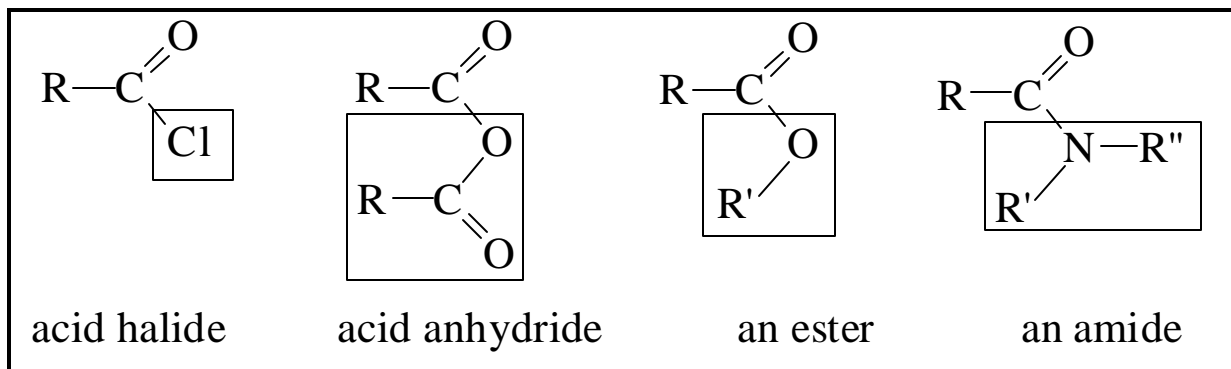


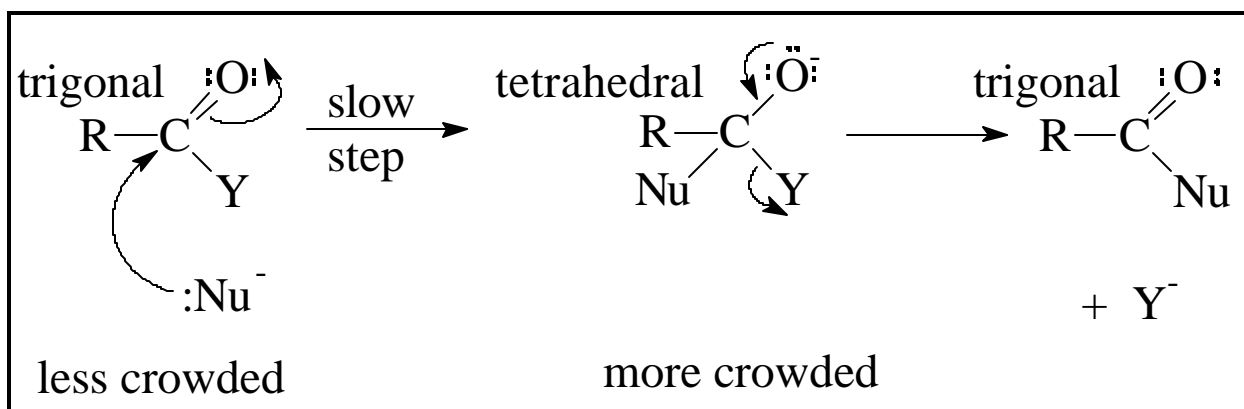
# Carboxylic Acid Derivatives

The most important derivatives of carboxylic acids are —



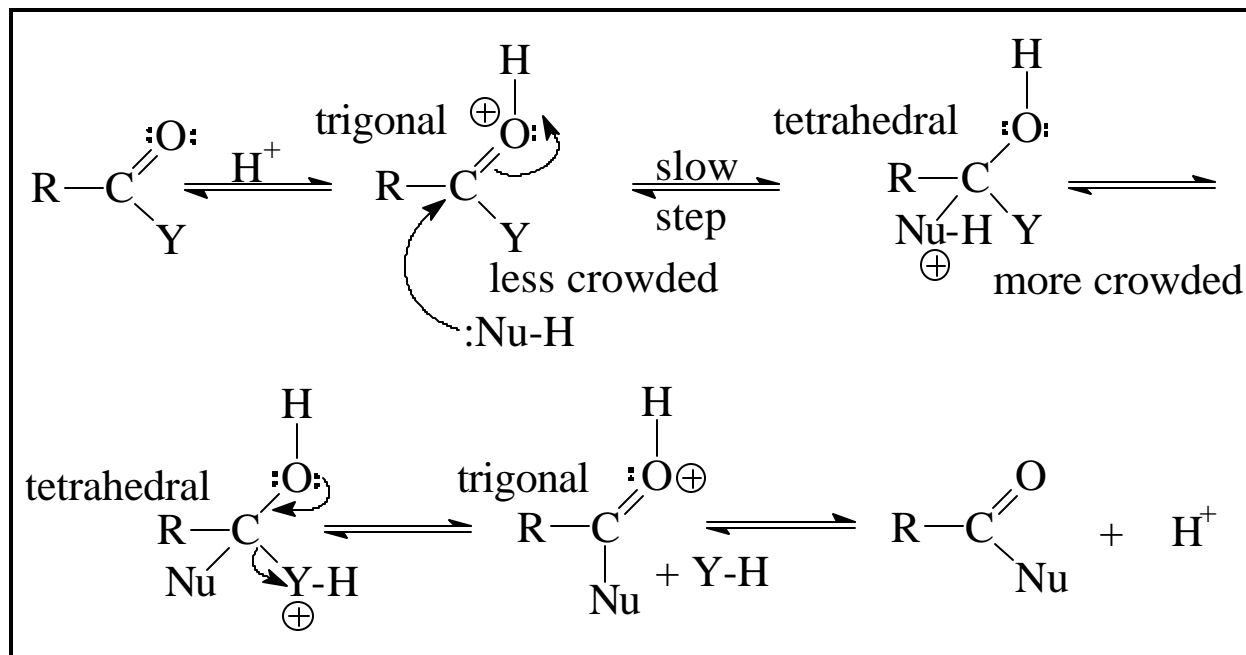
Although not direct derivatives, nitriles, R-CN, are related to carboxylic acids. They can be hydrolyzed to carboxylic acids and they can be prepared from carboxylic acids *via* dehydration of the amide.

