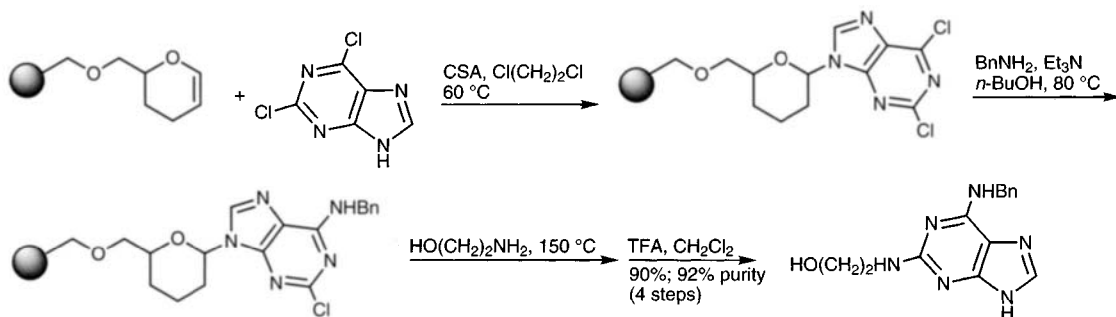


# 28 Heterocycles at work

The occurrence of heterocyclic compounds in nature is widespread, and the use of natural and synthetic heterocyclic compounds in many commercially important spheres, is enormous. Indeed even a book devoted entirely to ‘Heterocycles in Life and Society’<sup>1</sup>, can only cover some of the important uses. In the earlier chapters of this book, small selections of some of the significant heterocyclic substances in use as medicines have been cited. In this final chapter we choose to highlight three aspects of heterocyclic chemistry of commercial importance – the increasing use of solid phase chemistry for the discovery of new drugs, the problems associated with the scale up from discovery chemistry to production quantities of new drugs, and the relevance of heterocyclic chemistry to materials of actual or potential value in electroactive and related areas of materials science.

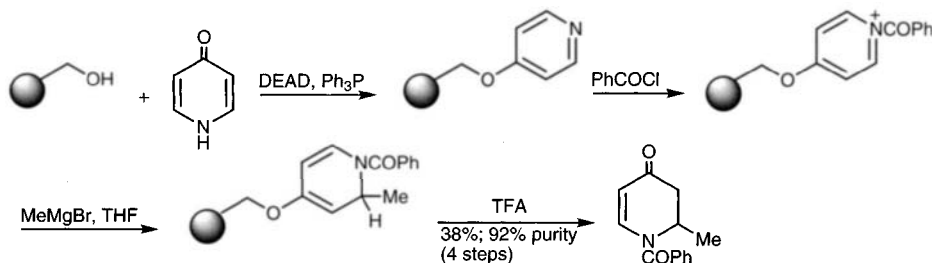
## 28.1 Solid phase reactions<sup>2</sup>

Reactions on solid phase – that is, where a substrate molecule is attached to an insoluble polymeric support – were originally developed for peptide synthesis but are now widely used in general synthetic and heterocyclic chemistry, particularly for application to combinatorial chemistry.



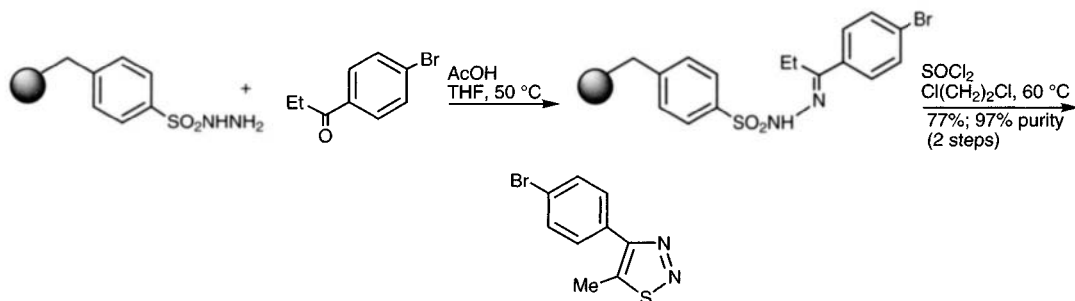
Scheme 1

The particular advantage of solid-supported chemistry is in purification: sequential reactions can be carried out and by-products washed away without the need for extractions, chromatography, or isolation of intermediates. The product is finally cleaved from the support with minimal impurities. Although some individual reactions may be slower on solid phase, overall processes are generally faster because only one isolation step is needed. These features also make reactions suitable for automation.



