Synthesis of aromatic heterocycles

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1 Introduction

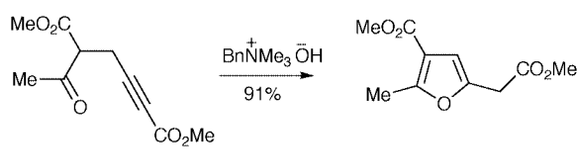
This review, as with previous ones in the series, has the aim of covering reports of new and improved methods of construction of aromatic heterocycles from acyclic precursors or by ring interconversion. The coverage cannot be comprehensive because of pressure of space. Many useful applications of existing methods are not included; in particular, several of those that make use of solid phase and polymer bound reagents, since the literature on these is now extensively covered elsewhere (for example, in *Perkin 1 Abstracts* and in other reviews[1]). As with the earlier literature surveys in this series the ring systems covered are mainly restricted to the more common monocyclic and bicyclic heterocycles.

New synthetic methods that make use of transition metals as catalysts or metal complexes (*e.g.*, carbene complexes) as reagents continue to appear; cyclisation reactions that are catalysed by palladium(0) species have been extended to the synthesis of many of the common ring systems. Some interesting new cycloaddition reactions have also been reported in this period. For example, Sauer's group has made extensive use of inverse electron demand Diels–Alder reactions of triazines and tetrazines for the synthesis of new pyridines and pyridazines and Wong and co-workers have made impressive use of cycloaddition reactions of trialkylsilyl- and trialkylstannylacetylenes to provide routes to 3,4-disubstituted furans, thiophenes and pyrroles. Rees and co-workers have continued to find new applications of trithiazyl chloride for the preparation of five-membered heterocycles containing sulfur and nitrogen.

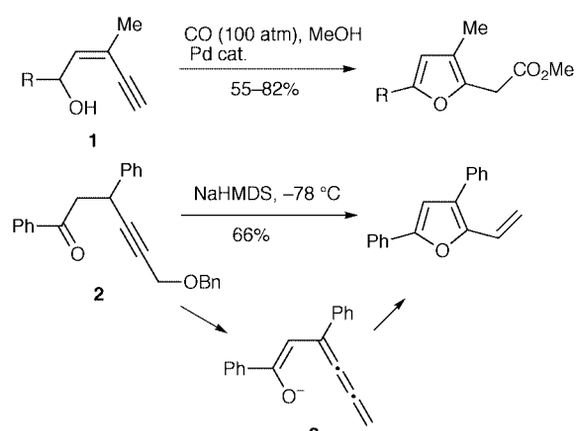
2 Furans and benzofurans

Methods for the synthesis of substituted furans, involving both construction of the ring and substitution reactions, have been reviewed.[2] The use of 3,4-bis(trialkylstannyl)furans and the corresponding bis(trimethylsilyl)furan for the synthesis of other 3,4-disubstituted furans has also been reviewed.[3] An improved version of Marshall's synthesis of furans from β-alkynyl allylic alcohols, making use of silver nitrate on silica gel as the catalyst, has been described.[4]

As in earlier reviews, several of the useful new routes to furans involve cyclisation reactions in which oxygen nucleophiles undergo addition to alkynes. The intramolecular addition of enolate anions to activated alkynes provides a simple and versatile route to several furans. An example is shown in Scheme 1; other terminal activating groups on the alkyne, including benzenesulfonyl and vinyl groups, are also effective in promoting the cyclisation.[5] Full details of the scope and limitations of the similar base catalysed cyclisation of 1-aryl- and 1-vinylpent-4-ynones to furans have also appeared.[6] Two other related cyclisations of alkynes are shown in Scheme 2. Methyl furan-2-acetates are formed by the palladium catalysed cyclisation and carbonylation of 5-hydroxyenynes **1**[7] and a related cyclisation, using potassium tetraiodopalladate as a catalyst, has been used in a new synthesis of rosefuran.[8] The base induced cyclisation of acetylenic ketones such as **2** provides a route to 2-alkenylfurans; the authors suggest that cumulenes such as **3** are intermediates.[9]

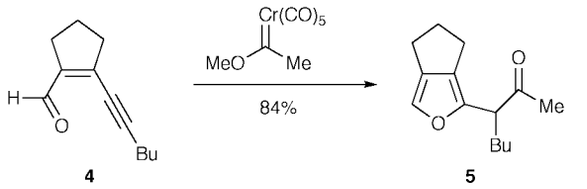


Scheme 1

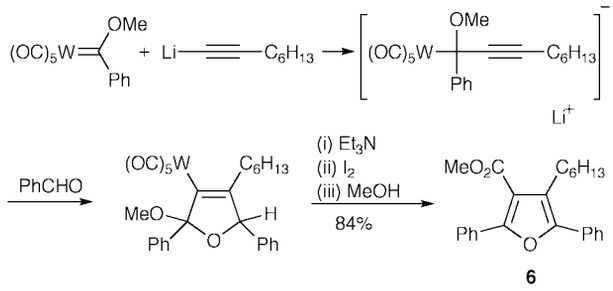


Scheme 2

Two furan syntheses involving metal carbene complexes are exemplified in Schemes 3 and 4. The aldehyde **4** reacts with the carbene complex $(CO)_5CrC(Me)OMe$ to give the bicyclic furan **5** in which the carbon atoms from the carbene complex are located in a side chain; an analogous cyclisation occurs with the



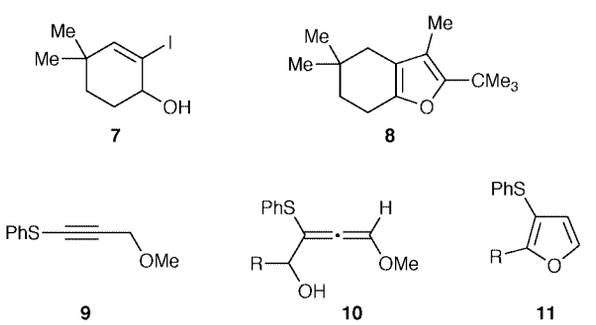
Scheme 3



Scheme 4

methyl ketone corresponding to **4**.[10] In an extension of a method reported earlier[11] Iwasawa and co-workers have described a synthesis of substituted methyl furan-3-carboxylates such as **6** from tungsten carbene complexes, lithium acetylides and aldehydes.[12] Tetrasubstituted furan-3-carboxylates have also been synthesised in moderate yield from 3-hydroxy-1,2-dioxane-4-carboxylates (cyclic peroxides) by reaction with acids.[13]

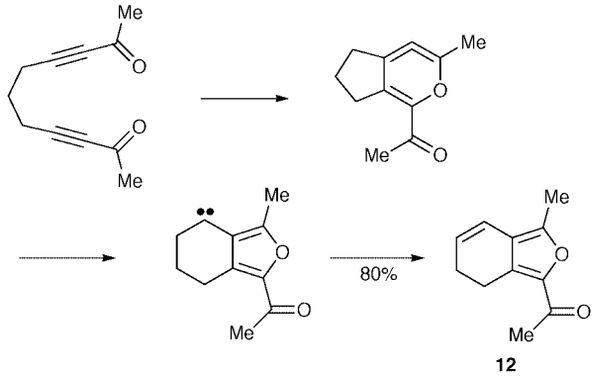
The palladium catalysed annelation of iodo compounds with internal alkynes, previously used by Larock's group to synthesise a variety of heterocycles, has now been applied to furan synthesis. For example, the tetrahydrobenzofuran **8** was produced (69%) from the vinyl iodide **7** and 4,4-dimethylpent-2-yne.[14] The mercury(II) catalysed cyclisation of the allenic alcohols **10**, generated *in situ* from 3-methoxy-1-phenylthioprop-1-yne **9** and aldehydes, leads to the 2,3-disubstituted furans **11**.[15]



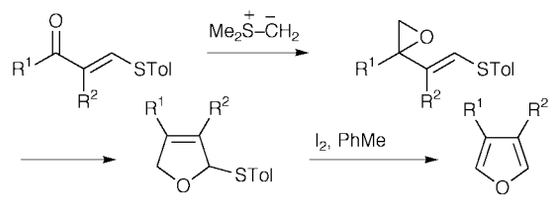
An unusual route to *c*-fused furans is illustrated in Scheme 5. Intramolecular cycloaddition of conjugated ynones to triple bonds leads to the formation of furans such as **12** which, the authors suggest, are formed by way of strained bicyclic allenes and carbenes.[16]

Two existing routes to 3,4-disubstituted furans have been improved. The Garst–Spencer furan annelation from 3-(butylthio)enones was modified by replacing the butyl group with a 4-tolyl group and by using iodine as the aromatising agent (Scheme 6).[17] The oxidation of 2-substituted and 2,3-disubstituted but-2-ene-1,4-diols **13** in a two phase system led to a variety of 3-substituted and 3,4-disubstituted furans in good yield; for example, 3,4-dibromofuran was prepared (83%) in this way.[18]

There are relatively few good methods for the synthesis of furans with specific substituents at the 2 and 4 positions and some useful new methods have been described. A simple

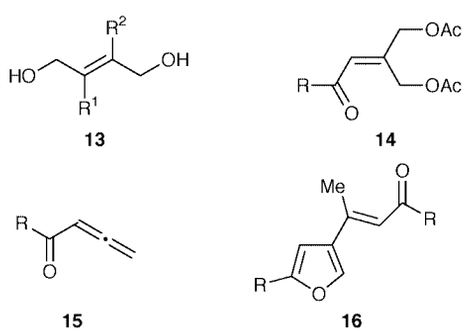


Scheme 5

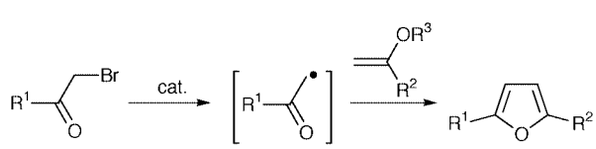


Scheme 6

synthesis of 2-substituted furan-4-methanols involves the intermediacy of enones **14**, which are prepared by a Horner–Wadsworth–Emmons reaction then cyclised by reaction with HCl.[19] The dimerisation of terminal allenic ketones **15** leads to 2,4-disubstituted furans **16** in preparatively useful yields when $PdCl_2(MeCN)_2$ is used as the catalyst in acetonitrile.[20] A potentially general route to 2,4-disubstituted furans has been used by Fürstner and his co-workers in a synthesis of the terpene ircinin-4, the structure of which incorporates a 2,4-dialkylfuran subunit.[21] This makes use of essentially the same methodology as was invented for 2,4-disubstituted pyrroles in Fürstner's route to roseophilin and which is outlined in Section 4 (see Scheme 26).



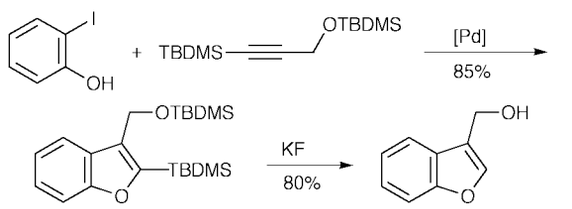
Several furans have been prepared in moderate to good yield by the reaction of α-bromomethyl ketones with enol ethers in the presence of the catalyst $[ReCl(N_2)(PMe_2Ph)_4]$. It is proposed that this generates acylmethyl radicals as the reactive intermediates (Scheme 7).[22]



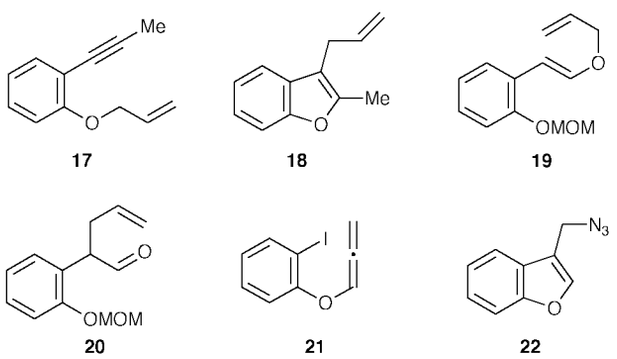
Scheme 7

Cyclisation reactions involving palladium catalysis are predominant among recently described methods for preparing benzofurans. Details have been published of the sequential palladium catalysed coupling of 2-iodophenols with alk-1-ynes

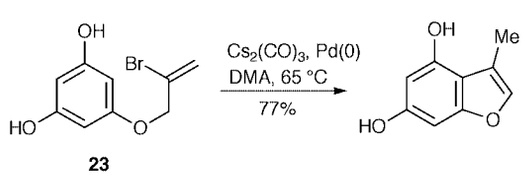
and *endo* cyclisation to 2-substituted benzofurans.[23] With silyl protected alkynols the method provides a route to benzofuran-3-methanol (Scheme 8) and to other alkan-3-ols.[24] A variant which leads to 2,3-disubstituted benzofurans is to carry out the reaction with allyl 2-alkynylphenyl ethers; for example, the ether **17** gave 3-allyl-2-methylbenzofuran **18** (76%) on palladium(0) catalysed cyclisation. A π-allylpalladium complex is suggested as an intermediate.[25] 3-Allenylbenzofurans have also been prepared by a similar method.[26] A different approach to 3-allylbenzofurans has been described that is based on salicylaldehyde derivatives; the aldehyde function is converted into an allyl vinyl ether (such as **19**) by Wittig olefination and this is then subjected to Claisen rearrangement. The aldehydes (such as **20**) so formed are then converted into 3-allylbenzofurans by acid catalysed cyclisation and dehydration.[27]



Scheme 8

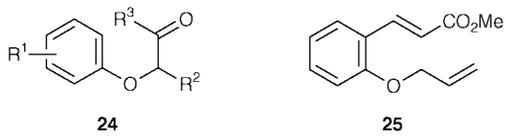


Palladium catalysed cyclisation reactions involving allenes have provided another route to 3-substituted benzofurans. The allene **21** gave 3-azidomethylbenzofuran **22** (71%) with sodium azide and a palladium(0) catalyst.[28] Other nucleophiles can be used to capture the intermediate organopalladium species; thus, with sodium benzenesulfinate, 3-(phenylsulfonylmethyl)benzofuran was isolated. Phenyl allyl ethers such as **23** have been cyclised to benzofurans by heating with caesium carbonate and a palladium catalyst (Scheme 9).[29] It is suggested that the reaction is promoted by the formation of phenolate anions, which are more reactive than free phenols in the cyclisation step. Intramolecular Heck reactions of allyl 2-iodophenyl ethers have been applied to a solid phase synthesis of benzofuran-3-ylacetamides.[30]

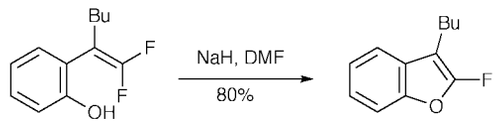


Scheme 9

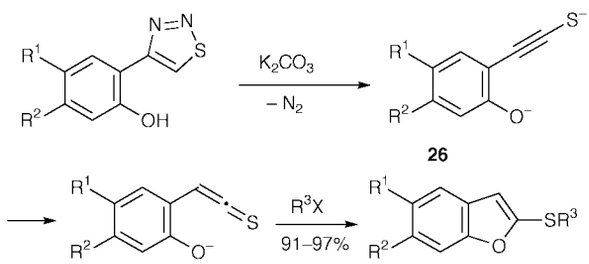
A standard route to benzofurans is the acid catalysed cyclodehydration of phenoxymethyl ketones **24**. A versatile route to these ketones, based on the reaction of anions of 1-phenoxymethylbenzotriazoles with aldehydes, has been described; the complete sequence leading to the benzofurans can be carried out in one pot.[31] Benzofuran has been isolated in 60% yield from the flash pyrolysis of the cinnamyl ester **25**; the reaction probably involves the generation and cyclisation of a phenoxy radical.[32]



Two base-induced cyclisation reactions that lead to benzofurans are illustrated in Scheme 10[33] and in Scheme 11.[34] The base induced fragmentation of 1,2,3-thiadiazoles is a precedented reaction and results in the generation of the anions **26** as intermediates in the route to 2-alkylthiobenzofurans.



