The use of lithium aluminum hydride (LiAlH₄) and sodium borohydride (NaBH₄) as reagents for the reduction of aldehydes and ketones to 1º and 2º-alcohols respectively has been noted. Of these, lithium aluminum hydride, often abbreviated LAH, is the most useful for reducing carboxylic acid derivatives. Thanks to its high reactivity, LAH easily reduces all classes of carboxylic acid derivatives, generally to the −1 oxidation state. Acids, esters, anhydrides and acyl chlorides are all reduced to 1º-alcohols, and this method is superior to catalytic reduction in most cases. Since acyl chlorides and anhydrides are expensive and time consuming to prepare, acids and esters are the most commonly used reactants for this transformation. As in the reductions of aldehydes and ketones, the first step in each case is believed to be the irreversible addition of hydride to the electrophilic carbonyl carbon atom. Coordinative bonding of the carbonyl oxygen to a Lewis acidic metal (Li or Al) undoubtedly enhances that carbon’s electrophilic character. This hydride addition is shown in the following diagrams, with the hydride-donating moiety being written as AlH₄⁻(−). All four hydrogens are potentially available to the reduction, but when carboxylic acids are reduced, one of the hydrides reacts with the acidic O–H to generate hydrogen gas. Although the lithium is not shown, it will be present in the products as a cationic component of ionic salts.

Amides are reduced to amines by treatment with LAH, and this has proven to be one of the most general methods for preparing all classes of amines (1º, 2º & 3º). Because the outcome of LAH reduction is so different for esters and amides, we must examine plausible reaction mechanisms for these reactions to discover a reason for this divergent behavior.

One explanation of the different course taken by the reductions of esters and amides lies in the nature of the different hetero atom substituents on the carbonyl group (colored green in the diagram). Nitrogen is more basic than oxygen, and amide anions are poorer leaving groups than alkoxide anions. Furthermore, oxygen forms especially strong bonds to aluminum. Addition of hydride produces a tetrahedral intermediate, shown in brackets, which has a polar oxygen-aluminum bond. Neither the hydrogen nor the alkyl group (R) is a possible leaving group, so if this tetrahedral species is to undergo an elimination to reform a hetero atom double bond, one of the two remaining substituents must be lost. For the ester this is an easy choice (described by the curved arrows). By eliminating an aluminum alkoxide (R'O–Al), an aldehyde is formed, and this is quickly reduced to the salt of a 1º-alcohol by LAH. In the case of the amide, aldehyde formation requires the loss of an aluminum amide (R₂N–Al), an unlikely process. Alternatively, the more basic nitrogen may act to
eject a metal oxide species (e.g. Al–O^(-)), and the resulting iminium double bond would then be reduced to an amine. This is the course followed by most amide reductions; but in the case of 1º-amides, the acidity of the nitrogen hydrogens coupled with the basicity of hydride enables a facile elimination of the oxygen (as an oxide moiety). The resulting nitrile intermediate is then reduced to a 1º-amine. Nitriles are in fact a major product when less than a full equivalency of LiAlH₄ is used. A mechanism will be shown above by clicking on the diagram.

Lithium aluminum hydride reduces nitriles to 1º-amines, as shown in the following equation. An initial hydride addition to the electrophilic nitrile carbon atom generates the salt of an imine intermediate. This is followed by a second hydride transfer, and the resulting metal amine salt is hydrolyzed to a 1º-amine. This method provides a useful alternative to the catalytic reduction of nitriles, described above, when alkene or alkyne functions are present.

\[
\begin{align*}
\text{C}=\text{N} & \quad \xrightarrow{\text{LiAlH}_4} \quad \text{C}=\text{N}^- + \text{AlH}_2^+ \\
\text{C}=\text{N}^- & \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{C}=\text{N}_2^- + \text{Al}(\text{OH})_2
\end{align*}
\]

In contrast to the usefulness of lithium aluminum hydride in reducing various carboxylic acid derivatives, sodium borohydride is seldom chosen for this purpose. First, NaBH₄ is often used in hydroxylic solvents (water and alcohols), and these would react with acyl chlorides and anhydrides. Furthermore, it is sparingly soluble in relatively nonpolar solvents, particularly at low temperatures. Second, NaBH₄ is much less reactive than LAH, failing to reduce amides and acids (they form carboxylate salts) at all, and reducing esters very slowly.

Since relatively few methods exist for the reduction of carboxylic acid derivatives to aldehydes, it would be useful to modify the reactivity and solubility of LAH to permit partial reductions of this kind to be achieved. The most fruitful approach to this end has been to attach alkoxy or alkyl groups on the aluminum. This not only modifies the reactivity of the reagent as a hydride donor, but also increases its solubility in nonpolar solvents. Two such reagents will be mentioned here; the reactive hydride atom is colored blue.

**Lithium tri-tert-butoxyaluminohydride** (LtBAH), LiAl[OC(CH₃)₃]₃H : Soluble in THF, diglyme & ether.

**Diisobutylaluminum hydride** (DIBAH), [(CH₃)₂CHCH₂]₂AlH : Soluble in toluene, THF & ether.

Each of these reagents carries one equivalent of hydride. The first (LtBAH) is a complex metal hydride, but the second is simply an alkyl derivative of aluminum hydride. In practice, both reagents are used in equimolar amounts, and usually at temperatures well below 0 ºC. The following examples illustrate how aldehydes may be prepared from carboxylic acid derivatives by careful application of these reagents. A temperature of -78 ºC is easily maintained by using dry-ice as a coolant. The reduced intermediates that lead to aldehydes will be displayed on clicking the "Show Intermediates" button. With excess reagent at temperatures above 0 ºC most carboxylic acid derivatives are reduced to alcohols or amines.
1. \[
\text{C}_{6}\text{H}_{5}\text{CH}_{3} \xrightarrow{\text{NaH}, \text{THF}, -78^\circ\text{C}} \text{C}_{6}\text{H}_{5}\text{CH}_{3} + \text{H} + \text{Li} + \text{C}_{6}\text{H}_{5}(\text{C}_{6}\text{H}_{5})\text{Li}
\]

2. \[
\text{CH}_{3}(\text{CH}_{2})_{5}\text{CO}_{2}\text{H} \xrightarrow{1. \text{DBU}, \text{toluene}, -78^\circ\text{C}} 2. \text{H}_{2}\text{O} \xrightarrow{2. \text{H}_{2}\text{O}} \text{CH}_{3}(\text{CH}_{2})_{5}\text{CO}_{2}\text{H} + \text{C}_{6}\text{H}_{5}\text{OH}
\]

3. \[
\text{C}_{6}\text{H}_{5}\text{CH}_{3} \xrightarrow{1. \text{DBU}, \text{toluene}, -78^\circ\text{C}} 2. \text{H}_{2}\text{O} \xrightarrow{2. \text{H}_{2}\text{O}} \text{C}_{6}\text{H}_{5}\text{CH}_{3}
\]

Contributors