Semester III (E-content)

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Department:	Department of Higher Education UT of Jammu & Kashmir	
Paper:	Organic Chemistry	
Class:	B. Sc. UG-General Semester 3rd	
University:	JU, CLUJ , Autonomous Colleges (JU)	
Unit:	2nd	**Amines (Aliphatic and Aromatic):** **Diazonium salts:**
Syllabus Covered:	**Amines (Aliphatic and Aromatic):** Preparation: from alkyl halides, Gabriel's Phthalimide synthesis, Hofmann Bromamide reaction. Reactions: Hofmann vs. Saytzeff elimination, Carbylamine test, Hinsberg test, with HNO2, Schotten – Baumann Reaction. Electrophilic substitution (case aniline): nitration, bromination, sulphonation. Diazonium salts: Preparation: From aromatic amines, Reactions: Conversion to benzene, phenol, dyes.	
Number of Modules	04	Number of Videos: 04

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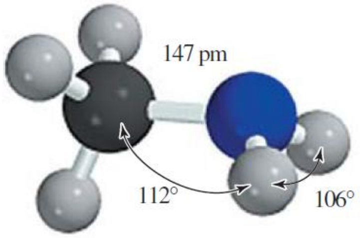
Chapter 2



By
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Course: UCHTP202

Unit 2: Amines (Aliphatic and Aromatic): (Upto 5 carbons)

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2.1 Learning outcomes:

2.1.1 To understand nomenclature, classification and types of amines.

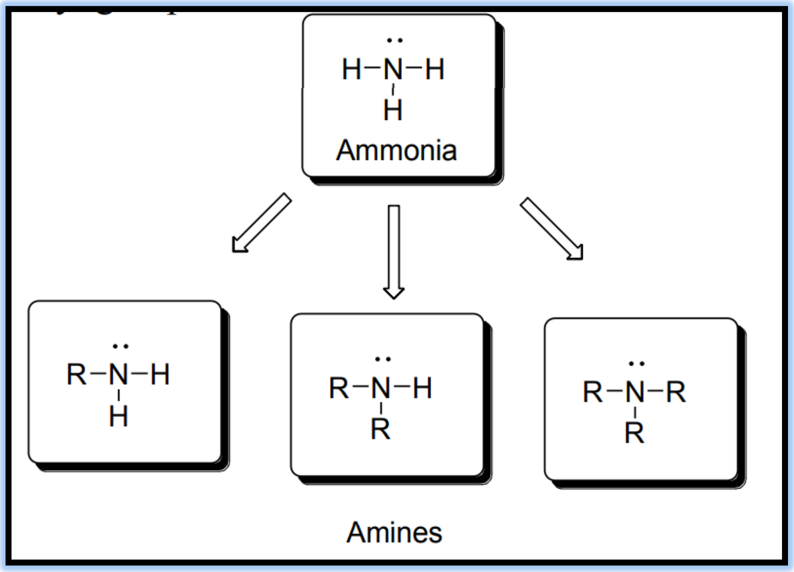
2.1.2 To discuss preparation of amines from alkyl halides and primary amides.

2.1.3 To study chemical reactions of amines with special reference to Hofmann vs. Saytzeff elimination, Carbylamine test, Hinsberg test, Reaction with HNO_2 and Schotten – Baumann Reaction.

2.1.4 To study electrophilic substitution reactions of aromatic amines

2.2 Amines (Introduction):

Amines are organic derivatives of ammonia in which one or more of the hydrogen atoms of ammonia have been replaced by alkyl or aryl groups. They are widely distributed in nature in form of proteins, vitamins, hormones and alkaloids. Amines are also used as dyes, polymers and drugs. In the present chapter, some important aspects regarding chemistry of amines will be discussed:



2.2.1 Types of amines:

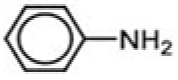
a) Aliphatic amines:

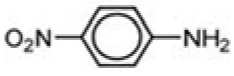
Aliphatic amines are the derivatives of ammonia in which one or more hydrogen atoms have been replaced by alkyl groups. Some examples of aliphatic amines are:

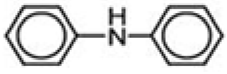
CH_3NH_2	$(CH_3)_2NH$	$(CH_3)_3N$
Methylamine	Dimethylamine	Trimethylamine

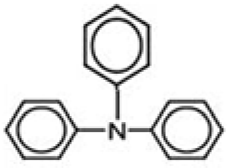
b) Aromatic amines: Aromatic amines can be aryl amines or aralkyl amines:

i) Aryl amines: Aryl amines are the derivatives of ammonia in which one or more hydrogen atoms have been replaced by aryl groups or aromatic rings. Some examples of aryl amines are:

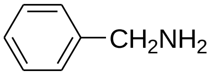

Aniline


p-Nitroaniline

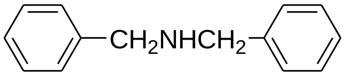

Diphenylamine


Triphenyl amine

ii) Aralkylamines: Aralkyl amines are the derivatives of ammonia in which one or more hydrogen atoms have been replaced by side chain/s of aromatic rings. Some examples of aralkyl amines are:



Benzyl amine

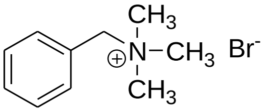


Dibenzylamine

2.2.2 Quaternary ammonium salt: A related class of compounds, quaternary ammonium salts is obtained by the replacement of all the four hydrogen atoms in ammonium ion (NH_4^+) by alkyl/aryl groups (NR_4^+). Some examples of quaternary ammonium compounds are:

$(CH_3CH_2)_4N^+ Cl^-$

Tetraethylammonium chloride



Benzyltrimethylammoniumbromide

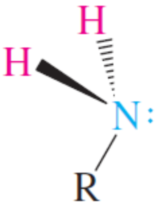
2.3 Classification of Amine:

Amines are classified according to the nature and number of substituents on nitrogen. **Aliphatic amines** contain only H and alkyl substituents whereas **Aromatic amines** have the nitrogen atom connected to an aromatic ring. Based on the number of carbon atoms adjacent to nitrogen, amines are classified as:

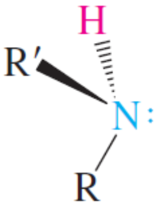
Primary (1^0) amines: Primary amines are those in which one of three hydrogen atoms in ammonia is replaced by an alkyl or aromatic group. Important primary alkyl amines include, methylamine, while primary aromatic amines include aniline.

Secondary (2^0) amines: Secondary amines are those in which two of three hydrogen atoms in ammonia are replaced by an alkyl or aromatic groups. For example, diethylamine is a secondary alkyl amine and diphenyl amine is secondary aromatic amine.

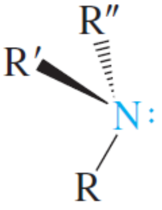
Tertiary (3^0) amines: In tertiary amines, all the three hydrogen atoms in ammonia are substituted by organic substituents. Examples include trimethylamine and triphenyl amine.



