

1

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The series *Topics in Heterocyclic Chemistry* presents critical reviews on “Heterocyclic Compounds” within topic-related volumes dealing with all aspects such as synthesis, reaction mechanisms, structure complexity, properties, reactivity, stability, fundamental and theoretical studies, biology, biomedical studies, pharmacological aspects, applications in material sciences etc. Metabolism will be also included which will provide information useful in designing pharmacologically active agents. Pathways involving destruction of heterocyclic rings will also be dealt with so that synthesis of specifically functionalized non-heterocyclic molecules can be designed.

The overall scope is to cover topics dealing with most of the areas of current trends in heterocyclic chemistry which will suit to a larger heterocyclic community.

As a rule contributions are specially commissioned. The editors and publishers will, however, always be pleased to receive suggestions and supplementary information. Papers are accepted for *Topics in Heterocyclic Chemistry* in English.

In references *Topics in Heterocyclic Chemistry* is abbreviated *Top Heterocycl Chem* and is cited as a journal.

Springer WWW home page: springer.com

Visit the THC content at springerlink.com

ISSN 1861-9282

ISBN-10 3-540-30983-7 Springer Berlin Heidelberg New York

ISBN-13 978-3-540-30983-3 Springer Berlin Heidelberg New York

DOI 10.1007/11497363

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Printed in Germany

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Cover design: *Design & Production* GmbH, Heidelberg

Typesetting and Production: LE-TeX Jelonek, Schmidt & Vöckler GbR, Leipzig

Printed on acid-free paper 02/3100 YL – 5 4 3 2 1 0

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Preface to the Series

Topics in Heterocyclic Chemistry presents critical accounts of heterocyclic compounds (cyclic compounds containing at least one heteroatom other than carbon in the ring) ranging from three members to supramolecules. More than half of the more than 10000 compounds listed in *Chemical Abstracts* are heterocyclic compounds. The branch of chemistry dealing with these heterocyclic compounds is called heterocyclic chemistry, which is the largest branch of chemistry and as such the chemical literature appearing every year as research papers and review articles is vast and can not be covered in a single volume.

This series in heterocyclic chemistry is being introduced to collectively make available critically and comprehensively reviewed literature scattered in various journals as papers and review articles. All sorts of heterocyclic compounds originating from synthesis, natural products, marine products, insects, etc. will be covered. Several heterocyclic compounds play a significant role in maintaining life. Blood constituents hemoglobin and purines, as well as pyrimidines, are constituents of nucleic acid (DNA and RNA). Several amino acids, carbohydrates, vitamins, alkaloids, antibiotics, etc. are also heterocyclic compounds that are essential for life. Heterocyclic compounds are widely used in clinical practice as drugs, but all applications of heterocyclic medicines can not be discussed in detail. In addition to such applications, heterocyclic compounds also find several applications in the plastics industry, in photography as sensitizers and developers, and the in dye industry as dyes, etc.

Each volume will be thematic, dealing with a specific and related subject that will cover fundamental, basic aspects including synthesis, isolation, purification, physical and chemical properties, stability and reactivity, reactions involving mechanisms, intra- and intermolecular transformations, intra- and intermolecular rearrangements, applications as medicinal agents, biological and biomedical studies, pharmacological aspects, applications in material science, and industrial and structural applications.

The synthesis of heterocyclic compounds using transition metals and using heterocyclic compounds as intermediates in the synthesis of other organic compounds will be an additional feature of each volume. Pathways involving the destruction of heterocyclic rings will also be dealt with so that the synthesis of specifically functionalized non-heterocyclic molecules can be designed. Each volume in this series will provide an overall picture of heterocyclic compounds

critically and comprehensively evaluated based on five to ten years of literature. Graduates, research students and scientists in the fields of chemistry, pharmaceutical chemistry, medicinal chemistry, dyestuff chemistry, agrochemistry, etc. in universities, industry, and research organizations will find this series useful.

I express my sincere thanks to the Springer staff, especially to Dr. Marion Hertel, executive editor, chemistry, and Birgit Kollmar-Thoni, desk editor, chemistry, for their excellent collaboration during the establishment of this series and preparation of the volumes. I also thank my colleague Dr. Mahendra Kumar for providing valuable suggestions. I am also thankful to my wife Mrs. Vimla Gupta for her multifaceted cooperation.

Jaipur, 31 January 2006

R.R. Gupta

Preface to Volume 1

The domestic microwave oven is one of the magnificent inventions used in the kitchen that contributes to simplifying the lives of many people, as the time for “cooking” an acceptable meal can be reduced to the time it takes to defrost and heat vacuum-packed food, altogether consuming less than half an hour.

It all started almost 60 years ago when P. Spencer, studying high-power microwave sources for radar applications, observed the melting of a chocolate bar in his pocket; at least that is the story told. The first patent in this field was filed by him in 1946 and one year later the first commercial microwave oven appeared on the market. We had to wait until 1955 for domestic models, but by 1976 almost 60% of US households already had a microwave oven.

Soon engineers and researchers realized that this technique possessed interesting applications for food processing, the drying industry, waste remediation, analytical chemistry, etc. Unfortunately organic chemists had to wait until 1986 before the first two publications concerning the application of microwaves in organic synthesis appeared in the literature, independently submitted by the groups of Gedye and Giguere/Majetich. Since then, the number of publications dealing with microwave-assisted organic synthesis (MAOS) has been growing steadily, having reached today a total of 2000, consisting of regular papers as well as several review articles and a few books describing the state of the art of microwave-assisted synthesis.

Especially since the appearance on the market at the end of the 1990s of dedicated single-mode systems, which are ideally suited for performing reactions under fully controlled conditions and on a small scale, microwave chemistry is also steadily finding its way into the labs of the more conservative amongst us. The main difference between conventional heating and microwave irradiation is the way the energy is transferred to the medium: in the former case this occurs via classical conduction, while in the latter an almost instantaneous transfer of energy to the reactants takes place.

There is still some dispute about how microwave irradiation accelerates reactions. Besides the generally accepted thermal effects, one believes that there are some specific (but also thermal) microwave effects, such as the formation of “hot spots”. There is still some controversy about the existence of non-thermal (athermal) microwave effects. At the present time, new techniques such as “cooling while heating” are being investigated and the problem of upscaling

for industrial purposes has been tackled with the introduction of continuous and stop-flow microwave systems, although there is certainly still a long way to go.

In the 1990s the technique of solid-phase organic synthesis (SPOS) became generally popular, but especially in the medicinal chemistry community, for lead detection and lead optimization via combinatorial techniques. The combination with microwave irradiation brought an elegant solution for the problem of the notoriously slower reactions compared to those in solution phase.

The aim of this book is to focus on the application of microwave irradiation in different fields of heterocyclic chemistry. As a result we are very proud to present eight selected contributions from eminent scientists in the field and one written by one of the editors (EVdE), dealing with different topics of heterocyclic chemistry. The first chapter describes the synthesis and functionalization of 2-pyridones, 2-quinolones and ring-fused 2-pyridones. An overview of microwave-assisted multicomponent reactions for the synthesis of heterocycles is given in the second chapter, followed by up-to-date reviews of the synthesis of sulfur and nitrogen-containing heterocycles in the third contribution, and solid-phase methods for the microwave-assisted synthesis of heterocycles in the fourth. The use of polymer-supported reagents is thoroughly discussed in the fifth chapter as well as the metal-based carbon-carbon and carbon-heteroatom bond formation for the synthesis and decoration of heterocycles. The final chapters are devoted to the synthesis of heterocycles via microwave-assisted cycloaddition and cyclocondensation reactions and an overview of 2(1*H*)-pyrazinone chemistry in solution and on solid support.

On this occasion we would like to thank all authors for sending their excellent contributions. We also would like to thank Springer for inviting us to be volume editors and for their valuable support during the production of this volume.

Heverlee and Graz, January 2006

Erik Van der Eycken
C. Oliver Kappe

Contents

Microwave-Assisted Synthesis and Functionalization of 2-Pyridones, 2-Quinolones and Other Ring-Fused 2-Pyridones N. Pemberton · E. Chorell · F. Almqvist	1
Microwave-Assisted Multicomponent Reactions for the Synthesis of Heterocycles M. C. Bagley · M. C. Lubinu	31
Microwave-Assisted Synthesis of Sulfur and Nitrogen-Containing Heterocycles T. Besson · V. Thiéry	59
Solid-Phase Methods for the Microwave-Assisted Synthesis of Heterocycles M. Erdélyi	79
Synthesis of Heterocycles Using Polymer-Supported Reagents under Microwave Irradiation S. Crosignani · B. Linclau	129
Transition-Metal-Based Carbon–Carbon and Carbon–Heteroatom Bond Formation for the Synthesis and Decoration of Heterocycles B. U. W. Maes	155
Synthesis of Heterocycles via Microwave-Assisted Cycloadditions and Cyclocondensations M. Rodriquez · M. Taddei	213

**The Chemistry of 2-(1*H*)-Pyrazinones
in Solution and on Solid Support**

N. Kaval · P. Appukkuttan · E. Van der Eycken	267
Author Index	305
Subject Index	307

Microwave-Assisted Synthesis and Functionalization of 2-Pyridones, 2-Quinolones and Other Ring-Fused 2-Pyridones

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1	Introduction	2
2	Synthesis of 2-Pyridone Containing Heterocycles	3
2.1	Synthesis of 2-Pyridone Containing Heterocycles Using Conventional Heating	3
2.2	Microwave-Assisted Synthesis of Monocyclic 2-Pyridones	6
2.3	Synthesis of 2-Quinolones	9
2.4	Microwave-Assisted Synthesis of Ring-Fused <i>N</i> -Substituted 2-Pyridones	13
3	Microwave-Assisted Functionalization of 2-Pyridones	15
3.1	Functionalization of 2-Pyridones Using Conventional Heating	16
3.2	Microwave-Assisted Substitution Reactions via Addition Elimination	17
3.2.1	Chloro Dehydroxylation	17
3.2.2	Amino Dehalogenation	18
3.3	Microwave-Assisted Substitution Reactions via Electrophilic Reagents	19
3.3.1	Mannich Reaction	19
3.3.2	Bromination	20
3.4	Microwave-Assisted Transition Metal Catalyzed Coupling Reactions	21
3.4.1	Suzuki Coupling	21
3.4.2	Heck Vinylation	22
3.4.3	Buchwald–Hartwig Coupling	22
3.4.4	Aminocarbonylation	23
3.4.5	Cyanodehalogenation	24
3.5	Microwave-Assisted Functional Group Transformations	25
3.5.1	Reduction and Hydrolysis of Nitriles	25
3.5.2	Decarboxylation Reactions	26
4	Concluding Remarks	27
	References	28

Abstract 2-pyridones are important heterocycles with great applicability in medicinal chemistry and this core structure can be found in compounds with various biological/medicinal applications. Here we show how microwave-assisted chemistry can be used to effectively synthesize and functionalize substituted monocyclic 2-pyridones, 2-quinolones and other ring-fused 2-pyridones. The chapter covers recent advancements in this field mainly describing methods developed with instruments specially designed for microwave-assisted organic synthesis (MAOS).

Keywords 2-Pyridone · 2-quinolone · Microwave-assisted reactions · Ring-fused 2-pyridone

Abbreviations

BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BMS	Borane methylsulfide
Bn	Benzyl
Bu	Butyl
dba	Dibenzylideneacetone
DCE	1,2-dichloroethane
DEAD	Diethyl azodicarboxylate
DMA	<i>N,N</i> -dimethylacetamide
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMFDMA	<i>N,N</i> -dimethylformamide dimethyl acetal
DMFDEA	<i>N,N</i> -dimethylformamide diethyl acetal
MAOS	Microwave-assisted organic synthesis
MW	Microwaves
NBS	<i>N</i> -bromosuccinimide
NMP	<i>N</i> -methyl-2-pyrrolidinone
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
rt	Room temperature

1

Introduction

This chapter describes microwave-assisted synthesis and functionalization of heterocycles that all have in common a 2-pyridone moiety. This core structure can be found in numerous biologically active compounds with diverse medicinal properties and is therefore considered a privileged structure in the pharmaceutical industry. The compounds represented in Fig. 1 are examples of a cardiotoxic agent for the treatment of heart failure **1** [1], a selective farnesyl protein inhibitor **2**, currently undergoing human clinical trials as an orally active antitumor agent [2], and a pilicide **3** that shows novel antibacterial properties by targeting bacterial virulence. They are also representatives of the three categories of 2-pyridones that will be covered in this chapter i.e., substituted 2-pyridones **4**, 2-quinolones **5** and other ring-fused 2-pyridones **6**.

Due to the importance of substituted 2-pyridones, many preparative methods have been reported (see Sect. 2.1), and some of these, but far from all, have been further developed into methods suitable for microwave-assisted organic synthesis (MAOS). Here we describe mainly methods performed with instruments specially designed for MAOS, thus excluding synthesis per-

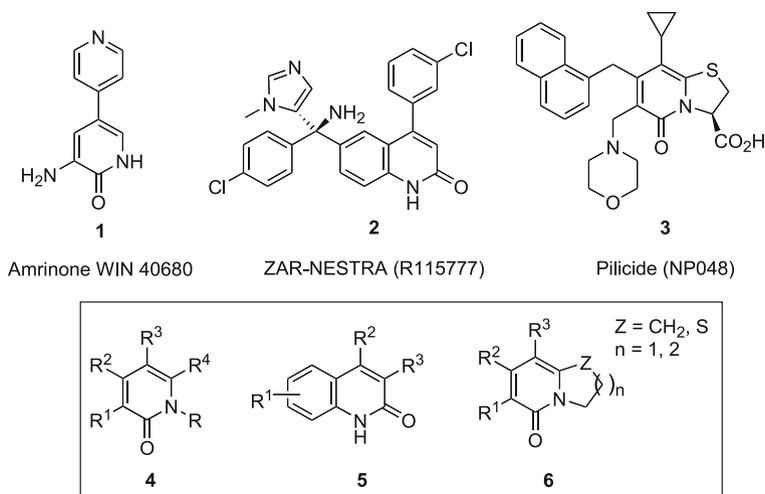


Fig. 1 Heterocycles bearing a 2-pyridone moiety with wide range of medicinal applications. Amrinone WIN 40680 **1** is a cardiotonic agent for the treatment of heart failure. ZAR-NESTRA **2** is a selective farnesyl protein inhibitor and NP048 **3** is a pilicide with novel antibacterial properties. The 2-pyridones **4**, **5** and **6** are schematic representations of the three categories of 2-pyridones that will be covered in this chapter i.e., substituted 2-pyridones **4**, 2-quinolones **5** and other ring-fused 2-pyridones **6**

formed in domestic microwave ovens. The experienced user of this technique will appreciate the fact that synthetic methods developed by conventional heating are not always directly transformable into MAOS. In this chapter, one will find examples where for instance the choice of solvent turns out to be crucial for an effective transformation. The methods described herein contain both reactions performed in solution as well as on solid supports and examples where different selectivities are obtained using microwave technique as compared to conventional heating are also shown. The last part of this chapter describes functionalization of 2-pyridones by microwave-assisted chemistry involving electrophilic and nucleophilic reagents, transition metal mediated cross-coupling reactions, and functional group transformations.

2

Synthesis of 2-Pyridone Containing Heterocycles

2.1

Synthesis of 2-Pyridone Containing Heterocycles Using Conventional Heating

The broad range of applications of 2-pyridone containing heterocycles has led to the development of numerous synthetic methods [3, 4], which dates back

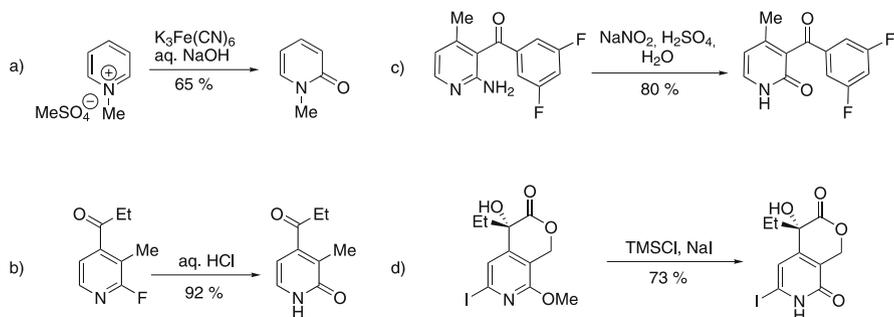
to 1892 when the oxidation of pyridinium salts to substituted 2-pyridones was reported (a, Scheme 1) [5,6]. The close relation to pyridine has been used in the preparation of 2-pyridones via hydrolysis of 2-fluoro-pyridines (b, Scheme 1) [7,8] or pyridine diazonium salts (c, Scheme 1) [9–11]. Many pathways based upon substituted pyridines can also be found in several approaches towards multi ring-fused natural products, such as Camptothecin and its analogues (d, Scheme 1) [12,13].

More general processes rely on variations of the Guareschi–Thorpe reaction [14] where condensations between 1,3-dicarbonyls and cyanoacetamide yield functionalized monocyclic 2(1*H*)-pyridones (a and b, Scheme 2) [15,16]. Unless the carbonyls are sufficiently different in reactivity, the reaction suffers from poor regioselectivity. The use of 3-alkoxy or 3-amino enones instead of 1,3-dicarbonyls has proven to be a versatile and reliable synthetic methodology where the 1,4-addition controls the regioselective outcome (c and d, Scheme 2) [17–19].

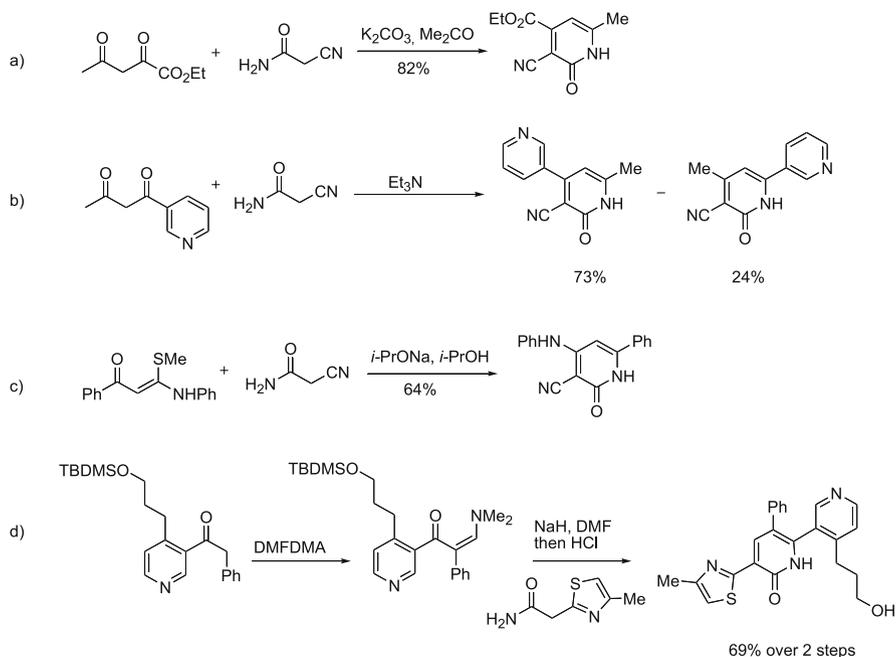
Other notable methods involve Hetero Diels–Alder reactions [20,21], and the reaction of vinyl isocyanates with enamines [22,23].

N-substituted 2-pyridones can be prepared by *N*-alkylation, under basic conditions (pK_a of the amide proton is ~ 11). The resulting anion can then react on either nitrogen or oxygen depending on the conditions employed [24–27]. Also, several direct methods for the construction of *N*-substituted 2-pyridones have been reported. Two such examples can be seen in Scheme 3 where the first example (a) is an intramolecular Dieckmann-type condensation [28] and the second (b) is a metal-mediated [2 + 2 + 2] reaction between alkynes with isocyanates [29,30].

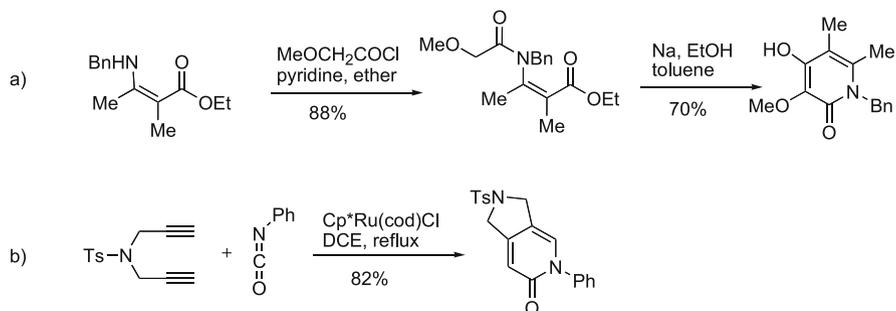
Bicyclic 2-pyridones fused over the nitrogen is another important heterocyclic scaffold. In the quest towards the total synthesis of Camptothecin, Danishefsky and co-workers developed a method where a vinylogous urethane was reacted with 1,3-dicarboxymethoxyallene generated in situ from dimethyl 3-chloroglutaconate to a bicyclic 2-pyridone intermediate [31–34]. This method has later been successfully applied in the synthesis of other



Scheme 1 A few routes for the synthesis of 2-pyridones from functionalized pyridines

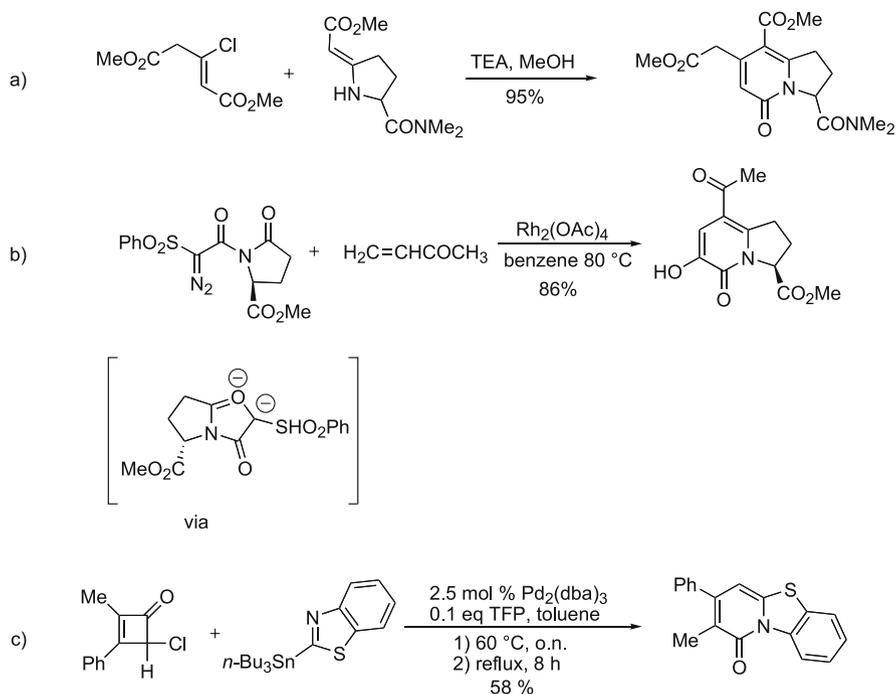


Scheme 2 Examples of synthesis of 2-pyridones either from 1,3-diketones (**a & b**) or from enamines (**c & d**)



Scheme 3 Examples of Dieckmann-type condensation (**a**) and [2 + 2 + 2] cycloaddition (**b**) leading to functionalized and ring-fused 2-pyridones

bicyclic 2-pyridones (**a**, Scheme 4) [35]. Another elegant approach is the Rh-catalyzed [3 + 2] cycloaddition between isomünchnone derivatives and alkenes applied in the synthesis of indolizine alkaloids (**b**, Scheme 4) [36, 37]. A third example of this category of reactions that result in bicyclic 2-pyridones is a Pd-catalyzed cross-coupling reaction (**c**, Scheme 4) developed in the Liebeskind laboratories [38].



Scheme 4 Synthesis of bicyclic 2-pyridones fused over the nitrogen

Obviously, some reactions are more suitable than others to be further developed into microwave-assisted methods. The following sections will cover some of the latest efforts made in this area but hopefully this previous section has shown that there are yet many other methods that are transformable into the more high throughput type of chemistry that MAOS can offer.

2.2

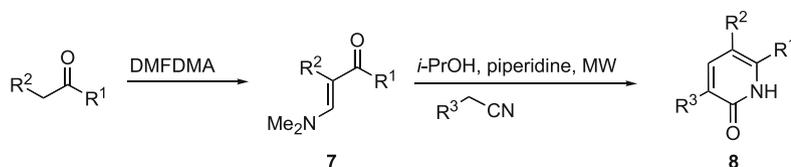
Microwave-Assisted Synthesis of Monocyclic 2-Pyridones

The condensation between enaminones and cyanoacetamide is a well-established method for the synthesis of 2-pyridones (see c, Scheme 2, Sect. 2.1), and the use of malonodinitrile instead of the amide component has also been shown to yield 2-pyridones [39–41]. Recently, Gorobets et al. developed a microwave-assisted modification of this reaction suitable for combinatorial synthesis, as they set out to synthesize a small library of compounds containing a 2-pyridone scaffold substituted at the 3, 5, and 6-positions [42]. The 2-pyridones were prepared by a three-component, two-step reaction where eight different carbonyl building blocks were reacted with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) to yield enaminones 7 (Fig. 2). The reactions were performed under solvent-free conditions at el-

evated temperatures and gave the desired enaminones in near-quantitative yields for the majority of the building blocks. Without further purification, these were then reacted with ten different methylene activated nitriles at 100 °C for 5 min using 2-propanol as solvent and catalytic amounts of piperidine as base. Out of the 80 possible diversely substituted 2-pyridones, 18 were isolated in moderate to high yields (27–96%), where the pure products **8** could be obtained by simple filtration in most of the cases.

As indicated, many of the more highly functionalized building blocks did not result in 2-pyridones. However, a thorough structure elucidation of by-products and intermediates was used to propose a mechanism for the formation of the 2-pyridone core based on a Michael addition followed by a “Dimroth-type” rearrangement (Fig. 3).

Another approach towards monocyclic *N*-unsubstituted 2-pyridones is based on a solid-phase supported Diels–Alder reaction where a resin-bound 2(1*H*)-pyrazinone **9** is reacted with acetylenic dienophiles (Fig. 4) [43]. The initially formed cycloadduct then undergoes a retro Diels–Alder reaction and depending on the substitution pattern of the starting pyrazinone the reaction



8 building blocks

10 building blocks

18 different 2-pyridones, 27–96%

Fig. 2 A library of 18 different functionalized 2-pyridones **8** were synthesized from enaminones **7** using microwave irradiation (single mode) [42]

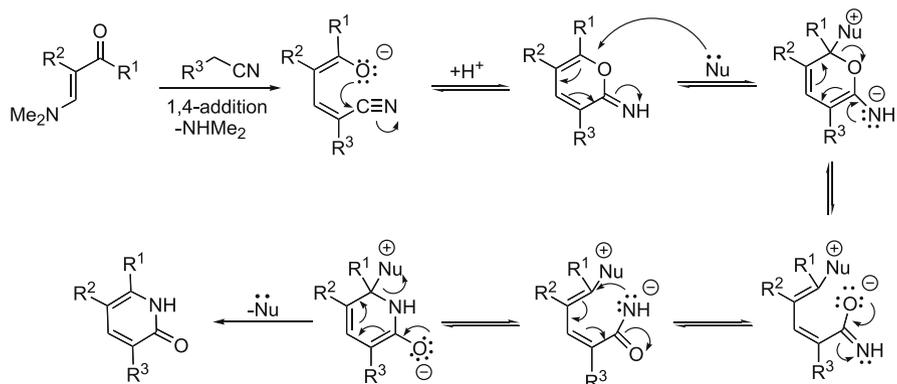


Fig. 3 Tentative mechanism for the formation of substituted 2-pyridones in the reaction between enaminones and methylene-activated nitriles

can take two directions thus rendering product mixtures. Either cyanogen chloride or isocyanate is lost, resulting in resin bound 2-pyridones **10** or pyridines **11**, respectively (Fig. 4). This method was first developed using conventional heating [44], and the chemistry has been applied in both solution and on solid-phase. In the case of the resin-bound method, the 2-pyridone is linked to the resin via the *N1* nitrogen, and cleavage under acidic conditions results in *N*-unsubstituted 2-pyridones.

It was also shown that the commercially available Wang resin is well suited for the reaction, but a tailor-made resin (based on syringealdehyde and Merrifield resin) offers milder cleavage conditions. By comparing conventional heating versus MAOS it was found that similar yields for the cycloaddition step were obtained, but the cleavage from the resin can be performed under much milder conditions when microwave irradiation is used, and in some cases the procedure only works using the microwave technique (Table 1).

The availability of functionalized 2(1*H*)-pyrazinone in combination with the use of microwave accelerated solid-phase chemistry constitutes a solid foundation for generating large libraries of compounds suitable for medicinal chemistry. The authors have also shown that the scaffold can be further functionalized using the principles of “click-chemistry”, thereby paving the way towards highly substituted 2-pyridone structures [45–47].

Table 1 Comparison between conventional heating and microwave irradiation for the cleavage of resin bound 2-pyridones under acidic conditions

Method A: Conventional heating		Yield (%) ^a	Method B: Microwave irradiation		Yield (%) ^a
Wang resin ^b	R ¹ = OMe	40%	Wang resin ^b	R ¹ = OMe	45%
	R ¹ = Ph	28%		R ¹ = Ph	27%
HMP-AM resin ^c	R ¹ = OMe	–	HMP-AM resin ^c	R ¹ = OMe	42%
	R ¹ = Ph	–		R ¹ = Ph	25%
Syringealdehyde	R ¹ = OMe	–	Syringealdehyde	R ¹ = OMe	41%
Resin	R ¹ = Ph	–	Resin ^d	R ¹ = Ph	25%

^a Isolated yields over two steps

^b refluxing in TFA

^c resulted in the formation of several by-products

^a Isolated yields over two steps

^b TFA:CH₂Cl₂ 1 : 2, 120 °C, 40 min

^c TFA:CH₂Cl₂ 1 : 9, 120 °C, 10 min

^d TFA:CH₂Cl₂ 5 : 95, 120 °C, 10 min

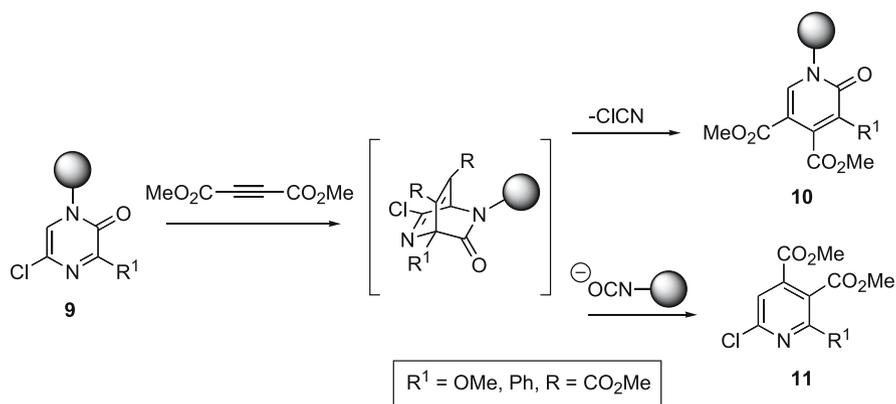


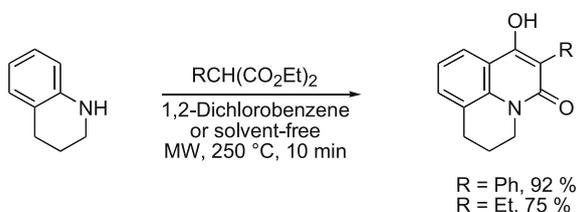
Fig. 4 Solid-phase synthesis of 2-pyridones via a Diels–Alder reaction and subsequent elimination of cyanogenchloride from the cycloadduct

2.3

Synthesis of 2-Quinolones

One frequently used method for synthesizing 2-quinolones is to react anilines with malonic esters. This reaction can be difficult to accomplish by conventional methods [48, 49] since high temperatures (250–350 °C) are required for the generation of an α -oxoketene intermediate **12** (Fig. 6). In a recent example of this type of reaction, Stadler et al. synthesized 4-hydroxyquinolin-2(1*H*)-ones by using a microwave-assisted procedure (Scheme 5) [50].

The reaction was performed in 1,2-dichlorobenzene, which dissolved the starting materials but not the product. Consequently, the precipitated product could be obtained in analytical purity by a simple filtration. The reaction also works by applying solvent-free microwave irradiation conditions, enlightening some green chemistry opportunities. It is worth noting that by mimicking the rapid heating obtained by microwave irradiation it is possible to get comparable yields of this type of 2-quinolones with other methods. This was shown by preheating an oil bath to 290 °C, which resulted in a temperature of 245 °C in the sealed process vial within 3 min, compared to 250 °C for the mi-



Scheme 5 Microwave-assisted synthesis of 2-quinolones

crowave irradiation method. However, the use of this method for larger scale reactions is obviously not recommended [50].

The reaction between anilines and malonic esters generates two equiv of ethanol, which could affect the equilibrium between the starting material and the product (Fig. 5). Therefore, in a sealed tube reaction, it is necessary to keep the volume and reactant concentrations low in order to shift the equilibrium towards product formation. Thus, large-scale experiments are not practical using this procedure (Fig. 5).

On the contrary, if the reaction is carried out using an open vessel technique, there is no pressure built up neither from the solvent nor from the ethanol formed in the reaction, and as a consequence the reaction can then be performed in larger scale [51, 52]. In agreement with the suggested mechanism, the synthesis of 4-hydroxyquinolin-2(1*H*)-ones **13** works best with an electron-donating group (R, Fig. 5) attached to the anilines. The nucleophilicity of the nitrogen then increases and both the condensation with the malonic ester as well as the ring closing acylation with the α -oxoketene **12** proceeds faster (Fig. 5). The presence of an aryl R²-group offers further conjugation and product stability resulting in higher yields (Fig. 5) [51].

However, when an electron-withdrawing group, e.g., a trifluoromethyl group, is attached to the anilines this procedure is not applicable. A way to circumvent this problem was enlightened by Glasnov et al. [53] who treated the malondianilide **14** with Eaton's reagent, a 7.7% solution of phosphorus pentoxide in methanesulfonic acid (a, Scheme 6) [54]. This reaction is, however, sensitive to time, temperature, and concentration. More reactive malondian-

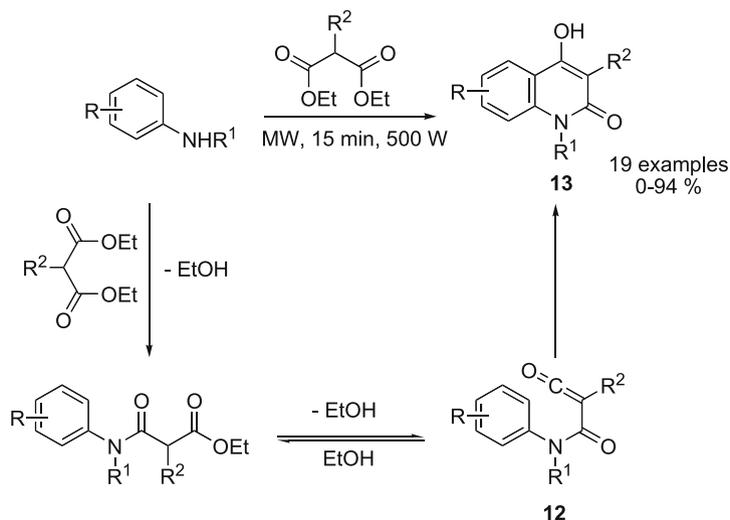
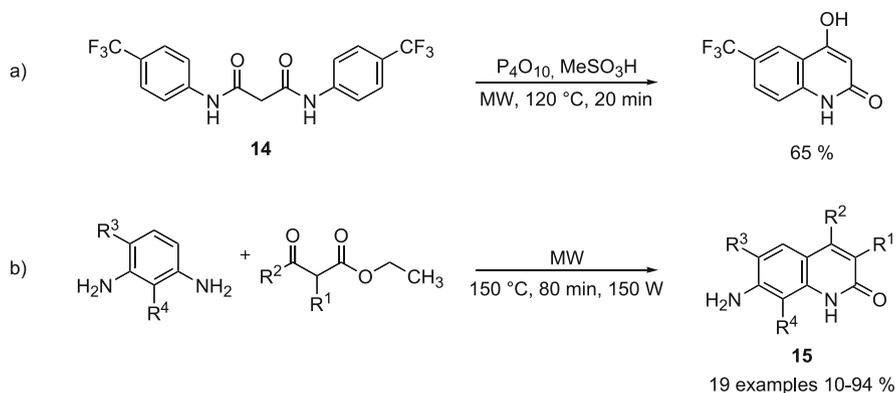


Fig. 5 Tentative mechanism for the formation of 3-substituted 4-hydroxyquinolones **13** in the reaction between anilines and substituted malonic esters via an α -oxoketene **12**



Scheme 6 Synthesis of 2-quinolones from 1,3-dicarbonyl compounds

ilides also work excellently with this method and result in 2-quinolones in isolated yields of 80–90%.

This technique has also been applied in the synthesis of carbostyryl analogues **15** and as in the previous example also this reaction is favored by an electron-rich group in the aniline-ring and an electron-poor group attached to the electrophilic specie (b, Scheme 6) [55]. The use of microwave irradiation can reduce the reaction times from 18–58 h to 80 min and the products are generally isolated in high yields and purities.

The methods described for synthesizing 2-quinolones has so far been dependent upon the formation of the intermediate α -oxoketene **12** (Fig. 5). There are, however, other methods for the formation of 2-quinolones. One

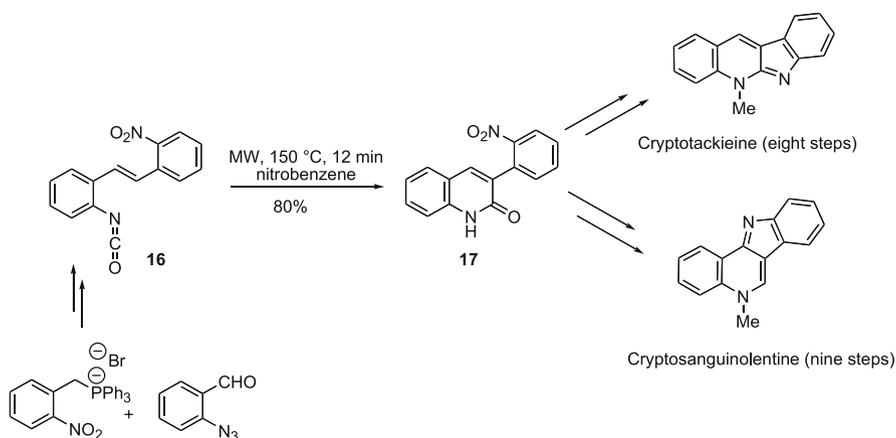
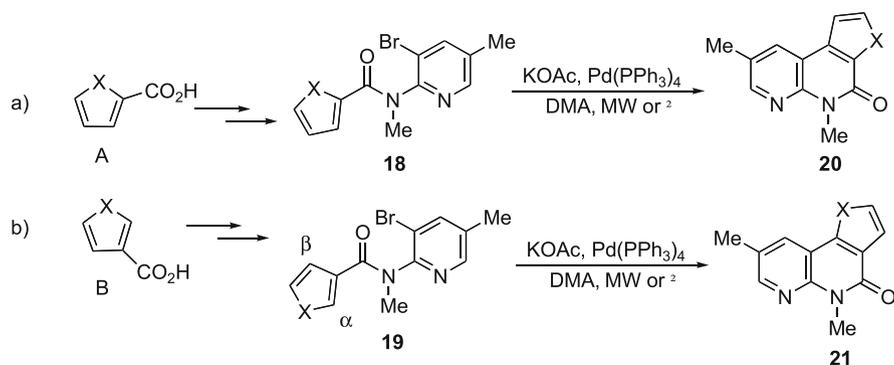


Fig. 6 Microwave promoted intramolecular cyclization of *o*-vinyl substituted isocyanates **16** leading to 2-quinolones

of these takes use of an *o*-vinyl substituted isocyanate **16**, which then yields the 3-aryl-substituted 2-quinolone **17** in 80% yield via a microwave-assisted electrocyclic ring-closure (Fig. 6) [56].

The last method for the preparation of 2-quinolones described in this chapter relies on an intramolecular Heck cyclization starting from heteroaryl-amides (Table 2) [57]. These are synthesized either from commercially available pyrrole- and thiophene-2-carboxylic acids (a, Table 2) or thiophene- and furan-3-carboxylic acids (b, Table 2) in three steps. The Heck cyclization is conventionally performed with *N,N*-dimethylacetamide (DMA) as solvent, KOAc as base and Pd(PPh₃)₄ as catalyst for 24 h at 120 °C resulting in the coupled products in 56–89% yields. As discussed in Sect. 3.4, transition metal-catalyzed reactions often benefit from microwave irradiation [58–61], and so is the case also for this intramolecular reaction. In fact, derivatives with an aryl iodide were successfully coupled by conventional methods, whereas the heteroaryl bromides **18** and **19**, shown in Table 2, could only be coupled in satisfying yields by using MAOS (Table 2).

Table 2 A comparison between conventional heating and microwave-assisted synthesis in an intramolecular Heck coupling to heterocyclic derivatives of 2-quinolones **20** and **21**. Note the high selectivity in (b), where two possibilities exist to fuse a six-membered ring



Starting-material	X	Conventional heating ^a		Microwave irradiation ^{a/b}	
		Yield [%]	<i>t</i> [h]	Yield [%]	<i>t</i> [min]
A	N – Me	52	24	90	30 ^b
A	S	49	24	92	12 ^a
B	S	49	24	96	12 ^a
B	O	36	24	91	30 ^b

^a 120 °C ^b 140 °C

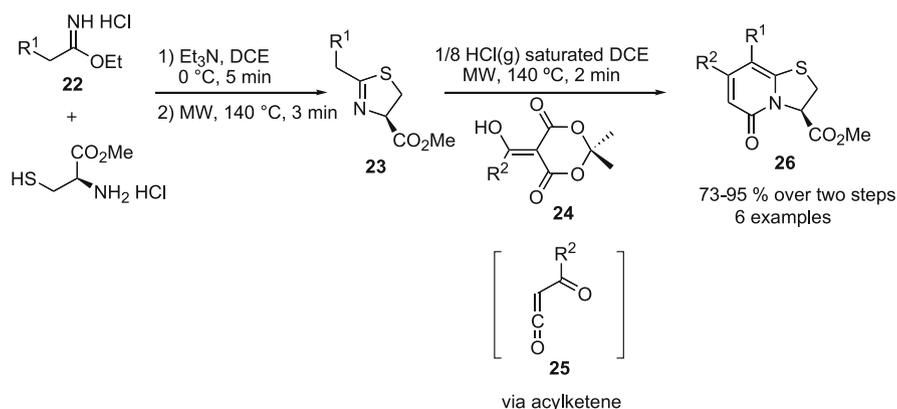
Hence, microwave irradiation in DMA for 12 min at 120 °C or 30 min at 140 °C, depending on the substrate, resulted in **20** or **21** in 90–96% yields, compared to yields around 50% and a 24 h reaction time for conventional heating. As can be seen in Eq. 2 in Fig. 5, two possibilities exist to connect the heteroaryl bromide part with the five-membered heterocycle (indicated by α and β , Table 2) that results in a six-membered 2-pyridone ring. Still, a very high selectivity was obtained yielding the 2-pyridones **21**, in which the new bond had been introduced at $C\alpha$. It should be noted that the obtained structures **20** and **21** represent heterocyclic derivatives of 2-quinolones rather than true 2-quinolones.

2.4

Microwave-Assisted Synthesis of Ring-Fused *N*-Substituted 2-Pyridones

Ring-fused 2-pyridone structures where the additional ring is fused over the nitrogen will be covered in this section. Other ring-fused systems can be obtained simply by using suitable cyclic starting materials or by conducting intramolecular reactions, examples for the preparation of such systems can be found in the papers discussed in Sect. 2.2 [42, 43].

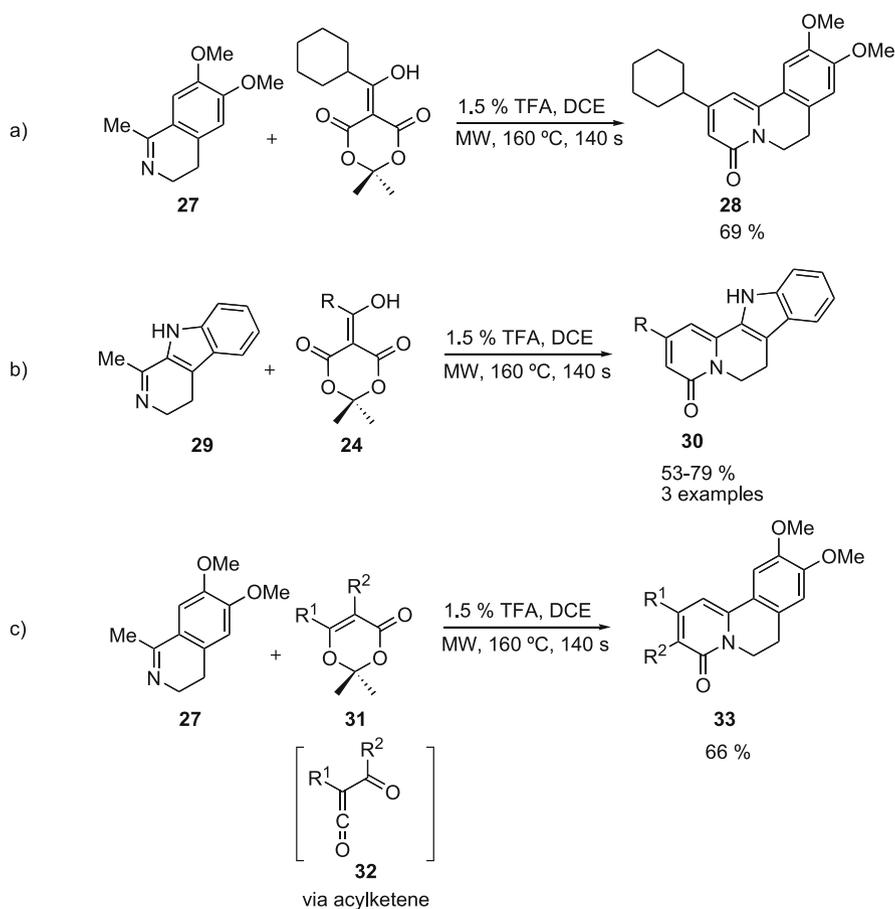
Optically active bicyclic 2-pyridones **26** have been prepared by a method based on reacting acyl-ketenes **25** with substituted Δ^2 -thiazolines **23** (Scheme 7) [62]. The thiazolines are prepared by reacting iminoethers **22** with cysteine and the acyl ketenes are generated in situ from acyl Meldrum's acid derivatives **24** (Scheme 7). The reaction has been performed both in solution [63] and by solid-phase techniques [64] using conventional thermal heating. The microwave-accelerated reaction, however, clearly offers advantages over the other two methodologies as the reaction can be performed in a two-step procedure shortening the reaction time to 8 + 2 min com-



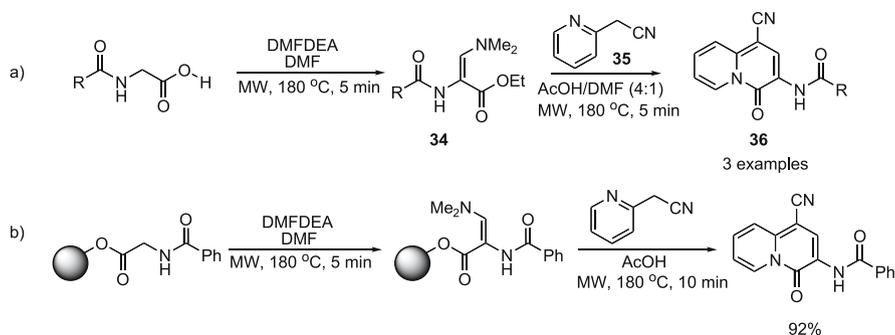
Scheme 7 Synthesis of chiral bicyclic 2-pyridones via acylketenes and Δ^2 -thiazolines

pared to 2 days when using conventional heating. In addition, less acid is needed in the microwave-assisted version, which results in milder conditions over all.

This method has been extended to include imines other than Δ^2 -thiazolines, hence enabling the synthesis of multi ring-fused 2-pyridones (**28**, **30**, and **33**, Scheme 8). Thus, by reacting dihydroisoquinolines **27** or β -carbolines **29** with acyl Meldrum's acid derivatives **24**, a set of new ring-fused heterocycles was prepared in moderate to excellent yields (a and b, Scheme 8). These systems were prepared by using trifluoro acetic acid (TFA) as a proton source instead of solutions saturated with HCl (g). The switch of acid proved to be advantageous since it reduced the formation of by-products and increased the isolated yields. From a practical point of view, TFA is also su-



Scheme 8 2-Pyridone synthesis from the reaction of acylketenes and imines



Scheme 9 Synthesis of ring-fused 2-pyridones via aminopropenoates using both solution-phase and solid-phase conditions

perior especially considering the potential of library synthesis in automated systems. Moreover, it was shown that a di-substituted acylketene **32** generated from the 5,6-disubstituted-1,3-dioxine-4-one **31** can be used to synthesize 3,4-substituted 2-pyridones **33** (c, Scheme 8), offering possibilities to prepare diversely substituted multi ring-fused systems in a direct manner.

Another method to synthesize ring-fused 2-pyridones relies on amino-propenoates **34** (Scheme 9) [65]. The aminopropenoates are prepared by reacting dimethylformamide diethyl acetal (DMFDEA) with CH-acidic carbonyl compounds (see also Sect. 2.2). Disubstituted quinolinones **36** are then formed by reacting these key intermediates **34** with bidentate C, N nucleophiles **35**, (a, Scheme 9). The method has also been performed on solid-phase support with the aminopropenoate anchored to the resin (b, Scheme 9) [66]. The heterocycle was released from the resin in an elegant cyclative cleavage step resulting in high purity and excellent yield (92%).

3

Microwave-Assisted Functionalization of 2-Pyridones

The previous sections have described methods to obtain 2-pyridone scaffolds. Both in the construction of new materials and especially in drug design and development, there is a desire to be able to derivatize and optimize the lead structures. In the following sections, some recent developments using MAOS to effectively substitute and derivatize 2-pyridone heterocycles are described. The reaction types described range from electrophilic-, and nucleophilic reactions to transition metal-catalyzed transformations (Fig. 7). To get an overview of how these systems behave, their characteristics under conventional heating is first described in brevity.

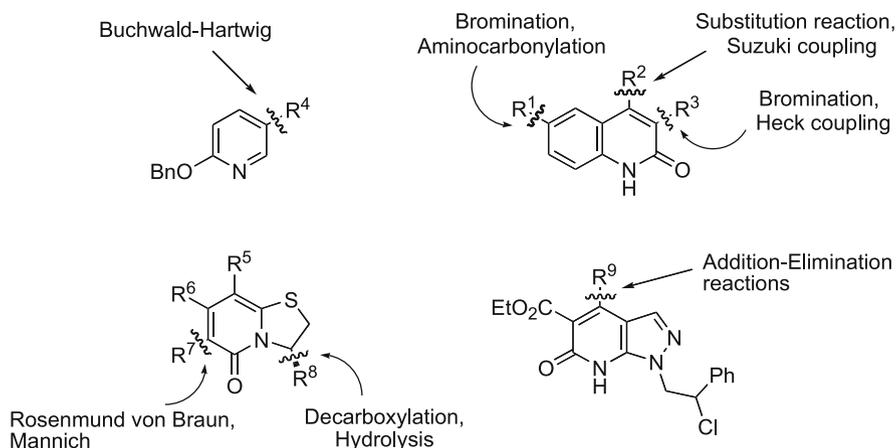
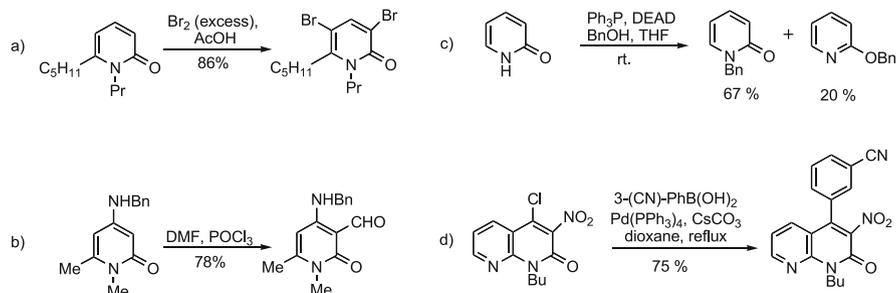


Fig. 7 Examples of microwave-assisted reactions and functional group transformations that are covered in Sect. 2

3.1

Functionalization of 2-Pyridones Using Conventional Heating

Taking into account the close relationship to pyridines one would expect 2-pyridones to express similar type of reactivities, but in fact they are quite different. 2-Pyridones are much less basic than pyridines (pK_a 0.8 and 5.2, respectively) and have more in common with electron-rich aromatics. They undergo halogenations (a, Scheme 10) [67] and other electrophilic reactions like Vilsmeier formylation (b, Scheme 10) [68, 69] and Mannich reactions quite easily [70, 71], with the 3 and 5 positions being favored. *N*-unsubstituted 2-pyridones are acidic and can be deprotonated (pK_a 11) and alkylated at nitrogen as well as oxygen, depending on the electrophile and the reaction conditions [24–26], and they have also been shown to react in Mitsunobu reactions (c, Scheme 10) [27].



Scheme 10 Various types of functionalizations of 2-pyridones using conventional heating

2-Pyridones can also be converted to 2-chloropyridines by exchanging the carbonyl functionality using phosphoroychloride (POCl_3) [72]. A combination of *N*-halosuccinimides and triphenylphosphine has also been applied to introduce halogens in this position [73]. The carbonyl functionality in 2-pyridones makes these systems reactive towards nucleophiles as well, which add in 1,4-reactions with displacement of halides [74]. The use of transition metal mediated couplings like Heck, and Suzuki have also been successfully applied on halogenated 2-pyridones (d, Scheme 10) [36, 75].

3.2

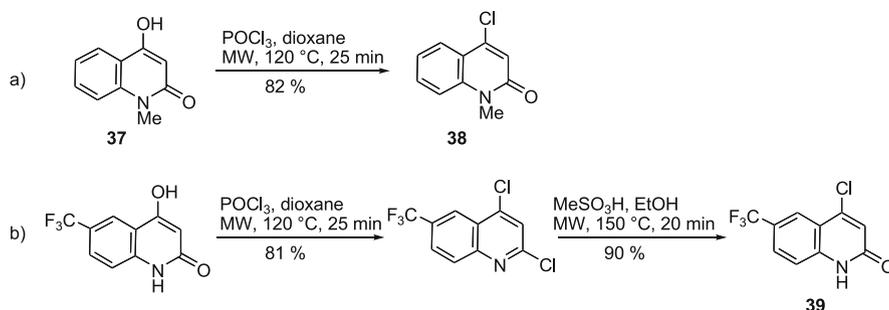
Microwave-Assisted Substitution Reactions via Addition Elimination

3.2.1

Chloro Dehydroxylation

Many types of reactions (e.g., organometallic transformations and nucleophilic substitution reactions) are performed with halogen containing starting materials wherefore effective methods to introduce halogens are desired. A common method to achieve this is to exchange a hydroxy group for a chloro substituent by using phosphoroychloride (POCl_3). This reagent has also proven successful for chlorination of hydroxy substituted 2-pyridones [48, 72, 75]. Under conventional heating conditions, this substitution reaction is typically carried out at elevated temperatures for 3 h using POCl_3 in excess. Glasnov et al. showed that this transformation could be effectively performed with microwave irradiation using dioxane as solvent and only 2 equiv of POCl_3 [53]. Hence, 4-hydroxyquinolin-2(1*H*)-one **37** was transformed into 4-chloroquinolin-2(1*H*)-one **38** in 82% yield with microwave irradiation at 120 °C for 25 min in dioxane and 2 equiv of POCl_3 (a, Scheme 11).

Selective C4 monochlorination can be accomplished when the reaction is performed with *N*1-substituted 2-quinolones, however, when performing the transformation on *N*-unsubstituted 2-quinolones both the 2 and



Scheme 11 Chloro dehydroxylation of 4-hydroxy-2-quinolones under microwave irradiation

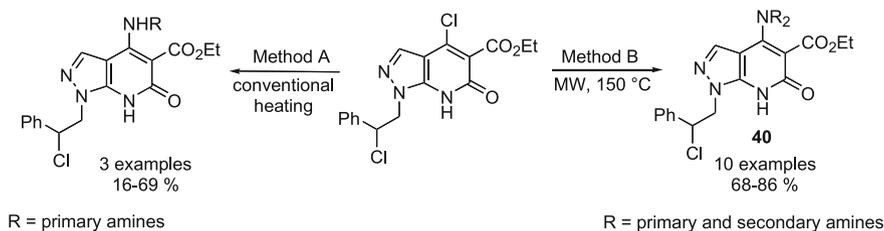
4 positions are chlorinated. A well-designed route to solve this problem was reported by Glasnov et al. who used a microwave-assisted two-step chlorination/hydrolysis sequence to get the monochlorinated product **39** in high yield (b, Scheme 11).

3.2.2

Amino Dehalogenation

Microwave-assisted synthesis has previously proved to be very efficient when performing nucleophilic addition elimination reactions [52, 74]. Fozza et al. applied this methodology to synthesize a set of ten different pyrazolo[3,4-*b*]pyridone derivatives **40** to obtain compounds with antagonistic activity on adenosine receptors (Fig. 8) [76]. The molecular diversity is introduced in the last step of the reaction protocol through a microwave-assisted amino dehalogenation. The displacement of the C4 chloro substituent was performed by irradiating different amines in glacial acetic acid and dioxane to a final temperature of 150 °C over 10 min (300 W). Washing and recrystallization from ethanol gave ten amino substituted pyrazolo[3,4-*b*]pyridones **40** in high yields (68–86%).

The use of microwave irradiation for this reaction, compared to conventional thermal heating, was investigated. Chloroform used as solvent under the conventional heating did only allow a temperature of 60 °C and a direct comparison between the two methods is therefore somewhat unfair under these circumstances. Nevertheless, the microwave-assisted method is attractive and proved useful for both primary and secondary amines resulting in highly substituted pyrazolo ring-fused pyridones **40** in 68–86% yields within only 10 min.



Method A: amine, CHCl₃, 60 °C, 2 h

Method B: amine, CH₃COOH, dioxane, MW, 300 W, 10 min

Fig. 8 A comparison of the results from microwave and conventional heating for amino-dehalogenation on 2-pyridones

3.3

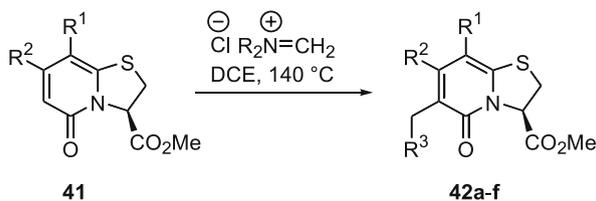
Microwave-Assisted Substitution Reactions via Electrophilic Reagents

3.3.1

Mannich Reaction

The Mannich reaction has been known since the early 1900s [77] and is an important C–C bond-forming reaction [78]. However, poor yields and formation of by-products sometimes appear as limitations of this reaction. These problems can sometimes be diminished by using preformed iminium salts and a shortened reaction time, and this strategy was utilized when Pemberton et al. introduced symmetrical dialkylaminomethylenes into highly substituted ring-fused 2-pyridones **41** (Table 3). Besides using preformed methyleneammonium chloride salts, microwave irradiation proved successful in the synthesis of the desired 2-pyridones **42** (48–93% yields, Table 3) [79]. The sterically more challenging 2-pyridones **42a–42d** were not obtained by conventional methods but by applying the microwave-assisted method these could be prepared in acceptable yields (48–66%, Table 3 entry 1–4). The optical purity was only affected to a small extent in this reaction and the tertiary amine **42c** was obtained with an ee drop of only 4% compared to the starting material.

Table 3 Highly substituted 2-pyridones were aminomethylated by utilizing a microwave-assisted Mannich reaction

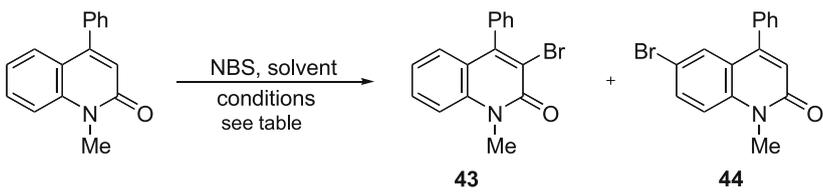


Entry	Product	R ¹	R ²	R ³	Time (s)	Eq. iminium salt	Yield (%)
1	42a	CH ₂ -1-naphthyl	phenyl	morpholine	800	2.2 + 1.1	64
2	42b	CH ₂ -1-naphthyl	phenyl	NMe ₂	800	2.2 + 1.1	48
3	42c	CH ₂ -1-naphthyl	cyclopropyl	morpholine	800	2.2 + 1.1	66
4	42d	CH ₂ -1-naphthyl	cyclopropyl	NMe ₂	800	2.2 + 1.1	55
5	42e	methyl	phenyl	morpholine	400	2.2	93
6	42f	methyl	phenyl	NMe ₂	400	2.2	92

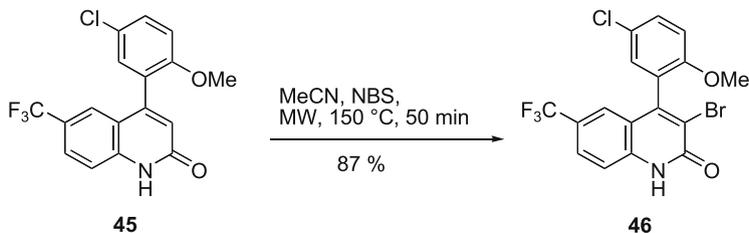
3.3.2 Bromination

There are many examples of brominations of 2-quinolones and other 2-pyridone containing structures [80–82]. Since 2-pyridones are easily brominated in positions 3 and/or 5 by using bromine in acetic acid at room temperature for 15 min [79], the need for improvements with MAOS appear limited. Still, Glasnov et al. reported an interesting selectivity observation when they performed microwave-assisted bromination of 2-quinolones with *N*-bromosuccinimide (NBS) (Table 4) [53]. When carried out at 25 °C for 4.5 h, a mixture of 3- and 6-bromo-quinolone (**43** and **44**, respectively) was obtained with a ratio of 83 : 17. However, microwave irradiation at 100 °C for 20 min in acetonitrile with 2.5 equiv of NBS favored the thermodynamically more stable 6-bromo-quinolone isomer **44** in a ratio of 95 : 5. The 3-bromoquinolone isomer **43** could be synthesized at low temperature, without MAOS, by using DMF as solvent at 0 °C for 17 h (79%).

Table 4 Results of the bromination of 2-quinolones under various conditions, including microwave irradiation



Solvent	Temp (°C)	Time (h)	Ratio 43 : 44
DMF	0 (Δ)	17	92 : 8
DMF	25 (Δ)	4.5	83 : 17
DMF	50 (Δ)	3.0	55 : 45
MeCN	100 (MW)	0.3	5 : 95



Scheme 12 Bromination of 2-quinolones using NBS and microwave irradiation

When position 6 on the 2-quinolone is blocked, bromination takes place selectively at the 3-position. Thus, microwave irradiation of **45** in acetonitrile at 150 °C for 50 min afforded the 3-bromo-quinolin-2(1*H*)-one **46** in 87% yield (Scheme 12).

3.4

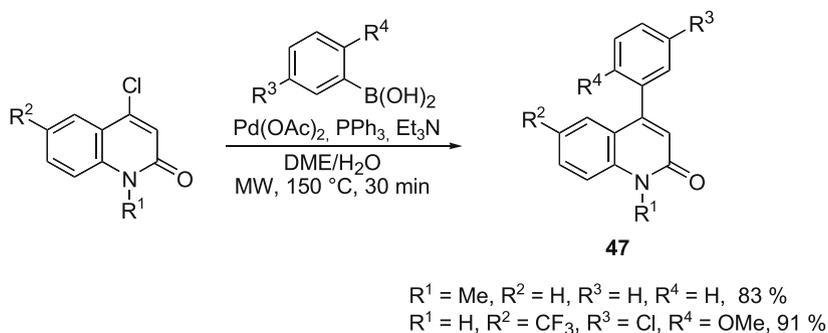
Microwave-Assisted Transition Metal Catalyzed Coupling Reactions

Halogen-substituted 2-pyridones are key intermediates for further metal-catalyzed coupling reactions and the halogenation of these scaffolds has already been described in previous sections. In the following section, a variety of C–C and C–N cross-coupling reactions under microwave-assisted conditions are described with some illustrative examples.

3.4.1

Suzuki Coupling

The Suzuki reaction has been successfully used to introduce new C–C bonds into 2-pyridones [75, 83, 84]. The use of microwave irradiation in transition-metal-catalyzed transformations is reported to decrease reaction times [52]. Still, there is, to our knowledge, only one example where a microwave-assisted Suzuki reaction has been performed on a quinolin-2(1*H*)-one or any other 2-pyridone containing heterocycle. Glasnov et al. described a Suzuki reaction of 4-chloro-quinolin-2(1*H*)-one with phenylboronic acid in presence of a palladium-catalyst under microwave irradiation (Scheme 13) [53]. After screening different conditions to improve the conversion and isolated yield of the desired aryl substituted quinolin-2(1*H*)-one **47**, they found that a combination of palladium acetate and triphenylphosphine as catalyst (0.5 mol %), a 3 : 1 mixture of 1,2-dimethoxyethane (DME) and water as solvent, triethylamine as base, and irradiation for 30 min at 150 °C gave the best result. Crucial for the reaction was the temperature and the amount of water in the



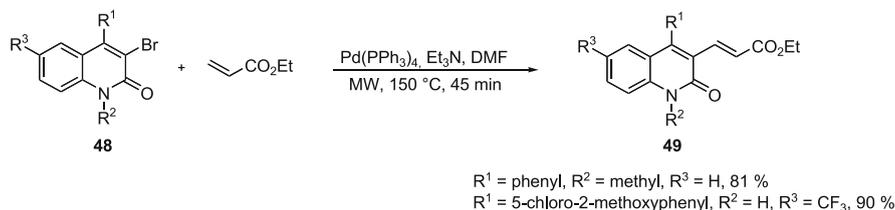
Scheme 13 Microwave-assisted Suzuki coupling of 4-chloro-2-quinolones

solvent mixture. A higher temperature leads to the formation of by-products and different water/DME ratios resulted in either incomplete conversion or hydrolysis of the starting material.

3.4.2

Heck Vinylation

As for the Suzuki reaction, the palladium-mediated Heck coupling has been reported to be a successful method to introduce new C–C bonds into 2-pyridone scaffolds [36, 85]. But here also, reports of using microwave irradiation are limited, even though it can drastically decrease the reaction times [58]. Scheme 14 shows a microwave-assisted Heck vinylation of 3-bromo-1-methyl-4-phenylquinolin-2(1*H*)-one **48** with ethyl acrylate [53]. Dehalogenations are often observed as undesired side reactions during Heck couplings. By performing the reaction with 3 mol % tetrakis(triphenylphosphine)palladium(0), 3 equiv of triethylamine, and DMF as solvent at 150 °C for 45 min, only minor amounts (less than 5%) of dehalogenated 2-quinolone was formed and the desired product **49** was isolated in a 81% yield (Scheme 14). Changing solvent or catalyst loadings resulted in incomplete conversion of starting material.



Scheme 14 Microwave-promoted Heck vinylation of 3-bromo-2-quinolones

3.4.3

Buchwald–Hartwig Coupling

Palladium-catalyzed aminations of aryl halides is now a well-documented process [86–88]. Heo et al. showed that amino-substituted 2-pyridones **54** and **55** can be prepared in a two-step procedure via a microwave-assisted Buchwald–Hartwig amination reaction of 5- or 6-bromo-2-benzyloxy pyridines **50** and **51** followed by a hydrogenolysis of the benzyl ether **52** and **53**, as outlined in Fig. 9 [89]. The actual microwave-assisted Buchwald–Hartwig coupling was not performed directly at the 2-pyridone scaffold, but instead at the intermediate pyridine. Initially, the reaction was performed at 150 °C for 10 min with $\text{Pd}_2(\text{dba})_3$ as the palladium source, which provided both the desired amino-pyridines (65% yield) as well as the debrominated pyridine. After improving the conditions, the best temperature and time to use proved

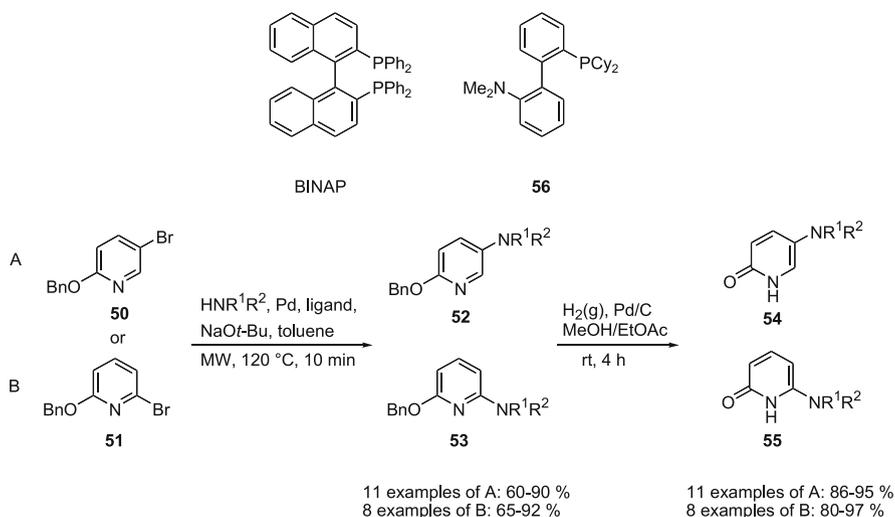


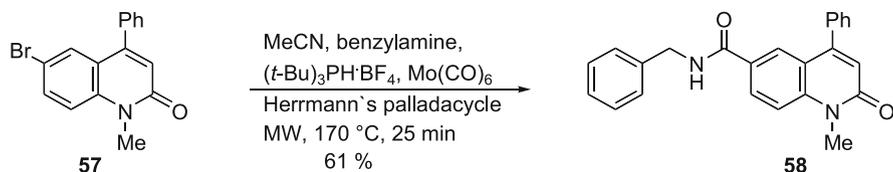
Fig. 9 Examples of Buchwald–Hartwig amination of bromo-pyridines and subsequent hydrogenolysis leading to amino-substituted 2-pyridones

to be 120 °C for 10 min. Different phosphine ligands and bases were examined for the reaction resulting in the use of $\text{Pd}_2(\text{dba})_3$ together with either BINAP or the amino phosphine ligand **56**, and NaOt-Bu as the best combinations. Thus, 5- or 6-aminosubstituted 2-benzyloxy-pyridines **52** and **53** were prepared in 60–90% yield. The corresponding amino-substituted 2-pyridones **54** and **55** were thereafter obtained in yields from 80–97% by hydrogenation with hydrogen gas, Pd/C in MeOH/EtOAc at room temperature for 4 h (Fig. 9).

3.4.4

Aminocarbonylation

An attractive method to synthesize amide substituted aryls is to perform an aminocarbonylation coupling where amines and a carbon monoxide source (e.g., molybdenum hexacarbonyl) together with an aryl halide and a catalyst, most commonly a Pd(0) specie, result in a one pot amido dehalogenation [90, 91]. As mentioned earlier for the Heck and Buchwald–Hartwig couplings, this reaction also sometimes suffers from a side reaction where dehalogenation occurs and aryl chlorides are often difficult to use. Herrero et al. have shown that MAOS, in combination with Herrmann's palladacycle [92] (5 mol %) and Fu's salt $[(t\text{-Bu})_3\text{PH}]\text{BF}_4$ as catalyst system together with molybdenum hexacarbonyl as a solid carbon monoxide source is very advantageous in aminocarbonylations [93]. It has recently been shown that this methodology can also be useful with aryl chlorides as starting materials [94]. Glasnov et al.



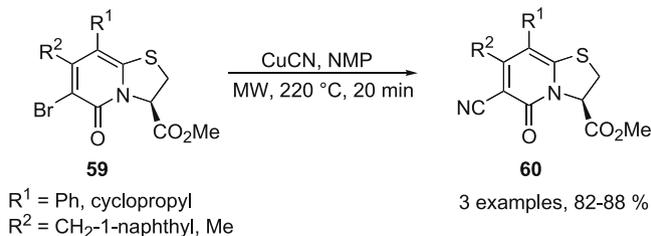
Scheme 15 Microwave-assisted aminocarbonylation of 2-quinolones

took use of this method to synthesize a 6-amido-4-phenylquinolin-2(1H)-one **58** from the corresponding 6-bromo derivative **57** (Scheme 15) [53]. The introduced carbonyl may serve as a handle for the synthesis of ZAR-NESTRA 2 (Fig. 1) and analogues thereof.

3.4.5

Cyanodehalogenation

The cyano group is a very attractive functionality due to the many possibilities to further transformations into a variety of functional groups. Various cyanodehalogenation procedures employing transition-metal catalysts e.g., palladium-catalyzed reactions together with zinc cyanide as the cyanide source have worked well with aryl halides [95, 96]. Another cyanodehalogenation method is the original Rosenmund von Braun cyanation, in which aryl halides are treated with CuCN in refluxing DMF [97]. Recent reports of alternative cyanodehalogenation reactions performed on aryl halides have shown that microwave-assisted organic synthesis can improve this reaction significantly [95, 98–100]. Pemberton et al. used this methodology for microwave-assisted cyanodehalogenation of highly substituted ring-fused 2-pyridones **59** (Scheme 16) [79]. The synthesis was first performed under conventional thermal heating conditions, but long reaction times and a harsh workup procedure resulted in low and irreproducible yields. The first attempts using microwave irradiation still gave rather low yields (< 30%) and a lot of unconsumed starting material, problems that were not solved by a prolonged reaction time. However, by increasing the temperature and using *N*-methyl-2-



Scheme 16 Cyanodehalogenation of ring-fused 2-pyridones

pyrrolidinone (NMP) as solvent, the reaction could be significantly improved and cyano-substituted 2-pyridones **60** were obtained in high yields within 20 min.

3.5

Microwave-Assisted Functional Group Transformations

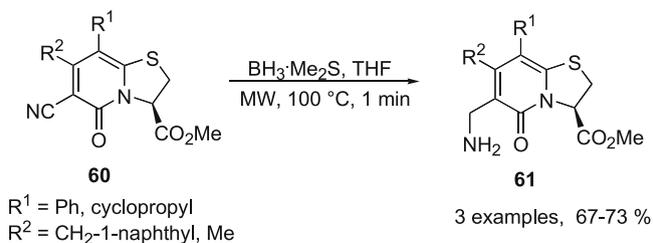
Simple functional group transformations are very effective in altering the characteristics of a compound. Hydrophobicity, acidity, etc. can easily be changed, by, for instance, an oxidation, a reduction, or a hydrolysis. Also, methods to remove a functional group can be of great importance since the functionality can be used either as a handle in solid-phase supported chemistry or as a blocking or directing group earlier in the synthetic route. Here, a couple of useful transformations are shown where microwave-assisted organic synthesis has been used as a powerful tool. Indeed, some of the transformations shown were only possible to perform with MAOS while others had a different outcome compared to conventional heating methodologies.

3.5.1

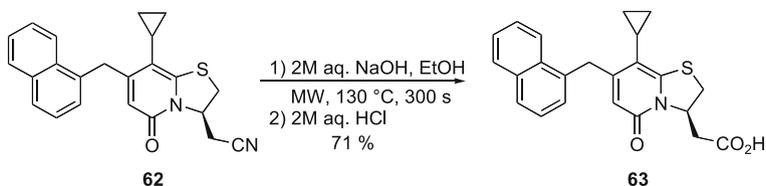
Reduction and Hydrolysis of Nitriles

Reduction of a nitrile is commonly used to synthesize primary amines and there are several methods reported for this transformation. Pemberton et al. applied several of these, including hydrogenation with different catalysts as well as nucleophilic and electrophilic reducing agents, in order to reduce a nitrile in ring-fused 2-pyridones **60** without success [79]. The only reagent that gave detectable amounts of product was $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (BMS) after long reaction times. Heating the reaction mixture overnight gave a substantial increase of product but still a lot of starting material remained and the conditions also led to significant amounts of by-products. However, these problems were solved by applying MAOS and the desired primary amines **61** could be isolated in 67–73% yield after irradiation at 100 °C for 60 s (Scheme 17).

Hydrolysis of nitriles normally requires quite harsh conditions and long reaction times [101, 102]. Applying microwave irradiation for this type of re-



Scheme 17 Reduction of nitriles using borane dimethyl sulfide and microwave irradiation



Scheme 18 Hydrolysis of nitriles to carboxylic acids under microwave irradiation

action is one way to shorten the reaction time. One successful example is the microwave-assisted alkaline hydrolysis of a nitrile, positioned in a ring-fused 2-pyridone **62** (Scheme 18) [103]. Full conversion of the starting material was observed within 5 min at 130 °C in a 3 : 1 mixture of EtOH and NaOH (2 M aq.) rendering the corresponding carboxylic acid **63** in 71% yield after acidic work up.

3.5.2

Decarboxylation Reactions

Decarboxylation reactions performed on activated or aromatic carboxylic acids, e.g., β -keto acids, is a well-known synthetic transformation. However, the reaction has also been applied on other systems, e.g., *N*-carboxythiopyridones, *N*-acyloxypthalimides and by thermolysis of preesters [104–106].

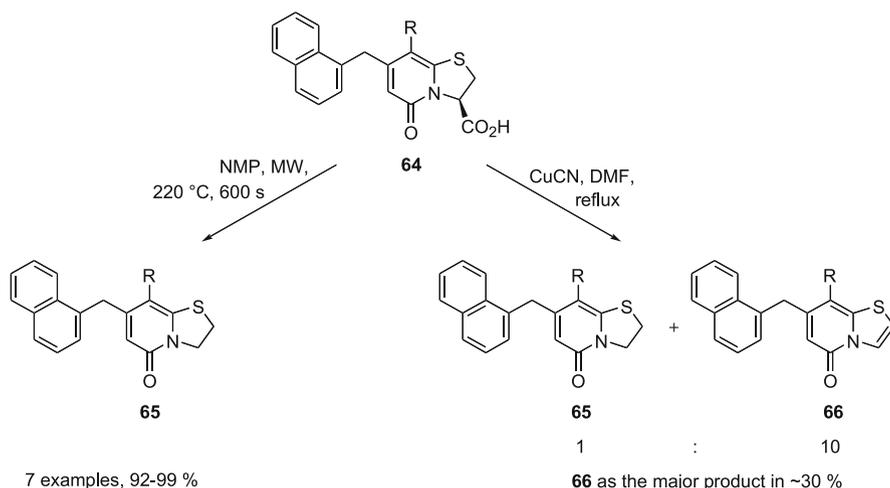


Fig. 10 2-Pyridone carboxylic acids **64** can be selectively decarboxylated to the saturated derivatives **65** via a reagent-free microwave-assisted method. Decarboxylation was also conducted under conventional heating but then copper cyanide was required resulting in mixtures of saturated and unsaturated 2-pyridones

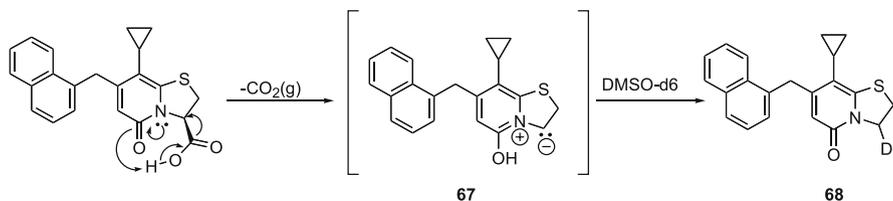


Fig. 11 A tentative mechanism for the reagent-free decarboxylation of ring-fused 2-pyridones obtained under MAOS conditions

The use of microwave irradiation for decarboxylation reactions is well appreciated [107–110]. Still, only one example of a decarboxylation performed on 2-pyridone starting materials has been reported (Fig. 10) [111]. Notably, this decarboxylation reaction is a selective and reagent-free method performed in *N*-methyl-2-pyrrolidinone (NMP) and microwave irradiation at 220 °C for 10 min. The products **65** were isolated in excellent yields (92–99%) by a simple aqueous work-up (Fig. 10).

It was shown in the same article that the decarboxylation could also be performed by conventional heating but then copper cyanide was required and a mixture of saturated and unsaturated 2-pyridones **65** and **66** was obtained in a ratio of 1 : 10 (Fig. 10). A tentative mechanism was suggested for the reagent-free MAOS method where the carbonyl in the 2-pyridone ring is supposed to assist in the decarboxylation yielding an ylide **67** (Fig. 11). The decarboxylated bicyclic 2-pyridone **68** is thereafter obtained after protonation by the solvent. In agreement with the mechanistic suggestion, it was shown that a selective deuteration occurred when deuterated dimethyl sulfoxide (DMSO-d₆) was used as solvent.

This microwave-assisted decarboxylation method may have broader applicability as indicated by Åberg et al. who showed two other successful examples of decarboxylations [111].

4

Concluding Remarks

This chapter has taken the reader through a number of microwave-assisted methodologies to prepare and further functionalize 2-pyridone containing heterocycles. A survey of inter-, intramolecular-, and pericyclic reactions together with electrophilic, nucleophilic and transition metal mediated methodologies has been exemplified. Still, a number of methods remain to be advanced into microwave-assisted organic synthesis and we hope that the “smorgasbord” of reactions presented in this chapter will inspire to more successful research in this area.

Acknowledgements We are very grateful to Prof. Dr. Basudeb Basu and M.Sc. Veronica Åberg for helpful discussions in the process of finalizing this book chapter.

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Microwave-Assisted Multicomponent Reactions for the Synthesis of Heterocycles

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1	Introduction	32
2	Classical Multicomponent Reactions	33
2.1	Biginelli Cyclocondensation	34
2.2	Hantzsch 1,4-Dihydropyridine Synthesis	36
2.3	Ugi Reaction	39
3	Synthesis of Simple Heterocycles	41
3.1	Five-Membered Heterocycles	42
3.2	Six-Membered Heterocycles and Benzo-Derivatives	46
4	Synthesis of Fused Heterocycles	49
4.1	Pyrido[2,3- <i>d</i>]pyrimidines and Related Heterocycles	49
4.2	Cycloaddition Reactions	51
5	Perspectives	55
	References	56

Abstract Multicomponent reactions offer convenient procedures for the introduction of many points of structural diversity into heterocyclic compounds prepared in a straightforward manner in a single synthetic step. Combining these features with the extremely fast reaction kinetics of microwave-assisted organic synthesis provides new methods for the rapid and efficient synthesis of heterocyclic libraries suitable for biological evaluation and SAR studies. This review describes recent discoveries in microwave-assisted multicomponent reactions, primarily carried out using modern microwave synthesizers, for the preparation of both simple and fused heterocyclic targets. Advances in our understanding and the application of traditional multicomponent processes, including the Biginelli, Hantzsch and Ugi condensation reactions, for the synthesis of heterocycles are described, as well as a number of newly discovered multicomponent reactions for the preparation of nitrogen-, oxygen- and sulfur-containing, five- and six-membered, partially unsaturated or fully aromatic, heterocyclic rings. Methods for the construction of more complex fused heterocyclic motifs, and the benzo-derivatives of simple heterocycles, are described, with particular emphasis on new combinatorial methodology and the introduction of structural diversity. In many cases, microwave irradiation offers considerable improvements in chemical yield and constitutes a very simple and extremely rapid method to access a diverse range of heterocyclic motifs.

Keywords Heterocycles · Multicomponent reactions · Microwave · Organic synthesis

Abbreviations

DCE	1,2-dichloroethane
DIPEA	Diisopropylethylamine
DHP	Dihydropyridine
DHPM	Dihydropyrimidine
F-SPE	Fluorous solid phase extraction
MAOS	Microwave-assisted organic synthesis
MCR	Multicomponent reaction
Nap	2-naphthyl
PEG	Polyethylene glycol
PS-DMAP	Polystyrene-bound dimethylaminopyridine
Rf ₈	Perfluorooctyl, C ₈ F ₁₇
RT	Room temperature
SAR	Structure-activity relationship

1

Introduction

The development of new methods in combinatorial chemistry for the rapid synthesis of heterocyclic compound libraries, both in solution and on solid phase, has attracted considerable attention in recent times [1] for the preparation of diverse structural motifs of biological and pharmaceutical importance [2]. By incorporating points of diversity in substituents, the heterocyclic motif and appended functional groups, the SAR of biologically relevant scaffolds can be evaluated. Many domino and multicomponent reactions (MCRs) enable three or more reactive partners to be combined, either sequentially or simultaneously in one pot, to give a target library that incorporates diversity simply by varying the constitution of the starting subsets. It is this feature that has made the discovery and development of new MCRs, as well as the reinvestigation of existing processes, an important focus of current synthetic research, directed towards improving their rapidity and facility, toleration of diverse precursors, chemical yield and library purity. The potential of microwave-assisted organic synthesis (MAOS) to address many of these needs is clear, as an alternative to the use of conductive heating for accelerating chemical reactions [3, 4]. From the pioneering experiments of Gedye [5] and Giguere [6], the use of microwave irradiation as an energy-efficient heat source for organic reactions has seen widespread application [7–15]. Reactions carried out under microwave-assisted conditions often benefit from short reaction times, higher yields, and improved selectivities, and so it is not surprising that these methods have been applied to the rapid synthesis of heterocyclic libraries using MCRs in combinatorial and medicinal chemistry.

The potential of MCRs to assemble compounds with high diversity, simply and efficiently, has been the subject of many recent reviews [16–24] and the use and further manipulation of these products have also been described [25]. This review describes the use of microwave irradiation to improve MCRs, in particular those carried out using modern microwave reactors. Although the majority of procedures reported for MAOS have been carried out using multimode domestic ovens, without utilizing specialized reactor design, these instruments experience fluctuating power cycles, unpredictable formation of hotspots, and a complex electric field pattern produced by the standing waves within the cavity, and thus the actual conditions experienced in the reaction are poorly understood at best, and irreproducible or hazardous at worst [26]. The use of a dedicated mono- or single-mode synthesizer overcomes most of these difficulties, by focusing the microwave irradiation using an accurately designed wave guide in a cavity located at a fixed distance from the radiation source, thus providing improved reproducibility, efficient energy transfer and greater control/monitoring of reaction parameters. The rapid optimization of procedures and ease of automation provided by this instrumentation has seen considerable application in combinatorial chemistry [27]. Furthermore, it has enabled the discovery of a number of new MCRs, for the preparation of both simple and fused nitrogen-, oxygen- and sulfur-containing five- and six-membered heterocycles, both partially unsaturated and fully heteroaromatic. The recent discovery of these processes, as well as the development of classical MCRs, for the high-throughput synthesis of combinatorial libraries using single-mode microwave synthesizers will be the focus of this review.

2

Classical Multicomponent Reactions

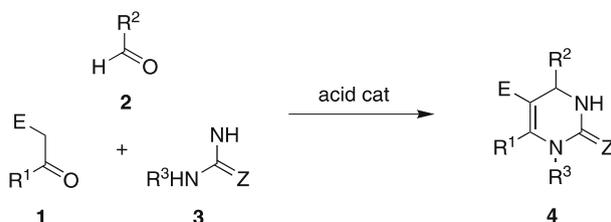
Most of the classical MCRs involve condensation processes of carbonyl compounds and their derivatives and were first reported a long time ago using traditional conductive heating methods. However, the discovery that these processes experience very fast reaction kinetics when coupled with microwave irradiation, and the later advent of single-mode microwave instruments, has reinvigorated research into their application in recent years. Equilibrium processes involving the synthesis of imines and enamines, as well as condensation and cyclocondensation reactions, with concomitant elimination of water, are traditionally promoted by forming an azeotrope with toluene or alcoholic solvent, but the expedition of these processes would appear to be greatly facilitated by microwave irradiation. This phenomenon has been utilized in the promotion of a number of classical MCRs, leading to new automated procedures and combinatorial methods to explore their biological properties.

2.1 Biginelli Cyclocondensation

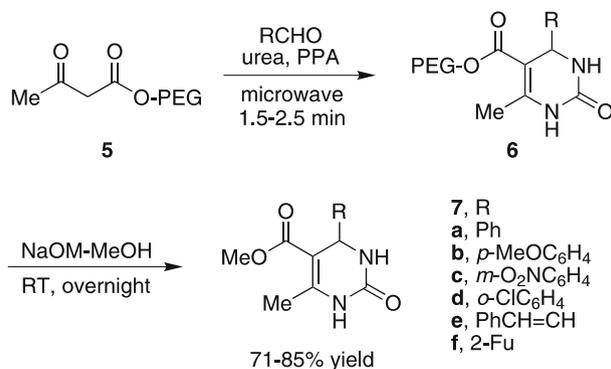
The three-component Biginelli cyclocondensation reaction (Scheme 1) combines a β -acidic ketone **1**, aldehyde **2** and urea **3** in the synthesis of functionalized dihydropyrimidines (DHPMs) **4** [28–30]. Biginelli DHPMs display a range of interesting biological properties, in particular as calcium channel blockers, prompting the development of a number of lead compounds based upon this motif [31]. The efficiency of this cyclocondensation reaction varies with substrate, often proceeding in low to moderate yield, and traditionally requires a strong Brønsted acid catalyst [29] in order to form the key *N*-acyliminium ion intermediate [32], although a number of alternative Lewis acid catalyzed processes have been reported [30].

Earlier reports on facilitating this reaction using microwave irradiation [33–39] focused on the use of solvent-free conditions in a domestic microwave oven [33–35], giving DHPMs in enhanced yield (up to 95%) [33] and short reaction times following an easy work up procedure. A similar approach has been applied to the parallel synthesis of a small targeted library of 10 DHPMs in only 1.5 min and in 61–95% yield by using polyphosphate ester (PPE) as a reaction mediator and an alumina bath heat sink [33], but these protocols do not lend themselves so well to the high throughput generation of DHPM libraries. Irradiation in a domestic oven can reduce reaction times from many hours down to a few minutes in ethanol in the presence of a mineral acid catalyst [36, 37], but these rate enhancements have been attributed to solvent evaporation and concentration and not to a non-thermal microwave effect [38].

The liquid phase synthesis of Biginelli DHPM derivatives **7** on the soluble polymer of polyethylene glycol (PEG) is also promoted using microwave irradiation [40]. PEG 4000 linked acetoacetate **5** reacted with urea and a range of aldehydes in the presence of polyphosphoric acid (PPA) in 1.5–2.5 min in a domestic oven to give the polymer bound DHPMs **6** (Scheme 2) in improved yield and very short reaction time compared with classical solution phase conditions. Subsequent cleavage from the PEG polymer using NaOMe – MeOH gave six DHPMs **7a–f** in 71–85% yield and > 90% purity.



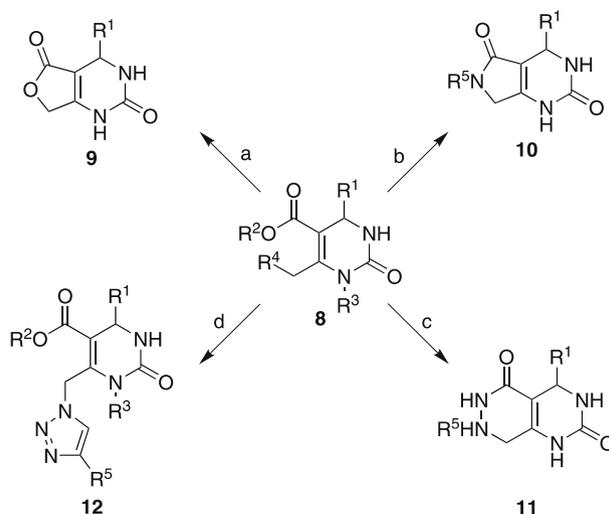
Scheme 1 Biginelli cyclocondensation reaction for the synthesis of DHPMs **4**



Scheme 2 Liquid-phase synthesis of DHPM derivatives 7a–f

The focus of recent work has been to develop new rapid procedures suitable for automation that are promoted in a modern microwave synthesizer. The sequential microwave-assisted synthesis of a DHPM library 4 from diverse subsets of 17 CH-acidic carbonyl compounds 1, 25 aldehydes 2, and 8 ureas/thioureas 3 ($Z = \text{O}$ or S) has been automated using a liquid handler and gripper in a single-mode microwave reactor [41]. The use of 10 mol % $\text{Yb}(\text{OTf})_3$ in $\text{AcOH} - \text{EtOH}$ (3 : 1) as solvent at 120°C for 10 min, and subsequent precipitation of the product on cooling or crystallization by addition of ice-water, was successful for many reagent combinations. However, the advantage of this approach was its flexibility: for each individual combination of building blocks, the solvent, catalyst, reaction temperature and/or irradiation time could be varied, based upon known reactivity trends, in order to optimize DHPM formation. Using this automated sequential process, a representative 48-membered library, out of the 3400 possible combinations, was synthesized within 12 h in an average isolated yield of 52% and > 90% purity.