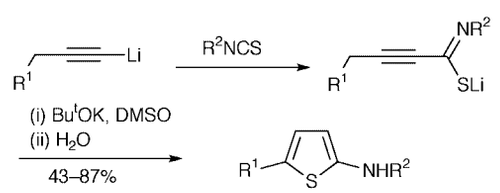
Scheme 10



Scheme 11

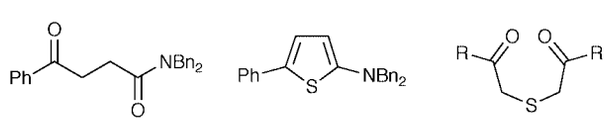
3 Thiophenes and benzothiophenes

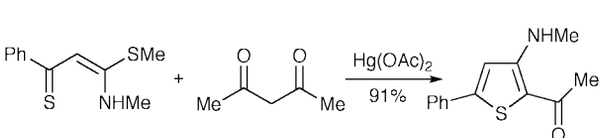
Several 2-alkylaminothiophenes have been prepared from terminal alkynes and alkyl or aryl isothiocyanates by the route shown in Scheme 12.[35] Similar syntheses of 2-alkylaminothiophenes bearing dialkylamino substituents at C-5[36] and heteroatom substituents at C-3[37] have also been described.



Scheme 12

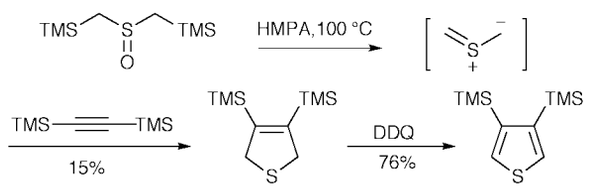
The tertiary amide **27** gave the 2-aminothiophene **28** (57%) on reaction with Lawesson's reagent.[38] When secondary amides were used mixtures of aminothiophenes and pyrroles were produced. 3-Alkylaminothiophenes were obtained in high yield from reactions of ketene *N*,*S*-acetals such as **29** with 1,3-dicarbonyl compounds and mercury(II) acetate; an example is shown in Scheme 13.[39]





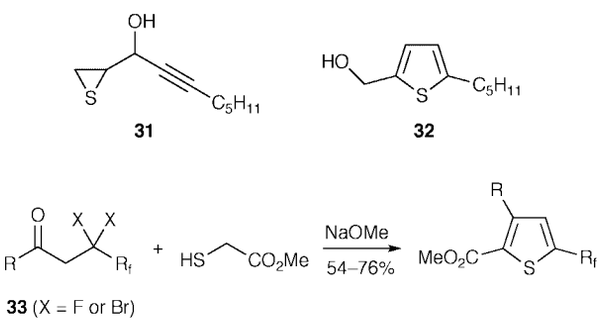
Scheme 13

Details have been published of the remarkably efficient synthesis of 3,4-bis(trimethylsilyl)thiophene by the high temperature Diels–Alder addition of bis(trimethylsilyl)acetylene to 4-phenylthiazole. The thiophene can be prepared in batches of up to 8 g by this method, which has also been extended to some other 3,4-disubstituted thiophenes.[40] A 1,3-dipolar cycloaddition approach was also investigated (Scheme 14) but was less efficient. Experimental details have also been provided for the preparation of 3,4-disubstituted thiophenes from the diketones **30** by reductive cyclisation using titanium reagents.[41] Thiophenes bearing bulky substituents (*tert*-butyl, 1-adamantyl, *etc*.) have been prepared by this route.



Scheme 14

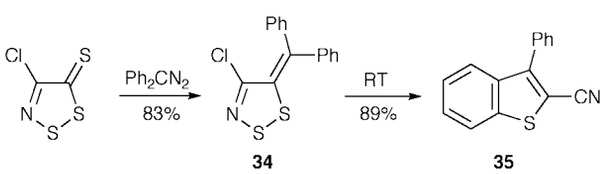
Two new thiophene syntheses have been described that make use of the methodology previously developed for the preparation of other heterocycles. Marson and Campbell have applied a synthesis of furans, based on the ring expansion of functionalised epoxides, to analogous episulfides; for example, the episulfide **31** gave the thiophene-2-methanol **32** (80%) when treated with a catalytic amount of mercury(II) oxide in dilute sulfuric acid at room temperature.[42] α-Fluoroalkylcarbonyl compounds **33**, which have previously been used in the synthesis of fluoroalkyl substituted pyrazoles and pyrimidines, gave 2-(α-fluoroalkyl)thiophenes on reaction with methyl mercaptoacetate and sodium methoxide (Scheme 15).[43]



33 (X = F or Br)

Scheme 15

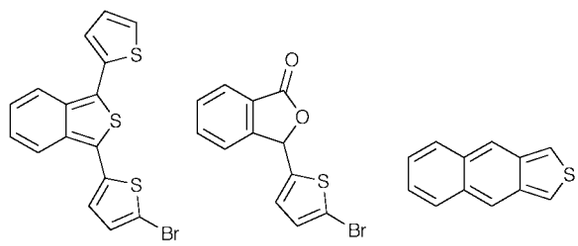
Relatively few new routes to benzothiophenes have been described in the period under review. The route to benzofurans described by Katritzky and co-workers has also been used as a one pot synthesis of benzothiophenes, the thioethers analogous to **24** being intermediates.[31] 6-Hydroxybenzothiophenes have been synthesised by a procedure in which the benzene ring is annelated to a 2-substituted thiophene by acid catalysed cyclisation.[44] 4-Chloro-1,2,3-dithiazole-5-thione, which is readily prepared from 4,5-dichlorodithiazolium chloride (Appel's salt) and hydrogen sulfide, reacts with diphenyldiazomethane to give the benzothiophene **35** by way of the isolable intermediate **34** (Scheme 16).[45]



34 **35**

Scheme 16

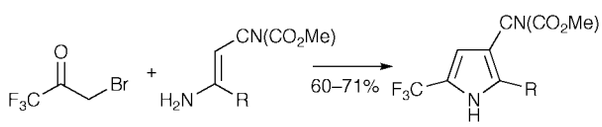
In a continuation of their work on benzo[*c*]thiophenes, Cava and his group have described a synthesis of the bis(2-thienyl)-benzo[*c*]thiophene **36** from the phthalide **37**.[46] They have also described a much improved synthesis of naphtho[2,3-*c*]thiophene **38** which makes use of a base catalysed Pummerer reaction.[47]



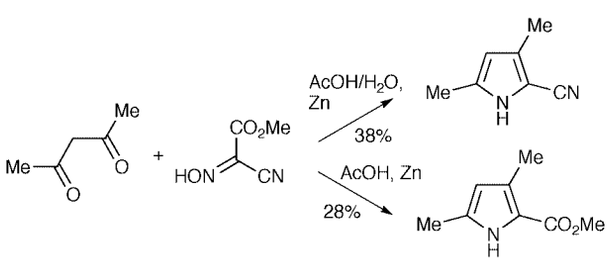
36 **37** **38**

4 Pyrroles

A review of routes to arylpyrroles covers both classical and recent methods, with particular emphasis on the Trofimov synthesis from aryl ketoximes and acetylenes.[48] Several useful variants of classical methods have been reported. The optimum conditions for the preparation of 1-benzylpyrroles from benzylamines and 2,5-dimethoxytetrahydrofuran require the use of a mixture of pyridine and acetic acid as solvent.[49] This synthetic method has also been adapted to provide a route to 3,4-dialkoxypyrroles.[50] 5-Trifluoromethylpyrroles have been prepared by a modified Hantzsch synthesis (Scheme 17) in which the use of preformed enamines avoids the side reaction that leads to furans.[51] The use of organotin enamines, which are stable enough to be isolated and stored, also leads to pyrroles in high yields.[52] The products of Knorr-type reductive condensation of 1,3-diketones with oximinocyanoacetate esters depend on whether dry or aqueous acetic acid is used as the solvent (Scheme 18).[53] Glyoxal monophenylhydrazone has been used in Knorr-type condensations with β-keto esters to give 1,2,3,4-tetrasubstituted pyrroles.[54] Atmospheric nitrogen has been used for the first time in place of the usual ammonia in the synthesis of pyrroles from 1,4-dicarbonyl compounds: the reaction involves the reduction of nitrogen by a mixture of titanium(IV) chloride, chlorotrimethylsilane and lithium metal.[55]

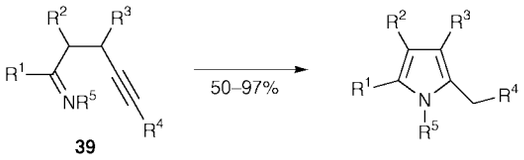


Scheme 17



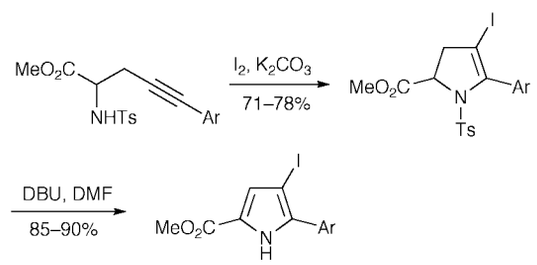
Scheme 18

Some cyclisation reactions that were previously used to synthesise furans have been successfully adapted to the preparation of pyrroles. Thus, the imines **39**, which are formed from the corresponding ketones and primary amines, spontaneously cyclise to pyrroles (Scheme 19).[6] Some related palladium

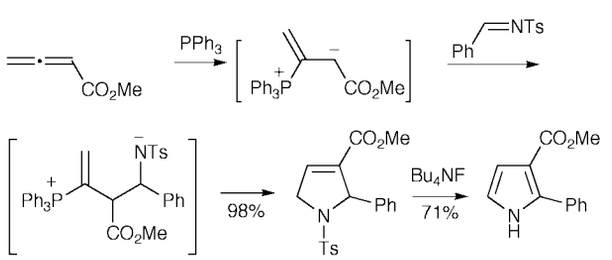


Scheme 19

catalysed cyclisations of ynone *p*-tolylsulfonylhydrazones to 1-(*p*-tolylsulfonylamino)aminopyrroles have been described.[56] Knight and co-workers have adapted their iodocyclisation reactions to provide routes 2,5-disubstituted pyrroles with or without an iodo substituent at C-3.[57,58] The methodology is illustrated in Scheme 20.[58] The synthesis of methyl 2-arylpyrrole-3-carboxylates from methyl buta-2,3-dienoate which is exemplified in Scheme 21 is conceptually quite different but probably involves the same kind of *endo*-cyclisation and aromatisation steps.[59]

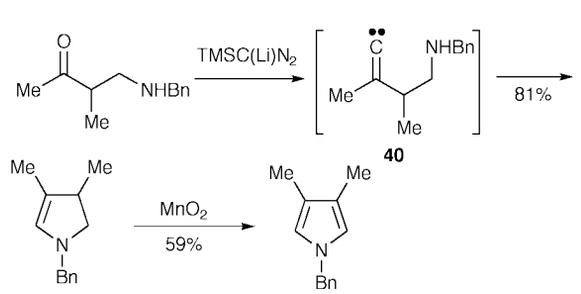


Scheme 20



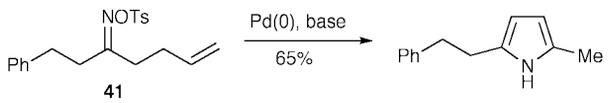
Scheme 21

Other new cyclisation reactions in which the N–C2 bonds of pyrroles are formed are illustrated in Scheme 22[60] and Scheme 23.[61] Trimethylsilyldiazomethyllithium is used to generate a vinylidene carbene **40** from which the five-membered ring is generated by intramolecular N–H insertion. The oxime tosylate **41** probably cyclises by N–O insertion of the palladium catalyst followed by an intramolecular Heck reaction. 2-Substituted-3-nitropyrroles were isolated in good yield from the reaction of aminoacetaldehyde dimethyl acetal with β-(methylthio)nitroalkenes.[62]

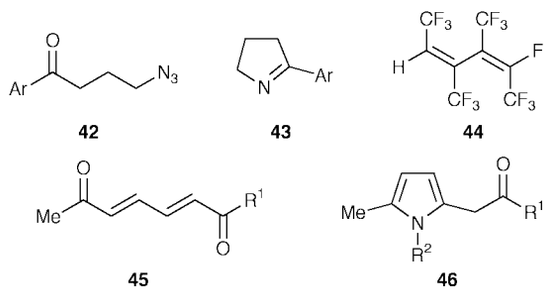


Scheme 22

The aza-Wittig reaction of azido ketones **42** has been previously reported as a route to pyrrolines **43**. These pyrrolines have now been efficiently converted into 2-aryl-3-halopyrroles by bis-halogenation at C-3 with NCS or NBS followed by base

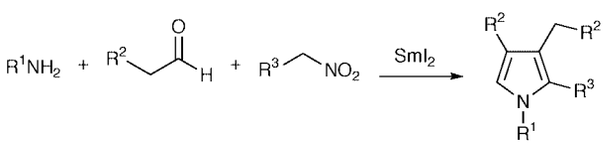


Scheme 23

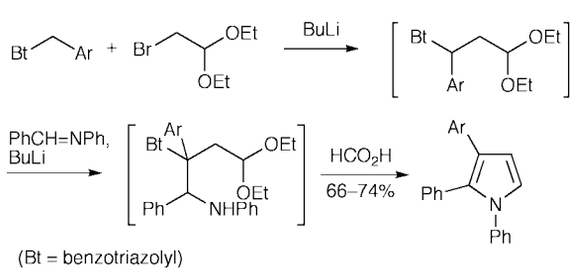


induced dehydrohalogenation.[63] Other cyclisation reactions that have been used for specifically substituted pyrroles include the reaction of the diene **44** with arylamines to give 1-aryl-2,3,4,5-tetrakis(trifluoromethyl)pyrroles,[64] the cyclisation of 5-chloropent-3-en-2-one with homochiral amines to give chiral 1-substituted 2-methylpyrroles[65] and the reaction of the dienones **45** with various amines to give 1,2,5-trisubstituted pyrroles **46**.[66]

Two three-component pyrrole syntheses are illustrated in Scheme 24[67] and in Scheme 25.[68] The samarium(II) iodide catalysed condensation of alkylamines, aldehydes and nitroalkanes gave 1,2,3,4-tetrasubstituted pyrroles in moderate to good yield. Katritzky and co-workers used benzotriazole methodology to construct intermediates from which 1,2,3-triarylpyrroles were obtained by acid catalysed cyclisation.[68]



Scheme 24

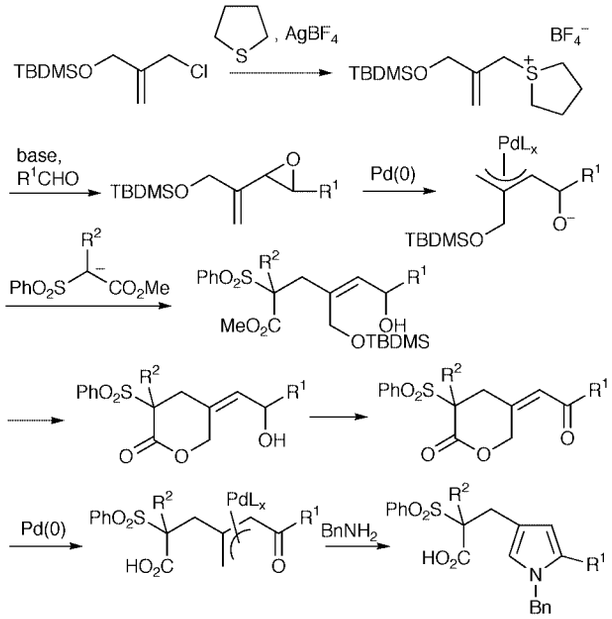


Scheme 25

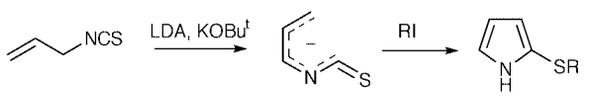
Fürstner's remarkably short synthesis of the macrotricyclic core of roseophilin, a pyrrolic antitumour agent, incorporates a new and potentially more general method of synthesis of 2,4-disubstituted pyrroles; the key steps are outlined in Scheme 26.[69,70] It includes the formation and reaction of two π-allylpalladium intermediates.

A simple route to 2-(alkylthio)pyrroles is the base catalysed cyclisation of allyl isothiocyanate followed by *S*-alkylation (Scheme 27).[71,72] The use of isothiocyanate anions has been extended to the synthesis of more highly substituted 2-(alkylthio)pyrroles.[73] A similarly mild synthesis of 2-arylpyrroles is the opening of cyclopropane-1,2-diammonium salts **47** with aromatic aldehydes.[74] The reactions go in buffered methanol at room temperature and bis(alkylammonium) salts can be used in the same way.

