# *Notes on Amines*

*By*

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Amines are derivatives of ammonia in which one or more hydrogen atoms have been replaced by alkyl, cycloalkyl, allyl or aryl groups. Amines are classified as 1º, 2º and 3º amines according to the number of hydrogen atoms replaced by the alkyl groups. Thus, the general formula of primary, secondary and tertiary amines may be written as $RNH_2$, $R_2NH$, and $R_3N$, respectively.

## General methods of preparation:

**1. Hofmann's method:** When a mixture of an alkyl halide and an ethanolic solution of ammonia is heated in a sealed tube, a mixture of three kinds of amine salts, 1º, 2º and 3º, and quaternary ammonium halide is obtained. The amine salts obtained by the process are converted to amines by distilling with strong alkali.

$$RX + NH_3 \longrightarrow RNH_2 + HX \longrightarrow R\overset{+}{N}H_3X^-$$

$$RNH_2 + RX \longrightarrow R_2NH + HX \longrightarrow R_2\overset{+}{N}H_2X^-$$

$$R_2NH + RX \longrightarrow R_3N + HX \longrightarrow R_3\overset{+}{N}HX^-$$

$$R_3N + RX \longrightarrow R_4\overset{+}{N}HX^-$$

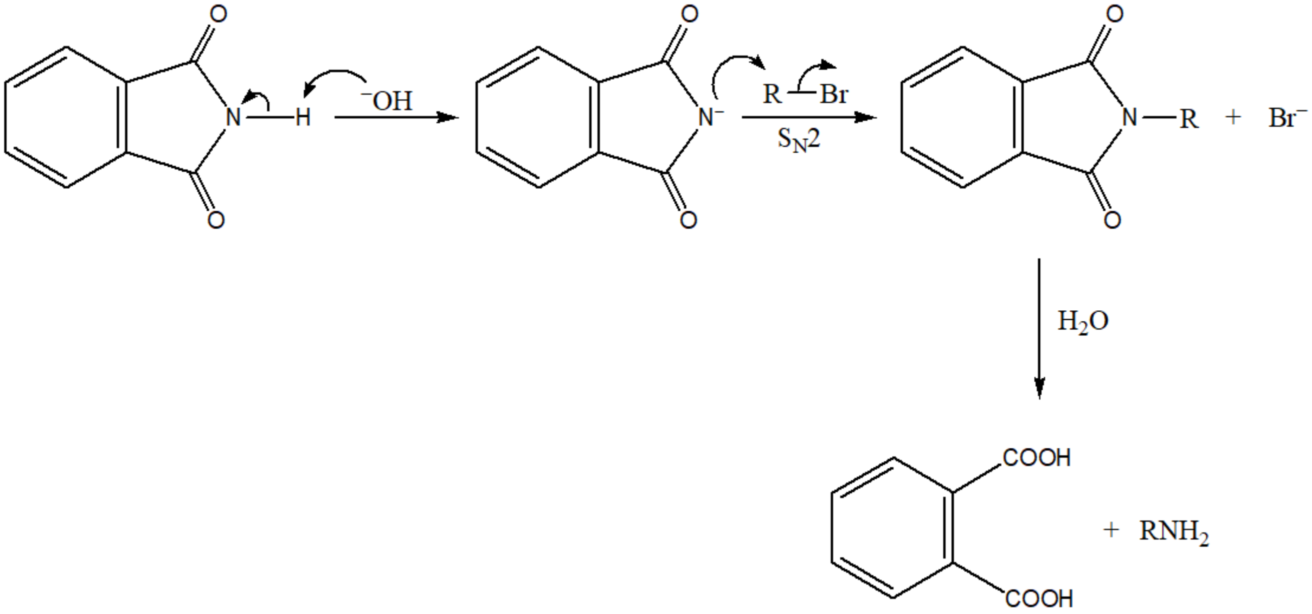
In many cases, a good yield of primary amine may be obtained by using a large excess of ammonia, and a good yield of tertiary amine by using alkyl halide in slight excess. The reactivity order of alkyl groups and halides are: methyl> 1º> 2º> 3º and iodide> bromide> chloride. In a modified process, a mixture of three types of amines may be prepared by heating alcohol and ammonia under pressure in presence of catalyst.

