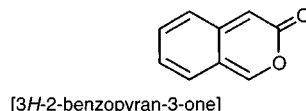
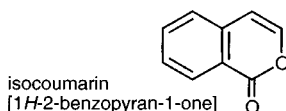
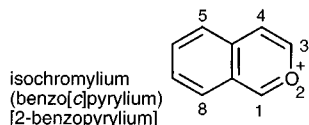
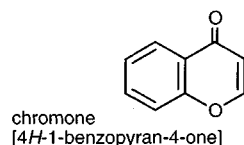
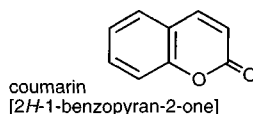
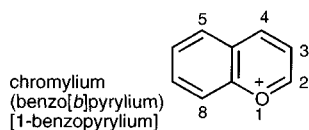
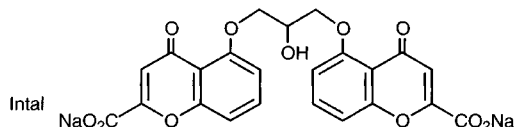
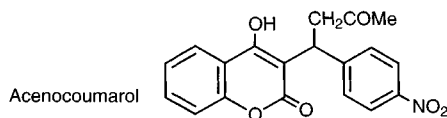


9 Benzopyryliums, benzopyrones: reactions and synthesis



1-Benzopyryliums, coumarins, and chromones are very widely distributed throughout the plant kingdom where many secondary metabolites contain them. Not the least of these are the anthocyanins¹ and flavones² which, grouped together, are known as the flavonoids,³ and make up the majority of the flower pigments. In addition, many flavone and coumarin⁴ derivatives have marked toxic and other physiological properties in animals, though they play no part in the normal metabolism of animals. The isomeric 2-benzopyrylium⁵ system does not occur naturally and only a few isocoumarins⁶ occur as natural products and as a consequence much less work on these has been described.

Chemotherapeutically valuable compounds in this group are a series of coumarins, of which Acenocoumarol is one, which are valuable as anticoagulants, and Intal, which is used in the treatment of bronchial asthma. One of the earliest optical brighteners was 7-diethylamino-4-methylcoumarin.⁷



Processes initiated by nucleophilic additions to the positively charged heterocyclic ring are the main, almost the only, types of reaction known for benzopyryliums. The absence of examples of electrophilic substitution in the benzene ring is to be contrasted with the many examples of substitution in quinolinium and isoquinolinium salts, emphasising the greater electron-withdrawing and thus deactivating effect of positively charged oxygen.

Coumarins, chromones, and isocoumarins react with both nucleophiles and electrophiles in much the same way as do quinolones and isoquinolones.

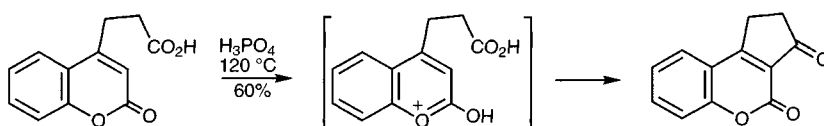
9.1 Reactions of benzopyryliums

Much more work has been done on 1-benzopyryliums than on 2-benzopyryliums, because of their relevance to the flavylum (2-phenyl-1-benzopyrylium) nucleus which occurs widely in the anthocyanins, and much of that work has been conducted on

flavylium itself. As with pyrylium salts, benzopyrylium salts usually add nucleophiles at the carbon adjacent to the oxygen.

9.1.1 Reactions with electrophilic reagents

No simple examples are known of electrophilic or radical substitution of either heterocyclic or homocyclic rings of benzopyrylium salts; flavylium⁸ and 1-phenyl-2-benzopyrylium⁵ salts nitrate in the substituent benzene ring. Having said this, the cyclisation of coumarin-4-propanoic acid may represent Friedel-Crafts type intramolecular attack on the carbonyl-*O*-protonated form i.e. on a 2-hydroxy-1-benzopyrylium system, at C-3.⁹



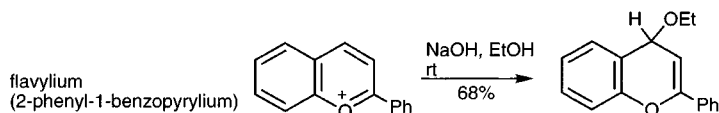
9.1.2 Reactions with oxidising agents

Oxidative general breakdown of flavylium salts was utilised in early structural work on the natural compounds. Baeyer-Villiger oxidation is such a process whereby the two 'halves' of the molecule can be separately examined (after ester hydrolysis of the product).¹⁰ Flavylium salts can be oxidised to flavones using thallium(III) nitrate¹¹ and benzopyrylium itself can be converted into coumarin with manganese dioxide.¹²

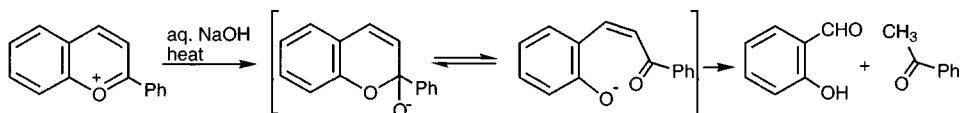
9.1.3 Reactions with nucleophilic reagents

9.1.3.1 Water and alcohols

Water and alcohols add readily at C-2, and sometimes at C-4, generating chromenols or chromenol ethers.¹³ It is difficult to obtain *2H*-chromenols pure since they are always in equilibrium with ring-opened chalcones.¹⁴

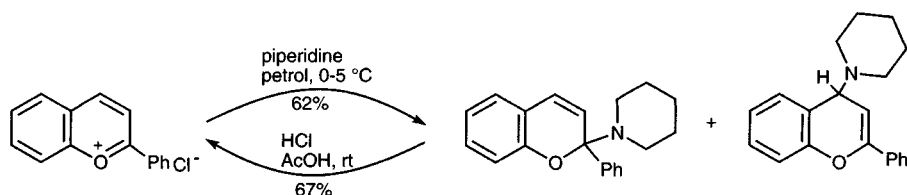


Controlled conditions are required for the production of simple adducts, for under more vigorous alkaline treatment, ring opening then carbon-carbon bond cleavage *via* a retro-aldol mechanism takes place and such processes, which are essentially the reverse of a route used for the synthesis of 1-benzopyryliums (section 9.3.1) were utilised in early structural work on anthocyanin flower pigments.

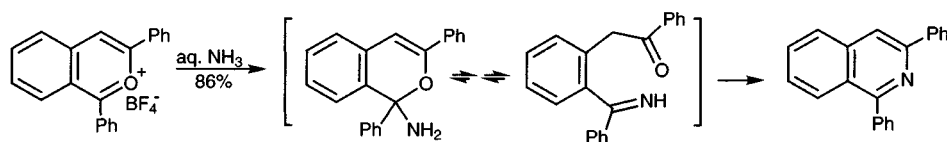


9.1.3.2 Ammonia and amines

Ammonia and amines add to benzopyryliums, and simple adducts from secondary amines have been isolated.¹⁵

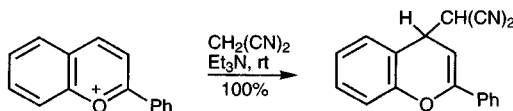


It is important to realise that 1-benzopyrylium salts cannot be converted into quinolines or quinolinium salts by reaction with ammonia or primary amines, whereas 2-benzopyrylium salts are converted, efficiently, into isoquinolines or isoquinolinium salts respectively.¹⁶

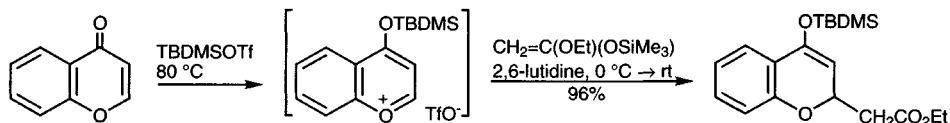


9.1.3.3 Carbon nucleophiles

Organometallic carbon nucleophiles add to flavylium salts¹⁷ as do activated aromatics like phenol,¹⁸ and enolates such as those from cyanoacetate, nitromethane,¹⁹ dimedone,²⁰ all very efficiently, at C-4. Cyanide and azide add to 2-benzopyryliums at C-1.²¹

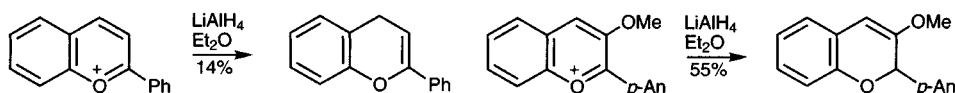


Silyl enol ethers, or allylsilanes will add at C-2 to benzopyrylium salts generated by *O*-silylation of chromones; in the case of silyl ethers of α,β -unsaturated ketones, cyclisation of the initial adduct is observed.²²



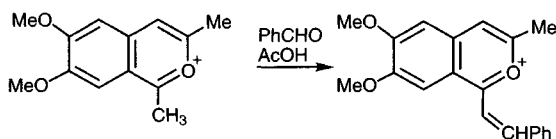
9.1.4 Reactions with reducing agents

Catalytic hydrogenation of flavylium salts is generally straightforward and results in the saturation of the heterocyclic ring. Lithium aluminium hydride reduces flavylium salts generating 4*H*-chromenes,²³ unless there is a 3-methoxyl, when 2*H*-chromenes are the products.²⁴ 2-Benzopyryliums add hydride at C-1.²⁵



