Aromatic and Heterocyclic Chemistry

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AROMATIC COMPOUNDS

- Besides the aliphatic compounds that were known since the very early days of the history of organic chemistry, a large number of compounds having distinct characteristics also exist.

- Such compounds were highly unsaturated and yet very stable.

- Most of these compounds possess pleasant odour, therefore, the new class of compounds were named aromatic compounds.

- Fragrances of oil from natural materials e.g oil of bitter almons, turpentine oil etc were attributed to the presence of certain aromatic compounds present in them.

- However, analytical study later revealed that the fundamental difference between aromatic and aliphatic compounds was structural rather than fragrance.
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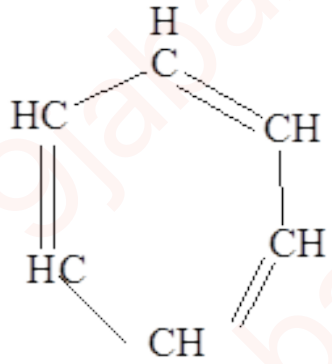
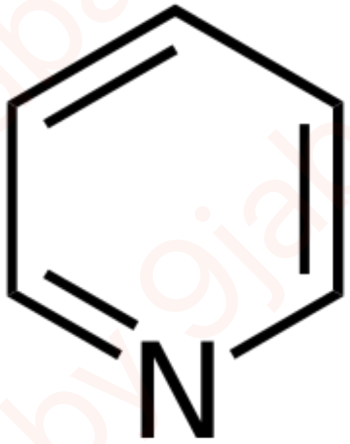
- Luischmidt (1961) reported that all aromatic compounds were derivatives of a cyclic hydrocarbons; benzene, which has a sextet of carbons bounded to each other in a specific fashion.



- The presence of the structure (benzene ring) in a compound conferred on it on aromatic behaviour e.g a carboxylic compound that contains at least a benzene ring is said to belong to the aromatic series.

- The scope of the term aromatic is now not limited to the benzenoid compounds; which do not have sextet carbons and yet possess aromatic properties.

- For example, pyridine is a non-benzenoid compound yet it is an aromatic compound because it is found to have similar electronic configuration with benzenoid compound.



Pyridine

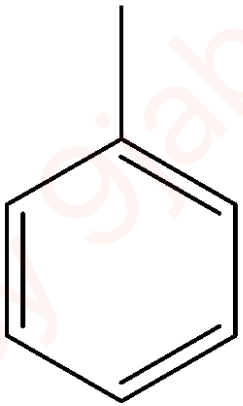
- Like their aliphatic counterparts, aromatic compounds include hydrocarbons, alcohols aldehyde, ketones, carboxylic acids, amino and their derivatives.

Nomenclature of Aromatic compounds

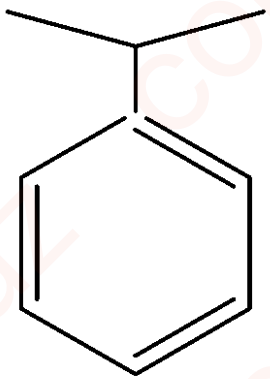
Aromatic hydrocarbons are referred to as arenes and they are divided into two classes.

- **A. Monocyclic Arenes**:- These include benzene and its derivatives in which one or more H-atom of benzene has been replaced by a substituent such as alkyl, alkenyl alkynl and aryl. They are further divided into

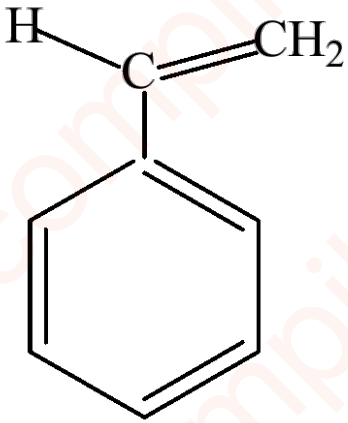
- (i) ***Monosubstituted Benzene:*** They are named by prefixing the name of the substituent group to the word benzene.



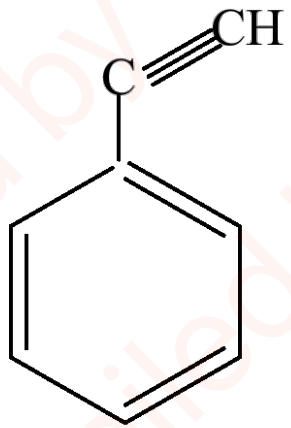
Methyl benzene
(Toluene)



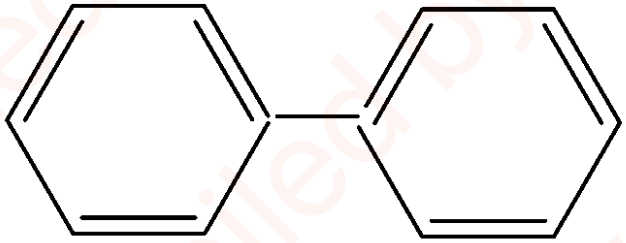
Isopropyl benzene



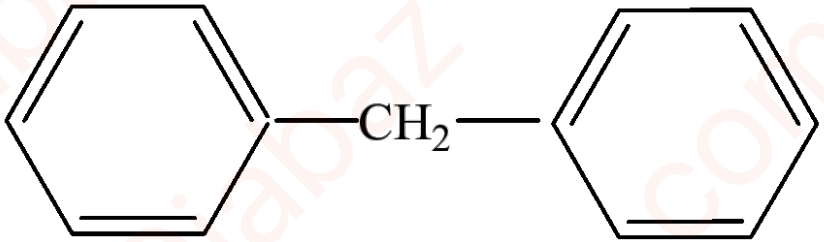
Ethenyl benzene
(Styrene)



Ethynyl benzene

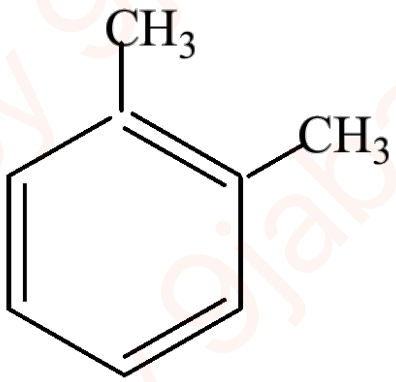


Phenyl benzene
(Biphenyl)

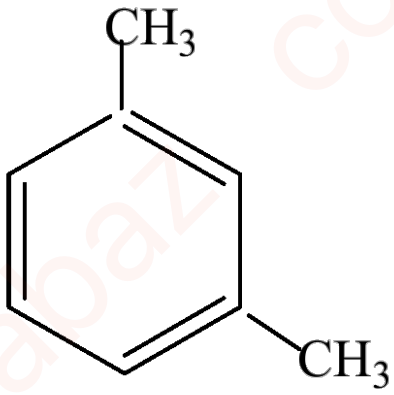


Benzyl benzene
(Diphenyl methane}

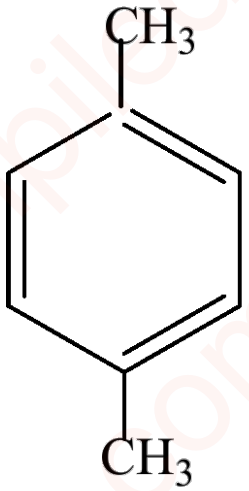
(ii) ***Disubstituted Benzene***: The most important of these type are dimethyl benzenes whose trivial names are xylenes.



1,2-Dimethylbenzene
(o-xylene)

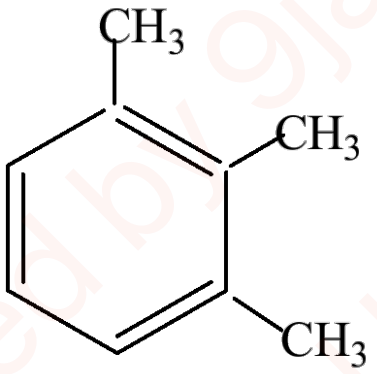


1,3-Dimethylbenzene
(m-xylene)

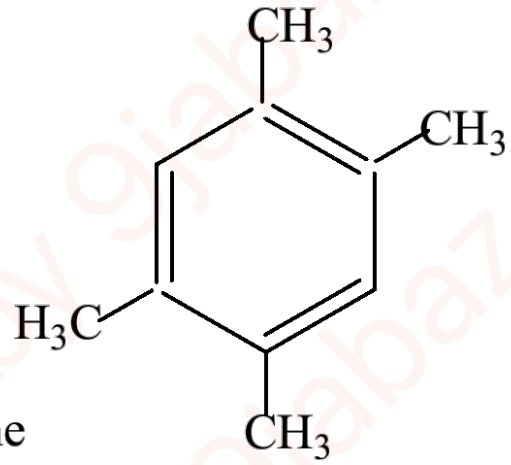


1,4-Dimethylbenzene
(p-xylene)

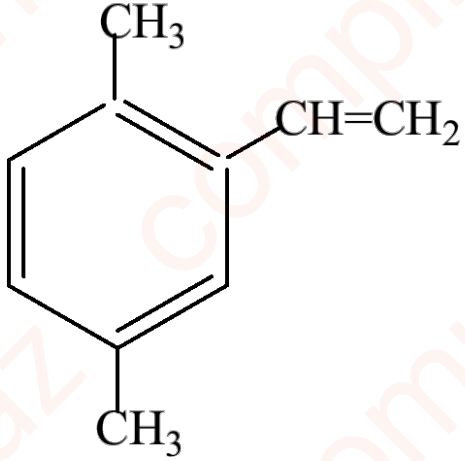
(iii) ***Polysubstituted Benzene***: They are named according to the IUPAC system. One of the substituent groups is placed at the top of the benzene ring and it carries position 1, the remaining substituents are numbered 2-6 either clockwise or anti-clockwise which ever gives lower numbers to the substituents.



1,2,3-Trimethylbenzene



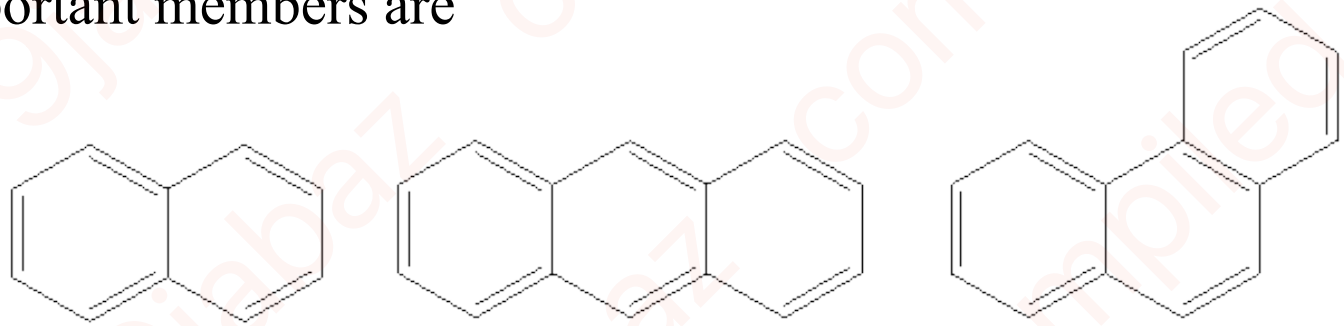
1,2,4,5-Tetramethylbenzene



1,4-Dimethyl-2-ethenylbenzene

B. Fused Polycyclic Arenes

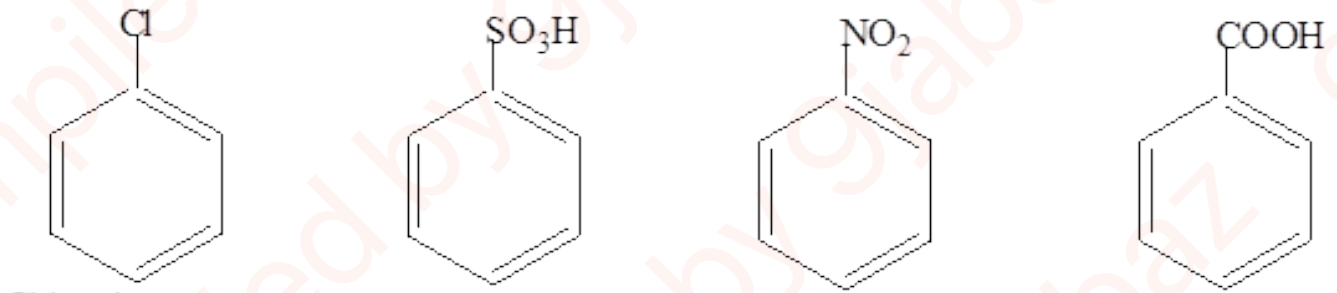
These contains two or more benzene rings in ortho position, some important members are



Naphthalene Anthracene Phenanthrene

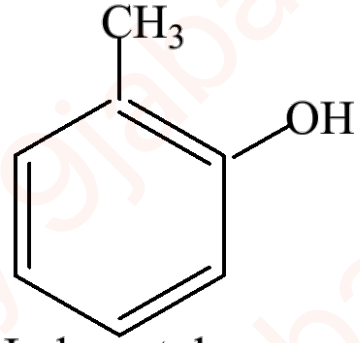
Functional Derivatives of Arenes

- The IUPAC names of these compounds are given either as the substituent products of arena or by naming the aryl group followed by the name of the functional groups. The groups are derived from toluene or benzene.
- ***Monosubstituted Functional Derivatives***

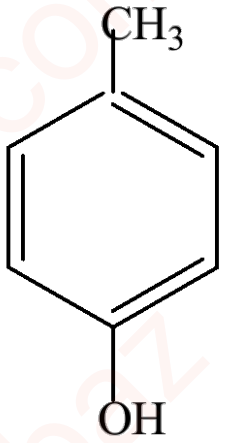


Chlorobenzene Benzenesulphonic acid Nitrobenene Benzoic acid

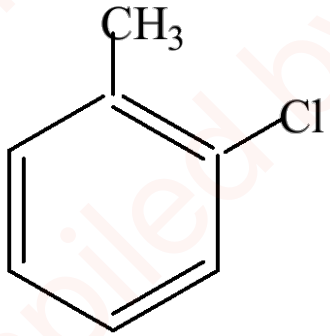
2. Monosubstituted Toluene



2-Hydroxytoluene

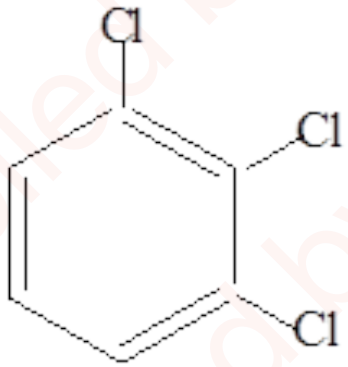


4-Hydroxytoluene
(p-cresol)

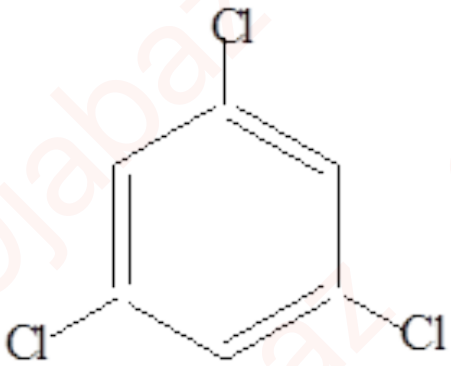


2-Chlorotoluene

3. Tri- and Tetra- Benzene Products



1,2,3-Trichlorobenzene



1,3,5-Trichlorobenzene

Sources of Aromatic Hydrocarbons

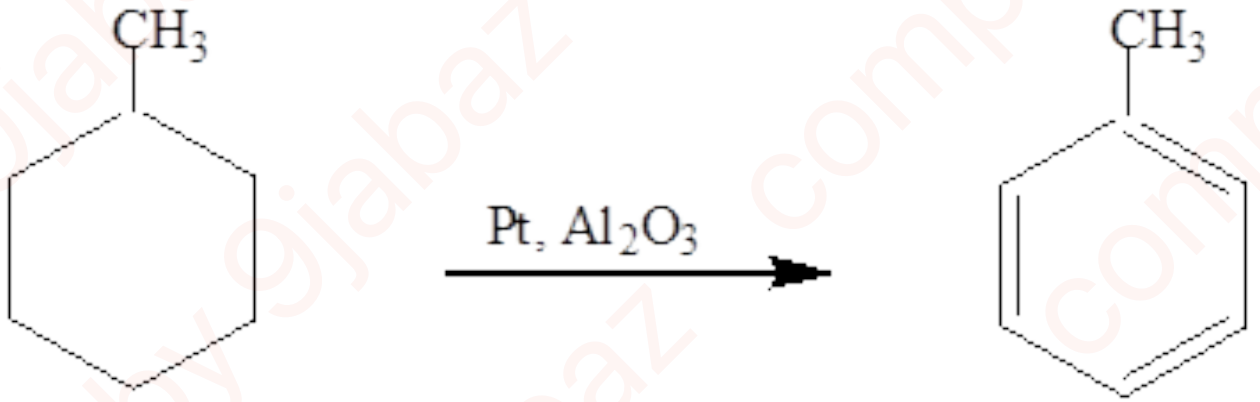
- There are two large reservoirs of organic materials, which are coal and petroleum.

- Aromatic compounds are obtained from both; the larger portion of coal that is mined today is converted into coke.

- When coal is heated in the presence of air, it is broken down into simpler volatile compounds, the residue is coke. The volatile materials consist of coal gas and a liquid known as coal tar. Aromatic compounds are obtained from the distillation of coal tar.

- Also, aromatic hydrocarbons are synthesized from alkenes through the process of catalytic reforming.

- This can bring about not only dehydrogenation as in the reformation of toluene from methyl cyclohexane but also cyclization and isomerization as in the formation of toluene from n-heptane or 1,2- dimethyl cyclohexane.

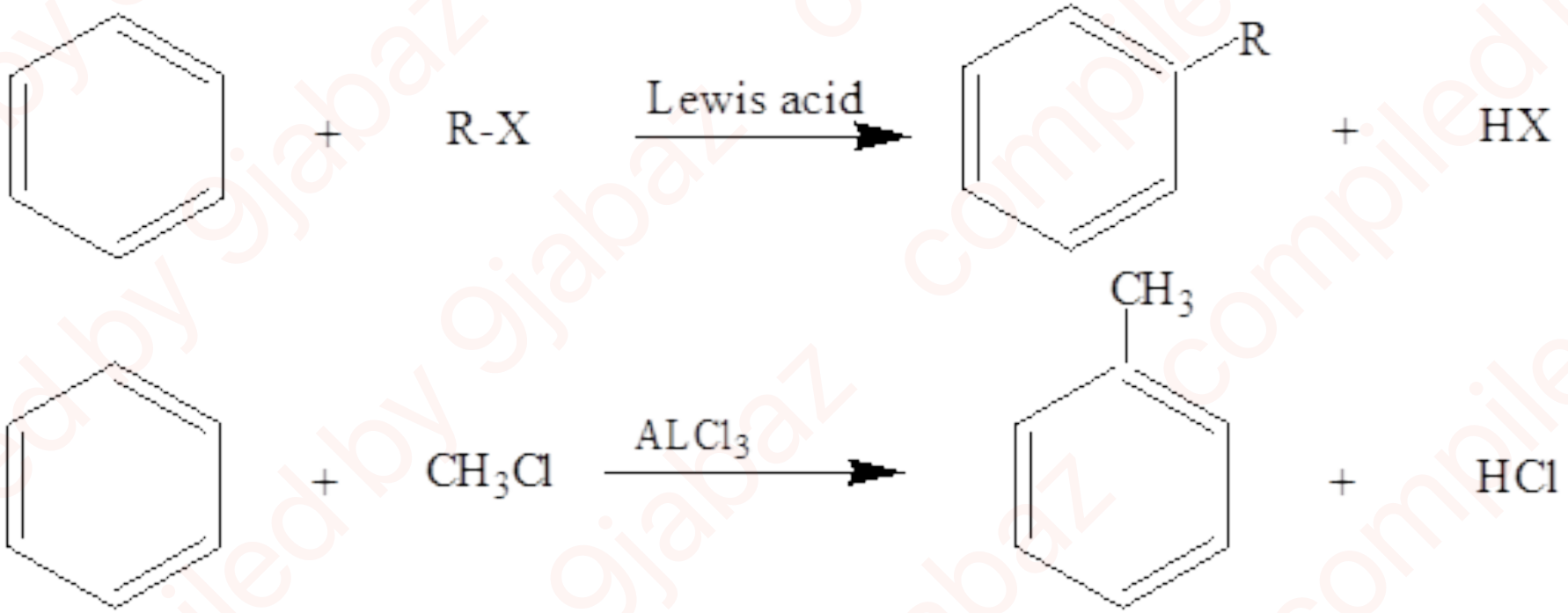


- In an analogous way, benzene is obtained from cyclohexane as well as from hydro-dealkylation of toluene.

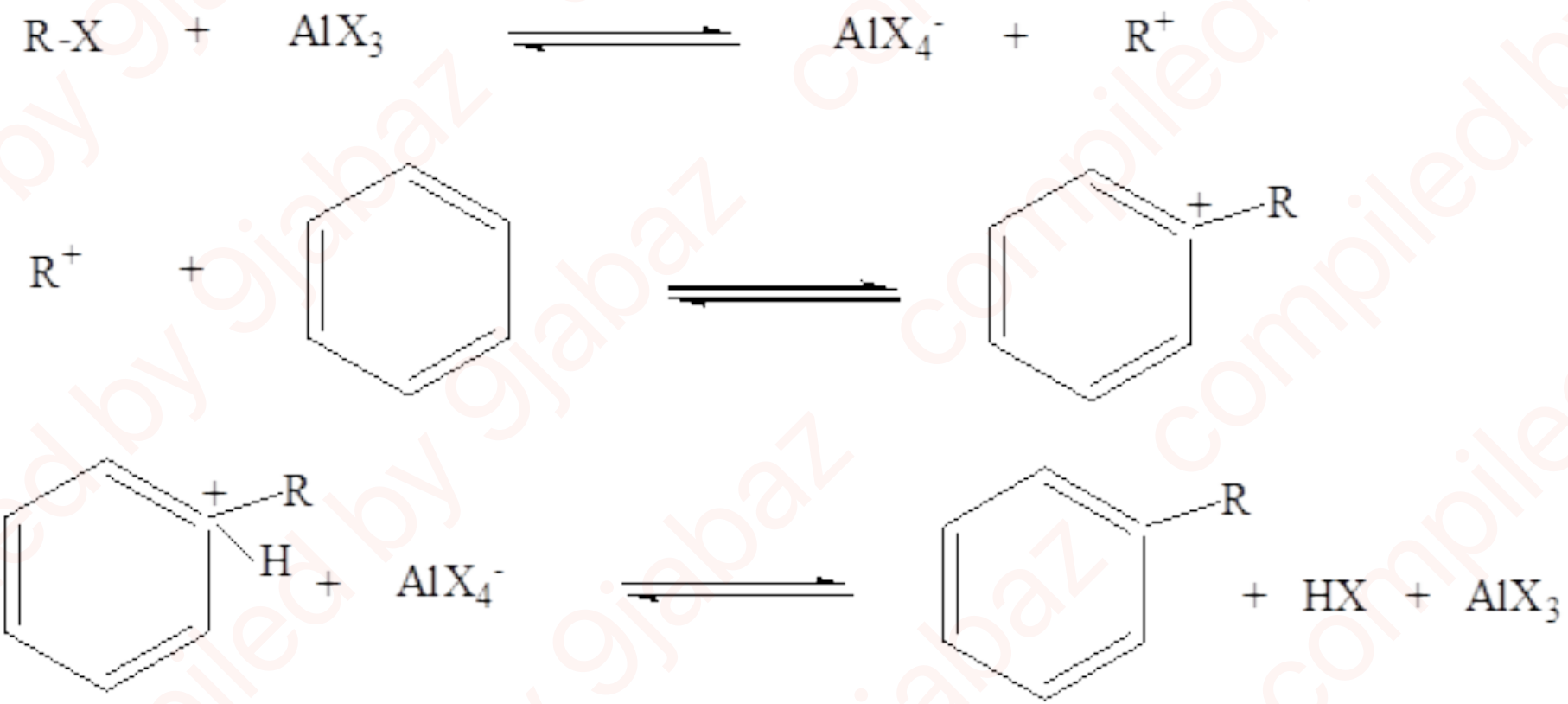
- Today, the main source of enormous quantity of benzene is petroleum.

Preparation of Alkyl Benzene

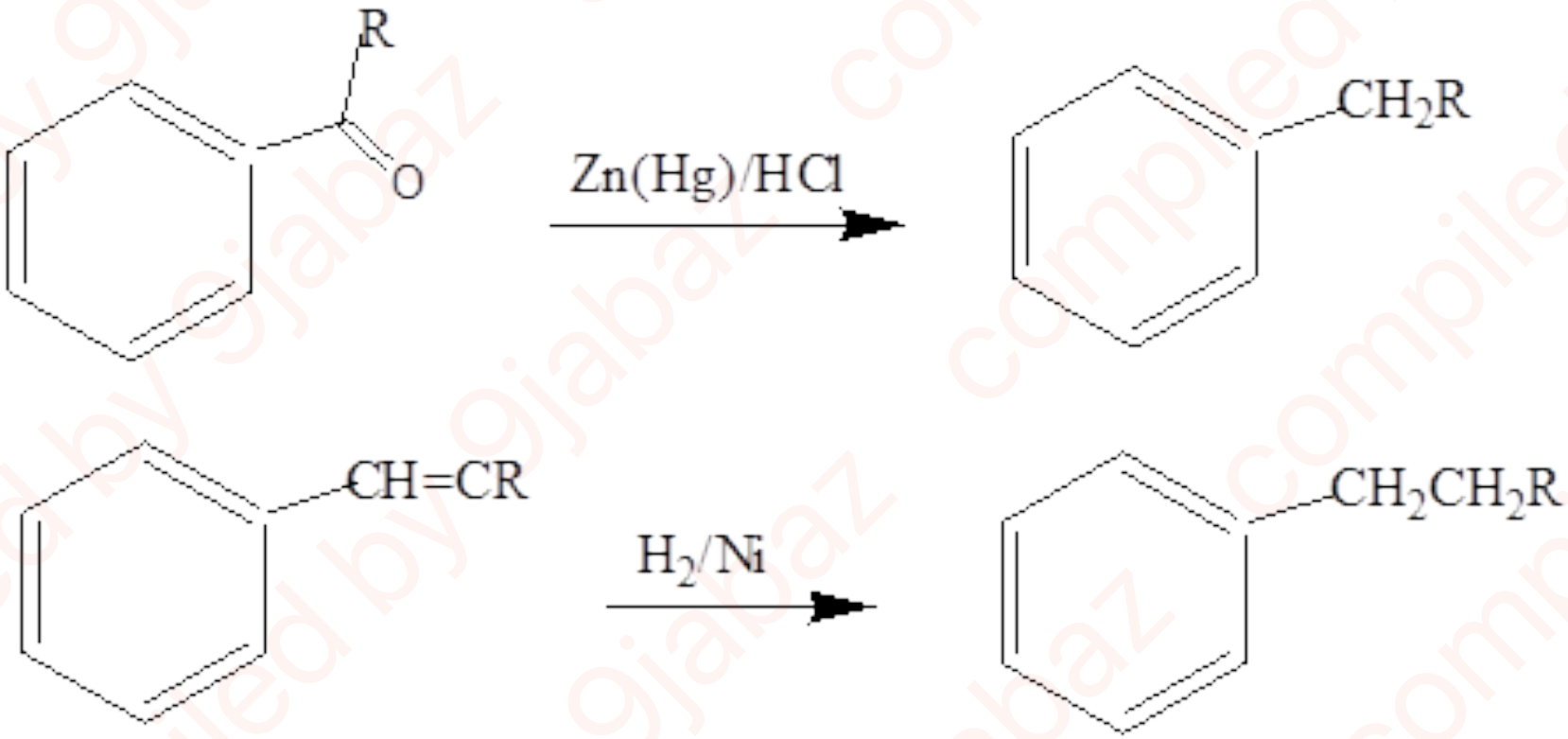
1. Friedel-Craft Alkylation



Mechanism of Friedel-Craft Alkylation

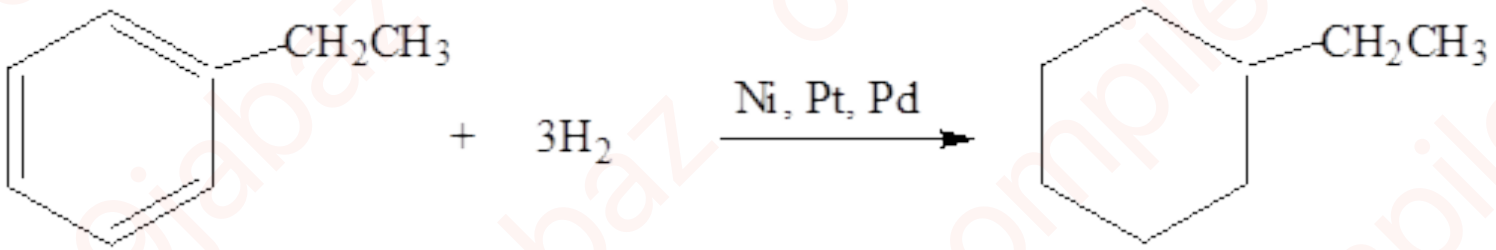


2. Conversion of Side Chain



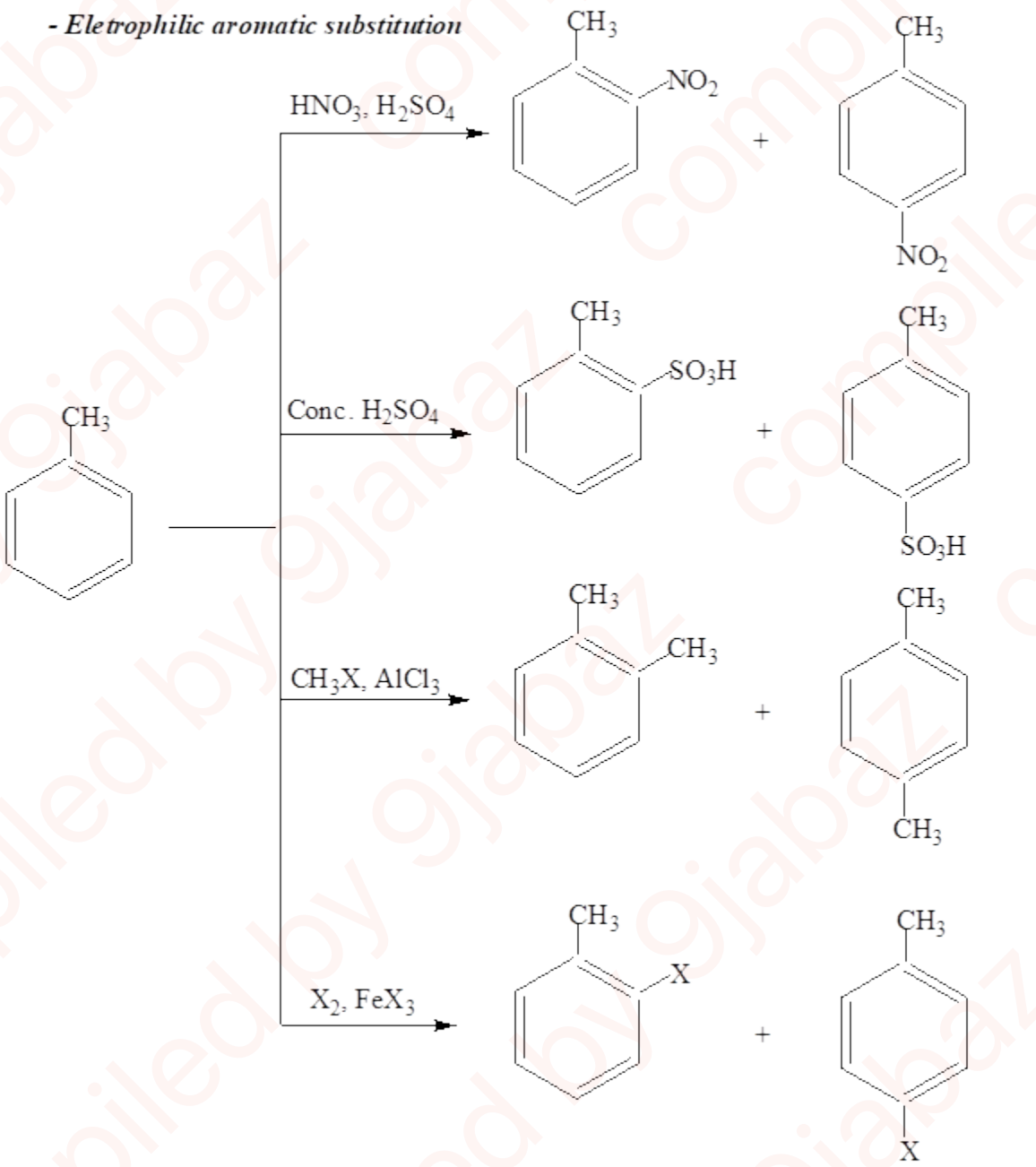
Reactions of Alkyl Benzene

1. Hydrogenation



3. Substitution Reaction

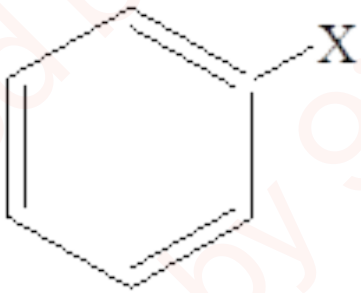
- *Eletrophilic aromatic substitution*



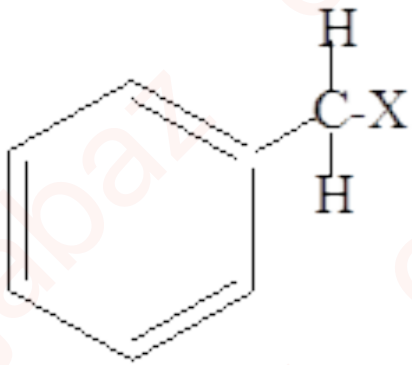
Aromatic Halogen Compounds

The halogen derivatives of aromatic hydrocarbon are divided into two classes.

- Aryl halides (Ar-X) in which the halogen atom is attached directly to carbon in the aromatic group.
- Arylalkylhalides – the halogen atom is attached to carbon on the side chain, then the aryl alkyl halides are more of alkyl halides.



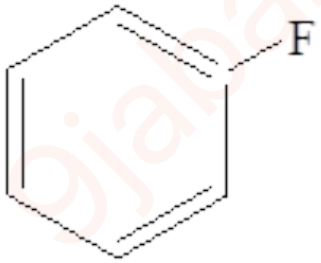
Aryl halide



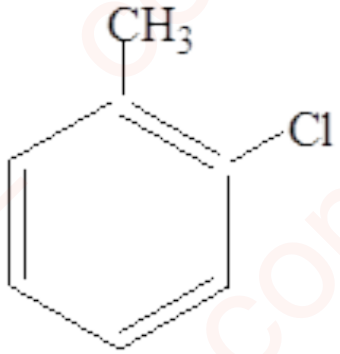
Aryl akyl halide

Nomenclature

- Nomenclature of Aryl halides are named by prefixing the name of substituent to parent hydrocarbon called halohydrocarbon

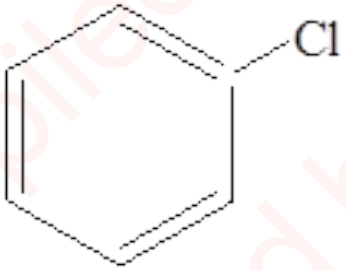


Fluorobenzene

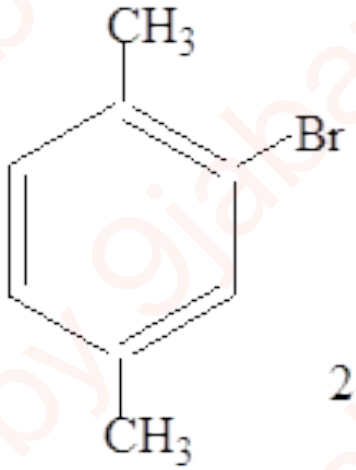


2-Chlorotoluene

- Simple halides are also assigned the common names



Phenylchloride

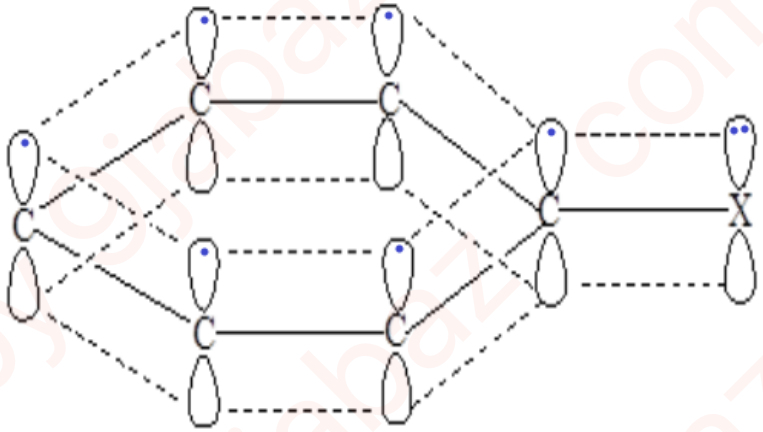


2-Bromo-p-xylene

Structure of Aryl halides (Ar-X)

(X = Cl, Br, F)

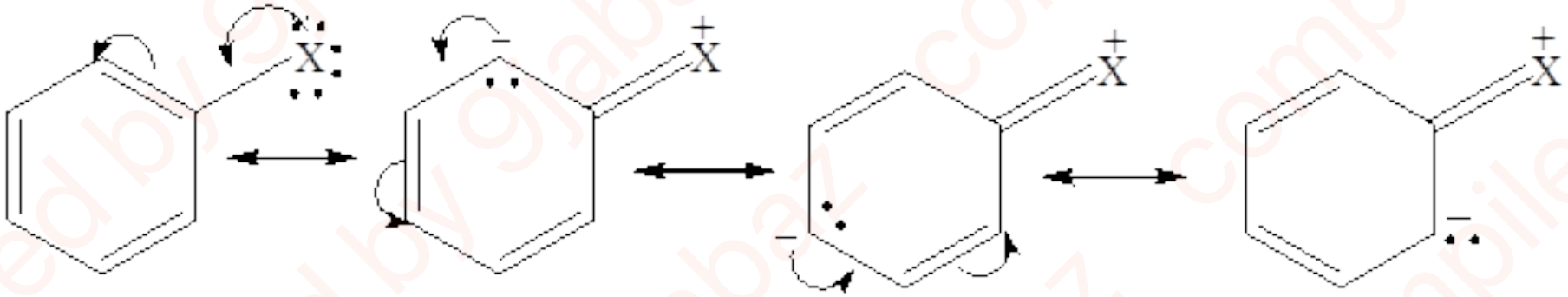
- The structure of arylzalides is basically the same with that of benzene except the halogen bonded to a carbon in the ring was a p-orbital containing lone pair of electrons.



- The p-orbital of the halogen interacts with the π orbital enveloping the ring, to form an extended π orbital.

- The extended orbital envelopes the six carbons of the ring as well as the halogen.

- In other words, the six electrons of the ring carbons (one belonging to each carbon) and two electrons of the halogen are now associated with all the seven atoms.
- This delocalization of electrons lends some double bond character to the carbon – halogen bond.
- The electronic structure of aryl halides could be represented by the following canonical forms.

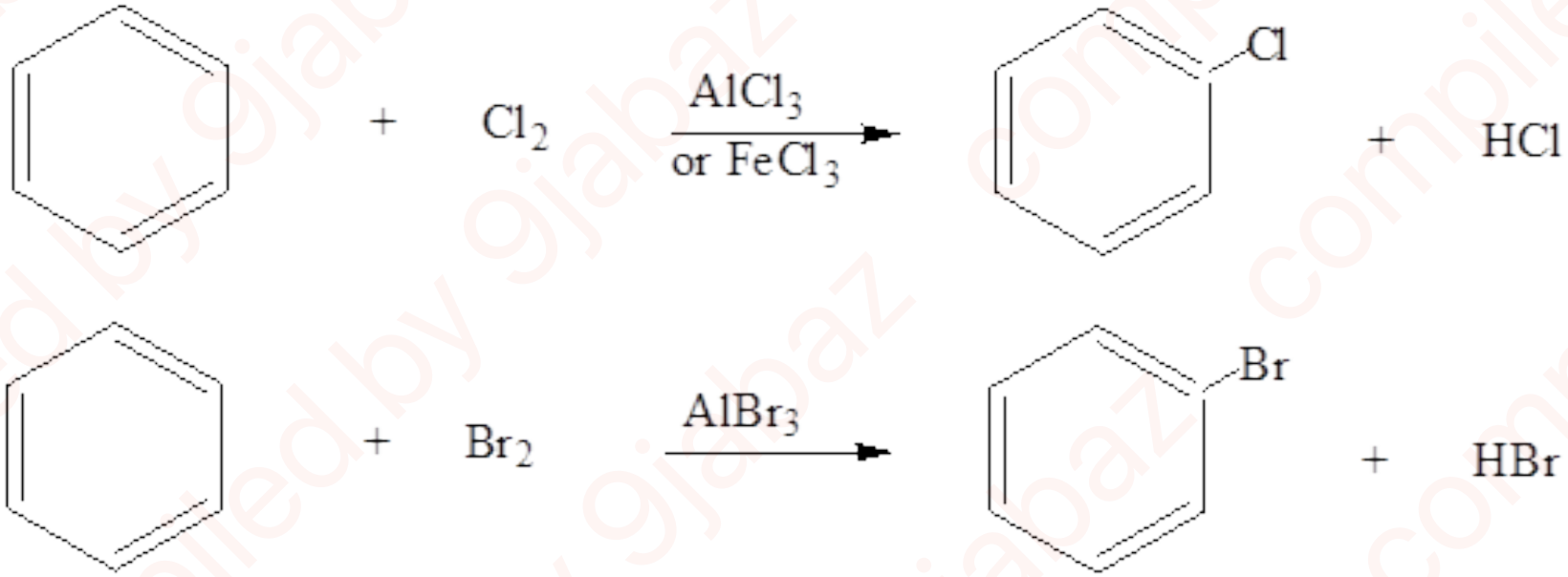


- Thus aryl halides are to be regarded as resonance hybrid of the 4 contributing forms shown above.
- Thus Ar-Xs are to be regarded as hybrid structure of the four canonical forms for this reason the C-X bonds of arylhalides can stronger than those in the alkylhalides.

