

Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution Reactions

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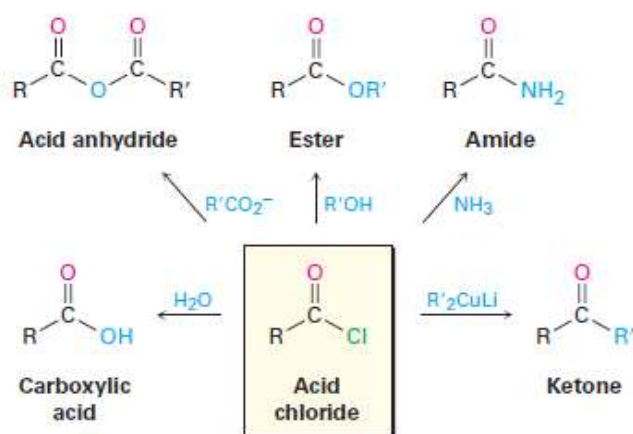
Chemistry of Acid Halides Preparation of Acid Halides

Acid chlorides are prepared from carboxylic acids by reaction with thionyl chloride (SOCl_2). Similar reaction of a carboxylic acid with phosphorus tribromide (PBr_3) yields the acid bromide.



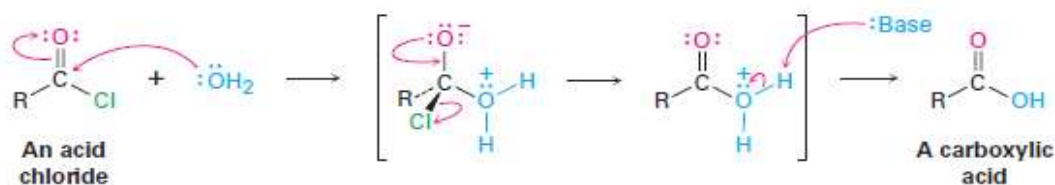
Reactions of Acid Halides

Acid halides are among the most reactive of carboxylic acid derivatives and can be converted into many other kinds of compounds by nucleophilic acyl substitution mechanisms. The halogen can be replaced by $-\text{OH}$ to yield an acid, by $-\text{OCOR}$ to yield an anhydride, by $-\text{OR}$ to yield an ester, by $-\text{NH}_2$ to yield an amide, or by R' to yield a ketone. In addition, the reduction of an acid halide yields a primary alcohol, and reaction with a Grignard reagent yields a tertiary alcohol. Although the reactions we'll be discussing in this section are illustrated only for acid chlorides, similar processes take place with other acid halides.



Conversion of Acid Halides into Acids: Hydrolysis

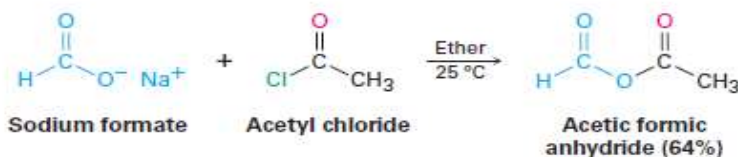
Acid chlorides react with water to yield carboxylic acids. This hydrolysis reaction is a typical nucleophilic acyl substitution process and is initiated by attack of water on the acid chloride carbonyl group. The tetrahedral intermediate undergoes elimination of Cl^- and loss of H^+ to give the product carboxylic acid plus HCl .



Because HCl is formed during hydrolysis, this reaction is often carried out in the presence of a base such as pyridine or NaOH to remove the HCl and prevent it from causing side reactions.

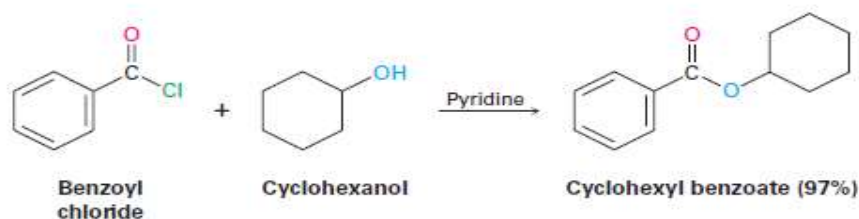
Conversion of Acid Halides into Anhydrides

Nucleophilic acyl substitution reaction of an acid chloride with a carboxylate anion gives an acid anhydride. Both symmetrical and unsymmetrical acid anhydrides can be prepared.

