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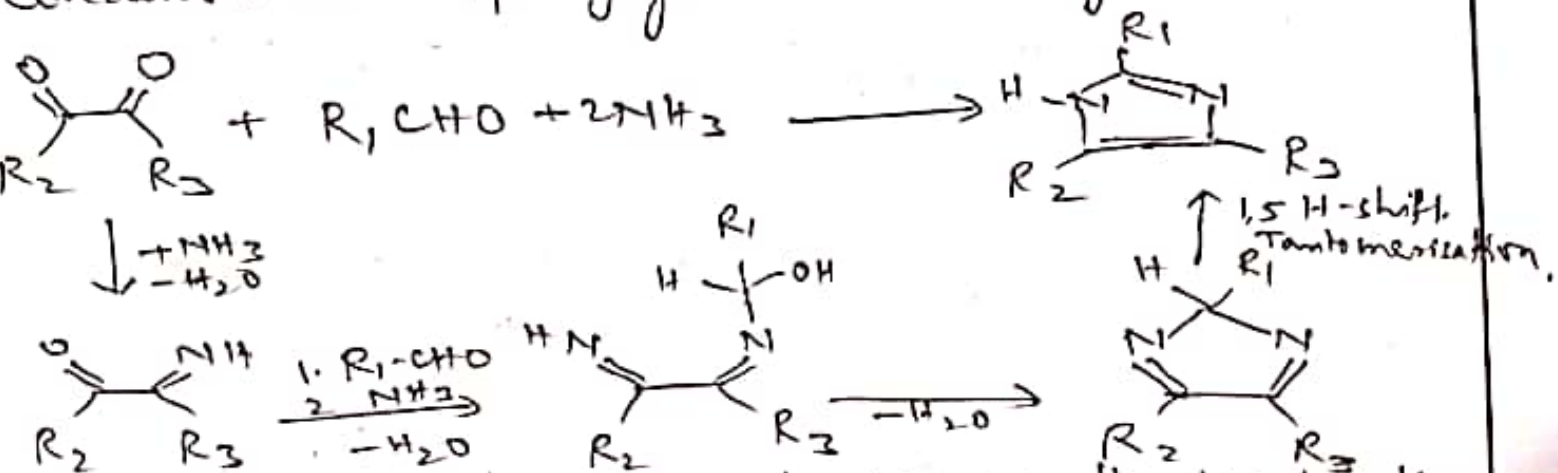
Topic: Imidazole

Imidazole

It contains one pyrrole and one pyridine like N-atom, located in 1- and 3-positions, respectively. Its systematic name is 1,3-diazole. Many natural products especially alkaloids, contain the imidazole ring.

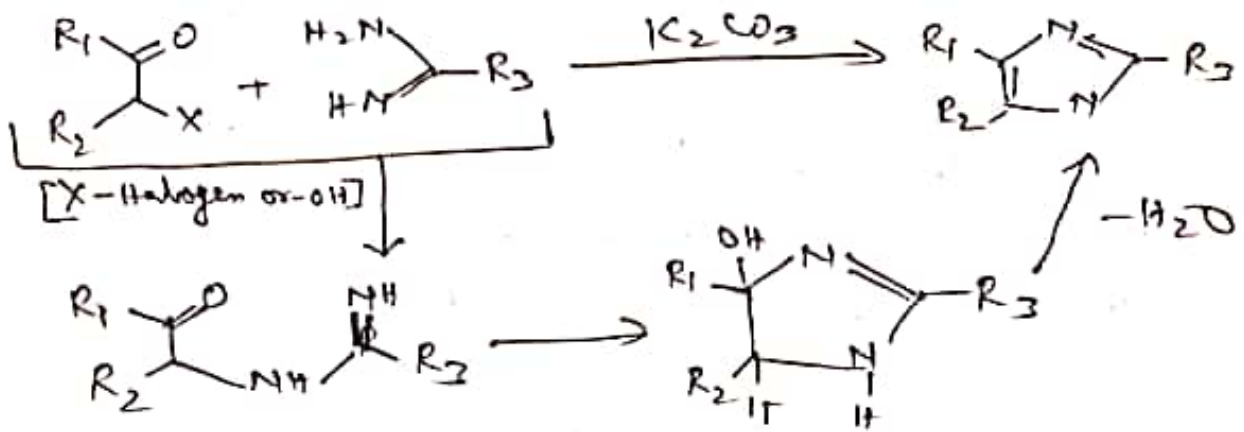
Synthesis

1. Debus method: Imidazole was first reported in 1858 by the German chemist Heinrich Debus although various imidazole derivatives had been discovered as early as 1840. It was originally named glyoxaline as they are formed by condensation of glyoxal, formaldehyde and ammonia.

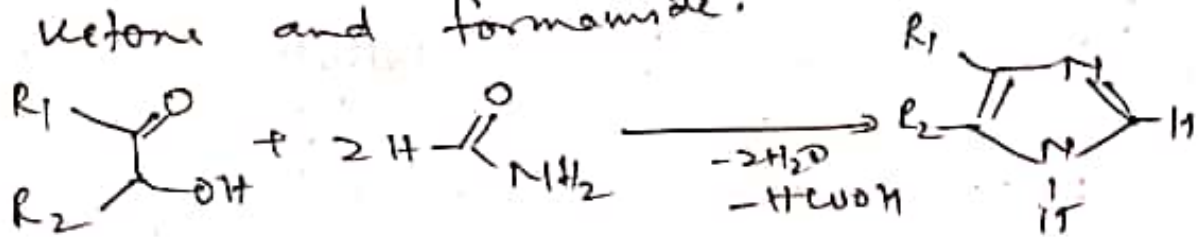


1,2-Dicarbonyl compound undergoes three component cyclodehydration with NH₃ and aldehyde to give 2,4-disubstituted or 2,4,5-trisubstituted imidazole.

