Chapter 20

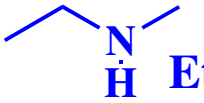
Amines

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

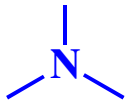
Amines are classified according to the number of R groups on the nitrogen.	$R\ddot{N}H_2$	$R_2\ddot{N}H$	$R_3\ddot{N}$
	primary	*secondary*	*tertiary*
	(1^o) amine	*(2^o) amine*	*(3^o) amine*
	The R groups may be alkyl or aryl.		

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.



Ethylmethylamine

N-Methylethanamine



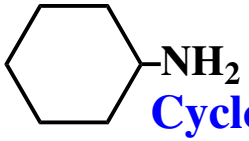
Trimethylamine

N,N-Dimethylmethanamine

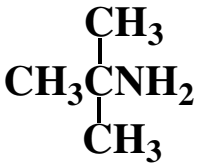
The systematic name is derived from the name of the longest alkane chain present by dropping the final "e" and adding the suffix "amine." Then designate smaller alkyl groups as shown, using the italicized locant "*N*."

Additional Examples

1º Amines

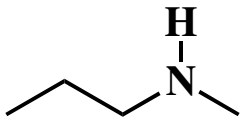


Cyclohexylamine
Cyclohexanamine

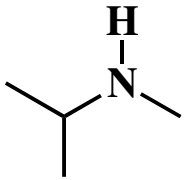


***tert*-Butylamine**
2-Methyl-2-propanamine

2º Amines

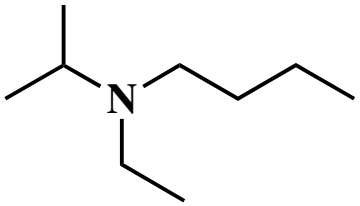


Methylpropylamine
***N*-Methylpropanamine**

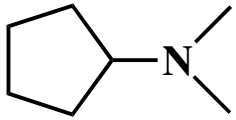


Isopropylmethylamine
***N*-Methyl-2-propanamine**

3º Amines



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



Cyclopentyldimethylamine
***N,N*-Dimethylcyclopentanamine**

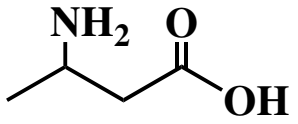
Polyfunctional Amines

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

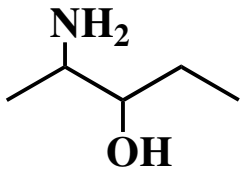
There is an established order of precedence of compound classes, which is used to determine which functional group is the principal one. A highly abbreviated list, in order of decreasing precedence, is:

Acids, aldehydes, ketones, alcohols, amines.

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



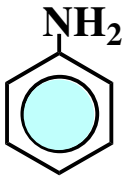
3-Aminobutanoic acid



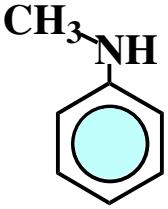
2-Amino-3-pentanol

Arylamines

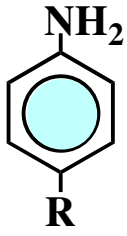
Aromatic amines are often named as derivatives of aniline.



Aniline
Benzenamine



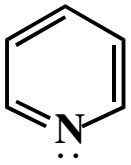
N-Methylaniline
N-Methylbenzenamine



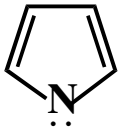
Additional unique common names:
When R = CH_3, *p*-toluidine.
When R = OCH_3, *p*-anisidine.

Heterocyclic Amines

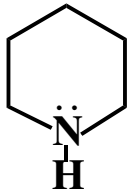
Examples



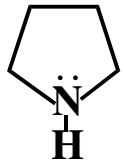
Pyridine



Pyrrole



Piperidine



Pyrrolidine

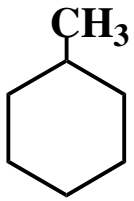
Physical Properties and Structure of Amines

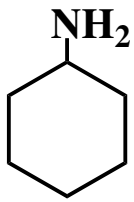
Amines are moderately polar compounds because of the greater electronegativity of nitrogen relative to carbon and hydrogen.

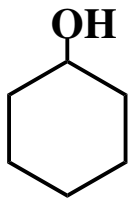
Since 1º and 2º amines have N-H bonds, they hydrogen bond intermolecularly causing their boiling points to be higher than those of alkanes of comparable molecular weight but lower than those of similar alcohols.

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

A COMPARISON:



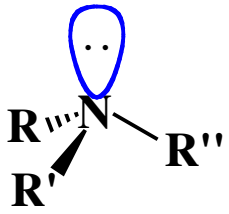




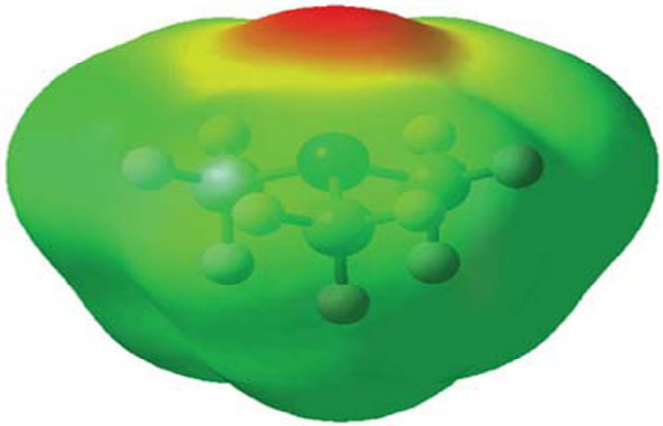
	Methylcyclohexane	Cyclohexylamine	Cyclohexanol
MW	98	99	100
BP	100 ºC	134 ºC	161.5 ºC
Water solubility	Insoluble	Slightly soluble	3.6 g/100 mL

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.



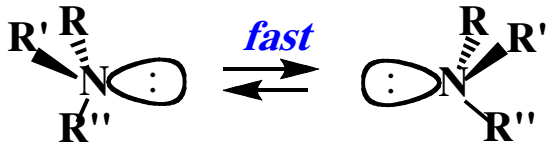
The geometry is described as trigonal pyramidal. Bond angles are close to 109.5°.



A calculated structure for trimethylamine
The electrostatic potential map shows charge associated with the nitrogen unshared electron pair.

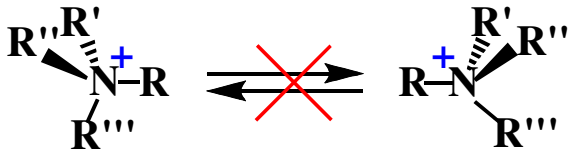
Stereochemical Features

When there are three (four, counting the unshared pair) different groups attached to the nitrogen, the structure is chiral. But because of very fast inversion at the stereocenter (the inversion rate in NH_3 is close to 10^{11} s^{-1}), it is not possible to resolve a chiral amine.



Interconversion of amine enantiomers by fast inversion at the nitrogen center

Quaternary ammonium salts (compounds of type R_4N^+ X^-) display stereochemical features similar to chiral tetravalent carbon. If they contain four different R groups, they are chiral and, being of stable, non-inverting form, can be resolved into their enantiomers.



Chiral quaternary ammonium salts can be resolved.

Interconversion of enantiomers would require bond breaking.

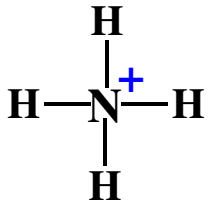
Basicity of Amines: Amine Salts

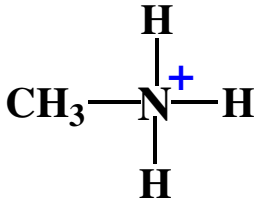
The greater the basicity of an amine, the weaker the acidity of its conjugate acid, the cation in its salts.

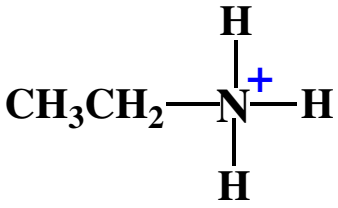
$$RNH_3^+ + H_2O \rightleftharpoons RNH_2 + H_3O^+$$

$$K_a = \frac{[RNH_2][H_3O^+]}{[RNH_3^+]} \qquad pK_a = -\log K_a$$

Influence of alkylation on the acidity of aminium ions:



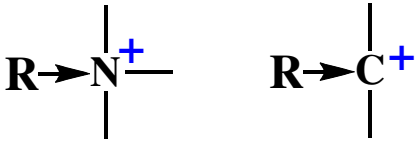




pK_a	9.26	10.64	10.75

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.

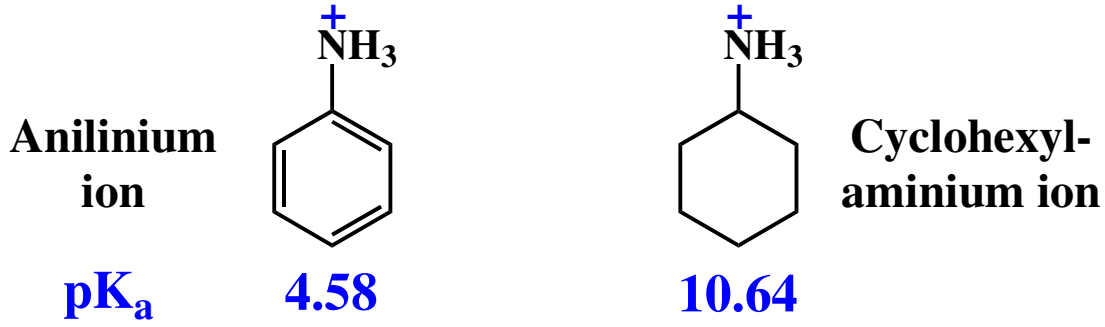


This increase in the basicity of an amine by alkylation is slightly enhanced by introduction of a second alkyl group. Further alkylation of a 2° amine does further increase basicity, but only if measured in the gas phase. In the usual aqueous media, aminium ions from 1° and 2° amines are very effectively 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: $NH_3 < RNH_2 < R_2NH < R_3N$

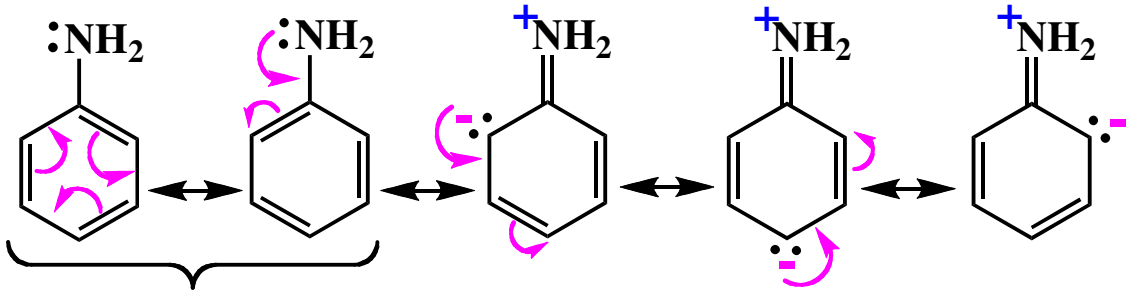
Order of increasing basicity in water: $NH_3 < R_3N < RNH_2 < R_2NH$

Basicity of Arylamines

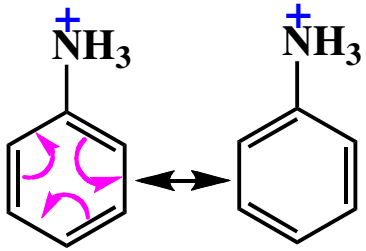


The greater acidity of the anilinium ion means that aniline is a markedly weaker base than is cyclohexylamine, a typical 1^{o} alkylamine.

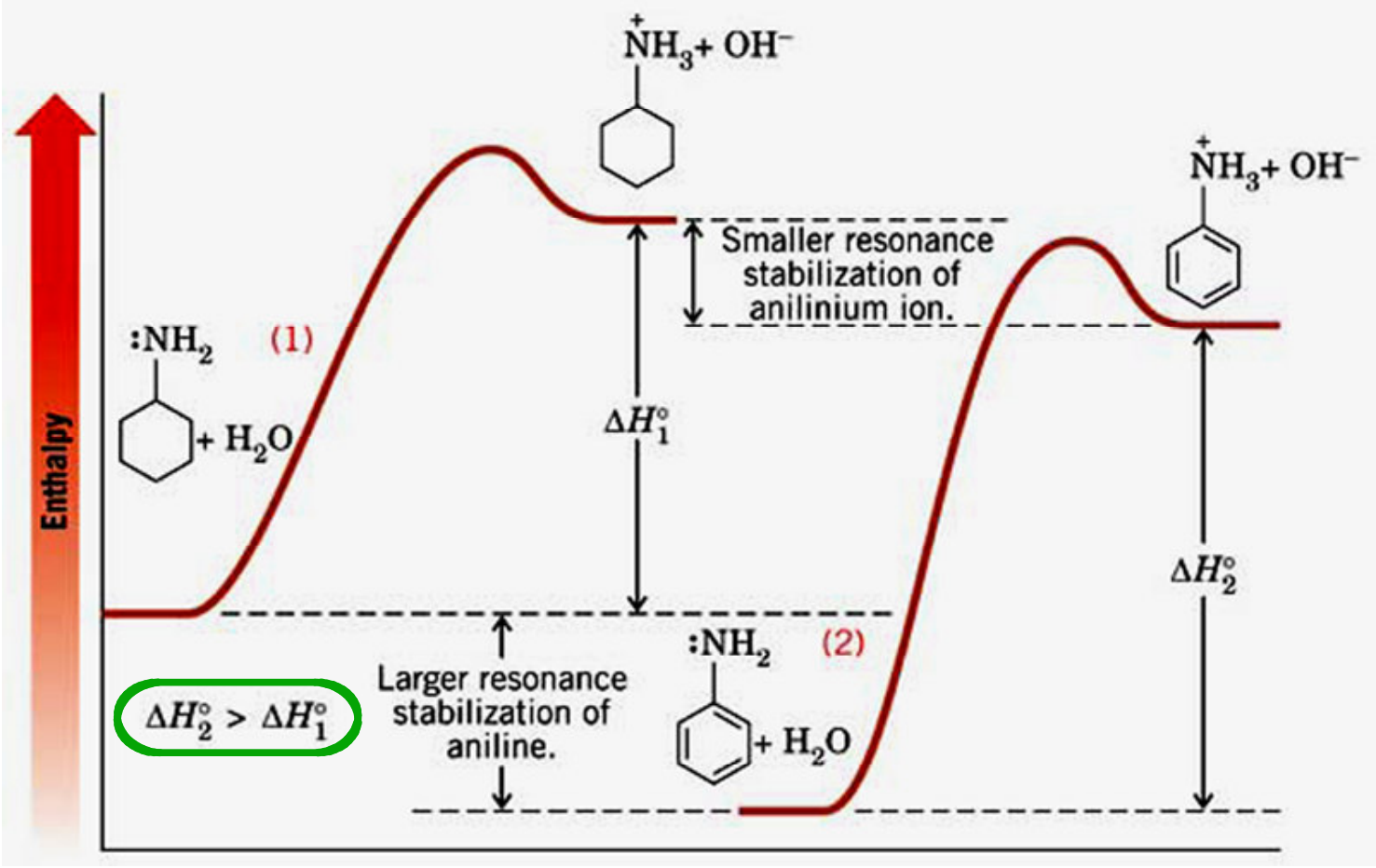
The decreased basicity of aniline is primarily due to the delocalization of the unshared pair on nitrogen by the benzene ring:



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



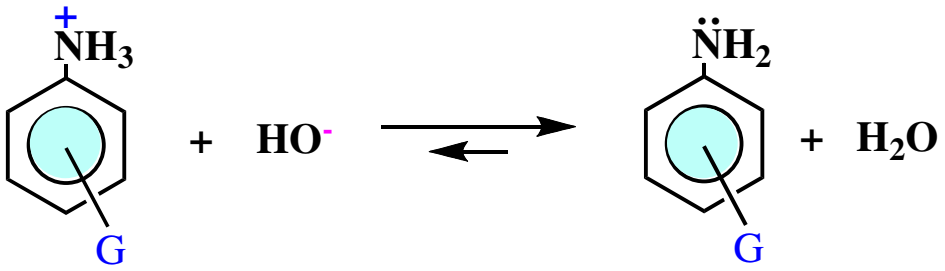
The smaller enthalpy change on protonation of cyclohexylamine (ΔH^{o}_{1}) than on protonation of aniline (ΔH^{o}_{2}) results from its net resonance stabilization and explains why the alkylamine is more basic than aniline.



Basicity of arylamines is also lowered by the sp^2-hybridized carbon attached to the amino group; it is more electronegative than the sp^3 carbon of an alkyl group.

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).



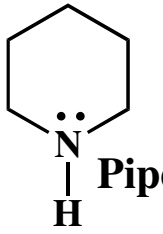
Aminium ion *Free base*

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.

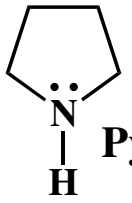
When G is electron-withdrawing, the *conjugate acid* is destabilized (i. e., base strength is decreased) leading to a sometimes considerably smaller value for its pK_a. E. g., when G is a *p*-nitro group, the pK_a drops to 1.00.

Basicity of Heterocyclic Amines

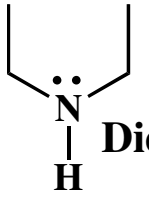
Nonaromatic amines have basicities like those of acyclic amines:



Piperidine



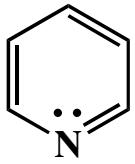
Pyrrolidine



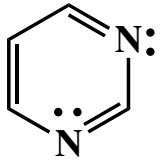
Diethylamine

	Piperidine	Pyrrolidine	Diethylamine
pK_a of aminium ion	11.20	11.11	10.98

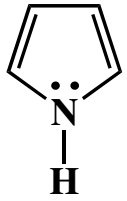
Aromatic amines, in aqueous solution, have much lower basicities, similar to that of aniline:



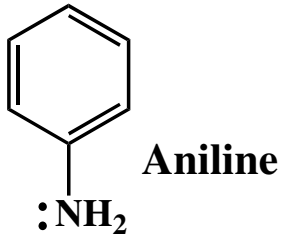
Pyridine



Pyrimidine



Pyrrole



Aniline

	Pyridine	Pyrimidine	Pyrrole	Aniline
pK_a of aminium ion	5.23	2.70	0.40	4.58

The basicity of pyrrole is especially low because its nominally unshared pair electrons are tied up in the "aromatic sextet" and delocalized about the ring.

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.

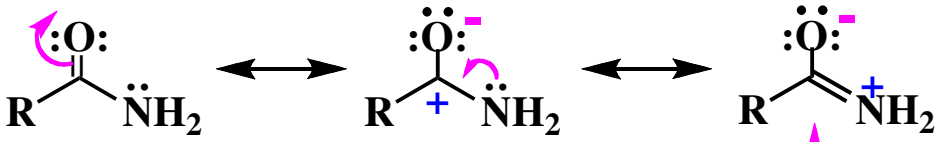
	$R\text{-}\ddot{N}H_2$	$RC(=O)\text{-}\ddot{N}H_2$
	Amine	***Amide***
pK_a (conjugate acid)	~ 10 (R = alkyl)	~ 0

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.

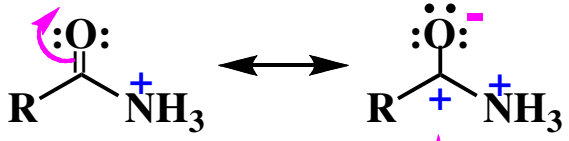
AMIDE



Large resonance stabilization

large contribution

PROTONATED AMIDE
(conjugate acid)



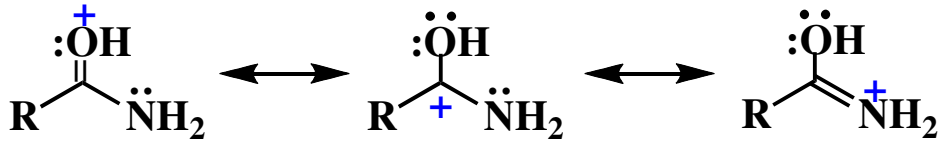
Small resonance stabilization

small contribution

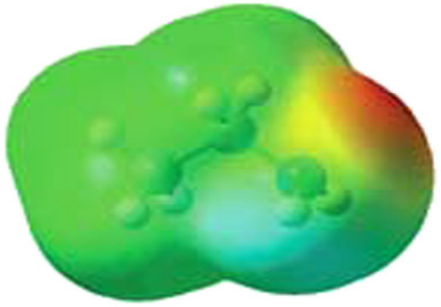
Therefore, resonance lowers the energy of the free base more than that of the protonated state, giving this conjugate acid a smaller pK_a (about zero) in comparison with aliphatic aminium ions (about 10).

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

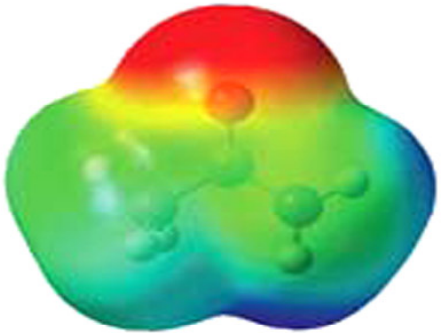
Protonation occurs on the carbonyl oxygen because that adduct is resonance stabilized:



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.



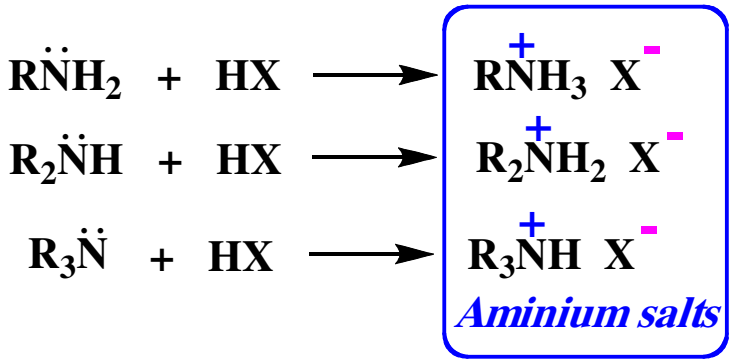
Ethylamine



Acetamide

Aminium Salts

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



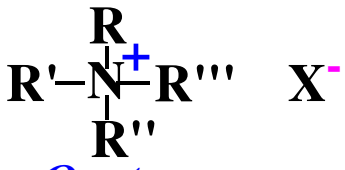
It is the formation of aminium salts that causes amines to dissolve in acidic aqueous media. Aminium salts are not basic because there is no longer a nonbonding electron pair on the nitrogen atom.

