The Chemistry of Heterocycles

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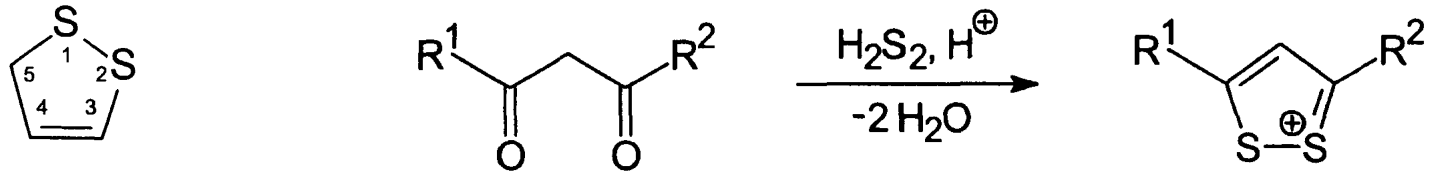
The Chemistry of Heterocycles, (Second Edition).

By Theophil Eicher and Siegfried Hauptmann, Wiley-VCH Veriag GmbH, 2003

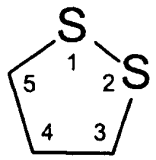
5.19 1,2-Dithiole

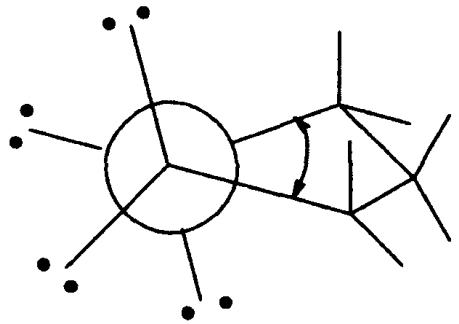
1,2-Dithiole is not a cyclic conjugated system. However, the 1,2-dithiolylium ions derived from it are aromatic. For instance, the corresponding salts are obtained from 1,3-dicarbonyl compounds and disulfane in acid solution:



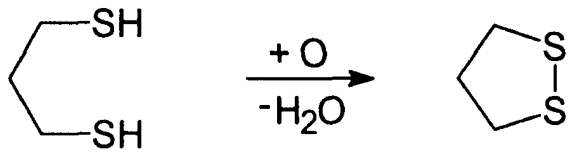
5.20 1,2-Dithiolane

[A-D] 1,2-Dithiolanes can be viewed as cyclic disulfanes. A C-S-S-C dihedral angle of 26.6° results from the elctronic interaction between the S-atoms. For this reason, a considerable ring strain is caused by the widening of the bond angles, as can be deduced from the Newman projection formula. The strain enthalpy was found to be 67 kJ mo^{-1}.





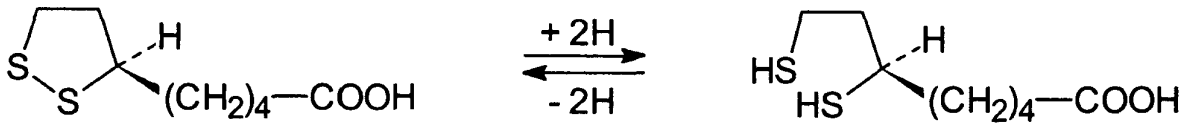
1,2-Dithiolanes are prepared by oxidation of 1,3-dithioles:



1,2-Dithiolanes are very reactive because of ring strain. 1,2-Dithiolane polymerizes at room temperature.

About 20 1,2-dithiolanes are found in nature. Among them, α-lipoic acid (6,8-disulfanyloctanoic acid) is of great biological importance. The crystalline compound was isolated for the first time in 1951 from the liver of cattle.

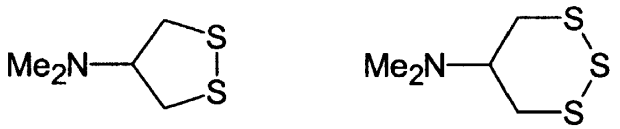
α-Lipoic acid, bound to proteins, acts as a coenzyme in the oxidative decarboxylation of pyruvic acid and 2-oxopentandioic acid. By taking up hydrogen, it is converted into the corresponding 1,3-dithiole, which is subsequently reoxidized to α-lipoic acid by flavine-adenine dinucleotide.



(R)-(+)-α-lipoic acid

Flies are killed upon contact with the marine worm Lumbriconereis. Nereistoxin **1** was identified as the active substance in this worm, and its constitution determined as 4-dimethylamino-1,2-dithiolane.

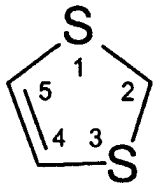
Consequently, structural analogues were synthesized and introduced as insecticides, e.g. thiocyclam **2**.

