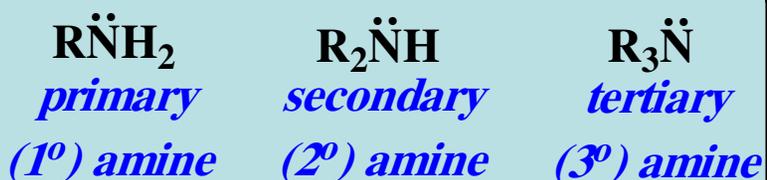


Amines

Amines are **organic bases**. They are found widely in nature. Trimethylamine occurs in animal tissue, and the distinctive odor of fish is due to amines. Amines isolated from plants are called alkaloids and many are pharmacologically important.

Nomenclature

Amines are **classified** according to the number of R groups on the nitrogen.

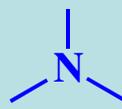


The R groups may be alkyl or aryl.

For the **common name** of simple aliphatic amines, name the alkyl group(s) on the nitrogen and attach "**amine.**" Use the prefixes "**di**" and "**tri**" as needed.



Ethylmethanamine
N-Methylethanamine

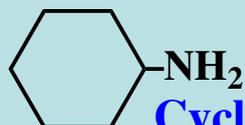


Trimethanamine
N,N-Dimethylmethanamine

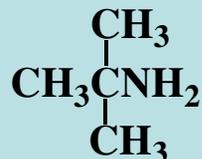
The **systematic name** is derived from the name of the longest alkane chain present by dropping the final "**e**" and adding the suffix "**amine.**" Then designate smaller alkyl groups as shown, using the italicized locant "**N**."

Additional Examples

1° Amines



Cyclohexylamine
Cyclohexanamine

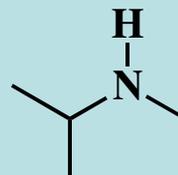


tert-Butylamine
2-Methyl-2-propanamine

2° Amines

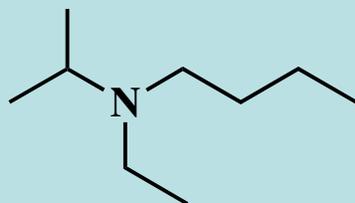


Methylpropylamine
N-Methylpropanamine

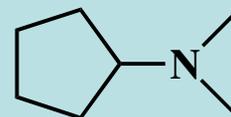


Isopropylmethylamine
N-Methyl-2-propanamine

3° Amines



Butylethylisopropylamine
N-Ethyl-N-(1-methylethyl)-butanamine



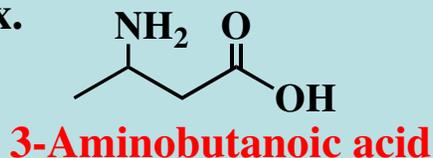
Cyclopentyl dimethylamine
N,N-Dimethylcyclopentanamine

Polyfunctional Amines When the amino function is not the **principal group**, it is designated by use of the prefix "**amino**."

There is an established order of precedence of compound classes, which is used to determine which functional group is the principal one. A highly abbreviated list, in order of decreasing precedence, is:

Acids, aldehydes, ketones, alcohols, amines.

So in most polyfunctional compounds, an amine function will be designated by use of the prefix.



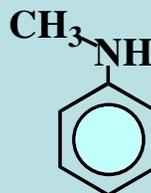
Arylamines

Aromatic amines are often named as derivatives of **aniline**.



Aniline

Benzenamine



N-Methylaniline

N-Methylbenzenamine



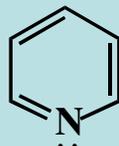
Additional unique common names:

When R = CH₃,
p-toluidine.

When R = OCH₃,
p-anisidine.

Heterocyclic Amines

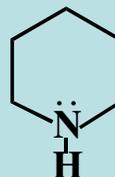
Examples



Pyridine



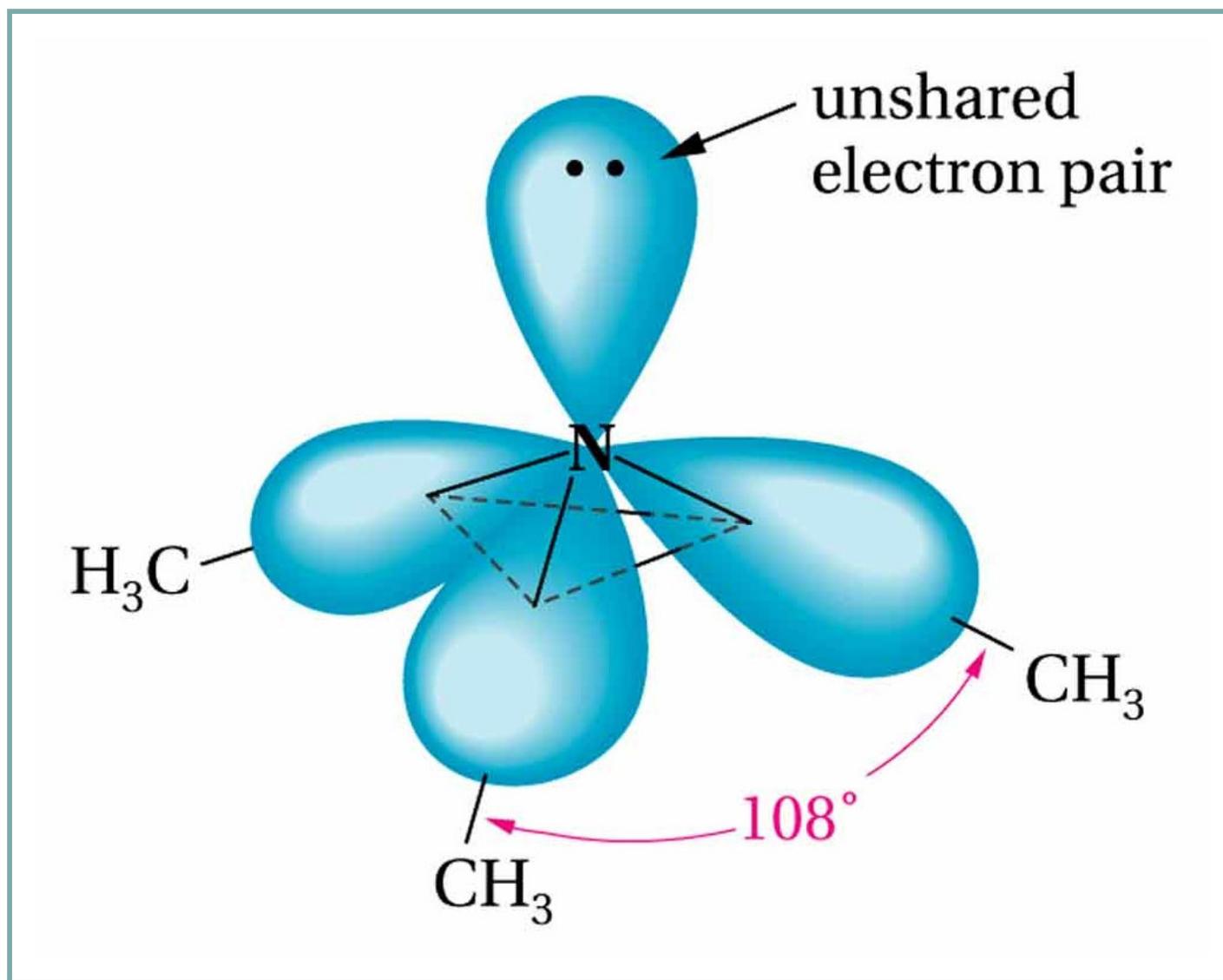
Pyrrole



Piperidine

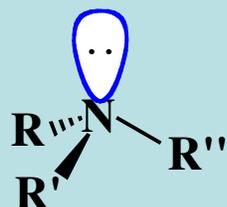


Pyrrolidine



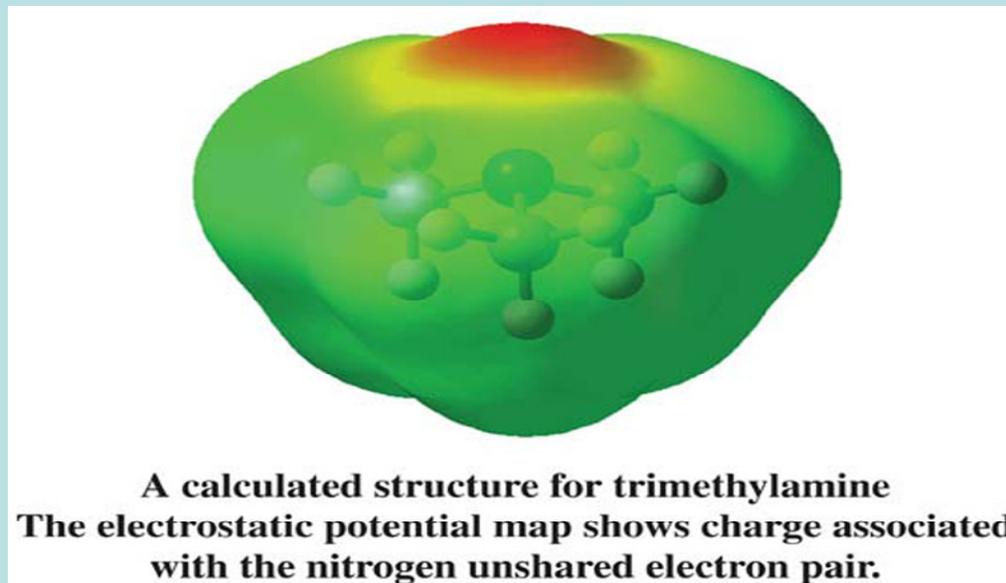
Structure of Amines

The nitrogen atom in most amines is similar to that in ammonia and can be considered to be sp^3 hybridized. The nonbonding electron pair is in an sp^3 orbital.



The geometry is described as **trigonal pyramidal**.

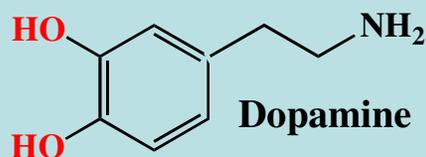
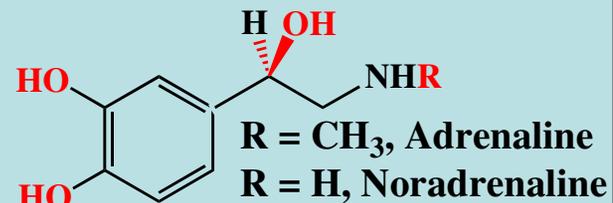
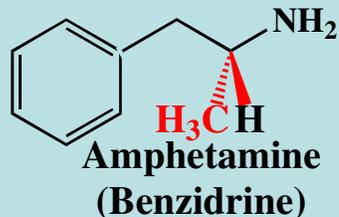
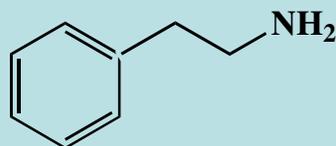
Bond angles are close to 109.5° .



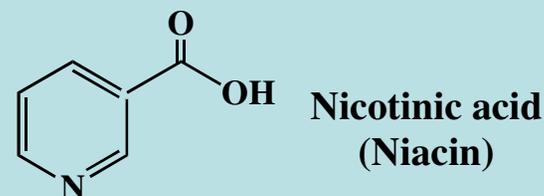
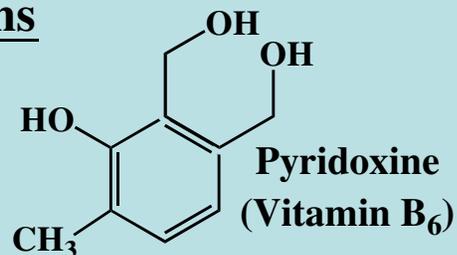
Some Biologically Important Amines

Amines are widely encountered in biological and pharmacological studies. Some important examples are the 2-phenylethylamines, some vitamins, antihistamines, tranquilizers, and neurotransmitters.