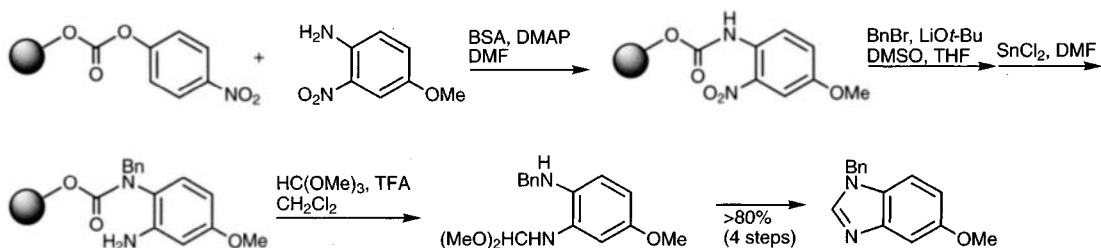
Scheme 2

Practically all types of reaction can be carried out (with choice of the appropriate support) including halogenations, lithiations, transition metal-catalysed reactions and reactions with such aggressive reagents as phosphorus pentachloride. Many standard heterocyclic ring synthesis methods can also be used successfully.



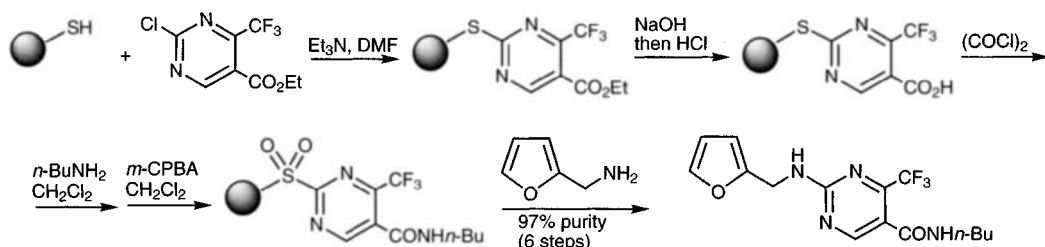
Scheme 3

The solid supports used are often derived from chloromethylated polystyrene resins, which can be used directly (Merrifield) for alkylation or for coupling via a linker, which may be cleavable selectively, by acid or base (*e.g.* Wang).



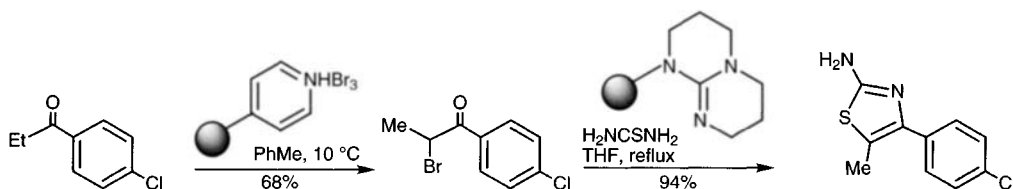
Scheme 4

The main question is how to attach the substrate to the polymer: in carboaromatic and aliphatic chemistry this is usually done through a functional group (Schemes 2 and 4) such as a carboxylic acid or an amine, which can restrict choice of substrate; an alternative method is through a 'traceless link' such as a silane, which can be removed, for example by protonolysis to leave a hydrogen at the point of attachment, but this may not be particularly convenient. Here, heterocycles have the advantage! Attachment to the support can be by methods<sup>3</sup> similar to those described above, but also via the ring heteroatom, particularly nitrogen in azoles<sup>4</sup> (Scheme 1) or by a heteroatom when the heterocyclic ring formation is the final step<sup>5</sup> – it is often easy to incorporate a final cyclisation (heterocycle formation) step in such a way that it results in cleavage of the product from the support (Scheme 3). Sulfur is a useful link for heterocycles because its use as a leaving group (or better, after conversion to sulfoxide<sup>6</sup> or sulfone<sup>7</sup>) can lead to cleavage from the support (Scheme 5). For full discussion of the heterocyclic reactivity involved in the examples shown, the reader should consult earlier chapters.



