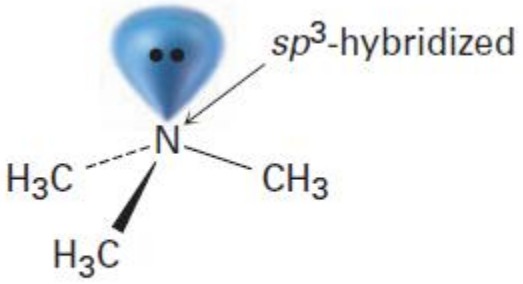
Amines

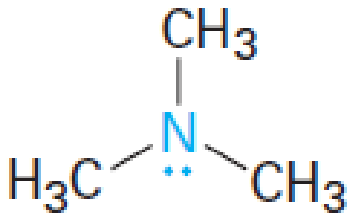
Amines are organic derivatives of ammonia

Amines contain a nitrogen atom with a lone pair of electrons, making amines both basic and nucleophilic.

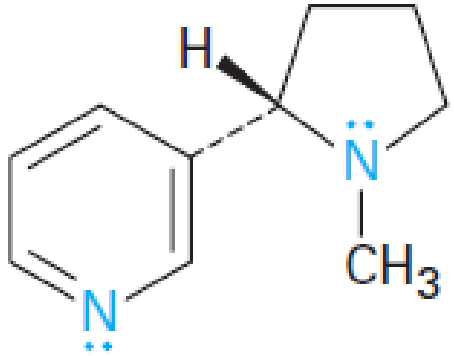


Trimethylamine

Amines occur widely in all living organisms. Trimethylamine, for instance, occurs in animal tissues and is partially responsible for the distinctive odor of fish; nicotine is found in tobacco

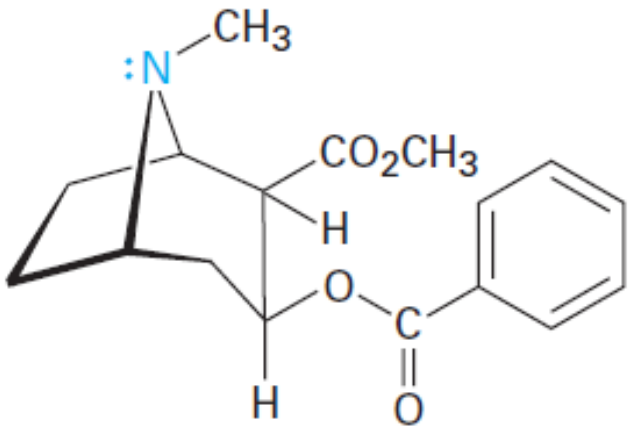


Trimethylamine



Nicotine

Cocaine is a stimulant found in the leaves of the South American coca bush.



Cocaine

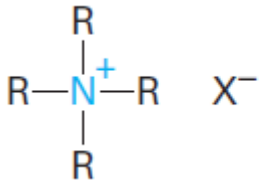
Amines are classified as primary (RNH_2), secondary (R_2NH), or tertiary (R_3N), depending on the number of organic substituents attached to nitrogen.

Methylamine (CH_3NH_2) is a primary amine

Dimethylamine $[(CH_3)_2NH]$ is a secondary amine

Trimethylamine $[(CH_3)_3N]$ is a tertiary amine.

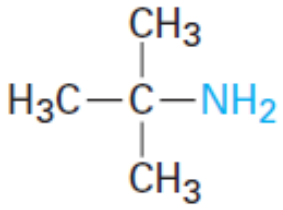
Compounds containing a nitrogen atom with four attached groups called quaternary ammonium salts.



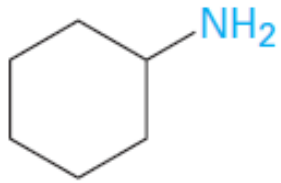
A quaternary ammonium salt

Naming Amines

Primary amines are named in the IUPAC system in several ways. For simple amines, the suffix *–amine* is added to the name of the alkyl substituent.

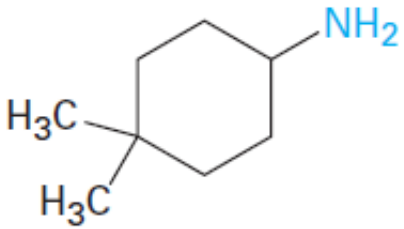


***tert*-Butylamine**



Cyclohexylamine

Alternatively, the suffix *-amine* can be used in place of the final *-e* in the name of the parent compound.

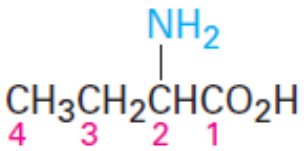


4,4-Dimethylcyclohexanamine

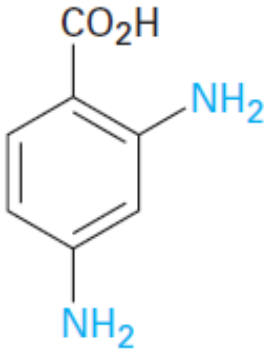
$H_2NCH_2CH_2CH_2CH_2NH_2$

1,4-Butanediamine

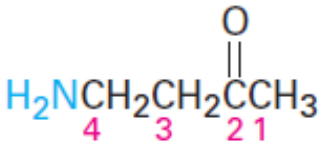
Amines with more than one functional group are named by considering the $-NH_2$ as an *amino* substituent on the parent molecule.



2-Aminobutanoic acid

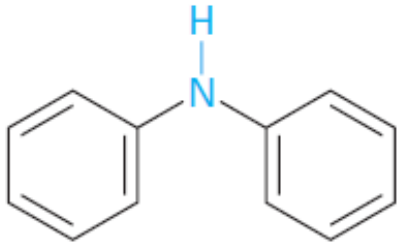


2,4-Diaminobenzoic acid

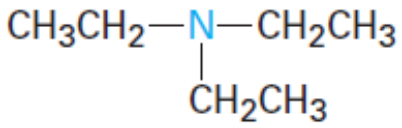


4-Amino-2-butanone

Symmetrical secondary and tertiary amines are named by adding the prefix *di-* or *tri-* to the alkyl group.

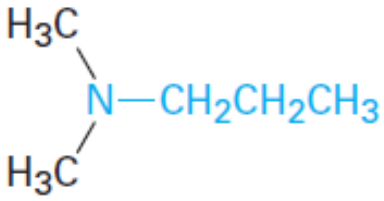


Diphenylamine

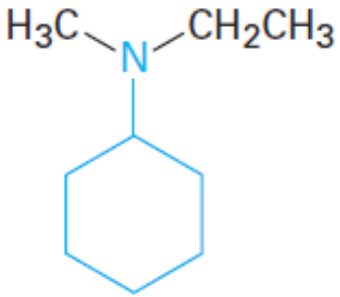


Triethylamine

Unsymmetrically substituted secondary and tertiary amines are named as *N*-substituted primary amines. The largest alkyl group is chosen as the parent name, and the other alkyl groups are considered *N*-substituents on the parent (*N* because they're attached to nitrogen).



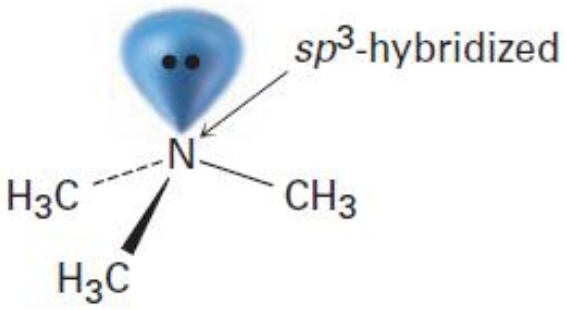
***N,N*-Dimethylpropylamine**



***N*-Ethyl-*N*-methylcyclohexylamine**

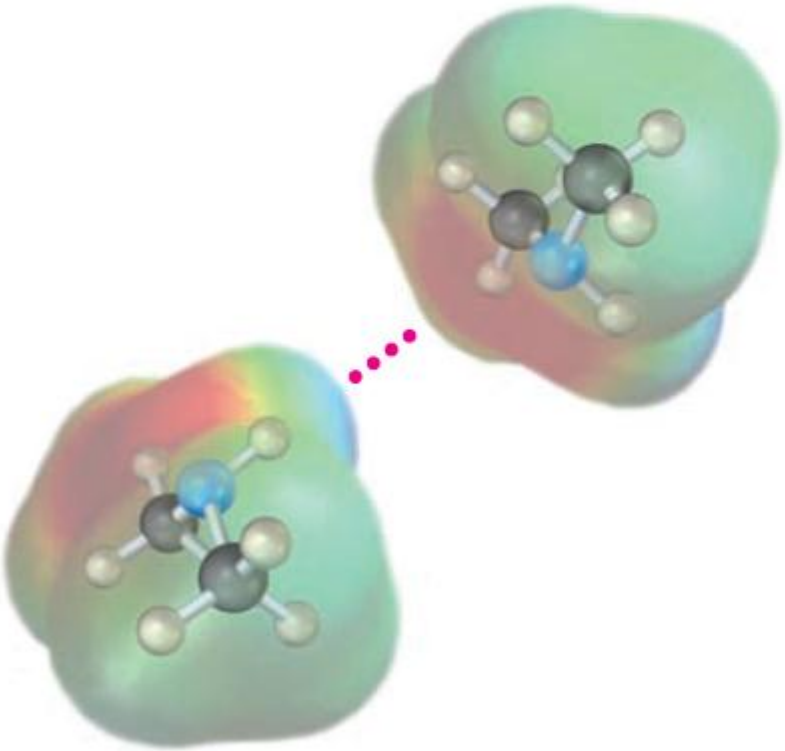
Structure and Properties of Amines

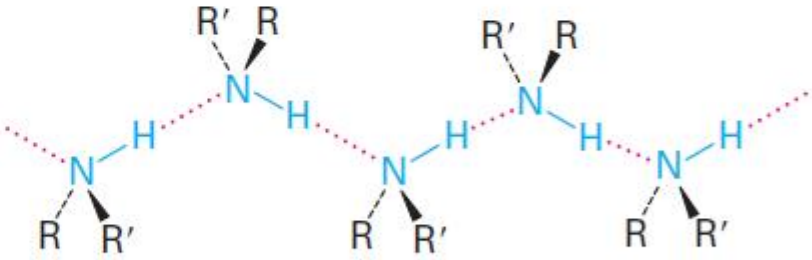
The bonding in alkylamines is similar to the bonding in ammonia. The nitrogen atom is sp^3-hybridized, with the three substituents occupying three corners of a regular tetrahedron and the lone pair of electrons occupying the fourth corner. As you might expect, the C–N–C bond angles are close to the 109° tetrahedral value. For trimethylamine, the C–N–C bond angle is 108° and the C–N bond length is 147 pm.



Trimethylamine

Like alcohols, amines with fewer than five carbon atoms are generally water-soluble. Also like alcohols, primary and secondary amines form hydrogen bonds and are highly associated. As a result, amines have higher boiling points than alkanes of similar molecular weight. Diethylamine (MW = 73 amu) boils at 56.3 °C, for instance, while pentane (MW = 72 amu) boils at 36.1 °C.





Basicity of Amines

The chemistry of amines is dominated by the lone pair of electrons on nitrogen, which makes amines both basic and nucleophilic.

