REVIEW

Synthesis of aromatic heterocycles

Thomas L. Gilchrist

Chemistry Department, The University of Liverpool, Liverpool, UK L69 7ZD.
E-mail: tlg57@liv.ac.uk

Received (in Cambridge, UK) 11th July 2001
First published as an Advance Article on the web 2nd October 2001

Covering March 1999 to February 2001. Previous review: *J. Chem. Soc., Perkin Trans. 1*, 1999, 2849.

1 Introduction
2 Furans and benzofurans
3 Thiophenes and benzothiophenes
4 Pyrroles
5 Indoles, indolizines and carbazoles
6 Oxazoles, benzoxazoles, thiazoles and benzothiazoles
7 Isoxazoles, isothiazoles and fused analogues
8 Imidazoles and benzimidazoles
9 Pyrazoles and indazoles
10 Oxadiazoles and thiadiazoles
11 Triazoles and tetrazoles
12 Pyrones, coumarins and chromones
13 Pyridines
14 Quinolines and isoquinolines
15 Pyrimidines and quinazolines
16 Other diazines, triazines and tetrazines
17 References

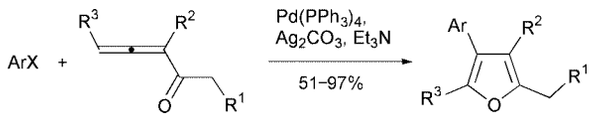
1 Introduction

This is a review of new or improved methods of construction of aromatic heterocycles from acyclic precursors or by ring interconversion that have been published in the primary literature between March 1999 and February 2001. The ring systems covered are mainly the more common monocyclic and bicyclic aromatic heterocycles. There is increasing emphasis in recent publications on methods that make use of supported reagents or that employ techniques such as microwave irradiation in the absence of solvents. Some of these methods have clear technical advantages over older solution phase methods in terms of yield, versatility, or environmental impact, but do not employ new chemistry in the construction of the ring systems. The coverage of these publications in this article is very selective since reviews of such methods are available elsewhere.

A major new reference work, *Science of Synthesis*, will eventually provide comprehensive coverage of the methods of preparation of aromatic heterocycles. Two volumes have appeared during the period under review, one covering monocyclic five membered hetarenes with one heteroatom[1] and the second, fused five membered hetarenes with one heteroatom.[2] Palladium catalysed reactions are now ubiquitous in heterocyclic chemistry and their applications have been described in a new book.[3]

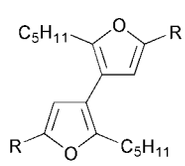
2 Furans and benzofurans

Fürstner has reviewed his catalysis based syntheses of furan and pyrrole natural products.[4] A versatile new synthesis of polysubstituted furans from allenic ketones (Scheme 1) results from their reaction with aryl bromides or iodides and palladium(0) catalysed cyclisation.[5] A related synthesis based on the cyclisation of allenic ketones with allylic bromides has been described; in these reactions a palladium(II) catalyst is used.[6] A palladium(0) catalysed synthesis of bifuranyls **1** from iodoenones **2** may also involve allenic ketones as intermediates.[7]

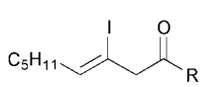


Scheme 1

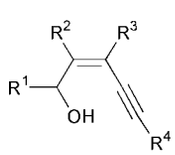
In comparison with other transition metal catalysts gold(III) chloride is highly effective for the cyclisation of propargyl (prop-2-ynyl) and allenyl ketones to furans.[8] Tetrasubstituted furans have also been synthesised by the palladium(II) catalysed *exo* cyclisation on to the triple bond of acetylenic alcohols **3** and full details of this work have been published.[9,10] Further examples of the synthesis of furans by intramolecular *exo* cyclisation of enolate anions, through oxygen, on to triple bonds have been described; these provide routes to 5-substituted furan-2-acetate esters[11] and to 2,5-disubstituted methyl furan-3-carboxylates **4**.[12] The alkylation of β-keto esters and β-ketonitriles by propargyl bromide followed by *exo* cyclisation on to the triple bond produces 2-methyl-4,5-disubstituted furans.[13] Tri- and tetra-substituted furans can also be formed from *tert*-butyl acetoacetate by a variant of the Feist–Benary reaction in which *C*-alkylation by an α-haloketone is followed by cyclisation in TFA.[14]



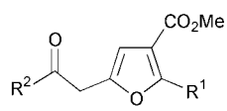
1



2



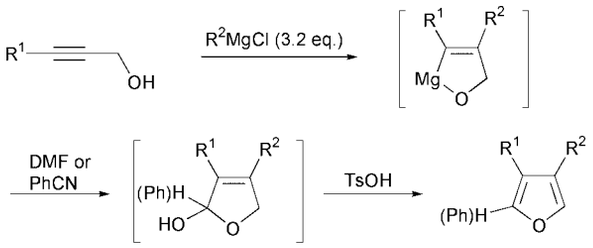
3



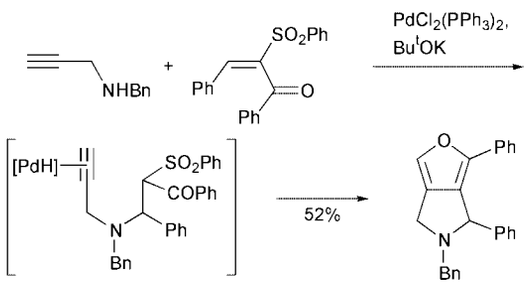
4

A new route to 3,4-disubstituted and 2,3,4-trisubstituted furans is based on the addition of Grignard reagents to propargyl alcohols (Scheme 2).[15] For example, 3-phenyl-4-vinylfuran was prepared in 72% yield from 3-phenylpropynol and vinylmagnesium chloride. The methodology was extended to the synthesis of tetrasubstituted furans by generating 1,3-disubstituted propynols *in situ*. Another method that provides a synthesis of furo[3,4-*c*]-fused heterocycles from propargylic alcohols or propargylic amines is illustrated in Scheme 3. Variations in the structures either of the propargylic component or of the vinyl sulfone give a range of fused furan derivatives.[16] A new synthesis of symmetrical 3,3-bifurans is based on the palladium(II) catalysed tandem dimerisation and *endo* cyclisation of acetylenic ketones.[17] A tandem reductive ring

DOI: 10.1039/a904578c

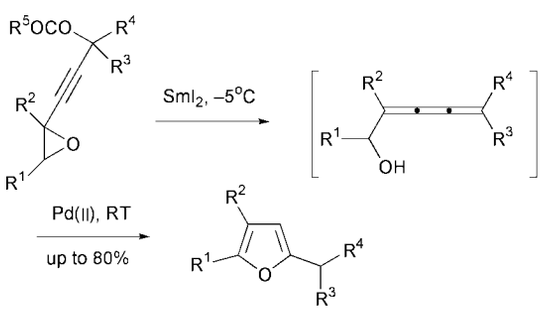


Scheme 2



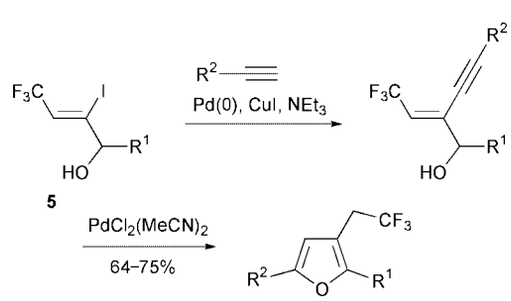
Scheme 3

opening of epoxypropargylic esters followed by palladium(II) catalysed cyclisation (Scheme 4) gives 2,3,5-trisubstituted furans, generally in good yield.[18]



Scheme 4

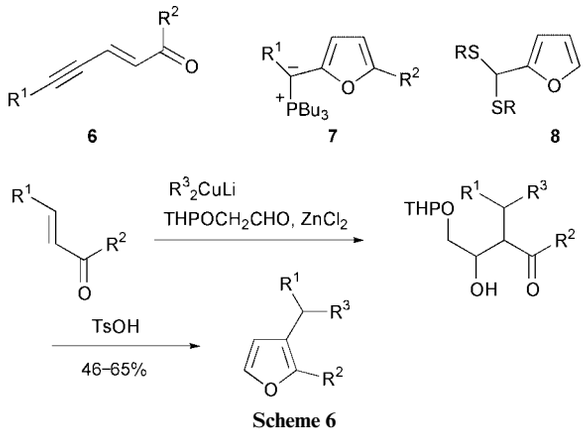
An efficient route to 3-trifluoroethylfurans is outlined in Scheme 5.[19] The iodoenol **5** was obtained from the corresponding propargyl alcohol by reaction with sodium iodide in acetic acid and the furan synthesis was completed by successive coupling reactions and palladium(II) catalysed cyclisation.



Scheme 5

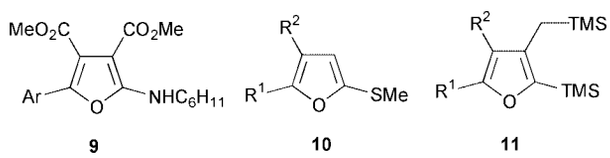
Two new conversions of ynenones **6** to furans have been reported, one involving the addition of tributylphosphine to the triple bond followed by cyclisation to give an intermediate ylide **7** which is intercepted by reaction with an aldehyde.[20] The second is the cyclisation of the sulfides **6** (R^1 = MeS or PhS, R^2 = H) to furan dithioacetals **8** in HCl. This unusual reaction is proposed to go through a series of ring closure and ring opening steps.[21]

2,3-Disubstituted furans have been synthesised from enones by a sequence involving conjugate addition and interception of the enolate anions (Scheme 6).[22] A series of 2,3,5-trisubstituted

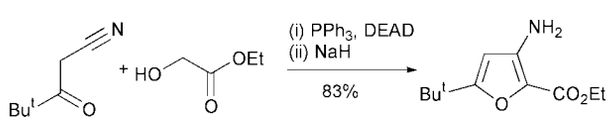


Scheme 6

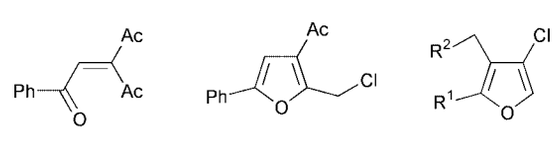
furans was also prepared from enones in moderate to high yield by the boron trifluoride catalysed addition of alkynyl boronates, followed by cyclisation.[23] Conjugate addition of cyclohexyl isocyanide to DMAD in the presence of an aromatic aldehyde gives the cyclohexylaminofuran diesters **9** in 54–68% yield.[24] 2-Aminoalkylfurans have been formed in a similar way starting from 2-acetylbenzoquinone and alkyl isocyanides.[25] 2-Methylthiofurans **10** are produced from ketones $R^1COCH_2R^2$ by a cyclisation reaction in which the key step is methylsulfenylation of thioacetals by the reagent $(MeS)Me_2S^+BF_4^-$.[26]



Trimethylsilylfurans **11** have been isolated in good yield as the major products from the reaction of *cis*-2,3-bis(trimethylsilyl)cyclopropanone and keto phosphonium ylides.[27] *O*-Alkylation of α-cyanoketones under Mitsunobu conditions provides intermediates that are converted by base into 3-aminofurans: an example is shown in Scheme 7. The sequence can be carried out as a one pot procedure.[28] The condensation of arylglyoxals with acetylacetone gives transient enones **12**; these intermediates are then converted into furans either by further addition of acetylacetone or by cyclisation with conc. HCl. For example, 3-acetyl-2-chloromethyl-5-phenylfuran **13** was formed in high yield from phenylglyoxal under the latter conditions.[29] A new route to 3-chlorofurans **14** starting from trichloroacetaldehyde and allylic alcohols has been described.[30]



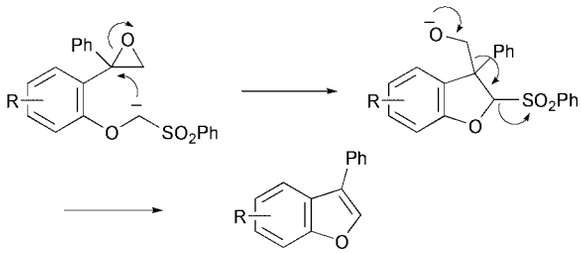
Scheme 7



3-Arylbenzofurans can be formed from α-aryloxyacetophenones in solvent free conditions on a reusable clay support and under microwave irradiation (Scheme 8).[31] A new general route to 3-arylbenzofurans, which can either be used in solution or adapted to a solid support, is illustrated in Scheme 9.[32]

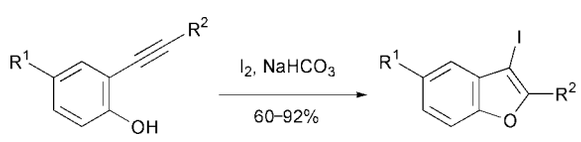
The palladium(II)–copper(I) catalysed coupling of 2-iodophenol to the triple bond of chiral α-phenylpropargylamines followed by cyclisation of the 2-alkynylphenols gives the

Scheme 8

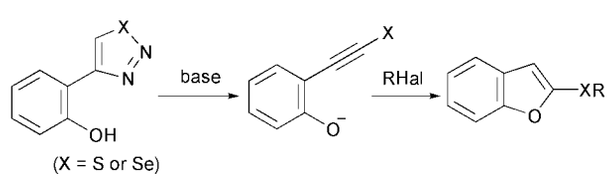


Scheme 9

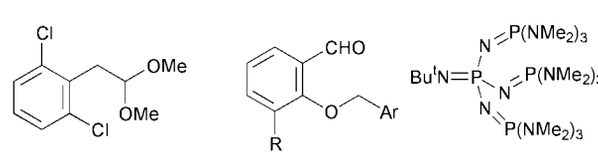
corresponding 2-(α-phenylaminomethyl)benzofurans with little loss of chirality.[33] The cyclisation of 2-alkynylphenols to benzofurans can also be carried out using iodine (Scheme 10) and this produces 2-substituted 3-iodobenzofurans which can then be further substituted at C-3 by palladium coupling.[34] A mechanistically related process, which leads to 2-alkylthio- and 2-alkylselenobenzofurans in good yield, is shown in Scheme 11: here the alkyne is generated *in situ* from a 1,2,3-thiadiazole or a 1,2,3-selenadiazole.[35] Carbonylative cyclisation under palladium catalysis leads directly to 2-substituted benzofuran-3-carboxylates and the reaction has been used to prepare precursors to adenosine receptor antagonists.[36] The yields in such reactions can be poor if electron withdrawing substituents are present on the benzene ring but a new catalyst system based on palladium(II) iodide, thiourea and carbon tetrabromide has been shown to be effective in such cases.[37] 2-Aryl-3-phenylbenzofurans have been prepared in high yield from 1,2-dibromobenzenes and aryl benzyl ketones by coupling and cyclisation with a palladium catalyst and caesium carbonate.[38] The first reported synthesis of 4-chlorobenzofuran starts from the dichlorophenylacetal **15**. This is converted into the corresponding mono-*tert*-butyl phenyl ether by heating with sodium *tert*-butoxide and a palladium catalyst; acid catalysed deprotection and ring closure then gives the benzofuran in 51% overall yield.[39] The closure of the aryl benzyl ethers **16** to the corresponding 2-arylbenzofurans can be achieved in good yield by heating with the strong phosphazene base **17**.[40]



Scheme 10



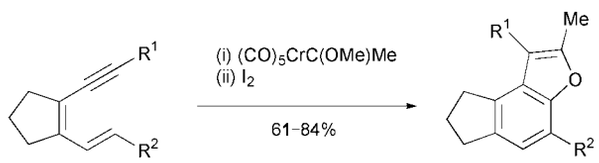
Scheme 11



15 **16** **17**

A general route to 4-arylbenzofurans from 3-aryl-1-(trimethylsilyloxy)cyclohexenones and ethyl vinyl ether has been described. The reaction sequence involves oxidative addition to the silyl enol ether followed by ring closure and aromatisation; overall yields are moderate (39–58%).[41] Procedures for the microwave assisted synthesis of benzofuran-2-carboxylic esters under solvent free conditions[42] and for the preparation of 3-arylbenzofurans using polymer supported reagents[43] have been described. Both procedures enable the benzofurans to be isolated in high yield.

A novel synthesis of furans from Fischer carbene complexes was outlined in the previous review in this series. The method has since been extended to the synthesis of benzofurans and isobenzofurans. A synthesis of benzofurans from dienylacetylenes is shown in Scheme 12[44] and a related synthesis from enediynes has been described.[45] In a more direct extension of the furan synthesis the isobenzofuran **19** was generated from the alkyne **18** and the same chromium carbene complex and was intercepted by Diels–Alder cycloaddition.[46] Several other isobenzofurans were generated in the same way. 5,6-Bis(trimethylsilyl)isobenzofuran has also been generated for the first time, using Warrener's established tetrazine methodology, and has been efficiently intercepted by a variety of dienophiles.[47]



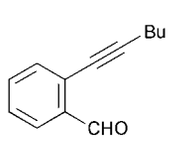
Scheme 12

Phenanthro[2,3-*c*]furan **20** has been synthesised from 2-bromo-3-methylphenanthrene. It is 15 times more reactive than isobenzofuran in competitive cycloaddition reactions, and is therefore described as the most reactive isolable diene so far reported.[48] Phenanthrofurans **21** have been prepared (45–70%) from phenanthraquinone and alkyl vinyl ketones by a novel Baylis–Hillman procedure with titanium(IV) chloride as the catalyst.[49]

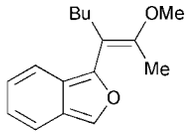
3 Thiophenes and benzothiophenes

Thermal methods of synthesis of thiophenes and selenophenes have been reviewed.[50] The Gewald synthesis of tetrasubstituted thiophenes has been carried out at room temperature by using pyridine as a solvent. The method has been used for the parallel synthesis of thiophenes.[51] In an extension of the Gewald synthesis, tetrasubstituted thiophenes **22** bearing an alkoxy group at C-5 have been prepared in moderate yield from ethyl cyanoacetate, an alkoxyacetone and sulfur with morpholine in ethanol.[52] The thiophene **24** was prepared (63%) from the ester **23** and methyl mercaptoacetate with KOH in methanol. It was then hydrolysed and decarboxylated to 4-hydroxy-2-trifluoromethylthiophene, an isostere of trifluoro-*m*-cresol.[53] A related route to 3-aminothiophene-2-carboxylic esters bearing a sulfone function at C-4 and a free 5-position has been described.[54]

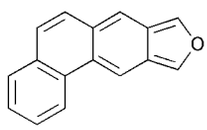
A synthesis of 5-dialkylaminothiophene-2-carboxylic esters from thioamides is illustrated in Scheme 13.[55] Several closely related methods for the synthesis of these thiophenes are described. 3-Alkylamino-5-arylthiophenes have also been synthesised by a new route, which is illustrated in Scheme 14 with a phosphonic ester as an activated methylene component. The method was generalised by using a wide range of other activated methylene components, including nitromethane and cyanoacetic acid.[56] The palladium(II) catalysed *exo* cyclisation of the thiol **25** to 2-pentyl-4-ethylthiophene **26** (89% yield) is an example of a general method of thiophene synthesis from allylic thiols of this type.[57] Similarly, the allylic sulfide **27** and



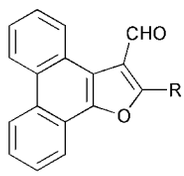
18



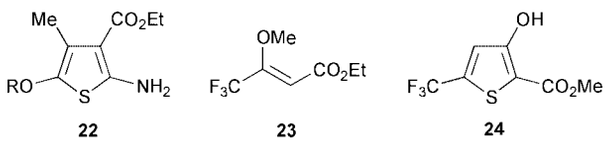
19



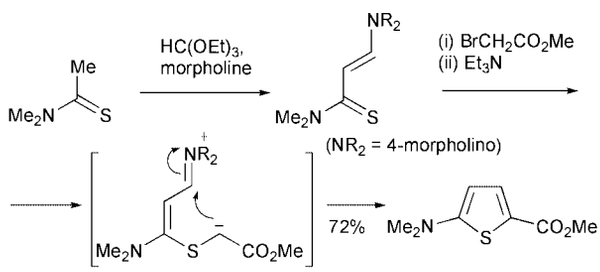
20



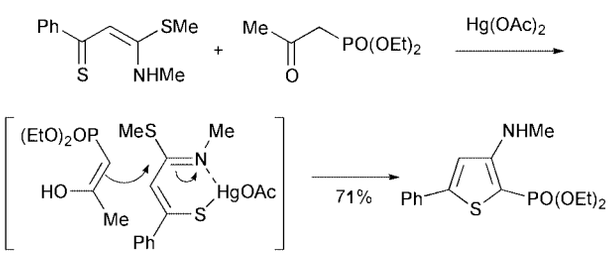
21



22 23 24

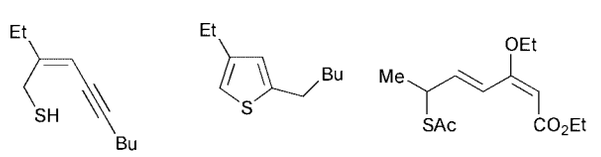


Scheme 13



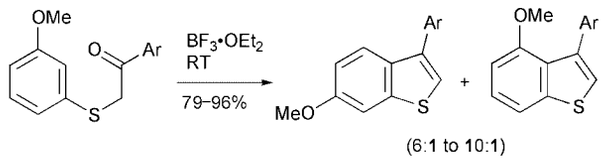
Scheme 14

related compounds have been converted into thiophenes under acidic conditions; the yield of ethyl 5-methylthiophene-2-acetate from the sulfide **27** was 84%.[58]

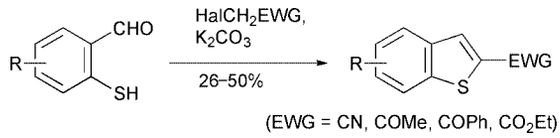


25 26 27

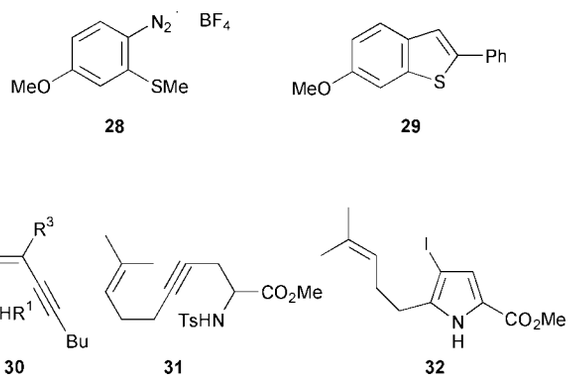
The cyclisation of (3-methoxyphenylthio)acetophenones to benzothiophenes shown in Scheme 15 is notable for the absence of 2-arylbenzothiophenes as products since they are commonly formed in other acid catalysed cyclisations.[59] 2-Mercaptobenzaldehydes can be formed from the corresponding benzaldehydes by *ortho* lithiation and reaction with sulfur. These are useful precursors to benzothiophenes bearing an electron withdrawing group at C-2, as shown in Scheme 16.[60] A route to 2-phenyl-6-methoxybenzothiophene **29** (55%) from the diazonium fluoroborate **28** involves its reaction with phenylacetylene in the presence of iron(II) sulfate in DMSO (radical forming conditions) and *endo* cyclisation of the alkynyl sulfide so produced.[61]



