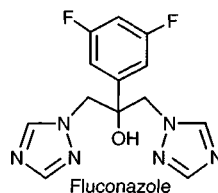
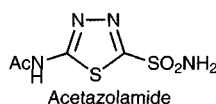
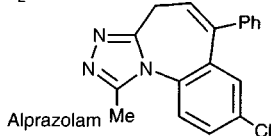
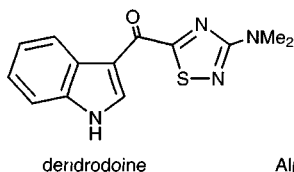


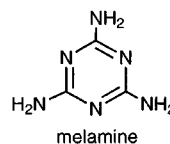
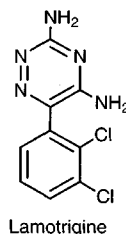
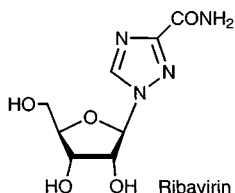
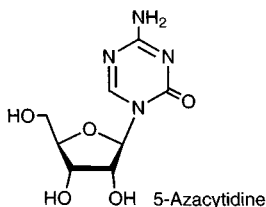
26 Heterocycles containing more than two hetero atoms

In systems which contain more than two hetero atoms in the same ring we find the trends in properties, which this book has described, taken to further extremes. In particular, the additional hetero atoms, in both six- and five-membered systems, lead to a suppression of electrophilic substitution and a slowing of electrophilic addition to nitrogen. On the other hand, further increases in tendencies for nucleophilic substitution and addition, and in the five-membered compounds, further increases in acidities of *N*-hydrogen are found.

Multihetero atom heterocycles are comparatively rare in nature, dendrodoine, a cytotoxic substance from a marine tunicate, is an example, however in medicinal chemistry they are of considerable significance: Alprazolam is a major drug for the treatment of anxiety, Acetazolamide is an inhibitor of the enzyme carbonic anhydrase and is used principally for the treatment of glaucoma, and Fluconazole, is an antifungal agent.



Analogues of the pyrimidine nucleosides have been extensively studied: 5-Azacytidine is antileukemic and Ribavirin, an antiviral agent, is used in the treatment of lung infections in infants. Lamotrigine is used for the treatment of epilepsy. Melamine, which on condensation with formaldehyde produces the melamine resins well known in kitchen utensils, is an important industrial intermediate.



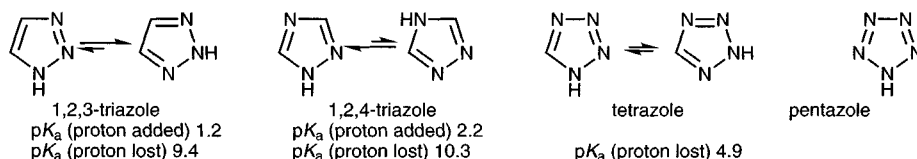
26.1 Five-membered rings

26.1.1 Azoles¹

The triazoles are numbered to indicate the relative positions of the nitrogen atoms, tetrazole and pentazole are unambiguous names. 1,2,3-Triazoles are surprisingly stable, when one considers that they contain three directly-linked nitrogen atoms, but on flash vacuum pyrolysis at 500°C they do lose nitrogen to give 2*H*-azirines,

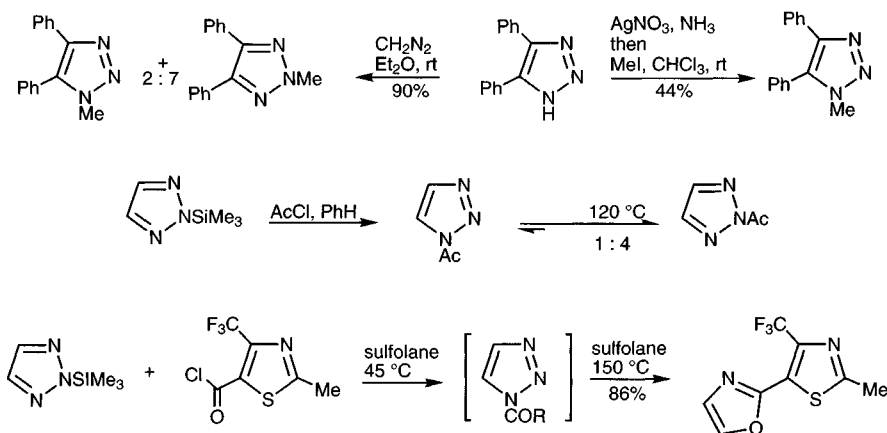
probably *via* the 1*H*-isomer.² Benzotriazole is similarly relatively stable and has been distilled *in vacuo* at 200 °C, though explosions have been reported during this process. Simple tetrazoles are also relatively stable, but the pentazole ring system is only known in a few aryl derivatives which generally decompose (possibly explosively) at or below room temperature.³

The additional hetero atoms make these systems less basic but more acidic than comparable 1,2- and 1,3-azoles. Each is subject to the same kind of tautomerism as discussed for the 1,2- and 1,3-azoles (section 21.1.1.1), in which the tautomers are equivalent (not shown) but also, in these systems, to tautomerism which generates different arrangements.

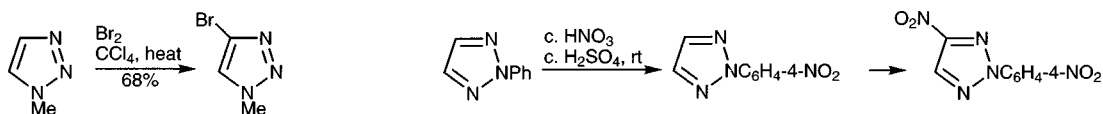


26.1.1.1 1,2,3-Triazole⁴

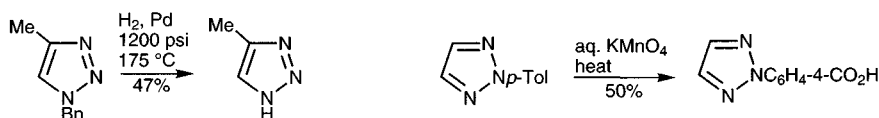
1,2,3-Triazole is fairly resistant to *N*-alkylation under neutral conditions however both acylations and alkylations involving *N*-anions occur readily, but mixtures of 1- and 2-substituted products are often obtained.^{1,5} Trimethylsilylation produces 2-trimethylsilyl-1,2,3-triazole and this can be alkylated at N-1 to produce 1-alkylated compounds following loss of silicon.⁶ An equilibrium mixture of *N*-acetyl-1,2,3-triazoles contains predominantly the 2-acetyl-isomer,⁷ as in the parent: this may reflect unfavourable *ortho* lone-pair/lone-pair interactions in the 1-isomer and is in agreement with calculations which suggest that the 2*H*-isomer is more aromatic.⁸ Heating in sulfolane at 150 °C converts the *N*-acyl compounds into oxazoles in a synthetically useful transformation.⁹



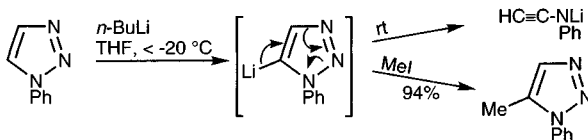
1-Methyl-1,2,3-triazole can be brominated at C-4, but the 2-methyl isomer is less reactive, requiring the use of an iron catalyst;¹⁰ the lower reactivity of the latter is probably related to the presence of two imine units. 1,2,3-Triazole itself forms a 4,5-dibromo derivative in high yield with bromine at 50 °C.¹¹ Nitration of 2-phenyl-1,2,3-triazole proceeds first on the benzene ring, but then does bring about hetero-ring substitution.¹²



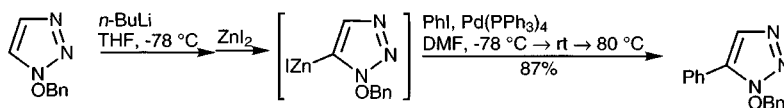
The ring system is relatively resistant to both oxidation and reduction as exemplified below.¹³



N-Substituted 1,2,3-triazoles can be lithiated directly at carbon, but low temperatures must be maintained to avoid ring cleavage by cycloreversion.^{14,15}



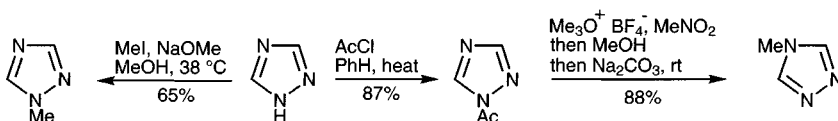
Metal exchange of 5-lithio-1-benzyloxy-1,2,3-triazole with zinc iodide gives a relatively stable zinc derivative which can be used in palladium-catalysed couplings. The corresponding tin compound is less stable and can be used only for palladium-catalysed acylations.¹⁶