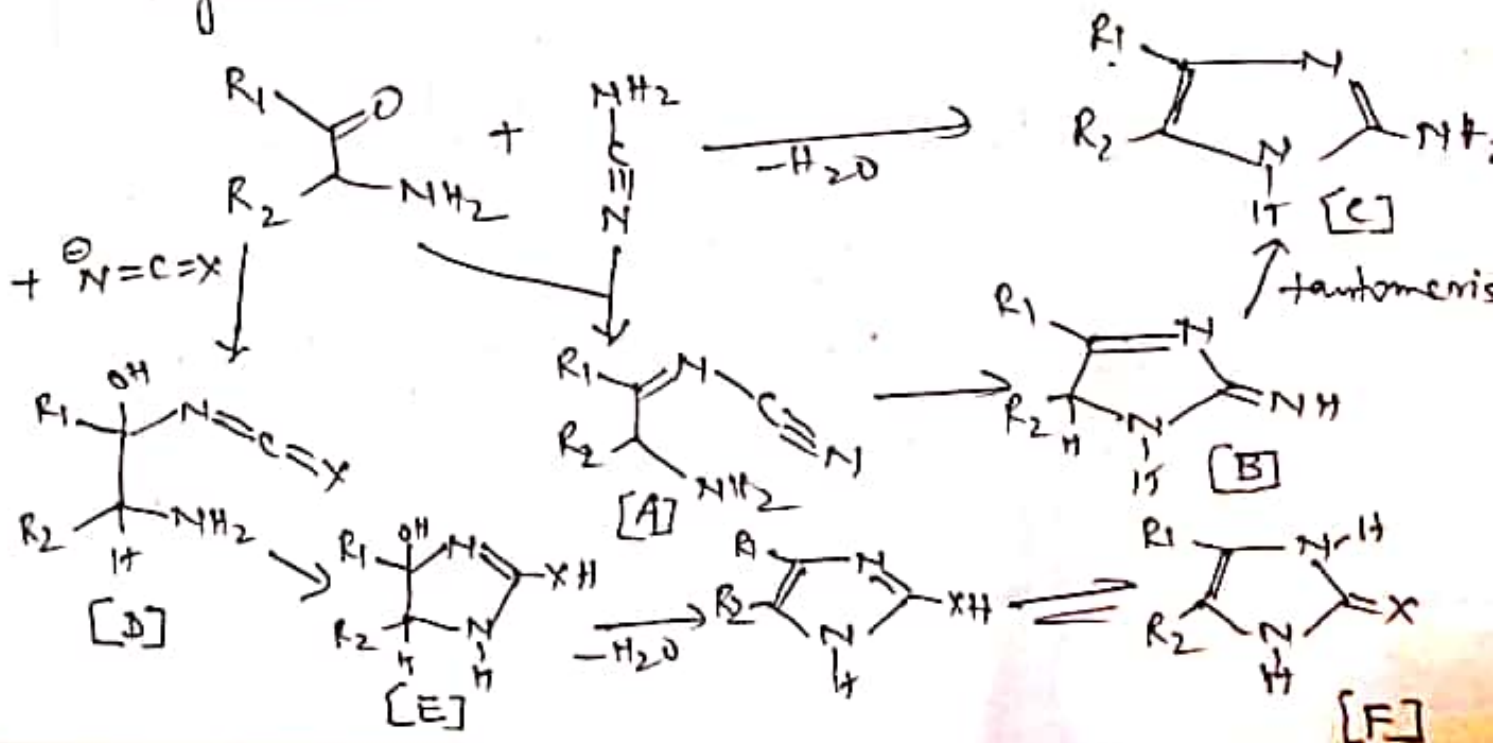
2. From α-halo or α-hydroxy ketones and amidines:
 This involves N-alkylation of the amidine followed by cyclisation and dehydration. 2,5-Disubstituted imidazole are obtained from amidines and α-halogeno ketones in the presence of base.



Analogously, α -hydroxy ketones cyclodehydrate with amidines, guanidines and urea or thiourea to give imidazole or 2-aminoimidazoles or imidazole-2(3H)-ones or thiones respectively. By Bredereck synthesis imidazoles unsubstituted at the 2-position are obtained from α -hydroxy ketone and formamide.



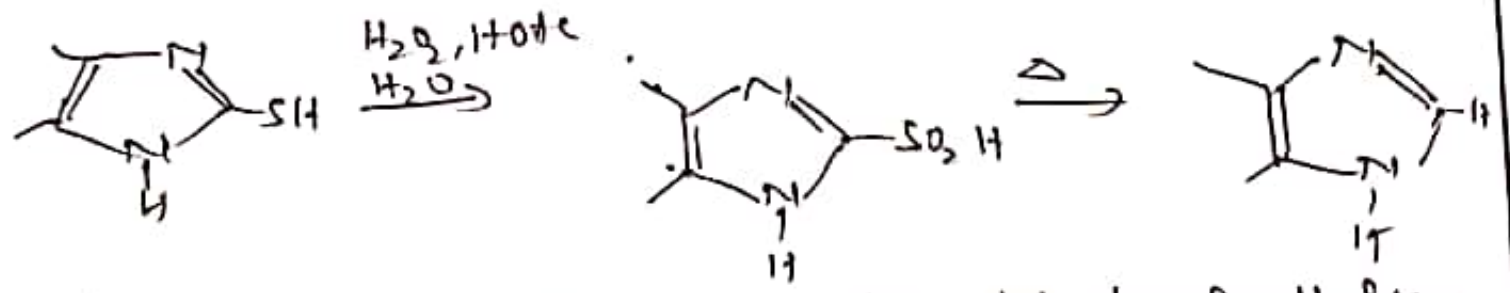
3. Marckwald synthesis: α -amino ketones react with cyanamide to afford 2-aminoimidazoles



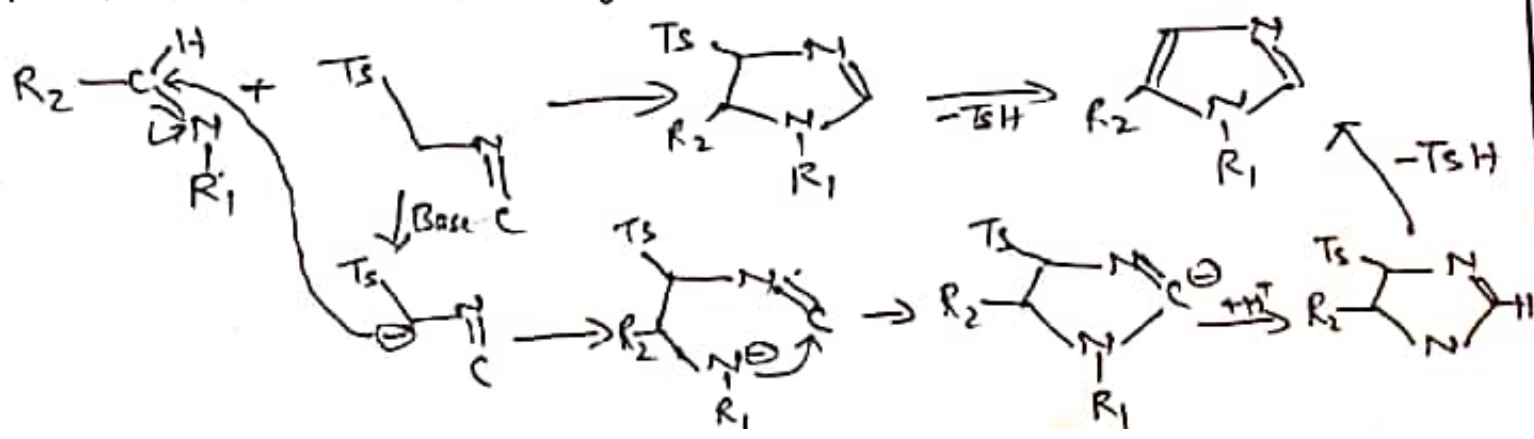
Formation of C can be interpreted by condensation of both reactant to give the imine [A] followed by intramolecular amine addition to the cyano group to get [B] which tautomerises to [C].