Preparation of Aryl halides

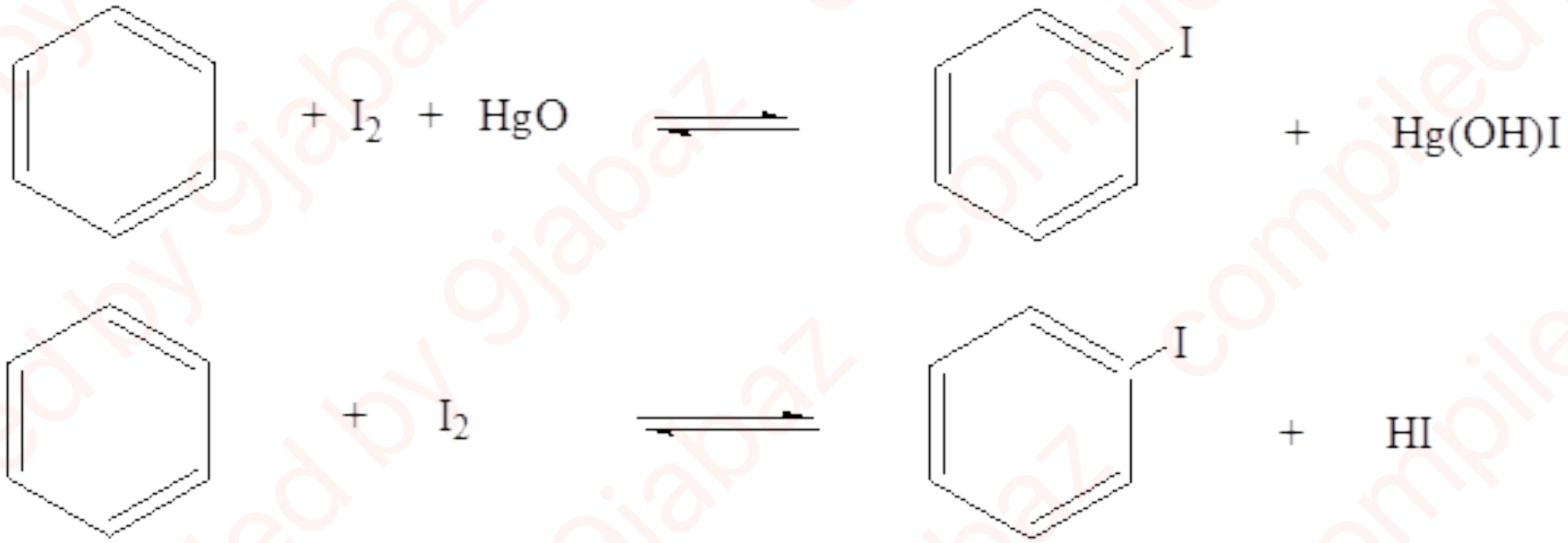
Direct halogenation

- Ar-Cl & Ar – Br are prepared by direct halogenation of aromatic hydrocarbon in the presence of Lewis acid catalyst.



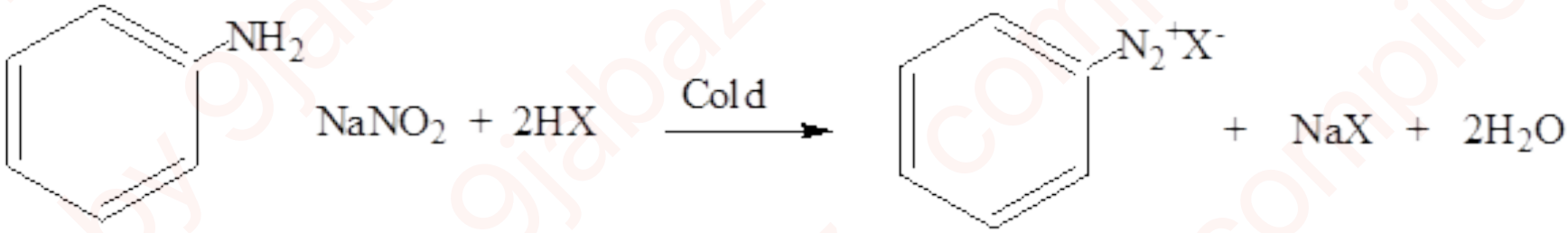
- In excess of the halogen di-halo is obtained.

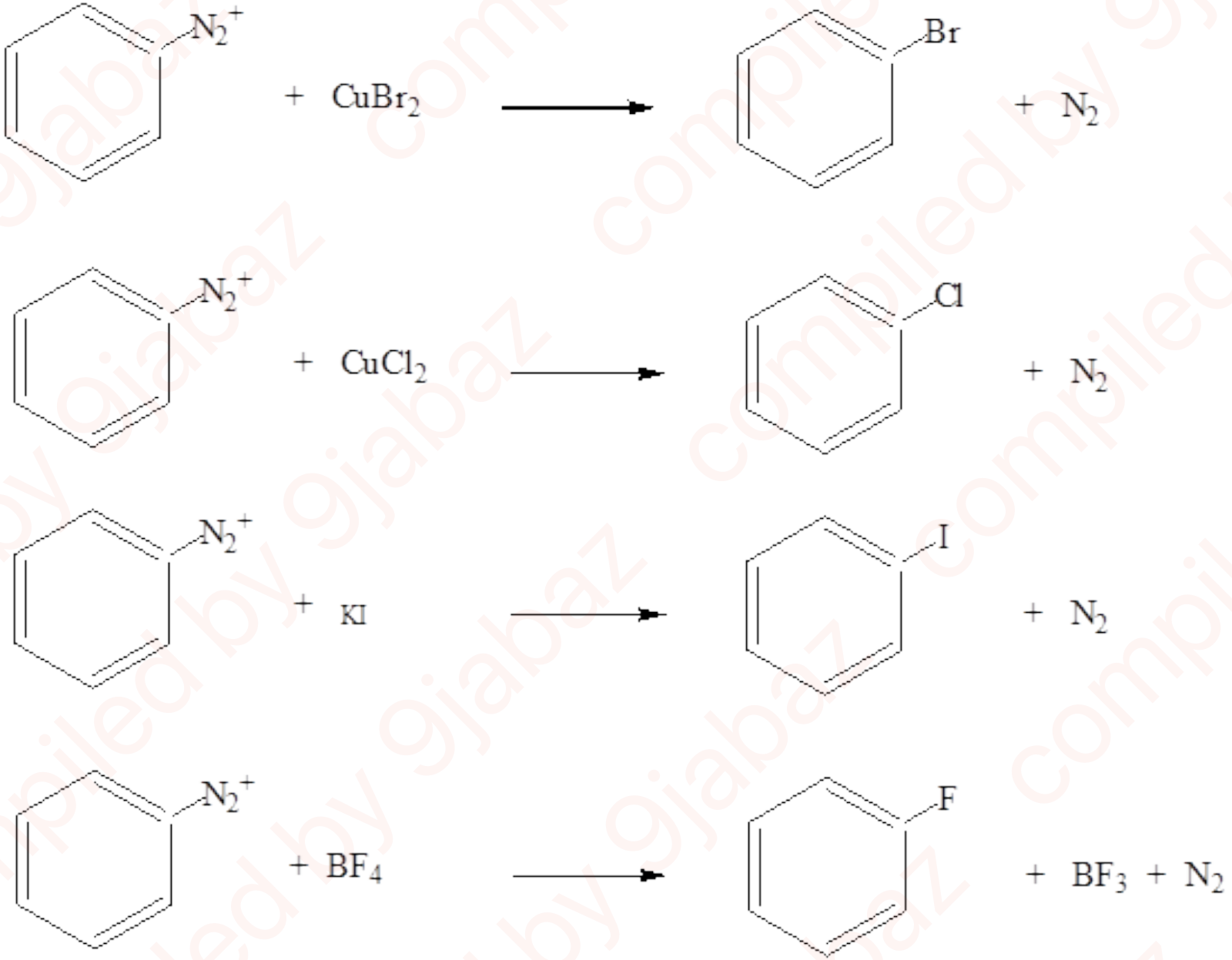
- Ar-I is obtained in huge yields in the presence of reagents like HgO, HNO_3, HIO_3 which remove HI produced in the reaction.



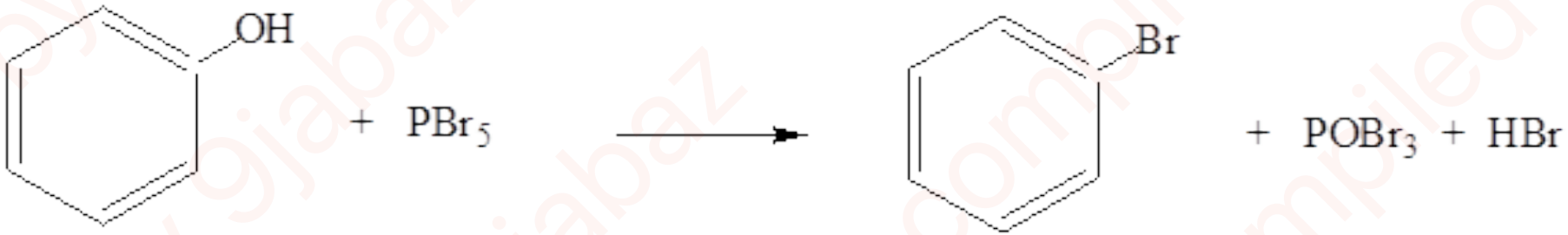
Decomposition of Diazonium salts

- The diazonium salts ($C_6H_5N_2^+X^-$) is obtained from the corresponding aromatic amine

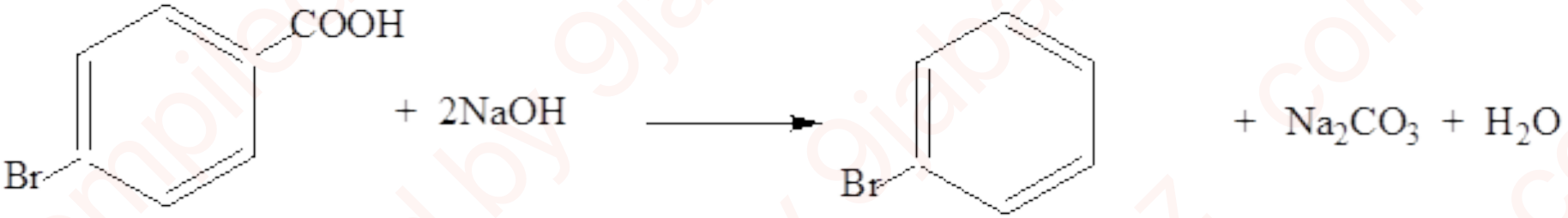



N_2^+
+ $CuBr_2$
Br
+ N_2
N_2^+
+ $CuCl_2$
Cl
+ N_2
N_2^+
+ KI
I
+ N_2
N_2^+
+ BF_4
F
+ BF_3 + N_2

- ***Substitution of –OH of phenol by a halide when phenol is treated with X^- generating agent such as PBr_5, $SOCl_2$ aryl halide is produced.***

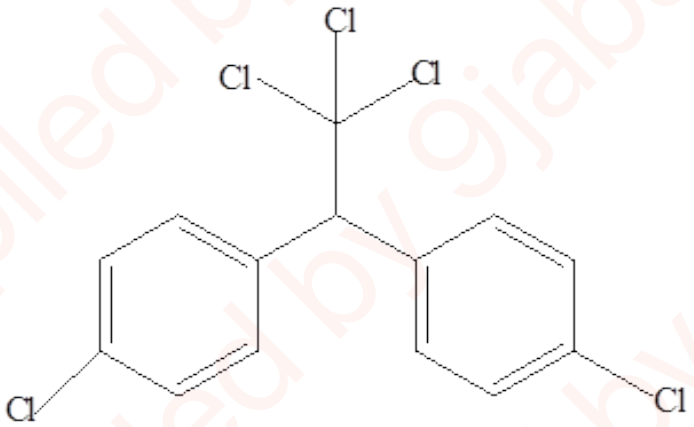


- ***Decarboxylation of halogenated acid***



Physical Properties

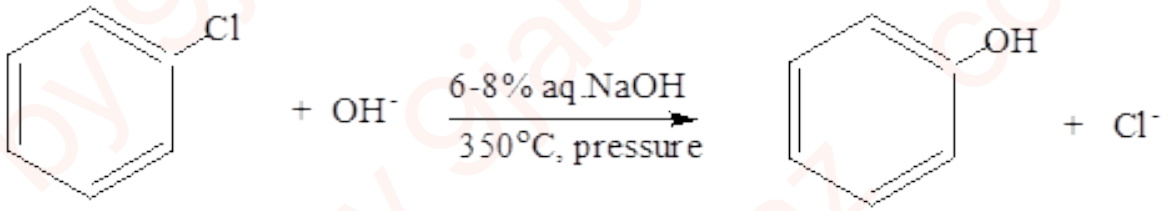
- Ar-Xs are colourless oily liquid
- They have low polarity therefore insoluble in water but soluble in common solvents.
- They have density greater than one.
- Boiling point, melting point and density are gradually from F (i.e. F < Cl < Br < I) of the same homologous series. The boiling point of ortho, meta and para isomers are so close that they are difficult to separate by distillation. Many of them have physiological activities and they are used as insecticides e.g. DDT (Dichlorodiphenyltrichloroethane)

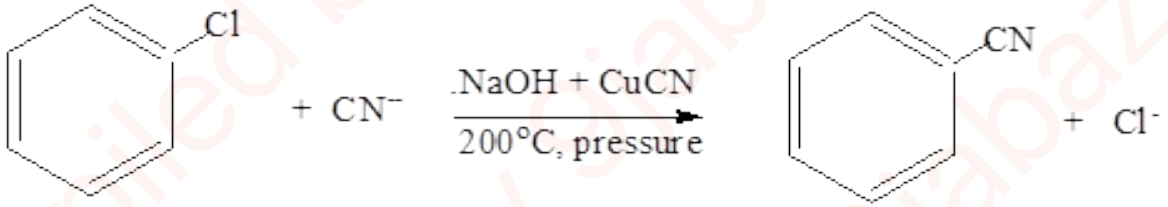


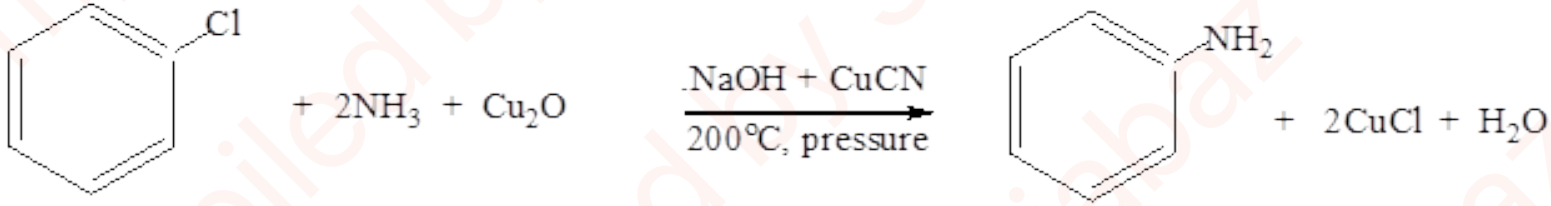
- ***Structure of DDT (Dichlorodiphenyltrichloroethane)***

Chemical Properties

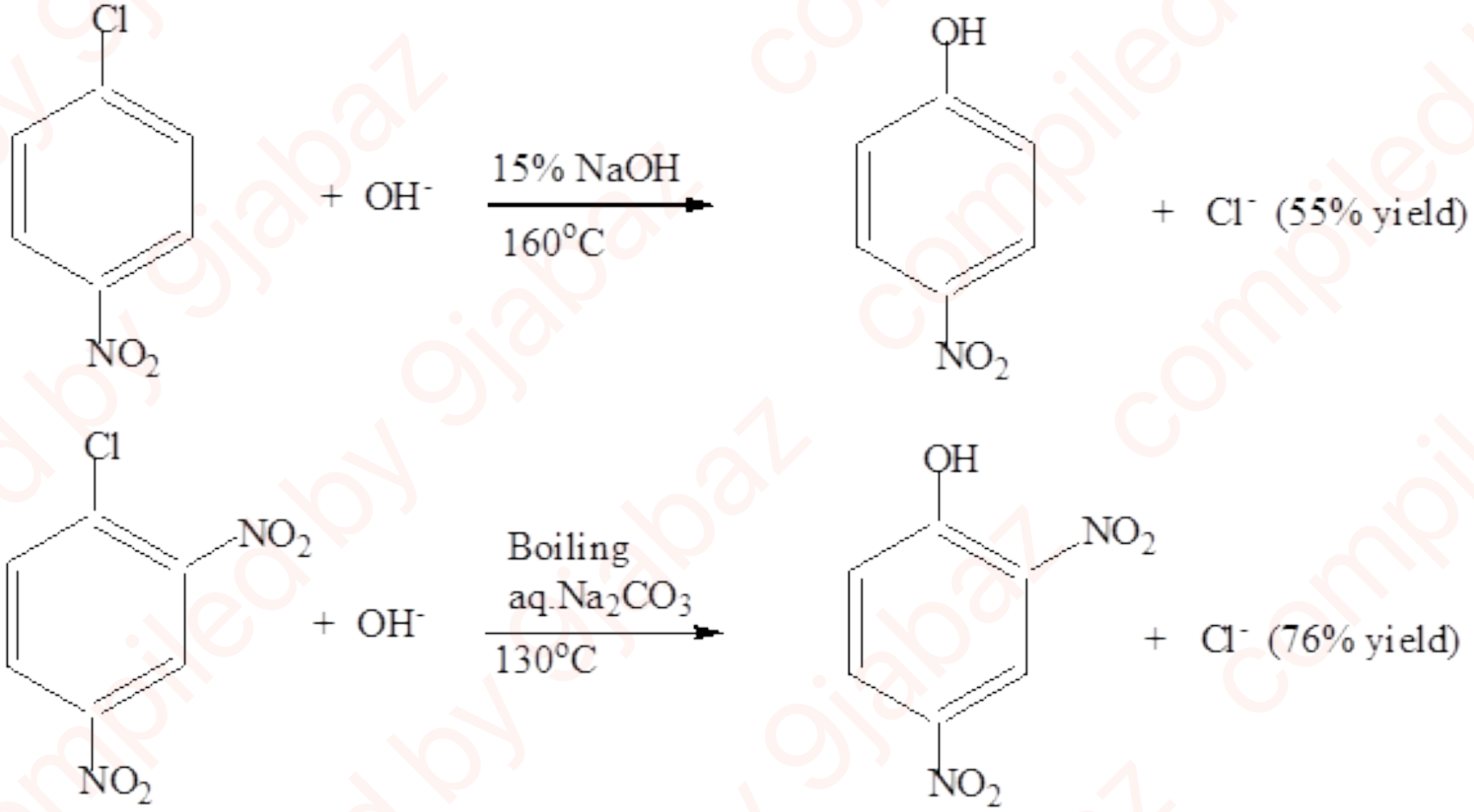
1. Nucleophilic substitution: aromatic halogen has low reactivity toward nucleophiles because it has a positive charge on it. Also, aryl halides could be represented as resonance hybrid where "C-X" bonds in them possess a double bond character and stronger than C-X bond in alkyl halides (R-X). However, at sufficient high temperature and pressure several nucleophilic substitution can be carried out.



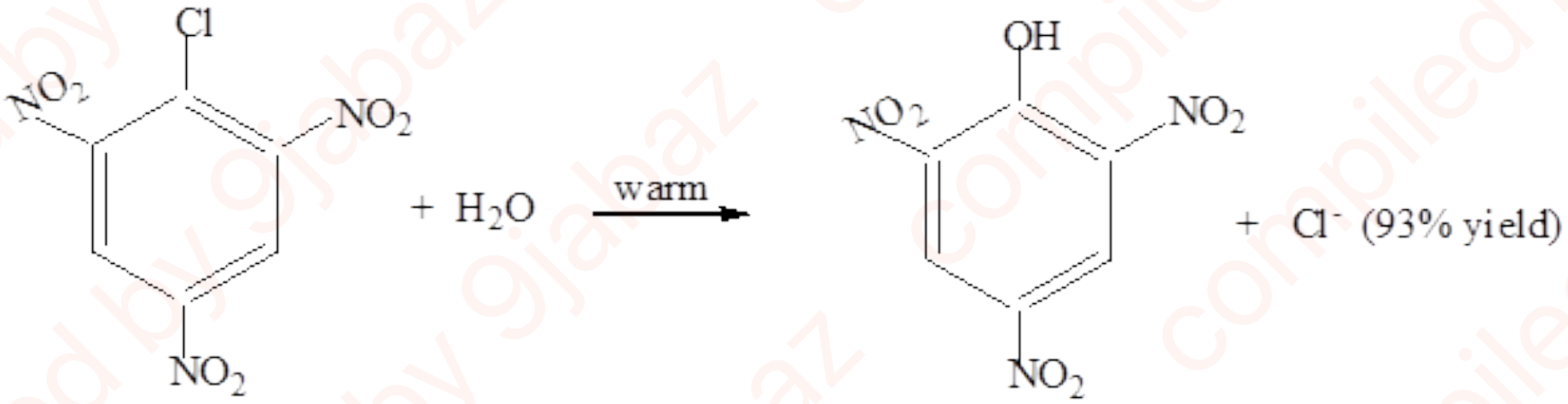




- Ar-X undergo nucleophilic displacement with increasing readiness, if a strong electron attracting group is present.

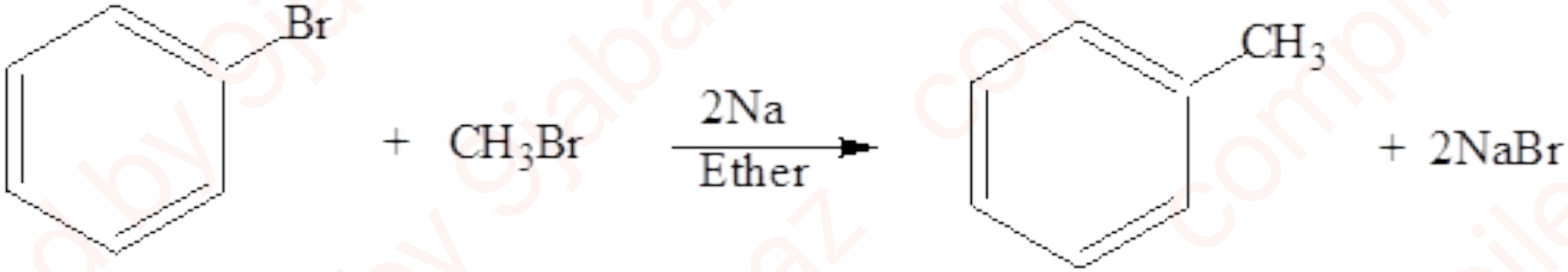


- When 3 NO_2 groups are placed at 2,4,6, positions to the halogen, the activity of Ar-X is greatly enhanced and is comparable to that of alkyl halides.



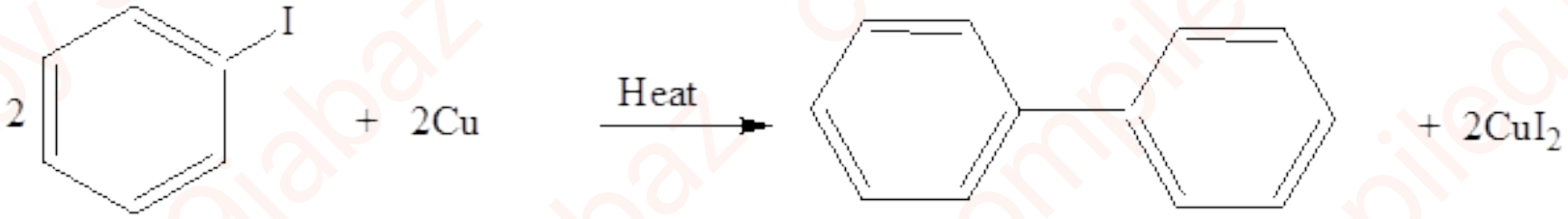
2. Wurtz-Fittig Reaction

- Ar-X and R-X undergo compiling reaction in the presence of Na in other to form alkylated aromatic hydrocarbon (arenes) referred to as Wurtz-Fittig reaction

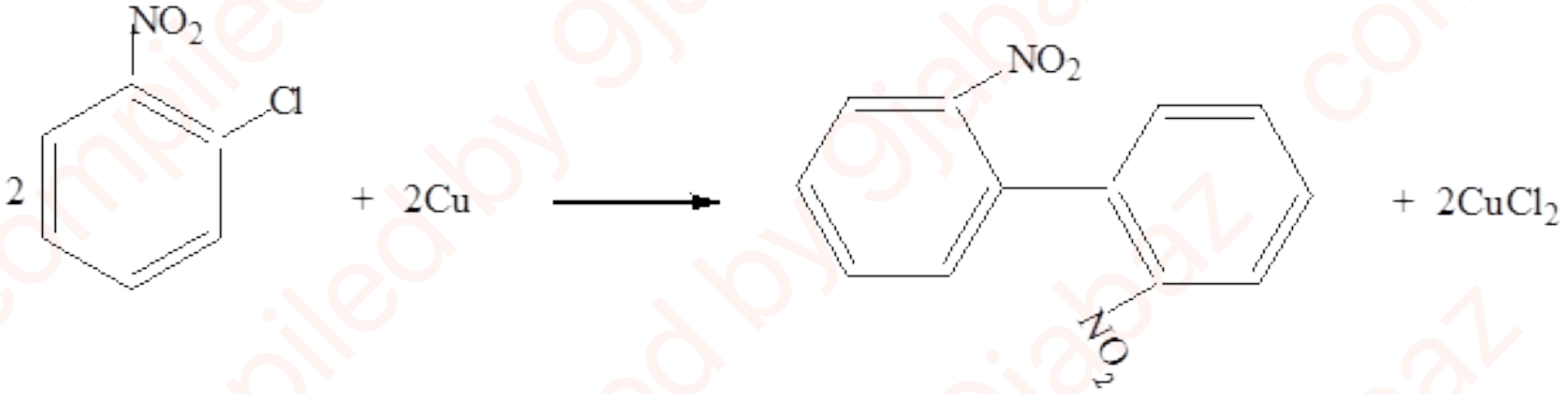


3. Ullmann Reaction

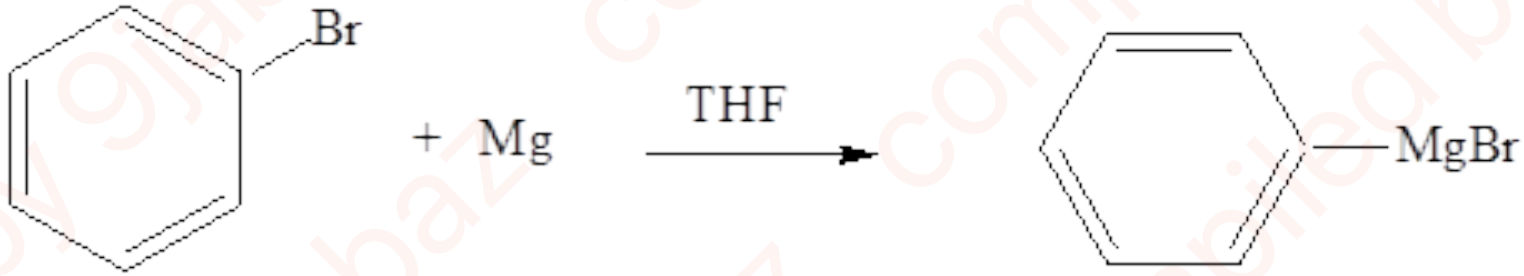
- When Ar – Xs are refluxed with Cu-powder, they undego compling reaction to form biaryls.

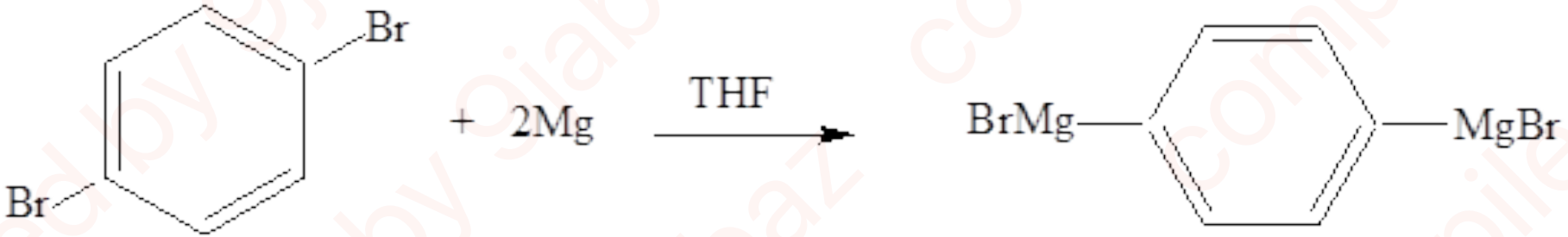


- Ar-X (X = Cl, Br) do not usually undergo this reaction except when activated with suitable substituent (electron attracting agent) are NO_2 is present as substituent on it.



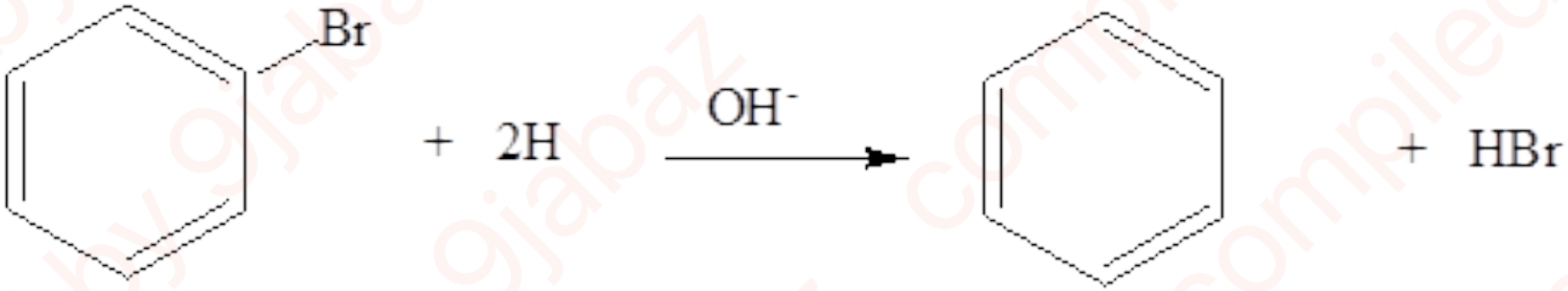
3. Formation of organometallic Compounds





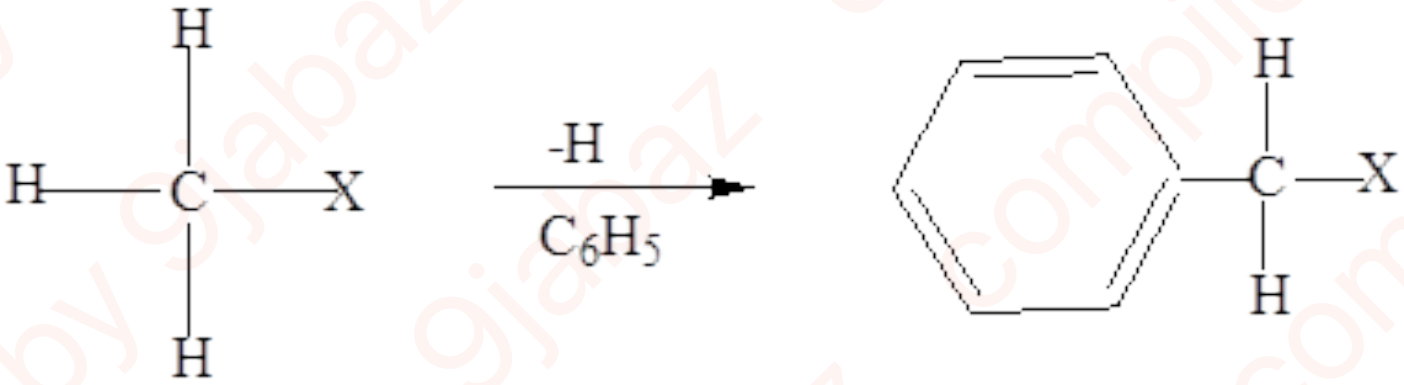
4. Reduction:

- When aryl halides are reduced by means of Ni/Al alloy in the presence of an alkali they yield parent hydrocarbon.



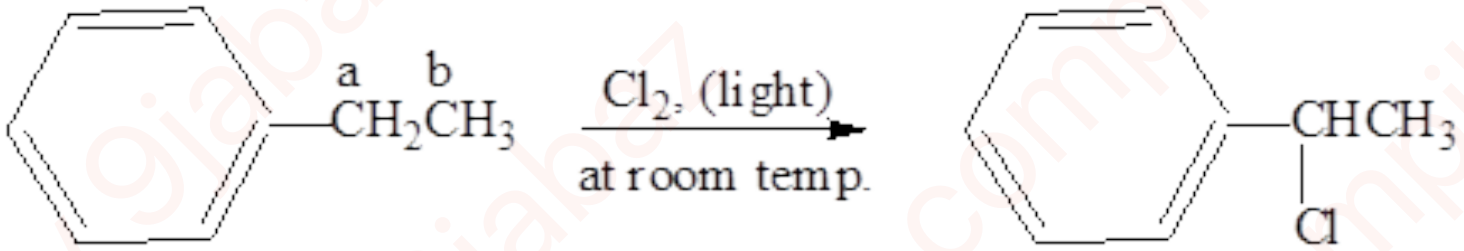
Arylalkyl halides or Arakyl halides

- This compound can be regarded as aryl and alkyl halide. i.e

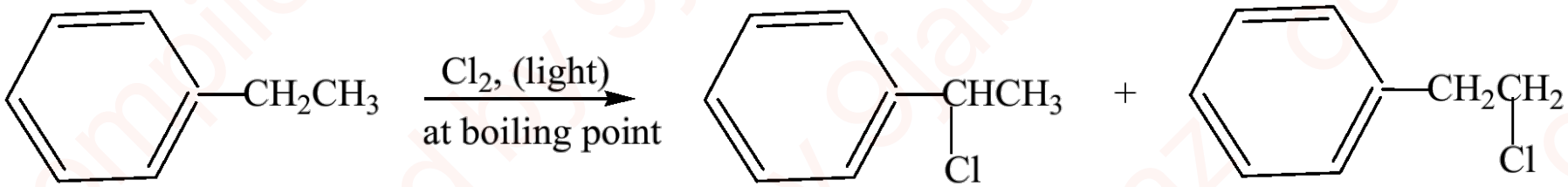


- The simplest anylalkyl halides are those derived from toluene. Ar-CH_2Cl; Ar-CH_2Br both compounds are obtained by direct halogenation of toluene in sunlight.

- Longer side chain of Cl and Br derivatives are obtained by halogenation with Cl_2 and Br_2 in the presence light when the halogen enters the position

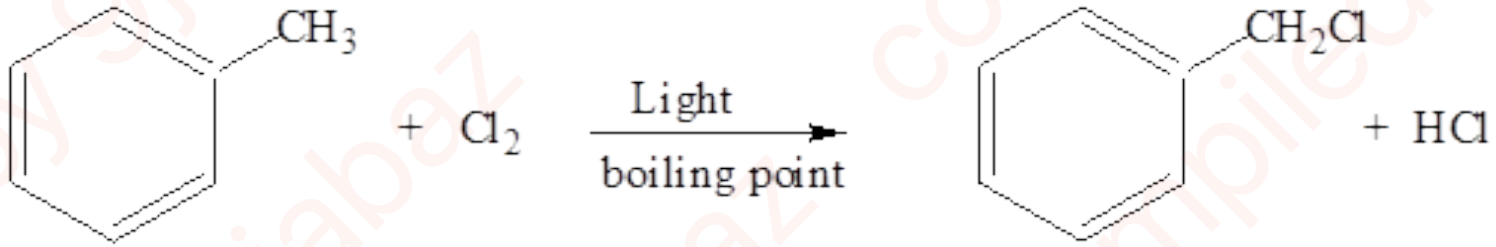


- At boiling, halogenation yields derivatives with halogen in other positions.

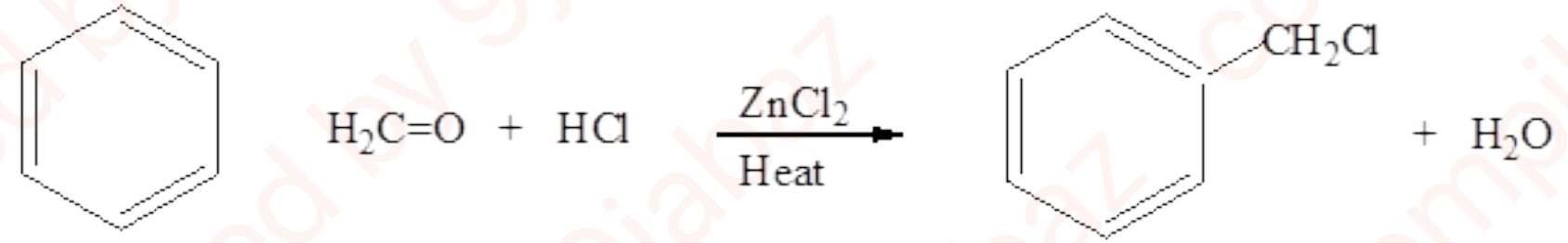


Preparation of Benzyl Chloride

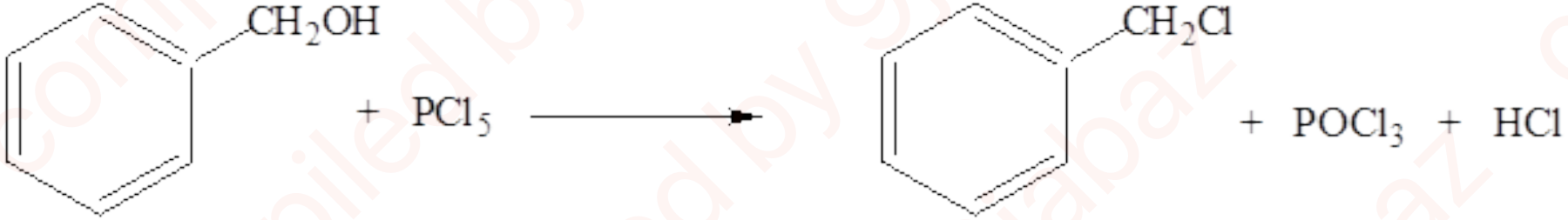
1. Direct chlorination of toluene by raising chlorine into boiling toluene in light.



2. Chloromethylation of benzene; heating benzene with formaldehyde (HCHO) and HCl in the presence of anhydrous $ZnCl_2$

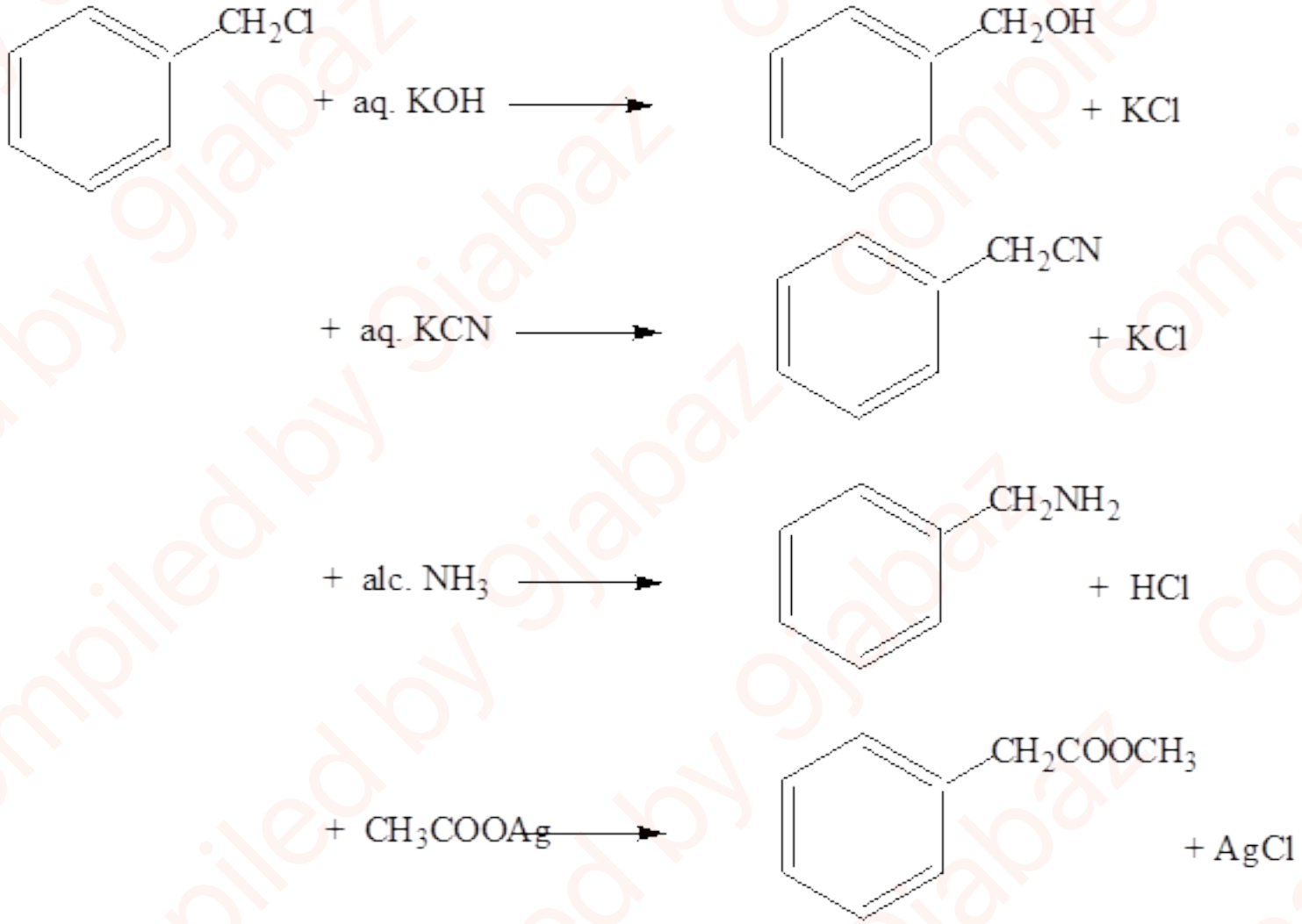


3. Action of PCl_5 on bemzyl alcohol

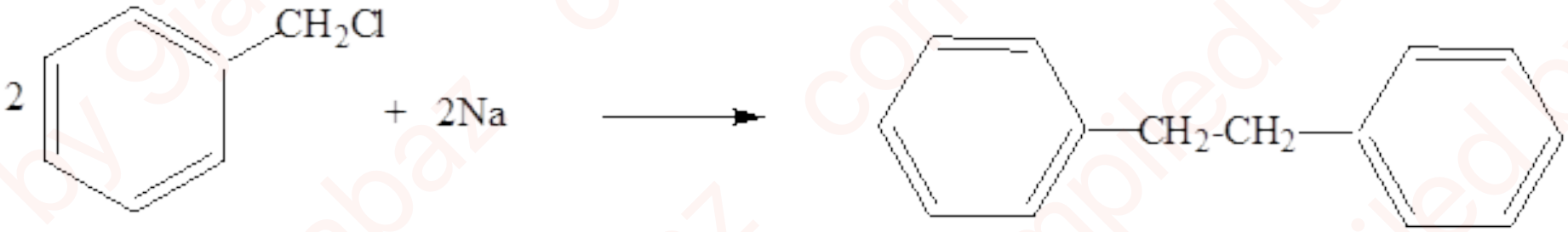


Reactivity of Aralkyl Halides

1. Nucleophilic substitution reaction: Benzyl chloride undergoes nucleophilic substitution reaction as readily as alkylchloride.