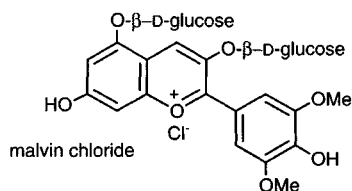
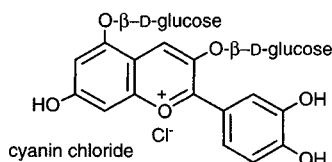
9.1.5 Alkylbenzopyryliums

Alkyl groups oriented α or γ to the positively charged oxygen in benzopyryliums have acidified hydrogens which allow aldol-type condensations.^{5,26}

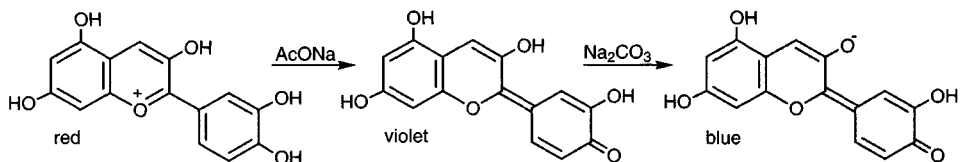


9.1.6 1-Benzopyrylium pigments; anthocyanins and anthocyanidins

The anthocyanidins are polyhydroxyflavylium salts. They occur in a large proportion of the red to blue flower pigments and in fruit skins, for example grapes and therefore in red wines made therefrom.²⁷ Anthocyanidins are generally bound to sugars, and these glycosides are known as anthocyanins. As an example, cyanin (isolated as its chloride) is an anthocyanin which occurs in the petals of the red rose (*Rosa gallica*), the poppy (*Papaver rhoeas*), and very many other flowers. Another example is malvin chloride which has been isolated from many species, including *Primula viscosa*, a mauvy-red alpine primula.



In the living cell these compounds exist in more complex bound forms, interacting with other molecules, for example flavones,²⁸ and the actual observed colour will depend on these interactions. However it is interesting that even *in vitro*, simple pH changes bring about extreme changes in the electronic absorption of these molecules. For example cyanidin is red in acidic solution, violet at intermediate pH and blue in weakly alkaline solution, the deep colours being the result of extensive resonance delocalisation in each of the structures.

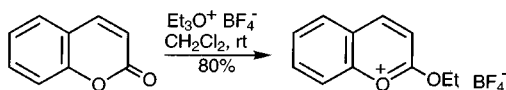
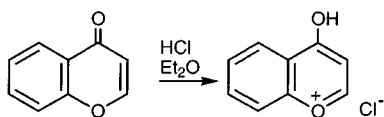


9.2 Benzopyrones (chromones, coumarins, and isocoumarins)

9.2.1 Reactions with electrophilic reagents

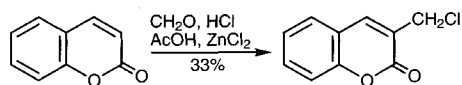
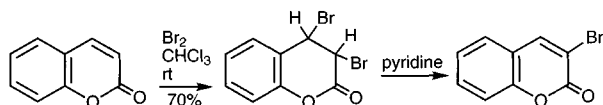
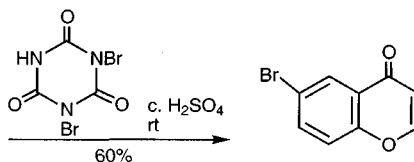
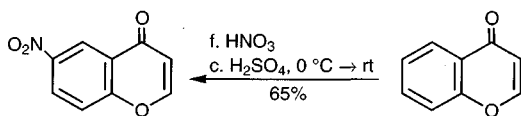
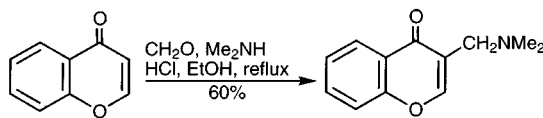
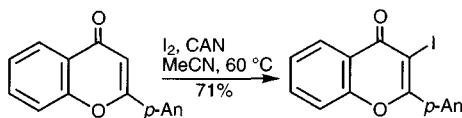
9.2.1.1 Addition to carbonyl oxygen

Addition to carbonyl oxygen of a proton produces a hydroxybenzopyrylium salt; chromones undergo this protonation more easily than the coumarins, for example passage of hydrogen chloride through a mixture of chromone and coumarin in ether solution leads to the precipitation of only chromone hydrochloride (i.e. 4-hydroxy-1-benzopyrylium chloride).²⁹ *O*-Alkylation requires the more powerful alkylating agents.^{5,30} *O*-Silylation of benzopyrones is easy (section 9.1.3.3).



9.2.1.2 C-Substitution

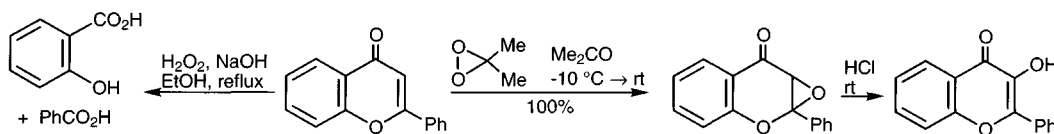
C-Substitution of coumarins and chromones has been observed in both rings: in strongly acidic media, in which presumably it is an hydroxybenzopyrylium cation which is attacked, substitution takes place at C-6, for example nitration.³¹ This can be contrasted with the dimethylaminomethylation of chromone³², iodination of flavones³³ or the chloromethylation of coumarin³⁴ where hetero-ring substitution takes place, presumably *via* the non-protonated (complexed) heterocycle (CAUTION: $\text{CH}_2\text{O}/\text{HCl}$ also produces some $\text{ClCH}_2\text{OCH}_2\text{Cl}$, a carcinogen).



Bromine in the presence of an excess of aluminium chloride (the 'swamping catalyst' effect) converts coumarin into 6-bromocoumarin.³⁵ Reaction of coumarin with bromine alone results in simple addition to the double bond in the heterocyclic ring; 3-bromocoumarin can be obtained by then eliminating hydrogen bromide.³⁶ Copper(II) halides with alumina in refluxing chlorobenzene is an alternative method for 3-halogenation of coumarins.³⁷ Chromone can be efficiently brominated at C-6 using dibromoisocyanuric acid (DBI),³⁸ treatment of chromone with bromine in carbon disulfide results in addition, elimination of hydrogen bromide on warming giving 3-bromochromone.³⁹

9.2.2 Reactions with oxidising agents

Non-phenolic coumarins are relatively stable to oxidative conditions. Various oxidative methods were used extensively in structure determinations of natural flavones.⁴⁰



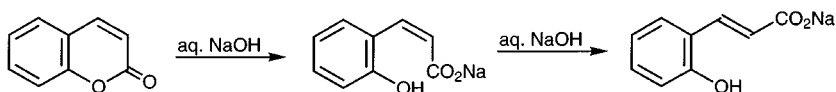
Flavones and isoflavones (3-arylchromones) are quantitatively converted into 2,3-epoxides by exposure to dimethyl dioxirane; such intermediates have obvious

synthetic potential, flavone oxides, for example, being quantitatively converted by acid into 3-hydroxyflavones, which are naturally occurring.⁴¹

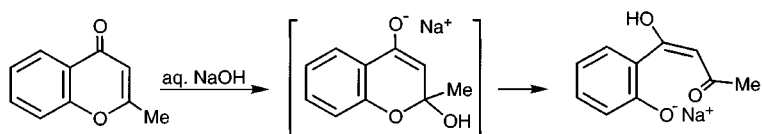
9.2.3 Reactions with nucleophilic reagents

9.2.3.1 Hydroxide

Coumarins (and isocoumarins) are quantitatively hydrolysed to give yellow solutions of the salts of the corresponding *cis* cinnamic acids (coumarinic acids) which cannot be isolated since acidification brings about immediate relactonisation; prolonged alkali treatment leads to isomerisation and the formation of the *trans* acid (coumaric acid) salt.

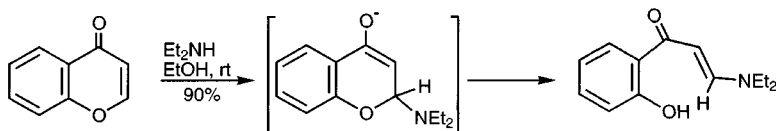


Cold sodium hydroxide comparably reversibly converts chromones into the salts of the corresponding ring-opened phenols, *via* initial attack at C-2, more vigorous alkaline treatment leading to reverse-Claisen degradation of the 1,3-diketo-side-chain.

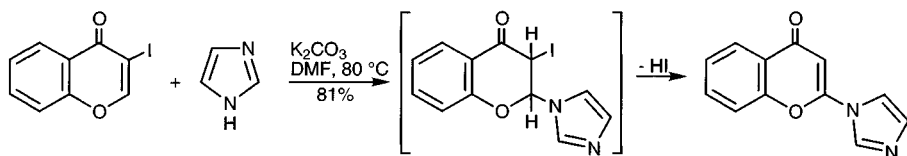


9.2.3.2 Ammonia and amines

Ammonia and amines do not convert coumarins into 2-quinolones nor chromones into 4-quinolones, but isocoumarins do produce isoquinolones.⁴² Ring-opened products from chromones and secondary amines can be obtained where again the nucleophile has attacked at C-2.

