Amines: Synthesis and Reactions

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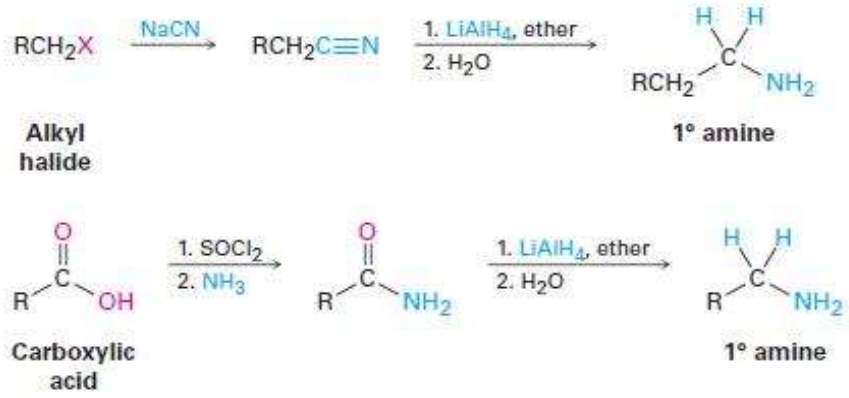
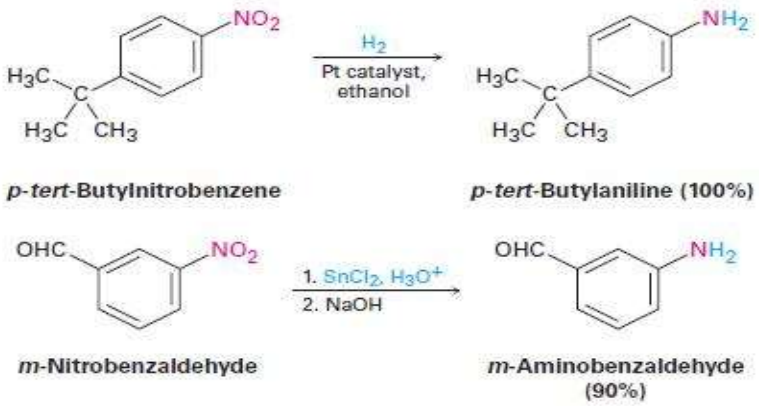
Synthesis of Amines

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.

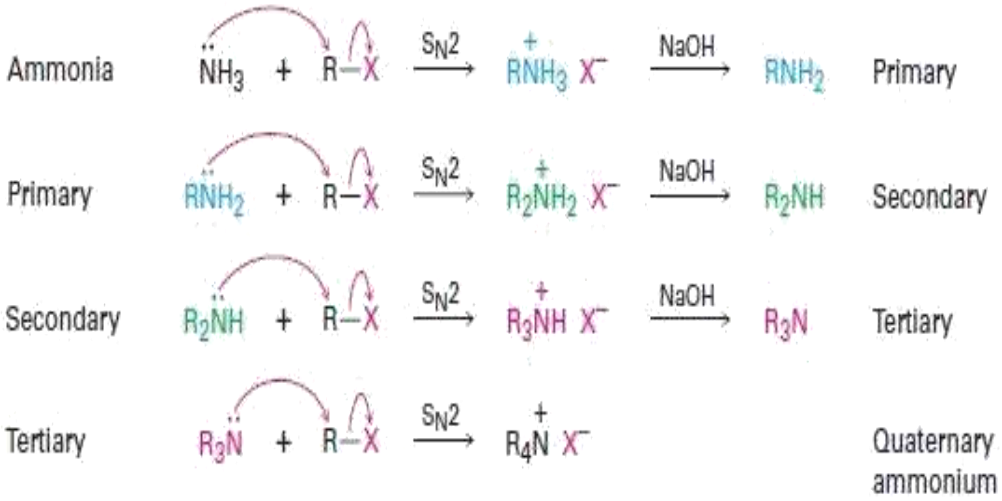


Arylamines are usually prepared by nitration of an aromatic starting material, followed by reduction of the nitro group. The reduction step can be carried out in many different ways, depending on the circumstances. Catalytic hydrogenation over platinum works well but is often incompatible with the presence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