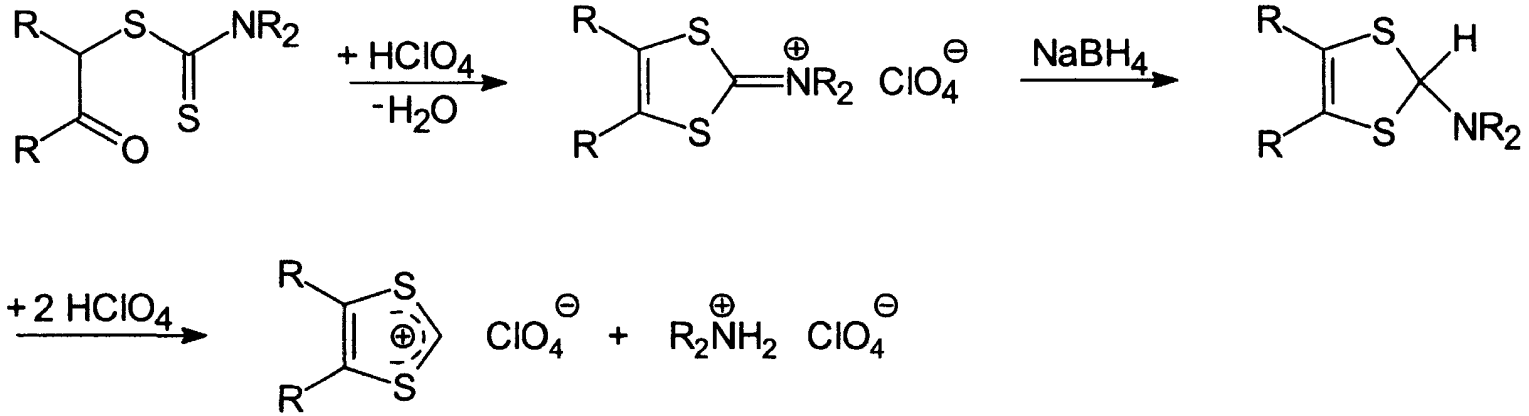


1 **2**

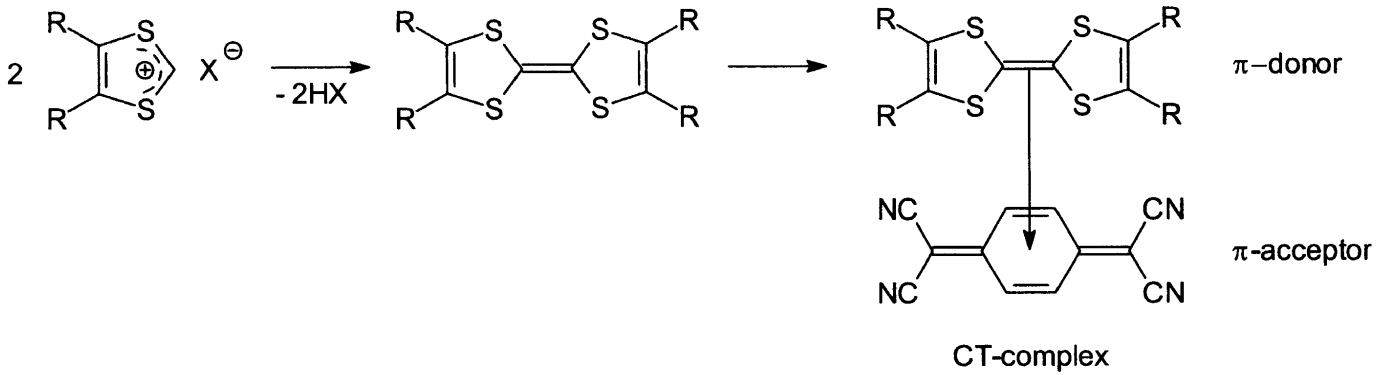
5.21 1,3-Dithiole

[A-C] 1,3-Dithiole, like its 1,2-isomer, is not a cyclic conjugated system. However, the aromatic 1,3-dithiolylium system is derived from it. For instance, salts with this cation can be obtained from 2-oxoalkyl dithiocarbamates as follows:



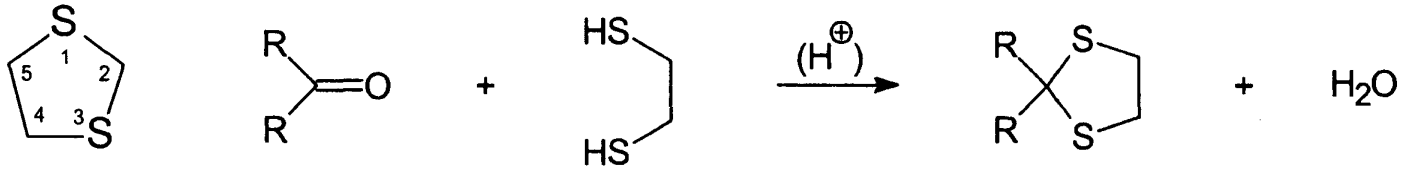


1,3-Dithiolylium salts react with tertiary amines to give tetrathiafulvalenes. Tetrathiafulvalenes form crystalline CT complexes (charge-transfer complexes, π--complexes) with e.g. 7,7,8,8-tetracyanoquinodimethane, which display high electric conductivity (organic metals).

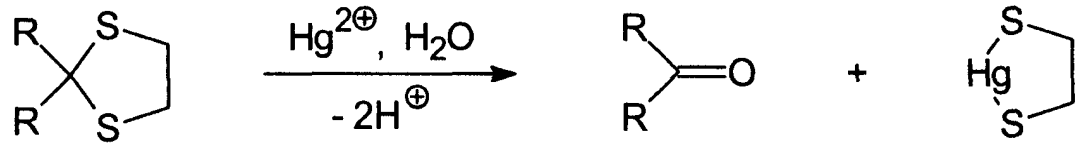


5.22 1,3-Dithiolane

[A-C] 1,3-Dithiolanes can also be regarded as cyclic dithioacetals or ketals. They are accordingly obtained by cyclocondensation of aldehydes or ketones with 1,2-dithiols in acetic acid with *p*-toluenesulfonic acid as catalyst:

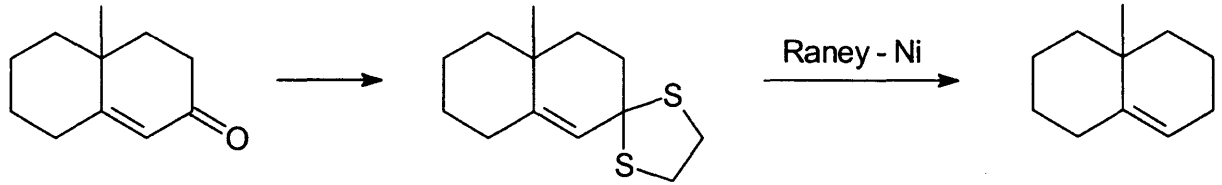


1,3-Dithiolanes are stable towards bases. They are hydrolyzed by dilute acids only slowly, in a reversal of their formation, faster in the presence of mercury(II) salts:



A better method for regenerating carbonyl compounds from 1,3-dithiolanes is the reaction with selenium dioxide in acetic acid.

1,3-Dithiolanes are subject to reductive desulfurization by the action of RANEY nickel in ethanol. A method for the chemoselective reduction of α,β-unsaturated ketones is based on this reaction, e.g.:

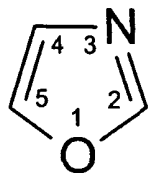


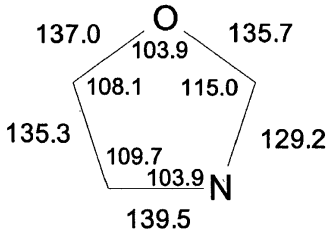
5.23 Oxazole

[A] Oxazole (1,3-Oxazole) contains an O-atom bonded as in furan, and also a pyridine-like N-atom. The univalent radical is known as oxazolyl. The oxazole molecule is planar and its structure can be represented by a distorted pentagon:

The differences in the bond lengths, especially between the bonds N/C-2 and N/C-4 indicate that the delocalization of the π-electrons is affected by the heteroatoms.