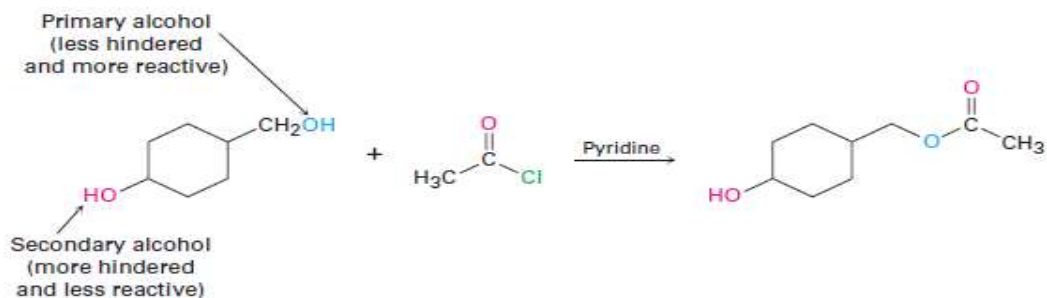


Conversion of Acid Halides into Esters: Alcoholysis

Acid chlorides react with alcohols to yield esters in a process analogous to their reaction with water to yield acids. In fact, this reaction is probably the most common method for preparing esters in the laboratory. As with hydrolysis, alcoholysis reactions are usually carried out in the presence of pyridine or NaOH to react with the HCl formed.

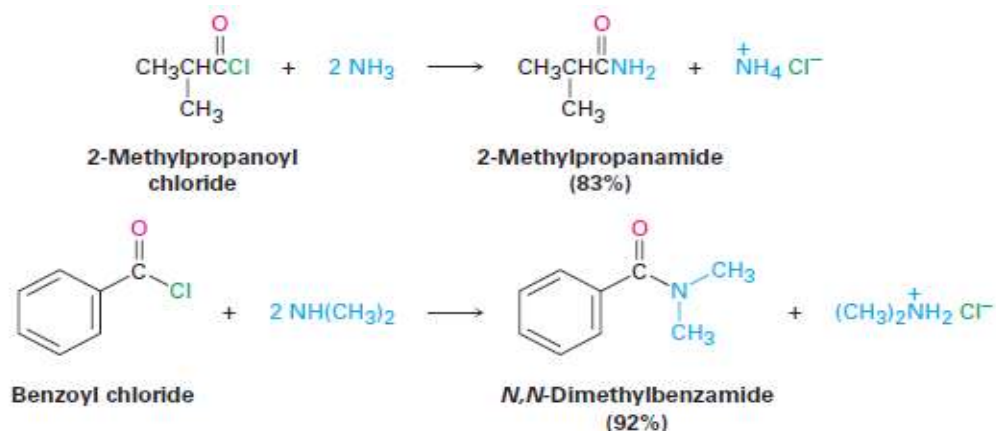


The reaction of an alcohol with an acid chloride is strongly affected by steric hindrance. Bulky groups on either partner slow down the reaction considerably, resulting in a reactivity order among alcohols of primary > secondary > tertiary. As a result, it's often possible to selectively esterify an unhindered alcohol in the presence of a more hindered one. This can be important in complex syntheses in which it's sometimes necessary to distinguish between similar functional groups. For example,

