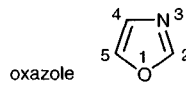
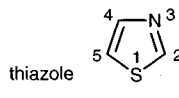
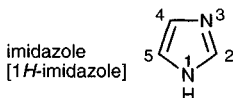
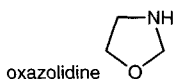
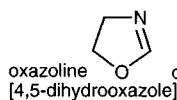
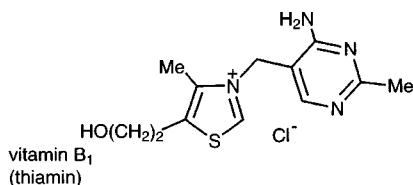
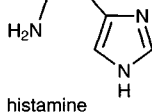
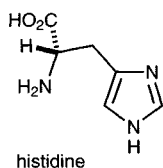


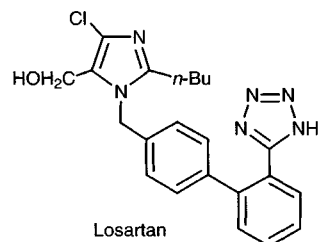
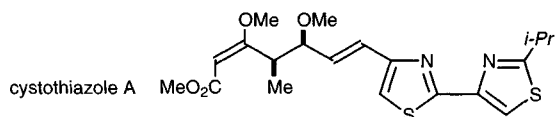
21 1,3-Azoles: imidazoles, thiazoles, and oxazoles: reactions and synthesis

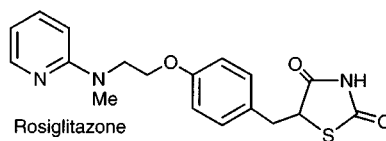
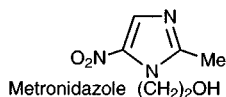
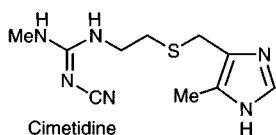


The three 1,3-azoles, imidazole,¹ thiazole and oxazole,² are all very stable compounds which do not autoxidise. Oxazole and thiazole are water-miscible liquids with pyridine-like odours. Imidazole, which is a solid at room temperature, and 1-methylimidazole are also water-soluble but are odourless. They boil at much higher temperatures (256 °C and 199 °C) than oxazole (69 °C) and thiazole (117 °C); this can be attributed to stronger dipolar association resulting from the very marked permanent charge separation in imidazoles (the dipole moment of imidazole is 5.6D; cf. oxazole, 1.4 D; thiazole, 1.6 D) and for imidazole itself, in addition, extensive intermolecular hydrogen bonding. The dihydro and tetrahydro heterocycles are named imidazoline/imidazolidine, thiazoline/thiazolidine, and oxazoline/oxazolidine.



Only oxazole, of the trio, does not play any part in normal biochemical processes, though there are secondary metabolites (especially from marine organisms) which incorporate thiazole (and oxazole) units – the antibiotic cystothiazole A, from the myxobacterium *Cyctobacter fuscus* is an example.³ Imidazole occurs in the essential amino acid histidine; histidines within enzymes are intimately involved in catalysis requiring proton transfers. The structurally related hormone, histamine, is a vasodilator and a major factor in allergic reactions such as hay fever. The thiazolium ring is the chemically active centre in the coenzyme derived from thiamin (vitamin B₁).





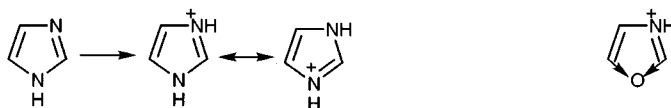
Amongst synthetic 1,3-azoles in use⁴ as therapeutic agents are Cimetidine, for the treatment of peptic ulcers, and Metronidazole, an antibacterial and an antiprotozoal, used for example in the treatment of amoebic dysentery. Rosiglitazone is used in the treatment of type 2 diabetes and Losartan is an angiotensin II antagonist – its use is as an antihypertensive agent.

21.1 Reactions with electrophilic reagents

21.1.1 Addition at nitrogen

21.1.1.1 Protonation

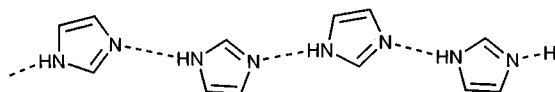
Imidazole, thiazole and alkyloxazoles, though not oxazole itself, form stable crystalline salts with strong acids, by protonation of the imine nitrogen, N-3, known as imidazolium, thiazolium, and oxazolium salts.



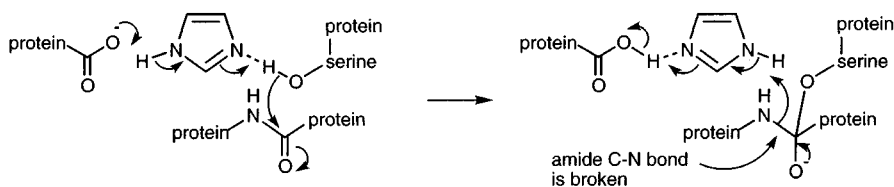
Imidazole, with a $\text{p}K_{\text{a}}$ of 7.1 is a very much stronger base than thiazole ($\text{p}K_{\text{a}}$ 2.5) or oxazole ($\text{p}K_{\text{a}}$ 0.8). That it is also stronger than pyridine ($\text{p}K_{\text{a}}$ 5.2) is due to the amidine-like resonance which allows both nitrogens to participate equally in carrying the charge. The particularly low basicity of oxazole can be understood as a combination of inductive withdrawal by the oxygen and weaker mesomeric electron release from it. The 1,3-azoles are stable in hot strong acid.

Hydrogen bonding in imidazoles

Imidazole, like water, is both a good donor and a good acceptor of hydrogen bonds; the imine nitrogen donates an electron pair and the *N*-hydrogen, being appreciably acidic (section 21.4.1), is an acceptor.

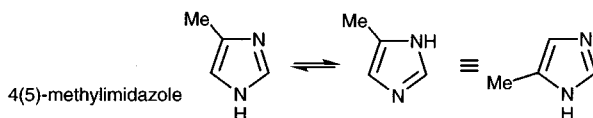


This property is central to the mode of action of several enzymes which utilise the imidazole ring of a histidine. These include the digestive enzyme chymotrypsin, which brings about amide hydrolysis of peptides in the small intestine: the enzyme provides a ‘proton’ at one site, while it accepts a ‘proton’ at another, making use of the ambivalent character of the imidazole ring to achieve this. The illustration shows how the heterocycle allows a proton to ‘shuttle’ from one site to another *via* the heterocycle.



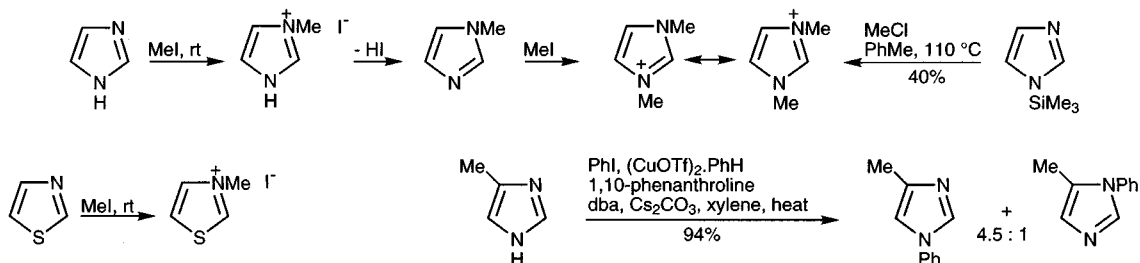
Tautomerism in imidazoles

Imidazoles with a ring *N*-hydrogen are subject to tautomerism which becomes evident in unsymmetrically substituted compounds such as the methylimidazole shown. This special feature of imidazole chemistry means that to write simply '4-methylimidazole' would be misleading, for this molecule is in tautomeric equilibrium with 5-methylimidazole, and quite inseparable from it. All such tautomeric pairs are inseparable and the convention used to cover this phenomenon is to write '4(5)-methylimidazole'. In some pairs, one tautomer predominates, for example 4(5)-nitroimidazole favours the 4-nitro-tautomer by 400:1.



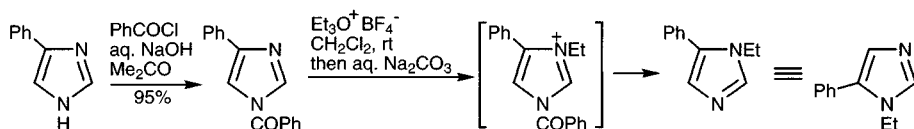
21.1.1.2 Alkylation at nitrogen

The 1,3-azoles are quaternised easily at the imine nitrogen with alkyl halides; the relative rates are: 1-methylimidazole:thiazole:oxazole – 900:15:1.⁵ Microwave irradiation makes the process particularly rapid.⁶ In the case of imidazoles which have an *N*-hydrogen, the immediate product is a protonated *N*-alkylimidazole; this can lose its proton to unreacted imidazole and react a second time, meaning that reactions with alkyl halides give a mixture of imidazolium, 1-alkylimidazolium and 1,3-dialkylimidazolium salts. Furthermore, an unsymmetrically substituted imidazole can give two isomeric 1-alkyl derivatives. The use of a limited amount of the alkylating agent, or reaction in basic solution,⁷ when it is the imidazolyl anion (section 21.4.1) which is alkylated, can minimise these complications. Clean formation of doubly alkylated derivatives can be achieved by reacting 1-trimethylsilylimidazole with an alkyl halide.⁸ *N*-Arylation of imidazoles, efficient when copper(I)-catalysed, shows the same regioselectivity with 4(5)-substituted imidazoles: generally the 1-aryl-4-substituted imidazole is the major product.⁹

