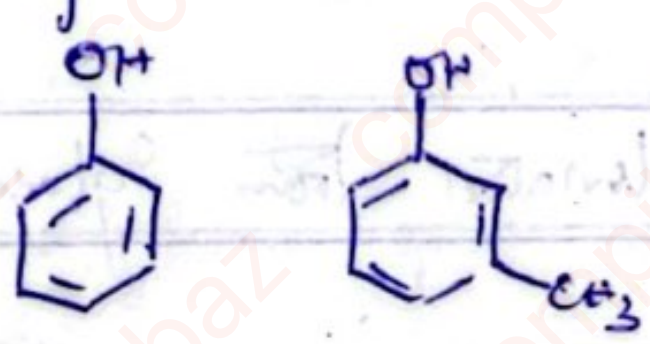
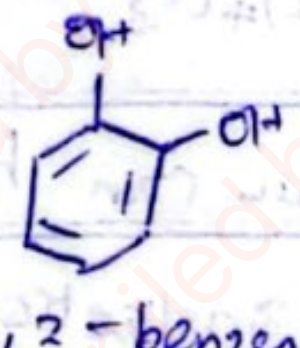
PHENOLS

Structure and Nomenclature: The FG of phenol is a hydroxyl group bonded directly to a benzene ring. Substituted phenols are named as either derivatives of phenols, benzenediols or by common names

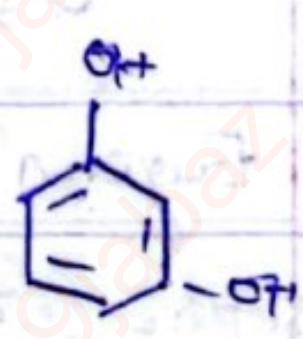


Phenol

3-methyl phenol
m-cresol



Catechol
1,2-benzenediol



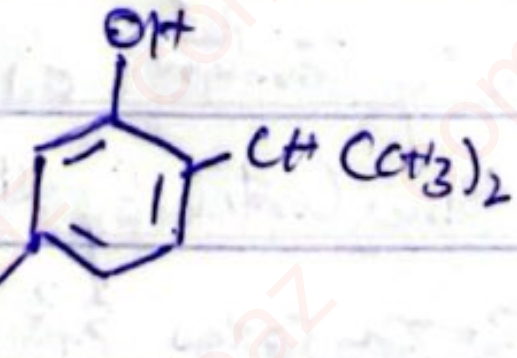
Resorcinol
1,3-benzenediol

Hydroquinone
1,4-benzenediol

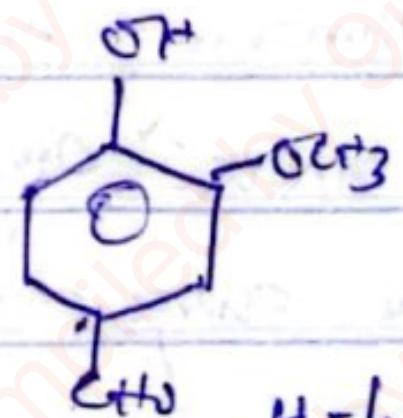
Benzoquinone

Quinone

Phenols are widely distributed in nature. Phenols itself and its homologues are found in coal tar and petroleum. Thymol and vanillin are important constituents of thyme & vanilla bean



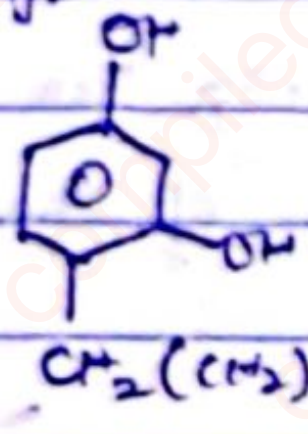
2-isopropyl-5-methyl phenol
(Thymol)



4-hydroxyl-3-methoxybenzaldehyde
(Vanillin)

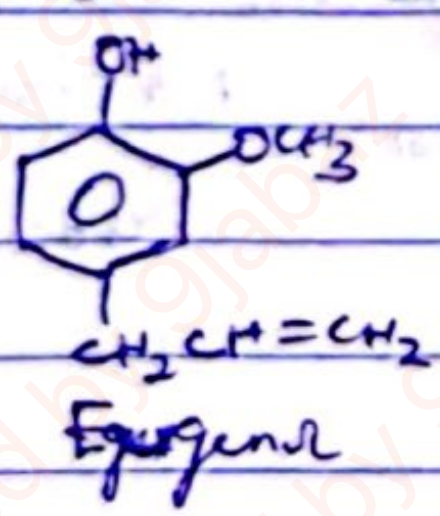
Phenols is a low melting point solid that is soluble in water. In sufficient concentrate it is corrosive to all types of cell.

Hexylresorcinol is used in Surgery as an antiseptic and disinfectant

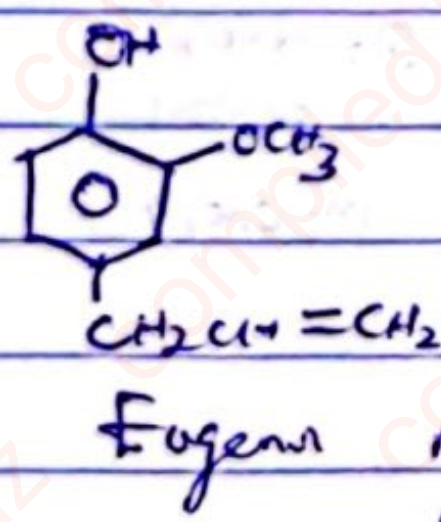


Hexylresorcinol

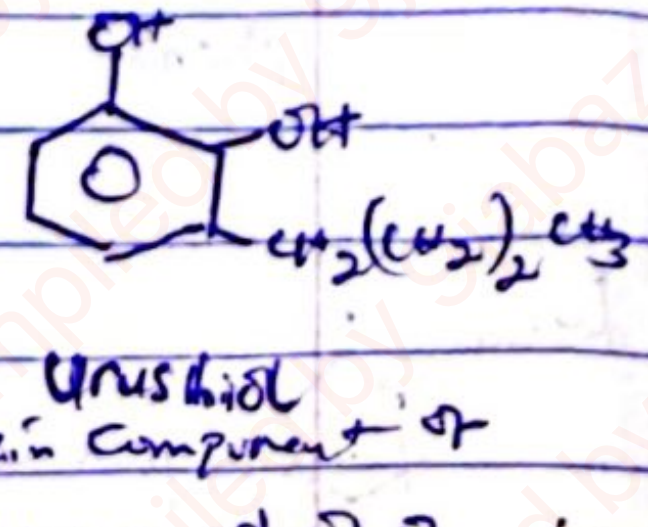
Eugenol which can be isolated from "gloves" is used as a dental antiseptic and analgetic



Eugenol



Eugenol



Urushiol main component of Poisoning

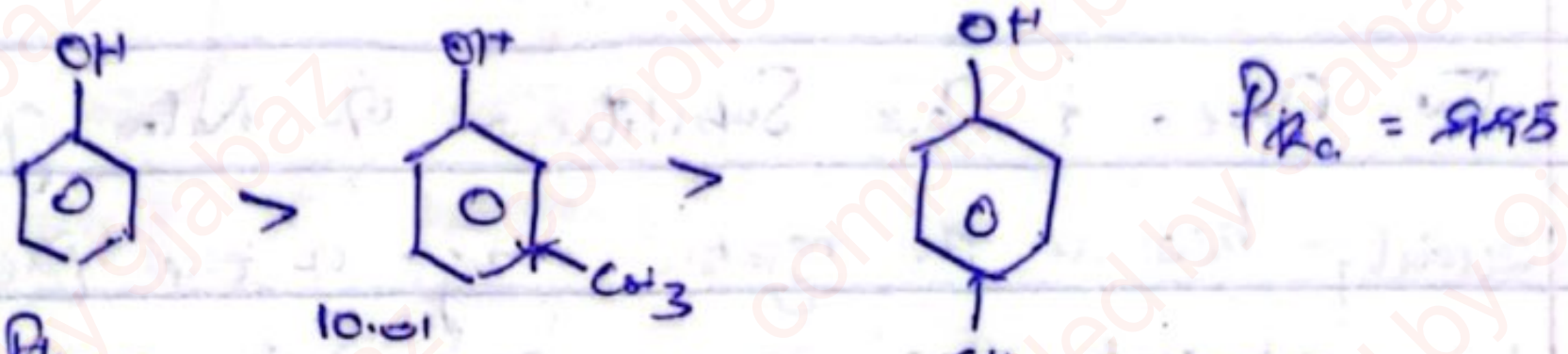
2 ACIDITY OF PHENOLS

Phenols are significantly acidic. The Acidity of phenols is due to a result of the greater stability of the Phenoxide ions. The negative charge on the Phenoxide ion is delocalized by resonance. The two Contributing structure on the left Place the negative charge on the Oxygen. The three Contributing structure on the right Place the negative charge on the Carbon at the Ortho & Para Positions of the ring. Taken together this Contributing structure delocalize the negative charge of the Phenoxide ion over four atoms

Ring substituent especially halogen and nitro groups have a significant effect on the acidity of phenols by a combined effect on the acidity of phenol by a combination of inductive and resonance effect

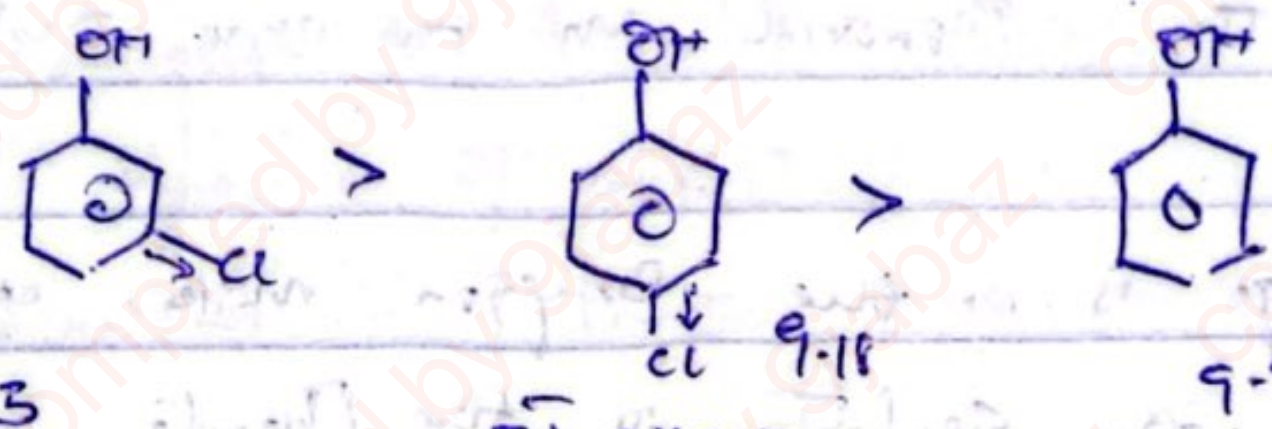
+I effect → Carbon get more electron from substituent

-I " → " loses " " " "



P_{Ka} = 9.95 Phenol m-cresol p-cresol P_{Ka} = 9.95

M-chloro phenol are stronger acid than phenol



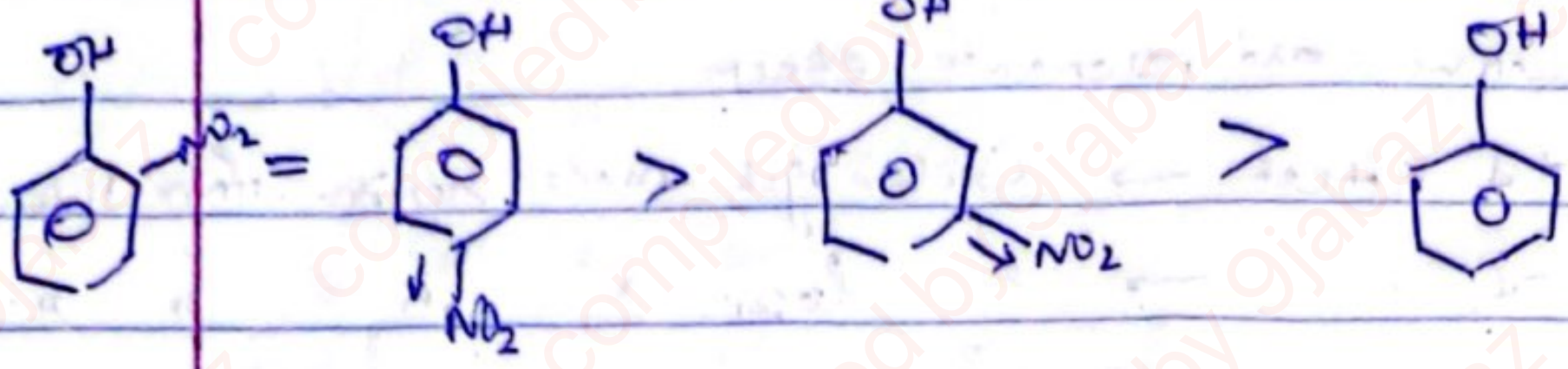
P_{Ka} = 8.83

The lower acidity of phenols carry methyl group due to polarization of C-C bond by the electron releasing inductive effect of the sp^3 carbon of the methyl group additionally the resonance structure contributes

The presence of halogen attracts electron away from the aromatic ring stabilizing the ring

Para Nitro phenol & meta-Nitro phenol are more acid

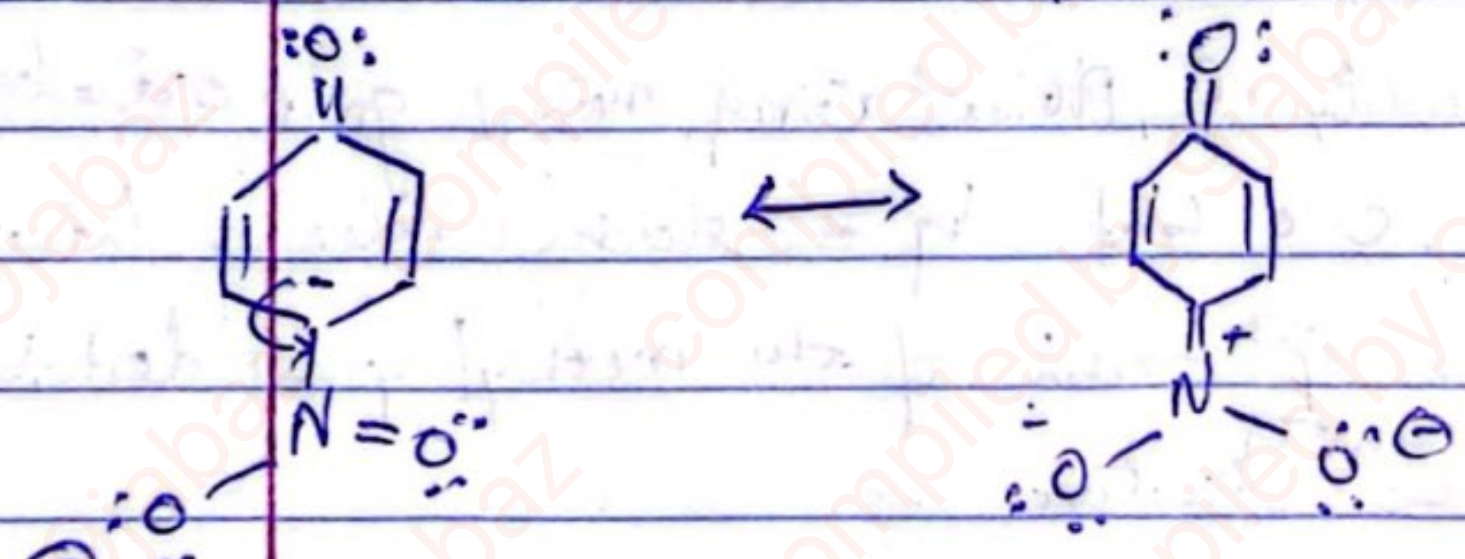
Acid than phenol due to their electron withdrawing effect hence stabilizing the ring or decolourizing making it more acid



The Ortho & Para Substitution of Nitro group, increase acidity because the negative charge of the phenoxide ion is delocalized unto the oxygen of the Nitro group hence further increase the resonance stabilization of the phenoxide ion

NB The more stable the Phenoxide ion the more acidity phenol become,

The negative charge is on the Oxygen makes it more stable & increase the acidity of the Phenolic



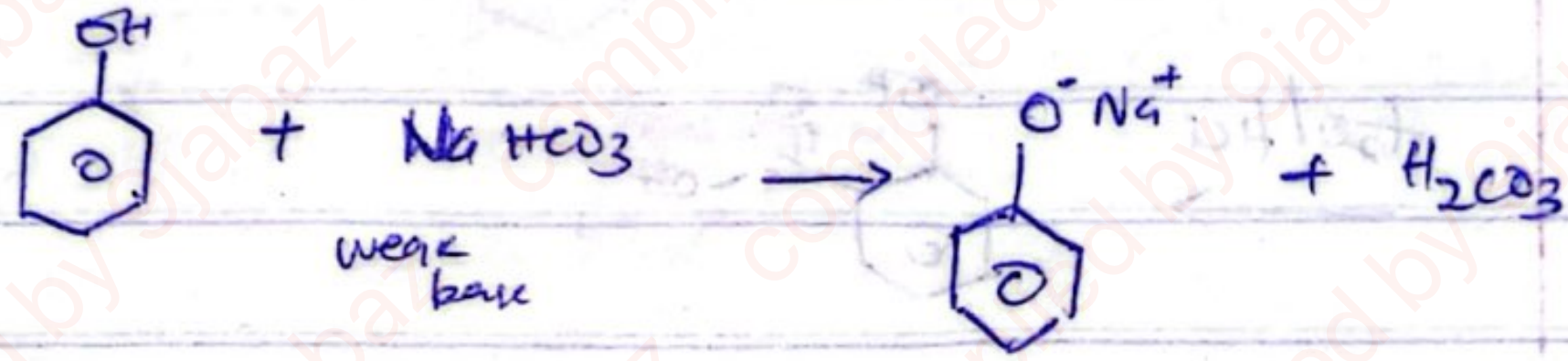
Arrange in increasing Acidity

2,4-dinitro phenol, 2,4,6-trinitro phenol, phenol and benzylalcohol

Arrange in order of increasing acidity

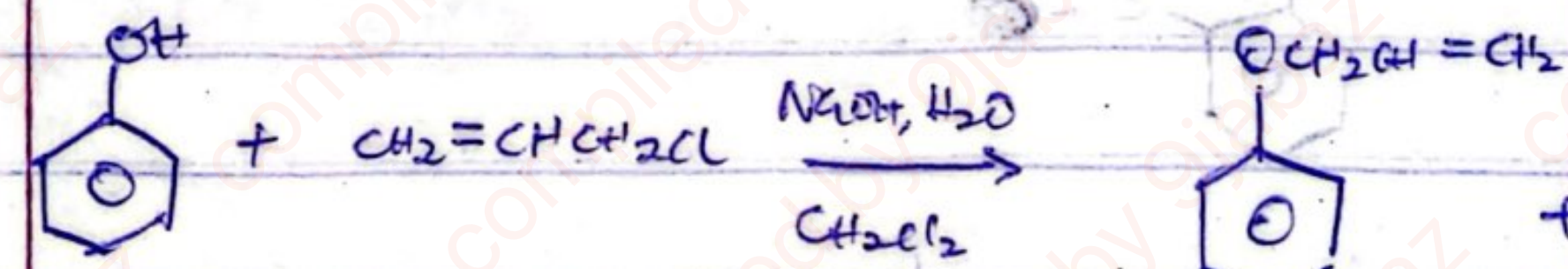
3 Acid-base Reaction of Phenols

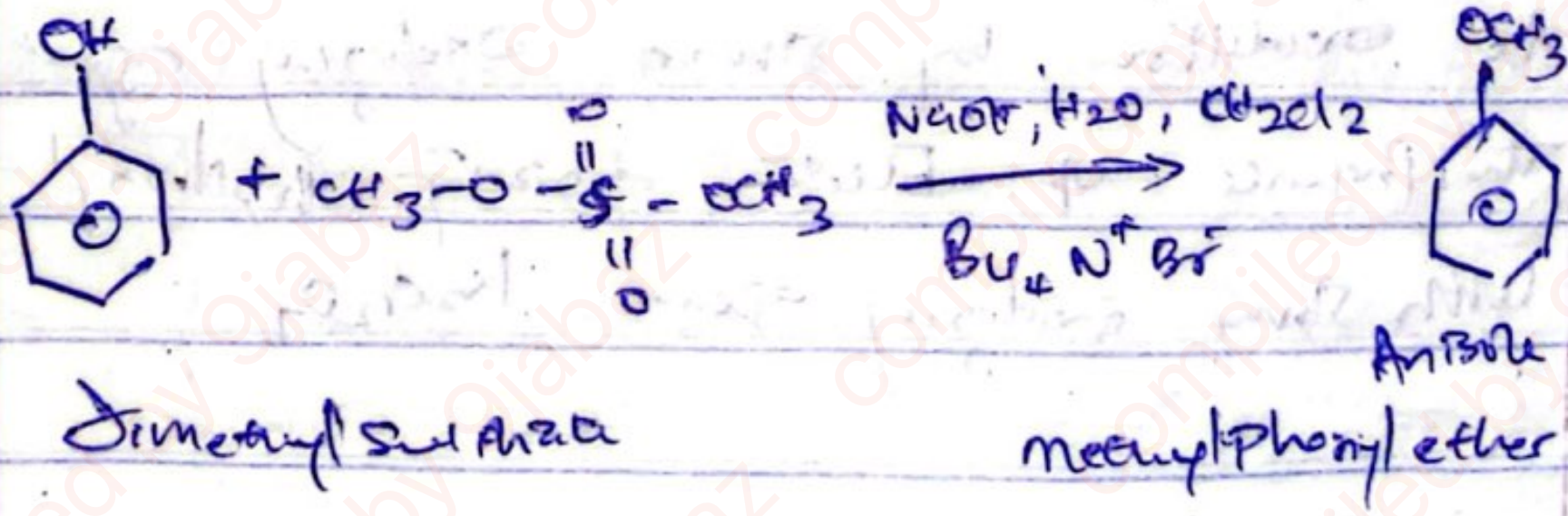
Phenols generally are weak acids and reacts with strong bases such as Sodium hydroxide NaOH to form a soluble salt. $HCl + NaOH \longrightarrow NaCl + H_2O$



4 PREPARATION OF ~~ALKYL~~ ~~ARYL~~ ETHERS

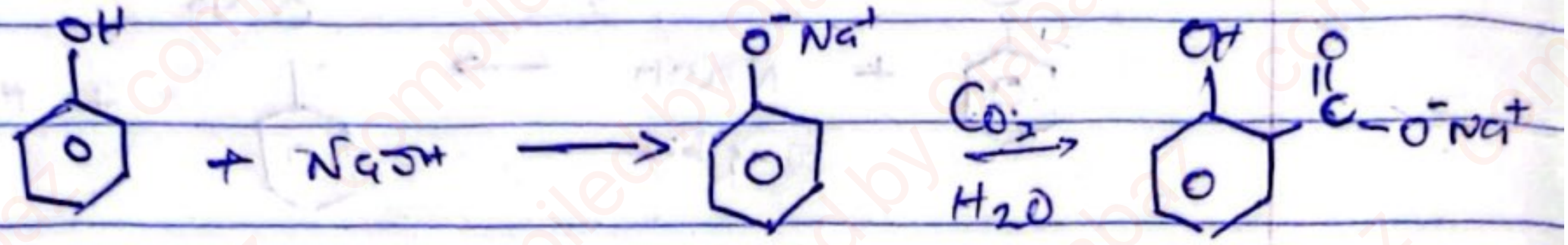
The Synthesis of alkyl phenyl ether involve nucleophilic displacement of a Primary halide in ⇒ typical ran called Williamson Synthesis

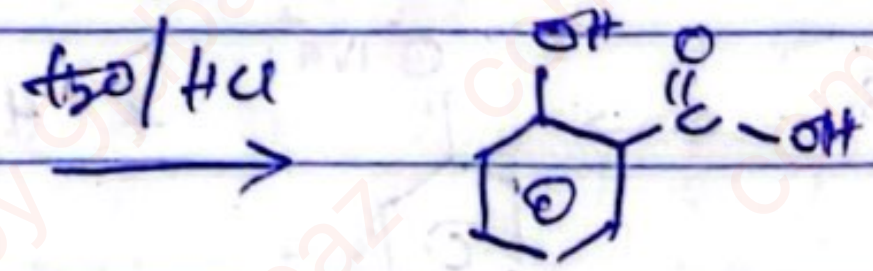




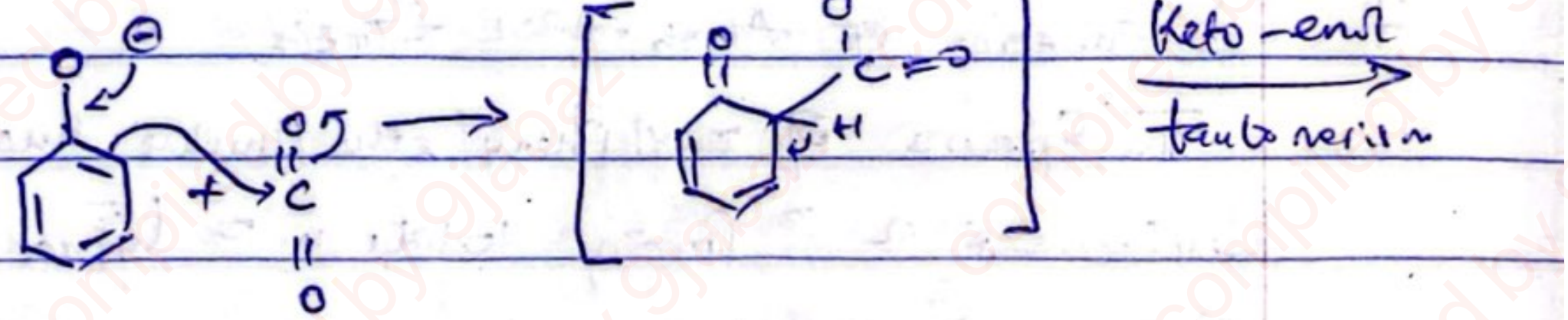
5 KOLBE CARBOXYLATION

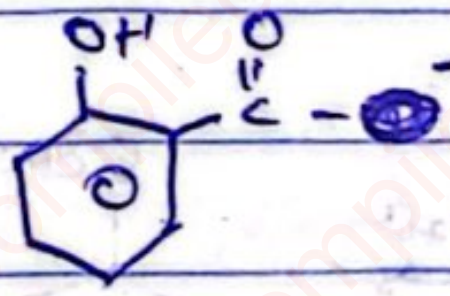
Kolbe carboxylation involves the synthesis of Salicylic acid whereby phenoxide ion reacts with Carbondioxide to give Carboxylate acid salt





Mechanism



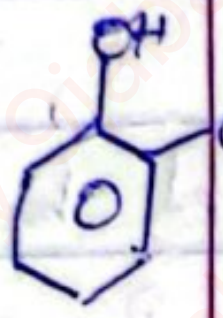


6 OXIDATION OF QUINONES: Phenols are susceptible to oxidation by strong oxidizing agent due to the presence of Electron donating hydroxyl group with strong oxidizing agent $K_2Cr_2O_7$

Hint: Structures Raw Corrections,
Products, Reactants,
- Mechanism of Rxn.
- Starting with (laboratory
Exp. from Plants show
how to Prepare organic
IUPAC names

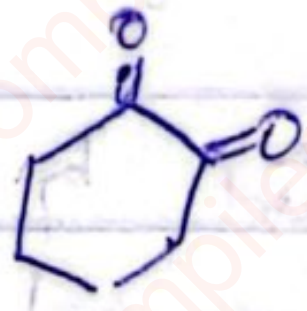
$K_2Cr_2O_7$
H_2SO_4

1,4-benzoquinone
(P-quinone)



Catechol

$Cr_2O_7^{2-}$
H^+

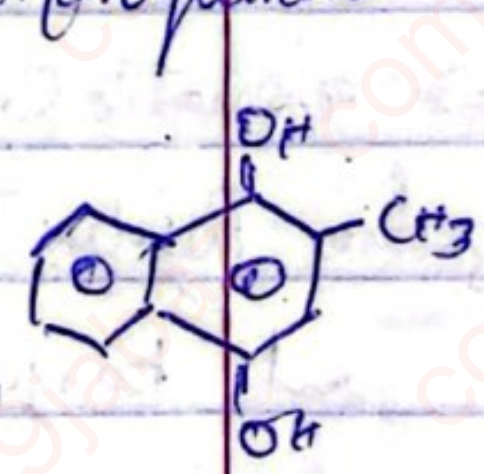


1,2-Benzoquinone
O-quinone

Hydroquinone

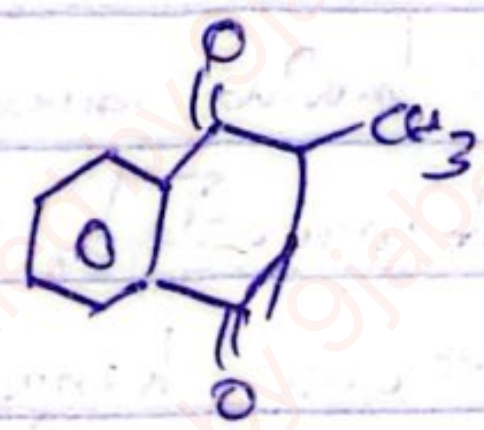
$Cr_2O_7^{2-}$
H^+

1,4 benzoquinone
P-quinone



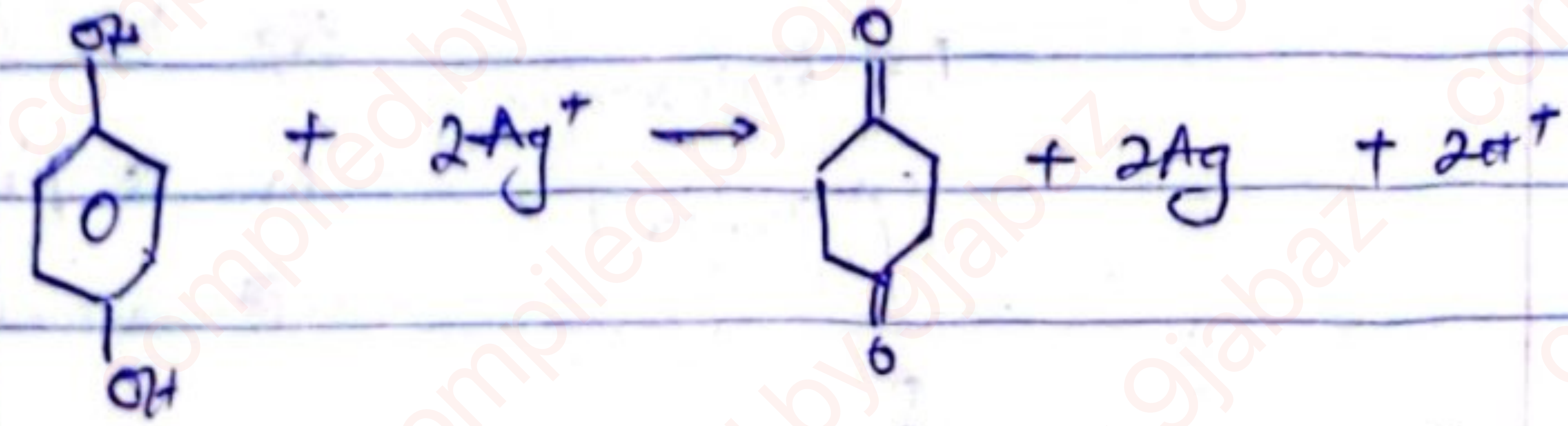
Menadione
2-methyl-1,4-naphthaquinone

CrO_3,



A commercial application of Quinone is the black and white Photography. The Black and white film is coated with the Emulsion of silver bromide or silver iodide crystals which become activated by exposure to light. The Activated

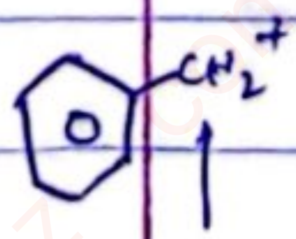
In the developing stage to metallic Silver Silver ion are reduced to their respective state by hydroquinone which at the same time is Oxidized to quinone



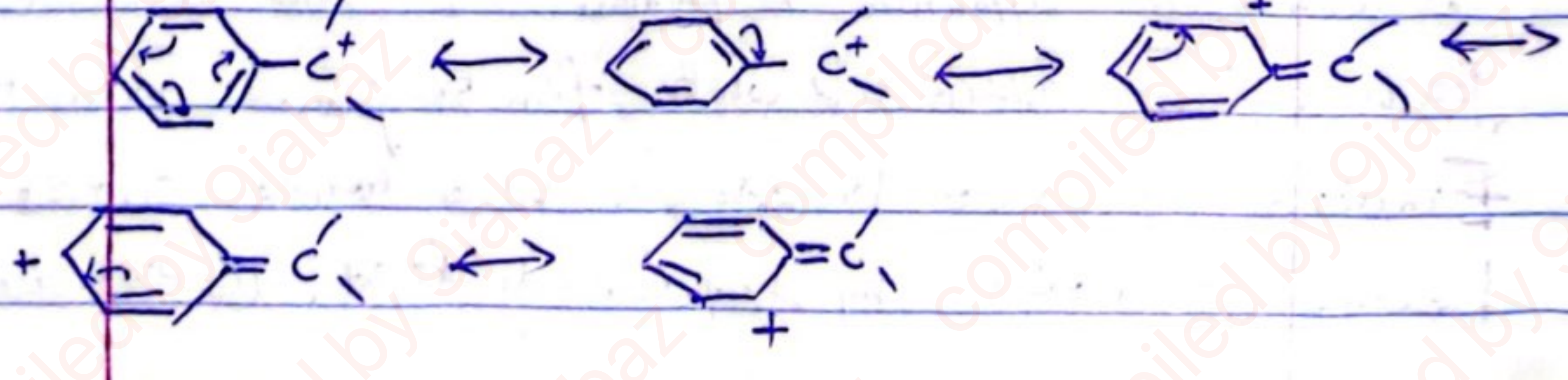
All Silver Halides not activated by light and reduced by Intermediate where hydroquinone is removed in the fixing Process and the result is a black image (-ve) left by deposited metallic Silver where the film have been struck by light.

A REACTIONS OF BENZENE

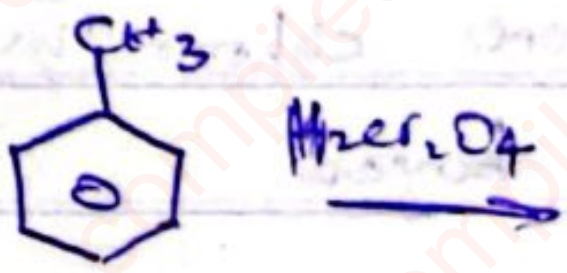
Reaction of a benzylic Position



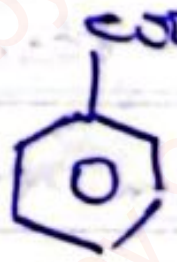
The reaction involving alkyl side chain of aromatic Compound Occur Predominately on the benzylic Position. This Benzylic Carbon is because benzylic Cation and benzylic radicals are easily formed because of resonance Stabilization of these Intermediates



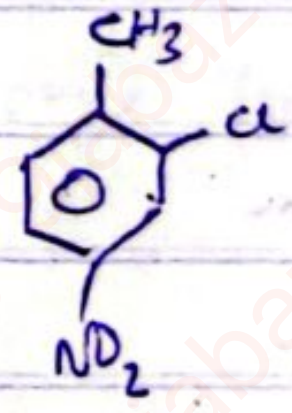
1. Oxidation: Toluene reacts  with strong oxidizing agent $H_2Cr_2O_4$ to form under vigorous conditi to form benzoic acid

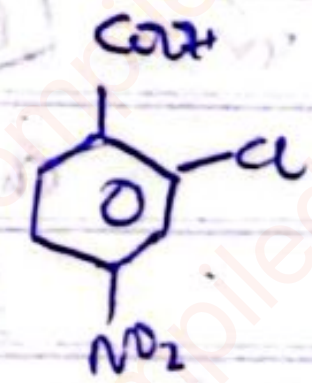


Toluene



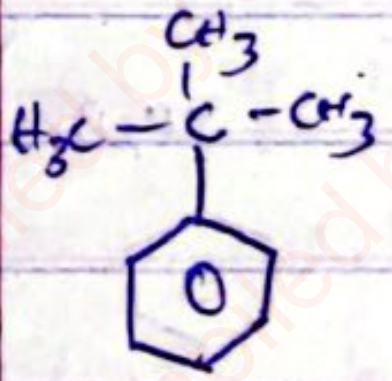
Benzoic acid





Condition

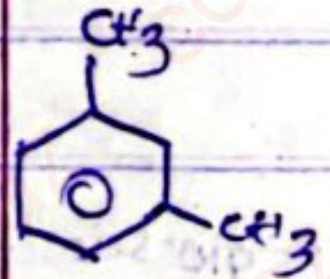
1. There must be presence of hydrogen. No hydrogen No Rxn.

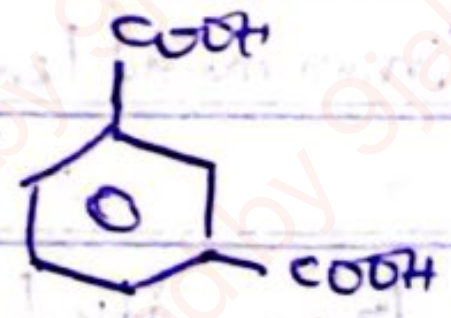


No Rxn.

3. p-butyl benzene

Oxidation of Xylene:



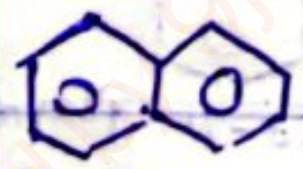


M-xylene

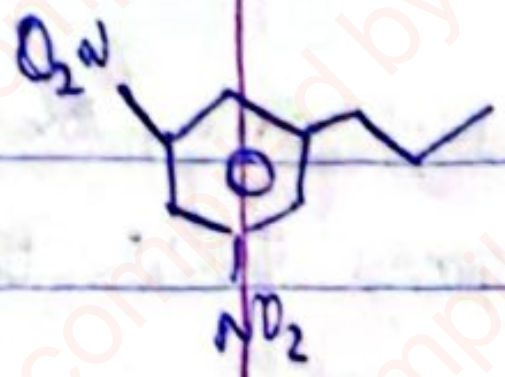
Isophthalic acid

1,3-benzene dicarboxylic acid.

Examples

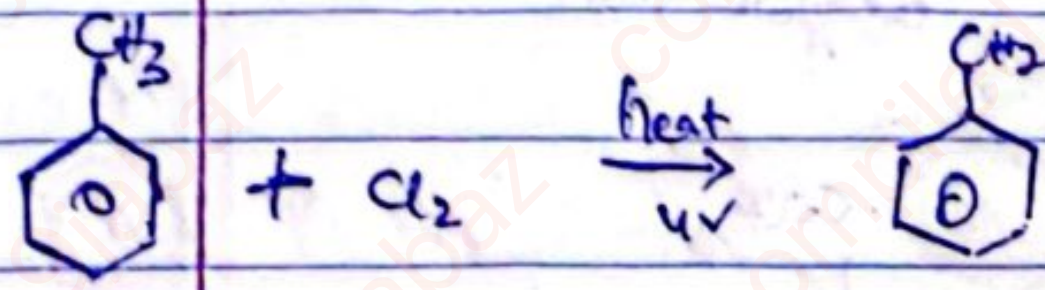
1.  + O_2 $\xrightarrow[350^\circ C]{V_2O_3}$ A

Naphthalene

ii 

$H_2Cr_2O_4$ B

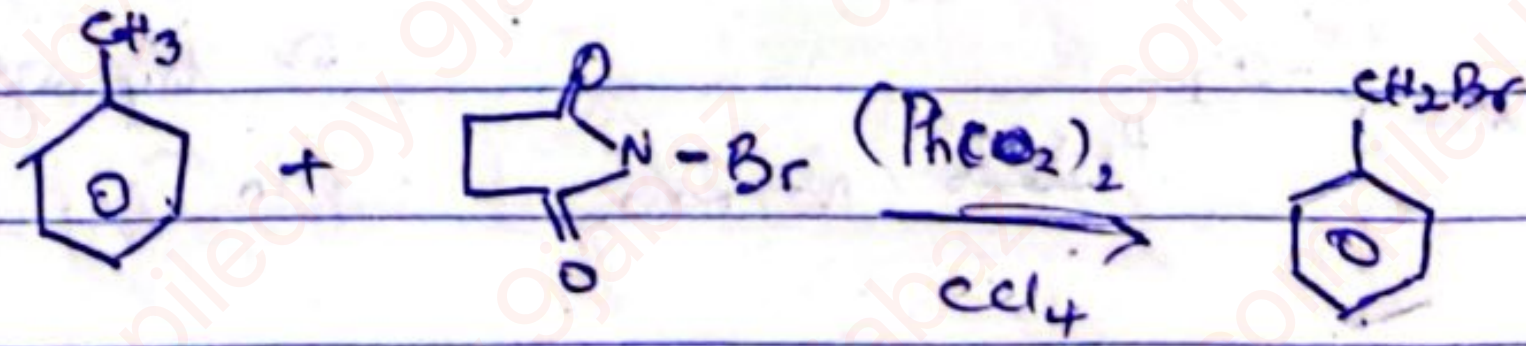
2 HALOGENATION : Toluene reacts with chlorine in the presence of heat / light to form chloro methyl benzene



Toluene + Cl_2 $\xrightarrow[uv]{Heat}$ Chloro methyl benzene

Benzyl chloride

• Toluene reacts with N-bromo succinimide in Presence of Peroxide

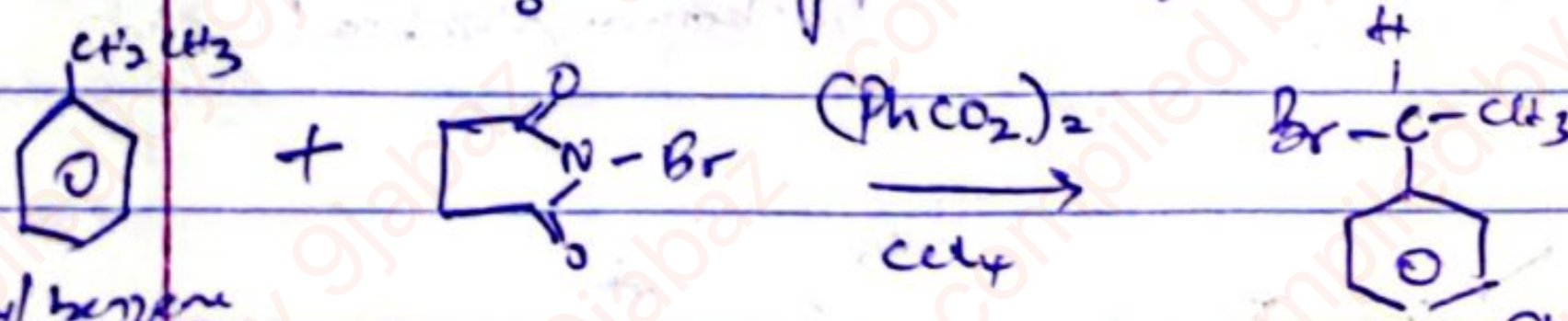


Toluene + N-bromo succinimide $\xrightarrow[CCl_4]{(PhCO_2)_2}$ Bromo methyl benzene

NBS

Catalyst is form bromo methyl benzene

Halogenation 2 → larger Alkyl side chain is regio-selective because of resonance stabilization of the benzylic radical intermediate

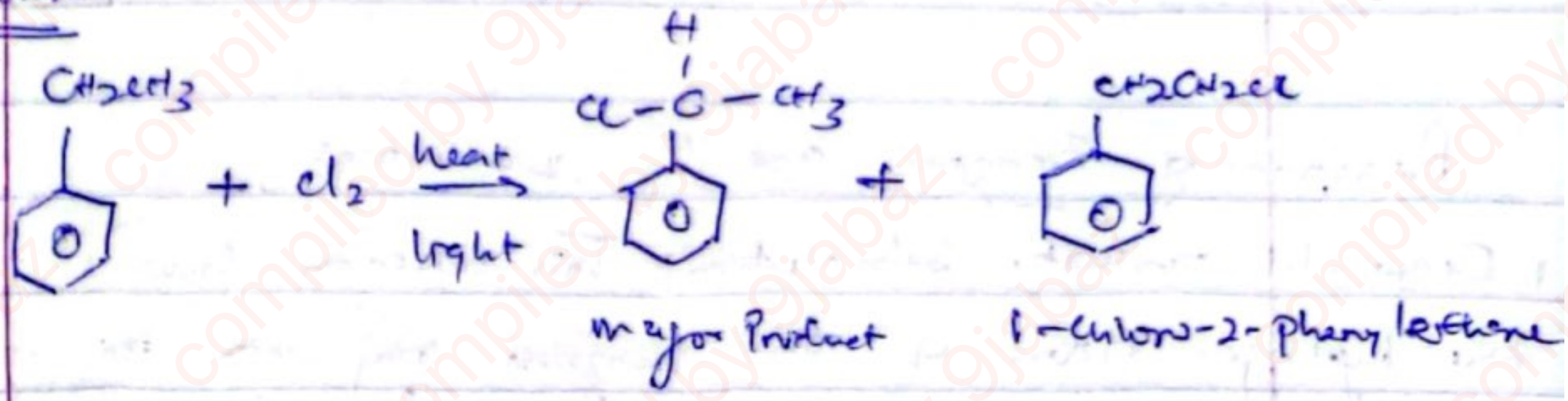


Ethyl benzene + N-Br $\xrightarrow[CCl_4]{(PhCO_2)_2}$ 1-bromo-1-phenyl ethane

Bromination is taking place on CH_2 not CH_3 because of resonance

stabilization and it is regio selective

With chlorine



NB With bromine you have one Product but in chlorine you have 2 products.

