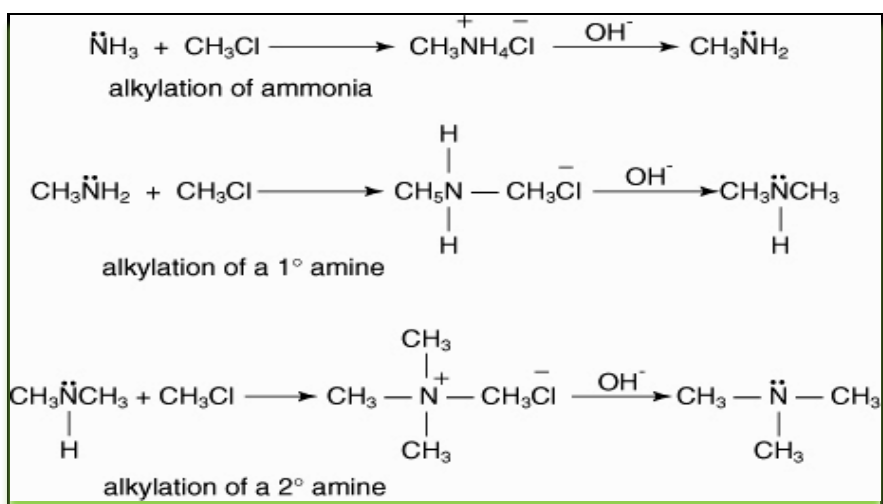


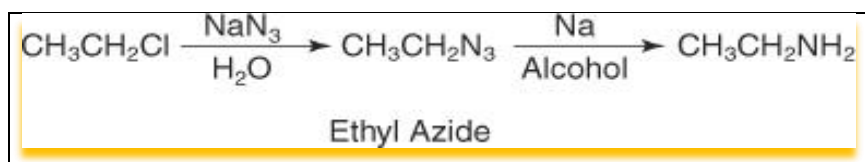
Aromatic and Aliphatic Amines

1. Preparation: Amines are prepared by the alkylation of ammonia, Gabriel synthesis, reduction of amides, reduction of nitriles, reduction of nitro-compounds, and reductive amination of aldehydes and ketones.

❖ **Alkylation of ammonia (Hoffmann's method):** Ethanolic solution of ammonia reacts with an alkyl halide to form primary amine which can further react with the alkyl halide to form a secondary amine that can further react to form a tri-substituted amine (i.e., 3° amine). Therefore a mixture of three classes of amines is obtained, alongwith some quaternary ammonium salts. The order of reactivity of halides is $RI > RBr > RCl$ and follow the S_N2 pathway.

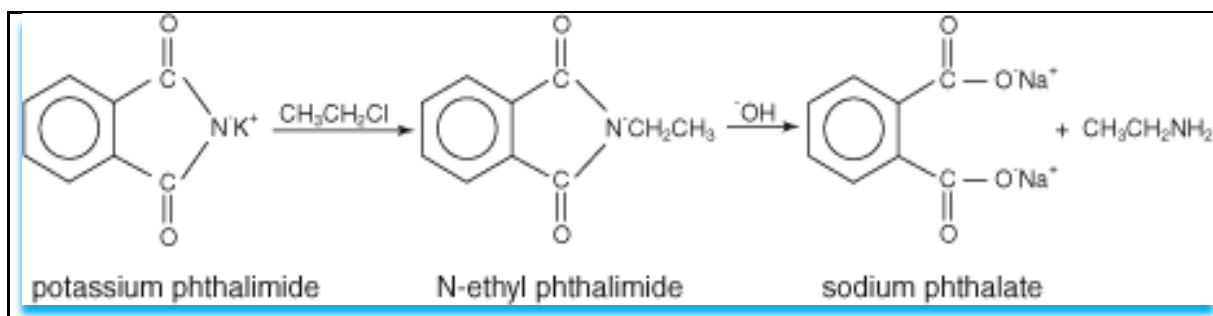


❖ **Reduction of alkylazides:** A primary amine can be best prepared from alkyl azide by reduction with Na /alcohol or Zn/CH_3COOH .