As in the case of furan, the structural formula with two π-bonds is a good representation of the electronic structure of the molecule.



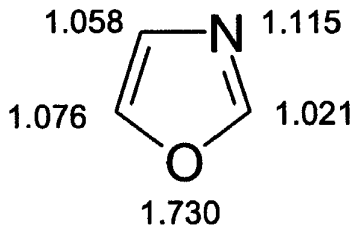


Structure of oxazole
(bond lengths in pm, bond angles in degrees)

The ionization energy of oxazole is 9.83 eV and its dipole moment is 1.5 D. The UV absorption and chemical shifts in the NMR spectra are as follows:

UV (methanol)	^{1}H-NMR (CCl_4)	^{13}C-NMR ($CDCl_3$)
λ (nm) (ε)	δ (ppm)	δ (ppm)
205 (3.59)	H-2: 7.95	C-2: 150.6
	H-4: 7.09	C-4: 125.4
	H-5: 7.69	C-5: 138.1

Oxazole is thus diatropic and aromatic. All ring atoms are sp^2-hybridized. Consequently, there are two nonbonding electron pairs, one on the O-atom and the other on the N-atom. The π-electron densities were calculated by various SCF/MO methods, e.g.:

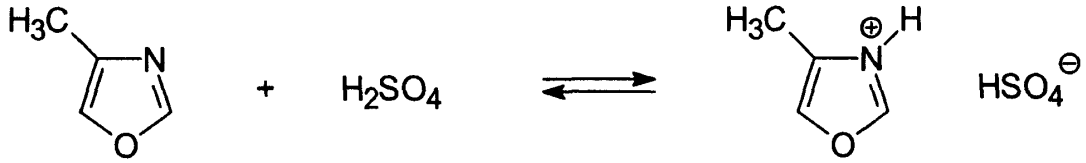


Oxazole, therefore, belongs to the family of π-electron excessive heterocycles. The electronegativity of the pyridine-like N-atom, however, causes the π-electron density to be low, especially on the C-2 atom. Electrophilic substitution should occur in the 5- or 4-position, while reaction with nucleophiles should occur in the 2-position.

[B] The reactions of five-membered heterocycles with two or more heteroatoms cannot be classified as easily as those systems possessing only one heteroatom. For this reason, they are described according to the system and importance of their reactions. For oxazoles, the following reactions are characteristic.

Salt formation

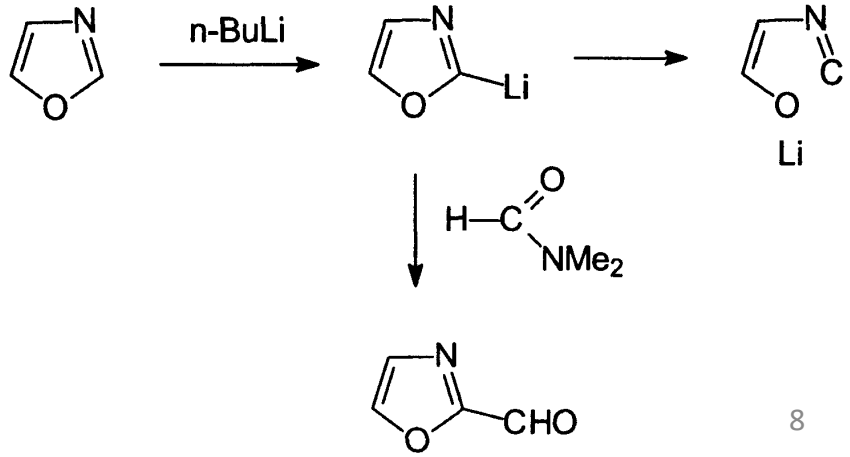
Oxazoles are weak bases. The pK_a value of oxazole is 0.8. They are protonated by strong acids on the N-atom. Oxazolium salts react faster with nucleophiles than oxazole.



Metallation

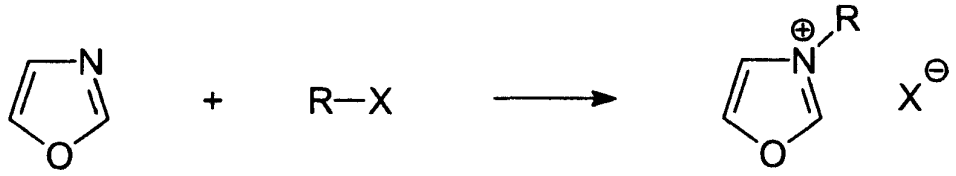
Oxazoles unsubstituted on the 2-position react with «-butyllithium in THF already at -75°C to give 2-lithiooxazoles.

2-Lithiooxazole is subject to slow ring-opening at room temperature to form the lithium enolate of 2-oxoethyl isocyanide. With DMF it reacts to give oxazole-2-carbaldehyde.



Reactions with electrophilic reagents

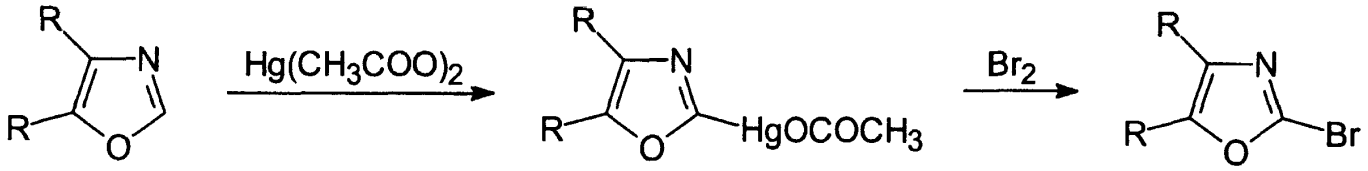
Oxazoles are quaternized by haloalkanes:



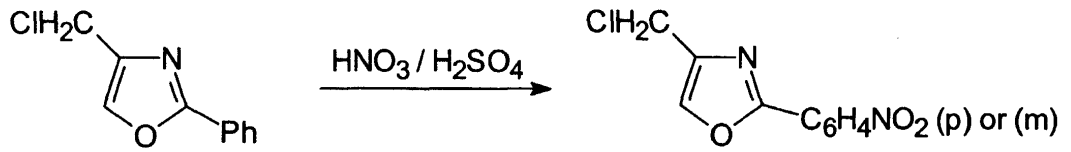
Although electrophilic substitution reactions are possible with oxazoles, they are frequently accompanied by addition reactions, as in furan.