Aminum salts are weak acids. As conjugate acids of the free base amines, the general conjugate relationship applies in which $pK_a + pK_b = 14$.

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

Quaternary Ammonium Salts

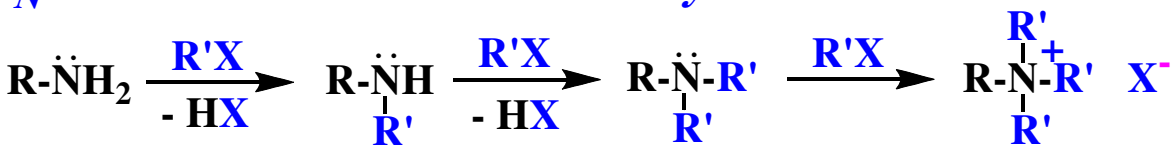
When there are four R groups (alkyl or aryl) attached to the nitrogen, the function is called a quaternary ammonium ion.



Quaternary ammonium salt

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

S_N2 reactions: "exhaustive" N-alkylation

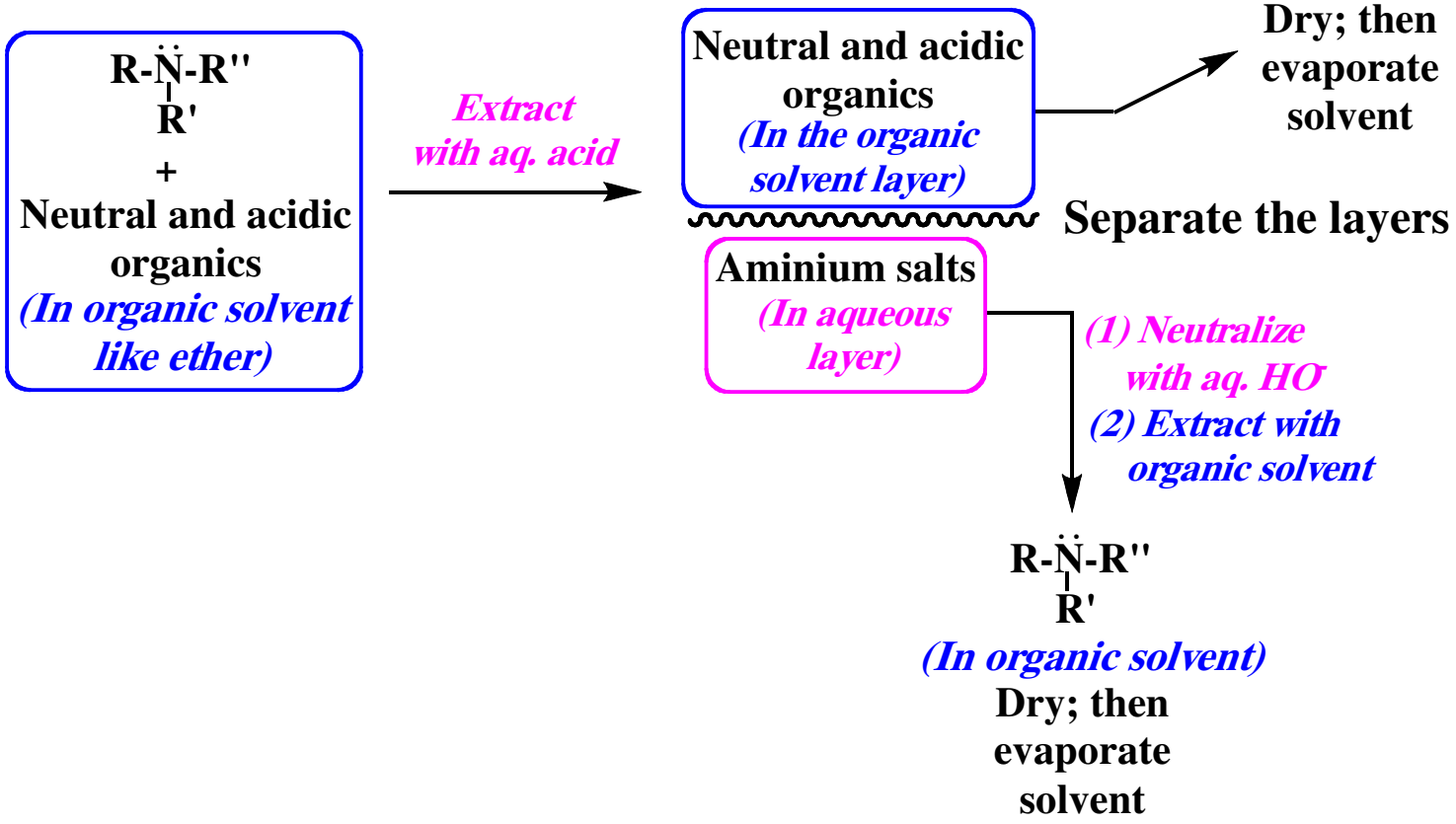


Quaternary ammonium halides, having no unshared pair on nitrogen, cannot act as bases. If, however, the halide ion is replaced with a hydroxide ion they are fully ionic, strong bases like NaOH or KOH.

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

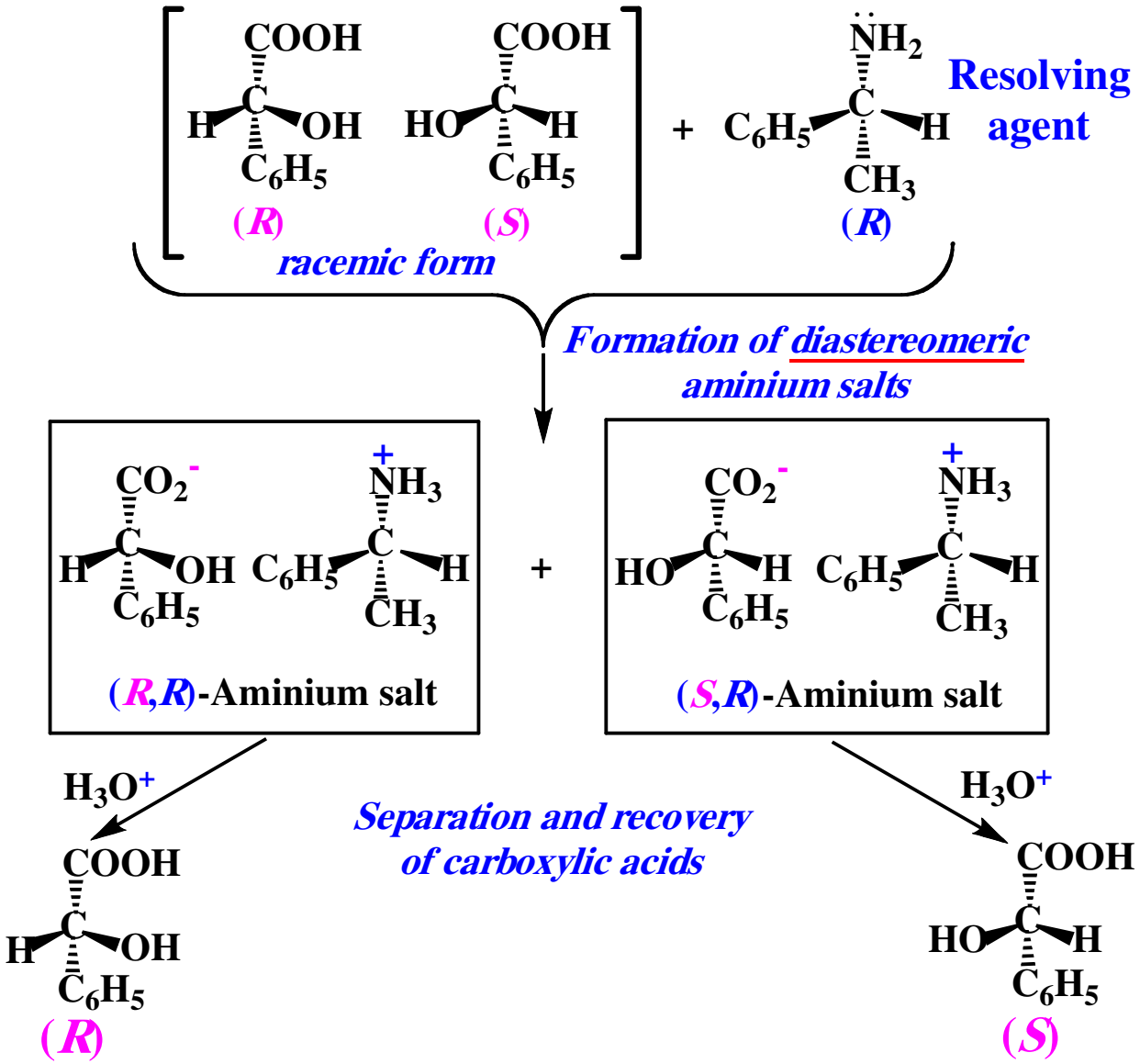
A type of amine called alkaloids is available from plant sources. Many are chiral and occur in single enantiomer form. Some of these compounds are pharmacologically important, e. g., quinine and atropine. Others have dangerous natures, e. g., morphine and strychnine.

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.

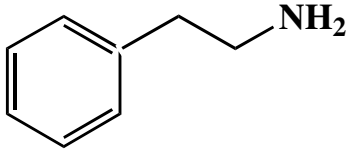
Resolution of α-Hydroxyphenylacetic acid by (*R*)-1-Phenylethylamine

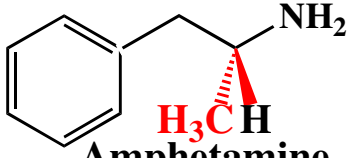


Some Biologically Important Amines

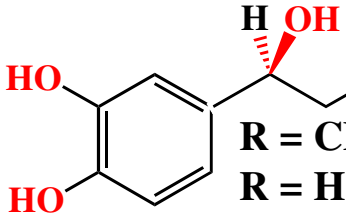
Amines are widely encountered in biological and pharmacological studies. Some important examples are the 2-phenylethylamines, some vitamins, antihistamines, tranquilizers, and neurotransmitters.

2-Phenylethylamines

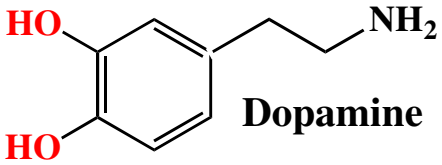




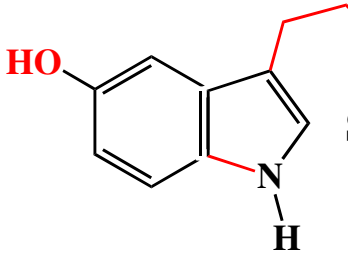
Amphetamine
(Benzidrine)



R = CH_3, Adrenaline
R = H, Noradrenaline

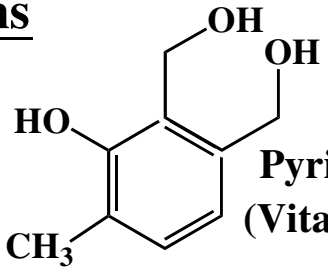


Dopamine

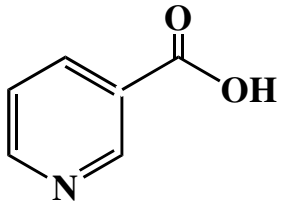


Serotonin

Vitamins

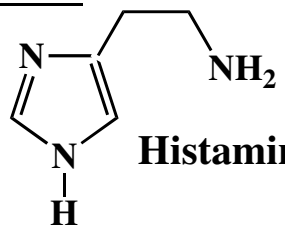


Pyridoxine
(Vitamin B_6)



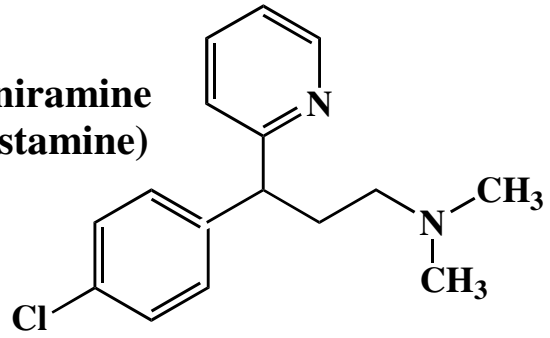
Nicotinic acid
(Niacin)

Antihistamines



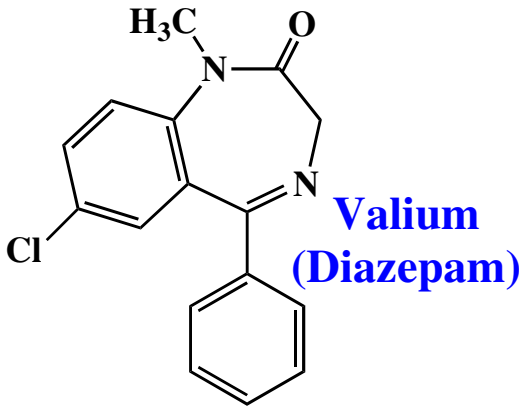
Histamine

Chlorpheniramine
(an antihistamine)

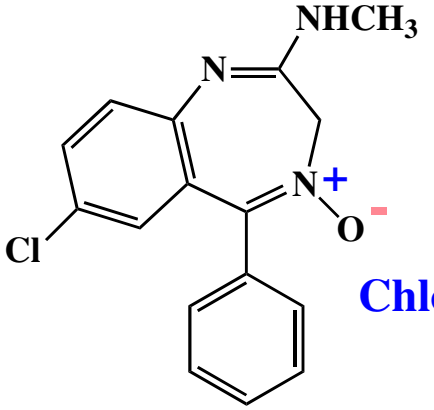


Tranquilizers

These examples are both 1,4-benzodiazepine anxiolytics.



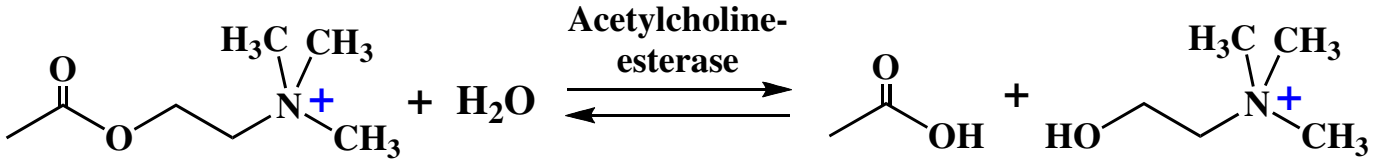
Valium (Diazepam)



Chlordiazepoxide

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.



Acetylcholine **Choline**

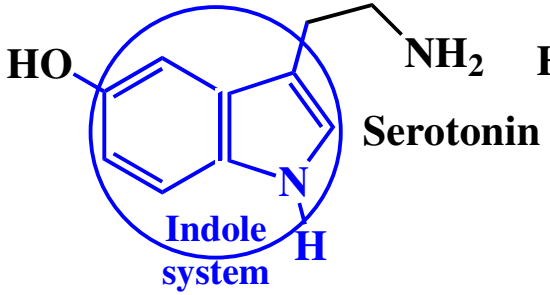
An essential feature of this system is that the esterase can almost immediately hydrolyze the neurotransmitter that has been received at the receptor site, freeing it to receive a later nerve impulse.

Structure-Reactivity Relationships

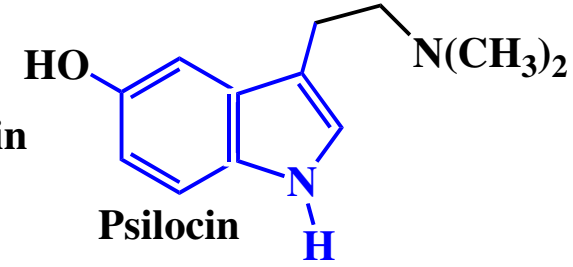
Medicinal chemists have long used structural features as a key to drug design. The structural similarity between the amphetamines and the natural brain hormones (like adrenaline, noradrenaline, and dopamine) is an example.

Serotonin Mimics

Another example of structure-reactivity relationships appears to be the hallucinogenic effect of a number of compounds of the indole type.

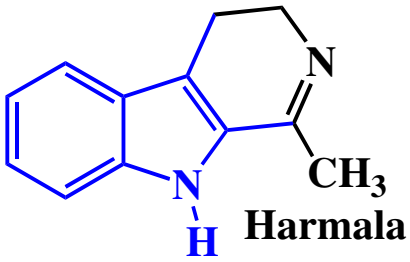


Serotonin



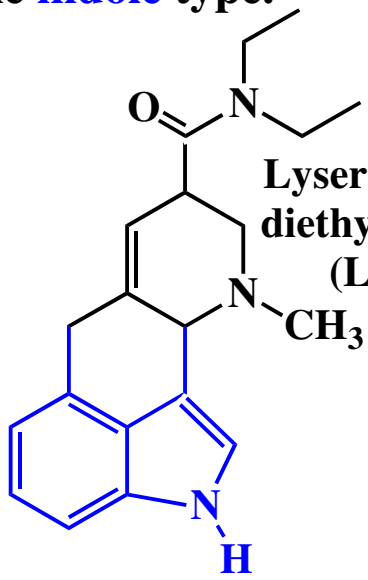
Psilocin

A hallucinogenic alkaloid obtained from the "sacred" mushrooms of Central America, *Psilocybe mexicana.*



Harmala alkaloids

Found in plants in Peru, Ecuador, Columbia and Brazil. Used as a hallucinogen by native indians.



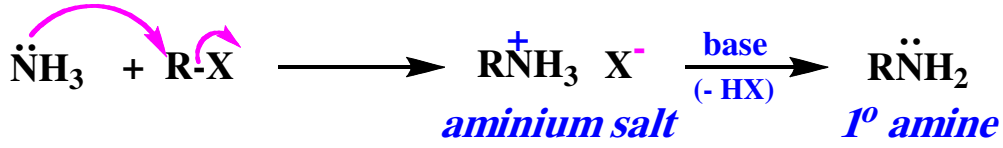
Lysergic acid diethyl amide (LSD)

First synthesized by Albert Hofmann in 1938 at Sandoz Pharmaceutical Co. while working on derivatives of the hallucinogenic ergot alkaloids .

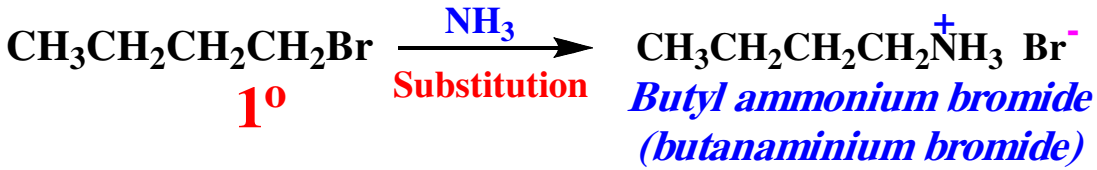
Synthesis of Amines

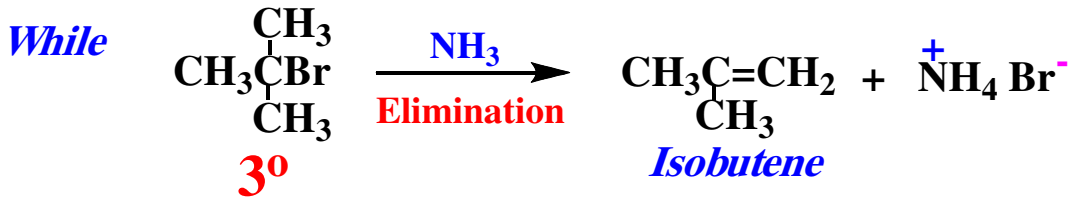
Nucleophilic Substitution Reactions: Direct Alkylation Method

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



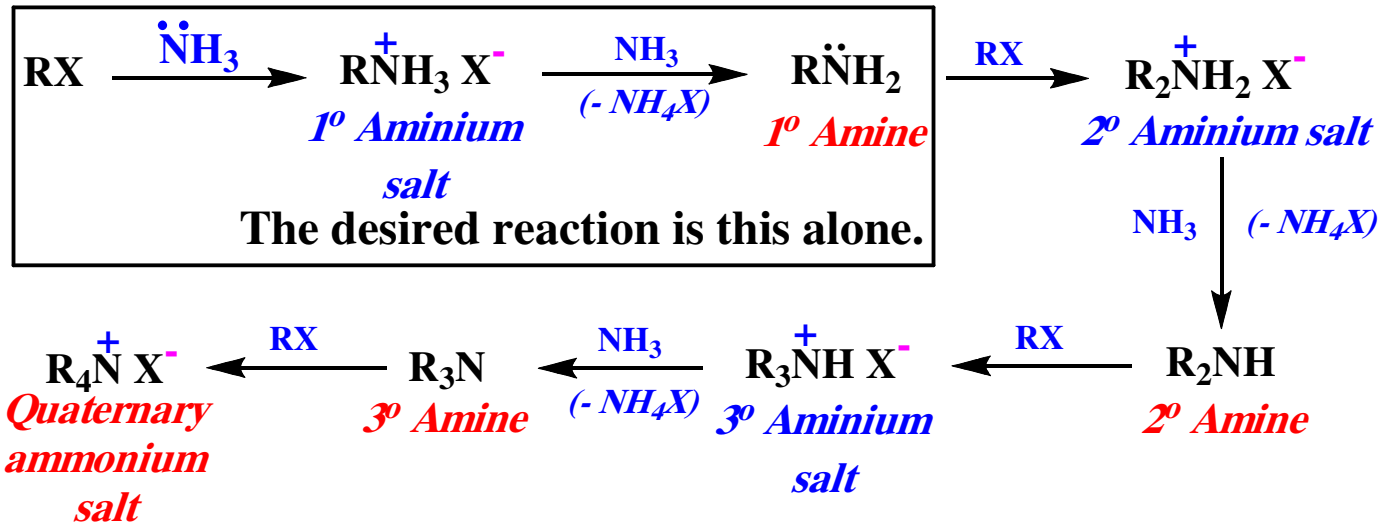
The reaction may be carried out in aqueous or alcoholic (to improve the solubility of RX) solutions of ammonia. All the usual structural limitations of an S_N2 reaction apply.