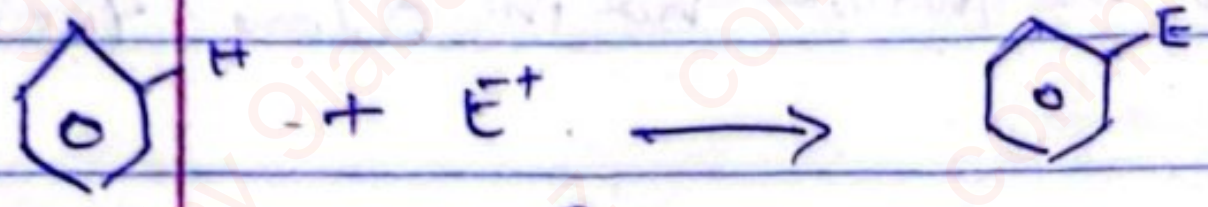
3. Hydrogenolysis of Benzyl ethers

Benzyl esters are formed by treatment of alcohol with phenol use benzyl chloride in the Presence of a base such as Triethyl amine or Pyridine. They are useful Protective agent for the hydroxyl groups of alcohols and phenols

Hint You can be able from Simple laboratory reagent Propose how the 2-(2-propenyl) phenol be converted to 2-(3-hydroxypropyl)

Reaction of Benzene and its Derivatives

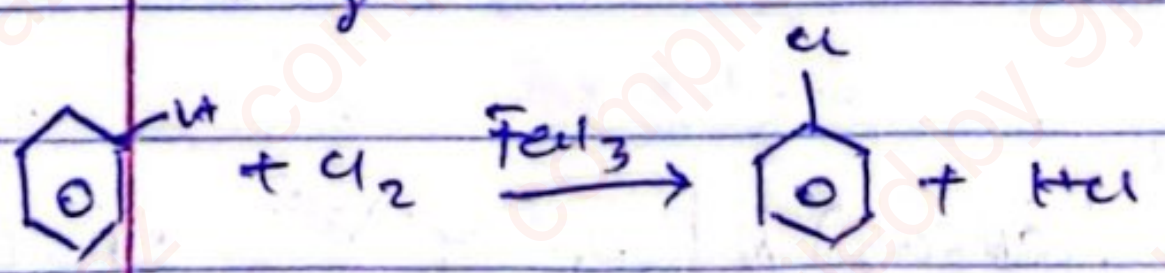
1. Electrophilic aromatic Substitution: This reaction involves replacing the hydrogen atom of the benzene ring with an electrophile to form electrophilic Substituted Product.



A. chlorination & Bromination

i. Cl_2-E ; it polarize and it is closer to the centre in the Positive side than -ve side

Chlorination reaction with benzene in Presence of $FeCl_3$ or $AlCl_3$ to form chlorobenzene

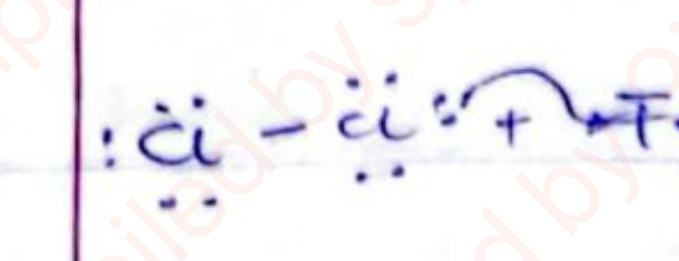


Mechanism:

It involves 3 steps

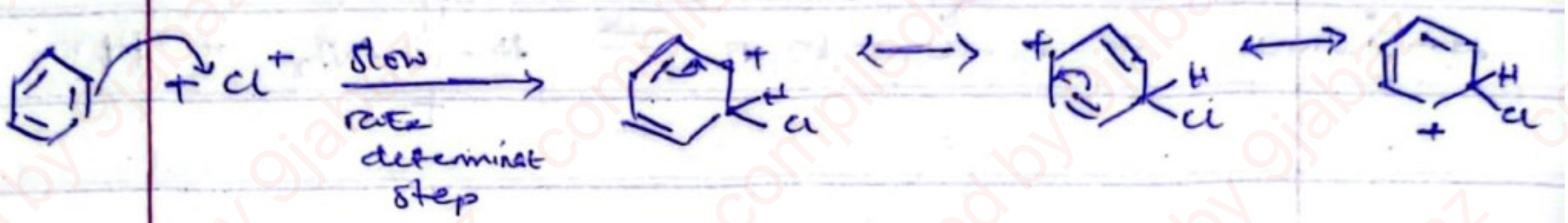
Step 1 : Reaction btw chlorine Lewis base and Fe^{3+} chloride

$FeCl_3$ Lewis acid to give Iron Pair containing chloronium ion

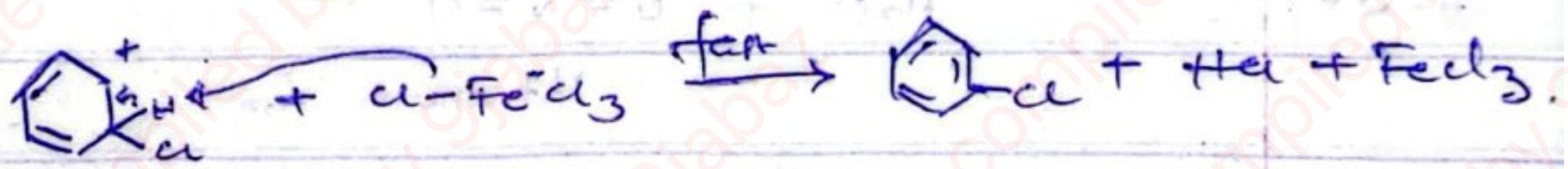


Chloronium ion

Step 2: Involves the attack of the chloronium ion on the Pi system on the aromatic ring gives a resonance stabilized cation intermediate



Step 3: Proton transfer from Cation intermediate to regenerate the aromatic ring

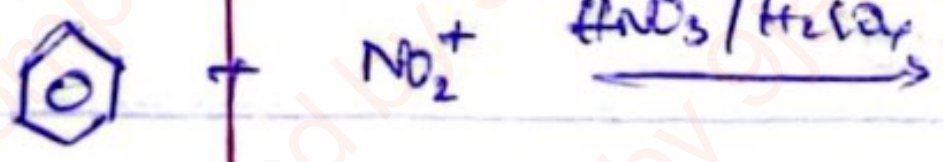


a For Bromination

* Hint
learn the mechanism similar as chlorination.

b. Nitration

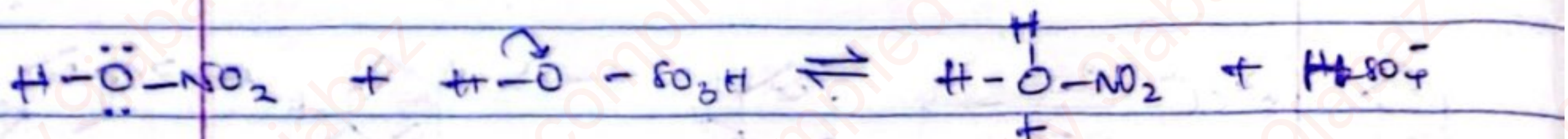
The Nitrating agent is called HONO (NO_2^+) : Nitronium ion NO_2^+ generated in situ from the mix of Nitric acid and Sulfuric acid



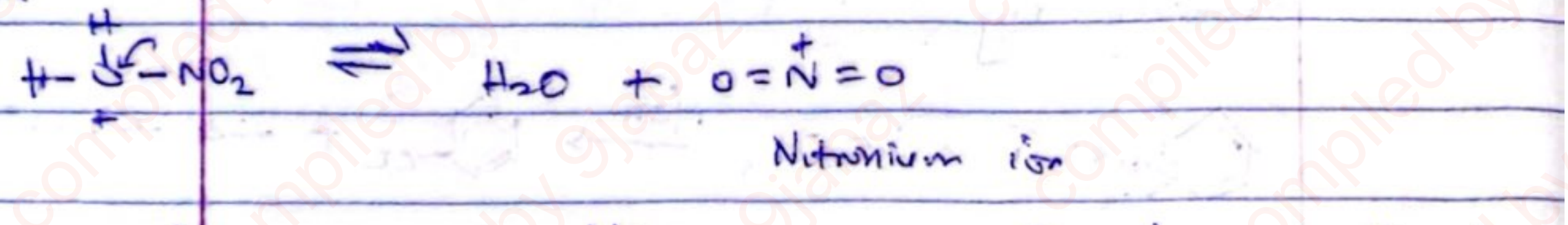
Example  + $HNO_3 \xrightarrow{H_2SO_4}$ A

Write the mechanism of the above. four steps

Step 1: Proton Transfer from Sulfuric acid to the -OH group of the Nitric acid to give a Conjugate acid of the nitric acid.

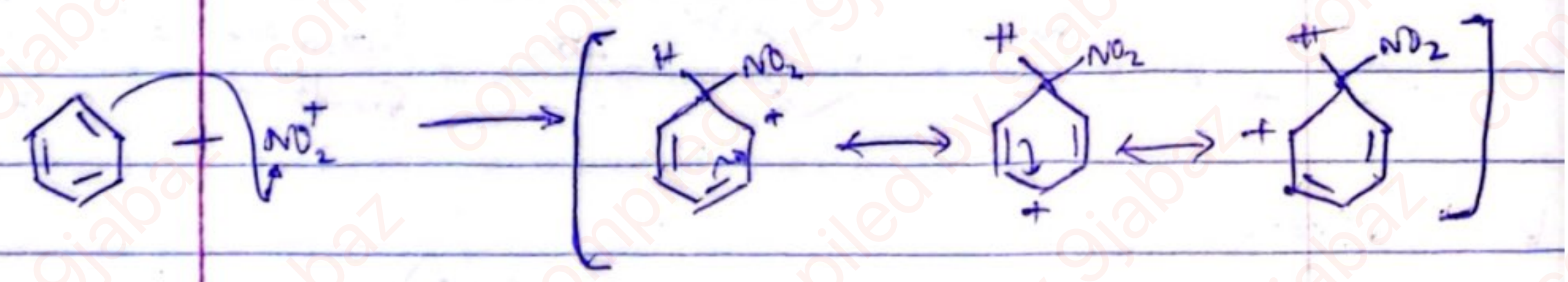


Step 2: Loss of H_2O to the Conjugate acid to give Nitronium ion

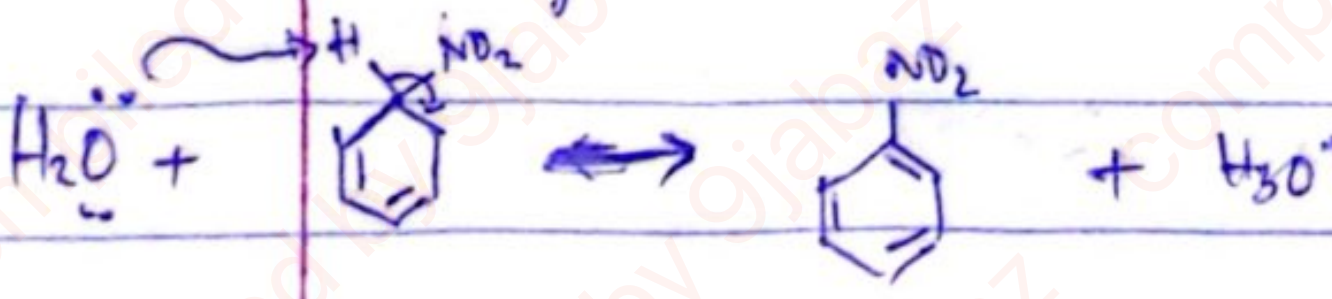


Nitronium ion

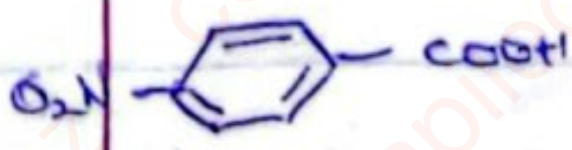
Step 3: Attack of the Nitronium ion on the benzene ring to Give the resonance stabilized carbon intermediate



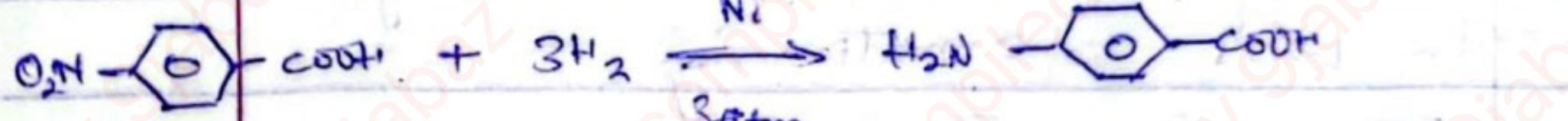
Step 4: Proton transfer to either H_2O or the HSO_4^- to give Nitrobenzene



Nitrobenzene can be reduced to amino benzene by hydrogenation in the presence of a transition metal catalyst such as Ni, Pd or Pt

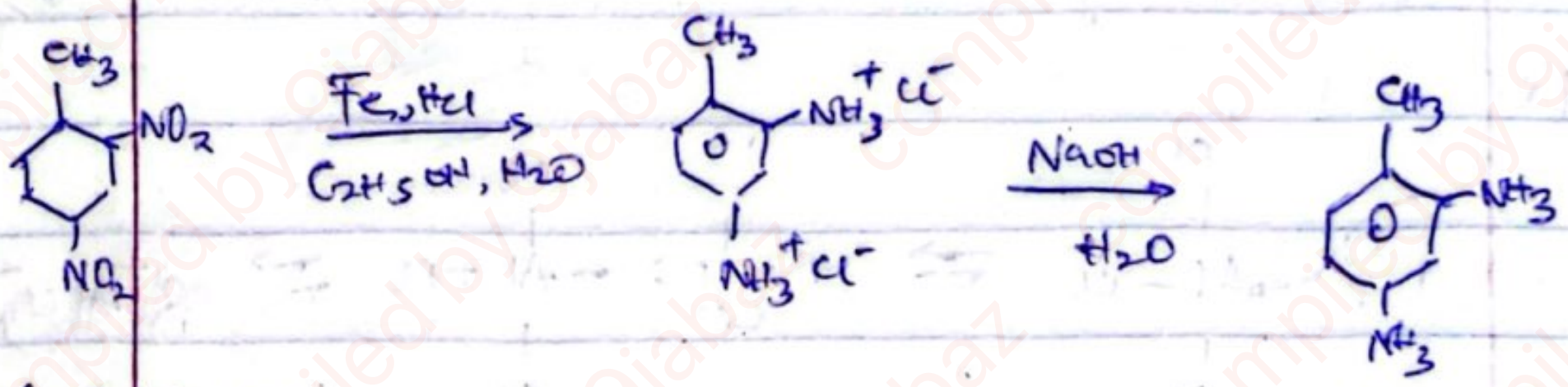


4-nitrobenzoic acid



4-nitrobenzoic acid

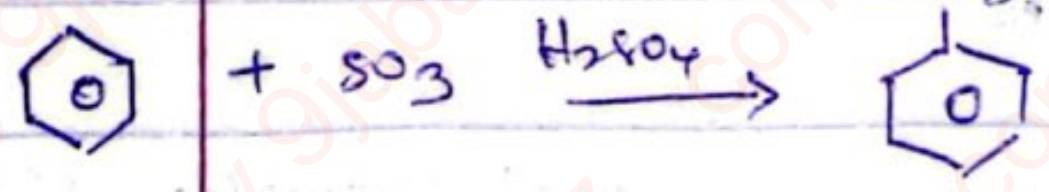
4-aminobenzoic acid



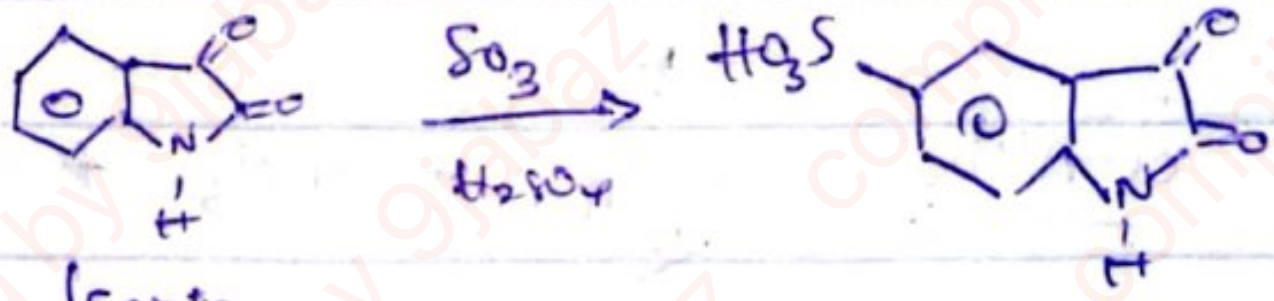
2,4-dinitrotoluene

2,4-diaminotoluene

Sulfonation : There are two ways to sulfonate benzene : i) fuming Sulfuric acid (SO_3) : Benzene is sulfonated by using conc H_2SO_4 containing SO_3 dissolve sulfur trioxide (Fuming sulfuric acid).



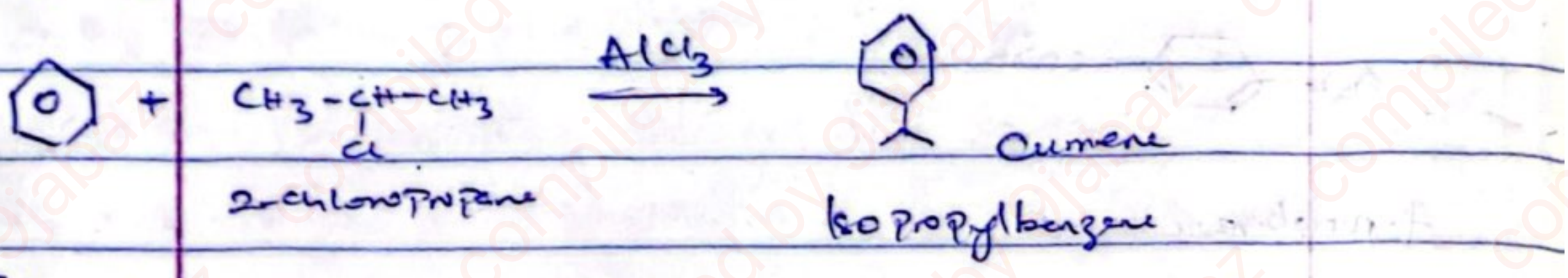
Example



Isatin

Hint Look for the mechanism of sulfonation.

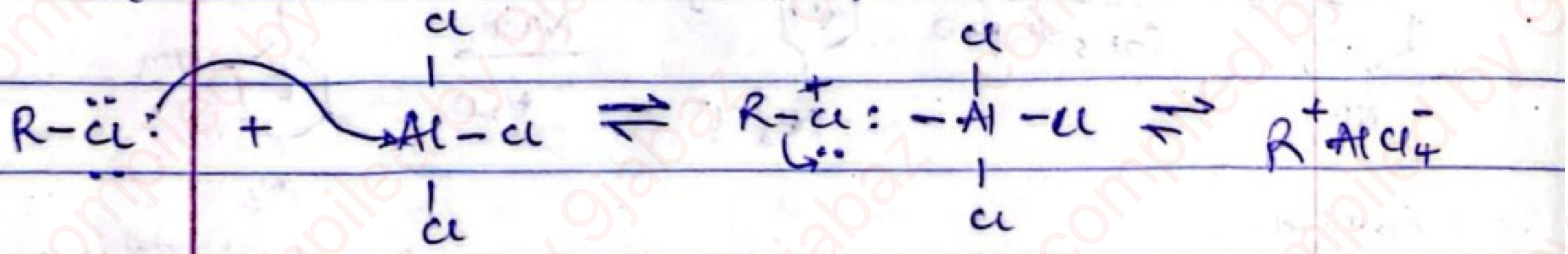
Friedel Craft Alkylation: This is the rxn of benzene with alkyl halide in the presence of aluminium chloride to form alkylbenzene



Friedel Craft Alkylation is the most efficient way of forming new Carbon-carbon bonds to aromatic ring

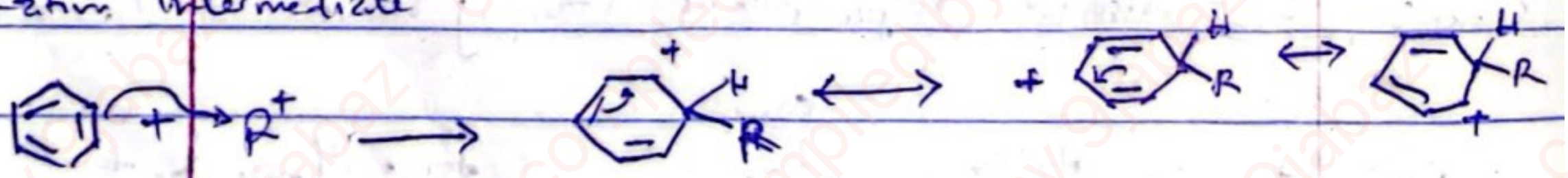
Mechanism For the Rxn: Involves 3 steps

Step 1: Rxn of the alkyl halide with aluminium trichloride to give an ion pair

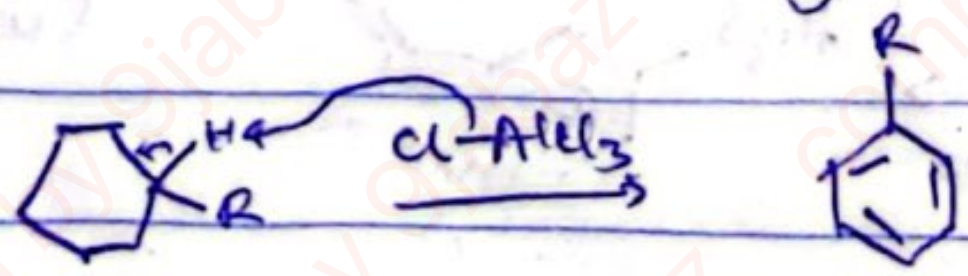


R^+ - electrophile R^- - nucleophile

Step 2: This is the reaction of the alkyl carbocation with the π cloud of the aromatic ring to give the resonance stabilized Cation intermediate



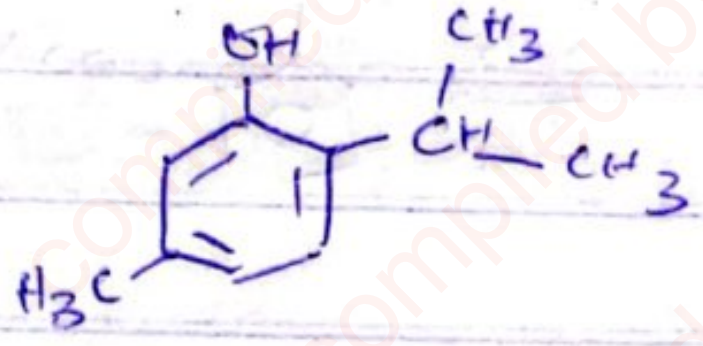
Step 3: Proton Transfer to regenerate the aromatic character of the ring



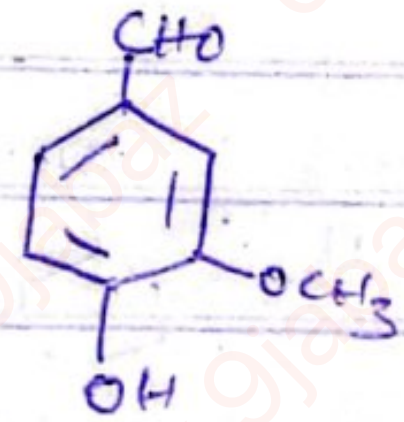
Correction of Test Quesita

Write the structure of the following Compounds

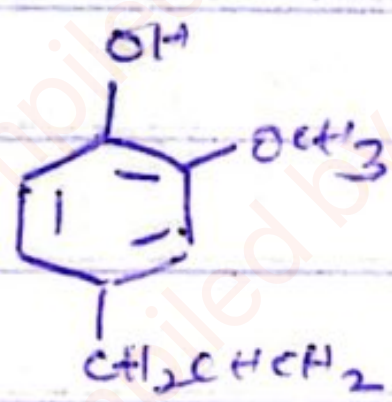
1. 2-Isopropyl-5-methylphenol



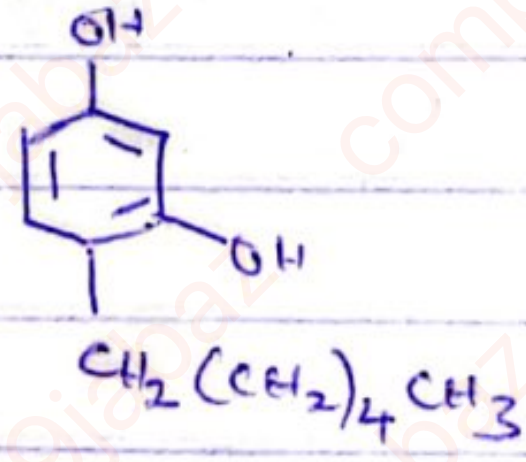
ii 4-hydroxy-3-methoxybenzaldehyde



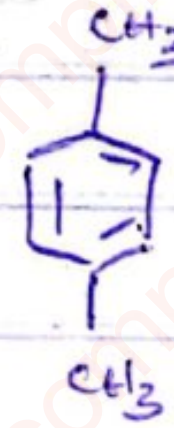
iii Eugenol



iv Hexylresorcinol



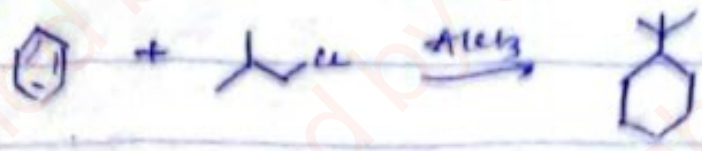
v P-xylene



b | By chemical equation outline the synthesis of synthesis of salicylic acid from phenol

CHM 306

Limitation to F.C Alkylation : 1. Rearrangement of an Alkyl halide

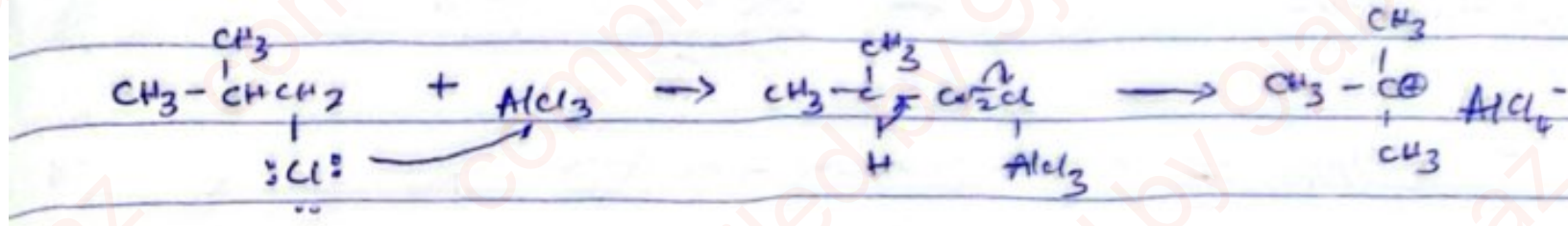


1-chloro-2-methyl chloride
Isobutyl chloride

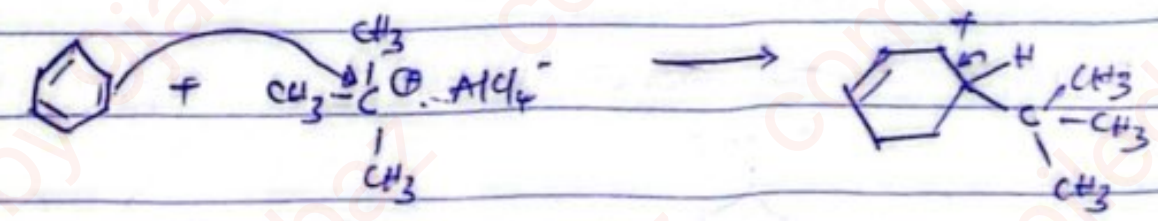
t-butyl benzene

Mechanism

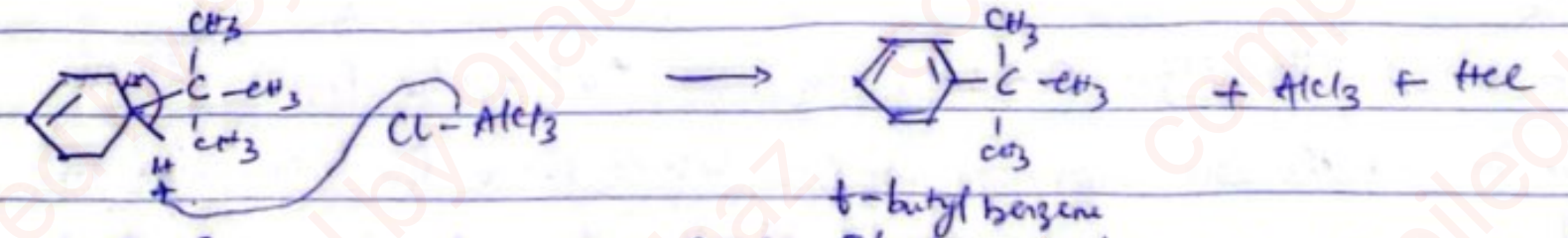
Step I: Rearrangement of the Isobutyl Chloride to tert butyl cation which serves as the electrophile



Step II : Electrophile attack on the Pi bond of the benzene ring



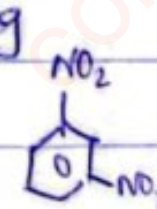
Step III : The Proton transfer to regenerate the aromatic character of the ring



t-butyl benzene

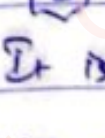
II. In the presence of 1 or more strongly Electron withdrawing groups on the benzene

where X = -CHO, $-SO_3H$, $-CF_3$, RCOR', -COOH, $-NO_2$, -CN, $-CCl_3$, $-NR_3^+$,



Eg

+ CH_3Cl ⟶ NO Reaction

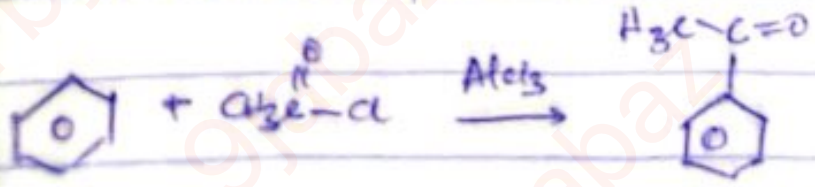


+ RX ⟶ NO Reaction

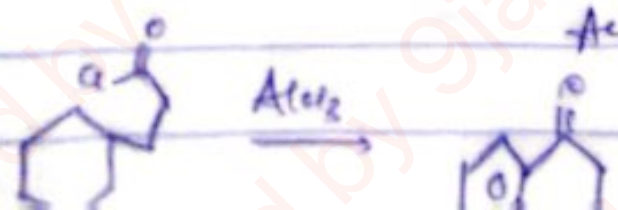
III. It is difficult to stop the reaction at mono alkylation because the Product is more reactive than the starting material

FRIEDEL CRAFT ACYLATION

This is the reaction between benzene with Acyl chloride in the Presence of Halogen Carrier ($AlCl_3$) to form a ketone

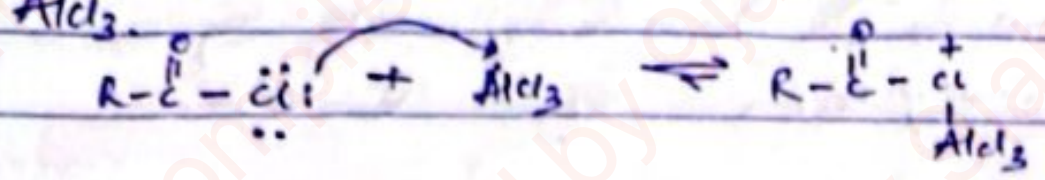


Acetophenone



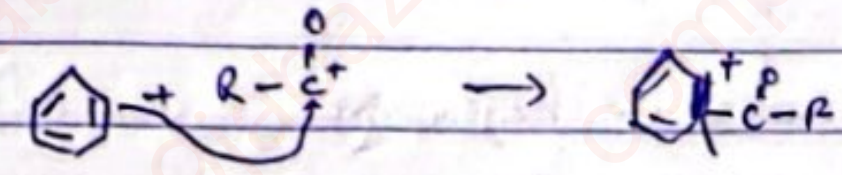
Mechanism for Acylation

Step I: The R₃N bit the Halogen atom of the acyl chloride & Aluminum trichloride

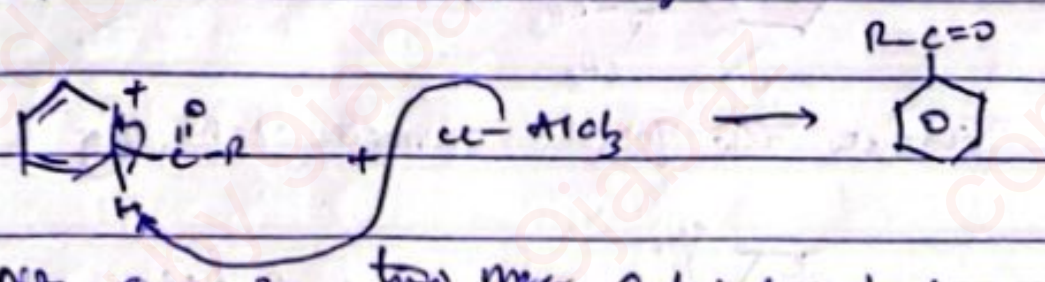


Step II: - Redistribute of Valence electron of the molecule. Complex to give an ion pair containing Acylium ion

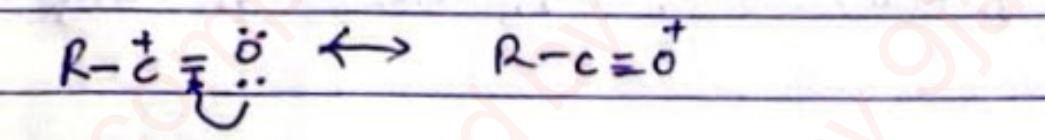
Step III: This is Attack of the Acyllium ion on an benzene ring



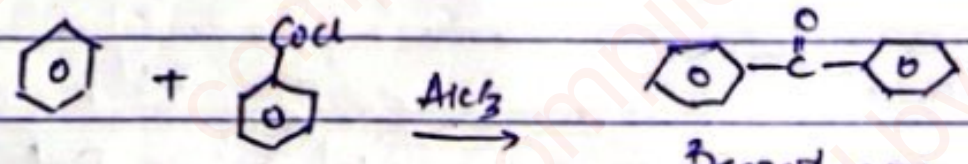
Step IV : Proton transfer to regenerate the aromatic system



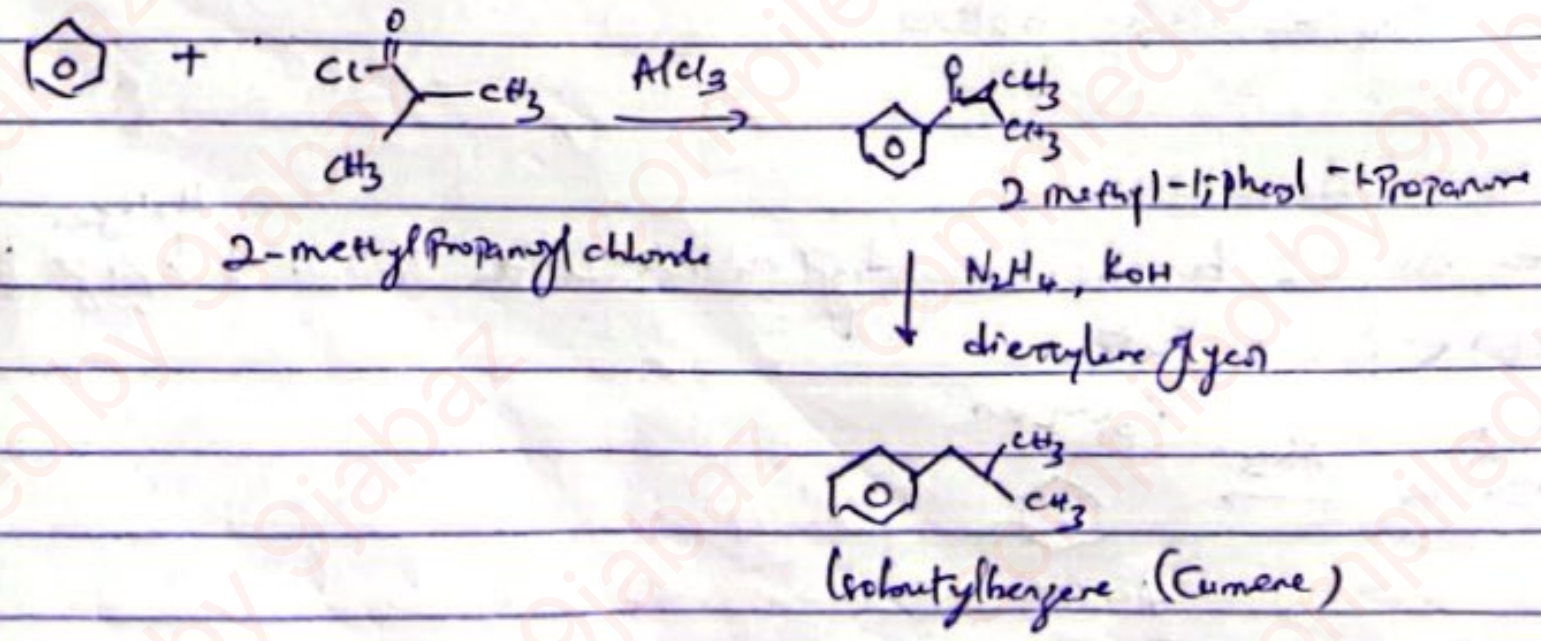
Note there are two Major Contributing structures that can be drawn for the Acylium ion but the one with the complete Valence Shells for both carbon and oxygen makes a greater Contribution to the hybrid



Some Specific Examples



Benzophenone

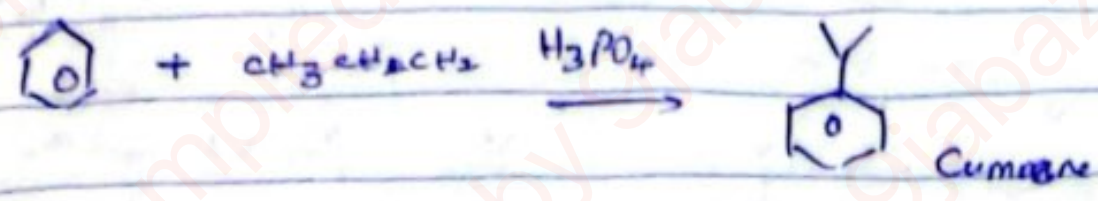


2-methylpropanoyl chloride

2 methyl-1-phenyl-1-Propanone

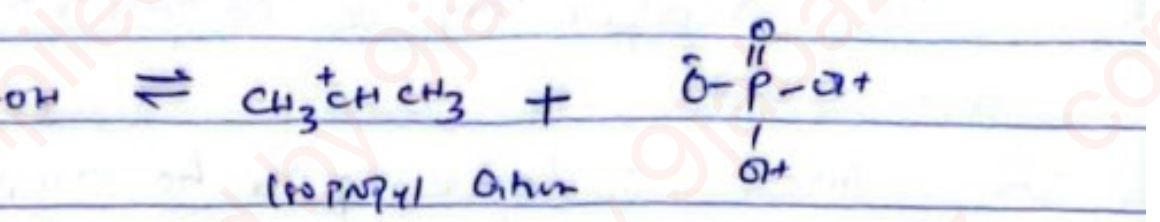
Isobutylbenzene (Cumene)

Cumene (Isopropylbenzene) can be prepared from the reaction of benzene and 2 methylpropan-2-ol chloride or Propylene in the presence of Phosphoric acid

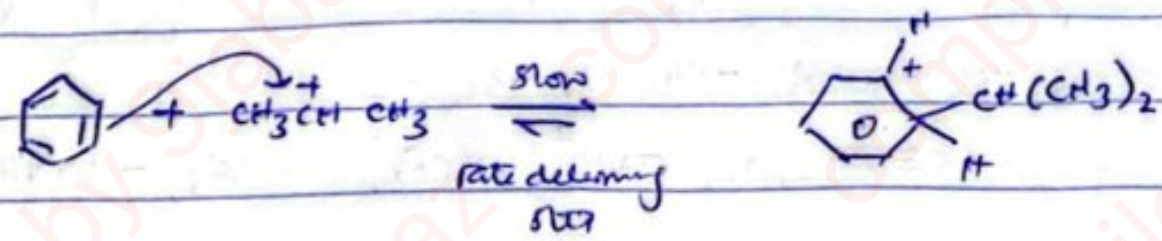


Mechanism

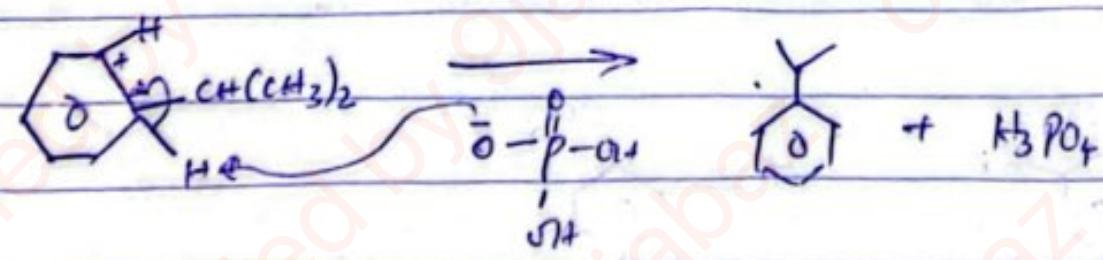
Step I: Proton transfer from the Phosphoric acid to the Propylene to give Isopropyl cation



Step II : This is the attack of the Isopropyl cation with the Pi electron on the benzene ring to give 2 resonance stabilize Carbocation Intermediate



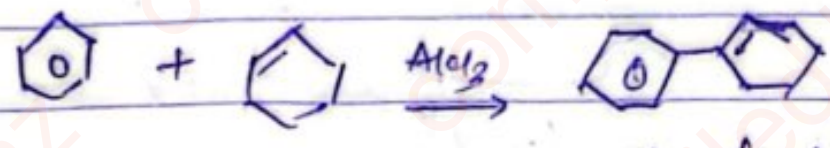
Step III : Proton transfer to dihydrogen phosphate to give Cumene



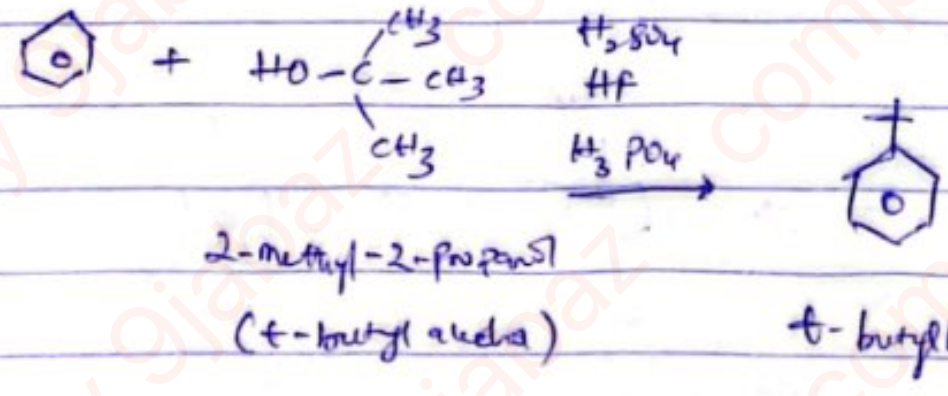
Other Electrophilic Aromatic Alkylation

1. Reaction of benzene with Propene in the Presence of Phosphoric acid to give Cumene

2. Treatment of Benzene with Cyclohexene in the Presence of Aluminium Trichloride to give Vinylcyclohexene

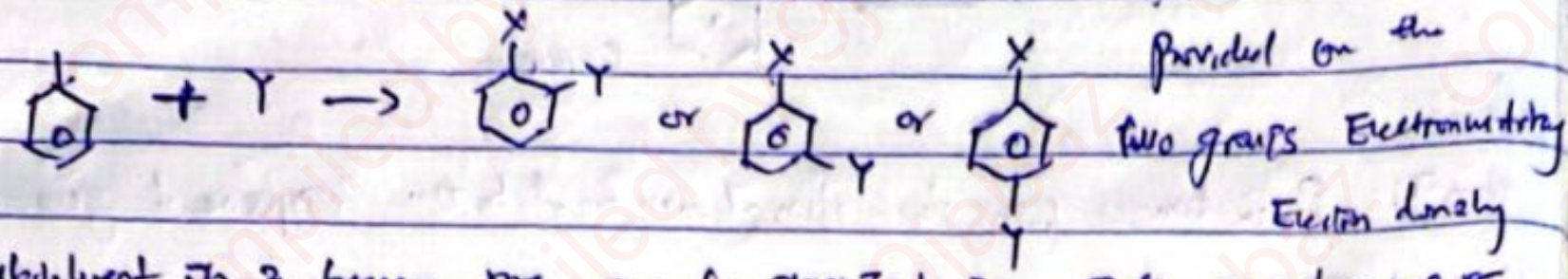


iii. Treatment of 2-methyl-2-propanol



DISUBSTITUTION AND POLYSUBSTITUTION

a. Effect of Substituent Group on further substitution: There are many possibilities when electrophilic substitution of a monosubstituted benzene is carried out. The new group may become oriented in the Ortho Position, meta or Para Position



Provided on the two groups Electron withdrawing Electron donating

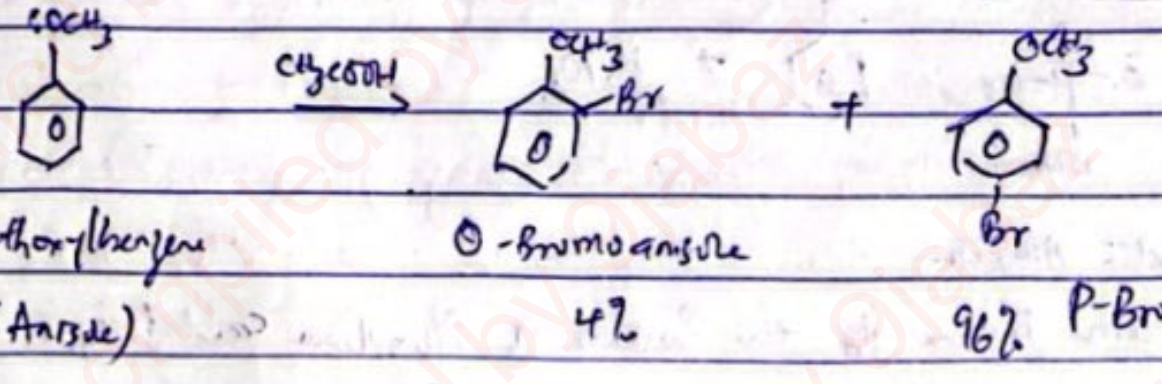
i. Substituent in a benzene ring can be classified as Ortho-para directing or as meta directing

ii. Certain groups on a benzene ring can be classified as activating or deactivating towards further substitution on the benzene ring

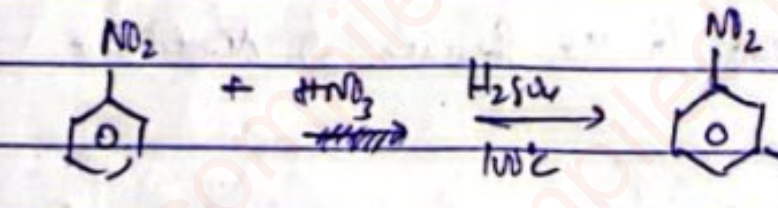
Ortho-Para Directing groups: $-NH_2$, $-NHR$, $-NR_2$, $-OH$, $-OR$, $-NHCOR$, $-NHCOAr$, $-OCOR$, $-OCOAr$, $-R$, $-Ph$, $-F$, $-Br$, $-I$

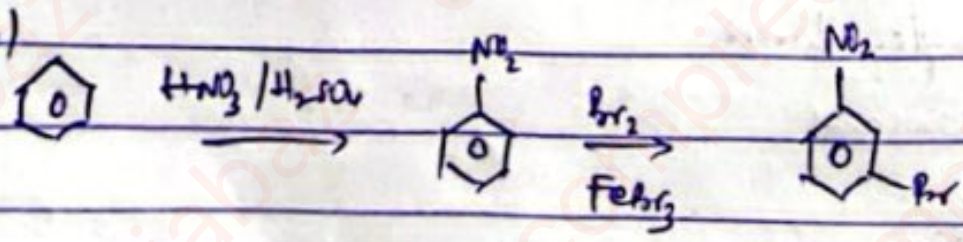
Meta Directing: $-COOR$, $-SO_3H$, $-C\equiv N$, $-NO_2$, $-NH_3^+$, $-CF_3$, $-CCl_3$, $-CONH_2$

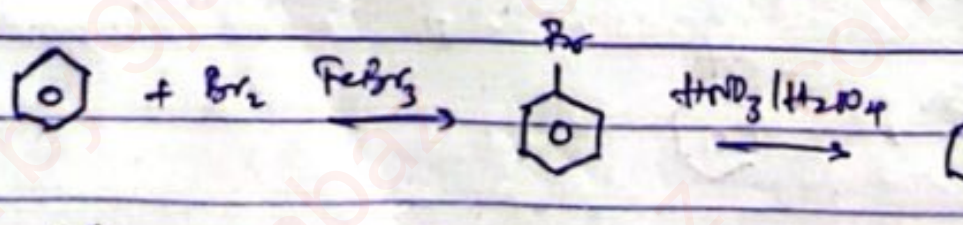
b. Bromination of Anisole in ethanoic acid which can serves as a catalyst gives two product; Orthobromoanisole 4% and Para bromo anisole 96%.