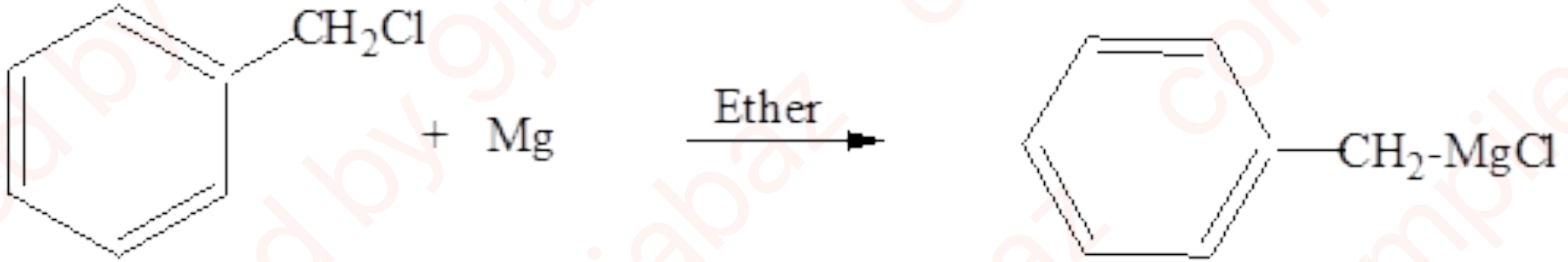


2. Wurtz reaction: Benzyl chloride on treatment with sodium metal given dibenzyl. Thus behaving like alkyl halides.

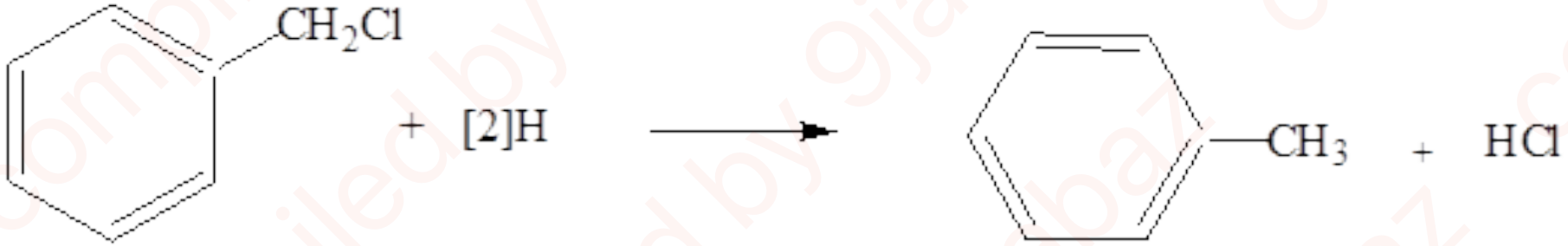


dibenzyl

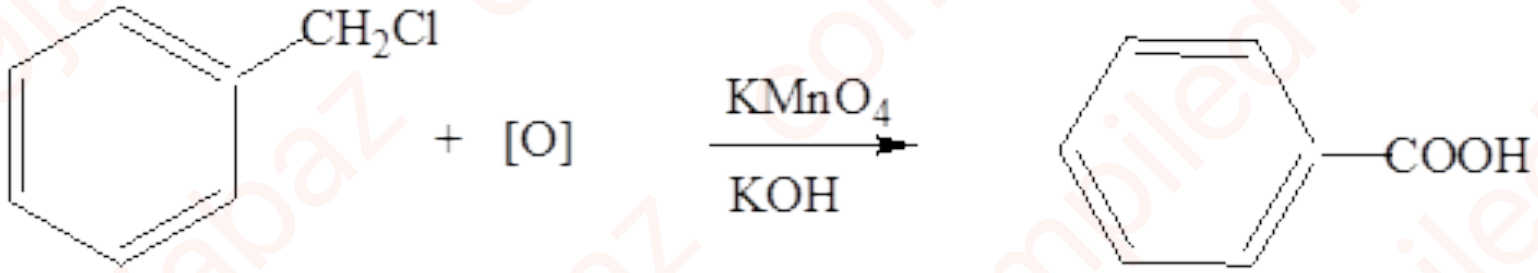
3. Formation of Grignards Reagent



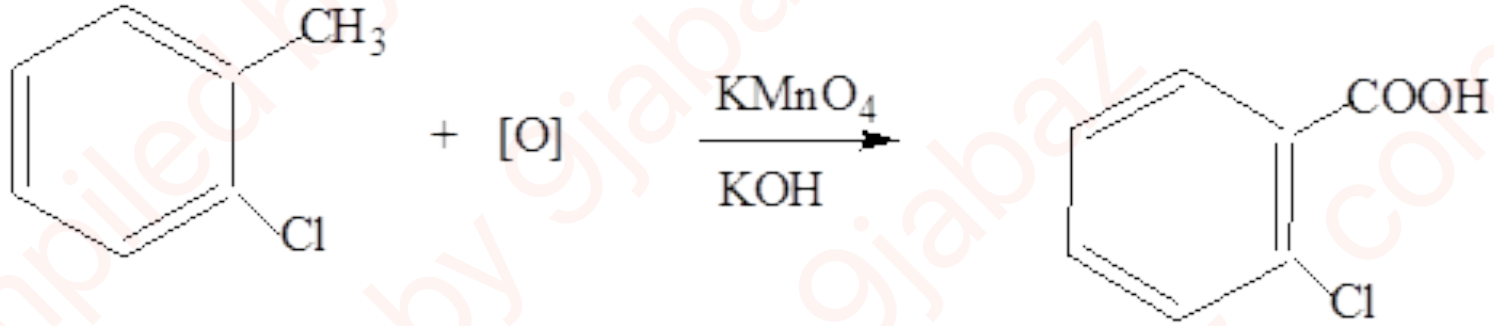
4. Reduction: It gives toluene when reduced with Zn, Cu metal.



Oxidation: The action of potassium permanganate in the presence of KOH will give benzoic acid.

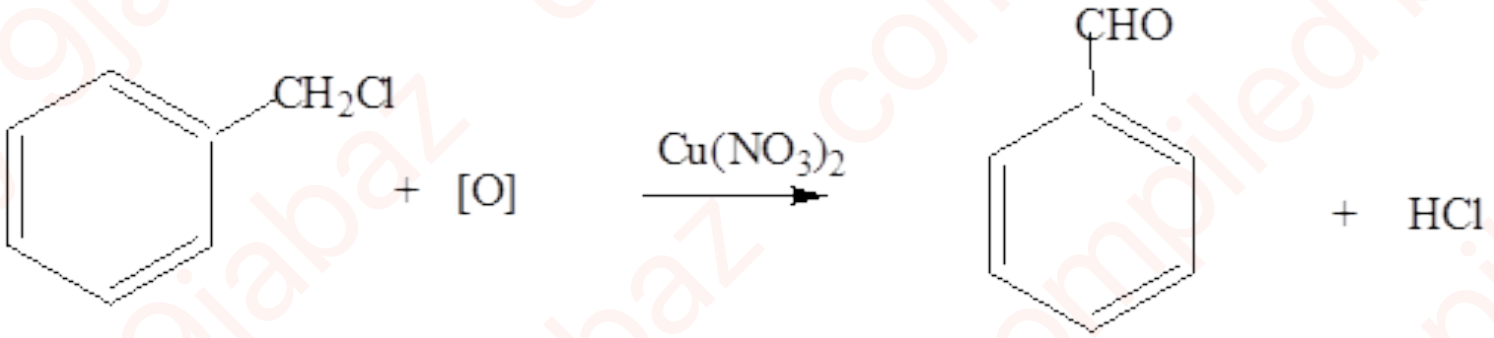


- This reaction can be used to distinguish benzyl chloride from the isomeric chlorotoluenes because chlorotoluenes will produced chlorobenzoic acid on oxidation

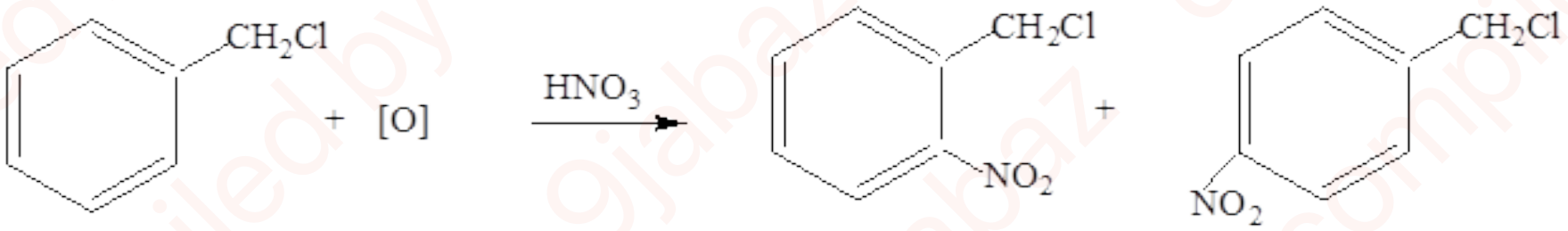


- The product obtained from o-cholorotoluene contains chlorine while that of benzyl chloride does not.

- For mild oxidation with Iron (III) nitrate [$Fe(NO_3)_3$], copper(II) nitrate [$Cu(NO_3)_2$]

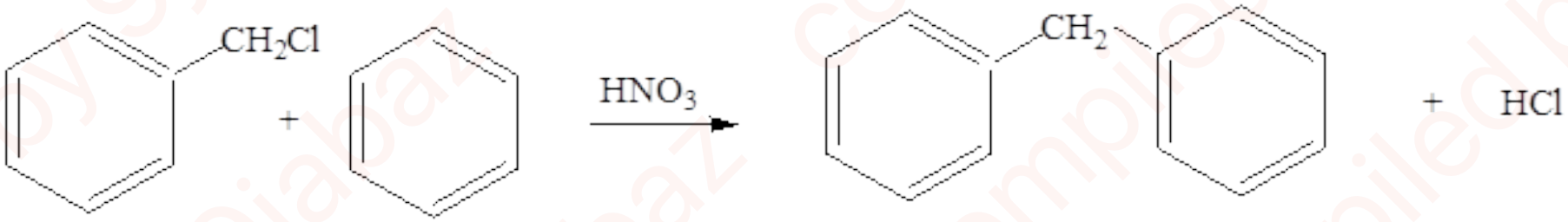


- ***6. Substitution in the Benzene Ring***



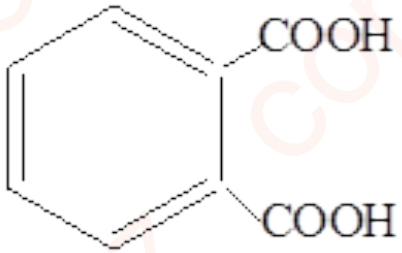
7. Fnedel – Crafts Reaction

- Like alkyl halides, it responds to fnedel craft reaction

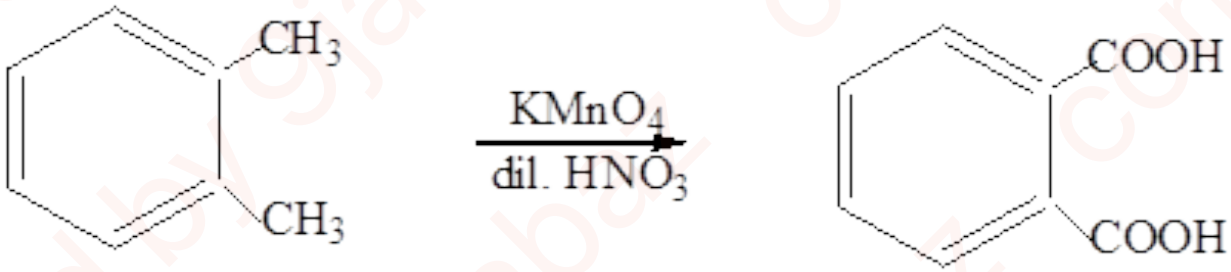


Dicarboxylic Acids

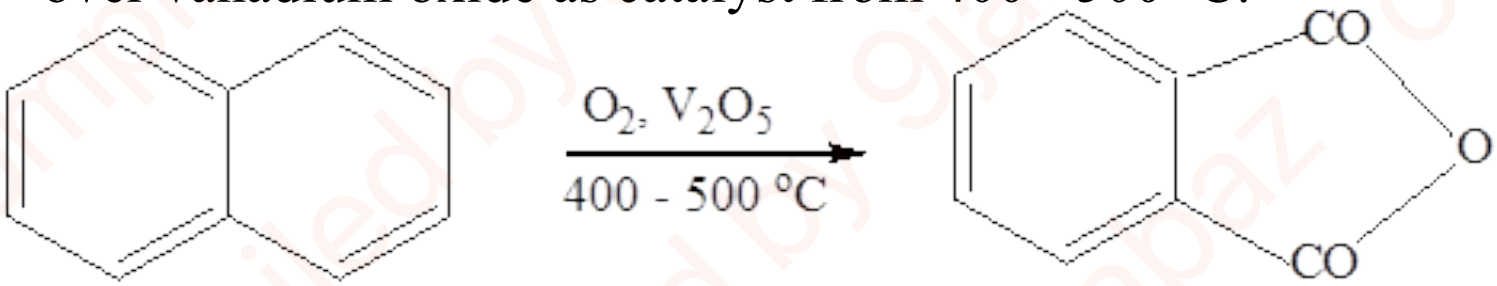
Phthalic Acid



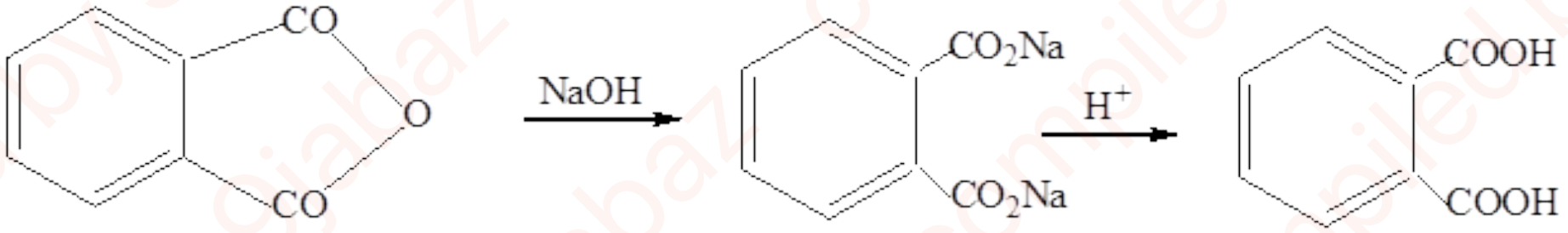
- It may be prepared by the oxidation of o-xylene with strong oxidizing agent.



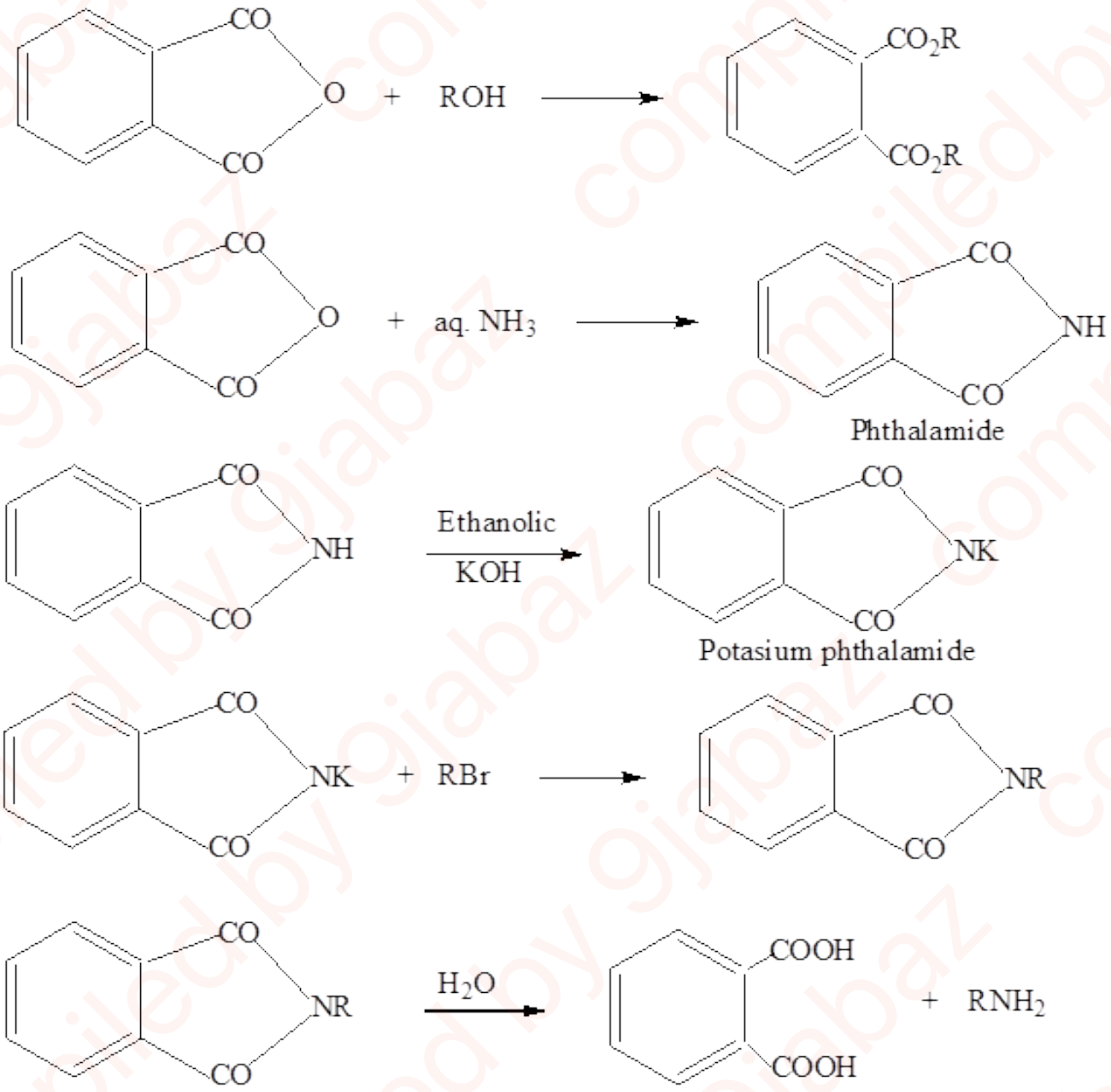
- Industrially phthalic acid is prepared by passing naphthalene vapour over vanadium oxide as catalyst from 400 - 500 °C.



- The anhydride is converted to phthalic acid by heating with NaOH and then acidified.



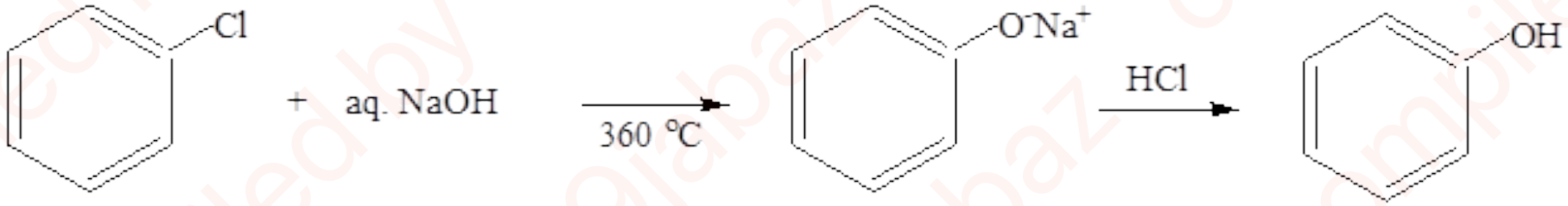
- The phthalic acid is a white crystalline solid with a melting point of 231 °C.



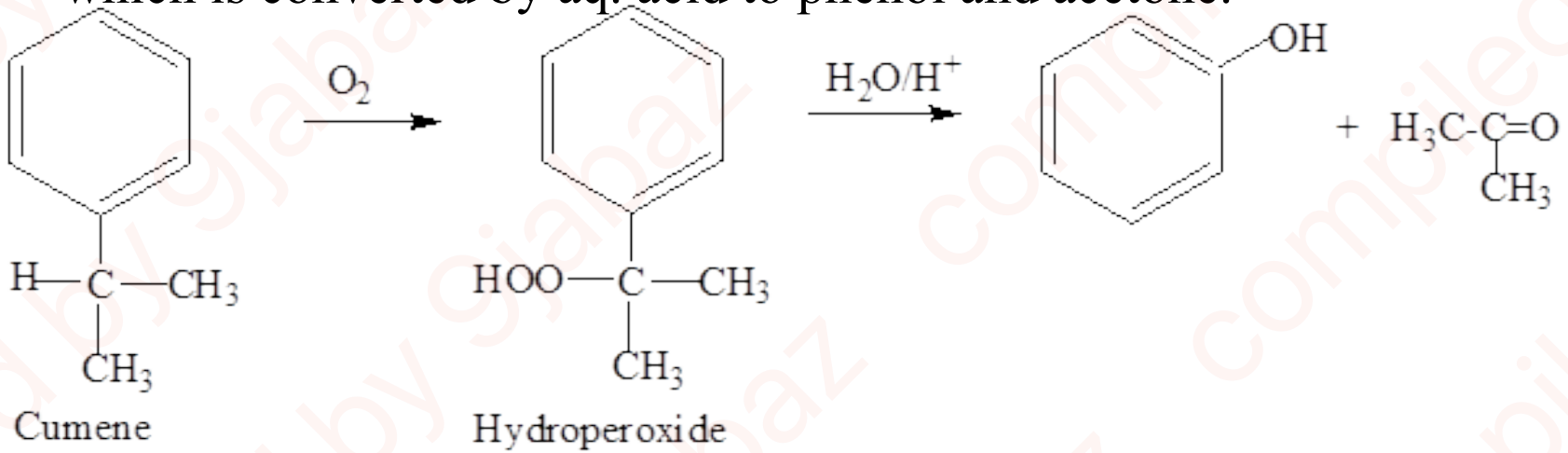
Phenols

- Most phenols are made industrially by the same methods that are used in the laboratory. However, there are several ways of obtaining certain of these compounds on a commercial scale.

- DOW Process: This is a process whereby chlorobenzene is allowed to react with aq. NaOH at about 350 ^{o}C.

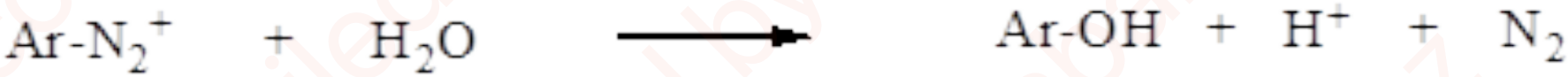


- Most phenols are made today by a newer process that starts with isopropyl benzene (cumene).
- Isopropyl benzene is converted by air oxidation to hydroperoxide, which is converted by aq. acid to phenol and acetone.

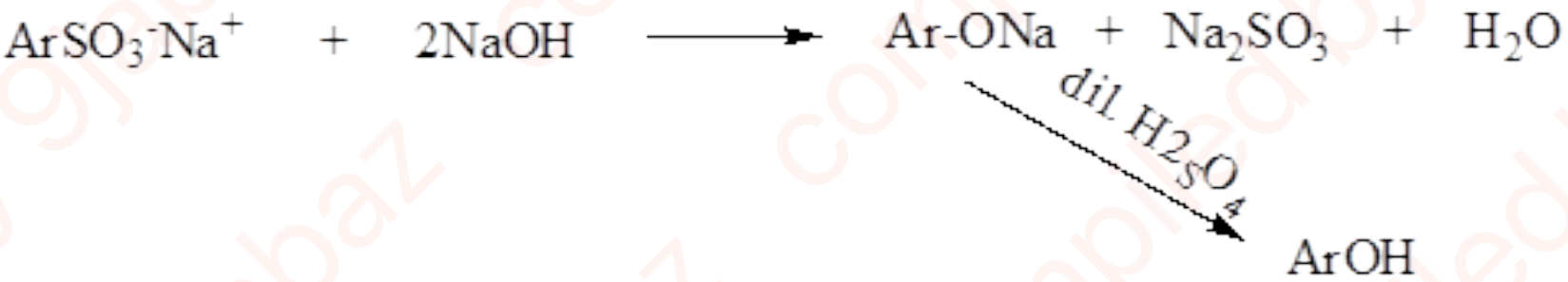


Preparation of Phenols

- 1. ***Hydrolysis of diazonium salt.***



2. Phenol may be obtained by fusion of sodium aryl sulphonate

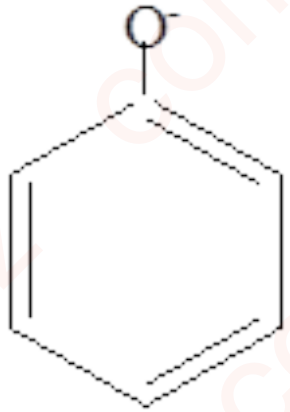


3. Reaction of diazonium sulphate solution: When the diazonium sulphate solution is steam distilled phenol as produced.

Reactivity of Phenols

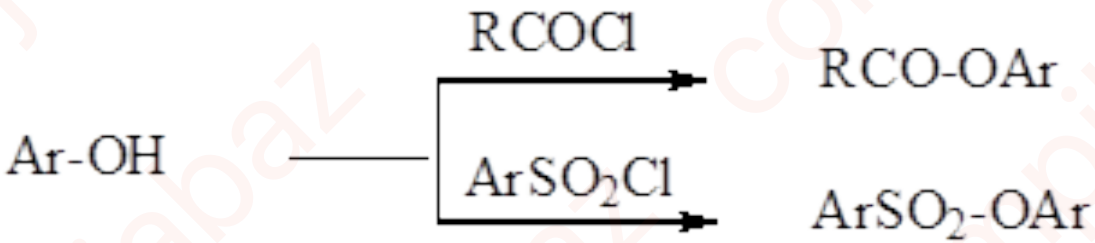
Asides from acidity, phenol has extremely high reactivity of its ring towards electrophilic substitution.

- Even in ring substitution, acidity plays an important role. Ionization of phenols gives O^- group as in

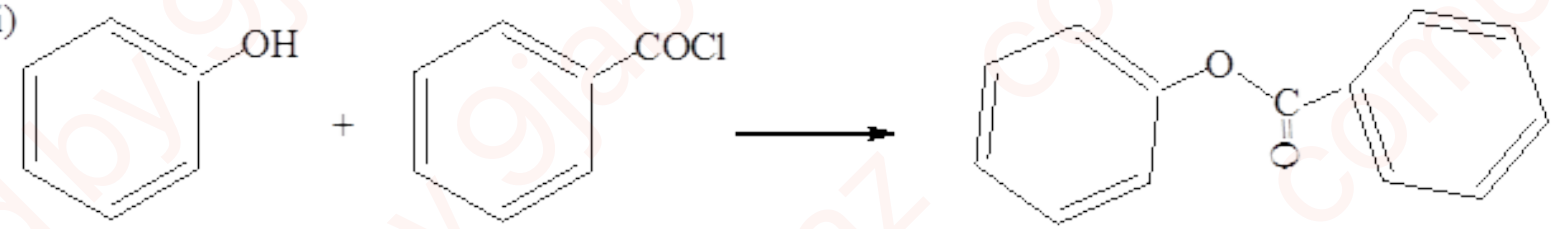


- and because of the full-fledged negative charge, it is even more strongly electron releasing than the OH group
- ***1. Acidity, Salt Formation***

- Since it behaves like an acid, it can form esters
- ***- Ester Formation***



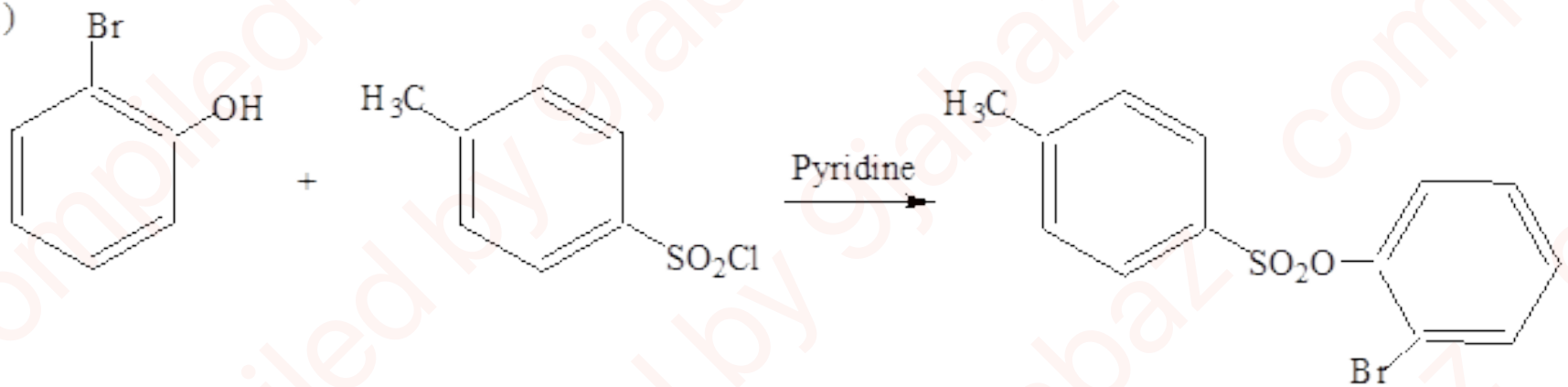
(i)



Benzoylchloride

Phenylbenzoate

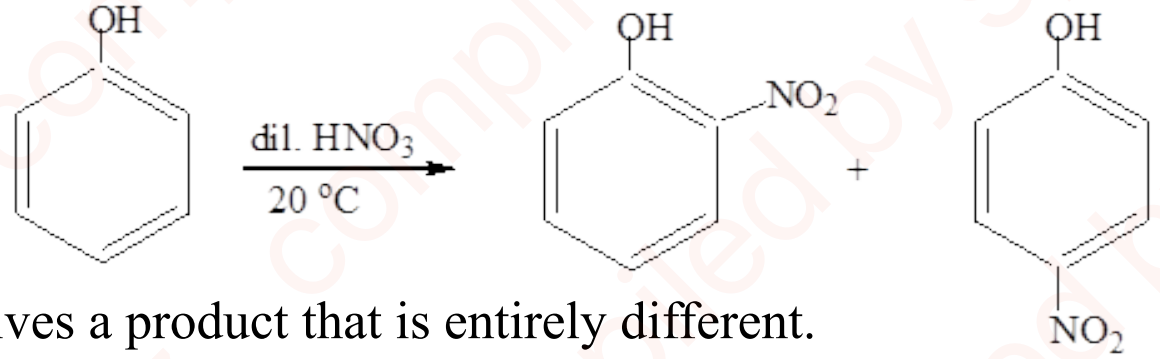
(ii)



Bromophenyl-p-toluene sulphonate

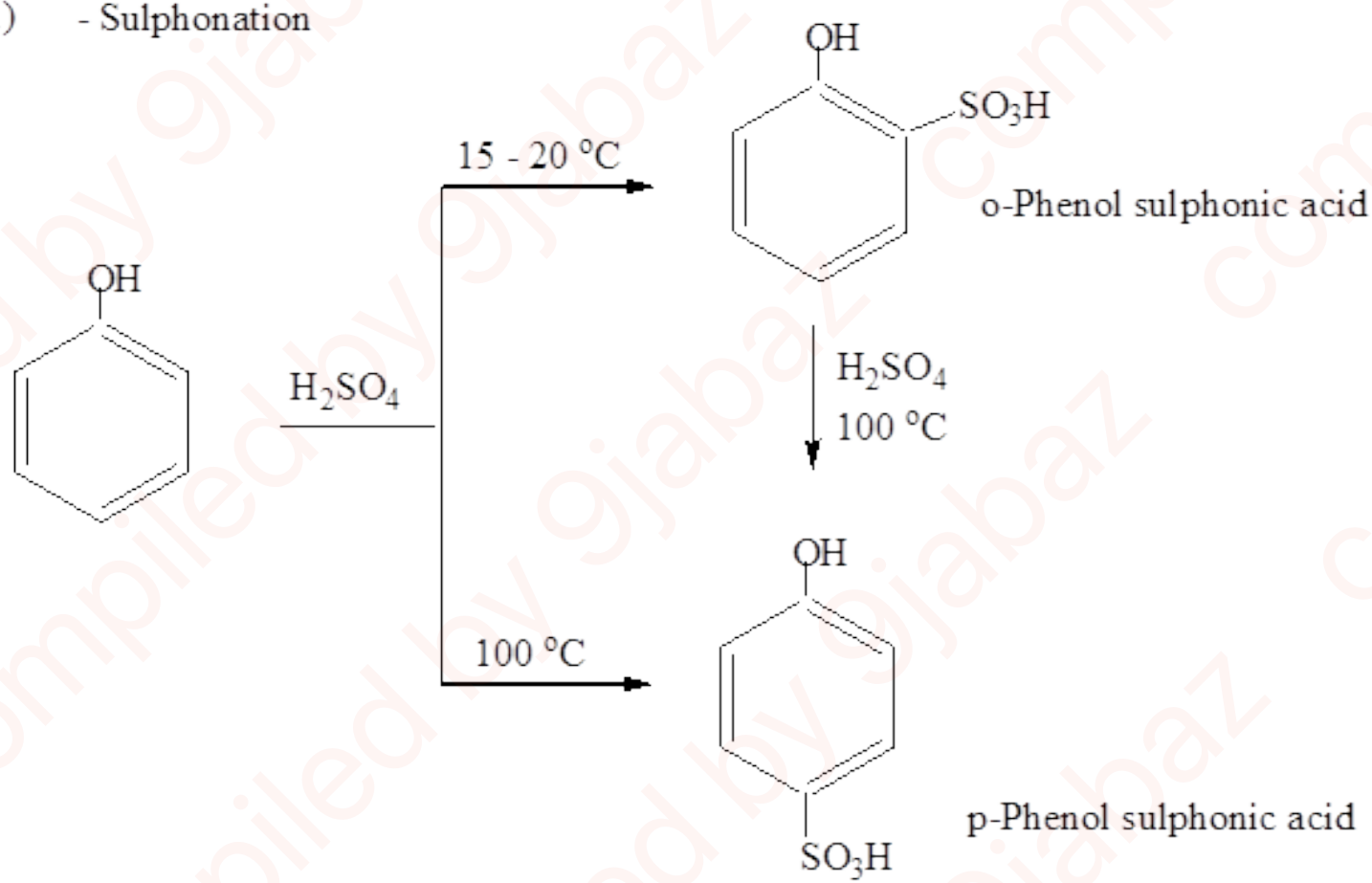
2. Ring Substitution

(i) - Nitration

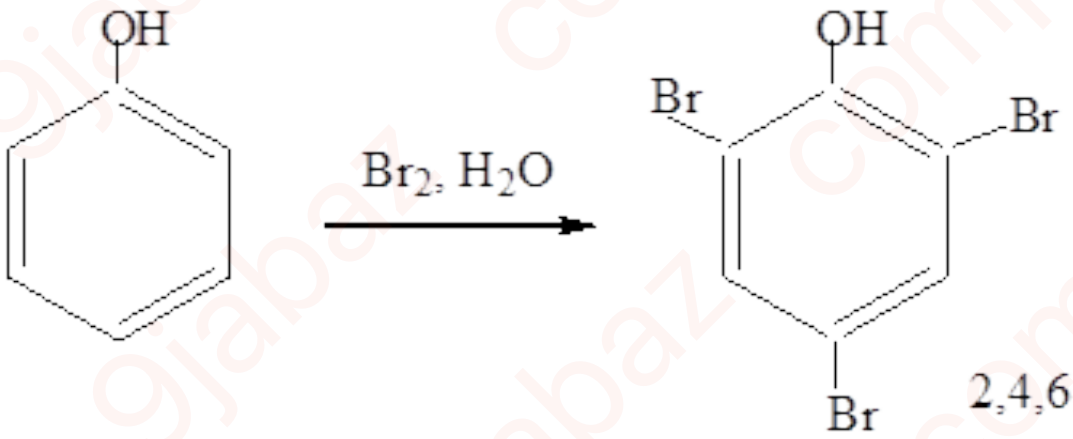


Changing the temperature gives a product that is entirely different.

(ii) - Sulphonation

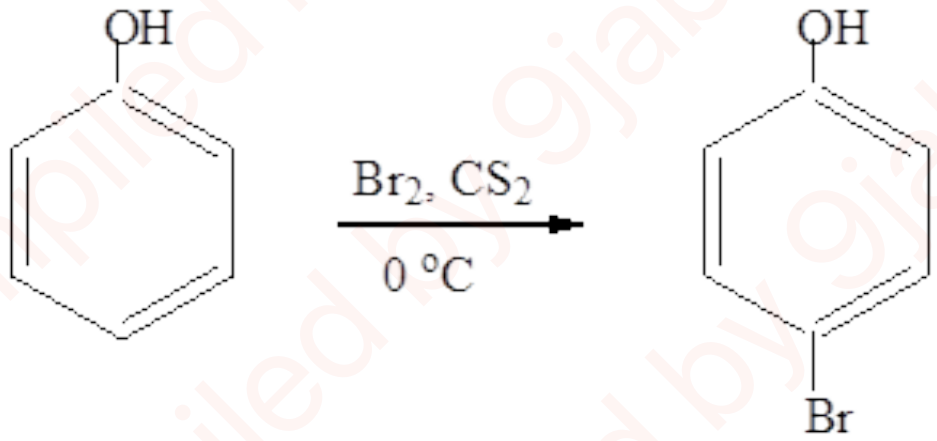


(iii) Halogenation



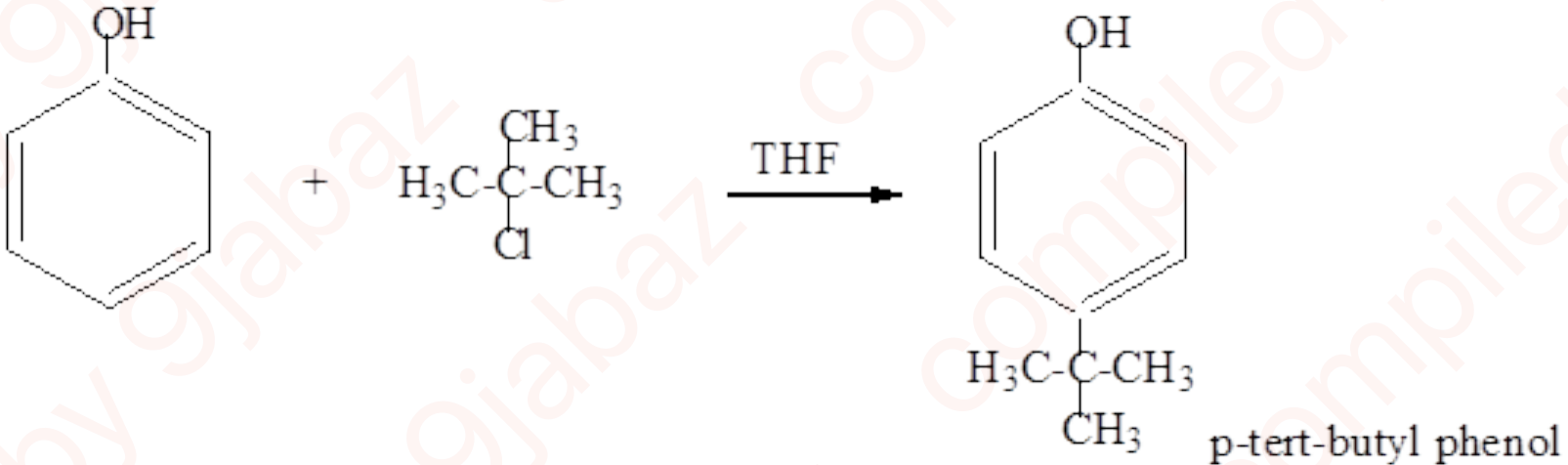
2,4,6-Tribromophenol

Similar reaction at 0 °C only gives a monosubstituted product



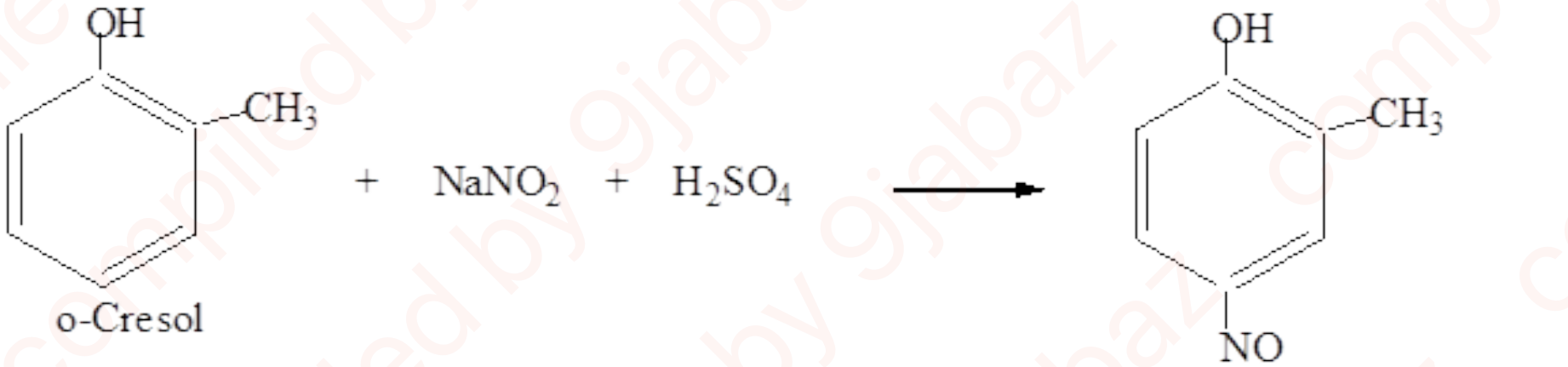
(iv) Friedel-Crafts Alkylation

- Reaction of phenol with 3º butyl chloride



p-tert-butyl phenol

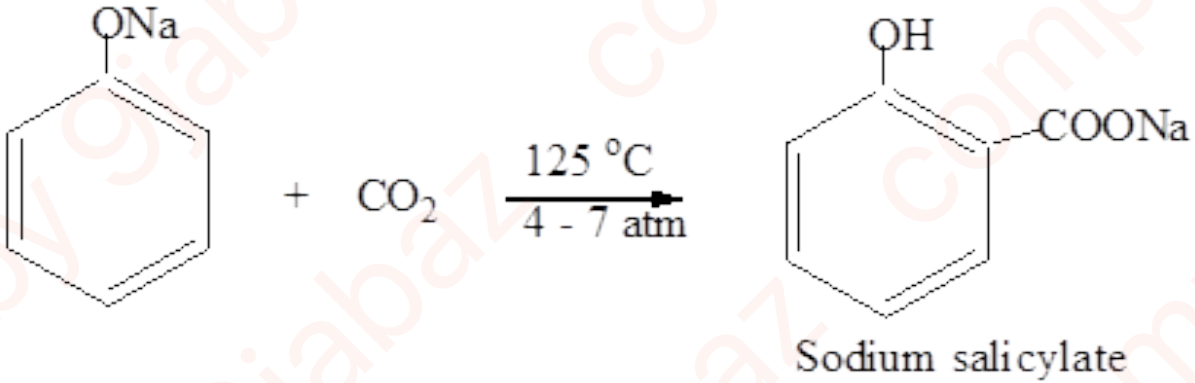
- (v) Nitrosation



o-Cresol

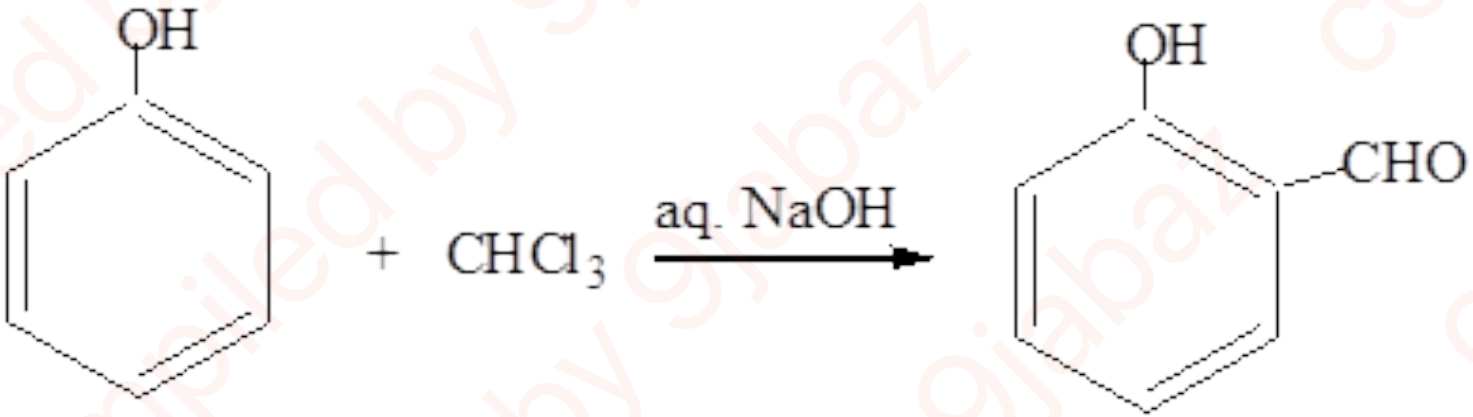
2-methyl-4-nitrosophenol

(vi) Kolbe Reaction



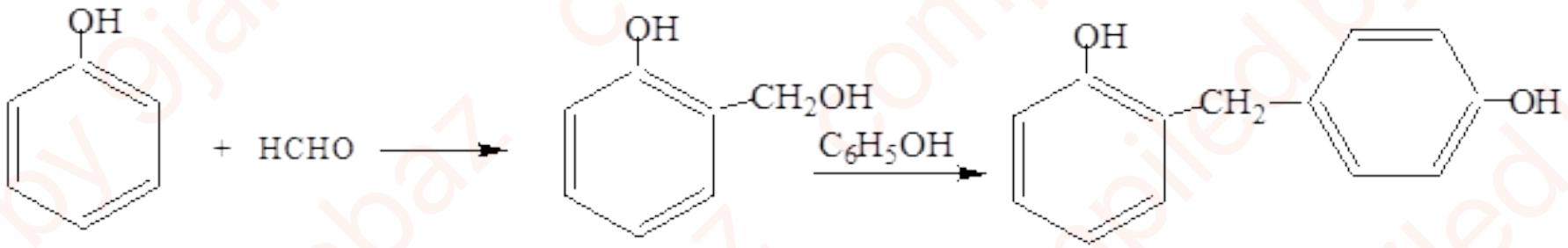
Sodium salicylate

vii) Aldehyde Formation



Salicylaldehyde

- (viii) Reaction with Formaldehyde



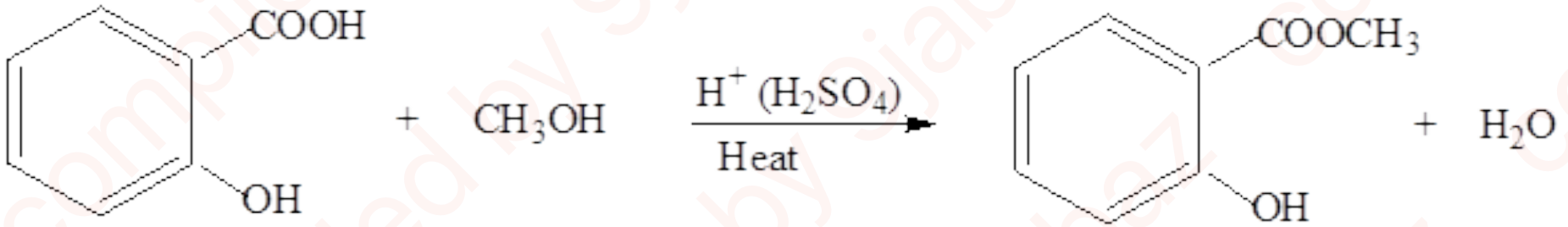
• Salicy Compounds

- They are bi-functional benzene derivatives

1. ***Methyl salicylate:*** The melting point is 224 ^{o}C. It is the principal constituent of oil of wintergreen and oil of sweet birch. It is colourless, pleasant smelling liquid.