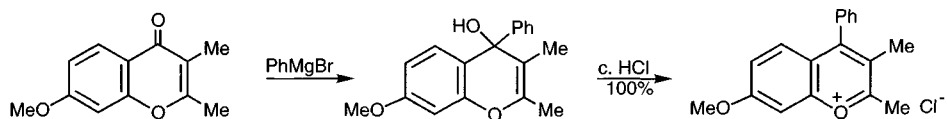


The interaction of 3-iodochromone with imidazole leads to substitution at the 2-position, presumably via an addition/elimination sequence as indicated.⁴³

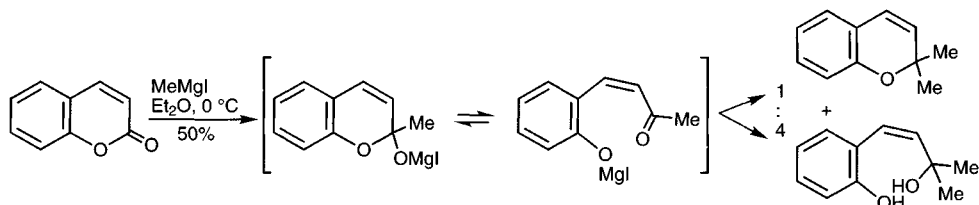


9.2.3.3 Carbon nucleophiles

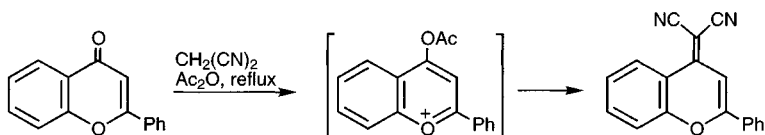
Grignard reagents react with chromones at carbonyl carbon; the resulting chromenols can be converted by acid into the corresponding 4-substituted 1-benzopyrylium salts.²⁶



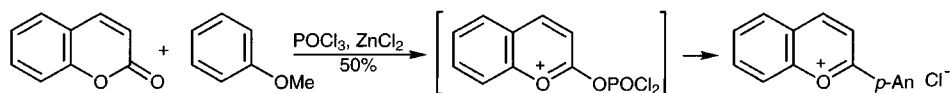
Coumarins, and isocoumarins,¹⁶ react with Grignard reagents, as do esters, and can give mixtures of products, resulting from ring opening of the initial carbonyl adduct; the reaction of coumarin with methylmagnesium iodide illustrates this.⁴⁴



By conversion into a benzopyrylium salt with a leaving group, nucleophiles can be introduced at the chromone 4-position: treatment with acetic anhydride presumably forms a 4-acetoxymethylbenzopyrylium.⁴⁵

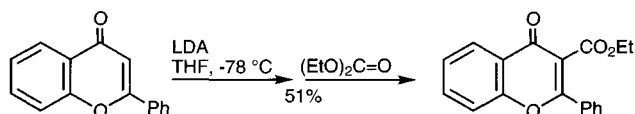


In efficient reactions, coumarin can be made to react with electron-rich aromatics using phosphoryl chloride, alone, or with zinc chloride.⁴⁶

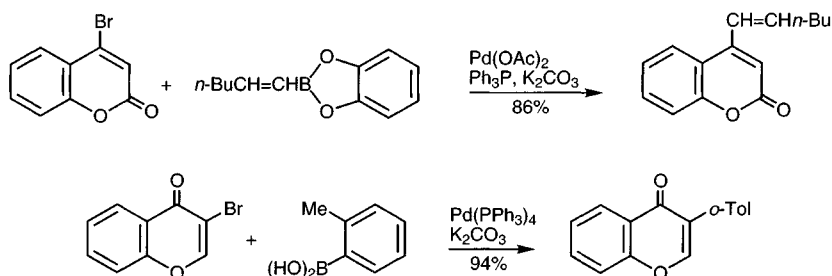


9.2.3.4 Organometallic derivatives

Flavone has been lithiated at C-3.⁴⁷

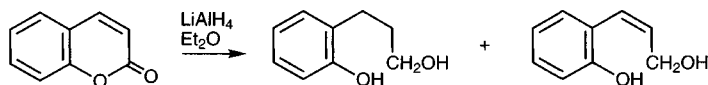


Both 3-bromochromone and 4-bromocoumarin have been successfully used in coupling reactions using palladium(0) methodology.⁴⁸



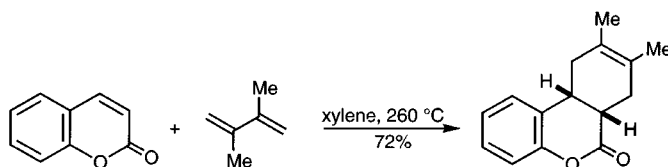
9.2.3.5 Reactions with reducing agents

Both coumarin and chromone are converted by diborane then alkaline hydrogen peroxide into 3-hydroxychroman.⁴⁹ Catalytic reduction of coumarin or chromone saturates the C–C double bond.⁵⁰ For both systems, hydride reagents can of course react either at carbonyl carbon or at the conjugate position and mixtures therefore tend to be produced. Zinc amalgam in acidic solution converts benzopyrones into 4-unsubstituted benzopyrylium salts.⁵¹

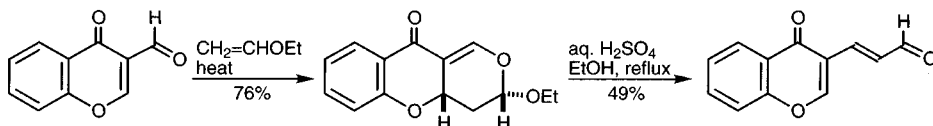


9.2.3.6 Reactions with dienophiles; cycloadditions

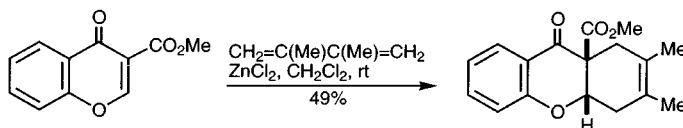
Coumarins, but not apparently, chromones, serve as dienophiles in Diels-Alder reactions, though under relatively forcing conditions.⁵²



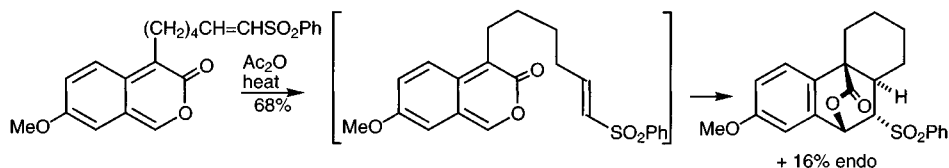
It can be taken as a measure of the low intrinsic aromaticity associated with fused pyrone rings, that 3-acylchromones undergo hetero Diels-Alder additions with enol ethers,⁵³ and ketene acetals,⁵⁴ 3-formylchromone reacting the most readily.



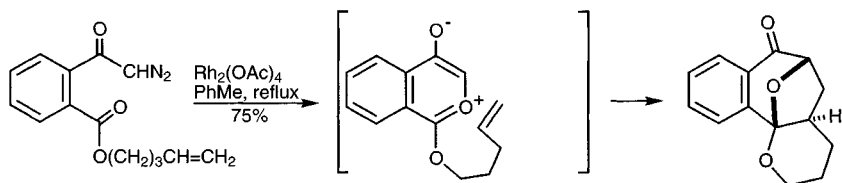
Chromone-3-esters, on the other hand, serve as dienophiles under Lewis acid catalysis.⁵⁵



2-Benzopyran-3-ones, generated by cyclising dehydration of an *ortho* formylar-lacetic acid take part in intramolecular Diels-Alder additions as shown below.⁵⁶

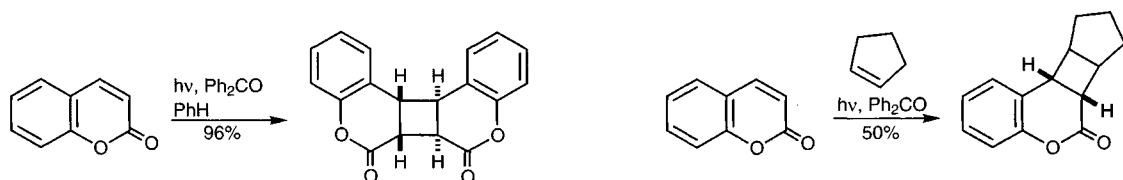


Decomposition of aryl diazoketones with an appropriately tethered alkene allows the intramolecular cycloaddition to the 4-oxidoisochromylium salts thus formed, as illustrated below.⁵⁷



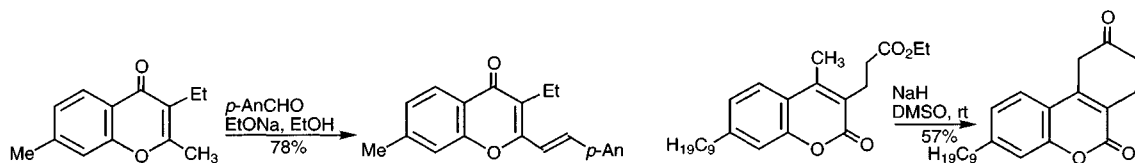
9.2.3.7 Photochemical reactions

Coumarin has been studied extensively in this context; in the absence of a sensitiser it gives a *syn* head-to-head dimer; in the presence of benzophenone, as sensitiser, the *anti* isomer is formed;⁵⁸ the *syn* head-to-tail dimer is obtained by irradiation in acetic acid.⁵⁹ Cyclobutane-containing products are obtained in modest yields by sensitiser-promoted cycloadditions of coumarins and 3-acyloxycoumarins with alkenes, ketene diethylacetal, and cyclopentene.⁶⁰



9.2.3.8 Alkylcoumarins and alkylchromones

Methyl groups at C-2, but not at C-3, of chromones undergo condensations with aldehydes, because only the former can be deprotonated to give conjugated enolates.⁶¹

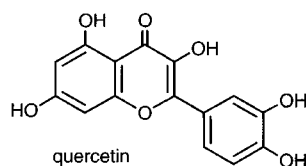
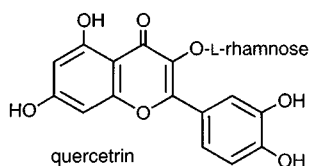


The 4-position of coumarins is the only one at which alkyl substituents have enhanced acidity in their hydrogens,⁶² and this is considerably less than that of the methyl groups of 2-methylchromones.⁶³

9.2.3.9 Flavone pigments

The naturally occurring flavones are yellow and are very widely distributed in plants. They accumulate in almost any part of a plant, from the roots to the flower petals.