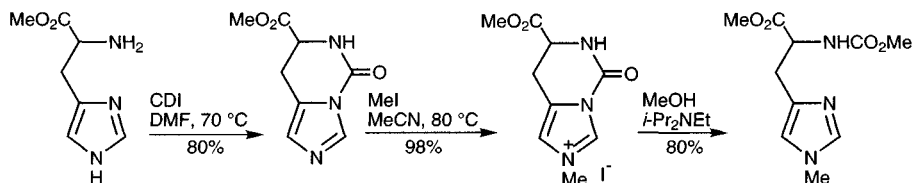


N-Alkylation of oxazoles,¹⁰ or imidazoles carrying, for example, a phenylsulfonyl or acyl¹¹ group on nitrogen, is more difficult, requiring methyl triflate or a Meerwein salt for smooth reaction. Subsequent simple alcoholysis of the imidazolium-

sulfonamide releases the *N*-substituted imidazole;¹² the process can be utilised in another sense for converting alcohols into carbamates.¹³ Moreover, since acylation of 4(5)-substituted imidazoles gives the sterically less crowded 1-acyl-4-substituted imidazoles, subsequent alkylation, then hydrolytic removal of the acyl group produces 1,5-disubstituted imidazoles.¹⁴ Complementarily, the 1,4-disubstitution pattern can be achieved by alkylating 1-protected-5-substituted imidazoles (see section 21.6.1) at *N*-3, then removing the *N*-protection.¹⁵ *N*-Tritylimidazoles can be *N*-alkylated with simple halides, removal of the triphenylmethyl group after alkylation requiring only simple acid treatment.¹⁶ Alkylation with acrylonitrile, via a Michael mechanism, is reversible and can also be made the means for the synthesis of 1,5-disubstituted imidazoles via *N*-alkylation of 1-(2-cyanoethyl)-4-substituted imidazoles then elimination of acrylonitrile.¹⁷



Another device to control the position of *N*-alkylation is applicable to histidine and histamine: a cyclic urea is first prepared by reaction with carbonyl dimidazole (section 21.1.1.3), forcing the alkylation onto the other nitrogen, ring opening then providing the *N*-1-alkylated, urethane-protected derivative.¹⁸

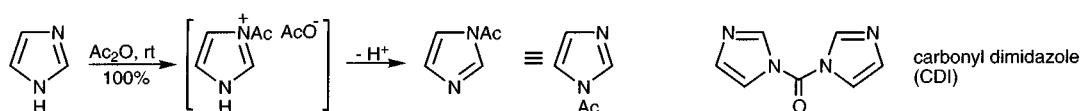


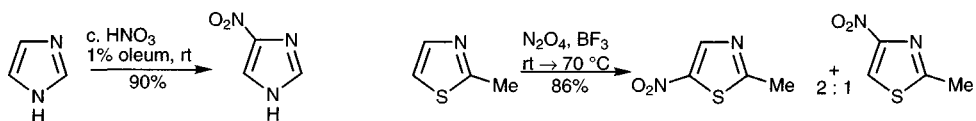
Exposure of imidazole to 'normal' Mannich conditions leads to *N*-dimethylaminomethylimidazole, presumably *via* attack at the imine nitrogen, followed by loss of proton from the other nitrogen.¹⁹

21.1.1.3 Acylation at nitrogen

Acylation of imidazole produces *N*-acylimidazoles *via* loss of proton from the initially-formed *N*-3-acylimidazolium salt.²⁰ A device which has been employed frequently for the synthesis of 1-acylimidazoles is to use two mol equivalents of the heterocycle for one of the acylating agent, the second mole of imidazole serving to deprotonate the first-formed *N*-acylimidazolium salt.

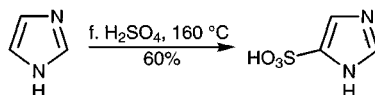
N-Acylimidazoles are even more easily hydrolysed than *N*-acylpyrroles, moist air is sufficient. The ready susceptibility to nucleophilic attack at carbonyl carbon has been capitalised upon: commercially available 1,1'-carbonyldiimidazole (CDI), prepared from imidazole and phosgene, can be used as a safe, phosgene equivalent, i.e. a synthon for $O=C^{2+}$, and also in the activation of acids for formation of amides and esters *via* the *N*-acylimidazole.²¹





21.1.2.3 Sulfonation

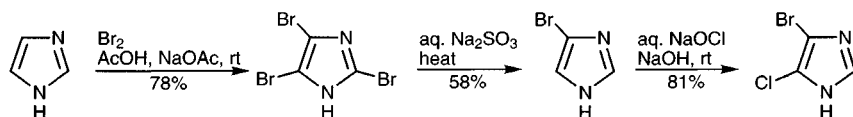
Here again, thiazoles are much less reactive than imidazoles,³⁵ generally requiring high temperatures and mercury(II) sulfate as catalyst for any reaction to take place,³⁶ oxazole sulfonations are unknown.



21.1.2.4 Halogenation

Imidazole,³⁷ and 1-alkyl imidazoles,³⁸ are brominated with remarkable ease at all free nuclear positions. 4(5)-Bromimidazole can be obtained by reduction of tribromimidazole,³⁹ *via* regioselective exchange of the 2- and 5-halogens then water quenching,⁴⁰ or by bromination with 4,4-dibromocyclohexa-2,5-dienone.⁴¹ Chlorination with hypochlorite in alkaline solution effects substitution only at the 4- and 5-positions.⁴² Iodination of imidazoles which have a free *N*-hydrogen, in alkaline solution and therefore *via* the imidazolyl anion, can also give fully halogenated products;⁴³ 4,5-diiodination of imidazole takes place in cold alkaline solution.⁴⁴

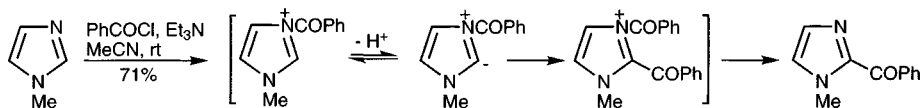
It is, at first sight, somewhat surprising that such relatively mild conditions allow bromination of imidazole at C-2, but it must be remembered that the neutral imidazole, not its protonic salt (*cf.* nitration and sulfonation), is available for attack. Electrophilic addition of bromine to nitrogen, then addition of bromide at C-2, and finally elimination of hydrogen bromide may be involved.



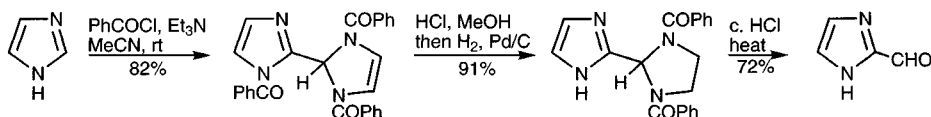
Thiazole does not undergo bromination easily, though 2-methylthiazole brominates at C-5; when the 5-position is not free no substitution occurs, thus 2,5-dimethylthiazole, despite its two activating substituents, is not attacked.⁴⁵ Halogenation of simple oxazoles has not been reported.

21.1.2.5 Acylation

Friedel-Crafts acylations are unknown for the azoles, clearly because of interaction between the basic nitrogen and the Lewis acid catalyst. It is, however, possible to 2-arylate 1-alkylimidazoles⁴⁶ or indeed imidazole itself⁴⁷ by reaction with the acid chloride in the presence of triethylamine, the substitution proceeding *via* an *N*-acylimidazolium ylide as shown below. It is similarly possible to introduce cyano to the 2-position by reaction with *N*-cyano-4-dimethylaminopyridinium chloride.⁴⁸ In the reverse sense, 2-acyl substituents can be cleaved by methanolysis, the mechanism again involving the imidazolium ylide.⁴⁹

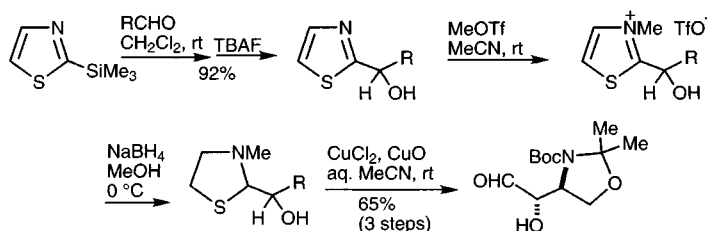


Another fascinating example of the utility of *N*-acylimidazolium ylides provides a means for synthesising 2-formylimidazole efficiently: the electrophile which attacks the ylide is in this case an *N*-benzoylimidazolium cation.⁵⁰



21.1.2.6 Reactions with aldehydes

The discovery of *ipso* displacement of silicon from the thiazole 2-position under mild conditions led to the development of this reaction as an essential component of a route to complex aldehydes. Subsequent quaternisation, saturation of the heterocyclic ring using sodium borohydride, and then mercury(II) or copper(II) catalysed treatment leads to the destruction of the thiazolidine and the formation of a new homologous aldehyde; an example is shown below.⁵¹



21.1.2.7 Reactions with iminium ions

The standard, acidic Mannich conditions do not allow simple *C*-substitutions of the imidazole. (*cf.* 21.1.1.2), thiazole, or oxazole systems.

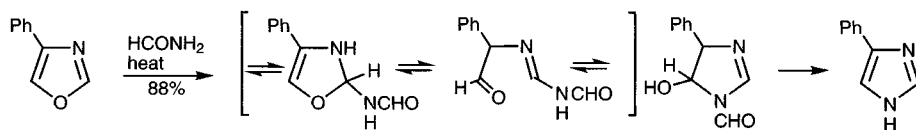
21.2 Reactions with oxidising agents

Resistance to oxidative breakdown falls off in the order thiazoles > imidazoles > oxazoles. 2-Substituted thiazoles can be converted into *N*-oxides,⁵² however peracids bring about degradation of imidazoles; oxazole *N*-oxides can only be prepared by ring synthesis.