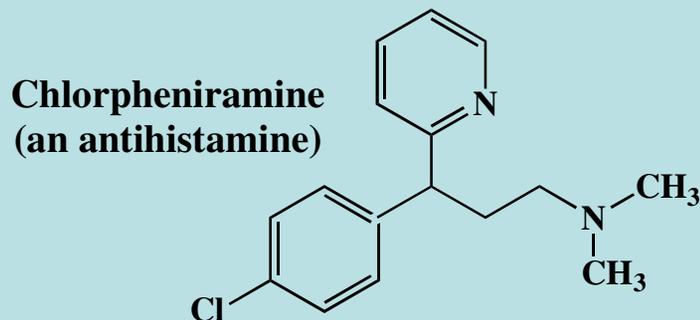
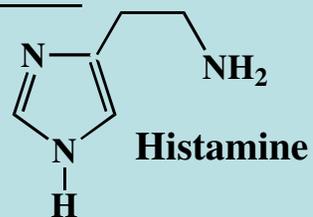
2-Phenylethylamines



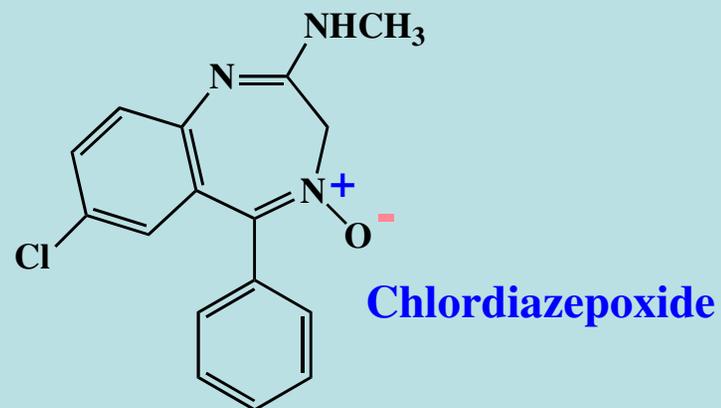
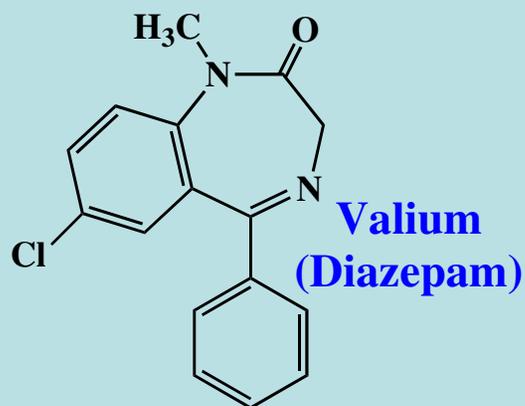
Vitamins



Antihistamines

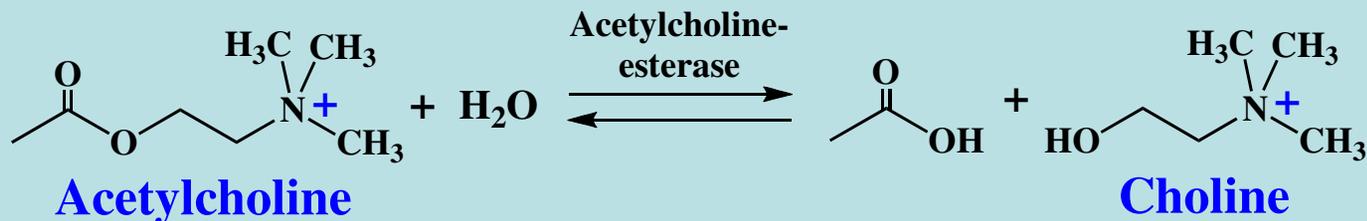


Tranquilizers These examples are both 1,4-benzodiazepine anxiolytics.



Neurotransmitters

Besides 2-phenylethylamines like noradrenaline, dopamine, and serotonin, the simpler amine-family compound acetylcholine is a neurotransmitter, one of great importance that acts at neuromuscular synapses.



An essential feature of this system is that the esterase can almost immediately hydrolyze the neurotransmitter that has been received at the receptor site, freeing it to receive a later nerve impulse.

Physical Properties and Structure of Amines

Amines are **moderately polar** compounds because of the greater electronegativity of nitrogen relative to carbon and hydrogen.

Since 1° and 2° amines have N-H bonds, they hydrogen bond intermolecularly causing their boiling points to be higher than those of alkanes of comparable molecular weight but lower than those of similar alcohols.

3° Amines boil at lower temperatures than 1° and 2°, but all amines can hydrogen bond to water, making low-molecular-weight amines water soluble.

A COMPARISON:

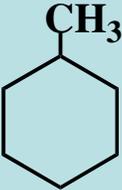
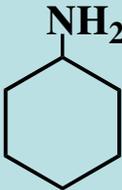
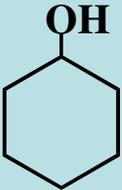
			
	Methylcyclohexane	Cyclohexylamine	Cyclohexanol
MW	98	99	100
BP	100 °C	134 °C	161.5 °C
Water solubility	Insoluble	Slightly soluble	3.6 g/100 mL

Table 11.1 The boiling points of some simple amines

Name	Formula	bp, °C
ammonia	NH ₃	-33.4
methylamine	CH ₃ NH ₂	-6.3
dimethylamine	(CH ₃) ₂ NH	7.4
trimethylamine	(CH ₃) ₃ N	2.9
ethylamine	CH ₃ CH ₂ NH ₂	16.6
propylamine	CH ₃ CH ₂ CH ₂ NH ₂	48.7
butylamine	CH ₃ CH ₂ CH ₂ CH ₂ NH ₂	77.8
aniline	C ₆ H ₅ NH ₂	184.0

Table 11.2 A comparison of alkane, amine, and alcohol boiling points*

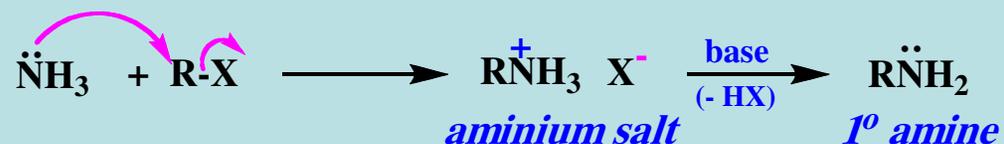
alkane	CH ₃ CH ₃ (30) bp -88.6°C	CH ₃ CH ₂ CH ₃ (44) bp -42.1°C
amine	CH ₃ NH ₂ (31) bp -6.3°C	CH ₃ CH ₂ NH ₂ (45) bp +16.6°C
alcohol	CH ₃ OH (32) bp +65.0°C	CH ₃ CH ₂ OH (46) bp +78.5°C

*Molecular weights are given in parentheses.

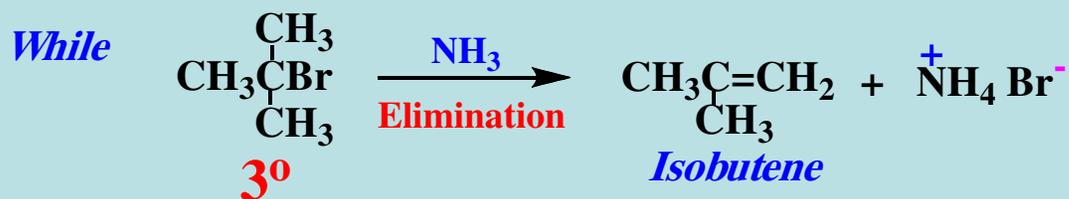
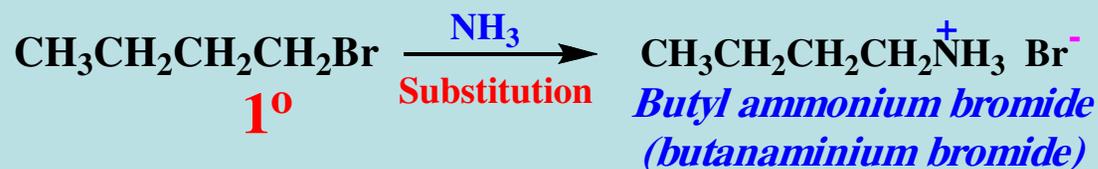
Synthesis of Amines

Nucleophilic Substitution Reactions: Direct Alkylation Method

The nucleophilic substitution of alkyl halides with ammonia is a general synthesis of primary amines.

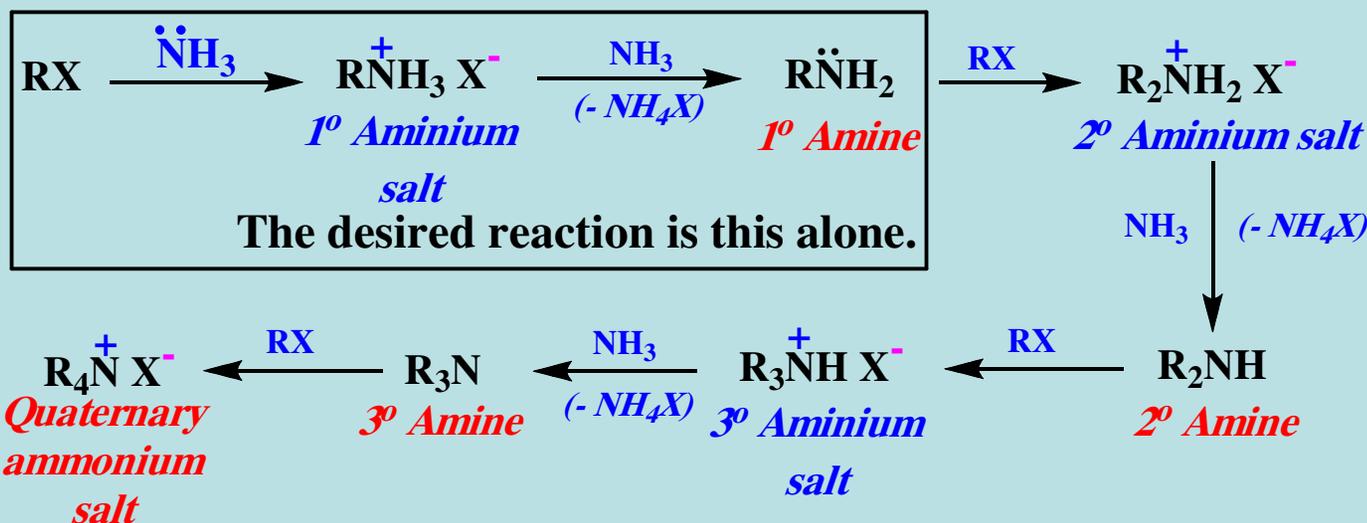


The reaction may be carried out in aqueous or alcoholic (to improve the solubility of RX) solutions of ammonia. All the usual structural limitations of an $\text{S}_{\text{N}}2$ reaction apply.



Side Products in the Direct Alkylation Synthesis of 1° Amines

A problem in synthesizing 1° amines by the direct alkylation reaction is the formation of more highly alkylated products from repetitive reaction.



While the direct alkylation synthesis of 1° amines is simple, the products are contaminated by the 2° and 3° amines and 4° ammonium salts. By using a very large excess of ammonia, good results sometimes can be achieved.

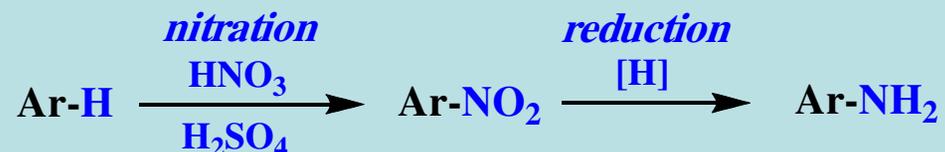
A similar alkylation method that yields 1° amines free of higher order amines reacts azide ion (N_3^-) with an alkyl halide to give an alkyl azide, which is then reduced to the 1° amine by use of Na/alcohol or LiAlH_4 .

Caution must be taken because azides are explosive.

