Amines

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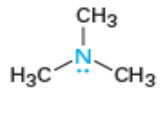
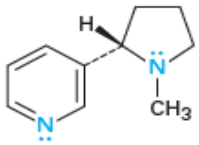
Amines are organic derivatives of ammonia in the same way that alcohols and ethers are organic derivatives of water. Like ammonia, amines contain a nitrogen atom with a lone pair of electrons, making amines both basic and nucleophilic. We'll soon see, in fact, that most of the chemistry of amines depends on the presence of this lone pair of electrons.

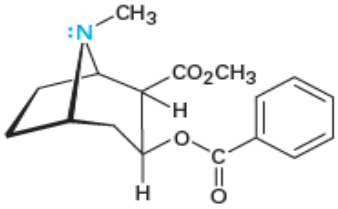
Amines occur widely in all living organisms. Trimethylamine, for instance, occurs in animal tissues and is partially responsible for the distinctive odor of fish; nicotine is found in tobacco; and cocaine is a stimulant found in the leaves of the South American coca bush. In addition, amino acids are the building blocks from which all proteins are made, and cyclic amine bases are constituents of nucleic acids.



Trimethylamine



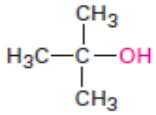
Nicotine



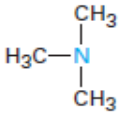
Cocaine

Naming Amines

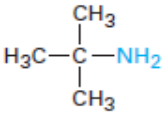
Amines can be either alkyl-substituted (**alkylamines**) or aryl-substituted (**arylamines**). Although much of the chemistry of the two classes is similar, there are also substantial differences. Amines are classified as **primary (RNH_2), secondary (R_2NH), or tertiary (R_3N),** depending on the number of organic substituents attached to nitrogen. Thus, methylamine (CH3NH2) is a primary amine, dimethylamine [$(CH_3)_2NH$] is a secondary amine, and trimethylamine [$(CH_3)_3N$] is a tertiary amine. Note that this usage of the terms ***primary, secondary,*** and ***tertiary*** differs from our previous usage. When we speak of a tertiary alcohol or alkyl halide, we refer to the degree of substitution at the alkyl carbon atom, but when we speak of a tertiary amine, we refer to the degree of substitution at the nitrogen atom.



tert-Butyl alcohol
(a tertiary alcohol)

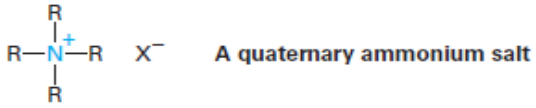


Trimethylamine
(a tertiary amine)



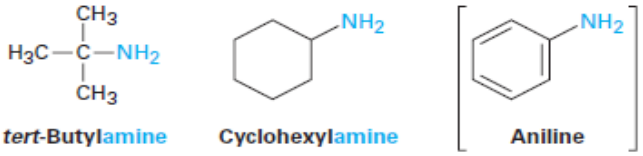
tert-Butylamine
(a primary amine)

Compounds containing a nitrogen atom with four attached groups also exist, but the nitrogen atom must carry a formal positive charge. Such compounds are called **quaternary ammonium salts**.



A quaternary ammonium salt

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. Phenylamine, $C_6H_5NH_2$, has the common name ***aniline.***

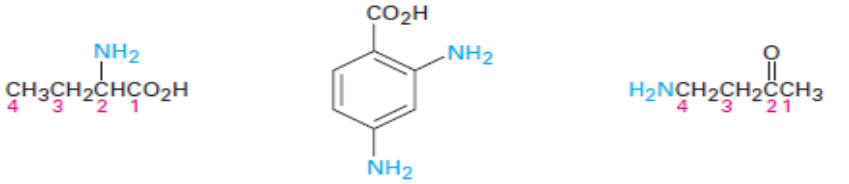


tert-Butylamine Cyclohexylamine Aniline

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

4,4-Dimethylcyclohexanamine 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

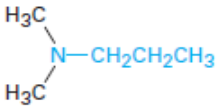


2-Aminobutanoic acid 2,4-Diaminobenzoic acid 4-Amino-2-butanone

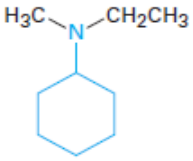
Symmetrical secondary and tertiary amines are named by adding the prefix ***di-*** or ***tri-*** to the alkyl group.

Diphenylamine Triethylamine

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



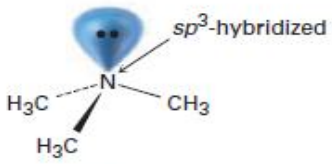
N,*N*-Dimethylpropylamine



N-Ethyl-*N*-methylcyclohexylamine

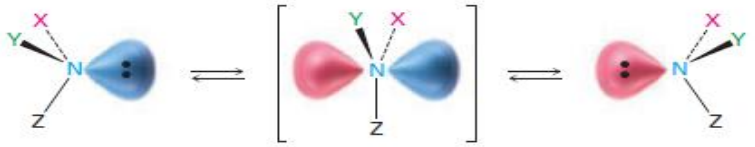
Structure and Properties of Amines

The bonding in alkylamines is similar to the bonding in ammonia. The nitrogen atom is sp^3-hybridized, with its 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

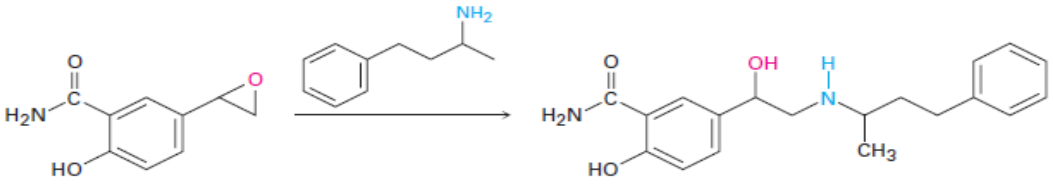
One consequence of tetrahedral geometry is that an amine with three different substituents on nitrogen is chiral. Unlike chiral carbon compounds, however, chiral amines can't usually be resolved because the two enantiomeric forms rapidly interconvert by a ***pyramidal inversion***, much as an alkyl halide inverts in an S_N2 reaction. Pyramidal inversion occurs by a momentary rehybridization of the nitrogen atom to planar, *sp*2 geometry, followed by rehybridization of the planar intermediate to tetrahedral, *sp*3 geometry **(Figure 24-1)**. The barrier to inversion is about 25 kJ/mol (6 kcal/mol), an amount only twice as large as the barrier to rotation about a C-C single bond.