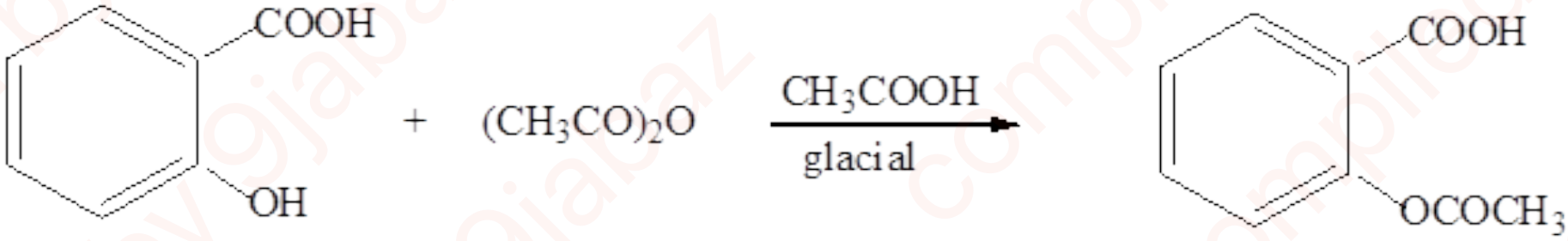
- It may be prepared by direct esterification. It is used in perfumery and as flavoring material It is used in healing aches and bruises

- It is prepared from salicylic acid.



*2. **Acetyl salicylic acid:***

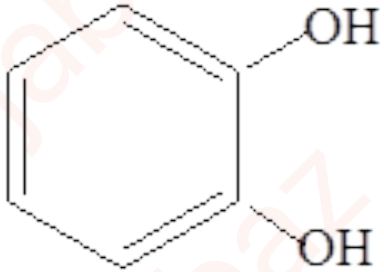
The melting point is 135 ºC and it may be prepared by acetylating salicylic acid by a mixture of acetic anhydride and glacial acetic acid.



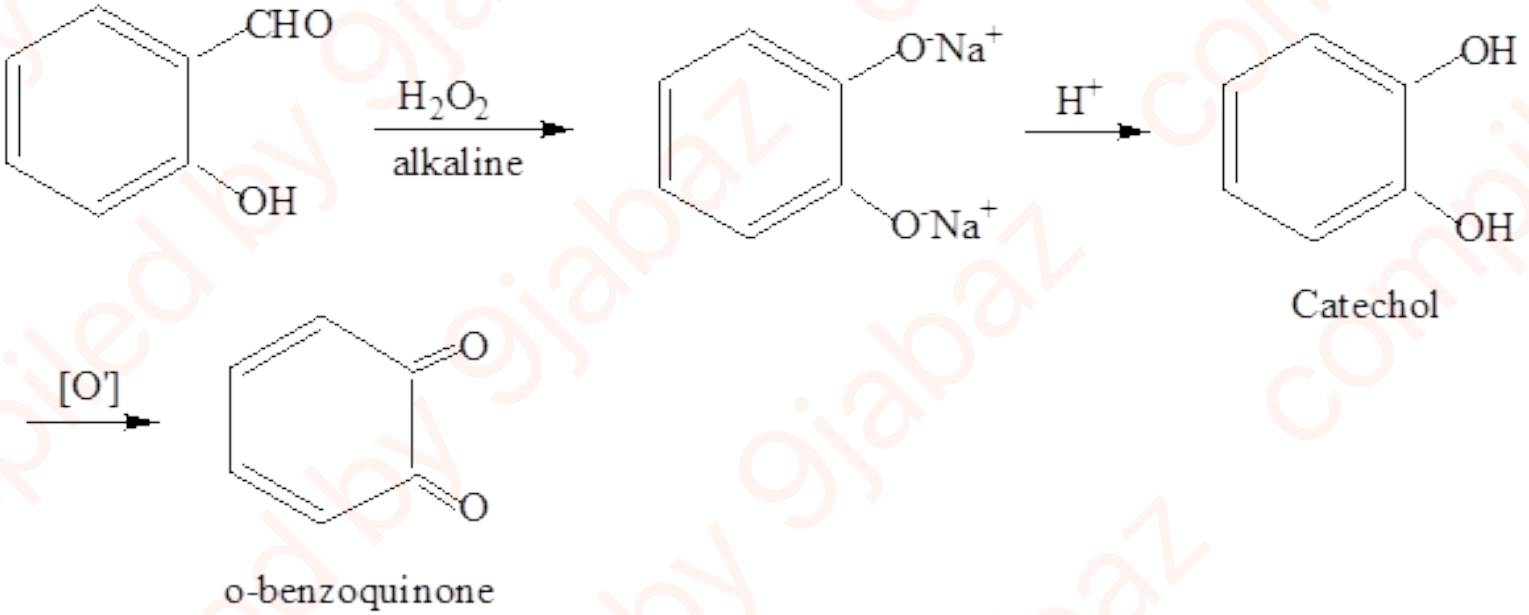
3. Dihydric Phenols

They are aromatic compounds with two hydroxy groups. These include catechol, resorcinol and quinol.

Catechol

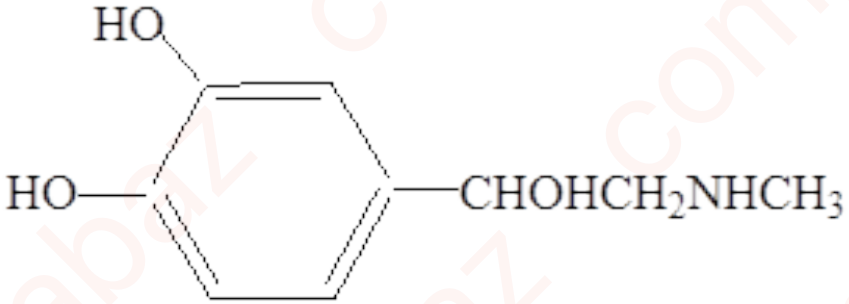


It is obtained by the oxidation of salicyaldehyde with alkaline hydrogen peroxide.



The oxidation of catechol gives a product called, o-benzoquinone

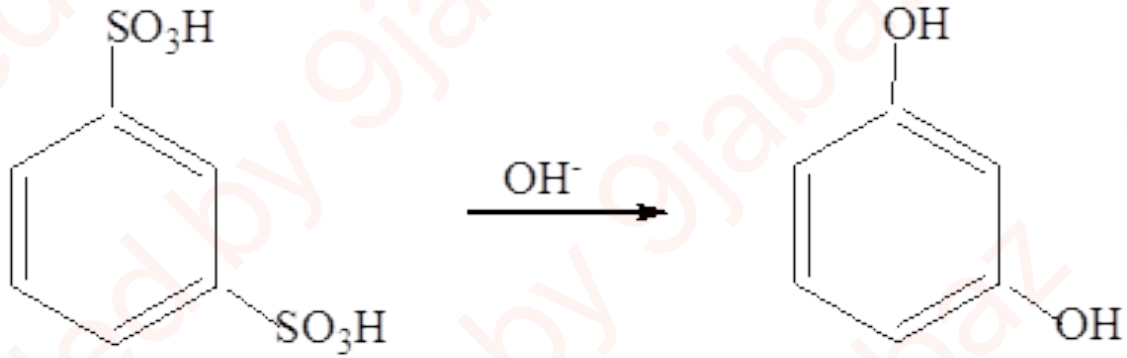
- An important derivative of catechol is adrenaline which is an harm one secreted by adrenal gland.



Adrenaline

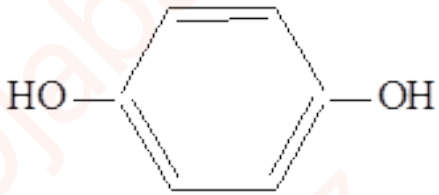
Resorcinol

- The melting point is 110 ^{o}C. It can be prepared industrially from benzene -1,3- disulphonic acid.



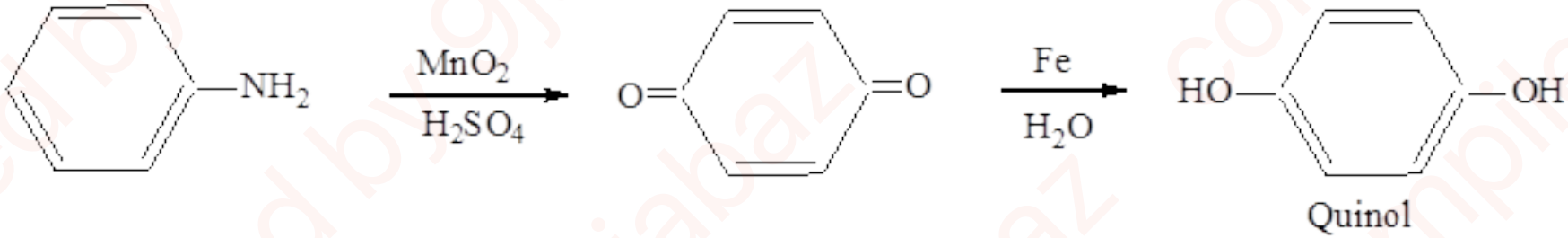
Resorcinol

Quinol



Quinol

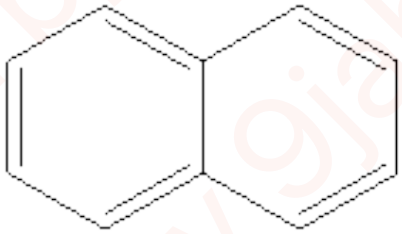
- It has a melting point of 170 ^{o}C and can be prepared industrially from aniline.



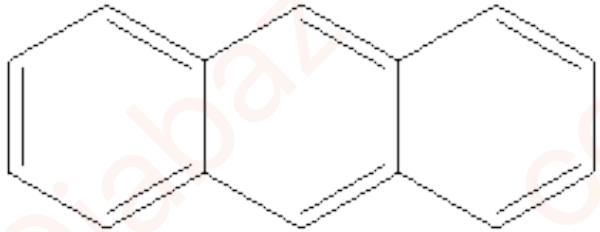
Quinol

- Quinol is a powerful reducing agent and it is used as a photographic developer. It is easily oxidized to para-benzoquinone.

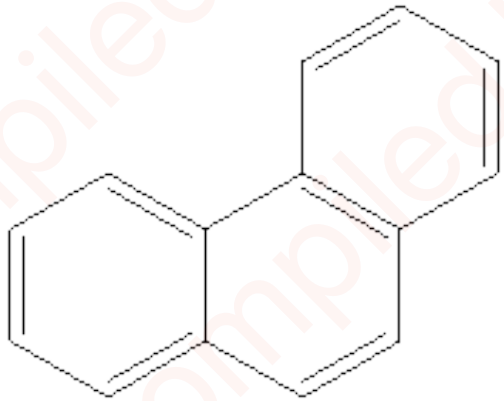
Fused Polynuclear Aromatic Hydrocarbons



Naphthalene



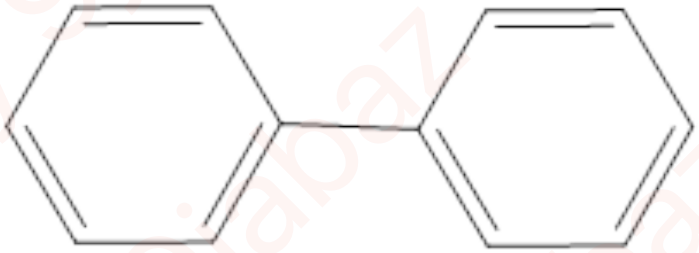
Anthracene



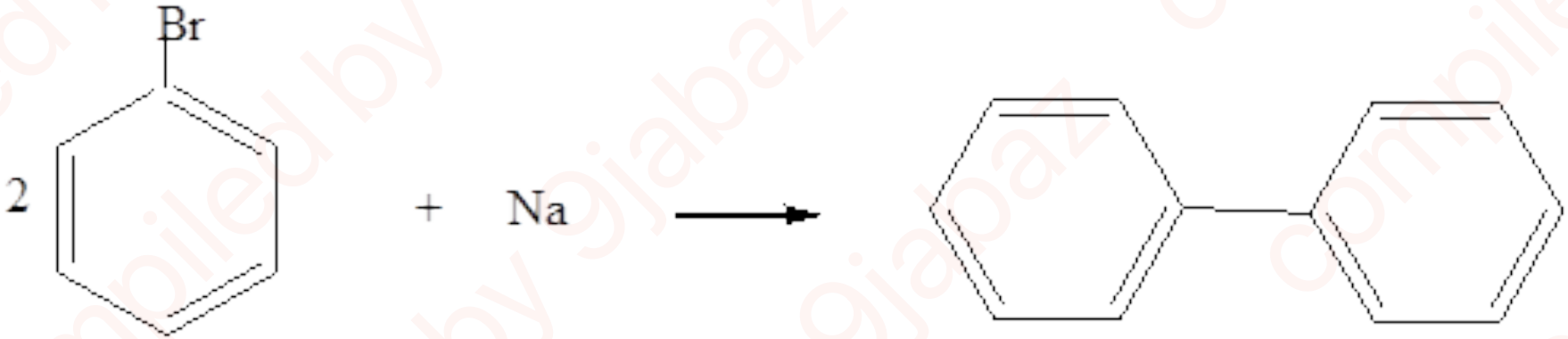
Phenanthrene

Isolated Polynuclear Aromatic Hydrocarbons

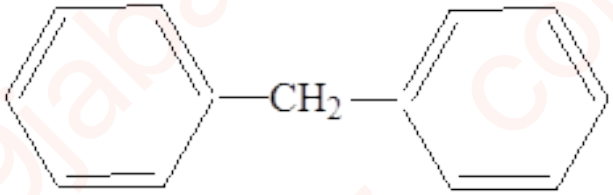
1. Biphenyl



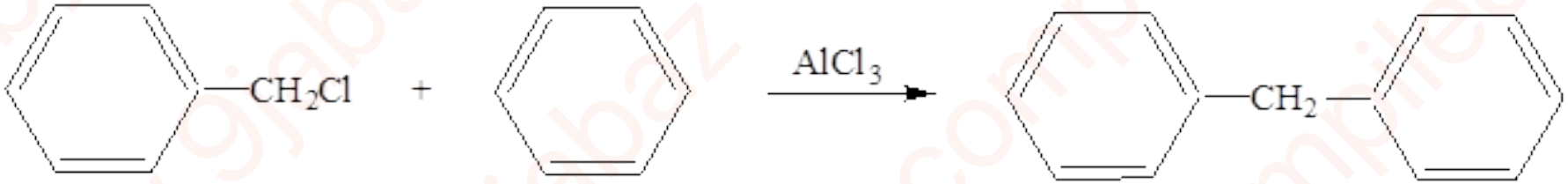
- Preparation



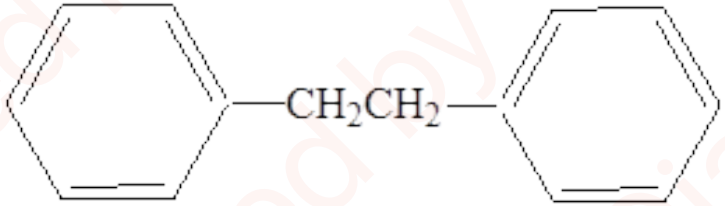
2. Diphenylmethane



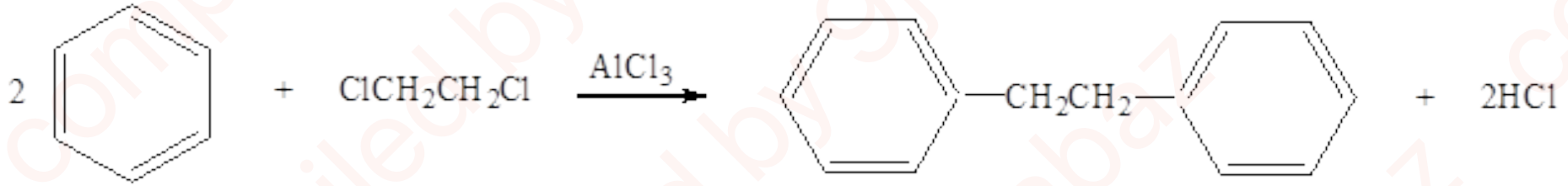
- Preparation



3. Bibenzyl



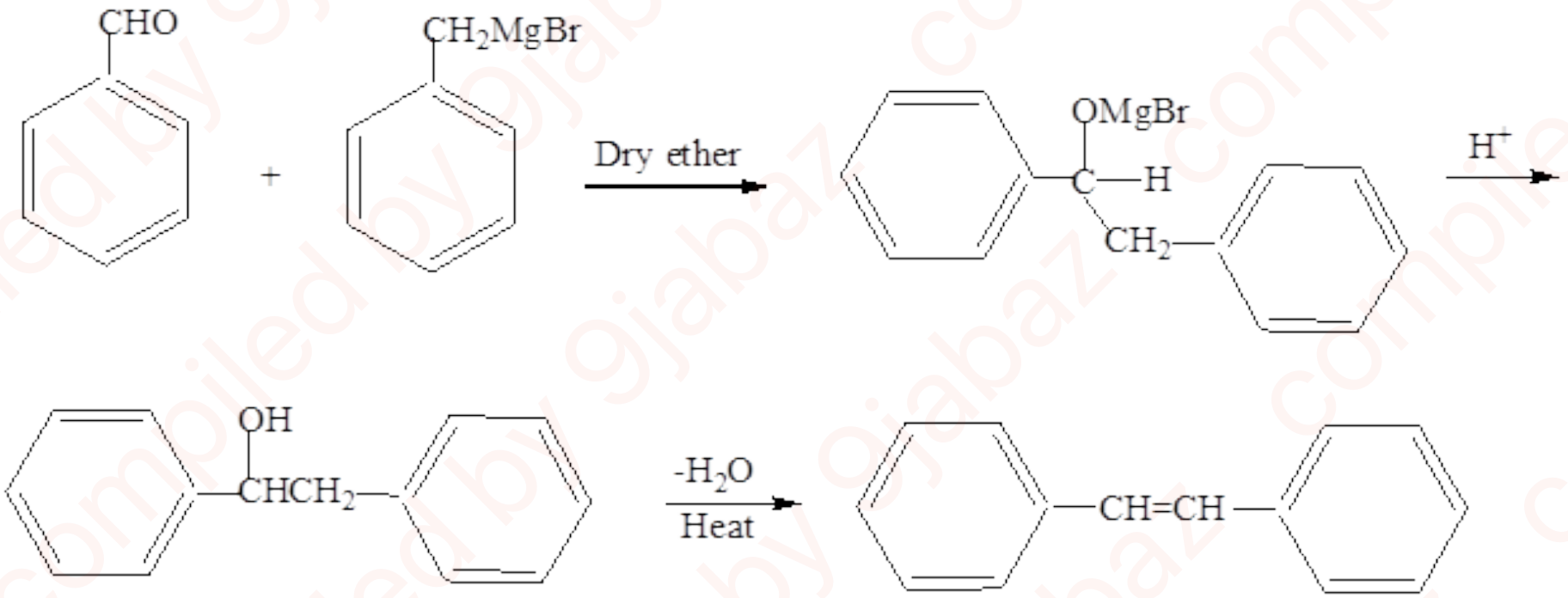
- Preparation



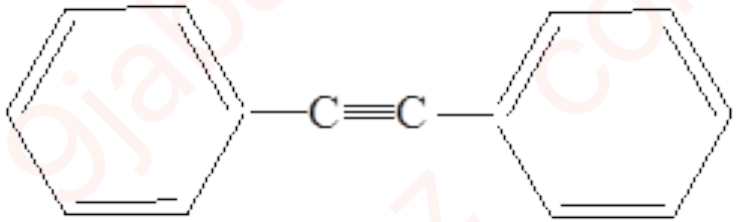
4. Trans-stilbene

Preparation

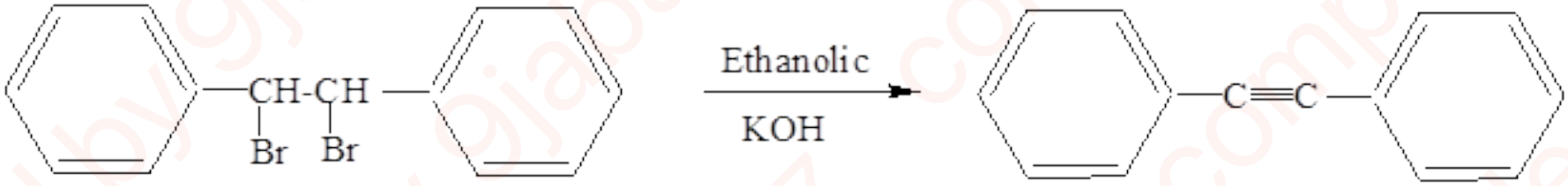
- It is stable and has a melting point of 154 ºC while the cis-isomer is unstable with a melting point of 145 ºC.
- It can be prepared using Grignard reagent and benzaldehyde.



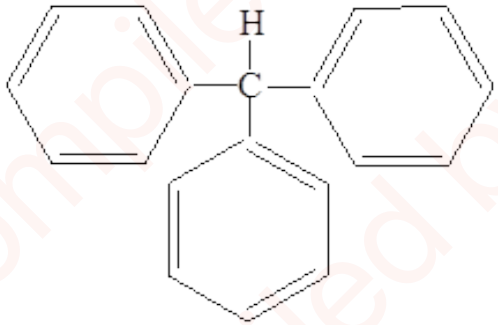
5. Diphenylacetylene



Preparation

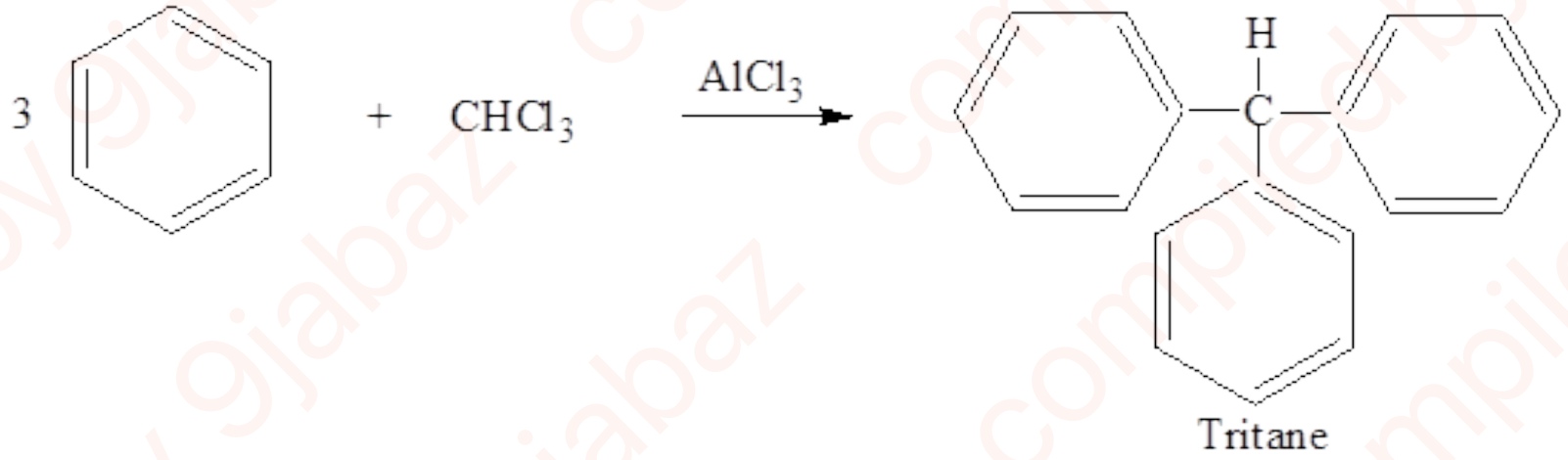


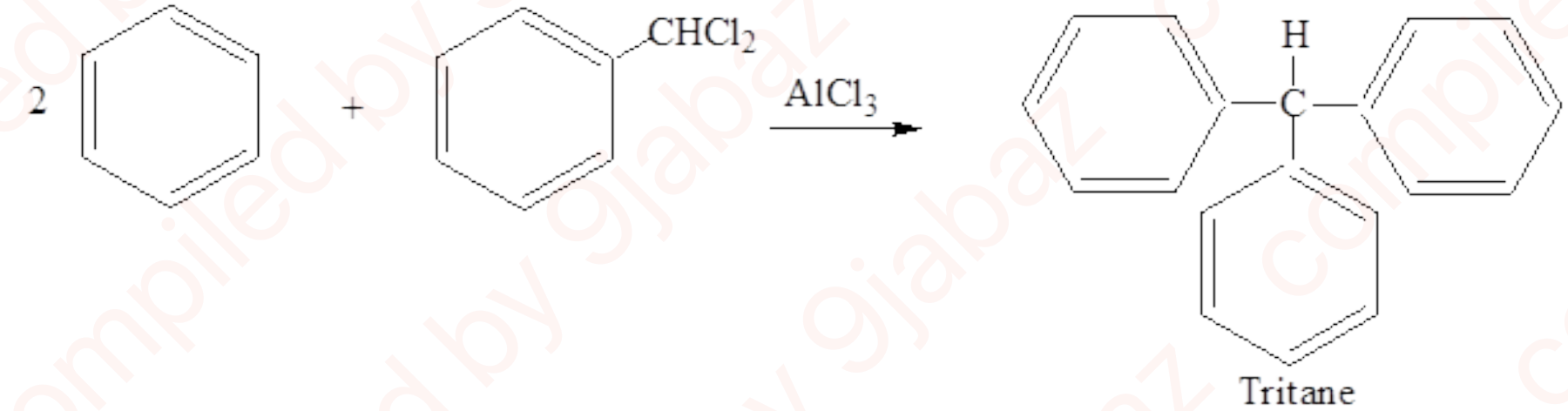
5. Triphenylmethane



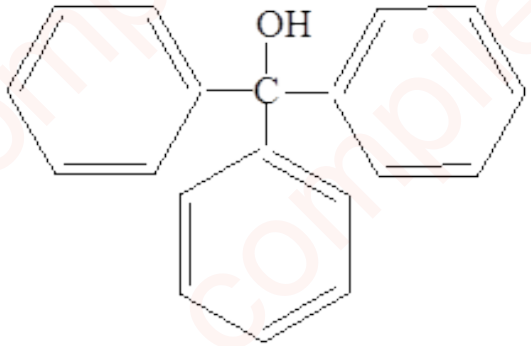
Tritane

- Preparation





7. Triphenyl carbinol

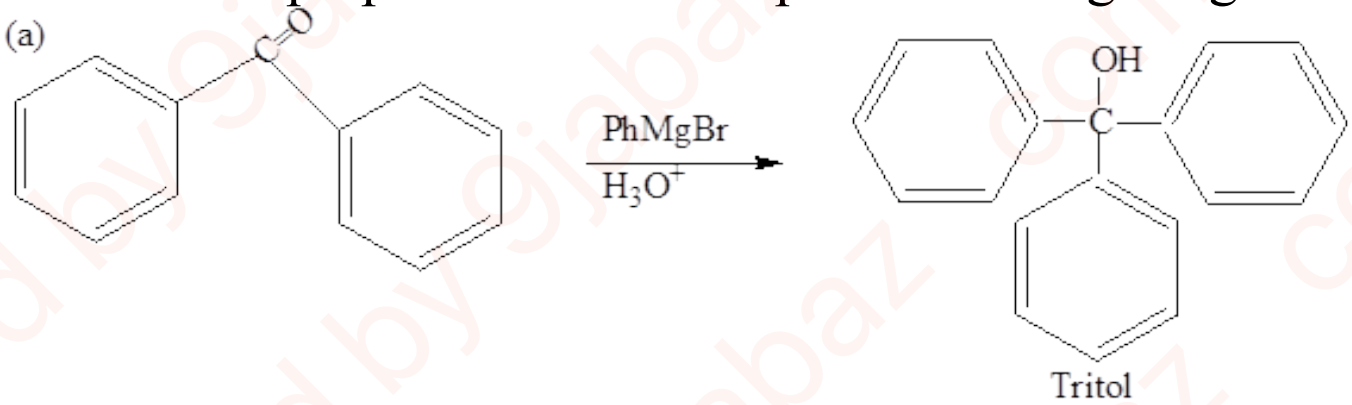


Tritol

Preparation

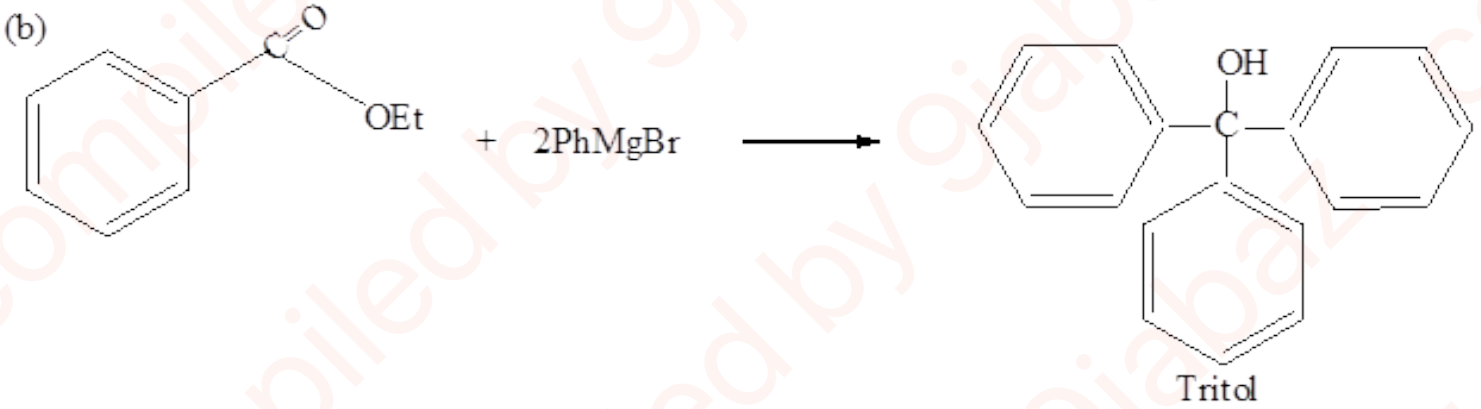
- It can be prepared from benzophenone using Grignard reagent

(a)



Tritol

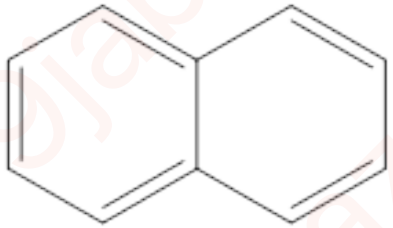
(b)



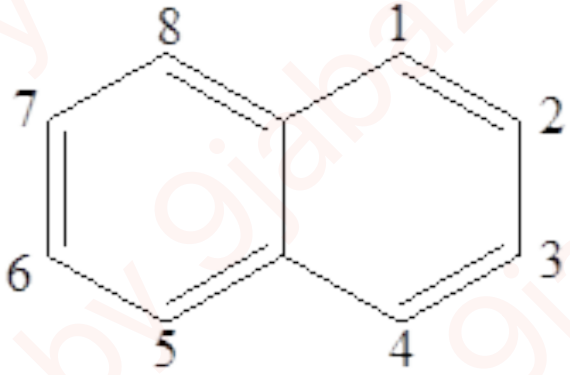
Tritol

Fused Polynuclear Aromatic Hydrocarbons (Condensed)

1. Naphthalene



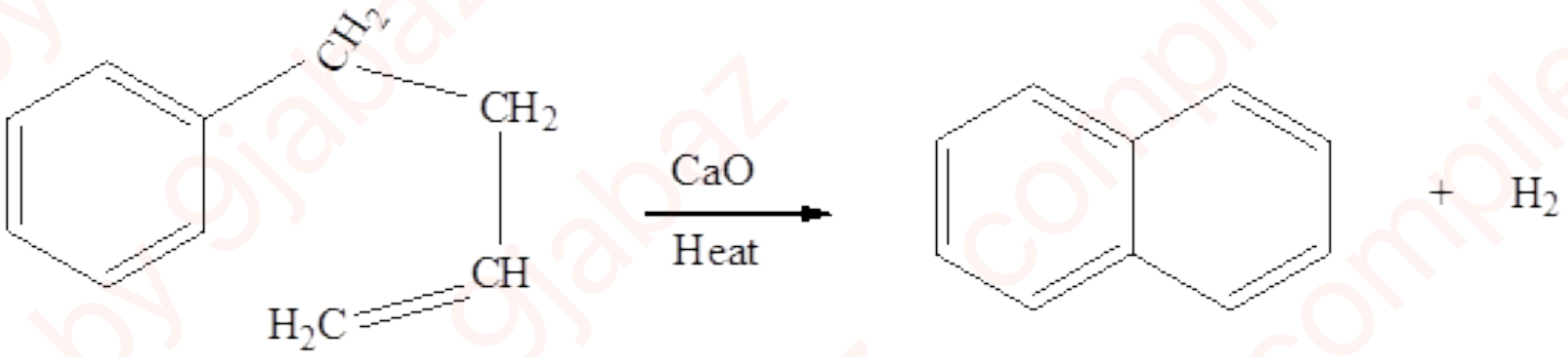
- Generally, there are n+1 principal resonating structure for the polynuclear hydrocarbons containing n benzene rings fused together in a linear manner.
- They are obtained by taking the average of the 3 resonating structures and the assuming that the 3 contribute equally to the resonance hybrid.



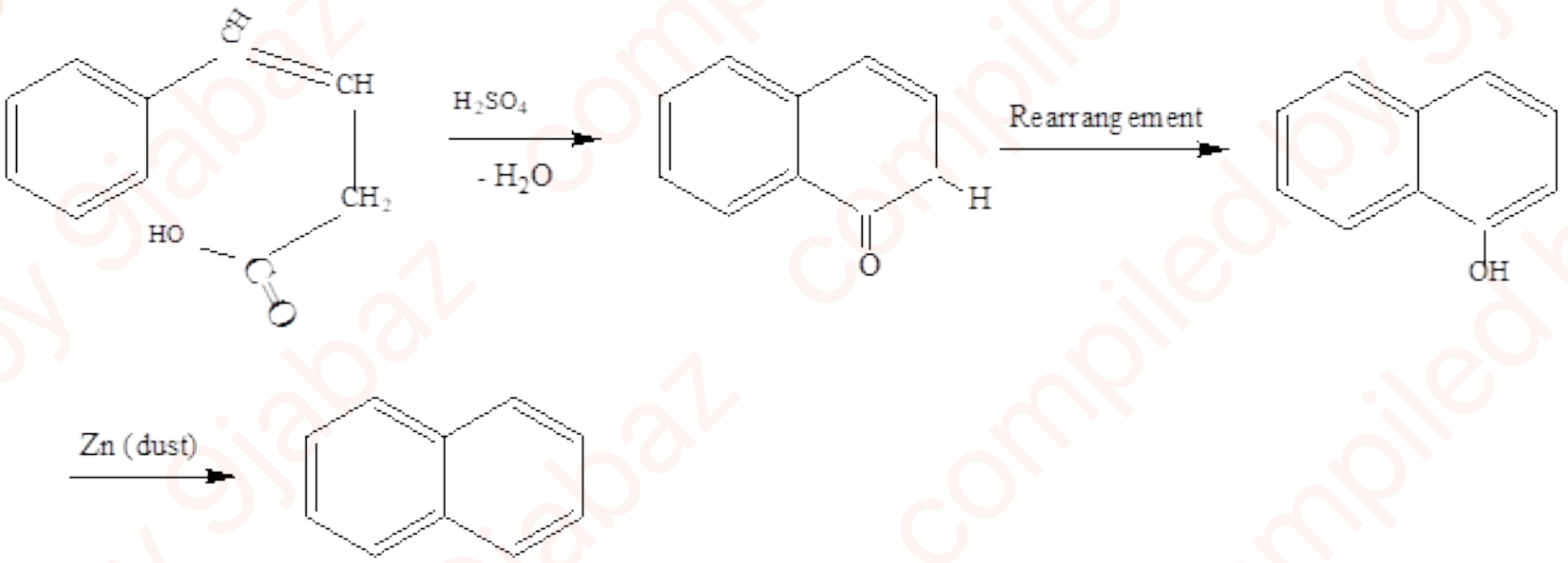
- Positions 1,4,5,& 8 are called alpha
- Positions 2,3,6 & 7 are called beta

Preparation of Naphthalene

1. When 4-phenyl-1-butene is passed over red hot calcium oxide naphthalene is produced.

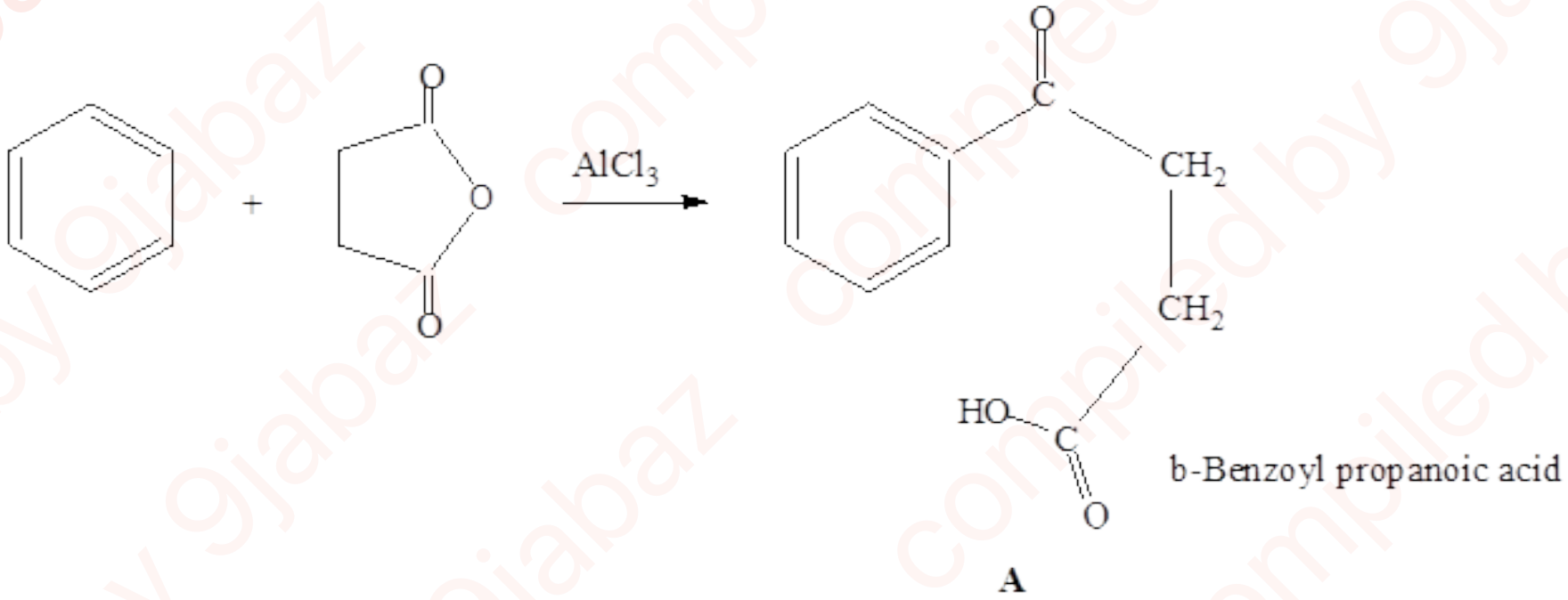


2. From: 4-phenyl-3- butenoic acid: when 4-phenyl -3- butanoic acid heated with conc. sulfuric acid, 1-naphthol is produced. 1-Naphthol on distillation with zinc dust gives naphthalene.