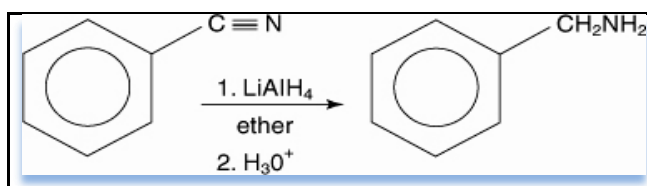


❖ **Gabriel synthesis:** In Gabriel synthesis, phthalimide is converted into its salt potassium phthalimide by the reaction of ethanolic KOH . That salt on heating with an alkyl halide

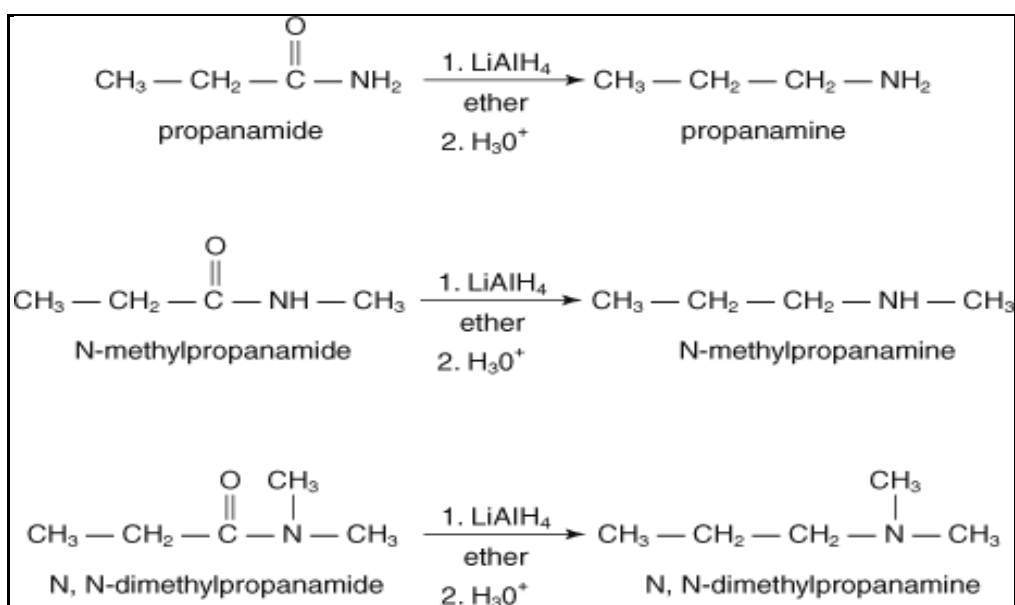
produces N-alkyl phthalimide. This can be hydrolyzed by aqueous acids or bases into the primary amine and phthalic acid.



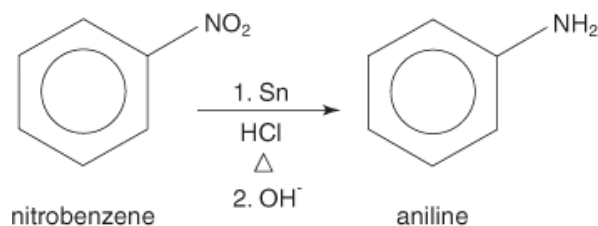
- ❖ **Reduction of nitriles:** Nitriles can be reduced by lithium aluminum hydride (LiAlH_4) or Na /ethanol to primary amines.



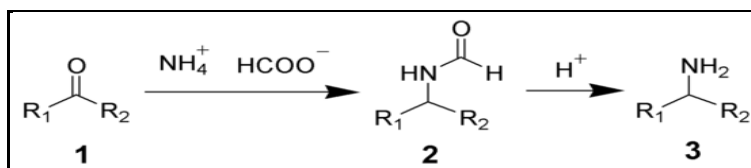
- ❖ **Reduction of amides:** Primary amines can be prepared from amides by reduction with lithium aluminum hydride, while N-substituted and N, N-disubstituted amides give secondary and tertiary amines, respectively.



