Carboxylic Acids

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Reactions of Carboxylic Acids:

Carboxylic acids are similar in some respects to both alcohols and ketones. Like alcohols, carboxylic acids can be deprotonated to give anions, which are good nucleophiles in S_N^2 reactions. Like ketones, carboxylic acids undergo addition of nucleophiles to the carbonyl group. However, carboxylic acids also undergo other reactions characteristic of neither alcohols nor ketones. **Figure 20-2** shows some of the general reactions of carboxylic acids.

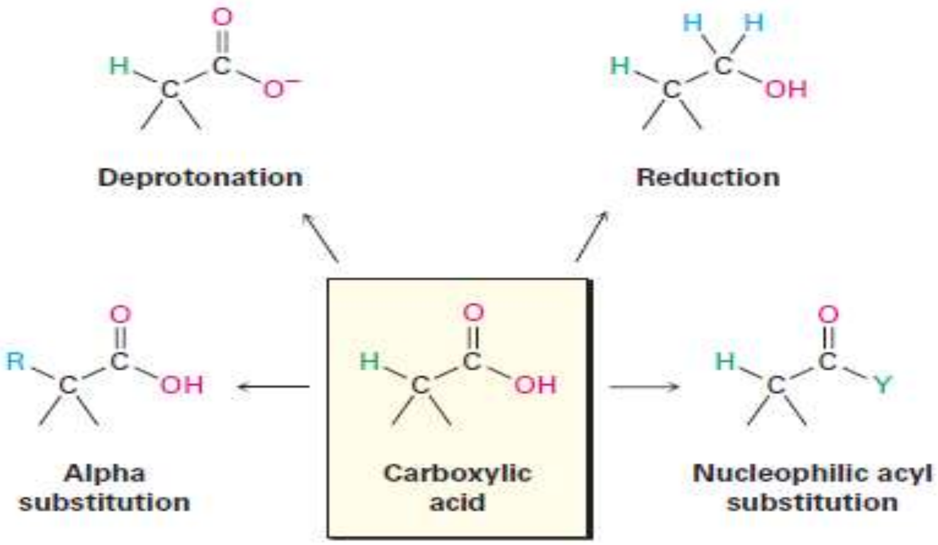
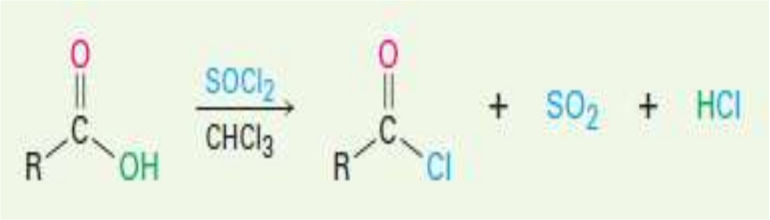


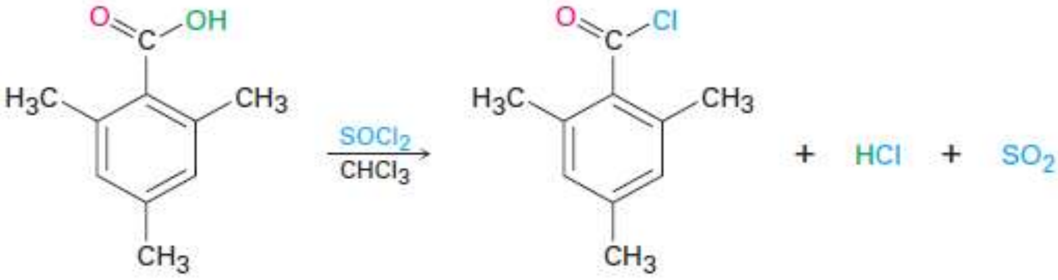
Figure 20-2 some general reactions of carboxylic acids.