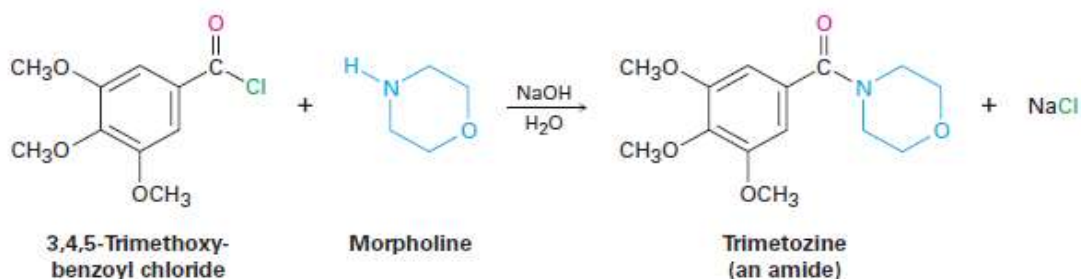


Conversion of Acid Halides into Amides: Aminolysis

Acid chlorides react rapidly with ammonia and amines to give amides. As with the acid chloride plus-alcohol method for preparing esters, this reaction of acid chlorides with amines is the most commonly used laboratory method for preparing amides. Both monosubstituted and disubstituted amines can be used, but not trisubstituted amines (R_3N).



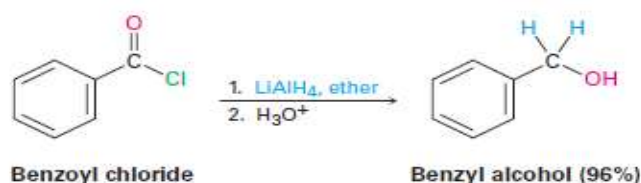
Because HCl is formed during the reaction, two equivalents of the amine must be used. One equivalent reacts with the acid chloride, and one equivalent reacts with the HCl by product to form an ammonium chloride salt. If the amine component is valuable, amide synthesis is often carried out using one equivalent of the amine plus one equivalent of an inexpensive base such as NaOH. For example, the sedative trimetozine is prepared commercially by reaction of 3,4,5-trimethoxybenzoyl chloride with the amine morpholine in the presence of one equivalent of NaOH.



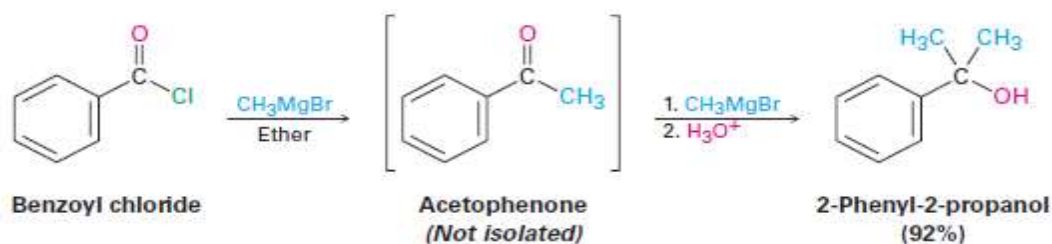
Conversion of Acid Chlorides into Alcohols: Reduction and Grignard Reaction

Acid chlorides are reduced by LiAlH_4 to yield primary alcohols. The reaction is of little practical value, however, because the parent carboxylic acids are generally more readily available and can themselves be reduced by LiAlH_4 to yield alcohols.

Reduction occurs via a typical nucleophilic acyl substitution mechanism in which a hydride ion (H^-) adds to the carbonyl group, yielding a tetrahedral intermediate that expels Cl^- . The net effect is a substitution of $-\text{Cl}$ by $-\text{H}$ to yield an aldehyde, which is then further reduced by LiAlH_4 in a second step to yield the primary alcohol.

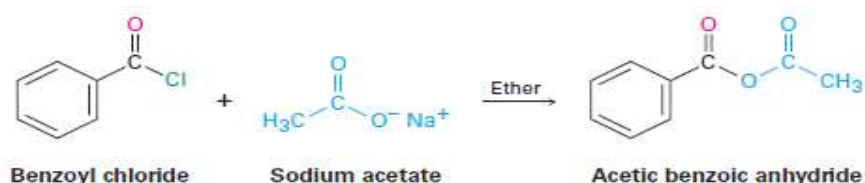


Grignard reagents react with acid chlorides to yield tertiary alcohols with two identical substituents. The mechanism of the reaction is similar to that of LiAlH_4 reduction. The first equivalent of Grignard reagent adds to the acid chloride, loss of Cl^- from the tetrahedral intermediate yields a ketone, and a second equivalent of Grignard reagent immediately adds to the ketone to produce an alcohol.