Methoxybenzene (Anisole) — O-Bromoanisole 4% — 96% P-Bromoanisole

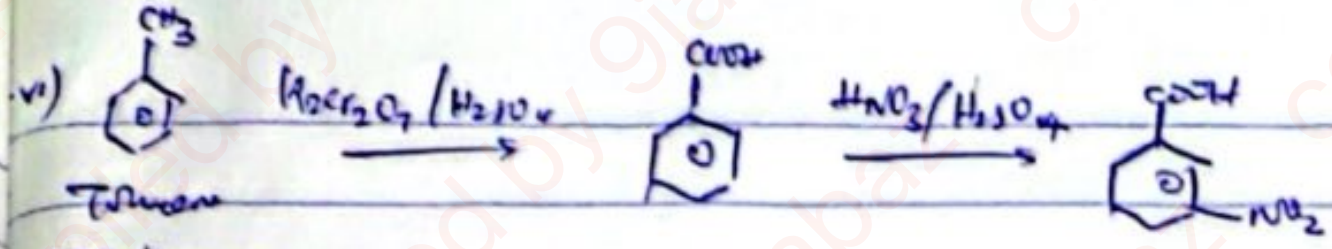
i. 

ii) 

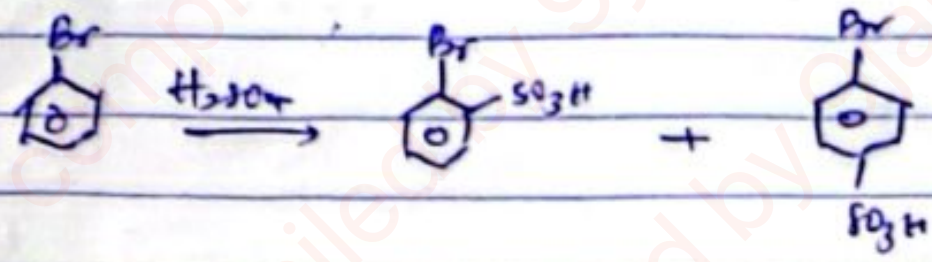
iii) 

iv)

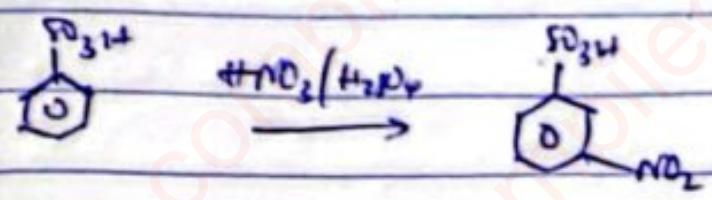
v)

vi) 

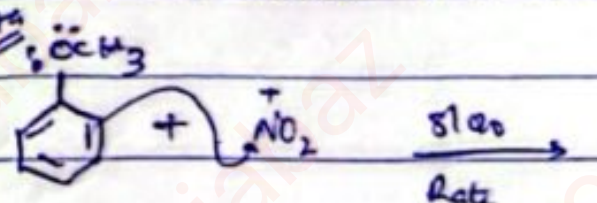
Toluene
Benzoic acid
m-nitrobenzoic acid

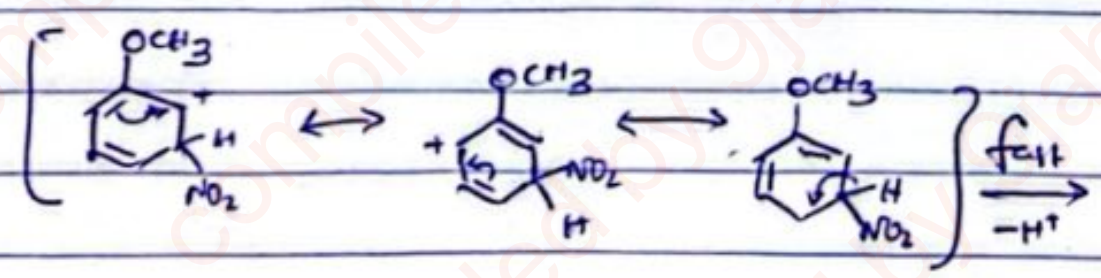
vii) 

Steric Product due to steric hindrance

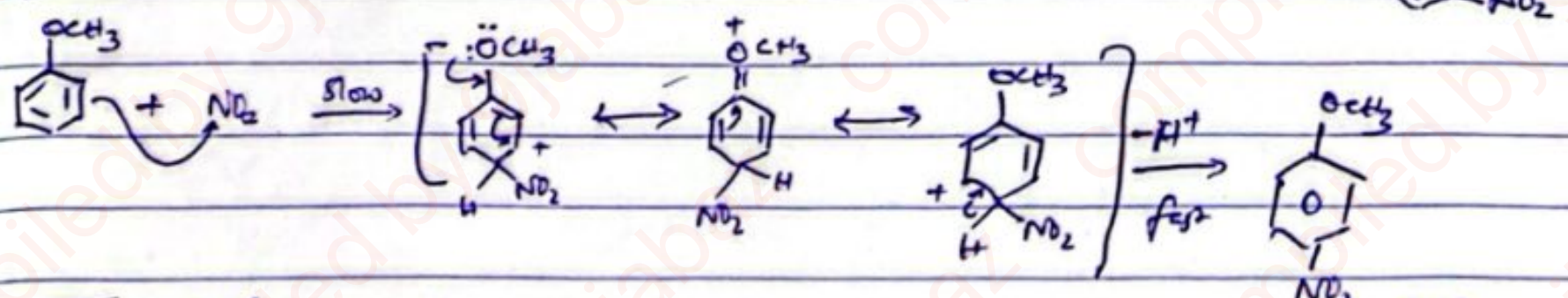
viii) 

Nitration of Anisole to check the Mechanism of ortho-para Directive

Meta




Para



major

Theory of Activating - Deactivating Effects

I. Any Resonance effect such as that of amino (NH_2) Hydroxyl ($-OH$) & Alkoxyl ($-OR$) that delocalize a Positive charge of the Carbocation intermediate lowers the activation energy for the formation and has an activating effect towards further electrophilic aromatic substitution

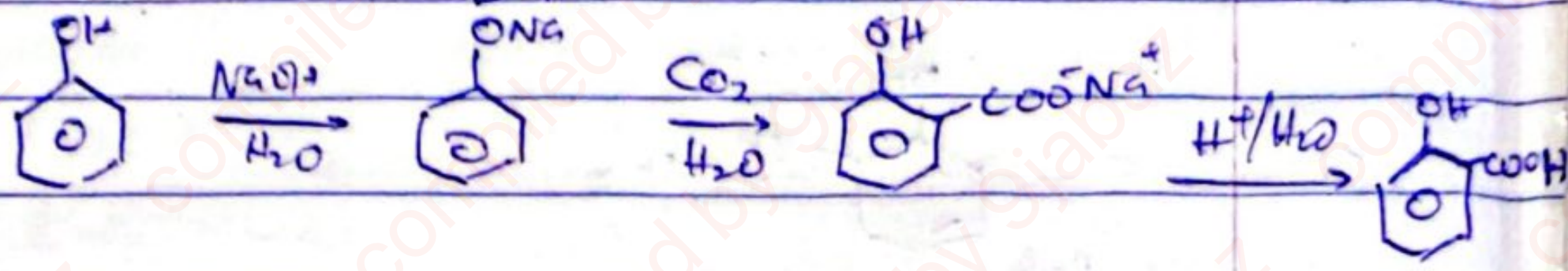
II. Any Inductive effect such as that of $-CH_3$, or another alkyl group that releases electron density towards the ring activate the ring towards further Substitution

+ I effect

III. Any resonance or Inductive effect such as that of $-NO_2$, $-C\equiv N$, $-C=O$, $-CO_2$, $-SO_3H$ that decreases electron density on the ring deactivate the ring to further Substitution.

IV. Any Inductive effect such as that of halogen Br_2, NR_3^+, $-CF_3$, $-CCl_3$ that decreases electron density on the ring deactivate the ring towards further Substitution.

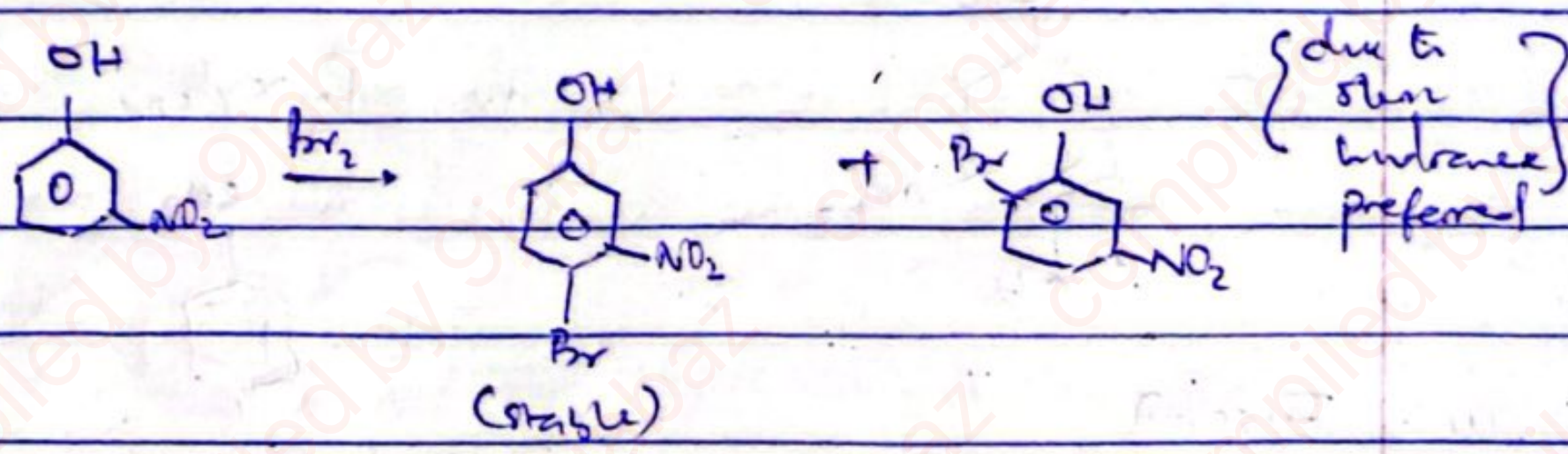
b By chemical equation outline the synthesis of synthesis of salicylic acid from phenol



CONTINUATION

Some examples

1



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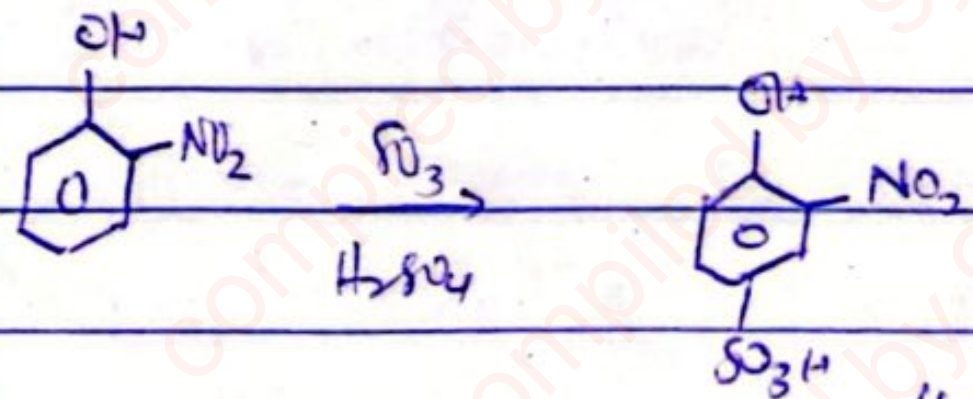


4-hydroxy-3-Nitrobenzenesulfonic acid

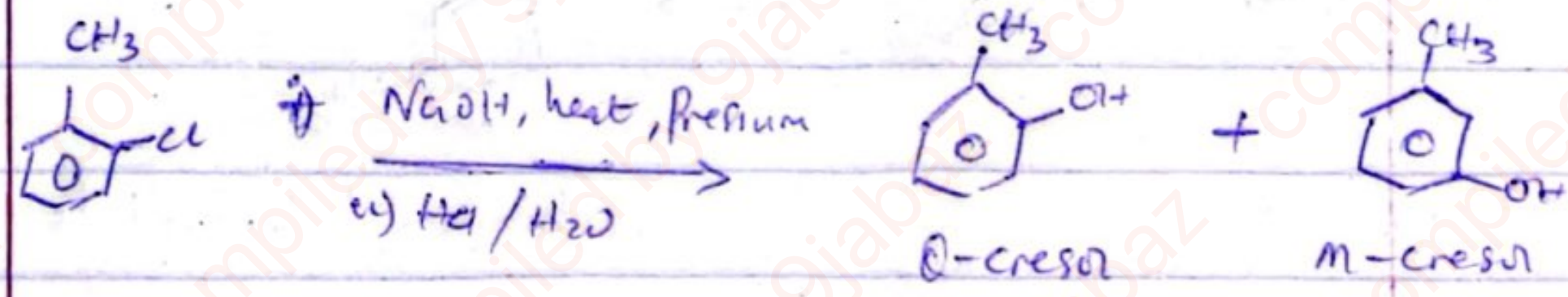
Nucleophilic Aromatic Substitution

This is a reaction in which a nucleophile most commonly a halogen on an aromatic ring is replaced by another nucleophile

(a) Nucleophilic substitution by way of benzyne Intermediate

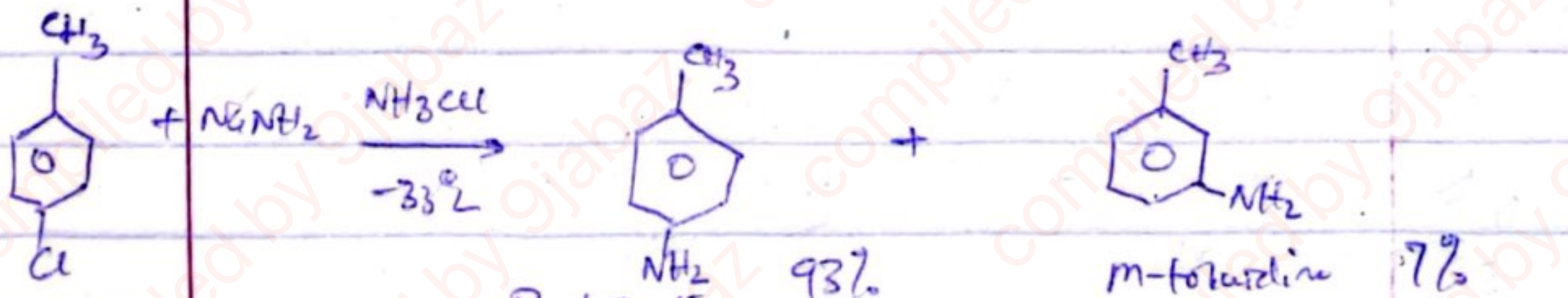
A benzyne Intermediate is a reactive Intermediate formed by β elimination from adjacent Carbon atom of a benzene ring and having a triple bond on the benzene ring. The second Pi bond of the benzyne triple bond is formed by overlap of Co-Planar Sp^2 orbitals on the adjacent carbons

Example 1: Ortho chlorotoluene (methyl) reacts with NaOH in the presence of HCl to give a mixture of 2-methyl phenol (O-cresol) & 3-methyl phenol



O-chlorotoluene

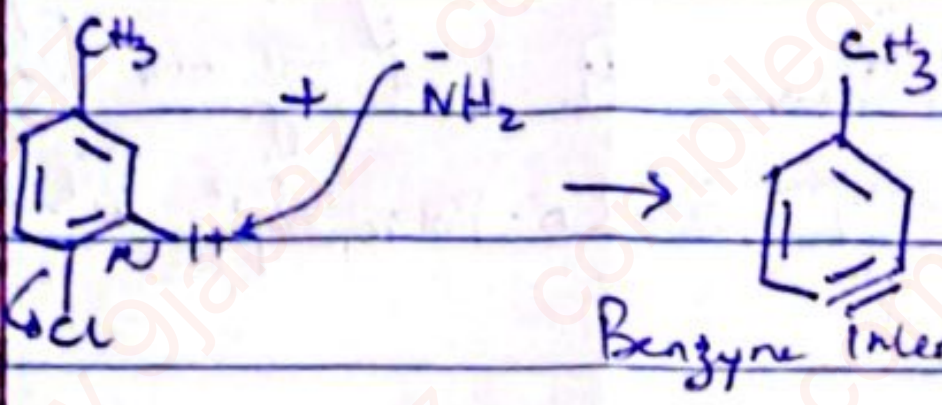
2. Para chlorotoluene reacts with Sodamide to give a mixture of (Para toluidine 4-methyl aniline and 3-methyl aniline (meta toluidine)



3. Chlorobenzene reacts with Sodium hydroxide in water at high pressure at 200°C to give Sodium phenoxide

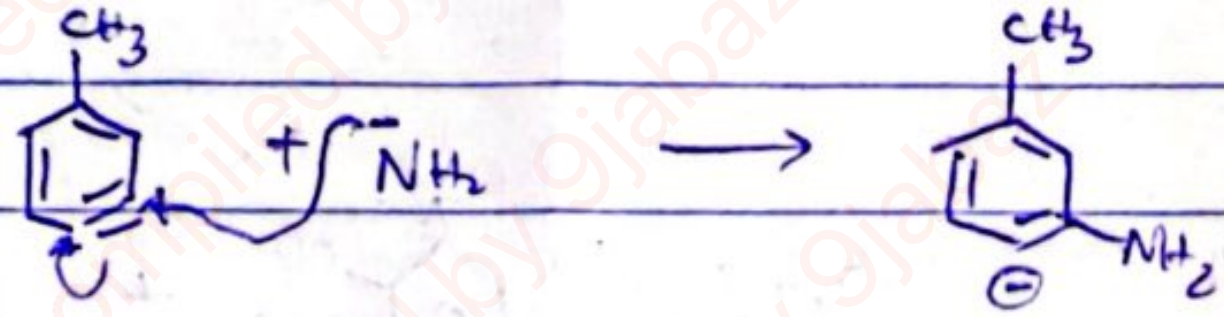
Mechanism

1. Step 1: Dehydrogenation of the benzene ring to give a benzyne Intermediate



Benzyne Intermediate

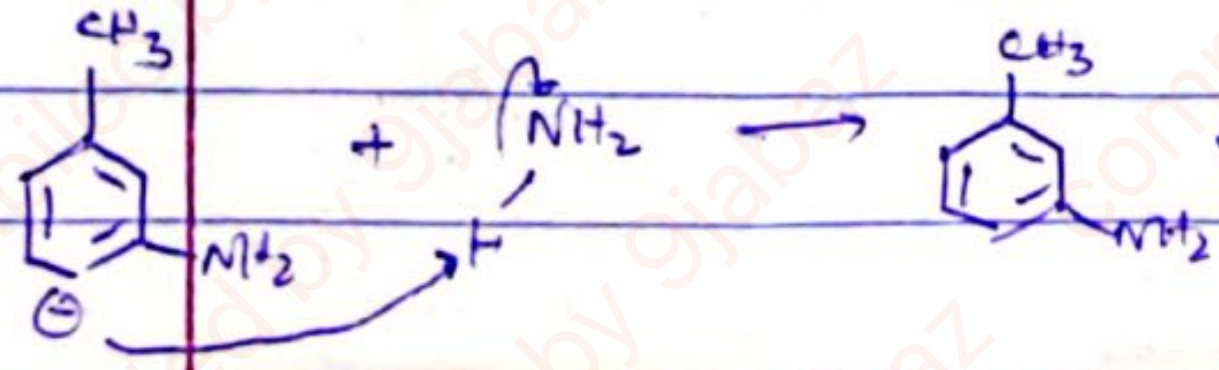
Step 2: Nucleophilic addition of the amide ion to a carbon of the benzyne triple bond to give a Carbanion Intermediate.



Carbanion Intermediate

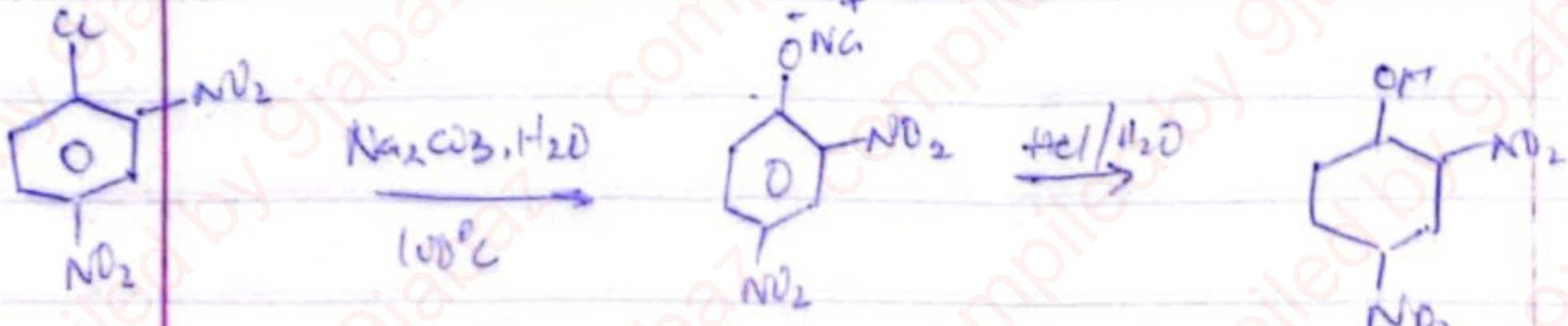
Addition of both ends of new triple bond occurs

Step 3: Proton transfer from ammonia to Carbanion intermediate gives one of the observed Substituted Product and generate a new amide ion



b Nucleophilic Substitution by Addition elimination when an aromatic Compound Containing strong electron withdrawing nitro groups Ortho or Para to the halogen Nucleophilic aromatic Substitution occurs readily

Ex: 1-chloro-2,4-dinitrobenzene undergo reflux reaction in aqueous Sodium Carbonate followed by treatment in aqueous acid results in formation of 2,4-dinitrophenol.

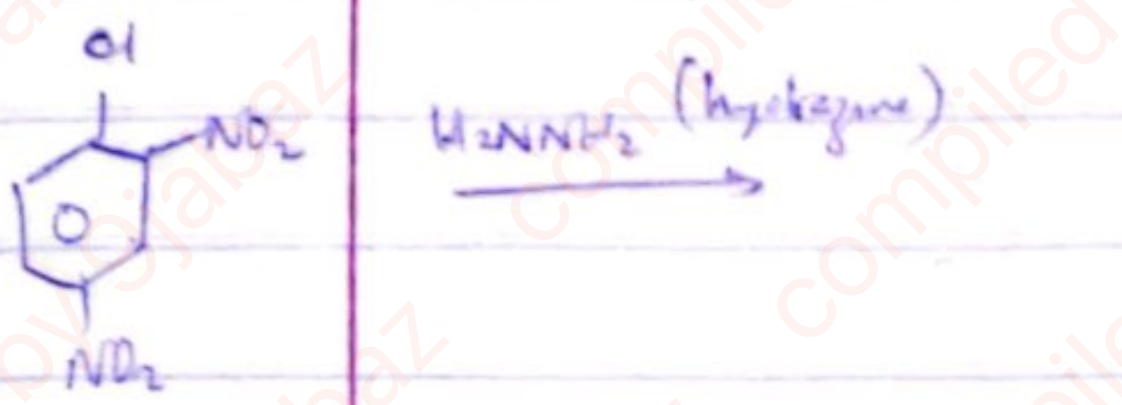


Sodium-2,4-dinitrophenoxide

2,4-dinitrophenol

Synthesis of 2,4-Dinitrophenyl hydrazine

Step 1: 1- Chloro-2,4-dinitrobenzene reacts with Hydrazine (H_2NNH_2) to form 2,4-dinitrophenylhydrazine



2,4-dinitrophenylhydrazine

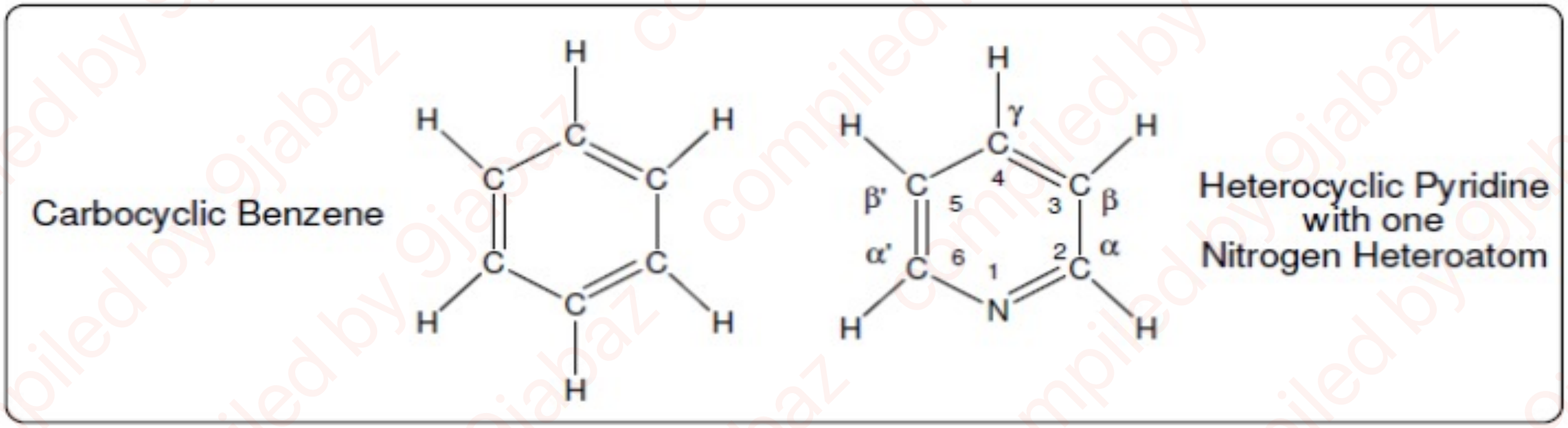
CHM 306

PART C- HETEROCYCLIC COMPOUNDS

INTRODUCTION TO HETEROCYCLIC COMPOUNDS

Cyclic compound having only carbons as the ring members, such as benzene are called carbocyclic compounds. As only carbon forms the backbone of the ring, it is also a homocyclic compound.

In contrast, cyclic compounds having at least one atom other than carbon as ring members, (e.g. Pyridine with nitrogen replacing one of the carbon atom) may be termed as heterocyclic compounds. These atoms are termed as heteroatoms. The structure of benzene and pyridine are provided in the figure below.



Classification

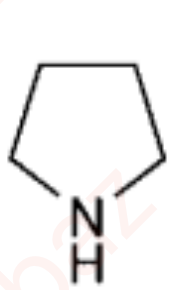
Based on the structural and electronic arrangement the heterocyclic compounds may be classified into two categories.

1. Aliphatic heterocyclic compounds
2. Aromatic heterocyclic compounds

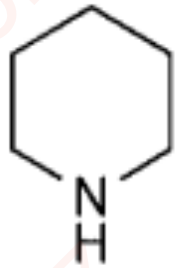
Based on the variety of structure, the heterocyclic compounds may also be divided in to:

3. Five membered heterocyclic compounds
4. Six membered heterocyclic compounds
5. Fused or condensed heterocyclic compounds

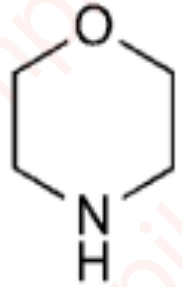
Aliphatic Heterocyclic Compounds



pyrrolidine

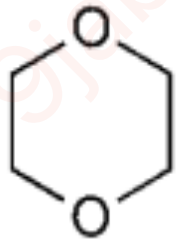


piperidine

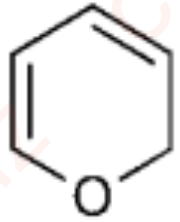


morpholine

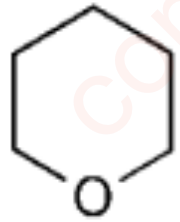
tetrahydrofuran
THF



dioxane
[1,4-dioxane]



2*H*-pyran



tetrahydropyran

azirine
[2*H*-azirine]

oxirane
(ethylene oxide)

aziridine
(ethylene imine)

thiirane
(ethylene sulfide)

azete

azetidine

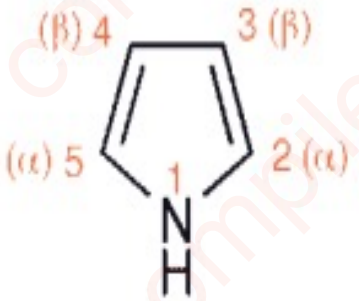
2*H*-oxete

oxetane

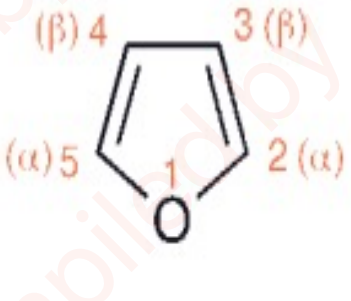
2*H*-thiete

thietane

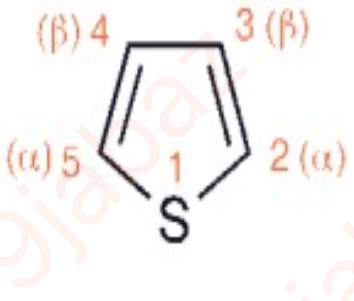
Aromatic Heterocyclic Compounds



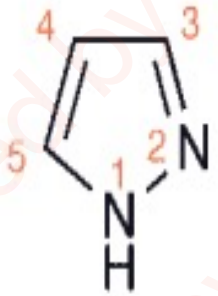
pyrrole



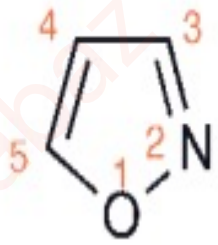
furan



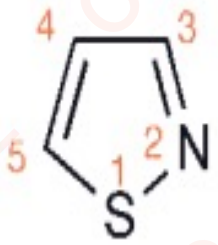
thiophene



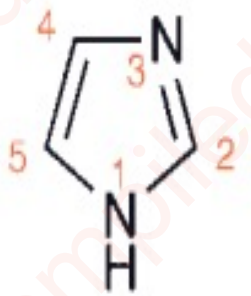
pyrazole



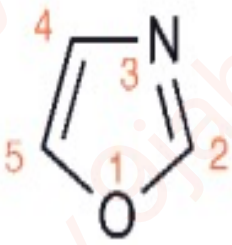
isoxazole



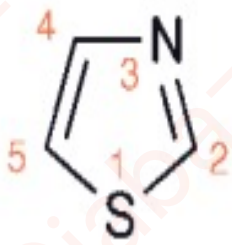
isothiazole



imidazole

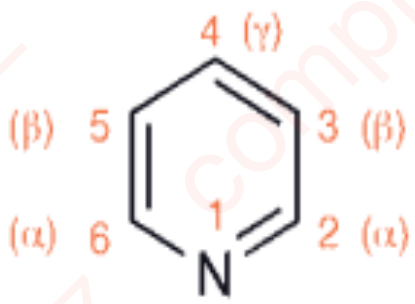


oxazole

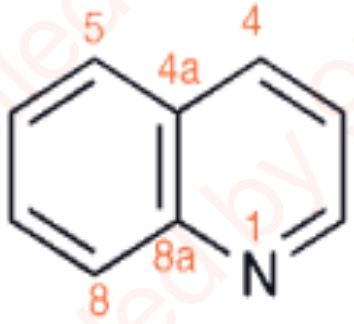


thiazole

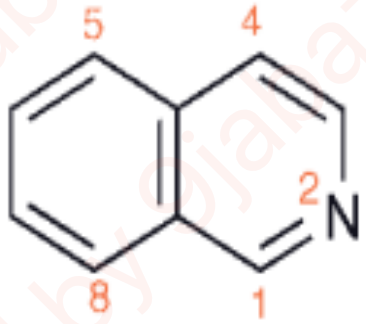
5-membered Ring



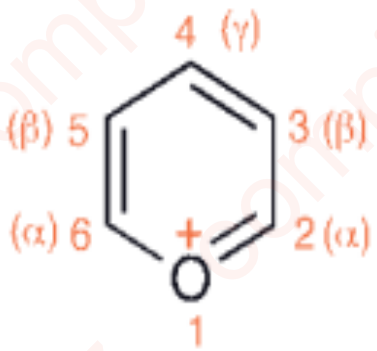
pyridine



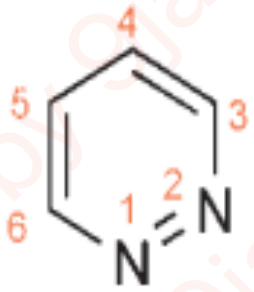
quinoline



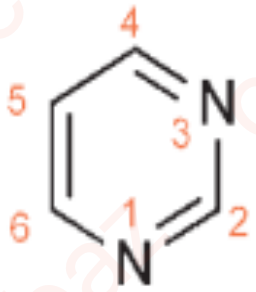
isoquinoline



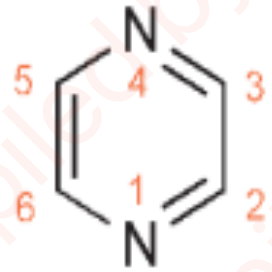
pyrylium cation



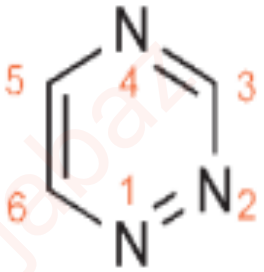
pyridazine



pyrimidine

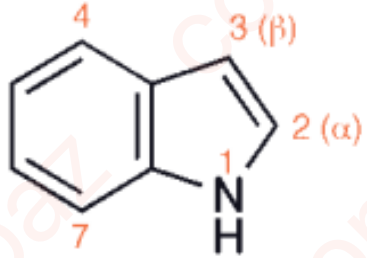


pyrazine

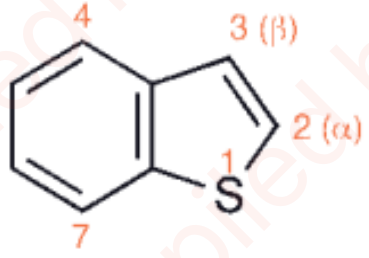


1,2,4-triazine

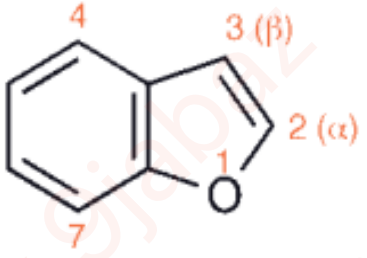
6-Membered Ring



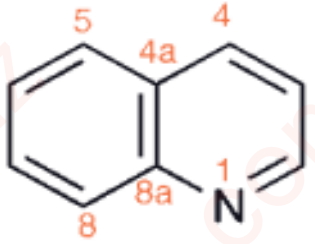
indole



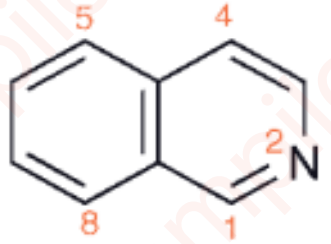
benzothiophene
[benzo[*b*]thiophene]



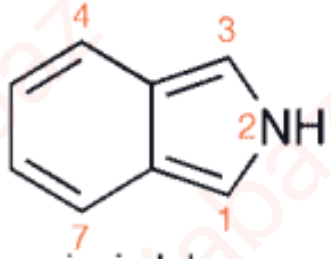
benzofuran
[benzo[*b*]furan]



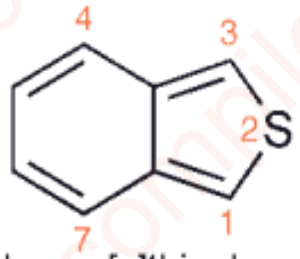
quinoline



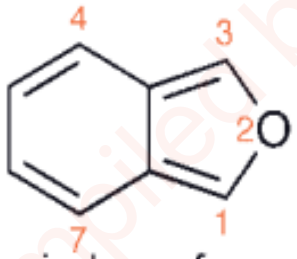
isoquinoline



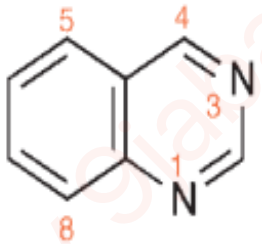
isoindole



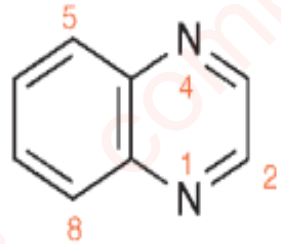
benzo[*c*]thiophene



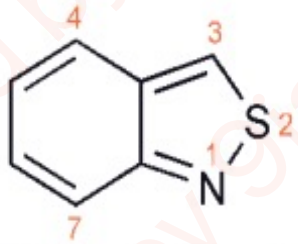
isobenzofuran



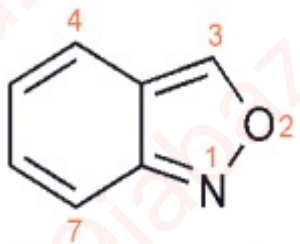
quinazoline



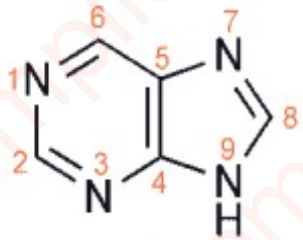
quinoxaline



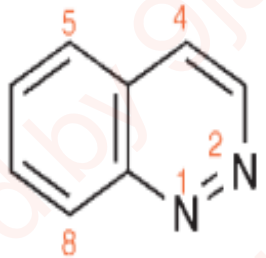
2,1-benzisothiazole



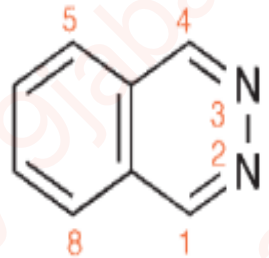
2,1-benzisoxazole
(anthranil)



purine
[9*H*-purine]



cinnoline



phthalazine

Fused Ring

Nomenclature Of Heterocyclic Compounds

1. Type of Heteroatom

The type of heteroatom is indicated by a prefix as shown below for common hetreroatoms:

Hetreroatom	Prefix
O	Oxa
N	Aza
S	Thia
P	Phospha

2 The ring size is indicated by a suffix. Some of the syllables are derived from Latin numerals, namely ir from tri, et from tetra, ep from hepta, oc from octa, on from nona, ec from deca.

Stems to indicate the ring size of heterocycles

Ring size	Suffix	Ring size	Suffix
3	ir	7	ep
4	et	8	oc
5	ol	9	on
6	in	10	ec

Common Prefix for Heteroatoms (arranged in the preferential order)

S. No.	Heteroatom	Symbol	Prefix
1	Oxygen	O	Oxa
2	Sulphur	S	Thia
3	Selenium	Se	Selena
4	Nitrogen	N	Aza
5	Phosphorous	P	Phospha
6	Arsenic	As	Arsa
7	Antimony	Sb	Stiba
8	Bismuth	Bi	Bisma
9	Silicon	Si	Silia

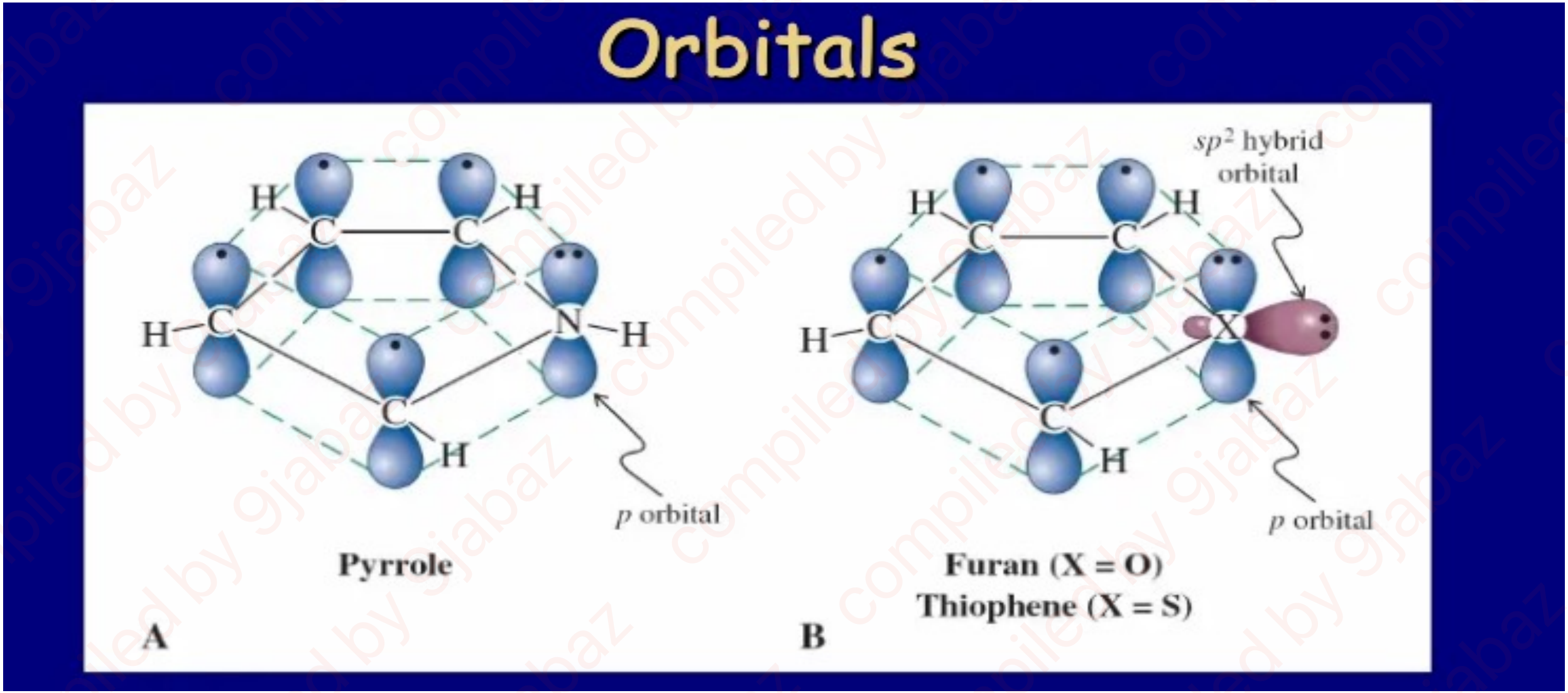
S.No	Ring Size	Unsaturated Ring	Saturated Ring
1	3	iren	Irane
2	4	ete	Etane
3	5	ole	Olane
4	6	ine	Inane
5	7	epine	Epane
6	8	ocine	Ocane
7	9	onine	Onane
8	10	ecine	Ecane

According to this system heterocycles are named by combining appropriate prefix/prefixes. The letter ‘a’ in the prefix is omitted when necessary.