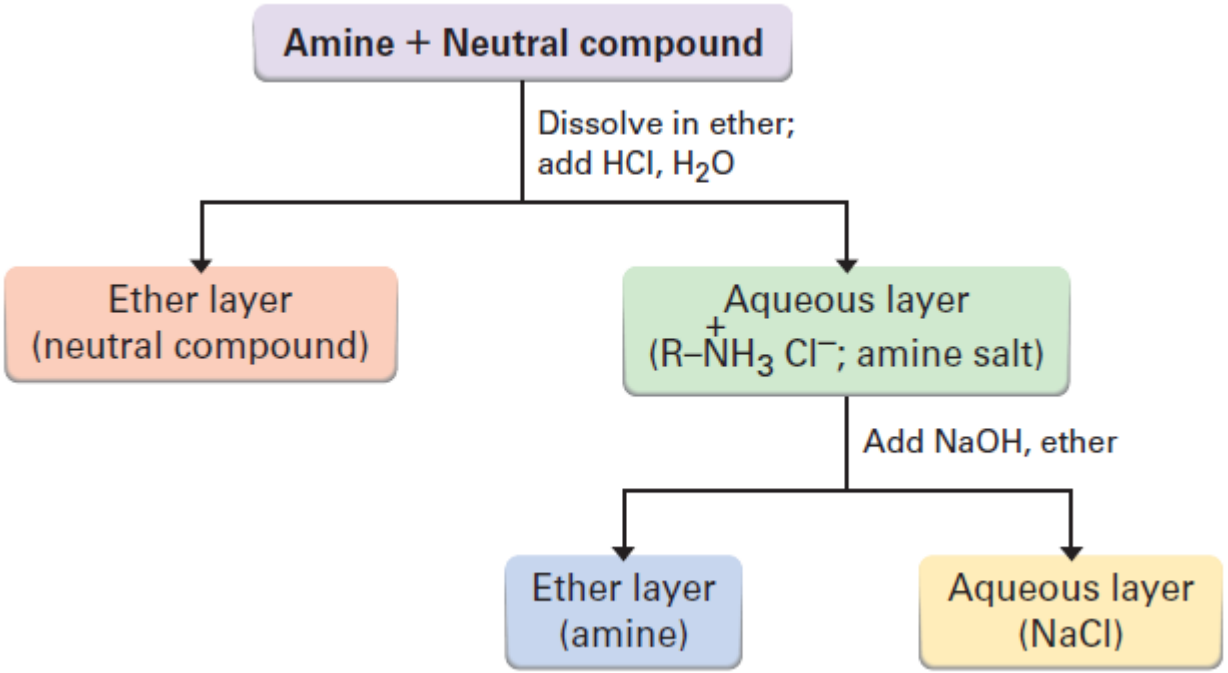
The base strength of an amine can be measured by defining an analogous *basicity constant* K_b. The larger the value of K_b and the smaller the value of pK_b, the more favorable the proton-transfer equilibrium and the stronger the base.

$$RNH_2 + H_2O \rightleftharpoons RNH_3^+ + OH^-$$

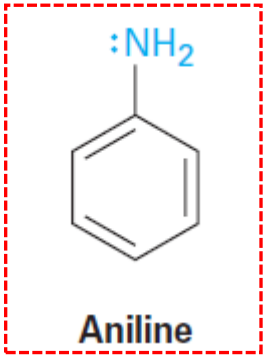
$$K_b = \frac{[RNH_3^+]\,[OH^-]}{[RNH_2]}$$

$$pK_b = -\log K_b$$

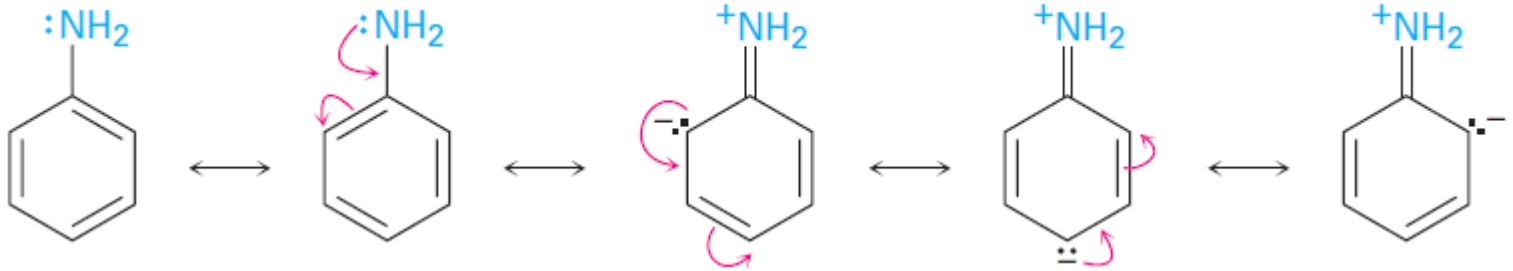
It's often possible to take advantage of their basicity to purify amines. For example, if a mixture of a basic amine and a neutral compound such as a ketone or alcohol is dissolved in an organic solvent and aqueous acid is added, the basic amine dissolves in the water layer as its protonated salt, while the neutral compound remains in the organic solvent layer. Separation of the water layer and neutralization of the ammonium ion by addition of NaOH then provides the pure amine



Basicity of Arylamines



Arylamines are generally less basic than alkylamines because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic ring π electron system and are less available for bonding to H^+.



Substituted Arylamines

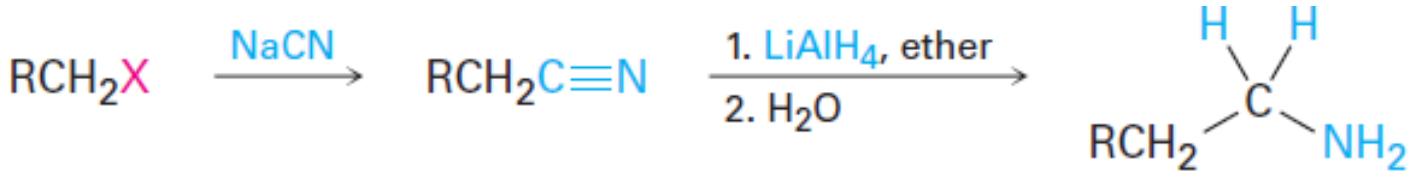
Electron-donating substituents (Activating Groups) increase the basicity

Electron-withdrawing substituents (Deactivating Groups) decrease the basicity.

	Substituent, Y	pK_a	
Stronger base	$-NH_2$	6.15	Activating groups
	$-OCH_3$	5.34	
	$-CH_3$	5.08	
	$-H$	4.63	
	$-Cl$	3.98	Deactivating groups
	$-Br$	3.86	
	$-CN$	1.74	
Weaker base	$-NO_2$	1.00	

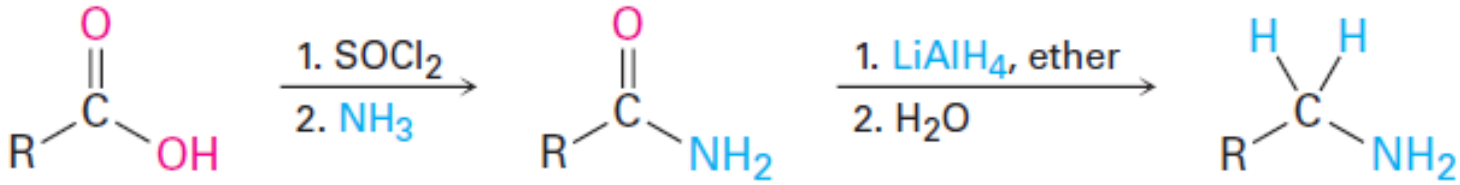
Synthesis of Amines

Reduction of nitriles and amides with LiAlH4



Alkyl halide

1° amine



Carboxylic acid

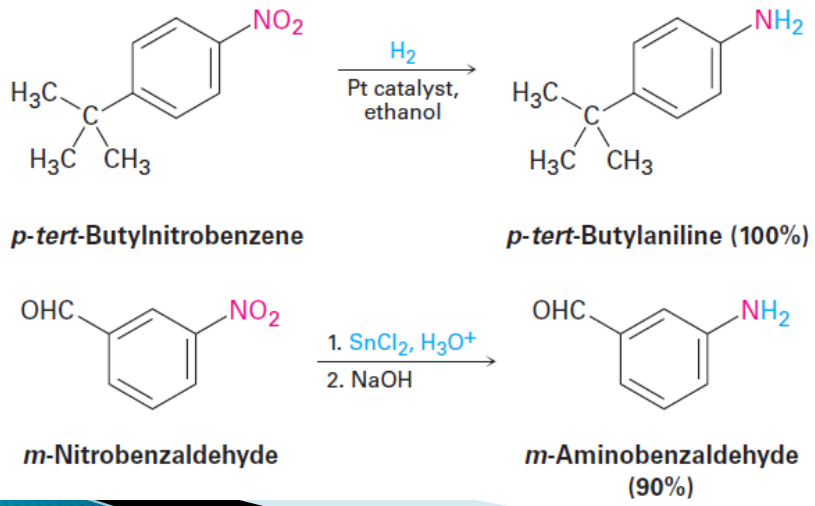
1° amine

Synthesis of Amines

Arylamines are usually prepared by nitration of an aromatic starting material, followed by reduction of the nitro group. The reduction step can be carried out in many different ways, depending on the circumstances. Catalytic hydrogenation over platinum works well but is often incompatible with the presence elsewhere in the molecule of other reducible groups, such as C=C bonds or carbonyl groups.

Iron, zinc, tin, and tin(II) chloride ($SnCl_2$) are also effective when used in acidic aqueous solution.

Tin(II) chloride is particularly mild and is often used when other reducible functional groups are present.



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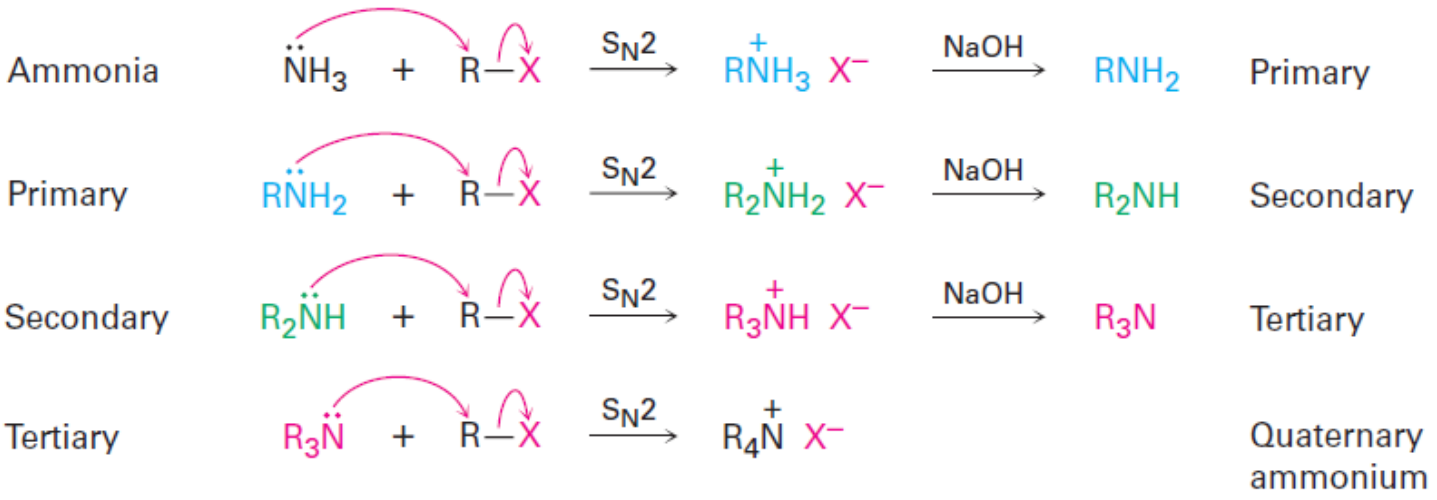
Synthesis of Amines

SN2 Reactions of Alkyl Halides

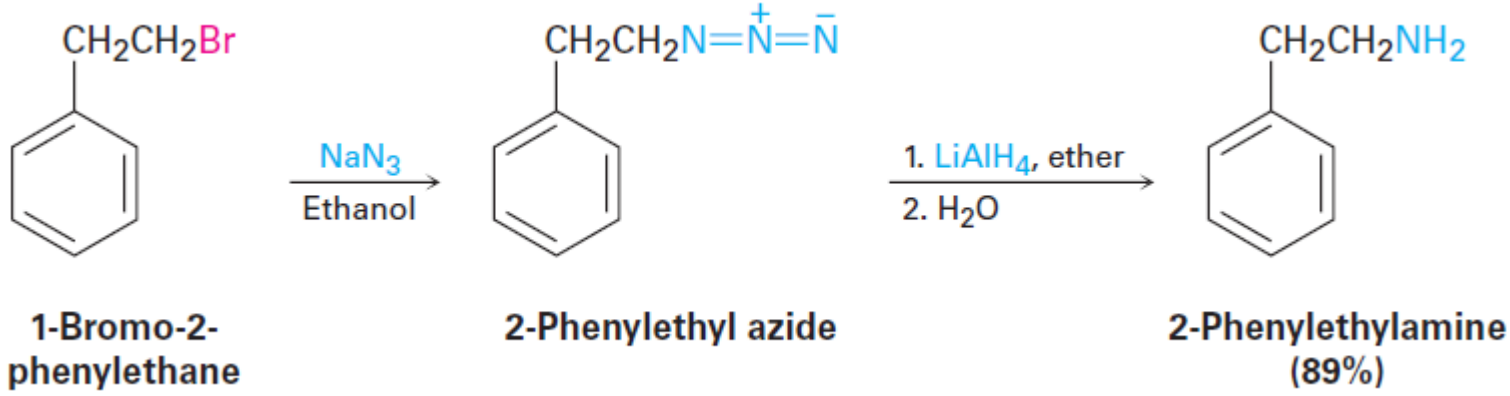
Ammonia and other amines are good nucleophiles in S_N2 reactions. As a result, the simplest method of alkylamine synthesis is by S_N2 alkylation of ammonia or an alkylamine with an alkyl halide. If ammonia is used, a primary amine results; if a primary amine is used, a secondary amine results; and so on. Even tertiary amines react rapidly with alkyl halides to yield quaternary ammonium salts, $R_4N^+ X^-$.



