Synthesis of aromatic heterocycles

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REVIEW PERKIN 1

Covering: March 1995 to February 1997

Previous review: *Contemp. Org. Synth.*, 1995, 2, 337

1 Introduction

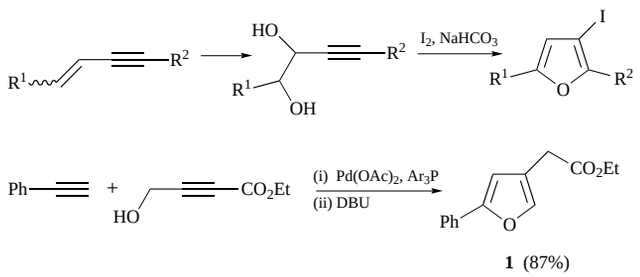
This review, the third in the series,[1] is a selection of new and improved methods for the formation of aromatic heterocycles from acyclic precursors or from other ring systems. The review is largely restricted to monocyclic and benzo-fused heterocycles.

A feature of the literature in the period covered by this review is the number of publications that describe combinatorial methods. Some examples are the formation of pyrroles by dipolar addition of polymer bound münchnones to alkynes,[2] Fischer indole syntheses,[3] Heck reactions leading to indoles[4] and preparations of thiophenes,[5] quinolines[6,7] and pyrimidines.[8] Many combinatorial syntheses of aromatic heterocycles are also described in two reviews.[9,10]

Intramolecular Wittig and aza-Wittig reactions are useful for the formation of several classes of aromatic heterocycles and both reactions have been reviewed.[11,12] The intramolecular Heck reaction is proving increasingly useful as a method of synthesis of indoles and other benzo-fused heterocycles and recent examples have been reviewed.[13] A review of intramolecular McMurry coupling as a method of pyrrole and indole ring synthesis has also appeared.[14]

2 Furans and benzofurans

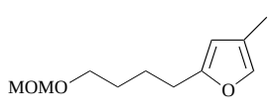
Cyclisation reactions of alkynes continue to provide useful methods of synthesis of furans. Bew and Knight have described a route to 3-iodofurans from conjugated enynes in which the double bond is first hydroxylated and the resulting diol is then cyclised with iodine (**Scheme 1**).[15] A related palladium(II)-catalysed cyclisation, leading to di- and tri-substituted furans, is illustrated by the synthesis of ethyl 5-phenylfuran-3-acetate **1**.[16] Earlier examples of the *endo*-cyclisation of β-hydroxy alkynes to furans have been brought about by a strong base such as potassium *tert*-butoxide, but the ring closure can also be achieved using silver nitrate on silica. This is useful for preparing furans, such as **2**, that bear a base sensitive protecting group.[17] Some conjugated allenyl ketones have also been shown to undergo palladium-catalysed *endo*-cyclisation to 2-substituted furans.[18]



1 (87%)

Scheme 1

The ketone **3** and related compounds are converted into furans by reaction with potassium *tert*-butoxide (**Scheme 2**).[19] In an extension of a route reported earlier, furans **4** have been prepared by palladium(0)-catalysed carbonylative arylation followed by *exo*-cyclisation of acetylenic ketones.[20] A full paper on the ruthenium- or palladium-catalysed *exo*-cyclisation of hydroxyenynes **5** to 5-substituted 2,3-dimethylfurans has been published.[21]



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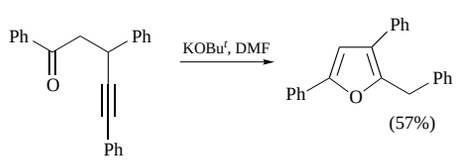

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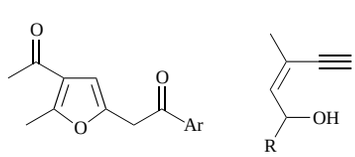
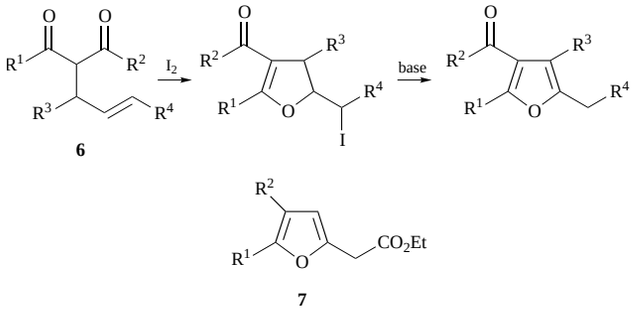
Scheme 2



4 **5**

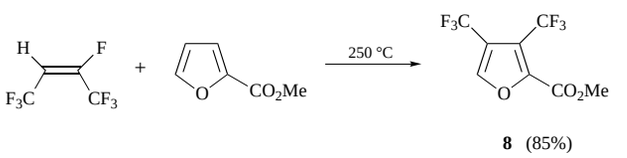
The iodine-catalysed cyclisation of the 1,3-diketones **6** provides a route to a variety of tetrasubstituted furans (**Scheme 3**).[22] There are several useful acid-catalysed cyclisations leading to 2,3,5-trisubstituted furans including the furanacetic esters **7**.[23,24]

Some 3,4-disubstituted furans are best prepared by Diels–Alder cycloaddition to simpler furans followed by retro addition, but the method is limited by the reactivity and availability of suitable acetylenic dienophiles. Chambers and co-workers have shown that heptafluorobut-2-ene is a suitable replacement for hexafluorobutyne.[25] Several furans, including the ester **8**, were formed from the appropriate furan and this fluoroalkene



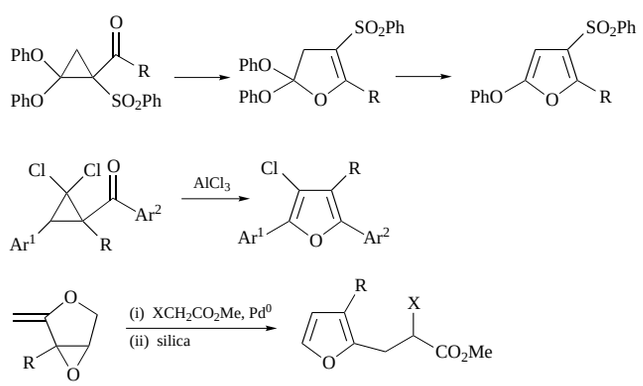
Scheme 3

when they were heated together in a sealed tube at 200–300 °C (**Scheme 4**).



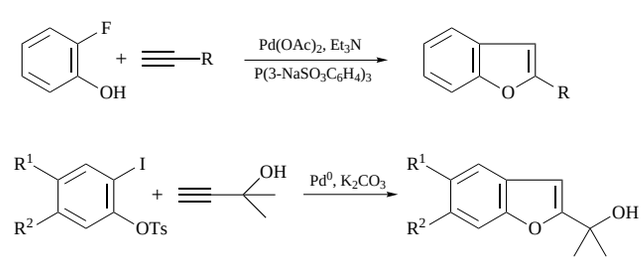
Scheme 4

Methods of furan synthesis based on the ring expansion of cyclopropyl ketones[26,27] and on the ring opening of oxiranes[28,29] are illustrated in **Scheme 5**.



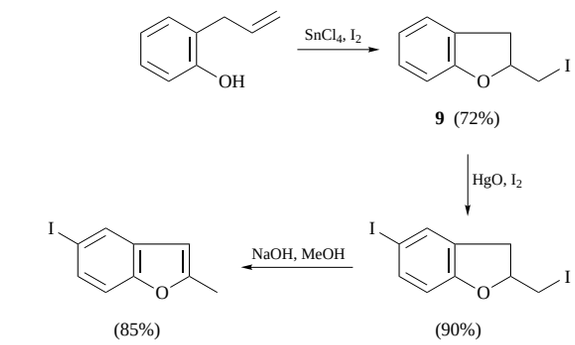
Scheme 5

2-Halophenols undergo palladium-catalysed coupling with terminal alkynes to give 2-alkynylphenols. These phenols have been shown to be converted into 2-substituted benzofurans by *endo*-cyclisation; two further illustrations of the methodology are shown in **Scheme 6**.[30,31] A related synthesis of 3-methylbenzofuran from 2-methoxyacetophenone has been described.[32]

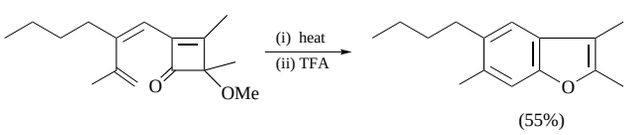


Scheme 6

The intermediate **9** formed from 2-allylphenol by cyclisation with iodine can be converted into 2-methylbenzofuran by reaction with sodium hydroxide, but it is also possible to iodinate it at C-5 in high yield before dehydrohalogenation (**Scheme 7**).[33] 3-Substituted benzofurans are conveniently prepared by intramolecular Heck reactions[13] and the method has been applied to the synthesis of chiral benzofurans by incorporating a chiral auxiliary into the precursor.[34] Polysubstituted benzofurans can be prepared by the rearrangement of dienylcyclobutenones; an example is shown in **Scheme 8**.[35] Benzofuran-3-acetic acid has been prepared by base-catalysed ring contraction of 4-chloromethylcoumarin.[36]

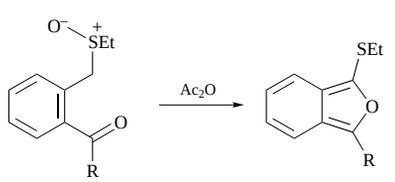


Scheme 7

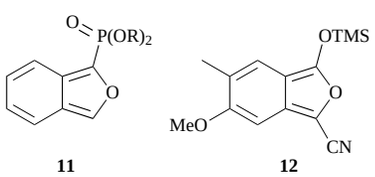


Scheme 8

Several new syntheses of isobenzofurans have been reported. Padwa and co-workers have made use of the Pummerer reaction to generate ethylthiobenzofurans **10** (**Scheme 9**)[37] and related *c*-fused furans.[38] The isobenzofuran **10** (R = Ph) was isolated by rapid chromatography, but in most cases these and other 1-(alkylthio)benzofurans[39] were intercepted by Diels–Alder cycloaddition. The isobenzofurans **11**[40] and **12**[41] have also been generated and trapped with dienophiles.