Unlike the anthocyanins, which are too reactive and short-lived, the much more stable flavones have, from time immemorial, been used as dyes, for they impart various shades of yellow to wool. As an example, in the more recent past the inner bark of one of the North American oaks, *Quercus velutina*, was a commercial material known as quercitron bark and much used in dyeing: it contains quercetrin.

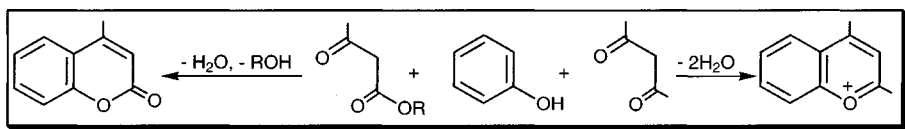


The corresponding aglycone, quercetin, is one of the most widely occurring flavones, found, for example, in *Chrysanthemum* and *Rhododendron* species, horse chestnuts, lemons, onions, and hops.

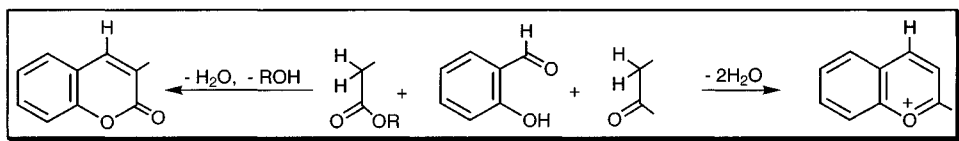
9.3 Synthesis of benzopyryliums, chromones, coumarins and isocoumarins

There are three important ways of putting together 1-benzopyryliums, coumarins, and chromones; all begin with phenols. The isomeric 2-benzopyrylium and isocoumarin nuclei require the construction of an *ortho*-carboxy- or *ortho*-formyl-arylacetaldehyde (homophthalaldehyde).

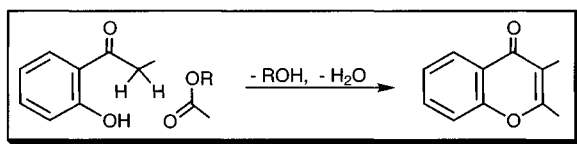
Subject to the restrictions set out below, phenols react with 1,3-dicarbonyl compounds to produce 1-benzopyryliums or coumarins depending on the oxidation level of the 1,3-dicarbonyl component.



ortho-Hydroxybenzaldehydes react with carbonyl compounds having an α -methylene, to give 1-benzopyryliums or coumarins depending on the nature of the aliphatic unit.



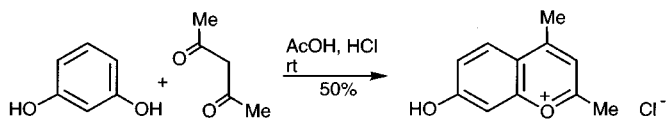
ortho-Hydroxyaryl alkyl ketones react with esters to give chromones.



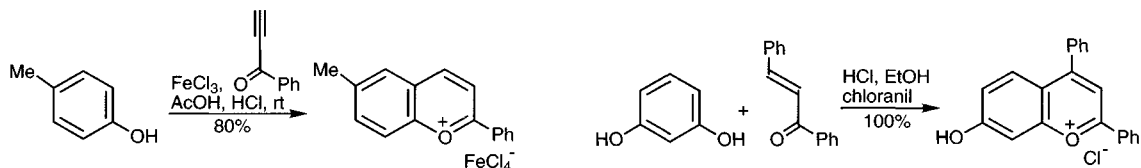
9.3.1 Ring synthesis of 1-benzopyryliums^{1b}

9.3.1.1 From phenols and 1,3-dicarbonyl compounds

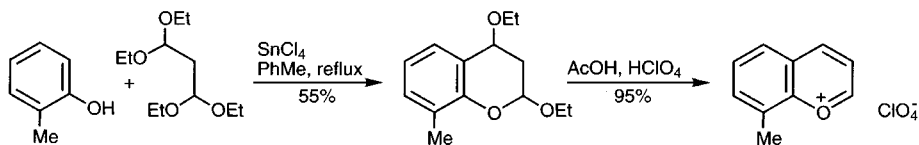
The simplest reaction, that between a diketone and a phenol, works best with resorcinol, for the second hydroxyl facilitates the cyclising electrophilic attack. This synthesis can give mixtures with unsymmetrical diketones, and it is therefore well suited to the synthesis of 1-benzopyryliums with identical groups at C-2 and C-4,⁶⁴ however diketones in which the two carbonyl groups are appreciably different in reactivity can produce high yields of single products.⁶⁵



Acetylenic ketones, synthons for 1,3-keto-aldehydes, also take part regioselectively in condensations,⁶⁶ as do chalcones, though of course an oxidant must be incorporated in this latter case.⁶⁷

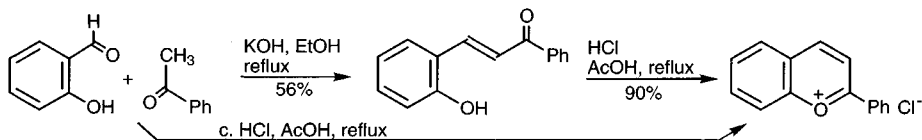


For hetero-ring-unsubstituted targets, the bis-acetal of malondialdehyde can be employed; in this variant a heterocyclic acetal-ether is first obtained, from which two mol equivalents of ethanol must then be eliminated.⁶⁸



9.3.1.2 From *ortho*-hydroxyaraldehydes and ketones

Salicylaldehydes can be condensed, by base or acid catalysis, with ketones which have an α -methylene. When base catalysis is used, the intermediate hydroxy-chalcones can be isolated,⁸ but overall yields are often better when the whole sequence is carried out in one step, using acid.⁶⁹ It is important to note that because this route does not rely upon an electrophilic cyclisation on the benzene ring, benzene-ring-unsubstituted 1-benzopyryliums can be produced.

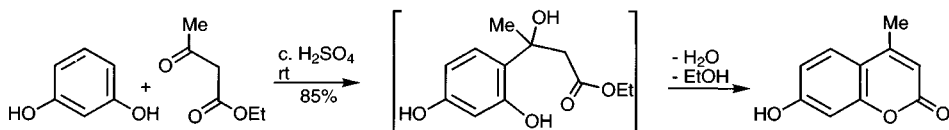


9.3.2 Ring synthesis of coumarins

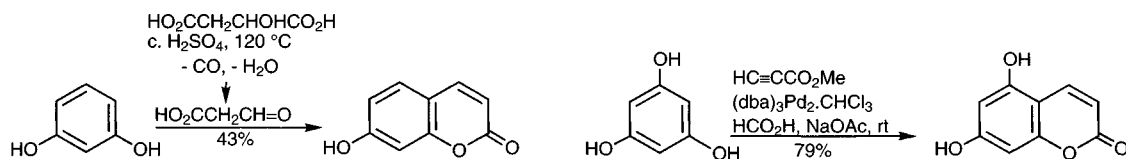
9.3.2.1 From phenols and 1,3-ketoesters

The Pechmann synthesis⁷⁰

Phenols react with β -ketoesters, including cyclic keto-esters,⁷¹ to give coumarins under acid-catalysed conditions – concentrated sulfuric acid,⁷² hydrogen fluoride,⁷³ or a cation exchange resin have been used.⁷⁴



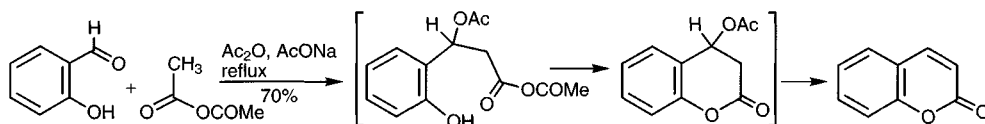
The Pechmann synthesis works best with the more nucleophilic aromatics such as resorcinols: electrophilic attack on the benzene ring *ortho* to phenolic oxygen by the protonated ketone carbonyl is the probable first step, though aryl acetoacetates, prepared from a phenol and diketene, also undergo ring closure to give coumarins.⁷⁵ The greater electrophilicity of the ketonic carbonyl determines the orientation of combination. The production of hetero-ring-unsubstituted coumarins can be achieved by condensing with formylacetic acid, generated *in situ* by the decarboxylation of malic acid.



