Ministry Of Higher Education
Baghdad College Of Medical Sciences
Assistant Prof: Ameen Waleed

Organic Chemistry
Lecture: 9, 10

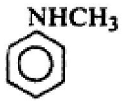
Amines I

Structure

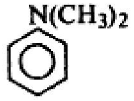
An amine has the general formula RNH_2, R_2NH, or R_3N, where R is any alkyl or aryl group. For example:

CH_3NH_2	$(CH_3)_2NH$	$(CH_3)_3N$	$H_2NCH_2CH_2NH_2$
Methylamine	**Dimethylamine**	**Trimethylamine**	**Ethylenediamine**
(1°)	**(2°)**	**(3°)**	**(1°)**

Aniline
(1°)



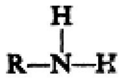
N-Methylaniline
(2°)



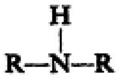
N,N-Dimethylaniline
(3°)

Classification

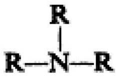
Amines are classified as primary, secondary, or tertiary, according to the number of groups attached to the nitrogen atom.


$$R-\overset{H}{\overset{|}{N}}-H$$

Primary
1°


$$R-\overset{H}{\overset{|}{N}}-R$$

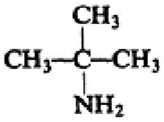
Secondary
2°


$$R-\overset{R}{\overset{|}{N}}-R$$

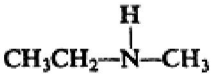
Tertiary
3°

Nomenclature

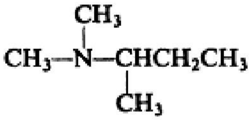
Aliphatic amines are named by naming the alkyl group or groups attached to nitrogen, and following these by the word -amine. More complicated ones are often named by prefixing amino- (or N-methylamino-, N,N-diethylamino-, etc.) to the name of the parent chain. For example:


$$CH_3-\underset{NH_2}{\overset{CH_3}{C}}-CH_3$$

***tert*-Butylamine**
(1°)


$$CH_3CH_2-\overset{H}{N}-CH_3$$

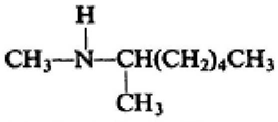
Methylethylamine
(2°)


$$CH_3-\overset{CH_3}{N}-\underset{CH_3}{C}HCH_2CH_3$$

Dimethyl-*sec*-butylamine
(3°)

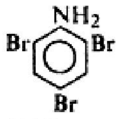
$H_2NCH_2CH_2CH_2COOH$
γ-Aminobutyric acid
(1°)

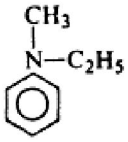
$H_2NCH_2CH_2OH$
2-Aminoethanol
(Ethanolamine)
(1°)

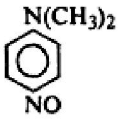

$$CH_3-\overset{H}{N}-\underset{CH_3}{C}H(CH_2)_4CH_3$$

2-(N-Methylamino)heptane
(2°)

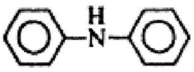
Aromatic amines those in which nitrogen is attached directly to an aromatic ring are generally named as derivatives of the simplest aromatic amine, **aniline**. An **aminotoluene** is given the special name of toluidine. For example:

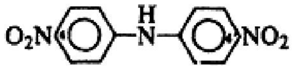

2,4,6-Tribromoaniline
(1°)


N-Methyl-N-ethylaniline
(3°)


p-Nitroso-N,N-dimethylaniline
(3°)


p-Toluidine
(1°)


Diphenylamine
(2°)


4,4′-Dinitrodiphenylamine
(2°)

Salts of amines are generally named by replacing -amine by -ammonium (or aniline by anilinium), and adding the name of the anion (chloride, nitrate, sulfate ,etc.). For example:

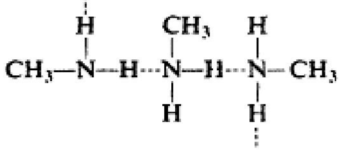
$(C_2H_5NH_3^+)_2SO_4^{--}$
Ethylammonium
sulfate

$(CH_3)_3NH^+NO_3^-$
Trimethylammonium
nitrate

$C_6H_5NH_3^+Cl^-$
Anilinium
chloride

Physical properties

Like ammonia, amines are polar compounds and, except for tertiary amines ,can form intermolecular hydrogen bonds. Amines have higher boiling points than non-polar compounds of the same molecular weight, but lower boiling points than alcohols or carboxylic acids. Amines are capable of forming hydrogen bonds with water.



As a result, smaller amines are quite soluble in water, with border line solubility being reached at about six carbon atoms. Amines are soluble in less polar solvents like ether, alcohol, benzene, etc. The methyl amines and ethyl amines smell very much like ammonia; the higher alkyl amines have decidedly "fishy" odors. Aromatic amines are generally very toxic; they are readily absorbed through the skin, often with fatal results. Aromatic amines are very easily oxidized by air, and although most are colorless when pure, they are often encountered discolored by oxidation products.

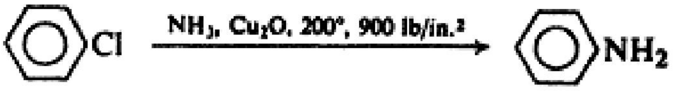
Industrial source

The most important of all amines, aniline is prepared in several ways :

(a) reduction of nitrobenzene by the cheap reagents, iron and dilute hydrochloric acid (or by catalytic hydrogenation)

Nitrobenzene Anilinium chloride Aniline

(b) treatment of chloro benzene with ammonia at high temperatures and high pressures in the presence of a catalyst.