sp^3-hybridized (tetrahedral) sp^2-hybridized (planar) sp^3-hybridized (tetrahedral)

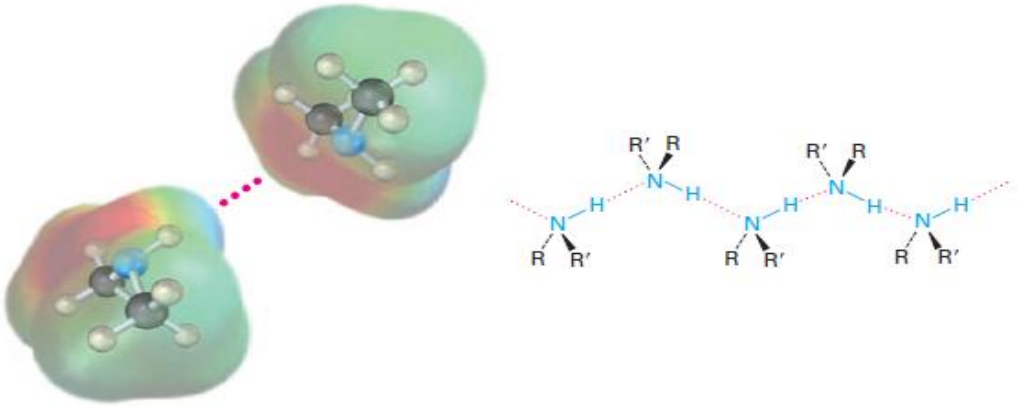
Figure 24-1 Pyramidal inversion rapidly interconverts the two mirror-image (enantiomeric) forms of an amine.

Alkylamines have a variety of applications in the chemical industry as starting materials for the preparation of insecticides and pharmaceuticals. **Labetalol**, for instance, a so-called *b*-blocker used for the treatment of high blood pressure, is prepared by S_N2 reaction of an epoxide with a primary amine. The substance marketed for drug use is a mixture of all four possible stereoisomers, but the biological activity results primarily from the (*R*,*R*) isomer.



Labetalol

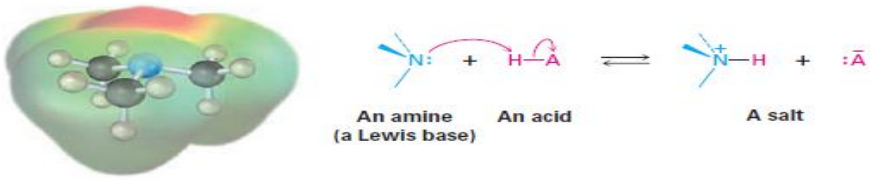
Like alcohols, amines with fewer than five carbon atoms are generally water-soluble. Also like alcohols, primary and secondary amines form hydrogen bonds and are highly associated. As a result, amines have higher boiling points than alkanes of similar molecular weight. Diethylamine (MW=73 amu) boils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



One other characteristic of amines is their odor. Low-molecular-weight amines such as trimethylamine have a distinctive fishlike aroma, while diamines such as cadaverine (1,5-pentanediamine) and putrescine (1,4-butanediamine) have the appalling odors you might expect from their common names. Both of these diamines arise from the decomposition of proteins.

Basicity of Amines

The chemistry of amines is dominated by the lone pair of electrons on nitrogen, which makes amines both basic and nucleophilic. They react with acids to form acid–base salts, and they react with electrophiles in many of the polar reactions seen in past chapters. Note in the following electrostatic potential map of trimethylamine how the negative (red) region corresponds to the lone pair of electrons on nitrogen.



Amines are much stronger bases than alcohols and ethers, their oxygen containing analogs. When an amine is dissolved in water, equilibrium is established in which water acts as an acid

and transfers a proton to the amine. Just as the acid strength of a carboxylic acid can be measured by defining an acidity constant *K*a, 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.

For the reaction

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

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

$$pK_b = -\log K_b$$

In practice, *K*b values are not often used. Instead, the most convenient way to measure the basicity of an amine (RNH_2) is to look at the acidity of the corresponding ammonium ion (RNH_3^+).

For the reaction

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

$$K_a = \frac{[RNH_2]\,[H_3O^+]}{[RNH_3^+]}$$

so

$$K_a \cdot K_b = \left[\frac{[RNH_2]\,[H_3O^+]}{[RNH_3^+]}\right]\left[\frac{[RNH_3^+]\,[OH^-]}{[RNH_2]}\right]$$

$$= [H_3O^+]\,[OH^-] = K_w = 1.00 \times 10^{-14}$$

Thus

$$K_a = \frac{K_w}{K_b} \quad \text{and} \quad K_b = \frac{K_w}{K_a}$$

and

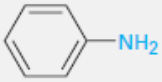
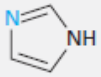
$$pK_a + pK_b = 14$$

These equations state that the K_b of an amine multiplied by the K_a of the corresponding ammonium ion is equal to K_w, the ion-product constant for water (1.00×10^{-14}). Thus, if we know K_a for an ammonium ion, we also know K_b for the corresponding amine base because $K_b = K_w/K_a$. The more acidic the ammonium ion, the less tightly the proton is held and the weaker the corresponding base. That is, a weaker base has an ammonium ion with a smaller pK_a and a stronger base has an ammonium ion with a larger pK_a.

Weaker base smaller pK_a for ammonium ion
Stronger base larger pK_a for ammonium ion

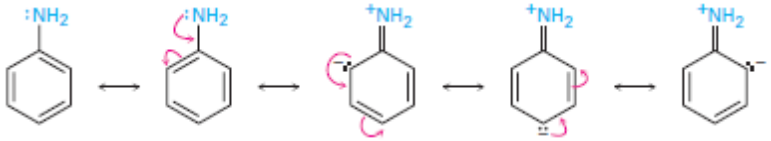
Table 24-1 lists p*K*a values of the ammonium ions from a variety of amines and indicates that there is a substantial range of amine basicities. Most simple alkylamines are similar in their base strength, with pK_a's for their ammonium ions in the narrow range 10 to 11. Arylamines, however, are considerably less basic than alkylamines, as are the heterocyclic amines pyridine and pyrrole.