Scheme 9

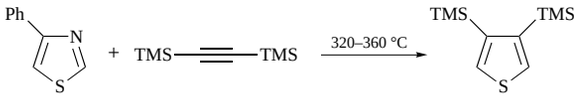


11 **12**

Dibenzofurans can be prepared from 2-phenoxybenzenediazonium salts by Pschorr ring closure. Iron(II) sulfate has been found to greatly improve the yield and to decrease the reaction time for this process.[42]

3 Thiophenes and benzothiophenes

Diels–Alder reactions of thiazoles have hitherto been virtually unknown, but 4-phenylthiazole has recently been shown to undergo Diels–Alder cycloaddition to bis(trimethylsilyl)acetylene and to some other alkynes in the temperature range 320–360 °C. The products isolated are 3,4-disubstituted thiophenes, such as **13**, formed by elimination of benzonitrile (**Scheme 10**).[43]

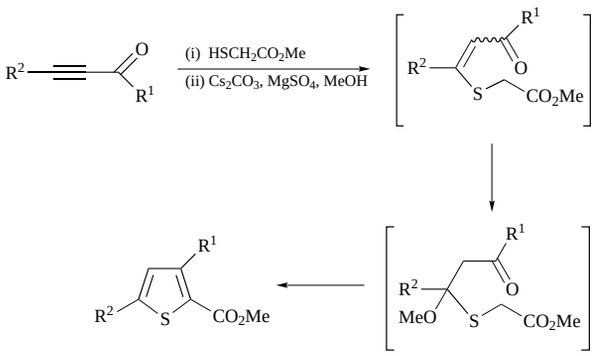


13 (92%)

Scheme 10

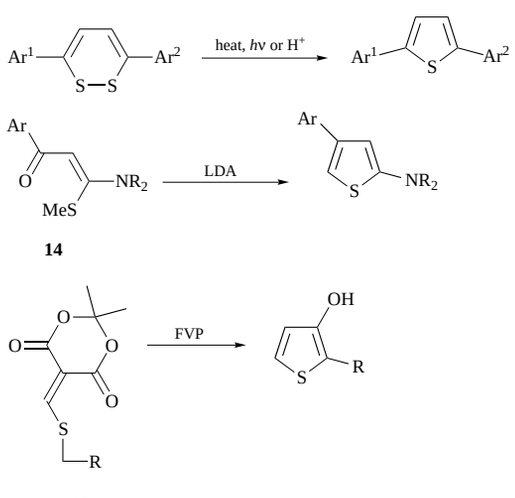
The trimethylsilyl substituents in the thiophene **13** can then be replaced by other substituents.

A good route to methyl thiophene-2-carboxylates is provided by the reaction sequence shown in **Scheme 11**.[44] Successive conjugate addition of methyl thioglycolate and methanol to the triple bond of an alkynone produces an intermediate suitable for intramolecular Knoevenagel condenstion.



Scheme 11

Some less general routes to thiophenes are shown in **Scheme 12**. 2,5-Diarylthiophenes are easily produced from the corresponding 1,2-dithiins by extrusion of sulfur.[45] 2-Dialkylaminothiophenes have been produced from the enones **14** by reaction with LDA[46] and 3-hydroxythiophenes are isolated in good yield from the flash vacuum pyrolysis of the Meldrum's acid derivatives **15**.[47]



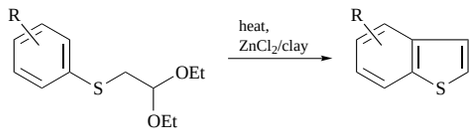
14

15

Scheme 12

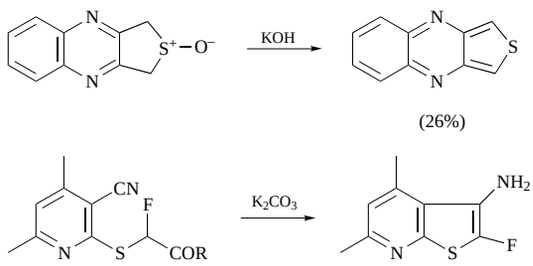
The synthesis of benzothiophenes by cyclisation of phenylthioacetals **16** (**Scheme 13**) is significantly improved by using zinc chloride impregnated montmorillonite clay for the cyclisation.[48] For example, under the best conditions 7-methylbenzothiophene was obtained in 85% yield, and 5-bromobenzothiophene in 87% yield.

Routes to two ring systems in which thiophene is fused to a six-membered heterocycle are shown in **Scheme 14**. Thieno[3,4-*b*]quinoxaline was isolated as acid sensitive orange crystals from the reaction of the corresponding dihydrothiophene *S*-oxide with potassium hydroxide[49] and the thieno[2,3-*b*]pyridine **17** was obtained in good yield from the base-catalysed cyclisation of the cyanopyridines **18** (R = Me or OEt).[50]



16

Scheme 13



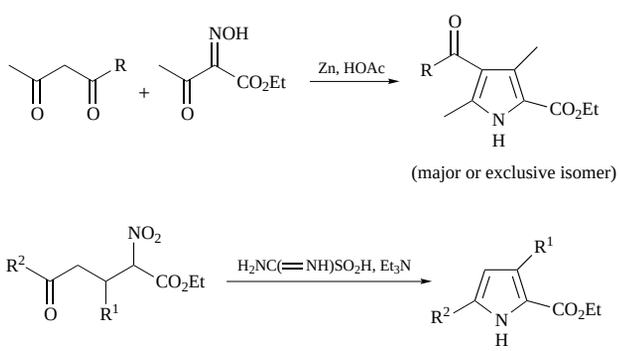
18 **17**

Scheme 14

4 Pyrroles

The classical methods of pyrrole ring synthesis continue to be widely used, and several variations in the methodology have been reported that either give new types of pyrroles or result in improved yields. For example, 1-aminopyrroles have been prepared cleanly in a Paal–Knorr reaction from alkoxycarbonylhydrazines and 1,4-dicarbonyl compounds, followed by removal of the alkoxycarbonyl protecting group.[51] Several 3-substituted pyrroles have also been prepared by a variation of the Paal–Knorr method in which 3-cyanopropionaldehyde acetals are intermediates.[52] 2,5-Dimethoxytetrahydrofuran reacts with a variety of amines to give 1-substituted pyrroles. A survey of a variety of catalysts for this reaction resulted in the selection of phosphorus pentoxide as the most efficient.[53] The reaction can be carried out using chiral amino acids as the amine components but the resulting 1-substituted pyrroles often show evidence of partial racemisation. Jefford and coworkers have found that this racemisation can be avoided by carrying out the reaction in a two phase system.[54]

The regioselectivity of the Knorr pyrrole synthesis with ethyl hydroxyiminoacetoacetate and unsymmetrical β-diketones has been studied.[55] The major or exclusive product has the larger alkyl substituent of the diketone incorporated as the 4-acyl substituent of the pyrrole (**Scheme 15**). An alternative method of producing unsymmetrical substituted pyrroles from hydroxyimino esters is also shown. This makes use of α-nitro esters as starting materials, these being reduced to the corresponding

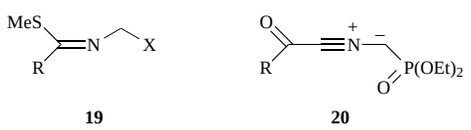


(major or exclusive isomer)

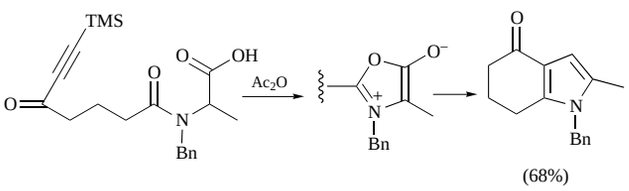
Scheme 15

oximes with formamidinesulfinic acid.[56] In a variant of the standard Knorr synthesis, ethyl hydroxyiminoacetoacetate was reduced electrolytically in the presence of an excess of ethyl acetoacetate.[57]