The typical reaction type of carboxylic acid derivatives is nucleophilic substitution at the carbonyl carbon. [Aldehydes and ketones usually undergo nucleophilic addition because they do not contain reasonable leaving groups:  $R^-$  and  $H^-$  are poor leaving groups.] A generalized reaction mechanism under basic conditions,  $B_{AC}2$  (basic, acyl, bimolecular) looks like this, where Y is a leaving group – one of the boxed groups above:



[If  $:Nu$  is neutral, the intermediate will be a neutral betaine ( $-O^-$ ,  $-Nu^+$ ), and the product will carry a + charge unless the  $-Nu^+$  expels an  $H^+$ .]

A generalized reaction mechanism under acidic conditions,  $A_{AC}2$  (acidic, acyl, bimolecular) looks like this:



Since the intermediate is more crowded than the reactant, bulky R-groups slow down the reaction: for a given Nu and Y, the rate of reaction is usually in the order:  $1^\circ > 2^\circ > 3^\circ$ .

The more electronegative Y the faster the reaction: for a given R and Nu, the rate of reaction is usually in the order:  $\text{Cl} > \text{OCOR} > \text{OR}' > \text{NR}'\text{R}''$ . The reason for this depends on the reaction type.

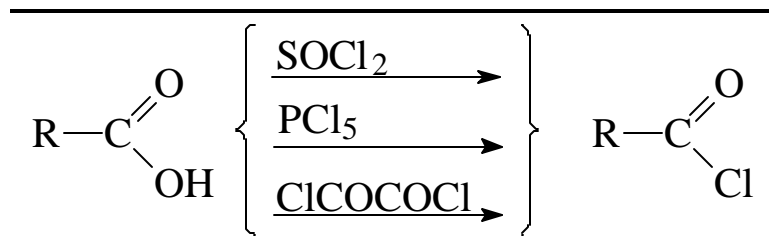
☞ If it is  $\text{B}_{\text{AC}}2$  with Nu<sup>-</sup>, the intermediate carries a negative charge and it (and the transition state leading to it) are stabilized by an electronegative group. The reacting molecule, on the other hand, is destabilized by electronegative groups because of the  $\delta+$  charge on the carbonyl carbon. These effects work together causing electronegative groups to reduce  $\Delta G^\ddagger$ .

☞ If it is  $\text{B}_{\text{AC}}2$  with Nu, the intermediate is neutral, but the starting material is destabilized by electronegative groups because of the  $\delta+$  charge on the carbonyl carbon, thus reducing  $\Delta G^\ddagger$ .

☞ If it is  $\text{A}_{\text{AC}}2$  (with Nu), the intermediate and reactant (the protonated starting material) are both positively charged. Electronegative groups would destabilize both. However, the effect may be greater on the reactant because the positive charge is transferred to the carbonyl carbon by *both* an inductive and resonance effect, while in the intermediate there is only an inductive effect. If the reactant is more destabilized than the intermediate,  $\Delta G^\ddagger$  is reduced.

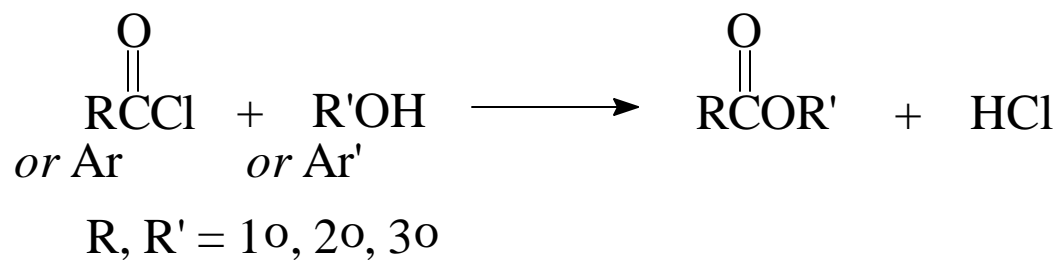
A consequence of this reactivity order is that acid chlorides can be directly converted into the other derivatives and anhydrides can be directly converted into esters and amides, but directly converting the less reactive derivatives into the more reactive ones is difficult.