The Synthesis of Amines by Reduction Methodologies

Reduction of Nitro Compounds

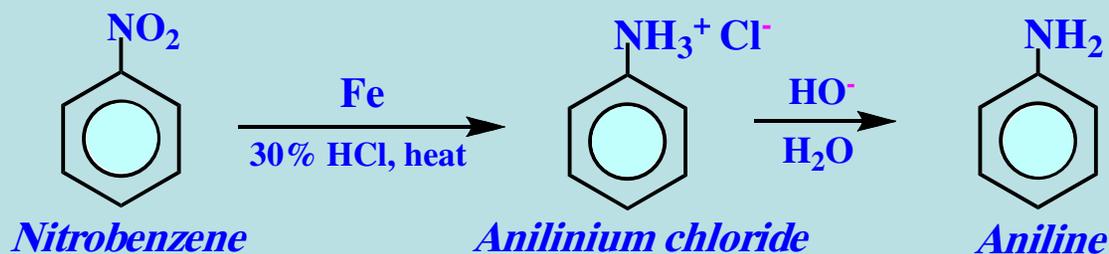
Anilines may be prepared by reduction of nitrobenzenes. The overall synthetic sequence begins with nitration of the starting arene.



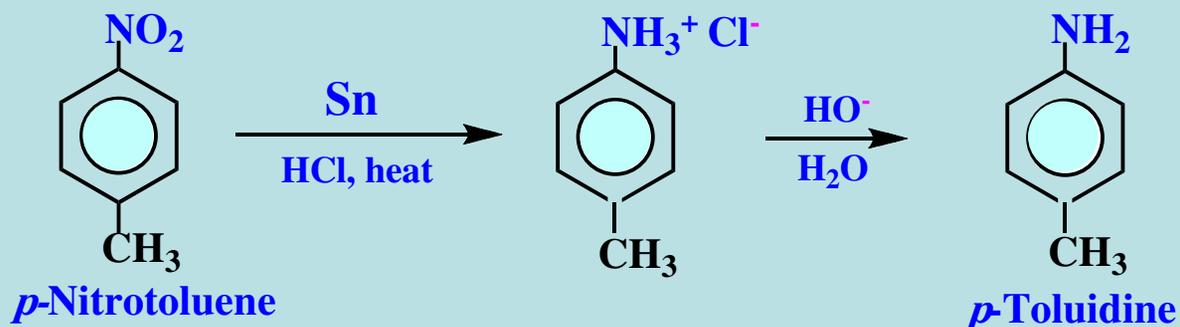
The Dissolving Metal Reduction of Nitrobenzenes to Anilines

These reactions use metals such as iron, zinc and tin and typically are carried out at reflux in hydrochloric acid solution, sometimes with added acetic acid to help dissolve the aromatic compound.

EXAMPLE

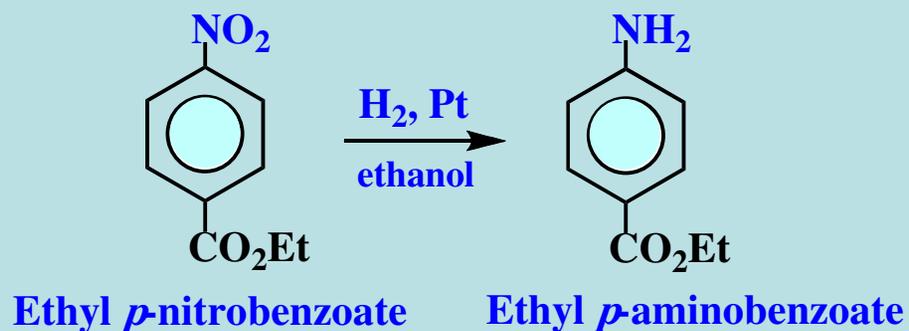


A SECOND EXAMPLE

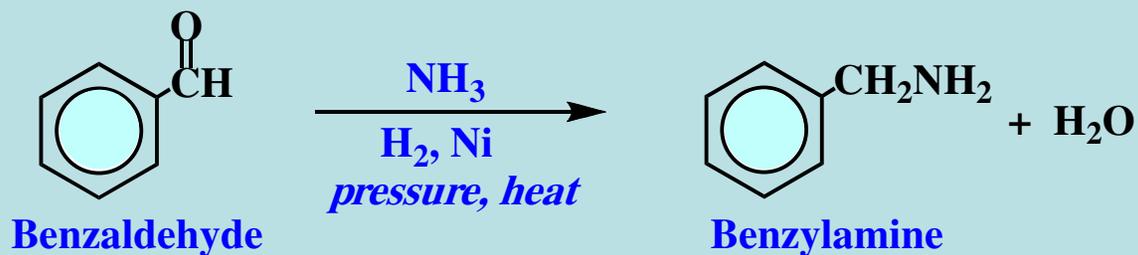


Catalytic Hydrogenation of Nitroaromatics

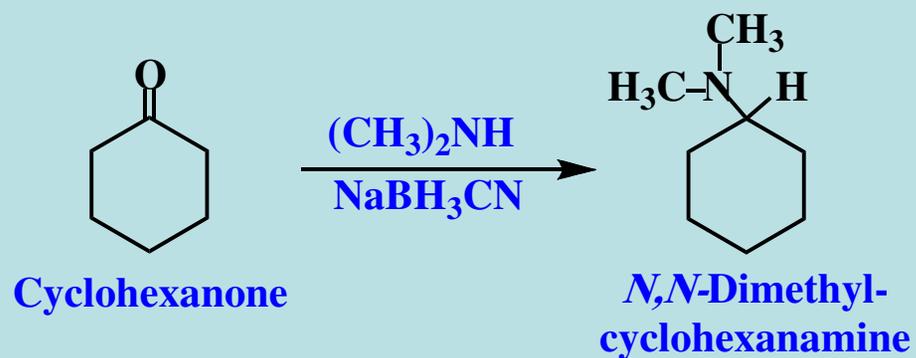
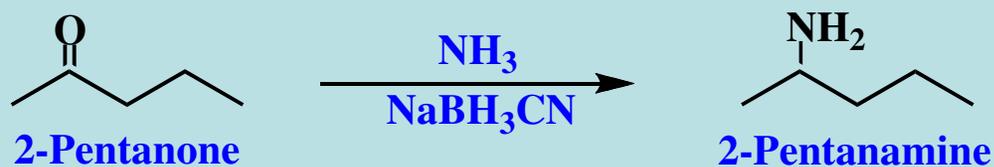
Anilines may also be prepared by catalyzed reaction of pre-formed hydrogen with nitroaromatics:



Examples



Amination of aldehyde OR alkylation of ammonia

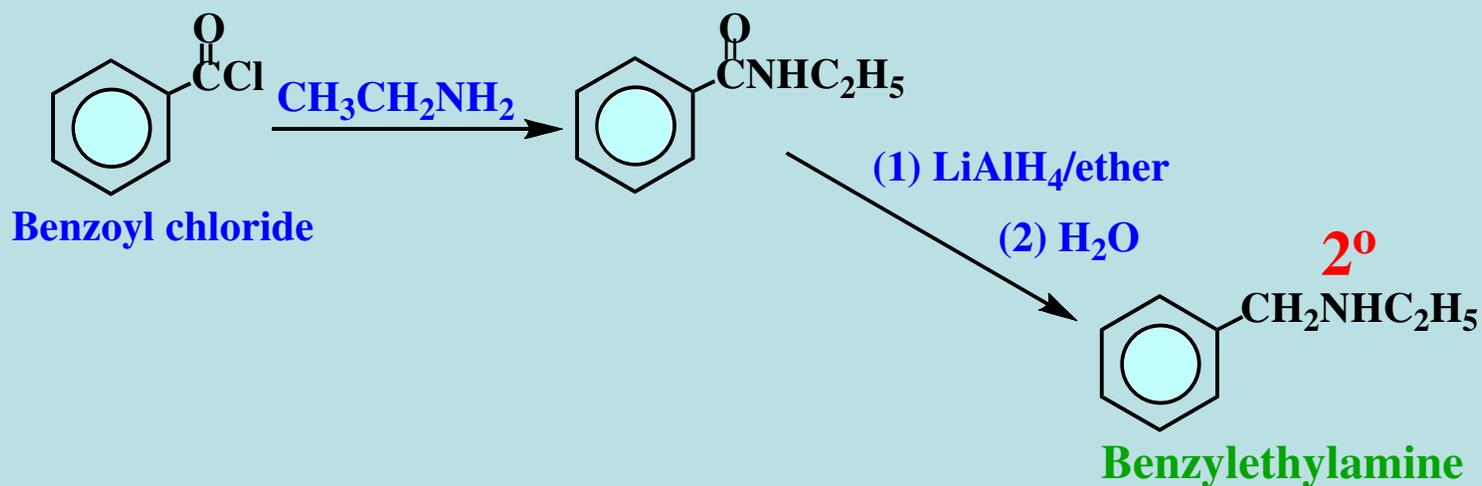
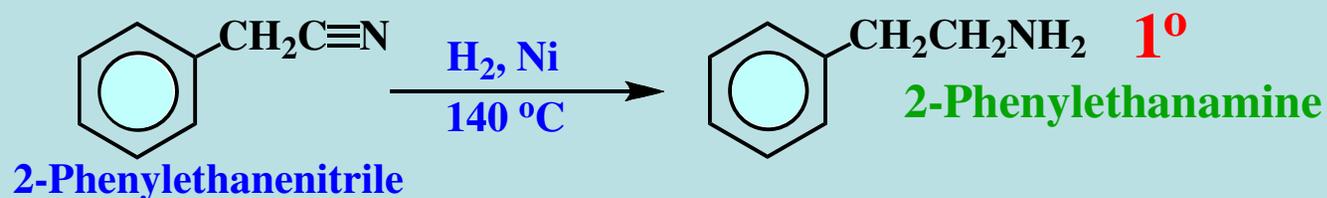
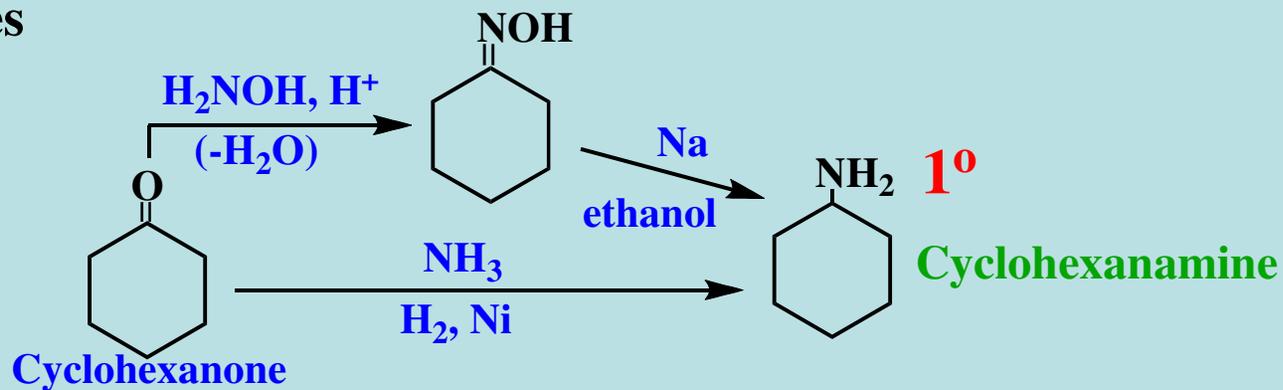


Reduction of Nitriles, Oximes, and Amides

Reduction of any of these functional groups by catalytic hydrogenation or lithium aluminum hydride (LiAlH_4) yields an amine.

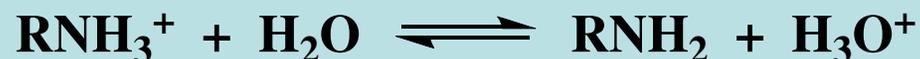


Examples



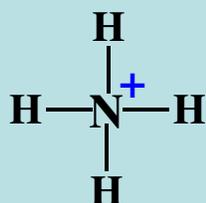
Basicity of Amines: Amine Salts

The greater the basicity of an amine, the weaker the acidity of its conjugate acid, the cation in its salts.

