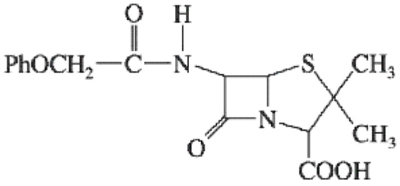
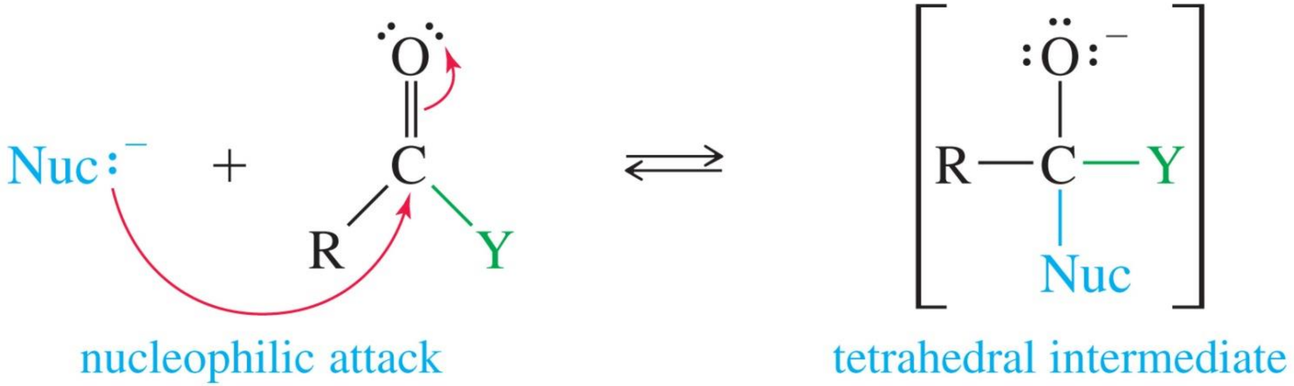


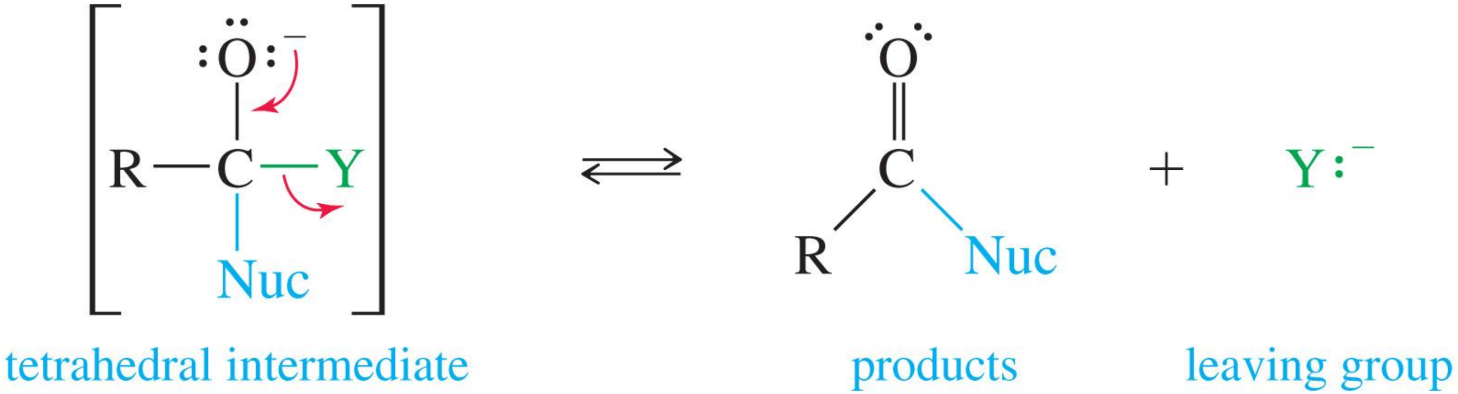
Reactions of Carboxylic Acid Derivatives

Nucleophilic Acyl Substitution

- Interconversion of acid derivatives occur by nucleophilic acyl substitution.
- Nucleophile adds to the carbonyl forming a tetrahedral intermediate.
- Elimination of the leaving group regenerates the carbonyl.
- Nucleophilic acyl substitutions are also called ***acyl transfer reactions*** because they transfer the acyl group to the attacking nucleophile.

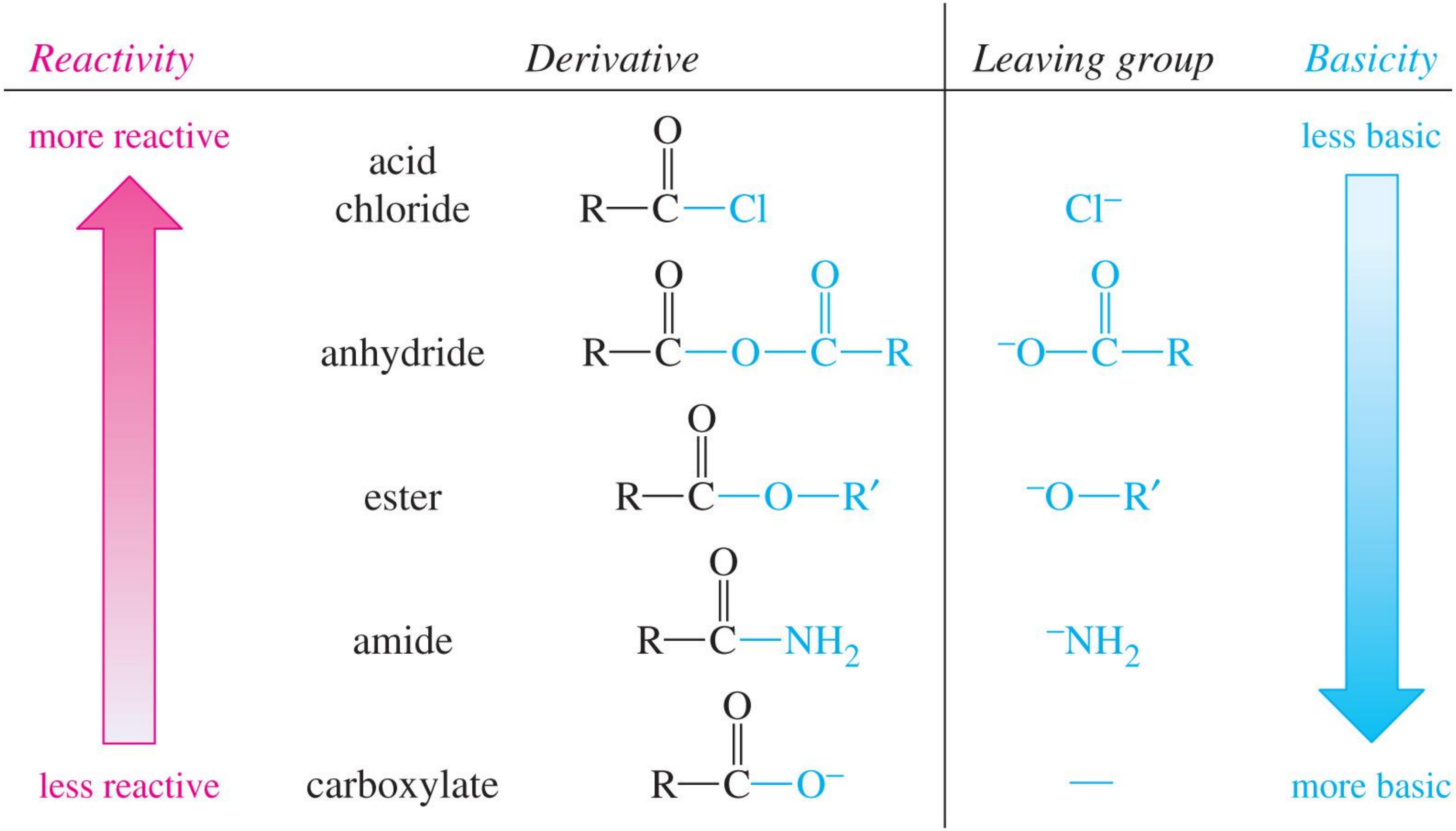
Mechanism of Acyl Substitution





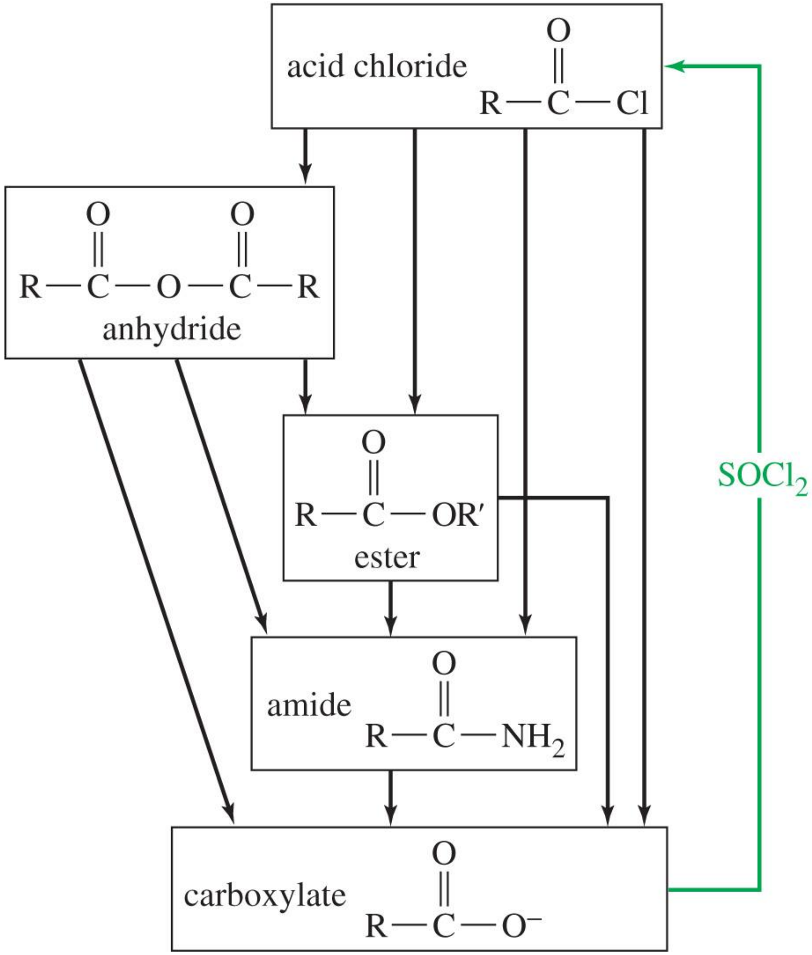
This is an addition–elimination mechanism.

Reactivity of Acid Derivatives



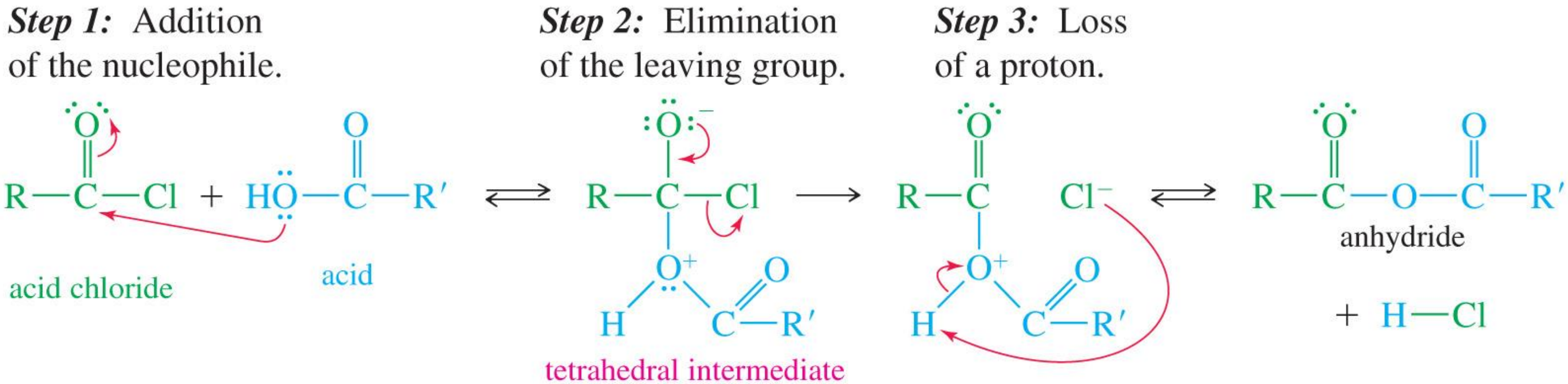
Reactivity	*Derivative*		*Leaving group*	*Basicity*
more reactive	acid chloride	$R-\overset{\overset{O}{\|}}{C}-Cl$	Cl^-	less basic
	anhydride	$R-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-R$	$^-O-\overset{\overset{O}{\|}}{C}-R$	
	ester	$R-\overset{\overset{O}{\|}}{C}-O-R'$	$^-O-R'$	
	amide	$R-\overset{\overset{O}{\|}}{C}-NH_2$	$^-NH_2$	
less reactive	carboxylate	$R-\overset{\overset{O}{\|}}{C}-O^-$	—	more basic

Interconversion of Derivatives


Interconversions of acid derivatives

- More reactive derivatives can be converted to less reactive derivatives.

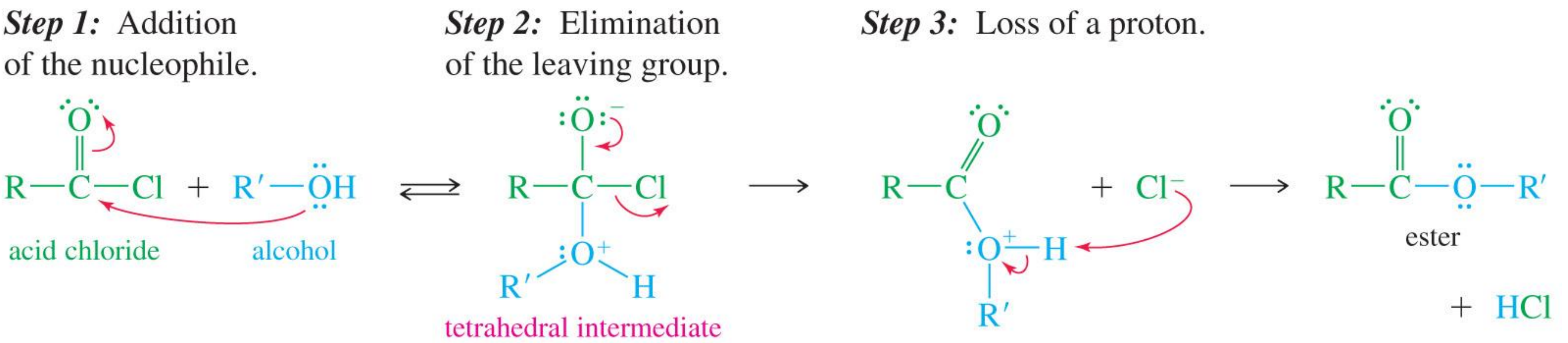
Acid Chloride to Anhydride



Copyright © 2010 Pearson Prentice Hall, Inc.

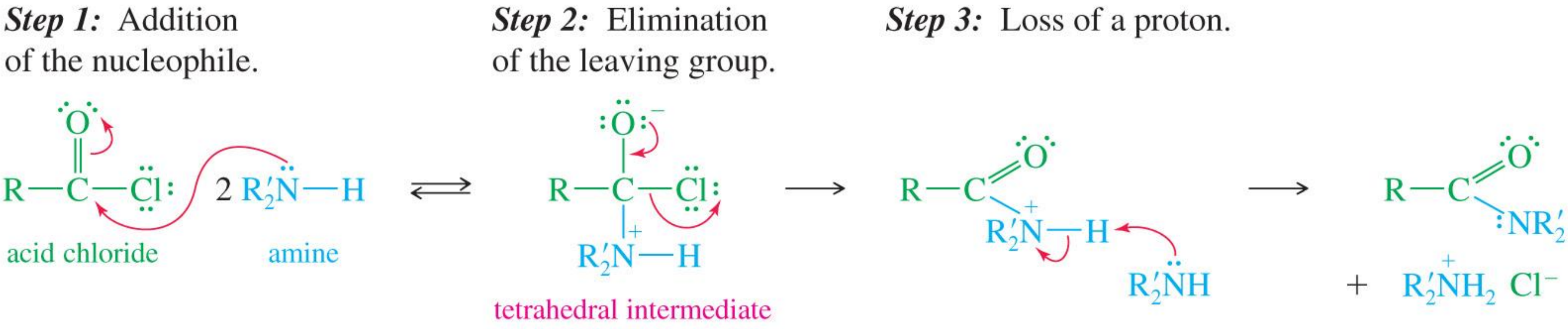
- The carboxylic acid attacks the acyl chloride, forming the tetrahedral intermediate.
- Chloride ion leaves, restoring the carbonyl.
- Deprotonation produces the anhydride.

