

Organic Chemistry
Semester-4, CBCS
Course: CEMG CC-4/GE-4

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Lecture Note prepared by Kaushik Basu, SPCMC

Chemistry of amines:

Introduction:

Amines are derivatives of ammonia in which one or more of the protons have been replaced with alkyl or aryl groups.

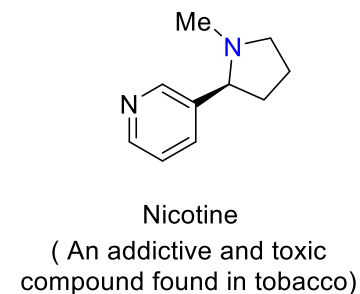
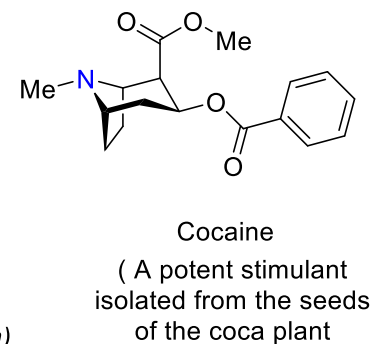
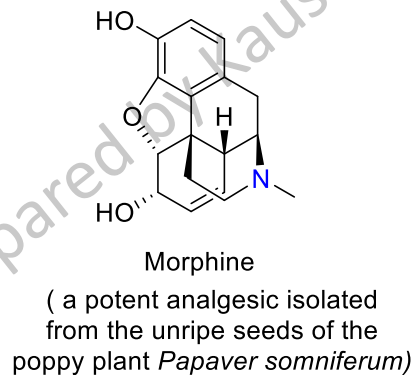
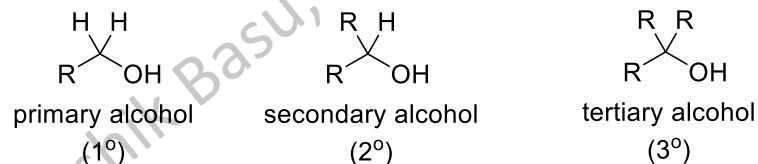
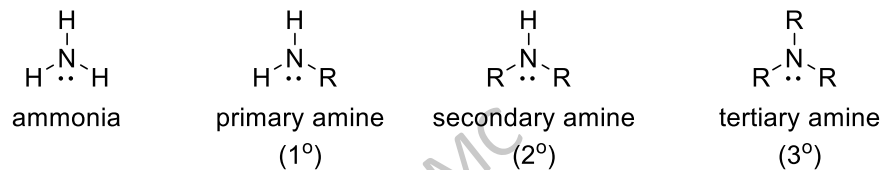
Amines are classified as primary, secondary, or tertiary, depending on the number of groups attached to the nitrogen atom.

Note that these terms have a different meaning than when they were used in naming alcohols.

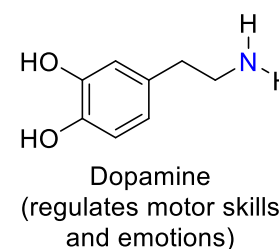
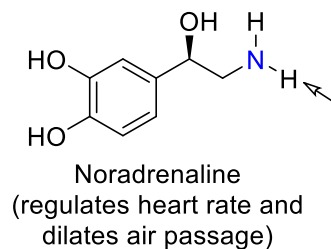
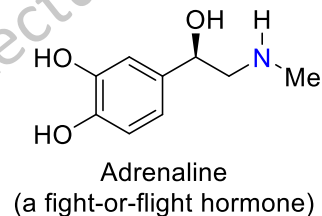
A tertiary alcohol has three groups attached to the α -carbon, while a tertiary amine has three groups attached to the nitrogen atom.

Amines are abundant in nature. Naturally occurring amines isolated from plants are called alkaloids. Below are examples of several alkaloids that have garnered public awareness as a result of their physiological activity:

amines: if R = alkyl, aliphatic amines, if R = aryl, aromatic amines



Many amines also play vital roles in neurochemistry (chemistry taking place in the brain). Below are a few examples:



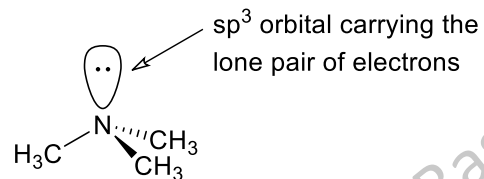
Chemistry of amines:

Structure and property:

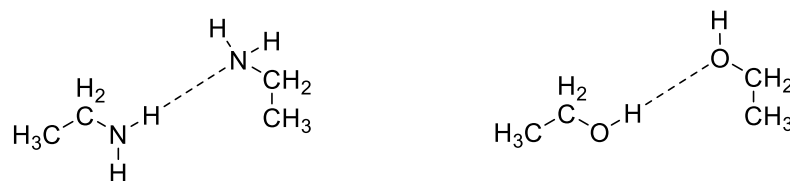
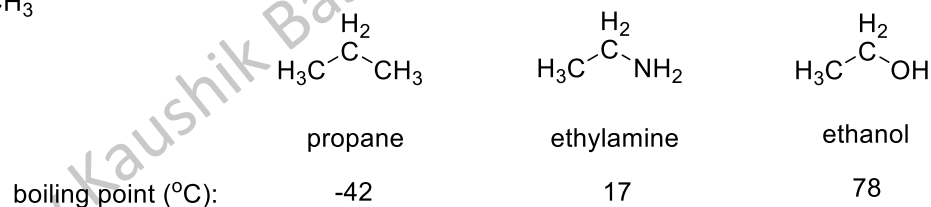
The nitrogen atom of an amine is typically sp^3 hybridized, with the lone pair occupying an sp^3 -hybridized orbital.

Consider trimethylamine as an example (shown below). The nitrogen atom exhibits trigonal pyramidal geometry, with bond angles of 108° .

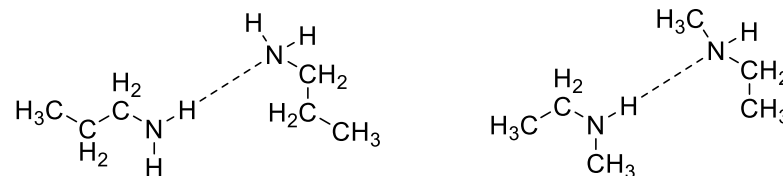
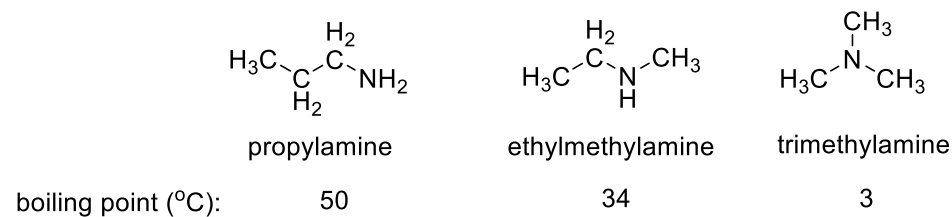
The C-N bond lengths are 147 pm, which is shorter than the average C-C bond of an alkane (153 pm) and longer than the average C-O bond of an alcohol (143 pm).