Two more recent methods of pyrrole ring synthesis that have become well established are 1,3-dipolar cycloaddition reactions of azomethine ylides or nitrile ylides to alkenes or alkynes and cyclisation reactions of isocyanides. There are several examples of pyrrole synthesis from thioimidates **19** (X = CO_2Et[58] or 1-benzotriazolyl[59]) and activated alkenes. The nitrile ylide **20** has been generated and its reaction with β-nitrostyrenes used as a route to pyrrole-2-phosphonic esters.[60] The regioselectivity of the cycloaddition of nitroalkenes to münchnones has been investigated[61] and some intramolecular additions of münchnones to alkynes have been explored as a route to bicyclic pyrroles; an example is shown in **Scheme 16**.[62]

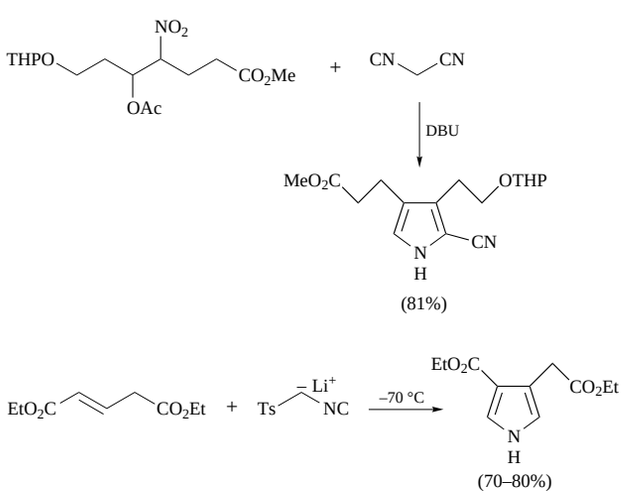


19 **20**



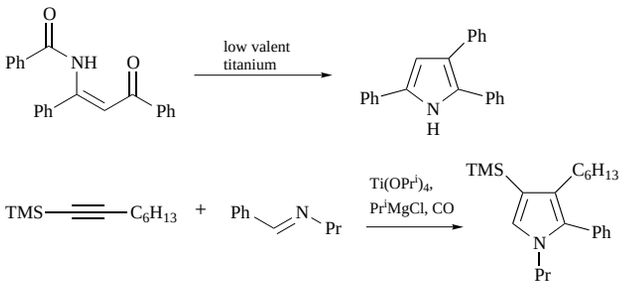
Scheme 16

Among the many new reports of the use of isocyanides in pyrrole synthesis, two have been specifically designed to provide a route to porphobilinogen.[63,64] The initial pyrrole syntheses are illustrated in **Scheme 17**. The methodology has been applied to a variety of other 3-substituted pyrroles including 3-nitro-,[65] 3-ethynyl-[66] and 3-(1-naphthyl)pyrroles.[67] Pyrroles of the last type are axially dissymmetric and can be resolved; they were used as catalysts for the enantioselective addition of diethylzinc to aromatic aldehydes.



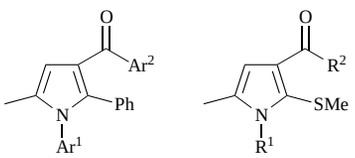
Scheme 17

The low valent titanium coupling of acylamino ketones, which has been shown to provide an excellent route to some indoles, has also been applied to pyrrole synthesis.[68] For example, 2,3,5-triphenylpyrrole was prepared (78%) by this method (**Scheme 18**). Titanium–acetylene complexes are intermediates in the synthesis of pyrroles from alkynes, imines and carbon monoxide with titanium isopropoxide and isopropylmagnesium chloride; an example is shown in Scheme 18.[69]

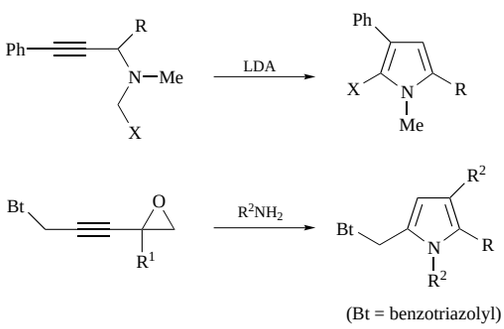


Scheme 18

Several syntheses of pyrroles involve *endo*- or *exo*-cyclisation on to a triple bond in the ring forming step. A full report of the reaction of 4-arylamino-1-azadienes and prop-2-ynyl bromide, which leads to pyrroles such as **21** in high yield by *exo*-cyclisation, has been published.[70] A related reaction of acylketene *N*,*S*-acetals with prop-2-ynyl bromide, catalysed by copper(I) bromide, provides a route to the pyrroles **22**.[71] Two examples of pyrrole synthesis by *endo*-cyclisation on to a triple bond are given in **Scheme 19**.[72,73]



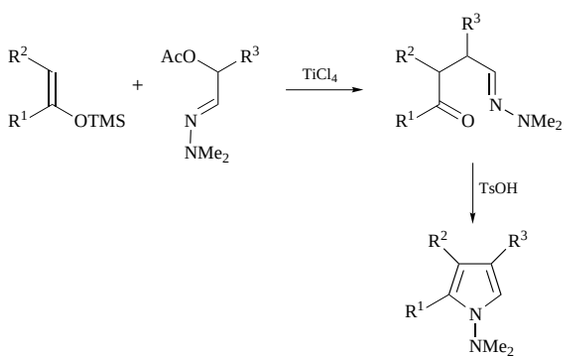
21 **22**



(Bt = benzotriazolyl)

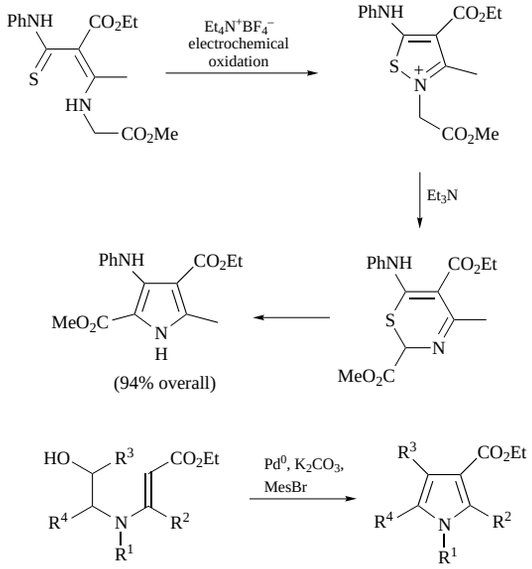
Scheme 19

A new synthesis of pyrroles from α-acetoxyaldehyde dimethylhydrazones and enol ethers, catalysed by titanium(IV) chloride, is illustrated in **Scheme 20**.[74] The preparation of pyrroles from azo alkenes and activated methylene compounds, which has been extensively investigated by Attanasi and co-workers,[75] is mechanistically quite similar, and further examples of the synthesis of 1-acylaminopyrroles by this method have been reported.[76]



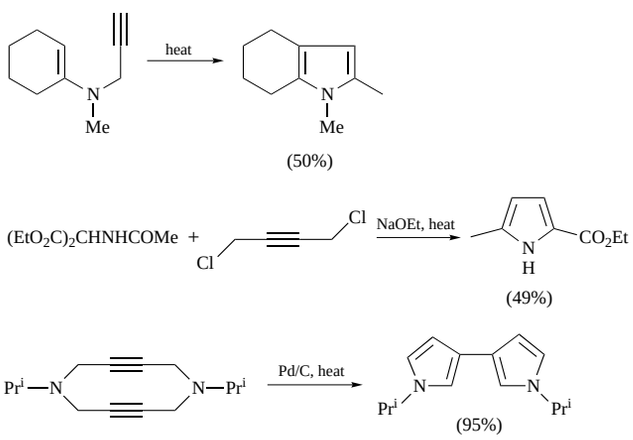
Scheme 20

A useful one pot synthesis of tetrasubstituted pyrroles from unsaturated thioamides involves isothiazolium salts as intermediates (**Scheme 21**).[77] The conversion of the isothiazolium salts into pyrroles involves extrusion of sulfur from a 1,3-thiazine.[78] The reaction is thus another example of the ring contraction of thiazines to pyrroles. A new synthesis of di-, tri- and tetra-substituted pyrroles also illustrated in Scheme 21 is the oxidative cyclisation of β-hydroxyenamines in the presence of a palladium(0) catalyst.[79]



Scheme 21

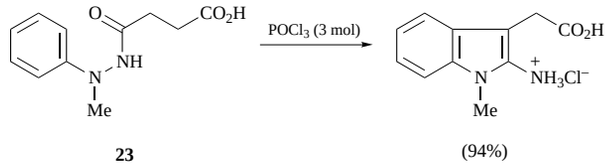
For those who enjoy mechanistic problems, the reaction pathways for the three pyrrole syntheses shown in **Scheme 22** should provide interesting exercises.[80,81,82]