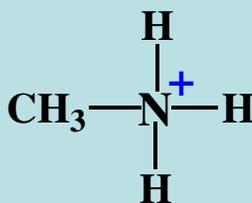


$$K_a = \frac{[\text{RNH}_2][\text{H}_3\text{O}^+]}{[\text{RNH}_3^+]} \quad \text{p}K_a = -\log K_a$$

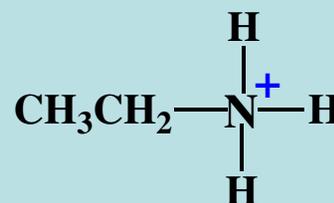
Influence of alkylation on the acidity of aminium ions:



pK_a 9.26



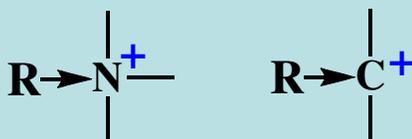
10.64



10.75

These experimentally determined pK_a values show that alkylation decreases the acidity of these conjugate acids, **which means that their parent amines became more basic on alkylation.**

This stabilization of positive charge on nitrogen by alkylation is parallel to the stabilization of carbocations by alkylation. It is another example of the electron-releasing nature of alkyl groups.

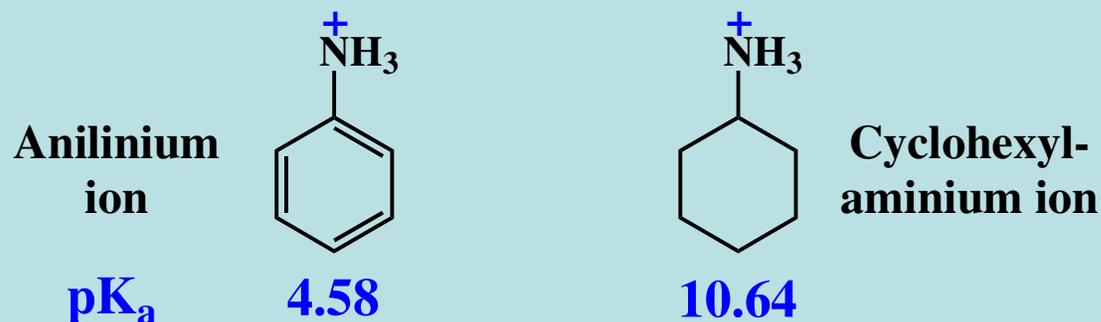


This increase in the basicity of an amine by alkylation is slightly enhanced by introduction of a second alkyl group. Further alkylation of a 2° amine does further increase basicity, but only if measured in the gas phase. In the usual aqueous media, aminium ions from 1° and 2° amines are very effectively stabilized by hydrogen-bonding with water molecules. Aminium ions from 3° amines, with only one N-H bond per ion, are not as well stabilized, so 3° amines in water cannot fully utilize their true basicity.

Order of increasing basicity in gas phase: $\text{NH}_3 < \text{RNH}_2 < \text{R}_2\text{NH} < \text{R}_3\text{N}$

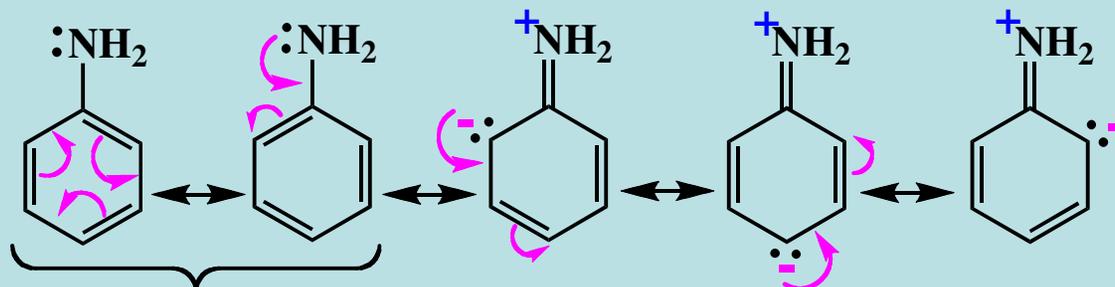
Order of increasing basicity in water: $\text{NH}_3 < \text{R}_3\text{N} < \text{RNH}_2 < \text{R}_2\text{NH}$

Basicity of Arylamines

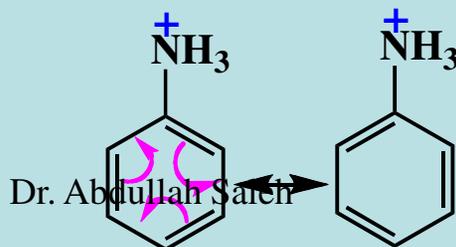


The greater acidity of the anilinium ion means that aniline is a markedly weaker base than is cyclohexylamine, a typical 1° alkylamine.

The decreased basicity of aniline is primarily due to the delocalization of the unshared pair on nitrogen by the benzene ring:

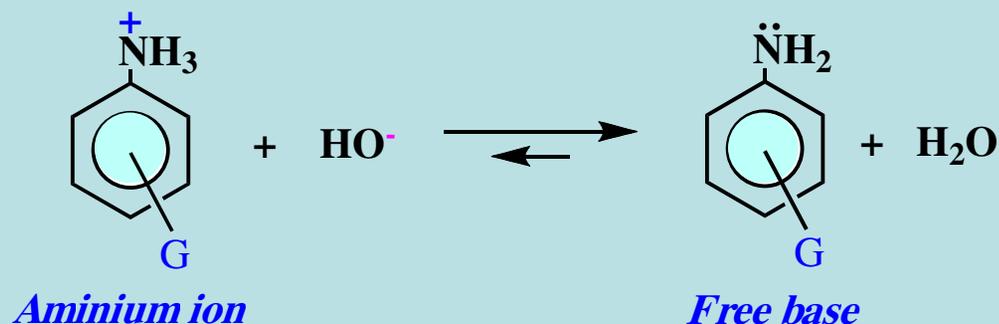


These two general types of benzene resonance forms are the only ones available to stabilize the anilinium ion:



Effect of Substituents on the Basicity of Anilines

Substituents, especially those that are electron-withdrawing, influence the basicity of anilines. The substituent effect is important in both the aminium ion (conjugate acid) and free base (see the aniline discussion).



When **G** is electron-releasing, the *conjugate acid* is **stabilized** (i. e., base strength is increased) leading to a slightly larger value for its **pK_a**. E.g., when **G** is a *p*-methyl group, the pK_a increases from 4.58 for the parent aniline to 5.08.

When **G** is electron-withdrawing, the *conjugate acid* is **destabilized** (i. e., base strength is decreased) leading to a sometimes considerably smaller value for its **pK_a**. E. g., when **G** is a *p*-nitro group, the pK_a drops to 1.00.

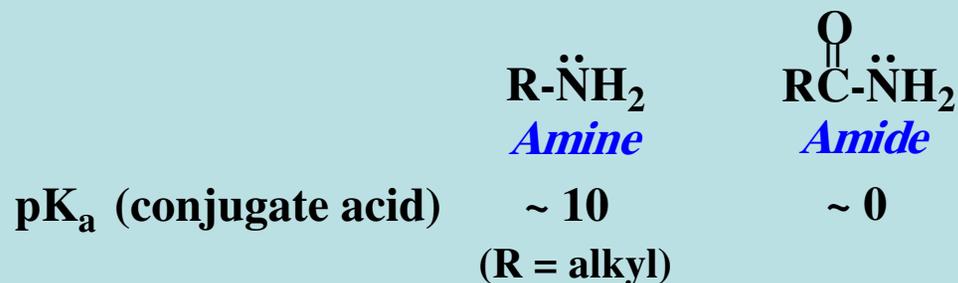
Table 11.3

Basicities of some common amines, expressed as pK_a of the corresponding ammonium ions

Name	Formula		pK_a of the ammonium ion
	Amine	Ammonium ion	
ammonia	$\ddot{\text{N}}\text{H}_3$	NH_4^+	9.30
methylamine	$\text{CH}_3\ddot{\text{N}}\text{H}_2$	CH_3NH_3^+	10.64
dimethylamine	$(\text{CH}_3)_2\ddot{\text{N}}\text{H}$	$(\text{CH}_3)_2\text{NH}_2^+$	10.71
trimethylamine	$(\text{CH}_3)_3\ddot{\text{N}}$	$(\text{CH}_3)_3\text{NH}^+$	9.77
ethylamine	$\text{CH}_3\text{CH}_2\ddot{\text{N}}\text{H}_2$	$\text{CH}_3\text{CH}_2\text{NH}_3^+$	10.67
propylamine	$\text{CH}_3\text{CH}_2\text{CH}_2\ddot{\text{N}}\text{H}_2$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_3^+$	10.58
aniline	$\text{C}_6\text{H}_5\ddot{\text{N}}\text{H}_2$	$\text{C}_6\text{H}_5\text{NH}_3^+$	4.62
<i>N</i> -methylaniline	$\text{C}_6\text{H}_5\ddot{\text{N}}\text{HCH}_3$	$\text{C}_6\text{H}_5\text{NH}_2(\text{CH}_3)^+$	4.85
<i>N,N</i> -dimethylaniline	$\text{C}_6\text{H}_5\ddot{\text{N}}(\text{CH}_3)_2$	$\text{C}_6\text{H}_5\text{NH}(\text{CH}_3)_2^+$	5.04
<i>p</i> -chloroaniline	$p\text{-ClC}_6\text{H}_4\ddot{\text{N}}\text{H}_2$	$p\text{-ClC}_6\text{H}_4\text{NH}_3^+$	3.98

Amines versus Amides

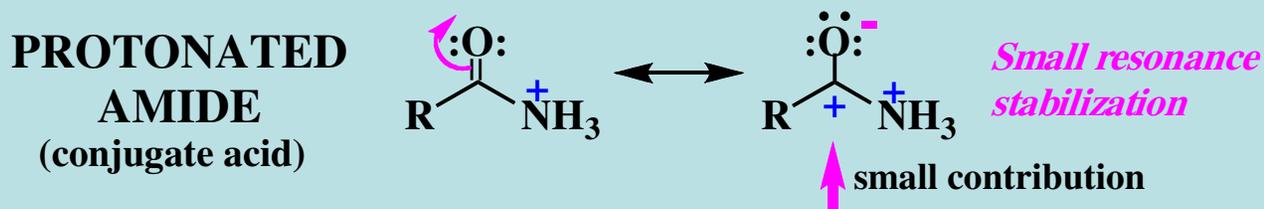
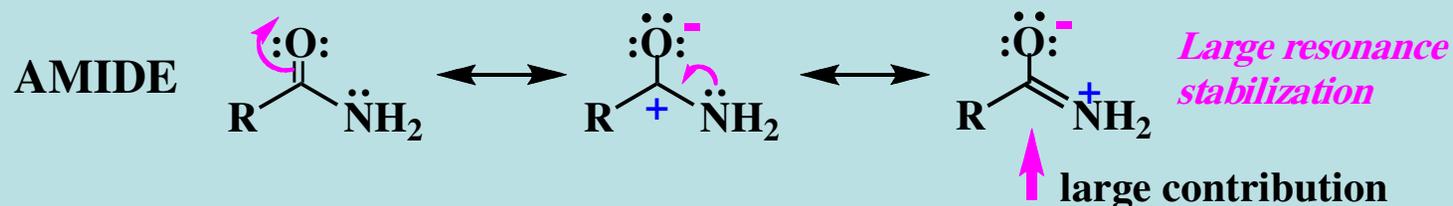
Amides are much less basic than amines even though their structural formulas both show an unshared pair of electrons on the nitrogen.



The decreased base strength of amides is **explained by both resonance and inductive influences**, as with aryl amines.

Resonance Stabilization of Amides

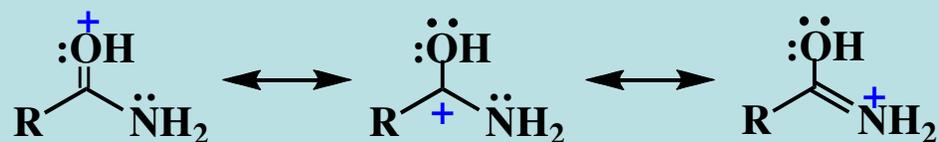
Stabilization by π -electron delocalization is important in amides, but relatively unimportant in their conjugate acids, as illustrated in these resonance structures.