21.3 Reactions with nucleophilic reagents

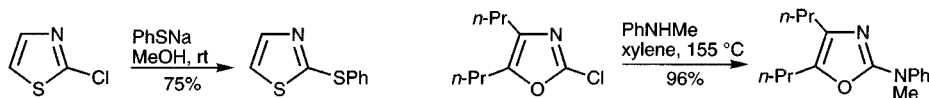
21.3.1 With ring opening

Generally speaking, the 1,3-azoles do not show the pyridine-type reactions in which hydrogen is displaced, although a Chichibabin substitution on 4-methylthiazole has been reported.⁵³ There are however reactions in which the heterocyclic ring is opened, for example phenylhydrazine attacks oxazoles leading to osazones.⁵⁴ Reaction of an oxazole with hot formamide also leads to a ring opening; a reclosure results in the formation of imidazoles; the example show reasonable intermediates.

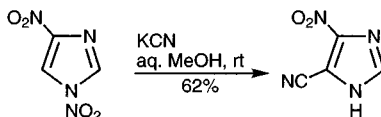


21.3.2 With replacement of halogen

There are many examples of halogen at a 2-position undergoing nucleophilic displacement, for example 2-halothiazoles with sulfur nucleophiles⁵⁵ (indeed, more rapidly than for 2-halopyridines), 2-halo-1-substituted imidazoles,⁵⁶ and 2-chlorooxazoles⁵⁷ with nitrogen nucleophiles.



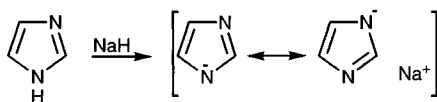
In the special situation where an imidazole nitrogen carries a nitro group which can act as a leaving group (as nitrite) *cine* substitution has been observed.⁵⁸



21.4 Reactions with bases

21.4.1 Deprotonation of *N*-hydrogen

The pK_a for loss of the *N*-hydrogen of imidazole is 14.2; it is thus an appreciably stronger acid than pyrrole (pK_a 17.5) because of the enhanced delocalisation of charge onto the second nitrogen in the imidazolyl anion.



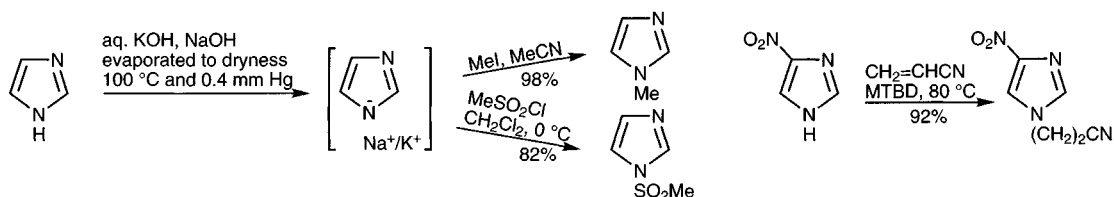
21.4.2. Deprotonation of *C*-hydrogen

The specific exchange at C-2 in the azoles in neutral solution, *via* an ylide, has already been discussed (section 21.1.2.1). In strongly basic solution, deprotonation takes place by direct abstraction of proton from the neutral heterocycle at the positions adjacent to the oxygen and the sulfur in oxazole and thiazole⁵⁹ and, less easily, at C-5 in *N*-methylimidazole.⁶⁰

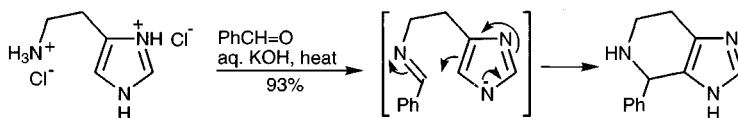
21.5 Reactions of *N*-metallated imidazoles

Salts of imidazoles can be alkylated or acylated on nitrogen. One convenient method is to use the dry sodium/potassium salt obtained by evaporation of an aqueous alkaline solution,⁶¹ sodium hydride in dimethylformamide also serves very well for this purpose. When there is a route for the entering group to be lost again, as in the addition to a carbonyl-conjugated alkene, a 2,4(5)-substituted imidazole will give the less hindered 1,2,4-trisubstituted product rather than the 1,2,5-isomer.⁶² The use of

1,3,4,6,7,8-hexahydro-1-methylpyrimido[1,2-*a*]pyridine (MTPD) is particularly effective at promoting the addition of imidazoles to unsaturated esters and nitriles.⁶³



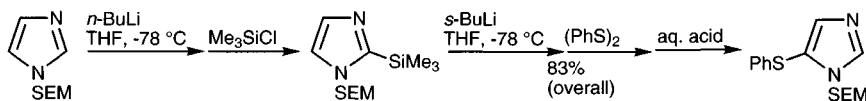
Imidazoles react with Mannich electrophiles at nitrogen, however the overall effect of Mannich *C*-substitution has been found in base-catalysed cyclisation of histamine Schiff bases; closure does not take place in the absence of base and it must be the imidazolyl anion which reacts intramolecularly with the side-chain imine.⁶⁴



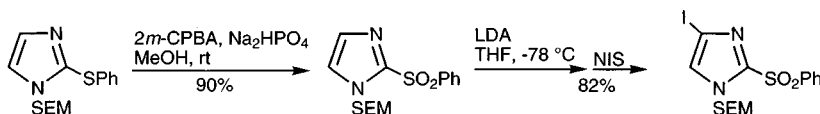
21.6 Reactions of C-metallated 1,3-azoles⁶⁵

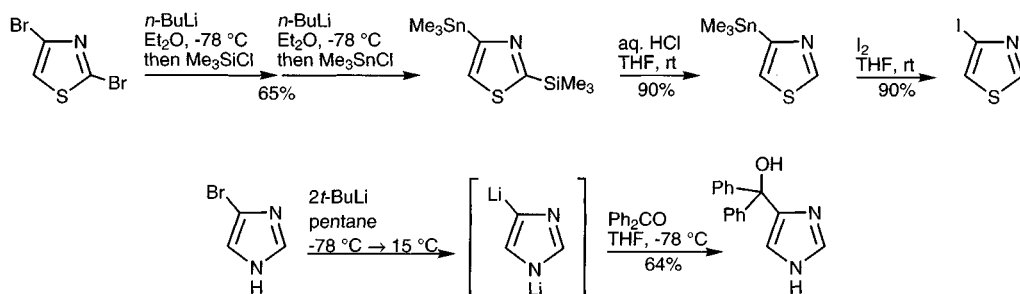
21.6.1 Lithium derivatives

In line with the exchange processes discussed above, preparative strong base deprotonation of oxazoles,⁶⁶ thiazoles,⁶⁷ and *N*-methylimidazole⁶⁸ takes place preferentially at C-2, or at C-5 if the former position is blocked,⁶⁹ and the lithiated derivatives can then be utilised in reactions with electrophiles. A variety of removable *N*-protecting groups have been used to achieve comparable transformations for the eventual synthesis of *N*-unsubstituted imidazoles, including phenylsulfonyl,⁷⁰ dimethylaminosulfonyl,⁷¹ dimethylaminomethyl,¹⁹ trimethylsilylethoxymethyl (SEM),⁷² diethoxymethyl,⁷³ 1-ethoxyethyl,⁷⁴ and trityl⁷⁵ (see also 21.13). The intrinsic tendency to lithiate at C-2, then C-5, taken with metal-halogen exchange processes for the 4-position are a powerful combination for elaborations of the 1,3-azoles. For example, the sequence shown below produces SEM-protected 5-substituted imidazoles,^{71,76} with retention of a 2-silyl substituent if required.⁷⁷ All three isomeric trimethylsilyl- and all three trimethylstannylthiazoles have been made in similar ways and provide means for subsequent regioselective *ipso* displacement with electrophiles under mild conditions.⁷⁸

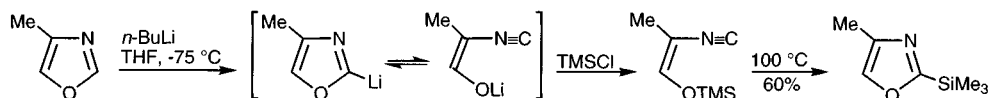


Complementarily, the lithiation of a SEM protected 2-phenylsulfonylimidazole takes place at C-4.⁷⁹ Metal-halogen exchange of 4(5)-bromoimidazole is possible without protection.⁸⁰

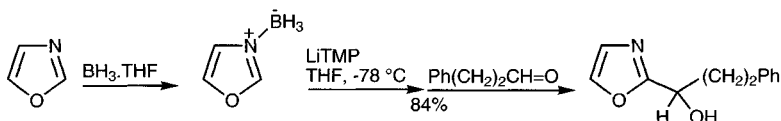




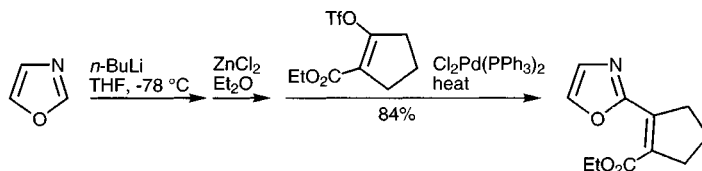
Although oxazoles follow the pattern and lithiate at C-2, 4-substituted products are produced with some electrophiles; this is interpreted by a ring opening of the anion, to produce an enolate, which after C-electrophilic attack, recloses. An estimate by NMR spectroscopy showed the ring cleaved tautomer to dominate the equilibrium.⁸¹ The open enolates can be trapped by reaction with chlorotrimethylsilane; the open, enol trimethylsilyl ether will undergo a thermal rearrangement to form a 2-trimethylsilyloxazole.⁸²



The ring opening of oxazoles can be avoided by transmetalation,⁸³ or by first forming a borane complex which is then lithiated as shown below.⁸⁴

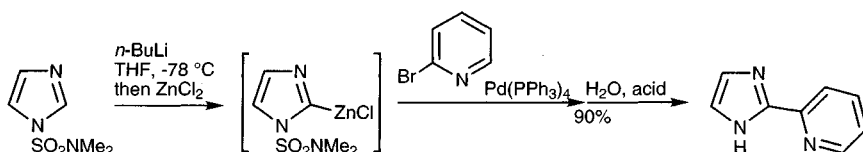


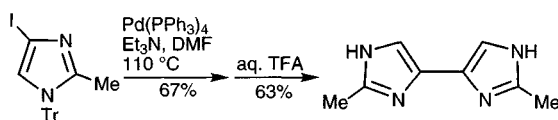
Oxazolylzinc compounds^{80,85} and oxazolyl tin compounds⁸⁶ take part in coupling processes (see also below) without problems over ring opening.