The bromination of 4-methyl-2-phenyloxazole with bromine or *N*-bromosuccinimide yields 5-bromo-4-methyl-2-phenyloxazole, and that of 2-methyl-5-phenyloxazole gives 4-bromo-2-methyl-5-phenyloxazole.

Mercury(II) acetate in acetic acid acetoxymercurates 4-substituted oxazoles in the 5-position, 5-substituted oxazoles in the 4-position, and 4,5-disubstituted oxazoles in the 2-position. The acetoxymercury group can be substituted by electrophiles.

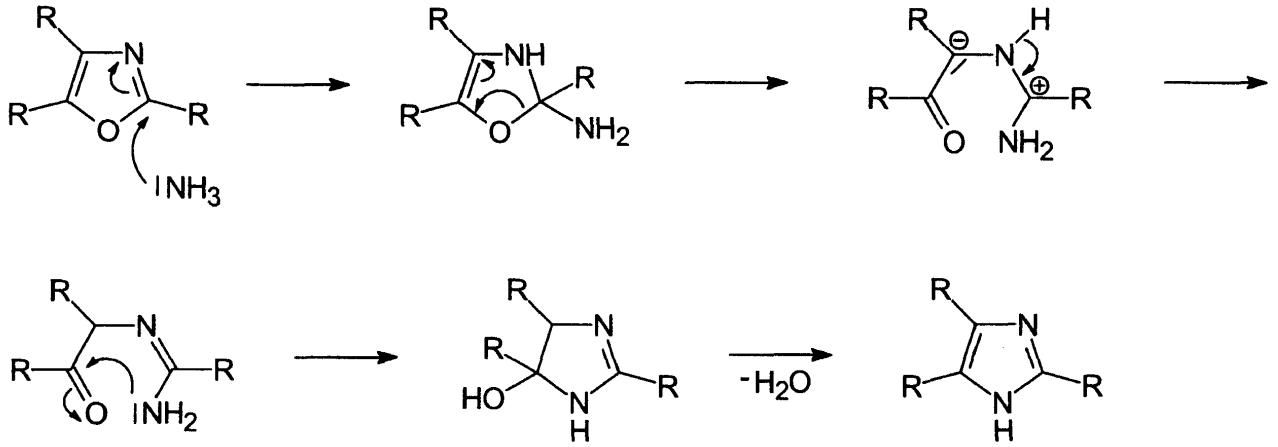


In general, it can be stated that the pyridine-like N-atom in the oxazole molecule impedes electrophilic substitution reactions. This is particularly evident in the nitration of phenyloxazoles. The substitution occurs on the benzene ring, e.g.:



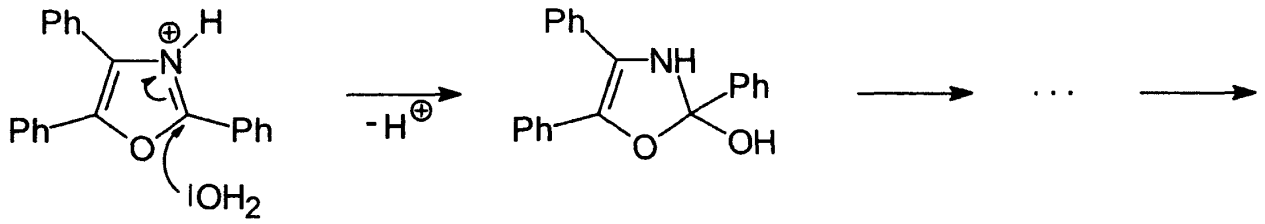
Reactions with nucleophilic reagents

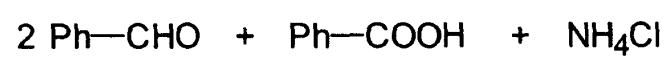
Oxazoles are attacked in the 2-position by nucleophiles, even if a substituent is already present. Ring-opening occurs and, depending on the reagent, is followed by ring-closure, e.g. with ammonia:



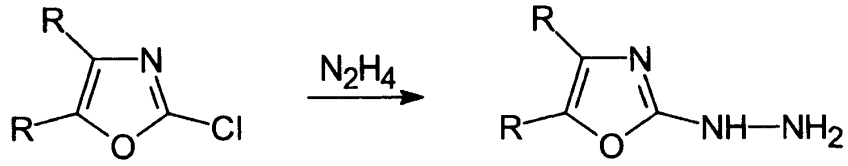
On heating with ammonia, formamide or primary amines, oxazoles thereby undergo a ring transformation into imidazoles.

With nucleophiles, oxazolium salts react much faster. For instance, the acid-catalyzed hydrolysis of 2,4,5-triphenyloxazole yields benzaldehyde, benzoic acid and ammonium chloride analogously to the mechanism described above:





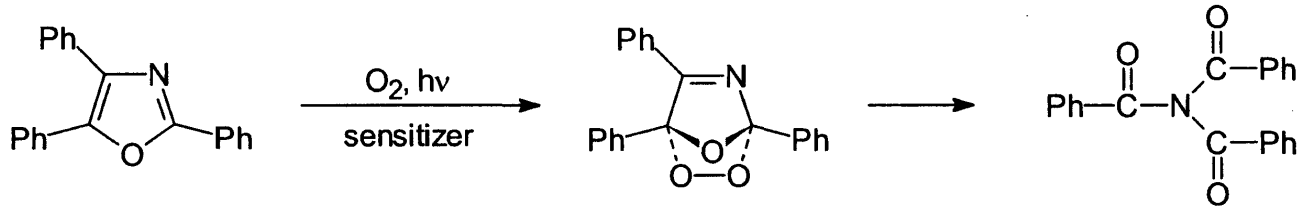
As a consequence of the low π-electron density on C-2, nucleophilic substitution reactions of 2-halooxazoles proceed rapidly.