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.



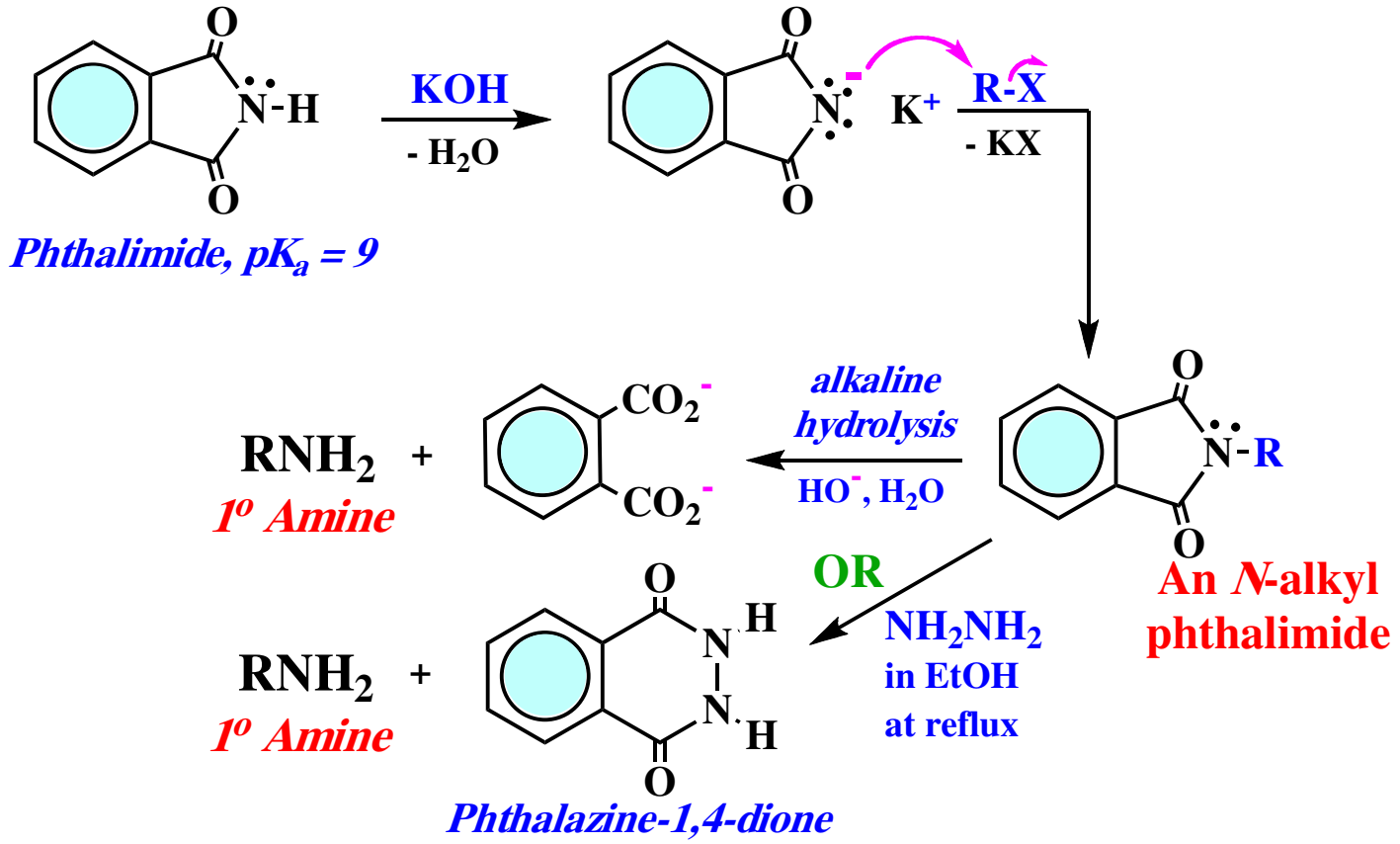
While the direct alkylation synthesis of 1° amines is simple, the products are contaminated by the 2° and 3° amines and 4° ammonium salts. By using a very large excess of ammonia, good results sometimes can be achieved.

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 Gabriel Synthesis of 1° Amines (S. Gabriel, 1887)

The Gabriel synthesis is a good choice when 1° amines are desired.

This synthesis utilizes the anion of phthalimide as a nucleophile in S_N2 reaction with alkyl halides. Alkaline hydrolysis of the *N*-alkylated phthalimide yields the 1° amine free of 2° and 3° amines.

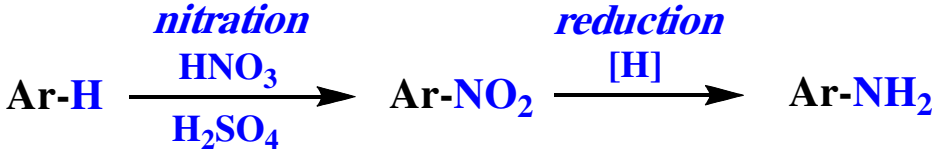


The alternative of using hydrazine, NH_2NH_2, to release the 1° amine often gives superior results.

The Synthesis of Amines by Reduction Methodologies

Reduction of Nitro Compounds

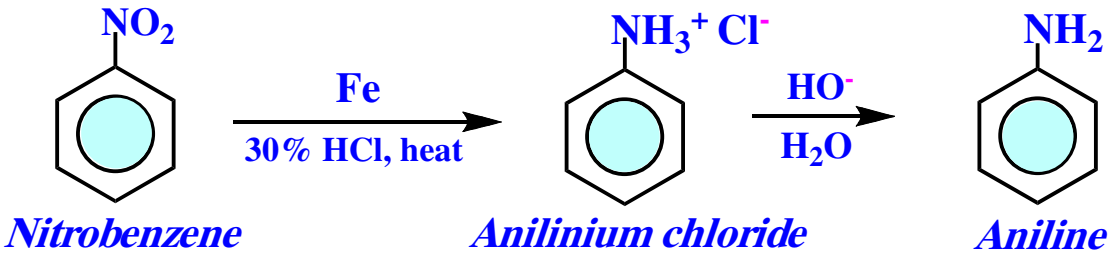
Anilines may be prepared by reduction of nitrobenzenes. The overall synthetic sequence begins with nitration of the starting arene.



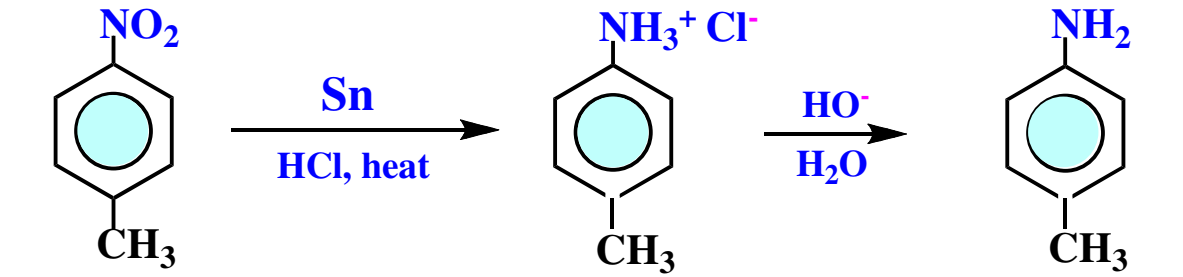
The Dissolving Metal Reduction of Nitrobenzenes to Anilines

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

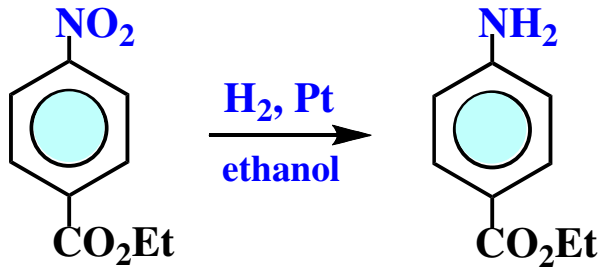


p-Nitrotoluene

p-Toluidine

Catalytic Hydrogenation of Nitroaromatics

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

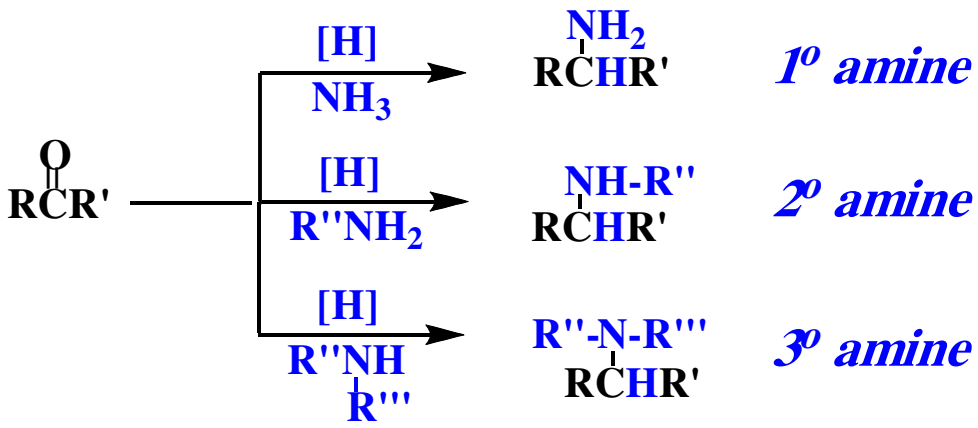


Ethyl *p*-nitrobenzoate

Ethyl *p*-aminobenzoate

Reductive Amination

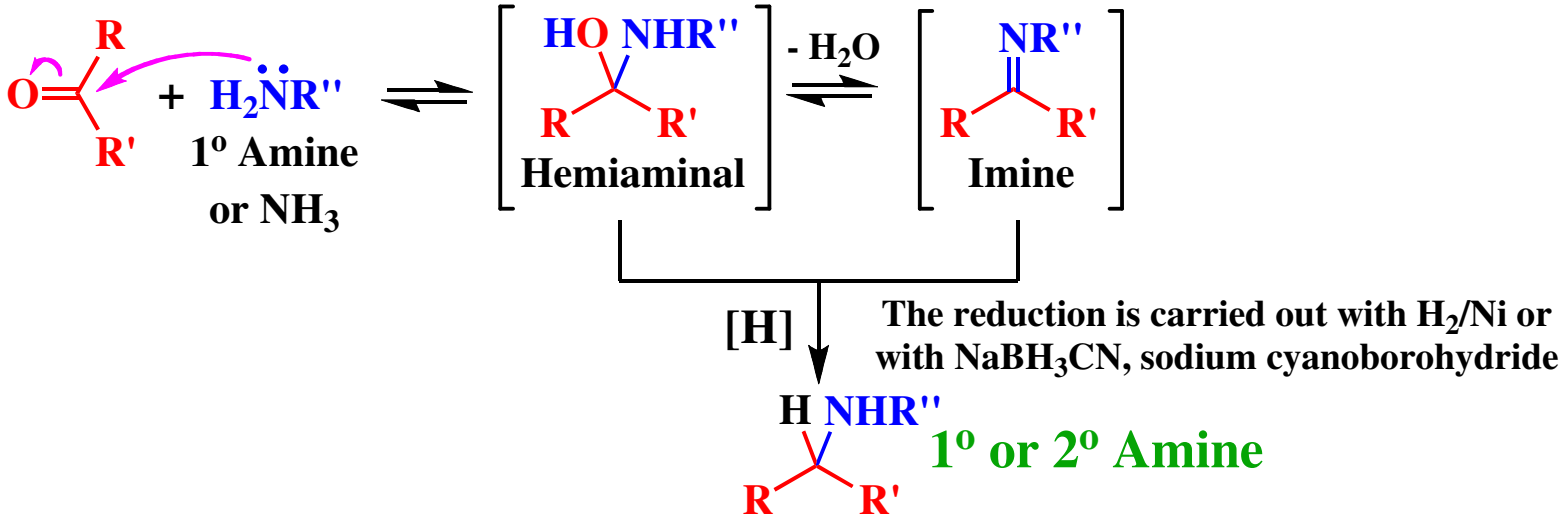
Aldehydes and ketones can be converted into amines by catalytic or chemical reduction in the presence of ammonia or a 1º or 2º amine. The overall synthetic schemes are these:

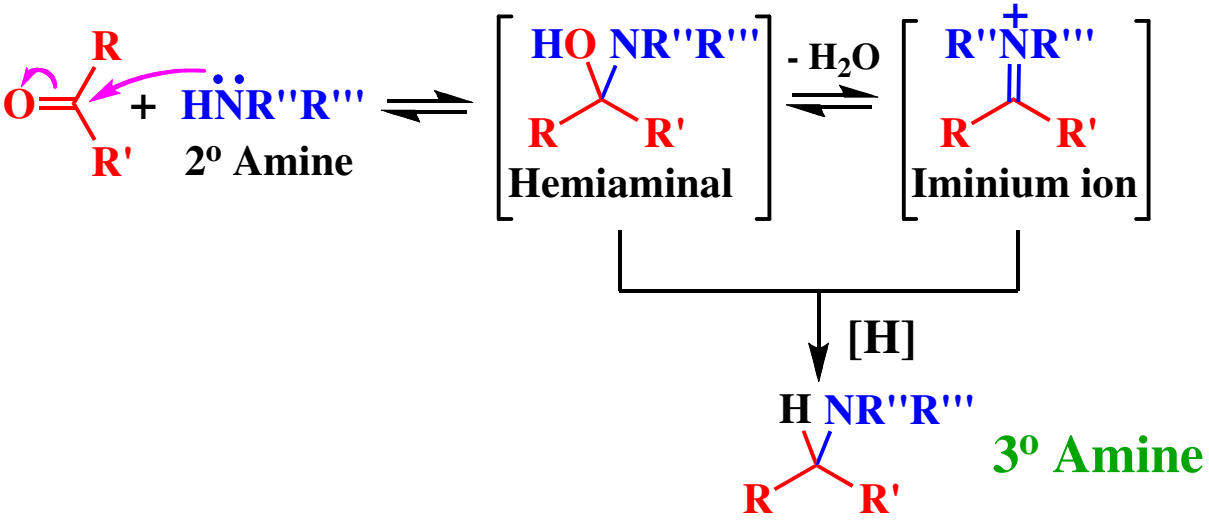


These conversions can alternatively be viewed as reductive alkylations of the starting amines.

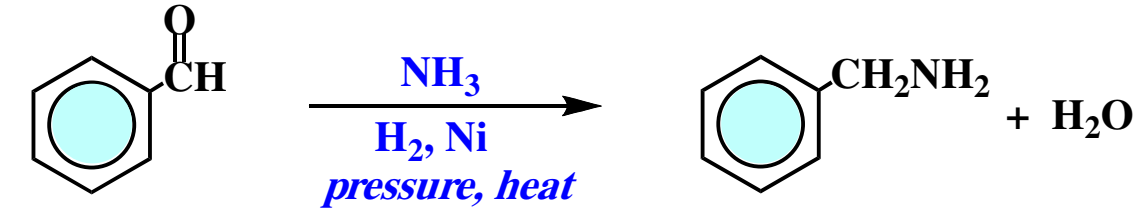
A Mechanism for Reductive Amination

Reductive amination involves addition of the amine to the carbonyl followed by reduction via the immediate aminal or its dehydration product, an imine.





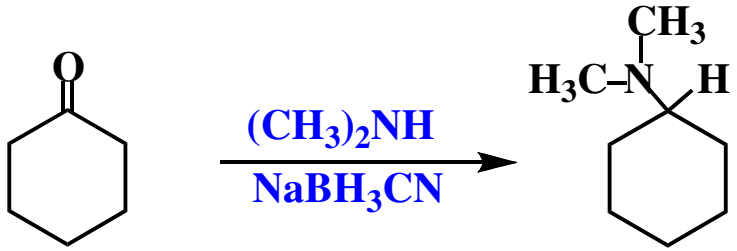
Examples



Benzaldehyde — Benzylamine

Amination of aldehyde OR alkylation of ammonia

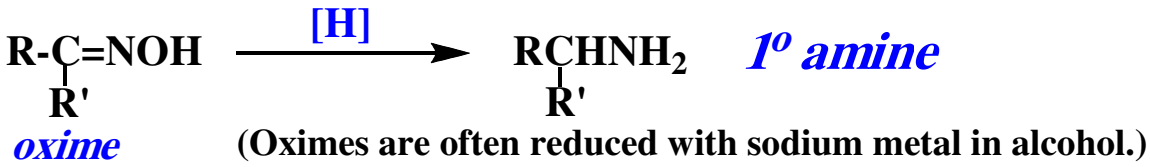
2-Pentanone — 2-Pentanamine



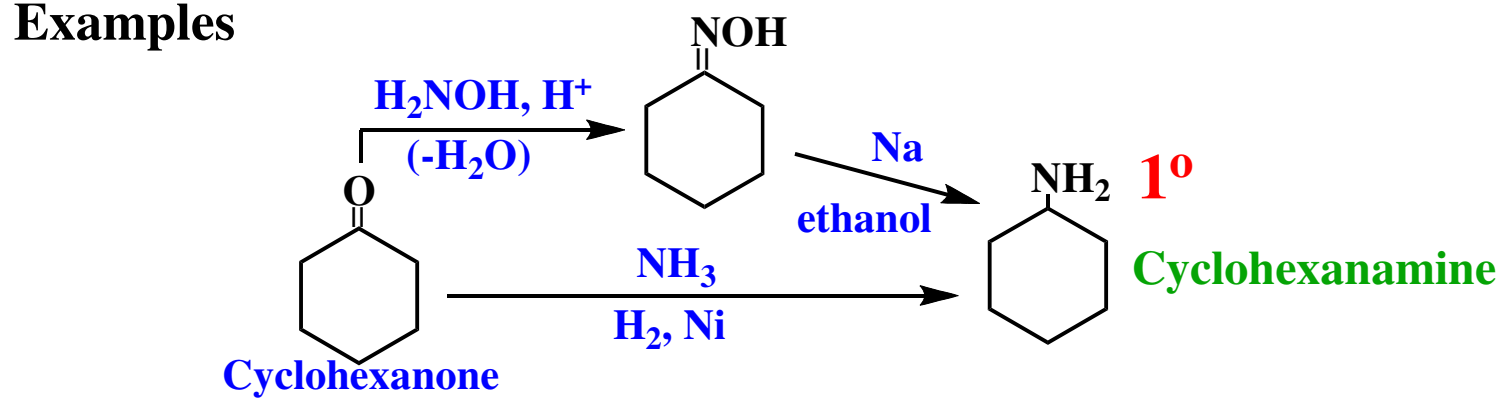
Cyclohexanone — *N,N*-Dimethyl-cyclohexanamine

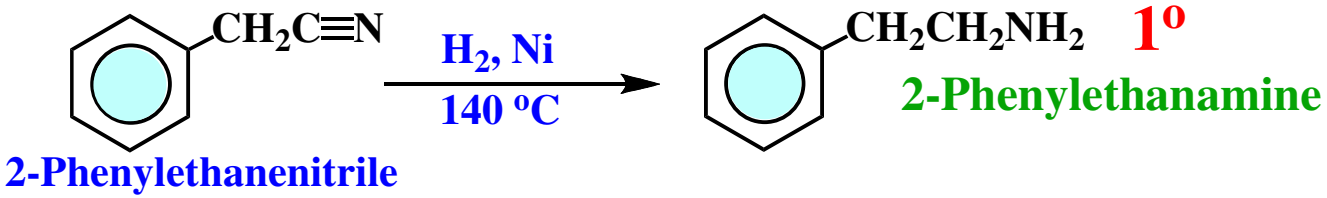
Reduction of Nitriles, Oximes, and Amides

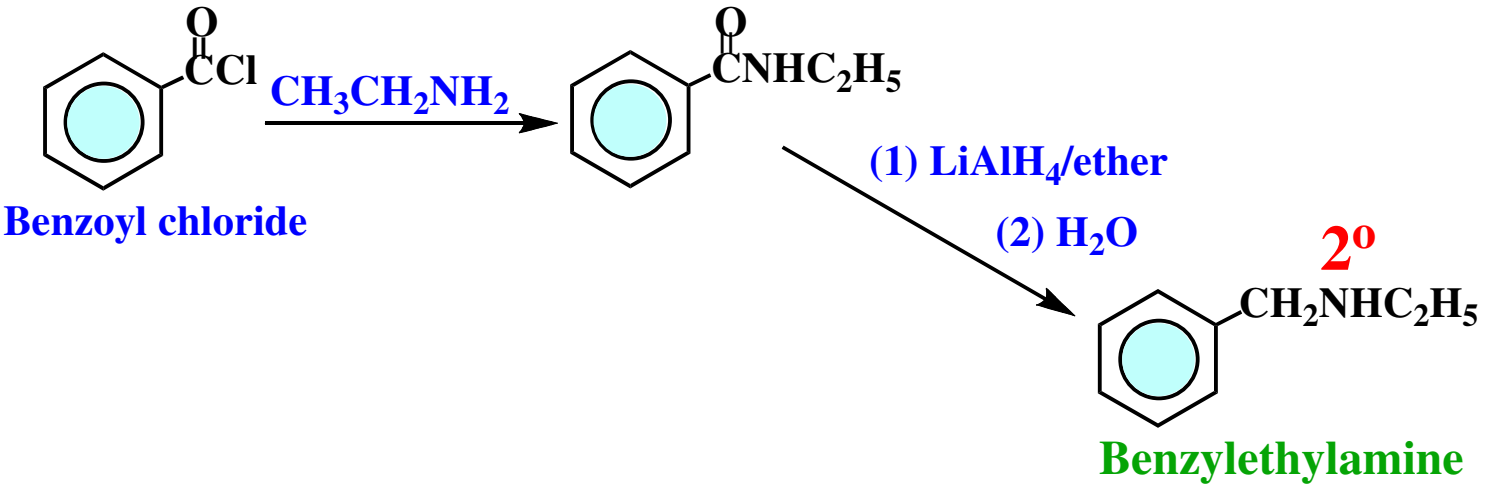
Reduction of any of these functional groups by catalytic hydrogenation or lithium aluminum hydride ($LiAlH_4$) yields an amine.