Primary and secondary amines can form intermolecular H bonds and typically have higher boiling points than analogous alkanes but lower boiling points than analogous alcohols.



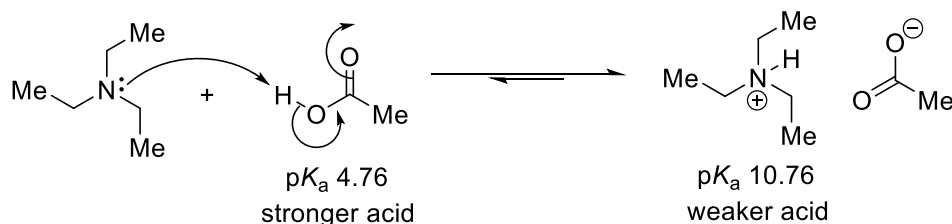
The boiling point of amines increases as a function of their capacity to form hydrogen bonds. As a result, primary amines typically have higher boiling points, while tertiary amines have lower boiling points. This trend can be observed by comparing the physical properties of the following three constitutional isomers:



Chemistry of amines:

Basicity:

One of the most important properties of amines is their basicity. Amines are generally stronger bases than alcohols or ethers, and they can be effectively protonated even by weak acids.



In this example, triethylamine is protonated using acetic acid.

Compare the pK_a values of acetic acid (4.76) and the ammonium ion (10.76).

Recall that the equilibrium will favour the weaker acid.

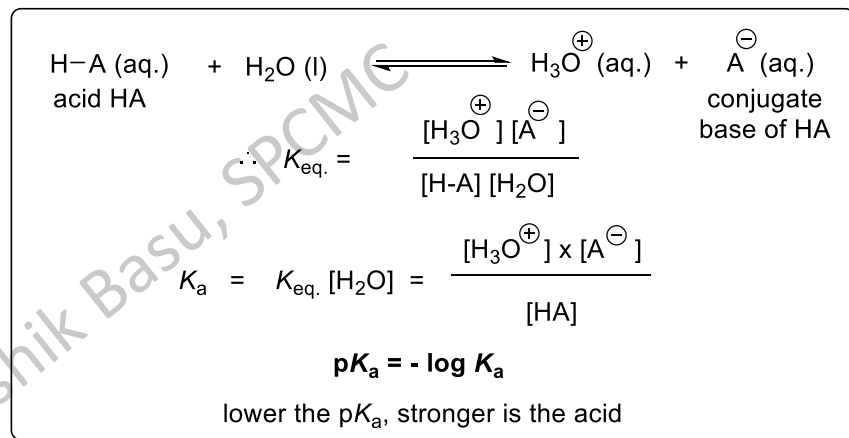
In this case, the ammonium ion is six orders of magnitude weaker than acetic acid, and therefore, the amine will exist almost completely in protonated form (one in every million molecules will be in the neutral form).

This example illustrates how the basicity of an amine can be quantified by measuring the pK_a of the corresponding ammonium ion.

A high pK_a indicates that the amine is strongly basic, while a low pK_a indicates that the amine is only weakly basic.

The following table shows pK_a values for the ammonium ions of many amines.

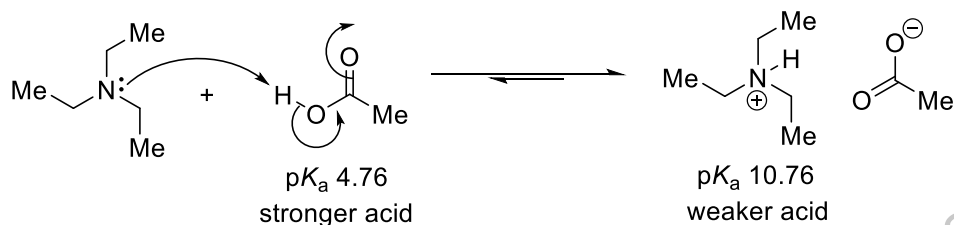
Amine	pK_a of ammonium ion	Amine	pK_a of ammonium ion	Amine	pK_a of ammonium ion
$\begin{array}{c} \text{H} \\ \\ \text{Me}-\text{N}:\text{H} \\ \\ \text{H} \end{array}$ methylamine	$\begin{array}{c} \text{H} \\ \\ \text{Me}-\text{N}^+\text{H} \\ \\ \text{H} \end{array}$ $pK_a = 10.6$	$\begin{array}{c} \text{H} \\ \\ \text{Me}-\text{N}:\text{H} \\ \\ \text{Me} \end{array}$ dimethylamine	$\begin{array}{c} \text{H} \\ \\ \text{Me}-\text{N}^+\text{H} \\ \\ \text{Me} \end{array}$ $pK_a = 10.7$	$\begin{array}{c} \text{Me} \\ \\ \text{Me}-\text{N}:\text{H} \\ \\ \text{Me} \end{array}$ trimethylamine	$\begin{array}{c} \text{H} \\ \\ \text{Me}-\text{N}^+\text{H} \\ \\ \text{Me} \end{array}$ $pK_a = 9.8$
$\begin{array}{c} \text{H} \\ \\ \text{Et}-\text{N}:\text{H} \\ \\ \text{H} \end{array}$ ethylamine	$\begin{array}{c} \text{H} \\ \\ \text{Et}-\text{N}^+\text{H} \\ \\ \text{H} \end{array}$ $pK_a = 10.6$	$\begin{array}{c} \text{H} \\ \\ \text{Et}-\text{N}:\text{H} \\ \\ \text{Et} \end{array}$ diethylamine	$\begin{array}{c} \text{H} \\ \\ \text{Et}-\text{N}^+\text{H} \\ \\ \text{Et} \end{array}$ $pK_a = 11.0$	$\begin{array}{c} \text{Et} \\ \\ \text{Et}-\text{N}:\text{H} \\ \\ \text{Et} \end{array}$ triethylamine	$\begin{array}{c} \text{H} \\ \\ \text{Et}-\text{N}^+\text{H} \\ \\ \text{Et} \end{array}$ $pK_a = 10.8$



Chemistry of amines:

Basicity:

One of the most important properties of amines is their basicity. Amines are generally stronger bases than alcohols or ethers, and they can be effectively protonated even by weak acids.



lower the pK_a , stronger is the acid

Aliphatic amines:

Amine	pK_a of ammonium ion	Amine	pK_a of ammonium ion	Amine	pK_a of ammonium ion
 methylamine	 $pK_a = 10.6$	 dimethylamine	 $pK_a = 10.7$	 trimethylamine	 $pK_a = 9.8$
 ethylamine	 $pK_a = 10.6$	 diethylamine	 $pK_a = 11.0$	 triethylamine	 $pK_a = 10.8$

Aromatic amines:

Amine	pK_a of ammonium ion	Amine	pK_a of ammonium ion
 aniline	 $pK_a = 4.6$	 <i>N,N</i> -dimethylaniline	 $pK_a = 5.1$
 <i>N</i> -methylaniline	 $pK_a = 4.8$		

