

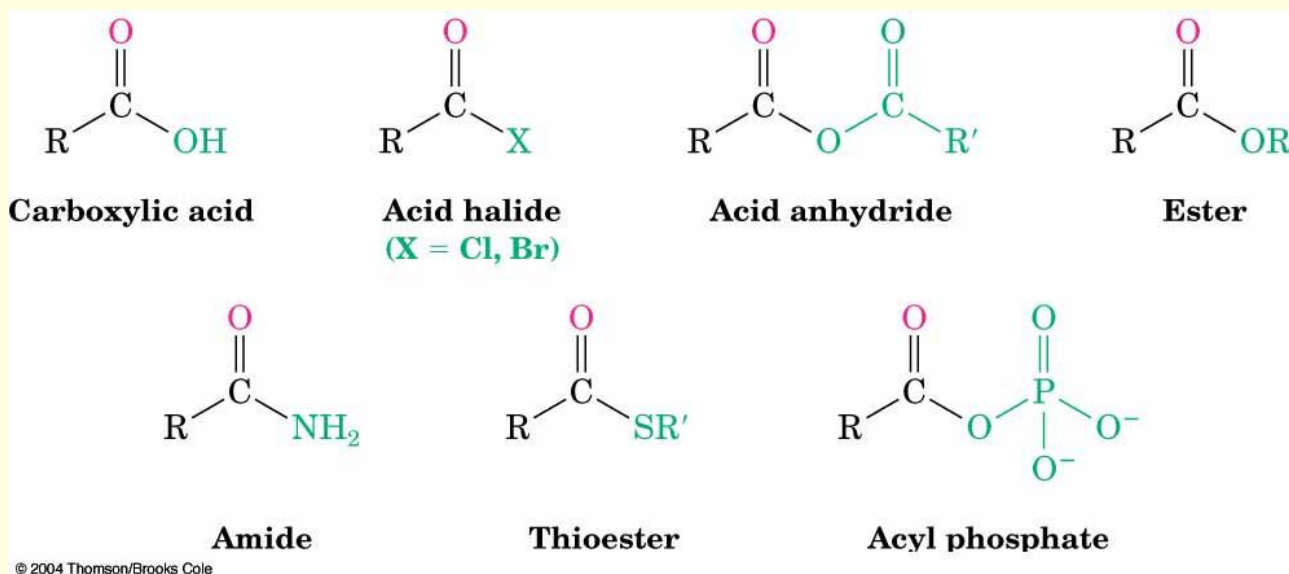
Chapter 21. Carboxylic Acid Derivatives and Nucleophilic Acyl Substitution Reactions

Based on McMurry's *Organic Chemistry*, 6th
edition

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Department of Chemistry
University of Toronto

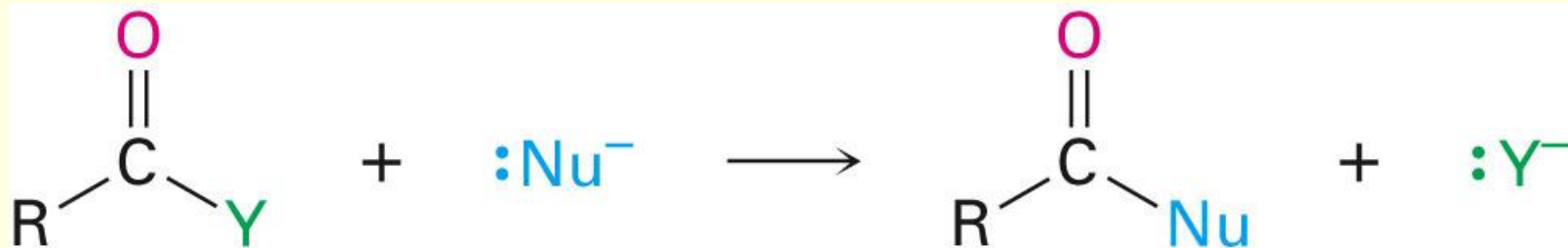
Carboxylic Compounds

- Acyl group bonded to Y, an electronegative atom or leaving group
- Includes: Y = halide (acid halides), acyloxy (anhydrides), alkoxy (esters), amine (amides), thiolate (thioesters), phosphate (acyl phosphates)



General Reaction Pattern

- Nucleophilic acyl substitution



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Why this Chapter?