Formation of [F] via [D] & [E] gives variable products. The cyanate or thiocyanate yields imidazol-2-one or 2-thiones and alkyl isocyanate gives 1-alkylimidazol-2-one.

Tautomer of thione i.e. thiole can be easily oxidised by H_2O_2 to sulfonic acid moiety which thermally eliminates SO_2 to give 2-substituted imidazole.

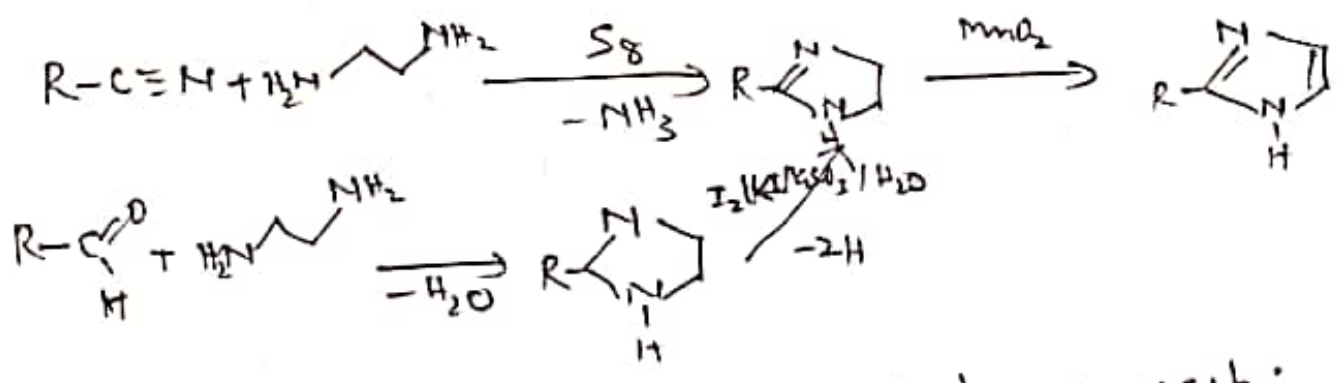


4. From Aldimine: Aldimine reacts with tosylmethylisocyanide (TSMIC) in the presence of K_2CO_3 giving 1,5-disubstituted imidazole. The carbanion formed from tosylmethylisocyanide add to the aldimine analogous to the van Leusen synthesis of oxazole.

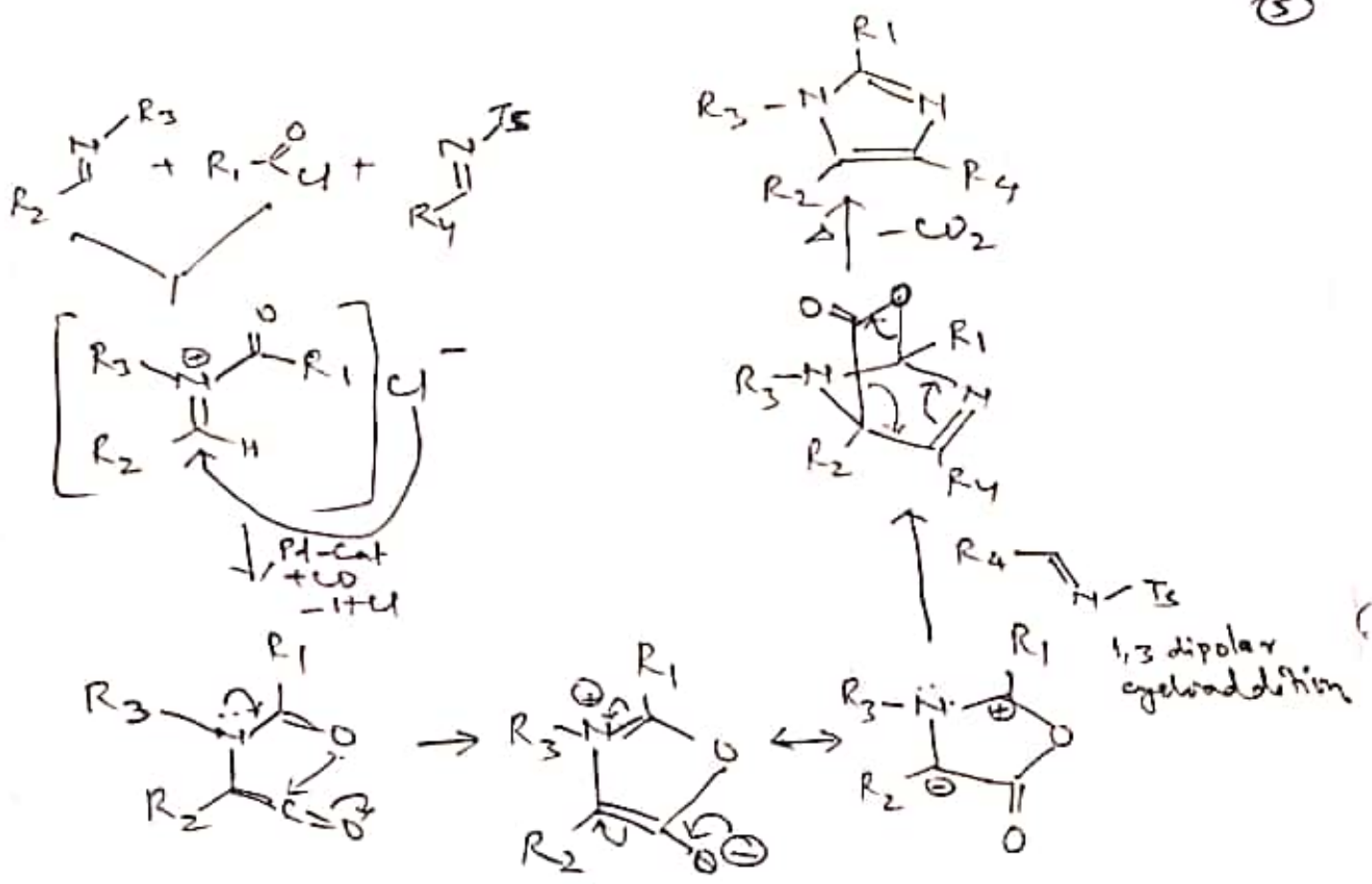


Here in analogy to the van Leusen oxazole synthesis, the anion of TMIC adds to the imine function and the addition product cyclizes to imidazoline which undergoes base induced elimination of sulfonic acid producing the imidazole.