Examples


NOH
H_2NOH, H^+
$(-H_2O)$
Na
ethanol
NH_2
1^o
O
NH_3
H_2, Ni
Cyclohexanamine
Cyclohexanone


$CH_2C\equiv N$
H_2, Ni
140 °C
$CH_2CH_2NH_2$
1^o
2-Phenylethanamine
2-Phenylethanenitrile


O
Cl
$CH_3CH_2NH_2$
O
$CNHC_2H_5$
(1) $LiAlH_4$/ether
(2) H_2O
2^o
$CH_2NHC_2H_5$
Benzoyl chloride
Benzylethylamine

The Hofmann Rearrangement: Amines from Primary Amides

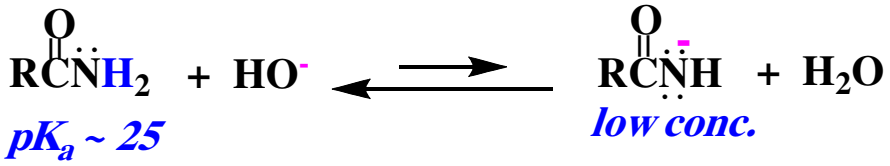
Primary amides are converted into amines by loss of the carbonyl group in aqueous basic solutions of Br_2 or Cl_2.

The Hofmann rearrangement of 1º amides provides 1º amines exclusively, with no contamination from 2º or 3º amines. This reaction also can be useful for shortening a carbon chain, which explains why it is sometimes referred to as a Hofmann degradation.

A Mechanism for the Hofmann Rearrangement

The proposed mechanism begins with base-promoted *N*-bromination, analogous to α-bromination of enolizable ketones.

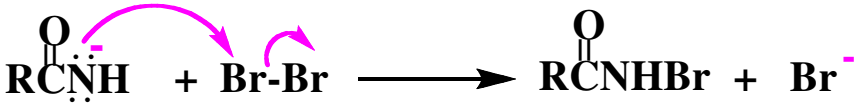
acid-base reaction



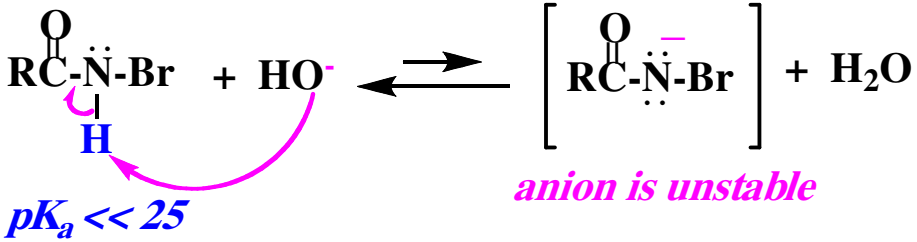
pK$_a$ ~ 25

low conc.

nucleophilic attack: N-bromination step



The *N*-bromoamide is more acidic than the unsubstituted amide and deprotonation readily occurs:

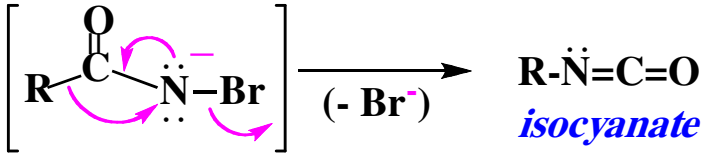


pK$_a$ << 25

anion is unstable

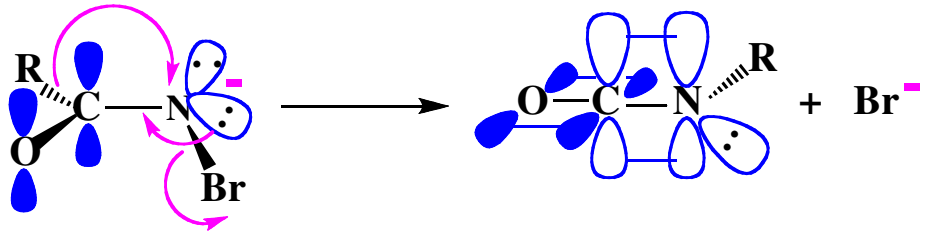
The Rearrangement Step

molecular rearrangement of unstable anion to isocyanate



The R group (alkyl or aryl) shifts from the carbonyl to the nitrogen with departure of the bromide ion. Formation of a π-bond produces the isocyanate.

ANOTHER VIEW:

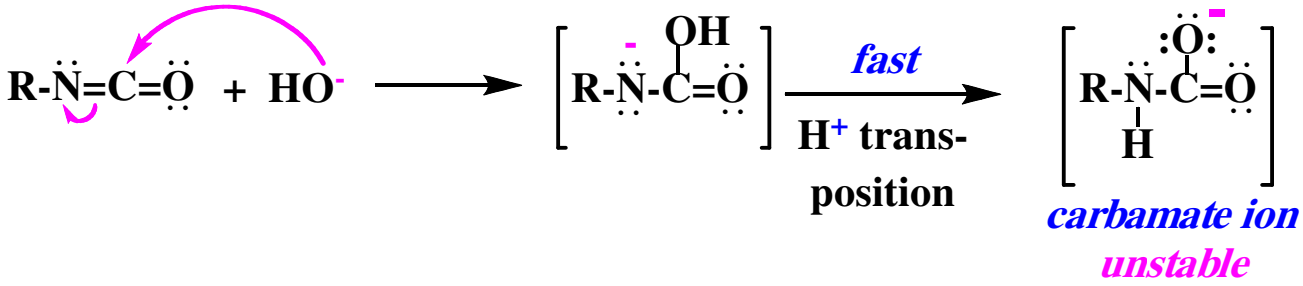


The R group shifts with its pair of bonding electrons as the bromide ion departs. If the R-group carbon that is immediately attached to the carbonyl is chiral, its stereochemistry is preserved during the rearrangement.

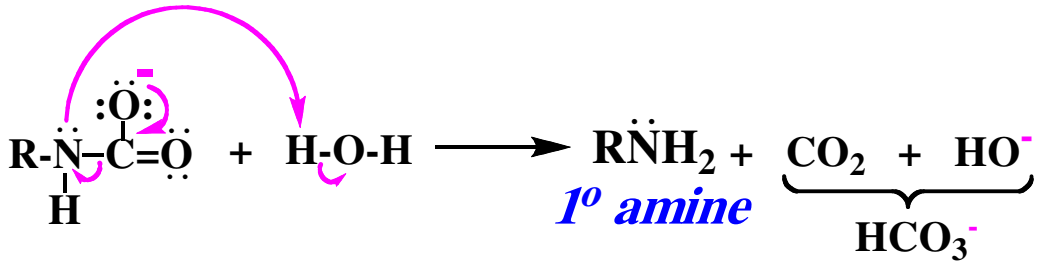
The nitrogen atom undergoes a change in hybridization from sp^3 to sp^2 as a nonbonding electron pair on nitrogen forms a π-bond with the carbon center that has transformed from sp^2 to sp hybridization.

Hydrolysis of Isocyanate to Obtain an Amine

Isocyanates undergo nucleophilic addition reactions at the electropositive carbon center.

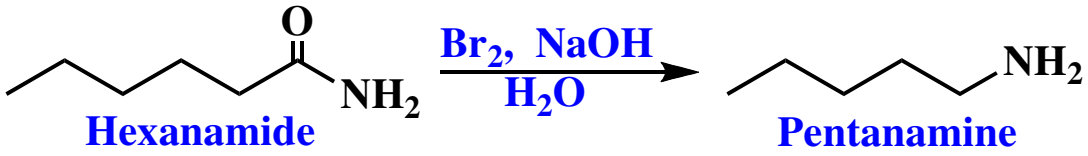


decarboxylation of carbamate anion

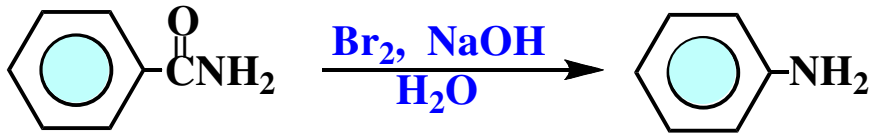


Some Features of the Hofmann Rearrangement

the migrating group may be alkyl or aryl

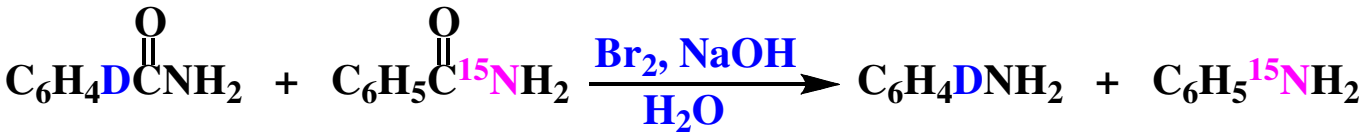


Hexanamide — Pentanamine



Benzamide — Aniline

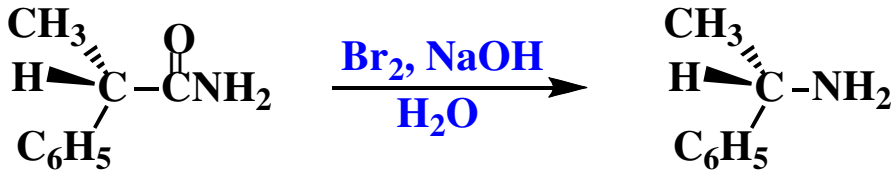
the rearrangement is intramolecular



A double label experiment — **No crossover of isotope labels**

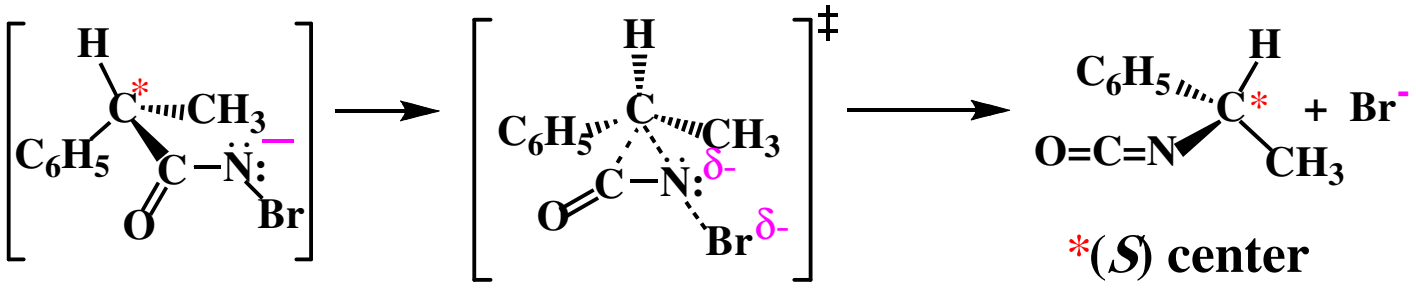
stereocenters migrate <u>with retention</u>

[That is, neither complete inversion nor racemization is observed.]



(*S*)-(+)-2-Phenylpropanamide **(*S*)-(-)-1-Phenylethanamine**

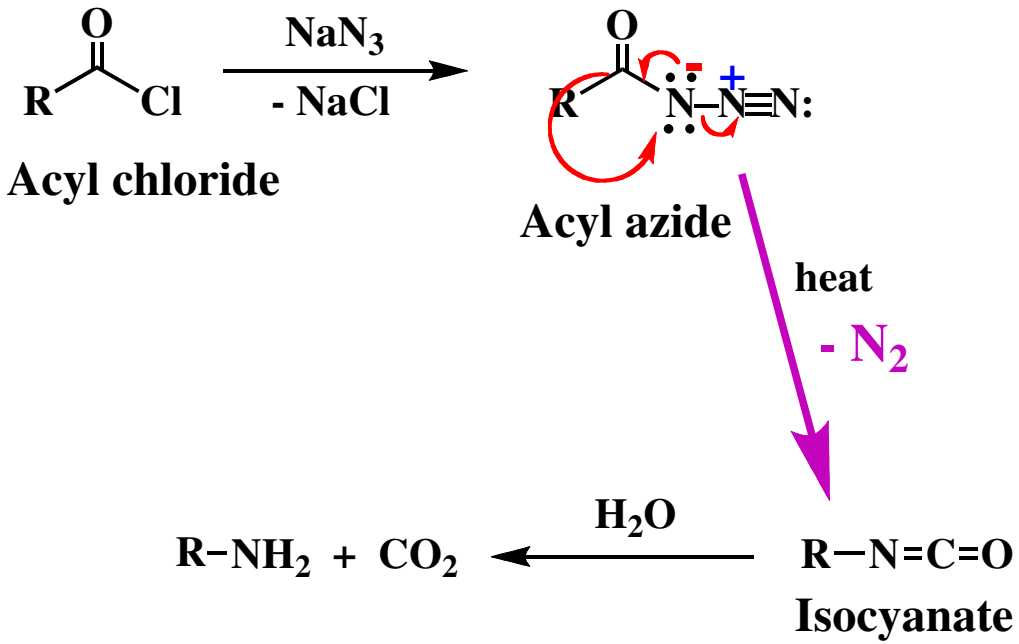
The evidence suggests that the migrating group never becomes detached.



(*S*) center** ***transition state ***(*S*) center**

The Curtius Rearrangement

This is a rearrangement of acyl azides that is analogous to the Hofmann rearrangement.

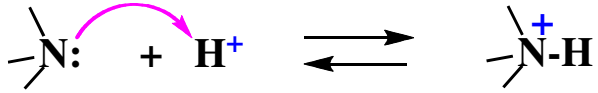


The driving force for the rearrangement is the elimination of the thermodynamically super stable N_2 molecule. Similarly, the driving force for the decarboxylation is the elimination of the very stable CO_2 molecule.

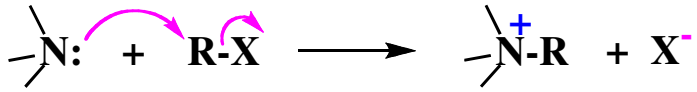
Reactions of Amines

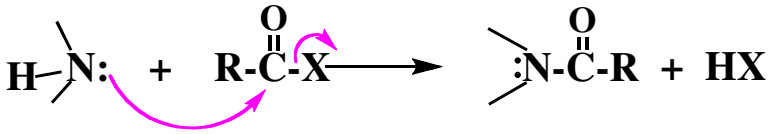
The chemistry of amines is determined by the unshared electron pair on nitrogen. Amines are bases and nucleophiles.

base

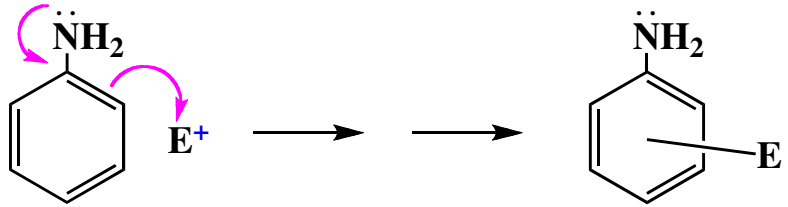


nucleophile





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

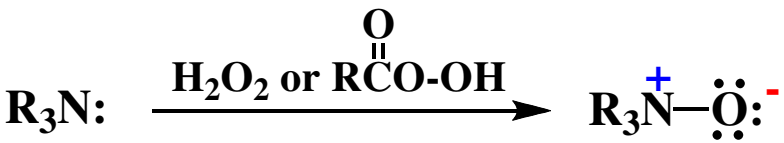


ortho* and *para

[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.]

Oxidation of Amines

With alkyl amines, the only useful oxidation reaction is that of 3° amines. By using hydrogen peroxide or peroxy acids, they can be converted to 3° amine oxides.



Amine oxides undergo the Cope syn elimination reaction, a useful alkene synthesis.

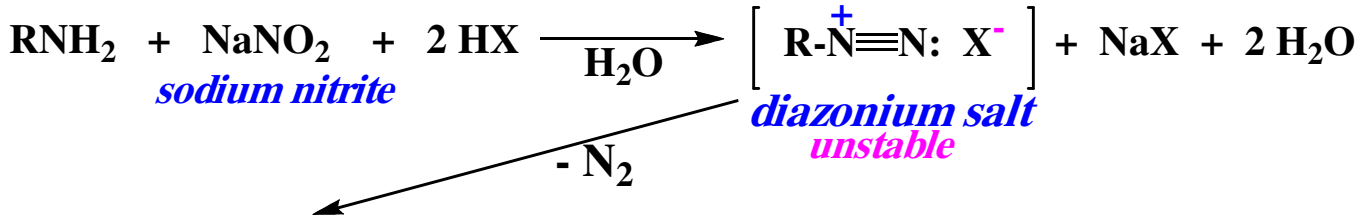
Arylamines are so electron rich that they readily undergo oxidation, but it occurs first on the ring and, as with 1° and 2° aliphatic amines, rarely gives useful products.

Reactions of Amines with Nitrous Acid

Nitrous acid, HNO_2, is unstable and is prepared in the reaction mixture from a nitrite salt and an acid such as HCl or HBr in the presence of the amine.

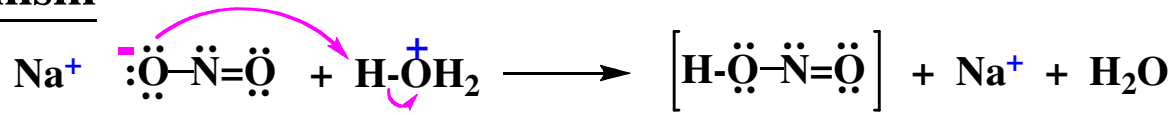
Diazotization of 1° Aliphatic Amines

overall chemistry

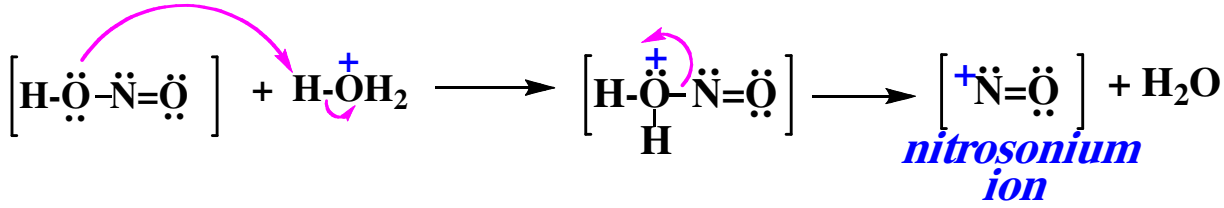


The complexity of the product mixture makes the reaction with 1° amines of no synthetic value.

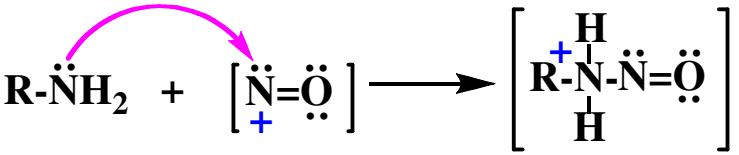
Mechanism



formation of nitrosonium ion



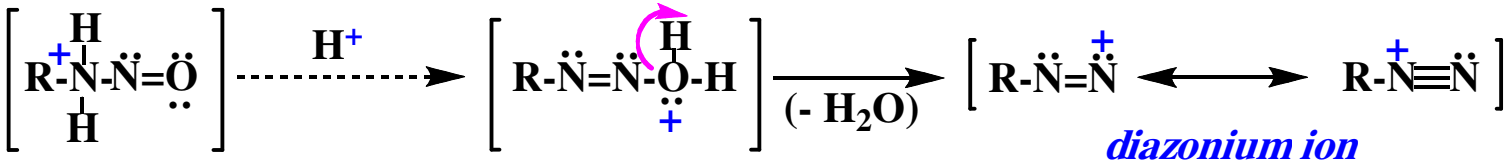
nitrosation of amine



N-nitrosoamine

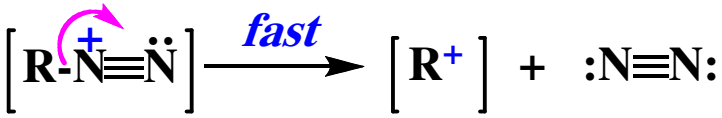
dehydration of N-nitrosoamine

A series of deprotonation and reprotonation steps leads to dehydration:



diazonium ion

Alkyl diazonium ions are unstable.

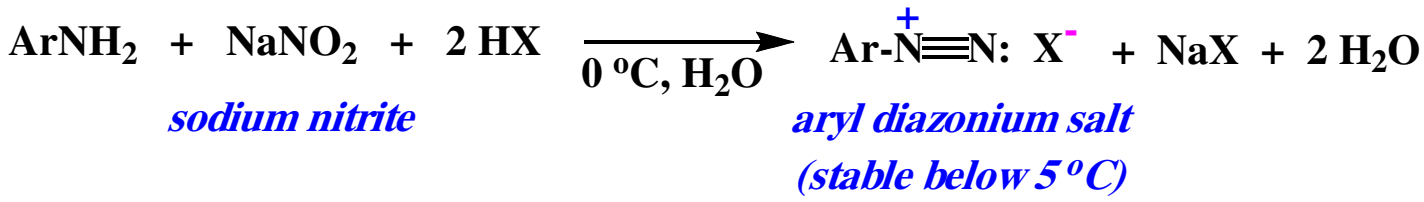


The measurement of the released N_2 gas from diazotization of primary amines is used in some analytical procedures.

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:

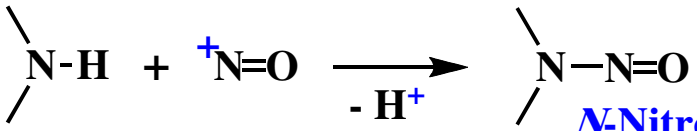


Note: Many dry aryl diazonium salts are explosive. Therefore, these compounds are typically not isolated but prepared and then used in the same solution.