Scheme 22

5 Indoles and other fused pyrroles

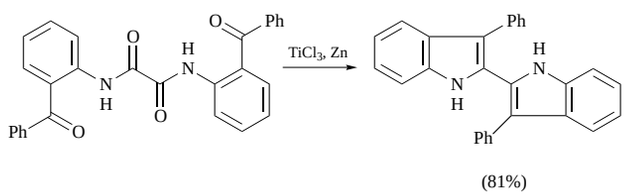
A few recent syntheses of indoles make use of simple anilines and related monosubstituted benzenes as starting materials. *N*-Alkylanilines react with triethanolamine when heated at 180 °C with a homogeneous ruthenium catalyst to give 1-alkylindoles; for example, *N*-methylaniline gives 1-methylindole in 78% yield.[83] Azobenzenes react with acetylene in the presence of Wilkinson's catalyst [$RhCl(PPh_3)_3$] to give 1-(arylamino)-indoles in good yield.[84] 2-Methyl-1-tosylindole has been obtained (66%) from the reaction of *N*-lithio-*N*-tosylaniline with the iodonium salt phenylpropynyliodonium triflate.[85] The acylhydrazine **23** gave 2-amino-1-methylindole-3-acetic acid (as the hydrochloride salt) in high yield when heated with an excess of phosphorus oxychloride (**Scheme 23**).[86]



23 (94%)

Scheme 23

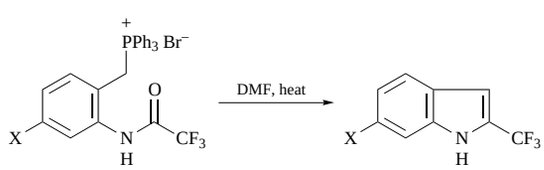
The original Madelung synthesis of 2,2′-biindolyl from the bis(*o*-toluoylamide) of oxalic acid has been improved; the product can be obtained in 80% yield when the amide is heated wth potassium *tert*-butoxide at 300 °C.[87] A milder route to biindolyls is represented by the intramolecular carbonylative coupling shown in **Scheme 24**.[88] This highly selective coupling is one of several examples of this type of indole synthesis. The reactions require only catalytic amounts of the low valent titanium catalyst when they are carried out in the presence of a chlorosilane.[89]



(81%)

Scheme 24

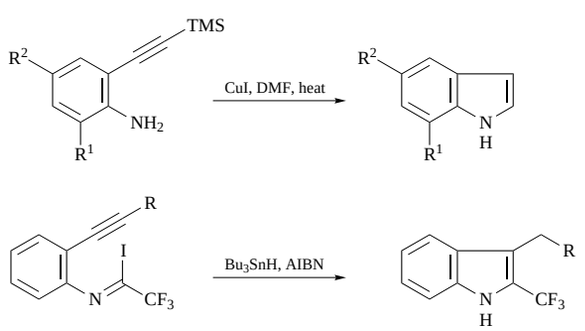
Intramolecular Wittig reactions are also useful for the synthesis of 2-substituted indoles and a 2-arylindole has been synthesised in this way from a polymer bound phosphonium salt.[90] 2-(Trifluoromethyl)indoles have also been prepared from the phosphonium salts **24** (**Scheme 25**) although, since no base was used, the authors question whether the products are formed by the intramolecular Wittig reaction.[91] 2-(Trifluoromethyl)indole has also been prepared in high yield from *N*-trimethylsilyl-*o*-toluidine, butyllithium and ethyl trifluoroacetate[92] and a similar method has been used to construct the five-membered rings of 5- and 6-azaindoles.[93]



24

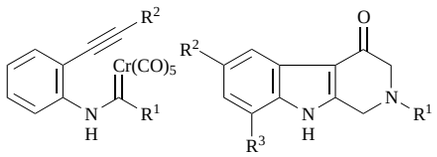
Scheme 25

Cyclisation reactions of 2-alkynylaniline derivatives continue to provide good routes to indoles. An example, shown in **Scheme 26**, provides a route to 5- and 7-substituted indoles[94] and similar *endo*-cyclisations have been used to prepare other indoles.[95,96] A radical cyclisation route to 3-alkyl-2-(trifluoromethyl)indoles is also illustrated in Scheme 26.[97] The cyclisation

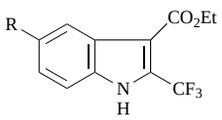


Scheme 26

of chromium aminocarbene complexes **25** provides another route to 2,3-disubstituted indoles, although the overall yields are moderate.[98]



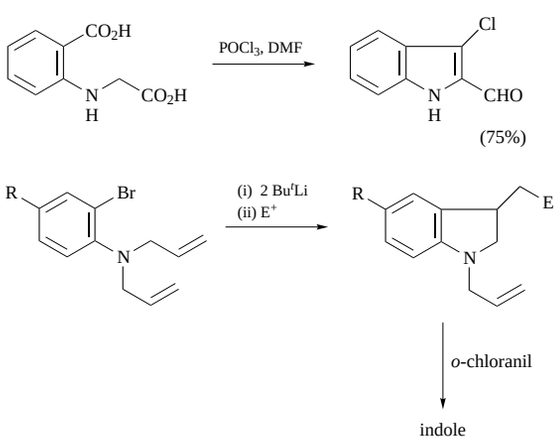
25 **26**



27

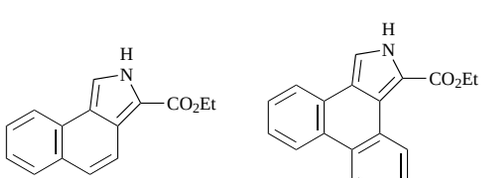
New examples of intramolecular Heck reactions leading to indoles have been described. The products are 1-acylindoles[99] and indoles having the general structures **26**[100] and **27**.[101]

An efficient one pot synthesis of 3-chloroindole-2-carbaldehyde is shown in **Scheme 27**.[102] The method is also applicable to the synthesis of the corresponding pyrroles, benzofurans and benzothiophenes. A useful route to a variety of 3-substituted indolines and indoles is also illustrated.[103,104]



Scheme 27

The isocyanide cyclisation route to pyrroles has also been applied to a number of fused pyrroles. The starting materials are a nitroarene and ethyl isocyanoacetate. The efficiency of the process depends upon the degree of double bond character in the starting nitroarene. Thus, 1-nitronaphthalene gave the ester **28** (12%) whereas 9-nitrophenanthrene gave the corresponding fused pyrrole ester **29** in 70% yield.[105]



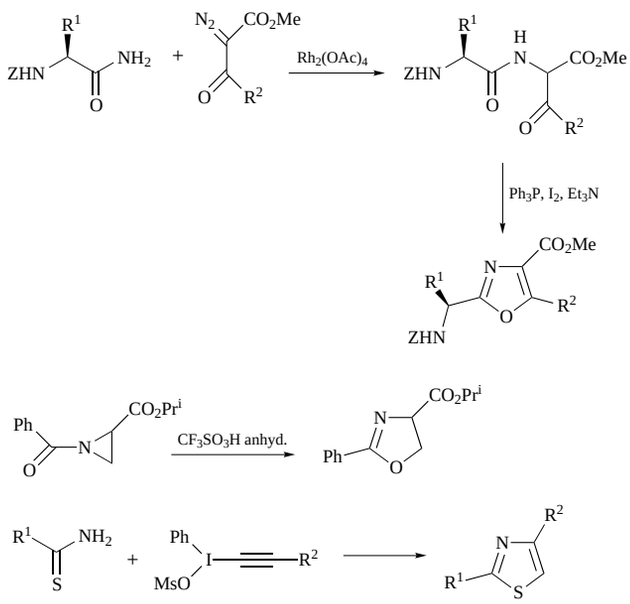
28 **29**

Although they fall outside the scope of this review, there are also several reports of useful syntheses of indoles that involve the construction or the modification of the six-membered ring.[106,107,108,109]

6 Oxazoles, thiazoles, benzoxazoles and benzothiazoles

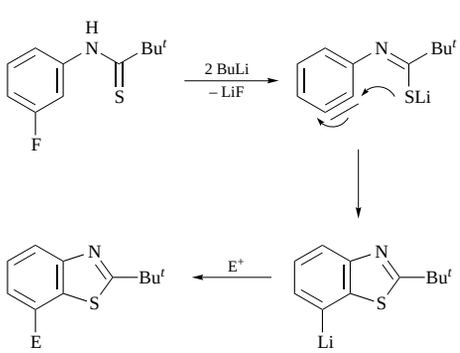
Methods of synthesis of 2,4-disubstituted oxazoles are assuming increasing significance because of the incorporation of this structural unit into several important natural products. The most popular approach has been to prepare a 2,4-disubstituted oxazoline from an *N*-β-hydroxyethyl amide by the method described earlier by Wipf and co-workers, and then to oxidise the oxazoline to an oxazole.[110,111] The oxidation step can prove difficult in this approach and several new methods have been described.[112,113,114] 2,4-Disubstituted thiazoles can be prepared by analogous procedures. It has been shown that *N*-trityl protection of an *O*-methylserine side chain during the synthesis prevents racemisation.[115]

A different method for the construction of the ring system, described by Moody and co-workers, makes use of the rhodium-catalysed insertion of carbenoids derived from diazoesters.[116] Insertion into the NH bond of a primary amide provides an intermediate suitable for cyclisation (**Scheme 28**). Other examples of oxazole and thiazole synthesis from diazocarbonyl compounds have been described.[117,118] 2,4-Disubstituted isoxazolines have also been made by the ring expansion of *N*-acylaziridines, as illustrated in Scheme 28. Anhydrous trifluoromethanesulfonic acid has been recommended as the catalyst for this ring expansion.[119] A new route to some 2,4-disubstituted thiazoles is also shown in Scheme 28.[120] 4-Substituted 2-phenyloxazole-5-carboxylates have been prepared by the reaction of *N*-benzoylamino acids with an excess of oxalyl chloride.[121]



Scheme 28

A method of synthesis of benzo-fused heterocycles that has not been widely used in recent years is intramolecular aryne addition. An application of the method to the synthesis of benzothiazoles has been described (**Scheme 29**), the aryne pre-

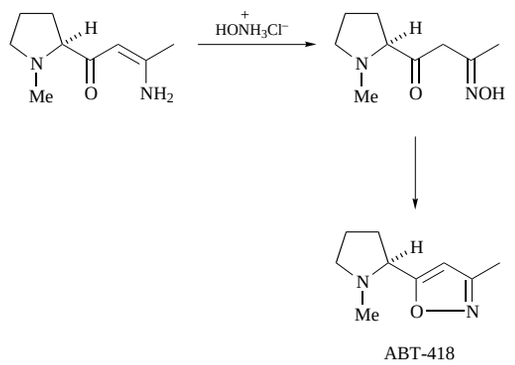


Scheme 29

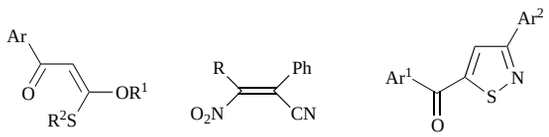
cursor being generated by directed lithiation.[122] One advantage of the method is that the aryl anion produced in the cyclisation process can be intercepted by an electrophile, thus allowing further specific substitution of the benzene ring. In this case, a range of substituents was introduced at the 7-position.

7 Isoxazoles, isothiazoles and fused analogues

A synthesis of the cholinergic channel activator ABT-418 from *N*-methylproline methyl ester in good overall yield and with high optical purity has been described.[123] The steps leading to the formation of the isoxazole with the required 3,5-substitution pattern are shown in **Scheme 30**. 3-Aryl-5-alkoxyisoxazoles have been obtained in moderate yield from the reaction of acylketene *O*,*S*-acetals **30** with hydroxylamine[124] and 5-aminoisoxazoles from the reduction of the nitroacrylonitriles **31** with Baker's yeast.[125]



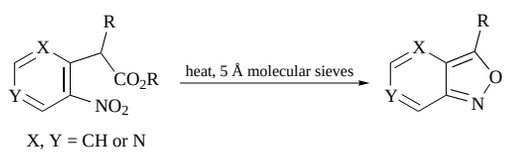
Scheme 30



30 **31** **32**

2,5-Diarylfurans react with trithiazyl chloride ($Cl_3N_3S_3$) to give the isothiazoles **32**.[126] The mechanism of this unusual ring transformation is postulated by the authors to involve the introduction of the S≡N functional group at C-3 of the furan followed by ring cleavage.

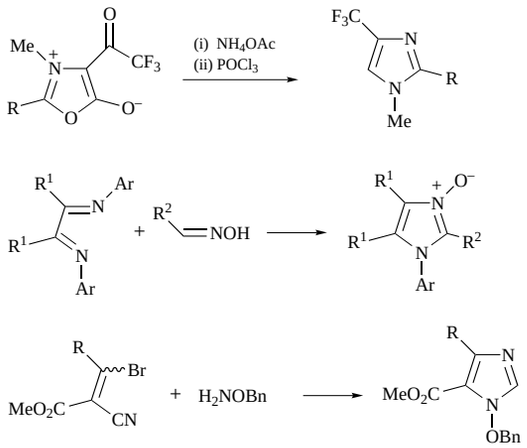
A new synthesis of 3,4-fused isoxazoles from 2-nitroacetic acids is illustrated in **Scheme 31**.[127] The proposed initial step is the generation of a ketene, which cyclises to the intermediate from which carbon dioxide is eliminated. 3-Aminobenzoisoxazoles have hitherto been virtually unknown but two routes to derivatives of this class, one starting with 2-fluorobenzonitriles[128] and the other from 2-fluorobenzamides,[129] have been described.



Scheme 31

8 Imidazoles and benzimidazoles

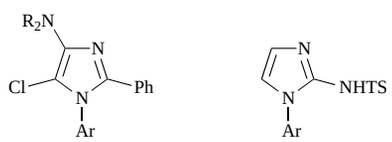
Some recent imidazole syntheses are outlined in **Scheme 32**. A good route to 4-(trifluoromethyl)imidazoles and other perfluoroalkylimidazoles involves ring opening of oxazolium 5-



Scheme 32

oxides.[130] Some 1-arylimidazole 3-oxides have been prepared from bis(arylimines) of glyoxal or butane-2,3-dione and aldoximes.[131,132] 1-Hydroxyimidazoles have been prepared from 3-bromo-2-isocyanoacrylates and *O*-benzylhydroxylamine;[133] the method has also been applied to the preparation of the analogous 1-aminoimidazoles.

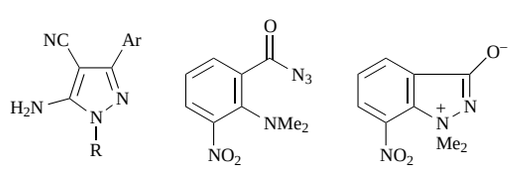
The tetrasubstituted imidazoles **33**, a new class of imidazoles, have been prepared from ketene aminals and *N*-chloroamidines.[134] The 1-aryl-2-(tosylamino)imidazoles **34** have been prepared in moderate yield starting from the diethyl acetal of isocyanoacetaldehyde[135] and *N*-alkyl- or *N*-aryl-*o*-phenylenediamines have been converted into the corresponding 2-cyanobenzimidazoles by reaction with 4,5-dichloro-1,2,3-dithiazolium chloride.[136]



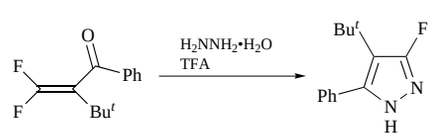
33 **34**

9 Pyrazoles and indazoles

The regioselectivity of the cyclisation of aroylmalononitriles to aminocyanopyrazoles on reaction with alkylhydrazines has been established by X-ray crystallography. The reactions lead exclusively to 1-alkyl-5-aminopyrazoles **35**.[137] These preparations were carried out in one pot from malononitrile. An efficient one pot synthesis of 3-ethoxycarbonylpyrazoles has also been reported.[138] Hydrazine and monosubstituted hydrazines react with β,β-difluoroenones to give fluoropyrazoles; an example, shown in **Scheme 33**, is the synthesis of 4-*tert*-butyl-3-fluoro-5-phenylpyrazole (95%).[139]



35 **36** **37**



Scheme 33

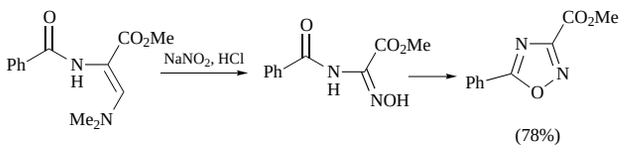
Benzoyl azides normally rearrange to phenyl isocyanates on heating, but the major product isolated when the azide **36** was

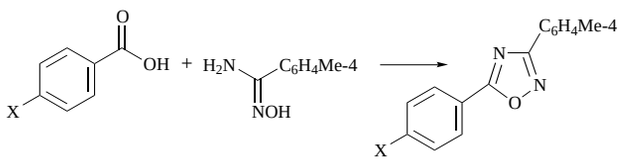
warmed in benzene was the indazol-1-ium-3-olate **37**, formed by trapping of the intermediate before rearrangement.[140]

10 Oxadiazoles and thiadiazoles

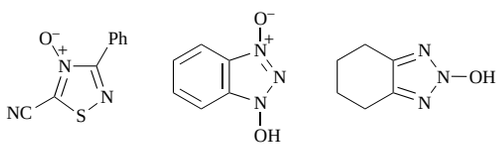
Two routes to 1,2,4-oxadiazoles are illustrated in **Scheme 34**.[141,142] The second, a variant on a standard method of synthesis, makes use of peptide coupling reagents to bring about the *O*-acylation of amidoximes by aromatic carboxylic acids.

The first 1,2,4-thiadiazole 4-oxide **38** has been isolated from the reaction of benzamidoxime with 4,5-dichloro-1,2,3-dithiazolium chloride.[143]



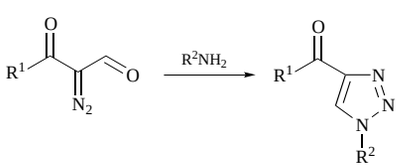


Scheme 34



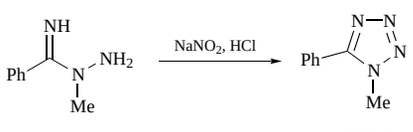
11 Triazoles, benzotriazoles and tetrazoles

1-Substituted 4-acyl-1,2,3-triazoles have been prepared from diazoaldehydes and ammonia, primary amines, hydroxylamine or hydrazines (**Scheme 35**).[144] Routes to the fused hydroxytriazoles **39**[145] and **40**[146] from nitroso compounds have been described; this is the first preparation of 1-hydroxybenzotriazole 3-oxide **39**.



