Synthesis of five-membered aromatic heterocycles

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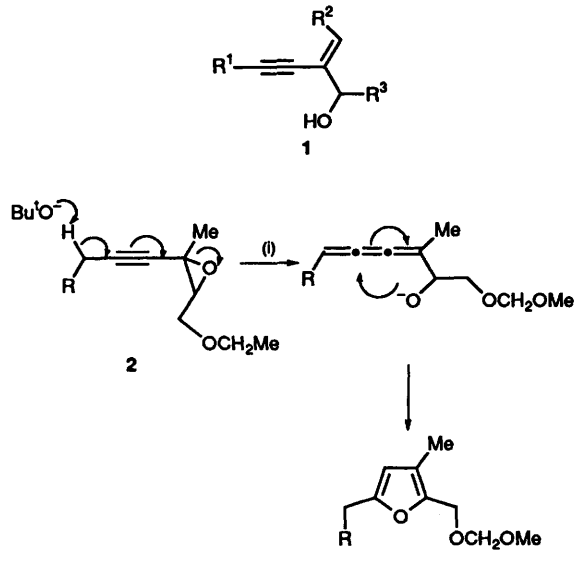
Reviewing the literature published between July 1991 and June 1993

1 Introduction

The aim of this review is to highlight advances in methods of formation of five-membered aromatic heterocycles. Because of the large number of publications the review has to be selective. In general, only methods which involve the construction of the ring systems, either from acyclic precursors or from other heterocycles, are covered: papers in which only functional group transformations are described are not included. The review is arranged according to the type of ring system being formed rather than according to the methods used.

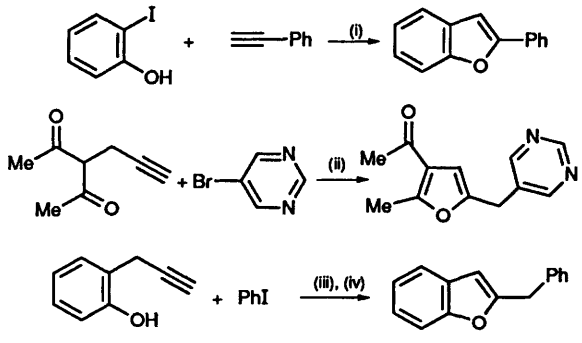
2 Furans and benzofurans

Several new furan syntheses involve a ring-forming step in which an oxygen–carbon bond is made by *endo* or *exo* cyclization of oxygen on to an *sp* hybridized carbon. Marshall and DuBay have described new routes to furans based on cyclization of unsaturated alcohols **1** with potassium t-butoxide.[1] A related route to furans is the ring opening and cyclization of the oxiranes **2** (**Scheme 1**).[2] The alcohols **1** are constructed by palladium-catalysed coupling of vinyl bromides or iodides with alkynes; a similar strategy is used to construct benzofurans from 2-iodophenol and alkynes (**Scheme 2**).[3,4] Related routes to furans[5] and to benzofurans[6] which make use of palladium(0) coupling and cyclization are also shown in (**Scheme 2**).



Reagents: (i) KOBu^t, Bu^{t}OH, 18-crown-6

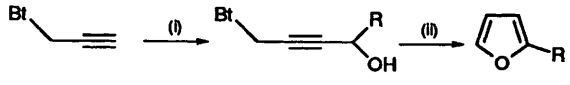
Scheme 1



Reagents: (i) $(Ph_3P)_2PdCl_2$, CuI, Et_3N, 60–80 °C, DMF (77%); (ii) $Pd(PPh_3)_4$, K_2CO_3, 60 °C, DMF (62%); (iii) BuLi; (iv) $Pd(PPh_3)_4$ (28%)

Scheme 2

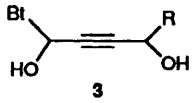
A simple route to 2-arylfurans (**Scheme 3**) makes use of the 1-benzotriazolyl function as an activating group and as a leaving group.[7] A conceptually similar route to 2,3-disubstituted furans has also been described,[8] and 2,5-disubsituted furans have been prepared from the propargylic diols **3** by reductive cyclization with tributylphosphine and a palladium(0) catalyst.[9]



(Bt = 1-benzotriazolyl)

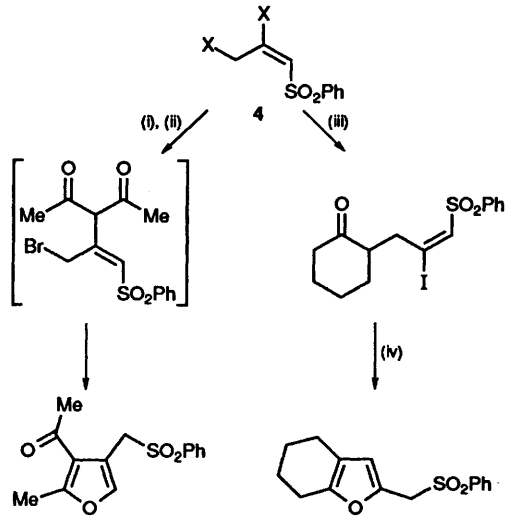
Reagents: (i) BuLi, RCHO; (ii) NaOH, EtOH (R = Ph, 81%; R = 4-ClC$_6$H$_4$, 62%; R = 2-furanyl, 53%)

Scheme 3



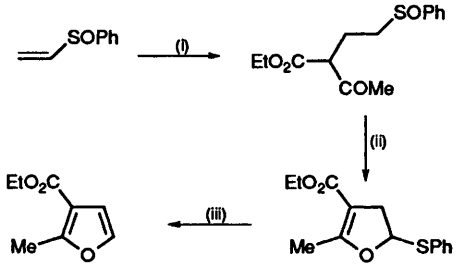
3

Padwa and co-workers have used vinylsulfones **4** (X = Br, I) for the synthesis of several new trisubstituted furans. The sulfones **4**, which are derived from benzenesulfonylallene by the addition of halogen, can react with enolate anions or their equivalent either by displacement of the allylic halide or by conjugate addition–elimination, the preference being determined by the choice of solvent and other reaction conditions.[10,11] Two examples are shown in **Scheme 4**. The conjugate addition of enolate anions to vinyl sulfoxides has also been used as a route to trisubstituted furans: in this method, cyclization is achieved by Pummerer rearrangement of the intermediate sulfoxide (**Scheme 5**).[12]



Reagents: (i) (X = Br) MeCOCH$_2$COMe, MeCN; (ii) K_2CO_3 (77%); (iii) (X = I) 1-(trimethylsilyloxy)cyclohexene, $AgBF_4$ (71%); (iv) Et_3N (65%)

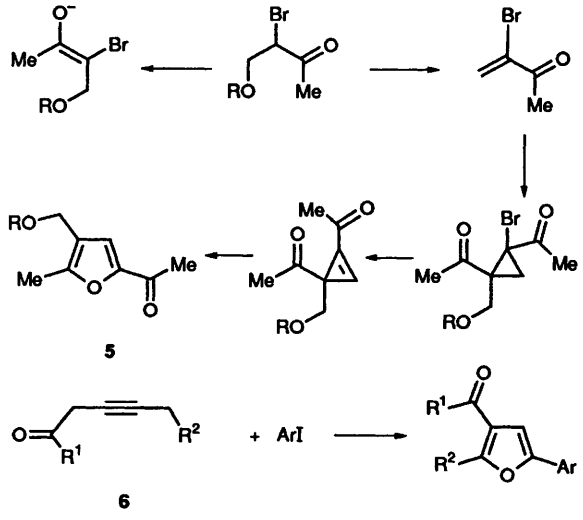
Scheme 4



Reagents: (i) ethyl 3-oxobutanoate, NaOMe (83%); (ii) $(MeCO)_2O$, Cl_3CCO_2H (84%); (iii) MCPBA (55%)

Scheme 5

Two further routes to trisubstituted furans which probably involve conjugate addition as a key step are illustrated in **Scheme 6**. α-Bromo-β-alkoxyketones react with DBU to give trisubstituted furans **5** (35–71%): the reaction sequence shown has been suggested.[13] Furans are also produced from ethynyl ketones **6** and aryl iodides by palladium-catalysed carbonylation.[14] It is likely that conjugate addition of an intermediate acylpalladium iodide, ArCOPdI, to the triple bond provides the carbon framework.