Each suffix consists of ring size root and an ending intended to designate the degree of unsaturation in the ring.

It is important to recognize that the saturated suffix applies only to completely saturated ring systems, and the unsaturated suffix applies to rings incorporating the maximum number of non-cumulated double bonds.

AROMATIC HETEROCYCLIC COMPOUNDS



For this group of heterocycles, ring strain is of little or no importance. All atoms of these molecules are sp^2-hybridized, lie in a plane thus forming the ring of an almost regular pentagon.

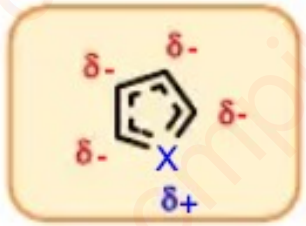
Furan, pyrrole and thiophene are aromatic π-excessive or electron-rich heterocycles. They possess 6π-electrons delocalized over the ring, so all of them comply with the Hückel rule. Conjugated system includes four electrons of ring carbon atoms and a lone pair of electrons of heteroatom. Note that in furan and thiophene, the heteroatom has two different types of lone pair – one involved in the aromatic sextet and the other, in the plane of the ring, in an sp^2 hybrid orbital, and NOT involved in the aromatic π-system.

Since 6π-electrons are distributed between 5 ring atoms, this fact makes them electron rich systems. The electron density is drifted from the heteroatom towards C-atoms, especially in α-positions, thus making them easily attacked by electrophiles.

The structural presentation of the heterocycles follows from the fact that the bond length between C-3 and C-4 is greater than that between C-2 and C-3 and between C-4 and C-5, and it complies with the contribution of resonance structures of furan, pyrrole and thiophene.

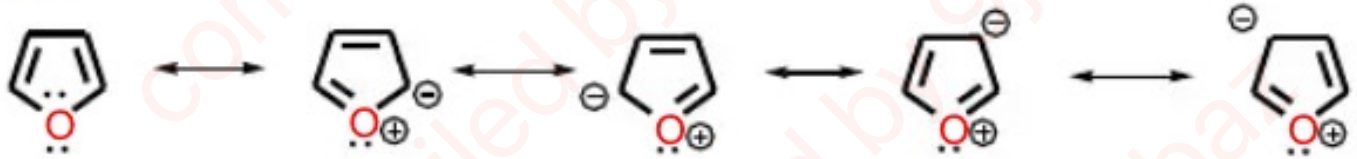
Electronic structure

Electron rich heterocycles

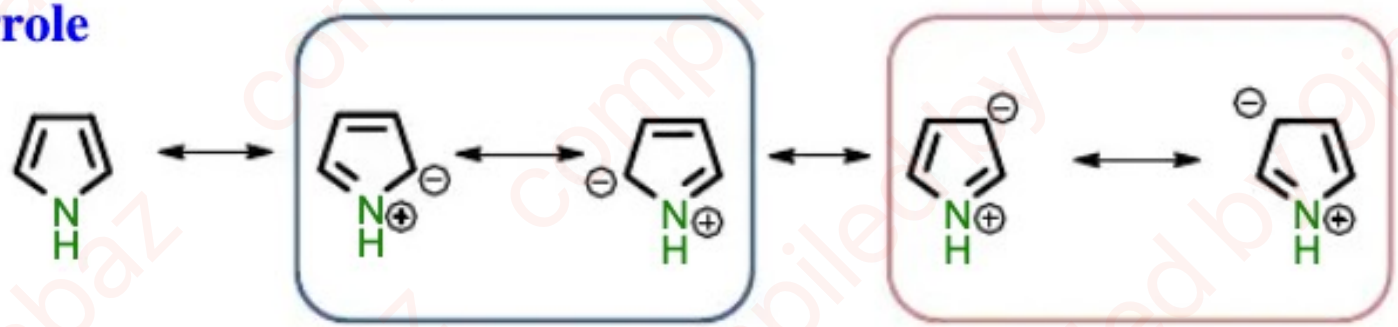


The increase of aromatic character

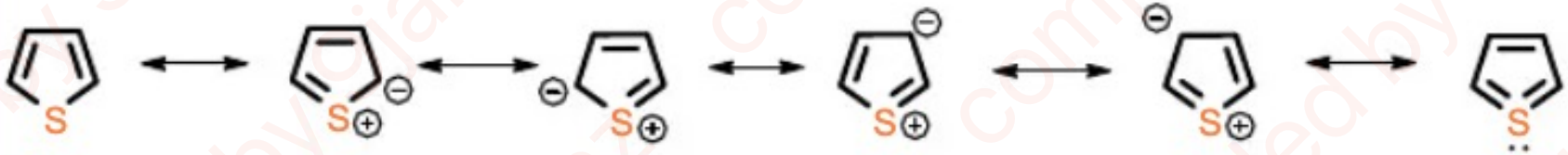
- **Furan**



- **Pyrrole**



- **Thiophene**



d-orbital participaton

Here you see all resonance structures which show the shift of electron density in the ring. The contribution of each of resonance structure into the real structure of the heterocycle is not equal. Thus in the case of pyrrole the more stable structures are marked in a blue square. In each case we see four resonance structures in which there is charge separation, indicating electron density drift away from the heteroatom.

If the extent of delocalization of the nonbonding electron pair is decisive for the aromaticity, then the grading of aromaticity, *i.e.* furan < pyrrole < thiophene < benzene, is correctly reflected by PAULING'S electronegativity values for oxygen (3.5), nitrogen (3.0) and sulfur (2.5). The other factors increasing the aromaticity and stability of thiophene are the greater atomic radius of sulfur and the presence of d-orbital. So, in this trio of heteroaromatic systems, thiophene is the 'most aromatic' – the most like benzene – and furan is the 'least aromatic' – the most like a 1,3-diene.

Important Heterocyclic Compounds

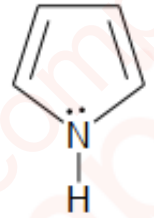
- - Pyrrole: Component of hemoglobin
- - Furan: Found in essential oils
- - Thiophene: Used in electronic materials
- - Pyridine: Base in organic synthesis

AROMATIC HETEROCYCLIC COMPOUNDS

A. PYRROLE

PYRROLE

1. Pyrrole and simple alkyl-pyrrole are simple liquids with relatively weak odour as aniline.



2. Pyrrole was first isolated from coal tar in 1834.

3. It is a five membered compound with molecular formula C_4H_5N.

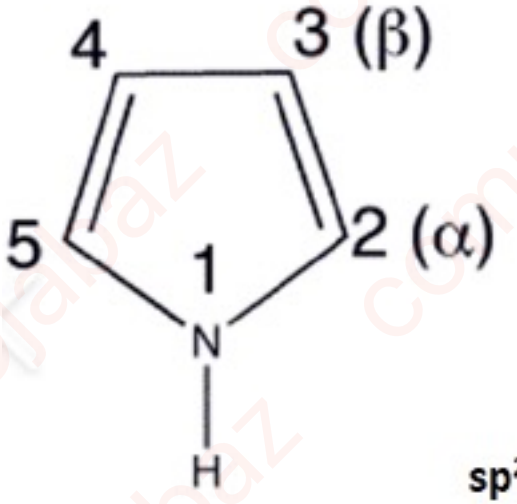
4. The Study of Pyrrole came into existence from the degradative work of the “Haem” and “Chlorophyll” synthesized from ”**Porphobilinogen**”

5. All the 4 carbon atom as well as N is SP^2 Hybridized (N- SP^2= $1e^-$ + SP^2=$1e^-$+ SP^2= $1e^-$ + P=$2e^-$) with planar geometry.

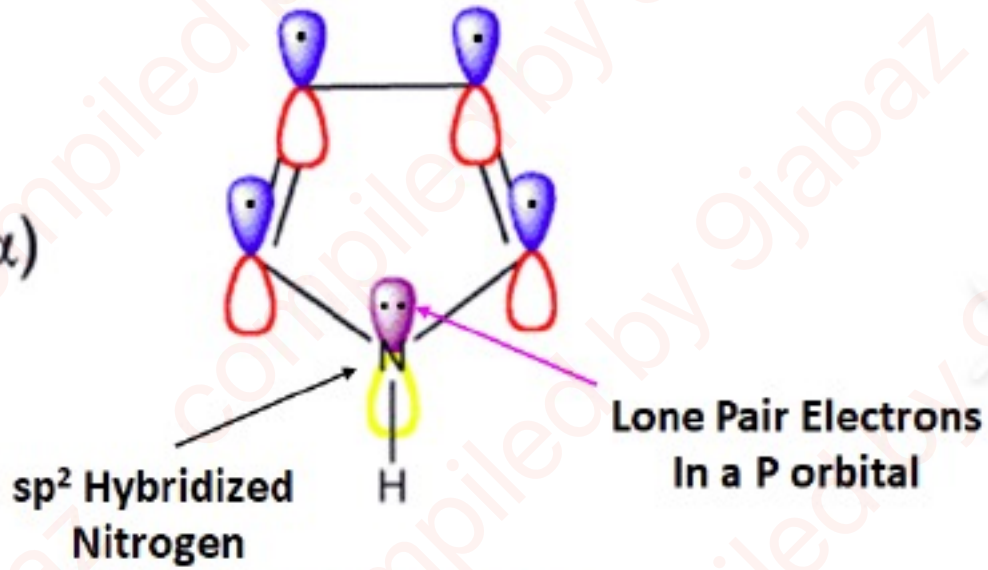
6. The lone pair on its nitrogen is not readily available, it participates in delocalization, it is an aromatic compound with $4n + 2\pi$ electrons. It is acidic and fairly basic.

7. Exhibits considerable aromatic character, its resonance energy is about 100 kJ/mol compared to that of conjugated diene 12.5 kJ/mol

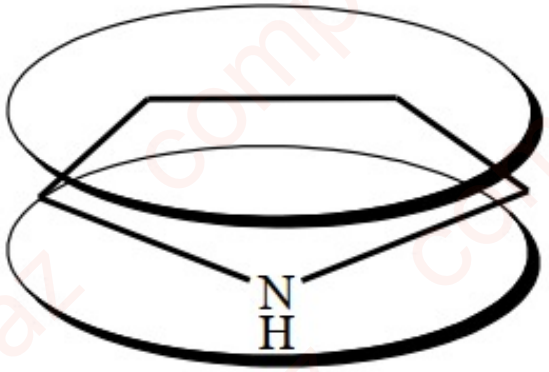
8. Pyrrole ring also occur in other natural compounds like pyrrole ring like chlorophyll of plants, nicotine, chalcone, vitamin B12, morphine and naturally occurring alkaloids.



Pyrrole

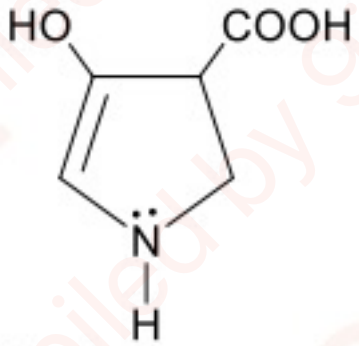


6 Π Electrons

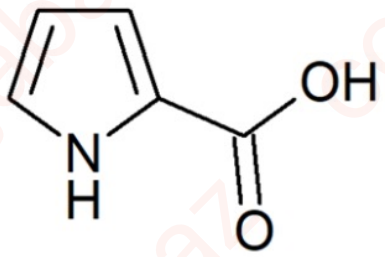


Delocalized electron cloud above and below the pyrrole ring

Derivatives of Pyrrole are 4-hydroxyl pyrroline carboxylic acid, pyrrole-2-carboxylic acid,

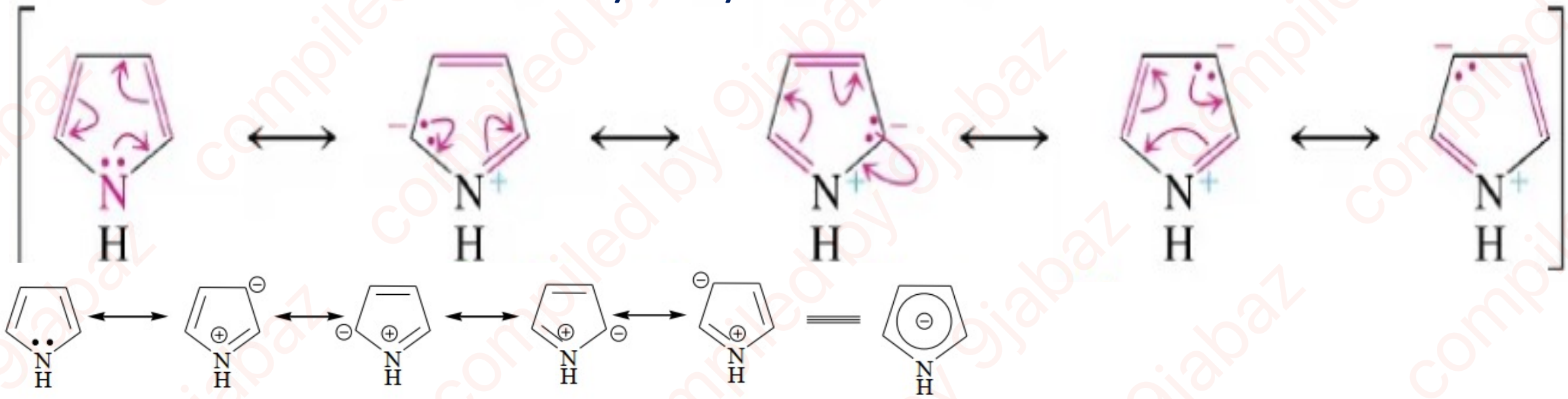


4-hydroxyl pyrroline carboxylic acid



Pyrrole-2-carboxylic acid

Stability of Pyrrole



The higher the resonance structure of pyrrole, the higher its stability. All the carbon atoms on pyrrole are electron rich i.e have higher electron density, while the nitrogen is highly electropositive. Thus, Pyrrole is highly susceptible to electrophilic substitution because all the carbon atoms are highly electron rich, but position 2 is more prone to electrophilic attack. The α-position is more susceptible because all the electrons are enhanced to move towards the positively charged nitrogen atom. The α-position has higher canonical structure than the β-position. However, when substitution takes place on the nitrogen atom, and hence it is said to be nucleophilic.

SYNTHESIS OF PYRROLE

The most obvious route to pyrroles, furans and thiophenes involves the use of 1,4-dicarbonyl compound. It is a general protocol called the Paal-Knorr synthesis.

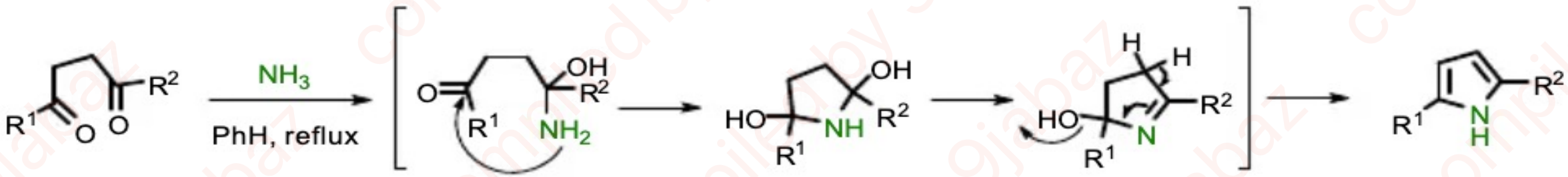
When treated with concentrated sulphuric acid, polyposphoric acid or other dehydrant agent 1,4-dicarbonyl compounds undergo cyclodehydration yielding 2,5-substituted furans.

To change this strategy into a thiophene or a pyrrole synthesis, all that is necessary is to expose 1,4-dicarbonyl compounds to the N-source reagent (ammonia and primary amines) or S-source reagent (P_4S_{10} or Lawesson's reagent).

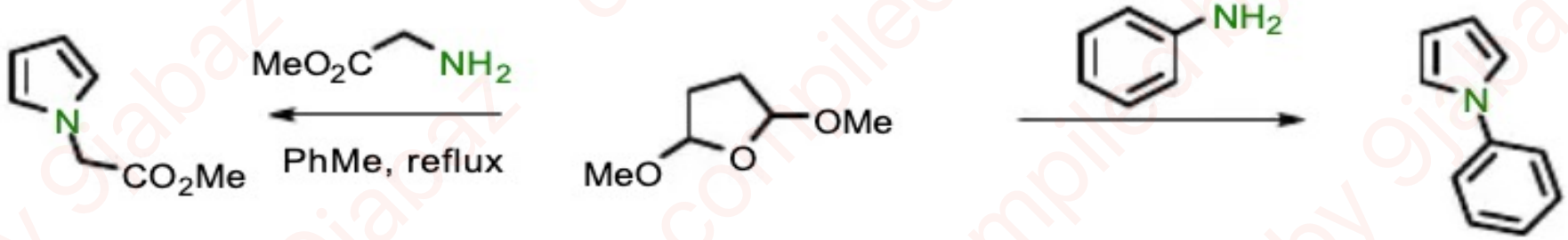
Furan, pyrrole and thiophene can be converted into one another under catalytic conditions and at high temperatures. The reaction is named after the Russian chemist Yuryev.

1. Paal-Knorr synthesis

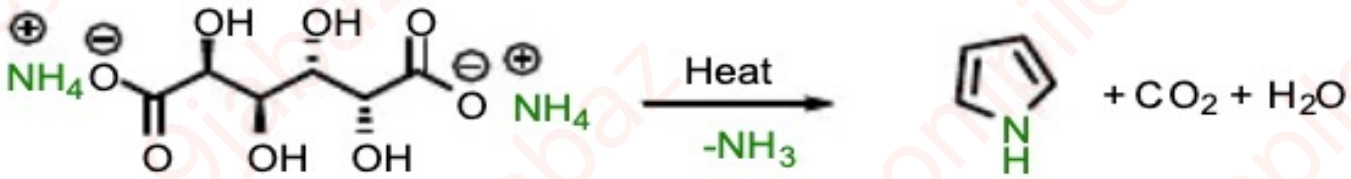
Universally applicable synthesis. 1,4-Dicarbonyl compounds react with ammonia or primary amines (or with ammoniom/alkylammonium salts) in ethanol, acetic acid or toluene to give corresponding pyrroles. The process represents nucleophilic addition with the following elimination.



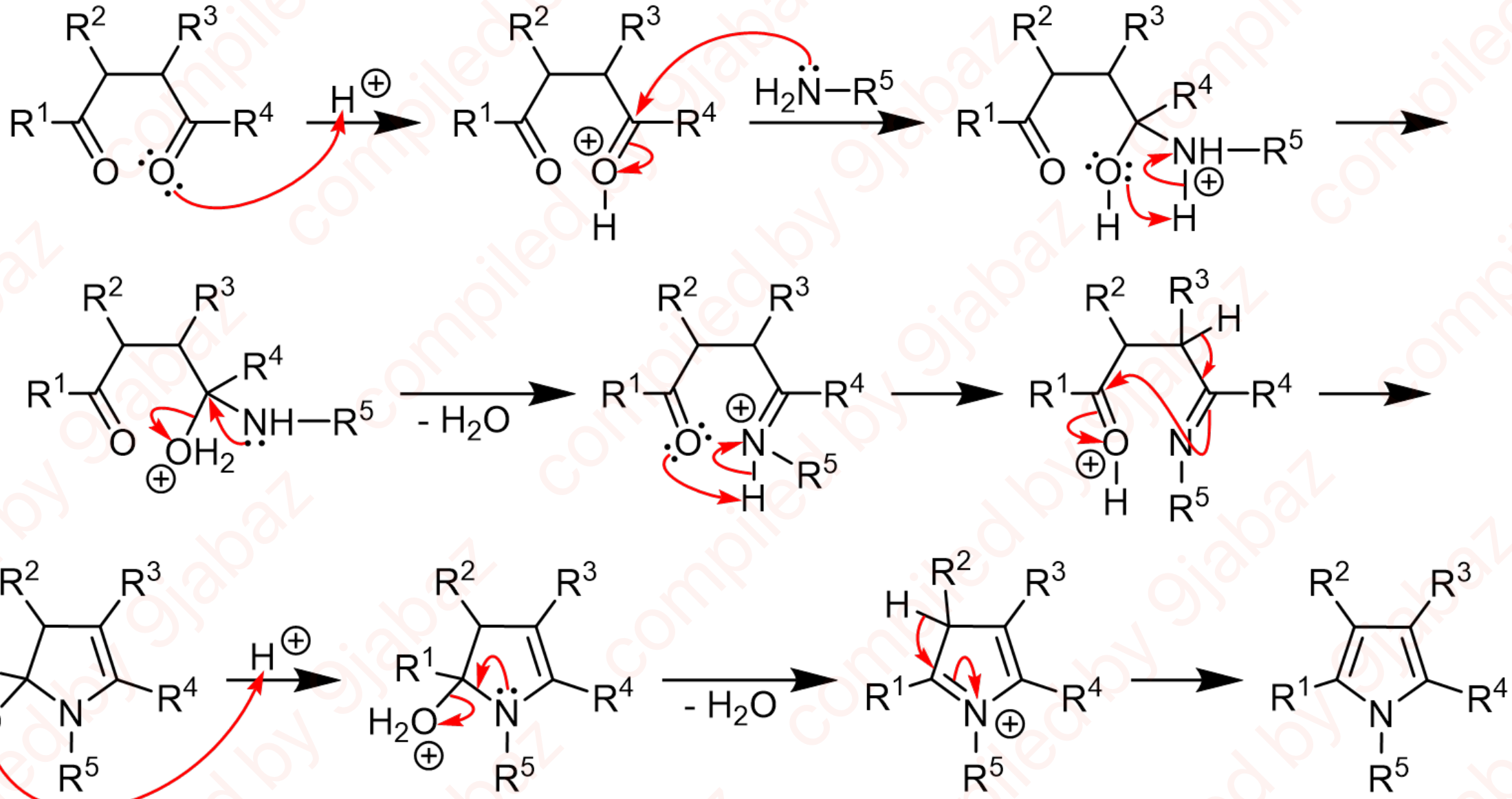
For the synthesis of unsubstituted pyrrole derivatives the 2,5-dimethoxytetrahydrofuran is used



Laboratory method (from ammonia salt of mucic acid)



MECHANISM OF PAAL KNORR SYNTHESIS OF PYRROLE



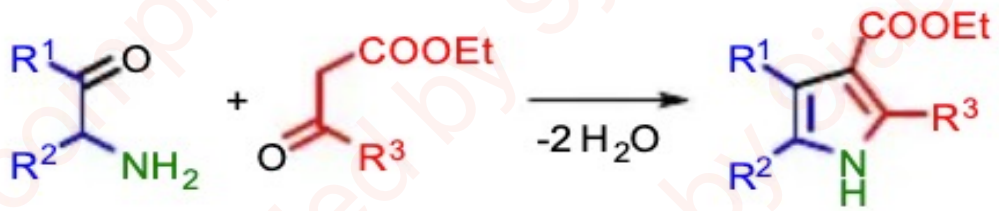
Since the Paal-Knorr synthesis is universally applicable we demonstrate its mechanism using the formation of the pyrrole ring as an example. The process represents nucleophilic addition of ammonia or primary amines (or with ammonium/alkylammonium salts) to 1,4-dicarbonyl compounds resulting into the double hemiaminal **1** which by the following elimination of water yields pyrrole **3** *via* enamine formation.

For the synthesis of unsubstituted pyrrole derivatives instead of unstable succindialdehyde 2,5-dimethoxytetrahydrofuran is used.

In the laboratory you can still use a simple and effective method for the synthesis of *N*-substituted pyrroles starting from ammonium salts of saccharic acids.

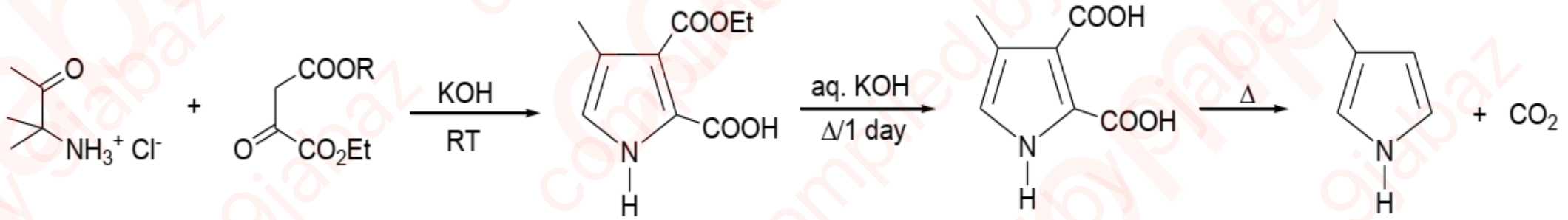
2. Knorr synthesis for pyrrole

Consists in reaction of α-amino ketones with β-keto esters or β-diketones



carbonyl compounds that has methylene group i.e. active methylene group.

For example:

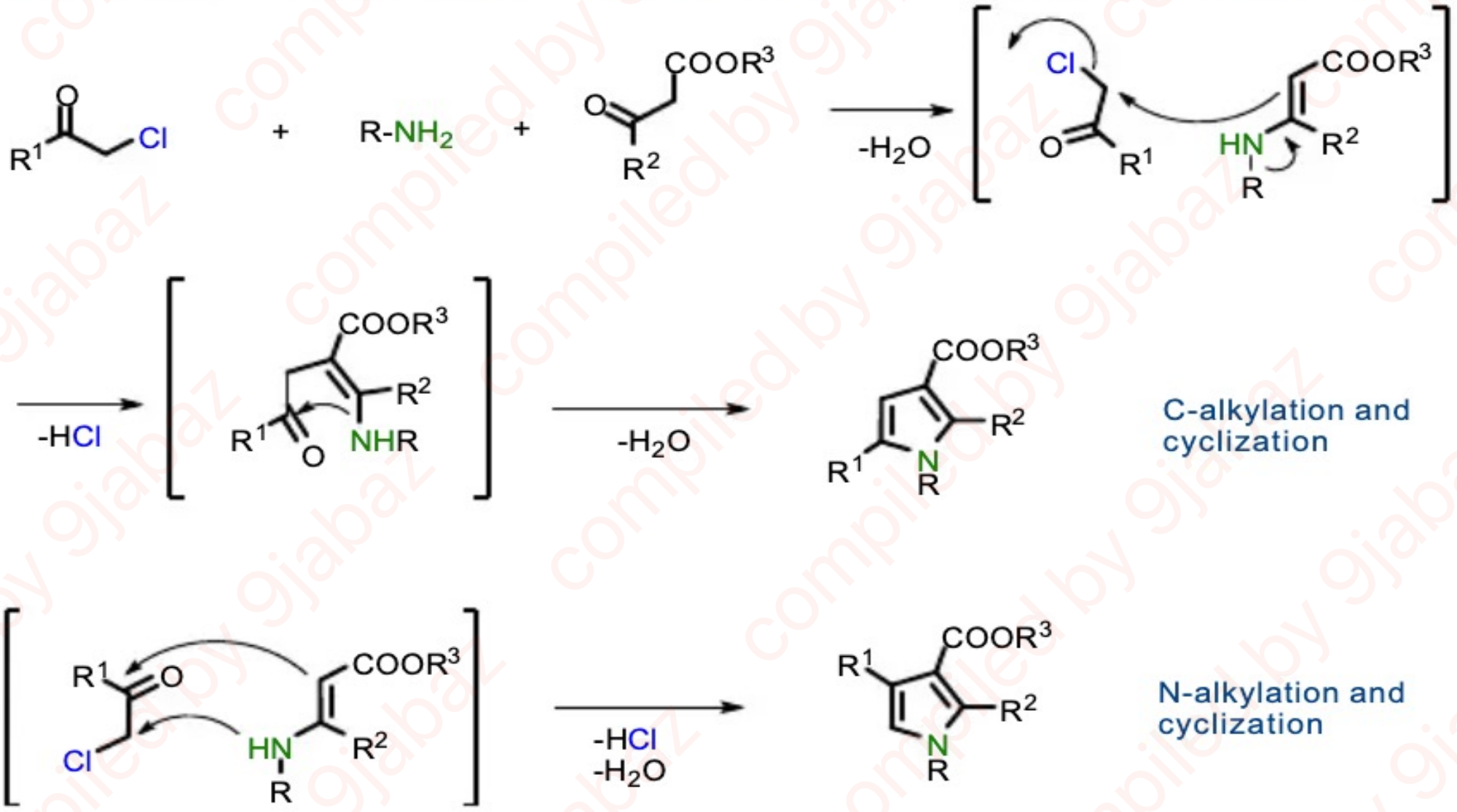


The presence of the base helps in hydrolysis and in the removal of the acidic proton.

Cyclocondensation of α-amino ketones with β-keto esters or β-diketones is known as the Knorr synthesis of pyrrole. The use of a free amino ketone is problematic, its dimerisation gives a by-product dihydropyrazine. The problem can be overcome by using amino carbonyl compound in an N-protected form, as a protonic salt for an example or as more frequently, α-amino ketones are generated *in situ* by reduction of α-oximo ketones obtained *via* nitrosation of ketones with alkyl nitrites. The classical variant of Knorr synthesis and its mechanism is demonstrated.

3. Hantzsch Pyrrole Synthesis

Three-component cyclocondensation reaction of α-halocarbonyl compounds, β-keto esters or β-diketones and ammonia or primary amines.



Another way for the synthesis of the pyrrole system is a modified version of the Feist-Benary method called Hantzsch synthesis. Hantzsch synthesis represents three-component cyclocondensation of α-halocarbonyl compounds with β-keto esters or β-diketones and ammonia or primary amines. The regio-selectivity depends on the substituents in the starting material. It was proved that the first step is the formation of β-aminoacrylic ester **1**. The further C-alkylation of it by the haloketone gives 1,2,3,5-substituted pyrrole, while N-alkylation yields 1,2,3,4-substituted pyrrole.

4. FROM FURAN

Industrially pyrrole is prepared by passing a mixture of furan and ammonia over alumina over 400° C.

Furan Pyrrole

PROPERTIES OF PYRROLE

Physical Properties:

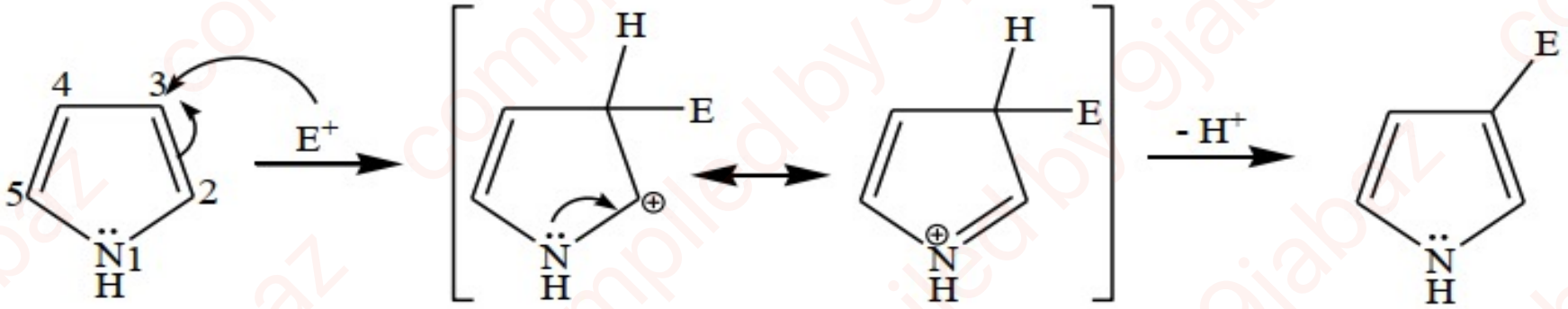
1. Pyrrole is a colorless liquid with boiling point 131° C.
2. It is highly sensitive to air, when pyrrole is exposed to air it turns brown and gradually resinifies.
3. Pyrrole is slightly soluble in water but completely miscible in ether and ethanol.

Chemical Properties:

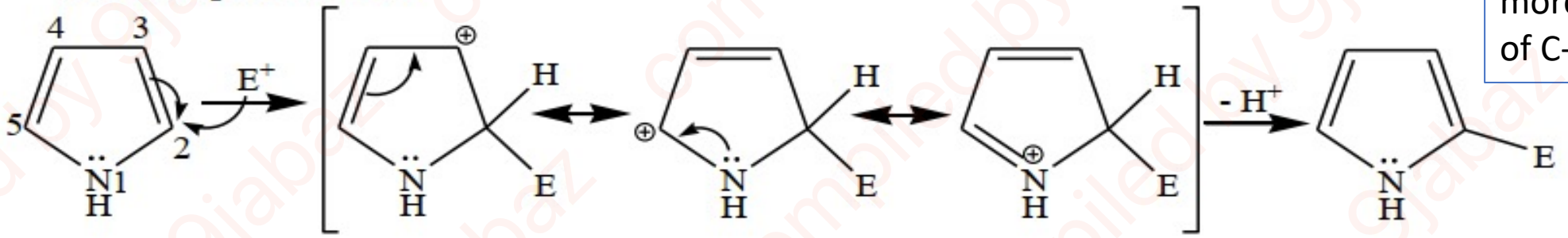
Pyrrole is an aromatic compound and more reactive than benzene. Because of the aromatic nature pyrrole gives all characteristic reactions (electrophilic substitution reactions) of aromatic compounds such as halogenation, nitration, sulphonation, Friedel-Crafts reactions etc

ELECTROPHILIC AROMATIC SUBSTITUTION OF PYRROLE

Attack at position C-3:

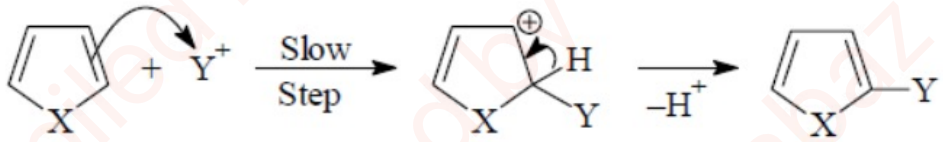


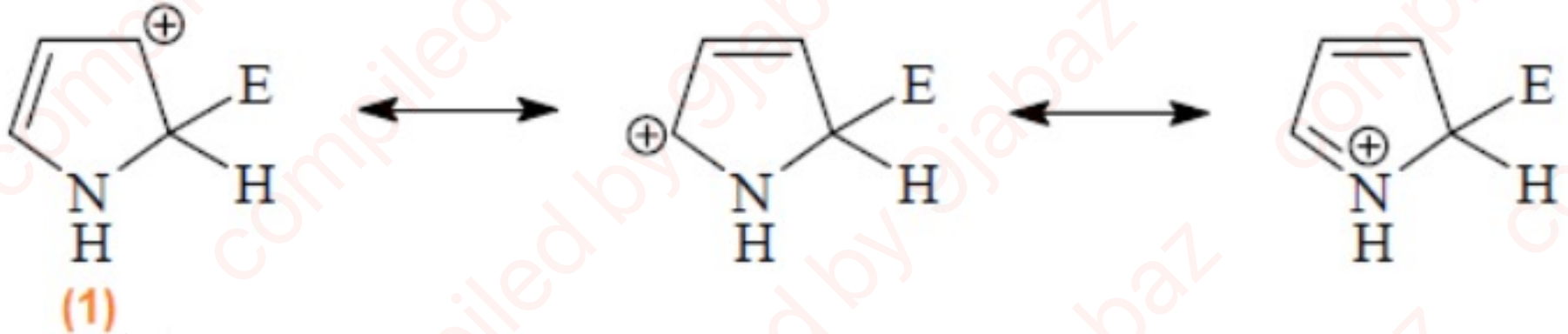
Attack at position C-2:



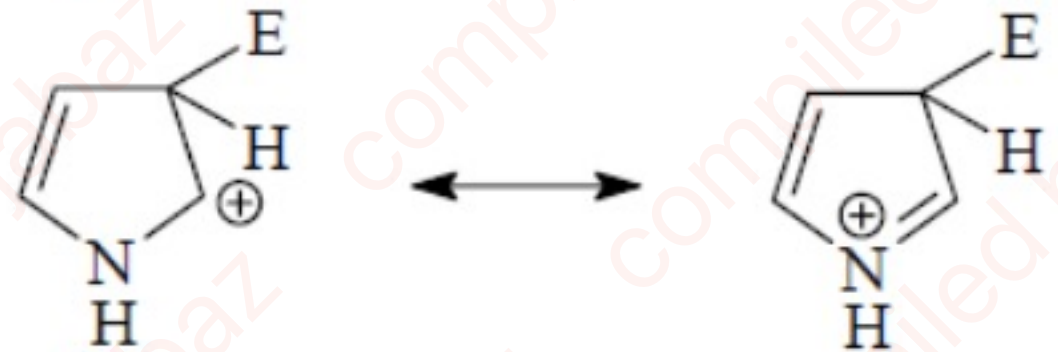
E= electrophile

1. Attack at C-3 give 2 while at C-2 gives 3 resonating structures;
2. the intermediate (the resonance stabilized carbocation) obtained by the approach of the electrophile at C-2 is more stable than that of C-3.





(1)



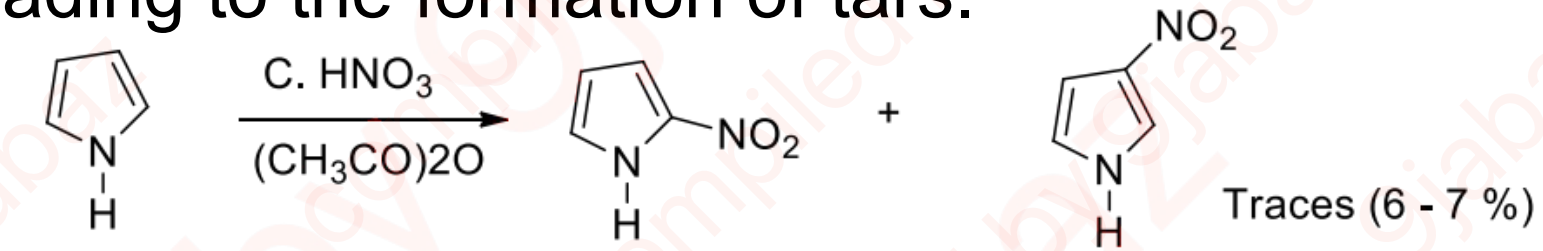
(2)

When position 2 is occuppied, the electrophile picks position 3

Electrophilic Substitution Reactions of Pyrrole

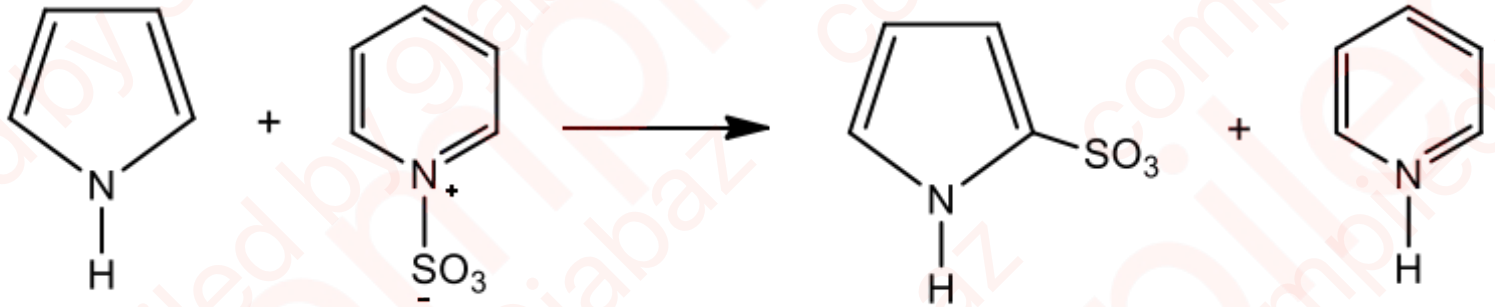
Pyrrole is more reactive than benzene due to the presence of the nitrogen a tom in its 5-membered ring.

1. **Nitration**: milder reagents such as conc. HNO_3 in acetic anhydride are used instead of the normal nitrating agents which are too strong for pyrrole leading to the formation of tars.



2-nitropyrrole

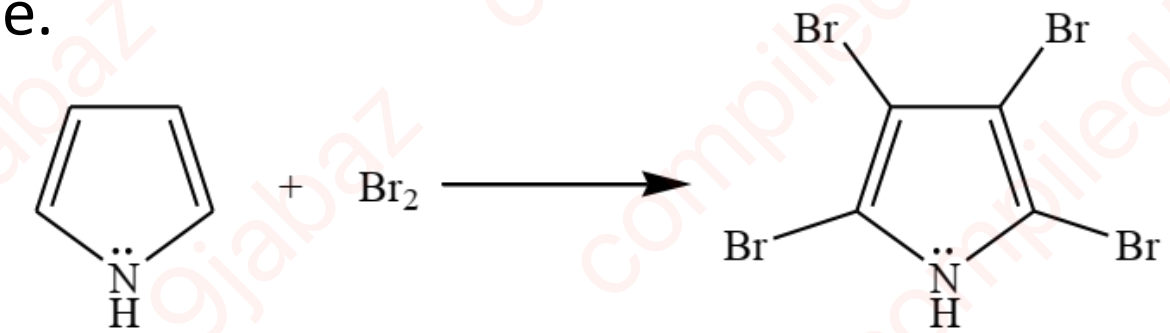
2. **Sulfonation**: milder reagents like pyridinium sulphonate is used to avoid polymerization under vigorous condition.



2-pyrrolesulfonic acid

3. **Friedel Craft Acylation**: Pyrrole react with acetic anhydride to form 2-acetylpyrrole without the need of a catalyst.

4. **Halogenation**: Pyrrole reacts with halogens [X_2 (X_2 = Cl_2, Br_2 and I_2)] to give tetrahalopyrrole.



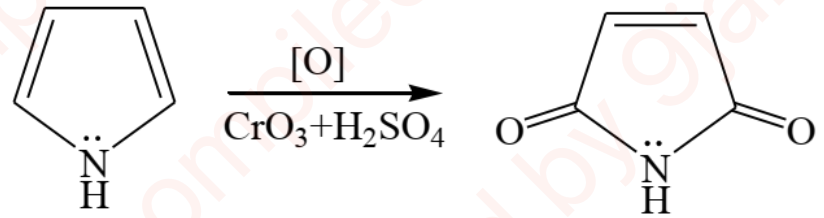
Pyrrole

2,3,4,5-tetrabromopyrrole

Other reactions of pyrrole include oxidation, reduction, diazotization etc.

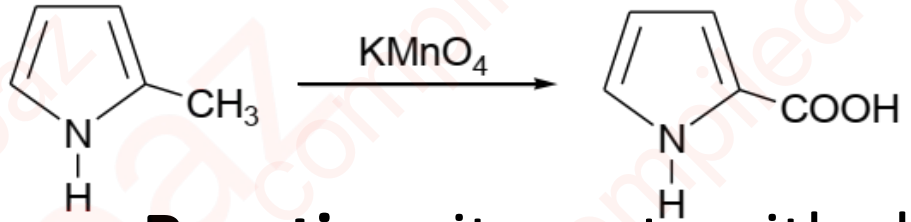
2. Oxidation: (i.) pyrrole is oxidized to form maleimide which is further reduced to fom pyrrolidine (ii) oxidized with $KMnO_4$ gives its carboxylic acid.

i.

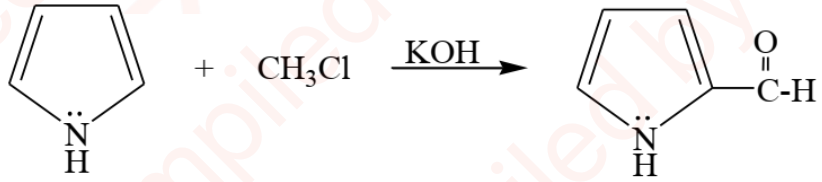


Pyrrole — Pyrrole-2,5-dione (Malecimide)

ii.