21.6.2 Palladium-catalysed reactions

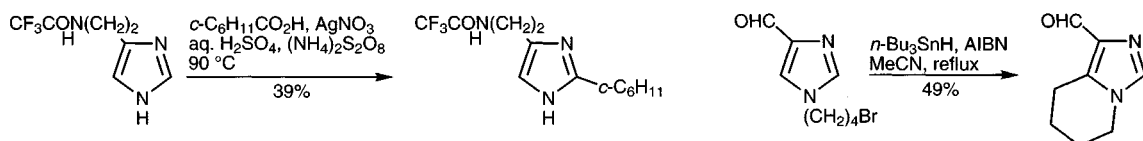
The palladium(0)-catalysed coupling of *N*-protected imidazoles has been extensively utilised, as illustrated by the examples below.⁸⁷ The coupling of 4,5-diiodoimidazole protected with trimethylsilylethoxymethyl on *N*-1, was completely selective for the 5-halogen.⁸⁸





21.7 Reactions with radical reagents

The preferred site for radical substitution of imidazoles in acid solution is C-2.⁸⁹ In contrast, intramolecular alkylation of a 4-formylimidazole in neutral solution took place at C-5.⁹⁰ Intramolecular displacement of tosyl as a C-2 substituent, has also been demonstrated.⁹¹

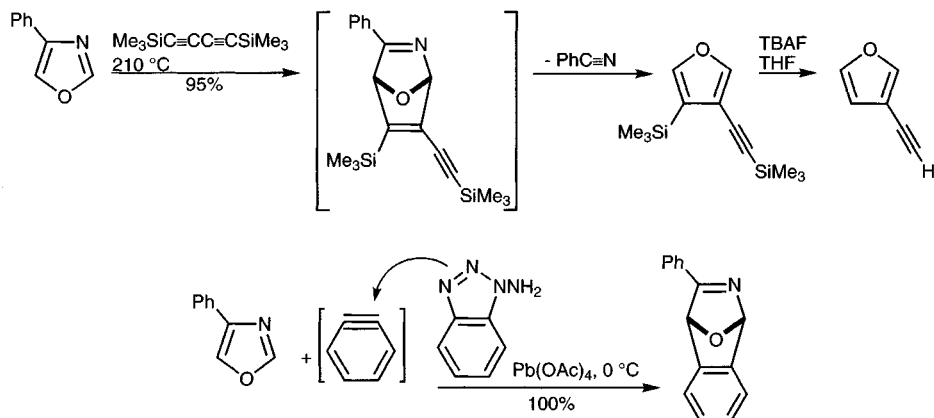


21.8 Reactions with reducing agents

Oxazoles are the most easily reduced, catalytic sequences also bringing about C–O bond cleavage. 1,3-Azolium salts are, of course, more easily attacked by hydride reducing agents: thiazolium salts produce tetrahydro-derivatives.⁹²

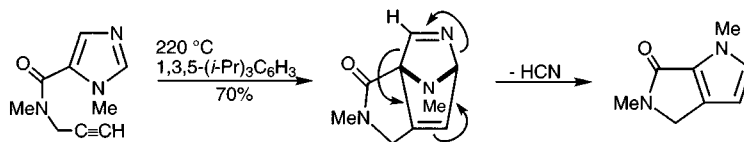
21.9 Electrocyclic reactions

Oxazoles readily undergo cycloaddition across the 2,5-positions, in parallel with the behaviour of furans (section 15.9); thiazoles react with alkynes in the same way (e.g. section 14.13.1.7) but there is only one example of such a cycloaddition in imidazole chemistry. Thiazole and imidazole react with highly electrophilic alkynes *via* initial electrophilic addition to the nitrogen then nucleophilic intramolecular cyclising addition.⁹³

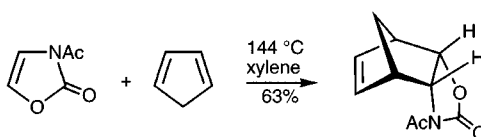


Oxazole cycloadditions have been reported with alkyne dienophiles⁹⁴ (tandem Diels-Alder addition and retro Diels-Alder loss of a nitrile leads on to furans), benzyne (the primary adduct can be isolated),⁹⁵ and with typical alkene dienophiles. The primary adducts from addition of singlet oxygen rearrange, by a mechanism

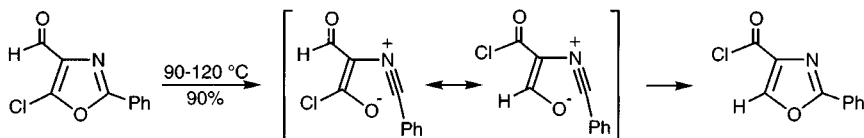
which is not definitely established, to form triamides, themselves useful synthetic intermediates.⁹⁶ The only example of this sort of process with an imidazole is an intramolecular example, the product in this case being a pyrrole after loss of hydrogen cyanide.⁹⁷



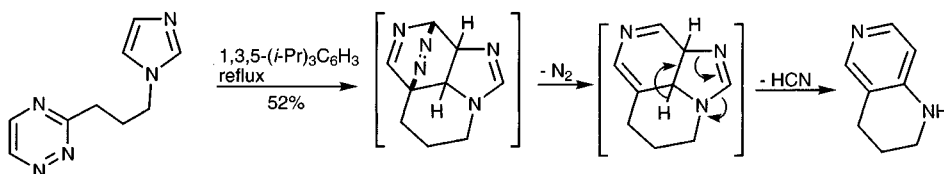
Considerable attention has been paid to the reactions of oxazoles with typical Diels-Alder alkene dienophiles.⁹⁸ The adducts can be transformed into pyridines by different routes (section 5.15.1.4). Electron-releasing substituents on the oxazoles increase the rate of reaction: 5-alkoxyoxazoles are comparable in reactivity to typical all-carbon dienes. Particularly useful dienophiles are *N*-acyl-oxazolones – synthons for *cis*-1,2-amino-alcohols.⁹⁹



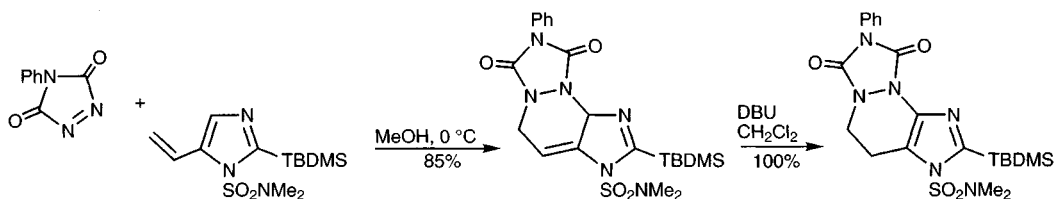
Thermally induced equilibration of oxazole-4-aldehydes and -ketones¹⁰⁰ and 5-ethoxy-4-amides¹⁰¹ takes place at remarkably low temperatures (90–120 °C) giving the more stable, isomeric carbonyl compound. The intermediates are believed to be nitrilium-enolates.



Isolated examples of 1,3-azoles serving as 2π components in cycloadditions include the reaction of 4-nitro-2-phenyloxazole with dienes across the 4,5-bond¹⁰² and the intramolecular imidazole example shown below where the diene is electron-deficient and the process is completed by loss of hydrogen cyanide.¹⁰³

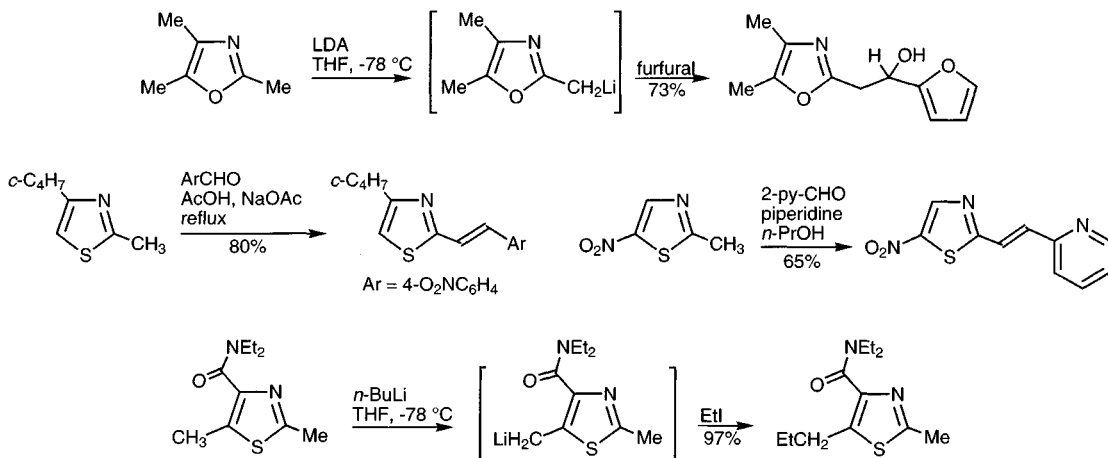


With a strong electron-withdrawing group on nitrogen (but much less efficiently with for example methoxymethyl on nitrogen) a 5-vinylimidazole will take part in a cycloaddition as a 4π component, as the example shows.¹⁰⁴

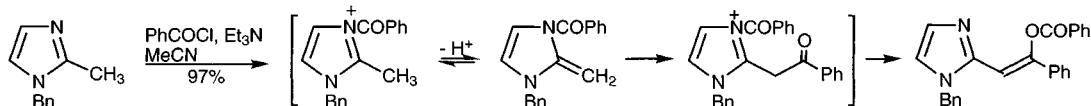


21.10 Alkyl-1,3-azoles

Protons on alkyl groups at the 1,3-azole 2-positions are sufficiently acidic for strong base deprotonation,¹⁰⁵ and are more acidic than methyl groups at other positions; even the assistance of an *ortho*-related carboxylate is usually insufficient to overcome the intrinsic tendency for 2-methyl-lithiation, though an adjacent tertiary amide can do this.¹⁰⁶ The side-chain metallated derivatives can be utilised in reactions with electrophiles. The presence of a 5-nitro group allows much milder, base-catalysed condensations to occur.³³ The condensation at the 2-methyl of thiazoles proceeds in organic acid solution.¹⁰⁷



N-Acylation also increases the acidity of 2-methyl groups, allowing *C*-acylation *via* a non-isolable enamide.¹⁰⁸

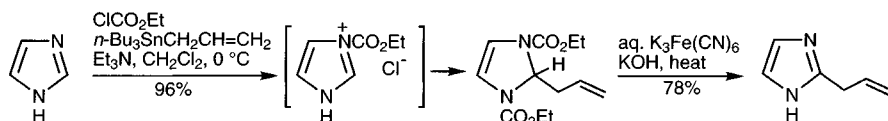


21.11 Quaternary 1,3-azolium salts

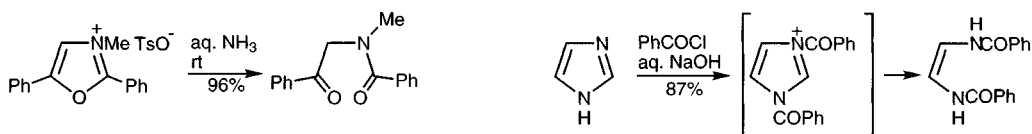
1-Butyl-3-methylimidazolium hexafluorophosphate, which is fluid at room temperature and stable to water, has been recommended as an 'ionic liquid' and shown to serve as the equivalent of a dipolar aprotic solvent in some base-catalysed alkylations; products can be simply extracted with an immiscible organic solvent in the usual way.¹⁰⁹

N-Alkoxy carbonyl 1,3-azolium salts, generated *in situ* by reaction with chloroformates, will react with allylstannanes,¹¹⁰ or allylsilanes¹¹¹ by addition of the

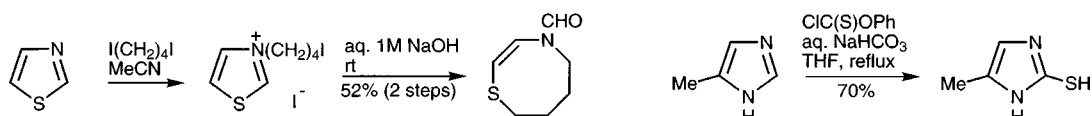
equivalent of an allyl anion. In the same way, silyl enol ethers add the equivalent of an enolate to give 2,3-dihydro-2-substituted imidazoles and thiazoles.¹¹²



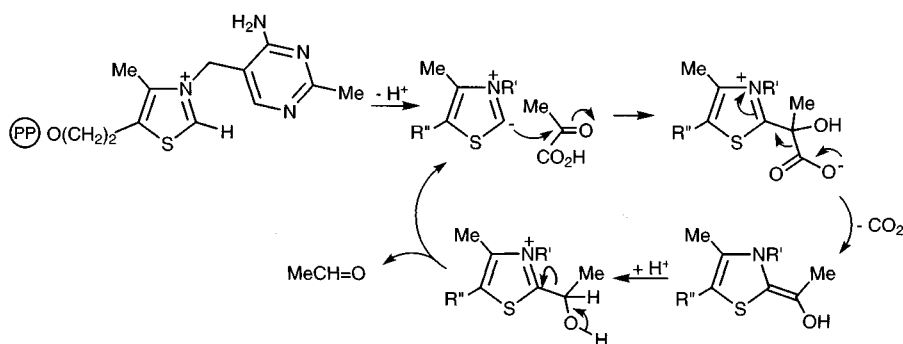
Azolium salts are readily attacked by nucleophiles, for example with hydroxide, addition at C-2 is followed by ring opening.¹¹³



Neat exploitations of this process, include the synthesis of medium-sized heterocycles as products of a three stage sequence involving addition of hydroxide to ω -iodoalkyl thiazolium salts, ring-opening and then reclosure by intramolecular *S*-alkylation, illustrated below for the formation of an eight-membered ring,¹¹⁴ and the introduction of sulfur to the imidazole 2-position using phenyl chlorothionoformate.¹¹⁵

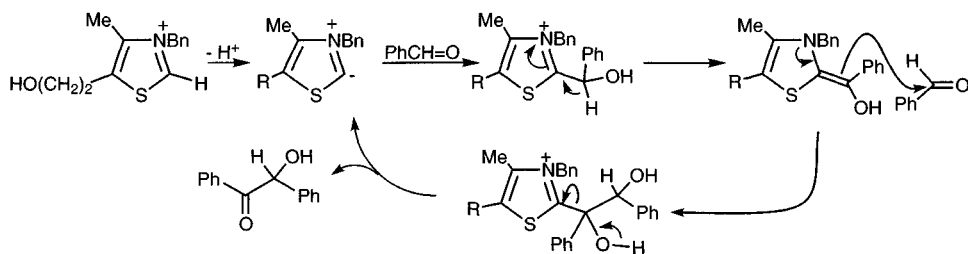


The C-2-exchange of azolium salts *via* an ylide mechanism has already been discussed (section 21.1.2.1). Thiamin pyrophosphate acts as a coenzyme in several biochemical processes and in these, its mode of action also depends on the intermediacy of a 2-deprotonated species. For example, in the later stages of alcoholic fermentation, which converts glucose into ethanol and carbon dioxide, the enzyme pyruvate decarboxylase converts pyruvate into ethanal and carbon dioxide, the former then being converted into ethanol by the enzyme, alcohol dehydrogenase. It is believed, that in the operation of the former enzyme, the coenzyme, thiamin pyrophosphate, adds as its ylide to the ketonic carbonyl group of pyruvate; this is followed by loss of carbon dioxide then the release of ethanal by expulsion of the original ylide.



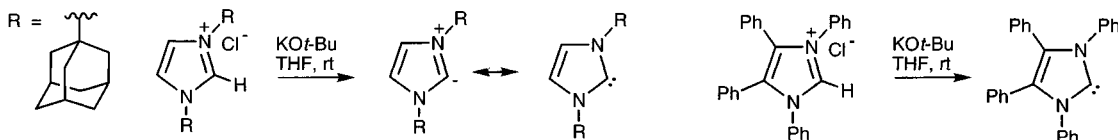
In the laboratory, thiazolium salts (3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride is commercially available) will act as catalysts for the benzoin

condensation, and in contrast to cyanide, the classical catalyst, allow such reactions to proceed with alkanals, as opposed to aryl aldehydes; the key steps in thiazolium ion catalysis for the synthesis of 2-hydroxyketones are shown below. Such catalysis, which also finds other applications, provides acyl anions, in effect.



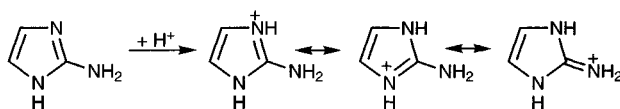
It is very interesting that replacing a thiazolium ring with an oxazolium ring gives a thiamin analogue in which there is no catalytic activity;¹¹⁶ similarly 3,4-dimethyloxazolium iodide does not catalyse a benzoin condensation.¹¹⁷ Nature has chosen the heterocyclic system with the correct balance – oxazolium ylides are formed faster, but because of the greater stability that this reflects, do not then add to carbonyl groups as is required for catalytic activity. In keeping with the carbenoid character of thiazolium ylides, they dimerise; the dimers, either in their own right, or by reversion to monomer, are also catalysts for the benzoin condensation.¹¹⁸

The 1,3-dimethylimidazolium ylide, generated using sodium hydride, allows the introduction of electrophiles to C-2.¹¹⁹ Isolable, crystalline carbenes have been derived from 1,3-bis(adamantanylimidazolium chloride,¹²⁰ and from 1,3,4,5-tetra-phenylimidazolium chloride.¹²¹ A stable thiazol-2-ylidene carried methyl groups at positions 4 and 5 and a 2,6-di-*i*-propylphenyl substituent on nitrogen.¹²²

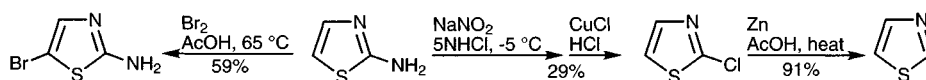


21.12 Oxy-^{123,124} and amino-¹²⁵ -1,3-azoles

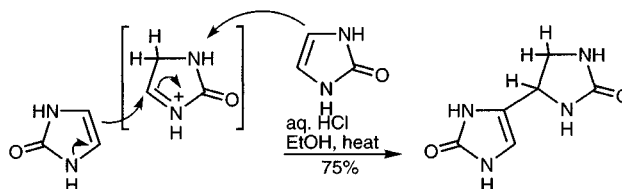
Amino-1,3-azoles exist as the amino tautomers, though 2-arylsulfonylaminothiazoles have been shown to exist as the imino tautomers.¹²⁶ 2-Amino-1,3-azoles tend to be more stable than other isomers. All amino-1,3-azoles protonate on the ring nitrogen. 2-Aminothiazole has a pK_a of 5.39 which compares with the value for 2-aminoimidazole of 8.46, reflecting the symmetry of the resonating guanidinium type system in the latter.



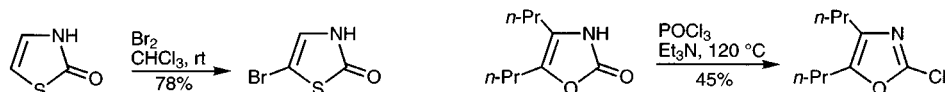
The amino-1,3-azoles behave as normal arylamines, for example undergoing carbonyl condensation reactions, easy electrophilic substitutions,¹²⁷ and diazotisation,¹²⁸ though 2-aminoxazoles cannot be diazotised,¹²⁹ presumably due to the greater electron withdrawal by the oxygen.



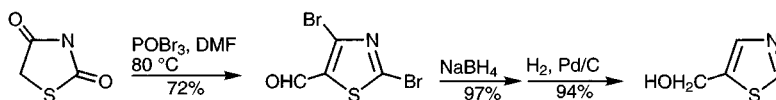
The oxygen-substituted 1,3-azoles exist in their carbonyl tautomeric forms. That there is little aromatic character left in such systems is nicely illustrated by the acid-catalysed dimerisation of imidazol-2-one, which acts as an enamide in the process.¹³⁰



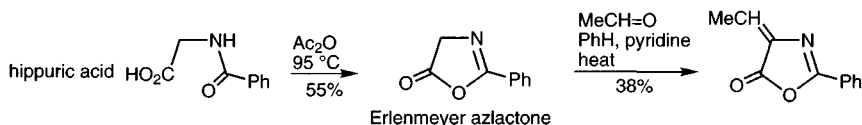
The bromination of thiazol-2-one, at C-5, is also a nice demonstration of relative reactivity: here the double bond carries both sulfur and nitrogen, and it is the latter, *i.e.* the enamide rather than the thioenol ester character, which dictates the site of electrophilic attack.¹³¹



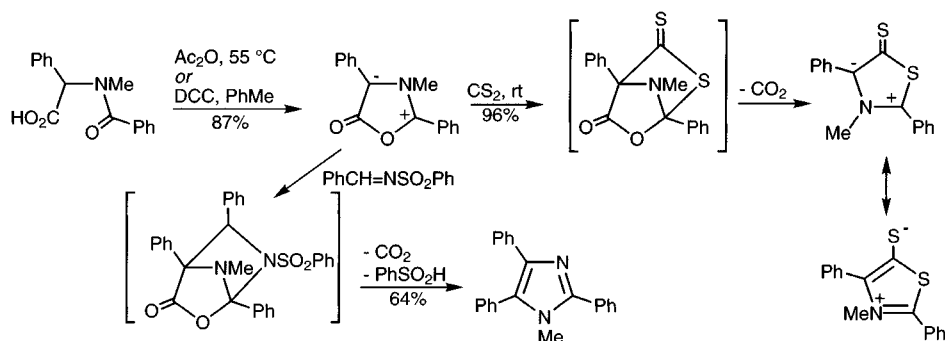
1,3-Azol-2-ones can be converted into the 2-haloazoles by reaction with phosphorus halides.⁵⁶ Thiazolidine-2,4-diones are converted into the dihalothiazoles on exposure to phosphorus halides; when accompanied by dimethylformamide, *i.e.* under Vilsmeier conditions, ring formylation also occurs and after hydrogenolytic removal of halogen the overall sequence can be seen to be a means for the hydroxyalkylation of a thiazole.¹³²



The 5-ones condense in an aldol fashion at C-4.¹³³ Alkylation of the 1,3-azolones can take place either on the oxygen, giving alkyloxyazoles, or on nitrogen; for example thiazol-2-one reacts with diazomethane giving 2-methoxythiazole, but with methyl iodide/methoxide, to give 3-methylthiazol-2-one.¹³⁰

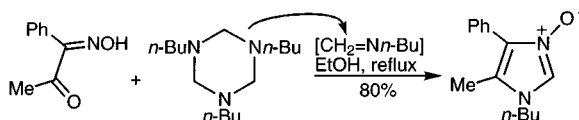


4(5)-Oxazolones are simply cyclic anhydrides of *N*-acyl- α -amino acids, and are constructed in the way that this implies. If the nitrogen also carries an alkyl group, cyclisation¹³⁴ can only lead to an overall neutral product by its adopting a zwitterionic structure, for which no neutral canonical form can be written – a mesoionic structure. Mesoionic oxazolones (named ‘münchnones’ by Huisgen after their discovery at the University of München, Germany) undergo ready dipolar cycloadditions,¹³⁵ with loss of carbon dioxide from initial adduct; the examples¹³⁶ show the conversion of a münchnone into a mesoionic thiazolone and into an imidazole.

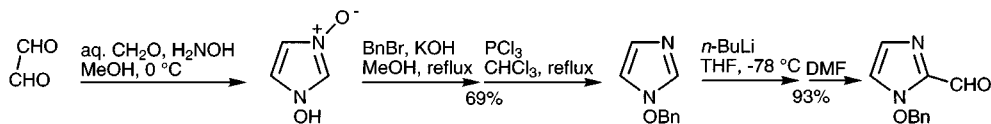


21.13 1,3-Azole *N*-oxides

The chemistry of azole *N*-oxides is relatively under developed compared, for example, with that of pyridine *N*-oxides, largely because of difficulty in their preparation from the azoles themselves. Some ring synthetic methods can be used, for example the reaction of 1,2-dicarbonyl mono-oximes with imines as shown.¹³⁷ 1-Substituted imidazole 3-oxides can be converted into nitriles with loss of the oxygen using trimethylsilyl cyanide, careful choice of solvent minimising a tendency for isomeric mixtures to be formed.¹³⁸



1-Hydroxyimidazole *N*-oxide can be transformed into 1-benzyloxyimidazole and this undergoes useful 2-lithiations; hydrogenolysis produces 2-substituted 1-hydroxyimidazoles and these, in turn, can be converted into the 2-substituted imidazole by reduction with titanium(III) chloride.¹³⁹



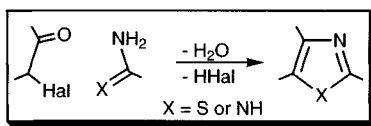
21.14 Synthesis of 1,3-azoles^{140,141}

21.14.1 Ring synthesis

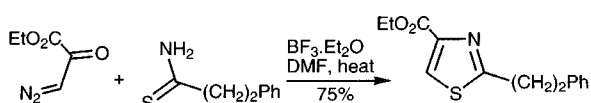
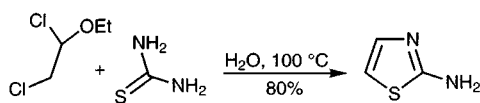
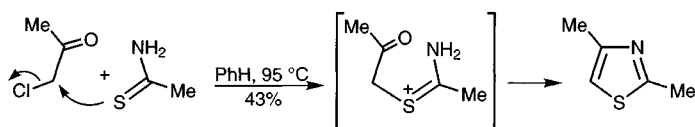
Considerable parallelism emerges from an examination of the major methods for the construction of oxazole, thiazole and imidazole ring systems.

21.14.1.1 From an α -halocarbonyl component (or an equivalent) and a three-atom unit supplying C-2 and the heteroatoms

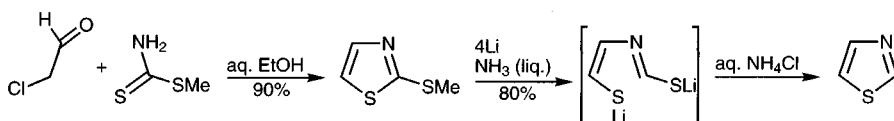
Reaction of an α -halocarbonyl component and a three-atom unit supplying C-2 and the heteroatoms gives the five-membered heterocycle; this route is particularly important for thiazoles.



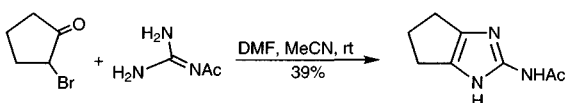
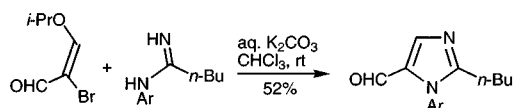
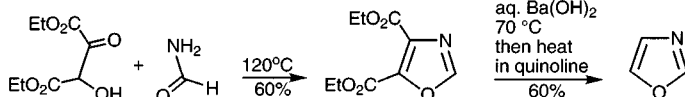
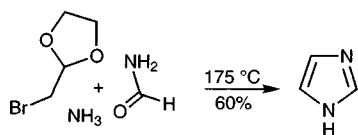
Simple examples of this strategy, which for the synthesis of thiazoles is known as the *Hantzsch synthesis*, are shown below: the syntheses of 2,4-dimethylthiazole where the heteroatoms are provided by thioacetamide,¹⁴² and 2-aminothiazole, in which 1,2-dichloroethyl ethyl ether is utilised as a synthon for chloroethanal and the heteroatoms derive from thiourea.¹⁴³ The use of thioureas as the sulfur component with 2-chloroacetamides as the second unit gives rise to 2,4-diaminothiazoles.¹⁴⁴ Conversion of 1,3-diketones into their 2-phenyliodonium derivatives and reaction of these with thioureas produces 2-amino-5-acylthiazoles.¹⁴⁵ The first step in such ring syntheses is *S*-alkylation.¹⁴⁶ A useful variant is the use of an α -diazo ketone in place of the α -halocarbonyl component.¹⁴⁷



The interaction of ammonia with carbon disulfide produces ammonium dithiocarbamate in solution, which reacts with 2-haloketones to produce thiazol-2-thiones;¹⁴⁸ similarly, methyl dithiocarbamate serves as a component for the construction of 2-methylthiothiazole, reducible to thiazole itself, thus providing a good route to the unsubstituted heterocycle.¹⁴⁹



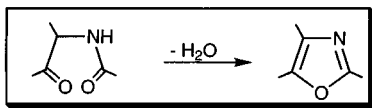
Imidazole itself can be prepared efficiently from bromoethanal ethylene acetal, formamide and ammonia; by analogy it is likely that displacement of halogen by ammonia occurs at an early stage.¹⁵⁰ An enol ether of bromomalonaldehyde reacts with amidines giving 5-formylimidazoles.¹⁵¹ 2-Acetylaminoimidazoles are formed efficiently from the interaction of 2-bromoketones and *N*-acetylguanidine.¹⁵²



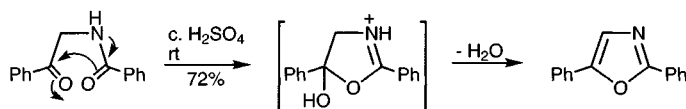
Oxazole itself has been prepared from its 4,5-diester, by hydrolysis then decarboxylation; though this formally falls into the same category of synthesis, it is probable that the ring oxygen derives from the 2-hydroxy-ketone, and not from the formamide;¹⁵³ the reaction of acylins with formamide can be looked on as a general approach to oxazoles.¹⁵⁴ The use of cyanamide gives 2-amino-oxazoles.¹⁵⁵

21.14.1.2 By cyclising dehydration of α -acylaminocarbonyl compounds

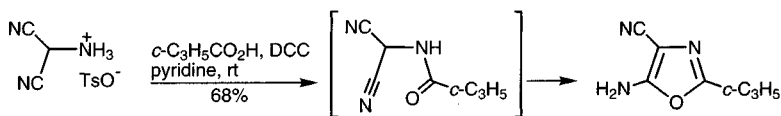
Cyclising dehydration of an α -acylaminocarbonyl compound is particularly important for oxazoles, and can be adapted for thiazole formation.



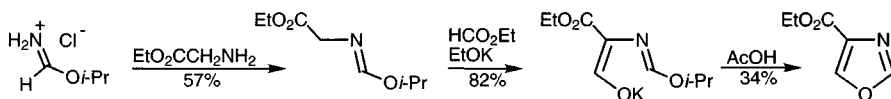
The classical method for making oxazoles, the *Robinson-Gabriel synthesis*, which is formally analogous to the cyclising dehydration of 1,4-dicarbonyl compounds to furans (section 15.13.1.1), is the acid-catalysed closure of α -acylamino carbonyl compounds.¹⁵⁶



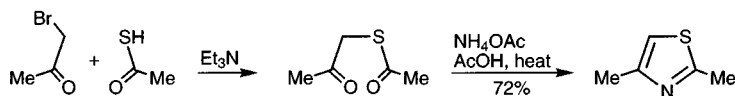
The construction of an amide using aminomalononitrile and a carboxylic acid under typical peptide coupling conditions, is accompanied by ring closure and the production of 5-aminooxazoles *in situ*.¹⁵⁷



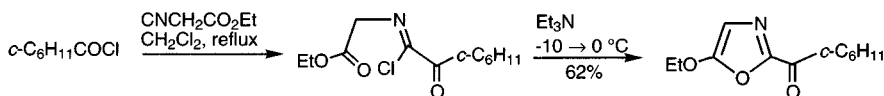
A synthesis shown below of ethyl oxazole-4-carboxylate illustrates a sophisticated use of this strategy.¹⁵⁸

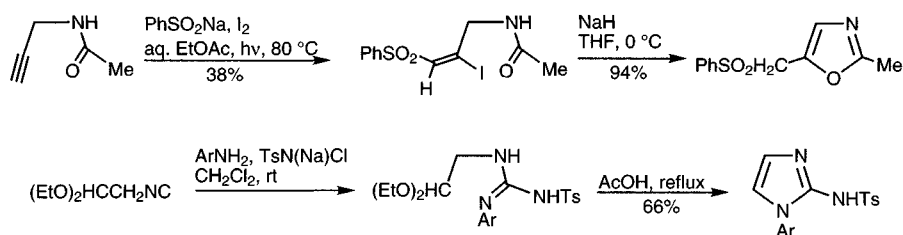


α -Acylothioketones close with ammonia to give thiazoles.¹⁵⁹

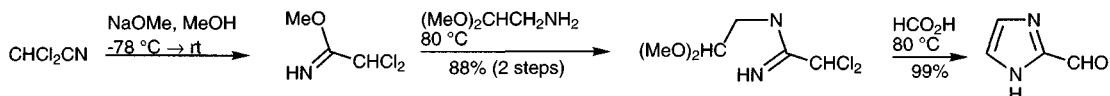


In two modern versions of ring closures in this category of ring synthesis, oxazoles are produced by base-catalysed closure of imino-chloride derivatives of glycine, obtained by acylation of ethyl isocyanoacetate¹⁶⁰ and in the second, by base-catalysed closure of 3-acylamino-2-iodo-1-phenylsulfonylalkenes.¹⁶¹ In yet another use of an isonitrile, 2-tosylaminoimidazoles can be prepared.¹⁶²



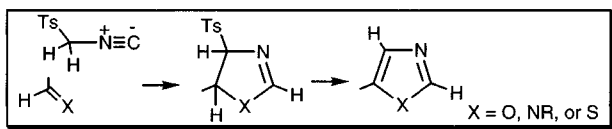


Iminoethers on reaction with aminoacetal give amidines which close in acid to give 2-substituted imidazoles.¹⁶³

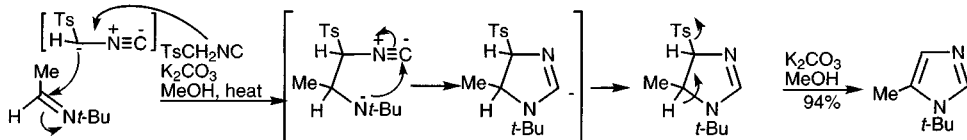


21.14.1.3 From isocyanides

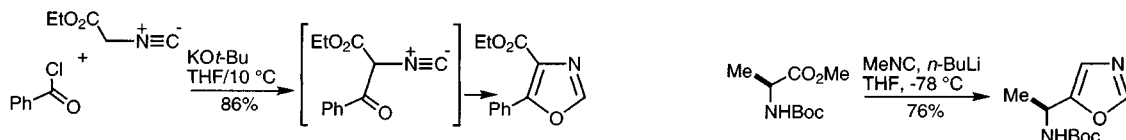
Tosylmethylisocyanide (TOSMIC), can be used for the synthesis of all three 1,3-azole types.



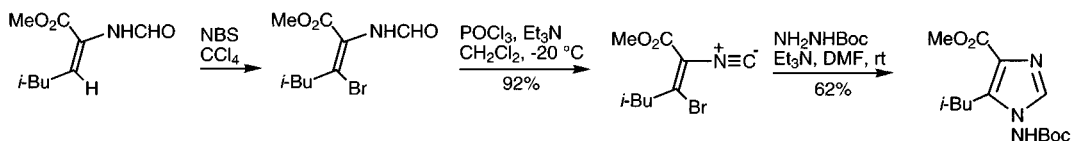
Tosylmethylisocyanide has been used in the synthesis of all three 1,3-azole types. It reacts with aldehydes affording adducts, which lose toluenesulfinate on heating giving oxazoles,¹⁶⁴ with carbon disulfide it produces 4-tosyl-5-alkylthiothiazoles (following a subsequent *S*-alkylation)¹⁶⁵ and, in analogy to its interaction with aldehydes, it adds to *N*-alkylimines¹⁶⁶ or *N*-dimethylaminosulfamylimines¹⁶⁷ when, following elimination of toluenesulfinate, imidazoles are formed. The analogous benzotriazolymethyl isocyanide can serve in the same way and has advantages in some situations.¹⁶⁸



Anions derived from other isocyanides have been acylated (and thioformylated¹⁶⁹), the products spontaneously closing to oxazoles¹⁷⁰ (thiazoles).

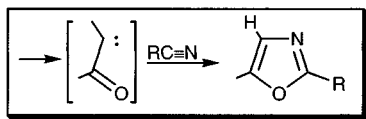


2-Isocyanoacrylates are proving to be versatile intermediates: they react with amines to give imidazoles, with thiols to give thiazoles, with protected hydrazine to give 2-aminoimidazoles (illustrated) and with *O*-benzylhydroxylamine to give 1-benzyloxyimidazoles.¹⁷¹

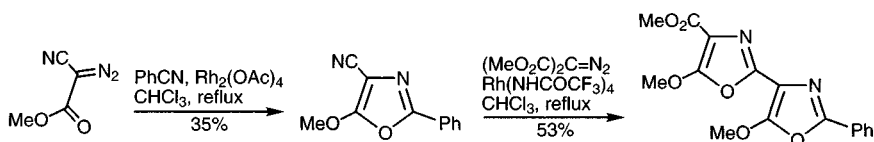


21.14.1.4 Oxazoles from α -diazocarbonyl compounds¹⁷²

The carbene or carbenoid derived from an α -diazocarbonyl compound cycloadds to nitriles to produce oxazoles with the nitrile substituent at C-2.

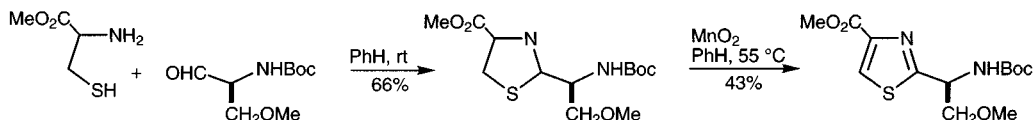


The generation of a carbene (or when using a metal catalyst, a carbenoid) from an α -diazocarbonyl compound, in the presence of a nitrile results in overall cycloaddition and the formation of an oxazole. Both α -diazoketones and α -diazooesters have been used, the examples in the sequence below showing that the result in the latter situation is the formation of a 5-oxygenated oxazole.¹⁷³ The exact sequence of events is not certain but may involve a nitrile ylide, the result of electrophilic addition of the carbene to the nitrile nitrogen.