To convert a carboxylic acid into an ester or amide, it is usually converted to a chloride first.

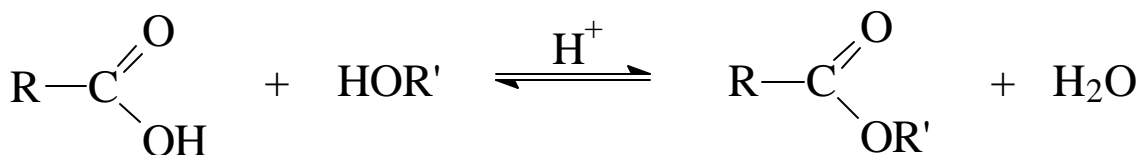


### Esters: Preparation

Reaction of an Acid Chloride with an Alcohol or Phenol –



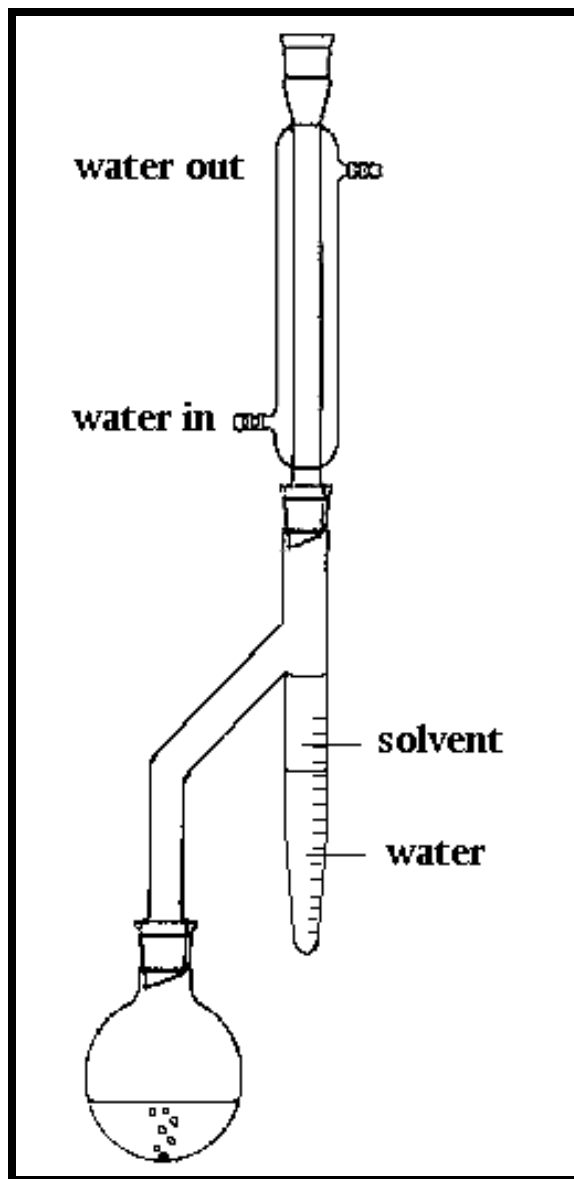
## Fisher Esterification —



The equilibrium constant for a Fisher Esterification is typically about 1. However, when phenols are employed  $K_{\text{eq}}$  is usually much less than 1; phenols are not usually acylated by the Fisher esterification.