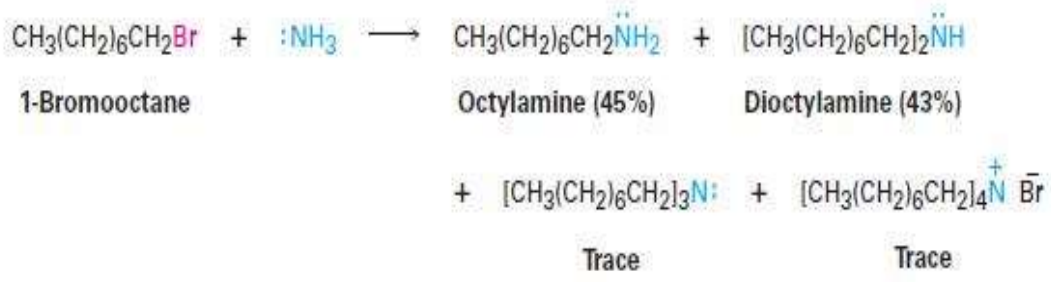


S_N2 Reactions of Alkyl Halides

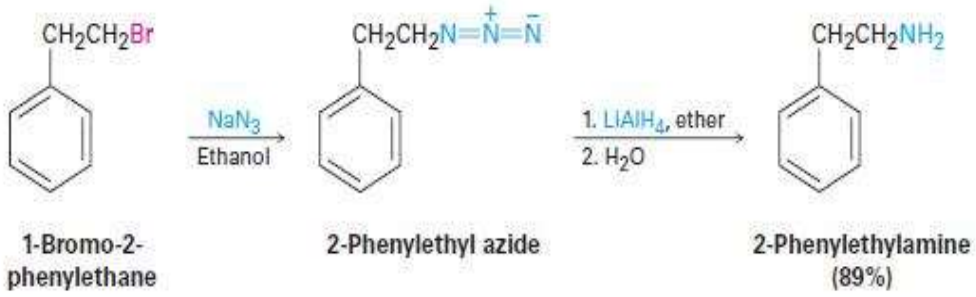
Ammonia and other amines are good nucleophiles in S_N2 reactions. As a result, the simplest method of alkylamine synthesis is by S_N2 alkylation of ammonia or an alkylamine with an alkyl halide. If ammonia is used, a primary amine results; if a primary amine is used, a secondary amine results; and so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



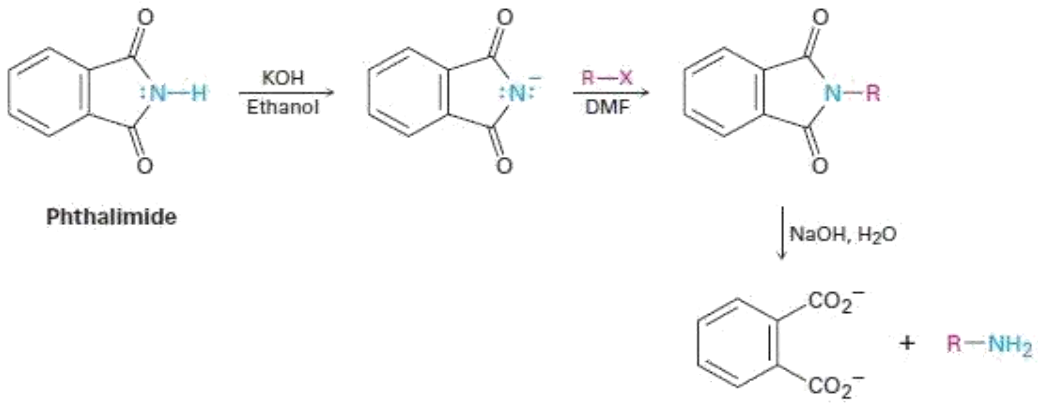
Unfortunately, these reactionshasdon'toccurred.Becausestop cle ammonia and primary amines have similar reactivity, the initially formed mono alkylated substance often undergoes further reaction to yield a mixture of products. Even secondary and tertiary amines undergo further alkylation, although to 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 occurntreduction.Subseque 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.

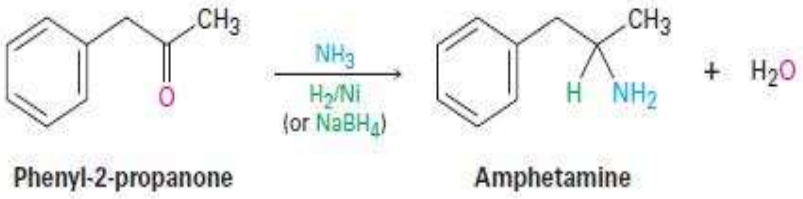


Another alternative for preparing a primary amine from an alkyl halide is the **Gabriel amine synthesis**, which uses a ***phthalimide*** alkylation. An **imide (-CONHCO-)** is similar to a β-keto ester in that the acidic N-H hydrogen is flanked by two carbonyl groups. Thus, imides are deprotonated by 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.



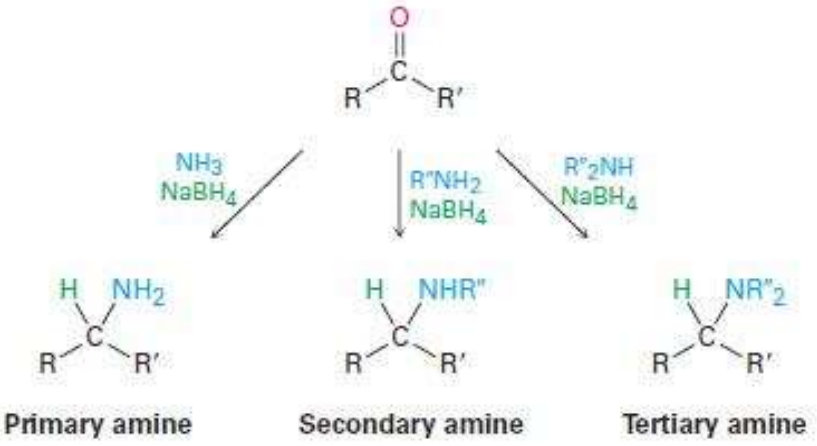
Reductive Amination of Aldehydes and Ketones

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).



Phenyl-2-propanone Amphetamine

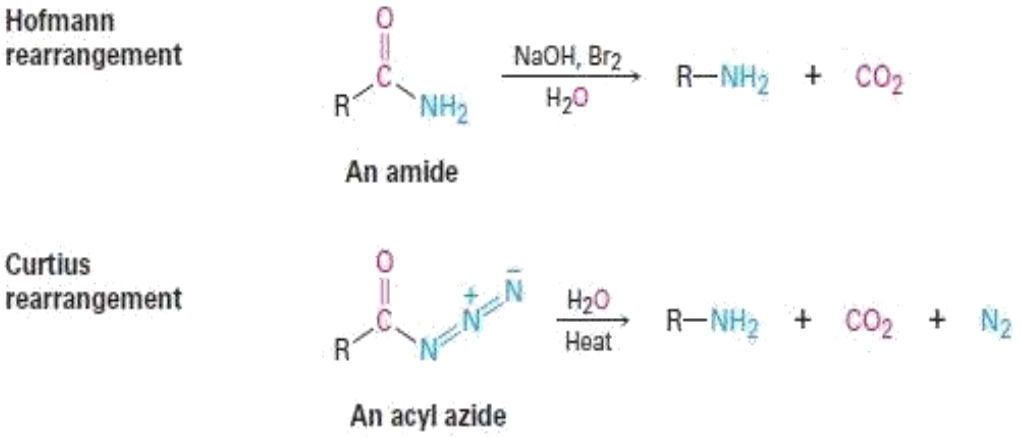
Ammonia, primary amines, and secondary amines can all be used in the reductive amination reaction, yielding primary, secondary, and tertiary amines, respectively.



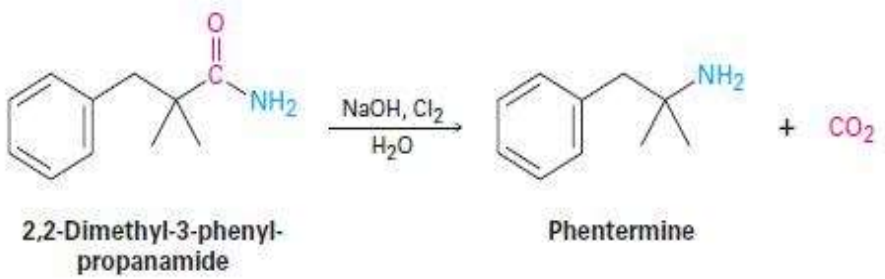
Primary amine Secondary amine Tertiary amine

Hofmann and Curtius Rearrangements

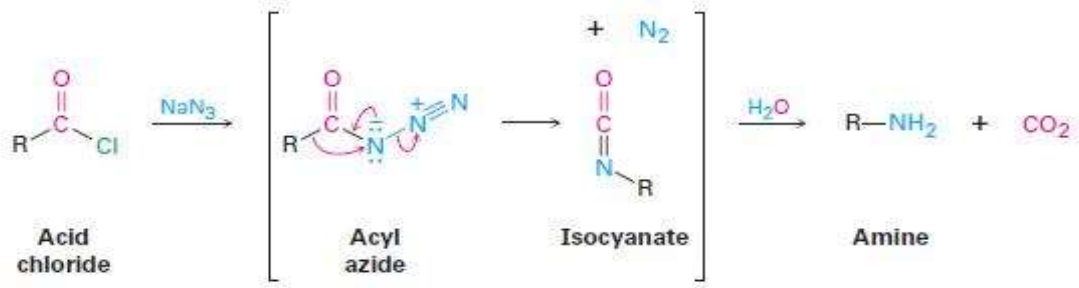
Carboxylic acid derivatives can be converted into primary amines with loss of one carbon atom by both **Hofmann rearrangement** and **Curtius rearrangement**. Although Hofmann rearrangement involves a primary amide and Curtius rearrangement involves an acyl azide, both proceed through similar mechanisms.



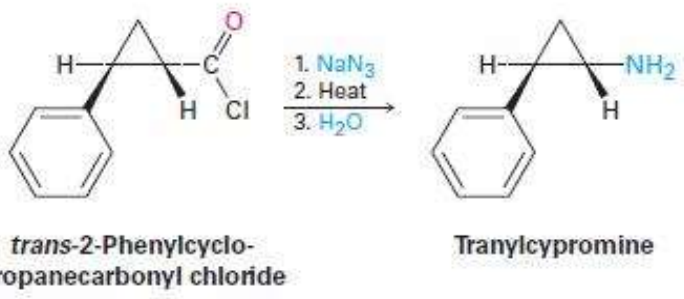
Hofmann rearrangement occurs when a primary amide, $RCONH_2$, is treated with Br_2 and base. Despite its mechanistic complexity, Hofmann rearrangement often gives high yields of both arylamines and alkylamines. For example, the appetite suppressant drug phentermine is prepared commercially by Hofmann 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.



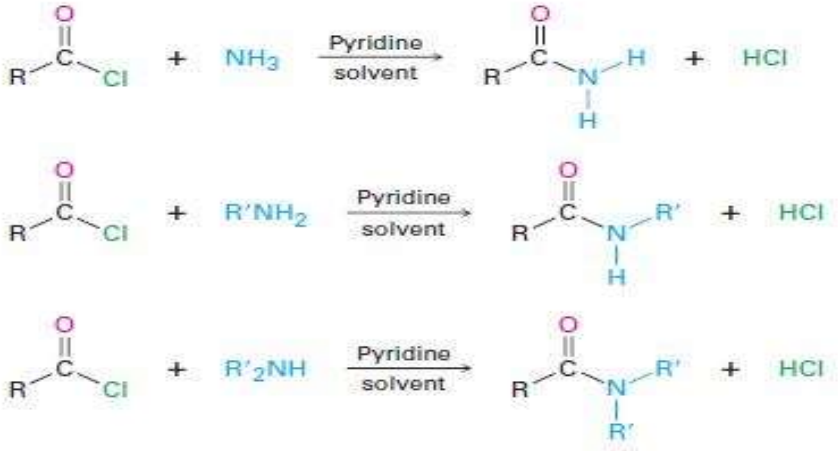
Also like Hofmann rearrangement, Curtius rearrangement is often used commercially. The antidepressant drug tranylcypromine, for instance, is made by Curtius rearrangement of 2-phenylcyclopropanecarbonyl chloride.



Reactions of Amines

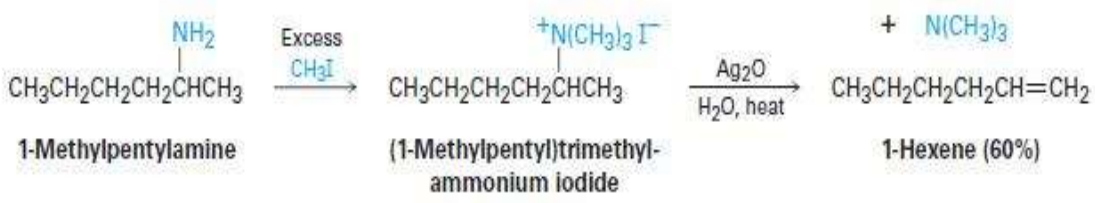
Alkylation and Acylation

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.

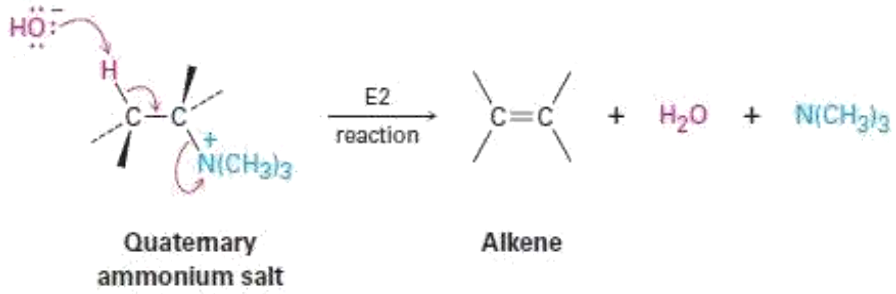


Hofmann Elimination

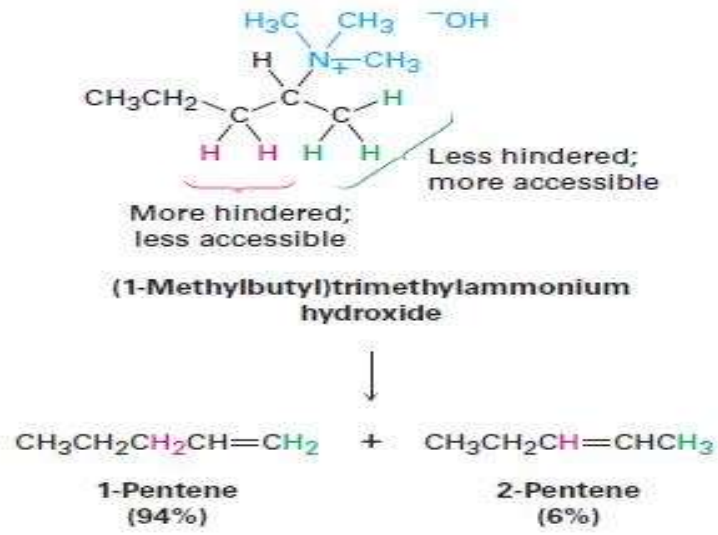
Like alcohols, amines can be converted into alkenes by an elimination reaction. But because an amide ion, NH_2^-, is such a poor leaving group, it must first be converted into a better leaving group. In the **Hofmann elimination reaction**, an amine is completely methylated by reaction with an excess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

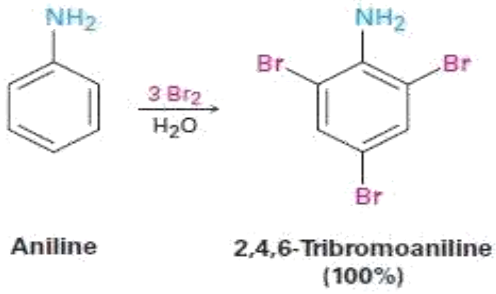


Unlike what happens in other E2 reactions, the major product of Hofmann elimination is the less highly substituted alkene rather than the more highly substituted one, as shown by the reaction of (1-methylbutyl) trimethyl ammonium hydroxide to give 1-pentene rather than the alternative 2-pentene. The 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

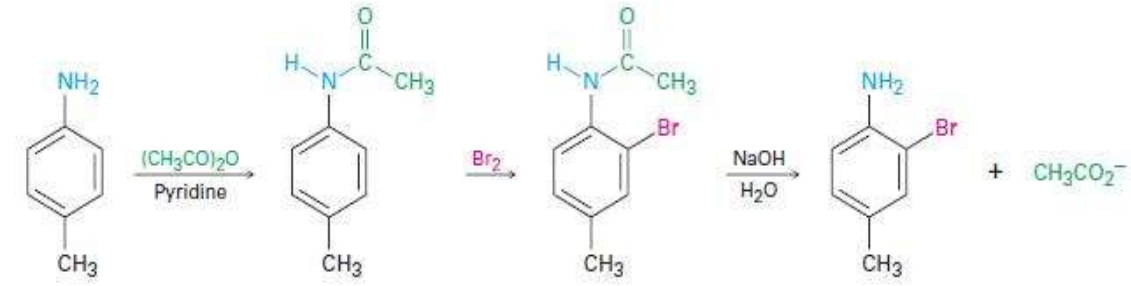
An amino group is strongly activating and ortho- and para-directing in electrophilic aromatic substitution reactions. This high reactivity of amino-substituted benzenes can be a drawback at times because it'stopreventoftenpolysubstitutiondifficult.Reactionofaniline with Br_2, for instance, takes place rapidly and yields the 2,4,6-tribrominated product. The amino group is so strongly activatingssibletostop at thethatmonobromoit'sstage.



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

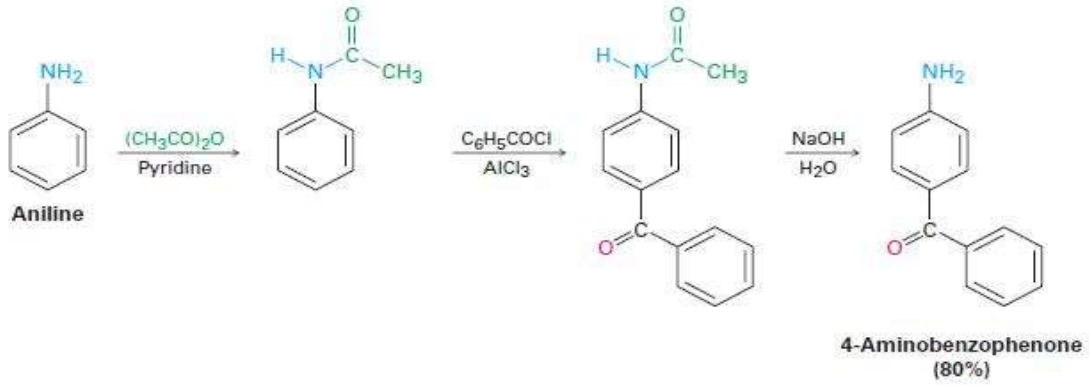
Another drawback to the use of amino-substituted benzenes in electrophilic aromatic substitution reactions is that Friedel–Crafts reactions are not successful. The amino group forms an acid–base complex with the $AlCl_3$ catalyst, which prevents further reaction. Both drawbacks can be overcome, however,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



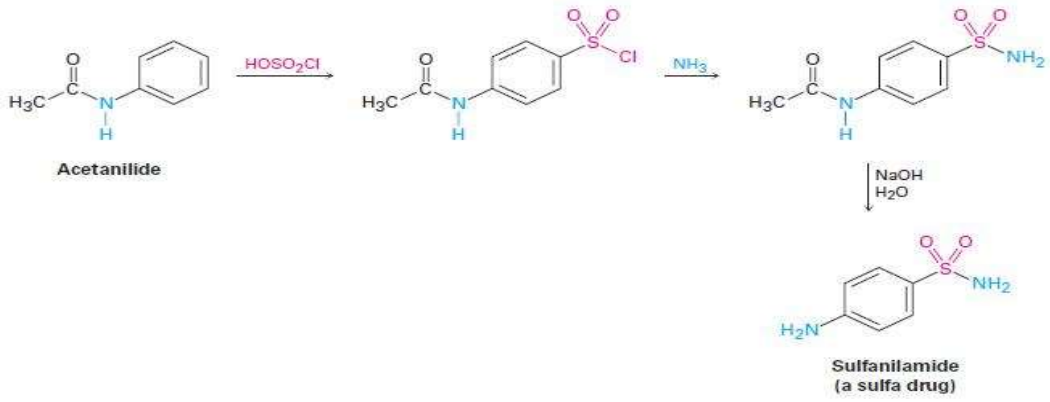
***p*-Toluidine** **2-Bromo-4-methyl-aniline (79%)**

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.



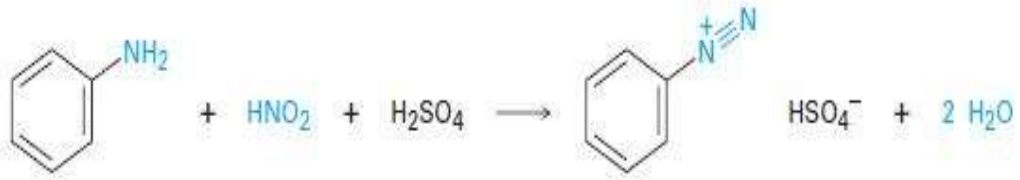
Modulating the reactivity of amino-substituted benzene by forming an amide is a useful trick that allows many kinds of electrophilic aromatic substitutions to be carried out that would otherwise be impossible. One example is the preparation of the sulfa drugs, such as sulfanilamide.

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.

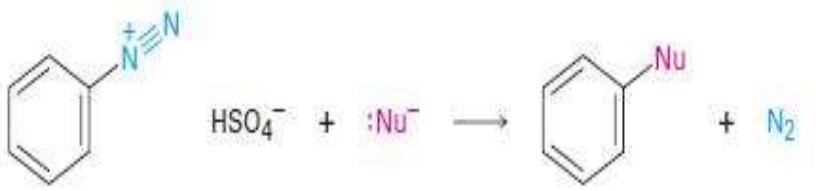


Diazonium Salts: The Sandmeyer Reaction

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 sobe isolatedreactive. 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.

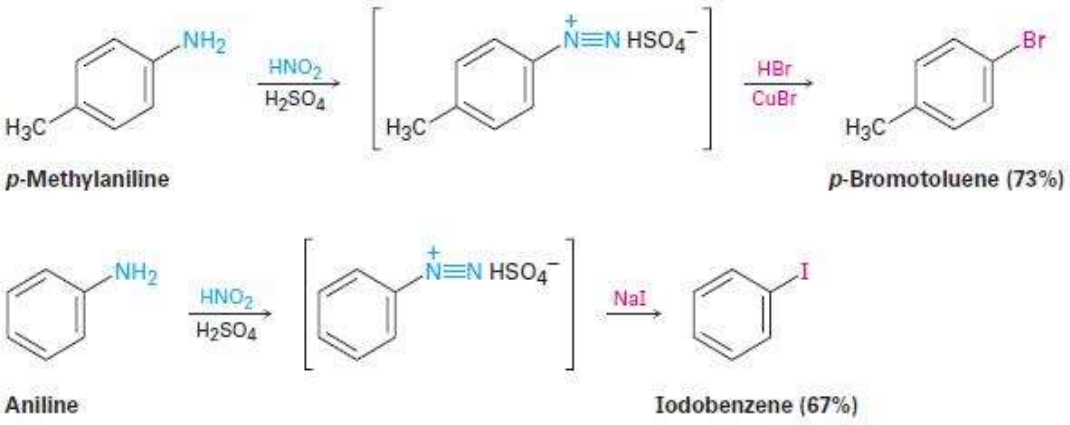


Arene diazonium salts are useful because the diazonio group (N_2) can be replaced by a nucleophile in a substitution reaction.

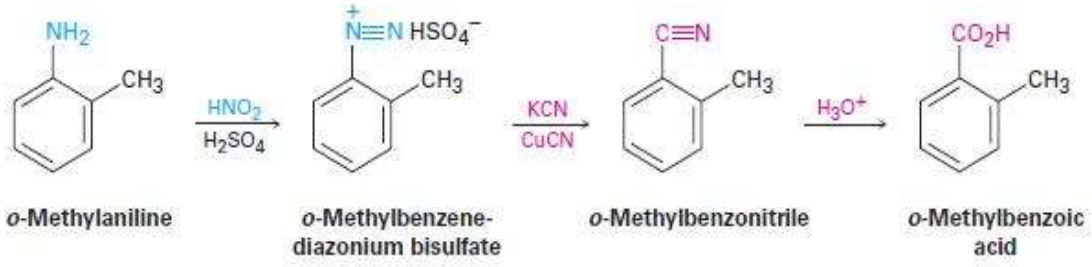


Many different nucleophiles—halide, hydride, cyanide, and hydroxide among others react with arene diazonium salts, yielding many different kinds of substituted benzenes. The overall sequence of (1) nitration, (2) reduction, (3) diazotization, and (4) nucleophilic substitution is perhaps the single most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

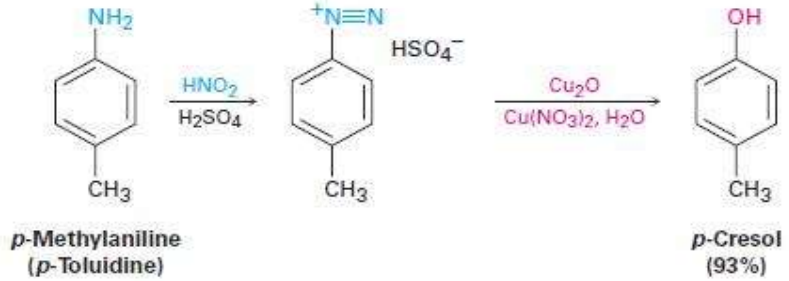
Aryl chlorides and bromides are prepared by reaction of an arene diazonium salt with the corresponding copper (I) halide, CuX, a process called the **Sandmeyer reaction**. Aryl iodides can be prepared by direct reaction with NaI without using a copper (I) salt. Yields generally fall between 60% and 80%.



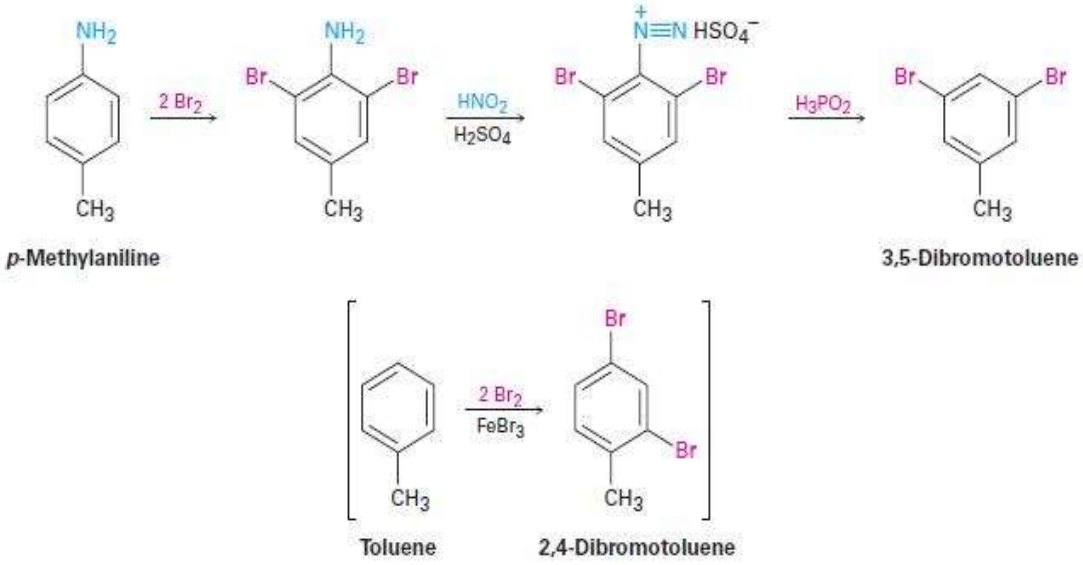
Similar treatment of an arene diazonium salt with CuCN yields the nitrile ArCN, which can then be further converted into other functional groups such as carboxyl. For example, Sandmeyer reaction of *o*-methyl benzene diazonium bisulfate with CuCN yields *o*-methyl benzonitrile, which can be hydrolyzed to give *o*-methylbenzoic acid. This*o*- produ xylene by the usual side-chain oxidation route because both methyl groups would be oxidized.



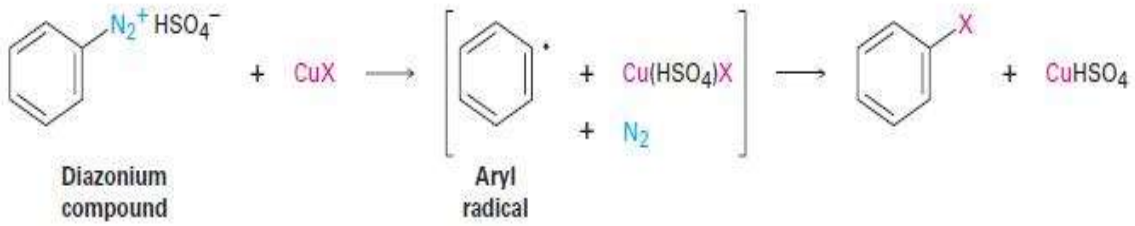
The diazonio group can also be replaced by -OH to yield a phenol and by -H to yield an arene. A phenol is prepared by reaction of the arene diazonium salt with copper (I) oxide in an aqueous solution of copper(II) nitrate, a reaction that is especially useful because few other general methods exist for 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 ontoa ring to take advantage of its directing effect. Suppose, for instance, that youneeded to make 3,5-dibromotoluene. This made by directproductbromination ofcan' 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.

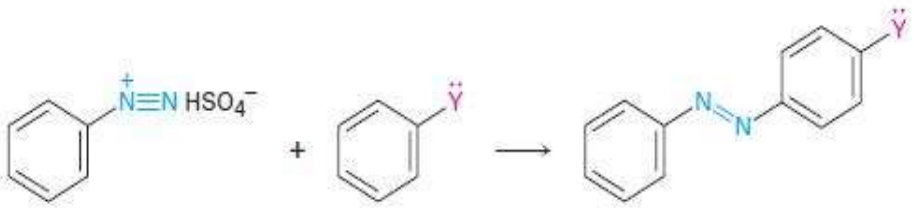


Mechanistically, these diazonio replacement reactions occur through radical rather than polar pathways. In the presence of a copper(I) compound, for instance, it's though diazonium ion is first converted to an aryl radical plus copper(II), followed by subsequent reaction to give product plus regenerated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



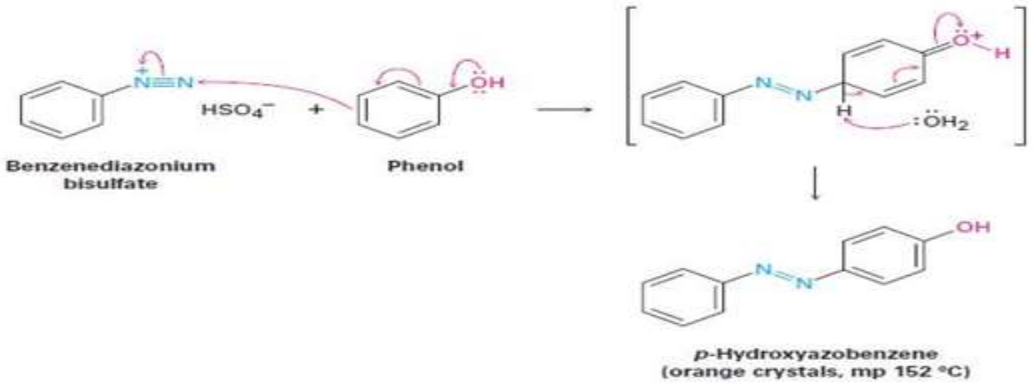
Diazonium Coupling Reactions

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



where Y = −OH or $-NR_2$

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.