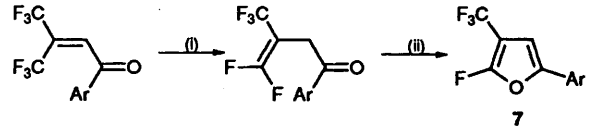


5

6

Scheme 6

A useful synthesis of 2-fluoro-3-trifluoromethylfurans **7** has been described starting from hexafluoroacetone (**Scheme 7**).[15] The cyclization step can be represented as a 5-*endo-trig* process or, perhaps, better, as an electrocyclic reaction of the enolate anion.

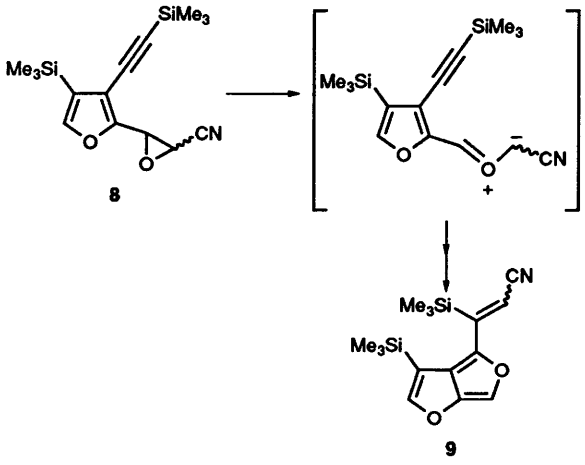


Reagents: (i) $SnCl_2$ then heat (80–90%); (ii) NaH or LDA (60–72%)

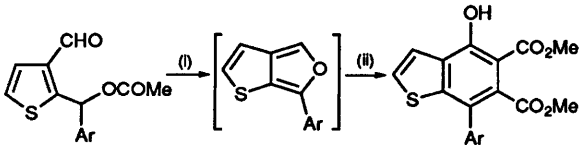
Scheme 7

An electrocyclic process is also probably involved in the rather complex sequence by which 2-furanyloxiranes **8** are isomerized thermally to furo[3,4-*b*]furans **9** (**Scheme 8**).[16] Several other unstable bicyclic furans, including thienofurans, furopyridines, and furoindoles, have been generated by acid catalysed cyclization: an example is shown in **Scheme 9**.[17] Another route to fused furans is the intramolecular addition of acylcarbenoids to triple bonds: an example of the reaction is shown in **Scheme 10** and several other types of polycyclic furans have been made using the same approach.[18]

Intramolecular radical addition reactions to carbon–carbon double bonds continue to provide useful routes to benzofurans.[19] Normally such additions involve carbon radicals, but a flash pyrolytic route to benzofurans has been described in which an

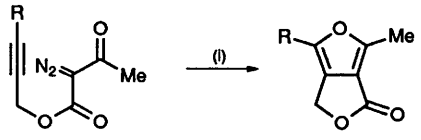


Scheme 8



Reagents: (i) CF_3CO_2H; (ii) dimethyl acetylenedicarboxylate (88%, Ar = 3,4-dimethoxyphenyl)

Scheme 9



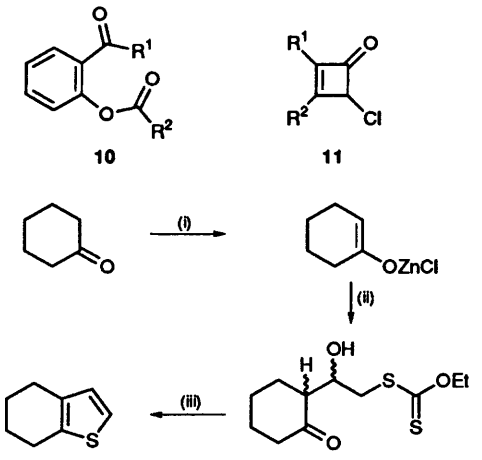
Reagents: (i) $Rh_2(OAc)_4$, 80 °C (>70%)

Scheme 10

aryloxyl radical adds to a double bond at the *ortho* position.[20] Another reaction which provides a good route to furans, benzofurans, and other heterocycles is intramolecular McMurry coupling of dicarbonyl compounds. For example, benzofurans were prepared in good yield by reductive cyclization of the ketoesters **10**.[21] A method of preparing benzofurans and dibenzofurans has been described in which the six-membered ring is constructed from a chlorocyclobutenone **11** by palladium(0) coupling to the five-membered heterocycle followed by ring expansion.[22]

3 Thiophenes and benzothiophenes

Methods of preparation of ethenyl- and ethynyl-thiophenes have been reviewed.[23] A general method of synthesis of 2,3-disubstituted thiophenes has been described starting from ketones.[24] The method is illustrated in **Scheme 11** for the preparation of 4,5,6,7-tetrahydrobenzothiophene; several other substituted thiophenes were prepared in an analogous manner from both cyclic and acyclic ketones. A procedure for preparing 3-substituted and 3,4-disubstituted thiophenes makes use of ketone dithioacetals **12** as starting materials. Reaction with diiodomethane and zinc–copper couple leads to the formation of 2-(methylthio)thiophenes **13** from which the methylthio substituent can be selectively removed with Raney nickel.[25]

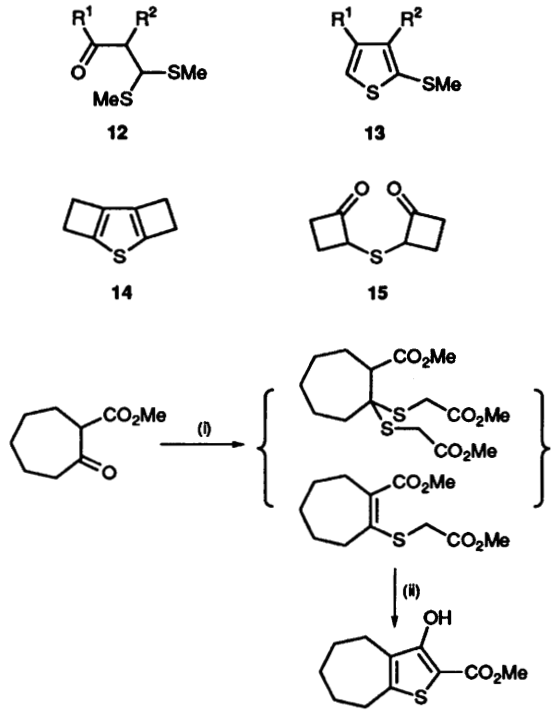


Reagents: (i) $(Me_3Si)_2NLi$, $ZnCl_2$; (ii) $EtOC(=S)SCH_2CHO$ (66%): (iii) conc. HCl (70%)