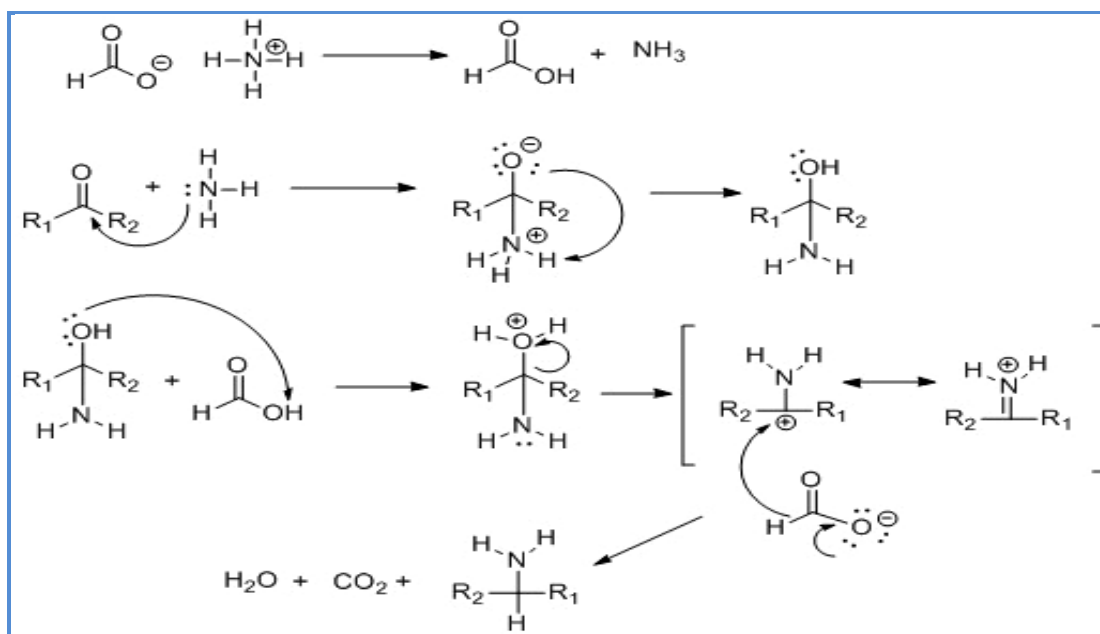
- ❖ **Reduction of nitrocompounds:** Aromatic amines are normally prepared by reduction of the corresponding aromatic nitrocompounds with metal/acid or Ni/H₂ or LAH.



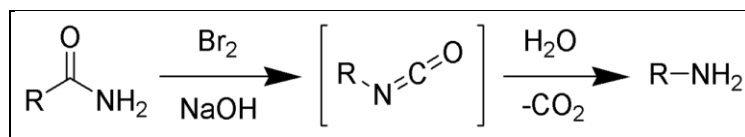
- ❖ **Reductive amination of aldehydes and ketones (Leuckart reaction):** The Leuckart reaction involves the conversion of aldehydes or ketones to amines by reductive amination in the presence of heat. The reaction takes place in two pathways: one using ammonium formate and the other using formamide as the reducing agent. It requires high temperatures, usually between 120 and 130°C, although under the presence of formamide, the temperature can be greater than 165 °C.



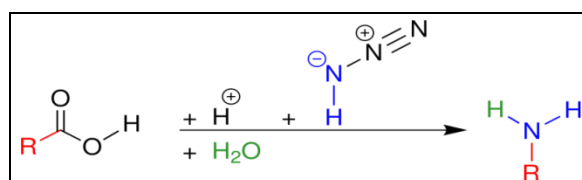
Mechanism:



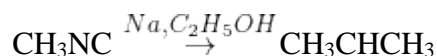
- ❖ **Hofmann rearrangement:** The Hofmann rearrangement is the organic reaction of a primary amide to primary amine with one fewer carbon atom



- ❖ **Schmidt rearrangement:** Carboxylic acid reacts with hydrazoic acid in presence of acid to give amine.