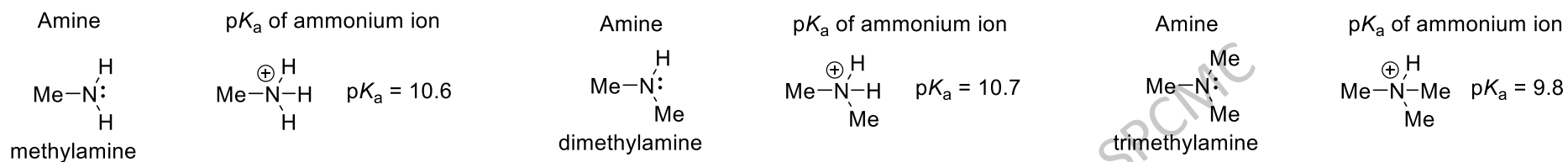
The ammonium ions of most alkyl amines are characterized by a pK_a value between 10 and 11,

Ammonium ions of aryl amines are more acidic (lower pK_a) than the ammonium ion of alkyl amines.

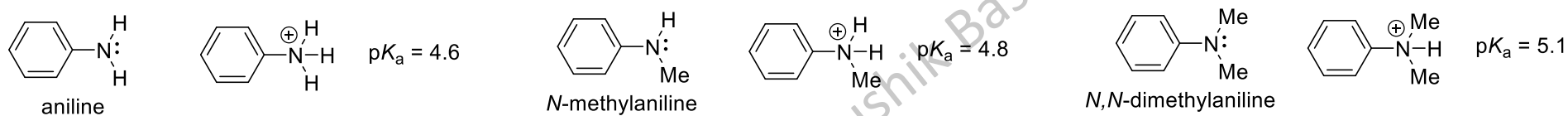
Chemistry of amines:

Basicity:

Aliphatic amines:



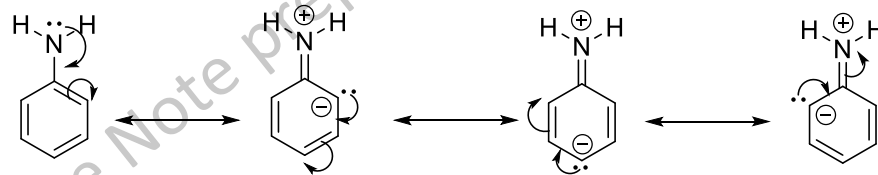
Aromatic amines:



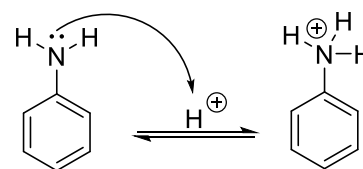
The ammonium ions of most alkyl amines are characterized by a pK_a value between 10 and 11,

Ammonium ions of aryl amines are more acidic (lower pK_a) than the ammonium ion of alkyl amines.

In other words, aryl amines are less basic than alkylamines. This can be rationalized by considering the delocalized nature of the lone pair of an aryl amine:



The lone pair occupies a p orbital and is delocalized by the aromatic system. This resonance stabilization is lost if the lone pair is protonated, and as a result, the nitrogen atom of an aryl amine is less basic than the nitrogen atom of an alkyl amine.

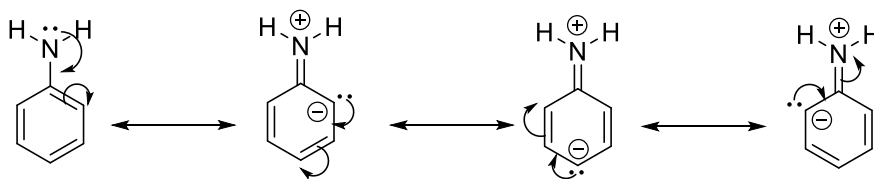


no l.p. of e available on N atom
 - no resonance with ring,
 - l.p. donation more difficult

The other way to consider this is to imagine the less availability of l.p. of an aryl amine as result of the conjugation with the benzene ring. This is absent for alkyl amines and thus, the l.p. is more available for protonation in case of alkyl amines, leading to the higher basicity.

Chemistry of amines:

Basicity:



The lone pair occupies a p orbital and is delocalized by the aromatic system. This resonance stabilization is lost if the lone pair is protonated, and as a result, the nitrogen atom of an aryl amine is less basic than the nitrogen atom of an alkyl amine.

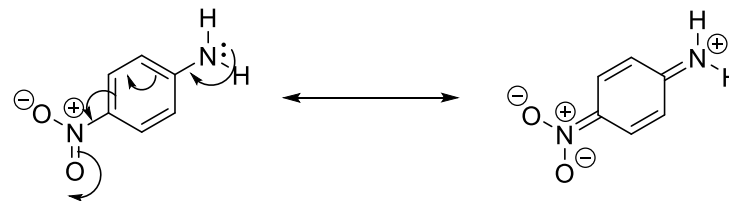
If the aromatic ring bears a substituent, the basicity of the amino group will depend on the identity of the substituent.

<i>para</i> -Substituted aniline	Ammonium ion
	 $pK_a = 6.2$
	 $pK_a = 5.3$
	 $pK_a = 5.1$
	 $pK_a = 4.6$
	 $pK_a = 4.0$
	 $pK_a = 1.7$
	 $pK_a = 1.0$

Increasing basicity (upward arrow) and Increasing acidity (downward arrow)

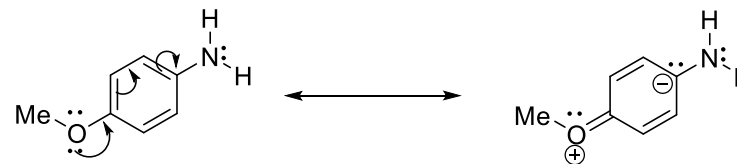
Electron-donating groups, such as methoxy, slightly increase the basicity of aryl amines, while electron-withdrawing groups, such as nitro, can significantly decrease the basicity of aryl amines.

This profound effect is attributed to the fact that the lone pair in *para*-nitroaniline is extensively delocalized:



Therefore, this lone pair is much less available for protonation, leading to weaker basicity of the nitroaniline.