Scheme 11

The strained thiophene **14** has been synthesized for the first time; the precursor was the diketone **15** which was subjected to reductive coupling and dehydration.[26] Unlike most thiophenes, compound **14** participates as a diene in the Diels–Alder reaction under mild conditions. One of the products obtained from it by flash pyrolysis is benzo[*b*]thiophene (a reaction which presents a mechanistic challenge!). A variant of the long established route to 2,5-disubstituted thiophenes from 1,4-diketones has been described in which bis(trialkylstannyl)sulfides [$(Bu_3Sn)_2S$, *etc.*] have been used as the source of sulfur; thiophenes are formed in high yield in the presence of boron trichloride.[27] An improvement to the published experimental procedure for the preparation of 3-hydroxythiophene-2-carboxylic esters from β-ketoesters has been described. In the modified method a mixture of the ketoester, its corresponding alcohol, and thioacetic acid is treated with dry hydrogen chloride and the crude product mixture is then cyclized by reaction with the corresponding sodium alkoxide.[28] An example is shown in **Scheme 12**. Thioacetic acid has also been used in the synthesis of ethyl thieno[2,3-*d*]thiazole-5-carboxylate **16** from the chloroaldehyde **17**.[29]

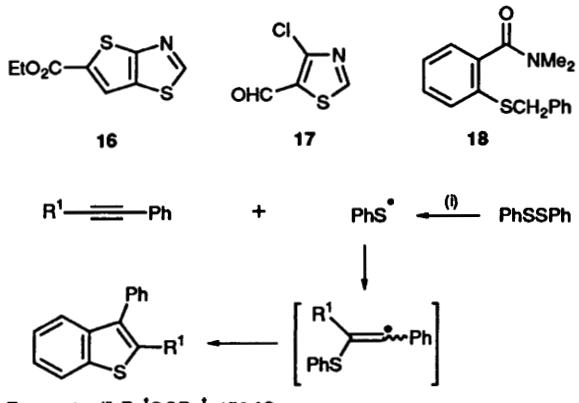
The technique of directed lithiation is playing an increasing role in the synthesis of benzo fused heterocycles. An example is the synthesis of the sulfide **18** from *N*,*N*-dimethylbenzamide by directed lithiation followed by reaction of the lithio intermediate with sulfur then alkylation. This sulfide was then cyclized in high yield to 3-hydroxy-2-phenylbenzothiophene using potassium t-butoxide.[30] The cyclization requires the presence of both the sulfur atom and the phenyl group to provide activation to the methylene group in compound **18**; a synthesis of the corresponding thieno[2,3-*b*]pyridine was also successful. A related synthesis of naphtho[1,2-*b*]thiophenes has been described.[31]



Reagents: (i) $HSCH_2CO_2H$, MeOH, Dry HCl; (ii) NaOMe (85%)

Scheme 12

Two reports have appeared of the preparation of benzo[*b*]thiophenes by the reaction of arylthio radicals with acetylenes. In one report, phenylthio radicals were generated from diphenyl disulfide at 150°C in the presence of phenylacetylenes (**Scheme 13**).[32] In the other report, a gas-phase reaction between acetylene, hydrogen sulfide, and aryl chlorides or bromides was carried out and this gave benzothiophenes in good yield; arylthio radicals were suggested as intermediates in the reaction.[33]



Reagents: (i) Bu^tOOBu^t, 150 °C

Scheme 13

Some of the procedures described for furans in Section 2 have also been applied to thiophenes. These include the base-catalysed cyclization of thiols analogous to compound **1**,[34] and a route to benzothiophenes based on the coupling of the cyclobutenone **11** with 2-(tributylstannyl)thiophenes.[22]

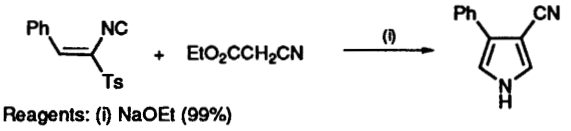
The Diels–Alder reaction shown in **Scheme 9** provides a method of synthesis of benzothiophenes substituted in the six-membered ring.

4 Pyrroles

Reviews of the synthesis of the following pyrroles have appeared: vinylpyrroles,[35] aminopyrroles,[36] and 3-hydroxypyrroles.[37]

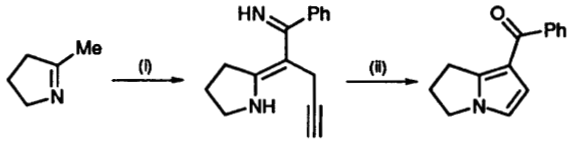
One of the best routes to 3,4-disubstituted pyrroles has proved to be the conjugate addition of the carbanion derived from tosylmethyl isocyanide (TOSMIC) to carbon–carbon double bonds followed by cyclization. A different use of TOSMIC has been described by van Leusen and co-workers in which it is first condensed with an aldehyde to produce an α,β-unsaturated isonitrile; this then acts as the electrophilic partner in reactions leading to pyrroles.[38,39] An example, shown in **Scheme 14**, is the synthesis of 3-cyano-4-phenylpyrrole in high yield from ethyl cyanoacetate. The use of the isonitrile $(EtO)_2P(O)CH_2NC$ as a nucleophilic partner in pyrrole synthesis has also been described.[40] A different *endo* cyclization procedure, which is claimed to be of wide scope, is illustrated in **Scheme 15**; the reaction can generally be carried out as a 'one-pot' procedure.[41] Hydroformylation of propargylamines has provided an efficient synthesis of 3-phenylpyrrole and of several other pyrroles;[42] a related method involves the use of propargylamines **19** which are converted into pyrroles **20** in moderate yield by conjugate addition followed by acylation (**Scheme 16**).[43]

The use of acylcarbenoids, derived by rhodium(II)-catalysed decomposition of diazocarbonyl



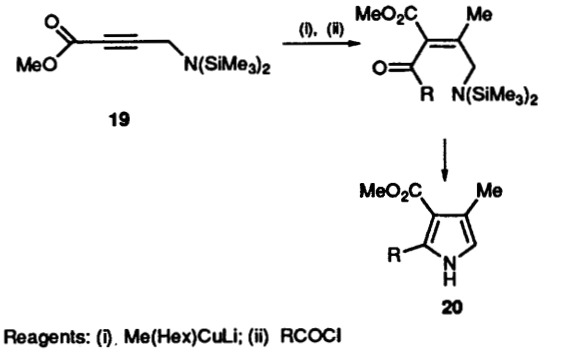
Reagents: (i) NaOEt (99%)

Scheme 14



Reagents:(i) LDA, PhCN, $BrCH_2C{\equiv}CH$; (ii) Et_3N (55%)

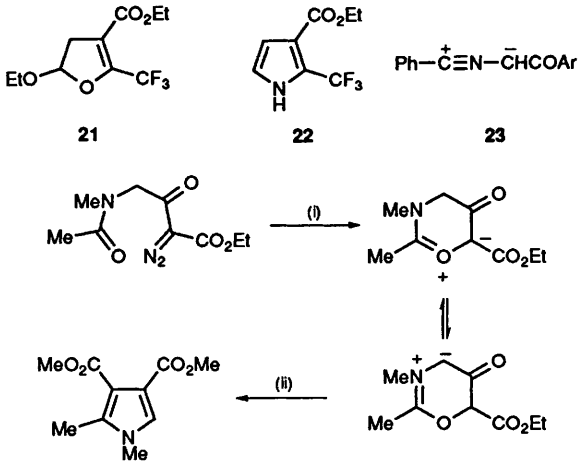
Scheme 15



Reagents: (i) Me(Hex)CuLi; (ii) RCOCl

Scheme 16

compounds, in the synthesis of furans has already been referred to in Section 2. The methodology can be adapted to produce pyrroles: for example, the dihydrofuran **21** was prepared by carbenoid addition to ethyl vinyl ether and this was then converted into the pyrrole **22** (69%) by reaction with ammonium chloride.[44] A more complicated use of the carbenoid reaction in pyrrole synthesis is illustrated in **Scheme 17**: a 1,3-dipole is generated by intramolecular addition to the carbonyl group of an amide and this tautomerizes to an azomethine ylide, which can be intercepted conventionally by reaction with acetylenic esters. Several pyrrolecarboxylic esters with a variety of substituents have been prepared in good yield by this method.[45] Rhodium-catalysed decomposition of diazoketones, $ArCOCHN_2$, in the presence of benzonitrile provides a more direct route to nitrile ylides **23**. These can be intercepted by dimethyl acetylenedicarboxylate to give pyrroles, although the major reaction is always electrocyclic ring-closure of the dipole to give a 2,5-diaryloxazole.[46]