$$ROH + NH_3 \longrightarrow RNH_2 + H_2O$$

$$RNH_2 + ROH \longrightarrow R_2NH + H_2O$$

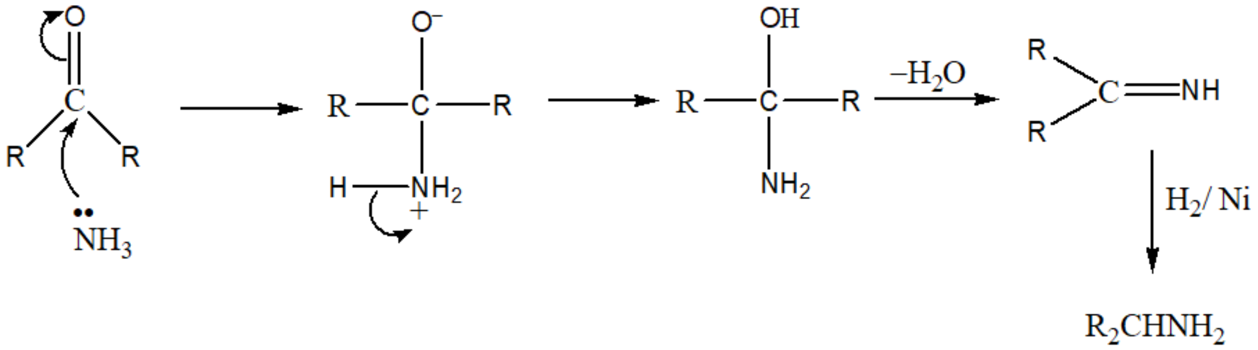
$$R_2NH + ROH \longrightarrow R_3N + H_2O$$

**2. Gabriel phthalimide synthesis:** In this method, phthalimide is converted by means of ethanolic potassium hydroxide into its salt, potassium phthalimide which on heating with an alkyl halide gives N-alkylphthalimide. This is then hydrolysed to phthalic acid and a primary amine by heating with hydrochloric acid under pressure or by refluxing with potassium hydroxide solution.



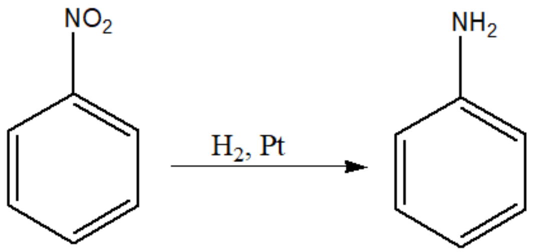
**3. Reductive amination of carbonyl compounds:** When a mixture of aldehyde or ketone and a large excess of ammonia and hydrogen is passed over Raney Ni at 40-50 ºC under 20-150 atmospheric pressure, a primary amine is formed. The reaction may also be carried out at 3 atmospheres in presence of excess ammonium chloride and Adam’s platinum catalyst.

$$R_2C{=}O + NH_3 + H_2 \xrightarrow{Ni} R_2CHNH_2 \xrightarrow{R_2C=O} (R_2CH)_2NH \xrightarrow{R_2C=O} (R_2CH)_3N$$



**4. Reduction of nitro compounds:** Nitro compounds can be reduced in two general ways: (a) by catalytic hydrogenation using molecular hydrogen, (b) by chemical reduction usually by a metal and acid. Hydrogenation of nitro compounds to amine takes place when a solution of nitro compound in alcohol is shaken with finely divided nickel or platinum under hydrogen gas. Chemical reduction is most often carried out by adding hydrochloric acid to a mixture of nitro compound and a metal, usually granulated tin.

$$RNO_2 + 3H_2 \xrightarrow{Ni} RNH_2 + 2H_2O$$



Reduction of nitro compounds is an essential step in synthesizing a number of aromatic compounds.

$$\begin{tikzcd}
 & & & & ArX \\
ArH \arrow[r] & ArNO_2 \arrow[r] & ArNH_2 \arrow[r] & ArN_2^+ \arrow[ur] \arrow[r] \arrow[dr] \arrow[ddr] & ArOH \\
 & & & & ArCN \\
 & & & & \text{azo dyes}
\end{tikzcd}$$