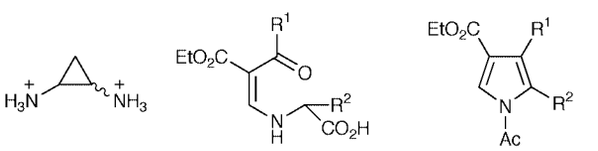
β-Enaminocarbonyl compounds have been used to construct



Scheme 26

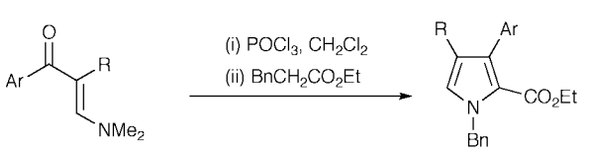


Scheme 27

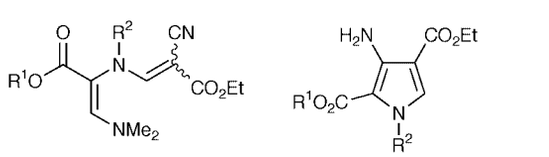


47 48 49

a variety of new pyrroles. The little-used Zav'yalov pyrrole synthesis, the cyclisation of enamino acids **48** to *N*-acetylpyrroles **49** with acetic anhydride and a base, has been reinvestigated and applied to the synthesis of some novel [*c*]-fused pyrroles.[75] Several new trifluoromethylpyrroles have been prepared by a related base catalysed cyclisation of trifluoroacetylenamines.[76] A synthesis of ethyl 3-arylpyrrole-2-carboxylates (Scheme 28) involves the intermediacy of vinylogous amidinium salts.[77] 3-Aminopyrrole-2,4-dicarboxylates **51** have been prepared by the acid catalysed cyclisation of enaminones **50**[78] and an efficient solid phase pyrrole synthesis is based on the condensation of resin bound enaminoamides with nitroalkenes.[79]

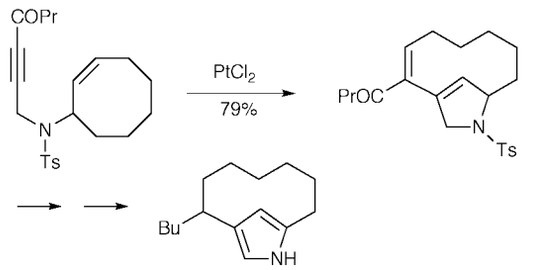


Scheme 28



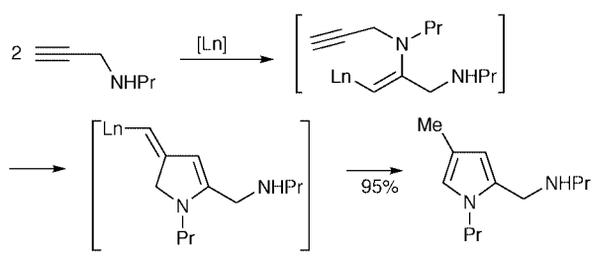
50 51

An interesting new pyrrole synthesis was developed as part of a route to the antibiotic streptorubin B.[80] An enyne metathesis reaction (Scheme 29) was used as the key step in constructing the pyrrolic core. Initially platinum(II) chloride was used as the



Scheme 29

catalyst but it was subsequently found that simple protic and Lewis acids could also be used to bring about such cyclisations. The dimerisation of propargylamines to pyrroles proceeds under the influence of a lanthanide catalyst; an example is shown in Scheme 30.[81]

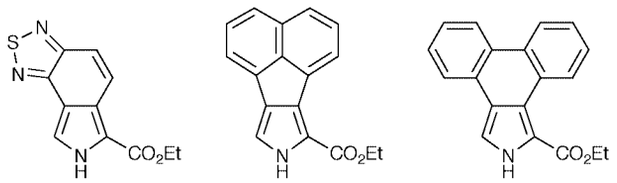


Scheme 30

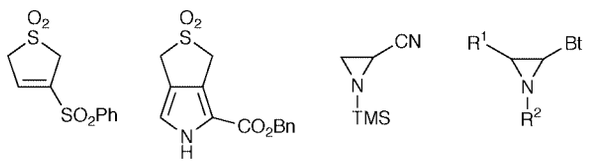
Isocyanides continue to be key intermediates in the synthesis of novel pyrroles. The Barton–Zard reaction (the base catalysed addition of alkyl isocyanoacetates to nitroalkenes) has been used to prepare a variety of new pyrroles;[82] in particular, Lash's group has made extensive use of the reaction as a route to pyrrolic intermediates for porphyrin synthesis starting from polycyclic aromatic nitro compounds.[83–85] The fused pyrroles **52**–**54** are examples of compounds that have been obtained in preparatively useful yields by this method. In an analogue of the Barton–Zard reaction, addition of the anions of alkyl isocyanoacetates to α,β-unsaturated sulfones led to the formation of a variety of unusually substituted pyrroles, including the bicyclic pyrrole **56** (60%) from the sulfone **55**.[86] Tosylmethyl isocyanide (TosMIC) has been used to make new [*c*]annelated pyrroles[87] and 3-arylpyrroles.[88] By prior reaction with base and chlorotrimethylstannane, its addition to enones provided a direct route to 2-trimethylstannylpyrroles.[89] This provides the basis for the preparation of other 2-substituted pyrroles. In a similar way, 3,4-bis(trimethylsilyl)pyrrole can be used as a precursor of other β-substituted pyrroles; this has been prepared efficiently by 1,3-dipolar cycloaddition of the azomethine ylide derived from the aziridine **57** to bis(trimethylsilyl)acetylene.[90] Pyrroledicarboxylic esters have been prepared by similar 1,3-dipolar addition of benzotriazolylaziridines **58** to acetylenic esters.[91]

5 Indoles, indolizines and carbazoles

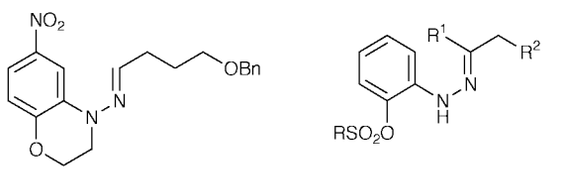
Several useful new modifications of classical methods of indole synthesis have been described. Two variants of the Fischer indole cyclisation enable the method to be used for the preparation of indoles bearing oxygen substituents at C-7 and thus avoid "abnormal" cyclisation on to the substituted carbon. A temporary tether was used in the cyclisation of the hydrazone **59**; the tether was subsequently removed by reaction with sodium ethoxide to provide a route to the 7-hydroxy-4-nitroindole.[92] A sulfonyloxy group in hydrazones **60** also directs cyclisation to give mainly 7-substituted indoles.[93] The N–H insertion reaction of rhodium carbenoids has been used by Moody and Swann to construct α-arylamino ketone inter-



52 53 54

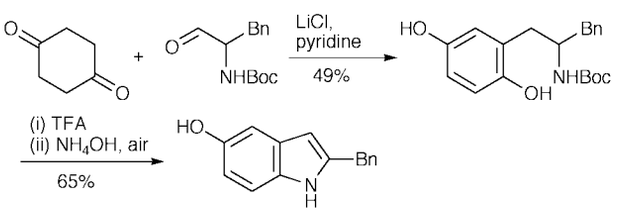


55 56 57 58



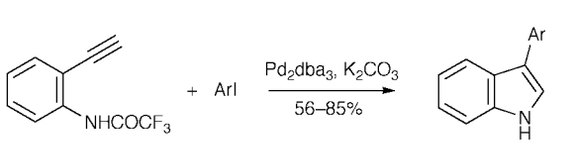
59 60

mediates similar to those in the Bischler indole synthesis; these were then cyclised under acidic conditions to produce a variety of indole-2-carboxylic acid esters.[94] A route to 2-substituted 5-hydroxyindoles that provides an alternative to the Nenitzescu synthesis makes use of cyclohexane-1,4-dione as the 6-membered ring component; an example is shown in Scheme 31.[95] The Sundberg indole synthesis has been used to provide the first preparation of 2-nitroindole: 2-azido-β-nitrostyrene was heated in xylene to give the indole in 54% yield.[96]



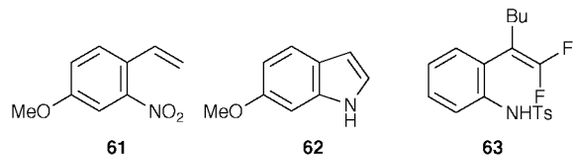
Scheme 31

The cyclisation of 2-alkynylaniline derivatives provides a versatile synthesis of indoles and several new variants of the reaction have been reported. 3-Arylindoles are obtained by the palladium catalysed *endo* cyclisation of 2-ethynyltrifluoroacetanilide and trapping of the intermediate palladium species with aryl iodides (Scheme 32).[97] 2-Substituted 3-allylindoles have also been prepared by a palladium catalysed cyclisation and capture of the intermediates by allylic esters.[98] Similar syntheses of 2,3,6-trisubstituted indoles have been carried out in the solid phase.[99] Such cyclisations can also be brought about by bases and this methodology has been applied to the synthesis of 4,5,7-trimethoxyindole and other oxygen substituted indoles.[100] Molybdenum catalysed cyclisations of this type have also been reported; indole itself has been prepared in good yield from 2-ethynylaniline with the aid of a molybdenum catalyst.[101] Cyclisations of 2-alkynylanilines to 2-substituted indoles can also be catalysed by TBAF, and in this mild procedure other reactive functional groups are unaffected.[102]



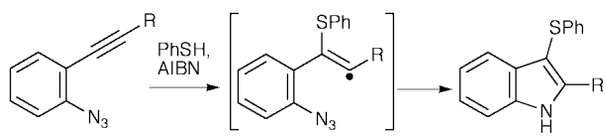
Scheme 32

The reductive palladium catalysed *endo* cyclisation of 2-nitrostyrenes has previously been shown to provide a route to indoles; new, milder conditions for the reaction, involving heating the precursor and catalyst at 70 °C under 4 atm carbon monoxide, have now been described. The indoles are isolated in moderate to excellent yield; for example, 4-methoxy-2-nitrostyrene **61** gave 6-methoxyindole **62** in 89% yield.[103] A base induced *endo* cyclisation of the difluoroalkene **63** led to the formation of 3-butyl-2-fluoro-1-(*p*-tolylsulfonyl)indole in high yield; a similar methodology was used to produce the corresponding benzofuran and benzothiophene.[33]

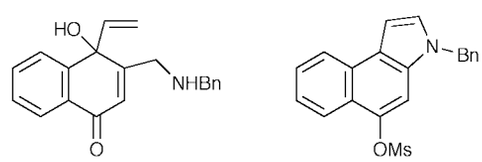


61 62 63

Although limited in scope, the radical cyclisation process shown in Scheme 33 represents an unusual method for the construction of the N–C2 bond of indoles.[104] Another reaction which is represented as a new method of constructing this bond (intramolecular nucleophilic addition to an allyl cation) is the cyclisation of the enaminone **64** to the benzindole **65** with methanesulfonyl chloride.[105]

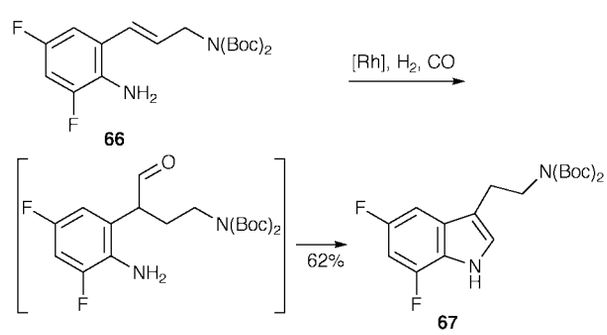


Scheme 33



64 65

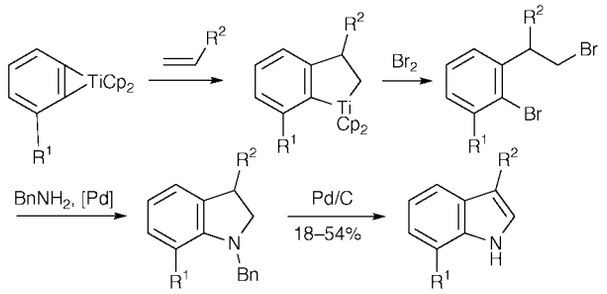
A route to substituted tryptamines from iodoanilines makes use of a Heck vinylation reaction followed by a hydroformylation to construct an intermediate aldehyde from which the N–C2 bond is formed. For example, the intermediate aniline **66**, formed from the iodoaniline by a Heck reaction, was converted into the substituted tryptamine **67** (Scheme 34).[106]



66 67

Scheme 34

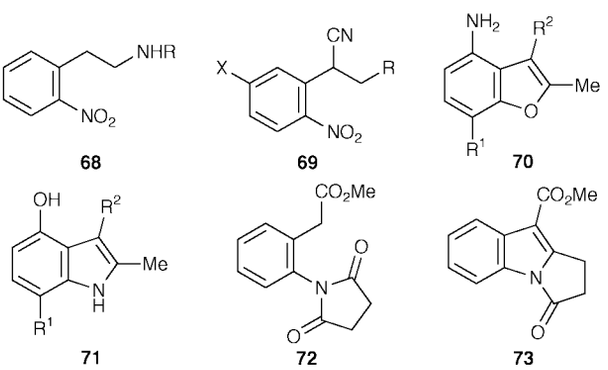
A new route to indoles, outlined in Scheme 35, makes use of the reaction of the air stable complex Cp_2TiCl_2 with aryl Grignard reagents to generate a titanocene–benzyne complex, which undergoes insertion reactions with alkenes. The indole ring is constructed by bromination followed by palladium catalysed amination of the resulting aryl bromide.[107]



Scheme 35

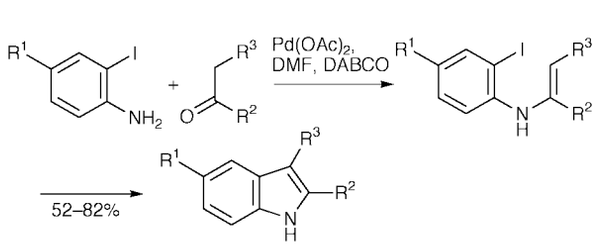
An electrochemical method, involving the use of a redox flow cell, has provided an efficient synthesis of 1-alkylaminoindoles from the nitroamines **68**.[108] 3-Cyano-1-hydroxyindoles have been prepared in good yield by base catalysed cyclisation of the aromatic nitro compounds **69**.[109] In concentrated hydrochloric acid 4-amino-2-methylbenzofurans **70** are converted in high yield into the isomeric 4-hydroxy-2-methylindoles **71**. The reaction requires the 2-methyl substituent and occurs only in the presence of concentrated acids, indicating that a tertiary carbocation intermediate is involved.[110] The known "lateral lithiation" of the methyl group of Boc-protected *o*-toluidines has been applied to the synthesis of ethyl indole-2-carboxylates by quenching the anion with diethyl oxalate; the reaction allows the preparation of indole esters bearing a range of substituents in the six-membered ring.[111]

New examples of base catalysed reactions which lead to formation of the indole C2–C3 bond include the cyclisation of the succinimide **72** to the indole **73**[112] and the intramolecular addition of benzyl sulfones to imines and carbodiimides.[113]

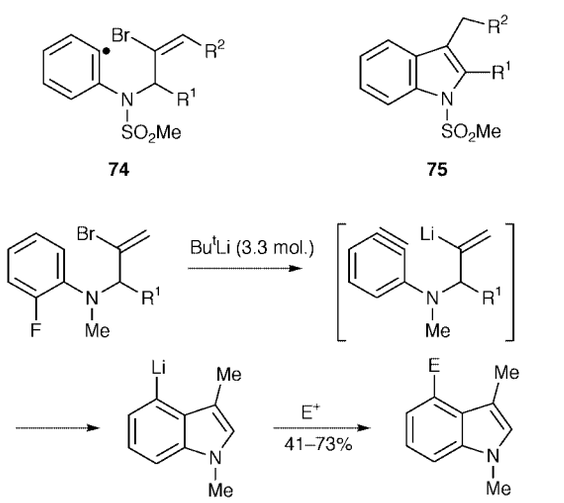


Palladium catalysed cyclisation reactions are increasingly important methods for the formation of the C3–C3a bond of indoles. The methodology illustrated in Scheme 9 for the construction of hydroxybenzofurans has also been applied to indole synthesis[29] as has the solid phase intramolecular Heck reaction.[30] A simple condensation–cyclisation procedure, shown in Scheme 36, is the palladium catalysed reaction of 2-iodoanilines with ketones.[114] Related cyclisations of preformed enamines to 2-trifluoromethylindole-3-carboxylic acid esters have been described.[115]

