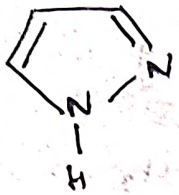
Heterocyclic Compounds

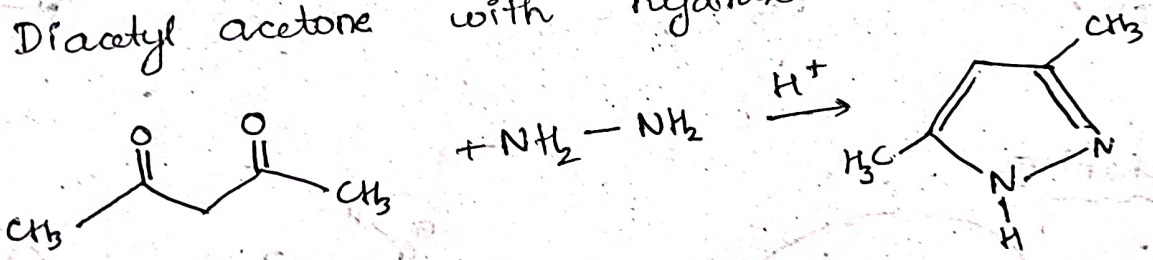
1) Pyrazole:



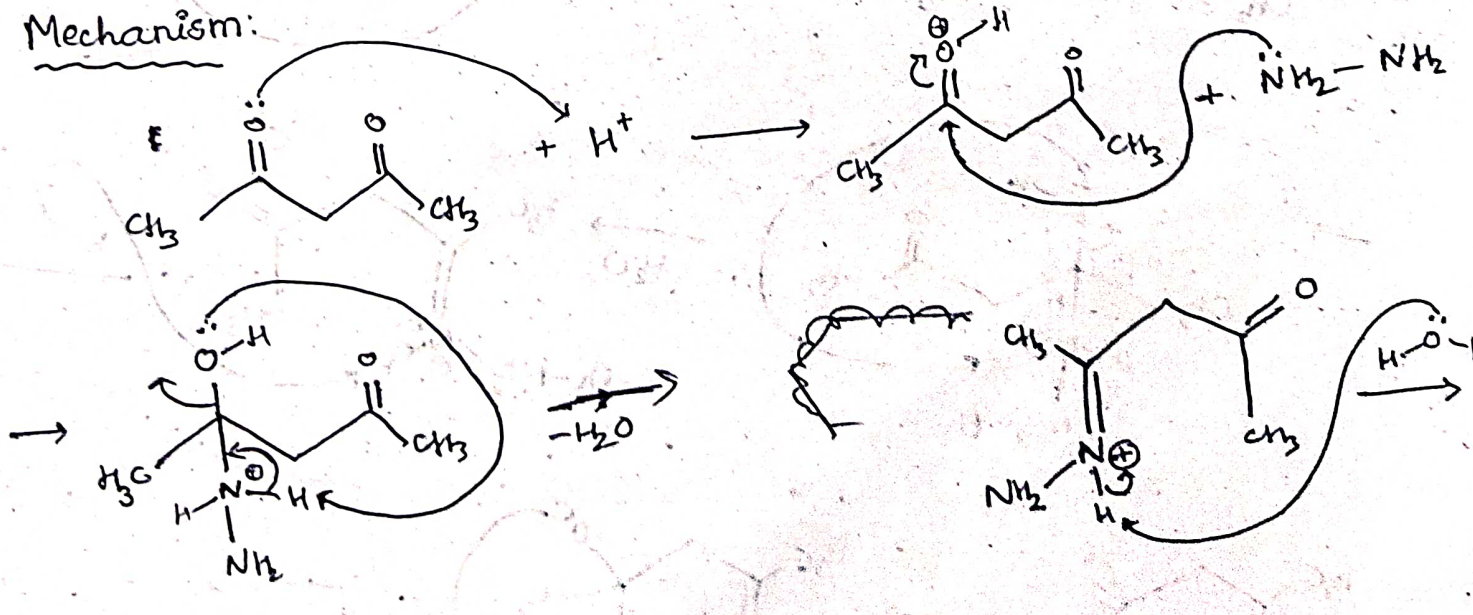
* Antipyretic nature
* synthesized by Buchner from the derivative of 3,4,5 - tricarboxylic acid decarboxylation

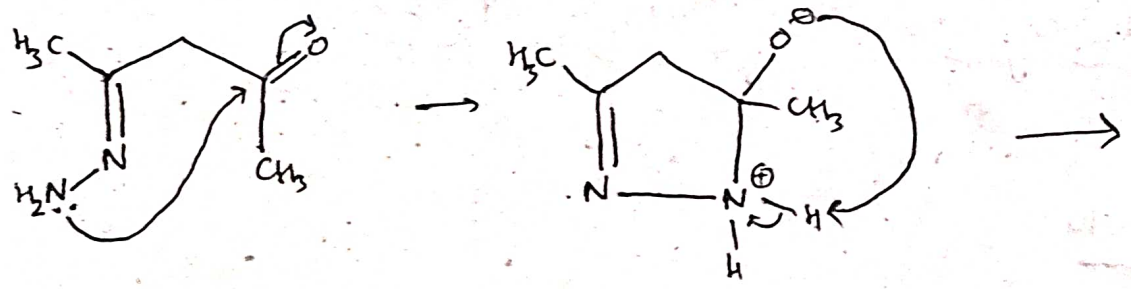
Preparation:

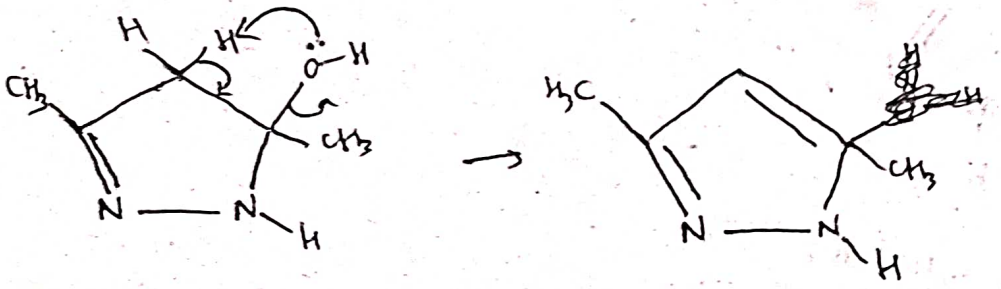
1) Diacetyl acetone with hydrazine



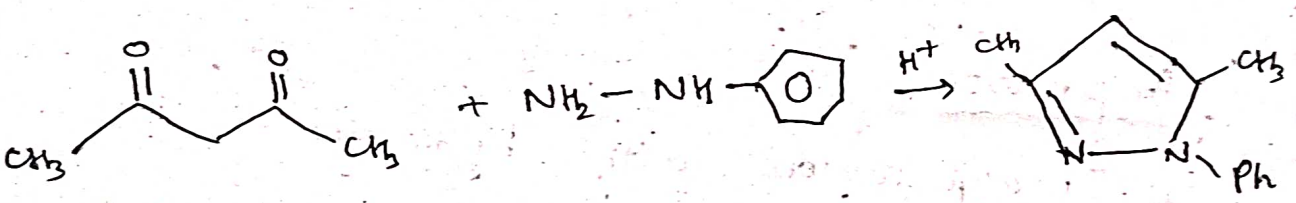
Mechanism:



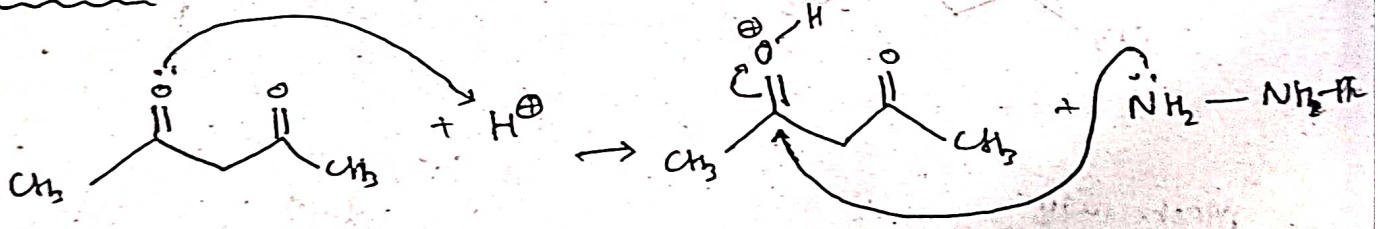


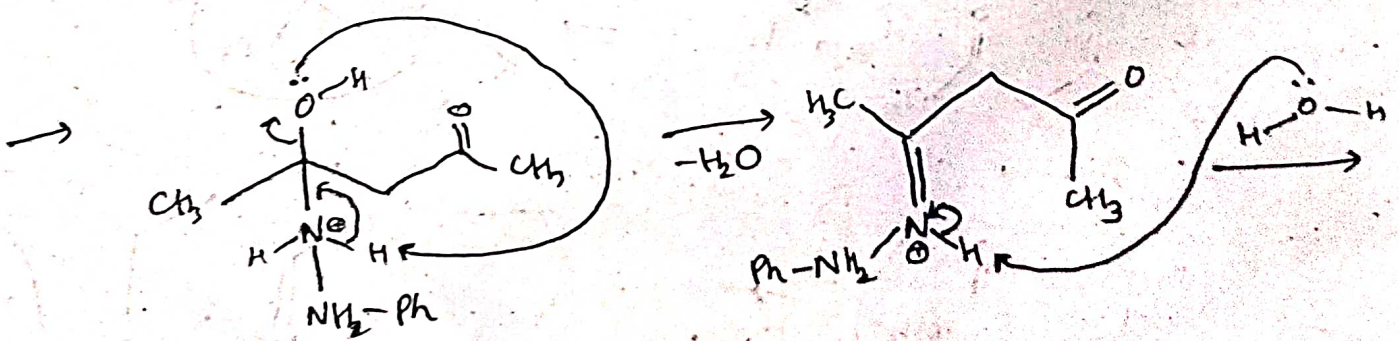


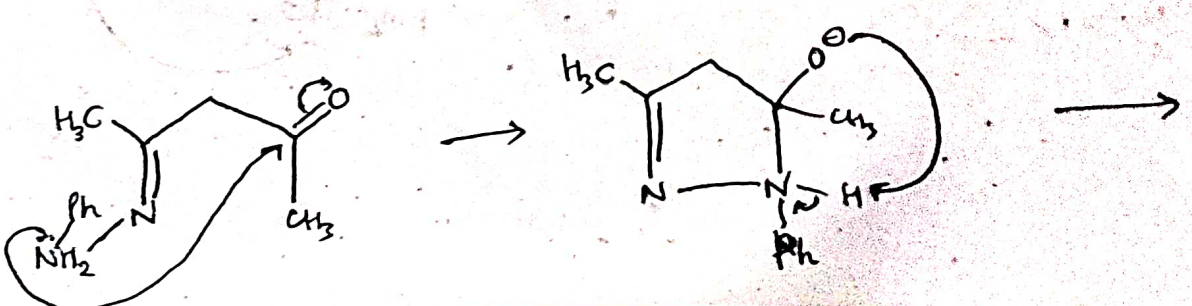
2)

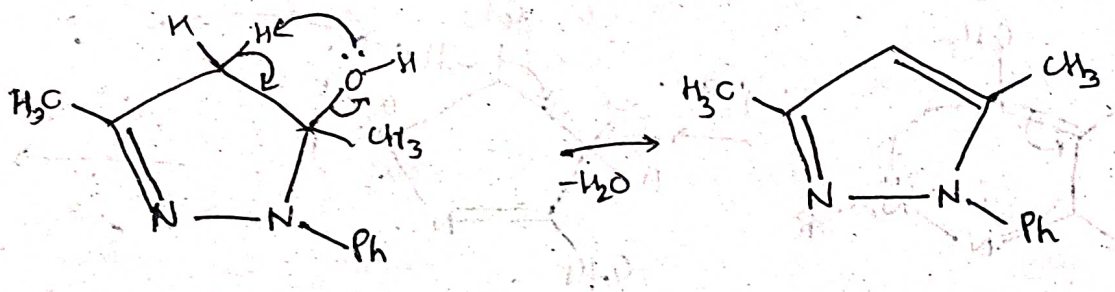


Mechanism



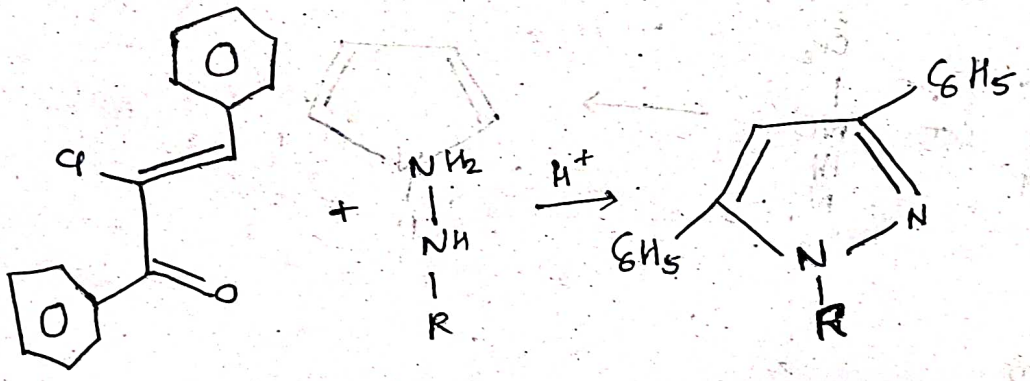




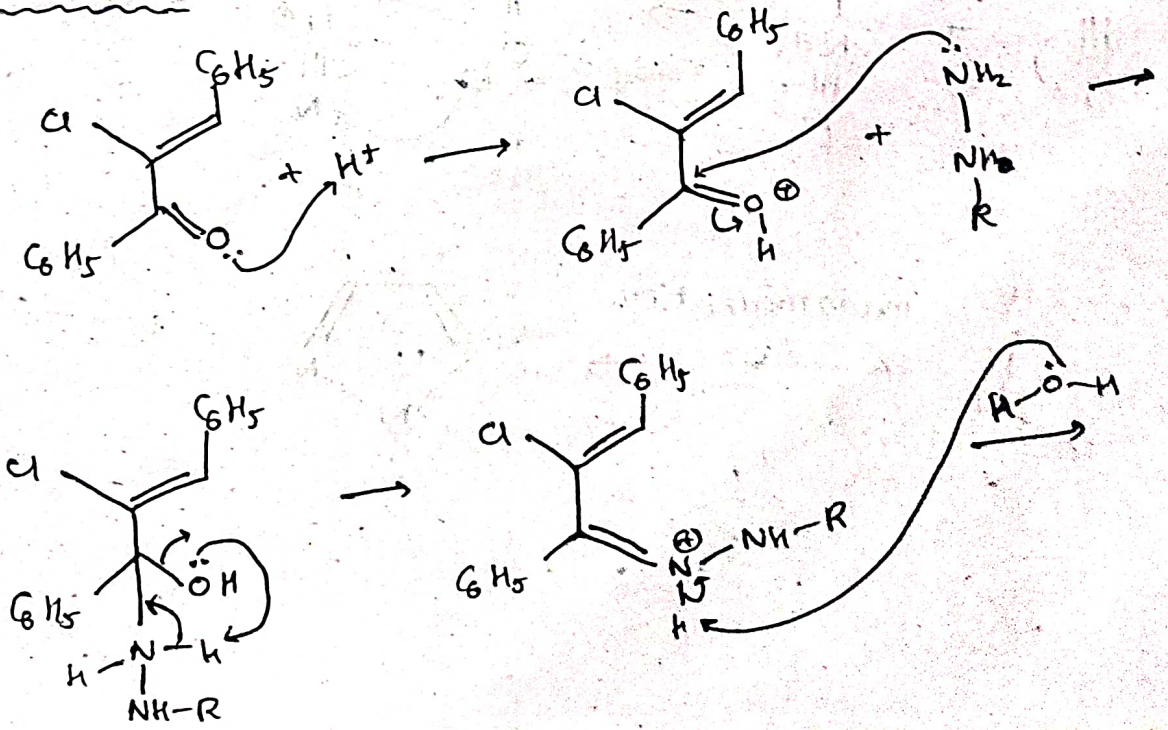


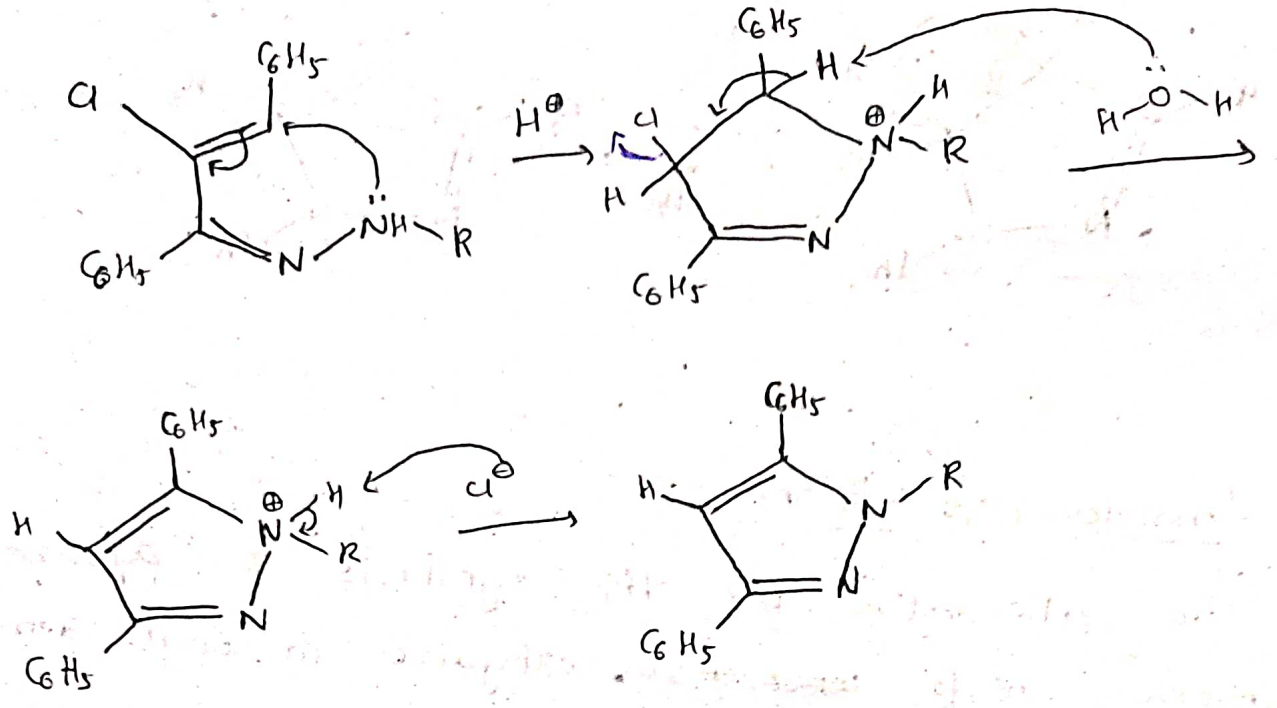
3) Unsaturated ketone

The alternative for the synthesis of pyrazole involves α-β ~~unsaturat~~ ethylinic carbonyl derivatives or α-β acetylinic carbonyl compound with hydrazine derivatives.

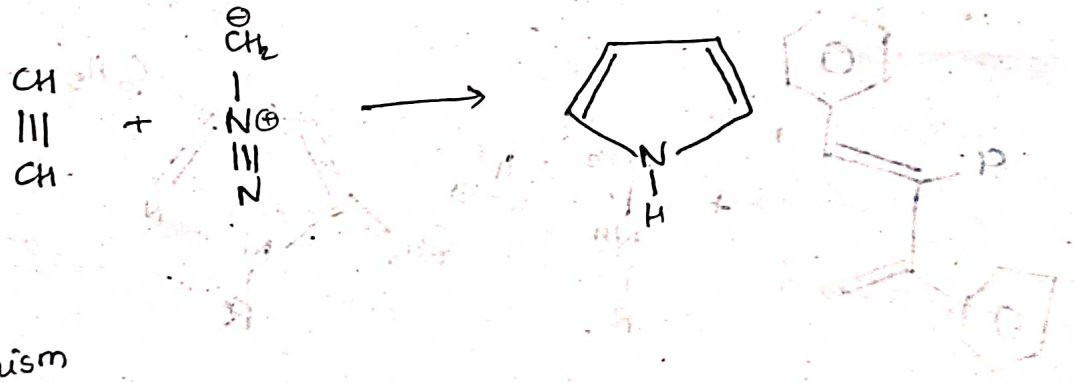


Mechanism:

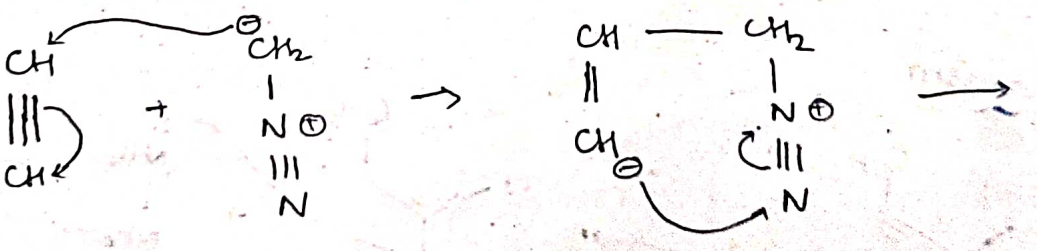


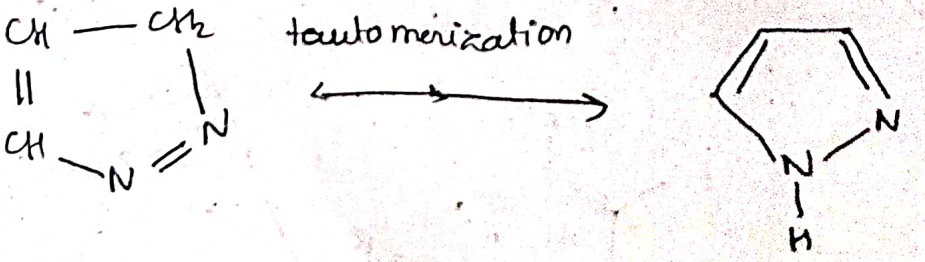


4).

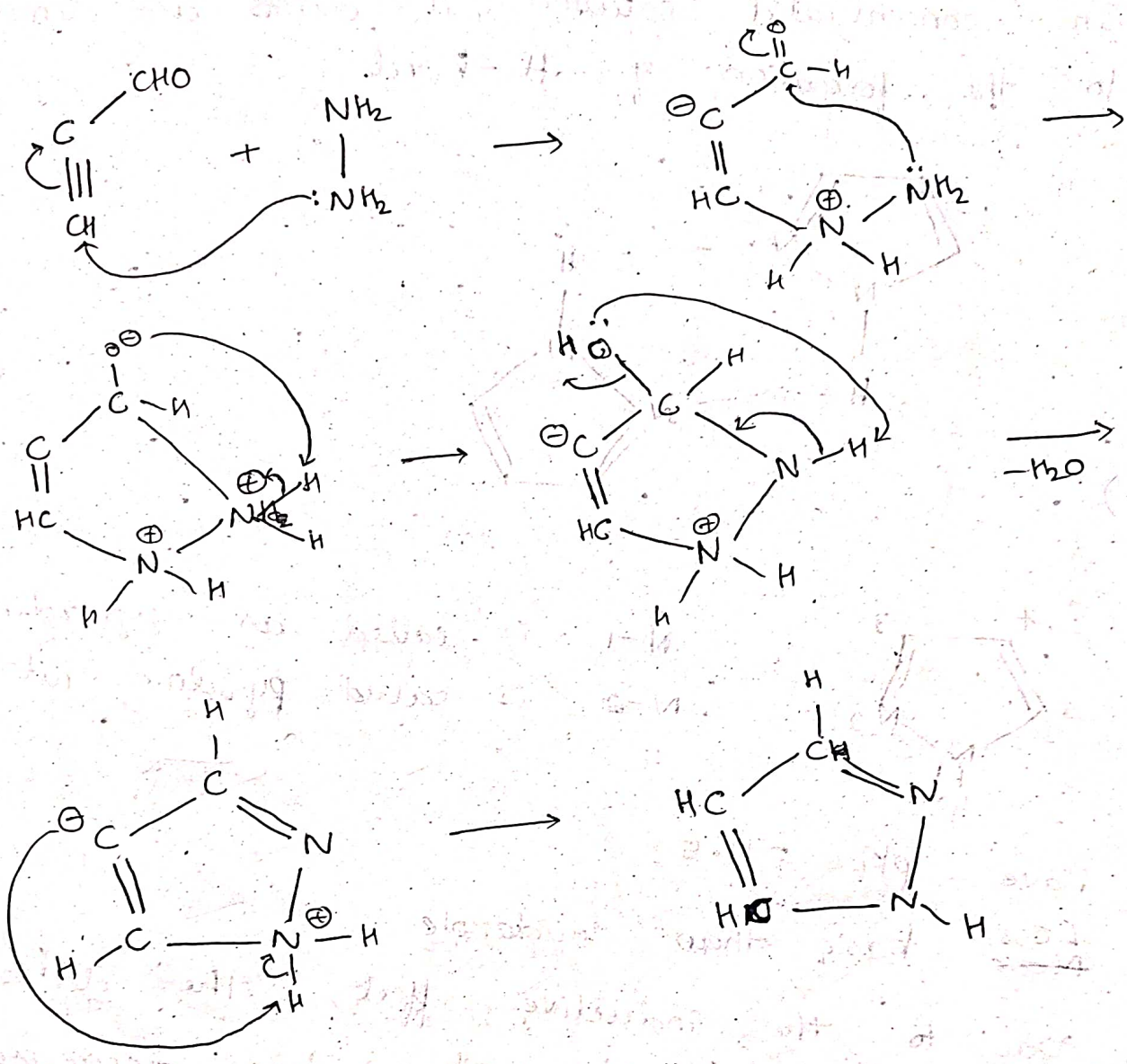


Mechanism



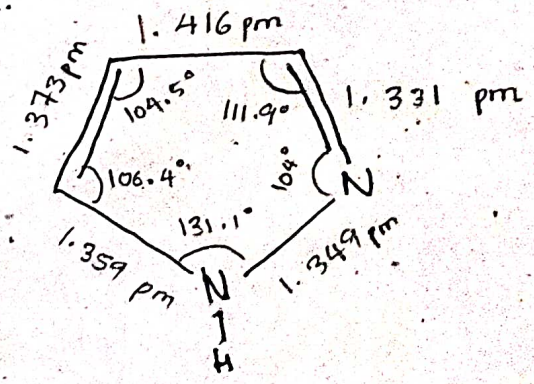


5) Acetylene with Hydrazine

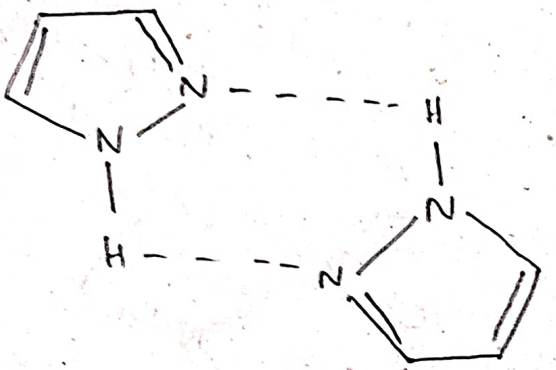


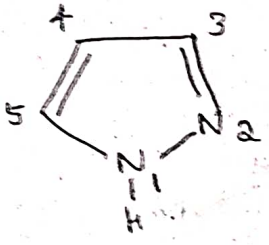
Physical & Chemical properties of pyrazole

* It has got the melting point of 70°C which crystallizes to colourless needle and possess a boiling point of 188°C, and has the odour of pyridine.