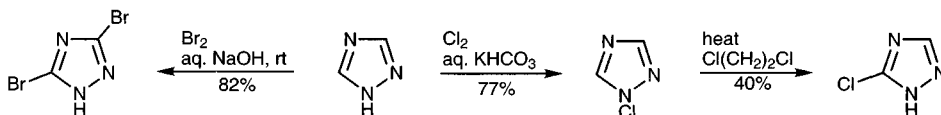
Both 4,5-dibromo-1-methoxymethyl- and 4,5-dibromo-2-methoxymethyl-1,2,3-triazole form 5-lithio compounds by exchange with *n*-butyllithium at -80°C .¹¹

26.1.1.2 1,2,4-Triazole¹⁷

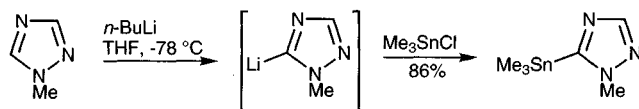
Alkylations and acylations generally occur at N-1, reflecting the higher nucleophilicity of N–N systems (cf. section 11.1.1.2), however 4-alkyl derivatives can be prepared *via* quaternisation of 1-acetyl-1,2,4-triazole¹⁸ or the acrylonitrile or crotononitrile adducts¹⁹ (Note that N-1 and N-2 are equivalent until substitution occurs).



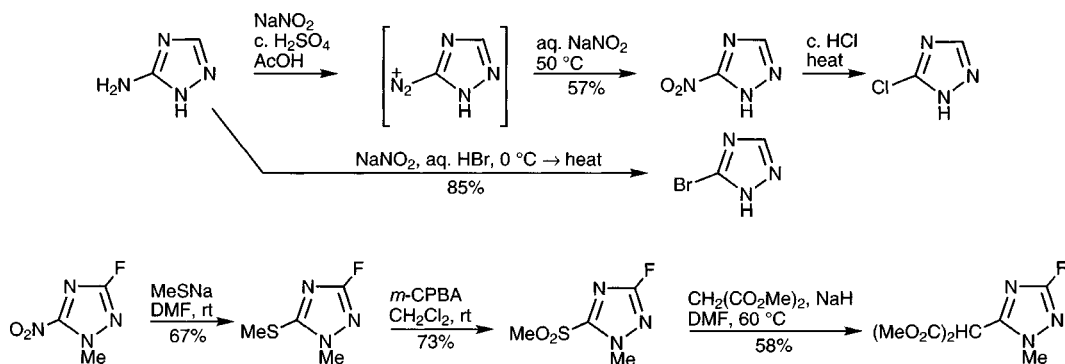
Bromination occurs readily in alkaline solution giving 3,5-dibromo-1,2,4-triazole;²⁰ the 3-monochloro-derivative can be obtained by thermal rearrangement of the *N*-chloro isomer;²¹ an analogous $\text{N} \rightarrow \text{C}$ 1,5-sigmatropic shift converts the 1- into the 3-nitro-compound.²²



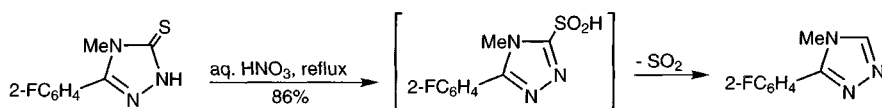
C-Lithiations can be easily effected on *N*-1-protected 1,2,4-triazoles, the resulting 5-lithio-derivatives being much more stable than lithiated-1,2,3-triazoles.²³



3-Amino-1,2,4-triazole can be diazotised normally: the resulting diazonium salt has been used for the production of azo dyes, and also loses nitrogen with easy replacement by nucleophiles. The bromo- and nitrotriazoles which can be thus prepared are themselves substrates for nucleophilic displacement reactions.^{18,24} 5-Bromo and 5-nitro²⁵ groups are good leaving groups in 1-alkyl-1,2,4-triazoles for hetero nucleophiles; for carbon nucleophiles, methanesulfonate is a better leaving group.²⁶



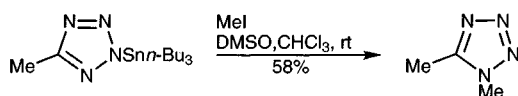
The oxidative desulfurisation of 1,2,3-triazole thiones using nitric acid is a type of reaction common to other electron-deficient nitrogen heterocycles. The process involves loss of sulfur dioxide from an intermediate sulfinic acid.²⁷

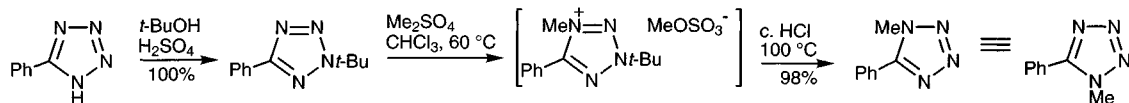


26.1.1.3 Tetrazole²⁸

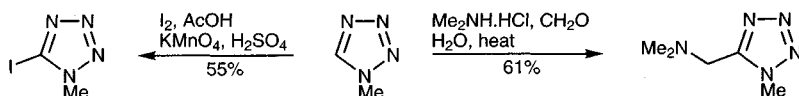
Noting the similarity of tetrazole pK_a s to those of carboxylic acids, tetrazoles have often been used as bioequivalent replacements for CO_2H in pharmacologically active compounds. Tetrazole and its alkyl and aryl derivatives generally begin significant decomposition at about 180 °C and the chloro and alkylthio derivatives at somewhat lower temperatures; 5-nitrotetrazole explodes unpredictably on storage.²⁹

Tetrazoles alkylate and acylate on *N*-1 or *N*-2 depending on substituents at *C*-5, however selective 1-alkylations by quaternisation of 2-tri-*n*-butylstannyl and 2-*t*-butyl derivatives is possible.³⁰ Unfortunately, in the latter case the quaternisation fails with alkyl halides and requires alkyl sulfates or more powerful alkylating agents.³¹

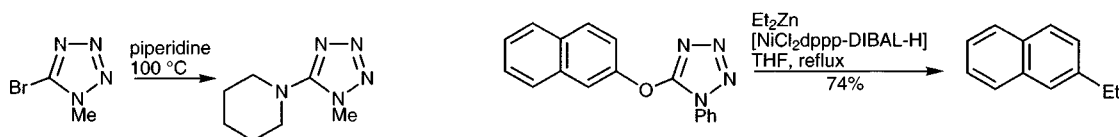




Remarkably, some *C*-electrophilic substitutions such as bromination,³² mercuration³³ and even Mannich reactions³⁴ (but not nitration) can be achieved, though the mechanisms for these substitutions may not be of the conventional type.

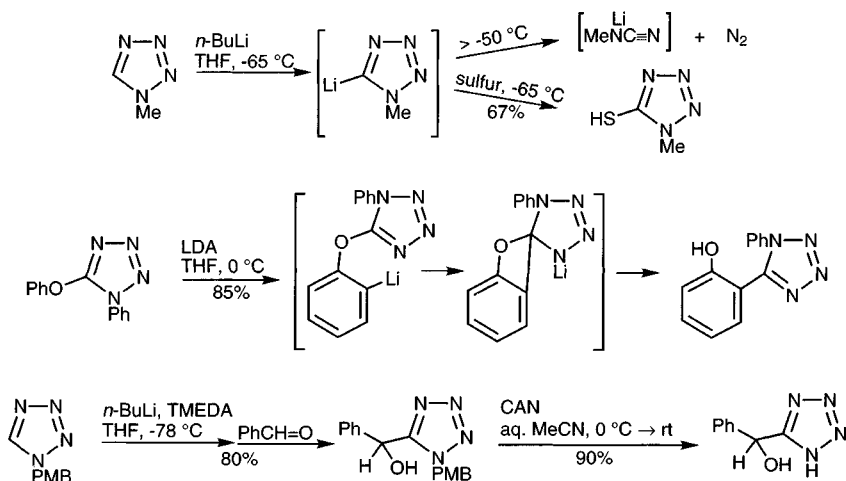


As would be expected from inductive effects, 5-bromo-1-methyltetrazole is more reactive in nucleophilic substitution than are the corresponding halo-1,2,4- and -1,2,3-triazoles, which in turn are more reactive than the corresponding haloimidazoles. 5-Bromo-2-methyltetrazole is significantly less reactive than its 1-methyl isomer due to less effective delocalisation of the negative charge in the intermediate adduct.³⁵