Primary amine



Secondary amine



Tertiary amine

Note: *The difference in classification of alcohols and amines: Unlike alcohols and alkyl halides, which are classified as primary, secondary, or tertiary according to the degree of substitution at the carbon that bears the functional group, amines are classified according to their degree of substitution at nitrogen.*

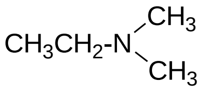
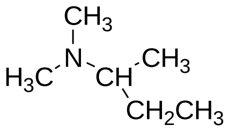
2.4 Nomenclature of Amines:

2.4.1 Aliphatic amines

In common system, aliphatic amines are named by adding word -*amine* to the name of the alkyl group that bears the nitrogen. Hence, aliphatic amines are called alkylamines.

In case of mixed secondary & tertiary amines (where both alkyl groups are different), the names of alkyl groups are arranged in alphabetical order and suffix amine is then added. More complicated ones are often named by prefixing amino- the name of the parent chain. For example: N,N-Dimethylaminoethane, N,N-Diethyl-2-aminopropane, etc.

In the IUPAC nomenclature, the names of amines are derived by adding the **amine** suffix to the systematic name of the parent alkane. Consequently, amines are named as **alkanamines**. The process begins by identifying the longest carbon chain that contains the amino group and then numbering from the end of the chain that gives the amino group the lowest locant.

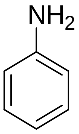
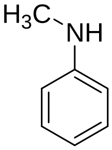
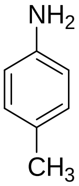
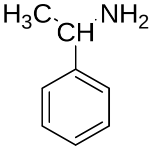
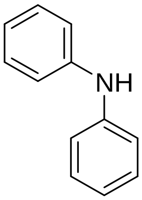
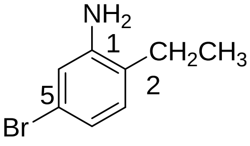
Structure	**Common Name**	**IUPAC Name**
$CH_3CH_2CH_2NH_2$	n-Propylamine or 1-Aminopropane	1-Propanamine
$CH_3CH_2CH(NH_2)CH_2CH_3$	3-Aminopentane	3-Pentanamine
$CH_3NHCH_2CH_3$	Ethylmethylamine	N-Methylethanamine
 $CH_3CH_2\text{-}N(CH_3)_2$	N,N-Dimethylaminoethane	N,N-Dimethylethanamine
 $(CH_3)_2N\text{-}CH(CH_3)CH_2CH_3$	2-(N,N-Dimethylamino)butane Or Dimethyl-*sec*-butylamine	2-(N,N-Dimethyl)butanamine

2.4.2 Aromatic amines

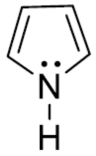
In common system, aromatic amines are called aryl amines. The simplest aromatic amine is aniline ($C_6H_5NH_2$). In some cases special names such as toluidine (for methyl aniline), anisidine(for methoxy aniline) are also used.

In the IUPAC System, aromatic amines are named as derivatives of aniline. *Aniline* is the parent IUPAC name for amino-substituted derivatives of benzene. Substituted anilines are numbered beginning at the carbon that bears the amino group. Substituents are listed in alphabetical order, and the direction of numbering is governed by the usual "first point of difference" rule. The name of arylamine in IUPAC system can also be obtained by replacing the terminal e from the name of the corresponding arene with amine. For example, $C_6H_5NH_2$ is called as benzenamine.

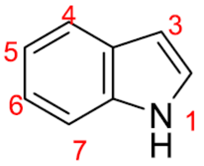
Name Aniline:
Aniline was first isolated in 1826 as a degradation product of indigo, a dark blue dye obtained from the West Indian plant *Indigofera anil*, from which the name *aniline* is derived.

Structure	**Common Name**	**IUPAC Name**
	Aniline	Aniline or Benzenamine
	N-Methylaniline	N-Methylaniline or N-Methybenzenamine
	p-Toluidine	4-Methybenzenamine or 4-methylaniline
	1-Phenylaminoethane	1-Phenylethanamine
	Diphenylamine	N-Phenylbenzenamine
	--	5-Bromo-2-ethylaniline

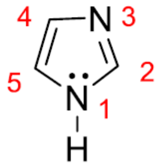
2.4.3 Aromatic hetero cyclic amines also exist. Heterocyclic amines are cyclic compounds in which one or more of the atoms of the ring are nitrogen atoms. The heterocyclic nitrogen is always numbered as position 1. IUPAC nomenclature of some heterocyclic amines is given below:



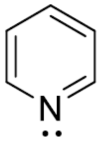
Pyrrole



Indole



Imidazole

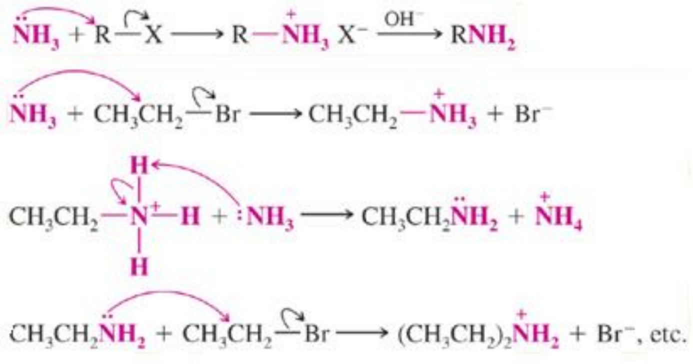


Pyridine

2.5 Methods of preparation of amines from alkyl halides and primary amides:

2.5.1 Hofmann's ammonolysis:

When an alcoholic solution of an alkyl halide and ammonia is heated at 373 K in a sealed tube primary amines are formed. The primary amine so produced reacts with another molecule of alkyl halide to yield secondary amine which then reacts with one more molecule of alkyl halide to produce tertiary amine and finally quaternary ammonium salt.



Drawback of Hofmann's ammonolysis:

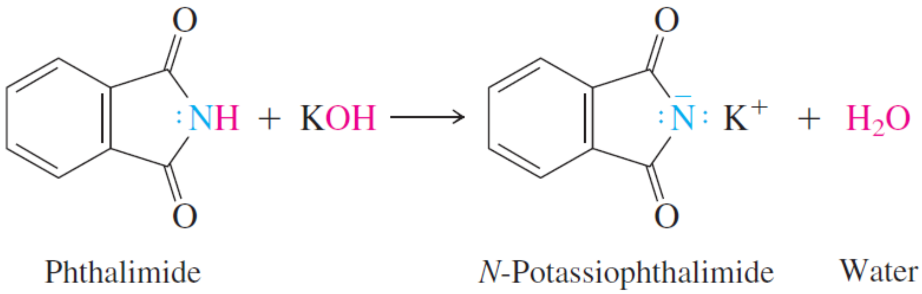
1. Competitive alkylation takes place leading to the production of mixture of primary, secondary & tertiary amines along with quaternary ammonium salts. Multiple alkylations can be minimized using excess of ammonia.

2. Aryl amines cannot be prepared by this method since aryl halides are less reactive than alkyl halides towards nucleophilic substitution reactions.