Chlorobenzene Aniline

Methylamine, dimethylamine, and trimethylamine are synthesized on an industrial scale from methanol and ammonia:

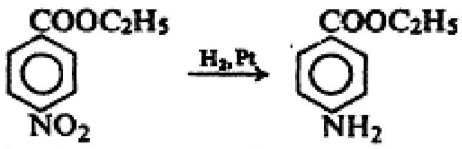
$$NH_3 \xrightarrow[Al_2O_3,\ 450°]{CH_3OH} CH_3NH_2 \xrightarrow[Al_2O_3,\ 450°]{CH_3OH} (CH_3)_2NH \xrightarrow[Al_2O_3,\ 450°]{CH_3OH} (CH_3)_3N$$

Ammonia Methylamine Dimethylamine Trimethylamine

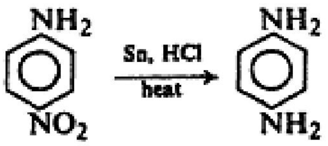
Preparation of Amines

1. Reduction of nitro compounds.

Examples:



Ethyl *p*-nitrobenzoate Ethyl *p*-aminobenzoate



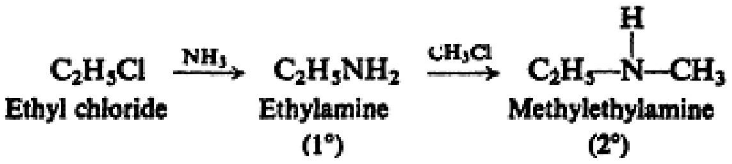
p-Nitroaniline *p*-Phenylenediamine

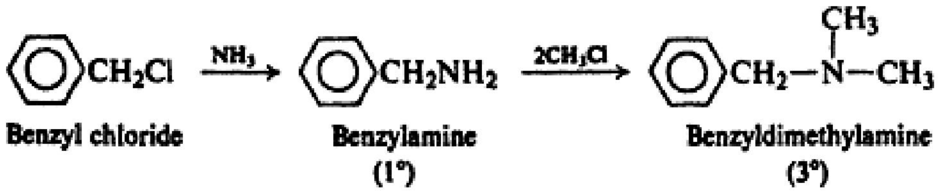
$$CH_3CH_2CH_2NO_2 \xrightarrow{Fe,\ HCl} CH_3CH_2CH_2NH_2$$

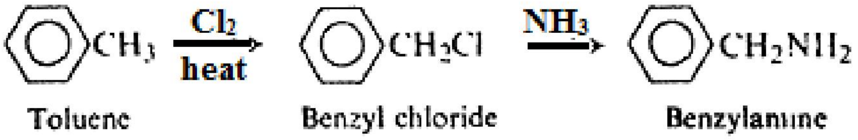
1-Nitropropane *n*-Propylamine

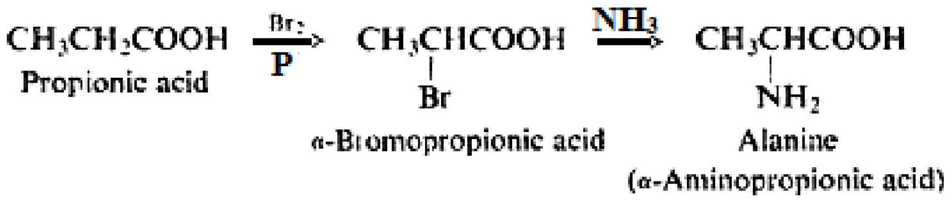
2. Reaction of halides with ammonia or amines.

Examples:



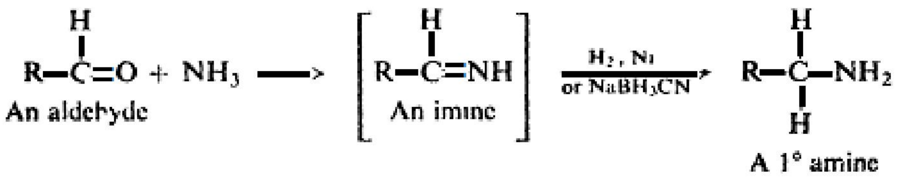






3. Reductive amination.

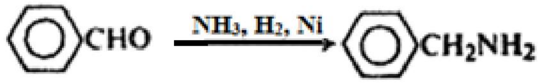
Many aldehydes (RCHO) and ketones (R_2CO) are converted into amines by **reductive amination:** reduction in the presence of ammonia. Reduction can be accomplished catalytically or by use of sodium cyanohydridoborate, $NaBH_3CN$.



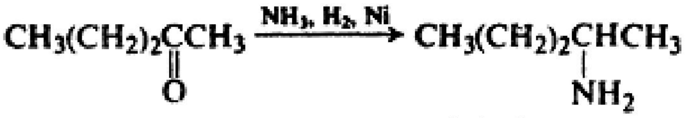
Examples:

$$CH_3(CH_2)_5CHO \xrightarrow{NH_3,\ H_2,\ Ni} CH_3(CH_2)_5CH_2NH_2$$

Heptaldehyde (Heptanal) → *n*-Heptylamine (1-Aminoheptane)

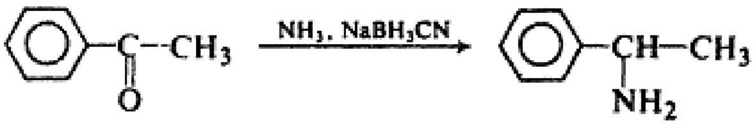


Benzaldehyde → Benzylamine

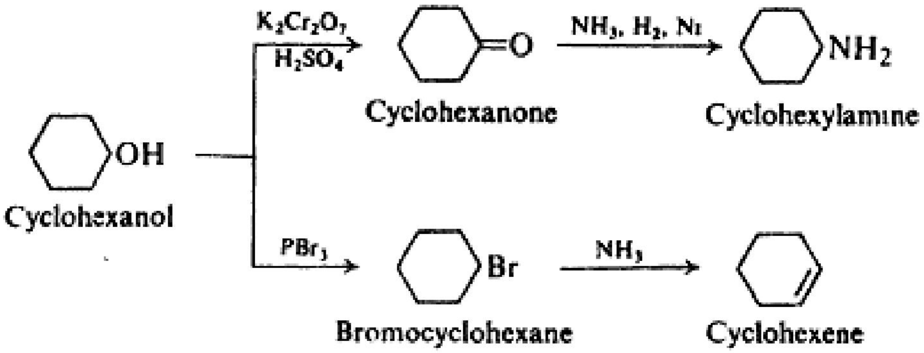


$$CH_3(CH_2)_2\underset{\displaystyle \overset{\|}{O}}{C}CH_3 \xrightarrow{NH_3,\ H_2,\ Ni} CH_3(CH_2)_2\underset{\displaystyle \overset{|}{NH_2}}{C}HCH_3$$

2-Pentanone (Methyl *n*-propyl ketone) → 2-Aminopentane

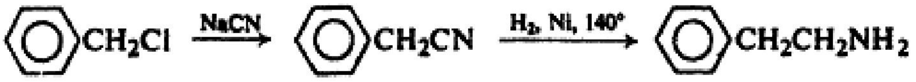


Acetophenone (Methyl phenyl ketone) → α-Phenylethylamine



4. Reduction of nitriles.

Examples:



Benzyl chloride → Phenylacetonitrile (Benzyl cyanide) → β-Phenylethylamine (1°)

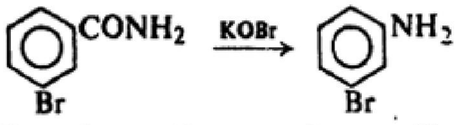
$$ClCH_2CH_2CH_2CH_2Cl \xrightarrow{NaCN} NC(CH_2)_4CN \xrightarrow{H_2,\ Ni} H_2NCH_2(CH_2)_4CH_2NH_2$$

1,4-Dichlorobutane → Adiponitrile → Hexamethylenediamine (1,6-Diaminohexane) (1°)

5. Hofmaim degradation of amides.

The Hofmann degradation of amides has the special feature of yielding a product containing one less carbon than the starting material. As we can see, reaction involves migration of a group from carbonyl carbon to the adjacent nitrogen atom, and thus is an example of a molecular rearrangement.