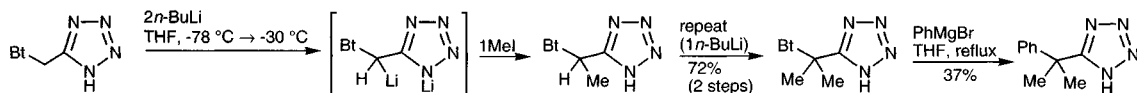
5-Tetrazolyl ethers can be used in two ways: to activate phenols for nickel- or palladium-catalysed coupling reactions, as illustrated above or to allow catalytic hydrogenolysis of the C–O bond of the phenol.³⁶

C-Lithiation occurs readily and the resulting lithio-derivatives can be trapped with electrophiles, despite a strong tendency for cycloreversion. Tetrazole can also act as an *ortho*-directing group, as in the lithiation of 5-phenyltetrazole.^{37,38} A tetrazolyl ether similarly directs *ortho*-metallation but here, the tetrazole migrates from the oxygen to the lithiated carbon.³⁹ *para*-Methoxybenzyl is a useful nitrogen protecting group for lithiations and it can be removed finally by hydrogenation, or oxidation as shown.⁴⁰

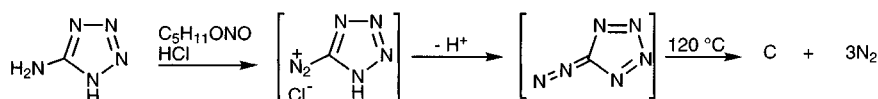


5-Alkyl groups in 1-substituted tetrazoles can be lithiated but in a 5-alkyl-2-methyltetrazole it is the *N*-methyl which is metallated⁴¹ but 5-methyl-2-trityltetrazole

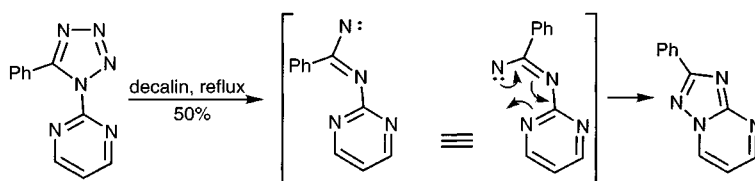
lithiates normally at the side chain methyl.⁴² The methylene group in 5-(benzotriazolylmethyl)tetrazole is sufficiently activated that *N*-protection is unnecessary – the benzotriazole can then act as a leaving group for displacement by Grignard reagents as shown below.⁴³



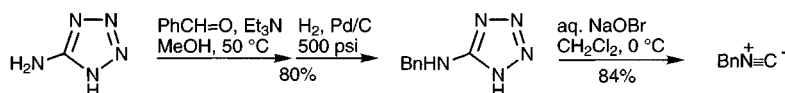
5-Aminotetrazole gives a diazonium salt (with the formula $\text{CN}_6\cdot\text{HCl}$!) (**CAUTION: EXPLOSIVE**) which has been used to generate atomic carbon!⁴⁴ 1-Substituted-5-aminotetrazoles seem to give relatively stable *N*-nitroso derivatives.



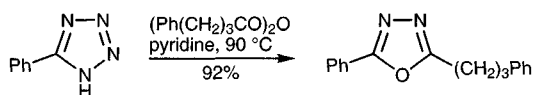
Flash vacuum pyrolysis of 5-aryltetrazoles generates aryl carbenes⁴⁵ but heating the pyrimidinyl phenyltetrazole shown below in refluxing decalin (180 °C) results in the formation of an intermediate nitrene which then cyclises onto the pyrimidine nitrogen.⁴⁶



Hypobromite oxidation of 5-benzylaminotetrazoles provides a useful synthesis of benzyl isonitriles, as illustrated below.⁴⁷



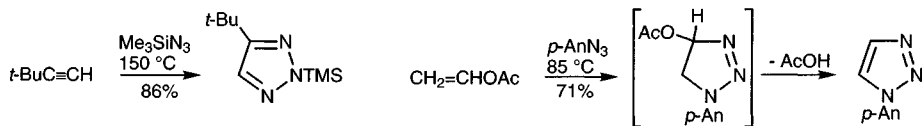
1,3,4-Oxadiazoles are formed on heating tetrazoles with acylating agents, via rearrangement of a first-formed 2-acyl derivatives.⁴⁸



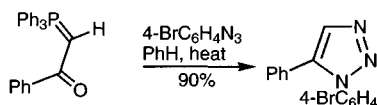
26.1.1.4 Ring synthesis of azoles

1,2,3-Triazoles

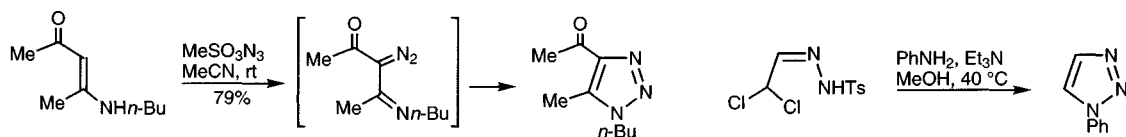
1,2,3-Triazoles are generally prepared by the cycloaddition of an alkyne with an azide, but the hazardous nature of some alkyl azides limits the method in these cases. A convenient synthesis which leads to *N*-hydrogen 1,2,3-triazoles utilises the stable (and relatively safe) trimethylsilyl azide.⁴⁹ For *C*-unsubstituted 1,2,3-triazoles, ethyne itself would be required but it is much more convenient to use, as starting material, vinyl acetate instead of the gaseous ethyne, or in general, an enamine or an enol ether as alkyne equivalents.^{50,51}



The condensation of azides with acyl-Wittig reagents offers a regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles.⁵²

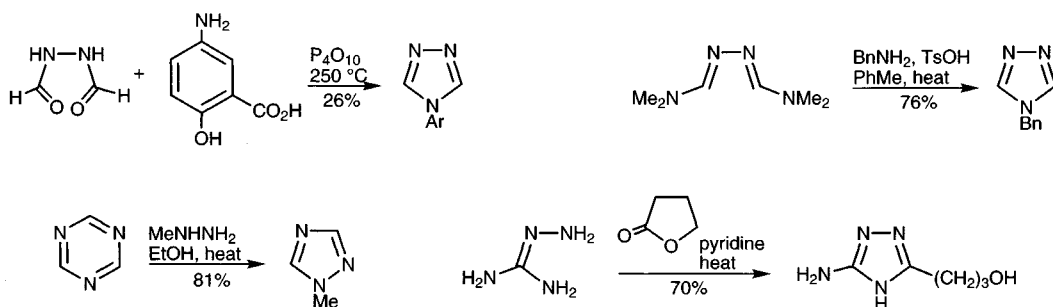


Other useful syntheses of 1,2,3-triazoles include diazo-transfer to enamino-ketones from either sulfonyl azides⁵³ (or 3-diazo-oxindole),⁵⁴ and reaction of dichloroacetaldehyde tosylhydrazone with amines and each of these is illustrated below.⁵⁵



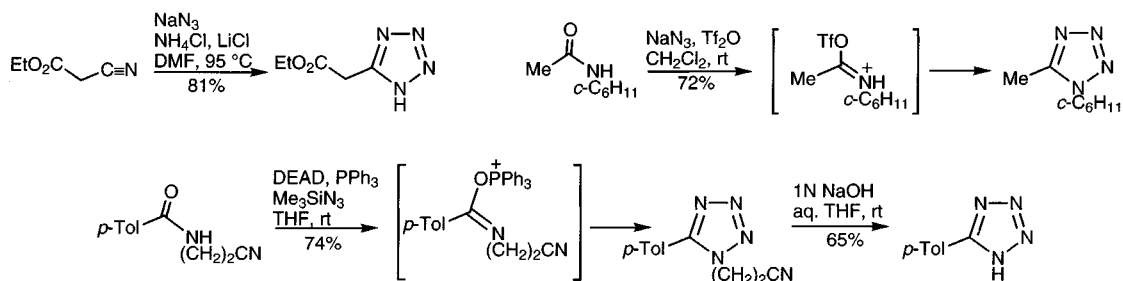
1,2,4-Triazoles

1,2,4-Triazoles are available *via* cyclodehydration reactions of *N,N'*-diacylhydrazine with amines, although the conditions are often quite vigorous.⁵⁶ An interesting variant utilises *sym*-triazine (1,3,5-triazine) as an equivalent of $\text{HN}(\text{CHO})_2$.⁵⁷ Condensations of aminoguanidine with esters give the versatile 3-amino compounds.⁵⁸