Scheme 15



Scheme 16

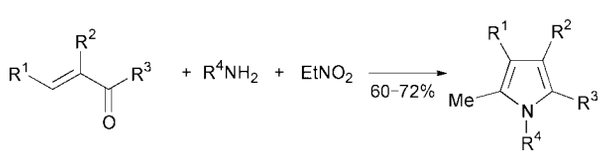


28 29 30 31 32

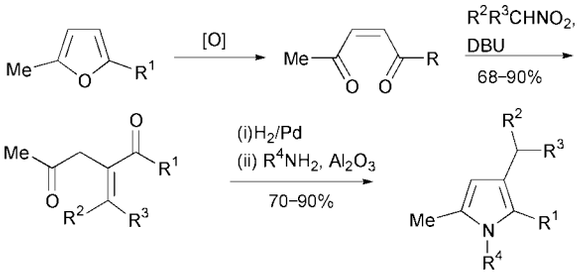
4 Pyrroles

By analogy with the formation of 2-pentylthiophenes from allylic sulfides such as **25**, palladium catalysed *exo* cyclisation of *Z*-enynes **30** leads to the formation of 2-pentylpyrroles. The ring closure goes at room temperature when $R^3 = H$, but otherwise heating is required.[62] As reported earlier, iodocyclisation can also be used to construct the N–C bond. Knight and coworkers have used their *endo* iodocyclisation to produce the iodopyrrole **32** from the alkyne **31**. The pyrrole was then converted into the core structure of roseophilin by further radical cyclisation.[63] A Paal–Knorr synthesis has also been used to construct the pyrrole ring in an asymmetric synthesis of roseophilin.[64] Simple Paal–Knorr reactions have been shown to go efficiently under microwave irradiation and without the need for an acid catalyst.[65]

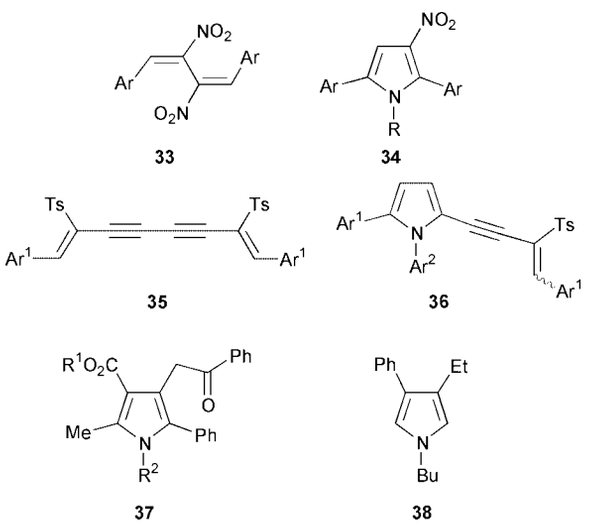
A related reaction is the three component coupling of enones, amines and nitroalkanes which leads to pentasubstituted pyrroles (Scheme 17) and this can also be carried out under microwave irradiation on the surface of silica gel.[66] The overall conversion of 2,5-dialkylfurans to pyrroles shown in Scheme 18 has some similar features in that key steps are conjugate addition of a nitroalkane and ring closure with a primary amine.[67] 2,3-Dinitrobutadienes **33** are available from 3,4-dinitrothiophene and these compounds can be converted into 3-nitro-2,5-diarylpyrroles **34** by reaction with a primary amine followed by treatment with an acid catalyst and DDQ.[68] The copper(I)–copper(II) catalysed addition of aromatic amines to the conjugated diacetylenic sulfones **35** has been reported to give the pyrroles **36** (47–63%).[69]



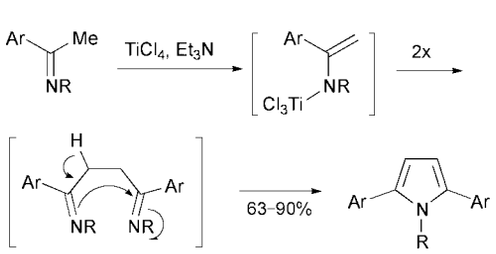
Scheme 17



Scheme 18

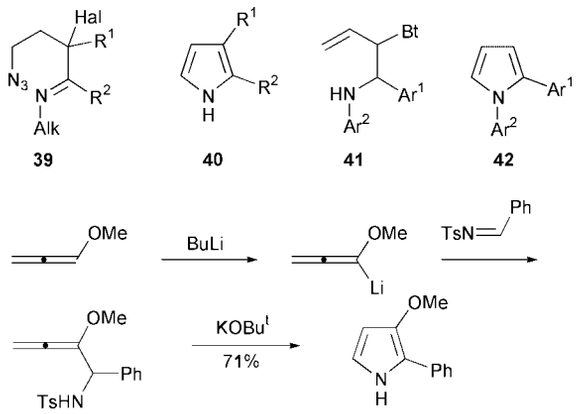


Imines and enamines are components in several new reports of pyrrole synthesis. The conjugate addition of alkyl 3-aminocrotonates to *trans*-1,2-dibenzoylethylene results in the formation of pyrroles with structure **37**. When the reactions were carried out in a ball mill without solvent the products were obtained in quantitative yield.[70] Addition of butyraldehyde *N*-butylimine to β-nitrostyrene is catalysed by samarium(III) isopropoxide and the pyrrole **38** is isolated (63%); several similar reactions are described.[71] Addition reactions of cyclohexanone *N*-benzylimine to nitroalkenes (without a catalyst) have also been reported.[72] 1-Substituted 2,5-diarylpyrroles are isolated in good yield from the reactions of acetophenone imines with titanium(IV) chloride and triethylamine. The reaction is proposed to go by coupling of a titanium enamine complex (Scheme 19).[73] The azides **39** are produced by alkylation of α-haloalkyl imines with 1-azido-2-iodoethane and they can be converted into 2,3-disubstituted pyrroles **40** by successive reaction with tin(II) chloride and sodium methoxide.[74] An improved route to 1,2-diarylpyrroles from *N*-allylbenzotriazole and *N*-arylimines of aromatic aldehydes has been described: the adducts **41** are isolated and cyclised under oxidative conditions [copper(II) chloride and catalytic palladium(II) acetate] to give a range of 1,2-diaryl pyrroles **42** in moderate to good yield.[75]



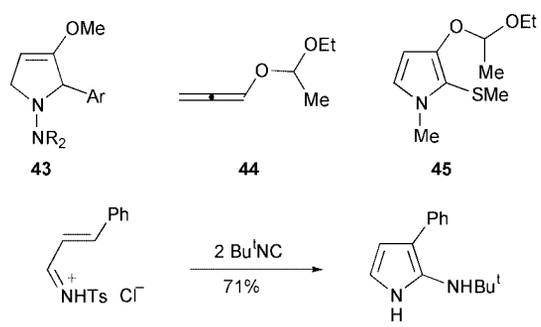
Scheme 19

Lithiated methoxyallenes have been used as a precursor to 2-aryl-3-methoxypyrroles. An example, in which *N*-tosylbenzaldimine is the electrophilic component, is shown in Scheme 20.[76] Other 2-substituted and 2,5-disubstituted 3-methoxy-



Scheme 20

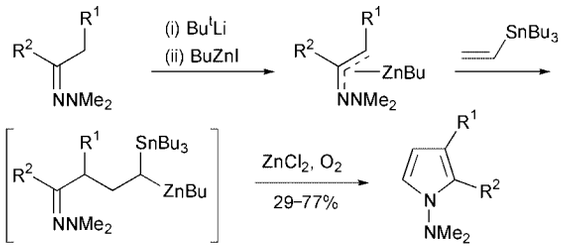
pyrroles were obtained in a similar way. In an analogous series of reactions, lithiated methoxyallene was reacted with benzaldehyde *N*,*N*-dialkylhydrazones to give dihydropyrroles **43**.[77] The *N*-morpholino derivatives were aromatised by MCPBA oxidation, or by treatment with dilute HCl when an unusual migration of the morpholino group to the 3-position occurred. In another related piece of work the alkoxypyrrole **45** was synthesised from the allene **44**, methyl isothiocyanate and iodomethane. The corresponding 3-hydroxypyrrole was obtained by hydrolysis of the acetal function.[78] Similar routes to 2-methylthio-5-methoxypyrroles have been described.[79] 2-Alkylaminopyrroles have been isolated in moderate to good yield from the reaction of isocyanides with conjugated iminium salts; an example is shown in Scheme 21.[80]



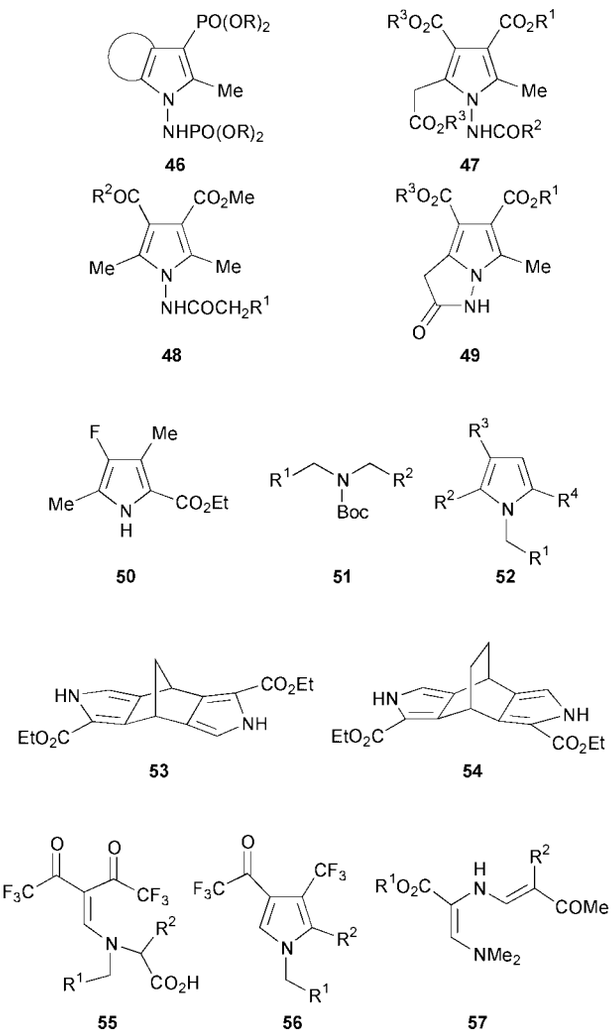
Scheme 21

A new route to 1-(dimethylamino)pyrroles from alkyl ketone *N*,*N*-dimethylhydrazones is shown in Scheme 22.[81] A versatile route to substituted 1-aminopyrroles is provided by nucleophilic addition reactions to conjugated vinylazo compounds. Diphosphorylated 1-aminopyrroles **46** have been obtained in this way from phosphorylated azoalkenes and cyclic enamines.[82] Attanasi and co-workers have extended the range of 1-aminopyrroles that can be formed from activated methylene compounds and vinylazo compounds derived from β-keto esters. For example, pyrroles of general structures **47**[83] and **48**[84] have been prepared. Compounds **47** were converted into the bicyclic structures **49** by cyclisation, and pyrroles **48** reacted further with the vinylazo compounds to give more complex 1-amino derivatives. Ketoximes are also sources of pyrroles through the Trofimov synthesis. Trofimov and co-workers have reviewed examples of the reaction that lead to bipyrroles, furylpyrroles and thienylpyrroles.[85] The first use of propyne or allene (interconvertible under the reaction conditions) to give 2-methylpyrroles in the Trofimov synthesis has been described.[86]

A novel synthesis of substituted pyrrole-2-carboxylates from ethyl isocyanoacetate and 1,3-dicarbonyl compounds under rhodium carbonyl catalysis has been reported: an example of its application is the formation of the fluoropyrrole **50** (40%).[87] α-Carbanions derived from carbamates **51** undergo copper



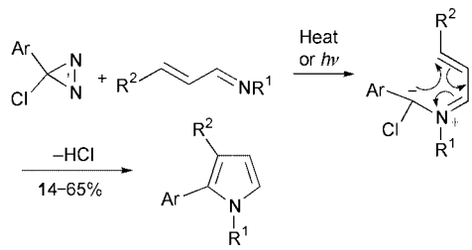
Scheme 22



catalysed conjugate addition to ynones and the intermediates are converted into substituted pyrroles **52** after removal of the Boc group.[88]

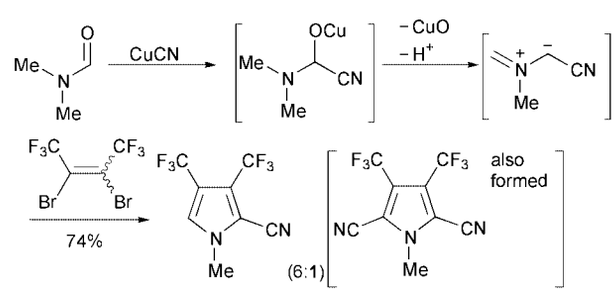
Applications of the Barton–Zard reaction and related reactions of isocyanides continue to provide important routes to 4-substituted and 3,4-disubstituted pyrrole-2-carboxylates. The reaction has been used to prepare pyrrolostatin and some analogues[89] and (+)-deoxypyrrololine (a potential biological marker for the diagnosis of osteoporosis).[90] One of the most important applications of the reaction is the synthesis of 3,4-fused pyrroles from ethyl isocyanoacetate and relatively unreactive nitro compounds such as 1-nitronaphthalene. It has been shown that the yields in such reactions can be significantly improved by using a phosphazene base instead of DBU.[91,92] Other reported examples of the reaction include the addition of ethyl cyanoacetate to 1,2-disubstituted-1-vinyl sulfones to give a variety of ethyl pyrrole-2-carboxylates with electron-withdrawing groups at the 4-position,[93] syntheses of 4-formyl-pyrrole-2-carboxylates,[94] and routes to novel bipyrroles such as **53** and **54** by double condensation reactions.[95]

A series of fluorinated pyrroles **56** has been obtained from the cyclisation of the activated enamino diketones **55** derived from secondary amino acids.[96] The enamino esters **57** have also been used as a source of a variety of 4-substituted 3-methylpyrrole-2-carboxylates.[97] Arylchlorocarbenes derived from diazirines react with conjugated imines to give conjugated azomethine ylides; these intermediates are detectable in solution but undergo 1,5-dipolar cyclisation and elimination to trisubstituted pyrroles, which are isolated in low to moderate yield (Scheme 23).[98,99]



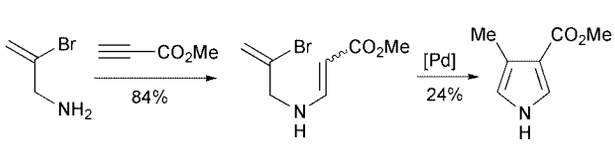
Scheme 23

Azomethine ylides have also been generated from aromatic imines and difluorocarbene. Both intermolecular[100] and intramolecular[101] dipolar cycloadditions of these intermediates to acetylenes have been reported and the products, 2-fluoropyrroles, have been isolated in moderate yield. An unusual method of generation of an azomethine ylide is illustrated in Scheme 24: reaction of DMF with copper(I) cyanide leads to the production of an intermediate that can be intercepted by activated dibromoalkenes.[102] The major products are 2-cyano-1-methylpyrroles. The cycloaddition reactions of azomethine ylides derived from glycine *N*-arylimines with β-nitrostyrenes provide good routes to 3,5-diarylpyrrole-2-carboxylic acids[103,104] and other useful new examples of the synthesis of 3,4-disubstituted 2-arylpyrroles by cycloaddition to azomethine ylides have been reported.[105,106]

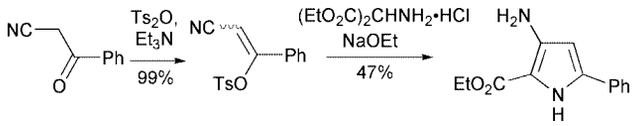


Scheme 24

In a modification of the Knorr pyrrole synthesis, Weinreb amide derivatives have been used in place of the amino ketone components in order to avoid self condensation reactions of the amino ketones.[107] The *N*-methoxymethyl function of the amide can then be displaced by a range of other groups. Several pyrroles have been isolated in moderate to good yield from a two step reaction sequence (exemplified in Scheme 25) in which ring formation is brought about by palladium catalysed coupling.[108] 5-Aryl-3-aminopyrrole-2-carboxylates have also been prepared in moderate yield by a two step sequence from benzoylacetonitrile, as illustrated in Scheme 26; an ethoxycarbonyl group is lost in the cyclisation step.[109]



Scheme 25

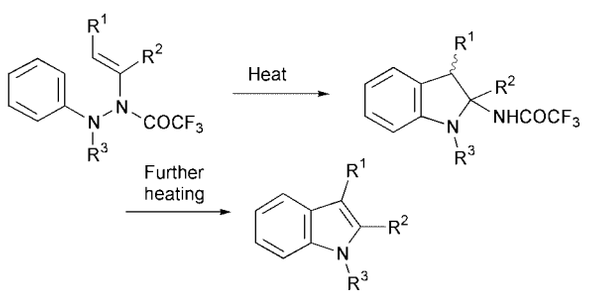


Scheme 26

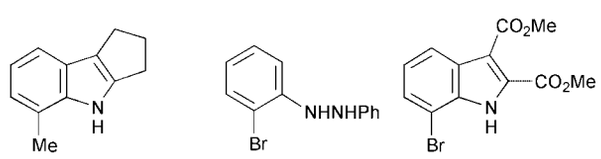
5 Indoles, indolizines and carbazoles

Gribble's updating review of recent developments in indole ring synthesis provides an excellent overview of the available methods.[110]

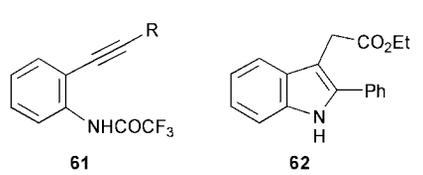
A new version of the Fischer indole synthesis avoids the use of an acid catalyst in the cyclisation step. Arylhydrazones are first converted into *N*-trifluoroacetyl enehydrazines by reaction with TFAA. These undergo the rearrangement and cyclisation on mild heating and in some cases at room temperature; the intermediate dihydropyrroles are aromatised at higher temperature (Scheme 27). The trifluoroacetyl substituent predictably increases the rate of the [3,3] sigmatropic rearrangement.[111] Substituted monoarylhydrazines suitable for use in the Fischer synthesis can be difficult to obtain. A solution to the problem has been found by converting benzophenone hydrazone into the terminal arylhydrazones $Ph_2C{=}NNHAr$ by palladium coupling; they are then deprotected under the conditions of the Fischer synthesis.[112] Another indole synthesis that can be represented as a [3,3] sigmatropic rearrangement is the Bartoli reaction. This is normally carried out with a nitroarene and vinylmagnesium bromide but the reaction has been extended to other vinylmagnesium halides. For example, the indole **58** was isolated in 49% yield from the reaction of 2-nitrotoluene with cyclopentenylmagnesium bromide.[113] The thermal reaction of 1,2-diarylhydrazines with DMAD to give dimethyl indole-2,3-dicarboxylates is a long known method that generally gives indoles in low yield. It has been found that 1-(2-bromophenyl)-2-phenylhydrazines give the indoles in much improved yield; for example the indole **60** was isolated in 62% yield when the hydrazine **59** was heated with DMAD in mesitylene. The bromo substituent was then transformed into other functional groups. The reaction presumably involves an enehydrazine intermediate and so this may also go by a [3,3] sigmatropic shift mechanism.[114]



Scheme 27



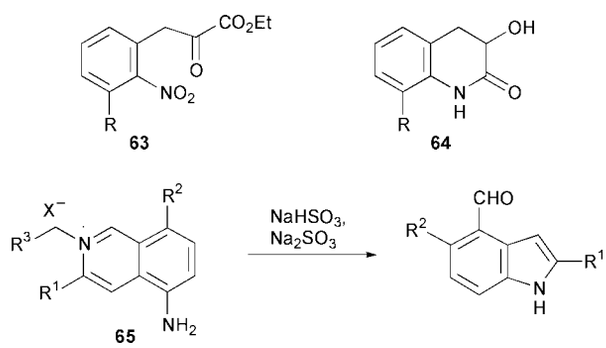
58 **59** **60**



61 **62**

Palladium catalysed *endo* cyclisation of 2-ethynyltrifluoroacetanilides **61** followed by *in situ* alkylation leads to 2,3-substituted indoles; for example, ethyl 2-phenylindole-3-acetate **62** was isolated (73%) after trapping of the intermediate derived from the amide **61** (R = Ph) with ethyl iodoacetate.[115] *endo* Cyclisations of 2-ethynylanilines to 2-substituted indoles have also been carried out using potassium *tert*-butoxide and other strong bases in *N*-methylpyrrolidinone at room temperature.[116] In a reaction that is analogous to the benzofuran synthesis shown in Scheme 11, 5-(2-aminophenyl)-1,2,3-thiadiazole was converted into 2-methylthioindole in high yield by reaction with potassium *tert*-butoxide.[35]

Several new examples of the synthesis of indoles by the reductive cyclisation of 2-nitrostyrenes have been described. These provide routes to 2,3-disubstituted indoles,[117] to 5,6-dihydroxyindole,[118] and to indoles with a bridging ring connecting C-3 and C-4.[119] The related synthesis of indoles by cyclisation of 2-azidostyrenes has been used as a route to several 4,6-dinitroindoles.[120,121] An attempt to prepare 7-substituted indole-2-carboxylates by the Reissert synthesis from the 2-nitroarylpyruvates **63** unexpectedly gave 3-hydroxydihydroquinolinones **64** as significant byproducts when the nitro group was hydrogenated over platinum oxide; palladium on carbon is therefore the preferred reducing agent.[122] A useful route to indole-4-carbaldehydes, which are otherwise difficult to obtain, is the cleavage and recyclisation of isoquinolinium salts **65** (Scheme 28).[123] Indole-4-carbaldehyde was prepared in 82% yield by this route.