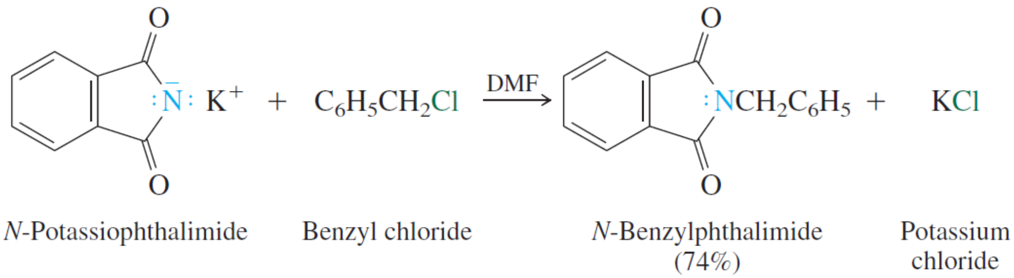
2.5.2 Gabriel's Phthalimide synthesis:

A method that attains the same end product as that of alkylation of ammonia but which avoids the formation of side products such as secondary & tertiary amines along with quaternary salts is the **Gabriel's Phthalimide** synthesis. This is a very suitable method for the preparation of pure aliphatic/aralkyl primary amines.

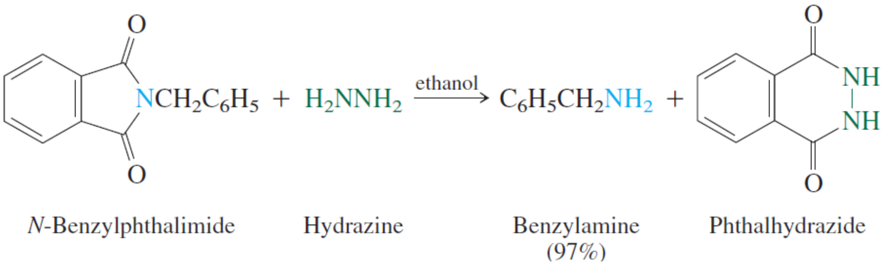
Step I. Preparation of key reagent: The key reagent i.e., potassium salt of phthalimide is prepared by treatment of phthalimide with an alcoholic solution of potassium hydroxide:



Step II. Bimolecular nucleophilic substitution (SN2) process: The potassium salt of phthalimide has a negatively charged nitrogen atom, which acts as a nucleophile toward primary alkyl halides in a bimolecular nucleophilic substitution (SN2) process. On heating with an alkyl or aralkyl halide, potassium phthalimide gets converted into N-alkyl/aralkyl phthalimide.



Step III. Hydrazinolysis of N-alkyl phthalimides: The product of above reaction is an imide, a diacyl derivative of an amine. Either aqueous acid or aqueous base can be used to hydrolyze its two amide bonds and liberate the desired primary amine. A more effective method of cleaving the two amide bonds is by reaction with hydrazine:



Note: Besides alkyl halides and aralkyl halides; α-halo ketones, α-halo esters, and alkyl *p*-toluenesulfonates have also been used in Gabriel's Phthalimide synthesis..

Drawback: Aryl halides cannot be converted to arylamines by the Gabriel synthesis because they do not undergo nucleophilic substitution with N-potassiophthalimide in the first step of the procedure.

2.5.3 Hofmann bromamide reaction (Hofmann degradation of amides):

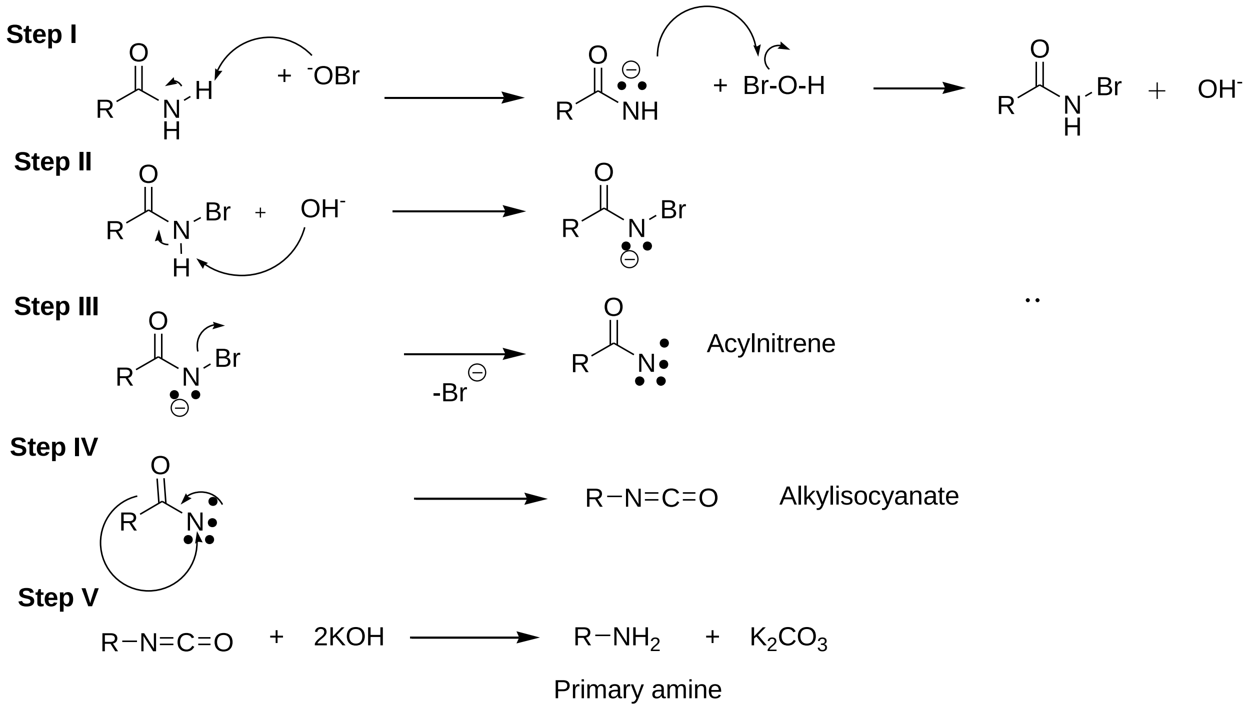
Hofmann degradation of amides has the special feature of yielding a product containing one carbon less than the starting material. The reaction involves migration of a group from carbonyl carbon to the adjacent nitrogen atom, and thus is an example of a **molecular rearrangement.** The reaction protocol involves the treatment of primary amide with bromine or chlorine in aqueous alkali to yield primary amine with one carbon less.

Mechanism:

The reaction is initiated by hypobromite ion (OBr^-) which is formed by reaction of bromine (Br_2) with alkali.

$$Br_2 + OH^- \longrightarrow {}^-OBr + Br^- + H_2O$$

Various steps involved in the reaction are:



Step (1) is the halogenation of an amide.

Step (2) is the abstraction of a hydrogen ion by hydroxide ion. This is reasonable behavior for hydroxide ion, especially since the presence of the electron withdrawing bromine increases the acidity of the amide.