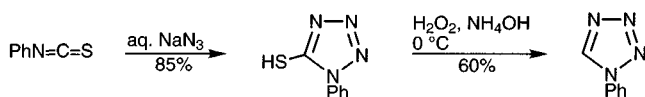


Tetrazoles

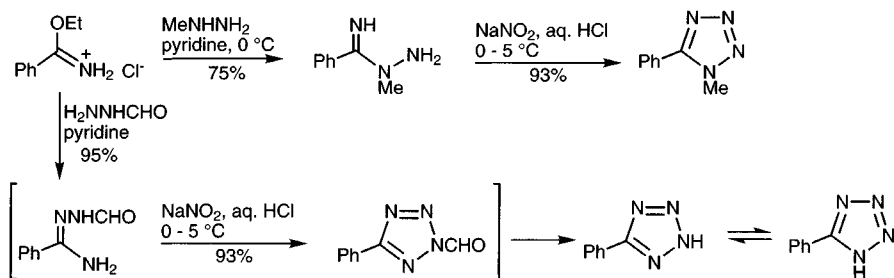
Tetrazoles are usually prepared by the reaction of an azide with a nitrile, or an activated amide; tri-*n*-butyltin azide and trimethylsilyl azide are more convenient and safer reagents than azide anion in some cases. The second example shown illustrates the use of a cyanoethyl group as a removable protecting group for amide nitrogen.⁵⁹ Other variations on this method from nitriles include the use of triethylammonium chloride (instead of ammonium chloride) to avoid the possible sublimation of potentially explosive azides,⁶⁰ and the use of micelles as reaction media.⁶¹ Amides can be activated with trifluoromethanesulfonic anhydride,⁶² or via formation of the thioamide,⁶³ or by the use of triphenylphosphine with diethyl azodicarboxylate; the equivalent imidochloride will react under phase transfer conditions.⁶⁴



Related methods can be used to prepare 5-hetero-substituted compounds: isonitriles with *N*-halosuccinimides and azide give halo derivatives,⁶⁵ aryl isothiocyanates with azide give the arylthio compounds⁶⁶ and isothiocyanates give thiols, as illustrated. The thiols can be converted into 5-unsubstituted tetrazoles by oxidation with hydrogen peroxide⁶⁷ or chromium trioxide.⁶⁸

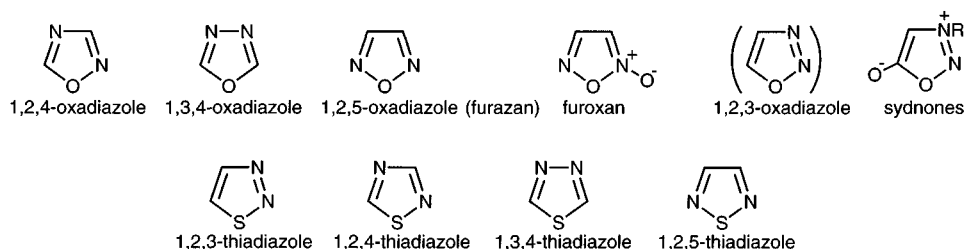


Nitrosation of amidrazones is a method which avoids the use of azide and also offers a regiospecific synthesis of 1- or 2-substituted compounds.⁶⁹



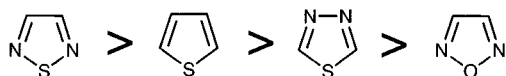
26.1.2 Oxadiazoles and thiadiazoles

Only one divalent hetero atom can be incorporated into a simple five-membered, aromatic heterocycle. These systems are named with the non-nitrogen atom numbered as 1, and the positions of the nitrogen atoms shown with reference to the divalent atom.

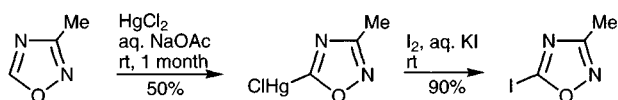


1,2,4-Oxadiazoles,⁷⁰ 1,3,4-oxadiazoles,⁷¹ and 1,2,5-oxadiazoles are well known, but the 1,2,3-oxadiazole system, which calculations indicate to be unstable relative to its ring-open diazoketone tautomer,⁷² is known only as a benzo-fused derivative (in solution) and in mesoionic substances, known as 'sydnones',⁷³ which have been well investigated. 'Furoxans',⁷⁴ which are formed by the dimerisation of nitrile oxides,

have also been extensively studied. 1,2,3-Thiadiazoles, 1,2,4-thiadiazoles,⁷⁵ 1,3,4-thiadiazoles,⁷⁶ and 1,2,5-thiadiazoles⁷⁷ are all represented by well characterised compounds. Estimates of aromaticity, based on bonds lengths and NMR data produced the following relative order.⁷⁸

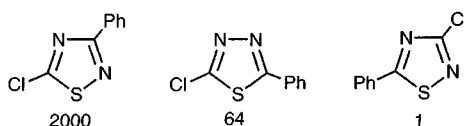


As with the azoles, oxa- and thiadiazoles are very weak bases due to the inductive effects of the extra hetero atoms, although *N*-quaternisation reactions can be carried out. For similar reasons, electrophilic substitutions on carbon are practically unknown, apart from a few halogenations and mercurations⁷⁹ – it is an intriguing paradox that mercurations, with what is generally thought of as a weak electrophile, are often successful in electron-poor heterocycles. Another important difference from the azoles is of course the absence of *N*-hydrogen, so that *N*-anion-mediated reactions are not possible.

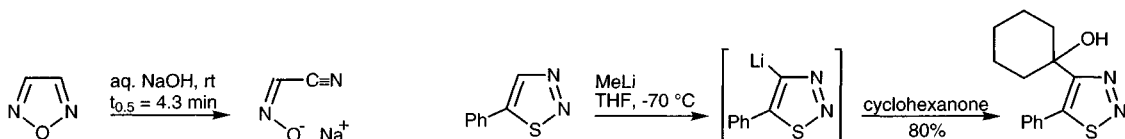


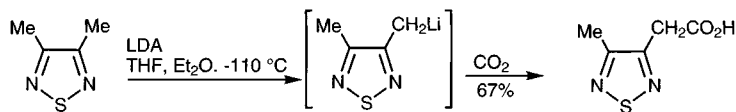
All these systems are susceptible to nucleophilic attack, particularly the oxadiazoles, which often undergo ring cleavage with aqueous acid or base unless both (carbon) positions are substituted. Similarly, leaving groups are generally displaced easily; there is substantial differential positional reactivity: in both 1,2,4-oxa- and -thiadiazoles a 5-chlorine is displaced much more easily than a 3-chlorine, no doubt due to the more effective stabilisation of the intermediate anionic adduct in the former situation. There is a far from complete set of comparisons of relative reactivities, but some data are available.⁸⁰

Relative rates of reaction with piperidine in ethanol



Base-catalysed proton exchange occurs readily, but decomposition *via* cycloreversion or β -elimination in the anion often competes.⁸¹ Direct lithiations at carbon are generally easy,⁸² but the resulting lithio derivatives vary greatly in stability, some being of no use synthetically.⁸³ Hydrogens on side-chain alkyl groups are 'acidified' by delocalisation of the charge in the deprotonated species onto ring nitrogens. There is an interesting difference between 1,2,5-oxa- and 1,2,5-thiadiazoles in this context: in the former, smooth metallation of a 3-methyl occurs with *n*-butyllithium, but for the latter, lithium diisopropylamide must be used to avoid competing nucleophilic addition to the sulfur, leading then to ring decomposition.⁸⁴

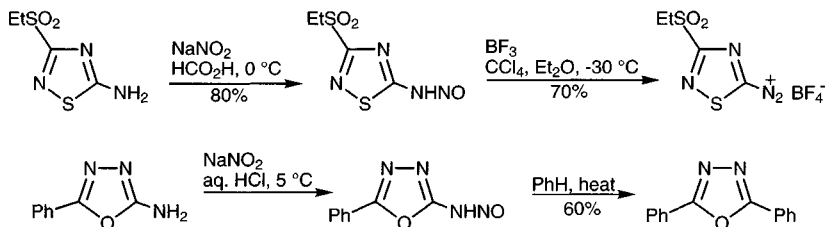




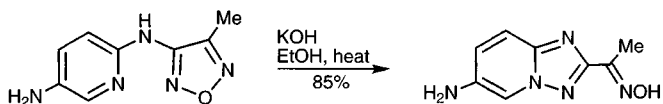
4-Substituted 5-chloro-1,2,3-thiadiazoles react with simple hetero nucleophiles by displacement of the chlorine, but reaction with aryl- and alkylolithiums gives alkynyl thioethers via attack at sulfur and then ring cleavage with loss of nitrogen. A similar ring cleavage occurs, but by a different mechanism, when the 5-unsubstituted analogue is treated with base.⁸⁵