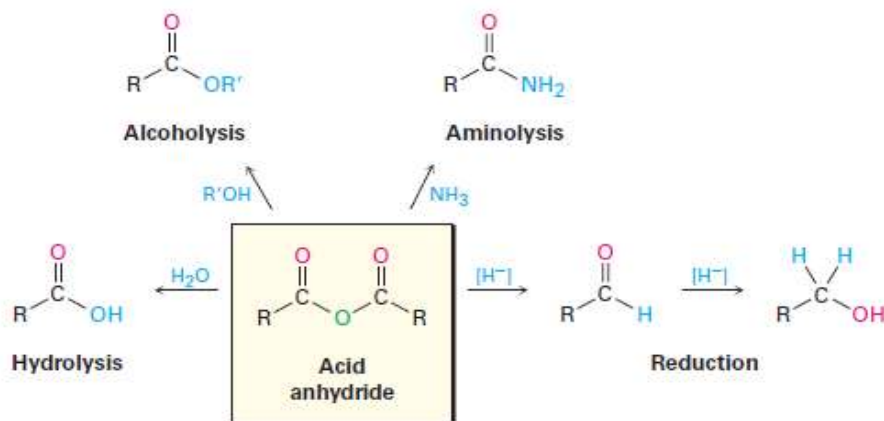
Chemistry of Acid Anhydrides Preparation of Acid Anhydrides

Acid anhydrides are typically prepared by nucleophilic acyl substitution reaction of an acid chloride with a carboxylate anion. Both symmetrical and unsymmetrical acid anhydrides can be prepared in this way.



Reactions of Acid Anhydrides

The chemistry of acid anhydrides is similar to that of acid chlorides, although anhydrides react more slowly. Thus, acid anhydrides react with water to form acids, with alcohols to form esters, with amines to form amides, and with LiAlH_4 to form primary alcohols. Only the ester- and amide-forming reactions are commonly used, however.



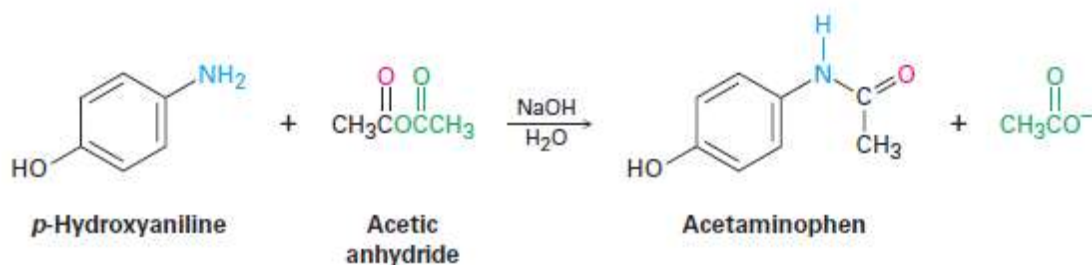
Conversion of Acid Anhydrides into Esters

Acetic anhydride is often used to prepare acetate esters from alcohols. For example, aspirin (acetylsalicylic acid) is prepared commercially by the acetylation of *o*-hydroxybenzoic acid (salicylic acid) with acetic anhydride.



Conversion of Acid Anhydrides into Amides

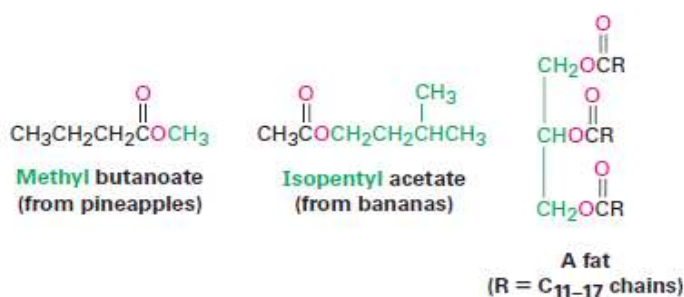
Acetic anhydride is also commonly used to prepare *N*-substituted acetamides from amines. For example, acetaminophen, a drug used in over-the-counter analgesics such as Tylenol, is prepared by reaction of *p*-hydroxyaniline with acetic anhydride. Only the more nucleophilic $-\text{NH}_2$ group reacts rather than the less nucleophilic $-\text{OH}$ group.