Acid Chloride to Ester



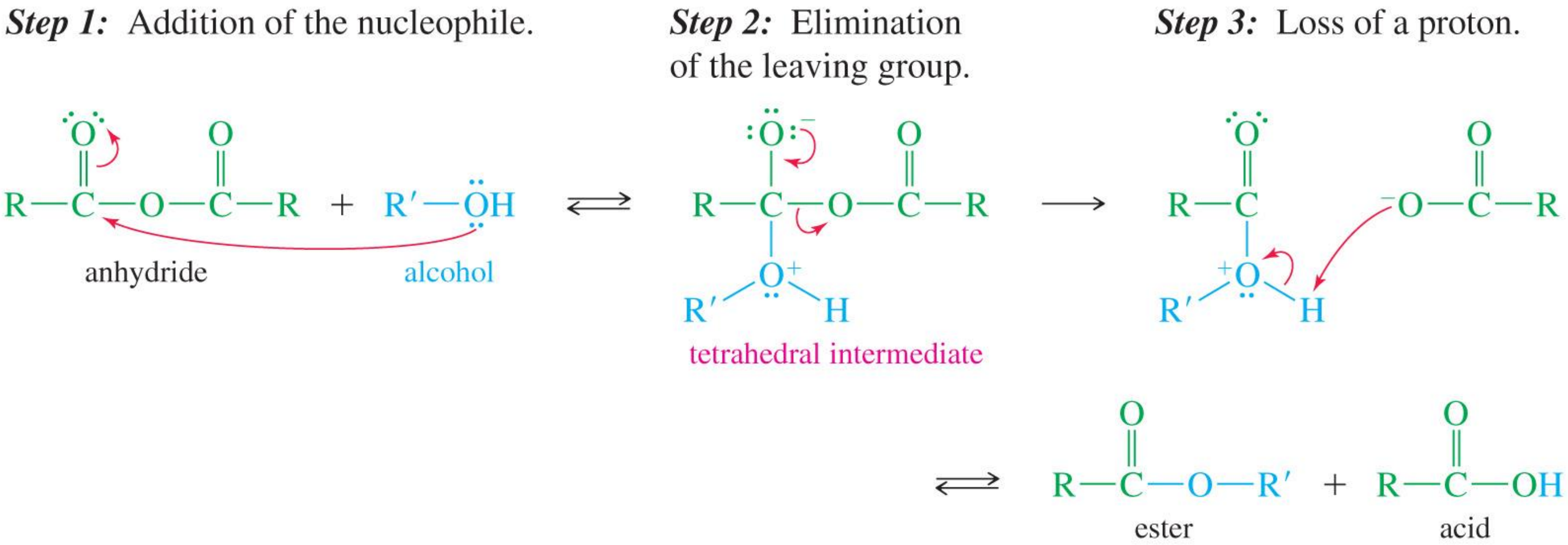
- The alcohol attacks the acyl chloride, forming the tetrahedral intermediate.
- Chloride ion leaves, restoring the carbonyl.
- Deprotonation produces the ester.

Acid Chloride to Amide



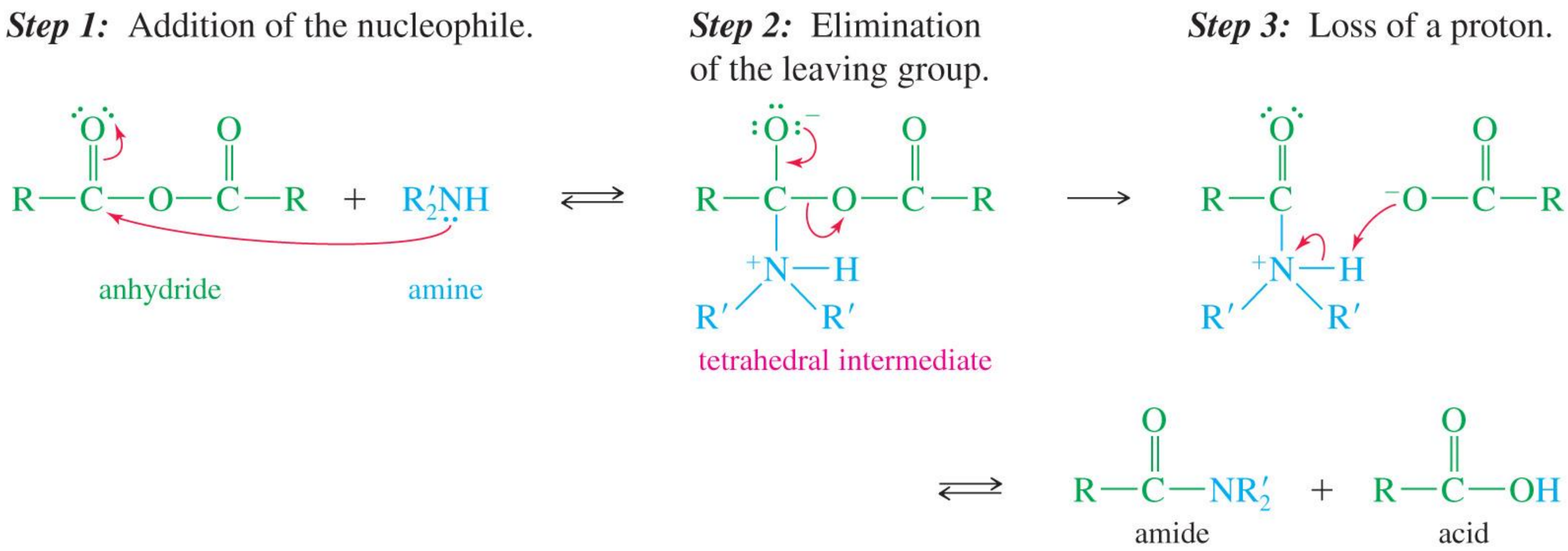
- Ammonia yields a 1° amide.
- A 1° amine yields a 2° amide.
- A 2° amine yields a 3° amide.

Anhydride to Ester



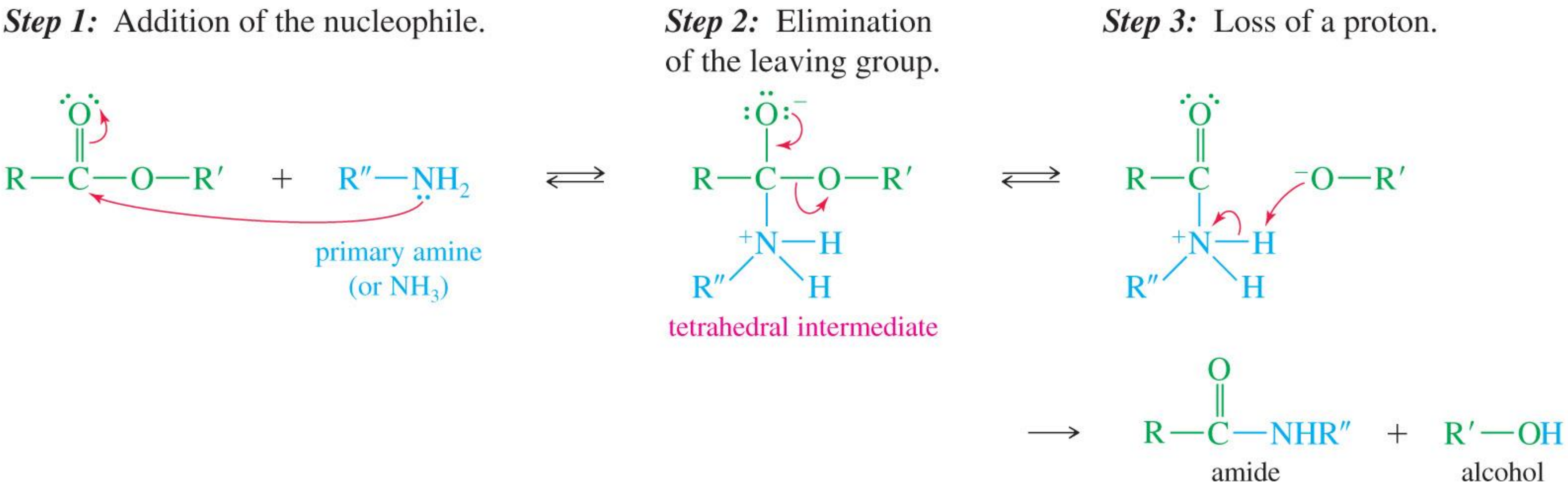
- Alcohol attacks one of the carbonyl groups of the anhydride, forming the tetrahedral intermediate.
- The other acid unit is eliminated as the leaving group.

Anhydride to Amide



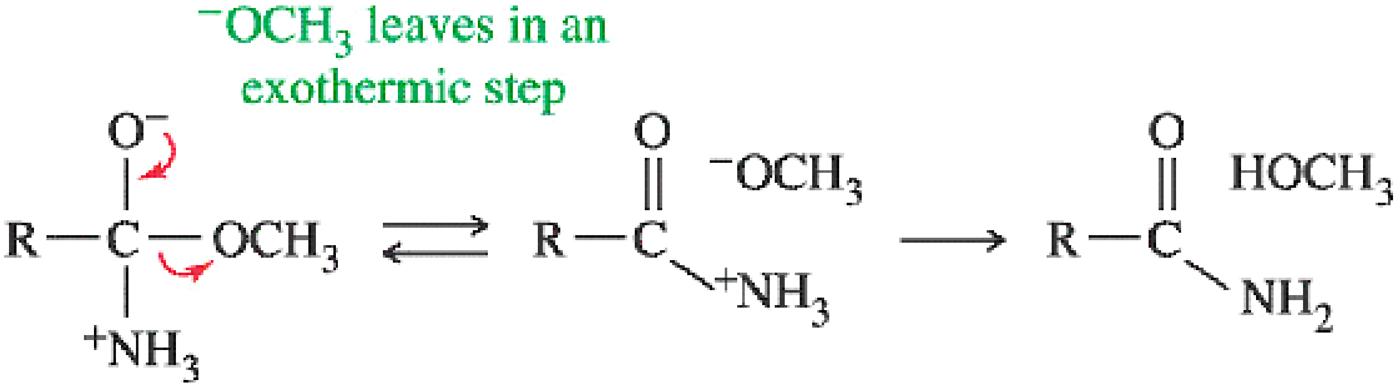
- Ammonia yields a 1° amide; a 1° amine yields a 2° amide; and a 2° amine yields a 3° amide.

Ester to Amide: Ammonolysis



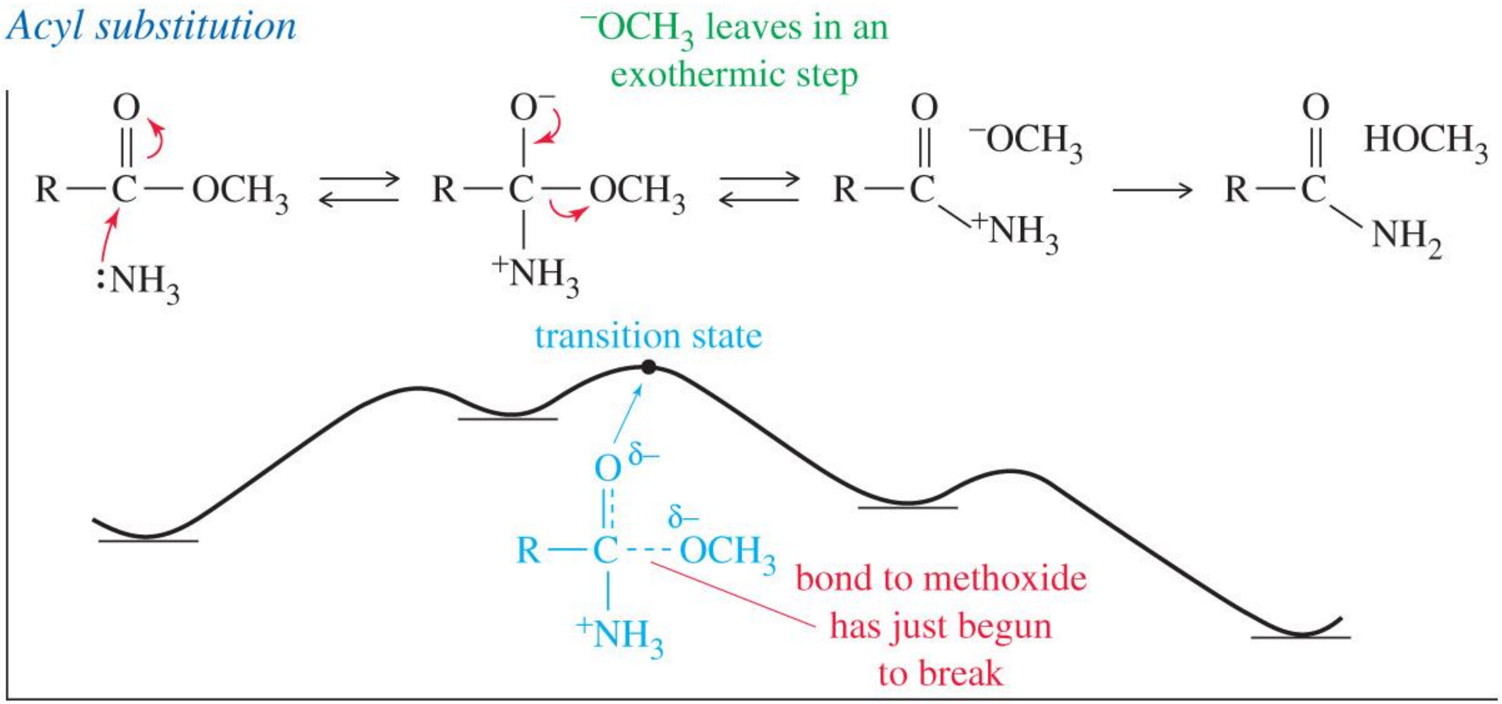
- Nucleophile must be NH_3 or 1° amine.
- Prolonged heating is required.