Unfortunately, these reactions don't stop cleanly after a single alkylation has occurred. Because ammonia and primary amines have similar reactivity, the initially formed monoalkylated substance often undergoes further reaction to yield a mixture of products.

Synthesis of Amines

A better method for preparing primary amines is to use azide ion, N32, as the nucleophile rather than ammonia for SN2 reaction with a primary or secondary alkyl halide. The product is an alkyl azide, which is not nucleophilic, so overalkylation can't occur. Subsequent reduction of the alkyl azide with LiAlH4 then leads to the desired primary amine. Although the method works well, lowmolecular weight alkyl azides are explosive and must be handled carefully.



1-Bromo-2-phenylethane

2-Phenylethyl azide

2-Phenylethylamine (89%)

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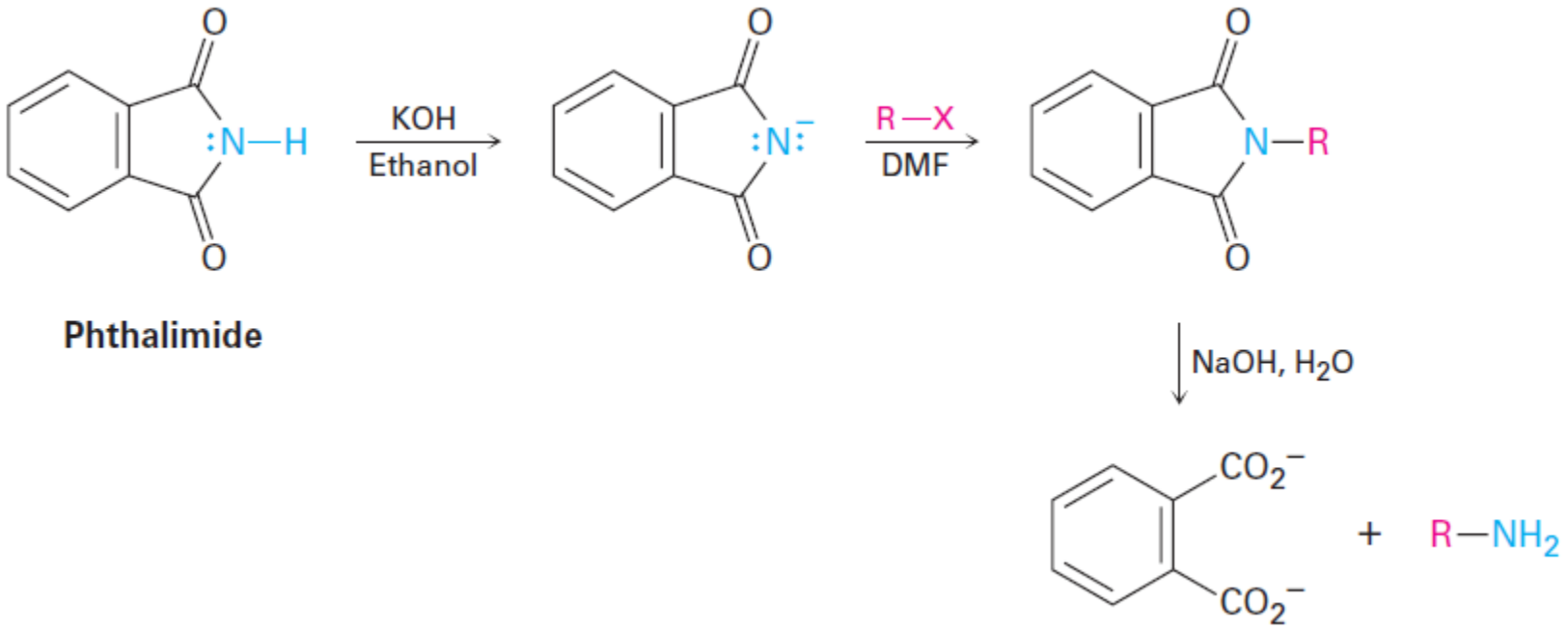
Synthesis of Amines

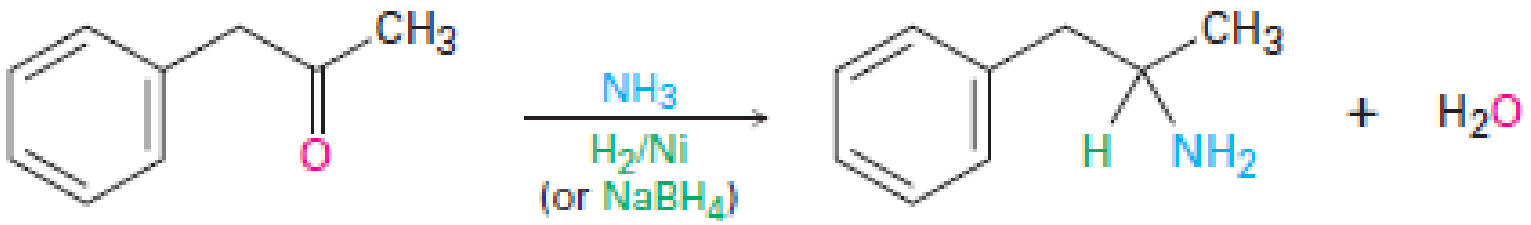
Gabriel amine synthesis



Synthesis of Amines

Reductive Amination of Aldehydes and Ketones

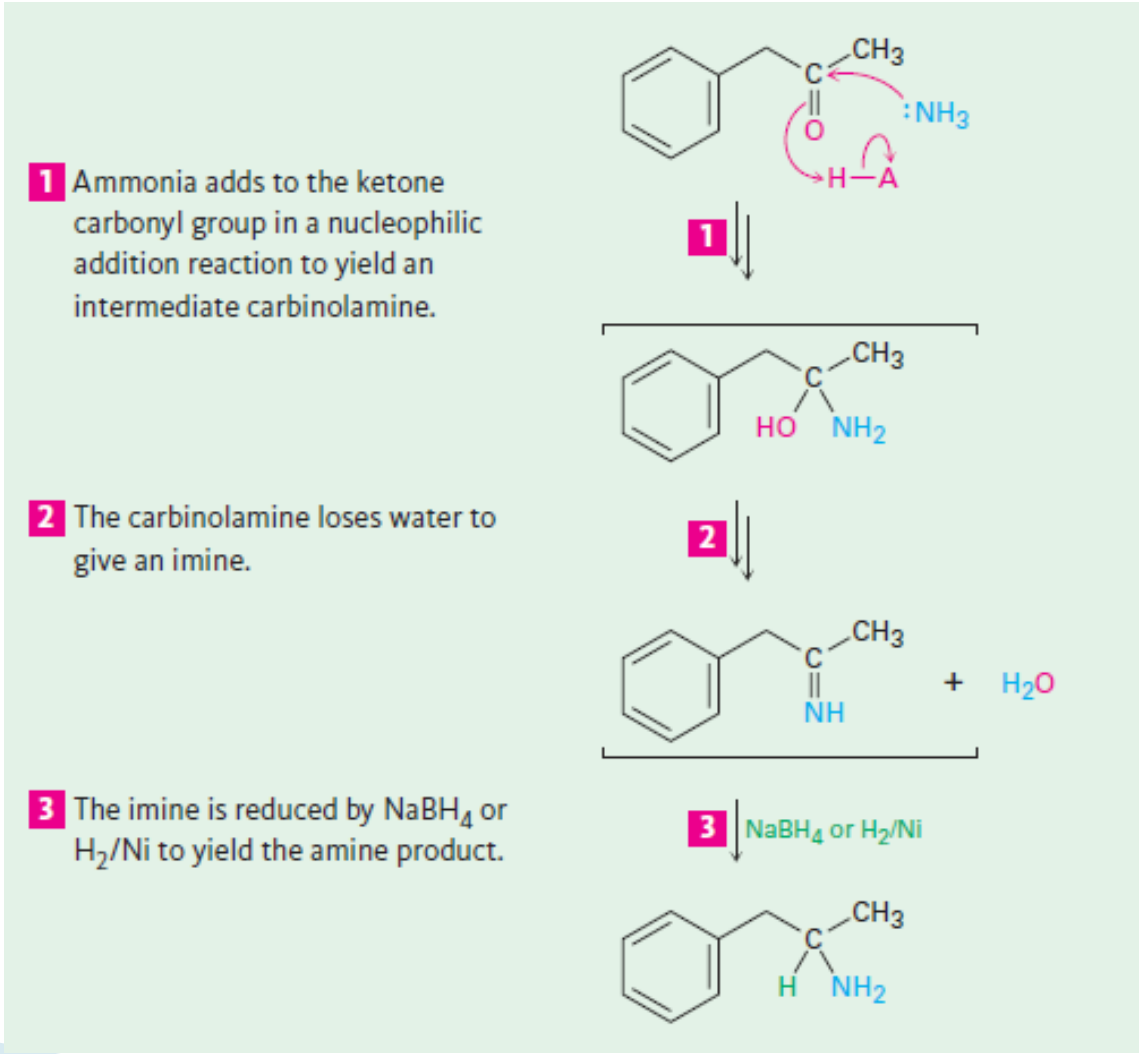
Amines can be synthesized in a single step by treatment of an aldehyde or ketone with ammonia or an amine in the presence of a reducing agent