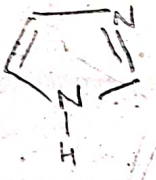


* It is partially soluble in water
* In concentrated solution, it exists as dimer due to the formation of H-bond





* N-1 is called as pyrazolin nitrogen
* N-2 is called pyridine nitrogen



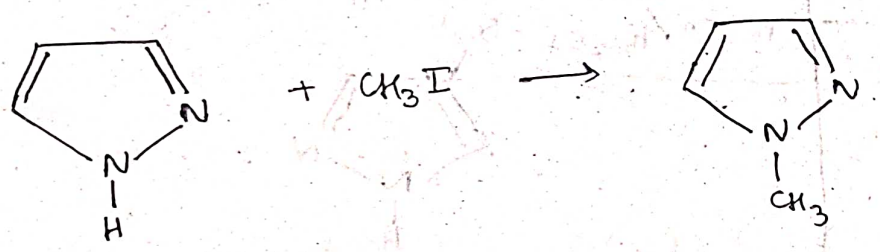
imidazole

* Have $pK_b = 11.5$
* ~~Less~~ More basic than imidazole
* Due to the inductive effect, the electron density around 3rd & 5th carbon decreases. But it does not alter the electron density of 4th carbon. So 4th carbon is vulnerable to electrophilic substitution

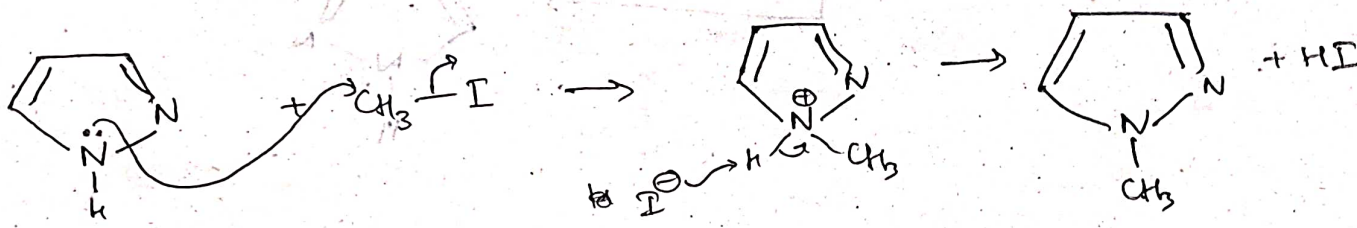
Reactions of Pyrazole

1) Electrophilic substitution at N-atom

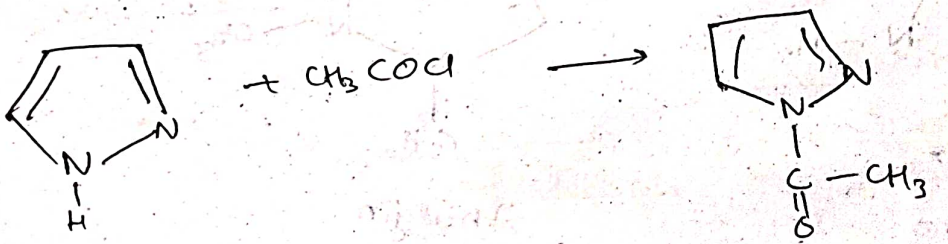
a) · Methylation



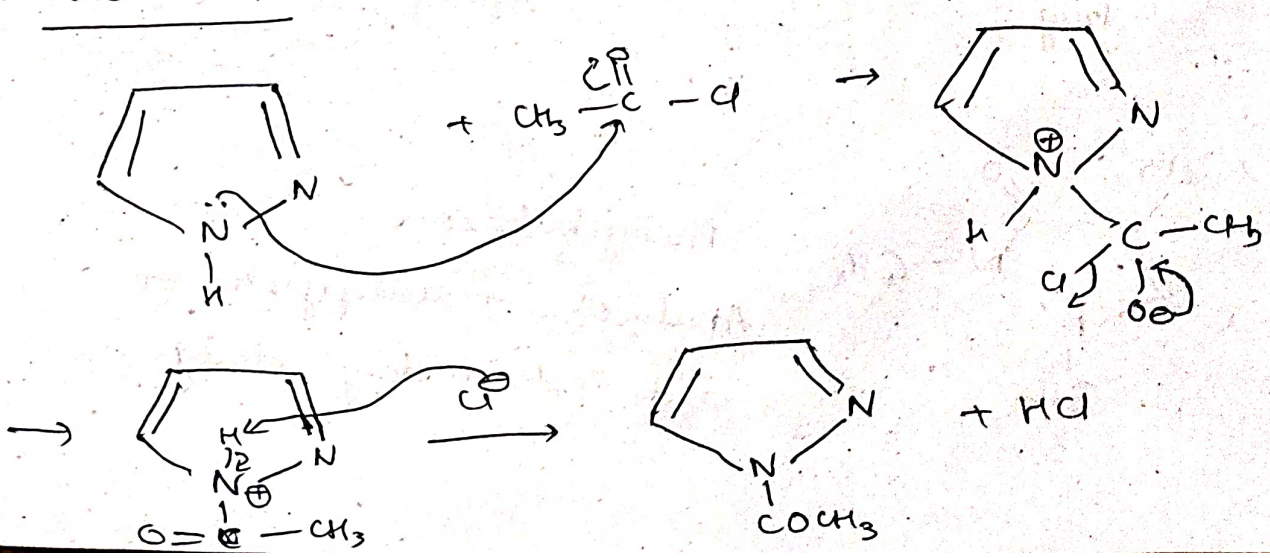
Mechanism:



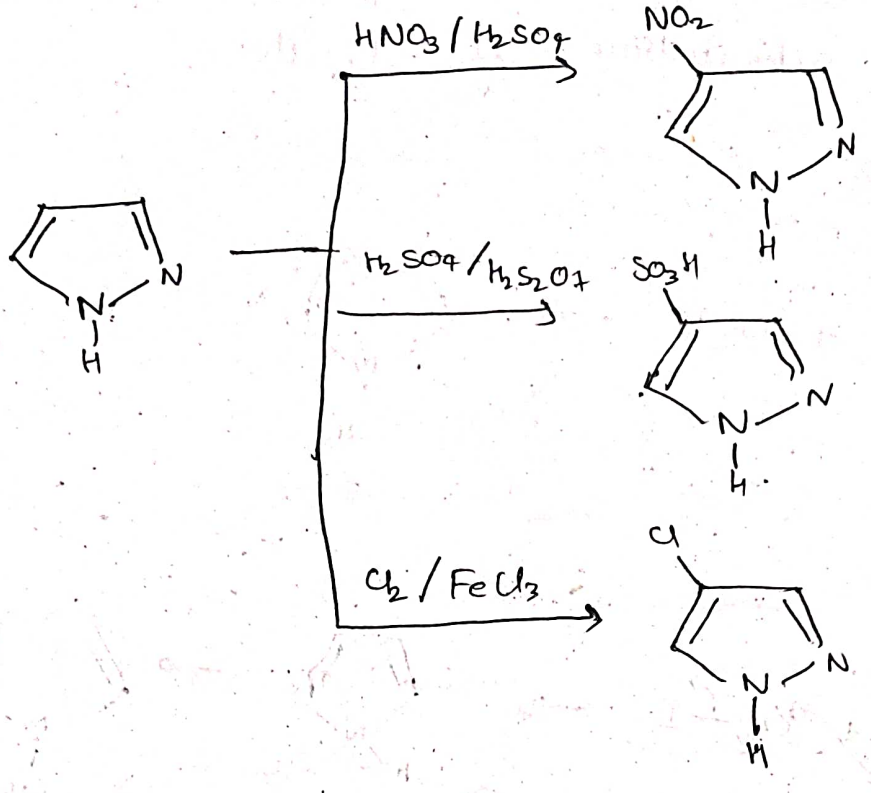
b) · Acetylation:



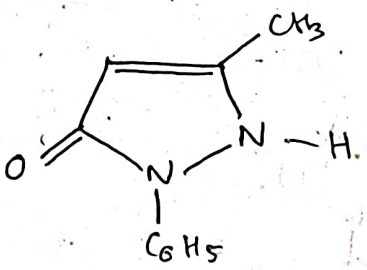
Mechanism:



2) Electrophilic substitution at 4th carbon

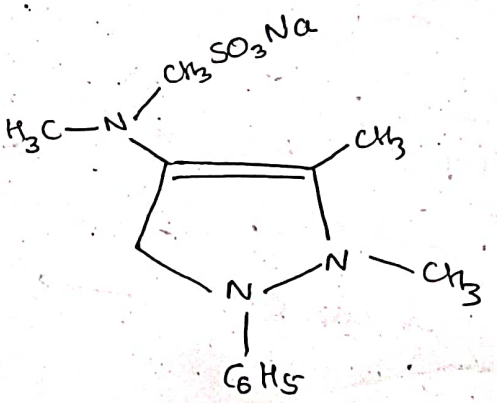


Medicinal uses:



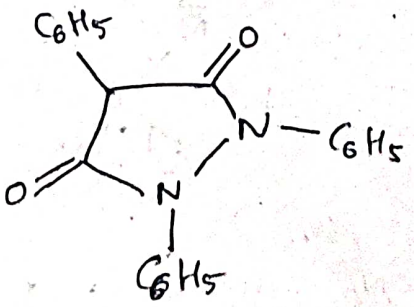
Antipyrene

Used as an antipyretic drug



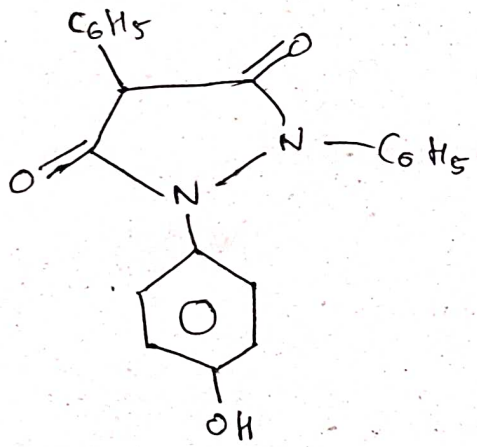
Analgin

Analgesic and antipyretic drug



Phenylbutazone

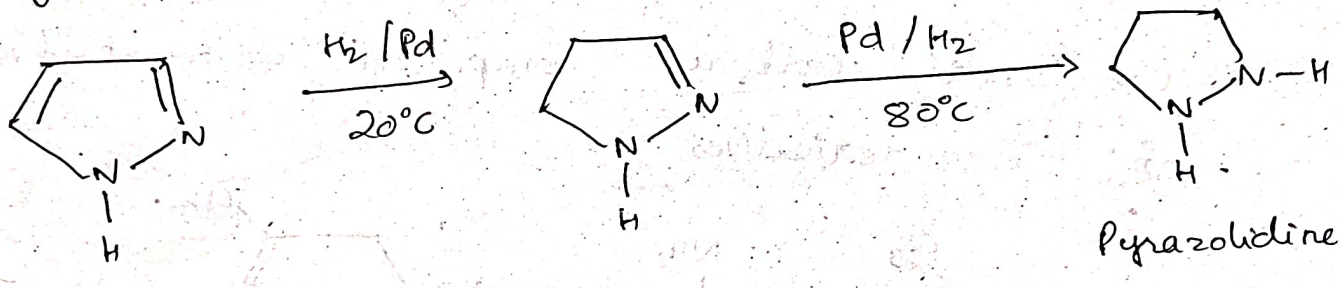
Analgesic + antipyretic + anti-inflammatory drug.



oxyphenbutazone

Same effect that of phenyl butazone

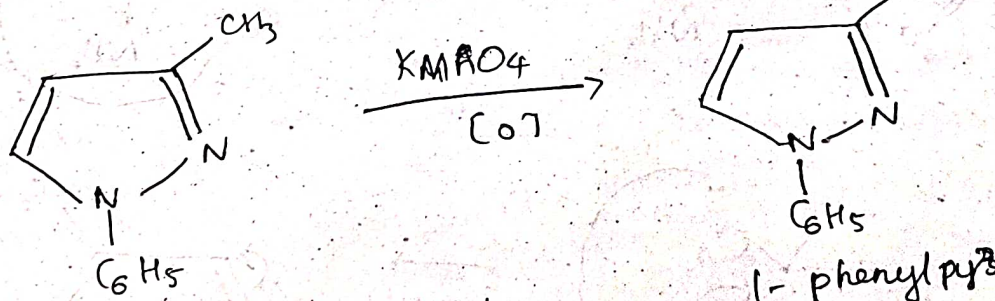
Catalytic reduction of pyrazole



Pyrazolidine

Oxidation of side chains:

Pyrazole is stable ~~for~~ in oxidizing agents

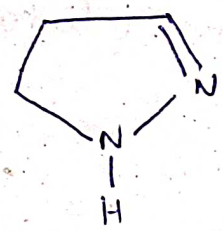


3-methyl-1-phenyl pyrazole

1-phenyl pyrazole-3-carboxylic acid

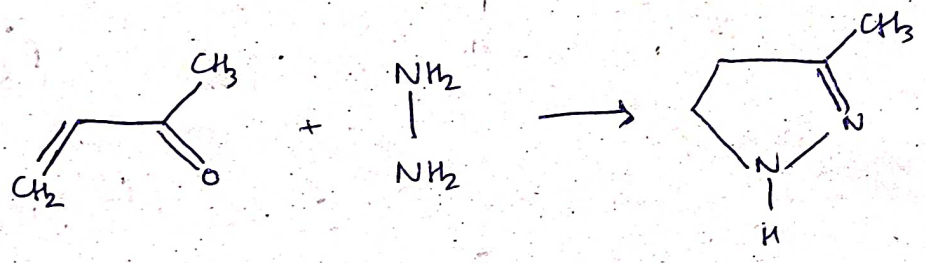
Derivatives of Pyrazole:

① 4,5 - dihydropyrazole

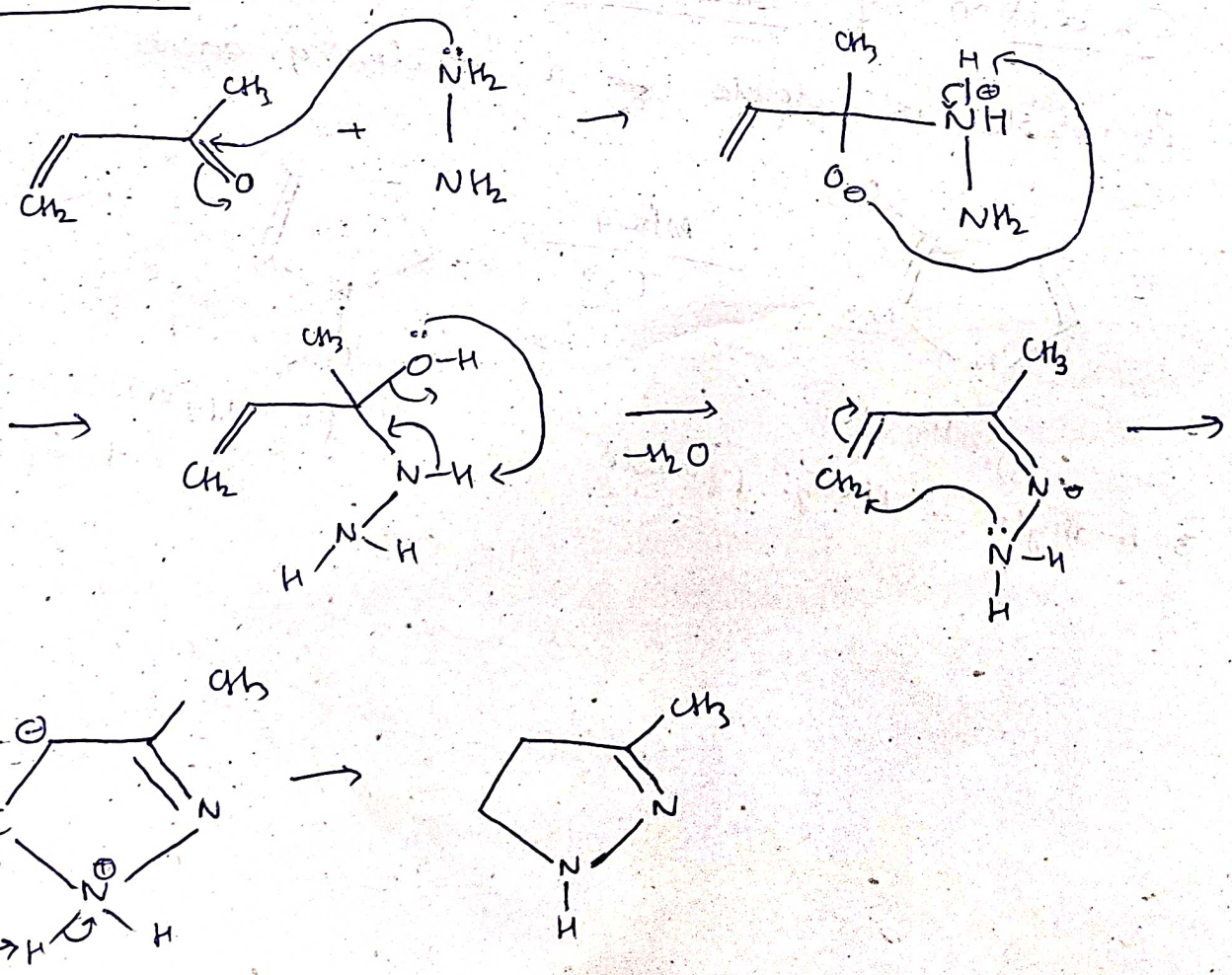


Synthesis:

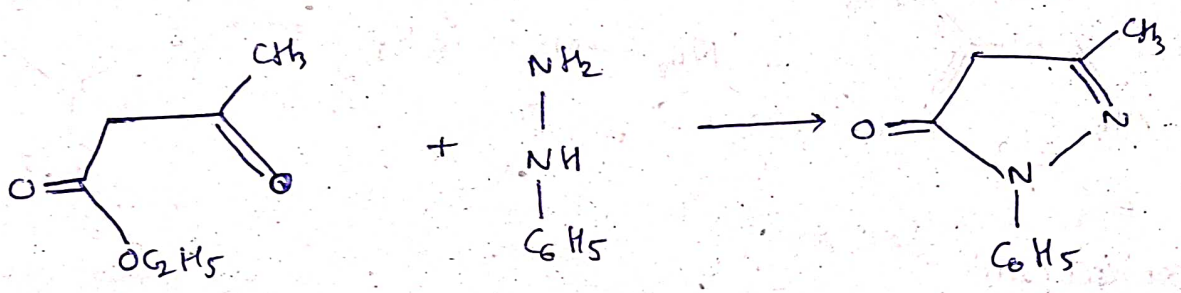
1. It is obtained from cyclocondensation of α, β unsaturated carbonyl compound with hydrazine or its derivatives.



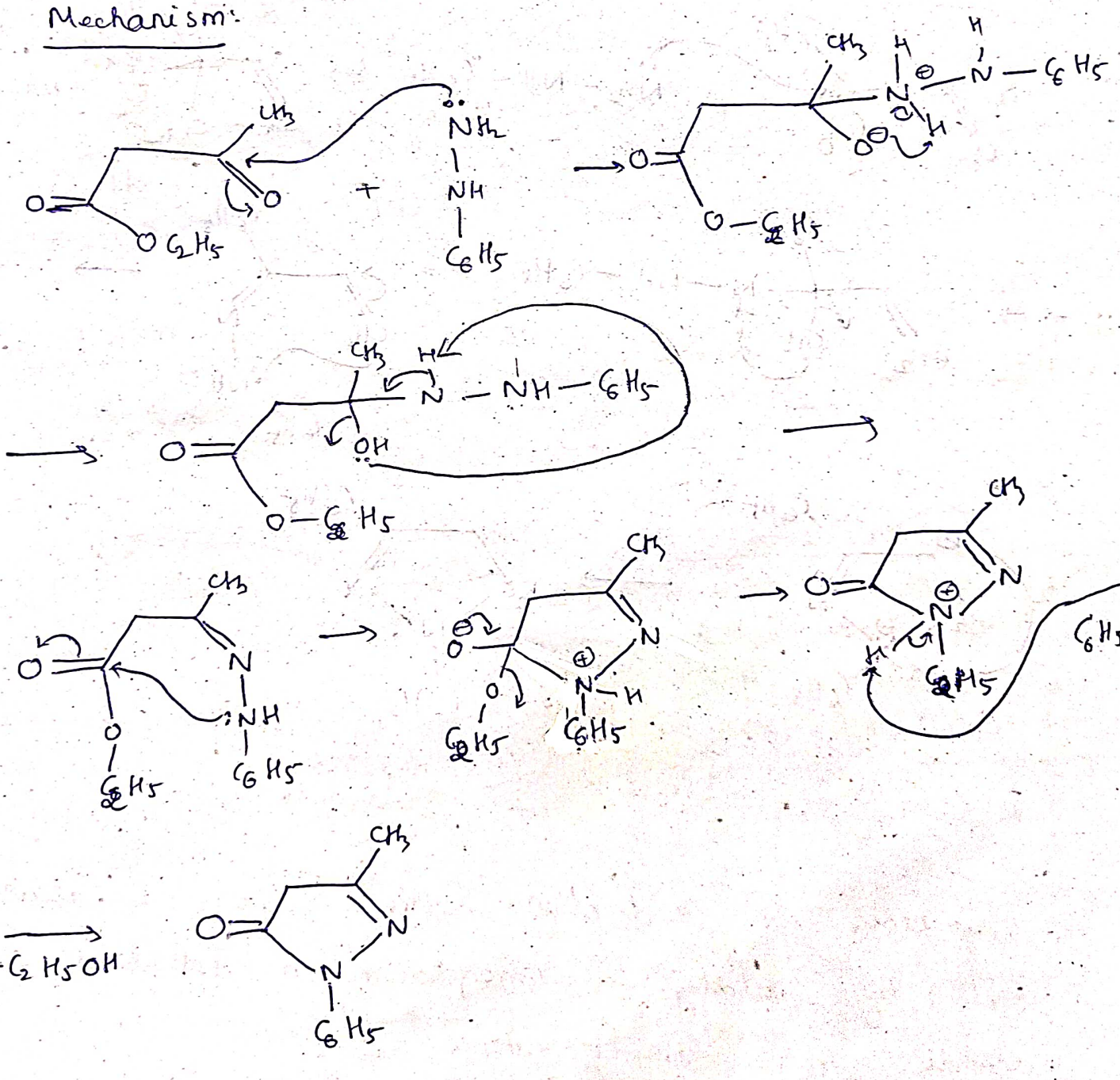
Mechanism:



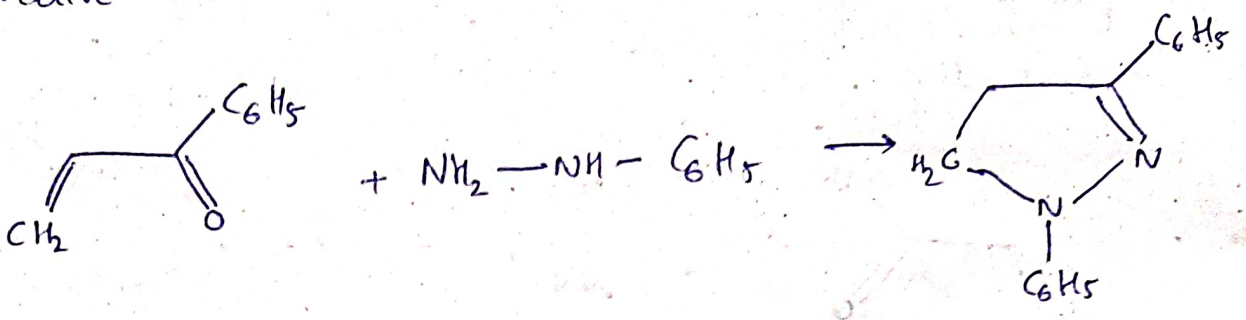
2. Acetoacetic ester undergoes cyclocondensation with phenyl hydrazine to give 5- pyrazolone derivative



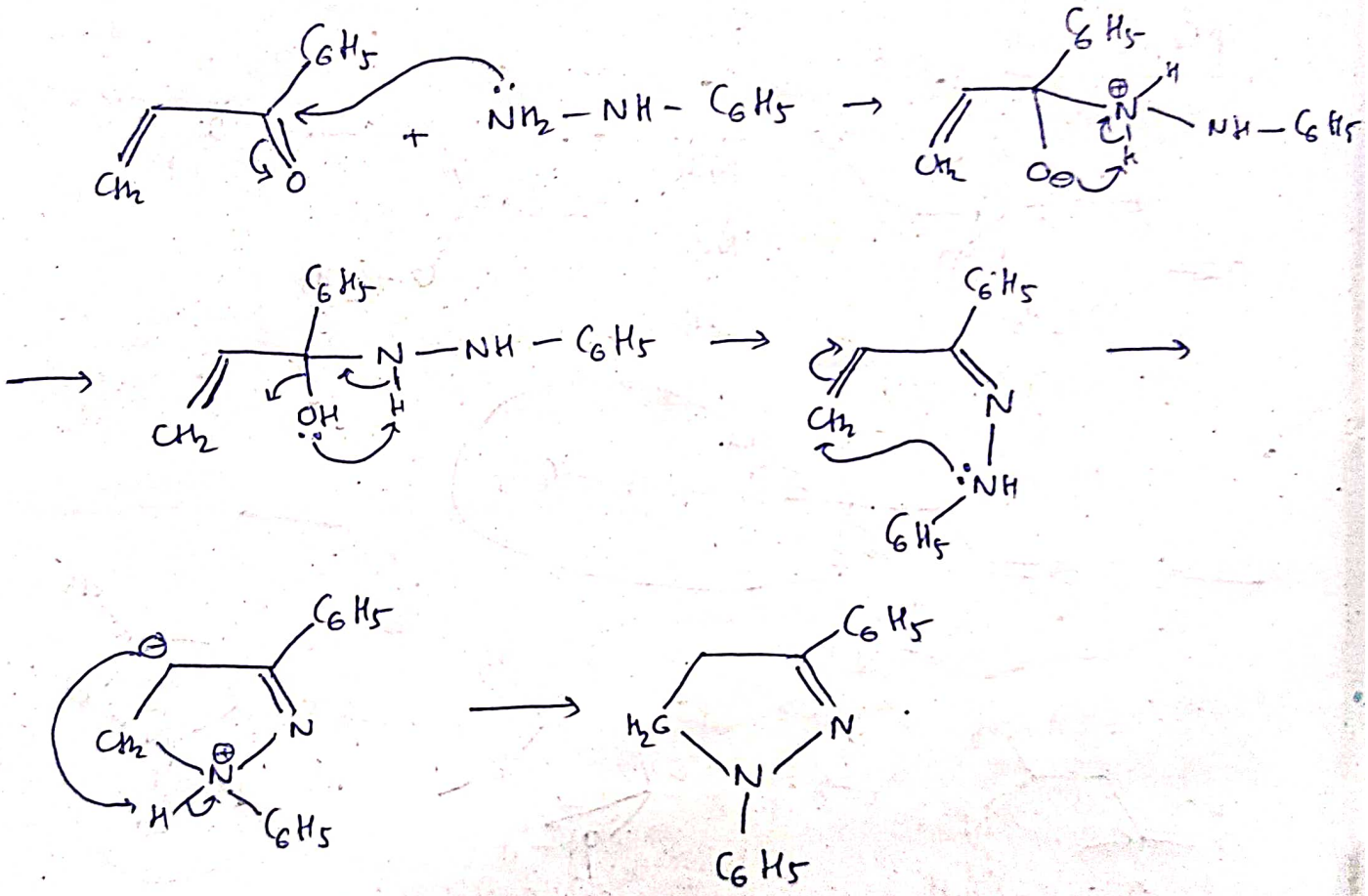
Mechanism:



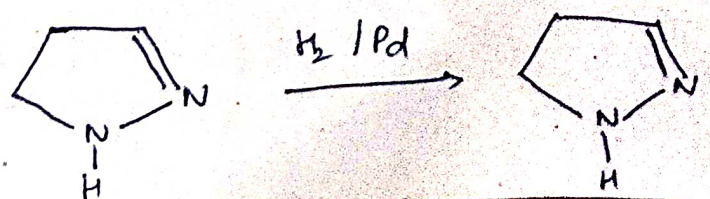
3. By the reaction of phenyl vinyl ketone with phenyl hydrazine to give 4,5 - dihydropyrazole derivative



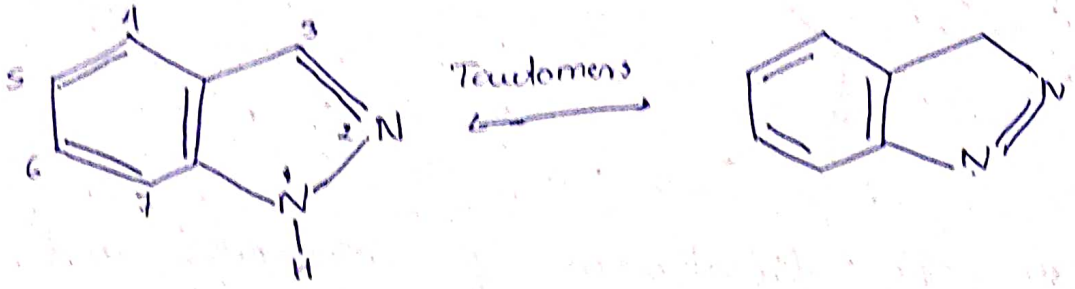
Mechanism:



4. Pyrazole on reduction with sodium & alcohol or by catalytic hydrogenation on Palladium catalyst yields 4,5 - dihydropyrazole.

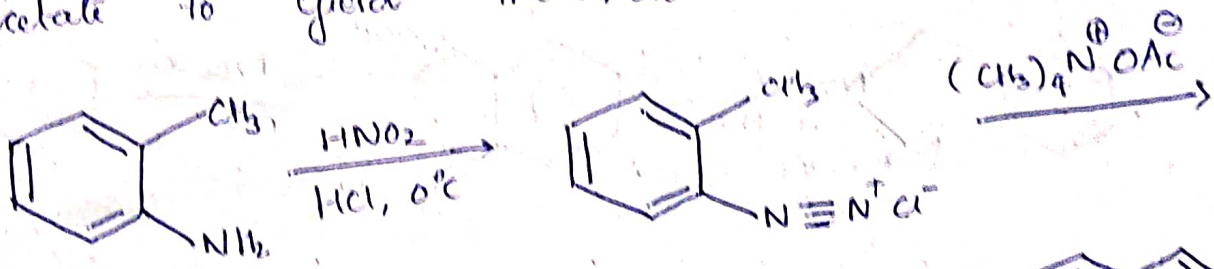


(2) Indazole

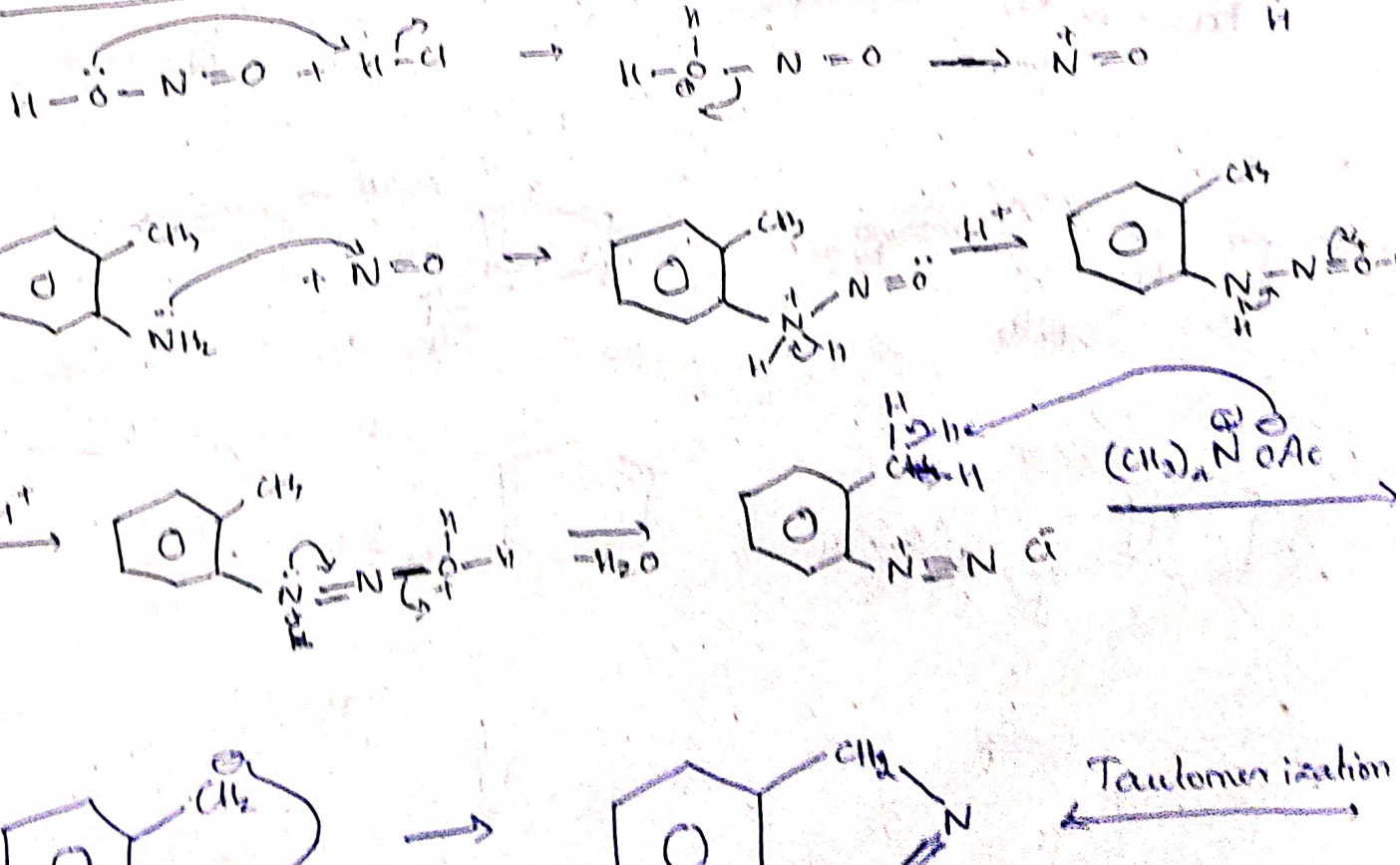


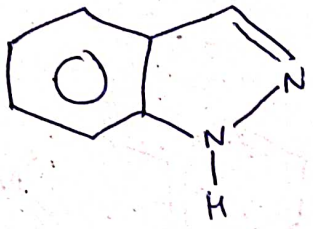
Synthesis

1. Orthotoluecline undergoes diazodization and subsequent cyclization using tetramethyl ammonium acetate to yield indazole.

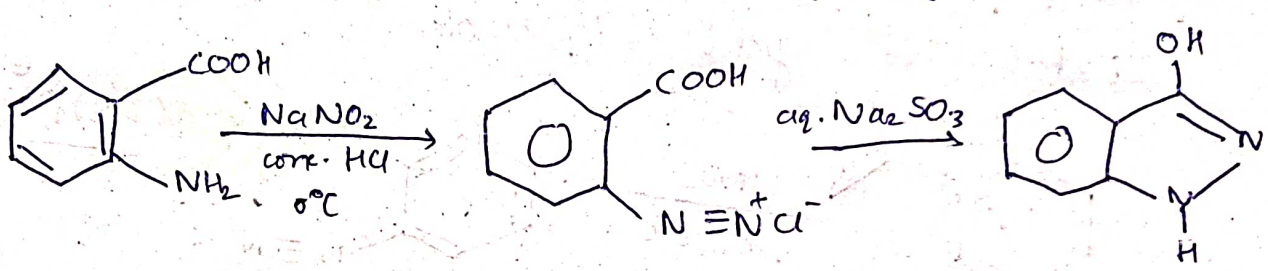


Mechanism:

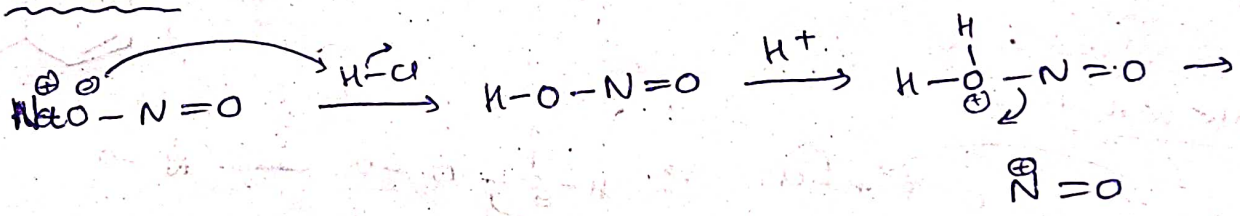


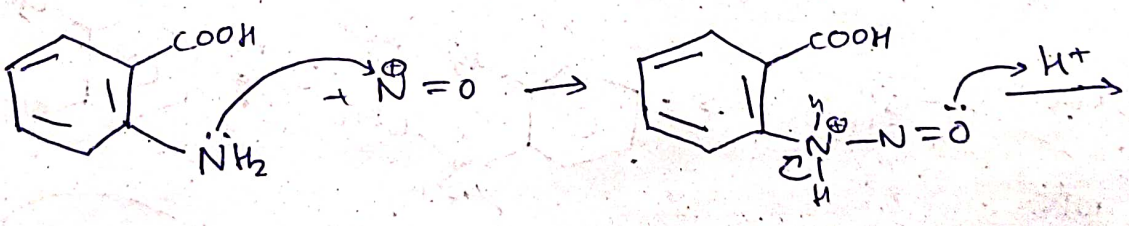


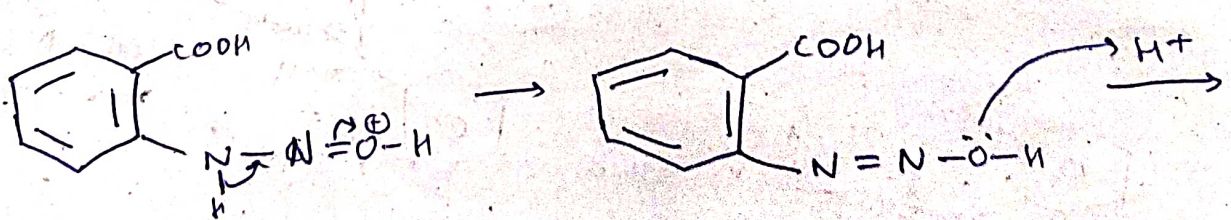
2. From the diazotization of anthranilic acid in the presence of sodium nitrite and conc. HCl at 0°C provides a diazocompound which on reduction with sodium sulphate to give 3-hydroxy indazole.