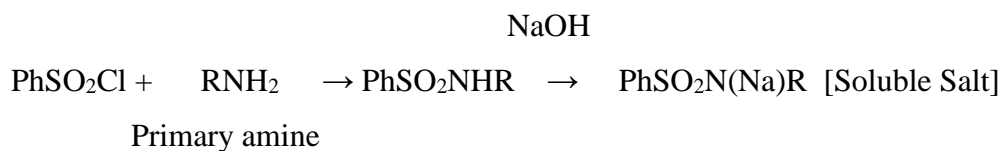


- ❖ **Secondary amine from cyanamide:** A convenient method for the preparation of secondary amines which are not contaminated with primary or tertiary amines is the reaction of cyanamide with alkyl halides to *N,N*-dialkylcyanamides which can easily be hydrolyzed by acid or alkali to dialkylamines.
- ❖ **Reduction of alkyl isocyanides** with Na/C₂H₅OH gives 2° amines

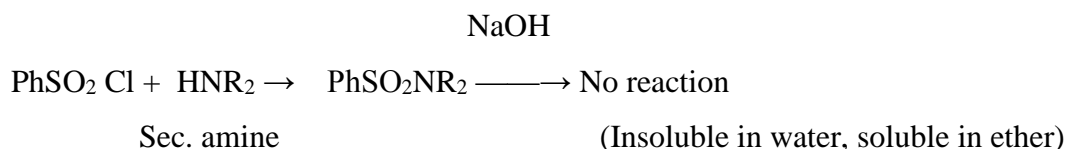


2. Separation and identification between primary, secondary and tertiary amine using Hinsberg reagent: (Hinsberg's method):

Separation of primary, secondary and tertiary amines is carried out by treating the mixture of three amines with benzene sulphonyl chloride, i.e., **Hinsberg's reagent** (PhSO₂Cl). The solution is then made alkaline with aqueous NaOH to form sodium salt of monoalkyl benzene sulphonamide (soluble in water).



The secondary amine forms N,N-dialkyl benzene sulphonamide which does not react to form any salt with NaOH and remains as insoluble in alkali solution.

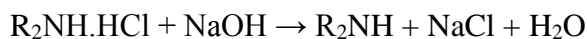
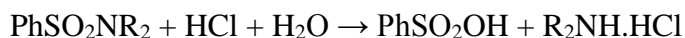


Tertiary amine does not react.

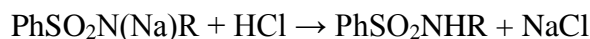


The above alkaline mixture of the amines is extracted with ether. Two distinct layers are observed where lower layer i.e., the aqueous layer contains sodium salt of N-alkyl benzene sulphonamide (primary amine) and upper layer i.e., the ether layer consists of N,N-dialkyl benzene sulphonamide (secondary amine) and tertiary amine.

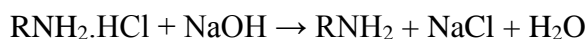
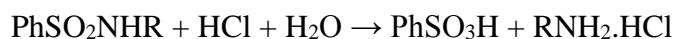
Two layers are separated using separating funnel. The upper layer is fractionally distilled. One fraction obtained is tertiary amine and the other fraction is treated with concentrated HCl to recover secondary amine hydrochloride which gives free secondary amine on distillation with NaOH.



The aqueous layer is acidified and hydrolysed with dilute HCl. The hydrochloride formed is then distilled with NaOH when primary amine distils over.



Sulphonamide of primary amine

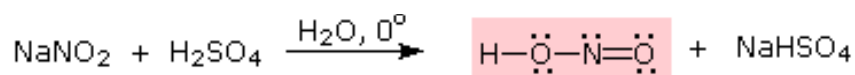


3. Reaction:

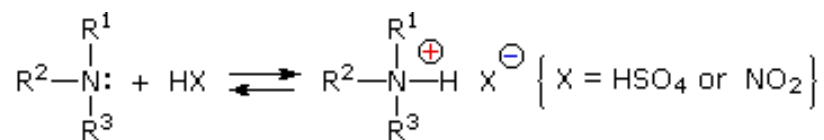
❖ **Reaction with Nitrous Acid:** Aliphatic amines react with nitrous acid (HNO₂) in a fashion that provides a useful test to distinguish the primary, secondary and tertiary amine.