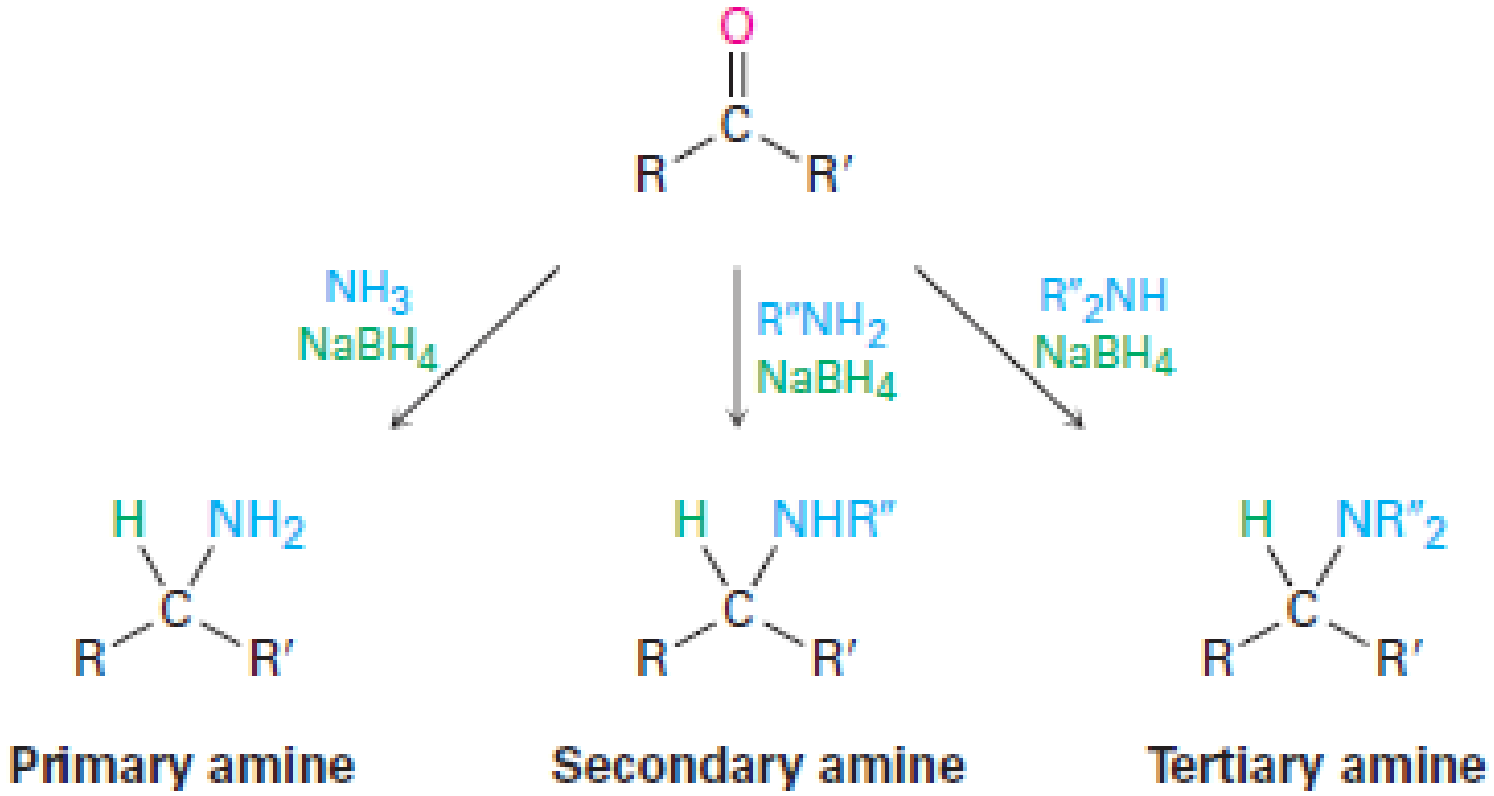
Phenyl-2-propanone

Amphetamine

Imine intermediate is first formed by a nucleophilic addition reaction and the C=N bond of the imine is then reduced to the amine

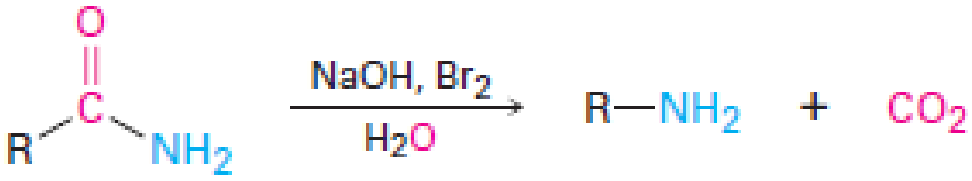


Ammonia, primary amines, and secondary amines can all be used in the reductive amination reaction, yielding primary, secondary, and tertiary amines, respectively.



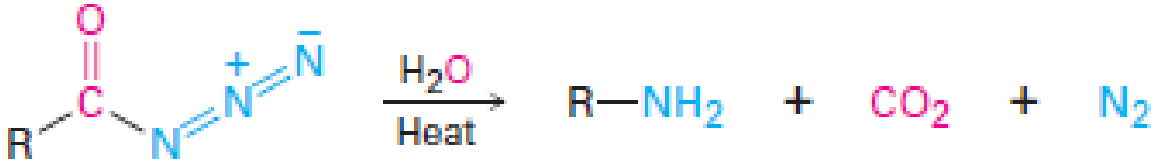
Hofmann and Curtius Rearrangements

Hofmann rearrangement



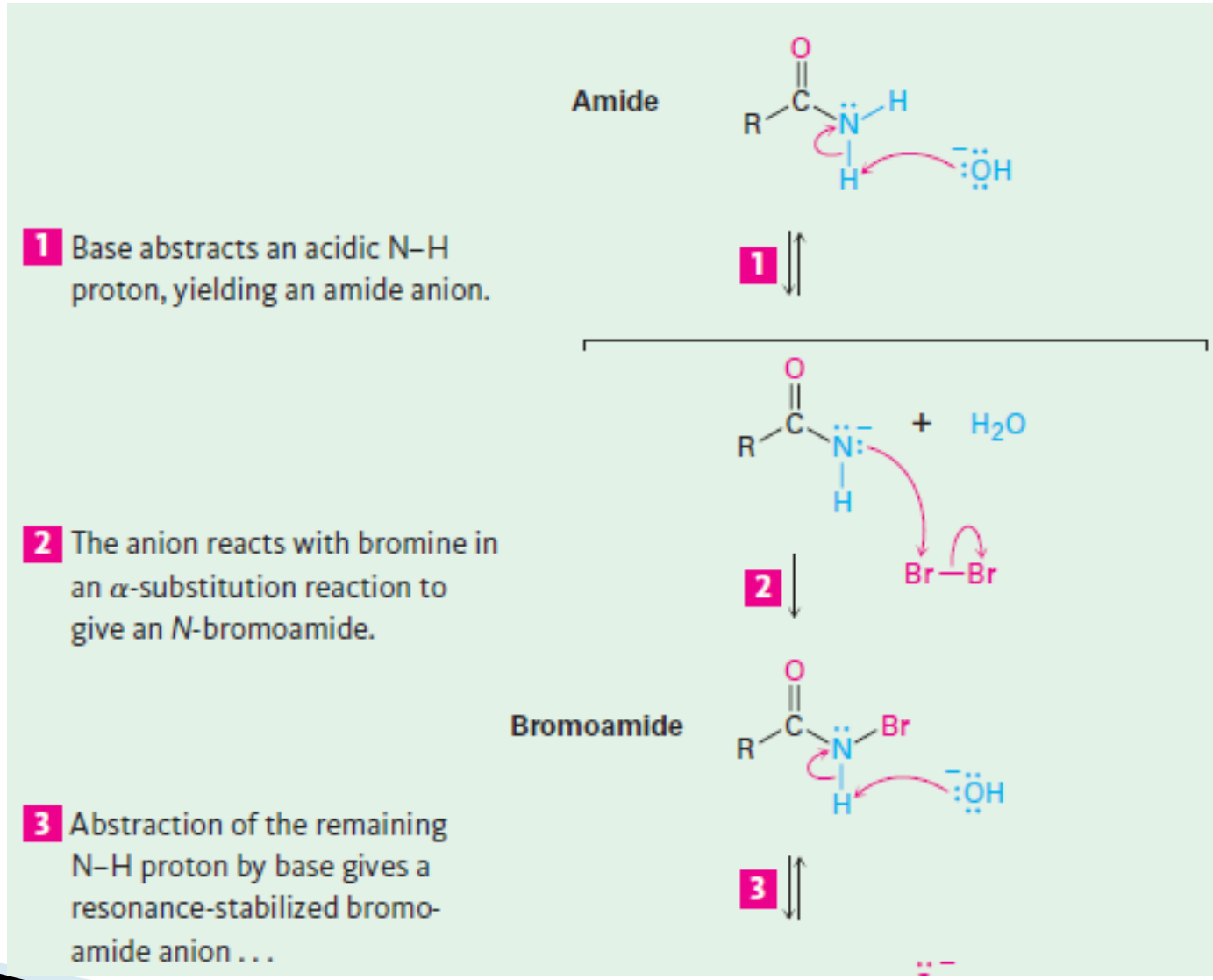
An amide

Curtius rearrangement

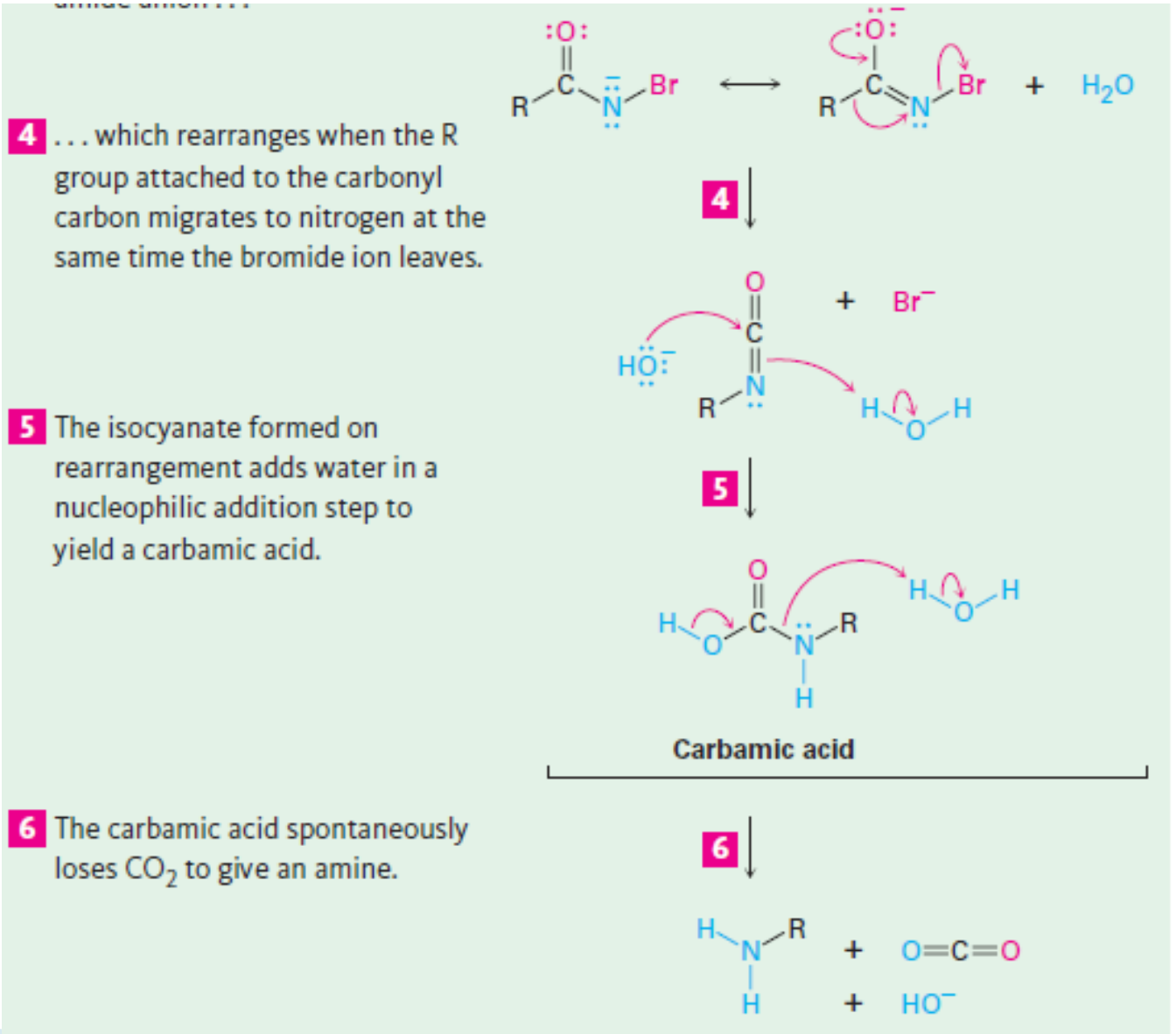


An acyl azide

Mechanism of the Hofmann rearrangement

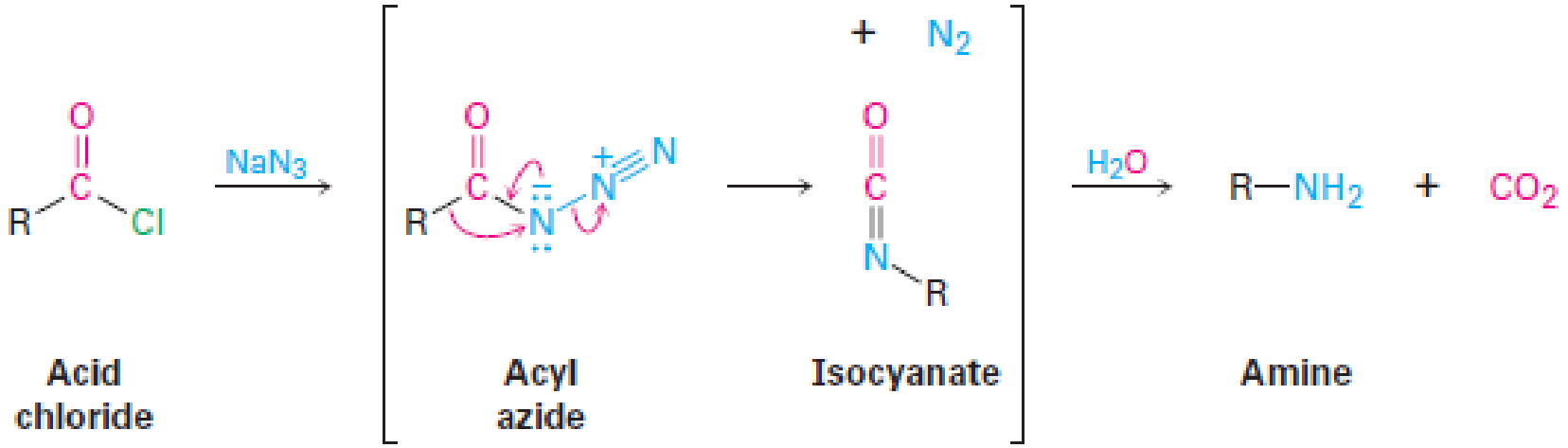


Mechanism of the Hofmann rearrangement



Curtius rearrangement

The Curtius rearrangement, like the Hofmann rearrangement, involves migration of an –R group from the C=O carbon atom to the neighboring nitrogen with simultaneous loss of a leaving group. The reaction takes place on heating an acyl azide that is itself prepared by nucleophilic acyl substitution of an acid chloride.