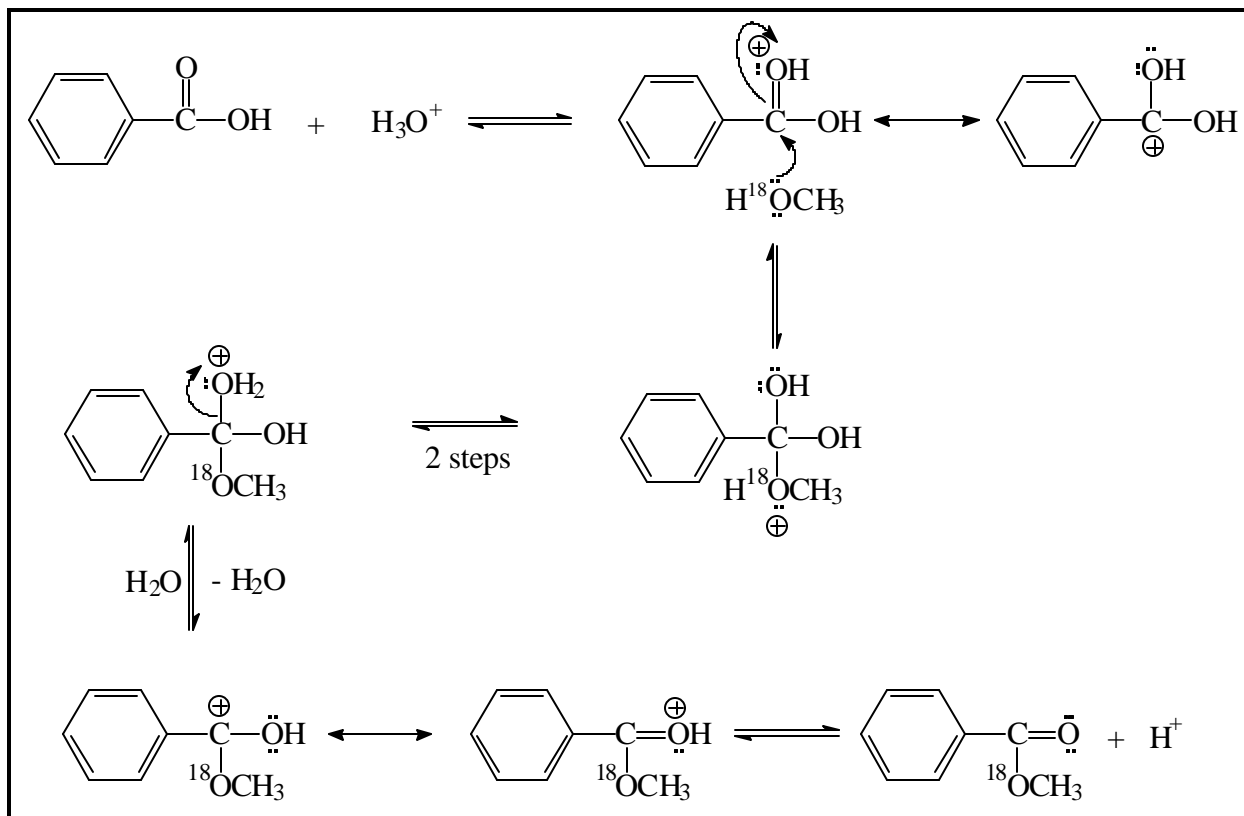
This reaction can be driven in the forward direction by using the alcohol as the solvent or by removal of water. Removal of water is often accomplished by use of a Dean-Stark trap.

This reaction can be driven in the reverse direction (hydrolysis of an ester) by use of an excess of water.



**Dean-Stark Apparatus**

# Mechanism of the Fisher Esterification (and Acid Catalyzed Hydrolysis of an Ester), $A_{AC}2$ —

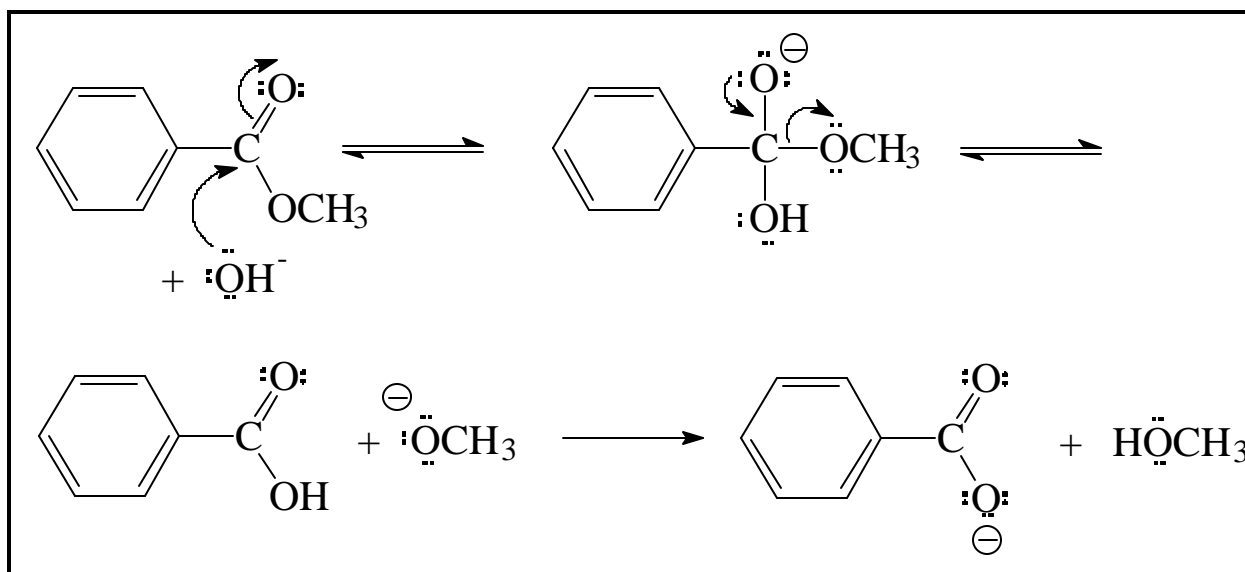


## Esters: Reactions

Hydrolysis: Conversion to Carboxylic Acids —

☞ Acidic: see Fisher Esterification.