5. From ethylenediamine: Ethylenediamine and nitrile in the presence of catalytic amount of sulfur under ultrasonic irradiation ~~can~~ or ethylene diamine and aldehyde in the system $I_2/KI/K_2S_2O_8/H_2O$ gives 2-substituted 4,5-dihydroimidazole which on dehydrogenation ^{by MnO_2 , $PhIOAc_2$ or Swern oxidation} gives 2-substituted imidazole.

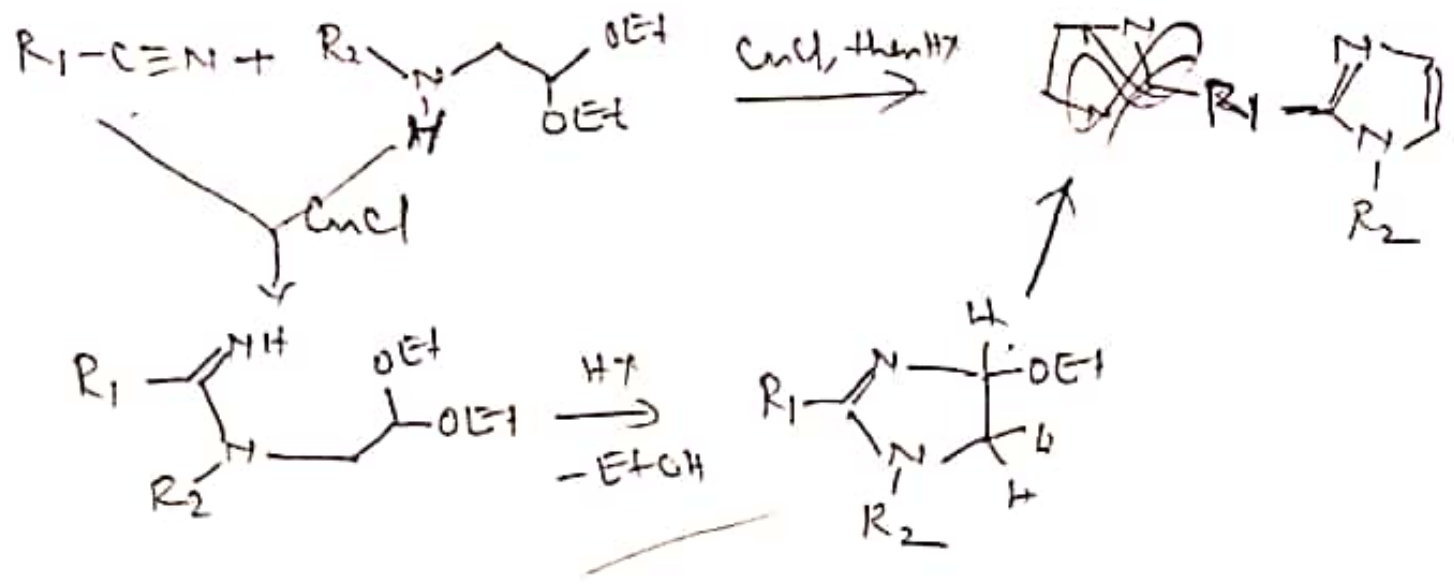


6. By transition metal mediated approach:
 a) In the Pd-catalyzed multicomponent approach N-alkylimines, acid chloride and ~~N-tosylimine~~ DIPEA/LiCl, CO, and a specific Pd(0) catalyst to give tetrasubstituted n-alkylimidazole.



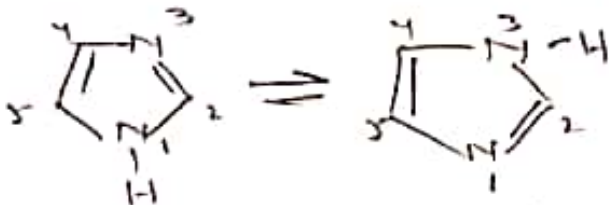
Here N-alkylimine is acylated to get acyliminium system which undergoes Pd-mediated and LiCl assisted CO transfer to get N-acylketene. The cyclisation of N-acylketene gives rise to Munchnone which undergoes 1,3-dipolar cycloaddition followed by elimination of p-toluenesulfonic acid and CO_2 to yield tetrasubstituted ~~imidazole~~ N-alkylimidazole.

b) 1,2-disubstituted imidazole can be obtained from nitriles by Cu(I) promoted addition of aminoacetaldehyde diethylacetal followed by acid induced eliminative cyclization of the intermediate formed amidineacetal.

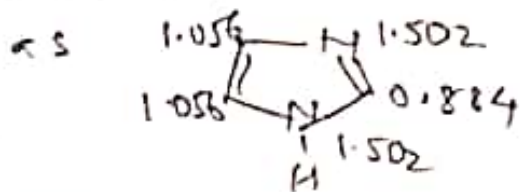


Properties

The ionization energy of imidazole (8.78 eV) is greater than that of Pyrrole (8.23 eV) explains the stabilization of π -system due to lowering of HOMO energy due to the pyridine like N-atom. It shows annular tautomerism based on ^{aromatic} nmr spectral signal for 4H and 5H as well as for C4 and C5.



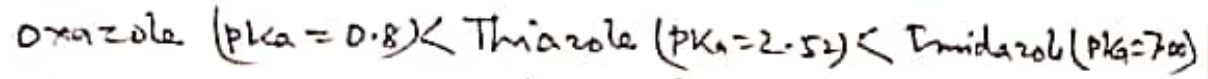
Imidazole is an aromatic system belongs to the class of π -excessive heterocycles with six electrons distributed over five atoms but mainly concentrated on the N-atoms. The electron densities have been calculated by self MD methods



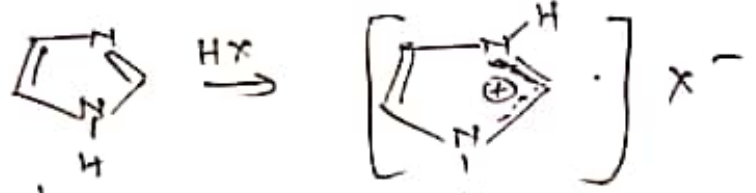
The 2-position between the two N-atoms shows the lowest π -electron density, thus nucleophilic attack would be expected to occur at 2-position while electrophilic ~~at~~ substitutions should be possible in the 4- or 5-positions.