1°-Amines + HONO (cold acidic solution)	Nitrogen Gas Evolution from a Clear Solution
2°-Amines + HONO (cold acidic solution)	An Insoluble Oil (N-Nitrosamine)
3°-Amines + HONO (cold acidic solution)	A Clear Solution (Ammonium Salt Formation)

Nitrous acid (pK_a = 3.3) is prepared immediately before use in the following manner due to its instability

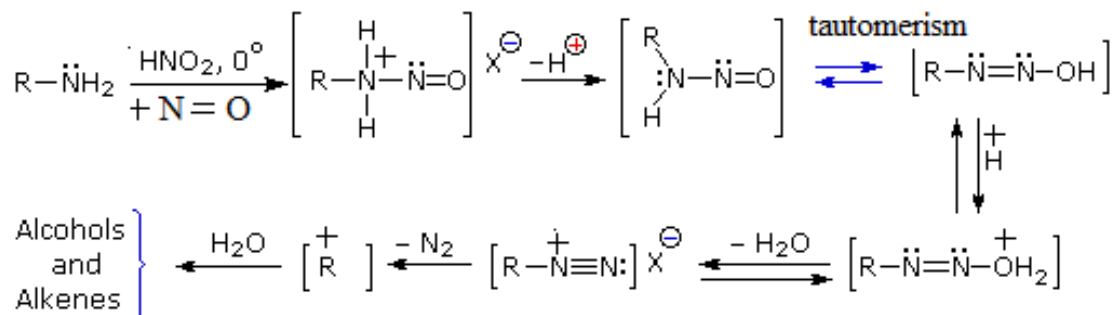


Under the acidic conditions of this reaction, all amines undergo reversible salt formation:

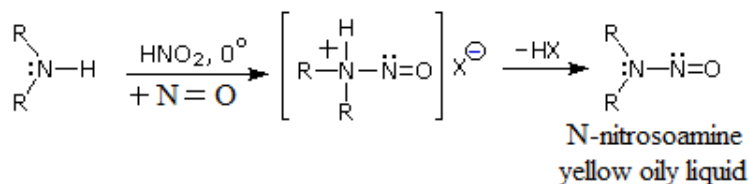


This happens with 3°-amines, and the salts are usually soluble in water. The reactions of nitrous acid with 1°- and 2°- aliphatic amines may be explained by considering their behavior with the nitrosonium cation, NO⁽⁺⁾, an electrophile, produced from nitrous acid solutions.

Primary Amines

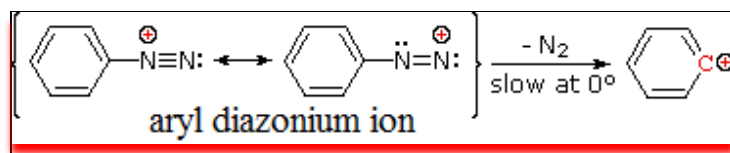


Secondary Amines

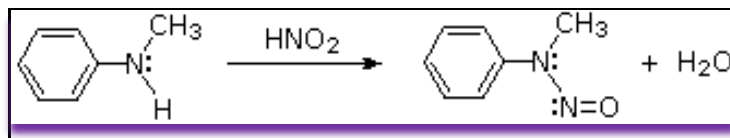


The distinct behavior of 1°, 2° & 3°-aliphatic amines is an instructive challenge to our understanding of their chemistry, but is of little importance as a synthetic tool. The S_N1 product mixtures from primary amines are difficult to control, and rearrangement is common when branched primary alkyl groups are involved. The N-nitrosamines formed from 2°-amines are carcinogenic, and are not generally useful as intermediates for subsequent reactions.

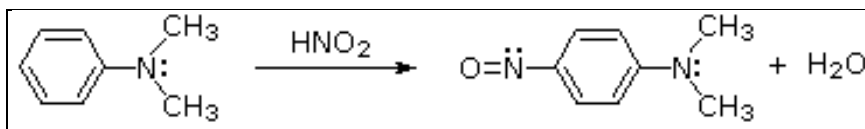
Aryl Amines: 1°-aryl amine reacts with nitrous acid to form relatively stable diazonium. Loss of nitrogen from it is slower than 1° aliphatic amines because the C-N bond is stronger due to attaining double bond character. Aqueous solutions of these diazonium ions have sufficient stability at 0° to 10 °C that they may be used as intermediates in a variety of nucleophilic substitution reactions.



2°-Aryl Amines: 2°-Aryl amines on reaction with nitrous acid give N-nitrosamine derivative.