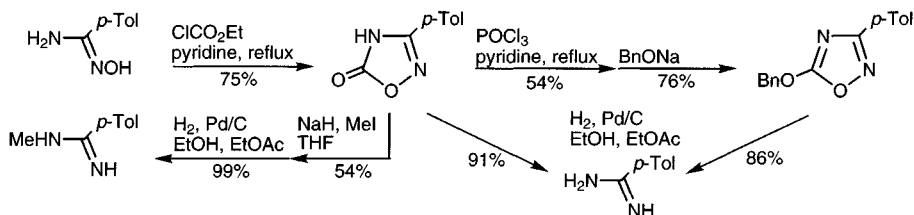
Generally, amines can be diazotised and converted, for example, into halides, but in some cases the intermediate, *N*-nitroso compound is stable, and only then subsequently converted into a diazonium salt by treatment with strong acid – this may reflect the lower stability of a positively charged group attached to an electron-deficient ring.⁸⁶



An interesting and fairly general type of reaction in ring systems such as these is ring interconversion *via* intramolecular attack on nitrogen.⁸⁷



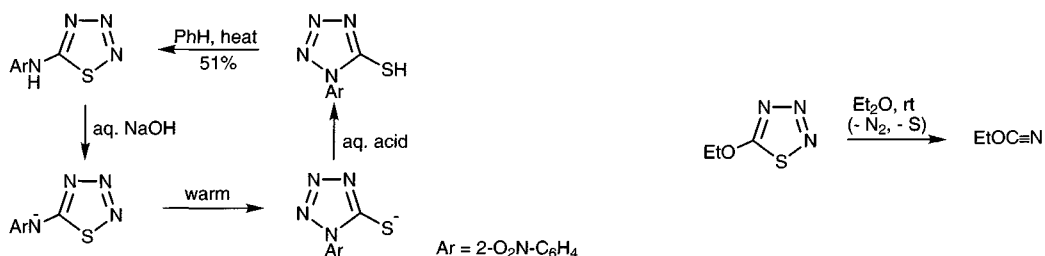
1,2,4-Oxadiazoles are useful as masked amidines where such strongly basic groups would be incompatible with reaction conditions – the amidine is easily liberated by hydrogenation, as illustrated below.⁸⁸



26.1.3 Other systems

Of the higher aza-compounds, only derivatives of 1,2,3,4-thiadiazole⁸⁹ are well defined, but even here alkyl derivatives decompose at or below 0 °C, though 5-aryl- and amino derivatives are generally fairly stable. Many other derivatives are,

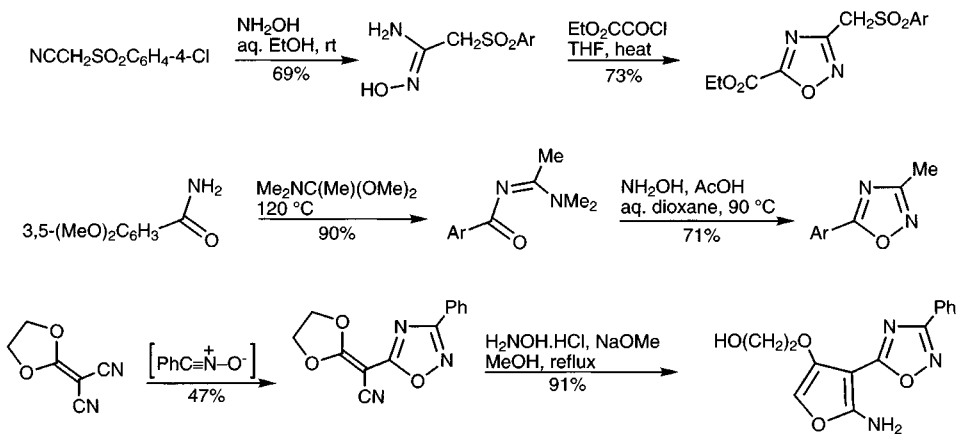
however, dangerously explosive, for example the 5-chloro and thiolate derivatives. The controlled decomposition of 5-alkoxy-1,2,3,4-thiatriazoles (for example the 5-ethoxy-derivative in ether at 20 °C) has been recommended as the best preparation of pure alkyl cyanates; thermal decomposition of 5-aryl compounds gives the corresponding nitrile.⁹⁰ An interesting isomerisation cycle interconverts aminothia-triazoles and tetrazole thiols.⁹¹



26.1.4 Ring synthesis

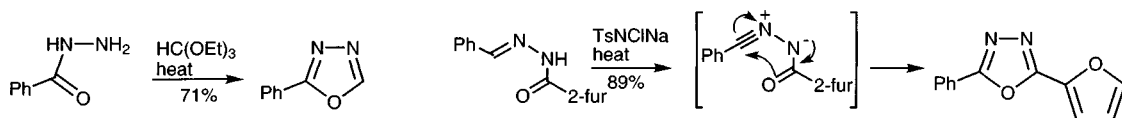
26.1.4.1 1,2,4-Oxadiazoles

1,2,4-Oxadiazoles can be prepared by acylation of amidoximes.⁹² A variation of this method gives a one-pot synthesis from the amidoxime, an organic acid and a peptide coupling agent; the method is sufficiently mild that there is no racemisation when mandelic acid is used.⁹³ 1,2,4-Oxadiazoles can also be prepared from amides *via* acylamidines,⁹⁴ or *via* the cycloaddition of nitrile oxides to nitriles, as illustrated, or to *O*-methyl oximes.⁹⁵



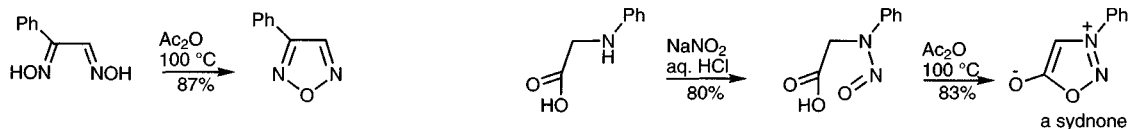
26.1.4.2 1,3,4-Oxadiazoles

1,3,4-Oxadiazoles are available by cyclodehydration of *N,N'*-diacylhydrazines or their equivalents.⁹⁶ They are also available from tetrazoles (section 26.1.1.3) or by oxidative cyclisation of acyl hydrazones.⁹⁷



26.1.4.3 1,2,5-Oxadiazoles

1,2,5-Oxadiazoles result from the dehydration of 1,2-bisoximes.

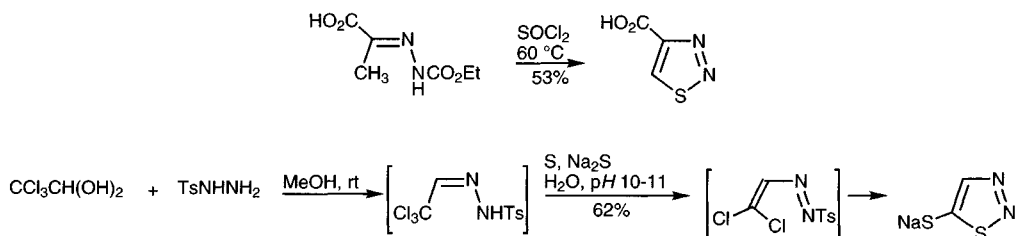


26.1.4.4 Sydnone

Sydnone is normally prepared by the dehydration of *N*-nitroso α -amino acids.⁹⁸

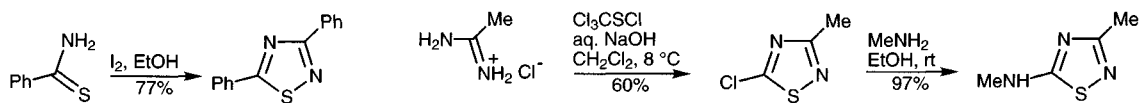
26.1.4.5 1,2,3-Thiadiazoles

1,2,3-Thiadiazoles are prepared by reaction of a hydrazone, containing an acidic methylene group, with thionyl chloride.⁹⁹ The 5-thiol can be prepared by reaction of chloral tosylhydrazone with polysulfide, as indicated below.¹⁰⁰