Reactions of 2° Amines and 2° Amides with Nitrous Acid

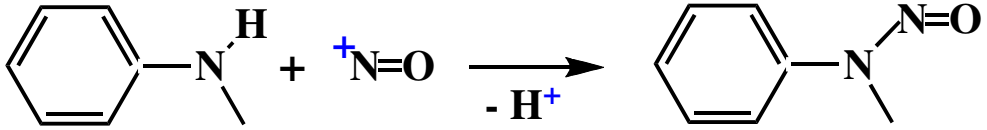
Secondary amines, both alkyl and aryl, and 2° amides are converted to *N*-nitroso derivatives on reaction with nitrous acid.

EXAMPLES: $[HO\text{-}N{=}O] + H_3O^+ \longrightarrow {}^+N{=}O + 2\,H_2O$



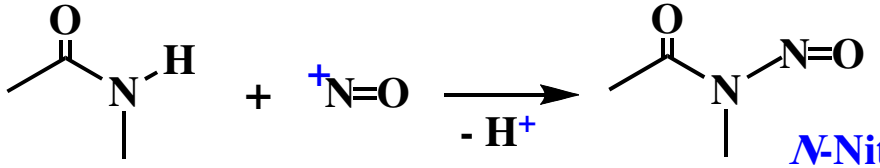
Dimethylamine

***N*-Nitrosodimethylamine**
a yellow oil



***N*-Methylaniline**

***N*-Nitroso-*N*-methylaniline**
a yellow oil



***N*-Methylacetamide**

***N*-Nitroso-*N*-methylacetamide**
a yellow crystalline solid

This compound, on reaction with aqueous NaOH, yields diazomethane, a powerful methylating agent (but one which is poisonous and explosive, requiring special precautions).

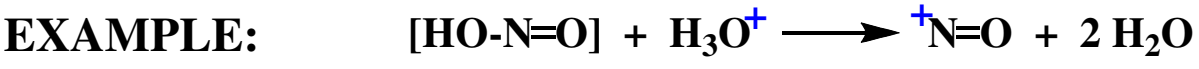
Reactions of 3° Amines with Nitrous Acid

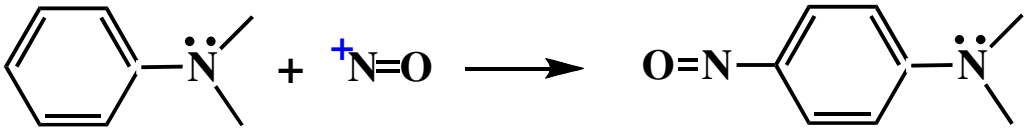
Aliphatic 3° amines afford *N*-nitrosoammonium compounds,

but these salts are of little importance.

Aryl 3° amines react with nitrous acid via their electron-rich aromatic rings, affording *C*-nitroso derivatives. This electrophilic aromatic substitution takes place almost exclusively at the *para* position or, if it is not available, at the *ortho* position.

EXAMPLE:



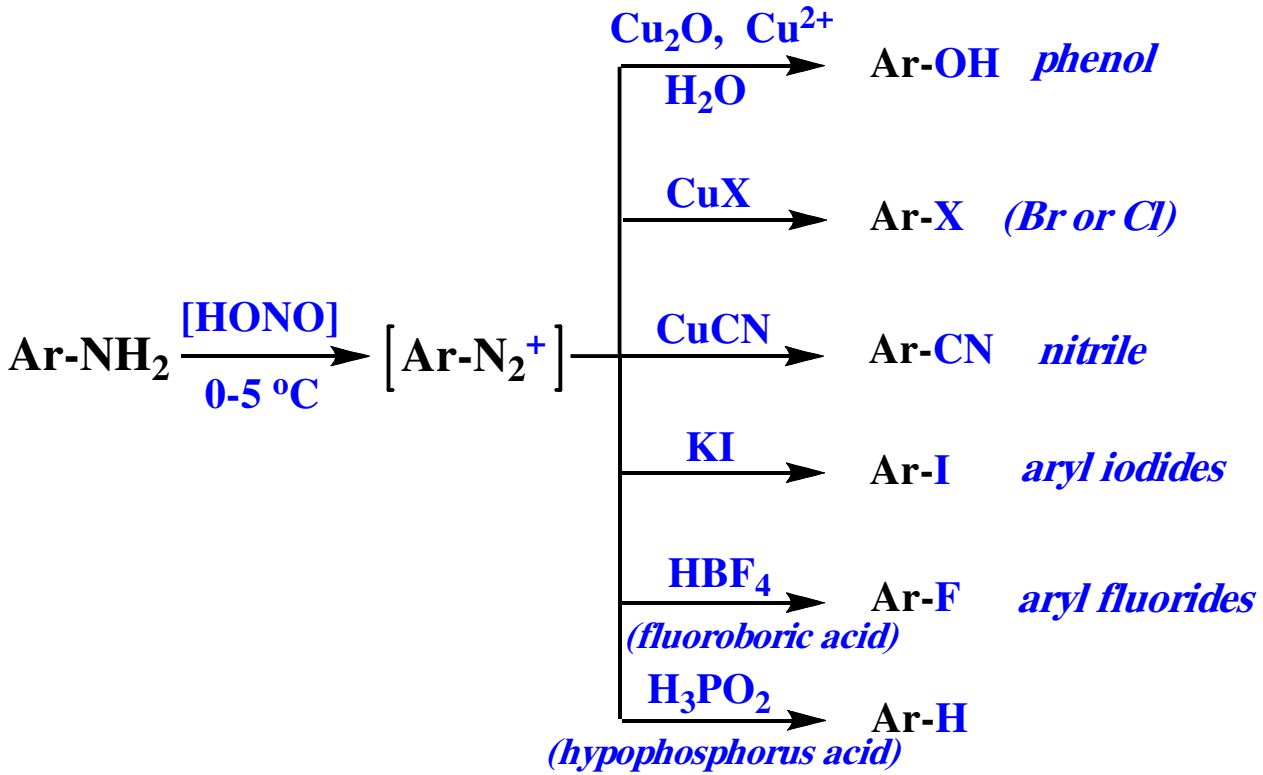


N,N-Dimethylaniline

4-Nitroso-*N,N*-Dimethylaniline

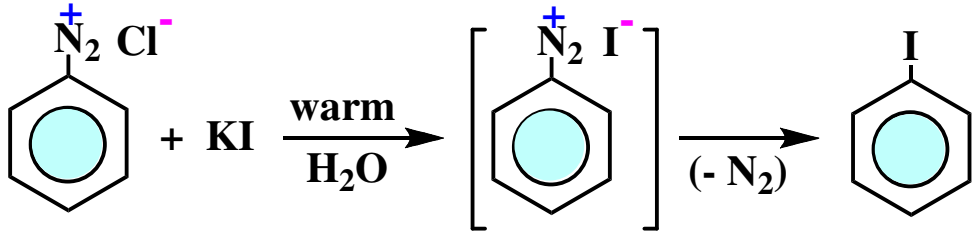
Replacement Reactions of Aryl Diazonium Salts

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

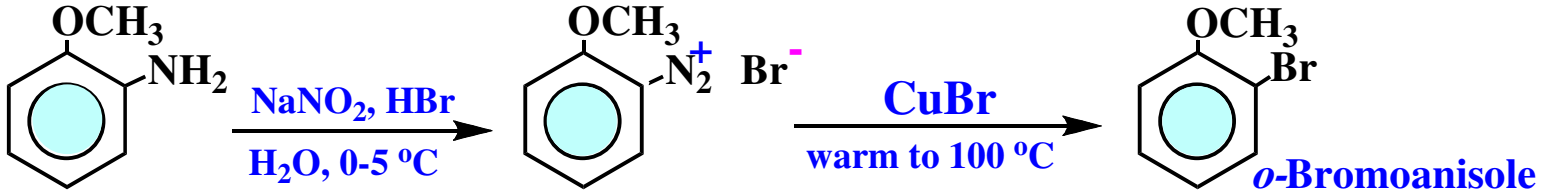


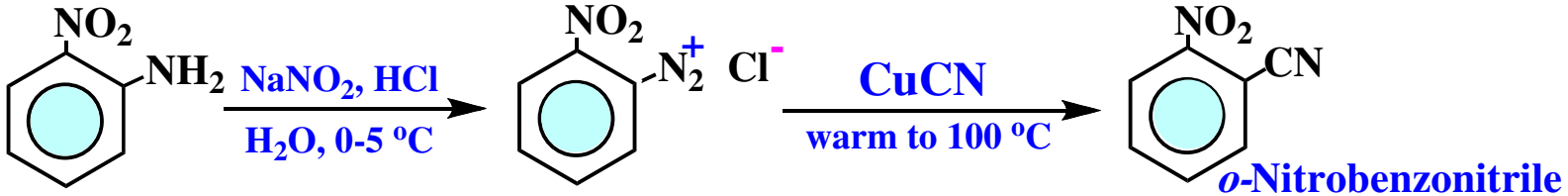
The Sandmeyer Reaction

When an aqueous solution of benzenediazonium chloride and KI is allowed to warm to room temperature, the benzenediazonium iodide produced decomposes with liberation of N_2 to give a good yield of iodobenzene.



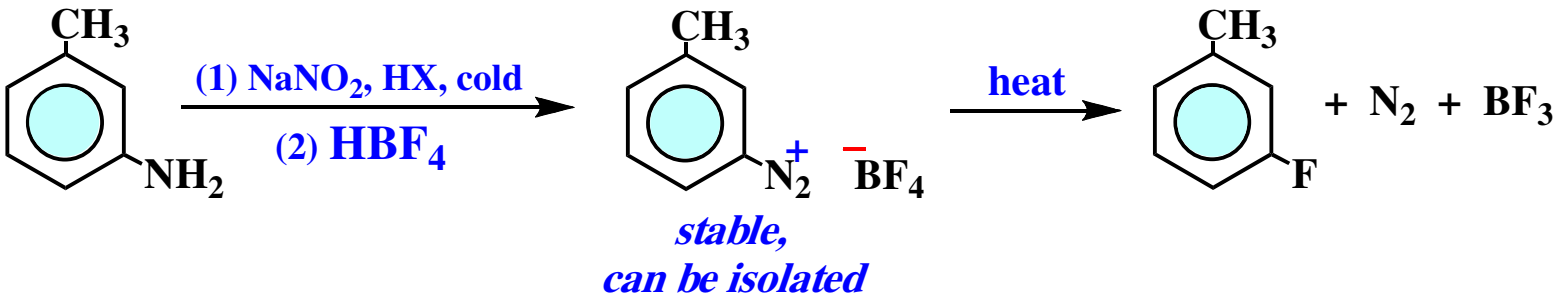
A similar reaction does not occur with the aryldiazonium chlorides and bromides. But in 1884, the Swiss chemist Traugott Sandmeyer discovered that replacement reactions are catalyzed by cuprous salts. With CuCl, CuBr, or CuCN added, replacement reactions occur as the diazonium salt is allowed to warm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





Aryl Fluorides via Aryldiazonium Tetrafluoroborates

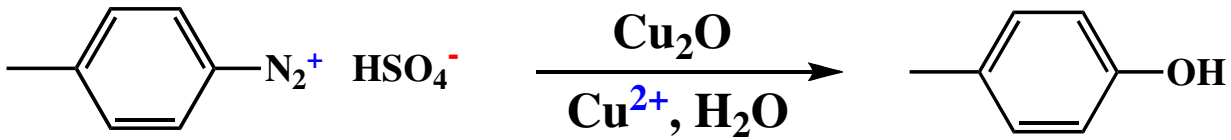
When aryldiazonium salts are reacted with fluoroboric acid (HBF_4), the aryldiazonium tetrafluoroborate salts often crystallize out and can be isolated. These salts are unique in their stability. When heated, they produce the aryl fluoride.



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:



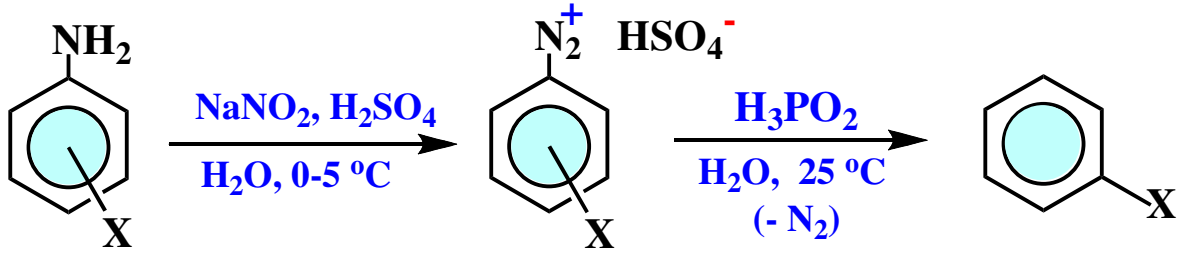
***p*-Toluenediazonium hydrogen sulfate**

***p*-Cresol**

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

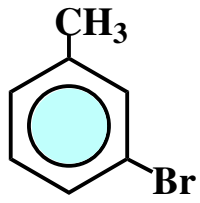
Arenediazonium salts react with hypophosphorous acid (H_3PO_2, HO-P(=O)(H)-H) to yield products in which the diazonium group has been replaced by a hydrogen atom.



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.

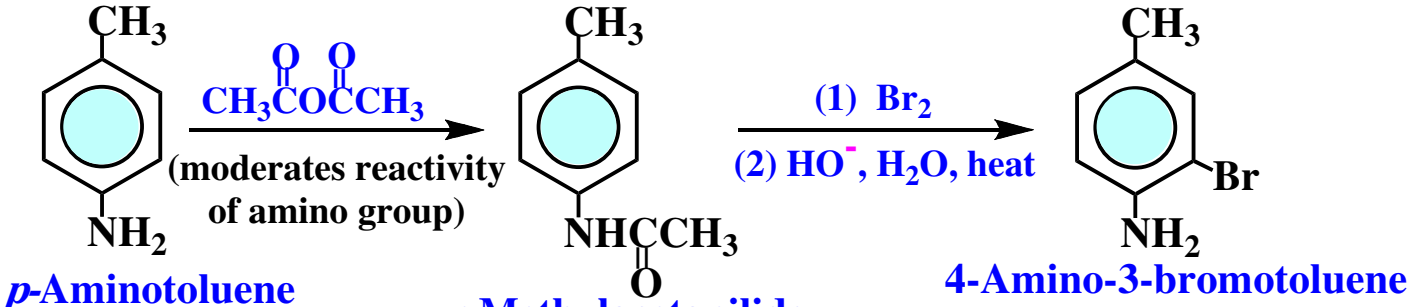
***m*-Bromotoluene cannot be prepared by simple bromination of toluene because of the *o*/*p* directing nature of the methyl group. However, use of an amination-deamination procedure can surmount this problem.**

Target compound



***m*-Bromotoluene**

Solution

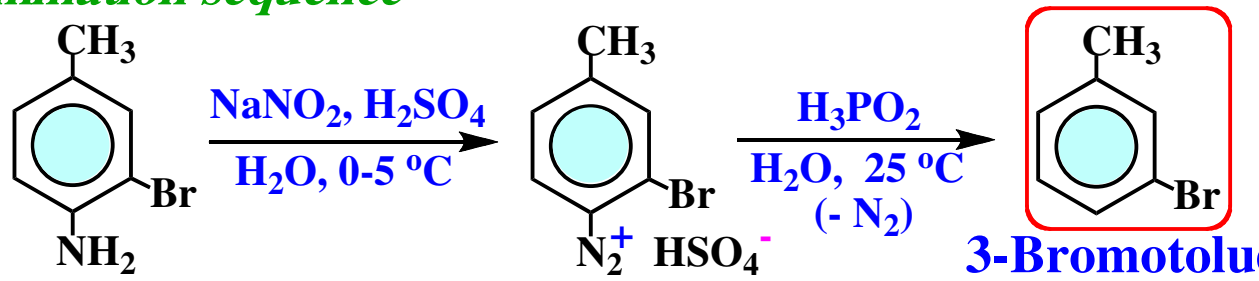


p-Aminotoluene

p-Methylacetanilide

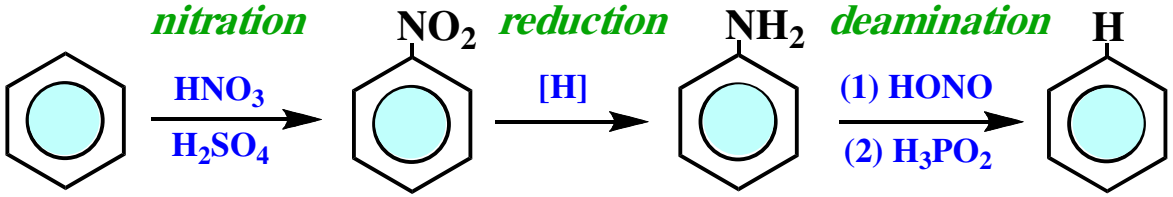
4-Amino-3-bromotoluene

Deamination sequence



3-Bromotoluene

Extended Synthetic Sequence:



meta-directing

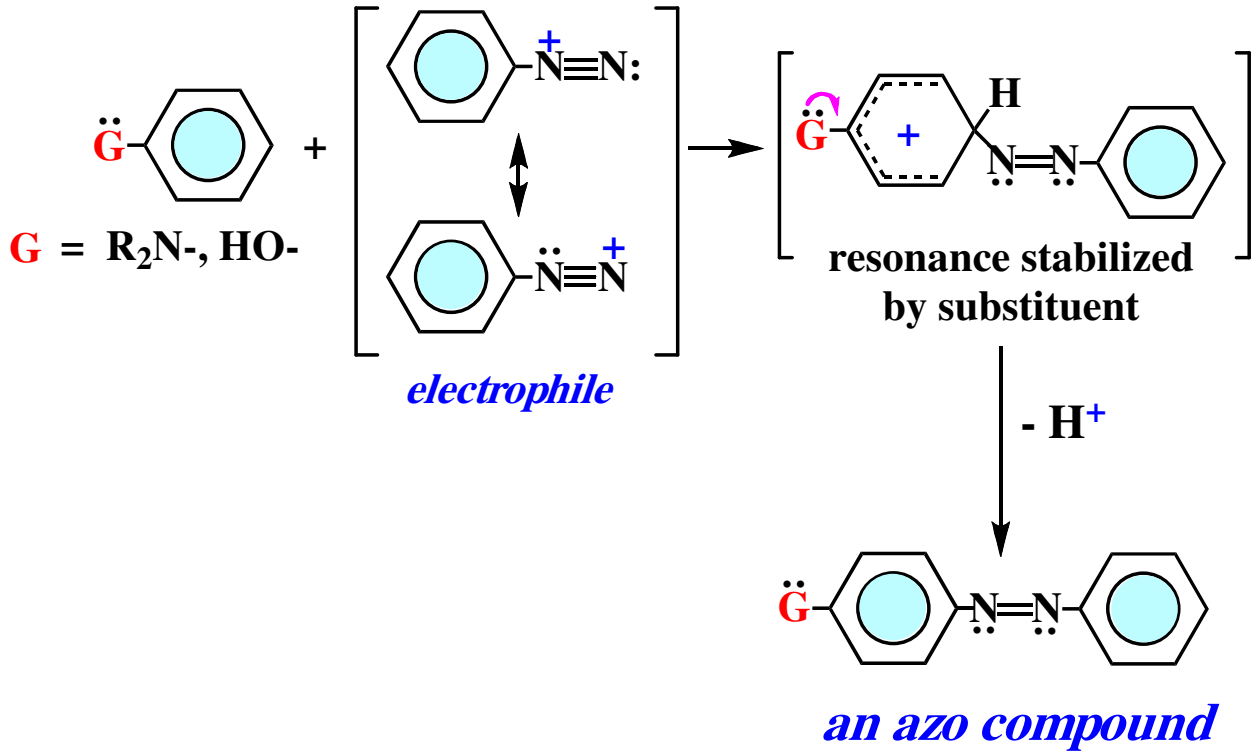
o,p-directing

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

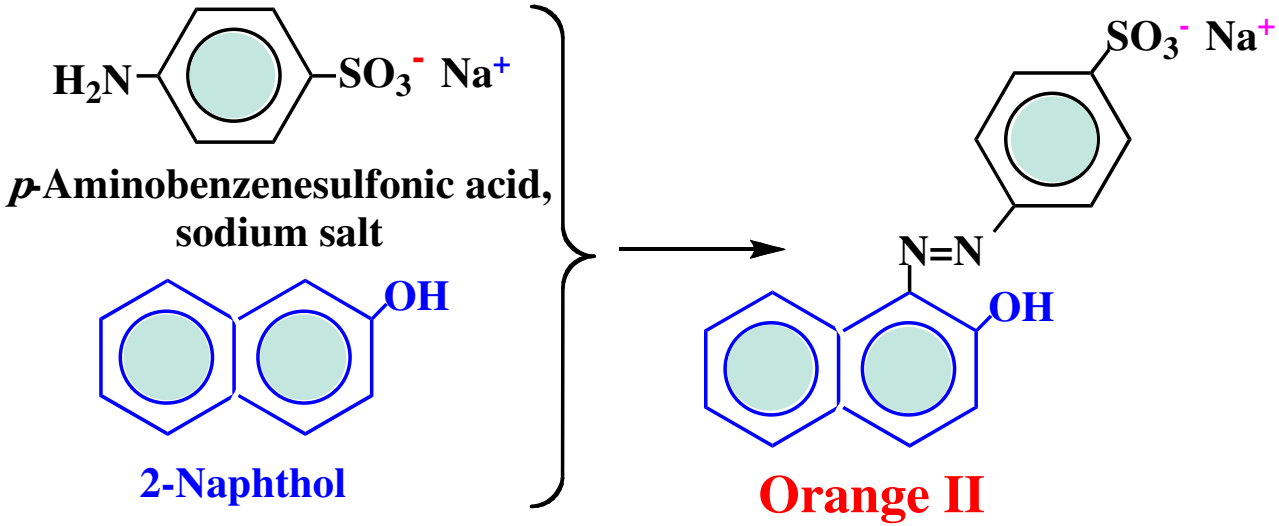
Aryldiazonium ions are weak electrophiles that react with electron-rich aromatics such as phenols and *N,N*-disubstituted aryl amines to give azo compounds.