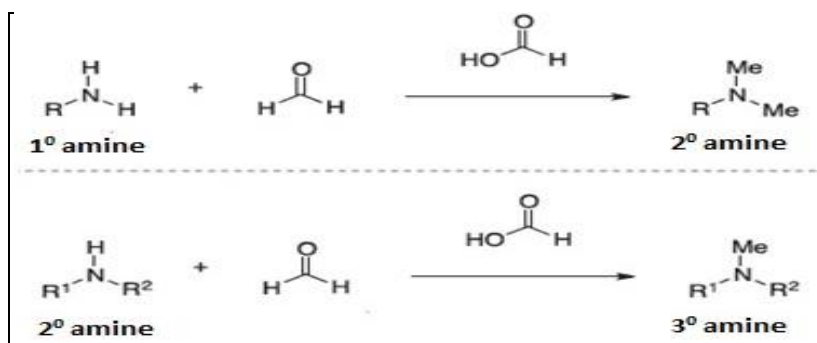


3°-Aryl Amines: 3°-aryl amines may undergo aromatic ring nitrosation at sites ortho or para with respect to -NH₂ group. The nitrosonium cation is not sufficiently electrophilic to react with benzene itself, or even toluene, but highly activated aromatic rings such as amines and phenols are capable of substitution. Of course, the rate of reaction of nitrosonium cation at nitrogen is greater than that of ring substitution, as shown in the previous example.