Leaving Groups in Nucleophilic Acyl Substitution



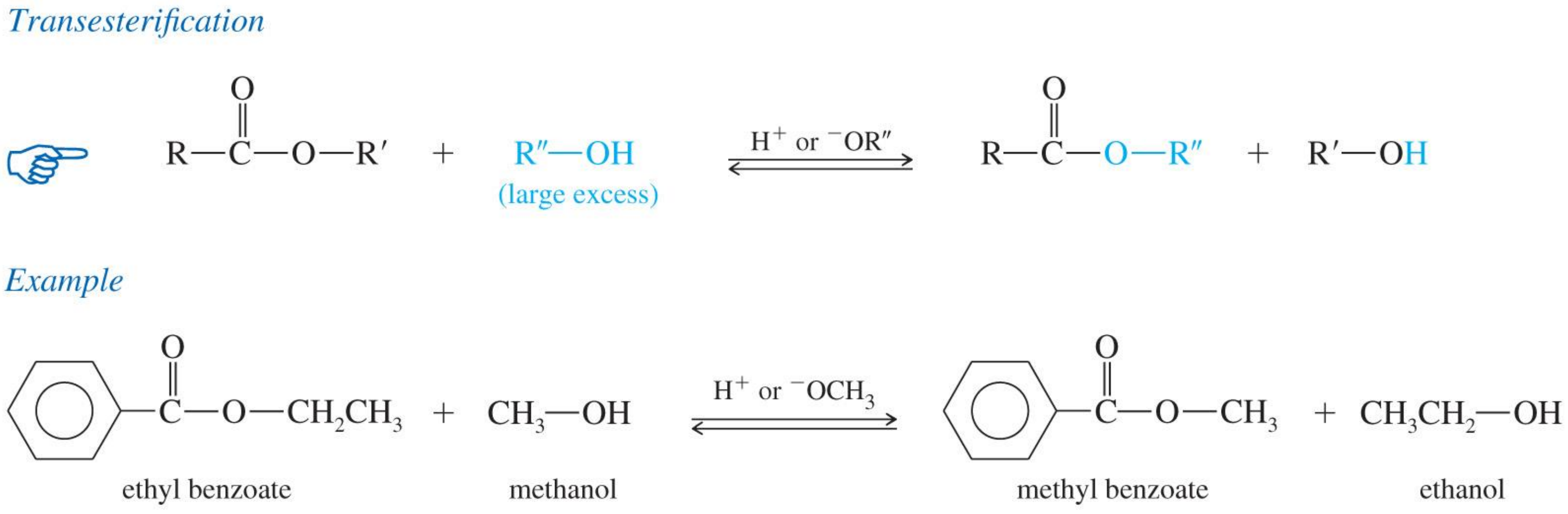
- A strong base, such as methoxide ($^{-}OCH_3$), is not usually a leaving group, except in an exothermic step.

Energy Diagram



- In the nucleophilic acyl substitution, the elimination of the alkoxide is highly exothermic, converting the tetrahedral intermediate into a stable molecule.

Transesterification



- One alkoxy group can be replaced by another with acid or base catalyst.
- Use large excess of preferred alcohol.

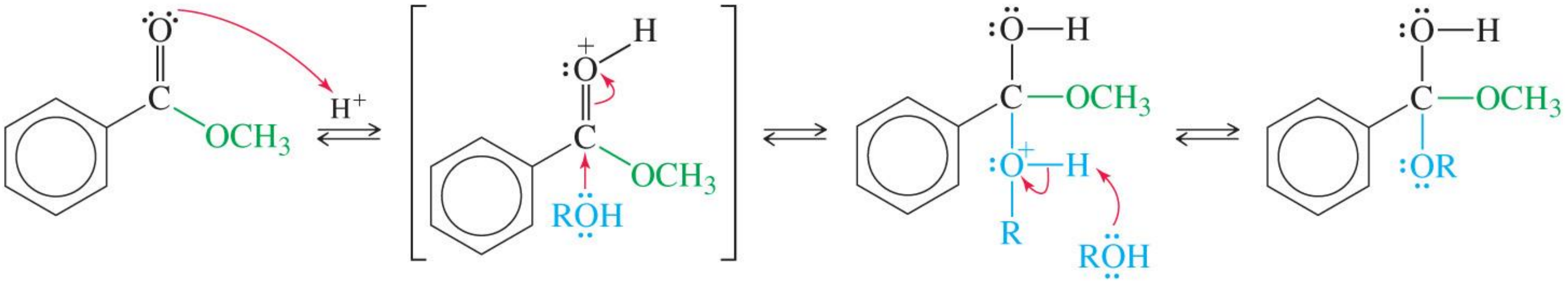
Transesterification Mechanism

First half: Acid-catalyzed addition of the nucleophile.

Step 1: Protonation of the carbonyl.

Step 2: Nucleophile attack.

Step 3: Deprotonation.

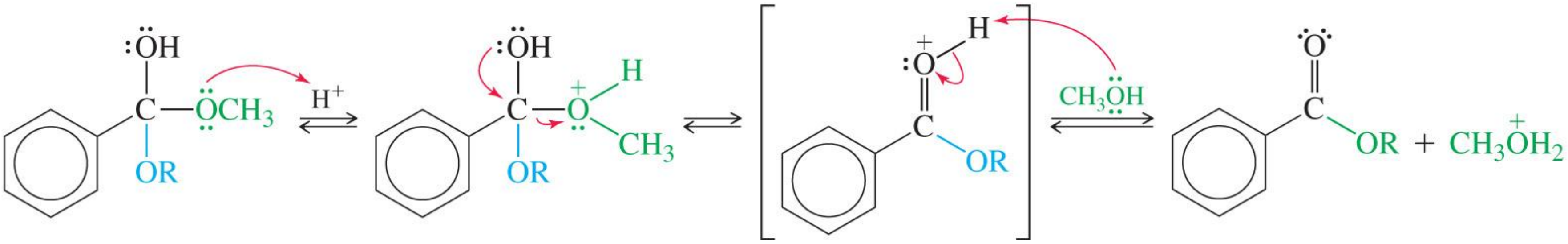


Second half: Acid-catalyzed elimination of the leaving group.

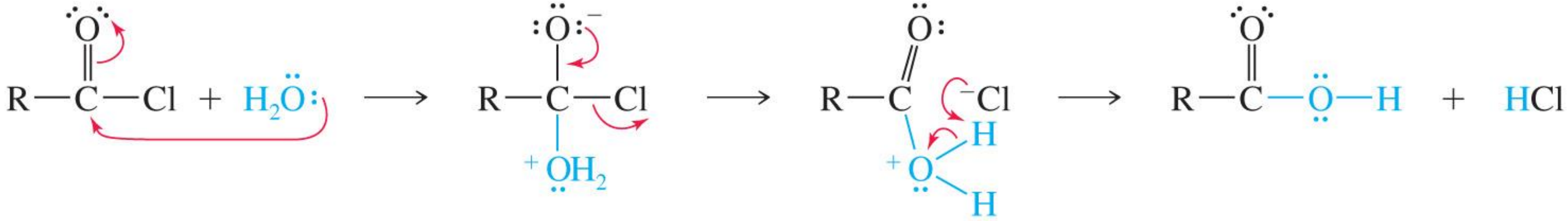
Step 1: Protonation of the leaving group.

Step 2: Elimination of the leaving group.

Step 3: Deprotonation.

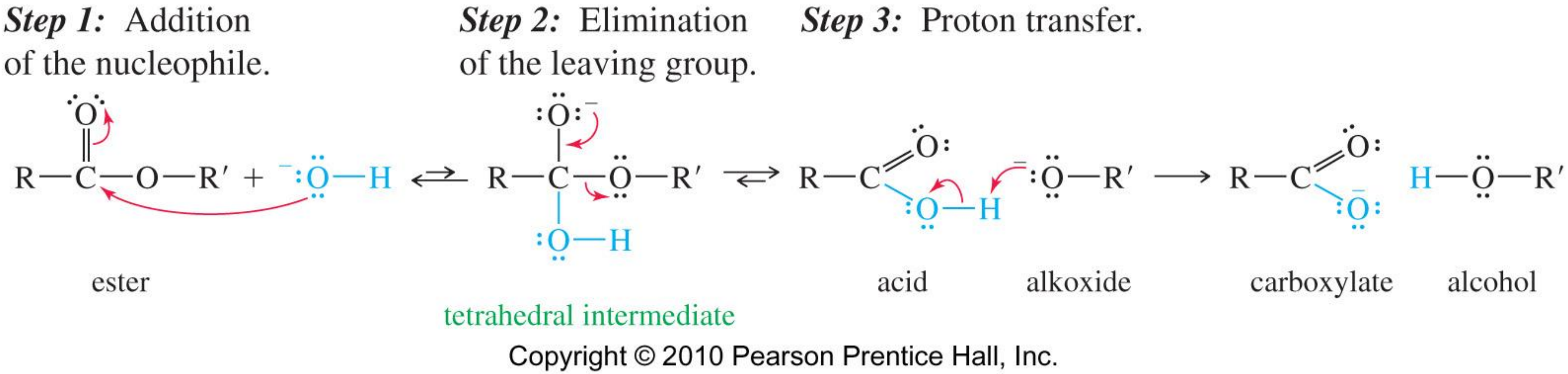


Hydrolysis of Acid Chlorides and Anhydrides



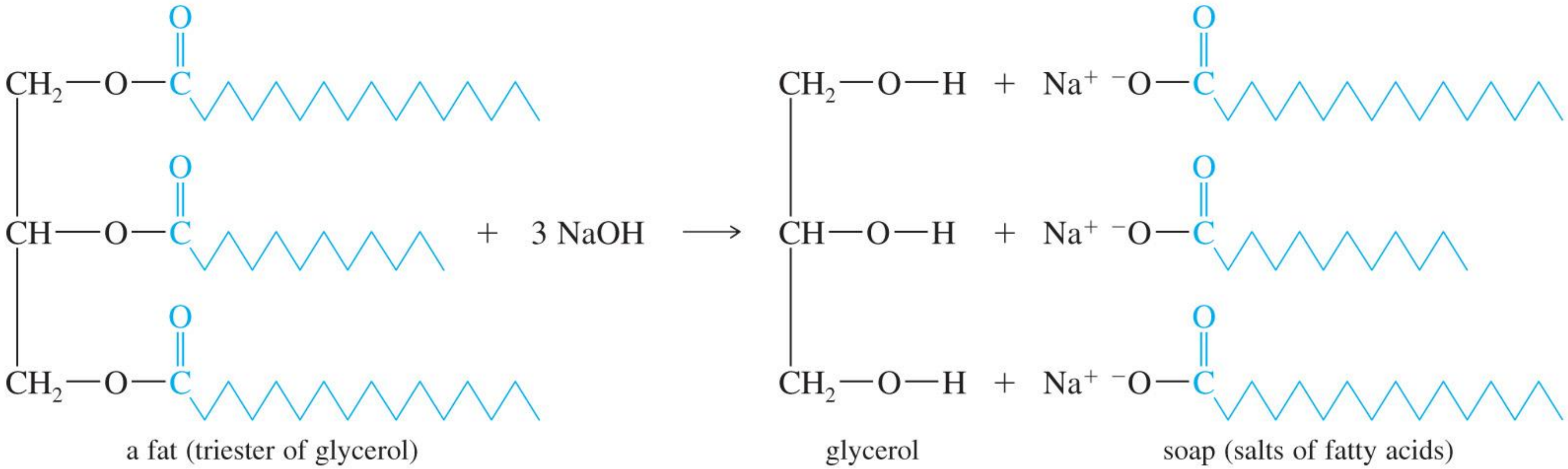
- Hydrolysis occurs quickly, even in moist air with no acid or base catalyst.
- Reagents must be protected from moisture.

Hydrolysis of Esters: Saponification



- The base-catalyzed hydrolysis of ester is known as ***saponification***.
- *Saponification* means “soap-making.”

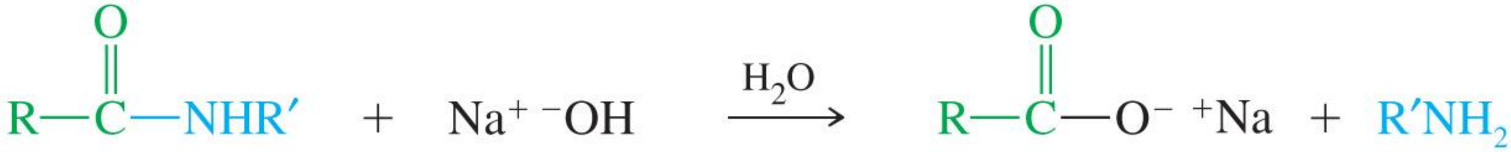
Saponification



- Soaps are made by heating NaOH with a fat (triester of glycerol) to produce the sodium salt of a fatty acid—a soap.

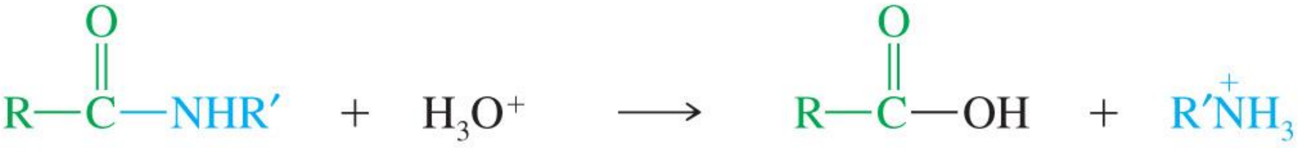
Hydrolysis of Amides

Basic hydrolysis



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-NHR' + Na^{+}\ {}^{-}OH \xrightarrow{H_2O} R-\overset{\overset{\displaystyle O}{\|}}{C}-O^{-}\ {}^{+}Na + R'NH_2$$

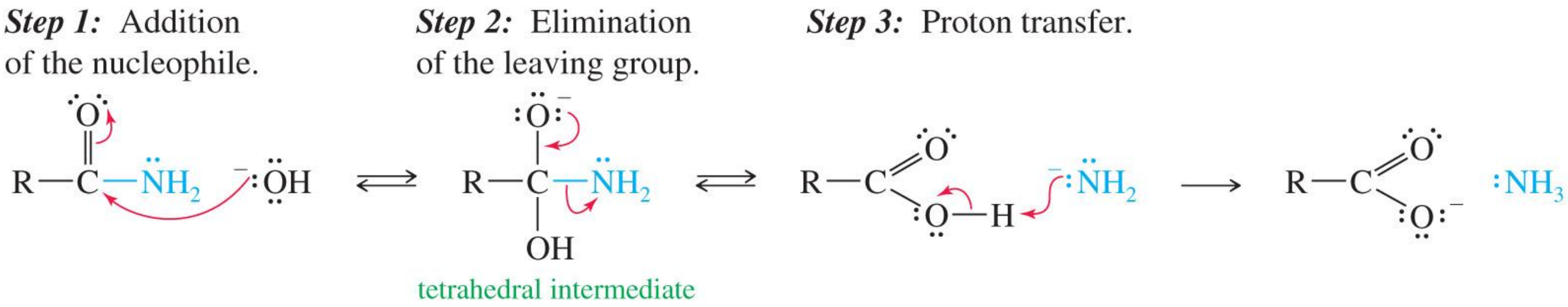
Acid hydrolysis



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-NHR' + H_3O^{+} \longrightarrow R-\overset{\overset{\displaystyle O}{\|}}{C}-OH + R'\overset{+}{N}H_3$$

Amides are hydrolyzed to the carboxylic acid under acidic or basic conditions.

Mechanism of Basic Hydrolysis of Amides



Step 1: Addition of the nucleophile.

Step 2: Elimination of the leaving group.

Step 3: Proton transfer.

- Similar to the hydrolysis of an ester.
- Hydroxide attacks the carbonyl forming a tetrahedral intermediate.
- The amino group is eliminated and a proton is transferred to the nitrogen to give the carboxylate salt.

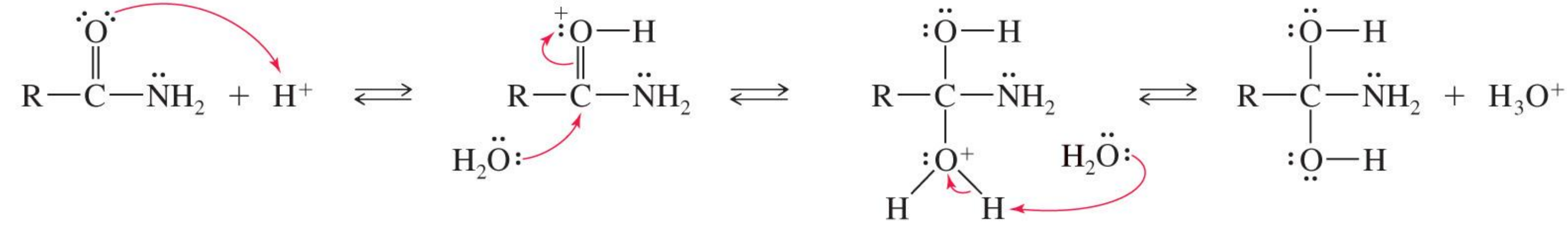
Acid Hydrolysis of an Amide

First half: Acid-catalyzed addition of the nucleophile (water).

Step 1: Protonation of the carbonyl.

Step 2: Addition of the nucleophile.

Step 3: Loss of a proton.