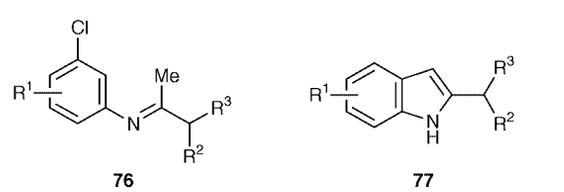
A new indole synthesis makes use of radical cyclisation for the construction of the C3–C3a bond. The radical intermediates **74** were generated from the corresponding diazonium tetrafluoroborates with sodium iodide in acetone and cyclised to the indoles **75**.[116] The cyclisation onto a vinyl bromide allows a wider variety of indoles to be constructed than the analogous radical cyclisation onto a triple bond. Vinyl bromides are also used as precursors in the synthesis of 3,4-disubstituted indoles shown in Scheme 37.[117] This reaction is rationalised as involving an aryne intermediate; after cyclisation the aryllithium species is intercepted by electrophiles such as benzaldehyde and ethyl chloroformate. Kuehm-Caubère and co-workers have also described an efficient synthesis of 2-substituted indoles by arynic cyclisation. The aryl imines **76** derived from methyl ketones gave the indoles **77** in the presence of the complex base derived from sodamide and sodium *tert*-butoxide.[118]



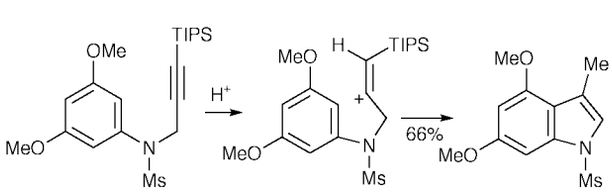
Scheme 36



Scheme 37

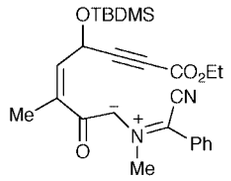


3-Methylindoles can be prepared from propargylanilines (prop-2-ynylanilines) by the new and conceptually simple method illustrated in Scheme 38.[119] There are several constraints on the method which were established experimentally: the trialkylsilyl group and the nitrogen protecting group were chosen in order to be stable to methanesulfonic acid, the cyclising agent, and the position at which the cation cyclises must be sufficiently activated by ring substituents. Another acid catalysed cyclisation procedure which leads to indoles unsubstituted in the five-membered ring, is the reaction of anilines with triethanolamine in the presence of tin(II) chloride and a ruthenium catalyst.[120]



Scheme 38

The indoloquinone **79** has been synthesised by a route in which the key step is intramolecular 1,3-dipolar addition of the azomethine ylide **78**.[121] The 1,3-dipole was generated from an *N*-methyloxazolium salt by ring opening with cyanide. A novel



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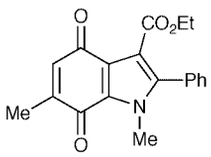
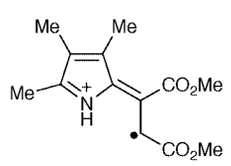


79

synthesis of 3-nitroindoles is based on the construction of the six-membered ring from a 3-nitropyrrole intermediate.[122]

One of the standard synthetic methods for indolizines is the reaction of activated alkenes or alkynes with pyridinium ylides. This method has been used to prepare some new 1-trifluoromethylindolizines from 2-bromo-3,3,3-trifluoropropene.[123] Methods of synthesis that start from pyrroles are much less common. A method involving (stepwise) cycloaddition of radical cations such as **80** to β-acceptor substituted enamines has been described. The cations were generated by electrochemical oxidation of the corresponding pyrroles and the final products were indolizines such as **81** (X = CN, CO_2Me, *etc.*).[124]



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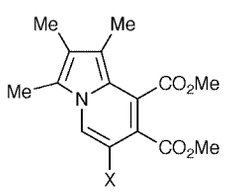
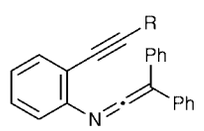


81



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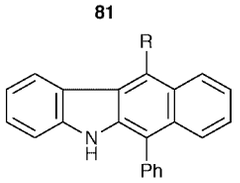
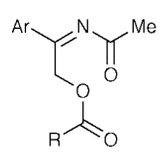


83

The thermal ring closure of *N*-arylketenimines **82** to benzo[*b*]carbazoles **83** is proposed to involve a diradical intermediate.[125,126] Cyclisations of this type can also lead to the formation of quinolines, depending on the nature of the substituents (Section 14). Examples of the formation of carbazoles by oxidative cyclisation of diphenylamines[127] and from pentacarbonylchromium carbene complexes[128] have also been reported.

6 Oxazoles, thiazoles and benzothiazoles

A synthesis of 5-amino-4-cyanooxazoles with a functionalised side chain at C-2 has been described; the procedure is simple and uses aminomalononitrile toluene-*p*-sulfonate, a carboxylic acid and DCC in pyridine (Scheme 39).[129] 2-Substituted 5-aryloxazoles are produced in good yield by the oxidation of aryl methyl ketones and trifluoromethanesulfonic acid in an aliphatic nitrile (Scheme 40). Both thallium(III) acetate[130] and iodosylbenzene diacetate[131] have been used as oxidants. The mechanism probably involves formation and cyclisation of a nitrilium salt. In a simple synthesis of 2-substituted 4-phenyloxazoles, phenacyl carboxylates were heated with acetamide and boron trifluoride–diethyl ether at about 140 °C. The *N*-acetylimines **84** are formed as intermediates.[132] *N*-Acylisoxazolones **85** lose carbon dioxide on flash pyrolysis or on photolysis to give trisubstituted oxazoles **86**.[133,134] When *N*-thioacylisoxazoles are used instead, they give thiazoles in an analogous manner.[135] 5-Arylisoxazole-4-carbaldehydes have been isolated in moderate yield from the reaction of aryl 2-azidomethyl ketones with the Vilsmeier reagent at 80–90 °C.[136]



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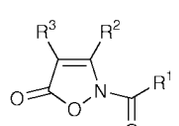

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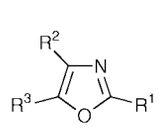

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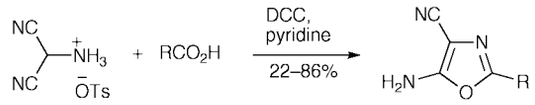
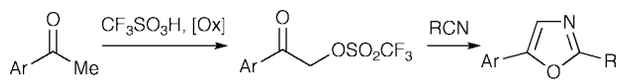


Scheme 39

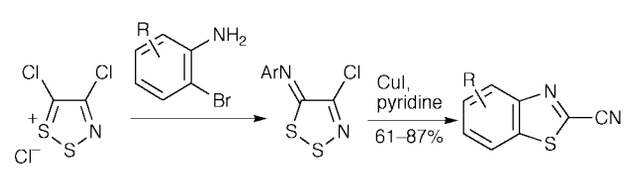


Scheme 40

A full paper has appeared on the insertion of rhodium carbenoids derived from diazocarbonyl compounds into the N–H bonds of amides.[137] This leads to dihydrooxazoles, which were oxidised by the use of triphenylphosphine, iodine and triethylamine, a method first described by Wipf. A comparative study of methods for the oxidation of 4,5-dihydrooxazoles to oxazoles has also been published.[138]

A solid phase adaptation of the Hantzsch synthesis of 2-aminothiazoles has been achieved.[139] The solution synthesis of *N*-substituted 2-aminothiazoles from α-haloketones, potassium thiocyanate and a primary amine has been simplified to an efficient one pot procedure.[140] Several *N*-substituted 2-aminothiazoles have also been prepared from *N*-thiocarbamoylimidates and activated haloalkanes.[141]

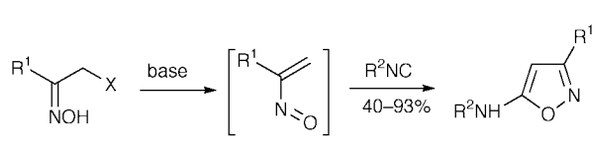
2-Cyanobenzothiazoles are formed by the sequence shown in Scheme 41. The second reaction step can be carried out by conventional heating, or, more efficiently, by microwave irradiation.[142]



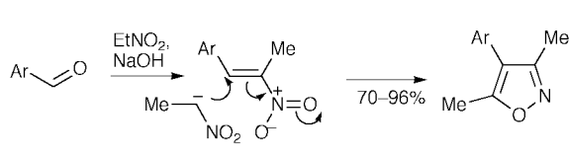
Scheme 41

7 Isoxazoles, isothiazoles and fused analogues

3-Substituted 5-aminoisoxazoles have been produced from oximes of α-haloketones and isocyanides (Scheme 42); transient vinylnitroso compounds are probably intermediates.[143] A synthesis of trisubstituted isoxazoles from aromatic aldehydes and nitroethane or nitropropane (Scheme 43) requires the incorporation of two moles of the nitroalkane in the product.[144]

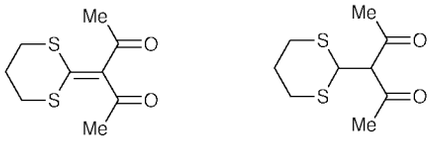


Scheme 42



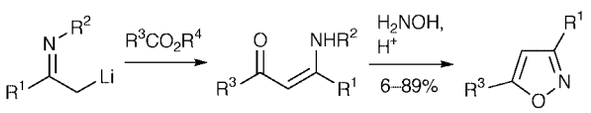
Scheme 43

A simple route to 3,5-disubstituted isoxazole-4-carbaldehydes, and also to the corresponding pyrazoles, depends upon the clean reduction of ketene dithioacetals with zinc and acetic acid. For example, the dithioacetal **87** was reduced to the diketone **88**, from which 3,5-dimethylisoxazole-4-carbaldehyde



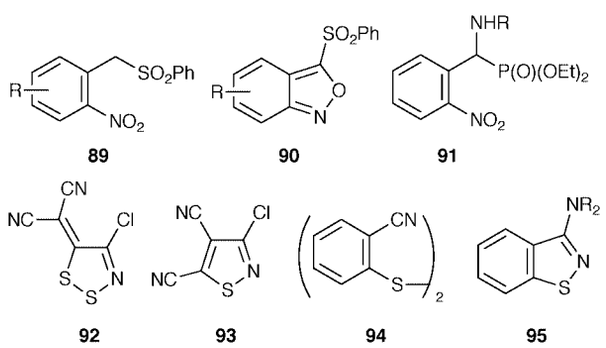
87 **88**

was formed by conventional reaction with hydroxylamine and deprotection.[145] A route to unsymmetrically 3,5-disubstituted isoxazoles, outlined in Scheme 44, avoids the problems of regiocontrol inherent in reactions of 1,3-diketones with hydroxylamine.[146]



Scheme 44

Anthranils can be prepared by dehydration of 2-nitrobenzyl derivatives and this method has been used as a route to the sulfones **90** from the readily available nitro compounds **89**.[147] 3-Alkylaminoanthranils have been obtained by cyclisation of the nitrobenzylphosphonates **91**.[148]



89 **90** **91**

92 **93** **94** **95**

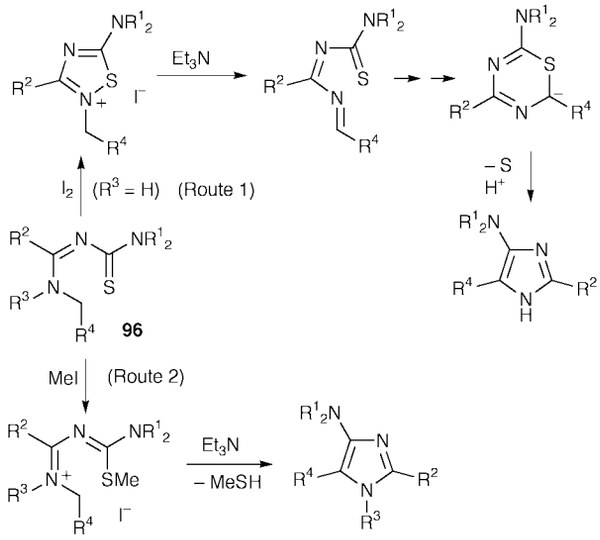
Further experimental and mechanistic details have appeared of the unusual conversion of 2,5-diarylfurans into 3,5-disubstituted isothiazoles which was described in the previous report.[149,150] The dithiazole **92**, which is easily prepared from Appel's salt and malononitrile, has been converted in high yield into the isothiazole **93** by heating with benzyltriethylammonium chloride.[45] 3-Dialkylamino-1,2-benzisothiazoles **95** are formed in excellent yields from the disulfide **94** by nucleophilic addition of the amide R_2NMgBr to the nitrile followed by oxidative cyclisation with copper(II) chloride.[151]

8 Imidazoles and benzimidazoles

A compilation of methods of synthesis of imidazoles and benzimidazoles is available.[152]

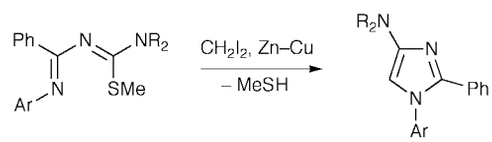
Several new routes to tri- and tetrasubstituted imidazoles are based on the cyclisation of amino(thiocarbonyl)amidines **96** and related species. Two of these routes are outlined in Scheme 45.[153] Oxidative cyclisation followed by treatment with base (Route 1) resulted in the extrusion of sulfur, probably by way of the thiadiazine shown. Alternatively the imidazole could be formed by *S*-methylation followed by the elimination of methanethiol (Route 2). This second route is related mechanistically to a different synthesis of imidazoles of this type which is shown in Scheme 46.[154] In this synthesis the carbenoid attacks the nitrogen and the reaction then follows the same course as in Route 2 above.

In a new application of their isocyanide methodology, van Leusen and his co-workers have prepared a series of 4(5)-monosubstituted imidazoles by the addition of tosylmethyl



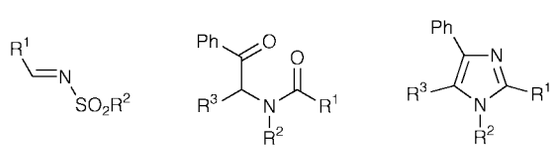
96

Scheme 45

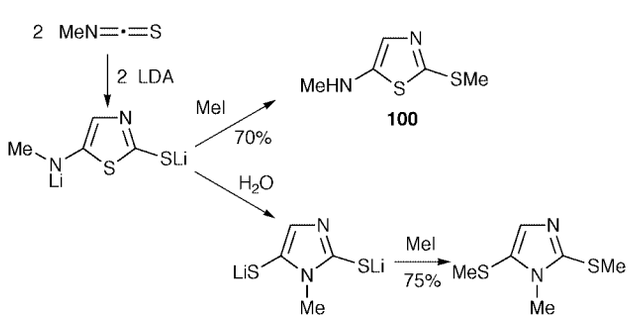


Scheme 46

isocyanide (TosMIC) to *N*-tosyl- or *N*-(dimethylsulfamoyl)-aldimines **97**.[155] The *N*-substituent is easily removed from the imidazoles, either spontaneously or by reaction with aqueous HBr. Tetrasubstituted imidazoles **99** have been prepared by heating the amides **98** with ammonium trifluoroacetate.[156] The reaction of methyl isothiocyanate with LDA can take different courses that are dependent on the reaction conditions (Scheme 47). The thiazole **100** is isolated after methylation of the reaction mixture with dimethyl sulfate, but the imidazole **101** is obtained if the reaction mixture is quenched with water before methylation.[157]



97 **98** **99**



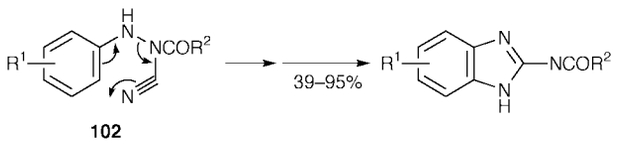
100

101

Scheme 47

A new synthesis of 2-acylaminobenzimidazoles has been described that is a refinement of a method first published 80 years ago by Pellizzari. Arylhydrazines were converted by successive cyanation and acylation into the hydrazides **102**. These rearranged cleanly to benzimidazoles when heated in diphenyl ether at 190 °C.[158] This method was earlier shown to go by way

of a [3,3] sigmatropic shift (Scheme 48). A new procedure for preparing 2-alkylaminobenzimidazoles from *o*-phenylenediamine and primary amines has also been described.[159] 2-Methylbenzimidazole has been prepared by irradiating *o*-dinitrobenzene with titanium dioxide in ethanol. The reaction goes by way of 2-nitroaniline which condenses with acetaldehyde (formed by oxidation of ethanol) and is then further reduced.[160]