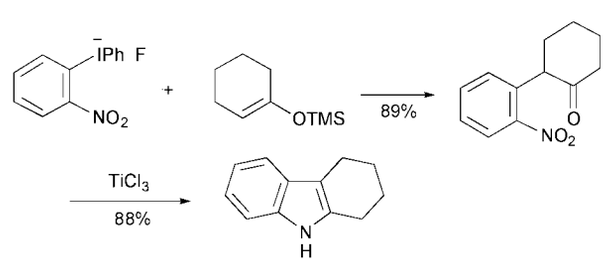


63 **64**

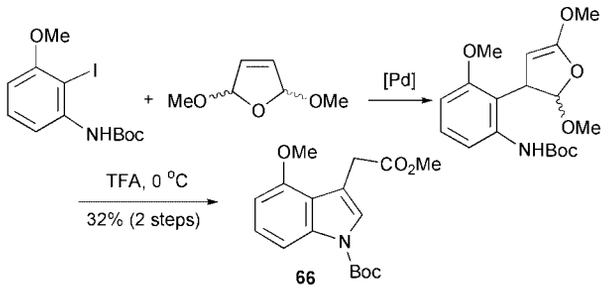
65

Scheme 28

The structures required for creation of the N–C2 bond of indoles can be constructed by *ortho* nucleophilic substitution of aromatic nitro compounds, followed by reduction of the nitro group. The reaction between diaryliodonium fluorides and silyl enol ethers, illustrated by a synthesis of tetrahydrocarbazole in Scheme 29, is a new example of this approach.[124] Vicarious nucleophilic substitution (substitution of a hydrogen adjacent to an aromatic nitro group) also provides a method of constructing suitable precursors and this method of preparing indoles has been reviewed.[125] Examples of nucleophilic substitution at a position adjacent to an amino group are also reported and in these cases a reduction step is unnecessary.[126–128] The synthesis of the indoleacetic ester **66**, a precursor to psilocin (Scheme 30), illustrates a related approach in which the precursor is constructed by palladium coupling.[129]

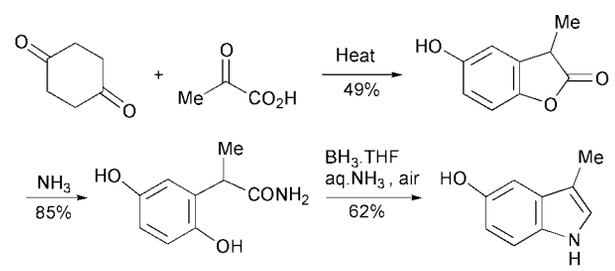


Scheme 29



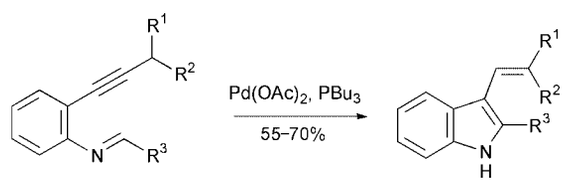
Scheme 30

In a synthesis related to the Nenitzescu reaction, 3-substituted 5-hydroxyindoles have been prepared from cyclohexane-1,4-dione and 2-oxocarboxylic acids.[130] The reaction sequence is illustrated in Scheme 31 for 5-hydroxy-3-methylindole. 5-Methoxy-1-tosylindole has been prepared (76%) from 4-tosylaminoanisole and phenyl vinyl sulfide by oxidative cyclisation.[131]

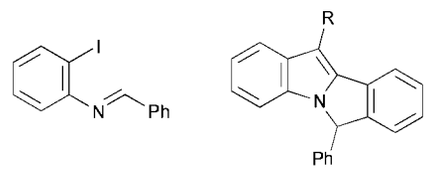


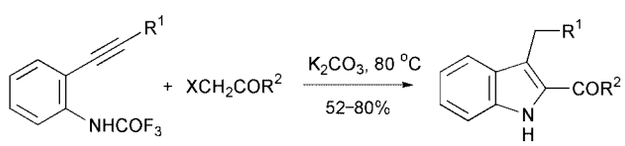
Scheme 31

A further variant on methods for preparing indoles by palladium catalysed cyclisation is illustrated in Scheme 32. Here the C2–C3 bond is created in the *exo* cyclisation of imines of 2-aminoarylacetylenes.[132] The imines can be generated *in situ* from the anilines and aldehydes. In a related process the tetracyclic indoles **68** were produced from alkyl aryl acetylenes and the 2-iodoaryl imine **67** in the presence of a palladium(0) catalyst.[133] A base induced cyclisation in which the C2–C3 bond is made is shown in Scheme 33. The trifluoroacetyl group acts as an activating group for the *N*-alkylation and it is lost after cyclisation.[134]



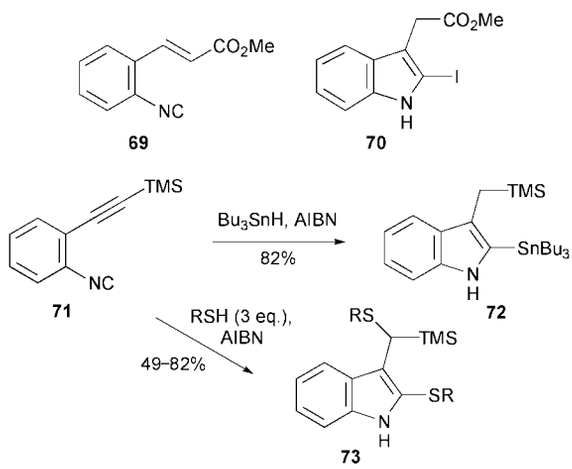
Scheme 32



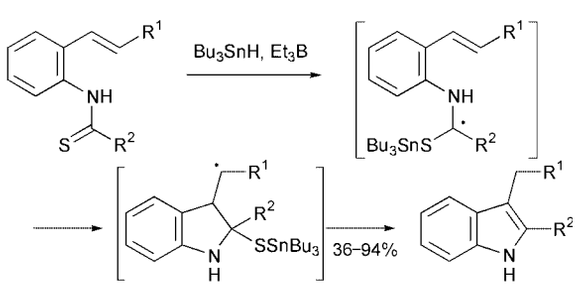


Scheme 33

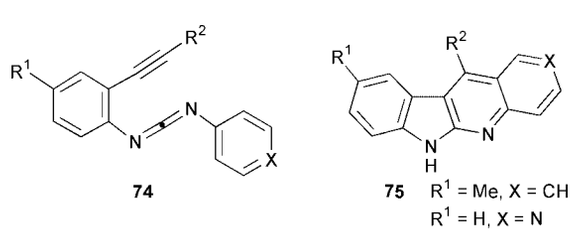
A powerful and versatile radical cyclisation method, first described by Fukuyama and co-workers, is the reaction of 2-alkenylaryl isocyanides with tributyltin hydride. Several new versions of the method have been published. Radical ring closure of the cinnamic ester **69** followed by addition of iodine gave the 2-iodoindole **70** in 91% yield, from which other 2-substituted indoles were prepared by palladium coupling.[135] Tin-mediated cyclisation on to the triple bond of the trimethylsilylacetylene **71** produced the indole **72** in 82% yield and with no *endo* cyclisation to a quinoline (Scheme 34).[136,137] The reaction was not so efficient with substituents other than trimethylsilyl. A related radical cyclisation with a thiol as a co-reagent led to the formation of the 2-substituted indoles **73**. Similar cyclisation reactions with thioamides as precursors have been used to produce 2,3-disubstituted indoles, as shown in Scheme 35. Following the reports, mentioned in the previous review, that acetylenic ketinimines could be converted thermally into benzo[*b*]carbazoles, similar thermal[138] and photochemical[139] cyclisations of diarylketinimines **74** to fused indoles **75** have been described.



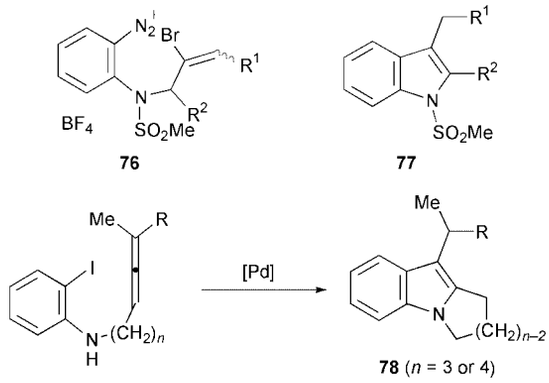
Scheme 34



Scheme 35

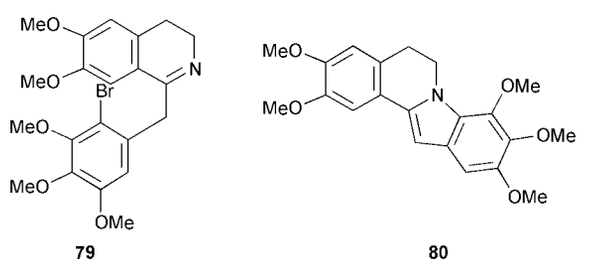


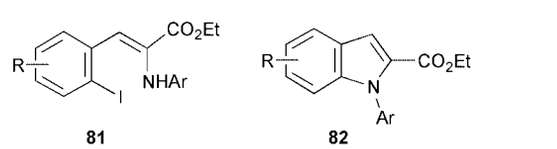
The indole synthesis developed by Murphy and co-workers in which the five membered ring is created by cyclisation of aryl radicals on to vinyl halides has been extended by the use of "clean" methods for the generation of the radicals. For example, the diazonium salts **76** were cyclised to indoles **77** (44–83%) with sodium iodide as the reagent used to generate the aryl radicals.[140] The C3–C4 bond can also be constructed by palladium catalysis, and an application to the synthesis of trisubstituted indoles **78**, which were isolated in high yield, is shown in Scheme 36.[141] Indoles that are unsubstituted in the five membered ring have been synthesised by heating anilines and triethanolammonium chloride with ruthenium(III) chloride, triphenylphosphine and tin(II) chloride as catalysts.[142]

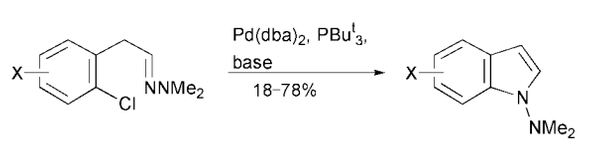


Scheme 36

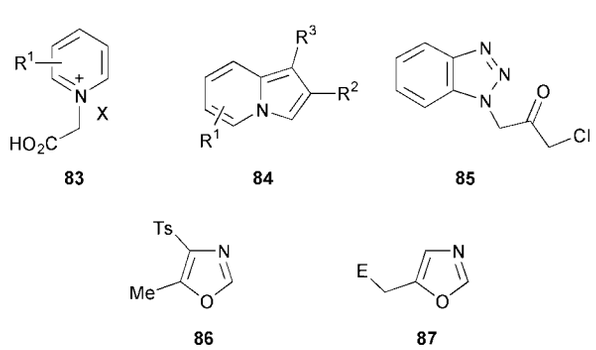
A few new methods of synthesis of indoles involve formation of the N–C7a bond. Because of steric repulsion between the methoxy substituents, the radical closure of the substituted dihydroisoquinoline **79** goes on to the nitrogen of the imine function instead of the usual cyclisation on to the adjacent aryl ring. The fused indole **80** was isolated in 68% yield.[143] Other hindered derivatives also cyclise in the same way. The ring closure has also been brought about by heating the substrates with potassium carbonate in DMF.[144] Ethyl 1-arylindole-2-carboxylates **82** have been isolated in high yield from intramolecular palladium catalysed amination reactions of the enamines **81**.[145] A versatile synthesis of 1-dimethylaminoindoles by palladium catalysed intramolecular amination is shown in Scheme 37.[146] Indoles have also been synthesised in moderate yield from 2- or 3-chlorostyrenes by base catalysed amination followed by cyclisation through aryne intermediates.[147] Carbazole can be obtained in 66% yield from diphenylamine by oxidation using oxygen and a palladium(II) acetate catalyst.[148]







Scheme 37

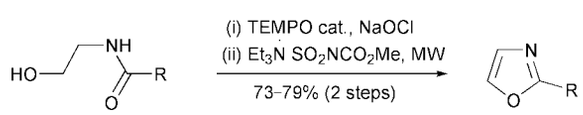


Indolizines **84** that are unsubstituted at C3 are produced in good yield from pyridinium salts **83** and activated alkenes by 1,3-dipolar addition followed by *in situ* oxidation with manganese(IV) oxide.[149] Indolizine-3-carboxamides have been synthesised in a similar way.[150] Indolizines have also been obtained by 1,3-dipolar addition reactions of pyridinium ylides bearing a stabilising benzotriazole substituent on the carbanionic carbon[151] and by condensation reactions between 2-alkylpyridines and the carbonyl group of 1-benzotriazol-1-yl-3-chloroacetone **85**.[152]

6 Oxazoles, benzoxazoles, thiazoles and benzothiazoles

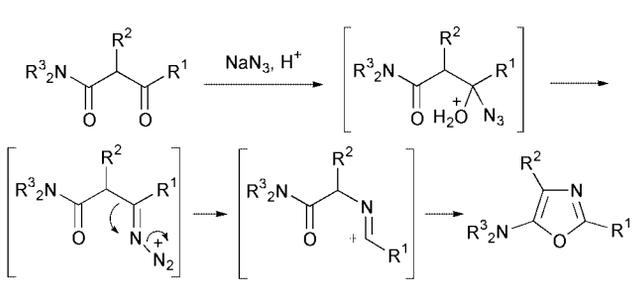
Tosylmethyl isocyanide (TosMIC) is an attractive reagent for the preparation of 2-unsubstituted oxazoles because of its stability and ready availability. A polymer supported version of the reagent has been used to prepare 5-aryloxazoles from aromatic aldehydes and an amidine base; this allows simple workup and the isolation of the oxazoles in good yield.[153] An alternative procedure is to use a resin supported quaternary ammonium hydroxide base, which also provides a simplified workup procedure.[154] The reaction of TosMIC with acetic anhydride gives 5-methyl-4-tosyloxazole **86**. Reaction with two equivalents of BuLi allows selective substitution of the methyl group by electrophiles. Since the tosyl group can then be removed reductively this provides a route to a variety of 5-substituted oxazoles **87** that avoids the use of methyl isocyanide.[155] In a similar way, ethyl isocyanoacetate has been used in a three step synthesis of the parent ring system. The isocyano ester is used with formic acid and carbonylbis(imidazole) in a literature synthesis of ethyl oxazole-4-carboxylate and this is then hydrolysed and decarboxylated.[156]

Cyclodehydration procedures provide another important general route to oxazoles. The Burgess reagent, in combination with microwave irradiation, is effective for the cyclisation of 2-acylamino ketones. The method has been adapted to the synthesis of 2-monosubstituted oxazoles (Scheme 38) by *in situ* oxidation of acylaminoethanols using TEMPO (tetramethylpiperidine-1-oxyl) as a catalyst, followed by cyclodehydration.[157] In effect this extends the classical Robinson–Gabriel oxazole synthesis to 2-acylaminoaldehydes. Cyclodehydration and oxidation steps have been carried out in the reverse order in a high yielding route to 2,5-disubstituted oxazole-4-carboxylates.[158]

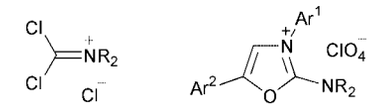


Scheme 38

An unusual route to 5-dialkylaminooxazoles is illustrated in Scheme 39: attack of azide on the ketone carbonyl group of a β-keto amide is followed by a Schmidt rearrangement and ring closure.[159] 3-Aryl-2-dialkylaminooxazolium salts **89** have been synthesised from imidoyl dichlorides **88** and α-(arylamino)-acetophenones by reaction with perchloric acid.[160]

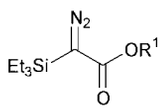


Scheme 39

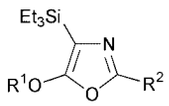


88

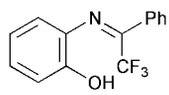
89



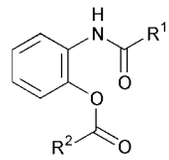
90



91



92



93

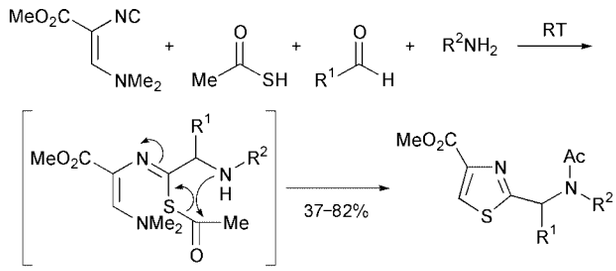
Indium(III) chloride has been used to promote the formation of oxazoles from diazomethyl ketones and nitriles.[161] Silyl substituted diazo esters **90** react with nitriles under rhodium catalysis to give the oxazoles **91**, from which the triethylsilyl group can either be removed or replaced by iodide. Further substituents can then be introduced at C-4 by coupling reactions.[162] A direct synthesis of 4-aryl-2-phenyloxazoles from aryl ketones and benzonitrile with mercury(II) tosylate and under microwave irradiation has been described.[163]

The reaction of the trifluoromethyl ketimines **92** with LiHMDS leads to 2-phenylbenzoxazoles in good yield.[164] 2-Substituted benzoxazoles are also formed in high yield from the acid catalysed ring closure of acylamino esters **93**. The major products have the 2-substituent derived from the acyl group of the amide and the minor components, the ester substituent. It is likely that the amide participates as a neighbouring group to assist the hydrolysis of the ester.[165]

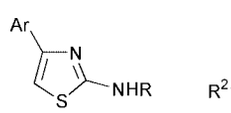
A one pot, multicomponent thiazole synthesis is illustrated in Scheme 40. Ring closure is probably preceded by intramolecular acyl transfer, as shown.[166] A one pot method for the synthesis of 2-alkylamino-4-arylthiazoles **94** from α-bromoacetophenones, sodium thiocyanate, and alkylamines provides a route to the products in moderate to good yield from a wide range of amines, including α-amino esters.[167] In a related synthesis of 2-arylamino-4-methylthiazoles from thioureas the use of α-bromoacetone was avoided by the use of acetone in the presence of HBr and DMSO.[168] The bromination of ketones using polymer supported reagents also proved highly effective.[169] A route to 2-arylselenazoles **95** is the reaction of aryl selenoamides with α-haloketones. This route has been improved by using the reagent **96** for the *in situ* α-tosyloxylation of ketones as an alternative to the use of haloketones.[170] 2-Phenylaminothiazoles **98** have previously been prepared from the thiourea derivatives **97** and α-haloketones but the range of such compounds has been limited to hydrogen, alkyl and aryl substituents (R^1) at C-4. A new route to the precursors **97** from amidines and phenyl isothiocyanate has widened the scope of the method.[171] The selenourea derivatives **99** are intermediates in a new, mechanistically related synthesis of 2-aminoselenazoles and these intermediates have been constructed from diarylimidoyl chlorides, potassium selenocyanate and amines.[172]

A route to 5-arylaminothiazoles from aryl isothiocyanates, illustrated in Scheme 41, makes use of the anion stabilising property of the benzotriazolyl (Bt) substituent.[173] A Claisen rearrangement is implicated in the efficient thermal conversion of 1,2,4-triazoles into thiazoles shown in Scheme 42.[174]

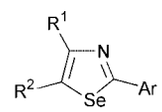
A one pot synthesis of 2-aminobenzothiazoles **101** in high yield from 3-alkylanilines **100** makes use of sodium thiocyanate and bromine as an oxidant.[175] 2-Aminothiophenol is a standard



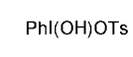
Scheme 40



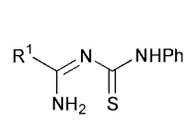
94



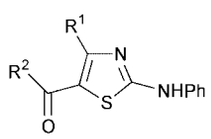
95



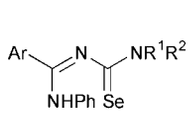
96



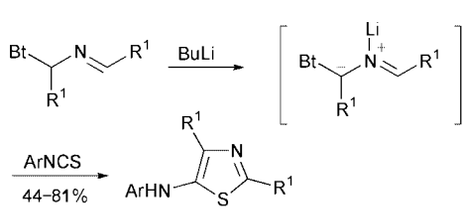
97



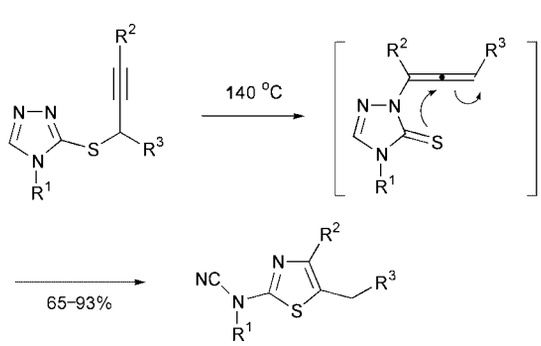
98



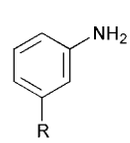
99



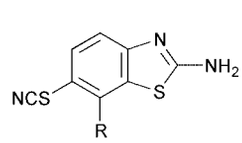
Scheme 41



Scheme 42



100



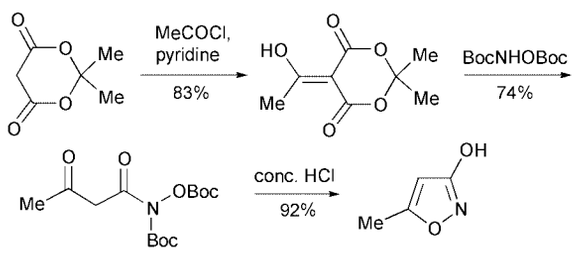
101

starting material for the synthesis of the parent benzothiazole or 2-substituted derivatives. The formation of benzothiazole using formaldehyde and an oxidant is achieved in high yield with scandium(III) triflate as a catalyst.[176] 2-Arylbenzothiazoles have been formed from the reaction of 2-aminothiophenol with dibenzyl disulfides in DMF.[177]

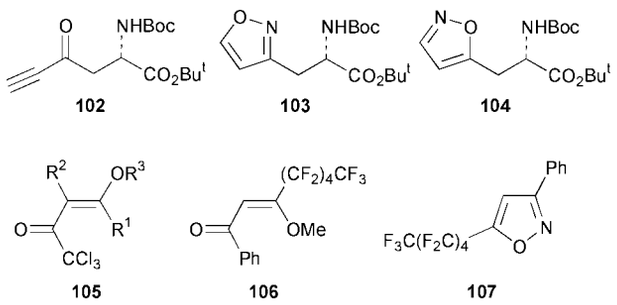
7 Isoxazoles, isothiazoles and fused analogues

A new and simple route to isoxazol-3-ols is illustrated in Scheme 43 for 5-methyloxazol-3-ol; other 5-alkyl derivatives were synthesised in good yield by the same method.[178] The use of the Meldrum's acid derivative solves the problem of regioselectivity in the nucleophilic addition of hydroxylamine derivatives. An alternative strategy is to use β-oxothionoesters, which react with hydroxylamine at the thiocarbonyl group and give 5-substituted 3-alkoxyisoxazoles after cyclisation.[179] In a route

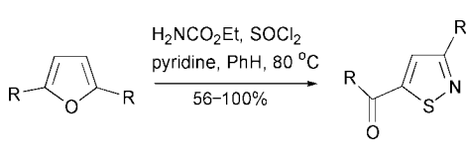
to protected amino acids bearing an isoxazole function the acetylenic ketone **102** was reacted with hydroxylamine under different conditions. Hydroxylamine hydrochloride alone, when heated in ethanol with the acetylene, gave exclusively the 3-substituted isoxazole **103** in 62% yield, whereas in the presence of pyridine the major product was the regioisomer **104**.[180] The unpredictable regioselectivity of such reactions is illustrated by the exclusive formation of isoxazole-5-carboxylic acids by conjugate addition of hydroxylamine to the enones **105** in acidic conditions followed by hydrolysis of the trichloromethyl group[181] and the contrasting selective attack on the carbonyl group of the enone **106** in a basic medium, leading to the formation of the isoxazole **107**.[182] There are further examples of the formation of isoxazoles by conjugate addition of hydroxylamine to enaminocarbonyl compounds: 4,5-diarylisoxazoles[183] and 5-methylisoxazole-3,4-dicarboxylic acid derivatives[184] have been synthesised in good yield by this method. A standard alternative approach to isoxazoles is the cycloaddition of nitrile oxides to acetylenes, but here also the control of regiochemistry can be a problem. Methyl (4-nitrophenyloxy)acrylate has been shown to be an alternative to methyl propiolate in 1,3-dipolar additions of aromatic nitrile oxides and it reverses the predominant regioselectivity of the acetylene addition, giving 3-arylisoxazole-4-carboxylic esters (43–96%).[185]



Scheme 43

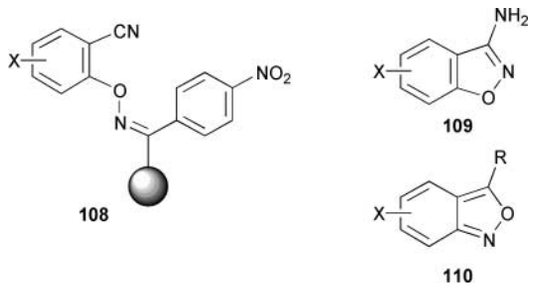


The conversion of 2,5-disubstituted furans into isothiazoles (Scheme 44) has previously been carried out with trithiazyl chloride as the reagent. A much simpler procedure has been described that makes use of a mixture of ethyl carbamate, thionyl chloride and pyridine in boiling benzene; this probably generates the reactive thiazyl chloride, NSCl, *in situ*.[186]



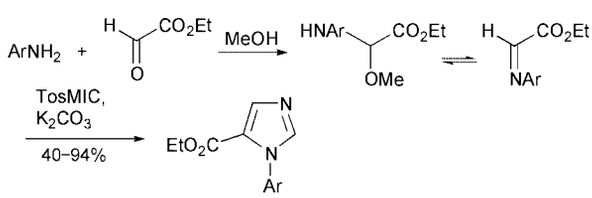
Scheme 44

3-Aminobenzisoxazoles **109** have been synthesised in high yield by the reaction of polymer bound oximes with 2-fluorobenzonitriles with displacement of fluoride. The *O*-2-cyanoaryl oximes **108** are then cleaved to the hydroxylamines and cyclised using TFA.[187] New reductive procedures have been described that convert 2-nitrobenzaldehydes and ketones efficiently into anthranils **110** (R = H or alkyl).[188, 189]