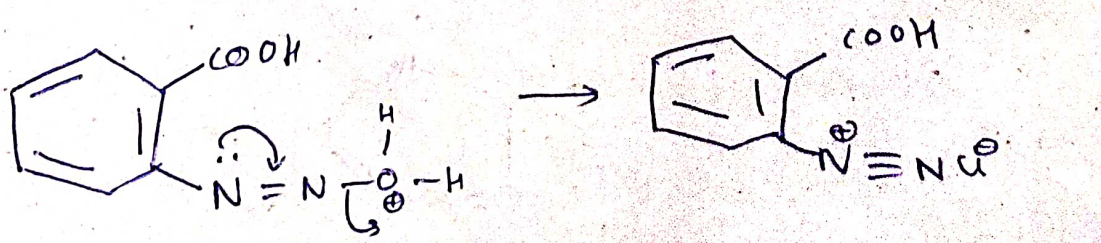


Mechanism:





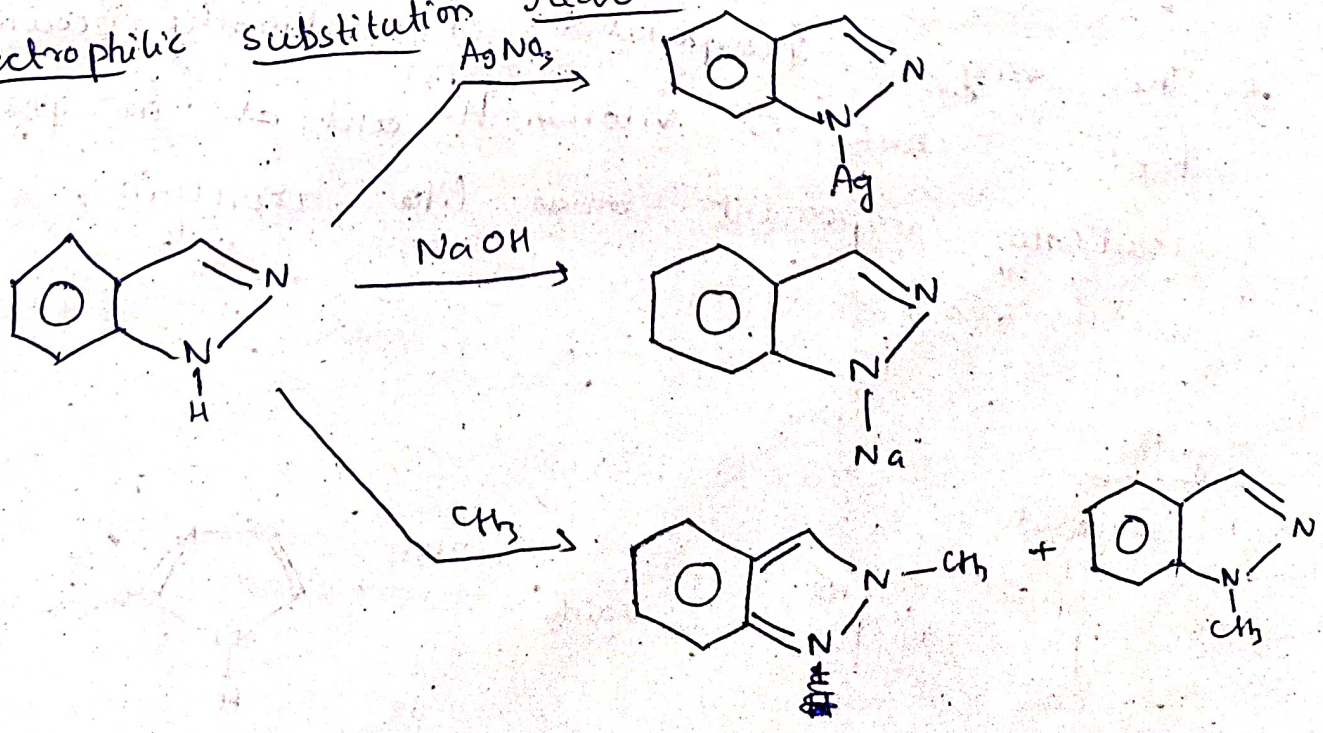




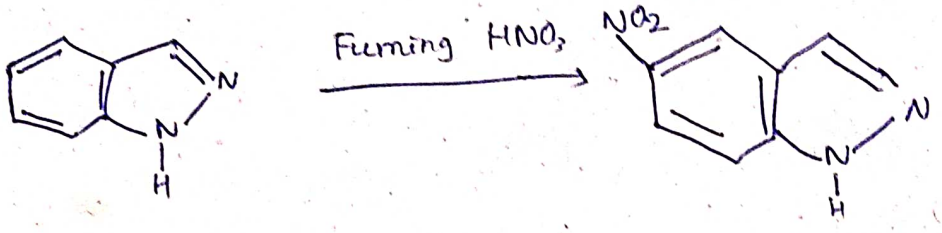
Physical & Chemical

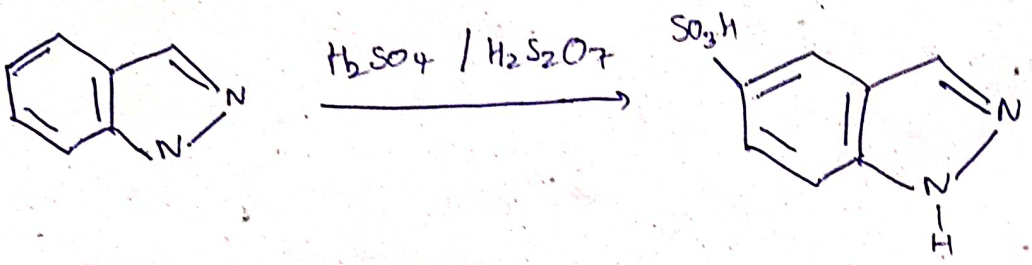
* It is a colourless crystalline compound having m.p = 145°C
* It is a weak base like pyrazole
* The aromaticity of the imidazole ring decreases due to the fusion of benzene ring, thus it is easier to ~~keep~~ cleave the the ring in comparison with pyrazole.

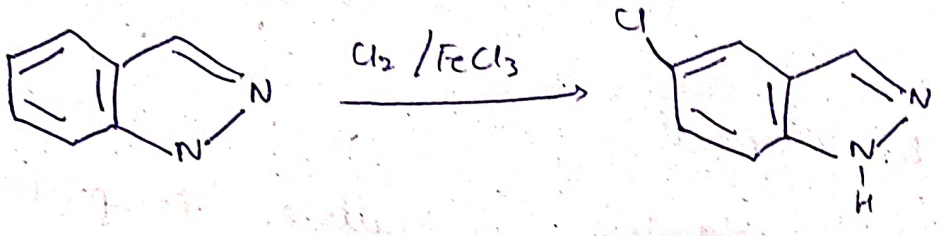
Electrophilic substitution reaction at Nitrogen



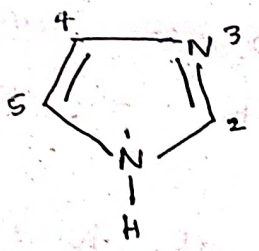
Electrophilic substitution at Carbon







Imidazole:



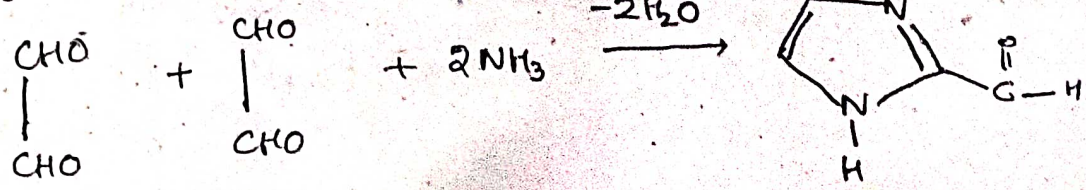
N-1 - pyrazole nitrogen

N-2 .

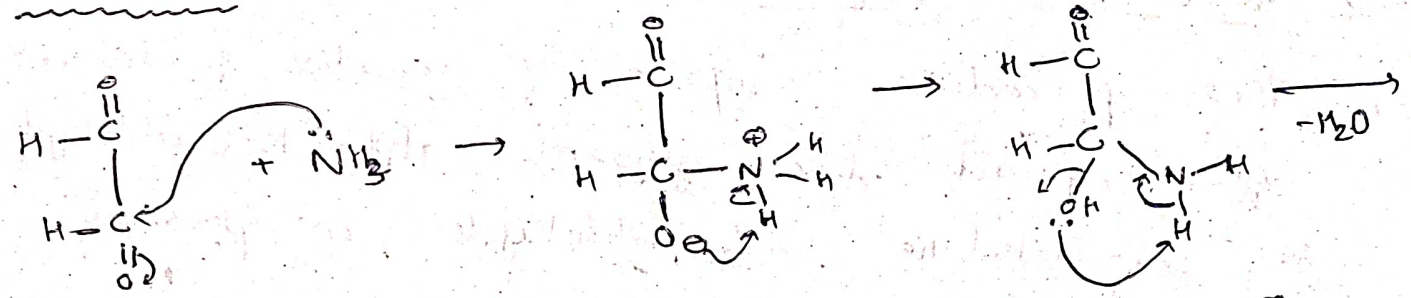
* the ring is incorporated in naturally occuring biotin which is Vitamin-H and also in pharm-aceutically important drugs like azomycin, metromidazole

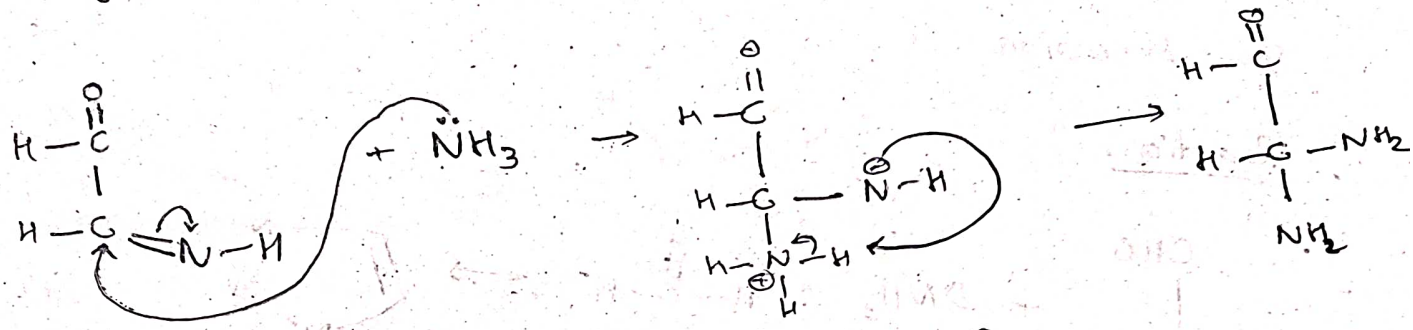
Synthes:

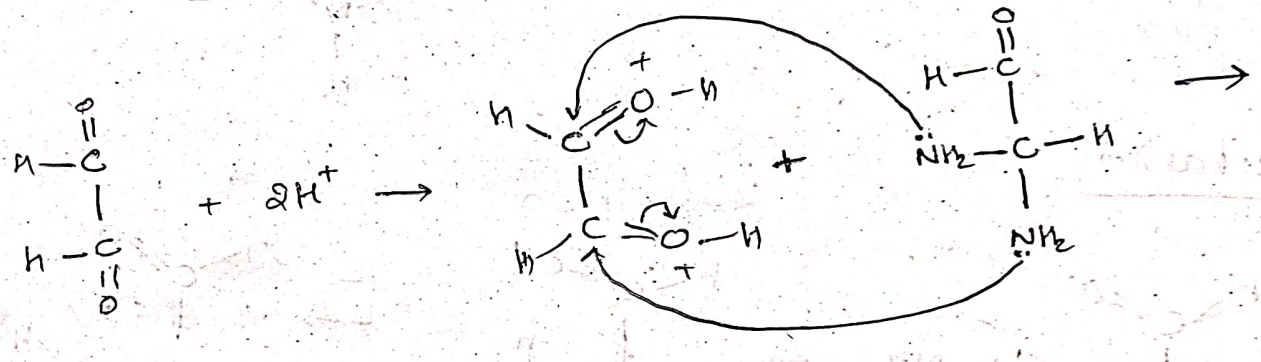
1. Glyoxal

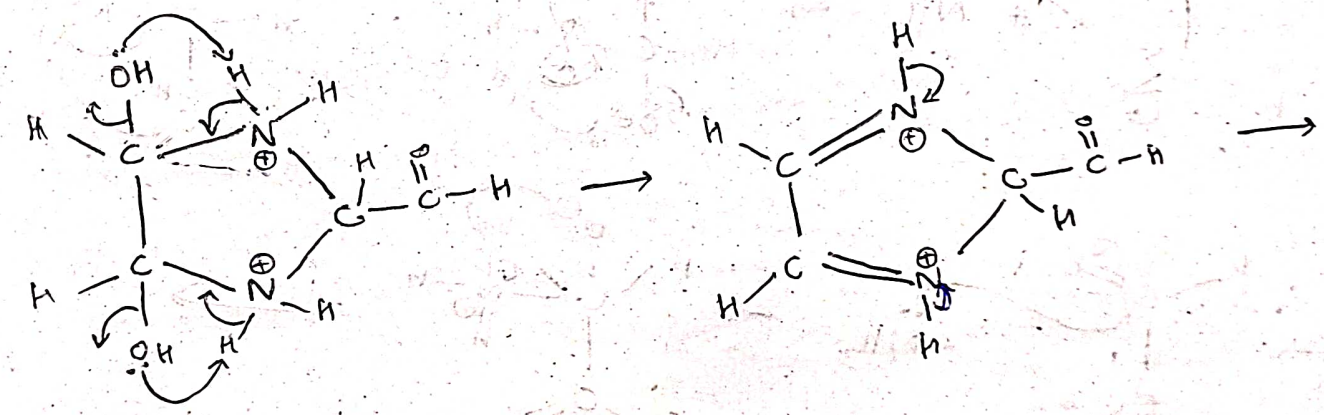


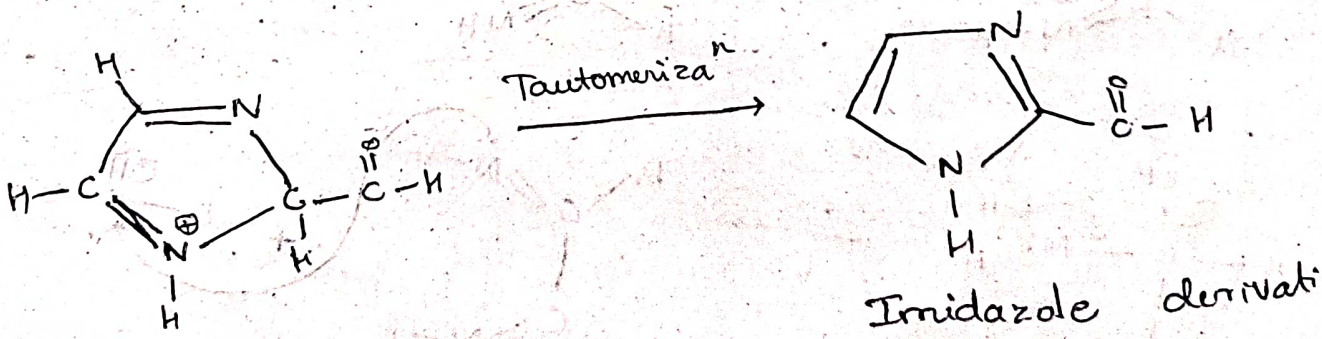
Mechanism:











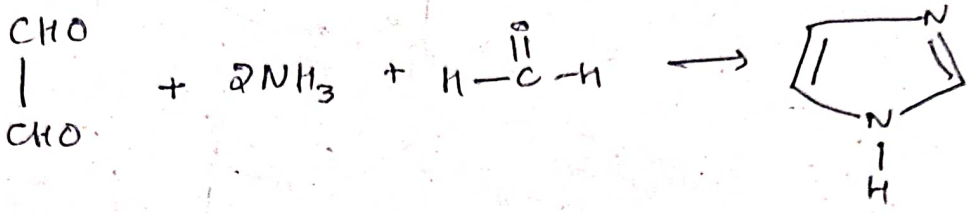
Tautomerization

Imidazole derivative

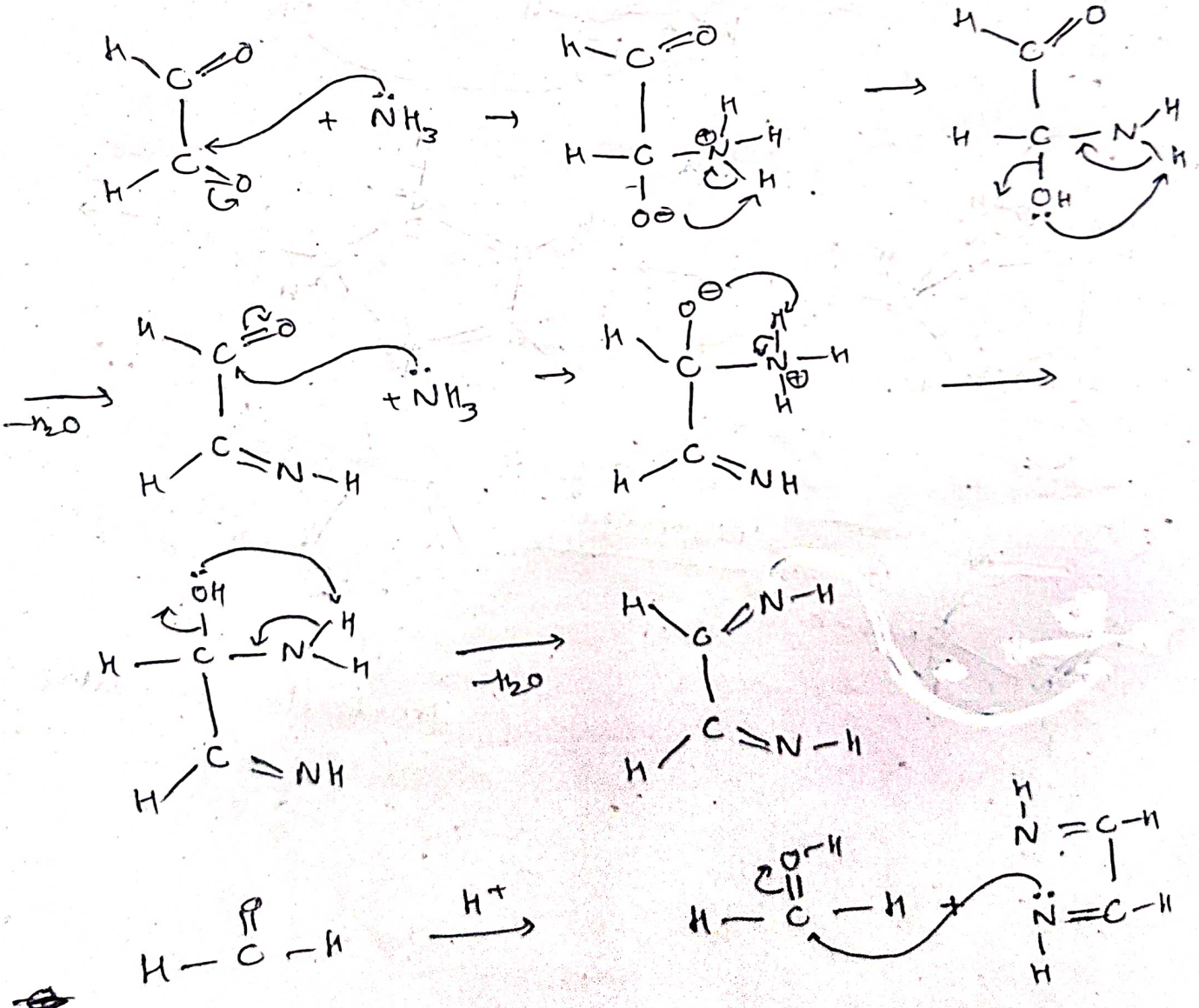
2. Radiszewski synthesis

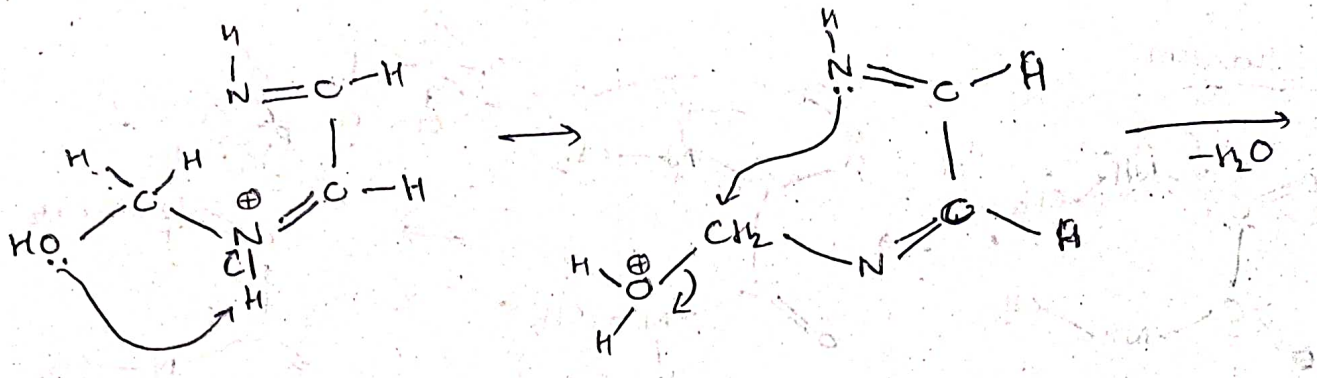
This procedure comprises of reaction of dicarbonyl compounds like glyoxal, alpha keto aldehyde or, α-diketone with aldehyde in presence of Ammonia

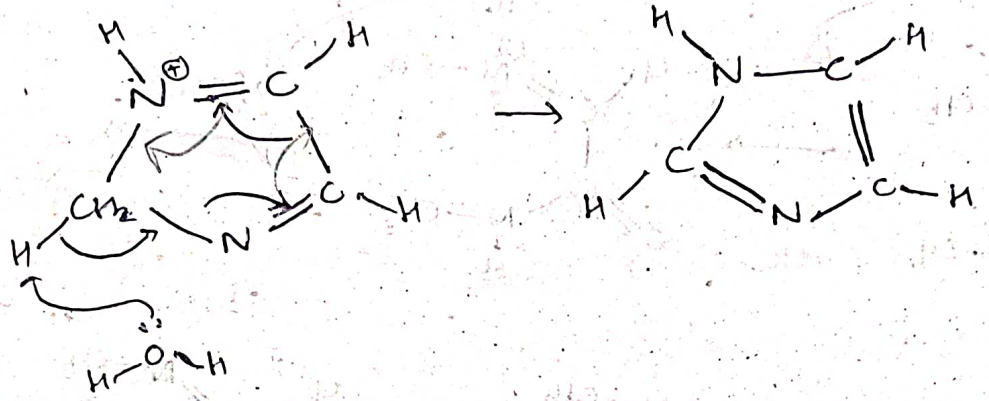
Reaction:



Mechanism:

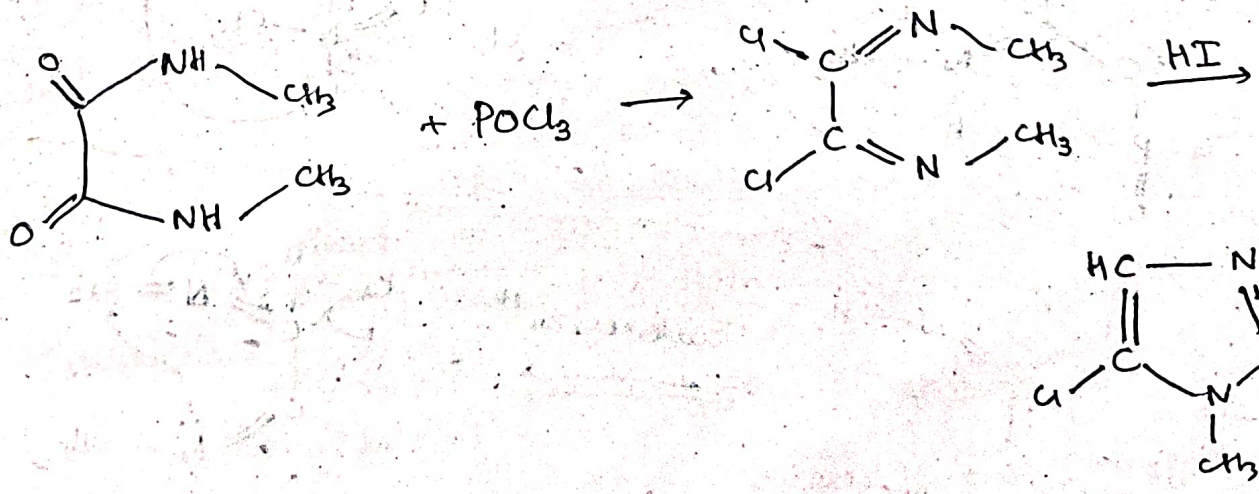




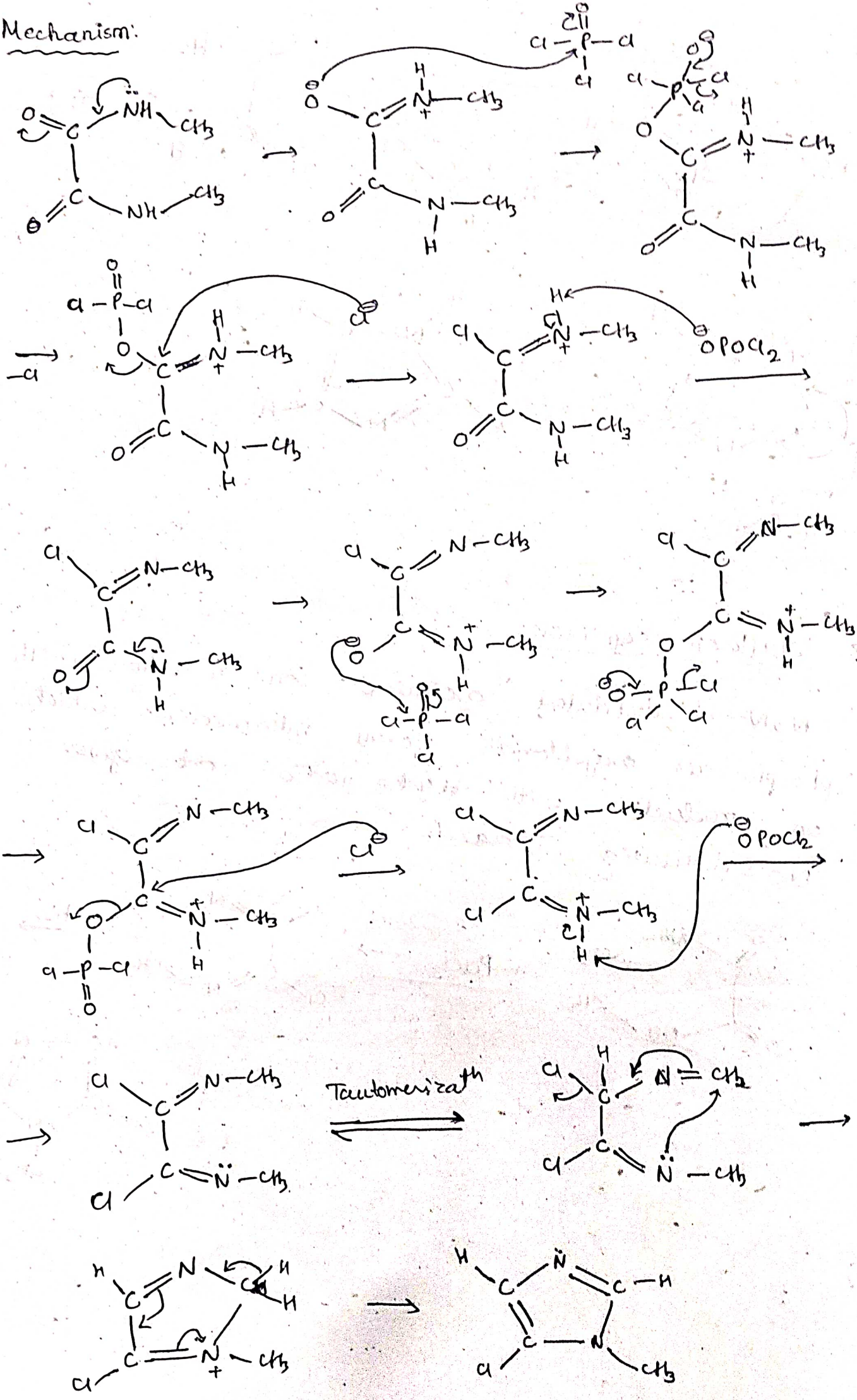


3. Wallach synthesis

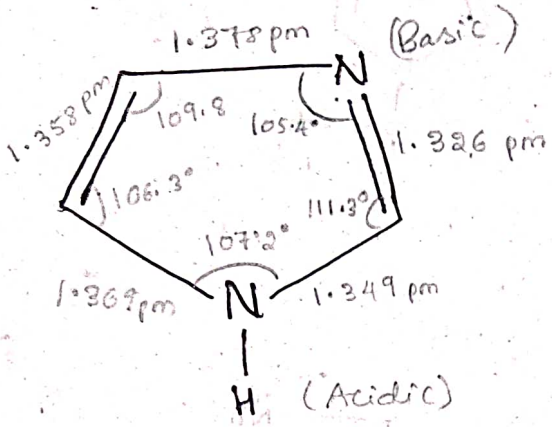
N,N-disubstituted oximine on reaction with phosphorous oxychloride forms intermediate which on reduction with Hydro iodic acid gives N-substituted imidazole



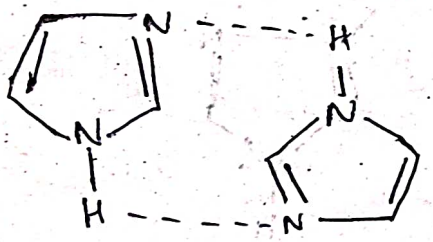
Mechanism:



Chemical and Physical properties of Imidazole



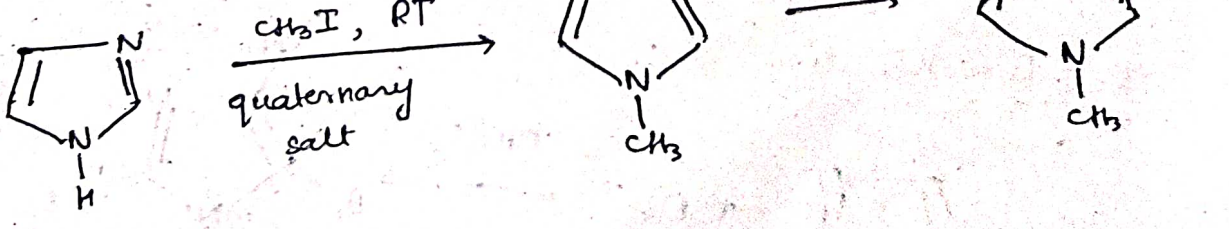
In aqueous solution imidazole behaves as good donor and good acceptor. The nitrogen at the 3rd position is the electron donor and nitrogen at first position is electron acceptor, due to which it can form hydrogen bonding