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 $-SO_3^-\ Na^+$ are introduced to make them water soluble and to promote their binding to polar fibers (wool, cotton, or nylon).

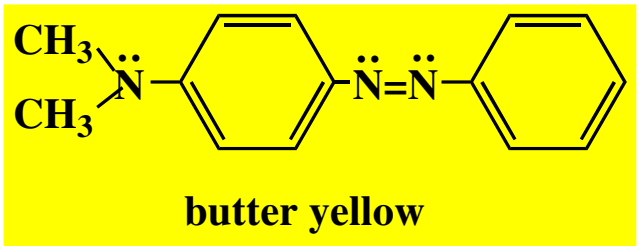


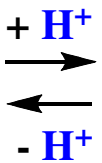
A particularly brilliant example

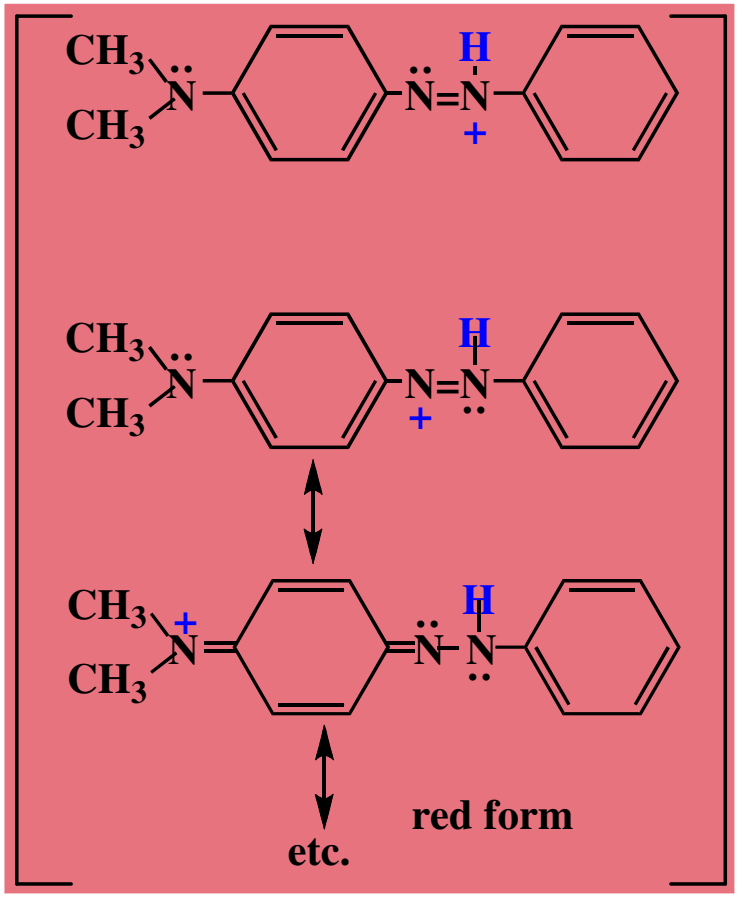
Azo Dyes as pH Indicators

Azo dyes are used as pH indicators because their π-electron systems change dramatically between the free base and conjugate acid forms, leading to different colors for the two forms.

Butter yellow, a dye once used to color margarine, is red below pH 3 (in the conjugate acid form) and yellow at and above pH 4 in the free base form).



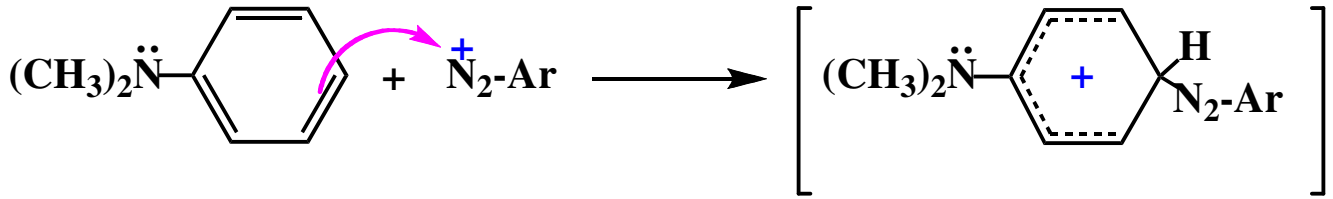


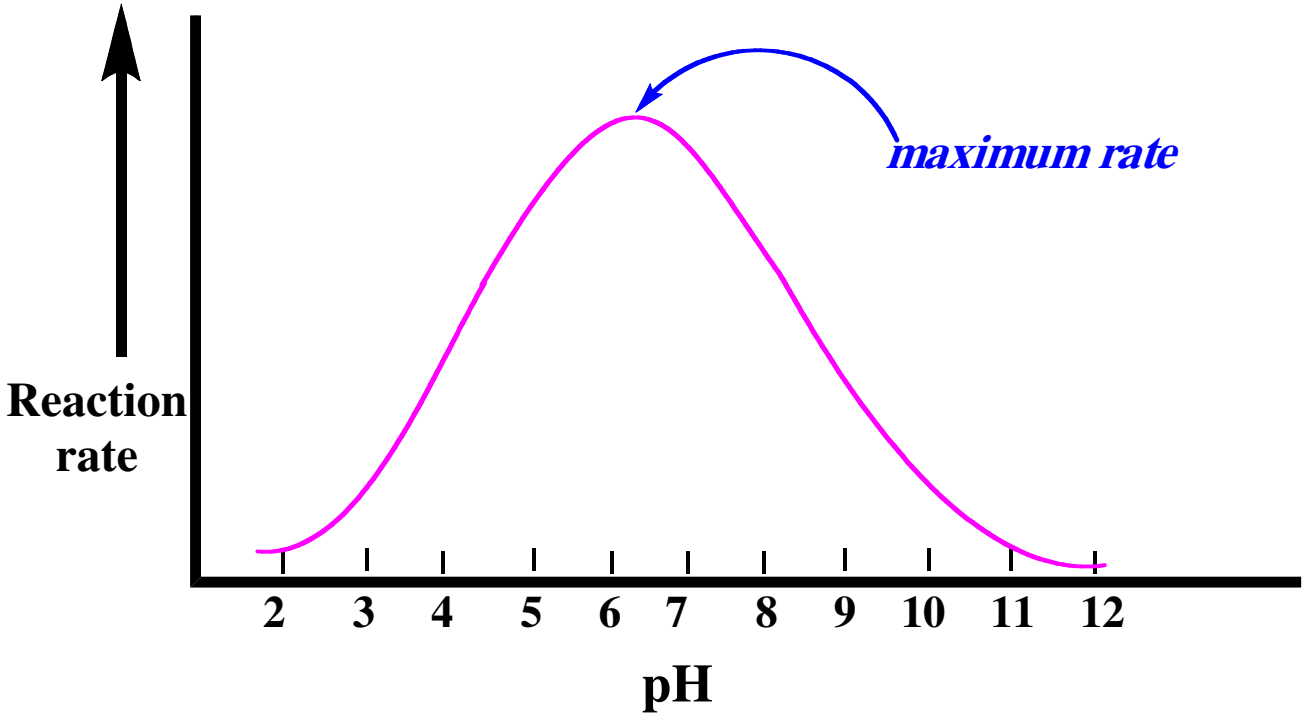


Protonation on the azo function is energetically favored because it produces a cation with more resonance stabilization than the cation produced by protonation on the amino nitrogen.

Effect of pH on a Diazo Coupling Reaction

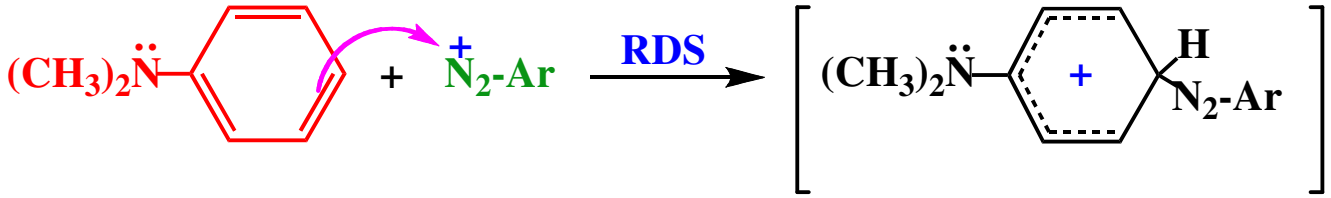
The coupling reaction between *N,N*-dimethylaniline and diazonium ions occurs fastest in the intermediate pH range 5.5 to 7, as shown below.



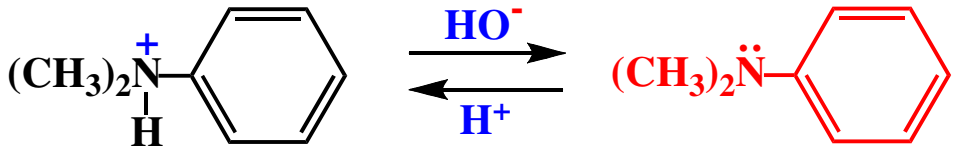


Effect of pH on Diazo Coupling Rate

The rate-determining step in the coupling reaction involves electrophilic attack by the diazonium ion on the *N,N*-dimethylaniline in its free base form:



The concentrations of these two reactants depend on the pH of the solution because of the equilibria below.



$pK_a = 5.15$

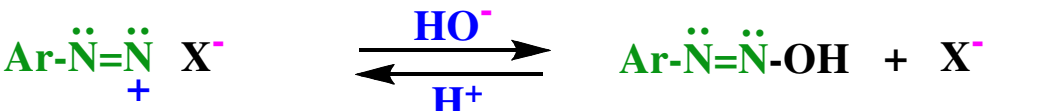
Dominates at low pH

reactive free base form

Dominates at high pH

The above equilibrium explains the rate increase as pH is raised to about 6.

The rate of coupling begins to decrease above pH 6-7 because of this second equilibrium that decreases the concentration of the electrophilic diazonium ion:



reactive electrophile

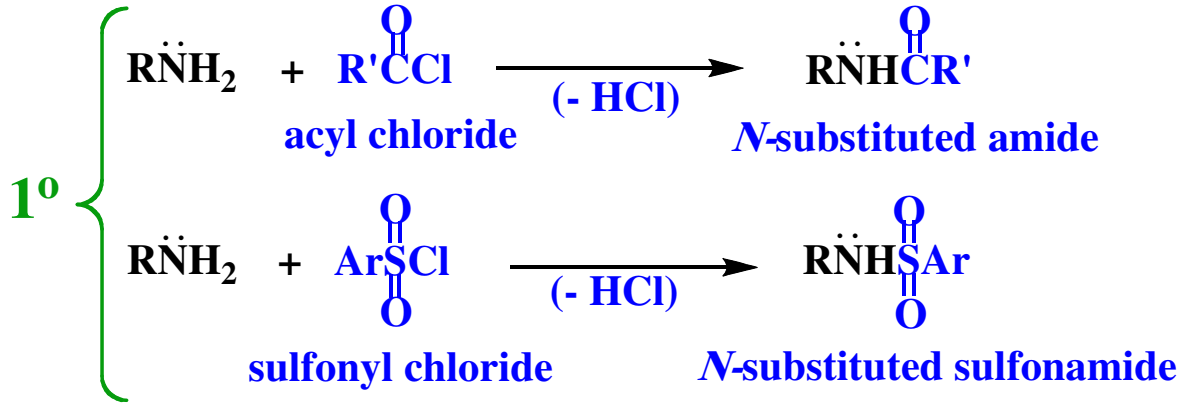
Dominates at low pH

does not undergo coupling

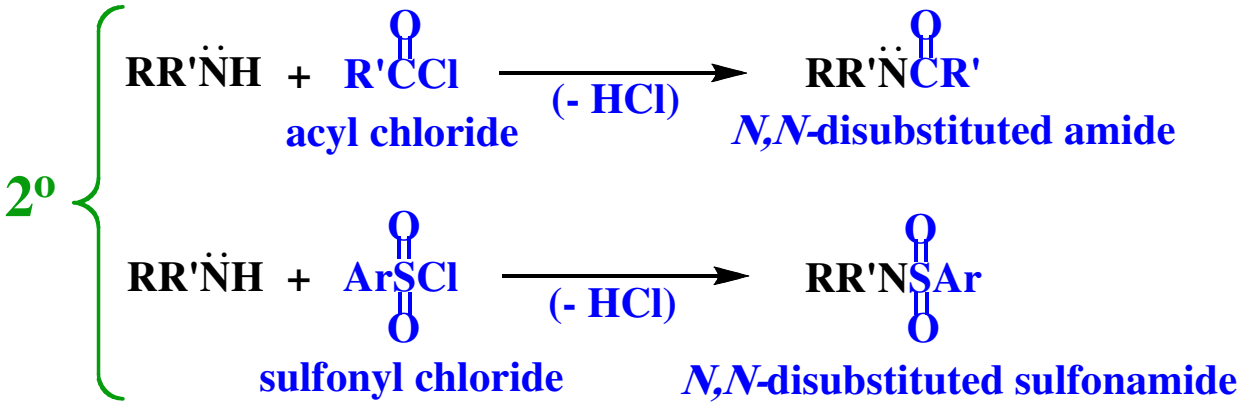
Dominates at high pH

Reactions of Amines with Sulfonyl Chlorides

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



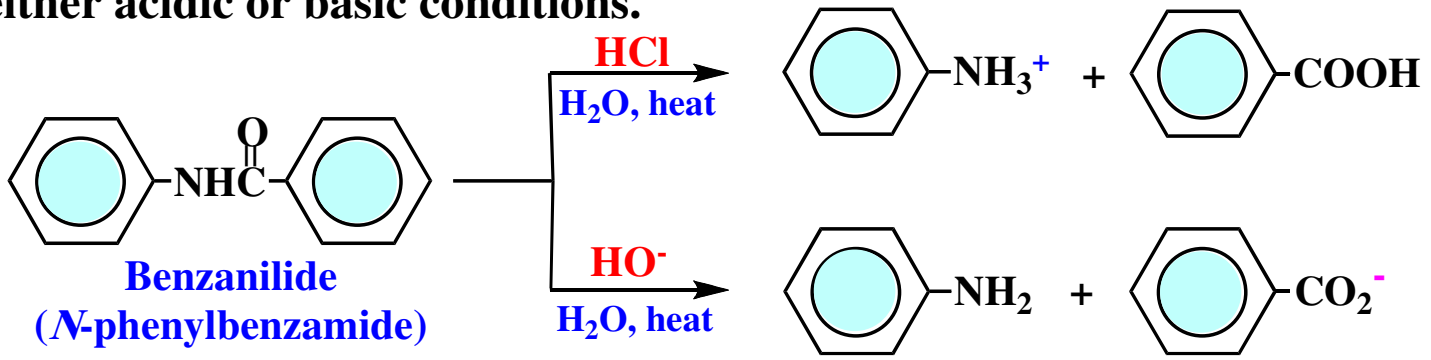
Similarly,



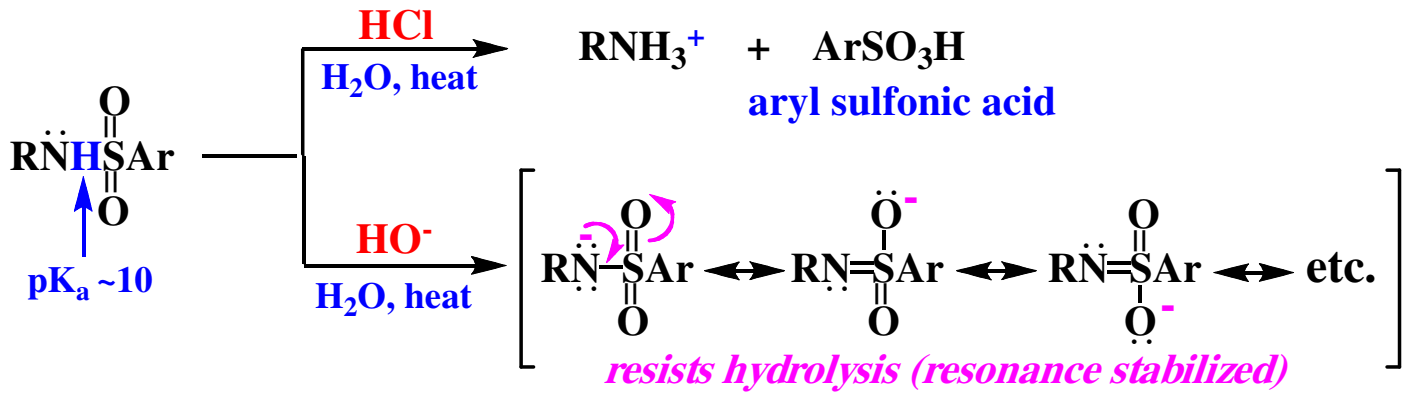
Tertiary amines do not give stable products.

Hydrolysis of Amides

Carboxamides (amides derived from carboxylic acids) hydrolyze under either acidic or basic conditions.



Sulfonamides hydrolyze much more slowly than carboxamides, but hydrolysis does occur under acidic conditions. Under basic conditions, the rapid formation of an anion (derived from the acidic H on nitrogen) inhibits nucleophilic attack and hydrolysis.



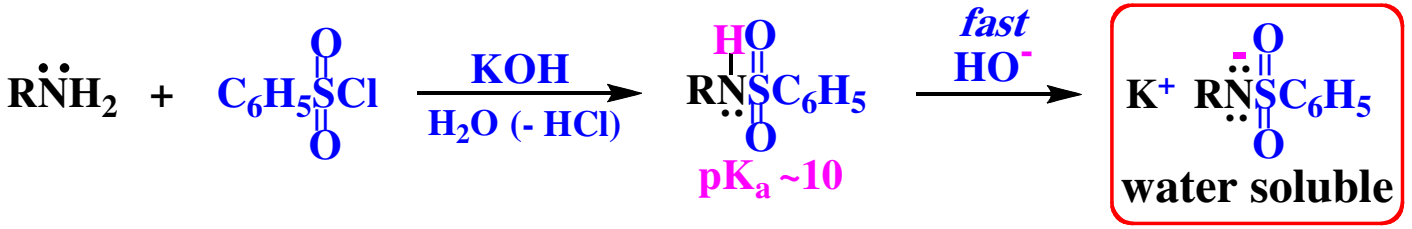
The Hinsberg Test: Distinguishing 1°, 2°, and 3° Amines

This test, a classic method of distinguishing among the amine classes, was developed in 1890 by O. Hinsberg in his studies with benzenesulfonyl chloride.

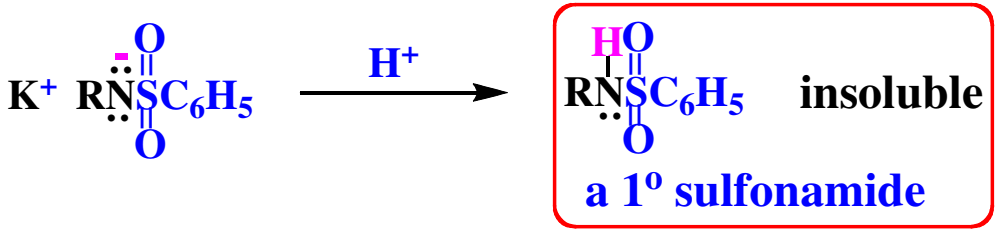
The test reagent is benzenesulfonyl chloride in aqueous KOH. It is important to use excess amounts of KOH to avoid false results with primary amines.

primary amines

When a 1° amine is added to the test reagent, a sulfonamide product is formed initially that rapidly is deprotonated by hydroxide ion because of the acidic H on nitrogen. The sulfonamide salt is soluble in water so a clear solution is observed. When acid is added, the insoluble sulfonamide product precipitates.

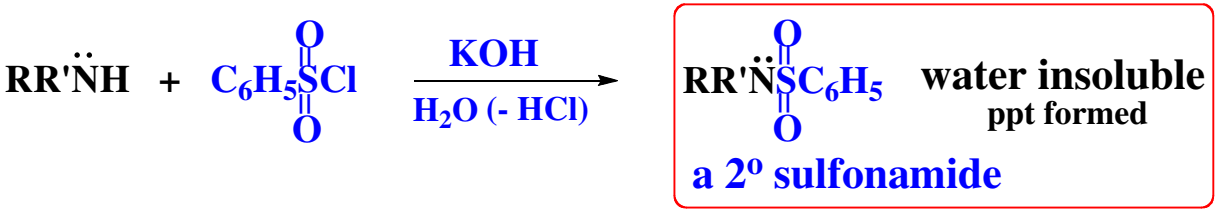


acidification



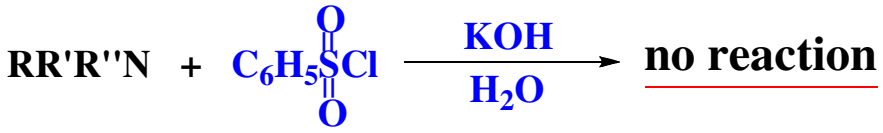
secondary amines

Secondary amines form water insoluble sulfonamides. They do not have an acidic H on nitrogen, so salts are not formed in the basic solution.

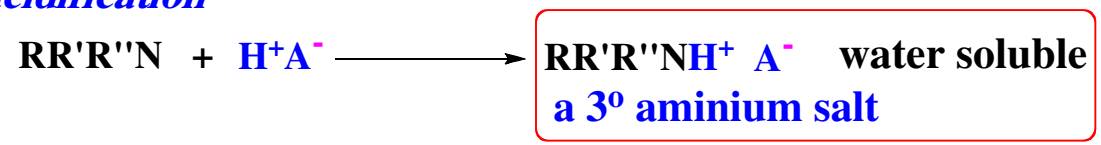


tertiary amines

With a 3° amine, there is no visual sign of reaction with the test reagent. However, if the amine is water insoluble, it will dissolve when the solution is made acidic.



acidification



Summary of Observations with the Hinsberg Test

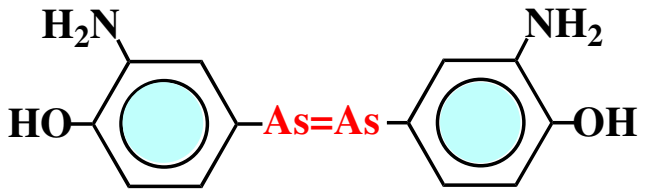
RNH_2	RR'NH	RR'R''N
clear solution, ppt with H^+	*immediate ppt*	*no reaction (but dissolves in acid)*

Chemotherapy and Sulfa Drugs

Chemotherapy is the use of chemical agents to destroy infectious organisms without harming the host. Typically, chemotherapy is used to kill bacteria responsible for a disease.