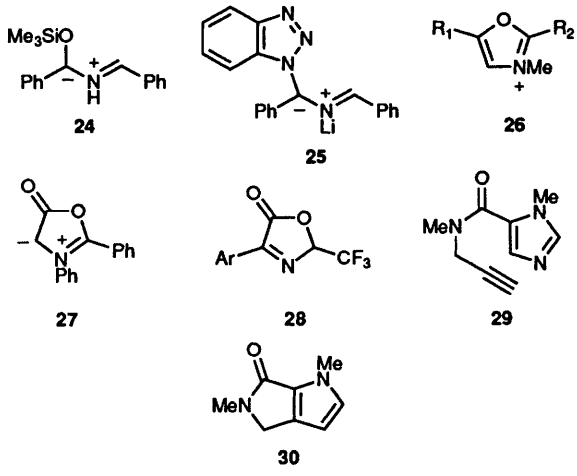


Reagents: (i) $Rh_2(OAc)_4$; (ii), dimethyl acetylenedicarboxylate (54%)

Scheme 17

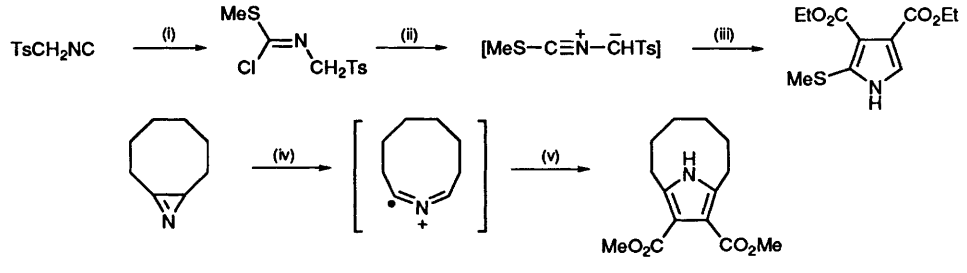
A more efficient pyrrole synthesis based on nitrile ylide cycloaddition is shown in **Scheme 18**; this also illustrates another use of TOSMIC.[47] 2*H*-Azirines are known to give nitrile ylides upon irradiation but when the process is carried out in the presence of an electron-acceptor the intermediate generated is a radical cation, which reacts with dipolarophiles in a stepwise manner.[48] An example of the synthesis of a pyrrole by this method is also shown in **Scheme 18**.

Azomethine ylides with appropriate leaving groups are, however, probably the most useful 1,3-dipoles for the synthesis of pyrroles. The transient intermediates shown in **Scheme 17** are of this type and several others have been used recently. The species **24**[49] and **25**[50] were generated *in situ* and were intercepted efficiently by dimethyl acetylenedicarboxylate. A versatile procedure, described by Vedejs and Piotrowski, is the ring-opening of the oxazolium salts **26** by nucleophiles (Z^-).[51] The azomethine ylides were then intercepted by acetylenic dipolarophiles, either inter- or intra-molecularly, to give a variety of polysubstituted pyrroles after the loss of the elements of HZ.



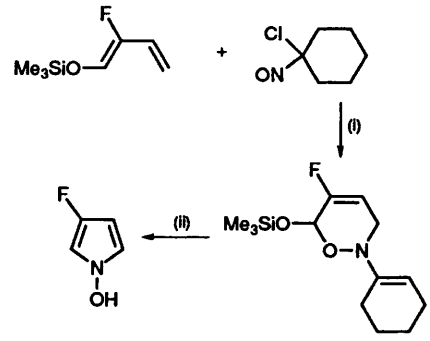
Münchnones such as **27** can be regarded as stabilized azomethine ylides and their cycloaddition reactions provide good routes to polysubstituted pyrroles; several β-trifluoromethylpyrroles have been prepared by this method.[52] The oxazolones **28** have also been used in pyrrole synthesis: reaction with α-chloroacrylonitrile gave β-cyanopyrroles.[53] This reaction was interpreted as a stepwise Michael addition–elimination process rather than as a cycloaddition.

A rare example of Diels–Alder reaction of an imidazole is the intramolecular cycloaddition of compound **29**, which takes place at 220°C to give the bicyclic pyrrole **30** in good yield.[54] A Diels–Alder reaction is the first step in a useful synthesis of 3-fluoropyrroles.[55] An example is shown in **Scheme 19**; nitrosobenzene was also used as the dienophile and gave 3-fluoro-1-phenylpyrrole by the same sequence.



Reagents: (i) MeSCl; (ii) KOH, alumina; (iii) diethyl fumarate (68%); (iv) *hν*, 1,4-dicyanonaphthalene; (v), dimethyl acetylenedicarboxylate (56%)

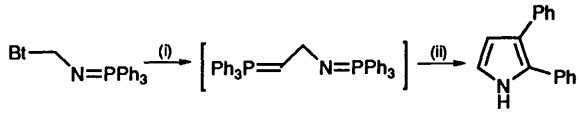
Scheme 18



Reagents: i, Et_3N; ii, $MeCO_2H$ aq. (72%)

Scheme 19

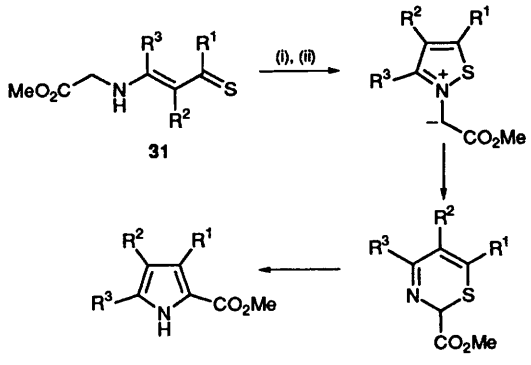
An unusual synthesis of 2,3-diarylpyrroles has been described by Katritzky and co-workers and this is illustrated in **Scheme 20**.[56] An ylide intermediate of a different kind is postulated in the route to pyrrole-2-carboxylic esters shown in **Scheme 21**.[57] This sequence can be carried out in one pot from the open chain species **31** and the overall yields are good. The loss of sulfur from the thiazines is a reaction which has been used before in pyrrole synthesis.