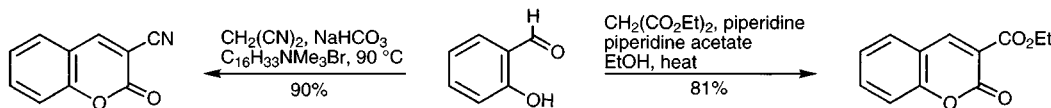
Coumarins can be obtained directly, in a one-pot procedure, from phenols and a propiolate using palladium(0) catalysis. The catalytic cycle is considered to involve a formyloxypalladium hydride reacting with the phenol to produce an aryloxypalladium hydride which adds to the alkyne.⁷⁶

9.3.2.2 From *ortho*-hydroxyaraldehydes and anhydrides (esters)

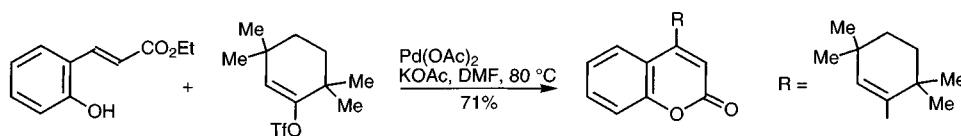
The simplest synthesis of coumarins is a special case of the Perkin condensation i.e. the condensation of an aromatic aldehyde with an anhydride. *ortho*-Hydroxy-*trans*-cinnamic acids cannot be intermediates since they do not isomerise under the conditions of the reaction; nor can *O*-acetylsalicylaldehyde be the immediate precursor of the coumarin, since it is not cyclised by sodium acetate on its own.⁷⁷



The general approach can be enlarged and conditions for condensation made milder by the use of further-activated esters, thus condensation with methyl nitroacetate produces 3-nitrocoumarins,⁷⁸ condensations with Wittig ylides⁷⁹ allow *ortho*-hydroxyaryl ketones to be used⁸⁰ and the use of diethyl malonate (or malonic acid⁸¹), malononitrile or substituted acetonitriles in a Knoevenagel condensation, produces coumarins with a 3-ester⁸² 3-cyano or 3-alkyl or -aryl substituent.⁸³ A 3-ester can be removed by hydrolysis and decarboxylation.⁸⁴

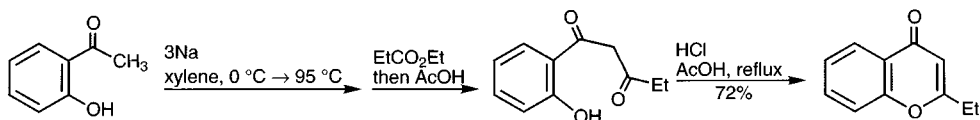


ortho-Hydroxy-*trans*-cinnamates can be converted into coumarins and with concomitant introduction of an aryl or alkenyl substituent into the 4-position; the sequence depends on a Heck reaction at the double bond.⁸⁵

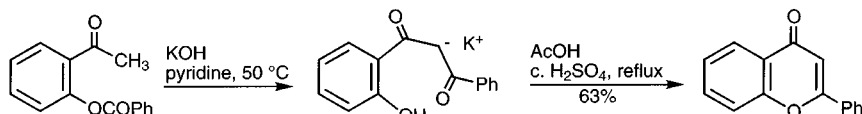


9.3.3 Ring synthesis of chromones from *ortho*-hydroxyacylarenes and esters

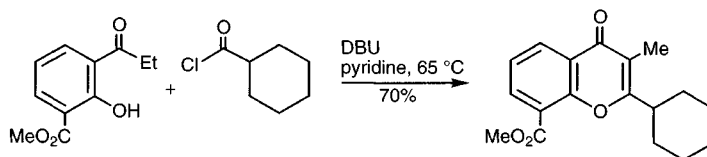
Most syntheses of chromones require the prior construction of a 1-(*ortho*-hydroxyaryl)-1,3-diketone, or equivalent, and it is in the manner in which this intermediate is generated that the methods differ.



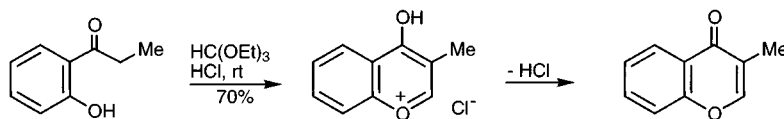
Claisen condensation between an ester and the methylene adjacent to the carbonyl of the acylarene produces a 1-(*ortho*-hydroxyaryl)-1,3-diketone. The Claisen condensation can be conducted in the presence of the acidic phenolic hydroxyl by the use of excess strong base;⁸⁶ triethylamine as solvent and base has also been utilised.⁸⁷ Alternatively, the process is conducted in two steps: first, acylation of the phenolic hydroxyl, and secondly, an intramolecular⁸⁸ base-catalysed Claisen condensation, known as the Baker-Venkataraman rearrangement: a synthesis of flavone itself is illustrative of the latter.⁸⁹



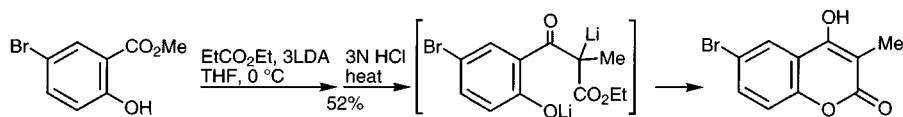
The use of diazabicycloundecene (DBU) allows the whole sequence, right through to the final heterocycle, to be conducted without isolation of intermediates as shown in the example below.⁹⁰



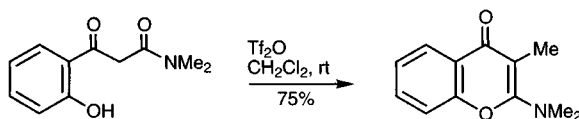
The production of a 2-unsubstituted chromone by this route requires the use of formate, or its equivalent, as the ester: a good method for this is the use of triethyl orthoformate as shown below,⁹¹ or dimethylformamide with methanesulfonyl chloride.⁹²



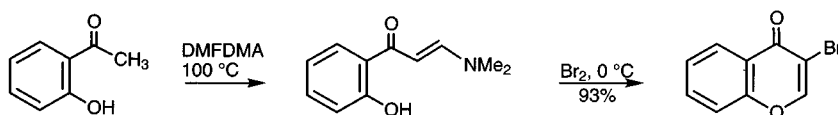
Another route to 2-unsubstituted chromones employs oxalic acid half-ester half-acid chloride, which gives a 2-ethoxycarbonyl chromone, hydrolysis and decarboxylation of which achieves the required result.⁹³ Diethyl carbonate as the ester gives rise to 2,4-dioxygenated heterocycles, which exist as 4-hydroxy-coumarins.⁹⁴ The condensation of a salicylate with an ester, using three mol equivalents of base also leads through to 4-hydroxycoumarins, as illustrated below.⁹⁵



2-Aminobenzopyrones result from the ring closure of 1-(*ortho*-hydroxyaryl)-1,3-ketoamides.⁹⁶

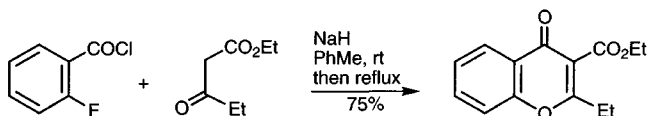


The variants on this route are many: for example condensation of *ortho*-hydroxyacetophenone with the Vilsmeier reagent produces 3-formylchromone,⁹⁷ and combination with dimethylformamide dimethyl acetal, then an electrophile, bromine in the example below, gives 3-substituted chromones.⁹⁸



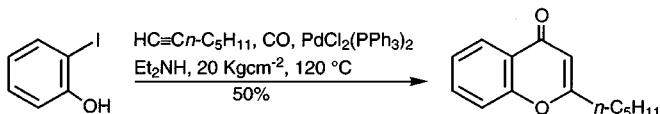
At a lower oxidation level, *ortho*-hydroxyacyl arenes undergo base-catalysed aldol condensations with aromatic aldehydes to give α,β -unsaturated ketones known as chalcones.⁹⁹ Chalcones can be cyclised to 2,3-dihydrochromones via an intramolecular Michael process; the dihydrochromones can in turn be dehydrogenated to produce chromones by a variety of methods, for example by bromination then dehydrobromination or by oxidation with the trityl cation, iodine, dimethyldioxirane, or iodobenzene diacetate.¹⁰⁰

Yet another variant uses *ortho*-fluorobenzoyl chloride in condensation with a 1,3-keto-ester;¹⁰¹ the fluoride is displaced in an intramolecular sense by enolate oxygen and the chromone obtained directly, as shown below.

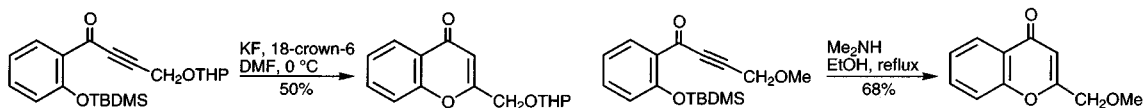


9.3.4 Ring synthesis of chromones from *ortho*-hydroxyaryl alkynyl ketones

ortho-Hydroxyaryl alkynyl ketones are intermediates in palladium(0)-catalysed coupling of *ortho*-hydroxyaryl iodides with terminal alkynes in the presence of carbon monoxide, ring closing to chromones *in situ*.¹⁰²

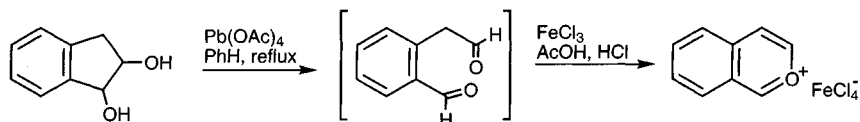


The alkynyl-ketones required for the 6-*endo-dig* cyclisation process¹⁰³ can be synthesised separately, and cyclise under mild conditions, as shown below. Enaminoketones also intervene in a very flexible sequence in which the cyclisation precursor is produced by coupling an acetylene with an *ortho* silyloxyaryl acid chloride; treatment of the resulting alkynone with a secondary amine leads to the chromone.¹⁰⁴

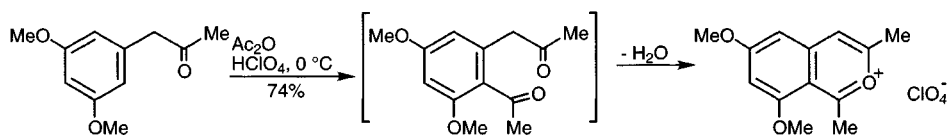


9.3.5 Ring synthesis of 2-benzopyryliums

The first synthesis¹⁰⁵ of the 2-benzopyrylium cation provided the pattern for subsequent routes in which it is the aim to produce a homophthalaldehyde, or diketone analogues, for acid-catalysed closure.