TABLE 24-1 Basicity of Some Common Amines

Name	Structure	pK_a of ammonium ion
Ammonia	NH_3	9.26
Primary alkylamine		
Methylamine	CH_3NH_2	10.64
Ethylamine	$CH_3CH_2NH_2$	10.75
Secondary alkylamine		
Diethylamine	$(CH_3CH_2)_2NH$	10.98
Pyrrolidine		11.27
Tertiary alkylamine		
Triethylamine	$(CH_3CH_2)_3N$	10.76
Arylamine		
Aniline		4.63
Heterocyclic amine		
Pyridine		5.25
Pyrimidine		1.3
Pyrrole		0.4
Imidazole		6.95

Basicity of Arylamines

Arylamines are generally less basic than alkylamines. Anilinium ion has p*K*a=4.63, for instance, whereas methylammonium ion has p*K*a=10.64. Arylamines are less basic than alkylamines because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic ring's *p* electron system and are less available for bonding to H1. In resonance terms, arylamines are stabilized relative to alkylamines because of their five resonance forms.



Much of the resonance stabilization is lost on protonation, however, so the energy difference between protonated and non-protonated forms is higher for arylamines than it is for alkylamines. As a result, arylamines are less basic. **Figure 24-3** illustrates this difference.

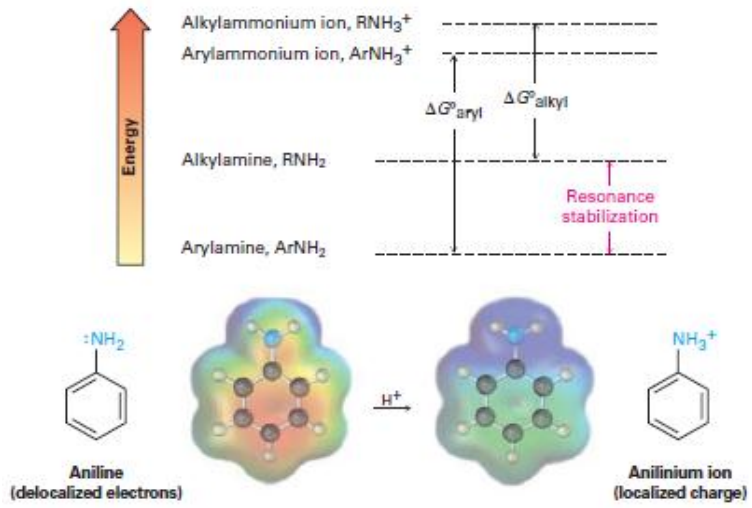


Figure 24-3 Arylamines have a larger positive $\Delta G°$ for protonation and are therefore less basic than alkylamines, primarily because of resonance stabilization of the ground state. Electrostatic potential maps show that lone-pair electron density is delocalized in the amine but the charge is localized in the corresponding ammonium ion.

Substituted arylamines can be either more basic or less basic than aniline, depending on the substituent. Electron-donating substituents, such as $-CH_3$, $-NH_2$, and $-OCH_3$, which increase the reactivity of an aromatic ring toward electrophilic substitution, also increase the basicity of the corresponding arylamine. Electron-withdrawing substituents, such as -Cl, $-NO_2$ and -CN, which decrease ring reactivity toward electrophilic substitution, also decrease arylamine basicity. **Table 24-2** considers only *p*-substituted anilines, but similar trends are observed for ortho and meta derivatives.

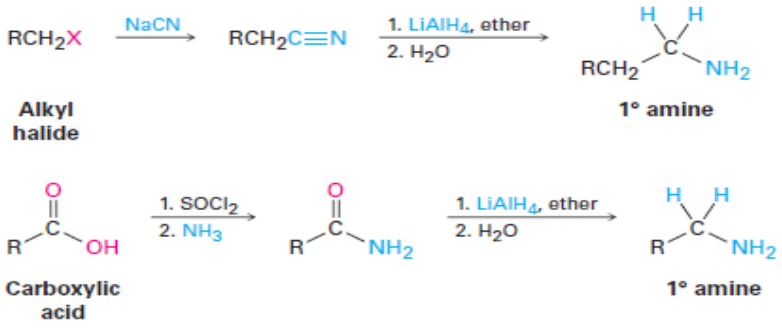
TABLE 24-2 Base Strength of Some *p*-Substituted Anilines

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

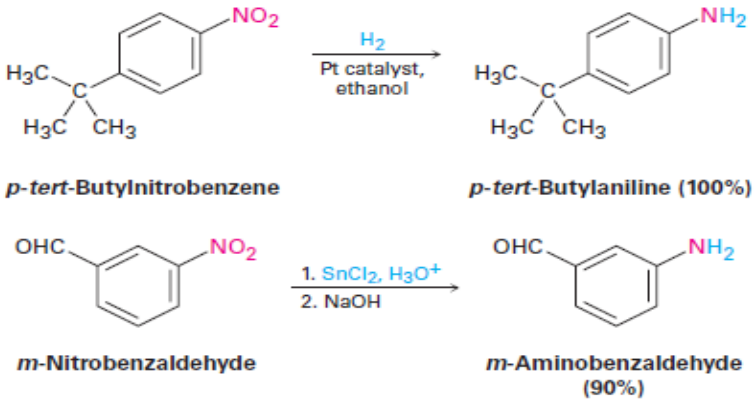
Synthesis of Amines

Reduction of Nitriles, Amides and Nitro Compounds

Amines can be prepared by reduction of nitriles and amides with $LiAlH_4$. The two-step sequence of S_N2 displacement with CN^- followed by reduction thus converts an alkyl halide into a primary alkylamine having an additional carbon atom. Amide reduction converts carboxylic acids and their derivatives into amines with the same number of carbon atoms.