(Bt = 1-benzotriazolyl)

Reagents: (i) $Ph_3P = CH_2$, BuLi; (ii) PhCOCOPh (67%)

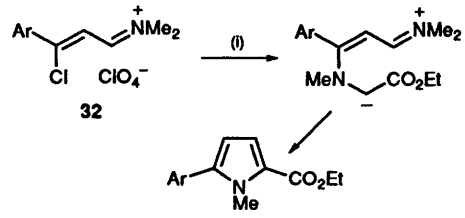
Scheme 20



Reagents: (i) Br_2; (ii) Et_3N

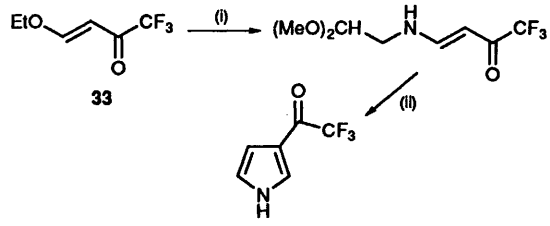
Scheme 21

Conjugate addition–*exo* cyclization sequences are widely used in pyrrole synthesis and two of the many useful recent examples are illustrated in **Schemes 22** and **23**. The conjugated iminium salts **32** react with glycine ethyl ester and with *N*-methylglycine ethyl ester and the adducts are cyclized in the presence of sodium hydride to give pyrrole-2-carboxylic esters in good yield.[58] A synthesis of 3-trifluoromethylpyrroles is achieved in good yield by conjugate addition to the enones **33**.[59] Several further examples of the synthesis of 1-(methoxycarbonylamino)pyrroles by conjugate addition of carbanions to conjugated azoalkenes have also been described.[60,61] Another reaction which is proving to be quite versatile as a pyrrole synthesis is the conjugate addition of oximes to acetylenes followed by the sigmatropic rearrangement of the *O*-vinyloximes; a recent example is shown in **Scheme 24**.[62]



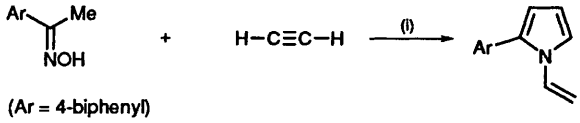
Reagents: (i) $MeNHCH_2CO_2Et$, NaH (67%, R = 4-ClC_6H_4)

Scheme 22



Reagents: (i) $(MeO)_2CHCH_2NH_2$; (ii) CF_3CO_2H aq. (87%)

Scheme 23



(Ar = 4-biphenyl)

Reagents: (i) KOH, Me_2SO (68%)

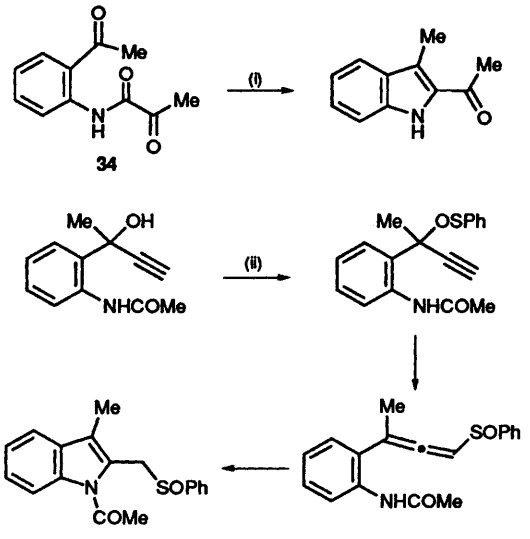
Scheme 24

Of all the methods available for pyrrole synthesis the Paal–Knorr procedure remains one of the most useful. An example of the synthesis of a highly functionalized, pentasubstituted pyrrole in good yield under carefully controlled conditions shows the versatility of the Paal–Knorr method.[63]

5 Indoles

Two new and mechanistically interesting methods of synthesis of 2,3-disubstituted indoles from *o*-acetylbenzamides have been reported; they are illustrated in **Scheme 25**. One is an intramolecular McMurry coupling of the amide **34**. This gives the indole in good yield; the coupling thus shows high chemoselectivity for the amide carbonyl despite the fact this functional group was previously believed to be inert in McMurry coupling, and despite the presence of a more activated carbonyl group.[21,64] In the second method the key step is the generation of an activated allene; this was achieved by a [2,3] sigmatropic rearrangement.[65]

Two other new indole syntheses based on *o*-substituted benzamides are shown in **Scheme 26**. The first makes use of directed lithiation into a 2-alkyl substituent and formylation of the alkyl-lithium intermediate. Several indoles were made in this way, including the 3,4-bridged compound **35**.[66] A Heck reaction is used in the second process to functionalize

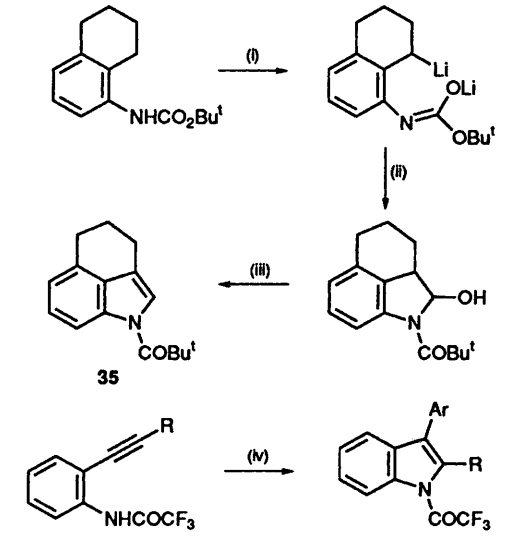


Reagents: (i) Ti/graphite; (ii) PhSCl, Et_3N (93%)

Scheme 25

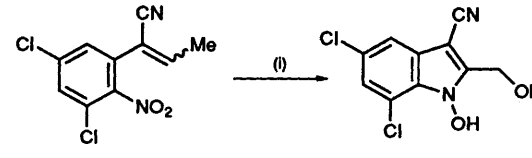
a 2-ethyl substituent and to activate it to nucleophilic attack.[67] 2-Phenylindole has been prepared in good yield by palladium-catalysed reductive cyclization of 2-nitrostilbene, and other 2-substituted indoles were prepared by the same method.[68] Activated 2-nitrostyrenes have also been used as precursors to 1-hydroxyindoles (**Scheme 27**).[69]

Several indole syntheses have been reported which make use of quinones as intermediates. Two intramolecular reactions, both leading to



Reagents: (i) Bu^tLi, TMEDA; (ii) DMF (88%); (iii) HCl (73%); (iv) ArI, $Pd(PPh_3)_4$, K_2CO_3, MeCN, 80 °C (80% for R = Ph, Ar = 4-ClC_6H_4)

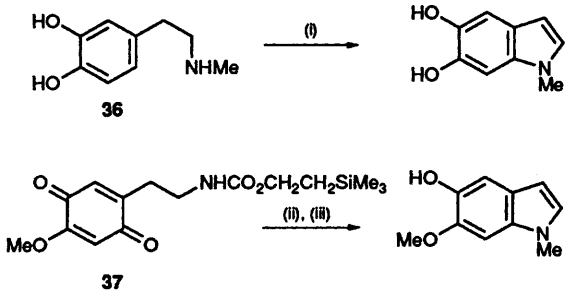
Scheme 26



Reagents: (i) K_2CO_3, MeOH (67%)

Scheme 27

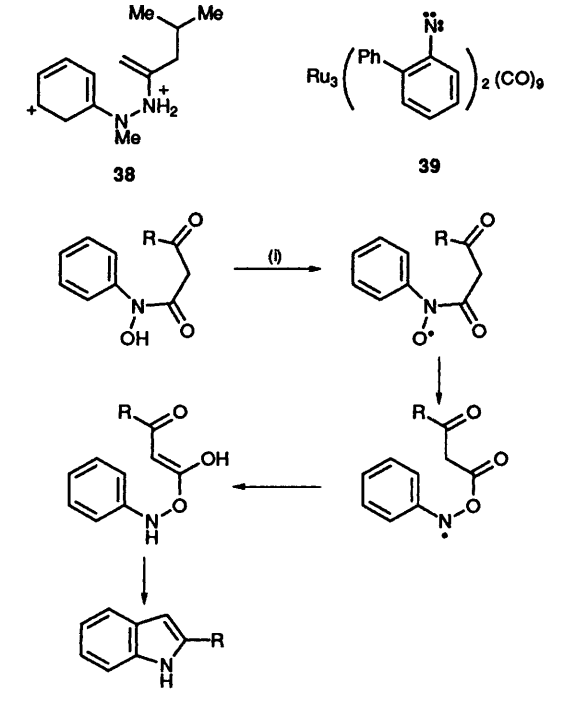
5,6-disubstituted indoles, are illustrated in **Scheme 28**. Epinine **36** was oxidized by manganese dioxide and intramolecular conjugate addition to the transient *o*-benzoquinone gave 1-methyl-5,6-dihydroxyindole.[70] The amino protecting group was removed from the quinone **37**, allowing the five-membered ring to form; dehydrogenation with palladium then gave 5-hydroxy-6-methoxyindole in high yield.[71] 6-Hydroxy-3-nitroindoles have also been isolated as products of the reactions of benzoquinone with nitroenamines, although the yields are low.[72]