**5.** By reduction of alkyl cyanides.

$$\mathrm{RCN} + 4[\mathrm{H}] \xrightarrow{\mathrm{Na/\ C_2H_5OH}} \mathrm{RCHNH_2}$$

**6.** By reduction of amides with sodium and ethanol or catalytically.

$$\mathrm{RCH{=}NOH} + 4[\mathrm{H}] \longrightarrow \mathrm{RCH_2NH_2}$$

$$\mathrm{R_2C{=}NOH} + 4[\mathrm{H}] \longrightarrow \mathrm{R_2CHNH_2}$$

**7. Leuckart reaction:** The reductive amination of aldehydes or ketones by ammonium formate or formamide is called Leuckart reaction.

$$\mathrm{RCOR'} + \mathrm{HCO_2NH_4} \longrightarrow \mathrm{RR'CHNH_2} + \mathrm{CO_2} + \mathrm{NH_3} + \mathrm{H_2O}$$

**8.** By hydrolysis of alkyl isocyanates with boiling alkali.

$$\mathrm{RNCO} + 2\mathrm{KOH} \longrightarrow \mathrm{RNH_2} + \mathrm{K_2CO_3}$$

**9. Hofmann’s degradation reaction:** This is generally the most convenient method of preparing primary amines. The conversion of carboxamide to a primary amine with a C atom less by the action of alkali and halogen (chlorine or bromine) or hypohalides (NaOCl or NaOBr) is known as Hofmann degradation of amide.

$$\mathrm{RCONH_2} + \mathrm{Br_2} + 4\mathrm{KOH} \longrightarrow \mathrm{RNH_2} + 2\mathrm{KBr} + \mathrm{K_2CO_3} + 2\mathrm{H_2O}$$

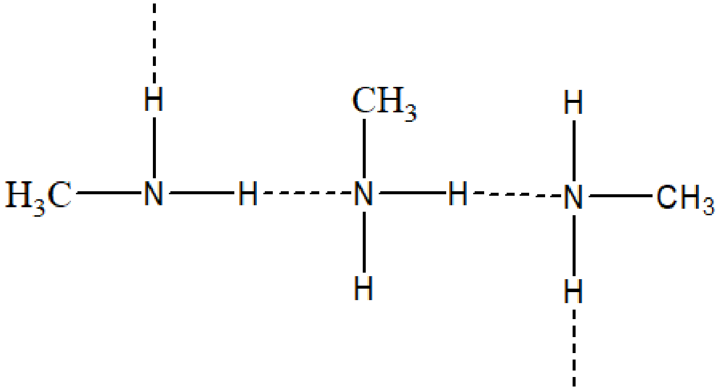
**10. Decarboxylation of amino acids:** This is carried out by distilling amino acid with barium hydroxides.

$$\mathrm{CH_2(NH_2)COOH} \xrightarrow{\mathrm{Ba(OH)_2}} \mathrm{CH_3NH_2}$$

**11.** By reduction of an alkyl isocyanide. $\mathrm{RNC} + 4[\mathrm{H}] \longrightarrow \mathrm{RNHCH_3}$

## General properties of amines:

Amines are polar compounds, except for tertiary amines, can form intermolecular H-bonds. This is reflected in their boiling points. Methylamine boils at -7 ºC, dimethylamine boils at 7 ºC while trimethylamine boils at 4 ºC. The boiling point of amines increases with increasing molecular weight. Aromatic amines boil at much higher temperature than its aliphatic analogue. Amines have higher boiling points than non-polar compounds of the same molecular weight, but lower boiling points than alcohols or carboxylic acids.