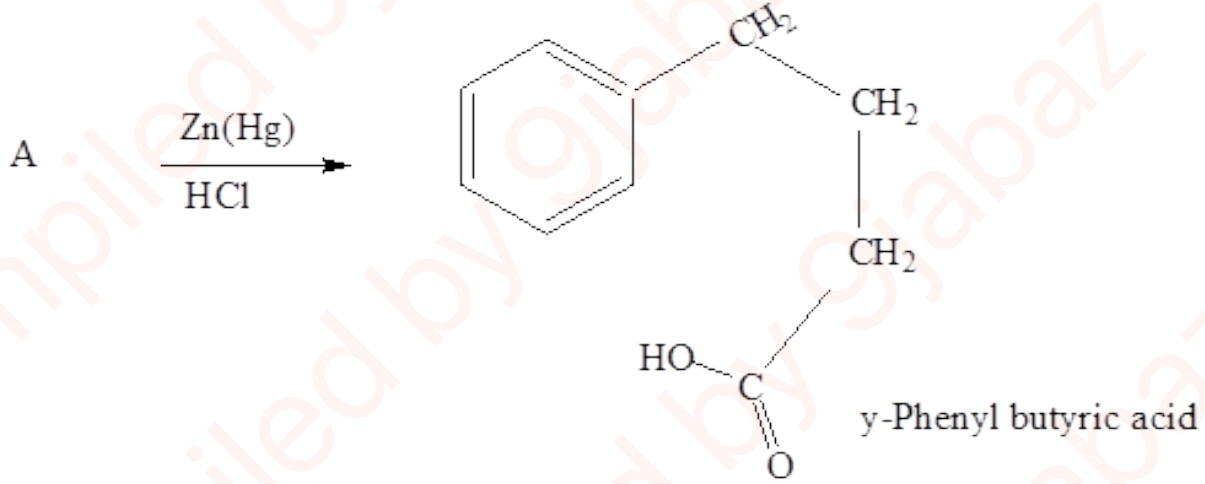
3. By Harworth synthesis: Synthesis of naphthalene by Harworth synthesis involves 5-steps.

Step 1. Benzene and succinic anhydride heated in the presence of aluminum chloride to form β-benzoyl propanoic acid.



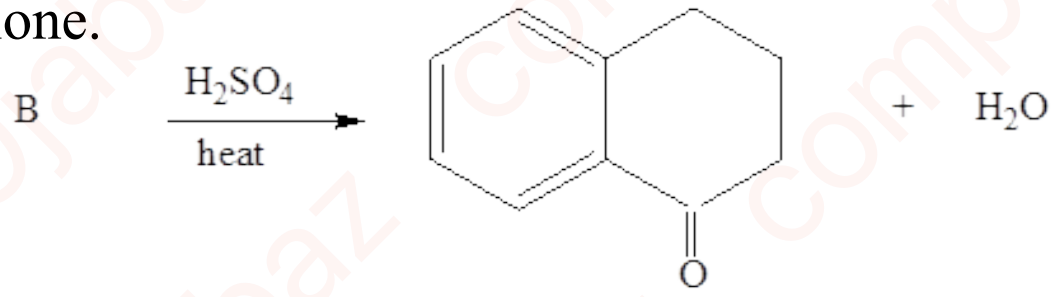
A

Step 2. β-benzoyl propanoic acid is treated with amalgam in the presence of hydrogen chloride to give gamma-phenyl butyric acid.



B

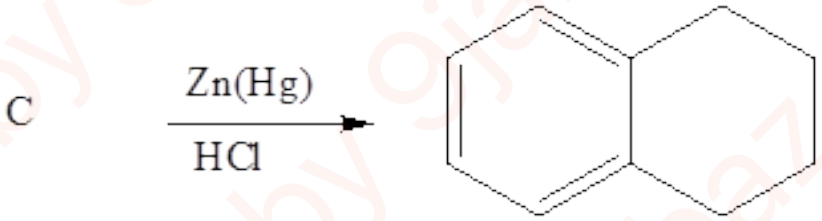
3. gamma-Phenyl butyric acid is heated with sulphuric acid to form α-tetralone.



a-Tetralone

C

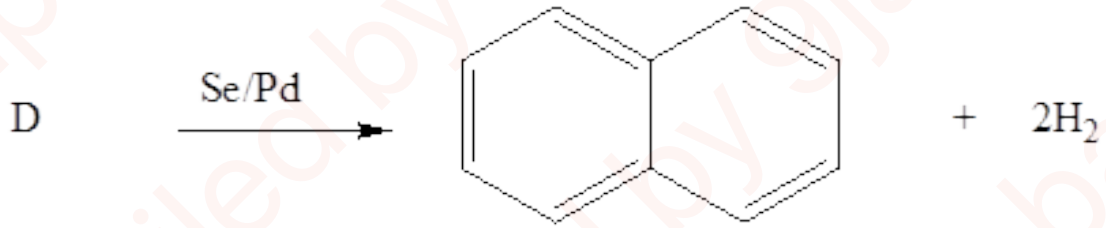
4. α-Tetralone is heated with zinc amalgam with HCl to give tetralin



Tetralin

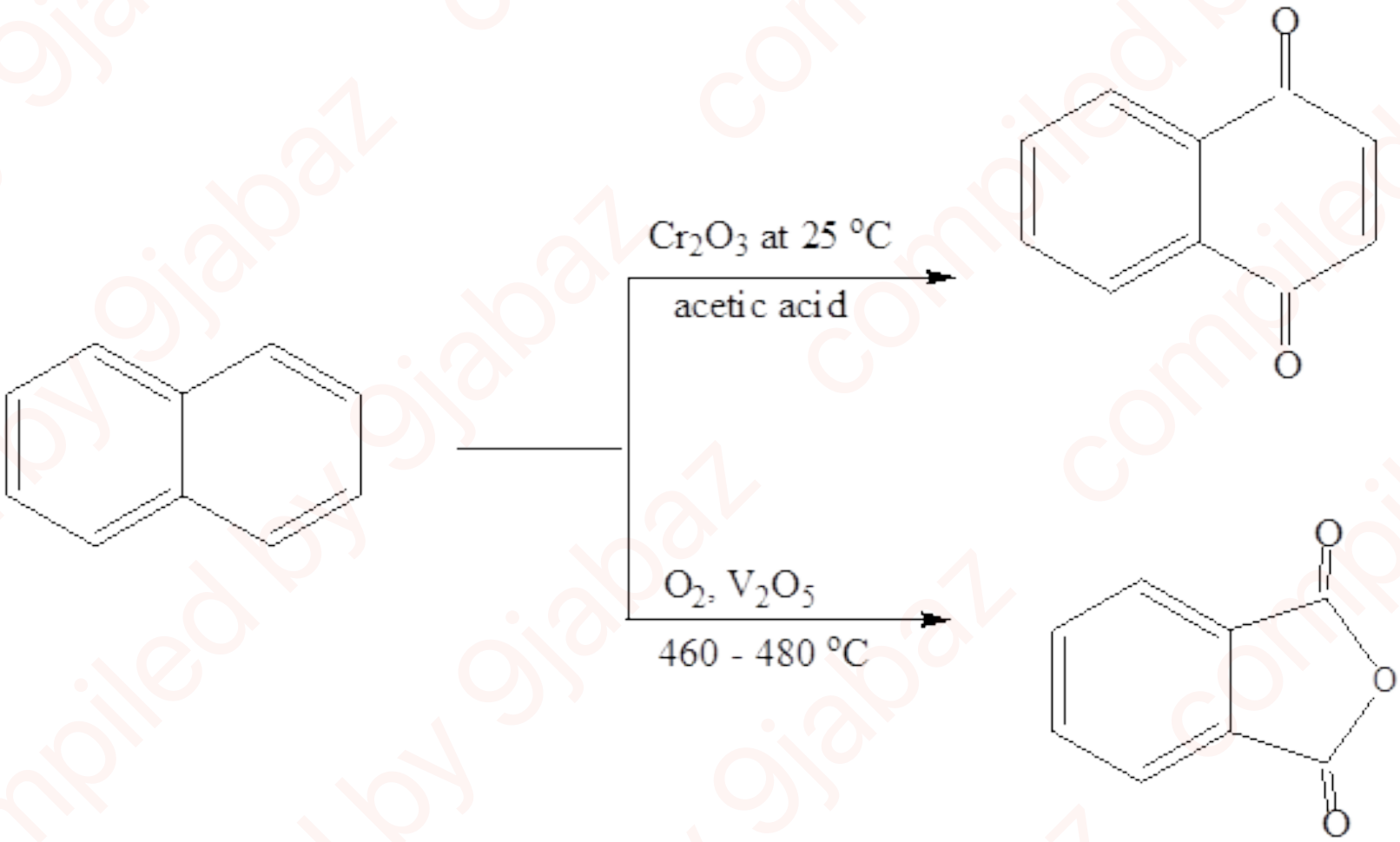
D

5. Tetralin is treated with selenium or palladium it yields naphthalene.

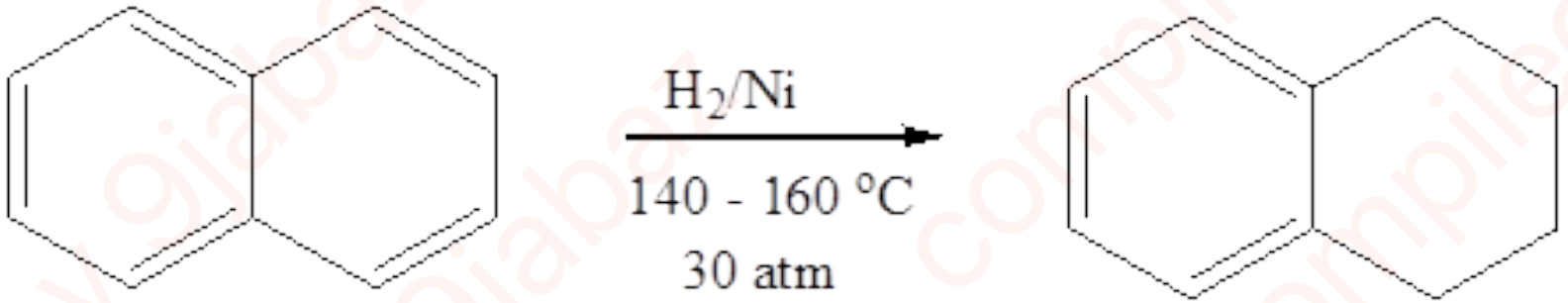


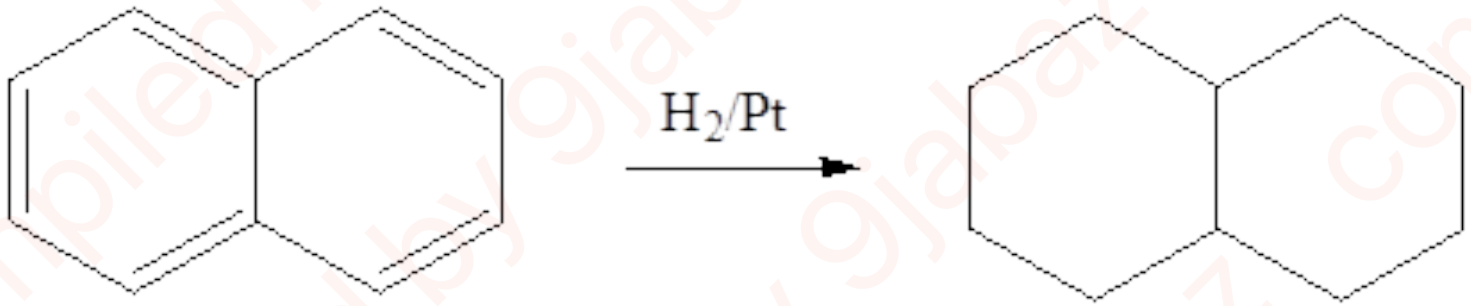
Reactions of Naphthalene

1. Oxidation reaction



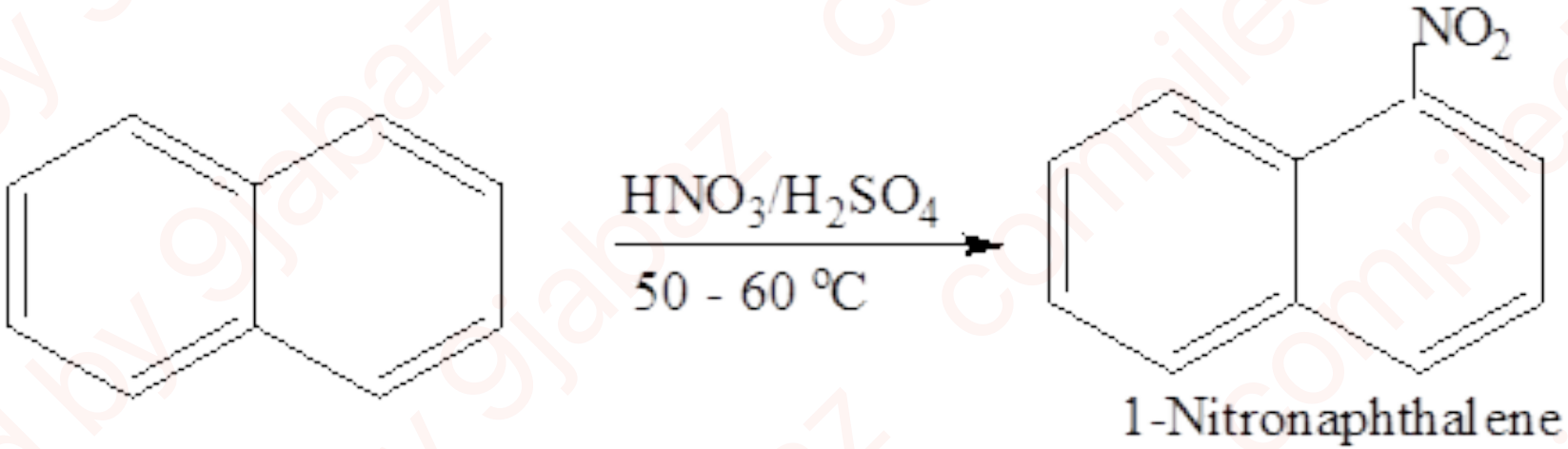
2. Reduction: A number of reduction products of naphthalene can be isolated and the product will depend one type of reducing agent used.



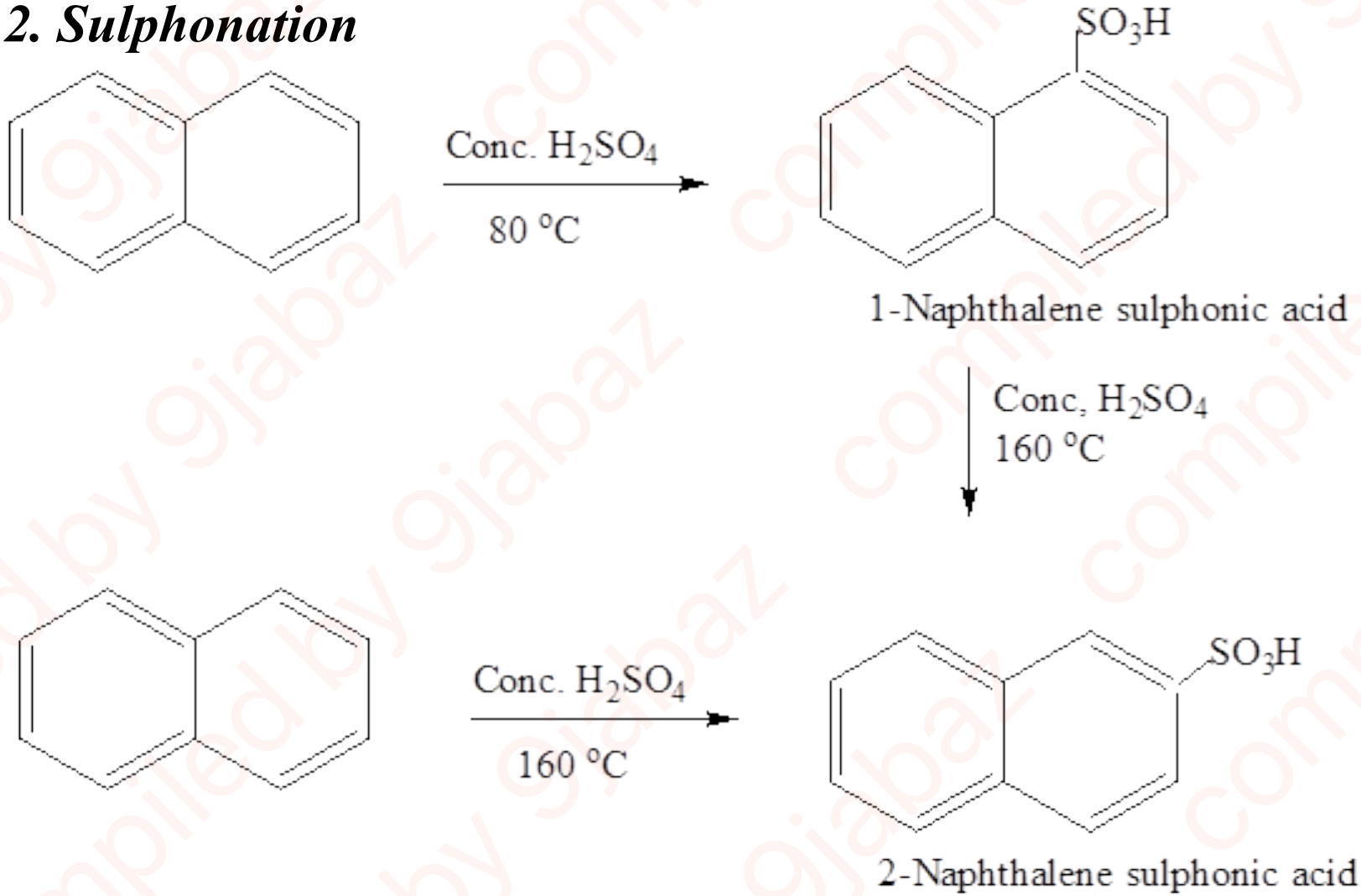


Electrophilic Substitution Reaction of Naphthalene

1. Nitration

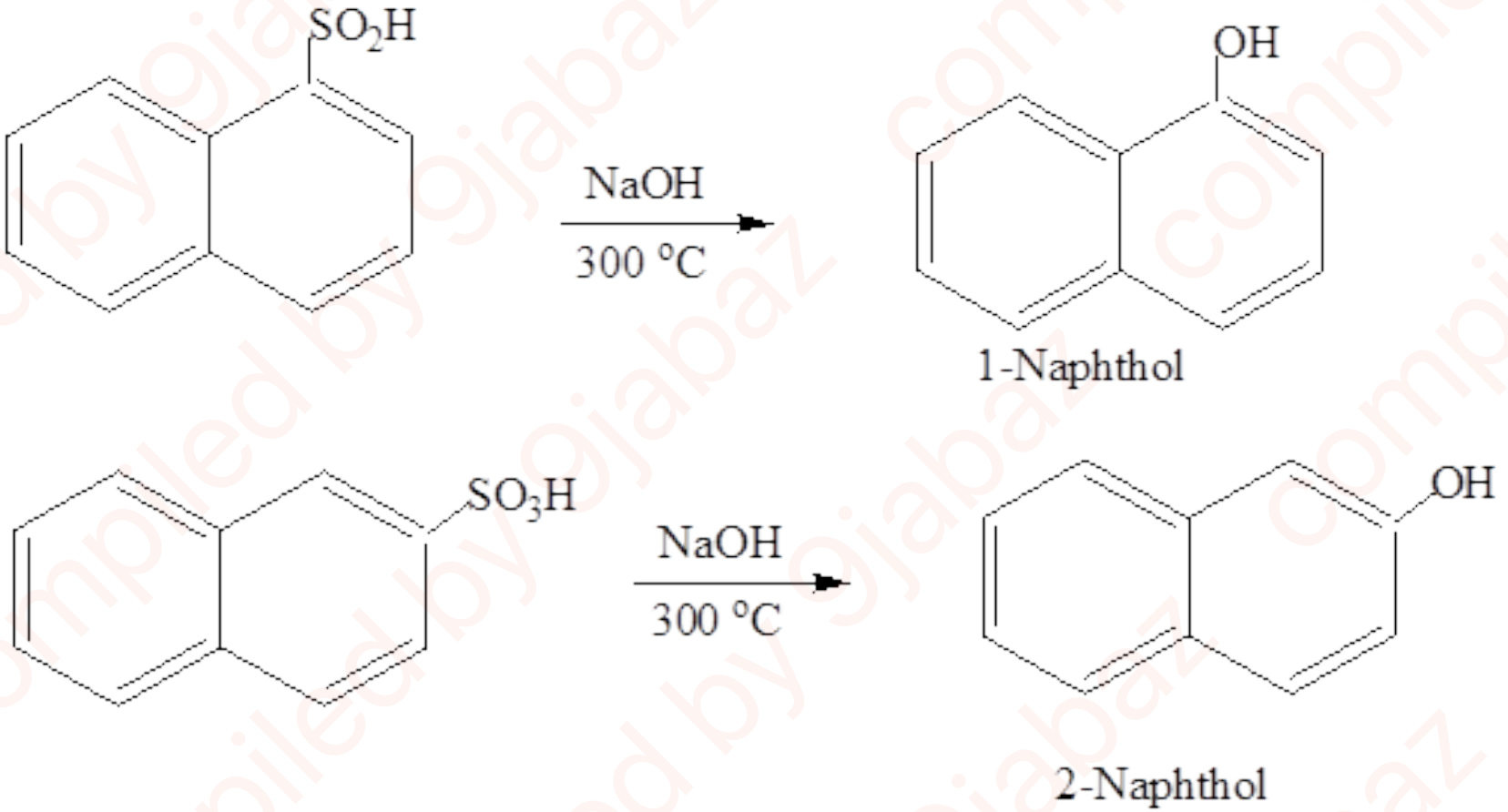


2. Sulphonation

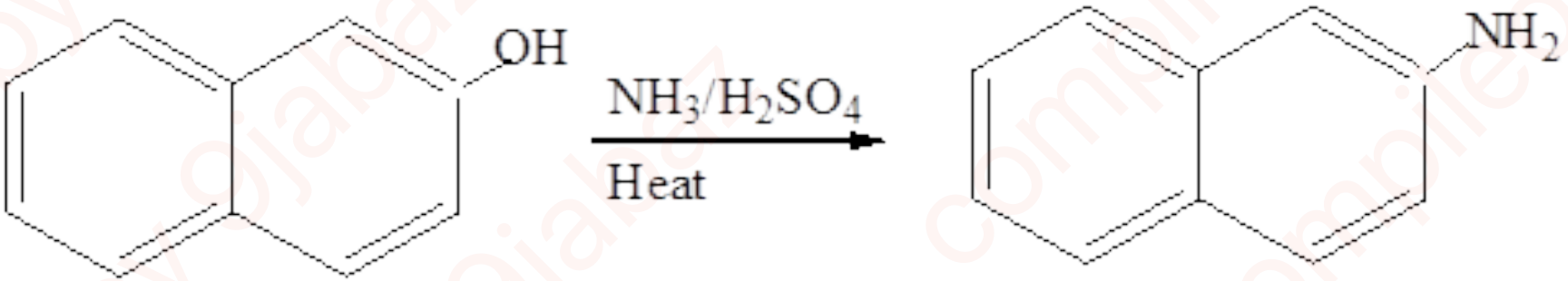


1-Naphthalene sulphonic acid is kinetically controlled product while 2-Naphthalene sulphonic acid is thermodynamically controlled product.

- The thermodynamically controlled product is more stable than the kinetically controlled product because increasing the temperature of the latter with yield the former which shows that it's unstable at high temperature of about 160°C or above
- The reaction both products with NaOH will yield naphthol.

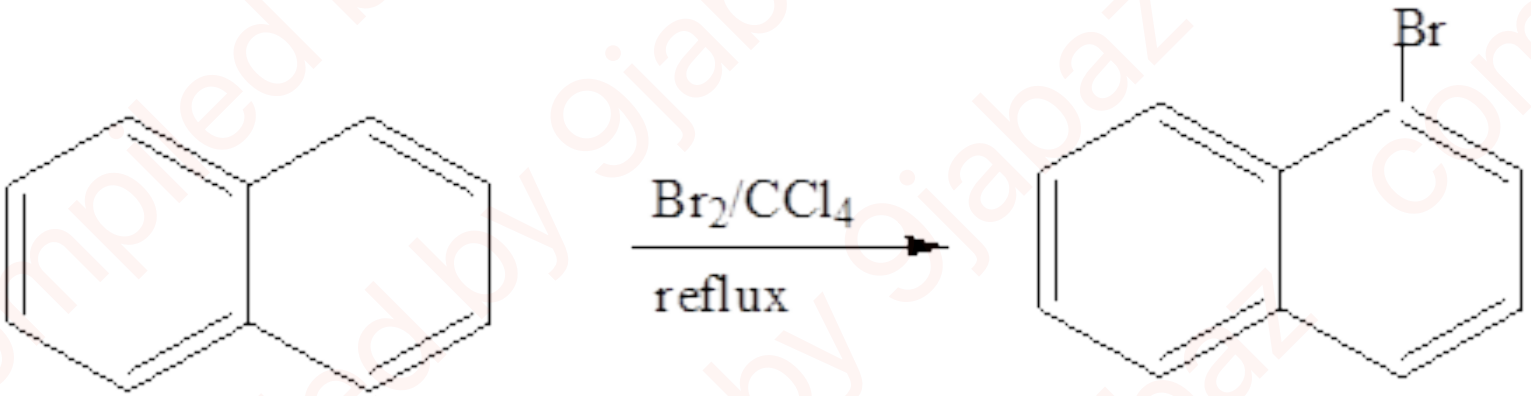


- 2-Naphthol is converted to 2-naphthylamine by heating with aqueous ammonia saturated with sulphur dioxide under pressure.



2-Naphthylamine

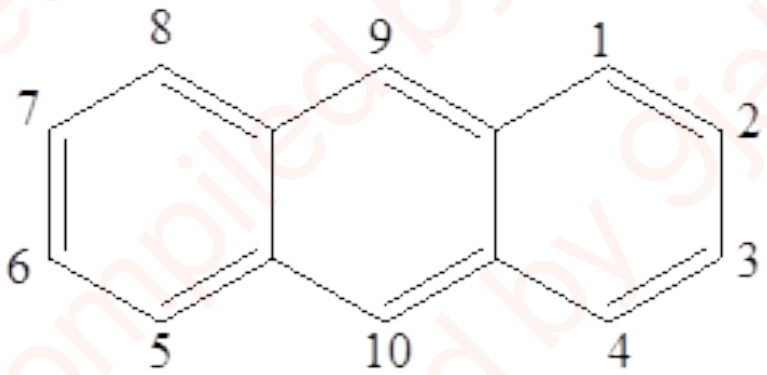
2. Halogenation



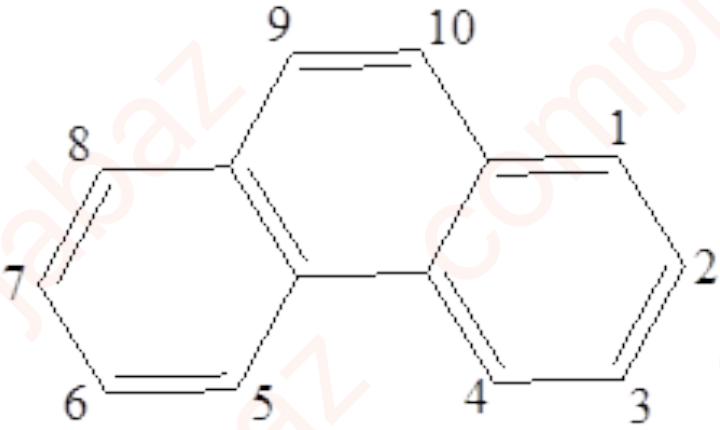
Anthracene and Phenanthrene

- In terms of valency bonds, anthracene is considered to be a resonance hybrid of four resonating structures, while phenanthrene is a resonance hybrid of five resonating structures.

- Heat of combustion indicates that anthracene has resonance energy of 84 $kcalmol^{-1}$ and phenanthrene has 92/$kcalmol^{-1}$. Anthracene & phenanthrene have 2 mono-substituted products.



Anthracene

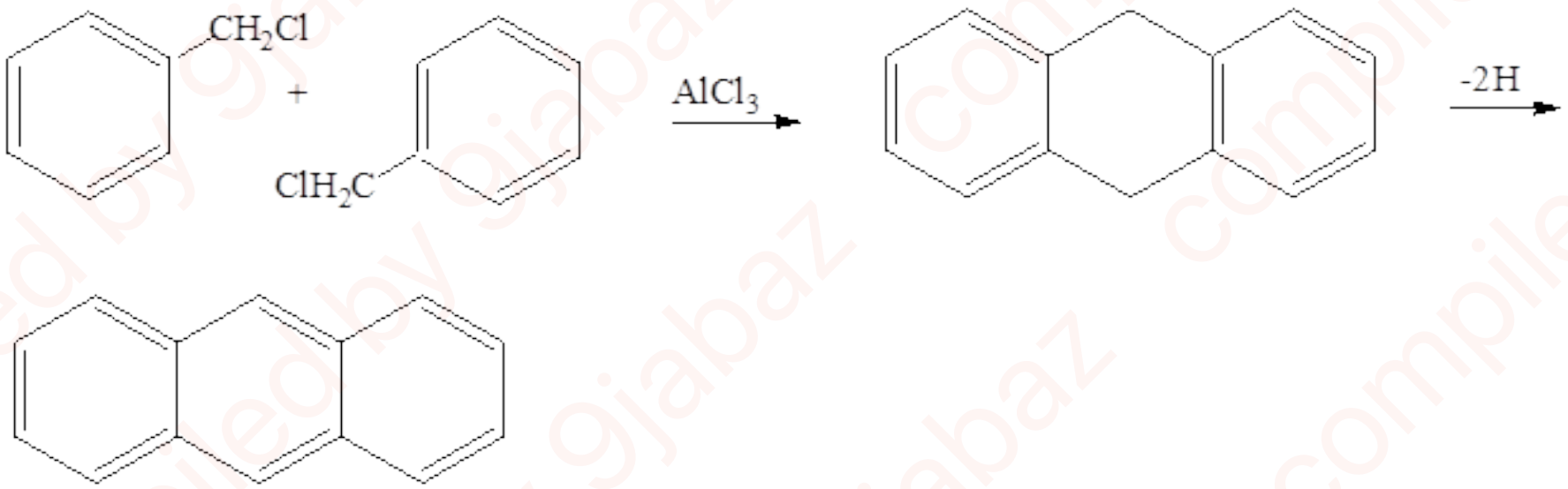


Phenanthrene

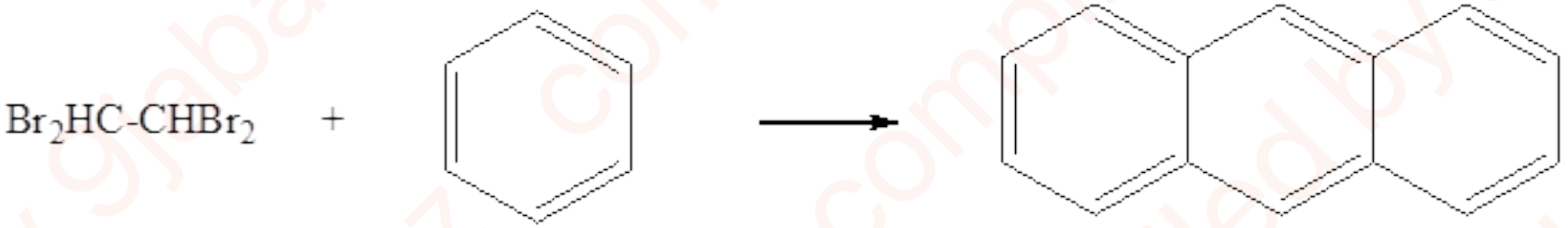
Anthracene

Synthesis of Anthracene

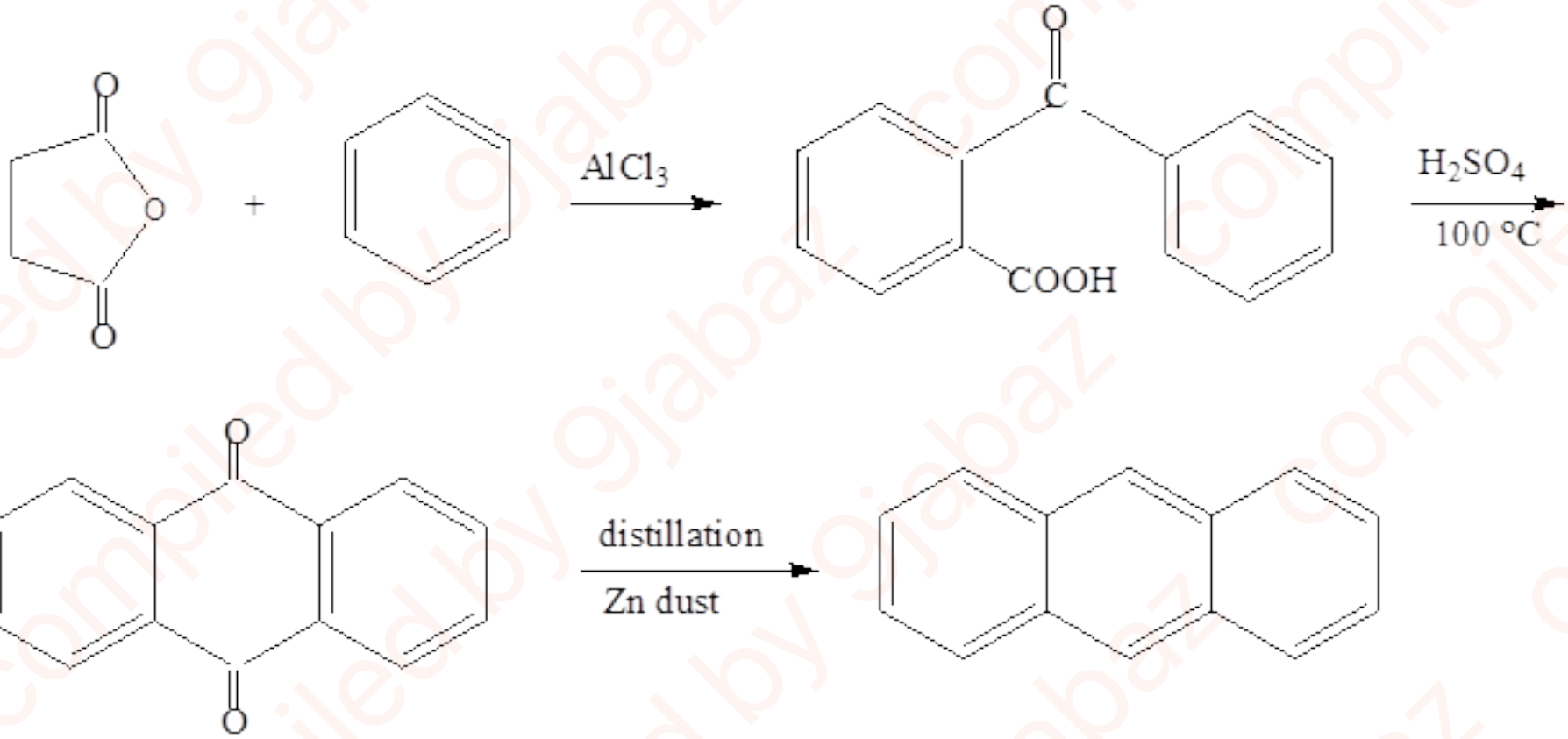
1. By Friedel-Crafts reaction using benzyl chloride



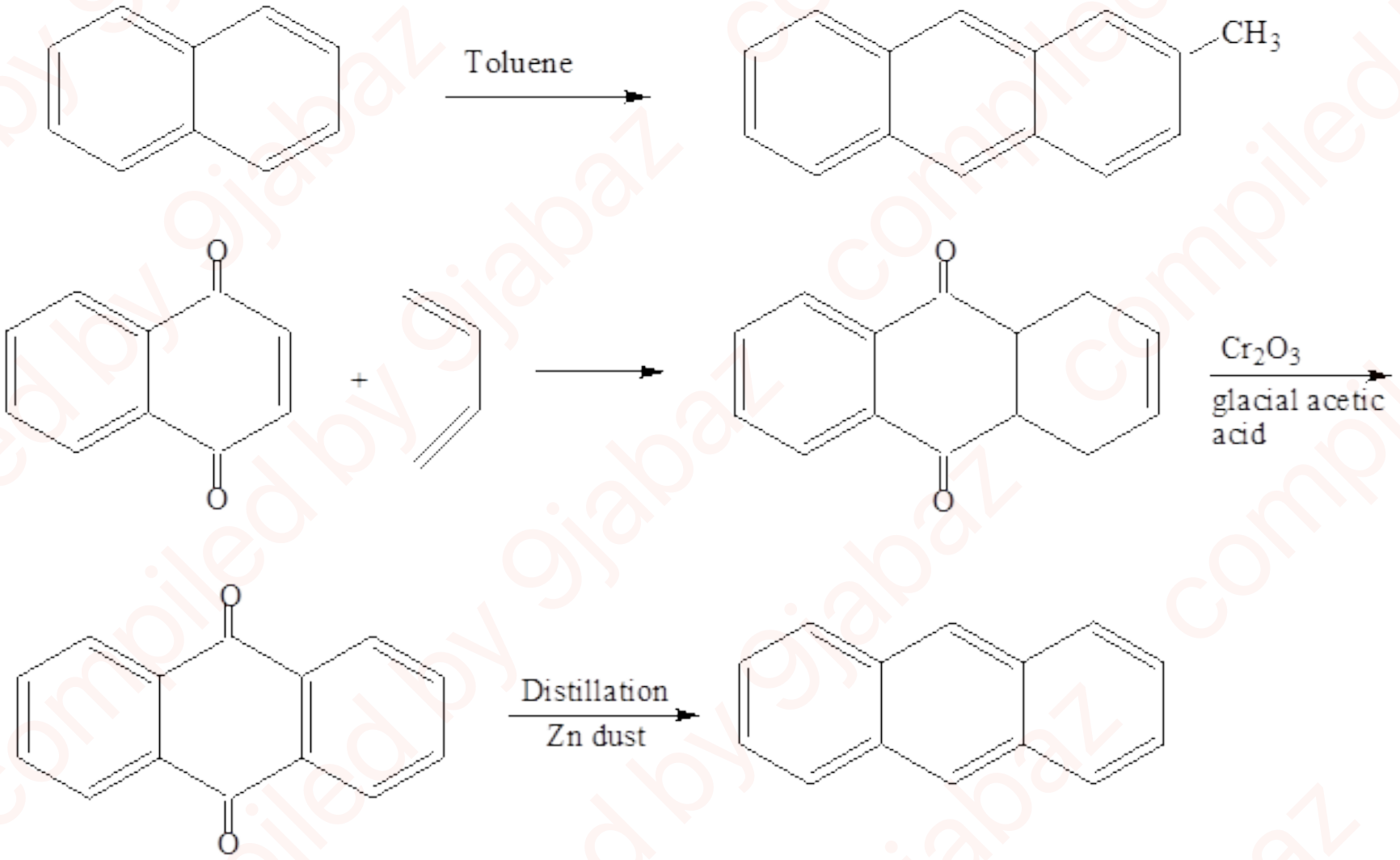
2. By a reaction between benzene and acetylene tetrabromide.



3. When phthalic anhydride in benzene solution is treated with $AlCl_3$.



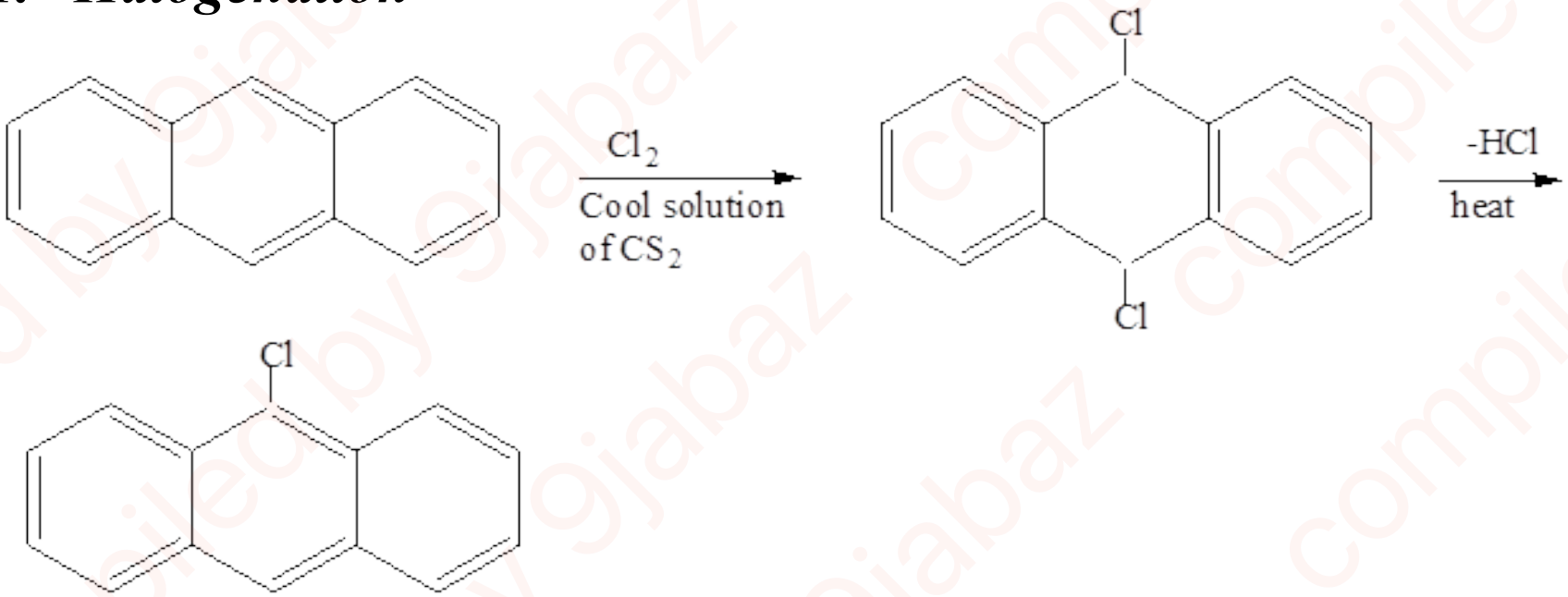
4. Anthracene derivatives could be prepared by using toluene and naphthalene.