Examples:

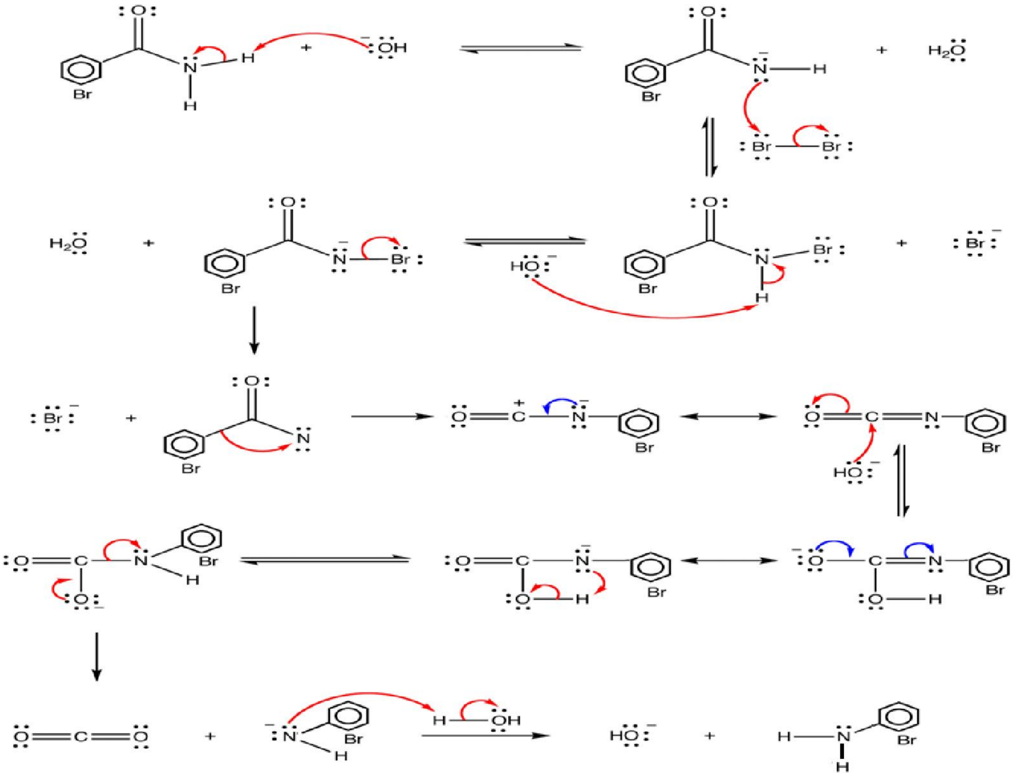


m-Bromobenzamide *m*-Bromoaniline

$$CH_3(CH_2)_4CONH_2 \xrightarrow{KOBr} CH_3(CH_2)_4NH_2$$

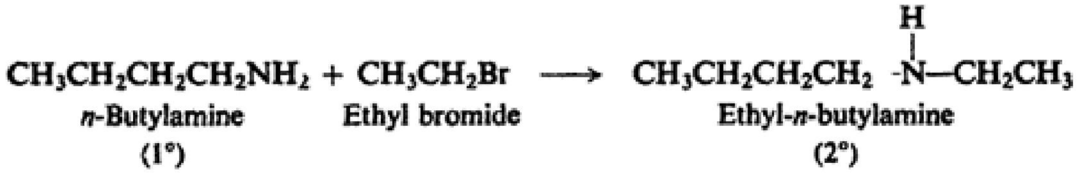
Caproamide (Hexanamide) *n*-Pentylamine

The reaction is believed to proceed by the following steps: Step (1) is the halogenation of an amide. Step (2) is the abstraction of a hydrogen ion by hydroxide ion. Step (3) involves the separation of a halide ion, which leaves behind an electron-deficient nitrogen atom. In Step (4) the actual rearrangement occurs. Steps (3) and (4) are generally believed to occur simultaneously, the attachment of R to nitrogen helping to push out halide ion. Step (5) is the hydrolysis of an isocyanate (R-N=C=O) to form an amine and carbonate ion.

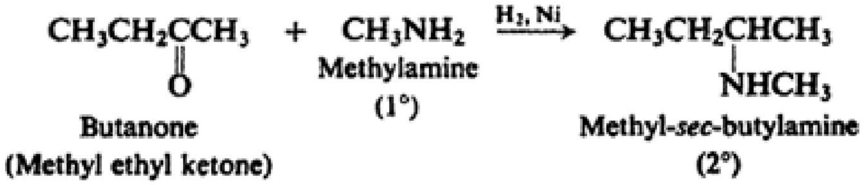


Synthesis of secondary and tertiary amines

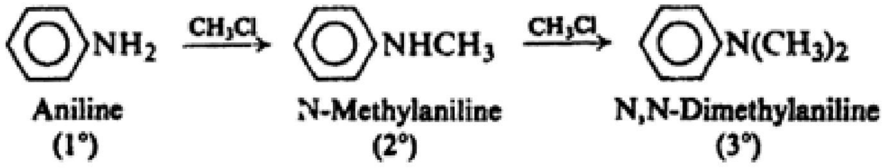
Secondary and tertiary amines are prepared by adaptations of one of the processes already described: ammonolysis of halides or reductive animation. For example:

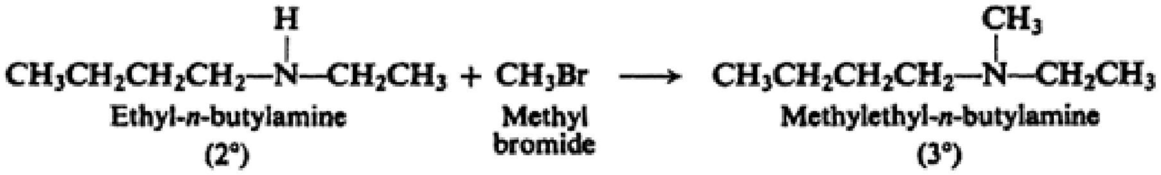


$$CH_3CH_2CH_2CH_2NH_2 + CH_3CH_2Br \longrightarrow CH_3CH_2CH_2CH_2\overset{H}{N}-CH_2CH_3$$



$$CH_3CH_2\underset{O}{C}CH_3 + CH_3NH_2 \xrightarrow{H_2, Ni} CH_3CH_2\underset{NHCH_3}{C}HCH_3$$





$$CH_3CH_2CH_2CH_2-\overset{H}{N}-CH_2CH_3 + CH_3Br \longrightarrow CH_3CH_2CH_2CH_2-\overset{CH_3}{N}-CH_2CH_3$$

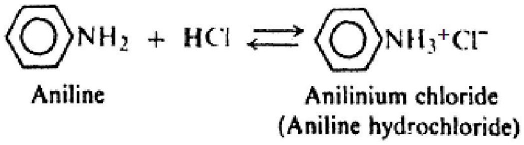
Amines II

Reaction of Amines

1. Basicity. Salt formation.

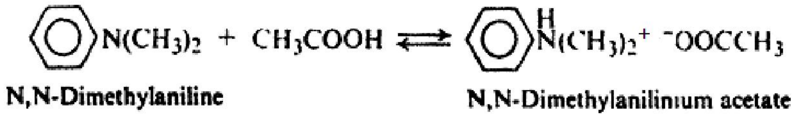
Like ammonia, amines are converted into their salts by aqueous mineral acids and are liberated from their salts by aqueous hydroxides. Like ammonia, therefore ,amines are more basic than water and less basic than hydroxide ion:

Examples:



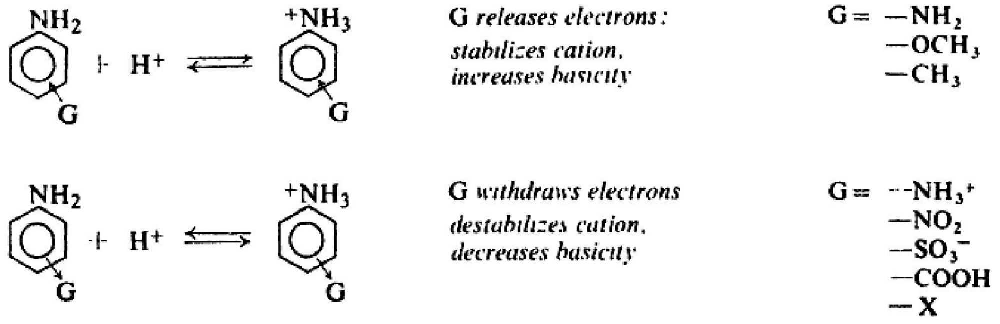
$$(CH_3)_2NH + HNO_3 \rightleftharpoons (CH_3)_2NH_2^+NO_3^-$$

Dimethylamine Dimethylammonium nitrate



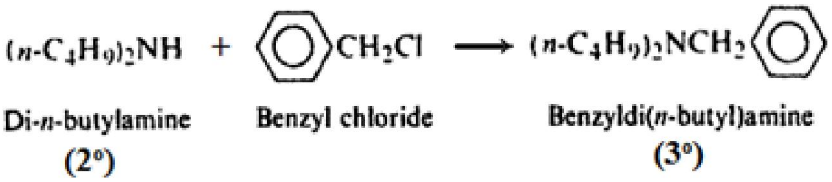
Effect of substituents on basicity of aromatic amines

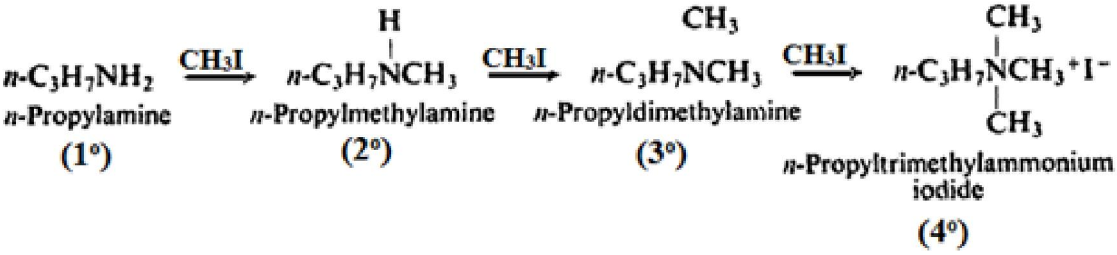
An electron-releasing substituent like -CH_3 increases the basicity of aniline, and an electron-withdrawing substituent like -X or NO_2 decreases the basicity .These effects are understandable. Electron release tends to disperse the positive charge of the anilinium ion, and thus stabilizes the ion relative to the amine. Electron withdrawal tends to intensify the positive charge of the, anilinium ion, and thus destabilizes the ion relative to the amine.



2. Alkylation.

Examples:

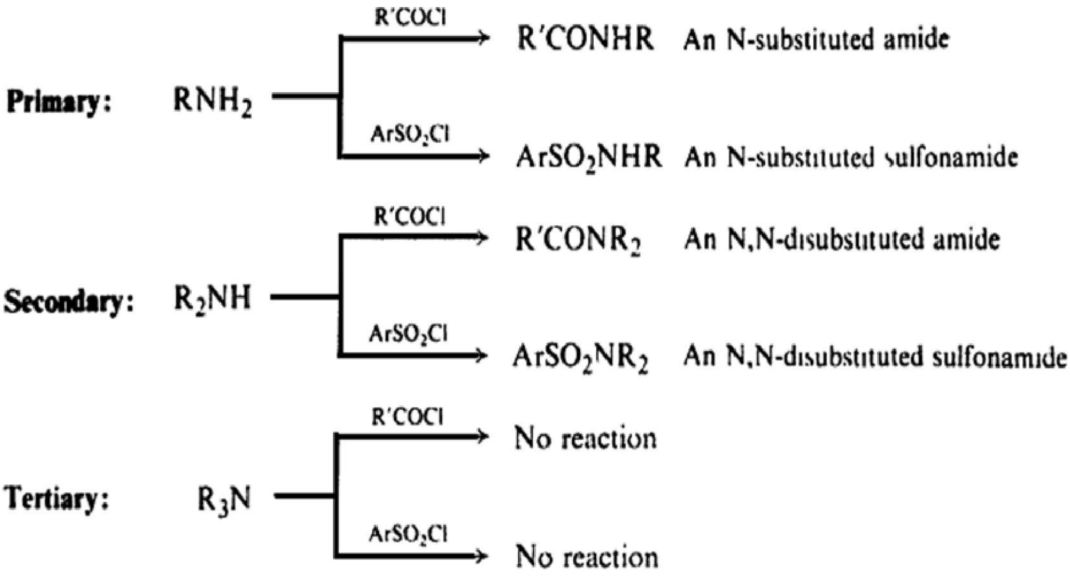




$$n\text{-}C_3H_7NH_2 \xrightarrow{CH_3I} n\text{-}C_3H_7\overset{H}{N}CH_3 \xrightarrow{CH_3I} n\text{-}C_3H_7\overset{CH_3}{N}CH_3 \xrightarrow{CH_3I} n\text{-}C_3H_7\overset{CH_3}{\underset{CH_3}{N}}CH_3{}^{+}I^{-}$$