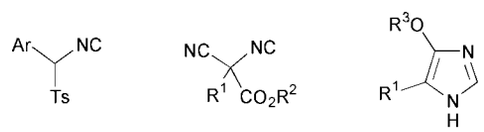


8 Imidazoles and benzimidazoles

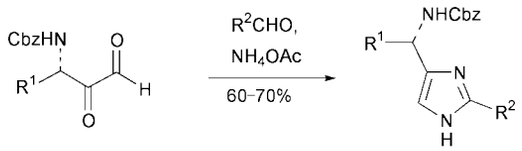
As with other five-membered heterocycles, TosMIC and other isocyanides are key reagents for the preparation of imidazoles unsubstituted at the 2-position, and several new examples have been described. The addition of aromatic amines to ethyl glyoxylate in methanol followed by reaction with TosMIC provides a route to 1-arylimidazole-5-carboxylates (Scheme 45).[190] The related reaction of ethyl glyoxylate or glyoxylic acid with primary amines or ammonia and aryl substituted TosMIC reagents **111** is a versatile method for the synthesis of 1,4- and 4,5-disubstituted imidazoles, and for substituted ethyl imidazole-5-carboxylates.[191] α-Cyano-α-isocyanoalkanoate esters **112** react with alcohols and potassium carbonate to give 4-alkoxyimidazoles **113** in good yield by loss of the alkoxycarbonyl function and addition of the alcohol to the cyano group.[192]



Scheme 45

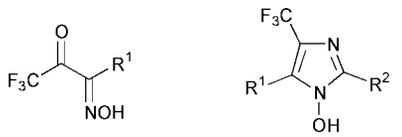


A synthesis of chiral 2-substituted 4-alkylaminoimidazoles is illustrated in Scheme 46.[193] The ketoaldehyde precursors were obtained from the corresponding diazocarbonyl compounds by oxidation with dimethyldioxirane. A similar synthesis of tri- and tetrasubstituted imidazoles from 1,2-diketones under microwave irradiation has been reported.[194] A related method was also used to prepare 1-hydroxy-4-trifluoromethylimidazoles **115** from the oximes **114**, aldehydes and ammonium acetate.[195]

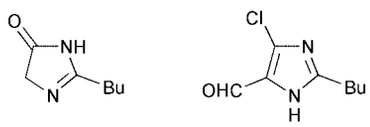


Scheme 46

The imidazole aldehyde **117**, a key intermediate for the synthesis of the angiotensin II antagonist Losartan, has been obtained by Vilsmeier formylation of the imidazolinone **116**. Compound **116** was produced by the reaction of glycine ethyl ester with ethyl pentanimidate at −10 °C.[196] Oxidation of imidazolines to imidazoles can be difficult, but in a new synthesis of 2-arylimidazoles from ethanediamines the intermediate 4,5-dihydroimidazoles were dehydrogenated *in situ* by heating with DMSO or by the action of palladium in boiling toluene.[197]

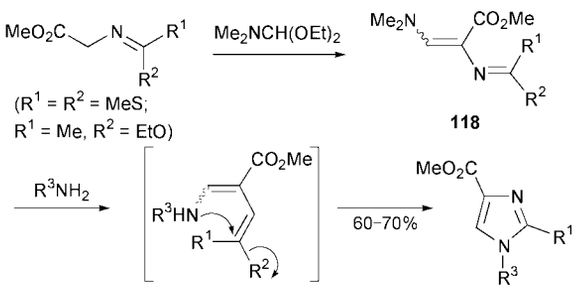


114 **115**



116 **117**

The 4-dimethylamino-2-azadienes **118** were converted into new imidazole-4-carboxylic acid derivatives by heating with hydrazines or amines in the absence of a solvent (Scheme 47).[198] Three methods for the synthesis of imidazoles from 2-azidoalkylcarbonyl compounds have been described. Ethyl 2-azido-3-phenylpropionate is converted into the transient guanidine derivatives **119** by successive reaction with triphenylphosphine, tosyl isocyanate and a primary amine. Ring closure followed by functional group manipulation gives the 1,4-disubstituted 2-aminoimidazoles **120** in good yield.[199] 3-Azidoacetyl-1-benzylindole is converted into the ketoamides **121** (55–60%) by reaction with methyldiphenylphosphine and acid chlorides. These are converted into imidazoles **122** (55–60%) by reaction with ammonium acetate under microwave irradiation.[200] This reaction sequence provided a short and simple synthesis of the antifungal agent nortopsentin D. Cathodic reduction of phenacyl azides gave the 2,5-disubstituted imidazoles **124** in good yield, probably through dimerisation of transient imines **123**.[201] A general synthesis of 2-aryl-4,5-dicyanoimidazoles **126** is provided by DDQ oxidation of the amidoximes **125**.[202] Base catalysed ring contraction of sulfur containing heterocycles, with extrusion of sulfur, provides a route to several heteroaromatic ring systems. An example is the ring contraction of thiadiazines **127** to imidazoles **128** upon heating with sodium ethoxide.[203]



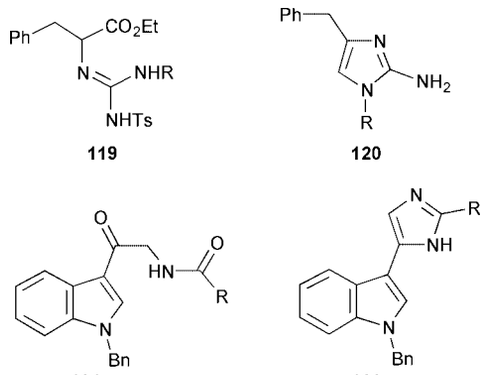
118

Scheme 47

Methods for preparing 2-substituted benzimidazoles in good yield from *o*-phenylenediamine derivatives on solid supports have been described.[204,205] 2-Aminobenzimidazoles **130** were synthesised from the alkoxyguanidines **129** by vicarious nucleophilic substitution with potassium *tert*-butoxide as the base. Nucleophilic attack takes place mainly *ortho* to the nitro substituent, leading to the benzimidazoles **130** as the major products.[206]

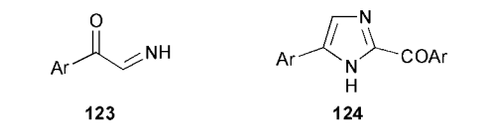
9 Pyrazoles and indazoles

A general synthesis of 3,4,5-trisubstituted pyrazoles, illustrated in Scheme 48, is based on the regioselective preparation and *in situ* cyclisation of unsaturated ketone tosylhydrazones.[207] The reactions can be carried out as a one pot procedure and yields are 17–88%. Phosphonylhydrazones have also been converted into 4-phosphonylpyrazoles by the Vilsmeier reagent.[208] The cyclisation route to pyrroles illustrated in Scheme 23 has been

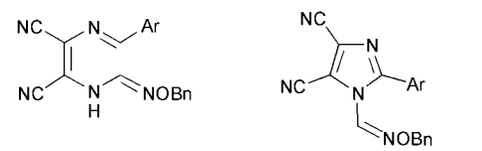


119 **120**

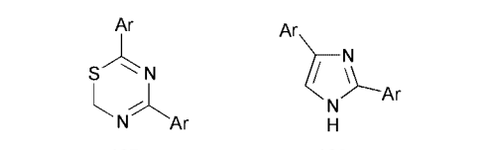
121 **122**



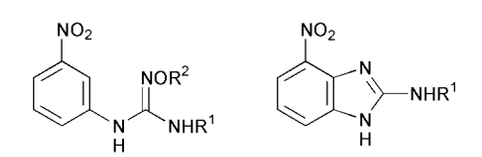
123 **124**



125 **126**

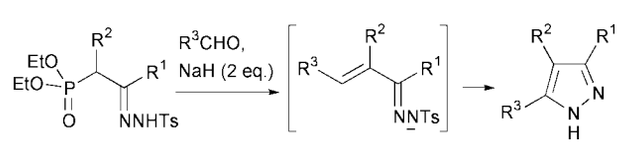


127 **128**

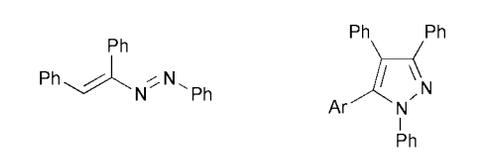


129 **130**

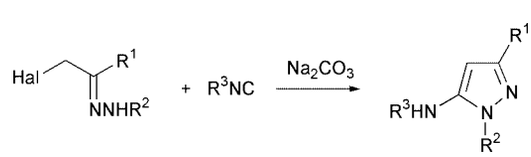
extended to the synthesis of tetraphenylpyrazole derivatives **132** (74–83%) from the vinylazo compound **131** and arylchlorodiazirines.[209] A related method in which the pyrazole ring system is constructed from a transient vinylazo compound and a one carbon fragment is illustrated in Scheme 49.[210] An analogous route to 5-aminoisoxazoles was reported earlier.



Scheme 48



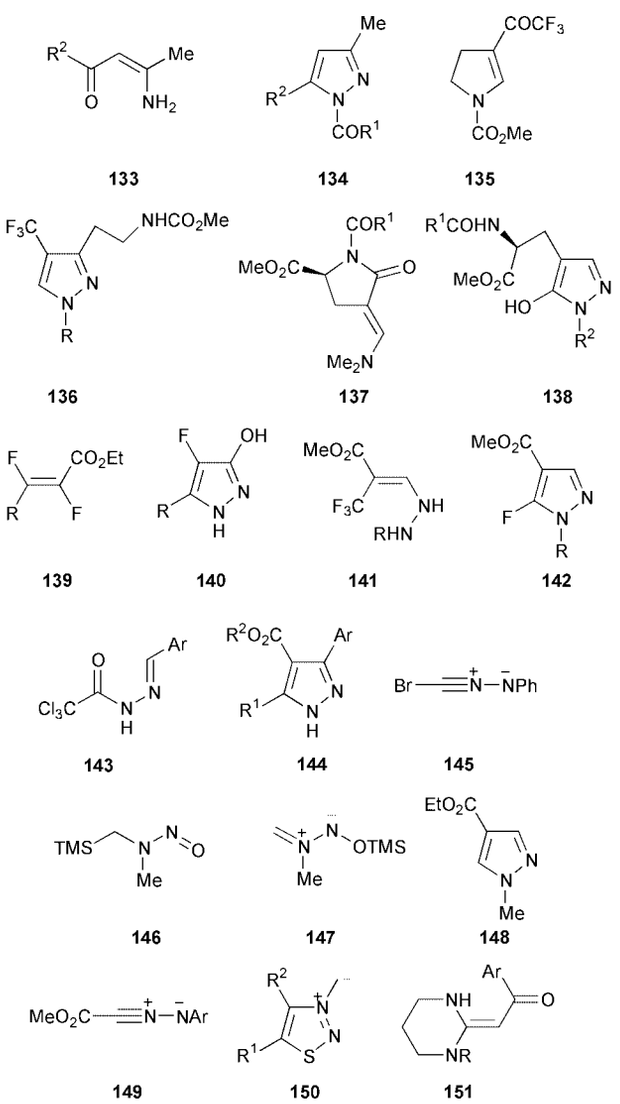
131 **132**



Scheme 49

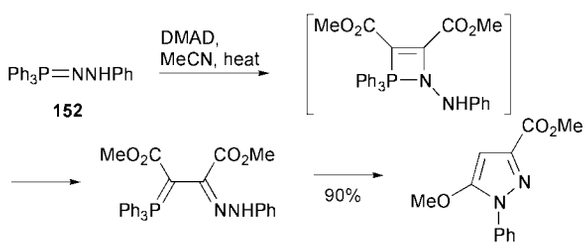
The conjugate addition of *N*-acylhydrazines to enaminones **133** followed by cyclisation on to the carbonyl function gave

1-acylpyrazoles **134** in good overall yield.[211] The addition of hydrazine or phenylhydrazine to the cyclic enaminone **135** results in opening of the ring followed by closure to the pyrazoles **136** (92–93%).[212] Similarly, the chiral amino acid derivatives **138** were formed in good yield from the enaminones **137** and monosubstituted hydrazines.[213] Several other new syntheses of pyrazoles bearing a chiral amino acid side chain have been reported, all based on the reaction of hydrazines with conjugated acetylenic ketones.[180,214–216] The synthesis of pyrazole-4-carboxylic acids by the conjugate addition of arylhydrazines to polymer bound enones has also been described.[217] 4-Fluoropyrazoles have been obtained from 2,3-difluoro-α,β-unsaturated carbonyl compounds;[218,219] an example is the synthesis of 4-fluoro-3-hydroxypyrazoles **140** (75–80%) from the difluoroacrylate esters **139** and hydrazine hydrate.[218] 5-Fluoropyrazole-4-carboxylates **142** were isolated in moderate yield from the reaction of methyl 3-methoxy-2-(trifluoromethyl)-acrylates with arylhydrazines and potassium carbonate.[220] The mechanism involves cyclisation of the intermediate unsaturated hydrazine **141** with double elimination of HF. Trichloroacetylhydrazones **143** derived from aromatic aldehydes react with β-ketoesters and sodium carbonate to give pyrazole-4-carboxylates **144** in good yield.[221]

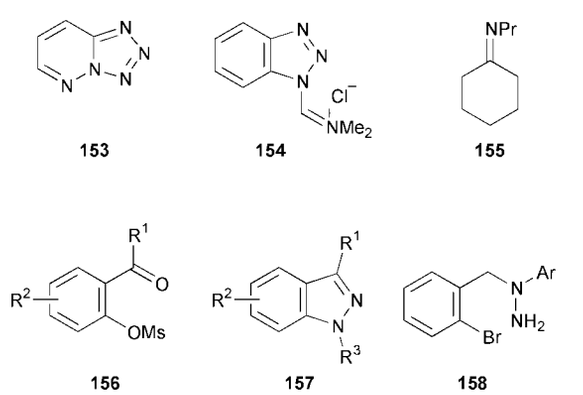


New examples of pyrazole synthesis by 1,3-dipolar addition have been described. A series of 3-bromopyrazoles has been synthesised (40–70%) by 1,3-dipolar addition reactions of the transient nitrile imide **145**.[222] Thermal rearrangement of the nitrosamine **146** produced the transient azomethine imide **147**. This and related 1,3-dipoles were intercepted by reaction with activated acetylenes; for example, ethyl propiolate gave ethyl 1-methylpyrazole-3-carboxylate **148** (83%).[223] Other examples of 1,3-dipolar addition include the reaction of the nitrile imides **149** with arenesulfonylallenes[224] and the interception of the cyclic azomethine imides **150** by DMAD.[203] The reaction of 1,3-diphenylnitrilimine with the enaminones **151** takes place not by dipolar addition but by a two step mechanism starting with nucleophilic addition to the enone and leading to 4-substituted 5-aryl-1,3-diphenylpyrazoles.[225]

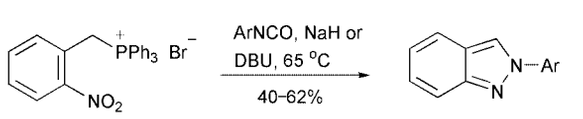
The reaction of the phosphazene **152** with DMAD and related acetylenes led to 5-methoxypyrazoles, probably by way of [2 + 2] addition and rearrangement (Scheme 50).[226] Thermal rearrangement and decomposition of tetrazolo[1,5-*a*]pyridazine **153** at 110–120 °C gave 1-cyanopyrazole in good yield; other 1-cyanopyrazoles were isolated from the thermolysis of substituted tetrazolopyridazines.[227] The modified Vilsmeier reagent **154** was used as a partner in reactions with ketone *N*-propylimines and hydrazine that led to the formation of pyrazoles; for example, 4,5,6,7-tetrahydroindazole was formed in 66% yield in a reaction with cyclohexanone *N*-propylimine **155**.[228]



Scheme 50



1*H*-Indazoles **157** have been isolated in 41–91% yield from the reaction of 2-mesyloxyaryl ketones **156** and monoalkylhydrazines in boiling xylene.[229] Two new routes to 2-aryl-2*H*-indazoles **160** have been reported; one a palladium catalysed intramolecular amination reaction of the hydrazines **158** (52–58% yield)[230] and the other, a reaction between the phosphonium salt **159** and aryl isocyanates (Scheme 51).[231] The second process is a mechanistic challenge.

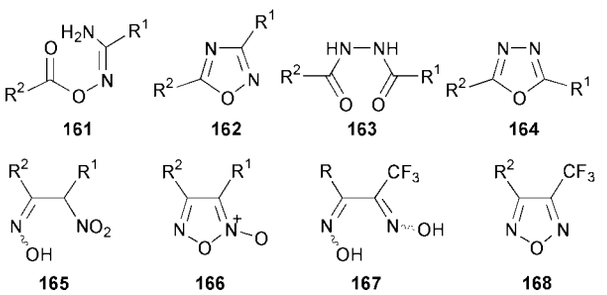


Scheme 51

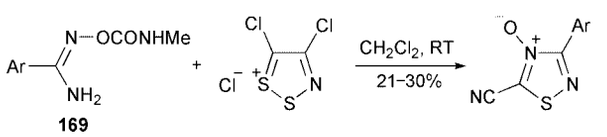
10 Oxadiazoles and thiadiazoles

The cyclisation of *O*-acylamidoximes **161** to 1,2,4-oxadiazoles **162** usually requires the use of a strong base or heating. Tetrabutylammonium fluoride has been found to be an effective catalyst for the transformation at room temperature.[232] A new procedure for the synthesis of the precursors **161** directly from carboxylic acids and amidoximes has been described.[233] New

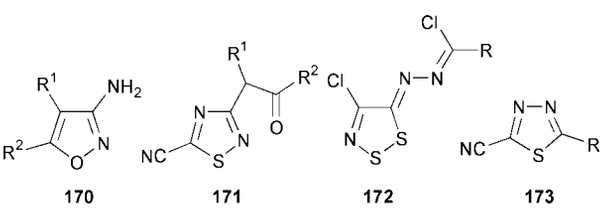
and mild procedures have also been used for the cyclodehydration of 1,2-diacylhydrazines **163** to 1,3,4-oxadiazoles **164**. Triflic anhydride at −10 to 0 °C[234] and a polymer supported Burgess reagent with microwave irradiation[235] both produce the oxadiazoles in greater than 70% yield. Symmetrically substituted 2,5-diaryl-1,3,4-oxadiazoles can be formed directly from aromatic carboxylic acids and hydrazine by reaction in a mixture of orthophosphoric acid, phosphorus pentoxide and phosphorus oxychloride.[236] Two other cyclodehydration procedures that produce 1,2,5-oxadiazole derivatives are the conversions of oximes **165** into oxadiazole 2-oxides **166** and of bis(oximes) **167** into oxadiazoles **168**. The cyclodehydration of compounds **165** has been reported before but the use of acidic alumina in acetonitrile at 60 °C is an improved method, giving the products **166** in 75–93% yield.[237] The dehydration of the bis(oximes) **167** was carried out by absorbing them on to silica gel and heating the material at 150 °C.[238]



A full description of the preparation of 5-cyano-1,2,4-thiadiazole 4-oxides from amidoximes and Appel's salt has appeared. The reaction (Scheme 52) gives the *N*-oxides in modest yield, the best precursors being the acylated amidoximes **169**.[239] 3-Aminoisoxazoles **170** behave as cyclic amidines and react with Appel's salt followed by base treatment to give the thiadiazoles **171** in good yield.[240] 5-Substituted tetrazoles react with Appel's salt to give the isolable intermediates **172** (56–95%) and these are converted into 5-cyano-1,3,4-thiadiazoles **173** in 72–99% yield by reaction with triphenylphosphine.[241] 3,5-Diaryl-1,2,4-thiadiazoles can be produced from thiobenzamides in high yield by self-condensation in acidic DMSO. A mechanistic investigation has led to the conclusion that thiobenzamide *S*-oxides are probably the key intermediates.[242] The same conversion has also been reported with an α-bromosulfone reagent.[243] A range of 4-substituted 3-acyl- and 3-alkoxycarbonyl-1,2,5-thiadiazoles were isolated in moderate yield from the reaction of primary enaminones and β-enamino esters with tetrasulfur tetranitride–antimony pentachloride complex in toluene at 100 °C.[244]

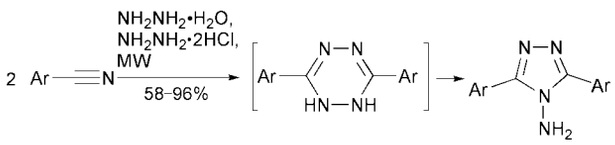


Scheme 52

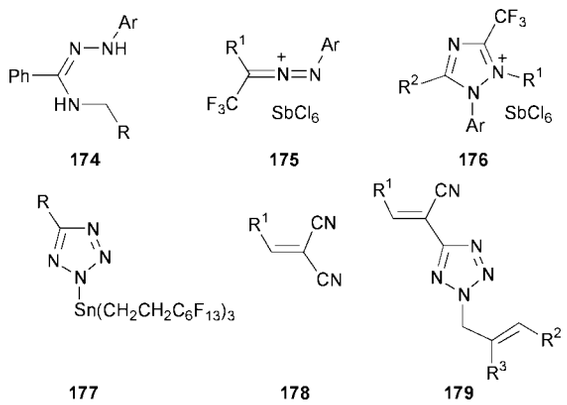


11 Triazoles and tetrazoles

A direct conversion of aromatic nitriles into 4-amino-3,5-diaryl-1,2,4-triazoles has been reported. The reaction takes place cleanly under microwave irradiation (Scheme 53).[245] The oxidative cyclisation of the amidrazones **174** to 1-aryl-3-phenyl-1,2,4-triazoles has been improved by the use of silver carbonate as a mild oxidising agent.[246] The salts **175**, which were prepared from arylhydrazones of trifluoromethyl ketones by successive α-chlorination with *tert*-butyl hypochlorite and ionisation with antimony pentachloride, react with nitriles R^2CN to give triazolium salts **176** in high yield.[247] Related syntheses of 2-trifluoromethyl-1,2,4-triazoles from trifluoroacetone ethoxycarbonylhydrazone have been reported.[248]

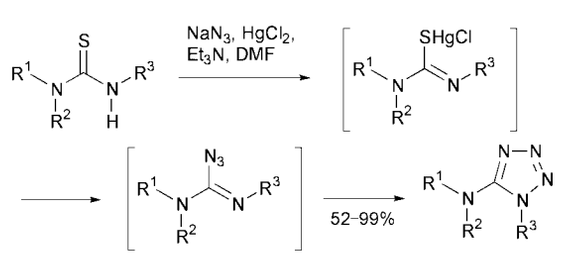


Scheme 53



Methods for the synthesis of *N*-unsubstituted tetrazoles have been reviewed.[249] Variations on the principal method, the reaction of nitriles with azides, continue to be reported. An efficient palladium catalysed conversion of aryl bromides into the corresponding nitriles using zinc cyanide is followed by a microwave promoted addition of sodium azide. This gives 5-aryltetrazoles in good overall yield.[250] Some 5-vinyltetrazoles were made in the same way. Trialkyltin azides are superior to alkyl azides in their reactivity towards unactivated nitriles and have the advantages that either further substitution reactions can be carried out on the products or the tin substituent can be removed by treatment with HCl.[251] One new aspect of this chemistry is a fluorous synthesis of tetrazoles **177** which can be purified by liquid–liquid extraction, thus providing pure products even from incomplete reactions.[252] 2-Allylated 5-substituted tetrazoles **179** have been prepared in 39–97% yield from malononitrile derivatives **178**, allylic acetates and trimethylsilyl azide in the presence of a palladium(0) catalyst.[253]