For ERGs like methoxy, the ring is already e-rich:

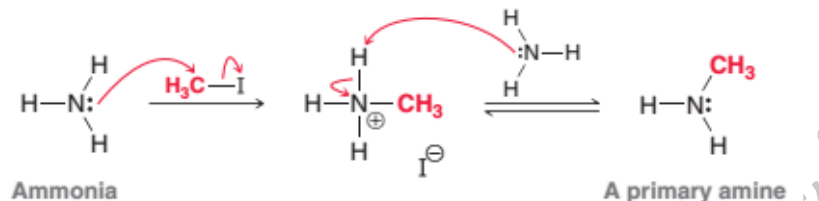


Chemistry of amines:

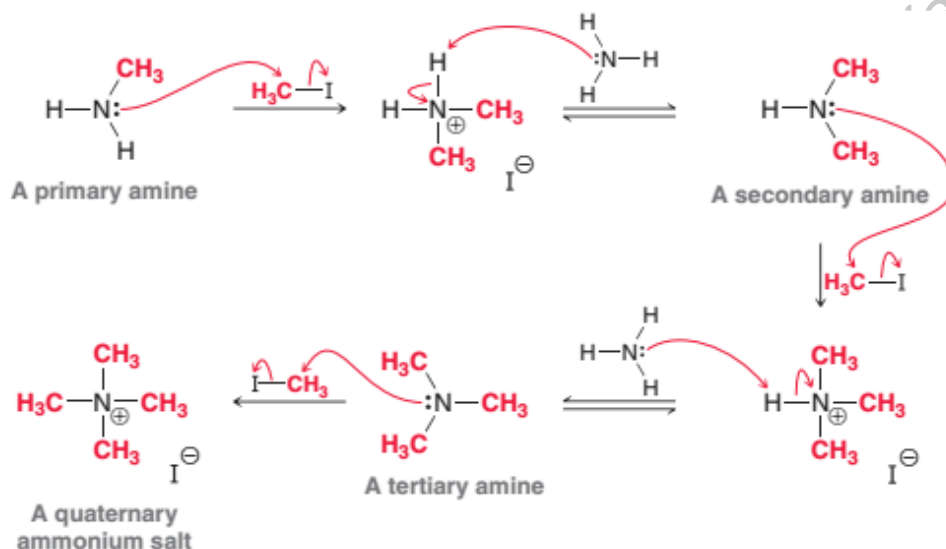
Preparation of amines:

i) Alkylation of ammonia and its modification: Gabriel's phthalimide synthesis:

Ammonia is a very good nucleophile and will readily undergo alkylation when treated with an alkyl halide.



This reaction proceeds via an S_N2 process followed by deprotonation to give a primary amine. As the primary amine is formed, it can undergo further alkylation to produce a secondary amine, which undergoes further alkylation to produce a tertiary amine. Finally, the tertiary amine undergoes alkylation one more time to produce a quaternary ammonium salt.



If the quaternary ammonium salt is the desired product, then an excess of the alkyl halide is used, and ammonia is said to undergo exhaustive alkylation. However, monoalkylation is difficult to achieve because each successive alkylation renders the nitrogen atom more nucleophilic.

If the primary amine is the desired product, then the process is generally not efficient because when 1 mol of ammonia is treated with 1 mol of the alkyl halide, a mixture of products is obtained.

For this reason, the alkylation of ammonia is only useful when the starting alkyl halide is inexpensive and the desired product can be easily separated or when exhaustive alkylation is performed to yield the quaternary ammonium salt.

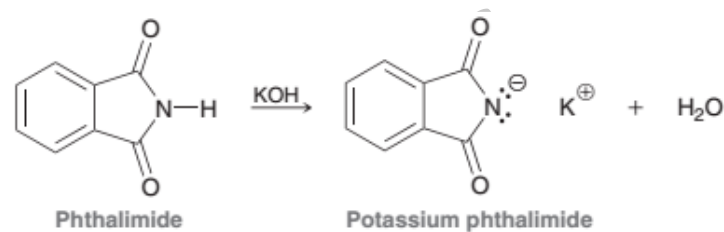
Chemistry of amines:

Preparation of amines:

i) Alkylation of ammonia and its modification: Gabriel's phthalimide synthesis:

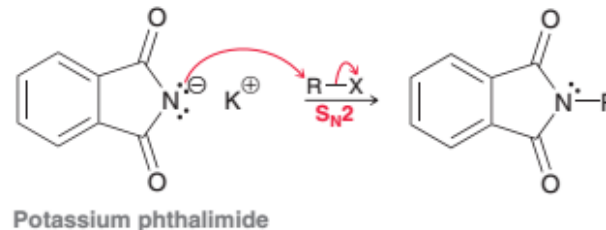
The Gabriel synthesis is one method for preparing primary amines while avoiding formation of secondary and tertiary amines.

The key reagent is potassium phthalimide, which is prepared by treating phthalimide with potassium hydroxide.



Hydroxide functions as a base and deprotonates phthalimide. The proton is relatively acidic ($pK_a=8.3$), because it is flanked by two C=O groups.

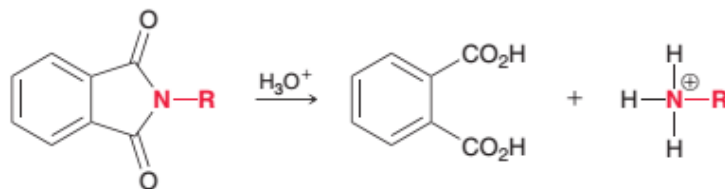
Potassium phthalimide can function as a nucleophile and is readily alkylated to form a C-N bond:



This reaction proceeds via an S_N2 process, so it works best with primary alkyl halides. It can be performed with secondary alkyl halides in many cases, but tertiary alkyl halides cannot be used. For tertiary halides, E2 elimination takes place and an alkene forms.

Acid-catalyzed or base-catalyzed hydrolysis needs to be performed to release the amine from the phthalimide derivative.

Acidic conditions are more common than basic conditions. Under acidic conditions, an ammonium ion is generated, which must be treated with a base to release the uncharged amine.

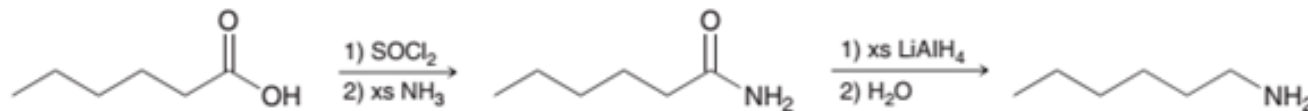


Chemistry of amines:

Preparation of amines:

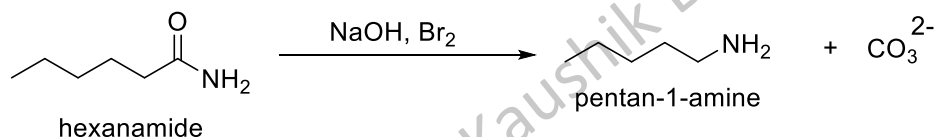
ii) From a carboxylic acid amide:

Amines can be prepared from carboxylic acids using the following approach:



The carboxylic acid is first converted into an amide, which is then reduced to give an amine. This approach for installation of an amino group does not involve introduction or removal of any additional carbon atoms; that is, the carbon skeleton is not changed.