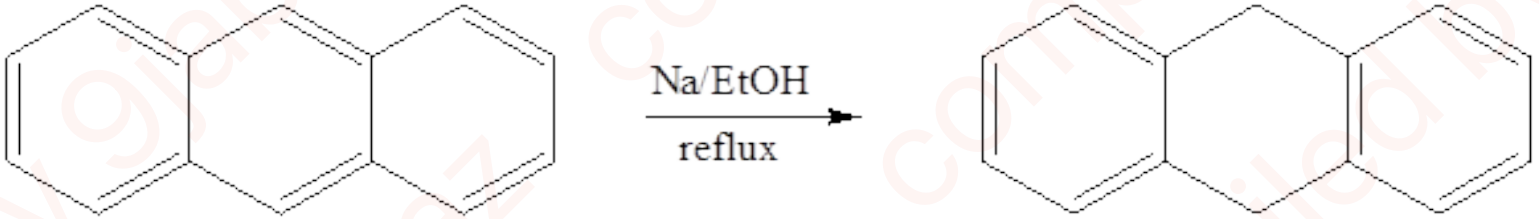
Reactions of Anthracene

- It has a melting point of 216 ºC with blue fluorescence and very reactive in positions 9 and 10.

1. Halogenation

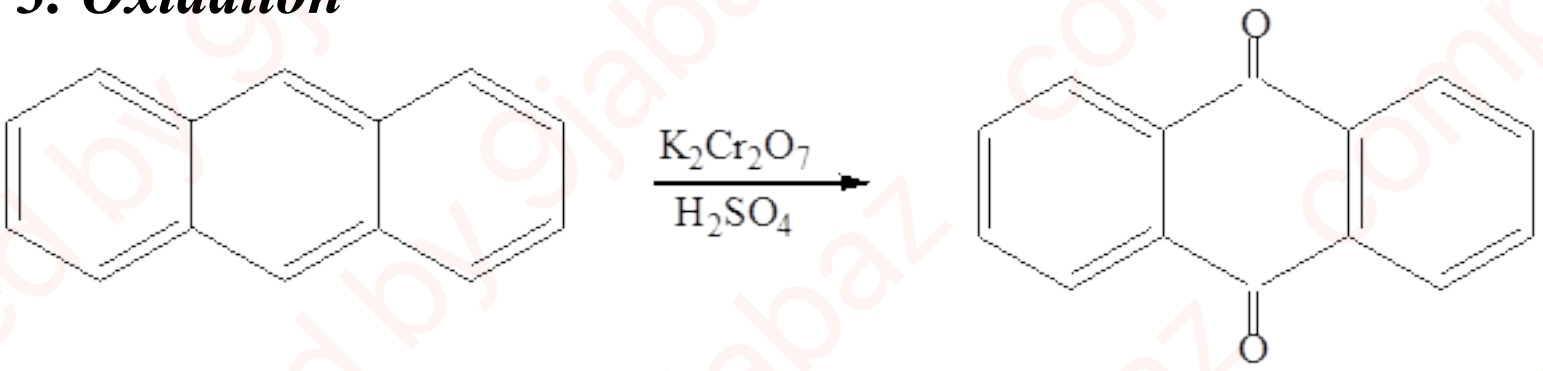


2. Reduction

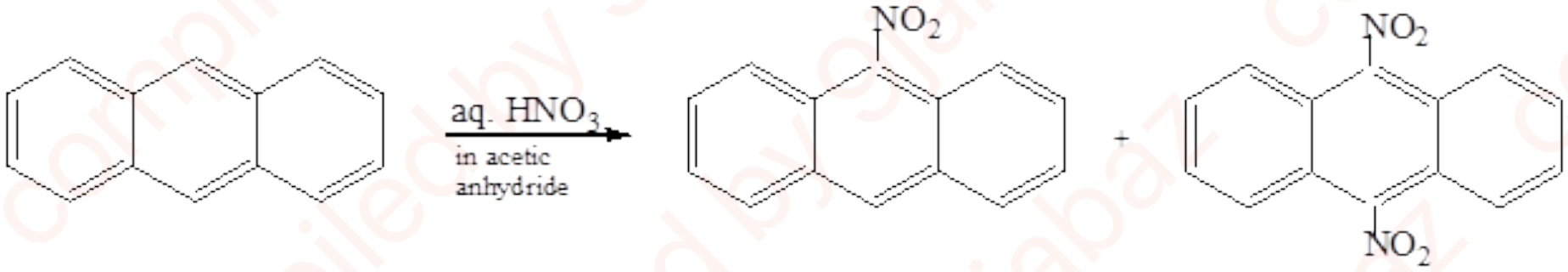


9,10-Dihydroanthracene

3. Oxidation



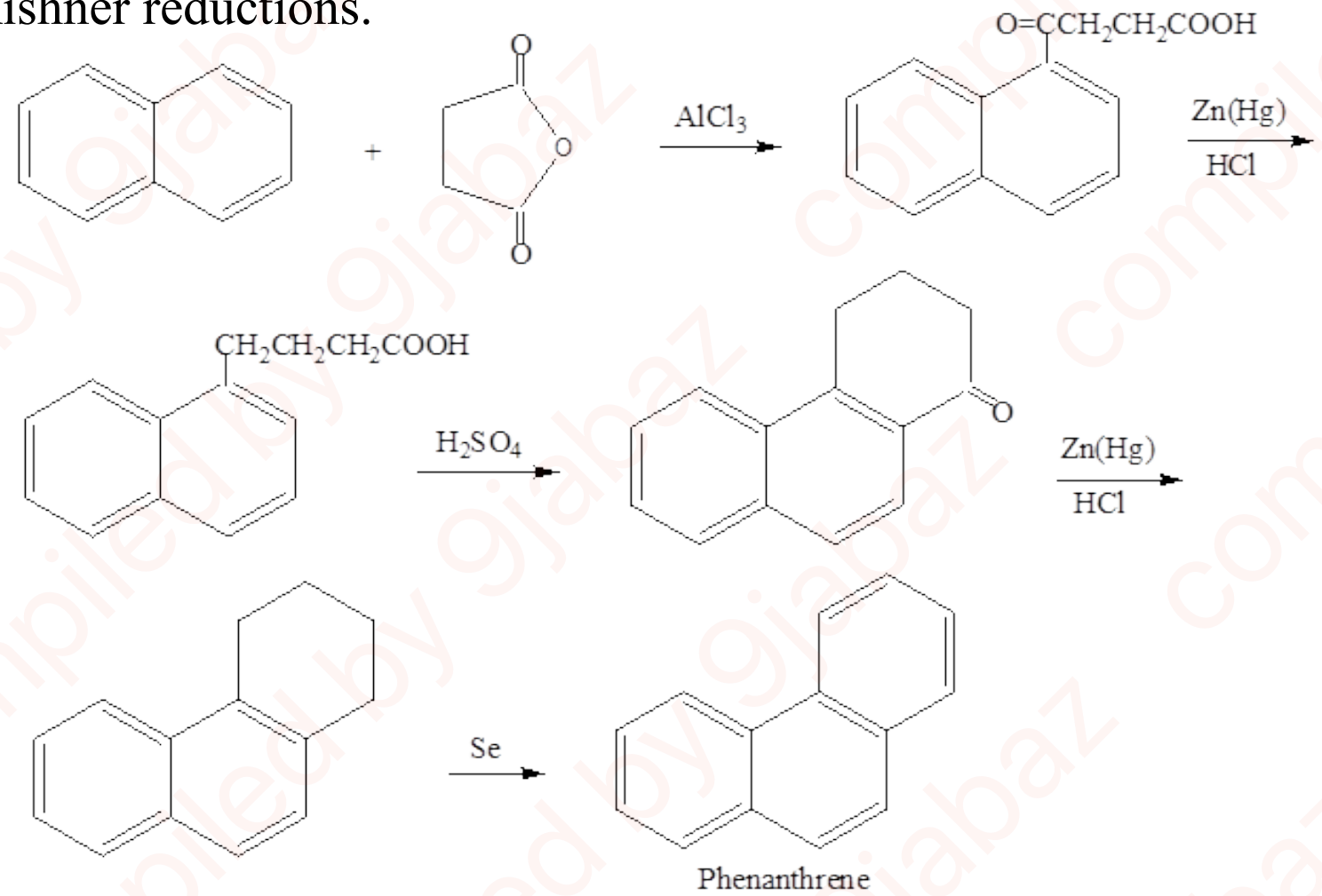
4.Nitration



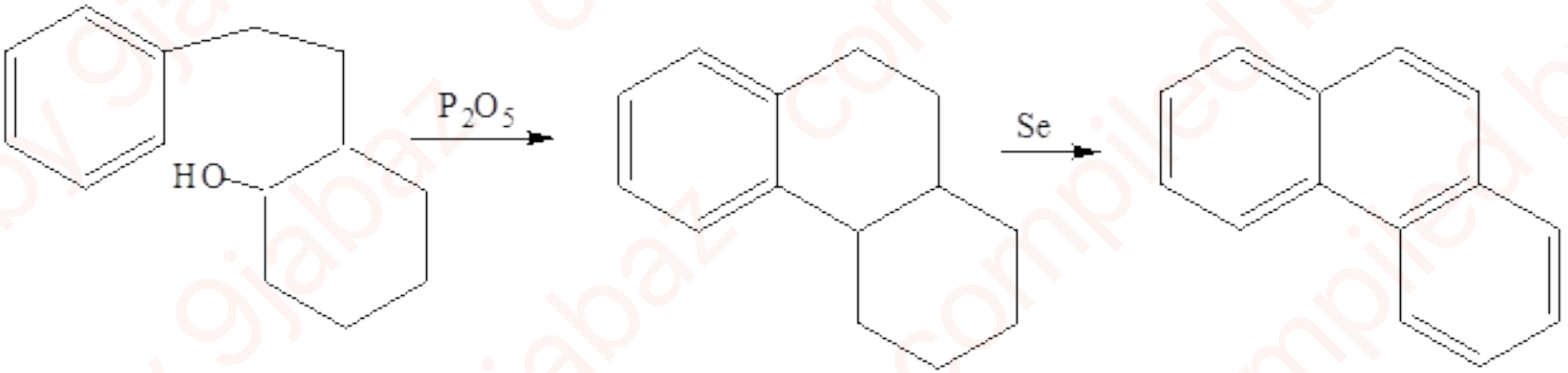
Phenanthrene

Preparation of Phenanthrene

- 1. Preparation of phenanthrene from naphthalene via a series of steps including Friedel-Crafts acylation and two Clemmensen or Wolff-Kishner reductions.



2. Bardhan-Sengupta Phenanthrene synthesis



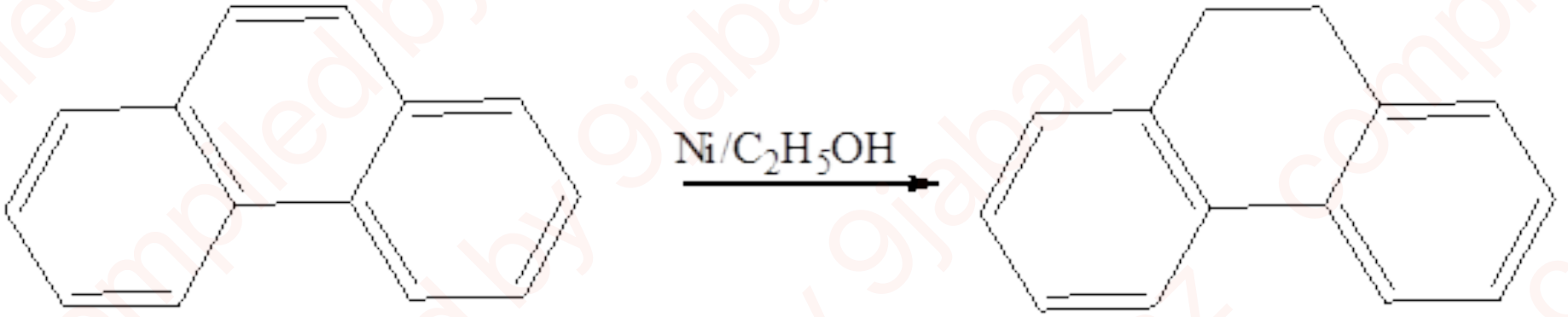
Properties & Reactions of Phenanthrene

Properties

1. It has a boiling point of 99 ^{o}C with blue fluorescence (effect of conjugation).
2. It is very reactive in positions 9 and10 just like anthracene.

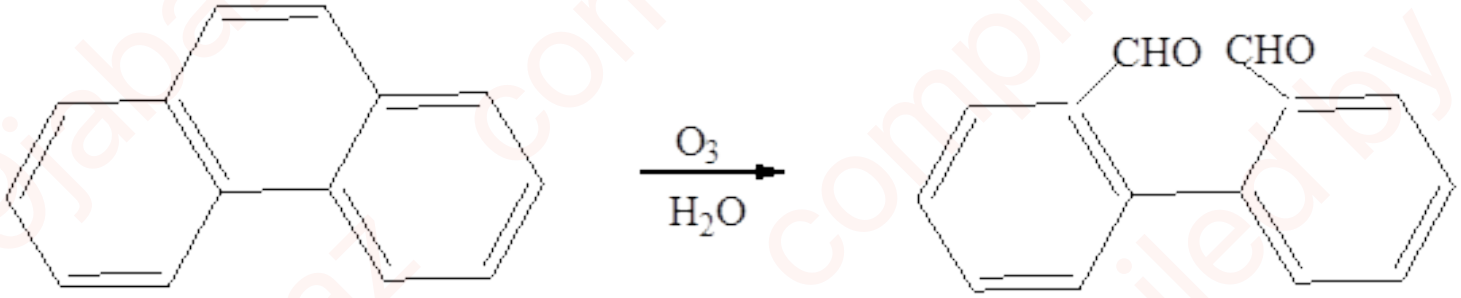
Reactions

1. Reduction

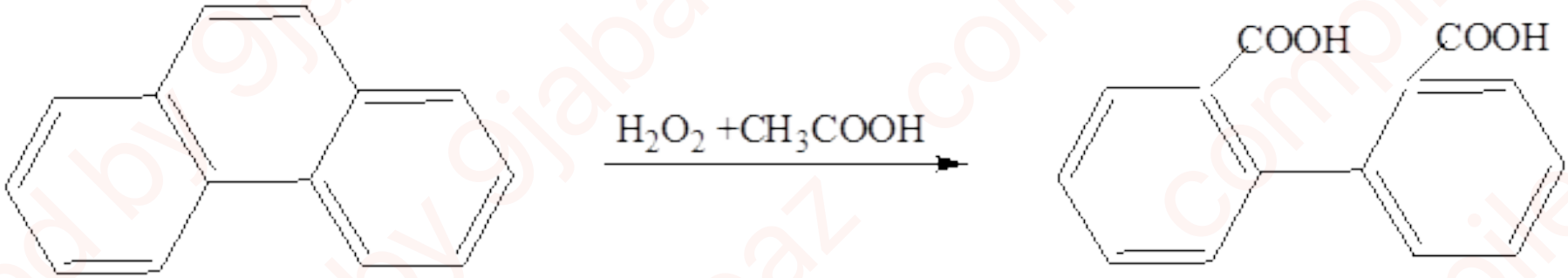


9,10-Dihydrophenathrene

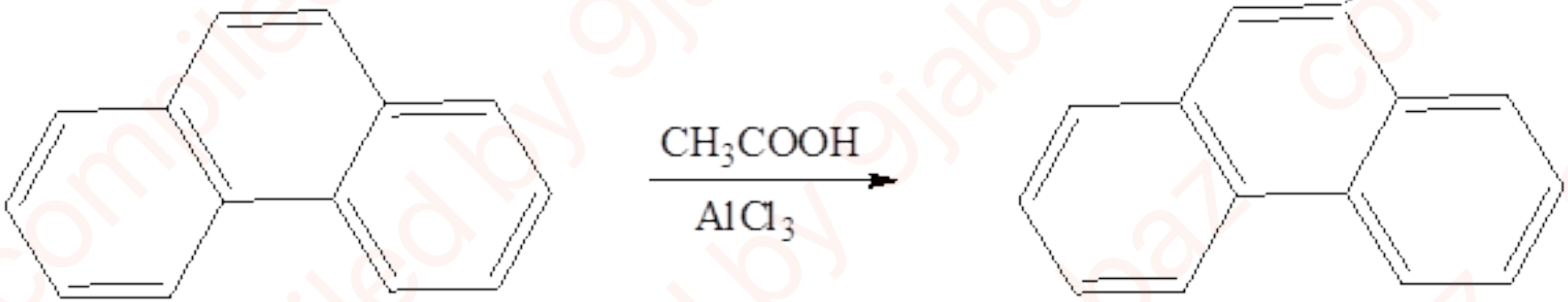
2. Phenathrene can undergo ozonolysis.



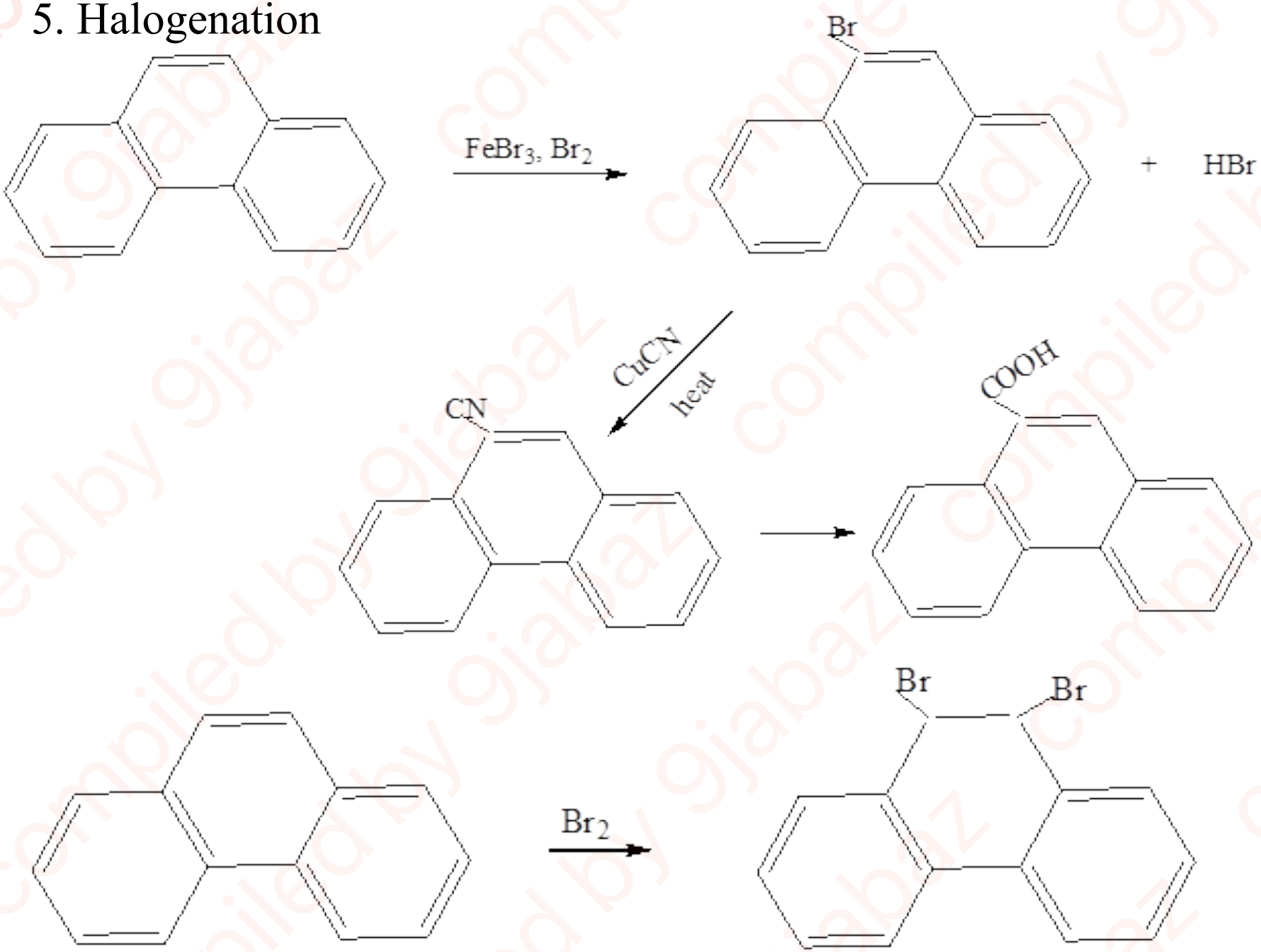
3. Reaction of Phenanthrene with peroacetic acid.



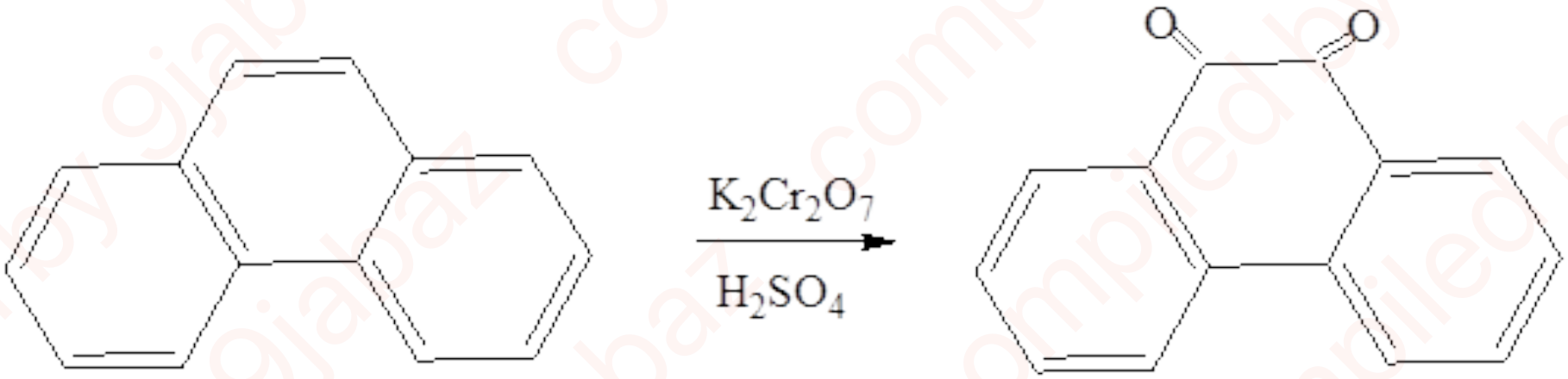
4. Friedel-Crafts reaction



5. Halogenation

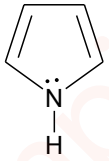


6. Oxidation



PYRROLE

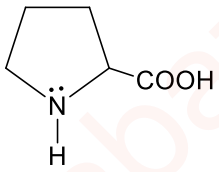
It is a five-membered compound and it has the structure shown below.



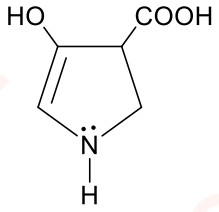
Pyrrole is aromatic because it obeys the Hückel's rule of aromaticity, which is defined as $(4n+2)\ \pi$ electrons, where n is a definite integral i.e. n = 1, 2, 3...

Aromaticity implies extra stability of compounds. Because the lone pair of electron on pyrrole's nitrogen atom is involved in aromatic delocalizaiton, its not readily available, therefore it is acidic and fairly basic.

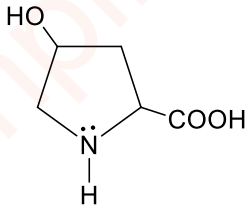
Derivatives of pyrrole include



proline carboxylic acid



4-hydroxyl pyrroline carboxylic acid

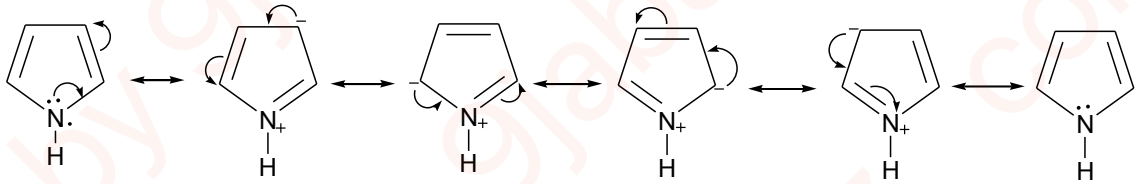


4-hydroxyl pyrrolidine carboxylic acid

Pyrrole ring also occur in other natural compounds like pyrrole ring like chlorophyll of plants, nicotine, chalcone, vitamin B_{12}, morphine and naturally occurring alkaloids.

Stability of Pyrrole

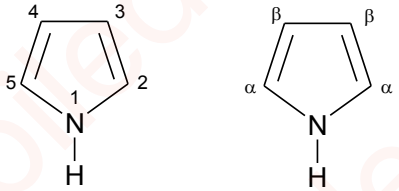
The higher the resonance or canonical structure of pyrrole, the higher the stability of pyrrole.



five canonical structures but four ionic canonical structures

All the carbon atoms on pyrrole has higher electron density (i.e. they are electron rich), while the nitrogen is highly electropositive.

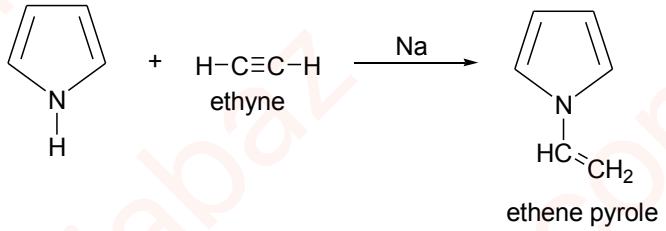
Pyrrole is highly susceptible to electrophilic substitution because all the carbon atoms are highly electron rich, but position 2 is more prone to electrophilic attack.



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.

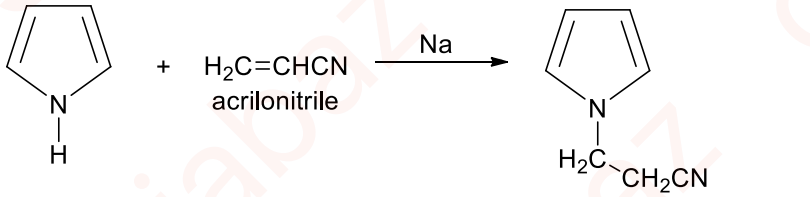
However, substitution takes place on the nitrogen atom, and hence it is said to be nucleophilic. Typical examples are reaction of pyrole with acetylenes and other unsaturated compounds e.g. acrylonitrile, acetylene, etc. in the presence of alkaline metal catalyst like sodium or potassium.

1. **Reaction with acetylene**



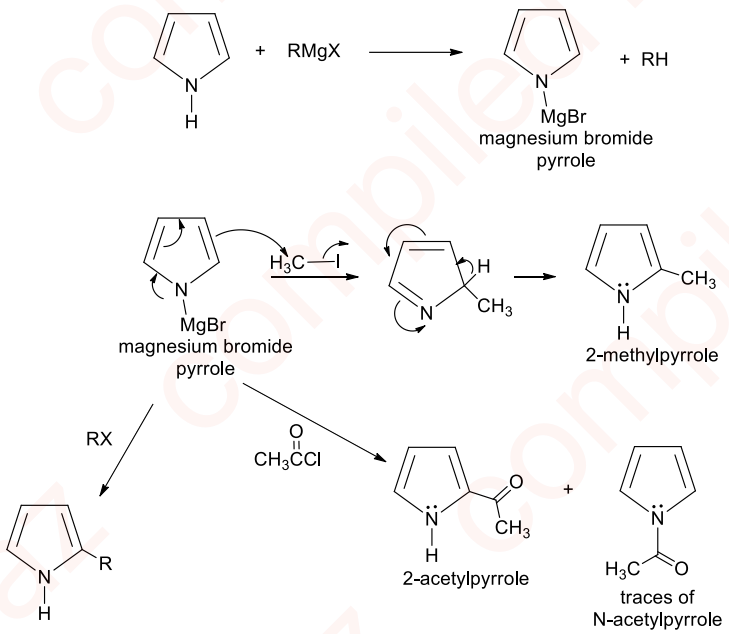
ethene pyrole

2. **Reaction with acrylonitrile**



ethylonitrile pyrrole
(N-ethylcyano pyrrole)

3. **Reaction with Grignard's Reagent or alkyl lithium**



These are reaction on nitrogen atoms of pyrrole. These reactions are only visible due to the presence of a stronger base like Na, K. N.

GENERAL REACTIONS OF PYROLE

Electrophilic substitution

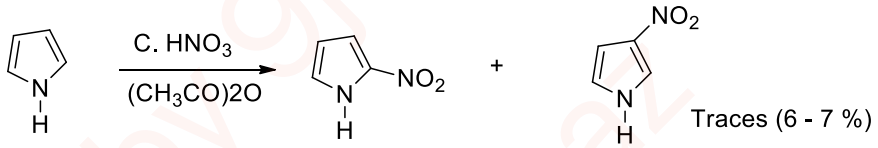
1. **Halogenation**:

Pyrole react extremely rapidly with halogens, i.e. iodine, in the presence of aqueous KI or bromine in the presence of methanol to give tetrahalogenated products.

2. **Nitration**: $HNO_3 + H_2SO_4$ ---------- $NO_2^+ + H_2O + HSO_4^-$

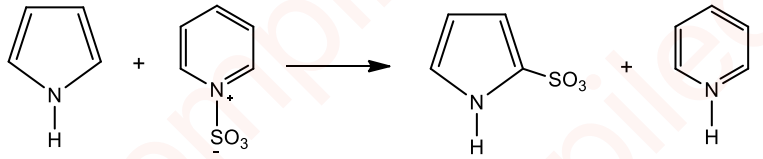
$HO\text{-}NO_2 + H\text{-}OSO_3H$ ------ $H_2O^+\text{-}NO_2 + HSO4^-$ ------- $NO_2^+ + H_2O + HSO_4^+$

Normal nitrating agents are usually too strong for pyrrole, which leads to the formation of tars. Therefore, milder reagents are used such as conc. HNO_3 in acetic anhydride. This gives 2-nitropyrole as the main product with some traces of 3-nitro products.



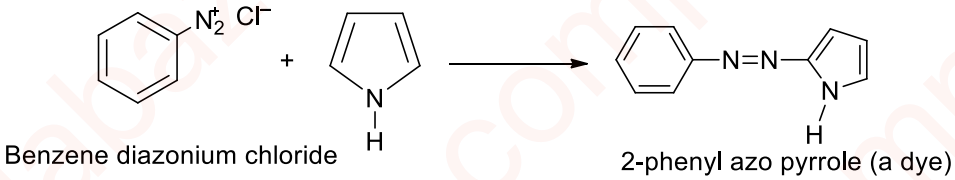
3. **Sulphonation**:

Pyrole cannot be sulphonated under vigorous condition, because polymerization might occur, hence, milder reagents like pyridinium sulphonate is used, and the product formed is pyrole-2-sulphonic acid.

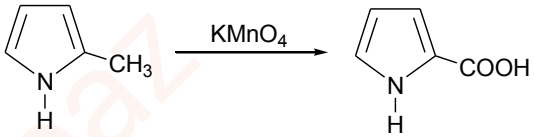


4. **Friedel-Crafts Acylation Reaction**:

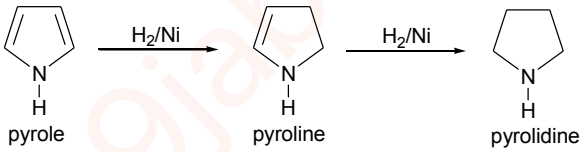
Under mild condition, reaction do take place i.e. pyrole with acetic anhydride gives pyrole-2-acetate. Because of its strong electrophilic ability, pyrole can be coupled with diazonium salts to form azo dyes.



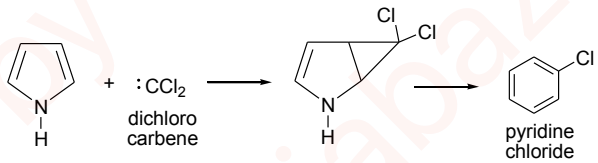
Alkyl pyrole can also be oxidized to the corresponding carboxylic acids.



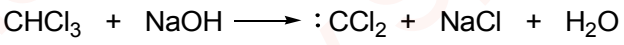
Pyrole can be reduced by catalytic hydrogen i.e. H_2/Ni or H_2/Pd, Zn/Acetic acid. Pyrole is partially reduced to pyroline, further reduction give pyrolidine.



Pyrole react with carbene



Carbene is obtained from the following chemical reaction

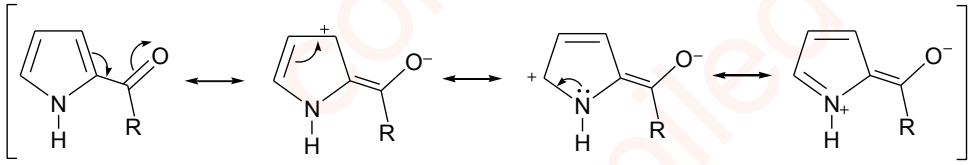


PYROLE ALDEHYDES AND KETONES

They are stable compounds. The carbonyl compounds are less reactive than normal especially at the α-position, because of the reduction of the positive charge of the carbonyl carbon as a result delocalization of electrons involving the ring nitrogen.

Normal carbonyl

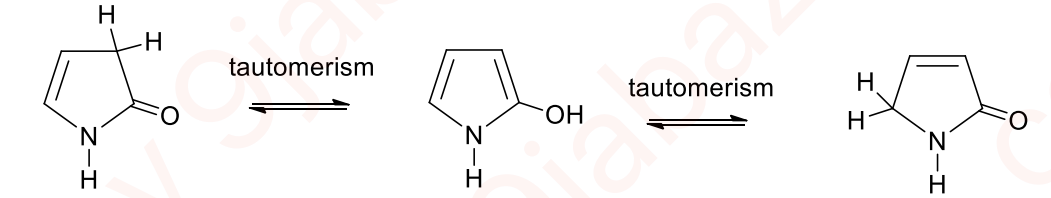
But for aldehyde carbonyl pyrole



Because of this phenomenon, pyrole aldehyde or ketones cannot undergo Perkin reaction and Canizarro reactions. However, pyrole aldehydes and ketons do undergo other reactions of aldehydes and ketones. For example, they can be reduced by sodium borohydride to the corresponding alcohol. They can also be reduced by Wolff-Kishner reagents to the corresponding hydrocarbons.

OXY PYROLES

A good example of oxy pyroles is given below

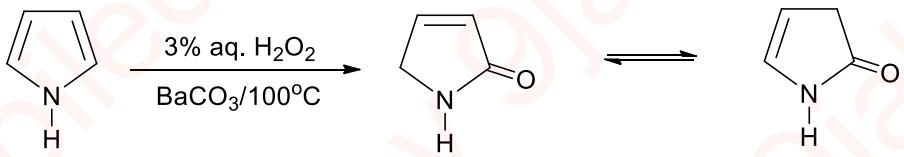


4-pyroline-2-one

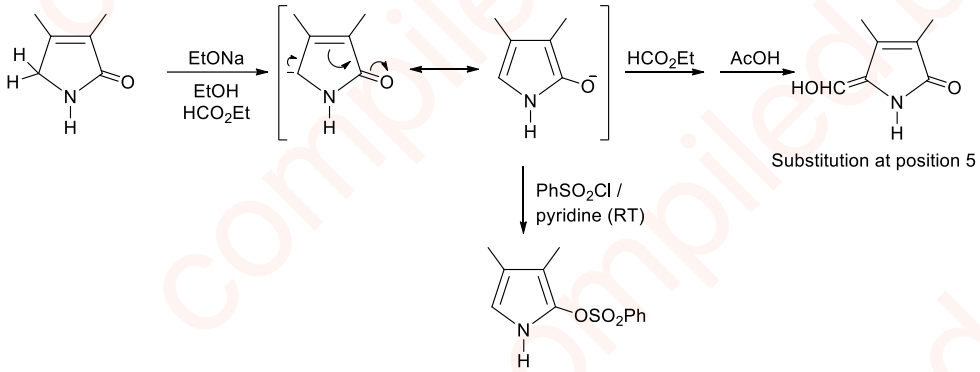
3-pyroline-2-one

Action of hydrogen peroxide on pyrole

H_2O_2 convert pyrole to a tautomeric mixture of pyrroline-2-ones i:e: 3-pyrroline-2-one or 4-pyroline-2-one



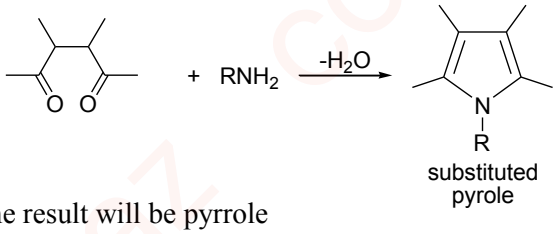
The 3-pyrroline-2-one is more stable and well know. Most pyrrolline-2-ones undergo base catalysed reactions and usually lead to substitution at position 5 or on the oxygen atom.



SYNTHESIS OF PYRROLE

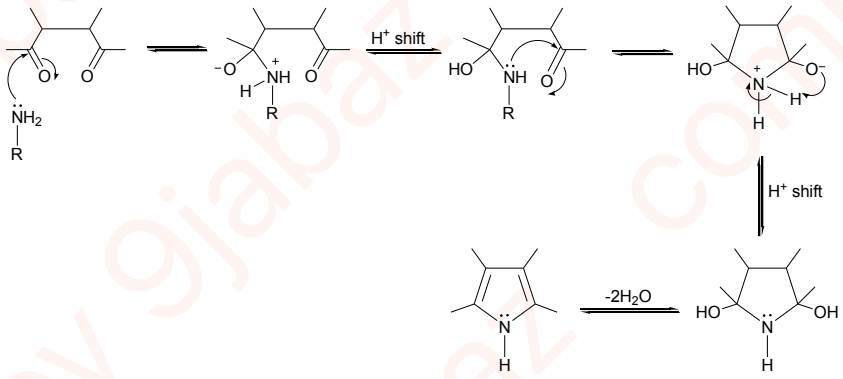
1. Paal-Knorr Synthesis

This is a general synthesis for pyrole and it involves the reaction between 1,4-dicarbonyl compound and ammonia or primary amines.



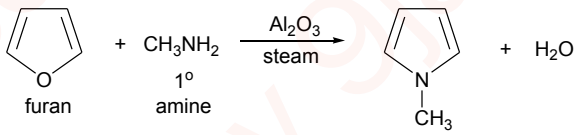
But if we use ammonia, the result will be pyrrole

Mechanism of the reaction



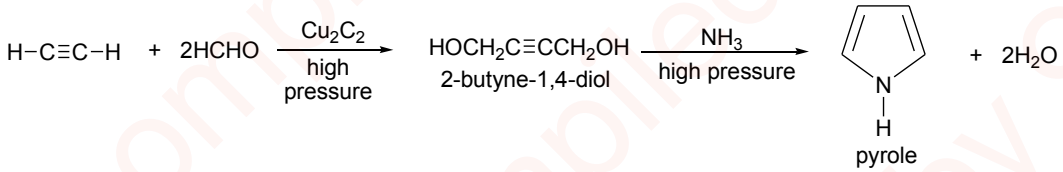
2. Conversion of Furan

Pyrole can be obtained commercially by passing furan, ammonia or 1° amine and steam (100°C) over heated alumina.



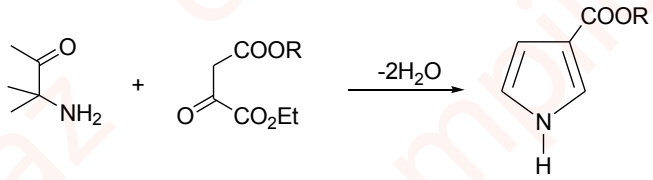
3. **Reppe's synthesis**

This is also an industrial method. It involves the reaction between acetylene and formaldehyde in the presence of copper carbide at a very high pressure. This reaction first yield but-2-yn-1,4-diol, which in the presence of ammonia at high pressure will give pyrole and water.

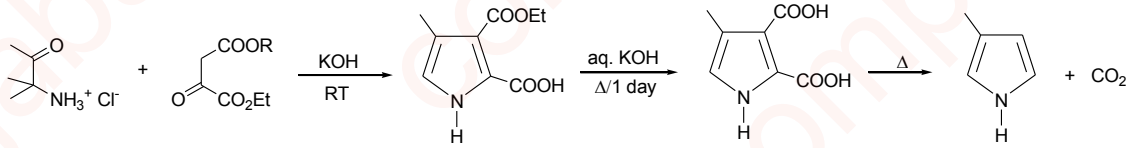


4. **Knorr synthesis**

This involves the reaction of α-aminoketone with carbonyl compounds that has methylene group i.e. active methylene group.

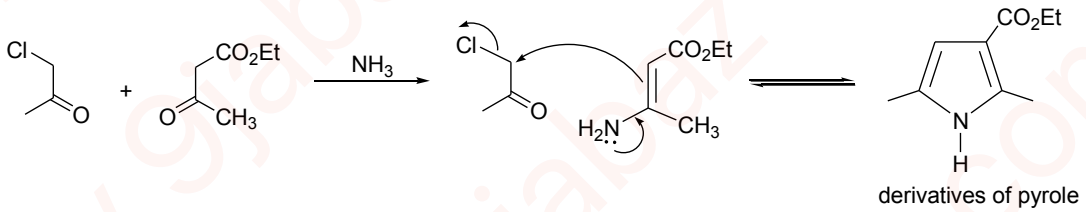


For example:



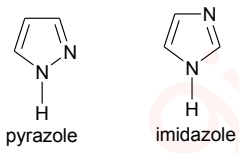
The presence of the base helps in hydrolysis and in the removal of the acidic proton.

5. **Synthesis from α-halocarbonyl compoun**



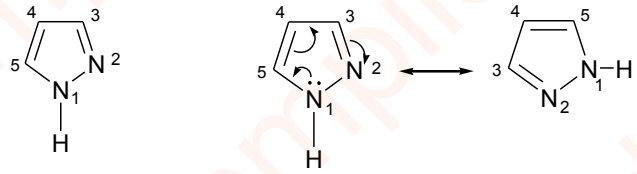
PYRAZOLES AND IMIDAZOLES

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



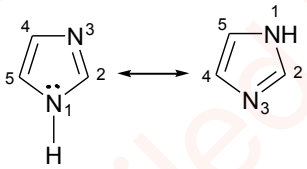
Both of them are aromatic because they obey the Huckel's $(4n+2)\pi$ rule, therefore the lone pair of electrons on the imino nitrogen atom are involved in aromaticity (aromatic stabilisation). However, they are more basic than pyrole because the lone pair of electrons on their other nitrogen atom (azo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

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



So in unsubstituted pyrazoles, the identity of position 3 and 5 are possible and major than the substituted pyrazole.