Scheme 5

Another application of solid phase chemistry is the use of polymer-bound reagents which offer similar advantages in requiring minimal purification: the thiazole synthesis shown below, which involved the use of a polymer-bound brominating agent and secondly a polymer-bound base, gave the intermediate and product in greater than 95% purity without the need for any chromatography.<sup>8</sup>



While these methods have been used very successfully on a small scale, they also have significant potential for rapid synthesis on medium scale (up to several kg) and possibly even larger. High loading resins can bind an equal weight of substrate and so are efficient in terms of volume.<sup>9</sup>

## 28.2 Heterocycles in the pharmaceutical industry: large scale heterocyclic synthesis

Heterocycles are the basis of the majority of medicines, with combined sales in tens of billions of pounds – about £60 billion for the top 100 drugs in 1998 – so for a chemist in the pharmaceutical and related industries, a thorough knowledge of heterocyclic chemistry is necessary at the discovery, development, and production stages. Most of the total cost is in discovery, development, testing and sales, the cost of production of the actual drug substance being a relatively minor part of the final cost. Production costs are tightly controlled so the synthetic route must be as efficient and cheap as possible – typical production prices are of the order of £1000 to £5000 per kilo for a new drug.

The requirements of scale-up and production are very different from those in medicinal chemistry and drug discovery and may lead to a very different approach to chemistry. The number of steps in the synthesis is a major determinant of cost, as are, of course, the costs of starting materials and reagents. Standard preliminary targets are for 90% hplc yields in each stage, with purification by crystallisation or possibly distillation in some cases; chromatographic purification on a production scale, which may be in ton quantities, is very rare.

A crucial aspect is the quality of the final product, with very rigorous criteria for reproducible levels of purity and of percentages of impurities, particularly metals. All impurities down to *ca.* 0.1% must be identified and possibly reference samples of the impurities separately synthesised, which provides another interesting challenge to the

development chemist. Some metal derivatives such as organotin compounds and mercury must be at almost undetectable levels; others, such as palladium may be acceptable at very low levels depending on dose.

Although some drugs have been produced using organotin reagents, as a general rule such reagents are avoided, particularly in the later steps. These requirements can greatly restrict the synthetic chemistry available for the production route – many elegant and ingenious reactions found, for example, in this book, though suitable for preliminary phases of drug discovery, may be of no use for production due to residual traces of such reagents in the final product.

Minimisation of environmental impact must also be considered – the composition of gaseous emissions and the content of toxic or prohibited substances in aqueous waste streams. These factors must therefore be taken into account when considering the production synthesis of a drug.

## 28.3 Electronic applications

An important area where technology and heterocyclic chemistry combine is that of electroactive organic materials.<sup>10</sup> The applications of these materials, which extend beyond simple replacements for metals, include use as conductors, superconductors, semiconductors, batteries, transistors, sensors, light emitting diodes (LEDs), and related electrochromic applications. This area is of great commercial importance.

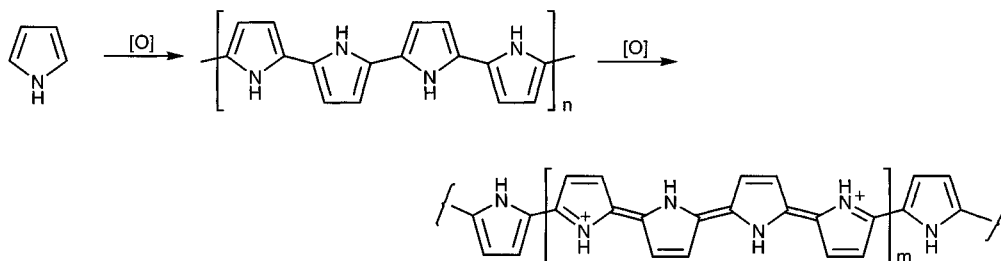
The use of organic conductors means that an essentially infinite supply of materials is available with minimum ecological impact and without strategic supply problems, which could arise with metals and rare elements. The resistance to corrosion, air and water stability, ease of preparation as very thin films, and suitability for incorporation into materials such as fabrics, are also significant advantages over metallic equivalents.