☞ Basic: typical nucleophilic acyl substitution via a tetrahedral intermediate,  $B_{AC}2$  —



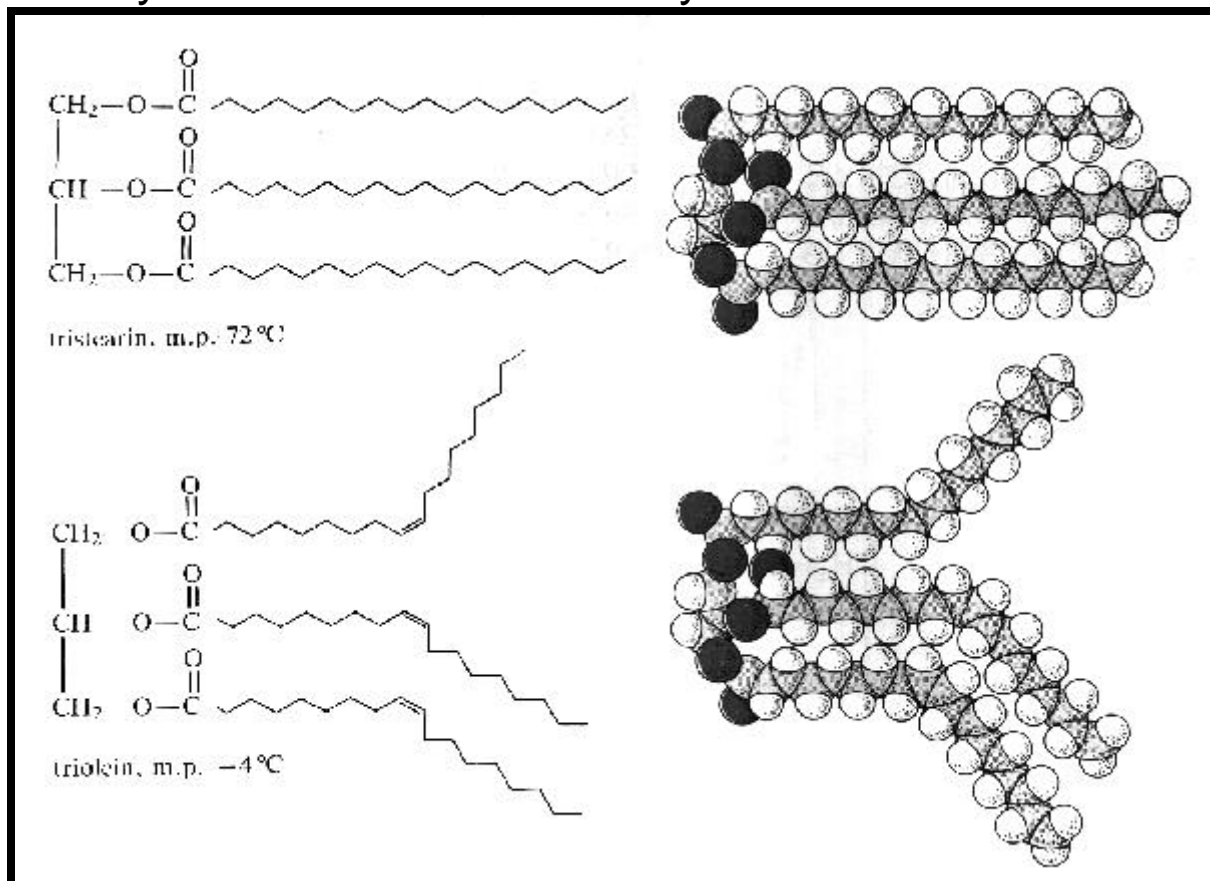


## Saponification —

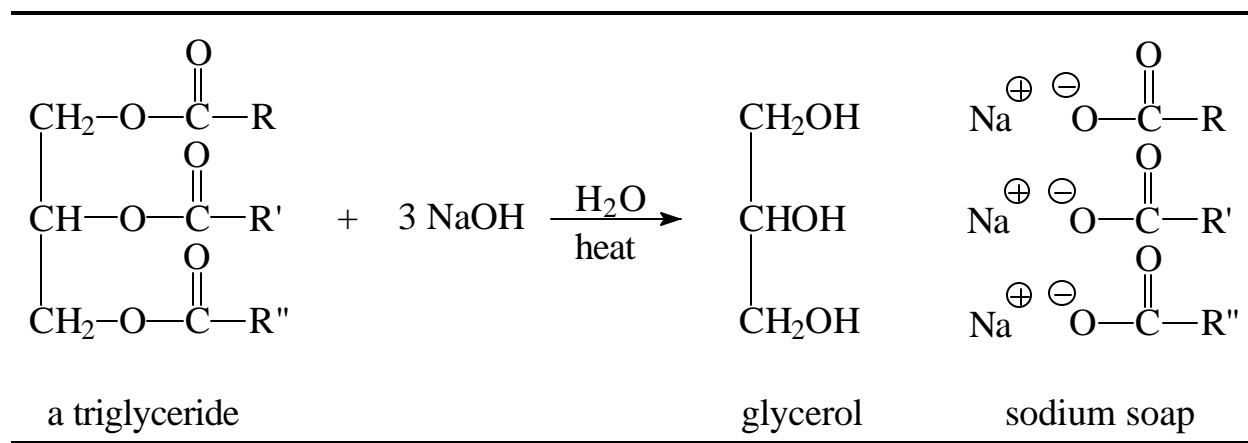
Hydrolysis of esters under basic conditions is known as *saponification*.

