Carboxylic Acid Derivatives

The most important derivatives of carboxylic acids are —

R—C(=O)—Cl	R—C(=O)—O—C(=O)—R	R—C(=O)—O—R'	R—C(=O)—N(R')—R''
acid halide	acid anhydride	an ester	an amide
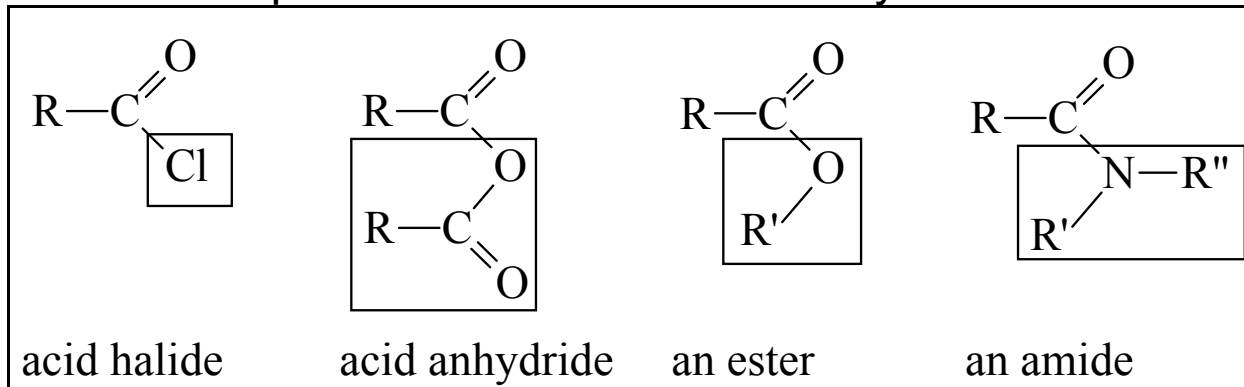
Although not direct derivatives, nitriles, R-CN, are related to carboxylic acids. They can be hydrolyzed to carboxylic acids and they can be prepared from carboxylic acids *via* dehydration of the amide.

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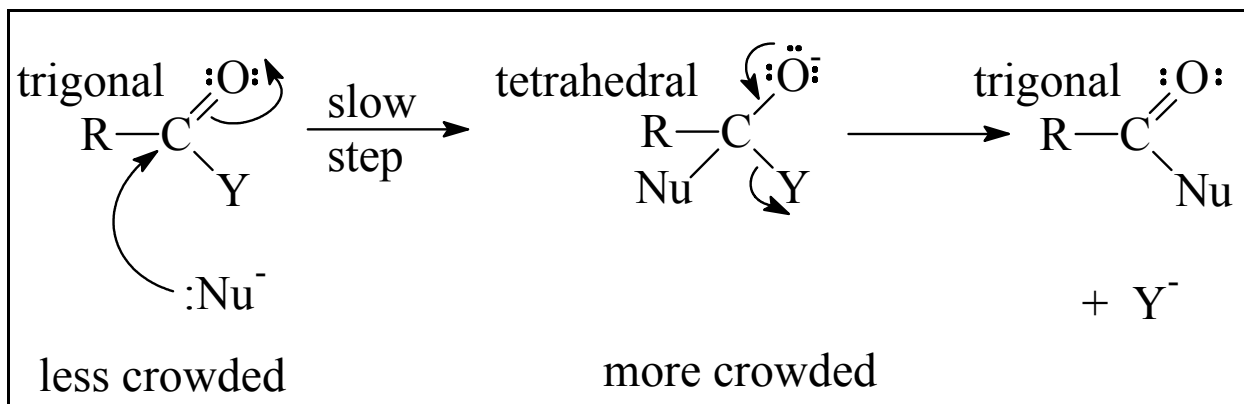
[If :Nu is neutral, the intermediate will be a neutral betaine (-O⁻, -Nu⁺), and the product will carry a + charge unless the -Nu⁺ expells an H⁺.]

A generalized reaction mechanism under acidic conditions, $A_{AC}2$ (acidic, acyl, bimolecular) looks like this:
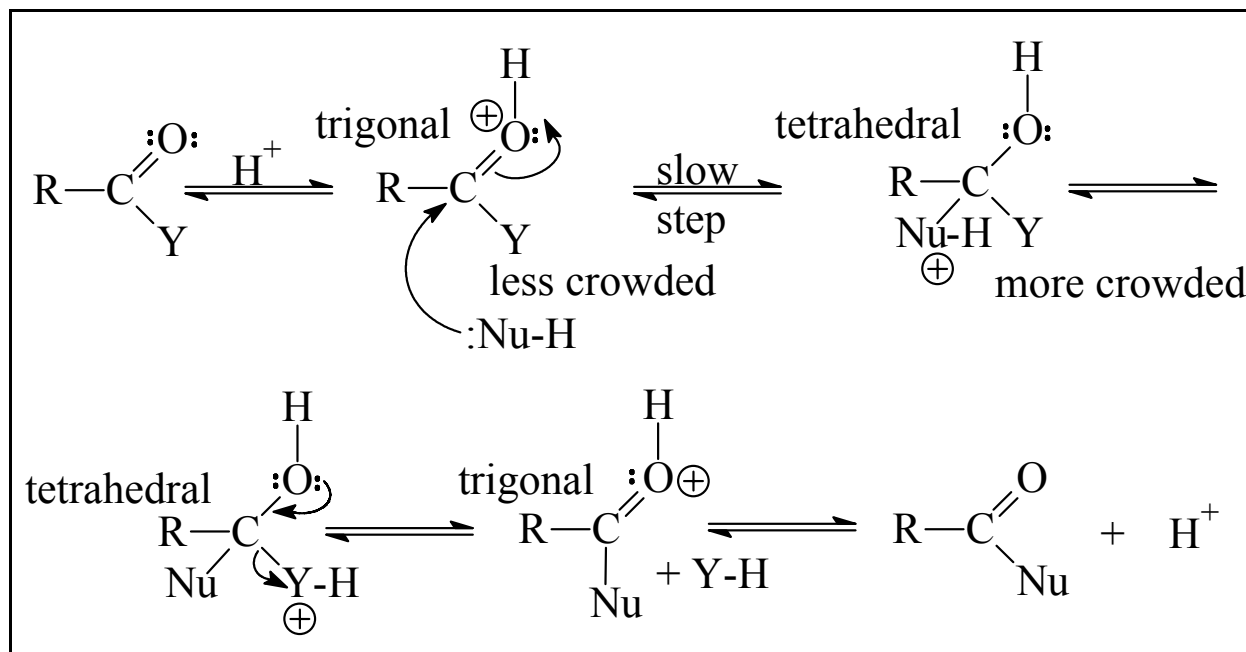
Since the intermediate is more crowded than the reactant, bulky R-groups slow down the reaction: for a given Nu and Y, the rate of reaction is usually in the order: $1° > 2° > 3°$.

The more electronegative Y the faster the reaction: for a given R and Nu, the rate of reaction is usually in the order: Cl > OCOR > OR' > NR'R". The reason for this depends on the reaction type.
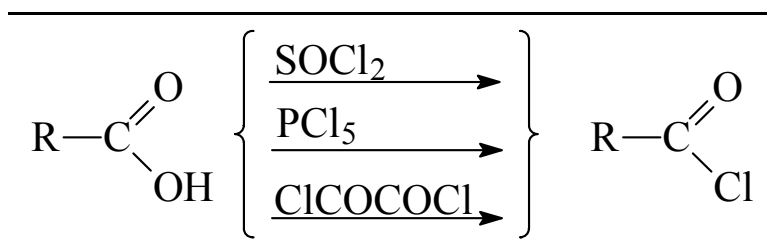
> If it is $B_{AC}2$ with Nu^-, the intermediate carries a negative charge and it (and the transition state leading to it) are stabilized by an electronegative group. The reacting molecule, on the other hand, is destabilized by electronegative groups because of the $\delta+$ charge on the carbonyl carbon. These effects work together causing electronegative groups to reduce $\Delta G^{\ddagger}$.