Further derivatization under microwave-assisted conditions of functionalized Biginelli compounds 8 has shown that the products of this useful MCR can be used to prepare diverse fused and bis-heterocyclic libraries (Scheme 3). The multidirectional traceless cyclative cleavage of 6-(chloromethyl)DHPM 8 ($\text{R}^4 = \text{Cl}$) immobilized on hydroxymethyl polystyrene resin (R^2) gave either furo[3,4-*d*]pyrimidines 9 by microwave flash heating in a thermally triggered release, pyrrolo[3,4-*d*]pyrimidines 10 by treatment with primary amines and subsequent nucleophilic cyclative cleavage by high-temperature microwave heating, or pyrimido[4,5-*d*]pyridazines 11 in a similar fashion through treatment with monosubstituted hydrazines [42]. The Biginelli multicomponent reaction can also be combined with so-called “click chemistry”, through microwave-assisted $\text{Cu}(\text{I})$ catalyzed azide-acetylene ligation of the 6-(azidomethyl)DHPM 8 ($\text{R}^4 = \text{N}_3$) derivatives. Azides 8 were prepared from the corresponding bromides, obtained by bromination of DHPMs 4 from the automated microwave-assisted Biginelli



Scheme 3 Combinatorial synthesis of heterocyclic libraries **9–12** from DHPM derivatives **8**. (a) Microwave, 150 °C, 10 min, DMF ($R^4 = \text{Cl}$) [42]; (b) $R^5\text{NH}_2$; microwave, 150–250 °C, 10 min, DMF ($R^4 = \text{Cl}$) [42]; (c) $R^5\text{NHNH}_2$; microwave, 150 °C, 10 min, DMF ($R^4 = \text{Cl}$) [42]; (d) $R^5\text{C} \equiv \text{CH}$, CuSO_4 , sodium ascorbate, microwave, 85 °C, 20 min, DMF ($R^4 = \text{N}_3$) [43]

cyclocondensation, followed by microwave-assisted azidation at 60 °C. Subsequent regiospecific cycloaddition with terminal acetylenes, gave rapid access to a 27-membered library of 1,2,3-triazole derivatives **12** with four points of diversity [43].

2.2

Hantzsch 1,4-Dihydropyridine Synthesis

The cyclocondensation of an aldehyde, CH-acidic ketone and ammonia provides symmetrical 1,4-dihydropyridine-3,5-dicarboxylate derivatives of pharmacological importance, often called Hantzsch 1,4-dihydropyridines (1,4-DHPs) following its original invention over a century ago (Scheme 4) [44, 45]. The 1,4-DHP motif is found in a number of chemotherapeutic agents for



Scheme 4 Hantzsch synthesis of 1,4-DHPs

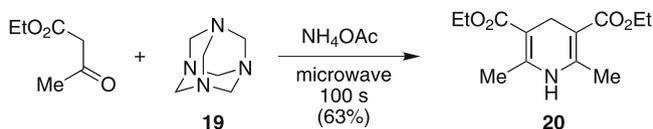


13-18: R¹, R², R³, R⁴, R⁵
 amlodipine **13**: Me, Cl, H, Et, OCH₂CH₂NH₂
 felodipine **14**: Me, Cl, Cl, Et, H
 nifedipine **15**: Me, NO₂, H, Me, H
 nicardipine **16**: Me, H, NO₂, CH₂CH₂N(Me)CH₂Ph, H
 nimodipine **17**: *i*-Pr, H, NO₂, CH₂CH₂OMe, H
 nitrendipine **18**: Me, H, NO₂, Et, H

Fig. 1 Structures of some 1,4-DHP derivatives of chemotherapeutic value

the treatment of cardiovascular disease (Fig. 1), such as hypertension and angina pectoris [46], including the 4-(2-chlorophenyl) derivatives amlodipine **13** and felodipine **14**, 4-(2-nitrophenyl)DHP derivative nifedipine **15** and the 4-(3-nitrophenyl) derivatives nicardipine **16**, nimodipine **17** and nitrendipine **18**, amongst others. The 1,4-DHP class of calcium channel antagonists relax the cardiac muscle by decreasing the transmembrane calcium current on binding [47]. This heterocyclic motif also plays a role in hydride transfer biotransformations from the reduced nicotinamide adenine dinucleotide coenzymes, and analogues thereof, that mediate hydrogen transfer reactions in biological systems [48–50]. In order to model and understand these biological properties, and in order to develop new chemotherapeutic agents based upon the 1,4-DHP motif, considerable effort has been devoted to establish efficient and rapid methods for their synthesis that are appropriate for the high-throughput generation of DHP libraries.

The use of microwave irradiation for the rapid synthesis of Hantzsch 1,4-DHPs has been the subject of recent review, along with the microwave-assisted oxidative aromatization or dealkylation of these derivatives for the synthesis of symmetrical pyridines [51], and so will not be exhaustively covered here. One of the first reports, carried out in a domestic oven, irradiated an aldehyde, alkyl acetoacetate and ammonium hydroxide in ethanol, or a ketone and aminocrotonitrile in acetic acid to obtain 1,4-DHP derivatives in a similar yield to comparative reactions carried out using traditional conductive heating, but in dramatically shorter time [52]. The use of ammonium acetate can give significant improvements in yield [53] and an aqueous hydrotrope solution can also serve as a safe reaction medium under microwave-assisted conditions, giving 1,4-DHPs in only 5 min [54]. The use of Zn[(L)-proline]₂ as a Lewis acid catalyst under solvent-free conditions in a domestic oven has also been reported recently [55], but it was Öhberg and Westman who first explored the use of a single-mode microwave reactor for this transformation [56]. In their method, a mixture of the aldehyde, CH-acidic ketone (5 equiv) and aqueous ammonium hydroxide (4 equiv) was irradiated at 140 °C for 10 min, followed by purification by both column chromatography and recrystallization. In comparison with both conventional methods and microwave-assisted reactions performed in a domestic oven, they reported that shorter reaction times and higher yields of the target 1,4-DHPs were ob-

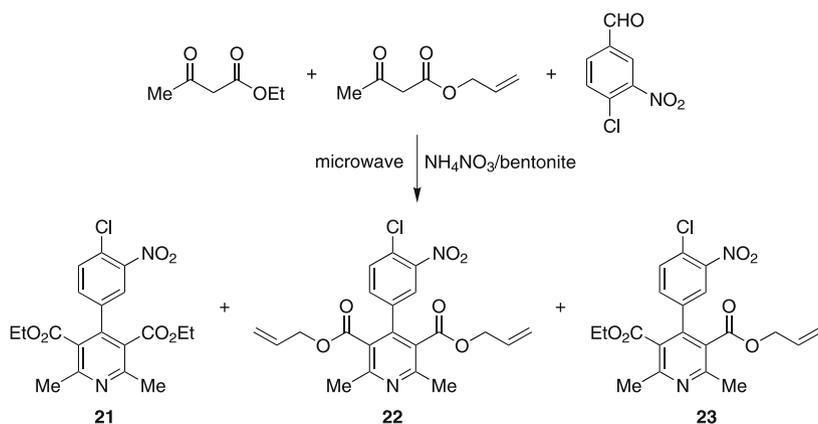


Scheme 5 Synthesis of 4-unsubstituted 1,4-DHP **20**

tained. Utilizing this methodology, a serial synthesis of 24 compounds was performed, but the yields and purities of library members, the latter as low as 53% in one case, varied considerably.

The synthesis of 4-unsubstituted DHPs in a focused microwave reactor has been reported using alkyl acetoacetates and hexamethylenetetramine **19** as the source of both formaldehyde and ammonia, with additional ammonium acetate to maintain the stoichiometry [57]. Irradiation for 100 s under solvent-free conditions gave, for example, 1,4-DHP **20** in 63% isolated yield (Scheme 5).

The rapid synthesis of heteroaromatic Hantzsch pyridines can be achieved by aromatization of the corresponding 1,4-DHP derivative under microwave-assisted conditions [51]. However, the domino synthesis of these derivatives has been reported in a domestic microwave oven [58, 59] using bentonite clay and ammonium nitrate, the latter serving as both the source of ammonia and the oxidant. In spite of some contradictory findings [51, 58, 59], this approach has been employed in the automated high-throughput parallel synthesis of pyridine libraries in a 96-well plate [59]. In each well, a mixture of an aldehyde, ethyl acetoacetate and a second 1,3-dicarbonyl compound was irradiated for 5 min in the presence of bentonite/ammonium nitrate. For some reactions, depending upon the specific 1,3-dicarbonyl compound used,



Scheme 6 Combinatorial domino synthesis of Hantzsch pyridines **21–23**

the combinatorial synthesis of symmetrical and unsymmetrical pyridines was observed, 21–23 for example (Scheme 6).

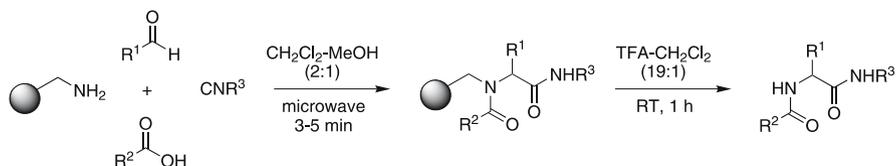
2.3

Ugi Reaction

The Ugi reaction is the four-component condensation of an amine, aldehyde or ketone, carboxylic acid and isocyanide to give an α -acylamino amide [22–24]. Although this process has the potential to introduce considerable diversity, the products themselves are not heterocycles but through appropriate choice of substrates, latent functionality in one of the precursors can intercept either an intermediate or further derivatize the acylamino amide Ugi product through post-modification. Thus variants of the Ugi reaction have been investigated under microwave-assisted conditions for the synthesis of diverse heterocyclic libraries [16, 19–24].

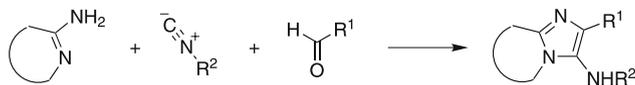
The microwave acceleration of Ugi condensations on a solid support have been utilized in the synthesis of an 18-membered targeted library of α -acylamino amides [60]. Irradiation of the four components, immobilizing the amine on TentaGel S RAM, for 3–5 min in a single-mode microwave synthesizer gave the products in moderate to excellent yields and high purity (Scheme 7).

A related three-component reaction, omitting the carboxylic acid and using an aminopyridine, -pyrimidine or -pyrazine for the amine component, occurs in the presence of montmorillonite K-10 clay under solvent-free conditions using microwave irradiation in a domestic oven [61]. Using these precursors, the nucleophilic N-1 of the heterocycle intercepts the product of isocyanide addition to give imidazo[1,2-*a*] annulated pyridines 24, pyrazines 25 and pyrimidines 26 in good yield (Scheme 8). A variety of fused three-aminoimidazoles have been prepared in up to 93% yield by microwave-assisted Ugi three-component coupling reactions, carried out in methanolic solvent in a single-mode microwave synthesizer, by irradiating the mixture at 160 °C for 10 min after pre-formation of the imine intermediate in the presence of scandium triflate [62]. Using this procedure, the reaction of 2-aminothiazole was found to give a thiazoloimidazole, albeit it in only 33% yield (Scheme 8).

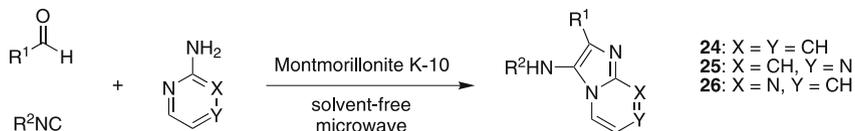


Scheme 7 Microwave-assisted Ugi reaction on solid phase

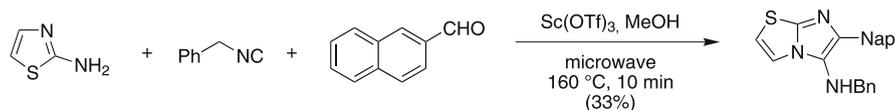
Ugi 3-component reaction for the synthesis of fused 3-aminoimidazoles:



Solvent-free synthesis of **24-26**:



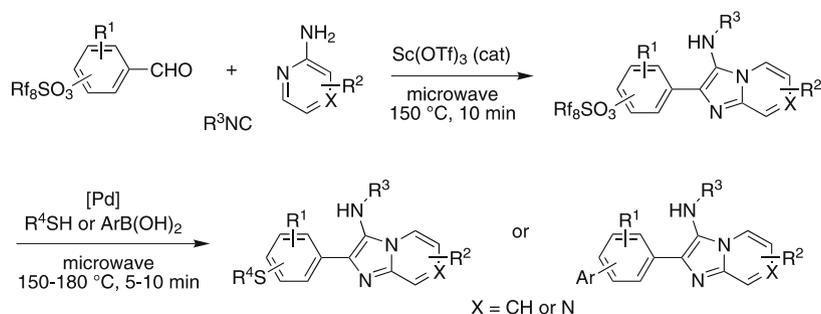
Reaction of 2-aminothiazole in a MW synthesizer:



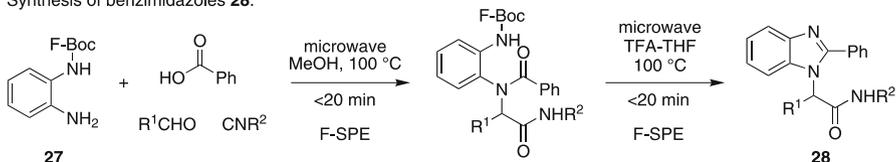
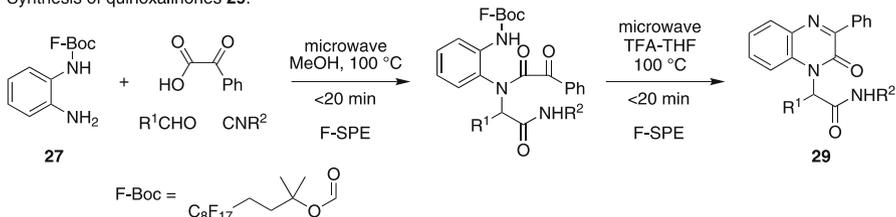
Scheme 8 Microwave-assisted synthesis of imidazo-annulated heterocycles

Microwave and fluorous technologies have been combined in the solution phase parallel synthesis of 3-aminoimidazo[1,2-*a*]pyridines and -pyrazines [63]. The three-component condensation of a perfluorooctane-sulfonyl ($Rf_8 = C_8F_{17}$) substituted benzaldehyde by microwave irradiation in a single-mode instrument at 150 °C for 10 min in CH_2Cl_2 – MeOH in the presence of $Sc(OTf)_3$ gave the imidazo-annulated heterocycles that could be purified by fluorous solid phase extraction (Scheme 9). Subsequent Pd-catalyzed cross-coupling reactions of the fluorous sulfonates with arylboronic acids or thiols gave biaryls or aryl sulfides, respectively, albeit it in relatively low yields.

The use of diamine **27**, bearing a fluorous-Boc protecting group, has been used with microwave irradiation in an Ugi/de-Boc/cyclization strategy for the synthesis of benzimidazoles **28** and quinoxalinones **29** [64]. Compared to the original procedures, which take 1–2 days, this approach avoids the use of



Scheme 9 Fluorous MCR and subsequent cross-coupling reactions

Synthesis of benzimidazoles **28**:Synthesis of quinoxalinones **29**:**Scheme 10** Fluorous Ugi and post-condensation reactions**Scheme 11** Microwave-assisted Ugi reaction of levulinic acid **30**

scavenging reagents and both the Ugi and post-condensation reaction can be facilitated in less than 20 min at $100\text{ }^\circ\text{C}$ under microwave-assisted conditions (Scheme 10), with purification by fluorous solid-phase extraction.

Linking the ketone and carboxylic acid components together in an Ugi reaction facilitates the synthesis of pyrrolidinones amenable to library design. The three-component condensation of levulinic acid **30**, an amine and isocyanide proceeds under microwave irradiation to give lactams **31** [65]. The optimum conditions were established by a “design of experiments” approach, varying the equivalents of amine, concentration, imine pre-formation time, microwave reaction time and reaction temperature, yielding lactams **31** at $100\text{ }^\circ\text{C}$ in poor to excellent yield, after only 30 min compared to 48 h under ambient conditions (Scheme 11).

3 Synthesis of Simple Heterocycles

A number of new MCRs, that are either facilitated or accelerated by microwave irradiation, have been reported recently for the synthesis of simple N-, O- and S-containing heterocycles. These one-pot domino processes offer

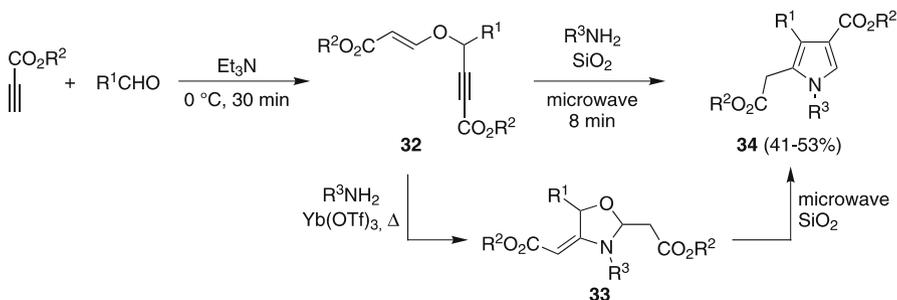
new methods for the rapid introduction of diversity into heterocyclic building blocks of pharmacological importance, and will be treated based upon the size of the target heterocycle.

3.1

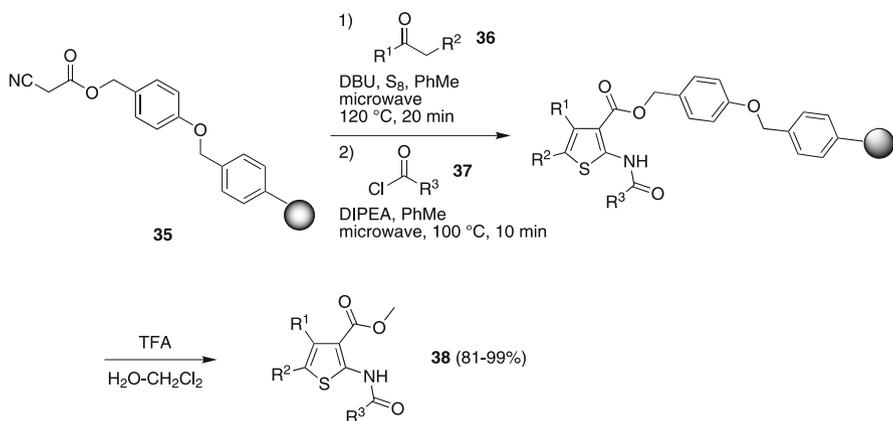
Five-Membered Heterocycles

Serendipity has often formed the basis of new routes to simple heterocyclic scaffolds. The discovery of the spontaneous rearrangement of 1,3-oxazolidines **33**, formed from the corresponding enol ethers **32** by ytterbium-catalyzed reaction with primary amines, to pyrroles **34** formed the basis of a new one-pot process for the synthesis of these five-membered heterocycles [66]. Although this rearrangement was very slow at room temperature, conductive heating could reduce the reaction time from months to hours, whereas microwave irradiation of a sample adsorbed on silica gel sped up this process still further. Combining these two coupled domino processes, the trialkylamine-catalyzed synthesis of propargylic enol ethers **32** and their transformation to pyrroles **34** through microwave-assisted reaction with a primary amine, gave a new one-pot procedure for the synthesis of tetrasubstituted pyrroles **34** (Scheme 12). The whole process was complete in less than 40 min, using a domestic oven to accelerate the rearrangement reaction, and proceeded in reasonable overall yield (41–53%).

Microwave irradiation has been used to accelerate the Gewald reaction for the one-pot synthesis of *N*-acyl aminothiophenes on solid support [67]. A suspension of cyanoacetic acid Wang resin **35**, elemental sulfur, DBU and an aldehyde or ketone **36** in toluene was irradiated for 20 min at 120 °C in a single-mode microwave synthesizer (Scheme 13). Acyl chloride **37** was added, followed by DIPEA, and the mixture was irradiated for 10 min at 100 °C. After cooling to room temperature, the washed resin was treated with a TFA solution to give *N*-acylated thiophenes **38** in 81–99% yield and purities ranging from 46–99%.



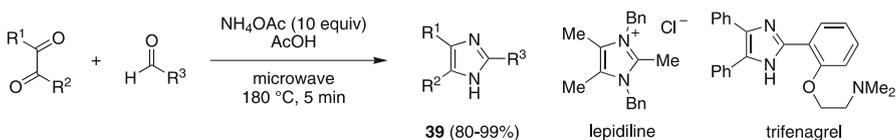
Scheme 12 Synthesis of tetrasubstituted pyrroles by coupled domino processes



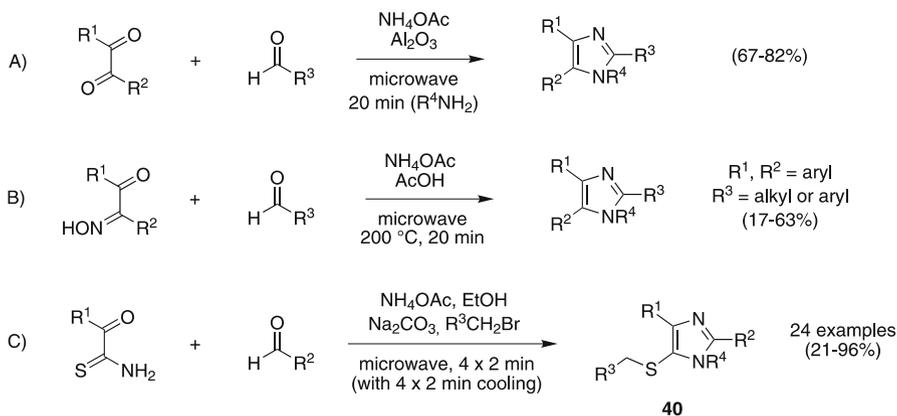
Scheme 13 Microwave-assisted Gewald synthesis on solid support

A number of microwave-assisted multicomponent methods for the synthesis of imidazoles have been reported [68–71]. The irradiation of a 1,2-diketone and aldehyde with ammonium acetate in acetic acid for 5 min at 180 °C in a single-mode reactor provides alkyl-, aryl-, and heteroaryl-substituted imidazoles **39** in excellent yield (Scheme 14) and this method has been used for the rapid and efficient preparation of two biologically active imidazoles, lepidiline B and trifenagrel [68].

This transformation can also be carried out under solvent-free conditions in a domestic oven using acidic alumina and ammonium acetate, with or without a primary amine, to give 2,4,5-trisubstituted or 1,2,4,5-tetrasubstituted imidazoles, respectively (Scheme 15A) [69]. The automated microwave-assisted synthesis of a library of 2,4,5-triarylimidazoles from the corresponding keto-xime has been carried out by irradiation at 200 °C in acetic acid in the presence of ammonium acetate (Scheme 15B) [70]. Under these conditions, thermally induced in situ N–O reduction occurs upon microwave irradiation, to give a diverse set of trisubstituted imidazoles in moderate yield. Parallel synthesis of a 24-membered library of substituted 4(5)-sulfonyl-1*H*-imidazoles **40** has been achieved by adding an alkyl bromide and base to the reaction of a 2-oxothioacetamide, aldehyde and ammonium acetate (Scheme 15C) [71]. Under microwave-assisted conditions, library generation time was dramatically re-



Scheme 14 Synthesis of lepidiline B and trifenagrel

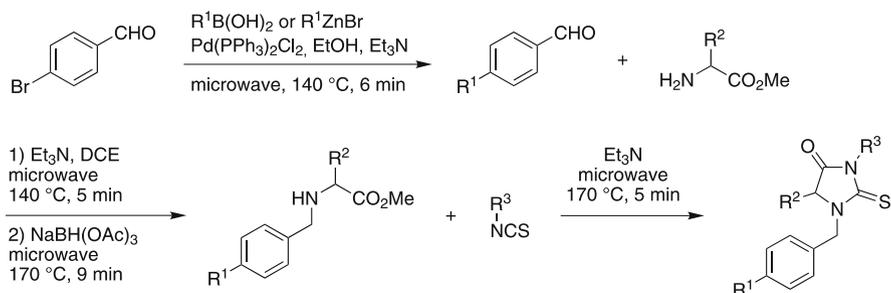


Scheme 15 Other microwave-assisted methods for the synthesis of imidazoles

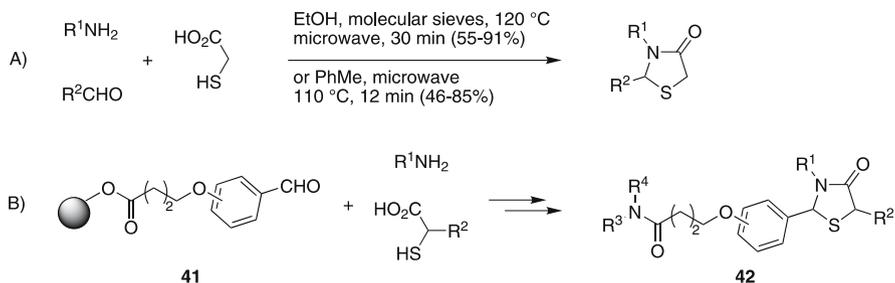
duced from 12 h to 16 min for each reaction event, giving the imidazoles in reasonable yield and purities that varied from 20–95%.

A one-pot synthesis of thiohydantoin has been developed using microwave heating [72]. A small subset of *p*-substituted benzaldehydes, prepared in situ from *p*-bromobenzaldehyde by microwave-assisted Suzuki or Negishi reactions, was reacted in one pot by reductive amination followed by cyclization with a thioisocyanate catalyzed by polystyrene-bound dimethylaminopyridine (PS-DMAP) or triethylamine, all carried out under microwave irradiation, to give the thiohydantoin products in up to 68% isolated yield (Scheme 16).

The rapid synthesis of 4-thiazolidinones by the MCR of an amine, aldehyde and mercaptoacetic acid has been developed under microwave-assisted conditions [73–75]. Irradiation of the three components in ethanol at 120 °C in the presence of molecular sieves [73] or in toluene at reflux under atmospheric conditions [74] in a single-mode microwave synthesizer gave the



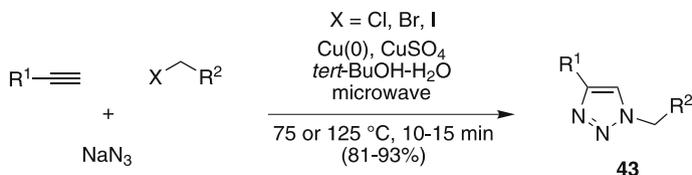
Scheme 16 One-pot solution phase synthesis of thiohydantoin



Scheme 17 Microwave-assisted synthesis of 4-thiazolidinones

4-thiazolidinones (Scheme 17A), in some cases in improved yield over conventional conductive heating procedures [74]. A similar approach has been adopted to prepare a small library of 4-thiazolidinones bound on a PEG-ionic liquid phase [75]. The three-component condensation of liquid phase bound aldehyde **41** with a subset of primary amines and mercaptoacetic acids (Scheme 17B) at 100 °C proceeded in 20 min. The ionic liquid-phase bound thiazolidinones could be cleaved under subsequent microwave irradiation with a primary or secondary amine to give a library of amides **42** in modest yield but without the need for further purification.

A microwave-assisted three-component reaction has been used to prepare a series of 1,4-disubstituted-1,2,3-triazoles with complete control of regioselectivity by “click chemistry”, a fast and efficient approach to novel functionalized compounds using “near perfect” reactions [76]. In this user-friendly procedure for the copper(I) catalyzed 1,3-dipolar cycloaddition of azides and alkynes, irradiation of an alkyl halide, sodium azide, an alkyne and the Cu(I) catalyst, produced by the comproportionation of Cu(0) and Cu(II), at 125 °C for 10–15 min, or at 75 °C for certain substrates, generated the organic azide in situ and gave the 1,4-disubstituted regioisomer **43** in 81–93% yield, with no contamination by the 1,5-regioisomer (Scheme 18).

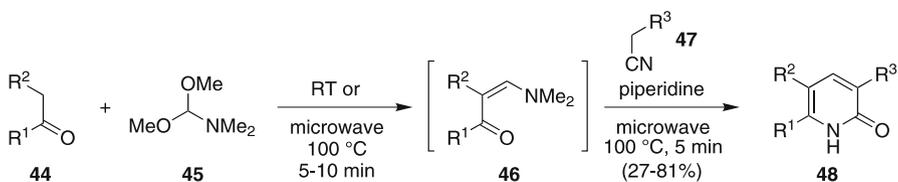


Scheme 18 Click chemistry synthesis of 1,4-disubstituted triazoles

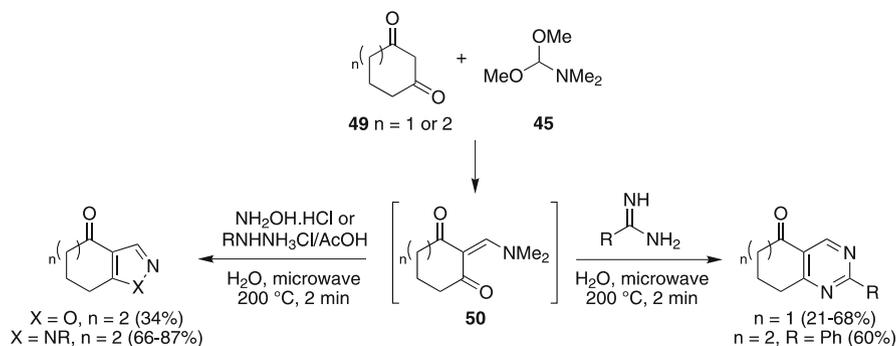
3.2 Six-Membered Heterocycles and Benzo-Derivatives

Fewer procedures have been explored recently for the synthesis of simple six-membered heterocycles by microwave-assisted MCRs. Libraries of 3,5,6-trisubstituted 2-pyridones have been prepared by the rapid solution phase three-component condensation of CH-acidic carbonyl compounds **44**, *N,N*-dimethylformamide dimethyl acetal **45** and methylene active nitriles **47** under microwave irradiation [77]. In this one-pot, two-step process for the synthesis of simple pyridones, initial condensation between **44** and **45** under solvent-free conditions was facilitated in 5–10 min at either ambient temperature or 100 °C by microwave irradiation, depending upon the CH-acidic carbonyl compound **44** used, to give enamine intermediate **46** (Scheme 19). Addition of the nitrile **47** and catalytic piperidine, and irradiation at 100 °C for 5 min, gave a library of 2-pyridones **48** in reasonable overall yield and high individual purities.

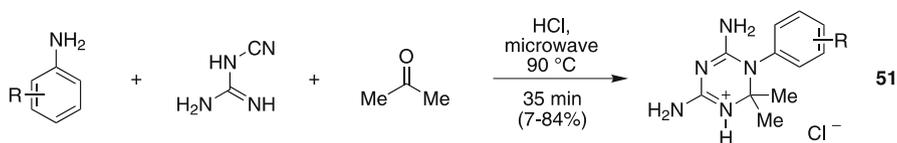
A similar strategy has been used to prepare pyrimidines, as well as pyrazoles and isoxazoles by reacting the enamine intermediate with a variety of bidentate nucleophiles [78]. Microwave irradiation of a cyclic 1,3-diketone **49** and acetal **45** in water generated the corresponding enamino-ketone **50** in situ which reacted with amidines, substituted hydrazines or hydroxylamine in only 2 min in a one-pot process to give 4-acylpyrimidines, pyrazoles or isoxazoles, respectively (Scheme 20).



Scheme 19 Synthesis of 2-pyridone libraries



Scheme 20 MCR for the synthesis of pyrimidines, pyrazoles and isoxazoles

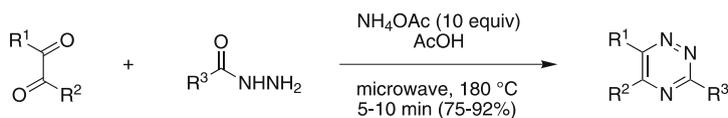


Scheme 21 One-pot three-component synthesis of dihydro-*s*-triazines

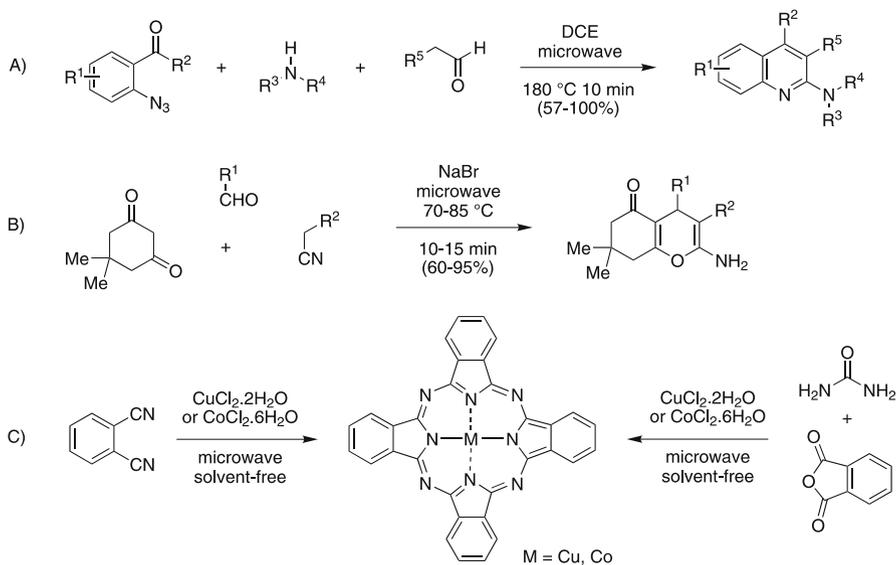
The one-pot, three-component synthesis of a 20-membered dihydrotriazine library was also dramatically accelerated through the use of microwave irradiation [79]. Heating a subset of substituted anilines, cyanoguanidine and acetone in the presence of concentrated hydrochloric acid for 35 min at 90 °C in a single-mode microwave reactor gave the corresponding 2,2-dimethyl-1,2-dihydro-*s*-triazine hydrochloride **51** in comparable yield to conventional conductive heating methods but in a much shorter reaction time and increased purity (Scheme 21).

The rapid synthesis of 1,2,4-triazines has also been developed under microwave-assisted conditions [80]. Irradiation of a 1,2-diketone with acyl hydrazides and ammonium acetate for 5–10 min at 180 °C in a single-mode microwave reactor gave 3,5,6-trisubstituted 1,2,4-triazines in excellent yield and purity and reaction times that were reduced 60–300 fold over conventional conductive heating methodology (Scheme 22).

An improved microwave-assisted method for the three-component synthesis of 2-aminoquinolines has been reported [81]. Microwave irradiation of a secondary amine and aldehyde generated an enamine intermediate, which was added to different 2-azidobenzophenones and irradiated in DCE in a single-mode microwave reactor (Scheme 23A). Purification by solid-phase extraction techniques gave the 2-aminoquinoline product in reasonable yield and both simplified and accelerated the overall process, with respect to comparable conductive heating procedures. Other benzo-derivatives have also been prepared under microwave-assisted conditions in a single-mode reactor. The sodium bromide catalyzed three-component cyclocondensation of aryl aldehydes, alkyl nitriles and dimedone proceeds at 70–85 °C under solvent-free conditions to give highly functionalized tetrahydrobenzo[*b*]pyrans in good yield (Scheme 23B) [82]. Microwave irradiation has also been shown to be a useful alternative to conventional conductive heating for the copper(II)- and cobalt(II)-templated synthesis of metallophthalocyanines from 1,2-



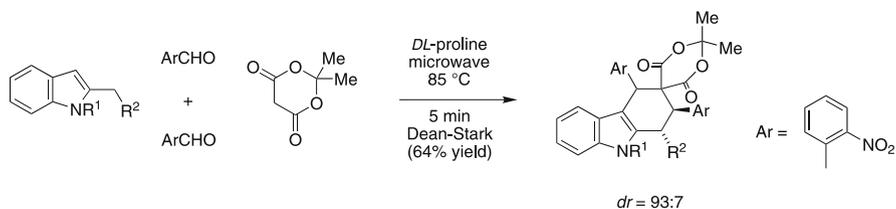
Scheme 22 Improved microwave-assisted method for the synthesis of 1,2,4-triazines



Scheme 23 Microwave-assisted synthesis of benzo-derivatives

phthalonitrile or phthalic anhydride [83], giving higher yields and reduced reaction times (Scheme 23C).

The synthesis of functionalized tetrahydrocarbazoles can be promoted by microwave irradiation [84]. The organocatalytic four-component reaction of a solution of 2-substituted indole, aromatic aldehyde (2 equiv) and Meldrum's acid in benzene in the presence of *DL*-proline proceeds when heated under Dean–Stark conditions for 5 min in a single-mode microwave reactor to give the tetrahydrocarbazole product as a mixture of diastereoisomers (Scheme 24).



Scheme 24 Synthesis of tetrahydrocarbazoles by four-component condensation

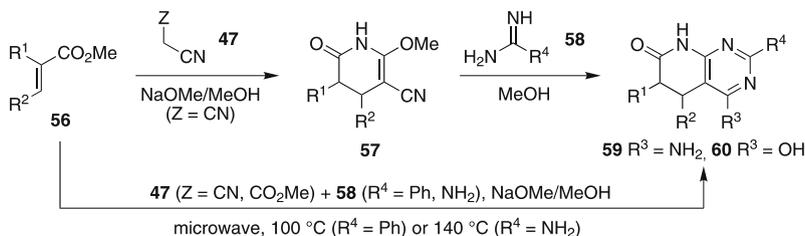
4 Synthesis of Fused Heterocycles

4.1 Pyrido[2,3-*d*]pyrimidines and Related Heterocycles

The synthesis of pyrido[2,3-*d*]pyrimidines has attracted considerable interest in heterocyclic chemistry. This ring system constitutes a deaza-analogue of the pyrazino[2,3-*d*]pyrimidine heterocyclic core of folic acid, analogues which can exhibit a wide range of biological properties as folate antagonists. Thus, the synthesis of this motif by MCR under microwave-assisted conditions has the potential to rapidly introduce diversity into a biologically relevant scaffold.

One of the first reports of a microwave-assisted cyclocondensation for the synthesis of pyridopyrimidines described the three-component reaction of an aminopyrimidin-4-one **52**, benzoylacetonitrile and benzaldehyde [85]. Irradiation for 15–20 min under solvent-free conditions in a domestic microwave oven gave 5,8-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **53** in good yield and as a single regioisomer (Scheme 26A). The related cyclocondensation of 2,6-diaminopyrimidin-4-one **54**, a CH-acidic ketone and an aromatic or aliphatic aldehyde has been carried out in a single-mode microwave reactor [86]. Irradiation in DMSO at 160 °C for 20 min, in the presence of zinc(II) bromide for aromatic aldehydes, gives 5-deaza-5,8-dihydropterins **55**, containing the pyrido[2,3-*d*]pyrimidine motif, in 59–91% yield with total regio-control (Scheme 26B).

The synthesis of pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones has also been achieved by a microwave-assisted MCR [87–89] that is based on the “Victory” reaction of 6-oxotetrahydropyridine-3-carbonitrile **57**, obtained by reaction of an α,β -unsaturated ester **56** and malonitrile **47** ($Z = \text{CN}$). The one-pot cyclocondensation of **56**, amidines **58** and methylene active nitriles **47**, either malonitrile or ethyl cyanoacetate, at 100 °C for benzamidine or 140 °C for reactions with guanidine, in methanol in the presence of a catalytic amount of sodium methoxide gave 4-oxo-**60** or 4-aminopyridopyrimidines **59**, respectively, in only 10 min in a single-mode microwave reactor [87, 88]

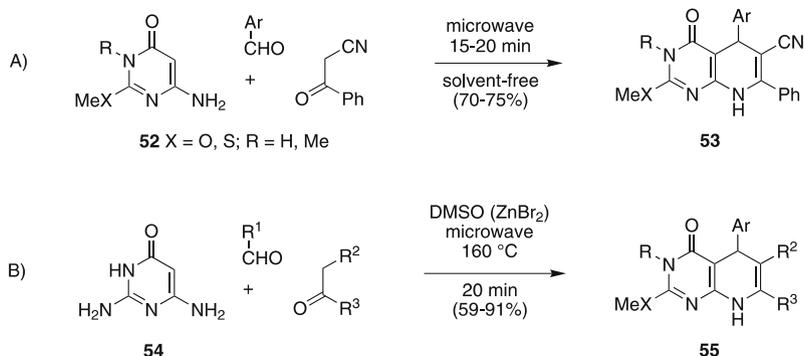


Scheme 25 Synthesis of pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones

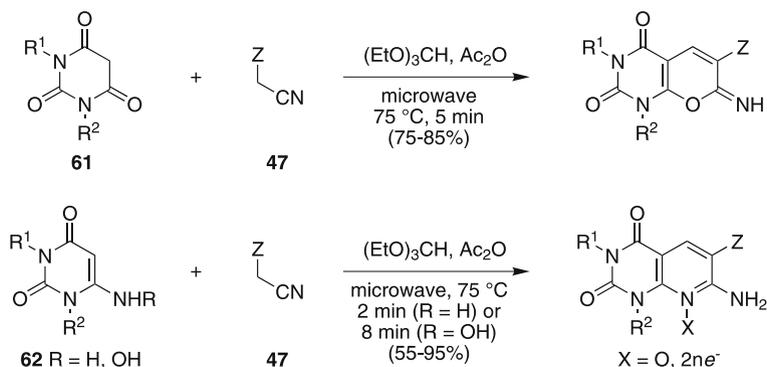
(Scheme 25). The introduction of greater diversity at C-2 and C-4 can be achieved by intercepting the tetrahydropyridinone intermediate in a multi-step sequence involving C-2 ammonolysis, microwave-assisted *N*-acylation, acid-catalyzed cyclization (to introduce diversity at C-2), treatment with POCl₃, and either microwave-assisted nucleophilic substitution or Suzuki coupling (to introduce diversity at C-4) [89].

The one-pot MCR of methylene active nitriles **47** has been used in the synthesis of both pyrano- and pyrido[2,3-*d*]pyrimidine-2,4-diones in a single-mode microwave reactor [90]. Microwave irradiation of either barbituric acids **61** or 6-amino- or 6-(hydroxyamino)uracils **62** with triethylorthoformate and nitriles **47** (Z = CN, CO₂Et) with acetic anhydride at 75 °C for 2–8 min gave pyrano- and pyrido[2,3-*d*]pyrimidines in excellent yield and also provided a direct route to pyrido[2,3-*d*]pyrimidine *N*-oxides (Scheme 27).

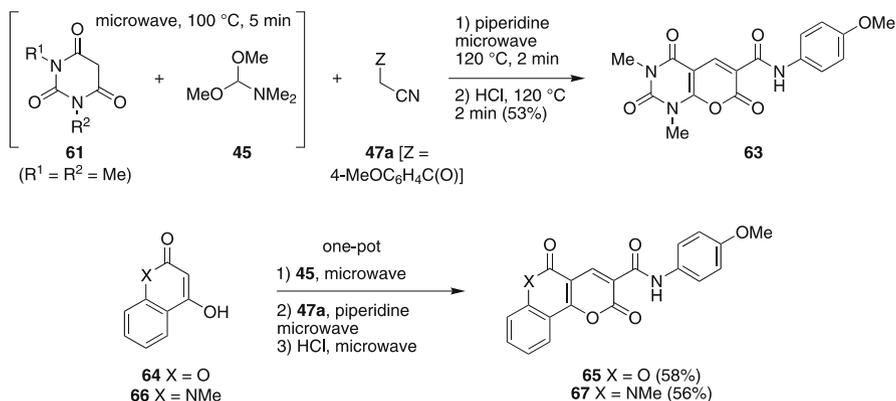
A related pyranopyrimidine **63** has been prepared by the irradiation of 1,3-dimethylbarbituric acid **61**, a methylene active nitrile **47a** and *N,N*-dimethylformamide dimethylacetal **45** [77]. After initial formation of the enam-



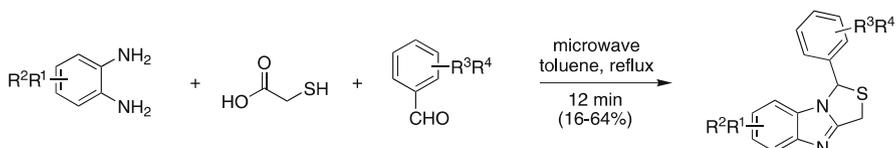
Scheme 26 Synthesis of pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones



Scheme 27 Synthesis of pyrano- and pyrido[2,3-*d*]pyrimidin-2,4-diones



Scheme 28 One-pot synthesis of fused pyran derivatives



Scheme 29 Three-component synthesis of thiazolobenzimidazoles

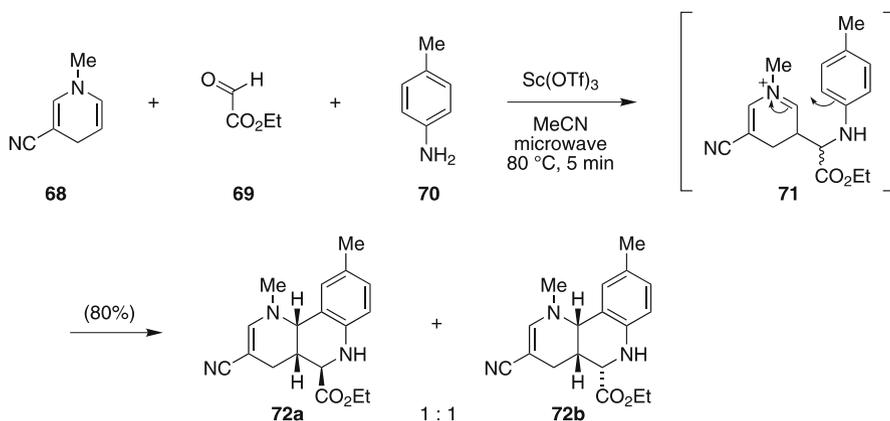
ine intermediate at $100\text{ }^\circ\text{C}$, the nitrile **47a** was added with a stoichiometric amount of piperidine and the mixture irradiated at $120\text{ }^\circ\text{C}$ for 2 min. Concentrated hydrochloric acid was added to the final reaction mixture, followed by microwave irradiation at $120\text{ }^\circ\text{C}$ for a further 2 min to give the pyranopyrimidine **63** in 53% yield (Scheme 28). This methodology also provided other fused pyran derivatives **65** and **67** from 4-hydroxycoumarin **64** and 4-hydroxyquinolinone **66**, in 58 and 56% yield, respectively.

The one-pot synthesis of thiazolo[3,4-*a*]benzimidazoles has been reported using a microwave-assisted condensation-cyclization (see Scheme 17) of a substituted 1,2-diamine, substituted benzaldehyde and mercaptoacetic acid [74]. Heating the mixture at reflux for 12 min using a single-mode microwave reactor for the most part gave the fused benzimidazoles in improved yield and dramatically shorter times, when compared to classical conditions of heating at reflux in benzene for 24–48 h (Scheme 29).

4.2

Cycloaddition Reactions

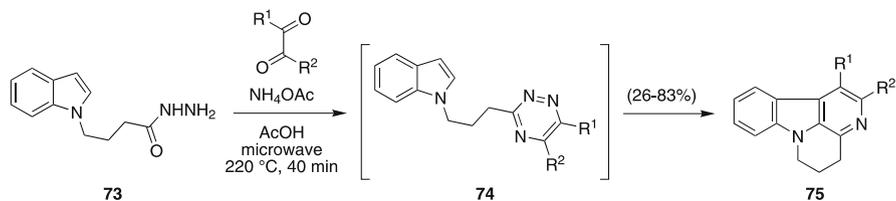
The use of microwave-assisted multicomponent cycloaddition reactions allows unique heterocyclic scaffolds to be assembled rapidly from readily accessible starting materials. The three-component reaction of *N*-alkyl-1,4-DHP



Scheme 30 Lewis acid catalyzed reaction of a 1,4-DHP, aldehyde and aniline

68, ethyl glyoxylate **69**, and *p*-methylaniline **70** is greatly accelerated under microwave irradiation [91]. This Lewis acid catalyzed MCR is formally a [4 + 2] cycloaddition between DHP **68** and the azadiene generated by condensation of an aniline and aldehyde, although the mechanism is probably stepwise, involving electrophilic intramolecular addition to iminium ion intermediate **71** (Scheme 30). Microwave irradiation of the three components in acetonitrile in the presence of Sc(OTf)_3 for 5 min at 80 °C gave an equimolar ratio of two diastereomeric pyrido-fused tetrahydroquinolines, **72a** and **72b**, in 80% overall isolated yield. Considering that this reaction takes 12 h at RT under conventional conditions, this represented a considerable improvement although no change in the diastereoselectivity was observed under microwave irradiation.

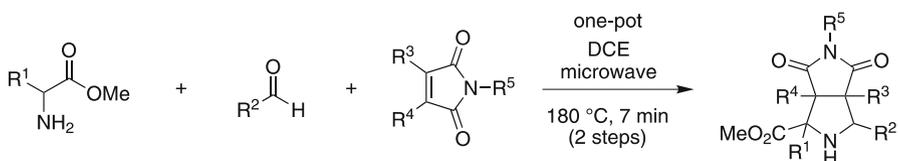
The inverse electron demand Diels–Alder reaction has also been used to provide expedient access to unnatural β -carboline alkaloids from 1,2,4-triazines, prepared by microwave-assisted MCR [92]. One-pot reaction of an acyl hydrazide-tethered indole **73**, 1,2-diketone and ammonium acetate in acetic acid provided triazines **74** (see Sect. 3.2, Scheme 22), bearing an electron-rich dienophilic indole moiety (Scheme 31). By carrying out the



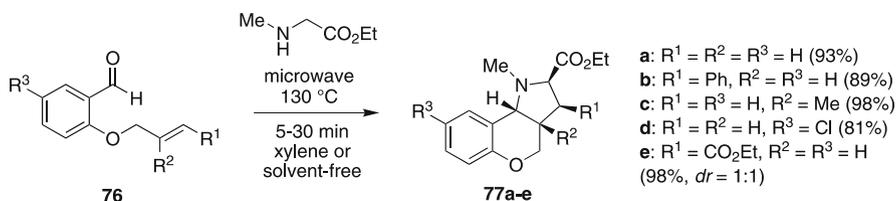
Scheme 31 Microwave-assisted cyclocondensation-cycloaddition- N_2 expulsion for the synthesis of the canthine skeleton

MCR at the higher temperature of 220 °C for 40 min, the subsequent cycloaddition was spontaneous under the reaction conditions, with chelotropic expulsion of N₂, to give canthine derivatives **75**. Functionalized aryl analogues (R¹ = R² = Ar) gave the highest yields (81–83%), followed by heteroaryl congeners (59–62%), whereas dialkyl derivatives were prepared in the lowest overall yields (26–34%). Although an unsymmetrical 1,2-diketone (R¹ = Ph, R² = *n*-Pr) did provide a reasonable overall yield (62%) of the tetracyclic product, no regioselectivity was observed.

The synthesis of [3 + 2] cycloaddition libraries can also be accelerated using microwave-assisted conditions, expediting the library development process by accelerating reaction rates and/or times. A simple, two-step, one-pot method for the conversion of α -aminoesters, aldehydes and maleimides by azomethine ylide mediated cycloaddition into fused pyrrolidine derivatives has been reported using microwave-assisted methods in a single-mode reactor [93]. Microwave irradiation of an amine and aldehyde in 1,2-dichloroethane at 180 °C for 2 min, followed by addition of a maleimide and irradiation at 180 °C for a further 5 min gave an 800-membered solution-phase library of substituted prolines without the need for any additional catalyst, greatly simplifying the purification process (Scheme 32). Library members were purified by solid-supported reagent scavenging with the addition of PS-TsNHNH₂ to give the resulting products with typical purities between 90 and 98% in twofold less time than by traditional thermal methods and with the facility for automation. It was found that aromatic aldehydes formed stable imines, allowing the subsequent cycloaddition to occur more readily, whereas aliphatic aldehydes performed poorly under these conditions. Furthermore, in comparison, the use of a domestic oven produced unacceptable results due to the poor absorption of microwave energy by the DCE sol-



Scheme 32 Microwave-assisted synthesis of a [3+2] cycloaddition library



Scheme 33 Rapid synthesis of hexahydrochromeno[4,3-*b*]pyrroles **77**

vent. Typical isolated yields in library validation using aromatic aldehydes in a single-mode microwave reactor were in the range 75–89%.

An intramolecular variant of this multicomponent azomethine ylide-mediated 1,3-dipolar cycloaddition reaction has been used for the synthesis of perhydrochromeno[4,3-*b*]pyrroles using microwave irradiation [94, 95]. The condensation of ω -unsaturated salicylaldehydes **76** with *N*-alkyl α -amino esters was compared (i) in toluene under traditional conductive heating procedures using Dean-Stark apparatus; (ii) in a preheated oil bath at 130 °C under solvent-free conditions or with a minimal amount of non-polar solvent xylene; and (iii) at 130 °C under microwave irradiation [95]. Almost all of the reactions performed under microwave-assisted conditions were complete after only 5–30 min, as compared to up to 24 h for traditional conditions at reflux in toluene, and the yields were almost always superior, with fewer side-products (Scheme 33). Similar findings were made at higher temperatures under solvent-free conditions [94]. Irradiating a mixture of *O*-allylsalicylaldehyde and ethyl *N*-benzylglycinate at 200 °C for 15 min gave the hexahydrochromeno[4,3-*b*]pyrrole **78** in 83% yield as a single diastereoisomer (Scheme 34). The yield of cycloadduct was largely unaffected by the addition of base to the reaction mixture or the use of a number different amines (R^4 = Bn, Et, *n*-Bu, *i*-Pr), although a less reactive aromatic amine (R^4 = Ph) or sterically bulky groups (R^4 = *tert*-Bu, adamantyl) failed to provide any yield of cycloadduct [94]. The reactions of activated *O*-allylic salicylaldehydes **76** (R^1 = Ph, CO₂Et; R^2 , R^3 = H) for the synthesis of cycloadducts **77b** and **e** were much faster, whereas the synthesis of cycloadduct **77c** with a quaternary bridgehead methyl group (R^2 = Me; R^1 , R^3 = H) required extended reaction times under both conductive heating and microwave conditions, but was considerably improved under microwave irradiation giving the hexahydrochromeno[4,3-*b*]pyrrole in 98% yield after only 30 min (Scheme 33) [95]. In the case of pyrrolidines **77a–d**, the all *cis* cycloadducts were accompanied by approximately 5% of a single diastereoisomer with a *trans* ring junction, whereas **77e** was formed as a 1 : 1 mixture of

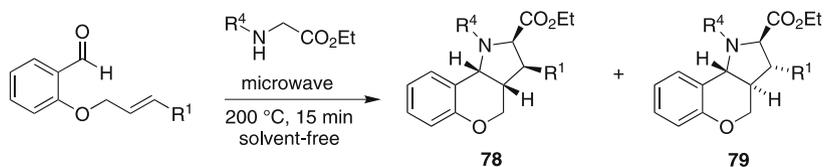
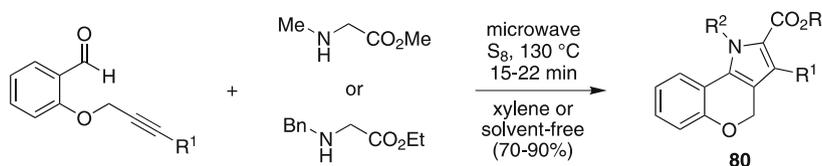


Table 1. Isolated Yield and Dr of Cycloadducts **78:79**.

	R^4 = Bn	R^4 = Et	R^4 = <i>n</i> -Pr	R^4 = <i>i</i> -Pr
R^1 = H	83	81	80	79
R^1 = CO ₂ Et	79 (3.8:1)	82 (3.8:1)	81 (4.0:1)	82 (2.8:1)

Scheme 34 Solvent-free synthesis of hexahydrochromeno[4,3-*b*]pyrroles **78** and **79**



Scheme 35 Microwave-assisted synthesis of benzopyrroles

diastereoisomers in which the ring junction was either *cis* or *trans* [95]. Some stereoselectivity has been observed in similar microwave-assisted azomethine ylide-mediated cycloadditions carried out at higher reaction temperatures with bulkier *N*-alkyl groups ($R^4 = \text{Bn, Et, } n\text{-Bu, } i\text{-Pr}$), *endo/exo* selectivities, **78** : **79**, ranging from 2.8–4 : 1 (Table 1, Scheme 34) [94]. More interestingly, it would appear that under microwave irradiation a change in the stereoselectivity was observed compared to classical conditions [94].

The condensation of ω -propargylic benzaldehydes with methyl sarcosinate or ethyl *N*-benzylglycinate followed by in situ oxidation was also more efficient under microwave-assisted conditions for the synthesis of benzopyrroles **80** [94]. Oxidation of the hexahydrochromeno[4,3-*b*]pyrrole cycloadducts could be facilitated by the addition of sulfur and further irradiation for 10 min at $130\text{ }^\circ\text{C}$ in a one-pot process to give pyrroles **80** in 70–90% yield (Scheme 35). Although there was little difference between reactions carried out under microwave irradiation and those using classical conductive heating methodology, in terms of product yield, the microwave-assisted reactions had considerably shorter reaction times. Furthermore, a more convenient one-pot procedure, in which a mixture of the aldehyde, α -amino ester, sulfur and a minimal amount of xylene was irradiated for 15 min at $130\text{ }^\circ\text{C}$, provided the pyrrole product without any reduction in yield (90%) in a one-pot MCR.

5 Perspectives

The use of microwave irradiation to accelerate chemical reactions has provided new alternative procedures for the synthesis of compounds of interest. The advantages that this methodology can offer over conventional conductive heating procedures, with the introduction of dedicated single-mode instruments, include accurate monitoring and control of reaction conditions, and thus reproducibility, the rapid optimization of procedures, the automation of multiple reactions with tailored variation in individual reaction parameters, changes in selectivity, improvements in product yield and purity and the rapid generation of compound libraries through considerable reduction in the reaction times of individual reaction events. These advantages apply

equally well to MCRs for the synthesis of heterocyclic compounds as they do to most other areas of organic synthesis carried out at elevated temperature. Recent advances have witnessed many new MCRs being developed, and provided more convenient and rapid procedures for carrying out existing MCRs, that are particularly amenable to library synthesis. The synthesis of simple 5- and 6-membered *N*-, *O*-, and *S*-containing heterocycles, as well as more complex fused heterocyclic scaffolds, by MCR have all been facilitated in recent years with the advent of new technology for microwave-assisted synthesis. With so many advances in such a short time, it is with eager anticipation that we can expect many more developments in the microwave-assisted synthesis of heterocycles by MCRs in the very near future.

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Microwave-Assisted Synthesis of Sulfur and Nitrogen-Containing Heterocycles

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1	Introduction	60
2	Five-Membered Systems	61
2.1	Thiophenes and Derivatives	61
2.2	1,3-Thiazoles and Derivatives	65
2.2.1	Thiazoles and Thiazolidines (2,3-Dihydrothiazole)	65
2.2.2	Benzothiazoles	67
2.3	1,3,4-Thiadiazoles	71
3	Six-Membered Systems	73
3.1	1,3-Thiazines	73
3.2	1,3,4-Thiadiazines	74
4	Seven-Membered Systems	74
4.1	1,5-Thiazepines and Derivatives	74
4.2	1,3,4-Thiadiazepines	76
5	Conclusion	77
	References	78

Abstract This chapter aims to review recent developments in the synthesis of sulfur and nitrogen-containing heteroaromatic compounds under conditions that include the application of microwave irradiation in the ring-forming step. The review is grouped according to the main heterocycle types in order of increasing complexity; commencing with five-membered sulfur-containing ring systems containing one, two, and three heteroatoms and their fused-ring analogues, followed by six- and seven-membered systems with more than one heteroatom, and then the analogous higher-membered ring systems. Fused-ring aromatic heterocycles and polycyclic molecules are also described.

Keywords Thiadiazines · Thiadiazepines · Thiazepines · Thiazines · Thiazoles · Thiophenes

Abbreviations

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Bu	Butyl

<i>t</i> -Bu	<i>tert</i> -butyl
Bz	Benzoyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N</i> -dicyclohexylcarbodiimide
DCM	Dichloromethane
DMAP	4-(dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
Me	Methyl
MW	Microwave(s)
Ph	Phenyl
Pr	Propyl
<i>i</i> -Pr	Isopropyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

1

Introduction

For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry. The presence of heterocycles in all kinds of organic compounds of interest in biology, pharmacology, optics, electronics, material sciences, and so on is very well known. Among them, sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers and their unique structures led to several applications in different areas. Sulfur and nitrogen organic aromatic heterocycles are formally derived from aromatic carbon cycles with a heteroatom taking the place of a ring carbon atom or a complete CH = CH group. Although the presence of many nitrogen and sulfur atoms in a ring was normally associated with instability and difficulties in the synthesis, stable sulfur and nitrogen heterocycles with unusual properties can be frequently obtained. The presence of heteroatoms results in significant changes in the cyclic molecular structure, due to the availability of unshared pairs of electrons, and in the reactivity, compared with the parent aromatic hydrocarbons. In contrast to the number and variety of such heterocycles, the number of synthetic methods to afford sulfur and nitrogen-containing molecules is, in practice, restricted to the availability of the appropriate sulfur or nitrogen reagent. Sometimes the preparation of these heterocyclic systems by conventional ways is difficult work that implies many synthetic steps and extensive starting material. For all these reasons, the various possibilities offered by the microwave technology are particularly attractive where fast, high-yielding protocols and the avoidance or facilitation of purification are highly desirable. Despite the area of microwave-assisted chemistry being 20 years old, the technique has only recently received widespread global acceptance in the academic and industrial

communities. This is a consequence of the recent availability of commercial microwave systems specific for synthesis, which offers improved opportunities for reproducibility, rapid synthesis, rapid reaction optimization and the potential discovery of new chemistries. The beneficial effects of microwave irradiation are finding an increased role in process chemistry, especially in cases when usual methods require forcing conditions or prolonged reaction times. Microwaves have also shown an advantage where processes involve sensitive reagents or when products may decompose under prolonged reaction conditions.

This chapter aims to review recent developments in the synthesis of sulfur and nitrogen-containing heteroaromatic compounds under conditions that include the application of microwave irradiation in the ring-forming step. Functionalization of pre-formed heteroaromatic core structures (e.g., *N*-alkylations, heteroaromatic substitution) and the generation of heteroaromatic species from existing non-aromatic ring systems (e.g., by dehydrogenation) will not be included. Many interesting reports of studies employing domestic microwave instruments have appeared in the literature; however, there is some debate over the safety and reproducibility aspects of the use of non-dedicated microwave instruments in the laboratory environment. Custom-designed microwave instruments for laboratory use are now commercially available and these offer superior control of the reaction conditions and enhanced reproducibility whilst also providing a key safety advantage. Wherever possible, this review will focus on chemistry carried out using the latter type of instrumentation.

This review is grouped according to the main heterocycle types in order of increasing complexity; commencing with five-membered sulfur containing ring systems containing one, two, and three heteroatoms and their fused-ring analogues, followed by six- and seven-membered systems with more than one heteroatom, and then the analogous higher-membered ring systems. Fused-ring aromatic heterocycles and polycyclic molecules are also described. Syntheses of heterocyclic systems of particular biological or commercial interest will be emphasized.

2

Five-Membered Systems

2.1

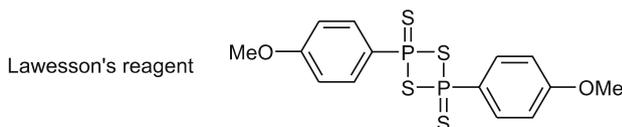
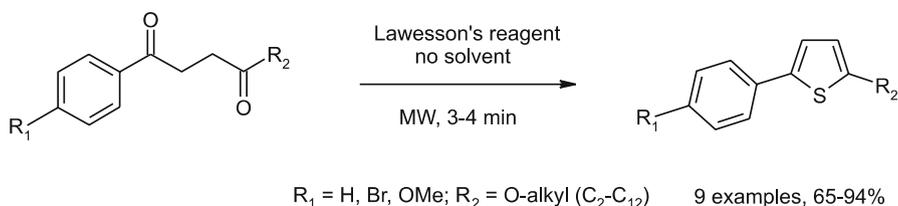
Thiophenes and Derivatives

Five-membered sulfur-containing heterocycles are important synthetic intermediates and have found a variety of applications in medical, agricultural, and material chemistry. Looking for potential candidates for ferroelectric display applications, Seed's group investigated the preparation of liquid crystals

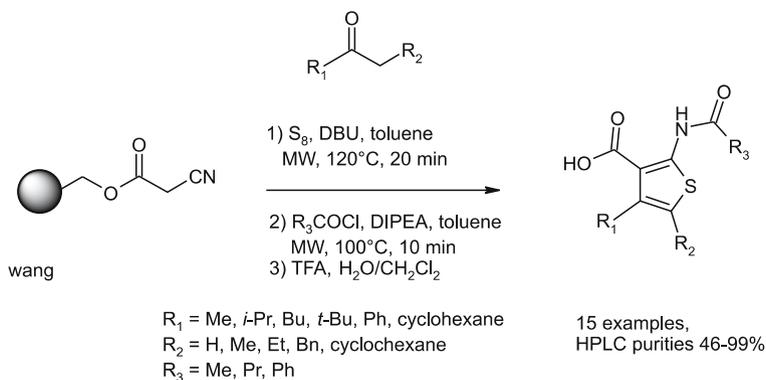
containing five-membered S-containing heterocycles containing thiophene derivatives. They demonstrate that when the Lawesson's reagent-mediated cyclization of various 1,4-dicarbonyl compounds is performed under microwave irradiation, high yields of the desired thiophenes are obtained (Scheme 1). Little or no by-products are formed and reaction times are extremely short (3–13 min) in these variants of the classical Paal–Knorr thiophene synthesis, which are performed in the absence of solvent in a conventional microwave oven [1].

The synthesis of polysubstituted thiophenes from a multi-component condensation of ketones or aldehydes, cyanoacetates, and elemental sulfur was originally published in 1961 by Gewald and co-workers. Beyond their industrial use in dyes and conducting polymers, 2,5-substituted thiophenes have shown extensive potential in the pharmaceutical industry. Most published Gewald thiophene synthetic procedures require reaction times between 8 and 48 h for the condensation step. The use of microwave irradiation in conjunction with resin-bound cyanoacetate is a notable improvement to this reaction. 2-Aminothiophene rings were rapidly constructed in 20 min at 120 °C as described in Scheme 2 [2]. In this variant of the Gewald transformation, toluene was the solvent of choice allowing the direct acylation of the primary amine generated in the first step. Cleavage from the Wang resin using TFA in DCM gave the desired products in 46–99% yield. Although these reactions were conducted in a single-mode reactor operating at 300 W, this chemistry offers numerous sites of diversity and is well suited for the preparation of a library of various thiophenes [2].

Benzothiophenes have always been of interest for medicinal chemistry and can be found in a number of marketed drugs such as Sertaconazole (Ginedermofix), Zileuton (Leutrol) and Raloxifene (Evista). The classical synthesis of benzothiophenes starts from thiophenols, reacting with bromoacetaldehyde dimethyl acetal, followed by cyclization using strong acid. An alternative and more convenient route was also described starting from benzaldehydes which



Scheme 1

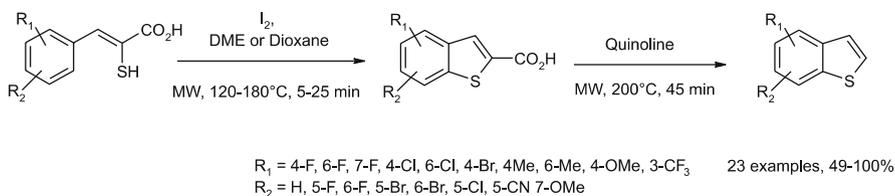


Scheme 2

can react with rhodanine and after hydrolysis in basic conditions affords the corresponding β -aryl- α -mercaptoacrylic acids (Scheme 3). The acids can be cyclized and decarboxylated to give the corresponding benzothiophenes. A recent paper described how both the cyclization and the subsequent decarboxylation were improved using microwave technology. This chemistry described was performed in a multimode CEM MARS microwave oven but the authors are claiming to investigate the possibility to perform the microwave irradiation with a focused reactor [3].

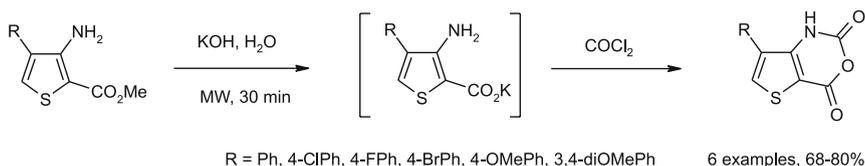
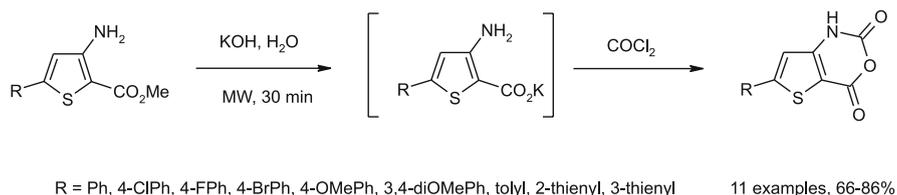
Despite that the thiophene ring is considered as a bioisoster of the benzene ring, the synthesis and chemistry of thiophene analogs of heterocycles with therapeutic interest remain poorly studied. One of the most recent examples concerns the synthesis of new substituted thioisatoic anhydrides (6 and 7-arylthieno[3,2-*d*] [1,3]oxazine-2,4-diones), which were prepared on a large scale under microwave irradiation conditions. A small library of thiophene ureidoacids was easily performed using a Normatron microwave reactor (500 W) with high yields and good purity [4, 5] (Scheme 4).

Imidazo[1,2-*c*]thieno[3,2-*e*]pyrimidines were investigated as possible bronchodilators. A facile microwave-assisted route for the synthesis of these tricyclic thieno derivatives was reported in quantitative yields via intermediate 4-chlorothieno[2,3-*d*]pyrimidines themselves synthesized under one-pot reaction conditions. The last step was performed for only 1 min



Scheme 3

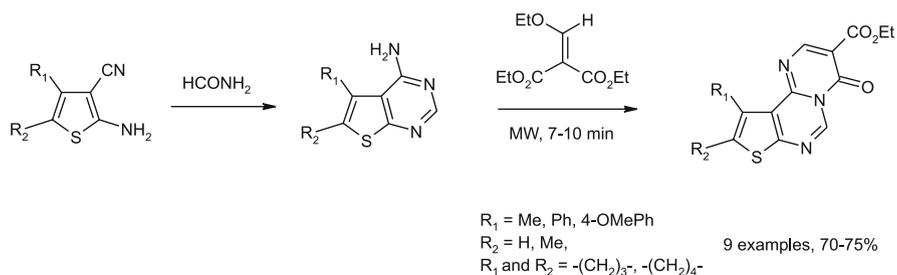
on silica gel as solid support in solvent-free conditions applying a multimode microwave oven (BPL 700T, Mumbai, India) irradiating at 600 W (Scheme 5). After extraction from the solid phase and an easy work-up procedure, a short library of 5-substituted-2,3-dihydroimidazo[1,2-*c*]8,9-



Scheme 4



Scheme 5



Scheme 6

dimethyl/tetrathieno[3,2-*e*]pyrimidines was obtained in improved yields (81–88%) compared to conventional heating methods [6].

With a similar approach, Dave and Shah have developed a simple, fast, solvent-free and high-yielding, variant of the Gould–Jacob type synthesis of thieno[3,2-*e*]pyrimido[1,2-*c*]pyrimidines. In this example the conventional condensation between 4-aminothieno-2,3-dyrimidines and diethyl ethoxymethylenemalonate via acyclic intermediates (usually performed in 5–6 h) was compared with a solvent-free single-step microwave procedure (7–10 min) applying a multimode microwave oven (BPL 700T, Mumbai, India) [7], Scheme 6.

2.2

1,3-Thiazoles and Derivatives

2.2.1

Thiazoles and Thiazolidines (2,3-Dihydrothiazole)

Thiazoles are important heterocycles and continue to be interesting synthetic targets because several classes of annulated thiazoles and thiazolyl (hetero)arenes display a diverse array of biological activities.

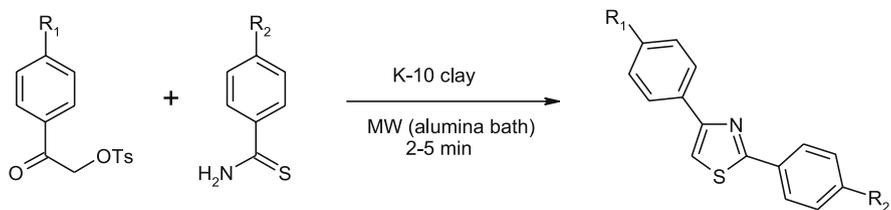
A solvent-free strategy for the synthesis of thiazoles involved mixing of thioamides with α -tosyloxy ketones in a clay-catalyzed reaction (Scheme 7). The typical procedure entailed mixing of thioamides and in situ produced α -tosyloxy ketones with montmorillonite K-10 clay in an open glass container. The reaction mixture was irradiated in a microwave oven for 2–5 min with intermittent irradiation and the product was extracted into ethyl acetate to afford 2-substituted thiazoles in 88–96% yields [8].

In the case of a diketone (e.g., 3-tosyloxy-pentane-2,4-dione), the formation of 5-acetyl-4-methyl-2-aryl-1,3-thiazole derivatives can be realized in very good yields (86–89%) (Scheme 7). All these experiments were performed in a Sears Kenmore unmodified household microwave oven (990 W) equipped with a turntable. The average bulk temperature was estimated by inserting a thermometer in the alumina bath housing the reaction vessel.

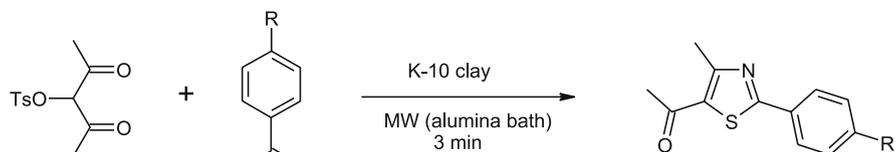
Following the same solvent-free approach, the synthesis of 2-aminothiazoles was described by short irradiation (2–3 min, approximate temperature 100–115 °C) of a mixture of thiourea and substituted α -bromoacetophenones, deposited over K_2CO_3 [9] (Scheme 8).

As described above for the synthesis of thiophenes, the microwave assisted Lawesson's reagent mediated cyclization of various 1,4-dicarbonyl compounds yielded the desired 2-alkoxythiazoles in 90% yields [1] (Scheme 9).

Thiazolines (2,3-dihydrothiazoles) were also prepared under microwave irradiation. Hamelin and coworkers have described the alumina-supported solvent-free synthesis of various 4-iminothiazolines by condensation of disymmetric thioureas and α -chloro ketone (Scheme 10). The experiments



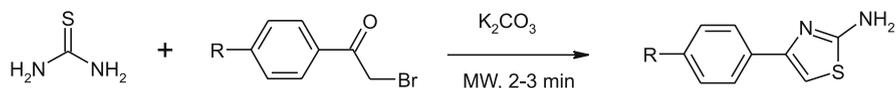
$R_1 = \text{H, Cl, Me, OMe}; R_2 = \text{Cl, OMe}$ 8 examples, 88-96%



$R = \text{Cl, OMe}$

2 examples, 86-89%

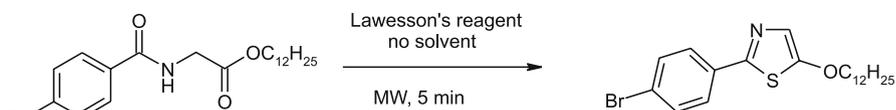
Scheme 7



$R = \text{Cl, NH}_2$

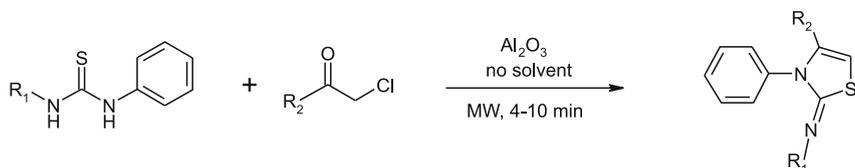
2 examples, 92-94%

Scheme 8



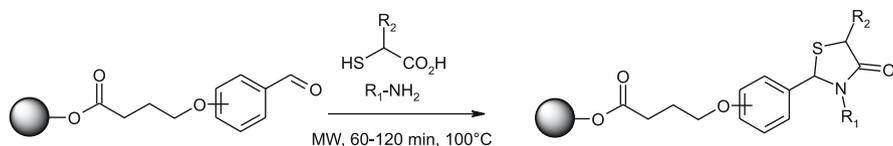
1 example, 90%

Scheme 9



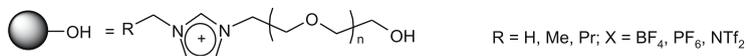
$R_1 = \text{Me, Ph}; R_2 = \text{Ph, Bn, } i\text{-Pr, } t\text{-Bu, Naphtyl}$ 12 examples, 77-98%

Scheme 10



$R_1 = \text{Bn}, \text{CH}_2\text{CH}=\text{CH}_2, \text{CH}_2(\text{OMe})_2, \text{piperonyl}; R_2 = \text{H}, \text{Me}, \text{CH}_2\text{CO}_2\text{H}$

12 examples, 25-61%



$R = \text{H}, \text{Me}, \text{Pr}; X = \text{BF}_4^-, \text{PF}_6^-, \text{NTf}_2^-$

[PEGn-Rmin][X] liquid phase: Poly(ethylene glycol)-ionic liquid matrix

Scheme 11

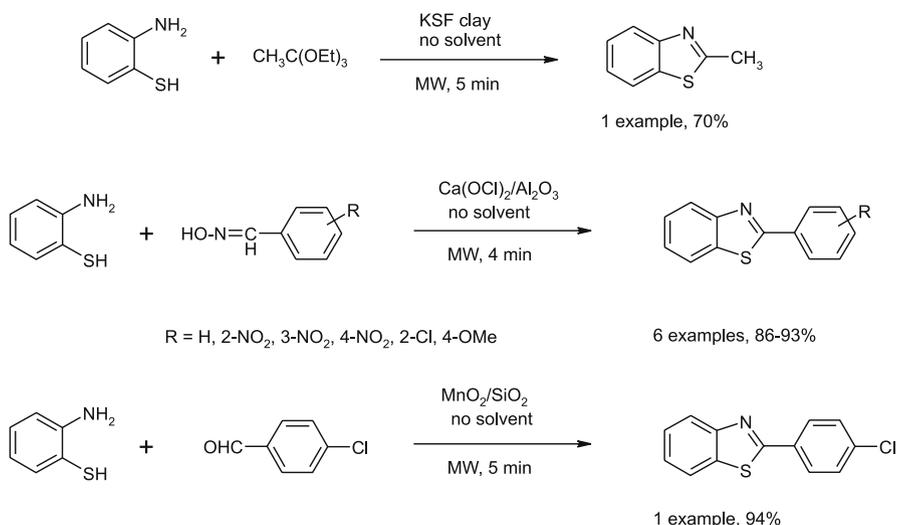
were performed in quartz tubes at 80 °C in a single-mode microwave reactor possessing an IR sensor for controlling the temperature [10].

Exploring the scope and potential of ionic liquids in microwave-assisted chemistry, authors from the same research institute recently published the first use of task-specific ionic liquids as a synthetic equivalent for ionic liquid-phase matrices for the preparation of a small library of 4-thiazolidinones. The starting (ethyleneglycol)ionic liquid-phase was functionalized in good yields with 4-(formylphenoxy)butyric acid by using usual esterification reaction conditions (DCC/DMAP as catalyst) (Scheme 11). The synthesis of the ionic liquid-phase bound 4-thiazolidinones was performed by a one-pot three-component condensation under microwave irradiation. Final cleavage under microwave/catalyst strategy (the procedure entails addition of a small amount of solid *tert*-butoxide) provided the expected 4-thiazolidinones in high purity after flash-chromatography purification [11].

2.2.2

Benzothiazoles

One of the first published microwave-assisted synthesis of benzothiazoles is the condensation of a dinucleophile such as 2-aminothiophenol, with an *ortho*-ester (neat) in the presence of KSF clay in a mono-mode microwave reactor operating at 60 W under a nitrogen atmosphere [12] (Scheme 12). Traditional heating (oil bath, toluene as solvent and KSF clay) gave the expected products in similar yields compared to the microwave experiments but more than 12 h were required for completion. Solvent-free microwave-assisted syntheses of benzothiazoles was also described by attack of the dinucleophiles cited above on benzaldehydes and benzaldoximes [13] (Scheme 12). This methodology was performed in a dedicated monomode microwave reactor

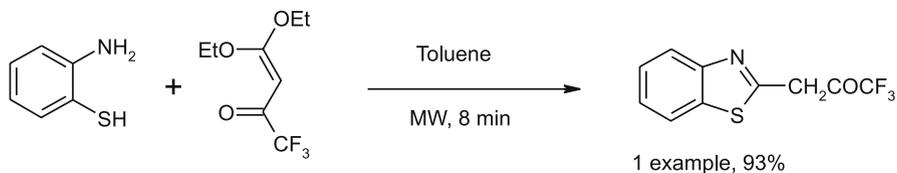


Scheme 12

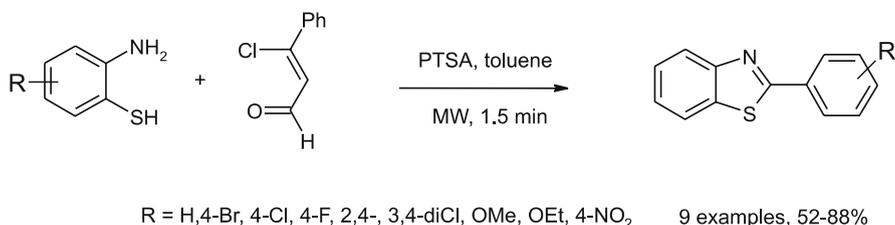
and has never been reported before. It complements the conventional processes described in the literature.

Following a similar strategy, trifluoroacetyl ketene diethyl acetal was successively condensed with 2-aminothiophenol in the presence of toluene in a multimode microwave oven (8 min at 980 W) to give the 2-(1,1,1-trifluoroacetyl)benzothiazole ring in an excellent yield (93%) [14] (Scheme 13). In this work, the temperature reached during reaction was not controlled reducing the reproducibility of the process.

Condensation of 2-aminothiophenol with the β -chlorocinnamaldehyde in the presence of *p*-toluene sulfonic acid (PTSA) gave good yield of benzothiazole (Scheme 14). The mechanism suggested in this work is believed to proceed via a nucleophilic attack of the sulfur atom in an addition-elimination sequence followed by a spontaneous cyclization and ejection of acetaldehyde [15]. These investigations were performed in a domestic microwave reactor and need 1.5 min for completion (65% yield). Here again, oil bath heating seems to be inferior, providing a maximum conversion of 53% after



Scheme 13

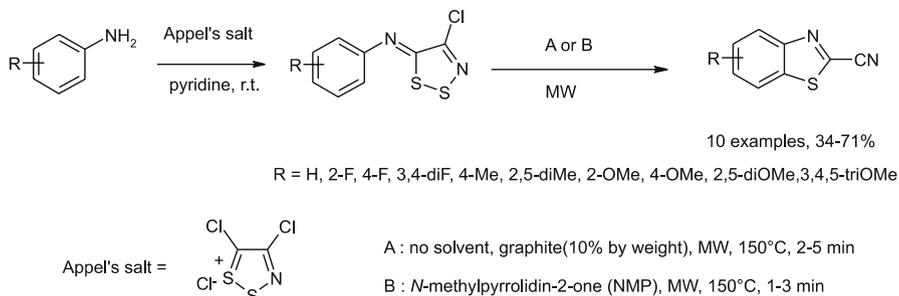
**Scheme 14**

1 h of reaction. The microwave-assisted protocol for this reaction was conducted with differently substituted aromatic compounds resulting in yields ranging from 52 to 88%.

Manganese(III)-promoted radical cyclization of arylthioformanilides and α -benzoylthio-formanilides is a recently described microwave-assisted example for the synthesis of 2-arylbenzothiazoles and 2-benzoylbenzothiazoles. In this study, manganese triacetate is introduced as a new reagent to replace potassium ferricyanide or bromide. The 2-substituted benzothiazoles are generated in 6 min at 110 °C under microwave irradiation (300 W) in a domestic oven with no real control of the temperature (reflux of acetic acid) (Scheme 15). Conventional heating (oil bath) of the reaction at 110 °C for 6 h gave similar yields [16].

One of the most studied microwave-assisted formations of the benzothiazole ring is initiated by an addition–elimination reaction. Treatment of aniline derivatives with 4,5-dichloro-1,2,3-dithiazolium chloride (commonly called Appel's salt) gave 4-chloro-5*H*-1,2,3-iminodithiazoles which are very versatile intermediates in the synthesis of various heterocycles (Scheme 16). Besson and co-workers demonstrated that heating of these compounds at elevated temperature gave benzothiazoles in good yields and in very short times. Depending on the nature of the substituents present on the aromatic ring, this procedure provided a number of benzothiazoles in 30–70% yields. Study of this reaction under microwave irradiation, varying the time and temperature was performed [17]. Under well-defined conditions methods for

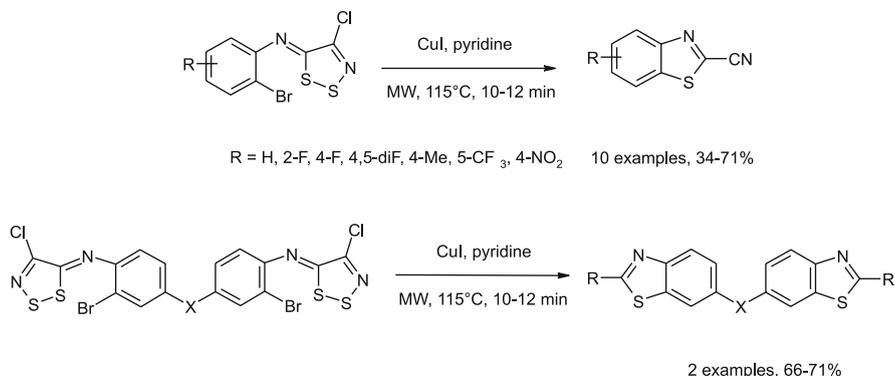
**Scheme 15**



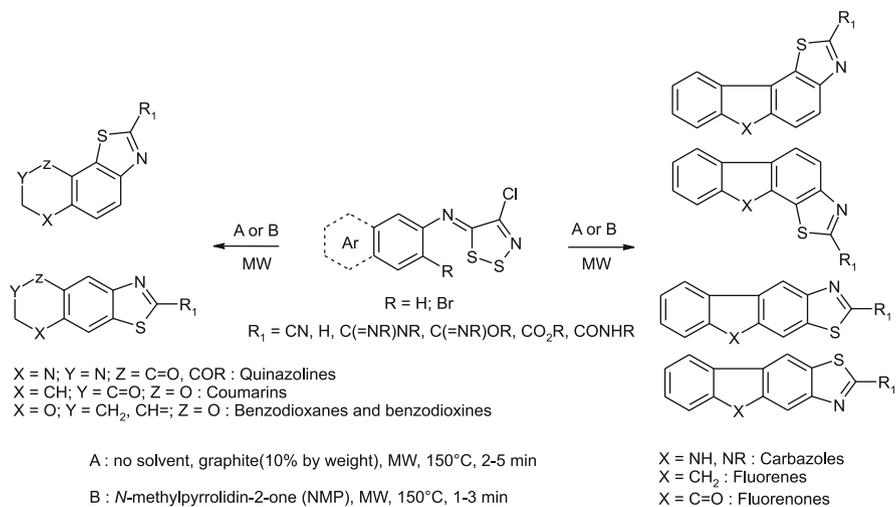
Scheme 16

scale-up were established. Comparisons were made between reactions performed under solvent-free conditions and in the presence of solvent [18]. In all cases the focused microwave methodologies were more productive than the traditional thermal reactions.

The major drawback in the preceding electrocyclization and fragmentation processes is the problem of the presence of strong electron withdrawing groups in the benzenic part. It prevents cyclization and results in the formation of a large number of by-products. Benzothiazoles possessing strong electron withdrawing substituents can be obtained from appropriate *o*-bromo substituted anilines in the presence of copper(I) iodide in pyridine at reflux [19,20] (Scheme 17). The mechanism may be facilitated by halogen complexation as described previously for the cyanation of aryl halides by copper(I) cyanide, where 2-cyanobenzothiazoles are also formed in the presence of copper(I) cyanide or copper(0). This reaction was performed with a focused microwave reactor at atmospheric pressure. Important reduction of the reaction time and comparable yields with those obtained under oil bath conditions were observed.



Scheme 17

**Scheme 18**

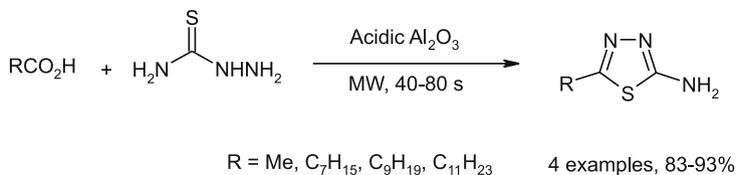
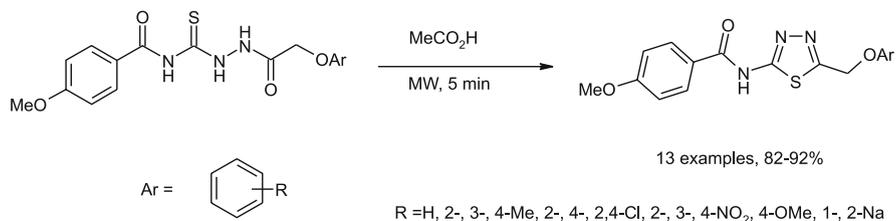
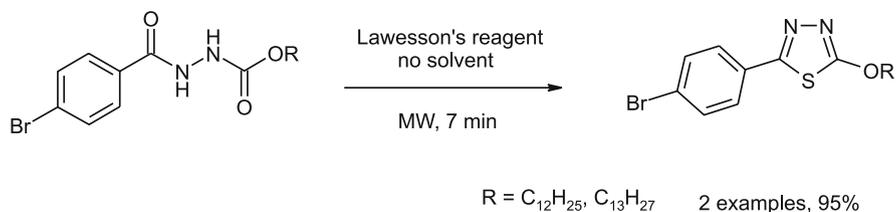
Possessing a large variety of microwave-assisted strategies to construct the benzothiazole ring [21], the authors extended their work and launched a research program dealing with the preparation and pharmacological evaluation of some original thiazolo derivatives. They focussed their studies on the regio-controlled synthesis of substituted thiazoloheterocycles mainly related to marine or terrestrial alkaloids (e.g., dercitine, kuanoniamine and ellipticine) in the hope to detect interesting cytotoxicity profiles and anti-cancer activity. Pursuing their efforts they reported the microwave-assisted synthesis of series of derivatives in which the thiazole ring was fused with carbazole [22–24], quinazoline [25, 26], benzodioxan [27], fluorenone, fluorene and anthraquinone [28] (Scheme 18).

In all cases, besides resulting in good to excellent yields, the microwave-assisted multistep syntheses resulted in much faster reactions compared to earlier published procedures at atmospheric pressure under conventional heating conditions. It is also noteworthy that in some cases the strong thermal effect due to graphite/microwave interaction, can efficiently be used for the synthesis of heterocyclic skeletons, especially benzothiazoles but, in fact, there is no general rule and some reactions performed in the presence of solvent may sometimes be more convenient than the same dry-media conditions.

2.3

1,3,4-Thiadiazoles

The microwave-assisted solid-supported synthesis of 1,3,4-thiadiazoles was described applying from acid and thiosemicarbazide on acidic alumina

**Scheme 19****Scheme 20****Scheme 21**

(Scheme 19). The reaction times were brought down from hours (5–7 h) to seconds (40–80 s) with improved yields compared to classical heating [29].

Li and co-workers introduced a rapid and efficient microwave-assisted method to prepare new disubstituted 1,3,4-thiazoles from 1,4-disubstituted thiosemicarbazides with the objective to obtain biologically active molecules. The intermediate 1-aryloxyacetyl-4-(4-methoxybenzoyl)thiosemicarbazide was irradiated in an excess of glacial acetic acid in a domestic microwave oven and led to the formation of 2-(methoxybenzoyl-5-aryloxymethyl)-1,3,4-dithiazoles in good yields [30] (Scheme 20).