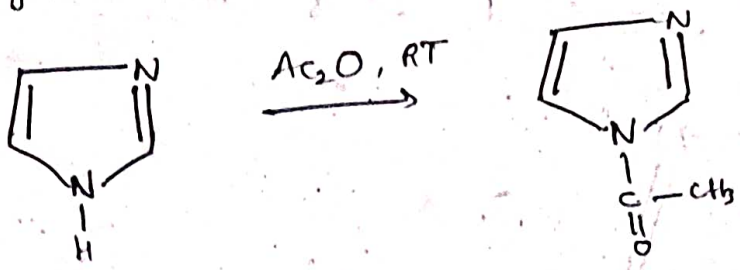
Have higher B.P – 256°C

Electrophilic attack on N

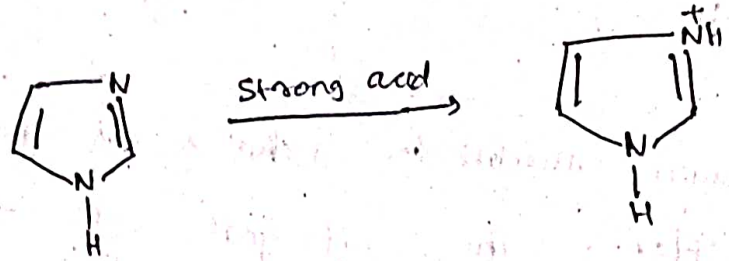
1. Alkylation



2. Acylation

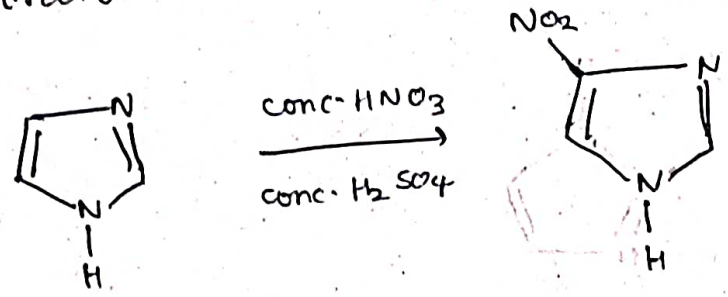


3. Protonation:

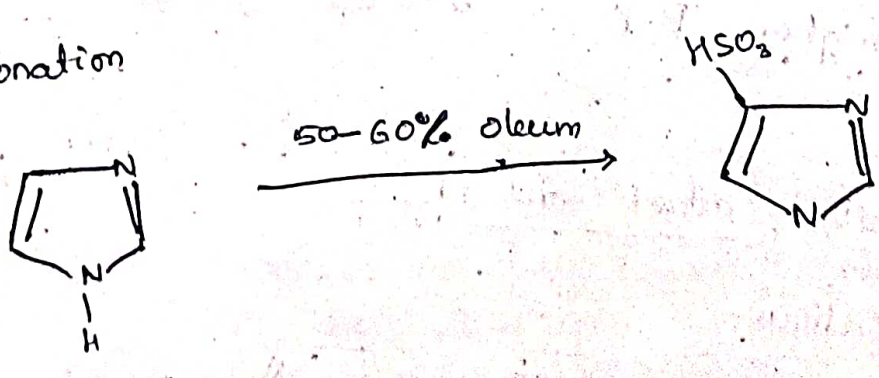


Electrophilic substitution at 4-th carbon

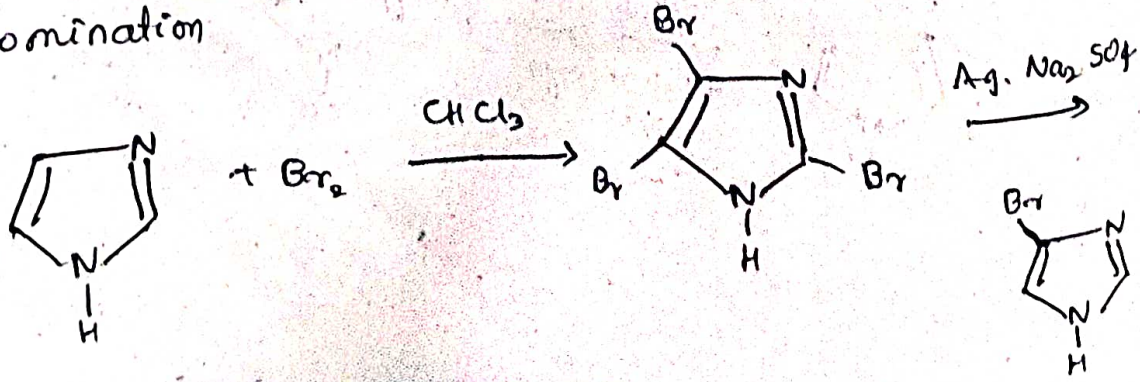
1. Nitration



2. Sulfonation

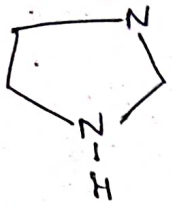


3. Bromination



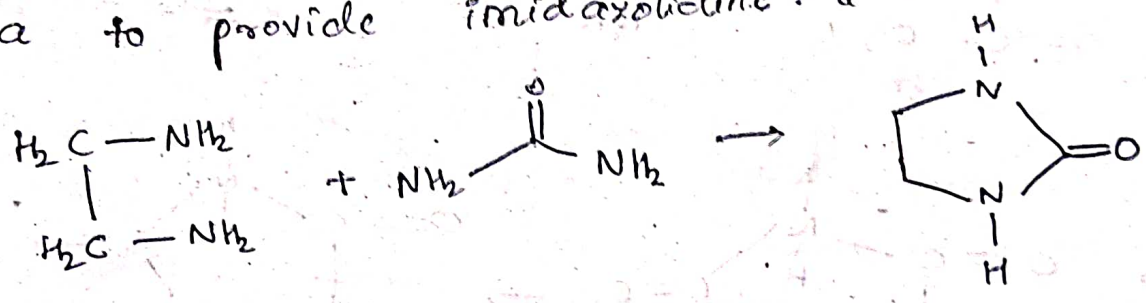
Derivatives of Imidazole

1) Imidazolidine :

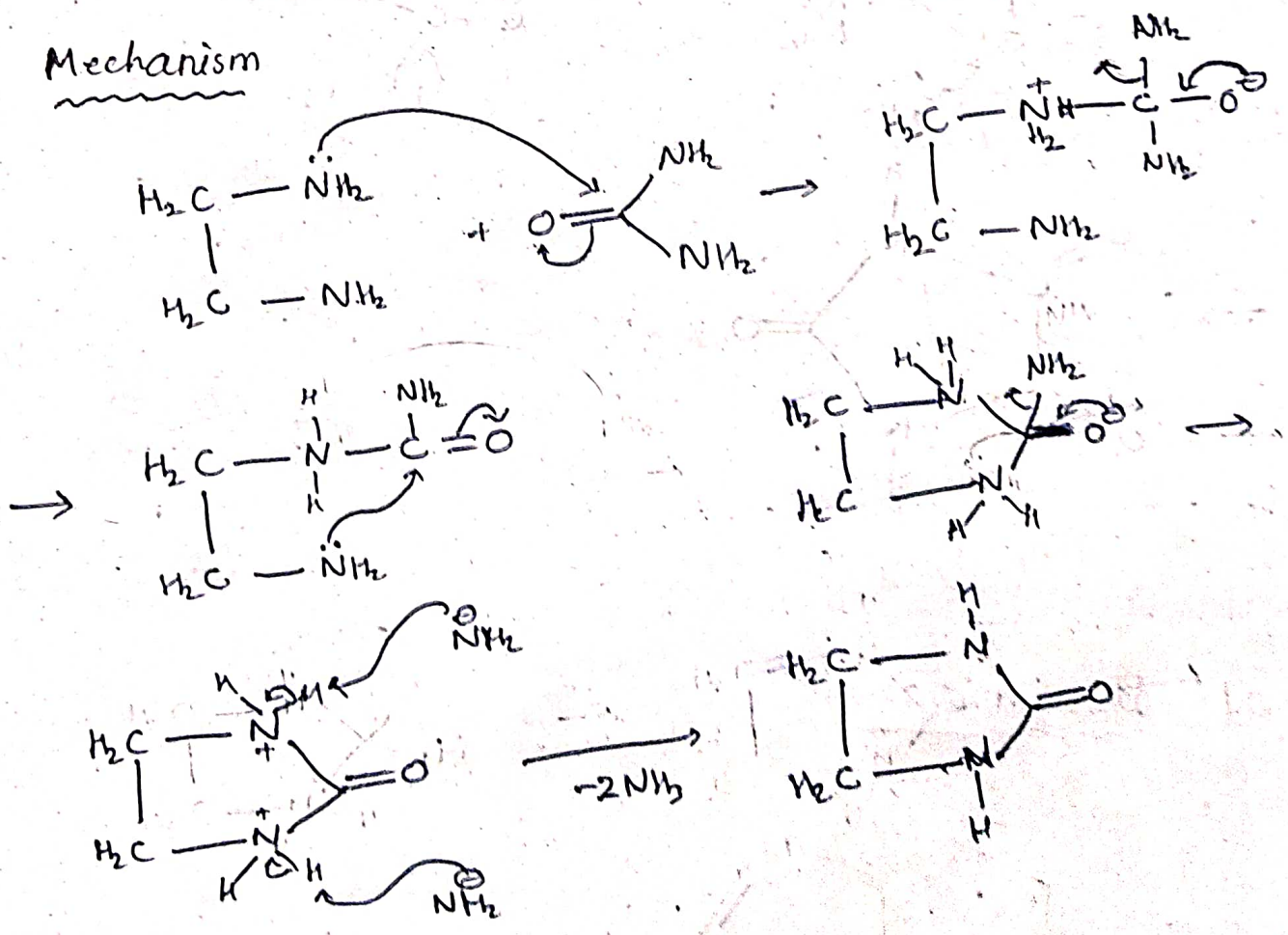


Synthesis

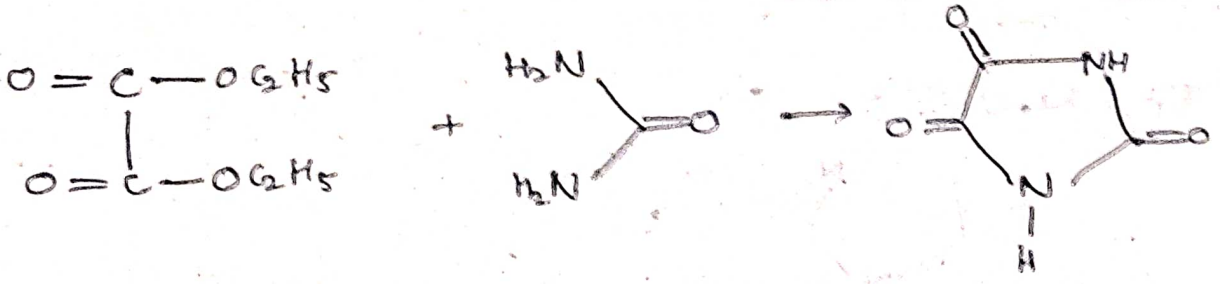
1) From the condenseation of ethylene diamine with urea to provide imidaxolidine - 2 - one



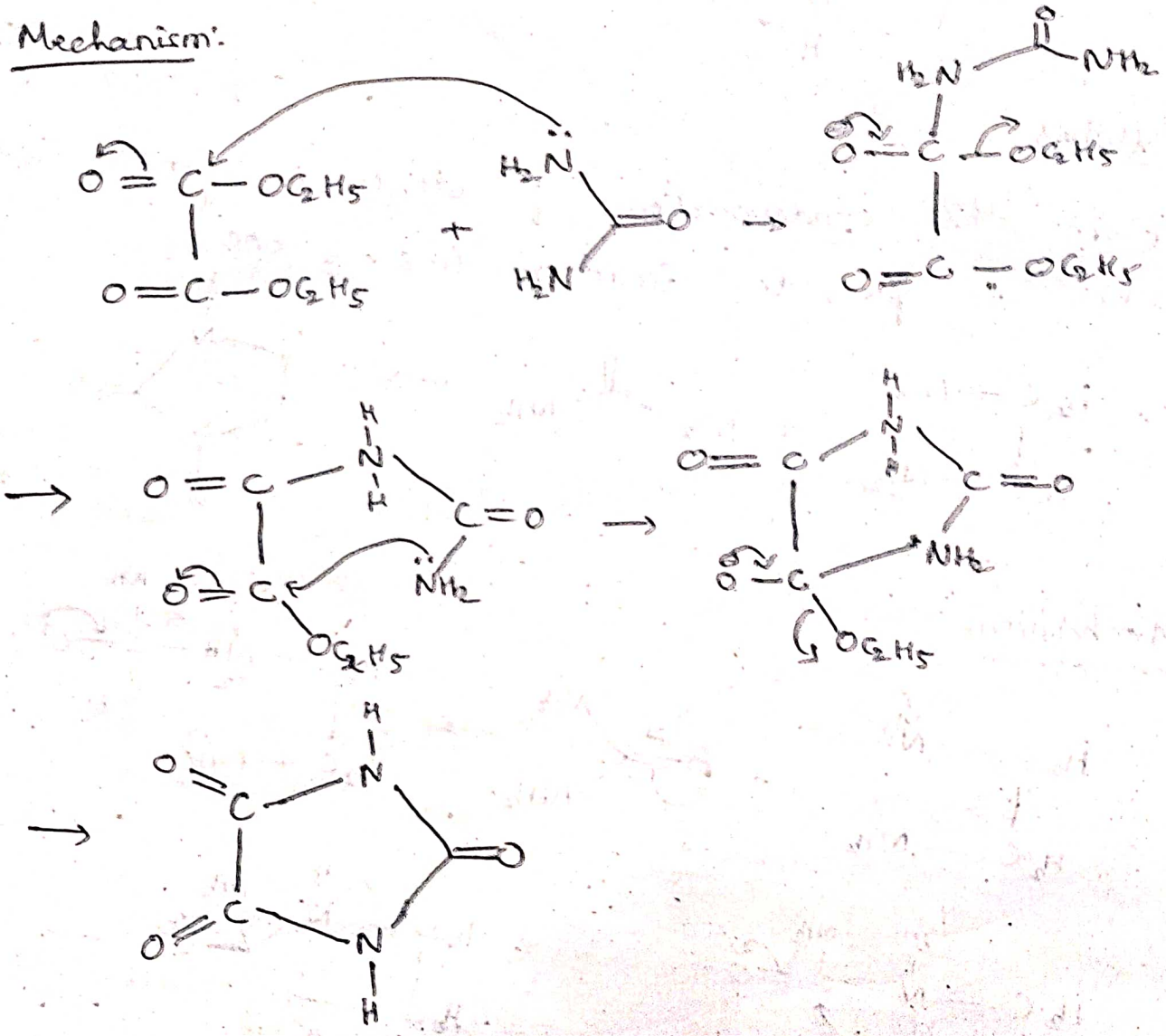
Mechanism



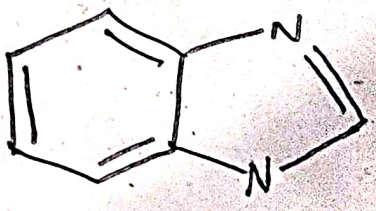
2) From Parabanic acid



Mechanism:

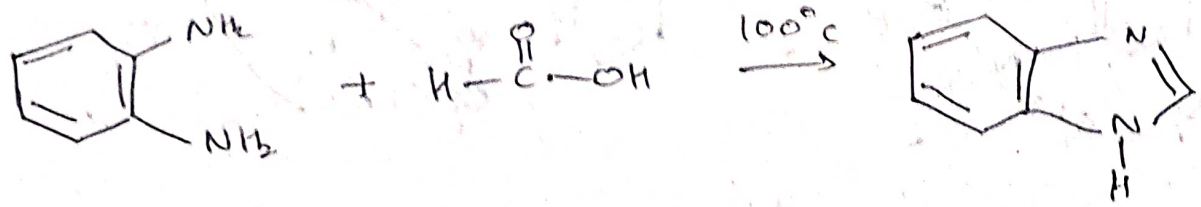


2] Benzimidazole

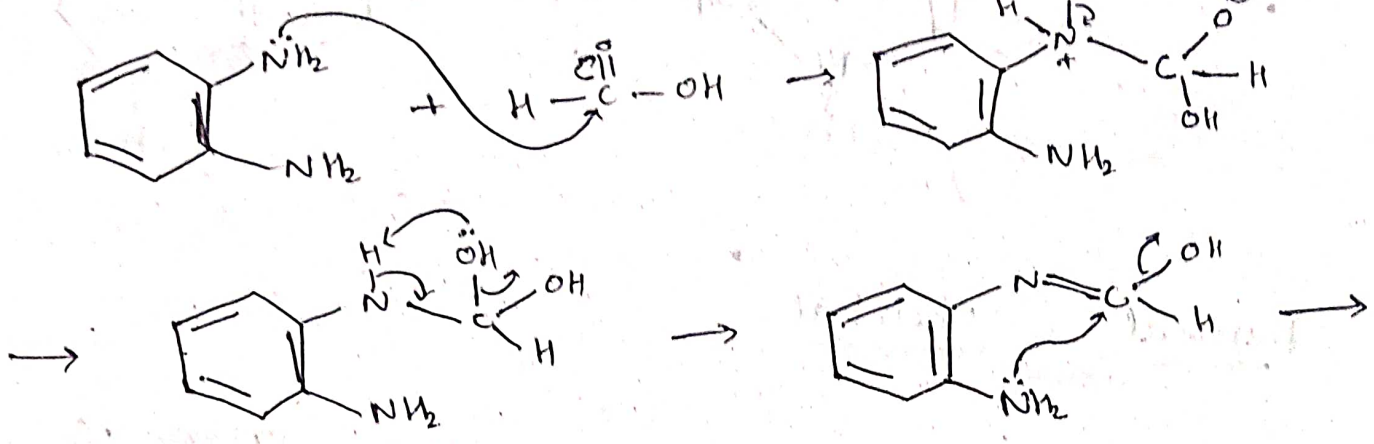


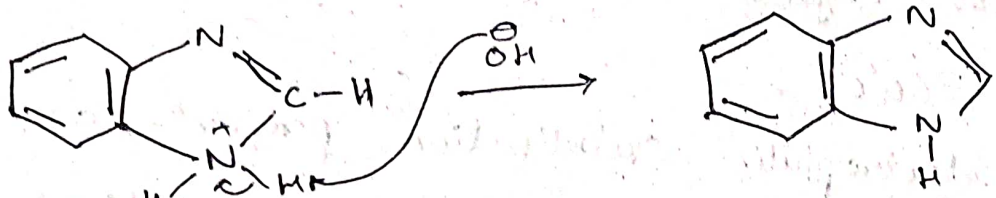
Synthesis

(1)

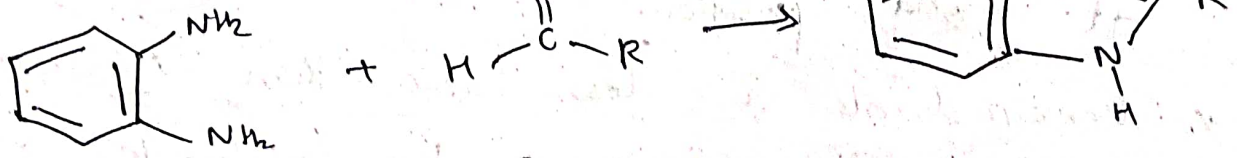


Mechanism:

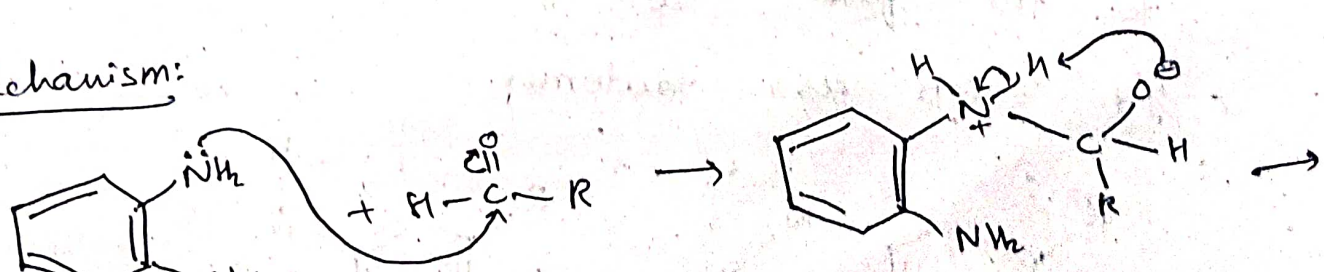


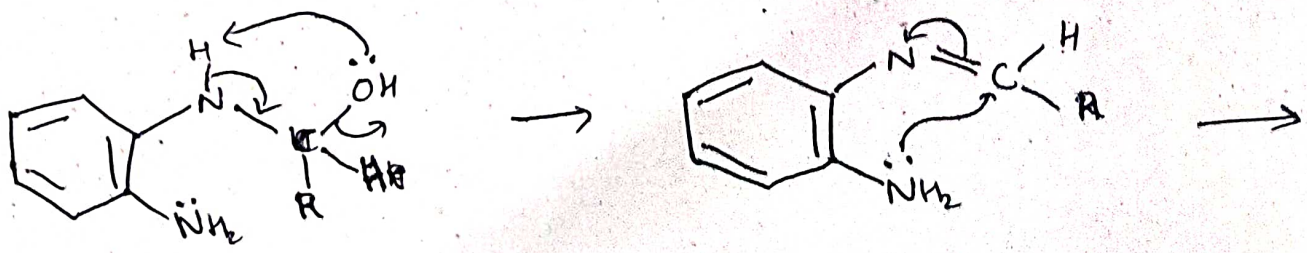


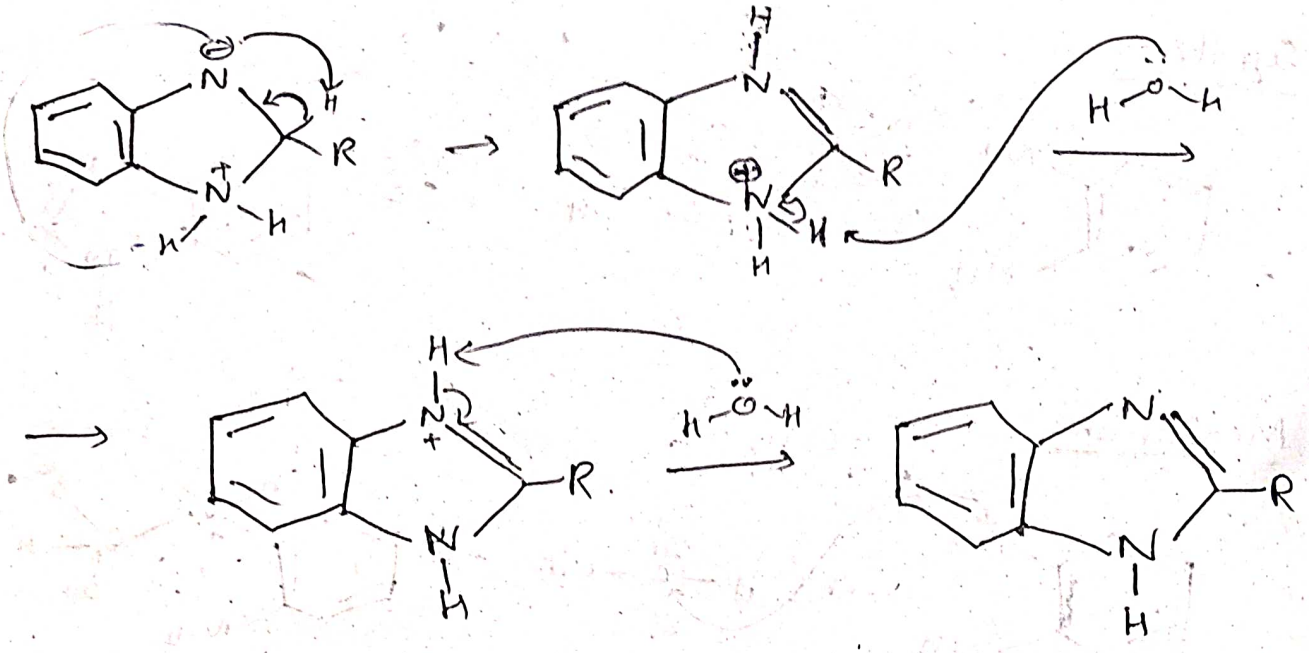
(2)



Mechanism:

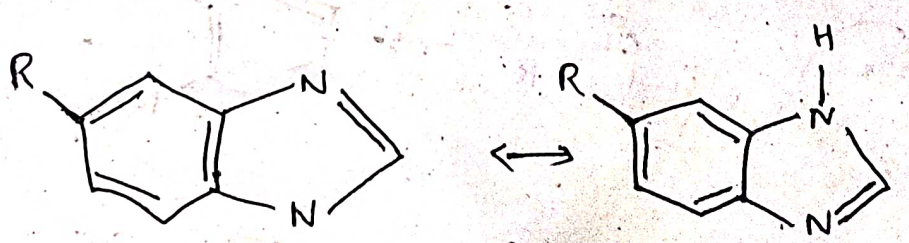






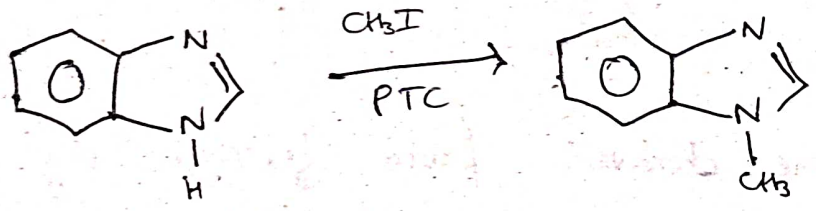
Physical & Chemical

* Colourless crystal having M.P = 171°C & BP = 360°C
* The electrophilic substitution proceeds at 5th position, while nucleophilic substitution occurs at 2nd position.
* Benzimidazole is less basic than imidazole due to the fused ring of benzimidazole
* It exists as tautomer

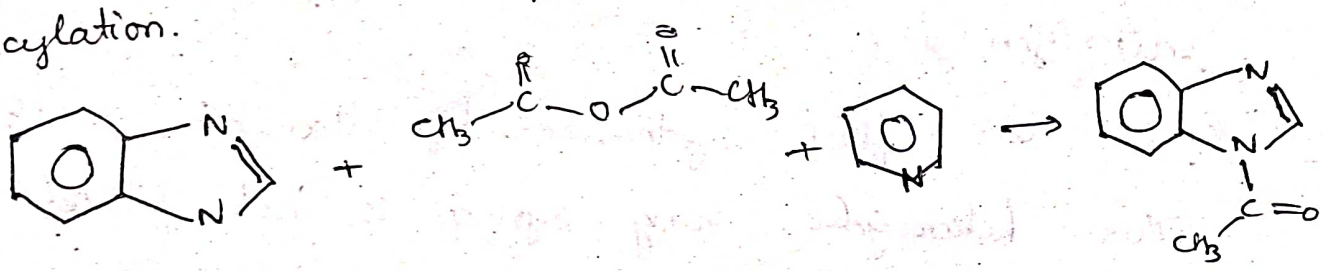


Electrophilic substitution at N

1. Alkylation

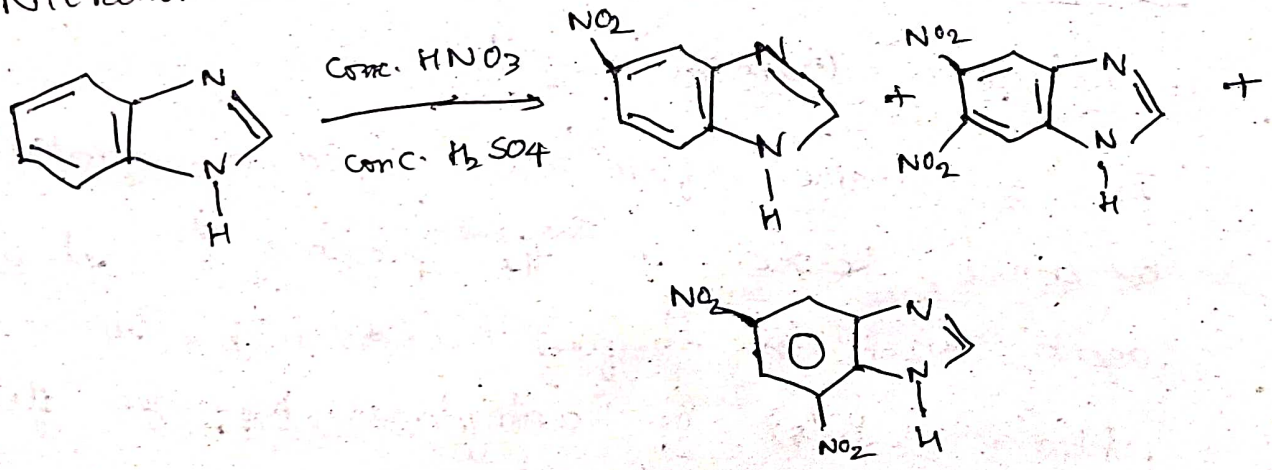


2. Acylation.

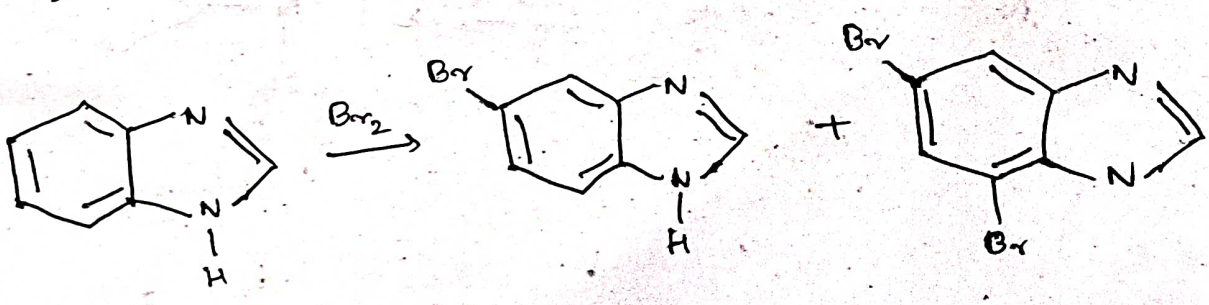


Electrophilic substitution at C

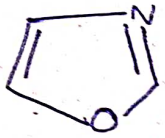
1. Nitration



2. Bromination



Oxazole:

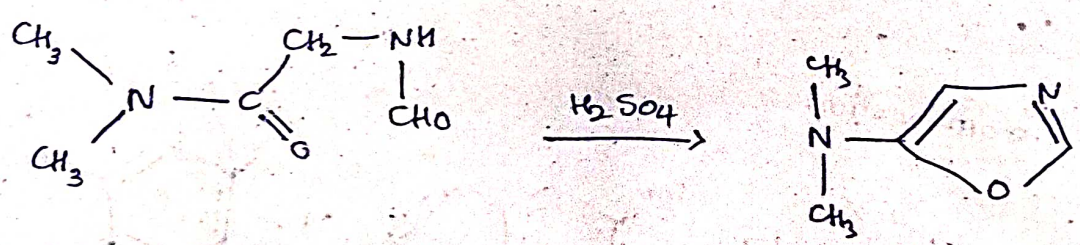


* It is a 1,3 azole derived from furan by the replacement of =CH group by azomethine nitrogen
* It was first synthesized by Hantzch in 1887. This heterocyclic ring system is not found in any natural product