- Carboxylic acids are among the most widespread of molecules.
- A study of them and their primary reaction “nucleophilic acyl substitution” is fundamental to understanding organic chemistry

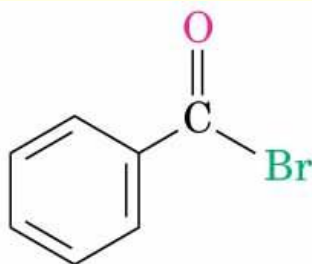
21.1 Naming Carboxylic Acid Derivatives

- Acid Halides, RCOX
 - Derived from the carboxylic acid name by replacing the *-ic acid* ending with *-yl* or the *-carboxylic acid* ending with *-carbonyl* and specifying the halide

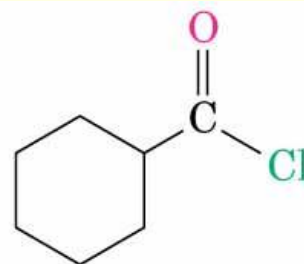


Acetyl chloride
(from acetic acid)

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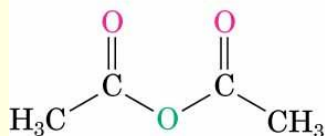
Benzoyl bromide
(from benzoic acid)



Cyclohexanecarbonyl chloride
(from cyclohexanecarboxylic acid)

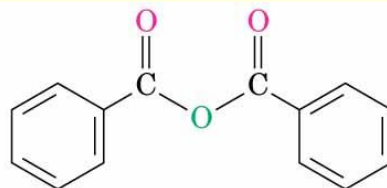
Naming Acid Anhydrides, $\text{RCO}_2\text{COR}'$

- If symmetrical replace “*acid*” with “*anhydride*” based on the related carboxylic acid (for symmetrical anhydrides)
- From substituted monocarboxylic acids: use *bis-* ahead of the acid name
- Unsymmetrical anhydrides— cite the two acids alphabetically

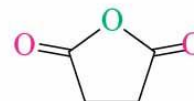


Acetic anhydride

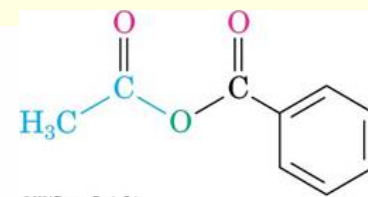
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Benzoic anhydride

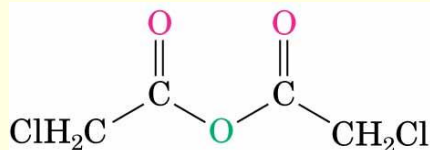


Succinic anhydride



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Acetic benzoic anhydride

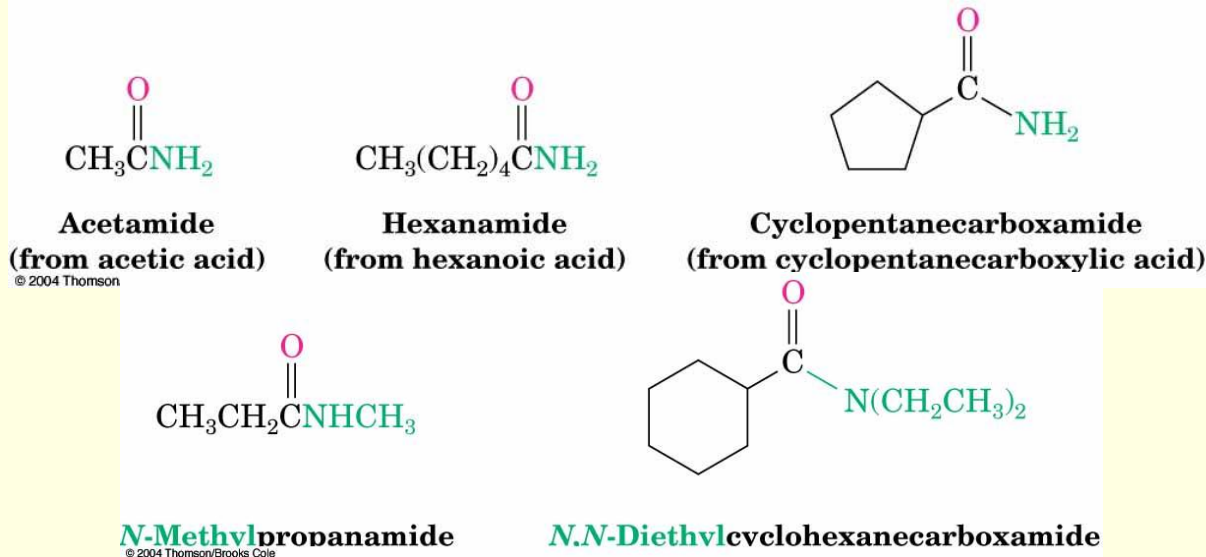


Bis(chloroacetic) anhydride

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Naming Amides, RCONH₂

- With unsubstituted —NH₂ group. replace *-oic acid* or *-ic acid* with *-amide*, or by replacing the *-carboxylic acid* ending with *-carboxamide*
- If the N is further substituted, identify the substituent groups (preceded by “N”) and then the parent amide



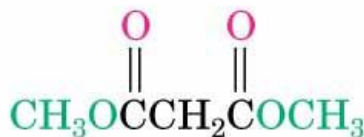
Naming Esters, $\text{RCO}_2\text{R}'$

- Name R' and then, after a space, the carboxylic acid (RCOOH), with the “*-ic acid*” ending replaced by “*-ate*”

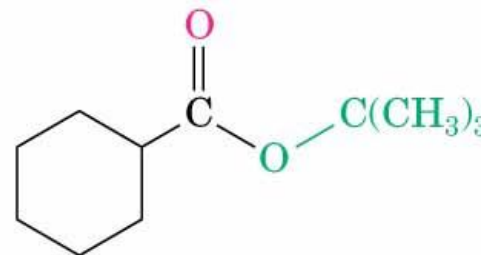


Ethyl acetate
(the ethyl ester of
acetic acid)

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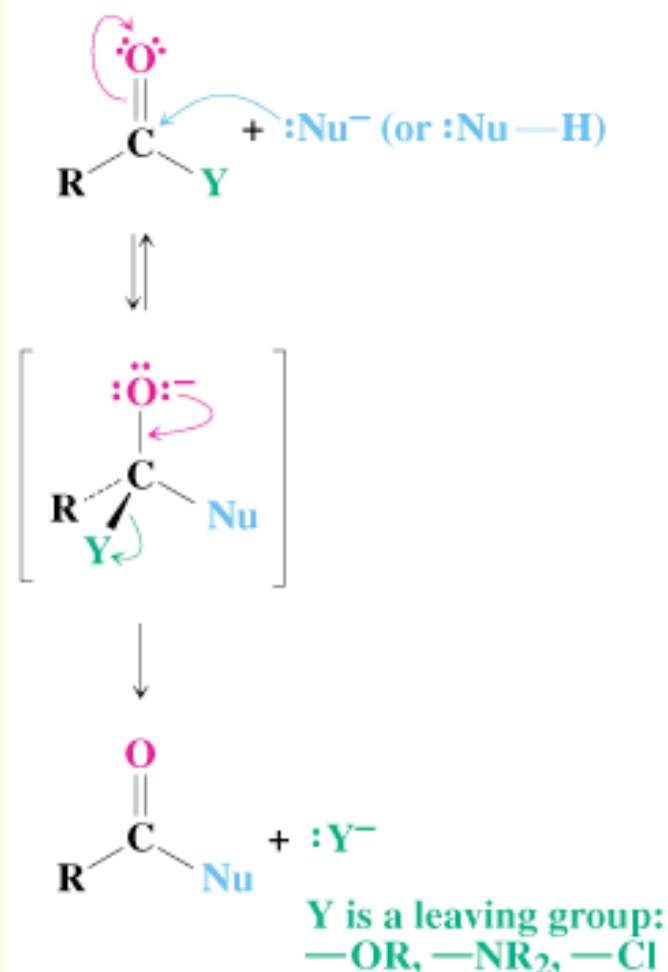
Dimethyl malonate
(the dimethyl ester of
malonic acid)