Scheme 35

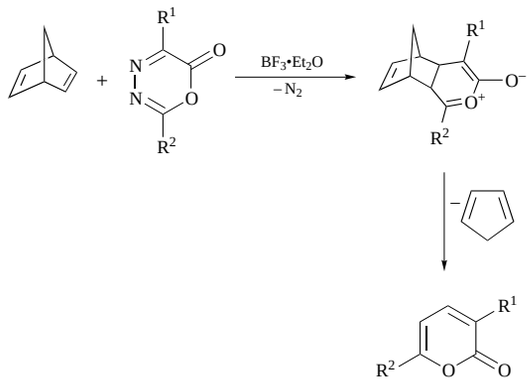
Several methods for the preparation of 1,5-disubstituted tetrazoles directly from ketones, a Lewis acid and a source of azide ions were described in the last report.[1] Another preparation of a similar type has been reported, in this case using silicon tetrachloride and sodium azide as the coreagents.[147] A route to 1,5-disubstituted tetrazoles that avoids the use of azides is the diazotisation of amidrazones. An example of the procedure is shown in **Scheme 36**.[148]



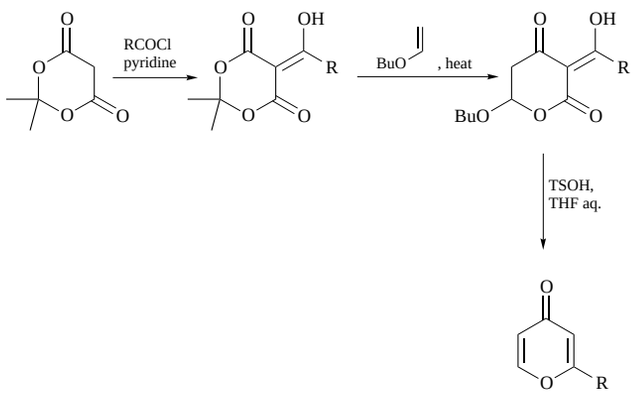
Scheme 36

12 Pyrones, coumarins and chromones

3,6-Disubstituted α-pyrones have been prepared by a new route (**Scheme 37**) involving the cycloaddition of oxadiazinones to norbornadiene followed by retro addition.[149] 2-Substituted γ-pyrones have been prepared in good yield from Meldrum's acid by the sequence shown in **Scheme 38**.[150]

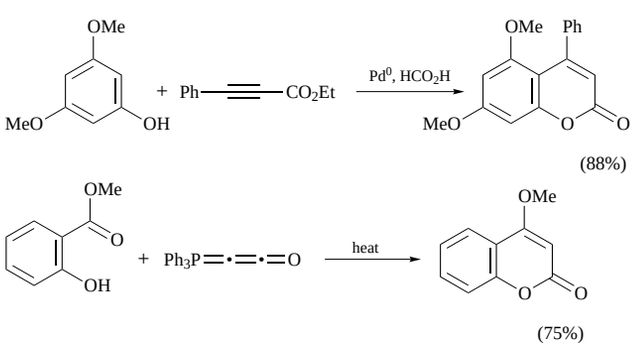


Scheme 37



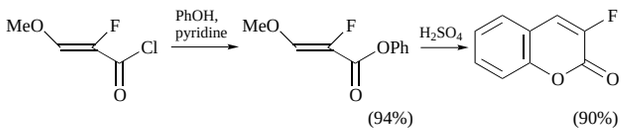
Scheme 38

An unusual coumarin synthesis from phenols and acetylenic esters has been described.[151] The reaction is carried out in formic acid with a palladium(0) catalyst, which in effect directs the acetylene to the ring position *ortho* to the hydroxy function. The resulting 2-hydroxycinnamic ester then cyclises in the usual way. An example is shown in **Scheme 39**; yields are generally better than those obtained using the classical Pechmann condensation. However, an 'environmentally friendly' version of the Pechmann condensation has been described in which a zeolite replaces the convential Lewis acid catalysts and the reaction is carried out without a solvent.[152] Another route to coumarins, also illustrated in Scheme 39, is based on the reaction of salicylic esters with a cumulated phosphorus ylide.[153] By starting with the appropriate 2-substituted benzoic esters the route can also be used to prepare the analogous sulfur and nitrogen heterocycles.



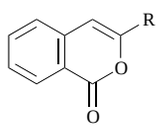
Scheme 39

A preparation of 3-substituted coumarins from salicylaldehyde and substituted acetonitriles has been carried out in water; the coumarins were obtained in high yield.[154] A good route to 3-fluorocoumarin (and to the analogous 3-fluorobenzothiin-2-one) has been described, and is illustrated in **Scheme 40**.[155]



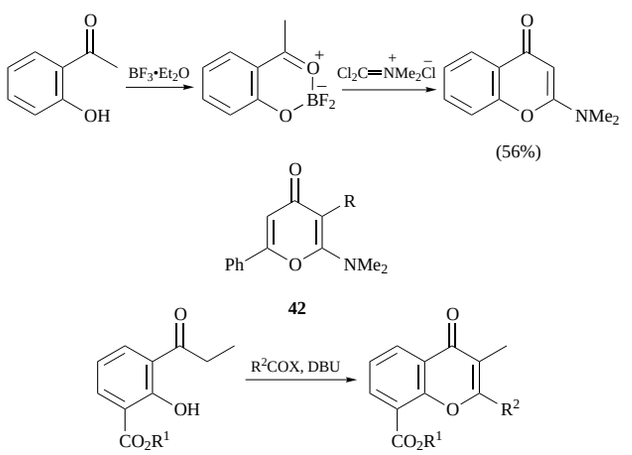
Scheme 40

Isocoumarins **41** (R = Ph or CH_2OH) are isolated in good yield from the palladium catalysed coupling of 2-iodobenzoic acid with the corresponding alkynes in the presence of zinc chloride.[156] The surprising feature of the reaction is the high *endo* selectivity of the cyclisation; the authors associate this with the presence of zinc chloride.



41

A new method of synthesis of 2-dimethylaminochromone from 2-hydroxyacetophenone is shown in **Scheme 41**.[157] The hydroxyketone is complexed with boron trifluoride and the resulting complex reacts with phosgeneiminium chloride at the activated methyl group. The product can be hydrolysed to 4-hydroxycoumarin. In the same way the dimethylamino-γ-pyrones **42** (R = H, Me) were synthesised from 1,3-diketones. An analogous chromone synthesis, also shown in Scheme 41, is a modified Baker–Venkataraman process in which an acyl chloride or acid anhydride reacts with a 2-hydroxyaryl ketone in the presence of DBU.[158]



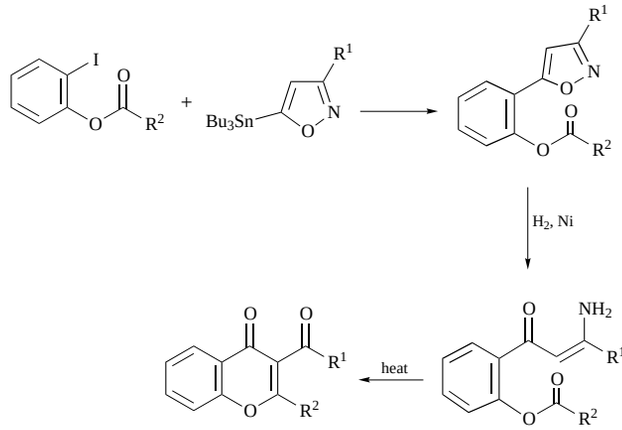
Scheme 41

The hydrogenolysis of isoxazoles to enamino ketones is exploited in a synthesis of 3-benzoylflavone (**Scheme 42**).[159] The isoxazole is coupled to 2-iodophenyl benzoate then cleaved to to provide the side chain necessary for cyclisation.