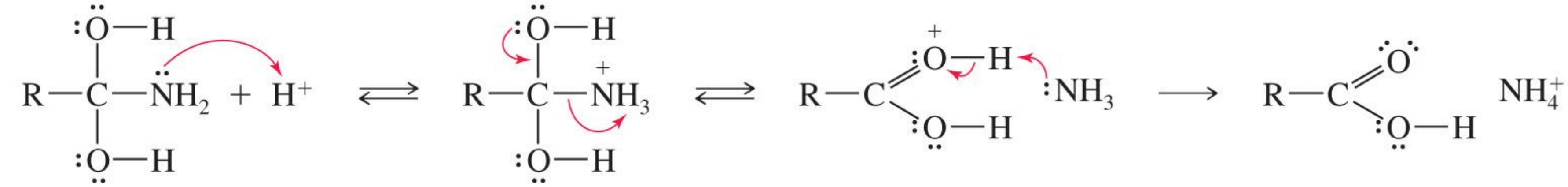


Second half: Acid-catalyzed elimination of the leaving group.

Step 1: Protonation of the leaving group.

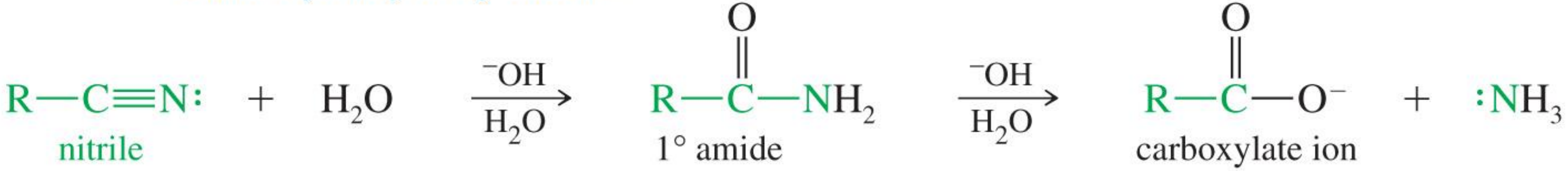
Step 2: Elimination of the leaving group.

Step 3: Deprotonation.



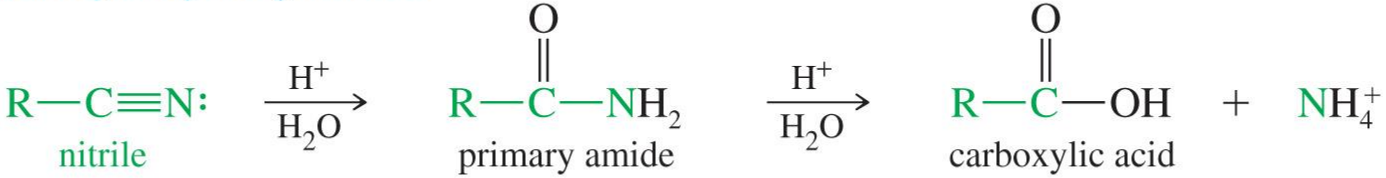
Hydrolysis of Nitriles

Basic hydrolysis of nitriles



$$\mathrm{R{-}C{\equiv}N{:}} + \mathrm{H_2O} \xrightarrow[\mathrm{H_2O}]{^{-}\mathrm{OH}} \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NH_2} \xrightarrow[\mathrm{H_2O}]{^{-}\mathrm{OH}} \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O^{-}} + \mathrm{{:}NH_3}$$

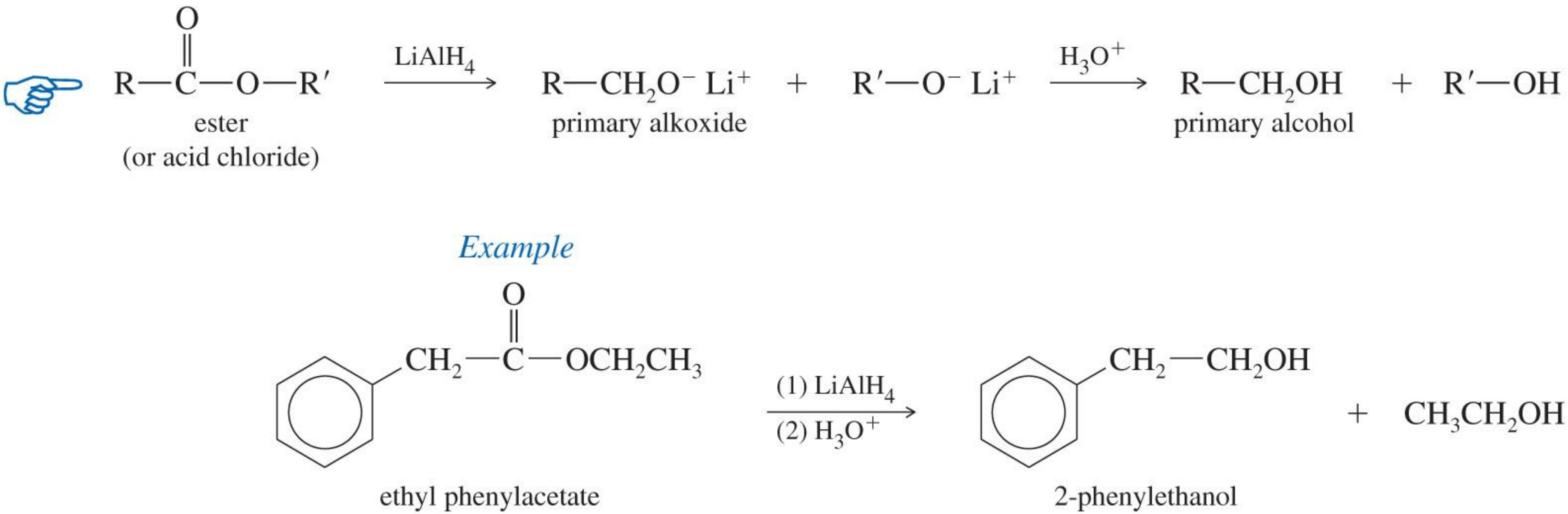
Acidic hydrolysis of nitriles



$$\mathrm{R{-}C{\equiv}N{:}} \xrightarrow[\mathrm{H_2O}]{\mathrm{H^+}} \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NH_2} \xrightarrow[\mathrm{H_2O}]{\mathrm{H^+}} \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH} + \mathrm{NH_4^+}$$

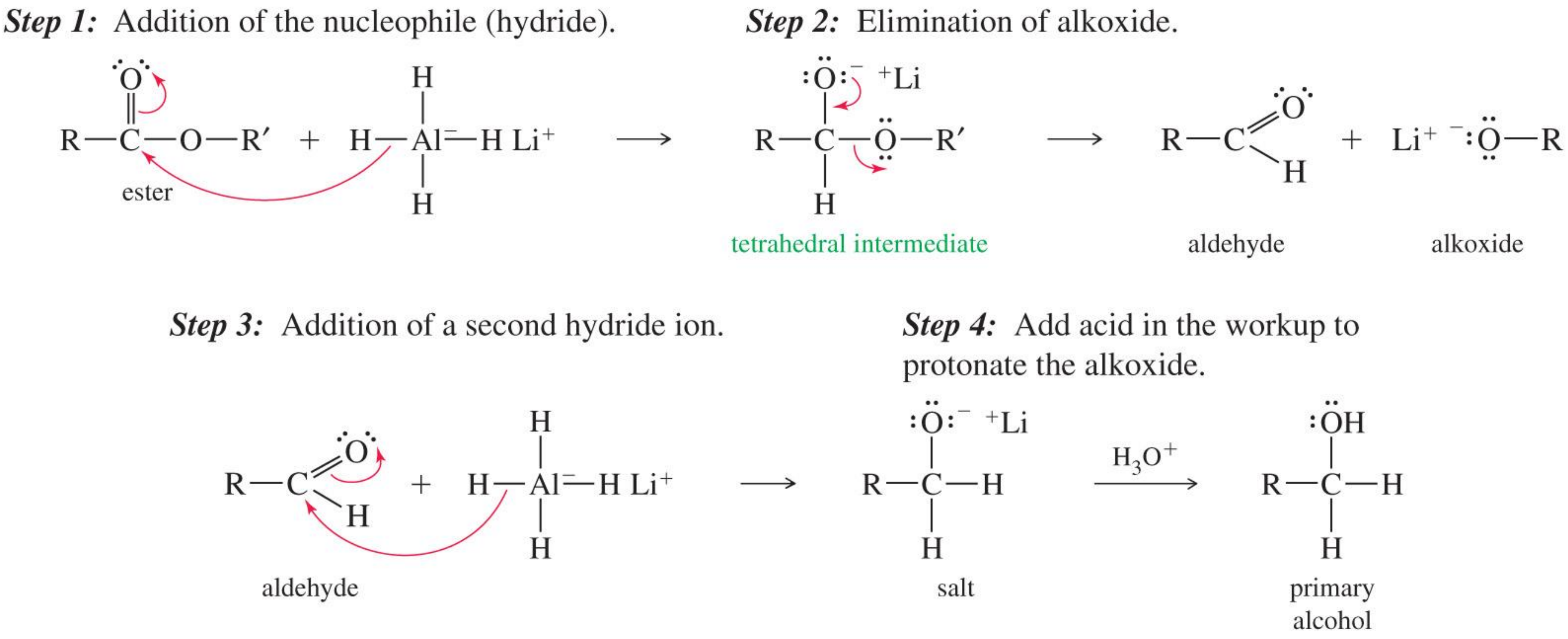
- Heating with aqueous acid or base will hydrolyze a nitrile to a carboxylic acid.

Reduction of Esters to Alcohols



- Lithium aluminum hydride ($LiAlH_4$) reduces esters to primary alcohols.

Mechanism of Reduction of Esters



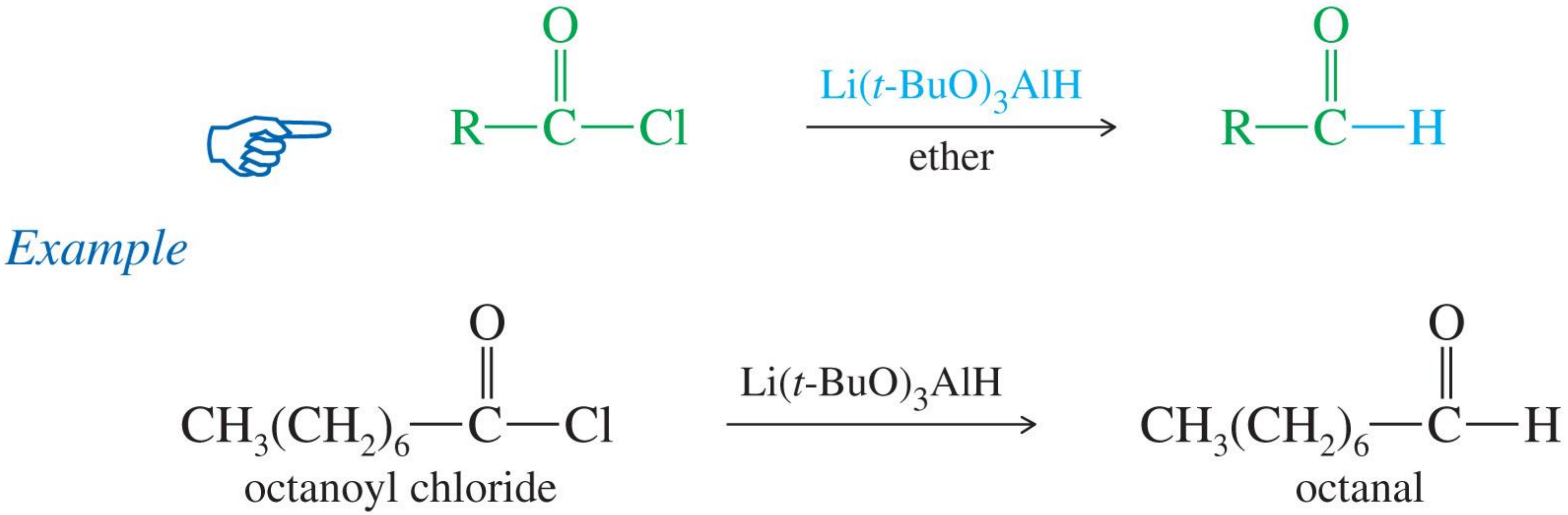
Step 1: Addition of the nucleophile (hydride).

Step 2: Elimination of alkoxide.

Step 3: Addition of a second hydride ion.

Step 4: Add acid in the workup to protonate the alkoxide.

Reduction to Aldehydes

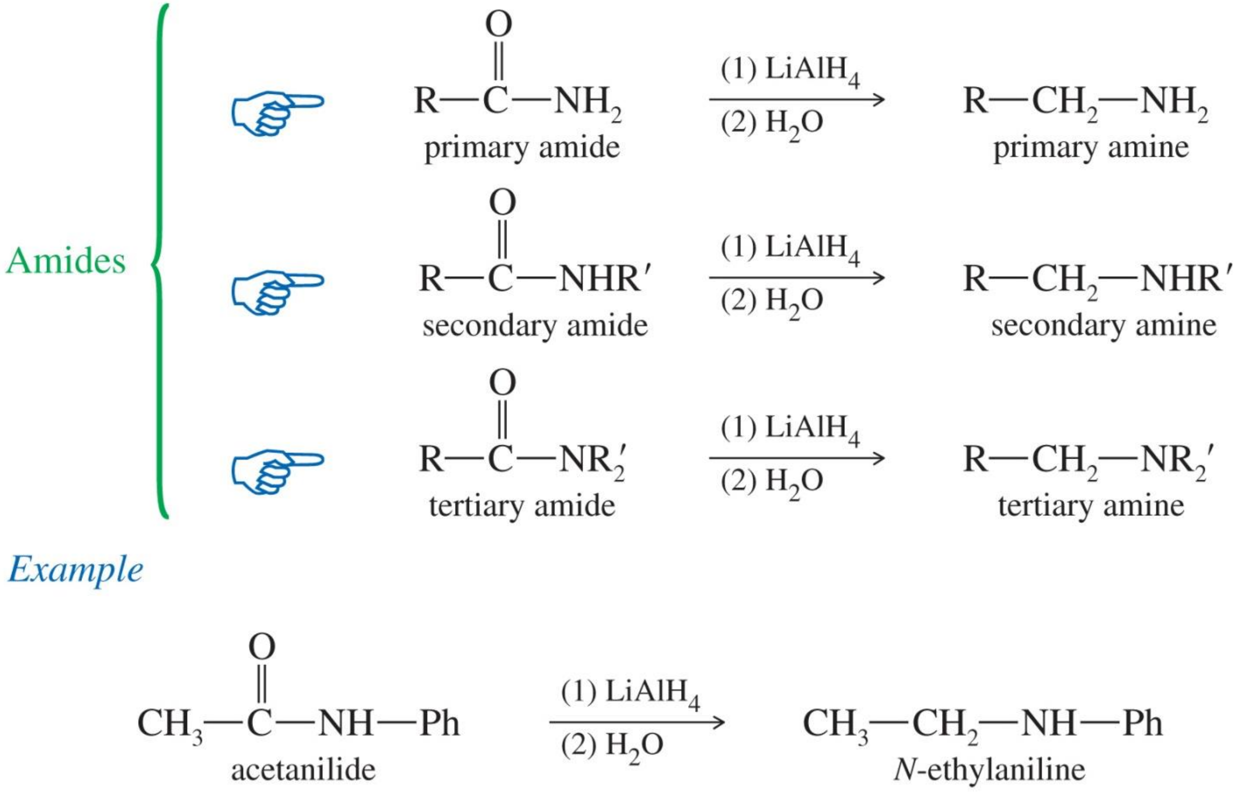


$$R-\overset{\displaystyle O}{\overset{\|}{C}}-Cl \xrightarrow[\text{ether}]{Li(t\text{-}BuO)_3AlH} R-\overset{\displaystyle O}{\overset{\|}{C}}-H$$

$$\underset{\text{octanoyl chloride}}{CH_3(CH_2)_6-\overset{\displaystyle O}{\overset{\|}{C}}-Cl} \xrightarrow{Li(t\text{-}BuO)_3AlH} \underset{\text{octanal}}{CH_3(CH_2)_6-\overset{\displaystyle O}{\overset{\|}{C}}-H}$$

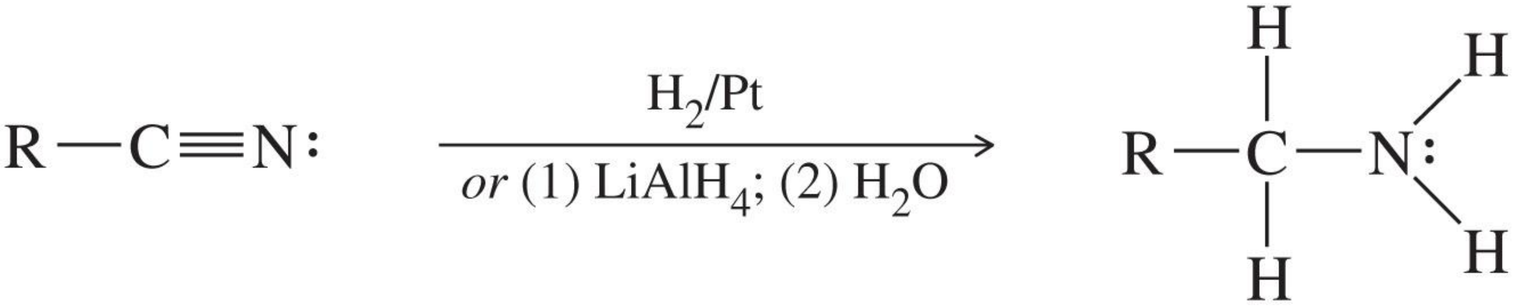
- Lithium aluminum tri(*t*-butoxy)hydride is a milder reducing agents.
- Reacts faster with acyl chlorides than with aldehydes.