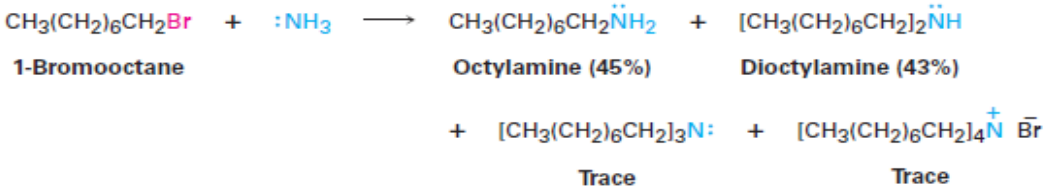
Arylamines are usually prepared by nitration of an aromatic starting material, followed by reduction of the nitro group. The reduction step can be carried out in many different ways, depending on the circumstances. Catalytic hydrogenation over platinum works well but is often incompatible with the presence 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.



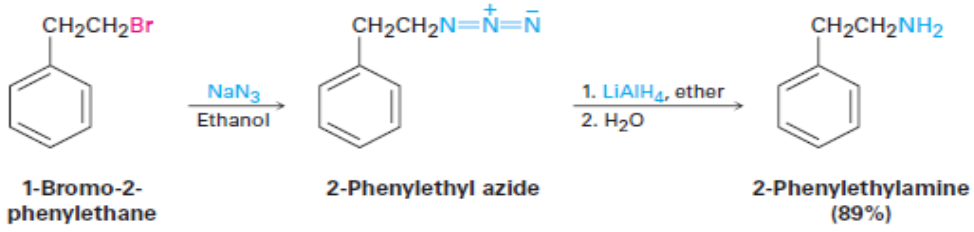
S_N2 Reactions of Alkyl Halides

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, $R_4N^+ X^-$.

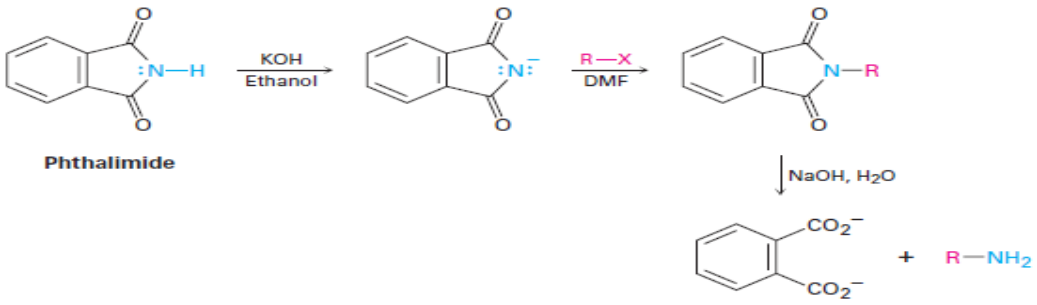
Unfortunately, these reactions don't stop cleanly after a single alkylation has occurred. Because ammonia and primary amines have similar reactivity, the initially formed mono alkylated substance often undergoes further reaction to yield a mixture of products. Even secondary and tertiary amines undergo further alkylation, although to a lesser extent. For example, treatment of 1-bromooctane with a twofold excess of ammonia leads to a mixture containing only 45% octylamine. A nearly equal amount of di octylamine is produced by double alkylation, along with smaller amounts of tri octylamine and tetra octylammonium bromide.



A better method for preparing primary amines is to use azide ion, $\mathbf{N_3^-}$, rather than ammonia, as the nucleophile for S_N2 reaction with a primary or secondary alkyl halide. The product is an alkyl azide, which is not nucleophilic, so over alkylation can't occur. Subsequent reduction of the alkyl azide with $LiAlH_4$ then leads to the desired primary amine. Although this method works well, low-molecular-weight alkyl azides are explosive and must be handled carefully.

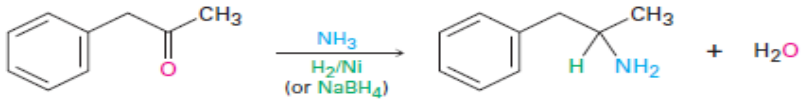


Another alternative for preparing a primary amine from an alkyl halide is the **Gabriel amine synthesis**, which uses a ***phthalimide*** alkylation. An **imide (-CONHCO-)** is similar to a β-keto ester in that the acidic N-H hydrogen is flanked by two carbonyl groups. Thus, imides are deprotonated by such bases as KOH, and the resultant anions are readily alkylated in a reaction similar to acetoacetic ester synthesis. Basic hydrolysis of the *N*-alkylated imide then yields a primary amine product. The imide hydrolysis step is analogous to the hydrolysis of an amide

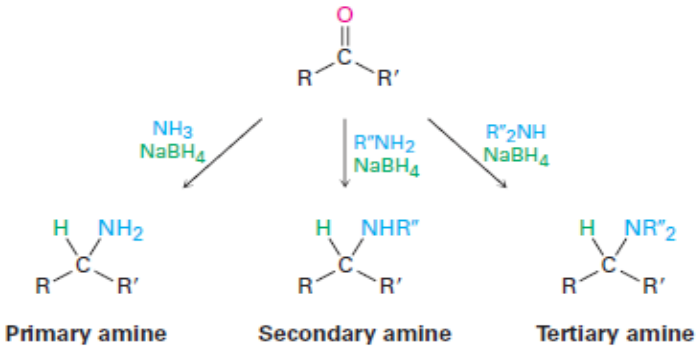


Reductive Amination of Aldehydes and Ketones

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, a process called **reductive amination**. For example, amphetamine, a central nervous system stimulant, is prepared commercially by reductive amination of phenyl-2-propanone with ammonia using hydrogen gas over a nickel catalyst as the reducing agent. In the laboratory, either $NaBH_4$ or the related $NaBH(OAc)_3$ is commonly used (OAc=acetate).

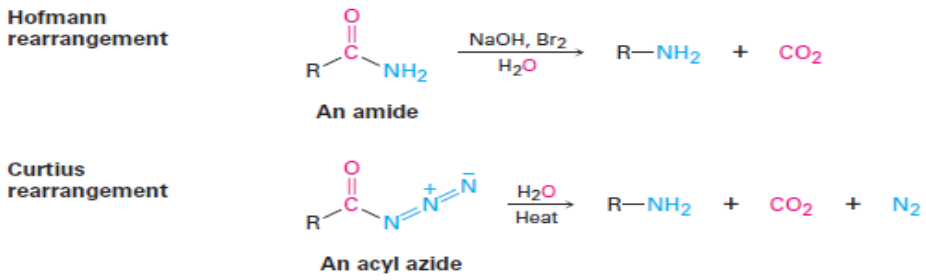


Ammonia, primary amines, and secondary amines can all be used in the reductive amination reaction, yielding primary, secondary, and tertiary amines, respectively.