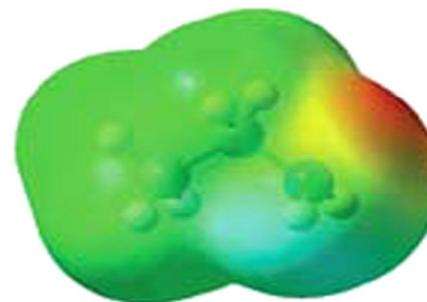
Therefore, resonance lowers the energy of the free base more than that of the protonated state, giving this conjugate acid a smaller pK_a (about zero) in comparison with aliphatic aminium ions (about 10).

Under sufficiently acidic conditions, amides do become protonated but on the oxygen atom, not the nitrogen.

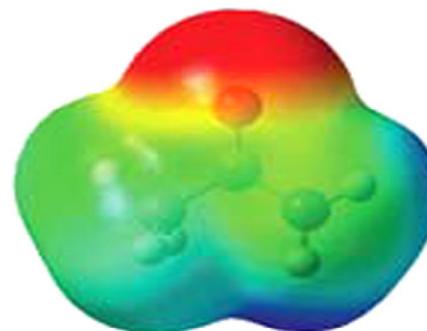
Protonation occurs on the carbonyl oxygen because that adduct is resonance stabilized:



This outcome can be further explained by comparing the electrostatic potential maps for ethylamine and acetamide, which show a shift of the high electron density from nitrogen in the amine to oxygen in the amide.



Ethylamine



Acetamide

Aminium Salts

Protonation of primary, secondary or tertiary amines produces **aminium salts**.



Aminium salts

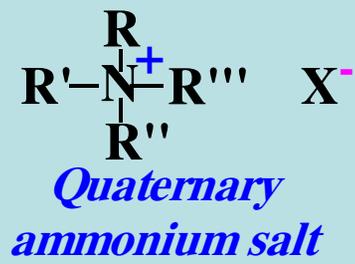
It is the formation of aminium salts that causes amines to dissolve in acidic aqueous media. Aminium salts are not basic because there is no longer a nonbonding electron pair on the nitrogen atom.

Aminium salts are **weak acids**. As conjugate acids of the free base amines, the general conjugate relationship applies in which **$\text{pK}_a + \text{pK}_b = 14$** .

The aminium salts of aliphatic amines ($\text{pK}_b \sim 4$) have pK_a values of ~ 10 (like phenols). The aminium salts of aryl amines ($\text{pK}_b \sim 9$) are about as acidic as carboxylic acids, $\text{pK}_a \sim 5$.

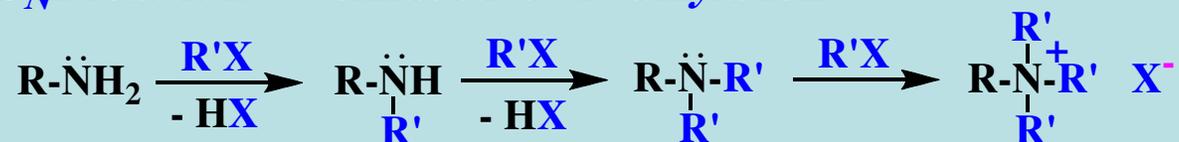
Quaternary Ammonium Salts

When there are four R groups (alkyl or aryl) attached to the nitrogen, the function is called a quaternary ammonium ion.



Quaternary ammonium salts are prepared by exhaustive N-alkylation of amines:

S_N2 reactions: "exhaustive" N-alkylation

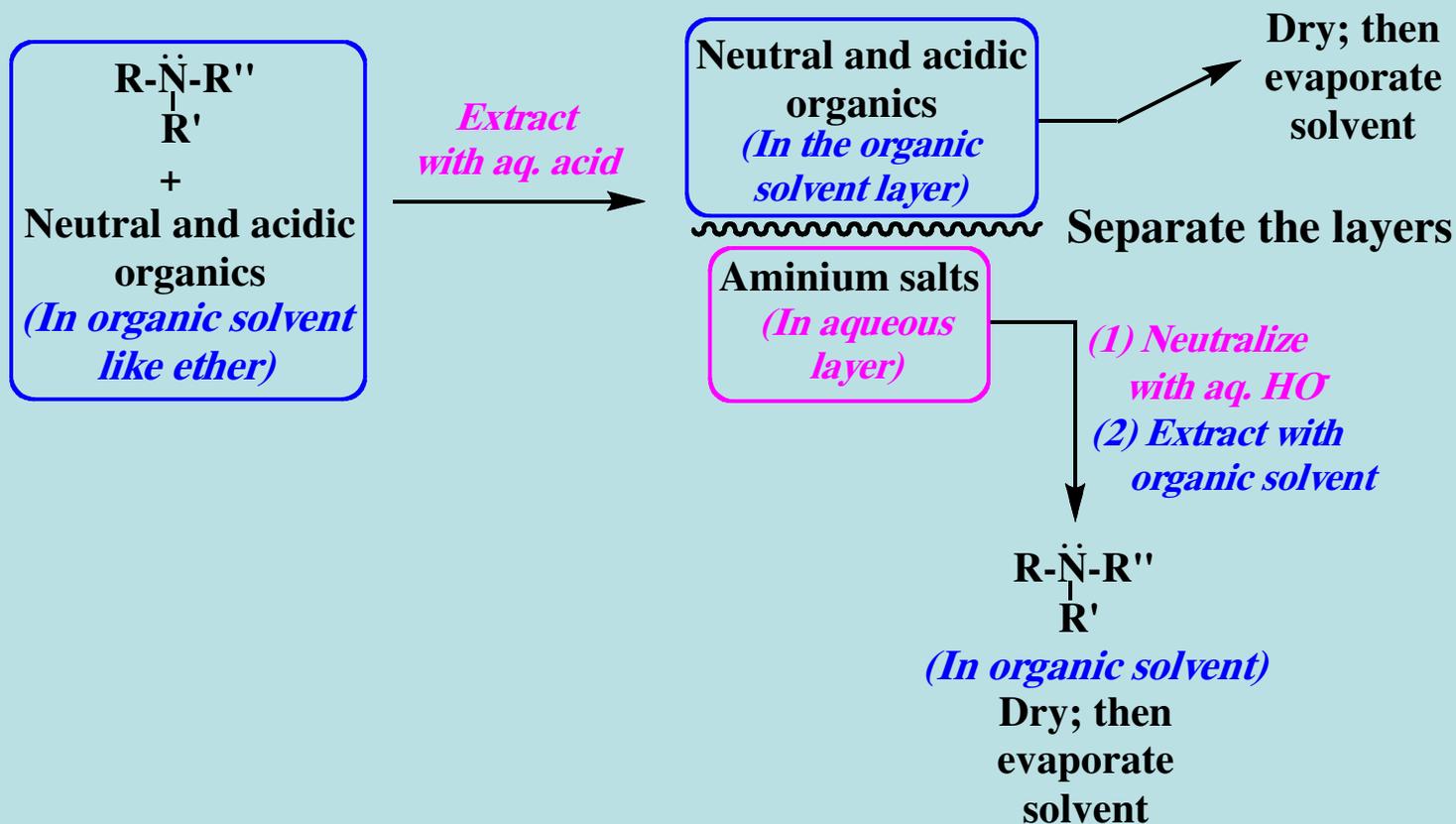


Quaternary ammonium halides, having no unshared pair on nitrogen, cannot act as bases. If, however, the halide ion is replaced with a hydroxide ion they are fully ionic, strong bases like NaOH or KOH.

Strong base ion exchange resins are of this hydroxide type, with the quaternary ammonium ion covalently bonded to the polymer matrix.

Solubility Properties and Separation Procedures

Because most aminium salts are soluble in water, it is possible to separate amines (whether they are water-soluble or water-insoluble) from other organic materials by extraction into an aqueous acid like dilute HCl.



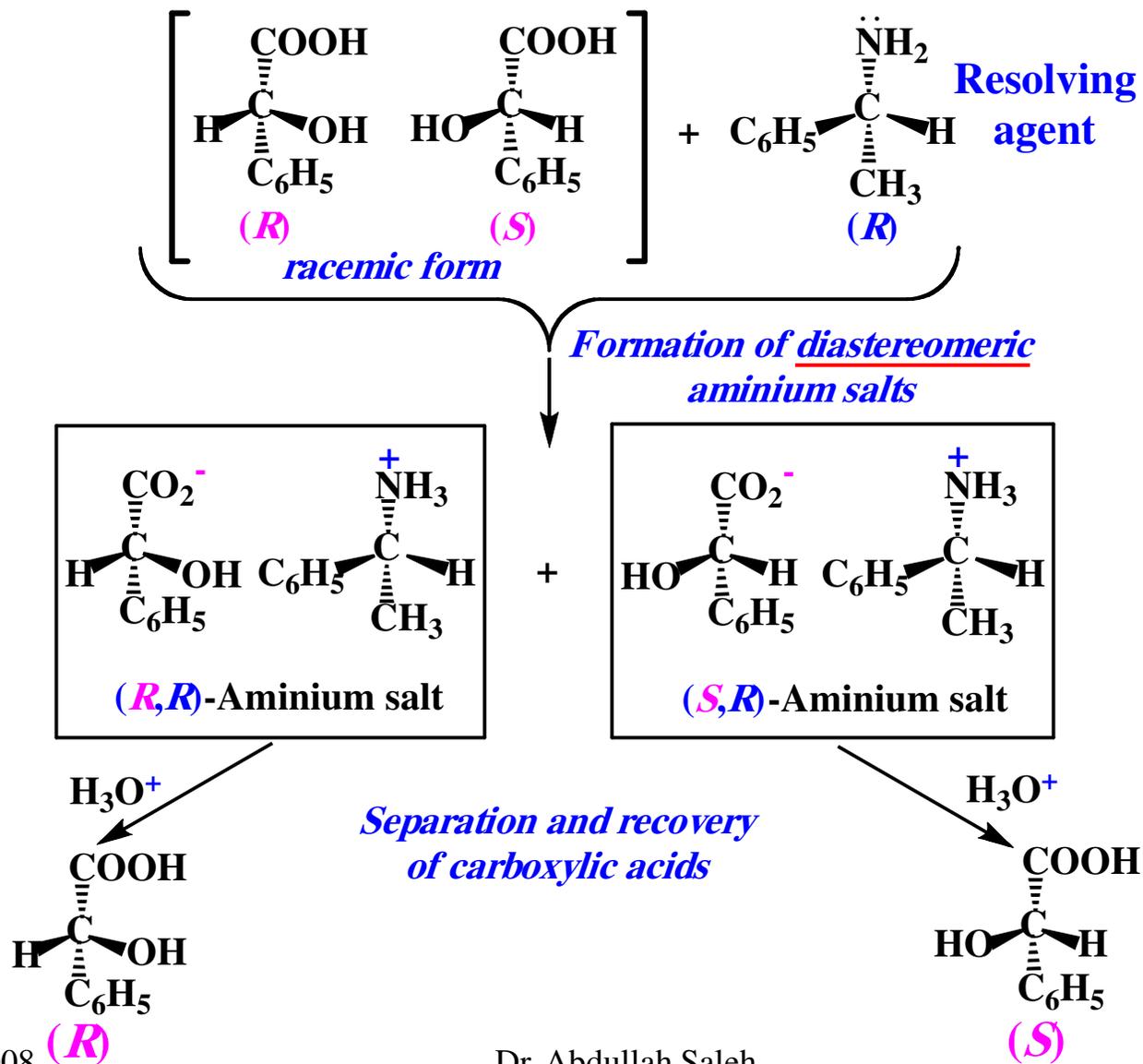
Amines as Resolving Agents

A type of amine called **alkaloids** is available from plant sources. Many are chiral and occur in single enantiomer form. Some of these compounds are pharmacologically important, e. g., quinine and atropine. Others have dangerous natures, e. g., morphine and strychnine.