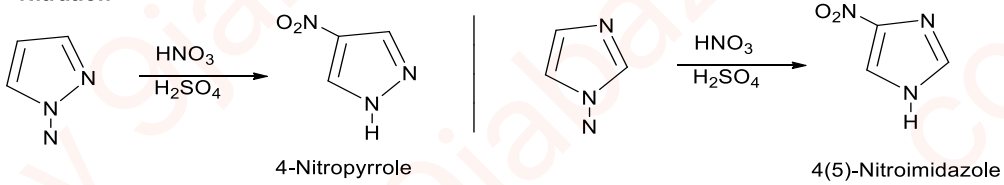
In imidazole, position 4 and 5 are identical i.e. for non-substituted imidazole



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.

Carbon-4 is readily used for electrophilic substitution reaction in pyrazole. In the case of imidazole, electrophilic substitution takes place both on the 4th and 5th carbon atoms because carbons 4 and 5 are identical. Electrophilic substitution in pyrazole and imidazole require strong reaction condition because they are not as susceptible towards electrophilic reactions as pyrrole.

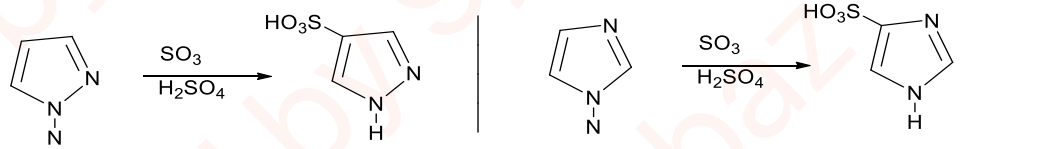
Nitration



4-Nitropyrrole

4(5)-Nitroimidazole

Sulphonation



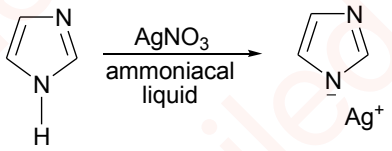
4-pyrrole sulphonic acid

4(5)-imidazole sulphonic acid

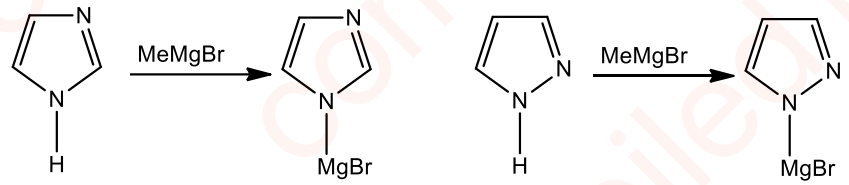
Imidazole & pyrazole are less susceptible to electrophilic reaction than pyrrole but more susceptible than pyridine. Imidazole is slightly more susceptible than pyrazole in electrophilic substitution reaction.

Reactions on N-atom – Reaction as a Base:

1. **Imidazole reaction with ammoniacal silver solution to form silver salt**

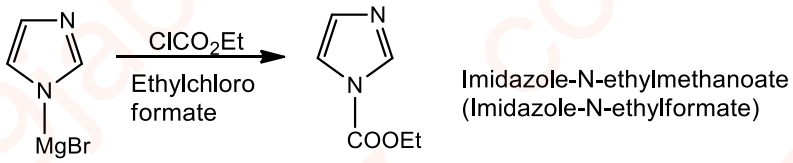


2. **Imidazole and pyrazole can also react with Grignard's reagents to form N-magnesium bromide imidazole/pyrazole:**



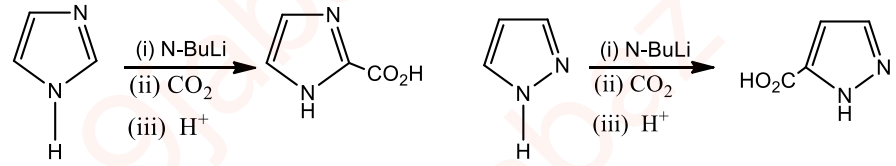
Imidazole Pyrazole

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



Imidazole-N-ethylmethanoate
(Imidazole-N-ethylformate)

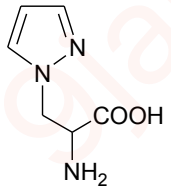
Both of them can also react with N-butyllithium followed by CO_2 in acidic medium to form pyrazole-5- or imidazole-2-carboxylic acid.



Imidazole Pyrazole

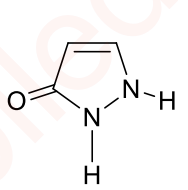
OCCURRENCE

1. Pyrazole derivatives have been isolated from water melon seed known as β-[1-pyrazolyl] alanine.

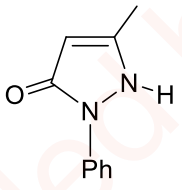


β–[1-pyrazolyl]alanine

Pyrazolone and antipyrine are also compounds of pyrazole



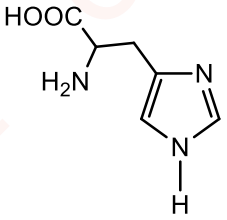
pyrazolone



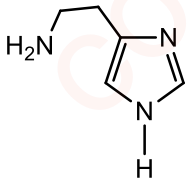
antipyrine

Antipyrine is derived from pyrazolone and used as an antipyretic.

2. Imidazole derivates include histidine, histamine, metroimidazole, allantoin etc

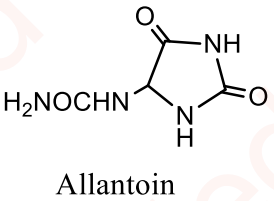


histidine



histamine

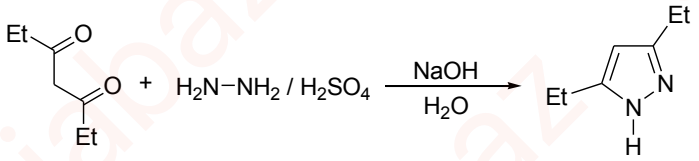
metroimidazole



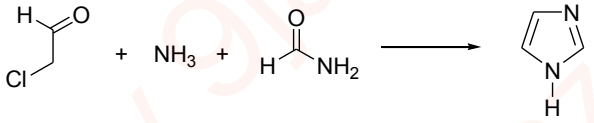
Allantoin

SYNTHESIS OF PYRAZOLES & IMIDAZOLE

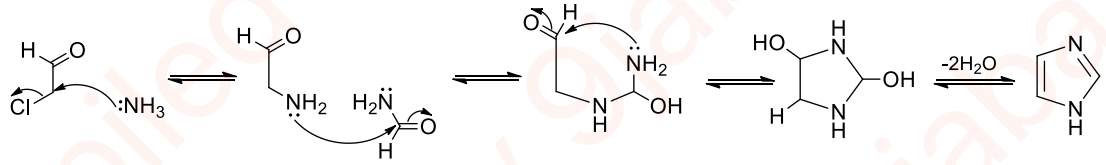
1. Pyrazoles can be obtained from 1,3-dicarbonyl compounds. The 1,3-dicarbonyl compounds react with hydrazines or methylhydrazines in the presence of a base to give pyrazoles.



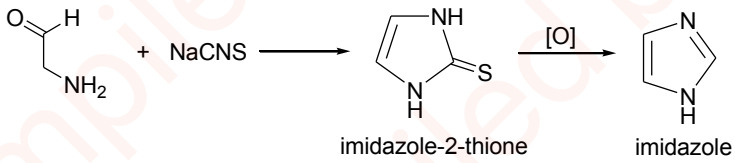
2. Imidazoles can be prepared from α-halocarbonyl compounds. On heating these α-halocarbonyl compounds with ammonia and formamide, imidazole is formed.



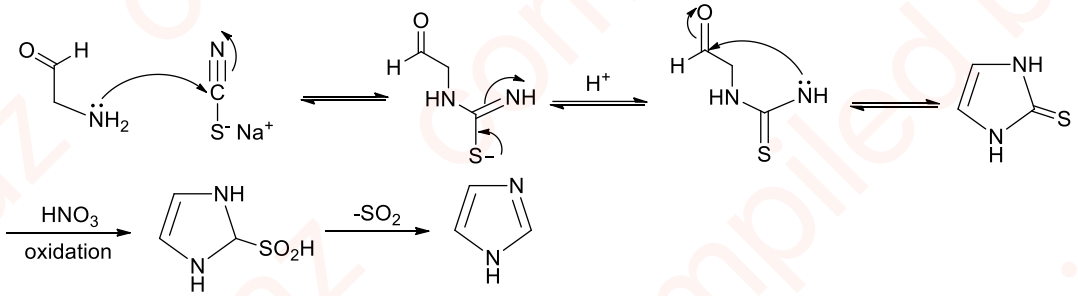
The mechanism involves the displacement of halogen atom by ammonia to form α-amino carbonyl compounds followed by attack by the formamide.



3. We can also obtain imidazole from α-aminocarbonyl compounds. This compound condenses with thiocyanate ion to form imidazole-2-thiones. Desulphurization takes place to get the imidazole



Mechanism of the reaction



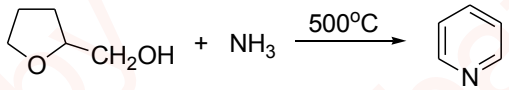
PYRIDINE

This is a six-membered heterocyclic nitrogen compound. It is aromatic. The nitrogen atom in pyridine has no hydrogen because of its π-electrons. Meanwhile, because the lone pair of electron in the nitrogen atom of pyridine is readily available, they are therefore basic.

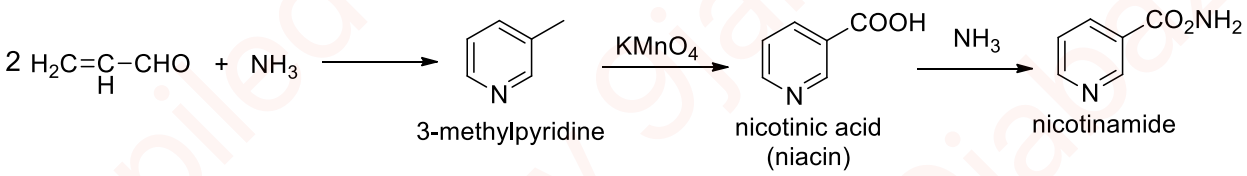
Pyridine is a colourless liquid with a disagreeable smell.

SYNTHESIS OF PYRIDINE

1. **It is prepared commercially by heating tetrahydro furfural alcohol with ammonia**

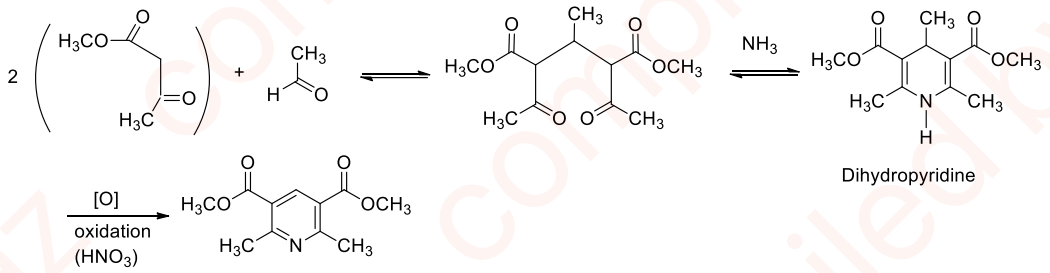


2. **Use of acrolein with ammonia**



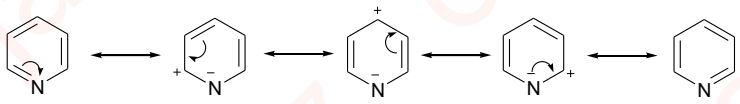
3. **Hantsch synthesis**

It involves the condensation of β-diketone or β-diketoester and aldehyde with ammonia to give dihydropyridine, which is then oxidized to pyridine.



REACTIONS OF PYRIDINE

Canonical structure of pyridine

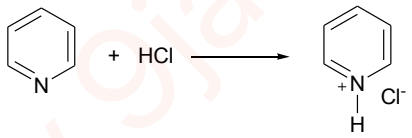


3 ionic canonical structure

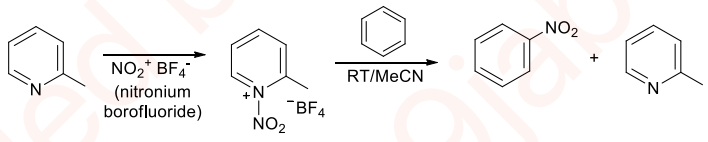
Electrophilic substitution of pyridine

Electrophilic reaction takes place on the nitrogen atom due to the availability of electrons, therefore pyridines are commonly known as organic bases.

1. **Reaction with HCl form pyridinium chloride (pyridinium hydrochloride)**



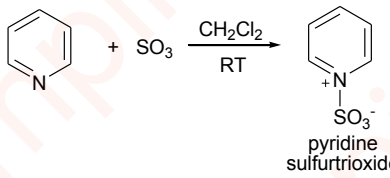
2. **Nitration:** Reaction of 2-methylpyridine with nitroniumborofluoride gives a product called



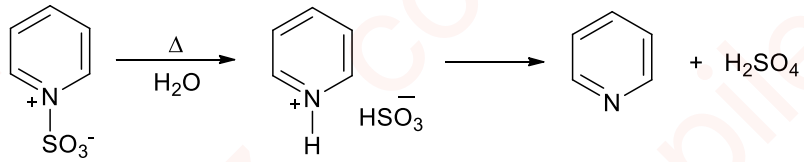
1-nitro-2-methylpyridinium borofluoride. It is a mild nonacidic nitrating agent.

3. **Sulphonation**

Pyridine react with sulphur trioxide in the presence of dichloromethane.

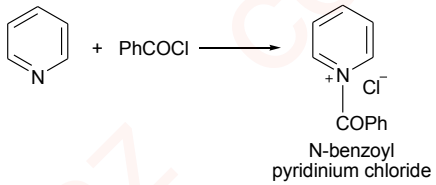


We can regenerate the starting material by reacting the product with water and then heat.

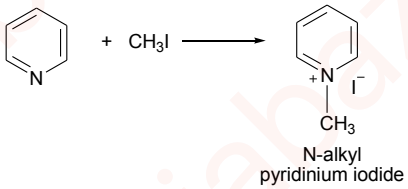


4. Another electrophilic reaction at the nitrogen atom is acylation and alkylation. Pyridine will react with acid chloride or aryl chloride to give N-benzoylpyridinium chloride.

i. With Aryl halide:

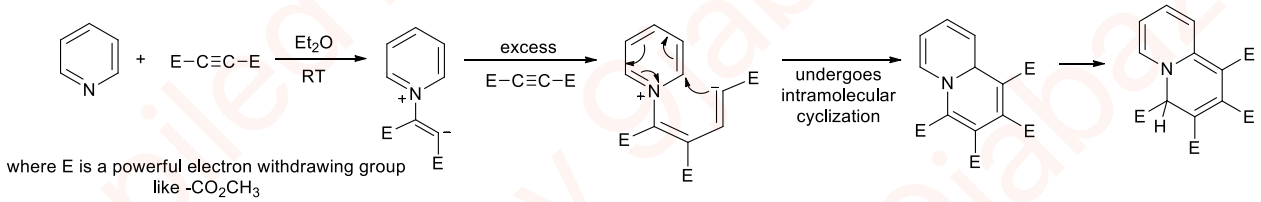


ii. With R – X : Used as acylating agent

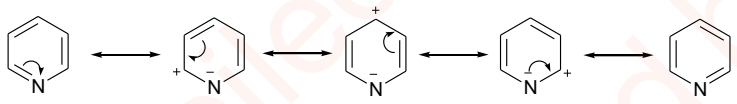


used as alkylating agent

5. **Reaction with activated acetylene**



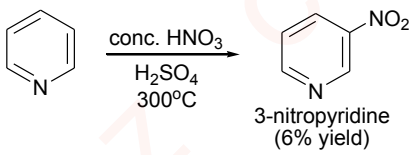
Canonical structures of pyridine shows that nucleophilic reactions are possible on positions 2, 4, and 6

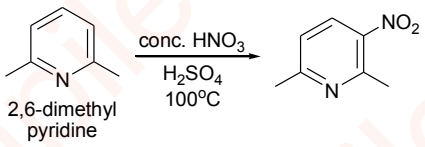


Therefore electrophilic substitution is difficult in pyridine and when it takes place it's only on C 3 & 5. Hence Friedel-Crafts alkylation, acylation, halogenation, sulphonation and nitration, hardly takes place in pyridine, and when it occurs, it's usually under rigorous conditions and it takes place on the third and fifth position.

Alkyl substitution on the ring do activate the ring towards electrophilic substitution reaction bcos of +I effect of R – group.

1. **Nitration**

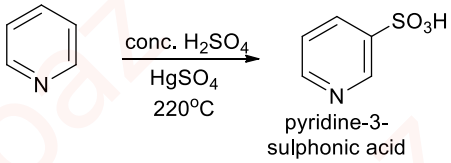




66% yield

2. **Sulphonation**

This usually occur in the presence of catalytic amount of mercuric sulphonate.

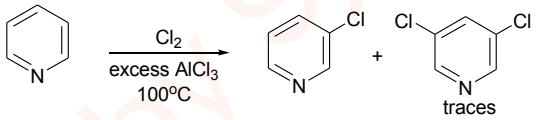


70% yield

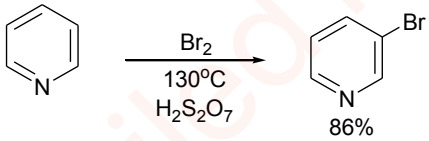
3. **Halogenation**

Pyridine reacts with chlorine in the presence of excess $AlCl_3$ at 100°C

a. **Chlorination**

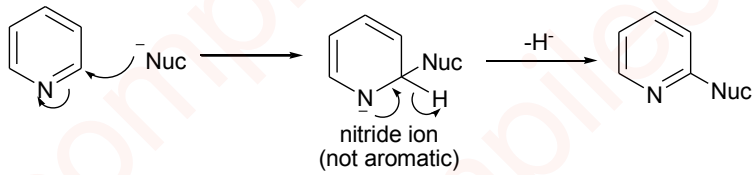


b. **Bromination**



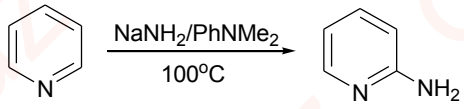
Nucleophilic substitution reaction of pyridine

Reaction with nucleophiles is characterisitic of pyridine as they are highly susceptible to nucleophilic attacks on position 2, 4 and 6.

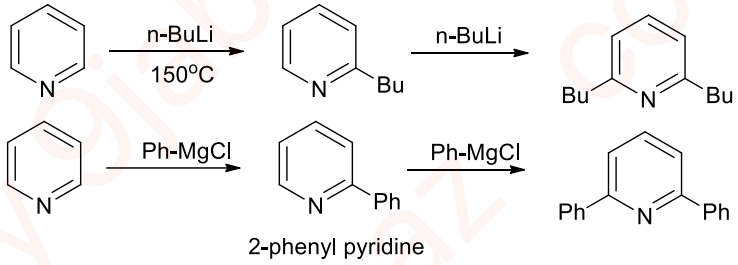


1. **Amination reaction**

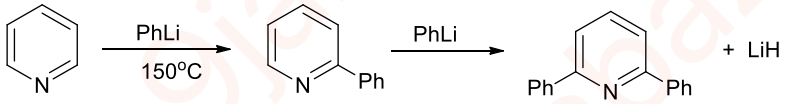
The reaction is referred to as Chichibabin reaction. It takes place in the presence of sodamide and dimethylalanine.



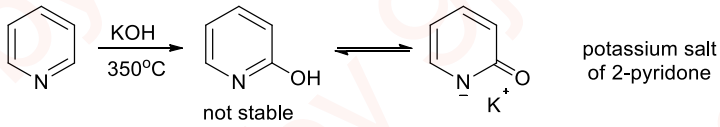
2. **Reaction with organometallic reagent such as N-butyllithium, we obtain 2-butylpyridine**



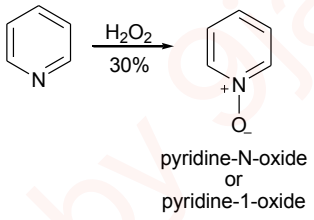
ii. Reaction with phenyllithium in diethylether



3. **Hydroxylation of pyridine**

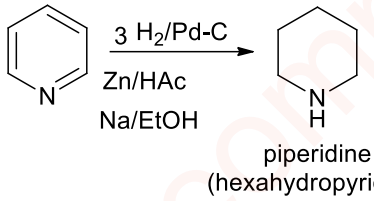


4. **Oxidation of pyridine with 30% hydrogen peroxide will give pyridine-N-oxide or pyridine-1-oxide**



5. **Reduction**

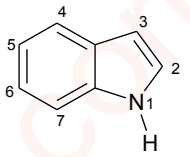
Pyridine can be reduced to piperidine.



Other hydrogenating agents are Zn/Acetic acid or Na/EtOH

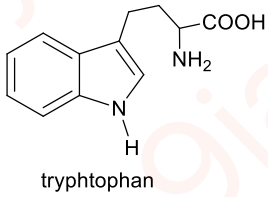
HETEROCYLIC COMPOUNDS WITH FUSED NUCLEUS

INDOLE

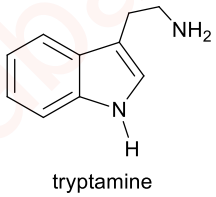


The lone pair of electron is involved in resonance stabilization

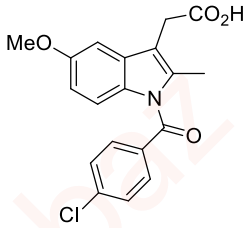
Common molecules that contain the indole moiety are tryptophan, tryptamine, indomethacin and scrotonini



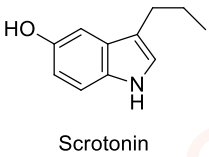
tryphtophan



tryptamine



indomethacin

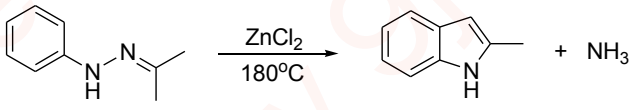


Scrotonin

SYNTHESIS OF INDOLE

1. **Fisher-Indole Synthesis**

This method is the most widely used method for preparing indole. The method works especially for preparing indole derivatives. It involves heating of phenylhydrazine of an aldehyde or ketone with an acidic catalyst such as $ZnCl_2$, BF_3, H_3PO_4, at 180°C. Ammonia is liberated during the process.

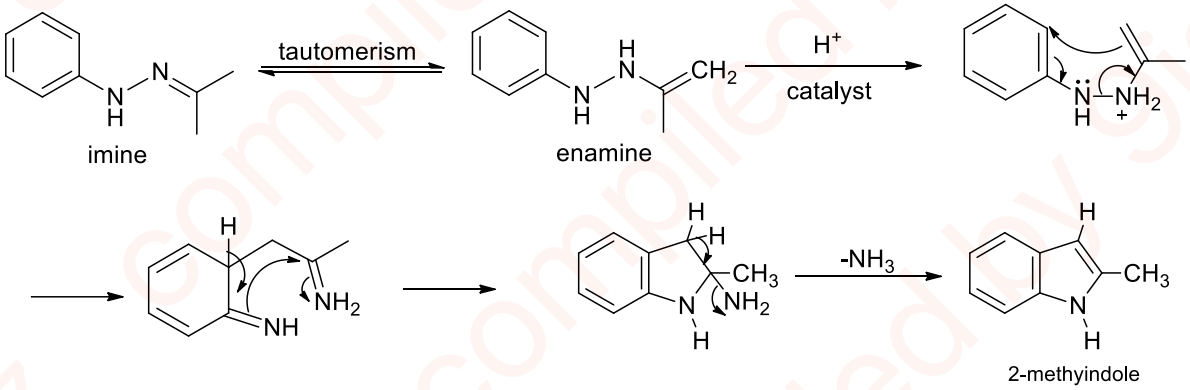


Acetone phenylhydrazone

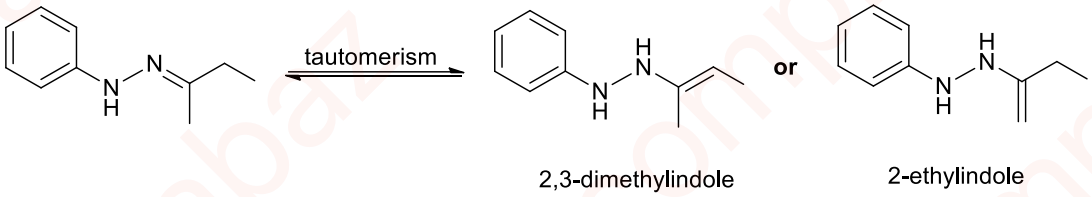
2-methylindole

Mechanism of the reaction

The hydrazone first undergoes tautomerism.

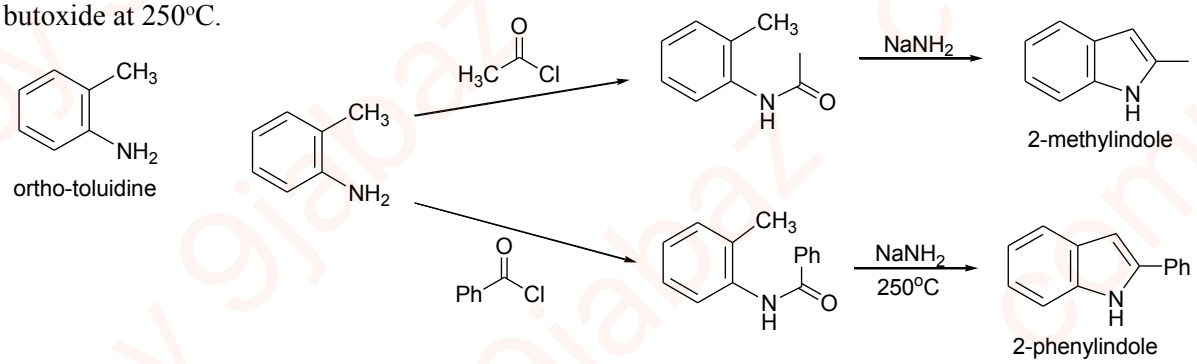


If we use a non-symmetical hydrazine, then we can form two different product



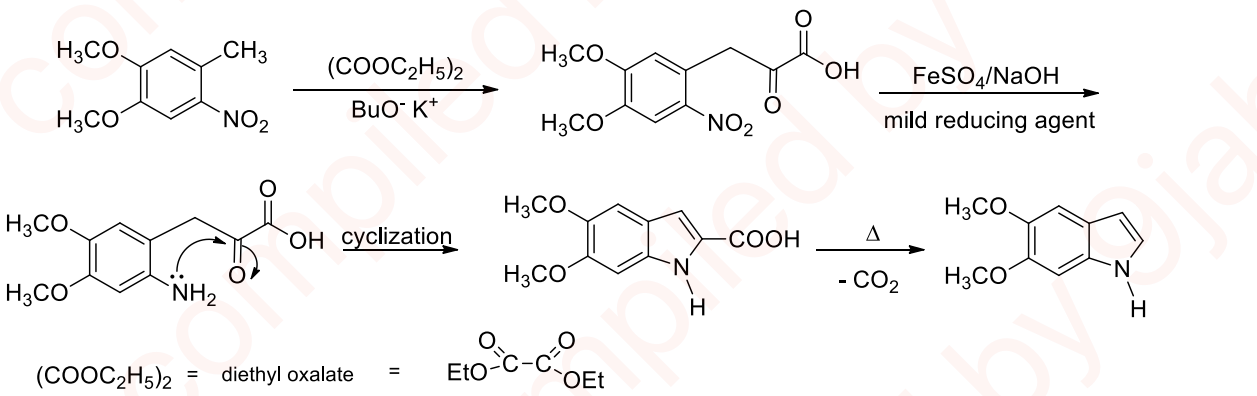
2. **Madelung's Synthesis**

It involves the cyclic dehydration of acyl or acetyl ortho-toluidine with strong base such as $NaNH_2$ or tert. butoxide at 250°C.



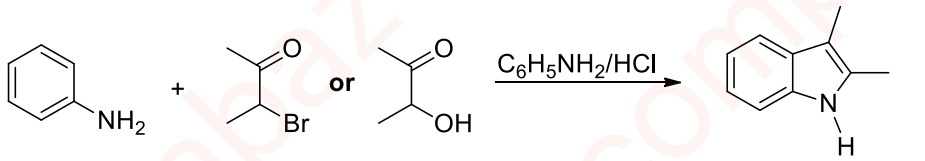
3. **Reissert Indole synthesis**

It depends on the fact that the methyl group that is ortho to the nitro group has an active hydrogen.



4. **Bishler Indole Synthesis**

This is acid catalysed reaction of an aryl amine with α-halo or α-hydroxylketone.



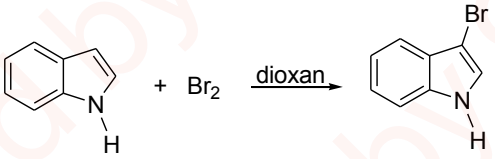
As the Br or OH group leaves, the NH_2 e attack the carbocation to form keto amine intermediate which undergoes electrophilic cyclisation with the aromatic ring.

REACTIONS OF INDOLE

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

1. **Halogenation**: It takes place under mild conditions to give 3-halogenated product

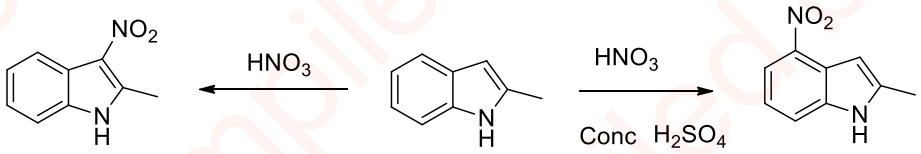
Bromination



2. **Nitration**

If the usual nitrating agent is used, it gives tar bcos indole is highly susceptible to electrophilic substitution reactio. However at very low temperature and using very mild nitrating agent like benzoyl nitrate, 3-nitro-indole is formed.

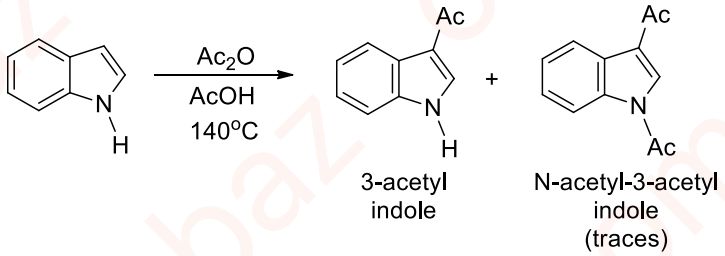
2-methylindole can react with HNO_3 to form 3-nitroindole, however, if we use an acidic conc. $H_2SO_4/NaNO_3$, nitration takes place at the benzene ring usually yielding 4-nitro derivatives.



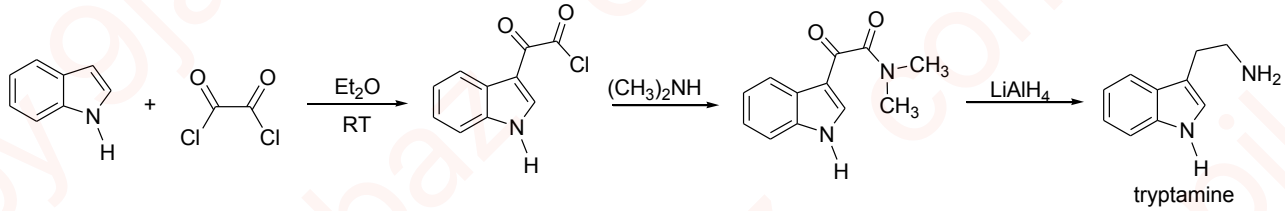
3. Sulphonation is carried out with N-pyridine sulphurtrioxide in pyridine to form indole-3-sulphonic acid.

4. **Acylation**

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

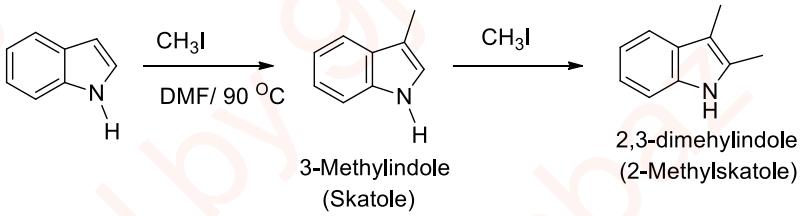


Indole can also react with oxalyl chloride.



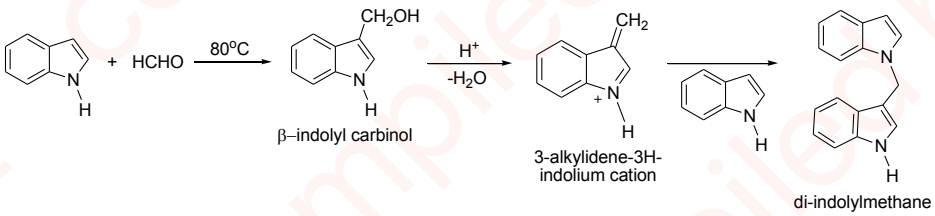
5. **Reactions of Indole with alkyl halide**

They react with alkyl halide at room temperature e.g. reaction with methyl iodide in the presence of dimethyl formamide gives skatole (3-methylindole). Reaction of skatole with excess of methyl iodide gives 2,3-dimethylindole.

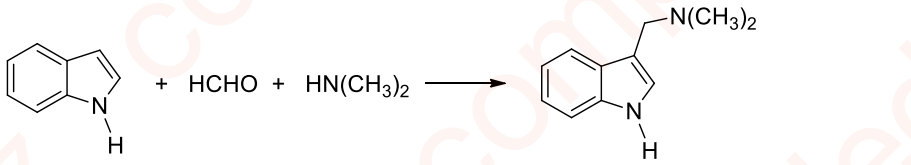


6. **Reactions with aldehydes and ketones**

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

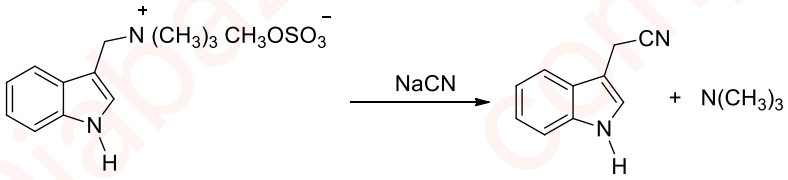


Methanal can also react with indole in the presence of dimethyl amine

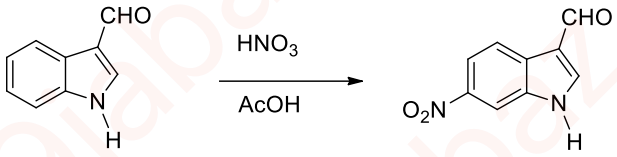


3-dimethylamino methylindole (gramine)

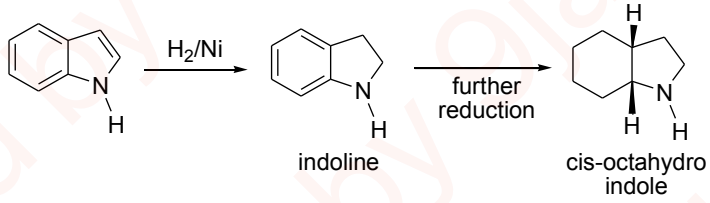
Gramine is a very important product as its quaternary salt are useful synthetic intermediate because the N-group is easily displaced by nucleophiles.



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.

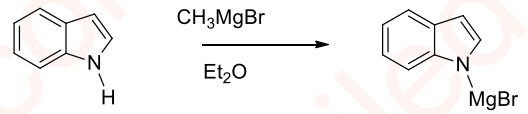


7. **Reduction of Indole**



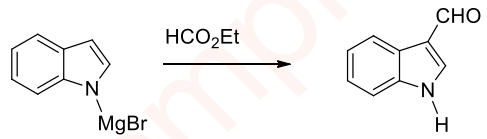
8. Reactions at N-atom: The N – H proton of indole like pyrrole is acidic and is easily attracted by metallic groups e.g NaOH; KOH; n-BuLi; Grignards rgt etc to give N-metalated derivatives.

a.

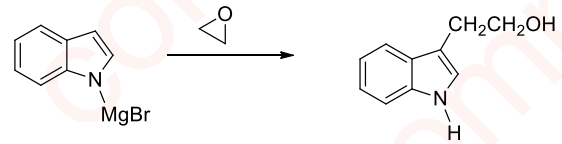


Indole-N-magnessium halide or N-halomagnesylindole is a very reactive intermediate which readily reacts with RCHO and R_2CO

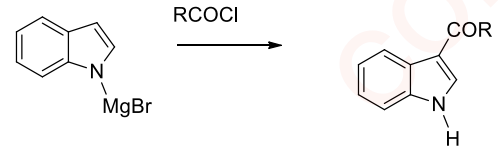
i



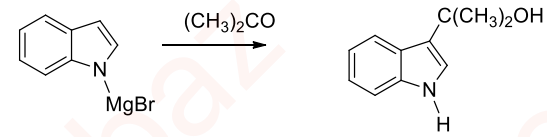
ii



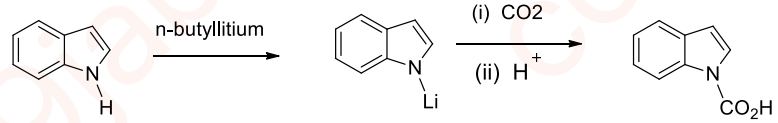
iii



iv



b.



INDOLE DERIVATIVES

1. ALKYL INDOLES

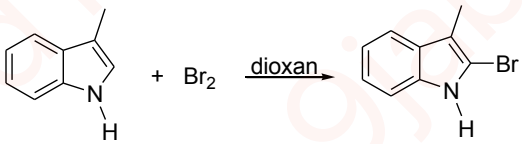
The best known alkyl indoles are the 2- and 3-methyl indoles. 2- and 3-methyl indole can be prepared by direct alkylation of indole. 2-methylindole undergoes electrophilic reactions to give 3-derivates.

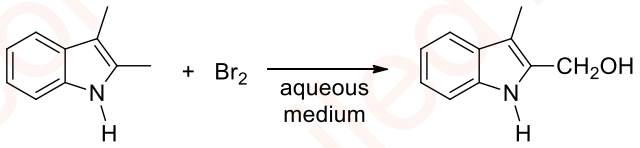
i. Nitration

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.

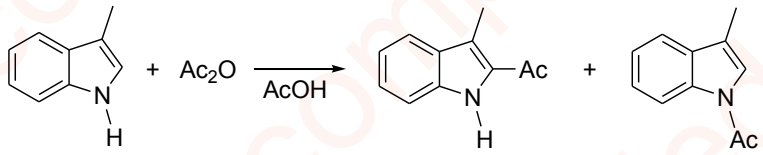




2-hydroxylmethyl-3-methylindole or
2-hydroxymethyl skatole

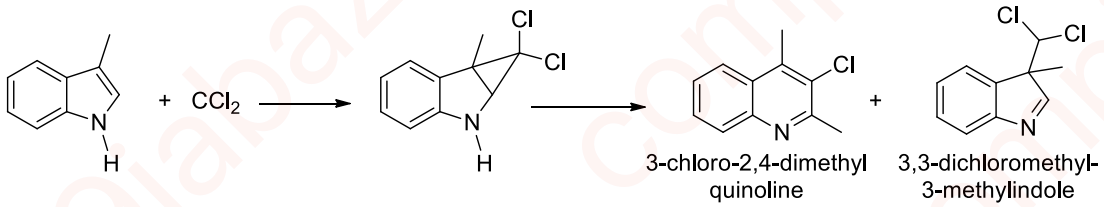
iii. **Acylation**

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

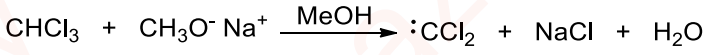


iv. **Reaction with carbene**

Skatole can also react with carbene.

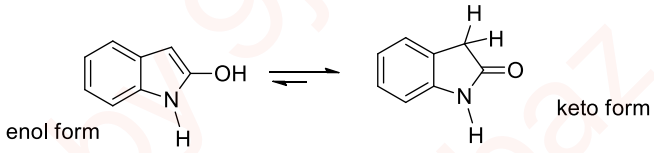


The carbene is obtained from the reaction of chloroform with sodium methoxide.

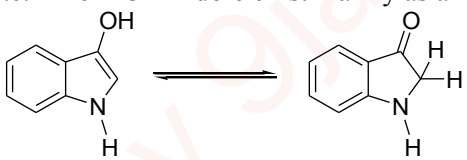


2. OXY INDOLE

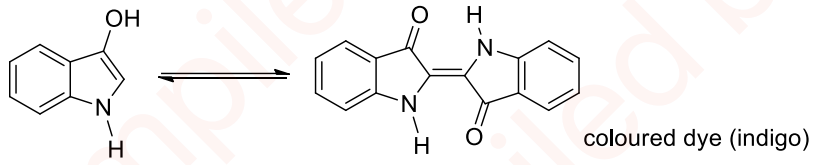
This is indole derivative that has a hydroxyl group present at position 2 or 3 of the indole ring. Indole with OH group in the benzene behaves like normal phenol. However if the hydroxyl group is on position 2 or 3, they exhibit different property e.g. 2-hydroxylindole behave more like an amide.



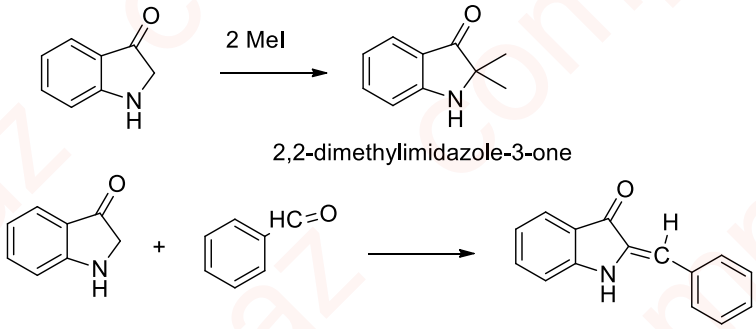
The methylene group of carbon 3 can easily be deprotonated and goes into condensation reaction with aldehyde, ketones, alkyl halides, etc. The 2-OH indole exist mainly as amide (keto form).



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.