Early in the 20th century, **Paul Ehrlich** (Nobel Prize 1908) discovered the first therapeutic chemicals. As a medical student, Ehrlich observed that certain dyes stained tissues selectively. He reasoned that staining was the result of selective chemical reactions between the dyes and the biological materials. He began a search for dyes with **selective affinities** for microorganisms hoping to find dyes that would be **selectively lethal** to specific microorganisms that cause disease...his "magic bullets."

Ehrlich discovered **salvarsan** as a treatment for syphilis in 1909.



salvarsan

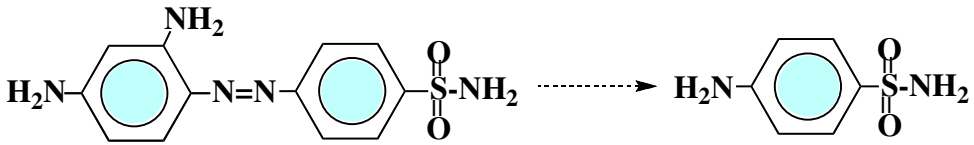
Note that this compound is an **arsenic analog** of a diazo compound. Recall that arsenic and nitrogen are both in Group VA of the Periodic Table, which explains why they can be interchanged in many structures.

Discovery of Sulfanilamide

Between 1909 and 1935, thousands of chemicals, including many dyes, were screened for activity. Very few "magic bullets" were found until a desperate father tried to save the life of his sick daughter in 1935.

Gerhard Domagk was a doctor employed by a German dye manufacturer (I. G. Farbenindustrie) when his daughter contracted a streptococcal infection. She became very ill and was near death when in one final desperate act, Domagk gave her a dose of a dye called prontosil. It was selected because tests at I. G. Farben had shown that prontosil inhibited the growth of streptococci in mice. The child recovered and a new generation of chemotherapeutics was discovered.

In 1936, Ernest Fourneau of the Pasteur Institute in Paris showed that prontosil breaks down in the human body to produce sulfanilamide, the active agent.



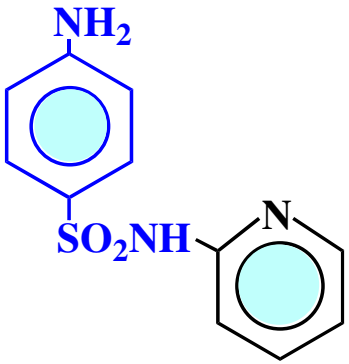
prontosil ***sulfanilamide***

the first sulfa drug

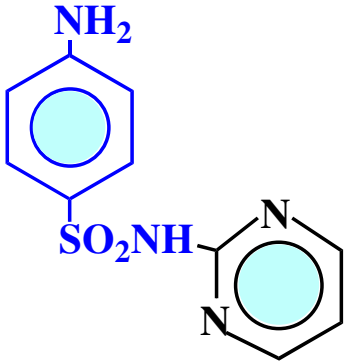
In the following years, many thousands of structural variations of sulfanilamide were synthesized in the search for additional drugs.

Some Sulfa Drugs

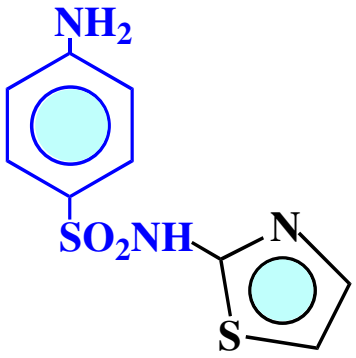
The sulfa drugs are broad spectrum antibacterial agents. They are effective against malaria, tuberculosis, leprosy, meningitis, pneumonia, scarlet fever, plague and a variety of respiratory infections.



***sulfa*pyridine**



***sulfa*diazine**

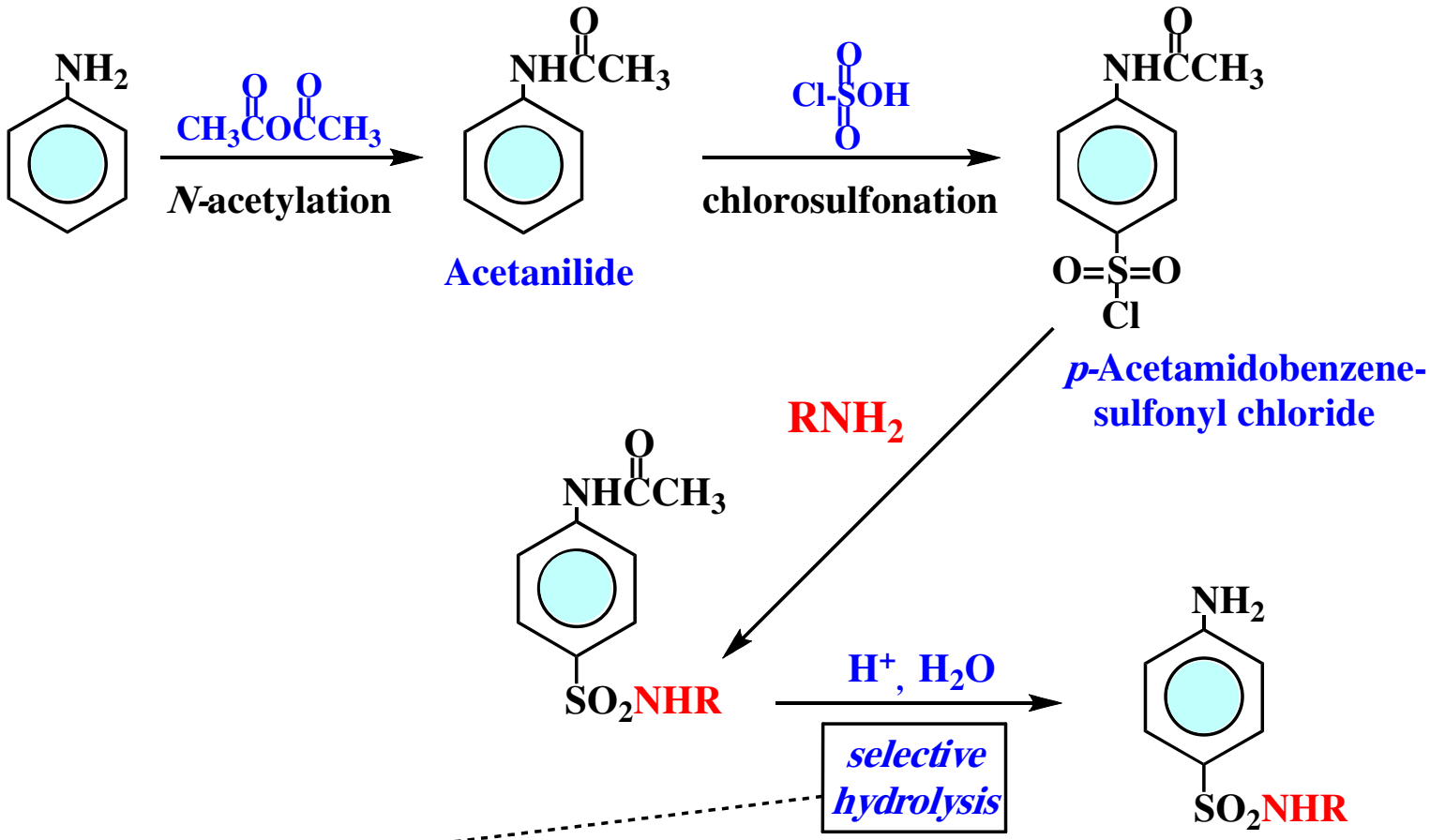


***sulfa*thiazole**

Synthesis of the Sulfanilamides

The classic synthetic route to these important compounds involves a key selective hydrolysis step that depends on the reactivity difference between carboxamides and sulfonamides.

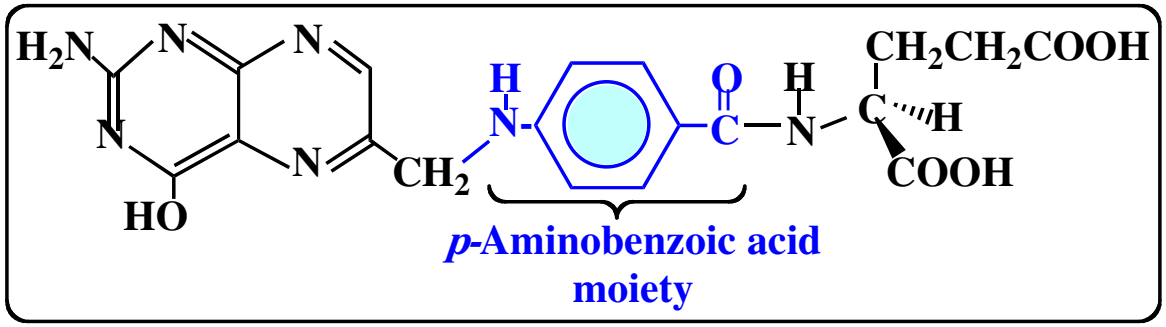
Synthesis of the Sulfanilamides



The success of this last step is dependent on the greater ease of hydrolysis of the carboxamide group than of the sulfonamide group.

The Drug Action of Sulfanilamides

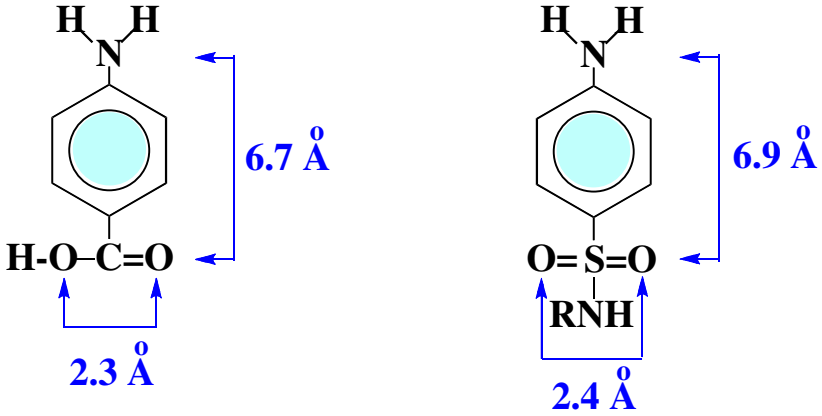
The sulfanilamides selectively kill bacteria but do not harm animal cells. Sulfanilamides function by blocking the enzymatic synthesis of folic acid in bacteria. Humans also need folic acid but derive it from their diet, so the action of sulfa drugs does not affect them.



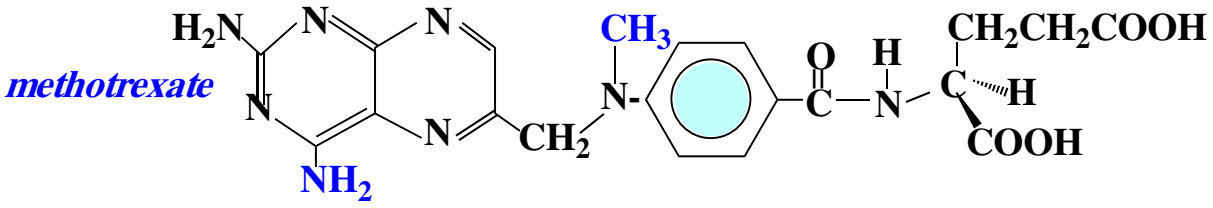
Folic Acid

In 1940, D. D. Woods observed that the inhibition of growth of certain microorganisms by sulfanilamide is competitively overcome by *p*-aminobenzoic acid. He reasoned that sulfanilamide competes with *p*-aminobenzoic acid in an essential metabolic step. It is now generally accepted that sulfanilamide becomes incorporated into a "mock" folic acid that blocks further folic acid synthesis at the active site of an enzyme.

It is suggested that the similar functionality and dimensions of *p*-aminobenzoic acid and sulfanilamide allow the latter to act at the active site of the enzyme that synthesizes folic acid, blocking or slowing folic acid synthesis. Such a compound is called an antimetabolite.



Another example of an antimetabolite is methotrexate, a mock folic acid effective in treating some cancers.



Because of its structural similarity to folic acid, it enters into similar reactions but cannot serve the same function. Methotrexate is toxic to all dividing cells, but it primarily acts against cancer cells because they divide more rapidly than normal cells.

Analysis of Amines

Infrared Spectroscopy

1º and 2º Amines show sharp, characteristic absorption bands between 3300-3500 cm^{-1} from N-H stretch. 1º Amines show two bands (symmetric and asymmetric stretches) while 2º amines show a single band. 3º Amines have, of course, no such bands.

Proton NMR Spectroscopy

N-H proton signals may appear anywhere between δ 0.5-5. The signals may be broad and are influenced by solvent, concentration and other factors. Because of rapid proton exchange among nitrogen atoms, N-H protons usually do not spin-spin couple to H on adjacent carbon atoms. They are best detected by adding D_2O, which results in exchange of N-H for N-D, with disappearance of any N-H signals.

Protons on the α carbon of an aliphatic amine are deshielded and absorb typically at δ 2.2-2.9.

^{13}C NMR Spectroscopy

The α carbon of an aliphatic amine is somewhat deshielded, appearing typically at δ 30-60.

MS Spectra of Amines

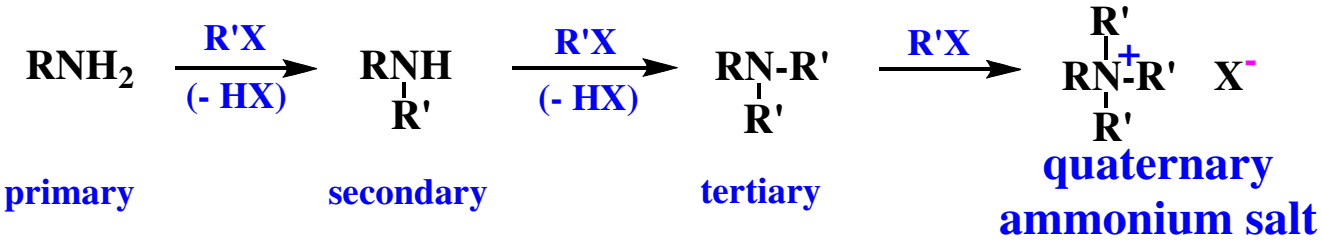
If there is an odd number of nitrogen atoms present, the molecular ion peak has an odd number mass. Cleavage between the α and β carbons is a common mode of fragmentation.

The Hofmann Elimination

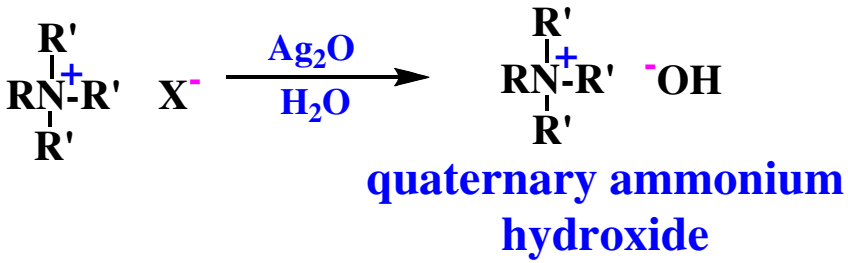
The starting material for Hofmann elimination reactions is a quaternary ammonium hydroxide.

Quaternary Ammonium Hydroxides

Exhaustive *N*-alkylation converts amines into quaternary ammonium salts:



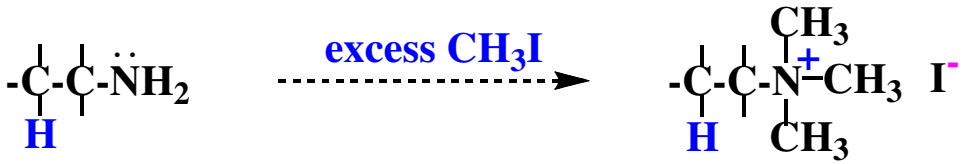
Treatment of a quaternary ammonium halide with an aqueous solution of silver oxide (actually AgOH), precipitates AgX and yields a solution containing the quaternary ammonium hydroxide.



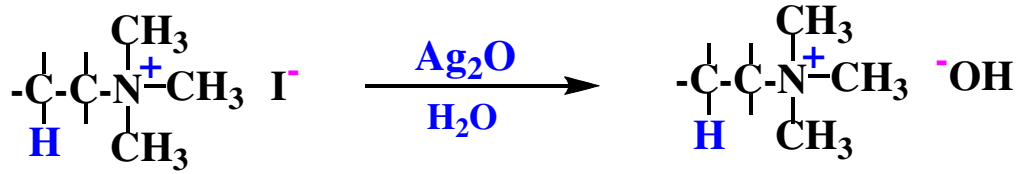
The Hofmann Elimination

In the late 19th century, the prominent German-born chemist, August W. von Hofmann (1818-1895) , discovered that quaternary ammonium hydroxides on heating undergo an elimination reaction to produce an alkene. Hofmann made many important contributions to organic chemistry as a professor at the Royal College of Chemistry in London.

In the traditional Hofmann elimination, a primary amine with a β-H is exhaustively methylated to give a trimethylalkylammonium salt:

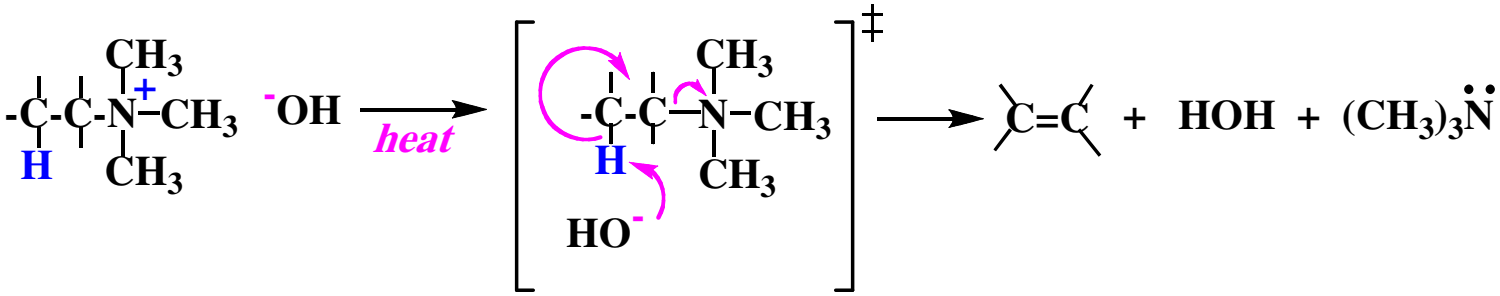


Treatment with aqueous silver oxide produces the hydroxide salt:

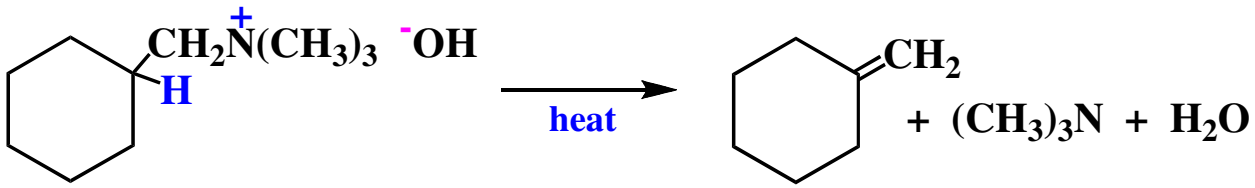


Hofmann Elimination, An E2 Reaction

The 4º ammonium hydroxide is stable and may be isolated and purified. When it is heated in the solid state or in solution to around 200 ºC an E2 reaction occurs. The availability of a β-H is, of course, a requirement for this reaction, and a trialkylamine (here trimethylamine) is the leaving group.



An Example



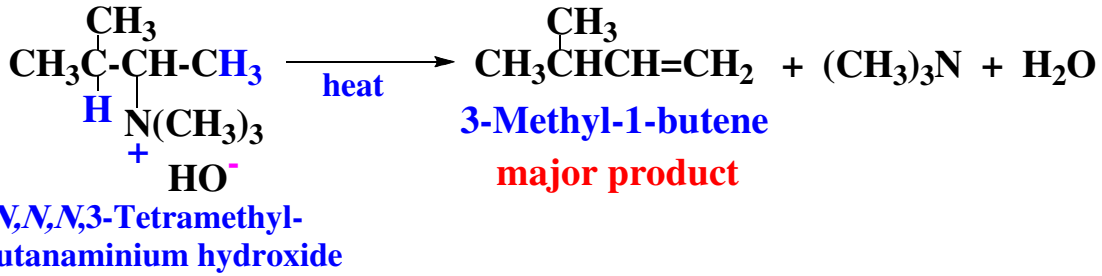
Cyclohexylmethyltrimethyl-ammonium hydroxide

Methylenecyclohexane

Regioselectivity in the Hofmann Elimination

In quaternary ammonium hydroxides that have two or more nonequivalent β-H's, the major product results from abstraction of the more or most acidic β-H. This is what is called the Hofmann rule. Since alkyl groups are electron-donating relative to H, a β-H is more acidic the fewer alkyl substituents are on the carbon to which it is attached.