1. Conversion into acid derivatives

a) Conversion into acid chlorides

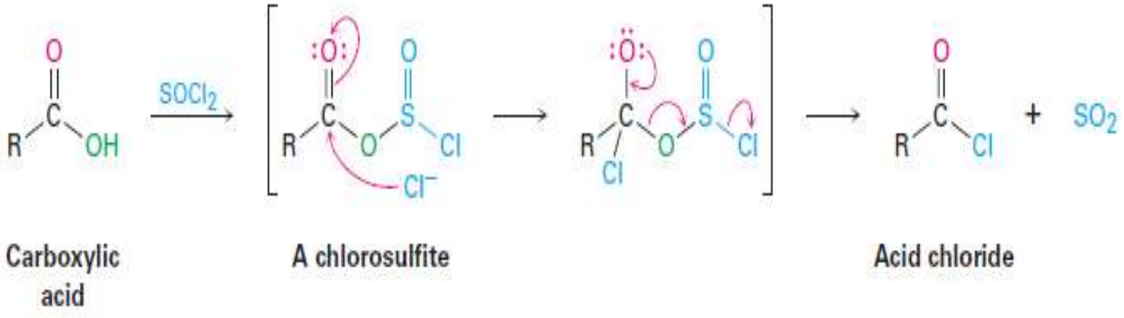
In the laboratory, carboxylic acids are converted into acid chlorides by treatment with thionyl chloride, $SOCl_2$.



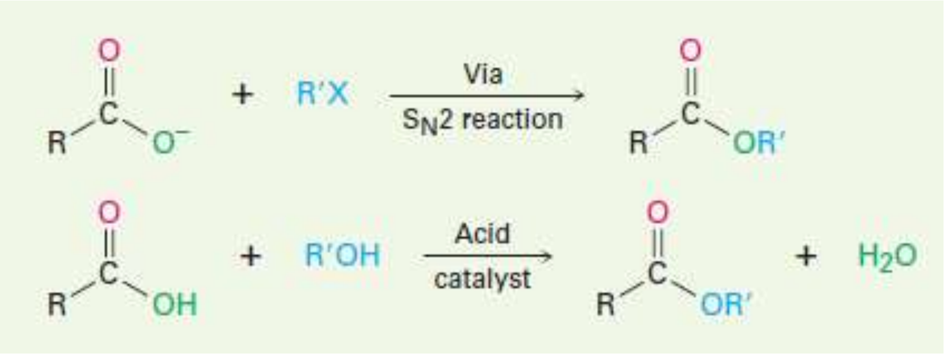


2,4,6-Trimethylbenzoic acid **2,4,6-Trimethylbenzoyl chloride (90%)**

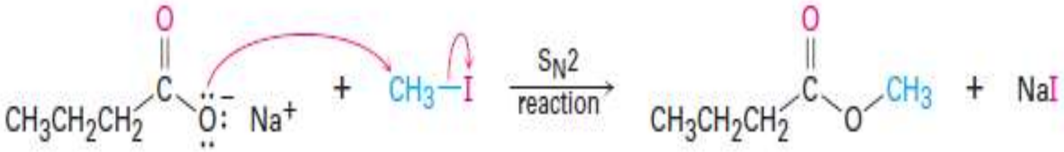
This reaction occurs by a nucleophilic acyl substitution pathway in which the carboxylic acid is first converted into an acyl chlorosulfite intermediate, thereby replacing the] OH of the acid with a much better leaving group. The chlorosulfite then reacts with a nucleophilic chloride ion. An analogous chlorosulfite is involved in the reaction of an alcohol with $SOCl_2$ to yield an alkyl chloride.



b) Conversion into esters

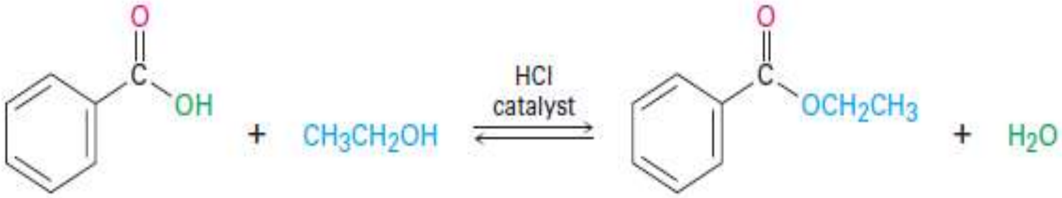


The most useful reaction of carboxylic acids is their conversion into esters. There are many methods for accomplishing this, including the SN2 reaction of a carboxylate anion with a primary alkyl halide.



Sodium butanoate **Methyl butanoate (97%)**

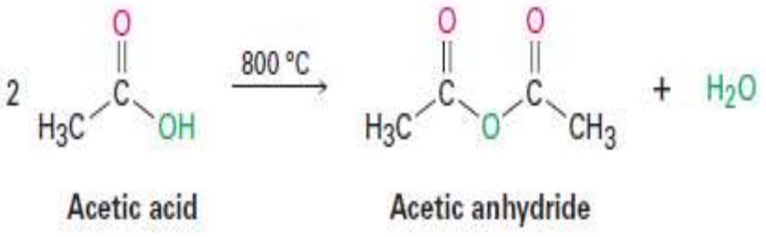
Esters can also be synthesized by an acid-catalyzed nucleophilic acyl substitution reaction of a carboxylic acid with an alcohol, a process called the **Fischer esterification reaction**. Unfortunately, the need for an excess of a liquid alcohol as solvent effectively limits the method to the synthesis of methyl, ethyl, propyl, and butyl esters.



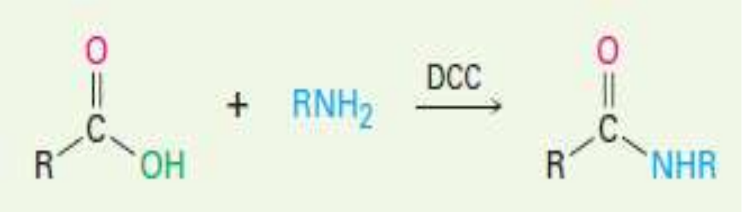
Benzoic acid **Ethyl benzoate (91%)**

c) Conversion into acid anhydrides

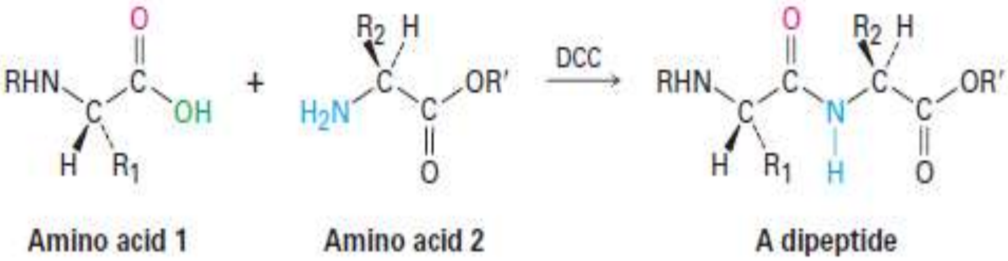
Acid anhydrides can be derived from two molecules of carboxylic acid by heating to remove 1 equivalent of water. Because of the high temperatures needed, however, only acetic anhydride is commonly prepared this way.