Step (3) involves the separation of a halide ion, which leaves behind an electron-deficient nitrogen atom i.e., nitrene.

In Step (4) the actual rearrangement occurs in which the migrating group shifts from carbon to nitrogen with retention of configuration.

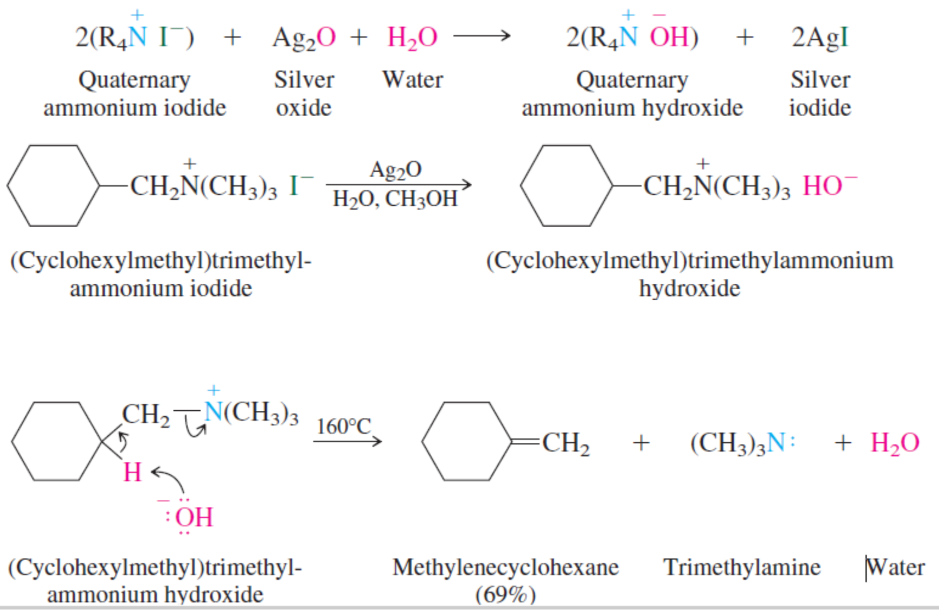
Step (5) involves the hydrolysis of an isocyanate (R -N - C=O) to form an amine and carbonate ion. This is a known reaction of isocyanates. If the Hofmann degradation is carried out in the absence of water, an isocyanate can actually be isolated.

2.6 Reactions:

2.6.1 Hofmann vs. Saytzeff elimination

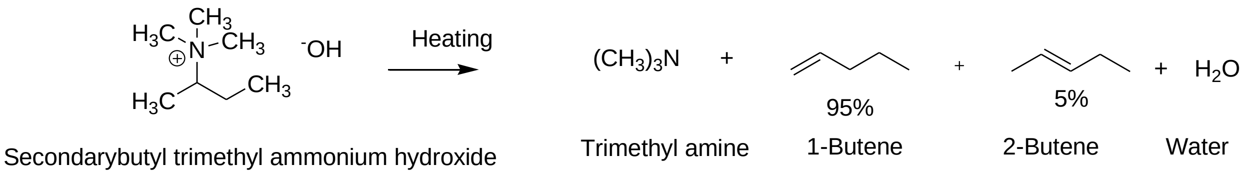
Hofmann elimination:

The halide anion of quaternary ammonium halides may be replaced by hydroxide by treatment with aqueous slurry of silver oxide. Silver halide precipitates, and a solution of the quaternary ammonium hydroxide is formed. Quaternary ammonium hydroxides so produced when heated to 400 K (127 °C) or higher, undergo E2 β elimination to form an alkene, water and a tertiary amine. For example;



This reaction was developed by August W. Hofmann and hence known as the **Hofmann elimination.** It is an anti elimination of the E2 type.

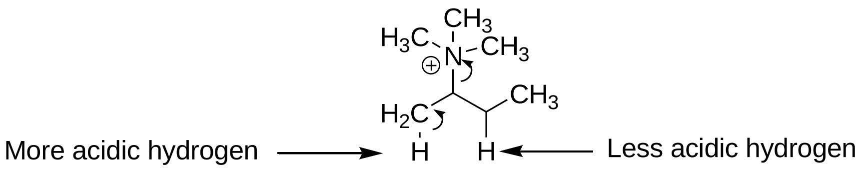
Regioselectivity in Hofmann elimination: Another aspect of the Hofmann elimination is its regioselectivity. The less sterically hindered β-hydrogen is removed by a base in Hofmann elimination i.e., elimination in alkyltrimethylammonium hydroxides proceeds in the direction that gives the *less* substituted alkene as the major product.



Note: *The formation of quaternary ammonium salts, followed by elimination in Hofmann reaction, is very useful in the determination of the structures of certain complicated nitrogen-containing compounds. The compound, which may be a primary, secondary, or tertiary amine, is* *converted into the quaternary ammonium hydroxide by treatment with excess methyl iodide and silver oxide. The number of methyl groups taken up by nitrogen depends upon the class of the amine; a primary amine will take up three methyl groups, a secondary amine will take up two, and a tertiary amine only one. This process is known as exhaustive methylation of amines.*

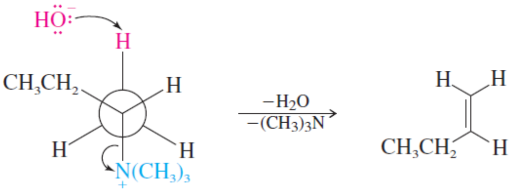
When heated, a quaternary ammonium hydroxide undergoes elimination to an alkene and a tertiary amine. From the structures of these products it is often possible to deduce the structure of the original amine.

Mechanism: In Hofmann's reaction, the direction of elimination is governed by the acidity of the β-hydrogens. For example, 1-butene is the major product in dehydrohalogenation of secondary butyl trimethyl ammonium hydroxide owing to greater acidity of β-hydrogens on the CH_3 group than CH_2 group.



Stereochemistry in Hofmann elimination:

Stereochemistry of Hofmann elimination is commonly anti. Given below is the conformation leading to 1-butene by anti elimination

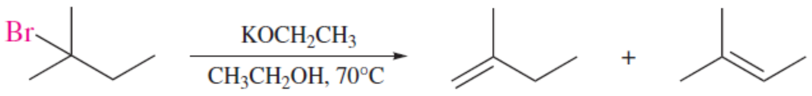


1-Butene
(major product)

Zaitsev (Saytzeff) elimination:

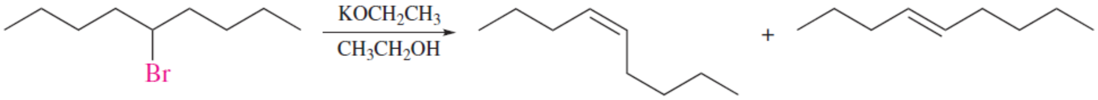
In 1875, Alexander M. Zaitsev of the University of Kazan (Russia) set forth a generalization describing the regioselectivity of β eliminations. Zaitsev's rule stated that "*The alkene formed in greatest amount is the one that correspond to removal of the hydrogen from the β-carbon having the fewest hydrogen substituents*"

In other words we can say that in base catalysed dehydrohalogenation or acid acatalysed dehydration of alcohols the major product is the one with the more highly substituted double bond (the more stable alkene).