Reagents: (i) MnO_2, phosphate buffer (61 % as diacetate); (ii) TsOH, MeCN; (iii) Pd/C (90%)

Scheme 28

The Fischer indole synthesis can be carried out in 96% formic acid under microwave irradiation.[73] A study of the mechanism of the Fischer indole synthesis has indicated that under strongly acidic conditions (phosphorus pentoxide in methanesulfonic acid) the intermediate which undergoes the [3,3] rearrangement is a dication **38** formed by protonation of the benzene ring.[74] A method of synthesis of 2-substituted indoles from *N*-acyl-*N*-phenylhydroxylamines has been described which, it is suggested, also involves a [3,3] shift as a key step (**Scheme 29**).[75]

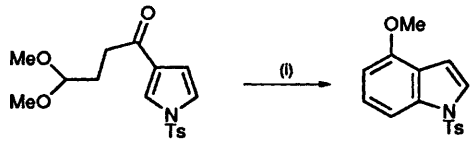


Reagents: (i) heat, AIBN (82% for R = CH_2Ph)

Scheme 29

A method of indole synthesis first reported in 1989 is the reaction of nitrobenzenes with an excess of vinylmagnesium bromide. This procedure has now been adapted to provide a large scale preparation of 7-formylindole in good yield from 2-nitrobenzaldehyde dibutyl acetal.[76]

The approach to indoles of building up the six-membered ring on to a substituted pyrrole has the advantage that it is possible to control the substitution pattern in the carbocylic part of the indole. This approach has been adopted in the synthesis of different 4-substituted indoles starting with 3-acyl-1-arenesulfonylpyrroles.[77–79] An example is shown in **Scheme 30**. A similar approach to the synthesis of 2,7-disubstituted indoles has been described although the yields were low.[80] The Diels–Alder reaction can also be used to construct the six-membered ring, as illustrated by the example in **Scheme 31**.[81]



Reagents: (i) H^+, MeOH (82%)

Scheme 30

Reagents: (i) dimethyl acetylenedicarboxylate, PhCl, heat (58%)

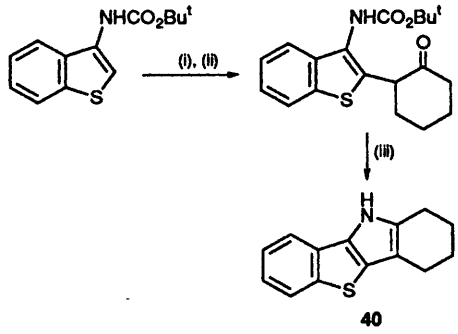
Scheme 31

6 Other fused pyrroles

The reductive cyclization of 2-nitrosobiphenyl to carbazole is well known and a mechanism involving a nitrene intermediate has been postulated. Reaction of 2-nitrosobenzene with $Ru_3(CO)_{12}$ has been shown to give a nitrene complex **39**, the structure of which was determined by *X*-ray analysis. This complex then gave carbazole when reacted with carbon monoxide.[82]

Some of the methods used for the preparation of indoles have been adapted to the preparation of aza-indoles (pyrrolopyridines) and other fused pyrroles. An example, shown in **Scheme 32**, is the preparation of a benzothienylpyrrole **40** by directed lithiation and cyclization.[83]

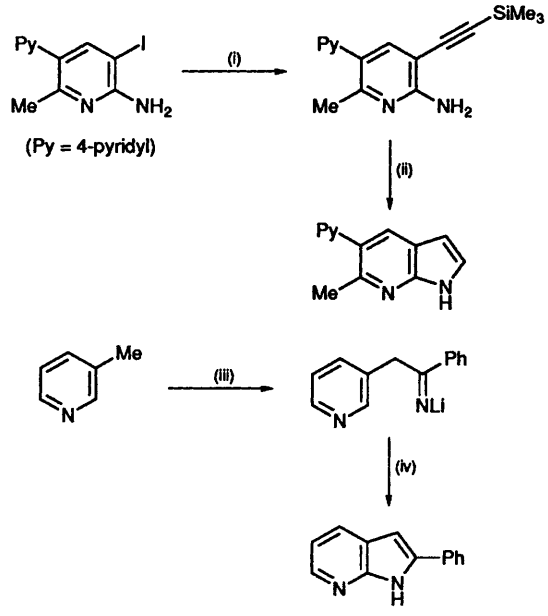
Another example is the construction of a 3-vinyl-2-aminopyridine by palladium coupling and its cyclization (**Scheme 33**).[84] A conceptually novel approach to this ring system is also illustrated in the Scheme. Here, an intermediate *N*-lithiated imine is generated and then cyclized in the presence of more LDA on to the activated 2-position of pyridine.[85] Several similar reactions, leading to other azaindoles, are described. A variety of methods has been used in an investigation of new and improved routes to 4-, 5-, 6-, and 7-azaindoles.[86]



40

Reagents: (i) BuLi; (ii) 2-chlorocyclohexanone; (iii) KOH, MeOH (90%)

Scheme 32



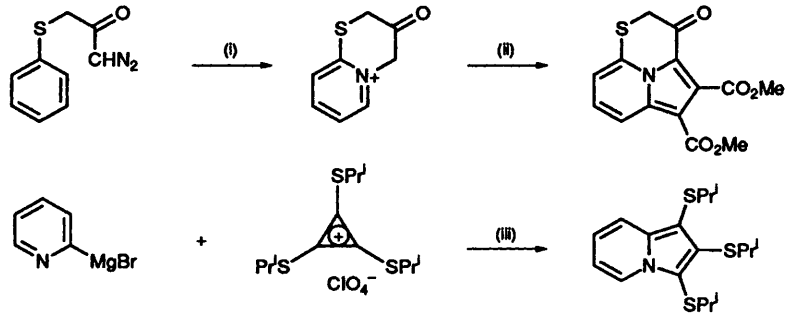
Reagents: (i) ethynyltrimethylsilane, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, DMF; (ii) CuI, DMF, heat (40%); (iii) PhCN, LDA; (iv) LDA, H^+, H_2O (90%)

Scheme 33

Padwa and co-workers have devised an indolizine synthesis (**Scheme 34**) as part of their continuing study of the applications of rhodium-catalysed reactions of diazoketones.[87] Another route to a special group of indolizines (and other 1,2-fused pyrroles) is also shown in the Scheme. This makes use of tris(alkylthio)cyclopropenium cations as annulating agents for 2-metallated aza heterocycles.[88]

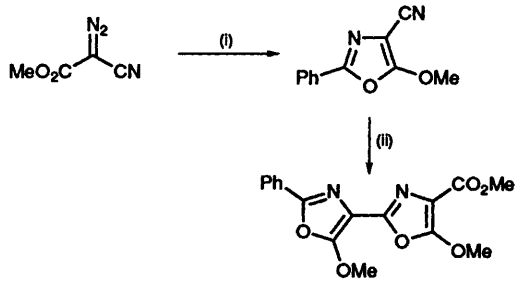
7 Oxazoles, isoxazoles, and benzoxazoles

Further examples have been reported of the preparation of oxazoles by the 1,5-dipolar cyclization of acylnitrile ylides; these intermediates were generated by the rhodium(II)-catalysed decomposition of diazo compounds in the presence of nitriles.[46,89,90] These reactions can be carried out sequentially to provide a route to bis-oxazoles, as in the example shown in **Scheme 35**.