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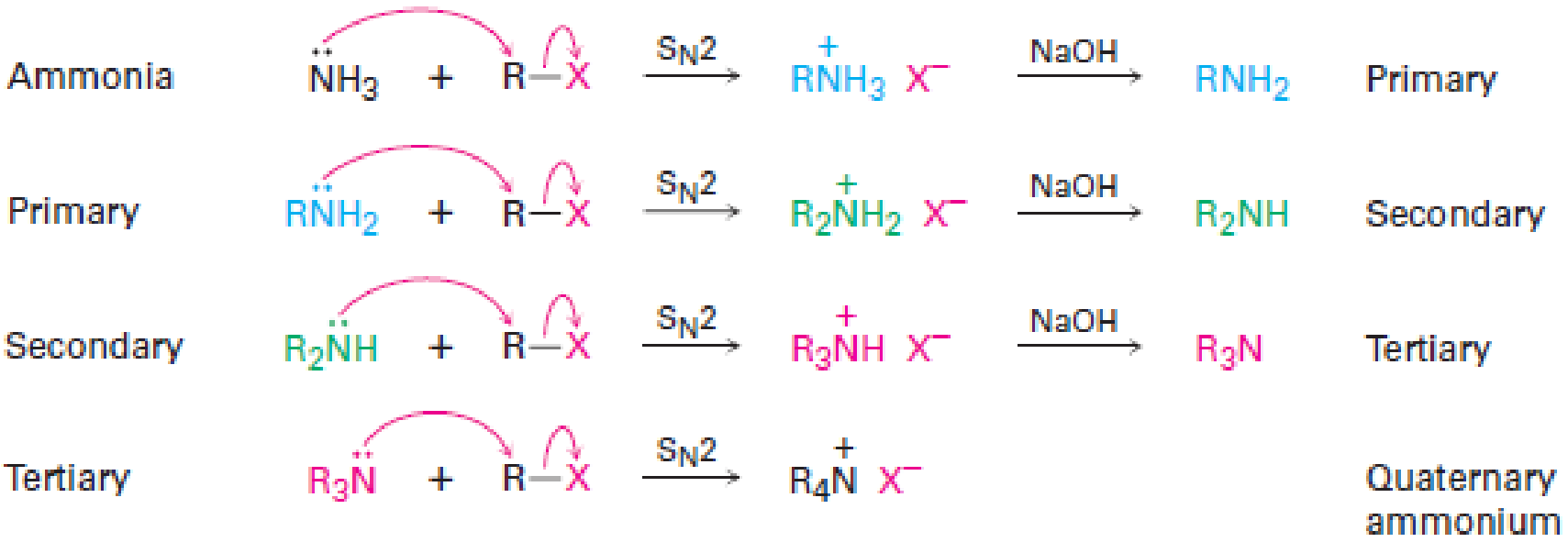
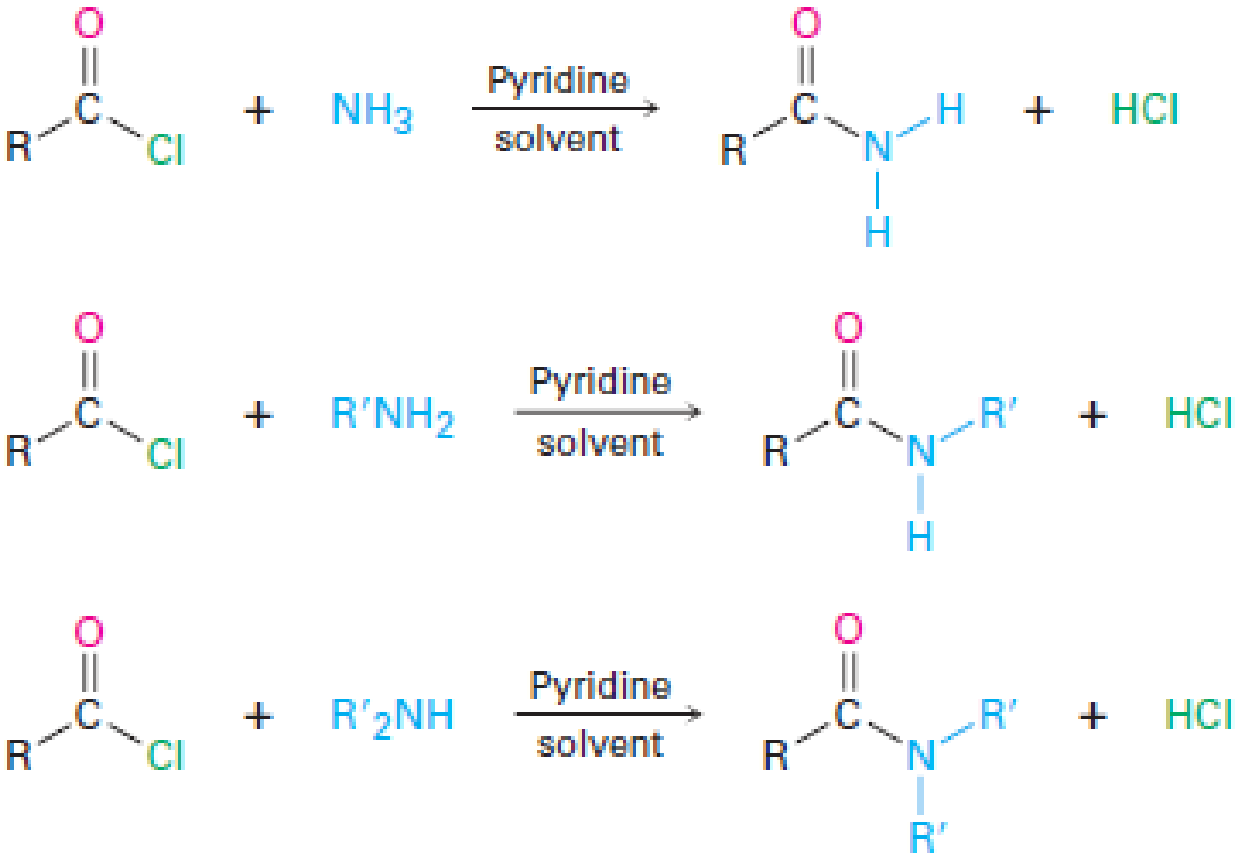
Reactions of Amines

Alkylation

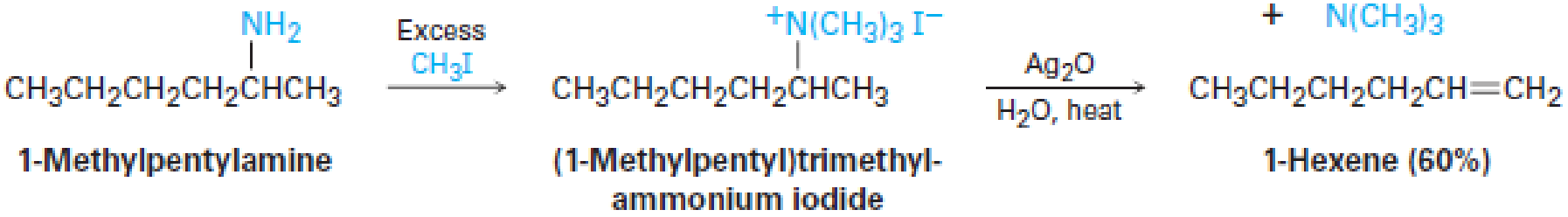


Acylation



Hofmann Elimination

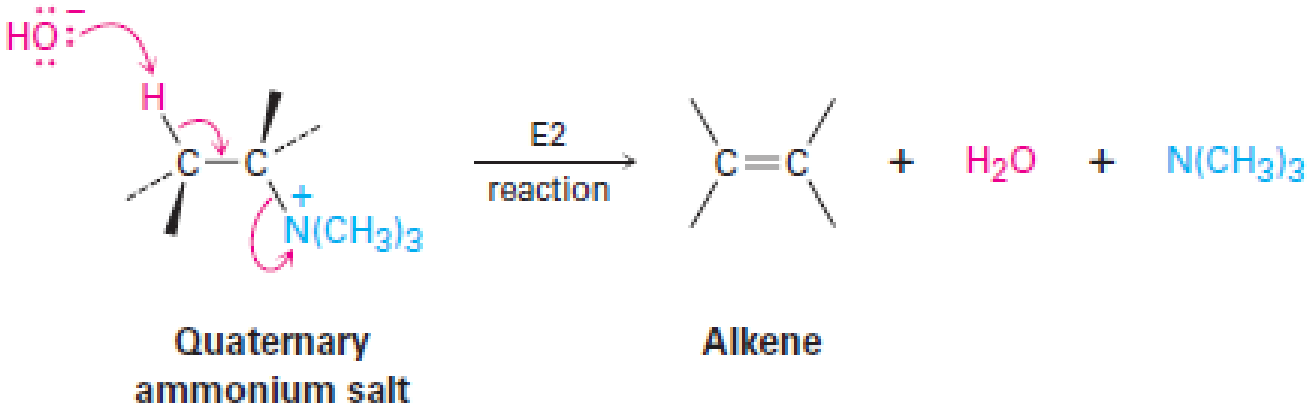
In the Hofmann elimination reaction, an amine is completely methylated by reaction with an excess amount of iodomethane to produce the corresponding quaternary ammonium salt. This salt then undergoes elimination to give an alkene on heating with a base, typically silver oxide, Ag_2O.



1-Methylpentylamine → **(1-Methylpentyl)trimethyl-ammonium iodide** → **1-Hexene (60%)**

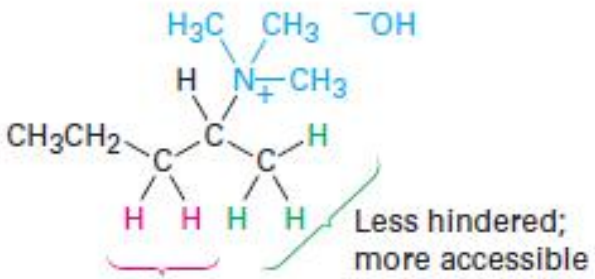
Hofmann Elimination

Silver oxide acts by exchanging iodide ion for hydroxide ion in the quaternary salt, thus providing the base necessary for elimination. The actual elimination step is an E2 reaction in which hydroxide ion removes a proton at the same time that the positively charged nitrogen atom leaves.