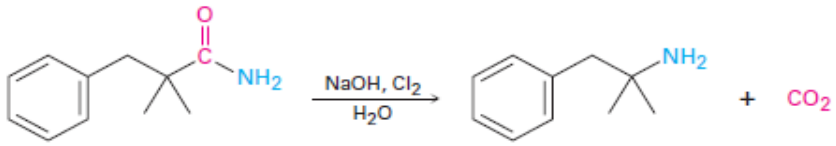


Hofmann and Curtius Rearrangements

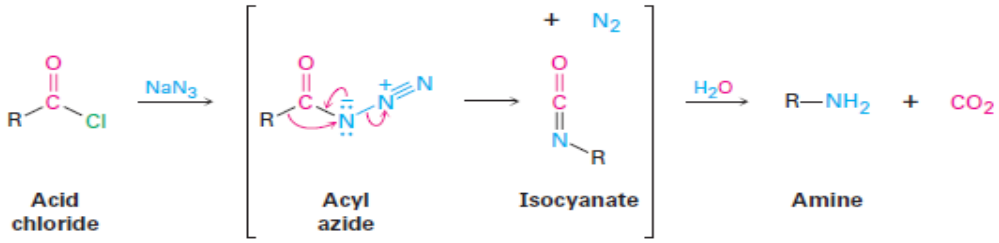
Carboxylic acid derivatives can be converted into primary amines with loss of one carbon atom by both **Hofmann rearrangement** and **Curtius rearrangement**. Although Hofmann rearrangement involves a primary amide and Curtius rearrangement involves an acyl azide, both proceed through similar mechanisms.



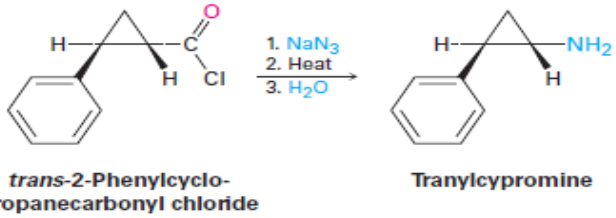
Hofmann rearrangement occurs when a primary amide, $RCONH_2$, is treated with Br_2 and base. Despite its mechanistic complexity, Hofmann rearrangement often gives high yields of both arylamines and alkylamines. For example, the appetite suppressant drug phentermine is prepared commercially by Hofmann rearrangement of a primary amide. Commonly known by the name Fen-Phen, the combination of phentermine with another appetite-suppressant, fenfluramine, is suspected of causing heart damage.



Curtius rearrangement, like 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.



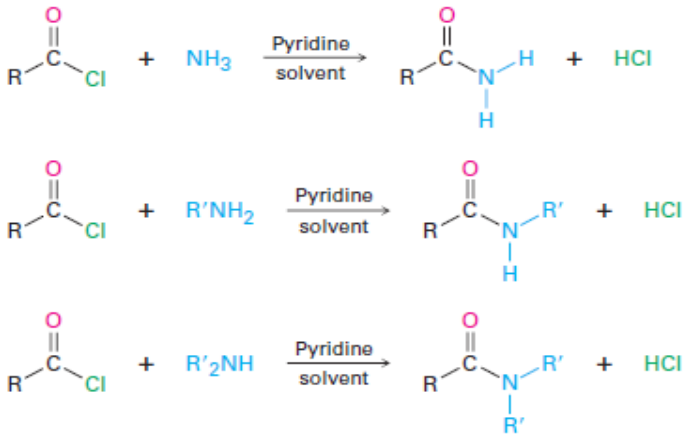
Also like Hofmann rearrangement, Curtius rearrangement is often used commercially. The antidepressant drug tranylcypromine, for instance, is made by Curtius rearrangement of 2-phenylcyclopropanecarbonyl chloride.



Reactions of Amines

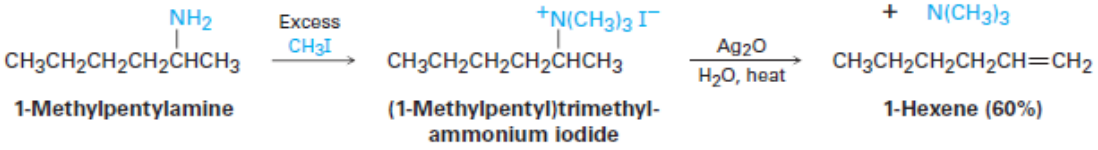
Alkylation and Acylation

Primary, secondary, and tertiary amines can be alkylated by reaction with a primary alkyl halide. Alkylations of primary and secondary amines are difficult to control and often give mixtures of products, but tertiary amines are cleanly alkylated to give quaternary ammonium salts. Primary and secondary (but not tertiary) amines can also be acylated by nucleophilic acyl substitution reaction with an acid chloride or an acid anhydride to yield an amide. Note that over acylation of the nitrogen does not occur because the amide product is much less nucleophilic and less reactive than the starting amine.

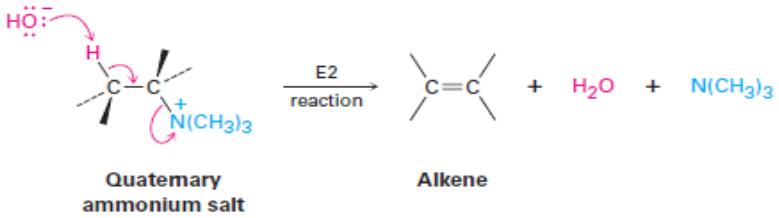


Hofmann Elimination

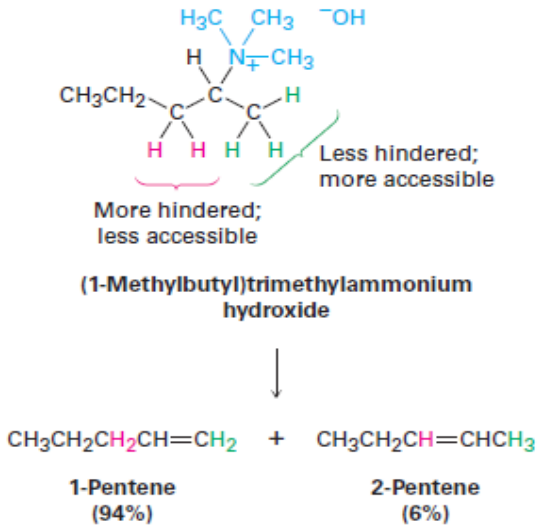
Like alcohols, amines can be converted into alkenes by an elimination reaction. But because an amide ion, NH_2^-, is such a poor leaving group, it must first be converted into a better leaving group. In the **Hofmann elimination reaction**, an amine is completely methylated by reaction with an excess 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. For example, 1-methylpentylamine is converted into 1-hexene.