Soap is made by saponification of oil or fat. Most soap is made from fat; Castile soap is made from olive oil.

Oils and fats are *triglycerides*, ie triesters of glycerol and fatty acids. Fatty acids are straight chain carboxylic acids, having an even number of carbons ranging from ~10 to ~20. The alkyl portion may be saturated or unsaturated; if unsaturated the double bond(s) are usually *cis* and there are usually not more than 3.



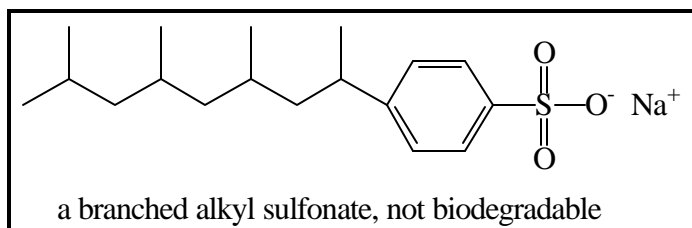
When triglycerides are saponified, soap and glycerol are produced —



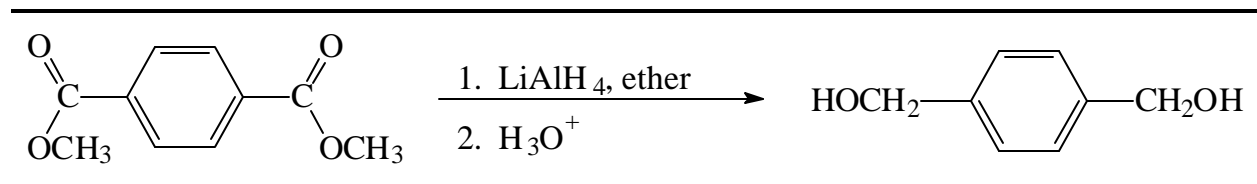
Sodium soap is a *surfactant*; it disperses into water in the form of micelles and is able to emulsify grease.

*Hard water* contains  $\text{Ca}^{+2}$ ,  $\text{Mg}^{+2}$  or iron ions. Sodium soap reacts with these ions forming an insoluble magnesium or calcium soap, *soap scum*. This problem can be remedied by replacing soap by a synthetic detergent which does not precipitate in the presence of the "hard water" ions.

Sodium sulfonates, having long alkyl chains, are sometimes used as detergents and are effective in hard water. Often the sulfonic acid group is on an aromatic ring which also holds the long alkyl group.

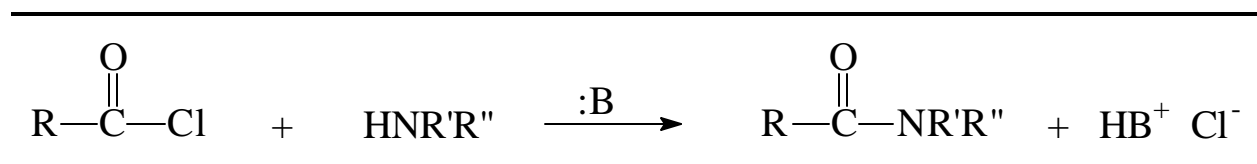


## Reduction to Primary Alcohols —



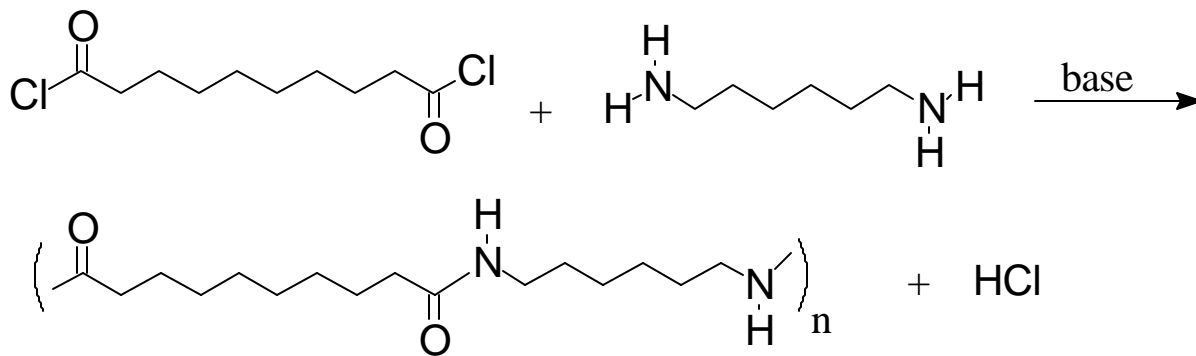
## Amides: Preparation

Amides can be prepared from acid chlorides by reaction with ammonia,  $\text{NH}_3$ , primary amines,  $\text{NH}_2\text{R}'$ , and secondary amines,  $\text{NHR}'\text{R}''$  —

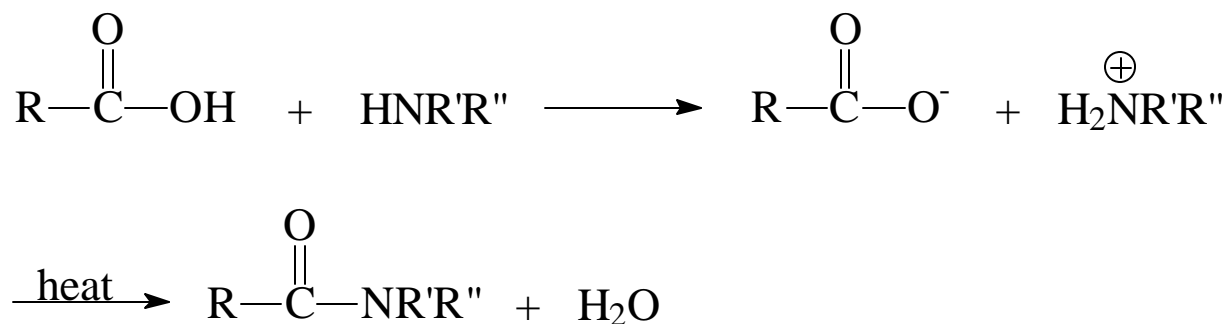


When a base, such as pyridine, is added to promote this reaction, it is known as the Schotten-Baumann reaction.

Nylon 6.10 can be made by interfacial (water and petroleum ether are insoluble in each other) polymerization of decanedioyl dichloride in petroleum ether and hexamethylenediamine and NaOH in water —

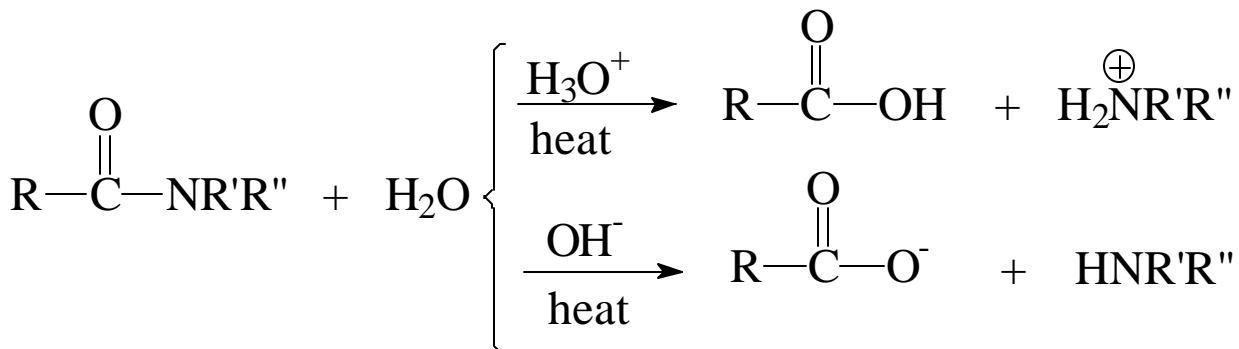


Sometimes, amides can be formed by reacting a carboxylic acid with a primary or secondary amine to form the salt and then heating this salt to expel water –