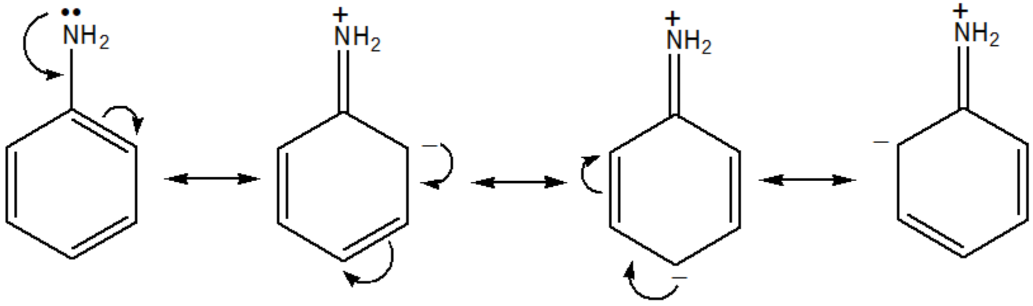
Amines of all three classes are capable of forming hydrogen bonding with water. As a result, smaller amines are quite soluble in water, borderline solubility of amines of about six carbon atoms. Amines are soluble in less polar solvents like ether, alcohol, benzene etc. The methylamines and ethyamines smell very much like ammonia; the higher alkylamines have fishy odors. Aromatic amines are generally very toxic; they are readily absorbed through the skin. Aromatic amines are very easily oxidized by air, although most are colorless when pure, they are often discolored by oxidation products.

## Structure and Basicity of amines:

Owing to the presence of lone pair of electrons on the N atom of amines, they are basic. Aliphatic amines are more basic than ammonia due to electron releasing effects of alkyl groups. Their relative basicity is due to the combination of solvation and electronic factors. Therefore, their relative basicity follows the order: $NH_3 < Me_3N < MeNH_2 < Me_2NH$. In case of trimethylamine, despite the presence of three methyl groups, it is a weaker base due to the steric crowding which makes difficult for bonding with proton.

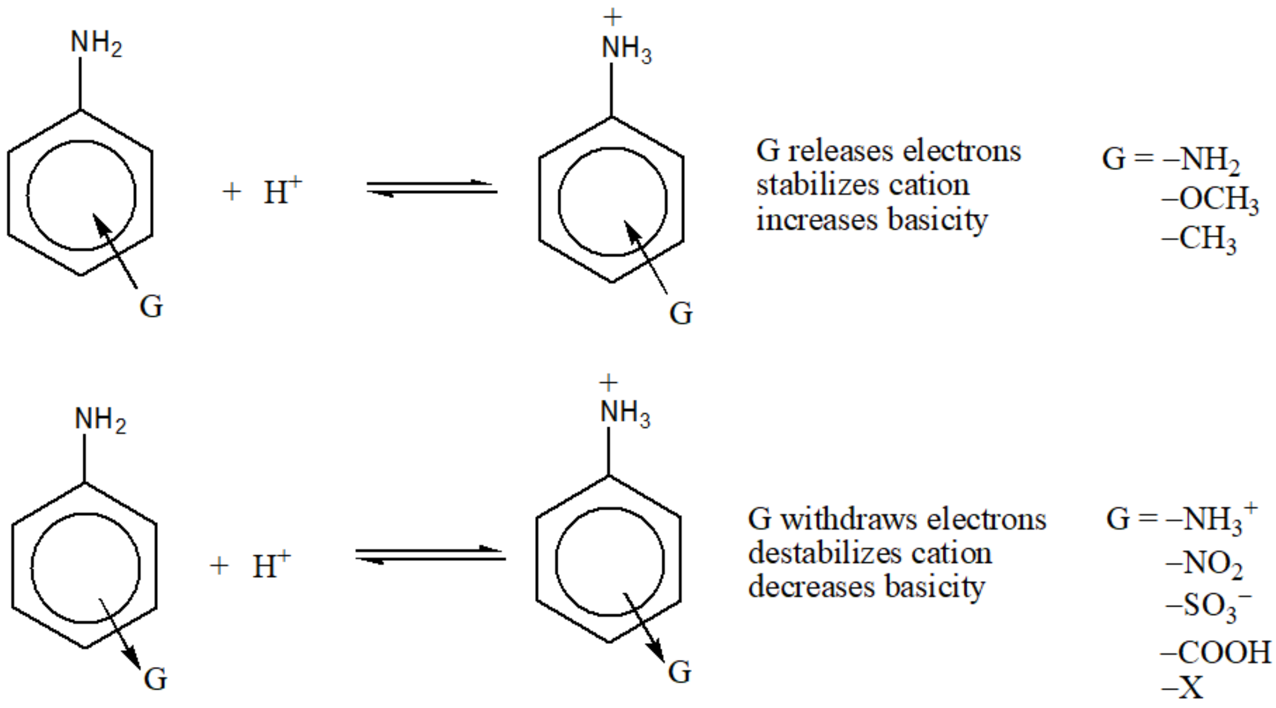
In solution, hydration effect stabilises dimethylammonium ion to a greater extent than trimethylammonium ion. Thus, the latter is more acidic than the former in the aqueous medium though + I effect of $–CH_3$ groups stabilises trimethylammonium ion to a more extent than dimethylammonium ion. Therefore, the conjugate base, dimethylamine is more basic than trimethylamine in aqueous medium.

Aromatic amines are weaker bases than ammonia. This low basicity is due to the fact that aromatic amine is stabilized to a greater extent. The lone pair of electrons on nitrogen is partly shared with the ring and is thus less available for sharing with hydrogen ion.



The tendency for the $–NH_2$ group to release electrons to the aromatic ring makes the ring more reactive toward electrophilic attack; at the same time this tendency makes the amine less basic. Similar considerations also apply to the other substituted aromatic amines.

# Basicity of aromatic amines



Electron release tends to disperse the positive charge of anilinium ion and thus stabilizes the ion relative to the amine. Electron withdrawal tends to intensify the positive charge of the anilinium ion and thus destabilizes the ion relative to amine.

## Reactions of amines:

**1. Hofmann exhaustive methylation:** The complete process of converting an amine, 1º, 2º, or 3º, to an unsaturated compound by pyrolytic decomposition of the quaternary ammonium hydroxide (obtained by treating amine with excess of alkyl halide and then hydrolysing the resulting quaternary ammonium iodide with moist silver oxide) is called Hofmann exhaustive methylation or Hofmann elimination.

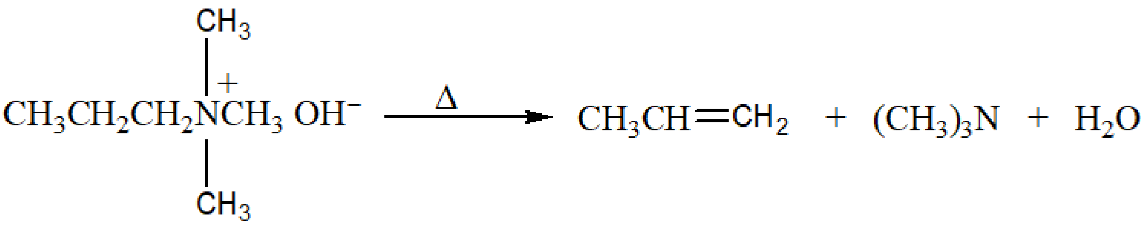
Quaternary ammonium salts are products of final stage of alkylation of nitrogen. The reaction of an amine with sufficient methyl iodide to convert the amine into a quaternary ammonium halide is called exhautive methylation.

$$RNH_2 \xrightarrow{RX} R_2NH \xrightarrow{RX} R_3N \xrightarrow{RX} R_4N^+X^-$$

When a solution of a quaternary ammonium halide is treated with silver oxide, silver halide precipitates and quaternary ammonium hydroxide forms as product.

$$R_4N^+X^- \xrightarrow{Ag_2O} R_4N^+OH^- + AgX$$

When quaternary ammonium hydroxide is heated strongly (to 125 º or higher), it decomposes to yield water, tertiary amine and an alkene. In case of trimethyl-n-propylammonium hydroxide, it decomposes to yield trimethylamine and propylene as product.