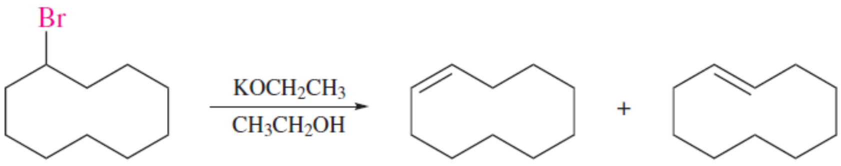
2-Bromo-2-methylbutane 2-Methyl-1-butene (29%) 2-Methyl-2-butene (71%)

Stereochemistry in Zaitsev (Saytzeff) elimination: In addition to being regioselective, dehydrohalogenation of alkyl halides is stereoselective and favors formation of the more stable stereoisomer. For example, in case of 5-bromononane, the *trans* (or *E*) alkene is formed in greater amounts than its *cis* (or *Z*) stereoisomer.



5-Bromononane *cis*-4-Nonene (23%) *trans*-4-Nonene (77%)

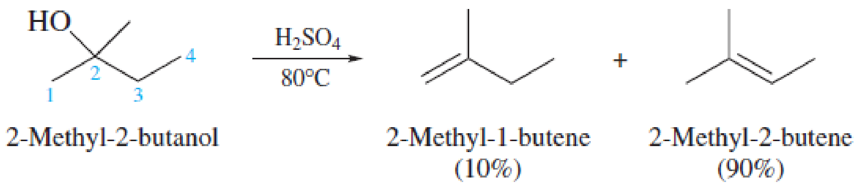
However, in case of cycloalkyl halides, dehydrohalogenation leads exclusively to *cis* cycloalkenes when the ring has fewer than ten carbons. For larger rings cycloalkyl halides give mixtures of *cis* and *trans* cycloalkenes.



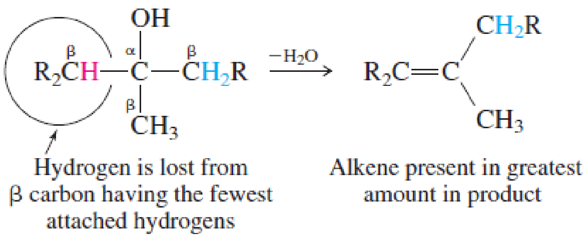
Bromocyclodecane *cis*-Cyclodecene (*Z*)-cyclodecene (85%) *trans*-Cyclodecene (*E*)-cyclodecene (15%)

Regioselectivity in dehydration of alcohols:

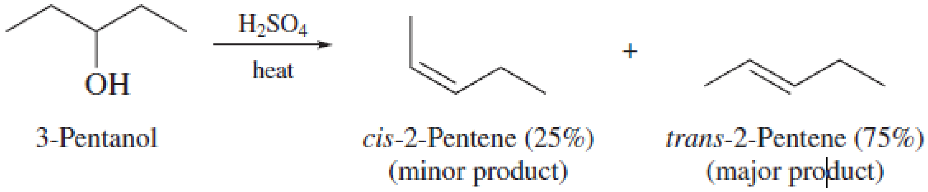
Acid catalyzed dehydration in 2-methyl- 2-butanol can occur in two different directions to give alkenes that are constitutional isomers. Here, a double bond can be created either between C-1 and C-2 or between C-2 and C-3. Under the usual reaction conditions 2-methyl-2-butene is the major product (90%), and 2-methyl-1-butene (10%) is the minor one.



According to Zaitsev (Saytzef) rule “β elimination reactions of alcohols yield the most highly substituted alkene as the major product” because, the most highly substituted alkene is also usually the most stable one.

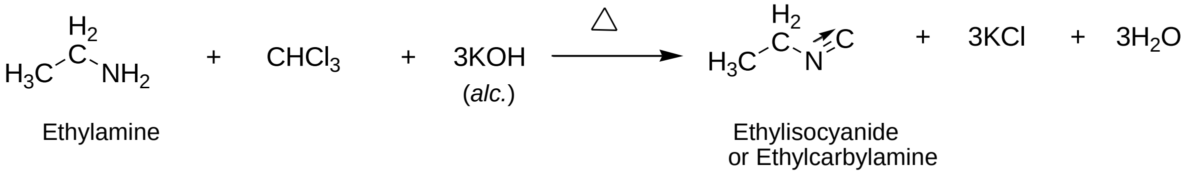


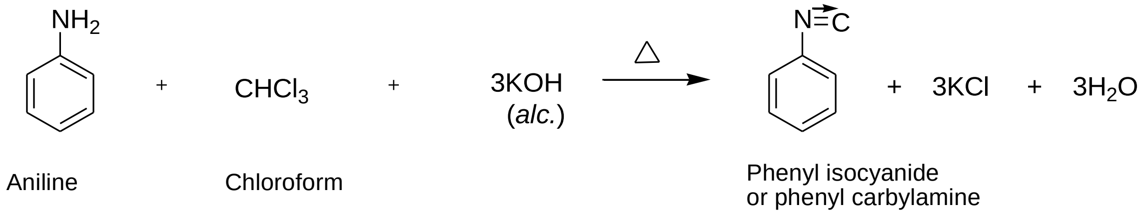
Dehydration reactions of alcohols are also **stereo selective** as more highly stable *trans* isomer predominates in dehydration of 3-pentanol.



2.6.2 Carbylamine test

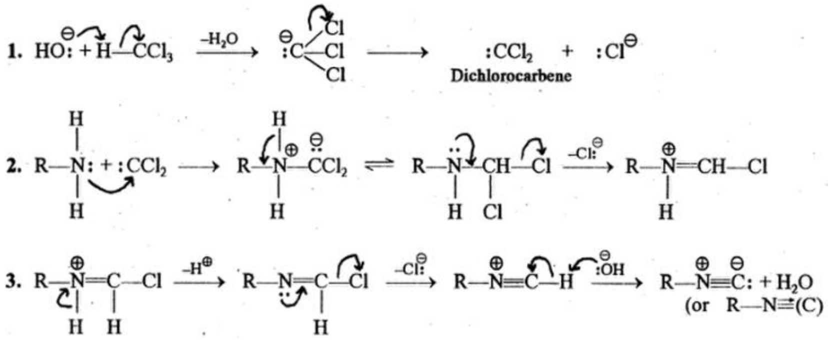
Both aliphatic and aromatic primary amines when warmed with chloroform and alcoholic KOH solution gives an unpleasant odour due to the formation of isocyanide or carbylamines. This reaction is called carbylamines reaction.





This reaction is used as a test to distinguish primary amines from secondary and tertiary amines.