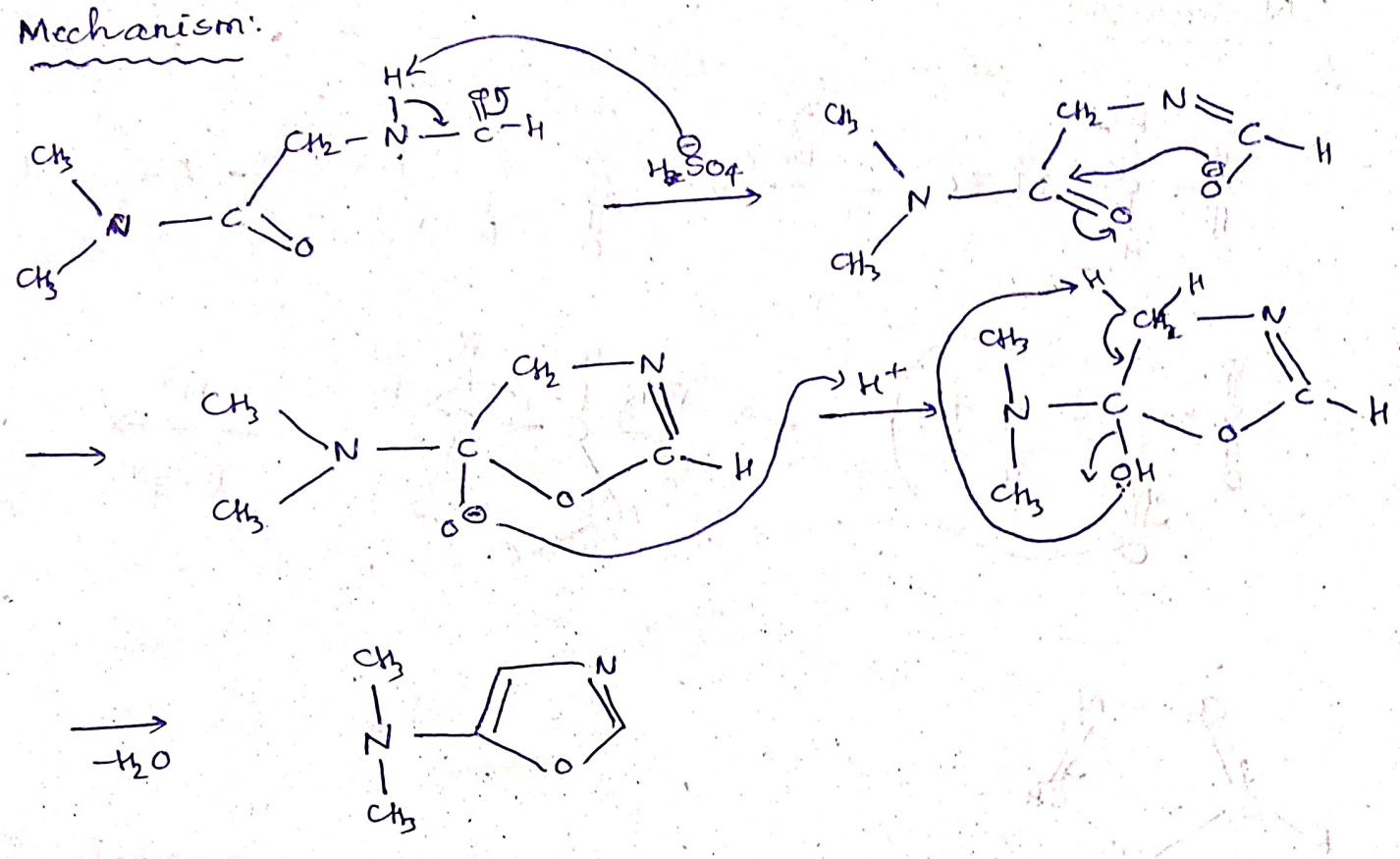
Synthesis:

1. Robinson - Gabriel synthesis

It is obtained from the cyclo dehydration of α- amino ketone in the presence of dehydrating agents such as sulfuric acid, Phosphorous penta chloride (PCl_5) or anhydrous hydrogen fluoride (HF)

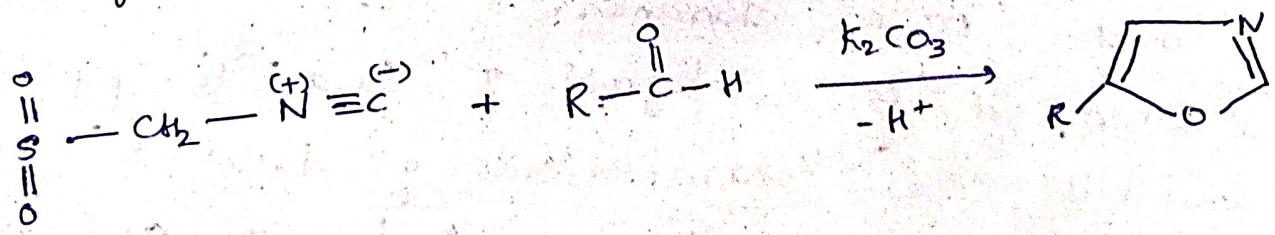


Mechanism:

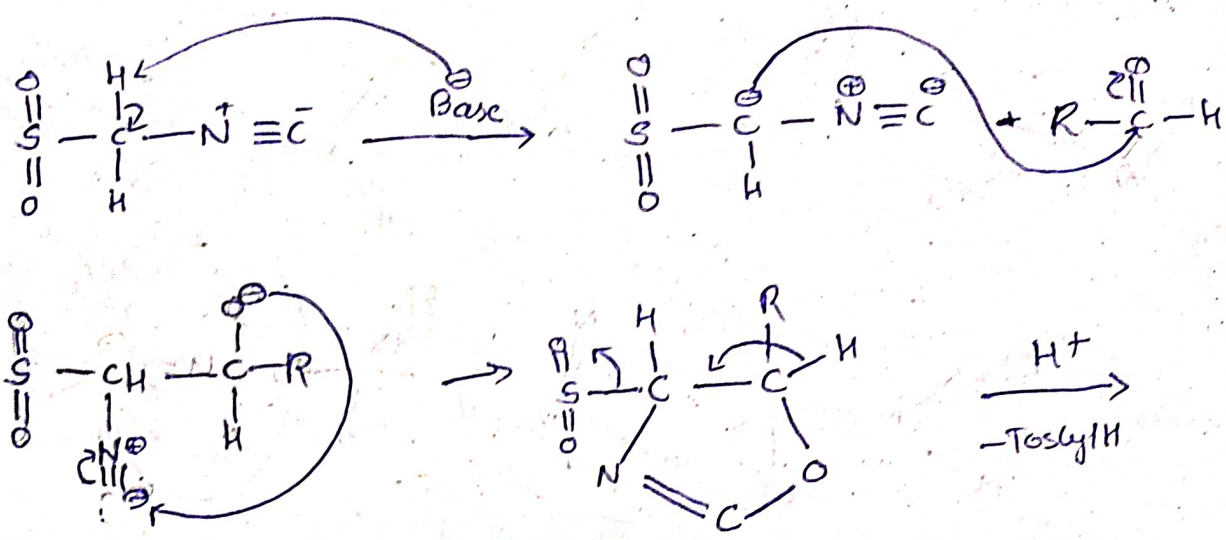


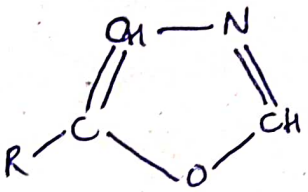
2. Van Leusen - Scholl kopf method

This reaction is based on tosyl methyl isocya-nide ~~metho~~ with aldehyde in the presence of potassium carbonate to afford ~~fine~~. ~~five alkyl~~ ~~or~~ of 5- alkyl or 5- aryl oxazole.



Mechanism:





Physical & Chemical properties of Oxazole

* It is a colourless liquid which has the odour of pyridine with boiling point 69- 70°C.
* It is a thermally stable compound possessing weak basic character.
* Since it is a hybrid of furan & pyridine, it exhibits the characteristics of both the compounds. Therefore it undergoes protonation and N-alkylation due to the presence of pyridine type nitrogen & diene type properties due to furan type oxygen
* It is less reactive towards electrophilic attack due to its electron defficiency due to the inductive effect of nitrogen & oxygen which causes electron

defficiency at 2nd carbon.

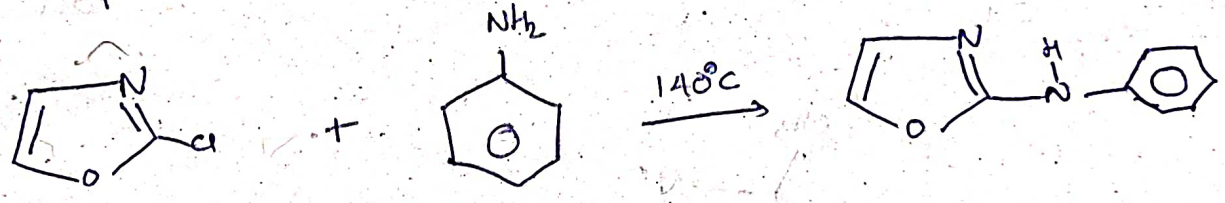
* Thees the nucleophilic attack takes place at 2nd carbon
* The electrophilic substitution preferably takes place at 4th & 5th carbon

Note: The electrophilic substitution of oxazole has not been investigated. Nitration, sulfonation reactions in acid media do not proceed in the oxazole due to the formation of highly electron deffi cient oxaxoleum cation.

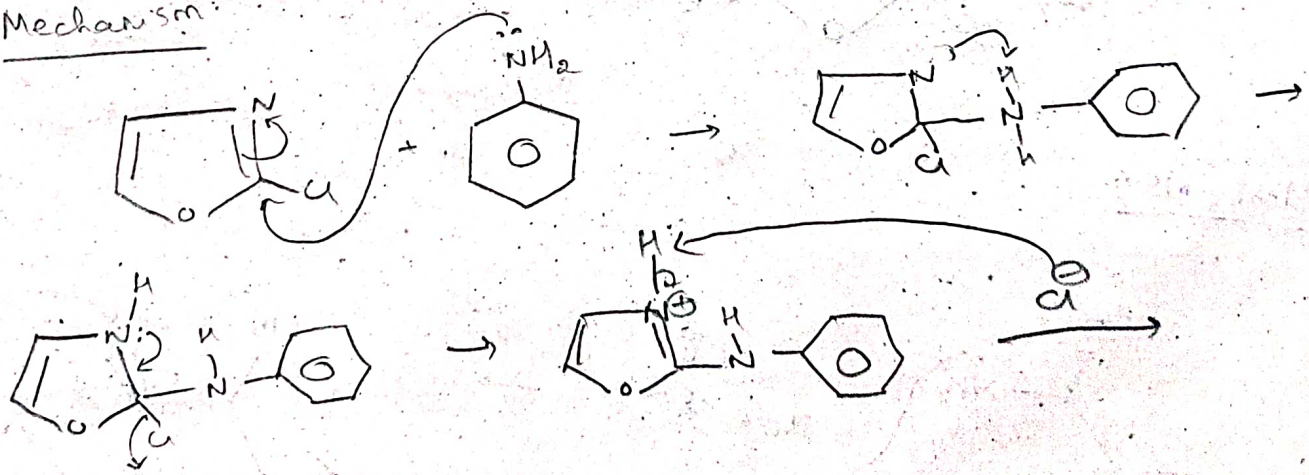
Reactions of oxazole

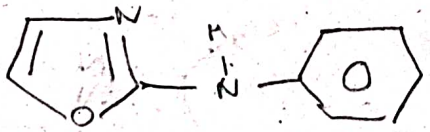
1) Nucleophilic substitution

i)

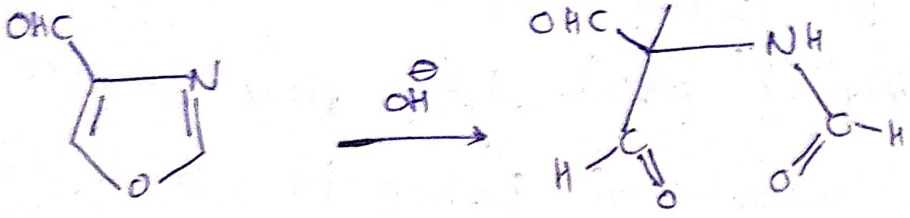


Mechanism:



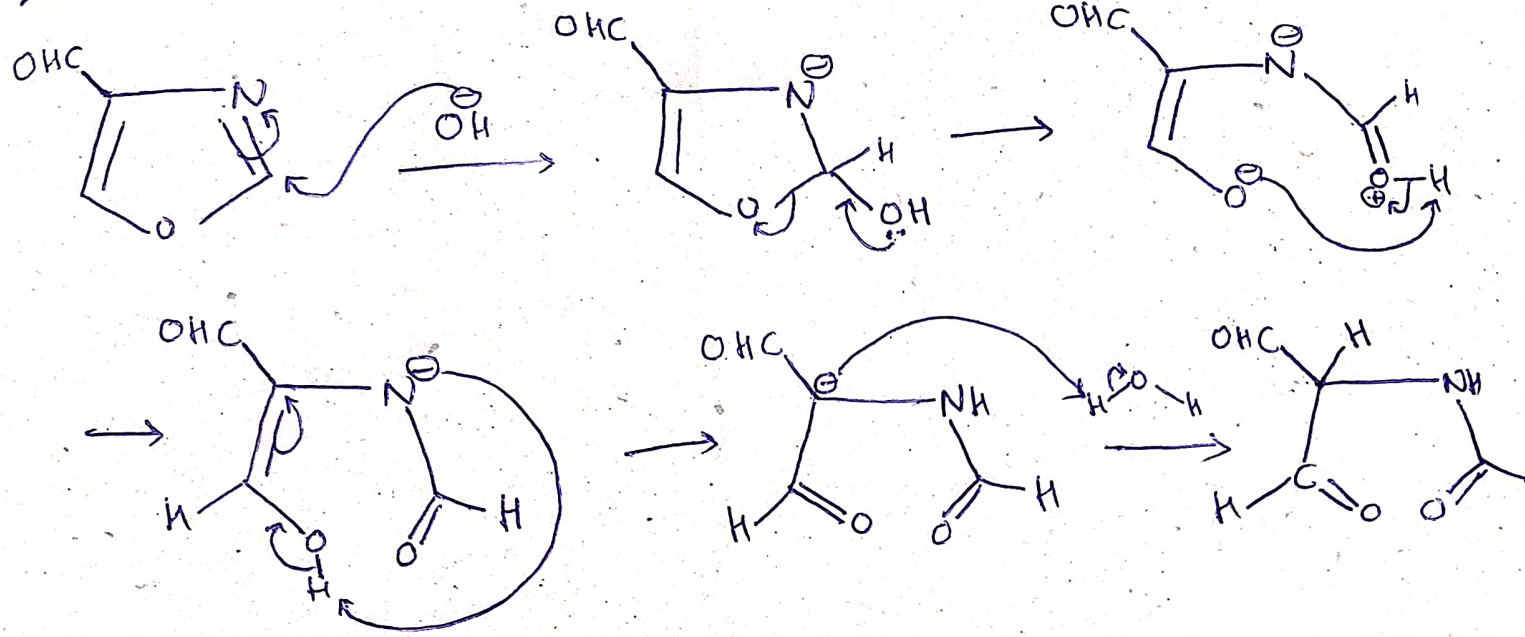


ii)



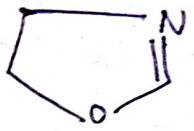
⇒ Mechanism

Mechanism:

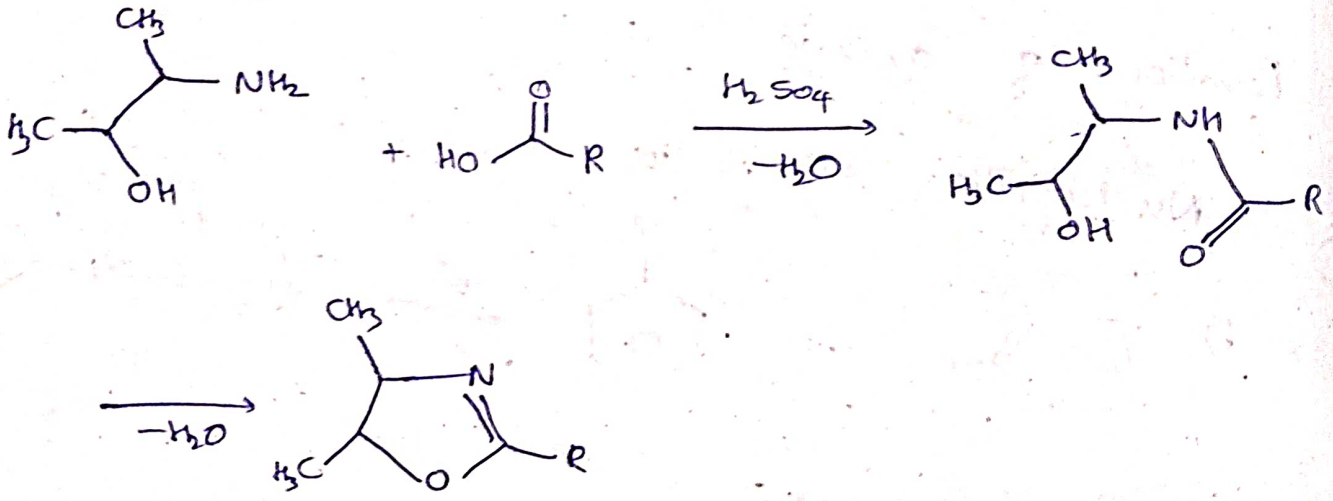

OHC
N
H
O
OH
OHC
N
H
O
OH
OHC
N
H
O
H
OHC
N
H
O
H
O
OHC
NH
H
O
H
O
H
OHC
H
NH
C
H
O
O

Derivative of oxazole:

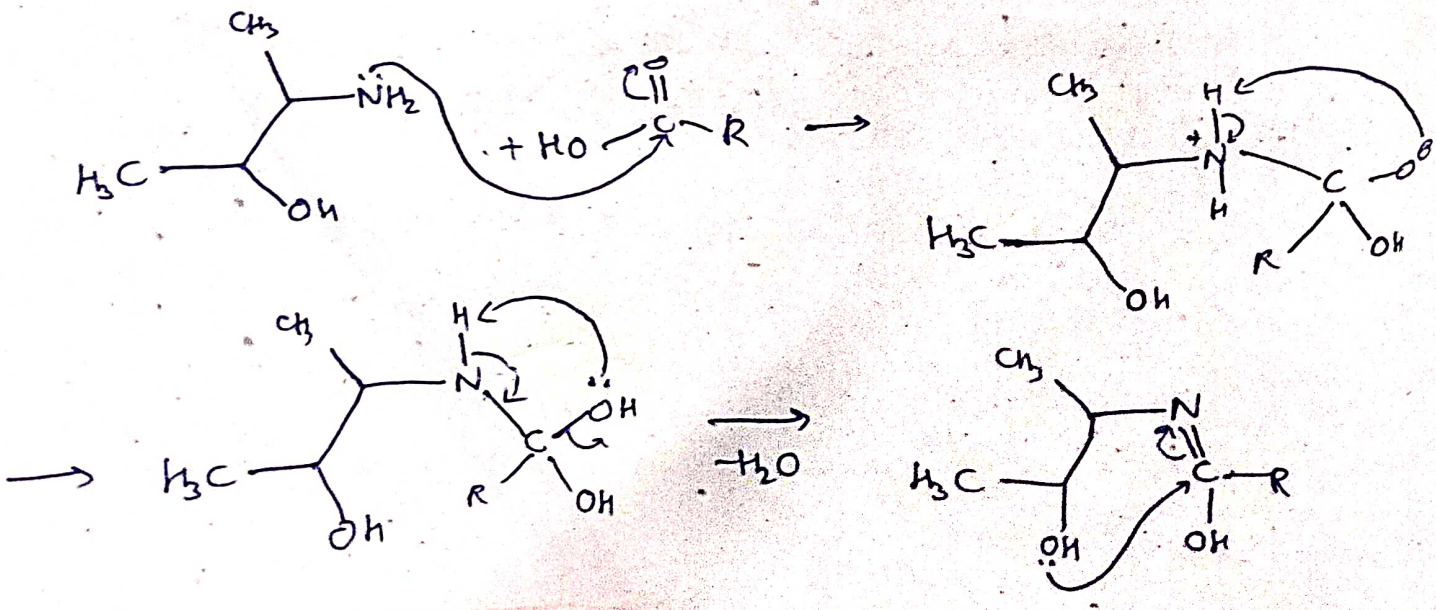
1. 4,5- dihydro-oxazole

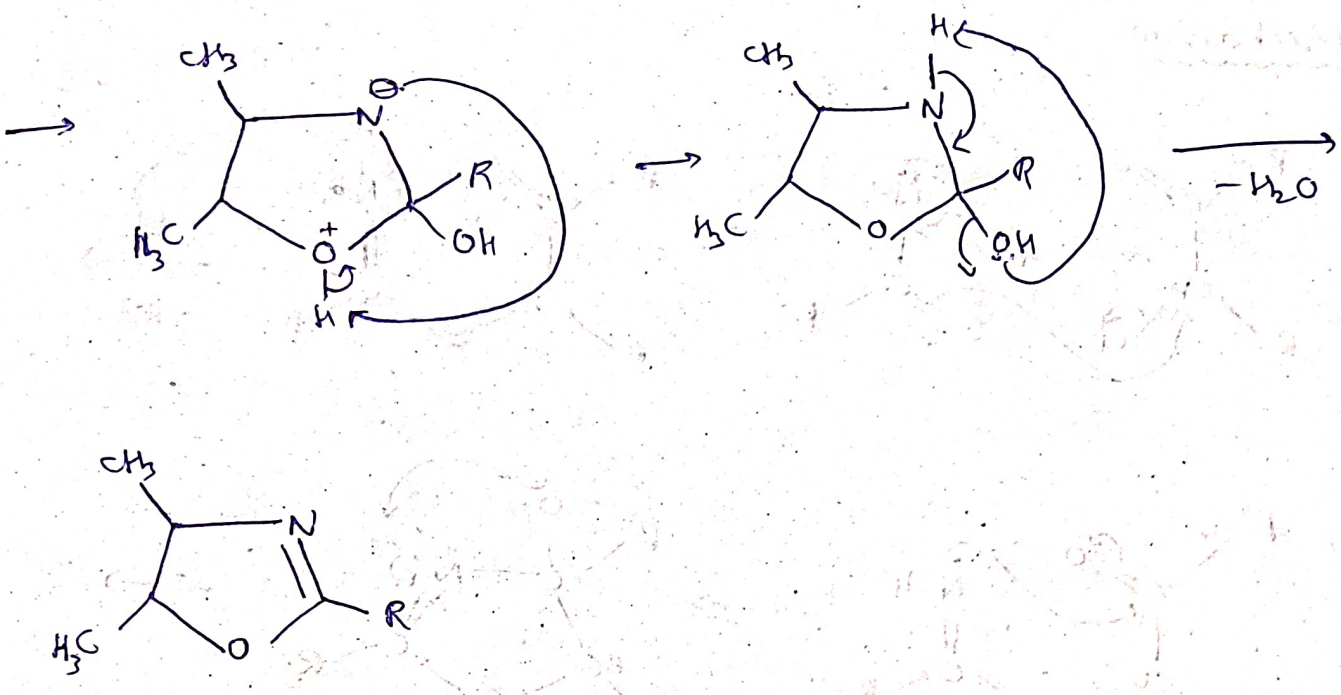


Synthesis

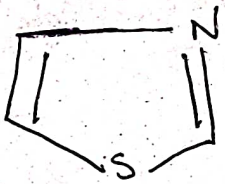


Mechanism:





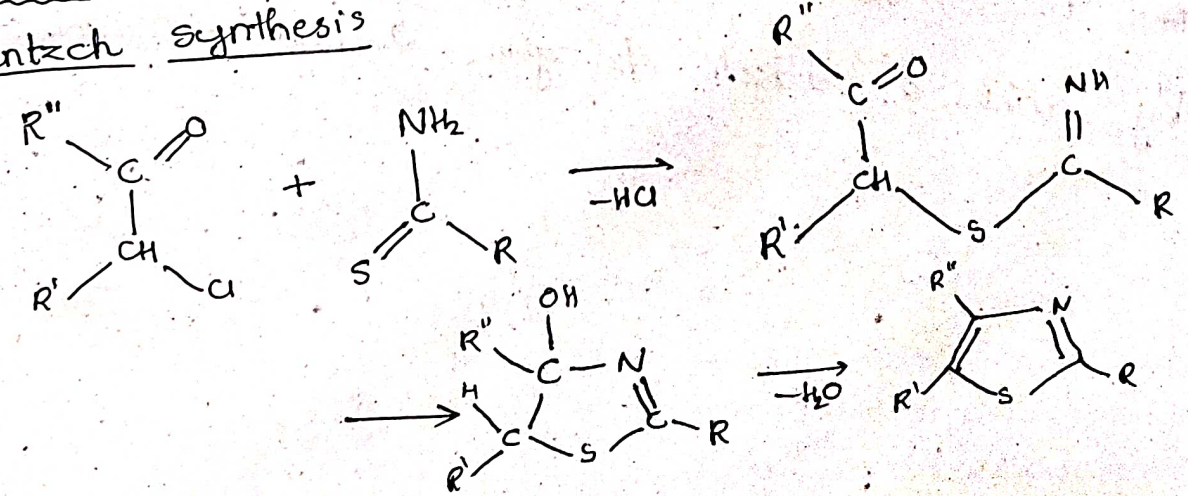
Thiazole:



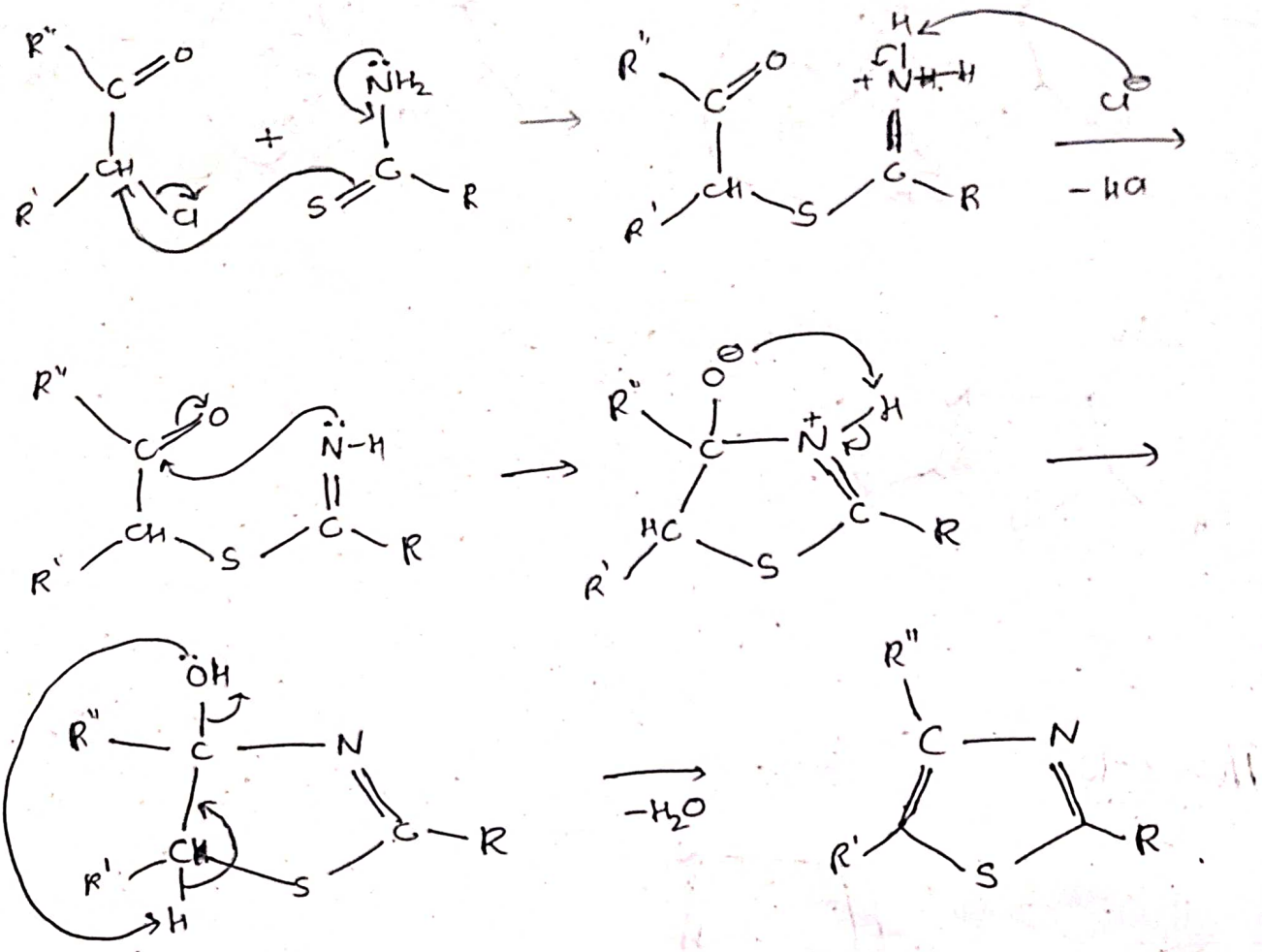
* It is a 5 membered ring with 5 excessive heterocyclic system which is derived from thiophene with the replacement of CH group by azomethyl nitrogen at the 3rd position.

Synthesis:

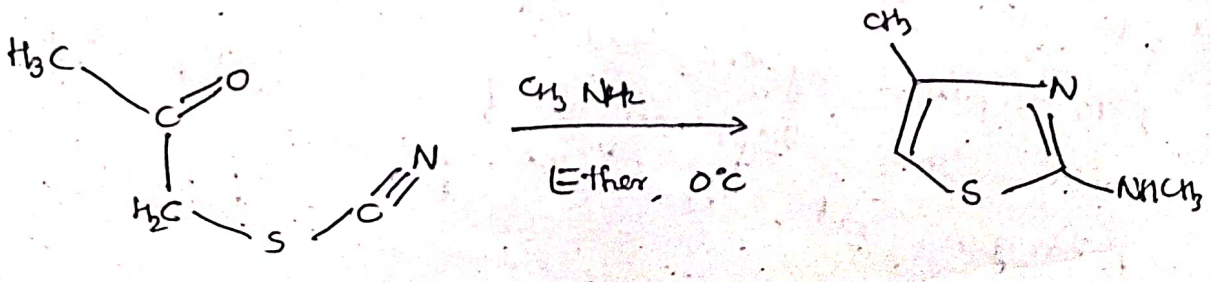
1. Hantzch synthesis



Mechanism:

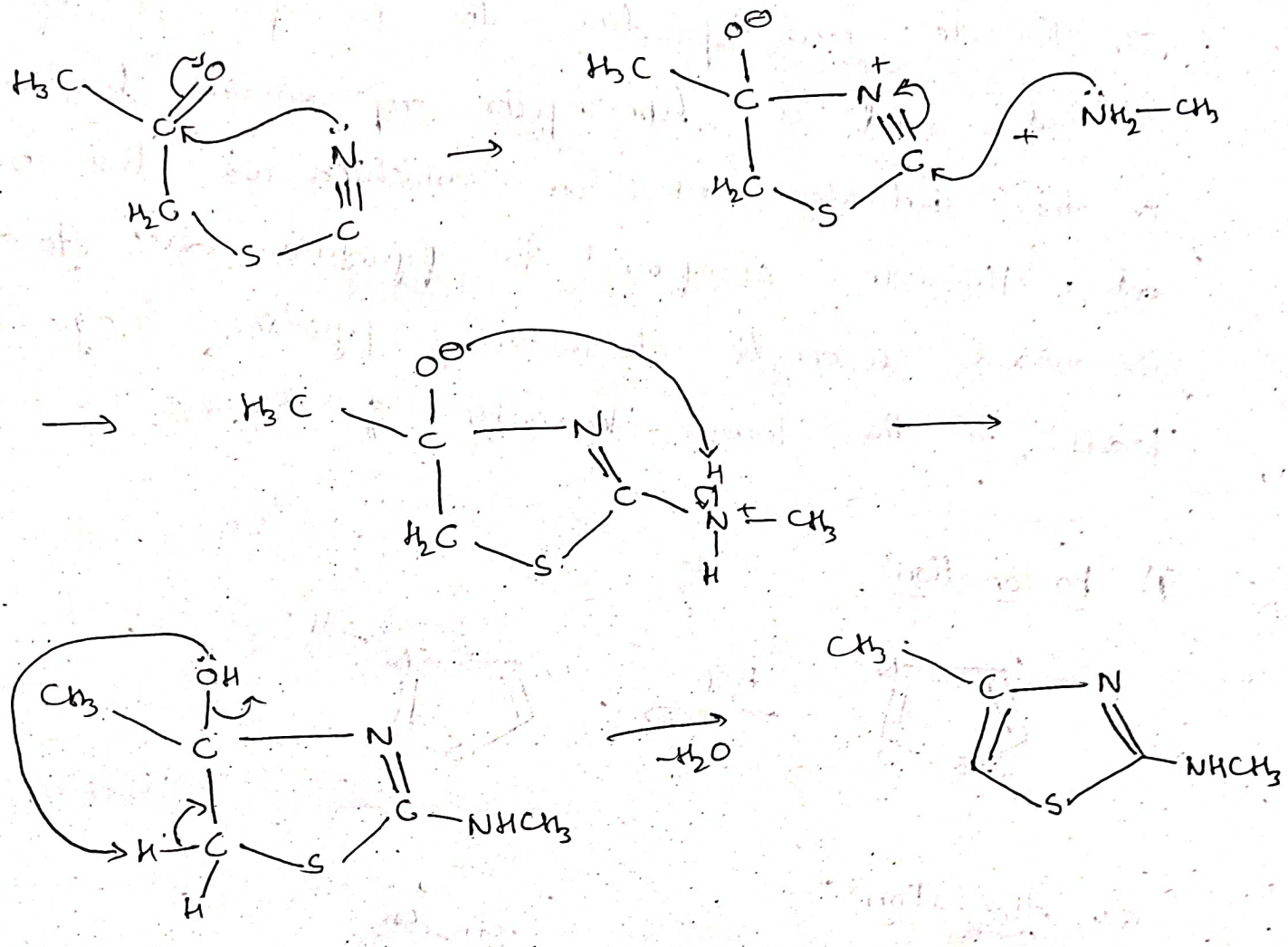


2. Tcherniac's Synthesis



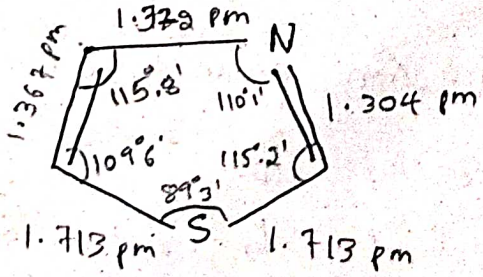
It involves the cyclization of α-thiocyano ketone by acid or alkali to give 2-hydroxythiazole derivative.