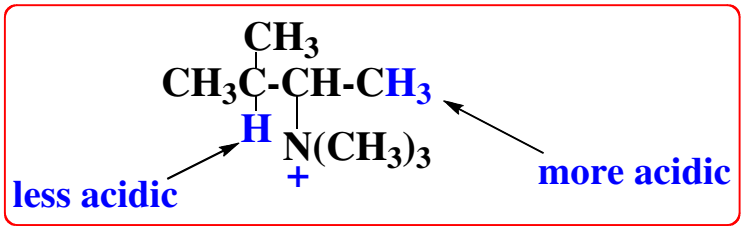
EXAMPLE



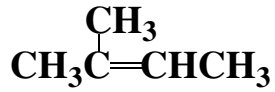
N,N,N,3-Tetramethyl-2-butanaminium hydroxide

3-Methyl-1-butene

major product

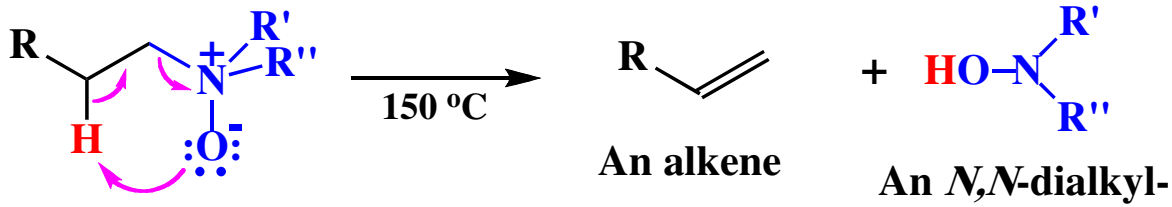


Recall that in eliminations involving neutral substrates, e. g., an alkyl bromide, the major product is that predicted by the Zaitsev rule: the most heavily substituted (the most stable) alkene possible. For example, if the leaving group above were bromide instead of $(CH_3)_3N$, the major product would involve loss of the alternative β-H and be 2-methyl-2-butene.



The Cope Elimination

Essentially a variation of the Hofmann elimination, the Cope starts with a 3º amine oxide, another type of compound that has a positive charge on a fully substituted nitrogen just as the 4º ammonium hydroxides that undergo Hofmann elimination do. The Cope is a syn elimination that proceeds through a cyclic transition state:

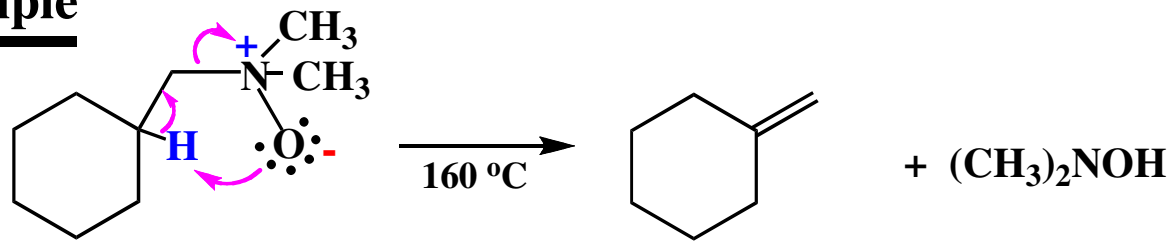


A 3º amine oxide

An alkene

An *N,N*-dialkyl-hydroxylamine

An Example



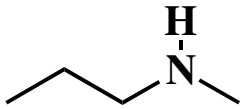
Cyclohexylmethyl-dimethylamine oxide

Methylenecyclohexane

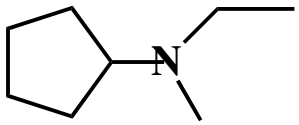
98%

Quiz 20.01

Provide both common and IUPAC names for these amines.



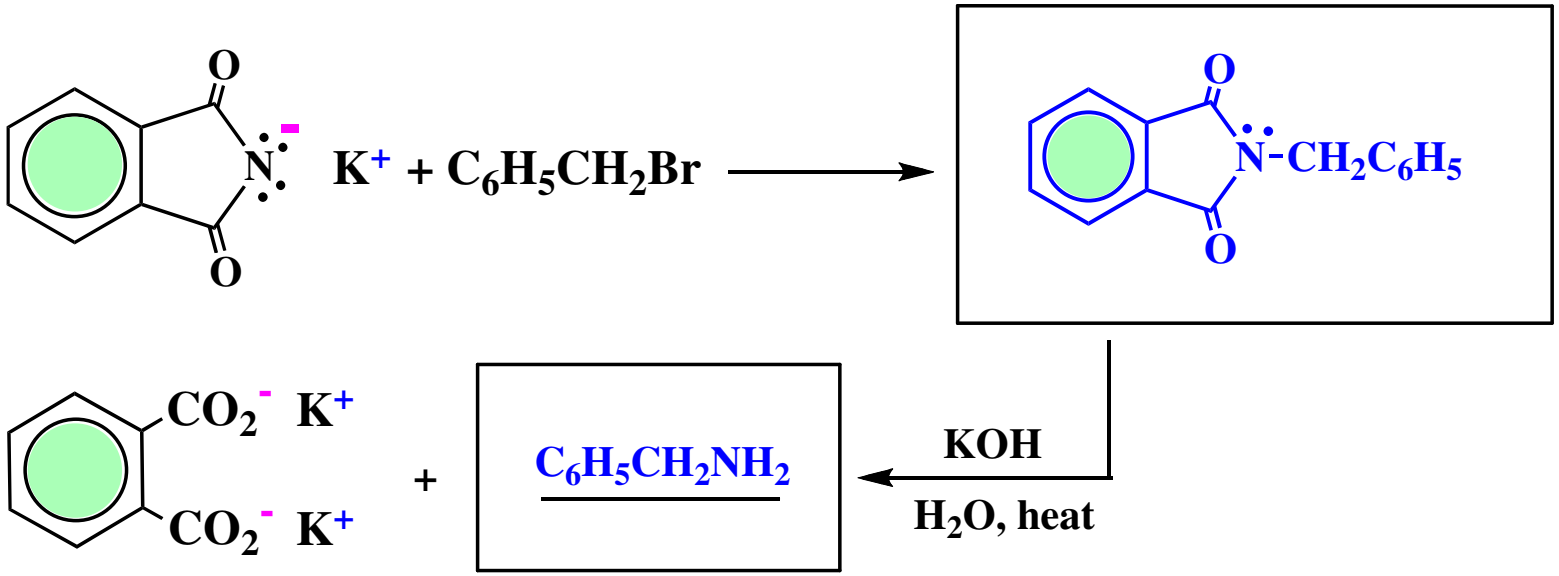
Methylpropylamine
***N*-Methylpropanamine**



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

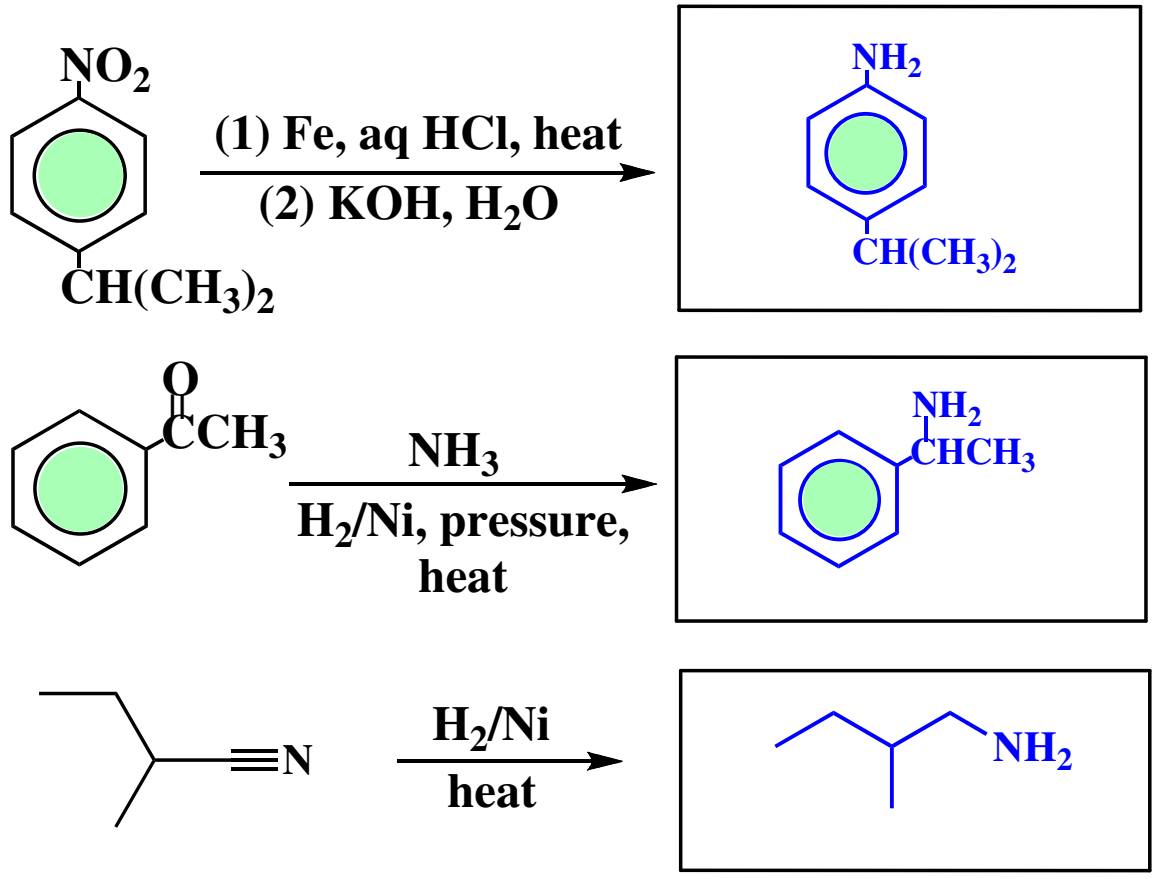
Quiz 20.02

Provide the missing structures in the reaction scheme below.



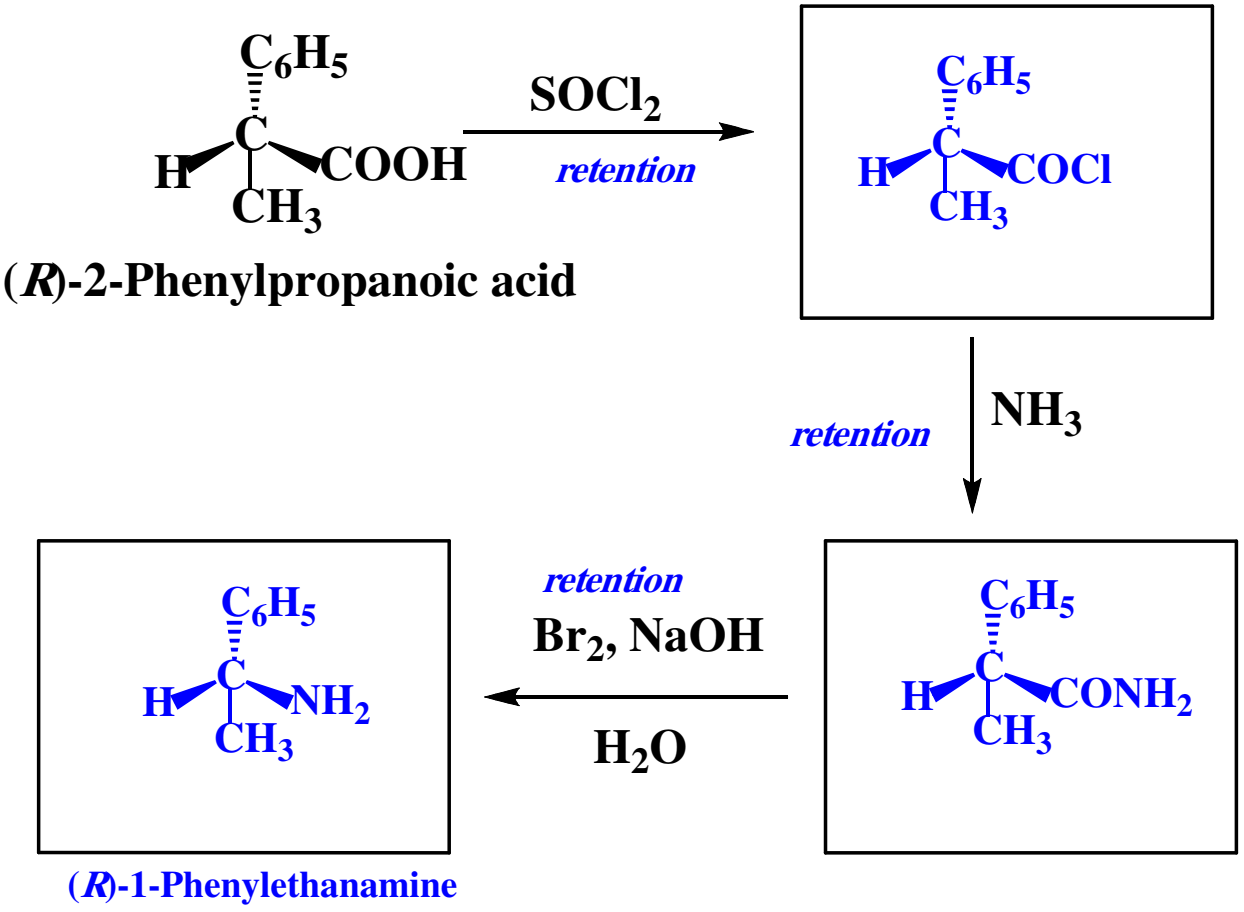
Quiz 20.03

Provide the structures of the products of the following reactions.



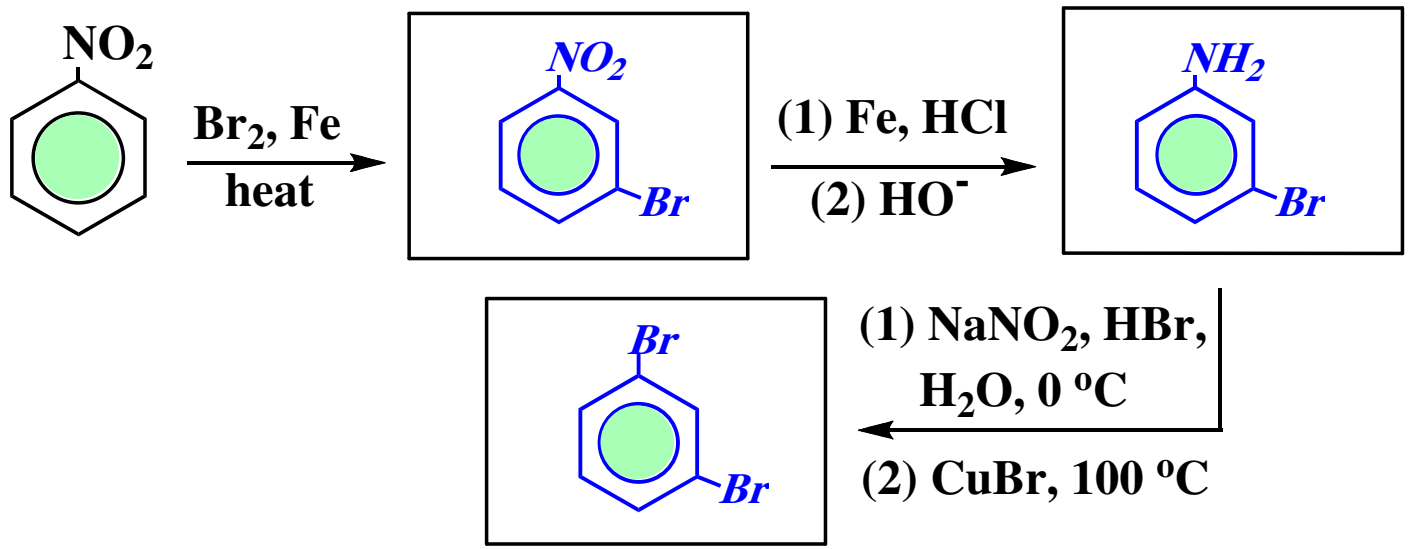
Quiz 20.04

Provide the missing structures in the following scheme.



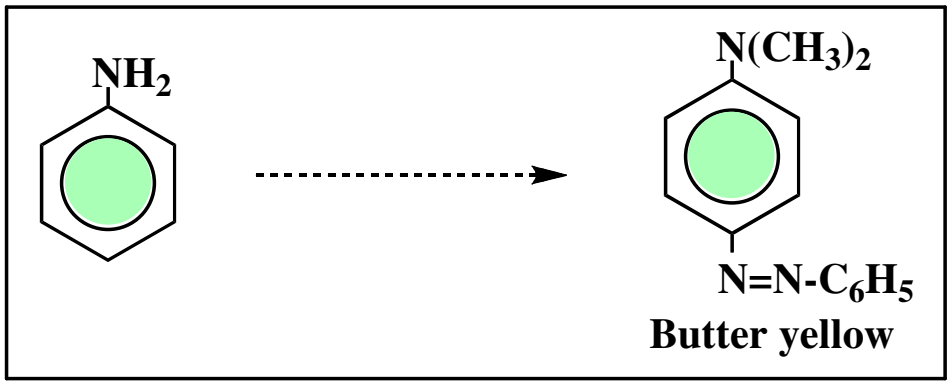
Quiz 20.05

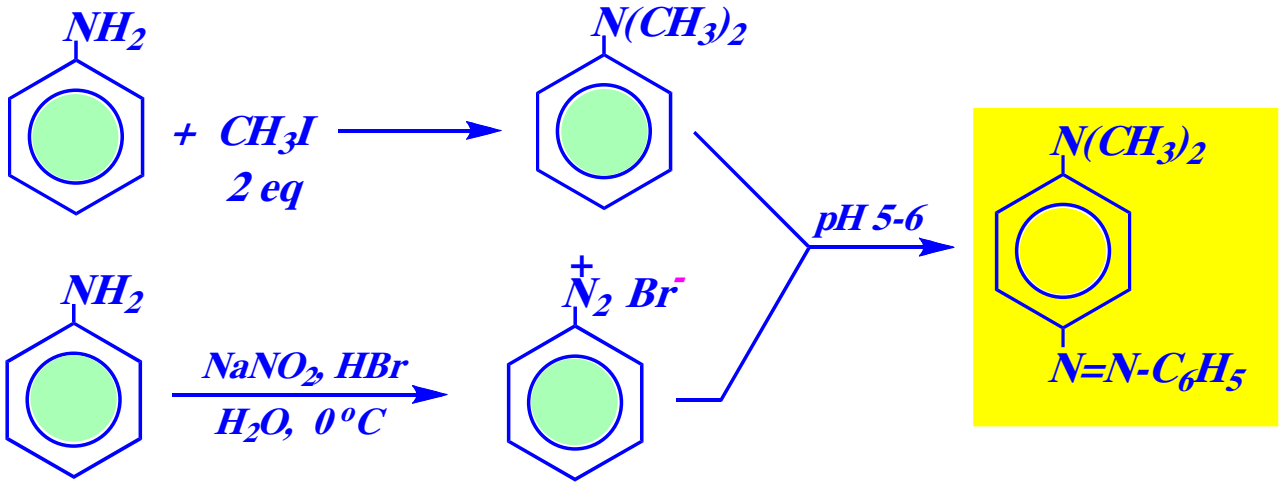
Provide the missing structures in the scheme below.



Quiz 20.06

Design a synthesis of the dye butter yellow from aniline.

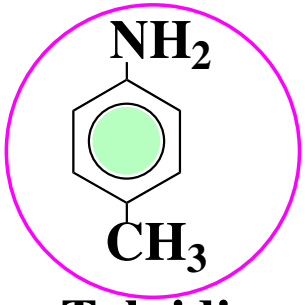




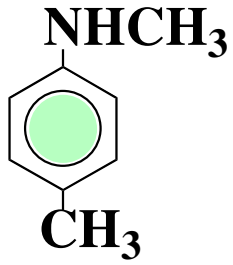
Quiz 20.07

An unknown amine is one of the three compounds below. When the Hinsberg test is run, the unknown amine dissolves completely in the Hinsberg reagent ($C_6H_5SO_2Cl$, KOH, H_2O), but a solid is formed when acid is added and the solution pH is adjusted to 7.

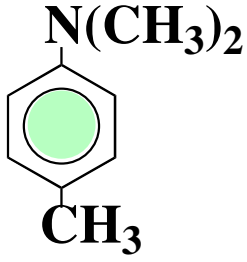
Circle the structure of the unknown amine.



***p*-Toluidine**



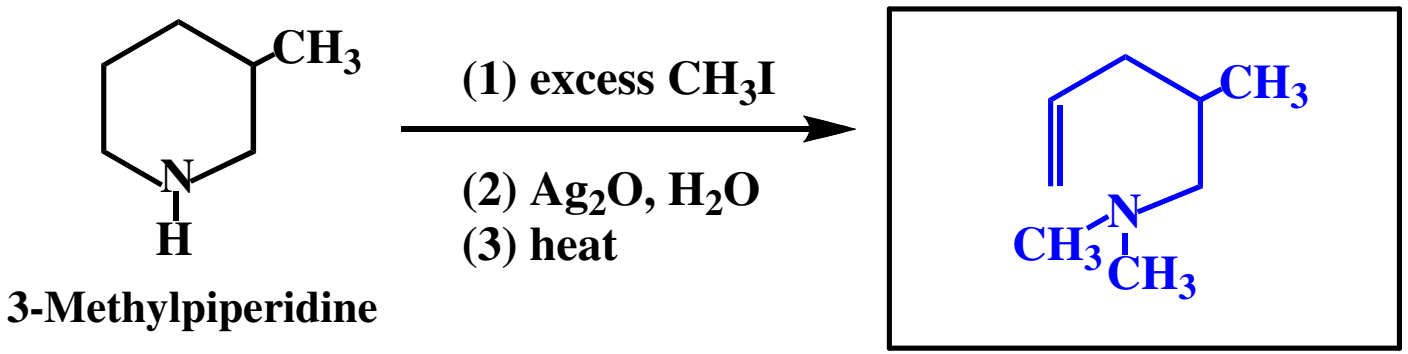
***N*-Methyl-*p*-toluidine**



***N,N*-Dimethyl-*p*-toluidine**

Quiz 20.08

Exhaustive methylation of 3-methylpiperidine, followed by treatment with aqueous silver oxide and heating, yields an amine product, $C_8H_{17}N$. What is its structure?



3-Methylpiperidine

$C_8H_{17}N$