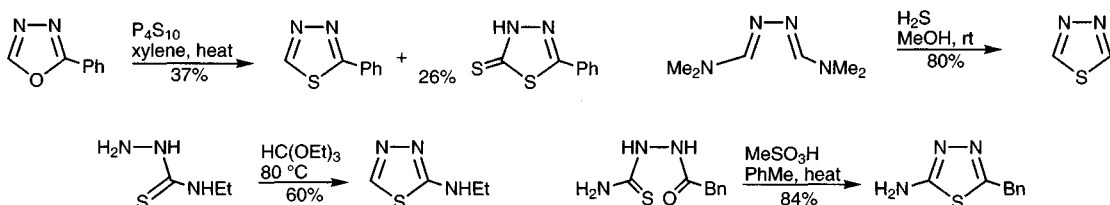
26.1.4.6 1,2,4-Thiadiazoles

1,2,4-Thiadiazoles carrying identical groups at the 3- and 5-positions are obtained by the oxidation of thioamides;¹⁰¹ 5-chloro-1,2,4-thiadiazoles result from the reaction of amidines with perchloromethyl mercaptan.¹⁰²



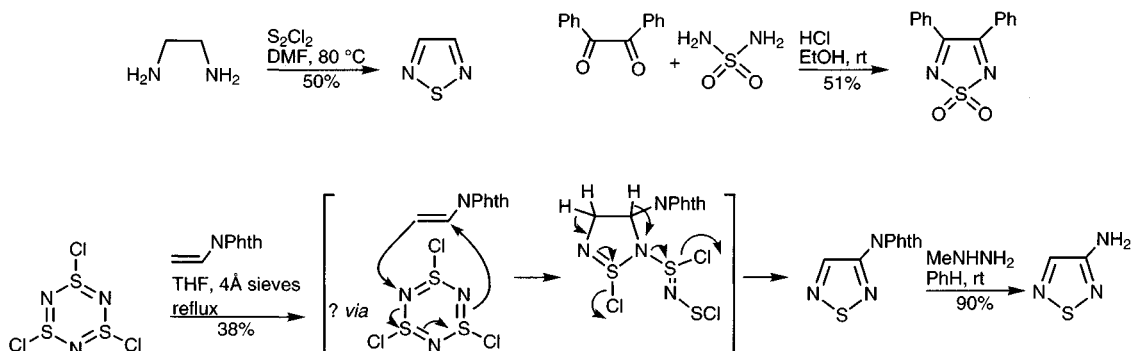
26.1.4.7 1,3,4-Thiadiazoles

1,3,4-Thiadiazoles are available by a number of convenient general routes including cyclisation of *N,N'*-diacylhydrazines, or 1,3,4-oxadiazoles, with phosphorus sulfides.¹⁰³ 3-Amino-1,3,4-thiadiazoles are prepared *via* acylation of thiosemicarbazides¹⁰⁴ and the parent compound is easily obtained from hydrogen sulfide and dimethylformamide azine.¹⁰⁵



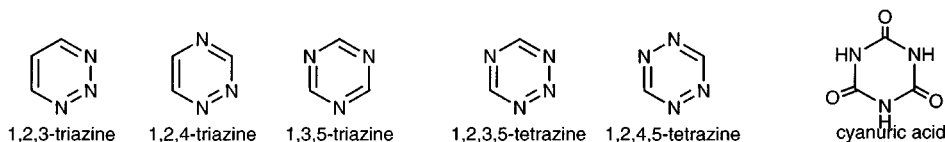
26.1.4.8 1,2,5-Thiadiazoles

1,2,5-Thiadiazoles can be prepared by the oxidative cyclisation of 1,2-diamines or aminocarboxamides.¹⁰⁶ Condensation of sulfamide ($\text{SO}_2(\text{NH}_2)_2$) with 1,2-diketones gives 1,2,5-thiadiazole 1,1-dioxides.¹⁰⁷ A good general method is the reaction of trithiazyl trichloride with activated alkenes and alkynes; this method is also useful for the fusion of a 1,2,5-thiadiazole onto other heterocycles such as pyrroles. The main drawback is that the reagent is not commercially available. The reaction possibly proceeds via cycloaddition to an N-S-N unit in the trithiazine ring.¹⁰⁸



26.2 Six-membered rings

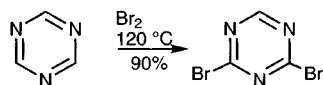
26.2.1 Azines



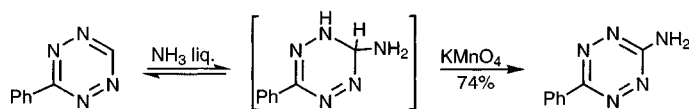
Neutral six-membered aromatic heterocycles cannot contain a divalent heteroatom. The azines are numbered to indicate the relative positions of the nitrogen atoms. 1,2,3,4-Tetrazine, pentazine and hexazine are unknown. Of the other systems, very little information is available on 1,2,3,5-tetrazine but on the other hand, derivatives of 1,3,5-triazazine are very well known and available in large quantities, indeed they are amongst the oldest known heterocycles: the trioxo-compound ('cyanuric acid') was first prepared in 1776 by Scheele by the pyrolysis of uric acid.

The thermal stabilities of the parent systems vary from 1,2,3-triazine, which decomposes at about 200 °C, to 1,3,5-triazazine, which is stable to over 600 °C – at this temperature it decomposes to give hydrogen cyanide, of which it is formally a trimer.

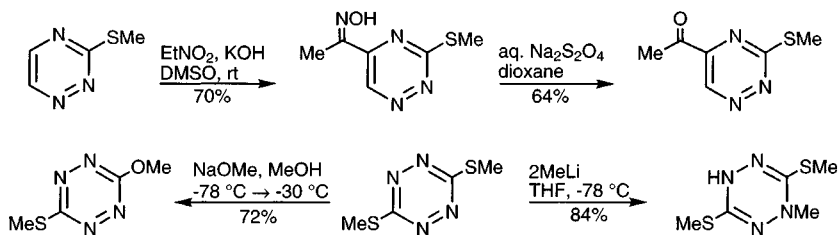
In comparison with the diazines, the inductive effects of the 'extra' nitrogen(s) lead to an even greater susceptibility to nucleophilic attack and as a result, all the parent systems and many derivatives react with water, in acidic or basic solution. Similarly, simple electrophilic substitutions do not occur; some apparent electrophilic substitutions, such as the bromination of 1,3,5-triazazine probably take place *via* bromide nucleophilic addition to an $\text{N}^+ - \text{Br}$ salt.¹⁰⁹ Attempted direct *N*-oxidation of simple tetrazines with the usual reagents generally results in ring cleavage however it can be achieved satisfactorily with methyl(trifluoromethyl)dioxirane.¹¹⁰



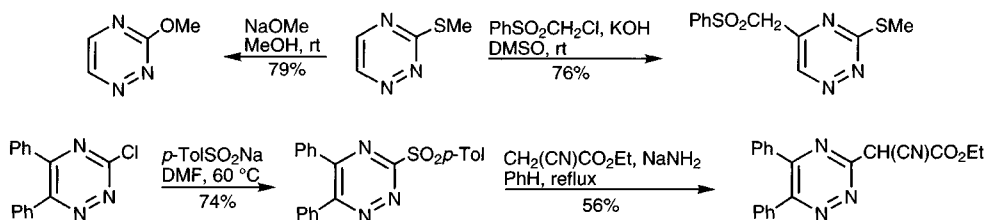
The examples shown below are illustrative of the many easy nucleophilic additions to the polyaza-azines: The reaction of 1,2,4,5-tetrazine with simple amines¹¹¹ can be contrasted with the requirement for sodamide (Chichibabin reaction) for the diazines and pyridine.



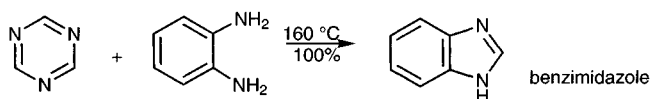
The easy addition at C-5 of 1,2,4-triazines¹¹² is shown by the VNS (section 2.3.3) reaction of the 3-methylthio-derivatives in the absence of activating groups; a closely related addition of nitroalkanes represents a very useful nucleophilic acylation.¹¹³ The ready displacement of methylthio from the same compound is also indicative.¹¹⁴ Nucleophilic displacement of methylthio in 1,2,4-triazines and 1,2,4,5-tetrazines by alkoxide and amines is very easy. Mono-displacement can be carried out on 3,6-bis(methylthio)-1,2,4,5-tetrazine but the reaction using methoxide requires careful control of reaction conditions to avoid formation of the dimethoxy derivative.¹¹⁵ However, reaction of the bis(methylthio) compound with methyllithium resulted¹¹⁶ in nucleophilic attack at nitrogen!