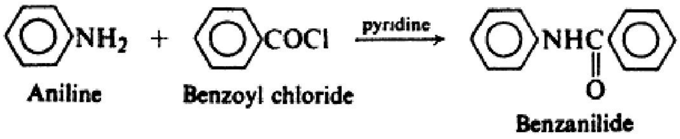
3. Conversion into amides.

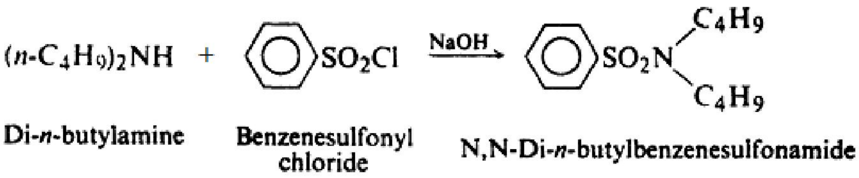
Primary and secondary amines can react with acid chlorides to form substituted amides, compounds in which -Cl has been replaced by the-NHR or -NR_2 group:

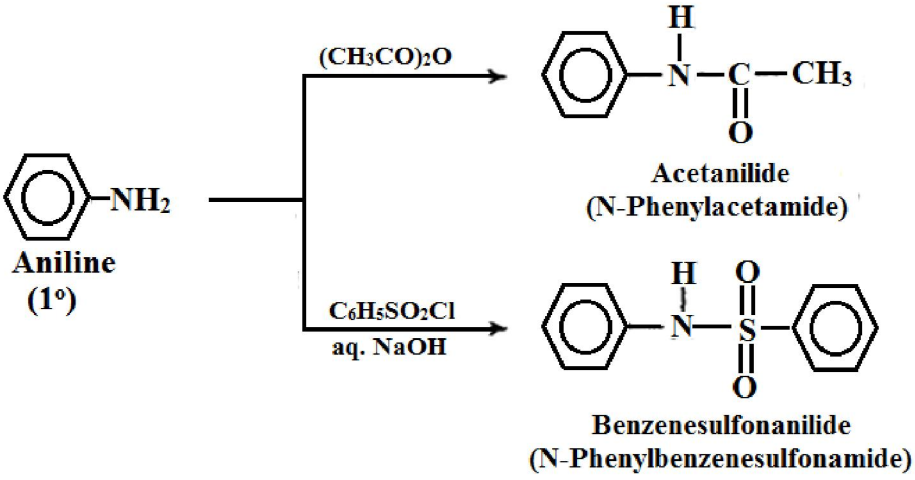


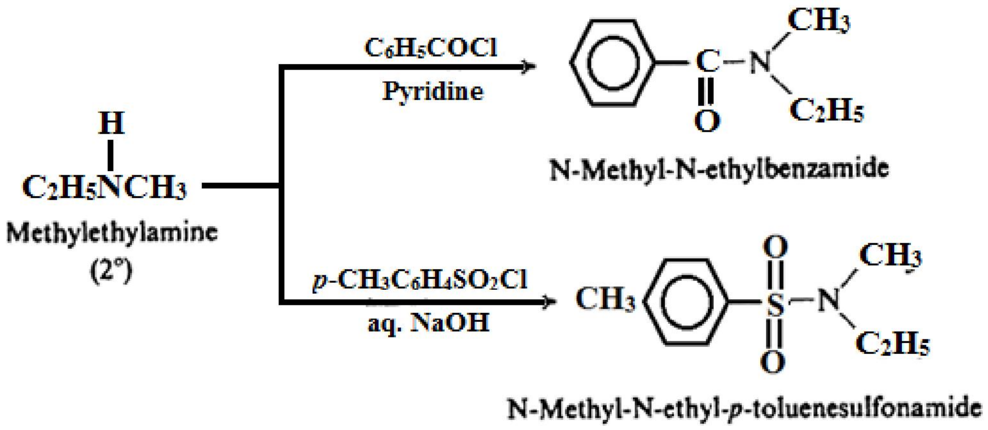
Tertiary amines, although basic, fail to yield amides, presumably because they cannot lose a proton (to stabilize the product) after attaching themselves to carbon or to sulfur.

Examples:

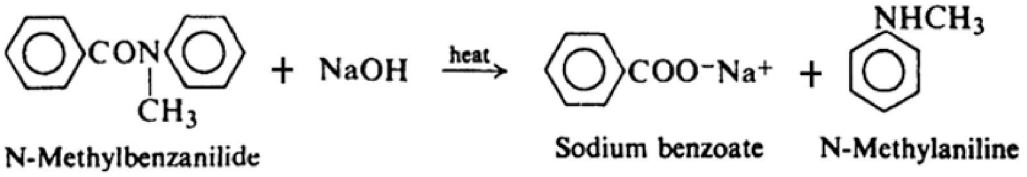


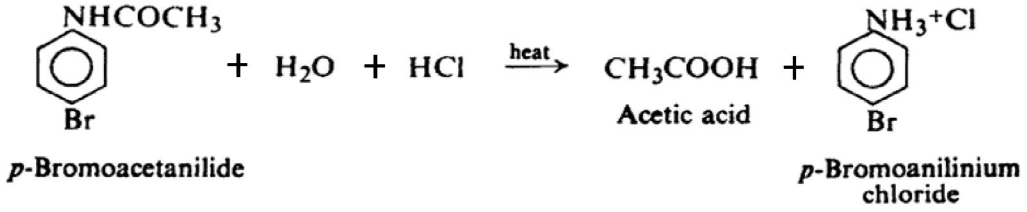






Like simple amides, substituted amides undergo hydrolysis; the products are the acid and the amine, although one or the other is obtained as its salt, depending upon the acidity or alkalinity of the medium.