Reduction to Amines



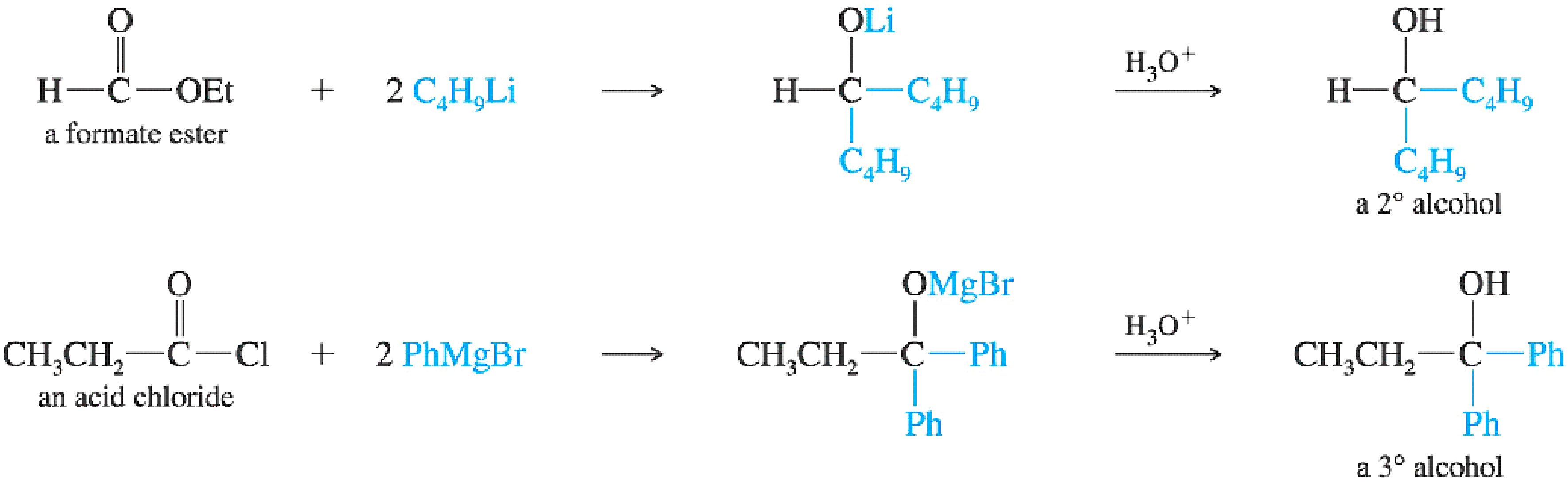
- Amides will be reduced to the corresponding amine by $LiAlH_4$.

Reduction of Nitriles to Primary Amines



- Nitriles are reduced to primary amines by catalytic hydrogenation or by lithium aluminum hydride reduction.

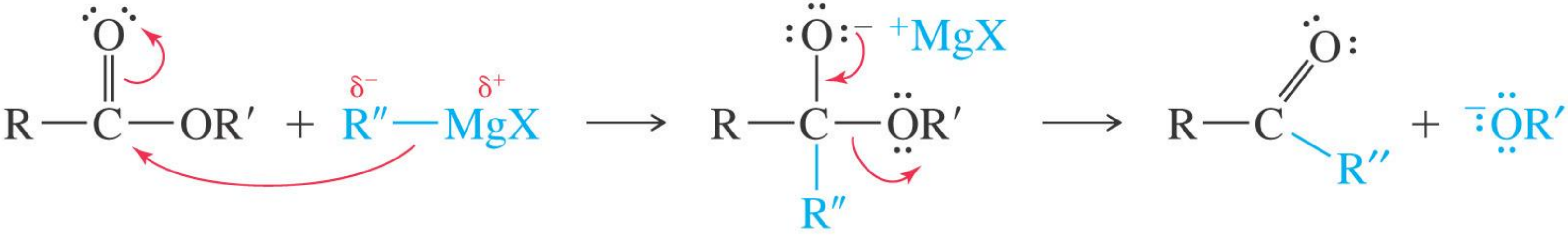
Organometallic Reagents



- Grignard and organolithium reagents add twice to acid chlorides and esters to give alcohols after protonation.

Mechanism of Grignard Addition

Step 1:

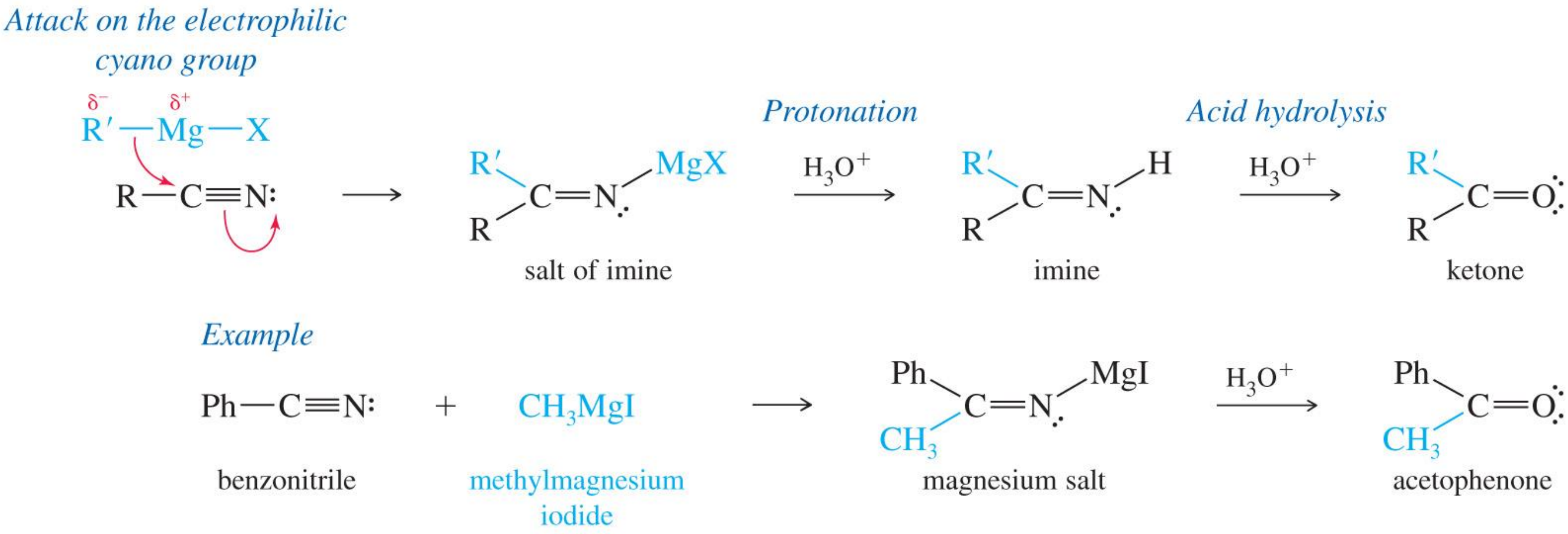


ester Grignard tetrahedral intermediate ketone

Reacts with a 2nd mole of Grignard.

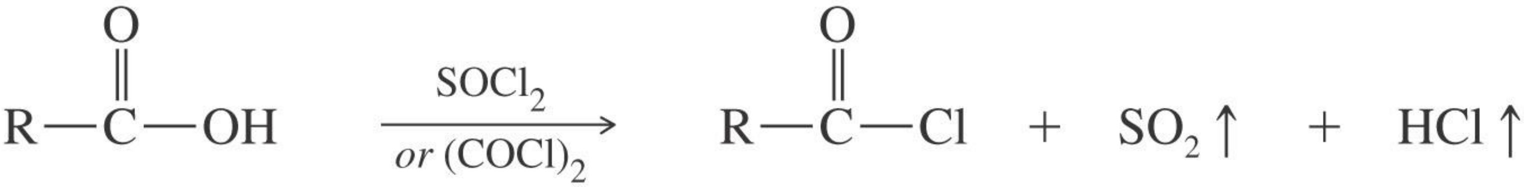
- Esters react with two moles of Grignards or organolithium reagents.
- The ketone intermediate is formed after the first addition and will react with a second mole of organometallic to produce the alcohol.

Reaction of Nitriles with Grignards



- A Grignard reagent or organolithium reagent attacks the cyano group to yield an imine, which is hydrolyzed to a ketone.

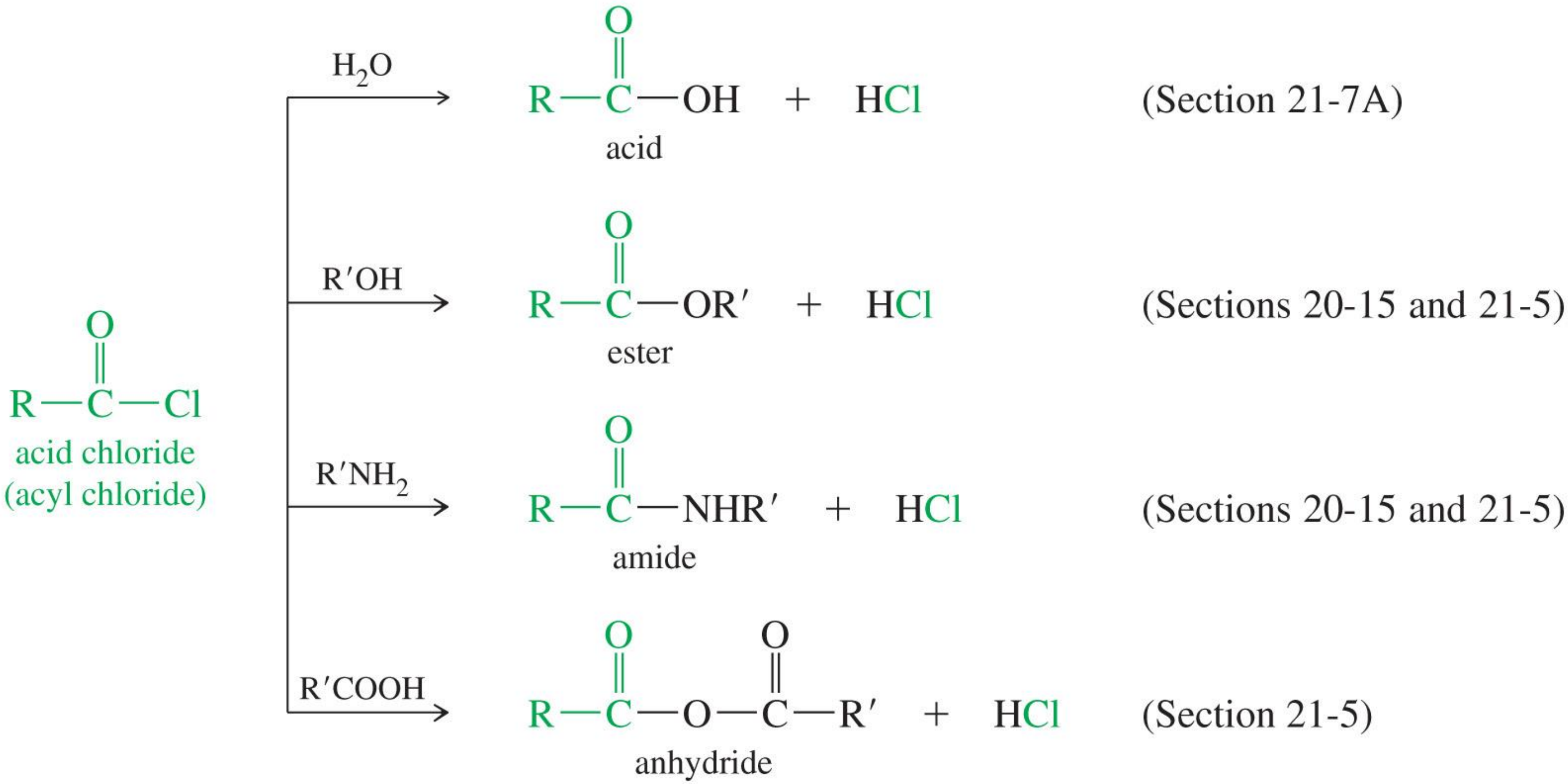
Acid Chloride Synthesis



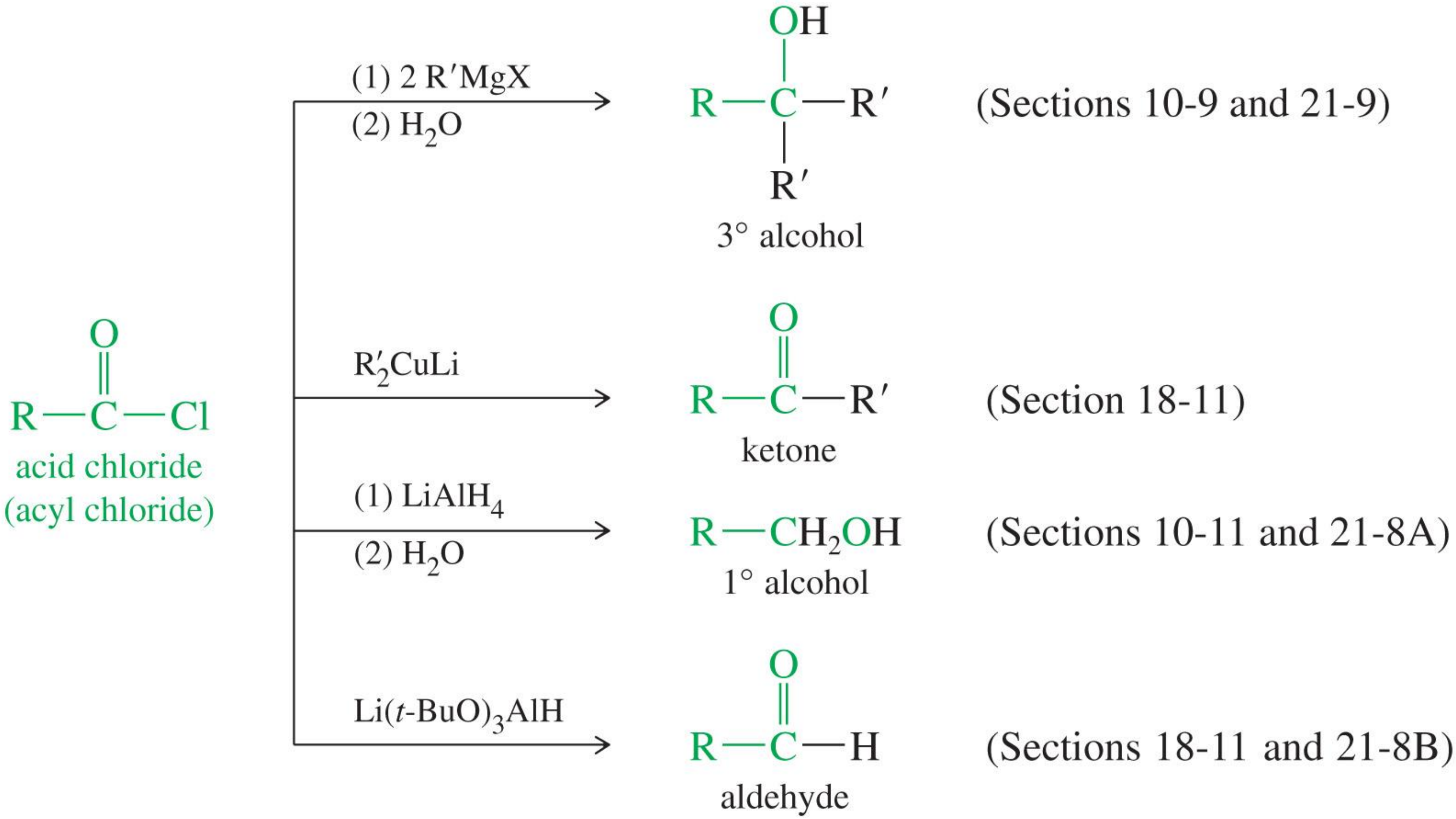
$$R-\overset{\overset{\displaystyle O}{\|}}{C}-OH \xrightarrow[or\ (COCl)_2]{SOCl_2} R-\overset{\overset{\displaystyle O}{\|}}{C}-Cl + SO_2\uparrow + HCl\uparrow$$

- Thionyl chloride ($SOCl_2$) and oxalyl chloride ($COCl_2$) are the most convenient reagents because they produce only gaseous side products.