The mechanism of conduction involves electronic conduction through long chains of conjugated molecules and/or  $\pi$ -stacked structures. A detailed discussion of the theory of conduction is beyond the scope of this book; this section is restricted to demonstrating the range of applications of heterocycles in this area.

The types of compound used in organic conductors cover a wide range of unsaturated molecules such as poly(acetylene) and poly(aniline), but of particular significance from the heterocyclic and commercial viewpoints are poly(pyrrole), poly(thiophene), and related polymers and  $\pi$ -stacked structures derived from tetrathiafulvalenes. An advantage of using heterocycles is that a wide range of electron-rich, electron-poor and mixed systems can be easily prepared, allowing for tuning of the electronic and electrical properties of such materials.<sup>11</sup>

### 28.3.1 Poly(pyrrole) and poly(thiophene)

Pyrrole, thiophene, and their derivatives can be oxidatively polymerised either electrochemically or chemically, for example using iron(III) chloride, to give mainly 2,5-coupled polymers. The initial neutral polymers are non-conducting but on further oxidation are converted partially into cation radicals or dications, with incorporation of counterions from the reaction medium – a process known as ‘doping’ – giving conducting materials. Reductive doping is also possible in other systems.

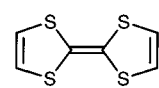


The conducting and physical properties can be modified by the use of 3- and/or 4-substituents, or *N*-substituents in the case of pyrrole. The counterions can be incorporated into a side-chain (self-doping) as in the polymer of 3-(thien-3-yl)propanesulfonic acid. Variation in the size of side-chains allows control of solubility. Mixed polymers with, for example, thiophenes and pyridines, are capable of both oxidative and reductive doping.

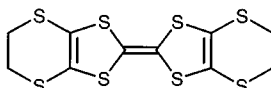
Oligo(thiophenes) are also useful in these applications and have been specifically synthesised up to 27 units long by palladium(0)-catalysed couplings or via the diacetylene synthesis (section 14.13.2.2).<sup>12</sup>

### 28.3.2 Tetrathiafulvalenes

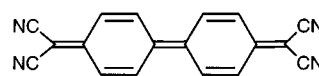
These unusual heterocycles and their analogues have been intensively studied – a search for the parent compound gives more than 1000 literature references – since the discovery<sup>13</sup> that single crystals of TTF.TCNQ (tetrathiafulvalene.tetracyanoquinodimethane) show electrical conductivity. TTF.TCNQ crystallises with segregated stacks, *i.e.* with the electron donor (TTF) and the electron acceptor (TCNQ) molecules aligned separately, in stacks of the planar molecules, rather than as alternating donors and acceptors as is found in conventional, non-conducting charge-transfer stacks. The partial transfer of charge between the segregated stacks is the key feature which allows the flow of current in the stack directions. ‘Electrons in crystalline ‘organic metals’ flow along supermolecular orbitals constructed from molecular orbitals of molecules arranged in columns’,<sup>14</sup> though intermolecular communication, not necessarily involving stacks, may be entirely sufficient.<sup>15,16</sup> Thus: ‘The structure of any successful organic conductor is probably dictated by two requirements. First, its molecular building blocks must fit closely together, so that the conduction electrons can move easily from one molecule to another. Second, the energy cost of partially filling or opening a valence energy band must be small’,<sup>17</sup> for example ‘stable open-shell (*i.e.* free radical) species are needed ... of planar molecules with ... delocalised  $\pi$ -molecular orbitals so that effective overlap ... can occur’.<sup>18</sup> Many variations on both the TTF and the TCNQ units have been prepared and studied, including selenium and tellurium analogues of TTF; and using electron-deficient heterocycles such as tetrazine instead of TCNQ. The bis(ethylenedithio) analogue of TTF, usually known as BEDT-TTF, has been particularly useful. Incidentally, the electron-donating ability of TTF allows its use as a radical initiator for diazonium salts.<sup>19</sup>



tetrathiafulvalene (TTF)