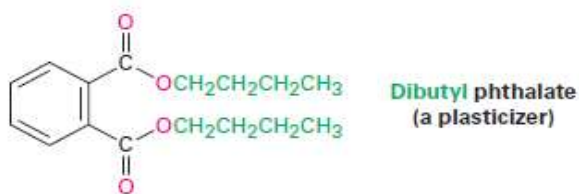
Notice in both of the previous reactions that only “half” of the anhydride molecule is used, while the other half acts as the leaving group during the nucleophilic acyl substitution step and produces acetate ion as a by-product. Thus, anhydrides are inefficient, and acid chlorides are normally preferred for introducing acyl substituents other than acetyl groups.

Chemistry of Esters

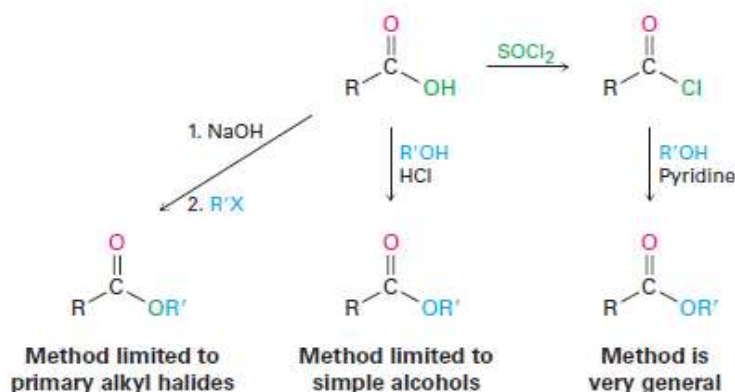
Esters are among the most widespread of all naturally occurring compounds. Many simple esters are pleasant-smelling liquids that are responsible for the fragrant odors of fruits and flowers. For example, methyl butanoate is found in pineapple oil, and isopentyl acetate is a constituent of banana oil. The ester linkage is also present in animal fats and in many biologically important molecules.



The chemical industry uses esters for a variety of purposes. Ethyl acetate, for instance, is a commonly used solvent, and dialkyl phthalates are used as plasticizers to keep polymers from becoming brittle. You may be aware that there is current concern about the possible toxicity of phthalates at high concentrations, although a recent assessment by the U.S. Food and Drug Administration found the risk to be minimal for most people, with the possible exception of male infants.

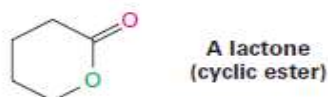


Esters are usually prepared from carboxylic acids by the methods already discussed. Thus, carboxylic acids are converted directly into esters by S_{N}^2 reaction of a carboxylate ion with a primary alkyl halide or by Fischer esterification of a carboxylic acid with an alcohol in the presence of a mineral acid catalyst. In addition, acid chlorides are converted into esters by treatment with an alcohol in the presence of base.



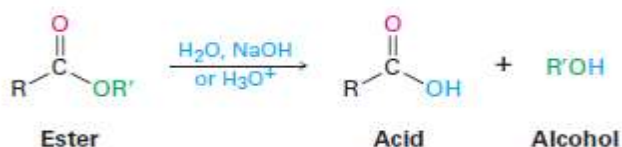
Reactions of Esters

Esters undergo the same kinds of reactions that we've seen for other carboxylic acid derivatives, but they are less reactive toward nucleophiles than either acid chlorides or anhydrides. All their reactions are applicable to both acyclic and cyclic esters, called **lactones**.