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 E_2 reaction in which hydroxide ion removes a proton while the positively charged nitrogen atom leaves.



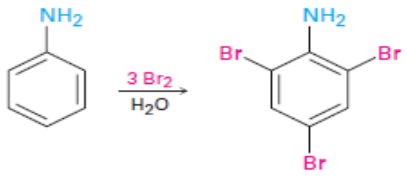
Unlike what happens in other E2 reactions, the major product of Hofmann elimination is the less highly substituted alkene rather than the more highly substituted one, as shown by the reaction of (1-methylbutyl) trimethyl ammonium hydroxide to give 1-pentene rather than the alternative 2-pentene. The reason for this non-Zaitsev result is probably steric. Because of the large size of the trialkylamine leaving group, the base must abstract hydrogen from the more accessible, least hindered position.



Reactions of Arylamines

Electrophilic Aromatic Substitution

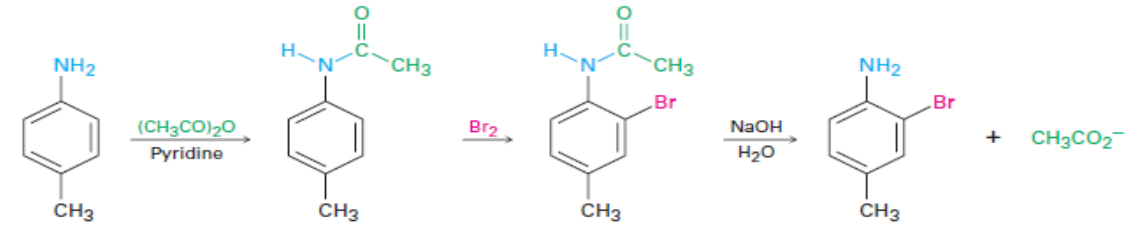
An amino group is strongly activating and ortho- and para-directing in electrophilic aromatic substitution reactions. This high reactivity of amino-substituted benzenes can be a drawback at times because it's often difficult to prevent poly substitution. Reaction of aniline with Br_2, for instance, takes place rapidly and yields the 2,4,6-tribrominated product. The amino group is so strongly activating that it's not possible to stop at the mono bromo stage.



Aniline **2,4,6-Tribromoaniline (100%)**

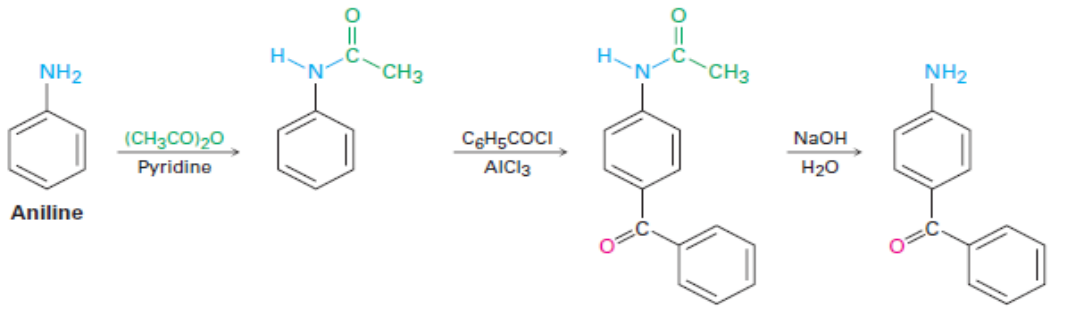
Another drawback to the use of amino-substituted benzenes in electrophilic aromatic substitution reactions is that Friedel–Crafts reactions are not successful. The amino group forms an acid–base complex with the $AlCl_3$ catalyst, which prevents further reaction. Both drawbacks can be overcome, however, by carrying out electrophilic aromatic substitution reactions on the corresponding amide rather than on the free amine.

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*-aryl amide occurs cleanly to give a mono bromo product, and hydrolysis of the amide with aqueous base then gives the free amine. For example, *p*-toluidine (4-methylaniline) can be acetylated, brominated, and hydrolyzed to yield 2-bromo-4-methylaniline. None of the 2,6-dibrominated product is obtained.



***p*-Toluidine** **2-Bromo-4-methyl-aniline (79%)**

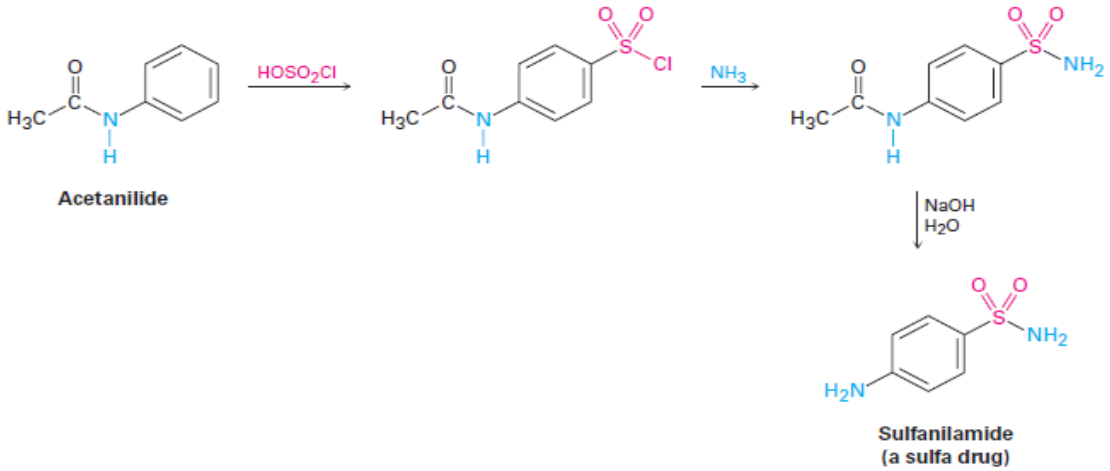
Friedel–Crafts alkylations and acylations of *N*-arylamides also proceed normally. For example, benzoylation of acetanilide (*N*-acetylaniline) under Friedel–Crafts conditions gives 4-aminobenzophenone in 80% yield after hydrolysis.