Iodosobenzene diacetate has been found to be a good reagent for the cyclodehydration of 2′-hydroxychalcones to flavones[160] and the methoxymethyl (MOM) protecting group is useful for protecting additional hydroxy substituents in acid catalysed cyclisations of this type.[161]

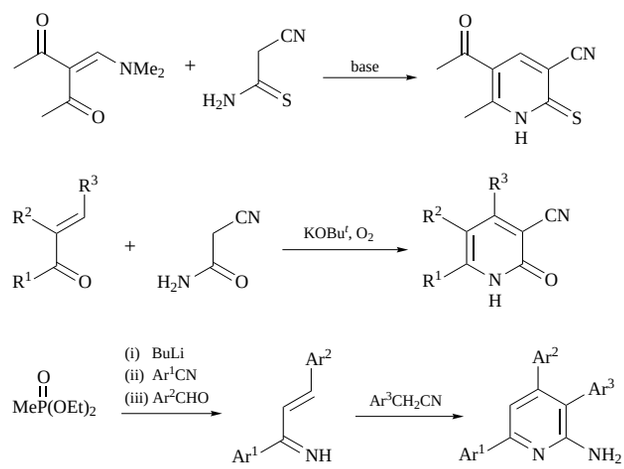
13 Pyridines

There are several examples of pyridine and pyridone synthesis



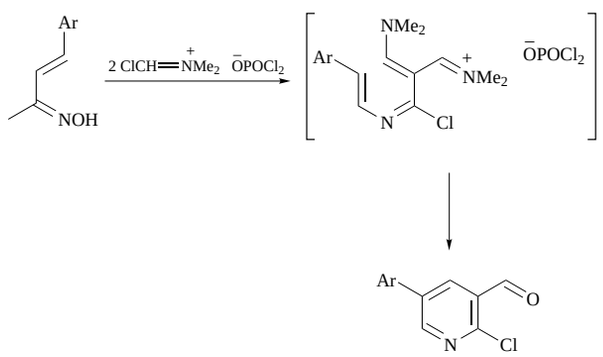
Scheme 42

involving conjugate addition of a cyano stabilised carbanion followed by ring closure and formation of the C–N bond. Examples that lead to 3-cyanopyridine-2-thiones,[162] 3-cyano-2-pyridones[163] and 2-aminotriarylpyridines[164] are shown in **Scheme 43**. Acid catalysed cyclisations of nitriles have provided good routes to a variety of aryl substituted 2-chloropyridines[165] and to the ethyl ester of 2-chloronicotinic acid.[166] Polyarylpyridines have been isolated from the conjugate addition of β-enaminophosphonates to enones.[167]



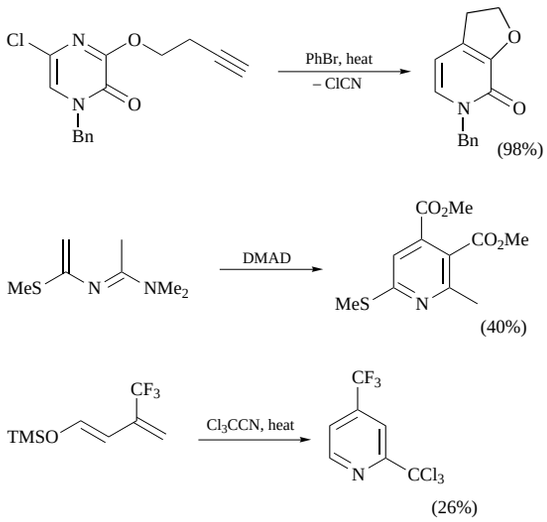
Scheme 43

Electrocyclic reactions of conjugated azatrienes, generated by aza-Wittig reactions or by other means, continue to be used as a means of synthesis of pyridines. Examples of the synthesis of pyridine-3-carboxylates[168] and of pyridine-2,3-dicarboxylates[169] have been reported. A synthesis of 2-chloropyridine-3-carbaldehydes that can be rationalised as a Beckmann rearrangement followed by an electrocyclic ring closure is the reaction of α,β-unsaturated methyl ketones with the Vilsmeier reagent (**Scheme 44**).[170]



Scheme 44

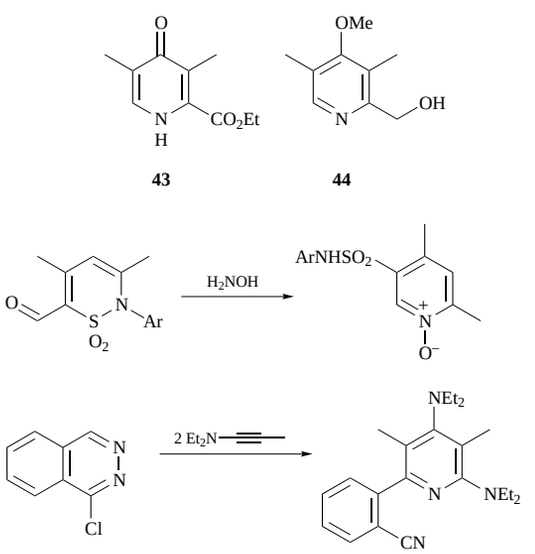
Several new pyridines have been synthesised by Diels–Alder cycloaddition reactions. There are examples of the use of 1,3-oxazin-6-ones[171,172] and of 1,2-dihydropyrazin-2-ones in reactions of this type; an example (**Scheme 45**) is a synthesis of a furopyridone by intramolecular cycloaddition.[173] Two other Diels–Alder reactions, to acyclic dienes, are also illustrated in Scheme 45.[174,175]



Scheme 45

The conversion of γ-pyrones into the corresponding pyridones has been used as a route to the pyridone **43**. This was then taken on to the pyridine **44**, a key intermediate for the preparation of omeprazole.[176] 3-Hydroxy-4-pyridones have also been synthesised from γ-pyrones.[177]

Two more pyridine syntheses from other heterocycles are shown in **Scheme 46**.[178,179a]

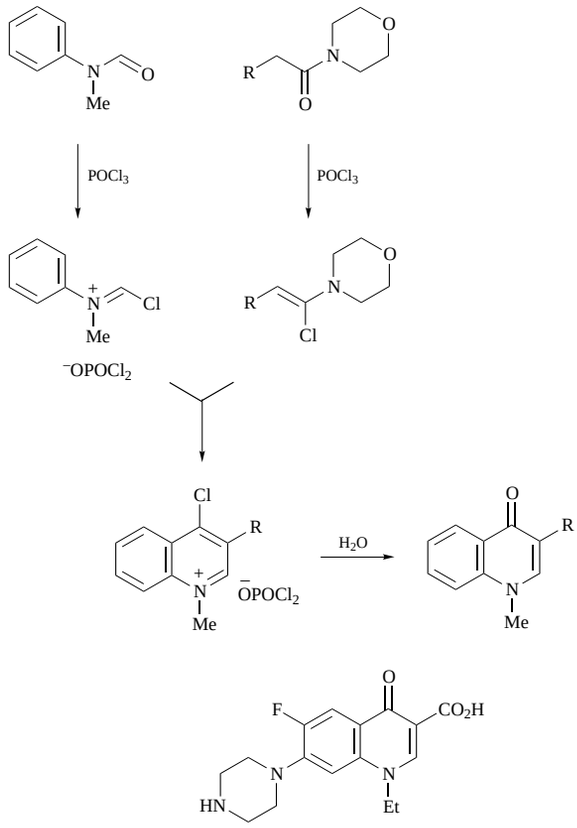


43 **44**

Scheme 46

14 Quinolines, isoquinolines, acridines and phenanthridines

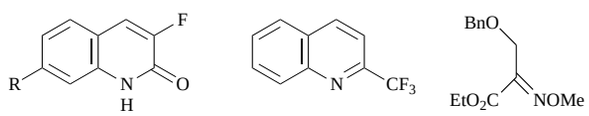
The reaction of *N*-alkylformanilides and alkyl morpholides in the presence of an excess of phosphorus oxychloride leads to *N*-alkylquinolinium salts, and hence to 1-alkyl-4-quinolones, in good yield (**Scheme 47**).[180] The alkylmorpholide is converted into a chloroenamine *in situ* and this then adds to the iminium salt generated from the *N*-alkylformanilide. The methodology has been adapted to provide a short and efficient route to norfloxacin **45** and to related quinolone antibiotics.[181] 6-Substituted 4-chloro-3-methylquinolines have also been synthesised in good yield from 2-acetamidophenylpropanones and the Vilsmeier reagent.[182]



45

Scheme 47

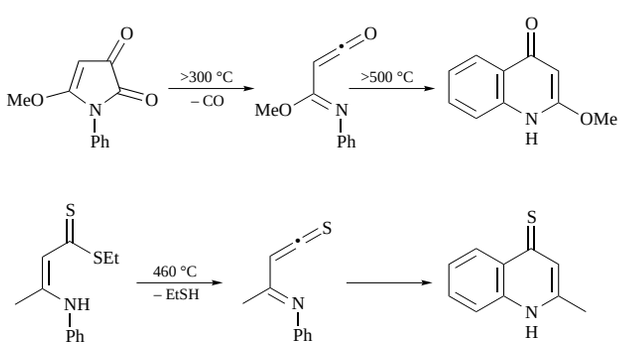
Routes to fluorinated quinolines **46**[183] and **47**[184] from substituted anilines have been reported. The oxime ether **48** has been used with salicylaldehyde in a modified Friedländer synthesis of 3-hydroxyquinoline-2-carboxylates when other routes to this type of quinoline proved unsuccessful.[185]



46 **47** **48**

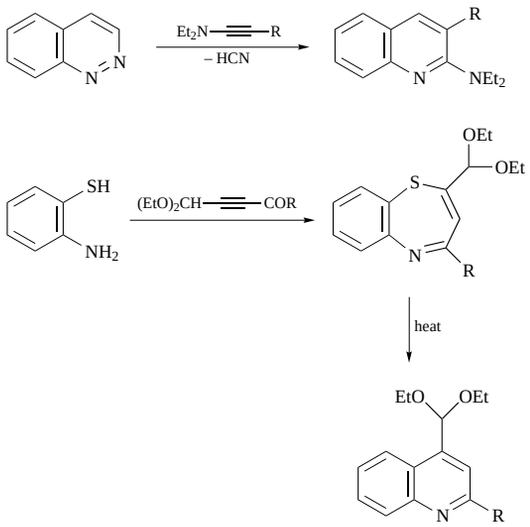
Two high temperature syntheses, one leading to 2-methoxy-4-quinolone[186] and the other to 2-methylquinoline-4-thione,[187] are illustrated in **Scheme 48**. Although the starting materials are quite different, similar cumulene intermediates are involved in the two processes.