Mechanism of carbylamine reaction: The mechanism involves hedydrohalogenation of chloroform to give dichlorocarbene intermediate. Dichlorocarbene being very reactive undergoes electrophilic attack on the nucleophilic nitrogen of the primary amine. The elimination of the hydrochloric acid leads to the formation of isonitrile. An illustration of the carbylamine reaction mechanism is provided below.



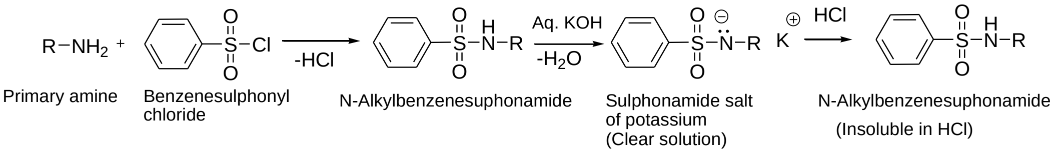
Alkylisocyanide

2.6.3 Hinsberg test (Analysis of amines)

Hinsberg test is used to distinguish between primary, secondary and tertiary amines. The test involves the treatment of amine with Hinsberg's reagent i.e., benzenesulfonyl chloride in the presence of aqueous potassium hydroxide.

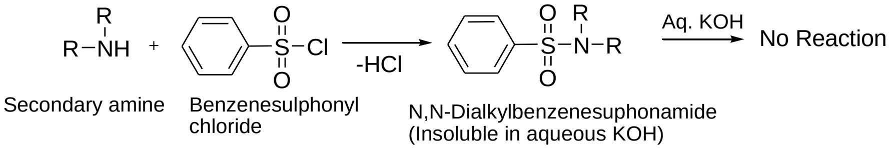
Primary amine forms monosubstituted sulfonamide which has acidic hydrogen attached to nitrogen. Reaction with potassium hydroxide converts this amide into a soluble salt (clear solution) which on acidification gives insoluble amide (N-alkylbenzenesulphonamide).

Primary amine:



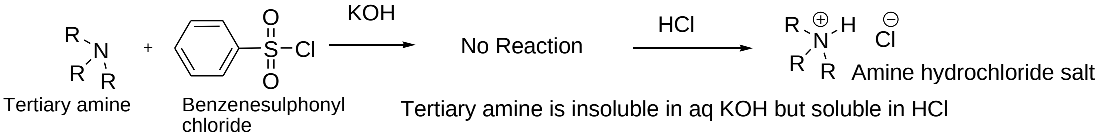
Secondary amine:

Secondary amine forms disubstituted sulfonamide which has no acidic hydrogen and hence remains insoluble in the alkaline reaction mixture. Addition of acid has no effect on it.



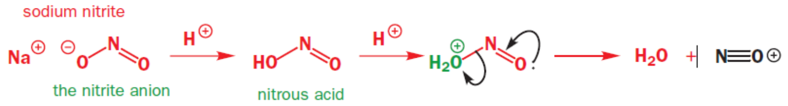
Tertiary amine:

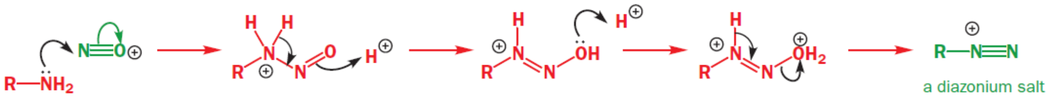
A tertiary amine does not react at all with Hinsberg’s reagent and hence yields an insoluble compound (the unreacted amine itself) which dissolves upon acidification of the mixture to give a clear solution.



2.6.4 Reaction with HNO_2

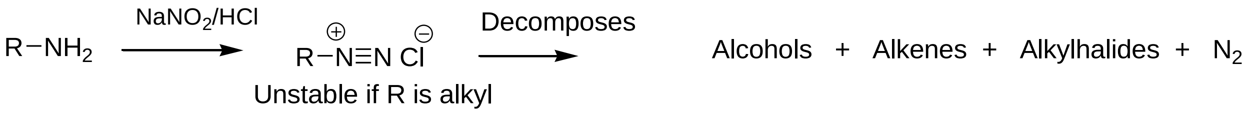
This reaction is used as the basis of a test to distinguish between primary, secondary and tertiary amines and is known as Nitrous Acid Test. Nitrous acid (HONO) is prepared *in situ* by reaction of sodium nitrite with a strong aqueous acid.





Primary Amine:

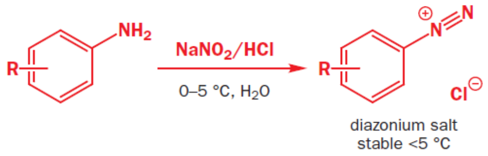
Primary alkylamines react with nitrous acid in cold to yield diazonium salt. This diazonium salt is very unstable and immediately loses nitrogen gas to give a planar carbocation, which normally reacts with a nucleophile in an SN1 process or loses a proton in an E1 process to give a complex mixture consisting of alcohols, alkenes, alkyl halides along with evolution of nitrogen (N_2) gas.



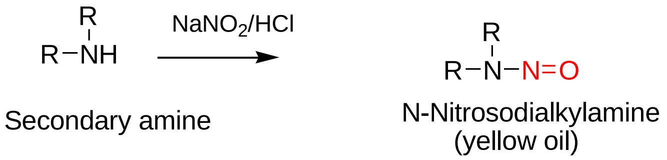
$$R{-}NH_2 \xrightarrow{NaNO_2/HCl} R{-}\overset{\oplus}{N}{\equiv}N\ \overset{\ominus}{Cl} \xrightarrow{\text{Decomposes}} \text{Alcohols} + \text{Alkenes} + \text{Alkylhalides} + N_2$$

Aliphatic primary amine reacts with HNO_2 to produce nitrogen gas (as bubbles) which is a test for aliphatic primary amines as no other class of amines liberate nitrogen gas on reaction with nitrous acid.

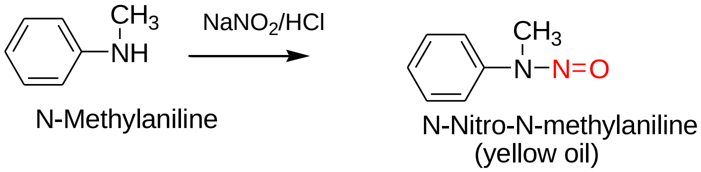
If R is an aryl group, the carbocation is much less stable (since the empty orbital is sp^2 rather than a p orbital) and that makes the loss of nitrogen slower. If the diazotization is done at low temperature (0° - 5 °C), the diazonium salt is stable and can be reacted with various nucleophiles.