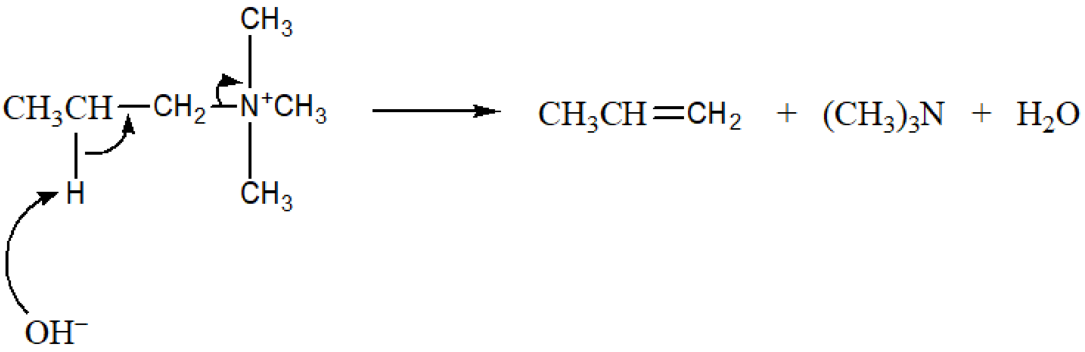


$$CH_3CH_2CH_2\overset{+}{N}(CH_3)_3\ OH^- \xrightarrow{\Delta} CH_3CH{=}CH_2 + (CH_3)_3N + H_2O$$

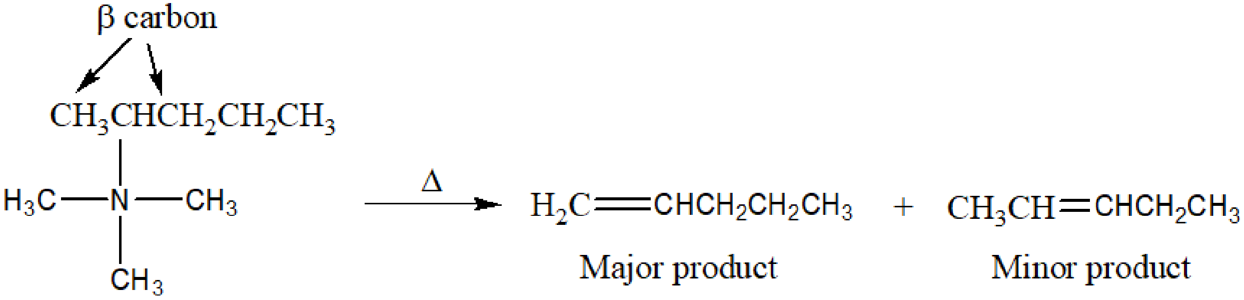
**** In order for quaternary ammonium ion to undergo elimination reaction, the counterion must be hydroxide ion because a strong base is needed to remove a proton from β carbon.***

This reaction, called Hofmann elimination, is quite analogous to dehydrohalogenation of alkyl halide. The above reaction is the basis of Hofmann exhaustive methylation. It is mainly a β-elimination reaction which usually follows E2 pathway. If there is no β-hydrogen in the quaternary hydroxide, then no olefin is formed.

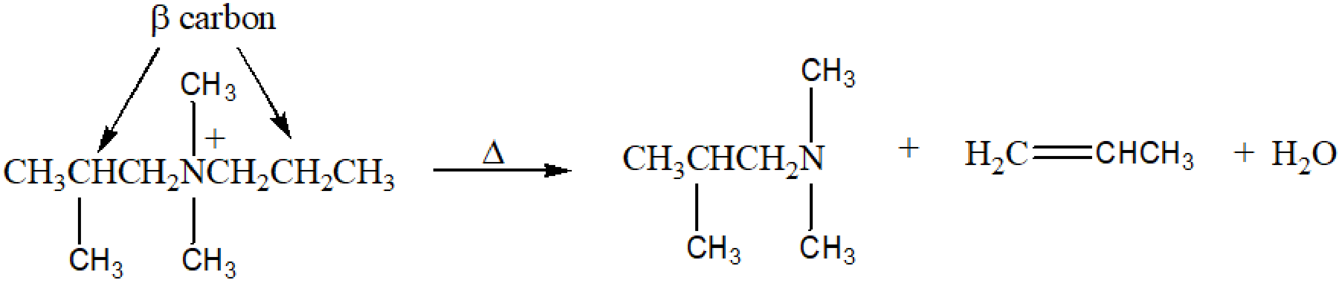
**Mechanism:**



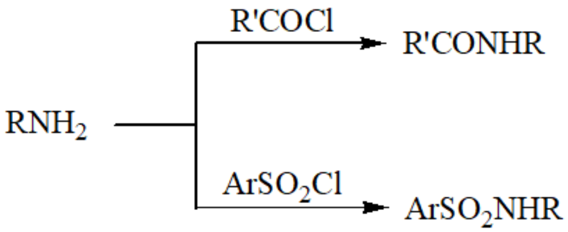
If the quaternary ammonium ion has more than one β carbon, the major alkene product is the one obtained by removing a proton from the β carbon bonded to the most hydrogen.