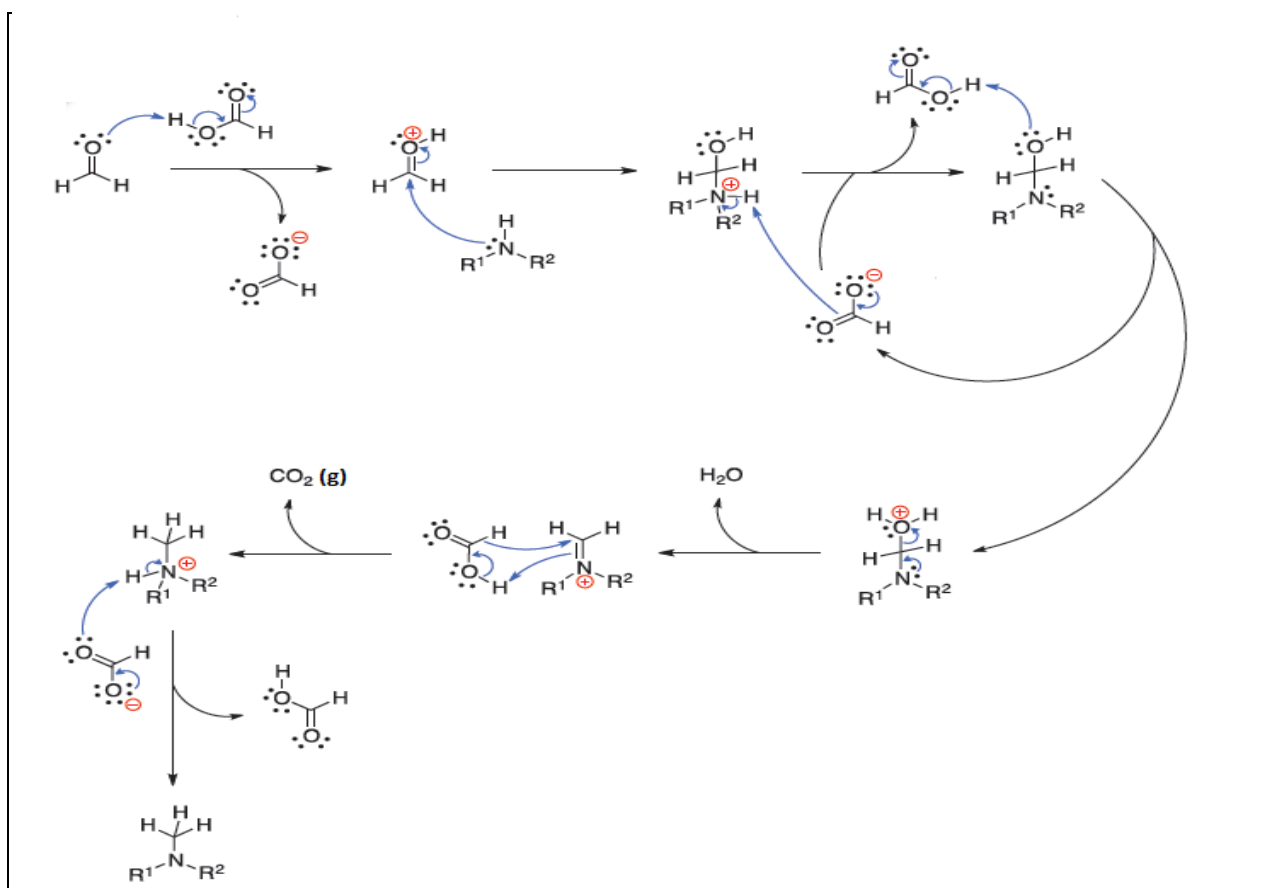


❖ **Eschweiler-Clarke methylation:**

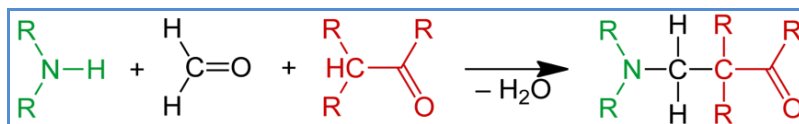
The Eschweiler-Clarke methylation involves the conversion of a primary or secondary amine to a tertiary amine using formaldehyde and formic acid. The reaction proceeds through iminium ion intermediate.



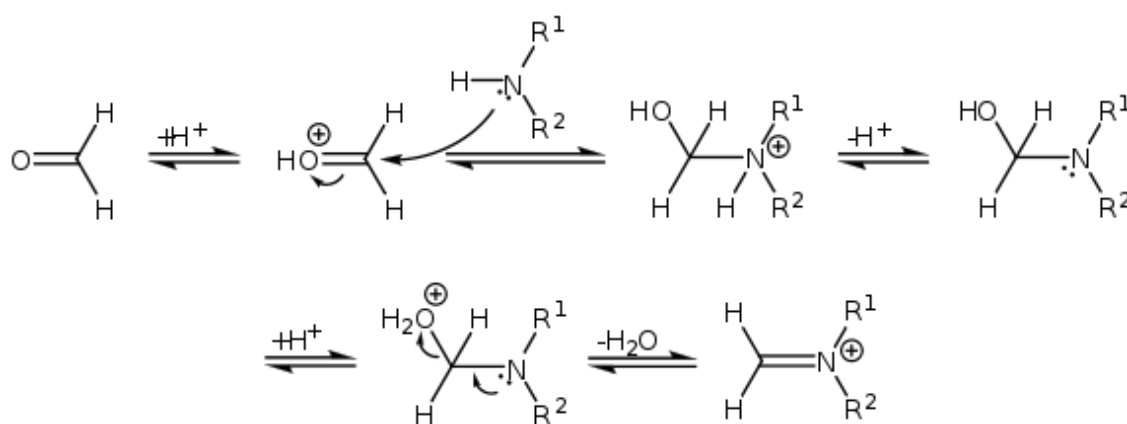
Mechanism:



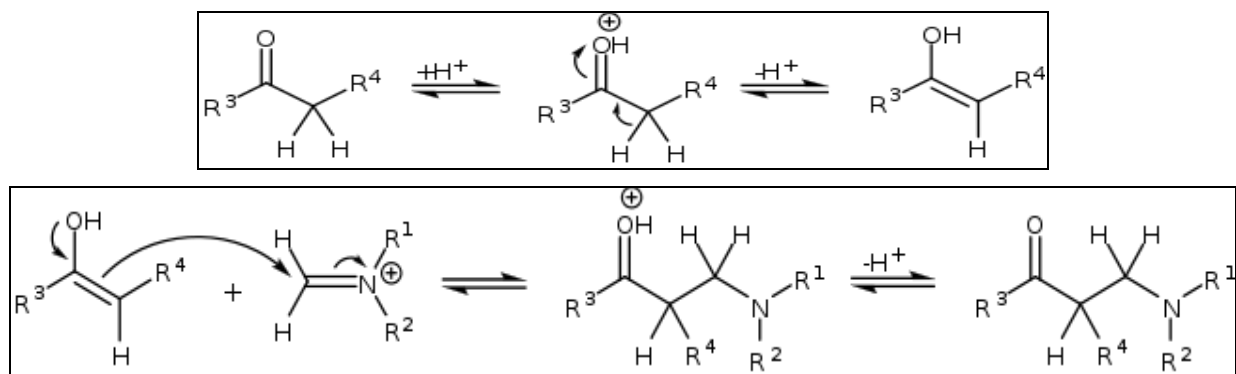
❖ **Mannich Reaction:** This reaction is the multi-component condensation of a non-enolisable aldehyde, a primary or secondary amine and an enolisable carbonyl compound to lead β -amino carbonyl compound also known as a Mannich base, using an acid or base catalyst.