A synthesis of 1-substituted 5-aminotetrazoles, in which the key step is a mercury(II) promoted attack of azide ion on thioureas, is illustrated in Scheme 54. This route has provided a series of new tetrazoles in good yield.[254]

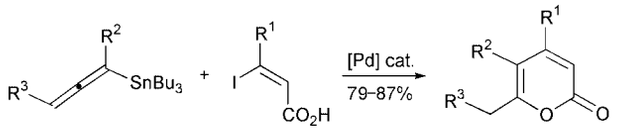


Scheme 54

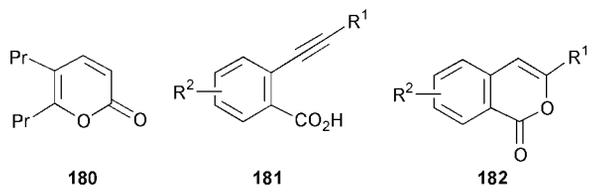
12 Pyrones, coumarins and chromones

As with many heterocycles, metal catalysed cyclisation reactions feature prominently among new methods of synthesis of these ring systems. A synthesis of 2-pyrones that is of this type

is shown in Scheme 55.[255] Further examples of the synthesis of pyrones and isocoumarins by the combination of β-halogeno-α,β-unsaturated and aromatic esters with alkynes have been reported. For example, methyl (*Z*)-3-iodoacrylate combined with oct-4-yne in the presence of a nickel catalyst and zinc chloride to give the pyrone **180** in 53% yield[256] and details of Larock's palladium catalysed synthesis of pyrones and isocoumarins by this method have been published.[257] The cyclisation of 2-ethynylphenylcarboxylic acids **181** under silver(I) or palladium(II) catalysis is predominantly an *endo* process, giving isocoumarins **182** as the major products.[258,259] However a combined cyclisation and alkylation reaction of the acids under palladium catalysis gave alkylidenephthalides as the major products as a result of *exo* attack on the triple bond.[260] A nickel(II) cyanide catalysed synthesis of 5-cyano-4,6-dimethyl-2-pyrone (86%) from propargyl bromide, CO and potassium cyanide in aqueous base has been reported[261] and 4,6-dimethyl-2-pyrone has been obtained in high yield from mesityl oxide and CO_2 under pressure in the presence of a diethylzinc–*N*-methylaniline complex.[262]

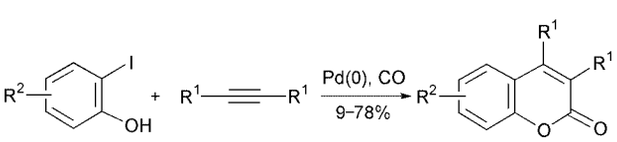


Scheme 55



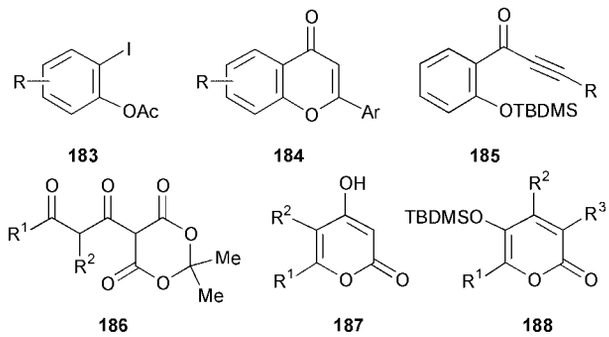
180 **181** **182**

Coumarins and chromones have also been synthesised by palladium coupling methods. The reaction of internal alkynes with 2-iodophenols and carbon monoxide produces 3,4-disubstituted coumarins (Scheme 56).[263] Symmetrically substituted alkynes are preferable since some unsymmetrical alkynes give both possible isomers. 4-Substituted coumarins have also been synthesised in good yield by palladium catalysed cyclisation of aryl esters of acetylenic acids.[264] This is also a route to 2-quinolones from the corresponding aryl amides **229**, as illustrated in Section 14. In contrast, palladium catalysed carbonylative cyclisation of 2-iodophenols or (better) 2-iodophenyl acetates **183** with monosubstituted alkynes leads to 2-substituted chromones. With arylacetylenes as the reaction partners this represents an efficient and versatile route to flavones **184**.[265] Another synthesis of 2-substituted chromones is based on the cyclisation of the ethynyl ketones **185**, which were obtained in good yield from the corresponding acid chlorides and monosubstituted acetylenes under copper and palladium catalysis. The cyclisation step was carried out by heating the ketones **185** with diethylamine and it gave the chromones in 54–96% yield. This step probably involves conjugate addition of diethylamine to the triple bond before cyclisation, thus avoiding the possible alternative *exo* attack on the triple bond.[266]



Scheme 56

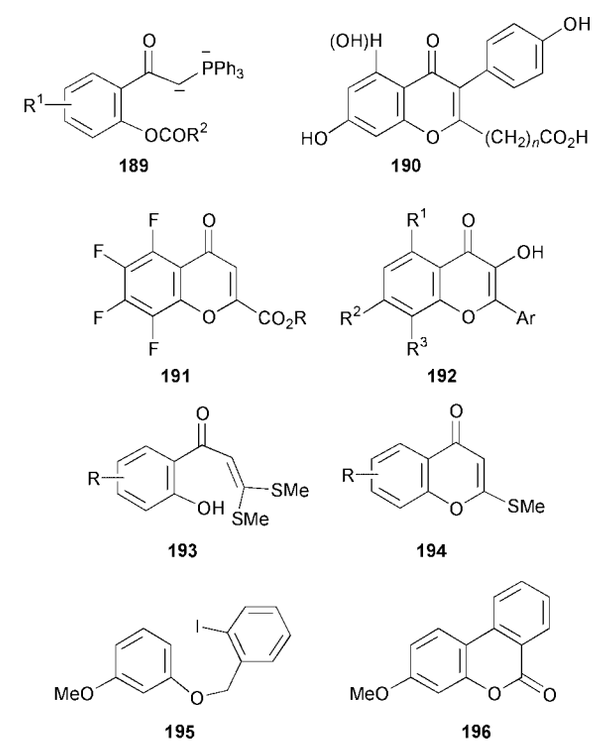
A new synthesis of 5,6-disubstituted 4-hydroxy-2-pyrones **187** is based on the Meldrum's acid derivatives **186**. When heated in toluene these compounds fragment, with elimination of CO_2 and acetone, to transient acylketenes which then cyclise to the pyrones.[267] Several protected 5-hydroxypyrones **188** were obtained in good yield from cyclobutenedione derivatives by nucleophilic attack of silylated cyanohydrins.[268]



183 **184** **185**

186 **187** **188**

The synthesis of coumarins from phenols and β-ketoesters or propiolic acid under solvent free conditions, and especially with assistance from microwave irradiation, has been reported to provide an improvement over conventional solution phase methods.[269,270] Two practicable syntheses of 4-hydroxycoumarin start from aspirin and involve the condensation of its acid chloride with the anions from either diethyl malonate or ethyl acetoacetate.[271] 3-Arylcoumarins have been prepared in high yield from salicylaldehydes and arylacetonitriles with an anion exchange resin as the catalyst.[272] A route to 2-substituted chromones starts from salicylic acids, the key step being an intramolecular Wittig reaction of the transient phosphonium ylide **189**.[273] The C2–C3 bond is more commonly formed by an intramoleculer aldol reaction and this approach has been used in a new synthesis of the 2-substituted polyhydroxyisoflavones **190** in which unprotected precursors are used.[274] New non-oxidative cyclisation reactions in which the O–aryl bond is created have been described for the chromone esters **191**[275] and for flavonols **192**.[276] The ketene dithioacetals **193**, which are generated from the corresponding 2-hydroxyacetophenones, CS_2 and iodomethane, cyclise to 2-methylthiochromones **194** in high yield.[277]



189 **190**

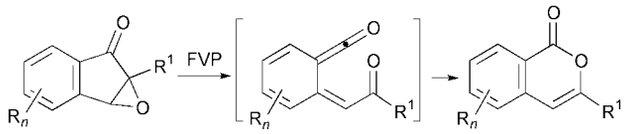
191 **192**

193 **194**

195 **196**

Benzochromones such as **196** were produced from aryl benzyl ethers **195** by tin mediated radical cyclisation followed

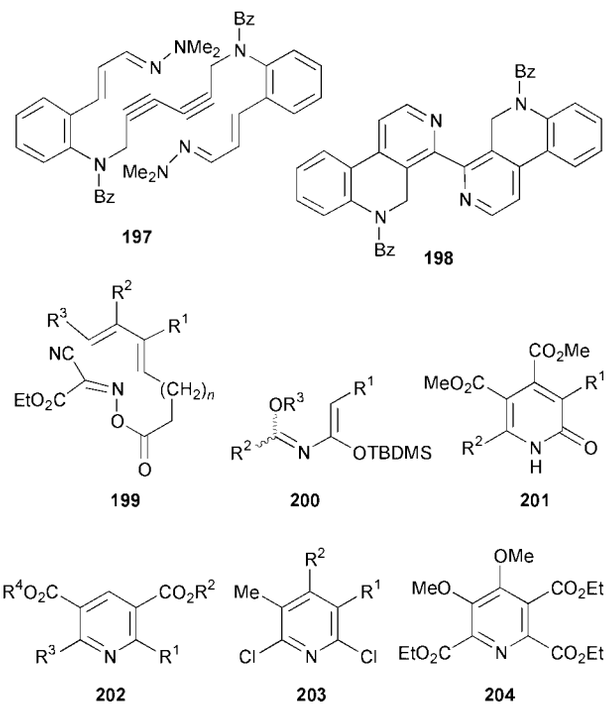
by oxidation to introduce the carbonyl group; they could not be synthesised directly by radical cyclisation of the diaryl esters corresponding to **195** because the esters adopt the incorrect conformation.[278] A new synthesis of isocoumarins, illustrated in Scheme 57, is based on the rearrangement of indenone epoxides under flash pyrolytic conditions.[279]



Scheme 57

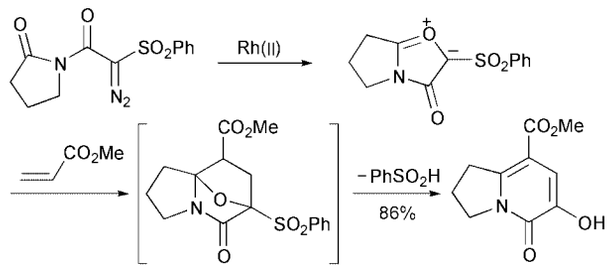
13 Pyridines

Review articles relevant to this section have been published on the synthesis of pyridones from vinyl isocyanates[280] and on the use of α,β-unsaturated *N*,*N*-dimethylhydrazones as 1-azadienes.[281] A spectacular application of the latter method is to a one step synthesis of polycyclic bipyridines, as illustrated by the assembly of the bipyridine **198** in 68% yield by heating the diyne **197** in xylene.[282] Intramolecular Diels–Alder reactions of *O*-acyloximes **199** have also been used in pyridine synthesis.[283]

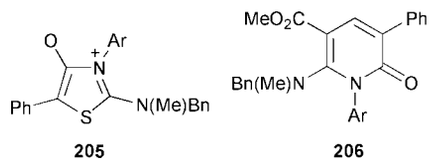


197 **198** **199** **200** **201** **202** **203** **204**

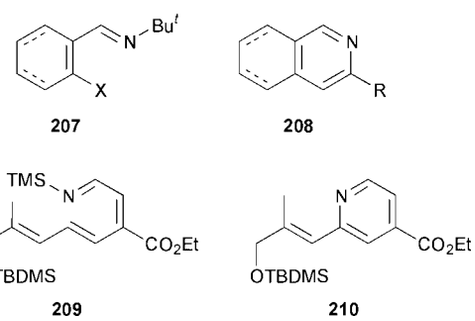
Nucleophilic 2-azadienes **200** are also good dienophiles. They can be generated *in situ* and react with DMAD to give 2-pyridones **201** (24–64%). They also add to activated nitriles to give pyrimidones.[284] 1,4-Diaryl-2-azabutadienes undergo analogous cycloaddition reactions with acetylenic esters.[285] Several other pyridines have been synthesised by Diels–Alder reactions of acyclic or cyclic 2-azadienes. These include pyridine-3,5-dicarboxylic esters **202**,[286] 2,6-dichloropyridines **203**,[287] and the pentasubstituted pyridine **204**.[288] This was synthesised from triethyl 1,2,4-triazine-3,5,6-tricarboxylate as a part of a total synthesis of an aza anthraquinone, phomazarin. Further examples of the LEGO system of constructing oligopyridines by cycloaddition reactions of 1,2,4-triazines to tributylstannylacetylene have also been published.[289,290] The cycloaddition reactions of isomünchnones provide a good route to a variety of highly substituted 2-pyridones. An example is shown in Scheme 58[291] and several others have been described.[292,293] The cycloaddition of mesoionic thiazolium 4-oxides **205** to methyl propiolate and other activated acetylenes might lead either to pyridones **206** (by loss of sulfur from the intermediate cycloadduct) or to thiophenes (by loss of an aryl isocyanate from the intermediate). The pyridones are the major or exclusive products and the reasons for the selectivity have been discussed.[294]



Scheme 58



205 **206**



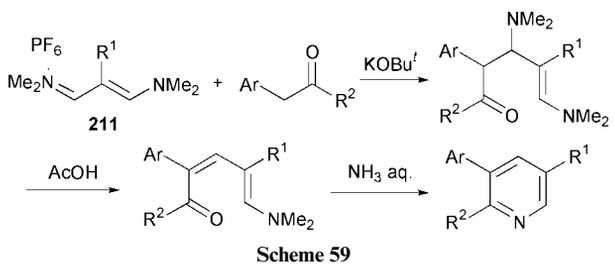
207 **208**

209 **210**

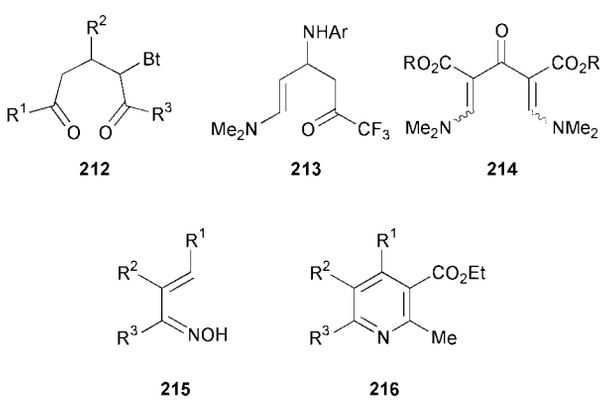
New syntheses of pyridines (and of isoquinolines) based on palladium coupling and cyclisation have been reported. The imines **207** (X = Br or I) are coupled with terminal alkynes in the presence of a palladium(II) and copper(I) catalyst and the ring synthesis is completed by heating the product residue in DMF with copper(I) iodide, giving compounds **208** in high yield.[295] A related palladium catalysed coupling of imines of this type with terminal allenes has been described.[296] Cyclisation reactions of a variety of azatrienes generated by other methods have also been used to produce pyridines.[297–299] An example is the spontaneous cyclisation of the *N*-trimethylsilylimine **209**, which was generated *in situ* from the corresponding aldehyde. This gives a dihydropyridine which, after oxidation by DDQ, is converted into the pyridine **210**.[300]

Vinylamidinium salts **211** have proved to be useful reagents for the synthesis of a number of 3-substituted 5-aryl- and 5,6-diarylpyridines. A reaction sequence with benzyl ketones as reaction partners is shown in Scheme 59.[301,302] For example, 3-chloro-5-phenylpyridine was formed in 80% yield with phenylacetaldehyde and the salt **211** (R^1 = Cl) as reagents. Salts bearing several other substituents R^1 have also been used. With hydroxylamine in place of ammonia, pyridine *N*-oxides are produced.[303] A variety of other methods can be used to assemble 1,5-dicarbonyl compounds or their equivalents which are then aromatised by reaction with ammonia or hydroxylamine. A frequently used method is sequential aldol condensation and conjugate addition reactions of carbonyl compounds and enolate anions. A one pot procedure of this type carried out in the absence of a solvent and with solid NaOH as the base gave 2,4,6-trisubstituted pyridines in high yield.[304] 1-Benzotriazolyl (Bt) stabilised enolates have been added to enones to give intermediates of general structure **212**, which

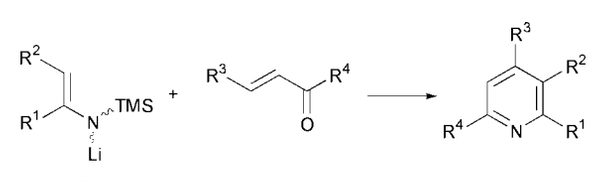
were cyclised to 2,4,6-trisubstituted pyridines by ammonium acetate.[305] Resin-bound enones have also been used as reagents in the Kröhnke synthesis of pyridines of this type.[217] 4-Arylamino-2-trifluoromethylpyridines were isolated in good yield from the cyclisation of the enaminones **213** with ammonium acetate.[306] 4-Oxopyridine-3,5-dicarboxylates were obtained from the reaction of amines with the bis(enaminoketones) **214**.[307] An alternative approach is to use a precursor that already contains the required nitrogen atom; for example, conjugate addition of ethyl acetoacetate to conjugated ketoximes **215** with iron(III) chloride as a catalyst gave ethyl 2-methylpyridine-3-carboxylates **216**.[308] The mechanism of the conjugate addition of malononitrile to β-aminoenones, which results in the formation of 6-cyano-2-pyridones, has been investigated[309] and some new examples of the synthesis of 2-pyridones by related methods have been described.[310,311]



Scheme 59

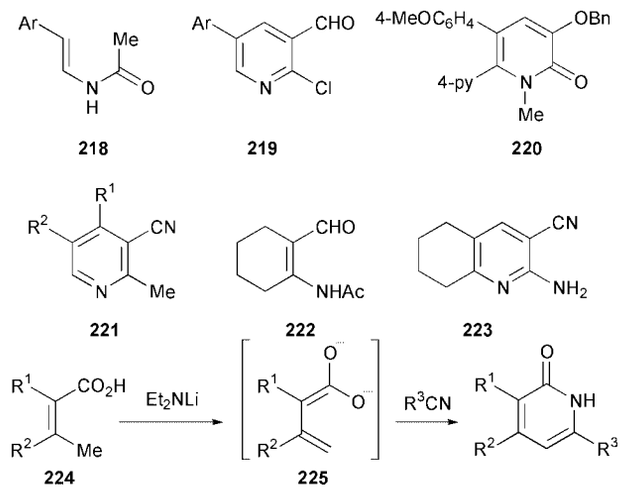


Another synthesis of 2-methylnicotinic esters (and then of 2-formylnicotinates by oxidation of the 2-methyl group) is based on the conjugate addition of β-aminocrotonic esters to aryl vinyl ketones or their precursors.[312] Methyl 3-aminocrotonate and 4-aminopent-3-en-2-one gave 2-pyridyl substituted amino acid derivatives analogous to **104** by conjugate addition to the ynone **102**.[180,214] Azaallyl anions **217** are useful building blocks for the synthesis of a variety of polysubstituted pyridines by addition to enones (Scheme 60).[313,314]



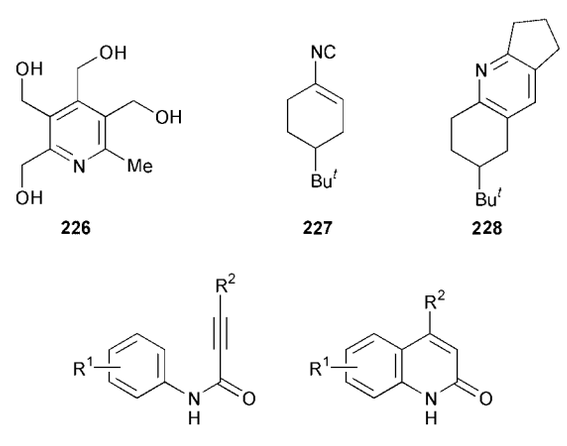
Scheme 60

The Vilsmeier formylation of enamines or activated methylene compounds has been used as a method of synthesis of several pyridines and 2-pyridones. The acetamides **218** were converted into the pyridines **219** in this way[315] and the pyridone **220** was constructed by a similar type of one carbon annulation reaction.[316] Nicotinonitriles **221** were synthesised in good yield from conjugated β-enaminonitriles and Katritzky's benzotriazole substituted equivalent of the Vilsmeier reagent, the iminium salt **154**.[317] β-Acylamino-α,β-unsaturated aldehydes such as **222** have been used in the construction of several pyridine derivatives.[318,319] For example, 2-amino-3-cyanotetrahydroquinoline **223** was isolated in 86% yield from a reaction of **222** and malononitrile on alumina under microwave irradiation.[318] A simple synthesis of 2-pyridones (Scheme 61) is based on the double deprotonation of carboxylic acids **224** and the reaction of the dianions **225** with nitriles.[320]



Scheme 61

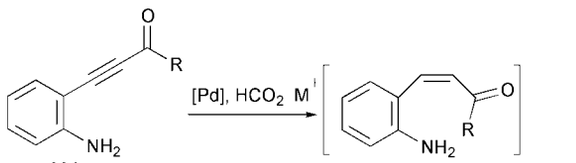
The synthesis of pyridines by cotrimerisation of alkynes and nitriles over a cobalt catalyst has been extended to the production of highly functionalised pyridines by using unprotected but-2-yne-1,4-diol and a water soluble catalyst in aqueous solution.[321] For example, the pyridine **226** was obtained in 76% yield with acetonitrile as the coreagent. An unusual radical cascade reaction of vinyl isocyanides and ω-iodoalk-1-ynes was used to construct a variety of fused pyridines in 20–72% yield.[322] This is illustrated by the reaction of the isocyanide **227** and 5-iodopent-1-yne to give the pyridine **228** in 66% yield when irradiated with hexabutylditin.