> If it is $B_{AC}2$ 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 $\Delta G^{\ddagger}$.
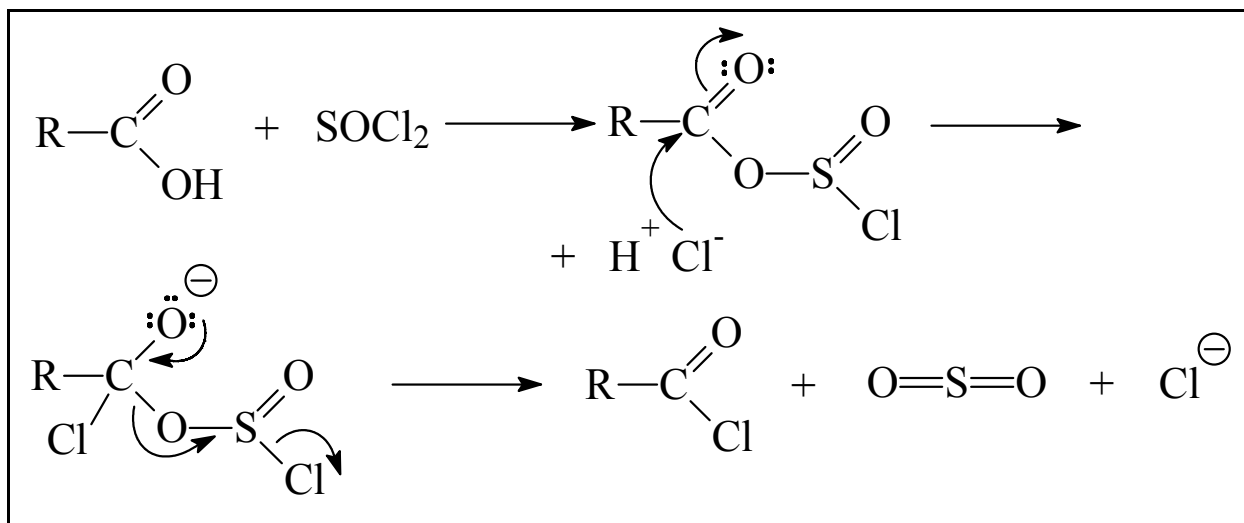
> If it is $A_{AC}2$ (with Nu), the intermediate and reactant (the protonated starting material) are both positively charged. Electronegative groups would destabilize both. However, the effect may be greater on the reactant because the positive charge is transferred to the carbonyl carbon by *both* an 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 derivates 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.

$$R-C\overset{O}{\underset{OH}{\Big\langle}} \quad \begin{array}{c} \underline{SOCl_2} \longrightarrow \\ \underline{PCl_5} \longrightarrow \\ \underline{ClCOCOCl} \longrightarrow \end{array} \quad R-C\overset{O}{\underset{Cl}{\Big\langle}}$$
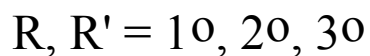
Mechanism (using thionyl chloride) —

Esters: Preparation

Reaction of an Acid Chloride with an Alcohol or Phenol—

$$\underset{or\ Ar}{\overset{\displaystyle O}{\overset{\|}{RCCl}}} \ + \ \underset{or\ Ar'}{R'OH} \ \longrightarrow \ \overset{\displaystyle O}{\overset{\|}{RCOR'}} \ + \ HCl$$

R, R' = 1o, 2o, 3o
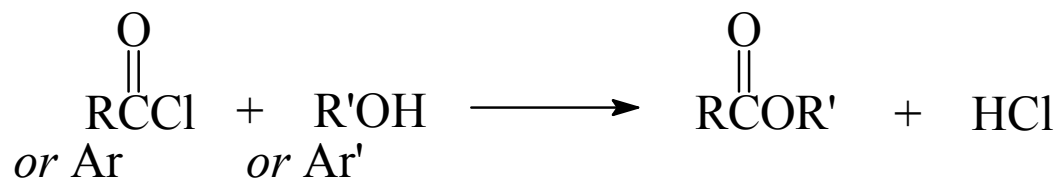
This reaction is catalyzed by pyridine —

Fisher Esterification —

$$R-C\!\!\underset{OH}{\overset{O}{\Big\langle}} \quad + \quad HOR' \quad \underset{\longleftarrow}{\overset{H^+}{\longrightarrow}} \quad R-C\!\!\underset{OR'}{\overset{O}{\Big\langle}} \quad + \quad H_2O$$
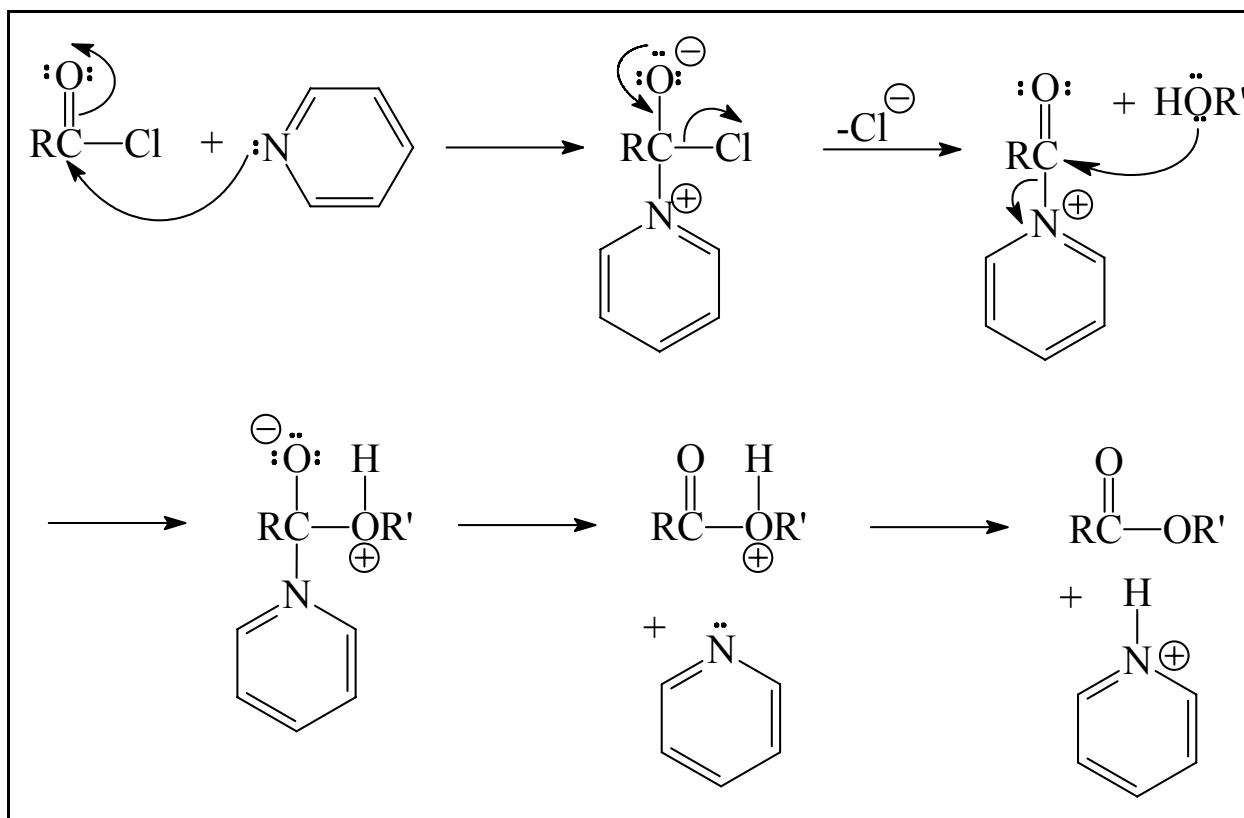
The equilibrium constant for a Fisher Esterification is typically about 1. However, when phenols are employed K_{eq} is usually much less than 1; phenols are not usually acylated by the Fisher esterification.
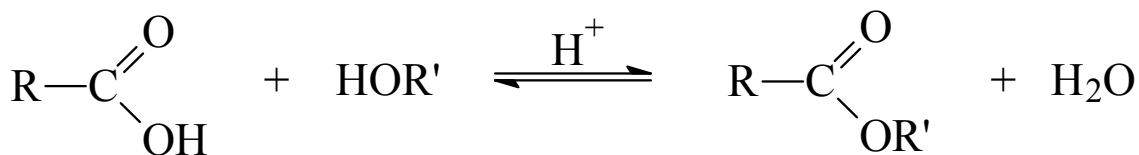
This reaction can be driven in the forward direction by using the alcohol as the solvent or by removal of water. Removal of water is often accomplished by use of a Dean-Stark trap.