In addition, thionation–cyclisation of 1,2-diacylhydrazidines to 1,3,4-thiadiazoles has been achieved by the action of Lawesson's reagent under solvent-free microwave irradiation in a domestic microwave oven (Scheme 21). This ring-closure methodology was extended for the synthesis of various liquid crystals [1].

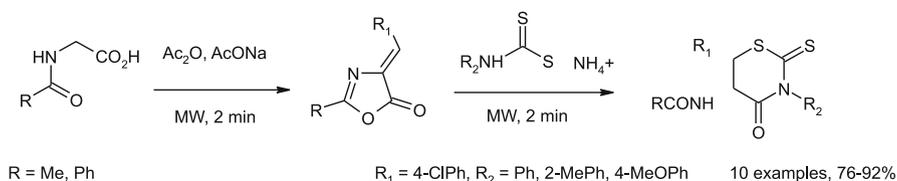
3 Six-Membered Systems

3.1

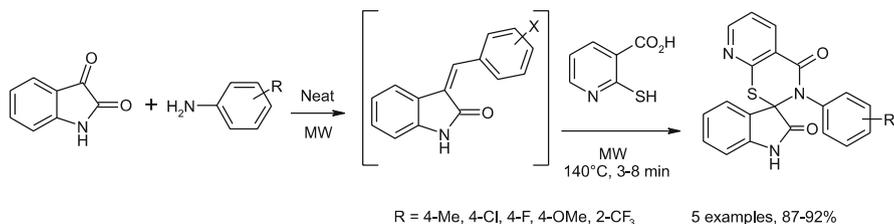
1,3-Thiazines

The 1,3-thiazine nucleus is the active core of cephalosporins which are among the widely used β -lactam antibiotics. Owing to their chemical and biological activity, novel syntheses of various 1,3-thiazine derivatives have generated some interest in the scientific community. The major drawback of the published work on this topic is the fact that all these processes use plenty of organic solvents and, in certain cases the yield does not exceed 30%. Considering all these results, Yadav and Singh have recently described a one-pot highly diastereoselective solvent-free synthesis of 1,3-thiazine derivatives using an unmodified domestic microwave oven at 480 W [31] (Scheme 22). These microwave-assisted cascade reactions of *N*-acylglycines, acetic anhydride, anhydrous sodium acetate, aromatic aldehydes and ammonium *N*-arylthiocarbamates afforded 5-acylamino-3,6-diarylperhydro-2-thioxo-1,3-thiazin-4-ones in good yields. A tentative of comparison between traditional heating and the microwave irradiation was performed. The measurement of the temperature in this kind of oven is not very easy and interpretation of the results may be really difficult.

Looking for novel 1,3-thiazines with biological interest, Dandia and co-workers have recently prepared fused pyrido-1,3-thiazine derivatives by treatment of in situ generated 3-indolyimine derivatives with 2-mercaptopyridine



Scheme 22



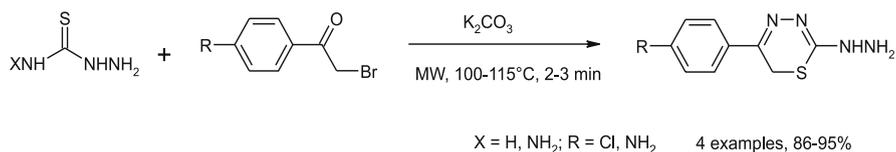
Scheme 23

acid under microwave irradiation in the absence of any solvent or solid support [32] (Scheme 23). This facile and short (3–8 min) one-pot reaction was generalized for a variety of ketones and amines to give pure pyrido-1,3-thiazines, which do not require further purification processes. In this case, the experiments were carried out in an open borosil glass vessel under atmospheric pressure applying a modified BMO-700T domestic microwave oven operating at 700 W. The use of microwave conditions seems absolutely essential in this transformation, as conventional heating fails.

3.2

1,3,4-Thiadiazines

Irradiating a mixture of thiocarbohydrazine with α -bromoacetophenone, deposited over K_2CO_3 , (approximate temperature 100–115 °C) for 2–3 min gave 2-hydrazino-1,3,4-thiadiazines which are therapeutically interesting compounds (Scheme 24). Reaction with thiosemicarbazide, which was unsymmetrically substituted at the thiocarbonyl unit with a hydrazine and an amino group, produced 1,3,4-thiadiazines in good yields. Comparison with classical heating conditions was investigated and afforded very impure product after 6–7 h of heating in an oil bath [9].



Scheme 24

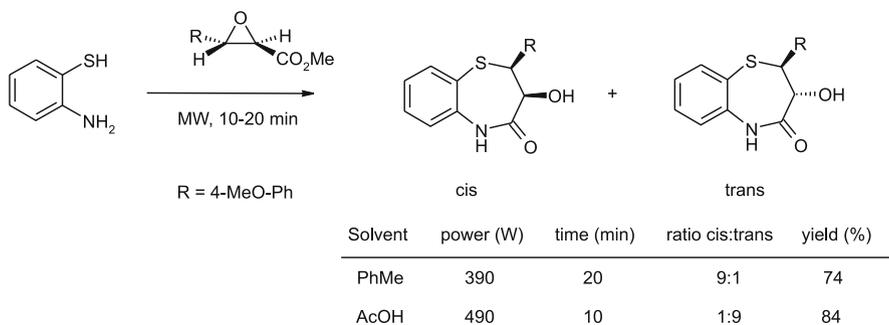
4

Seven-Membered Systems

4.1

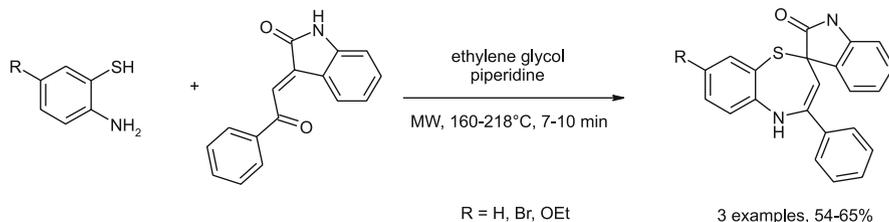
1,5-Thiazepines and Derivatives

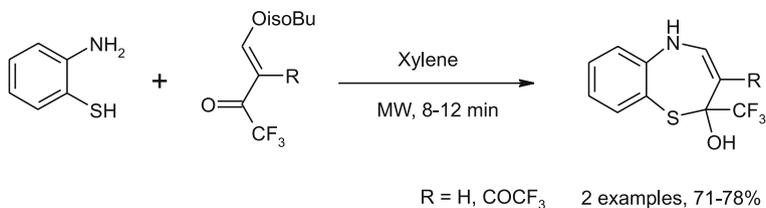
1,5-Benzothiazepines belong to the three classes of calcium channel blockers which are important cardiovascular drugs in the management of angina pectoris and hypertension. A diastereoselective one-pot synthesis of the *trans*- and *cis*-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4-one nucleus, a key intermediate in the preparation of the calcium channel blocker Diltiazem, was carried out under microwave irradiation in an open vessel (Scheme 25). Control of the diastereoselectivity was achieved by vary-

**Scheme 25**

ing the reaction time and power output as well as the nature of the solvent. A commercial microwave oven with 900 W of power output was used. The power generated by the oven was measured before every experiment by the method described by Watkins [33]. The authors observed that carrying out the process for 20 min at a power of 390 W in toluene led to a *cis/trans* ratio of 9 : 1 (yield: 74%). Raising the power to 490 W for 10 min involved an inversion of the ratio, increasing dramatically the amounts of the *trans*-isomer (yield: 84%). The traditional one-pot preparation of racemic target compounds produced less than 30% yield at 160 °C with prolonged reaction times [34].

Studying the biological activity of 3-spiroindolines incorporating a 1,5-benzothiazepine ring at the position 3 of the 2-indoline skeleton, Dandia and coworkers have investigated the reaction of 1,3-dihydro-3-(2-phenyl-2-oxoethylidene)indol-2-one with 2-aminobenzenethiols under thermal and microwave reaction conditions [35] (Scheme 26). In this work, ethylene glycol was used as the energy transfer medium under microwave irradiation conditions while the standard method involves reaction in ethanol saturated with hydrogen chloride gas. A discussion of the results obtained from the two synthetic approaches indicates a significant decrease of reaction times and cleaner reactions with the microwave methodology. The type of microwave reactor involved in these studies is not described by the authors but, reading the experimental conditions, probably a domestic microwave oven was used

**Scheme 26**



Scheme 27

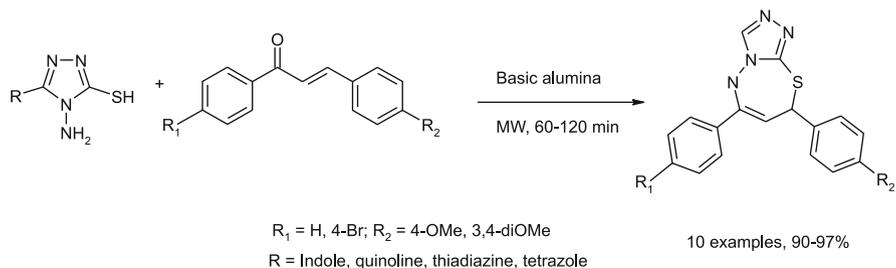
with no real control of the power applied and the temperature reached by the reactants.

Expecting to enhance the anxiolytic activity of some derivatives by introduction of a trifluoromethyl group in the dia-, oxa- or thiazepine segment, trifluoroacetyl ketene acetals were successively condensed with 2-aminothiophenol in the presence of xylene applying a multimode microwave oven (8–12 min at 980 W) following a similar procedure as this described for benzothiazoles [14] (Scheme 27). Although this methodology uses microwave inert solvents (e.g., toluene or xylene), which are not serving in the energy transfer processes, it gave the 3-substituted 2-hydroxy-2-trifluoromethyl-1,5-benzothiazepine ring in good yields (71–78%), suggesting absorption of the microwaves by the reactants. It is noteworthy that the temperature reached during the reaction was not controlled [14].

4.2

1,3,4-Thiadiazepines

Potent antimicrobial 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines derivatives were prepared from readily accessible substituted 2-mercapto-1-aminotriazoles and substituted chalcones on basic alumina in a solvent-free microwave-assisted synthesis (Scheme 28). Exposure of the reaction mixtures to microwaves led to an important decrease of the reaction time, which has been brought down from hours to seconds, accompanied by improved yields as compared with conventional heating [36]. This facile, rapid, and economic



Scheme 28

solvent-free methodology was carried out in a domestic microwave oven (Padimi Essentia, model Brownie) at 2450 MHz with no estimation of the temperatures reached during the reactions.

5 Conclusion

The examples described in this chapter demonstrate that microwave-assisted synthesis can allow easy and rapid access to various aromatic heterocyclic compounds, in particular sulfur- and nitrogen-containing molecules that may have interesting pharmaceutical potential. These aromatic heterocyclic compounds have been synthesized applying a variety of microwave systems, including domestic microwave ovens. This review is not intended to be exhaustive in its content, but rather to highlight significant examples where microwave irradiation has been either synthetically enabling or has provided a key advantage over conventional thermal methods. Despite the often-associated reproducibility problems associated with chemistries developed in a domestic microwave oven, these examples highlight opportunities for these chemical reactions to be investigated in a single-mode focussed microwave synthesizers now commercially available.

The description of the association of heterocyclic chemistry and microwave irradiation has also shown that performing microwave-assisted reactions should be considered with special attention. A few of these considerations can be applied generally for conducting microwave-assisted reactions and include the following: (a) the ratio between the quantity of the material and the support (e.g., graphite) or the solvent is very important; (b) for solid starting materials, the use of solid supports can offer operational, economical and environmental benefits over conventional methods. However, association of liquid/solid reactants on solid supports may lead to uncontrolled reactions which may result in worse results than the comparative conventional thermal reactions. In these cases, simple fusion of the products or addition of an appropriate solvent may lead to more convenient mixtures or solutions for microwave-assisted reactions.

The strategies explored and defined in the various examples presented open a way for wider application of microwave chemistry in industry. The most important problem for chemists today (in particular, drug discovery chemists) is to scale-up microwave chemistry reactions for a large variety of synthetic reactions with minimal optimization of the procedures for scale-up. At the moment, there is a growing demand from industry to scale-up microwave-assisted chemical reactions, which is pushing the major suppliers of microwave reactors to develop new systems. In the next few years, these new systems will evolve to enable reproducible and routine kilogram-scale microwave-assisted synthesis.

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Solid-Phase Methods for the Microwave-Assisted Synthesis of Heterocycles

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1	Introduction	80
1.1	Solid-Phase Organic Synthesis and Combinatorial Chemistry	80
1.2	Microwave-Assisted Synthesis	82
2	The Solid Support	83
2.1	Insoluble Polymer Supports	83
2.2	Soluble Polymer Supports	87
2.3	Microwave-Assisted Loading Reactions	87
3	Microwave Instrumentation for SPOS	89
4	Microwave-Mediated SPOS of Heterocyclic Compounds	94
4.1	Oxazoles	94
4.2	Preparation of Isoxazoles and Pyrazoles	95
4.3	Isoxazole Synthesis via On-Resin [3 + 2] Cycloaddition	96
4.4	Construction of Isoxazole, Pyrazole and Pyrimidine Rings from Aminopropenones	96
4.5	Rapid Preparation of Imidazole-4-Carboxylic Acids	97
4.6	Tetrazole Synthesis	98
4.7	“Catch and Release” Synthetic Route to 2,4,5-trisubstituted Pyrimidines	98
4.8	Domino Synthesis of Functionalized Tetronates	100
4.9	Preparation of Thiophenes by Microwave-Promoted Gewald Synthesis	101
4.10	Microwave-Promoted Synthesis of Bicyclic Pyrimidine Derivatives on Solid-Phase	102
4.11	Phthalimide Library Synthesis on Wang Resin	103
4.12	Indole Synthesis	104
4.13	Diverse Nitrogen and Oxygen Heterocycles via On-Resin Cyclization of Aminopropenones	108
5	Microwave-Accelerated SPOT Synthesis	109
6	Microwave-Promoted Synthesis on Soluble Supports	110
7	Microwave-Assisted Synthesis in Fluorous Phases	112
7.1	Fluorous Synthesis of Biaryl-Substituted Proline Analogs	112
7.2	Fluorous Synthesis of Dihydropteridinones by Microwave-Assisted Cyclative Cleavage	113
7.3	Fluorous Mixture Synthesis of Fused-Tricyclic Hydantoins	114
7.4	Microwave-Assisted Fluorous Ugi Reactions, Synthesis of Benzimidazoles and Quinoxalinones	115

8	Microwave-Enhanced Synthesis Using Functional Ionic Liquid Supports	115
8.1	Preparation of a 4-thiazolidinone Library Employing a Functional Ionic Liquid Support	116
8.2	Preparation of 2-thioxo Tetrahydropyrimidin-4-(1H)-ones on Ionic Liquid Support	117
8.3	Microwave-Assisted Synthesis of a Substituted Pyran Using Ionic Liquid Tagging	118
9	High-Speed Functionalization of Heterocycles	119
9.1	Rapid Nucleophilic Displacement on Purine C-2	119
9.2	Microwave-Promoted Route to Diverse 2(1H)-Pyrazinones and Pyridinones	120
9.3	Microwave-Assisted Substitution of Imidazole C-2 on Solid-Phase	122
9.4	Suzuki Couplings	122
10	Summary and Outlook	123
	References	123

Abstract Current microwave-assisted protocols for reaction on solid-phase and soluble supports are critically reviewed. The compatibility of commercially available polymer supports with the relatively harsh conditions of microwave heating and the possibilities for reaction monitoring are discussed. Instrumentation available for microwave-assisted solid-phase chemistry is presented. This review also summarizes the recent applications of controlled microwave heating to solid-phase and SPOT-chemistry, as well as to synthesis on soluble polymers, fluororous phases and functional ionic liquid supports. The presented examples indicate that the combination of microwave dielectric heating with solid- or soluble-polymer supported chemistry techniques provides significant enhancements both at the level of reaction rate and ease of purification compared to conventional procedures.

Keywords Microwave · Heterocyclic · Solid-phase · Solid-support · Soluble-support

1

Introduction

1.1

Solid-Phase Organic Synthesis and Combinatorial Chemistry

The fundamentals of solid-phase organic synthesis (SPOS) were introduced over 40 years ago for peptide chemistry by R. Bruce Merrifield [1, 2]. As a result, solid-phase peptide synthesis (SPPS) has been used to prepare a wide range of bioactive compounds [3]. For more than two decades, developments in solid-phase chemistry were almost entirely focused on the synthesis of biopolymers; however, early reports on the idea of “combinatorial chemistry” presented by peptide chemists in the late 1980s triggered a rapid growth and broadening of solid-phase methodology. Since the pioneering work of Árpád

Furka [4], combinatorial chemistry has been recognized as a major breakthrough in scientific research [5] and has resulted in revolutionary changes of the drug discovery paradigm. Thus, combinatorial chemistry has become simultaneously an answer and a part of the challenge of high throughput screening (HTS) technology [6, 7], which allows the quick exploration of huge numbers of potential drug candidates. Since the rapid preparation of novel low molecular weight compounds has become the bottleneck of modern drug development, continuing advances in SPOS are essential for the success of combinatorial chemistry. SPOS allows for the synthesis of drug-like molecules via innovative routes, which may be difficult, if not impossible, to achieve using traditional solution-phase methods. In addition, it offers less tedious and more time-efficient purification compared to traditional solution-phase chemistry. Thus, recent interest in the preparation of non-peptidic synthetic targets on solid support has grown. Solid-phase synthesis of heterocyclic compounds [8–10] has been an attractive field of academic as well as industrial pharmaceutical research since heterocycles offer well-defined spatial positioning of their substituents and, in general, have many characteristics common among bioactive compounds, such as good oral availability, the ability to cross membranes and high in vivo stability [11]. Furthermore, they are usually available via short, undemanding synthetic routes, and their preparation costs are typically lower than those of other drug candidates (i.e., peptide therapeutics for which the solid-phase methodology originally has been developed [12]). Hence, solid-phase combinatorial chemistry techniques are today frequently applied to the preparation of highly diverse libraries of heterocycles [13].

The main advantage of solid-phase organic synthesis is its simplicity. Reactions on solid phase are generally performed by shaking a substrate, which is covalently bound to an insoluble polymer, with a mixture of reagents for a given time, followed by filtration and washing to remove excess reagents. Then, the resin-bound compound can be reacted with another reagent mixture, filtered and washed as before. These steps can be repeated as many times as necessary and are amenable to automation. In addition, the support does not need to be dried between different reactions, only washed thoroughly with suitable solvents. Moreover, a large excess and high concentration of reagents can be used to drive chemical transformations to completion, since the surplus reagents are easily removed via filtration after each step. Reaction steps may be repeated several times, if necessary, to ensure full conversion. Cleavage of the final product is accomplished by the selective reaction of the linker, a unit connecting the compound of interest with the solid support. A linker is by definition stable under all reaction conditions used but allows for a selective release of the desired product at the end of the synthesis. The resulting product is usually of high purity and can be assayed directly; however it is commonly purified by chromatography or recrystallization. SPOS can in principle be performed with standard laboratory equipment. However,

manual synthesis is usually only performed if large amounts of resin have to be handled, with automation being employed for the generation of libraries in parallel. (Note: The term of “solid-phase” is occasionally misused in the literature since reaction sequences performed on inorganic solids are sometimes referred as if they would have been performed on solid-support.)

Although solid-phase organic synthesis provides a powerful means for the preparation of compound libraries, it still exhibits several weaknesses due to the nature of the heterogeneous reaction conditions. Nonlinear kinetic behavior, slow reactions, solvation difficulties, and degradation of the polymer support resulting from long reaction times being some of the frequently reported problems [14]. Another disadvantage of solid-phase synthesis is that it generally only allows for the preparation of small amount of product (μmol scale). In addition, impurities physically absorbed to the resin (not removed during washing) are typically desorbed during cleavage and may contaminate the product. Also, characterization of the resin-bound intermediates is rather difficult. Gel-phase NMR spectra usually suffers from extensive line-broadening, mainly originating from dipolar couplings and chemical shift anisotropy [15]. On the other hand, dried supports can be directly used for infrared spectroscopy, allowing the qualitative analysis of certain functional groups with intense and well-resolved absorptions [16]. Direct study of support-bound intermediates may also be available through TOF-SIMS and MALDI-TOF mass spectrometric analysis [17, 18]. Colorimetric methods have been developed for monitoring the detection of certain functionalities on a support. Kaiser’s test [19] was the very first method used for identifying small amounts of residual primary amines after the coupling of amino acids on solid-phase. A few analogous methods have been developed for other functionalities as well [20–22]. There are also some published examples of the use of elemental analysis of resin-bound compounds to determine a sample’s sulfur, nitrogen or halogen content [16, 23]. However, combustion analysis is not the first choice method for confirmation of completion of a reaction step. The most common alternative to the aforementioned techniques is the cleavage of intermediates from a small amount (1–20 mg) of the solid support and their characterization in solution.

1.2

Microwave-Assisted Synthesis

In recent years, parallel to the emergence of SPOS, microwave-mediated organic synthesis has come to light and has developed into a popular field [24–31]. The main advantage of microwave dielectric heating compared to other conventional methods, such as hot plate, oil bath or isomantle, is the tremendous rate enhancement generally observed under microwave irradiation conditions. Various theories have been proposed to explain the source of the rapidity of microwave chemistry [32, 33]. However, the gener-

ally accepted view is that most, if not all, observed rate enhancements can satisfactorily be explained by thermal effects, and even if “the existence of a ‘specific microwave effect’ cannot be completely ruled out, the effect appears to be a rarity and of marginal synthetic importance” [34]. The rate acceleration observed for microwave irradiation is often explained as being a result of the rapid, internal heating, a phenomenon that is extremely difficult, if not impossible to duplicate with conventional heating.

By linking solid-phase organic chemistry with microwave heating, a fast and efficient methodology is expected to arise. The advantages of the combination of these two techniques were first predicted by Caddick over 10 years ago [35]; he recognized that such a technique would be widely applicable to combinatorial chemistry. Since the basic principles and many of the major developments of combinatorial chemistry have their roots in peptide chemistry, the fact that the first microwave-assisted reaction on solid-phase was the synthesis of oligopeptides is not surprising [36]. Hence, Wang and coworkers demonstrated the potential of microwave heating for SPPS by performing peptide couplings on polystyrene Wang-resin in a domestic microwave oven with at least 2–3 fold rate enhancements (2–6 min) compared with standard room temperature conditions. Unfortunately, as in almost all early reports on microwave-mediated reactions, a reaction temperature was not reported. However, these results were later successfully reproduced under controlled microwave heating by several groups for peptidic [37–41], β -peptidic [42] as well as non-peptidic [43] compounds. Recently a microwave reactor dedicated to SPPS has been marketed [44], being applicable for general microwave-mediated SPOS and simple combinatorial chemistry purposes as well.

2 The Solid Support

2.1 Insoluble Polymer Supports

Solid-phase organic synthesis is a specific family of heterogeneous reactions, in which the chemical transformation takes place at the interface of a solid support and a reagent mixture. As a result, in addition to the properties of the solvent and reagents, the scope of chemical transformations is strongly affected by the properties of the solid support. The general requirements for a resin are chemical inertness under the conditions used, mechanical stability, sufficient permeability toward reagents and high swelling capacity. The polymer also needs to be functionalized with a suitable linker so that the starting materials can be attached to and removed from the support. For use in microwave-mediated SPOS, the resin needs to have good stability under high temperature conditions. Various supports have proven useful for SPOS,

and the scope of reaction conditions with which they are compatible has been explored [45–47].

The most common solid support in SPOS is hydrophobic, gelatinous resin beads (90–200 μm diameter) consisting of polystyrene (PS) cross-linked with 1–2% divinylbenzene (Fig. 1). Such polymers are insoluble but can swell in organic solvents, with a cross-linking dependent swelling capacity [48]. PS is cheap and commercially available as resin beads in a variety of sizes with a broad choice of pre-attached linkers uniformly distributed throughout the polymer matrix. In addition, cross-linked PS resins tolerate harsh reaction conditions, including strong bases like LDA, strong acids such as HBr or trifluoroacetic acid, and weak oxidants such as DDQ or ozone. However, due to its hydrophobicity, PS resin is less suitable for reactions involving ionic reagents. Kappe and Stadler have shown that PS resins tolerate microwave heating up to temperatures of 200 $^{\circ}\text{C}$ [38]. A wide variety of successful microwave-assisted transformations on PS support has been reported [37, 38, 49–68].

Microwave irradiation has recently been used to rapidly produce a combinatorial library via split-and-mix synthesis on PS macrobeads (500–600 μm) [69]. The high per-bead loading (80–200 nmol) of this solid support is attractive for preparation of one-bead-one-stock solution libraries; each bead contains sufficient material for multiple solution-based assays as well as analytical characterization [70]. Unfortunately, reaction rate decreases with increasing resin bead diameter, so library preparation on PS macrobeads can be hindered by slow reagent diffusion into the polymer matrix and sluggish reaction rates [71–73]. This problem is typically resolved by using extremely long reaction times and large excesses (20 equivalents) of reagents, neither of which is attractive [74]. Murray and coworkers applied multiple cycles of microwave irradiation to prepare a high-quality β -peptide library in reduced synthesis time as compared to conventional heating [69].

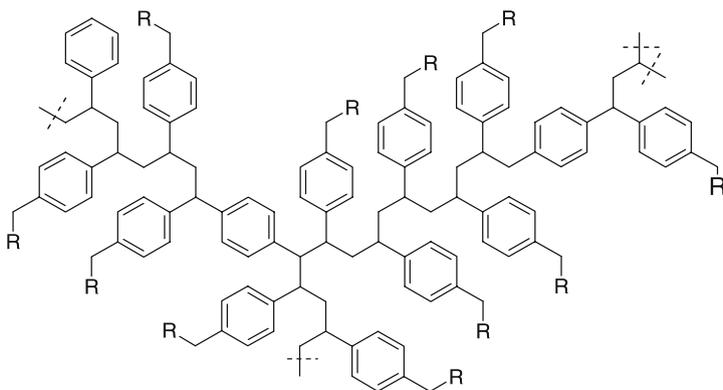


Fig. 1 The inner structure of a polystyrene solid support

A tetrahydrofuran cross-linked PS-based insoluble support (*JandaJel*) has also been developed and shown to tolerate microwave heating by Janda and coworkers [75]. *JandaJel* is commercially available and reported to offer better swelling characteristics, increased homogeneity and site-accessibility, as well as a more organic solvent-like environment compared to divinylbenzene cross-linked polymers.

A second class of solid support is the group of hybrid hydrophobic polystyrene beads, which are prepared by the grafting of poly(ethylene glycol) (PEG) to polystyrene (PS). The two most popular commercially available resins being the Argogel (Fig. 2) and the Tentagel families, these hybrid polymers combine the advantages of both types of polymers, such as the physical stability of insoluble PS and the solvent-like character of PEG, which improves swelling. Although these resins are more expensive than hydrophobic PS supports, they allow for the use of hydrophilic solvents, ionic reagents, and on-bead reaction monitoring by gel-phase ^{13}C NMR or MAS ^1H NMR. The disadvantages of PEG-PS resin is its low-loading capacity and easy leakage of PEG chains upon treatment with strong acids [76] or heating above 70°C [77]. The PEG moiety can also complicate drying of the support [76]. Despite its temperature sensitivity, microwave-assisted synthesis has been successfully performed on PS-PEG resins [52, 78], in most cases on Tentagel [79–82]. In addition, a convenient microwave-assisted method for PEGylation of PS resin was recently developed by mixing commercially available chloromethylated PS support (Merrifield resin) with excess poly(ethylene glycol) in the presence of solid sodium hydroxide under microwave irradiation at 170°C [78] (Fig. 3).

Another class of solid supports is based on rigid structures containing large pores and is often referred to as macroporous nonswelling beads.

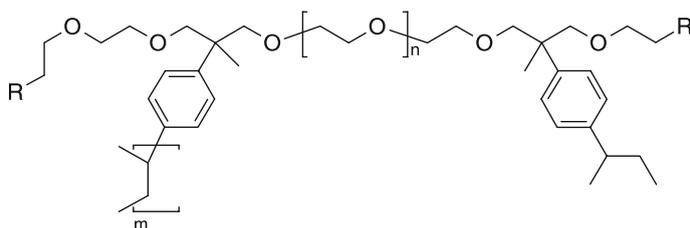


Fig. 2 The structure of Argogel, a typical hybrid PEG-PS resin

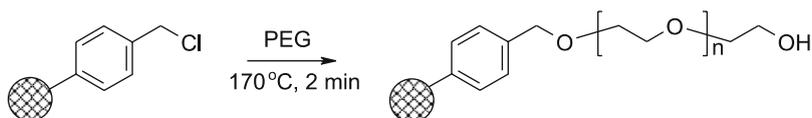


Fig. 3 Microwave-assisted synthesis of PEGylated PS resin

These supports are usually made of polyamide-containing Kieselguhr [83], polyamide-containing cross-linked polystyrene [84] or porous silica (controlled pore glass, CPG) [85]. Also within this polymer class is a highly cross-linked macroporous polystyrene designed specifically for SPOS [86]. It is available for a comparable price to the PEG-PS supports, but by design, can tolerate a wider range of reaction conditions. The use of macroporous nonswelling beads has several advantages, primarily the easy transfer of reaction conditions from solution to solid-phase and simpler washing. These, because reaction substrates are anchored to the surface, eliminating the need for reagent diffusion throughout the polymer matrix as required for classical swelling beads. Some disadvantages of macroporous nonswelling beads are the inability of performing on-resin NMR for reaction monitoring and their extreme rigidity. The fact that the beads do not swell makes these supports particularly interesting for continuous-flow applications. Of this group, the use of glass-surface as solid support for microwave mediated synthesis has been reported by Yates and coworkers [87].

Cross-linked polyacrylamides are a group of hydrophilic solid supports introduced primarily for preparation of biopolymers (Fig. 4). Unlike PS resins, polyacrylamides have excellent swelling capacity in both protic (water, alcohols) and aprotic (dichloromethane, dimethylformamide) solvents [88]. These beads are stable towards bases, acids, and weak reducing and oxidizing agents [89]. Predictably, conditions under which amide bonds are cleaved (i.e., sodium in liquid ammonia) [90] lead to rapid decomposition of the polymer.

Cellulose was the first type of solid support introduced for SPPS [91]; however, the scope of its use is limited by low loading capacity (~ 0.1 mmol/g) and chemical stability. In spite of these drawbacks, microwave-assisted synthesis was successfully performed on cellulose membranes [92–94] and beads [95].

A large variety of additional polymers and copolymers have been developed and evaluated for use as solid support. The most recently introduced and less-characterized resins are described elsewhere [96, 97].

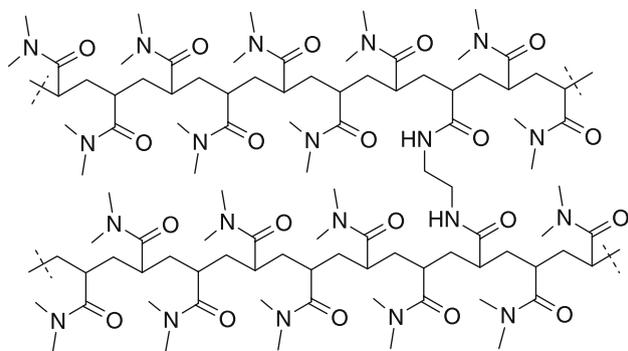


Fig. 4 Pepsyn, a cross-linked polyacrylamide resin

2.2

Soluble Polymer Supports

In addition to the insoluble polymers described above, soluble polymers, such as non-cross-linked PS and PEG have proven useful for synthetic applications. However, since synthesis on soluble supports is more difficult to automate, these polymers are not used as extensively as insoluble beads. Soluble polymers offer most of the advantages of both homogeneous-phase chemistry (lack of diffusion phenomena and easy monitoring) and solid-phase techniques (use of excess reagents and ease of isolation and purification of products). Separation of the functionalized matrix is achieved by either precipitation (solvent or heat), membrane filtration, or size-exclusion chromatography [98, 99].

PEG polymers are widely used as water soluble supports [99]. Although these polymers suffer from easy loss of PEG oligomers, they are frequently used for the preparation of small organic molecules [100–105] and biopolymers [106, 107]. The main benefit of PEG supports is their solubility in water as well as most organic solvents. Also, as opposed to most solid-phase techniques, PEG polymers allow for easy on-bead NMR monitoring. Soluble PEG supports have been used frequently in synthetic microwave chemistry protocols [108–122].

Linear non-cross-linked polystyrene has been used for organic synthesis since it is readily soluble in common organic solvents (i.e., dichloromethane, chloroform, tetrahydrofuran, toluene, ethyl acetate, and pyridine) but precipitates upon addition of water or methanol [123–126]. However, no examples of the use of this polymer in conjunction with microwave chemistry have been reported.

Fluorous tags are a novel type of soluble support introduced and recently commercialized by Curran et al. [127–129]. The popularity of this tagging methodology is growing because it enables the efficient purification technique fluorous solid-phase extraction (F-SPE). Fluorous tags were shown by Curran, Zhang and Hallberg to be compatible with high temperatures and microwave irradiation [129–136].

In addition to the examples described above, functionalized ionic liquids have been recently introduced as microwave-compatible soluble supports [137, 138].

2.3

Microwave-Assisted Loading Reactions

An important property of solid supports is their loading, which describes the amount of starting material (moles) that may be attached to a given mass of the polymeric beads (g). The loading of resins commonly used in SPOS is typically between 0.1–2.0 mmol/g. Interestingly, higher loadings and significant

rate enhancements have been observed when microwave-assisted protocols were compared to standard thermal loading procedures. In an early study, Stadler and Kappe performed the alkylation of polystyrene-bound benzyl chlorides with carboxylate anions using conventional and microwave heating (Fig. 5) [139].

Reaction times for the treatment of Merrifield resin or PS-bound 4-(benzyloxy)benzyl chloride (Wang-type linker) with 1.5–2.0 equivalents of the carboxylic acid in the presence of Cs_2CO_3 and KI using conventional thermal heating at 50–80 °C are usually very long (16–48 h) [140–143]. However, with slight modification of the reaction conditions (reducing the excess of reagents and changing the solvent to the microwave active, polar NMP) reaction times were reduced to 3–15 min by employing microwave heating at 200 °C in an open glass vessel. In this study, the absence of any non-thermal microwave effects was demonstrated by comparing the kinetics of the thermal coupling with the microwave-assisted reaction at 80 °C. At this temperature, both methods of heating required 12 h for the reaction to reach completion, although the reaction subjected to microwave irradiation progressed with a much higher initial rate because of the rapid, direct heating of the solvent with microwave energy [50]. In a related investigation, the reaction time needed for coupling symmetric anhydrides to hydroxymethyl polystyrene resin was decreased from days to 10 min by application of microwave irradiation (Fig. 6) [144]. Again, Stadler and Kappe demonstrated via kinetic studies that the increased loading rates did not originate from any non-thermal effects, but rather from rapid “in-core” heating of the solvent by the applied microwave irradiation.

Rapid loading of cross-linked PS Wang resin (4-(benzyloxy)benzyl alcohol PS) with a selection of β -ketoesters was shown to reach completion within 1–10 min if microwave irradiation at 170 °C was employed. The conventional thermal method for acetoacetylation of hydroxymethyl-functionalized polystyrene resins takes several hours; therefore, microwave heating allowed for

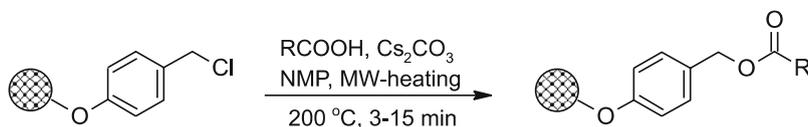


Fig. 5 Microwave-assisted loading protocol of carboxylic acids to chlorinated polystyrene Wang resin

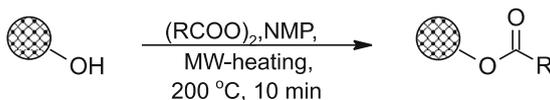


Fig. 6 Microwave-assisted loading protocol of symmetric anhydrides to hydroxymethyl PS resin

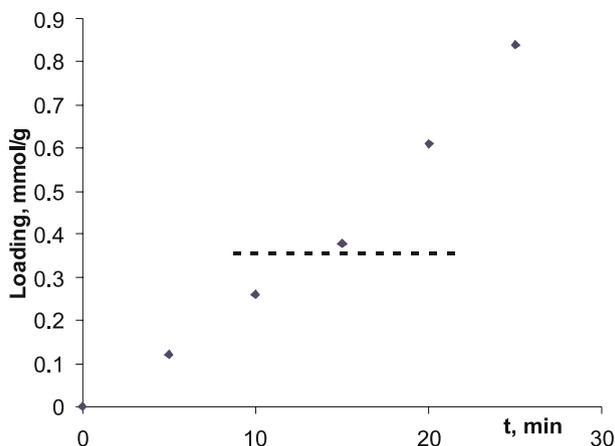


Fig. 7 Kinetics of microwave-assisted loading of 2-chlorotrityl chloride resin with Fmoc-isoleucine at 110 °C. For comparison, the *dashed line* indicates the level of loading after 1 h at room temperature

a significant improvement of the loading protocol by reducing the required synthesis time [145].

Investigation of the microwave-assisted attachment of Fmoc-protected amino acids onto 2-chlorotrityl chloride resin indicated higher loadings and increased rates compared to standard room temperature procedures [146]. In this comparative study standard procedures yielded 0.37 mmol/g loading after 1 hour, whereas at 110 °C using microwave dielectric heating, a similar result (0.38 mmol/g) was obtained after only 15 min (Fig. 7).

3 Microwave Instrumentation for SPOS

Since 1986, when the very first reports on the use of microwave heating to chemical transformations appeared [147, 148], microwave-assisted synthesis has been shown to accelerate most solution-phase chemical reactions [24–27, 32, 35]. The first application of microwave irradiation for the acceleration of reaction rate of a substrate attached to a solid support (SPPS) was performed in 1992 [36]. Despite the promising results, microwave-assisted solid-phase synthesis was not pursued following its initial appearance, most probably as a result of the lack of suitable instrumentation. Reproducing reaction conditions was nearly impossible because of the differences between domestic microwave ovens and the difficulties associated with temperature measurement. The technique became a “Sleeping Beauty”; interest awoke almost a decade later with the publication of several microwave-assisted SPOS protocols [37, 38, 73, 139, 144]. There has been an extensive

development in the field of microwave-mediated solid-phase organic synthesis over the recent 5 years and as a result, today practically every commercial supplier offers instrumentation applicable for controlled microwave mediated SPOS. Since the equipments for high-throughput microwave-assisted chemistry, both specialized for parallel and automated sequential processing, have been recently reviewed by Kappe and Stadler [32], no general discussion of the available instrumentation will be given in this review. Only the latest developments in the solid-phase handling systems will be overviewed.

Vessels designed for microwave-assisted SPOS must fulfill several requirements because of the harsh conditions (i.e., high temperatures and pressures) usually associated with microwave heating. Open vessels are often impractical because of the possible loss of solvent and/or volatile reagents during the heating process. However, in cases where a volatile byproduct inhibits a reaction, their use may be superior over closed systems. A sealed vessel retains the solvents and reagents, but must be sturdily constructed to avoid the obvious safety implications due to the buildup of pressure.

Monomode instruments (Initiator, Advancer, Emrys Synthesizer, Creator, Smith Synthesizer) for sequential processing of reaction vessels via an integrated robotic system that moves the reaction vials to and from the microwave cavity, while simultaneously offering advanced programmable liquid handling is available from Biotage AB [149, 150]. Although the standard vials (max. 20 bar, 250 °C) for these reactors do not offer simple resin handling, they were used in an early report on microwave-promoted SPPS [37]. The repeated transfer of reaction mixtures from the microwave vial into plastic columns equipped with a polypropylene frit for washing and deprotection steps caused significant loss of resin, decreasing the yield and efficiency of such procedures.

In 2003, the microwave-assisted coupling of aryl halides with acetylenes using a palladium catalyst were carried out employing a modified Smith Process vial [49]. These vessels, equipped with a polypropylene frit and screw cap at the bottom, and sealed with an aluminum crimp cap fitted with a silicon septum at the top (Fig. 8), facilitated the processing of approximately 1 g of solid support. Notably, they are compatible with stirring of the reaction mixture and monitoring of the temperature and pressure.



Fig. 8 Modified Smith process vial for microwave-assisted solid-phase organic synthesis

Synthos 3000, the multimode instrument available from Anton Paar [151], is dedicated to parallel scale up synthesis (max. 1 liter volume in 16 vessels) but also provides the possibility for small-scale experiments (min. 6 mL). These smaller reaction vessels consist of a non-adhesive teflon liner (max. 100 mL), placed inside a corresponding pressure jacket (max. 20 bar, 200 °C or max 40 bar, 250 °C), sealed by a screw cap with integrated lip-type seal. The vessels are suitable for solid-phase synthesis with a maximum of 5 g of solid support. For simplified handling of the polymer support, a screw-on filtration unit is available (Fig. 9). Thus, the polymer-bound compounds can be kept in the same reaction vessel throughout the reaction sequence, minimizing the loss of material and maximizing the yield. When using the filtration unit, an external pressure of up to 5 bar (compressed air or nitrogen) can be applied to speed up the filtration process. Temperature control is provided by an IR sensor, which detects the surface temperature of the vessel from the bottom. In addition, the inner temperature and pressure of one reference vessel can be measured as well. As an example, the microwave-assisted large-scale (20 g) batch synthesis of methylaminated Merrifield resin using the Synthos 3000 was reported recently [152]. The microwave-mediated protocol (150 °C, 5 min, 89% yield) is interesting because the reaction is carried out in water, a solvent in which PS resin has very poor swelling properties.

The Liberty (Fig. 10), a monomode microwave reactor for automated SPPS, was recently introduced by the CEM Corporation [153]. Although this instrument was originally developed for SPPS, it also allows for a broader scale of solid-phase applications. The solid-phase vial is equipped with a polypropylene frit and cap at one end (the entire assembly fitting into the standard 10 mL CEM reaction vessel) to allow the processing of 0.1 to 1.0 mmol quantities of resin attached substrates. An integrated fiber optic probe provides



Fig. 9 The SPOS-compatible reaction vessel for the Synthos 3000. Depicted from *left to right* is the filtration unit, the PTFE liner (*white*), the pressure jacket, and a fully assembled vessel with a ceramic pressure jacket



Fig. 10 Liberty (CEM Corporation), the first automated microwave solid-phase peptide synthesizer, is shown on the *left*; the available reaction vessel setup for solid-phase synthesis is depicted on the *right*

in situ control of the reaction temperature, and the heterogeneous mixture is agitated via magnetic stirring. To date, no published synthetic applications using this reaction vessel are available.

A simple predecessor of the CEM setup for microwave-mediated SPOS was employed by Murray and Gellman in their synthesis of 14-helical β -peptides [42]. A 4 mL polypropylene solid-phase extraction tube was inserted into a 10 mL CEM vessel, allowing for both microwave heating and simple resin manipulation (Fig. 11). While using this setup gave reproducible results for their experiments, a discrepancy between the reactions' target (set) temperatures and the actual temperatures was observed. Therefore, use

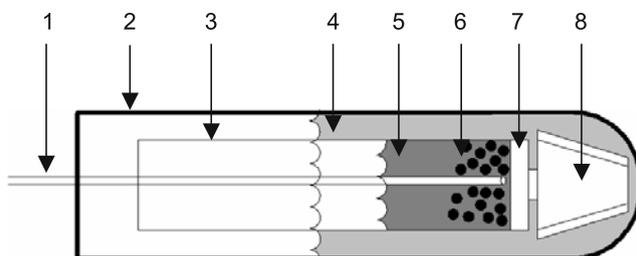


Fig. 11 Experimental set-up for small-scale microwave SPPS of β -peptides (SPE = solid-phase extraction). 1 Pasteur pipet for N_2 agitation; 2 10 mL glass vial; 3 4 mL solid-phase extraction tube; 4 DMF; 5 coupling solution; 6 resin; 7 polyethylene frit; 8 Luer-lock cap

of this arrangement in conjunction with the built-in IR sensor of the CEM Discover produces some inaccuracy in the temperature control of the reaction [42].

An expandable reaction vessel capable of accommodating pressure buildup without loss of solvents or reagents during microwave-mediated SPOS was developed by O'Shea et al. [154]. Importantly, these vials can be arrayed for parallel library generation. The setup is composed of a cylindrical reaction chamber (10 mL) fitted with a porous frit above the product outlet carrying a conventional Luer lock cap (Fig. 12). A piston mounted with a gastight seal and a straight hollow bore running the length of the piston is fitted in the upper opening of the chamber and the opening at the top of the piston bore is sealed with a Luer-lock cap. As microwave radiation is applied to the system, the pressure within the vessel may increase. Pressure buildup is alleviated by the rising of the piston (the setup allows for an expansion of 20 times the volume of the solvent/reagents within each vessel). The authors demonstrated the scope of the expandable vessel via the solution-phase preparation of a 24-membered imidazole library in a CEM MDS-200 microwave oven.

Microwave-assisted solid-phase parallel synthesis has also been reported using multi-well filter-bottom polypropylene plates [45, 155]. However, it should be mentioned that the thermal instability of the polypropylene plates is a limitation of this setup. In addition, uneven heating across the plate results in higher temperatures ($\Delta T \sim 10\text{--}20\text{ }^\circ\text{C}$) being observed at the center of the plate than at the edges.

Recently, Murray and Gellman demonstrated that parallel synthesis in inexpensive 96-well polypropylene filter plates with microwave irradiation in a multimode reactor is a simple and effective method for the rapid preparation of β -peptide libraries on solid support in acceptable purities [156].

Although Milestone [157] does not provide a special setup for microwave-assisted solid-phase organic chemistry, a few reports describe the use of their instruments in such synthetic procedures. For example, alkylation and acylation of standard polystyrene resins using the Ethos multimode reactor have provided excellent yields (> 99%) in 5 to 10 min [14]. The multiPREP rotors available for Milestone instruments house up to 80 atmospheric pressure or 36 sealed vessels with magnetic stirring in combination with temperature and pressure control by regulation of microwave power output. For combinatorial purposes a high throughput setup, CombiCHEM, was developed. The reac-

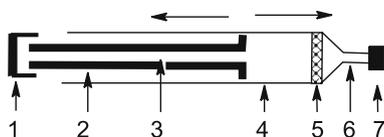


Fig. 12 Expandable microwave vessel. Components: 1 Luer-lock cap; 2 piston; 3 hollow bore; 4 reaction chamber; 5 frit; 6 product outlet; 7 Luer-lock cap

tion blocks composed of microwave-absorbent material were designed to be mountable on top of each other and allow the parallel processing of several hundred reaction mixtures. Unfortunately, the glass inserts (96/block) are incapable of bottom filtration.

4 Microwave-Mediated SPOS of Heterocyclic Compounds

Representative examples of the recent applications of controlled microwave heating in solid-phase synthesis of heterocyclic compounds are summarized. The preparation of monocyclic compounds is presented first, followed by a description of the synthesis of polycyclic structures.

4.1 Oxazoles

A constant interest in the development of new rapid methodologies for the preparation of oxazole libraries is motivated by their presence in numerous biologically active natural products. Janda and coworkers were first to show that oxazoles can be obtained by microwave-assisted treatment of polymer-bound α -acylamino- β -ketoesters with Burgess reagent [68]. Hydroxybutyl-functionalized JandaJel resin was used for this investigation, with key steps being monitored by on-bead FT-IR. First, a resin-bound acetoacetate was pre-

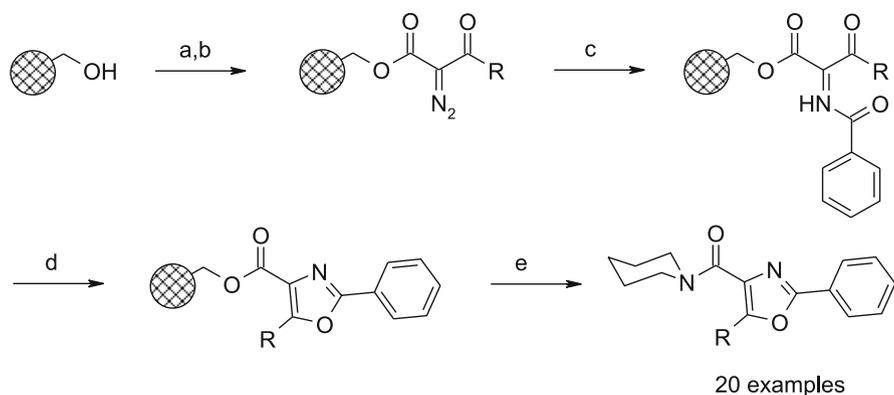


Fig. 13 Synthesis of oxazoles on JandaJel. Reagents and conditions: *a* toluene, alkyl acetoacetate ($\text{RO}(\text{CO})\text{CH}_2\text{COR}^1$; $\text{R} = t\text{-Bu}$), reflux, 6 h or alkyl acetoacetate ($\text{R} = \text{Me}, \text{Et}$), toluene, LiClO_4 , reflux, 6 h; *b* dodecylbenzenesulfonyl azide, Et_3N , toluene, rt, 16 h; *c* benzamide, $\text{Rh}_2(\text{oct})_4$, toluene, 65°C , 1 h; *d* Burgess' reagent, pyridine, chlorobenzene, MW 100°C , 15 min (or 80°C , 4 h with conventional heating); *e* AlCl_3 , piperidine, CH_2Cl_2 , rt, 16 h

pared (a) by refluxing the resin in the solution of alkyl acetoacetate in toluene for 6 h, (Fig. 13) followed by treatment with dodecylbenzenesulfonyl azide (b). Then, α -acylamino- β -ketoesters were produced using benzamide in the presence of a rhodium octanoate catalyst (c). The key cyclodehydration step (d) has proven to be a troublesome reaction and was therefore thoroughly optimized. The best conversions to the target oxazoles were obtained under microwave irradiation at 100 °C for 15 min. Cleavage of the oxazoles was performed using piperidine in the presence of aluminum chloride, yielding products in moderate yields (17–62%) and moderate to high purity (35–97%). It should be noted, though, that conventional thermal heating at 80 °C for 4 h was chosen for the production of the final 20 compound library, since it provided conversions comparable to the 15 min microwave reaction.

4.2

Preparation of Isoxazoles and Pyrazoles

Employing a Bredereck-type condensation De Luca and coworkers have recently prepared pyrazole and isoxazole libraries on cellulose beads using microwave irradiation [95]. A cellulose-bound aniline linker was treated with an excess of *N*-formylimidazole dimethylacetal in dimethylformamide in the presence of catalytic camphorsulfonic acid at 80 °C for 15 min (Fig. 14). This reaction was reported to provide higher yields when run in an open vessel (compared to closed systems) because that allows the removal of the methanol formed during the course of the reaction. Subsequent cyclization also carried out in an open vessel gave the desired pyrazoles and isoxazoles in high yields within 15 min using microwave heating at 82 °C. The progress of the reactions was monitored by colorimetric tests and on-bead FT-IR meas-

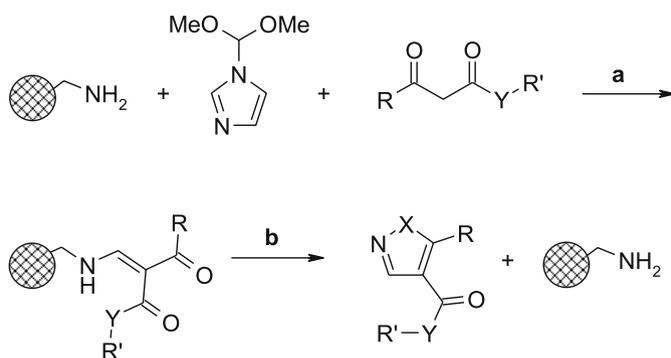


Fig. 14 Microwave-assisted synthesis of pyrazoles and isoxazoles on cellulose. Reagents and conditions: *a* Camphorsulfonic acid, DMF, MW 80 °C, 15 min, open vessel; *b* NH_2XH , MW 82 °C, 15 min, open vessel. $\text{X} = \text{N}, \text{O}$; $\text{Y} = \text{NH}, \text{NEt}, \text{O}$; $\text{R} = \text{Me}, i\text{-Pr}, \text{BuCH}_2, \text{PhCH}_2, \text{Et(Ph)CH}$, $\text{R}' = \text{alkyl}, \text{allyl}, \text{and aryl groups}$

urements. It should be noted that the applied resin, cellulose-bound aniline, could be recycled up to ten times without any reduction in yield (> 95%) or purity (> 98%).

4.3

Isoxazole Synthesis via On-Resin [3+2] Cycloaddition

Giacomelli et al. constructed 3-propylisoxazole-5-yl-methanol via a [3 + 2] cycloaddition (Fig. 15) [158]. Nitrobutane was converted to nitrile oxide in the presence of 4-(4,6-dimethoxy [1, 3, 5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) and catalytic 4-dimethylaminopyridine (DMAP). Trityl chloride resin-bound propargyl alcohol was employed as the dipolarophile to trap the nitrile oxide, forming the cycloadduct isoxazole ring under unusually mild conditions (i.e., microwave irradiation at 80 °C for five times 1 min). Disappearance of the starting material was monitored by FT-IR.

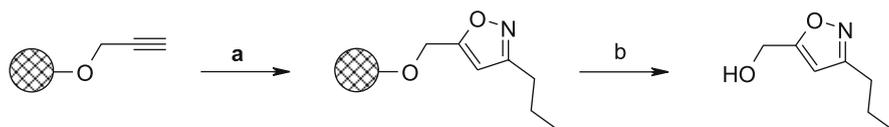


Fig. 15 Microwave-assisted isoxazole synthesis via on resin [3 + 2] cycloaddition. Reagents and conditions: *a* 1-nitrobutane, DMTMM, DMAP, MeCN, THF, MW 80 °C, 5 min, open vessel; *b* TFA : CH₂Cl₂ (5 : 95), rt, 20 min

4.4

Construction of Isoxazole, Pyrazole and Pyrimidine Rings from Aminopropenones

Westman and Lundin demonstrated an innovative concept for the synthesis of various isoxazole, pyrazole and pyrimidine compounds via a common three-component condensation reaction followed by a cyclization step initiated with nitrogen and/or oxygen dinucleophiles [61]. First, a benzylmethylamine linker was prepared from Merrifield resin via treatment with methylamine in water under microwave irradiation at 150 °C for 10 min (86%). The resin-bound amine was then reacted with an excess of *N,N*-dimethylformamide diethyl acetal and 4-phenoxyacetophenone with microwave irradiation at 180 °C for 10 min to form solid-supported benzyl methyl aminopropenones (step a, Fig. 16) as confirmed by on-bead MAS-NMR. Subsequently, the resin was treated with various dinucleophiles under microwave irradiation at 180 °C for 10 min to form the desired heterocycles in high yield (81–94%) and purity (85–93%). Depending upon the chosen dinucleophile, different types of heterocyclic rings systems were obtained: hydrazines yielded pyrazoles, hydroxylamines gave isoxazoles, and arylamidines formed pyrimidines. The major benefit of this approach is that diverse heterocyclic systems can be prepared in high purity in an overall reaction time of only 30 min.

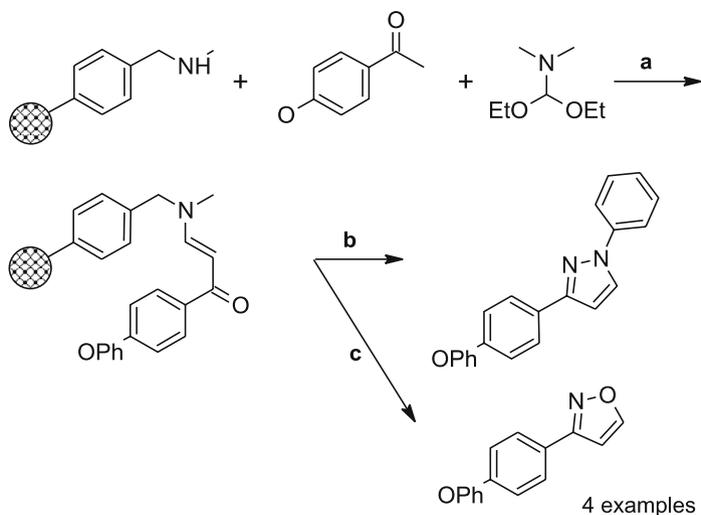


Fig. 16 Microwave-promoted route to pyrazoles and isoxazoles via resin-bound propenones. Reagents and conditions: *a* DMF, MW 150 °C, 10 min, closed vessel; *b* Ph-NH-NH₂, AcOH, MW 180 °C, 10 min, closed vessel; *c* HO-NH₂, AcOH, MW 180 °C, 10 min, closed vessel

4.5 Rapid Preparation of Imidazole-4-Carboxylic Acids

The imidazole ring is a privileged structure in medicinal chemistry since it is found in the core structure of a wide range of pharmaceutically active compounds; efficient methods for the preparation of substituted imidazole libraries are therefore of great interest. Recently, a rapid synthetic route to imidazole-4-carboxylic acids using Wang resin was reported by Henkel (Fig. 17) [64]. An excess aliphatic or aromatic amine was added to the commercially available Wang-resin-bound 3-*N,N*-(dimethylamino)isocyanacrylate, and the mixture was heated in a sealed vial with microwave irradi-

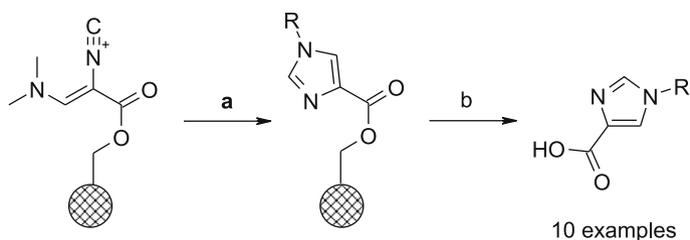


Fig. 17 Rapid preparation of imidazoles and thiazoles on solid-phase. Reagents *a* RNH₂, (CH₃OCH₂)₂, MW 220 °C, 15 min, closed vessel; *b* TFA in CH₂Cl₂, rt, 60 min. R = aliphatic, benzyl, or arylamines or arylhydrazine

ation to 220 °C for 15 min (a). Subsequent liberation of the *N*-alkylimidazole-4-carboxylates was performed by standard trifluoroacetic acid-mediated cleavage at room temperature, yielding imidazoles in 20–90% yield (b). The applied conditions allowed the use of aromatic and aliphatic amines as well as phenylhydrazine. The main limitation of the Henkel procedure is that the cyclization step is sensitive to steric hindrance, as hindered amines provided poor yields.

4.6

Tetrazole Synthesis

One of the earliest reports on the use of microwave-assisted SPOS methodology for the preparation of heterocyclic compounds was presented by Alterman and Hallberg in 2000 [80]. The authors reported the synthesis of an aryl tetrazole, a bioisostere to carboxylic acids, in 72% yield using a Rink linker on TentaGel resin. Although the two-step reaction was performed at high temperatures (~ 170 °C and 220 °C) and in presence of transition metal catalysts, only negligible decomposition of the solid support was observed, most likely due to the short reaction times (2–5 min) required for the microwave-promoted transformations (Fig. 18). First, 4-iodobenzoic acid (coupled to TentaGel resin) was mixed with $\text{Zn}(\text{CN})_2$ and $\text{Pd}(\text{PPh}_3)_4$ in dimethylformamide under nitrogen atmosphere and subjected to microwave irradiation. In the second step, NaN_3 , and NH_4Cl were added, and the mixture was irradiated for 15 more min at 200 °C, followed by trifluoroacetic acid-mediated cleavage of the aryl tetrazole product in a polypropylene tube. This synthesis was performed in a Microwell 10 monomode cavity, which produces continuous irradiation at a predetermined wattage and the temperature measurements were carried out using a fluoroptic probe. Thus, the reaction temperature and time may need reoptimization for use in a modern temperature-controlled microwave synthesizer.

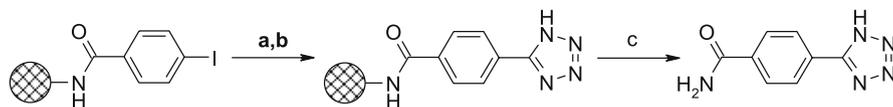


Fig. 18 Microwave-assisted synthesis of an aryl tetrazole. Reagents and conditions: *a* $\text{Zn}(\text{CN})_2$, $\text{Pd}(\text{PPh}_3)_4$, DMF, MW 60 W, ~ 170 °C, 2 min, closed vessel; *b* NaN_3 , NH_4Cl , DMF, MW 20 W ~ 220 °C, 15 min, closed vessel; *c* TFA, H_2O , rt, 5 min

4.7

“Catch and Release” Synthetic Route to 2,4,5-trisubstituted Pyrimidines

As cyclocondensation reactions generally require heating at high temperatures to achieve conversion, such procedures are expected to be well-suited

for the application of microwave technology. A representative example of the improvement in solid-phase synthesis and cyclative cleavage of heterocyclic compounds achieved with microwave heating was presented by Porcheddu and coworkers [159]. Cyclative cleavage is a popular approach (as demonstrated by the number of examples mentioned in this review) because it advantageously combines a synthetic step with the cleavage reaction and allows the selective release of the fully-formed target compound from the support, while potential byproducts are retained on-resin (if they are incapable of cyclizing). A combinatorial array of 2,4,5-trisubstituted pyrimidines were prepared through the resin-capture and release strategy summarized in Fig. 19. Resin-bound enaminones were prepared by condensation of solid-supported piperazine with β -ketoesters in the presence of catalytic camphorsulfonic acid and *N*-formylimidazole dimethyl acetal in an open vessel to allow the removal of the formed methanol from the reaction mixture (a). The time required for this reaction step to be complete was decreased from 48 hours using conventional heating to only 30 min with microwave heating at the same temperature. Pyrimidines, in an overall yield of 85–96% and high purity (> 95%), were released by cyclative cleavage with guanines (b) in a closed vessel under microwave irradiation at 130 °C for 10 min (conventional heating required 2 h at 65 °C). After product release, the solid-supported piperazine could be reused for at least 3–4 additional cycles, still providing the desired products in high yields and purity. The discussed synthetic procedure is attractive not only because it is capable of generating diverse pyrimidines but also for the reason that the enaminone intermediates are likely to be useful for the preparation of other heterocyclic systems using a similar strategy. Moreover, the “catch and release” approach requires minimal purification and allows for the economically beneficial reuse of the solid-support.

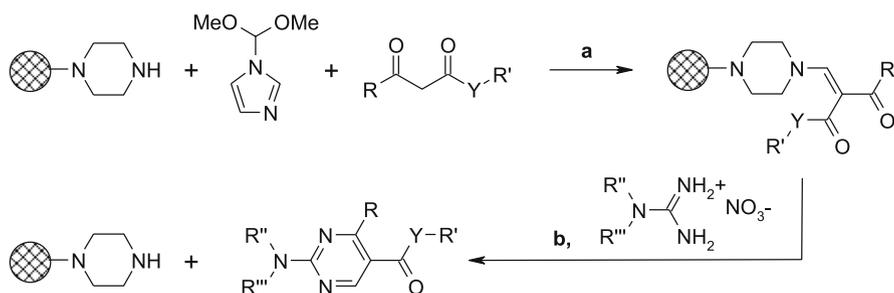


Fig. 19 Synthesis and cyclative cleavage of 2,4,6-trisubstituted pyrimidines using microwave-assisted solid-phase protocol. Reagents and conditions: *a* DME, camphorsulfonic acid, MW 80 °C, 30 min, open vessel; *b* EtONa, EtOH/THF (4/1), MW 130 °C, 10 min, closed vessel. Y = O, NEt₂; R = Me, *i*-Pr; R' = Et; R'' = H, alkyl, cycloalkyl, aryl, benzyl; R''' = H, Me, Et

4.8 Domino Synthesis of Functionalized Tetronates

A microwave-promoted solid-phase methodology for the preparation of functionalized tetronates (potential antibiotic, antiviral, antineoplastic and herbicidal agents) was recently demonstrated by Schobert and Jagusch [63]. Immobilized α -hydroxy esters were obtained by Lewis acid-catalyzed opening of the epoxide ring with either the hydroxyl group of Wang resin (microwave-assisted) or an amino-, or thiol-terminated Merrifield-type resin (Fig. 20, step a). Reaction progress was monitored by staining tests. In this step, the application of microwave irradiation allowed reduction of reaction times from several days to 30 min. Subsequently, microwave-mediated tandem addition – Wittig alkenation of hydroxy esters with the cumulated phosphorous ylide $\text{Ph}_3\text{P} = \text{C} = \text{C} = \text{O}$ was carried out in the presence of catalytic benzoic acid in tetrahydrofuran (b). Formation of the tetronates was monitored by on-bead FT-IR measurements and staining tests. Following step (b), 5-hydroxymethylenetetronates were liberated by trifluoroacetic acid-mediated cleavage (f) or converted in step (c) into resin-bound 3-allyltetronic acids. In addition, allyl esters [$\text{R}_2 = \text{CH}_2\text{C}(\text{R}_3) = \text{CH}_2$] could be converted not only to their respective tetronates under the aforementioned conditions but also directly to the Claisen-rearranged 3-allyltetronic acids by maintain-

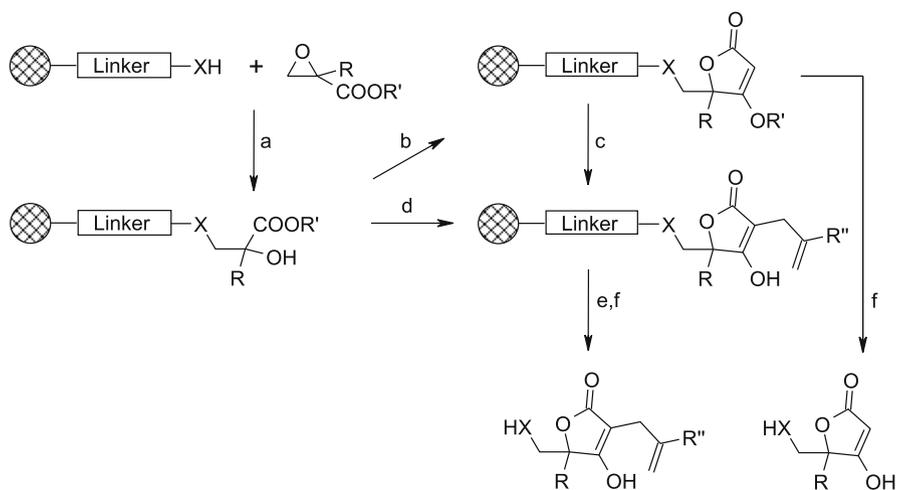


Fig. 20 Synthesis of tetronates via domino addition – Wittig olefination. Reagents and conditions: *a* X = O: LiClO_4 , DMF, MW 85°C , 30 min; X = NH: LiNTf_2 , CH_2Cl_2 , 25°C , 3 days; X = S: $\text{ZnCl}_2 \cdot \text{Et}_2\text{O}$, DMF/MeOH 9 : 1, 60°C , 4 days, 80–90%; *b* Ph_3PCCO , cat. PhCO_2H , THF, MW 80°C , 20 min, closed vessel; *c* $\text{CH}_2\text{C}(\text{CH}_2)\text{R}''$, MW 120°C , 1 h, closed vessel, or toluene, reflux, 48 h, *d* $\text{CH}_2\text{C}(\text{CH}_2)\text{R}''$, Ph_3PCCO , cat. PhCO_2H , THF, MW 120°C , 1 h; *e* $c\text{-C}_6\text{H}_{11}\text{NC}(\text{OBn})\text{NH}c\text{-C}_6\text{H}_{11}$, THF, 50°C , 16 h; *f* TFA : DCM (9 : 1), rt, 4 h. R = H, Me, R' = Me, CH_2CHCH_2 , $\text{CH}_2\text{C}(\text{Me})\text{CH}_2$; R'' = H, Me

ing 120 °C in the microwave apparatus for 1 h (d). Cleavage of the tetrionic acids from the resin in step (e) was only possible following benzylation of the hydroxyl group, thus providing 3,5-disubstituted tetrionic acids in almost quantitative yields.

4.9

Preparation of Thiophenes by Microwave-Promoted Gewald Synthesis

Highly substituted thiophenes occur in a variety of natural products and pharmaceutical lead compounds. Thiophenes are also frequently used in industrial dyes and conductors. The Gewald synthesis of polysubstituted thiophenes requires long reaction times and time-consuming purification of the products [160–162], and therefore, in its original form, it was not suitable for combinatorial chemistry. However, as a multicomponent condensation, the Gewald synthesis has potential for the generation of a diverse set of compounds with a core structure that displays substituents with well-defined positioning. Hence, the one-pot microwave-mediated solid-phase version of the Gewald reaction has opened new perspectives in thiophene-based library generation [56]. A two-step procedure was developed by Hoener et al. on commercially available cyanoacetylated Wang resin and was accomplished under 60 min. Departing from the standard conditions, toluene was used as the solvent (instead of ethanol), which allowed for both satisfactory swelling of the cross-linked PS resin and direct acylation of the primary amine generated in the first step. More specifically, the cyanoacetylated resin, elemental sulfur, DBU, and an aldehyde (or ketone) were suspended in toluene and heated at 120 °C for 20 min in a sealed vial with a Smith Creator monomode microwave reactor (Fig. 21, step a). An acyl chloride and diisopropylethylamine were then added (note: no filtration was required between steps), and the mixture was again treated with microwave irradiation at 100 °C for 10 min (b). The washed resin was transferred from the Smith Process Vial to a flask, and the products were cleaved for 2 h at room temperature. In this study various aldehydes, ketones, and acylating agents were employed to generate 12 desired thiophene products in high yields (81–99%) and good to excellent purities (70–99%). Although aliphatic and aromatic aldehydes, as well as ketones, generally gave good conversions, the substitution pattern of the carbonyl group involved in the cyclization was found to be the key factor. For example, acetaldehyde did not furnish the desired thiophenes, while branched chain aliphatic aldehydes provided the expected products in high yields. Thus, suffering from a few limitations, the procedure of Hoener and coworkers offers a rapid and clean route to 2-acyl aminothiophenes. Although solid-phase synthesis is superior for generation of libraries it should be noted that microwave-assisted solution-phase protocols of the Gewald reaction are available as well [163, 164]. An alternative microwave-mediated procedure on soluble polymer was also reported by Yang and coworkers [165, 166].

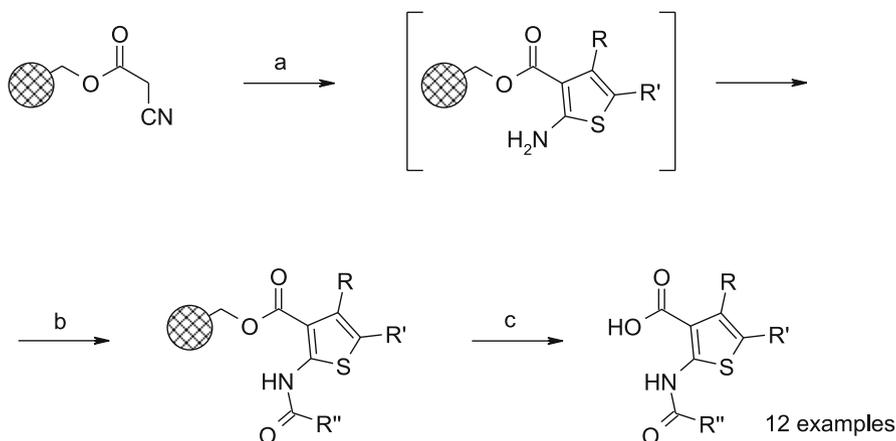


Fig. 21 Microwave-promoted multicomponent synthesis of polysubstituted thiophenes on solid-phase. Reagents and conditions: *a* $\text{RCOCH}_2\text{R}'$ ($\text{R} = \text{H, Me, Et, Bn}$; $\text{R}' = \text{Me, } i\text{-Bu, } i\text{-Pr, Ph, Bn, cyclohexyl}$), S_8 , DBU, toluene, MW 120°C , 20 min, closed vessel, 100%; *b* $\text{R}''\text{COCl}$ ($\text{R}'' = \text{Me, Pr, Ph or COOMe}$), diisopropylethylamine, toluene, MW 100°C , 10 min, closed vessel; *c* TFA, H_2O , CH_2Cl_2 , rt, 2 h

4.10

Microwave-Promoted Synthesis of Bicyclic Pyrimidine Derivatives on Solid-Phase

Solid-phase protocols using microwave-promoted SPOS for the synthesis of several types of bicyclic pyrimidine derivatives (i.e., furo[3,4-*d*]pyrimidines, pyrrolo[3,4-*d*]pyrimidines, and pyrimido[4,5-*d*]pyridazines) were reported by Kappe et al. (Fig. 22) [57]. A multistep, solid-phase sequence was employed, and the various bicyclic compounds were prepared from a common 6-chloromethyl-functionalized dihydropyrimidone precursor. This important intermediate was synthesized by acetoacetylation of hydroxymethylpolystyrene resin with methyl 4-chloroacetoacetate using microwave irradiation at 170°C (step a). (Note: This microwave-assisted transesterification needs to be carried out under open-vessel conditions so that the formed methanol is removed, driving the equilibrium toward the products. In closed vessel-systems significantly lower yields were obtained.) A three component Biginelli-type condensation followed, employing urea and a variety of aromatic aldehydes with conventional heating (b). The resulting 6-chloromethyl-functionalized resin-bound dihydropyrimidones were subjected to three different traceless cleavage strategies: Thus, furo[3,4-*d*]pyrimidines were obtained by a microwave-promoted, thermally-triggered nucleophilic substitution through cyclative release at 150°C (c). Treatment of the chloromethyl intermediates with a series of primary amines using conventional heating yielded methylamine derivatives of dihydropyrimidones (d), which could then be converted into pyrrolo[3,4-*d*]pyrimidines via nucleophilic cycla-

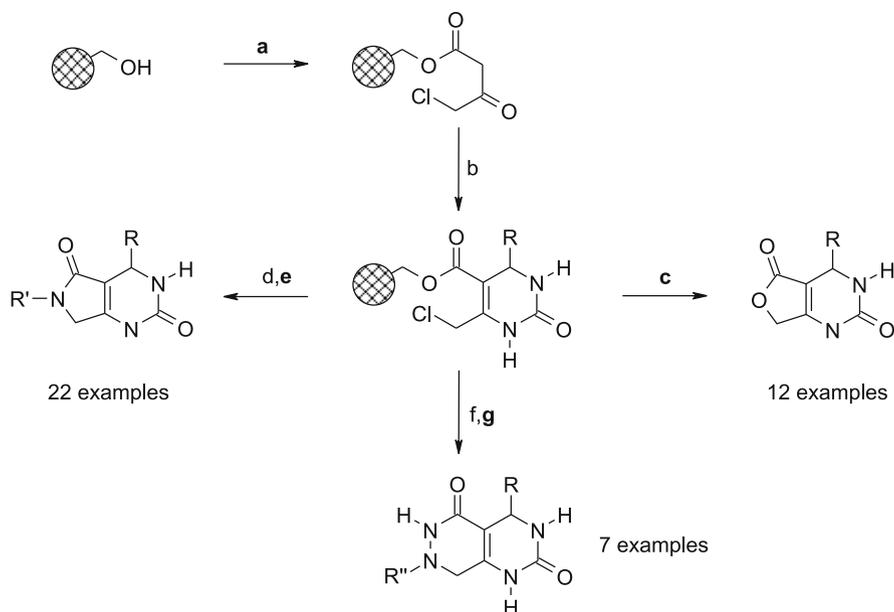


Fig. 22 Preparation of bicyclic dihydropyrimidinones from a common precursor by cyclative cleavage. Reagents and conditions: *a* Methyl-4-chloroacetoacetate, DCB, MW 170 °C, open vessel, 15 min; *b* R-CHO, urea, dioxane, HCl, 70 °C, 18 h; *c* DMF, MW 150 °C, 10 min, closed vessel; *d* R'-NH₂, DMF, rt to 70 °C, 18 h; *e* DMF, MW 150–250 °C, 10 min, closed vessel; *f* R''-NHNH₂, DMF, rt, 30 min; *g* DMF, MW 150 °C, 10 min, closed vessel

tive cleavage under controlled microwave heating at 150–250 °C (e). Lastly, pyrimido[4,5-*d*]pyridazines were similarly obtained by reaction of the intermediate with monosubstituted hydrazines at room temperature (f), followed by microwave-promoted nucleophilic cyclization and release at 150 °C (g). All final products were obtained in moderate to good overall yields and purities.

Kurth et al. applied an analogous strategy for the preparation of hydantoins via base-catalyzed microwave-mediated carbanilide cyclization; however, in their study the reactions were run without temperature/pressure control and will therefore not be discussed in further detail [59].

4.11

Phthalimide Library Synthesis on Wang Resin

A related microwave-assisted cyclative cleavage strategy was proposed for the synthesis of substituted phthalimide libraries by Chassaing et al. [60]. It should be noted that protocols using conventional heating [167, 168] were found to be unfeasible for large library production, as they required reaction times of several hours. Optimization of microwave-enhanced cyclative cleavage from Wang resin was first investigated through the synthesis of model

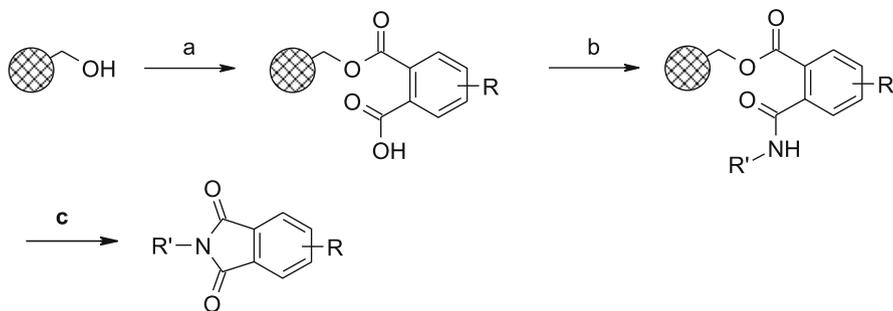


Fig. 23 Microwave-promoted SPOS of substituted phthalimides. Reagents and conditions: *a* phthalic acid ($R = \text{H, F, Br, CH}_3, \text{C}_4\text{H}_4$), DIAD, PPh_3 , THF, rt, 24 h; *b* primary amine ($R' = \text{C}_3\text{H}_6\text{Ph, CH}(\text{CH}_3)\text{C}_2\text{H}_4\text{Ph, C}_8\text{H}_{17}, 4\text{-CH}_3\text{OBn, 4-ClBn, C}_5\text{H}_9$) amine, EDC·HCl, HOAt, CH_2Cl_2 , rt, 18 h; *c* MW, DMF, 170°C , 20 min, closed vessel

compound 2-(3-phenyl-propyl)-isoindole-1,3-dione (Fig. 23). Phthalic acid was loaded on Wang resin using a Mitsunobu protocol, followed by a standard EDC/HOAt-mediated amide bond formation with 3-phenylpropylamine. Subsequently, complete release of the desired 2-(3-phenyl-propyl)-isoindole-1,3-dione was obtained by microwave irradiation of the resin-bound *N*-(3-phenyl-propyl)-phthalamic acid at 170°C for 20 min in dimethylformamide in a monomode microwave reactor (80% yield, 95% purity). The conversion in the microwave-mediated step was followed by on-bead FT-IR, and the isolated cyclized product was analyzed by LC-MS and ^1H NMR spectroscopy. The optimized conditions were then applied to various amines (6 compounds reported in detail, 56–90% yield with 54–97% purity) and phthalate derivatives (9 examples, 51% to quantitative yield with 49–99% purity). No resin degradation was detected under the reaction conditions. Good yields were obtained using aliphatic amines, but benzyl derivatives provided somewhat lower yields. Aromatic amines were found to be incompatible with the proposed route because of autoinduced ring closure in step (b). On the other hand, introduction of substituents on the aromatic ring was well-tolerated giving phthalimides in moderate to good yields and purities. Importantly, protocols available for the microwave-assisted solution-phase generation of phthalimides do not allow comparable variability of substituents [169, 170]. Previous attempts to synthesize the 4-fluoroaromatic derivatives had been unsuccessful, but these compounds were effectively furnished by Chassaings solid-phase procedure.

4.12

Indole Synthesis

Indoles are designated as privileged structures in medicinal chemistry because they are important constituents of bioactive natural products and

several marketed drugs and drug candidates. Thus, developments of rapid, general methods for preparation of indole derivatives are of high scientific value.

Berteina-Raboine and coworkers have described a microwave-assisted three-step protocol for the preparation of indole derivatives based on Pd-mediated cyclization of propargylamines to resin-bound iodoanilines using a monomode reactor and open-vessel technology (Fig. 24) [55]. The authors demonstrated that higher yields of the final products could be achieved in significantly shorter reaction times by utilizing a microwave protocol as compared to conventional heating. First, a peptidic coupling of 4-amino-3-iodobenzoic acid to Rink amide resin was performed at room temperature for 48 h. (Note: several rapid microwave-assisted procedures are available for amide bond formation on solid-phase [36–43]). Then, palladium-catalyzed coupling of the resin-bound iodoaniline and a protected propargylamine provided the indole core with excellent regioselectivity, indicating that the insertion of the intermediate arylpalladium species into the alkyne proceeded from the less-hindered side. Cleavage with 20% trifluoroacetic acid in dichloromethane yielded 3-(2-acetyl-amino-ethyl)-1H-indole-6-carboxylic acid amide in a good yield (conventional heating: 73%, microwave heating 90%). Moreover, treatment of the intermediate resin-bound indole with

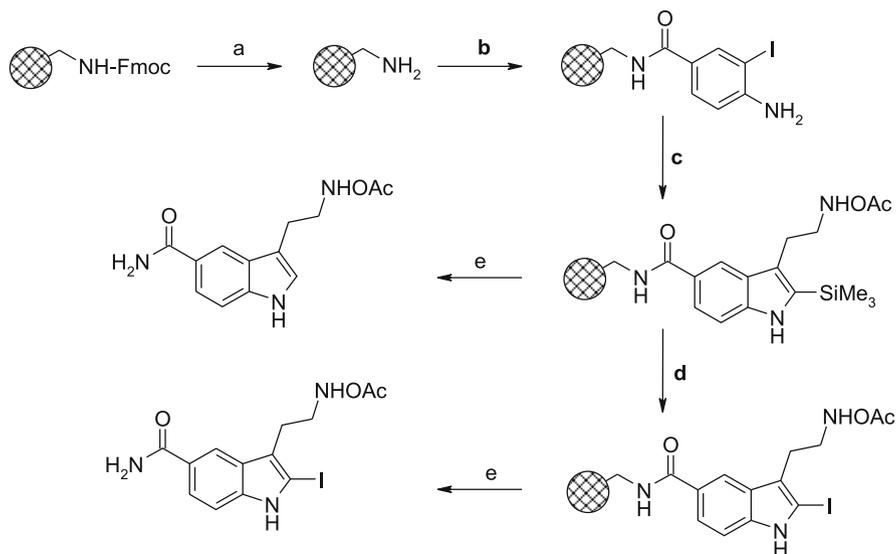


Fig. 24 Solid-phase synthesis of 5-carboxamido-*N*-acetyltryptamine. Reagents and conditions: *a* piperidine 20%, DMA, rt, 60 min; *b* 4-amino-3-iodo-benzoic acid, TBTU, HOBT, NEt₃, DMAP, dioxane, MW 45 W, 3 min, 100%, open vessel; *c* *N*-(4-Trimethylsilylbut-3-ynyl)-acetamide, Pd(OAc)₂, PPh₃, LiCl, NaOAc, DMA, MW 60 W, 2 × 13 min, 100%, open vessel; *d* NIS, CH₂Cl₂, MW 60 W, 14 min, 100%, open vessel; *e* cleavage, TFA, 20%, CH₂Cl₂, rt

three equivalents of *N*-iodosuccinimide in dichloromethane for 14 min in a microwave reactor (alternatively refluxing for 24 h using conventional heating) afforded the synthetically more useful 3-(2-acetylamino-ethyl)-2-iodo-1H-indole-6-carboxylic acid amide. This 2-iodo-indole derivative provides access to various pharmacologically important 2-substituted indoles via palladium-mediated coupling reactions for which experimental conditions (Heck [171], Suzuki [79], Stille [79] and Sonogashira [49] couplings and Heck-carbonylations [172]) using controlled microwave heating are well-established. It should be noted, that although the applied reactor provided temperature control via an IR sensor the authors did not report reaction temperatures, only the fact that it was kept under 140 °C.

Dai et al. have proposed an alternative synthetic route for the microwave-enhanced solid-phase preparation of substituted indole derivatives that employs a series of organometallic reaction steps (Fig. 25) [54]. The authors first synthesized a series of alkynes on Rink amide resin (b), followed by Sonogashira coupling of the acetylenic carbon with various aryl triflates using standard room temperature procedures (c). (Though not employed in this study, microwave assisted protocols are available for both steps b [36–43] and c [49].) Subsequently, arylsulfonamides were obtained by tin-mediated reduction of the nitro group followed by sulfonylation using either ortho, meta, or para-trifluoromethyl-benzene-sulfonyl chloride. The desired cyclization step (f) was extremely sluggish, and only partial ring closure was observed under conventional thermal conditions (80 °C, 4–5 h). Nevertheless, microwave heating for 10 min at 200 °C in NMP using $\text{Cu}(\text{OAc})_2$ catalyst afforded the desired indole in 82% yield and 98% purity after cleavage ($\text{Ar} = p\text{-CF}_3\text{C}_6\text{H}_4$, $n = 8$). Alternatively, $[\text{PdCl}_2(\text{CH}_3\text{CN})_2]$ -catalyzed cycli-

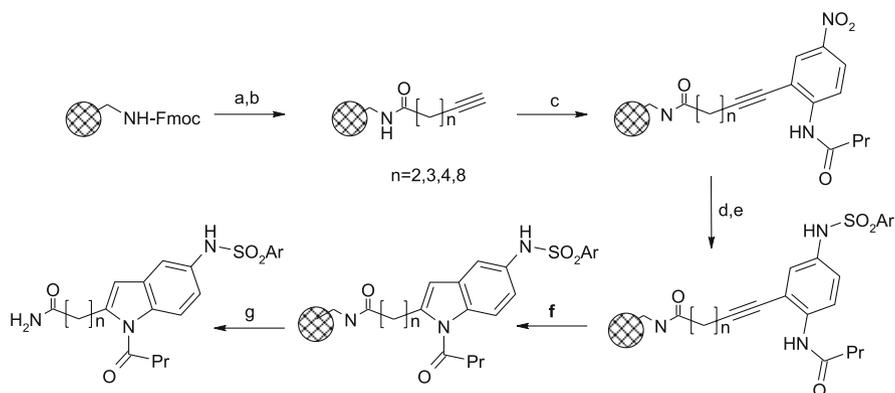


Fig. 25 SPOS of substituted indoles. Reagents and conditions: *a* 20% piperidine in DMF, rt, 1 h; *b* RCO_2H , DIC, HOBt, DMF-DCM (1 : 1), rt, 1 h; *c* ArOTf , $\text{Pd}(\text{PPh}_3)_4$, CuI , $n\text{-Bu}_4\text{NI}$, DMF- Et_3N (5 : 1), rt, 24 h; *d* $\text{SnCl}_2 \times 2\text{H}_2\text{O}$, NMP, rt, 24 h; *e* ArSO_2Cl , pyridine-DCM (1 : 5), rt, 20 h; *f* $\text{Cu}(\text{OAc})_2$, NMP, MW 200 °C, 10 min, or $\text{Pd}(\text{MeCN})_2\text{Cl}_2$, THE, MW 160 °C, 10 min, open vessel; *g* 20% TFA in DCM, rt, 1 h

zation in THF using microwave irradiation at 160 °C for 10 min yielded the product in 75% yield and 94% purity. The scope of the procedure was demonstrated by synthesizing a small library of 12 indoles using a combination of standard and microwave-assisted SPOS reactions, resulting in overall yields of 62–85% and purities over 95% in all cases.

A conceptually different approach to the synthesis of indole derivatives was recently presented by Fukase and coworkers. The authors applied microwave-mediated aryl radical cyclization reactions on a PS-support for the rapid generation of a diverse 40-membered 2-oxindole library [173]. The resin-bound benzyl chloride shown in Fig. 26 was prepared by coupling 4-(chloromethyl)benzoyl chloride to a Rink amide linker on PS beads. Resin-bound amides were then prepared by substitution of the benzoyl chloride with various *N*-(2-bromophenyl)-acrylamides in the presence of sodium hydride (a). Radical cyclization was carried out using Bu_3SnH and azoisobutyronitrile under microwave conditions at 170 °C for 45 min (the reaction temperature was reported to have risen to 100 °C within 3 min, to 120 °C within 10 min and to 170 °C within 20 min, and then remained constant). The resin was treated with 10% trifluoroacetic acid, and the eluted mixture was passed through an anion-exchange resin and concentrated in vacuo to give the desired indol-2-ones in 47–100% yield and 68–100% purity. It should be noted, that a similar radical cyclization scarcely proceeded in solution, opposing the general observation that reaction rates on solid support are slower compared to those in solution. The remarkable difference was proposed to originate from reagent concentration effects. Absorption of the applied tin reagent onto the solid-phase may have promoted the on-bead radical cycli-

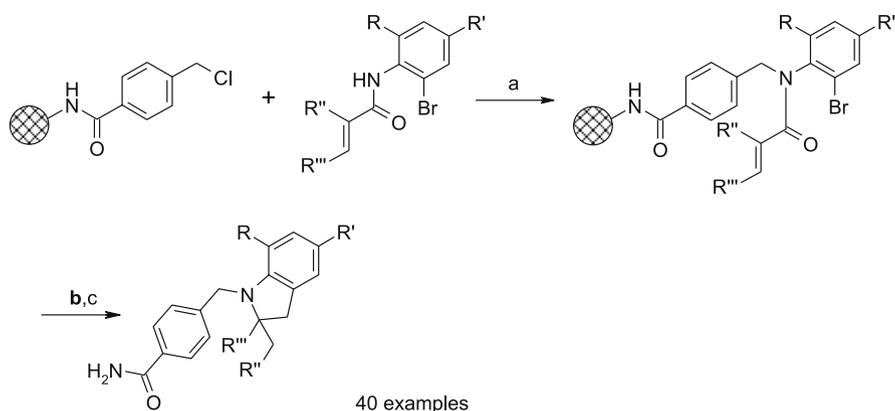


Fig. 26 Solid-phase synthesis of indol-2-ones by microwave-assisted radical cyclization. Reagents and conditions: *a* NaH, DMF; *b* Bu_3SnH , AIBN, DMF, MW 170 °C, 45 min, sealed vessel; *c* 10% TFA in CH_2Cl_2 . R = H, F, Me, OCF_3 ; R' = Phe, 3-OMe – Phe, 4-Me – Phe, 3,4- OCH_2O – Ph, $(\text{CH}_2)_4$, diMe; R'' = H, Me; R''' = H, Me

zation. However, this suggestion was not supported by any investigation of solution-phase reactions at higher reagent concentrations.

4.13

Diverse Nitrogen and Oxygen Heterocycles via On-Resin Cyclization of Aminopropenones

A general route to several types of bicyclic oxygen- and nitrogen-containing heterocycles on Merrifield resin was recently presented by Westman and Lundin [61]. Merrifield resin was treated with an excess of *N*-benzoylated glycine and cesium carbonate in dimethylformamide at 200 °C for 10 min (80%) with microwave irradiation, (Fig. 27), the formation of the resin-bound benzyl ester being optimized via on-bead MAS NMR analysis. This intermediate was mixed with *N,N*-dimethylformamide diethyl acetal, and the mixture was heated to 180 °C for 10 min in a closed vessel within a microwave reactor to form the dimethylamino propenoate species. Finally the resin was heated by microwave irradiation to 180 °C for 10 min in the presence of a dinucleophile; the resulting cyclative cleavage provided pyrido[1,2-*a*]pyrimidin-4-one, 4H-quinolizin-4-one or 5-oxo-5,6,7,8-tetrahydro-2H-1-benzopyran-2-one derivatives in high yields (77–95%) and purities (95–98%). This procedure has potential for the efficient construction of a large variety of diverse heterocycles using a simple three-step procedure.

In summary, microwave irradiation has been applied to several solid-phase syntheses of a large number of diverse and biologically relevant heterocycles.