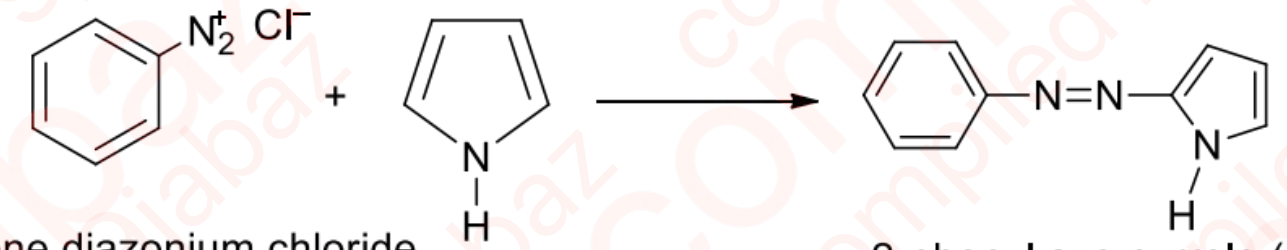


3. Reimer-Tiemann Reaction: it reacts with chloroform in the presence of a strong base to form 2-formylpyrrole



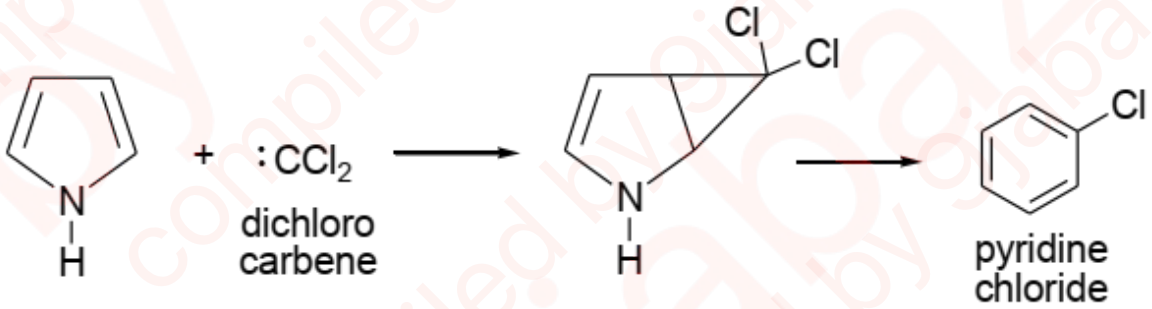
Pyrrole — 2-Formylpyrrole

4. Diazo Coupling: Pyrrole react with benzenediazonium chloride to form 2-phenylazopyrrole.

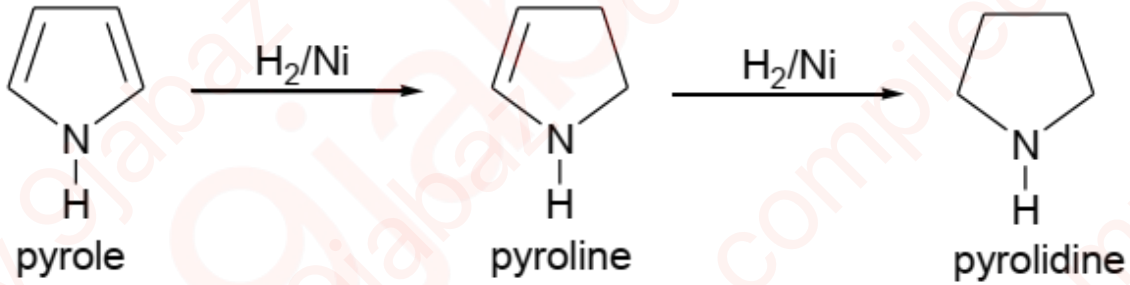


Benzene diazonium chloride — 2-phenyl azo pyrrole (a dye)

5. Reaction with carbene to give pyridine chloride.

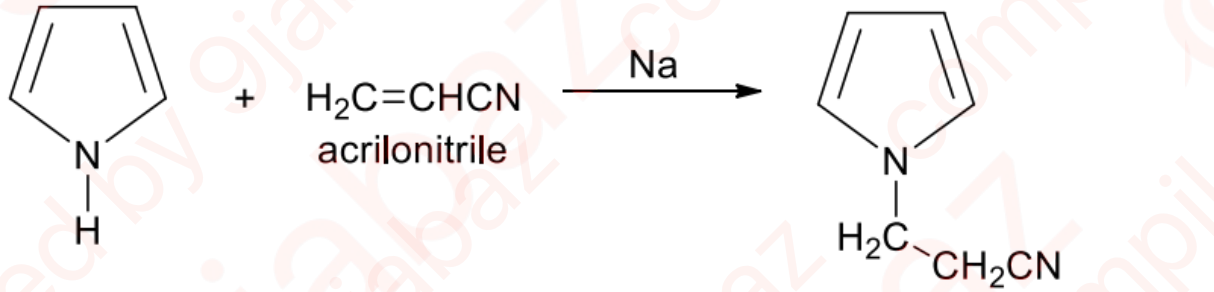


6. Reduction: Pyrole can be reduced by catalytic hydrogen i.e. H_2/Ni or H_2/Pd, Zn/Acetic acid. Pyrole is partially reduced to pyroline, further reduction give pyrolidine.



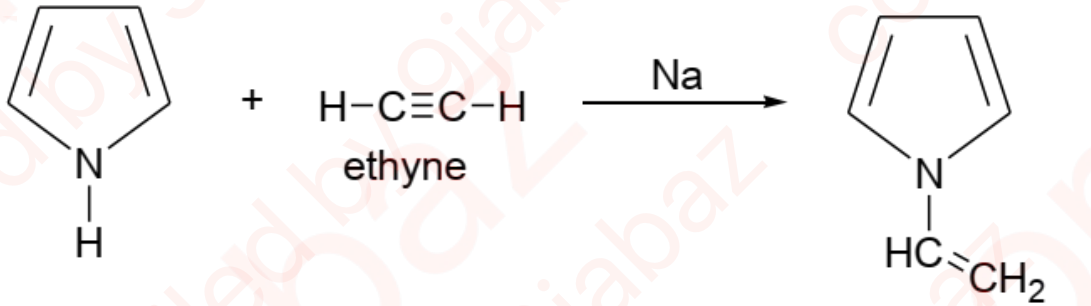
NUCLEOPHILIC REACTIONS OF PYRROLE

The 2/α-position is more susceptible because all the electrons are enhanced to move towards the positively charged nitrogen atom. However, substitution takes place on the nitrogen atom, and hence it is said to be nucleophilic, examples are reaction of pyrole with acetylenes and other unsaturated compounds e.g. acrylonitrile, acetylene, etc. in the presence of alkaline metal catalyst like sodium or potassium.



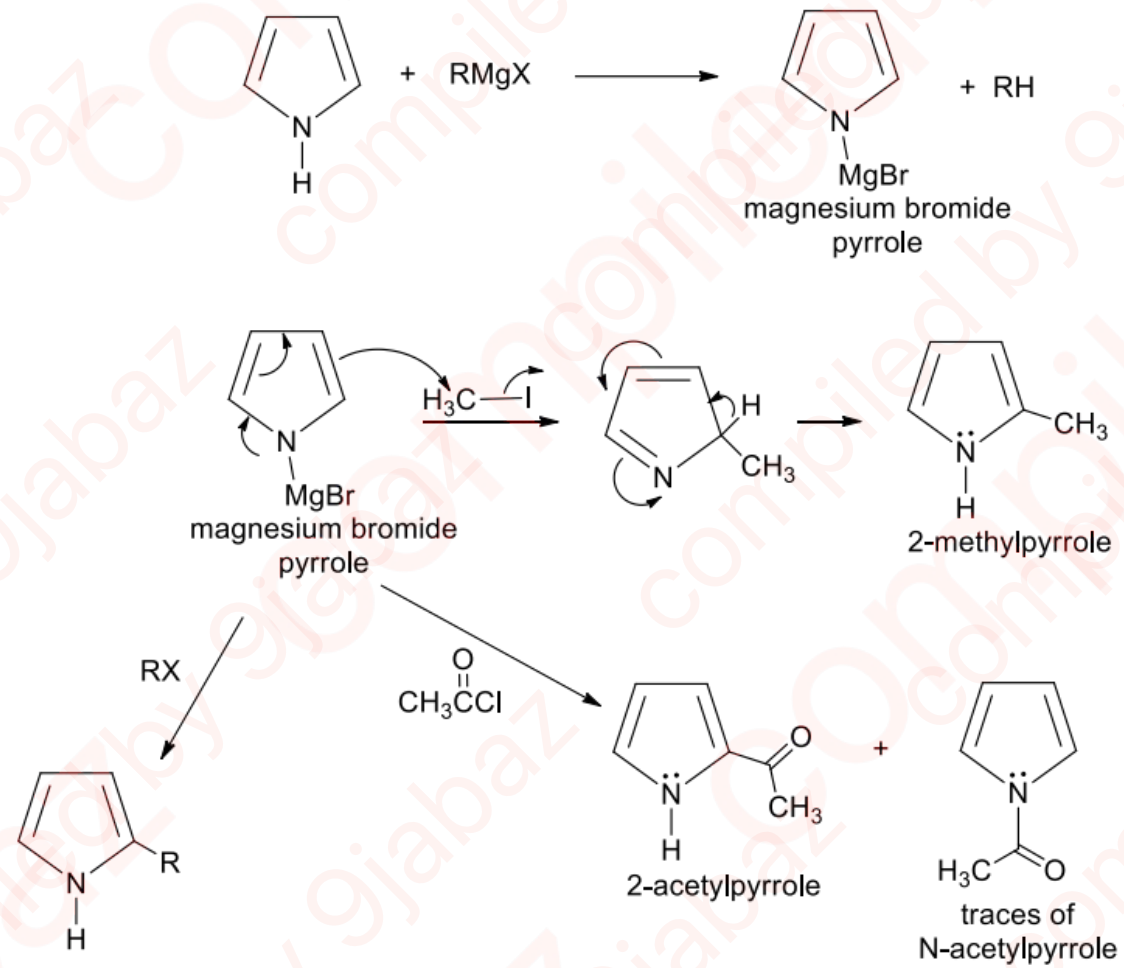
ethylonitrile pyrrole
(N-ethylcyano pyrrole)

A. Reaction with acrylonitrile



ethene pyrole

B. Reaction with acetylene



C. Reaction with Grignard reagent/alkyl lithium

ASSIGNMENT

1. Describe the synthesis of pyrrole from bone oil.
2. Draw the complete mechanism of the Paal Knorr synthesis of Pyrrole using a named 1,4-dicarbonyl compound with ammonia.
3. Explain why electrophilic substitution occurs preferentially at the α-position.
4. Discuss the biological significance of pyrrole-containing compounds.

Pyrrole: An Aromatic Heterocyclic Compound

1. Introduction

Pyrrole is a five-membered aromatic heterocyclic compound containing one nitrogen atom. Its molecular formula is C_4H_4NH, and it is classified as an *azole*. Pyrrole is the foundational unit of many biologically important molecules, including heme (in hemoglobin), chlorophyll, and vitamin B_{12}.

2. Structure and Aromaticity

Pyrrole has a planar, five-membered ring with the following structure:

- Four carbon atoms and one nitrogen atom form the ring.
- The nitrogen atom contributes its lone pair of electrons into the π-system.
- This gives pyrrole a total of 6 π-electrons (4 from the two double bonds + 2 from nitrogen's lone pair), satisfying Hückel's rule (4n + 2, where n = 1).

Because the nitrogen lone pair is delocalized into the ring, pyrrole fulfils the conditions for aromaticity:

1. Cyclic structure
2. Planar molecule
3. Fully conjugated (alternating single and double bonds + lone pair)
4. Obeys Hückel's rule (6 π-electrons)

3. Stability and Resonance

Pyrrole is stabilized by resonance. Five canonical structures can be drawn:

- The lone pair on nitrogen is delocalized across the entire ring.
- This delocalization makes all carbon atoms electron-rich (high electron density).
- The nitrogen atom, by donating its lone pair into the ring, becomes electropositive (electron-deficient relative to a typical amine).

Key consequence: Because nitrogen donates electrons into the ring, pyrrole is a much weaker base than typical amines (pKa of conjugate acid ≈ −3.8). Protonation on nitrogen would destroy aromaticity by removing the lone pair from conjugation.

α vs. β Positions

The ring has two types of positions:

- α-positions (C-2 and C-5): Adjacent to nitrogen

- β-positions (C-3 and C-4): Further from nitrogen

Electrophilic attack at the α-position generates an intermediate stabilized by 3 resonance structures, while attack at the β-position generates only 2 resonance structures. Therefore, Electrophilic substitution is strongly preferred at the α-position (C-2). When C-2 is already occupied, the electrophile attacks C-3 (the β-position).

4. Physical Properties

Property	Value/Description
Appearance	Colorless liquid
Boiling point	131°C
Air sensitivity	Turns brown on exposure to air; gradually resinifies
Solubility in water	Slightly soluble
Solubility in ether/ethanol	Completely miscible
Odor	Characteristic, chloroform-like

5. Synthesis of Pyrrole

5.1 Paal–Knorr Synthesis

The most important and widely used method.

Reagents: A 1,4-dicarbonyl compound + a primary amine (or ammonia)

Reaction:

$$\text{R-CO-CH}_2\text{-CH}_2\text{-CO-R'} + \text{NH}_3 \xrightarrow{\Delta} \text{Pyrrole} + 2\text{H}_2\text{O}$$

A classic example uses acetonylacetone (2,5-hexanedione) with ammonia to give 2,5-dimethylpyrrole.

Mechanism of Paal–Knorr Synthesis:

1. Step 1 — Nucleophilic addition: The amine (NH_3) attacks one of the carbonyl carbons of the 1,4-diketone, forming a hemiaminal (carbinolamine).
2. Step 2 — Dehydration: Loss of water forms an imine (Schiff base) intermediate.
3. Step 3 — Intramolecular cyclization: The imine nitrogen attacks the second carbonyl group intramolecularly, forming a 5-membered ring hemiaminal.

4. Step 4 — Second dehydration: Loss of a second water molecule forms the dihydropyrrole.
5. Step 5 — Tautomerization/aromatization: The ring aromatizes to give pyrrole.

5.2 Knorr Pyrrole Synthesis

Uses an α-amino carbonyl compound (e.g., ethyl glycinate or an α-aminoketone) condensed with a β-ketoester or active methylene compound.

- The α-amino group reacts with the active methylene group.
- Cyclization and dehydration yield a substituted pyrrole.
- This method is particularly useful for preparing pyrroles with specific substituents at defined positions.

5.3 From Furan (Industrial Method)

Reagents: Furan + ammonia, passed over alumina (Al_2O_3) catalyst at 400°C.

$$\text{Furan} + NH_3 \xrightarrow{Al_2O_3,\ 400^\circ C} \text{Pyrrole} + H_2O$$

The oxygen in furan is replaced by the nitrogen from ammonia. This is the primary industrial route to pyrrole.

5.4 From Bone Oil (Runge's Method)

Pyrrole was first isolated from bone oil (a product of the destructive distillation of bones). It was identified by the characteristic crimson-red color it produces when a pine chip moistened with hydrochloric acid is exposed to its vapors — the pine-chip test. In modern contexts, pyrrole can be fractionally distilled from bone oil, though this is not a practical synthetic route.

6. Chemical Properties and Reactions

Pyrrole is more reactive than benzene toward electrophilic aromatic substitution (EAS) because the ring is electron-rich due to nitrogen's lone pair donation.

6.1 Electrophilic Aromatic Substitution (EAS)

Principle

Electrophiles preferentially attack the α-position (C-2) because:

- The intermediate arenium ion (Wheland intermediate) at C-2 is stabilized by 3 resonance structures.

- At C-3, only 2 resonance structures stabilize the intermediate.
- When C-2 is blocked, substitution occurs at C-3 (β-position).

Note: Strong acids and strong reagents must be avoided because pyrrole polymerizes under acidic conditions (the nitrogen lone pair is not available for protonation since it is in the aromatic system — forcing protonation destroys aromaticity and leads to polymerization/tarring).

A. Nitration

- Reagent: Conc. HNO_3 in acetic anhydride (mild conditions)
- Product: 2-nitropyrrole
- Normal mixed acid (HNO_3/H_2SO_4) is avoided as it is too strong and causes decomposition/tarring.

B. Sulfonation

- Reagent: Pyridine–SO_3 complex (pyridinium sulfonate) — a mild sulfonating agent
- Product: Pyrrole-2-sulfonic acid
- Concentrated H_2SO_4 is avoided because it causes polymerization.

C. Friedel–Crafts Acylation

- Reagent: Acetic anhydride (no Lewis acid catalyst needed)
- Product: 2-Acetylpyrrole
- Pyrrole is reactive enough that no catalyst is required, unlike benzene.

D. Halogenation

- Reagent: X_2 (Cl_2, Br_2, or I_2)
- Product: Tetrahalopyrrole (all four positions halogenated)
- Pyrrole is so reactive that monohalogenation is difficult to control; all four ring carbons are halogenated under normal conditions.
- Controlled conditions can yield 2-halopyrrole.

6.2 Oxidation

i. Oxidation to Maleimide:

Pyrrole is oxidized (e.g., with H_2O_2 or peracids) to give maleimide, which can be further reduced to succinimide or to pyrrolidine.

$$\text{Pyrrole} \xrightarrow{[O]} \text{Maleimide} \xrightarrow{[H]} \text{Pyrrolidine}$$

ii. Oxidation with $KMnO_4$:

Gives the corresponding carboxylic acid (ring opening or side-chain oxidation depending on substituents).

6.3 Reduction

Pyrrole undergoes catalytic hydrogenation:

- Partial reduction (H_2/Ni or Zn/acetic acid): Gives 2-pyrroline or 3-pyrroline (one double bond reduced)
- Complete reduction (H_2/Ni or H_2/Pd under pressure): Gives pyrrolidine (fully saturated, no longer aromatic)

$$\text{Pyrrole} \xrightarrow{[H]} \text{Pyrroline} \xrightarrow{[H]} \text{Pyrrolidine}$$

6.4 Reimer–Tiemann Reaction

- Reagents: $CHCl_3$ + strong base (KOH)
- Product: Pyrrole-2-carbaldehyde (2-formylpyrrole)
- Mechanism involves formation of dichlorocarbene ($:CCl_2$) which attacks the electron-rich ring at C-2.

6.5 Diazo Coupling

- Reagent: Benzenediazonium chloride ($C_6H_5N_2^+Cl^-$)
- Product: 2-Phenylazopyrrole (an azo compound)
- The electrophilic diazonium ion attacks the α-position.

6.6 Reaction with Carbene

- Pyrrole reacts with dichlorocarbene ($:CCl_2$) to give pyridine (ring expansion) via the Ciamician–Dennstedt rearrangement.

7. Nucleophilic Reactions of Pyrrole

Although pyrrole is primarily known for EAS, N-substitution reactions involve nucleophilic behavior of the nitrogen:

When treated with strong bases (e.g., sodium or potassium metal), pyrrole forms the pyrrolyl anion (pyrrolyl potassium/sodium), which acts as a nucleophile at nitrogen.

A. Reaction with Acrylonitrile

$$\text{Pyrrole} + CH_2 = CHCN \xrightarrow{KOH} \text{N-(2-cyanoethyl)pyrrole}$$

The pyrrolyl anion attacks the electrophilic carbon of acrylonitrile (Michael addition at nitrogen).

B. Reaction with Acetylene

$$\text{Pyrrole} + HC{\equiv}CH \xrightarrow{K/Na} \text{N-vinylpyrrole}$$

C. Reaction with Grignard Reagent / Alkyl Lithium

Pyrrole reacts with Grignard reagents (RMgX) or organolithium (RLi) to form N-metallated pyrroles, which are useful synthetic intermediates. The N–H proton is acidic enough (pKa ≈ 17) to be removed by strong organometallic bases.

8. Derivatives of Pyrrole

Derivative	Notes
Pyrrole-2-carboxylic acid	Found in nature; decarboxylates readily on heating
4-Hydroxy-L-proline	Related amino acid found in collagen
Porphyrins	Tetrapyrrolic macrocycles; basis of heme and chlorophyll
Indole	Benzo[b]pyrrole; found in tryptophan
Bile pigments	Bilirubin and biliverdin contain pyrrole units

9. Biological Significance of Pyrrole-Containing Compounds

The pyrrole ring is one of the most biologically important structural units in nature:

Heme (Hemoglobin and Myoglobin)

- The heme group is an iron-containing porphyrin — a tetrapyrrolic macrocycle where four pyrrole rings are linked by methine bridges (=CH–).

- Heme is the oxygen-carrying unit in hemoglobin (blood) and myoglobin (muscle).
- The iron(II) center coordinates with oxygen reversibly.

Chlorophyll

- The chlorophyll molecule (central to photosynthesis in plants) contains a magnesium-porphyrin (magnesium coordinated within a modified tetrapyrrole called a chlorin).
- Responsible for the green color of plants and the capture of light energy.

Vitamin B_{12} (Cobalamin)

- Contains a corrin ring — a modified tetrapyrrole with cobalt at the center.
- Essential for DNA synthesis and neurological function.

Bile Pigments

- Bilirubin and biliverdin are open-chain tetrapyrroles formed from the breakdown of heme.
- Bilirubin gives bile its yellow color and is responsible for jaundice when elevated in the blood.

Amino Acids and Proteins

- Tryptophan contains an indole ring (benzo-fused pyrrole) and is an essential amino acid.
- Proline and hydroxyproline are pyrrolidine-containing amino acids critical to the structure of collagen (the most abundant protein in the human body).

Porphyrias

- Disruptions in porphyrin (pyrrole-based) biosynthesis lead to diseases called porphyrias, characterized by accumulation of porphyrin intermediates, causing photosensitivity, neurological symptoms, and other effects.

10. Conditions Required for Aromaticity (Summary)

A compound is aromatic if it satisfies all of the following:

1. Cyclic — The molecule must be in a ring.
2. Planar — All atoms in the ring must lie in the same plane (sp^2 or sp hybridization).
3. Fully conjugated — Every atom in the ring must contribute a p-orbital to the π-system (continuous conjugation around the ring).

4. Hückel's Rule — The number of π-electrons must equal 4n + 2, where n = 0, 1, 2, 3…

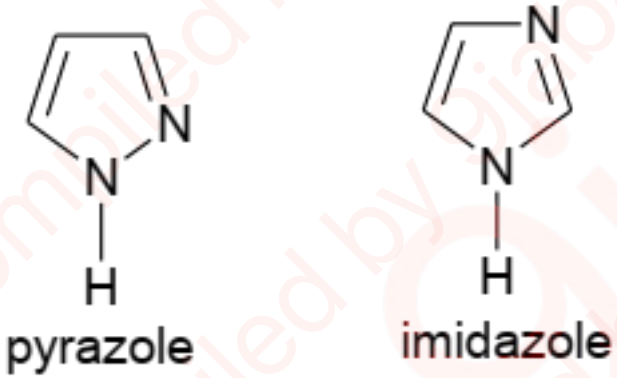
For pyrrole: 6 π-electrons (n = 1) with all conditions met.

(see all structures and mechanisms in the lecture slide)

AROMATIC HETEROCYCLIC COMPOUNDS

B. DIAZOLES (Pyrazole and Imidazole)

DIAZOLES- PYRAZOLE AND IMIDAZOLE

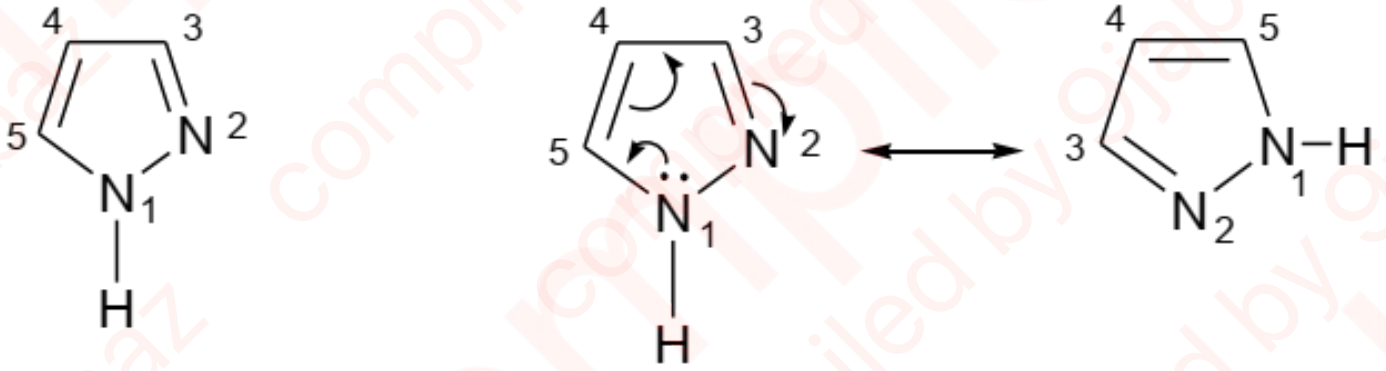


pyrazole imidazole

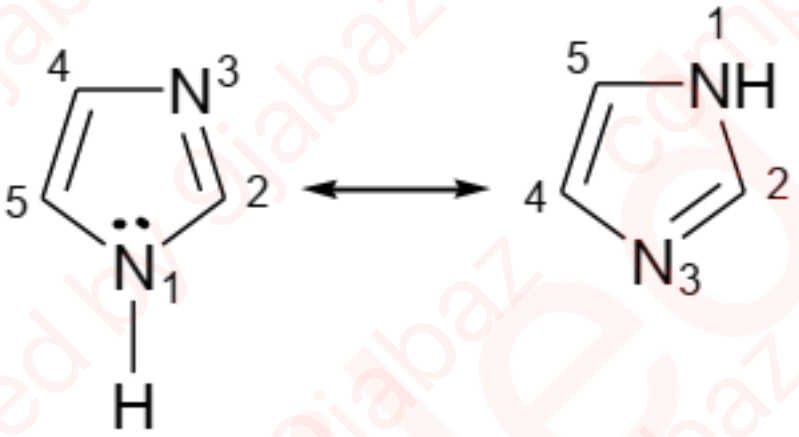
1. Pyrazoles are 1,2-diazoles while imidazoles are 1,3-diazoles.

2. Both of them are aromatic because they obey the Huckel's $(4n+2)\pi$ rule, therefore the lone pair of electrons on the imino nitrogen atom are involved in aromaticity (aromatic stabilisation). However, they are more basic than pyrole because the lone pair of electrons on their other nitrogen atom (azo methine group) are readily available for basic reactions.

Tautomerism in Diazoles



Tautomerism is more expressed in pyrazole than imidazole. Moreover, position 3 and 5 are identical i.e. for unsubstituted pyrazole at the N-position.

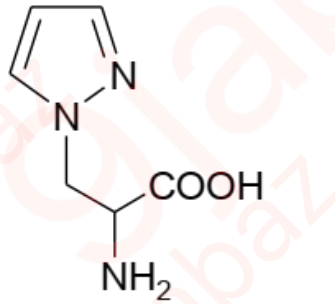


In imidazole, position 4 and 5 are identical i.e. for non-substituted imidazole.

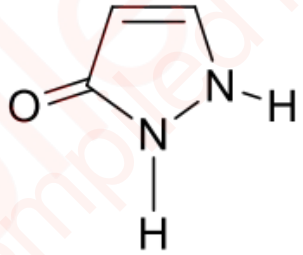
Both pyrazole and imidazole are basic but imidazole is more basic than pyrazole, because of the proximity of the nitrogen atoms in pyrazole, which by the inductive effect hold the lone pair of electrons on nitrogen firmly, therefore making it less basic than imidazole.

DERIVATIVES OF PYRAZOLE AND IMIDAZOLE

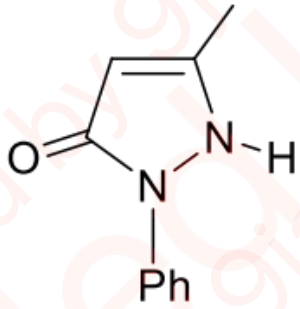
1. Pyrazole derivatives have been isolated from water melon seed known as β-[1-pyrazolyl] alanine. Pyrazolone, Antipyrine are also derivatives. Antipyrine is derived from pyrazolone and used as an antipyretic.



β–[1-pyrazolyl]alanine

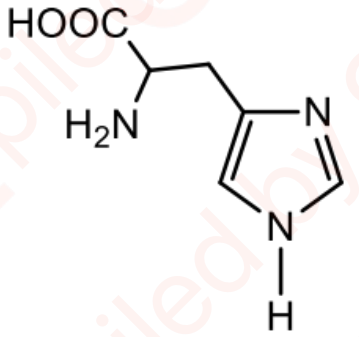


pyrazolone



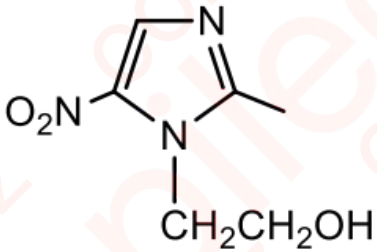
antipyrine

2. Imidazole derivatives include histidine, histamine, metroimidazole, allantoin e.t.c.



histidine

histamine

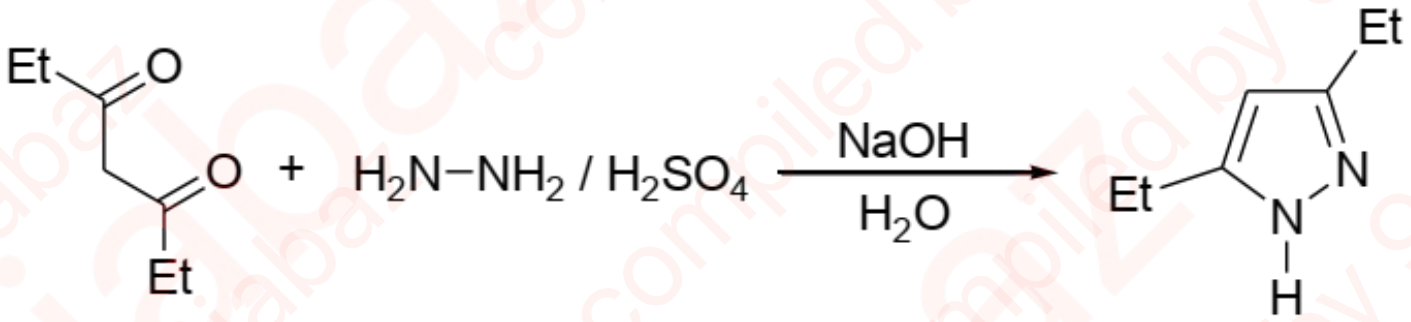


metroimidazole

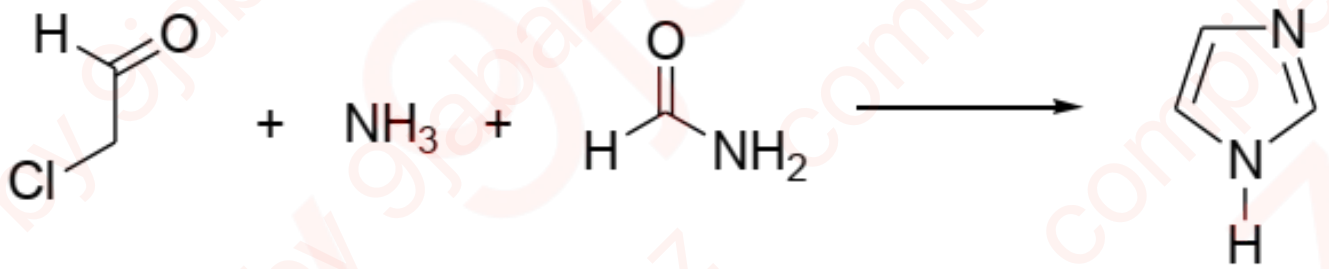
Allantoin

SYNTHESIS OF PYRAZOLE AND IMIDAZOLE

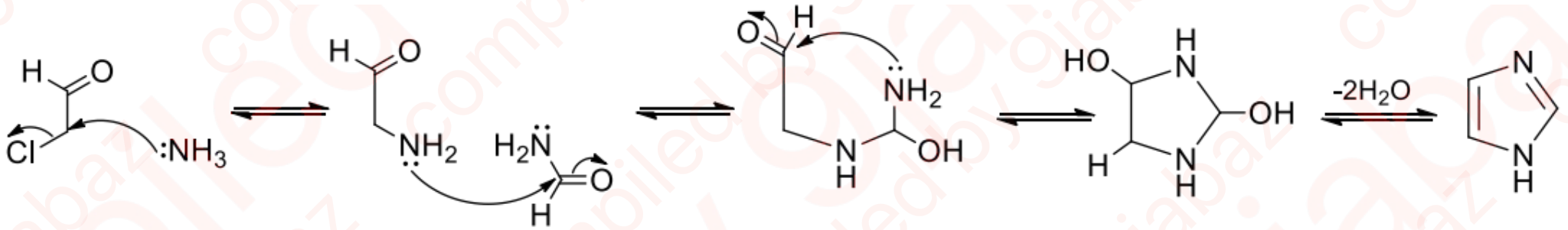
1. **Pyrazoles:** can be obtained from 1,3-dicarbonyl compounds. The 1,3-dicarbonyl compounds react with hydrazines or methylhydrazines in the presence of a base to give pyrazoles.



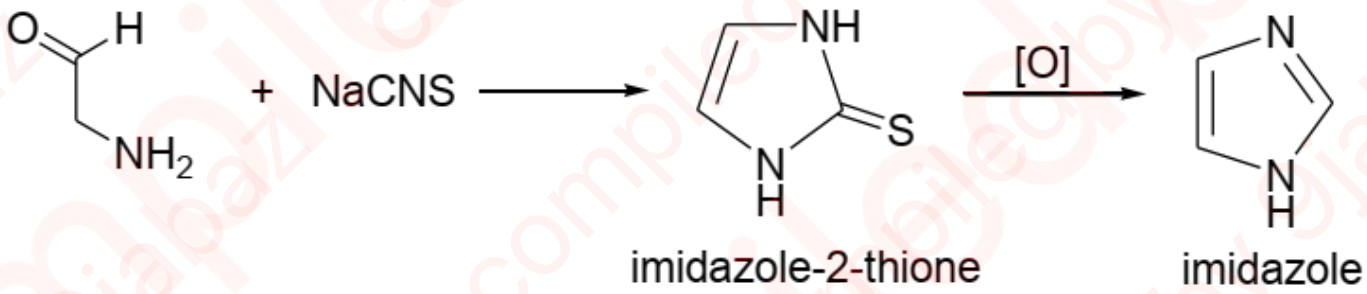
2. **Imidazoles:** can be prepared from α-halocarbonyl compounds. imidazole is formed upon heating the α-halocarbonyl compounds with ammonia and formamide.



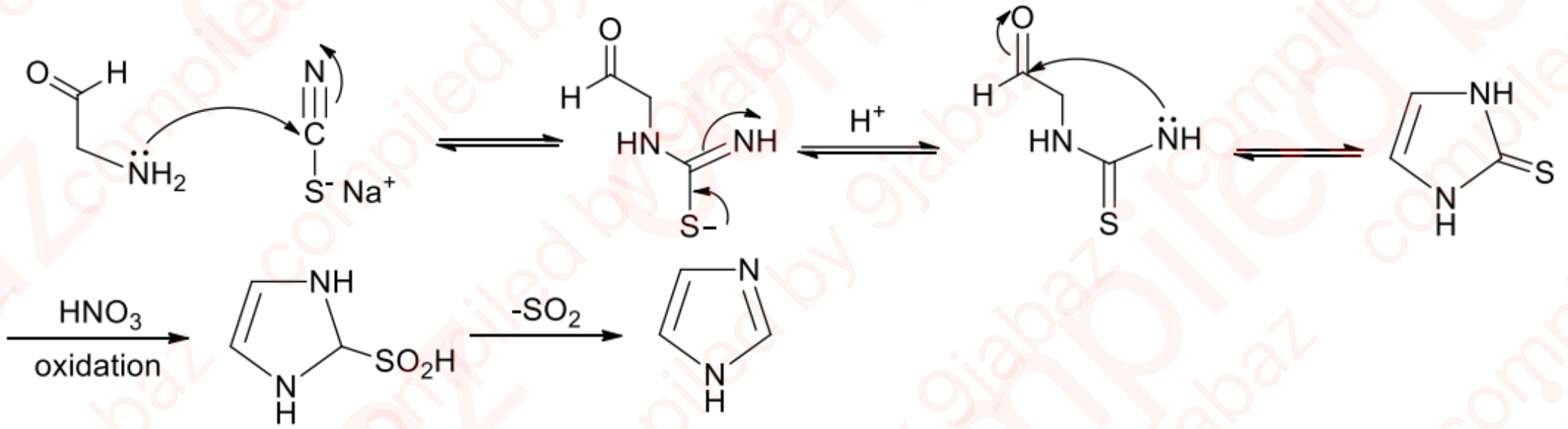
Mechanism: displacement of halogen atom by ammonia to form α-amino carbonyl compounds followed by attack by the formamide



B. Imidazole from α-aminocarbonyl compounds. This compound condenses with thio-cyanate ion to form imidazole-2-thiones. Desulphurization takes place to get the imidazole.

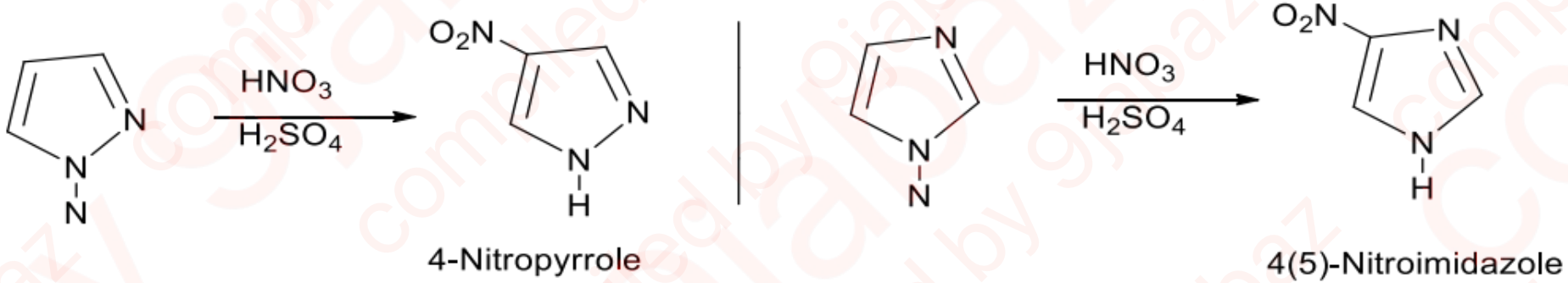


Mechanism:

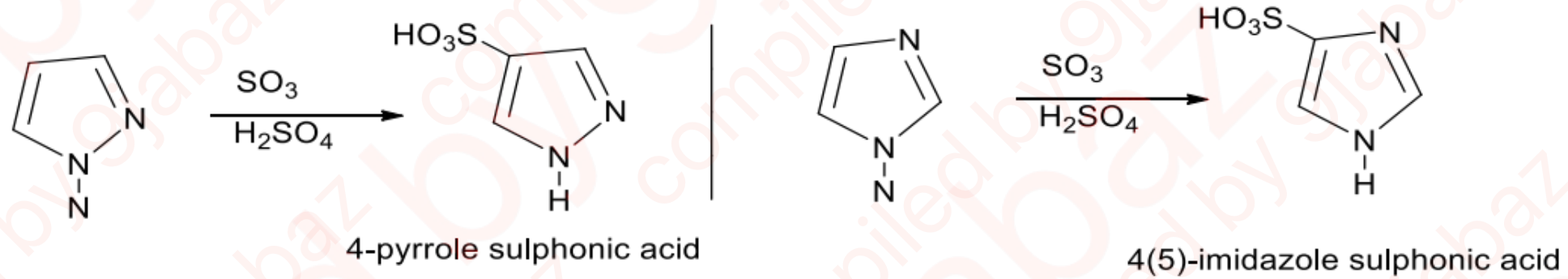


Electrophilic reaction of Pyrazole and Imidazole

Nitration



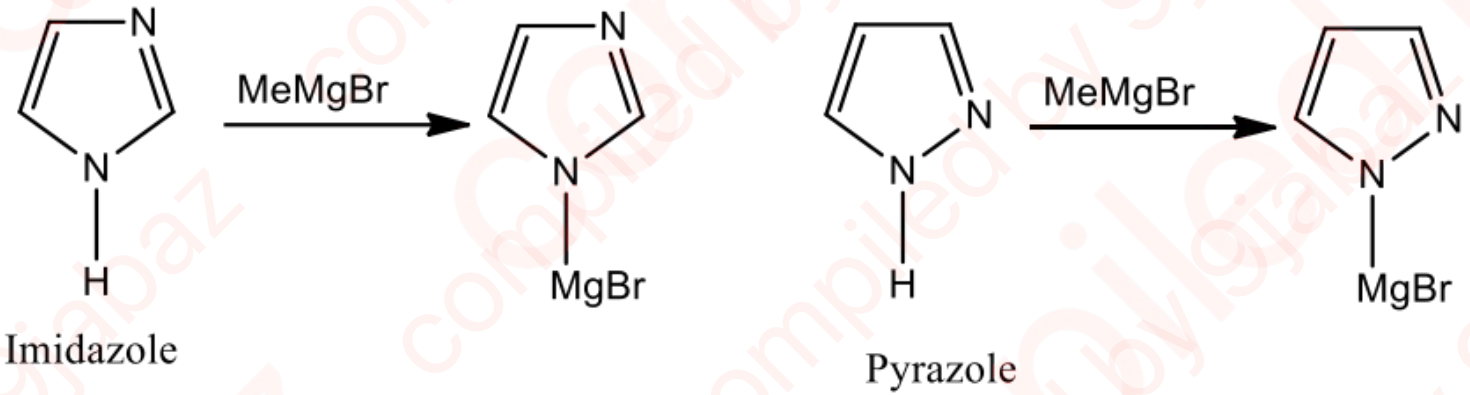
Sulphonation



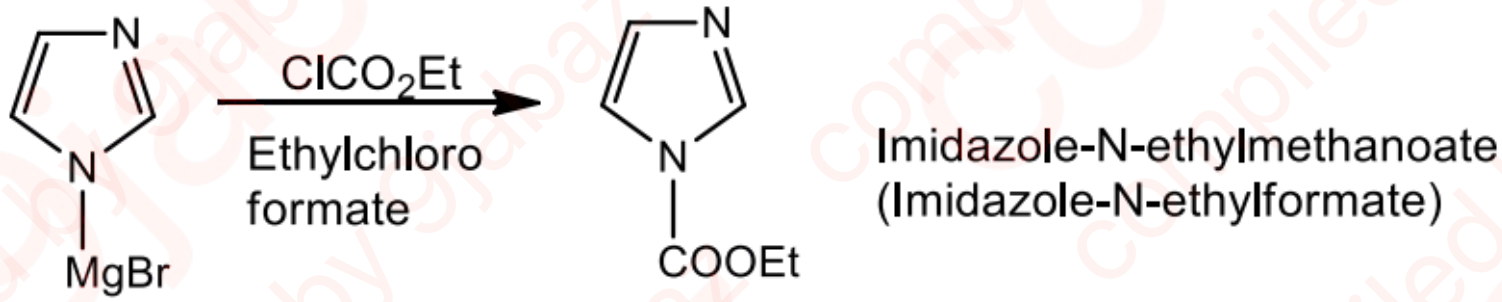
Position 4 is readily used for electrophilic substitution reaction in pyrazole while 4 and 5 which are identical in imidazole are used. Electrophilic substitution in pyrazole and imidazole require strong reaction condition because they are not as susceptible towards electrophilic reactions as pyrrole.

Nucleophilic reaction of Pyrazole and Imidazole

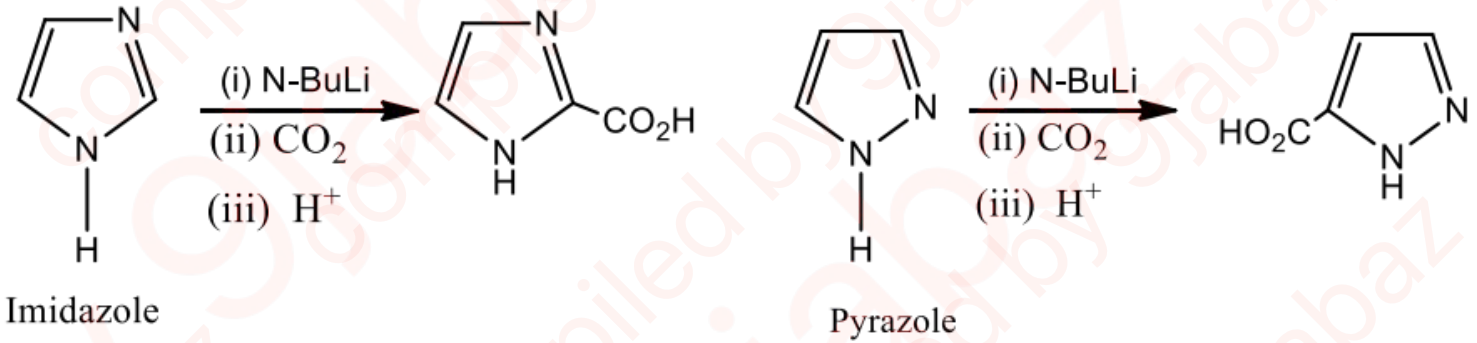
1. Imidazole and pyrazole reacts with Grignard's reagents to form N-magnesium bromide imidazole/pyrazole.



The two products are good synthetic intermediate which can be used to form a lot of chemical compound derivatives of imidazole and pyrazole.



Both of them can also react with N-butyllithium followed by CO_2 in acidic medium to form pyrazole-5- or imidazole-2-carboxylic acid



2. Imidazole react with ammoniacal silver solution to form silver salt.

ASSIGNMENT

1. Give 5 examples of 1,3-dicarbonyl compounds (with structures).
2. a. Write the mechanism for the reaction of a named 1,3-dicarbonyl compound with hydrazine/H_2SO_4 in the presence of NaOH.

   b. What is the name of the product formed?.