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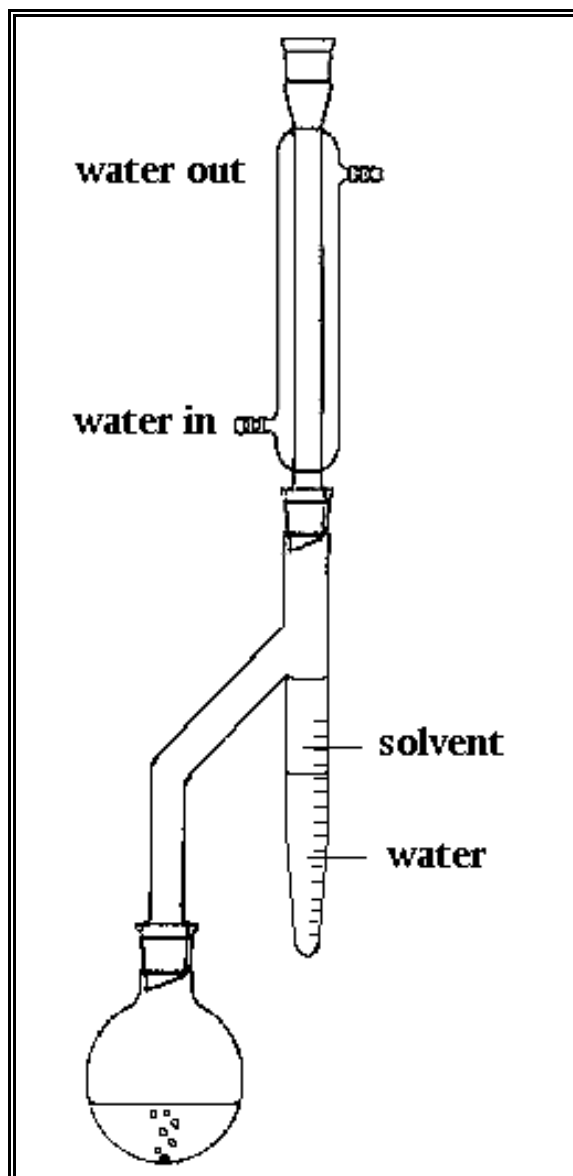
Dean-Stark Apparatus

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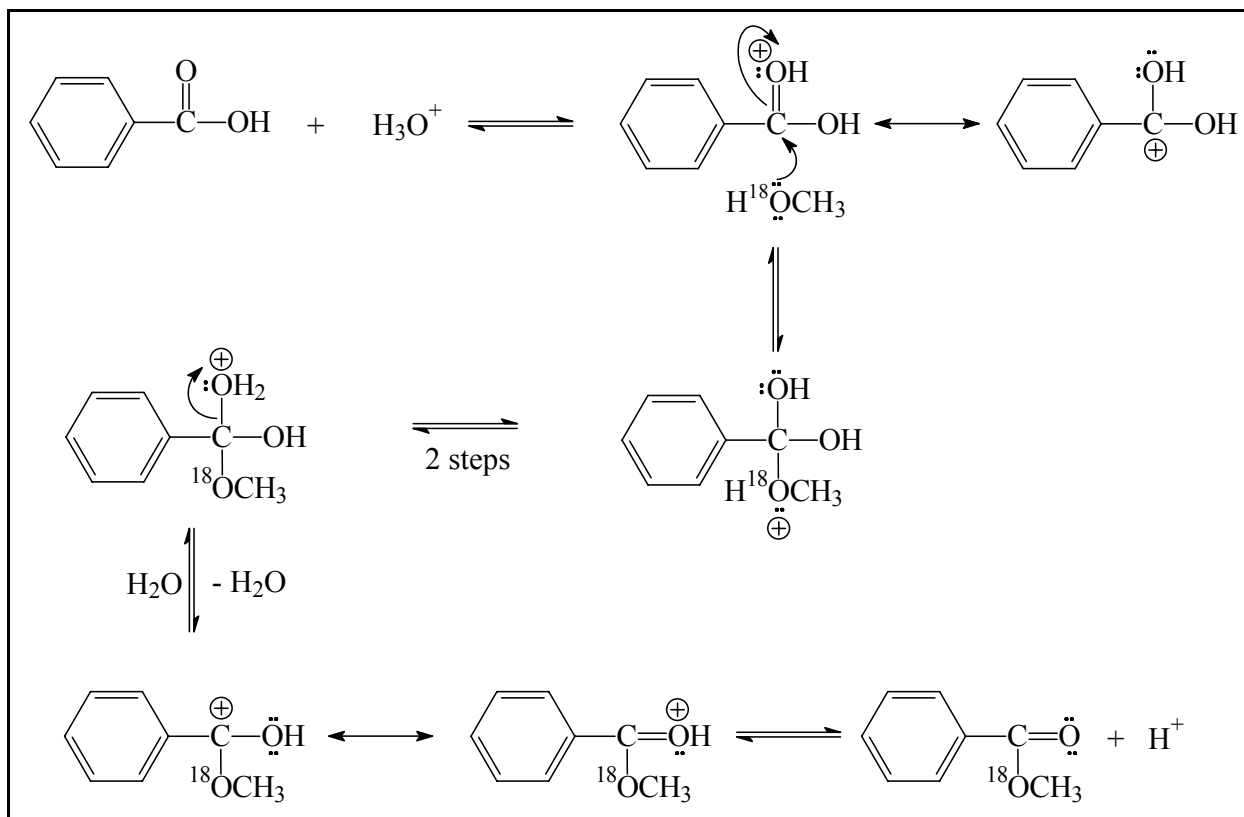
Esters: Reactions

Hydrolysis: Conversion to Carboxylic Acids —

> Acidic: see Fisher Esterification.

> Basic: typical nucleophilic acyl substitution via a
>   tetrahedral intermediate, $B_{AC}2$ —
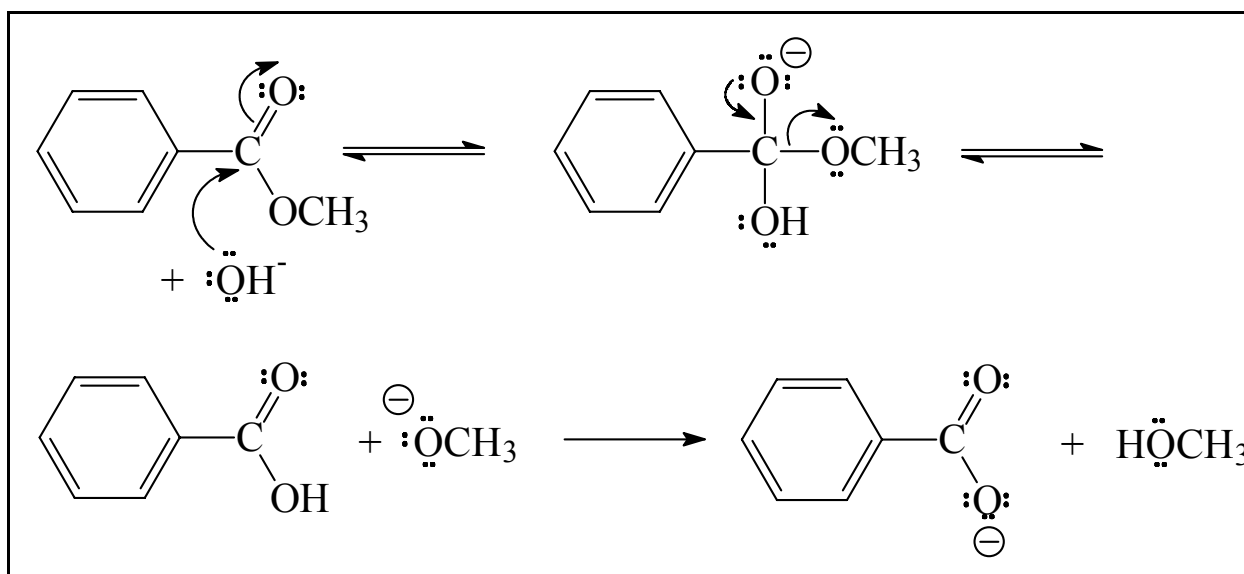
Evidence for this Mechanism for the Alkaline Hydrolysis of Esters —

rate = k_2[ester][OH$^-$], suggesting —

1.

2.