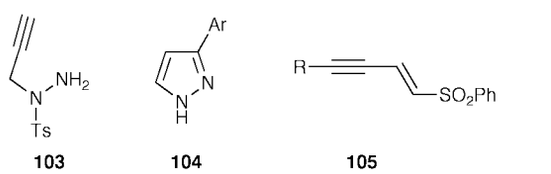


102

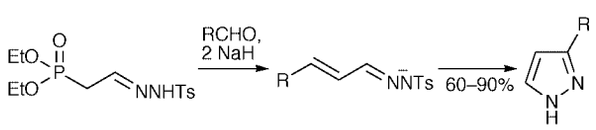
Scheme 48

9 Pyrazoles and indazoles

A new synthesis of 3-aryl- and 3-vinylpyrazoles is based on the palladium catalysed *endo* cyclisation previously used for pyrroles (Scheme 19) and for other five-membered heterocycles. *N*-Propargyl-*N*-tosylhydrazine **103** was successively arylated by reaction with iodoarenes and cyclised under the influence of palladium catalysts to give the 3-arylpyrazoles **104**. The steps could be carried out as a one pot procedure, giving the pyrazoles in 28–69% yield. Vinyl triflates were also used in place of aryl iodides in the first step.[161] Another simple synthesis of 3-substituted pyrazoles is based on the cyclisation of tosylhydrazone salts of α,β-unsaturated aldehydes which were produced from readily available starting materials by a Wadsworth–Emmons reaction (Scheme 49).[162] 4-Alkynylpyrazoles were prepared by regioselective addition of diazomethane to the double bond of the sulfones **105** followed by base catalysed elimination of benzenesulfinic acid.[163]



103 104 105

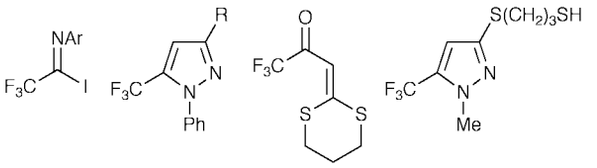


Scheme 49

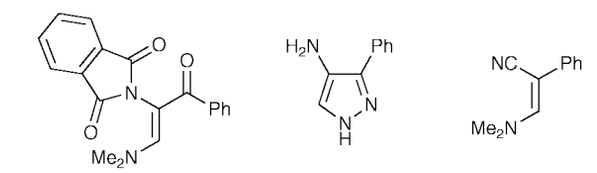
5-Trifluoromethylpyrazoles **107** have been isolated in good yield from reaction of the imidoyl iodides **106** with the dianions of methyl ketone phenylhydrazones; the methyl group of the phenylhydrazone becomes C-4 of the new pyrazole.[164,165] A different route to 5-trifluoromethylpyrazoles **109** is provided by the reaction of the ketene dithioacetal **108** with methylhydrazine.[166]

Several syntheses of new pyrazoles make use of the reaction of β-enaminocarbonyl compounds and related species with hydrazines. For example, 4-amino-3-phenylpyrazole **111** was isolated in 78% yield from the reaction of the enaminone **110** with an excess of hydrazine[167] and enaminonitriles such as **112** were similarly used for the synthesis of a variety of 5-aminopyrazoles.[168–170]

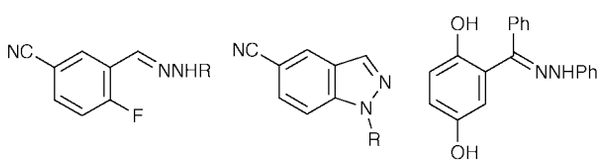
The hydrazones **113** cyclised to the indazoles **114** when heated to 250 °C;[171] an oxidative cyclisation of the hydrazone **115** to an indazoloquinone (a type of "aza-Nenitzescu reaction") has also been reported.[172] An example of indazole synthesis from pyrazoles by benzo annelation has been described.[173]



106 107 108 109



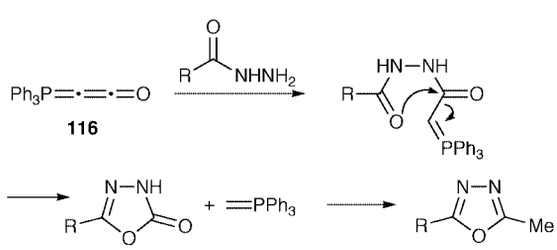
110 111 112



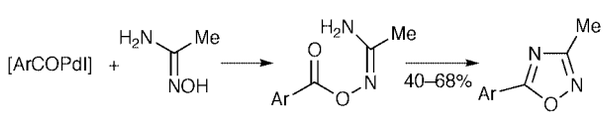
113 114 115

10 Oxadiazoles and thiadiazoles

Ketenylidene triphenylphosphorane **116** is easy to prepare and is storable. It has been found to react with acylhydrazides to give a series of 2-methyl-5-substituted 1,3,4-oxadiazoles in moderate to good yields.[174] An intriguing problem is to explain how the methyl substituent is produced. The authors favour a mechanism (Scheme 50) in which methylenetriphenylphosphorane is eliminated and then reincorporated into the product. Hydrogen chloride is eliminated in the base catalysed cyclisation of aldehyde trichloroacetylhydrazones, which leads to 5-substituted-2-dichloromethyl-1,3,4-oxadiazoles.[175] A more standard synthesis of 1,3,4-oxadiazoles is the cyclodehydration of 1,2-diacylhydrazines and this reaction has been carried out under palladium catalysis.[176] Palladium catalysis is also integral to another 1,3,4-oxadiazole synthesis: palladium catalysed carbonylation of aryl iodides followed by reaction with 5-phenyltetrazole gives 2-aroyl-5-phenyltetrazoles, from which 1,3-oxadiazoles are formed by thermal elimination of nitrogen.[177] A similar carbonylation procedure is involved in a one pot synthesis of 1,2,4-oxadiazoles (Scheme 51).[178]

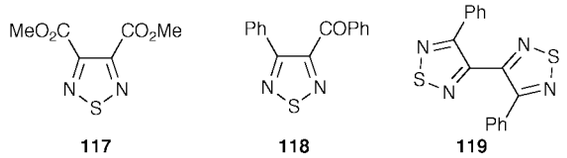


Scheme 50



Scheme 51

Trithiazyl chloride, $(NSCl)_3$, has proved to be a rich source of new 1,2,5-thiadiazoles. Alkenes and alkynes react readily with it to give mono- or disubstituted 1,2,5-thiadiazoles in one step; for example, DMAD gave the 3,4-dicarboxylic acid dimethyl ester **117** (84%).[179] Activated methylene compounds similarly give disubstituted 1,2,5-thiadiazoles; thus, the thiadiazole **118** was isolated (41%) from a reaction with dibenzoylmethane.[180] More exotic structures are obtained from reactions of trithiazyl



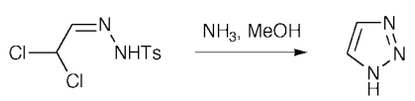
117 118 119

chloride with pyrroles; an example is the bis(thiadiazole) **119** formed (45%) with 1-methyl-2,5-diphenylpyrrole.[181] 1,2,5-Thiadiazoles have also been isolated in moderate yield from the reaction of tetrasulfur tetranitride or its antimony(v) chloride complex with oximes[182,183] and with isoxazoles.[184]

Ethyl diazoacetate and other diazo compounds react with thiocarbonylbis(imidazole) to give 1,3,4-thiadiazoles by 1,3-dipolar addition to the C=S bond, and not 1,2,3-thiadiazoles as was reported earlier.[185]

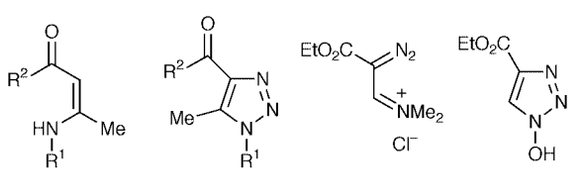
11 Triazoles, benzotriazoles and tetrazoles

1,2,3-Triazole has been isolated in up to 75% yield from the reaction of dichloroacetaldehyde tosylhydrazone with ammonia (Scheme 52). When primary amines are used in place of ammonia, 1-substituted triazoles are formed in good yield.[186] Another synthesis of 1,2,3-triazole starts from glyoxal[187] and a third new route is based on the 1,3-dipolar cycloaddition of 4-methoxybenzyl azide to acetylenedicarboxylic acid. The resulting triazole-4,5-dicarboxylic acid is decarboxylated and the nitrogen protecting group is subsequently removed by treatment with HBr.[188] These authors also describe a synthesis of 1-benzyloxy-1,2,3-triazole from glyoxal monobenzyloxime.

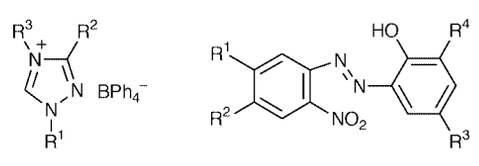


Scheme 52

Diazo transfer from methanesulfonyl azide to β-enaminocarbonyl compounds **120** led to the formation of the 1,2,3-triazoles **121** in moderate to high yields.[189] Ethyl 1-hydroxytriazole-4-carboxylate **123** was designed as a new coupling reagent for peptide synthesis; it was prepared from ethyl diazoacetate and the Vilsmeier reagent, followed by reaction of the iminium salt **122** with hydroxylamine.[190]



120 121 122 123



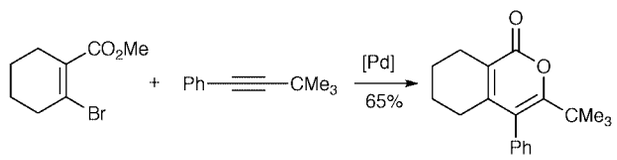
124 125

The previously unknown 1,4-dialkyl-1,2,4-triazolium salts **124** have been prepared from imidoyl chlorides and 1-alkyl-1-formylhydrazines.[191] Samarium diiodide was used as the reducing agent in the cyclisation of the 2-nitroazobenzene **125** to the corresponding 2-aryl-1,2,3-benzotriazole.[192]

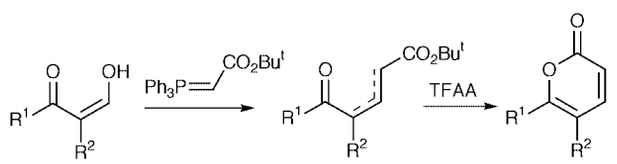
5-Substituted tetrazoles have been prepared in good yield from aliphatic and aromatic nitriles with sodium azide in toluene. Triethylamine hydrochloride acts as a catalyst and this allows a small amount of triethylammonium azide to be present in the organic solvent.[193] A micelle medium (hexadecyltrimethylammonium bromide) has also been used for the reaction.[194]

12 Pyrones, coumarins and chromones

A palladium catalysed synthesis of tri- and tetrasubstituted 2-pyrones has been described and is illustrated in Scheme 53. As shown in this example, when unsymmetrical alkynes are used in the reaction the bulkier group tends to be located at C-6 in the pyrone.[195] A simple route to 3,4-disubstituted 2-pyrones, based on a Wittig reaction and cyclisation, is illustrated in Scheme 54.[196]

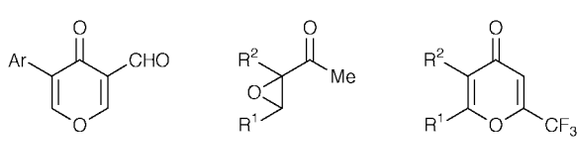


Scheme 53



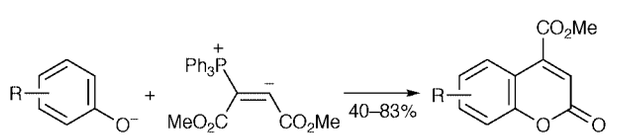
Scheme 54

A useful method for the conversion of 4-pyrones into pyrylium hydrobromides is to heat the pyrones in chloroform under reflux with *tert*-butyl bromide.[197] 3-Formyl-4-pyrones **126** have been prepared from 3-arylpropan-2-ones and four equivalents of the Vilsmeier reagent[198] and a synthesis of 2-trifluoromethyl-4-pyrones **128** is based on the base catalysed condensation of epoxyketones **127** with ethyl trifluoroacetate.[199]



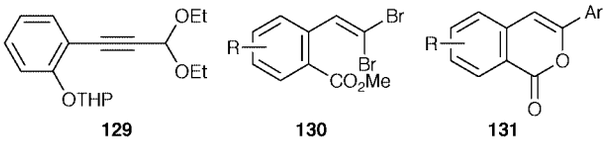
126 127 128

Coumarin and some derivatives can be synthesised by flash vacuum pyrolysis of methyl 2-hydroxycinnamates.[200] The (*E*)-configuration of the double bond normally precludes cyclisation but the barrier to isomerisation is overcome by the high temperature method. A simple synthesis of some coumarin-4-carboxylic esters, illustrated in Scheme 55, involves the reaction of phenols with the betaine formed by the addition of triphenylphosphine to DMAD.[201] 3-Arylcoumarins have been produced from the protected alkynylphenol **129** by palladium catalysed arylation followed by oxidative cyclisation.[202] A synthesis of isomeric 3-arylisocoumarins **131** also involves palladium catalysis: the styryl bromides **130** were coupled with aryltrimethylstannanes and the intermediate esters were then cyclised.[203]

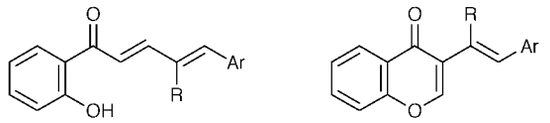


Scheme 55

A new route to 3-styrylchromones **133** from the hydroxyketones **132** and trimethyl orthoformate in methanol is based



129 130 131

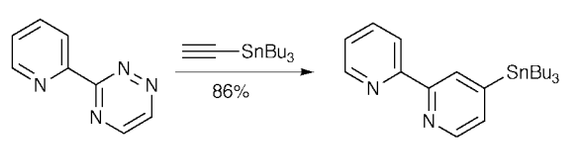


132 133

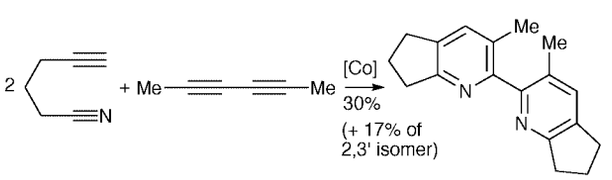
on the oxidative rearrangement of an intermediate ketone with thallium(III) nitrate.[204]

13 Pyridines

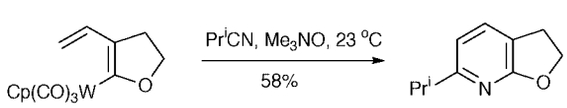
In a series of recent papers Sauer and his co-workers have greatly increased the scope of the known synthesis of pyridines by cycloaddition of electrophilic 1,2,4-triazines to alkynes. They have shown that stannylated acetylenes are particularly good partners in these reactions, with the added advantage of giving pyridines in which the trialkylstannyl group is available for coupling.[205,206] An example is shown in Scheme 56. By making use of reactions of this type, Sauer's group has been able to build up a series of oligopyridines and related oligomers.[207–210] Norbornadiene was also shown to be an effective synthetic equivalent of acetylene in these cycloadditions; it adds to the 1,2,4-triazines in boiling 1,2-dichlorobenzene and cyclopentadiene is spontaneously eliminated from the cycloadduct.[211] A different approach to bipyridines, illustrated in Scheme 57, is the cobalt catalysed [2 + 2 + 2] addition of alkynyl nitriles with mono- and diacetylenes.[212,213] A further application of the cobalt catalysed [2 + 2 + 2] addition of ynamines to chloropyridazines, described in the last report, has also been published.[214] A rare example of a [4 + 2] cycloaddition to an unactivated nitrile provides a synthesis of furopyridines; a tungsten substituted 1,3-diene is the reaction partner, as shown in Scheme 58.[215] Pentasubstituted pyridines have been obtained by the addition of ynamines to styryl carbodiimides and related cumulenes.[216]



Scheme 56

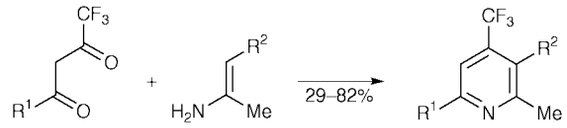


Scheme 57



Scheme 58

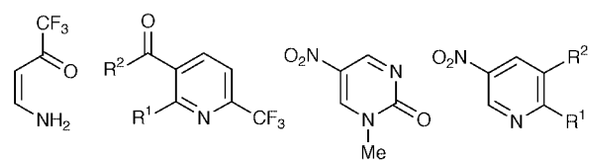
The classical methods of pyridine synthesis continue to be extended. A simple, regioselective synthesis of 4-trifluoromethylpyridines from β-diketones is shown in Scheme 59.[217] 2-Trifluoromethylpyridines and other trihalomethylpyridines have been synthesised in a similar way from α-trihalomethylenones and enamines.[218,219] Surprisingly, reaction of the



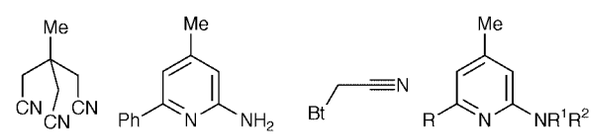
Scheme 59

enaminoketones **134** with β-dicarbonyl compounds and TFA led to the formation of 2-trifluoromethylpyridines **135** instead of the expected 4-trifluoromethyl isomers.[220] The pyrimidinone **136** has been shown to act as a synthetic equivalent of 2-nitropropane-1,3-dione in pyridine synthesis; in reactions with aliphatic ketones and ammonia, 3-nitropyridines **137** are formed.[221]

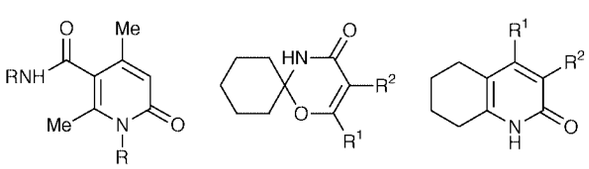
1,1,1-Ethanetriacetonitrile **138** reacts with Grignard reagents to give 2-aminopyridines; for example the aminopyridine **139** was formed (40%) with phenylmagnesium bromide.[222] 2-Alkylaminopyridines **141** have been prepared by the reaction of benzotriazolylacetonitrile **140** with enones and alkylamines.[223] When aqueous sodium hydroxide is used in place of the alkylamine, 2-pyridones are formed.