Some alkaloids have been used to separate the enantiomers of chiral carboxylic acids. This **resolution** is based on:

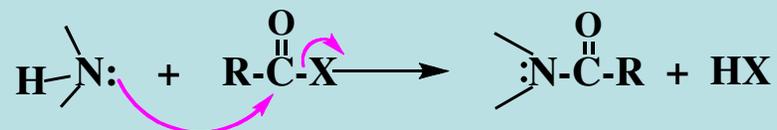
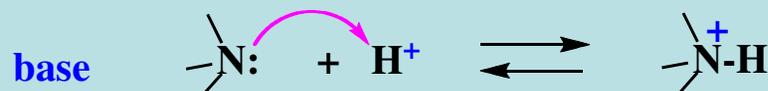
- (1) **Formation of the diastereomeric salts** from an enantiomeric alkaloid amine and a racemic carboxylic acid and
- (2) **Utilization of the differing physical properties** of the diastereomers.

Resolution of α -Hydroxyphenylacetic acid by (*R*)-1-Phenylethylamine

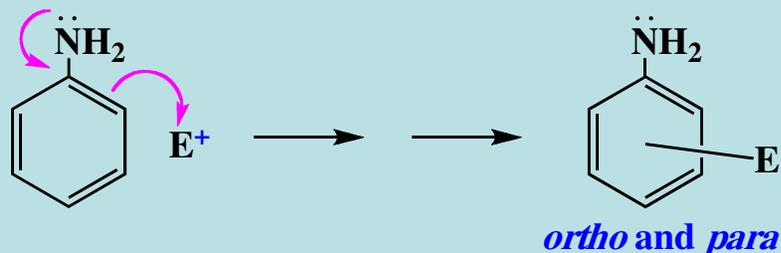


Reactions of Amines

The chemistry of amines is determined by the unshared electron pair on nitrogen. Amines are **bases** and **nucleophiles**.



The amino group as a substituent on a benzene ring is a powerful activating group and *ortho-para* director in electrophilic aromatic substitution:

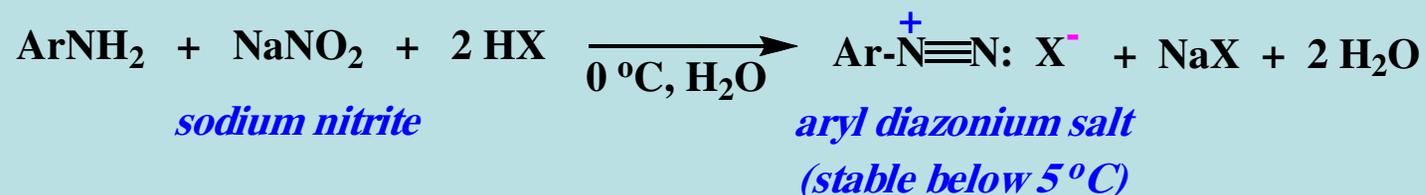


[This holds for reactions like bromination, but if the electrophile being used forms a stable aminium ion (as in the Friedel-Crafts reaction) by initial reaction with the basic amino group the benzene ring is very strongly deactivated.]

Reactions of 1° Arylamines with Nitrous Acid

This most important reaction of amines with nitrous acid yields **aryl diazonium ions**, which have many **replacement reaction** uses in organic synthesis.

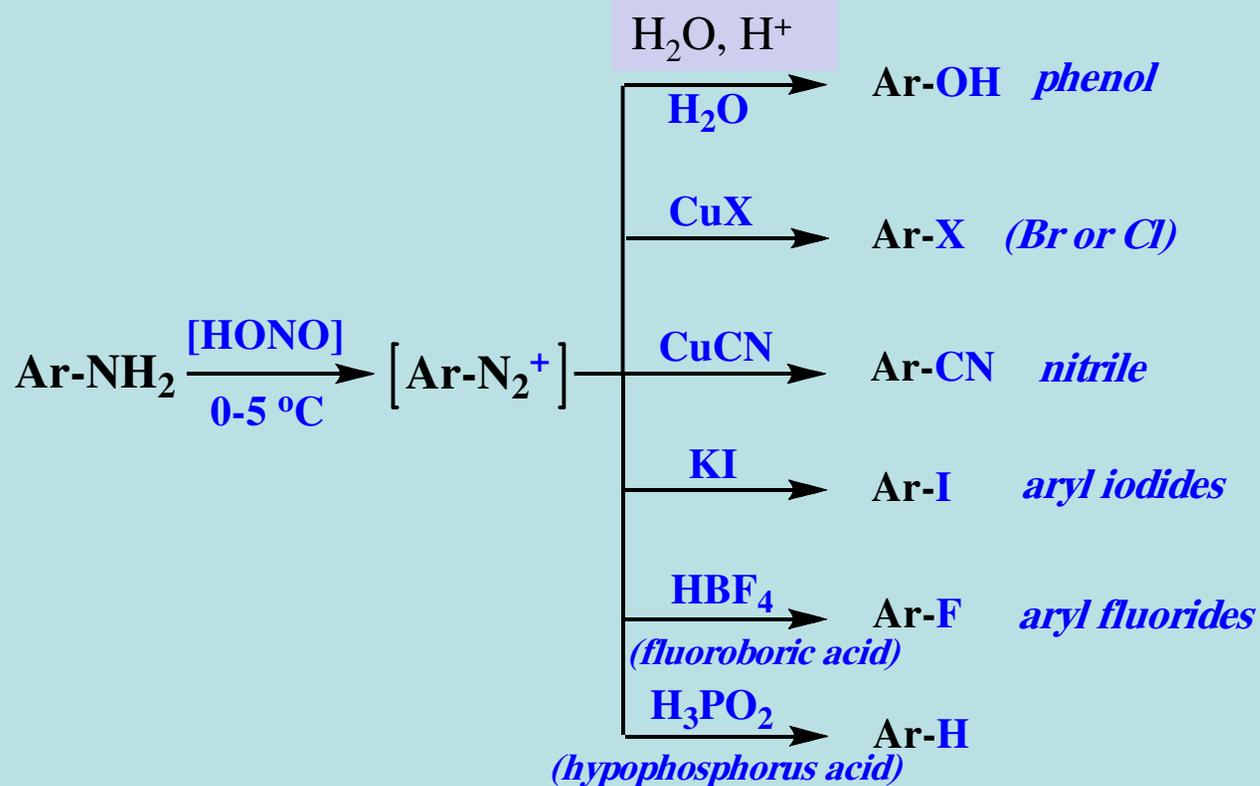
Aryl diazonium salts can be prepared and manipulated at 0 °C:



Note: Many dry aryl diazonium salts are **explosive**. Therefore, these compounds are typically not isolated but prepared and then used in the same solution.

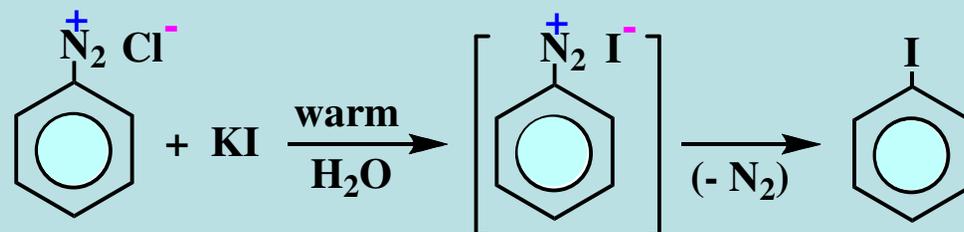
Replacement Reactions of Aryl Diazonium Salts

Reaction of aryl diazonium salts with various reagents results in replacement of the diazonium group by other groups.

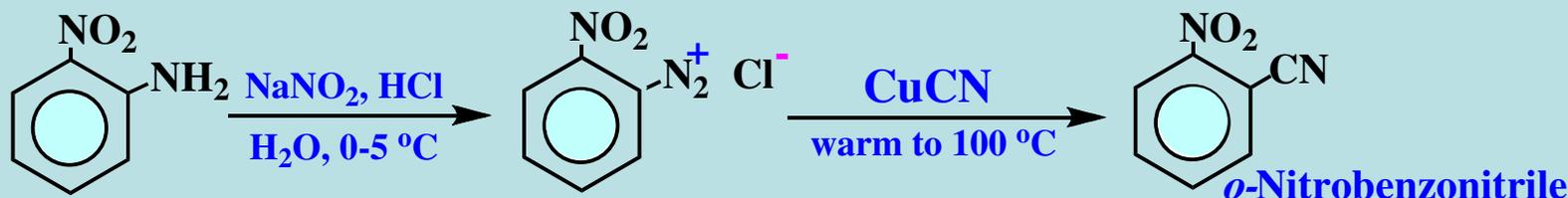
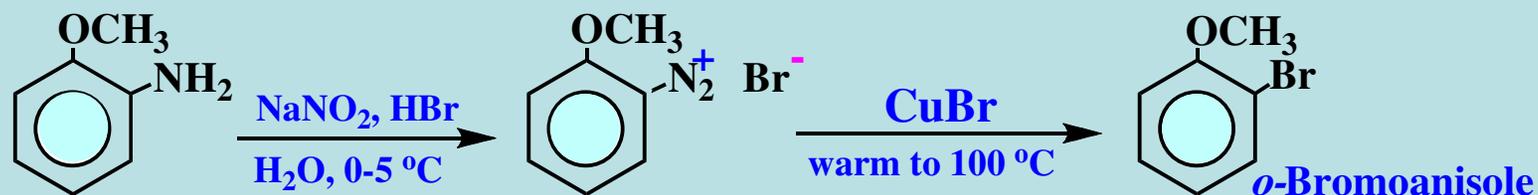


The Sandmeyer Reaction

When an aqueous solution of benzenediazonium chloride and KI is allowed to warm to room temperature, the benzenediazonium iodide produced decomposes with liberation of N₂ to give a good yield of iodobenzene.



A similar reaction does not occur with the aryldiazonium chlorides and bromides. But in 1884, the Swiss chemist Traugott Sandmeyer discovered that replacement reactions are catalyzed by cuprous salts. With **CuCl**, **CuBr**, or **CuCN** added, replacement reactions occur as the diazonium salt is allowed to warm to room temperature.



Aryl Fluorides via Aryldiazonium Tetrafluoroborates

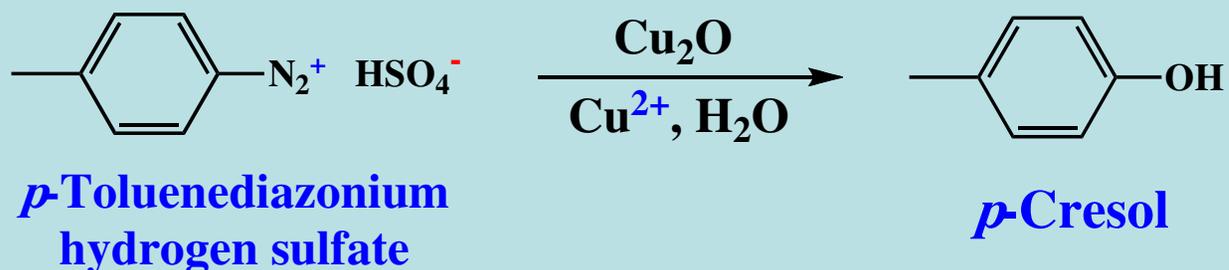
When aryldiazonium salts are reacted with fluoroboric acid (HBF_4), the **aryldiazonium tetrafluoroborate salts** often crystallize out and can be isolated. These salts are unique in their stability. When heated, they produce the aryl fluoride.



Note: Fluorine cannot be introduced by direct electrophilic aromatic substitution of toluene. Even if it could, toluene would yield *ortho* and *para* substitution products.

Phenols via Aryldiazonium Salts

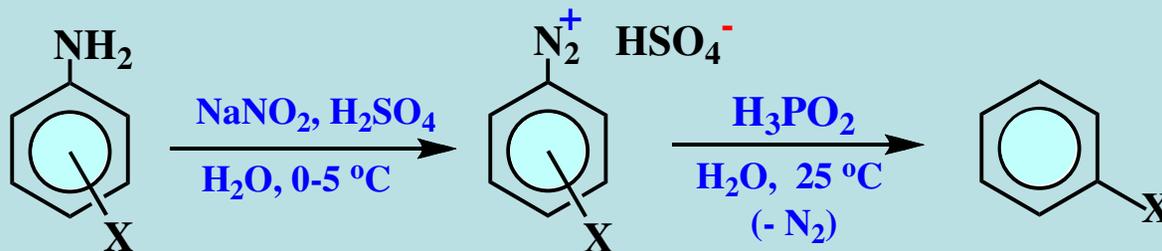
The diazonium group can be replaced with a hydroxyl group by adding cuprous oxide to a dilute solution of the diazonium salt that contains a large excess of cupric nitrate:



This variation of the Sandmeyer reaction was developed by T. Cohen of the University of Pittsburgh. It is simpler and safer than an older procedure.