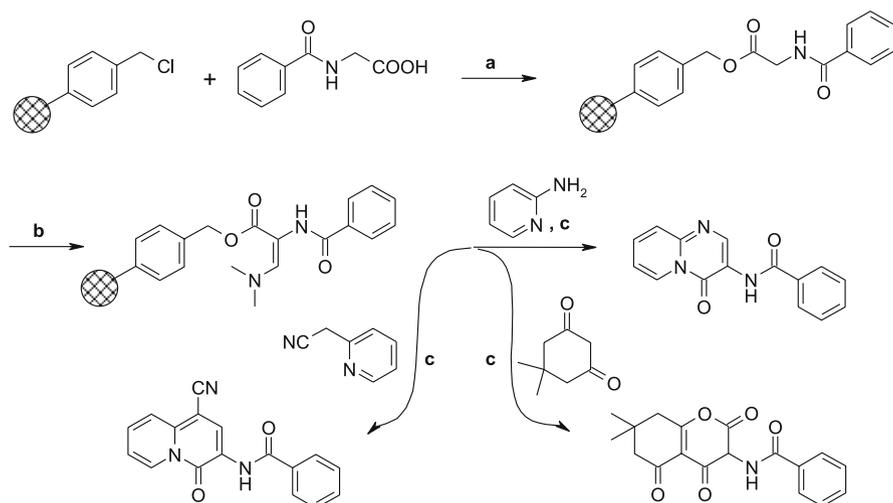


Fig. 27 Synthesis of heterocycles via propenoates. Reagents and conditions: *a* Hippuric acid, CsCO₃, DMF, 200 °C, 10 min, closed vessel; *b* DMFDEA in DMF, 180 °C, 10 min, closed vessel; *c* HOAc, 180 °C, 10 min, closed vessel

In most cases, the overall synthesis time was greatly reduced (from hours or days to minutes) by switching from conventional to microwave heating, facilitating the rapid preparation of novel chemical entities. The combination of solid-phase synthesis with microwave irradiation also allowed access to a few classes of molecules that had proven elusive via other synthetic strategies (traditional solution-phase synthesis).

5 Microwave-Accelerated SPOT Synthesis

SPOT-synthesis is a simple and flexible approach for parallel library synthesis involving spatially addressable, solid-phase synthesis on a planar cellulose solid support. The derivatized cellulose sheets are readily prepared from inexpensive filter paper. This methodology allows for the rapid generation of arrays of unique molecules (1–10 000 SPOTs) in nanomolar to micromolar scale, thus providing a sufficient amount of each product for analytical characterization and biological evaluation. Contrary to synthesis on traditional resin beads, different compounds prepared on the same cellulose sheet via SPOT-synthesis can be cleaved separately. SPOT-synthesis was originally developed by Frank for peptide synthesis [174], but Blackwell and coworkers have recently expanded the utility of SPOT-synthesis through combination with microwave heating to develop an excellent technique for the fast generation of small molecular weight heterocyclic libraries via multistep synthetic strategies (Fig. 28) [94]. In a representative synthesis, a Wang-type acid-labile linker was attached to the amino-cellulose support and subsequently functionalized with a diverse collection of hydroxyacetophenones via microwave-assisted nucleophilic substitution. The solutions of acetophenones and base were arrayed (SPOT size = 0.28 cm²) onto the activated support and subjected to microwave irradiation for 10 min. Analogous solid-phase nucleophilic displacements at 50 °C using conventional heating required 5 to 10 h. Although the experimental setup (i.e., planar membranes in glass vessels placed in a microwave oven) did not allow for accurate temperature measurement, reactions that were performed using an Ethos multimode microwave reactor provided reproducible acetophenone loadings ranging from 100 to 200 nmol/cm², but test experiments performed in a household microwave oven gave irreproducible results. Subsequent microwave-mediated Claisen-Schmidt condensation generated chalcones in good to excellent conversions (60–98%) within 20 min (c). The fact that such condensation reactions typically require 2–48 h with conventional solid-phase methods indicates the significant time-savings of the presented approach. Preparation of the library in a spatially addressable format permitted the application of different reaction conditions at different spots. For example, benzaldehydes of different reactivities required reaction conditions with various basicities for complete

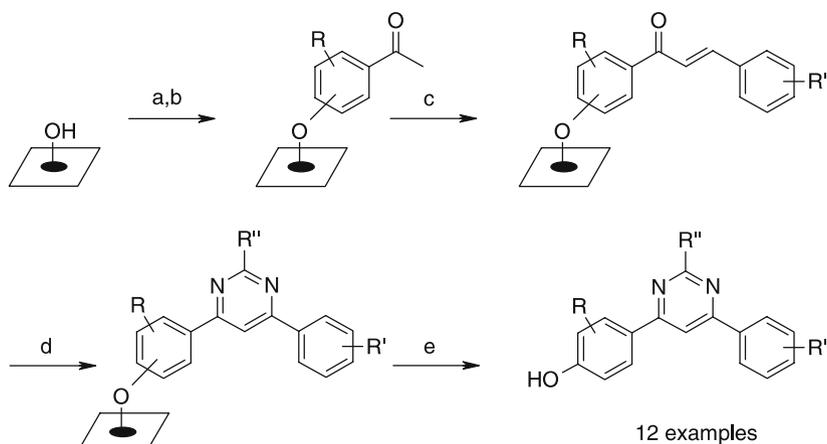


Fig. 28 Microwave-promoted SPOT-synthesis of dihydropyrimidines. Reagents and conditions: *a* TsCl, DME, 25 °C, 30 min; *b* R(OH)ArCOCH₃, KO-*t*-Bu, DMSO, MW 500 W, 10 min; *c* R'ArCHO, KOH, H₂O, MW 400 W, 20 min; *d* R''C(NH₂)NH₂·HCl, KO-*t*-Bu, DMA, MW 400 W, 30 min; *e* TFA. R = 3/4-OH, 3-OMe; R' = 3-Br, 4-Cl; R'' = Me, Ph

conversion, and hence 1.0 to 12.0 mol/dm³ potassium hydroxide solutions were added to different SPOTs depending on the reactivity of the substrate. Condensation of the membrane-attached chalcones with acetamidine or benzamidine hydrochloride furnished dihydropyrimidines in good to excellent purities (73–88%). Only trace amounts of related pyrimidines were formed using microwave-promoted SPOT methodology, while these products are formed exclusively under solid-phase conditions using conventional heating at 100 °C (20 h). The dihydropyrimidine library was liberated from the cellulose support via trifluoroacetic acid vapor-mediated cleavage in good yield and purity. Thus, a combination of microwave heating with SPOT-synthesis is a versatile tool for the extraordinarily rapid generation of highly diverse heterocyclic libraries. As the technique provides sufficient quantities of products for characterization and biological tests, it should be considered as an alternative to more conventional on-bead synthesis.

6

Microwave-Promoted Synthesis on Soluble Supports

Soluble support-based synthetic approaches offer the advantages of both homogeneous solution-phase chemistry (high reactivity, ease of analysis) and solid-phase synthesis (large excess of reagents, simple product isolation and purification) [98, 99]. As a representative example, PEG, one of the most widely used soluble polymers, has good solubility in most organic solvents (i.e., dichloromethane, acetonitrile, dimethylformamide, and toluene), but it

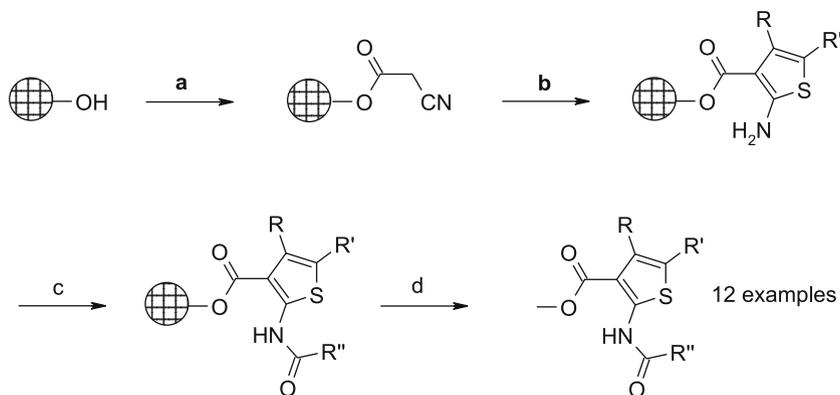


Fig. 29 Microwave-promoted multicomponent synthesis of polysubstituted thiophenes on soluble PEG support. Reagents and conditions: *a* NCCH_2OOH , DCC, DMAP, CHCl_3 , MW 130 W, 5 min; *b* $\text{RCOCH}_2\text{R}'$, S8, diisopropylethylamine, MW 130 W, 15 min; *c* $\text{R}''\text{COCl}$, diisopropylethylamine, 0°C to rt, 3 h; *d* 1% KCN in CH_3OH , o.n.; R = H or alkyl; R' = alkyl or acyl; R'' = CH_3 , Ph

is easily precipitated from diethyl ether, isopropyl alcohol and cold ethanol. Hence, after performing a reaction in the organic solvent, separation of the functionalized matrix is easily achieved by precipitation or filtration.

As previously indicated in Sect. 4.9, Gewald synthesis of highly substituted thiophenes has attracted increasing interest since originally published in 1961 [160]. In addition to traditional solid-phase procedures, a microwave-mediated approach on soluble PEG was described by Yang and coworkers [165]. Although all microwave-promoted steps were performed without proper control of temperature and pressure, this example of microwave-assisted synthesis on soluble support will be discussed as an alternative to the solid-phase methodology of Hoener [56] because the authors made excellent use of some advantages of the soluble support methodology. Thus, a cyanoacetylated polymer was prepared (Fig. 29) by microwave-promoted ester coupling (a); the progress of the reaction was followed with FT-IR and standard solution NMR methods. The Gewald reactions (b) were carried out with aldehydes, ketones and 1,3-dicarbonyl compounds under solvent-free microwave conditions, and again the reaction was monitored by FT-IR. The product was then purified via filtration and precipitation. Following acylation of the free amine (c), the products were cleaved with 1% KCN in methanol (d), and purified by column chromatography, yielding highly diverse thiophenes in 38–95% yields. In contrast with similar Gewald syntheses on insoluble beads [56], reaction steps on the soluble support could be easily monitored using standard techniques. Moreover, a combination of solution and solvent-free conditions for microwave irradiation could be applied.

7

Microwave-Assisted Synthesis in Fluorous Phases

Fluorous synthesis is a complementary technique to liquid-phase synthesis on soluble supports. By attaching perfluoroalkyl groups to the desired product as “phase tags”, the process of purification can be simplified. Products from a fluorous phase synthesis may easily be purified and separated by fluorous solid-phase extraction [130] or a simple three-phase extraction with an organic solvent, water, and a fluorocarbon solvent [127]. Separation of fluorous-tagged products from a complex mixture of untagged side-products is much more easily accomplished than separating the same (untagged) products from mixtures derived from soluble polymer supports [175]. Fluorous tags have excellent thermostability, and, in contrast to the constraints of solid supports, they do not diminish the solution-phase reactivity of their substrates. As fluorous supports combine many of the advantages of solution phase synthesis with the straightforward purification typical of solid-phase methodologies, their application is becoming increasingly popular in spite of the comparably high price of the perfluorinated tags.

7.1

Fluorous Synthesis of Biaryl-Substituted Proline Analogs

Most of the presently known microwave-assisted syntheses of heterocyclic libraries target aromatic systems. Of the few reports on the preparation of non-aromatic systems, the solution-phase synthesis of a highly diverse bicyclic proline library by 1,3-dipolar cycloaddition of perfluoroalkylsulfonyl-protected hydroxybenzaldehydes recently developed by Zhang and coworkers is noteworthy because of its utilization of fluorous methodology (Fig. 30). The bicyclic ring system was formed in a stereoselective manner with the *cis* ring-fused hydrogen atoms being *trans* to the phenyl group. The cycloaddition product was easily isolated using fluorous solid-phase extraction or fluorous column chromatography. The fluorous intermediates were analyzed via conventional TLC, NMR and LC-MS, methods known to be difficult/impossible to apply for polymer-supported intermediates. Subsequently, a Suzuki coupling reaction of the fluorous sulfonates was applied to add a further point of diversity and simultaneously effect the traceless cleavage of the bicyclic proline derivatives from the fluorous tag [176]. Final products were purified by solid-phase extraction on standard silica gel. The applied methodology is powerful and innovative, as the fluorous sulfonyl group plays three different roles in the multistep synthesis: being employed as a phase tag to ease purification, as a protecting group to mask the phenol functionality, and as a triflate equivalent to promote the Suzuki cross-coupling reaction. In addition, this strategy did not require an additional cleavage step to liberate the library products.

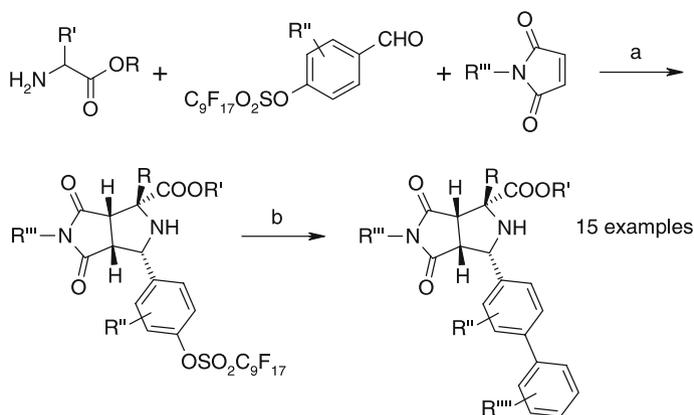


Fig. 30 Microwave-promoted fluorosynthesis of biaryl-substituted proline analogs. Reagents and conditions: *a* Et₃N, DME, MW 150 °C, 15 min, 40–75%, closed vials; *b* R^{''''}PhB(OH)₂, Pd(dppf)Cl₂, K₃PO₄, toluene: Acetone: H₂O, MW 120 °C, 12 min, sealed vial system, 19–79%. R = Me, Et; R' = Me, I-Pr; R'' = H, 3-MeO; R''' = Me, Et; R'''' = 4-MeO, 3-Cl, 4-Ac, 3,4-diCl, 3,4-methylenedioxy

7.2

Fluorous Synthesis of Dihydropteridinones by Microwave-Assisted Cyclative Cleavage

Nagashima and Zhang have reported the efficient synthesis of a 20-membered dihydropteridinone library in fluoros phase by a five-step procedure [177]. Among several room temperature transformations, the applied methodology featured the microwave-promoted creation of the bicyclic ring system (Fig. 31). Similar to the aforementioned synthesis of bicyclic prolines, the intramolecular nucleophilic cyclization released the product from the fluoros tag, and the dihydropteridinones could easily be isolated in crystalline form by precipitation with hexane (86–100% purity, 26–44% cumulative yields reported for four steps). The major advantages of the reported multistep procedure are that conventional chromatographic techniques were not required for purification of products and solution-phase monitoring (LC-MS or TLC) of each reaction step was feasible.

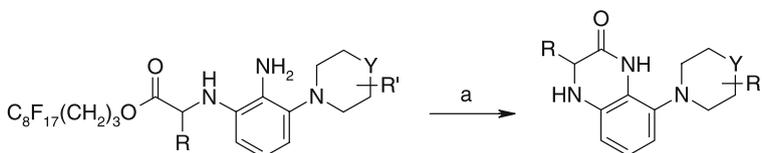


Fig. 31 Composition of dihydropteridinone ring system using cyclative cleavage in fluoros-phase. Reagents and conditions: *a* EtOAc, MeOH, THF, MW 150 °C, 15 min, sealed vials. Y = C, N, O; R = Me, Et, *i*-Bu, Bn; R' = H, aromatic or heteroaromatic ring

7.3

Fluorous Mixture Synthesis of Fused-Tricyclic Hydantoins

Very recently, Manku and Curran presented the synthesis of a small library of tricyclic hydantoins via a $[2 + 2 + 1]$ cycloaddition strategy and impressive deconvolution of the product mixtures through fluorous tagging techniques (Fig. 32) [178]. A mixture of six fluorous carbobenzyloxy-tagged alkynyl allenes was prepared (with four different tags) and subsequently treated with $\text{Mo}(\text{CO})_6$ and a catalytic amount of dimethylsulfoxide under microwave irradiation to undergo an allenic Pauson-Khand reaction (a), resulting in a complex mixture of α -alkylidenecyclopentenone stereoisomers along with 4-alkylidenecyclopentanones. Following deprotection of the *tert*-butyl ester (b), the carboxylic acid mixture was coupled with phenylethylamine (c). At this stage the mixture was separated via column chromatography into three submixtures containing predominantly the *syn* and *anti* isomers of α -alkylidenecyclopentenones, and 4-alkylidenecyclopentanones. These submixtures were then demixed by fluorous HPLC to give 17 individual products in 61–94% yield. Removal of the fluorous tag with concomitant hydantoin formation was then achieved by exposing the individual amides to diisopropylethylamine under microwave irradiation at 140 °C for 40 min (d). Products were then purified by fluorous solid-phase extraction, to remove the fluorous benzyl alcohol, and liquid-liquid extraction or HPLC. The *syn* isomers of the α -alkylidenecyclopentenone were isomerized to the more stable *anti* isomers during the base-promoted reaction, so 11 total products were obtained in 25–99% yield and 85–99% purity. The presented synthetic strategy provides an excellent technique for the quick synthesis of complex mixtures of heterocyclic compounds as well as easy purification and separation via fluorous tagging technology.

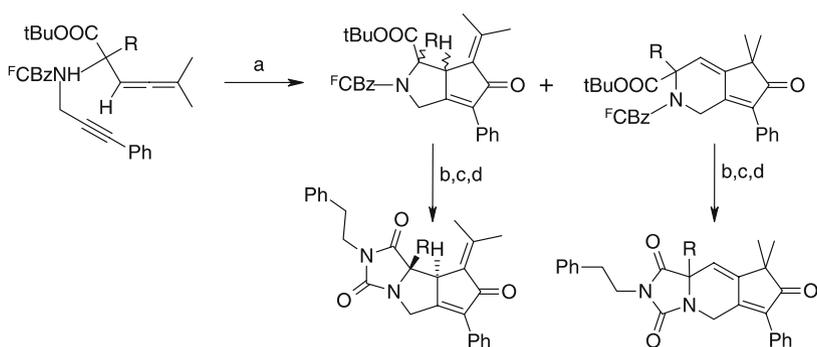


Fig. 32 Fluorous mixture synthesis of fused-tricyclic hydantoins. Reagents and conditions: *a* $\text{Mo}(\text{CO})_6$, DMSO, toluene, MW 150 °C, 35 min, closed system; *b* TFA : CH_2Cl_2 (1 : 1), rt; *c* $\text{PhC}_2\text{H}_4\text{NH}_2$, PyBOP, *i*-Pr₂EtN, MeOH, CH_2Cl_2 followed by flash chromatography and F-HPLC; *d* *i*-Pr₂EtN, MeOH, MW 140 °C, 40 min, followed by F-SPE

7.4

Microwave-Assisted Fluorous Ugi Reactions, Synthesis of Benzimidazoles and Quinoxalinones

Multicomponent reactions offer outstanding routes for preparation of heterocyclic libraries with high diversity. In a recent paper, Zhang and Tempest reported a microwave-promoted Ugi four-component condensation strategy in combination with fluorous protecting groups, an approach allowing both rapid synthesis and simple purification of complex heterocyclic compounds (Fig. 33) [179]. A methanolic solution of mono-F-Boc protected diamine with a slight excess of carboxylic acid, aldehyde, and isonitrile was irradiated at 100 °C for 10–20 min with a microwave apparatus, and the resulting mixture was purified by fluorous-SPE. The intermediates were then treated with a 1 : 1 mixture of trifluoroacetic acid and tetrahydrofuran at 100 °C for 10–20 min under microwave irradiation to give quinoxalinones (52–95%) or benzimidazoles (25–96%), which were subsequently purified by F-SPE. The presented methodology offers a superior strategy in terms of reaction and purification times compared to previous reports on Ugi reaction products [180, 181].

Additional examples of microwave-promoted fluorous synthesis are found in the following references [127–129, 182, 183].

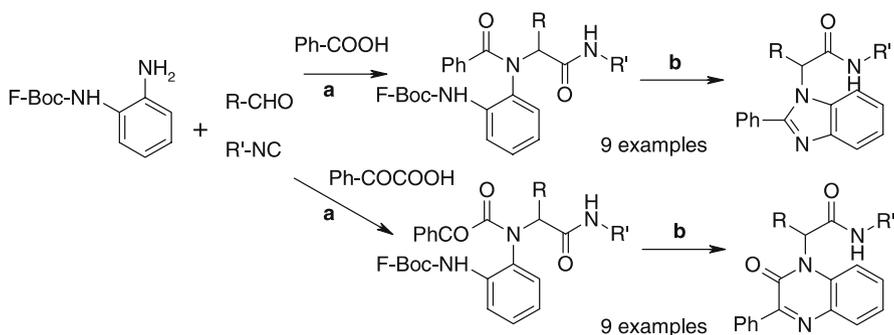


Fig. 33 Microwave-assisted fluorous Ugi condensations. Reagents and conditions: *a* MeOH, MW 100 °C, 10–20 min; *b* TFA-THF, MW 100 °C, 10–20 min. R = Ph, furyl, 3-Me-pyridil, *i*-Bu, MeSC₂H₄, PhC₂H₄; R' = *t*-Bu, cyclohexyl, Bn or Bu, *m*-xylil

8

Microwave-Enhanced Synthesis Using Functional Ionic Liquid Supports

Although solid-phase synthesis revolutionized synthetic organic chemistry and triggered the development of combinatorial chemistry, it still exhibits several shortcomings originating from the nature of heterogeneous conditions, such as lower reaction rates and difficulties in reaction monitoring.

By replacing insoluble cross-linked resins with soluble polymer supports, the well-established reaction conditions of classical organic chemistry can be more readily applied, while still facilitating product purification. However, soluble supports suffer from the limitation of low loading capacity. The recently introduced fluorous synthesis methodology overcomes many of the drawbacks of both the insoluble beads and the soluble polymers, but the high cost of perfluoroalkane solvents, limitation in solvent selection, and the need for specialized reagents may limit its applications.

An innovative approach for solution-phase synthesis employs ionic liquids as supports. This alternative combines many advantages of the more popular solid- and solution-phase techniques (i.e., homogeneous reaction conditions, high loading capacity, simple monitoring methods and a wide range of compatible solvents.) Ionic liquids are miscible with polar organic solvents but non-miscible with water and less-polar organic solvents (diethyl ether, aliphatic or aromatic hydrocarbons), so they offer the potential of easy separation. Ionic liquids also have a number of characteristics that make them uniquely suited to microwave-assisted synthesis, such as tolerance of high temperatures, excellent absorption of microwave energy, negligible vapor pressure, non-flammability, and low cost. The following examples will demonstrate their utility for the microwave-assisted synthesis of heterocycles.

8.1

Preparation of a 4-thiazolidinone Library Employing a Functional Ionic Liquid Support

The first example of the combination of a task-specific ionic liquid support with microwave dielectric heating was provided by Fraga-Dubreuil and Bazureau who prepared a small library of 4-thiazolidinones on a 3-methylimidazolium tetrafluoroborate based ionic liquid support (this functionalized ionic liquid was easily prepared by a microwave assisted procedure) [137]. Here, the 4-thiazolidinone ring was synthesized in a one-pot cyclization (stepwise reaction via an imine intermediate) using a 1 : 1 : 1 mixture of the ionic support, amine, and mercaptoacetic acid, giving products in 12–86% yield (Fig. 34). The authors noted that volatile amines gave lower yields in this step, probably due to the open-vessel conditions applied during the study. The progress of the three-component reaction could easily be monitored by standard ^1H NMR spectroscopy. Cleavage of the thiazolidinones from the ionic liquid support was performed by amidation with primary or secondary amines in the presence of potassium *tert*-butoxide under microwave irradiation in 10–20 min. This reaction was also monitored by standard solution NMR spectroscopy. The products were separated from the ionic tags by extraction into chloroform and purified by column chromatography, giving diverse thiazolidinones in 25–47% yields.

and converted into a support-bound thiourea by addition of an acetonitrile solution of isothiocyanate. The progress of the reaction was monitored with ^1H NMR or TLC. Cyclative cleavage of the 2-thioxo tetrahydropyrimidin-4(1H)-ones was then achieved by treatment with diethylamine using microwave irradiation at 120°C for 15–45 min under solvent-free conditions. Upon completion of the reaction, as evidenced by ^1H NMR, the crude reaction mixture was extracted with chloroform; purification using column chromatography afforded the desired 2-thioxo-tetrahydropyrimidin-4(1H)-ones in 67–85% yield. The applied ionic liquid-phase methodology allowed the use of standard analytical methods for reaction monitoring as well as greatly simplified product purification.

8.3

Microwave-Assisted Synthesis of a Substituted Pyran Using Ionic Liquid Tagging

Song and coworkers have achieved the microwave-assisted synthesis of methyl 6-amino-5-cyano-4-aryl-2-methyl-4H-pyran-3-carboxylate with ionic liquid supports (Fig. 36) [184]. In the first step, the ionic liquid 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate was treated with ethyl acetoacetate. Infrared monitoring of the mixture revealed that the coupling went to completion within 10 min under microwave irradiation but required 3 h reaction time for similar conversion using conventional heating. Subsequently, cyclization between the ionic liquid-bound acetoacetate and arylidenemalononitriles gave support-attached 4-H-pyran derivatives. The excess arylidenemalononitriles were easily removed by extraction with petroleum ether and dichloromethane (the ionic liquid is insoluble in this solvent mixture). Finally, the product was cleaved with sodium methoxide in methanol, the process being monitored by TLC. After removal of methanol from the reaction mixture under reduced pressure, the products were extracted from the residue with dichloromethane, giving methyl 6-amino-5-

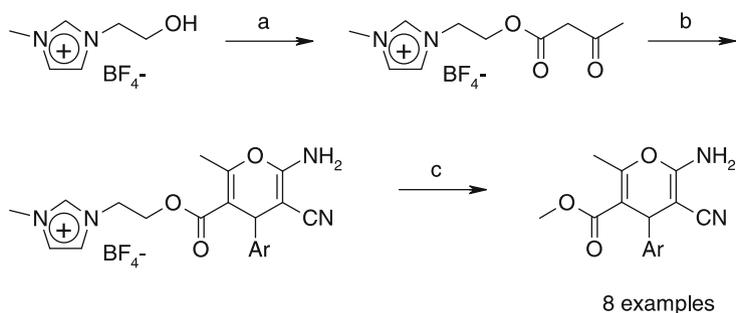


Fig. 36 Synthesis of a polysubstituted pyran on ionic liquid support. Reagents and conditions: *a* ethyl acetoacetate, MW 200 W, reflux, 10 min; *b* arylidenemalononitriles, pyridine, MeCN, MW 200 W, reflux, 15–20 min; *c* NaOMe, MeOH, rt, 6 h

cyano-4-aryl-2-methyl-4H-pyran-3-carboxylates in high yields (84–91%) and purities (95–99%). Besides the low cost, the main advantage of this procedure, and the use of ionic liquid supports in general, is that high purity products could be isolated by simple liquid-liquid extraction, a process readily amenable to automation. In addition, the ionic liquid could be recovered and reused without observable loss of activity. The authors did not report the exact temperature of the microwave-assisted reaction steps, only power setting values, greatly limiting the reproducibility of this attractive synthetic methodology.

Further examples of the creation of heterocyclic rings using microwave technology in combination with solid or soluble supports are found in references [108–115, 117, 119, 121, 123, 135, 185].

9

High-Speed Functionalization of Heterocycles

9.1

Rapid Nucleophilic Displacement on Purine C-2

The preparation of purine derivatives substituted at the C-2 position via amine displacement of a halogen is known as a difficult reaction step requiring several days of reaction time. However, Al-Obeidi and coworkers have recently prepared 2,6,9-trisubstituted purines on solid-phase by employing a synthetic route in which the critical step was performed with microwave irradiation (Fig. 37) [62]. PS resin-bound 2-iodosubstituted purine was treated with diethanolamine or propanolamine in NMP with microwave irradiation at 200 °C for 30 min. Trifluoroacetic acid-mediated cleavage resulted in the 2-amino substituted purines in 45–59% yields and 77–89% purities.

In a follow-up article, the authors have shown that, in addition to 2-iodopurines, fluoro and chloropurines can also be rapidly aminated under microwave-promoted conditions [186]. The conversion levels indicated that both fluorine and iodine were better choices than chlorine as the C-2 substituted halogen.

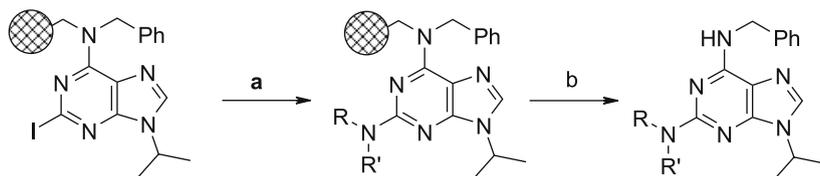


Fig. 37 Microwave-promoted rapid nucleophilic displacement of halogen on purine C-2. Reagents and conditions: *a* Diethanolamine or propanolamine, NMP, MW 200 °C, 30 min; *b* TFA : H₂O (92 : 8), 60 °C, 1 h. R, R' = HOC₂H₄ or R = H and R' = HOC₃H₆

9.2

Microwave-Promoted Route to Diverse 2(1H)-Pyrazinones and Pyridinones

The 2(1H)-pyrazinone scaffold has the potential to address a diverse set of biological targets. Hence, new methodologies for the generation of pyrazinone-based libraries are of exceptional interest. Van der Eycken and coworkers has developed a novel microwave-assisted solid-phase concept for the preparation of such libraries with variability at both the C-3 and C-6 positions (Fig. 38) [187]. In this approach, a Wang resin-attached pyrazinone was first prepared using modified Strecker conditions at ambient temperature (steps a and b). It should be noted that heating of the reaction mixture under these steps resulted in lower yields, possibly due to partial cleavage of the linker. The diversity of the resin-bound compound was extended through subse-

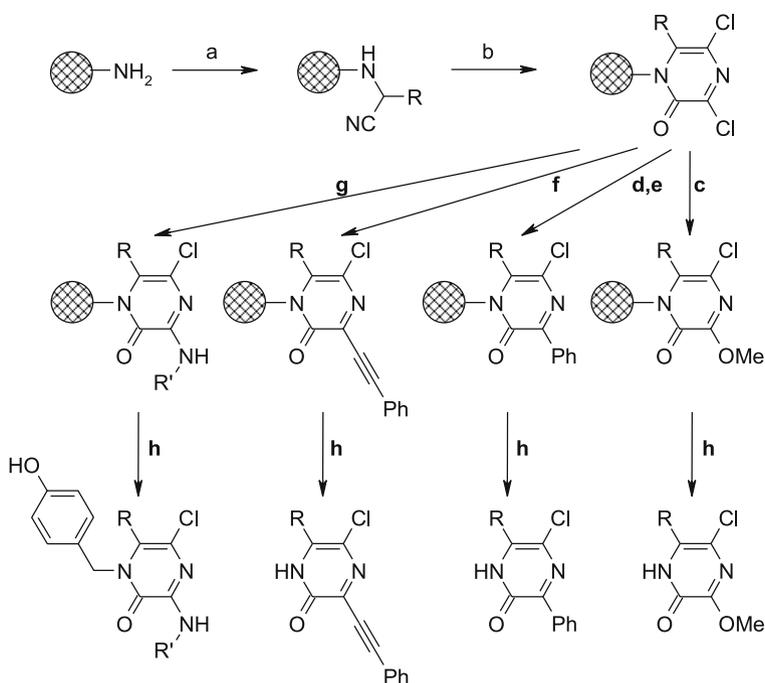


Fig. 38 Microwave-assisted synthesis of diverse 2(1H)-pyrazinones on solid-phase. Reagents and conditions: *a* R-CHO, TMSCN, CH₂Cl₂, rt, 24 h; *b* 1 M HCl/THF (1 : 1), rt, 30 min, then (COCl)₂, toluene, rt, 3 days; *c* NaH, MeOH/THF (1 : 1), rt, 3 h; *d* PhB(OH)₂, Na₂CO₃, Pd[P(Ph)₃]₄, MW 170 °C, 30 min, in sealed vessel or *e* Ph₄Sn, Pd[P(Ph)₃]₄, DMF, MW, 150 °C, 20 min, sealed vessel; *f* phenylacetylene, Pd[P(Ph)₃]₂Cl₂, CuI, toluene/TEA, MW, 120 °C, 30 min, sealed vessel; *g* *p*-anisidine, Cu, CuI, K₂CO₃, MW, 175 °C, 30 min, closed vessel; *h* TFA/CH₂Cl₂ (1 : 2), MW, 120 °C, 20 min, closed vessel; R = H, Me, 2-furyl, phenyl, 4-methoxyphenyl, 4-carbomethoxyphenyl, 3,4-methylenedioxyphenyl. For steps *d*, *e*, *f* and *g* R = phenyl. R' = 4-methoxyphenyl

quent derivatization. An addition-elimination with in situ-generated sodium methoxide provided the 3-methoxy derivative (c), which was then rapidly cleaved with trifluoroacetic acid using microwave heating (h). Although aryl chlorides are known to have limited reactivity in palladium-mediated couplings, substitution of the chloride attached to the electron deficient C-3 with organometallic reagents was feasible. Hence, treatment of the resin-bound pyrazinone under Suzuki (d) or Stille (e) conditions provided 3-phenyl-substituted products. Sonogashira coupling allowed the introduction of phenylalkynyl substituents at C-3 (f), and Ullman coupling with *para*-ansidine yielded (4-methoxyphenyl)amino-substituted pyrazinones (g). Cleavage of the latter compound gave the 1-*N*-*para*-hydroxyphenyl derivative (i). Following purification by silica gel chromatography, the products were obtained in 14–67% yields. The usefulness of solid-phase-bound pyrazinones for the generation of a broad scale of pyridinones and pyridines via microwave-assisted Diels-Alder/retro-Diels-Alder reactions was demonstrated in a separate work by Van der Eycken in cooperation with the group of Kappe and coworkers (Fig. 39) [68]. Microwave-assisted cycloaddition/retrocycloaddition of Wang resin-attached pyrazinones at 220 °C provided two different types of substituted pyridines (a), one being released into solution (2–49%) under the applied conditions, and the other being retained on the solid-phase (28–55%). Dihydrofuropyridinones could also be obtained from the resin-bound 3-(3-butynyloxy)-substituted pyrazinones (b). For each reaction step, microwave heating was used to shorten reaction times and achieve similar or higher yields compared to conventional heating. The observed rate enhancements were assumed to be a consequence of the rapid direct heating of the solvents to high

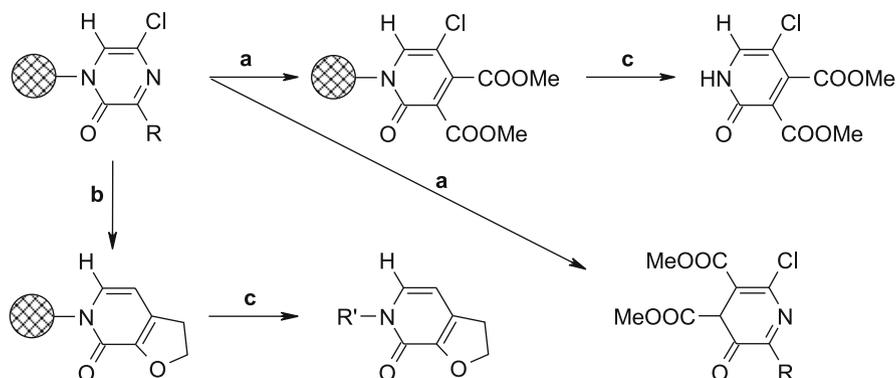


Fig. 39 Microwave-assisted synthesis of pyridinones from resin-bound 2(1H)-pyrazinones. Reagents and conditions: *a* dimethyl acetylenedicarboxylate, chlorobenzene, reflux (132 °C), 1–2 days or 1,2-dichlorobenzene, MW 220 °C, 20–40 min; *b* bromobenzene, reflux (156 °C), 2 h or 1,2-dichlorobenzene, MW 220 °C, 10 min R = OC₂H₄C₂H; *c* TFA, reflux (72 °C), 20–24 h or TFA/CH₂Cl₂, MW 120 °C, 10–40 min. R = OMe or Ph, R' = methoxyphenyl. All microwave-assisted reactions were run in sealed vessels

temperatures, and not due to any nonthermal microwave effects. It should also be noted that temperatures up to 220 °C were involved in the transformations on polystyrene-based supports without affecting resin stability.

9.3

Microwave-Assisted Substitution of Imidazole C-2 on Solid-Phase

Hlasta and Deng have developed a two-step solid-phase method for the decoration of azoles at C-2 [188]. First, imidazole was loaded onto a polystyrene-bound carbamyl chloride via a benzaldehyde bridge (Fig. 40). The 2-substituted imidazole was efficiently cleaved in good yields in the presence of various nucleophiles (i.e., water, alcohols, and amines), trifluoroacetic acid, and boron trifluoride under microwave irradiation in a closed vessel at 120 °C for 5 min.

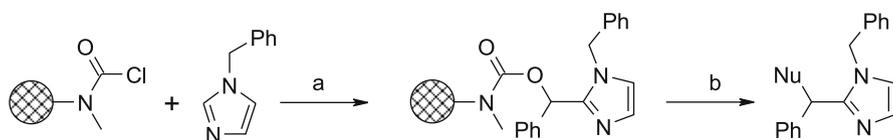


Fig. 40 Microwave-assisted substitution of imidazole on C-2 in solid-phase. Reagents and conditions: *a* benzaldehyde, *N,N*-diisopropylethylamine, CH₂Cl₂, 24 h, rt; *b* Nucleophile, TFA, BF₃Et₂O, THP, MW 120 °C, 5 min, closed vessel

9.4

Suzuki Couplings

The first example of microwave-promoted solid-phase methodology in heterocyclic chemistry was the arylation of thiophene and indole via Suzuki couplings on TentaGel S RAM resin, as demonstrated by Hallberg and co-workers in 1996, before temperature- and pressure-controlled microwave instruments were even available [189]. Three years later Schotten and co-workers presented analogous but aqueous Suzuki couplings of 5-bromothiophene anchored to PEG soluble support via a carboxylic function at its C-2 position [116]. Unfortunately, this work was performed in a do-

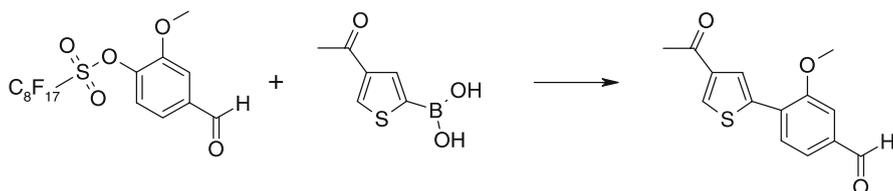


Fig. 41 Representative example of microwave-assisted Suzuki couplings in fluorous phase. Reagents and conditions: [Pd(dppf)Cl₂], K₂CO₃, toluene/acetone/H₂O, MW 130 °C, 10 min, closed system, 78%

mestic microwave oven, diminishing its reproducibility. Suzuki coupling of thiophene and quinoline derivatives attached to a fluororous tag was recently published by Zhang and coworkers [132]. In this example, [Pd(dppf)Cl₂] catalyst, K₂CO₃, an aryl perfluorooctylsulfonate, a boronic acid, and a mixture of toluene/acetone/H₂O were allowed to react in a sealed tube under monomode microwave irradiation at 130 °C for 10 min (Fig. 41). For purification of the product, the organic phase of the reaction mixture was loaded on a fluororous solid-phase extraction cartridge and eluted with a methanol-water mixture, yielding the product in high yield (75–95%) and purity (> 90%). Under these conditions the fluororous tag was retained on the cartridge.

Further examples of functionalization of heterocyclic systems using solid or soluble supports in combination with microwave technology are found in references [52, 92, 155, 190].

10

Summary and Outlook

In conclusion, the examples presented clearly indicate that bringing together microwave dielectric heating with solid- or soluble-supported chemistry techniques combines most advantages of the individual procedures. Thus, microwave-enhanced solid-phase synthesis provides significant enhancements both at the level of reaction rate and ease of purification. The number of publications in the field of microwave-assisted solid-phase synthesis is small but growing now that suitable instrumentation for the simultaneous application of temperature-controlled microwave heating and simple, automated resin handling has been developed and is becoming more widely available. Solid-phase microwave vessels are commercially available, and so rapid progress of this field is continued to be expected. New approaches to microwave-promoted synthesis, fluororous chemistry, soluble polymer, and functional ionic liquids are likely to attract the attention of combinatorial chemistry community as these methodologies promise straightforward transfer of conditions from standard solution-phase reactions with the benefit of easier product purification. In the future, the field will undoubtedly benefit from availability of less expensive instrumentation and continued innovation of solid supports and reaction methodology.

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Synthesis of Heterocycles Using Polymer-Supported Reagents under Microwave Irradiation

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1	Introduction	130
2	Polymer-Supported Reagents in Organic Synthesis	131
3	Using Polymer-Supported Reagents under Microwave Irradiation	135
4	Literature Survey	137
5	Concluding Remarks	151
	References	152

Abstract In this chapter, the microwave-assisted synthesis of heterocyclic systems using polymer-supported reagents is reviewed. After a brief introduction on the advantages of using polymer-supported reagents under microwave irradiation, a survey of the current literature on the field is given, highlighting whenever possible the differences in behavior when compared to the same reactions performed with conventional heating. The chapter will focus on the use of dedicated monomode microwave systems and on reactions run in the presence of solvents and involving either polymer-supported reagents, catalysts or scavengers. Reactions run in the absence of solvents, with the reagents impregnated on various kinds of supports, will not be included.

Keywords Combinatorial chemistry · Heterocycles · Microwave irradiation · Parallel chemistry · Polymer-supported reagents

Abbreviations

BEMP	2- <i>tert</i> -Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DIEA	Diisopropylethylamine
DMAP	<i>N,N'</i> -Dimethylaminopyridine
DMF	<i>N,N'</i> -Dimethylformamide

GC	Gas chromatography
HPLC	High performance liquid chromatography
HOBt	Hydroxybenzotriazole
HBTU	2-(1 <i>H</i> -benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
MALDI	Matrix assisted laser desorption ionization
MAOS	Microwave-assisted organic synthesis
MAS	Magic angle spinning
MCR	Multicomponent reaction
MS	Mass spectrometry
NMM	<i>N</i> -Methyl morpholine
NMR	Nuclear magnetic resonance
PASP	Polymer-assisted solution-phase chemistry
PEG	Polyethylene alcohol
PS-BEMP	Polymer-supported 2- <i>tert</i> -butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
PS-CPT	Polymer-supported chloropyridinium triflate
PS-FPT	Polymer-supported fluoropyridinium triflate
PS-NMM	Polymer-supported <i>N</i> -methyl morpholine
PS-TPP	Polymer-supported triphenylphosphine
PSR	Polymer-supported reagent
RCM	Ring-closing metathesis
SPOS	Solid-phase organic synthesis
TLC	Thin layer chromatography
TBD	1,3,4,6,7,8-hexahydro-1-methyl-2 <i>H</i> -pyrimido[1,2- <i>a</i>]pyrimidine
TEA	Triethylamine

1

Introduction

Along its history, the art of organic synthesis has evolved considerably, incorporating new reactions, new reagents or catalysts, and has permitted the preparation of molecules of incredible complexity and of great importance for the life of many people. However, until very recently, molecules were prepared one by one, in a successive rather than parallel way. Starting from the end of the 1980s, the need to keep pace with the development of high-throughput screening and to find good quality lead molecules for the pharmaceutical industry has generated an ever-increasing interest in finding new techniques that would allow the preparation of large numbers of compounds in short periods of time.

An important breakthrough in that respect was the use of solid-phase organic synthesis (SPOS) where the attachment of the substrate to an insoluble support allowed for easy workup (filtration) and for rapid generation of products via split-mix procedures [1, 2]. An important subsequent development consisted of the immobilization of reagents, scavengers and catalysts. This technique, coined polymer-assisted solution phase chemistry (PASP), allowed solution phase synthesis of compounds, yet still enjoying the bene-

fits of working with solid-supports [3–19]. Furthermore, the use of soluble supports, for example fluorous or polyethylene glycol (PEG) chains, further expanded the usefulness of product-, reagent- and scavenger tagging for library synthesis [19–27].

Finally, the introduction of focused microwave instruments further enabled to speed up the synthesis of libraries, by reducing the actual time needed for reaction [28–34]. The combination of using dedicated microwave instruments and solid or solution phase tagging subsequently became a very powerful tool for PASP and SPOS applications [25, 26, 33–51].

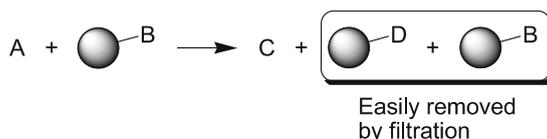
In this chapter attention is directed to the microwave-assisted synthesis of heterocyclic systems using polymer-supported reagents and/or scavengers. The chapter will focus on the use of dedicated monomode microwave systems and on reactions run in the presence of solvents and involving either insoluble polymer-supported reagents, catalysts or scavengers. Whereas possible comparison of microwave irradiation and conventional heating will be highlighted. Reactions run in the absence of solvents, with the reagents impregnated on various kinds of supports, will not be included.

2

Polymer-Supported Reagents in Organic Synthesis

The concept of using reagents linked to insoluble matrices to facilitate removal of excess or spent reagent is not new (Scheme 1). The first example was reported as early as 1946, although it is in the seventies that the first important results were obtained, thanks to the pioneering work by Frechet [52], Cainelli [53], Leznoff [54] and Sherrington [55], among others.

Despite these interesting results, the field remained of limited interest to the synthetic community. These reagents were generally considered to have slow kinetics and to be too expensive for effective use in organic synthesis. The advent of combinatorial chemistry has changed this. In the first place, the progress in the preparation of solid supports for solid-phase organic synthesis with better characteristics (higher loadings, uniform distribution of reactive sites, better reaction kinetics, lower cost) inevitably has had an impact on the area of polymer-supported reagents. Perhaps more importantly, the use of PSRs is proving to be an ideal methodology for the clean and



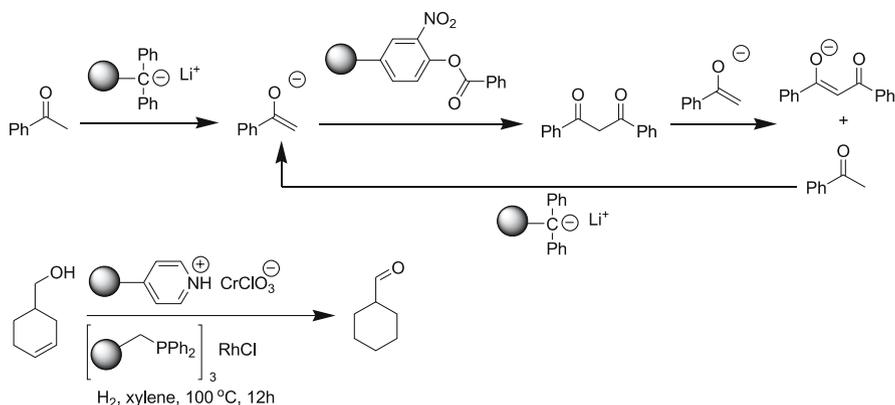
Scheme 1 Concept of the use of polymer-supported reagents

efficient preparation of smaller-sized (less than 10 000 compounds) chemical libraries. One of the main advantages of the use of polymer-supported reagents is the convenient use of an excess of reagent to drive the reaction to completion. If enough reagent is used, the variation in reactivity in an array of differently substituted substrates should be overcome, so that the library can be treated with the same reaction conditions. Subsequently, both the excess of reagent and the spent reagent can be easily removed by simple filtration. The fact that the workup can be reduced to simple filtrations and resin-washing routines is extremely important: these operations are very easily automated on relatively simple robots. Since preparation of large libraries relies heavily on automation to increase the throughput, it is obvious that this represents an essential requisite for employing these reagents in combinatorial chemistry.

It is worth noting that the use of polymer-supported scavengers offers a perfectly complementary technique to the use of PSRs, and in several cases the two have been successfully employed together [3, 9].

Compared to the other mainstream technique used for combinatorial chemistry, solid-phase organic synthesis, the use of polymer-supported reagents has a number of distinct advantages: as the substrate and product remain in solution, it is possible to follow the reaction progress with all the traditional analytical techniques (TLC, GC or GC-MS, HPLC or HPLC-MS, NMR etc.), while analysis of products which are attached to resins remains limited to few techniques, some of which require expensive and complex apparatus (e.g., gel-phase or MAS NMR, MALDI mass spectrometry), or are time consuming (cleavage off the resin of an analytical sample). Perhaps even more importantly, adaptation of literature conditions is often more straightforward from traditional solution-phase chemistry to the use of polymer-supported reagents than it is for SPOS, so that less time is spent optimizing the conditions prior to the actual library synthesis.

In 1977, Cohen described the first use of one of the most attractive features of polymer-supported reagents, namely what he described as the “wolf and lamb” principle [56]: two (or more) resins bearing mutually incompatible functionalities can be used together, as the site isolation provided by the support ensures that no reaction can occur between the various reagents. For example (Scheme 2), the lithiated solution-phase analogue (trityllithium) would not be compatible with the activated ester (in solution), but their immobilisation on insoluble support enables their simultaneous use. Furthermore, if this condensation is conducted in solution phase, the enolate has to be preformed and the yield does not exceed 50% as the product is more acidic than acetophenone itself. However, the site-isolation of the immobilised reagents allow using an excess of the lithiated resin so the acetophenone enolate can be formed and regenerated in situ, in which case dibenzoylmethane is isolated in 96% yield after workup. In another illustrative example, isolation on separate supports allows the simultaneous oxidation of an alcohol and reduction of a carbon-carbon double bond (Scheme 2) [57].



Scheme 2 Applications of the wolf-and-lamb principle

This means that several steps can be accomplished in the same pot, reducing significantly the time needed as well as the amount of work-up required.

It is important to notice that the use of polymer-supported reagents is by no means limited to applications of library generation. Recently, the Ley group published a number of total syntheses of natural products using polymer-supported reagents and/or scavengers in some or every step [8, 12–14, 18, 58–60]. These examples demonstrate first of all that polymer-supported reagents are compatible with complex structures and show the same kind of chemoselectivities exhibited by their soluble counterparts. They also illustrate that traditional chemistry can be translated to the use of these reagents. Even more importantly, they show that the advantages inherent to polymer-supported reagents (easy workups, no subsequent purifications, possibility for several steps to be accomplished together) can be useful not only to combinatorial chemists but also to the more widespread synthetic community. Perhaps the most complex natural product prepared using this strategy is epothilone C (Fig. 1) [59, 60]. The synthesis proposed by Ley comprises 29 overall steps (17 steps for the longest linear sequence) and involves only one purification by flash chromatography, to eliminate an unwanted minor diastereoisomer, in the very last step.

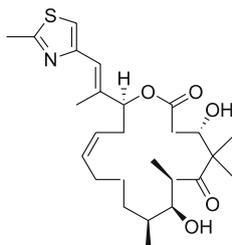
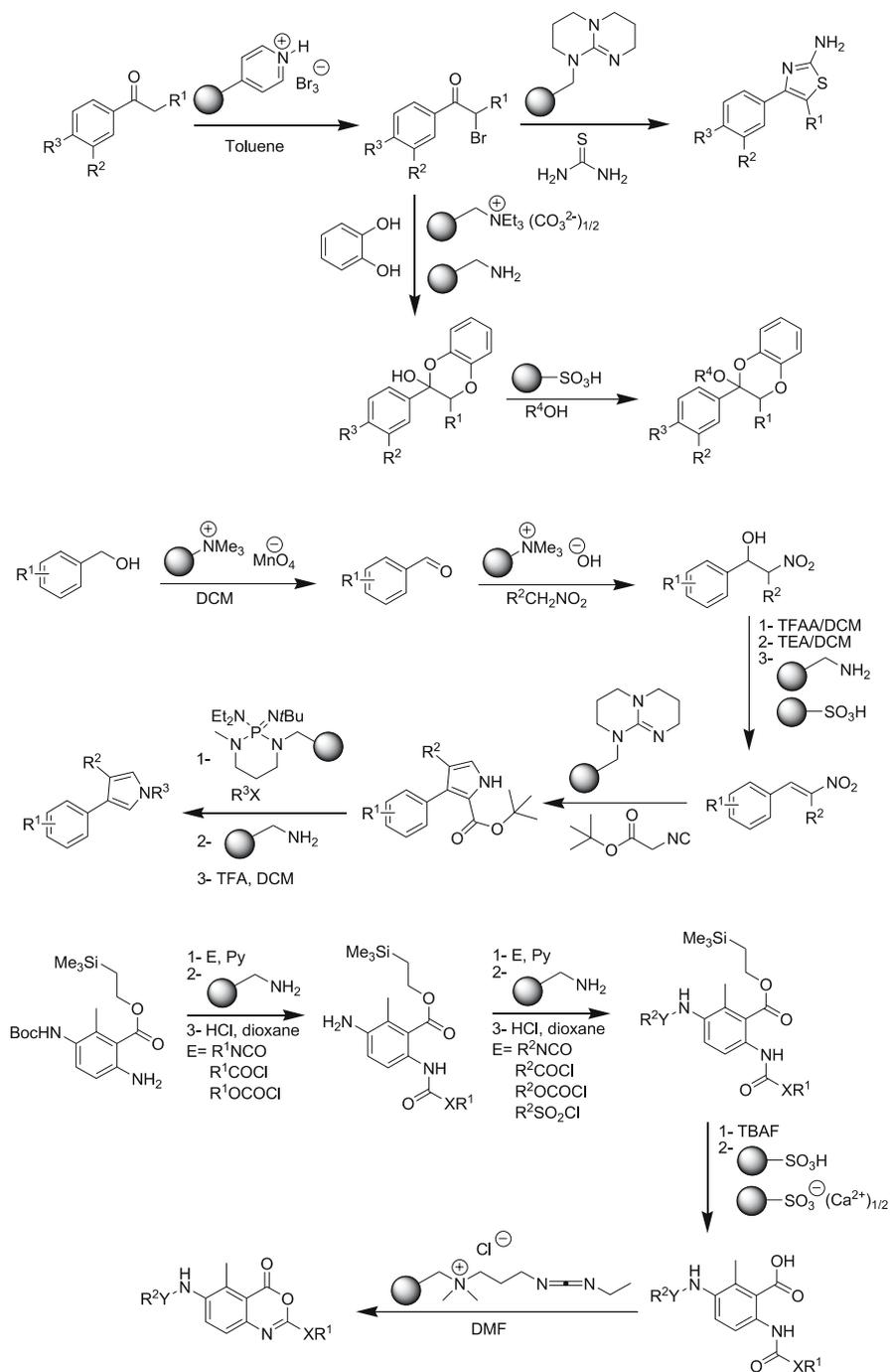


Fig. 1 Epothilone C



Scheme 3 Selected syntheses of heterocycles using polymer-supported reagents

Heterocyclic compounds are of great interest to the pharmaceutical industry, as they make up most of the known pharmacophores. As a result, a number of libraries of various heterocycles have been prepared using polymer-supported reagents. While an exhaustive list of all the heterocyclic cores that have been prepared using PSRs is beyond the scope of this chapter, some selected examples are depicted in Scheme 3.

3

Using Polymer-Supported Reagents under Microwave Irradiation

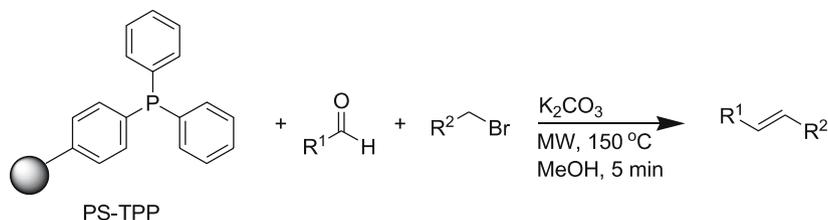
One of the undeniable drawbacks of the use of polymer-supported reagents is that the reaction kinetics are generally slower compared to traditional solution-phase chemistry. This is due to the necessity for the reactant to diffuse through the polymeric network in order to come in contact with the reagent, only at which point can the reaction take place. Therefore, when dedicated microwave equipment became available and reports describing the dramatic acceleration of organic reactions started to appear, it is hardly surprising that chemists researching the use of polymer-supported reagents became interested in the new technique.

A number of factors have to be taken into account for the integration of these two techniques (for discussions about the theory of microwave irradiation, see [33–36, 39, 41, 42, 47], in particular [49], in relation to using insoluble supports). The first question is whether the polymers used would be stable at the high temperatures achieved using microwave irradiation. In reality, most polymeric supports used in either SPOS or for PSRs (micro and macroporous polystyrene, TentaGel resins, cellulose) are stable to surprisingly high temperatures (generally up to 200 °C or even further). In addition, compared to resins heated by conventional means, the reduced reaction time significantly diminishes the risk of damage to the resins caused for example by magnetic stirring. However, other supports such as lanterns and crowns are relatively unstable at high temperature (> 160 °C), although it must be noted that these more exotic supports are mostly used for SPOS rather than for polymer-supported reagents.

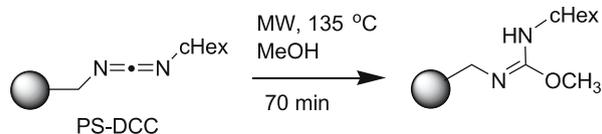
Another important aspect to be considered is the choice of the solvent. It is well known that the swelling of non-macroporous resins is heavily dependant on the solvent, so that reaction in low-swelling solvents (for example water for polystyrenic microporous resins) is prevented because the reactants cannot reach the reactive sites on the polymer. At the same time, the dielectric properties of the solvent are important for the interaction with the microwave radiation. Because of the particular heating mechanism, the presence of a solvent with a high loss tangent (related to the ability to absorb microwave energy) is important to achieve an effective conversion of radiation energy to heating. At first glance, the necessity to cater to these different require-

ments might seem a difficult task: for example, polystyrenic resins tend to swell better in low polarity solvents (for example DCM), which absorb poorly microwave radiation, than in polar solvents like methanol, which have a very good heating profile under microwave irradiation. In reality, a number of solvents, such as DMF or acetonitrile, are both high swelling for polystyrenic resins and good at absorbing microwave radiation. In addition, when a solvent which is transparent to microwave radiation must be employed, the microwave radiation can be converted to heat by adding another polar substance: either a polar co-solvent [35], an ionic liquid [61] or even a small graphite rod or a Weflon™ coated stirring bar, the latter two being the easiest to remove. Finally, it must be taken into consideration that the properties of the solvent in question might change dramatically at the high temperatures employed. In particular, the dielectric constants of solvents decrease with increasing the temperature. Probably one of the most striking examples is that of water, whose dielectric constant decreases from 78.5 at 25 °C to 20 at 300 °C, making it more similar to an organic solvent [62]. The importance of this behavior when performing reactions with polymer-supported reagents is dramatically illustrated with methanol as solvent. At room temperature this polar solvent is not capable of swelling polystyrene-based resins. However, Westman described how at high temperature it could be used as solvent for Wittig reactions involving a polystyrene-bound triphenylphosphine (Scheme 4) [63]. This property was also exploited by Linclau to develop a very simple and practical preparation of polymer-supported *O*-methyl isourea: simply suspending PS-carbodiimide (PS-DCC) in dry methanol followed by microwave irradiation cleanly gave the desired reagent (Scheme 5) [64].

The different interactions of the microwave radiation with the solvent and with the polymeric support might also cause interesting effects. Many authors



Scheme 4 Microwave-assisted Wittig reactions using polymer-supported triphenylphosphine in methanol



Scheme 5 Preparation of polymer-supported *O*-methyl isourea under microwave irradiation

have claimed the observation of so-called non-thermal effects caused by microwave irradiation [65]. While a discussion of these issues is beyond the scope of this chapter, it must be noted that working in a heterogeneous system, as is the case with PSRs [49], might give rise to observations that seem less easily explained by heating alone. For example, if a solvent which is transparent to microwaves is used in conjunction with a polymer-supported reagent with highly polar or ionic character, the temperature recorded in the bulk of the solution might be remarkably different from the local temperature within the polymer pores, where the reaction is actually taking place. This could lead to a larger than expected increase in the reaction rate if the temperature of the bulk solution is used as reference (as is with most modern dedicated microwave systems).

Finally, a problem for the integration of both SPOS and PASP with microwave irradiation is the integration of the respective hardware. As we have seen, one of the main advantages of using resins is that their handling can be easily performed by various robotic systems, with a marked increase in productivity. The integration of microwave vials, which must be able to work under considerable pressure (normally up to 20–25 bar), can become a major bottleneck. So far, only few reports have emerged into the literature concerning solutions to this particular problem, mostly for application for SPOS rather than for PASP. For multimode instruments, the use of 96-well polypropylene plates (equipped with frits for easy filtration of the resin) in household ovens has been described, although in this case the advantage of better control of the reaction conditions ensured by the more modern microwave systems is lost. Milestone is offering for its combiCHEM™ reactor system a range of 96, 48 or 24-well plates, using a proprietary microwave absorbing material (Weflon™), thus ensuring more homogeneous heating across the different plates. However, the plates are not equipped with frits so that easily automated resin filtration remains elusive. Anton Paar is also offering special vials to which a filtration unit can be connected via a screw cap for its Synthos 3000 model. For monomode microwave systems, a modification of the traditional microwave vials used for Personal Chemistry (now Biotage) systems bearing a polypropylene frit and a screw cap has been used for performing solid-phase chemistry [66], but to the best of our knowledge this product is not available for sale at the moment. For a more specialized application, CEM has put on the market a microwave system specifically adapted for peptide synthesis (CEM Liberty™).

4

Literature Survey

In this section, we will review the application of the combination of polymer-supported reagents and/or scavengers with microwave irradiation to the syn-

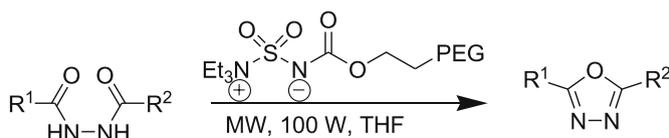
thesis of heterocycles. Particular interest will be given to those scaffolds that might be of interest because of their potential biological activities.

From a medicinal chemist's point of view, oxadiazoles are among the most important heterocycles as they are one of the most commonly used bioisosters for amide and ester groups [67]. As such it is hardly surprising that the two regioisomeric oxadiazole scaffolds received the most interest in the field of microwave-assisted synthesis using polymer-supported reagents.

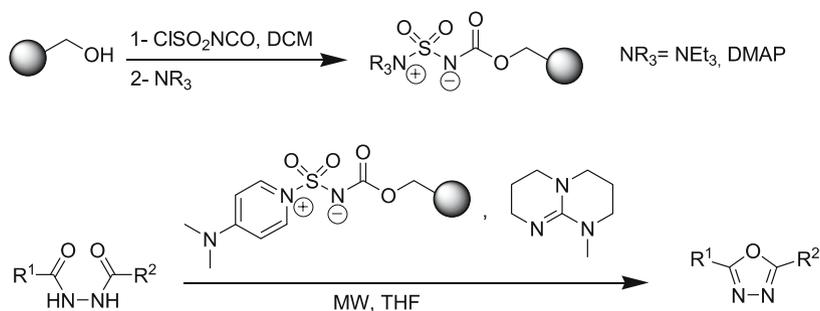
In 1999, the group of Brain in Novartis developed a novel preparation of 1,3,4-oxadiazoles, relying on the dehydration of 1,2-diacylhydrazines as the key step [68]. The intermediate 1,2-diacylhydrazines could be easily obtained by reaction of the corresponding hydrazide with an acyl chloride (to give the unsubstituted heterocycles as the final products) or with an isocyanate (to give 2-aminosubstituted oxadiazoles as the final product). In this first report, the cyclization was achieved using either soluble Burgess reagent or a Burgess reagent supported on polyethylene glycol (Scheme 6). The latter was prepared from MW750 polyethylene glycol monomethyl ether following the procedure reported by Wipf [69].

Under conventional heating, both reactions using either the traditional (1.2 equiv) or supported reagent (1.5 equiv) proceeded to ca. 40% conversion to the desired oxadiazole after 3 h. However, when the reaction with the supported reagent was repeated in a single-mode microwave reactor, the conversion was quantitative after only two min (fixed power 100 W, solvent THF). In order to remove the PEG-supported reagent, filtration on a silica plug followed by elution with ethyl acetate was found to be sufficient to afford the product in very high purity (minimum purity 89%, average 97% on 16 examples). The products were also obtained in high yields (70–96%, average 88%) and some of the most common protecting groups (benzylcarbamates, *tert*-butyldimethylsilyl and *tert*-butyl ethers) were found to be stable under the conditions used.

In 2000, the same group reported some further advances [70]. In order to facilitate work-up operations, the authors decided to change the support of the Burgess reagent from a PEG resin to a polystyrene resin. This way, the use of a silica plug would become superfluous and a simple filtration would be sufficient to remove the reagent. The required polystyrene-bound Burgess reagent was obtained by treatment of hydroxymethyl resin with chlorosulfonyl isocyanate followed by triethylamine (Scheme 7). However, this reagent failed to promote the cyclization of 1,2-dibenzoylhydrazine under either ther-



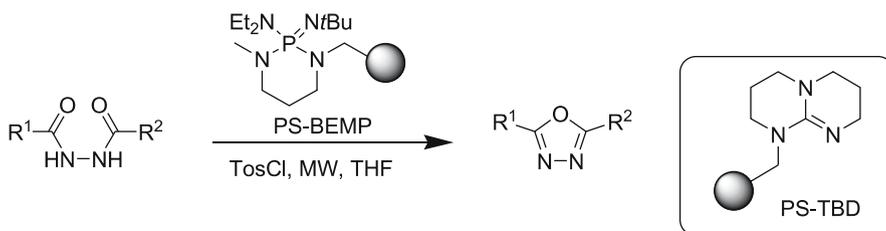
Scheme 6 Synthesis of 1,3,4-oxadiazoles using PEG-bound Burgess reagent



Scheme 7 Synthesis of 1,3,4-oxadiazoles using polystyrene-bound Burgess reagent

mal heating (refluxing THF for 18 h using 5 equiv of supported reagent) or microwave irradiation (20×1 min, 100 W). A variant of the supported Burgess reagent bearing a dimethylamino pyridine moiety was then prepared, and it proved more efficient. Although the reaction under thermal heating (reflux, THF, 18 h) gave only 20% conversion, under microwave irradiation 66% conversion could be obtained (20×1 min, 100 W) and complete conversion could be achieved when a strong guanidine base (but not a weaker base such as DIEA) was added (5×1 min, 100 W). The base and the DMAP formed during the reaction could be easily scavenged using a strong acidic ion-exchange resin (Amberlyst® 15). While this procedure gave excellent yields and purities over a range of substrates, still oxadiazoles possessing a basic site would remain trapped on the Amberlyst® resin. This being a very serious limitation, especially in view of applications in medicinal chemistry, the authors looked for an alternative strategy.

In order to activate the 1,2-diacylhydrazines towards cyclization, they were reacted with tosyl chloride (Scheme 8). While the reaction with tosyl chloride alone did not afford any of the desired product, and the cyclization in the presence of strong bases, although successful, posed the same problems of removal, excellent results were obtained in the presence of both tosyl chloride and a supported strong base, with polymer-bound BEMP giving better results than polymer-supported 1,3,4,6,7,8-hexahydro-1-methyl-2H-

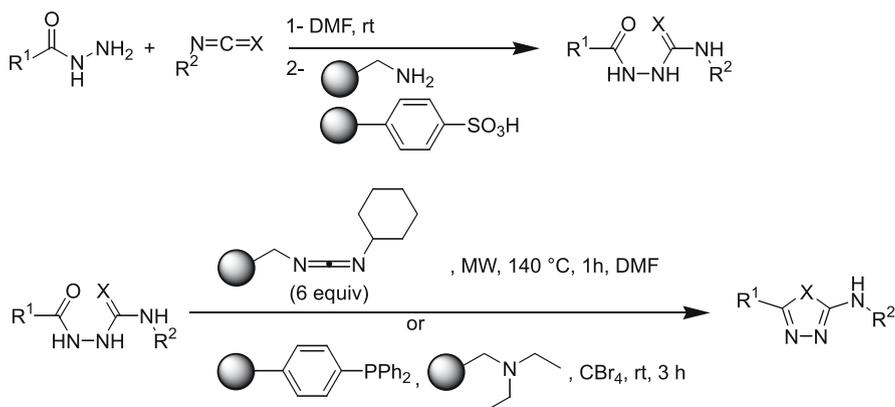


Scheme 8 Synthesis of 1,3,4-oxadiazoles using PS-BEMP and tosyl chloride

pyrimido[1,2-*a*]pyrimidine (PS-TBD). Using the combination of tosyl chloride and PS-BEMP the only work-up required was filtration of the reaction mixture followed by solvent evaporation, to give the desired products in high yields and purities (average 89%).

Recently, the Ley group has reported an alternative procedure for the synthesis of 2-amino-1,3,4-oxadiazoles [71]. First of all, a scavenging sequence involving both macroporous sulfonic acid resin and aminomethyl polystyrene was developed to give the intermediate 1,4-disubstituted semicarbazides in high purities (Scheme 9). Inspired by reports on the cyclodehydration of semicarbazides on solid-phase using carbodiimides [72, 73], the cyclization was carried out using polymer-supported carbodiimide. Even if the reaction was indeed successful under microwave irradiation (DMF, 140 °C, 1 h), the necessity to use 6 equiv of polymer-supported reagent in order for the reaction to go to completion proved to be a problem for the use in library production. As a comparison, similar results were obtained by Evans under thermal heating (80 °C, 60 h, 5 equiv of PS-DCC) [74]. However, Ley reported that better results were obtained using a combination of polymer-supported triphenylphosphine, CBr₄ and a polymer-supported base (3 h, rt) and a filtration through an amino-functionalized SPE cartridge was used to increase the purity of the products from 78–92% to > 95% (LC-MS) (Scheme 9).

The Ley group also investigated the PS-base/tosyl chloride methodology developed by Brain (see above, Scheme 8) for the synthesis of 2-aminooxadiazoles from semicarbazides, especially with a view to directly synthesize 2-aminosulfonamide substituted 1,3,4-oxadiazoles, a compound class of interest for agrochemical and pharmaceutical applications (Scheme 10) [71]. In this case, the choice of the supported base was crucial for the result of the reaction: weak bases (PS-DIEA, PS-NMM) could still afford the cyclized 2-aminooxadiazole product, but could not efficiently

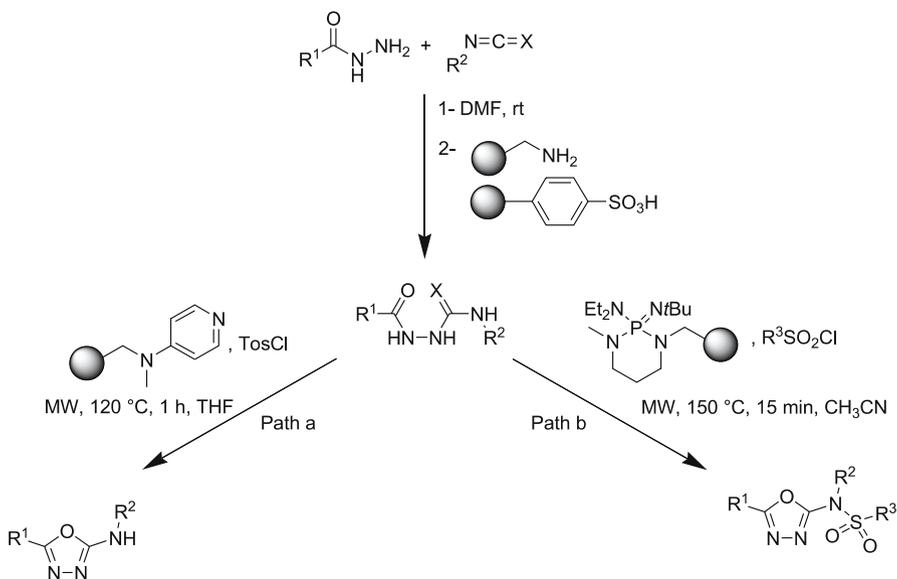


Scheme 9 Synthesis of 1,3,4-oxadiazoles from acyl hydrazines and isocyanates

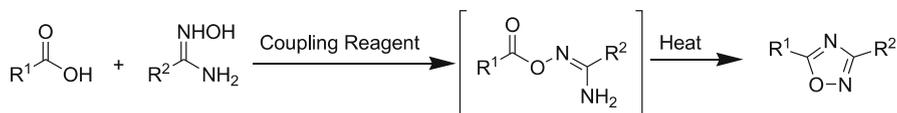
promote the sulfonamide formation (THF, 120 °C, 1 h) with mixtures of sulfonylated and free amino oxadiazoles as a result. However, polymer-supported dimethylaminopyridine could be used to form exclusively the unprotected 2-amino oxadiazoles (Scheme 10, path a), and it was used for the preparation of a 120-member library. Separation from residual starting material was efficiently achieved applying a product catch and release purification using solid-supported sulfonic acid.

Stronger bases (PS-BEMP, PS-TBD) promoted the subsequent sulfonylation to directly give the corresponding sulfonamides (Scheme 10, path b), but the reaction tended to give a variety of isomeric byproducts. However, good yields and purities of the desired isomers could be obtained using acetonitrile as solvent (150 °C, 15 min). This methodology was successfully applied for the preparation of an 850-member library. Importantly, the whole synthetic sequence (starting from acylhydrazide and isocyanates) can be performed in one pot, which greatly simplifies library production. Unfortunately, a similar cyclization protocol for thiosemicarbazides gave both the 2-amino-1,3,4-thiadiazole and the corresponding 2-amino-1,3,4-oxadiazoles in a substrate-dependant ratio [71].

In 2005, a group of researchers at Abbott turned their attention to the synthesis of a different regioisomer, the 1,2,4-oxadiazoles [75]. These heterocycles are normally prepared by reaction (mediated by a coupling reagent) of a carboxylic acid with an amidoxime, followed by base-catalyzed cyclization at high temperature (Scheme 11).



Scheme 10 Divergent synthesis of 2-amino-1,3,4-oxadiazoles and 2-sulfonamido-1,3,4-oxadiazoles

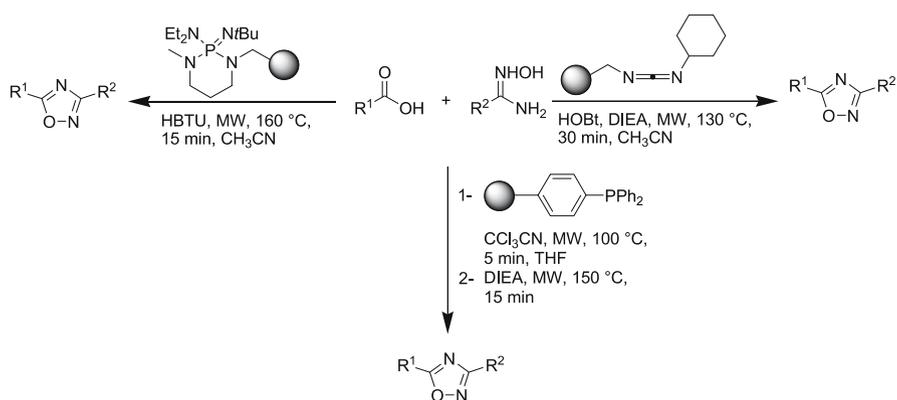


Scheme 11 General strategy for the synthesis of 1,2,4-oxadiazoles

Initially, PS-carbodiimide in the presence of HOBt and a base was used as coupling system (Scheme 12). Under microwave irradiation (CH₃CN, 130 °C, 30 min) a test reaction on (4-methylphenyl)-amidoxime was successful, giving a higher yield than the same reaction under thermal conditions (83% yield, against 66%, reaction time 30 min against 26 h). However, when an electron-poor amidoxime was employed, this coupling system proved insufficient to promote the acylation. A more efficient system was found in the combination of soluble coupling reagent HBTU and PS-BEMP (CH₃CN, 150 °C, 15 min). The best solvent for the reaction is acetonitrile, but up to 20% DMF can be added to ensure solubilisation of all building blocks (very important for parallel chemistry applications) without compromising the reaction (Scheme 12).

An alternative reported in the same publication involves the in situ conversion of the carboxylic acids to the corresponding acyl chlorides using PS-PPh₃ and CCl₃CN (THF, 10 °C, 5 min) before treatment with the amidoxime in the presence of DIEA (THF, 150 °C, 15 min). The resin-bound phosphine not interfering with the second step, and THF being the best solvent for both steps, the two-steps sequence could be performed one-pot with yields comparable to those obtained using the HBTU/PS-BEMP combination (Scheme 12).

A very interesting catch and release methodology has been developed by Porcheddu for the preparation of several interesting heterocycles [76, 77]. The



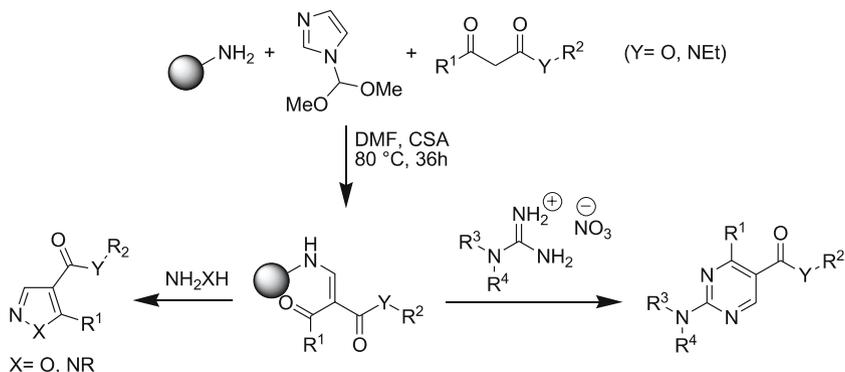
Scheme 12 Synthesis of 1,2,4-oxadiazoles from carboxylic acids and amidoximes using PS-reagents

key aspect resides in the easy preparation of resin-bound enaminones. These could be easily obtained in a one-pot process from a polymer-supported amine by reaction with formyl imidazole dimethyl acetal and a β -ketoester in the presence of CSA as catalyst (Scheme 13).

The resin-bound reagents thus obtained were reacted with a variety of nucleophiles to give different heterocycles (Scheme 13). So, reaction with hydrazine or hydroxylamine gave respectively pyrazoles and isoxazoles in excellent yields (94–99%, 34 examples) and excellent purities (> 95%). Reaction with guanidines afforded 2-aminopyrimidines.

All these reactions could be carried out under thermal heating conditions, but performed significantly better under microwave irradiation: not only were the reaction times significantly shorter, but for example the average purity for the 2-aminopyrimidine library could be increased from 88% to 98% just by switching from thermal heating to microwave irradiation, all other conditions being unchanged. It must be noted that, since the first step of the synthesis initially involves the in situ conversion of the dimethyl acetal moiety into the corresponding aldehyde, this step was carried out in an open vessel microwave apparatus to allow the removal of the methanol thus formed, while the second step could be carried out in a closed-vessel system, allowing for more flexibility in the choice of temperature.

As for the solid support, several polymer-supported amines were tested (Fig. 2). For either the pyrazole and isoxazole synthesis, the best results were given by aniline-functionalized cellulose, which has also the advantage of a relatively low cost. For the 2-aminopyrimidine library, polystyrene-based piperazine and piperidine gave products with a much higher purity compared with other secondary non-cyclic or primary amines. In both cases, the resins could be reused for up to four times before degradation in their behavior was observed. This reusability could be further enhanced (up to 10 cycles for cellulose-based aniline) when the microwave-assisted protocols were used.



Scheme 13 Divergent catch-and-release synthesis of heterocycles

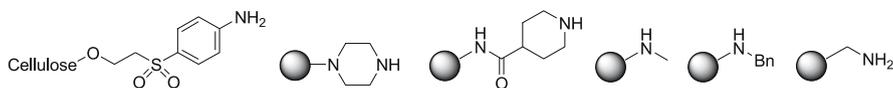
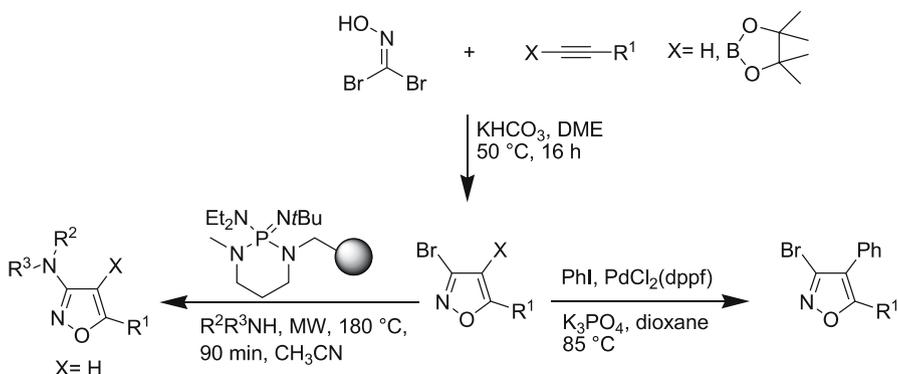


Fig. 2 Various polymer-supported bases used in the catch-and-release synthesis of pyrazoles, isoxazoles and 2-aminopyrimidines

Another approach for the parallel synthesis of isoxazoles has been described by Harrity [78]. The isoxazole core was assembled via a 1,3-dipolar cycloaddition between bromonitrile oxide (generated in situ) with alkynes or alkynyl boronates (Scheme 14). To introduce further diversity, the boronic ester moiety could be easily transformed via Suzuki reaction, but substitution of the bromine atom by different amines proved to be much more difficult. Eventually, the best conditions to perform this surprisingly difficult conversion were identified in the use of polymer-supported BEMP in conjunction with microwave irradiation (MeCN, 200 °C, 15 min). It is interesting to note that in this case the use of the polymer-supported reagent led to better yields compared to the soluble analogue (average yield 47% vs. 33%). As the mass balance that could be recovered after chromatography consisted of unreacted bromoisoxazole, the superior performance of the supported reagent compared to the soluble one cannot be attributed to lack of side reactions as is most common for such cases reported in the literature. On the other hand, under microwave irradiation, polymer-supported BEMP proved to be stable at higher temperatures compared to traditional BEMP, which started to cause unacceptable increases in pressure when heated at over 180 °C, so that the reactions of the former could be performed at higher temperatures (200 °C), leading to better conversions.

2-Oxazolines represent another very interesting scaffold for medicinal chemistry applications, since several molecules possessing this substructure show interesting biological activities [79–81]. As a result, considerable attention has been dedicated to the synthesis of these heterocycles.

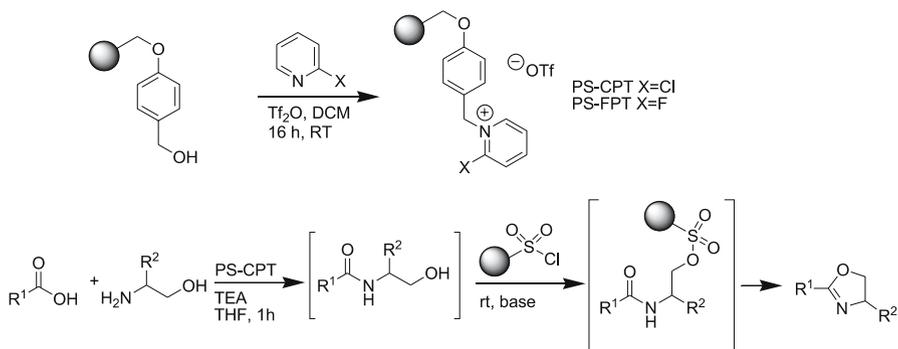


Scheme 14 Synthesis of 3-aminoisoxazoles

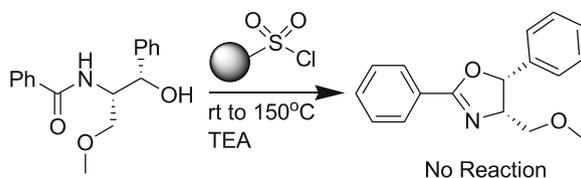
The most popular strategy relies on the preparation of the corresponding β -hydroxyamides, which can be cyclized using a variety of reagents [69, 82–84]. In 2000, Pirrung described an interesting catch and release method for the preparation of libraries of 2-oxazolines using polymer-supported reagents [85, 86]: the intermediate hydroxyamides, prepared by reaction of an aminoalcohol with an acyl chloride at 0 °C, were loaded on a sulfonyl chloride resin, and the polymer-supported intermediate sulfonates were washed to remove any impurities, before the final cyclization released the desired oxazolines in moderate yield (average yield 52%) but excellent purities (average purity 94%). More recently, Crosignani showed that, when the hydroxyamide was formed by reaction of the aminoalcohol with a carboxylic acid in the presence of a polymer-supported Mukaiyama reagent (polymer-supported 2-chloropyridinium triflate, PS-CPT) [87], the isolation of the polymer-supported tosylate intermediate was not necessary, and the whole sequence could be carried out in one-pot, giving the desired products in better yield (average yield 88%), without loss of purity (average purity 93%) (Scheme 15) [88].

A major limitation still remained in this methodology: cyclization of hydroxyamides substituted α to the hydroxy group could not be achieved except when the substituent was a mere methyl group, as anything bulkier would prevent the tosylation step. In this case, using microwave irradiation to force the reaction (Scheme 16) did not prove sufficient, and even after prolonged microwave irradiation at 150 °C no trace of the desired material could be observed.

Using a more reactive polymer-supported reagent (polymer-supported-2-fluoropyridinium triflate, PS-FPT) gave the desired product, but the reaction at room temperature was very slow and complete conversions could rarely be observed, which of course represents a serious limitation as the unreacted hydroxyamide would need to be removed in order to obtain the products in high



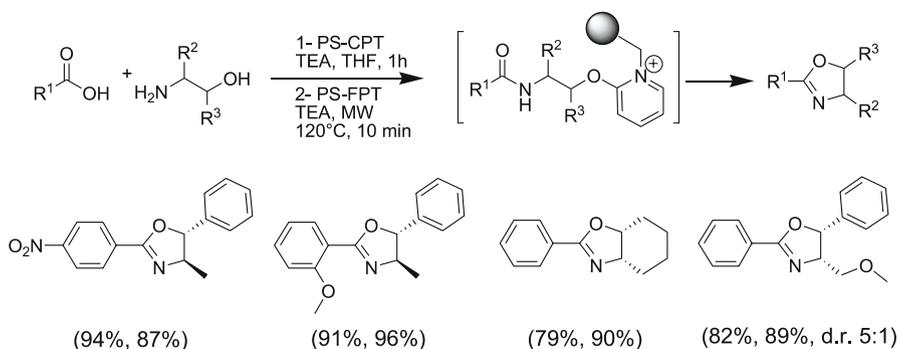
Scheme 15 Parallel synthesis of 2-oxazolines from carboxylic acids and aminoalcohols using PS-Mukaiyama reagent



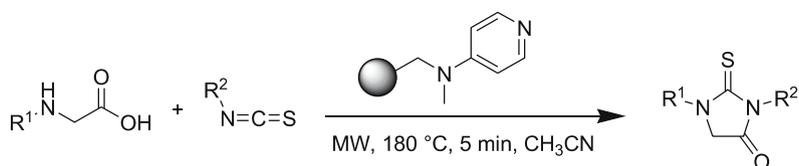
Scheme 16 Failed attempts for the synthesis of 5-substituted 2-oxazolines

purity. The ideal combination proved to be the use of the 2-fluoropyridinium resin in combination of microwave irradiation (Scheme 17) [88]. In this case, reactions were complete within 10 min at 120 °C, giving products in high yield and purity. In addition, the reaction proved to be remarkably stereoselective, giving in most cases exclusively the product with inversion of configuration at position 5 of the oxazoline. Only in one case, when reaction by an S_N1 mechanism was rendered possible by presence of a phenyl group α to the hydroxy group, was some quantity of the unwanted diastereoisomer observed (d.r. 5 : 1). In this case, performing the reaction under thermal heating or at room temperature led to an increase in the diastereomeric ratio (from 5 : 1 to 97 : 3), albeit at the expense of reaction time.

A study describing the parallel synthesis of thiohydantoins using microwave irradiation was published by Westman in 2001 [89]. The key step involves the reaction of *N*-substituted aminoacids and thioisocyanates in the presence of base (Scheme 18). The reaction could be performed either in the presence of a conventional base (TEA using DCE as solvent) or a polymer-supported base (PS-DMAP using acetonitrile as solvent). In both cases, the reactions could be performed in just 5 min. Similar isolated yields were observed using either method (average yield 76% for both), but the reactions run in the presence of the polymer-supported base were reported to be generally cleaner, making the subsequent purification step significantly easier.



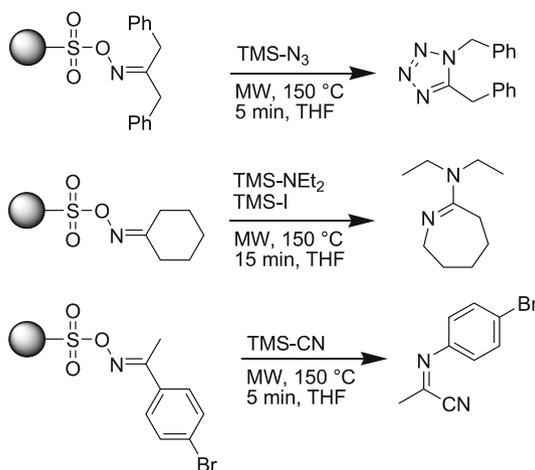
Scheme 17 Modified synthesis of 5-substituted-2-oxazolines



Scheme 18 Synthesis of thiohydantoin using PS-DMAP

The *N*-substituted amino acids required could be prepared by microwave-assisted reductive amination of amino acid methyl esters with aldehydes, and although in the Westman report soluble $\text{NaBH}(\text{OAc})_3$ was used to perform this step, other reports have shown how this transformation can be performed in using polymer-supported borohydrides (such as polymer-supported cyanoborohydride) under microwave irradiation [90]. An additional point of diversity could be inserted by use of a palladium-catalyzed reaction if suitably substituted aldehydes had been used. Again, these transformations might eventually be accomplished using supported palladium catalysts under microwave irradiation, as reported by several groups [91–93].

A catch and release synthesis of tetrazoles and cyclic amidines has been reported making use of solid-supported oximes [94]. When bound sulfonyloximes, obtained by reacting polymer supported sulfonyl chloride with oximes, were reacted with nucleophiles, tetrazoles or cyclic amidines were obtained (Scheme 19). Alternatively, the use of TMS-CN affords imino nitriles, which have been used as intermediates for the preparation of indoles, 1,2,3,4-tetrahydropyridines, quinoxalines and benzimidazoles.

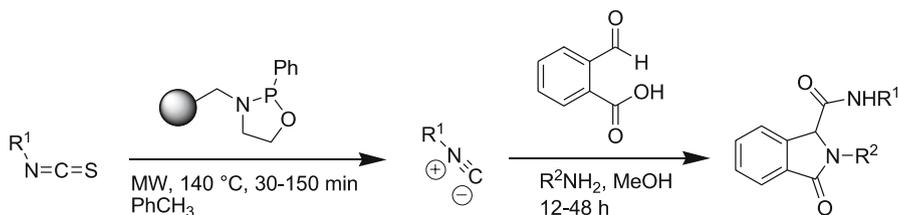


Scheme 19 Synthesis of different heterocycles from resin-bound intermediate sulfonyloximes

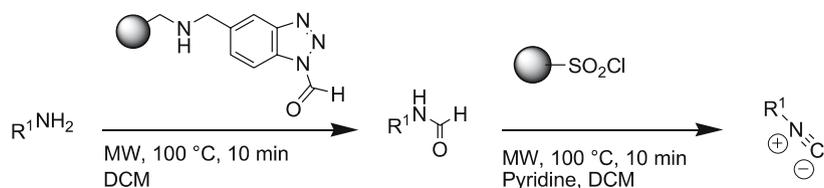
Over the last two decades, multicomponent reactions (MCRs) have emerged as a very powerful tool for the rapid generation of combinatorial libraries [95]. In particular, the Ugi [96] and Passerini [97] reactions and their more recent variants have proved to be very popular. For all these reactions, an indispensable ingredient is the presence of isocyanides, because of the very specific reactivity of these molecules capable of acting as both a nucleophile and an electrophile [98]. However, to this day only a limited number of isocyanides are commercially available, especially if confronted with the other reaction partners (carboxylic acids, aldehydes and amines for the Ugi reaction). This represents a serious limitation for the diversity of the libraries generated using this approach. As such, considerable effort has been recently put into finding ways to prepare these intermediates in a reliable, parallel chemistry friendly way. In this respect, the use of polymer-supported reagents would be of great utility, considering that the high reactivity of the isocyanides renders their purification troublesome.

The first approach towards this goal was reported by Ley [99]. A novel polymer-supported (1,3,2)-oxazaphospholidine was prepared in two steps from Merrifield resin, via reaction with aminoethanol followed by treatment with bis(diethylamino)phenyl phosphine at high temperature. The reagent was subsequently tested for the ability to convert isothiocyanates to isocyanides (Scheme 20). Under thermal heating, the desired reaction took indeed place, however the products were contaminated with the corresponding nitriles, resulting from a rearrangement process taking place during the prolonged heating required. By comparison, when the reactions were performed under microwave irradiation, not only could the reaction time be cut down by more than 40 times, but the products were obtained in very high purities (78–100%, average 95%) after a simple filtration operation. The building blocks obtained were directly used, without any further purification, for the preparation of a library of 2-isoinidolinone-7-carboxamides (yields 72–98%).

An alternative approach towards the PASP synthesis of isocyanides was developed by Bradley [100, 101]. It involved the use of a polymer-supported sulfonyl chloride in the presence of base to afford the dehydration of formamides (Scheme 21). The formamides required could be easily prepared by reaction of the corresponding amines with a formylated benzotriazole resin. Opti-



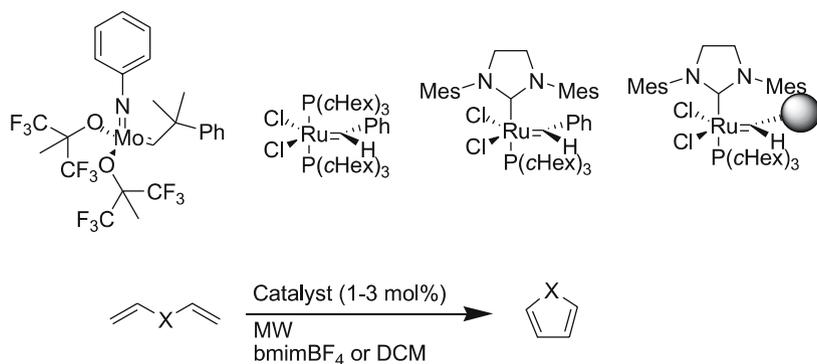
Scheme 20 Preparation of isocyanides using PS-oxazaphospholidine and their subsequent use in Ugi reaction to give substituted isoindolinones



Scheme 21 Synthesis of isocyanides from amines using PS-reagents

mization studies revealed that under microwave irradiation three equiv of the polymer-supported sulfonyl chloride were sufficient to drive the reaction to completion, while 50 equiv of pyridine were required. Of the six examples reported, only one resulted in a low purity of the desired isocyanide, probably because of high steric hindrance. In addition, the polymer-supported reagent could be readily regenerated by treatment with PCl_5 in DMF.

Among the different strategies available to synthetic chemists for the preparation of ring systems, ring-closing metathesis (RCM) has emerged as one of the most versatile, in particular because it can give access to both small and medium sized rings, as well as macrocycles [102–105]. Of the different catalysts available to achieve this important transformation, second-generation Grubbs catalysts have found the most use, thanks to their superior stability and tolerance to functional groups. In 2002, Kiddle reported the results of his investigations on the influence of microwave irradiation on RCM reactions (Scheme 22) [106]. Molybdenum-based catalysts, first and second generation Grubbs catalysts as well as a polymer-supported version of a second generation Grubbs catalyst were investigated, either using ionic liquids or DCM as solvent. This work shows clearly that the reaction is much accelerated under microwave irradiation, compared to thermal heating. Very interestingly, when DCM was used as a solvent, it was claimed that the internal temperature of



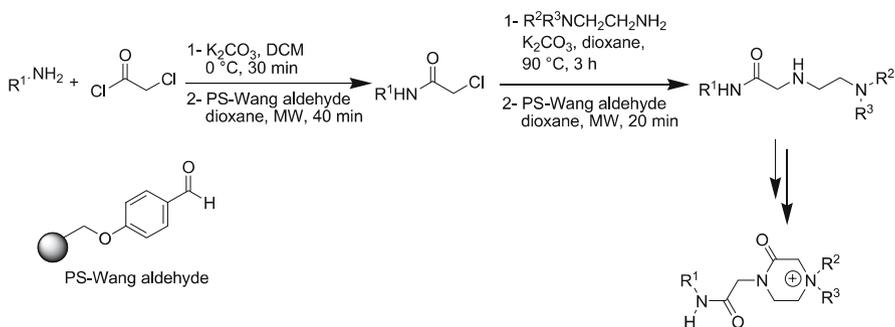
Scheme 22 Comparison between various catalysts for the RCM of 5-membered heterocycles

each vessel did not exceed 33 °C, but the reaction times were still significantly shorter than in the corresponding thermal reactions.

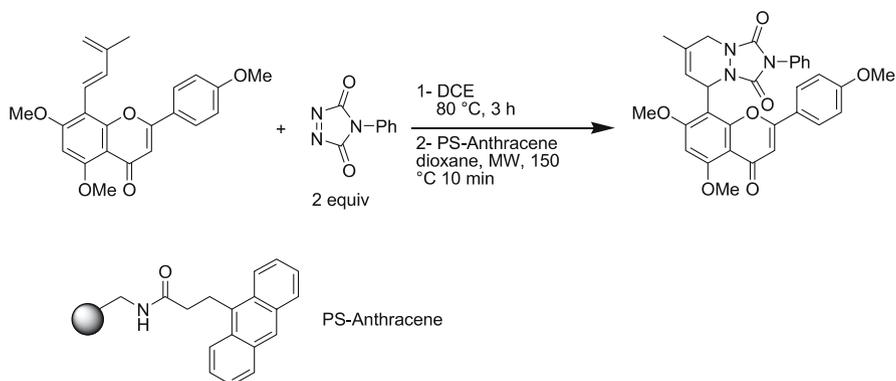
Starting from the appropriate diallyl amines or ethers, 4,5-dihydropyrroles and 4,5-dihydrofurans could be obtained in good yields in a matter of minutes.

Not unexpectedly, comparing the soluble catalysts to the polymer-bound analogue, the latter was found to be less reactive, with a 40% conversion after 60 s rather than the 100% conversion observed with conventional Grubbs catalyst (fixed power, 110 W, solvent bmimBF₄). This is in accordance to the behavior observed by Grubbs in the absence of microwave irradiation [107]. However, it must be noted that no attempt at optimizing the conversion for the polymer-supported reagent was reported, and it could be possible that a slightly longer reaction time or higher catalyst loading would give a more satisfactory conversion. Also, the eventual reusability of the supported catalyst was not investigated, something which could be of great importance considering the relatively high cost of these type of catalysts.

As we have seen in the introduction, an approach which is similar and complementary to the use of polymer-supported reagents is the use of polymer-supported scavengers. The main disadvantage of the latter technique is that, even after the desired conversion has been achieved, time must be allowed for the scavenger resin to sequester all the excess reagent, so that the overall time required in order to obtain the products is considerably lengthened. In some cases, the time required for the scavenging is considerably longer than the time needed for the reaction itself. It is therefore hardly surprising that several groups have started to employ microwave irradiation to accelerate not only the synthetic steps, but also the scavenging step. An interesting example has been reported by Messeguer for the preparation of a library of 3-oxopiperazinium salts (Scheme 23) [108]. The key steps for the preparation of the library involved reactions with a range of amines with first an acyl chloride and then with an aliphatic chloride, but in both cases an ex-



Scheme 23 Preparation of a library of 3-oxopiperazinium salts using microwave-assisted scavenging of excess amines



Scheme 24 Use of PS-anthracene to scavenge excess of dienophiles after a hetero Diels–Alder reaction

cess of amine had to be used. The excess of amine had to be removed, but reaction with a Wang aldehyde resin required 24 h at 40–50 °C to achieve products in good purity. However, the same scavenging operation could be satisfactorily carried out within a maximum of 40 min (cycles of 4 min at 350 W followed by 1 minute intervals).

Another interesting scavenger is polymer-supported anthracene, developed by Porco for the scavenging of dienophiles [109]. An example of its application to the synthesis of a complex 5,8-dihydro-(1,2,4)triazolo[1,2-a]pyridazine-1,3-diones via hetero-Diels–Alder reaction followed by removal of the excess of triazole-3,5-dione under microwave irradiation is depicted in Scheme 24. For this particular example, moving from thermal heating (toluene, 100 °C) to a microwave-assisted protocol (DCE, 150 °C) reduced scavenging time from 3 h to just 15 min.

5 Concluding Remarks

Both PASP and MAOS are by now recognized as powerful tools by synthetic chemists. The use of both techniques together is somewhat newer and has not yet reached widespread use, as the relatively small number of publications testifies. However, we feel that the examples presented clearly demonstrate how powerful this combination can be, in particular if we keep in mind how complementary these tools are, one simplifying work-up and purification procedures while the other one decreases the reaction time. Considering the ever-increasing interest in the pharmaceutical industry for focused, medium-sized, high purity combinatorial libraries, this combination should attract more and more interest from both academic and industrial laboratories. At the same time, the need to increase productivity should bring synthetic and

medicinal chemists to embrace techniques so far considered exclusive to combinatorial chemistry: as demonstrated by Ley, the combination of PASP and MAOS can bring big advantages even in the area of total synthesis. As such, we believe that such tools will gradually become an essential part of the arsenal of all organic chemists.

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Transition-Metal-Based Carbon–Carbon and Carbon–Heteroatom Bond Formation for the Synthesis and Decoration of Heterocycles

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1	Introduction	156
2	Cross-Coupling Reactions	157
2.1	Negishi Reaction	157
2.2	Stille Reaction	159
2.3	Suzuki–Miyaura Reaction	164
3	Sonogashira–Hagihara Reaction	182
4	Cyanation Reaction	189
5	Heck–Mizoroki Reaction	194
6	Buchwald–Hartwig Reaction	200
7	Goldberg Reaction	205
8	Ullmann Reaction	206
9	Pd-Catalyzed C–S Bond Formation	207
10	Cu-Mediated C–S Bond Formation	207
11	Conclusion	208
	References	208

Abstract A literature overview, up to the end of 2004, of the most important microwave-assisted transition-metal-mediated processes used for the decoration and construction of heterocycles is presented. The emphasis of the chapter lies in the use of palladium-assisted reactions but examples of copper- and nickel-mediated processes are also incorporated.

Keywords Copper · MAOS (Microwave assisted organic synthesis) · Nickel · Palladium · Transition-metal-mediated bond formation

Abbreviations

BARF tetra[3,5-bis(trifluoromethyl)phenyl]borate
BINAP 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl
BOC *t*-butoxycarbonyl

Cbz	benzyloxycarbonyl
DCE	1,2-dichloroethane
DCPAB	2-(dicyclohexylphosphanyl)-2'-(<i>N,N</i> -dimethylamino)biphenyl
DCPB	2-(dicyclohexylphosphanyl)biphenyl
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
dmphen	2,9-dimethyl-1,10-phenanthroline
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphanyl)ferrocene
DTPB	2-(di- <i>t</i> -butylphosphanyl)biphenyl
NIS	<i>N</i> -iodosuccinimide
NMM	<i>N</i> -methylmorpholine
NMP	<i>N</i> -methylpyrrolidinone
Ms	methanesulfonyl or mesyl
phen	1,10-phenanthroline
PPFA	<i>N,N</i> -dimethyl-1-[2-(diphenylphosphanyl)ferrocenyl]ethylamine
SPE	solid-phase extraction
SPOS	solid-phase organic synthesis
TBAB	tetrabutylammonium bromide
TBDPS	<i>t</i> -butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

1

Introduction

Transition-metal-catalyzed carbon–carbon and carbon–heteroatom bond formations have caused a real revolution in organic syntheses in the past decades [1–6]. A major part of the research in this highly important area has been devoted to palladium catalysis. Although Heck–Mizoroki [7, 8], Sonogashira–Hagihara [9], Suzuki–Miyaura [10], Stille [11, 12], and Buchwald–Hartwig [13, 14] reactions are now widely known and used, most chemists are unfamiliar with the fact that “modern” palladium-catalyzed synthetic chemistry began in 1960 with the ingenious invention of the Wacker process. Remarkably, palladium-mediated reactions were initially mainly used for the decoration of carbocyclic arenes, while its true economical relevant potential—as evidenced by the occurrence of heteroaromatic skeletons in numerous currently used drugs and agrochemicals—are undoubtedly heteroaromatic scaffolds. The broad functional group tolerance and variety of functional groups that can be created using this methodology make it a preferred tool in pharmaceutical and agrochemical discovery programs. The use of (pseudo)halogenated or metallated azines, 1*H*-imidazole, oxazole, thiazole, and diazines is certainly not self-evident, since these have to be considered as potential ligands for the metal causing possible catalyst deactivation. One major drawback currently remaining is the fact that standard reaction times

typically range from hours to a day. It is at this point that microwave irradiation can play a crucial role in the near future [15–19]. Although the use of transition metal catalysis in combination with microwave irradiation has been studied rather intensively during the past several years, the use of heteroaromatic coupling partners is remarkably underexplored. The current availability of thermally stable catalysts and dedicated microwave equipment will allow for the rapid creation of chemical diversity based on heteroaromatic scaffolds. Moreover, if flash heating by microwaves can be combined with high-speed purification techniques, it will be the method of choice for the creation of heterocyclic libraries. This chapter reviews the most important available literature up to the end of 2004 on the decoration and construction of heterocycles using a combination of transition-metal catalysis (homogeneous and heterogeneous) and microwave irradiation. This overview will mainly focus on palladium catalysis, although available examples of nickel- and copper-mediated processes are also included. Inspired by recent changes in ACS (American Chemical Society) guidelines, only literature examples making use of dedicated microwave equipment are incorporated.

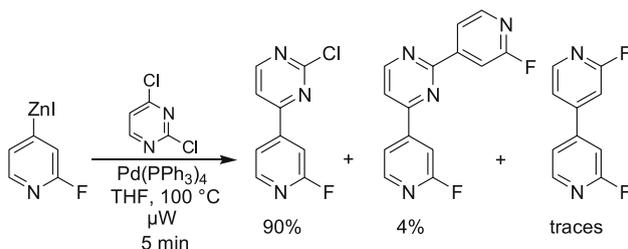
2

Cross-Coupling Reactions

2.1

Negishi Reaction

In 2003 Stanetty et al. published the use of (2-fluoropyridin-4-yl)zinc iodide in a microwave-assisted Negishi reaction [20]. The substrate 2,4-dichloropyrimidine could be regioselectively functionalized in the 4-position when one equivalent of the organometallic coupling partner was used at 100 °C in THF using $\text{Pd}(\text{PPh}_3)_4$ as the catalyst (Scheme 1). In only 5 min the conversion of starting material was completed, yielding a product of 90% 2-chloro-4-(2-fluoropyridin-4-yl)pyrimidine and 4% 2,4-bis(2-fluoropyridin-4-yl)pyrimidine. When a higher reaction temperature was selected, a larger amount of undesired 2,4-bis(2-fluoropyridin-4-yl)pyrimidine was formed



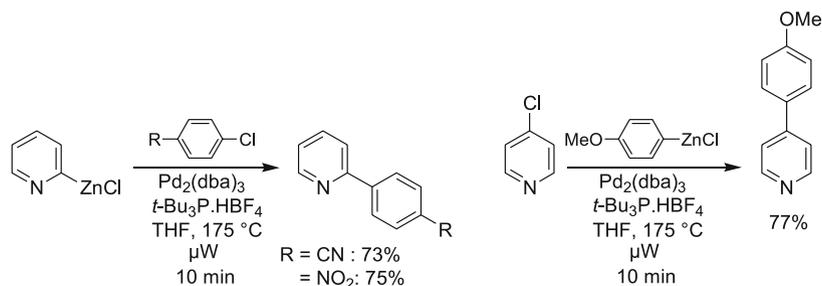
Scheme 1

in the same reaction time. As expected, a combination of a large excess (2.67 equiv) of (2-fluoropyridin-4-yl)zinc iodide and a higher reaction temperature (130 °C) yielded diarylated pyrimidine as the major reaction product (84%). Homo-coupling of the organometallic compound was also an important process under these conditions. Interestingly, the formation of the diarylated pyrimidine was not observed under thermal conditions (reflux), even when an excess of organozinc iodide (1.33 equiv) was used, but a reaction time of 240 min was required to get complete conversion of the starting material. Test reactions under microwave irradiation with the corresponding organozinc chloride revealed substantial amounts of 2,2'-difluoro-4,4'-bipyridine even with 1 equiv of organometallic compound at 100 °C. This poor result can be attributed to the inhomogeneous mixture of (2-fluoropyridin-4-yl)zinc chloride, leading to difficulties in reagent addition. Attempts to use Pd/C as a catalyst were disappointing, since a poor conversion and a low yield of the desired 2-chloro-4-(2-fluoropyridin-4-yl)pyrimidine were obtained. The major compound isolated was 2,2'-difluoro-4,4'-bipyridine.

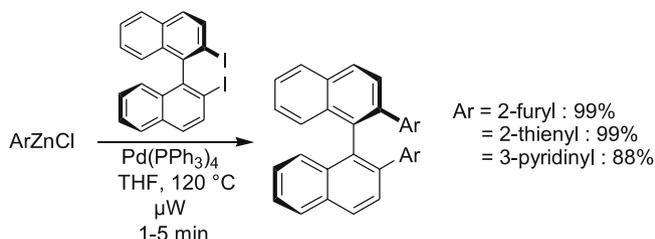
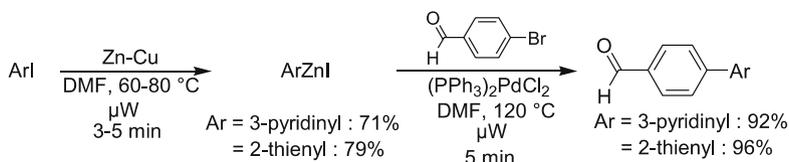
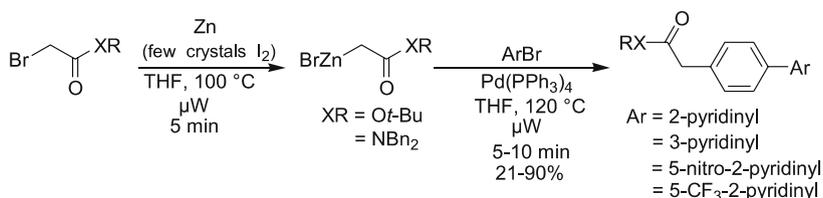
Similarly, Kappe and Walla showed that (2-pyridinyl)zinc chloride can be quickly cross-coupled with electron-deficient aryl chlorides using $\text{Pd}_2(\text{dba})_3/t\text{-Bu}_3\text{P.HBF}_4$ as a precatalyst in THF at 175 °C for 10 min (Scheme 2) [21]. In a reverse approach, 4-chloropyridine rapidly reacted with (4-methoxyphenyl)zinc chloride (Scheme 2).

2,2'-Diheteroaryl-1,1'-binaphthyls were prepared from 2,2'-diiodo-1,1'-binaphthyl via microwave assisted cross-coupling by Putala and Kappe using several heteroarylzinc chlorides: (2-thienyl)zinc chloride, (2-furyl)zinc chloride, and (3-pyridinyl)zinc chloride (Scheme 3) [22]. Importantly, no racemization occurred at the reaction temperature used, giving access to (*R*)-2,2'-diheteroaryl-1,1'-binaphthyls starting from (*R*)-2,2'-diiodo-1,1'-binaphthyl in excellent yields in 1 to 5 min of microwave irradiation.

Recently, the required heteroaromatic organozinc halides for the Negishi reaction have also been prepared using microwave irradiation [23]. Suna reported that a Zn – Cu couple (activated Zn), prepared using a slightly modified LeGoff procedure from Zn dust and cupric acetate monohydrate, allowed the smooth preparation of (3-pyridinyl)zinc iodide and (2-thienyl)zinc iodide



Scheme 2

**Scheme 3****Scheme 4****Scheme 5**

at 60 to 80 °C in DMF in 3 to 5 min (Scheme 4). The obtained heteroarylzinc iodide solutions have subsequently been coupled with 4-bromobenzaldehyde using (PPh₃)₂PdCl₂ as a precatalyst (Scheme 4).

Alkylzinc halides have also been prepared under microwave irradiation. The Reformatsky reagents (2-*t*-butoxy-2-oxoethyl)zinc bromide and [(2-dibenzylamino)-2-oxoethyl]zinc bromide were synthesized from the corresponding bromides via reaction with zinc in THF (Scheme 5) [24]. The oxidative addition was executed at 100 °C in 5 min. The obtained reagents were subsequently used in Negishi reactions on 2-bromopyridine, 3-bromopyridine, 2-bromo-5-nitropyridine, and 2-bromo-5-trifluoromethylpyridine using Pd(PPh₃)₄ as a catalyst (Scheme 5).

2.2

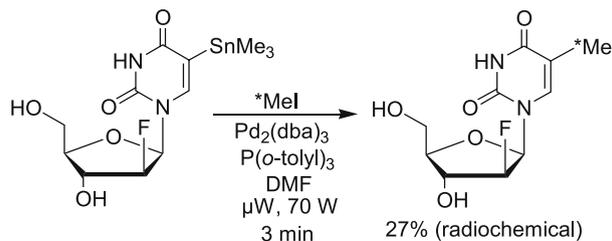
Stille Reaction

In 2003 Långström and Samuelsson described the synthesis of a radiopharmaceutical for PET (positron emission tomography) using a microwave-assisted Stille reaction [25]. 1-(2'-Deoxy-2'-fluoro-β-D-arabinofuranosyl)-

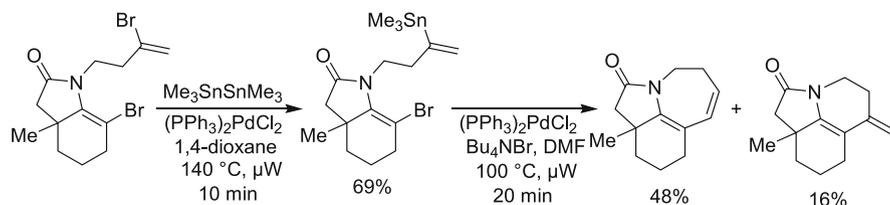
[Methyl- ^{11}C]thymine ([^{11}C]FMAU) could be obtained in modest radiochemical yields via cross-coupling of [^{11}C]methyl iodide with 1-(2'-deoxy-2'-fluoro- β -D-arabinofuranosyl)-5-(trimethylstannyl)uracil. Optimal power was found to be 70 W, since an increase to 100 W as well as a decrease to 50 W resulted in lower radiochemical yields (Scheme 6).

In the frame of a project dealing with the development of synthetic strategies for the construction of the D-ring of the pentacyclic alkaloid spgazzinidine, Padwa et al. used MAOS [26]. 7-Bromo-3a-methyl-1-(3-trimethylstannylbut-3-enyl)-1,3,3a,4,5,6-hexahydro-indol-2-one could be prepared from 7-bromo-1-(3-bromobut-3-enyl)-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one via a chemoselective Stille reaction using hexamethylditin as the transmetalating agent (Scheme 7). Microwave irradiation was also used for the subsequent intramolecular Stille reaction of the stannane yielding a mixture of a six- and seven-membered ring diene (Scheme 7).

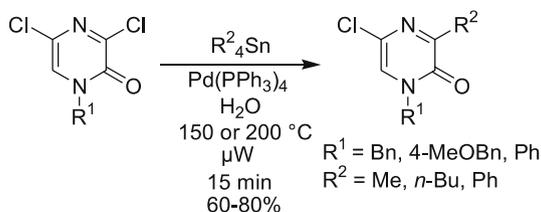
The *N*-substituted 3,5-dichloropyrazin-2(1*H*)-one scaffold has been smoothly decorated in the C-3 position by Van der Eycken et al. using chemoselective Stille reactions [27]. Aryl as well as alkyl groups can be transmetalated in just 5 min of irradiation when DMF is used as a solvent at 150 °C. The yields are similar to those obtained in refluxing toluene for 3 days under classical heating. Interestingly, water can also be used as the solvent (Scheme 8). Although the pyrazin-2(1*H*)-one substrates, R_4Sn as well as the catalyst $\text{Pd}(\text{PPh}_3)_4$ have only a very low solubility or are completely insoluble in water at low temperature, they smoothly dissolve at higher temperatures, allowing a complete conversion of substrate in only 15 min. For tetraalkylstannanes, 150 °C was sufficient, while tetraphenylstannane required 200 °C.



Scheme 6



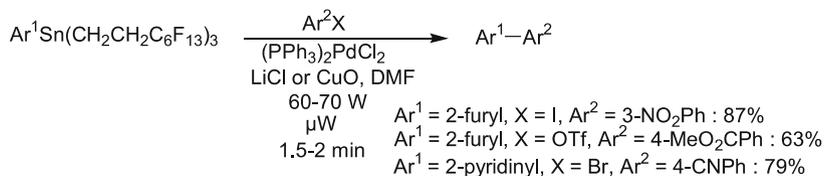
Scheme 7

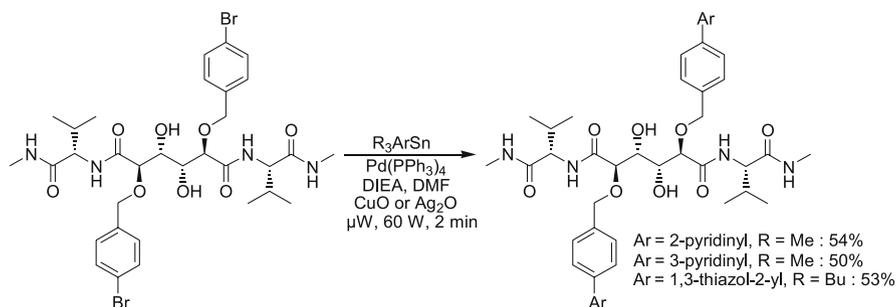
**Scheme 8**

Fluorous Stille reactions usually require long reaction times (typically about one day at 80 °C) [28]. The use of single-mode microwave irradiation allowed for a serious reduction of these reaction times to the order of a few minutes (Scheme 9). Interestingly, a higher Stille product-to-homocoupled biaryl (stannane) ratio was observed under microwave irradiation. Presumably, this originates from a predominance of Stille cross-coupling as compared to the competing homo-coupling at high reaction temperatures. Significantly, the microwave variant of the fluorous Stille reaction allows one to combine the ease of separation and the simple work-up associated with the fluorous stannane reactant with the rapid reactions related to microwave irradiation.

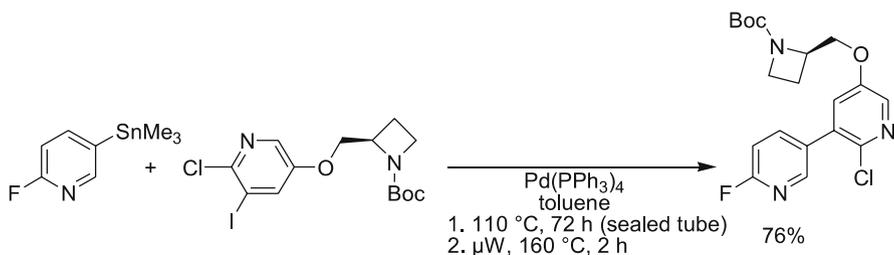
(2*R*,3*R*,4*R*,5*R*)-2,5-bis(benzyloxy)-3,4-dihydroxy-*N,N'*-bis{(1*S*)-2-methyl-1-[(methylamino)carbonyl]propyl}hexanediamide is a C_2 -symmetric HIV-1 protease inhibitor [29]. Derivatization in the *para* positions of the benzyloxy groups via microwave-assisted Stille reaction on the corresponding dibrominated inhibitor smoothly yielded the desired heteroarylated derivatives (Scheme 10). Interestingly, the 1,3-thiazole derivative showed a higher antiviral activity on the wild type virus than the lead compound. The activity remained at the same level in the presence of serum. Unfortunately, a low activity was observed on mutants.

In their search for new ligands with a very high binding affinity for the nicotinic acetylcholine receptor (nAChR), potentially useful in positron emission tomography (PET) when radiolabeled with [^{18}F], Horti et al. described the synthesis of BOC-protected 5-(azetidin-2-ylmethoxy)-2-chloro-6'-fluoro-3,3'-bipyridine via a sequential classical heating and microwave irradiation of (2-fluoro-5-pyridinyl)(trimethyl)stannane with *t*-butyl 2-[(6-chloro-5-

**Scheme 9**



Scheme 10

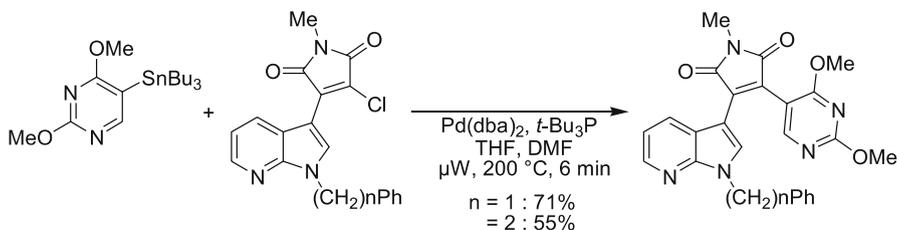


Scheme 11

iodopyridin-3-yl)oxy]methyl}azetidine-1-carboxylate (Scheme 11) [30]. No specific reason for this odd combination of events was given.

In the frame of a medicinal project at J & J Pharmaceutical Research and Development aimed at designing new potent and selective glycogen synthase kinase-3 β (GSK-3 β) inhibitors, the C-3 derivatization of the 1-methyl-4-[1-alkyl-1*H*-indol-3-yl]-1*H*-pyrrole-2,5-dione scaffold was explored [31]. Microwave-assisted Stille reaction of 3-chloro-1-methyl-4-[1-alkyl-1*H*-indol-3-yl]-1*H*-pyrrole-2,5-diones with (2,4-dimethoxy-5-pyrimidinyl)(tributyl)stannane at 200 °C yielded in 6 min the desired 3,4-diaryl-1*H*-pyrrole-2,5-diones in moderate yields (Scheme 12).

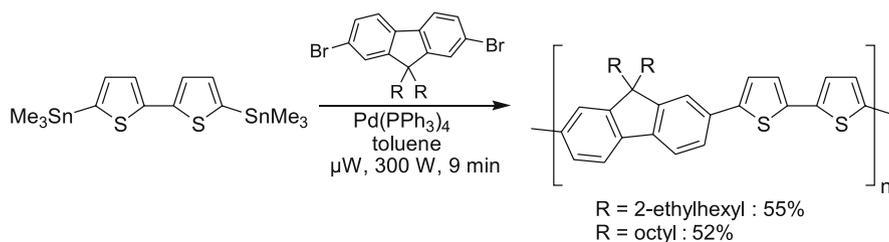
The synthesis of semiconducting polymers using microwave-assisted Stille reactions has also been studied [32]. The applied power was crucial for



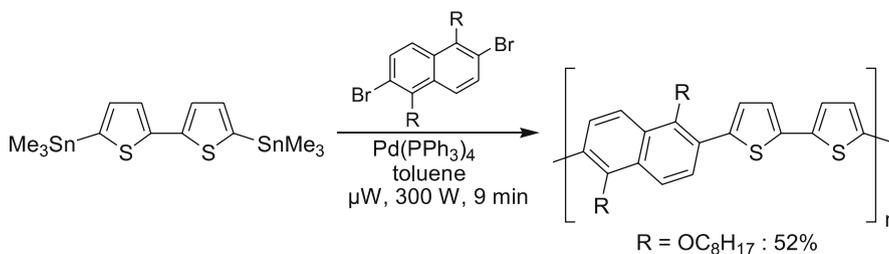
Scheme 12

the preparation of the dialkylfluorene/bisthiophene alternating copolymers (Scheme 13). Power levels higher than 170 W were required to receive appreciable degrees of polymerization. A molecular weight could be achieved, which was of similar magnitude to that achieved under conventional heating, albeit in a much shorter reaction time. Remarkably, when using a similar protocol for the construction of a naphthalene/bisthiophene copolymer, a substantially lower molecular weight and yield were obtained under conventional heating (Scheme 14). The comparison of classical heating and microwave irradiation is not meaningful, since the conventional experiments were executed under reflux for 72 h while the microwave reactions were performed in sealed 10 mL tubes in a single-mode microwave unit at full power for 9 min without temperature control.

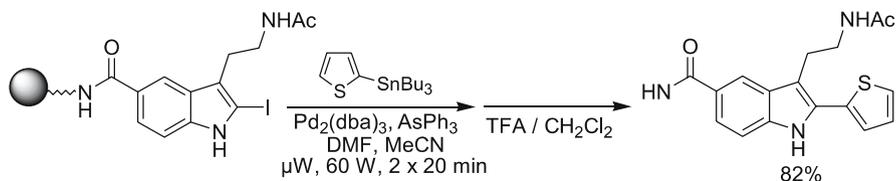
Pharmacomodulated melatonin analogs were prepared by Berteina-Raboin et al. using SPOS [33]. C-2 carbon functionalized 5-carboxamido-*N*-acetyltryptamines could be obtained via microwave-assisted transition-metal-catalyzed reactions such as the Stille reaction of resin-bound 3-[2-(acetylamino)ethyl]-2-iodo-1*H*-indole-5-carboxamide with (2-thienyl) (tributyl)stannane (Scheme 15). Resin-bound 3-[2-(acetylamino)ethyl]-2-iodo-1*H*-indole-5-carboxamide was generated starting from Polystyrene-Rink resin and 4-amino-3-iodobenzoic acid in only four steps [34]. Two cross-coupling reaction cycles (involving complete removal of reagents and by-products by washing off the resin) were required to get the desired Stille reaction to complete conversion at a constant power of 60 W.



Scheme 13



Scheme 14



Scheme 15

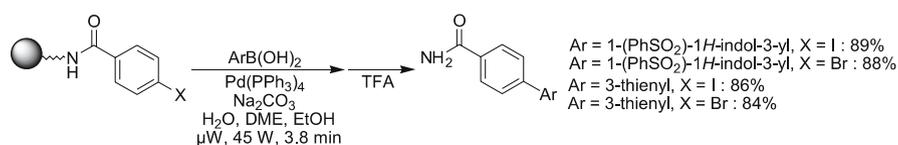
2.3

Suzuki–Miyaura Reaction

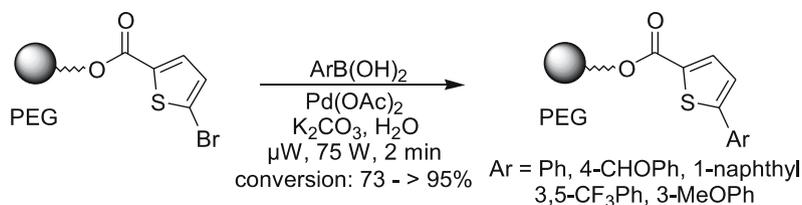
The first microwave-assisted Suzuki reactions involving heteroaromatic skeletons were reported in 1996 [35]. Hallberg et al. linked the substrates 4-iodo and 4-bromobenzoic acid to a TentaGel-Rink resin (Scheme 16). Suzuki reactions on these solid-phase-linked substrates were easily performed in less than 4 min using a constant microwave irradiation power (45 W) (no temperature control). Standard acidic cleavage with TFA yielded the corresponding biaryls with an excellent yield.

Soluble polymers have also been used as support. These exploit the combined advantage of homogeneous with those of solid-phase chemistry [36]. PEG linked 5-bromothiophene-2-carboxylic acid was cross-coupled with several arylboronic acids under microwave irradiation (constant power of 75 W) using water as the solvent (Scheme 17). Interestingly, microwave irradiation gave less ester cleavage than classical heating (70 °C). The polymeric support remained stable under both conditions.

(2*R*,3*R*,4*R*,5*R*)-2,5-bis(benzyloxy)-3,4-dihydroxy-*N,N'*-bis{(1*S*)-2-methyl-1-[(methylamino)carbonyl]propyl}hexanediamide is a C_2 -symmetric HIV-1



Scheme 16

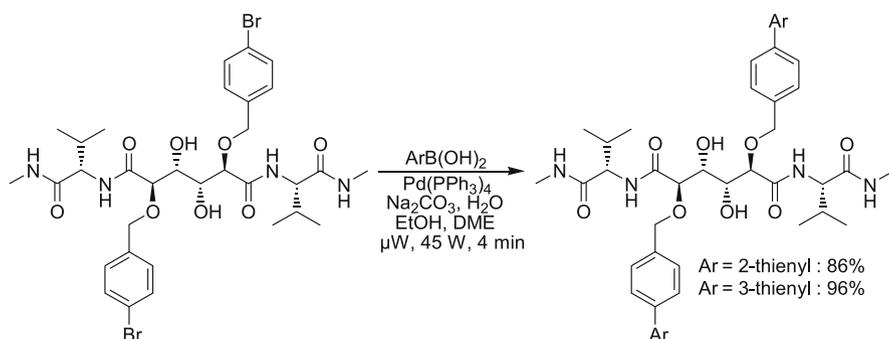


Scheme 17

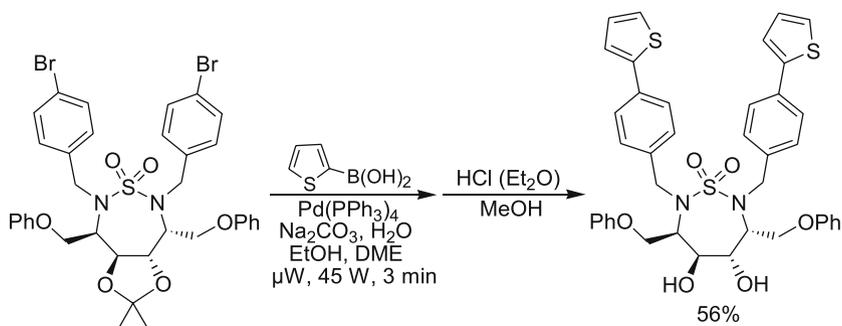
protease inhibitor [29]. Derivatization in the *para* positions of the benzyloxy groups via microwave-assisted Suzuki reaction on the corresponding dibrominated inhibitor smoothly yielded the desired heteroarylated derivatives (Scheme 18). The 2- and 3-thienyl derivatives were less potent (K_i) than the parent compound. However, both of these compounds demonstrated a pronounced antiviral activity on the wild type. They were similar in activity to ritonavir and indinavir.

Other types of HIV-1 protease inhibitors have also been prepared using microwave-promoted Suzuki reaction [37]. The symmetric cyclic sulfamide (3*R*,4*S*,5*S*,6*R*)-3,6-bis(phenoxymethyl)-2,7-bis[4-(2-thienyl)benzyl]-1,2,7-thiadiazepane-4,5-diol 1,1-dioxide, for instance, was synthesized via cross-coupling of (3*aS*,4*R*,8*R*,8*aS*)-5,7-bis(4-bromobenzyl)-2,2-dimethyl-4,8-bis(phenoxymethyl)hexahydro[1,3]dioxolo[4,5-*d*][1,2,7]-thiadiazepine 6,6-dioxide with 2-thienylboronic acid for 3 min at 45 W (Scheme 19).

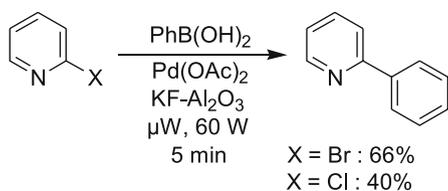
Solvent-free microwave-assisted Suzuki reaction on Al_2O_3 as solid support using KF as base has also been described in the literature by Villemin [38] (Scheme 20). Ligand-free $\text{Pd}(\text{OAc})_2$ was used as a precatalyst. In a reaction



Scheme 18



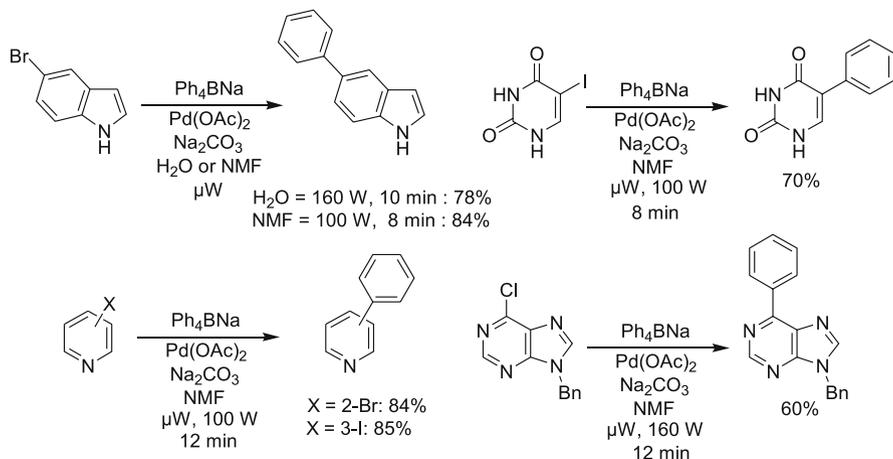
Scheme 19

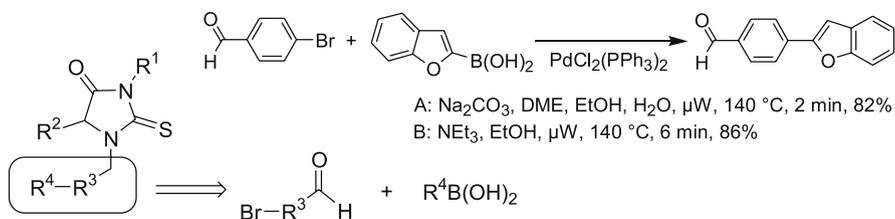
**Scheme 20**

time of 5 min, good results could be obtained on 2-halopyridine substrates using a constant power of 60 W.

The same group found that heteroaromatic halides can be smoothly phenylated using NaBPh_4 as the transmetallating agent and ligand-free Pd(OAc)_2 as a catalyst with water or *N*-methylformamide (NMF) as the solvent (Scheme 21) [39]. The experiments were all performed using power control.

Thiohydantoin s show a wide variety of biological properties such as antiviral, antibacterial, antifungal, and antitumour activity. Öhberg and Westman created a one-pot three-step solution phase protocol suitable for library synthesis of thiohydantoin s with four centers of diversity (R^1 – R^4) [40]. Microwave-assisted palladium-catalyzed cross-coupling reactions such as the Suzuki reaction have been used to prepare 4-heteroarylbenzaldehydes in only a few minutes allowing smooth R^3 – R^4 diversity (Scheme 22). To avoid work-up after Suzuki reactions, which is necessary when using aqueous conditions with Na_2CO_3 as a base (condition A), Öhberg and Westman used EtOH as solvent and NEt_3 as a base (condition B). The palladium catalyst was separated from the reaction mixture by filtration, and the solvent could easily

**Scheme 21**

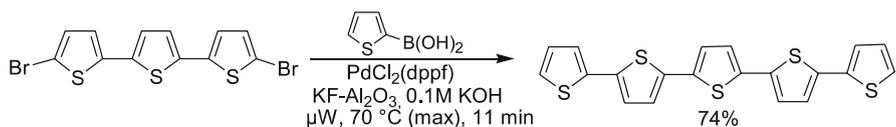


Scheme 22

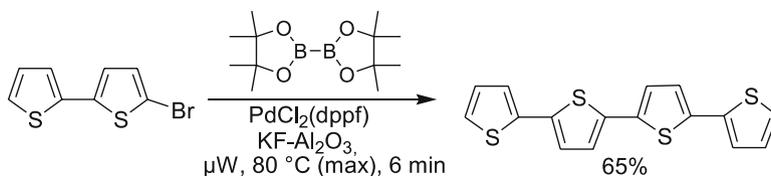
be evaporated in a Speedvac prior to the next step in the library production. Cross-coupling in EtOH with NEt_3 as a base gave similar yields when compared to the standard water-based system. Researchers from Boehringer-Ingelheim Pharmaceuticals studied the scale-up of the Suzuki-coupling of 4-bromobenzaldehyde with 2-benzofurylboronic acid, reported by Öhberg and Westman [41]. They used a continuous flow system based on a single-mode microwave unit and similar reaction conditions for this purpose at temperatures ranging from 120 to $140\text{ }^\circ\text{C}$. Although some palladium did not dissolve and precipitated as a mirror on the surface of the flow cell, no clogging of the lines and no temperature effects were observed. Interestingly, the yield obtained was similar to that of the small scale experiment of Öhberg and Westman.

Thiophene oligomers were efficiently synthesized via coupling of thienylboronic acids and esters with thienylbromides under solvent-free microwave irradiation [42]. Microwave-assisted couplings were executed on an Al_2O_3 solid support using KF as a base. Sometimes aqueous KOH was added to accelerate the reaction. Quinquethiophene, for instance, was synthesized in 11 min by reaction of 5,5''-dibromo-2,2':5',2''-terthiophene with 2-thienylboronic acid (Scheme 23). Quaterthiophene was obtained in only 6 min via homo-coupling of 5-bromo-2,2'-bithiophene using 0.5 equiv of bis(pinacolato)diboron (Scheme 24). Mechanistically the homo-coupling process is a borylation reaction followed by subsequent Suzuki cross-coupling.

Two years later, the same research group published an alternative to the solvent-free method, since this method cannot be applied to the synthesis of insoluble thiophene oligomers such as sexithiophene [43]. Obviously, their insolubility prevents separation of the Al_2O_3 solid support. The effectiveness of $\text{PdCl}_2(\text{dppf})/\text{KF}$ in solution phase was tested in the synthesis of soluble quinquethiophene from diiodoterthiophene and 2-thi-

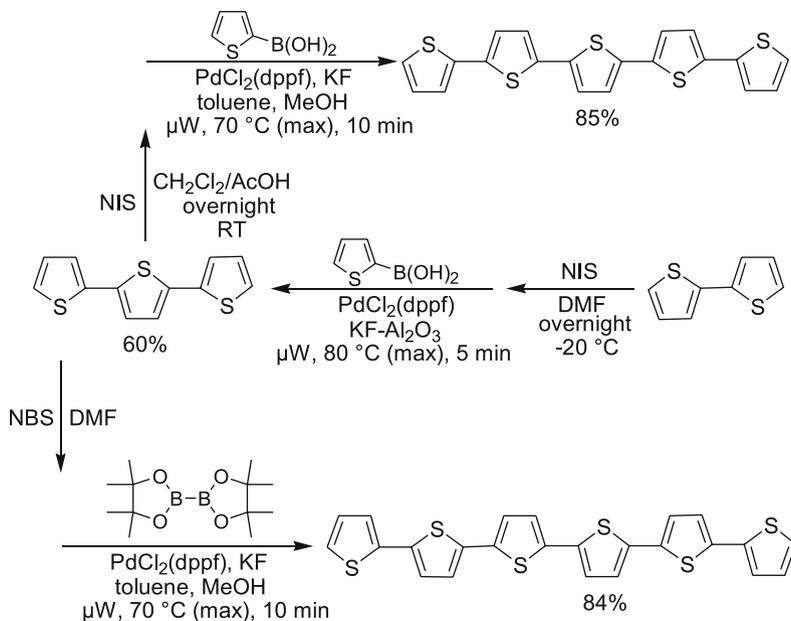


Scheme 23

**Scheme 24**

enylboronic acid (Scheme 25). Interestingly, the obtained yield was higher than via the solvent-free procedure described earlier. Unsubstituted sexithiophene could be obtained via one-pot borylation/Suzuki reaction of 5-bromoterthiophene with bis(pinacolato)diboron (Scheme 25). Quinque- and sexithiophenes substituted in the terminal thiophene rings were also synthesized following the solution-phase microwave protocol. A sexithiophene with a central 3,3'-dimethyl-2,2'-bithiophene subsystem could be constructed via microwave-accelerated Suzuki coupling of 5,5'''-dibromo-3'',4'-dimethyl-2,2':5',2'':5'',2'''-quaterthiophene with 2-thienylboronic acid [44]. For this coupling, ligandless Pd(OAc)₂, as a base K₂CO₃ in a mixture of water, and toluene in combination with the phase transfer agent TBAB were used. In 5 min of irradiation time, a yield of 65% of the desired hexamer was achieved.

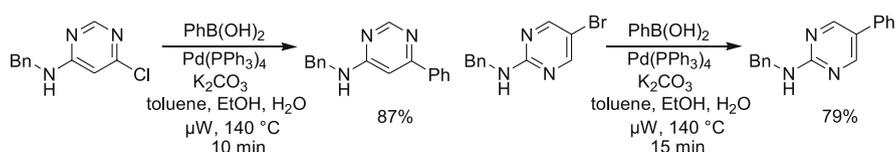
Researchers at the Bristol-Myers Squibb Pharmaceutical Research Institute in Wallingford investigated the use of microwave irradiation for the rapid

**Scheme 25**

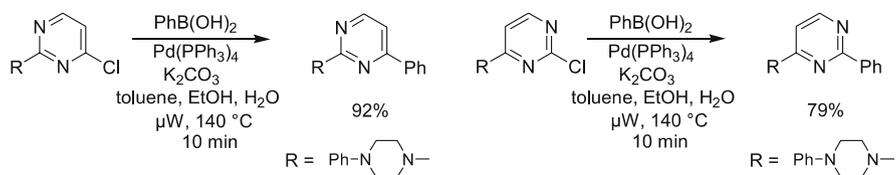
synthesis of various substituted aminopyrimidines [45]. The aminopyrimidine entity is medicinally very relevant, since it can be found in several drugs on the market such as aronixil (anti-atherosclerotic), thonzylamine (anti-histaminic), buspirone (anxiolytic), and enzadrem (anti-psoriatic). Suzuki phenylation of halogenated 2-amino- and 4-aminopyrimidines using standard cross-coupling conditions under microwave irradiation yielded the corresponding phenylated derivatives in good to excellent yields (Schemes 26 and 27).

4-Heteroarylphenylalanines could be smoothly obtained via microwave-promoted Suzuki reaction of heteroaryl halides with 2-amino-3-[4-(dihydroxyboryl)phenyl]propanoic acid (Scheme 28) [46]. Interestingly, the free amino acid could be used without any protection of the amine and carboxylic acid functionality. When 4-(dihydroxyboryl)-*L*-phenylalanine was used as organometallic partner no racemization was observed. The carboxylate anion and free amino group seem to shield the α -C – H from deprotonation and thus limit racemization.

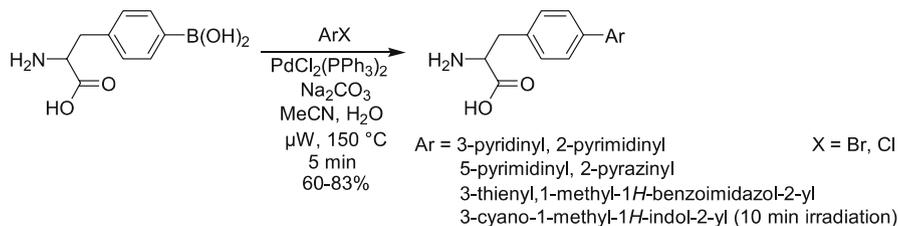
Heteroarylboronic esters, useful as organometallic partners in Suzuki reactions, have also been prepared under microwave irradiation by Fürst-



Scheme 26



Scheme 27

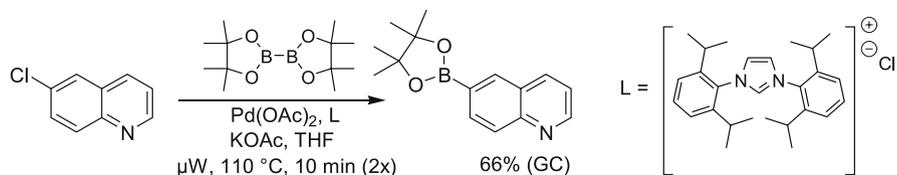


Scheme 28

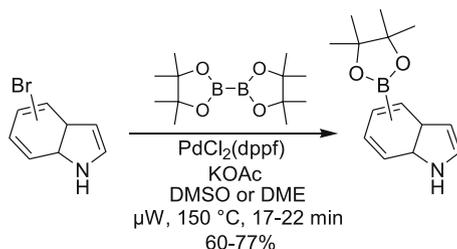
ner [47]. Unfortunately, only one example on a heteroaryl halide substrate was included. Borylation of 6-chloroquinoline was achieved using the in-situ-generated carbene ligand 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene as the palladium catalyst (Scheme 29). Two runs of 10 min, with the addition of equal amounts of $\text{Pd}(\text{OAc})_2$ and imidazolium chloride after the first run, were necessary to achieve good results. Unfortunately, the higher catalyst loadings required under microwave irradiation turned out to be necessary because of a fast precipitation of Pd black using dielectric heating.

One year later Van der Eycken and Dehaen described the smooth microwave-assisted borylation of 4, 5, 6 and 7-bromo-1*H*-indole using $\text{PdCl}_2(\text{dppf})$ as a precatalyst and KOAc as a base (Scheme 30) [48]. With 5, 6, and 7-bromo-1*H*-indole, DMSO was used as solvent at a temperature of 150 °C (with a set power of 150 W) for 17–27 min, resulting in the corresponding boronate esters in good yields. For 4-bromo-1*H*-indole, DME gave a better result at the same temperature (with a set power of 250 W).

In 2002 Leadbeater described the synthesis of biaryls using 0.4 mol % $\text{Pd}(\text{OAc})_2$ in water under microwave irradiation [49]. The aryl halide/arylboronic acid ratio used for the ligand-free process was only 1 : 1, while usually an excess of the arylboronic acid is used in aqueous Suzuki reactions. An equimolar amount of the phase-transfer agent TBAB was used to facilitate solvation of the organic substrate as well as for the enhancement of the coupling reaction by activation of the boronic acid ($[\text{ArB}(\text{OH})_3]^-[\text{R}_4\text{N}]^+$). A temperature of 150 °C was found optimal for aryl iodide and bromide substrates while aryl chlorides required a higher temperature (175 °C). Interestingly, the ligandless Pd-catalyzed process can be performed in air without degassing the water prior to use. Unfortunately, only one example of a heteroaryl halide



Scheme 29



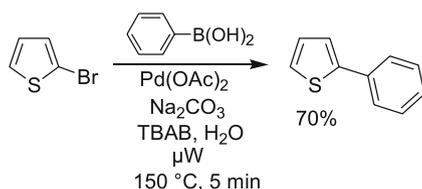
Scheme 30

substrate was included (Scheme 31). Similarly, Bryson described a Suzuki process for the synthesis of aterpyridine using glycol as a phase-transfer agent at 200 °C [50].

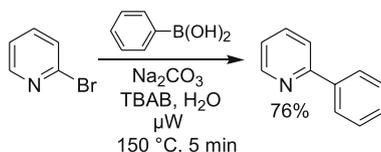
Remarkably, one year later Leadbeater described that biaryls can be synthesized via a Suzuki-type coupling under transition-metal free conditions [51, 52]. The reaction conditions were almost identical to those reported for the ligand-free process, with the difference being that a larger amount of Na_2CO_3 and arylboronic acid were used. Only one successful example of a heteroaryl halide substrate is shown; namely, the coupling of 2-bromopyridine with phenylboronic acid (Scheme 32). 3-Bromothiophene did not couple under the same reaction conditions. Unfortunately, attempts to use heteroarylboronic acids such as 3-pyridinylboronic acid, 3-thienylboronic acid, and 1*H*-indol-5-ylboronic acid on 4-bromoacetophenone completely failed.

Early 2005, Leadbeater's team reported that the previously claimed transition-metal-free Suzuki-type protocol was definitely palladium-catalyzed [53]. Palladium contaminants down to the level of 50 ppb found in commercially available sodium carbonate were responsible for the generation of the biaryl. For good product yields in a short reaction time under microwave irradiation, a loading of 1 ppm Pd was required.

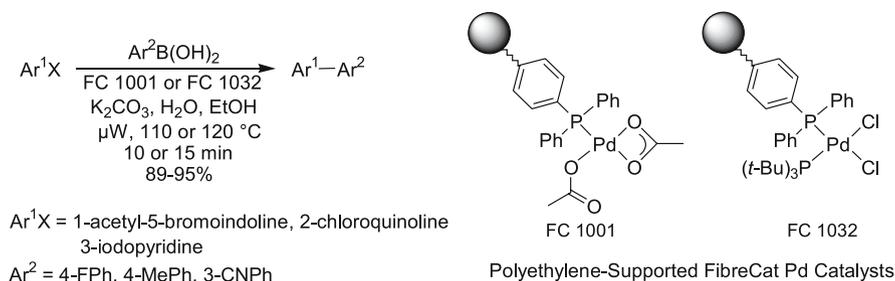
The use of polymer-supported palladium catalysts (FC 1001, FC 1032) in combination with microwave irradiation for the performance of Suzuki reactions has been shown to be highly attractive for routine library generation via parallel synthesis. Researchers from Abbott Laboratories showed that commercially available polyethylene-supported FibreCat Pd-catalysts gave cleaner reactions in comparison to homogeneous systems such as the precatalyst $\text{PdCl}_2(\text{PPh}_3)_2$ (Scheme 33) [54]. Interestingly, using the supported catalysts, there was no need to work under nitrogen atmosphere. Excess arylboronic



Scheme 31

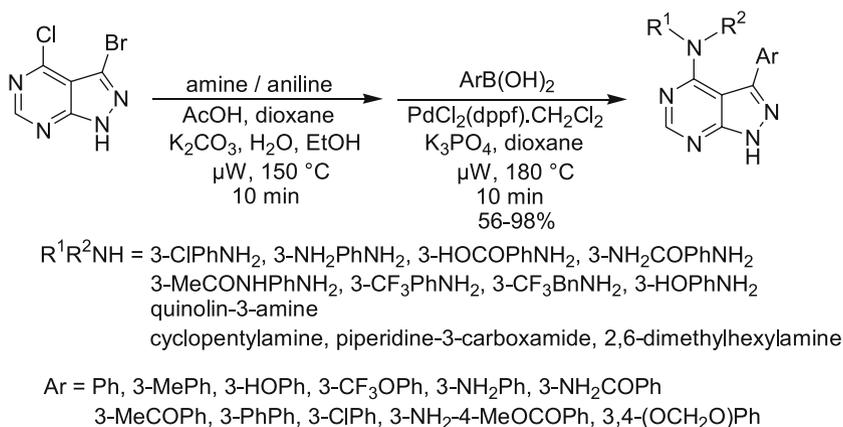


Scheme 32

**Scheme 33**

acid was easily removed after the microwave-assisted Suzuki reaction via SPE using a prepacked column of Si-carbonate. During this SPE the polymer-supported catalyst was also removed. The described approach allowed one to obtain the desired reaction products in high yield and purity. When quantitative conversion of substrate was reached there was no need for further purification of the reaction product after passing the reaction mixture through a plug of Si-carbonate. The simple work-up, by filtering off the heterogeneous catalyst after the cross-coupling reaction, makes this method suitable for (semi)automated Suzuki reactions, since in homogeneous catalysis Pd residues can clog probes and frits used to transfer and filter reaction mixtures. In addition, when using homogeneous catalysis, the work-up can be tedious due to the metal and associated ligands.

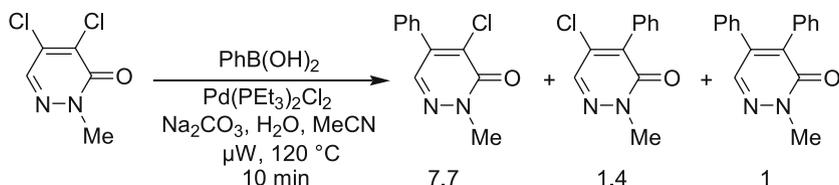
3-Bromo-4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine could be easily functionalized at C-3 and C-4 in a one-pot two-step microwave-assisted process (Scheme 34) [55]. Ding and Schultz reported that nucleophilic substitution of the addition-elimination type at the C-4 position with amines and anilines smoothly occurred under acidic conditions in dioxane upon irradiation

**Scheme 34**

(150 °C) for 10 min in a single-mode microwave. After the reaction vials were cooled down to ambient temperature using a propelled air flow, arylboronic acid, catalyst, and base were added. Subsequently, the glass vial was sealed and heated at 180 °C for another 10 min. Reversal of the reaction sequence gave significantly lower yields due to the fact that the palladium catalyst can also give oxidative addition in the C-4 position. Under conventional thermal conditions, longer reaction times are necessary, which would lead to significant decomposition of the desired product. For instance, the consecutive reaction of 3-bromo-4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine with 3-chloroaniline and 3-acetylphenylboronic acid requires 12 h of heating at 100 °C for both steps and the yield of the final compound is less than 50%, while the microwave protocol gives the same reaction product in only 20 min with a 73% yield. The presented method will allow for rapid access to libraries of disubstituted pyrazolopyrimidines. This is important since substituted pyrazolopyrimidines are well known as scaffolds for selective kinase inhibition. Interestingly, the method could also be extended to 5-bromo-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine without modification of reaction parameters.

In 2004 Gong and He investigated the C-5 selective Suzuki arylation of 2-methyl-4,5-dichloropyridazin-3(2*H*)-one with phenylboronic acid under microwave irradiation (Scheme 35) [56]. Best results were obtained with a ratio of 2 : 1 of pyridazin-3(2*H*)-one and phenylboronic acid using Pd(PEt₃)₂Cl₂ as a precatalyst. Additional enhancement of selectivity was accomplished via a careful optimization of the reaction temperature and co-solvent. A reaction at room temperature in DMF as a co-solvent with an extended reaction time (5 h) finally gave 4-chloro-2-methyl-5-phenylpyridazin-3(2*H*)-one with a selectivity greater than 300 fold over products 5-chloro-2-methyl-4-phenylpyridazin-3(2*H*)-one and 2-methyl-4,5-diphenylpyridazin-3(2*H*)-one. Besides a good selectivity a good isolated yield of 4-chloro-2-methyl-5-phenylpyridazin-3(2*H*)-one was obtained (77%). Unfortunately, the general applicability of these optimized reaction conditions, when other arylboronic acids or 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones are used, remains unknown.

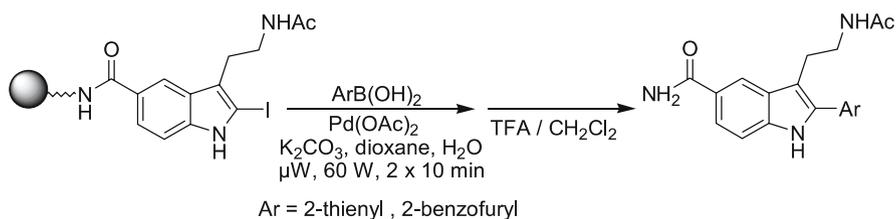
Pharmacomodulated melatonin analogs were prepared by Berteina-Raboin et al. using SPOS [33]. C-2 carbon functionalized 5-carboxamido-



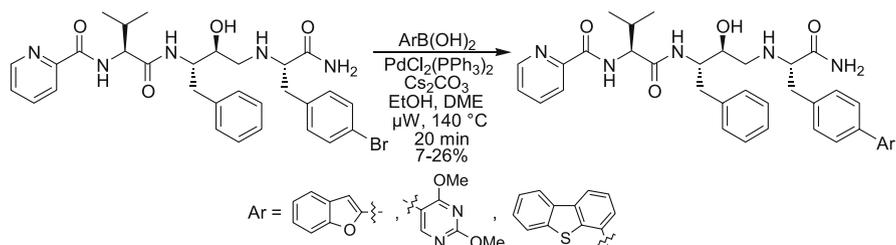
Scheme 35

N-acetyltryptamines could be obtained via microwave-assisted transition-metal-catalyzed reactions on resin bound 3-[2-(acetylamino)ethyl]-2-iodo-1*H*-indole-5-carboxamide. While acceptable reaction conditions for the application of microwave irradiation have been identified for Stille heteroarylation reactions, the related Suzuki protocol on the same substrate gave poor results, since at a constant power of 60 W, no full conversion (50–60%) of resin-bound 3-[2-(acetylamino)ethyl]-2-iodo-1*H*-indole-5-carboxamide could be obtained even when two consecutive cross-coupling reaction cycles (involving complete removal of reagents and by-products by washing off the resin) were used (Scheme 36). Also under conventional heating at 110 °C, and otherwise identical conditions, the Suzuki reactions proved to be difficult since two cross-coupling reaction cycles of 24 h had to be used to achieve full conversion.

Inhibitors for proteases plasmepsin I and II of the malaria parasite *Plasmodium falciparum*, with a good plasmepsin/human protease cathepsin D selectivity, have been identified via library construction involving rapid microwave-accelerated Suzuki reactions [57]. The phenyl ring of the biphenyl unit in the lead compound *N*-((1*S*)-1-{[(1*S*,2*S*)-3-{(1*S*)-2-amino-1-(4-phenylbenzyl)-2-oxoethyl]amino}-2-hydroxy-1-phenoxypropyl)amino]carbonyl}-2-methylpropyl)pyridine-2-carboxamide has been altered by performing Suzuki reactions on *N*-((1*S*)-1-{[(1*S*,2*S*)-3-{(1*S*)-2-amino-1-(4-bromobenzyl)-2-oxoethyl]amino}-2-hydroxy-1-phenoxypropyl)amino]carbonyl}-2-methylpropyl)pyridine-2-carboxamide (Scheme 37). In particular, a 2-benzofuryl moiety proved to be interesting since a K_i value of 13 nM for plasmepsin I and



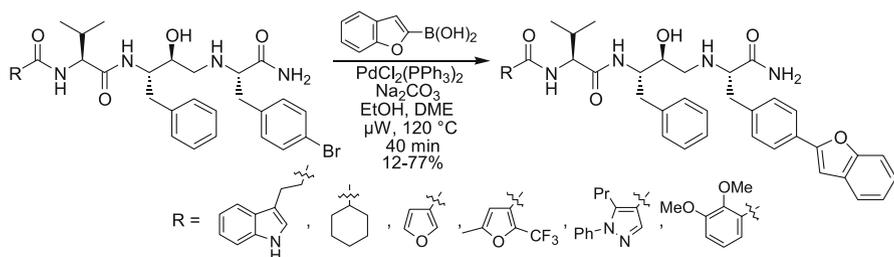
Scheme 36



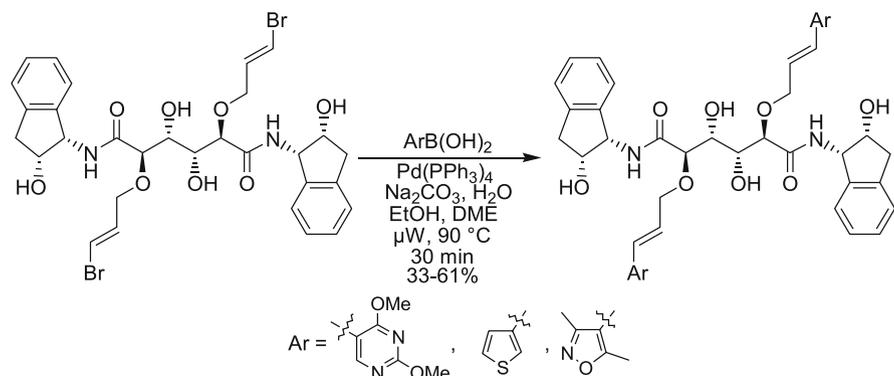
Scheme 37

a K_i value of 30 nM for plasmepsin II were measured. Moreover, for the human protease cathepsin D, the compound gave a K_i of 1400 nM thus showing a good selectivity. Replacement of the pyridine moiety by other groups did not give compounds with higher activity against the plasmepsins, although for plasmepsin I a single-digit nanomolar active compound was obtained ($R = 1H$ -indol-3-ylethyl) (Scheme 38).

Besides hydroxyethylamine-based inhibitors, 1,2-dihydroxyethylene-based inhibitors were also explored [58]. Only compounds with the (*R,R,R,R*)-configuration at the four central carbon atoms demonstrated any inhibitory potency, and a hydroxyindan substituent at the terminal nitrogen atoms improved activity. Hence (2*R*,3*R*,4*R*,5*R*)-2,5-bis[(prop-2-en-1-yl)oxy]-3,4-dihydroxy-*N,N'*-bis[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]hexanediamide was selected for an optimization study ($K_{i \text{ plasmepsin I}} = 163 \text{ nM}$, $K_{i \text{ plasmepsin II}} = 96 \text{ nM}$ and $K_{i \text{ Cathepsin D}} > 2000 \text{ nM}$). Microwave-assisted transition-metal-catalyzed reactions on (2*R*,3*R*,4*R*,5*R*)-2,5-bis{[(2*E*)-3-bromoprop-2-en-1-yl]oxy}-3,4-dihydroxy-*N,N'*-bis[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]hexanediamide allowed for the rapid creation of a diverse library of analogs as exemplified by microwave-promoted Suzuki reactions (Scheme 39).



Scheme 38

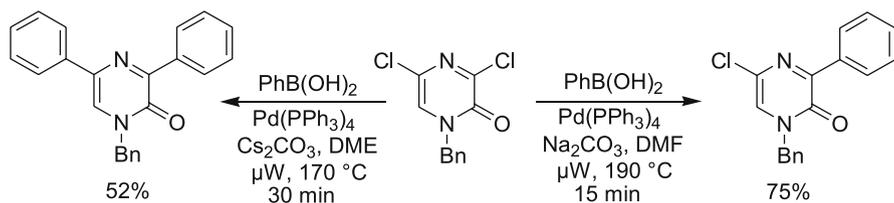


Scheme 39

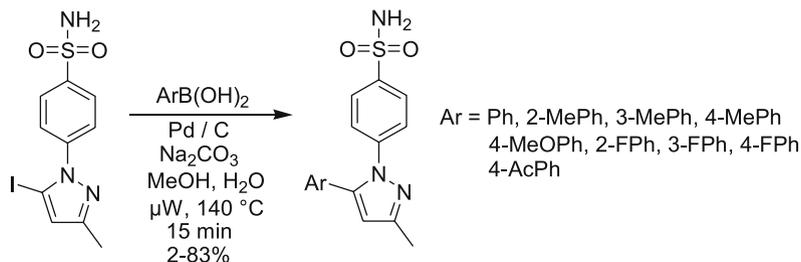
Interestingly plasmepsin inhibitors with a good activity (low nM) were obtained with no measurable affinity to the human protease enzyme.

The *N*-substituted 3,5-dichloropyrazin-2(1*H*)-one scaffold has been smoothly decorated in the C-3 position by Van der Eycken et al. using chemoselective Suzuki reactions [27]. When a mixture of 3,5-dichloro-1-benzylpyrazin-2(1*H*)-one, 1.1 equiv of phenylboronic acid, and Na₂CO₃ as the base in DMF was irradiated for 15 min at 190 °C, the desired 1-benzyl-5-chloro-3-phenylpyrazin-2(1*H*)-one could be isolated with a 75% yield (Scheme 40). Performing the reaction in DME gave a slower reaction, and the yield was lower. Interestingly, when Na₂CO₃ was replaced by Cs₂CO₃, a mixture of 3-mono- and 3,5-disubstitution occurred. When 2.2 equiv of phenylboronic acid were used in combination with this base, 1-benzyl-3,5-diphenylpyrazin-2(1*H*)-one could be obtained at a 52% yield (Scheme 40). For this double-phenylation reaction, DME was a preferential solvent since it gave a higher yield than DMF. When aqueous conditions were applied (DME/H₂O) at 150 °C for 20 min, only bis-phenylated product was obtained, independent of the carbonate base (Na₂CO₃ or Cs₂CO₃).

Organ et al. from York University demonstrated that a diarylated 1*H*-pyrazole-based library, based on the structure of the potent COX II inhibitor Celecoxib [4-(3-trifluoromethyl-5-(4-methylphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide], could be rapidly prepared using MAOS [59]. Microwave-accelerated Suzuki reaction on 4-(5-iodo-3-methyl-1*H*-pyrazol-1-yl)benzenesulfonamide using heterogeneous Pd/C was the principal diversification step investigated (Scheme 41). The interest of the team in microwave



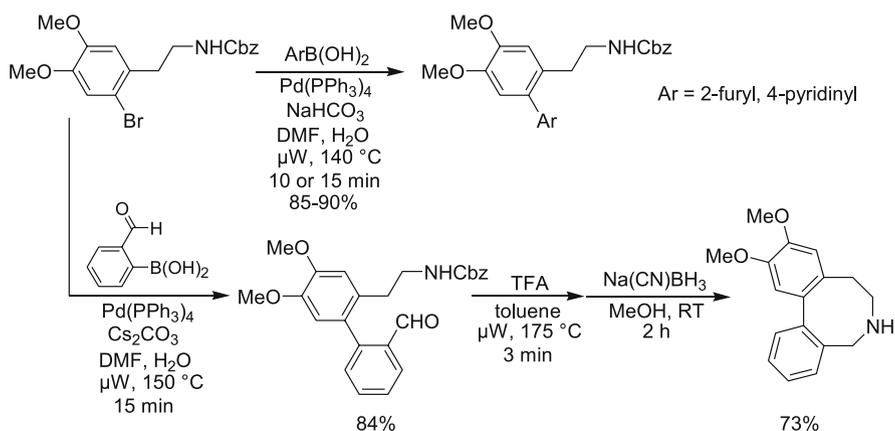
Scheme 40



Scheme 41

irradiation is based on the observed slow cross-coupling reactions on 4-(5-iodo-3-methyl-1*H*-pyrazol-1-yl)benzenesulfonamide under classical heating. Generally electron-deficient arylboronic acids coupled well under microwave irradiation but typically coupled very slowly under classical heating. Ortho-substituted arylboronic acids, on the other hand, were very poor coupling partners under microwave irradiation (mainly unreacted substrate was recovered) while they gave very good results under conventional heating, albeit after a long reaction time. Surprisingly, electron-rich arylboronic acids revealed a better performance conventionally. Interestingly, in the cases where microwave reactions worked well, cleaner crude products were obtained (reduction of the substrate to 4-(3-methyl-1*H*-pyrazol-1-yl)benzenesulfonamide was minimal (< 1%)), which allows for the isolation of the compounds by a simple precipitation.

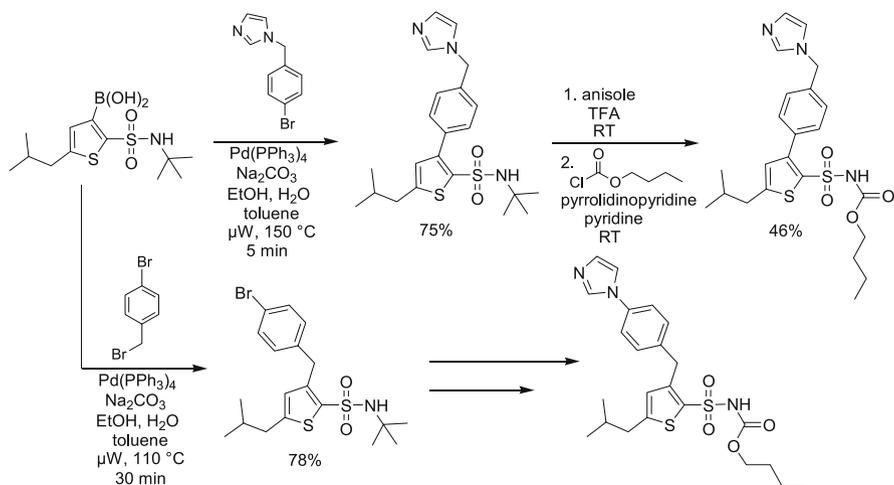
Van der Eycken generated a small library of electron-rich 2-(hetero)arylphenethylamines exploring the potential of microwave irradiation [60]. The biaryl axis was created via straightforward Suzuki cross-coupling of (hetero)arylboronic acids with easily accessible benzyl [2-(2-bromo-4,5-dimethoxyphenyl)ethyl]carbamate (Scheme 42). The reaction conditions were optimized using phenylboronic acid. Pd(PPh₃)₄ and NaHCO₃ were identified to be the catalyst and base of choice, respectively, though Cs₂CO₃ gave an equivalent result, in a mixture of DMF and water at 140 °C for 10 min. Other precatalysts such as PdCl₂(dppf) gave a substantially lower yield. It is surprising that the standard Pd(PPh₃)₄ can be smoothly inserted (oxidative addition) into the C – Br bond of the electron-rich arene. When arylboronic acids with electron-withdrawing groups were used a longer reaction time was required. Arylboronic acids with electron-donating substituents as well as electron-rich heteroarylboronic acids could be coupled using the standard reaction time. Electron-deficient heteroarylboronic acids, as exemplified

**Scheme 42**

by the use of 4-pyridinylboronic acid, seem to require the 15 min protocol. Also, sterically hindered and electron-deficient 2-formylphenylboronic acid could be used as an organometallic partner under similar reaction conditions. Interestingly, performing the same reaction in a preheated oil bath of 150 °C gave only 22% reaction product in 14 h compared to 84% under microwave irradiation for 15 min. Increasing the oil bath temperature to 200 °C only slightly increased the yield to 37%. Reaction of benzyl [2-(2'-formyl-4,5-dimethoxybiphenyl-2-yl)ethyl]carbamate with TFA in toluene gave a smooth ring-closure via imine formation (Scheme 42). Reduction of the imine functionality with NaBH₃(CN) in MeOH gave access to an apogalanthamine analog. This reduction could be easily performed by adding the crude imine reaction mixture to a methanolic solution of NaBH₃(CN) (Scheme 42).

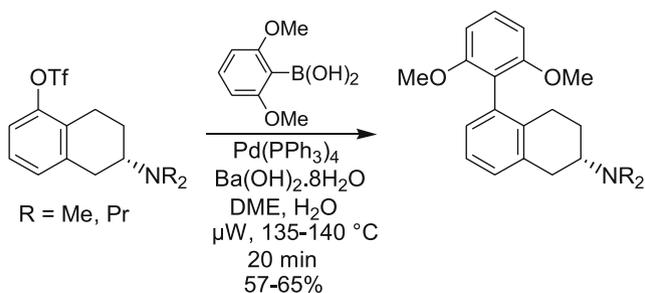
The first druglike selective angiotensin II AT₂ receptor agonist, butyl ({3-[4-(1*H*-imidazol-1-ylmethyl)benzyl]-5-isobutyl-2-thienyl}sulfonyl)carbamate, with a K_i value of 0.4 nM for the AT₂ receptor and a K_i > 10 μM for the AT₁ receptor has been synthesized using a Suzuki arylation promoted by microwave irradiation [61]. Cross-coupling of {2-[(*t*-butylamino)sulfonyl]-5-isobutyl-3-thienyl}boronic acid with 1-(4-bromobenzyl)-1*H*-imidazole under microwave irradiation, using Pd(PPh₃)₄ and aqueous Na₂CO₃ in a mixture of toluene and ethanol, yielded *N*-(*t*-butyl)-3-[4-(1*H*-imidazol-1-ylmethyl)phenyl]-5-isobutylthiophene-2-sulfonamide in 75% in only 5 min (Scheme 43). Deprotection of the sulfonamide followed by carbamate formation via reaction with butyl chloroformate finally gave the target compound (Scheme 43). An analog of this compound with an extra methylene group between the thiophene and phenyl ring and lacking the methylene group between the phenyl and the 1*H*-imidazole nucleus was also prepared. To achieve this 3-(4-bromobenzyl)-*N*-(*t*-butyl)-5-isobutylthiophene-2-sulfonamide was synthesized via a chemoselective Suzuki reaction of {2-[(*t*-butylamino)sulfonyl]-5-isobutyl-3-thienyl}boronic acid with 1-bromo-4-bromomethyl-benzene under similar conditions as was used for the coupling with 1-(4-bromobenzyl)-1*H*-imidazole (Scheme 43). Introduction of the 1*H*-imidazole ring via Ullmann-type chemistry followed by deprotection and carbamate formation finally gave butyl ({3-[4-(1*H*-imidazol-1-yl)benzyl]-5-isobutyl-2-thienyl}sulfonyl)carbamate (Scheme 43). This compound showed only a low affinity for the AT₂ receptor (K_i value > 10 μM).

The understanding of the physiological role of the G-protein coupled serotonin 5-HT₇ receptor is largely rudimentary. The lack of further insight into the pharmacology of this receptor has been hampered by the absence of chemical tools. Even though some nonselective 5-HT₇ agonists have been reported, no potent and selective 5-HT₇ receptor agonists have emerged. 8-Aryl-3-aminochromans and 5-aryl-2-aminotetralins have been identified as compounds with high affinity and good selectivity for this receptor [62]. These novel structures show efficacies ranging from antagonists to full agonists. The sterically hindered 2,6-dimethoxyphenyl has been smoothly in-

**Scheme 43**

produced at the C-8 position by rapid microwave-enhanced Suzuki arylation of (*R*)-3-dipropylamino- and (*R*)-3-dimethylamino-8-(trifluoromethanesulfonyloxy)chroman (Scheme 44). The substitution pattern of the aryl ring in the chromans and tetralins played a crucial role in the selectivity toward the 5-HT_{1A} receptor. Through the introduction of ortho substituents, the aryl group was forced out of the plane of the chroman and tetralin, which seems to reduce favorable interactions with the 5-HT_{1A} receptor while keeping a good affinity for the 5-HT₇ receptor.

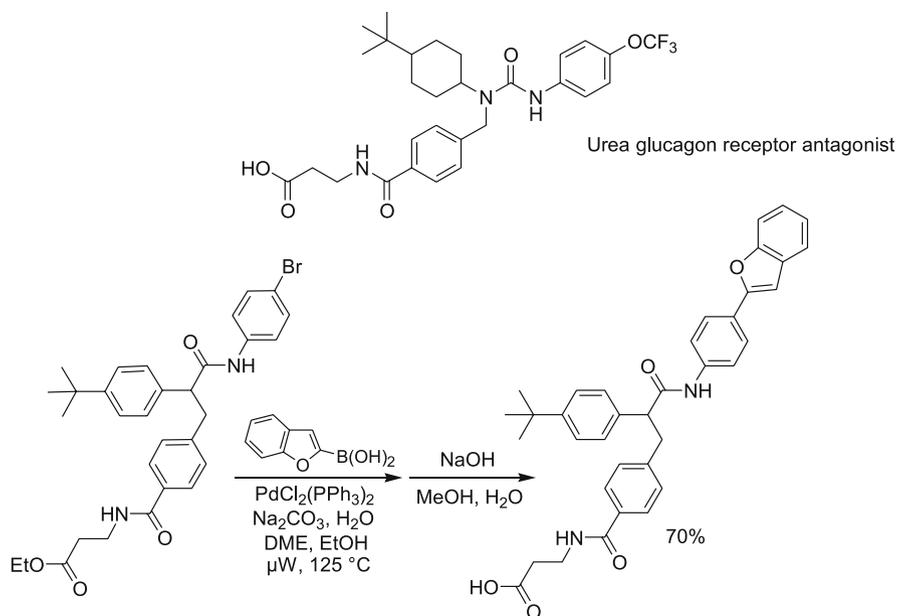
As the incidence of type 2 diabetes reaches epidemic proportions, the search for potential treatments has intensified. One useful target is the development of glucagon receptor (GlucR) antagonists. Researchers at Abbott Laboratories in the USA used a patented urea-based glucagon receptor antagonist of Novo Nordisk as template for further modification in order to increase binding and functional activity and to improve the pharmacokinetic profile [63]. Initially,

**Scheme 44**

the replacement of the tertiary nitrogen (and substituent) of the urea by a carbon atom was investigated. In addition, the effect of a 4-[(hetero)aryl]anilino moiety on the binding was studied. The preparation of such derivatives was achieved via Suzuki reaction on ethyl 3-({4-[3-[(4-bromophenyl)amino]-2-(4-*t*-butylphenyl)-3-oxopropyl]benzoyl}amino)propanoate under microwave irradiation (Scheme 45).

Pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones have attracted considerable interest due to the wide range of biological activities (kinase inhibitors, telomerase inhibitors, treatment of arthritis, etc.) associated with this scaffold. A set of 4-chloro-5,8-dihydro-6*H*-pyrido[2,3-*d*]pyrimidin-7-ones substituted in the 2, 5, and 6 position were recently prepared by Borrell et al. [64]. To illustrate that a wide variety of C-4-substituted derivatives can be easily and rapidly prepared starting from these compounds, thus opening the way for smooth library creation, a microwave-assisted Suzuki reaction on 4-chloro-5,5-dimethyl-2-phenyl-5,8-dihydro-6*H*-pyrido[2,3-*d*]pyrimidin-7-one was executed (Scheme 46). For the precatalyst, Pd(OAc)₂ and PPh₃ were selected. A mixture of glyme and some water was used as the solvent in combination with Na₂CO₃ as the base. Heating for 15 min at 180 °C resulted in 5,5-dimethyl-2,4-diphenyl-5,8-dihydro-6*H*-pyrido[2,3-*d*]pyrimidin-7-one at a 74% yield after chromatographic purification.

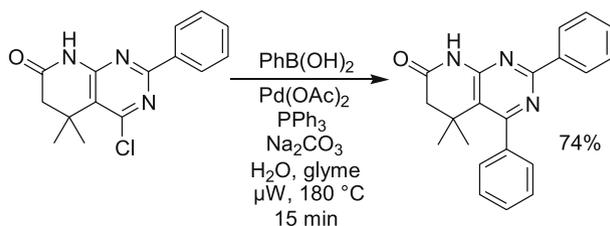
A library of biologically relevant 2-aryl-3-aminoimidazo[1,2-*a*]pyridines and 2-aryl-3-aminoimidazo[1,2-*a*]pyrazines was created using a combina-



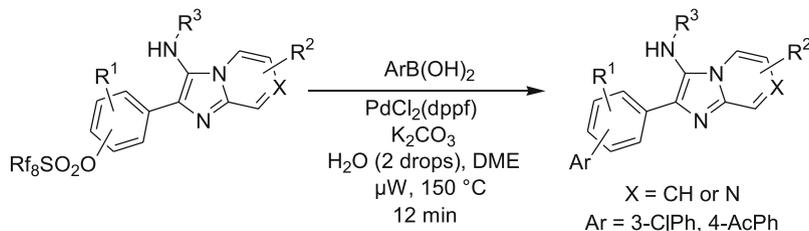
Scheme 45

tion of MAOS and fluoros chemistry [65]. While microwave chemistry is the champion in easily speeding up organic reactions, fluoros synthesis delivers the possibility of performing fast and easy purifications. A marriage of both techniques therefore has a great potential of further improving the efficiency of organic synthesis. The main advantage of fluoros over “classical” solid-phase synthesis is that the former is a homogeneous technique, which is highly favorable from a reaction kinetics point of view. Additional advantages are that no resin swelling is involved, and intermediates tagged with a fluoros tag can easily be analyzed. The 2-aryl-3-aminoimidazo[1,2-*a*]pyridines and 2-aryl-3-aminoimidazo[1,2-*a*]pyrazines were synthesized from perfluorooctanesulfonyl-tagged hydroxybenzaldehydes via a microwave-assisted three-component reaction involving isocyanides and 2-aminopyridines or aminopyrazines. The perfluoralkylsulfonyl tag did not only function as a phenol protecting group for the condensation reaction, and as a phase tag for purification in the multicomponent reaction, but was afterwards also used as an activating group for cross-coupling reactions. For instance, detagging via microwave-promoted Suzuki reactions smoothly yielded a biaryl unit (Scheme 47). A similar tagging strategy was followed for the synthesis of biaryls and a biaryl-substituted hydantoin [66].

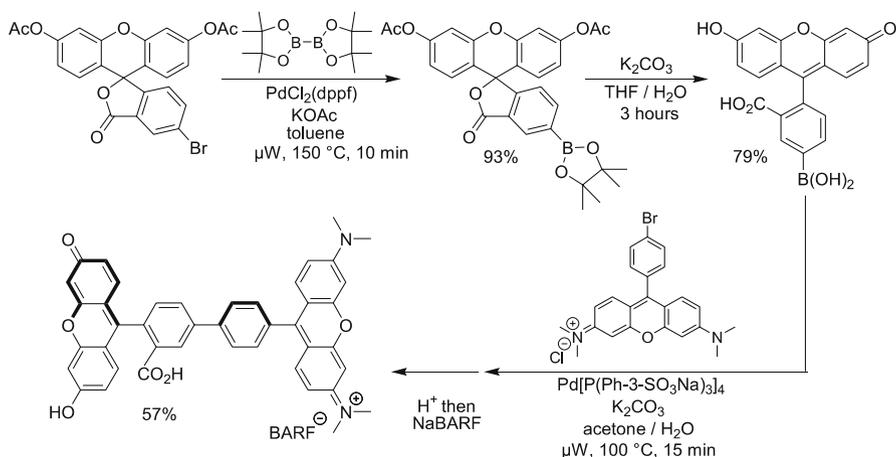
Fluorescent tags for labeling and observation of several biomolecules in one system inspired Burgess et al. to develop ways to link fluorescein and rosamine (rhodamine lacking a carboxylic acid functionality) fragments [67]. More specifically, they were linked in such a way that they would be conjugated if they became planar. To achieve this goal boryla-



Scheme 46



Scheme 47

**Scheme 48**

tion of 5-bromofluorescein diacetate was investigated. While initial experiments with pinacolborane using conventional heating gave a lot of reduced compound, microwave-assisted borylation with dipinacolatodiboron worked nicely (Scheme 48). Complete conversion of starting material and no formation of reduced product could be achieved using $\text{PdCl}_2(\text{dppf})$ as precatalyst with KOAc as a base in toluene. In only a 5 min irradiation at 150°C , a conversion with 98% selectivity for the desired boronate ester was observed relative to the debrominated compound. When this reaction was executed on a 1 mmol scale for 10 min under otherwise similar reaction conditions, a 93% yield was obtained. Hydrolysis to the deacylated boronic acid yielded the organometallic partner desired for coupling with a brominated rosamine (Scheme 48). The optimal conditions for coupling reactions with the borylated fluorescein were revealed from test experiments using 4-bromoanisole as substrate. The water soluble sulfonated variant of $\text{Pd}(\text{PPh}_3)_4$ gave the best results with a superior yield under microwave irradiation in comparison to conventional heating. Fortunately, these optimized cross-coupling conditions were also found to be suitable to link the fluorescein and rosamine entities (Scheme 48).

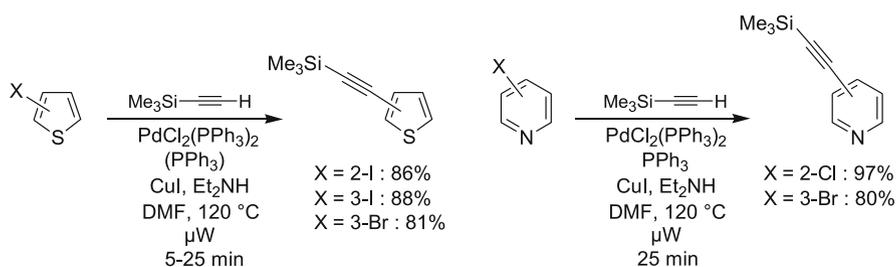
3 Sonogashira–Hagihara Reaction

In 2001 the first microwave-enhanced Sonogashira protocol including examples of heteroaromatic skeleta appeared. Trimethylsilylacetylene could be efficiently introduced on electron-rich and electron-deficient heteroaromatics as exemplified by thiophene and pyridine, respectively (Scheme 49) [68].

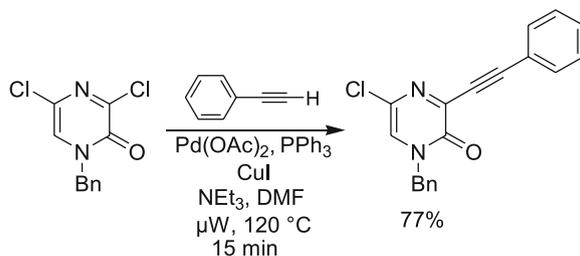
$\text{PdCl}_2(\text{PPh}_3)_2$ and CuI in a mixture of Et_2NH and DMF at 120°C for 5–25 min were found to be suitable as a general protocol. For less reactive (hetero)aryl bromides and 2-chloropyridine, extra triphenylphosphine was added to improve the stability of the palladium catalyst (Scheme 49).

Chemoselective alkylation in the C-3 position of *N*-substituted 3,5-dichloropyrazin-2(1*H*)-one has been described by Van der Eycken et al. [27]. When a mixture of 3,5-dichloro-1-benzylpyrazin-2(1*H*)-one and phenylacetylene in a mixture of NEt_3 and DMF, using $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ as precatalyst and CuI as a co-catalyst, was irradiated for 15 min at 120°C , the desired 1-benzyl-5-chloro-3-phenylethynylpyrazin-2(1*H*)-one could be isolated with a 77% yield (Scheme 50). Although 2.4 equiv of alkyne were used, no trace of the 1-benzyl-3,5-diphenylethynylpyrazin-2(1*H*)-one could be detected.

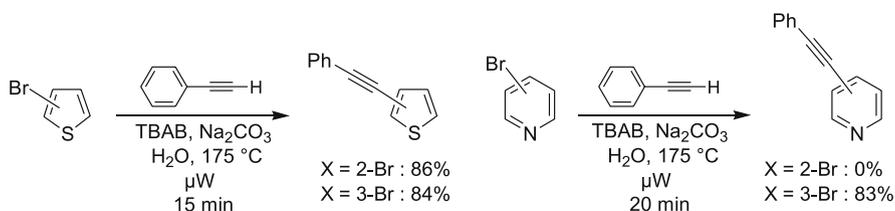
In 2003, Van der Eycken published a copper- and palladium-free microwave-assisted Sonogashira-type protocol in water with phenylacetylene as the alkyne (Scheme 51) [69]. The phase-transfer agent TBAB was used to facilitate



Scheme 49



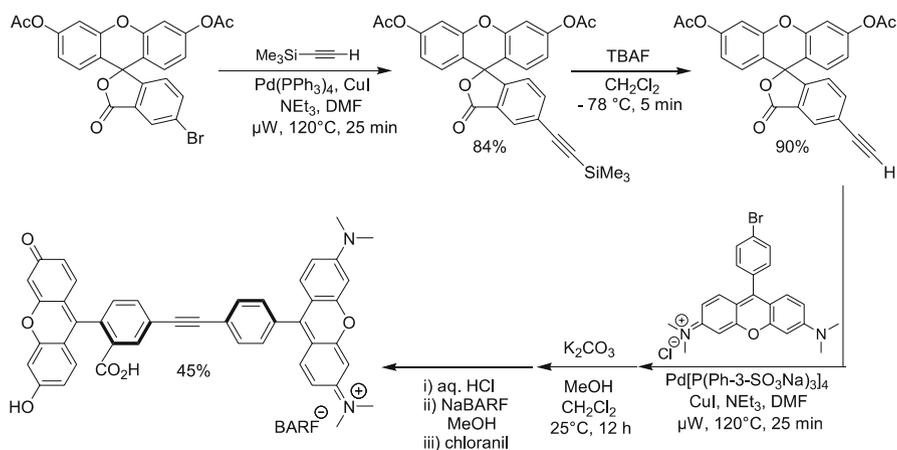
Scheme 50



Scheme 51

solvation of the organic substrate. The use of an excess of Na_2CO_3 was found to be critical. Remarkably, 2-bromopyridine substrate gave no 2-phenylethynylpyridine, even at 210°C , while 3-bromopyridine yielded 83% 3-phenylethynylpyridine under the same reaction conditions (Scheme 51). Although Leadbeater independently described a similar protocol in water with poly(ethylene glycol) as phase-transfer agent, no heteroaromatic skeleta were incorporated in his study [70]. It might be that the reported transition-metal-free Sonogashira-type protocols are nevertheless metal-catalyzed since palladium contaminants down to the level of 50 ppb found in commercially available sodium carbonate were identified to be responsible for biaryl formation via a transition-metal free Suzuki-type protocol mentioned earlier. Interestingly, Van der Eycken tried the coupling of 2-bromonaphthalene with phenylacetylene also under conventional heating. Remarkably, in this case, no reaction product could be observed, even at prolonged heating and an oil bath temperature of 210°C , while a smooth coupling was observed under microwave irradiation. Further study will be necessary to find out if specific microwave effects are involved for these reaction conditions.

Fluorescent tags for labeling and observation of several biomolecules in one system inspired Burgess et al. to develop ways to link fluorescein and rosamine (rhodamine lacking a carboxylic acid functionality) fragments [67]. More specifically, they were linked in such a way that they would be conjugated if they became planar. One of the possibilities investigated is an alkyne linker. To achieve this goal, microwave-promoted Sonogashira alkylation of 5-bromofluorescein diacetate with trimethylsilylthyne was performed in only 25 min (Scheme 52). Subsequent deprotection of the alkyne with TBAF yielded 5-ethynyl-substituted fluorescein diacetate (Scheme 52). Microwave-assisted coupling with a brominated rosamine using the sulfonated variant



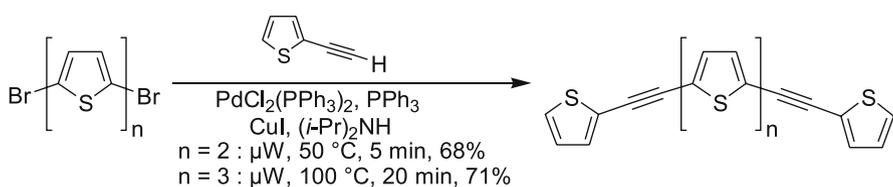
Scheme 52

of $\text{Pd}(\text{PPh}_3)_4$ as a catalyst in combination with a CuI co-catalyst followed by direct hydrolysis and counterion exchange gave the expected ethynyl-linked fluorescein and rosamine (Scheme 52).

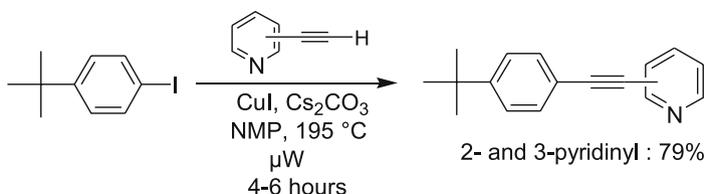
For the preparation of thiophene oligomers containing acetylenic spacers, microwave-assisted Sonogashira coupling of 2-ethynylthiophene with 5,5'-dibromo-2,2'-bithiophene and 5,5''-dibromo-2,2':5',2''-terthiophene was investigated (Scheme 53) [43]. $\text{PdCl}_2(\text{PPh}_3)_2$ with extra added triphenylphosphine and CuI in pure (*i*-Pr) $_2\text{NH}$ at 50 °C for 5 min or 100 °C for 20 min were found suitable for dibromothiophene and dibromoterthiophene, respectively. For coupling onto 5,5'-dibromo-2,2'-bithiophene, conventional heating in THF was also attempted but gave only 26% yield—homo-coupling of 2-ethynylthiophene was the major process taking place—while a much higher yield of desired compound could be obtained using the microwave-assisted protocol.

A microwave-assisted Cu-catalyzed Sonogashira-type protocol on aryl iodide substrates without the involvement of a palladium catalyst has also been published (Scheme 54) [71]. Reactions were executed using CuI and Cs_2CO_3 in NMP at 195 °C. The application seems to be fairly limited since there are indications that only (hetero)arylacetylenes are suitable coupling partners for this protocol. In addition, aryl bromides react more sluggishly than aryl iodides. Moreover, even on aryl iodides the reaction times required are on the order of hours.

Extended tetrathiafulvalenes with acetylenic cores are interesting compounds because of their redox and chromophoric properties. Such molecules are both interesting from materials and supramolecular chemistry perspectives. A tetraethynylethene-extended tetrathiafulvalene, for instance, was prepared using a microwave-promoted Sonogashira reaction [72]. Coup-



Scheme 53

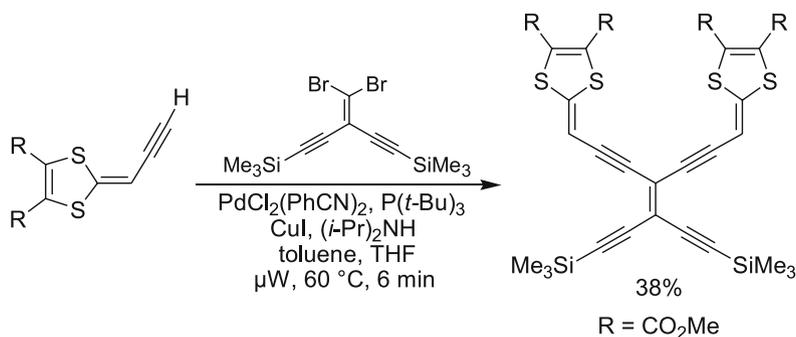


Scheme 54

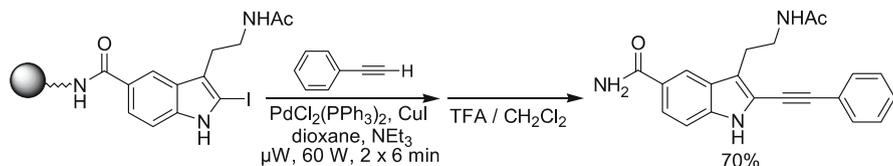
ling of dimethyl 2-prop-2-yn-1-ylidene-1,3-dithiole-4,5-dicarboxylate with [3-(dibromomethylene)penta-1,4-diyne-1,5-diyl]bis(trimethylsilane) at 60 °C for 6 min, using $\text{PdCl}_2(\text{PhCN})_2/\text{P}(t\text{-Bu})_3$ as a precatalyst system in combination with CuI as a co-catalyst, gave the desired extended tetrathiafulvalene with a yield of 38% (Scheme 55). A higher yield (84%) could be achieved using ultrasonication at 30 °C, albeit a longer reaction time of 4 h is required. The beneficial traits of ultrasonication in this case are likely a result of the high viscosity of the reaction mixture. Interestingly, the coupling reaction also worked at room temperature without microwave or ultrasonication but a much longer reaction time (24 h) was necessary, and the yield varied considerably.

Pharmacomodulated melatonin analogs were prepared by Berteina-Raboin et al. using SPOS. C-2 alkyne functionalized 5-carboxamido-*N*-acetyltryptamines could be obtained via microwave-assisted Sonogashira reaction of resin bound 3-[2-(acetylamino)ethyl]-2-iodo-1*H*-indole-5-carboxamide with phenylacetylene (Scheme 56) [33]. Two cross-coupling reaction cycles (involving complete removal of reagents and by-products by washing off the resin) were required to get the desired Sonogashira reaction to complete conversion at a constant power of 60 W. Interestingly, under conventional heating at 110 °C, a similar result (74%) could only be obtained using two reaction cycles of 24 h.

Nucleoside analogs substituted at the C-5 position of the pyrimidine base have been identified as antiviral and anticancer agents. In this context new



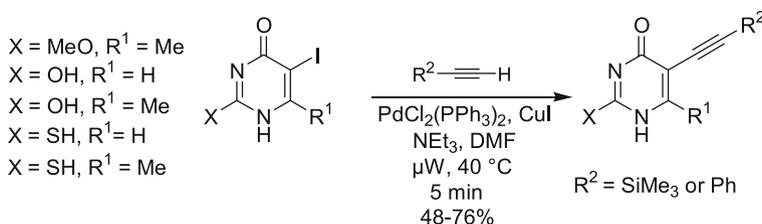
Scheme 55



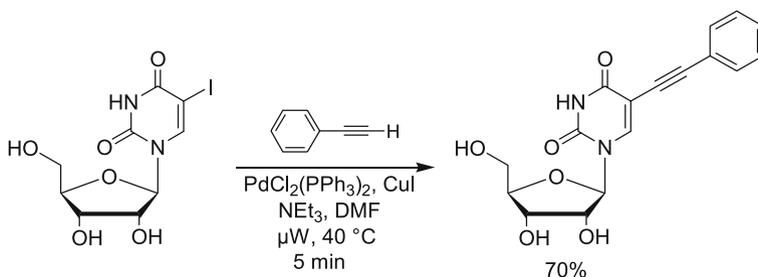
Scheme 56

C-5 alkynyl-substituted pyrimidinones were prepared via Sonogashira reaction on substituted 5-iodopyrimidin-4(1*H*)-ones under microwave irradiation [73]. In a typical experiment, substituted 5-iodopyrimidin-4(1*H*)-one, alkyne, PdCl₂(PPh₃)₂, CuI, and NEt₃ in DMF were irradiated for 5 min at 40 °C (Scheme 57). Even an alkynyluridine could be prepared without the requirement of protecting the sugar hydroxyl groups (Scheme 58). Interestingly, when propargyl alcohol was used as coupling partner no alkynyl derivatives were obtained, since ring-closure to furo[2,3-*d*]pyrimidines occurred in a one-pot process (Scheme 59).

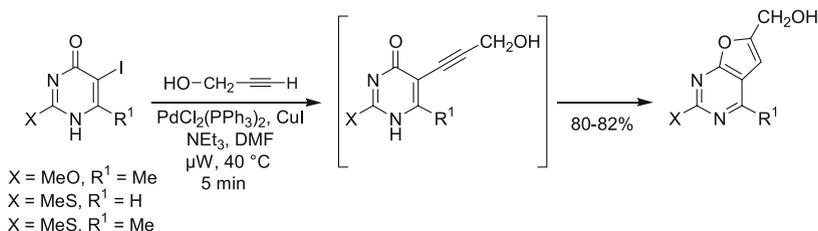
Besides furo[2,3-*d*]pyrimidines, 6-substituted 5*H*-pyrrolo[2,3-*b*]pyrazines have also been obtained in a microwave-promoted one-pot process starting from *N*-mesyl protected 2-amino-3-chloropyrazine (Scheme 60) [74]. The



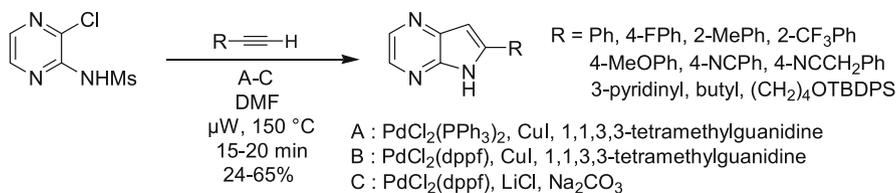
Scheme 57



Scheme 58



Scheme 59

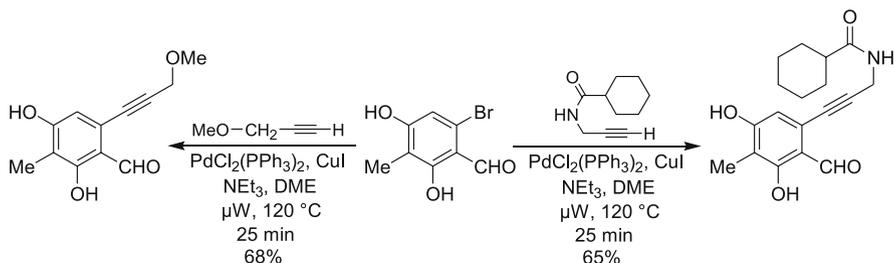


Scheme 60

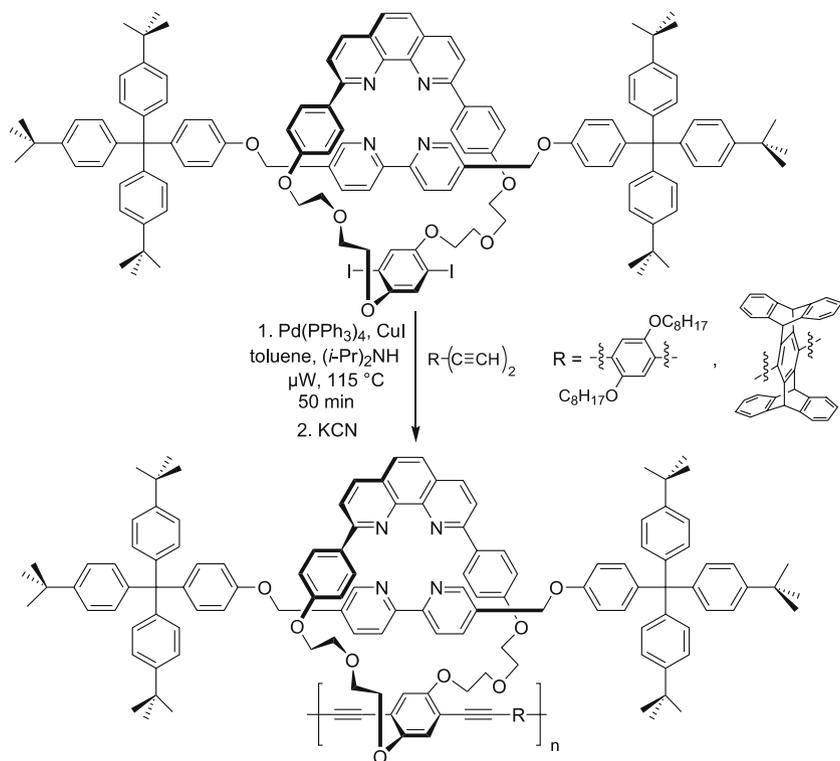
process involves three steps: Sonogashira reaction, cyclization, and deprotection. Several reaction conditions were identified to be suitable to establish the desired one-pot three-step transformation with a good yield. Notable are the copper-free conditions (condition C), which also worked smoothly. Comparison with conventional heating revealed that similar yields can normally only be obtained in much longer reaction times (on the order of hours). In particular, the alkylalkynes gave the most drastic reduction in time. In one case, a substantially higher yield was observed using conventional heating (2-methylphenylacetylene and condition B).

Azaphilones are a family of structurally diverse natural products containing a highly oxygenated bicyclic core and a quaternary center. They exhibit a wide range of biological activities. Porco recently reported a new synthetic approach for azaphilones involving cycloisomerization of *o*-alkynylbenzaldehydes to 2-benzopyrylium salts and subsequent oxidation to a 6*H*-isochromeno system [75]. The required *o*-alkynylbenzaldehydes were prepared via Sonogashira reaction. While phenylacetylene and 1-ethynylcyclohexene could be smoothly coupled with 6-bromo-2,4-dihydroxy-3-methylbenzaldehyde at room temperature, using $\text{P}(t\text{-Bu})_3$ as a ligand for the palladium catalyst and CuI as a co-catalyst, methyl propargyl ether and *N*-prop-2-yn-1-yl cyclohexanecarboxamide required a microwave-assisted Sonogashira reaction for efficient coupling (Scheme 61).

Swager et al. prepared conjugated polymers with tethered rotaxane groups [76]. As a substrate, a rotaxane containing a diiodobiphenyl unit was synthesized for this purpose. Polymerization via microwave-assisted Sono-



Scheme 61



Scheme 62

gashira coupling using substituted 1,4-diethynylbenzenes as alkynes was subsequently investigated (Scheme 62). Significantly, the use of microwave irradiation is highly preferential over conventional heating in this process since it reduced the reaction times of polymerization from 2 days to less than one hour. The obtained poly(*p*-phenyleneethynylene)s show potential as chemosensors as exemplified by the attenuation of fluorescence in the presence of phenols due to hydrogen bonding. Zn-doped poly(*p*-phenyleneethynylene)s exposed to alcohol vapor resulted in an increase in emission.

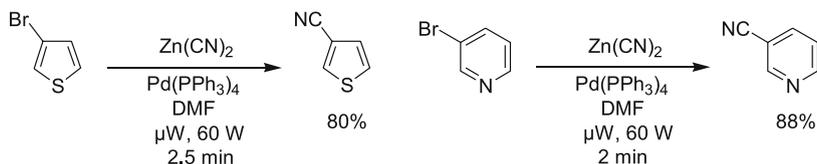
4 Cyanation Reaction

The synthesis of (hetero)aryl cyanides from (hetero)aryl halides via transition-metal catalysis is a very valuable reaction since a nitrile can be easily transformed into several other functional groups. Not until 2000 were the first examples on microwave-assisted cyanation reported in the literature. Alterman and Hallberg found that 3-bromopyridine and 3-bromothiophene were

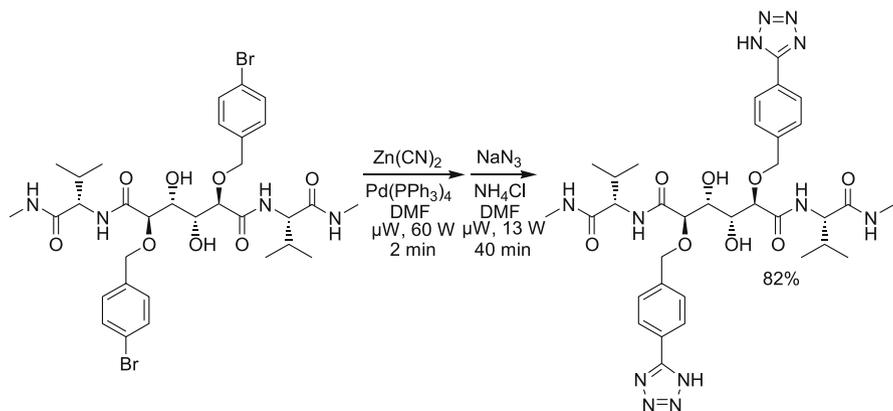
suitable substrates for a cyanation protocol involving $\text{Pd}(\text{PPh}_3)_4$ catalyst and $\text{Zn}(\text{CN})_2$ as an organometallic source of cyanide (Scheme 63) [77]. Heating at 60 W for only 2 min was usually sufficient for most (hetero)aryl bromide substrates but the electron rich 3-bromothiophene required a slightly longer reaction time to achieve a full conversion. The observed conversion rates were substantially larger than those of metal-catalyzed protocols found in the literature involving conventional heating.

As a direct application a potent C_2 -symmetric HIV-1 protease inhibitor (with two tetrazoles as carboxyl group bioisosteres) was prepared in one pot [77]. The process involved microwave-promoted cyanation followed by conversion of the nitrile group in a tetrazole with azide (Scheme 64). It is notable that the functionalization was achieved so smoothly without side reactions such as the elimination of water.

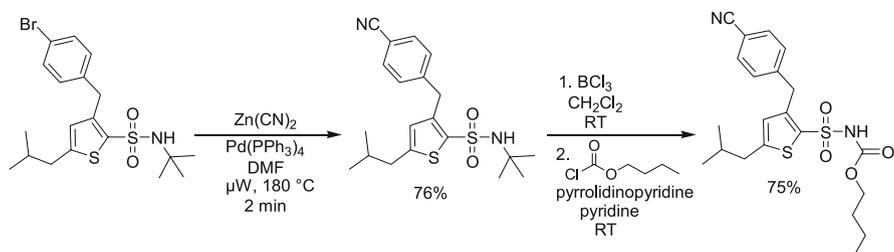
In 2004, Alterman et al. applied their cyanation protocol to the synthesis of *N*-(*t*-butyl)-3-(4-cyanobenzyl)-5-isobutylthiophene-2-sulfonamide [61]. De-protection of the sulfonamide followed by carbamate formation via reaction with butyl chloroformate finally gave the target compound for biological evaluation as a selective angiotensin II AT_2 receptor agonist (Scheme 65). The cyano derivative, however, showed only a low affinity for the AT_2 receptor (K_i value $> 10 \mu\text{M}$).



Scheme 63



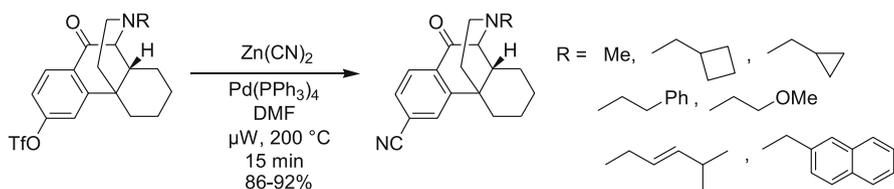
Scheme 64



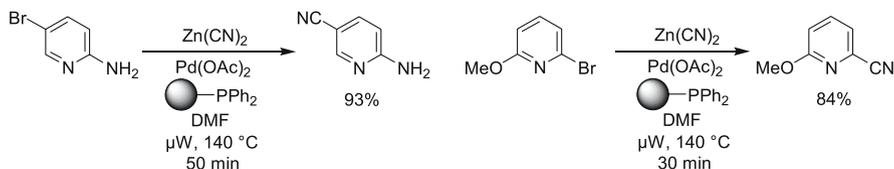
Scheme 65

In the course of studies on the design and synthesis of novel ligands for opioid receptors, 3-cyano-3-desoxy-*N*-alkyl-10-ketomorphinans were prepared from the corresponding triflates by applying the microwave cyanoation protocol developed by Alterman and Hallberg (Scheme 66) [76]. In a similar way 3-cyano-3-desoxy-*N*-alkylmorphinans were synthesized [79]. These 3-cyanomorphinans are important precursors for a series of opioid receptor agonist/antagonists via further transformation of the cyano group. Interestingly, the synthesis of 3-cyano-3-desoxy-10-keto-*N*-methylmorphinan was unsuccessful using traditional heating conditions for 24 h at 200 °C (< 5%) while a yield of 89% was achieved using microwave irradiation at the same temperature for 15 min. Unfortunately, the authors did not mention if the 200 °C under conventional heating was achieved in an oil bath or reaction mixture (in vessel) temperature.

A heterogeneous variant of the rapid microwave assisted homogeneous Pd-catalyzed cyanoation process of Alterman and Hallberg was developed by Srivastava and Collibee (Schemes 67 and 68) [80]. The heterogeneous cat-



Scheme 66



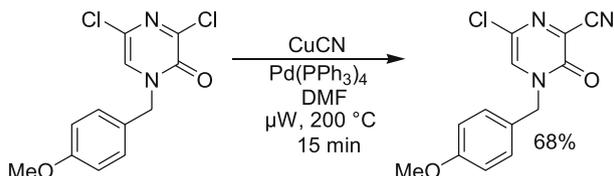
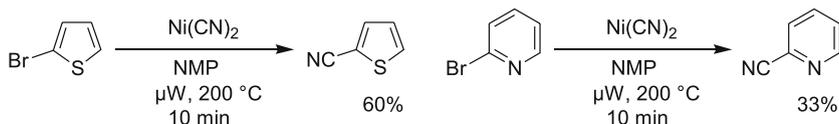
Scheme 67

**Scheme 68**

alyst was prepared by mixing a commercially available polymer-supported triphenylphosphine resin with Pd(OAc)_2 in DMF for 2 h. Significantly, initial experiments revealed that precatalyst formation is indeed important since it gave a better catalytic activity. The nitriles were obtained in high yields and with excellent purity (> 90%) by simply filtering off the resin and rinsing it with ether followed by aqueous extractions. No additional chromatography was required.

Chemoselective cyanation in the C-3 position of 3,5-dichloro-*N*-(4-methoxybenzyl)-pyrazin-2(1*H*)-one has been described by Van der Eycken et al. [27]. The procedure is similar to that reported by Alterman and Hallberg. The only difference is that CuCN was selected as transmetalating agent instead of Zn(CN)_2 . When a mixture of 3,5-dichloro-*N*-(4-methoxybenzyl)-pyrazin-2(1*H*)-one and CuCN in DMF, using $\text{Pd(PPh}_3)_4$ as a catalyst, was irradiated for 15 min at 200 °C, the desired 5-chloro-3-cyano-*N*-(4-methoxybenzyl)pyrazin-2(1*H*)-one could be isolated with a 68% yield (Scheme 69).

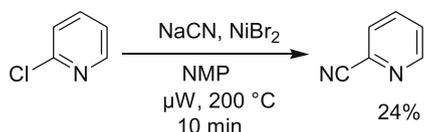
Leadbeater described the use of Ni(CN)_2 for the microwave-assisted cyanation of (hetero)aryl bromides [81]. The use of 0.6 equiv of Ni(CN)_2 was found to be optimal. Unfortunately, the heteroaryl bromides reported in the study gave relatively low yields due to significant decomposition (Scheme 70).

**Scheme 69****Scheme 70**

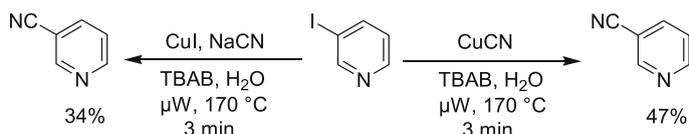
This is a problem that has been reported by several researchers in other cyanation methods on heteroaromatic halides. (Hetero)aryl chlorides have also been tackled via in situ halogen exchange to (hetero)aryl bromides followed by sequential cyanation (Scheme 71). For this microwave-assisted process an equimolar amount of NiBr_2 and a two-fold excess of NaCN were used. The only heteroaromatic chloride tested was 2-chloropyridine. Although the procedures described involve the use of significant amounts of nickel salts, a clear advantage is that the reactions can be performed in air. Moreover, the cyanating reagents are easily removed since they are water soluble.

The same group also described the rapid cyanation of aryl iodides in water using CuCN (Scheme 72) [82]. The addition of the phase-transfer agent TBAB was crucial for the reactions; otherwise, no reaction occurred. CuCN can also be generated in situ from NaCN and CuI (Scheme 72). While aryl iodides gave good results, the yield obtained with 3-pyridinyl iodide was poor.

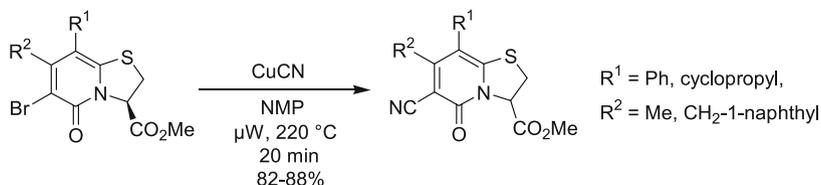
A microwave-assisted variant of the Rosenmund von Braun reaction has also been developed (Scheme 73) [83]. DMF at $200\text{ }^\circ\text{C}$ proved not very useful for the cyanodehalogenation of methyl (3*R*)-6-bromo-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylates since only low yields of the corresponding nitrile were obtained, and there were substantial amounts of unconverted starting material. Extending the reaction time from 10 to 20 min gave more desired reaction product but also significant amounts of



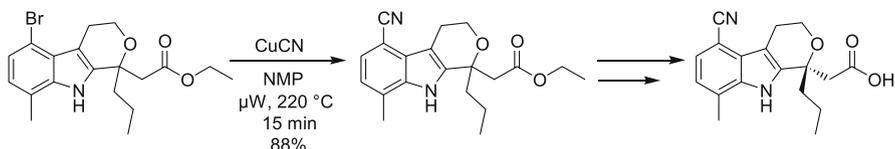
Scheme 71



Scheme 72



Scheme 73

**Scheme 74**

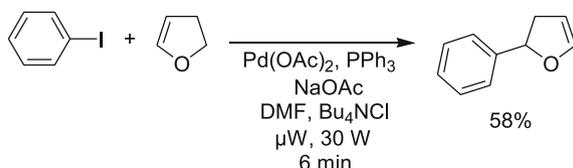
by-products. Finally, switching to NMP as a solvent and increasing the reaction temperature to 220 °C gave high yields and no detectable competing side reactions. Unfortunately, under these reaction conditions racemization was a problem, since a serious decrease in enantiomeric excess was observed.

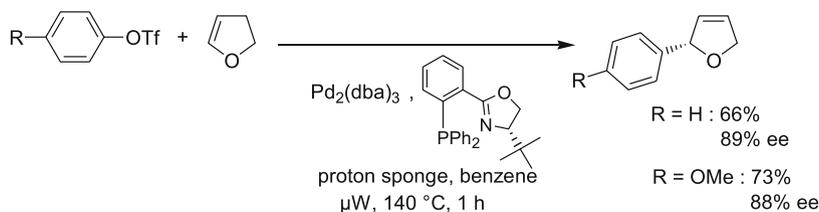
These modified Rosenmund von Braun reaction conditions were also used by Gopalsamy et al. for the rapid cyanation of the 1,3,4,9-tetrahydropyrano-[3,4-*b*]indole skeleton while searching for potent and selective Hepatitis C virus polymerase inhibitors (Scheme 74) [84].

5 Heck–Mizoroki Reaction

In 1996, the first examples of intermolecular microwave-assisted Heck reactions were published [85]. Among these, the successful coupling of iodobenzene with 2,3-dihydrofuran in only 6 min was reported (Scheme 75). Interestingly, thermal heating procedures (125–150 °C) resulted in the formation of complex product mixtures affording less than 20% of the expected 2-phenyl-2,3-dihydrofuran. The authors hypothesize that this difference is the result of well-known advantages of microwave irradiation, e.g., elimination of wall effects and low thermal gradients in the reaction mixture.

Larhed et al. investigated enantioselective Heck reactions with 2,3-dihydrofuran as alkene [86]. In the coupling with phenyl triflate, conditions previously reported by Pfaltz [87] were attempted under microwave irradiation. Interestingly, the catalytic system $\text{Pd}_2(\text{dba})_3/(4S)\text{-4-}t\text{-butyl-2-[2-(diphenylphosphanyl)phenyl]-4,5-dihydro-1,3-oxazole}$, identified by the Swiss team, was found suitable for high-temperature microwave-assisted enantioselective Heck reactions (Scheme 76). Using a proton sponge as a base and benzene as a solvent gave the best conversions (Scheme 76). At tempera-

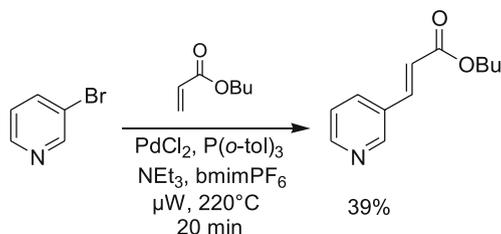
**Scheme 75**

**Scheme 76**

tures above 145 °C, catalyst decomposition occurs before complete conversion. Although in the optimized procedure the reaction time is still 1 hour, it is substantially shorter than the days required under conventional heating in Pfaltz's original protocol. Moreover, no inert atmosphere is required. Unfortunately, the obtained enantiomeric excess dropped from 97% to 89% going from 70 °C to 140 °C. The electronic properties of the triflate proved to be important since 4-methoxyphenyl triflate gave a high yield with a high enantiomeric excess, whereas the use of 4-cyanophenyl triflate gave only small amounts of an arylated Heck product.

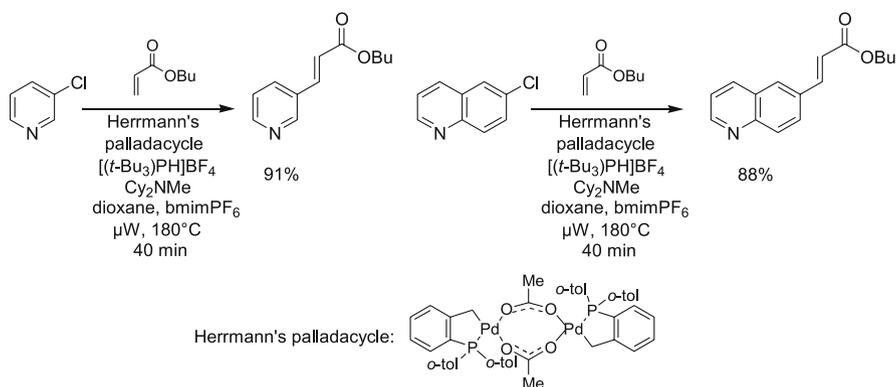
Besides conventional solvents, ionic liquids have also been selected as reaction media for microwave-assisted Heck reactions [88]. $\text{PdCl}_2/\text{P}(o\text{-tolyl})_3$ precatalyst in 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF_6) using triethylamine as a base proved to be very efficient for the rapid vinylation of aryl bromides and iodobenzenes with butyl acrylate. Interestingly, no inert atmosphere is required. Unfortunately, heteroaryl bromides such as 3-bromopyridine reacted much less efficiently (Scheme 77). Product separation could be easily achieved via distillation from the high-boiling bmimPF_6 . Ionic liquids such as bmimPF_6 are very attractive for MOAS, since they have the clear advantage of transforming microwave energy into heat very efficiently, giving rise to extremely short ramp times. In addition, they allow one to perform reactions at very high temperatures in closed vials without the creation of extreme pressures due to their negligible vapor pressure.

One year later the same team described the rapid alkenylation of 3-chloropyridine and 6-chloroquinoline with butyl acrylate based on Herrmann's palladacycle employing a mixture of dioxane and bmimPF_6 as a medium

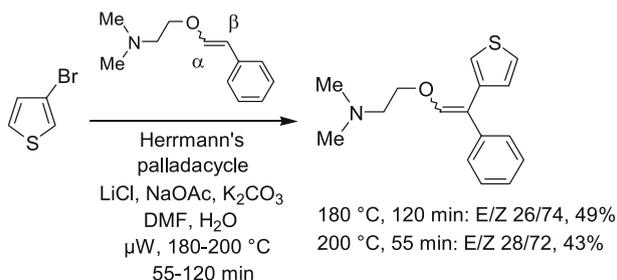
**Scheme 77**

(Scheme 78) [89]. Aryl chlorides with activating as well as deactivating substituents could also be coupled under the same conditions in high yields, ranging from 60% to 95%, within 30–60 min of microwave irradiation. The process does not require an inert atmosphere. The increased conversion observed with the addition of the ionic liquid reveals that it might have an additional function besides simply acting as a “molecular irradiator”. It cannot be excluded for instance that carbene palladium complexes are formed in situ and implicated in the catalytic cycle.

Microwave-assisted Heck reaction of (hetero)aryl bromides with *N,N*-dimethyl-2-[(2-phenylvinyl)oxy]ethanamine, using Herrmann’s palladacycle as a precatalyst, yielded the corresponding β -(hetero)arylated Heck products in a good *E/Z* selectivity (Scheme 79) [90]. The α/β -regioselectivity can be explained by the chelation control in the insertion step. This selectivity is better than 10/90 when no severe steric hindrance is introduced in the (hetero)aryl bromides. The process does not require an inert atmosphere. There is evidence that a Pd(0)/Pd(II)- and not Pd(II)/Pd(IV)-based catalytic cycle is involved. Similarly, other β -amino-substituted vinyl ethers such as



Scheme 78



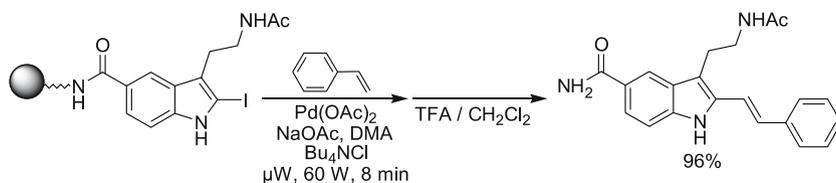
Scheme 79

(*S*)-*N*-methyl-2-vinylloxymethylpyrrolidine have also been used as an alkene partner in Heck reactions on vinyl triflates under microwave irradiation [91].

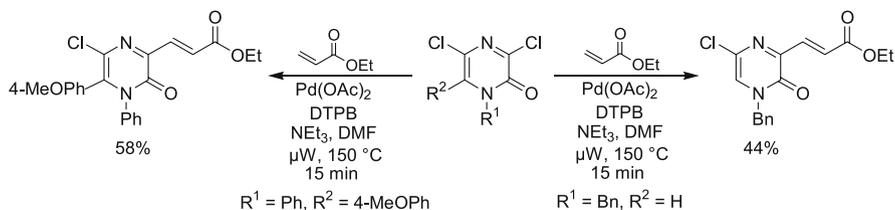
Pharmacomodulated melatonin analogs were prepared by Berteina-Raboin et al. using SPOS [33]. C-2 vinylated 5-carboxamido-*N*-acetyltryptamines could be smoothly obtained via a microwave-assisted Heck reaction as exemplified by the rapid coupling of resin-bound 3-[2-(acetyl-amino)ethyl]-2-iodo-1*H*-indole-5-carboxamide with styrene (Scheme 80). Interestingly, under conventional heating at 100 °C a similar result (90%) could only be obtained using two reaction cycles (involving complete removal of reagents and by-products by washing off the resin) of 24 h.

Chemoselective alkenylation in the C-3 position of *N*-substituted 3,5-dichloropyrazin-2(1*H*)-ones has been described by Van der Eycken et al. [27]. When a mixture of *N*-substituted 3,5-dichloropyrazin-2(1*H*)-one, ethyl acrylate, and NEt₃ in DMF, using Pd(OAc)₂/DTPB [2-(di-*t*-butylphosphanyl)biphenyl] as a precatalyst, was irradiated for 15 min at 150 °C, the desired β -functionalized ethyl acrylates could be obtained in moderate yields (Scheme 81). When styrene was used as an alkene, a mixture of *E* and *Z* products was isolated. The type of catalyst used proved to be important to avoid competitive Diels–Alder reaction of ethyl acrylate with the hetero-diene system of 3,5-dichloro-1-benzylpyrazin-2(1*H*)-one.

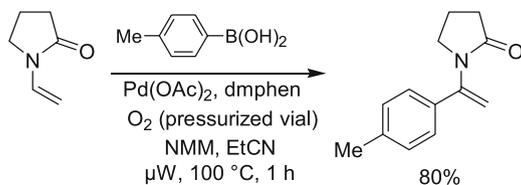
Oxidative Heck arylation of enamides with arylboronic acids, using oxygen gas as a reoxidant for Pd(0) and 2,9-dimethyl-1,10-phenanthroline as a chelating regiocontrolling ligand, yielded α (= internally) arylated reaction product as the major compound with a very good α/β selectivity [92]. Microwave irradiation with prepressurized sealed vials proved useful in reducing the reaction time (Scheme 82).



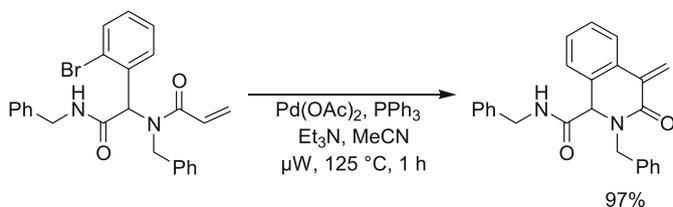
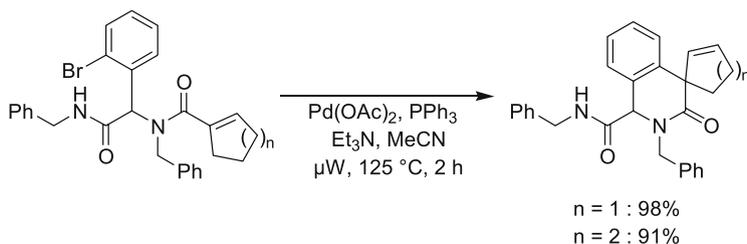
Scheme 80

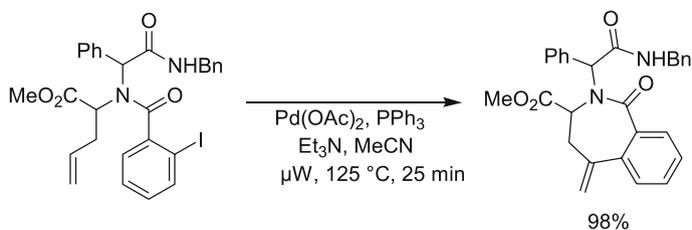


Scheme 81

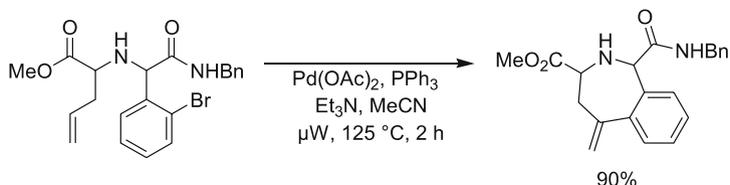
**Scheme 82**

The effect of microwave irradiation on intramolecular Heck reactions has also been studied. Gracias et al. prepared *N*,2-dibenzyl-4-methylene-3-oxo-1,2,3,4-tetrahydroisoquinoline-1-carboxamide via intramolecular alkenylation using a combination of $\text{Pd}(\text{OAc})_2$ and PPh_3 as a precatalyst in acetonitrile at 125 °C (Scheme 83) [93]. In a similar way, spiro compounds were prepared with good diastereoselectivity (Scheme 84). Two separate submissions to the Heck reaction conditions were required in this case (2 h total reaction time). Interestingly, the microwave-assisted approach was clearly superior for the synthesis of the spiro compounds since oil bath experiments under reflux took 16–18 h for completion and resulted in products at lower yields. The diastereoselectivities under microwave and conventional heating were similar. Also, seven-membered 5-methylene-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one and 5-methylene-2,3,4,5-tetrahydro-1*H*-2-benzazepine ring systems could be smoothly synthesized using the same protocol (Schemes 85 and 86). All the required Heck substrates were obtained by a simple Ugi multi-component reaction. The authors also demonstrated that the sequential Ugi/Heck procedure can be extended to SPOS (Wang resin); however, a low yield was obtained (Scheme 87).

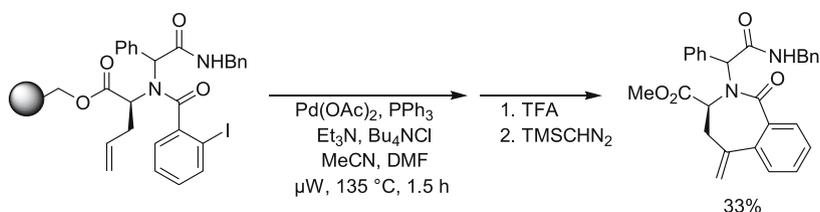
**Scheme 83****Scheme 84**



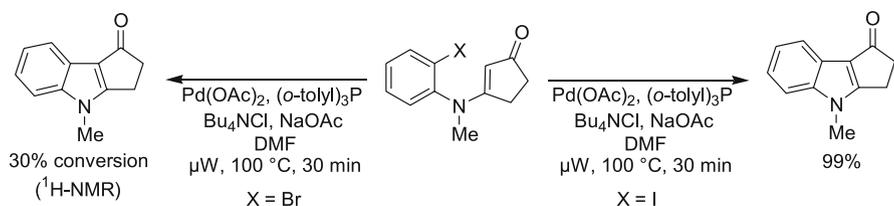
Scheme 85



Scheme 86



Scheme 87



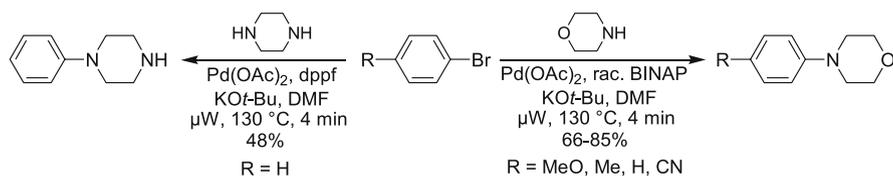
Scheme 88

9-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one, the key building block of the neuroactive compound alosetron, was easily obtained from 3-[(2-halophenyl)(methyl)amino]cyclohex-2-en-1-one by pyrrole ring formation via Heck reaction under microwave irradiation [94]. While the iodo substrate gave an excellent yield in only 30 min at 100 °C the corresponding bromo derivative converted only poorly under the same reaction conditions (Scheme 88).

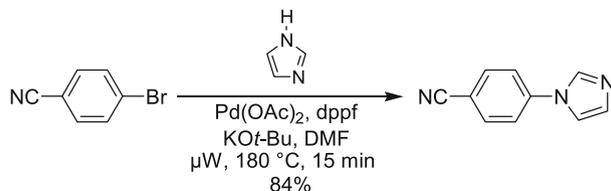
6 Buchwald–Hartwig Reaction

Not until 2002 were the first Buchwald–Hartwig reactions using dedicated microwave equipment reported [95]. The cyclic aliphatic amine morpholine was coupled with activated, electronically neutral and deactivated aryl bromides using $\text{Pd}(\text{OAc})_2/\text{rac. BINAP}$ as a precatalyst and $\text{KO}-t\text{-Bu}$ as a base in DMF (Scheme 89). DMF was selected as a solvent since it shows a good coupling efficiency with microwaves. Unprecedented rates for C–N coupling reactions were achieved with this standard precatalyst since a complete conversion of aryl bromides was achieved in a reaction time of only 4 min. For piperazine as an amination partner, *dppf* was used as a ligand for the palladium catalyst (Scheme 89). In this case, the obtained yield is rather low, which can be attributed to a competing *N*-diarylation reaction. The same precatalyst also proved useful for the rapid *N*-arylation of 1*H*-imidazole with 4-bromobenzonitrile when a higher temperature (180 °C) and a longer reaction time (15 min) were applied (Scheme 90). Unfortunately, electron-rich aryl bromides did not react with 1*H*-imidazole under these conditions. Interestingly, performing some of the microwave-assisted amination reactions in a pre-heated oil bath at the same temperature revealed that similar yields can be obtained in the same reaction time. In none of the reported examples were the reactions run under an inert atmosphere.

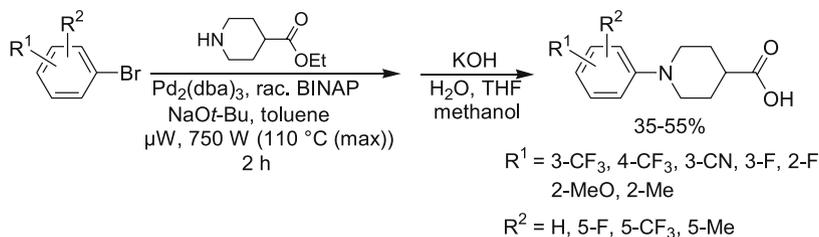
Independently, Antane reported that arylisonipecotic acids were obtained from aryl bromides in a two-step process involving microwave-assisted palladium-catalyzed amination with ethyl isonipecotate followed by ester hydrolysis with KOH (Scheme 91) [96]. Interestingly, toluene, which is the standard solvent for Buchwald–Hartwig aminations under conventional heating, was used as the sole reaction medium, although it is a very weak



Scheme 89



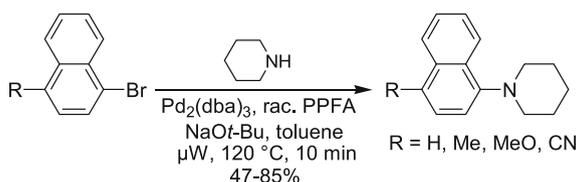
Scheme 90

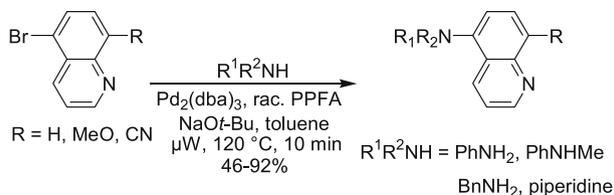
**Scheme 91**

microwave absorber. Multiple parallel reactions could be run by using a rotor with several vessels (5 mmol scale each). A drawback of the developed procedure is that rather long reaction times were required.

Rapid aminations of 1-bromonaphthalenes with piperidine under microwave irradiation were reported by Hamann using $\text{Pd}_2(\text{dba})_3/\text{rac. PPFA}$ (*N,N*-dimethyl-1-[2-(diphenylphosphanyl)ferrocenyl]ethylamine) precatalyst in combination with NaO-*t*-Bu in toluene at 120 °C (Scheme 92) [97]. Typically, reactions performed under conventional heating at 120 °C (oil bath) were still progressing after 16 h and were essentially complete by 24 h, whereas the microwave reactions appeared to be finished after 10 min. The same reaction conditions were also useful to functionalize 5- and 8-bromoquinolines with anilines and aliphatic amines (Schemes 93 and 94). Remarkably, no product formation was observed with 5-bromo-8-cyanoquinoline and 5-bromo-8-methoxyquinoline under conventional heating for 24 h at the same temperature, while the desired 5-aminoquinolines were smoothly obtained under microwave irradiation in a reaction time of only 10 min.

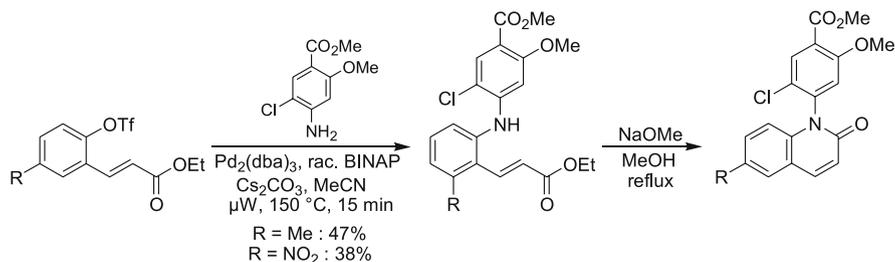
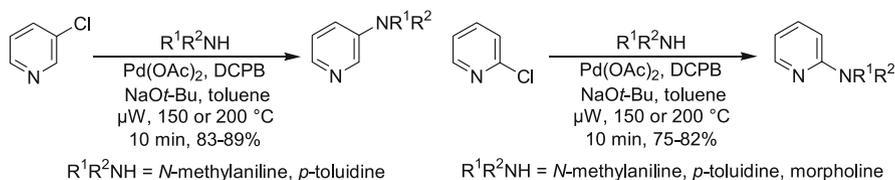
N-Arylquinolin-2(1*H*)-ones have been prepared in a four step process from commercially available coumarins, utilizing a Buchwald–Hartwig ami-

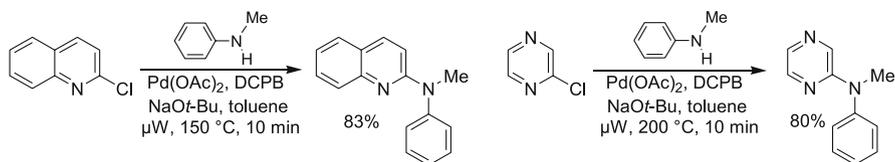
**Scheme 92****Scheme 93**

**Scheme 94**

nation for the key reaction [98]. Microwave-assisted C – N bond formation on ethyl (*2E*)-3-(2-[(trifluoromethyl)sulfonyl]oxy)phenyl)acrylate with methyl 4-amino-5-chloro-2-methoxybenzoate at 150 °C for 15 min smoothly yielded the desired substrates for a subsequent ring closure (Scheme 95). The obtained yields were similar to those achieved under conventional heating in toluene at reflux for 24 h. For the aminations performed with the microwave apparatus, toluene was substituted for acetonitrile, which is a much better microwave absorber.

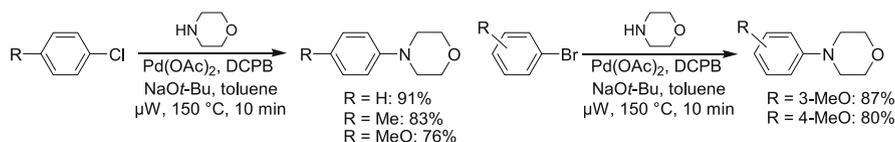
More challenging are the (hetero)aryl chlorides, since they are cheaper and more widely available than the corresponding bromides and iodides. Maes et al. published the first examples of microwave-assisted Buchwald–Hartwig aminations on (hetero)aryl chlorides in a communication in 2003 [99]. The substrates 2- and 3-chloropyridine as well as 2-chloroquinoline were smoothly coupled with *N*-methylaniline and *p*-toluidine within only 10 min using a catalyst loading of only 1 mol % (Schemes 96 and 97). The diazine

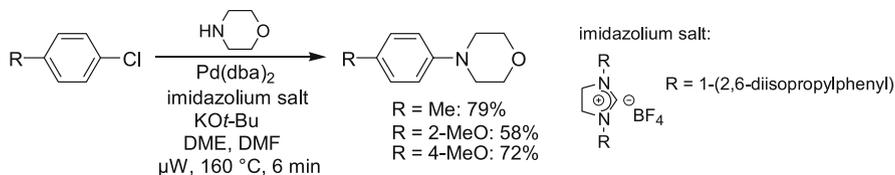
**Scheme 95****Scheme 96**

**Scheme 97**

chloropyridazine could also be used, albeit a higher catalyst loading (1.5 mol %) was required (Scheme 97). In the initial study only one aliphatic amine was tested, namely morpholine. Later, the same team published a full paper with more examples involving electron-neutral and -rich aryl chlorides and all types of aliphatic amines (primary and secondary cyclic and acyclic) (Scheme 98) [100]. Moreover, the protocol was extended to aryl bromides (Scheme 98). Interestingly, the results of the researchers revealed the remarkable temperature stability of palladium catalysts based on the Buchwalds biphenyl-type ligands 2-(dicyclohexylphosphanyl)biphenyl (DCPB) and 2-(di-*t*-butylphosphanyl)biphenyl (DTPB). To investigate the existence of non-thermal MW effects, several coupling reactions optimized for microwave irradiation were also studied in an oil bath at the same temperature. To mimic the flash heating rate of the MW experiments, the loaded vessels were immersed in a preheated oil bath. All the oil bath experiments performed clearly revealed a similar yield as obtained under microwave irradiation in the same reaction time. These results indicate that, for this type of reaction, no specific microwave effects have to be taken into account to explain the rapid aminations; the studied microwave-assisted reactions are only governed by thermal effects (Arrhenius).

Independently, Caddick et al. reported microwave-assisted amination of aryl chlorides using a palladium-*N*-heterocyclic carbene complex as the catalyst (Scheme 99) [101]. Initial experiments in a domestic microwave oven (reflux conditions) revealed that the solvent is crucial for the reaction. The Pd source also proved very important, since Pd(OAc)₂ at high power in DMF gave extensive catalyst decomposition and using it at medium and low power gave no reaction at all. Pd(dba)₂/imidazolium salt (1 mol % catalyst loading) in DME with the addition of some DMF was found to be suitable. Oil bath experiments indicated that only thermal effects are governing the amination reactions.

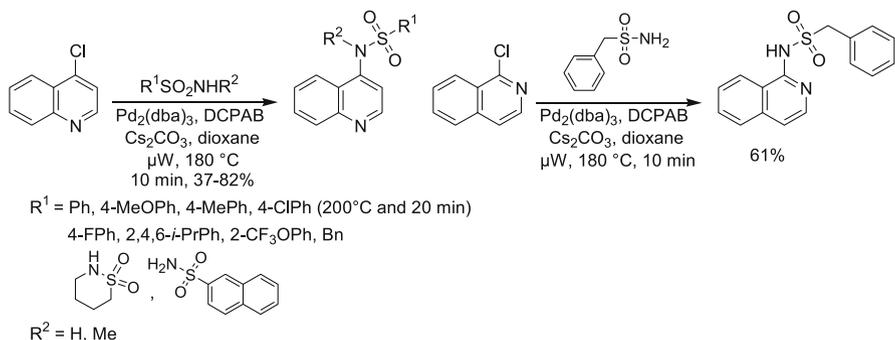
**Scheme 98**



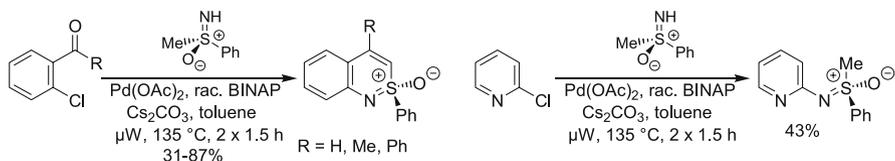
Scheme 99

Sulfonamides have been *N*-arylated with 4-chloroquinoline and 1-chloroisoquinoline using a microwave-assisted Buchwald–Hartwig amination protocol [102]. $\text{Pd}_2(\text{dba})_3/2\text{-}(\text{dicyclohexylphosphanyl})\text{-2'-(}N,N\text{-dimethylamino})\text{biphenyl}$ (DCPAB) precatalyst with Cs_2CO_3 as base in dioxane at 180°C gave the expected *N*-quinolin-2-yl- and *N*-isoquinolin-2-ylsulfonamides in moderate to good yields in a short reaction time (Scheme 100). The coupling protocol is fairly general since arenesulfonamides with a variety of electronic and steric factors as well as alkanesulfonamides are well tolerated. Surprisingly, attempts to use 2-chloro- and 3-chloropyridine as substrates were unsuccessful.

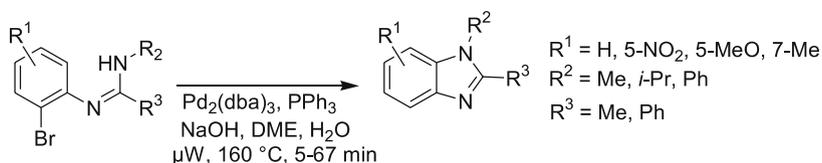
Besides sulfonamides, chiral sulfoximines have also been used in C–N bond formation under microwave irradiation [103]. The only heteroaryl chloride used in the study—namely, 2-chloropyridine—gave the desired *N*-(pyridin-2-yl)sulfoximine at a yield of 43% (Scheme 101). Interestingly,



Scheme 100



Scheme 101

**Scheme 102**

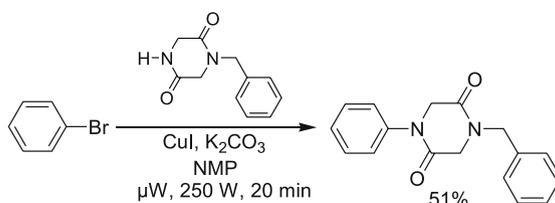
the use of 2-chlorobenzaldehyde, 2-chloroacetophenone, and 2-chlorobenzophenone gave amination followed by a subsequent condensation yielding the corresponding benzothiazines in moderate to good yields (Scheme 101). Remarkably, two reaction cycles of 1.5 hour at 135 °C were required to get the reactions to complete conversion. The second cycle involves addition of extra precatalyst.

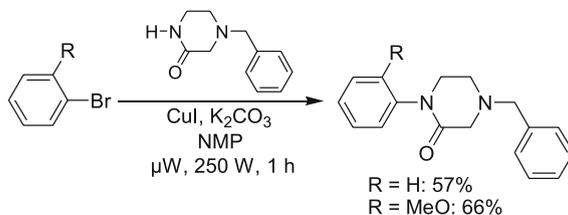
Microwave-assisted intramolecular C – N bond formations have also been studied. Substituted benzimidazoles were easily prepared from the corresponding *N*-(2-bromophenyl)imidoforamides by Brian et al. (Scheme 102) [104]. The protocol involved the use of a combination of $\text{Pd}_2(\text{dba})_3$ and PPh_3 in a mixture of DME and water using NaOH as the base at 160 °C. It was applicable for electron poor, neutral and rich as well as sterically hindered amidines. The fastest reactions were obtained with an electron withdrawing substituent R^1 and substituents located near the reacting centers.

7

Goldberg Reaction

N-Arylpiperazin-2-ones, *N*-arylpiperazin-2,5-diones and *N*-aryl-3,4-dihydroquinolin-2(1*H*)-ones have been synthesized via a microwave-enhanced Goldberg reaction [105]. *N*-arylation reactions with 4-benzylpiperazin-2-one and 4-benzylpiperazin-2,5-dione performed in the microwave (reflux conditions) were tremendously accelerated in comparison with the same transformations performed under classical heating at reflux (Schemes 103 and 104). The phenylation of 3,4-dihydroquinolin-2(1*H*)-one under microwave irradiation was also faster but less pronounced.

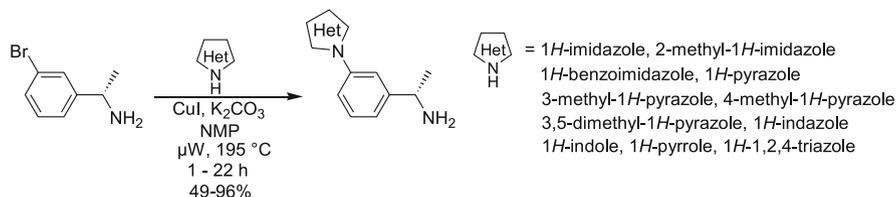
**Scheme 103**



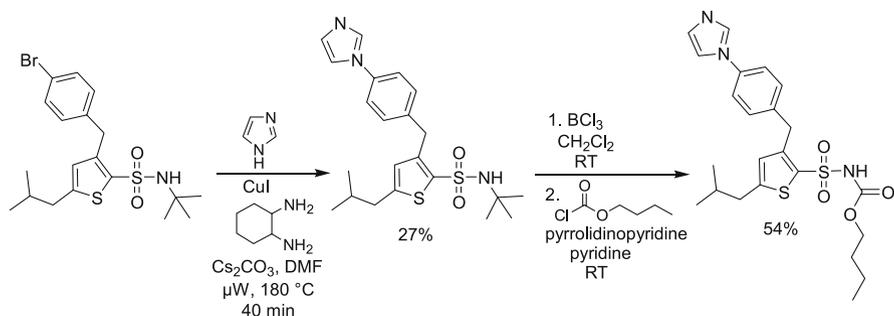
Scheme 104

8 Ullmann Reaction

Wu et al. studied the Ullmann coupling of (*S*)-[1-(3-bromophenyl)] ethylamine with a variety of *N*-H-containing heteroarenes (Scheme 105) [106]. In most cases the microwave-assisted Cu-catalyzed *N*-arylations were finished in 1 to 3 h of heating at 195 °C. For 3-methylpyrazole and 3,5-dimethylpyrazole, very long reaction times (17 and 22 h respectively) as well as the addition of extra heteroarene were required, presumably due to steric effects. The former diazole gave a 1 : 1 mixture of regioisomers. Interestingly, the free amino group of (*S*)-[1-(3-bromophenyl)] ethylamine is well tolerated in this protocol and no epimerization occurred under the reported reaction conditions.



Scheme 105



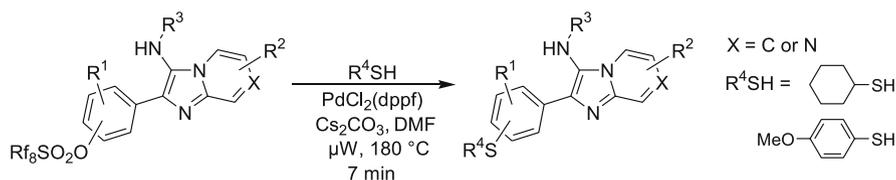
Scheme 106

In 2004, Alterman et al. used a microwave-assisted Ullmann-type protocol for the synthesis of *N*-(*t*-butyl)-3-[4-(1*H*-imidazol-1-yl)benzyl]-5-isobutylthiophene-2-sulfonamide (Scheme 106) [61]. Deprotection of the sulfonamide followed by carbamate formation via reaction with butyl chloroformate finally gave the target compound for biological evaluation as selective angiotensin II AT₂ receptor agonist. The 1*H*-imidazole derivative, however, showed only a low affinity for the AT₂ receptor (K_i value > 10 μ M).

9

Pd-Catalyzed C–S Bond Formation

A library of biologically relevant 2-aryl-3-aminoimidazo[1,2-*a*]pyridines and 2-aryl-3-aminoimidazo[1,2-*a*]pyrazines was created using a combination of MAOS and fluoros chemistry. The 2-aryl-3-aminoimidazo[1,2-*a*]pyridines and 2-aryl-3-aminoimidazo[1,2-*a*]pyrazines were synthesized from perfluorooctanesulfonyl-tagged hydroxybenzaldehydes via a microwave-assisted multi-component reaction involving isocyanides and 2-aminopyridines or aminopyrazines [65]. The perfluoralkylsulfonyl tag did not only have a function as a phenol-protecting group for the condensation reaction and as a phase tag for purification in the multi-component reaction but was afterwards used as an activating group for cross-coupling reactions. For instance, detagging via microwave-promoted palladium-catalyzed C–S bond formation smoothly yielded a thioether unit (Scheme 107).

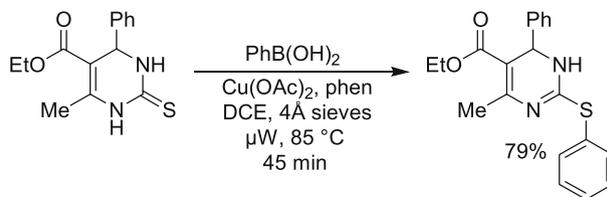


Scheme 107

10

Cu-Mediated C–S Bond Formation

Ethyl 6-methyl-4-phenyl-2-(phenylthio)-1,4-dihydropyrimidine-5-carboxylate was easily synthesized from ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate and phenylboronic acid via microwave-assisted Cu-mediated S-phenylation (Scheme 108) [107]. The reaction involves the use of a stoichiometric amount of $\text{Cu}(\text{OAc})_2$ and a two-fold excess of 1,10-phenanthroline as a ligand.



Scheme 108

11 Conclusion

In summary, the microwave-assisted decoration of heteroarenes via transition-metal-based carbon–carbon and carbon–heteroatom bond formation is underexplored in comparison with the work devoted to arenes. The main reported advantages of the combination of microwave irradiation and transition-metal-mediated processes are the substantially shorter reaction times, the higher yields, and the greater purity of the crude reaction mixtures. Interestingly, most transition metal complexes classically used under reflux conditions show a remarkable thermal stability at higher temperature in closed vials. When comparing the availability of published literature examples, carbon–carbon bond construction is better studied than carbon–heteroatom bond formation. This is not really surprising, since a metal-mediated C – X bond-forming process only makes sense when classical nucleophilic substitution fails or gives poor yields (due to less reactive nucleophiles and/or electron rich heteroarene substrates). Unfortunately, examples of the construction of heterocyclic cores via palladium- or copper-mediated processes under microwave irradiation are scarce.

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Synthesis of Heterocycles via Microwave-Assisted Cycloadditions and Cyclocondensations

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1	Introduction	214
2	Four-Membered Rings	216
3	Five-Membered Rings – Aromatic	217
3.1	Pyrrole	217
3.2	Thiophene	220
3.3	Furan	221
3.4	1,3-Azoles	222
3.4.1	Imidazole	222
3.4.2	Oxazole	224
3.4.3	Thiazole	225
3.5	1,2-Azoles	225
3.5.1	Pyrazole	225
3.6	Five-Membered Heterocycles with More than Two Heteroatoms	227
4	Five-Membered Rings – Non Aromatic	230
4.1	Tetrahydrofurans and Furanones	230
4.2	Pyrrolines and Pyrrolidines	232
4.3	Saturated Imidazoles and Pyrazoles	235
4.4	Saturated Oxazole, Thiazole, and Oxadiazole Derivatives	237
4.5	Hydantoins	240
4.6	Other Saturated Five-Membered Heterocycles	240
5	Six-Membered Rings – Aromatic	241
5.1	Pyridines	241
5.2	Diazines	242
5.3	Triazines	243
6	Six-Membered Rings – Non Aromatic	244
7	Five-Membered Benzocondensed Heterocycles	246
7.1	Phthalimides	246
7.2	Indoles	246
7.3	Benzo[b]furans	247

7.4	Benzo[b]thiophenes	248
7.5	Benzimidazoles	248
7.6	Benzoxazoles	249
7.7	Benzocondensed Heterocycles with More than Two Heteroatoms	249
7.8	Purines	251
8	Six-Membered Benzocondensed Heterocycles	252
8.1	Quinolines and Isoquinolines	252
8.2	Benzoxazines	253
8.3	Quinoxalines	254
8.4	Coumarins and Flavones	254
9	Tricyclic Systems	256
10	Tetracycles and Polycycles	258
11	Diazepines	259
12	Macrocycles	260
	References	262

Abstract Controlled microwave heating has found many important applications in the synthesis of heterocycles. Almost all kinds of heterocycles have been prepared (or their preparation attempted) with the aid of microwaves. Many examples of cyclocondensations, reactions where two or more functional groups combine with the loss of another small molecule (usually water), have been described. Moreover, microwave irradiation successfully induces cycloaddition reactions, especially in the cases where high temperatures are required. This review collects the most representative examples of the application of microwaves to these two kinds of transformations. Except for a few examples, all the reactions selected have been carried out under controlled microwave irradiation using dedicated instruments.

Keywords Cycloaddition reactions · Cyclocondensation reactions · Heterocycles · Microwaves

1

Introduction

The use of microwaves to heat organic reactions has attracted considerable interest in the last 15 years. This technique allows to reduce the time of chemical transformations and, consequently, the formation of by-products is reduced, often with improved yields and purity of the products. Practically every kind of transformation has been tested under microwave irradiation, in many instances giving better results than conventional heating [1].

An additional interest in the applications of microwave-assisted organic synthesis is related to the possibility of having more rapid access to large libraries of diverse small molecules and heterocyclic compounds

with biological activities [2–5]. Consequently, it has been demonstrated that the synthesis of a variety of heterocyclic compounds can be carried out safely in dedicated microwave reactors with remarkable rate enhancements. This is mainly due to the superheating effect—the ability of microwaves to rapidly heat the reactions much above the boiling point of the solvent [6, 7].

Although microwave irradiation might seem simply an alternative to conventional heating for introducing energy into reactions, the use of this technology has launched a new concept in organic synthesis because the transmission and absorption of energy is different from conventional thermal heating [6]. Moreover, several reaction types have been carried out successfully under solvent-free conditions, in which case the energy is not dispersed in the solvents, but directly absorbed by the reagents. This last possibility is attractive in offering reduced pollution and lower cost together with the simplicity of processing and handling [8–10]. The temperature profiles achieved by microwave heating cannot easily be duplicated with traditional heating and can allow kinetic control. Moreover, several reactions have been reported in which the chemo-, regio- and stereo-selectivity changed under microwave conditions in comparison to conventional heating in an oil bath.

This review collects the synthesis of different heterocycles formed through cyclocondensation or cycloaddition reactions. The term cyclocondensation is related to a reaction in which the heterocycle is formed with elimination of one or more simple molecular species (generally water) [11]. Examples in which the heterocycle is formed through a cycloaddition have also been selected. Most of the examples reported deal with cyclocondensations, as efficient heating may induce a better elimination of water or other simple, volatile compounds. On the other hand, microwave irradiation induces cycloadditions with great success, as these reactions involve, in many cases, very high temperatures and long reaction times. The rapid heating, induced by microwave irradiation, avoids the decomposition of reagents and instable intermediates leading to cleaner reactions and often the yields are higher than those obtained by conventional heating.

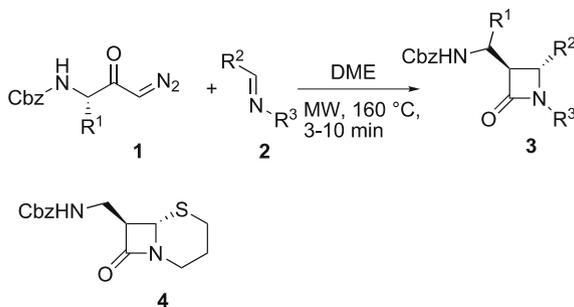
The material is organized according to the class of heterocycle formed, independent of the kind of reaction employed. The classification is taken from the book of Joule and Mills [12].

Except for a few examples, all the reactions reported herein have been carried out under controlled microwave heating using dedicated instruments for organic synthesis that register the temperature and pressure of the reaction mixture, giving more reproducible results and allowing to work under safe conditions.

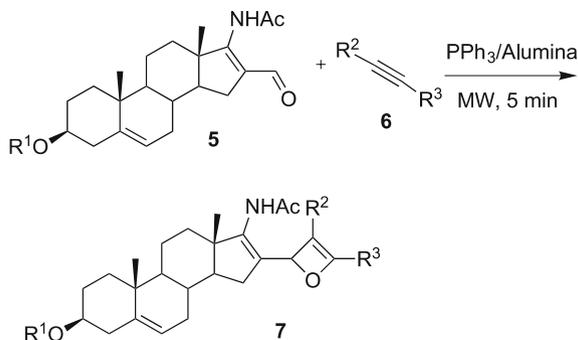
The application of microwaves to organic synthesis has been the subject of several books [13–16] and review articles [17–25] where the principles of the technique have been described.

2 Four-Membered Rings

The azetidinone ring is the key component of β -lactam antibiotics and other biologically active natural and synthetic molecules. One of the most popular methods to prepare β -lactams is the Staudinger reaction, the cycloaddition of a ketene and an imine. The reaction has been described first by Bose, using a domestic microwave oven, generating the ketenes from acyl chlorides and a tertiary amine [26]. Recently, Podlech and Linder reacted diazoketones **1** derived from *N*-protected amino acids with different imines **2** at 160–180 °C in 1,2 dimethoxyethane in a sealed tube under microwave condition (Scheme 1). The reaction gave predominantly the trans-lactam, the yields were much better than using conventional heating and no differences in the stereochemical outcome were observed [27]. Xu and co-workers later reinvestigated the same reaction. They observed that the reaction carried out under microwave irradiation gave the same products and the same stereoselectivity as the photochemically induced Staudinger reaction [28]. Moreover, the microwave-assisted reaction was applicable to the synthesis of bicyclic β -lactams (as



Scheme 1 Synthesis of β -lactams via Staudinger reaction



Scheme 2 Synthesis of steroid oxetanes

product **4** in Scheme 1) without the formation of the by-products observed in the photochemical transformation.

Oxetanes are present in several biologically active natural compounds as, for example, the taxol ring skeleton. An interesting method used to obtain this particular ring is the thermal [2 + 2] cycloaddition reaction. Longchar and co-workers reported a novel [2 + 2] cycloaddition of β -formil enamides **5**, often used in other cycloaddition and condensation processes, with acetylenic dienophiles **6** under microwave irradiation (in a domestic oven) to afford oxetenes **7** in 80% yields [29]. This reaction was directed towards the synthesis of D-ring annelated heterosteroids (Scheme 2).

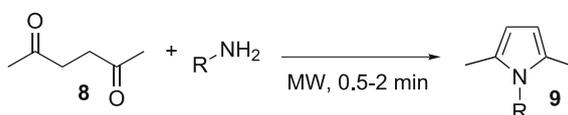
3 Five-Membered Rings – Aromatic

The use of microwaves for the preparation of aromatic five-membered heterocycles has been intensely investigated with excellent results in terms of yields and purities of the products prepared. The Paal-Knorr reaction, namely the cyclocondensation of a 1,4-dicarbonyl compound to give furans, pyrroles and thiophenes has been successfully carried out with the aid of microwaves.

3.1 Pyrrole

The first report appeared in 1999 when Danks described the basic reaction of 2,5-hexanedione and aniline, which was successfully carried out mixing the neat reagents and irradiating for 30 s in a domestic microwave oven. Several 2,5 dimethylpyrroles **9** were prepared starting from the same 1,4 diketone [30] (Scheme 3).

Two other examples of microwave-assisted Paal-Knorr reactions were reported in 2004, describing the synthesis of a larger set of pyrroles with different substituents around the ring. The methods differ mainly in the syntheses employed to produce the 1,4 dicarbonyl compounds required for the cyclization. A variation of the Stetter reaction between an acyl silane and dif-

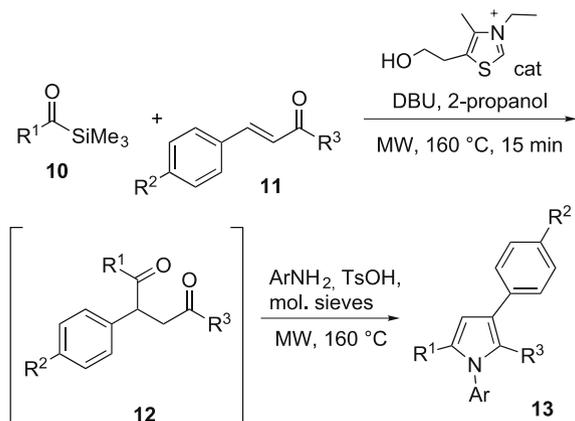


Scheme 3 Synthesis of 1,4-disubstituted pyrroles via Paal-Knorr reaction

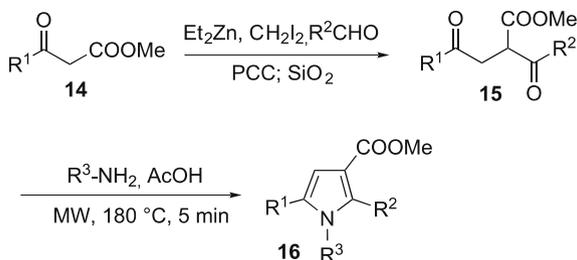
ferent α , β -unsaturated ketones was carried out under microwave irradiation (Scheme 4) to give the intermediate diketone, which could be cyclized in situ in the presence of aniline to a tetrasubstituted pyrrole [31].

A two-step procedure was required for the preparation of a diverse set of pyrrole-3-carboxylic acid derivatives. The diketone **15** was prepared using a functional homologation of a β -ketoester **14** with different aldehydes followed by oxidation with PCC. The Paal–Knorr reaction was carried out in AcOH in a sealed tube under microwave irradiation (180 °C, 5–10 min) to give differently substituted pyrroles with a COOMe group in position 3 (Scheme 5). This group was further transformed to expand the diversity of the products prepared with this method [32].

A modified 1,4 diketone **17** was employed for the microwave-assisted preparation of amino acids containing the pyrrole ring (Scheme 6). The products were further employed for the introduction of this original moiety into a peptide sequence [33].

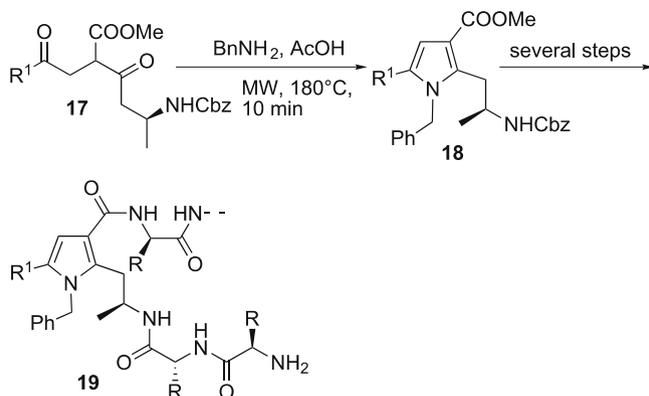


Scheme 4 Synthesis of 1,2,3,5-tetrasubstituted pyrroles



R^1 , R^2 and R^3 = Aliphatic or Aromatic

Scheme 5 Microwave-assisted Paal–Knorr reaction

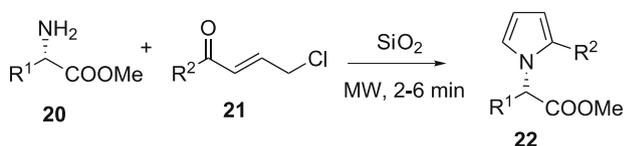


Scheme 6 Synthesis of peptidomimetics containing the pyrrole ring

Another series of pyrroles, structurally related to amino acids, was obtained in a microwave-assisted solvent-free condensation of α -amino acid methyl esters with chloroenones, which provided the four-carbon unit of the pyrrole. The reaction was carried out by mixing the reagents on silica gel and irradiating for 2–6 min inside a multimode microwave cavity (Scheme 7). The authors reported higher yields and cleaner products when microwaves were used instead of conventional heating [34].

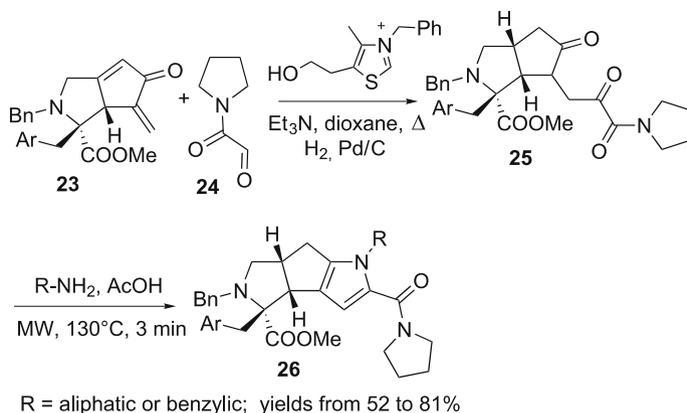
An interesting family of polycyclic pyrroles was described in 2005 using again the synthetic sequence of a Stetter reaction for the preparation of the starting 1,4 diketones followed by a microwave-assisted Paal-Knorr condensation [35]. For example, cyclopentenone **23** (obtained in a Pauson-Khand cyclization) reacted under Stetter reaction conditions to give the amino ketone **25** (Scheme 8). The microwave-assisted Paal-Knorr cyclization of **25** with different amines gave a small collection of tricyclic pyrrole 2-carboxamides.

Tetrasubstituted pyrroles were also obtained in a coupled domino process carried out under solvent-free conditions on silica gel (Scheme 9). The process involved the transformation of the alkynoate **27** into the 1,3-oxazolidine **28** that could be further rearranged (through loss of one molecule of water)

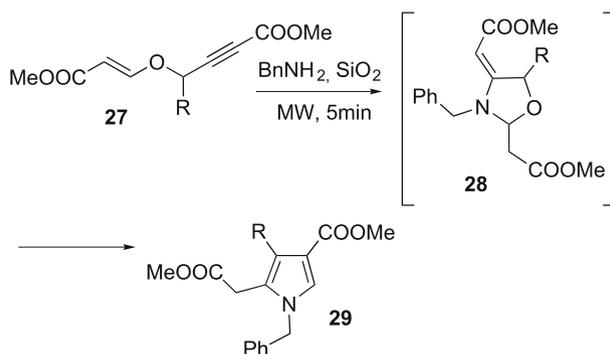


$R_1 = -\text{Me}, -\text{CH}_2\text{CH}_2-\text{SMe}, -\text{CH}_2\text{OH}$; $R_2 = -\text{Me}, -\text{Et}, \text{cyclo-}, \text{C}_6\text{H}_{11}, -\text{CHMe}_2$
yields from 68 to 88%

Scheme 7 Solvent-free synthesis of pyrroles



Scheme 8 Synthesis of polycyclic pyrrole carboxamides



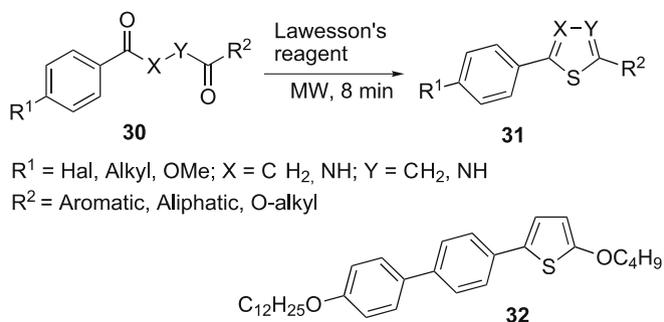
Scheme 9 Domino synthesis of pyrroles

into pyrrole **29**. When the reaction was carried out on silica gel without solvent and under microwave irradiation, the pyrrole **29** was directly obtained in approximately 45–59% yield [36].

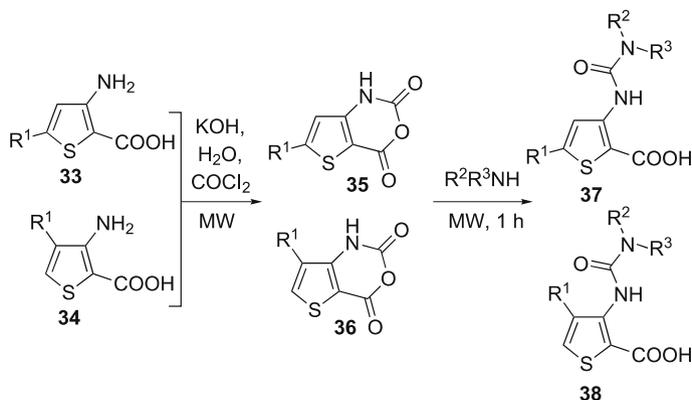
3.2

Thiophene

Thiophenes of type **31** (X-Y = CH) were generated via Lawesson's reagent-mediated cyclization of 1,4-dicarbonyl compounds **30** under microwave irradiation in the absence of solvent [37]. The reaction was carried by mixing the two solid reagents in a glass tube inserted inside a household microwave apparatus and irradiating until the evolution of H₂S ceased. An interesting application of this method is the preparation of liquid crystals and other ferro- and antiferroelectric material such as compound **33** (Scheme 10).



Scheme 10 Solvent-free synthesis of thiophenes



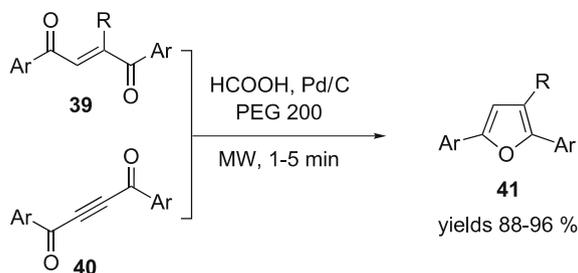
Scheme 11 Solvent-free synthesis of polysubstituted thiophenes

A different approach to polysubstituted thiophenes was described by Rault and co-workers who prepared thioisatoic anhydrides **35** or **36** starting from the corresponding thiophene amino esters **33** and **34** (Scheme 11), carrying out a cyclization in the presence of phosgene and KOH/H₂O under microwave irradiation for 1 h with a multimode apparatus [38]. The anhydrides **35** and **36** were reacted with different nucleophiles (mainly amines) to give ureas **37** and **38**. Although the irradiation time was longer with respect to the standard protocols, several products were obtained through a parallel approach that avoided purification procedures by selective acid-base extraction.

3.3

Furan

The same procedure used for the synthesis of pyrroles **16** was applied to prepare furans, namely heating 1,4-diketones **15** in AcOH under microwave



Scheme 12 Synthesis of furans via reductive Paal–Knorr reaction

irradiation [32]. A reductive version of the Paal–Knorr reaction produced furans. The reaction was carried out under microwave irradiation (multimode system) using PEG 200 as the solvent in the presence of HCOOH and Pd/C as the reducing agent via transfer hydrogenation (Scheme 12). The starting compounds can be either but-2-ene-1,4-diones **40** or but-2-yne-1,4-diones **41**. The reaction takes less than 2 min and also proceeds with hindered systems such as triphenylfuran. In some difficult cases, a catalytic amount of H_2SO_4 was needed [39].

3.4

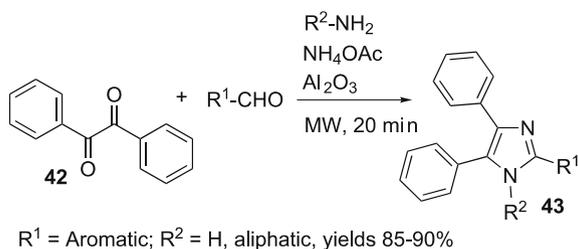
1,3-Azoles

3.4.1

Imidazole

The synthesis of imidazoles is another reaction where the assistance of microwaves has been intensely investigated. Apart from the first synthesis described since 1995 [40–42], recently a combinatorial synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles has been described on inorganic solid support under solvent-free conditions [43]. Different aldehydes and 1,2 dicarbonyl compounds **42** (mainly benzil and analogues) were reacted in the presence of ammonium acetate to give the trisubstituted ring **43**. When a primary amine was added to the mixture, the tetrasubstituted imidazoles were obtained (Scheme 13). The reaction was done by adsorption of the reagent on a solid support, such as silica gel, alumina, montmorillonite K10, bentonite or alumina followed by microwave irradiation for 20 min in an open vial (multimode reactor). The authors observed that when a non-acid support was used, addition of acetic acid was necessary to obtain good yields of the products.

An analogous approach starting from monoximes **44** derived from 1,2 diketo derivatives was described in 2004 [44]. Reaction with different aldehydes in the presence of NH_4OAc in acetic acid at 200°C under microwave irradiation for 20 min gave the corresponding trisubstituted imidazoles **45**

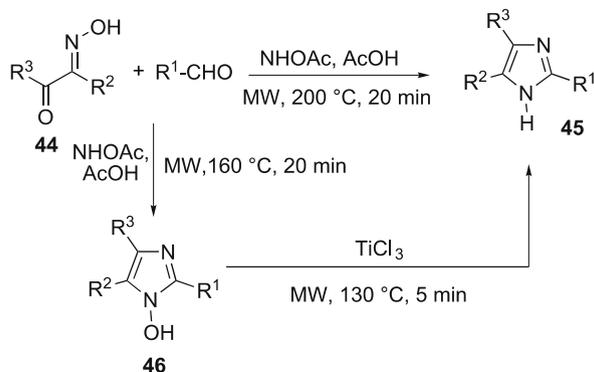


Scheme 13 Synthesis of imidazoles on alumina

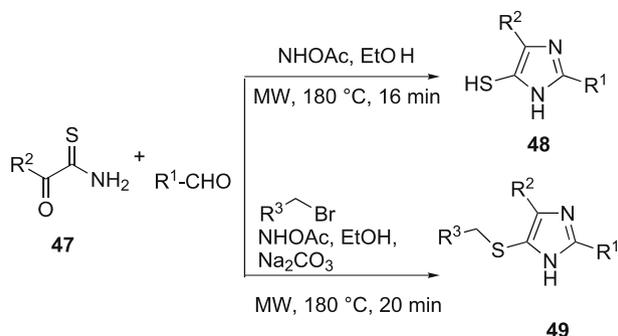
(Scheme 14). The diversity of the collection of imidazoles prepared was relatively high, and yields ranged from 17 to 83%. It is interesting to observe that the intermediate *N*-hydroxyimidazole **46** was obtained when the reaction was carried out at temperature lower than 200 °C.

The cyclization of 1,2-dicarbonyl compounds with aldehydes in the presence of NH_4OAc to give imidazoles was employed in a combinatorial study that compared conventional and microwave heating in the preparation of a library of sulfanyl-imidazoles (Scheme 15). The study employed an array of expandable reaction vessels that could accommodate a pressure build-up system for heating without loss of volatile solvents or reagents. A 24-membered library of imidazoles (**48** and **49**) was prepared in 16 min instead of the 12 h required using conventional heating [45].

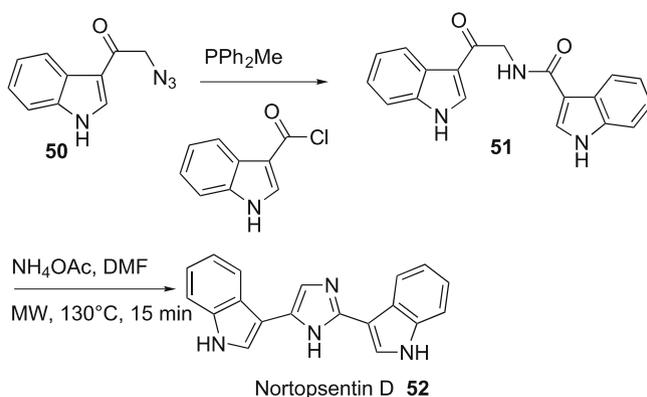
A similar microwave-assisted cyclization in the presence of ammonium acetate of an α -ketoamide, obtained by acylation of an α -aminoketone, was recently described for the synthesis of the antifungal agent Nortopsedin D [46]. The problem of the instability of the α -amino ketones was successfully resolved by in situ acylation of the amine derived from Staudinger reaction of the azide **50** with a phosphine (Scheme 16). This ketoamide was



Scheme 14 Imidazole synthesis



Scheme 15 Combinatorial synthesis of imidazoles



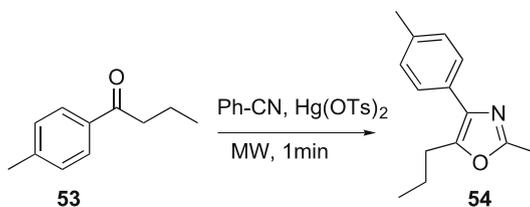
Scheme 16 Synthesis of the antifungal compound Nortopsedin

reacted in DMF in the presence of NH_4OAc under microwave irradiation for 15 min to give the required 2,4-disubstituted imidazole. In addition to Nortopsedin D, several other 2,4-disubstituted imidazoles were prepared using this method.

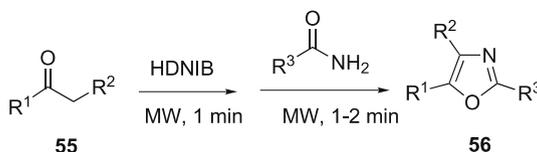
3.4.2 Oxazole

Oxazoles have attracted considerable interest due their presence as subunits of several biologically active compounds or as rigid mimetics of a peptidic ring. A first synthesis of 2-phenyl-4,5-substituted oxazoles **54** [47] was described by microwave-assisted reaction of enolizable ketones with benzoni-trile in the presence of mercury(II) *p*-toluenesulfonate (Scheme 17).

A similar approach was carried out reacting an enolizable ketone with amides in the presence of the hypervalent iodine(III) reagent (hydroxy(tosyl-oxy)iodobenzene, HDNIB) [48]. The reaction was carried out under solvent-



Scheme 17 Solvent-less mercury(II)-assisted synthesis of oxazoles



Scheme 18 Solvent-free synthesis of oxazoles mediated by hypervalent iodine(III) sulfonates

free conditions by mixing the ketone and the hypervalent iodine reagent and irradiating for 20 s to 1 min (domestic microwave oven). The amide was added and the mixture was irradiated for an additional 3 min to give oxazoles in yields of 62–94% [49]. The method seemed versatile as trisubstituted oxazoles **56** with aliphatic, aromatic and carboxyl group were prepared (Scheme 18).

3.4.3

Thiazole

Reaction of β -carbonyl amides with the Lawesson's reagent under microwave irradiation gave thiazoles in acceptable yields [37]. The reaction was the same one previously reviewed for the synthesis of thiophenes and was also employed for the preparation of thiadiazoles (Scheme 10, X = NH, Y = CH).

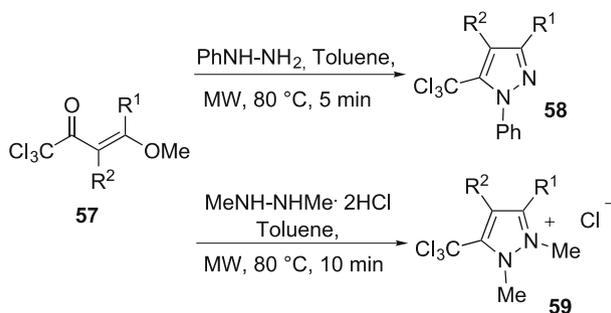
3.5

1,2-Azoles

3.5.1

Pyrazole

Different approaches towards pyrazoles have been described using microwave-accelerated cyclizations. A classical approach to pyrazoles is the cyclization of a β -diketone with hydrazines. A series of 5-trichloromethyl-pyrazoles **58** and pyrazolium chlorides **59** were synthesized by reaction of a 4-methoxy-trihalo-3-alken-one **57** with differently substituted hydrazines (Scheme 19). The use of microwave and conventional heating for making pyrazoles gave

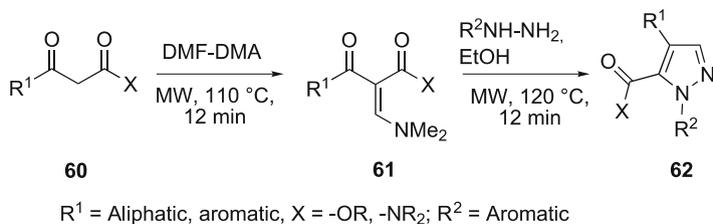


Scheme 19 Synthesis of pyrazoles and pyrazolium ions

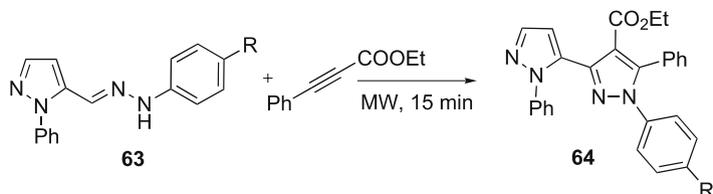
comparable results, whereas the formation of the pyrazolium chlorides was achieved in a significantly shorter time and better yields using microwave irradiation [50].

β -Keto esters and keto amides **60**, prepared by acylation of Meldrum's acid followed by ring opening with alcohols or amines, were the starting materials for the preparation of a small library of 1,4,5-trisubstituted pyrazoles [51]. Initial microwave-assisted reaction with DMF-DMA (used as the solvent) gave the unsaturated compounds **61** that cyclized with monosubstituted hydrazines under microwave irradiation in EtOH, to give pyrazoles in a regiocontrolled way (Scheme 20).

One of the first studies carried out on cycloadditions accelerated by microwaves describing a synthesis of an aromatic heterocycle was a preparation



Scheme 20 Two step synthesis of pyrazoles from β -ketoesters



Scheme 21 Synthesis of pyrazoles via 1,3-dipolar cycloaddition

of bipyrazoles (**64**) in 30 min [52]. The 1,3-dipolar cycloaddition was carried out starting from pyrazolyl hydrazones (**63**), which isomerized in situ to azomethine imines, and different dipolarophiles (Scheme 21). The authors reported that some of these cycloadditions were not possible under classical thermal conditions.

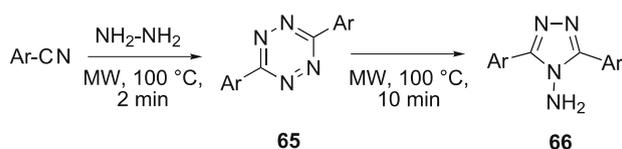
3.6

Five-Membered Heterocycles with More than Two Heteroatoms

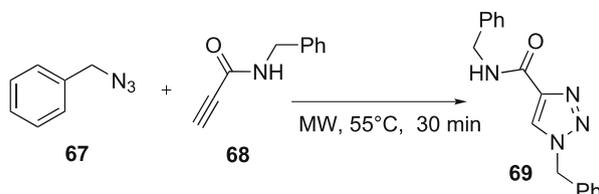
Regarding the series of heteroaromatic pentacyclic compounds with three heteroatoms, an accelerated synthesis of 3,5-disubstituted 4-amino-1,2,4-triazoles **66** under microwave irradiation has been reported by thermic rearrangement of dihydro-1,2,4,5 tetrazine **65** (Scheme 22). This product was obtained by reaction of aromatic nitriles with hydrazine under microwave irradiation [53]. The main limitation of the method is that exclusively symmetrically 3,5-disubstituted (aromatic) triazoles can be obtained.

Triazoles have been obtained via microwave-assisted [3 + 2] cycloaddition, under solvent-free conditions [54], starting from organic azides and acetylenic amides at 55 °C for 30 min (Scheme 23). The complete conversion of the reagents into *N*-substituted-1,2,3-triazoles **69** was achieved without decomposition and side products. A control reaction carried out at the same temperature in an oil bath did not give the cyclic products, not even after 24 h of reaction time.

The same azide **67** was utilized to study the microwave-assisted synthesis of triazoles using the thermal cycloaddition with acetylenes. To achieve high yields in a short time and avoiding side reactions, the authors analyzed the effects of time, temperature, and concentration (in toluene) on the synthesis of triazoles [55].



Scheme 22 Synthesis of symmetrically substituted triazoles



Scheme 23 Solvent-free synthesis of triazoles

Kappe and co-workers proposed an application of a microwave-assisted Huisgen 1,3-dipolar cycloaddition of terminal acetylenes and azides **70**, under Cu(I) catalysis, as an example of “click chemistry” to obtain a collection of 1,2,3-triazoles with potential biological activity (Scheme 24) [56]. The same reaction was carried out also under conventional conditions requiring 1 h reaction time at room temperature as compared to 1 min under microwave heating to 80 °C.

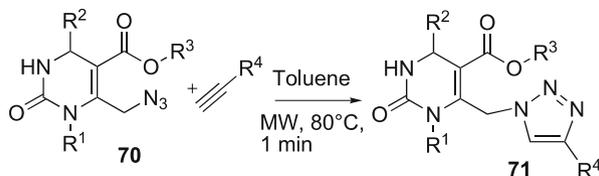
In another paper, the same authors investigated the 1,3-dipolar cycloaddition on 2-(1*H*)-pyrazine scaffolds **72** and electron-rich azides, using Cu(0) and CuSO₄ as pre-catalysts. To demonstrate the versatility of this approach, they reported the generation of different templates (**73** in Scheme 25) as an application of “click chemistry”. They also investigated the Diels–Alder reaction of the so obtained triazoles with dimethyl acetylenedicarboxylate (DMAD), under microwave irradiation. The latter reaction allowed obtaining various pyridinones in good yields (**74** and **75** in Scheme 25) [57].

The Cu(I)-catalyzed Huisgen [3 + 2] dipolar cycloaddition was also utilized by Van der Eycken and co-workers to obtain a new class of glycopeptidomimetics based on the 1,2,3-triazole ring system **78** starting from glucopyranosyl azide **75** and the pyrazinone compound **76** (Scheme 26) [58].

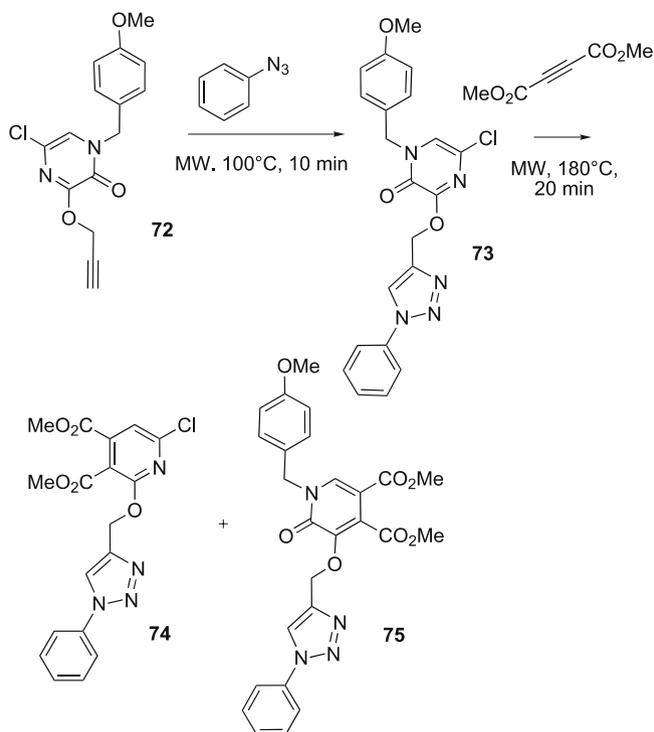
Several methods have been described for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles by microwave-assisted cyclodehydration of 1,2-diacylhydrazines using different dehydrating agents. The Burgess reagent (the original reagent and a supported version of it) was employed in two publications [59, 60] describing the preparation of non-symmetrically substituted oxadiazoles **80** (Scheme 27). A symmetric oxadiazole was obtained, on the other hand, by direct reaction of an aromatic carboxylic acid and hydrazine in the presence of orthophosphoric acid and phosphorous pentoxide [61] under microwave irradiation.

Finally, a series of 2-chloromethyl-5-aryl-1,3,4-oxadiazoles **82** were prepared by reaction of aromatic hydrazides **81** and a chloromethylorthoformate used as the solvent under microwave activation [62]. Potentially, the chloromethyl group could undergo nucleophilic substitution expanding the scope of this reaction (Scheme 28).

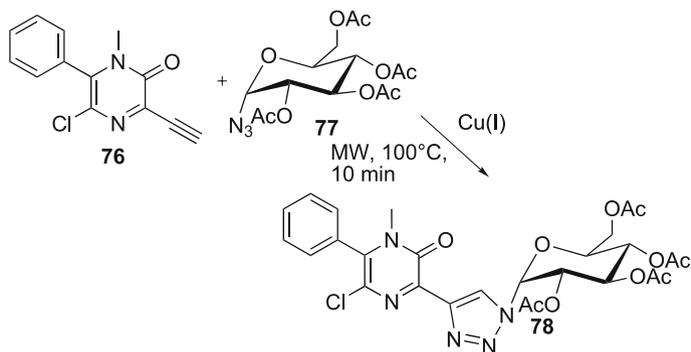
Tetrazoles are a very interesting family of aromatic five-membered heterocycles for their ability to be a mimetic of the carboxy group with metabolic



Scheme 24 “Click chemistry”

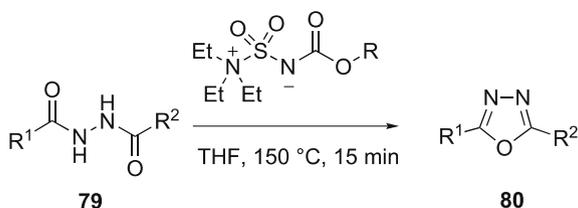


Scheme 25 Cu(I) catalyzed cycloaddition of azides

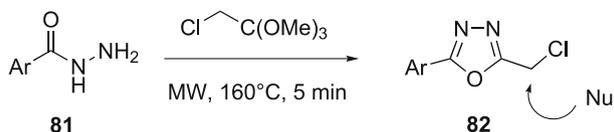


Scheme 26 Cu(I) catalyzed synthesis of glycopeptidomimetics

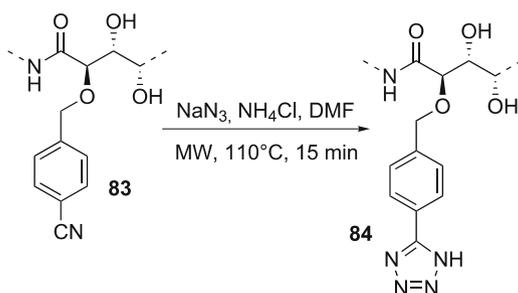
stability. For this reason, tetrazoles often replace carboxylic acid functionalities in peptidomimetic molecules with biological activity. Flash microwave heating allowed to produce aryl and vinyl nitriles **83**, starting from the corresponding halides, which were reacted with sodium azide once again under microwave exposure for 15 min (Scheme 29) to give aryl and vinyl tetrazoles **84** in good yields and faster than previously reported with conventional heating [63].



Scheme 27 Oxadiazole synthesis using the Burgess reagent



Scheme 28 Synthesis of 2-chloromethyl-oxadiazoles



Scheme 29 Synthesis of triazoles on a peptide strand

4 Five-Membered Rings – Non Aromatic

4.1 Tetrahydrofurans and Furanones

The application of 1,3-dipolar cycloaddition processes to the synthesis of substituted tetrahydrofurans has been investigated, starting from epoxides and alkenes under microwave irradiation. The epoxide **85** was rapidly converted into carbonyl ylide **86** that behaved as a 1,3-dipole toward various alkenes, leading to quantitative yields of tetrahydrofuran derivatives **87** (Scheme 30). The reactions were performed in toluene within 40 min instead of 40 h under classical conditions, without significantly altering the selectivities [64].

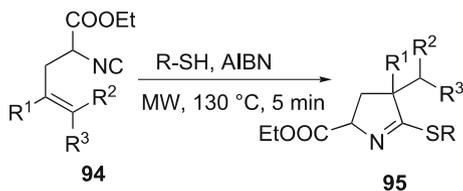
A rapid and efficient one-pot synthesis of substituted 2(5H)-furanones has been reported starting from 3-hydroxy-3-methyl-2-butanone **88** and ethyl

4.2 Pyrrolines and Pyrrolidines

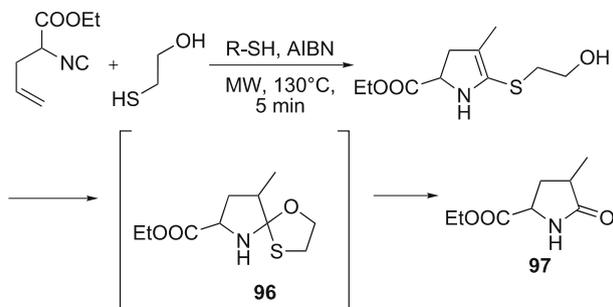
A small library of highly functionalized pyrrolines **95** was synthesized by reaction of allylic and propargylic isocyanides **94** with thiols followed by radical cyclization (Scheme 33). The radical reaction was carried out using a radical initiator (AIBN) under flash heating microwave irradiation [67].

When mercaptoethanol was used, the pyrrolidinone **97** (formally a derivative of pyroglutamic acid) was obtained through the intramolecular cyclization of the pyrroline formed under standard conditions. The spiroderivative **96** is hydrolyzed in situ to give the alkylated pyroglutamic derivative **97** (Scheme 34). The diversity and the yields of the products obtained with this method were high, especially if compared with results obtained under conventional heating.

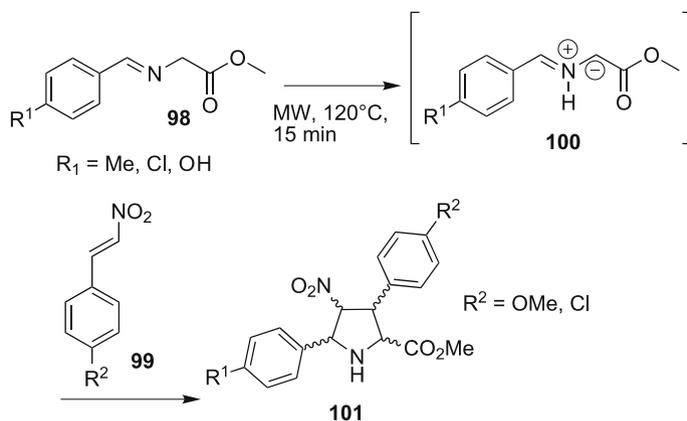
Dipolar [3 + 2] cycloadditions are one of the most important reactions for the formation of five-membered rings [68]. The 1,3-dipolar cycloaddition reaction is frequently utilized to obtain highly substituted pyrrolidines starting from imines and alkenes. Imines **98**, obtained from α -amino esters and nitroalkenes **99**, are mixed together in an open vessel microwave reactor to undergo 1,3-dipolar cycloaddition to produce highly substituted nitroprolines esters **101** (Scheme 35) [69]. Imines derived from α -aminoesters are thermally isomerized by microwave irradiation to azomethine ylides **100**,



Scheme 33 Pyrroline synthesis via a radical process



Scheme 34 Synthesis of a pyroglutamic acid derivative



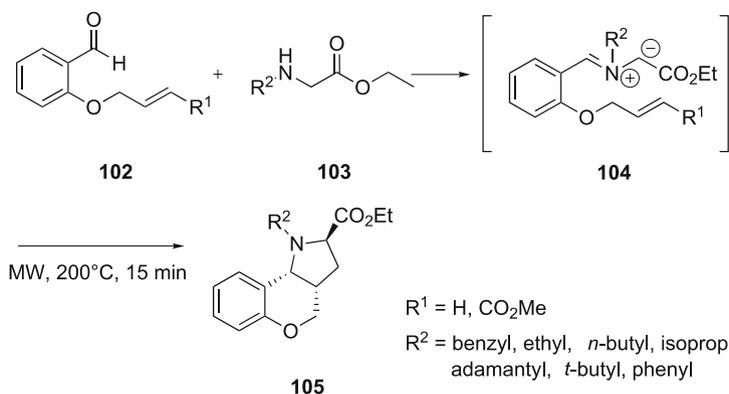
Scheme 35 Combinatorial approach towards substituted prolines

which consequently undergo cycloaddition with substituted β -nitrostyrenes. The cycloaddition was solvent-free and was carried out within 10–15 min at a temperature of 120 °C. The results under microwave irradiation were compared to the same reaction performed in refluxing toluene in an oil bath for 24 h. The main differences that appear from the comparison of the reactions with the two heating methods were:

- the yields, ranging from 81 to 86% when microwaves were used, versus 50% for the conventional heating
- the reaction times (15 min vs. 24 h)
- the observed stereoselectivities.

In fact, three different relative configurations were generated by each 1,3-dipolar cycloaddition using microwave irradiation. Starting from two imines and three alkenes, it was possible to create a small collection of 18 racemic proline derivatives. On the other hand, using conventional heating, only two diastereoisomers were produced in each cycloaddition, thus giving rise to 12 nitroproline esters. The authors proposed that an epimerization of the *endo/exo* adducts occurred through a microwave-induced rotation of the carboxyl group around the ylide bond, leading to two alternative hydrogen bonding patterns.

Another example of a microwave-assisted 1,3-dipolar cycloaddition using azomethine ylides and a dipolarophile was the intramolecular reaction reported for the synthesis of hexahydrochromeno[4,3-*b*]pyrrolidine **105** [70]. It was the first example of a solvent-free microwave-assisted intramolecular 1,3-dipolar cycloaddition of azomethine ylides, obtained from aromatic aldehyde **102** and *N*-substituted glycinate **103** (Scheme 36). The dipole was generated in situ (independently from the presence of a base like TEA) and reacted directly with the dipolarophile present within the same molecule. The intramolecu-

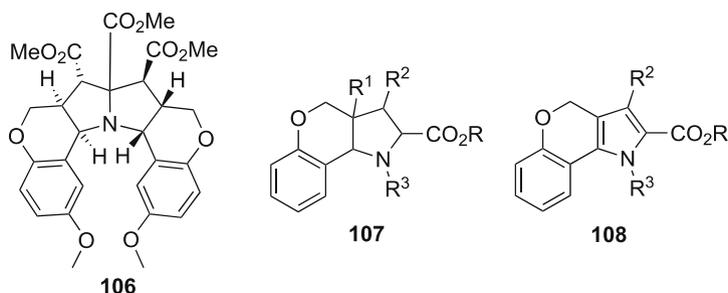


Scheme 36 Cyclo-condensed prolines via intramolecular cycloaddition

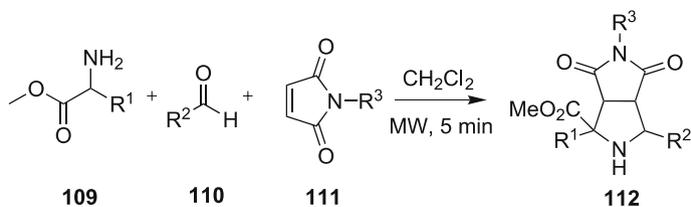
lar cycloaddition was also carried out at 200 °C within 15 min providing 83% yield of cycloadduct. At this temperature, decomposition of the product was observed. On the other hand, when the reaction was carried out at 150 °C in an oil bath for 1 h, decomposition of the reagents was observed, leading to a low yield (16%) of the cycloadduct.

A family of interesting polycyclic systems **106** related to pyrrolidines was obtained in a one-pot double intermolecular 1,3-dipolar cycloaddition, irradiating derivatives of *o*-allyl-salicylaldehydes with microwaves in toluene for 10 min in presence of the TFA salt of glycine esters [71]. A very similar approach was previously proposed by Bashiardes and co-workers to obtain a one-pot multicomponent synthesis of benzopyrano-pyrrolidines **107** and pyrrole products **108** (Scheme 37). The latter cycloadducts were obtained when *o*-propargylic benzaldehydes were utilized instead of *o*-allylic benzaldehydes, followed by in situ oxidation [72].

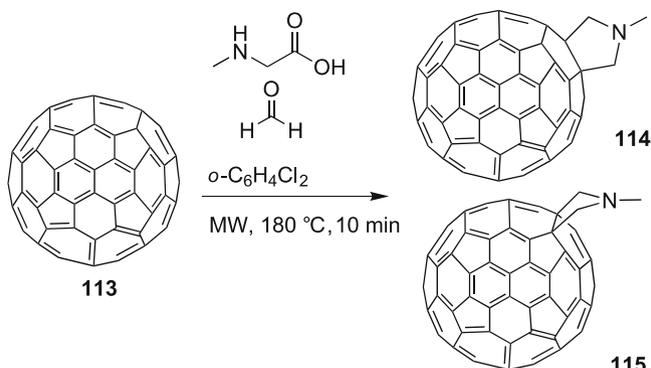
A library of 800 substituted prolines of type **112** was described using a similar synthetic approach. The [3 + 2] cycloaddition occurred via a multicomponent reaction of α -amino esters, aldehydes, and maleimides (Scheme 38).



Scheme 37 Benzopyrano-condensed prolines



Scheme 38 Multicomponent synthesis of a library of prolines



Scheme 39 Regioselection in cycloadditions on fullerenes

The pyrrolidines were obtained in a two-step, one-pot reaction in good yields and short reaction time (5 min vs. 36 h reported for the conventional heating) [73], using a single-mode microwave apparatus [74].

In 2000, it was proposed that the regioselectivity of the [3 + 2] cycloaddition of fullerenes could be modified under microwave irradiation. Under conventional heating, *N*-methylazomethine ylide and fullerene-(C_{70}) gave three different isomeric cycloadducts because of the low symmetry of C_{70} vs. C_{60} . Using microwave irradiation and *o*-dichlorobenzene as a solvent, only two isomers were obtained, the major cycloadduct 114 being kinetically favored (Scheme 39) [75]. The same authors had previously reported the 1,3-dipolar cycloaddition of pyrazole nitrile oxides, generated in situ, to C_{60} under either conventional heating or microwave irradiation. The electrochemical characteristics of the cycloadduct obtained with this method made this product a candidate for photophysical applications [76].

4.3

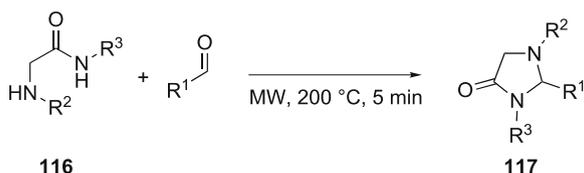
Saturated Imidazoles and Pyrazoles

A series of imidazolidin-4-ones 117 were prepared from α -amino amides 116 that reacted with aldehydes without solvent at 200 °C under microwave irradi-

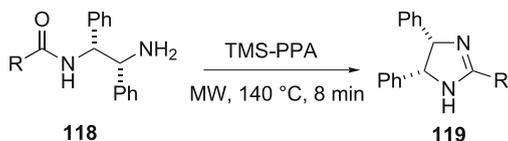
ation in an open vessel, probably to facilitate the removal of the water formed in the reaction [77]. Yields were good and aliphatic and aromatic groups can be used for the decoration of the final heterocycle (Scheme 40).

Diarylimidazolines **119** that act as potential P2X receptor antagonists have been prepared by microwave-assisted cyclization of amino amides in the presence of TMS-polyphosphate at 140 °C for 8 min [78]. This reaction seems quite general (for variations on R) as more than 35 compounds have been prepared with this method (Scheme 41).

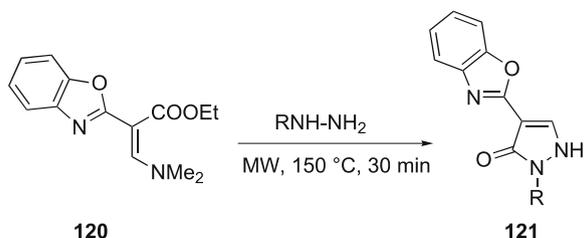
Dihydropyrazoles were prepared by reaction of a monosubstituted hydrazine with benzimidazole amino acrylates **120**. The reaction was carried



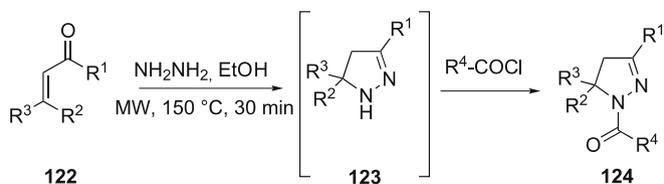
Scheme 40 Solvent-free synthesis of imidazolidinones



Scheme 41 Synthesis of potential P2X receptor antagonists



Scheme 42 Solvent-free synthesis of pyrazolones



Scheme 43 Synthesis of 1-acyl-pyrazolines

out without solvent at 150 °C for 30 min to give the required dihydropyrazolones **121** (Scheme 42) [79].

The same reaction, carried out with conventional heating at the same temperature, took more than 6 h to give comparable yields of the products. Dihydropyrazoles were also obtained by microwave-assisted reaction of poly-substituted vinyl ketones **122** with hydrazines, followed by reaction of the unstable pyrazole **123** with electrophiles (Scheme 43) [80].

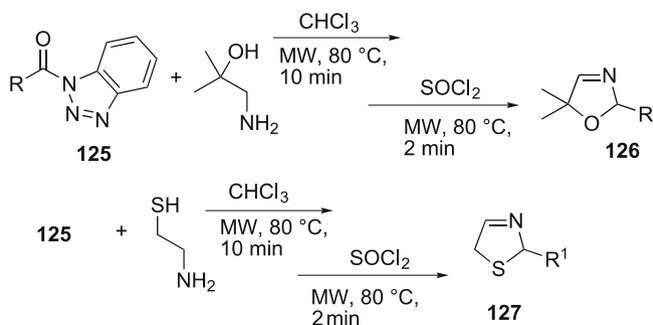
4.4

Saturated Oxazole, Thiazole, and Oxadiazole Derivatives

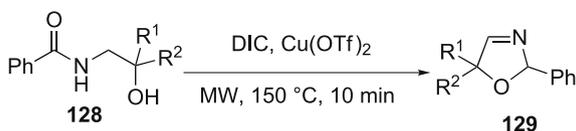
Oxazolines constitute a broad family of five-membered heterocycles with important applications as synthetic intermediates or as parts of biologically active compounds. Consequently, there are several syntheses of this heterocycle using microwave-facilitated cyclocondensations. The classical method is the reaction of a carboxylic acid with a β -amino alcohol in the presence of a Lewis acid. A solvent-free procedure that employs ZnO as solid support for this reaction has been described in 2003 [81]. This reaction proceeded under microwave irradiation with very good yields and high molecular diversity in the oxazolines formed. An analogous reaction was reported using carboxylic acids activated as benzotriazolyl derivatives **125** in CHCl_3 at 80 °C for 10 min [82]. A microwave mediated dehydration with SOCl_2 followed, to provide oxazolines **126** and, in the case when a β -amino thiol was used, β -thiazolines **127** (Scheme 44).

A further modification of the same reaction pattern has been described [83] starting from the β -hydroxyamide **128** that cyclized in the presence of DIC and $\text{Cu}(\text{OTf})_2$ under microwave irradiation at 100–175 °C within 5–15 min to give compound **129** (Scheme 45).

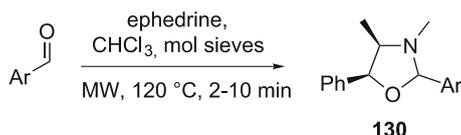
Oxazolidines **130** were obtained by reaction of (-)-ephedrine with aldehydes under microwave irradiation and in the presence of molecular sieves in order to remove the water formed in the reaction (Scheme 46) [84, 85]. As expected,



Scheme 44 Two-step synthesis of oxazolines and thiazolines



Scheme 45 Cu(II)-mediated synthesis of oxazolines

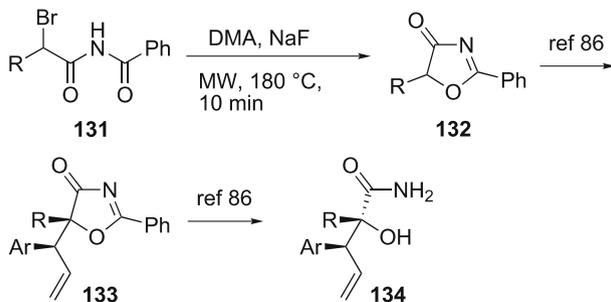


Scheme 46 Heterocycles derived from ephedrine

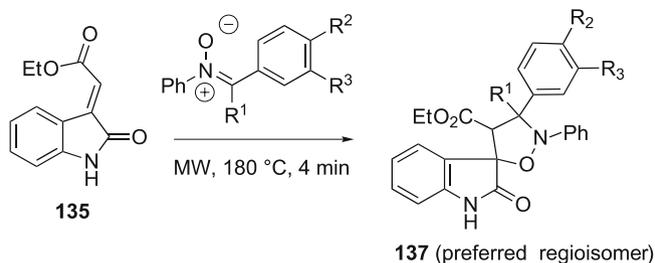
a significant decrease in the reaction time was observed using microwaves. Moreover, several differences in the diastereomeric ratios between conventional and microwave heating were found when aromatic aldehydes carrying an electron withdrawing group were used. For example, 2-NO₂-C₆H₄-CHO gave a 84/16 ratio of **130** after 24 h at room temperature and a 98/2 ratio under microwave irradiation at 120 °C for 10 min.

Oxazol-4-ones **132** have been prepared by Trost and co-workers via a microwave-assisted cyclocondensation of bromo imides in the presence of NaF [86]. These products were then employed for a Mo-catalyzed asymmetric synthesis of α -hydroxycarboxylic acid derivatives **134** (Scheme 47).

Spiro-(indoline-isoxazolidines) **137**, exhibiting interesting biological activities, were prepared in modest yields, by the cycloaddition reaction between ethyl (3-indolylidene)-acetate **135** and various substituted α,N -diphenylnitrones **136** under solvent-free conditions (Scheme 48). The reaction conducted under conventional heating in an oil bath did not proceed even after 20 h, especially when it was carried out without solvent [87].



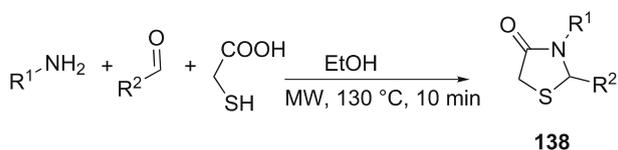
Scheme 47 Synthesis of enantiomerically pure azalactones



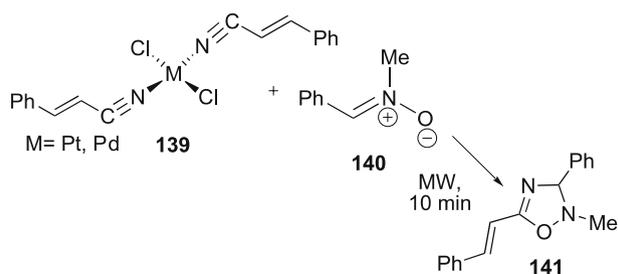
Scheme 48 Synthesis of spiro oxindoles

A small library of thiazolidinones **138** has been prepared mixing directly a primary amine (as the HCl salt), an aldehyde and mercaptoacetic acid in EtOH in the presence of Hünig's base and molecular sieves (120 °C for 30 min) [88]. Working with a chiral amine, a 1 : 2 mixture of diastereoisomers was obtained (Scheme 49).

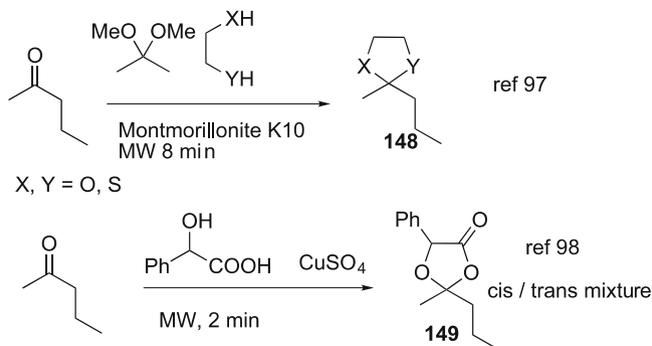
Wagner and co-workers explored the different selectivity of 1,3-dipolar cycloadditions of nitrones **140** and cinnamitrile **139** leading to oxadiazolines **141** derived from an exclusive CN attack instead of a C = C attack (Scheme 50). This behavior was observed when cinnamitrile was coordinated to a transition metal like Pt or Pd [89]. A similar approach to platinum-promoted nitrile-nitron cycloadditions was reported using cyclic nitrones. In this case, the authors reported a higher stereoselectivity of cyclic nitrones with respect to the acyclic nitrones, due to a rigid *E* conformation adopted by cyclic nitrones [90].



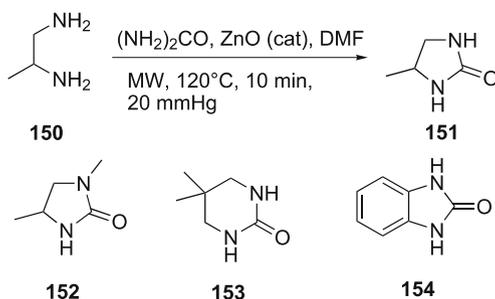
Scheme 49 Synthesis of a library of thiazolidines



Scheme 50 Pd-mediated cycloaddition for the synthesis of oxadiazolines



Scheme 52 Synthesis of dioxolanes and dithianes



Scheme 53 Synthesis of cyclic ureas

(water pump) in order to facilitate the removal of ammonia. Again, the use of conventional heating gave poor yields of the cyclic ureas. Polysubstituted and aromatic condensed cyclic ureas (such as **152–154**) were also prepared using this method [96].

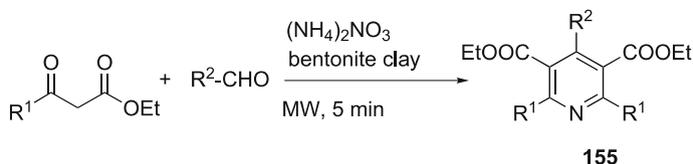
5

Six-Membered Rings – Aromatic

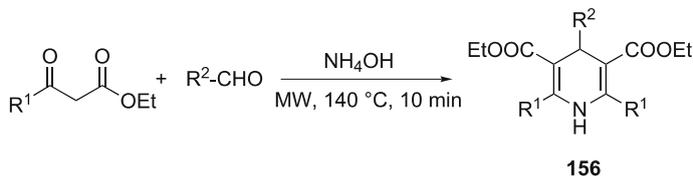
5.1

Pyridines

Pyridines are traditionally prepared using the Hantzsch reaction, a condensation between 2 mol of a β -ketoester, 1 mol of an aldehyde and 1 mol of ammonia. The product of this reaction is a 1,4-dihydropyridine which can be further oxidized to the corresponding pyridine compound (as **155** in Scheme 54). A first report described the Hantzsch reaction carried out under microwave irradiation on Bentonite clay and ammonium nitrate as ammonia



Scheme 54 Solvent-free synthesis of pyridines



Scheme 55 Hantzsch reaction

source and oxidant (Scheme 54) [97]. This reaction was further optimized for the synthesis of a library on a 96 well plate using different substituted keto esters and aliphatic and aromatic aldehydes [98].

Of course, the Hantzsch reaction can be used for the preparation of 1,4-dihydropyridines **156** and this transformation was carefully investigated in order to find the best reaction conditions using a focused microwave reactor (Scheme 55). In this report, using aqueous ammonia as the solvent, several methods of heating were compared [99]. The authors found that refluxing for 12 h gave 50% of the product, heating in an autoclave at 110 °C gave no products, 4 min in a domestic microwave (sealed tube) afforded 50% of the product and finally the use of the controlled microwave system gave 80% of product after 10 min at 140 °C.

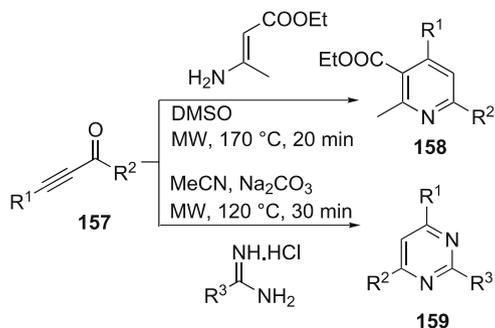
An interesting application of this reaction to the synthesis of bifunctional pyridines was investigated using a dialdehyde as the precursor with the aim of finding new calcium channel modulators [100]. This reaction has been also scaled up using a continuous microwave reactor where the solution of the reagent was pumped continuously through the microwave reactor using a peristaltic pump [101].

Pyridines **158** have been also prepared by cyclocondensation of alkynyl ketones **157** and amino acrylates in DMSO as the solvent at 170 °C for 20 min (Scheme 56 and Sect. 5.2 for more details) [102, 103].

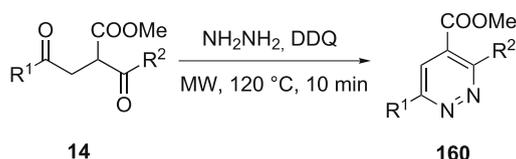
5.2

Diazines

Alkynyl ketones **157** were also used for the synthesis of pyrimidines **159** by reacting amidines in acetonitrile at 120 °C in a dedicated microwave synthesizer without the requirement of additional purification (Scheme 56) [104].



Scheme 56 Synthesis of pyridines and pyrimidines from alkynyl ketones



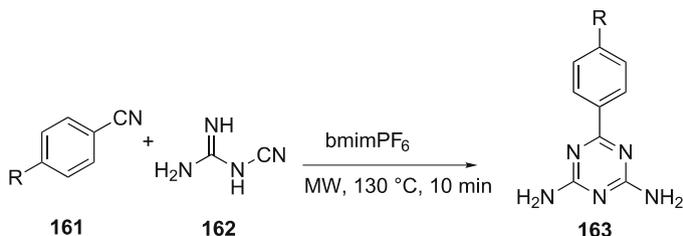
Scheme 57 Paal-Knorr synthesis of pyridazines

Pyridazines **160** were obtained by microwave-assisted reaction of 1,4-dicarbonyl compounds and hydrazine in AcOH and in the presence of DDQ as oxidant in order to obtain the aromatic compound in a one pot reaction [105]. The yields reported were relatively low although the method can be applied to the preparation of arrays of trisubstituted pyridazines with high molecular diversity (Scheme 57).

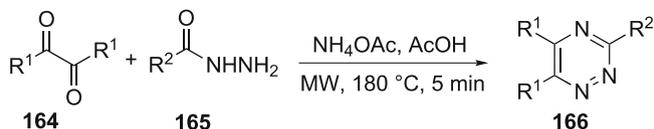
5.3

Triazines

1,3,5-Triazines have been prepared by microwave-assisted reaction of substituted benzonitriles **161** and cyanoguanidines **162** using the ionic liquid [bmim][PF₆] as the solvent at 130 °C for 10–15 min [106]. Nine differently



Scheme 58 Synthesis of triazines in ionic liquid



Scheme 59 Synthesis of 3,5,6-differently substituted triazines

substituted diamino triazines were obtained with a single point of diversity on the aromatic ring at position 4 (Scheme 58).

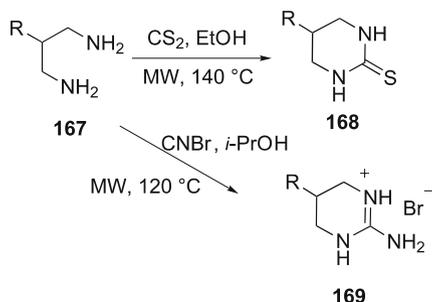
A different kind of triazine, 3,5,6-trisubstituted 1,2,4-triazines **166**, were prepared by reaction of 1,2-diketones **164** with acyl hydrazide in the presence of ammonium acetate and acetic acid at 180 °C for 5 min under microwave irradiation in a sealed tube [107]. Different substituents can be introduced in the final triazines providing a general approach for this kind of heterocycles (Scheme 59).

6 Six-Membered Rings – Non Aromatic

Two examples of non aromatic six-membered heterocycles have been recently reported using cyclocondensations mediated by microwave irradiation.

Cyclic isothioureas **168** were prepared simply by reaction of 1,3 diamines **167** and CS₂ in EtOH under microwave irradiation at 140 °C with elimination of one molecule of H₂S (Scheme 60).

When cyanogen bromide was used instead of CS₂, the corresponding guanidines **169** were obtained under analogous conditions [108]. Moreover, differently substituted guanidines **171** could be obtained in very good yields when the isothiourea **168** was alkylated with MeI under microwave irradiation and the product treated with a primary amine. An intramolecular version of this reaction was also described for the preparation of structure **172** present in several important natural products (Scheme 61).



Scheme 60 Synthesis of isothioureas

pared with the aid of microwave irradiation [110], was first reacted with DMF-DMA to obtain the product 175 that was finally transformed into the required compounds by treatment with a series of primary amines through exchange of the dimethylenamines and further cyclization [111]. The method is general and demonstrates the possibility of using microwaves in several consecutive steps of a synthetic procedure, therefore providing a significant shortening of the overall processing time.

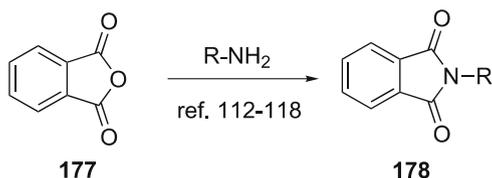
7

Five-Membered Benzocondensed Heterocycles

7.1

Phthalimides

The transformation of phthalic anhydride 177 into phthalimides 178 by reaction with primary amines under microwave irradiation has been one of the first reactions investigated using a household microwave apparatus [112], one procedure being even published on Organic Synthesis [113]. Other authors studied this reaction with or without solvents [114–116] or in the presence of the rather unusual $\text{TaCl}_5 - \text{SiO}_2$ catalyst [117]. In 2000, the reaction was re-examined by Loupy and co-workers in the absence of solvent or with at least one of the component being a liquid [118]. They observed that the reaction occurred exclusively after melting of the anhydride and subsequent solubilization of the amines. The reaction between two solids that did not melt at the reaction temperature (150–160 °C), occurred exclusively in the presence of a high boiling solvent. In all the observed cases, this reaction (Scheme 64) proceeds in excellent yields and purity, proving to be one of the most suitable for microwave activation.

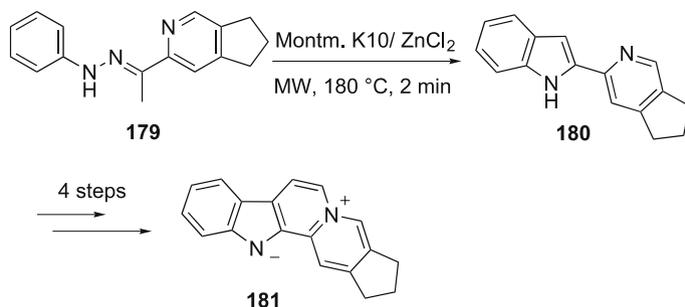


Scheme 64 Microwave-assisted synthesis of phthalimides

7.2

Indoles

A microwave-assisted version of the Fischer indole synthesis was described by reaction of the hydrazone 179 [119]. The reaction was carried out on Montmorillonite K10 doped with ZnCl_2 giving reasonable yields of compound



Scheme 65 Fisher indole synthesis

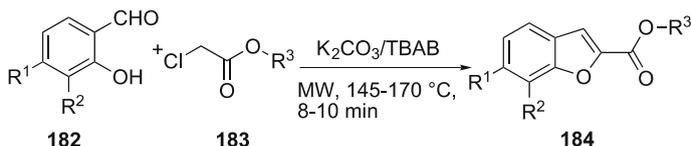
180 that is an intermediate for the synthesis of Sempervirine analogues **181** (Scheme 65).

7.3

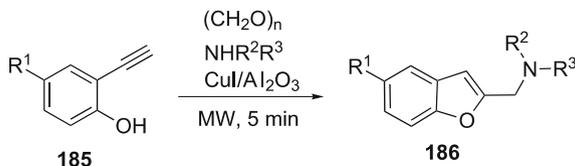
Benzo[b]furans

Benzofurans have been prepared by microwave-accelerated cyclocondensation of differently substituted salicylaldehydes **182** with esters of chloroacetic acid **183** in the presence of K_2CO_3 (used as the solid support) and tetrabutylammonium bromide (TBAB) as phase transfer catalyst [120]. This method seemed general regarding the variations at the benzene ring and the nature of the ester moiety (Scheme 66).

An alternative preparation of benzofurans was carried out via a microwave-assisted Mannich condensation of paraformaldehyde and a secondary amine followed by cyclization with an alkynyl phenol **185** mediated by alumina doped with CuI (Scheme 67). The reaction can be carried out in a single-step



Scheme 66 Phase-transfer catalyzed synthesis of benzofuran carboxylates



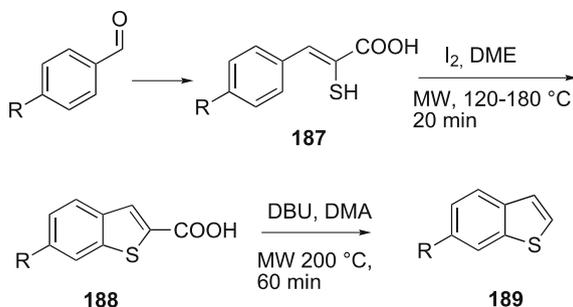
Scheme 67 Solvent-free synthesis of benzofurans

mixing of all the components in a sealed tube inserted inside a microwave cavity (monomode irradiation) and heating for 5 min [121].

7.4

Benzo[b]thiophenes

Benzothiophenes have been prepared by cyclization of an aryl mercaptoacrylic acid **187** with iodine in 1,2-dimethoxyethane at 120 °C under microwave irradiation (Scheme 68) with yields much higher than under conventional heating [122]. The following decarboxylation to give product **189** was also carried out at 200 °C using DBU in DMA as the solvent in 93% yield. The method was general, several benzothiophenes were prepared, some of them showing also interesting biological activities [123].

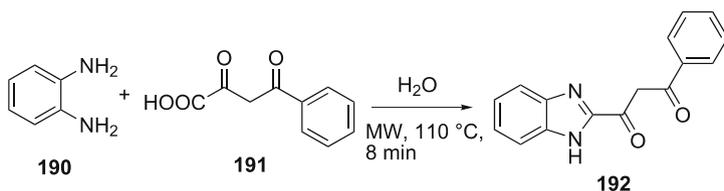


Scheme 68 Two-step microwave-assisted synthesis of benzothiophenes

7.5

Benzimidazoles

Benzimidazoles have been prepared by direct condensation of *o*-phenylenediamine **190** with a carboxylic acid at 110 °C in water and under microwave irradiation (Scheme 69) [124]. Differently functionalized benzimidazoles **192** were obtained with this method especially regarding the nature of the substituent on the imidazole ring.

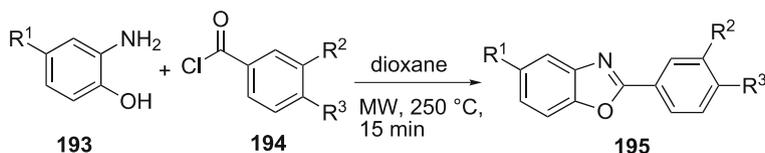


Scheme 69 Benzimidazole synthesis in water

7.6

Benzoxazoles

As in the case of benzimidazole, a parallel synthesis of benzoxazoles was described. The authors report that mixing directly differently substituted *o*-amino phenols **193** with acylating agents **194** and heating at 200 °C for 10–15 min under microwave irradiation, a collection of benzoxazoles **195** was obtained (Scheme 70). With this reaction, a 48-member library of benzoxazoles with different substituents on the aromatic rings was obtained [125].



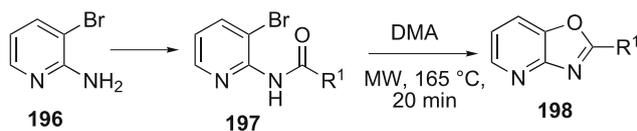
Scheme 70 Synthesis of a library of benzoxazoles

7.7

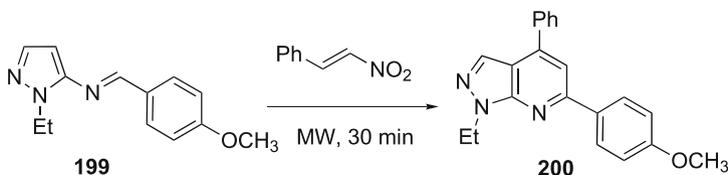
Benzocondensed Heterocycles with More than Two Heteroatoms

Pyridino-oxazoles **198** were obtained in an analogous way starting from *o*-bromoaminopyridine **196**, which was first acylated and then cyclized under microwave irradiation at 165 °C in DMA via an aromatic nucleophilic substitution (Scheme 71) [126].

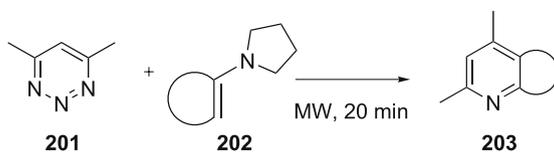
The first microwave-assisted hetero-Diels–Alder cycloaddition reaction was described by Diaz-Ortiz and co-workers in 1998 between 2-azadiene **198** and the same electron-poor dienophiles as for the preparation of pyrazolo[3,4-*b*]pyridines **200** (Scheme 72) [127]. These dienes reacted with



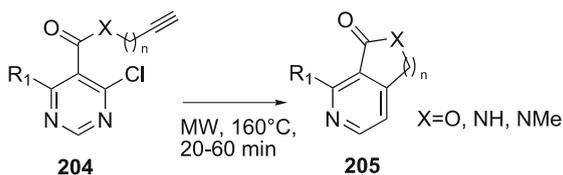
Scheme 71 Synthesis of pyridino-oxazoles



Scheme 72 Solvent-free synthesis of pyrazolo-pyridines



Scheme 73 General scheme for cycloaddition of triazines with enamines



Scheme 74 Diels–Alder reaction for the synthesis of fused pyridines

nitroalkenes under solvent-free conditions in 5–10 min to afford the corresponding cycloadducts in good yields, avoiding the usual degradation of the dienic pyrazole that always occurred under conventional heating. To evaluate the feasibility of this approach, the authors investigated the synthesis of tricyclic heterocycles using cycloalkenes, aliphatic and aromatic nitroalkenes, which did not undergo cycloaddition under classical heating [128].

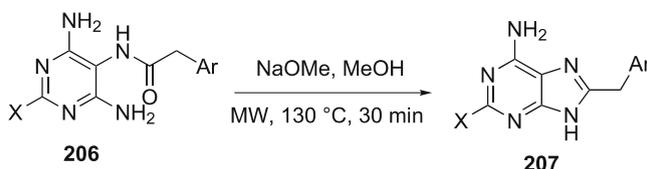
In 2001, the same authors described the cycloaddition of dimethyl-1,2,3-triazine **201** with enamines **202**, derived from cyclic ketones and pyrrolidines, under microwave irradiation in open vessels and under solvent-free conditions (Scheme 73) [129]. A remarkable improvement compared to the classical method was achieved allowing the preparation of heterocyclic derivatives in good yields without alterations of the reagents. Following their interests in microwave-assisted cycloaddition reactions, the authors carried out Diels–Alder reactions of (*E*)- and (*Z*)-3-styrylchromones with *N*-methyl and *N*-phenylmaleimide under solvent-free conditions providing 4-aryl-1,3-dioxopyrrolo[3,4-*c*]-3a,4,11a,11b-tetrahydroxanthenes in good yields [130]. The reaction gave the corresponding cycloadducts in a stereoselective manner.

Shao reported the microwave-assisted hetero-Diels–Alder cycloaddition reaction of a series of acetylenic pyrimidines to introduce a fused lactone/lactam ring, with no degradation of either reactants or products typical for the harsh thermal conditions (150–190 °C, 15–144 h) [131]. In contrast to the results reported when conventional heating was applied, the Diels–Alder cycloaddition under microwave irradiation gave a high yield of the desired fused lactones or lactams [132]. This reaction provided a practical and general method for the preparation of fused bicyclic pyridines **205** (Scheme 74).

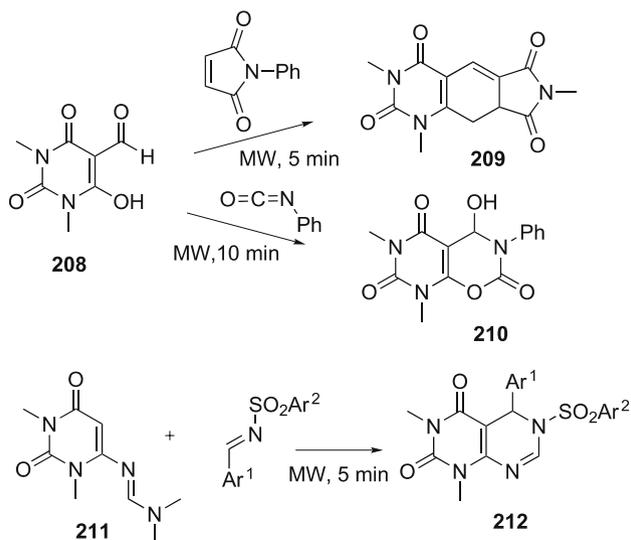
7.8 Purines

The cyclization of *o*-substituted amides **206** was used for the preparation of a series of purine derivatives **207**. In this case, the amine behaved as a nucleophile toward the amide function followed by ring closure to the imidazole ring (Scheme 75) [133].

Several syntheses of annulated uracils of biological value were recently reported. The key reaction was a microwave-assisted one-pot [4 + 2] cycloaddition of oxazino[4,5-d]-, pyrano-[2,3-d]-, pyrido[2,3-d]- and pyrimido[4,5-d]pyrimidines, in the solid state [134] and under solvent-free conditions [135]. The synthetic approach was based on the reaction of *N,N*-dimethyl-5-formylbarbituric acid **208** with maleimide in the solid state for 5 min under microwave irradiation at 120 °C to give the pyrano[2,3-d]pyrimidine derivative **209** in 90% yield (Scheme 76). The reaction of **208** with phenyl isocyanate in the absence of solvent



Scheme 75 Purine synthesis



Scheme 76 Solvent-free synthesis of polycyclic heterocycles

gave the corresponding oxazino[4,5-d]pyrimidine **210** in 87% yield. The 6-[(dimethylamino)methylene]amino-1,3-dimethyl uracil **211** was readily obtained by reaction of 6-amino-1,3-dimethyl barbituric acid with DMF-DMA under microwave irradiation. Treatment of **211** with an equimolar amount of *N*-(arenesulfonyl)benzaldimines gave the corresponding pyrimido[4,5-*d*]pyrimidine derivative **212** in 98% yield (Scheme 76). This hetero-Diels–Alder cycloaddition reaction was carried out in few minutes in a microwave reactor under solvent-free conditions.

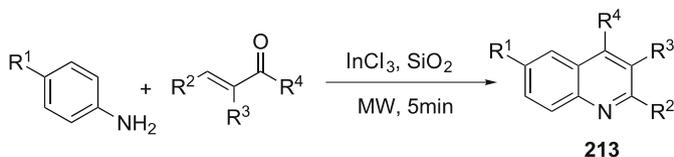
8 Six-Membered Benzocondensed Heterocycles

8.1 Quinolines and Isoquinolines

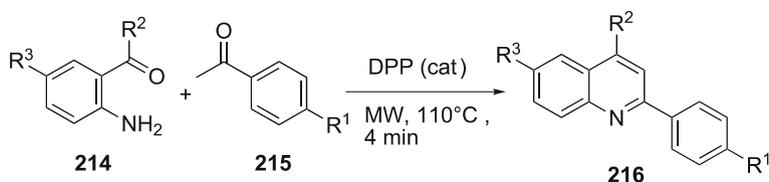
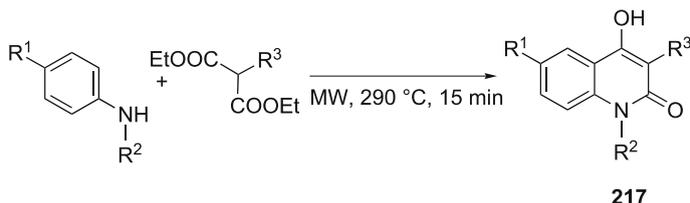
For the synthesis of quinolines and isoquinolines the classical approaches are the Skraup and the Bischler–Napieralski reactions. The reaction of substituted anilines with different carbonyl compounds in acid medium has been reported to be accelerated under microwave irradiation to give differently substituted quinolines and dihydroquinolines [137]. Although the yields are much better and the conditions are milder than under conventional heating, the acidity of the medium may prevent the preparation of acid-sensitive compounds. Thus, alternative approaches have been investigated. Substituted anilines and alkyl vinyl ketones reacted under microwave irradiation on the surface of silica gel doped with InCl_3 without solvent [137] to furnish good yields of quinolines **213** (Scheme 77).

Aryl substituted quinolines **216** have also been prepared through a microwave-assisted Friedländer condensation between various acetophenones **215** and 2-aminoacetophenones **214** in the presence of a catalytic amount of diphenylphosphate (Scheme 78). These conditions are less acidic than the others reviewed here for the synthesis of quinolines [138].

A related reaction has been described for the synthesis of 2-quinolones, reacting substituted secondary anilines with malonic acid derivatives. The reaction was carried out neat under microwave irradiation at 290 °C for 15 min. These harsh conditions were required for the elimination of two



Scheme 77 Solvent-free Skraup synthesis

**Scheme 78** Quinolines synthesis**Scheme 79** Microwave-assisted synthesis of quinolones

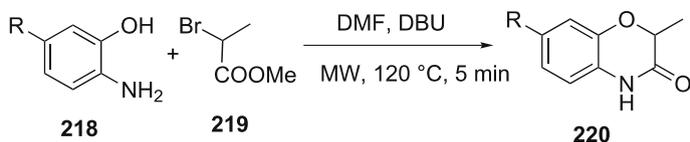
molecules of ethanol (Scheme 79). More than 15 examples of different 4-hydroxyquinolones **217** have been described with a good level of diversity at the three positions [139].

The Bischler–Napieralski reaction has been described to proceed under microwave irradiation to give very good yields of dihydroisoquinolines [140] and other polycyclic compounds (see below) in the presence of POCl₃ and P₂O₅ (classical conditions) in toluene (10 cycles of 60 s each using a dedicated microwave reactor).

8.2

Benzoxazines

1,4-Benzoxazine, an heterocycle present as structural subunit in many naturally occurring and synthetic bioactive compounds, was prepared under microwave irradiation from a mixture of 2-aminophenol **218** and an α -bromoester **219** (Scheme 80). The reaction proceeded through an initial base-catalyzed alkylation of the phenolic OH followed by spontaneous amidation. Yields from 44 to 78% were reported for 17 different benzoxazines **220** [141].

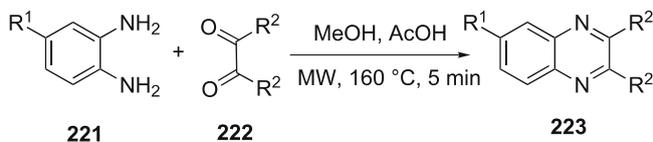
**Scheme 80** Synthesis of benzoxazines

8.3

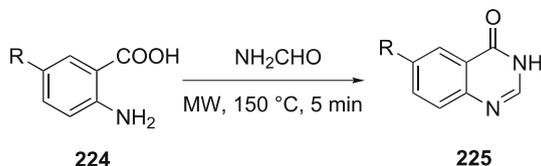
Quinoxalines

Quinoxalines have been prepared starting from common 1,2-diketones and 1,2-aryldiamines in MeOH/AcOH at 160 °C for 5 min under microwave irradiation (Scheme 81). Several differently substituted quinoxalines **223** and pyrido[2,3-*b*]pyrazines were prepared with this method, which limitation may be the symmetry of the diketone **221** or the diamine **222** employed, in order to avoid the formation of a mixture of regioisomers [142].

Microwave irradiation of a mixture of substituted anthranilic acid **224** with formamide (5 equiv) at 150 °C for 5 min gave quinazolinones **225** in good yields (Scheme 82). This microwave version of the Niementowski reaction [143] showed significantly improved yields compared to the conventional reaction conditions [144].



Scheme 81 Synthesis of quinoxalines



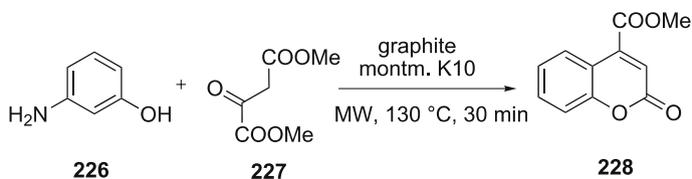
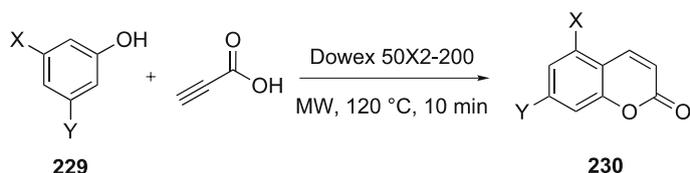
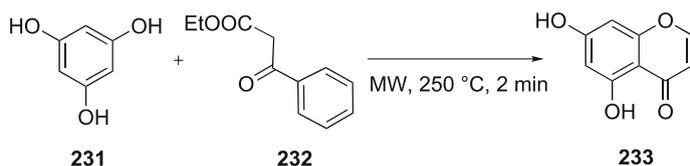
Scheme 82 Synthesis of quinazolinones

8.4

Coumarins and Flavones

Coumarins and flavonoids are common in nature and find their main applications as pharmaceuticals, fragrances, and agrochemicals.

For the synthesis of coumarins, the Pechmann reaction [145] is one of the most popular synthetic routes. As the reaction is conventionally carried out at high temperature, two microwave-assisted versions have been recently described. Besson and co-workers described the cyclocondensation of different *m*-amino phenols **226** with β -ketoesters **227** on graphite/montmorillonite K10 support (Scheme 83). The use of graphite was crucial in the development of the reaction conditions. In fact, microwave irradiation of the reagents using different conditions gave poor results in terms of yields and purity. The optimized conditions, using a monomode microwave system, employed

**Scheme 83** Coumarin synthesis**Scheme 84** Pechmann microwave-assisted reaction**Scheme 85** Solvent-free synthesis of flavones

a mixture of graphite and montmorillonite K10 (as acid catalyst) at 130 °C for 30 min [146]. Under these conditions, compound **228** was obtained in 75–98% yield.

A modified Pechmann microwave-assisted reaction has been reported using an electron-rich phenol **229** and an α,β -unsaturated acid in order to obtain coumarins without a substituent in position 4 [147]. Even in this case, the use of an acid solid catalyst (the support) was needed. Best results were obtained with Dowex or Amberlite-15 at 120 °C for 15 min (Scheme 84).

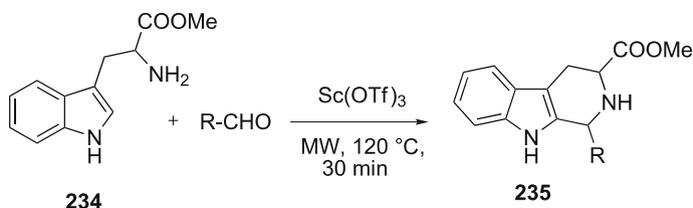
A solvent-free synthesis of flavones was recently reported by microwave-assisted reaction of phloroglucinol **231** and differently substituted β -ketoesters **232** [148]. The reaction was simply carried out by mixing the phenol and the ester in an open test tube followed by irradiation for 2–3 min. The internal temperature reached 240 °C and yields were in the range from 68 to 96%. Scheme 85 describes the application of this procedure to the synthesis of the natural product chrysin **233**.

9 Tricyclic Systems

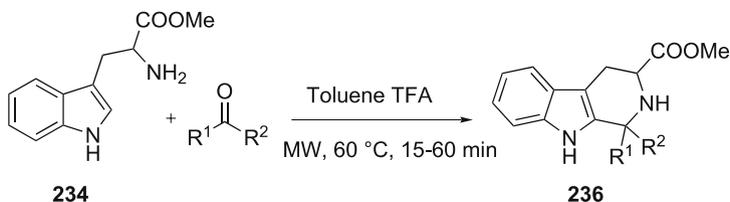
The Pictet–Spengler reaction has mainly been investigated as a potential source of polycyclic heterocycles for combinatorial applications or in natural product synthesis [149]. Tryptophan or differently substituted tryptamines are the preferred substrates in a cyclocondensation that involves also aldehydes or activated ketones in the presence of an acid catalyst. Several versions of microwave-assisted Pictet–Spengler reactions have been reported in the literature. Microwave irradiation allowed the use of mild Lewis acid catalysts such as $\text{Sc}(\text{OTf})_3$ in the reaction of tryptophan methyl esters **234** with different substituted aldehydes (aliphatic or aromatic) [150]. Under these conditions the reaction was carried out in a one-pot process without initial formation of the imine (Scheme 86).

The same kind of results were obtained using the ionic liquid $[\text{bmim}][\text{PF}_6]$ as the medium to carry out the reaction in the presence of TFA at 60°C for 30 s under microwave irradiation [151, 152]. Toluene can be also used as the solvent as well TFA as the acid [153]. Heating at 60°C for a longer period also allowed the reaction of different ketones, thus increasing the potential of the reaction for the generation of molecular diversity around a tricyclic scaffold such as **236** in Scheme 87.

An interesting modification of the Pictet–Spengler reaction has been described by Besson and co-workers that employed the degradation of DMSO under microwave irradiation [154]. DMSO undergoes decomposition by prolonged microwave heating, generating dimethyl sulfide, dimethyl disulfide,



Scheme 86 Microwave-assisted one-pot Pictet–Spengler reaction



Scheme 87 Pictet–Spengler reaction on ketones

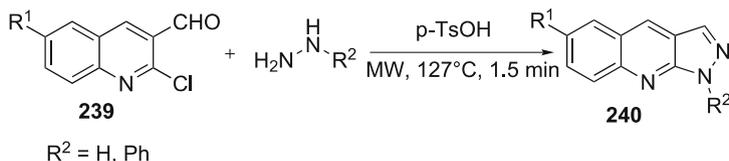
bismethylthiomethane, formaldehyde and water [155]. Formaldehyde is the key intermediate of the decomposition and it can be trapped with suitable substrates in order to generate additional compounds. Thus, reaction of benzothiophene **237** in DMSO as the solvent and in the presence of TsOH under reflux for 3 h (under microwave irradiation) gave the tricyclic compound **238** (Scheme 88). With this method, the synthesis of a rigidified analogue of melatonin was carried out.

Tricyclic pyrazolo-quinolines **239** were prepared from β -chloro arylaldehydes and hydrazine derivatives under microwave irradiation with an acid support [156]. The method, applied to a series of tricyclic compounds (Scheme 89), can be used, in principle, also for the synthesis of bicyclic and even monocyclic pyrazoles.

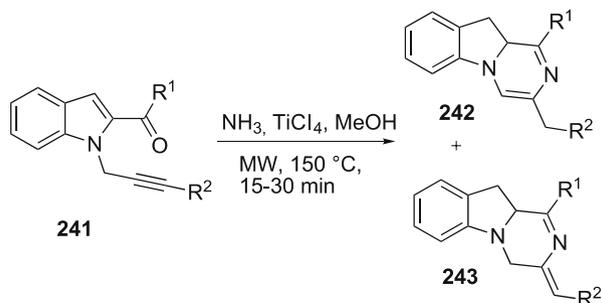
The synthesis of pyrazino-indoles has been described starting from 2-carbonyl-1-propargylindoles **241** and ammonia. The reaction gave a mixture of isomers, **242** and **243** in Scheme 90, and was optimized using



Scheme 88 Benzothiophene synthesis via degradation of DMSO



Scheme 89 Synthesis of polycyclic pyrazoles



Scheme 90 Synthesis of pyrazino-indoles

microwave irradiation in the presence of TiCl_4 as the catalyst or—more probably—the water scavenger [157]. The presence of the Lewis acid increased the amount of the dihydropyrazino indole **243** that in some cases was the exclusive product formed in the reaction.

A case study on the influence of microwave-assisted reactions carried out in open or closed vessel has been described by Kappe and co-workers [158]. One of the examples deals with the cyclocondensation of tetrahydroquinoline and malonic esters. The reaction gave tricyclic hydroxyquinolones with loss of two molecules of ethanol, similar to the reaction described in Scheme 79. The results showed clearly that this reaction carried out in an open vessel gave more reproducible results.

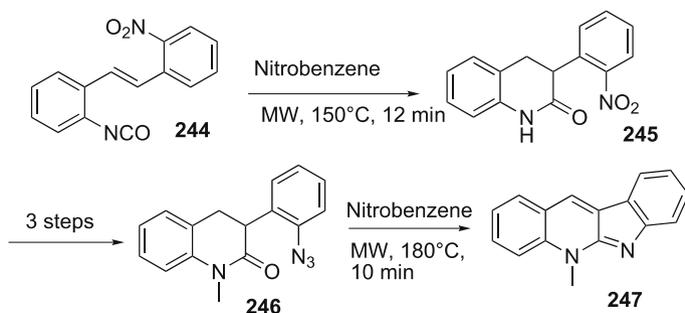
10 Tetracycles and Polycycles

A new approach to indoloquinoline alkaloids from *Cryptolepis sanguinolenta* has been reported based on the cyclization of an *o*-substituted vinyl isocyanate **244** under microwave irradiation and further additional cyclization based on an Aza-Wittig reaction carried out in the presence of microwaves [159]. The application of this synthetic scheme to the synthesis of Cryptotackienine **247** is reported in Scheme 91.

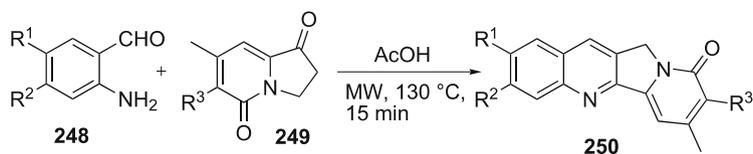
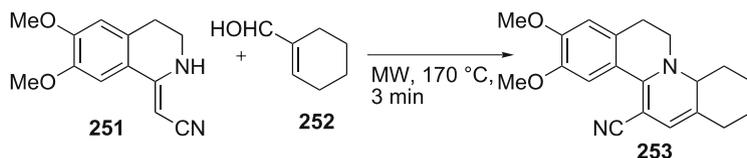
Indolizino-quinoline **250**, the ring system present in camphotecine and mappicine, has been prepared using classical Friedländer reaction under microwave irradiation conditions [160]. The reaction was successfully carried out in AcOH as the solvent and gave good results even with unstable *o*-amino benzaldehydes **248** (Scheme 92).

An improvement from 40% yield, working under conventional heating, to 70% was achieved working with microwaves.

β -Enaminonitriles are useful intermediates in the synthesis of a wide variety of heterocyclic systems. The microwave-enhanced reaction of a cyano-



Scheme 91 Synthesis of Cryptotackienine

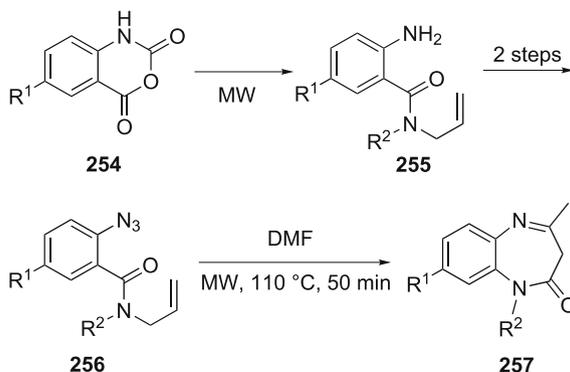
**Scheme 92** Friedländer reaction**Scheme 93** Synthesis of aza-tetracyclic compounds

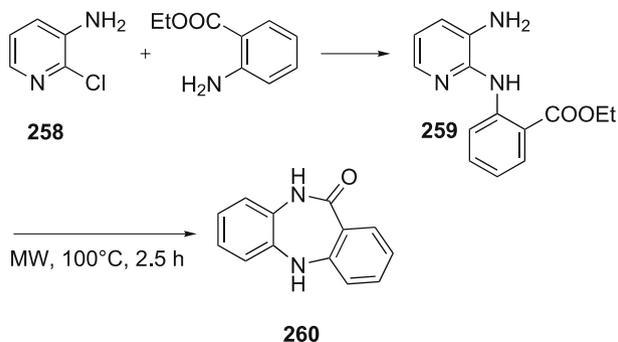
methylene tetrahydroquinoline **251** with different α,β unsaturated carbonyl compounds has been reported [161]. This procedure was employed for the preparation of the interesting tetracyclic compound **253**, starting from 1-cyclohexene-1-carboxaldehyde **252** (Scheme 93). The reaction was carried out in an open vessel without solvent at 170 °C for 3 min.

11

Diazepines

The benzodiazepine nucleus is extremely important, as it is the base of several drugs and other biologically active compounds with different properties. A facile synthesis of 2-methyl-1,4-benzodiazepin-5-ones has been described by Santagada and co-workers [162]. Isatoic anhydride **254** was reacted with *N*-substituted allylamines under microwave irradiation to give compound **255**

**Scheme 94** Synthesis of 1.5-benzodiazepin-2-ones



Scheme 95 Synthesis of dibenzo-diazepinones

and the $-\text{NH}_2$ transformed into an azide (**256**). The cyclization of the arylnitrene intermediate on the double bond at $80\text{--}110^\circ\text{C}$ for a period of approximately 50 min gave the benzodiazepinone **257** in good yields (Scheme 94). The same reaction can be carried out under conventional heating, but with lower yields.

Another synthesis of diazepines (tricyclic) was carried out by reaction of an amino chloropyridine (**258**) and anthranilic acid [163]. First, a nucleophilic substitution occurred (Scheme 95) followed by an intramolecular amidation on compound **259** by microwave irradiation to give structure **260**. The reaction was carried out at 100°C for more than 2 h, a remarkably long time for a microwave-assisted reaction.

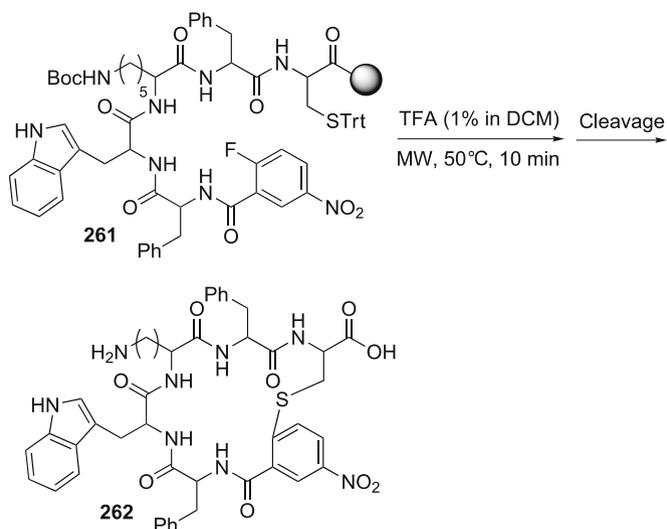
12

Macrocycles

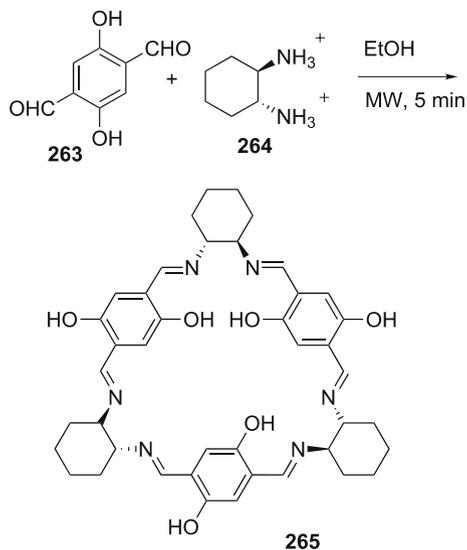
At the end of this review, it is interesting to report that even macrocyclic compounds can be obtained under microwave irradiation.

The macrocyclization of a peptide was carried out by nucleophilic substitution on a fluorobenzene by the sulfide group of the terminal cysteine of a pentapeptide [164]. The peptide **261** was prepared by standard SPPS and was cyclized under microwave irradiation at 50°C for 10 min in DMF (Scheme 96). The yields of **262**, after cleavage with TFA, were remarkably high for a macrocyclic peptide (70%) and also the resulting HPLC purity was very high.

A completely different kind of macrocycle, a calix-salen type macrocycle, was obtained in good yield by microwave irradiation of various dialdehydes and diamines [165]. This was the first example of a calix-type synthesis under microwave conditions and without the presence of a metal template. An example of a [3 + 3] cyclocondensed macrocycle **265**, obtained from a bis aldehyde and a chiral diamine is reported in Scheme 97.



Scheme 96 Synthesis of cyclic peptides



Scheme 97 Synthesis of a calixarene type macrocycle

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The Chemistry of 2-(1*H*)-Pyrazinones in Solution and on Solid Support

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1	Introduction	268
2	Transition-Metal-Catalyzed Decoration of the 2(1 <i>H</i>)-Pyrazinone Scaffold	274
3	Diels–Alder Reactions of the 2(1 <i>H</i>)-Pyrazinone Scaffold in Solution	280
3.1	Diels–Alder Reactions of 2(1 <i>H</i>)-Pyrazinone Scaffold with Acetylenes	280
3.2	Diels–Alder Reactions of the 2(1 <i>H</i>)-Pyrazinone Scaffold with Ethylenes	281
4	Decoration of the 2(1 <i>H</i>)-Pyrazinone Scaffold Applying “Click Chemistry”	285
5	Synthesis and Decoration of the 2(1 <i>H</i>)-Pyrazinone Scaffold on Solid Support	292
6	Diels–Alder Reactions of 2(1 <i>H</i>)-Pyrazinones with Acetylenes on Solid Support	295
7	Summary and Overview	300
	References	301

Abstract An overview on the microwave-enhanced synthesis and decoration of the 2(1*H*)-pyrazinone system is presented. Scaffold decoration using microwave-enhanced transition-metal-catalyzed reactions for generating structural diversity, as well as the conversion of the 2(1*H*)-pyrazinone skeleton applying Diels–Alder reactions to generate novel heterocyclic moieties are discussed. The transfer of the solution phase to polymer-supported chemistry (SPOS) is also described in detail.

Keywords 2(1*H*)-Pyrazinone · Diels–Alder reaction · Microwave · Solid support · Transition metal-catalyzed reaction

Abbreviations

BBN	Borabicyclononane
DCB	Dichlorobenzene
DCM	Dichloromethane
DMAD	Dimethyl acetylenedicarboxylate
DMF	<i>N,N</i> -Dimethyl formamide
Dppf	(Diphenylphosphono)ferrocene

HMPB	4-Hydroxymethyl-3-methoxyphenoxybutyric acid
MAOS	Microwave-assisted organic synthesis
NBS	<i>N</i> -Bromosuccinimide
NIS	<i>N</i> -Iodosuccinimide
PTFE	Poly(tetrafluoroethylene)
SPOS	Solid-phase organic synthesis
TBAF	<i>N,N,N,N</i> -Tetrabutylammoniumfluoride
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TNF- α	Tumor necrosis factor- α

1

Introduction

In the last two decades, 2(1*H*)-pyrazinones emerged as useful starting materials for the elaboration of different types of skeletons of biologically interesting compounds [1]. The 2(1*H*)-pyrazinone scaffold allows for the easy introduction of a wide range of pharmacologically active groups with the ability to address the diverse set of biological targets. Fused pyridine pyrazinones [2] and 3-indolyl pyrazinones [3] can function as corticotropin releasing factor (CRF) receptor antagonists and can be useful for the treatment of various neurological disorders (Fig. 1). Pyrazinones bearing an alkyl amino substituent at position C-3 are known tissue factor VIIa and thrombin inhibitors [4, 5]. Pyrazinones with (*o*-chloro)phenyl group at position 6 are discovered ligands that bind to a new site of GABA_A/chloride ionophore complex [6]. Pyrazinones substituted with anilines at position C-3 and phenols at position C-5 can be useful in inhibiting HIV replication [7]. A number of pyrazinones with an alkyl group at position N-1 and phenyl group at position C-3 show inhibitory action on platelet aggregation, vasodilating activity, and inhibitory action on liperoxide generation [8]. Some 1,2,4-triazolo[4,5-*b*]pyrazinones and 3-thiopyrazinones can act as antibacterial and antifungal agents [9].

3-Amino-2(1*H*)-pyrazinones are often preferred over the analogues 2-pyridinones in view of air-sensitivity of the latter and their oxidizability in neutral and alkaline media [10]. The additional nitrogen of the pyrazine system decreases the reactivity, stabilizing the heterocycle. Recently it has been shown that the 3-amino-2(1*H*)-pyrazinone framework can effectively replace a dipeptide segment in a peptide lead [11–13]. Because of the correct alignment of the CO- and NH-groups coupled with the rigidity of the pyrazinone ring, this scaffold can act as a general β -sheet mimetic that can find use in peptide chemistry and protease inhibitor design. Further constrain using a more rigid bicyclic pyrazinone can create more potent compounds [4]. A series of pyrazinone mono-amides as selective non-peptide caspase-3 in-

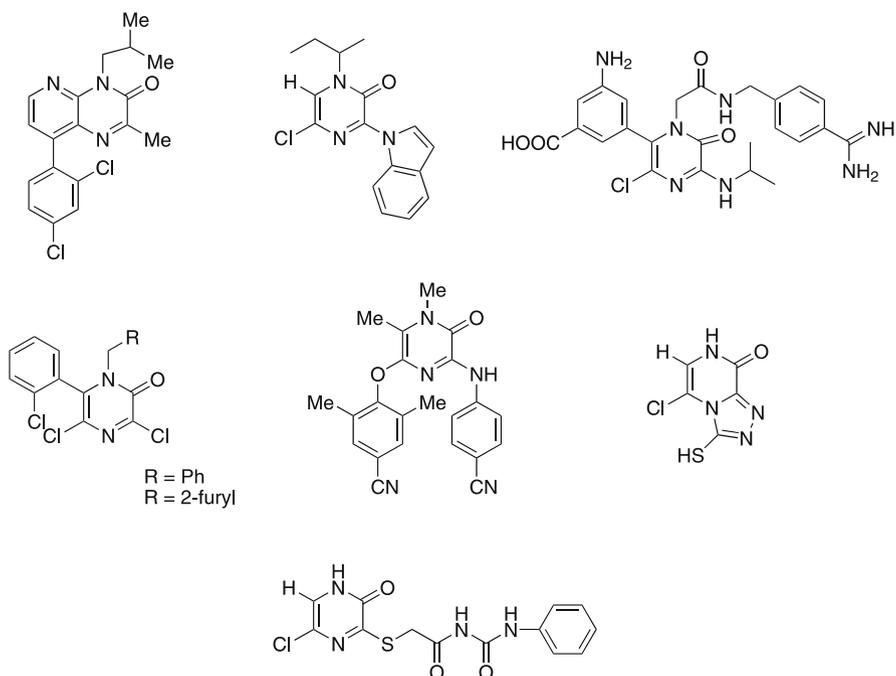
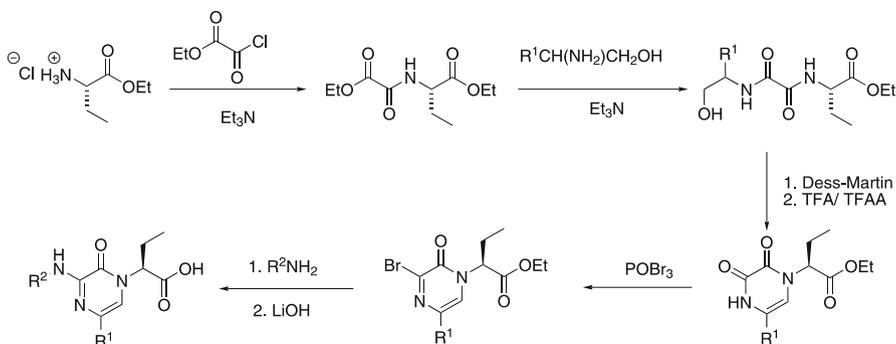


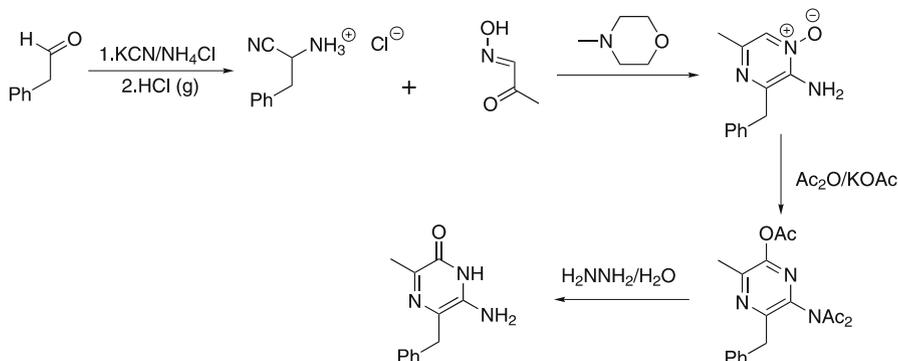
Fig. 1 Some biologically active 2(1*H*)-pyrazinones

hibitors was synthesized starting from readily available starting materials as illustrated in Scheme 1.

Reaction of (S)-(+)-2-aminobutyrate hydrochloride with ethyl oxalyl chloride followed by replacing of the ethyl ester with amino alcohol, oxidation with Dess-Martin periodinate and cyclization using TFA/TFAA in acetic acid gave the cyclic product, which was further converted to the bromide. Sub-



Scheme 1 Synthesis of non-peptide caspase-3 inhibitors



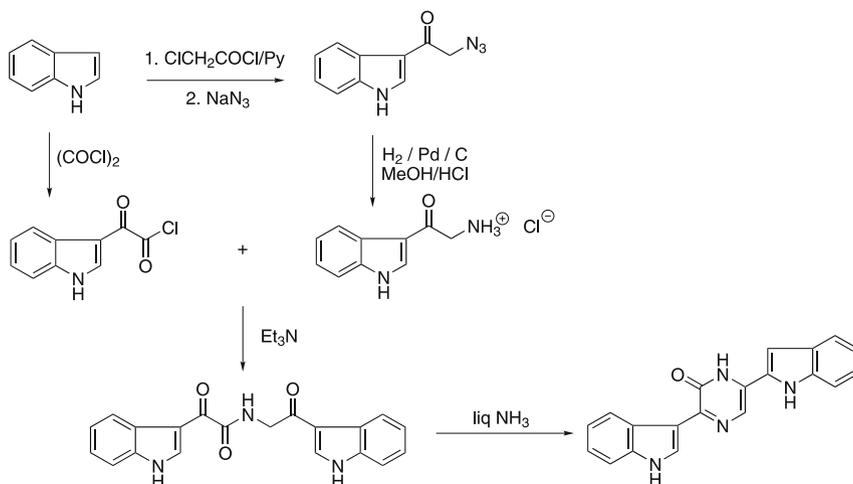
Scheme 2 Synthesis of 6-aminopyrazinones

stitution of bromide with amine R^2NH_2 , followed by saponification of the ethyl ester, afforded the acid template which mimics the hydrogen bond array of the peptide, resulting in the discovery of new protease inhibitors with dramatically improved activities both *in vitro* and *in vivo*.

It has been found that 6-aminopyrazinone (Scheme 2), when incorporated as a pyrimidine base analog into an oligonucleotide, might participate in a nonstandard base pair that retains Watson-Crick geometry [14].

Condensation of phenylalaninenitrile, prepared from phenyl acetaldehyde, with 1-oxime of pyruvaldehyde afforded the pyrazine *N*-oxide, which was further rearranged to give the *N*-acetyl pyrazinone. The acetyl groups were removed by treatment with hydrazine to give the target 6-aminopyrazinone.

During the last decade, a large number of natural products containing the indole nucleus have been isolated from the marine environment and it has been found that some bis(indole) secondary metabolites containing a heterocyclic spacer unit, exhibit a broad spectrum of biological activities [15]. So, antitumor active dramacidin d isolated from *spomgosorties* sp. has a structure of a central pyrazinone ring linked with two indolyl groups and shows antiviral activities [16, 17]. Recently, several methods have been developed to synthesize racemic, naturally occurring bis(indole) alkaloids by construction the central heterocyclic moiety between the indole residues via condensation of two suitable indolyl precursors as a key step. Reaction of indole with chloroacetyl chloride in toluene containing pyridine, followed by treatment with sodium azide afforded azidoketone, which was further hydrogenated over 10% Pd/C in methanol containing concentrated HCl to give 3-(α -aminoacetyl)indole hydrochloride salt as the first indolyl precursor (Scheme 3) [18]. 3-Indolylglyoxylic chloride, obtained from indole, was coupled with the 3-(α -aminoacetyl)indole hydrochloride salt and the central pyrazinone ring was successfully constructed by treatment of the compound with an excess of ammonia.