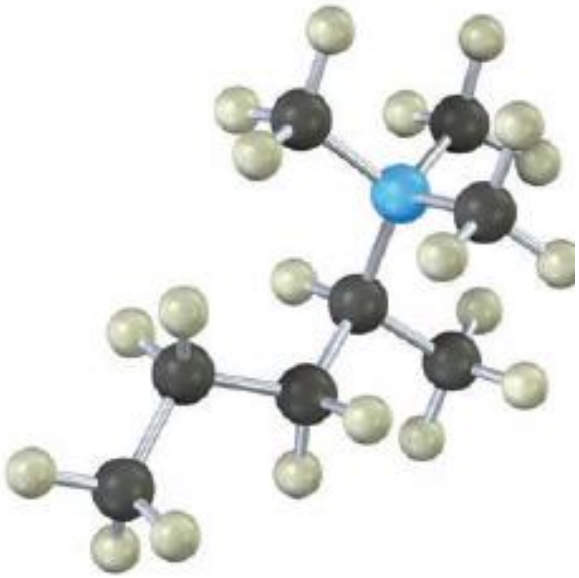
Hofmann Elimination

The major product of the Hofmann elimination is the less highly substituted alkene. The reason for this non-Zaitsev result is probably steric.

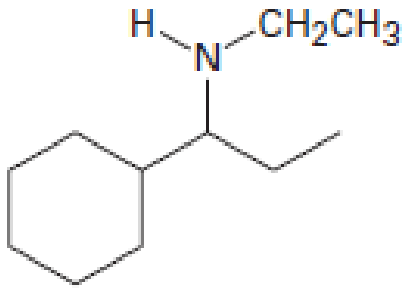


(1-Methylbutyl)trimethylammonium hydroxide

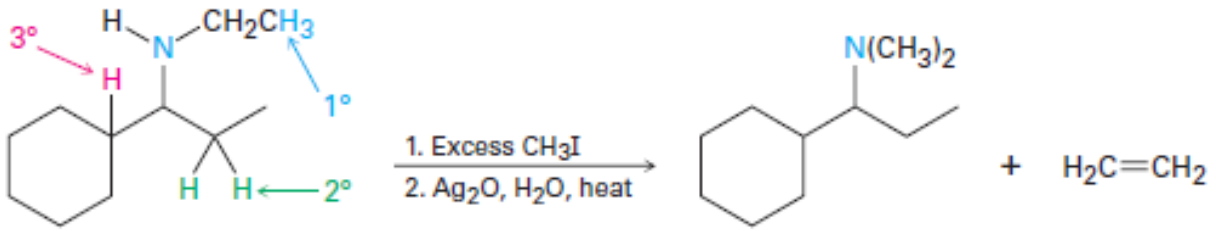
1-Pentene (94%) + **2-Pentene (6%)**



What product would you expect from Hofmann elimination of the following amine?



Solution



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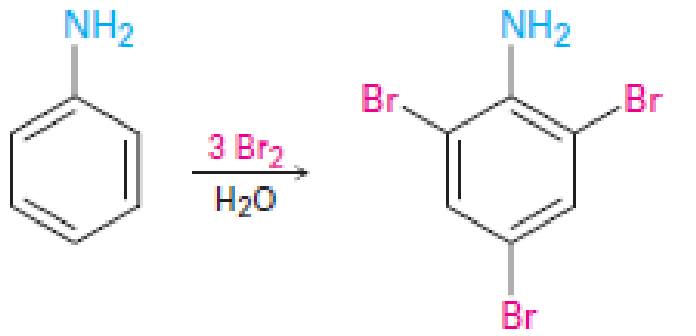
Reactions of Arylamines

Electrophilic Aromatic Substitution

An amino group is strongly activating and ortho- and para-directing in electrophilic aromatic substitution reactions.

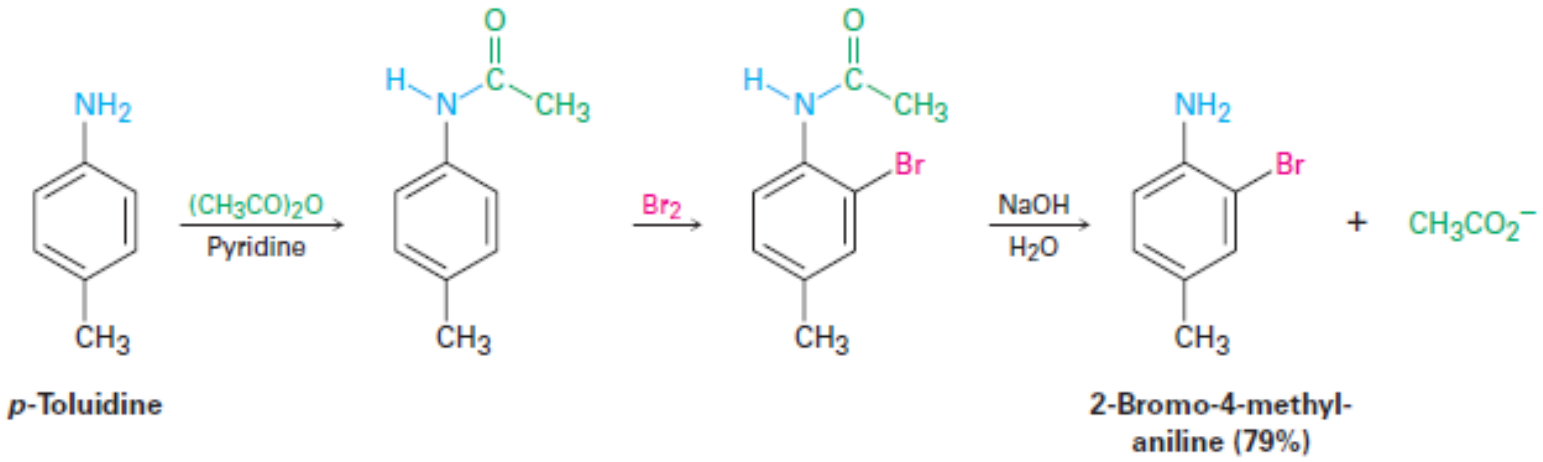


Aniline

2,4,6-Tribromoaniline
(100%)

Electrophilic Aromatic Substitution

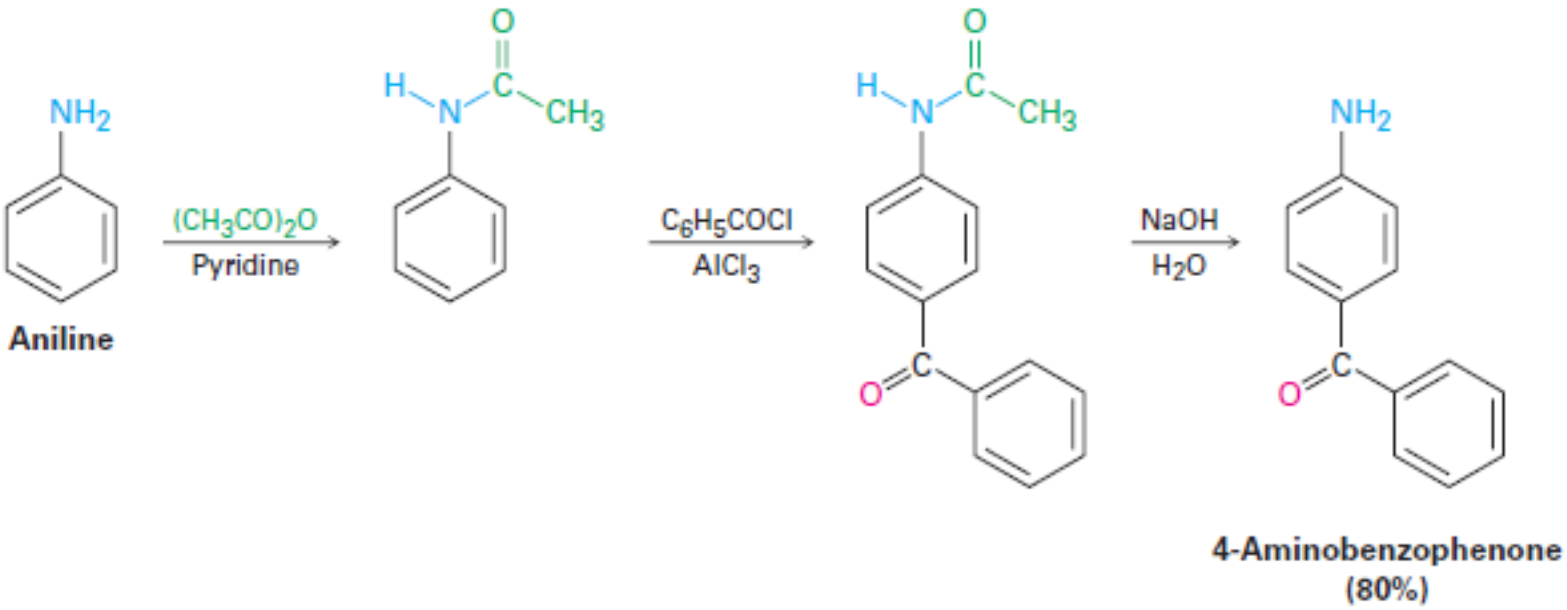
Treatment of an amine with acetic anhydride yields the corresponding acetyl amide, or acetamide. Although still activating and ortho-, para-directing, amido substituents ( ] NHCOR) are less strongly activating and less basic than amino groups because their nitrogen lone-pair electrons are delocalized by the neighboring carbonyl group. As a result, bromination of an *N*-arylamide occurs cleanly to give a monobromo product, and hydrolysis of the amide with aqueous base then gives the free amine.



p-Toluidine

2-Bromo-4-methyl-aniline (79%)

Electrophilic Aromatic Substitution



Aniline

4-Aminobenzophenone
(80%)

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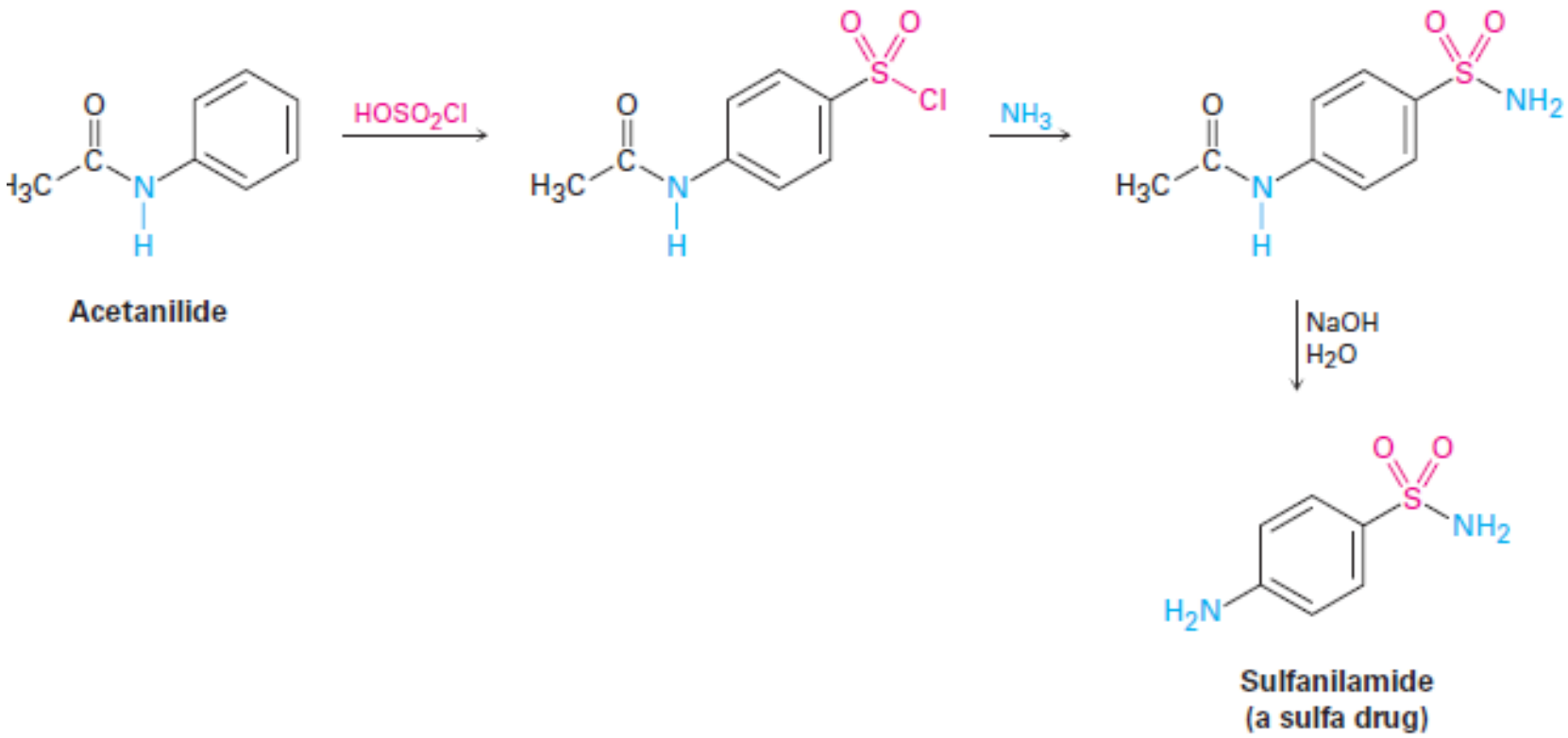
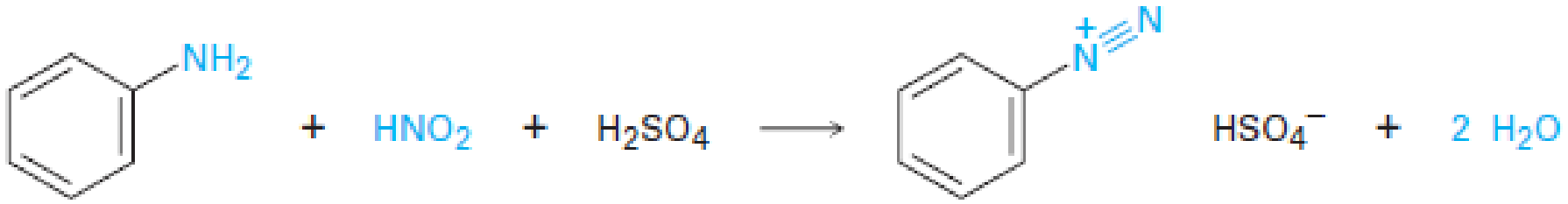
Sulfa Drugs