Acid base reactions, anular tautomerism:

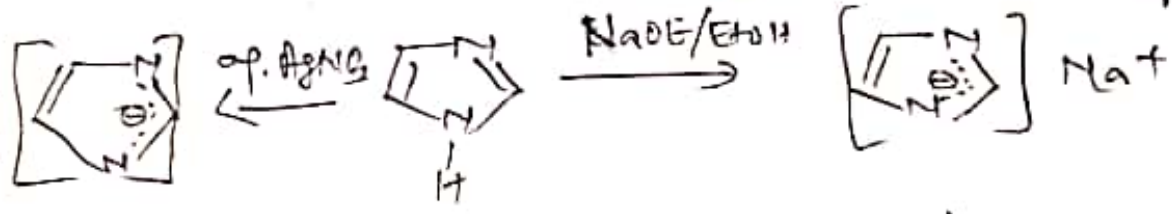
Imidazole possess the highest basicity than oxazole and thiazole. An order of basicity is



Imidazole reacts with acid to form salt with symmetrical delocalization of the positive charge

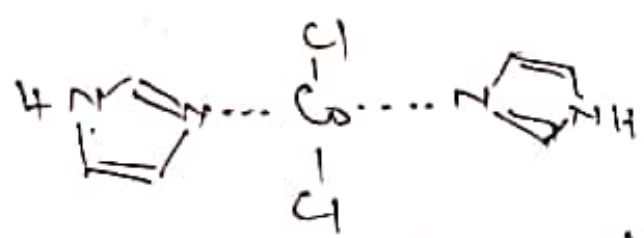


Imidazole unsubstituted at 1-N-position is weak NH acid. However their acidity is higher than that of pyrrole. Imidazole reacts with NaOEt in EtOH to form Na-salt and Ag salt with AgNO3.



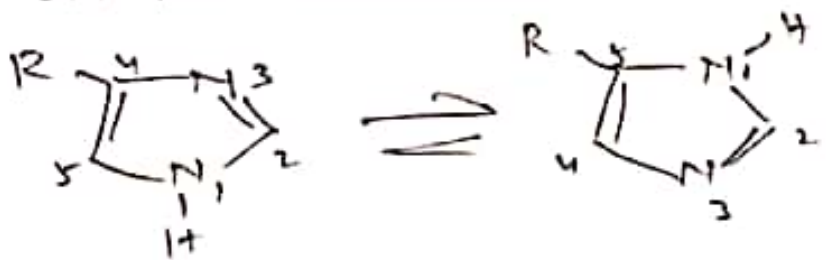
Therefore imidazole behaves as ambiprotic Complex formation

Imidazole forms complexes with many metal ion in which the pyridine like N-atom functions as donor



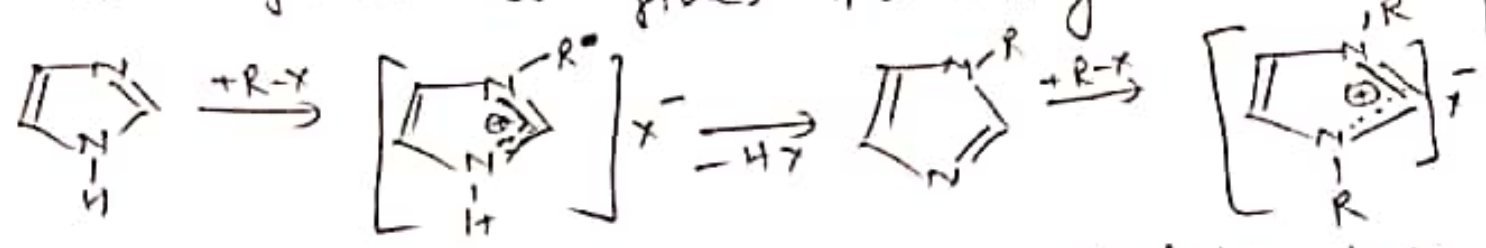
Hemoglobin is an Fe(II) complex of heme with the imidazole moiety of the amino acid histidine contained in the protein globin.

Annular tautomerism: The special case of prototropy is known as annular tautomerism in which proton transfer from N-1 to position N-3, 4-substituted 1,3-unsubstituted imidazole equilibrates with the corresponding 5-isomers. The equilibrium depends on the substituents.

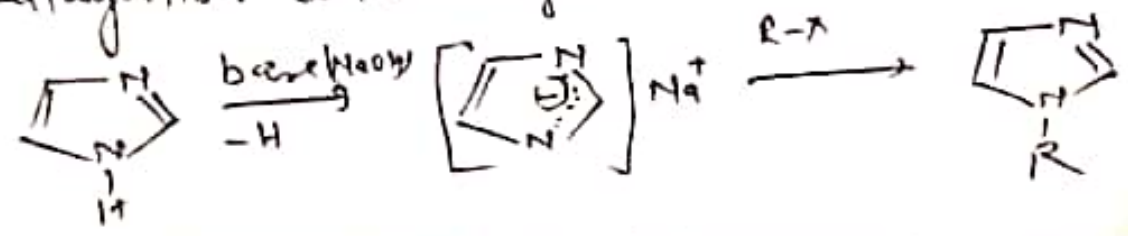


Reactions with electrophilic reagents

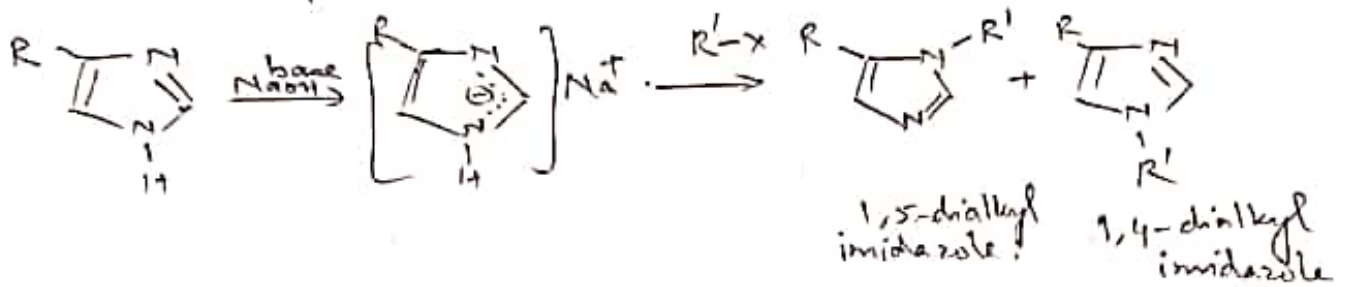
(a) Alkylation - ~~imid~~ Imidazole on alkylation by halogenoalkane gives quaternary salt initially which undergoes rapid deprotonation to 1-alkyl-imidazole and on further reaction with a second ~~at~~ halogenoalkane gives 1,3-dialkylimidazolium salt



In the presence of strong-base, alkylation takes place via the imidazolyl anion yielding 1-alkylation with halogenoalkanes and dialkyl sulfate.