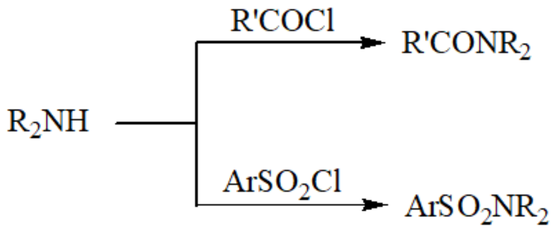


In case of next reaction, the major alkene product comes from removing a H from β carbon bonded to two hydrogens.



**2. Conversion of amines into substituted amides:** Primary and secondary amines react with acid chlorides to form substituted amides, compounds in which –Cl has been replaced by –NHR or $-NR_2$ group.





**3. Reaction with nitrous acid:** Each class of amines yields different kind of products in its reaction with nitrous acid, HONO. This unstable reagent is generated in presence of amine by the action of mineral acid on sodium nitrite.

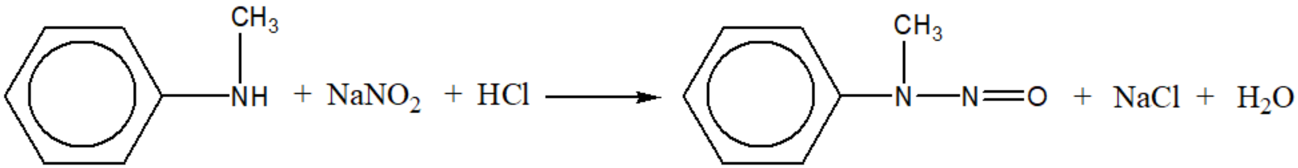
Primary aromatic amines react with nitrous acid to yield diazonium salts; this is one of the most important reactions in organic chemistry.

$$ArNH_2 + NaNO_2 + HX \longrightarrow ArN_2^+X^- + NaX + 2H_2O$$

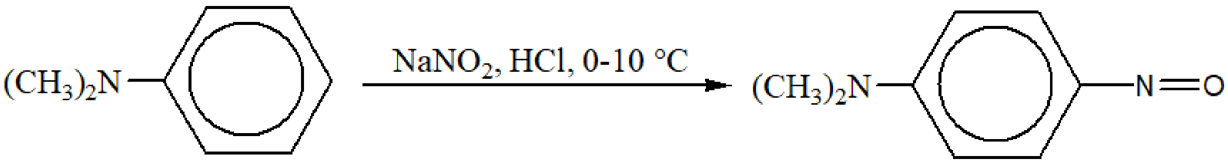
Primary aliphatic amines also react with nitrous acid to yield diazonium salts, but due to the instability of aliphatic diazonium salts, it breaks down to yield a complicated mixture of organic products.

$$RNH_2 + NaNO_2 + HX \longrightarrow \underset{\text{Unstable}}{\left[ RN_2^+X^- \right]} \longrightarrow N_2 + \text{mixture of alcohols and alkenes}$$

Secondary amines, both aliphatic and aromatic, react with nitrous acid to yield N-nitrosoamines.



Tertiary aromatic amines undergo ring substitution to yield compounds in which a nitroso group is joined to carbon.

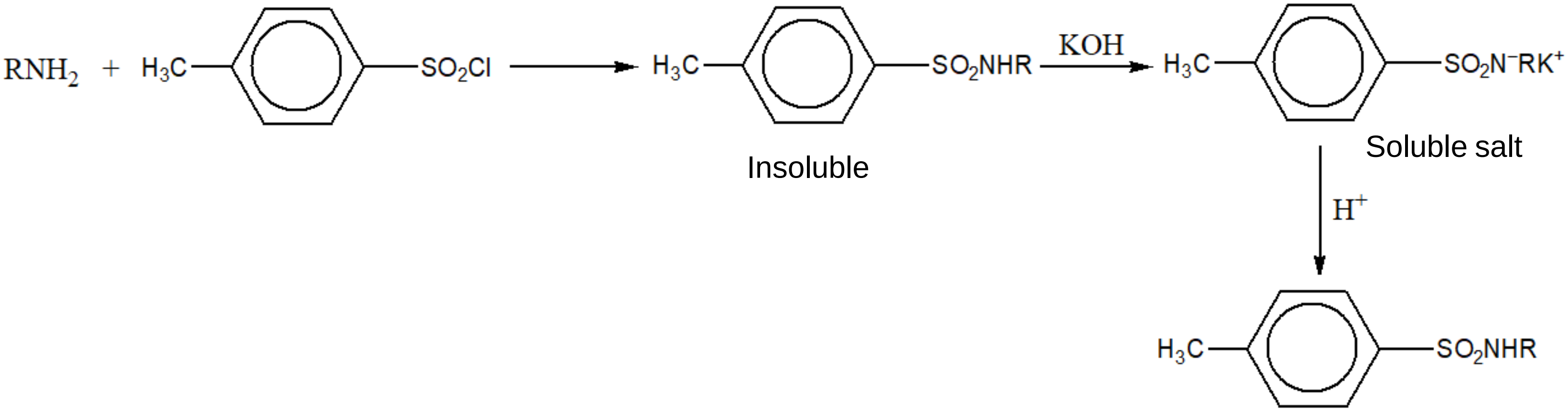


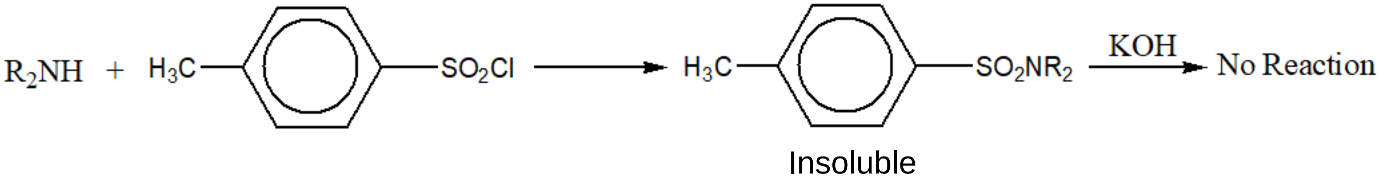
Tertiary aliphatic amines react with nitrous acid to yield N-nitroso derivative of secondary amine; the group that is lost from nitrogen appears as an aldehyde or ketone.

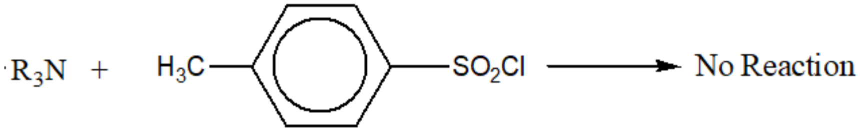
This reaction of amines with nitrous acid is a good means for differentiating three types of amines.

**3. Reaction with p-toluenesulfonyl chloride. Hinsberg reaction:** This reaction also differentiate three types of amines- whether an amine is primary, secondary and tertiary. The amine is shaken with p-toluenesulfonyl chloride in presence of aqueous potassium hydroxide. Primary and secondary amines form substituted sulfonamides, while tertiary amines do not.

The monosubstituted sulphonamide from primary amine has an acidic hydrogen attached to nitrogen. Reaction with potassium hydroxide converts this amide into soluble salt. Acidification of this solution also regenerates the insoluble amide. The disubstituted sulfonamide from secondary amine has no acidic hydrogen and remains insoluble in alkaline reaction mixture. A 3º amine does not react at all with the reagent due to the absence of active H.




R2NH
+
H3C
SO2Cl
H3C
SO2NR2
KOH
No Reaction
Insoluble


R3N
+
H3C
SO2Cl
No Reaction