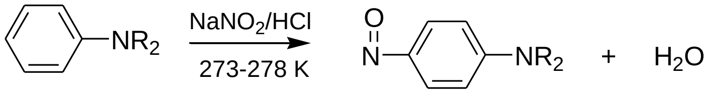
Secondary amines: On treatment with nitrous acid secondary amines (both aliphatic and aromatic) give N-nitrosoamines which separate out as a yellow oil layer. These on warming with a small crystal of phenol and a few drops of H_2SO_4(conc.) provide green coloured solution which turns blue with NaOH and red on dilution. This reaction, known as Libermann's nitroso raction, is used as a test from secondary amines.



$$R_2NH \xrightarrow{NaNO_2/HCl} R_2N{-}N{=}O$$



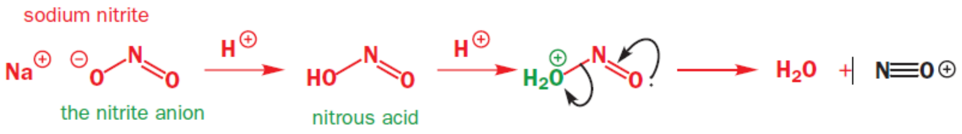
Tertiary amines: Aromatic tertiary amines undergo electrophilic substitution at *p*-position to yield *p*-nitrosamines. For example,



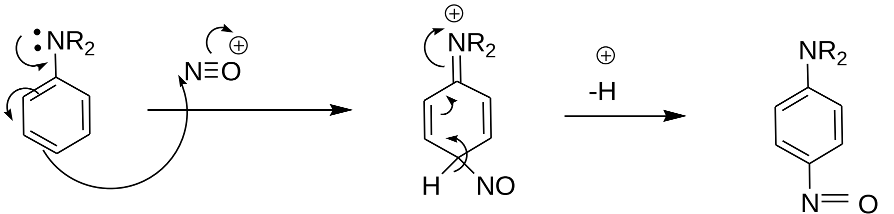
N,N-Dialkylaniline   *p*-Nitroso-N,N-dialkylaniline

Mechanism:

Step 1: Nitrous acid prepared *insitu* from sodium nitrite and hydrochloric acid was followed by loss of water to produce nitrosonium ion.

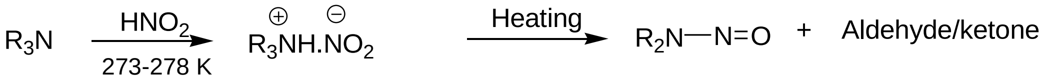


Step 2: Nitrosonium ion attacks the benzene ring at the less hindered para position to yield *p*-nitroso amines.



N,N-Dialkylaniline   p-Nitroso-N,N-dialkylaniline

Aliphatic tertiary amines, on the other hand, react with nitrous acid to produce trialkylammonium nitrite salt which is water soluble. These nitrite salts sometimes decomposes on heating to generate N-nitroso derivative along with a carbonyl compound (aldehyde or ketone).

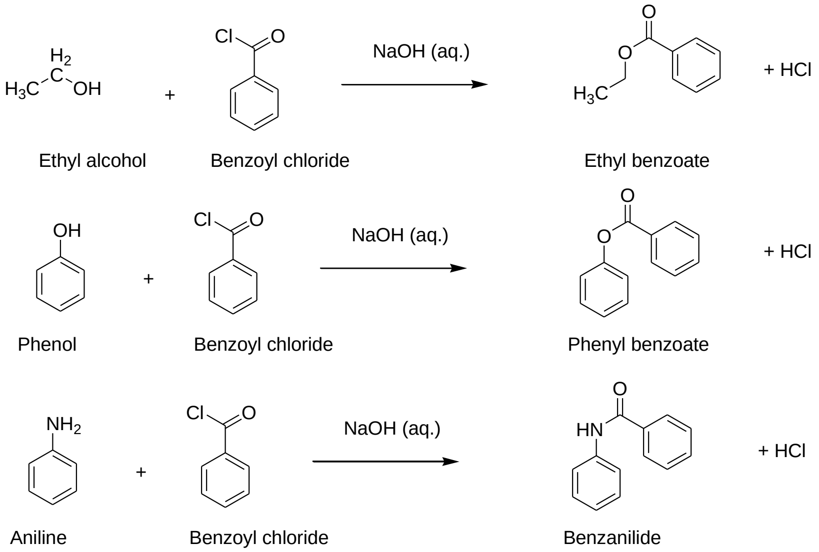


$$R_3N \xrightarrow[273\text{-}278\ K]{HNO_2} R_3\overset{\oplus}{N}H.\overset{\ominus}{NO_2} \xrightarrow{\text{Heating}} R_2N{-}N{=}O + \text{Aldehyde/ketone}$$

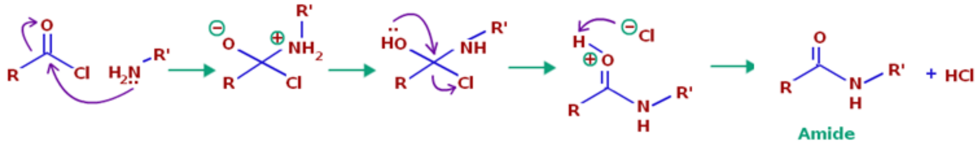
Trialkylammonium nitrite   N-Nitroso derivative

2.6.5 Schotten – Baumann Reaction

Schotten – Baumann Reaction involves the benzoylation of compounds containing active hydrogen atom such as aniline, phenol, alcohol etc. with benzoyl chloride in the presence of either aqueous NaOH or pyridine. The function of base is to neutralize the liberated HCl and also to catalyze the reaction. Moreover, the base is necessary to encourage an equilibrium shift towards the formation of amides. For example,

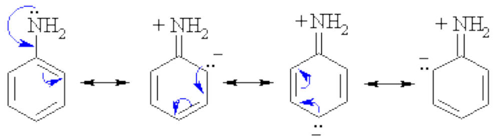


Mechanism:

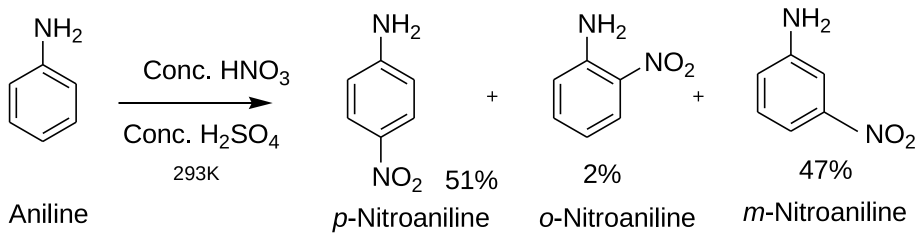


2.6.6 Electrophilic substitution reactions (case aniline):

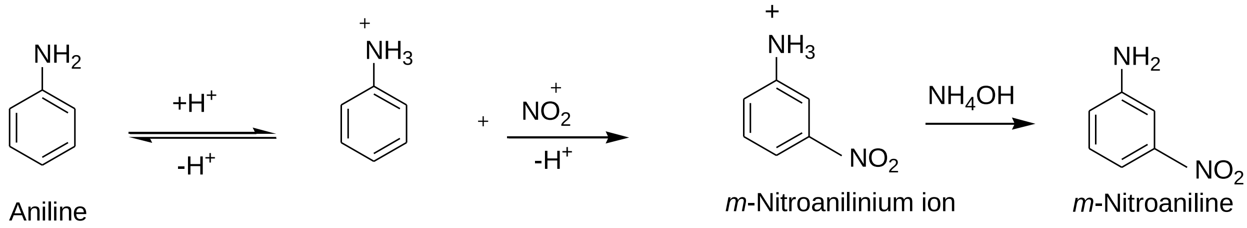
Aniline undergoes electrophilic substitution reactions readily due to strong activating effect of amino group. Amino group increases the electron density in the aromatic ring and makes arylamines extremely reactive toward electrophilic aromatic substitution. The delocalization of the lone pair of electrons of nitrogen atom over the ring results in increase in electron density at *ortho*- and *para*- positions as compared to meta position. Thus, NH_2 is an *ortho*-, *para*- directing group.