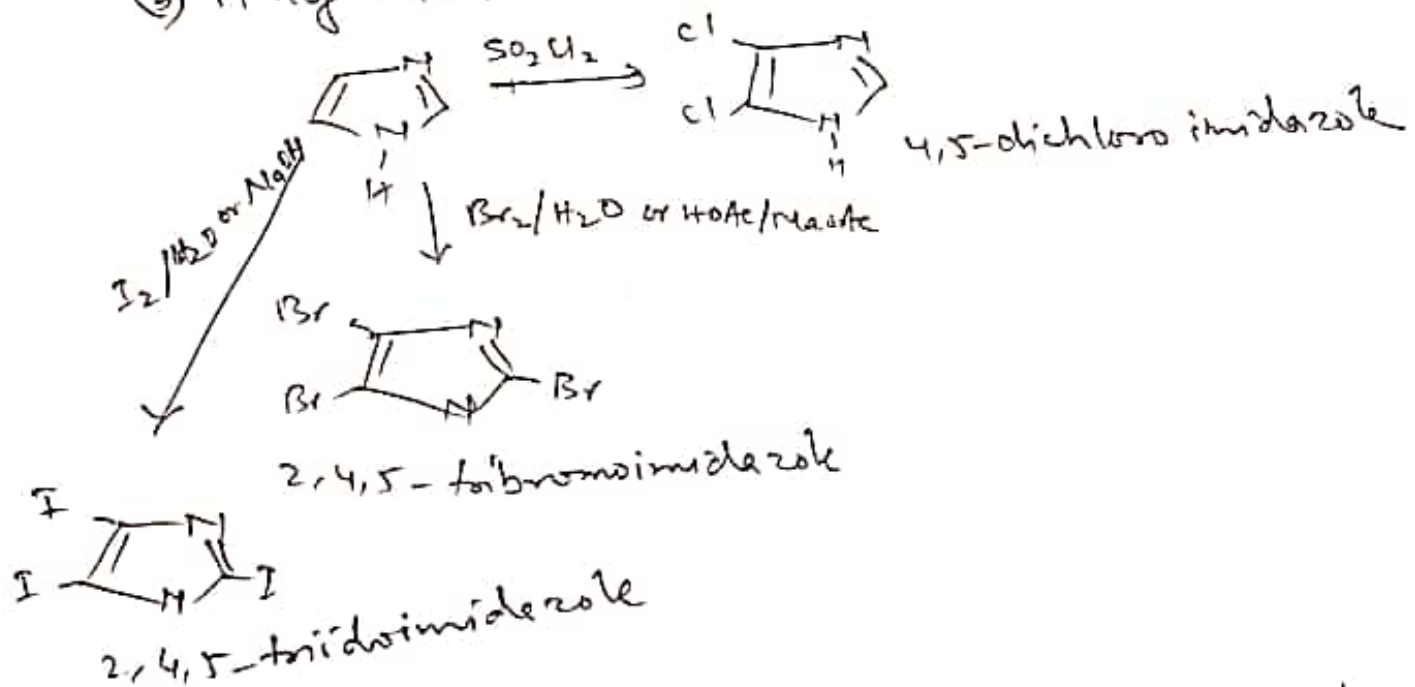


But in case of unsymmetrical imidazolyl anion mixture of disubstituted products are formed.

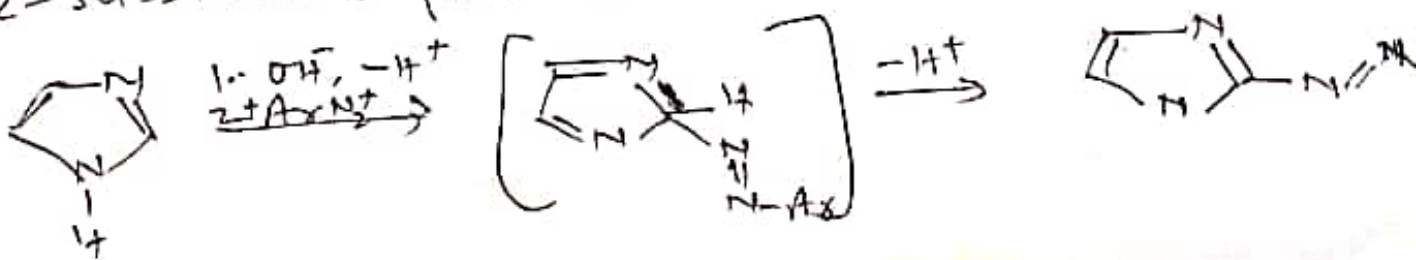


Sodium salt of imidazole can also be reacted with acid chloride, sulfonyl chlorides and trialkylchlorosilane to give the corresponding 1-substituted imidazole.

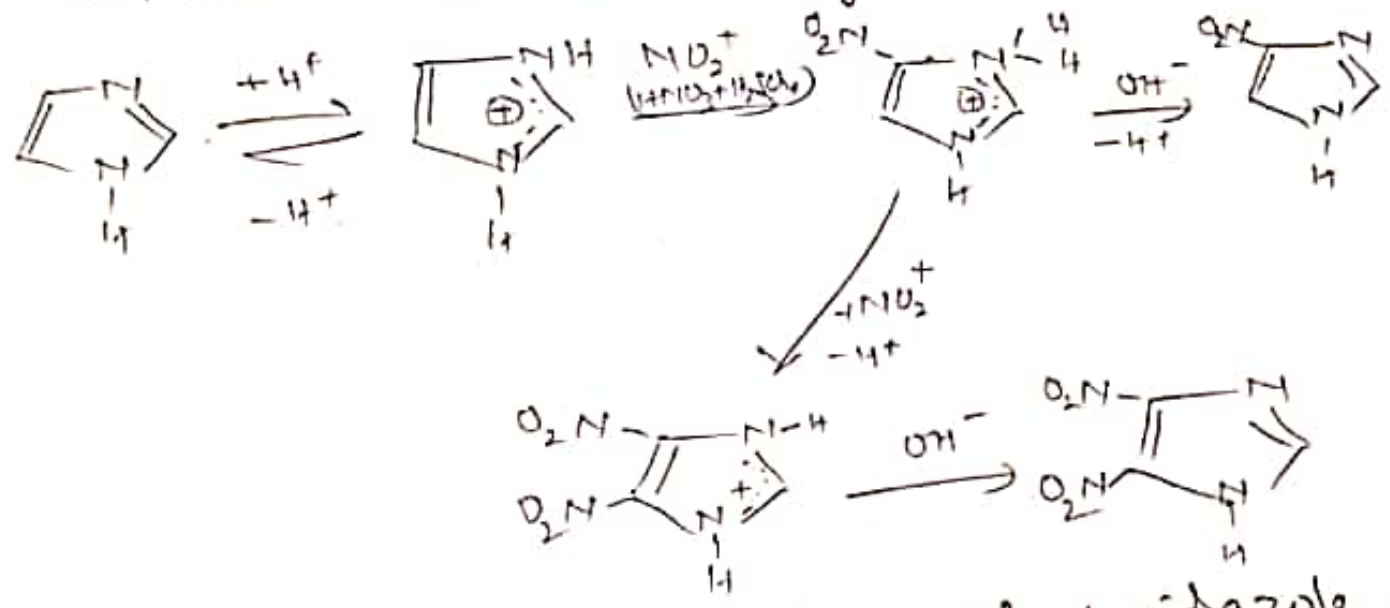
b) Halogenation:



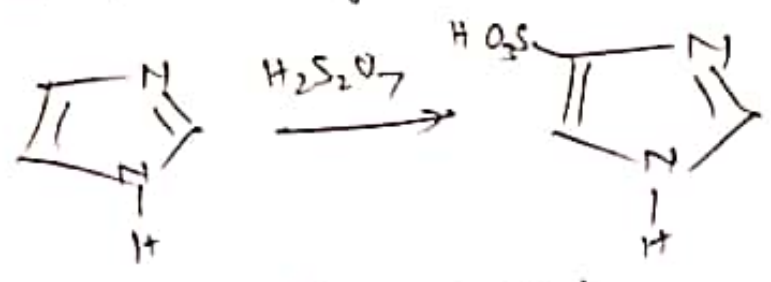
c) Azo coupling: In aqueous alkaline solution, imidazole undergoes azo coupling to give 2-substituted product.



(d) Nitration: Imidazole produces 4-nitroimidazole on nitration but under drastic condition gives rise to 4,5-dinitroimidazole. However nitration proceeds very slowly due to formation of Imidazolium ion in strongly acidic medium.

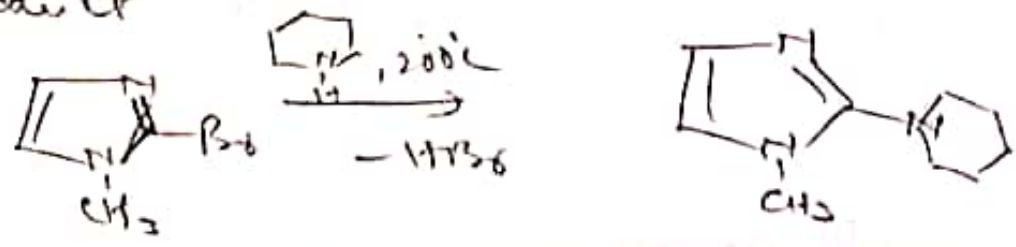


(e) Sulfonation: Sulfonation of imidazole in oleum at 160°C yields imidazole-4-sulfonic acid.

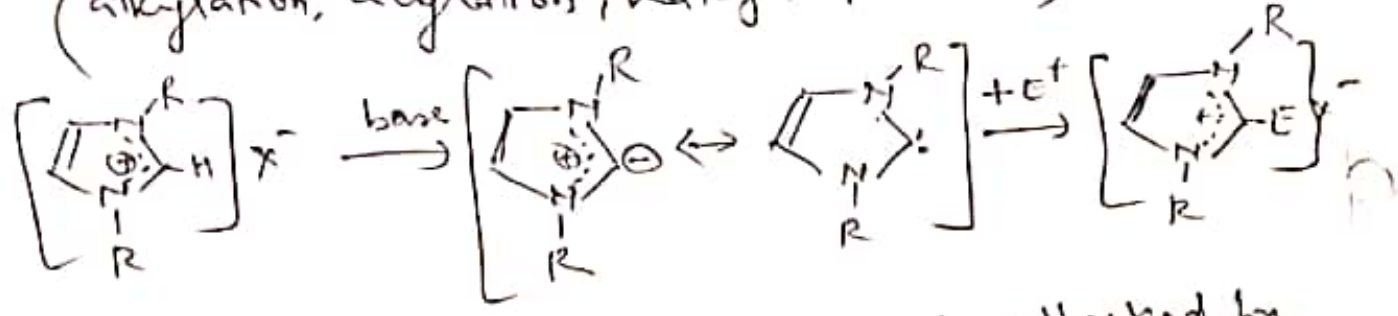


Reaction with nucleophilic reagent:

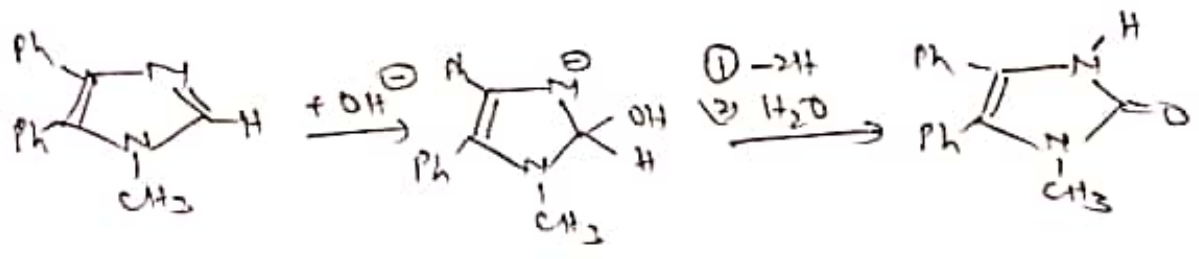
(f) 2-halogeno-1-alkylimidazole reacts with Piperidine at high temperature (200°C) yielding 2-substituted product



(b) 1,3-dialkylimidazolium salt undergoes deprotonation in the 2-position on treatment with strong base (t-BuOK) to yielding 1,3-dialkylimidazolium ylides which exhibit the behaviour of nucleophilic carbenes and undergoes electrophilic reaction (alkylation, acylation, halogenation etc) at C-2.

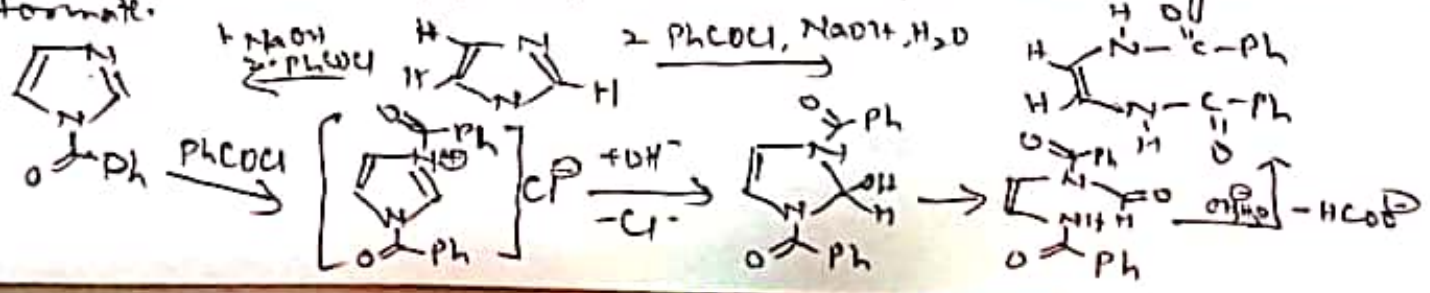


(c) 1-methyl-4,5-diphenylimidazole is attacked by KOH at 300°C in the 2-position to give the imidazole-2-one after addition and dehydrogenation.