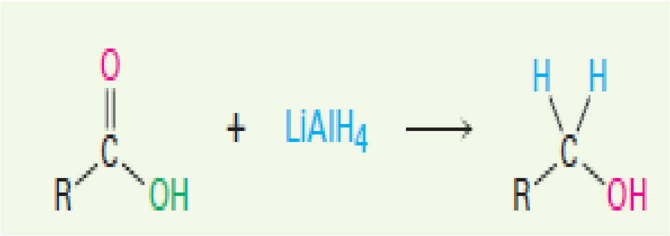
d) Conversion into amides



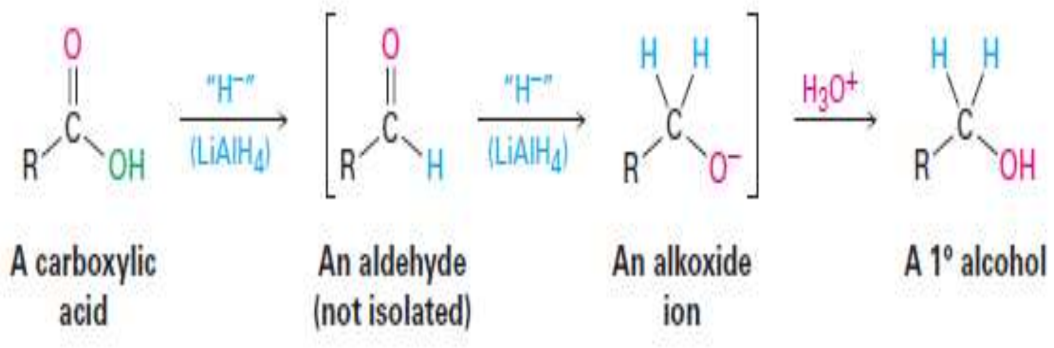
This DCC-induced method of amide formation is the key step in the laboratory synthesis of small proteins, or ***peptides***. For instance, when one amino acid with its NH_2 rendered unreactive and a second amino acid with its $-CO_2H$ rendered unreactive are treated with DCC, a dipeptide is formed.



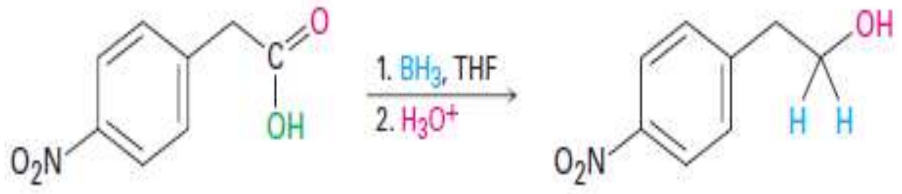
2. Reduction to yield primary alcohols



Carboxylic acids are reduced by $LiAlH_4$ to give primary alcohols, but we deferred a discussion of the reaction mechanism at that time. In fact, the reduction is a nucleophilic acyl substitution reaction in which -H replaces -OH to give an aldehyde, which is further reduced to a primary alcohol by nucleophilic addition. The aldehyde intermediate is much more reactive than the starting acid, so it reacts immediately and is not isolated.

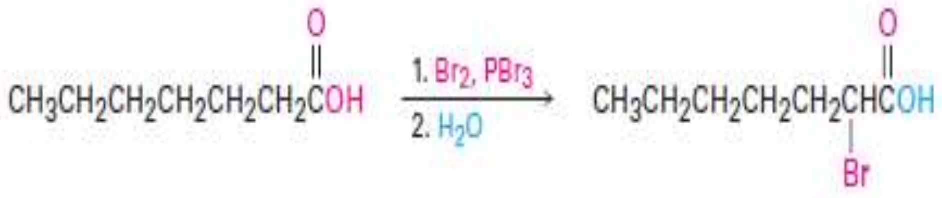


Alternatively, borane in tetrahydrofuran (BH_3/THF) is a useful reagent for reducing carboxylic acids to primary alcohols. Reaction of an acid with BH_3/THF occurs rapidly at room temperature, and the procedure is often preferred to reduction with $LiAlH_4$ because of its relative ease and safety. Borane reacts with carboxylic acids faster than with any other functional group, thereby allowing selective transformations such as that on *p*-nitrophenylacetic acid. If the reduction of *p*-nitrophenylacetic acid were done with LiAlH4, both the nitro and carboxyl groups would be reduced.