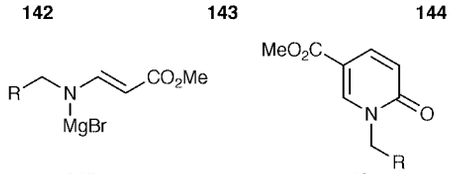
134 135 136 137



138 139 140 141

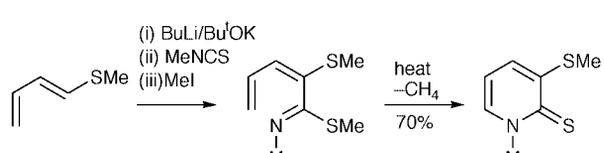


142 143 144



145 146

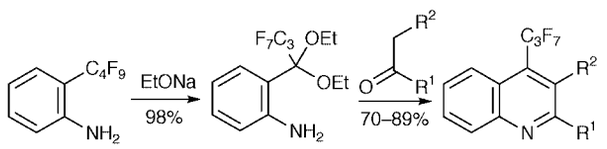
A simple route to 2-pyridones which, surprisingly, has not been carried out before in satisfactory yield is the dimerisation of substituted acetoacetamides. This has now been achieved by heating the compounds with toluene-*p*-sulfonic acid in the absence of a solvent; yields of the pyridones **142** are high.[224] 2-Pyridones **144** have been isolated in moderate yield from the acid catalysed dehydration of the spiro compounds **143**, which are derived from β-oxonitriles and cyclohexanone.[225] The pyrid-2-one esters **146** have been synthesised from methyl propiolate and magnesium salts **145** of β-aminoacrylates.[226] A new route to pyridine-2-thiones, illustrated in Scheme 60, makes use of an electrocyclic ring closure to construct the ring system.[227]



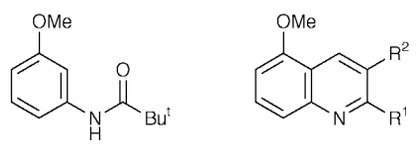
Scheme 60

14 Quinolines and isoquinolines

Several 4-perfluoroalkylquinolines have been prepared by Friedländer-type syntheses from 2-perfluoroalkylanilines; one such route is illustrated in Scheme 61.[228,229] A modified Friedländer synthesis is also used to prepare a series of 5-methoxyquinolines **148**. The amide **147** is formylated at C-2 by directed lithiation and reaction with DMF; the aldehyde is then condensed with ketones to give the quinolines.[230] Several examples of the synthesis of 2-aminoquinolines by reductive cyclisation of *o*-nitrocinnamonitriles have also been reported.[231,232] Quinoline and a few substituted quinolines have been isolated from the Baker's yeast reductive cyclisation of *o*-nitrocinnamyl ketones.[233]

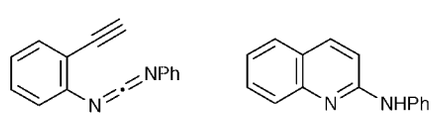


Scheme 61

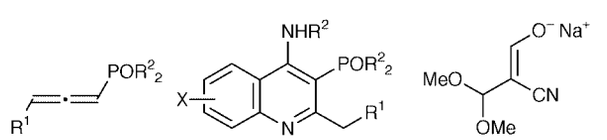


147 **148**

As indicated in Section 5, alkynyl ketenimines of structure **82** can cyclise to fused indoles by way of biradical intermediates; they can also give quinolines when R = H. Similarly, the carbodiimide **149** cyclised to the aminoquinoline **150** (49%) when heated with a hydrogen donor.[234]



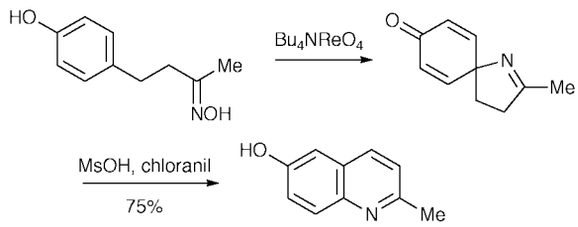
149 **150**



151 **152** **153**

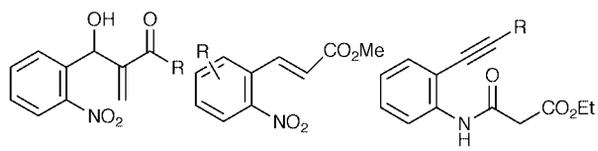
Several syntheses of new quinolines are based on the *N*-alkylation of anilines followed by acid catalysed cyclisation. Thus, reaction of the allenylphosphine oxides **151** with anilines, followed by reaction with an isocyanate and cyclodehydration, gives the quinolylphosphine oxides **152**.[235,236] The ruthenium catalysed reaction of triallylamine with anilines results in the formation of 2-ethyl-3-methylquinolines.[237] 3-Cyanoquinolines have been formed from the condensation of the sodium salt **153** of 3,3-dimethoxy-2-formylpropanenitrile with activated anilines followed by acid catalysed cyclisation.[238] Other cyclisation processes involving formation of the C4–C4a bond have been reported.[239–241]

Methods of forming the quinoline ring by cycloaddition are not common, an exception being the reaction of activated acetylenes and alkenes with *N*-aryliminium cations. These cations have been generated by benzotriazole methodology and *N*-alkylquinolinium salts were formed by cycloaddition to acetylenes.[242] A cycloaddition process that is mainly of mechanistic interest is the Diels–Alder reaction of 1,2,3-benzotriazine with enamines, from which 2- and 3-substituted quinolines were isolated in low yields.[243] Cyclisation reactions in which the N–C8a bond is formed are also fairly uncommon, but a series of such reactions involving cyclisation of oximes has been reported.[244,245] The example in Scheme 62 has been shown to go by way of an isolable spiro intermediate.[245]



Scheme 62

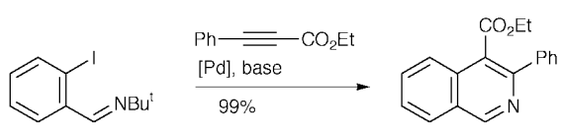
The Baylis–Hillman reaction of 2-nitrobenzaldehyde with but-3-en-2-one and other enones leads to the allylic alcohols **154**, which can be reduced and cyclised to 2-substituted quinoline 1-oxides. When methyl acrylate is used in the Baylis–Hillman reaction the product is 3-methyl-2-quinolone.[246] 2-Quinolones have also been formed by reductive cyclisation of the nitrocinnamate esters **155**[247] and by base catalysed cyclisation of the amides **156**.[248] Both these precursors were obtained by palladium catalysed coupling reactions.



154 **155** **156**

The Jackson variation of the Pomeranz–Fritsch isoquinoline synthesis results in the formation of 2-tosyl-1,2-dihydroisoquinolines, but the tosyl group can be difficult to remove. By replacing the tosyl group with the isomeric benzylsulfonyl group the method has been improved: the protecting group can be removed by brief heating with Raney nickel without reducing the ring system.[249]

Palladium coupling methods have been applied to isoquinoline synthesis. An example of the coupling of 2-iodobenzaldehyde *N*-*tert*-butylimine with an acetylene is shown in Scheme 63[250] and Grigg's group has used intramolecular palladium catalysed addition to allenes (analogous to the conversion of **21** into **22**) in a synthesis of isoquinolones.[28]

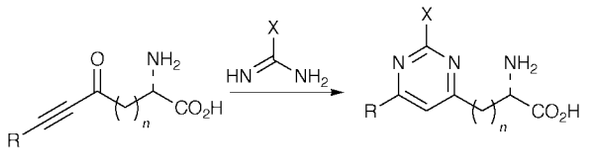


Scheme 63

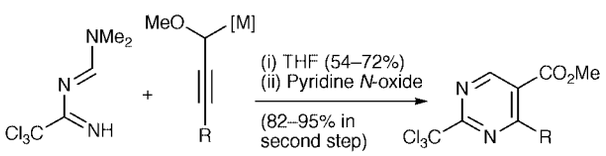
15 Pyrimidines and quinazolines

In a recent solid phase synthesis of pyrimidines, referred to in the last report, the ring system is constructed from alkynyl ketones and amidines. This methodology has now been adapted to the synthesis of pyrimidin-4-yl substituted α-amino acids (Scheme 64).[251] 2-Substituted pyrimidines have been isolated in good yield from the reaction of amidine hydrochlorides with malonodialdehyde tetramethyl acetal when the reactions are carried out in a sealed tube.[252] A new synthesis of 2-trichloromethylpyrimidines, illustrated in Scheme 65, involves alkynyl Fischer carbene complexes {[M] = $Cr(CO)_5$, $W(CO)_5$} as dienophiles.[253] Reactions of azadienes of this type with β-keto esters and with isocyanates have also been used in the synthesis of pyrimidinones and quinazolinones.[254]

New routes to 4-arylaminoquinazolines from 2-amino-*N*-

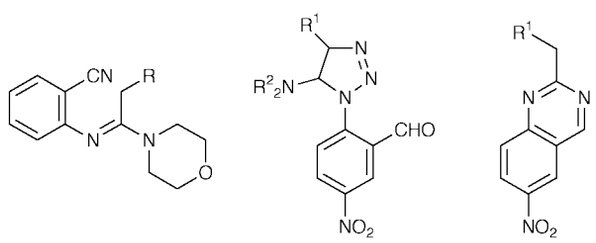


Scheme 64

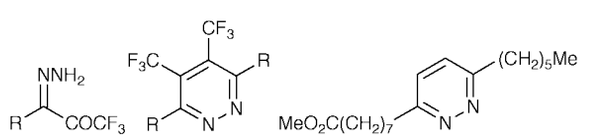


Scheme 65

arylbenzamidines[255] and from the amidines **157** with anilines[256] have been described. These amidines are formed by thermal decomposition of intermediate triazolines; by analogy, the decomposition of the triazolines **158** in the presence of ammonium acetate leads to the formation of the quinazolines **159**.[257] A cyclisation route to 2-diethylaminoquinazolines from imidoyl chlorides has also been reported.[258]



157 **158** **159**



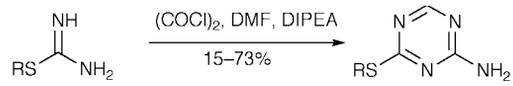
160 **161** **162**

16 Other diazines, triazines and tetrazines

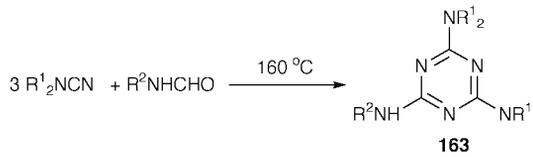
An optimised procedure for the formation of the parent 1,2,4,5-tetrazine from formamidine acetate and hydrazine has been described.[259] The tetrazine undergoes Diels–Alder cycloaddition to a variety of acetylenes and cyclic alkenes. The reaction is of the inverse electron demand type and bis(trimethylstannyl)-acetylene is amongst the most reactive with this tetrazine. This study provides data on the relative reactivities of electron rich dienophiles which should have more general applicability. Related routes to 3-aryltetrazines[260] and 3,6-dichlorotetrazine[261] are also reported. The bis(trifluoromethyl)pyridazines **161** have been isolated in moderate yield after heating the hydrazones **160** in TFA[262] and the pyridazine ester **162** was formed in high yield from methyl 9,12-dioxostearate and aqueous hydrazine under ultrasound irradiation.[263]

A new route to unsymmetrically 2,6-disubstituted 1,3,5-triazines is shown in Scheme 66.[264] This synthesis probably involves the condensation of two moles of the isothioureas with the Vilsmeier reagent. The alkylthio substituent can be oxidised to the sulfoxide and displaced by amines, making the method suitable for combinatorial synthesis. The 1,3,5-triazines **163** are formed from cyanamides and formamides by heating them together under high pressure (Scheme 67).[265]

An unusual synthesis of cinnolines is illustrated in Scheme 68. The reaction is limited to TCNE and the choice of

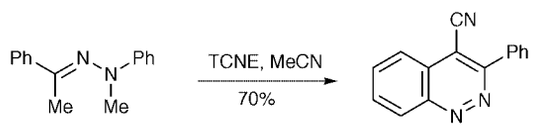


Scheme 66



163

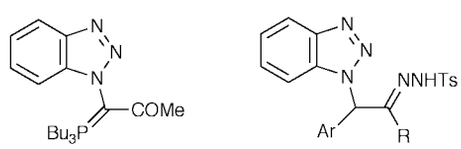
Scheme 67



Scheme 68

acetonitrile as a solvent is important; the mechanism has not been established.[266]

Cyclisation reactions that lead to 2,3-diphenylquinoxaline 1-oxides,[267] 1,2,4-benzotriazine 1-oxides[268] and phthalazinones[269] have been reported. Two syntheses of 1,2,4-benzotriazines make use of 1-substituted benzotriazoles as precursors. Flash pyrolysis of the ylide **164** gave 3-acetyl-1,2,4-benzotriazine in moderate yield[270] and reaction of the tosylhydrazones **165** with butyllithium in excess led to the isolation of 3-aryl-1,2,4-benzotriazines.[271] In both procedures the triazine ring is formed by cleavage and recyclisation of the benzotriazole.



164 **165**

17 References

1 J. W. Corbett, *Org. Prep. Proced. Int.*, 1998, **30**, 489.
2 X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. Tong and H. N. C. Wong, *Tetrahedron*, 1998, **54**, 1955.
3 X.-S. Ye, P. Yu and H. N. C. Wong, *Liebigs Ann./Recl.*, 1997, 459.
4 J. A. Marshall and C. A. Sehon, *Org. Synth.*, 1998, **76**, 263.
5 D. I. Ma Gee and J. D. Leach, *Tetrahedron Lett.*, 1997, **38**, 8129.
6 A. Arcadi and E. Rossi, *Tetrahedron*, 1998, **54**, 15253.
7 B. Gabriele, G. Salerno, F. DePascali, G. T. Sciano, M. Costa and G. P. Chiusoli, *Tetrahedron Lett.*, 1997, **38**, 6877.
8 B. Gabriele and G. Salerno, *Chem. Commun.*, 1997, 1083.
9 P. Wipf, L. T. Rahman and S. R. Rector, *J. Org. Chem.*, 1998, **63**, 7132.
10 J. W. Herndon and H. X. Wang, *J. Org. Chem.*, 1998, **63**, 4564.
11 N. Iwasawa, K. Maeyama and M. Saitou, *J. Am. Chem. Soc.*, 1997, **119**, 1486.
12 N. Iwasawa, T. Ochiai and K. Maeyama, *J. Org. Chem.*, 1998, **63**, 3164.
13 S. Kajikawa, Y. Noiri, H. Shudo, H. Nishino and K. Kurosawa, *Synthesis*, 1998, 1457.
14 R. C. Larock, M. J. Doty and X. J. Han, *Tetrahedron Lett.*, 1998, **39**, 5143.
15 H.-H. Tso and H. Tsay, *Tetrahedron Lett.*, 1997, **38**, 6869.
16 M. S. B. Wills and R. L. Danheiser, *J. Am. Chem. Soc.*, 1998, **120**, 9378.
17 M. Kurosu, L. R. Marcin and Y. Kishi, *Tetrahedron Lett.*, 1998, **39**, 8929.
18 G. A. Kraus and X. M. Wang, *Synth. Commun.*, 1998, **28**, 1093.
19 R. Díaz-Cortés, A. L. Silva and L. A. Maldonado, *Tetrahedron Lett.*, 1997, **38**, 2207.
20 A. S. K. Hashmi, T. L. Ruppert, T. Knofel and J. W. Bats, *J. Org. Chem.*, 1997, **62**, 7295.