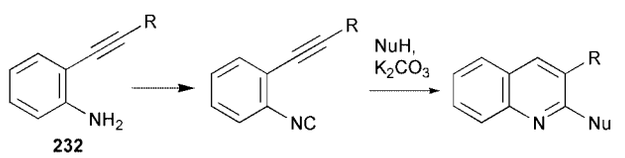
14 Quinolines and isoquinolines

The new methods of synthesis of quinolines and quinolones include several that are mediated by transition metals. Intramolecular hydroarylation of the triple bonds of acetylenic amides **229** is catalysed by palladium acetate and leads to the formation of 4-substituted quinolones **230** in high yield.[264] The acetylenic ketones **231** were assembled by palladium catalysed carbonylative acylation of the alkynes and were then reductively cyclised under palladium catalysis (Scheme 62).[323] Alternatively, the addition of nucleophiles to the triple bond followed by cyclisation produced 2,4-disubstituted quino-

lines.[324] Palladium catalysed coupling of 2-iodoaniline to trimethylsilylacetylenes and other terminal alkynes was used to produce the alkynes **232**. These were then converted into the corresponding aryl isocyanides. Addition of nucleophiles (MeOH, Et_2NH, *etc.*) to the isocyanides and cyclisation gave 2-substituted quinolines (R = TMS) or 2,3-disubstituted quinolines in high yield (Scheme 63).[325] Other methods of cyclisation of 2-isocyanostyrenes to quinolines and quinolones have also been reported.[326,327] The preliminary report of the formation of 2-ethyl-3-methylquinoline from aniline and triallylamine in the presence of a ruthenium(III) catalyst that was referred to in the previous review has since been supplemented by several other examples of quinoline syntheses of this type.[328–331]

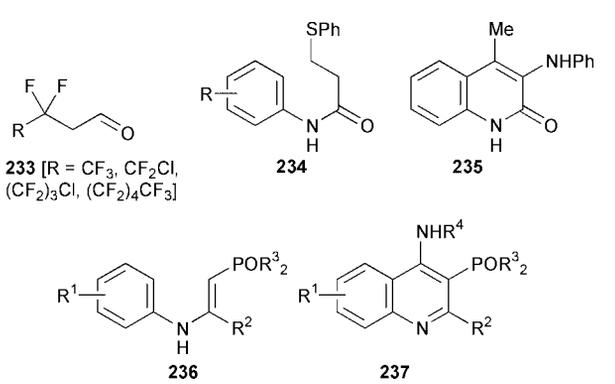


Scheme 62

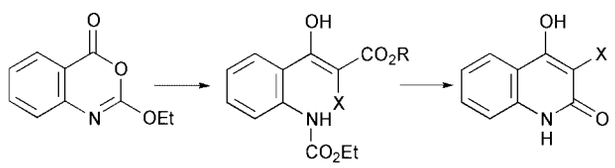


Scheme 63

Anilines are the starting materials in several classical quinoline syntheses, and improvements to these reactions have appeared. As an alternative to the Doebner–von Miller synthesis of quinoline from aniline and acrolein the aniline was first mesylated or tosylated and then condensed with acrolein in the presence of a base. By using this method 7-methoxyquinoline was prepared in 63% yield from *m*-anisidine on a large scale and without purification of any intermediates.[332] The formation of 2-methylquinolines from anilines and crotonaldehyde was improved by using a two phase system of toluene and 6 M HCl for the reaction.[333] 2-Fluoroalkyl substituted quinolines have been produced by the conjugate addition of anilines to β-fluoroacroleins, which were generated *in situ* from the aldehydes **233**.[334] The acylation of anilines with 3-(phenylthio)propionyl chloride gave the amides **234** which were then cyclised to 2-quinolones by a Pummerer type reaction sequence.[335] The product of condensation of ethyl 2-chloroacetoacetate with two moles of aniline has been shown to be the 2-quinolone **235** and not the isomeric 4-quinolone as was reported previously.[336] Efficient microwave assisted syntheses of quinolones from anilines and enones[66] and of 4-hydroxy-2-quinolones from anilines and malonic esters[337] have been described. The cyclisation of acetanilides to 2-chloroquinoline-3-carboxaldehydes by the Vilsmeier–Haack reagent has been carried out with a phase transfer catalyst in micellar conditions; this gives the products in improved yield, especially those derived from deactivated anilines.[338]

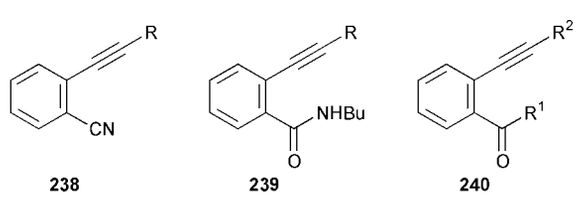


A route to 4-amino-3-phosphonylquinolines **237** from the enamides **236** has been reported. The conversion was carried out by acylation at the phosphorus bearing carbon with an isocyanate followed by dehydrative cyclisation.[339] A general method for the synthesis of 4-hydroxy-2-quinolones from benzoxazinones and activated esters is outlined in Scheme 64.[340] Further examples of known types of quinoline synthesis that have been reported include the following: vicarious nucleophilic substitution of nitroarenes followed by cyclisation leading to 4-arenesulfonylquinolines,[341] the reductive cyclisation of 2-nitrocinnamaldehydes,[342] the conversion of flavylium perchlorates to 2-aryl-4-quinolones with ammonia,[343,344] the cyclisation of Baylis–Hillman adducts of nitroarenes and ethyl acrylate to 4-hydroxyquinoline *N*-oxides,[345] and the formation of 2-trifluoromethylquinolines by the acid catalysed addition of enol ethers to Schiff bases of trifluoroacetaldehyde.[346]

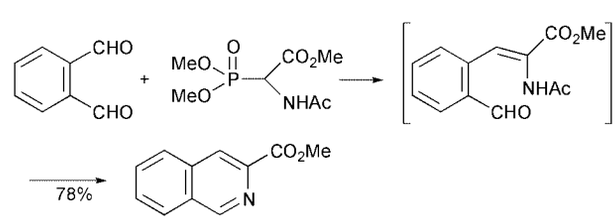


Scheme 64

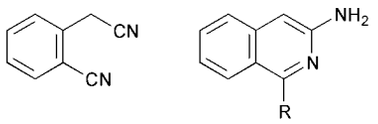
There are several new reports of the use of methods of isoquinoline ring synthesis that are based on palladium catalysed or base catalysed *endo* cyclisation onto a triple bond, but the reactions are sometimes complicated by competing *exo* cyclisation leading to isomeric five-membered ring products. This is a problem with the cyclisation of 2-cyanophenylalkynes **238** to 3-substituted isoquinolones[347] and to 1-methoxyisoquinolines.[348] The corresponding *N*-butylamides **239** apparently cyclise exclusively by the *endo* mode.[259] An alternative, used for 3-aryl substituted or 1,3-disubstituted isoquinolines, is to cyclise the ketones **240** to benzopyrylium salts with HBF_4 and then to treat the salts with ammonia.[349] A thermal procedure for cyclisation of the alkyne **238** (R = CH_2SO_2Ph) that may go by way of a diradical intermediate has also been described.[350]



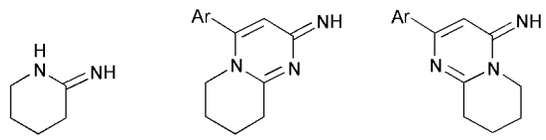
An improved experimental procedure for carrying out the Pomeranz–Fritsch isoquinoline synthesis on alkoxy substituted benzaldehydes has enabled 6- and 7-alkoxyisoquinolines to be prepared in good yield on a large scale.[351] Two new methods for the preparation of isoquinoline-3-carboxylic esters from phthalaldehydes have been reported. One makes use of a Horner–Wittig reaction, as illustrated for methyl isoquinoline-3-carboxylate in Scheme 65;[352] the other uses aminomalonic



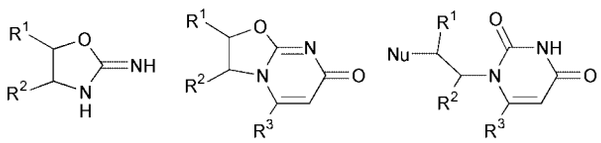
Scheme 65



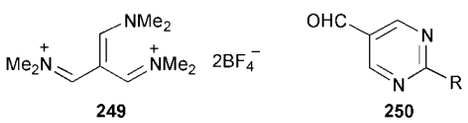
241 242



243 244 245



246 247 248



249 250

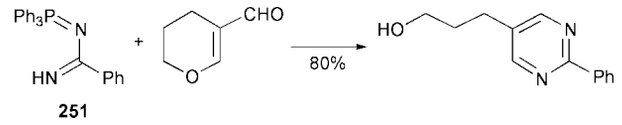
ester or an imidate derivative of it as the coreagent.[353] 1-Substituted 3-aminoisoquinolines **242** can be synthesised in good yield by reaction of the nitrile **241** with alkyllithium or (dialkylamino)lithium reagents.[354] It is possible to incorporate an additional propenyl or allyl substituent at C-4 by prior allylation at the activated methylene group of the nitrile **241**.[355]

A new synthesis of phenanthridines is based on the palladium–copper coupling of nitroarylstannanes to 2-bromobenzaldehyde followed by reductive ring closure.[356]

15 Pyrimidines and quinazolines

The addition of amidines to suitably functionalised acetylenic ketones has previously been reported as a route to new amino acids bearing pyrimidine substituents. A full paper on this work has appeared[357] and the methodology has been applied to the synthesis of novel pyrimidinyl substituted C-nucleosides.[358] Other syntheses of functionalised pyrimidines have also made use of the addition of amidines to activated acetylenes. The addition of the cyclic amidine **243** to aryl cyano acetylenes gave the 4-aminopyridines **244** almost exclusively in the absence of a base, but the opposite regioisomers **245** with NaHMDS.[359] The oxazolin-2-imines **246**, which are derived from amino alcohols by reaction with cyanogen bromide, react with acetylenic esters to give the fused pyrimidones **247**. The five membered ring can then be cleaved by reaction with nucleophiles, the products being 1,6-disubstituted pyrimidine-2,4-diones **248**.[360,361] The reactions of amidines with vinyl trifluoroacetyl ketones produced 2,6-disubstituted 4-trifluoroacetylpyrimidines in good yield. The use of phosphorus oxychloride and manganese dioxide as dehydrating and oxidising agents allowed the reactions to be carried out as a "one pot" procedure.[362] 4-Trifluoroacetylpyrimidines have also been formed from β-(dialkylamino)trifluoroacetyl ketones and guanidines or isothioureas.[363] The vinylamidinium tetrafluoroborate **249** reacted with amidines in the presence of sodium ethoxide to give the pyrimidine-5-carbaldehydes **250**.[364] The tetrafluoroborate is a safer alternative to the perchlorate that has been used previously in this synthesis.

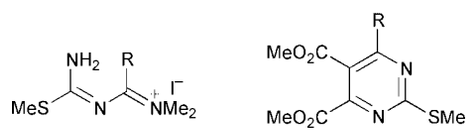
The iminophosphorane **251** is used in place of benzamidine as a reagent for the synthesis of 2-phenylpyrimidines. It reacts with unsaturated aldehydes to give pyrimidines in high yield; an example is shown in Scheme 66.[365]



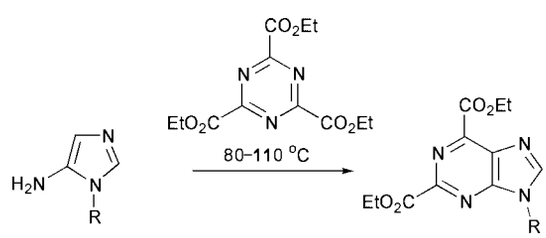
251

Scheme 66

The amidinium salt **252** reacted with DMAD to give the pyrimidine **253** (63%) by a stepwise mechanism: an intermediate formed by conjugate addition of the amidine to the acetylene can be isolated.[366] 5-Aminoimidazoles act as electron rich 2π components in a new purine synthesis that is formulated as a cycloaddition reaction with inverse electron demand (Scheme 67). The imidazoles are unstable and so are generated by decarboxylation of the corresponding imidazole-4-carboxylic acids.[367]

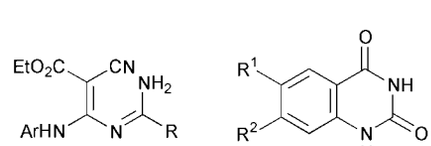


252 253

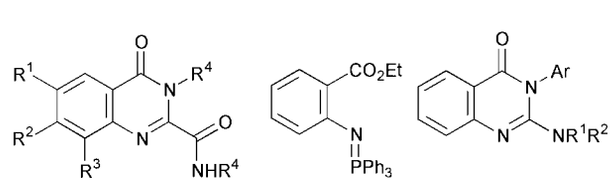


Scheme 67

Two new routes to 6-substituted uracils from α,β-unsaturated esters have been described.[368] One pot syntheses of 4-bromopyridines from the amidines **254** and HBr[369] and of 4-alkoxypyridines from aliphatic esters, acetonitrile and triflic† anhydride[370] have also been reported. The Leuckart reaction between formamide and acetophenone normally results in reductive amination of the ketone, but by carrying out the reaction in the presence of copper(I) chloride the course of the reaction has been diverted to give 4-phenylpyrimidine in 61% yield.[371]



254 255



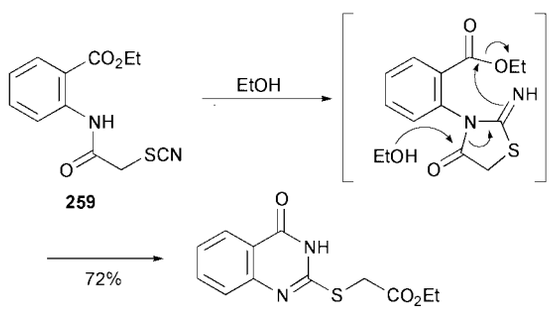
256 257 258

2-Aminobenzonitrile is a starting material for several syntheses of quinazolines. Its reaction with nitriles and potassium *tert*-butoxide, carried out in a domestic microwave oven, gave 2-substituted 4-aminoquinazolines in 73–93% yield.[372] The cyano function can be converted to an *N*-arylbenzamidine by reaction with an aniline and aluminium chloride; further reaction with an aldehyde followed by oxidation with $KMnO_4$ produces 2-

† The IUPAC name for triflic anhydride is trifluoromethanesulfonic anhydride.

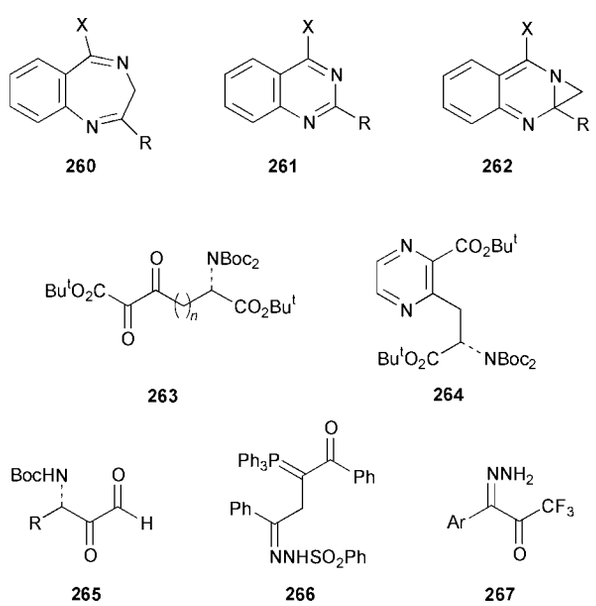
substituted 4-arylaminoquinazolines.[373] A traceless solid phase synthesis of 2,4-diaminoquinazolines from 2-aminobenzonitriles makes use of resin bound acyl isothiocyanates which acylate the amino function. After reaction with an amine the ring is closed, and the resin bound acyl function cleaved, by TFA.[374]

A simple procedure for preparing quinazoline-2,4-diones **255** from 2-aminobenzonitriles involves reaction of the nitriles with CO_2 and DBU in DMF at room temperature.[375] Another new route to quinazoline-2,4-diones is from 2-iodoanilines and isocyanates under a pressure of CO and with palladium acetate as a catalyst.[376] Quinazolin-4-ones **256** have been obtained from anthranilic acid derivatives and bis(imines) of oxalyl chloride.[377] *N*-Arylimidoyl chlorides reacted with cyanamide in the presence of titanium(IV) chloride to give 4-amino-2-phenylquinazolines.[378] The iminotriphenylphosphorane **257** derived from ethyl anthranilate has been converted into the 2-aminoquinazolin-4-ones **258** by reaction with an aryl isocyanate (to give a carbodiimide) then an amine (which becomes the 2-amino substituent).[379] The ethyl anthranilate derivative **259** (which was obtained by reaction of the corresponding chloroacetamide with KSCN) gave 2-substituted 4-quinazolones under mild conditions. The reaction with ethanol, and a possible mechanism, is illustrated in Scheme 68.[380]



Scheme 68

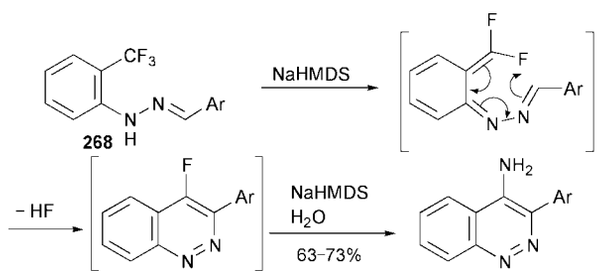
A simple synthesis of 2,6-disubstituted quinazolines is provided by the reaction of 2-fluorobenzaldehydes bearing an activating 5-substituent (NO_2 or CN) with amidines.[381] The 3*H*-1,4-diazepines **260** (X = OMe or NEt_2) were converted into quinazolines **261** in moderate yield when heated to 140–170 °C. The ring contraction probably goes by a valence tautomerism of the seven membered ring to a bicyclic intermediate **262** from which methylene is eliminated.[382]



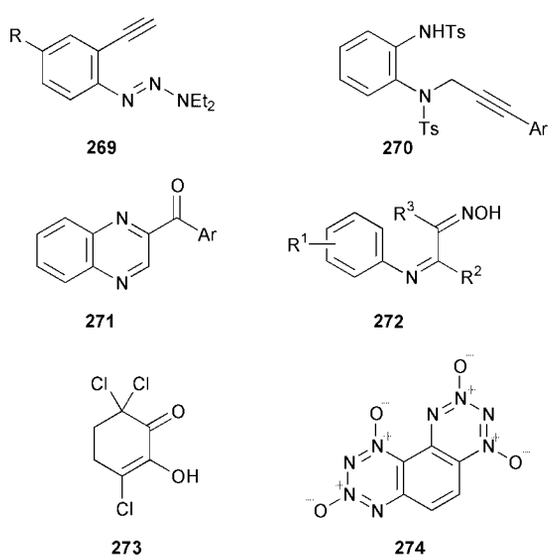
16 Other diazines, triazines and tetrazines

The protected amino acids **263** (*n* = 1 or 2) have been generated and used as precursors to new amino acid derivatives bearing pyrazine, triazine or quinoxaline substituents. For example, the pyrazine **264** was produced in 77% yield by reaction of the diester **263** (*n* = 1) with ethylenediamine followed by dehydrogenation over palladium.[383] A similar strategy was used to produce pyrazines and quinoxalines from the ketoaldehydes **265**.[384] 3,6-Diphenylpyridazine was formed as the major product (61%) when the phosphorane **266** was heated in benzene; other pyridazines were also prepared by this reaction.[385] The hydrazones **267** gave 3,6-diaryl-4,5-bis(trifluoromethyl)pyridazines when heated in TFA. A mechanism was proposed by the author in which protonated enol tautomers of the hydrazone **267** act as diene and dienophile in a Diels–Alder type cycloaddition.[386] In a related investigation, trifluoroacetaldehyde *N*,*N*-dimethylhydrazone was reacted in the presence of TFA to generate the mono(dimethylhydrazone) of hexafluorobutane-2,3-dione. This was then used as a building block for bis(trifluoromethyl)-pyrazines and -quinoxalines by reaction with appropriate diamines.[387]

A new synthesis of 4-amino-3-arylcinnolines from the arylhydrazones **268** and NaHMDS has been described. The mechanism proposed for the reaction (Scheme 69) involves three steps in which fluoride is lost, the key step being electrocyclic ring closure of a diazatriene intermediate.[388] The classical Richter reaction of cinnolines from 2-ethynylaryldiazonium salts has been adapted to the solid phase.[389] Cinnolines were the major products of thermolysis of the ethynyltriazines **269** when they were heated at or above 170 °C.[390] A new synthesis of 3-aroylquinoxalines **271** is provided by heating the benzene-1,2-diamine derivatives **270** with copper(I) iodide and potassium carbonate in DMF.[391] The oximes **272** also cyclised to 2,3-disubstituted quinoxalines when heated in acetic anhydride.[392]



Scheme 69



A new synthesis of 1-chlorophenazines, which have previously been obtained only in low yield, is based on the condensation

of the trichloroketone **273** with benzene-1,2-diamine derivatives.[393] There are few 1,2,3,4-tetrazine derivatives in the literature but a synthesis of the tetra-*N*-oxide **274** has been reported.[394]