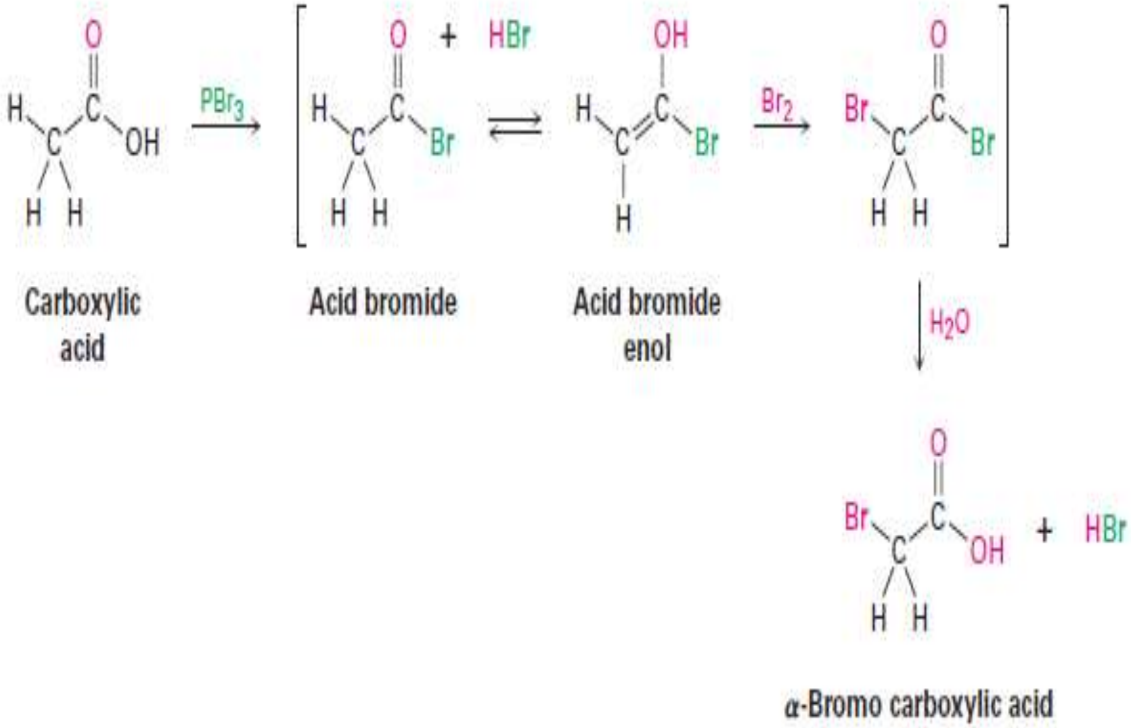
3. Alpha bromination of carboxylic acids

Carboxylic acids, however, can be *a* brominated by a mixture of Br_2 and PBr_3 in the ***Hell–Volhard–Zelinskii (HVZ) reaction***



$$CH_3CH_2CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH \xrightarrow[2.\ H_2O]{1.\ Br_2,\ PBr_3} CH_3CH_2CH_2CH_2CH_2\underset{Br}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}OH$$

The Hell–Volhard–Zelinskii reaction is a bit more complex than it looks and actually involves *a* substitution of an acid bromide enol rather than a carboxylic acid enol. The process begins by reaction of the carboxylic acid with PBr_3 to form an acid bromide plus HBr. The HBr then catalyzes enolization of the acid bromide, and the resultant enol reacts with Br_2 in an *a*-substitution reaction to give an *a*-bromo acid bromide. Addition of water hydrolyzes the acid bromide in a nucleophilic acyl substitution reaction and yields the *a*-bromo carboxylic acid product.


Carboxylic acid
PBr3
Acid bromide
HBr
Acid bromide enol
Br2
H2O
HBr
α-Bromo carboxylic acid