Aniline **4-Aminobenzophenone (80%)**

Modulating the reactivity of amino-substituted benzene by forming an amide is a useful trick that allows many kinds of electrophilic aromatic substitutions to be carried out that would otherwise be impossible. One example is the preparation of the sulfa drugs, such as sulfanilamide.

Sulfa drugs were among the first pharmaceutical agents to be used clinically against bacterial infection. Although they have largely been replaced today by safer and more powerful antibiotics, sulfa drugs are credited with saving the lives of thousands of wounded during World War II and is still prescribed for urinary tract infections. They are prepared by chlorosulfonation of acetanilide, followed by reaction of *p*-(*N*-acetylamino) benzenesulfonyl chloride with ammonia or some other amine to give a sulfonamide. Hydrolysis of the amide then yields the sulfa drug. Note that hydrolysis of the amide can be carried out in the presence of the sulfonamide group because sulfonamides hydrolyze very slowly.



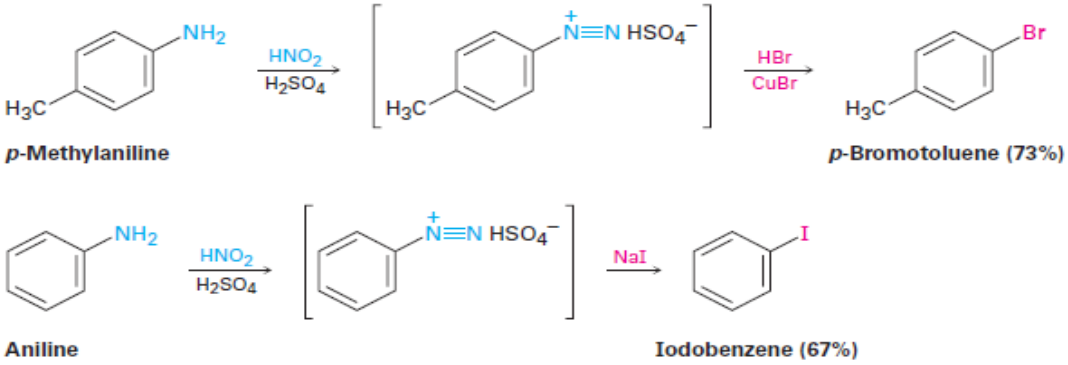
Diazonium Salts: The Sandmeyer Reaction

Primary arylamines react with nitrous acid, HNO_2, to yield stable ***arene diazonium salts***, $Ar—\dot{N}{\equiv}N\ X^-$, a process called a ***diazotization*** reaction. Alkylamines also react with nitrous acid, but the corresponding alkane diazonium products are so reactive they can't be isolated. Instead, they lose nitrogen instantly to yield carbocations. The analogous loss of N_2 from an arene diazonium ion to yield an aryl cation is disfavored by the instability of the cation.

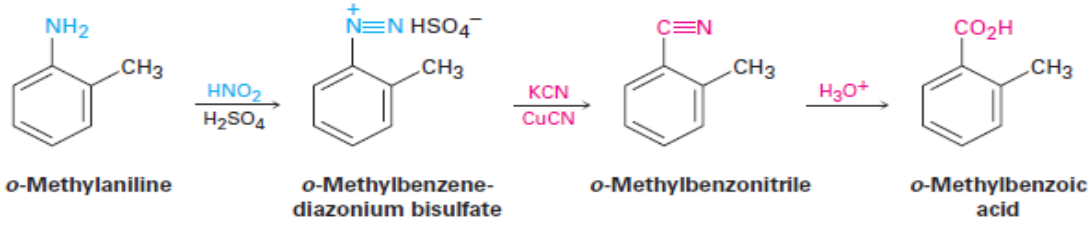
Arene diazonium salts are useful because the diazonio group (N_2) can be replaced by a nucleophile in a substitution reaction.

Many different nucleophiles—halide, hydride, cyanide, and hydroxide among others react with arene diazonium salts, yielding many different kinds of substituted benzenes. The overall sequence of (1) nitration, (2) reduction, (3) diazotization, and (4) nucleophilic substitution is perhaps the single most versatile method of aromatic substitution.

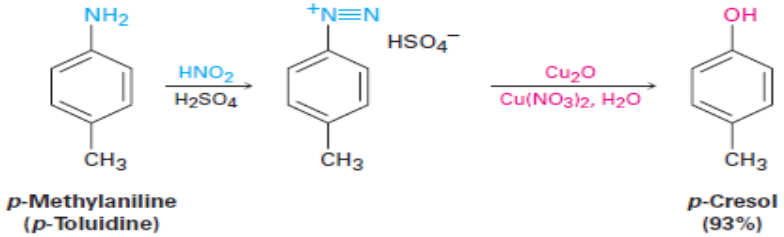
Aryl chlorides and bromides are prepared by reaction of an arene diazonium salt with the corresponding copper (I) halide, CuX, a process called the **Sandmeyer reaction**. Aryl iodides can be prepared by direct reaction with NaI without using a copper (I) salt. Yields generally fall between 60% and 80%.