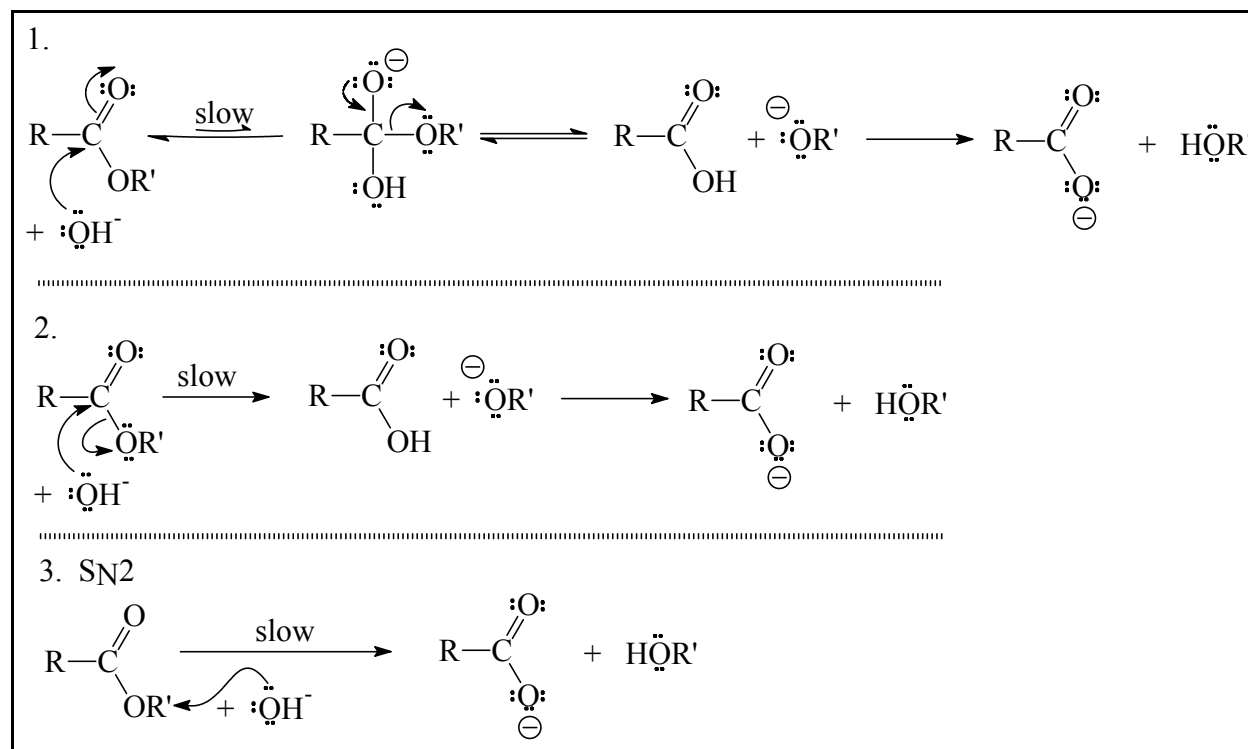3. S$_N$2

Narrowing down the field —

> If 1 or 2 is correct, inversion of configuration is not expected in R', since the O-R' bond is not broken. However, if 3 (an S_N2 mechanism) is correct, a Walden inversion is predicted. Experiment and observation:

$$Ph-\underset{O}{\overset{\|}{C}}-\boxed{Cl \quad + \quad H-O}-\underset{\underset{H}{|}}{\overset{C_2H_5}{\overset{|}{C}}}\cdots CH_3 \longrightarrow Ph-\underset{O}{\overset{\|}{C}}-O-\underset{\underset{H}{|}}{\overset{C_2H_5}{\overset{|}{C}}}\cdots CH_3$$

(S)-2-butanol

configuration retained: S

$$\xrightarrow[H_2O]{OH^-} \quad Ph-\underset{O}{\overset{\|}{C}}-O^- \quad + \quad H-O-\underset{\underset{H}{|}}{\overset{C_2H_5}{\overset{|}{C}}}\cdots CH_3$$

(S)-2-butanol
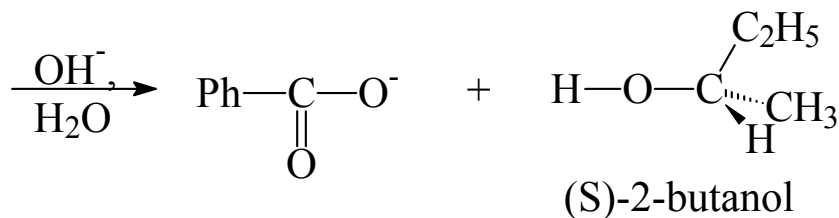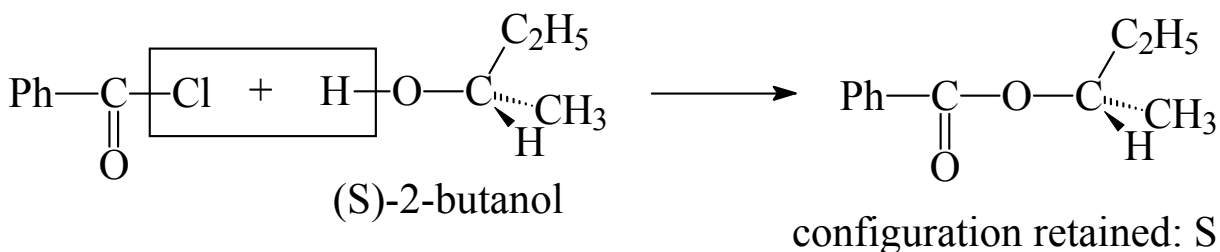
Configuration is retained: <u>mechanism 3 (S_N2) is incorrect</u>. This is confirmed by an isotopic tracer experiment—

$$C_2H_5-\underset{}{\overset{O}{\overset{\|}{C}}}-{}^{18}OC_2H_5 \quad + \quad OH^- \longrightarrow C_2H_5-\underset{}{\overset{O}{\overset{\|}{C}}}-O^- \quad + \quad H^{18}OC_2H_5$$
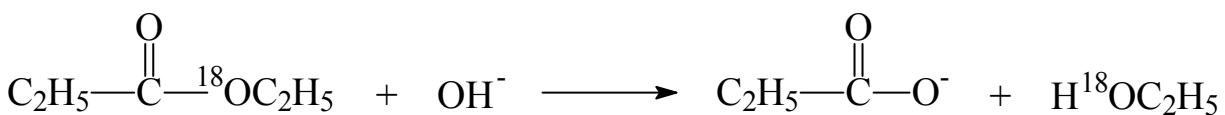
> To distinguish between 1 and 2 (*ie*, is there a tetrahedral intermediate?) —

Treat $R-\overset{\overset{18O}{\|}}{C}-OR'$ with OH⁻ and recover some ester before it is all consumed. If mechanism 2 is correct we would expect all of the ester to be labeled, even if the reaction is reversible:

$$R-\overset{\overset{18O}{\|}}{C}-OR' \ + \ OH^- \ \rightleftharpoons \ R-\overset{\overset{18O}{\|}}{C}-OH \ + \ OR'^-$$
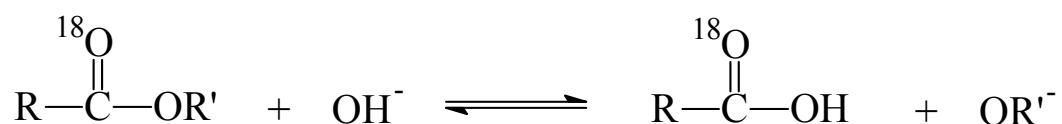
However, if mechanism 1 is correct, we might expect to recover ester, part of which is unlabeled, *via* the following mechanism —

$$
\underset{\substack{\| \\ R-C-OR'}}{\overset{^{18}O}{}} + OH^- \rightleftharpoons \underset{\substack{| \\ OH \\ R-C-OR'}}{\overset{^{18}O^-}{}} \rightleftharpoons \underset{\substack{\| \\ R-C-OH}}{\overset{^{18}O}{}} + OR'^-
$$

$$OH^- \upharpoonleft \downharpoonright H_2O$$

$$
\boxed{\underset{\substack{| \\ OH \\ R-C-OR'}}{\overset{^{18}OH}{}}}
$$

$$\underset{\substack{\| \\ R-C-O^-}}{\overset{^{18}O}{}}$$

$$H_2O \upharpoonleft \downharpoonright OH^-$$

$$\updownarrow$$

$$\underset{\substack{\| \\ R-C=O}}{\overset{^{18}O^-}{}}$$

$$+ \quad HOR'^-$$

$$
\underset{\substack{| \\ O^- \\ R-C-OR'}}{\overset{^{18}OH}{}} \rightleftharpoons \underset{\substack{\| \\ O \\ R-C-{}^{18}OH}}{} + OR'^-
$$