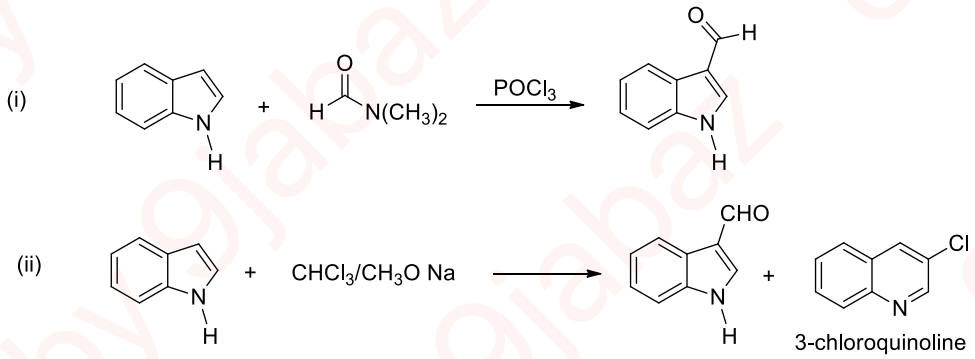


The protons at C2 of keto form are also acidic hence can be methylated at this point and it can also react with RCHO & R_2CO:

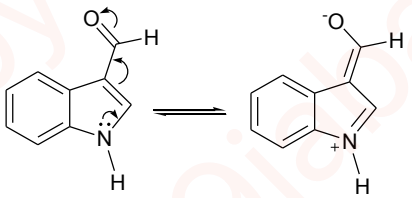


3. INDOLE ALDEHYDE

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

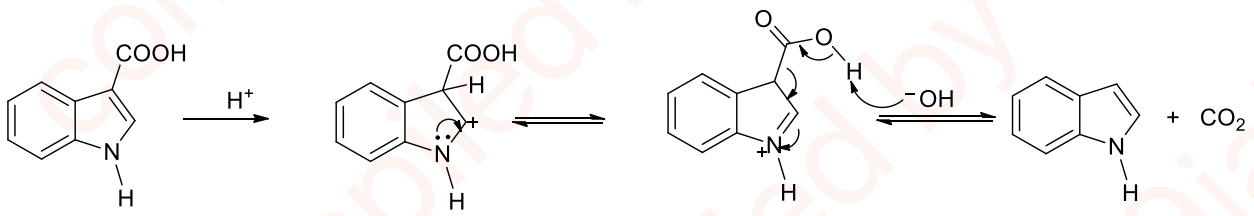


Indole-3-adehyde does not behave like typical CHO e.g. does not form cyanohydrin with hydrogen cyanide and won't undergo Cannizzaro rxn.



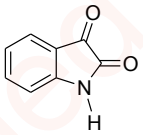
Indole Carboxylic Acids:

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

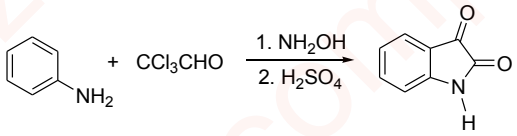


This reaction takes place in mineral acid.

ISATIN



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

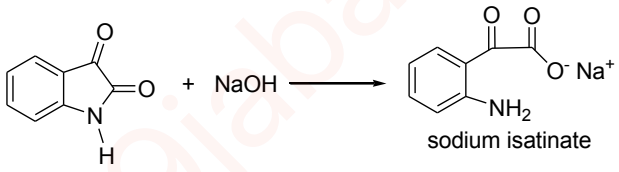


The two carbonyl groups on isatin are not identical, hence they differ in chemical properties.

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.

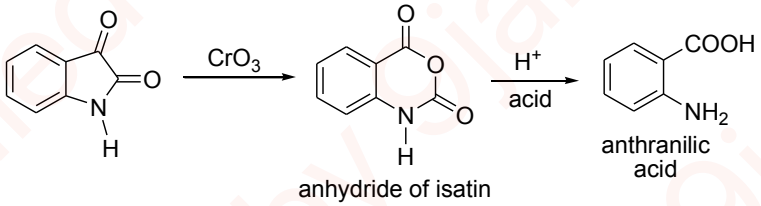
The keto group on position 2 will react with NaOH to form sodium salt of isatinic acid i.e. sodium isatinate.



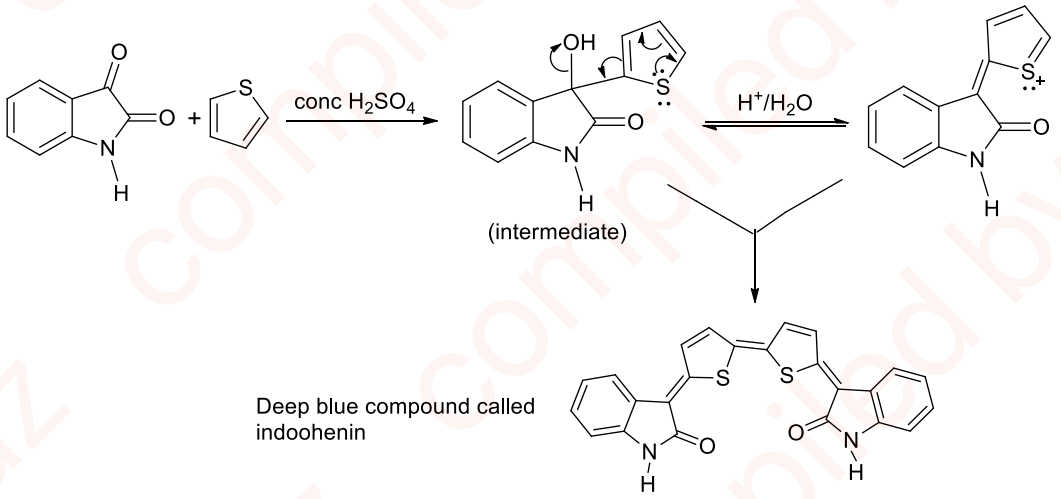
SOME OF THE REACTIONS OF ISATIN

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**



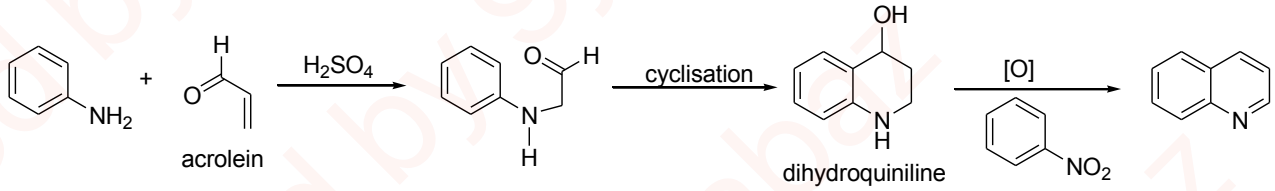
QUINOLINE

It is a fused ring heterocyclic compound (a [6+6] ring), a benzene and pyridine rings fused together. We can call it benzopyridine. It is also aromatic with 10π electrons in the cyclic system. The lone pair of electron in pyridine ring of the quinolone is not involved in aromatic stabilization so it is available for basic reaction. Therefore, it is basic.

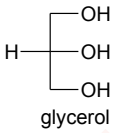
SYNTHESIS OF QUINOLINE

1. **Skraup's Synthesis**

This is the most popular method in the synthesis of quinolone and it involves heating an aryl amine which has a vacant ortho position with an α,β-unsaturated carbonyl compound in the presence of conc. H_2SO_4 and an oxidizing agent such as nitrobenzene, stanic chloride, ferric salt, $SnCl_2$ or Lewis acid.

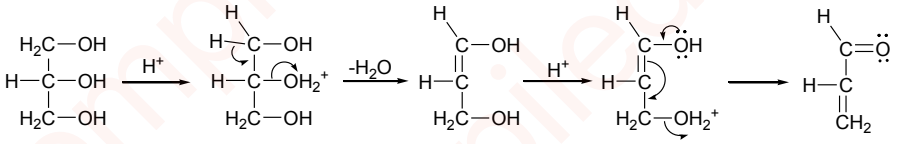


2. **From Glycerol**

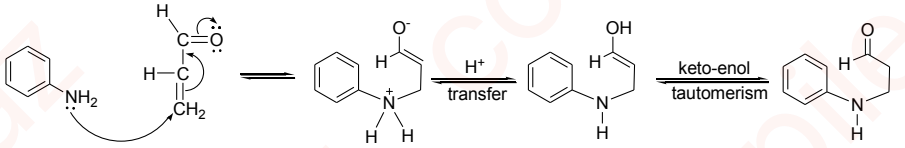


Mechanism of the reaction

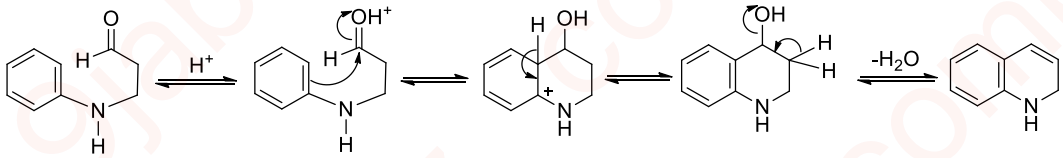
Step 1: Dehydration of glycerol to acrolein



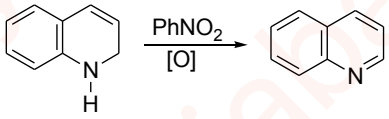
Step 2: Michael addition of aryl amine with the α,β-unsaturated carbonyl compound.



Step 3: Eletrophilic adition to the protonated carbonyl

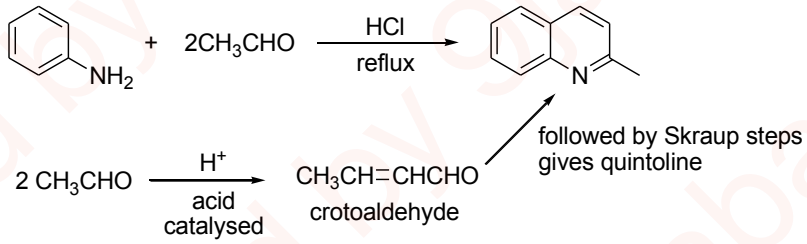


Step 4: Dehydrogenation of dihydroQ to Q by oxidising agent



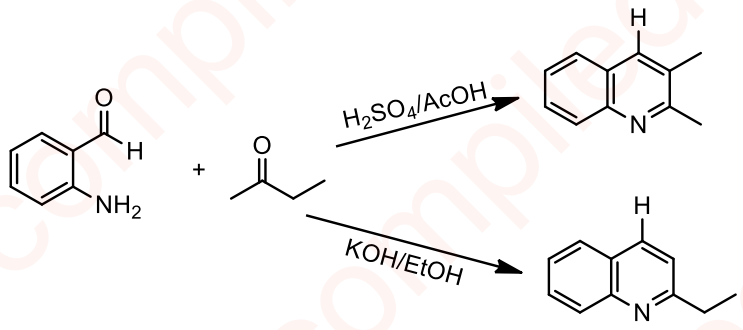
2. Dobner von Miller synthesis

It involves heating aromatic amines with an aldehyde in the presence of HCl, atmospheric air is used as the oxidant.

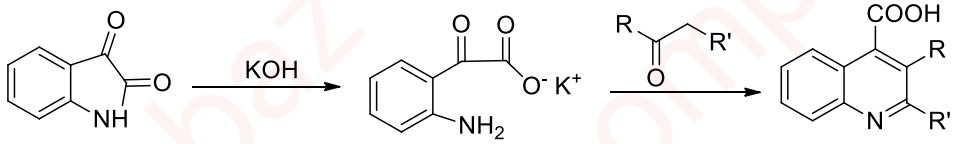


3. **Friedlaender and Pfitzinger method**

This involves the condensation of ortho-amino aromatic aldehyde or ketone with a carbonyl compound possessing α-methylene group. The reaction can either be acid or base catalysed.



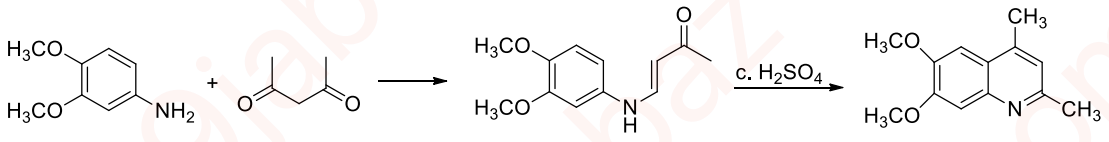
This method was modified by Pfitzinger starting with isatin and a base.



This method gives a variety of substituted quinolone, the carbonyl compound reagent must contain α-methylene group. The quinoline carboxylic acid obtained is not easily decarboxylated.

4. **From 1,3-dicarbonyl compound**

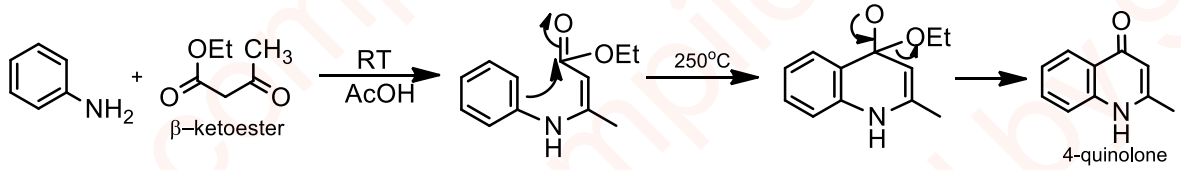
Aryl amine react with 1,3-dicarbonyl compounds or β-keto esters to give a wide range of quinoline compounds.



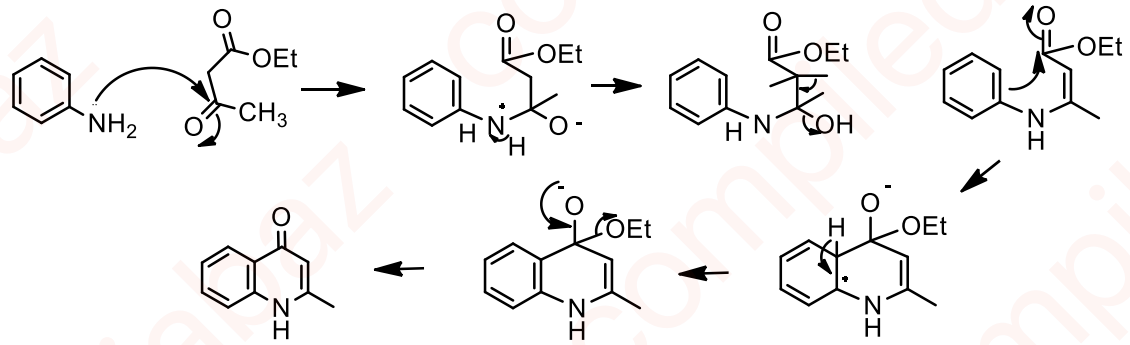
Mech:

i) Condensation followed by ii) Dehydration with conc. H_2SO_4

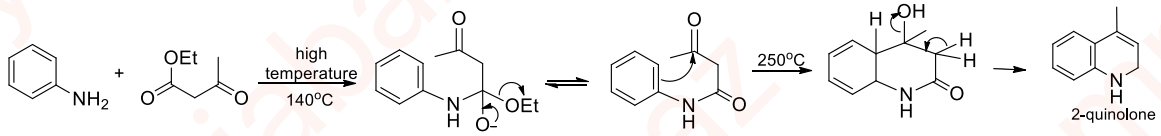
At room temperature:



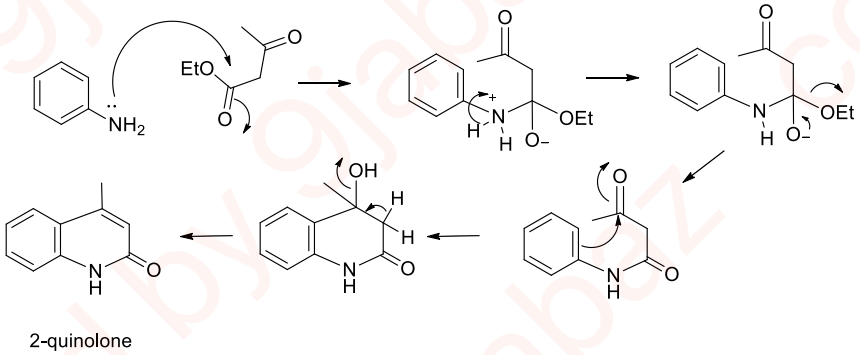
Mechanism:



At high temperature:



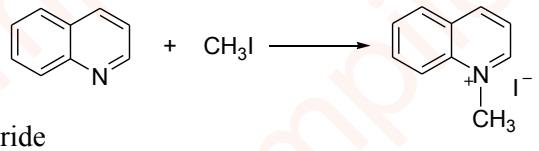
Mechanism:



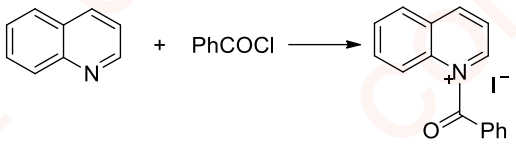
REACTIONS OF QUINOLINE

Reactions at N-atom (Basic Rxn):

The chemistry of pyridine is analogous to that of quinoline. It also react with alkyl halide to form N-alkyl quinolinium halide.

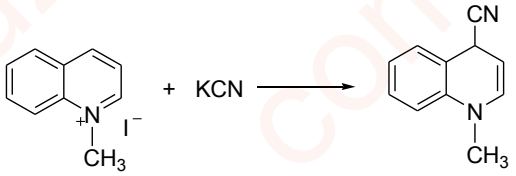


It also react with acyl chloride



N-benzoid quinolinium chloride

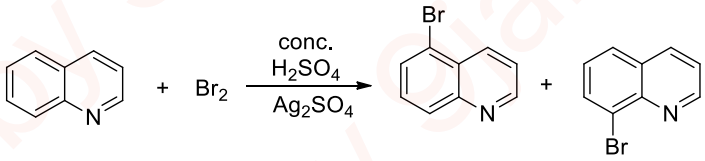
The importance of this reaction is that they are good intermediate for synthesizing derivatives of quinoline.



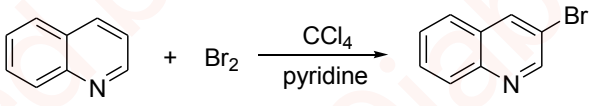
Electrophilic Substitution Reaction:

Generally, in very strong acidic medium electrophilic substitution reaction occur at position 5 and 8, where as in weak acids or non-acidic medium, substitution takes place at position 3. The reason is that in strong acid, the N-atom get protonated which deactivates the pyridine ring towards electrophilic substitution reaction.

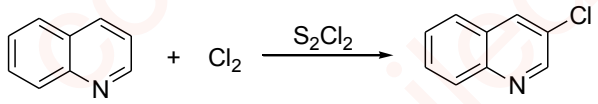
Halogenation: In the presence of conc H_2SO_4/Hg_2SO_4, bromination takes place on the benzene ring yielding 5 and 8-bromo products.



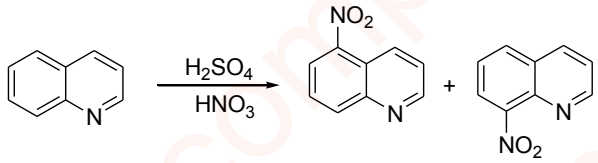
But in the presence of CCl_4/pyridine, 3-bromo is the main product.



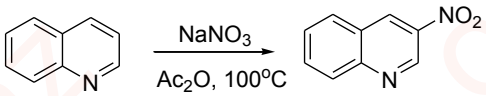
Chlorination using sulphur dicloride



Nitration using H_2SO_4/HNO_3 will give a mix of 5 and 8 nitro product

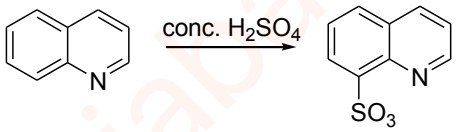


However, if sodium nitrate/Ac_2O is used at 100°C, 3-nitro product is formed



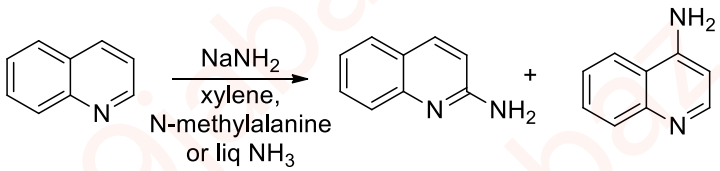
Sulphonation

Reaction with conc H_2SO_4, gives **mainly the 8-substituted** product.

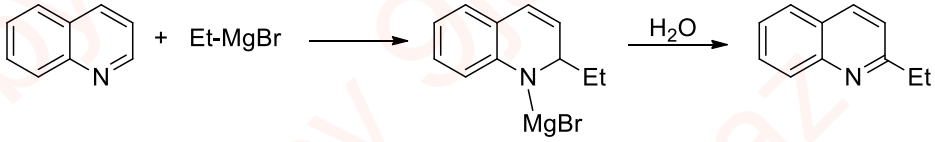


Reaction with nucleophilic reagent

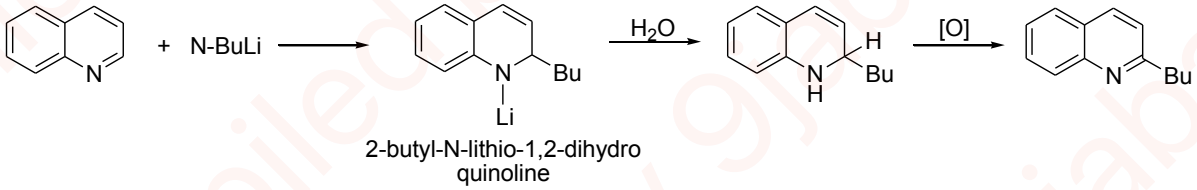
1. Chichibabin (Tschitschibabin) reaction



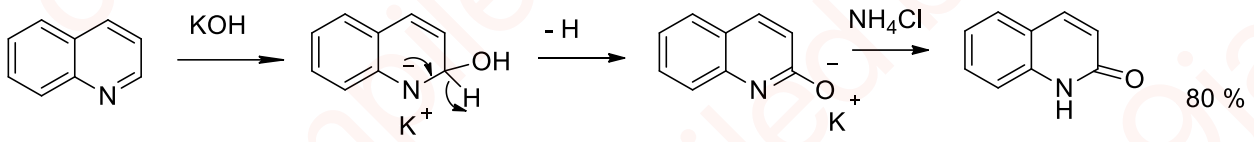
2. Reaction with Grignard reagent and organometallic compounds



With n-BuLi:



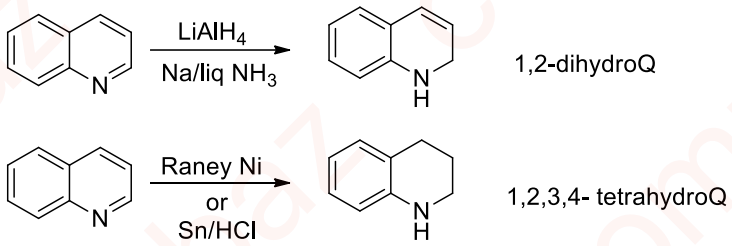
With KOH:



The hydroxyquinoline can tautomerise to the keto form, thus forming a much stabilized substrate

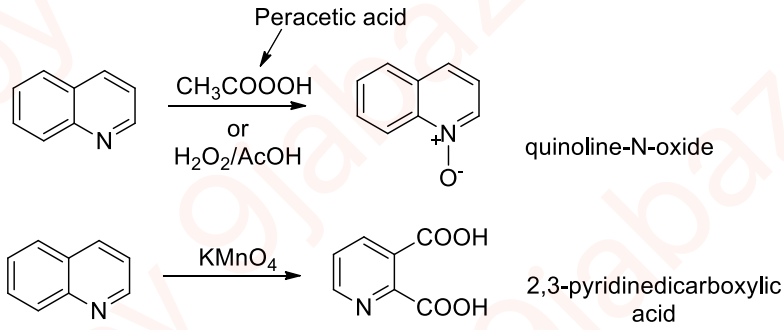
Reduction

Quinolone can be reduced to dihydro or tetrahydro product.



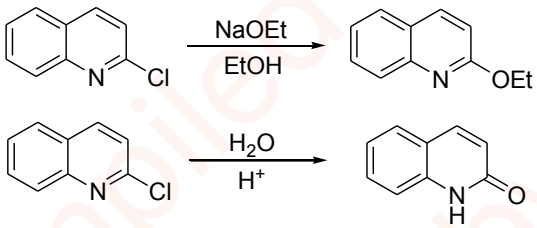
Reaction with oxidizing agent

Hydrogen peroxide and per acid usually oxidize quinolone.

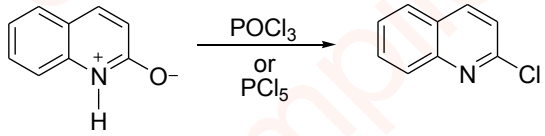


Substitution with displacement reaction

Halogen atoms on position 2 and 4 are easily replaced on reaction with other nucleophiles



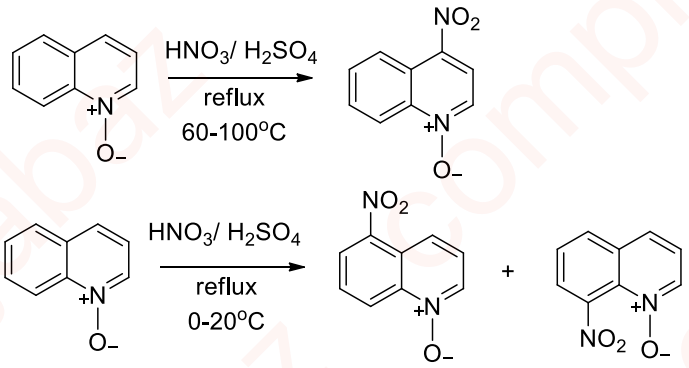
The 2 and 4-halo quinoline are readily prepared by reacting quinoline-2-oxide with $POCl_3$ or PCl_5



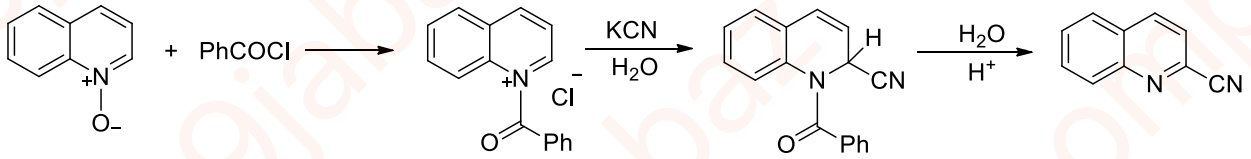
DERIVATIVES OF QUINOLINE

1. Quinoline-1-oxide: Prepared by oxidation of Q using peracid or hydrogen peroxide in acetic acid as shown above. It has similar reactions with Q with few differences:

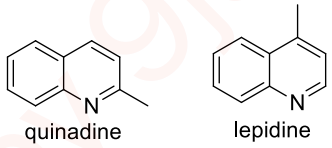
Nitration: At 0-20 ºC 5- & 8-nitroproducts are formed but at higher temp. (60-100 ºC) 4nitroproduct is mainly formed.



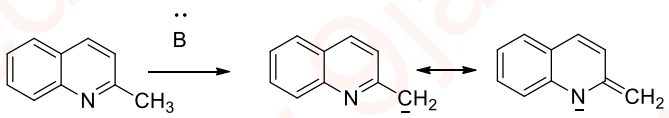
Quinoline-N-oxide react with weak and strong nucleophile:



2. Alkyl derivatives



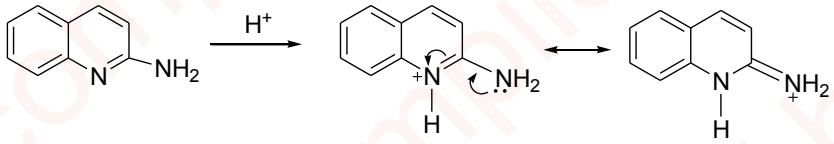
The methyl protons on 2 and 4-methyl quinolines are acidic and easily deprotonated. Both 2 & 4 meQ occur in coal tar.



Because of this quinaldine and lepidine can condense with RCHO & R_2O.

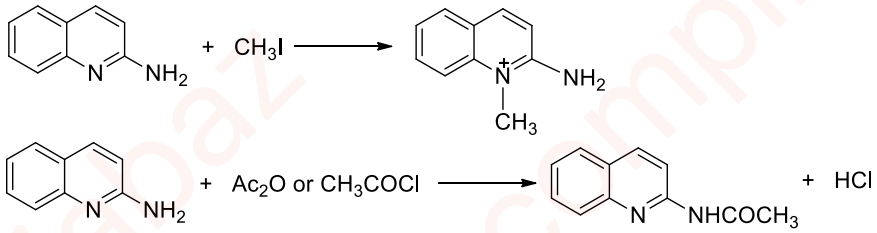
3. Amino quinolines

Both the 2 and 4-amino quinoline exist in the tautomeric forms, all amino quinolines protonate first on the ring nitrogen atom.



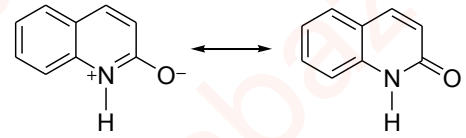
All the amino quinolilne except 2 and 4 qminoquinoline are simiar to aniline and so, they can be diazothized.

All amino quinolines are alkylated at the ring nitrogen with methyl iodide but acetylation usually takes place at the amino group.



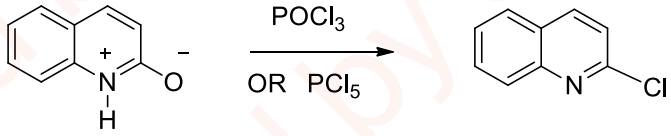
4. Hydroxyl quinoline

All the hydroxyl quinolines except 2 and 4 behaves like phenol. 2 and 4-hydroxyl quinoline do exist as tautomeric equilibrium with their keto form.



2-hydroxylquinoline (enol) 2-quinolone (keto)

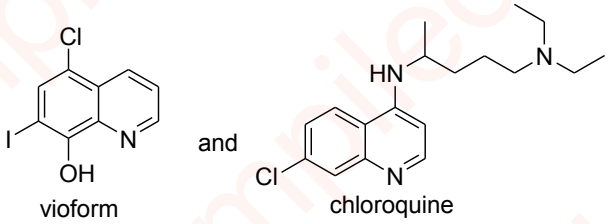
2 and 4-hydroxyl quinoline react with $POCl_3$ or PCl_5 to give the 2 & 4- halides.



The product, 2-chloroQ, is suceptible to substitution with displacement reaction

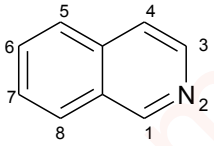
OCCURRENCE OF QUINOLINE DERIVATIVES

A number of alkaloids with quinoline nucleus are found in compounds used as drugs like chloroquine and vioform (used to treat gastrointestinal problems).



vioform chloroquine

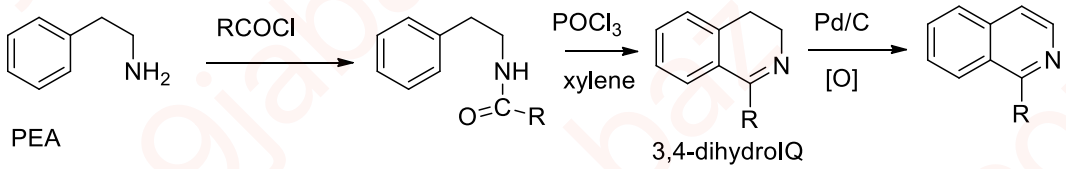
ISOQUINOLINE



SYNTHESIS

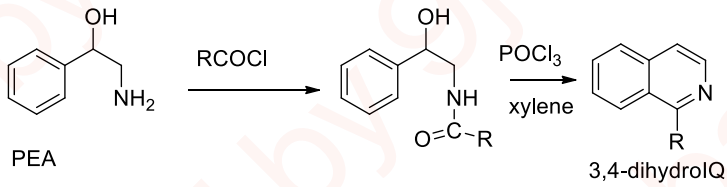
The synthesis of isoQ can be classified into two: (A) from phenyl ethyl amine (PEA) and (B) from aromatic aldehyde

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

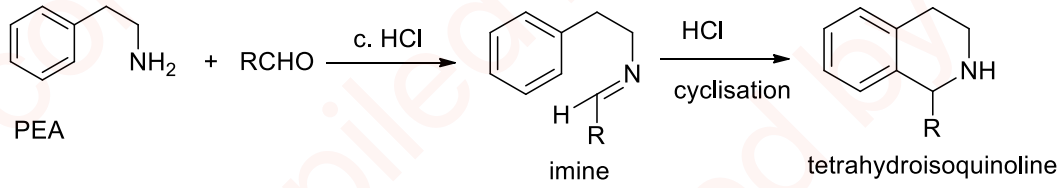
2. Pictet & Gams Modification: Uses α-hydroxy PEA



PEA 3,4-dihydroIQ

3. Pictet-Spengler synthesis

It involves the reaction between phenyl ethyl amine with an aldehyde under acidic condition.

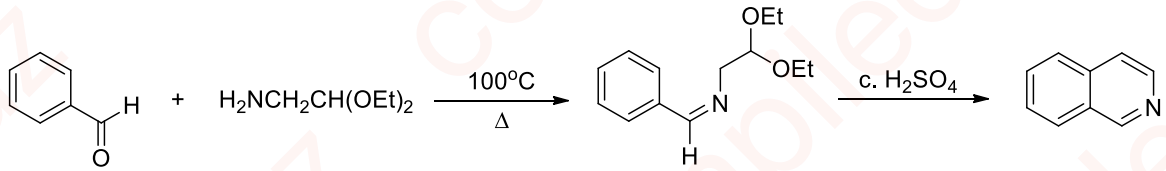


cyclisation involves protonation of the imine intermediate then intramolecular electrophilic cyclisation

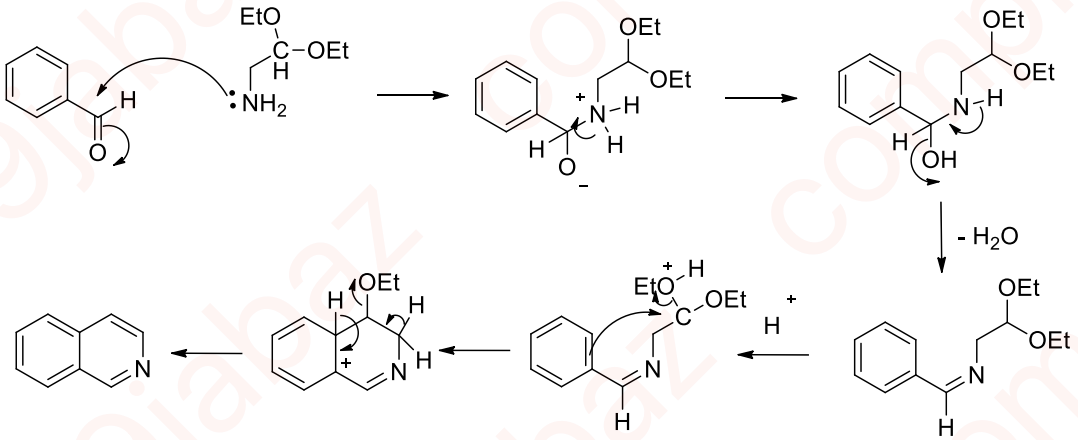
Category B: Synthesis from aromatic aldehyde

4. Pomeranz-Fritsh synthesis

This is a two stage synthesis in which aromatic aldehyde condense with amino acetal to form an aldimine, followed by cyclisation in the presence of appropriate acid i.e. conc H_2SO_4 to give isoquinoline directly.



Mechanism:

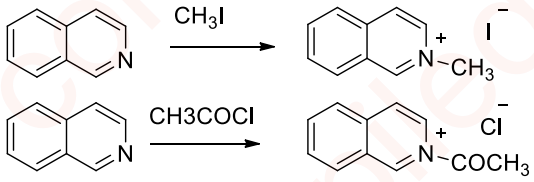


REACTIONS OF ISOQUINOLINE

Reactions with electrophilic reagents

1. **Reaction at nitrogen atom (Reactions as Base)**

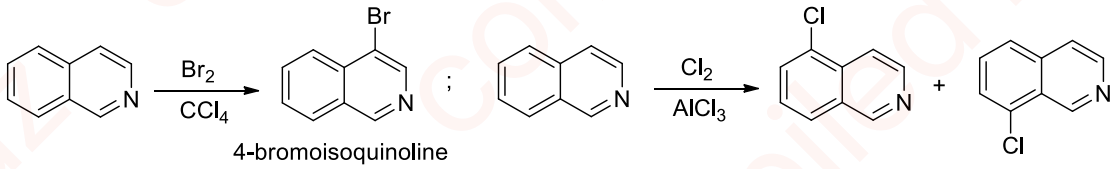
Generally, the reaction which occurs at position 1 in isoquinoline are usually an analogous to position 2 of quinolone, e.g Rxn with RX (X= sulphates): IQ gives quaternary salts



2. **Electrophilic Aromatic Substitution Reaction**

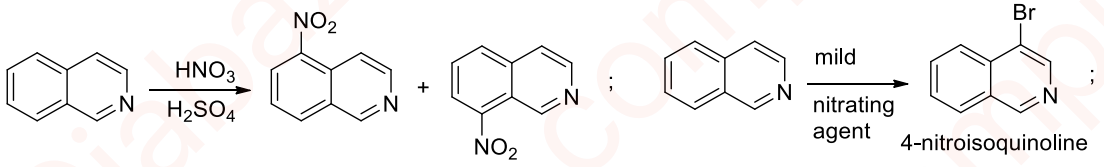
In strong acids (acidic medium), electrophilic substitution takes place at position 5 and 8 but in non-acidic or in weak acid, electrophiles attack at position 4.

(i) Halogenation



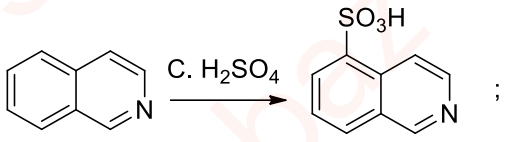
4-bromoisoquinoline

(ii) Nitration



4-nitroisoquinoline

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

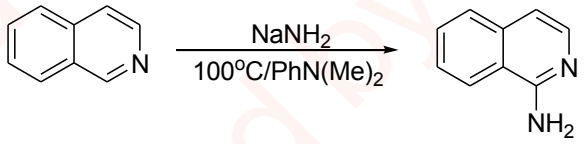


Isoquinoline-5-sulphonic acid

2. Reactions with nucleophiles

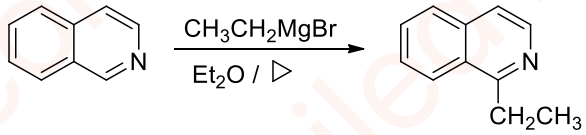
Nucleophiles attack isoquinolines at position 1 except if the position is occupied

i. **Chichibabin reaction**



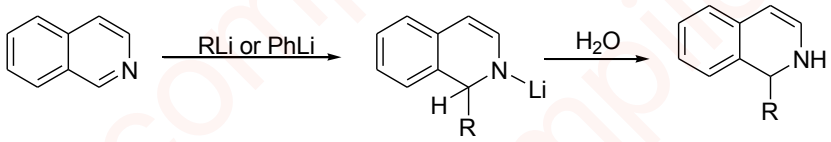
1-aminoisoquinoline

ii. **Grignard Reagent and other organometallic compound usually gives the 1-product**

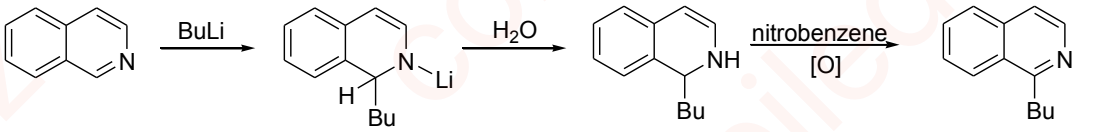


1-ethylisoquinoline

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

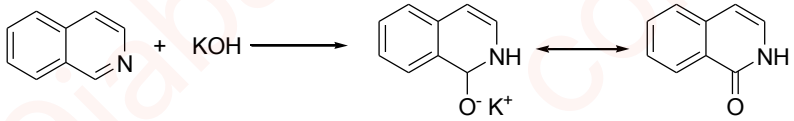


For example:



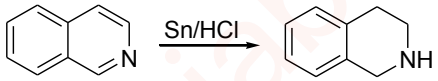
1-butylisoquinoline

iii. Hydroxylation of isoquinoline will give 1-hydroxyl product which tautomerises to the keto form.

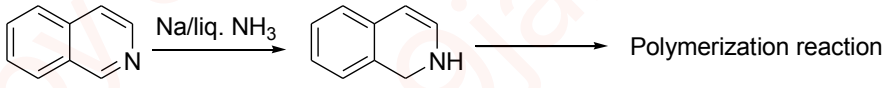


3. Reduction

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.



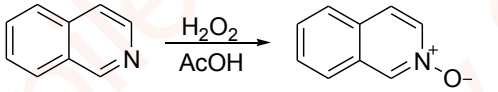
But Na/liq. NH_3 will yield 1,2-dihydro product



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

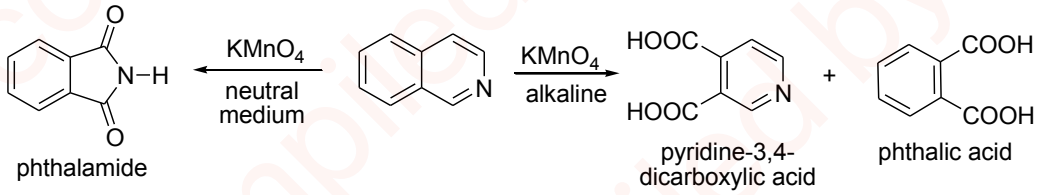
Reaction with oxidizing agent

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

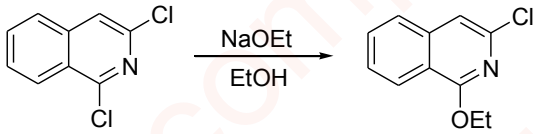


isoquinoline-N-oxide

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.

OBAFEMI AWOLOWO UNIVERSITY, ILE-IFE, NIGERIA
DEPARTMENT OF CHEMISTRY
B.Sc (Chemistry) RAIN SEMESTER EXAMINATION 2023/2024 SESSION

CHM 306: AROMATIC AND HETEROCYCLIC CHEMISTRY

Date: 25th April 2025 **TIME ALLOWED:** 30 Minutes

INSTRUCTIONS: Attempt ALL questions.

1. a. Write the structures of the following compounds (i) 1,4-dimethyl-2-ethenyl benzene (ii) ethynyl benzene (iii) dichlorodiphenyltrichloroethane

b. (i) Which of the oxidative products of coal can yield aromatic hydrocarbons?
(ii) Outline by chemical equations only, the synthesis of benzoic acid from acetophenone.

c. Explain by chemical equations, how to obtain bromobenzene from isopeopyl benzene?

OBAFEMI AWOLOWO UNIVERSITY, ILE-IFE, NIGERIA
DEPARTMENT OF CHEMISTRY
BSc, Degree (Chemistry) Examination Part III
CHM 306: Nitrogen Heterocyclic Compounds
Mid Rain Semester Examination 2023/2024 Session Time: 30 mins. Tuesday 13th May 2025

INSTRUCTION: Attempt all questions.

1. Give the structure of the following nitrogen heterocyclic compounds
   (i). Imidazole; (ii). 3-methylindole (skatole); (iii). Pyridine-3-carboxylic acid (nicotinic acid); (iv). 2-aminoquinoline and (v). isoquinoline
2. Write equation for the following reactions and give expected product(s) of the reactions in the equation:

(i). Ethylmagnesim bromide reacts with pyrrole at its N-atom to form an intermediate, which was later treated with ethylbromide.
(ii). 3-methylpyrrole treated with potassium permanganate
(iii). Two moles of acroleine (2-propenal) react with one mole of ammonia
(iv). Ethanal was made to react with phenylhyrazine, the product formed reacted with $ZnCl_2$ (a lewis acid) at about 180 °C to give one main compound

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KMnO4