17 References

1 Hetarenes and Related Ring Systems, *Science of Synthesis*, Category 2, vol. 9, ed. G. Maas, Georg Thieme Verlag, Stuttgart, 2001.
2 Hetarenes and Related Ring systems, *Science of Synthesis*, Category 2, vol. 10, ed. E. J. Thomas, Georg Thieme Verlag, Stuttgart, 2000.
3 J. J. Li and G. W. Gribble, *Palladium in Heterocyclic Chemistry*, Pergamon, Oxford, 2000.
4 A. Fürstner, *Synlett*, 1999, 1523.
5 S. M. Ma and J. L. Zhang, *Chem. Commun.*, 2000, 117.
6 S. M. Ma and L. T. Li, *Org. Lett.*, 2000, **2**, 941.
7 F. T. Luo, A. C. Bajji and A. Jeevanandam, *J. Org. Chem.*, 1999, **64**, 1738.
8 A. S. K. Hashmi, L. Schwarz, J. H. Choi and T. M. Frost, *Angew. Chem., Int. Ed.*, 2000, **39**, 2285.
9 B. Gabriele, G. Salerno and E. Lauria, *J. Org. Chem.*, 1999, **64**, 7687.
10 B. Gabriele, G. Salerno, F. De Pascali, M. Costa and G. P. Chiusoli, *J. Org. Chem.*, 1999, **64**, 7693.
11 T. Nicola, R. Vieser and W. Eberbach, *Eur. J. Org. Chem.*, 2000, 527.
12 J. A. Marshall and D. Zou, *Tetrahedron Lett.*, 2000, **41**, 1347.
13 A. Arcadi, G. Cerichelli, M. Chiarini, S. Di Giuseppe and F. Marinelli, *Tetrahedron Lett.*, 2000, **41**, 9195.
14 F. Stauffer and R. Neier, *Org. Lett.*, 2000, **2**, 3535.
15 P. Forgione, P. D. Wilson and A. G. Fallis, *Tetrahedron Lett.*, 2000, **41**, 17.
16 N. Monteiro and G. Balme, *J. Org. Chem.*, 2000, **65**, 3223.
17 A. Jeevanandam, K. Narkunan, C. Cartwright and Y. C. Ling, *Tetrahedron Lett.*, 1999, **40**, 4841.
18 J. M. Aurrecoechea, E. Pérez and M. Solay, *J. Org. Chem.*, 2001, **66**, 564.
19 F. L. Qing, W. Z. Gao and J. W. Ying, *J. Org. Chem.*, 2000, **65**, 2003.
20 H. Kuroda, E. Hanaki and M. Kawakami, *Tetrahedron Lett.*, 1999, **40**, 3753.
21 C. Bacilieri and M. Neuenschwander, *Helv. Chim. Acta*, 2000, **83**, 1191.
22 J. Méndez-Andino and L. A. Paquette, *Org. Lett.*, 2000, **2**, 4095.
23 C. D. Brown, J. M. Chong and L. X. Shen, *Tetrahedron*, 1999, **55**, 14233.
24 V. Nair and A. U. Vinod, *Chem. Commun.*, 2000, 1019.
25 A. Shaabani, S. Ajabi, F. Farrokhzad and H. R. Bijanzadeh, *J. Chem. Res. S*, 1999, 582.
26 A. Padwa, J. D. Ginn and M. S. McClure, *Org. Lett.*, 1999, **1**, 1559.
27 T. Takanami, A. Ogawa and K. Suda, *Tetrahedron Lett.*, 2000, **41**, 3399.
28 A. M. Redman, J. Dumas and W. J. Scott, *Org. Lett.*, 2000, **2**, 2061.
29 S. Onitsuka, H. Nishino and K. Kurosawa, *Tetrahedron Lett.*, 2000, **41**, 3149.
30 R. N. Ram and I. Charles, *Chem. Commun.*, 1999, 2267.
31 H. M. Meshram, K. C. Sekhar, Y. S. S. Ganesh and J. S. Yadav, *Synlett*, 2000, 1273.
32 K. C. Nicolaou, S. A. Snyder, A. Bigot and J. A. Pfefferkorn, *Angew. Chem., Int. Ed.*, 2000, **39**, 1093.
33 M. Botta, F. Corelli, F. Gasparrini, F. Messina and C. Mugnaini, *J. Org. Chem.*, 2000, **65**, 4736.
34 A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli and L. Moro, *Synlett*, 1999, 1432.
35 M. A. Abramov, W. Dehaen, B. D'Hooge, M. L. Petrov, S. Smeets, S. Toppet and M. Voets, *Tetrahedron*, 2000, **56**, 3933.
36 H. Lütjens and P. J. Scammells, *Synlett*, 1999, 1079.
37 Y. Nan, H. Miao and Z. Yang, *Org. Lett.*, 2000, **2**, 297.
38 Y. Terao, T. Satoh, M. Miura and M. Nomura, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 2345.
39 M. Watanabe, M. Nishiyama and Y. Koie, *Tetrahedron Lett.*, 1999, **40**, 8837.
40 G. A. Kraus, N. Zhang, J. G. Verkade, M. Nagarajan and P. B. Kisanga, *Org. Lett.*, 2000, **2**, 2409.
41 A. B. Paolobelli and R. Ruzziconi, *J. Org. Chem.*, 1999, **64**, 3364.
42 D. Bogdal and M. Warzala, *Tetrahedron*, 2000, **56**, 8769.
43 J. Habermann, S. V. Ley and R. Smits, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2421.
44 J. W. Herndon, Y. Zhang, H. X. Wang and K. Wang, *Tetrahedron Lett.*, 2000, **41**, 8687.
45 Y. Zhang and J. W. Herndon, *Tetrahedron*, 2000, **56**, 2175.
46 D. L. Jiang and J. W. Herndon, *Org. Lett.*, 2000, **2**, 1267.
47 C. Y. Yick, S. H. Chan and H. N. C. Wong, *Tetrahedron Lett.*, 2000, **41**, 5957.
48 M. E. Thibault, L. A. Pacarynuk, T. L. L. Closson and P. W. Dibble, *Tetrahedron Lett.*, 2001, **42**, 789.
49 D. Basavaiah, B. Sreenivasulu and J. S. Rao, *Tetrahedron Lett.*, 2001, **42**, 1147.
50 E. N. Deryagina and M. G. Voronkov, *Khim. Geterotsikl. Soedin.*, 2000, 3.
51 B. P. McKibben, C. H. Cartwright and A. L. Castelhano, *Tetrahedron Lett.*, 1999, **40**, 5471.
52 I. L. Pinto, R. L. Jarvest and H. T. Serafinowska, *Tetrahedron Lett.*, 2000, **41**, 1597.
53 G. M. Karp, D. Samant, S. Mukhopadhyay, M. E. Condon and A. Kleemann, *Synthesis*, 2000, 1078.
54 C. E. Stephens, M. B. Price and J. W. Sowell, *J. Heterocycl. Chem.*, 1999, **36**, 659.
55 C. Heyde, I. Zug and H. Hartmann, *Eur. J. Org. Chem.*, 2000, 3273.
56 B. S. Kim and K. Kim, *J. Org. Chem.*, 2000, **65**, 3690.
57 B. Gabriele, G. Salerno and A. Fazio, *Org. Lett.*, 2000, **2**, 351.
58 T. Kawano, T. Ogawa, S. M. Islam and I. Ueda, *Heterocycles*, 2000, **52**, 1279.
59 S. K. Kim, J. Yang and F. DiNinno, *Tetrahedron Lett.*, 1999, **40**, 2909.
60 T. Gallagher, D. A. Pardoe and R. A. Porter, *Tetrahedron Lett.*, 2000, **41**, 5415.
61 F. E. McDonald, S. A. Burova and L. G. Huffman, *Synthesis*, 2000, 970.
62 B. T. Gabriele, G. Salerno, A. Fazio and M. R. Bossio, *Tetrahedron Lett.*, 2001, **42**, 1339.
63 M. A. Fagan and D. W. Knight, *Tetrahedron Lett.*, 1999, **40**, 6117.
64 B. M. Trost and G. A. Doherty, *J. Am. Chem. Soc.*, 2000, **122**, 3801.
65 T. N. Danks, *Tetrahedron Lett.*, 1999, **40**, 3957.
66 B. C. Ranu, A. Hajra and U. Jana, *Tetrahedron Lett.*, 2000, **41**, 531.
67 R. Ballini, L. Barboni, G. Bosica and M. Petrini, *Synlett*, 2000, 391.
68 C. Dell'Erba, A. Mugnoli, M. Novi, M. Pani, G. Petrillo and C. Tavani, *Eur. J. Org. Chem.*, 2000, 903.
69 M. Takeda, S. Matsumoto and K. Ogura, *Heterocycles*, 2001, **55**, 231.
70 G. Kaupp, J. Schmeyers, A. Kuse and A. Atfeh, *Angew. Chem., Int. Ed.*, 1999, **38**, 2896.
71 H. Shiraishi, T. Nishitani, T. Nishihara, S. Sakaguchi and Y. Ishii, *Tetrahedron*, 1999, **55**, 13957.
72 S. Lim, I. Jabin and G. Revial, *Tetrahedron Lett.*, 1999, **40**, 4177.
73 M. Periasamy, G. Srinivas and P. Bharathi, *J. Org. Chem.*, 1999, **64**, 4204.
74 W. Aelterman, N. De Kimpe, V. Tyvorskii and O. Kulinkovich, *J. Org. Chem.*, 2001, **66**, 53.
75 A. R. Katritzky, L. H. Zhang, J. C. Yao and O. V. Denisko, *J. Org. Chem.*, 2000, **65**, 8074.
76 M. O. Amombo, A. Hausherr and H. U. Reissig, *Synlett*, 1999, 1871.
77 V. Breuil-Desvergnes, P. Compain, J. M. Vatèle and J. Goré, *Tetrahedron Lett.*, 1999, **40**, 8789.
78 L. Brandsma, N. A. Nedolya and B. A. Trofimov, *Russ. Chem. Bull.*, 2000, **49**, 1634.
79 L. Brandsma, N. A. Nedolya and B. A. Trofimov, *Eur. J. Org. Chem.*, 1999, 2663.
80 E. Marchand, G. Morel and S. Sinbandhit, *Eur. J. Org. Chem.*, 1999, 1729.
81 M. Nakamura, K. Hara, G. Sakata and E. Nakamura, *Org. Lett.*, 1999, **1**, 1505.
82 F. Palacios, D. Aparicio and J. M. de los Santos, *Tetrahedron*, 1999, **55**, 13767.
83 O. A. Attanasi, L. De Crescentini, P. Filippone and F. Mantellini, *Synlett*, 2000, 955.
84 O. A. Attanasi, L. De Crescentini, P. Filippone, B. Guidi, F. R. Perrulli and S. Santeusanio, *Synlett*, 1999, 1367.
85 S. E. Korostova, A. I. Mikhaleva and B. A. Trofimov, *Russ. Chem. Rev.*, 1999, **68**, 459.
86 B. A. Trofimov, O. A. Tarasova, A. I. Mikhaleva, N. A. Kalinina, L. M. Sinegovskaya and J. Henkelmann, *Synthesis*, 2000, 1585.
87 H. Takaya, S. Kojima and S. I. Murahashi, *Org. Lett.*, 2001, **3**, 421.
88 R. K. Dieter and H. Y. Yu, *Org. Lett.*, 2000, **2**, 2283.
89 Y. Fumoto, T. Eguchi, H. Uno and N. Ono, *J. Org. Chem.*, 1999, **64**, 6518.
90 M. Adamczyk, D. D. Johnson and R. E. Reddy, *Angew. Chem., Int. Ed.*, 1999, **38**, 3537.
91 T. D. Lash, M. L. Thompson, T. M. Werner and J. D. Spence, *Synlett*, 2000, 213.
92 T. Murashima, R. Tamai, K. Nishi, K. Nomura, K. Fujita, H. Uno and N. Ono, *J. Chem. Soc., Perkin Trans. 1*, 2000, 995.

93 H. Uno, M. Tanaka, T. Inoue and N. Ono, *Synthesis*, 1999, 471.
94 Y. Fumoto, H. Uno, S. Ito, Y. Tsugumi, M. Sasaki, Y. Kitawaki and N. Ono, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2977.
95 H. Uno, S. Ito, M. Wada, H. Watanabe, M. Nagai, A. Hayashi, T. Murashima and N. Ono, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4347.
96 R. J. Andrew and J. M. Mellor, *Tetrahedron*, 2000, **56**, 7267.
97 L. Selič and B. Stanovnik, *Synthesis*, 1999, 479.
98 Y. N. Romashin, M. T. H. Liu and R. Bonneau, *Chem. Commun.*, 1999, 447.
99 Y. N. Romashin, M. T. H. Liu, W. Ma and R. A. Moss, *Tetrahedron Lett.*, 1999, **40**, 7163.
100 M. S. Novikov, A. F. Khlebnikov, E. S. Sidorina and R. R. Kostikov, *J. Chem. Soc., Perkin Trans. 1*, 2000, 231.
101 M. S. Novikov, A. F. Khlebnikov, O. V. Besedina and R. R. Kostikov, *Tetrahedron Lett.*, 2001, **42**, 533.
102 J. P. Fitzgerald, H. Nanda, P. Fitzgerald and G. T. Yee, *J. Org. Chem.*, 2000, **65**, 2222.
103 I. Fejes, L. Töke, G. Blaskó, M. Nyerges and C. S. Pak, *Tetrahedron*, 2000, **56**, 8545.
104 C. S. Pak and M. Nyerges, *Synlett*, 1999, 1271.
105 K. Washizuka, S. Minakata, I. Ryu and M. Komatsu, *Tetrahedron*, 1999, **55**, 12969.
106 A. R. Katritzky, T. B. Huang, M. V. Voronkov, M. Y. Wang and H. Kolb, *J. Org. Chem.*, 2000, **65**, 8819.
107 A. Alberola, A. G. Ortega, M. L. Sádaba and C. Sañudo, *Tetrahedron*, 1999, **55**, 6555.
108 R. Grigg and V. Savic, *Chem. Commun.*, 2000, 873.
109 N. Chen, Y. L. Lu, K. Gadamasetti, C. R. Hurt, M. H. Norman and C. Fotsch, *J. Org. Chem.*, 2000, **65**, 2603.
110 G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, 2000, **7**, 1045.
111 O. Miyata, Y. Kimura, K. Muroya, H. Hiramatsu and T. Naito, *Tetrahedron Lett.*, 1999, **40**, 3601.
112 S. Wagaw, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 10251.
113 A. P. Dobbs, M. Voyle and N. Whittall, *Synlett*, 1999, 1594.
114 Y. Miki, K. Matsushita, H. Hibino and H. Shirokoshi, *Heterocycles*, 1999, **51**, 1585.
115 A. Arcadi, S. Cacchi, G. Fabrizi and F. Marinelli, *Synlett*, 2000, 394.
116 A. L. Rodriguez, C. Koradin, W. Dohle and P. Knochel, *Angew. Chem., Int. Ed.*, 2000, **39**, 2488.
117 Y. Nishiyama, R. Maema, K. Ohno, M. Hirose and N. Sonoda, *Tetrahedron Lett.*, 1999, **40**, 5717.
118 L. Novellino, M. d'Ischia and G. Prota, *Synthesis*, 1999, 793.
119 B. C. Söderberg, S. R. Rector and S. N. O'Neil, *Tetrahedron Lett.*, 1999, **40**, 3657.
120 V. V. Rozhkov, A. M. Kuvshinov, V. I. Gulevskaya, I. I. Chervin and S. A. Shevelev, *Synthesis*, 1999, 2065.
121 V. V. Rozhkov, A. M. Kuvshinov and S. A. Shevelev, *Org. Prep. Proced. Int.*, 2000, **32**, 94.
122 H. Suzuki, H. Gyoutoku, H. Yokoo, M. Shinba, Y. Sato, H. Yamada and Y. Murakami, *Synlett*, 2000, 1196.
123 J. M. Muchowski, *J. Heterocycl. Chem.*, 2000, **37**, 1293.
124 T. Iwama, V. B. Birman, S. A. Kozmin and V. H. Rawal, *Org. Lett.*, 1999, **1**, 673.
125 M. Makosza and K. Wojciechowski, *Heterocycles*, 2001, **54**, 445.
126 M. T. Baumgartner, M. A. Nazareno, M. C. Murguía, A. B. Pierini and R. A. Rossi, *Synthesis*, 1999, 2053.
127 N. Moskalev and M. Makosza, *Tetrahedron Lett.*, 1999, **40**, 5395.
128 N. Moskalev and M. Makosza, *Heterocycles*, 2000, **52**, 533.
129 H. Sakagami and K. Ogasawara, *Heterocycles*, 1999, **51**, 1131.
130 Y. Ozaki, Z. S. Quan, K. Watabe and S. W. Kim, *Heterocycles*, 1999, **51**, 727.
131 H. Tohma, H. Watanabe, S. Takizawa, T. Maegawa and Y. Kita, *Heterocycles*, 1999, **51**, 1785.
132 A. Takeda, S. Kamijo and Y. Yamamoto, *J. Am. Chem. Soc.*, 2000, **122**, 5662.
133 K. R. Roesch and R. C. Larock, *Org. Lett.*, 1999, **1**, 1551.
134 A. Arcadi, S. Cacchi, G. Fabrizi and F. Marinelli, *Synlett*, 2000, 647.
135 H. Tokuyama, Y. Kaburagi, X. Q. Chen and T. Fukuyama, *Synthesis*, 2000, 429.
136 J. D. Rainier, A. R. Kennedy and E. Chase, *Tetrahedron Lett.*, 1999, **40**, 6325.
137 J. D. Rainier and A. R. Kennedy, *J. Org. Chem.*, 2000, **65**, 6213.
138 Q. Zhang, C. S. Shi, H. R. Zhang and K. K. Wang, *J. Org. Chem.*, 2000, **65**, 7977.
139 M. Schmittel, D. Rodríguez and J. P. Steffen, *Angew. Chem., Int. Ed.*, 2000, **39**, 2152.
140 J. A. Murphy, K. A. Scott, R. S. Sinclair, C. G. Martin, A. R. Kennedy and N. Lewis, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2395.
141 K. Hiroi, Y. Hiratsuka, K. Watanabe, I. Abe, F. Kato and M. Hiroi, *Synlett*, 2001, 263.
142 C. S. Cho, J. H. Kim and S. C. Shim, *Tetrahedron Lett.*, 2000, **41**, 1811.
143 K. Orito, S. Uchiito, Y. Satoh, T. Tatsuzawa, R. Harada and M. Tokuda, *Org. Lett.*, 2000, **2**, 307.
144 K. Orito, R. Harada, S. Uchiito and M. Tokuda, *Org. Lett.*, 2000, **2**, 1799.
145 J. A. Brown, *Tetrahedron Lett.*, 2000, **41**, 1623.
146 M. Watanabe, T. Yamamoto and M. Nishiyama, *Angew. Chem., Int. Ed.*, 2000, **39**, 2501.
147 M. Beller, C. Breindl, T. H. Riermeier and A. Tillack, *J. Org. Chem.*, 2001, **66**, 1403.
148 H. Hagelin, J. D. Oslob and B. Åkermark, *Chem. Eur. J.*, 1999, **5**, 2413.
149 L. D. Zhang, F. Liang, L. Z. Sun, Y. F. Hu and H. W. Hu, *Synthesis*, 2000, 1733.
150 B. X. Wang, X. C. Zhang, J. Li, X. Xiang, Y. F. Hu and H. W. Hu, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1571.
151 A. R. Katritzky, G. F. Qiu, B. Z. Yang and H. Y. He, *J. Org. Chem.*, 1999, **64**, 7618.
152 A. R. Katritzky, D. O. Tymoshenko, D. Monteux, V. Vvedensky, G. Nikonov, C. B. Cooper and M. Deshpande, *J. Org. Chem.*, 2000, **65**, 8059.
153 A. G. M. Barrett, S. M. Cramp, A. J. Hennessy, P. A. Procopiou and R. S. Roberts, *Org. Lett.*, 2001, **3**, 271.
154 B. A. Kulkarni and A. Ganesan, *Tetrahedron Lett.*, 1999, **40**, 5637.
155 M. S. Addie and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2000, 527.
156 C. M. Shafer and T. P. Molinski, *Heterocycles*, 2000, **53**, 1167.
157 C. T. Brain and J. M. Paul, *Synlett*, 1999, 1642.
158 A. J. Phillips, Y. Uto, P. Wipf, M. J. Reno and D. R. Williams, *Org. Lett.*, 2000, **2**, 1165.
159 M. Lautens and A. Roy, *Org. Lett.*, 2000, **2**, 555.
160 T. Moschny and H. Hartmann, *Helv. Chim. Acta*, 1999, **82**, 1981.
161 S. Sengupta and S. Mondal, *Tetrahedron Lett.*, 1999, **40**, 8685.
162 P. C. Ducept and S. P. Marsden, *Synlett*, 2000, 692.
163 J. C. Lee and I. G. Song, *Tetrahedron Lett.*, 2000, **41**, 5891.
164 A. S. Kiselyov, *Tetrahedron Lett.*, 1999, **40**, 4119.
165 M. R. DeLuca, I. B. Taraporewala and S. M. Kerwin, *Heterocycles*, 1999, **51**, 979.
166 S. Heck and A. Dömling, *Synlett*, 2000, 424.
167 J. Rudolph, *Tetrahedron*, 2000, **56**, 3161.
168 C. Boga, L. Forlani, C. Silvestroni, A. B. Corradi and P. Sgarabotto, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1363.
169 J. Habermann, S. V. Ley, J. J. Scicinski, J. S. Scott, R. Smits and A. W. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2425.
170 P. F. Zhang and Z. C. Chen, *Synthesis*, 2000, 1219.
171 M. Romero-Ortega, A. Aviles, R. Cruz, Y. Fuentes, R. M. Gomez and A. Plata, *J. Org. Chem.*, 2000, **65**, 7244.
172 Y. H. Zhou, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, 2000, **83**, 1576.
173 A. R. Katritzky, X. J. Wang and R. Maimait, *J. Org. Chem.*, 2000, **65**, 8077.
174 D. K. Bates, M. D. Xia, M. Aho, H. Mueller and R. R. Raghavan, *Heterocycles*, 1999, **51**, 475.
175 J. Prasad, A. Panapoulous and J. R. Rubin, *Tetrahedron Lett.*, 2000, **41**, 4065.
176 T. Itoh, K. Nagata, M. Miyazaki and A. Ohsawa, *Heterocycles*, 2000, **52**, 1037.
177 V. Z. Shirinian, S. Y. Melkova, L. I. Belenkii and M. M. Krayushkin, *Russ. Chem. Bull.*, 2000, **49**, 1859.
178 U. S. Sorensen, E. Falch and P. Krogsgaard-Larsen, *J. Org. Chem.*, 2000, **65**, 1003.
179 T. Ohta, H. Fujisawa, Y. Nakai and I. Furukawa, *Bull. Chem. Soc. Jpn.*, 2000, **73**, 1861.
180 R. M. Adlington, J. E. Baldwin, D. Catterick, G. J. Pritchard and L. T. Tang, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2311.
181 M. A. P. Martins, A. F. C. Flores, G. P. Bastos, A. Sinhorin, H. G. Bonacorso and N. Zanatta, *Tetrahedron Lett.*, 2000, **41**, 293.
182 M. Ohkoshi, M. Yoshida, H. Matsuyama and M. Iyoda, *Tetrahedron Lett.*, 2001, **42**, 33.
183 R. Olivera, R. SanMartin, E. Dominguez, X. Solans, M. K. Urtiaga and M. I. Arriortua, *J. Org. Chem.*, 2000, **65**, 6398.
184 C. B. Vicentini, M. Mazzanti, C. F. Morelli and M. Manfrini, *J. Heterocycl. Chem.*, 2000, **37**, 175.
185 K. Zong, S. I. Shin, D. J. Jeon, J. N. Lee and E. K. Ryu, *J. Heterocycl. Chem.*, 2000, **37**, 75.