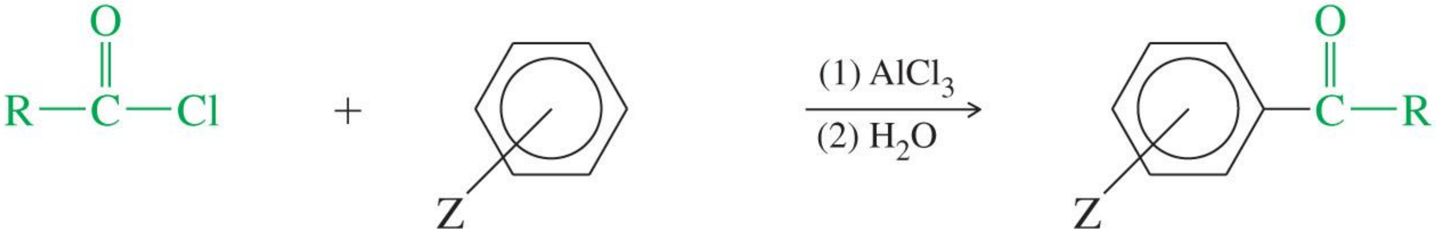
Acid Chloride Reactions (1)



Acid Chloride Reactions (2)



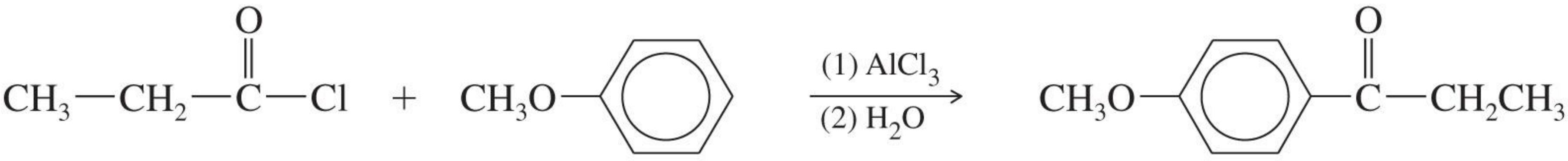
Friedel–Crafts Acylation



(Z = H, halogen, or an activating group)

an acylbenzene

Example

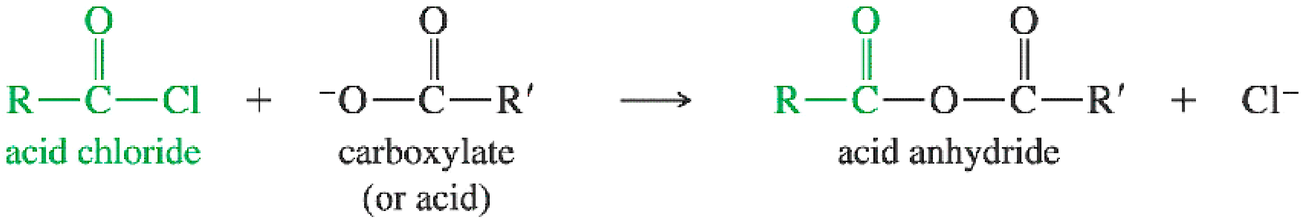


propionyl chloride

anisole

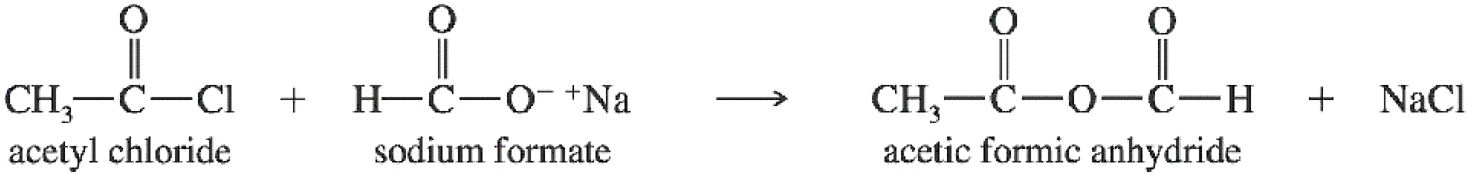
p-methoxypropiophenone
(major product)

General Anhydride Synthesis



$$R-\overset{O}{\overset{\|}{C}}-Cl \;+\; {}^{-}O-\overset{O}{\overset{\|}{C}}-R' \longrightarrow R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R' \;+\; Cl^{-}$$

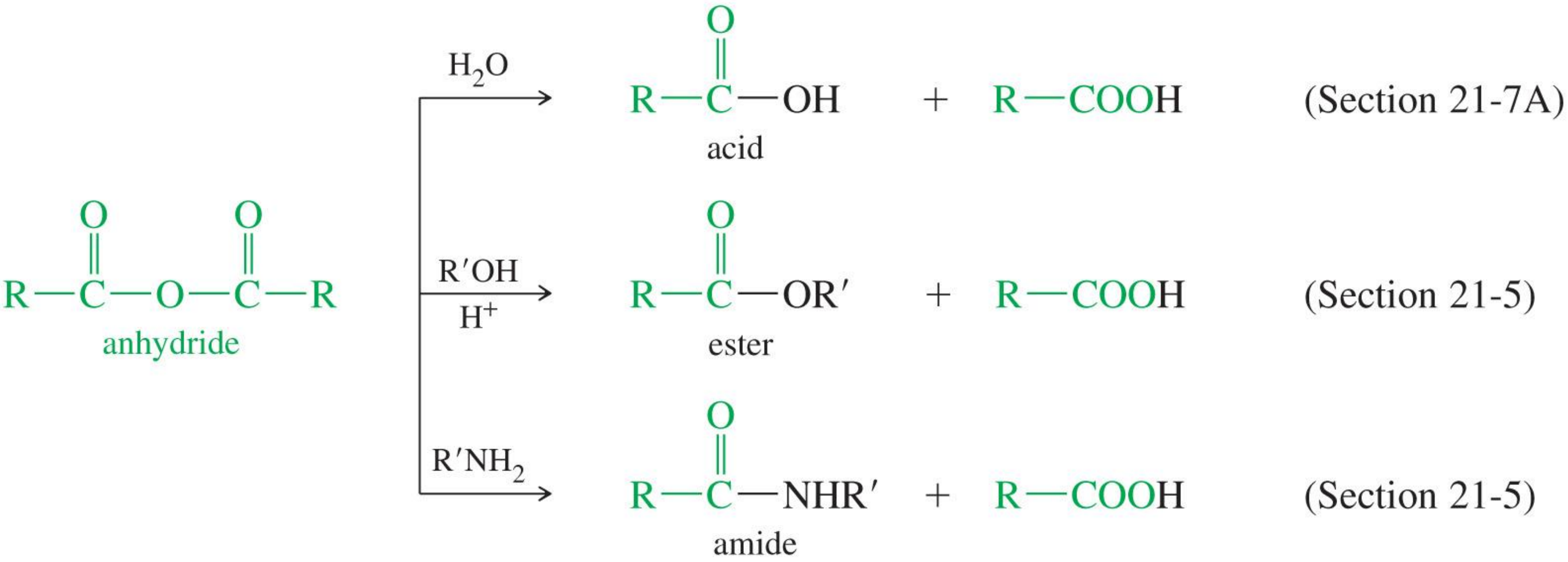
Examples



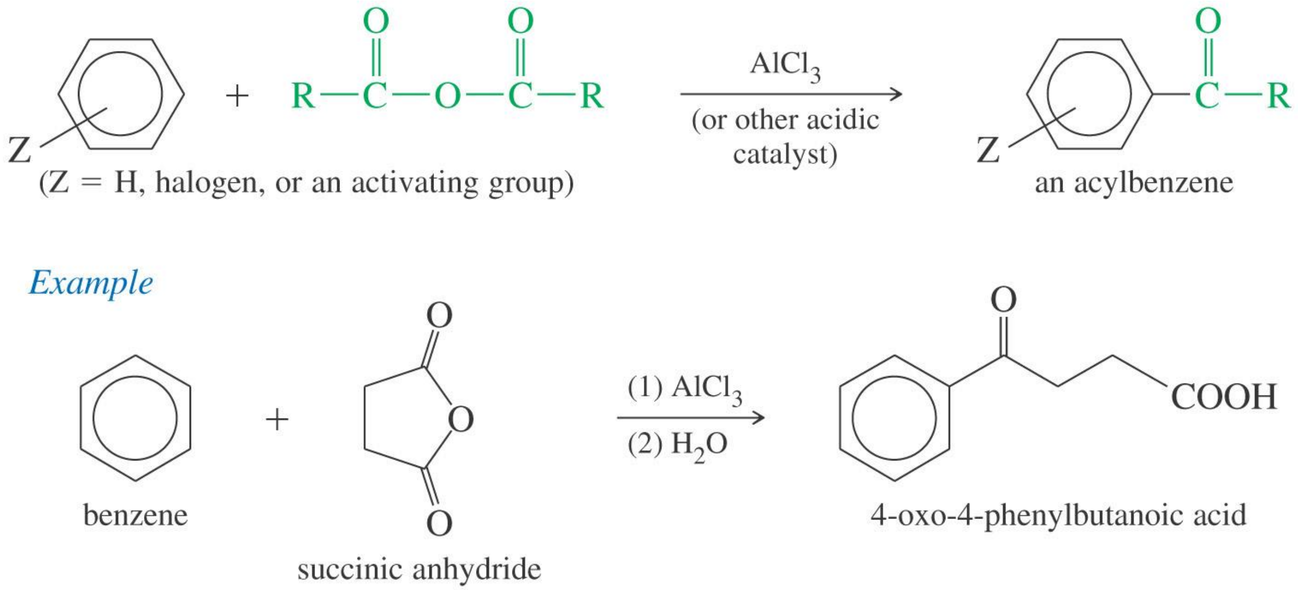
$$CH_3-\overset{O}{\overset{\|}{C}}-Cl \;+\; H-\overset{O}{\overset{\|}{C}}-O^{-}\;{}^{+}Na \longrightarrow CH_3-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-H \;+\; NaCl$$

- The most generalized method for making anhydrides is the reaction of an acid chloride with a carboxylic acid or a carboxylate salt.
- Pyridine is sometimes used to deprotonate the acid and form the carboxylate.

Reaction of Anhydrides

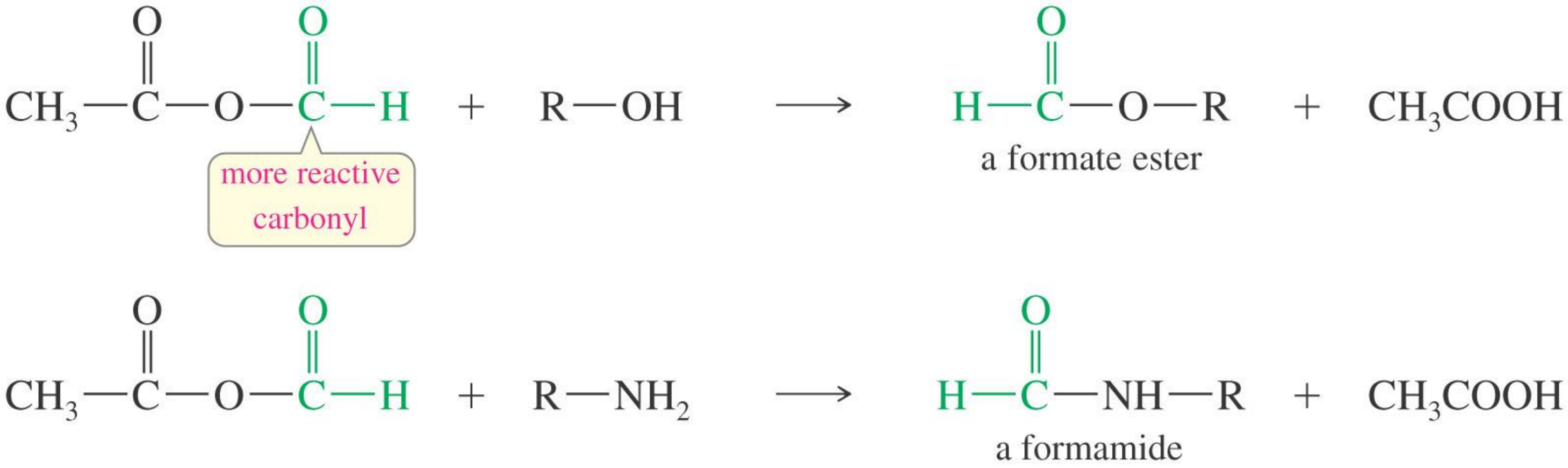


Friedel–Crafts Acylation Using Anhydrides



- Using a cyclic anhydride allows for only one of the acid groups to react, leaving the second acid group free to undergo further reactions.