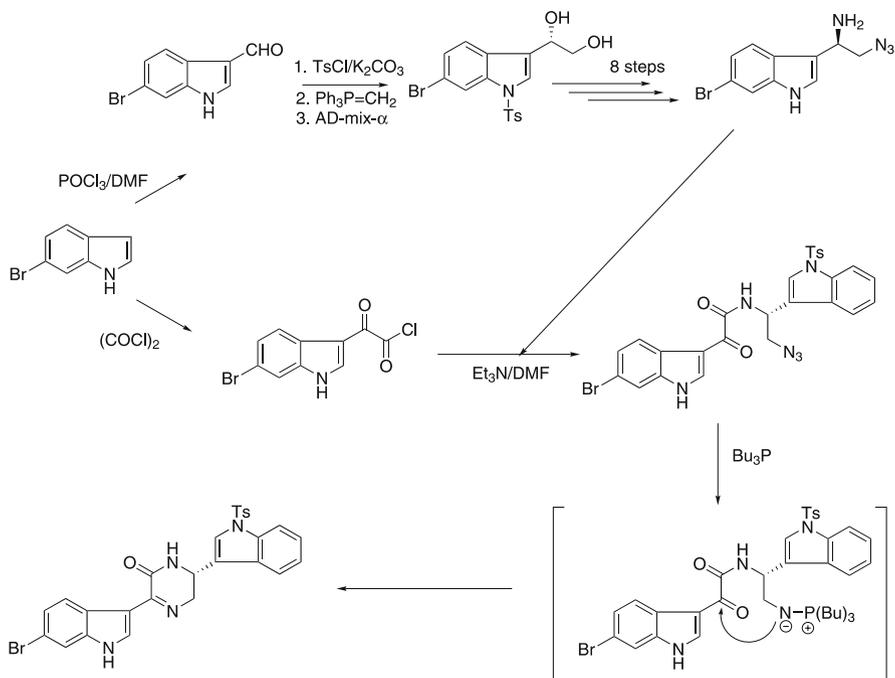
Scheme 3 Synthesis of bis(indole)alkaloids

In order to develop more active clinical candidates, a novel and general method for the synthesis of optically active 3,6-bis(indol-3-yl)-5,6-dihydro-2(1*H*)-pyrazinone derivatives has been reported, using a Staudinger-aza Wittig sequence as a key step for the formation of chiral pyrazinone ring [19] (Scheme 4). Coupling of 3-indolyl- α -oxoacetyl chloride and 3-indolyl-azidoethylamine, both obtained from easily available 6-bromoindole, resulted in the formation of bis(indolyl)azido-diketone. Reaction of the azido group with tributylphosphine gave the corresponding iminophosphorane, which directly cyclized to afford the expected central chiral dihydropyrazinone, a protected (-)- antipode of hamacanthin A isolated from *Hamacantha* sp. exhibiting significant antimicrobial activity.

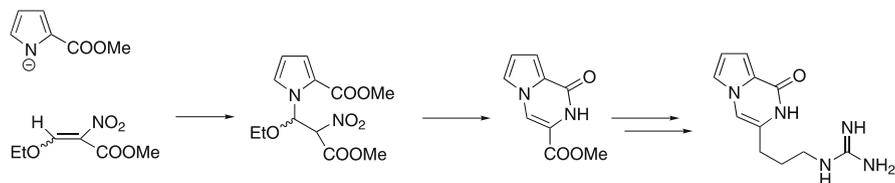
Bicyclic pyrazinones found in several natural products were synthesized via Michael addition of heterocyclic amines to nitro olefin followed by reduction/cyclization of the nitro group of the adduct [20] (Scheme 5). Further elaboration of the C-6 methoxycarbonyl group in pyrazinone to the *n*-propyl guanidine group could result in the synthesis of indoloperamine.

Substitution of a dipeptide unit by a cyclic dipeptide derivative within a peptide chain can induce certain conformational restraints that may alter the biological response via changing receptor selectivity. A facile procedure for synthesis of pyrazinone ring-containing opioid mimetics [21] has been elaborated, based on the cyclization of readily available dipeptidyl chloromethyl ketones [22] (Scheme 6). This method affords 2(1*H*)-pyrazinone derivatives containing substituents with desired functional groups at positions 3 and 6 in high yield.

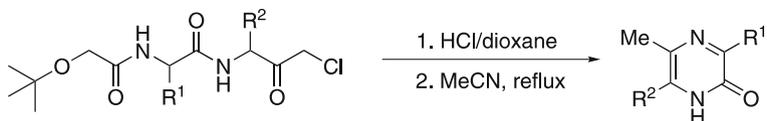
It has been shown that the stereochemistry of starting dipeptidyl chloromethyl ketones does not influence the cyclization reaction, but the chlorine



Scheme 4 Synthesis of the protected (-)-antipode of hamacanthin



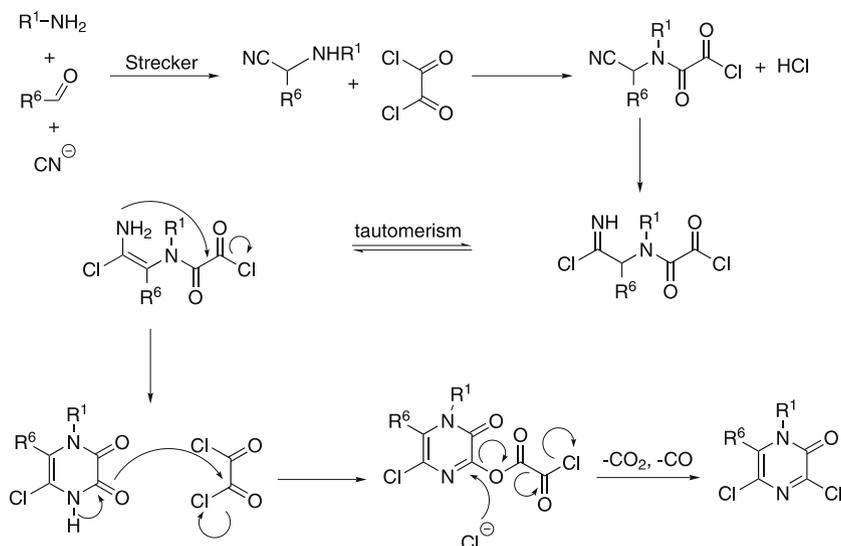
Scheme 5 Synthesis of bicyclic pyrazinones



Scheme 6 Synthesis of pyrazinone ring-containing opioid mimetics

atom has a remarkable effect on the desired cyclization. All attempts to obtain pyrazinones from the corresponding methyl ketones failed, resulting in isolation of amino acid residues.

A versatile synthesis of the 2(1*H*)-pyrazinone scaffold was developed starting from a suitable amine, an aldehyde and cyanide to give an α -aminonitrile,

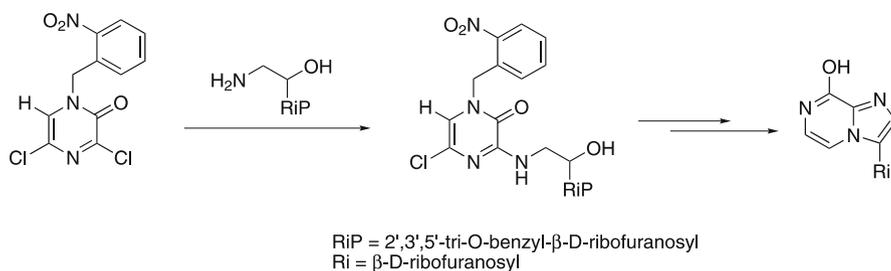


Scheme 7 Synthesis of 3,5-dichloro-2(1*H*)-pyrazinones

which was further cyclized with oxalyl chloride to afford the desired 2(1*H*)-pyrazinone in moderate to good yield [23] (Scheme 7). With regard to the mechanism of pyrazinone formation, it is presumed that the acylation of the amino group of the α -aminonitrile occurs first. After HCl addition on the nitrile function followed by imine-enamine tautomerism of the intermediate oxamoyl derivative, ring closure resulted in the formation of a cyclic dione. The latter is converted into 3,5-dichloro-2(1*H*)-pyrazinone by subsequent reaction with a second molecule of oxalyl chloride.

This approach offers unique opportunities for the generation of multifunctionalized cyclic 2-azadiene systems. A wide variation of the substitution pattern at the positions N-1 and C-6 can be determined by an appropriate choice of the aldehyde and amine. Various substituents can easily be introduced at the C-3 position via addition/elimination reactions on the sensitive imidoyl chloride moiety [24]. Upon reaction with bi-functional reagent, an adequately *N*-protected 2(1*H*)-pyrazinone was elaborated into *C*-nucleoside analogues (Scheme 8). The desired skeleton and functionalities were obtained by oxidation-cyclization reaction followed by photochemical removal of the protective *o*-nitrobenzyl group [25].

It has been shown that cross-coupling reactions constitute a very mild method to introduce different alkyl and aryl groups to the most active C-3 position of the pyrazinone ring [26]. The broadly functionalized 2-azadiene system of the title compounds was studied in cycloaddition reactions with various electron-rich and electron-poor dienophiles to provide highly substituted heterocycles [24].



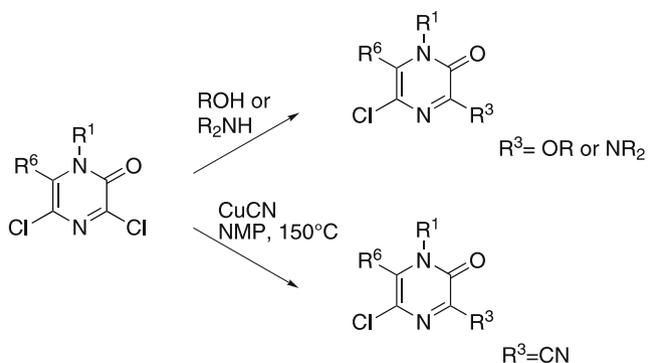
Scheme 8 Synthesis of C-nucleoside analogues

Due to its remarkably fast and clean reaction profiles, microwave-assisted organic synthesis (MAOS) could be regarded as a major breakthrough in modern chemistry, especially in the field of synthetic organic chemistry. The development of dedicated microwave instruments caused an exponential increase in the literature output regarding the application of microwave irradiation in promoting chemical transformations. The application of such apparatuses allows precise control of the power, temperature, and pressure, ensuring the reproducibility of reactions. These dedicated instruments are a handy tool for academic research as well as for the rapid parallel synthesis of medium-sized compound libraries for lead identification and drug discovery processes in industry. The application of microwave irradiation has been demonstrated with great success in the synthesis of various biologically active heterocyclic systems, exciting the interest of the pharmaceutical and medicinal chemistry community. Microwave-enhanced heterocyclic synthesis offers great potential for the rapidly increasing demand for novel drug candidates. However, until recently, the chemistry of 2(1*H*)-pyrazinones, an interesting scaffold in generating a number of various biologically active heterocyclic systems, has not been investigated under microwave irradiation conditions.

2

Transition-Metal-Catalyzed Decoration of the 2(1*H*)-Pyrazinone Scaffold

There has been a plethora of recent literature regarding the synthetic manipulations of the 2(1*H*)-pyrazinone skeleton. Even though the addition-elimination reactions at the C-3 position to decorate the pyrazinone scaffold are well documented [24], the versatility of such approaches can be found somewhat limited. Selective attack of nucleophiles on the chloroimine group of the pyrazinone system can generate 3-alkoxy- and 3-amino-pyrazinones (Scheme 9) [27, 28]. The 3-CN group was introduced via a Rosemund-von Braun reaction with copper(I)cyanide under harsh conditions (heating in NMP at 150 °C) [27] (Scheme 9).

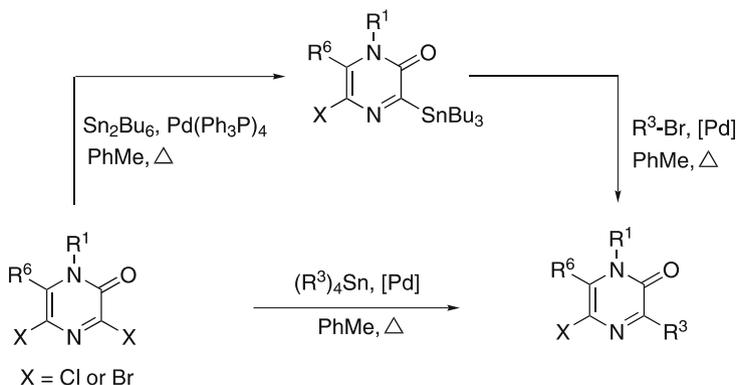


Scheme 9 Introduction of substituents to the position C-3 of the 2(1*H*)-pyrazinone scaffold

The use of transition-metal-catalyzed reactions under conventional heating conditions has been demonstrated for the decoration of the C-3 position of the pyrazinone system, though the C-5 position appeared to be more reluctant towards reaction.

For example, the sensitive imidoyl chloride moiety at the C-3 position of the pyrazinone scaffold is known to undergo Stille reactions with a variety of tetraaryltin reagents, generating the corresponding 3-substituted pyrazinones (Scheme 10) [26]. Furthermore, the transition-metal-catalyzed stannylation at the C-3 position is also documented in the literature, in view of cross-coupling with a variety of alkyl and (hetero)aryl halides [26]. However, this strategy is completely restricted to the C-3 position, while the Cl atom of C-5 position was found to be inert under these conditions.

It has recently been shown that the transition metal-mediated decoration of the pyrazinone scaffold can greatly benefit from microwave irradi-

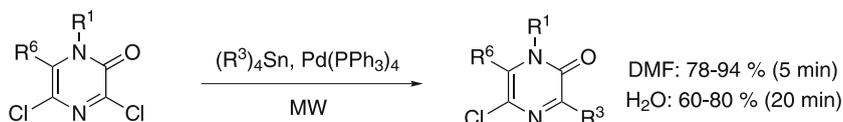


Scheme 10 Stannylations and Stille reactions at the C-3 position

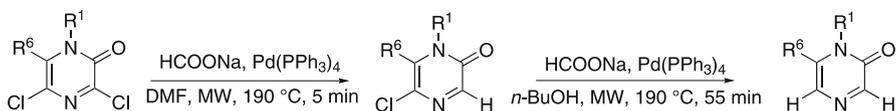
ation. Microwave-enhanced transition-metal-catalyzed reactions were found to be cleaner and faster than their counterparts under conventional heating conditions, often resulting in higher yields in remarkably shorter reaction times. Furthermore, microwave irradiation was found to facilitate the cross-coupling reactions at the relatively inert chloro group of the C-5 position, which was deemed impossible under conventional heating conditions. The reaction times for the Stille couplings could be brought down from the order of hours to mere minutes [29] with good to excellent yields in DMF as solvent (Scheme 11). The use of DMF was due to the fact that the high $\tan \delta$ value of the solvent facilitates strong microwave absorption and thus contributes to the efficient flash heating [30]. Furthermore, the authors carried out the Stille reactions in water as the sole solvent with high yields under microwave-enhanced conditions. While microwave-irradiated Pd-catalyzed Suzuki-Miyaura [31] and Heck [32] reactions have been frequently reported in the literature applying aqueous media, examples of microwave-enhanced Stille coupling reactions in water as the solvent have scarcely been described [33]. Even though there are examples reported under conventional heating conditions, they often demand the use of hydrolytically labile alkyltrichlorostannanes (R_3SnCl_3 and $PdCl_2$), [34, 35] water-soluble sulfonated phosphines [36] or the use of polyethylene glycol as a support and a phase-transfer catalyst in aqueous palladium-catalyzed liquid-phase synthesis [37]. Thus, the Stille reactions were performed via the microwave irradiation of an aqueous suspension of the 3,5-dichloro-2(1*H*)-pyrazinones applying the water insoluble $Pd(PPh_3)_4$ as catalyst and the very low water soluble, lipophilic R_4Sn or Ar_4Sn reagents at an elevated temperature of 200 °C (Scheme 11) to generate the 3-substituted analogues.

The dechlorination of the C-3 and C-5 position of the pyrazinone system was described to be fast under microwave irradiation [29]. Contrary to the reported de-chlorination [26] via palladium-catalyzed reaction with sodium formate 100 °C for 2–4 h and at the C-5 position in 2–3 days, a dramatic rate enhancement was observed under microwave irradiation (Scheme 12). The mono-reduction at C-3 was performed at 190 °C in DMF in merely 5 min, and the reduction of C-5, starting from the mono-reduction product, was performed in *n*-butanol in 55 min to afford the *bis*-reduction product in good overall yield.

Transition-metal-catalyzed cyanation [38] at the C-3 position for the decoration of the pyrazinone scaffold was also reported by the same authors,



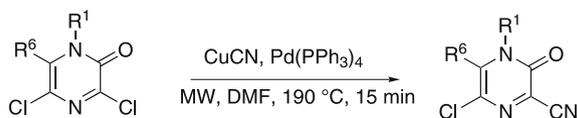
Scheme 11 Stille reactions under microwave irradiation



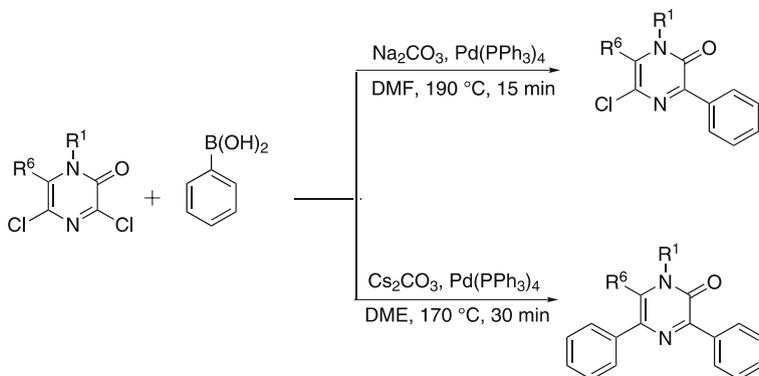
Scheme 12 Microwave-assisted dechlorination

applying focused microwave irradiation. The reactions were performed (Scheme 13), using CuCN and Pd(Ph₃P)₄ in DMF at 200 °C in 15 min [29].

The Suzuki–Miyaura coupling was performed at the 2(1*H*)-pyrazinone scaffold applying microwave irradiation [29]. Contrary to the Suzuki–Miyaura reactions under conventional heating conditions [39, 40], microwave irradiation was successful in directing the coupling not only to the reactive C-3 position of the 3,5-dichloro-pyrazinone, but also to the unreactive C-5 position of the molecule (Scheme 14). Mono-arylated product was isolated in good to excellent yield, when the cross-coupling was carried out with phenylboronic acid in the presence of Na₂CO₃ as the base and Pd(Ph₃P)₄ as the catalyst. The reaction was performed in DMF at a pre-selected maximum temperature of 190 °C for 15 min. Bis-arylated product was observed by switching the base to Cs₂CO₃ and the solvent to DME, the latter being necessary to avoid undesired amination of the C3-position due to thermal decomposition of the DMF during prolonged heating. The reaction was finished in a slightly longer time of 30 min at a pre-selected maximum temperature of 170 °C (Scheme 14).



Scheme 13 Microwave-assisted cyanation

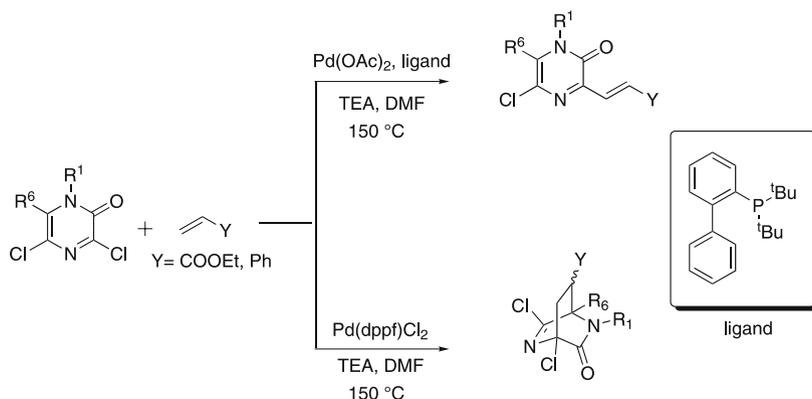


Scheme 14 The mono- and bis-Suzuki reaction under microwave irradiation

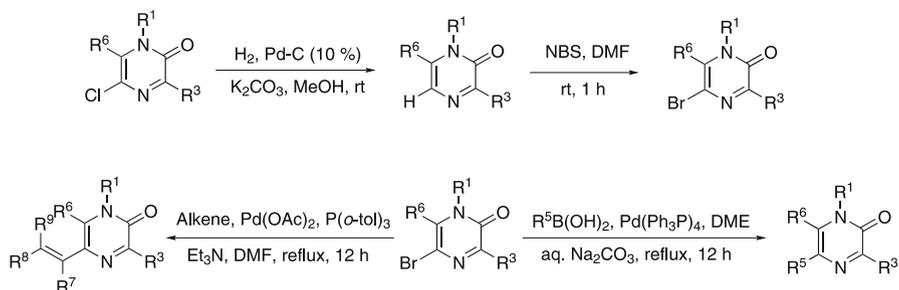
An interesting parallel was found while the microwave-enhanced Heck reaction was explored on the C-3 position of the pyrazinone system [29]. The additional problem here was caused by the capability of the alkene to undergo Diels–Alder reaction with the 2-azadiene system of the pyrazinone. An interesting competition between the Heck reaction and the Diels–Alder reaction has been noticed, while the outcome solely depended on the substrates and the catalyst system. Microwave irradiation of a mixture of pyrazinone ($R_6 = H$), ethyl acrylate ($Y = COOEt$) and $Pd(dppf)Cl_2$ resulted in the formation of a mixture of the starting material together with the cycloaddition product in a 3 : 1 ratio (Scheme 15). On the contrary, when $Pd(OAc)_2$ was used in combination with the bulky phosphine ligand 2-(di-*t*-butylphosphino)biphenyl [41–44], the Heck reaction product was obtained as the sole product. When a mixture of the pyrazinone ($R_6 = Ar$) with ethyl acrylate or styrene and $Pd(dppf)Cl_2$ was irradiated at 150 °C for 15 min, both catalytic systems favored the Heck reaction product with no trace of Diels–Alder adduct.

The Suzuki–Miyaura and Heck reactions were recently also reported under conventional heating conditions [39, 40]. A variety of 3-chloro pyrazinones were reacted with commercially available (hetero)aryl boronic acids or the alkyl-9-BBN derivatives under either classical or slightly modified Suzuki conditions to generate the 3-substituted analogues, however having the drawback of longer reaction times of up to 12 h of reflux.

In contrast to the results found under microwave irradiation conditions [29], the cross-couplings at the C-5 position, applying conventional heating conditions, could only be achieved by replacing the unreactive Cl group for the more reactive Br group [39, 40]. Thus, the Cl group at the C-5 position of the pyrazinone was first replaced by hydrogen under palladium-catalyzed hydrogenation conditions (Scheme 16) in the presence of K_2CO_3 as



Scheme 15 Heck vs. Diels–Alder under microwave irradiation



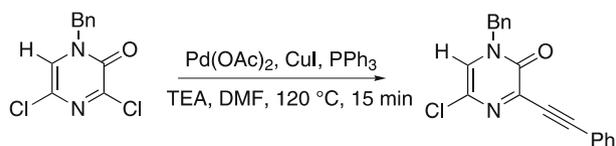
Scheme 16 Suzuki–Miyaura and Heck reactions at the C-5 position under conventional heating conditions

the base. The Br or I group was introduced at the C-5 position via a NBS- or NIS-mediated halogenation protocol. The bromo-analogue was then decorated at the C-5 position via palladium-catalyzed Suzuki–Miyaura or Heck reactions, with moderate to good yields, to generate the corresponding 5-substituted compounds.

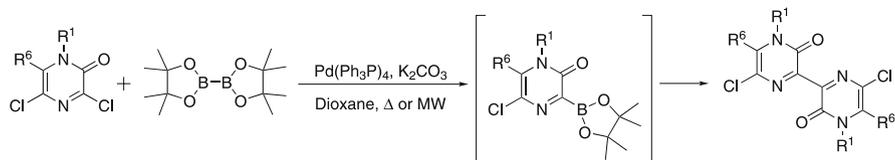
For the further decoration of the pyrazinone scaffold via transition metal-catalyzed chemistry, the Sonogashira reaction [45–50] has also been investigated on the C-3 position of the pyrazinone, applying microwave irradiation conditions (Scheme 17) [29]. It was found that microwave irradiation at 120 °C for 15 min of a mixture of the starting material, Pd(OAc)₂, CuI and PPh₃ in TEA/DMF were the appropriate reaction conditions.

Even though the reaction proceeded smoothly at the C-3 position of the pyrazinone scaffold providing the alkyne derivative in good yields, no reaction was observed at the C-5 position under similar conditions.

An alternative protocol for the transition-metal-catalyzed decoration of the C-3 position of the pyrazinone scaffold has recently been discovered, based on the homo-dimerization reaction [51–53]. An efficient synthesis was elaborated using the Suzuki-type cross-coupling protocol which gives rise to highly functionalized symmetric bi-2(1*H*)-pyrazinones (Scheme 18) [54]. A variety of richly substituted 3,5-dichloro-2(1*H*)-pyrazinones was treated with bis(pinacolato)diboron [B(pin)₂] in the presence of Pd(Ph₃P)₄ as catalyst and K₂CO₃ as base in refluxing dioxane. The in situ formed 3-borono derivatives, which cannot be isolated, were observed to directly undergo



Scheme 17 Sonogashira reaction at the C-3 position



Scheme 18 Palladium-catalyzed homo-dimerization of 2(1*H*)-pyrazinones

a Suzuki–Miyaura reaction with the starting 3-chloro-pyrazinones to furnish the corresponding symmetric bis-2(1*H*)-pyrazinones.

Microwave irradiation was found to be highly beneficial in this regard, and the reaction times could be shortened from 4 h under conventional heating to merely 12–15 min in most of the cases (Scheme 18). It is noteworthy that the 6-*H* pyrazinones gave sluggish reactions under conventional heating conditions providing < 10% yield. On the contrary, when microwave irradiation was used in combination with NaOH as the base in ethanol, the resulting bi-2(1*H*)-pyrazinones were obtained in good yields of 49–69%.

3

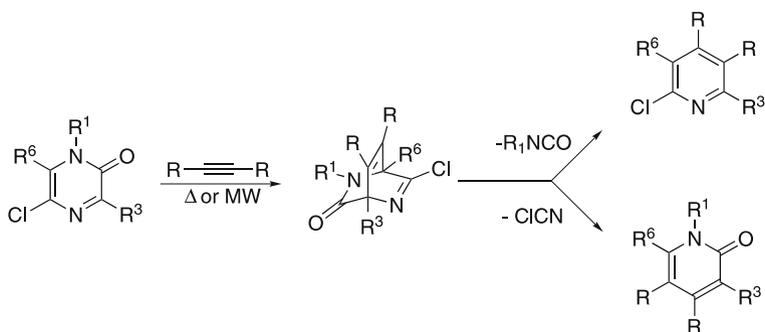
Diels–Alder Reactions of the 2(1*H*)-Pyrazinone Scaffold in Solution

3.1

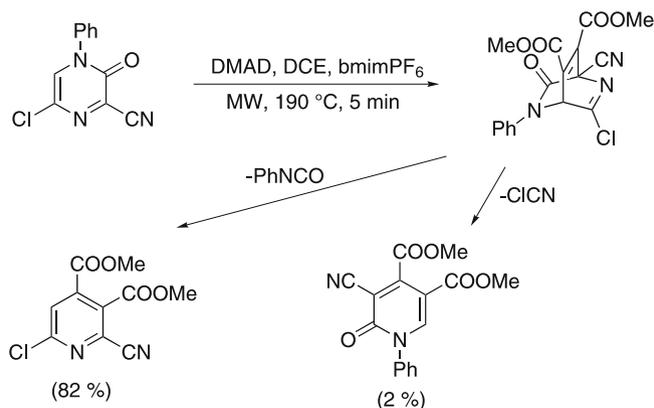
Diels–Alder Reactions of 2(1*H*)-Pyrazinone Scaffold with Acetylenes

In the course of the last two decades, it has been demonstrated that the 2-azadiene system of the 2(1*H*)-pyrazinones can participate in a number of inter- and intramolecular Diels–Alder reactions giving rise to versatile and richly decorated (fused) heterocyclic systems with potent biological and pharmacological activities [55, 56]. Diels–Alder reactions of highly functionalized pyrazinone scaffold with a variety of diversely functionalized acetylenes are reported in the literature, in view of generating elegantly functionalized heterocyclic systems with interesting biological and pharmacological activities. The pyrazinone scaffold undergoes Diels–Alder reaction with a number of acetylenes followed by a retro-Diels–Alder fragmentation (Scheme 19), either eliminating the corresponding isocyanate or cyanogen chloride, to furnish the pyridines or pyridinones.

However, most of the reactions are reported to be slow, taking up to 12 h for complete conversion of the starting materials. A Diels–Alder reaction of the pyrazinone scaffold with dimethyl acetylenedicarboxylate (DMAD) [57] has been studied in view of investigating the swiftness of this cycloaddition-fragmentation protocol (Scheme 20). The authors investigated the reaction with DMAD (10 equiv) under microwave irradiation at an elevated temperature of 190 °C, using small amounts of ionic liquid (bmimPF₆) in



Scheme 19 Diels–Alder reactions of the 2(1*H*)-pyrazinone scaffold with acetylenes



Scheme 20 Microwave-enhanced Diels–Alder reaction of the pyrazinone scaffold with DMAD

1,2-dichloroethane, to enhance the absorption of microwave energy. The corresponding pyridine and pyridinone were obtained in 82% and 2% isolated yields, respectively, after only 5 min of microwave irradiation. These results were found to be comparable in terms of product yields and ratio, with the data obtained under thermal conditions, where DMAD was utilized as the solvent (140 °C, 30 min).

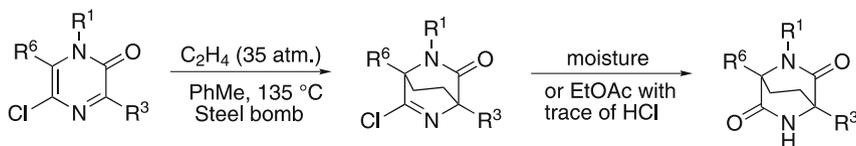
3.2

Diels–Alder Reactions of the 2(1*H*)-Pyrazinone Scaffold with Ethylenes

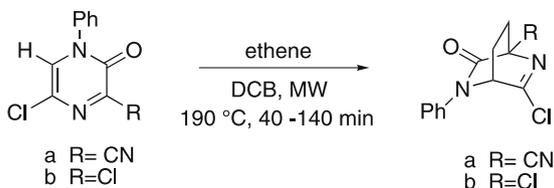
The 2-azadiene system of the pyrazinone scaffold undergoes inter- and intramolecular cycloaddition reactions with a variety of (functionalized) alkenes forming bicyclic adducts, leading to the stereoselective generation of a variety of natural product analogues as well as peptidomimetics [58]. These bicyclic compounds could serve as key intermediates in the synthesis

of the aminopiperidine carboxylate-derived β -turn mimetics of the substance P [59], an undecapeptide neurotransmitter implicated in several diseases like arthritis, asthma, and depression [60, 61]. Also, the tricyclic core skeleton of the brevianamide class of natural products was synthesized in this way [62]. For example, it has been demonstrated [62] that a variety of pyrazinones undergo a cycloaddition reaction with ethylene, albeit requiring rather harsh steel bomb conditions, applying 25–35 atm initial ethene pressure before the setup is heated to 110–135 °C for 12–64 h (Scheme 21). The thus-generated bicyclic adducts undergo a very slow moisture-promoted hydrolysis resulting in the formation of the bis-lactams.

It has been demonstrated [57] that the rates of these Diels–Alder reactions could be greatly enhanced under focused microwave irradiation. Since the microwave reactor setup used in the study, a mono-mode CEM Discover microwave apparatus, did not allow pre-pressurization of the reaction vessel with ethene, the authors saturated the solution of the 2-(1*H*)-pyrazinone, with gaseous ethene at atmospheric pressure, before sealing the vial with the standard aluminum/Teflon crimp. The strongly microwave-absorbing 1,2-dichlorobenzene (DCB) was chosen as a suitable solvent, allowing the cycloaddition chemistry to be carried out in the range of 180–250 °C utilizing microwave flash heating (Scheme 22). Diels–Alder addition of ethene in the sealed microwave vial was completed after irradiation of the pyrazinone precursors for 40–140 min at 190 °C resulting in high isolated yields. Interestingly, it was not possible to further increase the reaction rate by raising the temperature, as, at temperatures above 200 °C, the authors noticed an equilibrium between the cycloaddition and the competing retro-Diels–Alder fragmentation process. This was confirmed by subjecting a sample of cycloadduct to microwave irradiation (without ethene) in DCB at 250 °C, pro-



Scheme 21 Diels–Alder reactions of the pyrazinone scaffold with ethylene gas



Scheme 22 Microwave-enhanced Diels–Alder reaction of the pyrazinone scaffold with ethene

viding a mixture of the 2(1*H*)-pyrazinone precursor and the cycloadduct in a ratio of ca. 1 : 3. It is noteworthy that these microwave-assisted cycloadditions did not require a significant ethene pressure (measured pressure in the microwave vial during reaction at 190 °C is 1–2 bar), but are nevertheless significantly faster than the earlier published autoclave methods (25–35 atm ethene pressures at 110–135 °C for 12–64 h).

An interesting case study regarding the microwave-enhanced Diels–Alder reactions of the 2(1*H*)-pyrazinone scaffold was recently reported, concerning the effect of pressure on these cycloadditions. In view of examining the use of gaseous reagents in the microwave-enhanced reactions under pre-pressurized conditions, ethylene gas was used as the olefin [63]. Though there is a vast amount of literature related to the use of various techniques employed in microwave-enhanced reactions, like solvent-free experiments, adsorbing the reagents into a microwave transparent inorganic supports and phase-transfer catalyst-assisted reactions, the use of gaseous reagents in microwave instruments is relatively rare. Even though there are several examples in the context of heterogeneous gas-phase catalytic reactions important for industrial processes, the use of pre-pressurized reactions in a microwave-heated environment is relatively scarce [64, 65]. All reactions were carried out using a bench-top multimode microwave apparatus [66, 67], which allows the processing in either quartz or PTFE-TEM process vials with maximum operating limits of 300 °C and 80 bar (Fig. 2).

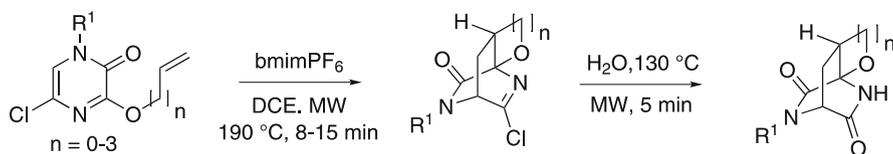


Fig. 2 Synthos 3000 bench-top multimode microwave apparatus of Anton Paar

When a blank reaction was run by purging the solution of pyrazinone (Scheme 22, pyrazinone b) in *o*-DCB with ethylene gas and irradiating it at 190 °C for 100 min, only a mere 53% conversion of the starting material was observed. Microwave-enhanced hydrolysis of the sensitive imidoyl chloride moiety of the cycloadduct using aqueous NaOH resulted in a yield of only 12%. However, the situation changed dramatically when the vial was pre-pressurized with ethylene gas at 5 bar. The reaction was completed after 30 min of microwave irradiation at 190 °C, and the hydrolyzed product was isolated in 87% yield. The reaction could be completed in a mere 10 min when carried out at 220 °C at an increased ethylene pressure of 10 bar, or in 20 min at 190 °C at 10 bar ethylene pressure.

The scope and limitations of the microwave process were evaluated by studying the Diels–Alder reactions on a number of pyrazinones and the yields of the cycloadducts were found to be comparable with those obtained under conventional heating conditions, while the reaction was found to proceed much faster under microwave irradiation. The nature of the substituent at the C-3 position was found to be crucial for the Diels–Alder reactions. While an electron withdrawing group like CN tended to favor the reaction greatly, completing the cycloaddition in a mere 10 min, an electron donating 4-methoxyphenyl group tended to retard the rate of cycloaddition to 100 min (12 h and 10 days, respectively, under conventional heating conditions). Furthermore, the Cl atom at the C-5 position was found to be important for the cycloaddition, as no reactions were observed when it was replaced by hydrogen. All the cycloadducts thus formed were found to be moisture sensitive, and the products were hydrolyzed into the corresponding bis-lactams prior to the isolation and purification protocols.

The intramolecular Diels–Alder reactions of a variety of alkene-tethered pyrazinone scaffolds were explored [57]. These reactions were known to proceed rather slowly under conventional heating conditions, in some cases requiring 2 days when refluxed in *o*-dichlorobenzene (*o*-DCB). However, microwave irradiation was found to accelerate the reactions dramatically and the cycloadditions were found to be complete in ca. 50 min instead of 48 h, when the alkene tethered pyrazinone scaffold was irradiated in 1,2-dichloroethane (DCE) at 170 °C. It is noteworthy that the $\tan(\delta)$ value of DCE is close to that of water and therefore it is absorbing the microwave radiation much better than *o*-DCB [30], while the low boiling point of the solvent (83 °C instead of the 132 °C of *o*-DCB) makes it easier to handle and manipulate during the purification procedures. In view of accelerating the reactions to a still higher degree, the cycloaddition was carried out in an ionic liquid-doped medium [57]. It is well demonstrated that ionic liquids promote a variety of reactions under conventional heating and under microwave irradiation, including Diels–Alder cycloadditions. Due to their ionic nature, the ionic liquids couple very effectively with the microwaves through an ionic conduction mechanism [68]. Thus, the addition of small amounts of ionic li-



Scheme 23 Microwave-enhanced Diels–Alder reactions of alkene-tethered 2(1*H*)-pyrazinones in ionic liquid doped solvents

quids to a relatively non-polar solvent increases the dielectric nature of the mixture and provides a much faster heating profile.

Based on the properties of ionic liquids in high-temperature microwave-enhanced reactions, the authors chose 1-butyl-3-methylimidazolium tetrafluorophosphate ($[\text{bmim}]\text{PF}_6$) as the suitable ionic liquid (Scheme 23). The addition of 0.15 mmol of $[\text{bmim}]\text{PF}_6$ to a reaction in 2.0 mL of DCE was found to increase the reaction rate dramatically and a set-temperature of 190 °C was reached in a mere 1 min, while the reactions programmed at 190 °C, in the absence of the ionic liquid, reached only 170 °C in 10 min. The reactions were finished in a mere 18–25 min of irradiation time, including the hydrolysis of the sensitive imidoyl chloride moiety with water. The formed bis-lactams were isolated in good yield and purity.

4

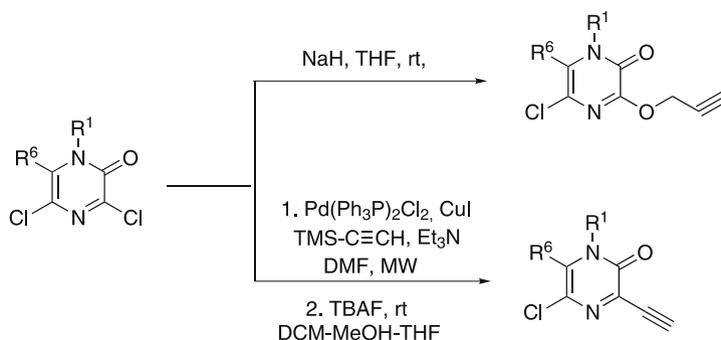
Decoration of the 2(1*H*)-Pyrazinone Scaffold Applying “Click Chemistry”

Another interesting protocol for the decoration of the pyrazinone scaffold has recently been demonstrated, making use of the well-known “click chemistry” approach [72]. The authors have chosen the Huisgen 1,3-dipolar cycloaddition of alkynes and azides [73–76] for the preparation of triazoles. This is of particular interest, as the 1,2,3-triazoles are important target molecules due to their widespread use and their value as potent pharmacophores [77–82]. It has been shown that several pyridyl and pyrimidyl substituted triazoles exhibit sub-micromolar activity against LPS-induced tumor necrosis factor- α (TNF- α) [83] and some *N*-substituted-phenyl-1,2,3-triazole-4-acylhydrazones show significant anti-platelet activity on arachidonic acid- and collagen-induced platelet aggregation [84]. Furthermore, 1,2,3-triazoles have found extensive industrial use as corrosion inhibitors, dyes, photostabilizers, photographic materials and agrochemicals [85]. Traditionally, 1,2,3-triazoles are prepared via a non-regioselective thermal 1,3-dipolar cycloaddition of an azide with an alkyne to afford a mixture of 1,4- and 1,5-di-substituted isomers [73–76]. This could be advantageous if a library of compounds is targeted, but it represents a severe drawback in preparative chemistry. Recently it was demonstrated that upon Cu(I) catalysis this

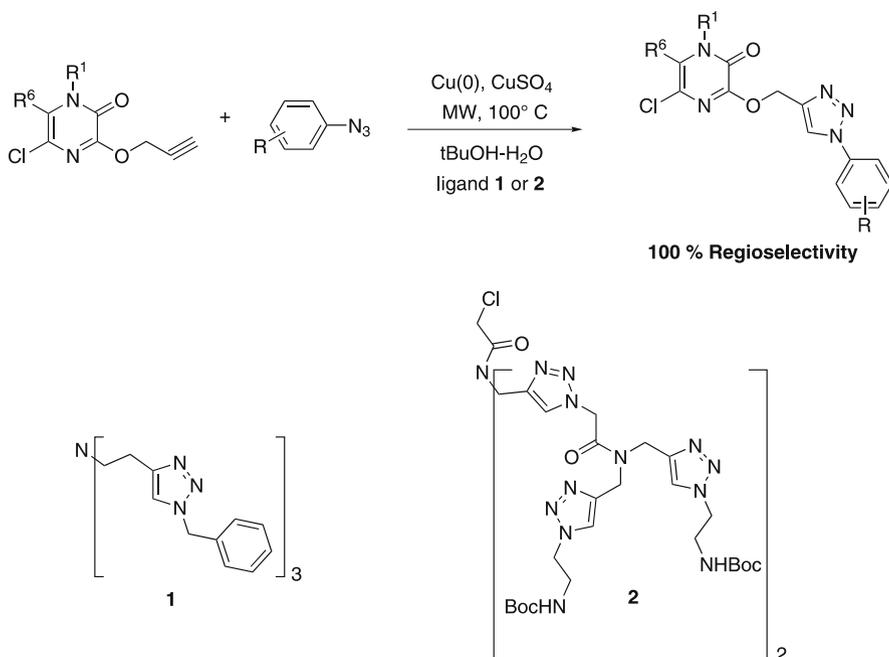
cycloaddition could be performed regioselectively, affording exclusively the 1,4-disubstituted 1,2,3-triazoles [86, 87]. Furthermore, the high yields, lack of laborious purification protocols as well as mild conditions has rendered the Huisgen 1,3-dipolar cycloaddition as the fittest reaction for “click chemistry” [88].

Two different methods are described for the decoration of the pyrazinone skeleton; one is based on the reaction of acetylene-tethered pyrazinones via a C–O or C–C linkage at position C-3 with a variety of aryl or benzyl azides, while in the other method the 3-azide functionalized pyrazinones are treated with various acetylenes, rendering the triazoles attached to the core via a C–N linkage. For the synthesis of starting materials, 3,5-dichloro pyrazinones were reacted with propargyl alcohol in the presence of NaH to afford the alkyne-functionalized compounds (Scheme 24). Alternatively, the 3,5-dichloro pyrazinones were subjected to a microwave-enhanced Sonogashira reaction with (trimethylsilyl)acetylene to furnish the alkyne substituted scaffold via a C–C linkage. This was followed by desilylation upon treatment with tetrabutylammonium fluoride (TBAF) affording the required compound with the terminal triple bond at position C-3 of pyrazinone ring.

The conditions for the 1,3-dipolar cycloaddition were investigated and optimized with the electron-rich 4-methoxyphenylazide and a pyrazinone with a triple bond connected via C–O linkage (Scheme 25). The Cu(I) catalyst was generated in situ using copper wire and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (2 mol %) in a solvent mixture of *t*BuOH, water and THF (1 : 1 : 1). However, the reactions were found to be slow at RT, requiring 1.5 days to afford the 1,4-triazole as the sole product. In contrast, upon microwave irradiation at a pre-selected maximum temperature of 100 °C, the reaction time could be drastically reduced to 15 min. It is noteworthy that this reaction could be carried out in water as the sole solvent without influencing the yield noticeably, but resulting in a slightly longer reaction time of 20 min. The addition of Cu(II) seemed to be critical as running this microwave-assisted reaction with copper wire as the sole copper



Scheme 24 Introduction of the C–O and C–C linked alkyne handles at the C-3 position of the 2(1*H*)-pyrazinone scaffold

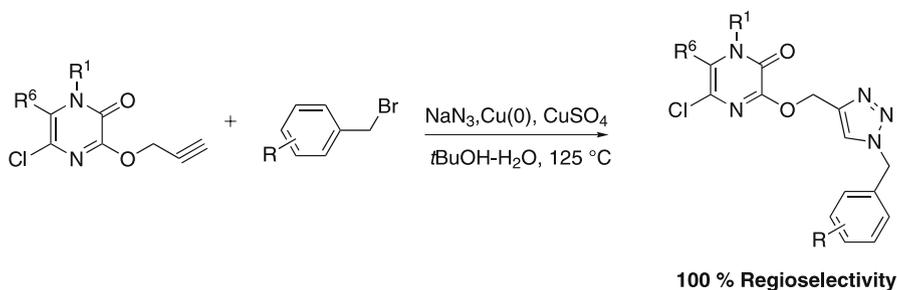


Scheme 25 Synthesis of 2(1H)-pyrazinone-triazoles using a C – O linkage

source resulted in almost no conversion. To stabilize the air-sensitive Cu(I), the influence of two different types of triazole-based ligands, also synthesized using “click chemistry”, was investigated (Scheme 25) [89]. Addition of one of the ligands resulted in a dramatic increase of the rate without having a noticeable influence on the yield. For the reaction in a *t*-BuOH/H₂O mixture, the reaction time was reduced to only 5 min (compared to 15 min), while upon performing the reaction in water as the sole solvent only 10 min (compared to 20 min) were needed to reach completion.

The authors have also elaborated a microwave-enhanced one-pot procedure [90] for the Huisgen 1,3-dipolar cycloaddition reaction. In a typical procedure, a pyrazinone with a triple bond connected to the core via C – O linkage, was reacted with a suitable benzylic bromide and NaN₃ in presence of the Cu(I) catalyst in a *t*-BuOH/H₂O system under microwave irradiation (Scheme 26). The cycloaddition was found to proceed cleanly and with full regioselectivity. As the azide is generated in situ, this procedure avoids the isolation and purification of hazardous azides, which is especially important when handling the aliphatic ones, which are known to be toxic and explosive in nature.

An alternative pathway to impart diversity at the C-3 position of the pyrazinone scaffold is possible via the linkage of the triazole moiety to the core using a C – C bond (Scheme 27). The C-3 acetylenic pyrazinone

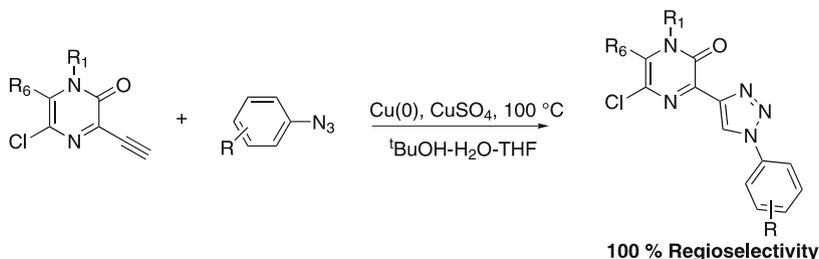


Scheme 26 Synthesis of 2(1*H*)-pyrazinone-triazoles using a one-pot procedure

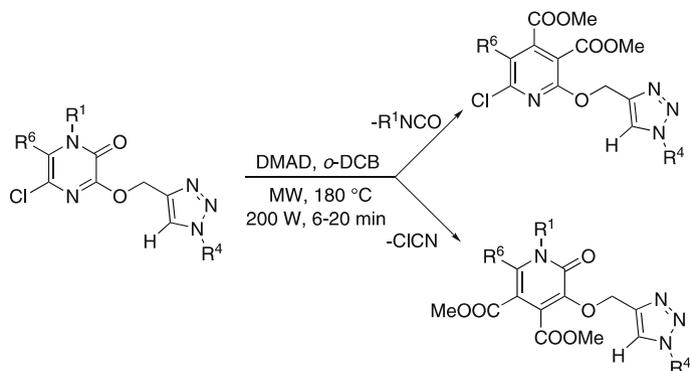
is demonstrated to undergo fast, efficient, and regioselective microwave-assisted Huisgen 1,3-dipolar cycloaddition reaction with a variety of aromatic azides, to generate the corresponding 1,2,3-triazole derivatives in 27–71% yield and in a completely regioselective manner.

As the Diels–Alder reactions of 2(1*H*)-pyrazinones with richly substituted acetylenes can be used to generate diversely substituted pyridines and pyridinones, these cycloadditions were investigated under microwave irradiation conditions on the 1,2,3-triazole decorated pyrazinone scaffold. As a proof of concept, the pyrazinones bearing a 1,4-disubstituted-1,2,3-triazole unit, linked via a C–O bond, were reacted with the symmetrical dienophile dimethyl acetylenedicarboxylate (DMAD), in view of minimizing regioselectivity problems (Scheme 28).

In a typical reaction, a series of C–O linked pyrazinone-triazoles were irradiated with an excess (3.5 equiv) of DMAD in *o*-DCB. The reactions were completed in 6–20 min at 180 °C, using a maximum irradiation power of 200 W. After spontaneous elimination of the corresponding isocyanate or cyanogen chloride, the pyridines and pyridinones were formed in combined yields of 71–99%. It is noteworthy that the pyrazinones with an aryl moiety at the N-1 position yielded pyridines as major products, while those with benzylic or alkyl ester moieties at the N-1 position furnished the corresponding pyridinones as major products.



Scheme 27 Synthesis of 2(1*H*)-pyrazinone-triazoles using a C–C linkage

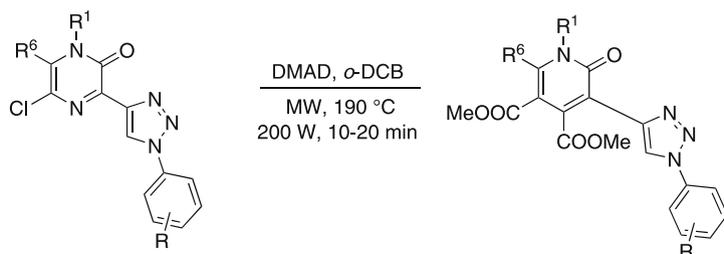


Scheme 28 Diels–Alder reactions of C–O linked 2(1*H*)-pyrazinone-triazoles with DMAD

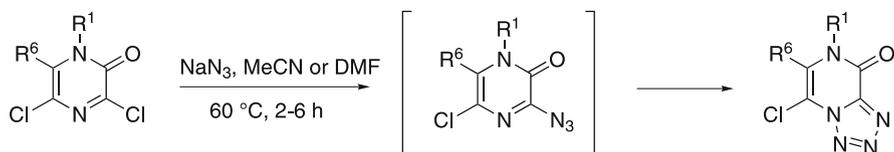
In a similar fashion, the C–C linked pyrazinone-triazoles were reacted with an excess of DMAD (3.5 equiv) under microwave irradiation conditions at a pre-selected temperature of 190 °C (Scheme 29). The reactions proceeded smoothly in *o*-DCB in 10–20 min, using a maximum irradiation power of 200 W. Differing from the C–O analogues, the C–C linked pyrazinone-triazoles generated the corresponding pyridinones as the exclusive products.

Another interesting reaction for the decoration of the C-3 position of the pyrazinone scaffold was demonstrated, using a 1,2,3-triazole-based approach via a C–N linkage strategy (Scheme 30). The synthesis involved the generation of the corresponding pyrazinone azides via a simple addition-elimination reaction using NaN_3 in MeCN or DMF at 60 °C. These azides are shown to cyclize directly into the corresponding more stable tetrazole analogues at RT, as detected by the absence of characteristic absorption peaks for the azide group in the FT-IR spectrum [72, 91].

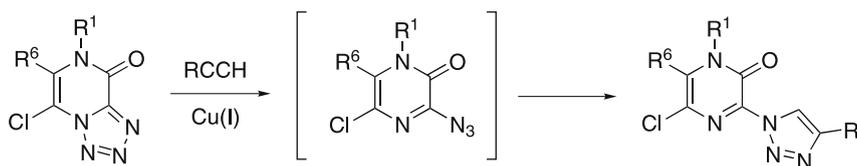
These tetrazoles undergo the Huisgen 1,3-dipolar cycloaddition reaction after ring-opening into the corresponding C-3 azides. A variety of aryl and alkyl acetylenes were reacted in the presence of in situ-generated Cu(I) catalyst to furnish the corresponding triazoles in good yields and with full regioselectivity (Scheme 31).



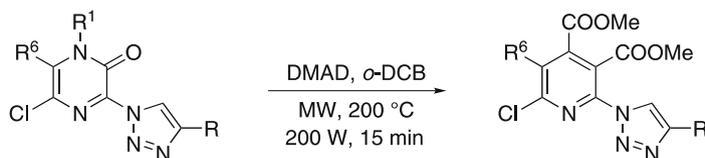
Scheme 29 Diels–Alder reactions of C–C linked 2(1*H*)-pyrazinone-triazoles with DMAD



Scheme 30 Synthesis of tetrazole analogues



Scheme 31 Synthesis of 2(1H)-pyrazinone-triazoles using a C – N linkage



Scheme 32 Diels–Alder reactions of C – N linked 2(1H)-pyrazinone-triazoles with DMAD

These triazolo-pyrazinones were reacted with DMAD under microwave irradiation (Scheme 32). The reactions were carried out in *o*-DCB at a slightly elevated temperature of 200 °C for 15 min. Interestingly, the opposite selectivity to the C–C linked analogues was observed during the Diels–Alder reactions of C – N linked pyrazinone-triazoles with DMAD, as pyridines were found to prevail over the corresponding pyridinones. These compounds were isolated in combined yields of 39–68%.

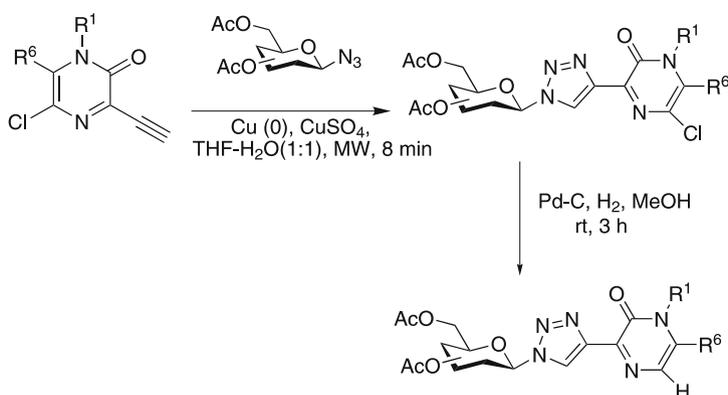
The click strategy for the decoration of the 2(1H)-pyrazinones has been further elaborated by incorporating sugar moieties into the scaffold [92]. The authors investigated the coupling of different glycosyl β -azides [93] with various 3-ethynyl-2(1H)-pyrazinones for the purpose of generating a variety of interesting structures as glycopeptide mimetics [94]. In general, the (oligo)saccharide and peptide part in the glycopeptidomimetics are directly connected with each other via a glycosidic linkage [95, 96]. However, the synthesis of this type of analogues is dealing with specific problems and the obtained compounds mostly suffer from instability upon in vivo applications. Therefore, stable glycopeptidomimetics were often elaborated via the synthesis of C-linked analogues [97–99]. Most of these syntheses, however, are rather complex and often feature low overall yields. In another approach, the peptide chain is replaced by a peptidomimetic derivative which exhibits

in vitro activity against HL-60 human leukemia and HT-29 human colon carcinoma as well as antineoplastic activities [100]. Interestingly, this peptidomimetic is indirectly linked with the sugar nucleus via a 1,2,3-triazole ring [101–103].

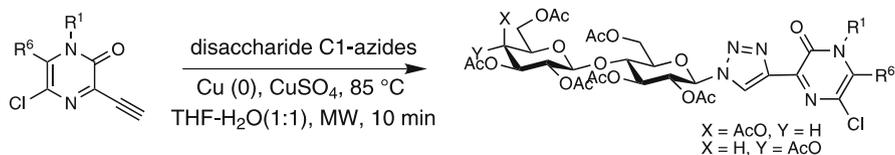
In this approach [92], the glycosyl β -azides were prepared according to literature procedure [93] and the acetylenes were synthesized in excellent yields via previously reported Pd-catalyzed microwave-assisted Sonogashira cross-coupling protocol with trimethylsilylacetylene, followed by desilylation upon treatment with TBAF.

The Cu(I)-catalyzed 1,3-dipolar cycloaddition reactions of the terminal acetylenes with the glycosyl β -azides occur with full regioselectivity, resulting in the formation of the corresponding 1,4-disubstituted 1,2,3-triazoles (Scheme 33). Applying microwave irradiation at a moderate ceiling temperature of 85 °C, using the β -azide (up to 1.8 equiv), this cycloaddition reaction was dramatically sped up and the compounds were isolated in moderate to good yields. The dechlorination of the thus obtained triazoles was easily performed upon reaction with hydrogen on Pd/C, yielding the products in satisfactory yields (Scheme 33).

The coupling of the protected disaccharides lactose and cellobiose with the pyrazinone scaffold via the 1,3-dipolar cycloaddition reaction was further investigated (Scheme 34). To run the reaction to completion, the use of 2 equiv



Scheme 33 Microwave-enhanced introduction of sugar moieties



Scheme 34 Introduction of disaccharides into the pyrazinone skeleton

of disaccharide β -azide as well as a longer irradiation time was required. For example, the C-1-azides of lactose and cellobiose were successfully coupled with the 3-ethynyl-2(1*H*)-pyrazinones upon microwave irradiation at a ceiling temperature of 85 °C for 10–12 min, resulting in the formation of the corresponding triazoles in good yields.

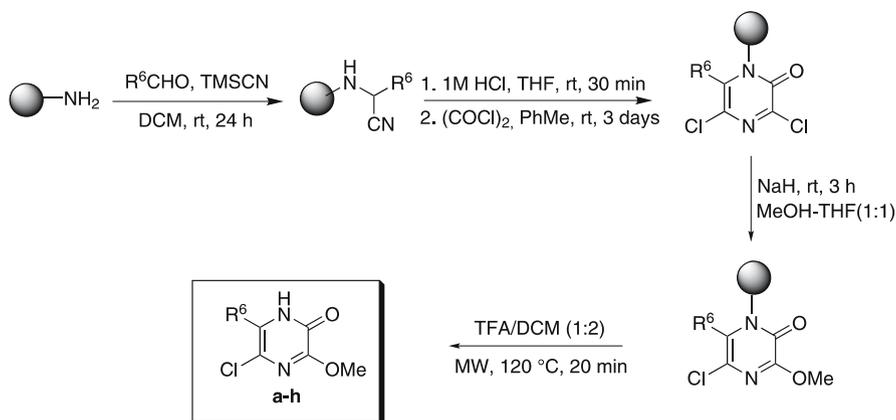
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Synthesis and Decoration of the 2(1*H*)-Pyrazinone Scaffold on Solid Support

Combinatorial chemistry along with high-throughput synthesis has emerged as a powerful tool for the developing of new drug candidates [104, 105]. One of the most widely used strategies for library preparation is solid-phase organic synthesis (SPOS), with a wide range of reactions successfully applied to various solid supports. The huge interest in resin-bound chemistry is based on the possibility to drive reactions to completion by using an excess of reagents and then removing it together with by-products by simple filtration, affording the target molecules in high purities. However, owing to the heterogeneous conditions, reactions performed on insoluble polymer supports generally require longer reaction times, which is considered as a severe shortcoming compared to the standard solution-phase synthesis. Moreover, thermal instability of polystyrene-based supports limits the optimization of the reactions by increasing the temperature. Instead of conventional heating, solid-phase procedures can be accelerated by using microwaves via selective absorption of microwave energy by polar molecules [106, 107]. Because of the fast and homogeneous heating, microwave-assisted solid-phase synthesis can provide not only significant rate enhancements, but also cleaner reactions, and therefore higher yields, which makes it attractive for the preparation of libraries of novel drug candidates.

Recently it has been shown that the microwave-assisted decoration of the 2(1*H*)-pyrazinone scaffold can allow an easy introduction of different substituents at the C-3 and even to the less reactive C-5 position [29]. Taking full advantage of combinatorial principles, some of these pathways were transferred to microwave-enhanced solid-phase chemistry, opening the way for the generation of many biologically interesting structures [108].

The solid-phase synthesis of the 2(1*H*)-pyrazinone scaffold is based on a Strecker reaction of commercially available Wang amide linker with appropriate aldehyde and tetramethylsilyl (TMS) cyanide, followed by cyclization of α -aminonitrile with oxalyl chloride resulting in the resin linked pyrazinones. This approach allows a wide diversity at the C-6-position of pyrazinone scaffold (Scheme 35, Table 1). As it has been shown for the solution phase, the sensitive imidoyl chloride moiety can easily undergo an addition/elimination reaction with in situ-generated sodium methoxide affording the resin-linked



Scheme 35 Solid-phase synthesis of the 2(1*H*)-pyrazinone scaffold

Table 1 Solid-phase synthesis of 2(1*H*)-pyrazinone scaffold

Entry	Compound	R ₆	Yield (%) ^a
1	a	phenyl	53
2	b	(4-methoxy)phenyl	67
3	c	(4-carbomethoxy)phenyl	47
4	d	(3,4-methylenedioxy)phenyl	29
5	e	(3,4,5-trimethoxy)benzaldehyde	traces
6	f	2-furyl	14
7	g	H	45
8	h	methyl	20

^a All yields are isolated yields after purification

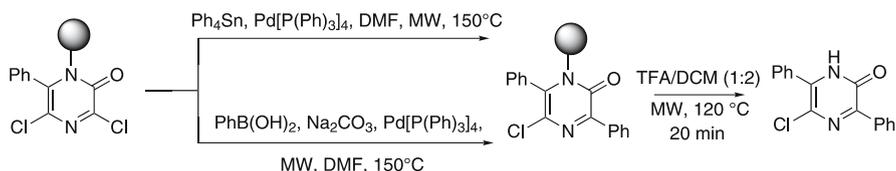
pyrazinones. Smooth cleavage of the pyrazinones from the solid support was carried out under microwave irradiation, using mixture of TFA-DCM (2 : 1). The major impurity in the obtained compounds **a–h** appeared to be a fragment of the linker and this could easily be removed by filtration through a plug of silica gel. To evaluate the scope and limitation of this method, the previously described “scaffold decoration” applying microwave-assisted transition-metal-catalyzed reactions, was evaluated. Stille reaction of pyrazinone was performed in DMF using 4 equiv of tetraphenyl tin and Pd[P(Ph)₃]₄ (20 mol %) as the catalyst (Scheme 36). The whole procedure was repeated and the resin-bound product was extensively washed with a mixture of AcOH-DCM (2 : 1) to remove all tin impurities. The pyrazinone was released into the solution upon microwave irradiation in a TFA/DCM mixture

at 120 °C for 20 min, yielding the desired compound in 65% yield based on the loading of the starting Wang amide resin.

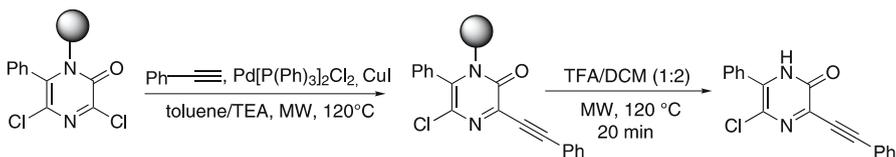
Alternatively, 3-phenyl pyrazinone was prepared via Suzuki reaction, when a polymer-bound pyrazinone was irradiated with 4 equiv of phenylboronic acid, 5 equiv of Na₂CO₃ and 20 mol % of Pd[P(Ph)₃]₄ as the catalyst in DMF as the solvent (Scheme 36). Contrary to the results obtained in solution phase [29], all attempts to drive the reaction toward the formation of disubstituted compound, using higher equivalents of reagents or longer reaction times, were unsuccessful. Application of aqueous conditions afforded mixtures of 3-mono and 3,5-disubstituted pyrazinones.

Pyrazinone bearing a phenylalkynyl substituent at position C-3, was prepared in 47% yield via Sonogashira reaction with 7 equiv of phenylacetylene in a mixture of toluene/triethylamine (2 : 1) using Pd[P(Ph)₃]₂Cl₂ and CuI as the catalyst system (Scheme 37).

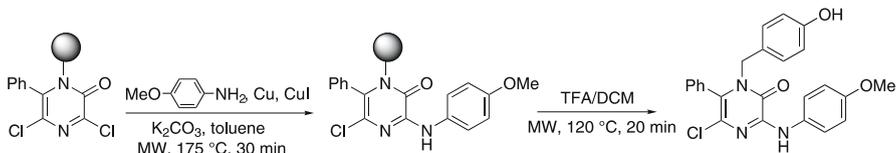
It has been shown that the imidoyl chloride moiety of 2(1*H*)-pyrazinones can undergo an easy addition/elimination reaction with alkyl amines [24], while reactions with anilines proceed under harsher conditions. Ullmann coupling [109–113] of 2(1*H*)-pyrazinones with substituted anilines could open the way to the libraries of physiologically active compounds useful in inhibiting HIV replication [7]. Polymer-bound pyrazinone was successfully



Scheme 36 Scaffold decoration via Stille and Suzuki-Miyaura reactions on solid support



Scheme 37 Scaffold decoration via Sonogashira reaction on solid support



Scheme 38 Scaffold decoration via Ullmann-type reaction

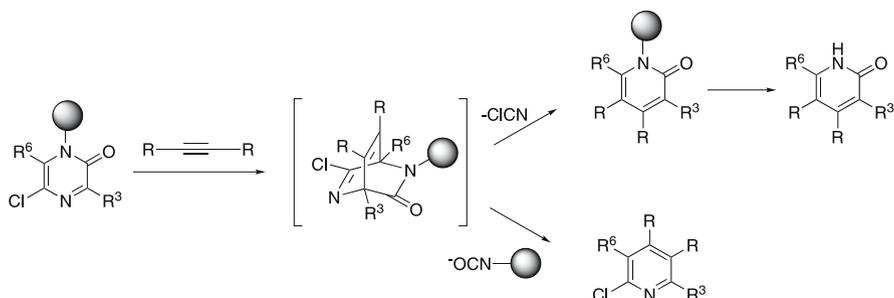
reacted with *p*-anisidine in toluene in the presence of K_2CO_3 using copper wire and CuI as the catalyst (Scheme 38). Microwave irradiation of the sample without the copper catalyst afforded a complex mixture without noticeable traces of the desired product. It should be noted that the resulting pyrazinone was cleaved from the resin as its *p*-hydroxybenzyl derivative under both conventional and microwave-assisted conditions.

6 Diels–Alder Reactions of 2(1*H*)-Pyrazinones with Acetylenes on Solid Support

Among the strategies applied for the solid-phase synthesis of combinatorial libraries of heterocyclic compounds, traceless cleavage of the target molecules and cyclative cleavage strategy [114] are the most commonly used. Since the cycloaddition of 2(1*H*)-pyrazinones with acetylenic compounds is known to give labile bicyclic adducts, which directly undergo retro Diels–Alder reactions providing pyridinones and/or pyridines, the application of this approach to the solid-phase chemistry could represent an easy separation procedure based on the concept of the “traceless linking”, whereby the pyridinone stays on solid support with the concomitant release of the pyridine into solution (Scheme 39).

A very detailed comparison for every single step of the whole sequence (linking of a pyrazinone to the solid support, Diels–Alder reaction with acetylenic dienophile and cleavage of a formed pyridinone from the resin) was made between microwave irradiation and conventional heating conditions [115].

To perform Diels–Alder reactions on solid phase, the 2(1*H*)-pyrazinone scaffold is linked to a suitable support via its amide nitrogen atom. While *N*-1-substituted pyrazinones are readily accessible by the choice of an appropriate amine, it is not possible to prepare *N*-1-unsubstituted pyrazinones using the general strategy as previously outlined in the introduction. How-



Scheme 39 Diels–Alder reaction of 2(1*H*)-pyrazinones with acetylenes on solid support

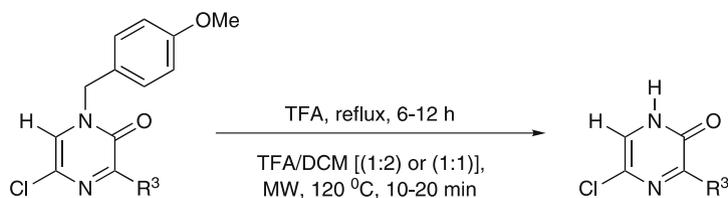
ever, these compounds can easily be synthesized via deprotection of the corresponding pyrazinones bearing a 4-methoxybenzyl at the N-1-position, upon reflux in neat TFA [116] (Scheme 40).

All attempts to use milder reaction conditions such as mixtures of TFA in DCM (95 : 5) at RT or DDQ failed, while microwave irradiation of compounds at 120 °C in a (1 : 1) or (1 : 2) TFA/DCM mixtures provided deprotected products in yields comparable to those obtained under conventional heating (69–96%). It should be noted that this microwave-enhanced procedure not only resulted in milder reaction conditions, but also represents a considerable shortening of reaction time (10–20 min compared to 6–12 h).

For the solid-phase experiments [115], the commercially available Wang and HMPB-AM resins were chosen due their stability under the applied reaction conditions and an easy cleavage with TFA/DCM mixtures. Moreover, a novel, tailor-made and readily available linker, derived from inexpensive syringaldehyde was designed and proven to be superior to both standard Wang and HMPB-AM resins. For an initial study, as a “proof of concept”, the Wang linker was mimicked with a 4-methoxybenzyl group at N-1 position of a pyrazinone, and the sequence was evaluated in solution (Scheme 41).

To avoid problems with the separation of regioimers, dimethyl acetylene dicarboxylate (DMAD) was chosen as a dienophile. The intermolecular Diels–Alder reactions were performed in refluxing dichlorobenzene (bp 132 °C), while the intramolecular reaction of alkyne tethered pyrazinone required a solvent with a higher boiling point (bromobenzene, bp 156 °C). In the case of 3-methoxy or 3-phenyl pyrazinones a mixture of pyridinones and pyridines was obtained, while for the alkyne tethered analogue only the dihydrofuropyridinone was isolated as the single reaction product.

For the microwave-assisted experiments, both solvents were replaced by 1,2-dichlorobenzene, as it couples very effectively with microwaves (loss-tangent ($\tan \delta$) at 20 °C: 1,2-dichlorobenzene 0.280 as compared to 0.101 for chlorobenzene). Diels–Alder reactions of 3-methoxy or 3-phenyl pyrazinones with DMAD were performed at a pre-selected maximum temperature of 200 °C, whereas the intramolecular reaction of alkyne tethered pyrazinone required a higher temperature (220 °C). The yields obtained under microwave irradiation are comparable with those obtained under conventional conditions, while for the dihydrofuropyridinone the yield was improved from

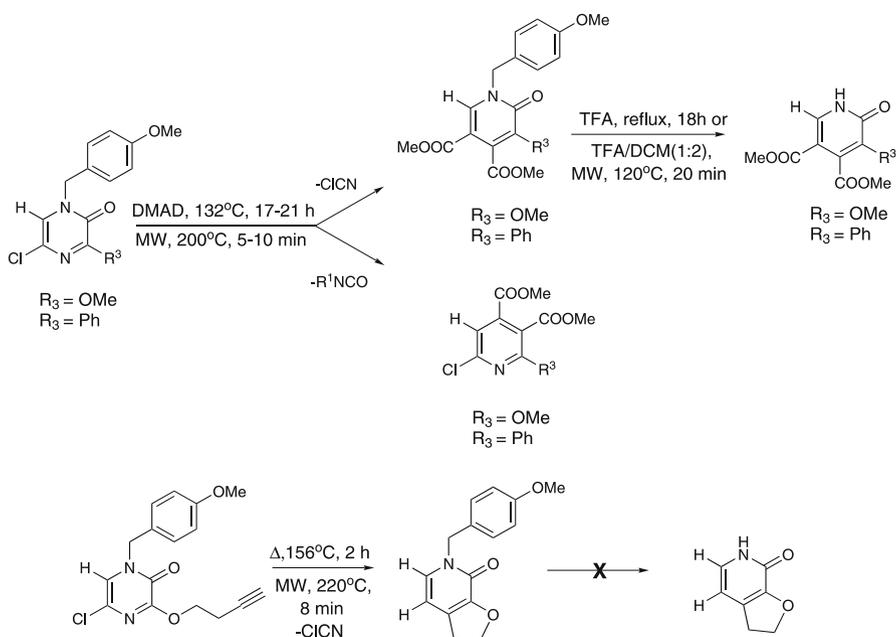


Scheme 40 Cleavage of the 4-methoxybenzyl group

65% to 91%. In both cases, a similar product distribution was observed. Microwave-assisted protocols represent a dramatic reduction of the reaction time as compared to conventional reflux conditions (5–10 min vs. 17–21 h for intermolecular cycloadditions and 8 min vs. 2 h for intramolecular Diels–Alder reaction).

Finally, we tried to deprotect the amide nitrogen of the obtained pyridinones upon reflux in neat trifluoroacetic acid (TFA) for 18 h [116]. Products were isolated in 73% and 79% yield, respectively. In contrast, upon microwave irradiation at 120 °C for only 20 min, a (1 : 2) TFA/DCM mixture sufficed to deprotect the pyridinones (isolated yields 75% and 73% respectively). Surprisingly, deprotection with either refluxing neat TFA (18 h) or microwave irradiation in neat TFA with a catalytic amount of methanesulfonic acid (20 min) did not work for dihydrofuropyridinone.

Most of the commercial acid-sensitive benzylic linkers have one or two methoxy groups in *ortho*-position of the benzyl group. For steric reasons this could be disadvantageous for linking the 2(1*H*)-pyrazinones to the resin. Therefore, a new acid-labile linker based on Merrifield resin derivatized with syringaldehyde was developed (Scheme 42). Coupling of Merrifield resin with syringaldehyde was performed in DMF at 60 °C within 24 h in the presence of Cs₂CO₃ and KI. The reaction time could be dramatically reduced to 5 min when the reaction mixture was irradiated at 220 °C. After work-up the alde-

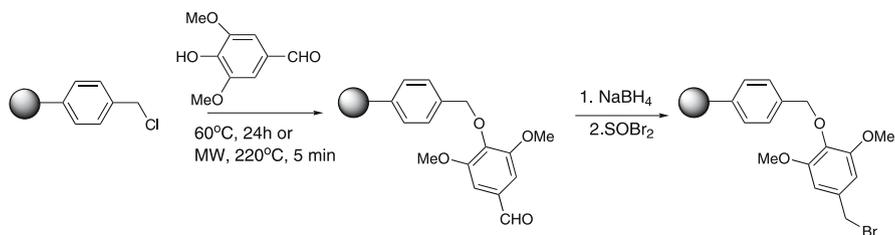


Scheme 41 Mimic of the Wang linker in solution

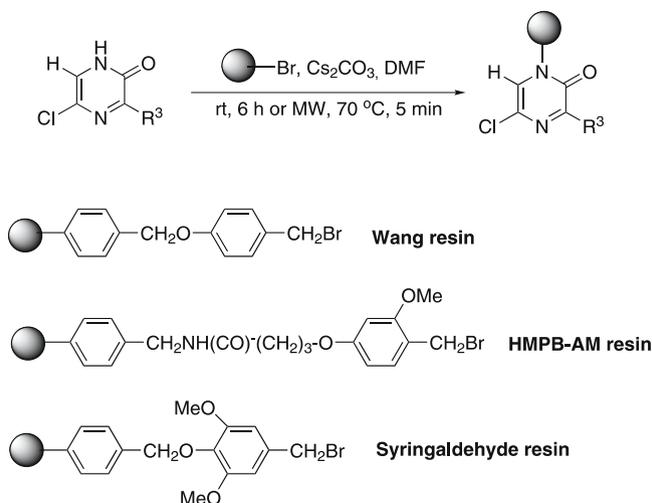
hyde moiety was reduced with NaBH_4 and finally the benzylic position was brominated with thionyl bromide prior to use, to furnish the linker.

To perform the cycloaddition on solid-phase, N-1-unprotected pyrazinones were coupled with the solid support by treatment of the brominated linker in DMF for 6 h at ambient temperature, using Cs_2CO_3 as a base (Scheme 43). The reaction time for complete loading could be dramatically shortened to only 5 min under microwave irradiation at a pre-selected maximum temperature of 70°C .

As in the case of the solution-phase protocol, Diels–Alder reactions of the polymer-bound pyrazinones **1a,b** were carried out in refluxing chlorobenzene (132°C) and it required 1–2 days to drive these reactions to the completion (Scheme 44). Intramolecular cycloaddition of pyrazinone **1c** was carried out in refluxing bromobenzene (bp 156°C). Microwave-assisted cycloadditions of these substrates were performed in 1,2-dichlorobenzene at 220°C and in significantly shorter reaction times (10–40 min). The product distribu-



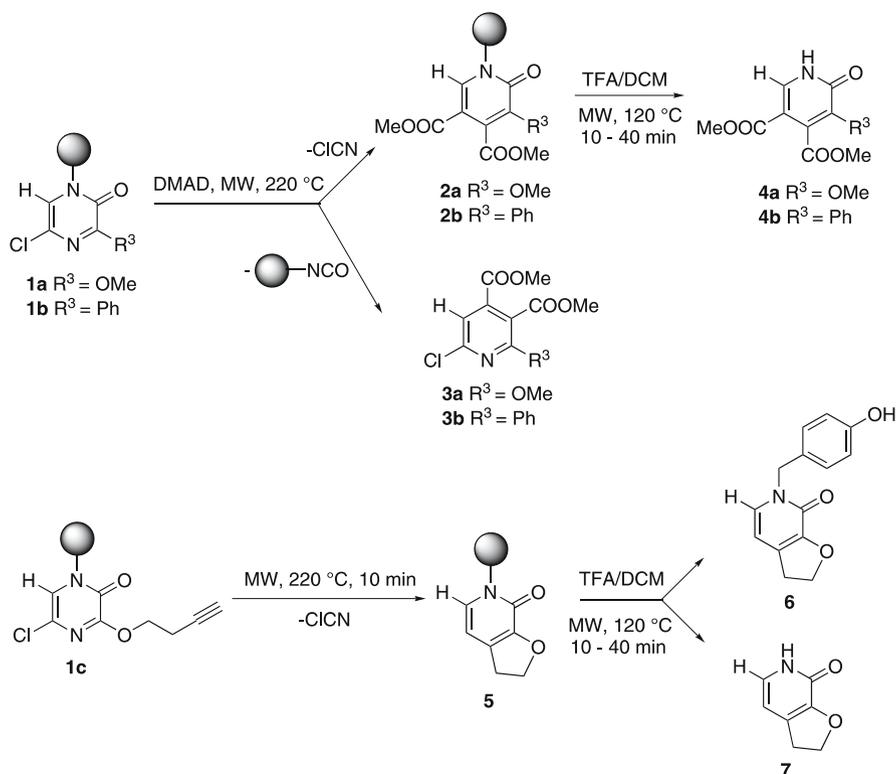
Scheme 42 Synthesis of the syringaldehyde-based linker



Scheme 43 Attachment of the pyrazinone scaffold to various linkers

tion of the cycloaddition/retro-cycloaddition reaction in solution phase and on solid support appeared to be comparable.

The final cleavage of compounds from the resin was performed with neat TFA under reflux. However, under these conditions, dihydrofuropyridinone was cleaved as its *N*-*p*-hydroxybenzylated derivative **6**. Microwave irradiation of resin-bound pyridinones **2a,b** in a mixture TFA/DCM (1 : 2) at 120 °C for 40 min resulted in complete cleavage from the Wang solid support (Table 2). In the case of pyridinone **5**, a mixture of *N*-1-unprotected compound **7** and its *N*-*p*-hydroxybenzylated pyridinone **6** was formed. All attempts to use concentrated TFA solutions or longer reaction times resulted in formation of complex mixtures. Microwave-assisted cleavage of pyridinones **2a,b** from HMPB-AM resin required significantly less acidic conditions compared to Wang resin (TFA/DCM (1 : 9), 10 min) (Table 2). Moreover, microwave irradiation of the dihydrofuropyridinone **5** in a mixture TFA/DCM (1 : 4) gave exclusively the desired *N*-1-unsubstituted compound **7** but required a slightly longer reaction time of 20 min. These cleavage conditions are considerably milder than those needed for Wang linker, although cleavage of pyridinone **6**



Scheme 44 Diels–Alder reactions of resin-bound pyrazinones

Table 2 Product distribution and microwave cleavage conditions from the three different types of resins

	Wang resin			HMPB-AM resin			Syringaldehyde resin		
	Ratio ^a	Min	Yield (%) ^b	Ratio ^a	Min	Yield (%) ^b	Ratio ^a	Min	Yield (%) ^b
1a	1 : 2	40	3a (~ 2)	1 : 9	10	3a (2)	5 : 95	10	3a (2)
			2a (45)			2a (42)			2a (41)
1b	1 : 2	40	3b (53)	1 : 9	10	3b (52)	5 : 95	10	3b (49)
			2b (27)			2b (25)			2b (25)
1c	1 : 2	40	6 (31)	1 : 4	20	7 (77)	1 : 9	20	7 (67)
			7 (16)						

^a Ratio of TFA/DCM^b All yields are isolated yields after purification

resulted from intramolecular reaction, still requires a significant concentration of TFA. Cleavage of pyridinones **2a,b** from syringaldehyde resin under conventional conditions gave unsatisfactory results, whereas microwave irradiation of resin-bound pyridinones **2a,b** in TFA/DCM (5 : 95) at 120 °C for only 10 min gave the desired compounds **4a,b**. For dihydrofuropyridinone **5**, a slightly higher concentration of TFA in DCM (1 : 9) was needed (Table 2). These very mild cleavage conditions, its stability towards different reaction conditions, and its ease of accessibility from low-cost, commercially available starting materials, makes this linker (based on Merrifield resin derivatized with syringaldehyde) highly suitable for microwave-assisted chemistry of 2(1*H*)-pyrazinones.

It has to be noted that the temperatures up to 220 °C involved in the transformations on polystyrene-based support do not affect the resin stability. The controlled microwave irradiation appeared to be very effective in speeding up the linking of 2(1*H*)-pyrazinones to an appropriate resin as well as in accelerating the rate of subsequent solid-phase Diels–Alder reaction and the following cleavage of a resulting pyridinone from the solid support.

7

Summary and Overview

The 2(1*H*)-pyrazinone system has received increased interest in the past two decades by both synthetic and biological research, due to its presence in a variety of natural and non-natural products as well as pharmacologically active compounds. The easy and diverse methods for the generation of this versatile scaffold make it a prime choice for the current pharmaceutical research like thrombin inhibitors, substance P antagonists, etc. The rich 1,4-azadiene

system of the 2(1*H*)-pyrazinone scaffold has attracted considerable current studies due to its readiness in undergoing Diels–Alder reactions and retro-Diels–Alder fragmentations to generate both synthetically and medicinally valuable targets and intermediates. Furthermore, the highly reactive imidoyl-halide moiety at the C-3 position enables easy and diverse functionalizations of this valuable scaffold via traditional addition–elimination reactions or the recently demonstrated transition-metal-catalyzed reactions. Microwave irradiation has recently emerged as a very valuable tool in promoting this wide range of reactions, increasing the scope of the pyrazinone scaffold exponentially. The transition-metal-catalyzed reactions on pyrazinone scaffold are demonstrated as very valuable tools when carried out under focused microwave irradiation, providing both acceleration and efficiency to the diverse range of reactions. The cycloaddition reactions, both Diels–Alder types and 1,3-dipolar ones, are presented to be highly influenced by focused microwave irradiation in both increasing the rate of the reactions and providing cleaner outcomes. Even though the C-5 position of the pyrazinone scaffold is relatively inert compared to the C-3 position for the decoration, the diversity and utility of the pyrazinone systems still remains of ever-growing interest.

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Author Index Volume 1

The volume numbers are printed in italics

Almqvist F, see Pemberton N (2006) *I*: 1–30

Appukkuttan P, see Kaval N (2006) *I*: 267–304

Bagley MC, Lubinu MC (2006) Microwave-Assisted Multicomponent Reactions for the Synthesis of Heterocycles. *I*: 31–58

Besson T, Thiéry V (2006) Microwave-Assisted Synthesis of Sulfur and Nitrogen-Containing Heterocycles. *I*: 59–78

Chorell E, see Pemberton N (2006) *I*: 1–30

Crosignani S, Linclau B (2006) Synthesis of Heterocycles Using Polymer-Supported Reagents under Microwave Irradiation. *I*: 129–154

Erdélyi M (2006) Solid-Phase Methods for the Microwave-Assisted Synthesis of Heterocycles. *I*: 79–128

Van der Eycken E, see Kaval N (2006) *I*: 267–304

Kaval N, Appukkuttan P, Van der Eycken E (2006) The Chemistry of 2-(1*H*)-Pyrazinones in Solution and on Solid Support. *I*: 267–304

Linclau B, see Crosignani S (2006) *I*: 129–154

Lubinu MC, see Bagley MC (2006) *I*: 31–58

Maes BUW (2006) Transition-Metal-Based Carbon–Carbon and Carbon–Heteroatom Bond Formation for the Synthesis and Decoration of Heterocycles. *I*: 155–211

Pemberton N, Chorell E, Almqvist F (2006) Microwave-Assisted Synthesis and Functionalization of 2-Pyridones, 2-Quinolones and Other Ring-Fused 2-Pyridones. *I*: 1–30

Rodriguez M, Taddei M (2006) Synthesis of Heterocycles via Microwave-Assisted Cycloadditions and Cyclocondensations. *I*: 213–266

Taddei M, see Rodriguez M (2006) *I*: 213–266

Thiéry V, see Besson T (2006) *I*: 59–78

Subject Index

- α -Acylamino amides 39
- Amino dehalogenation 18
- 2-Amino-1,3,4-oxadiazoles 141
- Aminocarbonylation 23
- 3-Aminoisoxazoles 144
- Aminopropenones 96
- 6-Aminopyrazinones 270
- 2-Aminothiazoles 65
- Amrinone WIN 40680 3
- 1,2-Azoles 225
- 1,3-Azoles 222

- Benzimidazoles 248
 - fluorous Ugi reactions 115
- Benzo[*b*]furans 247
- Benzo[*b*]thiophenes 248
- Benzocondensed heterocycles 246, 249, 252
- Benzo-derivatives 46, 48
- Benzopyranopyrroles 55
- Benzothiazoles 67
- Benzothiophenes 62
- Benzoxazines 253
- Benzoxazoles 249
- Biginelli cyclocondensation 34
- Bis(indole)alkaloids 271
- Bromination 20
- Buchwald–Hartwig reaction/coupling 22, 200

- Canthine skeleton 52
- Cardiotonic agent, heart failure 3
- Caspase-3 inhibitors, non-peptide 269
- “Catch and release”, 2,4,5-trisubstituted pyrimidines 98
- Chloro dehydroxylation 17
- Click chemistry, 1,4-disubstituted triazoles 45
 - , 2(*1H*)-pyrazinone 285

- Coumarins 254
- Coupling reactions, transition metal catalyzed 21
- Cross-coupling reactions 157
- C–S bond formation,
 - Cu-mediated/Pd-catalyzed 207
- Cyanation 189, 277
- 2-Cyanobenzothiazoles 70
- Cyanodehalogenation 24
- Cycloaddition 51
- Cyclocondensation 34

- Decarboxylation reactions 26
- Dechlorination 277
- DHPMs 34
- Diazepines 259
- Diazines 242
- 3,5-Dichloro-2(*1H*)-pyrazinones 273
- Dihydropteridinones, fluorous synthesis,
 - cyclative cleavage 113
- 1,4-Dihydropyridine synthesis 36
- 2,3-Dihydrothiazole 59, 65
- Dihydro-*s*-triazines 47

- Epothilone C 134

- Farnesyl protein inhibitor 2
- Flavones 254
- Fluorous phases 112
- Fluorous Ugi reactions 115
- Functional group transformations 25
- Furan 221
- Furanones 230

- Gewald synthesis 43
- Goldberg reaction 205

- Hamacanthin 272

- Hantzsch 1,4-dihydropyridine synthesis 36
- Heck vinylation 22
- Heck vs. Diels–Alder 278
- Heck–Mizoroki reaction 194
- Heterocycles, benzocondensed 246, 249, 252
- five-membered 42
 - –, saturated 240
 - fused 49
 - high-speed functionalization 119
 - imidazo-annulated 40
 - polymer-supported reagents 134
 - simple 41
 - six-membered 46
- Hexahydrochromeno[4,3-*b*]pyrroles 53
- Hydantoins 240
- fused-tricyclic, fluoros mixture synthesis 114
- Imidazole C-2, substitution, solid phase 122
- Imidazole-4-carboxylic acids 97
- Imidazoles 44, 222
- saturated 235
- Indoles 104, 246
- Ionic liquid supports, functional 115
- Isocyanides, PS-oxazaphospholidine 148
- Isoquinolines 252
- Isoxazoles 95
- MCR 46
 - on-resin [3+2] cycloaddition 96
- Lepidiline B 43
- Levulinic acid 41
- Loading reactions 87
- Macrocycles 260
- Mannich Reaction 19
- MCR, pyrimidines/pyrazoles/isoxazoles 46
- O-Methyl isourea, polymer-supported 136
- Minopropenones 108
- Negishi reaction 157
- Nitriles, reduction/hydrolysis 25
- Nitrogen heterocycles, on-resin cyclization, minopropenones 108
- C-Nucleoside analogues 274
- Opioid mimetics 272
- Oxadiazoles, PEG-bound Burgess reagent 139
- saturated 237
- Oxazoles 94, 224
- saturated 237
- 3-Oxopiperazinium salts 150
- Oxygen heterocycles, on-resin cyclization, minopropenones 108
- Phthalimides 246
- library, Wang resin 103
- Pilicide 2
- Polycycles 258
- Polyethylene glycol 131
- Polymer-assisted solution phase chemistry 130
- Polymer-supported chemistry (SPOS) 131, 267
- Polymer supports, insoluble 83
- –, soluble 87
- Proline analogs, biaryl-substituted, fluoros synthesis 112
- PS-anthracene, dienophiles 151
- PS-carbodiimide 136
- Purine C-2, nucleophilic displacement 119
- Purines 251
- Pyrans 51
- substituted, ionic liquid tagging 118
- 2(*1H*)-Pyrazinones 120, 269
- Diels–Alder reactions 280
 - scaffold, ethene 282
 - transition-metal-catalyzed decoration 274
- Pyrazoles 95, 225
- isoxazoles and 2-aminopyrimidines 144
 - MCR 46
 - saturated 235
- Pyridines 241
- Pyridinones 120
- Pyrido[2,3-*d*]pyrimidines 49
- 2-Pyridones 1, 15
- libraries 46
- Pyrimidines, aminopropenones 96
- bicyclic, solid-phase 102
 - MCR pyrazoles 46
 - 2,4,5-trisubstituted, “catch and release” 98
- Pyrrole 217

- Pyrrolidines 232
Pyrrolidinones 41
Pyrrolines 232
- Quinolines 252
2-Quinolones 1, 9
Quinoxalines 254
Quinoxalinones, fluorous Ugi reactions 115
- Solid support 83
Solid-phase organic synthesis (SPOS) 80, 89
– –, heterocyclic compounds 94
Soluble supports 110
Solution phase chemistry, polymer-assisted 130
Sonogashira reaction 182, 279
SPOT synthesis 109
Stille reaction 159
Substitution reactions, electrophilic reagents 19
2-Sulfonamido-1,3,4-oxadiazoles 141
Sulfonyloximes 147
Supports, functional, ionic liquid 115
Suzuki couplings 21, 122
Suzuki–Miyaura reaction 164
- Tetracycles 258
Tetrahydrocarbazoles 48
Tetrahydrofurans 230
Tetrazole 98
Tetronates, functionalized, domino synthesis 100
1,3,4-Thiadiazepines 59, 76
1,3,4-Thiadiazines 59, 74
1,3,4-Thiadiazoles 59, 71
1,5-Thiazepines 59, 74
1,3-Thiazines 59, 73
Thiazoles 59, 65, 225
– saturated 237
Thiazolidines 59, 65
Thiazolidinones 45, 67
library, functional ionic liquid support 116
Thiazolobenzimidazoles 51
Thiazoloimidazole 39
Thiohydantoins 44, 147
Thiophene 220
Thiophenes 61
– Gewald synthesis 101
2-Thioxo tetrahydropyrimidin-4-(1H)-ones, ionic liquid support 117
Triazines 47, 243
Triazoles, 1,4-disubstituted, click chemistry 45
Tricyclic systems 256
Trifenagrel 43
Triphenylphosphine 136
- Ugi reactions 39
– –, fluorous 115
Ullmann reaction 206
- Wang linker, mimic 297
Wang resin, phthalimide library synthesis 103
ZAR-NESTRA 3