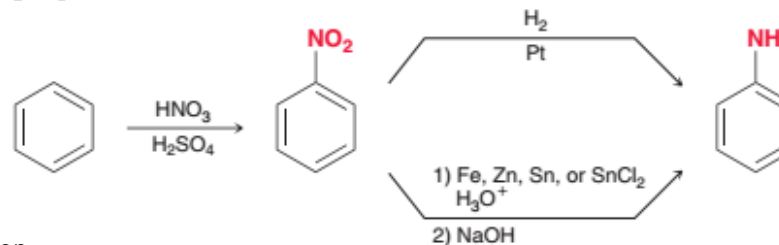
However, one can choose to synthesise a primary amine that will contain one carbon less than the parent amide, through the reaction known as Hofmann amide degradation:



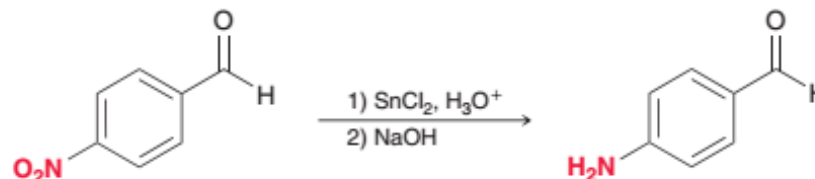
The amide carbon is lost as carbon dioxide which is trapped in the alkaline reaction medium as the carbonate.

iii) Reduction of nitro compounds: Way to access aromatic amines:

Aryl amines, such as aniline, can be prepared from benzene using the following approach:



The first step involves nitration of the aromatic ring, and the second step involves reduction of the nitro group. Several reagents can be used to accomplish this reduction, including hydrogenation in the presence of a catalyst or reduction with iron, zinc, tin, or tin(II) chloride (SnCl_2) in the presence of aqueous acid. The latter method is a milder approach that is used when other functional groups are present that would otherwise be susceptible to hydrogenation. For example, a nitro group can be selectively reduced in the presence of a carbonyl group:



When reducing a nitro group in acidic conditions, the reaction must be followed up with a base, such as sodium hydroxide, because the resulting amino group will be protonated under acidic conditions.

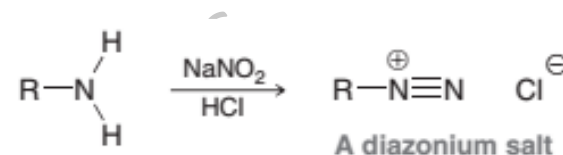
Chemistry of amines:

Reactions of amines:

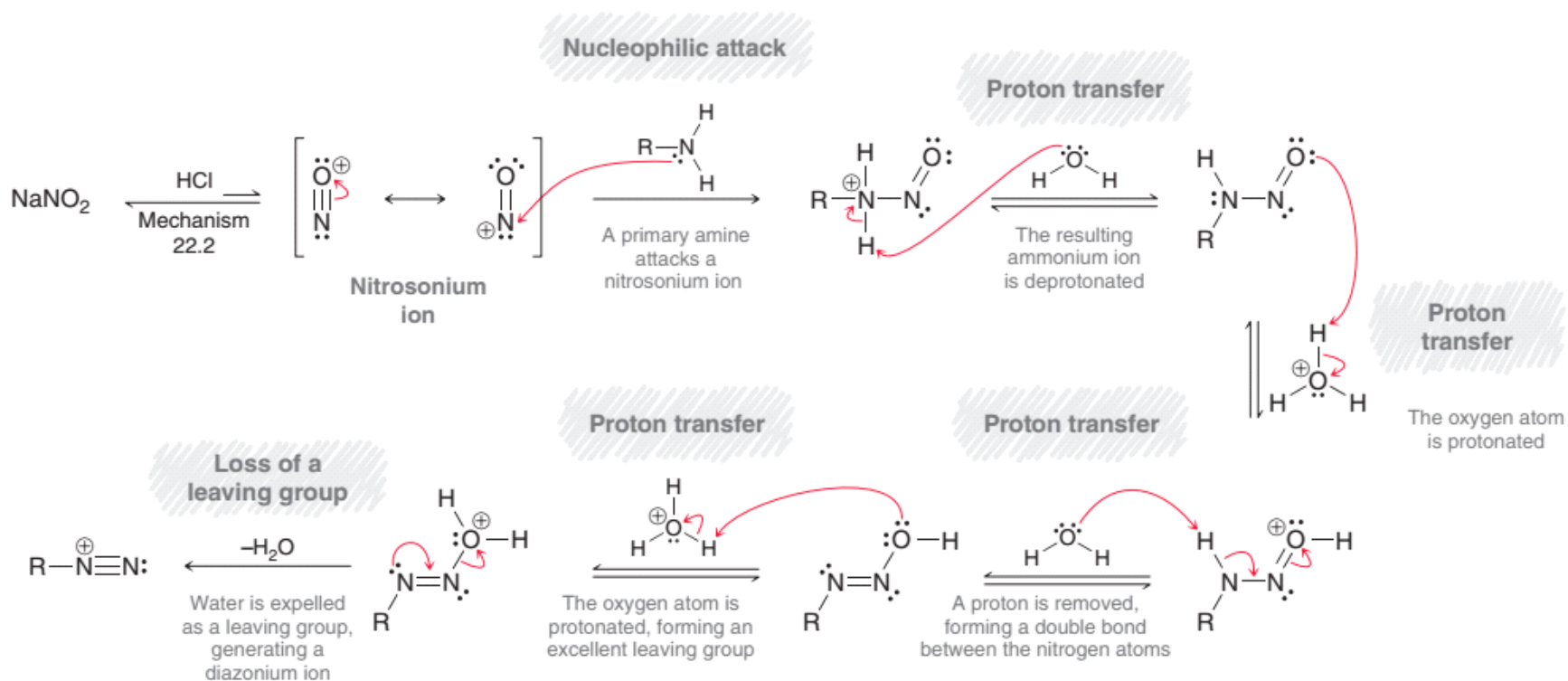
Reaction with HNO_2 - distinction between three classes of amines:

A) Primary amines:

When a primary amine is treated with sodium nitrite and HCl, the reaction produces a **diazonium salt** (azo indicates a nitrogen atom, diazo indicates two nitrogen atoms, and diazonium indicates two nitrogen atoms with a positive charge).



This process is called diazotization and is believed to proceed via the following mechanism. The amine functions as a nucleophile and attacks a nitrosonium ion, which was generated *in situ* from sodium nitrite and HCl. Several proton transfers follow, and the last step involves loss of water to generate the diazonium salt.



Chemistry of amines:

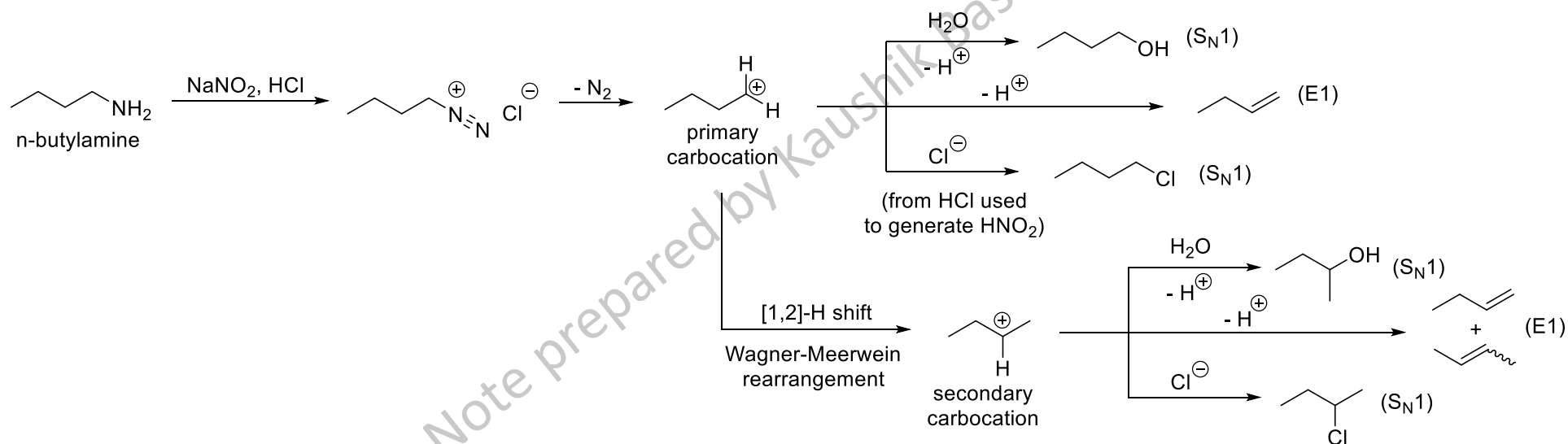
Reactions of amines:

Reaction with HNO_2 - distinction between three classes of amines:

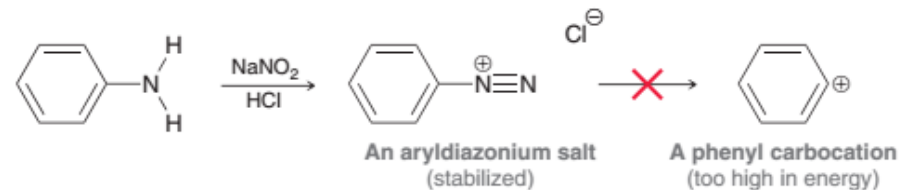
A) Primary amines (contd.):

When the R group of the primary amine is an alkyl group as opposed to an aryl group, then the resulting diazonium salt is highly unstable and is too reactive to be isolated. It can spontaneously liberate nitrogen gas to form a carbocation, which then reacts in a variety of ways.

For example, the carbocation can be captured by water to form an alcohol or it can lose a proton to form an alkene. The reaction generates a mixture of products and is therefore not useful. In addition, the process is also dangerous, because the expulsion of nitrogen gas can be an explosive process.



If, however, the primary amine is an aryl amine, then the resulting aryldiazonium salt is stable enough to be useful. It does not liberate nitrogen gas, because that would involve formation of a high-energy aryl cation.



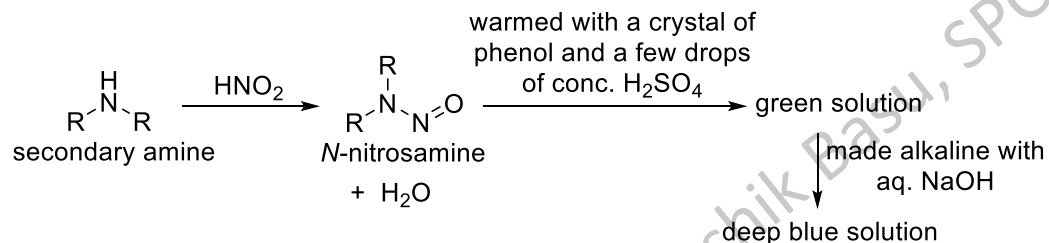
Aryldiazonium salts are extremely useful, because the diazonium group can be readily replaced with a number of other groups that are otherwise difficult to install on an aromatic ring. Reactions of aryldiazonium salts will be discussed later.

Chemistry of amines:

Reactions of amines:

Reaction with HNO_2 - distinction between three classes of amines:

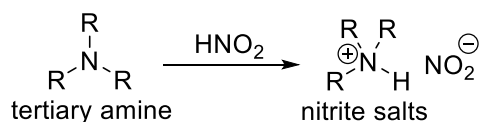
B) Secondary amines: Secondary amines react with nitrous acid to form *N*-nitrosamines which have oil-like appearance and are steam-volatile. This, on Liebermann's nitroso test responds favourably.



It is important to note that secondary amines *do not liberate nitrogen gas* when treated with nitrous acid but *forms yellow oil* which is strongly indicative of the presence of such amines; this can be confirmed the colour reaction mentioned above.

C) Tertiary amines:

Upon reacting with nitrous acid, tertiary amines neither liberate any nitrogen gas, nor do they separate any oil. They dissolve in the aqueous reaction medium forming nitrite salts.

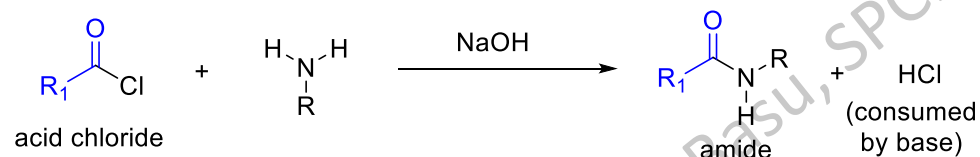


Chemistry of amines:

Reactions of amines:

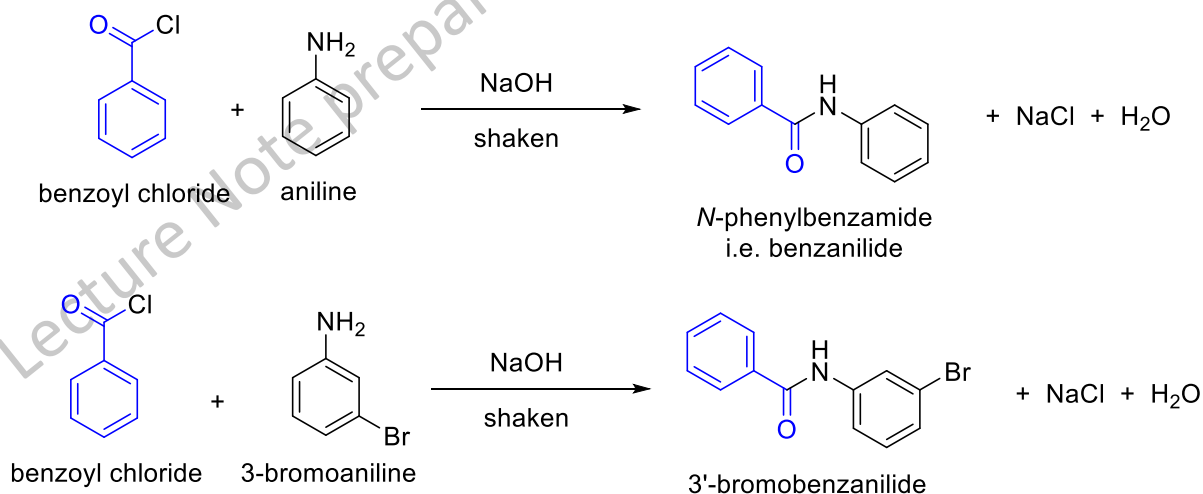
Schotten-Baumann Reaction:

Reaction of a primary or secondary amine with an acid chloride in presence of a base to yield an amide derivative is known as the Schotten-Baumann reaction. This is a nucleophilic acyl substitution where the chloride is exchanged with -NHR or -RN₂ group.