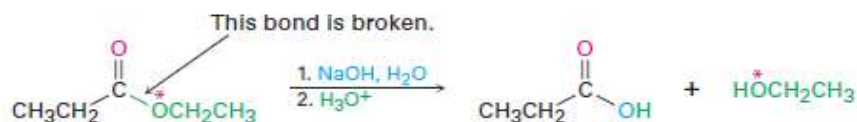


Conversion of Esters into Carboxylic Acids: Hydrolysis

An ester is hydrolyzed, either by aqueous base or aqueous acid, to yield a carboxylic acid plus an alcohol. Ester hydrolysis in basic solution is called **saponification**, after the Latin word *sapo*, meaning "soap." soap is in fact made by boiling animal fat with aqueous base to hydrolyze the ester linkages. Ester hydrolysis occurs through a typical nucleophilic acyl substitution pathway in which hydroxide ion is the nucleophile that adds to the ester carbonyl group to give a tetrahedral intermediate. Loss of alkoxide ion then gives a carboxylic acid, which is deprotonated to give the carboxylate ion. Addition of aqueous HCl, in a separate step after the saponification is complete, protonates the carboxylate ion and gives the carboxylic acid.

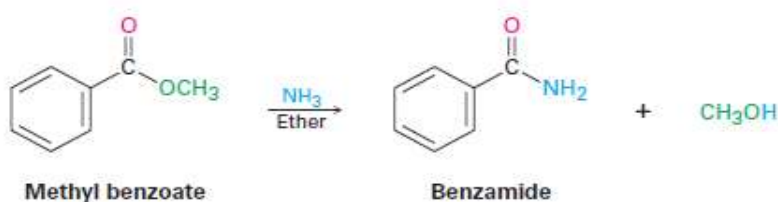


The mechanism is supported by isotope-labeling studies. When ethyl propanoate labeled with ^{18}O in the ether-like oxygen is hydrolyzed in aqueous NaOH, the ^{18}O label shows up exclusively in the ethanol product. None of the label remains with the propanoic acid, indicating that saponification occurs by cleavage of the **C-OR'** bond rather than the **CO-R'** bond.



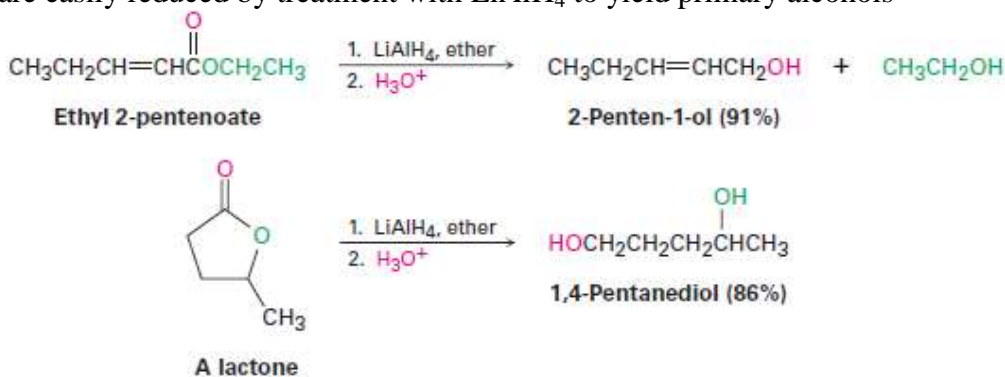
Conversion of Esters into Amides: Aminolysis

Esters react with ammonia and amines to yield amides. The reaction is not often used, however, because it's usually easier to prepare an amide by starting with an acid chloride