$$\upharpoonleft \downharpoonright$$

$$\boxed{\text{unlabeled ester} \quad \underset{\substack{\| \\ O}}{R-C-OR'}} + {}^{18}OH^-$$
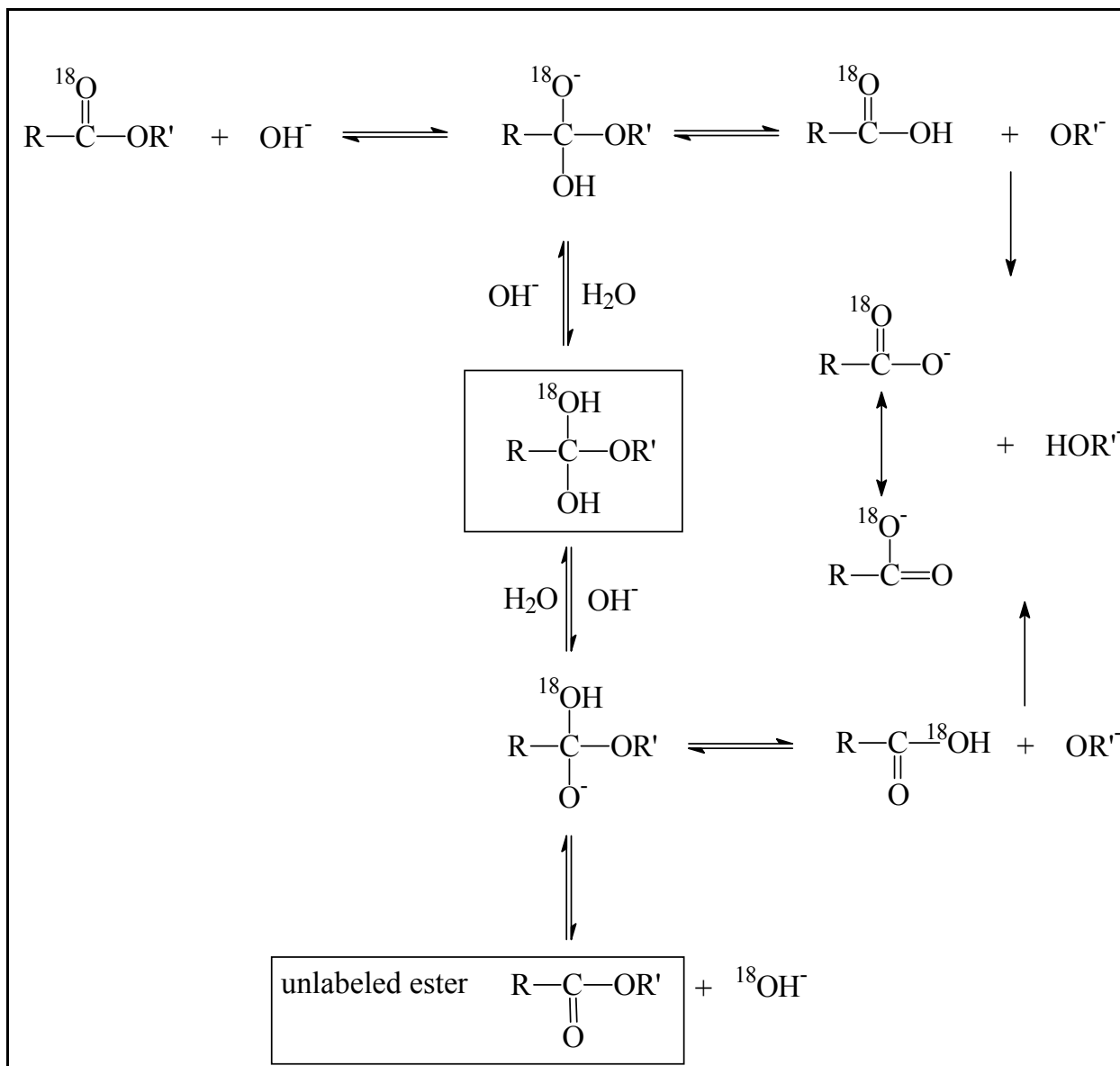
When unreacted ester is recovered, some *is* unlabeled. This rules out mechanism 2.
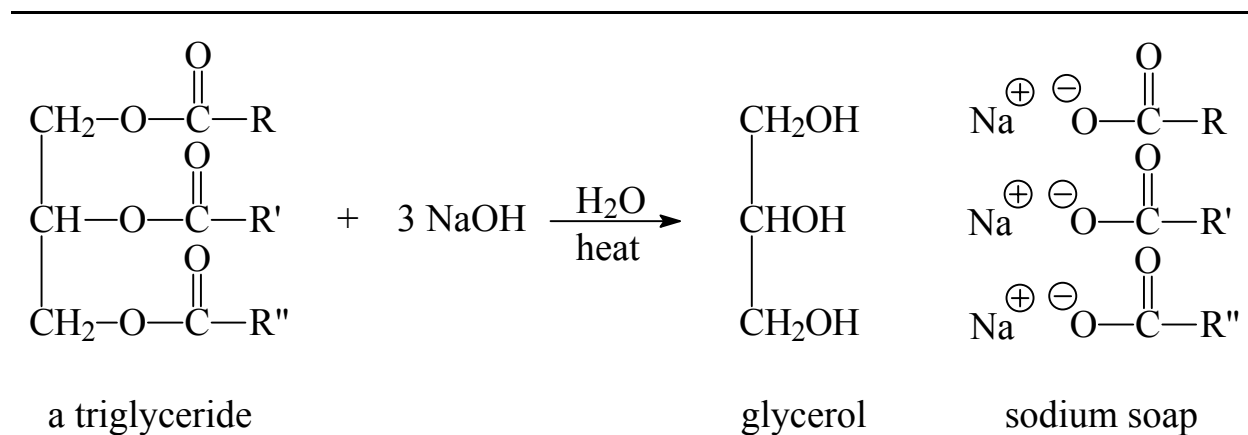
Saponification —

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.
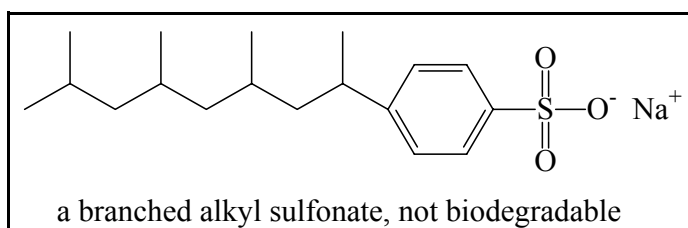

