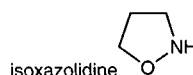
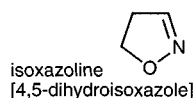
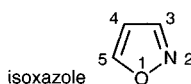
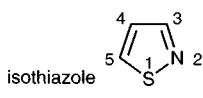
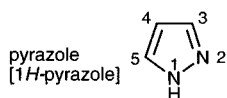
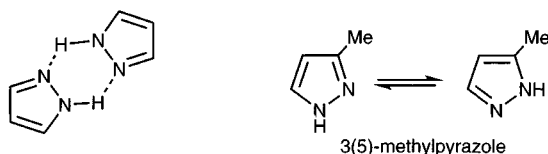


22 1,2-Azoles: pyrazoles, isothiazoles, isoxazoles: reactions and synthesis

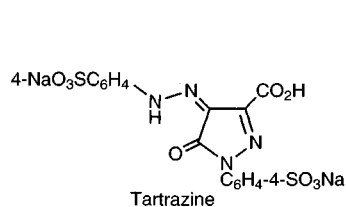
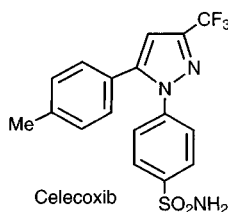
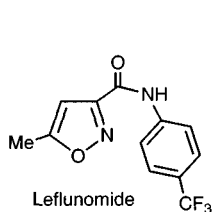
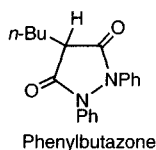


The physical properties of the three 1,2-azoles, pyrazole,¹ isothiazole² and isoxazole³ can be usefully compared and contrasted with those of their 1,3-isomeric counterparts. Echoing the higher boiling point of imidazole, pyrazole, which is the only one of the trio to be solid at room temperature, also has a much higher boiling point (187°C) than isothiazole or isoxazole (114°C and 95°C) again reflecting the intermolecular hydrogen bonding available only to pyrazole. This association probably takes the form of dimers, trimers, and oligomers; dimeric forms are of course not available to imidazole. Each 1,2-azole has a pyridine-like odour but is only partially soluble in water. The dihydro and tetrahydro heterocycles are named pyrazoline/pyrazolidine, isothiazoline/isothiazolidine, and isoxazoline/isoxazolidine.

Rapid tautomerism, involving switching of hydrogen from one nitrogen to the other, as in imidazoles, means that substituted pyrazoles are inevitably mixtures, and a nomenclature analogous to that used for imidazoles, is employed to signify this: 3(5)-methylpyrazole, for example.



Phenylbutazone has been utilised for some time in the treatment of severe arthritis, which, incidentally, afflicted such notables as Casanova, Goethe, and Luther. Leflunomide is used in the therapy of autoimmune diseases, such as active rheumatoid arthritis. Celecoxib is the first to market of a number of selective cyclooxygenase 2 (COX 2) inhibitors which show great promise as anti-inflammatory and analgetic agents, without the undesirable side effects associated with other non-steroidal anti-inflammatories. There are many pyrazole dyestuffs – the food colourant tartrazine is one such substance.

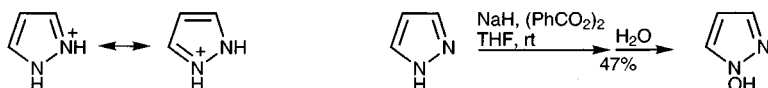


22.1 Reactions with electrophilic reagents

22.1.1 Addition at nitrogen

22.1.1.1 Protonation

Direct linking of two heteroatoms has a very marked base-weakening effect, as in hydrazine and hydroxylamine (pK_a s: NH_3 , 9.3; H_2NNH_2 , 7.9; HONH_2 , 5.8), and this is mirrored in the 1,2-azoles: pyrazole with a pK_a of 2.5 is some 4.5 pK_a units weaker than imidazole; isothiazole (−0.5) and isoxazole (−3.0) are some 3 pK_a units weaker than their 1,3-isomers. The higher basicity of pyrazole reflects the symmetry of the cation with its two equivalent contributing resonance structures. Clearly, again, oxygen has a larger electron-withdrawing effect than sulfur.



22.1.1.2 Oxidation at nitrogen

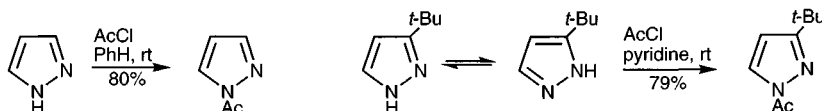
The preparation of 1-hydroxypyrazoles can employ peracidic conditions⁴ or basic conditions,⁵ when it is the pyrazolyl anion which reacts with the oxidising agent, dibenzoyl peroxide.

22.1.1.3 Alkylation at nitrogen

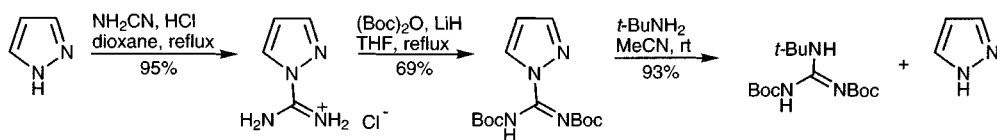
The 1,2-azoles are more difficult to quaternise than their 1,3-analogues: isothiazoles, for example, require reactive reagents such as benzyl halides or Meerwein salts.⁶ Additionally, isoxazolium salts are particularly susceptible to ring cleavage (see section 22.11). 3(5)-Substituted pyrazoles which have an *N*-hydrogen, can in principle give rise to two isomeric *N*-alkyl pyrazoles, after loss of proton from nitrogen, and there is the further complication that this initial product can undergo further reaction producing an *N,N'*-disubstituted quaternary salt.⁷ However, the quaternisation of an already 1-substituted pyrazole generally requires more vigorous conditions, no doubt because of steric impediment to reaction due to the substituent on the adjacent nitrogen. Microwave irradiation improves the rate of *N*-alkylation.⁸

22.1.1.4 Acylation at nitrogen

The introduction of an acyl⁹ or phenylsulfonyl¹⁰ group onto a pyrazole nitrogen is usually achieved in the presence of a weak base such as pyridine; such processes proceed *via* imine nitrogen acylation, then N^+-H -deprotonation. Since acylation, unlike alkylation, is reversible, the more stable product is obtained.



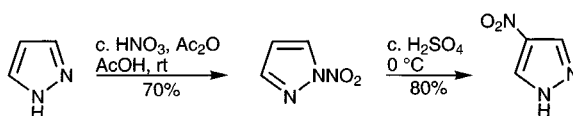
Pyrazole reacts with cyanamide very efficiently to produce an *N*-derivative which can be utilised, by reaction with primary or secondary amines, to synthesise guanidines.¹¹ Conversion of the pyrazolyl guanidine to a doubly *t*-butoxycarbonyl-protected pyrazolyl guanidine then allows this to be used for the direct synthesis of protected guanidines, as illustrated.¹²



22.1.2 Substitution at carbon

22.1.2.1 Nitration

Pyrazole¹³ and isothiazole¹⁴ undergo straightforward nitration, at C-4, but the less reactive isoxazole nitrates in negligible yield; 3-methylisoxazole, however, has sufficient extra reactivity that it can be satisfactorily nitrated, at C-4.¹⁵ With acetyl nitrate or dinitrogen tetroxide/ozone,¹⁶ 1-nitropyrazole is formed but this can be rearranged to 4-nitropyrazole in acid at low temperature.¹⁷



22.1.2.2 Sulfonation

Electrophilic sulfonation of isoxazole is of no preparative value; the substitution of only the phenyl substituent of 5-phenylisoxazole with chlorosulfonic acid makes the same point.¹⁸ Both isothiazole^{2a,19} and pyrazole²⁰ can be satisfactorily sulfonated.

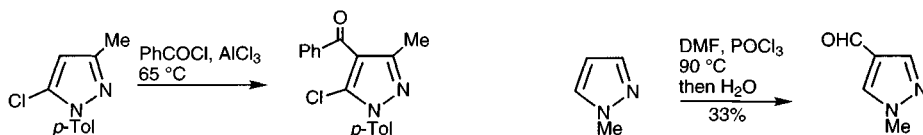


22.1.2.3 Halogenation

Halogenation of pyrazole gives 4-monohalopyrazoles, for example 4-iodo-,²¹ or 4-bromopyrazole²² under controlled conditions. Poor yields are obtained on reaction of isothiazole²³ and isoxazole²⁴ with bromine, again with attack at C-4, but with activating groups present, halogenation proceeds better.²⁵ 3,4,5-Tribromopyrazole is formed efficiently in alkaline solution, presumably the pyrazolyl anion is the reacting species.²⁶

22.1.2.4 Acylation

Only for pyrazole, of the trio, have any useful electrophilic substitutions involving carbon electrophiles been described,^{10,27} and even here only *N*-substituted pyrazoles react well, perhaps because of inhibition of N^+ -salt formation.

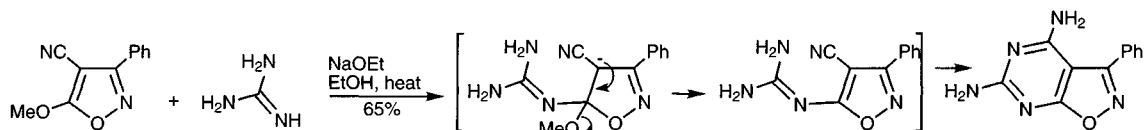
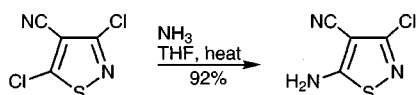


22.2 Reactions with oxidising agents

The 1,2-azole ring systems are relatively stable to oxidative conditions, allowing substituent alkyl, or more efficiently, acyl groups to be oxidised up to carboxylic acid.²⁸ Ozone cleaves the isoxazole ring.²⁹

22.3 Reactions with nucleophilic reagents

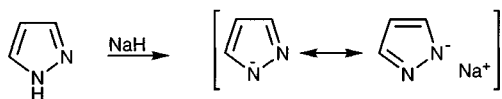
The 1,2-azoles do not generally react with nucleophiles with replacement of hydrogen; there is a limited range of examples of displacements of leaving groups from the 5-position³⁰ when it is activated by a 4-keto or similar group, but interestingly, 3-halo groups are less easily displaced; 4-halides behave like halobenzenes.



22.4 Reactions with bases

22.4.1 Deprotonation of pyrazole *N*-hydrogen

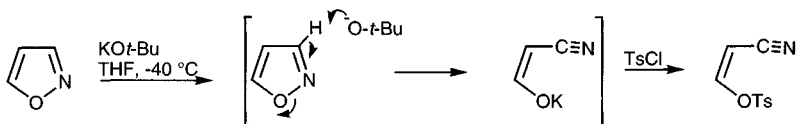
The pK_a for loss of the *N*-hydrogen of pyrazole is 14.2, compared with 17.5 for imidazole, though there are again two, equally-contributing resonance forms.



22.4.2. Deprotonation of C-hydrogen³¹

The C-5-deprotonation of pyrazoles requires the absence of the *N*-hydrogen; removable *N*-protecting groups which have been used include phenylsulfonyl,³² trimethylsilylethoxymethyl,³³ hydroxymethyl,³⁴ methylsulfonyl,³⁵ and pyrrolidin-1-ylmethyl.³⁶ The use of 1-benzyloxypyrazole gives 5-substituted-1-hydroxypyrazoles after subsequent hydrogenolytic removal of the benzyl group.³⁷ Dimethylaminosulfonyl has been used frequently and the 5-lithiated derivative transformed into the zinc compound and this coupled using palladium(0) catalysis.³⁸ Isothiazole undergoes rapid exchange at C-5 with sodium deuterioxide in DMSO.³⁹

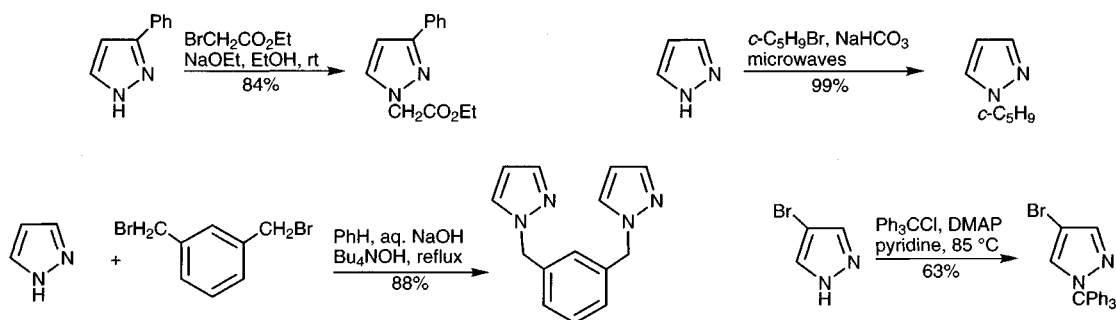
Attempted C-deprotonation of isoxazoles with hydrogen at C-3 leads inevitably to ring opening, with the oxygen as anionic leaving group,⁴⁰ indeed this type of cleavage was first recognised as long ago as 1891, when Claisen found that 5-phenylisoxazole was cleaved by sodium ethoxide⁴¹ (see section 22.11 for ring cleavage of isoxazolium salts). Comparable cleavages of isothiazoles can also be a problem.



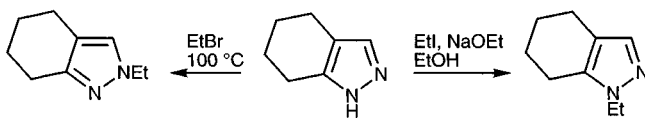
2-Methoxymethoxy-5-phenylisoxazole lithiates at C-4⁴² as does 3-amino-5-methylisoxazole, protected as a *t*-butoxycarbonyl urethane, but using two equivalents of *n*-butyllithium.⁴³

22.5 Reactions of *N*-metallated pyrazoles

N-Alkylations can be conducted in strongly basic,⁴⁴ or phase-transfer conditions⁴⁵ or in the presence of 4-dimethylaminopyridine,⁴⁶ and it seems likely that under these conditions it is the pyrazolyl anion (section 22.4.1) which is alkylated. The use of sodium hydrogen carbonate, without solvent, but with microwave heating is highly recommended.⁴⁷

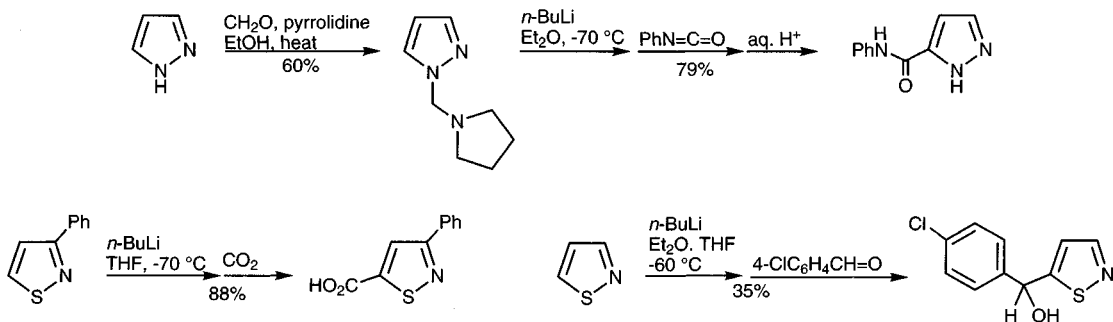


3(5)-Substituted pyrazoles may give a product isomeric with that which is obtained by reaction in neutral solution.⁷

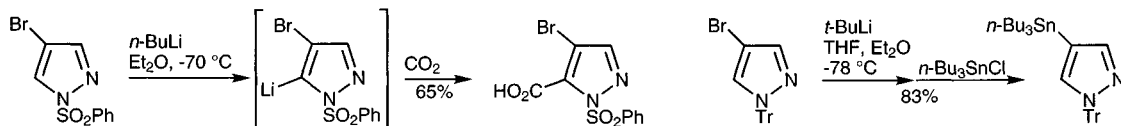


22.6 Reactions of *C*-metallated 1,2-azoles

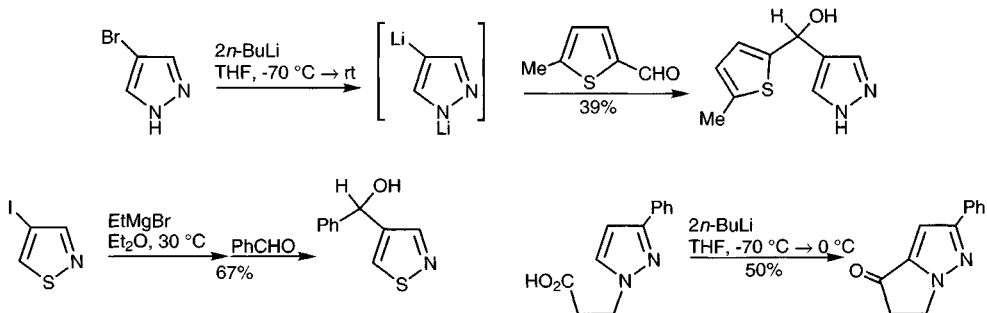
The reactions of 5-lithiated isothiazoles and of 5-lithiated-1-substituted pyrazoles allow the introduction of substituents at that position by reaction with a range of electrophiles; two examples are shown below.^{36,48,49}



It is significant that treatment of 4-bromo-1-phenylsulfonylpyrazole with *n*-butyllithium results in 5-deprotonation and not metal halogen exchange,³² however 4-bromo-1-triphenylmethylpyrazole undergoes normal exchange and in this way a tin derivative is obtained which undergoes routine palladium-catalysed couplings.⁴⁶

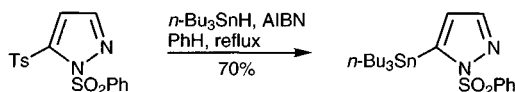


Metal-halogen exchange has been achieved in the formation of 3-lithio-1-methylpyrazole from the bromopyrazole,⁵⁰ and reaction of 4-bromopyrazole with two equivalents of *n*-butyllithium produced a 1,4-dilithiopyrazole which reacts normally with electrophiles at C-4.⁵¹ 4-Iodoisothiazole can be converted into a magnesium compound which shows normal nucleophilic Grignard properties.⁵² An intramolecular acylation, involving the lithium salt of an acid, is observed when pyrazoles carrying a suitable length chain on nitrogen are lithiated with two mol equivalents of the strong base.⁵³



22.7 Reactions with radicals

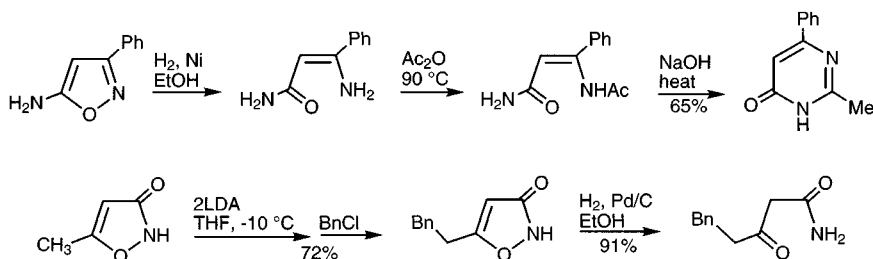
The interaction of 1,2-azoles with radical reagents is an area in which little is known so far. Displacement of tosyl from the 5-position of a protected pyrazole shows that there is potential for further development.⁵⁴



22.8 Reactions with reducing agents

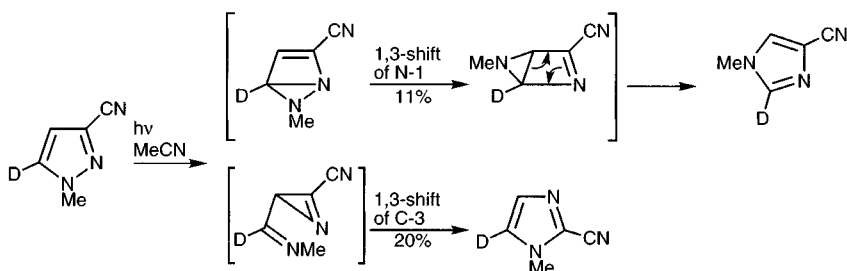
Pyrazoles are relatively stable to catalytic and chemical reductive conditions, particularly when there is no substituent on nitrogen, though catalytic reduction can be achieved in acid solution.⁵⁵ Isothiazoles are reductively desulfurised using Raney nickel, with loss of the ring.⁵⁶ Catalytic hydrogenolysis of the N–O bond in isoxazoles takes place readily over the usual noble metal catalysts,⁵⁷ and this process is central to the stratagem in which isoxazoles are employed as masked 1,3-dicarbonyl compounds. The immediate products of N–O hydrogenolysis, β -aminoenones, can often be isolated as such, or further processed. The use of this

ring cleavage to provide routes to pyrimidinones,⁵⁸ and 3-keto-carboxamides, is illustrated below.⁵⁹

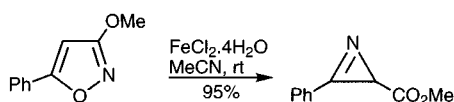


22.9 Electrocyclic reactions

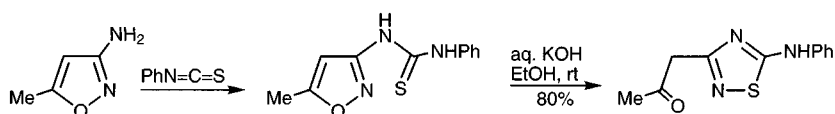
There are examples of 1,2-azoles being converted into their 1,3-isomers by irradiation, though such processes are of limited preparative value. The conversion of cyanopyrazoles into cyanoimidazoles was studied using 3-cyano-5-deuterio-1-methylpyrazole, the resulting mixture of products requiring a duality of mechanism.⁶⁰



In a similar way, irradiation converts many simpler pyrazoles into imidazoles,⁶¹ phenylisothiazoles⁶² and methylisothiazoles⁶³ partially into the corresponding thiazoles, and 3,5-diarylisoxazoles converted into 2,5-disubstituted oxazoles.⁶⁴ 3-Alkoxyisoxazoles undergo an extraordinary ring contraction with iron(II) chloride, producing azirine esters.⁶⁵

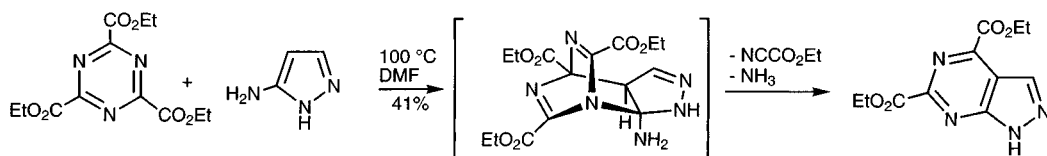


The transformation of 1,2-azoles carrying, at C-3, a side-chain of three atoms terminating in a doubly-bonded heteroatom, into isomeric systems with a new five-membered ring is a general process,⁶⁶ though there is no definitive view as to the details of its mechanism.



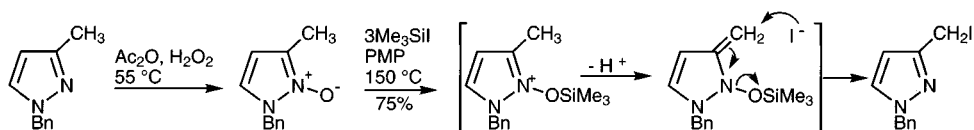
There do not appear to be any examples of 1,2-azoles acting as 1-azadienes in cycloadditions. 4-Nitroisoxazoles react with dienes across the 4,5-bond⁶⁷ and in processes useful for the synthesis of purine analogues, 3(5)-aminopyrazoles add to

electron-deficient 1,3,5-triazines, across the pyrazole 4,5-bond, subsequent eliminations giving the final aromatic product.⁶⁸



22.10 Alkyl-1,2-azoles

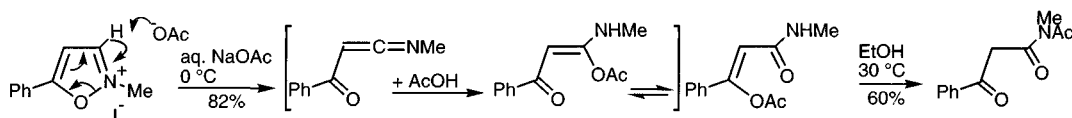
4-Methylisothiazoles are not especially acidic, but it is rather surprising that 3-methylisothiazoles are also not reactive whereas 5-methyl substituents will undergo condensation reactions.⁶⁹ This same effect is also found in isoxazoles. In order to study methyl group acidity in isoxazoles, the 3-position was blocked to prevent ring degradation (section 22.4.2), thus 3,5-dimethylisoxazole was shown to exchange, with methoxide in methanol, 280 times faster at the 5- than at the 3-methyl group. Preparative deprotonations of this same isoxazole proceed exclusively at the 5-methyl substituent, allowing subsequent reactions with electrophiles at that position. So strong is this tendency, that reaction of 3,5-dimethylisoxazole with three equivalents of base and three equivalents of iodomethane produces only 5-*t*-butyl-3-methylisoxazole, no alkylation of the 3-methyl being observed, even in competition with the 5-isopropyl group which is present in a penultimate intermediate.⁷⁰ By working at low temperature, thus avoiding ring degradation, 5-methylisoxazole can be deprotonated at the methyl, without the 3-deprotonation which would cause ring degradation.⁷¹ Conversion to *N*-oxide⁷² activates adjacent methyl groups, for example subsequent reaction with trimethylsilyl iodide permits side-chain iodination.⁷³



On subjection of 3-methyl-5-phenylisothiazole or 3-methyl-5-phenylisoxazole to lithiation conditions, competitive side-chain and C-4 deprotonation is observed except when lithium *i*-propyl(cyclohexyl)amide (LICA) is used – this allows exclusive side-chain lithiation.⁷⁴

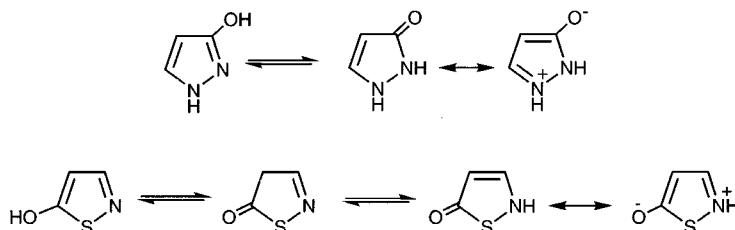
22.11 Quaternary 1,2-azolium salts

The base-catalysed degradation of the ring of isoxazolium salts is particularly easy, requiring only alkali metal carboxylates to achieve it. The mechanism,⁷⁵ illustrated for the acetate-initiated degradation of 2-methyl-5-phenylisoxazolium iodide, involves initial 3-deprotonation with cleavage of the N–O bond; subsequent rearrangements lead to an enol acetate which rearranges to a final keto-imide.

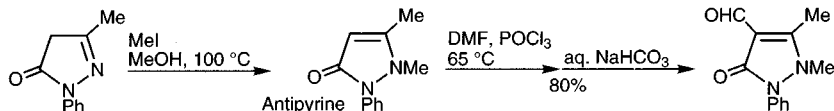


22.12 Oxy- and amino-1,2-azoles

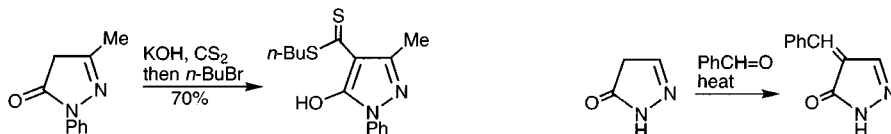
Only 4-hydroxy-1,2-azoles can be regarded as being phenol-like.⁷⁶ 3- and 5-Hydroxy-1,2-azoles exist mainly in carbonyl tautomeric forms, encouraged by resonance involving donation from a ring heteroatom, and are therefore known as pyrazolones, isothiazolones, and isoxazolones, though for all three systems, and depending on the nature of other substituents, an appreciable percentage of hydroxy tautomer exists in solution.



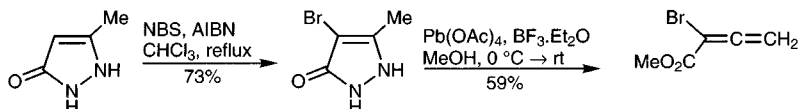
The reactivity of the 3- and 5-azolones centres mainly on their ability to react with electrophiles such as halogens,⁷⁷ (giving 4,4-dihalo-derivatives with excess reagent – 4,4-dibromo-3-methylpyrazol-5-one is a *para*-selective brominating agent for phenols and anilines⁷⁸), or to nitrate,⁷⁹ or undergo Vilsmeier formylation;⁸⁰ the example shown below is the formylation of ‘Antipyrine’ once used as an analgesic. Many dyestuffs have been synthesised *via* coupling of aryldiazonium cations with 5-pyrazolones at C-4 – tartrazine is such an example.



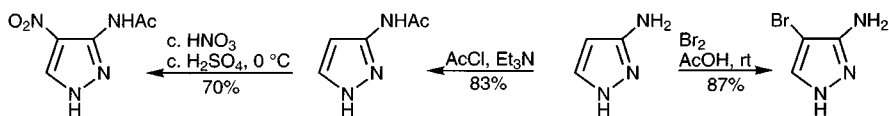
Pyrazolones also condense with aldehydes⁸¹ in aldol-type processes, or react with other electrophiles such as carbon disulfide,⁸² in each case reaction presumably proceeding *via* the enol tautomer, or its anion. In basic solution oxazol-3-ones alkylate either on oxygen or nitrogen and the choice of base can influence the ratio.⁴²



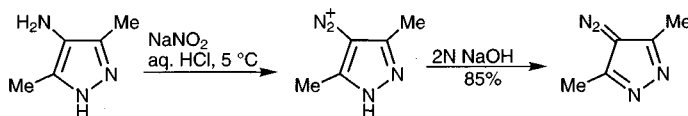
An intriguing and simple synthesis of a useful bromo-allene depends on the lead(IV) acetate oxidation of a bromopyrazolone, as shown.⁸³



Amino-1,2-azoles exist as the amino tautomers. Aminopyrazoles and amino-isothiazoles are relatively well behaved aromatic amines, for example 3(5)-aminopyrazole undergoes substituent-*N*-acetylation and easy electrophilic bromination at C-4.⁸⁴ Diazotisation and a subsequent Sandmeyer reaction provides routes to halo-isothiazoles,⁵² and azidopyrazoles.⁸⁵



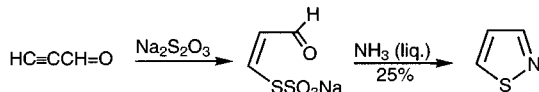
Diazotisation of 4-aminopyrazoles, then deprotonation yields stable diazopyrazoles.⁸⁶



22.13 Synthesis of 1,2-azoles⁸⁷

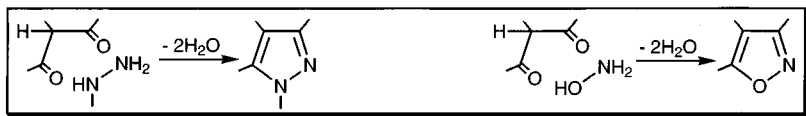
22.13.1 Ring synthesis

There are parallels, but also methods unique to particular 1,2-azoles, in the principal methods available for the construction of pyrazoles, isothiazoles and isoxazoles: neither the reaction of propene with sulfur dioxide and ammonia at 350 °C which gives isothiazole itself⁸⁸ in 65% yield, nor a synthesis⁸⁹ from propargyl aldehyde and thiosulfate (shown below) have direct counterparts for the other 1,2-azoles.

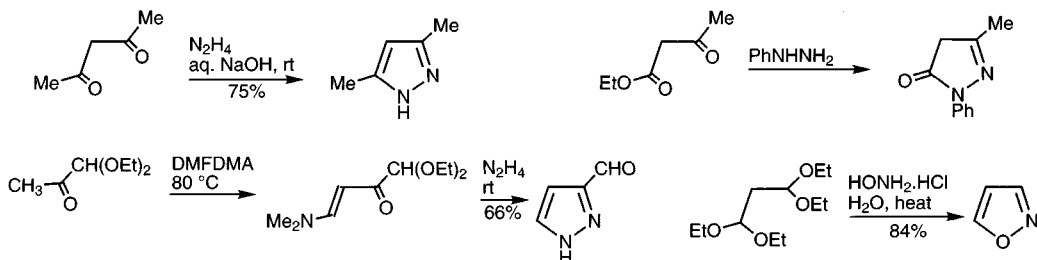


22.13.1.1 From 1,3-dicarbonyl compounds and hydrazines or hydroxylamine

Pyrazoles and isoxazoles can be made from a 1,3-dicarbonyl component and a hydrazine or hydroxylamine respectively.

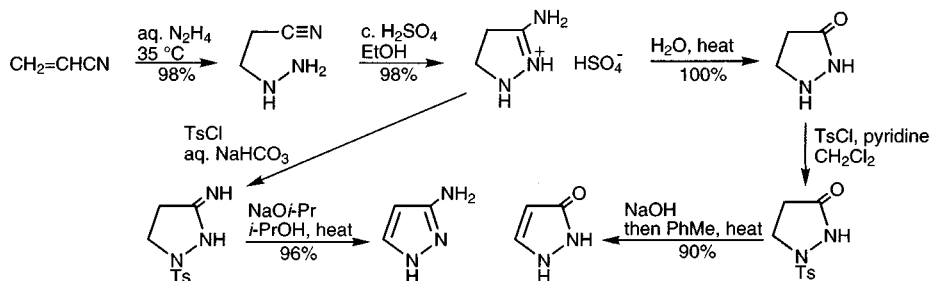


This, the most widely used route to pyrazoles and isoxazoles rests on the doubly nucleophilic character of hydrazines and hydroxylamines, allowing them to react in turn with each carbonyl group of a 1,3-diketone⁹⁰ or 1,3-keto-aldehyde, often with one of the carbonyl groups (especially when aldehyde) masked as enol ether,⁹¹ acetal, imine,⁹² or enamine,⁹³ or another synthon for one of these.

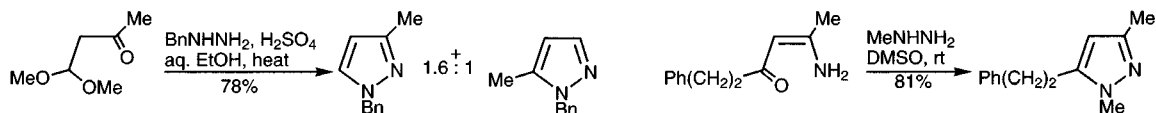


When β -keto-esters are used, the products are pyrazolones⁹⁴ or isoxazolones;⁹⁵ similarly, β -ketonitriles with hydrazines give 3(5)-aminopyrazoles.⁹⁶ 3(5)-Aminopyrazole itself is prepared *via* a dihydro-precursor formed by addition of hydrazine to

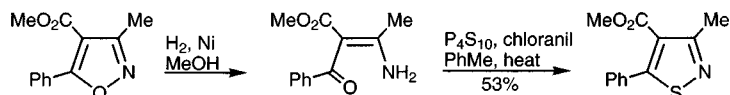
acrylonitrile then cyclisation;⁹⁷ hydrolysis of the first cyclic intermediate in this sequence and dehydrogenation *via* elimination of *p*-toluenesulfate allows preparation of 3(5)-pyrazolone.⁹⁸



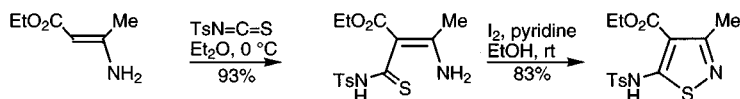
Generally speaking, unsymmetrical 1,3-dicarbonyl components produce mixtures of 1,2-azole products.⁷⁶ Sometimes this difficulty can be circumvented by the use of acetylenic-aldehydes or -ketones, for here a hydrazone or oxime can be formed first by reaction at the carbonyl group and this can then be cyclised in a separate, second step.⁹⁹ Pyrazole itself can be formed by the reaction of hydrazine with propargyl aldehyde.⁸ Using β -chloro-,¹⁰⁰ β -alkoxy-¹⁰¹ or β -amino-¹⁰² -enones as 1,3-dicarbonyl synthons is another way to influence the regiochemistry of reaction, and in favourable situations this can be effective.¹⁰³



When a β -aminoenethione, which can be produced from an isoxazole *via* hydrogenolysis then reaction of the β -aminoenone with a thionating agent, is treated with a dehydrogenating agent such as chloranil¹⁰⁴ or sulfur,¹⁰⁵ ring closure to an isothiazole results.



The ring closure of β -amino α,β -unsaturated thioamides comparably leads to 5-aminoisothiazoles.¹⁰⁶



In another oxidative closure, the oximes of chalcones close to isoxazoles using tetrakis(pyridine)cobalt(II) bis(chromate),¹⁰⁷ and in an interesting variant, isoxazoles and pyrazoles are formed from 1,3-diynes.¹⁰⁸

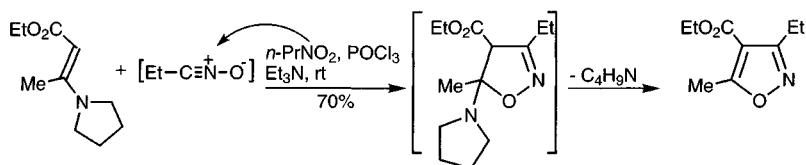


22.13.1.2 Dipolar cycloadditions of nitrile oxides and nitrile imines

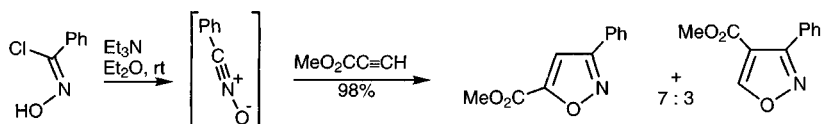
Isoxazoles are produced by the dipolar cycloaddition of nitrile oxides to alkynes; pyrazoles result from the comparable interaction of alkynes with nitrile imines.



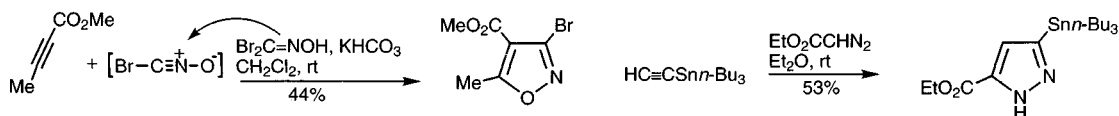
Nitrile oxides ($R-C\equiv N^+-O^-$),¹⁰⁹ which can be generated by base-catalysed elimination of hydrogen halide from halooximes ($RC(Hal)=NOH$), or by dehydration of nitro compounds¹¹⁰ (RCH_2NO_2), readily add to alkenes and to alkynes generating five-membered heterocycles. Addition to an alkene produces an isoxazoline, unless the alkene also incorporates a group capable of being eliminated in a step after the cycloaddition as shown below;¹¹¹ isoxazolines can be dehydrogenated to the aromatic system.^{112,113}



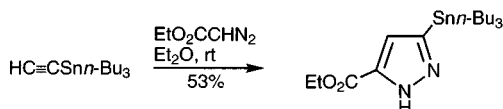
Cycloaddition of a nitrile oxide to an alkyne generates an aromatic isoxazole directly. Monoalkyl- or -aryl-substituted alkynes lead to 5-substituted isoxazoles;¹¹⁴ with other mono-substituted alkynes, mixtures are obtained.¹¹⁵



A useful route to 3-bromoisoxazoles rests on the cycloaddition of bromonitrile oxide.¹¹⁶



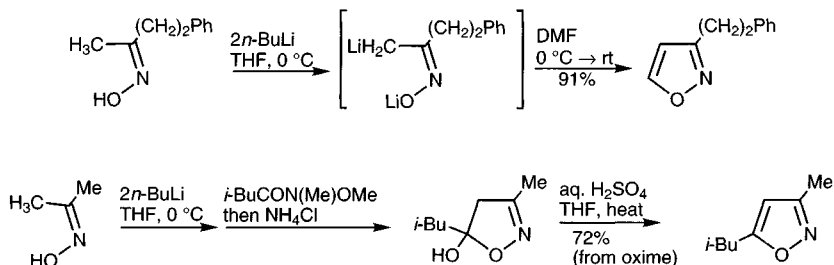
The cycloaddition of diazoalkanes with alkynes gives pyrazoles; the use of stannyl alkynes¹¹⁷ produces tin derivatives of the heterocycle, for use in subsequent electrophilic *ipso* displacements, or in palladium(0)-catalysed couplings.



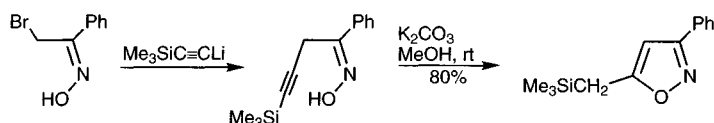
22.13.1.3 From oximes and hydrazones

Exposure of ketone oximes which have an α -hydrogen, to two mol equivalents of *n*-butyllithium leads to *O*- and *C*-lithiation (*syn* to the oxygen); reaction with dimethylformamide as electrophile then allows *C*-formylation and ring closure *in situ*

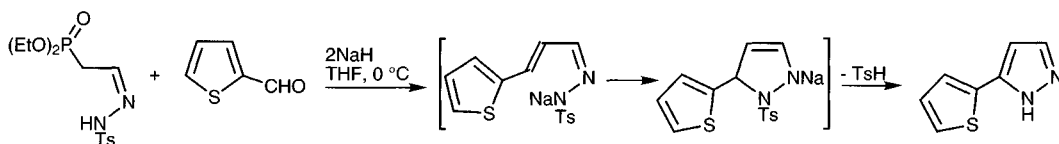
to a 5-unsubstituted isoxazole.¹¹⁸ Similarly, reaction of the dianion to an acylating agent (an ester¹¹⁹ or a Weinreb amide¹²⁰) leads through to 5-substituted isoxazoles.



Displacement of the halogen of an α -bromoketone oxime with an alkyne leads to an intermediate which closes to an isoxazole simply on treatment with mild base.¹²¹ Acylation of the di-anions of ketone *t*-butoxycarbonylhydrazones produces pyrazoles, and an example of this methodology is shown below.¹²²



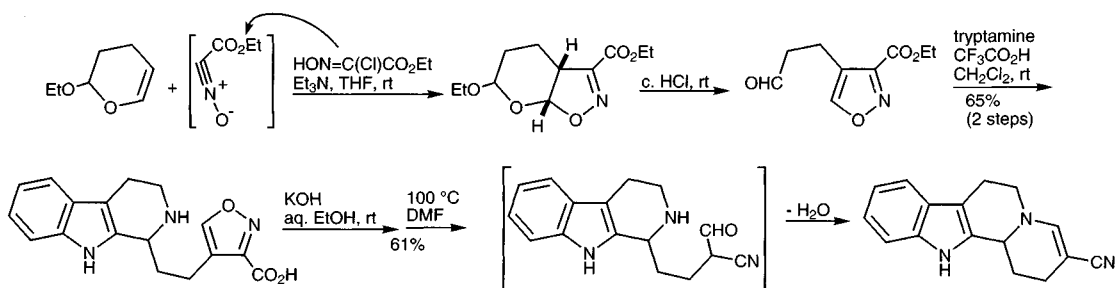
An extremely elegant route to pyrazoles which allows control over all three substituents, involves forming a ring closure precursor by Horner/Emmons condensation of a tosylhydrazone-phosphonate with an aldehyde, which become the 5-substituent; intramolecular Michael addition and then loss of toluenesulfinate, completes the sequence.¹²³



22.13.2 Notable syntheses using 1,2-azoles

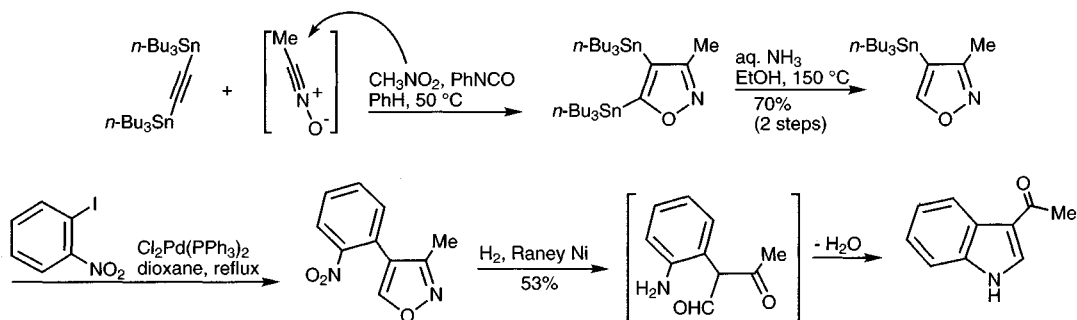
22.13.2.1 5-Cyano-1,2,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine¹²⁴

In this sequence, a nitrile oxide addition to an enol ether then elimination formed the isoxazole. Ring cleavage of the isoxazole accompanying decarboxylation, showed how the heterocycle can serve as a synthon for an α -cyano aldehyde.



22.13.2.2 3-Acetylidole¹²⁵

In view of the C-5 selectivity observed in lithiations, the selective 5-destannylation of a 4,5-di(tri-*n*-butylstannyl)isoxazole is useful. This nice sequence utilised a coupling to a 2-iodonitrobenzene; hydrogenation/hydrogenolysis caused ring cleavage of the isoxazole and produced an intermediate which cyclised with loss of water to give the indole.



Exercises for chapter 22

Straightforward revision exercises (consult chapters 20 and 22)

- Compare 1,2- with 1,3-azoles in pairs – which is the more basic? Why?
- What is incorrect about the name: ‘3-methylpyrazole’?
- Name some groups which can be used to mask the *N*-hydrogen in pyrazoles during C-lithiation.
- For what functionality are isoxazoles synthons if the *N*–*O* bond is cleaved? How could one cleave the *N*–*O* bond?
- How are 1,3-dicarbonyl compounds used for the synthesis of isoxazoles and pyrazoles?
- Describe a method involving an electrocyclic process for the ring synthesis of an isoxazole.
- Describe a method for the utilisation of the oxime of a dialkyl ketone, to make an isoxazole.

More advanced exercises

- Suggest structures for the isomeric products, $\text{C}_9\text{H}_7\text{N}_3\text{O}_2$ formed when 1-phenylpyrazole is reacted with (i) c. H_2SO_4 /c. HNO_3 or (ii) $\text{Ac}_2\text{O}/\text{HNO}_3$. Explain the formation of different products under the two conditions.
- Draw structures for the products obtained by reacting 3,5-dimethylisoxazole with NaNH_2 then (i) *n*-PrBr; (ii) CO_2 ; or (iii) PhCO_2Me .
- Deduce structures for the products obtained by treating 5-methylisoxazole with $\text{SO}_2\text{Cl}_2 \rightarrow \text{C}_4\text{H}_4\text{ClNO}$, and this with aqueous sodium hydroxide $\rightarrow \text{C}_4\text{H}_4\text{ClNO}$ (which contains no rings).
- Draw the structures of the products which would be formed from the reaction of BnNHNH_2 with $\text{MeCOCH}_2\text{COCO}_2\text{Me}$.
- Deduce structures for the products formed in the following sequence: pyrazole/ $\text{Me}_2\text{NSO}_2\text{Cl}/\text{Et}_3\text{N} \rightarrow \text{C}_5\text{H}_9\text{N}_3\text{O}_2\text{S}$ then this with $n\text{-BuLi}/-70^\circ\text{C}$ then $\text{TMSCl} \rightarrow \text{C}_8\text{H}_{17}\text{N}_3\text{O}_2\text{SSi}$ then this with $\text{PhCH=O}/\text{CsF} \rightarrow \text{C}_{12}\text{H}_{15}\text{N}_3\text{SO}_3$.

6. Draw the structures of the two products which are formed when hydroxylamine reacts with $\text{PhCOCH}_2\text{CH}=\text{O}$; suggest an unambiguous route for the preparation of 5-phenylisoxazole.
7. Deduce the structures of the heterocyclic substances produced: (i) $\text{C}_7\text{H}_9\text{NO}$, from cyclohexanone oxime with 2 mol equivalents of *n*-BuLi then dimethyl formamide; (ii) $\text{C}_{11}\text{H}_{15}\text{NOSSi}$ from thien-2-ylC(=NOH)CH₂Br and $\text{Me}_3\text{SiC}\equiv\text{CLi}$ then $\text{K}_2\text{CO}_3/\text{MeOH}$; (iii) $\text{C}_{11}\text{H}_{12}\text{N}_2$ from $\text{MeCOC}(=\text{NNHPh})\text{Me}$ with $(\text{EtO})_2\text{POCH}_2\text{SEt}/n\text{-BuLi}$.
8. Suggest a structure for the heterocyclic product, $\text{C}_7\text{H}_{13}\text{NOSi}$, formed by reaction of $\text{Me}_3\text{SiC}\equiv\text{CC}\equiv\text{CSiMe}_3$ and hydroxylamine.

References

1. 'Progress in pyrazole chemistry', Kost, A. N. and Grandberg, I. I., *Adv. Heterocycl. Chem.*, **1966**, 6, 347; 'The Azoles', Schofield, K., Grimmett, M. R., and Keene, B. R. T., Cambridge University Press, **1976**.
2. (a) 'Isothiazoles', Hübenett, F., Flock, F. H., Hansel, W., Heinze, H., and Hofmann, H., *Angew. Chem., Int. Ed. Engl.*, **1963**, 2, 714; (b) 'Isothiazoles', Slack, R. and Wooldridge, K. R. H., *Adv. Heterocycl. Chem.*, **1965**, 4, 107; 'Recent advances in the chemistry of mononuclear isothiazoles', Wooldridge, K. R. H., *ibid.*, **1972**, 14, 1.
3. 'Recent developments in isoxazole chemistry', Kochetkov, N. K. and Sokolov, S. D., *Adv. Heterocycl. Chem.*, **1963**, 2, 365; 'Isoxazole chemistry since 1963', Wakefield, B. J. and Wright, D. J., *ibid.*, **1979**, 25, 147; 'Synthetic reactions using isoxazole compounds', Kashima, C., *Heterocycles*, **1979**, 12, 1343.
4. Begtrup, M. and Vedso, P., *J. Chem. Soc., Perkin Trans. 1*, **1995**, 243.
5. Reuther W., and Baus, V., *Liebigs Ann.*, **1995**, 1563.
6. Chaplen, P., Slack, R., and Wooldridge, K. R. H., *J. Chem. Soc.*, **1965**, 4577.
7. v. Auwers, K., Buschmann, W., and Heidenreich, R., *Justus Liebigs Ann. Chem.*, **1924**, 435, 277.
8. Pérez, E., Sotelo, E., Loupy, A., Mocelo, R., Suarez, M., Pérez, R., and Autié, M., *Heterocycles*, **1996**, 43, 539.
9. Hüttel, R. and Kratzer, J., *Chem. Ber.*, **1959**, 92, 2014; Williams, J. K., *J. Org. Chem.*, **1964**, 29, 1377.
10. Finar, I. L. and Lord, G. H., *J. Chem. Soc.*, **1957**, 3314.
11. Bernatowicz, M. S., Wu, Y., and Matsueda, G. R., *J. Org. Chem.*, **1992**, 57, 2497.
12. Drake, B., Patek, M., and Lebl, M., *Synthesis*, **1994**, 579.
13. Hüttel, R., Büchele, F., and Jochum, P., *Chem. Ber.*, **1955**, 88, 1577.
14. Caton, M. P. L., Jones, D. H., Slack, R., and Woolridge, K. R. H., *J. Chem. Soc.*, **1964**, 446.
15. Quilico, A. and Musante, C., *Gazz. Chim. Ital.*, **1941**, 71, 327.
16. Suzuki, H. and Nonoyama, N., *J. Chem. Res. (S)*, **1996**, 244.
17. Olah, G. A., Narang, S. C., and Fung, A. P., *J. Org. Chem.*, **1981**, 46, 2706.
18. Woodward, R. B., Olofson, R., and Mayer, H., *J. Am. Chem. Soc.*, **1961**, 83, 1010.
19. Pain, D. L. and Parnell, E. W., *J. Chem. Soc.*, **1965**, 7283.
20. Knorr, L., *Justus Liebigs Ann. Chem.*, **1894**, 279, 188.
21. Hüttel, R., Schäfer, O., and Jochum, P., *Justus Liebigs Ann. Chem.*, **1955**, 593, 200.
22. Lipp, M., Dallacker, F., and Munnes, S., *Justus Liebigs Ann. Chem.*, **1958**, 618, 11.
23. Finley, J. H. and Volpp, G. P., *J. Heterocycl. Chem.*, **1969**, 6, 841.
24. Pino, P., Piacenti, F., and Fatti, G., *Gazz. Chim. Ital.*, **1960**, 90, 356.
25. Blount, J. F., Coffen, D. L., and Katonak, D. A., *J. Org. Chem.*, **1978**, 43, 3821.
26. Juffermans, J. P. H., and Habraken, C. L., *J. Org. Chem.*, **1986**, 51, 4656.
27. Tojahn, C. A., *Chem. Ber.*, **1922**, 55, 291.
28. Benary, E., *Chem. Ber.*, **1926**, 59, 2198; Holland, A., Slack, R., Warren, T. F., and Buttimore, J. *Chem. Soc.*, **1965**, 7277; Quilico, A., and Stagno d'Alcontres, G., *Gazz. Chim. Ital.*, **1949**, 79, 654.
29. Kashima, C., Takahashi, K., and Hosomi, A., *Heterocycles*, **1994**, 37, 1075.

30. Dornow, A. and Teckenburg, H., *Chem. Ber.*, **1960**, 93, 1103; Hatchard, W. R., *J. Org. Chem.*, **1964**, 29, 660.
31. Iddon, B., 'Synthesis and reactions of lithiated monocyclic azoles containing two or more hetero-atoms. Part I: Isoxazoles', *Heterocycles*, **1994**, 37, 1263; Grimmett, M. R. and Iddon, B., 'Part III: Pyrazoles', *ibid.*, **1994**, 37, 2087; Iddon, B., 'Part V: Isothiazoles and thiazoles', *ibid.*, **1995**, 41, 533.
32. Heinisch, G., Holzer, W., and Pock, S., *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1829.
33. Fugina, N., Holzer, W., and Wasicky, M., *Heterocycles*, **1992**, 34, 303.
34. Katritzky, A. R., Lue, P., and Akutagawa, K., *Tetrahedron*, **1989**, 45, 4253.
35. Effenberger, F., Roos, M., Ahmad, R., and Krebs, A., *Chem. Ber.*, **1991**, 124, 1639.
36. Katritzky, A. R., Rewcastle, G. W., and Fan, W.-Q., *J. Org. Chem.*, **1988**, 53, 5685.
37. Vedso, P. and Begtrup, M., *J. Org. Chem.*, **1995**, 60, 4995.
38. Yagi, K., Ogura, T., Numata, A., Ishii, S., and Arai, K., *Heterocycles*, **1997**, 45, 1463.
39. White, J. A. and Anderson, R. C., *J. Heterocycl. Chem.*, **1969**, 6, 199.
40. Hessler, E. J., *J. Org. Chem.*, **1976**, 41, 1828.
41. Claisen, L. and Stock, R., *Chem. Ber.*, **1891**, 24, 130.
42. Alzeer, J., Nock, N., Wassner, G., and Masciadri, R., *Tetrahedron Lett.*, **1996**, 37, 6857.
43. Konoike, T., Kando, Y., and Araki, Y., *Tetrahedron Lett.*, **1996**, 37, 3339.
44. Jones, R. G., Mann, M. J., and McLaughlin, K. C., *J. Org. Chem.*, **1954**, 19, 1428.
45. e.g. Hartshorne, C. M. and Steel, P. J., *Aust. J. Chem.*, **1995**, 48, 1587.
46. Elguero, J., Jaramillo, C., and Pardo, C., *Synthesis*, **1997**, 563.
47. Almena, I., Diez-Barra, E., de la Hoz, A., Ruiz, J., and Sánchez-Migallón, A., *J. Heterocycl. Chem.*, **1998**, 35, 1263.
48. Layton, A. J. and Lunt, E., *J. Chem. Soc.*, **1968**, 611.
49. Béringer, M., Priejs, B., and Erlenmeyer, H., *Helv. Chim. Acta*, **1966**, 49, 2466.
50. Pavlik, J. W. and Kurzweil, E. M., *J. Heterocycl. Chem.*, **1992**, 29, 1357.
51. Hahn, M., Heinisch, G., Holzer, W., and Schwarz, H., *J. Heterocycl. Chem.*, **1991**, 28, 1189.
52. Guilloteau, F. and Miginiac, L., *Synth. Commun.*, **1995**, 25, 1383.
53. Larsen, S. D., *Synlett*, **1997**, 1013.
54. Caddick, S. and Joshi, S., *Synlett*, **1992**, 805.
55. Thoms, H. and Schnupp, J., *Justus Liebigs Ann. Chem.*, **1923**, 434, 296.
56. Adams, A. and Slack, R., *J. Chem. Soc.*, **1959**, 3061.
57. Baraldi, P. G., Barco, A., Benetti, S., Moroder, F., Pollini, G., and Simoni, D., *J. Org. Chem.*, **1983**, 48, 1297.
58. Shaw, G. and Sugowdz, G., *J. Chem. Soc.*, **1954**, 665.
59. Oster, T. A. and Harris, T. M., *J. Org. Chem.*, **1983**, 48, 4307.
60. Barltrop, J. A., Day, A. C., Mack, A. G., Shahrissa, A., and Wakamatsu, S., *J. Chem. Soc., Chem. Commun.*, **1981**, 604.
61. Tiefenthaler, H., Dörscheln, W., Göth, H., and Schmid, H., *Helv. Chim. Acta*, **1967**, 50, 2244; Pavlik, J. W., Kebede, N., Bird, N. P., Day, A. C., and Barltrop, J. A., *J. Org. Chem.*, **1995**, 60, 8138.
62. Maeda, M., Kawahara, A., Kai, M., and Kojima, M., *Heterocycles*, **1975**, 3, 389.
63. Pavlik, J. W., Pandit, C. R., Samuel, C. J., and Day, A. C., *J. Org. Chem.*, **1993**, 58, 3407.
64. Singh, B. and Ullman, E. F., *J. Am. Chem. Soc.*, **1967**, 89, 6911.
65. Auricchio, S., Biri, A., Pastormerlo, E., and Truscetto, A. M., *Tetrahedron*, **1997**, 53, 10911.
66. 'Mononuclear heterocyclic rearrangements', Ruccia, M., Vivona, N., and Spinelli, D., *Adv. Heterocycl. Chem.*, **1981**, 29, 141.
67. Turchi, S., Giomi, D., and Nesi, R., *Tetrahedron*, **1995**, 51, 7085.
68. Dang, Q., Brown, B. S., Erion, M. D., *J. Org. Chem.*, **1996**, 61, 5204.
69. Hofmann, H., *Justus Liebigs Ann. Chem.*, **1965**, 690, 147.
70. Kashima, C., Yamamoto, Y., Tsuda, Y., and Omote, Y., *Bull. Chem. Soc. Jpn.*, **1976**, 49, 1047.
71. Xia, X., Knerr, G., and Natale, N. R., *J. Heterocycl. Chem.*, **1992**, 29, 1297.
72. Parnell, E. W., *Tetrahedron Lett.*, **1970**, 3941; Begtrup, M., Larsen, P., and Vedso, P., *Acta Chem. Scand.*, **1992**, 46, 972.
73. Begtrup, M. and Vedso, P., *J. Chem. Soc., Perkin Trans. 1*, **1992**, 2555.

74. Alberola, A., Calvo, L., Rodriguez, T. R., and Sañudo, C., *J. Heterocycl. Chem.*, **1995**, 32, 537.
75. 'The reaction of isoxazolium salts with nucleophiles', Woodward, R. B. and Olofson, R., *Tetrahedron, Suppl. No. 7*, **1966**, 7, 415.
76. Naito, T., Nakagawa, S., Okumura, J., Takahashi, K., and Kasai, K., *Bull. Chem. Soc. Jpn.*, **1968**, 41, 959; Fagan, P. J., Neident, E. E., Nye, M. J., O'Hare, M. J., and Tang, W.-P., *Can. J. Chem.*, **1979**, 57, 904.
77. Westöö, G., *Acta Chem. Scand.*, **1952**, 6, 1499.
78. Mashraqui, S. H., Mudalian, C. D., and Hariharasubrahmanian, H., *Tetrahedron Lett.*, **1997**, 38, 4865.
79. Iseki, T., Sugiura, T., Yasunaga, S., and Nakasina, M., *Chem. Ber.*, **1941**, 74, 1420.
80. Ledrut, J., Winternitz, F., and Combes, G., *Bull. Soc. Chim. Fr.*, **1961**, 704.
81. Knorr, L., *Chem. Ber.*, **1896**, 29, 249.
82. Oliva, A., Castro, I., Castillo, C., and León, G., *Synthesis*, **1991**, 481.
83. Gilmann, T., Heckhoff, S., and Weeber, T., *Synth. Commun.*, **1994**, 24, 2133.
84. Dorn, H. and Dilcher, H., *Justus Liebigs Ann. Chem.*, **1967**, 707, 141.
85. Morgan, G. T. and Reilly, J., *J. Chem. Soc.*, **1914**, 435.
86. Patel, H. P. and Tedder, J. M., *J. Chem. Soc.*, **1963**, 4589.
87. 'Synthesis of pyrazoles and condensed pyrazoles', Makino, K., Kim, H. S., and Kurasawa, Y., *J. Heterocycl. Chem.*, **1999**, 36, 321.
88. Hübenett, F., Flock, F. H., and Hofmann, H., *Angew. Chem., Int. Ed. Engl.*, **1962**, 1, 508.
89. Wille, F., Capeller, L., and Steiner, A., *Angew. Chem., Int. Ed. Engl.*, **1962**, 1, 335.
90. Wiley, R. H. and Hexner, P. E., *Org. Synth., Coll. Vol. IV*, **1963**, 351.
91. Martins, M. A. P., Freitag, R., Flores, A. F. C., and Zanatta, N., *Synthesis*, **1995**, 1491.
92. Hoffmann, M. G., *Tetrahedron*, **1995**, 51, 9511.
93. Brederick, H., Sell, R., and Effenberger, F., *Chem. Ber.*, **1964**, 97, 3407; Domínguez, E., Ibeas, E., Martínez de Marigorta, E., Palacios, J. K., and SanMartín, R., *J. Org. Chem.*, **1996**, 61, 5435.
94. Knorr, L., *Chem. Ber.*, **1884**, 17, 546.
95. Rupe, H. and Grünholz, J., *Helv. Chim. Acta*, **1923**, 6, 102.
96. Longemann, W., Almirante, L., and Caprio, L., *Chem. Ber.*, **1954**, 87, 1175; Tupper, D. E. and Bray, M. R., *Synthesis*, **1997**, 337.
97. Dorn, H. and Zubek, A., *Org. Synth., Coll. Vol. V*, **1973**, 39.
98. Dorn, H., Zubek, A., and Hilgetag, G., *Angew. Chem., Int. Ed. Engl.*, **1966**, 5, 665.
99. Nightingale, D. and Wadsworth, F., *J. Am. Chem. Soc.*, **1945**, 67, 416; Bowden, K. and Jones, E. R. H., *J. Chem. Soc.*, **1946**, 953.
100. Barnes, R. P. and Dodson, L. B., *J. Am. Chem. Soc.*, **1943**, 65, 1585.
101. Claisen, L., *Chem. Ber.*, **1926**, 59, 144.
102. Bunnelle, W. H., Singam, P. R., Narayanan, B. A., Bradshaw, C. W., and Lion, J. S., *Synthesis*, **1997**, 439.
103. Alberola, A., González-Ortega, A., Sáadaba, L. L., and Sañudo, M. C., *J. Chem. Soc., Perkin Trans. 1*, **1998**, 4061; Valduga, C. J., Braibante, H. S., and Braibante, M. E. F., *J. Heterocycl. Chem.*, **1998**, 35, 189.
104. McGregor, D. N., Corbin, U., Swigor, J. E., and Cheney, L. C., *Tetrahedron*, **1969**, 25, 389.
105. Bruno, A. and Purrello, G., *Gazz. Chim. Ital.*, **1966**, 96, 1009.
106. Goerdeler, J. and Krone, U., *Chem. Ber.*, **1969**, 102, 2273.
107. Wei, X., Fang, J., Hu, Y., Hu, H., *Synthesis*, **1992**, 1205.
108. Birkofer, L. and Richzenhain, K., *Chem. Ber.*, **1979**, 112, 2829.
109. 'The nitrile oxides', Grundmann, C. and Grünanger, P., Springer-Verlag, Berlin and New York, **1971**; 'Cycloaddition reactions of nitrile oxides with alkenes', Easton, C. J., Merric, C., Hughes, M., Savage, G. P., and Simpson, G. W., *Adv. Heterocycl. Chem.*, **1994**, 60, 261.
110. For the use of (Boc)₂O/DMAP for this see Basel, Y. and Hassner, A., *Synthesis*, **1997**, 309.
111. McMurray, J. E., *Org. Synth., Coll. Vol. VI*, **1988**, 592.
112. Hiraoka, T., Yoshimoto, M., and Kishida, Y., *Chem. Pharm. Bull.*, **1972**, 20, 122; Barco, A., Benetti, S., Pollini, G. P., and Baraldi, P. G., *Synthesis*, **1977**, 837.
113. For dehydrogenation of pyrazolines with 'clayfen' see Bougrin, K., Sonfiaoni, M., and El Yazid, M., *Tetrahedron Lett.*, **1995**, 36, 4065.

114. Iddon, B., Suschitzky, H., Thompson, A. W., Wakefield, B. J., and Wright, D. J., *J. Chem. Res.*, **1978**, (S) 174; (M) 2038.
115. Sasaki, T. and Yoshioka, T., *Bull. Chem. Soc. Jpn.*, **1968**, 41, 2212; Christl, M., Huisgen, R., and Sustmann, R., *Chem. Ber.*, **1973**, 106, 3275.
116. Hanson, R. N. and Mohamed, F. A., *J. Heterocycl. Chem.*, **1997**, 34, 345.
117. Sakamoto, T., Shiga, F., Uchiyama, D., Kondo, Y., and Yamanaka, H., *Heterocycles*, **1992**, 33, 813.
118. Barber, G. N. and Olofson, R. A., *J. Org. Chem.*, **1978**, 43, 3015.
119. He, Y. and Liu, N.-H., *Synthesis*, **1994**, 989.
120. Nitz, T. J., Volkots, D. L., Aldous, D. J., and Oglesby, R. C., *J. Org. Chem.*, **1994**, 59, 5828.
121. Short, K. M. and Ziegler, C. B., *Tetrahedron Lett.*, **1993**, 34, 75.
122. Church, A. C., Koller, M. U., Hines, M. A., and Beam, C. F., *Synth. Commun.*, **1996**, 26, 3659.
123. Almirante, N., Cerri, A., Fedrizzi, G., Marazzi, G., and Santagostino, M., *Tetrahedron Lett.*, **1998**, 39, 3287; Almirante, N., Benicchio, A., Cerri, A., Fedrizzi, G., Marazzi, G., and Santagostini, *Synlett*, **1999**, 299.
124. Perez, C., Janin, Y. L., and Grierson, D. S., *Tetrahedron*, **1996**, 52, 987.
125. Uchiyama, D., Yabe, M., Kameyama, H., Sakamoto, T., Kondo, Y., and Yamanaka, H., *Heterocycles*, **1996**, 43, 1301.