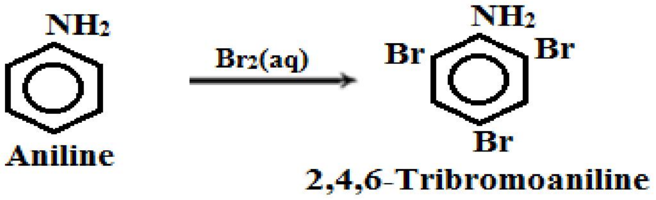
4. Ring substitution in aromatic amines.

—NH$_2$
—NHR
—NR$_2$

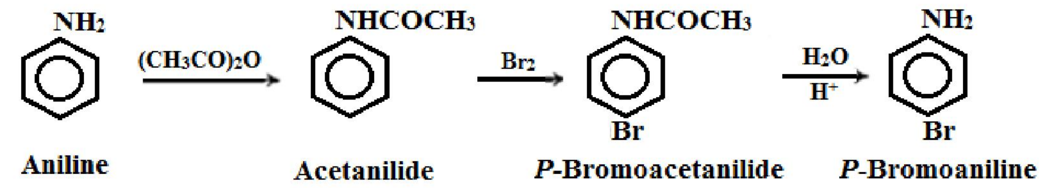
Activator powerfully, and direct *ortho, para* in electrophilic aromatic substitution

—NHCOR: Less powerful activator than —NH$_2$

Examples:



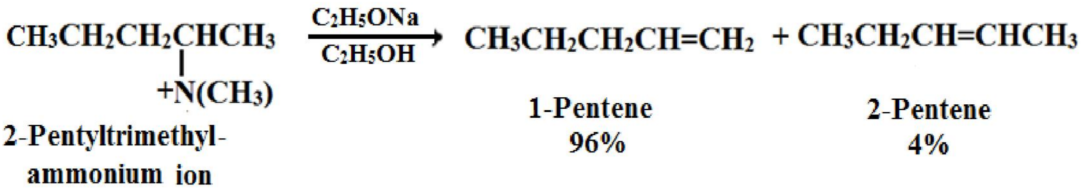
Acetylation is generally carried out using acetic anhydride rather than acetyl chloride.



5. Hofmann elimination from quaternary ammonium salts.

Hofmann elimination: is quite analogous to the dehydrohalogenation of an alkyl halide. Most commonly, reaction is E2 :hydroxide ion abstracts a proton from carbon; a molecule of tertiary amine is expelled, and the double bond is generated. Bases other than hydroxide ion can be used.

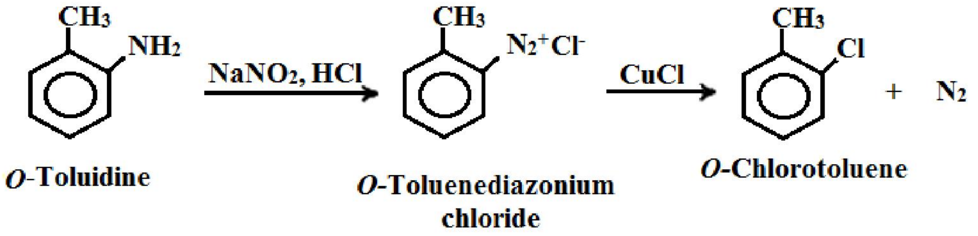
Example:



$$\underset{+N(CH_3)}{CH_3CH_2CH_2CHCH_3} \xrightarrow[C_2H_5OH]{C_2H_5ONa} CH_3CH_2CH_2CH{=}CH_2 + CH_3CH_2CH{=}CHCH_3$$

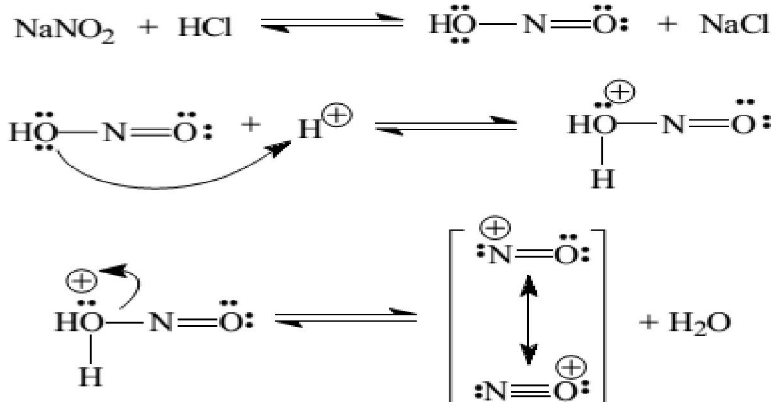
6. Reactions with nitrous acid.

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

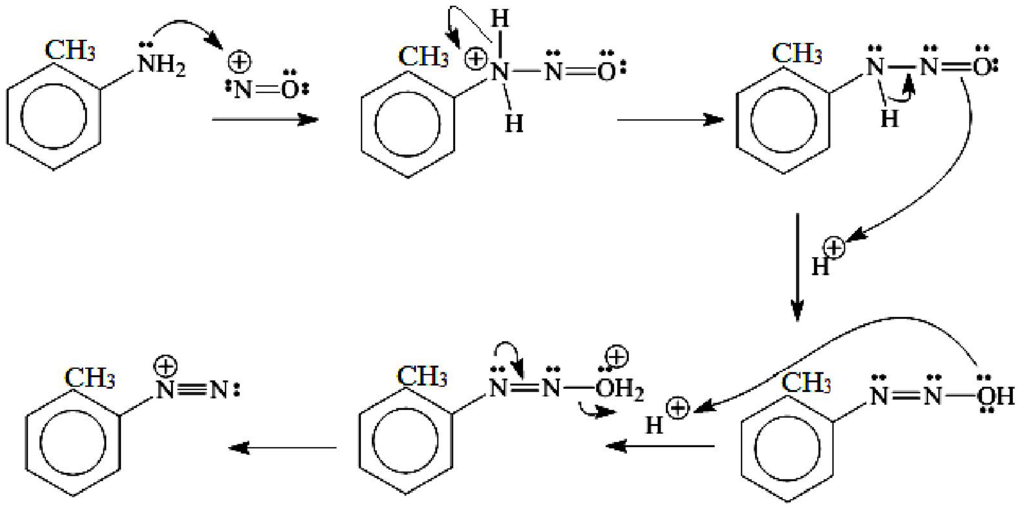


The reaction mechanism:

The electrophile used to react with the amine to form the aryl diazonium salt is the mild ⊕NO electrophile. The following mechanism shows how the aryl diazonium salt forms from HCl and $NaNO_2$. The ⊕NO ion is resonance-stabilized, so it forms relatively easily.