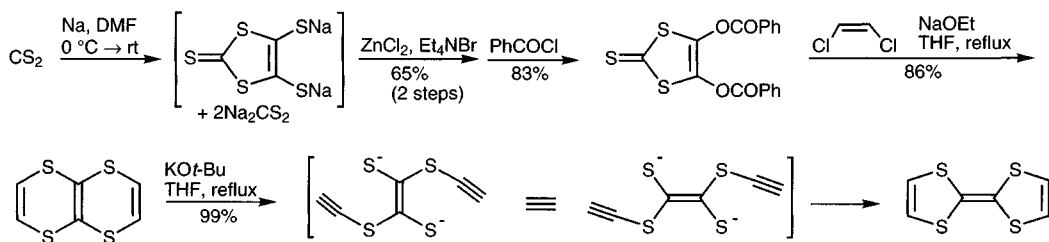


BEDT-TTF

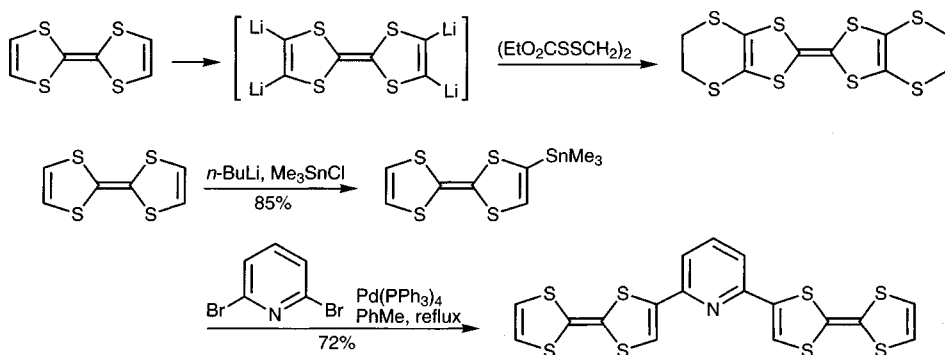


tetracyanoquinodimethane (TCNQ)

Tetrathiafulvalenes can be prepared in a number of ways,<sup>20</sup> for example from 1,3-dithiole-2-thione-4,5-dithiolate – the simple salts of this dianion are not very stable but it can be stored for later use, as a zinc complex, or as a dibenzoate as shown below.

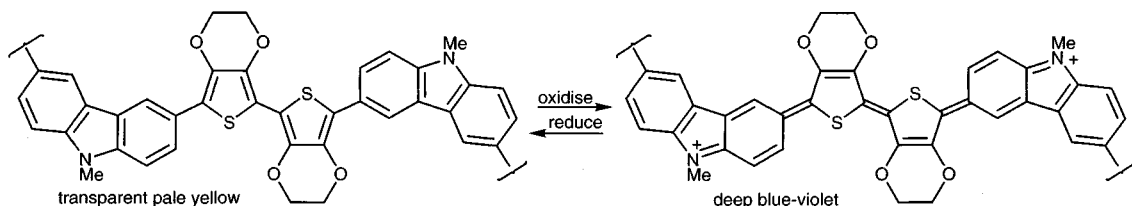


Most chemical transformations of TTF are based on lithiations – even a tetralithio derivative is easily formed. Palladium(0)-catalysed couplings utilising trialkyltin derivatives<sup>21</sup> can also be carried out without difficulty.<sup>22</sup>



### 28.3.3 Applications

In addition to the straightforward application of conductors and semi-conductors, there are some interesting examples of other uses. Polymers derived from 3,4-ethylenedioxythiophene are produced commercially as anti-static agents and substituted compounds have found particular application in electrochromic devices – substances which change colour on application of an electric current. Electrochromic devices can be used, for example, for switchable shading or colouring of glass and have been suggested as advanced forms of ‘stealth’ camouflage for fighter aircraft, where a computer-controlled array of electrochromic coatings would match the colour of the aircraft to that of its immediate surroundings; some of the original stealth coatings contained radar-absorbing poly(pyrroles).<sup>23</sup>



The conductivity of the polymer may change when organic vapours are absorbed and this has been put to use in the delightfully-named ‘electronic nose’.<sup>24</sup> In one

commercial form, this consists of an array of twelve different polymers, such as poly(pyrrole), with differential responses to absorption of different organic molecules; electronic processing of these responses generates a fingerprint for each compound, allowing identification. One application of the electronic nose is in the food industry, where it can be used to detect spoilage or faulty fermentations; it has a major advantage over current methods such as gas chromatography in being faster and cheaper and much simpler to operate. In a related way, biosensors, for example for the estimation of glucose levels, can be produced by attachment of enzymes to conducting polymer surfaces.

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