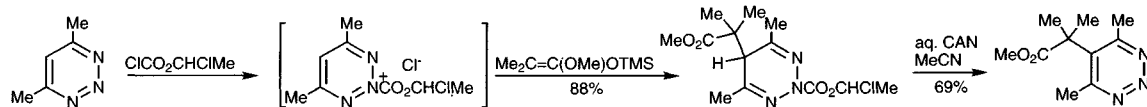
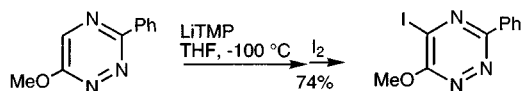
In triazine chemistry, sulfone is a better leaving group than halide for displacement with carbanions.¹¹⁷



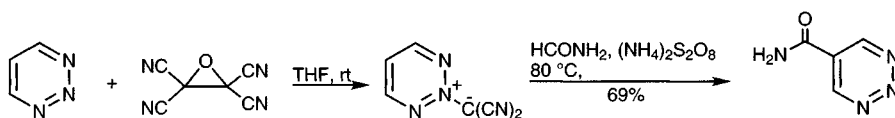
The susceptibility of 1,3,5-triazine to nucleophilic attack with ring-opening makes it a synthetically useful equivalent of formate, or formamide, particularly for the synthesis of other heterocycles such as imidazoles and triazoles¹¹⁸ (section 26.1.1.4; 1,2,4-triazoles).



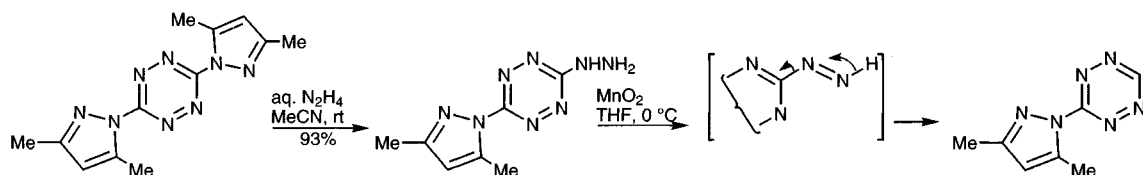
Despite the high susceptibility of 1,2,4-triazines to nucleophilic addition, 3-substituted-5-methoxy-1,2,4-triazines can be successfully lithiated.¹¹⁹



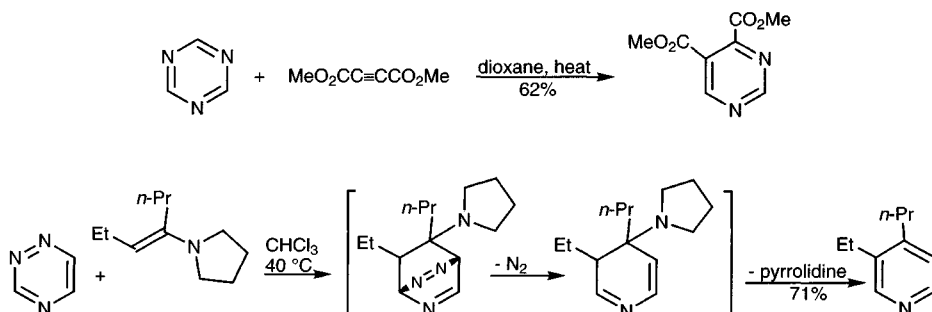
An interesting variant of the Minisci reaction has been reported for 1,2,3-triazine, which is unstable to the usual acidic conditions: here, activation of the heterocycle to attack by the nucleophilic radical is brought about by the agency of a dicyanomethylene ylide.¹²¹

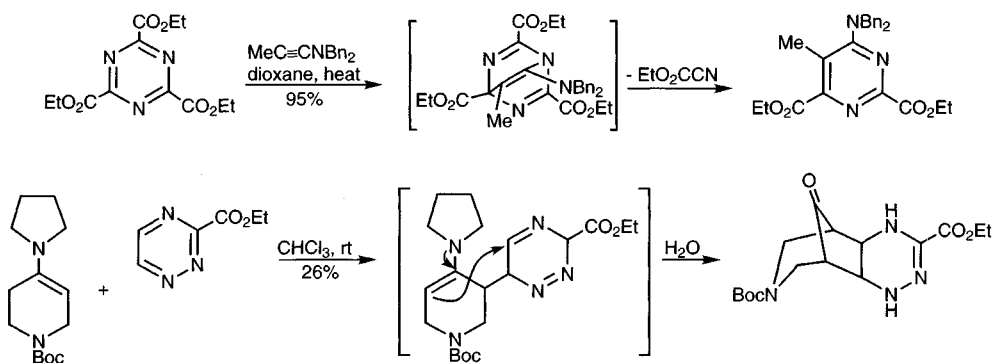


The reductive removal of hydrazine substituents under oxidising conditions is conceptually related to oxidative removal of thiols in other systems (e.g. section 26.1.1.2). In this case, the intermediacy of a diimide seems likely, as illustrated below.¹²²



Probably the most useful and general reaction of all these systems is the inverse-electron demand Diels-Alder reaction with acetylenes (or equivalents) to produce either pyridines or diazines *via* elimination of hydrogen cyanide or nitrogen.¹²³ Abnormal reactions occasionally occur through non-concerted mechanisms, as the last example shows.¹²⁴

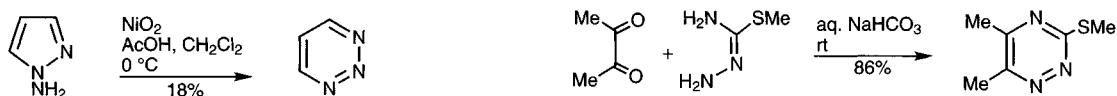




26.2.2 Ring syntheses

26.2.2.1 1,2,3-Triazine

1,2,3-Triazine has been prepared by the oxidation of 1-aminopyrazole.¹²⁵

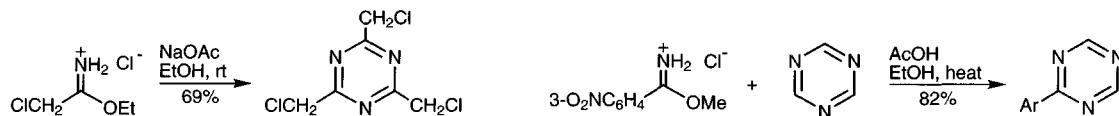


26.2.2.2 1,2,4-Triazines

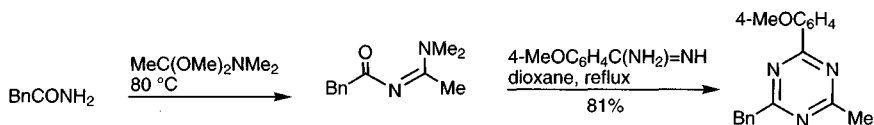
1,2,4-Triazines have been prepared by the condensation of amidrazones with diketones or halo-ketones, as shown above.¹²⁶

26.2.2.3 1,3,5-Triazines

1,3,5-Triazines are usually most easily obtained by substitution reactions on 2,4,6-trichloro-1,3,5-triazine, but the ring system can also be synthesised by cyclocondensation reactions. Trimerisation of nitriles (a common industrial method) or imidates¹²⁷ gives symmetrically substituted compounds; mono-substituted-1,3,5-triazines can be obtained *via* reaction of imidates with 1,3,5-triazine itself.¹²⁸

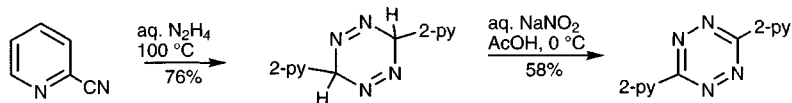


A route which allows the synthesis of 1,3,5-triazines with different substituents at each carbon is exemplified below – an *N'*-acyl-*N,N*-dimethylamidine reacts with an amidine (shown) or guanidine to form a 1,3,5-triazine.¹²⁹



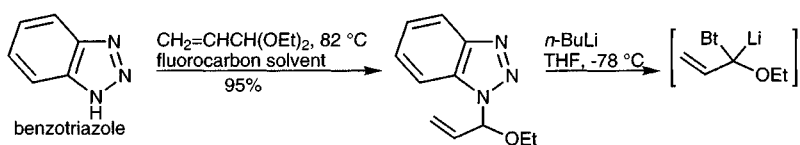
26.2.2.4 1,2,4,5-Tetrazines

1,2,4,5-Tetrazines can be produced by condensation of hydrazine with carbonyl compounds at acid oxidation level, followed by oxidation of the dihydroproducts: this generally produces 3,6-identically-substituted derivatives, crossed condensation reactions being inefficient.^{105,130}