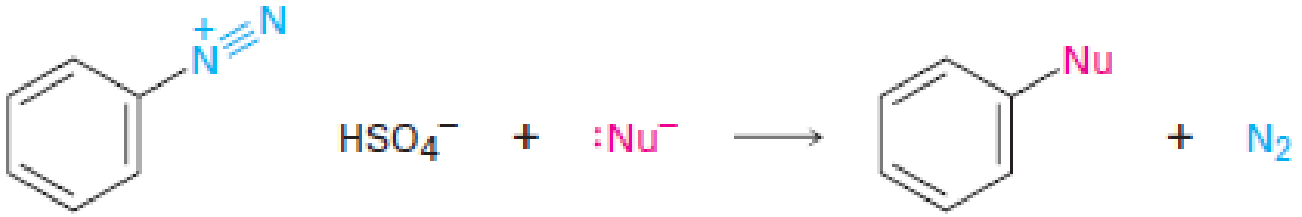


Diazonium Salts

Primary arylamines react with nitrous acid, HNO_2 , to yield stable *arenediazonium* salts, a process called a *diazotization* reaction.



Arenediazonium salts are useful because the diazonio group (N_2) can be replaced by a nucleophile in a substitution reaction.



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Reactions of Diazonium Salts

1. Replacement of nitrogen

$$Ar{-}N_2^+ + :Z \longrightarrow Ar{-}Z + N_2$$

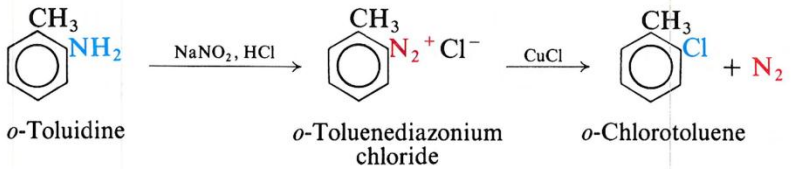
(a) Replacement by —Cl, —Br, and —CN. Sandmeyer reaction.

$$Ar{-}N_2^+ \xrightarrow{CuCl} Ar{-}Cl + N_2$$

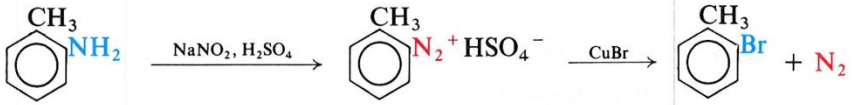
$$Ar{-}N_2^+ \xrightarrow{CuBr} Ar{-}Br + N_2$$

$$Ar{-}N_2^+ \xrightarrow{CuCN} Ar{-}CN + N_2$$

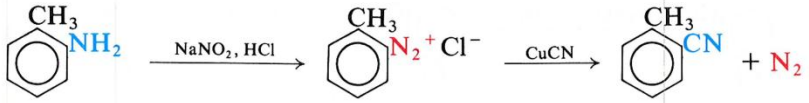
Examples:



o-Toluidine — *o*-Toluenediazonium chloride — *o*-Chlorotoluene



o-Toluidine — *o*-Bromotoluene

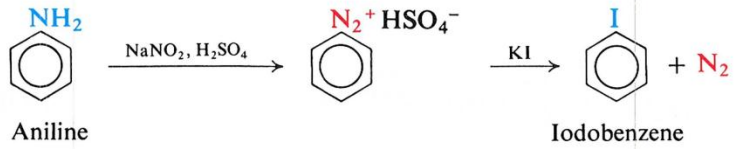


o-Toluidine — *o*-Tolunitrile

(b) Replacement by —I. Discussed in Sec. 23.13.

$$Ar{-}N_2^+ + I^- \longrightarrow Ar{-}I + N_2$$

Example:

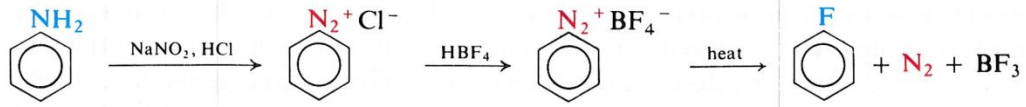


Aniline — Iodobenzene

(c) Replacement by —F. Discussed in Sec. 23.13.

$$Ar{-}N_2^+ BF_4^- \xrightarrow{\text{heat}} Ar{-}F + N_2 + BF_3$$

Example:



Aniline — Benzenediazonium chloride — Benzenediazonium fluoroborate — Fluorobenzene

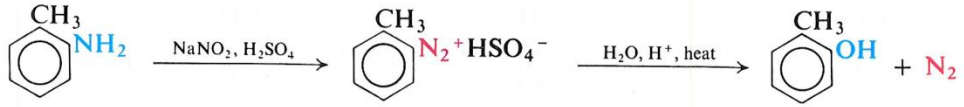
Isolated as crystalline salt

(d) Replacement by —OH. Discussed in Sec. 23.15.

$$Ar{-}N_2^+ + H_2O \xrightarrow{H^+} Ar{-}OH + N_2$$

A phenol

Example:



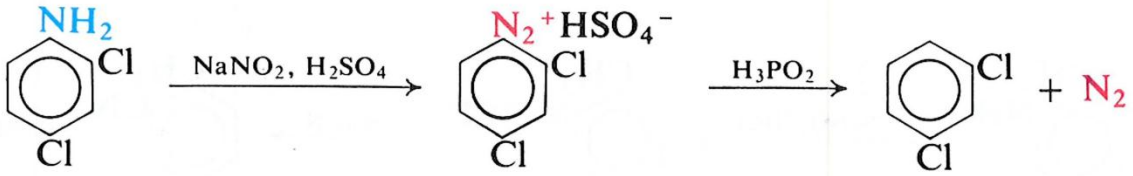
o-Toluidine — *o*-Cresol

(e) Replacement by —H. Discussed in Sec. 23.16.

$$Ar{-}N_2^+ + H_3PO_2 \xrightarrow{H_2O} Ar{-}H + H_3PO_3 + N_2$$

Hypophosphorous acid

Example:



2,4-Dichloroaniline

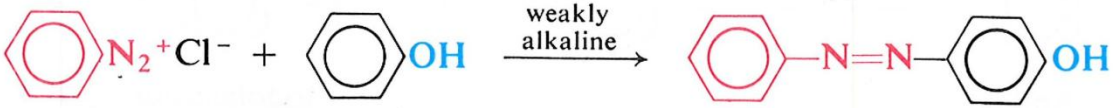
m-Dichlorobenzene

2. Coupling. Discussed in Sec. 23.18.

An azo compound

G must be a strongly electron-releasing group:
OH, NR_2, NHR, NH_2

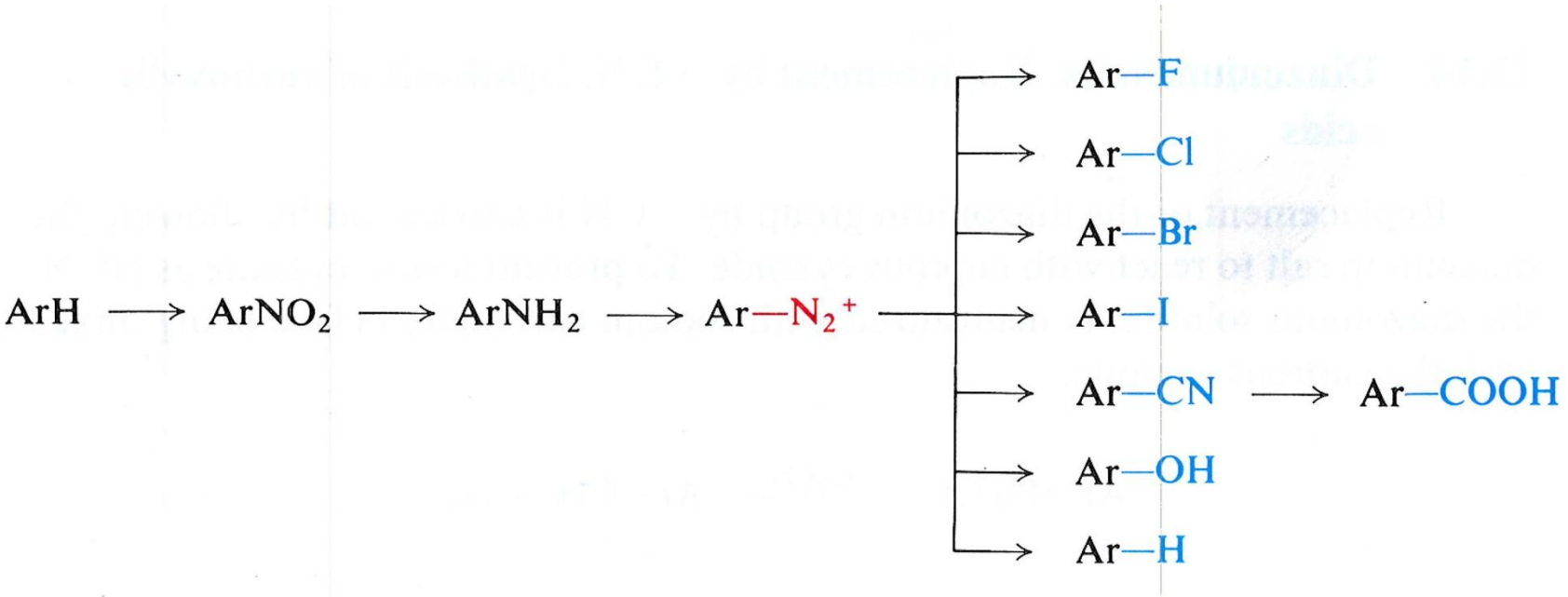
Example:



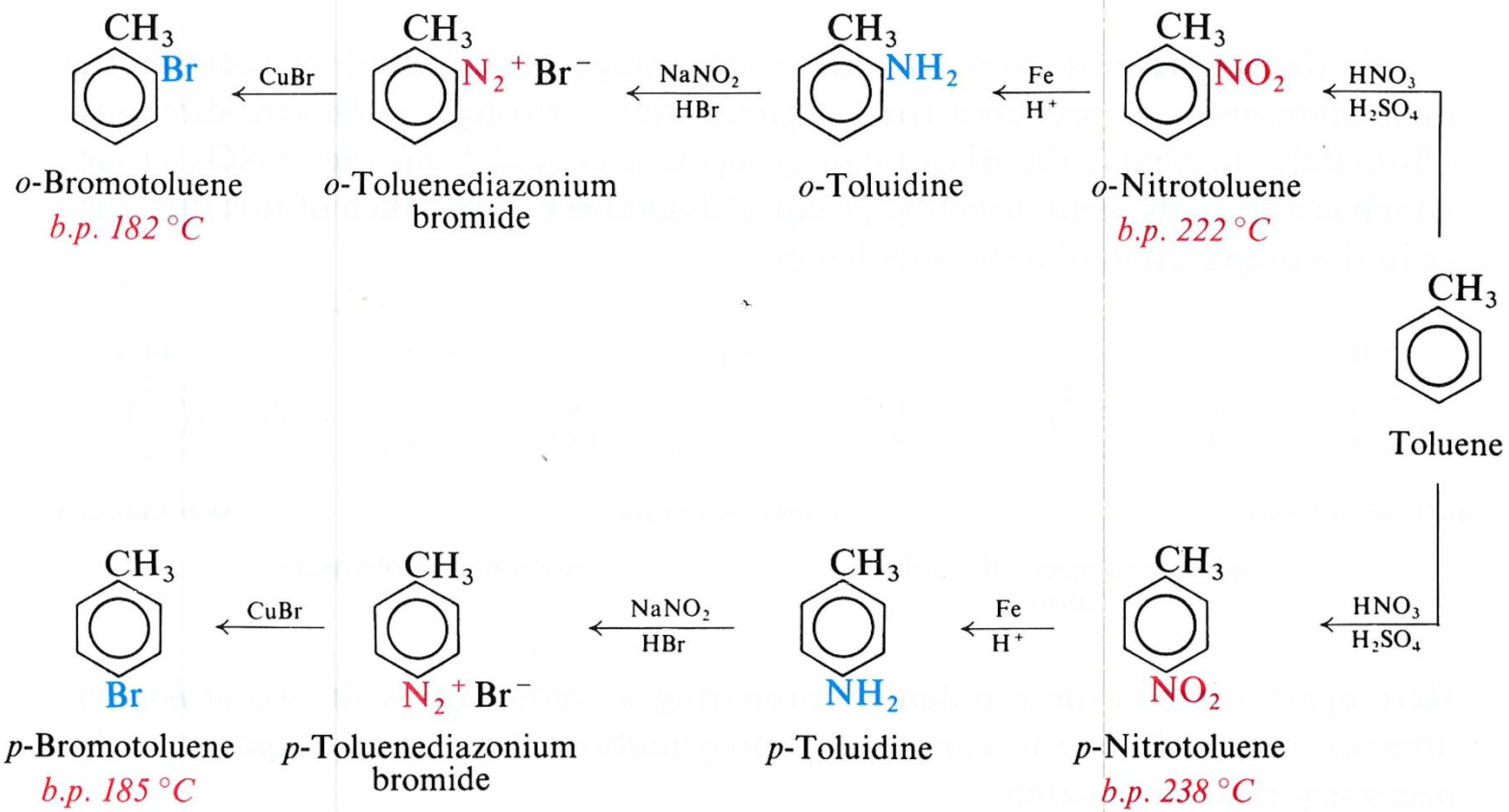
Benzenediazonium chloride

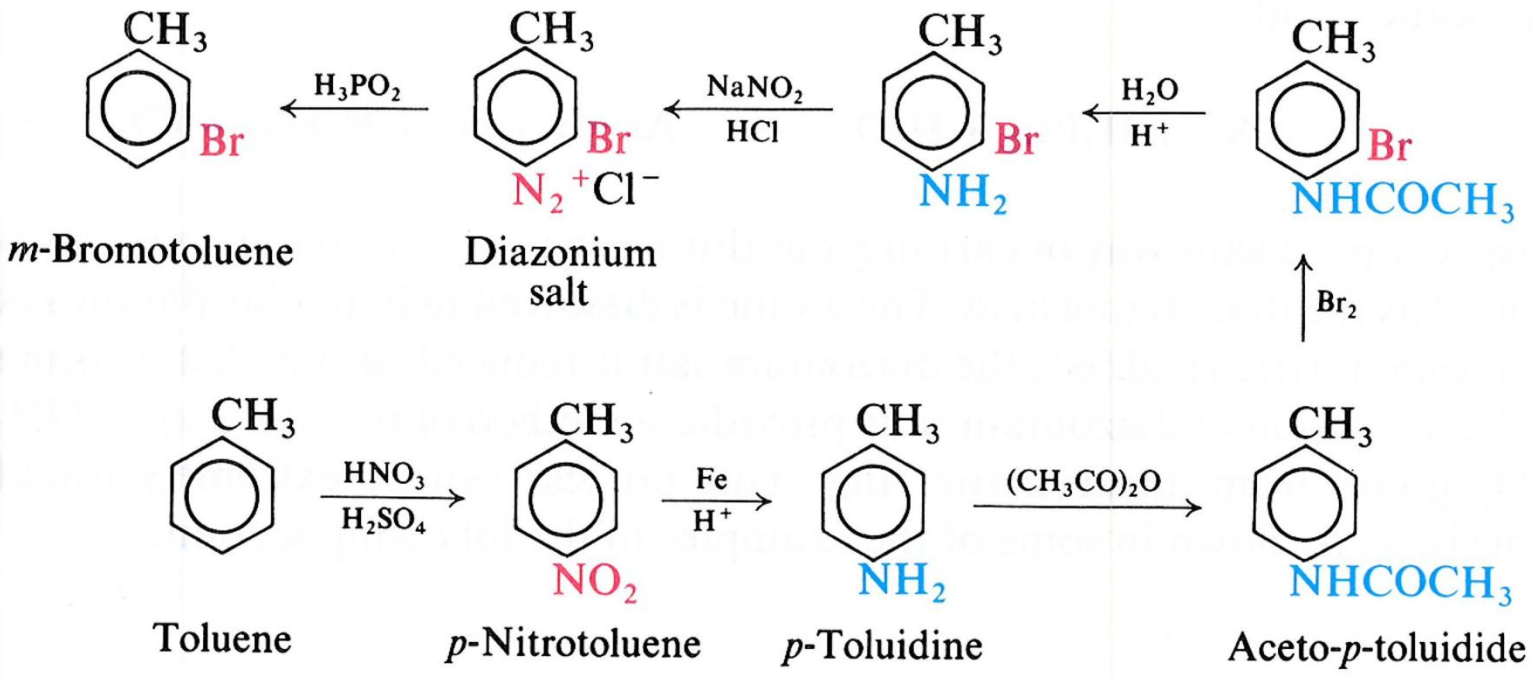
Phenol

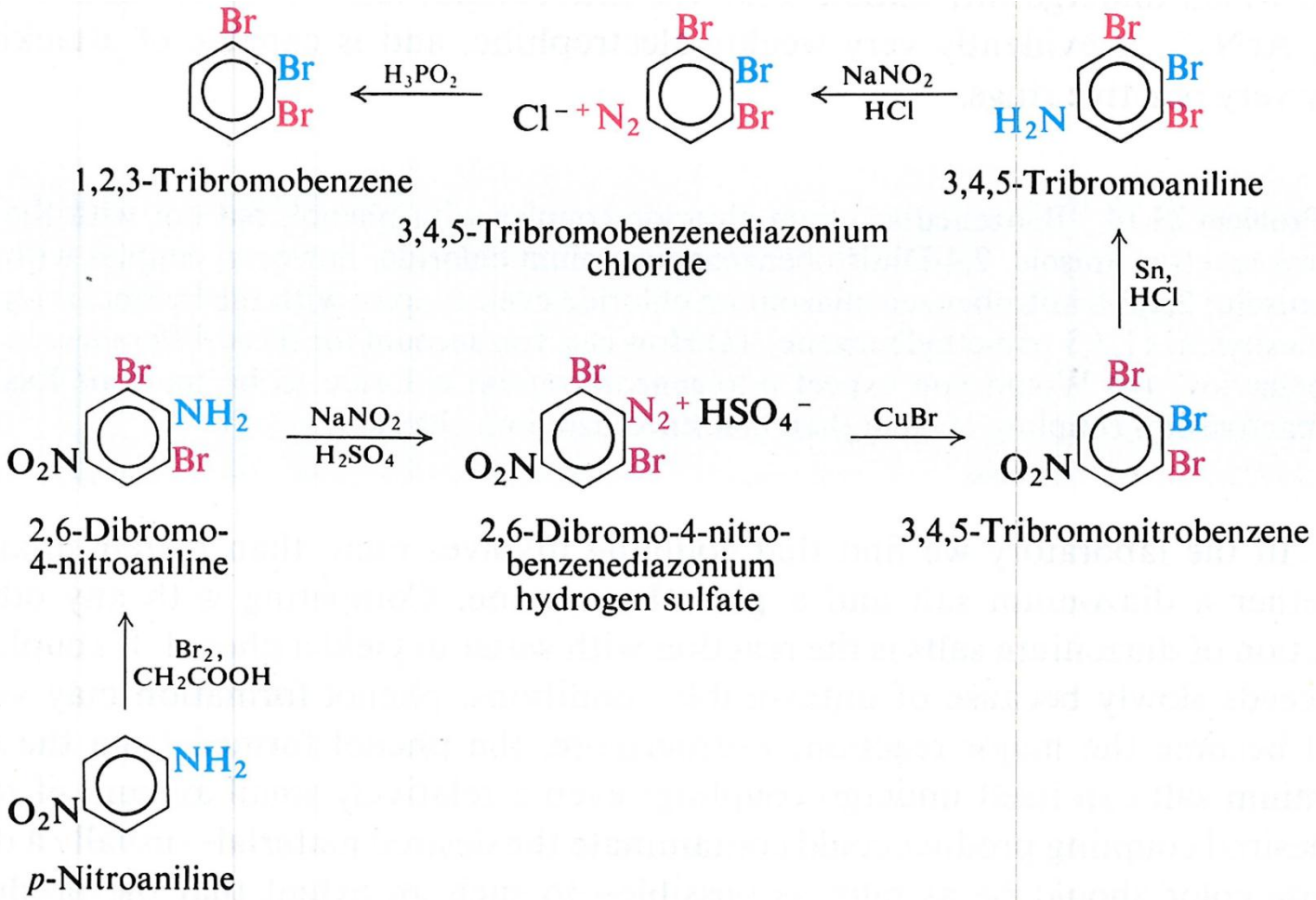
p-Hydroxyazobenzene
p-(Phenylazo)phenol


ArH
ArNO2
ArNH2
Ar—N2+
Ar—F
Ar—Cl
Ar—Br
Ar—I
Ar—CN
Ar—COOH
Ar—OH
Ar—H

Syntheses using diazonium salts




CH3
Br
H3PO2
CH3
Br
N2+Cl−
NaNO2
HCl
CH3
Br
NH2
H2O
H+
CH3
Br
NHCOCH3
Br2
m-Bromotoluene
Diazonium salt
CH3
HNO3
H2SO4
CH3
NO2
Fe
H+
CH3
NH2
(CH3CO)2O
CH3
NHCOCH3
Toluene
p-Nitrotoluene
p-Toluidine
Aceto-p-toluidide


Br
Br
Br
H_3PO_2
1,2,3-Tribromobenzene
$Cl^- {}^+N_2$
$NaNO_2$
HCl
H_2N
3,4,5-Tribromoaniline
3,4,5-Tribromobenzenediazonium chloride
Sn, HCl
O_2N
NH_2
2,6-Dibromo-4-nitroaniline
$NaNO_2$
H_2SO_4
$N_2^+ HSO_4^-$
2,6-Dibromo-4-nitrobenzenediazonium hydrogen sulfate
CuBr
3,4,5-Tribromonitrobenzene
Br_2, CH_2COOH
p-Nitroaniline