Cycloadditions

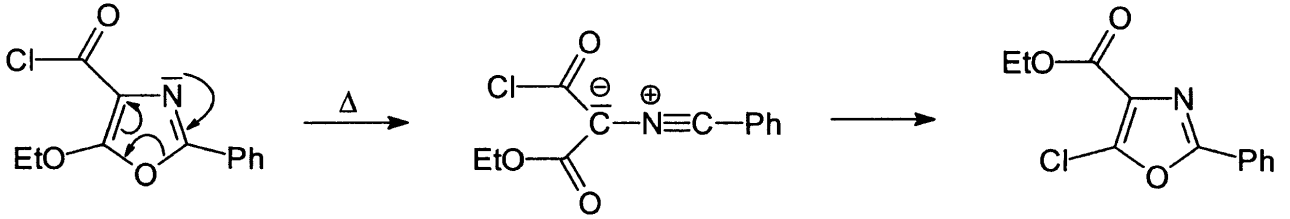
Oxazoles can react as 1,3-dienes, and with dienophiles such as maleic acid derivatives undergo DIELS- ALDER reactions. With acetylene dienophiles, furans are formed via the corresponding DIELS-ALDER adducts.

The photooxygenation of oxazoles also occurs as a [4+2] cycloaddition. The primary products decompose in various ways depending on the solvent. 2,4,5-Triphenyloxazole in methanol yields *N*,*N*-dibenzoylbenzamide:



Cornforth rearrangement

Oxazoles in which the C-4 atom is bonded to a carbonyl group isomerize on heating. Two substituents change places in this process, e.g.:



Results of experiments carried out with isotopically labelled compounds indicate an intermediate which is derived from the ring-opened starting material. It has the structure of a nitrile ylide and is converted into the final product by ring-closure.

To summarize, the reactivity of oxazoles closely resembles that of the furans, especially in their readiness to undergo ring-opening reactions and [4+2] cycloadditions. The pyridine-like N-atom impedes electrophilic substitution reactions.

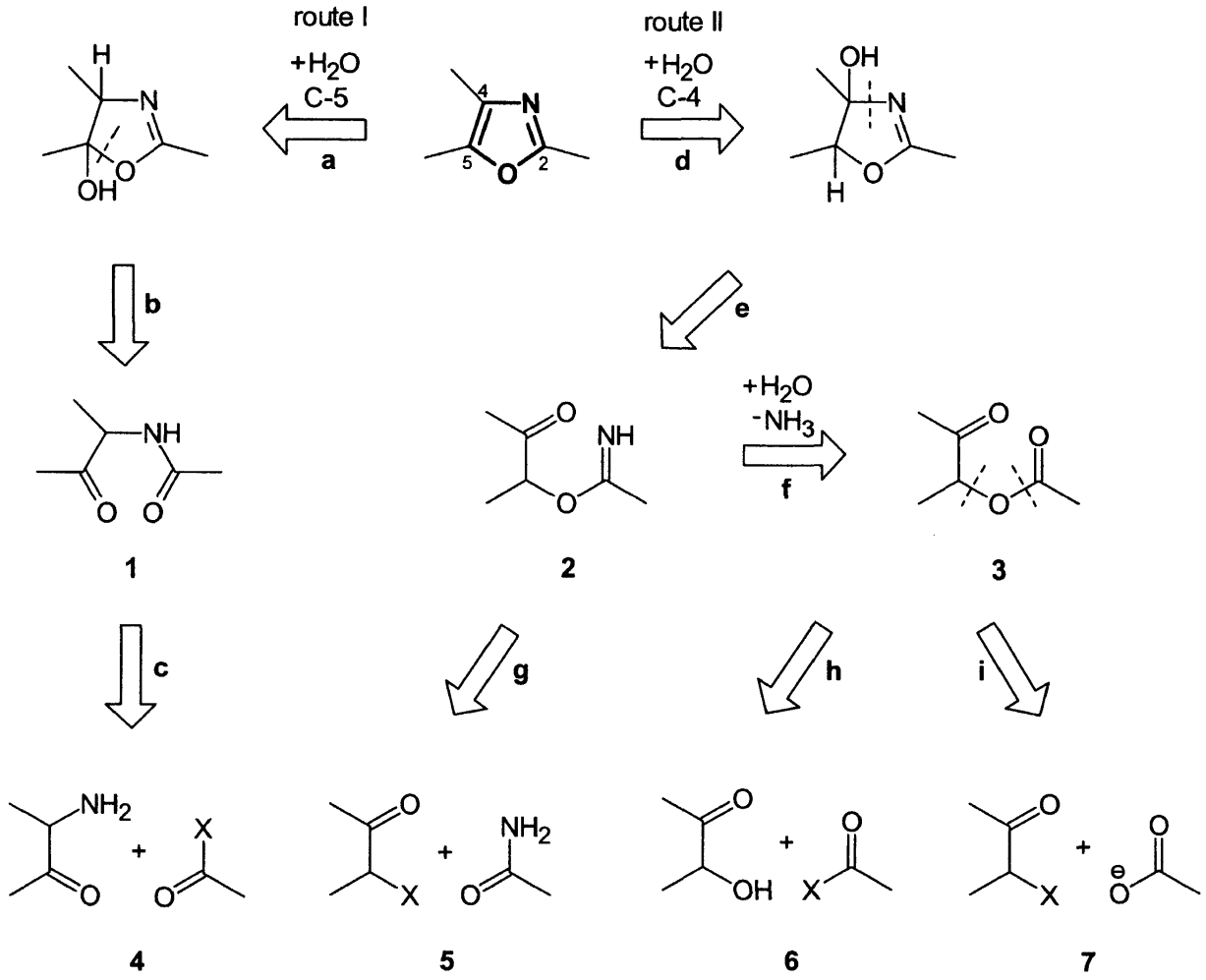
On the other hand, it facilitates the attack of nucleophiles onto the C-2 atom. Although oxazole is considered to be a heteroarene, because of its six delocalized ring electrons, its aromaticity is low and comparable to that of furan.

[C] When considering the retrosynthesis, it must be borne in mind that the oxazole structure combines the functionalities of an imido ester (C-2) and of an enediol ether (C-4 and C-5). Retrosynthetic considerations can then move in two directions (**I**/**II**) by analogy to furan-thiophene-pyrrole.

According to route **I**, addition of water after the retrosynthetic steps **a**/**b** leads to the α-acylamino-carbonyl system **1** which should be formed according to c from the two fragments **4**.

The more productive retroanalytical route is **II**, in which water is added, according to **d**. After cleavage of the N/C-4 bond (i.e. via **e**), this leads to the intermediate stage **2**.