21 A. Fürstner, T. Gastner and J. Rust, *Synlett*, 1999, 29.
22 Y. Koga, H. Kusama and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 475.
23 N. G. Kundu, M. Pal, J. S. Mahanty and M. De, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2815.
24 B. C. Bishop, I. F. Cottrell and D. Hands, *Synthesis*, 1997, 1315.
25 N. Monteiro and G. Balme, *Synlett*, 1998, 746.
26 N. Monteiro, A. Arnold and G. Balme, *Synlett*, 1998, 1111.
27 M. G. Kulkarni and R. M. Rasne, *Synthesis*, 1997, 1420.
28 M. Gardiner, R. Grigg, V. Sridharan and N. Vicker, *Tetrahedron Lett.*, 1998, **39**, 435.
29 D. D. Hennings, S. Iwasa and V. H. Rawal, *Tetrahedron Lett.*, 1997, **38**, 6379.
30 H.-C. Zhang and B. E. Maryanoff, *J. Org. Chem.*, 1997, **62**, 1804.
31 A. R. Katritzky, L. Serdyuk and L. H. Xie, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1059.
32 M. Black, J. I. G. Cadogan, H. McNab, A. D. MacPherson, V. P. Roddam, C. Smith and H. R. Swenson, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2483.
33 J. Ichikawa, Y. Wada, T. Okauchi and T. Minami, *Chem. Commun.*, 1997, 1537.
34 B. D'hooge, S. Smeets, S. Toppet and W. Dehaen, *Chem. Commun.*, 1997, 1753.
35 O. A. Tarasova, L. V. Klyba, V. Y. Vvedensky, N. A. Nedolya, B. A. Trofimov, A. Brandsma and H. D. Verkruijsse, *Eur. J. Org. Chem.*, 1998, 253.
36 O. A. Tarasova, N. A. Nedolya, V. Y. Vvedensky, L. Brandsma and B. A. Trofimov, *Tetrahedron Lett.*, 1997, **38**, 7241.
37 L. Brandsma, V. Y. Vvedensky, N. A. Nedolya, O. A. Tarasova and B. A. Trofimov, *Tetrahedron Lett.*, 1998, **39**, 2433.
38 T. Nishio, *Helv. Chim. Acta*, 1998, **81**, 1207.
39 B. S. Kim, K. S. Choi and K. Kim, *J. Org. Chem.*, 1998, **63**, 6086.
40 X.-S. Ye and H. N. C. Wong, *J. Org. Chem.*, 1997, **62**, 1940.
41 J. Nakayama, R. Hasemi, K. Yoshimura, Y. Sugihara, S. Yamaoka and N. Nakamura, *J. Org. Chem.*, 1998, **63**, 4912.
42 C. M. Marson and J. Campbell, *Tetrahedron Lett.*, 1997, **38**, 7785.
43 H.-P. Guan, B.-H. Luo and C.-M. Hu, *Synthesis*, 1997, 461.
44 A. V. Kelin and Y. Y. Kozyrkov, *Synthesis*, 1998, 729.
45 K. Emayan, R. F. English, P. A. Koutentis and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3345.
46 A. K. Mohanakrishnan, M. V. Lakshmikantham, C. McDougal, M. P. Cava, J. W. Baldwin and R. M. Metzger, *J. Org. Chem.*, 1998, **63**, 3105.
47 A. K. Mohanakrishnan, M. V. Lakshmikantham, M. P. Cava, R. D. Rogers and L. M. Rogers, *Tetrahedron*, 1998, **54**, 7075.
48 S. E. Korostova, A. I. Mikhaleva, A. M. Vasiltsov and B. A. Trofimov, *Russ. J. Org. Chem.* (*Engl. Transl.*), 1998, **34**, 967.
49 C. D'Silva and D. A. Walker, *J. Org. Chem.*, 1998, **63**, 6715.
50 A. Merz and T. Meyer, *Synthesis*, 1999, 94.
51 V. Kameswaran and B. Jiang, *Synthesis*, 1997, 530.
52 M. Yasuda, J. Morimoto, I. Shibata and A. Baba, *Tetrahedron Lett.*, 1997, **38**, 3265.
53 L. J. Cheng and D. A. Lightner, *Synthesis*, 1999, 46.
54 S. Jolivet-Fouchet, J. Hamelin, F. Texier-Boullet, L. Toupet and P. Jacquault, *Tetrahedron*, 1998, **54**, 4561.
55 M. Mori, K. Hori, M. Akashi, M. Hori, Y. Sato and M. Nishida, *Angew. Chem., Int. Ed.*, 1998, **37**, 636.
56 A. Arcadi, R. Anacardio, G. Danniballe and M. Gentile, *Synlett*, 1997, 1315.
57 D. W. Knight, A. L. Redfern and J. Gilmore, *Synlett*, 1998, 731.
58 D. W. Knight, A. L. Redfern and J. Gilmore, *Chem. Commun.*, 1998, 2207.
59 Z. R. Xu and X. Y. Lu, *J. Org. Chem.*, 1998, **63**, 5031.
60 T. Yagi, T. Aoyama and T. Shioiri, *Synlett*, 1997, 1063.
61 H. Tsutsui and K. Narasaka, *Chem. Lett.*, 1999, 45.
62 N. Terang, B. K. Mehta, H. Ila and H. Junjappa, *Tetrahedron*, 1998, **54**, 12973.
63 N. De Kimpe, K. A. Tehrani, C. Stevens and P. De Cooman, *Tetrahedron*, 1997, **53**, 3693.
64 R. D. Chambers, W. K. Gray, S. J. Mullins and S. R. Korn, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1457.
65 A. S. Demir, I. M. Akhmedov, C. Tanyeli, Z. Gercek and R. A. Gadzhili, *Tetrahedron: Asymmetry*, 1997, **8**, 753.
66 C. W. Ong, C. M. Chen, L. H. Wang, J. J. Jan and P. C. Shieh, *J. Org. Chem.*, 1998, **63**, 9131.
67 H. Shiraishi, T. Nishitani, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 1998, **63**, 6234.
68 A. R. Katritzky, Z. Q. Wang, J. Q. Li and J. R. Levell, *J. Heterocycl. Chem.*, 1997, **34**, 1379.
69 A. Fürstner and H. Weintritt, *J. Am. Chem. Soc.*, 1997, **119**, 2944.
70 A. Fürstner and H. Weintritt, *J. Am. Chem. Soc.*, 1998, **120**, 2817.
71 N. A. Nedolya, L. Brandsma, H. D. Verkruijsse and B. A. Trofimov, *Tetrahedron Lett.*, 1997, **38**, 7247.
72 N. A. Nedolya, L. Brandsma and B. A. Trofimov, *Russ. J. Org. Chem.* (*Engl. Transl.*), 1998, **34**, 950.
73 N. A. Nedolya, L. Brandsma, O. A. Tarasova, H. D. Verkruijsse and B. A. Trofimov, *Tetrahedron Lett.*, 1998, **39**, 2409.
74 W. von der Saal, R. Reinhardt, J. Stawitz and H. Quast, *Eur. J. Org. Chem.*, 1998, 1645.
75 C. D. Gabbutt, J. D. Hepworth, B. M. Heron, M. R. J. Elsegood and W. Clegg, *Chem. Commun.*, 1999, 289.
76 R. Bartnik, A. Bensadat, D. Cal, R. Faure, N. Khatimi, A. Laurent, E. Laurent and C. Rizzon, *Bull. Soc. Chim. Fr.*, 1997, **134**, 725.
77 J. T. Gupton, K. E. Krumpe, B. S. Burnham, K. A. Dwornik, S. A. Petrich, K. X. Du, M. A. Bruce, P. Vu, M. Vargas, K. M. Keertikar, K. N. Hosein, C. R. Jones and J. A. Sikorski, *Tetrahedron*, 1998, **54**, 5075.
78 L. Selič and B. Stanovnik, *Helv. Chim. Acta*, 1998, **81**, 1634.
79 A. W. Trautwein and G. Jung, *Tetrahedron Lett.*, 1998, **39**, 8263.
80 A. Fürstner, H. Szillat, B. Gabor and R. Mynott, *J. Am. Chem. Soc.*, 1998, **120**, 8305.
81 Y. W. Li and T. J. Marks, *J. Am. Chem. Soc.*, 1998, **120**, 1757.
82 J. Boëlle, R. Schneider, P. Gérardin and B. Loubinoux, *Synthesis*, 1997, 1451.
83 T. D. Lash, C. Wijesinghe, A. T. Osuma and J. R. Patel, *Tetrahedron Lett.*, 1997, **38**, 2031.
84 T. D. Lash, P. Chandrasekar, A. T. Osuma, S. T. Chaney and J. D. Spence, *J. Org. Chem.*, 1998, **63**, 8455.
85 B. H. Novak and T. D. Lash, *J. Org. Chem.*, 1998, **63**, 3998.
86 Y. Abel, E. Haake, G. Haake, W. Schmidt, D. Struve, A. Walter and F.-P. Montforts, *Helv. Chim. Acta*, 1998, **81**, 1978.
87 H. Spreitzer, W. Holzer, C. Puschmann, A. Pichler, A. Kogard, K. Tschetschkowitsch, T. Heinze, S. Bauer and N. Shabaz, *Heterocycles*, 1997, **45**, 1989.
88 N. P. Pavri and M. L. Trudell, *J. Org. Chem.*, 1997, **62**, 2649.
89 H. P. Dijkstra, R. ten Have and A. M. van Leusen, *J. Org. Chem.*, 1998, **63**, 5332.
90 H.-W. Chan, P.-C. Chan, J.-H. Liu and H. N. C. Wong, *Chem. Commun.*, 1997, 1515.
91 A. R. Katritzky, J. C. Yao, W. L. Bao, M. Qi and P. J. Steel, *J. Org. Chem.*, 1999, **64**, 346.
92 B. G. Szczepankiewicz and C. H. Heathcock, *Tetrahedron*, 1997, **53**, 8853.
93 Y. Murakami, T. Watanabe, H. Takahashi, H. Yokoo, Y. Nakazawa, M. Koshimizu, N. Adachi, M. Kurita, Y. Yoshino, T. Inagaki, M. Ohishi, M. Watanabe and M. Tani, *Tetrahedron*, 1998, **54**, 45.
94 C. J. Moody and E. Swann, *Synlett*, 1998, 135.
95 Y. Ozaki, K. Okamura, A. Hosoya and S. W. Kim, *Chem. Lett.*, 1997, 679.
96 E. T. Pelkey and G. W. Gribble, *Tetrahedron Lett.*, 1997, **38**, 5603.
97 S. Cacchi, G. Fabrizi, F. Marinelli, L. Moro and P. Pace, *Synlett*, 1997, 1363.
98 S. Cacchi, G. Fabrizi and P. Pace, *J. Org. Chem.*, 1998, **63**, 1001.
99 M. D. Collini and J. W. Ellingboe, *Tetrahedron Lett.*, 1997, **38**, 7963.
100 Y. Kondo, S. Kojima and T. Sakamoto, *J. Org. Chem.*, 1997, **62**, 6507.
101 F. E. McDonald and A. K. Chatterjee, *Tetrahedron Lett.*, 1997, **38**, 7687.
102 A. Yasuhara, Y. Kanamori, M. Kaneko, A. Numata, Y. Kondo and T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, 1999, 529.
103 B. C. Söderberg and J. A. Shriver, *J. Org. Chem.*, 1997, **62**, 5838.
104 P. C. Montevecchi, M. L. Navacchia and P. Spagnolo, *Eur. J. Org. Chem.*, 1998, 1219.
105 T. A. Kshirsagar and L. H. Hurley, *J. Org. Chem.*, 1998, **63**, 5722.
106 Y. Dong and C. A. Busacca, *J. Org. Chem.*, 1997, **62**, 6464.
107 K. Aoki, A. J. Peat and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 3068.
108 B. A. Frontana-Uribe, C. Moinet and L. Toupet, *Eur. J. Org. Chem.*, 1999, 419.
109 Z. Wróbel and M. Makosza, *Tetrahedron*, 1997, **53**, 5501.
110 A. Chilin, P. Rodighiero and A. Guiotto, *Synthesis*, 1998, 309.
111 D. A. Allen, *Synth. Commun.*, 1999, **29**, 447.
112 G. Kim and G. Keum, *Heterocycles*, 1997, **45**, 1979.
113 M. Takahashi and D. Suga, *Synthesis*, 1998, 986.
114 C. Y. Chen, D. R. Lieberman, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *J. Org. Chem.*, 1997, **62**, 2676.
115 E. J. Latham and S. P. Stanforth, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2059.
116 J. A. Murphy, K. A. Scott, R. S. Sinclair and N. Lewis, *Tetrahedron Lett.*, 1997, **38**, 7295.