After the ⊕NO electrophile forms, it reacts in acid/base fashion with the amine nitrogen. The intermediate then loses water and forms the diazonium salt.

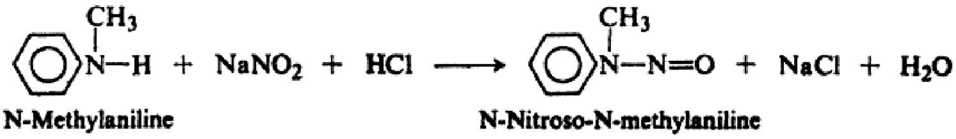


Primary aliphatic amines also react with nitrous acid to yield diazonium salts but since aliphatic diazonium salts are quite unstable and break down to yield a mixture of complicated organic products

$$\underset{\text{1° aliphatic amine}}{RNH_2} + NaNO_2 + HX \longrightarrow \underset{\textit{Unstable}}{[RN_2^+X^-]} \xrightarrow{H_2O} N_2 + \text{mixture of alcohols and alkenes}$$

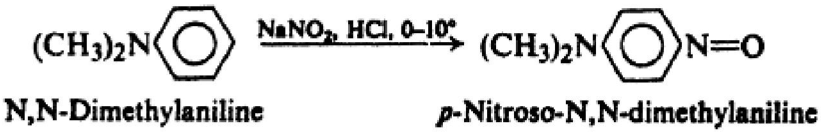
Secondary amines, both aliphatic and aromatic, react with nitrous acid to yield N-nitrosoamines.

Example:



Tertiary aromatic amines undergo ring substitution, to yield compounds in which a nitroso group-N=O, is joined to carbon; thus N,N-dimethylaniline yields chiefly *P*-nitroso-N,N-dimethylaniline.

Example:



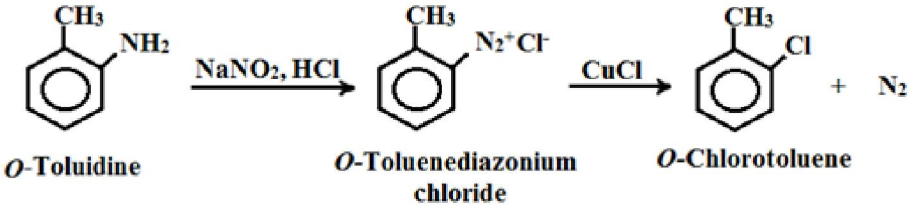
Tertiary aliphatic amines (and, to an extent, tertiary aromatic amines, too, particularly if the para position is blocked) react with nitrous acid to yield an N-nitroso derivative of a secondary amine; the group that is lost from nitrogen appears as an aldehyde or ketone.

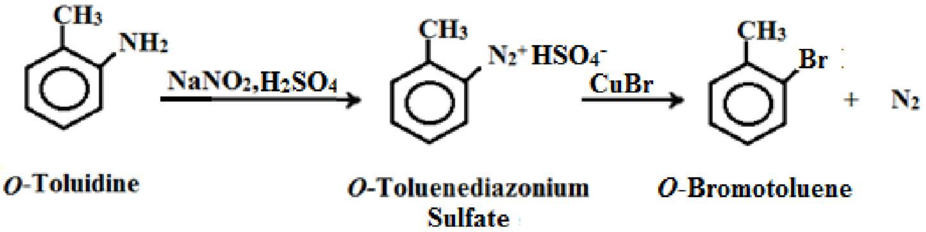
Reactions of diazonium salts

1. Replacement of nitrogen

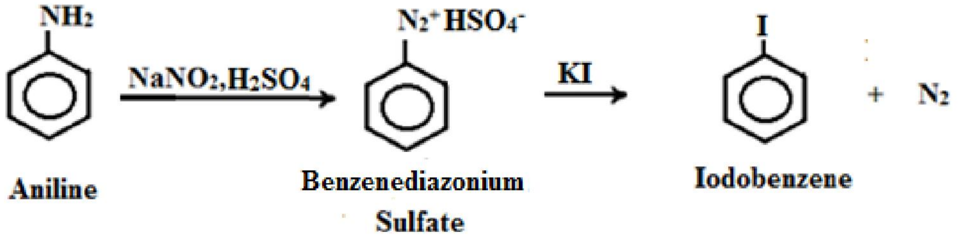
(a) Replacement by halogen. Sandmeyer reaction.

Examples:

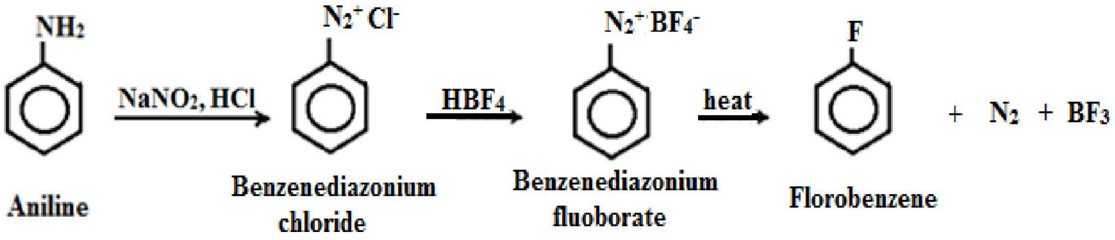




Replacement of the diazonium group by I does not require the use of a cuprous halide or copper; the diazonium salt and potassium iodide are simply mixed together and allowed to react.

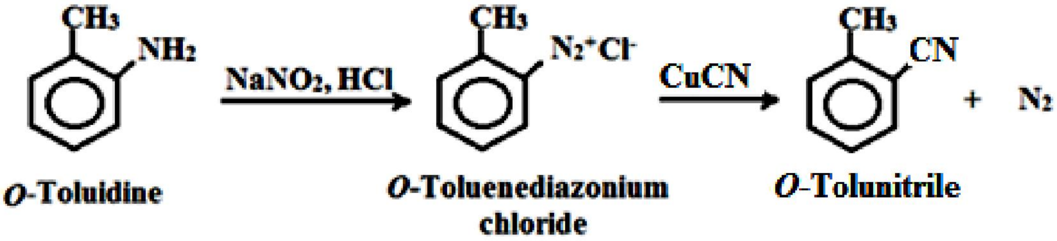


Replacement of the diazonium group by F is carried out in a somewhat different way. Addition of fluoboric acid, HBF_4 to the solution of diazonium salt causes the precipitation of the diazonium fluoborate which can be collected on a filter, washed, and dried.



(b) Replacement by -CN. Synthesis of carboxylic acids

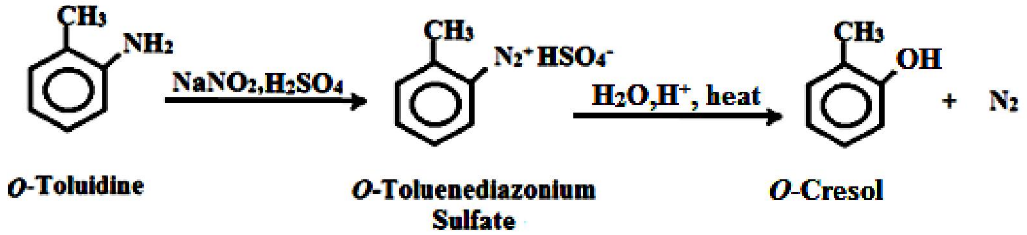
Replacement of the diazonium group by CN is carried out by allowing the diazonium salt to react with cuprous cyanide.



(c) Replacement by -OH.

Diazonium salts react with water to yield phenols.

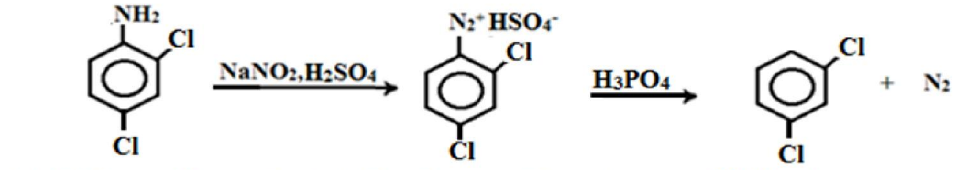
Example:



(d) Replacement by -H.

Replacement of the diazonium group by-H can be brought about by a number of reducing agents; may be the most useful of these is phosphoric acid H_2SO_4

Example:



2,4-Dichloroaniline **2,4-Dichlorobenzenediazonium sulfate** ***m*-Dichlorobenzene**

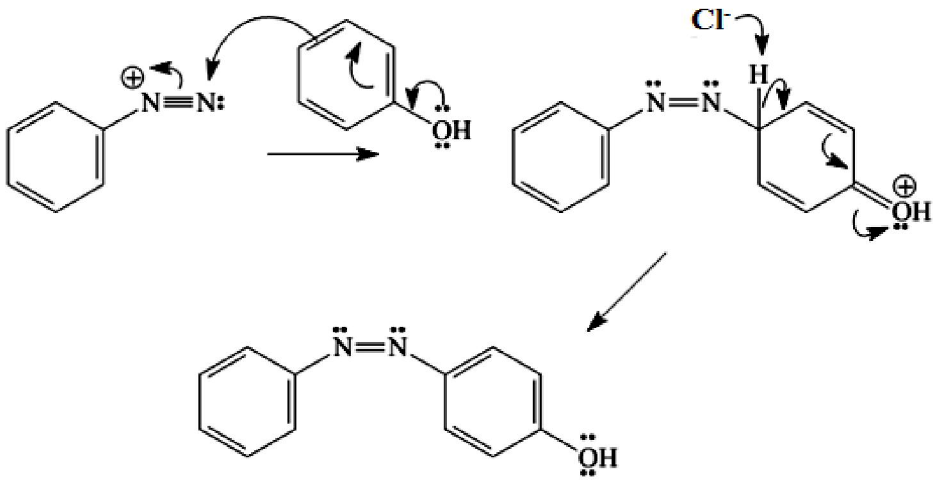
2. Coupling.

Coupling of diazonium salts.

Under the proper conditions, diazonium salts react with certain aromatic compounds to yield products of the general formula ArN=NAr', called azo compounds. The aromatic ring (Ar'H) undergoing attack by the diazonium ion must, in general, contain a powerfully electron-releasing group, generally-OH, $-NR_2$, -NHR, or $-NH_2$. Substitution usually occurs para to the activating group .Typically, coupling with phenols is carried out in mildly alkaline solution, and with amines in mildly acidic solution.

Benzenediazonium chloride **Phenol** ***p*-Hydroxyazobenzene *p*-(Phenylazo)phenol**

The reaction mechanism:

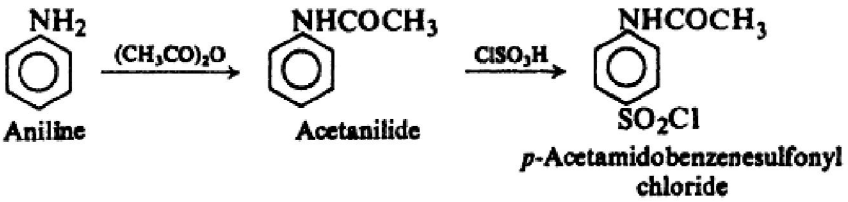


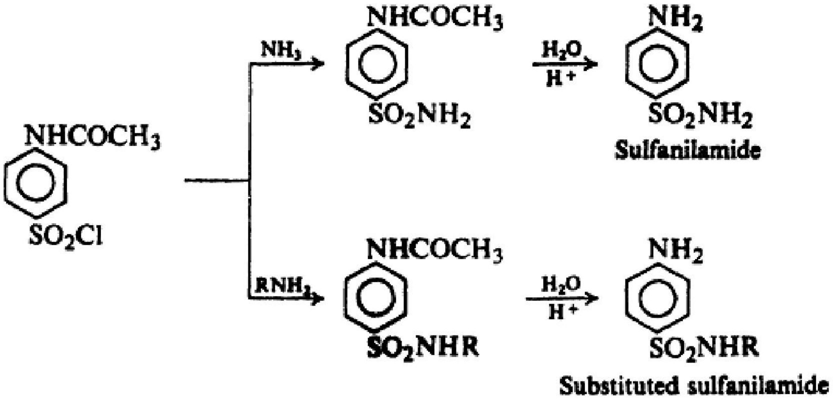
4-Phenylazophenol
An azo compound

Sulfanilamide. The sulfa drugs

The amide of sulfanilic acid (sulfanilamide) and certain related substituted amides are of considerable medical importance as the sulfa drugs. Although they have been supplanted to a wide extent by the antibiotics (such as penicillin, Terramycin, Chloromycetin, and Aureomycin).

Sulfonamides are prepared by the reaction of a sulfonyl chloride with ammonia or an amine. Sulfanilamide and related compounds are generally prepared in the following way:





The selective removal of the acetyl group in the final step is consistent with the general observation that amides of carboxylic acids are more easily hydrolyzed than amides of sulfonic acids.