The reaction can be done with aliphatic as well as aromatic amines, and with alcohols (ROH) and phenols (Ar-OH), where the final product is an alkyl or a phenyl ester (R₁COR or R₁COAr). A two-phase solvent system is often used, to enable the acid generated during the reaction to be neutralised by the aqueous base, while the starting materials and products remain in the organic phase.

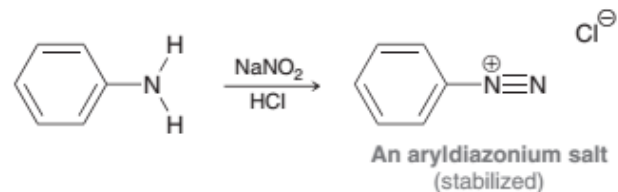
Example: benzoylation of aromatic primary amines,:



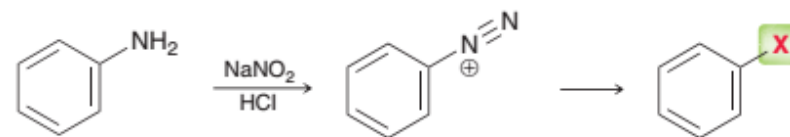
Chemistry of amines:

Reactions of aryldiazonium salts:

In the previous section, we saw that aryl amines can be converted into aryl diazonium salts upon treatment with nitrous acid.



As mentioned earlier, this reaction is extremely useful, because many different reagents will replace the diazo group, allowing for a simple procedure for installing a wide variety of groups on an aromatic ring:

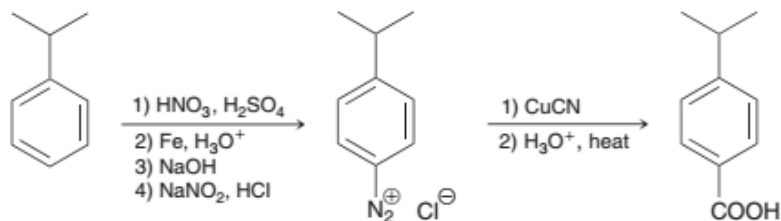
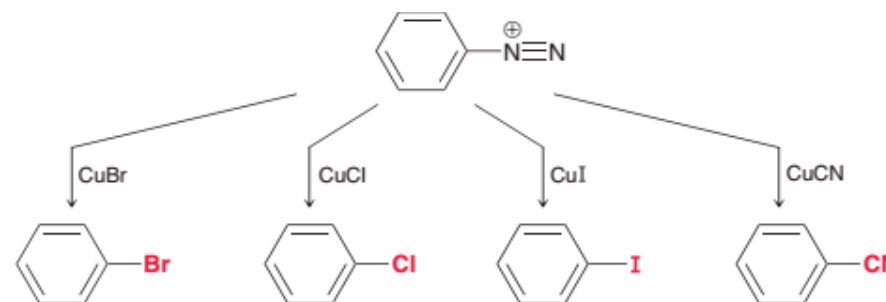


In this section, we will explore some of the groups that can be installed on an aromatic ring using this procedure.

Sandmeyer reactions:

The Sandmeyer reactions utilize copper salts (CuX) and enable the installation of a halogen or a cyano group on an aromatic ring:

Notice the installation of a cyano group. Recall that a cyano group can be hydrolyzed in aqueous acid or base, which provides a method for installing a carboxylic acid group on an aromatic ring.



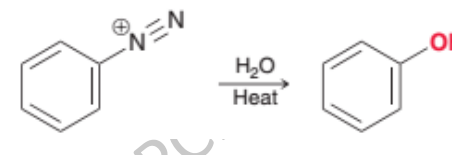
If one wants to make benzoic acid through this method, one would have to start from aniline.

Chemistry of amines:

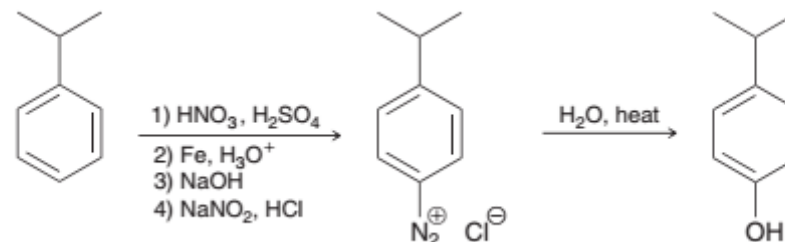
Reactions of aryldiazonium salts:

Other substitution reactions of aryldiazonium salts:

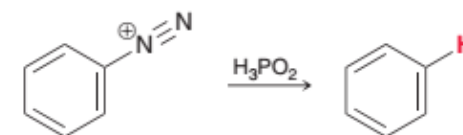
i) Synthesis of phenols: When an aryldiazonium salt is heated in the presence of water, the diazo group is replaced with a hydroxyl group.



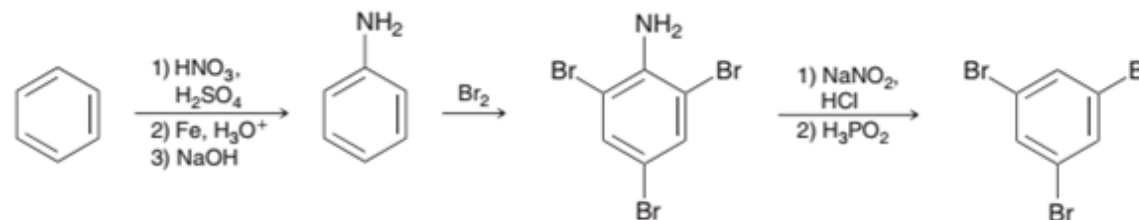
This procedure is very useful, because there are not many other ways to install an OH group on an aromatic ring. An example of this process is shown below.



ii) Replacing diazo group with H: When treated with hypophosphorus acid (H_3PO_2), the diazo group of an aryldiazonium salt is replaced with a hydrogen atom:



This reaction can be useful for manipulating the directing effects of a substituted aromatic ring. For example, consider the following synthesis of 1,3,5-tribromobenzene:



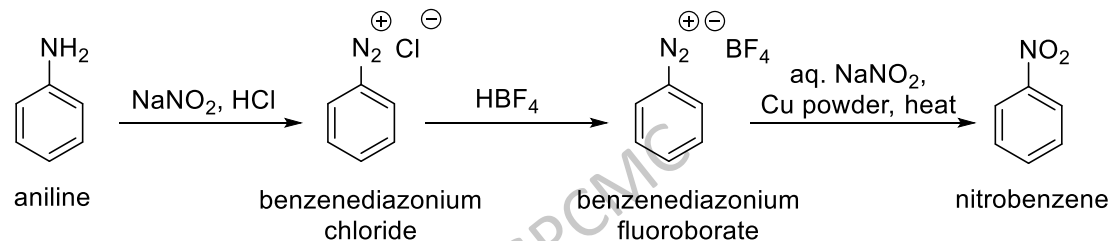
The amino group is first installed, its activating and directing effects are exploited, and then it is completely removed. The product of this sequence cannot be easily prepared from benzene via successive halogenation reactions because halogens are *ortho-para* directors.

