Preparation of Primary Amines

Although direct alkylation of ammonia by alkyl halides leads to 1º-amines, alternative procedures are preferred in many cases. These methods require two steps, but they provide pure product, usually in good yield. The general strategy is to first form a carbon-nitrogen bond by reacting a nitrogen nucleophile with a carbon electrophile. The following table lists several general examples of this strategy in the rough order of decreasing nucleophilicity of the nitrogen reagent. In the second step, extraneous nitrogen substituents that may have facilitated this bonding are removed to give the amine product.

<table>
<thead>
<tr>
<th>Nitrogen Reactant</th>
<th>Carbon Reactant</th>
<th>1st Reaction Type</th>
<th>Initial Product</th>
<th>2nd Reaction Conditions</th>
<th>2nd Reaction Type</th>
<th>Final Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₃⁻</td>
<td>RCH₂-X or R₂CH-X</td>
<td>Sn2</td>
<td>RCH₂-N₃ or R₂CH-N₃</td>
<td>LiAlH₄ or 4 H₂ &amp; Pd</td>
<td>Hydrogenolysis</td>
<td>RCH₂-NH₂ or R₂CH-NH₂</td>
</tr>
<tr>
<td>C₆H₅SO₂NH⁻</td>
<td>RCH₂-X or R₂CH-X</td>
<td>Sn2</td>
<td>RCH₂-NHSO₂C₆H₅ or R₂CH-NHSO₂C₆H₅</td>
<td>Na in NH₃ (liq)</td>
<td>Hydrogenolysis</td>
<td>RCH₂-NH₂ or R₂CH-NH₂</td>
</tr>
<tr>
<td>CN⁻</td>
<td>RCH₂-X or R₂CH-X</td>
<td>Sn2</td>
<td>RCH₂-CN or R₂CH-CN</td>
<td>LiAlH₄</td>
<td>Reduction</td>
<td>RCH₂-CN or R₂CH-CN</td>
</tr>
<tr>
<td>NH₃</td>
<td>RCH=O or R₂C=O</td>
<td>Addition / Elimination</td>
<td>RCH=NH or R₂C=NH</td>
<td>H₂ &amp; Ni or NaBH₃CN</td>
<td>Reduction</td>
<td>RCH₂-NH₂ or R₂CH-NH₂</td>
</tr>
<tr>
<td>NH₃</td>
<td>RCOX</td>
<td>Addition / Elimination</td>
<td>RCO-NH₂</td>
<td>LiAlH₄</td>
<td>Reduction</td>
<td>RCH₂-NH₂</td>
</tr>
<tr>
<td>NH₂CONH₂ (urea)</td>
<td>R₃C⁺</td>
<td>SN1</td>
<td>R₃C-NHCONH₂</td>
<td>NaOH soln.</td>
<td>Hydrolysis</td>
<td>R₃C-NH₂</td>
</tr>
</tbody>
</table>

A specific example of each general class is provided in the diagram below. In the first two, an anionic nitrogen species undergoes an Sn2 reaction with a modestly electrophilic alkyl halide reactant. For example #2 an acidic phthalimide derivative of ammonia has been substituted for the sulfonamide analog listed in the table. The principle is the same for the two cases, as will be noted later. Example #3 is similar in nature, but extends the carbon system by a methylene group (CH₂). In all three of these methods 3º-alkyl halides cannot be used because the major reaction path is an E2 elimination.
The methods illustrated by examples #4 and #5 proceed by attack of ammonia, or equivalent nitrogen nucleophiles, at the electrophilic carbon of a carbonyl group. A full discussion of carbonyl chemistry is presented later, but for present purposes it is sufficient to recognize that the C=O double bond is polarized so that the carbon atom is electrophilic. Nucleophile addition to aldehydes and ketones is often catalyzed by acids. Acid halides and anhydrides are even more electrophilic, and do not normally require catalysts to react with nucleophiles. The reaction of ammonia with aldehydes or ketones occurs by a reversible addition-elimination pathway to give imines (compounds having a C=N function). These intermediates are not usually isolated, but are reduced as they are formed (i.e. in situ). Acid chlorides react with ammonia to give amides, also by an addition-elimination path, and these are reduced to amines by LiAlH₄.

The 6th example is a specialized procedure for bonding an amino group to a 3º-alkyl group (none of the previous methods accomplishes this). Since a carbocation is the electrophilic species, rather poorly nucleophilic nitrogen reactants can be used. Urea, the diamide of carbonic acid, fits this requirement nicely. The resulting 3º-alkyl-substituted urea is then hydrolyzed to give the amine.

One important method of preparing 1º-amines, especially aryl amines, uses a reverse strategy. Here a strongly electrophilic nitrogen species (NO₂⁺) bonds to a nucleophilic carbon compound. This nitration reaction gives a nitro group that can be reduced to a 1º-amine by any of several reduction procedures.

The Hofmann rearrangement of 1º-amides provides an additional synthesis of 1º-amines. To learn about this useful procedure Click Here.

### Preparation of Secondary and Tertiary Amines

Of the six methods described above, three are suitable for the preparation of 2º and/or 3º-amines. These are


Examples showing the application of these methods to the preparation of specific amines are shown in the following diagram. The sulfonamide procedure used in the first example is similar in concept to the phthalamide example #2.
presented in the previous diagram. In both cases the acidity of the nitrogen reactant (ammonia or amine) is greatly enhanced by conversion to an imide or sulfonamide derivative. The nucleophilic conjugate base of this acidic nitrogen species is then prepared by treatment with sodium or potassium hydroxide, and this undergoes an $S_N_2$ reaction with a $1^\circ$ or $2^\circ$-alkyl halide. Finally, the activating group is removed by hydrolysis (phthalimide) or reductive cleavage (sulfonamide) to give the desired amine. The phthalimide method is only useful for preparing $1^\circ$-amines, whereas the sulfonamide procedure may be used to make either $1^\circ$ or $2^\circ$-amines.

Examples #2 & #3 make use of the carbonyl reductive amination reaction (method #4 in the preceding table). This versatile procedure may be used to prepare all classes of amines ($1^\circ$, $2^\circ$ & $3^\circ$), as shown here and above. A weak acid catalyst is necessary for imine formation, which takes place by amine addition to the carbonyl group, giving a 1-aminoalcohol intermediate, followed by loss of water. The final reduction of the C=N double bond may be carried out catalytically (Pt & Pd catalysts may be used instead of Ni) or chemically (by NaBH$_3$CN). The imine or enamine intermediates are normally not isolated, but are immediately reduced to the amine product.

Another general method for preparing all classes of amines makes use of amide intermediates, easily made from ammonia or amines by reaction with carboxylic acid chlorides or anhydrides. These stable compounds may be isolated, identified and stored prior to the final reduction. Examples #4 & #5 illustrate applications of this method. As with the previous method, $1^\circ$-amines give $2^\circ$-amine products, and $2^\circ$-amines give $3^\circ$-amine products. The last example (#6) shows how $4^\circ$-ammonium salts may be prepared by repeated (exhaustive) alkylation of amines.

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**Contributors**