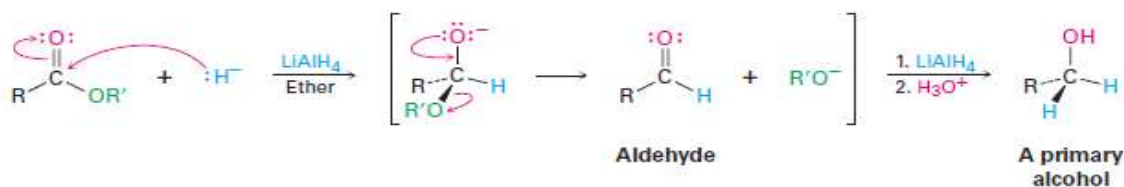


Conversion of Esters into Alcohols: Reduction

Esters are easily reduced by treatment with LiAlH₄ to yield primary alcohols

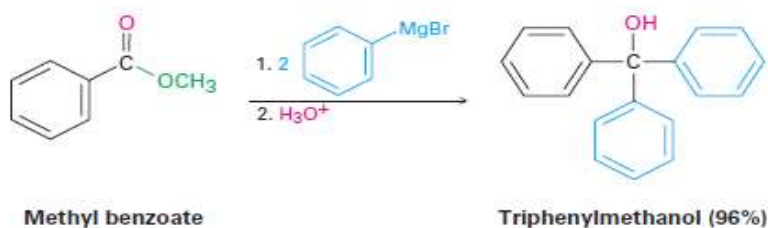


The mechanism of ester reduction is similar to that of acid chloride reduction in that a hydride ion first adds to the carbonyl group, followed by elimination of alkoxide ion to yield an aldehyde. Further reduction of the aldehyde gives the primary alcohol.



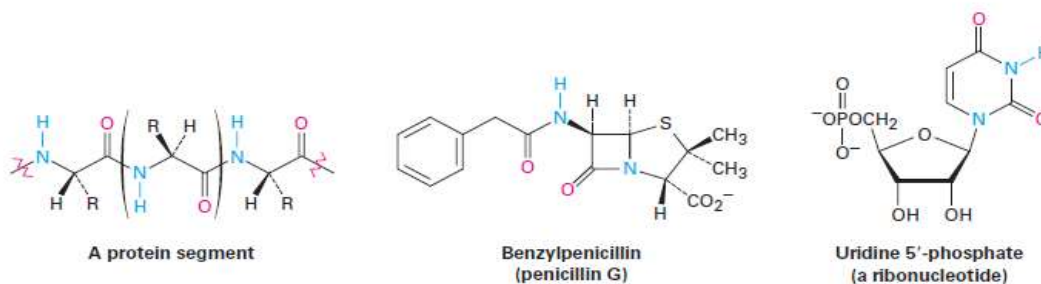
Conversion of Esters into Alcohols: Grignard Reaction

Esters react with 2 equivalents of a Grignard reagent to yield a tertiary alcohol in which two of the substituents are identical. The reaction occurs by the usual nucleophilic substitution mechanism to give an intermediate ketone, which reacts further with the Grignard reagent to yield a tertiary alcohol.



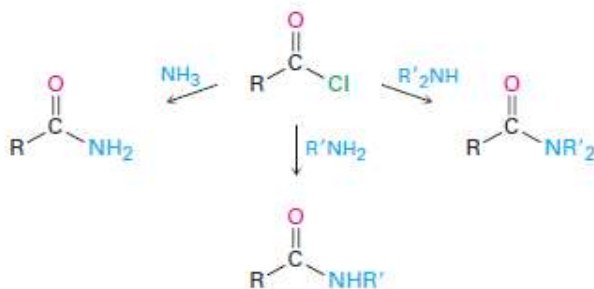
Chemistry of Amides

Amides, like esters, are abundant in all living organisms. Proteins, nucleic acids, and many pharmaceutical agents have amide functional groups. The reason for this abundance of amides is that they are stable in the aqueous conditions found in living organisms. Amides are the least reactive of the common acid derivatives and undergo relatively few nucleophilic acyl substitution reactions.



Preparation of Amides

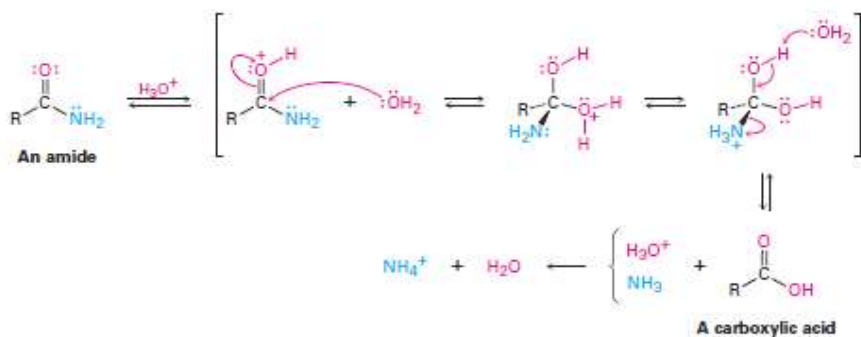
Amides are usually prepared by reaction of an acid chloride with an amine. Ammonia, monosubstituted amines, and disubstituted amines all undergo this reaction.