Two unusual methods of synthesis of quinolines are illus-



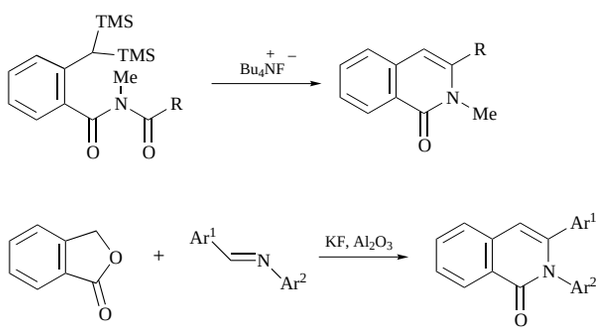
Scheme 48

trated in **Scheme 49**. Cinnoline reacts with ynamines in boiling dioxan with elimination of hydrogen cyanide.[179b] A route to 2-substituted quinoline-4-carbaldehydes has been devised starting from 2-aminothiophenol and ynones.[188] Unstable benzothiazepines can be isolated but they extrude sulfur when heated.[78b]



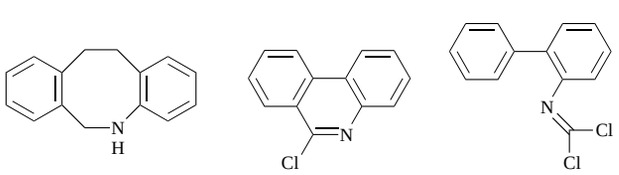
Scheme 49

Routes to isoquinolin-1(2*H*)-ones are shown in **Scheme 50**. The trimethylsilyl groups in the first precursor were introduced by directed lithiation. The method allows a variety of substituents to be incorporated at the 3-position.[189] The reaction of phthalide with Schiff bases leads to 2,3-diarylisoquinolones.[190]



Scheme 50

Acridine has been isolated in 75% yield from the flash pyrolysis of the dibenzazocine **49**. A radical mechanism, involving the initial homolysis of the NH–CH_2 bond, has been proposed.[191] 6-Chlorophenanthridine **50** has been synthesised in high yield by means of the Lewis acid-catalysed cyclisation of the imidoyl dichloride **51**.[192]

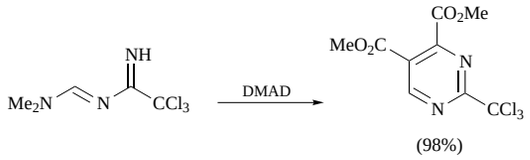


49 **50** **51**

15 Pyrimidines and quinazolines

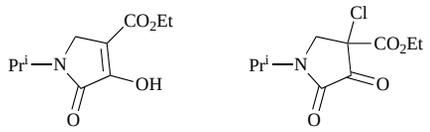
A range of pyrimidine-4,5-dicarboxylic esters has been synthesised by the Diels–Alder addition of dimethyl acetylenedicarboxylate to transient 1,3-diazabutadienes; an example is shown in **Scheme 51**.[193] Pyrimidines have also been assembled from 4-amino-1-azadienes and acylating agents.[194]

In a classical pyrimidine synthesis from guanidines and the



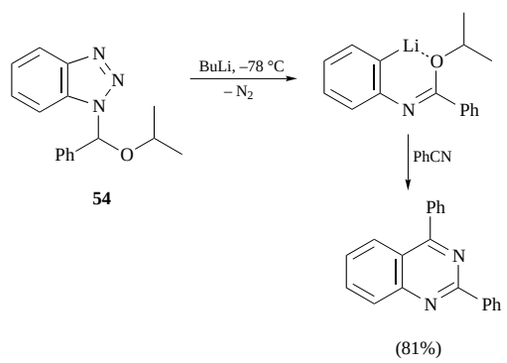
Scheme 51

keto ester **52**, the keto ester proved to be unreactive. A novel solution was found by chlorinating the keto ester to give the chloro ester **53**. This was then successfully condensed with the guanidines in the presence of a reducing agent, chromium(II) chloride, to give the required pyrimidines in good yield.[195]



52 **53**

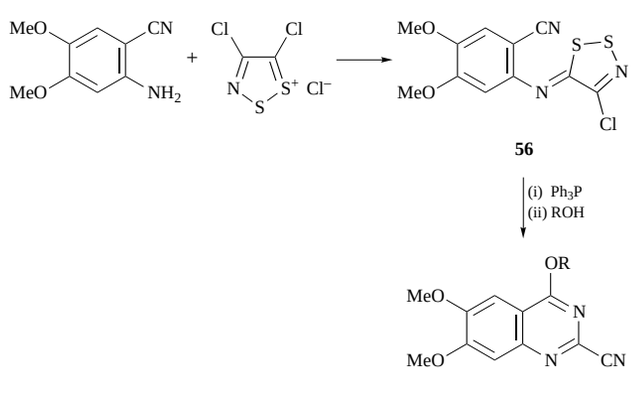
A new route to 2-phenylquinazoline derivatives starts with the 1-alkylbenzotriazole **54** (**Scheme 52**). This is cleaved by butyllithium to give an aryllithium species that can be intercepted by benzonitrile or by phenyl isothiocyanate.[196] The synthesis of 2,4-diphenylquinazoline is illustrated.



54

Scheme 52

There are several new syntheses of quinazolines from *ortho*-disubstituted benzenes. The quinazolines **55** have been prepared in good yield from the corresponding 2-aminobenzonitriles by condensation with 4,5-dichloro-1,2,3-dithiazolium chloride to give the intermediates **56**, which are then reductively cyclised in the presence of an alcohol (**Scheme 53**).[197] 6-Chloro-4-phenylquinazoline has been prepared in high yield from 2-amino-5-chlorobenzophenone by heating it with urea in formic acid. This procedure is claimed to be a general one that avoids the formation of side products.[198] The reaction of



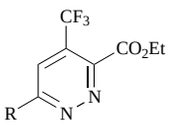
56 **55**

Scheme 53

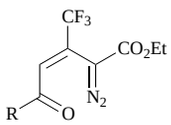
2-aminobenzaldoximes with ortho esters gives quinazoline-3-oxides.[199]

16 Pyridazines, cinnolines, pyrazines and triazines

Several 6-substituted 4-(trifluoromethyl)pyridazine-3-carboxylic esters **57** have been prepared from the diazo esters **58** by reaction with triphenylphosphine.[200] 3-Phenylpyridazines have been prepared from the dichloroacetophenone hydrazone **59** and enamines with Hünig's base.[201] This synthesis involves cycloaddition of the enamines to the chloro azo alkene **60**.



57



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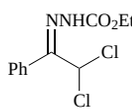
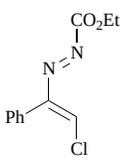
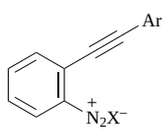


59



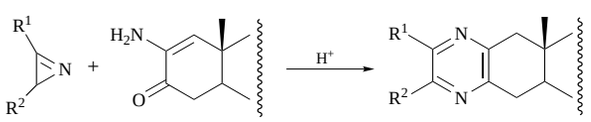
60



61

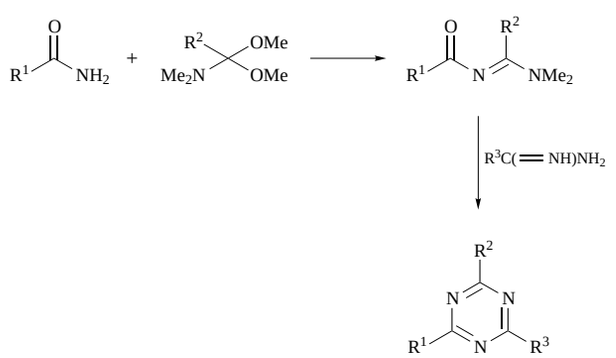
A route to 3-arylcinnolines bearing a chloro- or bromo-substituent at C-4 has been described from the alkynyldiazonium salts **61** and the appropriate hydrogen halide.[202]

In an approach to the synthesis of the steroidal pyrazine cephalostatin and analogues, a new approach to the synthesis of unsymmetrical pyrazines was devised that should have more general applicability (**Scheme 54**).[203] 2*H*-Azirines were condensed with unsaturated amino ketones in the presence of an acid catalyst to give the pyrazines regioselectively.



Scheme 54

A new route to 1,3,5-triazines bearing three different substituents is shown in **Scheme 55**.[204] There are few previous methods for preparing triazines of this type.



Scheme 55

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