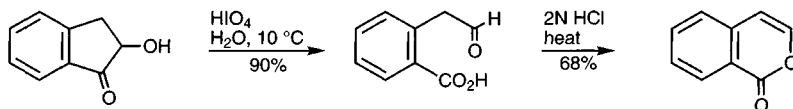


Most of the 2-benzopyrylium salts which have been synthesised subsequently have been 1,3-disubstituted and their precursors have been prepared by Friedel-Crafts acylation of activated benzyl ketones.^{6,106}

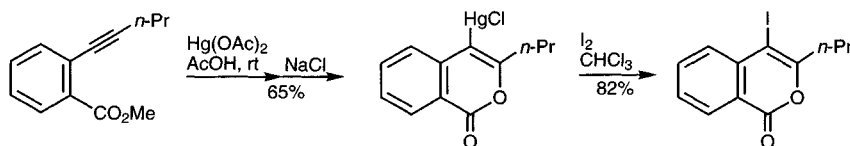


9.3.6 Ring synthesis of isocoumarins

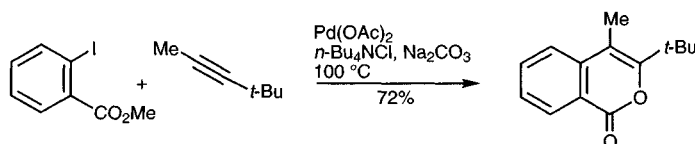
One approach to isocoumarins is comparable to that above for 2-benzopyryliums, only the aromatic aldehyde needing to be changed to acid.¹⁰⁷



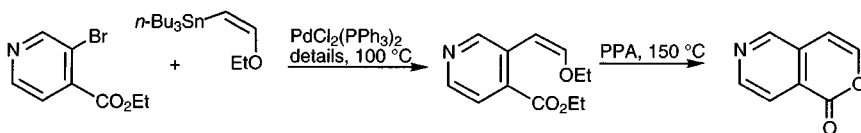
The direct introduction of the two-carbon unit of the heterocyclic ring, *ortho* to an existing carboxylic acid (ester) can be achieved in two ways: *ortho*-bromobenzoates can be coupled with π -(2-methoxyallyl)nickel bromide for the introduction of acetonyl,¹⁰⁸ or thallation of benzoic acids, *ortho* to the carboxyl, can be followed by palladium-catalysed coupling with alkenes.¹⁰⁹ Benzoates carrying an *ortho* acetylenic substituent can be ring closed using mercuric acetate, as shown below.¹¹⁰



The most general route so far described involves coupling an alkyne with *ortho*-iodobenzoic acid or with methyl *ortho*-iodobenzoate.¹¹¹ Both mono- and disubstituted alkynes will serve allowing considerable flexibility for the construction of substituted isocoumarins.



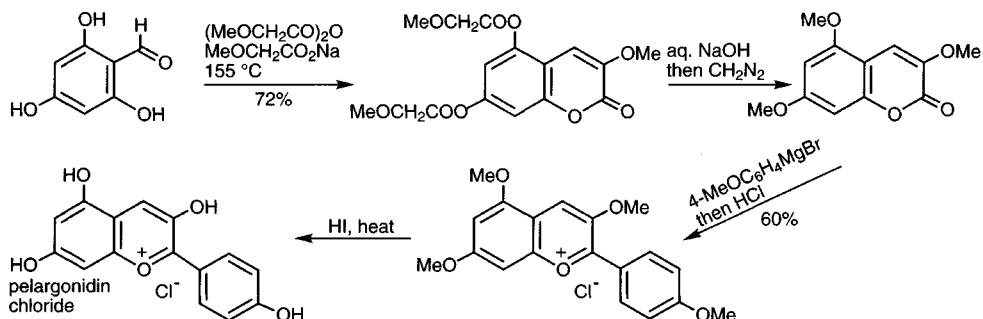
In a related process an *ortho* bromo ester is coupled with 1-tri-*n*-butylstannyl-2-ethoxyethene then acid used to close the ring; the example below shows how this sequence is applied to a pyridine ester.¹¹²



9.3.7 Notable examples of benzopyrylium and benzopyrone syntheses

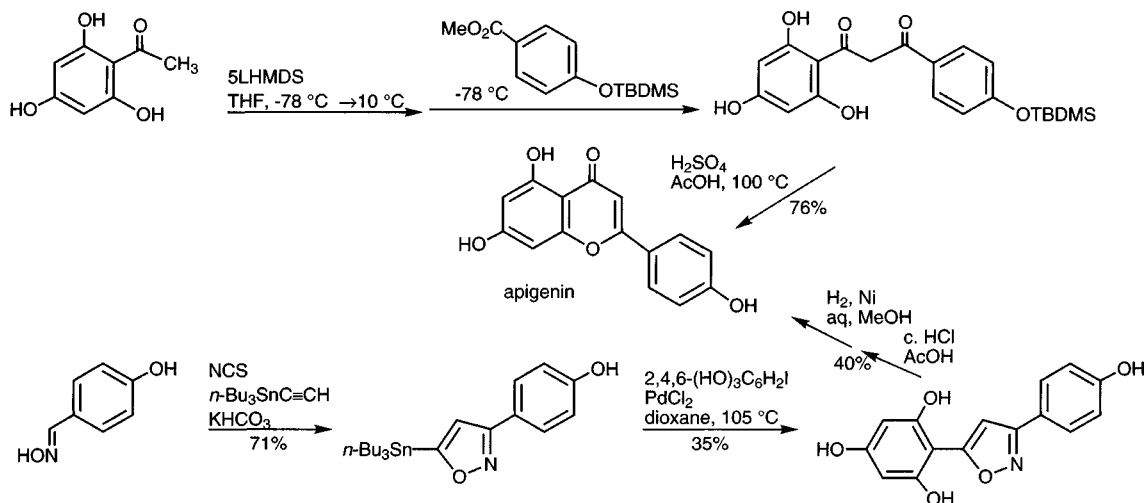
9.3.7.1 Pelargonidin chloride

The first synthesis of pelargonidin chloride used methyl ethers as protecting groups for the phenolic hydroxyls during the Grignard addition step.¹¹³



9.3.7.2 Apigenin

The scheme below shows two contrasting routes to apigenin. The modern use of excess of a very strong base, and the reaction of the resulting 'polyanion' obviated the need for phenolic protection in one synthesis.¹¹⁴



An elegant and flexible strategy for the assembly of a synthon for the *ortho*-hydroxyaryl-1,3-diketone required for a chromone synthesis depends on the use of an isoxazole as surrogate for the 1,3-diketone unit (section 22.8). An isoxazole is

produced by the cycloaddition of an aryl nitrile oxide to tri-*n*-butylstannylacetylene (section 22.13.1.2), the product coupled with an aryl halide and then the N–O bond hydrogenolytically cleaved (section 22.8).¹¹⁵

Exercises for chapter 9

Straightforward revision exercises (consult chapters 7, 8, and 9)

- At which position(s) do benzopyrylium ions react with nucleophiles, for example water?
- What is the typical structure of an anthocyanin flower pigment? What is the typical structure of a flavone flower pigment?
- At which atom do coumarins and chromones protonate?
- At which positions do coumarins and chromones undergo electrophilic substitution?
- Describe a cycloaddition reaction in which (i) a coumarin and (ii) a chromone take part.
- How could one construct a 1-benzopyrylium salt from a phenol?
- How can *ortho*-hydroxyaryl aldehydes be used to prepare coumarins?
- How can *ortho*-hydroxyaryl ketones be used to prepare chromones?

More advanced exercises

- When salicylaldehyde and 2,3-dimethyl-1-benzopyrylium chloride are heated together in acid, a condensation product $C_{18}H_{15}O_2^+ Cl^-$ is formed. Treatment of the salt with a weak base (pyridine) generates a neutral compound, $C_{18}H_{14}O_2$. Suggest structures for these two products.
- When ethyl 2-methylchromone-3-carboxylate is treated with NaOH, then HCl, a product $C_{11}H_8O_4$ is produced which does not contain a carboxylic acid group but does dissolve in dilute alkali: suggest a structure and the means whereby it could be formed.
- Deduce the structures of intermediate and final product in the sequence: salicylaldehyde/MeOCH₂CO₂Na/Ac₂O/heat → $C_{10}H_8O_3$, this then with 1 mol equivalent of PhMgBr → $C_{16}H_{14}O_3$ and finally this with HCl → $C_{16}H_{13}O_2^+ Cl^-$.
- Predict the structure of the major product from the interaction of resorcinol (1,3-dihydroxybenzene) and (i) PhCOCH₂COMe in AcOH/HCl; (ii) methyl 2-oxocyclopentanecarboxylate/H₂SO₄.