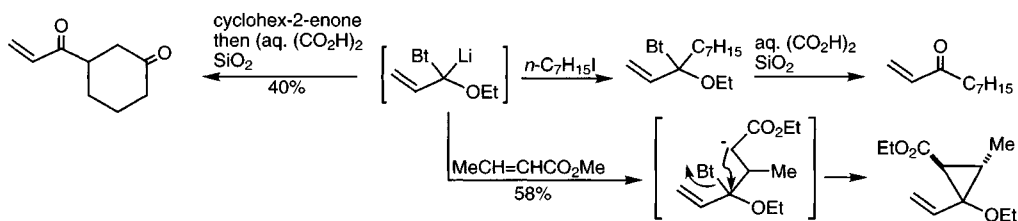
26.3 Benzotriazoles

The chemistry of benzotriazole has been developed to the point where it has now found extensive use for heterocyclic¹³¹ and general synthesis.¹³² A useful set of properties give it this role: (i) α -carbanions are stabilised to the same extent as at the benzylic position of a benzene compound; (ii) α -carbocations are also stabilised; (iii) the benzotriazolyl anion is also a good leaving group with a combination of good reactivity and stability/ease of handling. Sequential combinations of these reactivities have been applied to the synthesis of a wide variety of molecules – some illustrative examples are shown below.

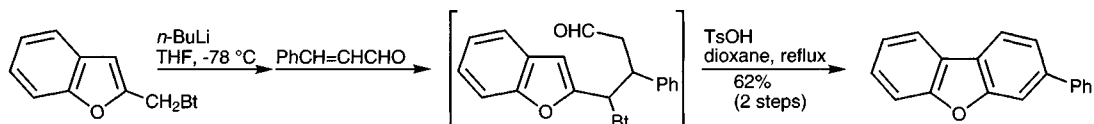


The starting benzotriazole derivatives are usually prepared from the parent heterocycle by *N*-alkylation with a halide, or via reaction with aldehydes or acetals, which can lead to mixtures of 1- and 2-substituted benzotriazoles, however the reactivities of the two isomers are similar. For clarity, only reactions of 1-substituted compounds are shown.

Alkylation of lithiated 1-(1-ethoxyprop-2-enyl)benzotriazole leads to enones after hydrolytic removal of the heterocycle; addition of the lithiated species to cyclohexenone then hydrolytic cleavage of the heterocycle produces an unsaturated 1,4-diketone.¹³³ Addition of the same anion to methyl but-2-enoate generates an anion in which the benzotriazole is displaced intramolecularly and a cyclopropane results.¹³⁴

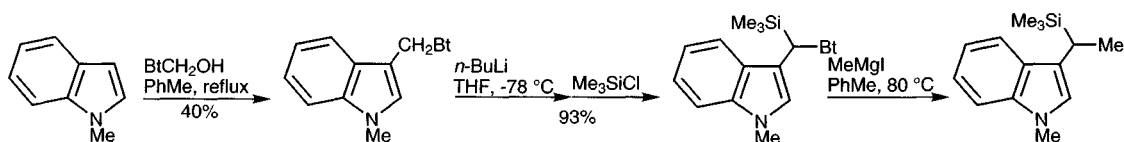


In the next example the benzotriazole unit facilitates benzylic lithiation and in the final step acts as a leaving group.¹³⁵

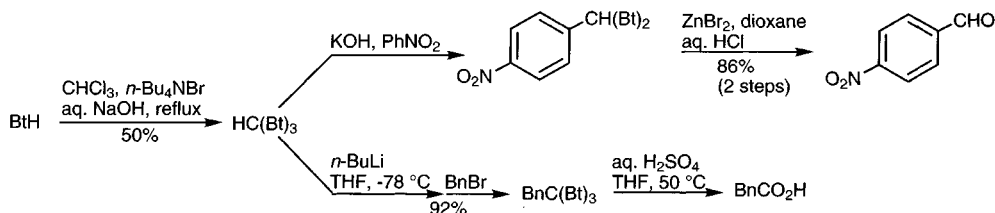


Next, the ability of benzotriazole to stabilise a cation allows 1-hydroxymethylbenzotriazole to alkylate indole; the product is then lithiated to allow substitution by

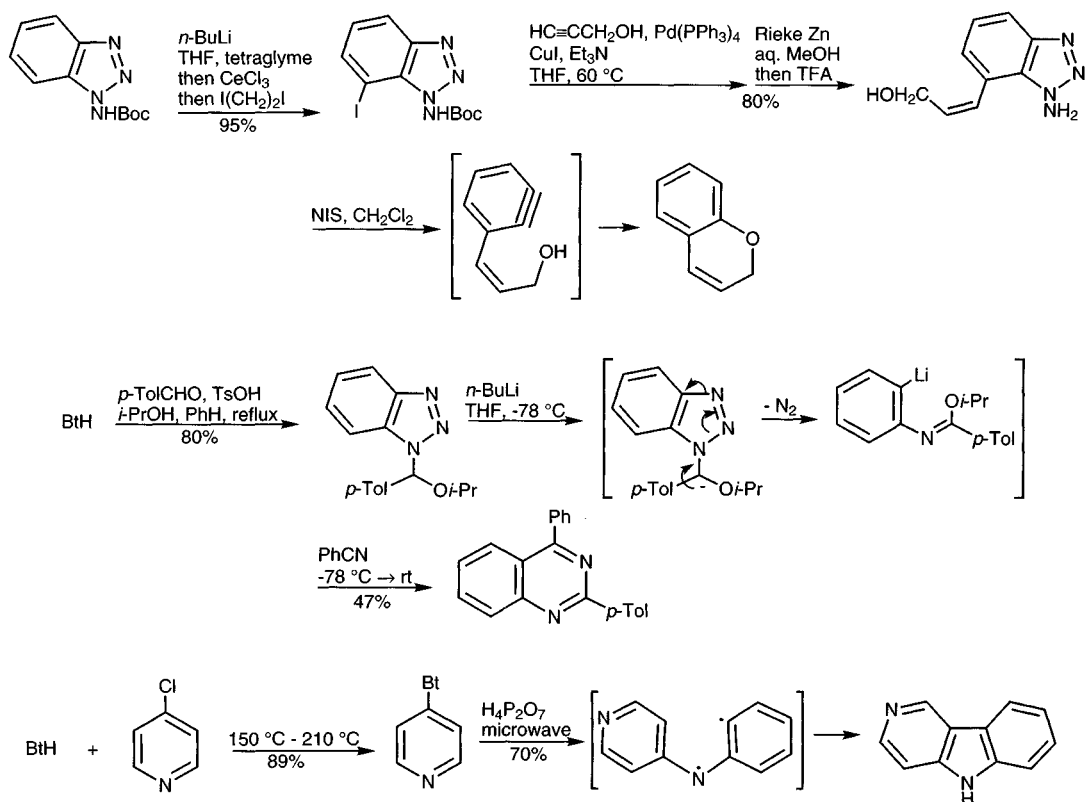
an electrophile and then finally the benzotriazole unit is displaced by a Grignard reagent.¹³⁶



Tris(benzotriazol-1-yl)methane anion will add to nitrobenzene in a VNS process in which the benzotriazole unit is both the anion-stabilising unit and also the leaving group;¹³⁷ another use for this compound is illustrated by alkylation of its anion then hydrolysis forming an acid.¹³⁸



Benzotriazoles also have interesting reactivity in their own right and can be used to form other heterocyclic compounds via various ring cleavage reactions leading to reactive intermediates such as benzyne,¹³⁹ aryllithiums,¹⁴⁰ and diradicals, as illustrated below.¹⁴¹



Exercises for chapter 26

1. What are the products of the following (Diels-Alder) reactions: (i) 1-pyrrolidinylcyclopentene with (a) 1,3,5-triazine, (b) 1,2,4-triazine; (ii) 3-phenyl-1,2,4,5-tetrazine with 1,1-diethoxyethene?
2. Thiophosgene ($\text{S}=\text{CCl}_2$) reacts at low temperature with sodium azide to give a product which contains no azide group; on subsequent reaction with methylamine this compound is converted into $\text{C}_2\text{H}_4\text{N}_4\text{S}$ – suggest structures.
3. What are the products of the reaction of PhCONH_2 with DMFDMA then (a) N_2H_4 and (b) H_2NOH ?
4. 1,3,5-Triazine reacts with (i) aminoguanidine to give 4-amino-1,3,4-triazole and with (ii) diethyl malonate to give ethyl 4-hydroxypyrimidine 5-carboxylate. Write mechanisms for these transformations.

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