1,3-dialkyl or 1,3-diacylimidazolium ion in contrast usually shows addition at C-2 followed by ring cleavage in presence of OH- ion, and shows higher reactivity against OH- ion.

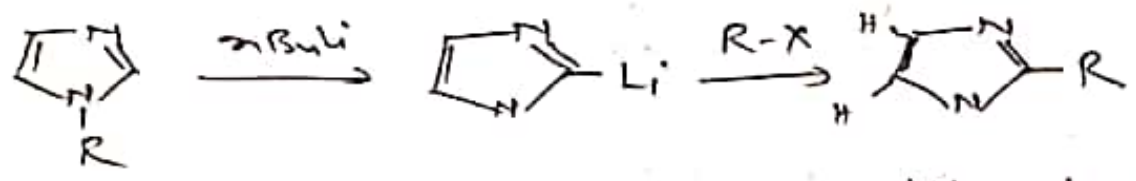
(d) In Schotten-Baumann condition (NaOH/H2O), imidazole reacts with Ph-COCl leads to 1,2-dibenzoylamidobenzene and formate.



Primarily, imidazolyl-Na formed from imidazole and NaOH, is acylated by PhCOCl to give 1-benzoylimidazole. Quaternization of 1-benzoylimidazole by a second PhCOCl moiety leads to the 1,3-dibenzoylimidazolium salt which undergoes addition of OH⁻ at C-2 with subsequent ring opening at C-2/N-3 to give triacylated diamine which finally hydrolysed to give 1,2-dibenzoylamidomethane, and formate.

Metalation and metal mediated reactions.

(a) 1-alkylimidazole can be metalated in the 2-position by n-BuLi to give the corresponding 2-lithioimidazole.

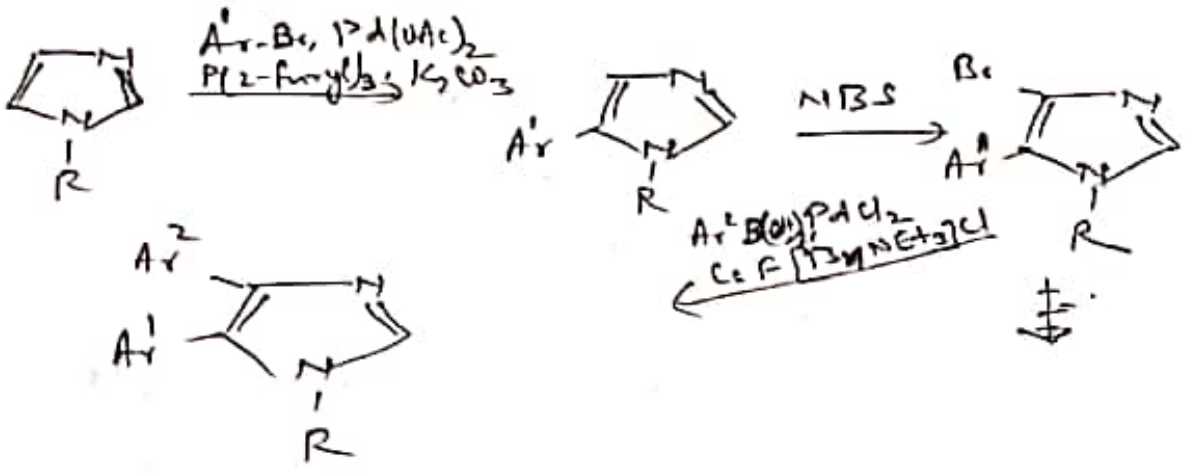


2-lithiated imidazoles can be utilized for introduction of other functionality.

- (i) alkylation with -R-X
- (ii) silylation with R₃Si-Cl

→ 1,2-dialkylated imidazole are metalated by R-Li in the 5-position.

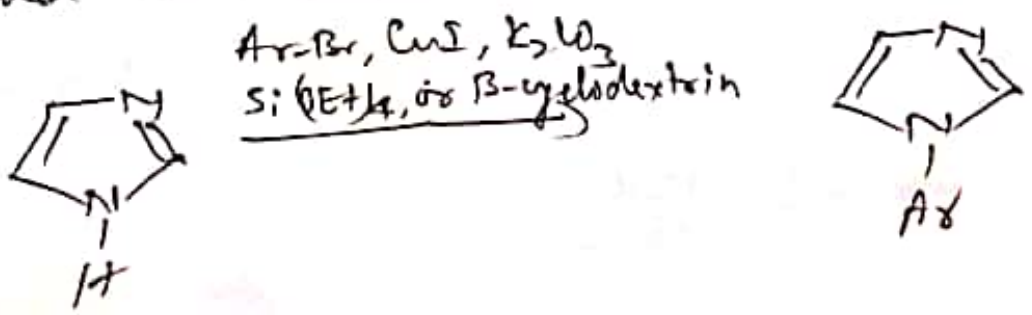
(b) 1-alkylimidazole undergoes direct regioselective arylation in the 5-position by aryl bromide in the presence of K₂CO₃ and a Pd(II) catalyst.



The 5-arylated imidazole can be further subjected to a second arylation by bromination with NBS followed by Pd-catalyzed Suzuki-Miyaura coupling with arylboronic acid to give 1-alkyl-4,5-diarylimidazole.

(C) N-arylation of imidazole can be obtained by various methods.

- (i) In a Cu(I) catalysed, ligand free and microwave assisted process with arylbromide in the presence of K_2CO_3 and $\text{Si}(\text{Et})_4$
- (ii) In a Cu(I) catalysed K_2CO_3 promoted process with arylbromide and heptakis(6-amino-6-deoxy) cyclodextrin as an highly efficient supramolecular ligand and host.



Use

The wide application of the imidazole pharmacophore can be attributed to its hydrogen bond donor-acceptor capability ^{like water} as well as high affinity for metals like Zn, Fe, Mg that are present in many protein active sites. The imine nitrogen of imidazole donates an electron pair and N-hydrogen being appreciably acidic is an acceptor.