Reagents: (i) $Rh_2(OAc)_4$; (ii) DMAD, air (65%); (iii), (99%)

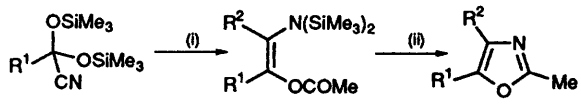
Scheme 34



Reagents: (i) PhCN, $Rh_2(OCOMe)_4$ (35%); (ii) $(MeO_2C)_2C=N_2$ $Rh_2(NHCOCF_3)_4$ (53%)

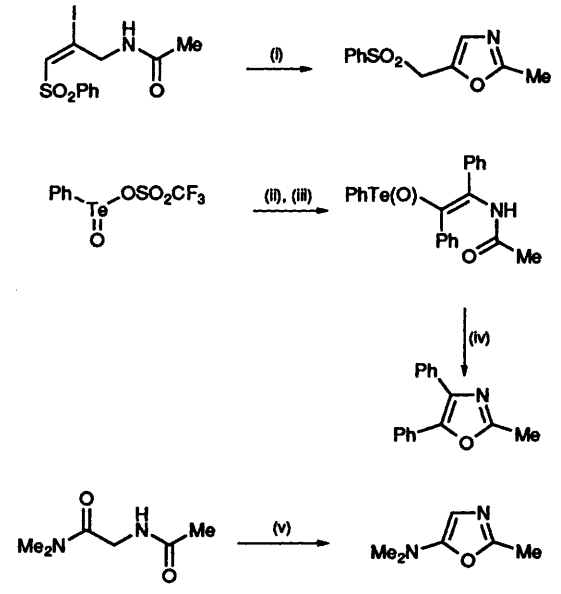
Scheme 35

A range of trisubstituted oxazoles has been prepared in good yield by the route outlined in **Scheme 36**.[91,92] Three other methods for 2-methyloxazoles are illustrated in **Scheme 37**:[93-95] the first is represented as a conjugate addition reaction to the vinyl sulfone and is analogous to the furan synthesis of Padwa and co-workers described in Section 2. Oxazole-4-carboxylic esters have been synthesized by cyclization of *N*-acylserine methyl esters **41** with diphenyl sulfoxide and triflic anhydride, followed by oxidation of the resulting oxazolines with nickel peroxide.[96] Oxazolines **42** are also formed by the reaction of the hydrazones **43** with wet silica.[97] The mechanism of this unusual reaction has not been established but the C-2 methylene group is derived from the *N*-methyl substituent of the hydrazone. The oxazolines **42** were aromatized by reaction with phosphorus oxychloride and a base, giving 5-trifluoromethyloxazoles in good yield. The ketoamides **44** are produced by a three component reaction of arylglyoxals with carboxylic acids and isonitriles RNC; these compounds have been cyclized to oxazoles **45** in moderate yield with ammonium formate.[98,99]



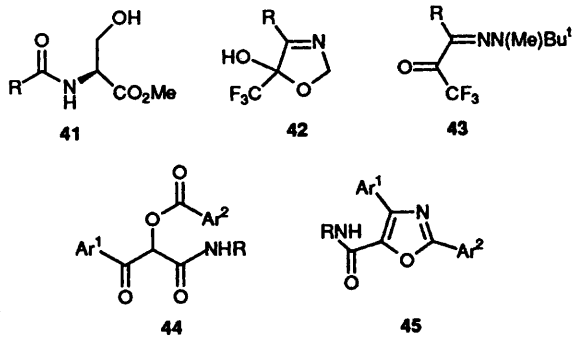
Reagents: (i) R^2Li, $(MeCO_2)O$; (ii) 600 °C/1 mmHg (72-80%)

Scheme 36



Reagents: (i) NaH, THF (94%); (ii) diphenylacetylene, MeCN; (iii) H_2O; (iv) (75%); (v) Ph_3PBr_2, Et_3N (61%)

Scheme 37



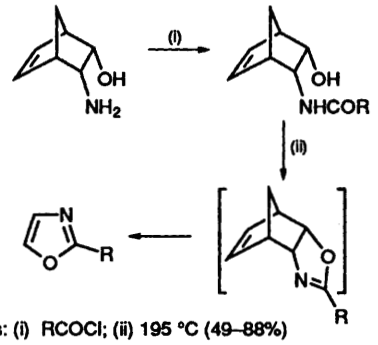
41 **42** **43**

44 **45**

2-Substituted oxazoles have been prepared in good yield by a reaction sequence (**Scheme 38**) with the retro Diels–Alder reaction as the final step.[100] A method of preparation of 2-arylbenzoxazoles **46** from anilines **47** (X = F or OH) makes use of a palladium-catalysed *N*-acylation with aryl iodides and carbon monoxide followed by cyclization.[101,102]

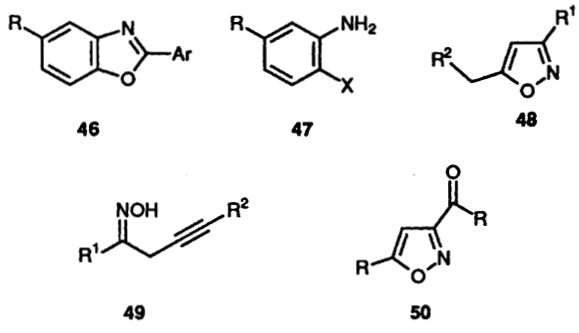
The known method of preparation of 3,5-disubstituted isoxazoles from α,β-unsaturated oximes has been carried out by using a new oxidant,

tetrakis(pyridine)cobalt(II)dichromate.[103] A different approach to 3,5-disubstituted isoxazoles **48** is the *exo* cyclization of oximes **49** of propargylic ketones with potassium carbonate.[104] An unusual method of preparation of isoxazoles **50** is the reaction of monosubsituted acetylenes with nitric acid in the presence of the catalyst $Bu_4N^+AuCl_4^-$. The ring system is produced by 1,3-dipolar cycloaddition of an intermediate acylnitrile oxide to the alkyne.[105]



Reagents: (i) RCOCl; (ii) 195 °C (49–88%)

Scheme 38

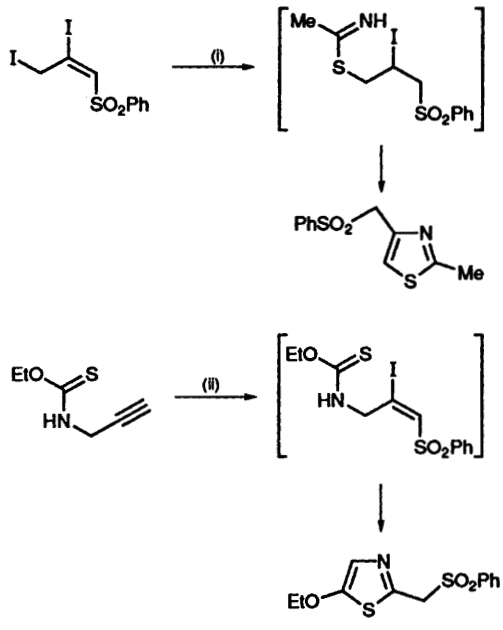


8 Thiazoles and selenazoles

Two approaches to the preparation of thiazoles from vinylsulfones are shown in **Scheme 39**.[11,93] The methods are complementary in terms of the substitution pattern of the thiazoles. A modification of the Hantzsch thiazole synthesis has been described which avoids the need to use α-halocarbonyl compounds: instead, the carbonyl compound and the oxidant PhI(OH)OTs are used.[106] An example is the preparation of the aminothiazole **51** (78%) from thiourea and hexane-2,5-dione. The corresponding selenadiazole was prepared in the same way.