Chemistry of amines:

Reactions of aryldiazonium salts:

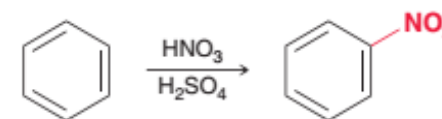
Other substitution reactions of aryldiazonium salts:

iii) Synthesis of nitrobenzene from benzenediazonium salt:



Nitrobenzene and its reduction:

When benzene is treated with a mixture of nitric acid and sulfuric acid, a nitration reaction occurs in which nitrobenzene is formed.



This reaction proceeds via an electrophilic aromatic substitution in which a nitronium ion (NO_2^+) is believed to be the electrophile.

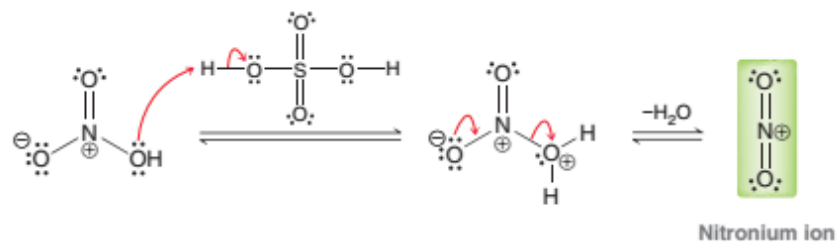
This strong electrophile is formed from the acid-base reaction that takes place between HNO_3 and H_2SO_4 .

Nitric acid functions as a base to accept a proton from sulfuric acid, followed by loss of water to produce a nitronium ion.

It might seem strange that nitric acid functions as a base rather than an acid, but remember that acidity is relative.

Sulfuric acid is a much stronger acid than nitric acid, and it will protonate nitric acid when mixed together.

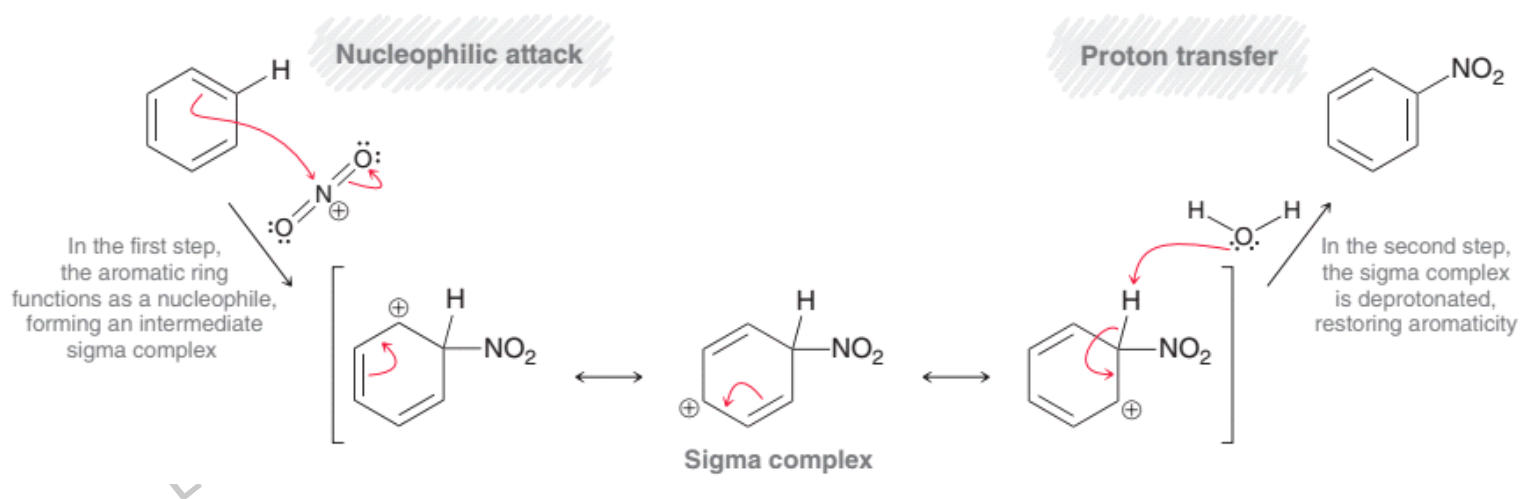
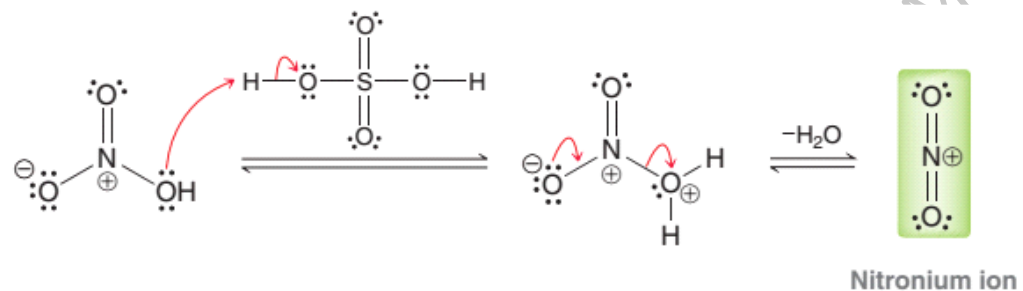
The resulting nitronium ion then serves as an electrophile in an electrophilic aromatic substitution reaction.



Chemistry of amines:

Nitrobenzene and its reduction:

The generation of nitronium ion and consequent nitration of benzene to nitrobenzene:



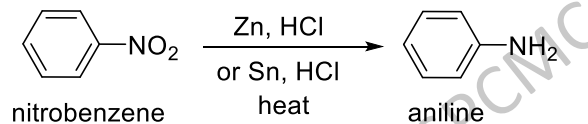
Aromaticity of the benzene ring is lost on introduction of the electrophile (here, nitronium ion). Loss of proton from the carbon attached to the electrophile restores the aromaticity - the cyclic arrangement of 6 π -electrons,

Chemistry of amines:

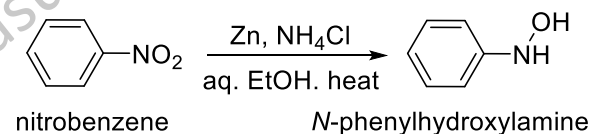
Reduction of nitrobenzene:

Reduction of nitro group is very important in organic synthesis. By the reduction of nitro compounds under different conditions, we may obtain a variety of products which can be manipulated further. Let us take a close look at the following series of reactions:

i) Under acid condition: aniline is formed, as discussed earlier:



ii) Under neutral (actually slightly acidic) condition: phenylhydroxylamine is the end product, this is what you do in the Mulliken-Barker's test in your qualitative analysis:



iii) Under alkaline condition: a variety of products are formed, depending upon the exact reagent used:

