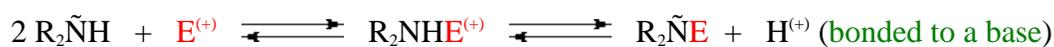


Electrophilic Substitution at Nitrogen

Ammonia and many amines are not only bases in the Brønsted sense, they are also nucleophiles that bond to and form products with a variety of electrophiles. A general equation for such **electrophilic substitution of nitrogen** is:

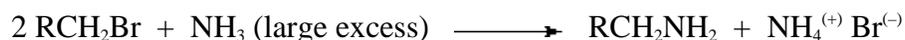


A list of some electrophiles that are known to react with amines is shown here. In each case the electrophilic atom or site is colored red.

Electrophile	$\text{RCH}_2\text{-X}$	$\text{RCH}_2\text{-OSO}_2\text{R}$	$\text{R}_2\text{C=O}$	R(C=O)X	$\text{RSO}_2\text{-Cl}$	HO-N=O
Name	Alkyl Halide	Alkyl Sulfonate	Aldehyde or Ketone	Acid Halide or Anhydride	Sulfonyl Chloride	Nitrous Acid

Alkylation

It is instructive to examine these nitrogen substitution reactions, using the common alkyl halide class of electrophiles. Thus, reaction of a primary alkyl bromide with a large excess of ammonia yields the corresponding 1°-amine, presumably by an S_N2 mechanism. The hydrogen bromide produced in the reaction combines with some of the excess ammonia, giving ammonium bromide as a by-product. Water does not normally react with 1°-alkyl halides to give alcohols, so the enhanced nucleophilicity of nitrogen relative to oxygen is clearly demonstrated.

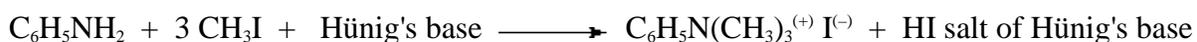


It follows that simple amines should also be more nucleophilic than their alcohol or ether equivalents. If, for example, we wish to carry out an S_N2 reaction of an alcohol with an

alkyl halide to produce an ether ([the Williamson synthesis](#)), it is necessary to convert the weakly nucleophilic alcohol to its more nucleophilic conjugate base for the reaction to occur. In contrast, amines react with alkyl halides directly to give N-alkylated products. Since this reaction produces HBr as a co-product, hydrobromide salts of the alkylated amine or unreacted starting amine (in equilibrium) will also be formed.



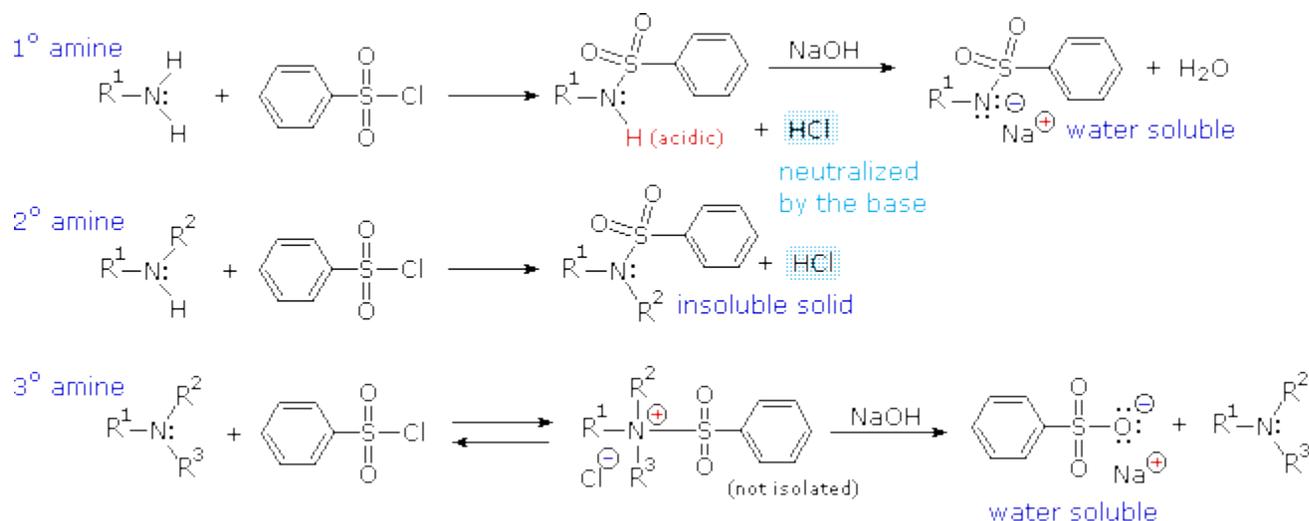
Unfortunately, the direct alkylation of 1° or 2°-amines to give a more substituted product does not proceed cleanly. If a 1:1 ratio of amine to alkyl halide is used, only 50% of the amine will react because the remaining amine will be tied up as an ammonium halide salt (remember that one equivalent of the strong acid HX is produced). If a 2:1 ratio of amine to alkylating agent is used, as in the above equation, the HX issue is solved, but another problem arises. Both the starting amine and the product amine are nucleophiles. Consequently, once the reaction has started, the product amine competes with the starting material in the later stages of alkylation, and some higher alkylated products are also formed. Even 3°-amines may be alkylated to form quaternary (4°) ammonium salts. When tetraalkyl ammonium salts are desired, as shown in the following example, Hünig's base may be used to scavenge the HI produced in the three S_N2 reactions. Steric hindrance prevents this 3°-amine (Hünig's base) from being methylated.



Reaction with Benzenesulfonyl chloride (The Hinsberg test)

Another electrophilic reagent, benzenesulfonyl chloride, reacts with amines in a fashion that provides a useful test for distinguishing primary, secondary and tertiary amines (the Hinsberg test). As shown in the following equations, 1° and 2°-amines react to give sulfonamide derivatives with loss of HCl, whereas 3°-amines do not give any isolable products other than the starting amine. In the latter case a quaternary "onium" salt may

be formed as an intermediate, but this rapidly breaks down in water to liberate the original 3^o-amine (lower right equation).



The **Hinsberg test** is conducted in aqueous base (NaOH or KOH), and the benzenesulfonyl chloride reagent is present as an insoluble oil. Because of the heterogeneous nature of this system, the rate at which the sulfonyl chloride reagent is hydrolyzed to its sulfonate salt in the absence of amines is relatively slow. The amine dissolves in the reagent phase, and immediately reacts (if it is 1^o or 2^o), with the resulting HCl being neutralized by the base. The sulfonamide derivative from 2^o-amines is usually an insoluble solid. However, the sulfonamide derivative from 1^o-amines is acidic and dissolves in the aqueous base. Acidification of this solution then precipitates the sulfonamide of the 1^o-amine.

Source : <http://www2.chemistry.msu.edu/faculty/reusch/VirtTxtJml/amine1.htm#aminom>