Acetic Formic Anhydride



$$\mathrm{CH_3-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-H} + \mathrm{R-OH} \longrightarrow \mathrm{H-\overset{O}{\overset{\|}{C}}-O-R} + \mathrm{CH_3COOH}$$

more reactive carbonyl

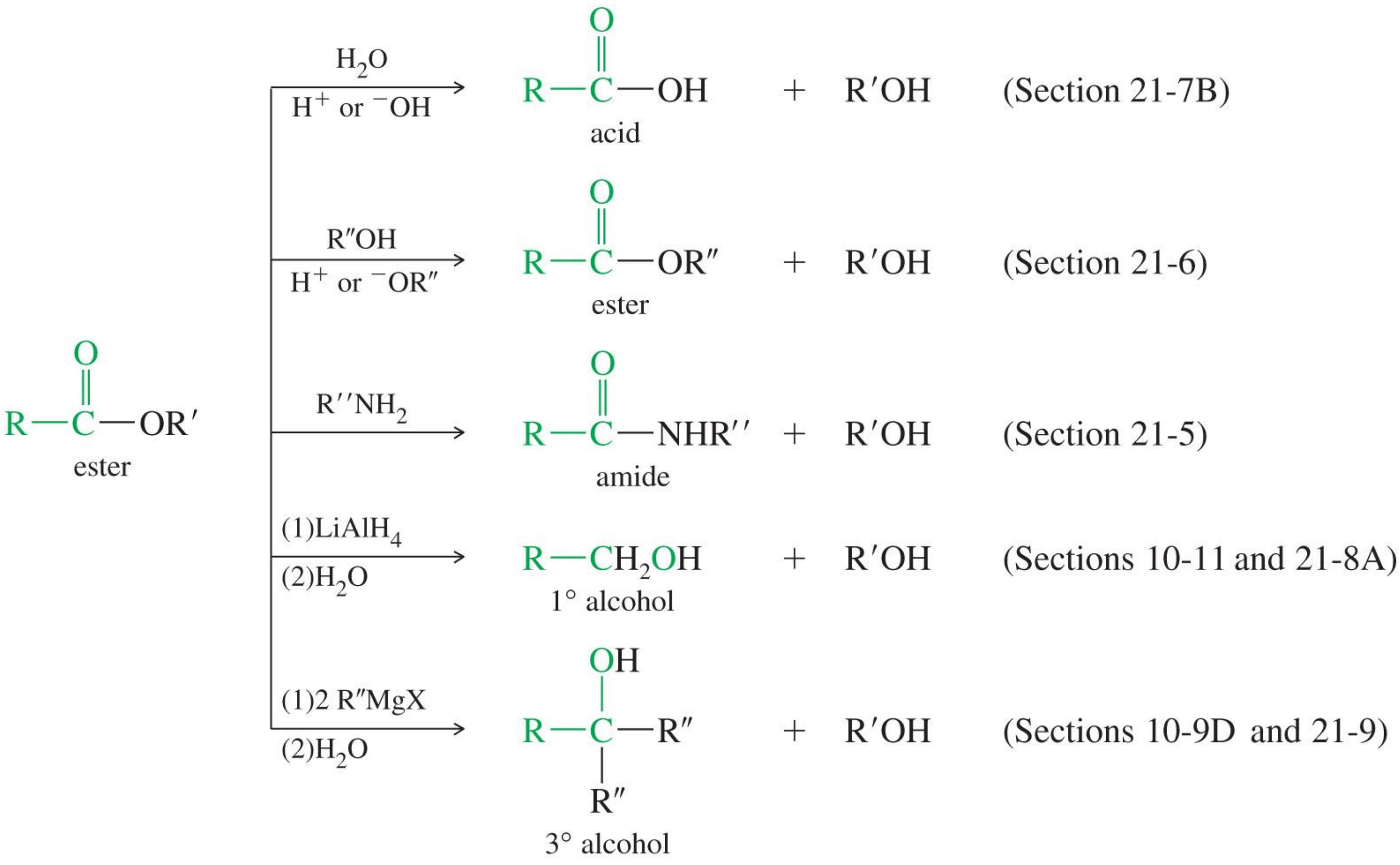
a formate ester

$$\mathrm{CH_3-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-H} + \mathrm{R-NH_2} \longrightarrow \mathrm{H-\overset{O}{\overset{\|}{C}}-NH-R} + \mathrm{CH_3COOH}$$

a formamide

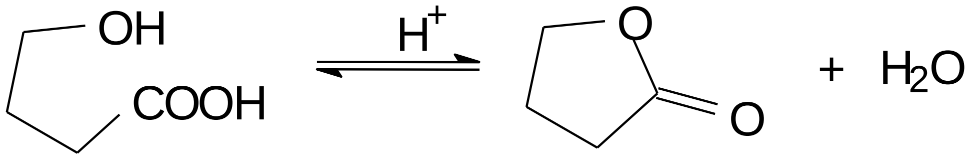
- Acetic formyl anhydride, made from sodium formate and acetyl chloride, reacts primarily at the formyl group.
- The formyl group is more electrophilic because of the lack of alkyl groups.

Reactions of Esters

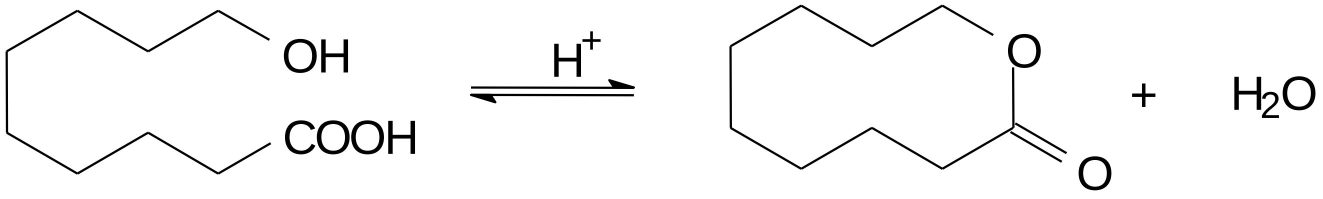


Formation of Lactones

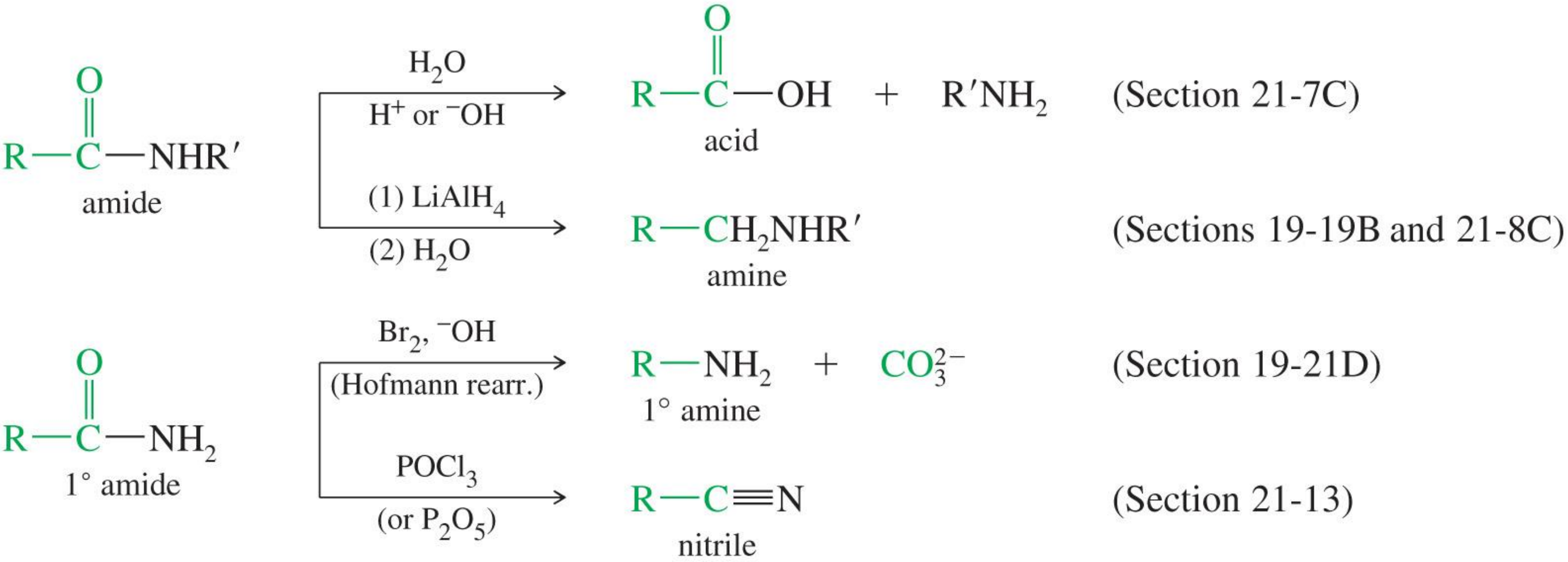
- Formation favored for five- and six-membered rings.



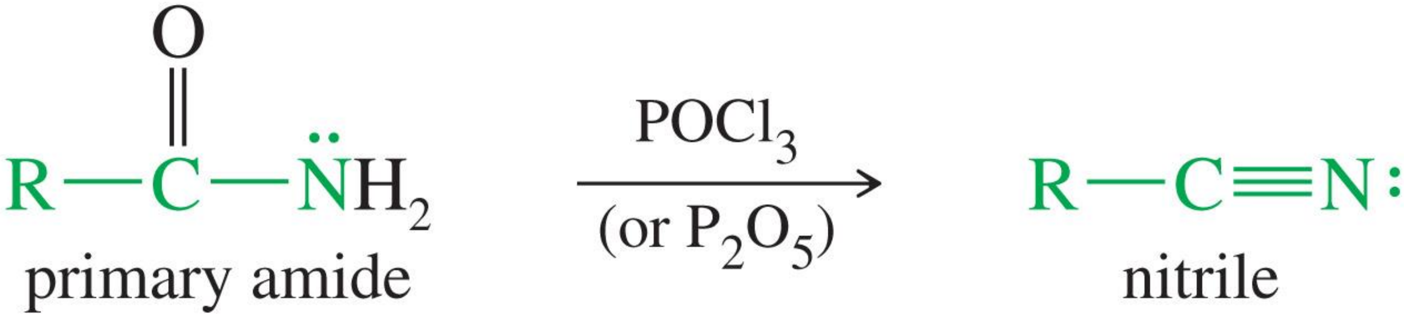
- For larger rings, remove water to shift equilibrium toward products.



Reactions of Amides



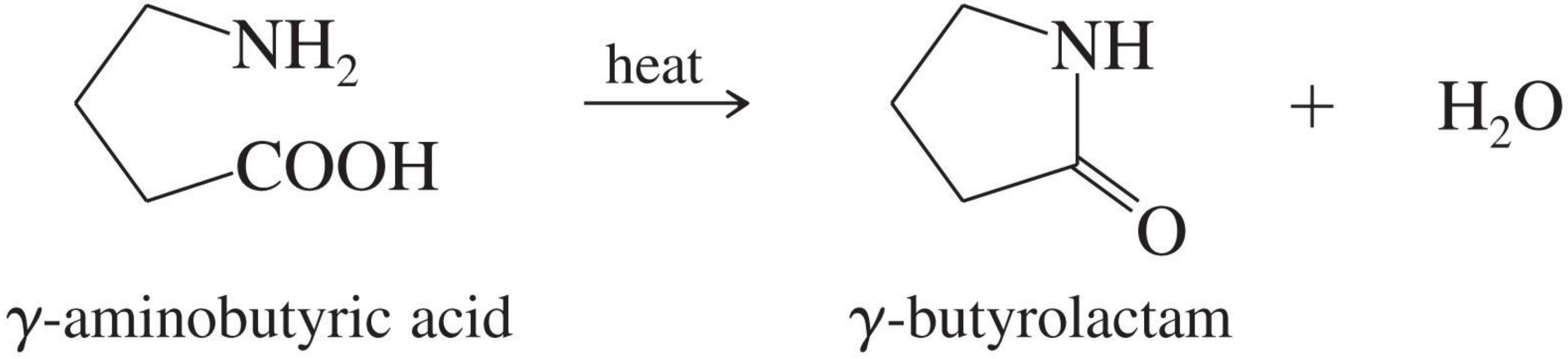
Dehydration of Amides to Nitriles



$$R-C(=O)-NH_2 \xrightarrow[\text{(or } P_2O_5)]{POCl_3} R-C\equiv N:$$

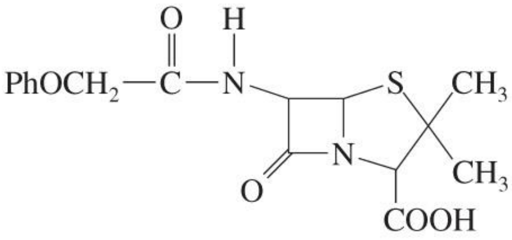
- Strong dehydrating agents can eliminate the elements of water from a primary amide to give a nitrile.
- Phosphorus oxychloride ($POCl_3$) or phosphorus pentoxide (P_2O_5) can be used as dehydrating agents.

Formation of Lactams

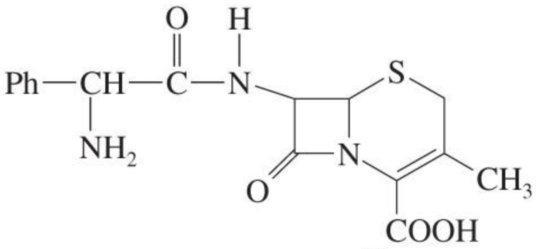


- Five-membered lactams (γ-lactams) and six-membered lactams (δ-lactams) often form on heating or adding a dehydrating agent to the appropriate γ-amino acid or δ-amino acid.

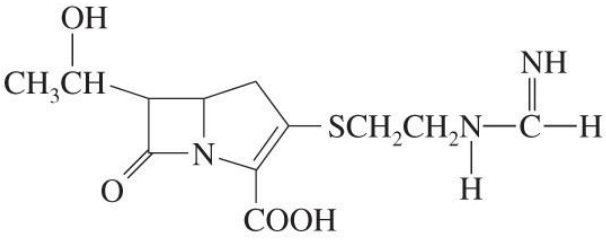
β-Lactams



penicillin V
a penicillin



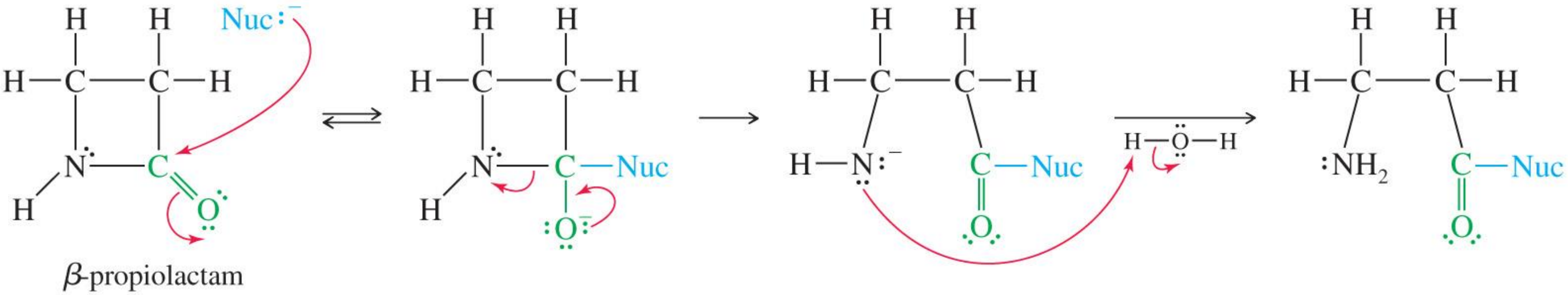
cephalexin (Keflex®)
a cephalosporin



imipenem (Primaxin®)
a carbapenem

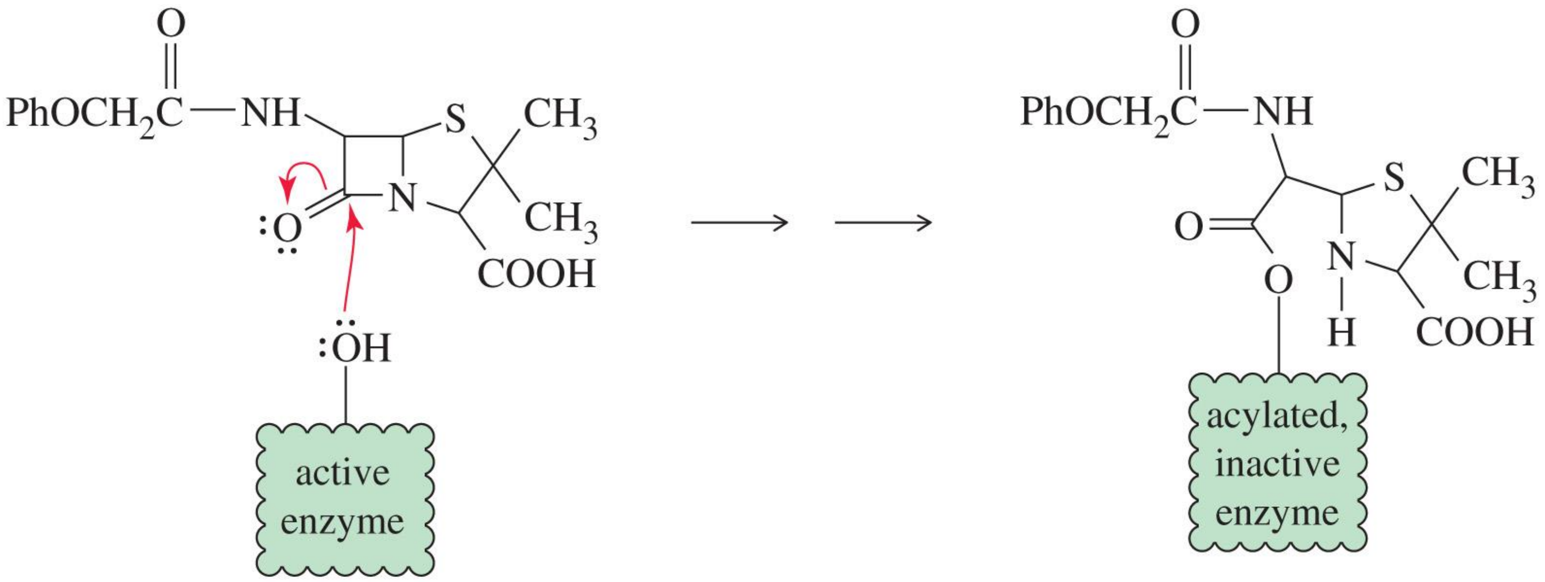
- Unusually reactive four-membered ring amides are capable of acylating a variety of nucleophiles.
- They are found in three important classes of antibiotics: *penicillins, cephalosporins, and carbapenems*.