186 S. M. Laaman, O. Meth-Cohn and C. W. Rees, *Synthesis*, 1999, 757.
187 S. D. Lepore and M. R. Wiley, *J. Org. Chem.*, 1999, **64**, 4547.
188 B. H. Kim, T. K. Kim, J. W. Cheong, S. W. Lee, Y. M. Jun, W. Baik and B. M. Lee, *Heterocycles*, 1999, **51**, 1921.
189 B. H. Kim, Y. Jin, Y. M. Jun, R. B. Han, W. Baik and B. M. Lee, *Tetrahedron Lett.*, 2000, **41**, 2137.
190 B. C. Chen, M. S. Bednarz, R. L. Zhao, J. E. Sundeen, P. Chen, Z. Q. Shen, A. P. Skoumbourdis and J. C. Barrish, *Tetrahedron Lett.*, 2000, **41**, 5453.
191 J. Sisko, A. J. Kassick, R. Mellinger, J. J. Filan, A. Allen and M. A. Olsen, *J. Org. Chem.*, 2000, **65**, 1516.
192 M. Bergemann and R. Neidlein, *Helv. Chim. Acta*, 1999, **82**, 909.
193 M. Groarke, M. A. McKervey and M. Nieuwenhuyzen, *Tetrahedron Lett.*, 2000, **41**, 1275.
194 A. Y. Usyatinsky and Y. L. Khmelnitsky, *Tetrahedron Lett.*, 2000, **41**, 5031.
195 Y. Kamitori, *Heterocycles*, 2000, **53**, 107.
196 C. J. Griffiths, M. B. Hauck, R. Imwinkelried, J. Kohr, C. A. Roten and G. C. Stucky, *J. Org. Chem.*, 1999, **64**, 8084.
197 M. Anastassiadou, G. Baziard-Mouysset and M. Payard, *Synthesis*, 2000, 1814.
198 S. Jouneau and J. P. Bazureau, *Tetrahedron Lett.*, 1999, **40**, 8097.
199 P. Molina, P. M. Fresneda and M. A. Sanz, *J. Org. Chem.*, 1999, **64**, 2540.
200 P. M. Fresneda, P. Molina and M. A. Sanz, *Synlett*, 2001, 218.
201 B. Batanero, J. Escudero and F. Barba, *Org. Lett.*, 1999, **1**, 1521.
202 B. L. Booth, F. A. T. Costa, R. Pritchard and M. F. Proença, *Synthesis*, 2000, 1269.
203 R. N. Butler, M. O. Cloonan, J. M. McMahon and L. A. Burke, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1709.
204 G. Penieres, I. Bonifas, J. G. López, J. G. García and C. Alvarez, *Synth. Commun.*, 2000, **30**, 2191.
205 K. Bougrin, A. Loupy, A. Petit, B. Daou and M. Soufiaoui, *Tetrahedron*, 2001, **57**, 163.
206 F. Esser, P. Ehrengart and H. P. Ignatow, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1153.
207 N. Almirante, A. Benicchio, A. Cerri, G. Fedrizzi, G. Marazzi and M. Santagostino, *Synlett*, 1999, 299.
208 H. Chen, D. Q. Qian, G. X. Xu, Y. X. Liu, X. D. Chen, X. D. Shi, R. Z. Cao and L. Z. Liu, *Synth. Commun.*, 1999, **29**, 4025.
209 Y. N. Romashin, M. T. H. Liu, S. S. Nijjar and O. A. Attanasi, *Chem. Commun.*, 2000, 1147.
210 V. Atlan, C. Buron and L. El Kaïm, *Synlett*, 2000, 489.
211 A. Alberola, L. Calvo, A. G. Ortega, M. L. Sádaba, M. C. Sanudo, S. G. Granda and E. G. Rodríguez, *Heterocycles*, 1999, **51**, 2675.
212 M. Kawase, M. Hirabayashi, S. Saito and K. Yamamoto, *Tetrahedron Lett.*, 1999, **40**, 2541.
213 M. Škof, J. Svete and B. Stanovnik, *Heterocycles*, 2000, **53**, 339.
214 R. M. Adlington, J. E. Baldwin, D. Catterick, G. J. Pritchard and L. T. Tang, *J. Chem. Soc., Perkin Trans. 1*, 2000, 303.
215 L. De Luca, M. Falorni, G. Giacomelli and A. Porcheddu, *Tetrahedron Lett.*, 1999, **40**, 8701.
216 L. De Luca, G. Giacomelli, A. Porcheddu, A. M. Spanedda and M. Falorni, *Synthesis*, 2000, 1295.
217 P. Grosche, A. Höltzel, T. B. Walk, A. W. Trautwein and G. Jung, *Synthesis*, 1999, 1961.
218 Q. S. Zhang and L. Lu, *Tetrahedron Lett.*, 2000, **41**, 8545.
219 J. P. Bouillon, B. Didier, B. Dondy, P. Doussot, R. Plantier-Royon and C. Portella, *Eur. J. Org. Chem.*, 2001, 187.
220 J. N. Volle and M. Schlosser, *Eur. J. Org. Chem.*, 2000, 823.
221 L. El Kaïm and S. Lacroix, *Synlett*, 2000, 353.
222 F. Foti, G. Grassi and F. Risitano, *Tetrahedron Lett.*, 1999, **40**, 2605.
223 K. Washizuka, K. Nagai, S. Minakata, I. Ryu and M. Komatsu, *Tetrahedron Lett.*, 1999, **40**, 8849.
224 G. Broggini and G. Molteni, *J. Chem. Soc., Perkin Trans. 1*, 2000, **11**, 1685.
225 B. Liu, M. X. Wang and Z. T. Huang, *Tetrahedron Lett.*, 1999, **40**, 7399.
226 F. Palacios, A. M. O. de Retana and J. Pagalday, *Tetrahedron*, 1999, **55**, 14451.
227 D. Simoni, R. Rondanin, G. Furnò, E. Aiello and F. P. Invidiata, *Tetrahedron Lett.*, 2000, **41**, 2699.
228 A. R. Katritzky, A. Denisenko, S. N. Denisenko and M. Arend, *J. Heterocycl. Chem.*, 2000, **37**, 1309.
229 S. Caron and E. Vázquez, *Synthesis*, 1999, 588.
230 J. J. Song and N. K. Yee, *Org. Lett.*, 2000, **2**, 519.
231 A. Taher, S. Ladwa, S. T. Rajan and G. W. Weaver, *Tetrahedron Lett.*, 2000, **41**, 9893.
232 A. R. Gangloff, J. Litvak, E. J. Shelton, D. Sperandio, V. R. Wang and K. D. Rice, *Tetrahedron Lett.*, 2001, **42**, 1441.
233 R. F. Poulain, A. L. Tartar and B. P. Déprez, *Tetrahedron Lett.*, 2001, **42**, 1495.
234 S. Liras, M. P. Allen and B. E. Segelstein, *Synth. Commun.*, 2000, **30**, 437.
235 C. T. Brain, J. M. Paul, Y. Loong and P. J. Oakley, *Tetrahedron Lett.*, 1999, **40**, 3275.
236 F. Bentiss and M. Lagrenée, *J. Heterocycl. Chem.*, 1999, **36**, 1029.
237 M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati, R. Ballini and G. Bosica, *Tetrahedron Lett.*, 2000, **41**, 8817.
238 Y. Kamitori, *Heterocycles*, 1999, **51**, 627.
239 L. S. Konstantinova, O. A. Rakitin, C. W. Rees, T. Torroba, A. J. P. White and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2243.
240 T. Iwakawa and A. Murabayashi, *Heterocycles*, 1999, **51**, 811.
241 V. D. Le, C. W. Rees and S. Sivadasan, *Tetrahedron Lett.*, 2000, **41**, 9407.
242 L. Forlani, A. Lugli, C. Boga, A. B. Corradi and P. Sgarabotto, *J. Heterocycl. Chem.*, 2000, **37**, 63.
243 A. Shafiee, M. A. Ebrahimzadeh and A. Maleki, *J. Heterocycl. Chem.*, 1999, **36**, 901.
244 S. H. Bae, K. Kim and Y. J. Park, *Heterocycles*, 2000, **53**, 159.
245 F. Bentiss, M. Lagrenée and D. Barbry, *Tetrahedron Lett.*, 2000, **41**, 1539.
246 K. Paulvannan, T. Chen and R. Hale, *Tetrahedron*, 2000, **56**, 8071.
247 X. J. Liu, J. P. Zou, Y. B. Fan and Q. R. Wang, *Synthesis*, 1999, 1313.
248 Q. R. Wang, X. J. Liu, F. G. Tao and C. Z. Zhang, *Synth. Commun.*, 2000, **30**, 4255.
249 V. Y. Zubarev and V. A. Ostrovskii, *Khim. Geterotsikl. Soedin.*, 2000, 867.
250 M. Alterman and A. Hallberg, *J. Org. Chem.*, 2000, **65**, 7984.
251 P. A. Bethel, M. S. Hill, M. F. Mahon and K. C. Molloy, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3507.
252 D. P. Curran, S. Hadida and S. Y. Kim, *Tetrahedron*, 1999, **55**, 8997.
253 Y. S. Gyoung, J. G. Shim and Y. Yamamoto, *Tetrahedron Lett.*, 2000, **41**, 4193.
254 R. A. Batey and D. A. Powell, *Org. Lett.*, 2000, **2**, 3237.
255 S. Rousset, M. Abarbri, J. Thibonnet, A. Duchêne and J. L. Parrain, *Chem. Commun.*, 2000, 1987.
256 M. Kotora, M. Ishikawa, F. Y. Tsai and T. Takahashi, *Tetrahedron*, 1999, **55**, 4969.
257 R. C. Larock, M. J. Doty and X. J. Han, *J. Org. Chem.*, 1999, **64**, 8770.
258 F. Bellina, D. Ciucci, P. Vergamini and R. Rossi, *Tetrahedron*, 2000, **56**, 2533.
259 H. Sashida and A. Kawamukai, *Synthesis*, 1999, 1145.
260 R. Rossi, F. Bellina, M. Biagetti, A. Catanese and L. Mannina, *Tetrahedron Lett.*, 2000, **41**, 5281.
261 N. Rosas, M. Salmon, P. Sharma, C. Alvarez, R. Ramirez, J. L. Garcia and H. Arzoumanian, *J. Chem. Soc., Perkin Trans. 1*, 2000, **10**, 1493.
262 M. Zhou, Y. Yoshida, S. Ishii and H. Noguchi, *Synth. Commun.*, 1999, **29**, 2241.
263 D. V. Kadnikov and R. C. Larock, *Org. Lett.*, 2000, **2**, 3643.
264 C. Jia, D. Piao, T. Kitamura and Y. Fujiwara, *J. Org. Chem.*, 2000, **65**, 7516.
265 H. Miao and Z. Yang, *Org. Lett.*, 2000, **2**, 1765.
266 A. S. Bhat, J. L. Whetstone and R. W. Brueggemeier, *Tetrahedron Lett.*, 1999, **40**, 2469.
267 I. P. Lokot, F. S. Pashkovsky and F. A. Lakhvich, *Tetrahedron*, 1999, **55**, 4783.
268 P. Mingo, S. J. Zhang and L. S. Liebeskind, *J. Org. Chem.*, 1999, **64**, 2145.
269 A. de la Hoz, A. Moreno and E. Vázquez, *Synlett*, 1999, 608.
270 T. Sugino and K. Tanaka, *Chem. Lett.*, 2001, 110.
271 J. C. Jung, J. C. Kim and O. S. Park, *Synth. Commun.*, 1999, **29**, 3587.
272 C. Mhiri, F. Ladhar, R. El Gharbi and Y. Le Bigot, *Synth. Commun.*, 1999, **29**, 1451.
273 P. Kumar and M. S. Bodas, *Org. Lett.*, 2000, **2**, 3821.
274 N. Al-Maharik, I. Mutikainen and K. Wähälä, *Synthesis*, 2000, 411.
275 V. I. Saloutin, Y. V. Burgart, C. O. Kappe and O. N. Chupakhin, *Heterocycles*, 2000, **52**, 1411.
276 A. Fougerousse, E. Gonzalez and R. Brouillard, *J. Org. Chem.*, 2000, **65**, 583.
277 G. H. Lee and C. S. Pak, *Synth. Commun.*, 1999, **29**, 2539.
278 W. R. Bowman, E. Mann and J. Parr, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2991.

279 D. Mal, M. Bandyopadhyay, S. K. Ghorai and K. Datta, *Tetrahedron Lett.*, 2000, **41**, 3677.
280 J. H. Rigby, *Synlett*, 2000, 1.
281 F. Pautet, P. Nebois, Z. Bouaziz and H. Fillion, *Heterocycles*, 2001, **54**, 1095.
282 N. Bushby, C. J. Moody, D. A. Riddick and I. R. Waldron, *Chem. Commun.*, 1999, 793.
283 D. C. Bland, B. C. Raudenbush and S. N. Weinreb, *Org. Lett.*, 2000, **2**, 4007.
284 L. Ghosez, E. Jnoff, P. Bayard, F. Sainte and R. Beaudegnies, *Tetrahedron*, 1999, **55**, 3387.
285 J. L. Paparin, C. Crévisy, R. Grée and L. Toupet, *J. Heterocycl. Chem.*, 2000, **37**, 411.
286 F. Palacios, E. Herrán and G. Rubiales, *J. Org. Chem.*, 1999, **64**, 6239.
287 W. De Borggraeve, F. Rombouts, E. Van der Eycken and G. J. Hoornaert, *Synlett*, 2000, 713.
288 D. L. Boger, J. Y. Dong, M. Hikota and M. Ishida, *J. Am. Chem. Soc.*, 1999, **121**, 2471.
289 G. R. Pabst, O. C. Pfüller and J. Sauer, *Tetrahedron*, 1999, **55**, 5047.
290 G. R. Pabst and J. Sauer, *Tetrahedron*, 1999, **55**, 5067.
291 A. Padwa, S. M. Sheehan and C. S. Straub, *J. Org. Chem.*, 1999, **64**, 8648.
292 A. Padwa, T. M. Heidelbaugh and J. T. Kuethe, *J. Org. Chem.*, 1999, **64**, 2038.
293 C. S. Straub and A. Padwa, *Org. Lett.*, 1999, **1**, 83.
294 M. J. Arévalo, M. Avalos, R. Babiano, P. Cintas, M. B. Hursthouse, J. L. Jiménez, M. E. Light, I. López and J. C. Palacios, *Tetrahedron*, 2000, **56**, 1247.
295 K. R. Roesch and R. C. Larock, *Org. Lett.*, 1999, **1**, 553.
296 J. J. H. Diederen, R. W. Sinkeldam, H. W. Frühauf, H. Hiemstra and K. Vrieze, *Tetrahedron Lett.*, 1999, **40**, 4255.
297 E. M. Beccalli, F. Clerici and M. L. Gelmi, *Tetrahedron*, 2000, **56**, 4817.
298 P. J. Campos, E. Añón, M. C. Malo and M. A. Rodríguez, *Tetrahedron*, 1999, **55**, 14079.
299 F. Palacios, M. J. Gil, E. M. de Marigorta and M. Rodríguez, *Tetrahedron*, 2000, **56**, 6319.
300 K. Tanaka and S. Katsumura, *Org. Lett.*, 2000, **2**, 373.
301 J. F. Marcoux, E. G. Corley, K. Rossen, P. Pye, J. Wu, M. A. Robbins, I. W. Davies, R. D. Larsen and P. J. Reider, *Org. Lett.*, 2000, **2**, 2339.
302 I. W. Davies, J. F. Marcoux, E. G. Corley, M. Journet, D. W. Cai, M. Palucki, J. Wu, R. D. Larsen, K. Rossen, P. J. Pye, L. DiMichele, P. Dormer and P. J. Reider, *J. Org. Chem.*, 2000, **65**, 8415.
303 I. W. Davies, J. F. Marcoux and P. J. Reider, *Org. Lett.*, 2001, **3**, 209.
304 G. W. V. Cave and C. L. Raston, *Chem. Commun.*, 2000, 2199.
305 A. R. Katritzky, A. A. A. Abdel-Fattah, D. O. Tymoshenko and S. A. Essawy, *Synthesis*, 1999, 2114.
306 M. T. Cocco, C. Congiu and V. Onnis, *Tetrahedron Lett.*, 1999, **40**, 4407.
307 S. Zupancic, J. Svete and B. Stanovnik, *Heterocycles*, 2000, **53**, 2033.
308 A. M. Chibiryaev, N. De Kimpe and A. V. Tkachev, *Tetrahedron Lett.*, 2000, **41**, 8011.
309 A. Alberola, L. A. Calvo, A. G. Ortega, M. C. S. Ruíz, P. Yustos, S. G. Granda and E. Garciá-Rodríguez, *J. Org. Chem.*, 1999, **64**, 9493.
310 A. Nadin and T. Harrison, *Tetrahedron Lett.*, 1999, **40**, 4073.
311 F. Bondavalli, O. Bruno, E. Lo Presti, G. Menozzi and L. Mosti, *Synthesis*, 1999, 1169.
312 E. Gräf and R. Troschütz, *Synthesis*, 1999, 1216.
313 T. Konakahara, M. Hojahmat and S. Tamura, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2803.
314 M. Hojahmat, T. Konakahara and S. Tamura, *Heterocycles*, 2000, **53**, 629.
315 R. R. Amaresh and P. T. Perumal, *Synth. Commun.*, 2000, **30**, 2269.
316 I. Collins and J. L. Castro, *Tetrahedron Lett.*, 1999, **40**, 4069.
317 A. R. Katritzky, A. Denisenko and M. Arend, *J. Org. Chem.*, 1999, **64**, 6076.
318 U. Sharma, S. Ahmed and R. C. Boruah, *Tetrahedron Lett.*, 2000, **41**, 3493.
319 R. C. Boruah, S. Ahmed, U. Sharma and J. S. Sandhu, *J. Org. Chem.*, 2000, **65**, 922.
320 E. M. Brun, S. Gil, R. Mestres and M. Parra, *Synthesis*, 2000, 273.
321 A. W. Fatland and B. E. Eaton, *Org. Lett.*, 2000, **2**, 3131.
322 I. Lenoir and M. L. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2000, 641.
323 S. Cacchi, G. Fabrizi and F. Marinelli, *Synlett*, 1999, 401.
324 A. Arcadi, F. Marinelli and E. Rossi, *Tetrahedron*, 1999, **55**, 13233.
325 M. Suginome, T. Fukuda and Y. Ito, *Org. Lett.*, 1999, **1**, 1977.
326 K. Kobayashi, T. Kitamura, K. Yoneda, O. Morikawa and E. Konishi, *Chem. Lett.*, 2000, 798.
327 K. Kobayashi, J. Yonemori, A. Matsunaga, T. Kitamura, M. Tanmatsu, O. Morikawa and H. Konishi, *Heterocycles*, 2001, **55**, 33.
328 C. S. Cho, B. H. Oh and S. C. Shim, *J. Heterocycl. Chem.*, 1999, **36**, 1175.
329 C. S. Cho, B. H. Oh, J. S. Kim, T. J. Kim and S. C. Shim, *Chem. Commun.*, 2000, 1885.
330 C. S. Cho, B. H. Oh, S. C. Shim and D. H. Oh, *J. Heterocycl. Chem.*, 2000, **37**, 1315.
331 C. S. Cho, J. S. Kim, B. H. Oh, T. J. Kim, S. C. Shim and N. S. Yoon, *Tetrahedron*, 2000, **56**, 7747.
332 H. Tokuyama, M. Sato, T. Ueda and T. Fukuyama, *Heterocycles*, 2001, **54**, 105.
333 M. Matsugi, F. Tabusa and J. Minamikawa, *Tetrahedron Lett.*, 2000, **41**, 8523.
334 Q. F. Wang, Y. Y. Mao, C. Y. Qin, S. Z. Zhu and C. M. Hu, *Monatsh. Chem.*, 2000, **131**, 55.
335 J. Toda, M. Sakagami, Y. Goan, M. Simakata, T. Saitoh, Y. Horiguchi and T. Sano, *Chem. Pharm. Bull.*, 2000, **48**, 1854.
336 H. Fretz, M. Gaugler and J. Schneider, *Helv. Chim. Acta*, 2000, **83**, 1145.
337 J. H. M. Lange, P. C. Verveer, S. J. M. Osnabrug and G. M. Visser, *Tetrahedron Lett.*, 2001, **42**, 1367.
338 M. M. Ali, Tasneem, K. C. Rajanna and P. K. S. Prakash, *Synlett*, 2001, 251.
339 F. Palacios, A. M. O. de Retana and J. Oyarzabal, *Tetrahedron*, 1999, **55**, 5947.
340 C. Mitsos, A. Zografos and O. Igglessi-Markopoulou, *Heterocycles*, 1999, **51**, 1543.
341 Z. Wróbel, *Eur. J. Org. Chem.*, 2000, 521.
342 C. Boix, J. M. de la Fuente and M. Poliakoff, *New J. Chem.*, 1999, **23**, 641.
343 S. Sato, H. Kumagai, S. Matsuba, T. Kumazawa, J. Onodera and M. Suzuki, *J. Heterocycl. Chem.*, 1999, **36**, 1345.
344 S. Sato, T. Watanabe, H. Kumagai, N. Kitamura, S. Matsuba, T. Kumazawa, J. Onodera and M. Suzuki, *J. Heterocycl. Chem.*, 1999, **36**, 1189.
345 J. N. Kim, K. Y. Lee, H. S. Kim and T. Y. Kim, *Org. Lett.*, 2000, **2**, 343.
346 B. Crousse, J. P. Bégué and D. Bonnet-Delpon, *J. Org. Chem.*, 2000, **65**, 5009.
347 M. J. Wu, L. J. Chang, L. M. Wei and C. F. Lin, *Tetrahedron*, 1999, **55**, 13193.
348 L. M. Wei, C. F. Lin and M. J. Wu, *Tetrahedron Lett.*, 2000, **41**, 1215.
349 J. D. Tovar and T. M. Swager, *J. Org. Chem.*, 1999, **64**, 6499.
350 M. J. Wu, C. F. Lin, S. H. Chen and F. C. Lee, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2875.
351 R. Kucznierz, J. Dickhaut, H. Leinert and W. von der Saal, *Synth. Commun.*, 1999, **29**, 1617.
352 J. Hiebl, H. Kollmann, S. H. Levinson, P. Offen, S. B. Shetzline and R. Badlani, *Tetrahedron Lett.*, 1999, **40**, 7935.
353 M. A. A. Meziane, S. Royer and J. P. Bazureau, *Tetrahedron Lett.*, 2001, **42**, 1017.
354 A. L. Wang, H. M. Zhang and E. R. Biehl, *Heterocycles*, 2000, **53**, 291.
355 S. Tandel and E. R. Biehl, *Heterocycles*, 2000, **53**, 1183.
356 D. J. Li, B. P. Zhao and E. J. LaVoie, *J. Org. Chem.*, 2000, **65**, 2802.
357 R. M. Adlington, J. E. Baldwin, D. Catterick and G. J. Pritchard, *J. Chem. Soc., Perkin Trans. 1*, 1999, 855.
358 R. M. Adlington, J. E. Baldwin, G. J. Pritchard and K. C. Spencer, *Tetrahedron Lett.*, 2000, **41**, 575.
359 J. A. McCauley, C. R. Theberge and N. J. Liverton, *Org. Lett.*, 2000, **2**, 3389.
360 C. Agami, L. Dechoux, L. Hamon and M. Melaimi, *J. Org. Chem.*, 2000, **65**, 6666.
361 C. Agami, L. Dechoux and M. Melaimi, *Org. Lett.*, 2000, **2**, 633.
362 K. Funabiki, H. Nakamura, M. Matsui and K. Shibata, *Synlett*, 1999, 756.
363 M. Soufyane, S. van den Broek, L. Khamliche and C. Mirand, *Heterocycles*, 1999, **51**, 2445.
364 J. A. Ragan, R. E. McDermott, B. P. Jones, D. J. A. Ende, P. J. Clifford, S. J. McHardy, S. D. Heck, S. Liras and B. E. Segelstein, *Synlett*, 2000, 1172.
365 E. Rossi, G. Abbiati and E. Pini, *Synlett*, 1999, 1265.

366 C. Landreau, D. Deniaud, A. Reliquet, F. Reliquet and J. C. Meslin, *J. Heterocycl. Chem.*, 2001, **38**, 93.
367 Q. Dang, Y. Liu and M. D. Erion, *J. Am. Chem. Soc.*, 1999, **121**, 5833.
368 S. P. Keen and S. M. Weinreb, *Tetrahedron Lett.*, 2000, **41**, 4307.
369 M. T. Chhabria and C. J. Shishoo, *Heterocycles*, 1999, **51**, 2723.
370 A. G. Martínez, A. H. Fernández, R. M. Álvarez, M. D. M. Vilchez, M. L. L. Gutierrez and L. R. Subramanian, *Tetrahedron*, 1999, **55**, 4825.
371 I. Helland and T. Lejon, *Heterocycles*, 1999, **51**, 611.
372 J. A. Seijas, M. P. Vázquez-Tato and M. M. Martinez, *Tetrahedron Lett.*, 2000, **41**, 2215.
373 W. Szczepankiewicz, J. Suwinski and R. Bujok, *Tetrahedron*, 2000, **56**, 9343.
374 L. J. Wilson, *Org. Lett.*, 2001, **3**, 585.
375 T. Mizuno, N. Okamoto, T. Ito and T. Miyata, *Tetrahedron Lett.*, 2000, **41**, 1051.
376 C. Larksarp and H. Alper, *J. Org. Chem.*, 2000, **65**, 2773.
377 J. Wuckelt, M. Doring, R. Beckert and P. Langer, *Synlett*, 1999, 1100.
378 W. Zielinski and A. Kudelko, *Monatsh. Chem.*, 2000, **131**, 895.
379 M. W. Ding, G. P. Zeng and T. J. Wu, *Synth. Commun.*, 2000, **30**, 1599.
380 M. Gruner, M. Rehwald, K. Eckert and K. Gewald, *Heterocycles*, 2000, **53**, 2363.
381 H. Kotsuki, H. Sakai, H. Morimoto and H. Suenaga, *Synlett*, 1999, 1993.
382 M. Kaname, T. Tsuchiya and H. Sashida, *Heterocycles*, 1999, **51**, 2407.
383 R. M. Adlington, J. E. Baldwin, D. Catterick and G. J. Pritchard, *J. Chem. Soc., Perkin Trans. 1*, 2000, 299.
384 P. Darkins, M. Groarke, M. A. McKervey, H. M. Moncrieff, N. McCarthy and M. Nieuwenhuyzen, *J. Chem. Soc., Perkin Trans. 1*, 2000, 381.
385 S. Ito, A. Kakehi and K. Okada, *Heterocycles*, 1999, **51**, 2949.
386 Y. Kamitori, *Heterocycles*, 2000, **53**, 1065.
387 Y. Kamitori, *Tetrahedron Lett.*, 2000, **41**, 9267.
388 A. S. Kiselyov and C. Dominguez, *Tetrahedron Lett.*, 1999, **40**, 5111.
389 S. Bräse, S. Dahmen and J. Heuts, *Tetrahedron Lett.*, 1999, **40**, 6201.
390 D. B. Kimball, A. G. Hayes and M. M. Haley, *Org. Lett.*, 2000, **2**, 3825.
391 R. Mukhopadhyay and N. G. Kundu, *Tetrahedron Lett.*, 2000, **41**, 9927.
392 N. P. Xekoukoulotakis, C. P. Hadjiantoniou-Maroulis and A. J. Maroulis, *Tetrahedron Lett.*, 2000, **41**, 10299.
393 A. Guirado, A. Cerezo and R. Andreu, *Tetrahedron Lett.*, 2000, **41**, 6579.
394 A. E. Frumkin, A. M. Churakov, Y. A. Strelenko, V. V. Kachala and V. A. Tartakovsky, *Org. Lett.*, 1999, **1**, 721.