AROMATIC HETEROCYCLIC COMPOUNDS

INDOLE

INDOLE

1. Indole is an aromatic heterocyclic organic compound with formula C_8H_7N. It is a Fused bicyclic system of benzene + pyrrole.

2. The name Indole is a combined name of the words “indigo and oleum”, since Indole was first isolated by treatment of the indigo dye with oleum. Indigo can be converted to Isatin and then to Oxindole.

3. Indole is widely distributed in the natural environment. It is found in coal tar and in essential oils (Jesamine oil, orange oil) of many plants. The pure form of Indole has very pleasant smell and this is the reason it is used as a perfumery base.

4. Indole was first synthesized in 1866, when Adolf von Baeyer reduced Oxindole to Indole using zinc dust.

4. Indole and its derivatives are being extensively used in medicinal and pharmaceutical industry.

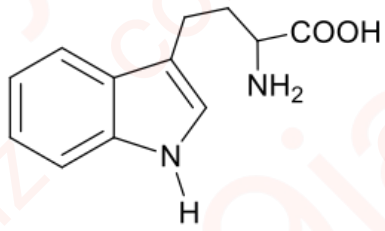
5. The IUPAC name of Indole is 1H-benzo[b] pyrrole, it is being the b-face benzo-fused isomer.

6. Indole is a π-excessive aromatic heterocycles with ten π-electrons since it follows the Huckel’s rule (i.e. 4n+2π electron rule) for n=2.

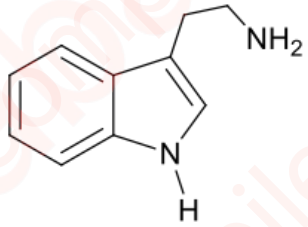
7. All the ring atoms in Indole are sp^2 hybridized. It is a Planar and conjugated structure with the nitrogen lone pair contributes to its aromaticity.

8. Indole is Colorless to pale yellow crystals, it has melting point between 52–54 °C and Boiling point of 253–254 °C.

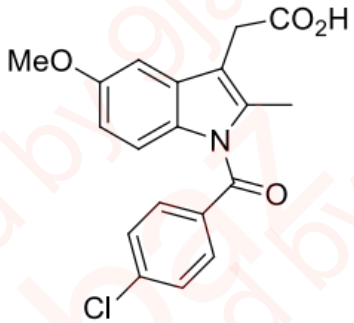
Some molecules with indole moiety include tryptamine, tryptophan, serotonin e.t.c



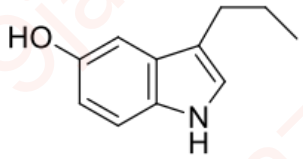
tryphtophan



tryptamine



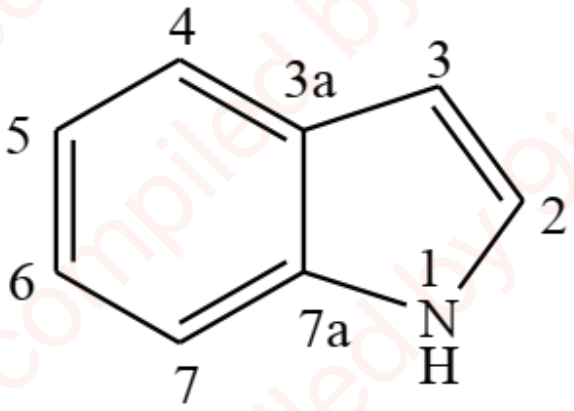
indomethacin



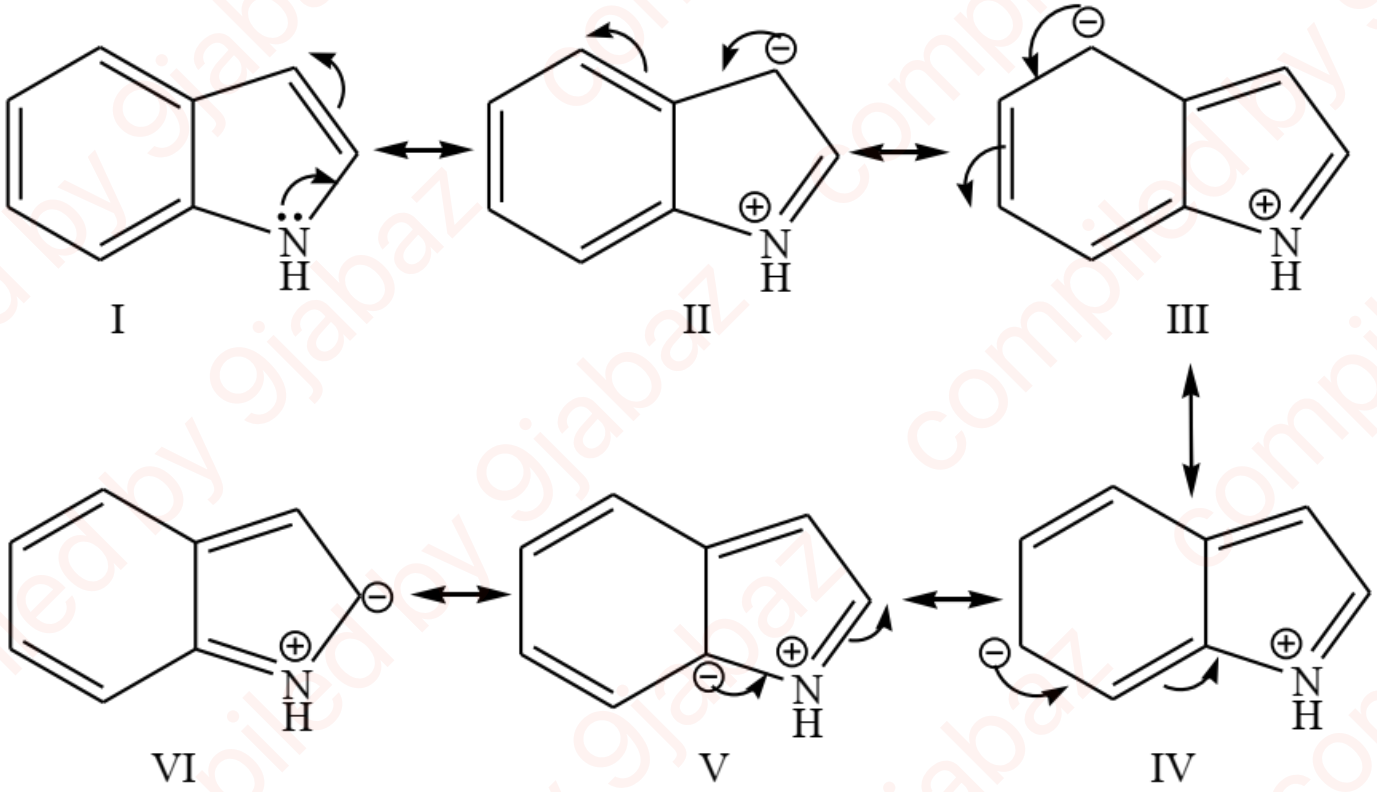
Serotonin

Some important indole drugs are Indomethacin, Sumatriptan, Reserpine, Vincristine and Vinblastine

STRUCTURE OF INDOLE



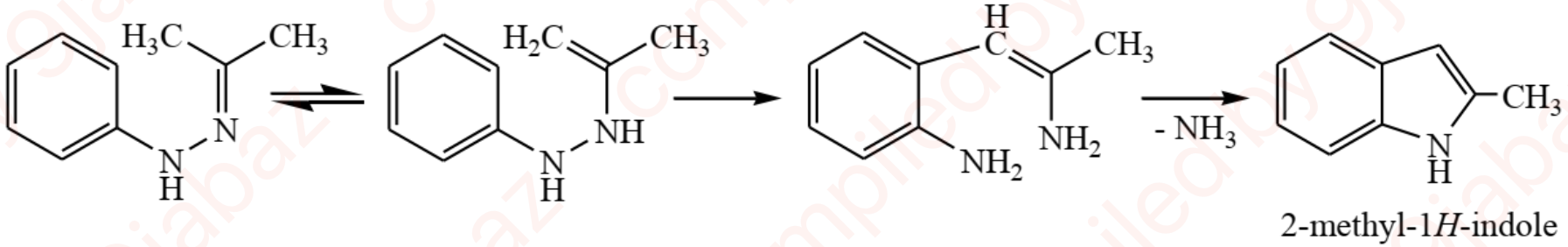
RESONANCE/CANONICAL STRUCTURES OF INDOLE



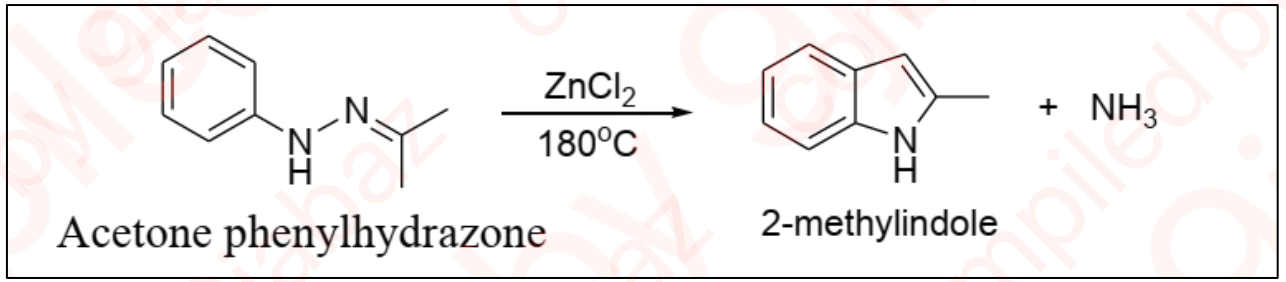
Structures IV, V and VI involve the formation of a nonbenzenoid system in which the aromaticity of benzene ring is not retained. Hence, these structures contribute less in the resonance.

Synthesis of Indole

1. Fischer-Indole synthesis: This is the most widely used method for the synthesis of Indole. It involves an acid (Lewis acid) catalyzed rearrangement of a phenylhydrazone of an aldehyde or ketone, with the elimination of a molecule of ammonia. The conventional catalysts used in this process are zinc chloride, polyphosphoric acid or a Lewis acid (BF_3) at 180 ^oC. Synthesis of 2-methyl indole can be achieved by taking the phenylhydrazone of acetone. The starting material arylhydrazones can be obtained from aldehydes, ketones, keto acids, keto esters and diketones. The reaction is as shown below.



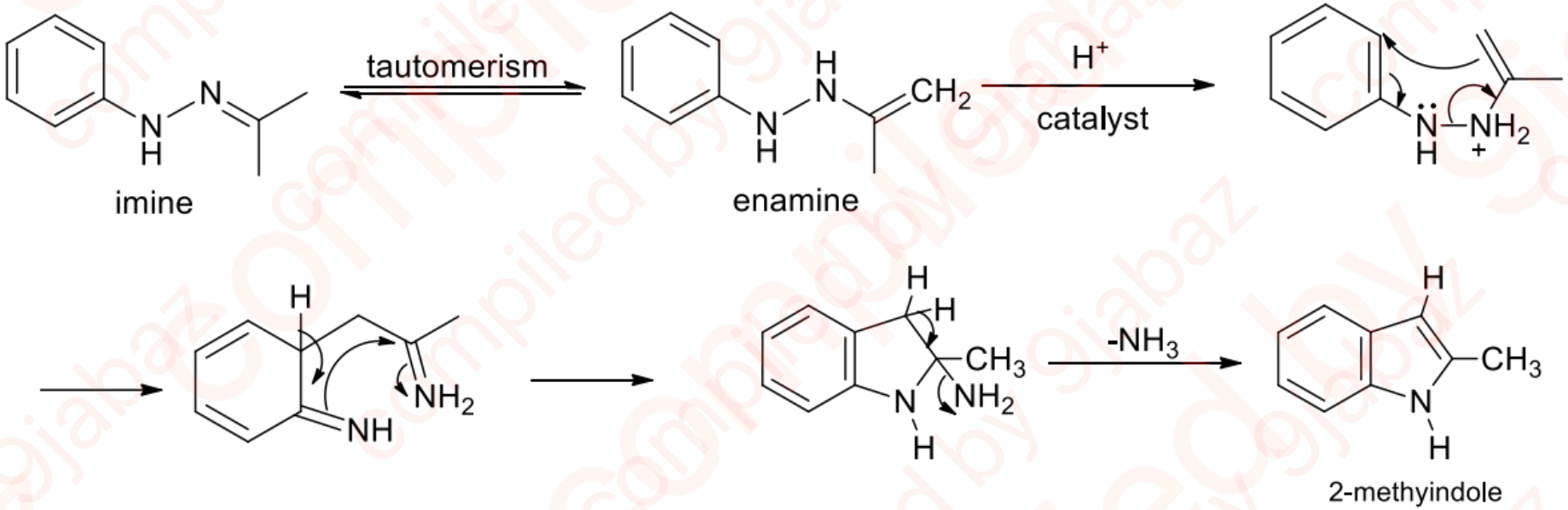
2-methyl-1*H*-indole



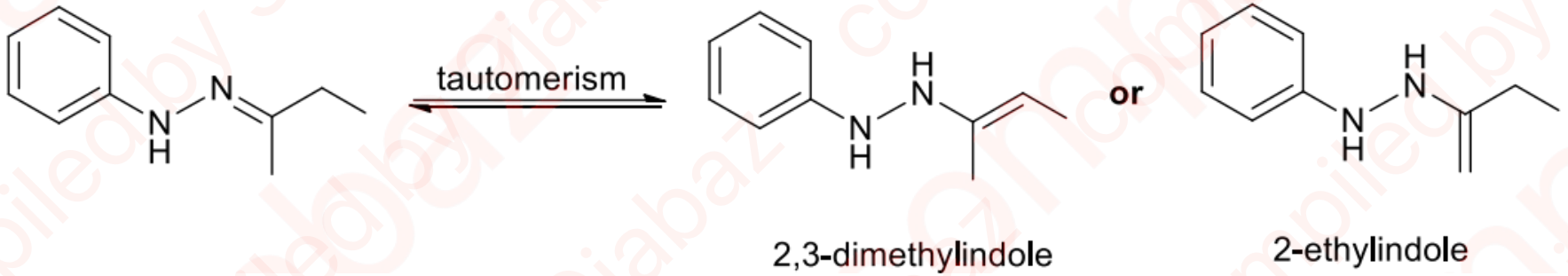
Acetone phenylhydrazone

2-methylindole

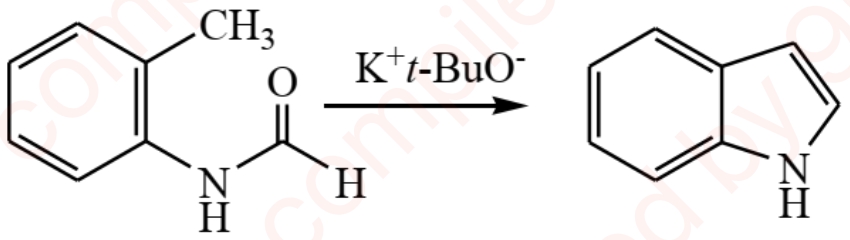
Mechanism of Fischer- Indole synthesis: takes place by acid catalyzed rearrangement of the tautomeric form of the starting phenylhydrazone as shown below:



If we use a non-symmetical hydrazine, then we can form two different products



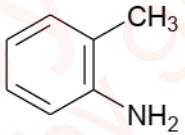
2. Madelung Synthesis: cyclic dehydration of an acetyl or acyl o-toludine in presence of a strong base and at high temperature.



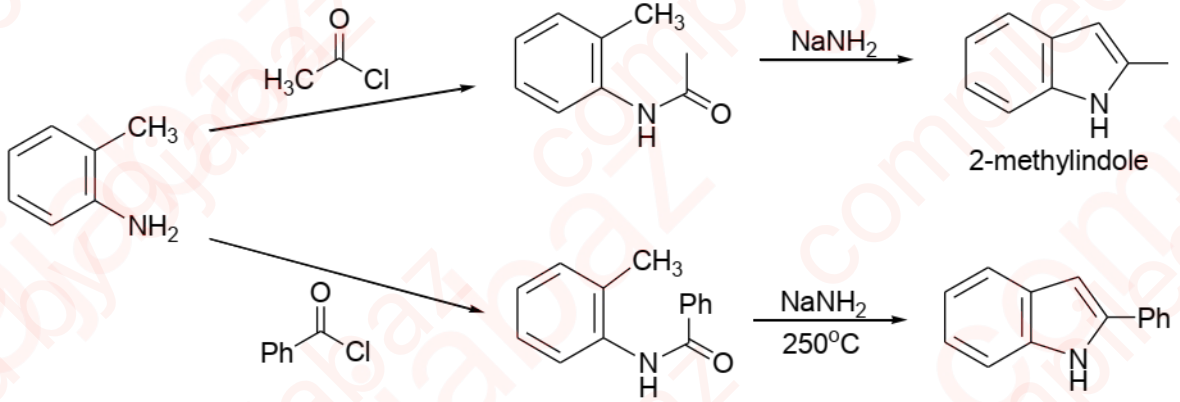
N-*o*-tolylformamide

Indole

butoxide at 250°C.



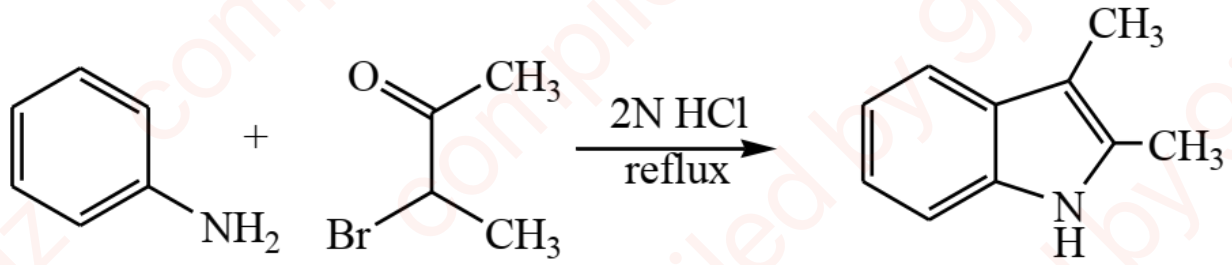
ortho-toluidine



2-methylindole

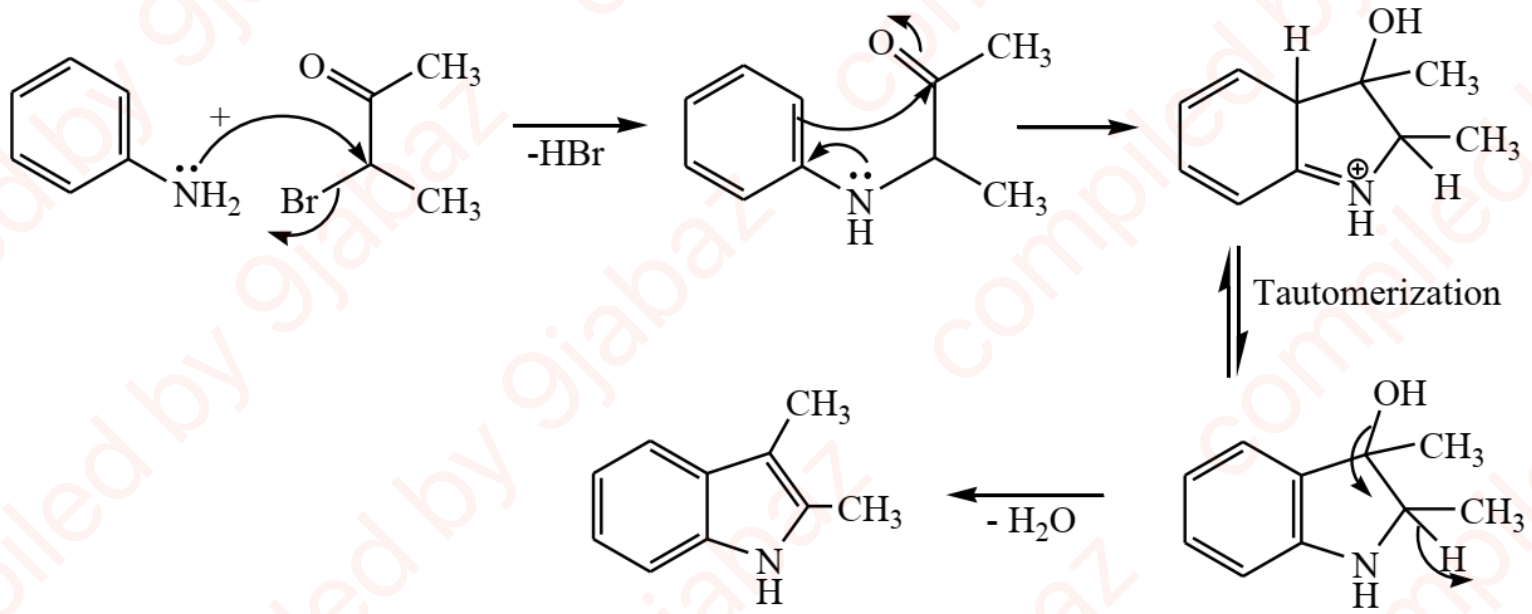
2-phenylindole

3. The Bischler's synthesis: This method involves the reaction of an aryl amine and α-haloketone or α-haloaldehyde in presence of zinc chloride under thermal or heating condition (reflux).

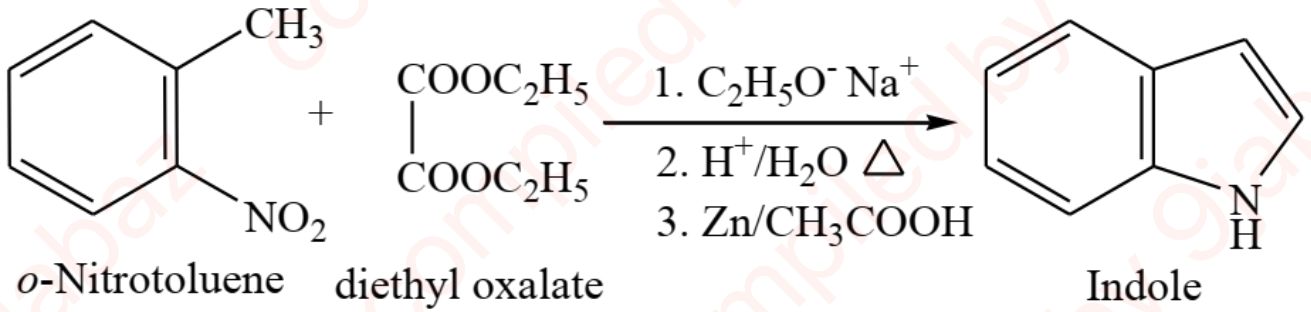


aniline 3-bromobutan-2-one 2,3-dimethyl-Indole

Mechanism

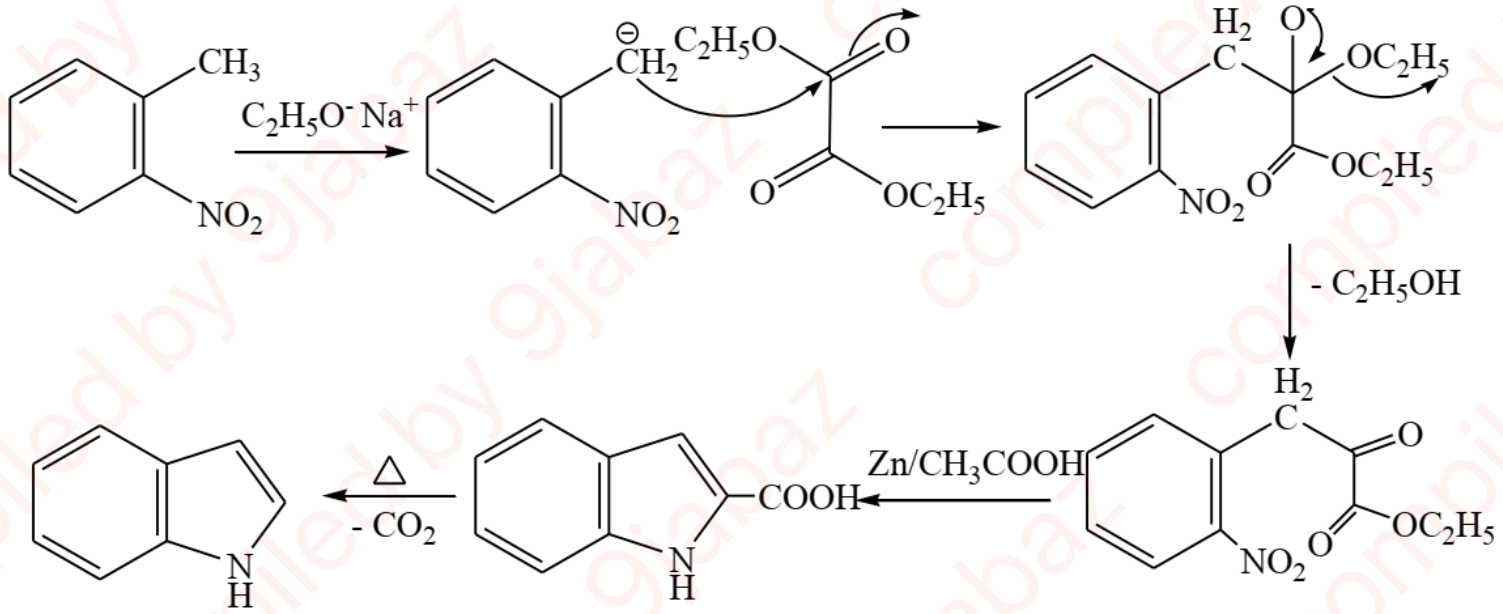


4. Reissert Synthesis: involves the base catalyzed condensation of o-nitrotoluene with oxalic acid ethyl ester (diethyl oxalate) in presence of strong base like sodium ethoxide. This condensation leads the formation of onitro-phenylpyruvate which on hydrolysis gives the corresponding acid. The resultant acid on reductive cyclization in presence of Zn/CH_3COOH yields the Indole.



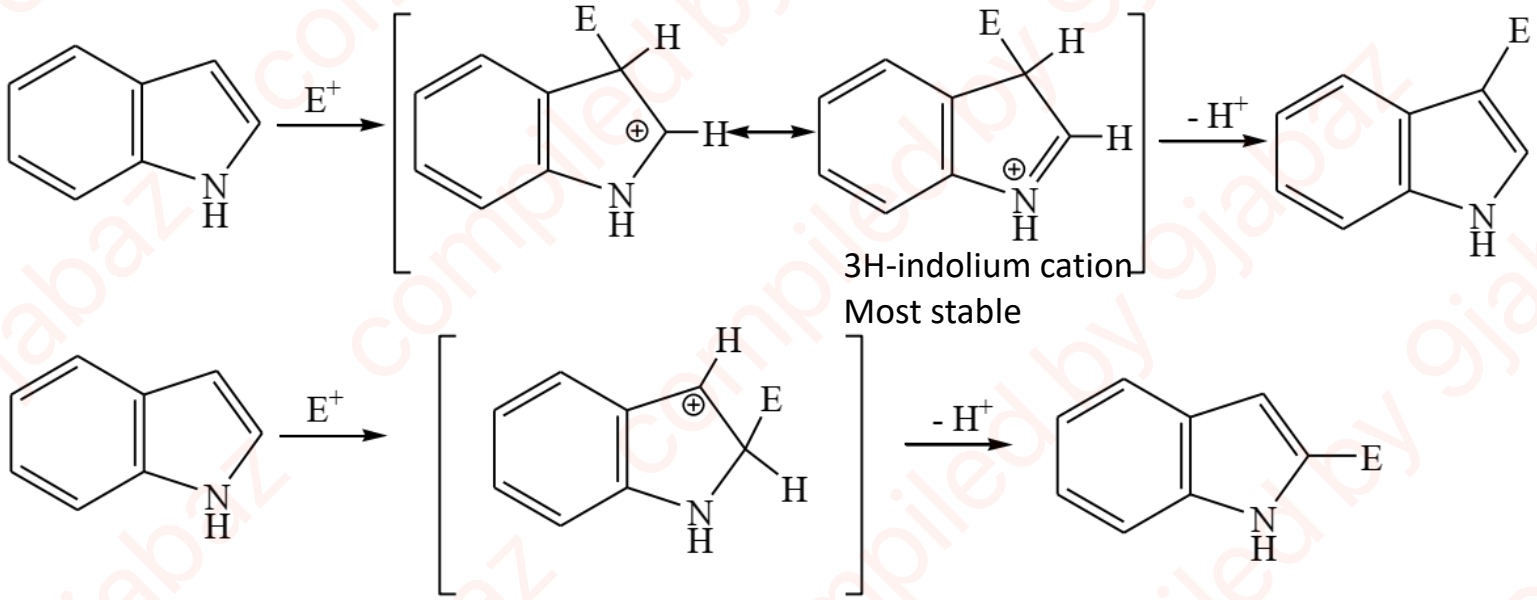
o-Nitrotoluene diethyl oxalate Indole

Mechanism

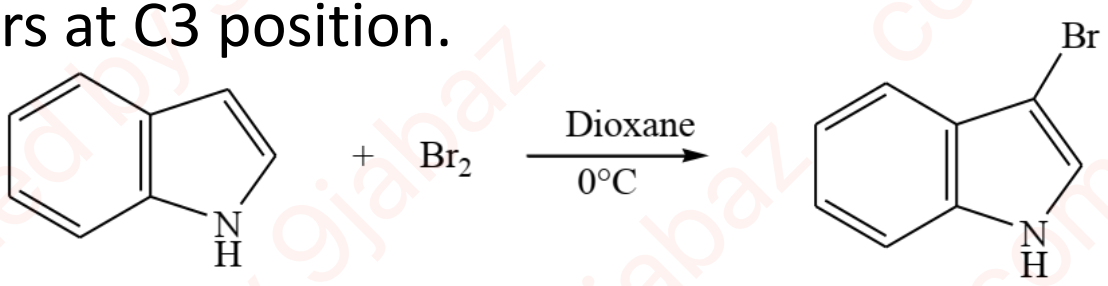


Electrophilic Substitution of Indole

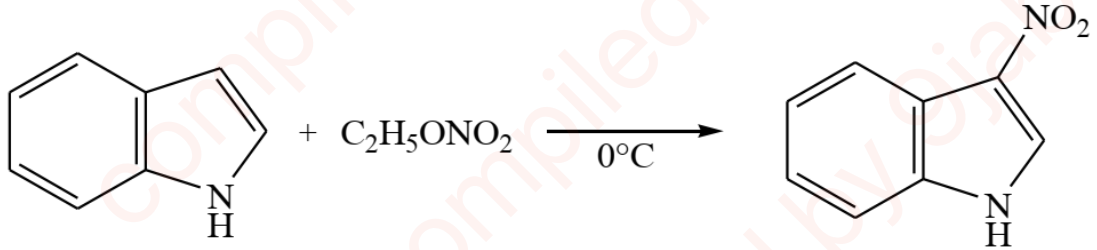
Electrophilic substitution in Indole takes place preferentially at C3. Because the lone pair of electrons on the nitrogen of the indole is not readily available, indole like pyrrole is a very weak base. However, if position 3 is occupied, position 2 can accommodate an electrophile.



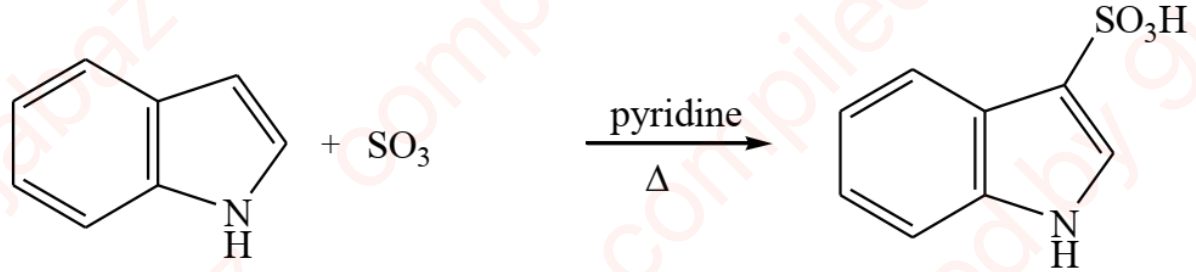
1. Bromination: Indole undergoes bromination at very low temperature (0°C) in dioxane. The bromination occurs at C3 position.



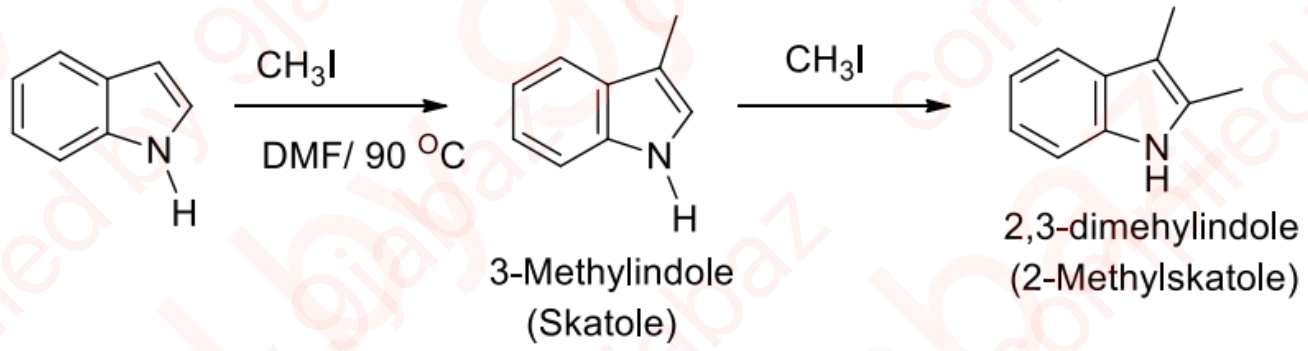
2. Nitration: Indole undergoes nitration in presence of ethyl nitrate at low temperature (0 - 5°C). Nitration of Indole also occurs at C3 with the similar mechanism as discussed above.



3. Sulphonation: Sulphonation of Indole is carried out only under milder conditions using pyridine-sulphur trioxide complex in order to minimize the acidity of the reagent.

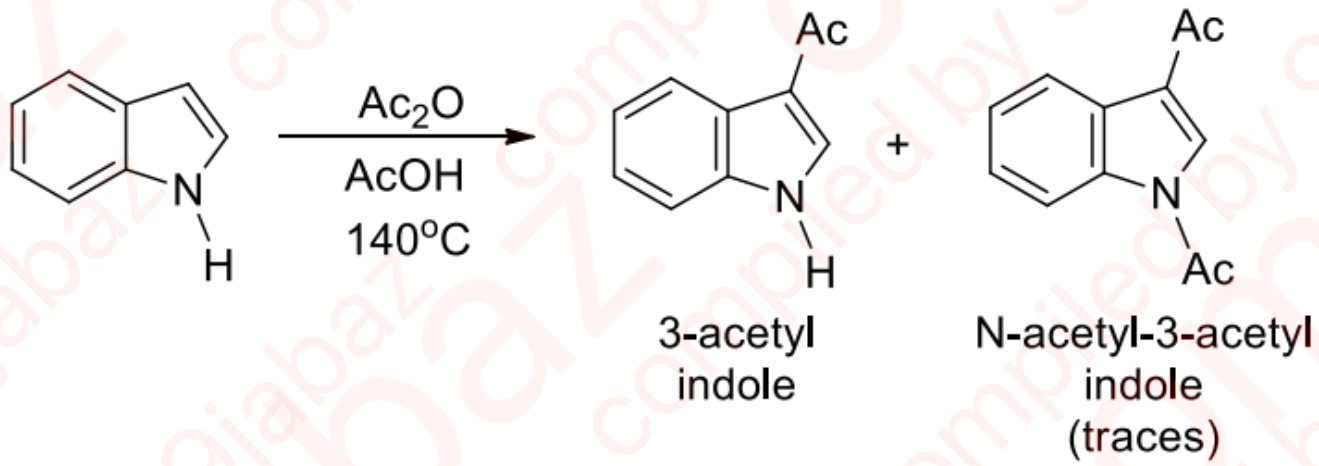


4. Friedel crafts alkylation: Indole undergoes alkylation at C3 position with alkyl iodide in N,N-dimethyl formamide (DMF) or dimethyl sulphoxide (DMSO) as solvent to give **skatole**.

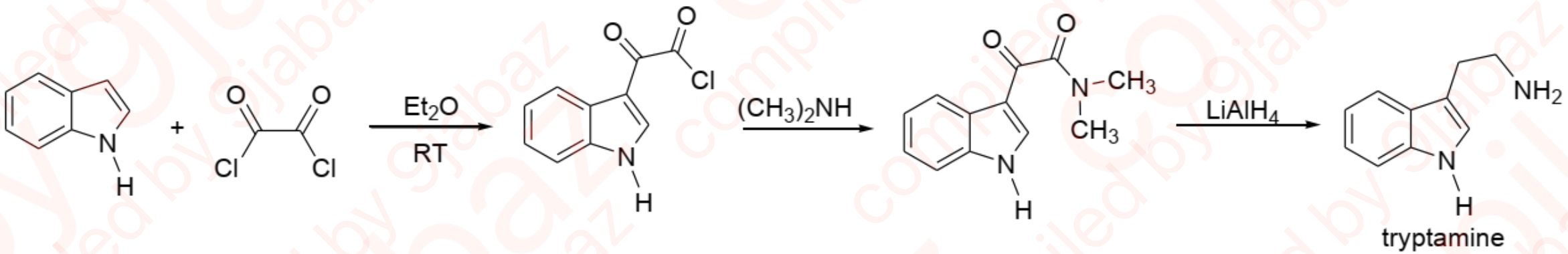


5. Acylation

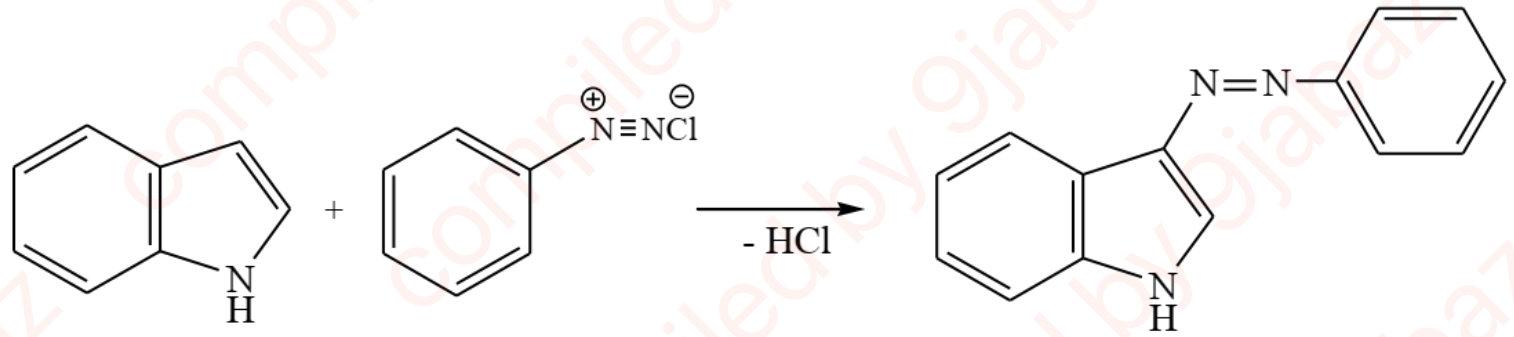
Acetic acid and acetic anhydride will react with indole to form 3-acetylindole and N-acetylindole.



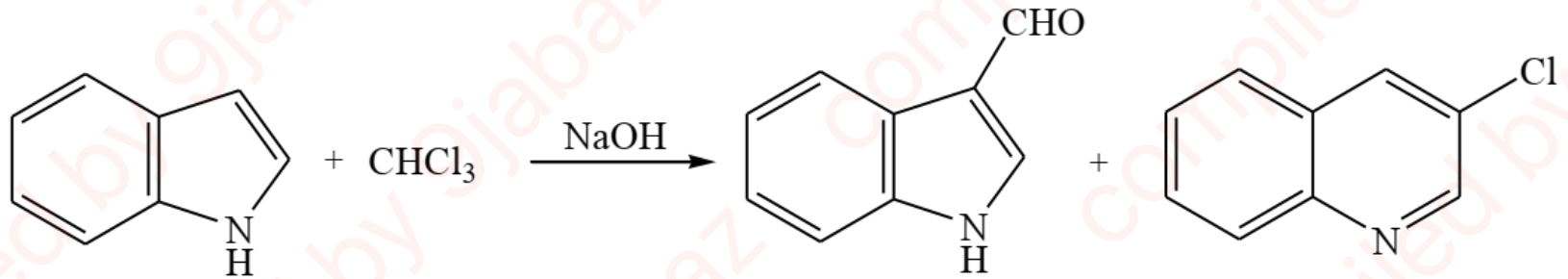
Indole can also react with oxalyl chloride.



5. Diazocoupling or Diazotization reaction: Indole reacts with benzene diazonium chloride to give 3-phenylazoindole, a diazotized coupled product.



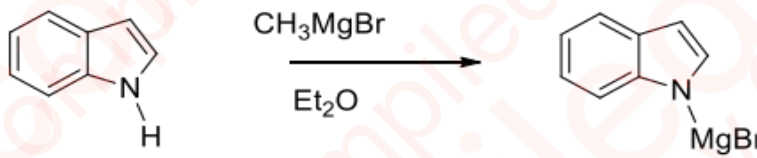
6. Reimer Tiemann formylation: Indole, like other aromatic compounds, reacts with Chloroform ($CHCl_3$) in presence of alkali to give formylated product at C3 position. This reaction proceeds via carbine intermediate. In general two products are obtained in this reaction, first, the C3 formylated product (Indole-3-cabaldehyde) and second, the rearranged product (3-Chloroquinoline).



Indole-3-carbaldehyde 3-Chloroquinoline

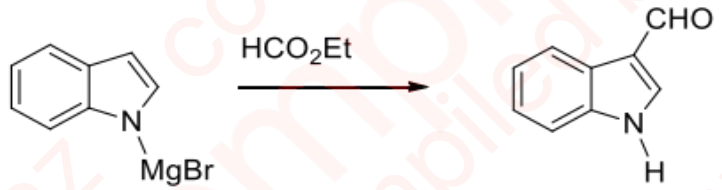
6. Reactions at N-atom: The N – H proton of indole like pyrrole is acidic and is easily attracted by metallic groups e.g NaOH; KOH; n-BuLi; Grignards reagent etc to give N-metalated derivatives

a.

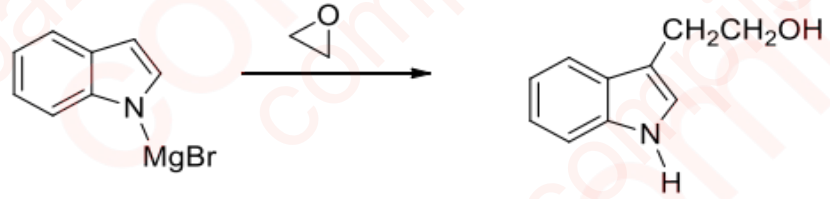


Indole-N-magnessium halide or N-halomagnesylindole is a very reactive intermediate which readily reacts with RCHO and R_2CO

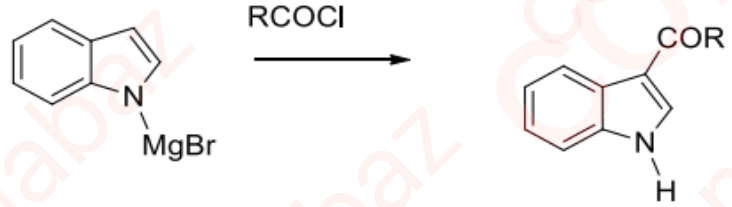
i



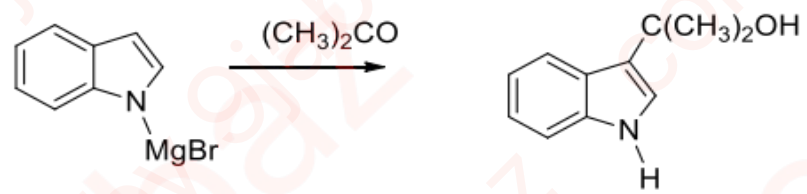
ii



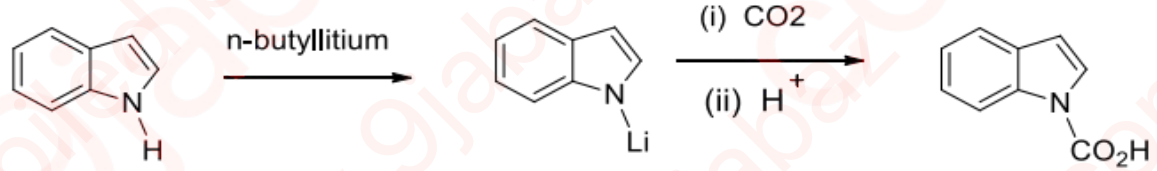
iii



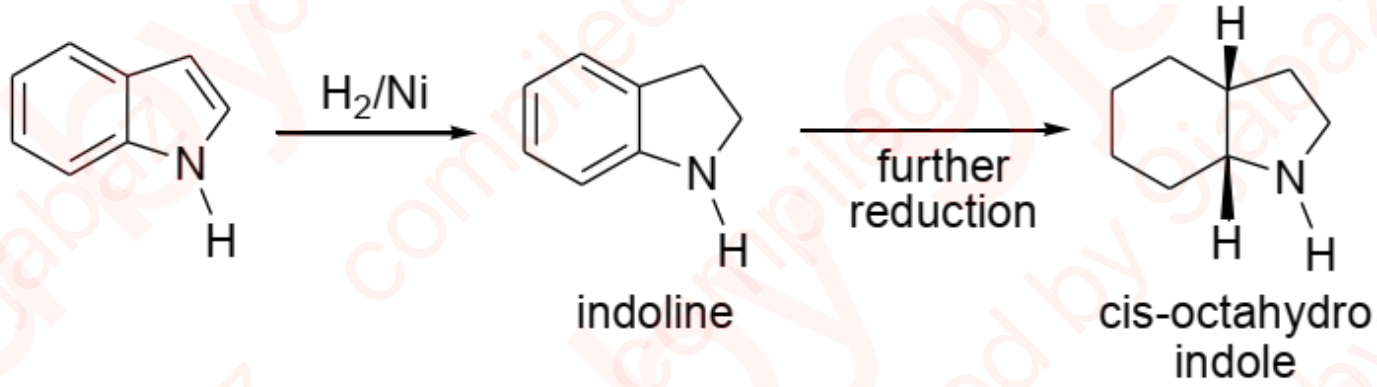
iv



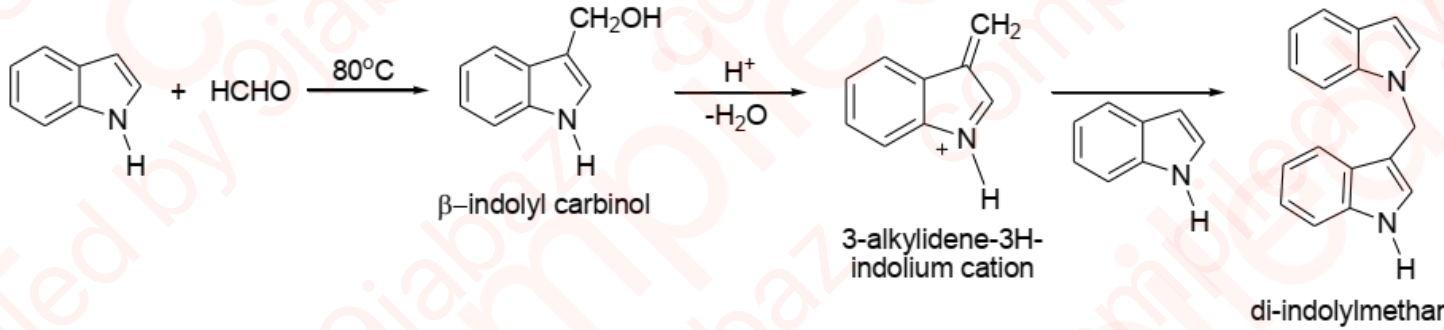
b.