21.14.1.5 By dehydrogenation

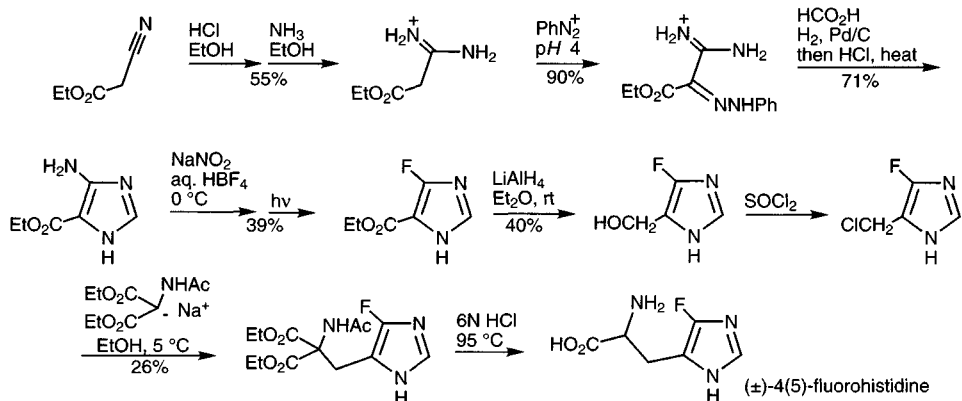
The ring synthesis of the tetrahydro-1,3-azoles is simply the formation of *N,N*-, *N,O*- or *N,S*-analogues of aldehyde cyclic acetals; the ring synthesis of the 4,5-dihydro-heterocycles requires an acid oxidation level in place of aldehyde. A good route to the aromatic systems is therefore the dehydrogenation of these reduced and partially reduced systems. Nickel peroxide,¹⁷⁴ manganese(IV) oxide,¹⁷⁵ copper(II) bromide/base,¹⁷⁶ and bromotrichloromethane/diazabicycloundecane¹⁷⁷ have been used. The example shown uses cysteine methyl ester with a chiral aldehyde to form the tetrahydrothiazole.



21.14.2 Examples of notable syntheses involving 1,3-azoles

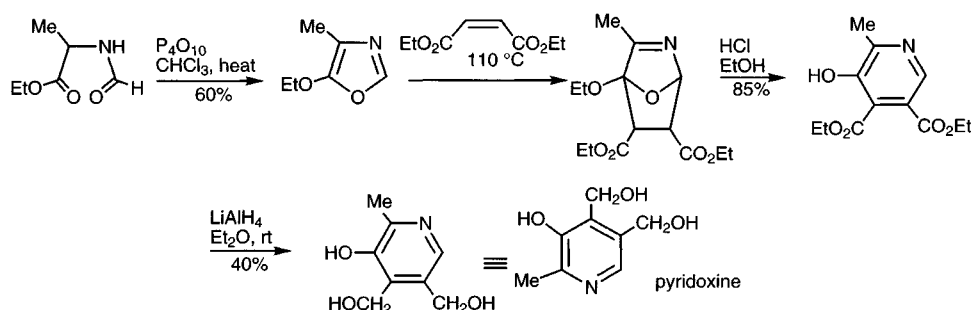
21.14.2.1 4(5)-Fluorohistamine

4(5)-Fluorohistamine¹⁷⁸ was synthesised via nucleophilic displacement of a side-chain leaving group (cf. pyrroles, section 14.12).



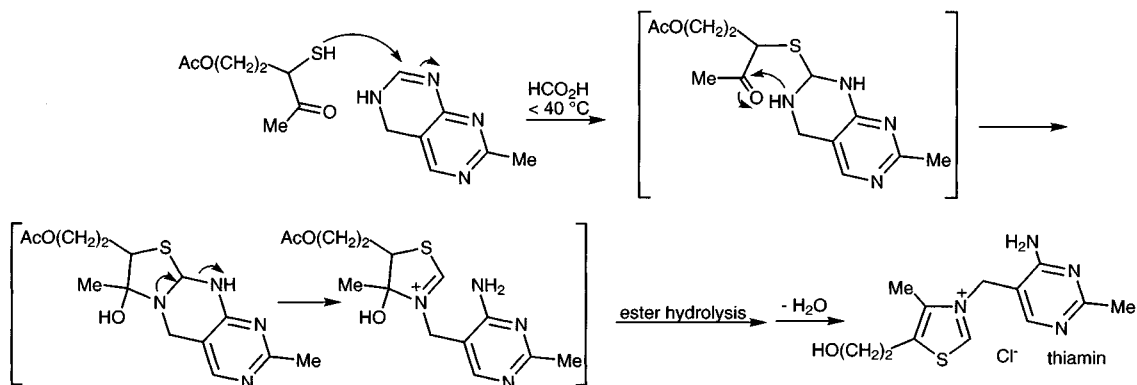
21.14.2.2 Pyridoxine¹⁷⁹

This synthesis illustrates the use of an oxazole undergoing a Diels-Alder addition, leading on to a pyridine.



21.14.2.3 Thiamin

Thiamin was first synthesised in 1937.¹⁸⁰ It is widely used as a feed/food additive and in pharmaceutical preparations. A modern synthesis¹⁸¹ of thiamin utilised an α -keto-thiol; the C-2 carbon was neatly delivered as the carbon of an amidine, one of the nitrogens providing the thiazole ring nitrogen and the other being the eventual amino group of the substituent pyrimidine.



- (e) What is the positional order of selectivity for deprotonation of 1,3-azoles? How, then, would you make 5-methylthiazole from thiazole?
- (f) What is the most typical electrocyclic process undergone by the 1,3-azoles and which of them show this tendency to the highest degree?
- (g) Describe one typical synthesis for (i) an imidazole, (ii) a thiazole, and (iii) an oxazole.

More advanced exercises

1. Suggest structures for the halo compounds formed in the following ways: (i) imidazole with $\text{NaOCl} \rightarrow \text{C}_3\text{H}_2\text{Cl}_2\text{N}$; (ii) 1-methylimidazole with excess Br_2 in $\text{AcOH} \rightarrow \text{C}_4\text{H}_3\text{Br}_3\text{N}_2$ then this with EtMgBr followed by water $\rightarrow \text{C}_4\text{H}_4\text{Br}_2\text{N}_2$ and this in turn with $n\text{-BuLi}$ then $(\text{MeO})_2\text{CO}$ gave $\text{C}_6\text{H}_7\text{BrN}_2\text{O}_2$.
2. Draw structures for the intermediates and final products which are formed when (i) 4-phenyloxazole is heated with but-1-yn-3-one $\rightarrow \text{C}_6\text{H}_6\text{O}_2$; (ii) 5-ethoxyoxazole is heated with dimethyl acetylenedicarboxylate $\rightarrow \text{C}_{10}\text{H}_{12}\text{O}_6$.
3. When the cyclic acyloin, $c\text{-(CH}_2\text{)}_{10}\text{COCH(OH)}$ was heated with formamide, in the presence of acid, a bicyclic oxazole, $\text{C}_{13}\text{H}_{21}\text{NO}$, was formed; what is its structure? This bicyclic oxazole was converted by exposure to $^1\text{O}_2$, then heating, into the acyclic cyano-acid, $\text{HO}_2\text{C(CH}_2\text{)}_{10}\text{CN}$; draw a mechanism for the transformation.
4. Deduce structures for the products formed at each stage of the following syntheses: 1,2-dimethyl-5-nitroimidazole heated with $\text{Me}_2\text{NCH(O}t\text{-Bu)}_2 \rightarrow \text{C}_8\text{H}_{12}\text{N}_4\text{O}_2$; this then heated with $\text{Ac}_2\text{O} \rightarrow \text{C}_{10}\text{H}_{14}\text{N}_4\text{O}_3$. This product reacted (i) with guanidine $[\text{H}_2\text{NC(NH}_2\text{)=NH}] \rightarrow \text{C}_9\text{H}_{10}\text{N}_6\text{O}_2$, and (ii) with $\text{MeNHNH}_2 \rightarrow \text{C}_9\text{H}_{11}\text{N}_5\text{O}_2$.
5. Deduce structures for the products formed in the following sequences: 1-methylimidazole/ $n\text{-BuLi}/-30^\circ\text{C}$ then $\text{TMSCl} \rightarrow \text{C}_7\text{H}_{14}\text{N}_2\text{Si}$ then $n\text{-BuLi}/-30^\circ\text{C}$ then $\text{TMSCl} \rightarrow \text{C}_{10}\text{H}_{22}\text{N}_2\text{Si}_2$, then this with $\text{MeOH}/\text{rt} \rightarrow \text{C}_7\text{H}_{14}\text{NSi}$, which was different to the first product.
6. Explain the following: 4-bromo-1-methylimidazole treated with $n\text{-BuLi}/-78^\circ\text{C}$ then DMF gave $\text{C}_5\text{H}_6\text{N}_2\text{O}$. Carrying out the same sequence but allowing the solution to warm to 0°C before addition of DMF gave an isomeric product.
7. Thiazole-2-thione reacted with $\text{Br(CH}_2\text{)}_3\text{Br}$ to give, mainly, a salt $\text{C}_6\text{H}_8\text{NS}_2^+ \text{Br}^-$; suggest a structure and a mechanism for its formation.
8. Deduce structures for the 1,3-azoles which are produced from the following reactant combinations: (i) 1-chlorobutan-2-one and thiourea; (ii) thiobenzamide and chloroethanal; (iii) thioformamide and ethyl bromoacetate.
9. Write structures for the intermediates in the following synthesis of 3,4-bis(acetoxymethyl)furan: phenacyl bromide/ $\text{NH}_4^+ \text{HCO}_2^- \rightarrow \text{C}_9\text{N}_7\text{NO}$; this then heated with $\text{AcOH}_2\text{CC}\equiv\text{CCH}_2\text{OAc}$.
10. What imidazoles would be formed from the following reactant combination: (i) $\text{MeN}\equiv\text{C}/n\text{-BuLi}$ and $\text{PhC}\equiv\text{N}$; (ii) 2-amino-1,2-diphenylethanone and $\text{H}_2\text{NC}\equiv\text{N}$?

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