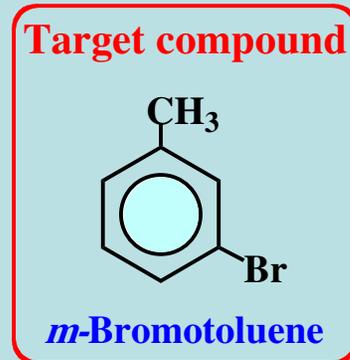
Replacement by Hydrogen: Deamination by Diazotization and Its Use in Synthetic Strategy

Arenediazonium salts react with **hypophosphorous acid** (H_3PO_2 , $\text{HO}-\overset{\text{O}^-}{\underset{\text{H}}{\text{P}}}-\text{H}$) to yield products in which the diazonium group has been replaced by a hydrogen atom.

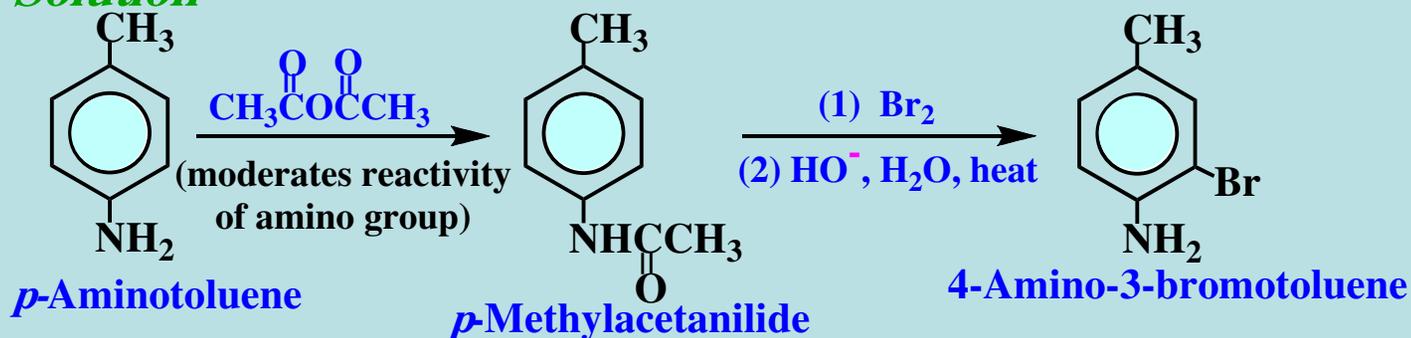


Deamination refers to such a removal of the amino function. In synthetic design, the *ortho-para* directing ability of the amino function can be exploited before it is removed (or replaced) by another group using diazotization chemistry.

m-Bromotoluene cannot be prepared by simple bromination of toluene because of the *o/p* directing nature of the methyl group. **However, use of an amination-deamination procedure can surmount this problem.**



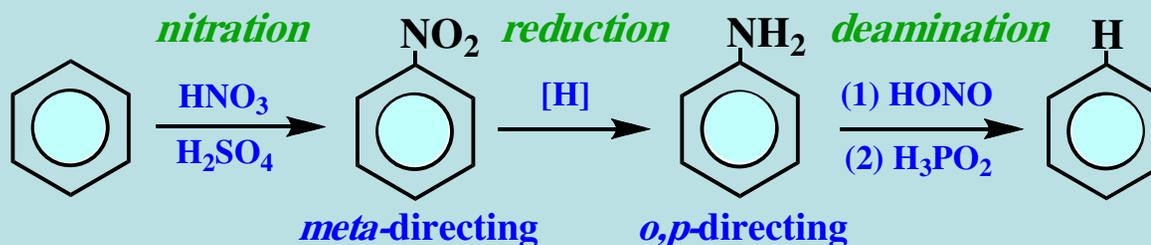
Solution



Deamination sequence



Extended Synthetic Sequence:

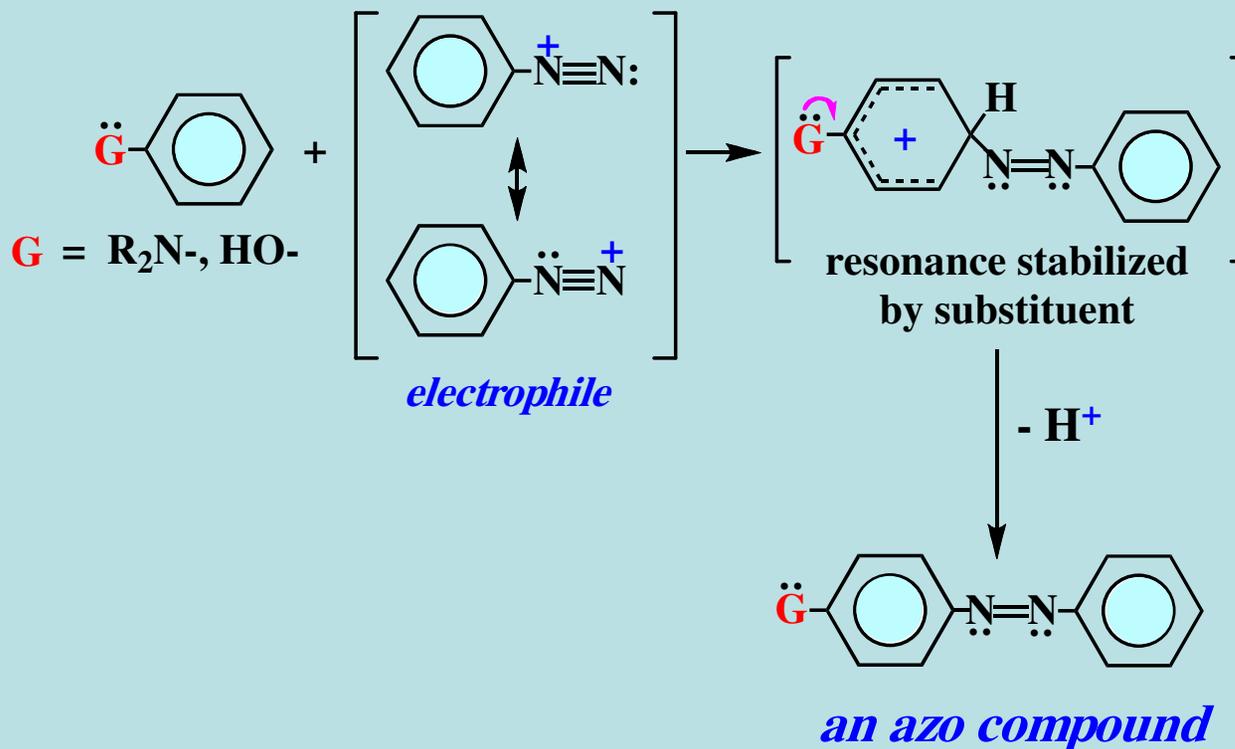


When this sequence is carried out on substituted benzenes, it is possible to design synthetic routes to aromatics with a variety of substitution patterns.

Coupling Reactions of Aryldiazonium Salts

Aryldiazonium ions are **weak electrophiles** that react with electron-rich aromatics such as phenols and *N,N*-disubstituted aryl amines to give **azo compounds**.

Electrophilic aromatic substitution



Azo Dyes

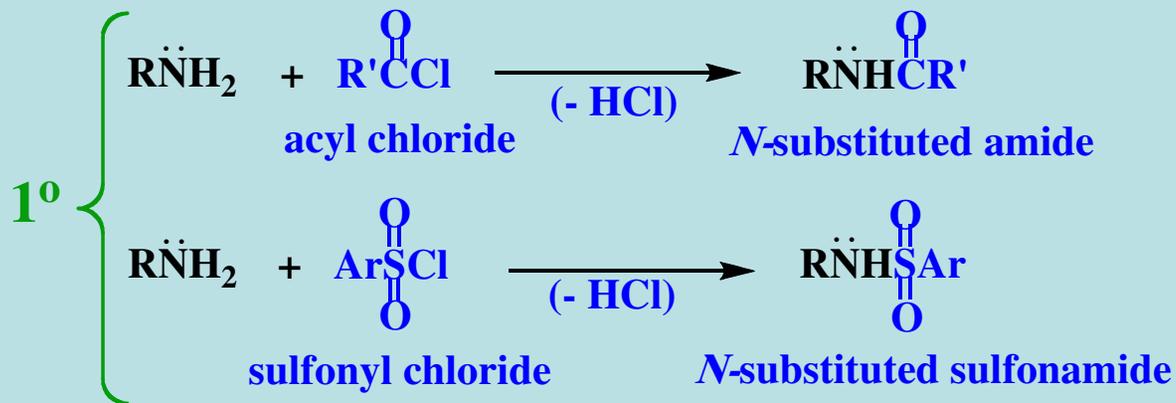
Azo compounds are typically **intensely colored** because of their extended π -electron systems that absorb radiation in the visible region. They are used commercially as dyes. Substituent groups such as $-\text{SO}_3^- \text{Na}^+$ are introduced to make them water soluble and to promote their binding to polar fibers (wool, cotton, or nylon).



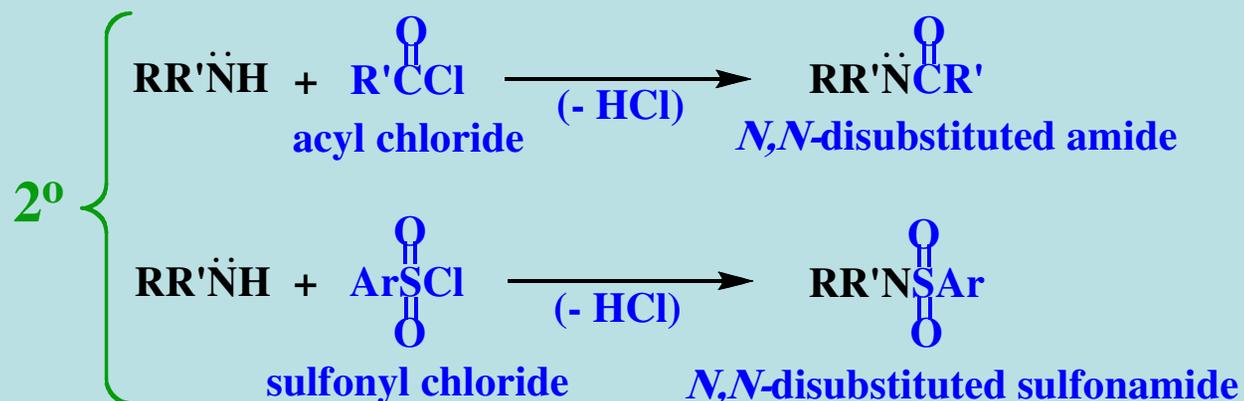
Orange II
A particularly brilliant example

Reactions of Amines with Sulfonyl Chlorides

Primary and secondary amines react readily with **sulfonyl chlorides** just as they do with **acyl chlorides**:



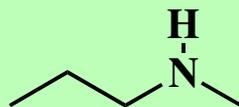
Similarly,



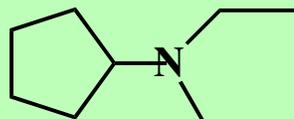
Tertiary amines do not give stable products.

Quiz 20.01

Provide both common and IUPAC names for these amines.