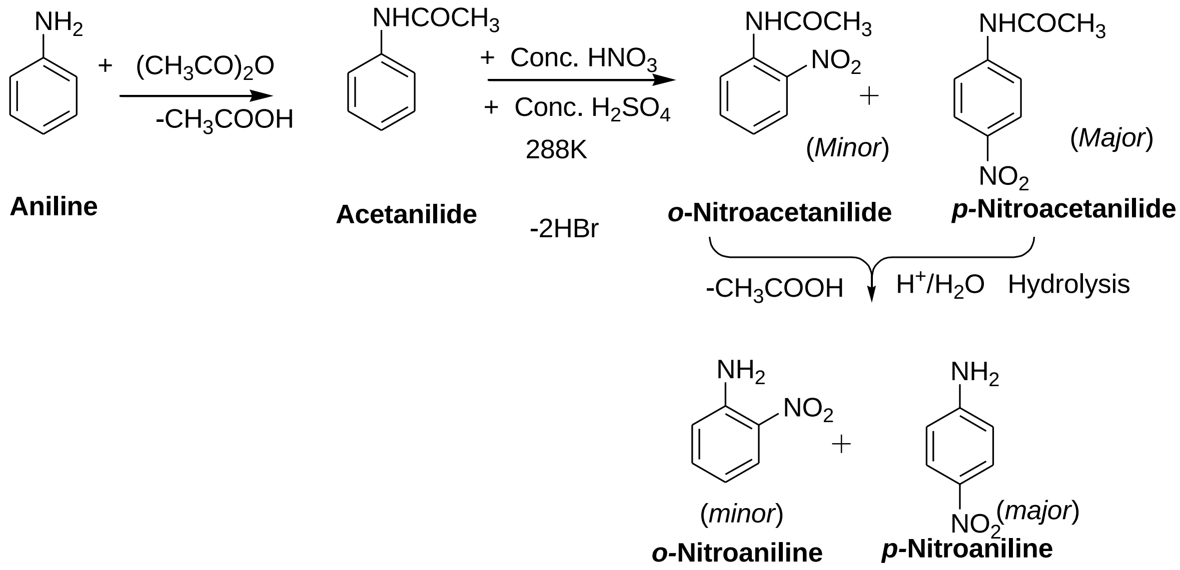
2.6.6.1 Nitration: Direct nitration with nitric acid is not a useful method as nitric acid not only acts as nitrating agent but also as a strong oxidizing agent. However, under controlled conditions, nitration of aniline yields a mixture of *o*-, *m*-, and *p*- products.



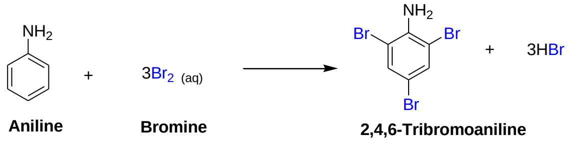
The formation of *meta*- product is due to protonation of -NH_2 group to give -$^+NH_3$ group which directs the incoming electrophile to *meta*- position due to nonavailability of lone pair on nitrogen.

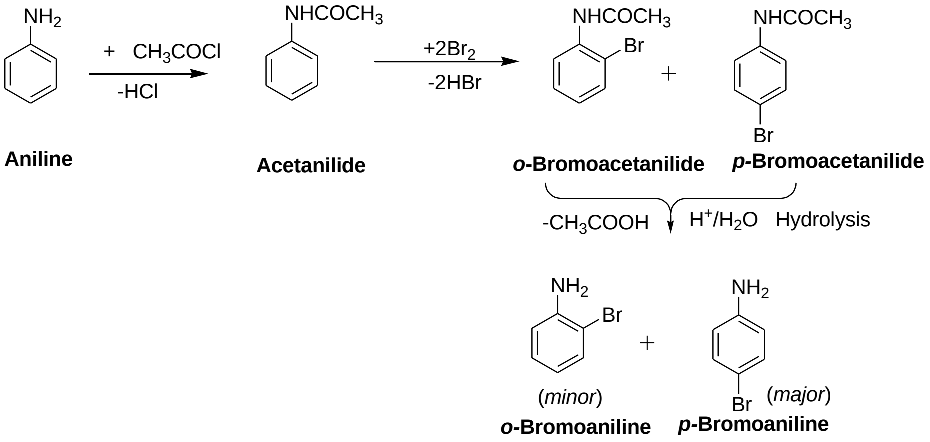


Therefore to avoid the formation of *m*-product in nitration, it is more convenient to first protect the amino group in aniline by acetylation. The acetyl group is removed in the final step by hydrolysis.



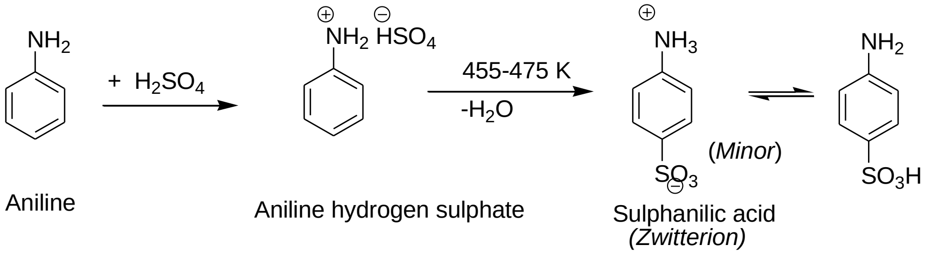
2.6.6.2 Halogenation: Due to strong activating effect of amino group, the halogenations reaction of aniline proceeds very fast to provide 2,4,6-trisubstituted amines and it is often difficult to stop the reaction at the monosubstitution stage, therefore to stop the reaction at this stage the activity of amino group is reduced by protection of NH_2 group with acetic anhydride or acetyl chloride. Acetyl group is removed in the final step by hydrolysis.





2.6.6.3 Sulphonation

Sulphonation of aniline takes place under drastic conditions i.e., treatment with conc. H_2SO_4 at 455 -475 K for 4-5 hours, to give *p*-aminobenzenesulphonic acid also called sulphanilic acid.



Sulphanilic acid is insoluble in water as well as in organic solvents and has high melting point due to its Zwitterion character.

References:

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3. Morrison, R. T. & Boyd, R. N. Organic Chemistry, Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).

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