References

- (a) 'The chemistry of plant pigments', Chichester, C. O., Ed., Academic Press, NY, **1972**;
(b) 'The chemistry of anthocyanins, anthocyanidins, and related flavylum salts', Iacobucci, G. A. and Sweeny, J. E., *Tetrahedron*, **1983**, 39, 3005.
- 'Natürlich vorkommende chromone', Schmid, H., *Fortschr. Chem. Org. Naturst.*, **1954**, 11, 124.
- 'The flavonoids', Harborne, J. B., Mabry, T. J., and Mabry, H., Eds., Chapman and Hall, London, **1975**; 'Flavonoids: chemistry and biochemistry', Morita, N. and Arisawa, M., *Heterocycles*, **1976**, 4, 373; 'The flavonoids: advances in research since 1980', Harborne, J. B. and Mabry, T. J., Eds., Chapman and Hall, London & NY, **1988**.
- 'Synthesis of coumarins with 3,4-fused ring systems and their physiological activity', Darbarwar, M. and Sundaramurthy, V., *Synthesis*, **1982**, 337; 'Naturally occurring coumarins', Dean, F. M., *Fortschr. Chem. Org. Naturst.*, **1952**, 9, 225; 'Naturally occurring plant coumarins', Murray, R. D. H., *Fortschr. Chem. Org. Naturst.*, **1978**, 35,

- 199; 'The natural coumarins: occurrence, chemistry, and biochemistry', Murray, R. D. H., Méndez, J., and Brown, S. A., Chichester, Wiley, **1982**.
5. A large proportion of work on benzo[c]pyryliums is by Russian and Hungarian workers and is described in relatively inaccessible journals, however it is well reviewed as: 'Benzo[c]pyrylium salts: syntheses, reactions and physical properties', Kuznetsov, E. V., Shcherbakova, I. V., and Balaban, A. T., *Adv. Heterocycl. Chem.*, **1990**, *50*, 157.
6. 'Isocoumarins. Developments since 1950', Barry, R. D., *Chem. Rev.*, **1964**, *64*, 229.
7. 'Heterocycles as structural units in new optical brighteners', Dorlans, A., Schellhammer, C.-W., and Schroeder, J., *Angew. Chem., Int. Ed. Engl.*, **1975**, *14*, 665.
8. Le Fèvre, R. J. W., *J. Chem. Soc.*, **1929**, 2771.
9. Holker, J. S. E. and Underwood, J. G., *Chem. Ind. (London)*, **1964**, 1865.
10. Jurd, L., *Tetrahedron*, **1966**, *22*, 2913; *ibid.*, **1968**, *24*, 4449.
11. Meyer-Dayman, M., Bodo, B., Deschamps-Valley, C., and Molho, D., *Tetrahedron Lett.*, **1978**, 3359.
12. Degani, I. and Fochi, R., *Ann. Chim. (Rome)*, **1968**, *58*, 251.
13. Hill, D. W. and Melhuish, R. R., *J. Chem. Soc.*, **1935**, 1161.
14. Jurd, L., *Tetrahedron*, **1969**, *25*, 2367.
15. Sutton, R., *J. Org. Chem.*, **1972**, *37*, 1069.
16. Dimroth, K. and Odenwälder, H., *Chem. Ber.*, **1971**, *104*, 2984.
17. Lowenbein, A., *Chem. Ber.*, **1924**, *57*, 1517.
18. Pomilio, A. B., Müller, O., Schilling, G., and Weinges, K., *Justus Liebigs Ann. Chem.*, **1977**, 597.
19. Kröhnke, F. and Dickoré, K., *Chem. Ber.*, **1959**, *92*, 46.
20. Jurd, L., *Tetrahedron*, **1965**, *21*, 3707.
21. Shcherbakova, I. V., Kuznetsov, E. V., Yudilevich, I. A., Kompan, O. E., Balaban, A. T., Abolin, A. H., Polyakov, A. V., and Struchkov, Yu. T., *Tetrahedron*, **1988**, *44*, 6217; Le Roux, J.-P., Desbene, P.-L., and Cherton, J.-C., *J. Heterocycl. Chem.*, **1981**, *18*, 847.
22. Lee, Y.-G., Ishimaru, K., Iwasaki, H., Okhata, K., and Akiba, K., *J. Org. Chem.*, **1991**, *56*, 2058.
23. Marathe, K. G., Philbin, E. M., and Wheeler, T. S., *Chem. Ind. (London)*, **1962**, 1793.
24. Clark-Lewis, J. W. and Baig, M. I., *Aust. J. Chem.*, **1971**, *24*, 2581.
25. Müller, A., Lempert-Streter, M., and Karczag-Wilhelms, A., *J. Org. Chem.*, **1954**, *19*, 1533.
26. Heilbron, I. M. and Zaki, A., *J. Chem. Soc.*, **1926**, 1902.
27. 'A curious brew', Allen, M., *Chem. Brit.*, **1996** (May), 35.
28. 'Structure, stability and color variation of natural anthocyanins', Goto, T., *Fortschr. Chem. Org. Naturst.*, **1987**, *52*, 113; Goto, T. and Kondo, T., 'Structure and molecular stacking of anthocyanins - flower colour variation', *Angew. Chem., Int. Ed. Engl.*, **1991**, *30*, 17; 'The chemistry of rose pigments', Eugster, C. H. and Märki-Fischer, E., *ibid.*, 654; 'Nature's palette', Haslam, E., *Chem. Brit.*, **1993** (Oct.), 875.
29. Wittig, G., Baugert, F., and Richter, H. E., *Justus Liebigs Ann. Chem.*, **1925**, 446, 155.
30. Meerwein, H., Hinz, G., Hofmann, P., Kroenigard, E., and Pfeil, E., *J. Prakt. Chem.*, **1937**, *147*, 257.
31. Clayton, A., *J. Chem. Soc.*, **1910**, 2106; Joshi, P. P., Ingle, T. R., and Bhide, B. V., *J. Ind. Chem. Soc.*, **1959**, *36*, 59.
32. Wiley, P. F., *J. Am. Chem. Soc.*, **1952**, *74*, 4326.
33. Zhang, F. J. and Li, Y. L., *Synthesis*, **1993**, 565.
34. Dean, F. M. and Murray, S., *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1706.
35. Pearson, D. E., Stamper, W. E., and Suthers, B. R., *J. Org. Chem.*, **1963**, *28*, 3147.
36. Fuson, R. C., Kneisley, J. W. and Kaiser, E. W., *Org. Synth., Coll. Vol. III*, **1955**, 209; Perkin, W. H., *Justus Liebigs Ann. Chem.*, **1871**, 157, 115.
37. Thapliyal, P. C., Singh, P. K., and Khauna, R. N., *Synth. Commun.*, **1993**, *23*, 2821.
38. Ellis, G. P. and Thomas, I. L., *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2781.
39. Arndt, F., *Chem. Ber.*, **1925**, *58*, 1612.
40. For the use of singlet oxygen see Matsuura, T., *Tetrahedron*, **1977**, *33*, 2869.
41. Adam, W., Golsch, D., Hadjarapoglou, L., and Patonay, T., *J. Org. Chem.*, **1991**, *56*, 7292; Adam, W., Hadjarapoglou, L., and Levai, A., *Synthesis*, **1992**, 436.
42. Muller, E., *Chem. Ber.*, **1909**, *42*, 423.
43. Sugita, Y. and Yokoe, I., *Heterocycles*, **1996**, *43*, 2503.