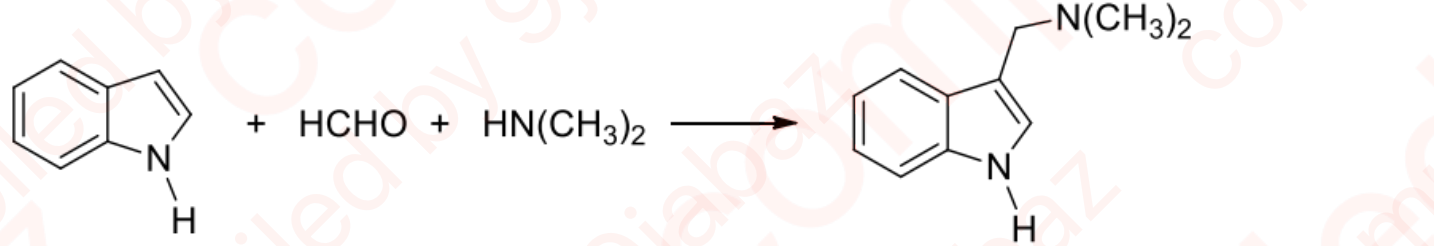
7. Reduction of Indole



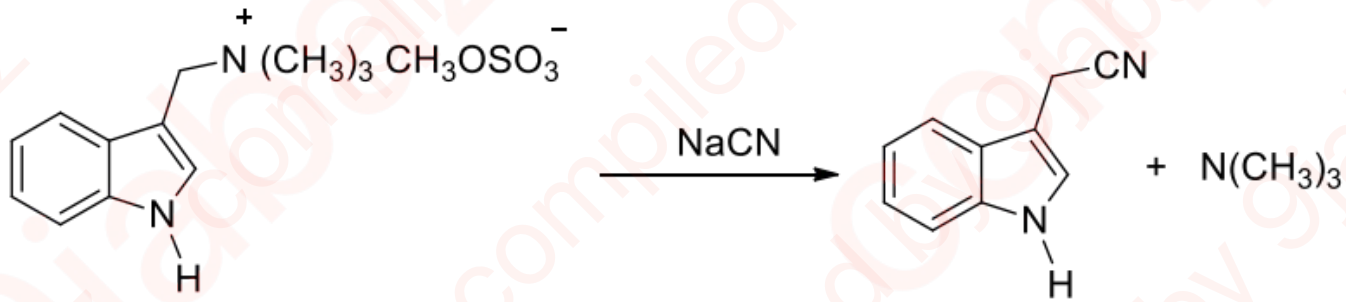
8. Reactions with aldehydes and ketones: Indole condenses with aldehydes and ketones i.e. formalin/formaldeyde to form β-indolyl carbinol



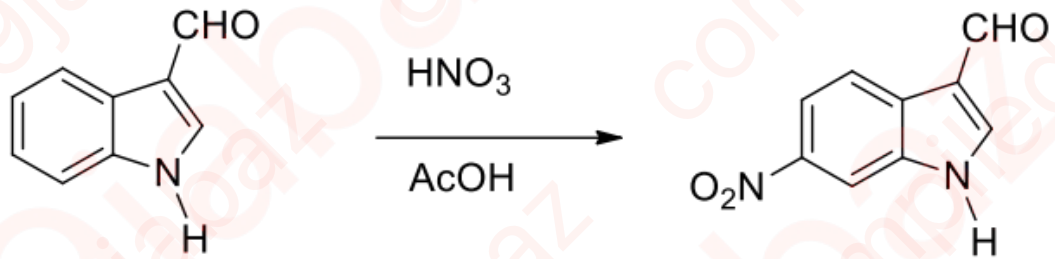
Methanal can also react with indole in the presence of dimethyl amine



Gramine is a very important product as its quaternary salt are useful synthetic intermediate because the N-group is easily displaced by nucleophiles.



With the presence of electron withdrawing group on the heterocyclic ring of indole, the ring is deactivated and further attack occurs in the benzene ring e.g. nitrating of indole-3-aldeyde, using HNO_3/AcOH will yield 6-nitro derivative.



INDOLE DERIVATIVES

1. ALKYL INDOLES

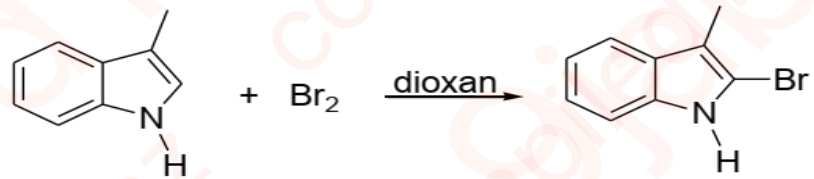
The best known alkyl indoles are the 2- and 3-methyl indoles. 2- and 3-methyl indole can be prepared by direct alkylation of indole. 2-methylindole undergoes electrophilic reactions to give 3-derivates.

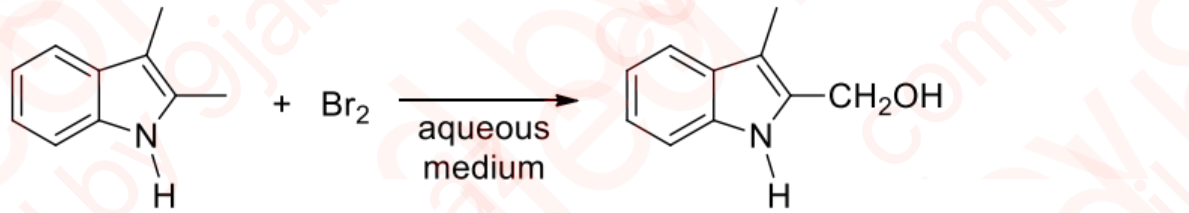
i. Nitration

It gives 3-nitro-2-methylindole but if the usual reagent is used i.e. H_2SO_4/HNO_3, we get 5-nitro-2-methylindole. If the 2 and 3 positions are occupied, any incoming electrophile will not have space on the heteroaromatic ring, hence substitution takes place at position 5 i.e. on the benzene ring.

ii. Halogenation of Alkyl Indole

Halogenation of 3-methylindole gives 2-bromo derivatives. If 2,3-dimethylindole is brominated in aqueous medium, an unusual product is obtained.

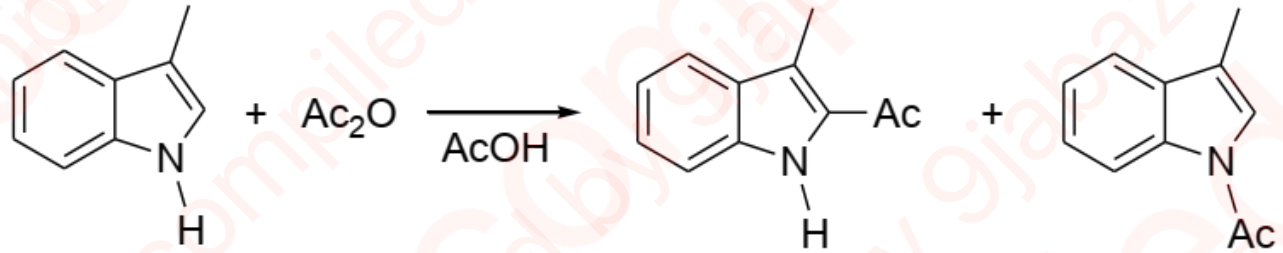




2-hydroxylmethyl-3-methylindole or
2-hydroxymethyl skatole

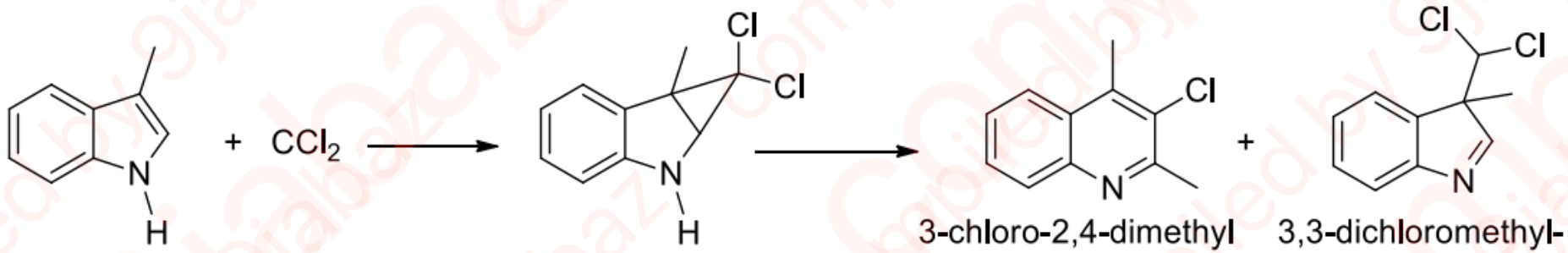
iii. **Acylation**

Acylation with acetic anhydride and acetic acid gives a mixture of acyl derivatives.

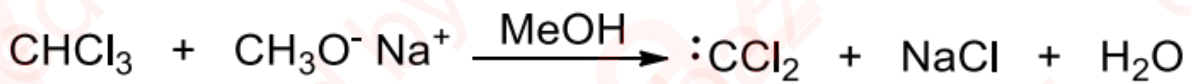


iv. **Reaction with carbene**

Skatole can also react with carbene.

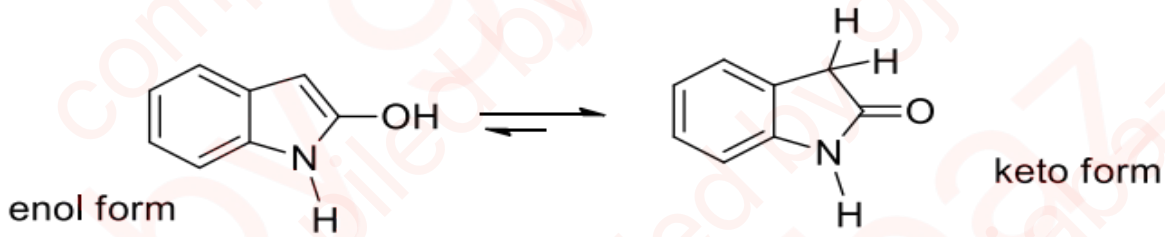


The carbene is obtained from the reaction of chloroform with sodium methoxide.



2. OXY INDOLE

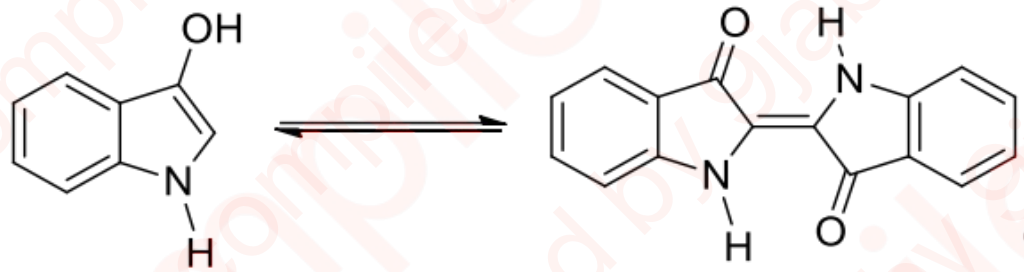
This is indole derivative that has a hydroxyl group present at position 2 or 3 of the indole ring. Indole with OH group in the benzene behaves like normal phenol. However if the hydroxyl group is on position 2 or 3, they exhibit different property e.g. 2-hydroxylindole behave more like an amide.



enol form keto form

The methylene group of carbon 3 can easily be deprotonated and goes into condensation reaction with aldehyde, ketones, alkyl halides, etc. The 2-OH indole exist mainly as amide (keto form).

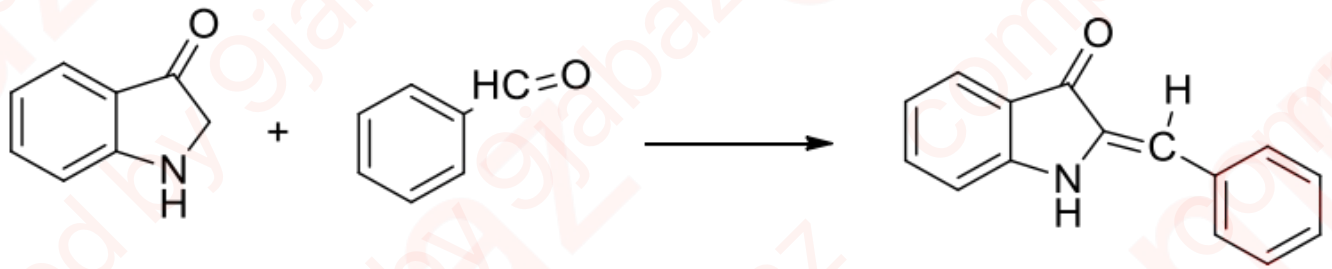
The 3-OH indole also exist in keto-form but it has appreciable enol form, thus it exhibits phenolic reactions (it gives purple colouration with $FeCl_3$). 3-OH indole is easily oxidized to indigo.



coloured dye (indigo)

The protons at C2 of keto form are also acidic hence can be methylated at this point and it can also react with RCHO & R_2CO:

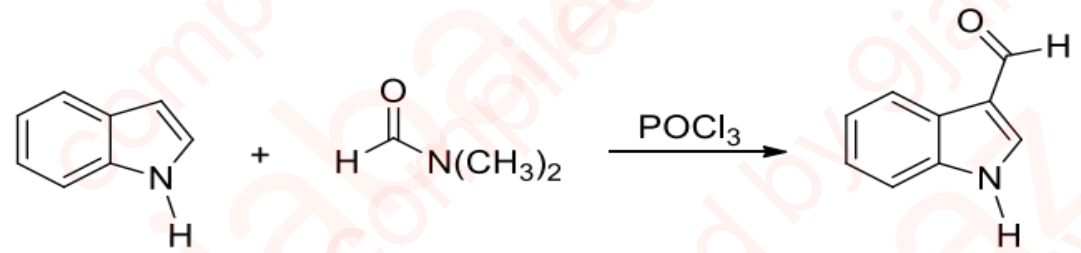
2,2-dimethylimidazole-3-one



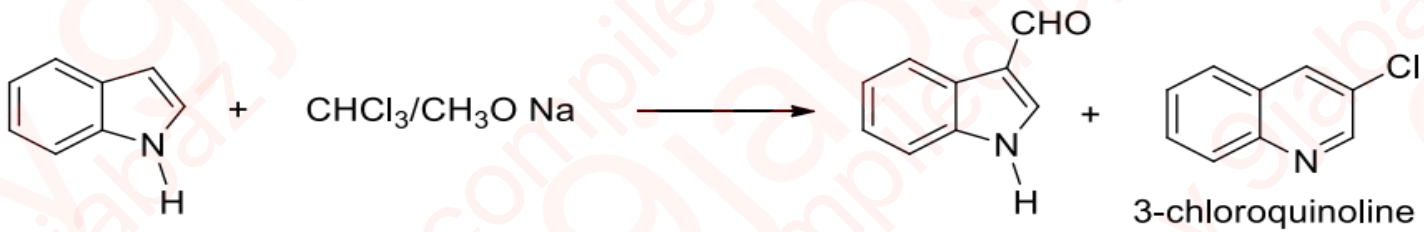
3. INDOLE ALDEHYDE

When indole is treated with DMF in the presence of phosphorus oxo chloride, it forms indole-3-aldehyde.

(i)

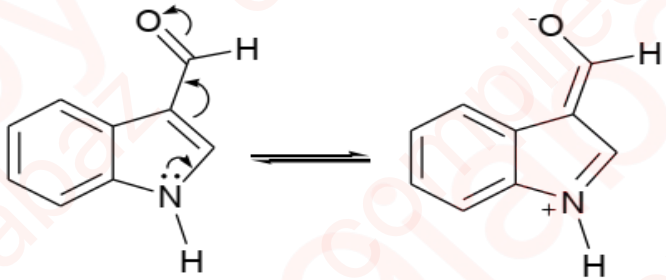


(ii)



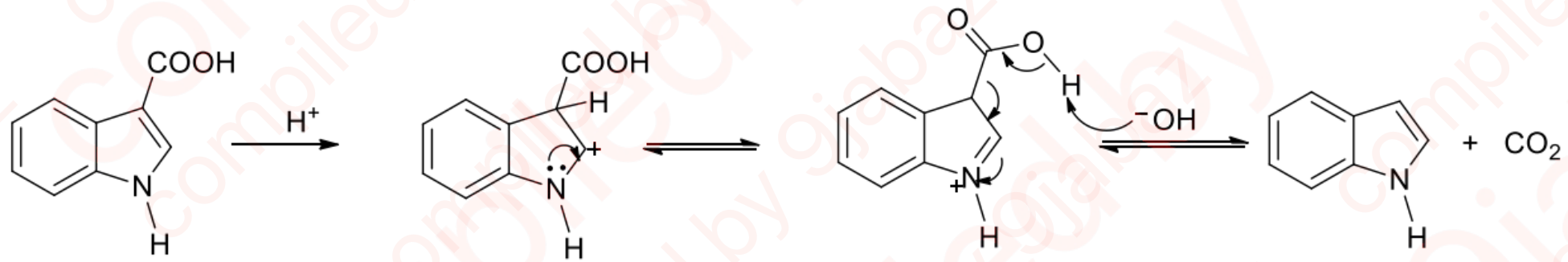
3-chloroquinoline

Indole-3-adehyde does not behave like typical CHO e.g. does not form cyanohydrin with hydrogen cyanide and won't undergo Cannizzaro rxn.



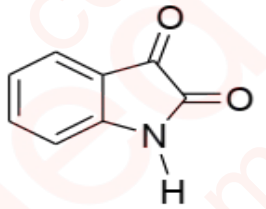
Indole Carboxylic Acids:

Indole-2 and 3-carboxylic acids are readily decarboxylated, but 3-carboxylic acid is much more labile.

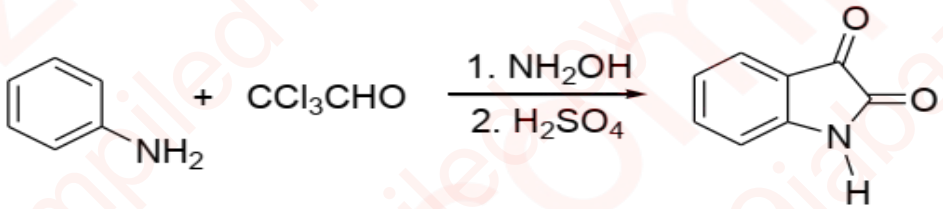


This reaction takes place in mineral acid.

ISATIN



It can be obtained by oxidation of indigo, which is a dimer of 3-hydroxyl indole. We can also obtain isatin from aniline.

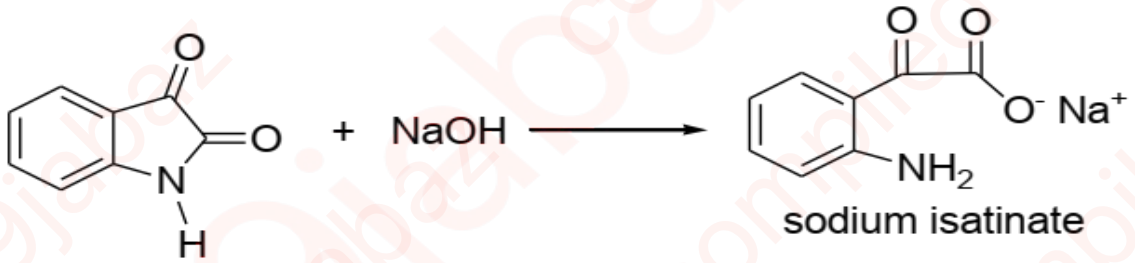


The two carbonyl groups on isatin are not identical, hence they differ in chemical properties.

Isatin is basic enough to dissolve in HCl and the hydrogen of isatin is acidic enough to be replaced by strong basic metals like Na and Ag. The 3-keto group behaves like a typical carbonyl while the 2-keto grp behaves like a typical amide.

The usual reaction of normal carbonyl group can take place on the 3-keto group i.e. reacting with hydrazine derivatives, however the keto group on position 2 cannot undergo such.

The keto group on position 2 will react with NaOH to form sodium salt of isatinic acid i.e. sodium isatinate.

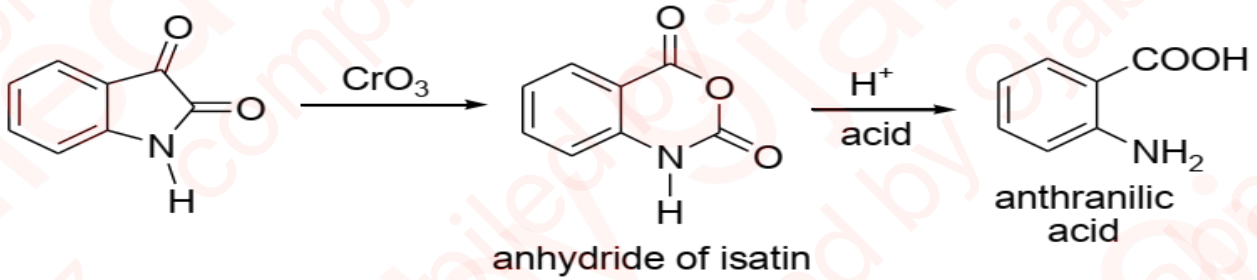


sodium isatinate

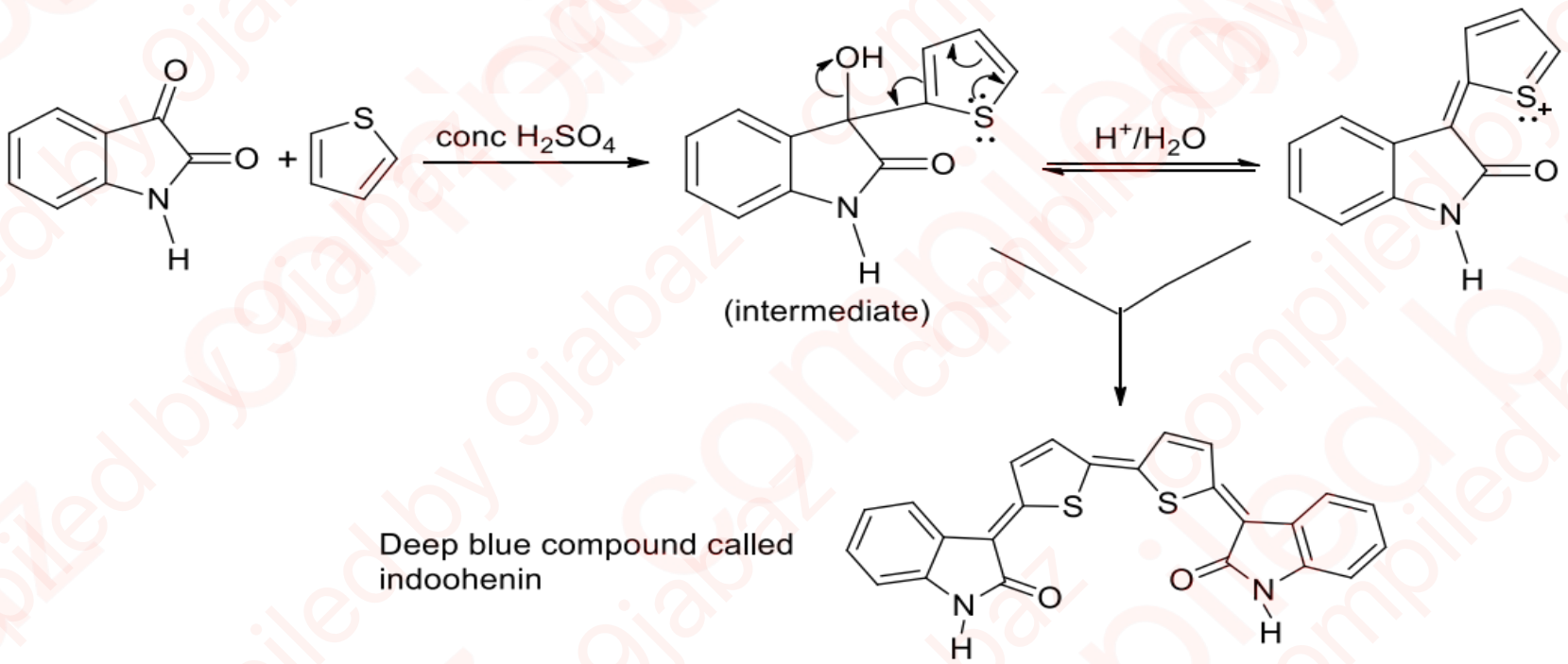
SOME OF THE REACTIONS OF ISATIN

1. Oxidation reactions

Isatin is oxidized by chromic acid to form the anhydride which in the presence of acid affords anthranilic acid.



2. Reactions with thiophene



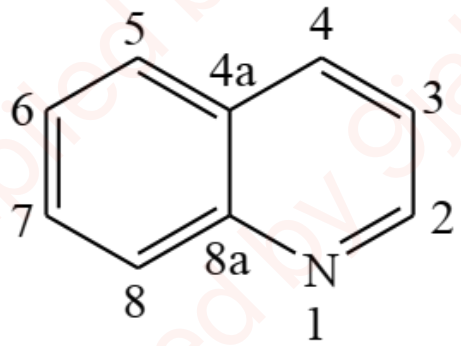
Assignment

1. Outline a synthetic route for preparing indole starting from benzene.
2. Why common Nitrating agent (H_2SO_4 + HNO_3) is not used in the nitration of indole ?.
3. Write the mechanism for the reaction between acetophenone and phenylhydrazine to form indole derivative.

AROMATIC HETEROCYCLIC COMPOUNDS

QUINOLINE

QUINOLINE



1. Quinoline is a heterocyclic aromatic organic compound with the chemical formula C_9H_7N.

2. It is also called 1-azanaphthalene or benzo[b]pyridine.

3. Quinoline was first extracted from coal tar in 1834 by German chemist Friedlieb Ferdinand Runge.

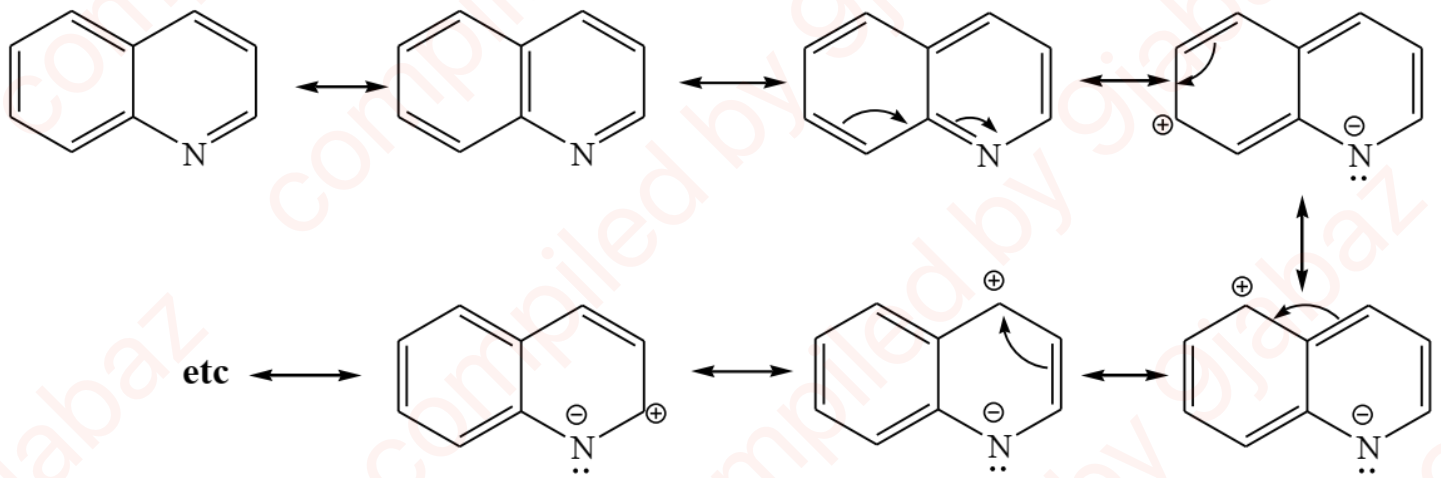
4. Quinoline is an aromatic compound since it follows the Huckel's rule (i.e. $4n+2\pi$ electron rule) for n=2. It contains 10 π electrons and it is planar

5. All the ring atoms in Quinoline are sp2 hybridized. Unlike Indole, the lone pair of nitrogen of quinoline does not participate in the delocalization

6. Quinoline is colorless to pale yellow liquid, it has a boiling point ≈ 238°C

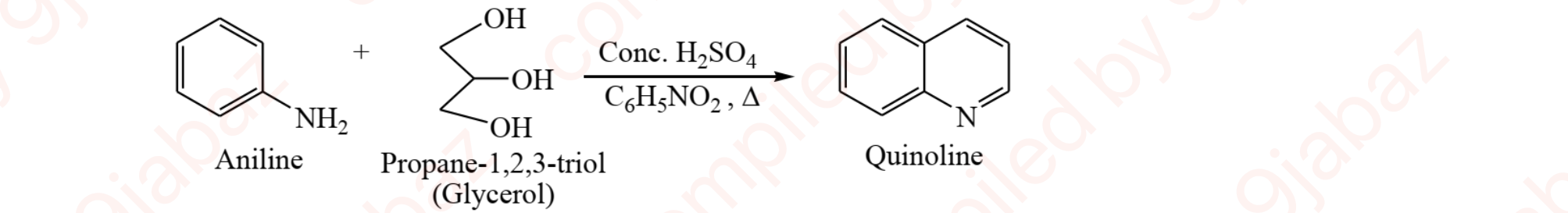
7. It is weakly basic compound and slightly soluble in water.

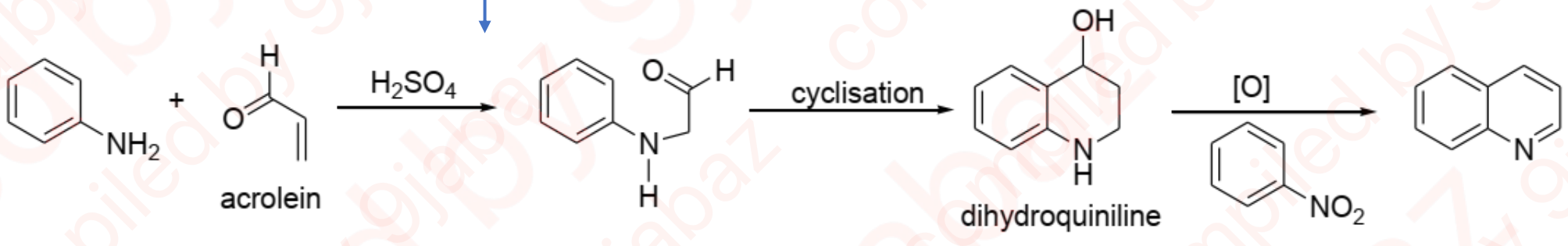
Resonance Structures of Quinoline



SYNTHESIS OF QUINOLINE

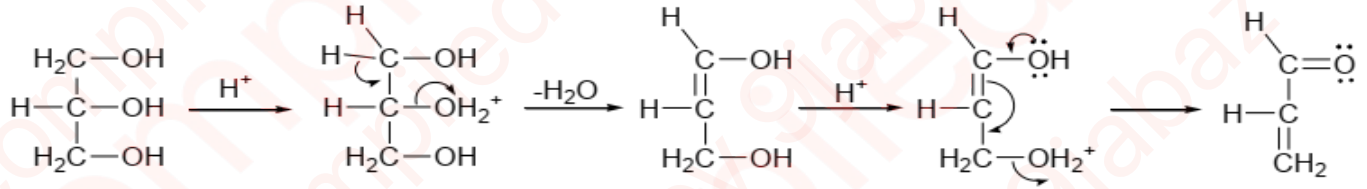
1. Skraup Synthesis: This is one of the most important methods for the preparation of quinoline. This method involves heating an aryl amine (aniline) which has a vacant ortho position with α,β-unsaturated carbonyl compound glycerol, Conc. H_2SO_4 and an oxidizing agent the resultant product is obtained as quinoline or its derivatives. The nitrobenzene, stanic chloride, ferric salt, $SnCl_2$ or Lewis acid is generally used as mild oxidizing agent in Skraup synthesis. Glycerol when heated with concentrated H_2SO_4 gives the acroline after dehydration. Condensation of acroline thus obtained with aniline or its derivatives followed by oxidation gives the quinoline.



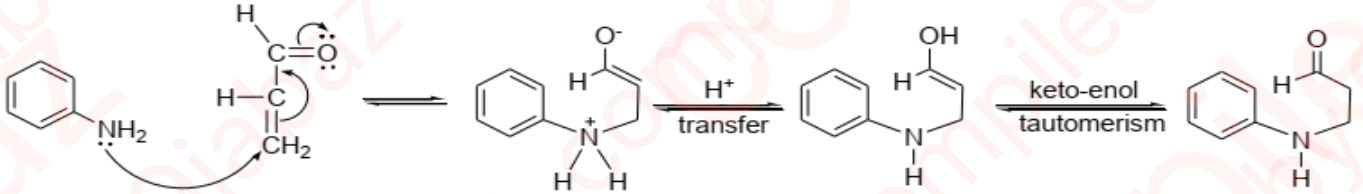


Mechanism

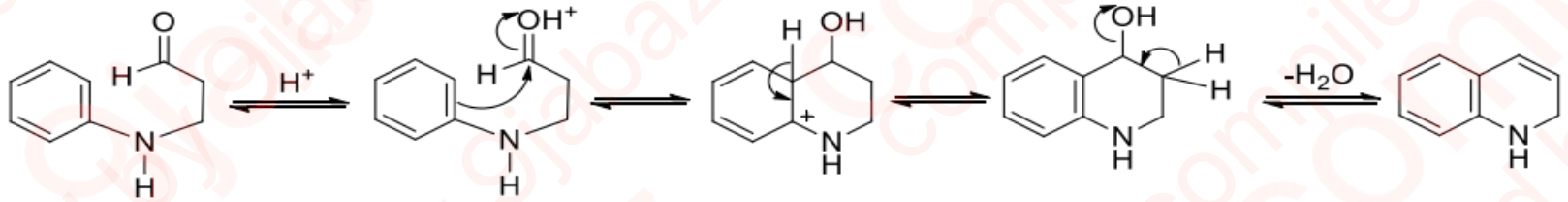
Step 1: Dehydration of glycerol to acrolein



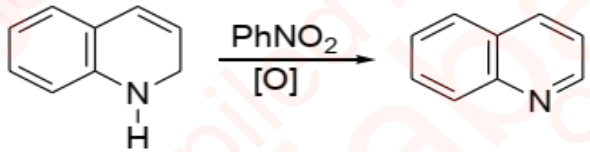
Step 2: Michael addition of aryl amine with the α,β-unsaturated carbonyl compound.



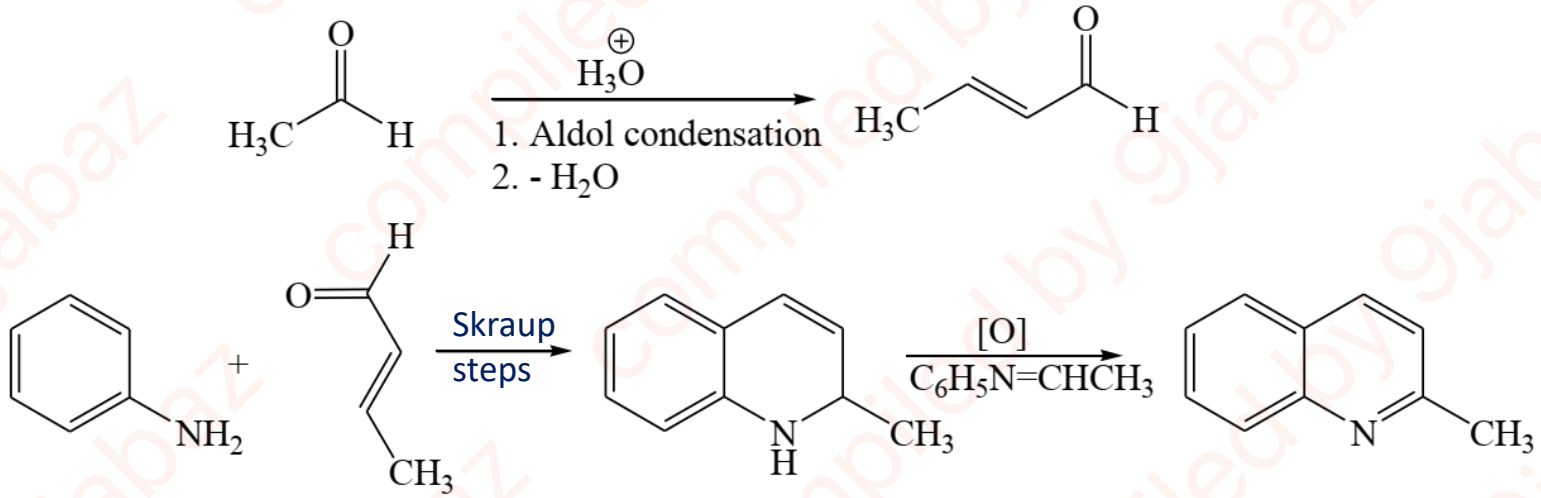
Step 3: Eletrophilic adition to the protonated carbonyl



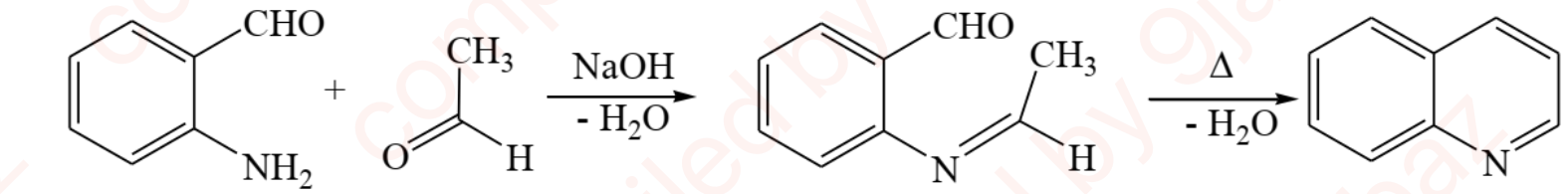
Step 4: Dehydrogenation of dihydroQ to Q by oxidising agent



2. Dobner-Miller Synthesis: This is a modified form of the Skraup synthesis. In this reaction the simple aldehydes and ketones act as precursor of α, β-unsaturated carbonyl compounds. The reaction follows the similar reaction course as in the Skraup synthesis to produce derivatives of quinoline. When acetaldehyde is used as precursor of α, β - unsaturated carbonyl compound 2-methylquinoline is formed.

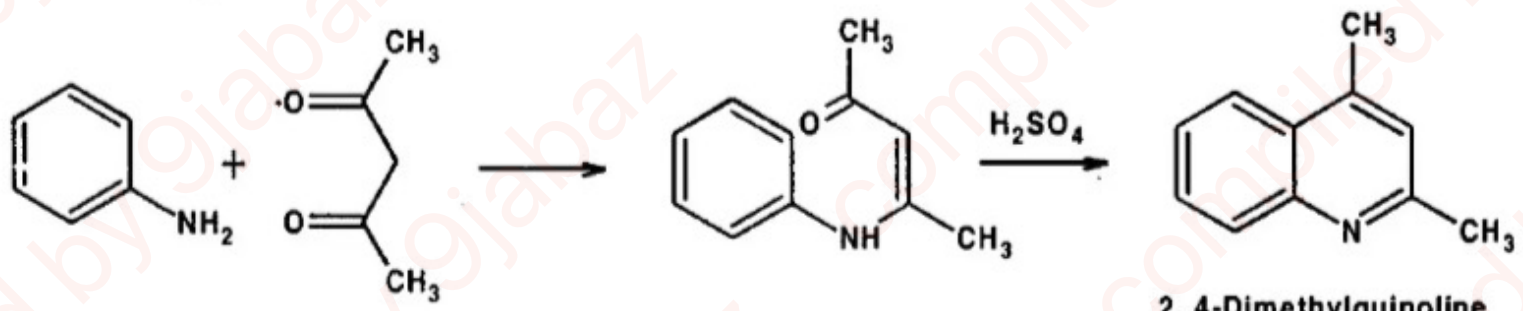


3. Friedlander and Pfitzinger synthesis: Quinoline can also be prepared by the condensation of ortho-amino aromatic aldehyde or ketone with a carbonyl compound having α-methylene group (e.g acetaldehyde) in sodium hydroxide solution.



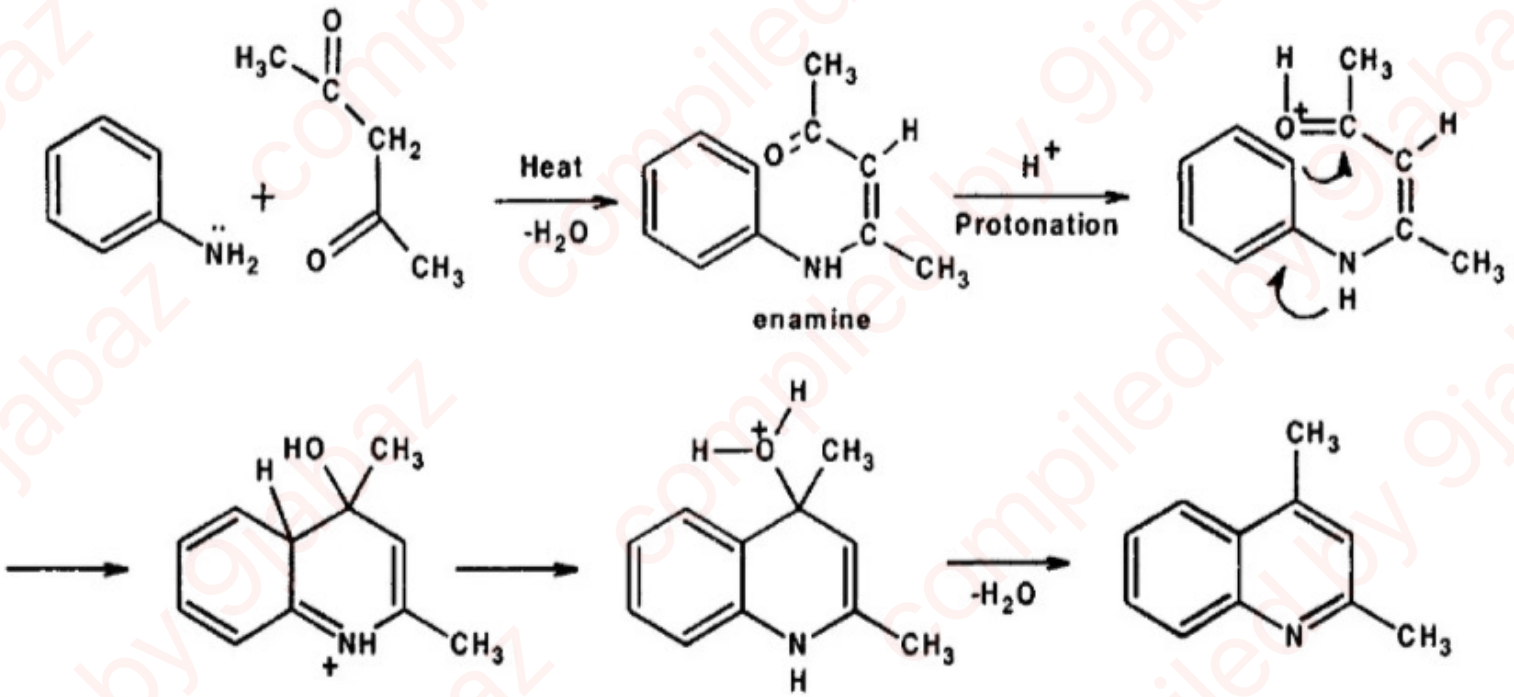
o-aminobenzaldehyde Acetaldehyde Quinoline

4. Combes Synthesis: aromatic amines react with 1,3-dicarbonyl compounds or β-keto esters to give a wide range of quinoline compounds.