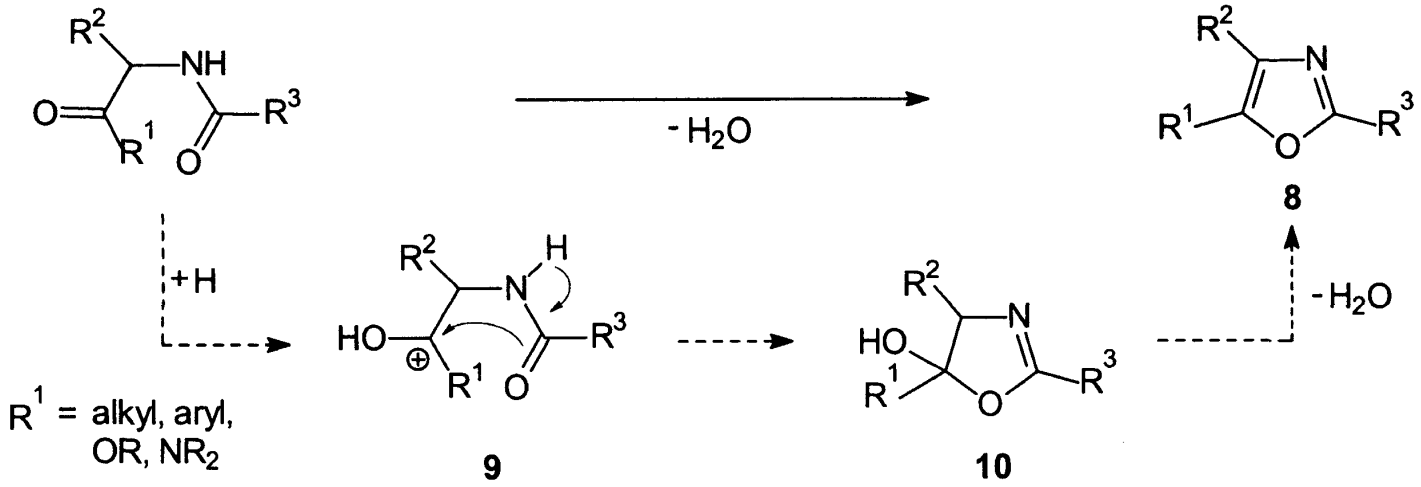
This can split further in several ways, namely **g**, which leads to an α-halo ketone and an acid amide (fragments **5**), or alternatively **f**, which yields NH_3 and the α-hydroxy- or α-halocarbonyl compound, i.e. by combination of the fragment pair in **6** or **7** in a reversal of the retrosynthetic operation indicated by **h** and **i**.



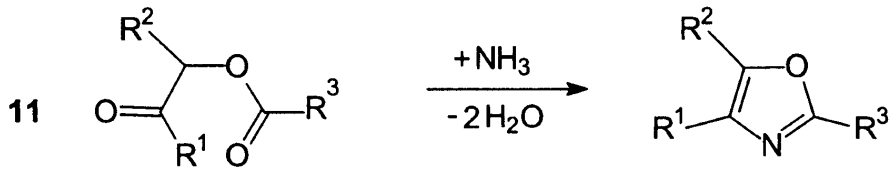
(1) α-Acylamino ketones, esters or -amides are cyclodehydrated by H_2SO_4 or polyphosphoric acid to give oxazoles **8** (Robinson-Gabriel synthesis).

α-Acylamino ketones are accessible, for instance, by the DAKIN-WEST reaction (heating acid anhydrides with α-amino acids in the presence of pyridine).

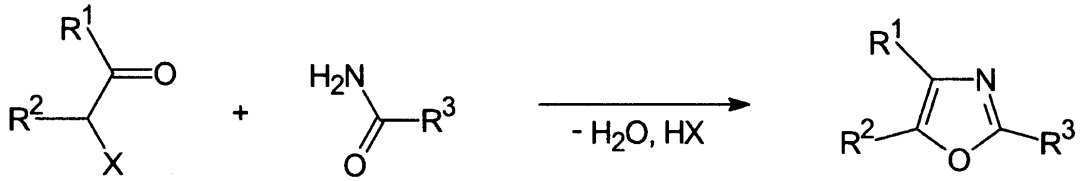
Labelling the α-acylamino ketones with ^{18}O in the keto carbonyl group does not produce ^{18}O-labelled oxazoles. However, if the acyl carbonyl group is labelled with ^{18}O, then all the label is found in the oxazole. These experiments support the suggested mechanism (intermediates **9** and **10**).



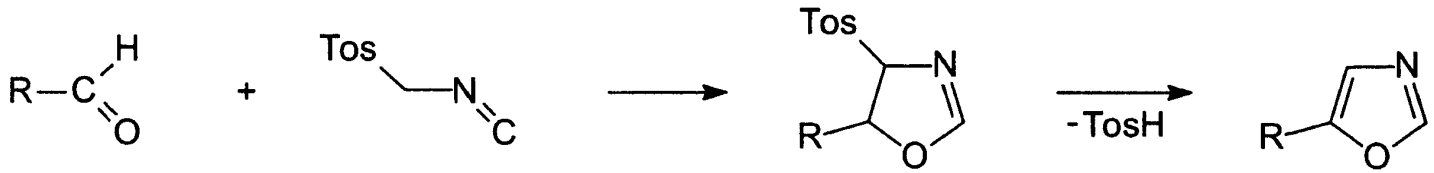
(2) α-Acyloxy ketones **11**, obtainable from a-halo ketones and salts of carboxylic acids, form oxazoles on treatment with ammonia. An enamine is formed from **11** which dehydrates to give the heterocycle.



(3) α-Halo and α-hydroxy ketones condense with acid amides via an *O*-alkylation to give oxazoles (Blümlein-Lewy synthesis). Formamide yields oxazoles unsubstituted in the 2-position, urea yields 2-aminooxazoles:

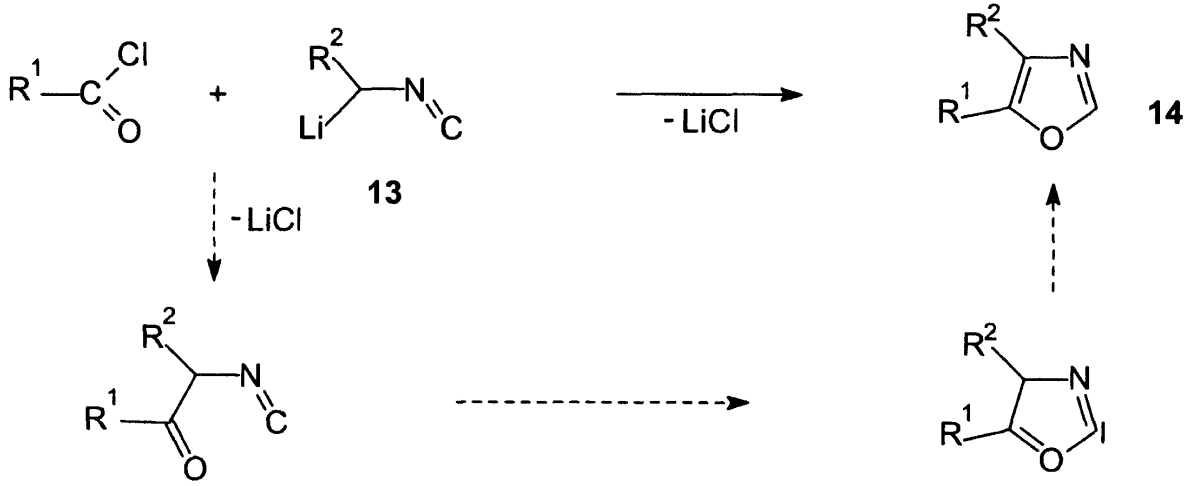


(4) Oxazole syntheses employing isocyanides as starting materials are of considerable preparative value. In the *van Leusen synthesis*, tosylmethyl isocyanide (TosMIC) reacts with aldehydes under base catalysis, e.g. in the presence of K_2CO_3. The primary products are 4,5-dihydro-1,3-oxazoles **12**, which are converted into oxazoles by elimination of sulfinic acid:



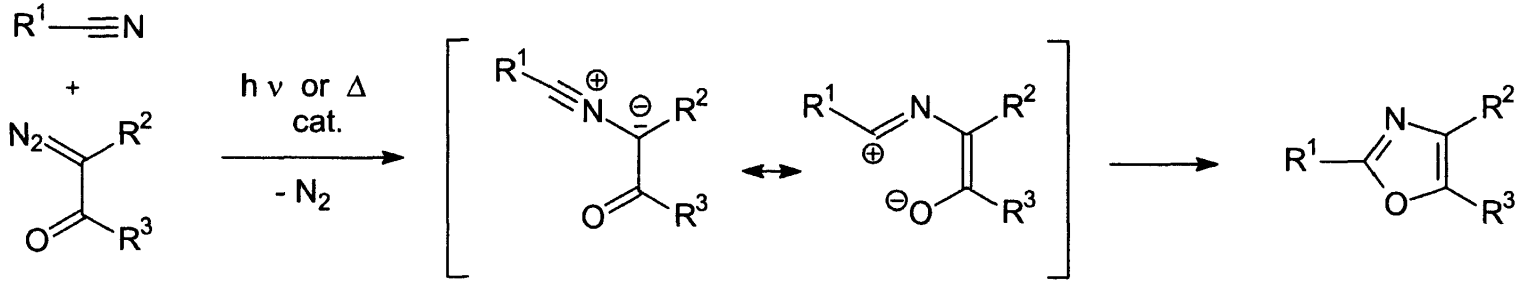
12

In the Schöllkopf synthesis, α-metalated isocyanides **13** (from isocyanides and *n*-butyllithium) react with acid chlorides to give 4,5-disubstituted oxazoles **14** via *C*-acylation and electrophilic C-O bond formation.



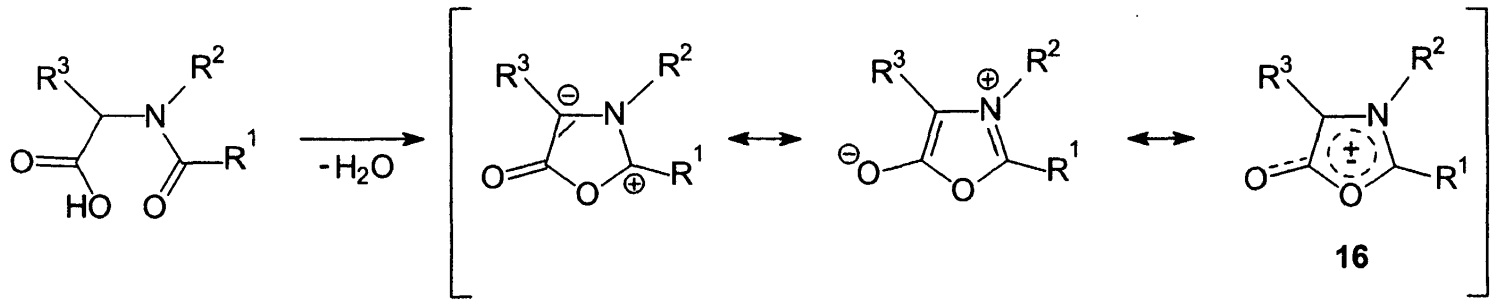
(5) α-Diazocarbonyl compounds undergo addition to nitriles with elimination of N_2 in the presence of LEWIS acids or transition metal compounds [Cu(II), Pd(II), especially Rh(II)] as catalysts to give oxazoles.

This reaction is likely to proceed via intermediate formation of nitrile ylides **15** and their electrocyclic ring closure as 1,5-dipoles yielding the oxazole system.

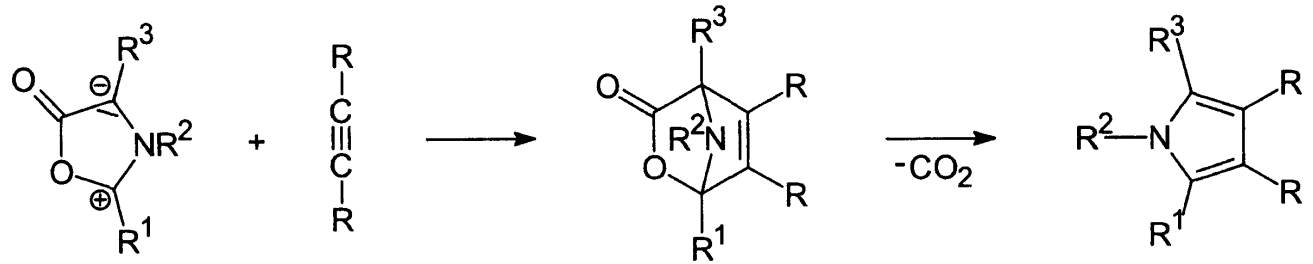


[D] Oxazole is a colorless liquid with a smell similar to pyridine, of bp 69-70 °C, and is soluble in water.

1,3-Oxazolium-5-olates **16** are known by the trivial name of Münchnones. Their reactions have been extensively studied by HUISGEN in Munich. They are prepared by cyclodehydration of *N*-substituted *N*-acyl α-amino acids with acetic anhydride:

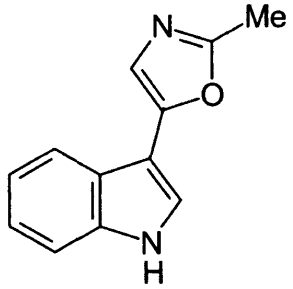


Mesomeric zwitterions like Münchnones are known as mesoionic compounds, which also occur in other heterocyclic systems. Münchnones are crystalline compounds and are reactive 1,3-dipoles. For instance, they react with acetylenes via the corresponding cycloadducts **17** to give pyrroles **18**.

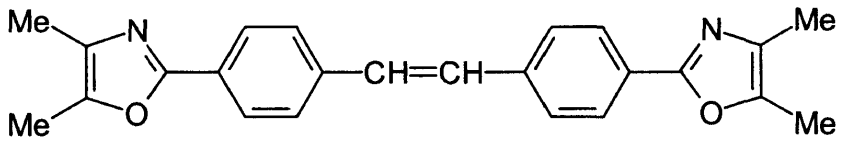


Oxazoles are rarely found in natural products. Pimprinin **19**, isolated from Streptomyces pimprina, provides an example. The oxazole ring is found in some macrocyclic antibiotica and several alkaloids.

Only a few pharmaceuticals derived from oxazole are in use. The anti-inflammatory and analgesic action of 2-diethylamino-4,5-diphenyloxazole is known.



19



20

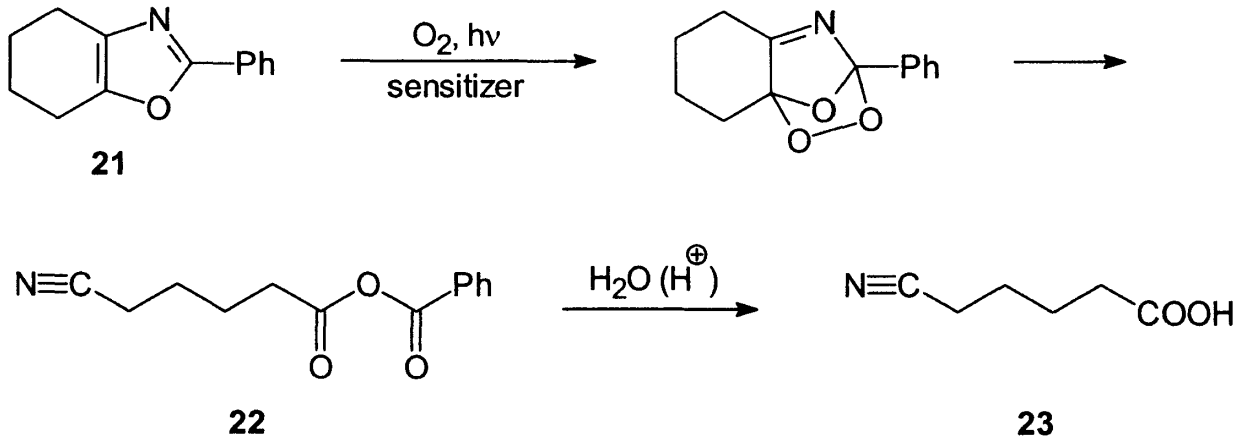
Aryl-substituted oxazoles are strongly fluorescent. In solution, they are therefore suitable as luminous substances for liquid scintillation counters and also as optical brighteners (brightening agents).

4,4'-bisoxazol-2-ylstilbenes (**20**) are added to washing agents. During the washing process, they are absorbed by the fibers, so that the clothes appear to be 'whiter than white' as a result of the blue fluorescence.

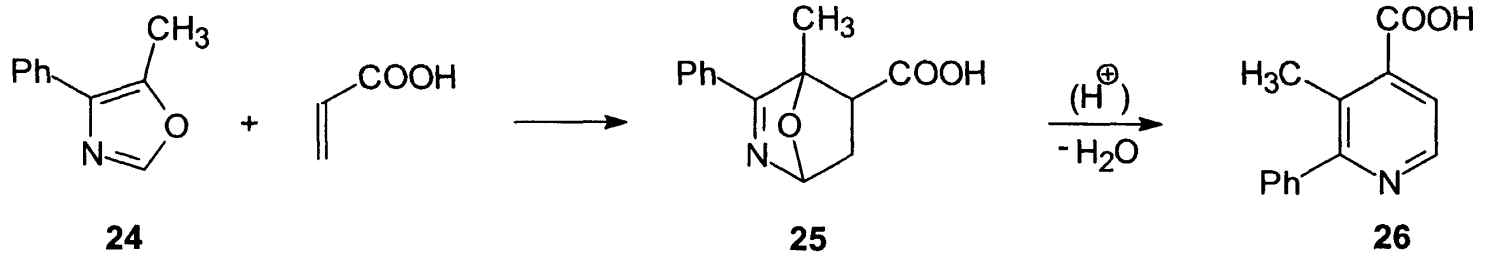
Polymethine dyes with oxalyl terminal groups are used as photographic sensitizers of silver halogen emulsions. 2,5-Diphenyloxazole is added as antioxidant to hydraulic fluids and high temperature lubricating oils.

[E] Oxazoles are used as auxiliaries for transformations in organic synthesis in various ways.

(1) The photooxygenation with singlet oxygen, when applied to 4,5-cycloalkeno-l,3-oxazoles, e.g. **21**, leads via **22** to mononitriles of dicarboxylic acids **23**:



(2) Transformations of DIELS-ALDER adducts from oxazoles and activated multiple bond systems are important. In this case, alkynes lead to furan derivatives. Alkenes lead to adducts, regioselectively in the case of unsymmetrical alkenes, which eliminate H_2O in acidic media and are thereby converted into pyridine derivatives; in this way, acrylic acid and oxazole **24** furnish pyridine-4-carboxylic acid **26** via the DIELS-ALDER adduct **25**.



If the oxazole contains cyano or alkoxy groups in the 5-position, or if the dienophile possesses appropriate leaving groups, then these groups can be eliminated and 3-hydroxypyridines are formed.

The industrial synthesis of pyridoxine **27** (vitamin B_6) is based on these reactions.