tristearin, m.p. 72 °C

triolein, m.p. −4 °C
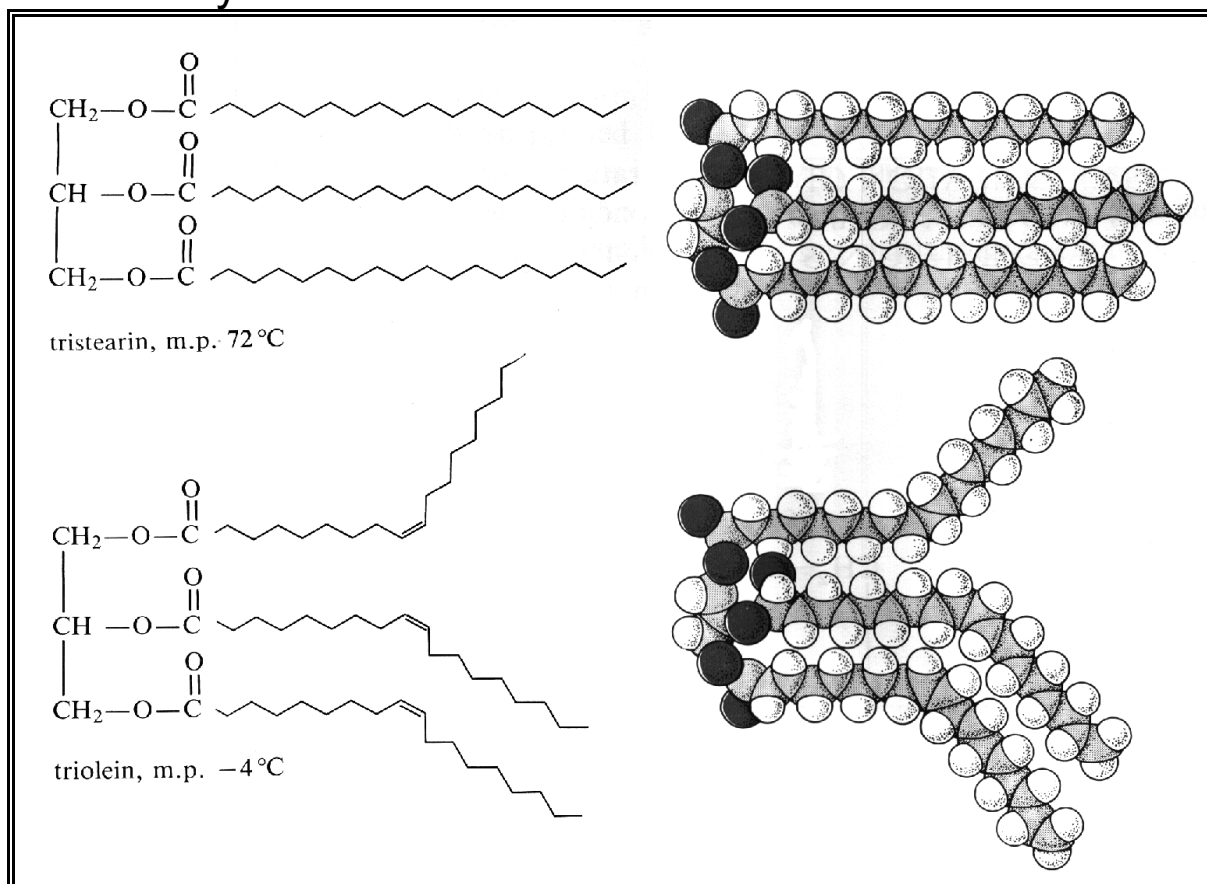
When triglycerides are saponified, soap and glycerol are produced —

$$
\begin{array}{c}
\underset{\text{a triglyceride}}{
\begin{array}{l}
CH_2-O-\overset{\displaystyle O}{\overset{\|}{C}}-R \\
CH-O-\overset{\displaystyle O}{\overset{\|}{C}}-R' \\
CH_2-O-\overset{\displaystyle O}{\overset{\|}{C}}-R''
\end{array}}
\quad + \quad 3\ NaOH \quad \xrightarrow[\text{heat}]{H_2O} \quad
\underset{\text{glycerol}}{
\begin{array}{l}
CH_2OH \\
CHOH \\
CH_2OH
\end{array}}
\quad
\underset{\text{sodium soap}}{
\begin{array}{l}
Na^{\oplus}\ {}^{\ominus}O-\overset{\displaystyle O}{\overset{\|}{C}}-R \\
Na^{\oplus}\ {}^{\ominus}O-\overset{\displaystyle O}{\overset{\|}{C}}-R' \\
Na^{\oplus}\ {}^{\ominus}O-\overset{\displaystyle O}{\overset{\|}{C}}-R''
\end{array}}
\end{array}
$$

Sodium soap is a *surfactant*; it disperses into water in the form of micelles and is able to emulsify grease.
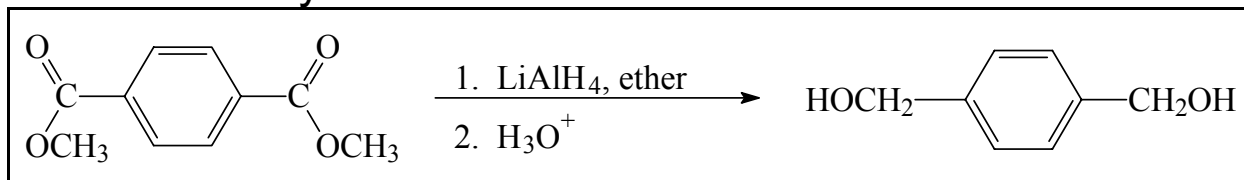
Hard water contains Ca^{+2}, Mg^{+2} or iron ions. Sodium soap reacts with these ions forming an insoluble magnesium or calcium soap, *soap scum.* This problem can be remedied by replacing soap by a synthetic detergent which does not precipitate in the presence of the "hard water" ions.

Sodium sulfonates, having long alkyl chains, are sometimes used as detergents and are effective in hard water.

a branched alkyl sulfonate, not biodegradable

Often the sulfonic acid group is on an aromatic ring which also holds the long alkyl group.

Reduction —

> to Primary Alcohols:

$$\text{(dimethyl terephthalate)} \xrightarrow[\text{2. } H_3O^+]{\text{1. LiAlH}_4, \text{ ether}} \text{HOCH}_2\text{—(benzene)—CH}_2\text{OH}$$

> to Aldehydes:

$$\xrightarrow[\text{2. } H_3O^+]{\text{1. DIBAH, toluene, -78}^o}$$

$$\text{DIBAH} = [(\text{CH}_3)_2\text{CHCH}_2]_2\text{AlH}$$
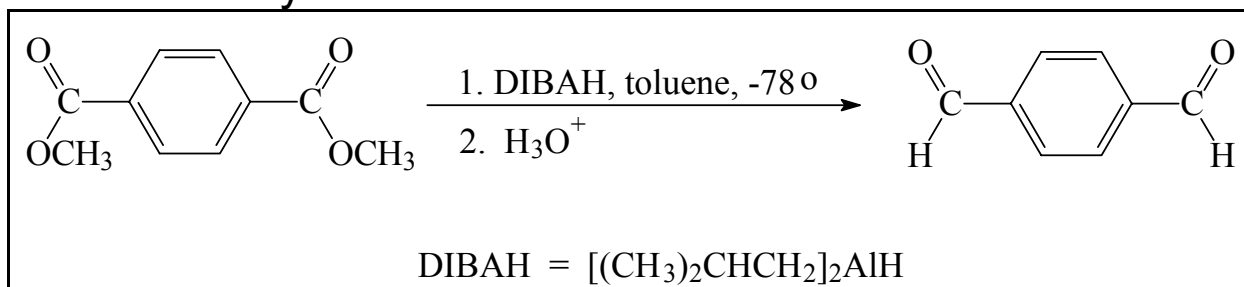
> to 2° or 3° Alcohols *via* Grignard Reagents:

$$\underset{H}{\overset{O}{\text{C}}}\text{—OCH}_3 \quad + \quad 2 \;\; \text{(C}_6\text{H}_5)\text{—MgBr} \quad \xrightarrow{H_3O^+} \quad \text{(C}_6\text{H}_5)_2\text{CH—OH}$$

$$\text{(C}_6\text{H}_5)\overset{O}{\text{C}}\text{—OCH}_3 \quad + \quad 2 \;\; \text{(C}_6\text{H}_5)\text{—MgBr} \quad \xrightarrow{H_3O^+} \quad \text{(C}_6\text{H}_5)_3\text{C—OH}$$
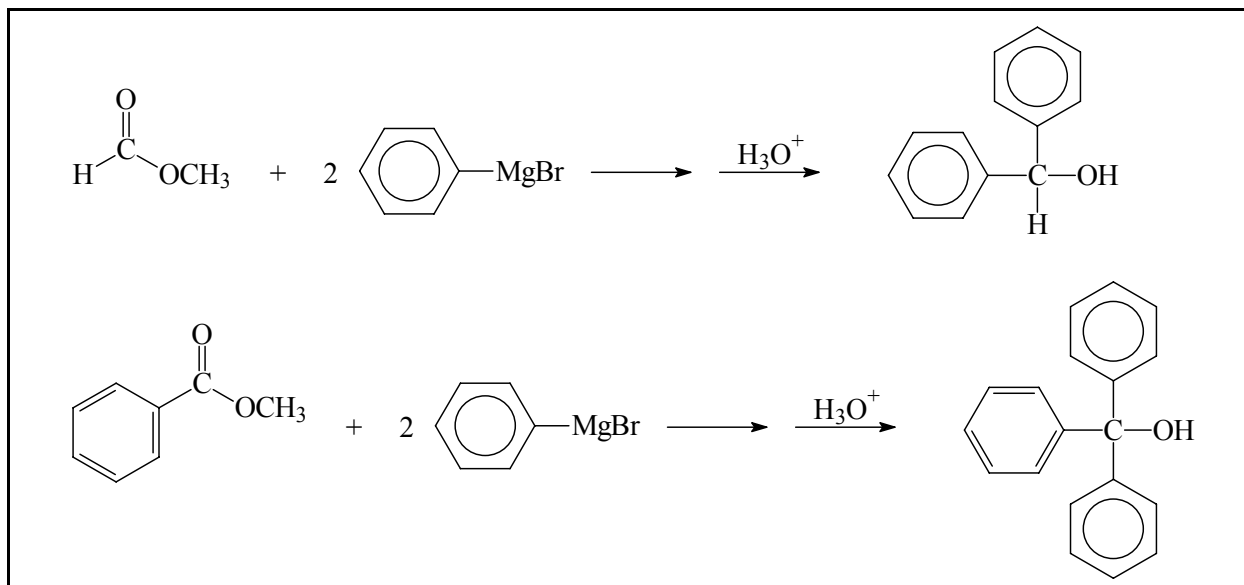
## Amides: Preparation