2, 4-Dimethylquinoline

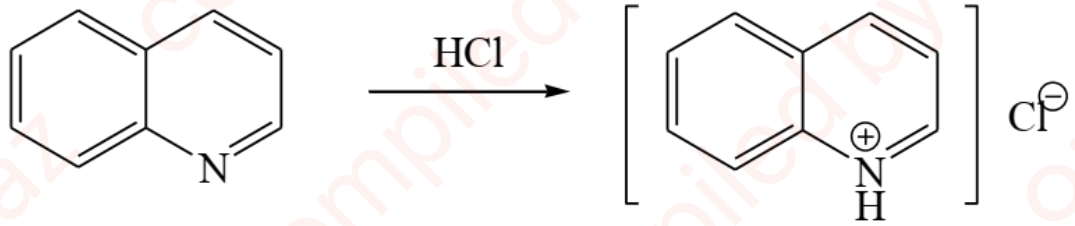
Mechanism



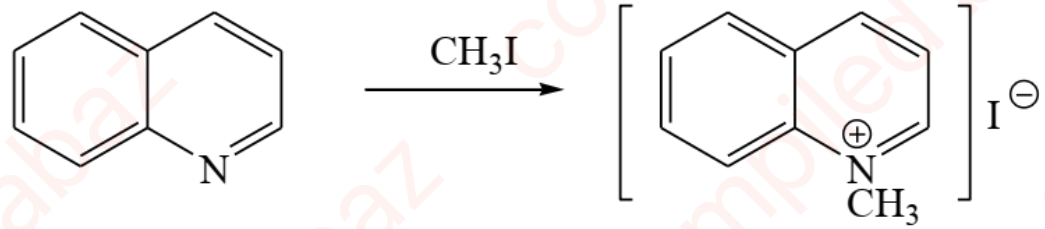
Chemical Properties of Quinoline

1. **Basicity:** quinoline acts as a base and forms salts with acids and quaternary salts with alkyl halides due to availability of lone pair of electrons on nitrogen.

a. Reaction with acids:

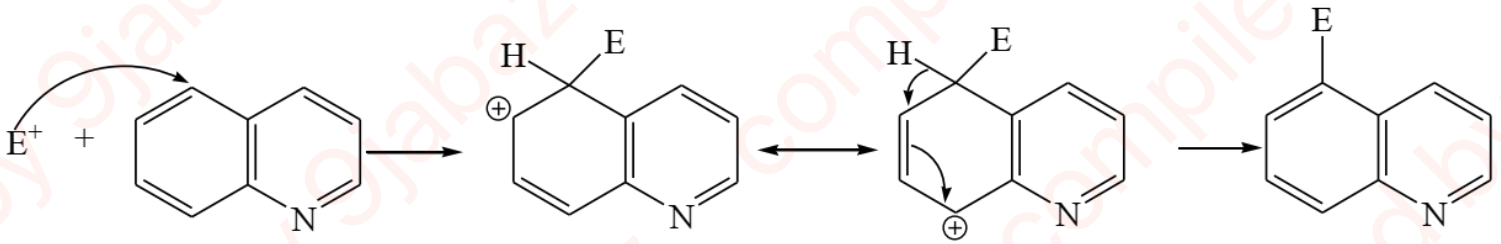


b. Reaction with methyl iodide:

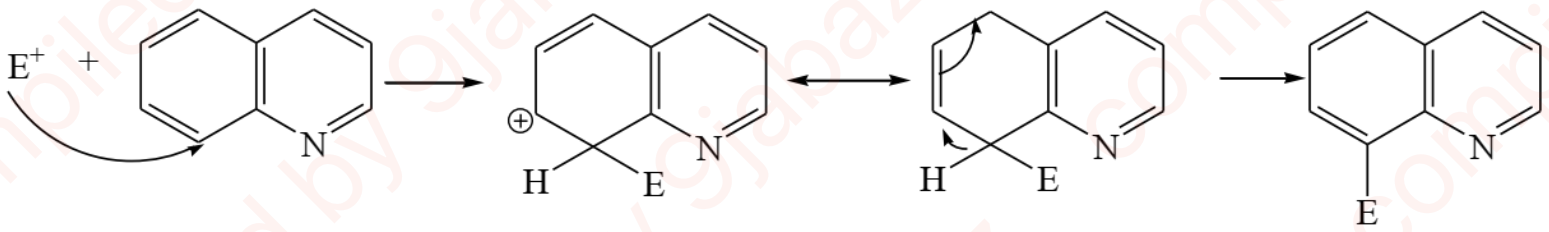


2. Electrophilic substitution: the carbocyclic (benzene) ring in the quinoline is relatively more electron rich and resembles benzene ring while the nitrogen containing ring is less electron rich and resembles pyridine ring. Thus, electrophilic substitution takes place more readily at position 5 and 8 of benzene ring rather than the pyridine ring. Thus if both the positions in benzene ring are vacant than mixture of substituted product is obtained.

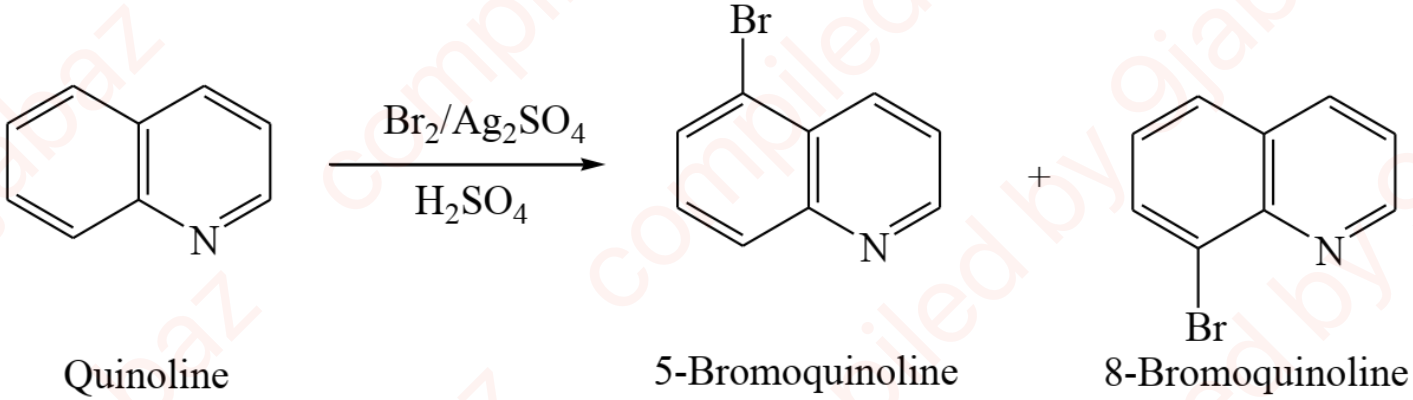
a. At position 5



b. At position 8

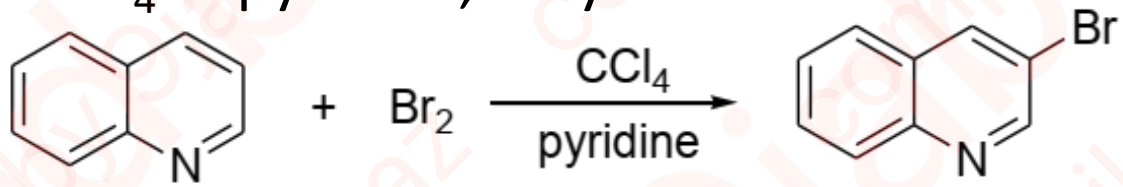


a. Halogenation: with Br_2 in the presence of silver sulphate (Ag_2SO_4) and H_2SO_4, bromination occurs at position 5 and 8 hence mixture of products is formed.

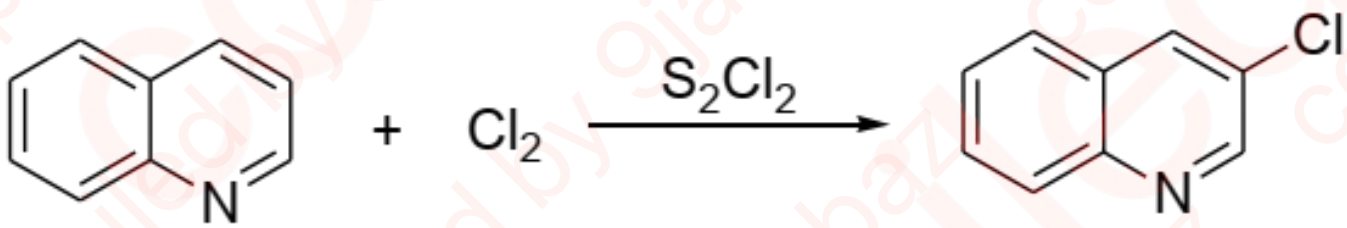


Quinoline 5-Bromoquinoline 8-Bromoquinoline

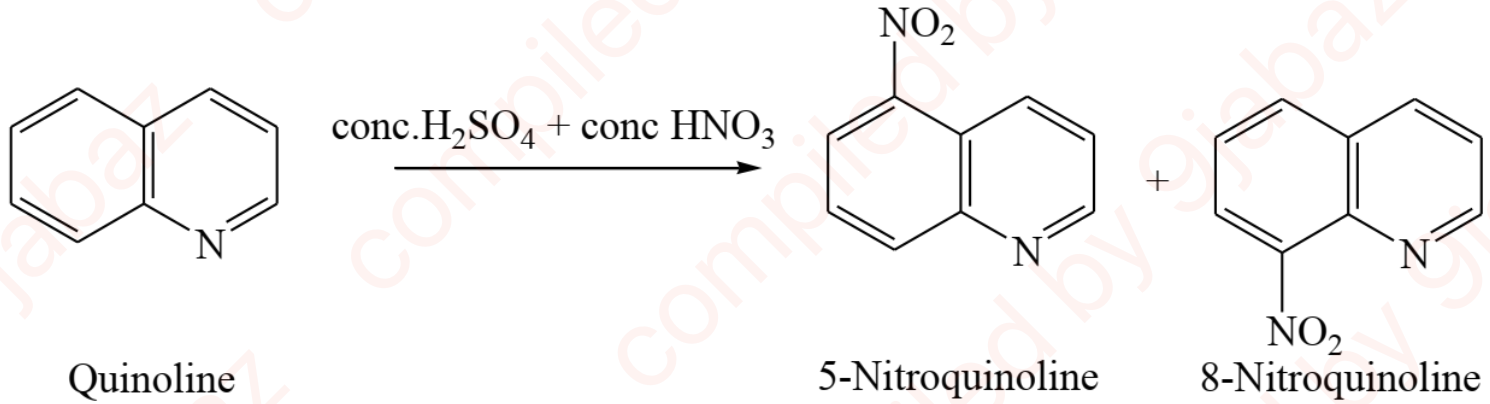
But with CCl_4 in pyridine, only the 3-bromo is formed.



Chlorination occurs with sulphur dichloride

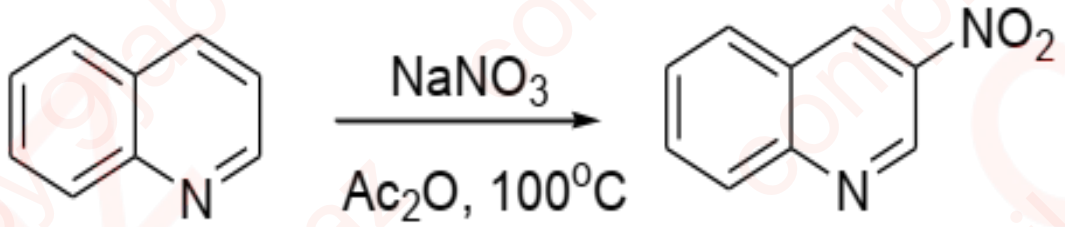


b. Nitration: occurs with the nitrating reagent to give the 5 and 8-nitro product.

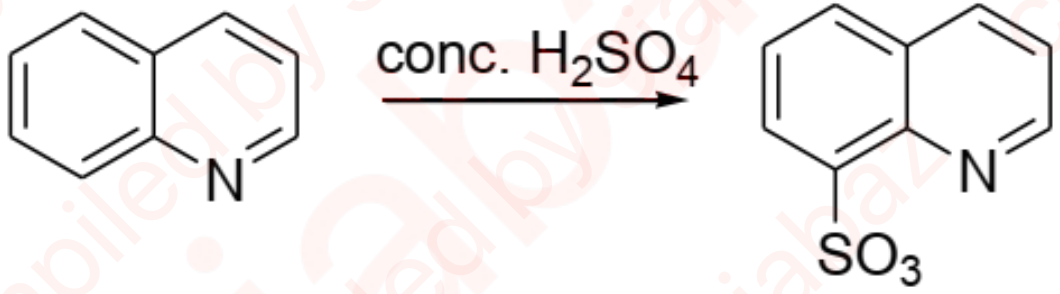


Quinoline 5-Nitroquinoline 8-Nitroquinoline

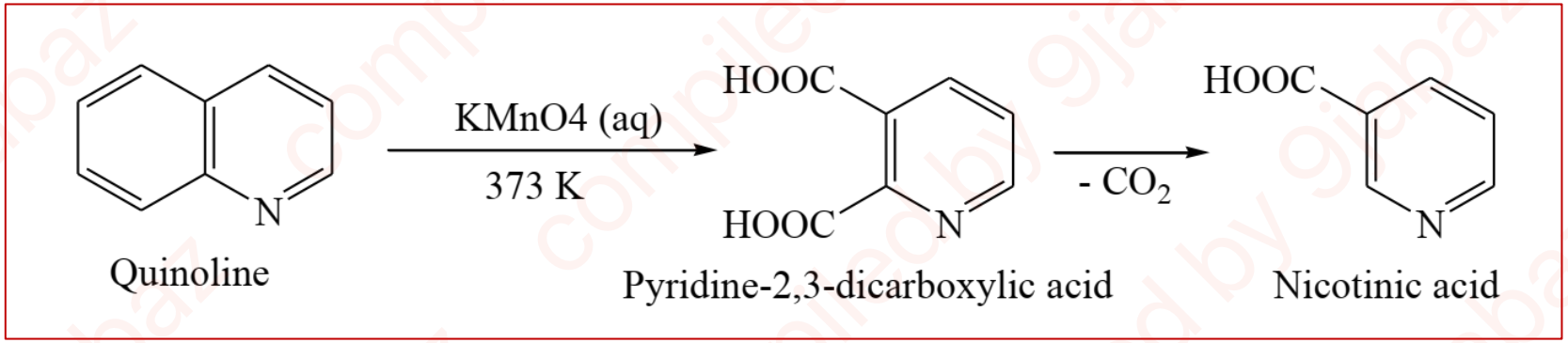
With Sodium nitrate/Ac_2O at 100 °C, 3-nitro is formed.



c. Sulphonation: with conc. Sulphuric acid to obtain mainly the 8-substituted product.

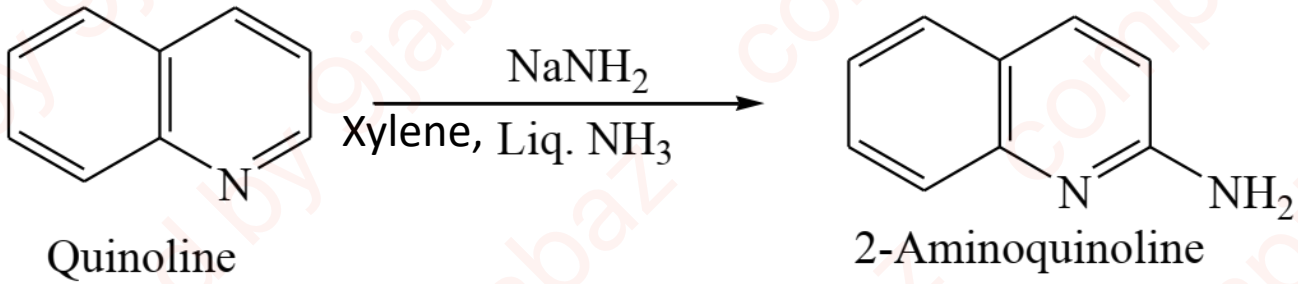


3. **Oxidation**: in the presence of $KMnO_4$ quinoline is oxidized to pyridine-2,3-dicarboxylic acid which upon decarboxylation gives nicotinic acid.



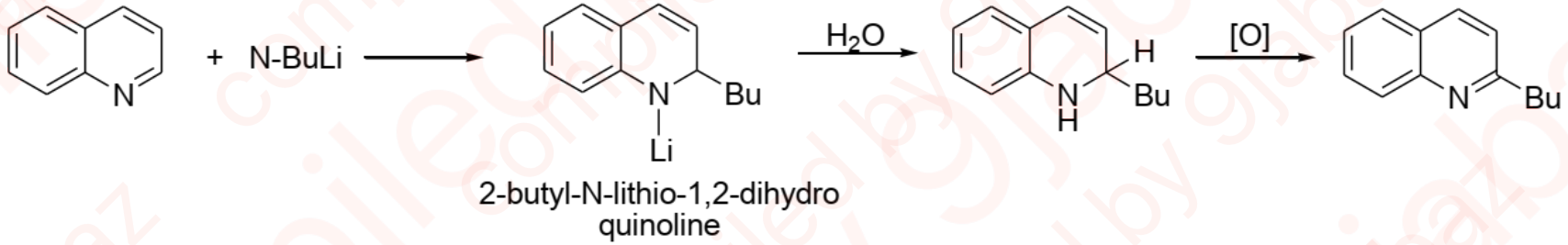
4. **Nucleophilic substitution**: Quinoline undergo nucleophilic substitution reactions at the pyridine ring since it is less electron rich compared to the benzene ring. The substitution takes place at position 2 of the pyridine ring, but if occupied, takes position 4.

A. Chichibabin (Tschitschibabin) reaction

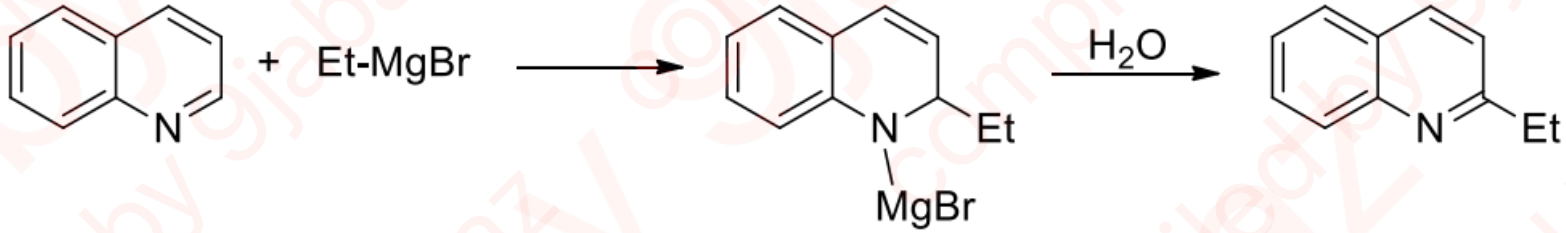


B. Reaction with organometallic compounds and Grignard reagent

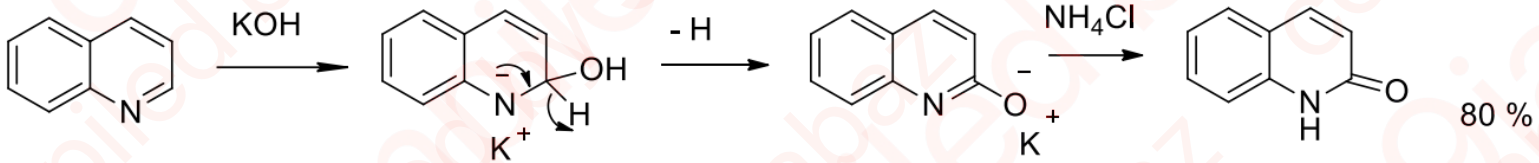
With n-BuLi:



2-butyl-N-lithio-1,2-dihydro quinoline

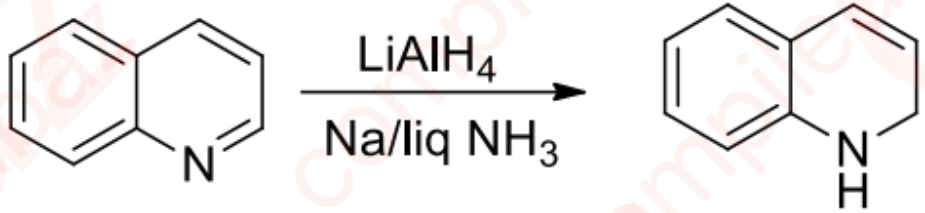


C. Reaction with KOH: the hydroxyquinoline tautomerises to the keto form to form a much stabilized substrate

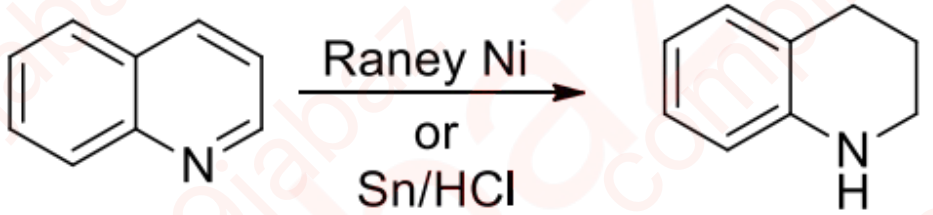


80 %

5. Reduction

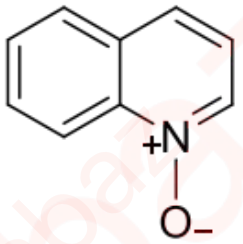


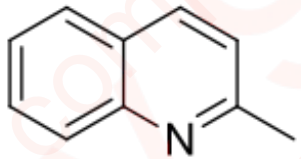
1,2-dihydroquinoline



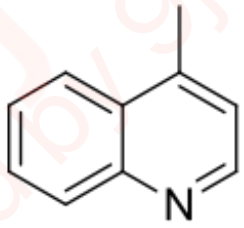
1,2,3,4-tetrahydroquinoline

DERIVATIVES OF QUINOLINE

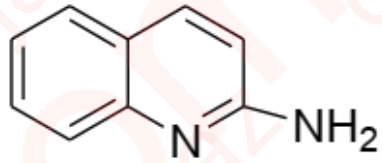


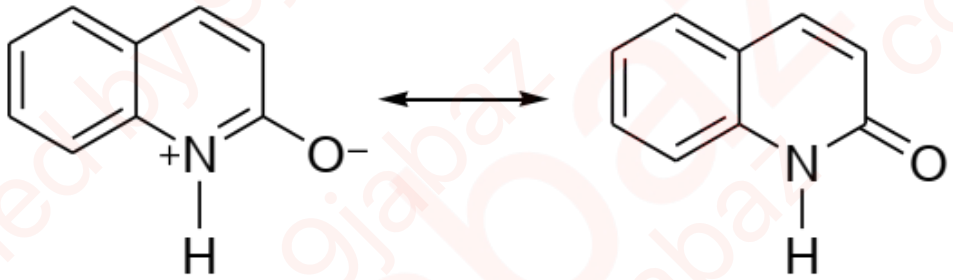


quinadine



lepidine



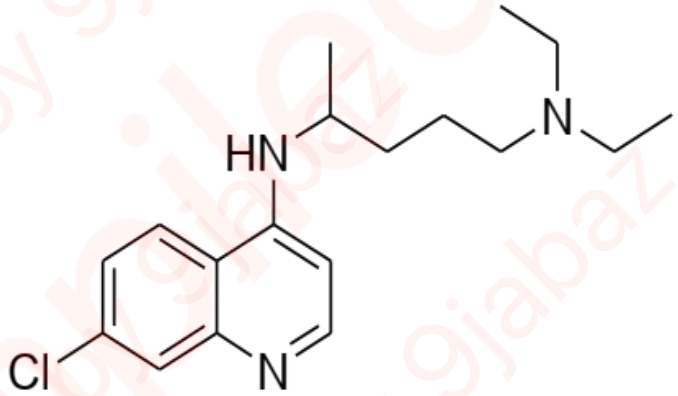


2-hydroxylquinoline
(enol)

2-quinolone
(keto)

vioform

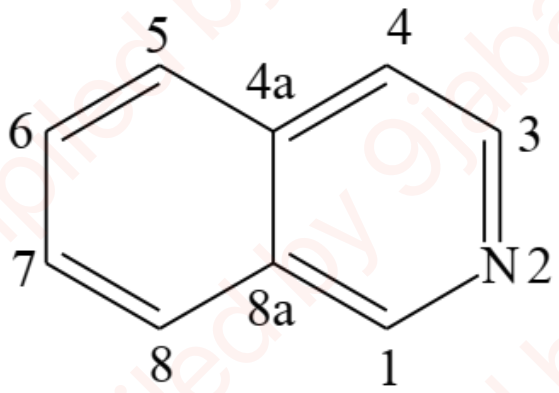
and



chloroquine

ALKALOID DRUGS WITH QUINOLONE NUCLEUS

ISOQUINOLINE

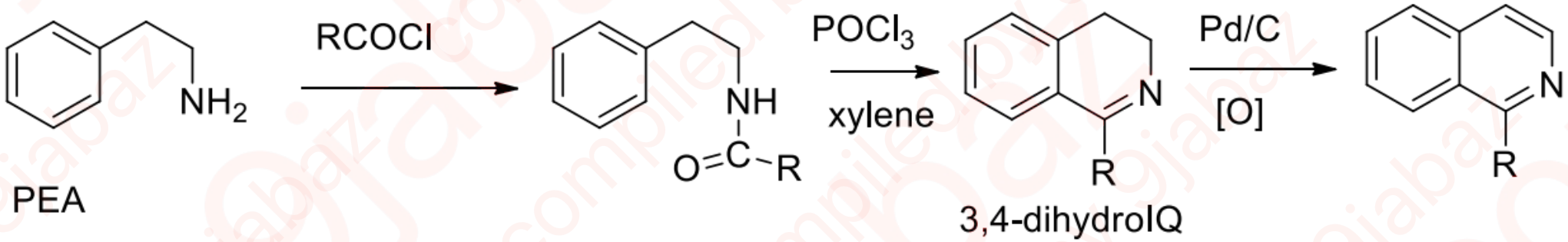


Isoquinoline

Isoquinoline is a structural isomer of quinoline, It was first isolated by Hoogewerff and Drop from the quinoline fraction of coal tar in 1885. It does not occur free in nature but found frequently in several alkaloids. It is called 2-azanaphthalene or benzo[b]pyridine. The numbering of the atoms in Isoquinoline is similar as followed in quinoline; however, the nitrogen atom is assigned position-2. Isoquinoline has close similarities in the structure with quinoline; therefore both have a close relationship in their physical and chemical properties.

SYNTHESIS OF QUINOLINE-(A) from phenyl ethyl amine (PEA) and (B) from aromatic aldehyde

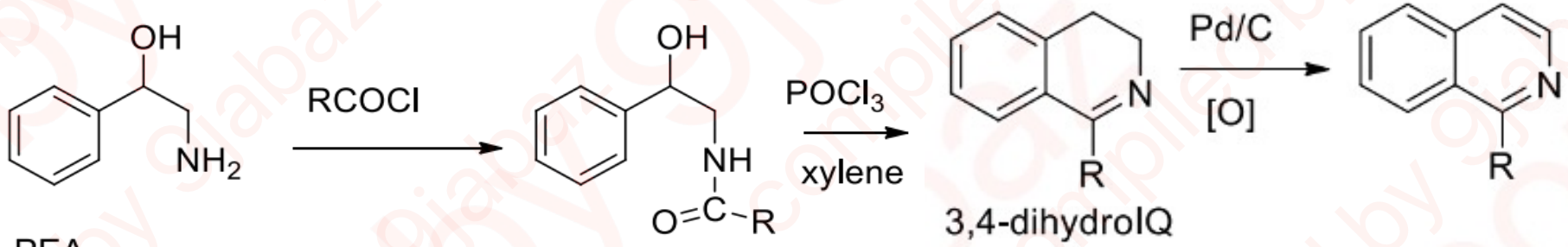
1. **Bischler-Napieralski Synthesis**: This involves reaction of acyl halide or carboxylic acid with phenyl ethylamine (PEA) to form acyl derivative of PEA which undergoes cyclisation when heated with P2O5, POCl3 or PCl5 in an inert medium to form the corresponding isoQ:



PEA

3,4-dihydroIQ

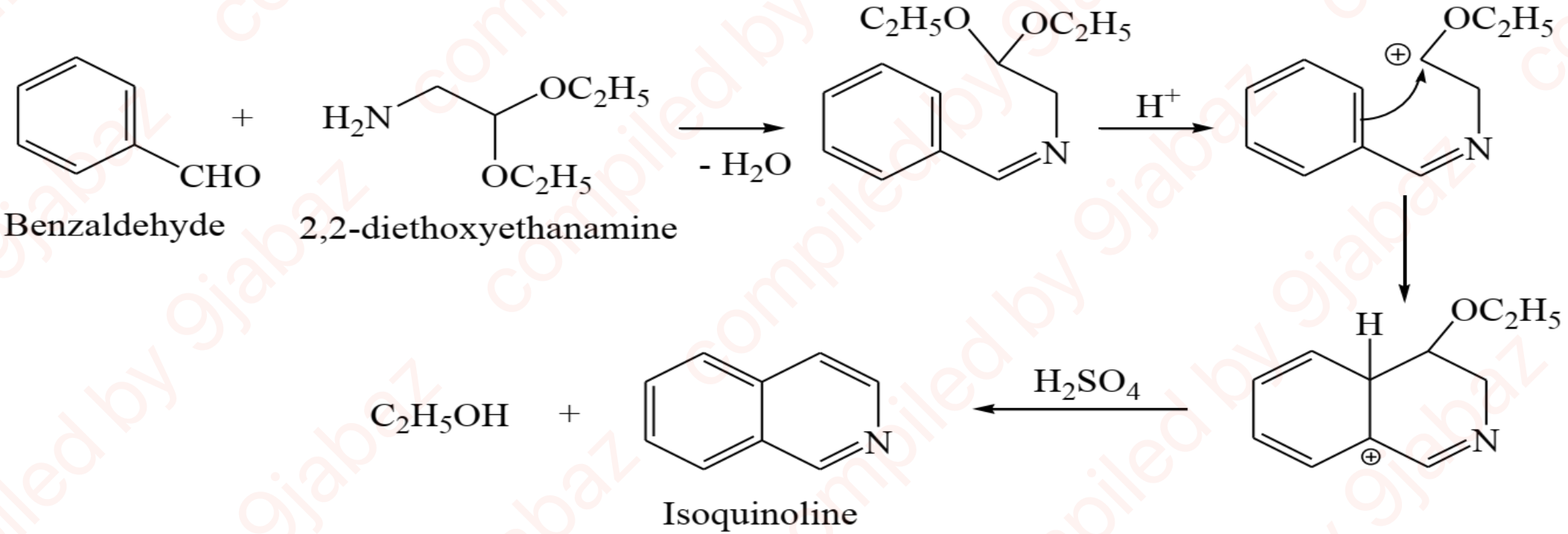
2. Pictet & Gams Modification: Uses α-hydroxy PEA



PEA

3,4-dihydroIQ

2. **The Pomeranz Fritsch synthesis:** an aromatic aldehyde or a substituted Benzaldehyde is condensed with aminoacetal to give Schiff's base. The Schiff's base thus formed is cyclized in the presence of H_2SO_4 or P_2O_5. The last step of this reaction is similar to the Skraup synthesis of quinoline.

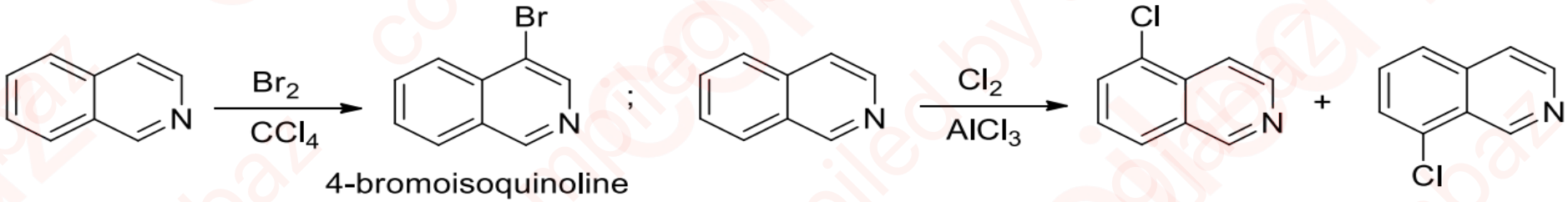


Benzaldehyde 2,2-diethoxyethanamine Isoquinoline

1. Electrophilic Aromatic Substitution Reaction

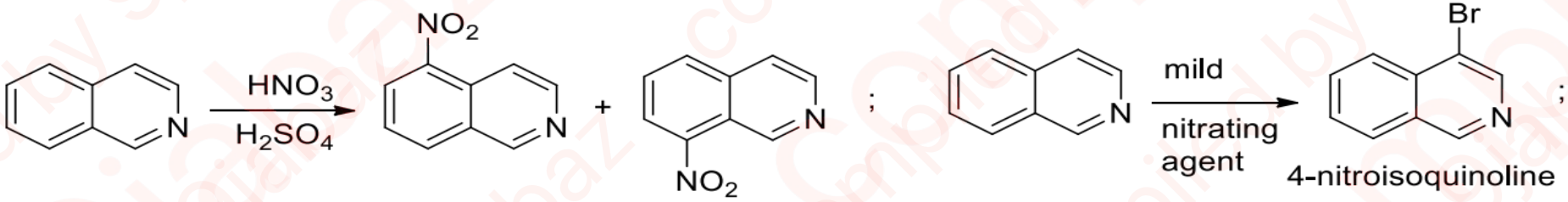
In strong acids (acidic medium), electrophilic substitution takes place at position 5 and 8 but in non-acidic or in weak acid, electrophiles attack at position 4.

(i) Halogenation



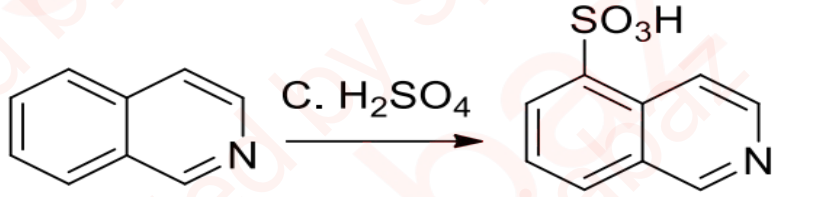
4-bromoisoquinoline

(ii) Nitration



4-nitroisoquinoline

(iii) Sulphonation: Unlike in Q, where 8-sulphonic acid is obtd. In IQ, 5-product is obtd.

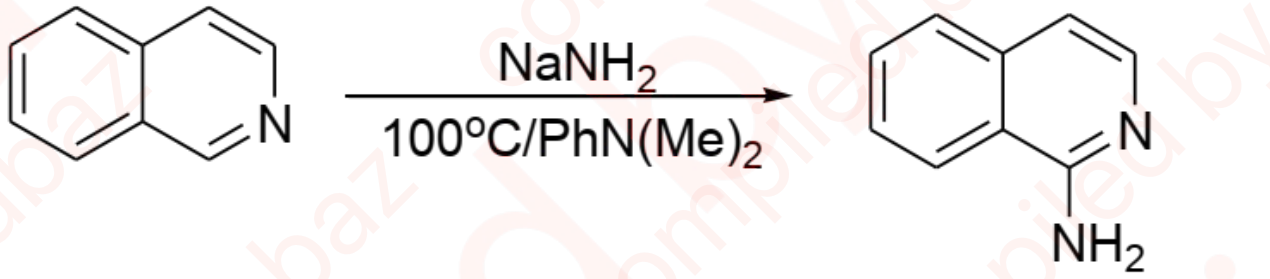


Isoquinoline-5-sulphonic acid

2. Reactions with nucleophiles

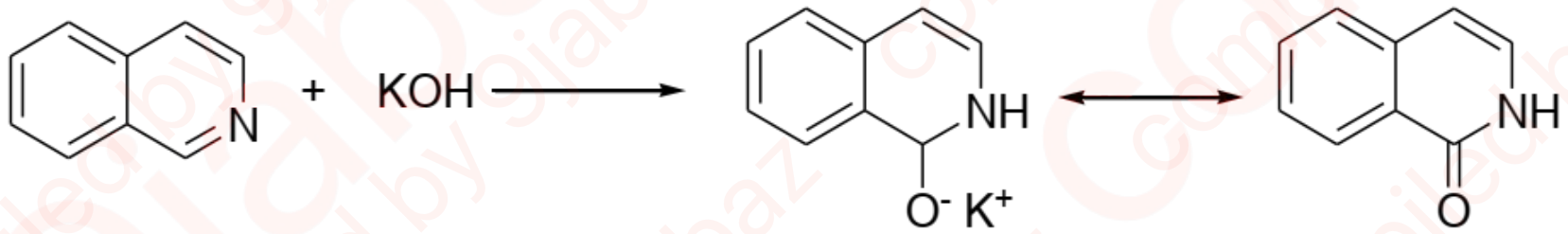
Nucleophiles attack isoquinolines at position 1 except if the position is occupied

i. Chichibabin reaction

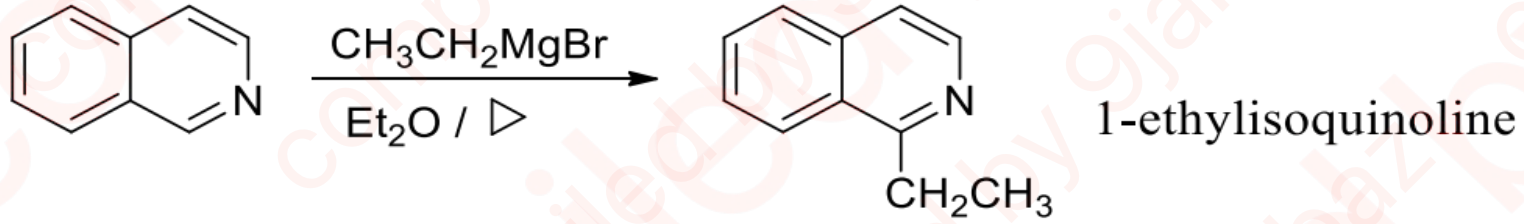


1-aminoisoquinoline

ii. Hydroxylation

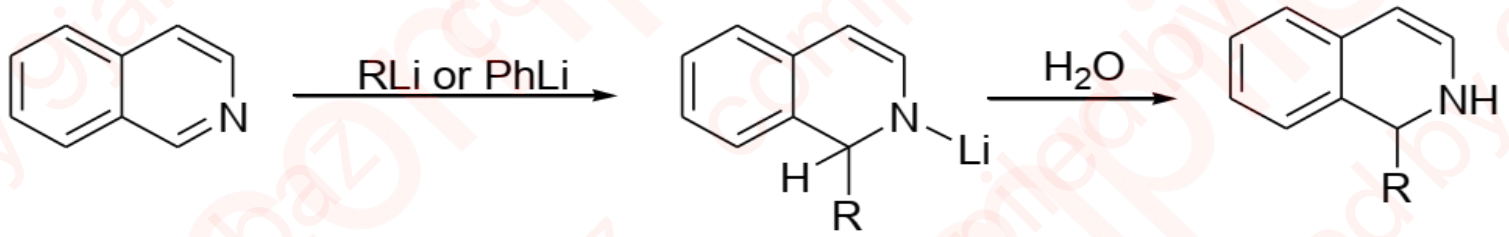


iii. Grignard reagent

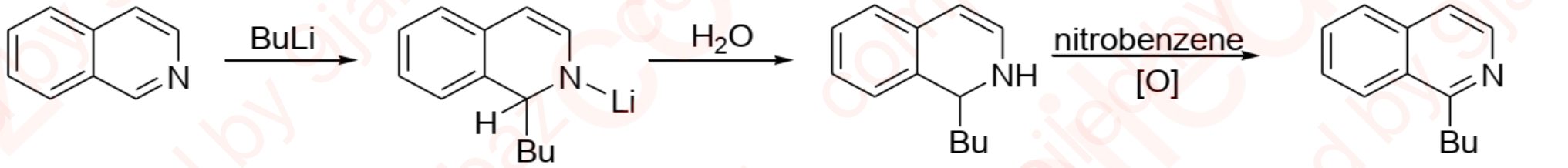


1-ethylisoquinoline

Alkyl or aryl Lithium react as in Q to give 1,2-dihydro product:



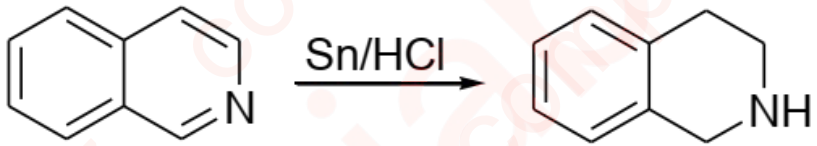
For example:



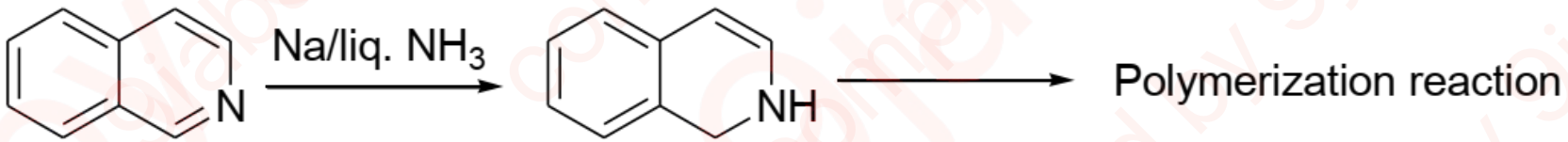
1-butylisoquinoline

3. Reduction

It react with reducing agent to give different product depending on the nature of the reducing agent i.e. Sn/HCl to give 1,2,3,4-tetrahydro product.



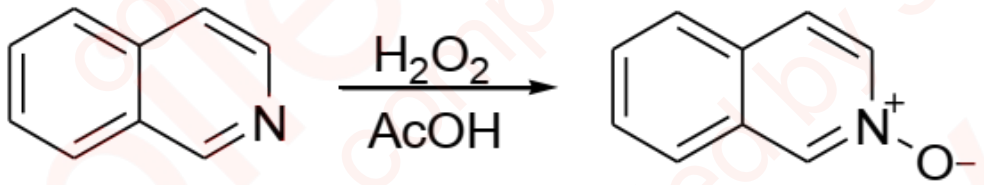
But Na/liq. NH_3 will yield 1,2-dihydro product



1,2-dihydroproduct
(not stable and readily
undergoes polymerization)

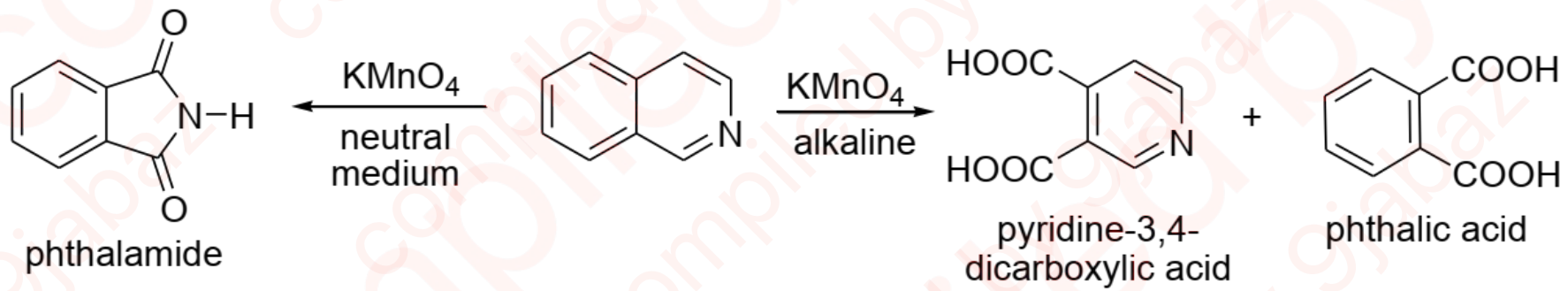
Reaction with oxidizing agent

Isoquinoline when treated with H_2O_2 in acetic acid give the N-oxide as in Q.

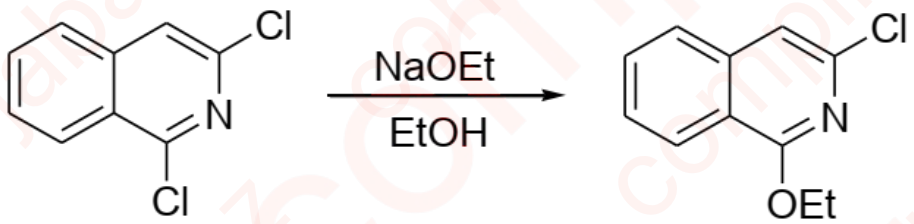


isoquinoline-N-oxide

When treated with alkaline $KMnO_4$. It gives pyridine-3,4-dicarboxylica acid and pthalic acid.



It undergoes substitution with replacement. In this case, halogen atom at position 1 are readily replaced with nucleophiles, while halogen atom at position 3 are not.



Alkyl grp in position 1 of IQ behaves as alkyl grp in position 2 of Q, hence 1-alkyl IQ will undergo condensation reaction with RCHO, R_2O, acid chlorides etc.