44. Shriner, R. C. and Sharp, A. G., *J. Org. Chem.*, **1939**, 4, 575; Hepworth, J. D. and Livingstone, R., *J. Chem. Soc., C*, **1966**, 2013.
45. Reynolds, G. A., VanAllan, J. A., and Petropoulos, C. C., *J. Heterocycl. Chem.*, **1970**, 7, 1061.
46. Goswami, M. and Chakravarty, A., *J. Ind. Chem. Soc.*, **1932**, 9, 599; Michaelidis, Ch. and Wizinger, R., *Helv. Chim. Acta*, **1951**, 34, 1761.
47. Costa, A. M. B. S. R. C. S., Dean, F. M., Jones, M. A., and Varma, R. S., *J. Chem. Soc., Perkin Trans. 1*, **1985**, 799.
48. Hoshino, Y., Miyaura, N., and Suzuki, A., *Bull. Chem. Soc. Jpn.*, **1988**, 61, 3008; Yanagi, T., Oh-e, T., Miyaura, N., and Suzuki, A., *ibid.*, **1989**, 62, 3892.
49. Kirkiacharian, B. S. and Raulais, D., *Bull. Soc. Chim. Fr.*, **1970**, 1139.
50. Smith, L. I. and Denyes, R. O., *J. Am. Chem. Soc.*, **1936**, 58, 304; John, W., Günther, P., and Schmeil, M., *Chem. Ber.*, **1938**, 71, 2637.
51. Elhabiri, M., Figueiredo, P., Fougerousse, A., and Brouillard, R., *Tetrahedron Lett.*, **1995**, 36, 4611.
52. Adams, R., McPhee, W. D., Carlin, R. B., and Wicks, Z. W., *J. Am. Chem. Soc.*, **1943**, 65, 356; Adams, R. and W. D., Carlin, R. B., *ibid.*, 360.
53. Ghosh, C. K., Tewari, N., and Bhattacharya, A., *Synthesis*, **1984**, 614; Coutts, S. J. and Wallace, T. W., *Tetrahedron*, **1994**, 50, 11755.
54. Wallace, T. W., Wardell, I., Li, K.-D., Leeming, P., Redhouse, A. D., and Challand, S. R., *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2293.
55. Ohkata, K., Kubo, T., Miyamoto, K., Ono, M., Yamamoto, J., and Akiba, K., *Heterocycles*, **1994**, 38, 1483.
56. Bush, E. J., Jones, D. W., and Ryder, T. C. L. M., *J. Chem. Soc., Perkin Trans. 1*, **1997**, 1929.
57. Plüg, C., Friedrichsen, W., Debaerdemaecker, T., *J. prakt. Chem.*, **1997**, 339, 205.
58. Schenk, G. O., von Willucki, I., and Krauch, C. H., *Chem. Ber.*, **1962**, 95, 1409; Anet, R., *Canad. J. Chem.*, **1962**, 40, 1249; Hammond, G. S., Stout, C. A., and Lamola, A. A., *J. Am. Chem. Soc.*, **1964**, 86, 3103.
59. Krauch, C. H., Farid, S., and Schenk, G. O., *Chem. Ber.*, **1966**, 99, 625.
60. Hanifen, J. W. and Cohen, E., *Tetrahedron Lett.*, **1966**, 1419; Kobayashi, K., Suzuki, M., and Sugimoto, H., *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2837.
61. Heilbron, I. M., Barnes, H., and Morton, R. A., *J. Chem. Soc.*, **1923**, 2559.
62. Archer, R. A., Blanchard, W. B., Day, W. A., Johnson, D. W. Lavagnino, E. R., Ryan, C. W., and Baldwin, J. E., *J. Org. Chem.*, **1977**, 42, 2277.
63. Mahal, H. S. and Venkataraman, K., *J. Chem. Soc.*, **1933**, 616.
64. Bülow, C. and Wagner, H., *Chem. Ber.*, **1901**, 34, 1189.
65. Bülow, C. and Wagner, H., *Chem. Ber.*, **1901**, 34, 1782; Sweeny, J. G. and Iacobucci, G. A., *Tetrahedron*, **1981**, 37, 1481.
66. Johnson, A. W. and Melhuish, R. R., *J. Chem. Soc.*, **1947**, 346.
67. Robinson, R. and Walker, J., *J. Chem. Soc.*, **1934**, 1435.
68. Bigi, F., Casiraghi, G., Casnati, G., and Sartori, G., *J. Heterocycl. Chem.*, **1981**, 18, 1325.
69. Pratt, D. D. and Robinson, R., *J. Chem. Soc.*, **1923**, 745.
70. 'The Pechmann reaction', Sethna, S. and Phadke, R., *Org. React.*, **1953**, 7, 1.
71. Sen, H. K. and Basu, U., *J. Ind. Chem. Soc.*, **1928**, 5, 467.
72. Russell, A. and Frye, J. R., *Org. Synth., Coll. Vol. III*, **1955**, 281.
73. Dann, O. and Mylius, G., *Justus Liebigs Ann. Chem.*, **1954**, 587, 1.
74. John, E. V. O. and Israelstam, S. S., *J. Org. Chem.*, **1961**, 26, 240.
75. Lacey, R. N., *J. Chem. Soc.*, **1954**, 854.
76. Trost, B. M. and Toste, F. D., *J. Am. Chem. Soc.*, **1996**, 118, 6305.
77. Crawford, M. and Shaw, J. A. M., *J. Chem. Soc.*, **1953**, 3435.
78. Dauzonne, D. and Royer, R., *Synthesis*, **1983**, 836.
79. Harayama, T., Nakatsuka, K., Nishioka, H., Murakami, K., Hayashida, N., and Ishii, H., *Chem. Pharm. Bull.*, **1994**, 42, 2170.
80. Mali, R. S. and Yadav, V. J., *Synthesis*, **1977**, 464.
81. Steck, W., *Canad. J. Chem.*, **1971**, 49, 2297.
82. Horning, E. C., Horning, M. G., and Dimmig, D. A., *Org. Synth., Coll. Vol. III*, **1955**, 165.
83. Brufola, G., Friguelli, F., Piermatti, O., and Pizzo, F., *Heterocycles*, **1996**, 43, 1257.
84. Rouessac, F. and Leclerc, A., *Synth. Commun.*, **1993**, 23, 1147.

85. Arcadi, A., Cacchi, S., Fabrizi, G., Marinelli, F., and Pace, P., *Synlett*, **1996**, 568.
86. Wiley, P. F., *J. Am. Chem. Soc.*, **1952**, 74, 4329; Schmutz, J., Hirt, R., and Lauener, H., *Helv. Chim. Acta*, **1952**, 35, 1168; Mozingo, R., *Org. Synth., Coll. Vol. III*, **1955**, 387; Hirao, I., Yamaguchi, M., and Hamada, M., *Synthesis*, **1984**, 1076; Banerji, H. and Goomer, N. C., *ibid.*, **1980**, 874.
87. Looker, J. H., McMechan, J. H., and Mader, J. W., *J. Org. Chem.*, **1978**, 43, 2344.
88. Baker, W., *J. Chem. Soc.*, **1933**, 1381; Schmid, H. and Banholzer, K., *Helv. Chim. Acta*, **1954**, 37, 1706.
89. Wheeler, T. S., *Org. Synth., Coll. Vol. IV*, **1963**, 478.
90. Riva, C., De Toma, C., Donadel, L., Boi, C., Peunini, R., Motta, G., and Leonardi, A., *Synthesis*, **1997**, 195.
91. Becket, G. J. P., Ellis, G. P., and Trindade, M. I. U., *J. Chem. Res.*, **1978** (S) 47; (M) 0865.
92. Bass, R. J., *J. Chem. Soc., Chem. Commun.*, **1976**, 78.
93. Baker, W., Chadderton, J., Harborne, J. B., and Ollis, W. D., *J. Chem. Soc.*, **1953**, 1852.
94. Boyd, J. and Robertson, A., *J. Chem. Soc.*, **1948**, 174.
95. Davis, S. E., Church, A. C., Tummons, R. C., and Beam, C. F., *J. Heterocycl. Chem.*, **1997**, 34, 1159.
96. Morris, J., Wishka, D. G., and Fang, Y., *Synth. Commun.*, **1994**, 24, 849.
97. Harnisch, H., *Justus Liebigs Ann. Chem.*, **1972**, 765, 8; Nohara, A., Umetani, T., and Sanno, Y., *Tetrahedron*, **1974**, 30, 3553.
98. Gammill, R. B., *Synthesis*, **1979**, 901; *Chem. Pharm. Bull.*, **1994**, 42, 1697.
99. Geissman, T. A. and Clinton, R. O., *J. Am. Chem. Soc.*, **1946**, 68, 697.
100. Lorette, N. B., Gage, T. B., and Wender, S. H., *J. Org. Chem.*, **1951**, 16, 930; Schönberg, A. and Schutz, G., *Chem. Ber.*, **1960**, 93, 1466; Patonay, T., Cavaleiro, J. A. S., Lévai, A., and Silva, A. M. S., *Heterocycl. Commun.*, **1997**, 3, 223; Bernini, R., Mincione, E., Sanetti, A., Bovicelli, P., and Lupattelli, P., *Tetrahedron Lett.*, **1997**, 38, 4651; Prakash, O. and Tanwer, M. P., *J. Chem. Res (S)*, **1995**, 143, (M), 1429; Litkei, G., Gulácsis, K., Antus, A., and Blaskó, G., *Justus Liebigs Ann. Chem.*, **1995**, 1711.
101. Coppola, G. M. and Dodsworth, R. W., *Synthesis*, **1981**, 523; Cremins, P. J., Hayes, R., and Wallace, T. W., *Tetrahedron*, **1993**, 49, 3211.
102. Torii, S., Okumoto, H., Xu, L. H., Sadakane, M., Shostakovsky, M. V., Ponomaryov, A. B., and Kalinin, V. N., *Tetrahedron*, **1993**, 49, 6773.
103. Nakatani, K., Okamoto, A., and Saito, I., *Tetrahedron*, **1996**, 52, 9427.
104. Bhat, A. S., Whetstone, J. L., and Brueggemeier, R. W., *Tetrahedron Lett.*, **1999**, 40, 2469.
105. Blount, B. K. and Robinson, R., *J. Chem. Soc.*, **1933**, 555.
106. Bringmann, G. and Jansen, J. R., *Justus Liebigs Ann. Chem.*, **1985**, 2116.
107. Schöpf, C. and Kühne, R., *Chem. Ber.*, **1950**, 83, 390.
108. Korte, D. E., Hegedus, L. S., and Wirth, R. K., *J. Org. Chem.*, **1977**, 42, 1329.
109. Larock, R. C., Varaprath, S., Lau, H. H., and Fellows, C. A., *J. Am. Chem. Soc.*, **1984**, 106, 5274.
110. Larock, R. C. and Harrison, L. W., *J. Am. Chem. Soc.*, **1984**, 106, 4218.
111. Liao, H.-Y. and Cheng, C.-H., *J. Org. Chem.*, **1995**, 60, 3711; Larock, R. C., Yum, E. K., Doty, M. J., and Sham, K. K. C., *ibid.*, 3270.
112. Sakamoto, T., Kondo, Y., Yasuhara, A., and Yamanaka, H., *Tetrahedron*, **1991**, 47, 1877.
113. Willstätter, R., Zechmeister, L., and Kindler, W., *Chem. Ber.*, **1924**, 47, 1938.
114. Nagarathnam, D. and Cushman, M., *J. Org. Chem.* **1991**, 56, 4884.
115. Gothelf, K., Thomsen, I., and Torssell, K. B. G., *Acta Chem. Scand.*, **1992**, 46, 494; Gothelf, K. V. and Torssell, K. B. G., *ibid.*, **1994**, 48, 165; Ellemose, S., Kure, N., and Torssell, K. B. G., *ibid.*, **1995**, 49, 524.