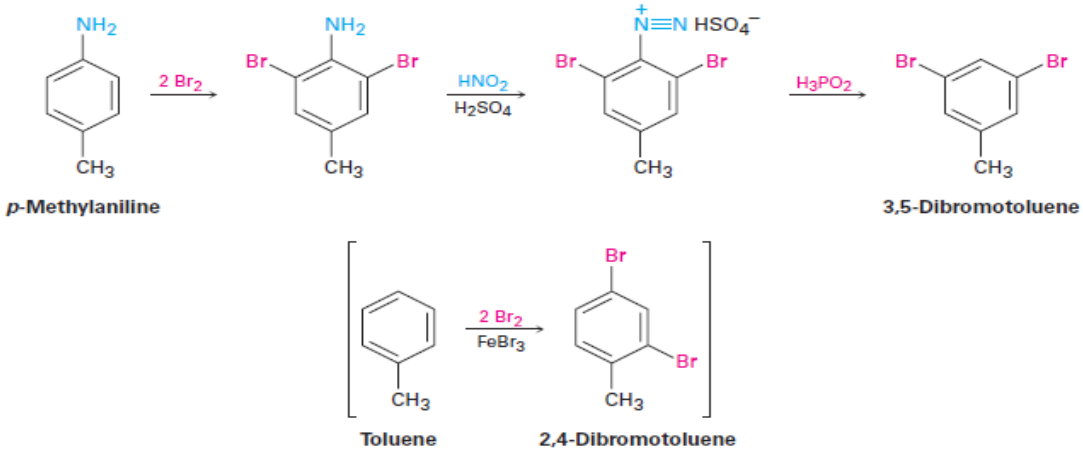
Similar treatment of an arene diazonium salt with CuCN yields the nitrile ArCN, which can then be further converted into other functional groups such as carboxyl. For example, Sandmeyer reaction of *o*-methyl benzene diazonium bisulfate with CuCN yields *o*-methyl benzonitrile, which can be hydrolyzed to give *o*-methylbenzoic acid. This product can't be prepared from *o*-xylene by the usual side-chain oxidation route because both methyl groups would be oxidized.



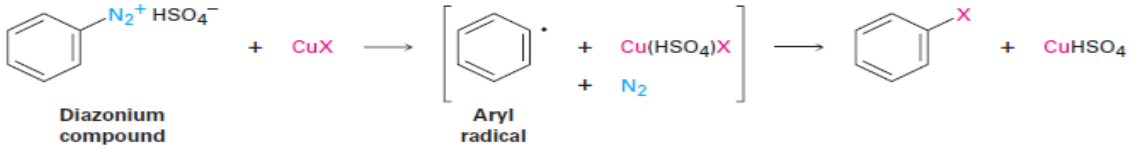
The diazonio group can also be replaced by -OH to yield a phenol and by -H to yield an arene. A phenol is prepared by reaction of the arene diazonium salt with copper (I) oxide in an aqueous solution of copper(II) nitrate, a reaction that is especially useful because few other general methods exist for introducing an -OH group onto an aromatic ring.



Reduction of a diazonium salt to give an arene occurs on treatment with hypo phosphorous acid, H_3PO_2. This reaction is used primarily when there is a need for temporarily introducing an amino substituent onto a ring to take advantage of its directing effect. Suppose, for instance, that you needed to make 3,5-dibromotoluene. This product can't be made by direct bromination of toluene because reaction would occur at positions 2 and 4. Starting with *p*-methyl aniline (*p*-toluidine), however, dibromination occurs ortho to the strongly directing amino substituent, and diazotization followed by treatment with H_3PO_2 to remove the amino group yields the desired product.

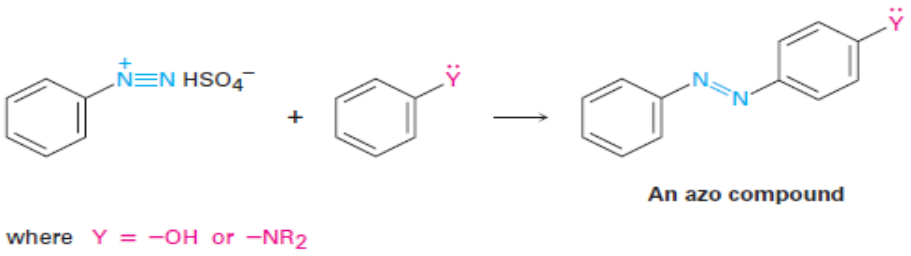


Mechanistically, these diazonio replacement reactions occur through radical rather than polar pathways. In the presence of a copper(I) compound, for instance, it's thought that the arene diazonium ion is first converted to an aryl radical plus copper(II), followed by subsequent reaction to give product plus regenerated copper(I) catalyst.

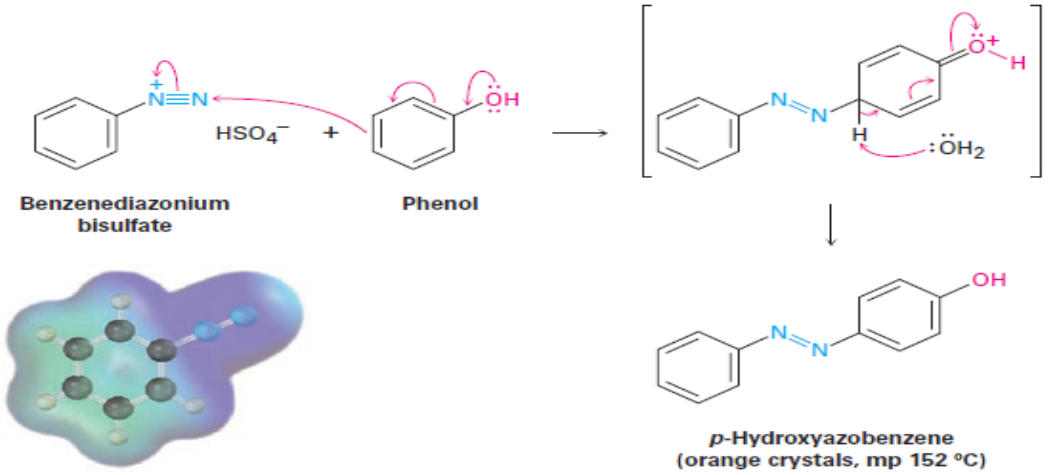


Diazonium Coupling Reactions

Arene diazonium salts undergo a coupling reaction with activated aromatic rings such as phenols and arylamines to yield brightly colored **azo compounds**,



Diazonium coupling reactions are typical electrophilic aromatic substitutions in which the positively charged diazonium ion is the electrophile that reacts with the electron-rich ring of a phenol or arylamine. Reaction usually occurs at the para position.



Azo-coupled products are widely used as dyes for textiles because their extended conjugated π electron system causes them to absorb in the visible region of the electromagnetic spectrum. *p*-(Dimethyl amino)-azobenzene, for instance, is a bright yellow compound that was at one time used as a coloring agent in margarine.