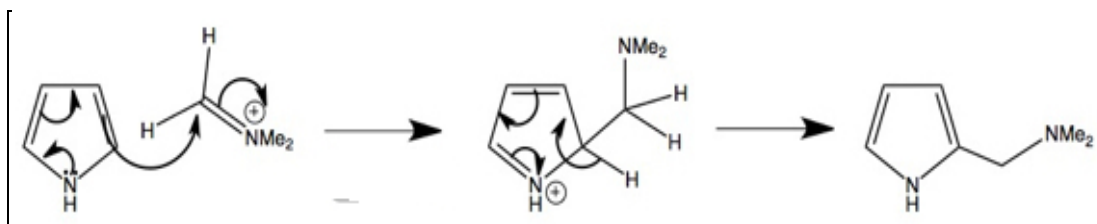
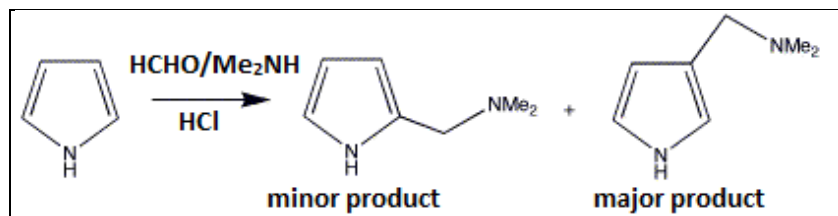
Mechanism: The mechanism of this reaction starts with the formation of an iminium ion from the amine and the formaldehyde.



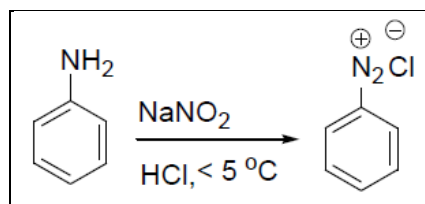
The compound containing the carbonyl functional group can tautomerize to the enol form, after which it can attack the iminium ion.



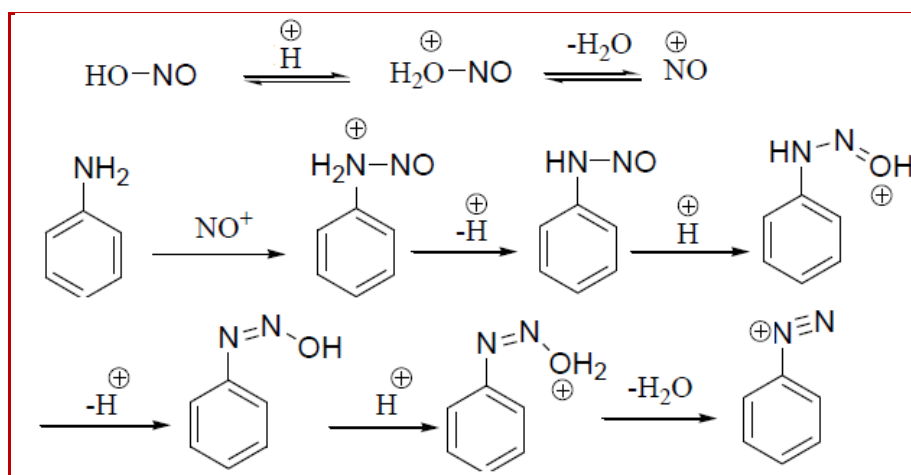
Mannich reaction of Pyrrole:



- ❖ **Diazo-coupling reaction:** Addition of aqueous solution of NaNO₂ to a solution of amine hydrochloride in presence of excess of HCl which is cooled by an ice-bath such that the temperature of the reaction remains below 5⁰C leads to diazotization of primary aromatic amine.



Mechanism:



If aromatic nucleus contain electron withdrawing groups then the aromatic amines are difficult to diazotize because the nucleophilicity of the amino-nitrogen is reduced by the conjugation of unshared electron pair with pi electrons of aromatic nucleus.