Mechanism:



Physical and chemical properties of Thiazole

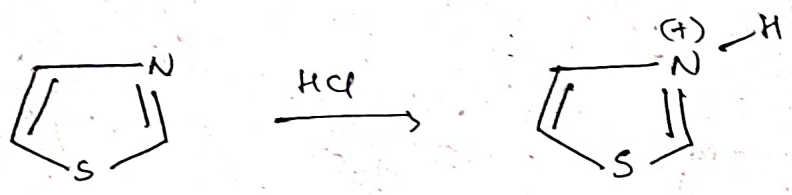
The chemistry of thiazole has the similarity with thiophene and pyridine due to the presence of thiophene-type sulfur at 1st position and pyridine type nitrogen at the 3rd position.



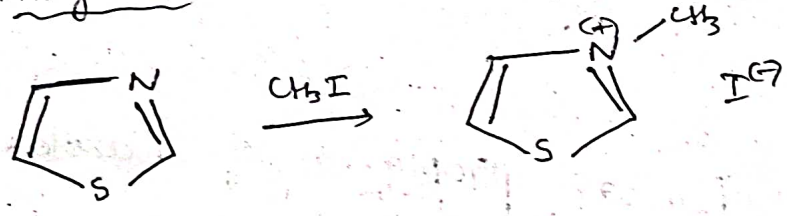
Electrophilic substitution at nitrogen:

In thiazole and pyridine, the nitrogen is sp^2 hybridized and a lone pair remains localized on the nitrogen atom which is less reactive at thiazole compared to pyridine due to the increased aromatic character of pyridine ring. This leads to the lower basicity of thiazole

1) Protonation:

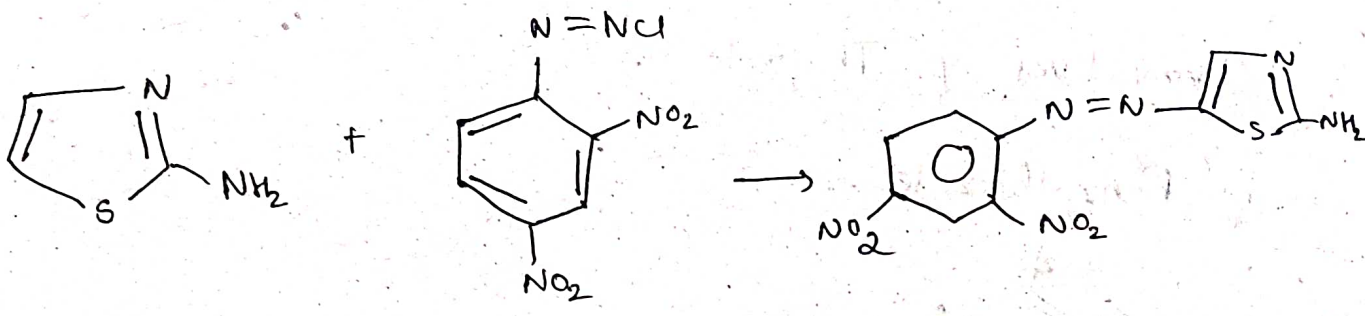


2). Alkylation



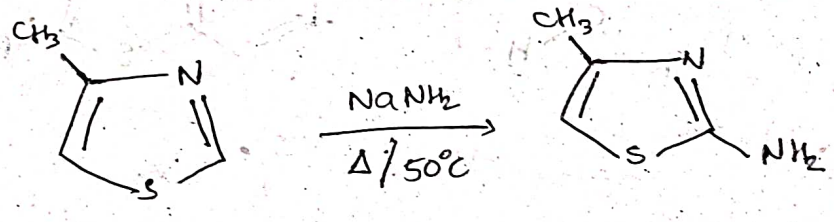
Electrophilic substitution at carbon:

* The presence of electron donating group favours this type of reaction
* Electrophilic substitution proceeds at 5th position or at the 4th position if it is occupied.
* Thiazole is resistant to nitration with classical nitrating agent, however 2 or 4 -substituted thiazole can be nitrated.

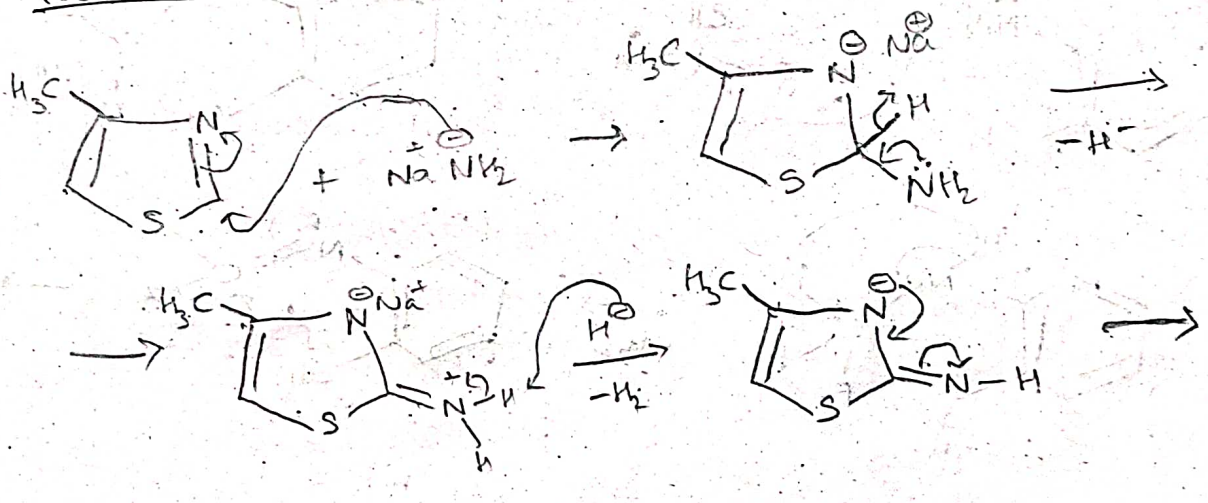


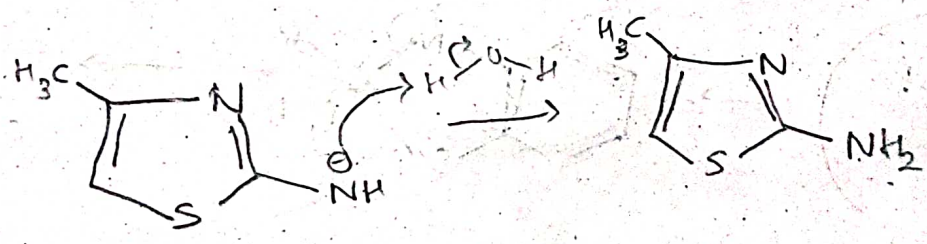
Nucleophilic substitution at carbon:

* 4-methyl thiazole reacts with sodamide



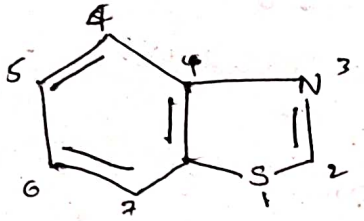
Mechanism:





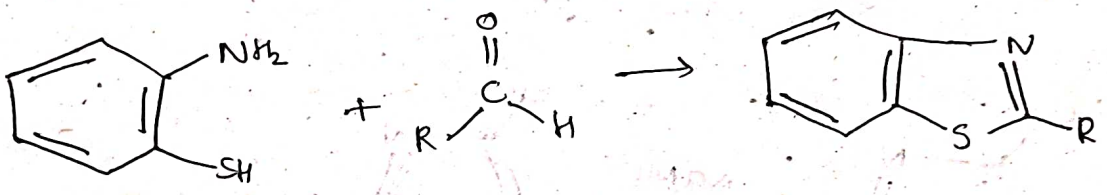
Derivatives of Thiazole

1. Benzothiazole

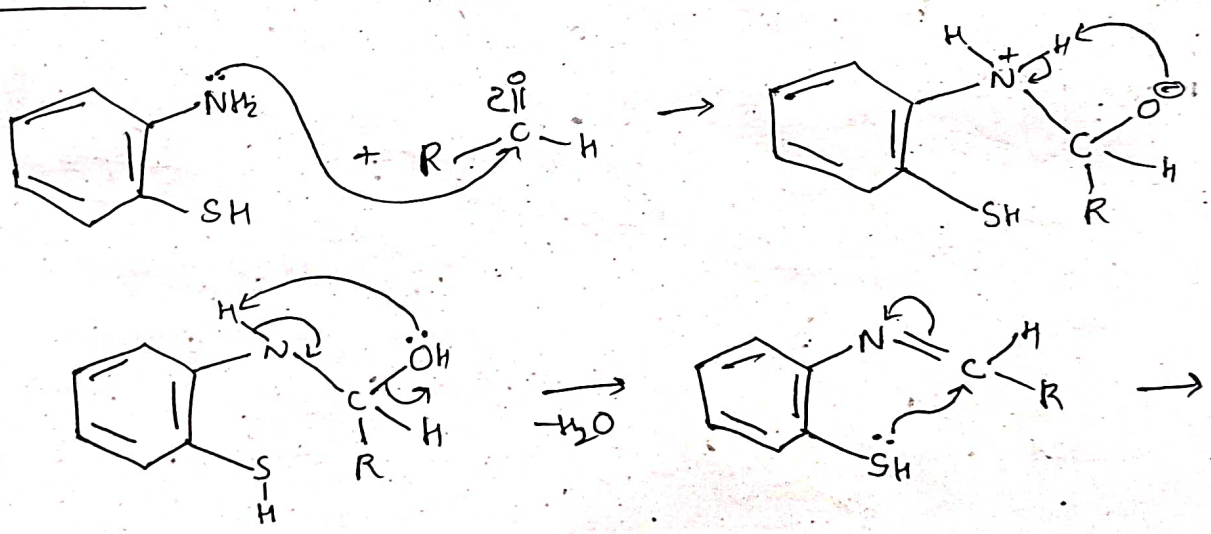


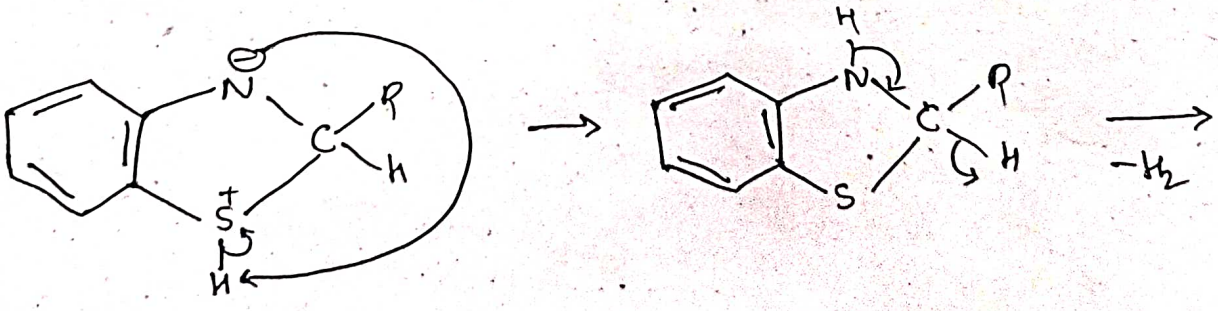
Synthesis:

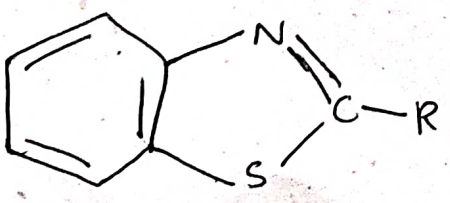
1.



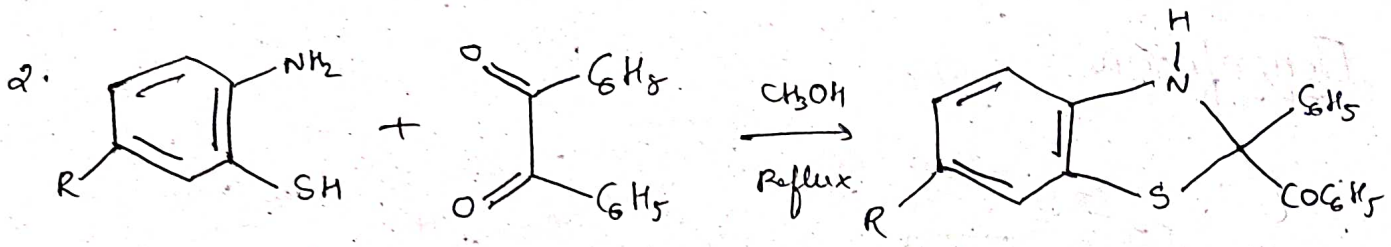
Mechanism:

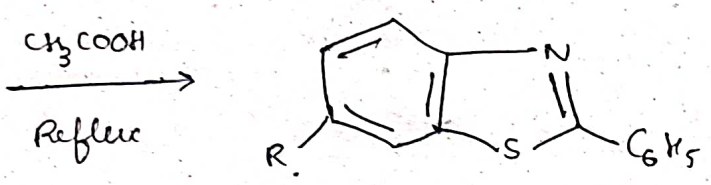




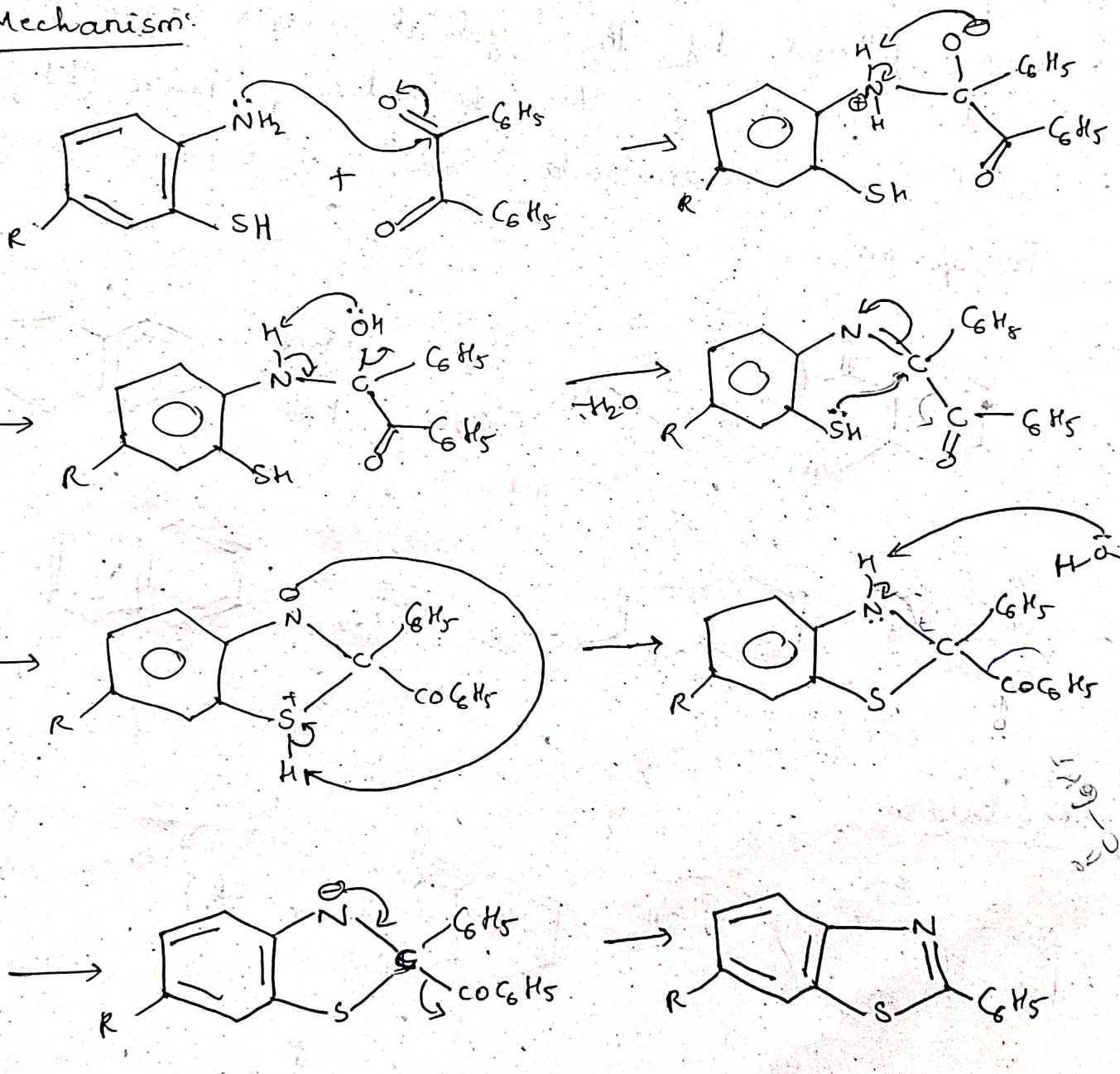


2.

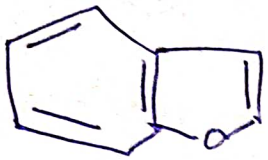




Mechanism:

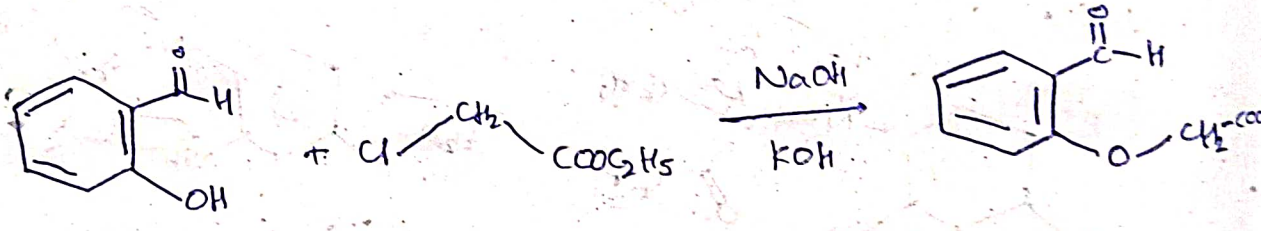


Benzofuran:

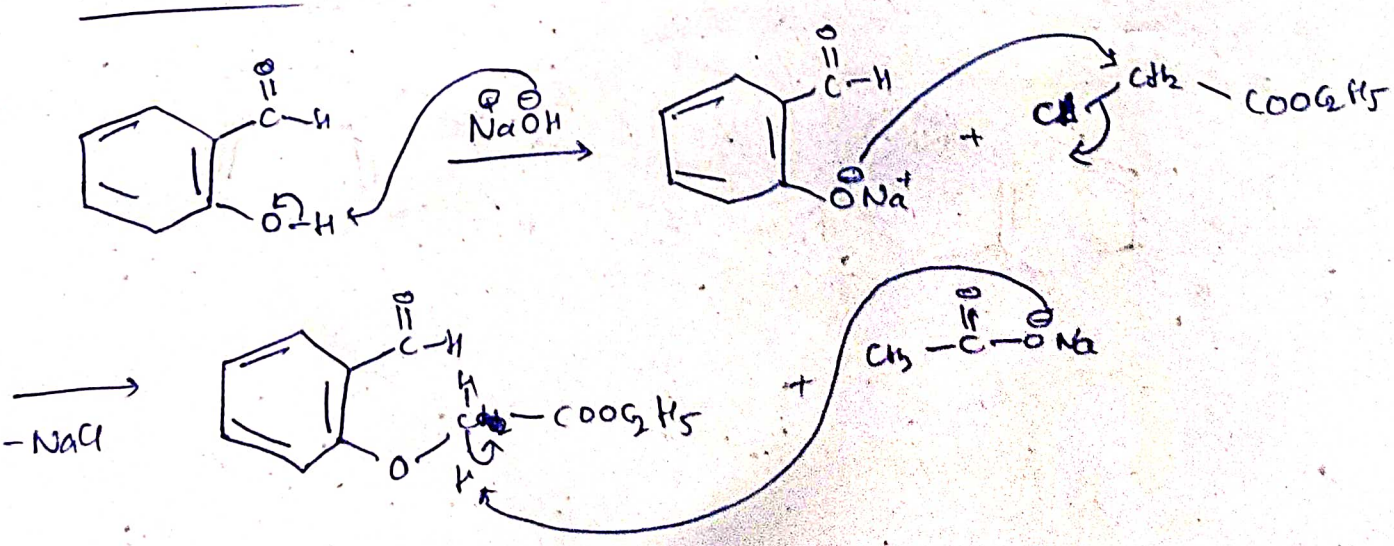


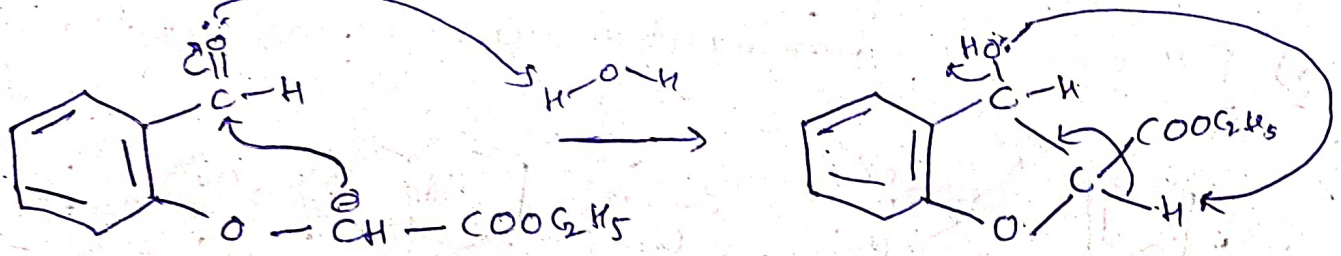
Synthesis:

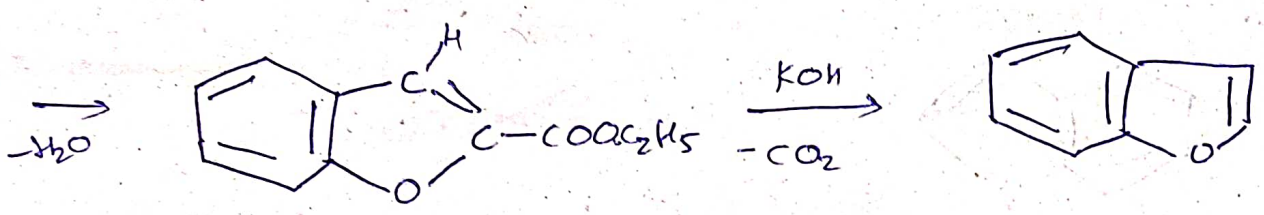
1. The reaction of salicylaldehyde & α-haloketones or esters followed by the cyclization and dehydration which results in the formation of Benzo [b] furan, which on intramolecular aldol condensation to give benzofuran



Mechanism





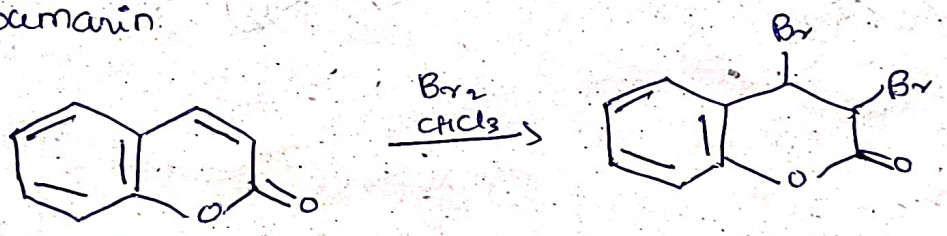


2. Perkin's synthesis of Benzofuran (Imp)

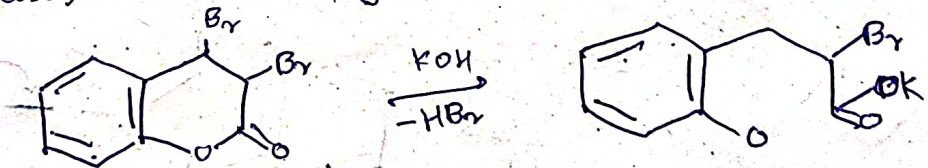
Conversion of Coumarin into Benzofuran

The steps involved are

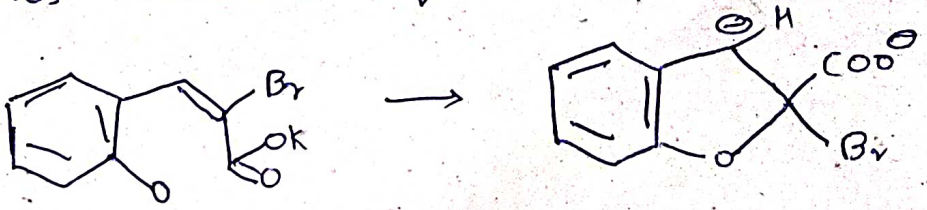
i) Bromination of coumarin to yield 3,4-dibromo coumarin



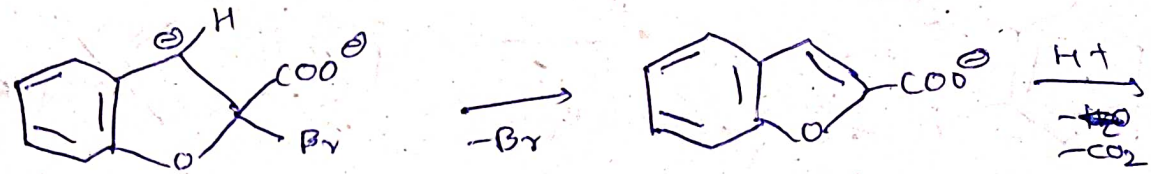
ii) Action of KOH onto the 3,4-dibromo coumarin causes the ring opening

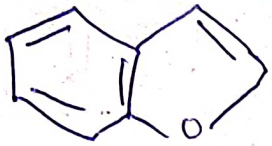


iii) which undergoes cyclization to form coumaric acid followed by subsequent decarboxylation gives benzo[b] furan

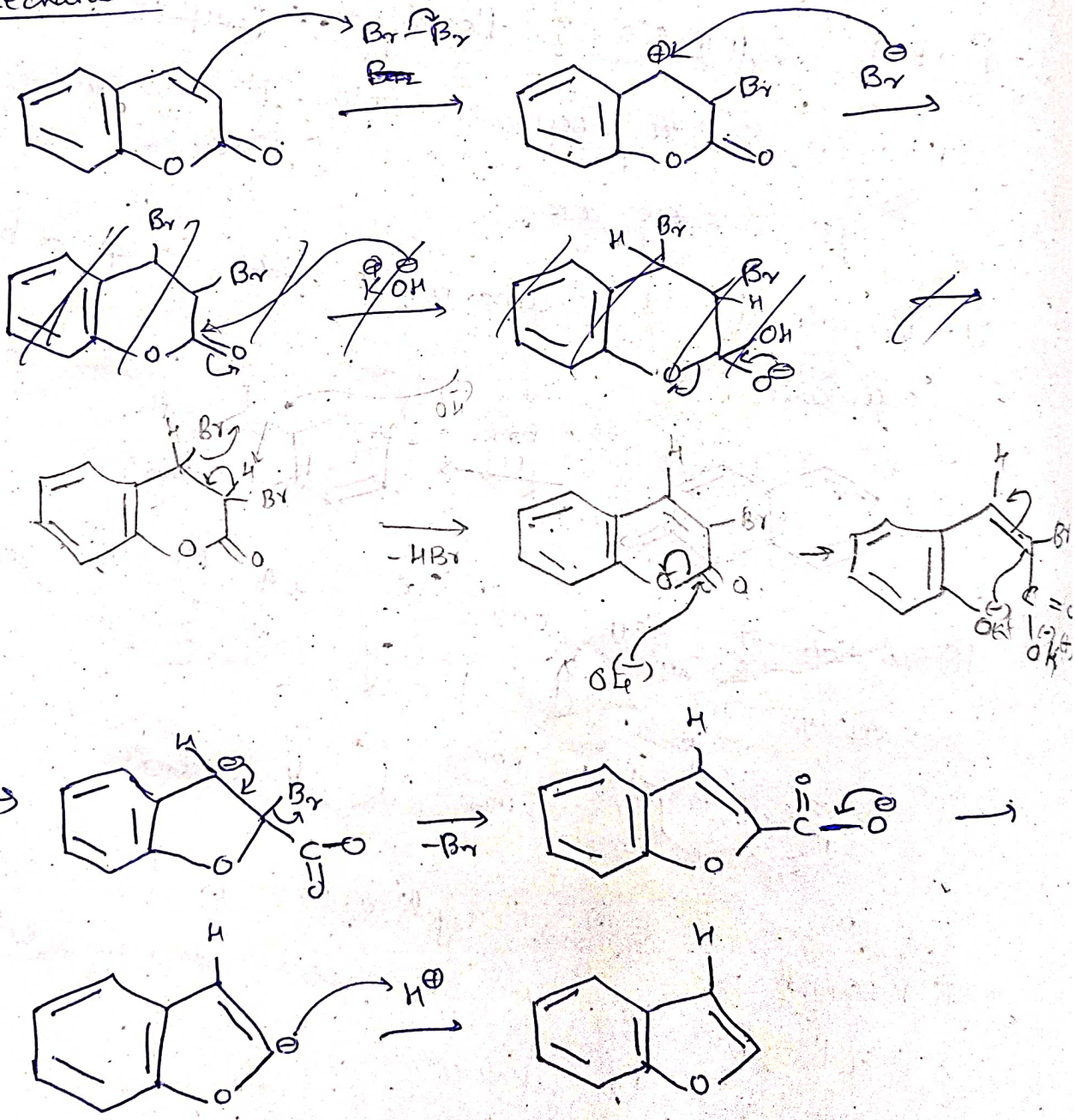


iv) Followed by debromination and decarboxylation.





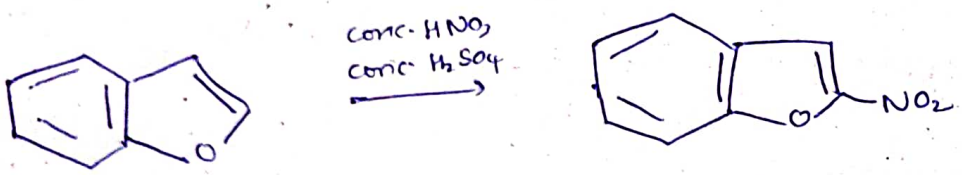
Mechanism:



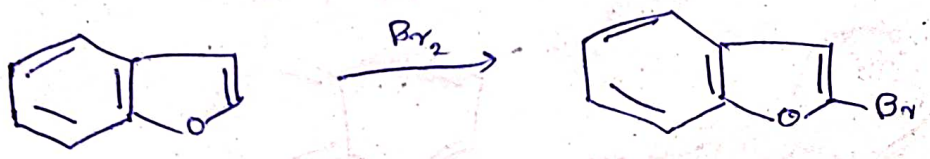
Physical & Chemical properties

* Benzofuran is the colourless oil and water soluble compound with B.P of 173°C
* It is more stable ~~than~~ as compared to furan in the presence of acid, however it undergoes polymerization with conc. H_2SO_4.

Electrophilic substitution reaction

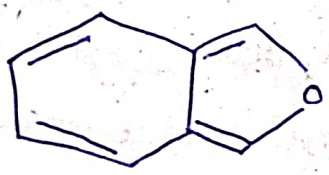


The electrophilic substitution occur at 2nd position while in the case of indole it occurst 3rd position. this is due to the higher electrone-getivity of ring oxygen as compared to nitrogen

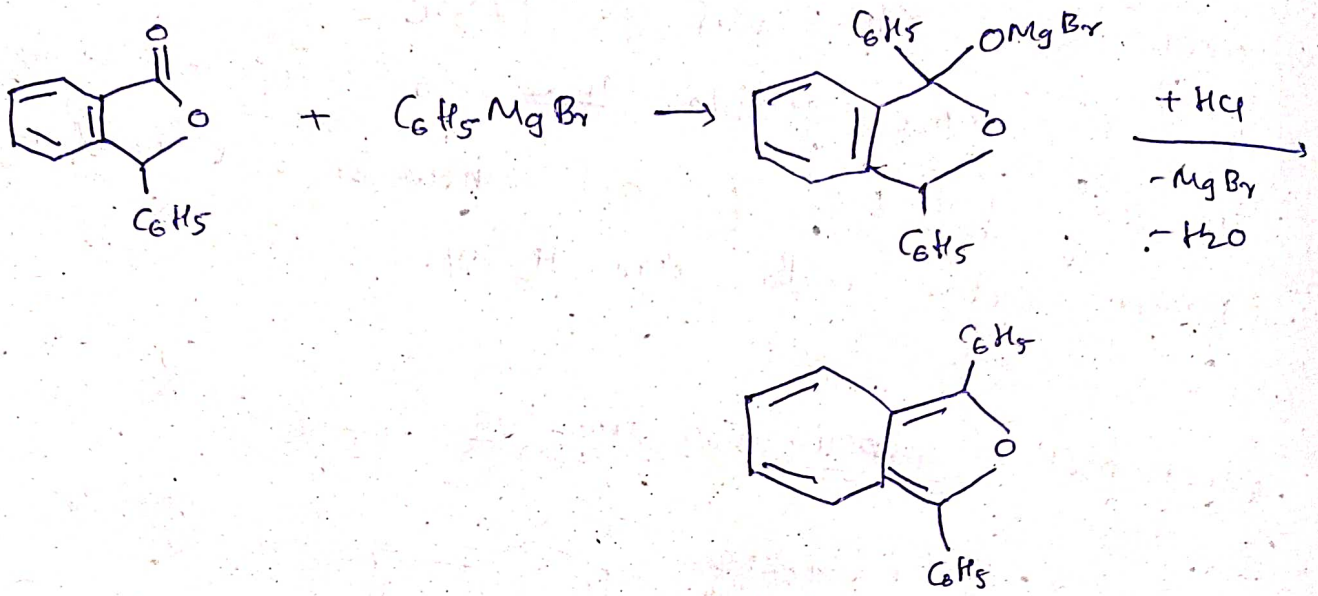


Derivatives of Benzofuran

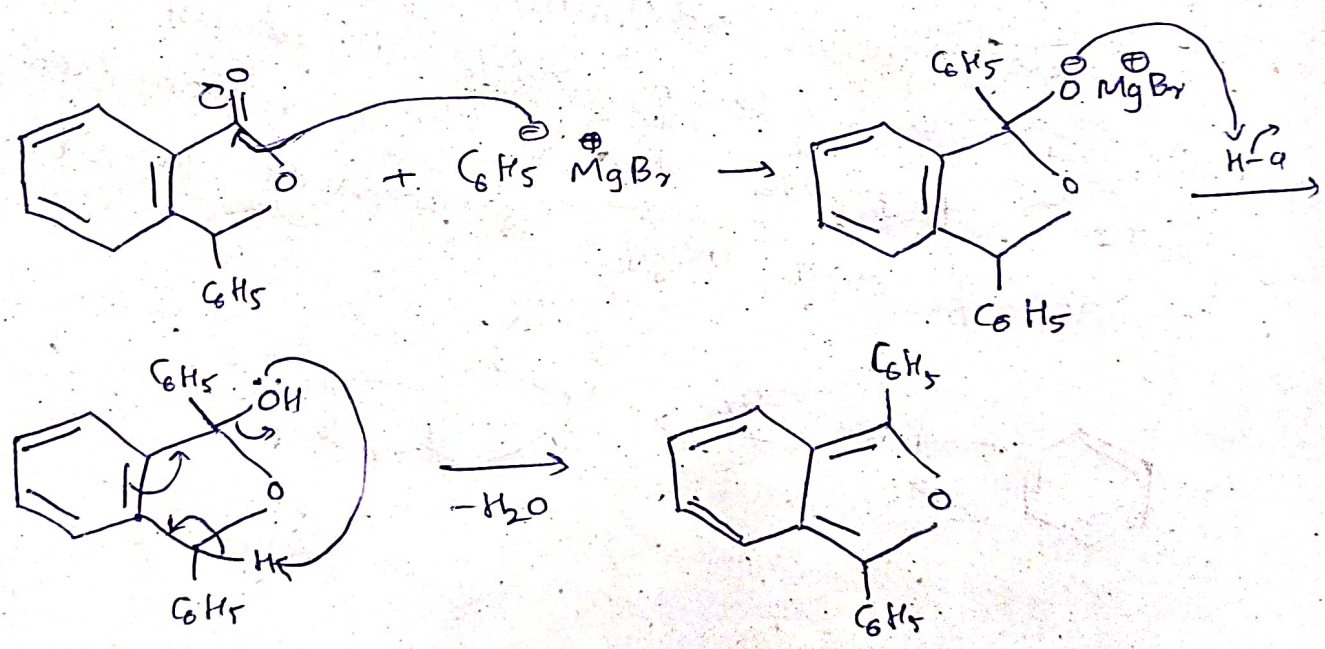
1. Isobenzofuran



* It is unstable and highly reactive form, and is not been isolated in the pure form



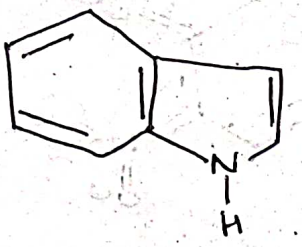
Mechanism:



Physical & Chemical properties:

* 1, 3- diphenyl benzofuran is yellow solid with m.p of 127°C and its solution has blue-green fluorosence.
* It is a highly reactive diene which undergoes [4+2] cycloaddition reaction

Indole:



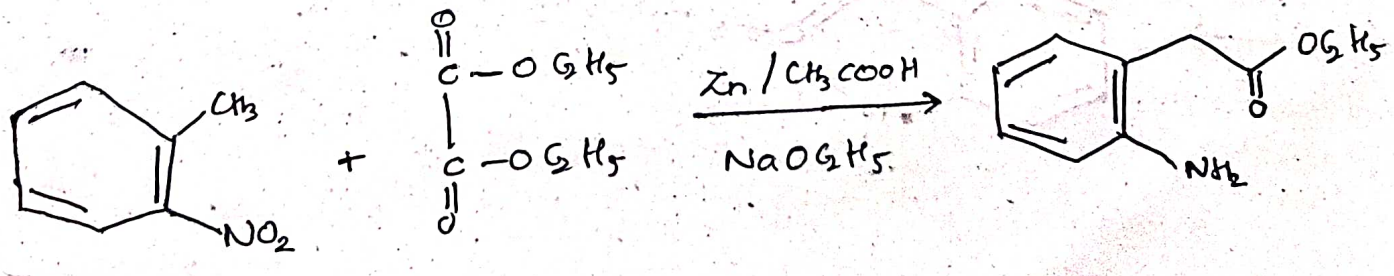
Indole is the most common member of benzopyrrole class which is present in large variety of natural products.

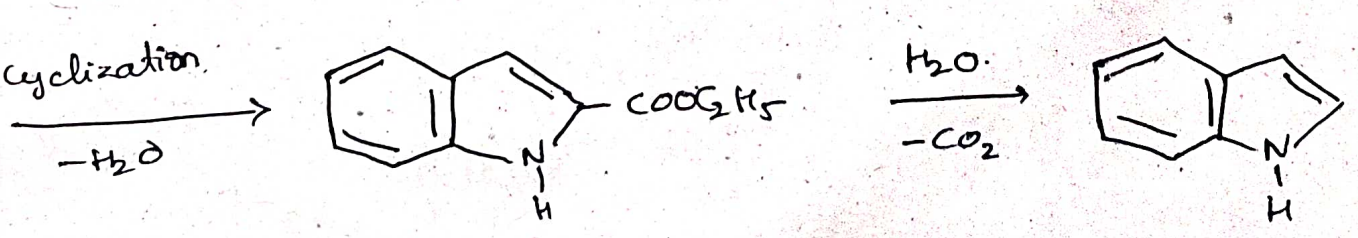
Name indole is derived from India

Synthesis

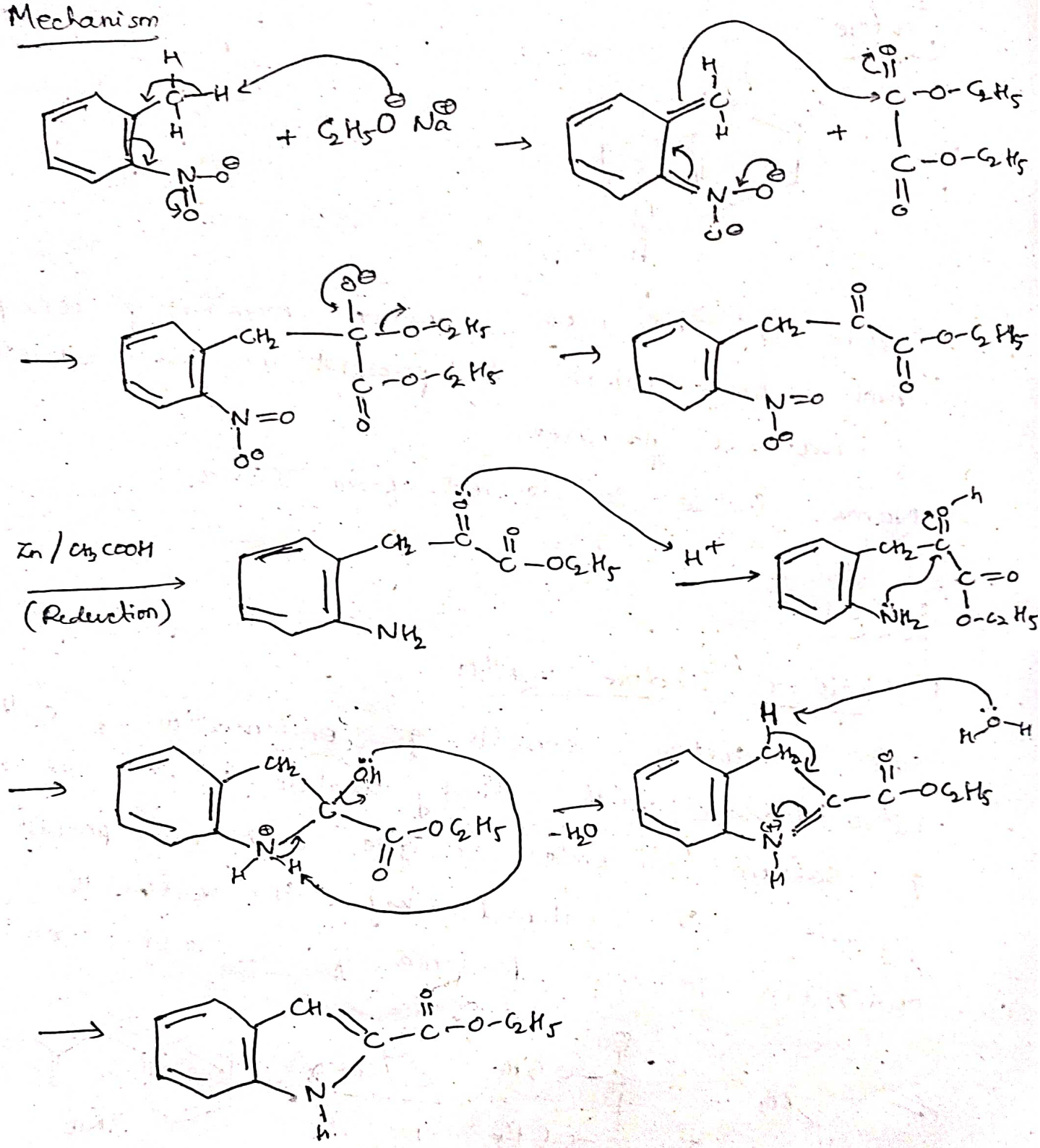
1. Reissert Indole synthesis:

This reaction consists of condensation of ortho nitro toluene with diethy oxalate in the presence of sodium ethoxide to give ortho nitro phenyl pyruvic ester followed by the reductive cyclization in the presence of Zn and acetic acid





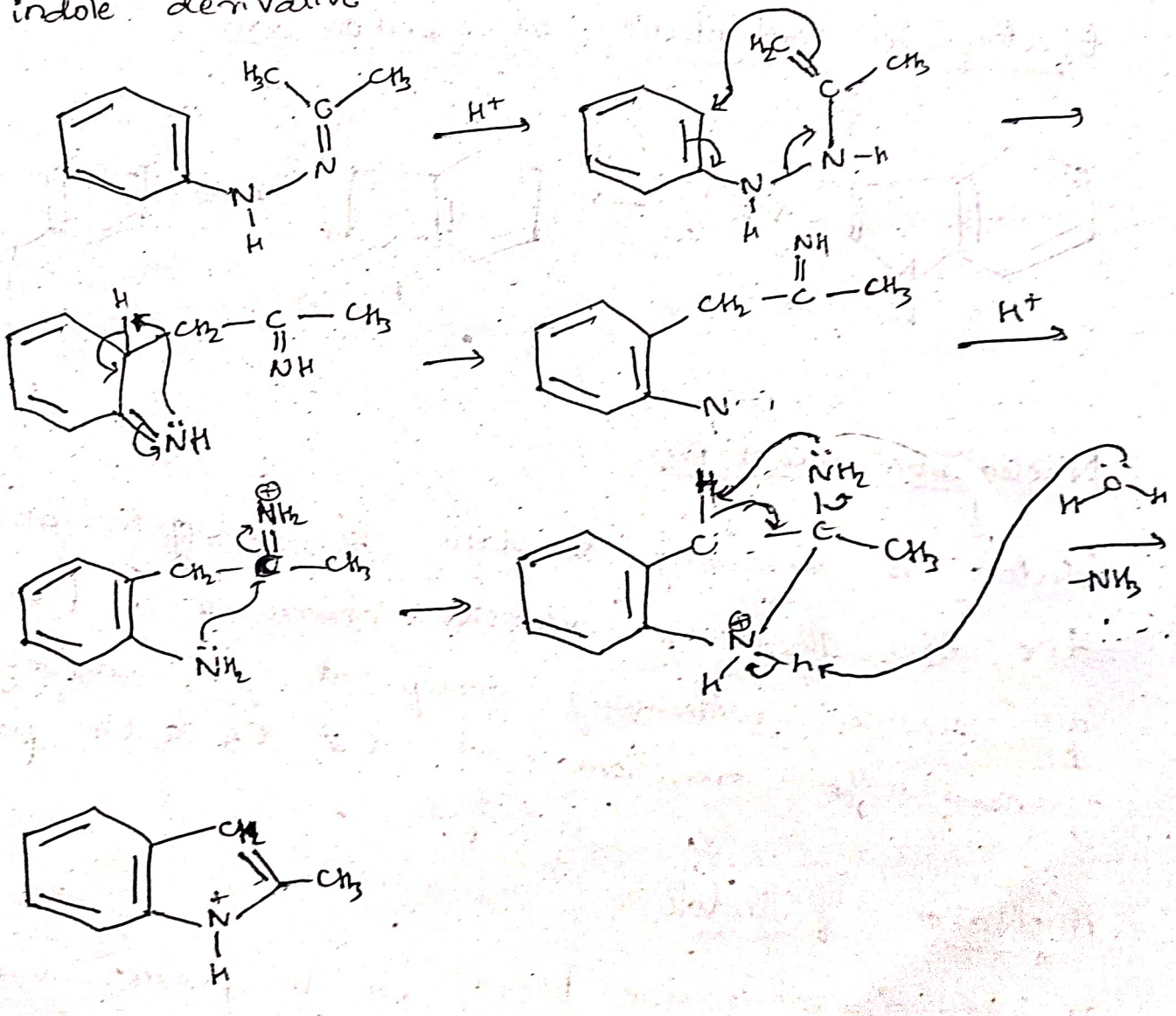
Mechanism



Imp

2. Fischer Indole synthesis

Fischer synthesis was first discovered in 1883 by Emil Fischer which is one of the oldest and reliable method to get indole. It involves the rearrangement of aryl hydrazone derived from aldehydes or ketones by an acid catalyst to form indole derivative

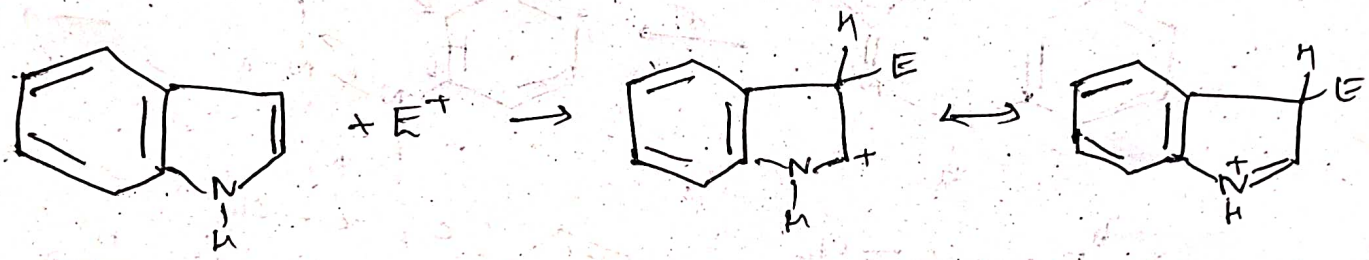


Physical & Chemical properties:

* Colourless crystalline solid with M.P of 52°C and B.P of 254 °C, having pleasant smell and used as perfume.

* Less reactive compared to pyrrole.
* Electrophilic substitution takes place at 3rd carbon, because the cation formed at 3rd carbon is more stable and the positive charge can be delocalized without inverting benzenoid structure.

Electrophilic substitution at carbon atom:



Nucleophilic reactions:

Indole is relatively resistant to nucleophilic attack due to π-electro excessive character. Presence of electron withdrawing group at the nitrogen favours the reactions at C2, C4 & C7 positions.

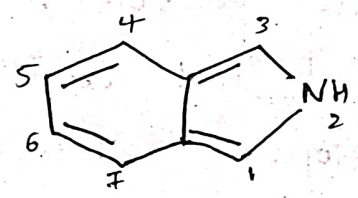
Applications of Indole

* Indole derivatives are known for its pharmaceutical and industrial applications.
* The indole alkaline reserpine is one of the first drug used for the treatment of anxiety and metal illness. They also possess the activity of anti-tumor.

* Indomethacin is well known for anti-inflamatory agent
* Other examples of anti-inflamatory agents are indoxyl and intrazole

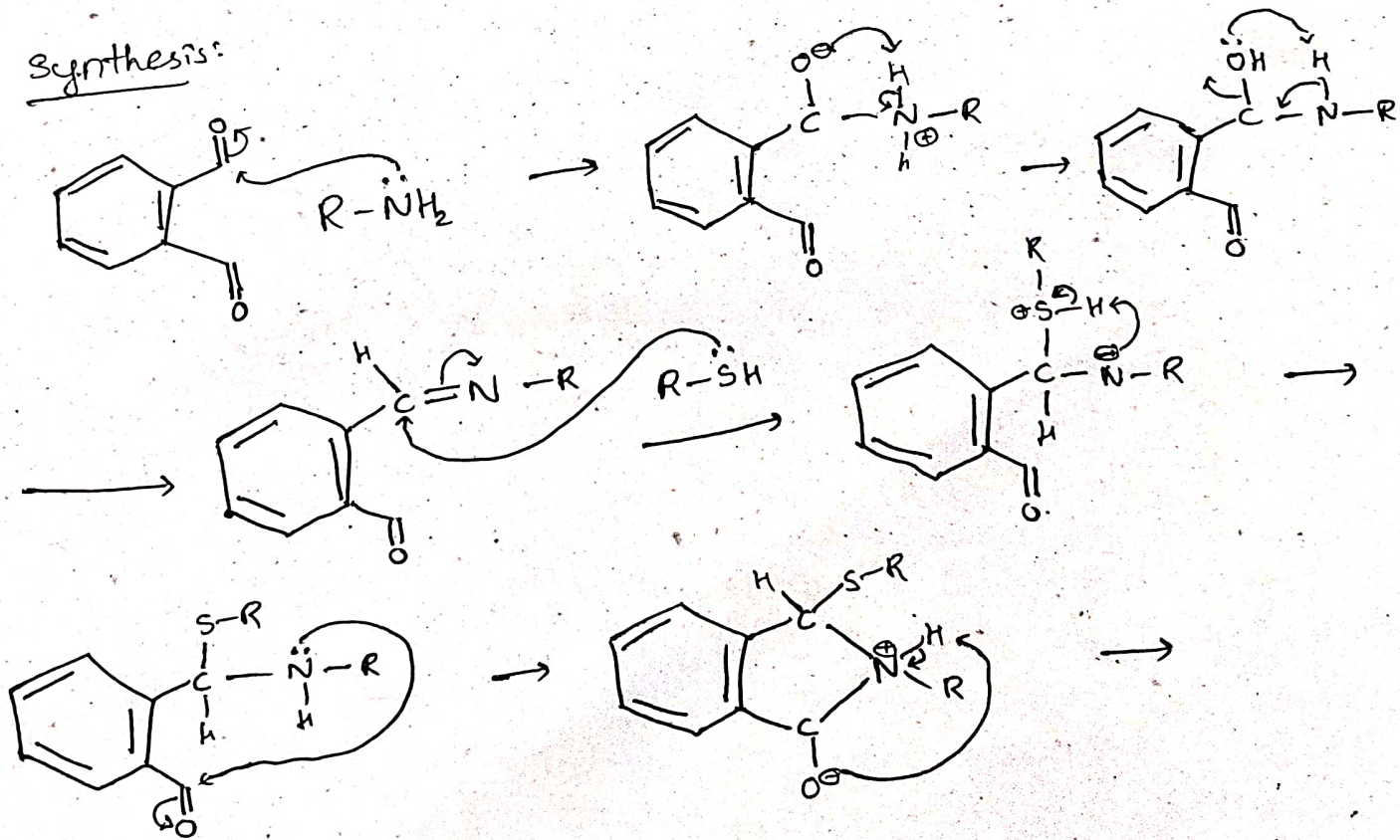
Derivative of Indole

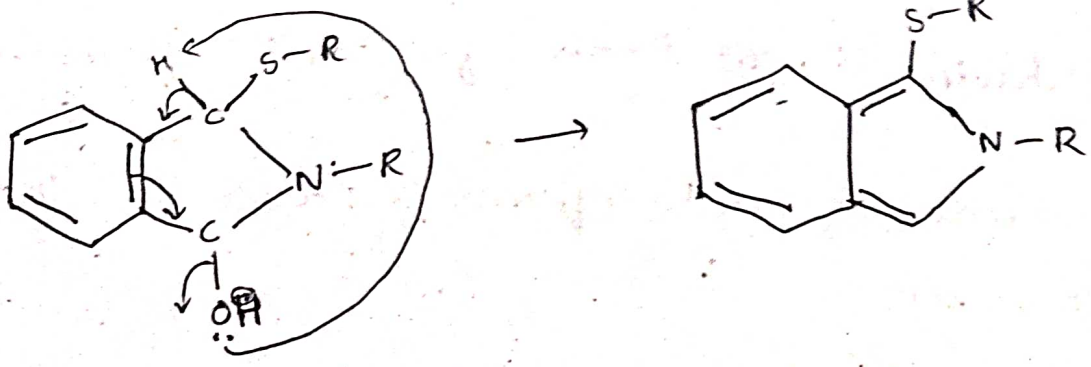
Isoindole:



It is derived by the ortho fusion of benzene ring across the 4,5 position of the pyrrole ring. It exists in two tautomeric form. i.e. 2H-isoindole and 1H-isoindole

Synthesis:



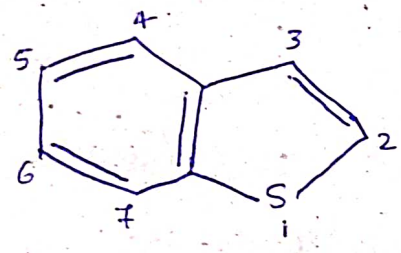


Physical & Chemical properties of isoindole:

Electrophilic reactions: As the π-electron density is high in indole ring at first carbon, it undergoes electrophilic substitution at C-1 and disubstitution at C_1 and C_3 positions.

Eg:- Protonation, Acetylation

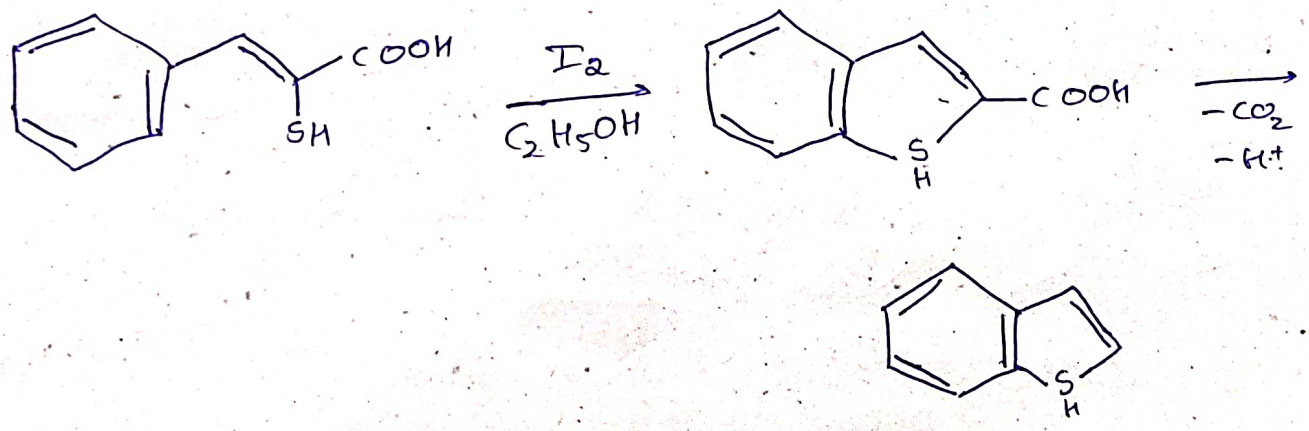
Benzothiophene



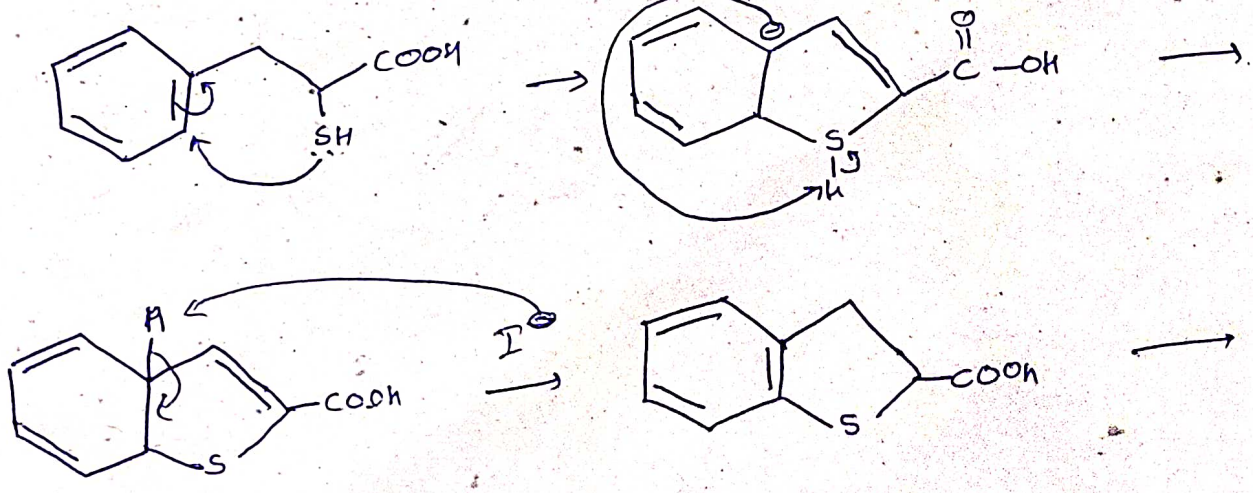
It is also known as thianaphthalene which is a colourless solid with M.P = 32°C and B.P = 221°C

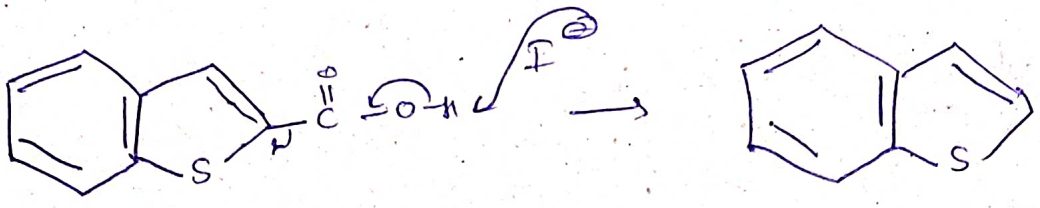
Preparation:

α-mercaptocinnamic acid on oxidative cyclization with iodine ethanol results in the formation of benzothiophene.

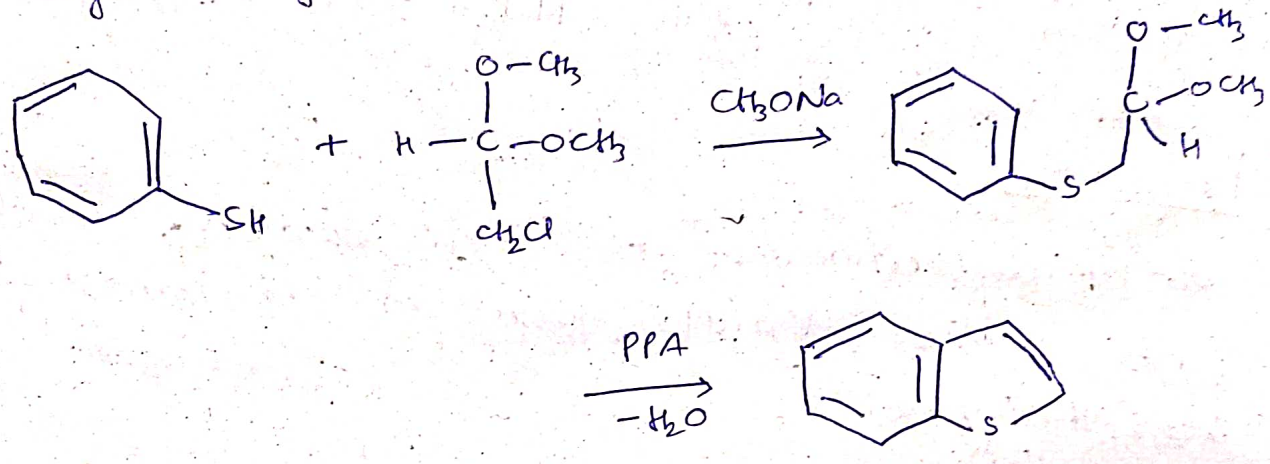


Mechanism:

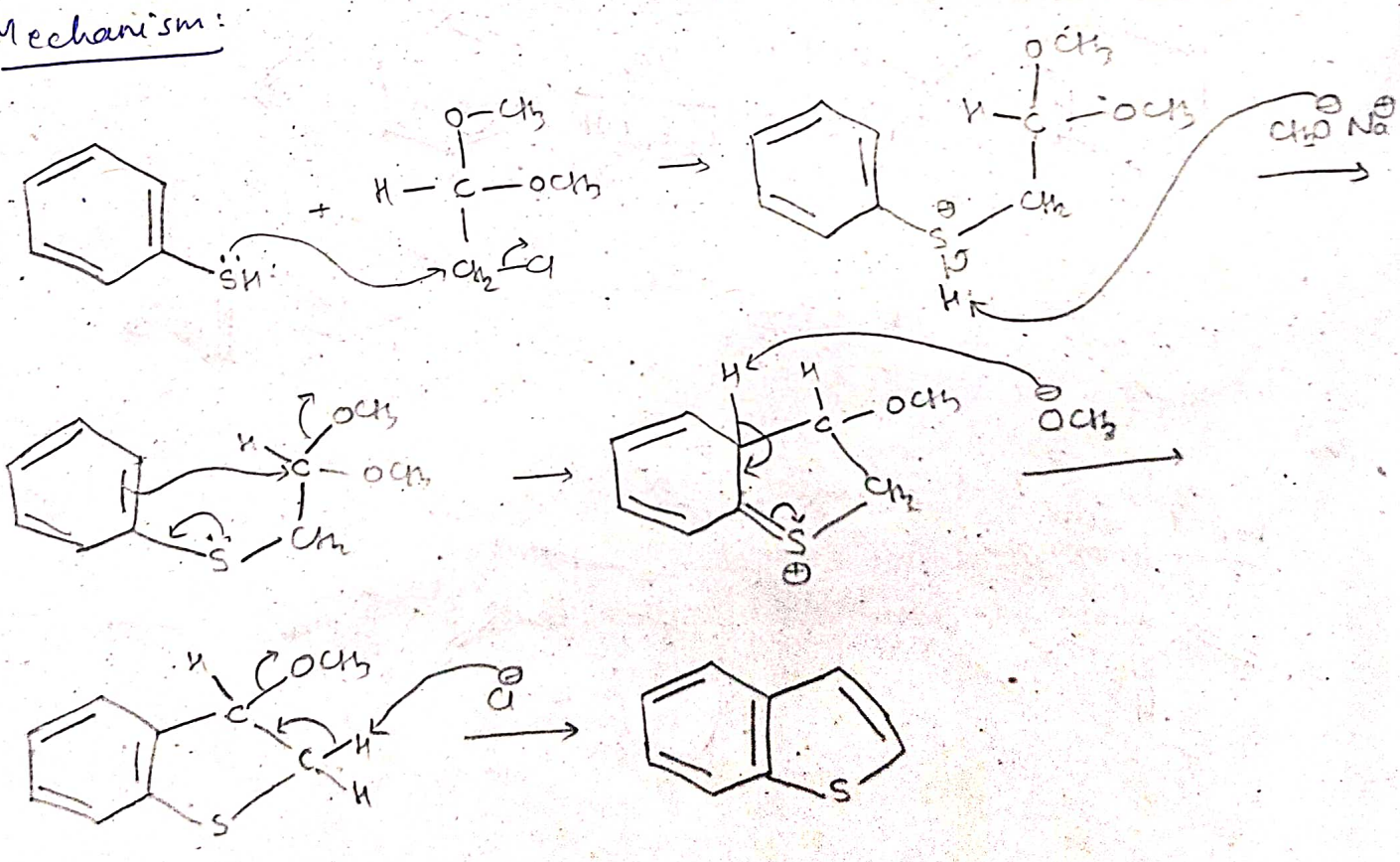




2. Arylthioacetaldehyde acetal undergoes cyclization in the presence of polyphosphoric acid as a catalyst to give benzothiophene

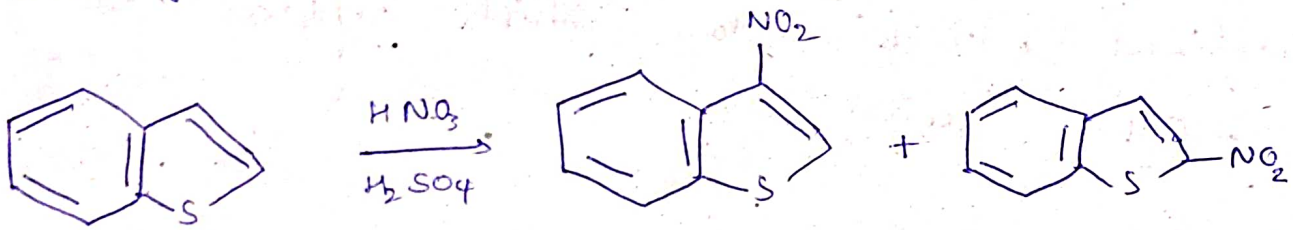


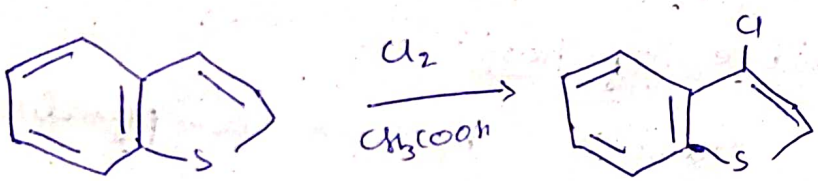
Mechanism:

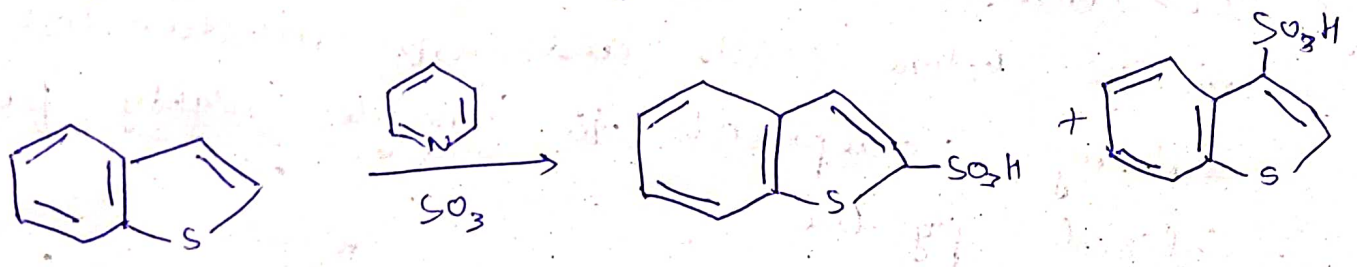


Physical & chemical pro

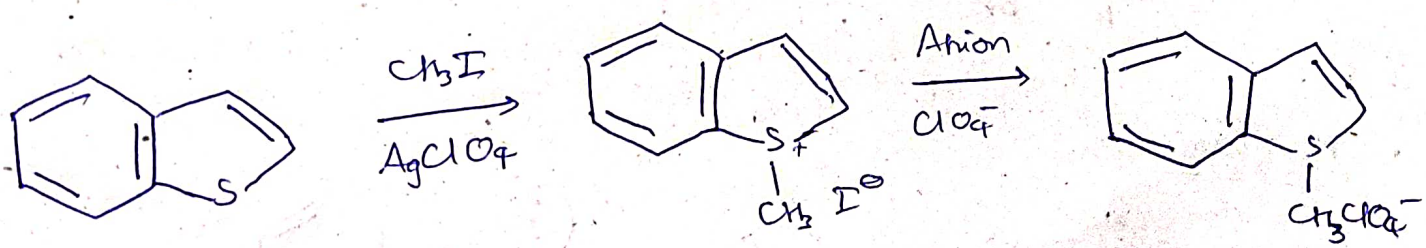
* Benzothiophene is less reactive than thiophene
* Same reactive as benzofuran electrophilic substi-tutions
* Usually electrophilic substitution occurs at 3rd carbon







Electrophilic substitution at S



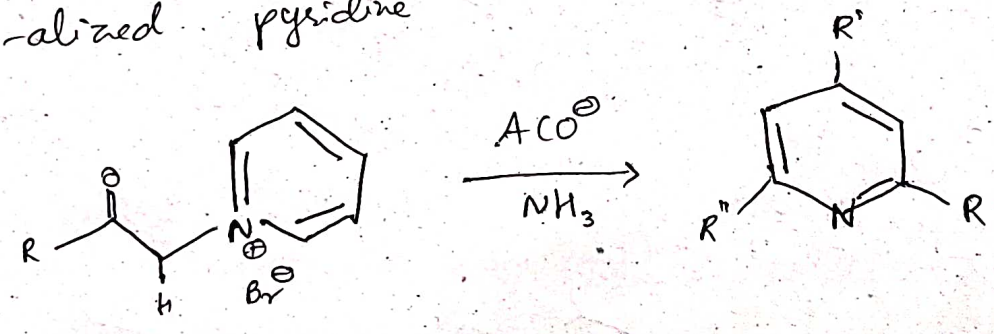
Pyridine:

* It is also called as Azabenzene or Azine
* It is a heterocyclic aromatic tertiary amine
* It is characterized by a six membered ring composed of 5 carbon atoms and a sp^2 hybri-dized nitrogen atom which replaces one of the $-CH=$ units.

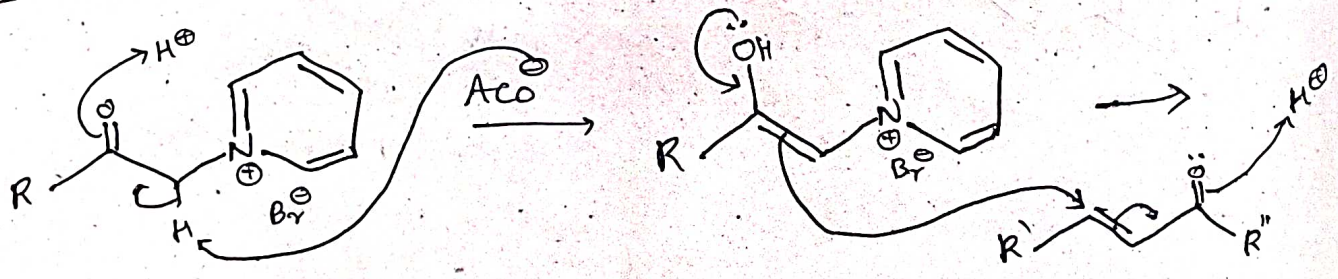
Synthesis:

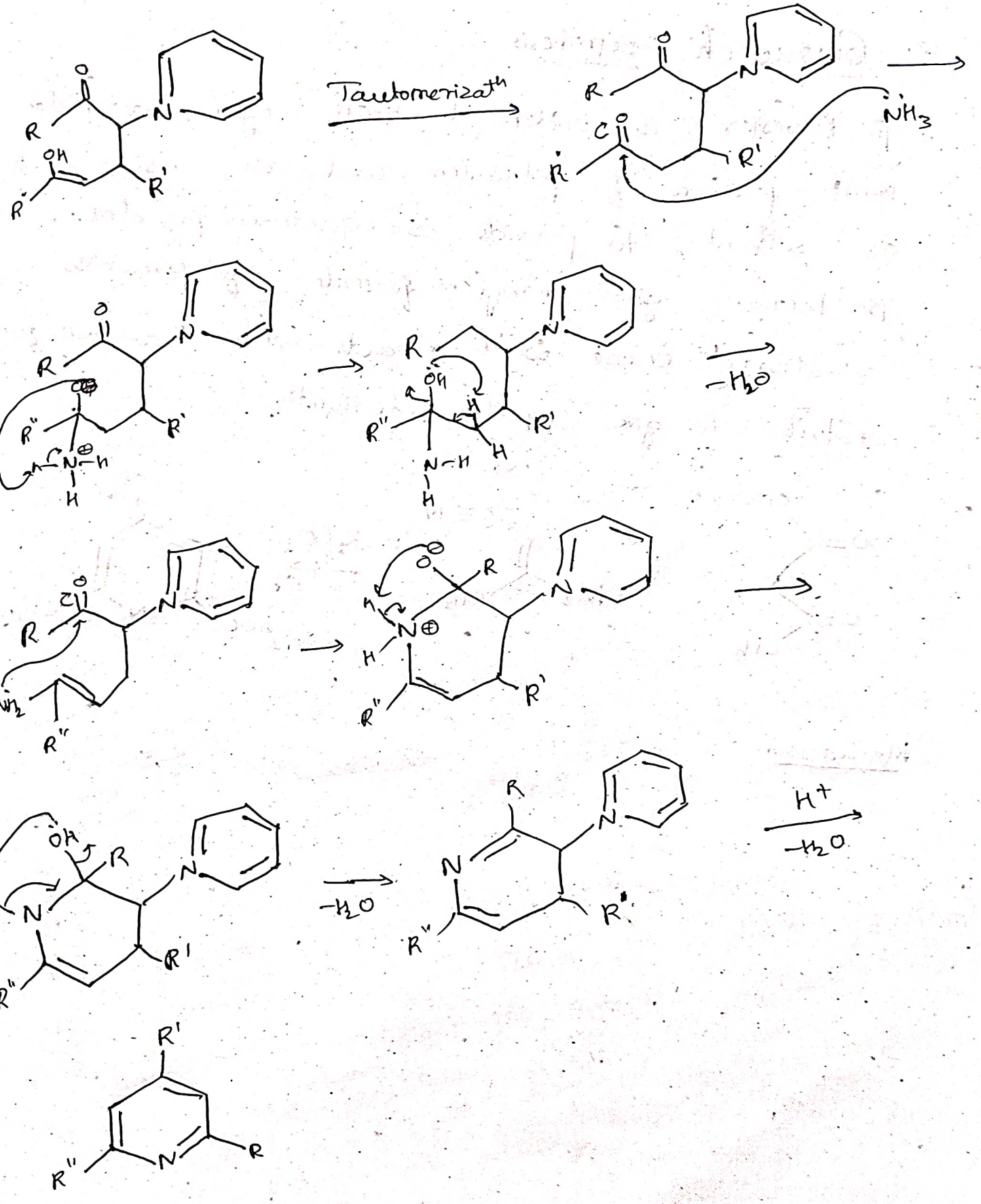
1. Krohnke pyridine synthesis:

It involves the reaction between α-pyridinium methyl ketone salts and α,β-unsaturated carbonyl compounds to generate highly function-alized pyridine



Mechanism:

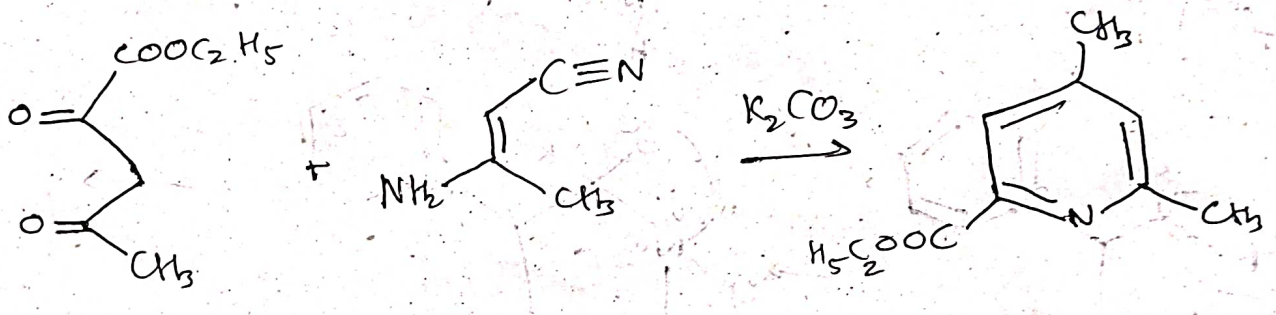



Tautomerizat^n
NH3
-H2O
-H2O
H+
-H2O

2. Guraeschi synthesis

β- Ketoester is condensed with cyanoacetamide with presence of potassium carbonate using acetone as solvent to provide 3-cyano-α-pyridone.

β- Ketoester give ethyl α-formate to provides 3-ethoxy enone which reacts with 3-aminocroty nitrile to give pyridine derivative



Mechanism:

Physical & Chemical properties

Presence of electronegetive nitrogen in the ring causes π-electron defficiency at the positions 2, 4 and 6 while electron density is greater at nitrogen and 3rd position. This deactivates the ring towards the electrophilic attack. Hence electrophilic substitution reactions occur with great difficulty and under forced reaction conditions.

Electrophilic attack at nitrogen

1. Alkylation
2. Sulfonation
3. Acylation

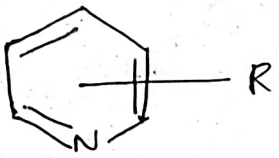
Nucleophilic attack at carbon:

* The nucleophilic reaction takes place at 2nd & 4th positions.

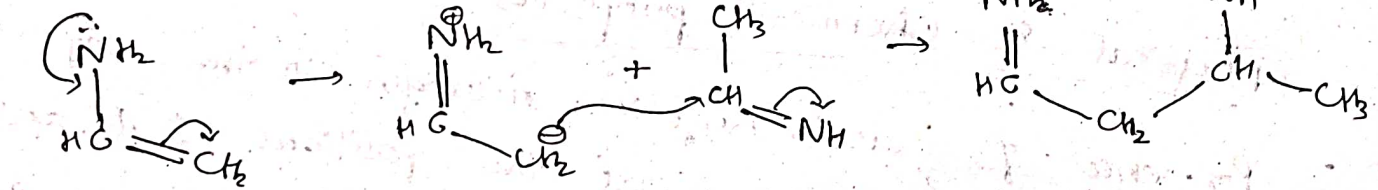
Eg:- Chichibabin reaction.

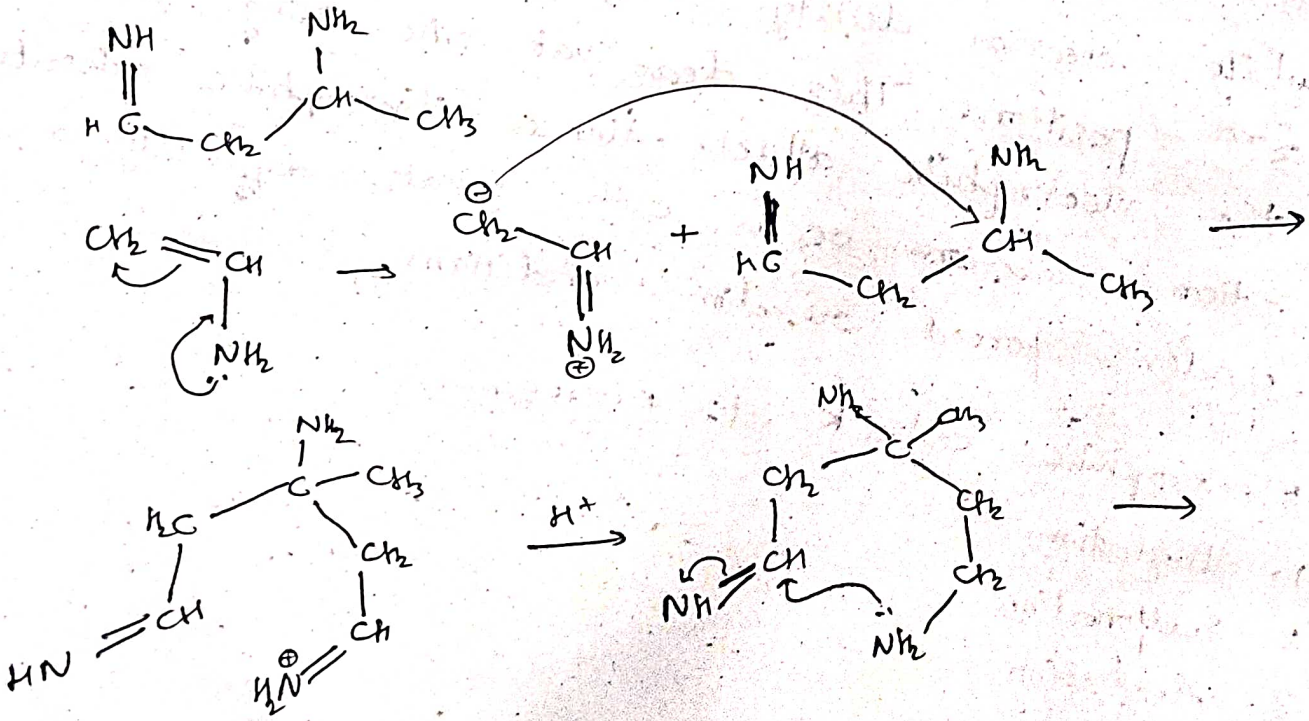
Derivatives of pyridine

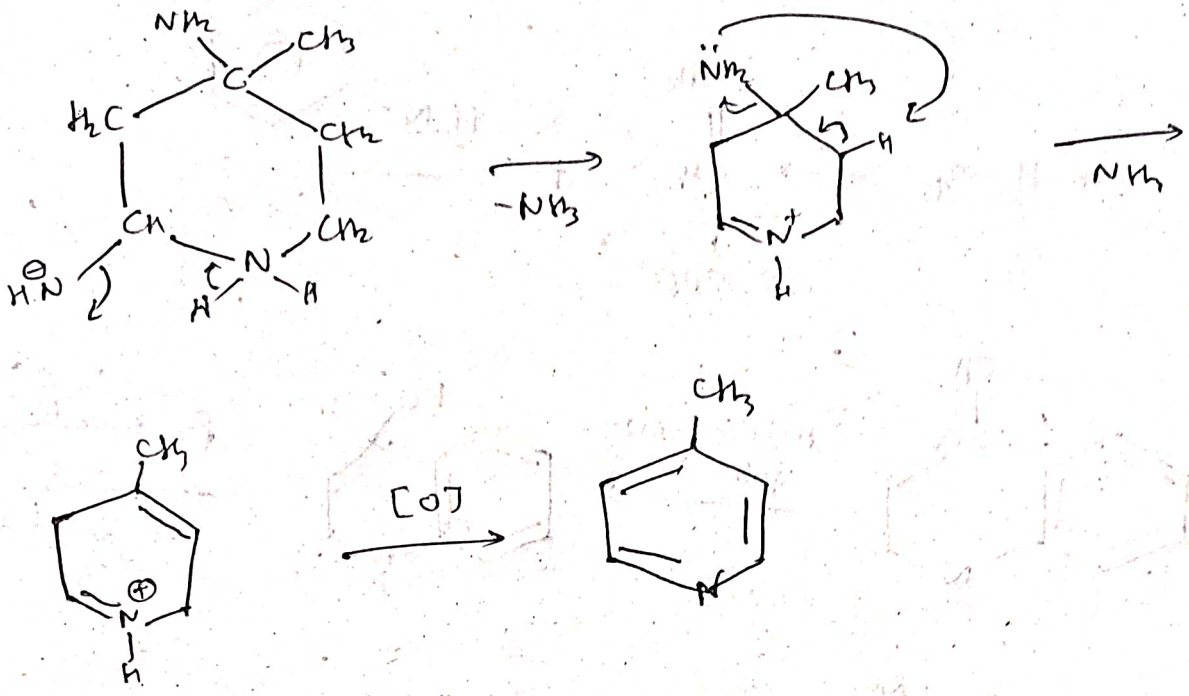
1. Picolines (methyl pyridines)



Mechanism:



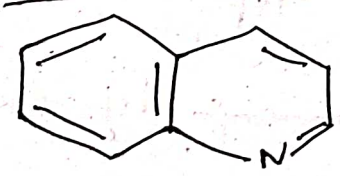




Physical & Chemical properties of Picolines

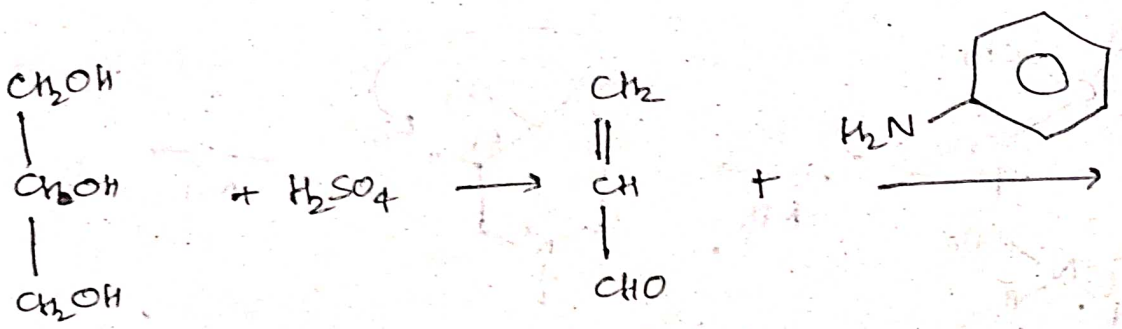
* Picoline is a liquid with B.P- 129°C. They have high Boiling point.
* They undergo electrophilic substitution such as sulfonation, chlorination and alkylation

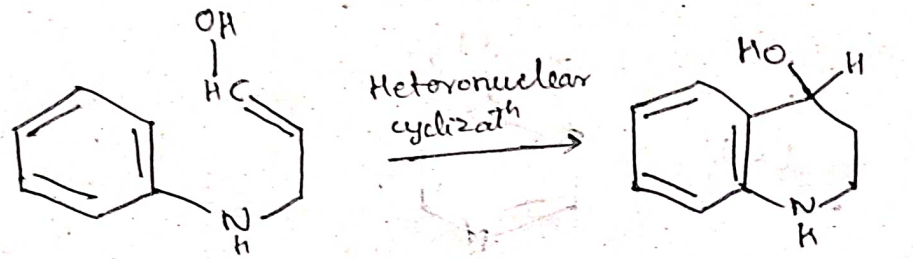
2. Quinoline

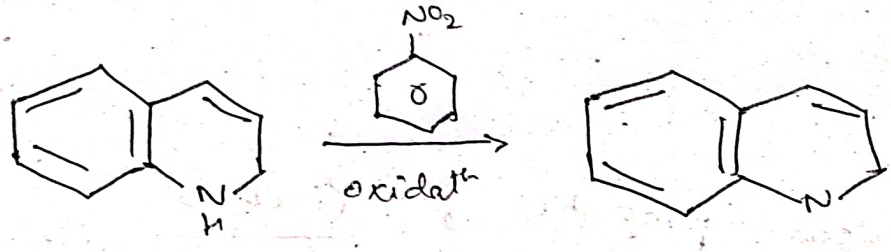


Synthesis:

1. Skraup synthesis







This reaction involves the reaction of aniline with glycerol in the presence of sulfuric acid and a mild oxidizing agent like nitrobenzene. The reaction is proceeded by the dehydration of glycerol to acroline which reacts with aniline to yield 1,2-dihydroquinoline

The mechanism includes following steps.

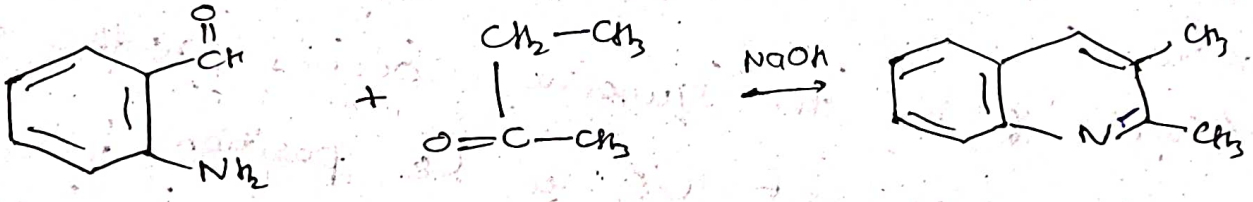
Step 1: Formation of acroline by the reaction of sulfuric acid with glycerine

Step 2: Action of acroline on aryl amine forming addition product.

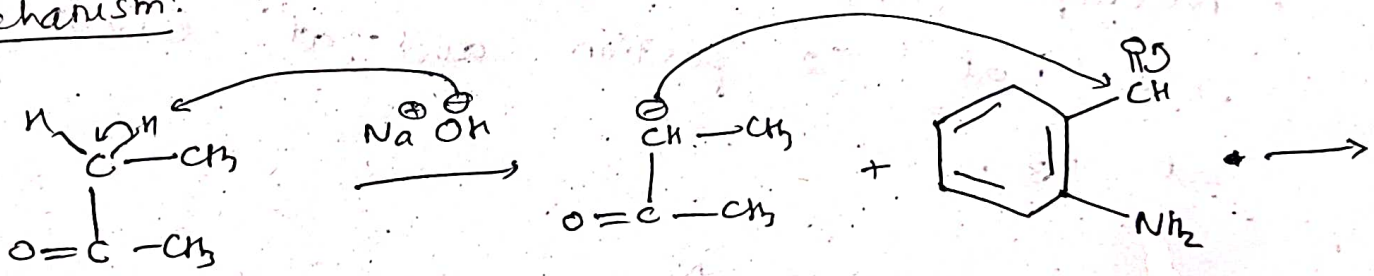
Step 3: Intramolecular electrophilic addition followed be the protonation, dehydration and oxidation to yield quinoline

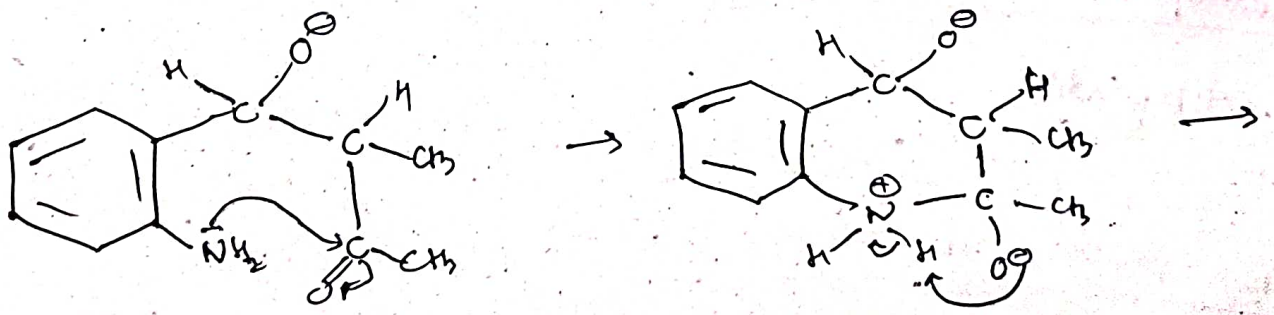
Friedlander synthesis

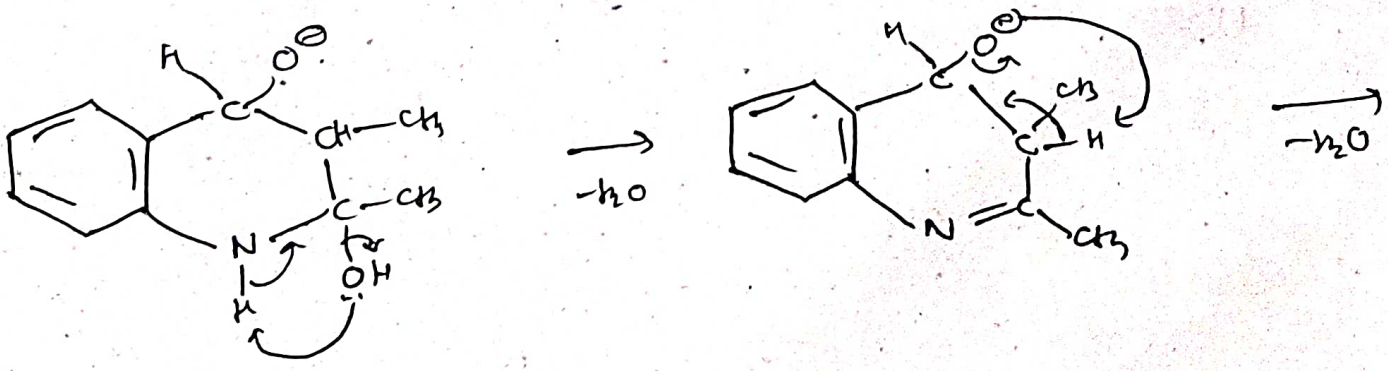
It involves the reaction of with ketone or aldehyde containing active methylene group by base or acid to furnish quinolines

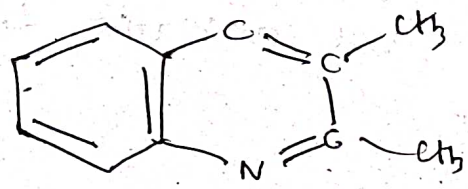


Mechanism:









Physical & Chemical properties of Quinoline

* Most of the reactions of quinoline are analogous to pyridine. It displayes the properties of tertiary amine.
* Attack of on the quinoline occurs in the carbocyclic ring at C-5 & C8 positions.
* Nucleophilic attack is favored in the pyridine ring, at C2 position and at lessere extent at C_3.

Electrophilic sub at N

1. Alkylation

Electrophilic sub at C

1. Halogenation
2. sulfonation