9 Pyrazoles, indazoles, imidazoles, and benzimidazoles

The 1,3-dipolar cycloaddition of diazomethane to carbon–carbon multiple bonds provides one of the most straightforward methods of preparation of pyrazoles. Addition to vinylsulfones gives pyrazolines which can be converted into aromatic pyrazoles by reaction with a base.[107] Further examples of the synthesis of pyrazoles using (trimethylsiyl)diazomethyl-lithium, $Me_3SiC(Li)N_2$, have been published.[108,109]



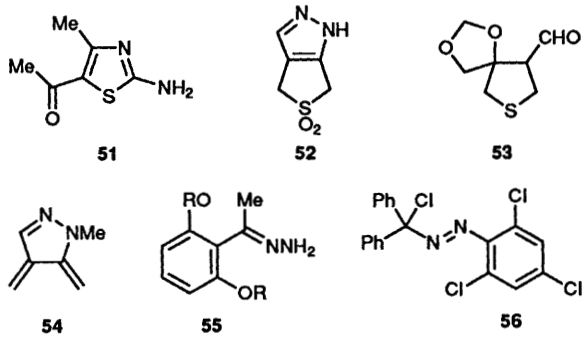
Reagents: (i) $MeCSNH_2$, DMF, pyridine (75%); (ii) I_2, $NaSO_2Ph$ (95%)

Scheme 39

Two approaches to the bicylic pyrazole **52** have been described, one using the cycloaddition of diazomethane to a vinylsulfone (analogous to that described above)[110] and the other, condensation of the aldehyde **53** with t-butoxycarbonylhydrazine followed by *S*-oxidation.[111] Compound **52** was used as a precursor to new reactive dienes such as **54**. Monosubstituted hydrazines have also been used to prepare pyrazoles from the alkenes $YCH=C(COCF_3)_2$ (Y = isobutoxy, ethylthio, or dimethylamino).[112]

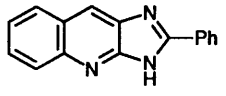
Indazoles have been produced in good yield by the cyclization of acetophenone hydrazones **55** with polyphosphoric acid.[113] The azo compound **56** was cyclized to 3-phenyl-1-(2,4,6-trichlorophenyl)indazole by reaction with antimony(V) chloride.[114]

Aminomalonamide, $H_2NCH(CONH_2)_2$, reacts with 1,2-diketone mono(phenylhydrazones) to give imidazole-2-carboxamides in moderate to good yield.[115]



A large number of methods exists for the preparation of benzimidazoles from benzenes with *ortho* nitrogen substituents and some recent syntheses are based on this approach.[116–118] The intramolecular amination approach to fused pyrroles shown in

Scheme 33 has also been investigated as a method of preparation of fused imidazoles.[119] It was less successful as a route to aminoazoles, although the imidazoquinoline **57** was prepared in moderate yield from 3-aminoquinoline. A route to imidazothiazoles **58** and other fused imidazoles has been described in which the imidazole ring is constructed by base-catalysed cyclization of the salts **59** followed by opening of the pyrrolidine ring.[120]



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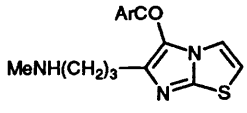

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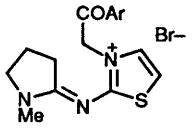
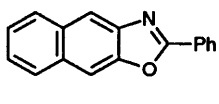


59

10 Oxadiazoles

The first 1,2,3-oxadiazole to be isolated is the naphtho fused compound **60**; it is stable below −20°C.[121] Examples of another new class of heterocycles, 3,4,5-trisubstituted 1,2,4-oxadiazolium salts **61**, have been prepared by the addition of isolable nitrile oxides to nitrilium salts.[122] Further examples of the synthesis of 1,3,4-oxadizoles from acylhydrazines have been described.[123,124]



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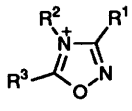


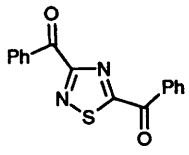
61

11 Thiadiazoles, dithiazoles, and dithiadiazoles

The cyclization of acylhydrazones of alkyl ketones with thionyl chloride (the Hurd–Mori reaction) represents the best general method of synthesis of 1,2,3-thiadiazoles. One problem with the procedure is that with unsymmetrical hydrazones (those having differently substituted methylene groups adjacent to the hydrazono group) the reaction often produces a mixture of isomeric thiadiazoles. A study of the effects of substituents has shown that the major product can, to some extent, be predicted on the basis of the relative rates of acid-catalysed enolization of the two methylene groups.[125] An improved synthesis of 1,2,3-thiadiazole-4-carbaldehyde by the Hurd–Mori reaction has also been reported.[126] A different approach to 1,2,3-thiadiazoles is the cycloaddition of diazomethane to compounds containing C=S bonds; examples of addition to ROCSCl and RSCSCl to give 5-subsituted 1,2,3-thiadiazoles have been described.[127]

Tetrasulfur tetranitride (S_4N_4) has proved to be a rich source of novel sulfur-nitrogen heterocycles. Ketones normally react with it to give 1,2,5-thiadiazoles as the major products, but phenacyl chloride gave the 1,2,4-thiadiazole **62** (60%) in boiling chlorobenzene.[128] Doubly alkylated 1,3,4-thiadiazolium salts **63** have been prepared for the first time by the cyclization of hydrazides **64** with triethyloxonium tetrafluoroborate.[129]

The reagent $[SNS]^+AsF_6^-$ has previously been shown to undergo cycloaddition to aliphatic alkynes and nitriles. It has now been shown to react with diphenylacetylene and with aromatic nitriles to give the heterocycles **65** and **66**.[130]



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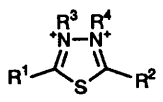

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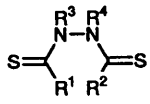

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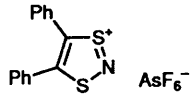

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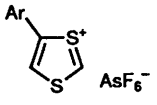
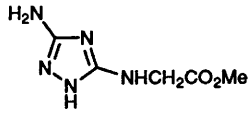


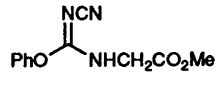
66

12 1,2,4-Triazoles

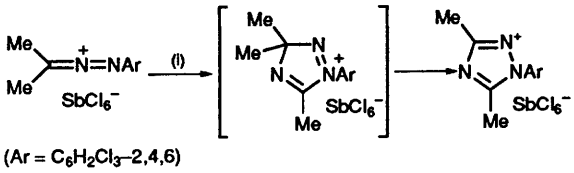
A useful route to disubstituted 1,2,4-triazoles is the reaction of *N*-cyanoisoureas and related compounds with hydrazine. Several new reactions of this type have been described, an example being the synthesis of the glycine derivative **67** in high yield from the isourea **68**.[131,132] A route to 1,2,4-triazolium salts illustrated in **Scheme 40** makes use of 1-aza-2-azonia-allene salts as electrophiles.[114]



67



68



(Ar = $C_6H_2Cl_3$-2,4,6)

Reagents: (i) MeCN (97%)

Scheme 40

13 References

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