117 J. Barluenga, F. J. Fananas, R. Sanz and Y. Fernandez, *Tetrahedron Lett.*, 1999, **40**, 1049.
118 C. Kuehm-Caubère, I. Rodriguez, B. Pfeiffer, P. Renard and P. Caubère, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 2857.
119 P. Magnus and I. S. Mitchell, *Tetrahedron Lett.*, 1998, **39**, 4595.
120 C. S. Cho, H. K. Lim, S. C. Shim, T. J. Kim and H.-J. Choi, *Chem. Commun.*, 1998, 995.
121 E. Vedejs and S. D. Monahan, *J. Org. Chem.*, 1997, **62**, 4763.
122 R. ten Have and A. M. van Leusen, *Tetrahedron*, 1998, **54**, 1913.
123 X. C. Zhang and W. Y. Huang, *Synthesis*, 1999, 51.
124 T. Peglow, S. Blechert and E. Steckhan, *Chem. Eur. J.*, 1998, **4**, 107.
125 M. Schmittel, J. P. Steffen, M. A. W. Ángel, B. Engels, C. Lennartz and M. Hanrath, *Angew. Chem.*, *Int. Ed.*, 1998, **37**, 1562.
126 C. S. Shi and K. K. Wang, *J. Org. Chem.*, 1998, **63**, 3517.
127 A. B. Mandal, F. Delgado and J. Tamariz, *Synlett*, 1998, 87.
128 K. H. Dotz and T. Leese, *Bull. Soc. Chim. Fr.*, 1997, **134**, 503.
129 F. Freeman, T. Chen and J. B. van der Linden, *Synthesis*, 1997, 861.
130 J. C. Lee and T. Y. Hong, *Tetrahedron Lett.*, 1997, **38**, 8959.
131 R. S. Varma and D. Kumar, *J. Heterocycl. Chem.*, 1998, **35**, 1533.
132 W. W. Pei, S. H. Li, X. P. Nie, Y. W. Li, J. Pei, B. Z. Chen, J. Wu and X. L. Ye, *Synthesis*, 1998, 1298.
133 R. H. Prager, J. A. Smith, B. Weber and C. M. Williams, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 2665.
134 J. Khalafy, C. E. Svensson, R. H. Prager and C. M. Williams, *Tetrahedron Lett.*, 1998, **39**, 5405.
135 R. H. Prager, M. R. Taylor and C. M. Williams, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 2673.
136 V. J. Majo and P. T. Perumal, *J. Org. Chem.*, 1998, **63**, 7136.
137 M. C. Bagley, R. T. Buck, S. L. Hind and C. J. Moody, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 591.
138 P. M. Pihko and A. M. P. Koskinen, *J. Org. Chem.*, 1998, **63**, 92.
139 P. C. Kearney, M. Fernandez and J. A. Flygare, *J. Org. Chem.*, 1998, **63**, 196.
140 J. G. Schantl and I. M. Lagoja, *Synth. Commun.*, 1998, **28**, 1451.
141 K. Dridi, M. L. El Efrit, B. Baccar and H. Zantour, *Synth. Commun.*, 1998, **28**, 167.
142 T. Besson, M.-J. Dozias, J. Guillard and C. W. Rees, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 3925.
143 C. Buron, L. El Kaïm and A. Uslu, *Tetrahedron Lett.*, 1997, **38**, 8027.
144 W. M. Best, E. L. Ghisalberti and M. Powell, *J. Chem. Res.* (*S*), 1998, 388.
145 J. M. Mellor, S. R. Schofield and S. R. Korn, *Tetrahedron*, 1997, **53**, 17151.
146 W. H. Bunnelle, P. R. Singam, B. A. Narayanan, C. W. Bradshaw and J. S. Liou, *Synthesis*, 1997, 439.
147 Z. Wróbel, *Synthesis*, 1997, 753.
148 B. Boduszek, A. Halama and J. Zon, *Tetrahedron*, 1997, **53**, 11399.
149 X.-L. Duan, R. Perrins and C. W. Rees, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 1617.
150 C. W. Rees and T. Y. Yue, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 2247.
151 T. Nakamura, H. Nagata, M. Muto and I. Saji, *Synthesis*, 1997, 871.
152 M. R. Grimmett, *Imidazole and Benzimidazole Synthesis*, Academic Press, London, 1997.
153 A. Rolfs and J. Liebscher, *J. Org. Chem.*, 1997, **62**, 3480.
154 S. Jayakumar, M. P. S. Ishar and M. P. Mahajan, *Tetrahedron Lett.*, 1998, **39**, 6557.
155 R. ten Have, M. Huisman, A. Meetsma and A. M. van Leusen, *Tetrahedron*, 1997, **53**, 11355.
156 C. F. Claiborne, N. J. Liverton and K. T. Nguyen, *Tetrahedron Lett.*, 1998, **39**, 8939.
157 N. A. Nedolya, L. Brandsma and B. A. Trofimov, *Tetrahedron Lett.*, 1997, **38**, 6279.
158 M. Carvalho, A. M. Lobo, P. S. Branco and S. Prabhakar, *Tetrahedron Lett.*, 1997, **38**, 3115.
159 J. J. Perkins, A. E. Zartman and R. S. Meissner, *Tetrahedron Lett.*, 1999, **40**, 1103.
160 H. Y. Wang, R. E. Partch and Y. Z. Li, *J. Org. Chem.*, 1997, **62**, 5222.
161 S. Cacchi, G. Fabrizi and A. Carangio, *Synlett*, 1997, 959.
162 N. Almirante, A. Cerri, G. Fedrizzi, G. Marazzi and M. Santagostino, *Tetrahedron Lett.*, 1998, **39**, 3287.
163 M. Yoshimatsu, M. Kawahigashi, E. Honda and T. Kataoka, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 695.
164 H.-B. Yu and W.-Y. Huang, *Synlett*, 1997, 679.
165 H.-B. Yu and W.-Y. Huang, *J. Fluorine Chem.*, 1997, **84**, 65.
166 J. M. Mellor, S. R. Schofield and S. R. Korn, *Tetrahedron*, 1997, **53**, 17163.
167 C. Chen, K. Wilcoxen and J. R. McCarthy, *Tetrahedron Lett.*, 1998, **39**, 8229.
168 R. D. Wilson, S. P. Watson and S. A. Richards, *Tetrahedron Lett.*, 1998, **39**, 2827.
169 C. Reidlinger, R. Dworczak and H. Junek, *Monatsh. Chem.*, 1998, **129**, 1207.
170 C. Reidlinger, R. Dworczak, H. Junek and H. Graubaum, *Monatsh. Chem.*, 1998, **129**, 1313.
171 F. Halley and X. Sava, *Synth. Commun.*, 1997, **27**, 1199.
172 V. M. Lyubchanskaya, L. M. Alekseeva and V. G. Granik, *Tetrahedron*, 1997, **53**, 15005.
173 P. G. Baraldi, B. Cacciari, G. Spalluto, R. Romagnoli, G. Braccioli, A. N. Zaid and M. J. P. de las Infantas, *Synthesis*, 1997, 1140.
174 J. Löffler and R. Schobert, *Synlett*, 1997, 283.
175 L. El Kaïm, I. Le Menestrel and R. Morgentin, *Tetrahedron Lett.*, 1998, **39**, 6885.
176 S. Lutun, B. Hasiak and D. Couturier, *Synth. Commun.*, 1999, **29**, 111.
177 A. Kraft, *Liebigs Ann./Recl.*, 1997, 1463.
178 J. R. Young and R. J. DeVita, *Tetrahedron Lett.*, 1998, **39**, 3931.
179 X.-G. Duan, X.-L. Duan, C. W. Rees and T.-Y. Yue, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 2597.
180 X.-G. Duan, X.-L. Duan and C. W. Rees, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 2831.
181 X.-G. Duan and C. W. Rees, *Chem. Commun.*, 1997, 1493.
182 S. C. Yoon, J. Cho and K. Kim, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 109.
183 K.-J. Kim and K. Kim, *Heterocycles*, 1999, **50**, 147.
184 K.-J. Kim and K. T. Kim, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 2175.
185 G. Mloston, T. Gendek, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, 1998, **81**, 66.
186 K. Harada, M. Oda, A. Matsushita and M. Shirai, *Heterocycles*, 1998, **48**, 695.
187 K. Harada, M. Oda, A. Matsushita and M. Shirai, *Synlett*, 1998, 431.
188 P. Uhlmann, J. Felding, P. Vedsø and M. Begtrup, *J. Org. Chem.*, 1997, **62**, 9177.
189 G. A. Romeiro, L. O. R. Pereira, M. C. B. V. de Souza, V. F. Ferreira and A. C. Cunha, *Tetrahedron Lett.*, 1997, **38**, 5103.
190 L. Jiang, A. Davison, G. Tennant and R. Ramage, *Tetrahedron*, 1998, **54**, 14233.
191 J. H. Teles, K. Breuer, D. Enders and H. Gielen, *Synth. Commun.*, 1999, **29**, 1.
192 B. H. Kim, S. K. Kim, Y. S. Lee, Y. M. Jun, W. Baik and B. M. Lee, *Tetrahedron Lett.*, 1997, **38**, 8303.
193 K. Koguro, T. Oga, S. Mitsui and R. Orita, *Synthesis*, 1998, 910.
194 B. S. Jursic and B. W. LeBlanc, *J. Heterocycl. Chem.*, 1998, **35**, 405.
195 R. C. Larock, X. J. Han and M. J. Doty, *Tetrahedron Lett.*, 1998, **39**, 5713.
196 T. Dubuffet, B. Cimetiere and G. Lavielle, *Synth. Commun.*, 1997, **27**, 1123.
197 E. A. Cioffi and W. F. Bailey, *Tetrahedron Lett.*, 1998, **39**, 2679.
198 Josemin, K. N. Nirmala and C. V. Asokan, *Tetrahedron Lett.*, 1997, **38**, 8391.
199 V. I. Tyvorskii, D. N. Bobrov, O. G. Kulinkovich, N. De Kimpe and K. A. Tehrani, *Tetrahedron*, 1998, **54**, 2819.
200 G. A. Cartwright and H. McNab, *J. Chem. Res.* (*S*), 1997, 296.
201 I. Yavari, R. Hekmat-Shoar and A. Zonouzi, *Tetrahedron Lett.*, 1998, **39**, 2391.
202 S. Cacchi, G. Fabrizi, L. Moro and P. Pace, *Synlett*, 1997, 1367.
203 L. Wang and W. Shen, *Tetrahedron Lett.*, 1998, **39**, 7625.
204 A. M. S. Silva, J. A. S. Cavaleiro and J. Elguero, *Liebigs Ann./Recl.*, 1997, 2065.
205 J. Sauer and D. K. Heldmann, *Tetrahedron Lett.*, 1998, **39**, 2549.
206 J. Sauer, D. K. Heldmann and G. R. Pabst, *Eur. J. Org. Chem.*, 1999, 313.
207 G. R. Pabst, K. Schmid and J. Sauer, *Tetrahedron Lett.*, 1998, **39**, 6691.
208 G. R. Pabst and J. Sauer, *Tetrahedron Lett.*, 1998, **39**, 8817.
209 O. C. Pfüller and J. Sauer, *Tetrahedron Lett.*, 1998, **39**, 8821.
210 G. R. Pabst, O. C. Pfüller and J. Sauer, *Tetrahedron Lett.*, 1998, **39**, 8825.
211 G. R. Pabst and J. Sauer, *Tetrahedron Lett.*, 1998, **39**, 6687.
212 J. A. Varela, L. Castedo and C. Saá, *J. Org. Chem.*, 1997, **62**, 4189.
213 J. A. Varela, L. Castedo and C. Saá, *J. Am. Chem. Soc.*, 1998, **120**, 12147.
214 K. Iwamoto, E. Oishi, T. Sano, A. Tsuchiya, Y. Suzuki, T. Higashino and A. Miyashita, *Heterocycles*, 1997, **45**, 1551.
215 W.-T. Li, F.-C. Lai, G.-H. Lee, S.-M. Peng and R.-S. Liu, *J. Am. Chem. Soc.*, 1998, **120**, 4520.
216 J. Barluenga, M. Ferrero and F. Palacios, *Tetrahedron*, 1997, **53**, 4521.

217 I. Katsuyama, S. Ogawa, Y. Yamaguchi, K. Funabiki, M. Matsui, H. Muramatsu and K. Shibata, *Synthesis*, 1997, 1321.
218 J. W. B. Cooke, M. J. Coleman, D. M. Caine and K. P. Jenkins, *Tetrahedron Lett.*, 1998, **39**, 7965.
219 I. Katsuyama, S. Ogawa, H. Nakamura, Y. Yamaguchi, K. Funabiki, M. Matsui, H. Muramatsu and K. Shibata, *Heterocycles*, 1998, **48**, 779.
220 E. Okada, T. Kinomura, Y. Higashiyama, H. Takeuchi and M. Hojo, *Heterocycles*, 1997, **46**, 129.
221 N. Nishiwaki, Y. Tohda and M. Ariga, *Synthesis*, 1997, 1277.
222 S. Mathé and A. Rassat, *Tetrahedron Lett.*, 1998, **39**, 383.
223 A. R. Katritzky, S. A. Belyakov, A. E. Sorochinsky, S. A. Henderson and J. Chen, *J. Org. Chem.*, 1997, **62**, 6210.
224 I. Furukawa, H. Fujisawa, M. Kawazome, Y. Nakai and T. Ohta, *Synthesis*, 1998, 1715.
225 J. F. Stambach, L. Jung and R. Hug, *Synthesis*, 1998, 265.
226 T. Koike, N. Takeuchi and S. Tobinaga, *Chem. Pharm. Bull.*, 1999, **47**, 128.
227 N. A. Nedolya, L. Brandsma, A. van der Kerk, V. Yu. Vvedensky and B. A. Trofimov, *Tetrahedron Lett.*, 1998, **39**, 1995.
228 A. Czarny, H. Lee, M. Say and L. Strekowski, *Heterocycles*, 1997, **45**, 2089.
229 L. Strekowski, S.-Y. Lin, H. Lee, Z.-Q. Zhang and J. C. Mason, *Tetrahedron*, 1998, **54**, 7947.
230 J. I. Úbeda, M. Villacampa and C. Avendaño, *Synthesis*, 1998, 1176.
231 R. S. Compagnone, A. I. Suárez, J. L. Zambrano, I. C. Piña and J. N. Domínguez, *Synth. Commun.*, 1997, **27**, 1631.
232 L. H. Zhou and Y. M. Zhang, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 2899.
233 W. Baik, D. I. Kim, H. J. Lee, W.-J. Chung, B. H. Kim and S. W. Lee, *Tetrahedron Lett.*, 1997, **38**, 4579.
234 C. S. Shi, Q. Zhang and K. K. Wang, *J. Org. Chem.*, 1999, **64**, 925.
235 F. Palacios, D. Aparicio and J. Garciá, *Tetrahedron*, 1997, **53**, 2931.
236 F. Palacios, D. Aparicio and J. Garciá, *Tetrahedron*, 1998, **54**, 1647.
237 C. S. Cho, B. H. Oh and S. C. Shim, *Tetrahedron Lett.*, 1999, **40**, 1499.
238 P. Charpentier, V. Lobrégat, V. Levacher, G. Dupas, G. Quéguiner and J. Bourguignon, *Tetrahedron Lett.*, 1998, **39**, 4013.
239 M. Schlosser, H. Keller, S. Sumida and J. Yang, *Tetrahedron Lett.*, 1997, **38**, 8523.
240 L. Brandsma, N. A. Nedolya, H. D. Verkruijsse, N. L. Owen, D. Li and B. A. Trofimov, *Tetrahedron Lett.*, 1997, **38**, 6905.
241 H.-J. Ha, Y.-S. Lee and Y.-G. Ahn, *Heterocycles*, 1997, **45**, 2357.
242 A. R. Katritzky, D. Semenzin, B. Z. Yang and D. P. M. Pleynet, *J. Heterocycl. Chem.*, 1998, **35**, 467.
243 J. Koyama, I. Toyokuni and K. Tagahara, *Chem. Pharm. Bull.*, 1998, **46**, 332.
244 K. Uchiyama, Y. Hayashi and K. Narasaka, *Synlett*, 1997, 445.
245 H. Kusama, Y. Yamashita, K. Uchiyama and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 1997, **70**, 965.
246 O. B. Familoni, P. T. Kaye and P. J. Klaas, *Chem. Commun.*, 1998, 2563.
247 C. W. Holzapfel and C. Dwyer, *Heterocycles*, 1998, **48**, 215.
248 A. Arcadi, S. Cacchi, G. Fabrizi, F. Manna and P. Pace, *Synlett*, 1998, 446.
249 E. L. Larghi and T. S. Kaufman, *Tetrahedron Lett.*, 1997, **38**, 3159.
250 K. R. Roesch and R. C. Larock, *J. Org. Chem.*, 1998, **63**, 5306.
251 R. M. Adlington, J. E. Baldwin, D. Catterick and G. J. Pritchard, *Chem. Commun.*, 1997, 1757.
252 T. S. Wang and I. S. Cloudsdale, *Synth. Commun.*, 1997, **27**, 2521.
253 J. Barluenga, L. A. López, S. Martínez and M. Tomás, *Synlett*, 1999, 219.
254 P. Dalla Croce, R. Ferraccioli and C. La Rosa, *Heterocycles*, 1997, **45**, 1309.
255 W. Szczepankiewicz and J. Suwinski, *Tetrahedron Lett.*, 1998, **39**, 1785
256 E. Erba and D. Sporchia, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 3021.
257 E. Erba, D. Pocar and M. Valle, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 421.
258 W. K. Zielinski, A. Kudelko and E. M. Holt, *Heterocycles*, 1998, **48**, 319.
259 J. Sauer, D. K. Heldmann, J. Hetzenegger, J. Krauthan, H. Sichert and J. Schuster, *Eur. J. Org. Chem.*, 1998, 2885.
260 J. Sauer and D. K. Heldmann, *Tetrahedron*, 1998, **54**, 4297.
261 T. J. Sparey and T. Harrison, *Tetrahedron Lett.*, 1998, **39**, 5873.
262 Y. Kamitori, M. Hojo and T. Yoshioka, *Heterocycles*, 1998, **48**, 2221.
263 M. S. F. Lie Ken Jie and P. Kalluri, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 3485.
264 T. Masquelin, Y. Delgado and V. Baumlé, *Tetrahedron Lett.*, 1998, **39**, 5725.
265 I. Shibuya, A. Oishi and M. Yasumoto, *Heterocycles*, 1998, **48**, 1659.
266 Y. Matsubara, A. Horikawa and Z. Yoshida, *Tetrahedron Lett.*, 1997, **38**, 8199.
267 A. J. Maroulis, K. C. Domzaridou and C. P. Hadjiantoniou-Maroulis, *Synthesis*, 1998, 1769.
268 H. Suzuki and T. Kawakami, *Synthesis*, 1997, 855.
269 A. M. Bernard, M. T. Cocco, C. Congiu, V. Onnis and P. P. Piras, *Synthesis*, 1998, 317.
270 R. A. Aitken, I. M. Fairhurst, A. Ford, P. E. Y. Milne, D. W. Russell and M. Whittaker, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 3107.
271 A. R. Katritzky, J. Wang, N. Karodia and J. Q. Li, *Synth. Commun.*, 1997, **27**, 3963.

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