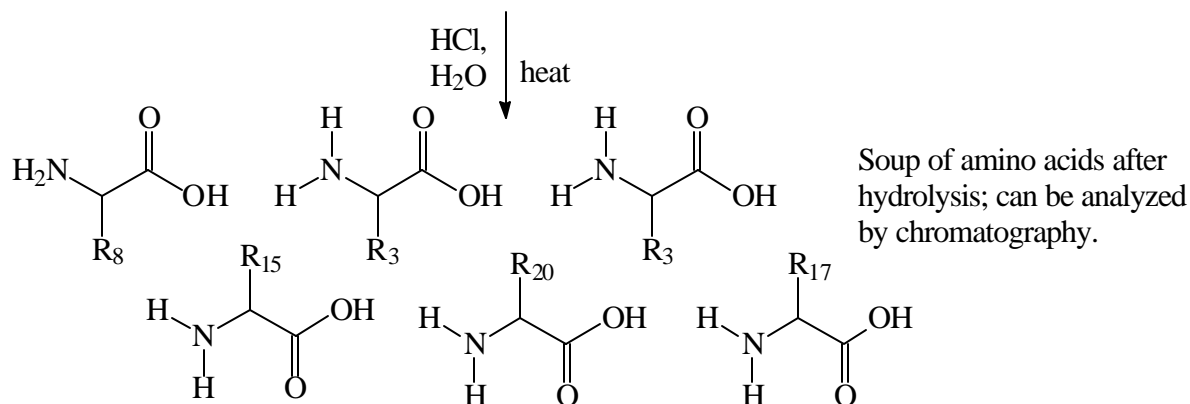
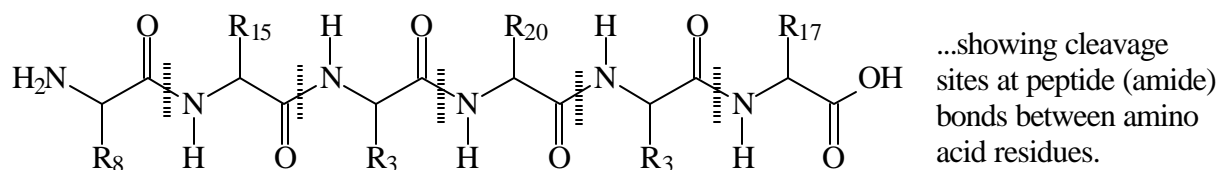
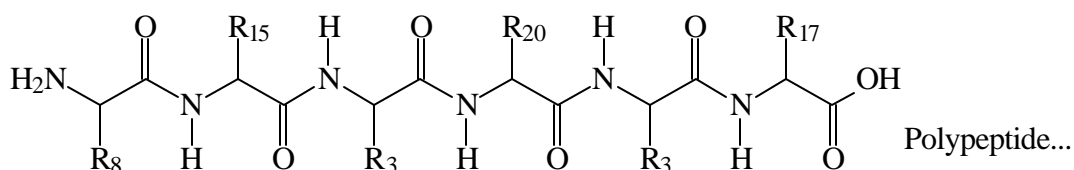


## Reactions of Amides

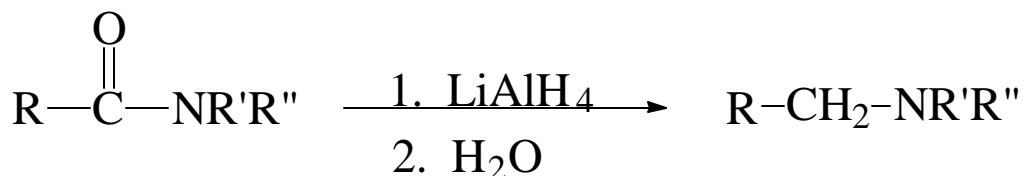
### Hydrolysis —



Acid hydrolysis is used to determine which *amino acid residues* are present in a *polypeptide* or *protein*.



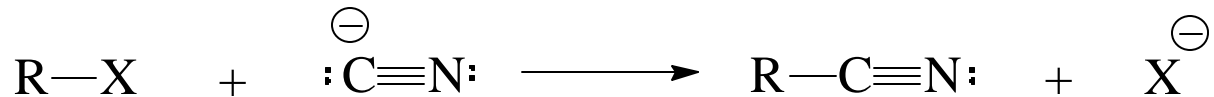
## Reduction to Amines —



## Nitriles

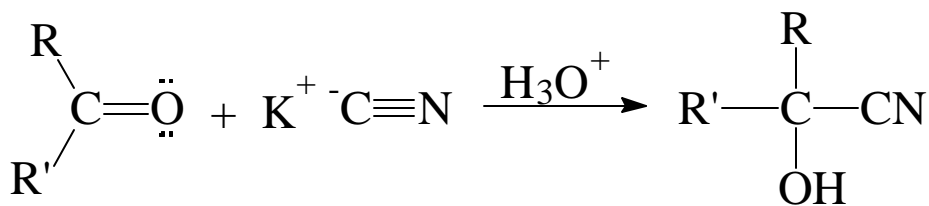
### *Preparation* —

Reaction of cyanide ion with alkyl halides (usually S<sub>N</sub>2):



Works best for 1° R.

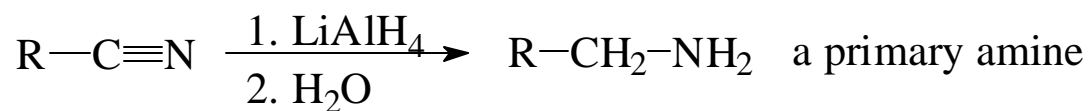
Cyanohydrin synthesis from aldehydes and unhindered ketones:



*Reactions* —

Acidic or basic hydrolysis to give carboxylic acids —  
discussed earlier.

Reduction —



Reaction with Grignard reagents to give ketones —