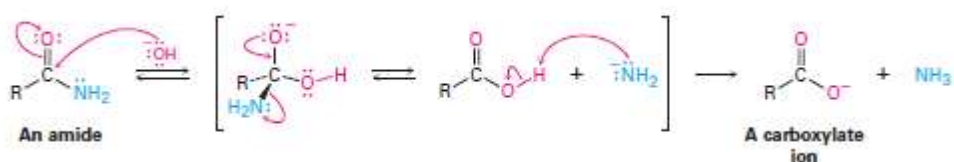
Reactions of Amides

Conversion of Amides into Carboxylic Acids: Hydrolysis

Amides undergo hydrolysis to yield carboxylic acids plus ammonia or an amine upon heating in either aqueous acid or aqueous base. The conditions required for amide hydrolysis are more extreme than those required for the hydrolysis of acid chlorides or esters, but the mechanisms are similar. Acidic hydrolysis reaction occurs by nucleophilic addition of water to the protonated amide, followed by transfer of a proton from oxygen to nitrogen to make the nitrogen a better leaving group, and subsequent elimination. The steps are reversible, with the equilibrium shifted toward product by protonation of NH₃ in the final step.

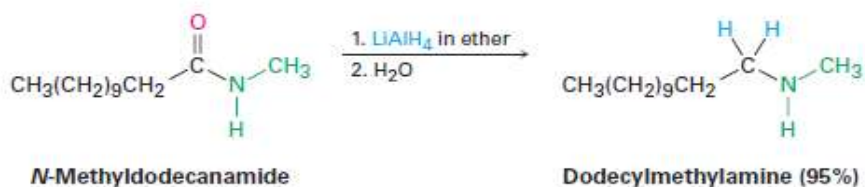


Basic hydrolysis occurs by nucleophilic addition of **OH⁻** to the amide carbonyl group, followed by elimination of amide ion (**NH₂⁻**) and subsequent deprotonation of the initially formed carboxylic acid by ammonia. The steps are reversible, with the equilibrium shifted toward product by the final deprotonation of the carboxylic acid. Basic hydrolysis is substantially more difficult than the analogous acid-catalyzed reaction because amide ion is a very poor leaving group, making the elimination step difficult.

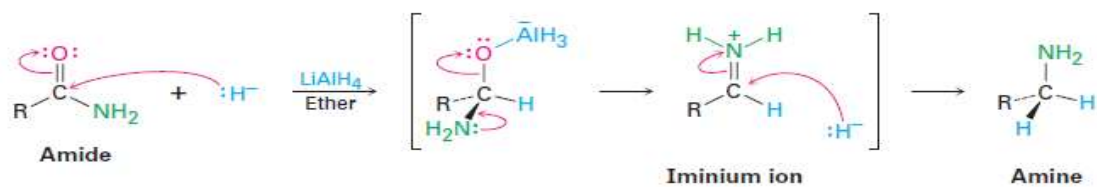


Conversion of Amides into Amines: Reduction

Like other carboxylic acid derivatives, amides can be reduced by LiAlH₄. The product of the reduction, however, is an amine rather than an alcohol. The net effect of an amide reduction reaction is thus the conversion of the amide carbonyl group into a methylene group (**C=O** → **CH₂**). This kind of reaction is specific to amides and does not occur with other carboxylic acid derivatives.



Amide reduction occurs by nucleophilic addition of hydride ion to the amide carbonyl group, followed by expulsion of the **oxygen** atom as an aluminate anion leaving group to give an iminium ion intermediate. The intermediate iminium ion is further reduced by LiAlH₄ to yield the amine.



The reaction is effective with both acyclic and cyclic amide (**lactams**), and is a good method for preparing cyclic amines.