Mechanism of β-Lactam Acylation



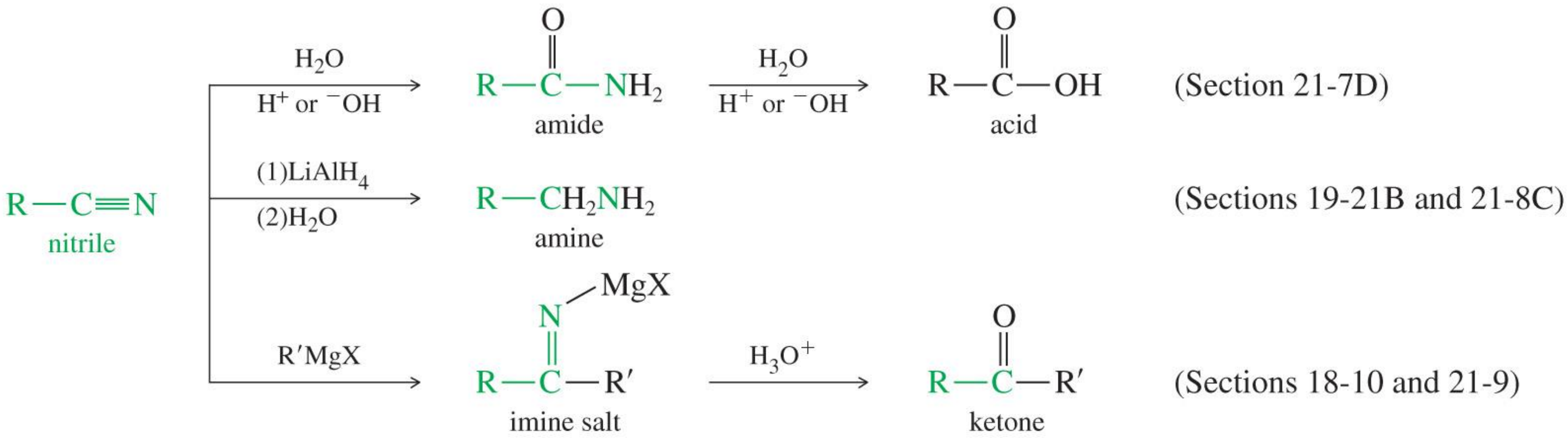
- The nucleophile attacks the carbonyl of the four-membered ring amide, forming a tetrahedral intermediate.
- The nitrogen is eliminated and the carbonyl reformed.
- Protonation of the nitrogen is the last step of the reaction.

Action of Antibiotics

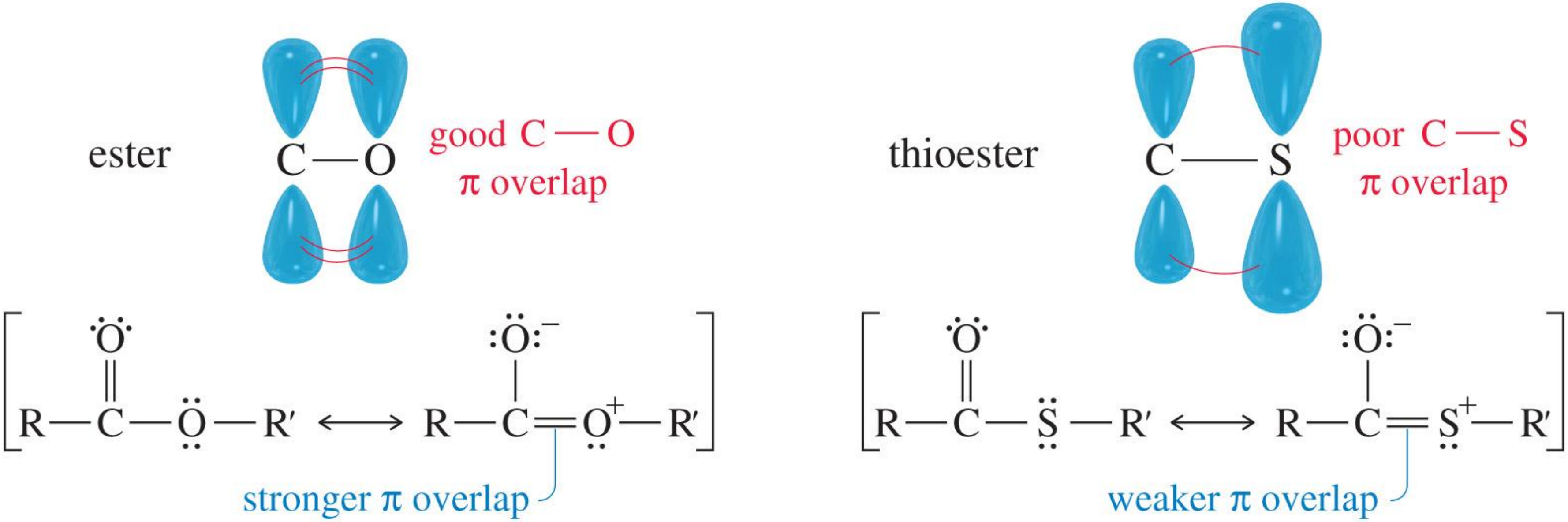


- The β-lactams work by interfering with the synthesis of bacterial cell walls.
- The acylated enzyme is inactive for synthesis of the cell wall protein.

Reactions of Nitriles

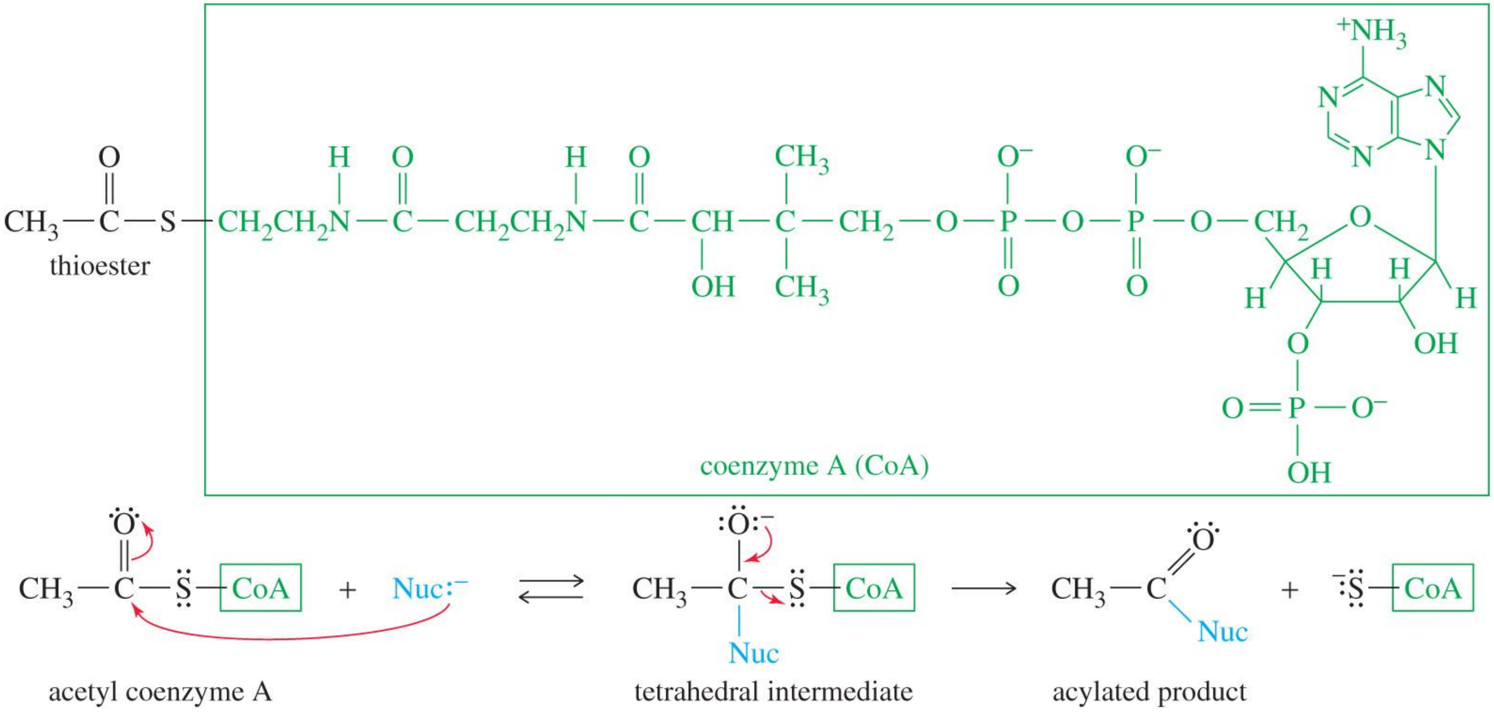


Resonance Overlap in Ester and Thioesters



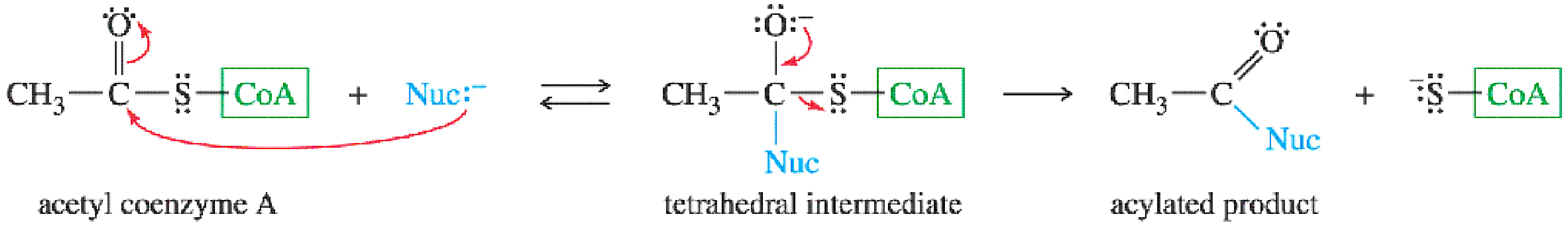
- The resonance overlap in a thioester is not as effective as that in an ester.

Structure of Coenzyme A (CoA)



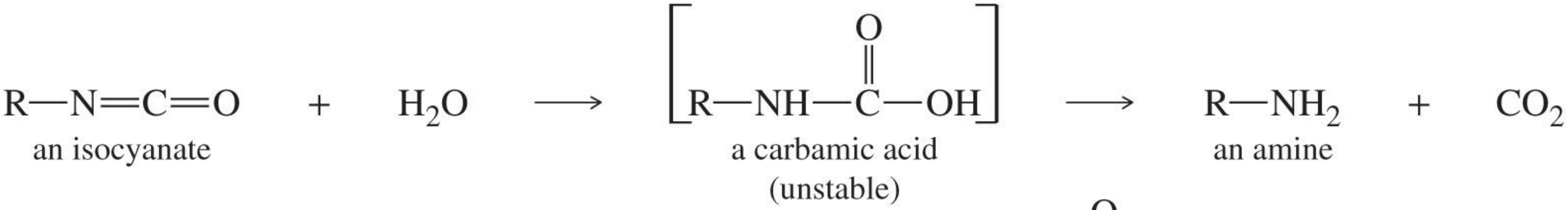
- Coenzyme A (CoA) is a thiol whose thioesters serve as a biochemical acyl transfer reagents.

Mechanism of Action of Acetyl CoA



- Acetyl CoA transfers an acetyl group to a nucleophile, with coenzyme A serving as the leaving group.
- Thioesters are not so prone to hydrolysis, yet they are excellent selective acylating reagents; therefore, thioesters are common acylating agents in living systems.

Synthesis of Carbamate Esters from Isocyanates

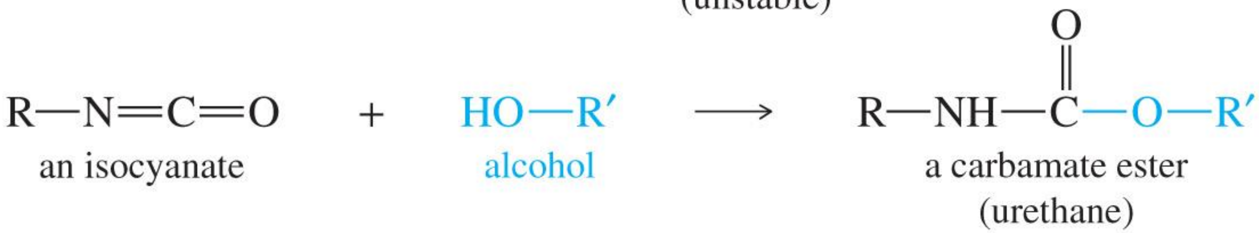


$$R{-}N{=}C{=}O + H_2O \longrightarrow \left[R{-}NH{-}\overset{\overset{O}{\|}}{C}{-}OH\right] \longrightarrow R{-}NH_2 + CO_2$$

an isocyanate

a carbamic acid
(unstable)

an amine



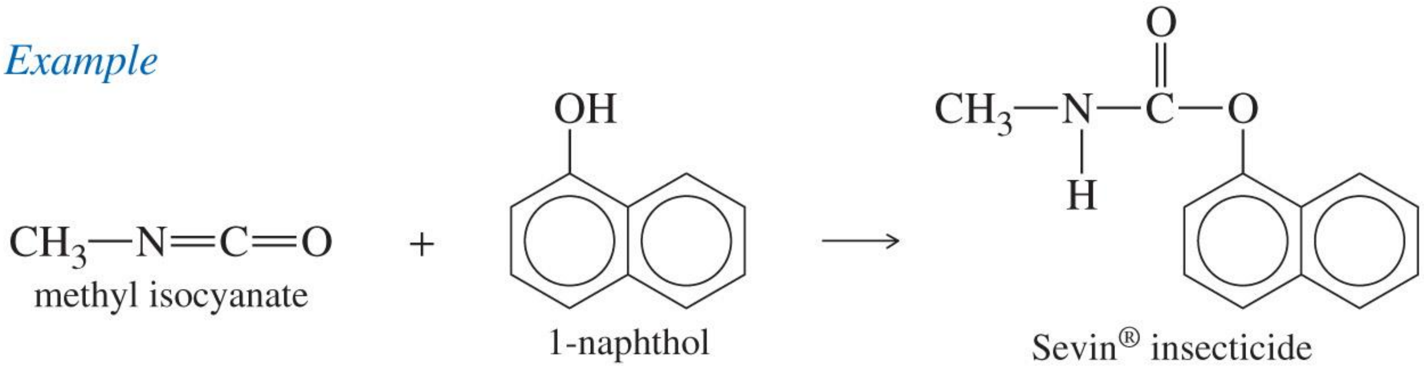
$$R{-}N{=}C{=}O + HO{-}R' \longrightarrow R{-}NH{-}\overset{\overset{O}{\|}}{C}{-}O{-}R'$$

an isocyanate

alcohol

a carbamate ester
(urethane)

Example



methyl isocyanate

1-naphthol

Sevin® insecticide