Amides can be prepared from acid chlorides by reaction with ammonia, NH_3, primary amines, NH_2R', and secondary amines, $NHR'R''$ —

$$R-\overset{\overset{O}{\|}}{C}-Cl \quad + \quad HNR'R'' \quad \xrightarrow{:B} \quad R-\overset{\overset{O}{\|}}{C}-NR'R'' \quad + \quad HB^+ \; Cl^-$$
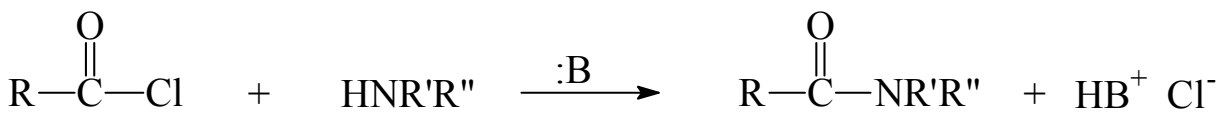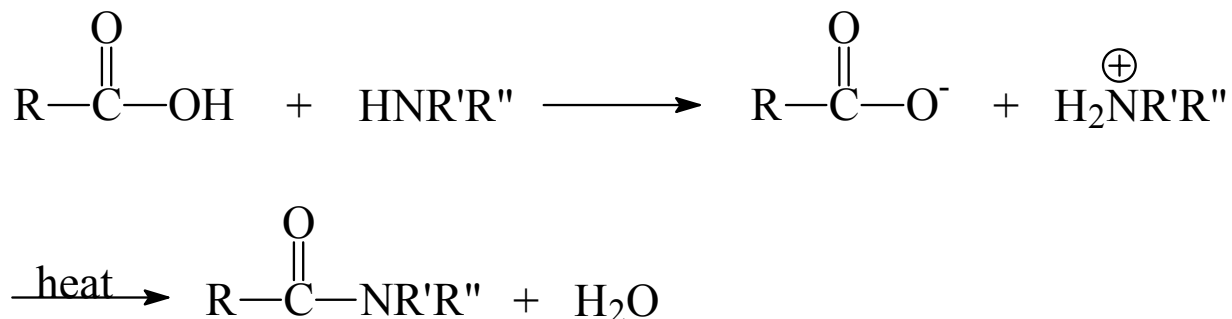
When a base, such as pyridine, is added to promote this reaction, it is known as the Schotten-Baumann reaction.

Nylon 6.10 can be made by interfacial polymerization of decanedioyl dichloride in petroleum ether and hexamethylenediamine and NaOH in water —
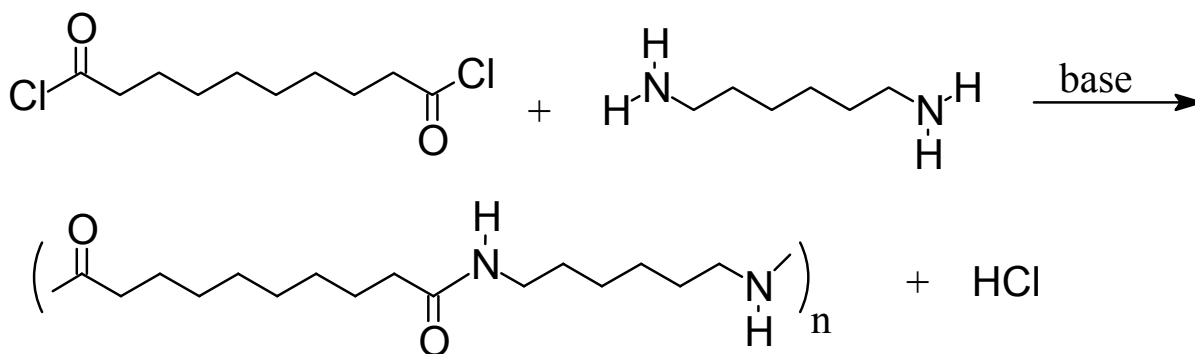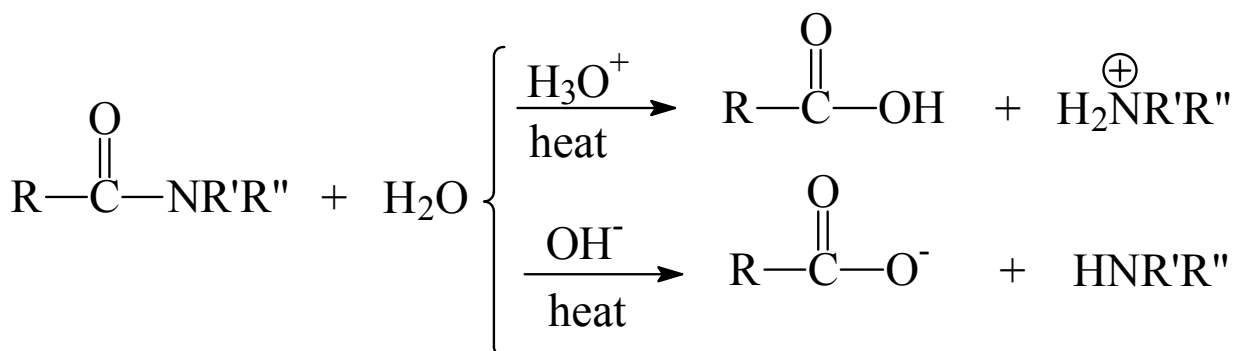
Sometimes, amides can be formed by reacting a carboxylic acid with a primary or secondary amine to form the salt and then heating this salt to expel water —
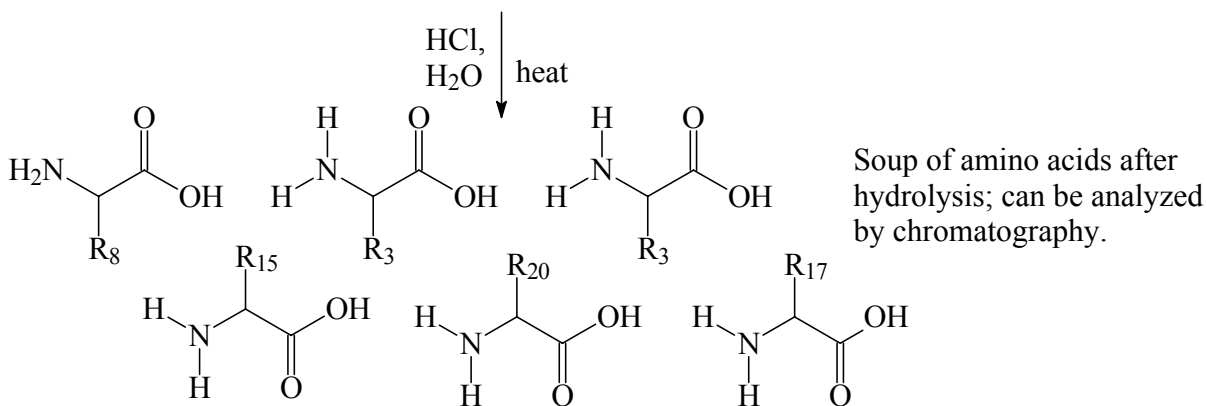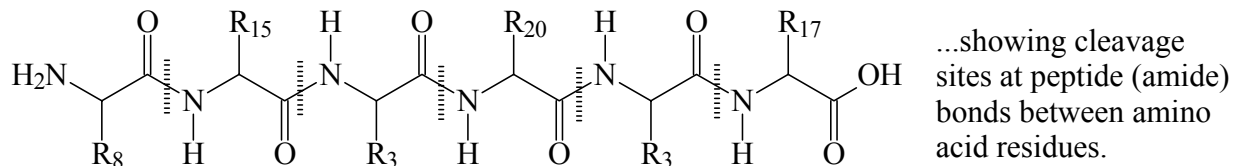
$$\underset{\substack{\| \\ \text{O}}}{R-C-OH} \;+\; HNR'R'' \longrightarrow \underset{\substack{\| \\ \text{O}}}{R-C-O^-} \;+\; H_2\overset{\oplus}{N}R'R''$$

$$\xrightarrow{\text{heat}} \underset{\substack{\| \\ \text{O}}}{R-C-NR'R''} \;+\; H_2O$$