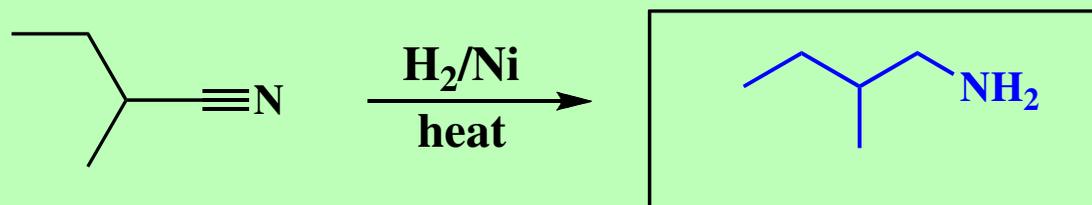
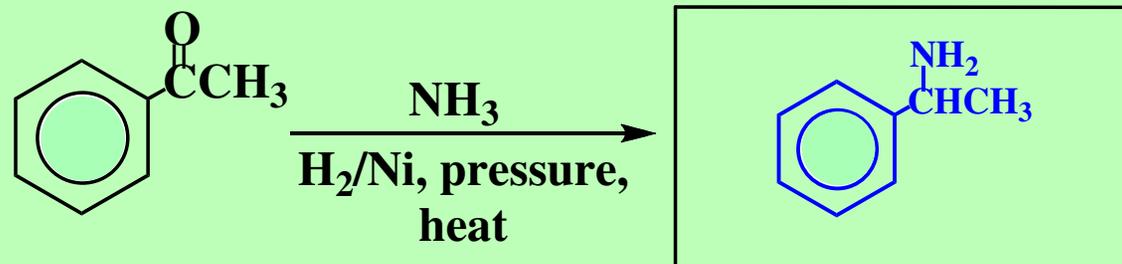
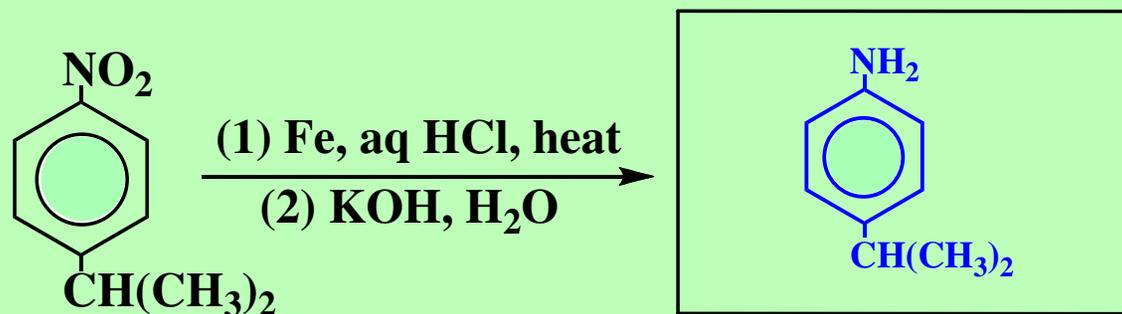
Methylpropylamine
***N*-Methylpropanamine**



Cyclopentylethylmethylamine
***N*-Ethyl-*N*-methylcyclopentanamine**

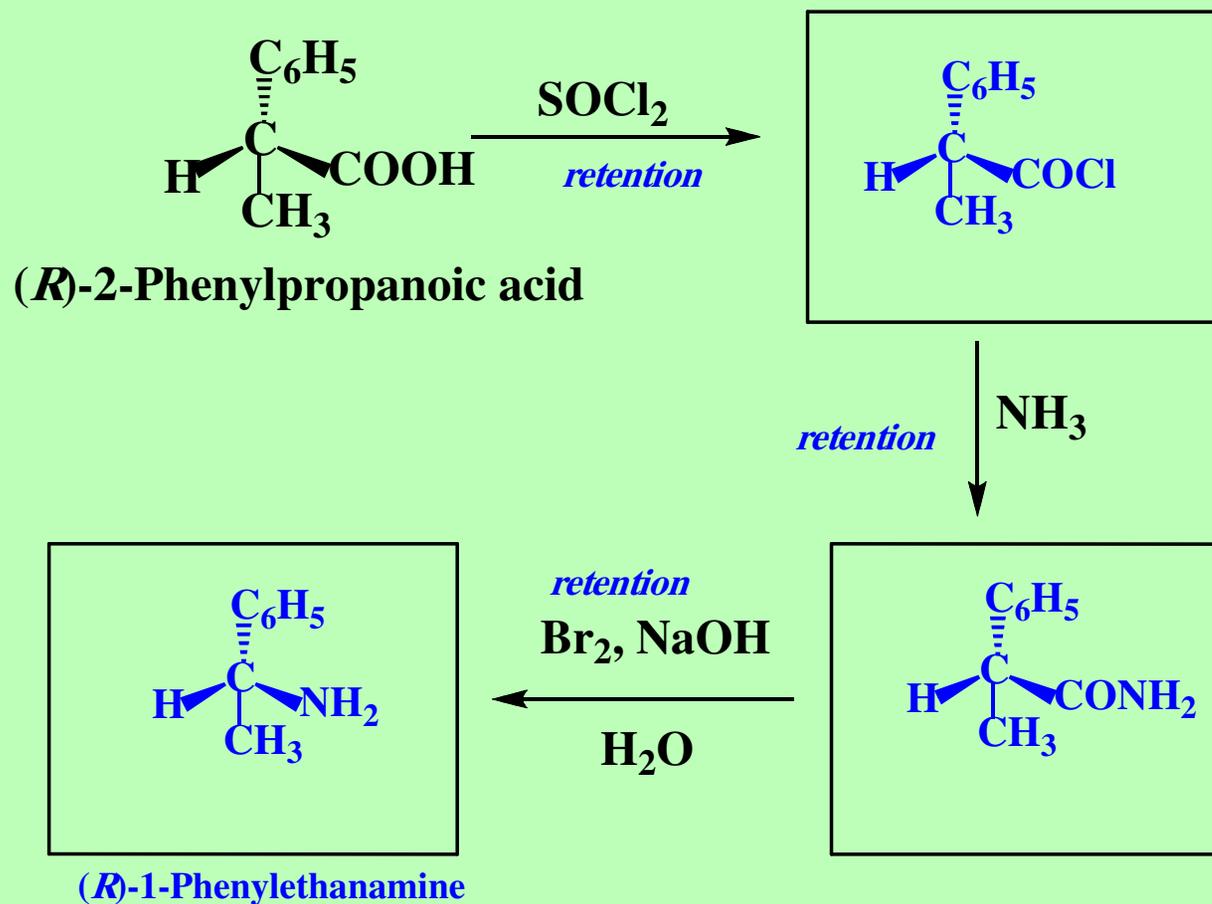
Quiz 20.03

Provide the structures of the products of the following reactions.



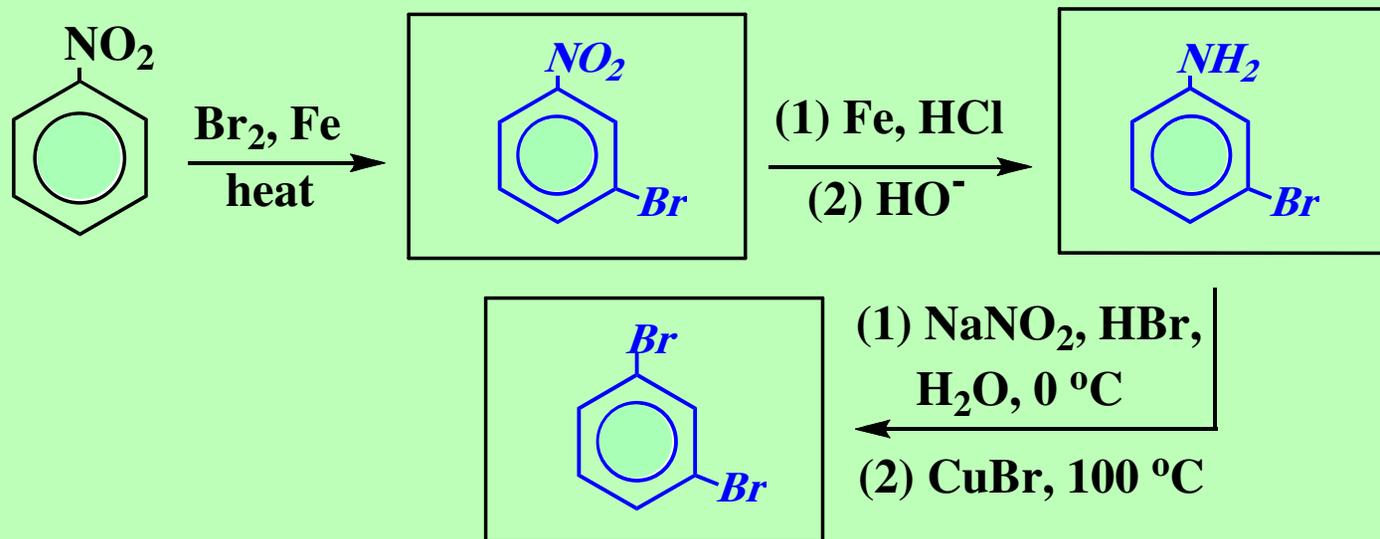
Quiz 20.04

Provide the missing structures in the following scheme.



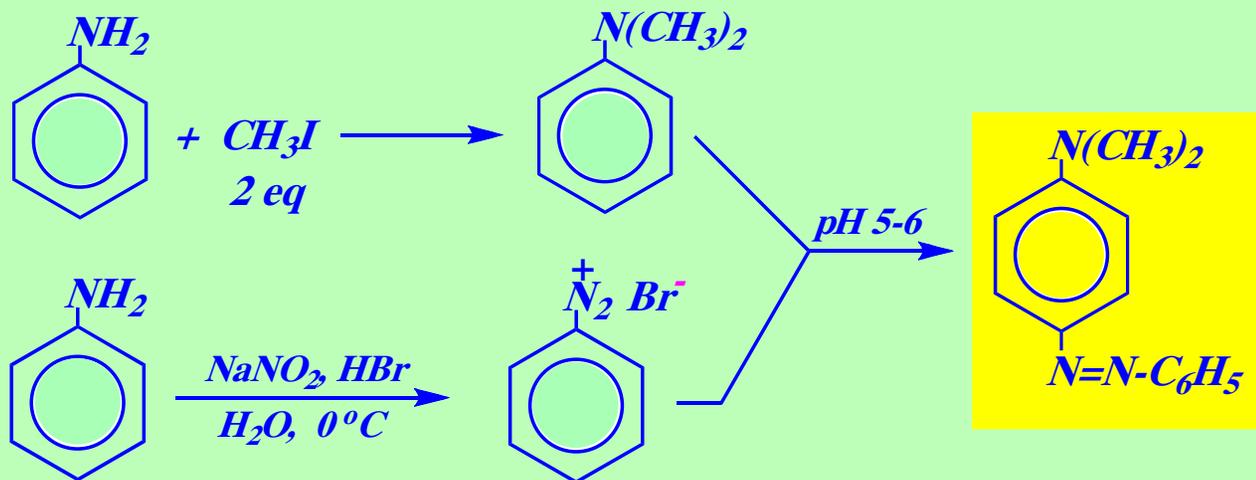
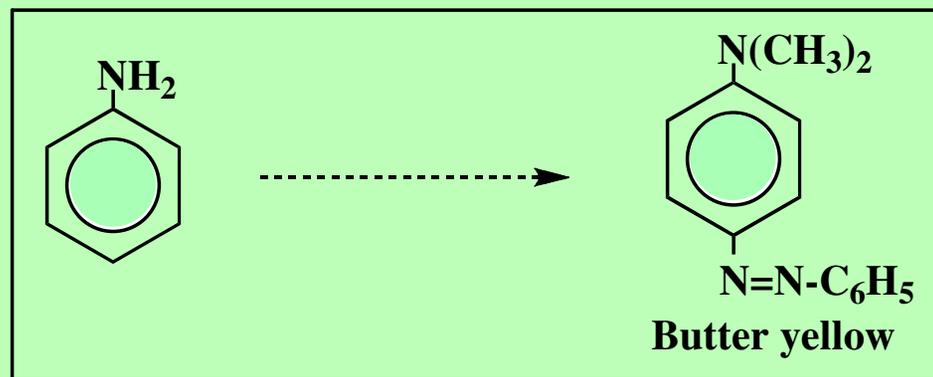
Quiz 20.05

Provide the missing structures in the scheme below.



Quiz 20.06

Design a synthesis of the dye butter yellow from aniline.



End of
Chapter 11

Dr. Abdullah I. Saleh