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Topic: Azoles

Azoles: Five membered ring ^{compounds} containing two ~~atoms~~ hetero atoms ^{besides C-atom} in which one hetero atom is nitrogen and other hetero atom may be nitrogen, oxygen or sulphur are called azoles.

Azoles may be therefore of three types

- (a) Oxazoles containing nitrogen and oxygen as hetero atoms.
- (b) Pyrazoles ^{and imidazoles} containing two nitrogen as hetero atoms.
- (c) Thiazoles containing nitrogen and sulfur as hetero atoms.

Hence these azoles may be derived from pyrrole, furan and thiophene by replacing methine (=CH-) group with pyridine ^{type} nitrogen (=N) atoms from the different positions. Generally they are 1,2- and 1,3- azoles as given below



Imidazole



Thiazole



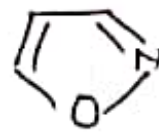
Oxazole



Pyrazole



Isothiazole



Isoxazole

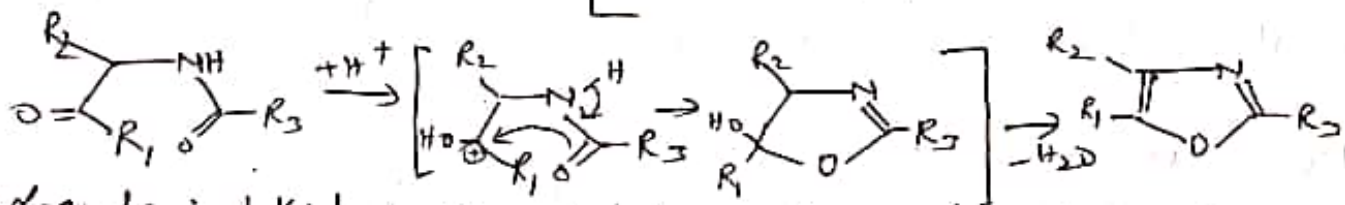
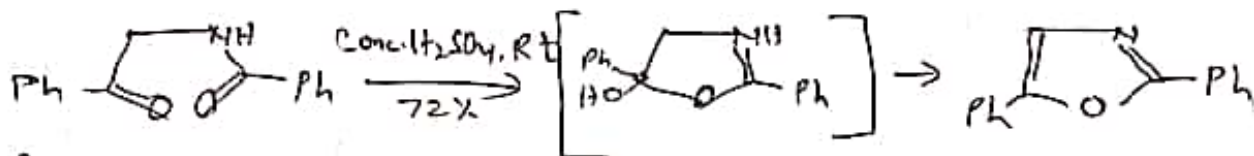
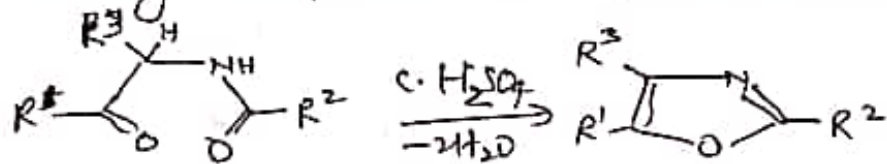
1,3-azoles

1,2-azoles

The 1,2-azoles are less basic than their 1,3-isomers due to direct linking of the two heteroatoms with substantial inductive influence and hence 1,2-azoles tend to be less nucleophilic than 1,3-azoles.

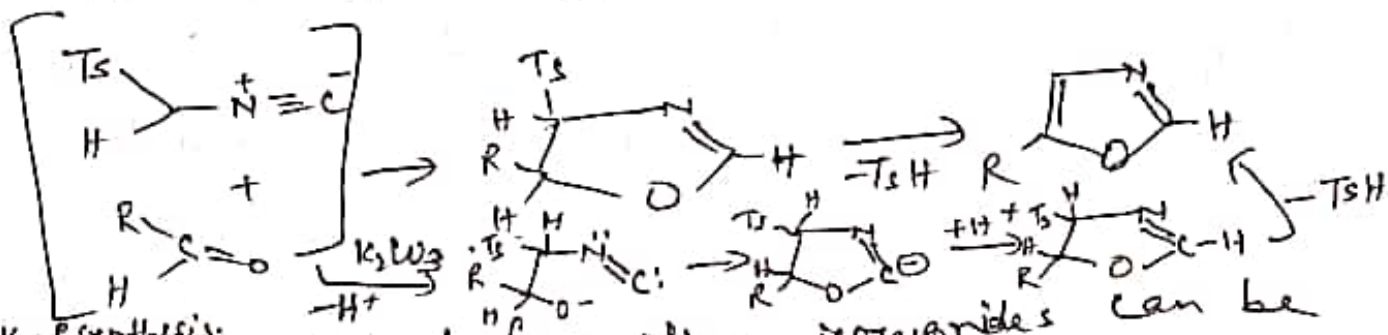
Oxazole Synthesis

1. By ~~dehydration~~ ^{the acid catalysed} cyclising dehydration of α -acylamino-carbonyl compounds - (Robinson-Gabriel Synthesis)

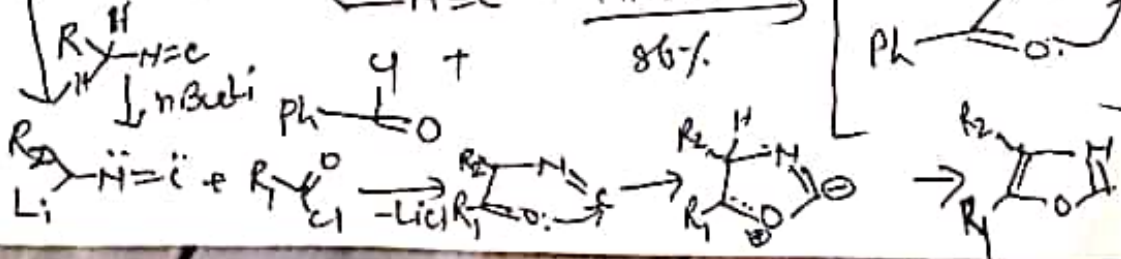
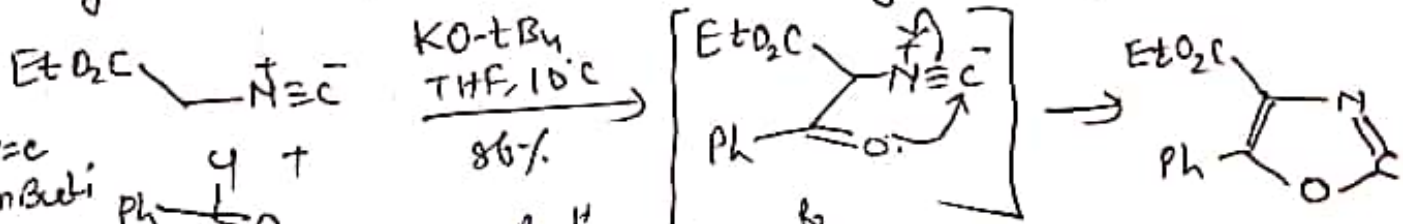


(α -acylamino) ketone are obtained by the Dakin-West reaction by heating acid anhydride with α -amino acid in the presence of pyridine.

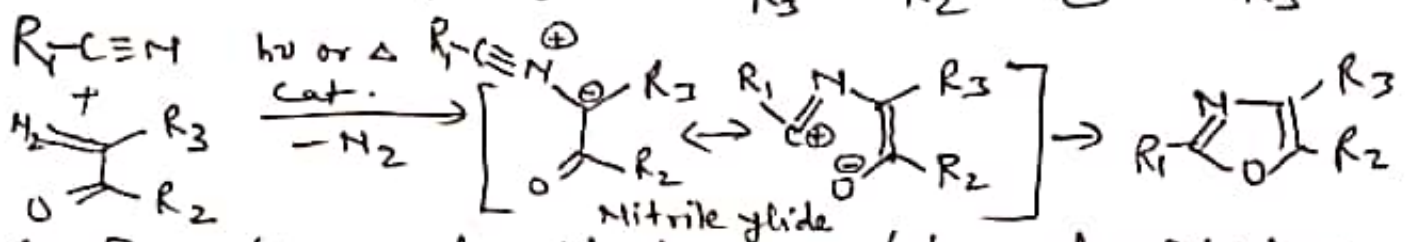
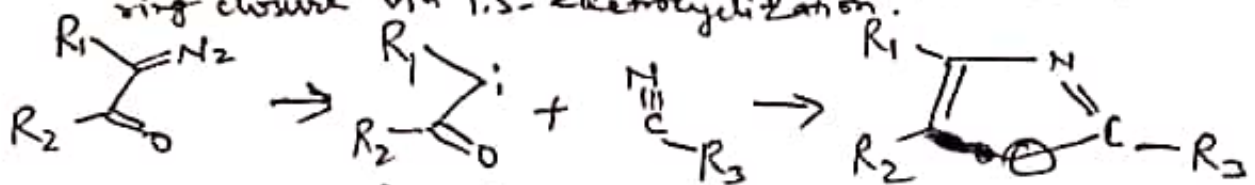
2. From Isocyanides a) Tosylmethylisocyanide reacts with aldehydes ^{under base catalyst} on heating by losing toluenesulfinic acid gives oxazoles. (Van-Lensen Synthesis)



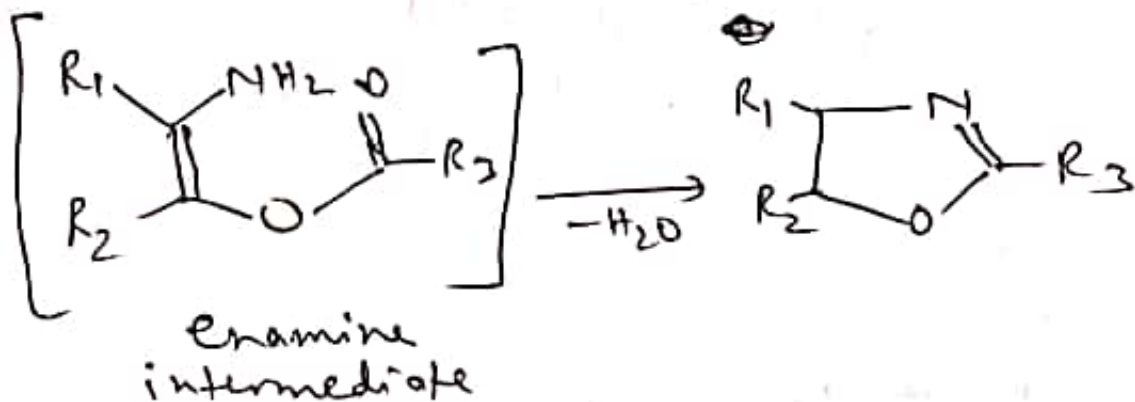
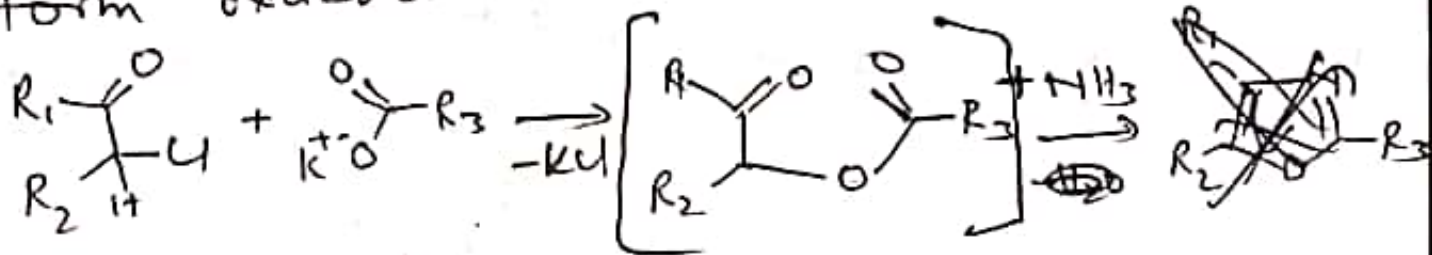
Schollkopf synthesis: Anions derived from other isocyanides can be acylated, the product spontaneously closing to oxazoles.



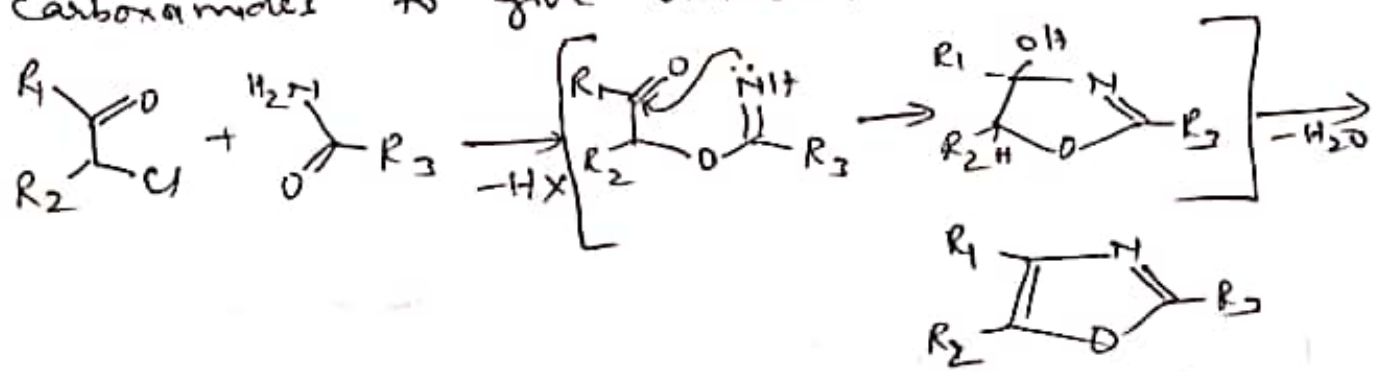
3 From α -Diazocarbonyl compounds - The generation of a carbene from an α -diazocarbonyl compound, in the presence of nitrile, results in overall cycloaddition and the formation of an oxazole. The reaction proceeds via nitrile ylide intermediate and then ring closure via 1,5-electrocyclization.



4. From (α -acyloxy) ketone - (α -acyloxy) ketone obtained from (α -halogeno) ketone, and salts of carboxylic acids, on treatment with ammonia form oxazole.

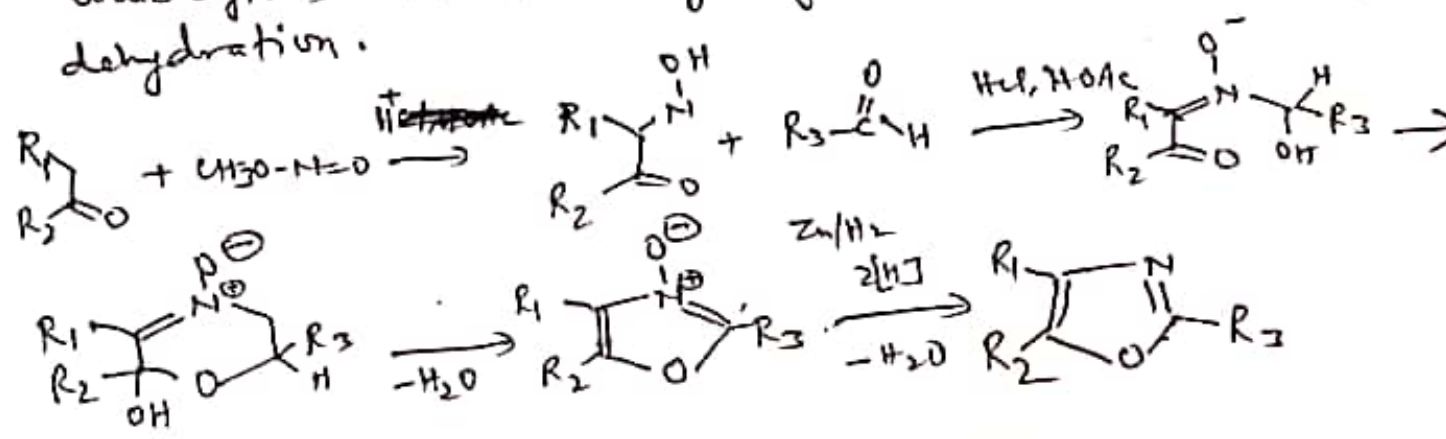


5. Blumlein - Levy synthesis: - Halogeno and α -hydroxyketone undergo cyclocondensation with carboxamides to give oxazoles.

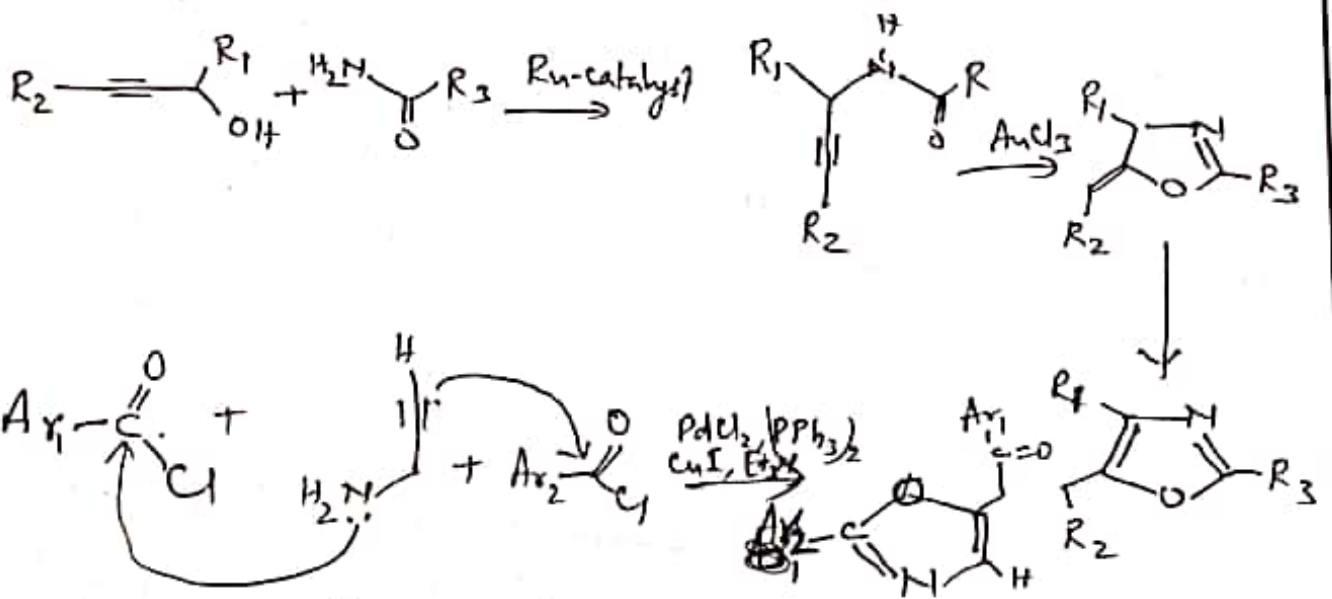


First step is O-alkylation of the carboxamide and then cyclization via N \rightarrow C=O attack followed by elimination of H₂O.

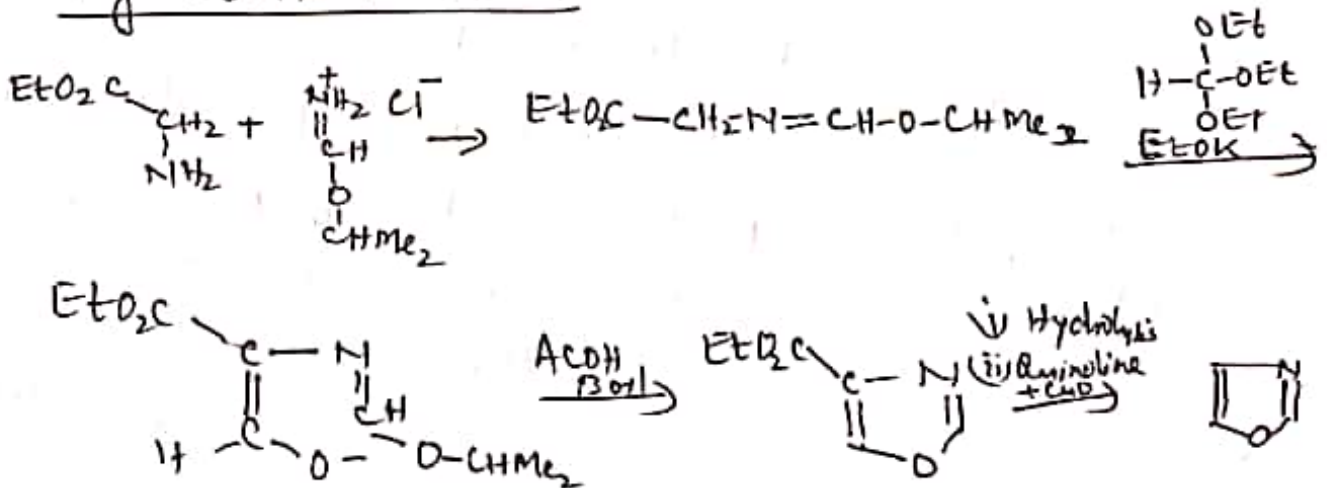
6. From α -Diketone monooximes: α -Diketone monooxime is obtained from methylene ketone by nitrosation with methyl nitrite in acidic medium which then subjected to condensation with aldehyde in acetic acid saturated with dry HCl. The unstable N-oxide intermediate is formed which are reduced by Zn or catalytic hydrogenation to get trisubstituted oxazole. Here condensation of the oxime with aldehyde involves acid catalyzed formation of a nitron intermediate which gives N-oxide by cyclisation followed by dehydration.



7. From Propargylic amide: Propargylic alcohol and amides forms propargylic amide which on sequential action of Ru and Au-catalyst forms oxazoles. ~~This involves~~ Amidation-coupling-cyclisation sequence from propargylamine and acid chloride also gives oxazole.

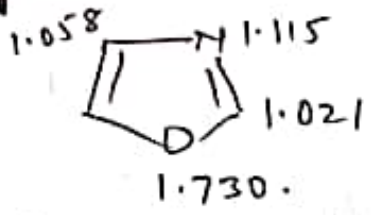


8. By Cornforth et. al.



Properties.

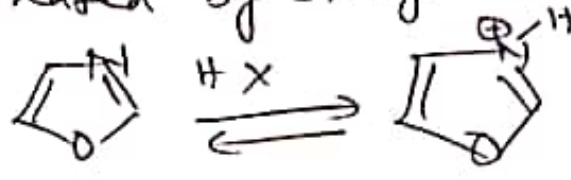
Oxazole is a colourless, water soluble liquid having boiling point 70°C with a smell similar to pyridine. The bond N-C₄ is longer than N-C₂ which indicates the delocalization of the π -electrons is affected by the heteroatom. Its dipole moment is 1.5D. It is diatropic and aromatic. All ring atoms are sp² hybridised. There are two non-bonding electron pairs, one on the O-atom and the other on the N-atom. The π -electron density over atom ring atoms are



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 therefore should occur in the 5 or 4-position while reaction with nucleophile should occur over the 2-position. The interaction of pyridine type N with pyrrole type oxygen affects electrophilic attack at N-3.

Reaction with electrophiles

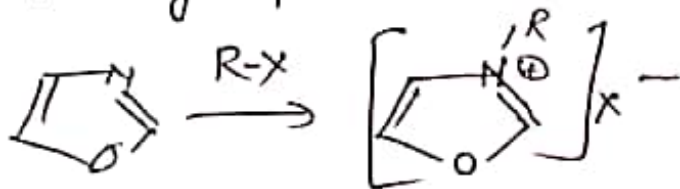
1. Oxazole is weak base (pK_a = 0.8) and are protonated by strong acid at the N-atom.



* The inductive effect is stronger when second heteroatom is oxygen and thus lowers electron density on nitrogen.

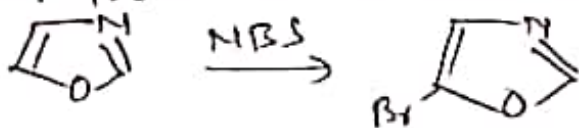
Oxazole is alkylated/acetylated with the formation of quaternary salts (7)

2. Oxazole reacts with alkyl halide to form quaternary product.



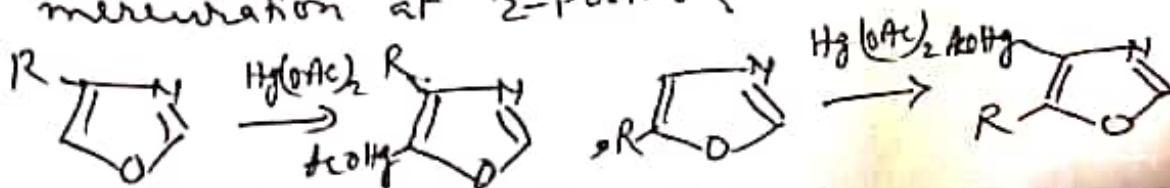
3. Apart from electrophilic substitution, oxazole frequently gives addition reactions. The pyridine like N-atom in the oxazole impedes electrophilic substitution reactions

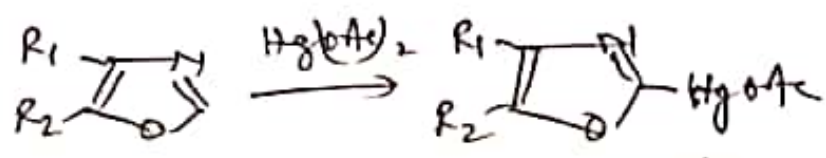
(a) Halogenation - It undergoes bromination by NBS or Br₂ at 5-position, and if this is occupied then at the 4-position.



(b) Ni

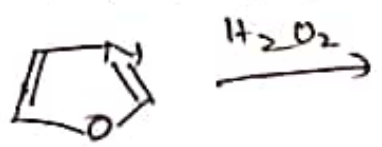
(c) Mercuration - 4-substituted oxazole gives mercuration at 5-position, 5-substituted oxazole gives mercuration at 4-position while 4,5-disubstituted oxazole gives mercuration at 2-position





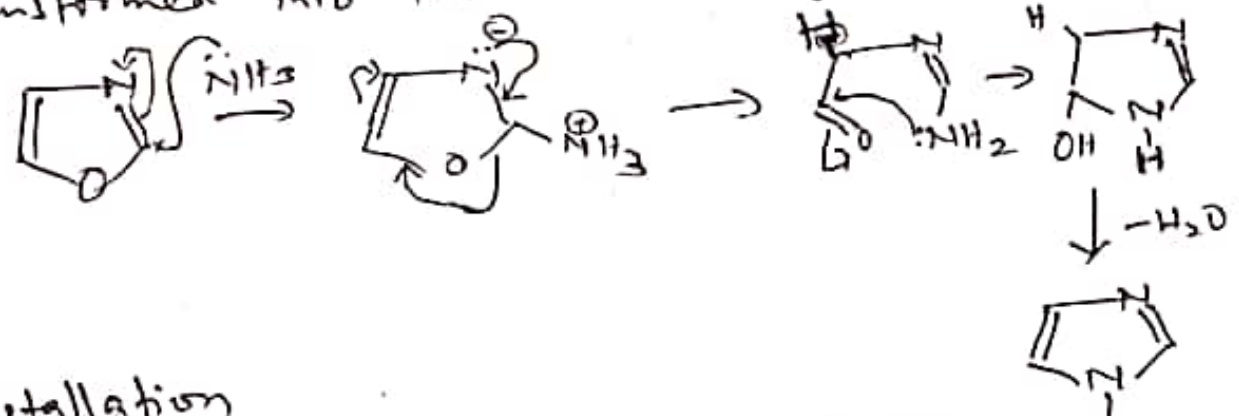
Reaction with oxidising agent.

The oxazole ring is cleaved by oxidising agents such as KMnO_4 , chromic acid or H_2O_2 to give acid and amide



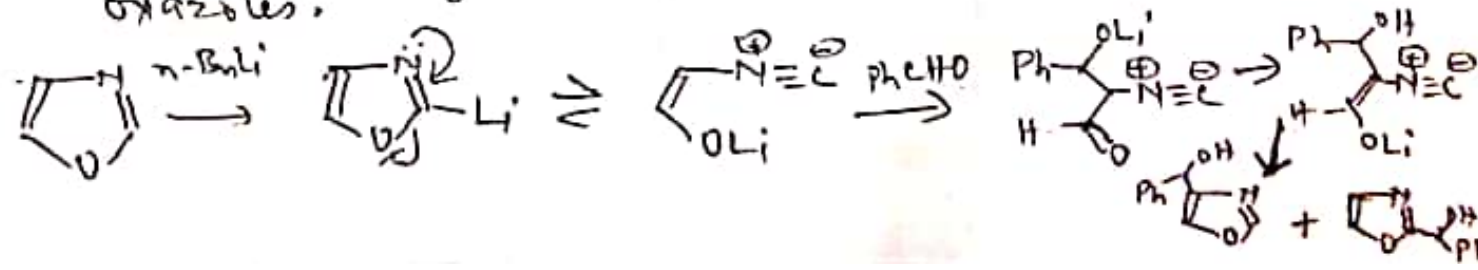
Reaction with nucleophilic reagent

Oxazole when treated with NH_3 at 200°C undergo nucleophilic attack at the 2-position and are transformed into the corresponding imidazoles.

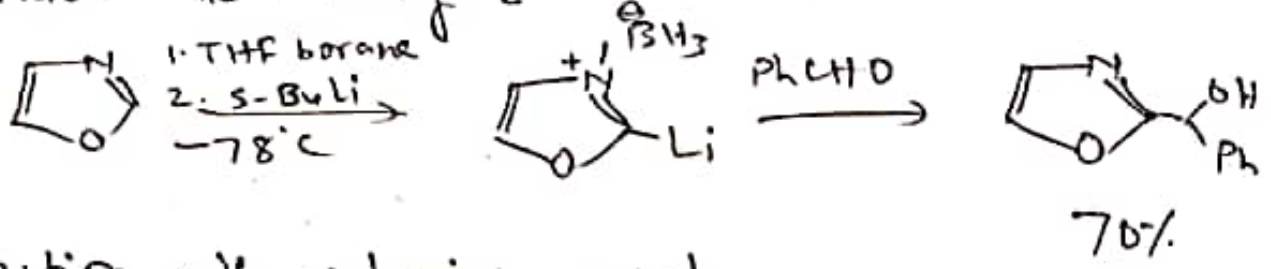


Metallation

~~is~~ Oxazole are prone to be lithiated at C2 but if this is already occupied then at C5. But attempt to trap 2-lithiooxazole with electrophiles fails due to ring opening followed by elimination to produce the β -cyano enolate. However in many case enolate cyclizes back after the C-electrophilic attack giving mixtures of C2 and C4 substituted oxazoles.

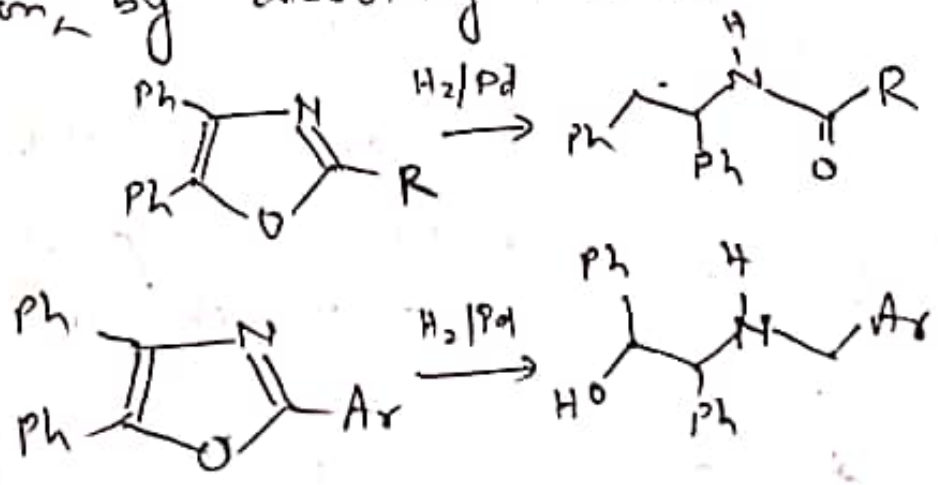


In this electrophilic ring opening, it is possible to lock the electron pair at the oxazole nitrogen by complexation with a Lewis acid, such as borane, which allow ~~the~~ C-2 substituted oxazole as major.



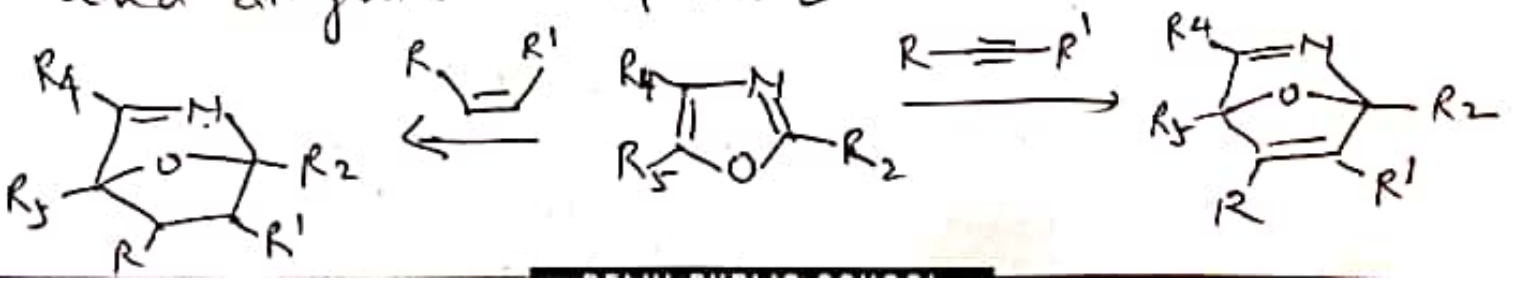
Reaction with reducing agent

Oxazole is readily reduced usually with ring scission. From the reduction with complex metal hydride of oxazoles gives acyclic product. This has been also obtained by using catalytic hydrogenation ^{or reduction} by dissolving metals.

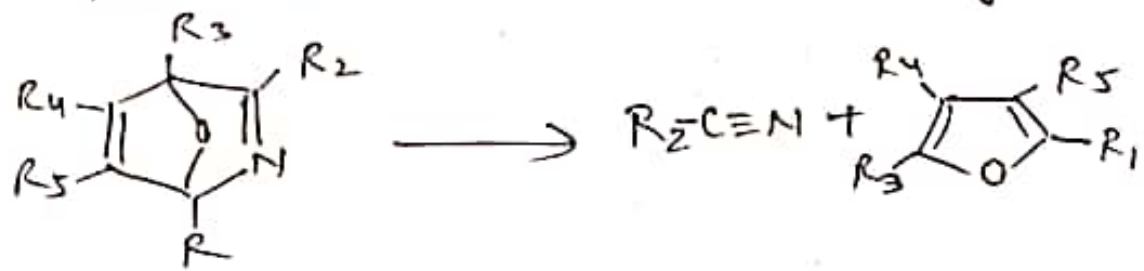


Diels Alder reaction

Oxazole exhibit diene type characteristics and undergoes Diels Alder reaction with alkenic and alkynic dienophiles [HOMO-oxazole, LUMO-Dienophile]

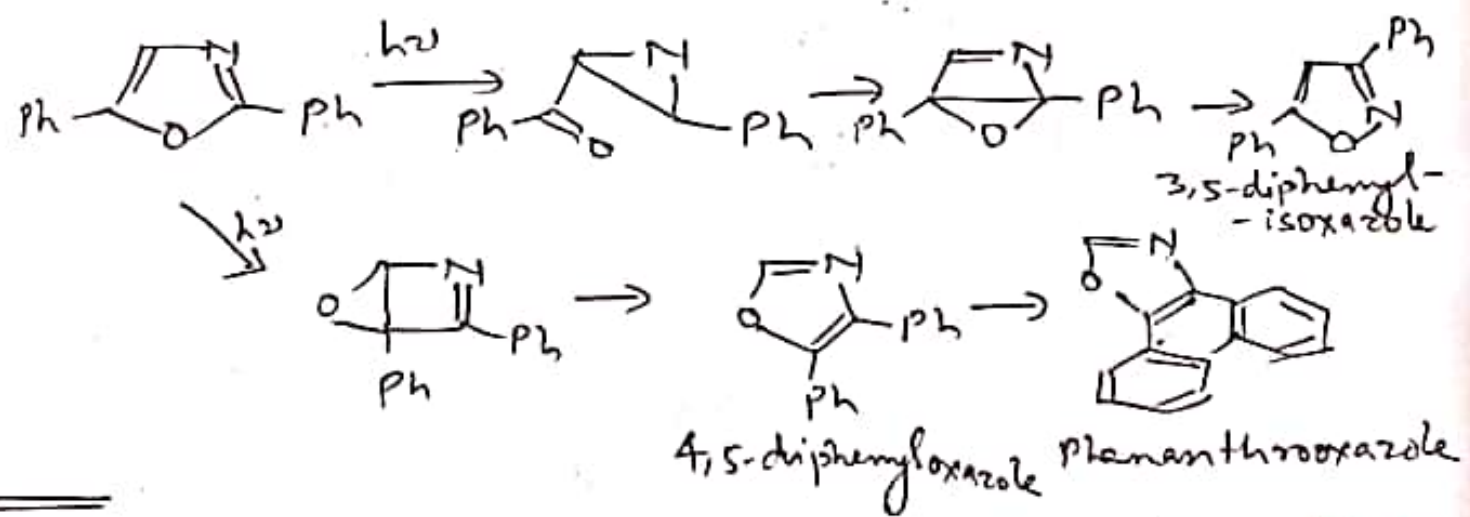


The ~~most~~ primary ~~pro~~ adduct of oxazole are usually too unstable to be isolated and undergoes retro Diels Alder reactions to give furan with elimination of cyanide.



Photochemical reaction.

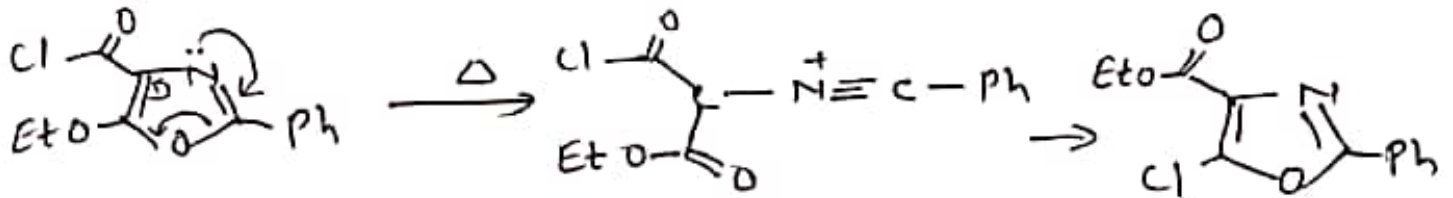
Oxazoles are generally photostable. However 2,5-diphenyloxazole in ethanol on irradiation gives mixture of 3,5-diphenylisoxazole, 4,5-diphenyloxazole, the phenanthrooxazole and traces of benzoic acid.



Oxazole was first prepared by Cornforth in 1947. about 100 years after the first synthesis of substituted oxazole 1,4,5-triphenylisoxazole reported by Zenin in 1840. Oxazole was not easily synthesised earlier. Oxazole chemistry was stimulated in the 1940 by the synthesis of penicillin which was presumed to contain the oxazole nucleus.

Cornforth rearrangement

Oxazoles in which the C-4 atom is bonded to a carbonyl group isomerize on heating. Two substituents change place in this process.



Usage

1. The anti-inflammatory and analgesic action of 2-diethylamino-4,5-diphenyloxazole.
2. Aryl substituted oxazoles are strongly fluorescent. 4,4-bisoxazol-2-ylstilbene is added to washing soda so that the clothes appear to be whiter than white as a result of the blue fluorescence.
3. 2,5-Diphenyloxazole is added as antioxidant to hydraulic fluids and high temperature lubricating oils.