Reactions of Amides

Hydrolysis —

$$\underset{\substack{\| \\ \text{O}}}{R-C-NR'R''} \;+\; H_2O \begin{cases} \xrightarrow[\text{heat}]{H_3O^+} & \underset{\substack{\| \\ \text{O}}}{R-C-OH} \;+\; H_2\overset{\oplus}{N}R'R'' \\ \\ \xrightarrow[\text{heat}]{OH^-} & \underset{\substack{\| \\ \text{O}}}{R-C-O^-} \;+\; HNR'R'' \end{cases}$$
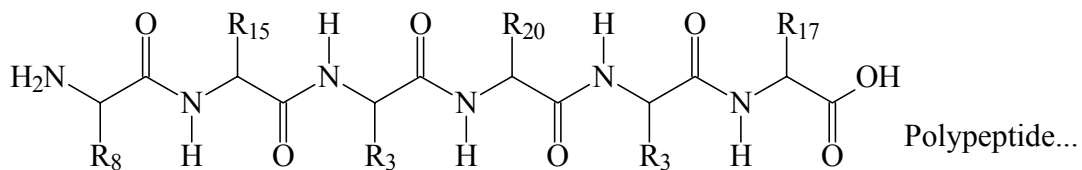
Acid hydrolysis is used to determine which *amino acid residues* are present in a *polypeptide* or *protein.*

Polypeptide...

...showing cleavage sites at peptide (amide) bonds between amino acid residues.

HCl, H_2O | heat

Soup of amino acids after hydrolysis; can be analyzed by chromatography.

Reduction to Amines —

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-NR'R'' \quad \xrightarrow{\text{1. LiAlH}_4 \quad} \quad R-CH_2-NR'R''$$
$$\text{2. } H_2O$$
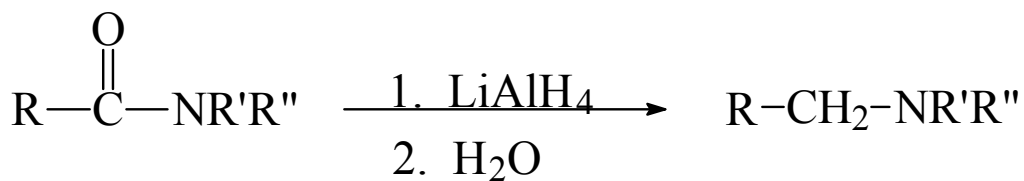
Nitriles

Preparation —

Reaction of cyanide ion with alkyl halides (usually S_N2):

$$R-X \quad + \quad :C{\equiv}N: ^{\ominus} \longrightarrow R-C{\equiv}N: \quad + \quad X^{\ominus}$$
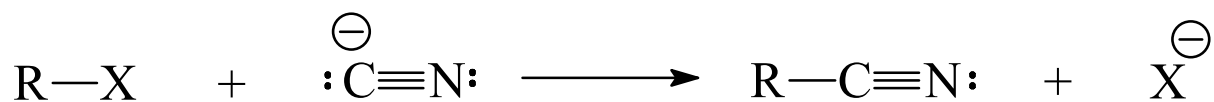
Works best for 1° R.

Cyanohydrin synthesis from aldehydes and unhindered ketones:

$$\underset{R'}{\overset{R}{\diagdown}}C{=}\ddot{O} \; + \; K^+ \; {}^-C{\equiv}N \xrightarrow{H_3O^+} R'-\underset{OH}{\overset{R}{\underset{|}{\overset{|}{C}}}}-CN$$
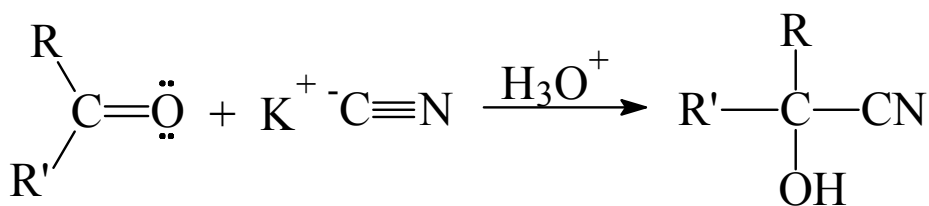
Dehydration of primary amides:

$$\underset{or \; Ar}{R}-\overset{\overset{O}{\|}}{C}-NH_2 \xrightarrow[\begin{array}{c}or \; POCl_3\\or \; P_2O_5\end{array}]{SOCl_2} \underset{or \; Ar}{R}-C{\equiv}N$$
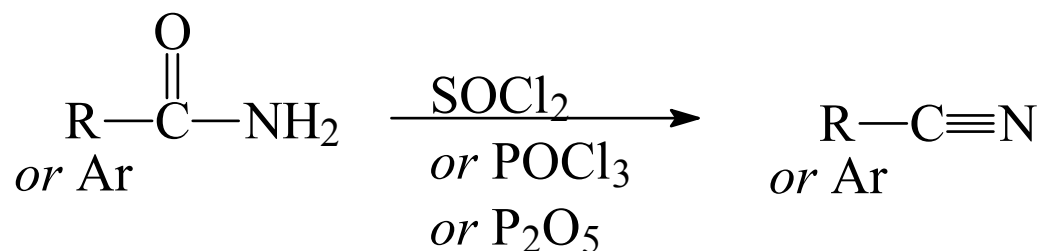
Diazotization of primary aromatic amines, followed by the Sandmeyer reaction:

$$\text{Ar—NH}_2 \xrightarrow[\text{HCl}]{\text{NaNO}_2} \text{Ar—}\overset{\oplus}{\text{N}}\text{≡N:} \quad \overset{\ominus}{\text{Cl}} \xrightarrow{\text{CuCN}} \text{Ar—C≡N}$$
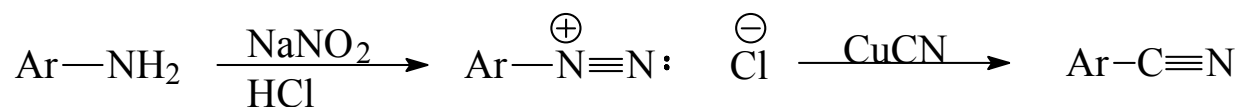
Reactions —

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

Reduction —

$$\text{R—C≡N} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. LiAlH}_4} \text{R—CH}_2\text{—NH}_2 \quad \text{a primary amine}$$

$$\text{R—C≡N} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. DIBAH, -78}^\text{o}} \text{R—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—H}$$
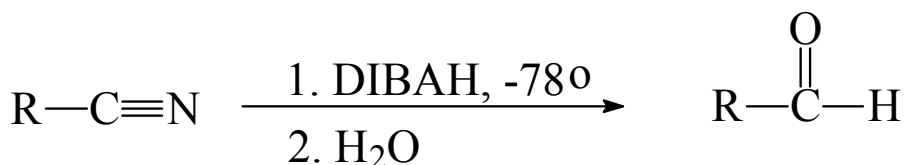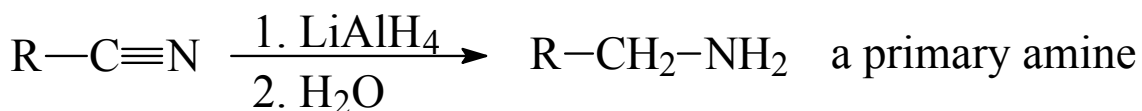
Reaction with Grignard reagents to give ketones —

$$\text{R—C≡N} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. R'MgX}} \text{R—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—R'}$$