***tert*-Butylcyclohexanecarboxylate**
(the *tert*-butyl ester of
cyclohexanecarboxylic acid)

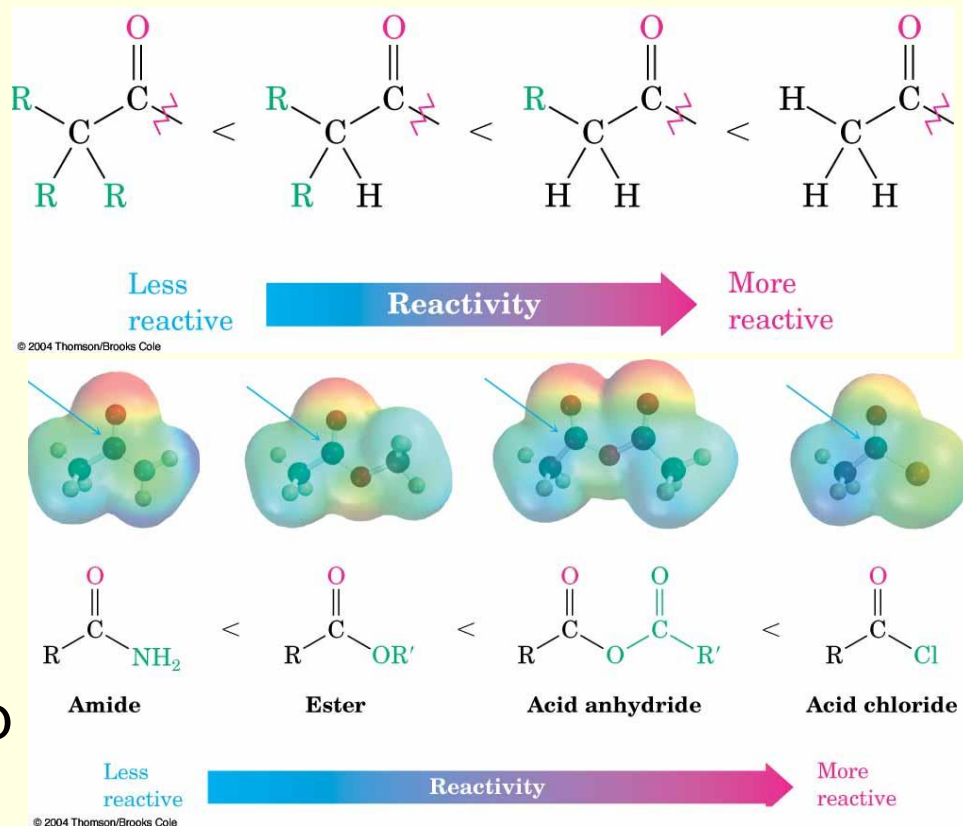
21.2 Nucleophilic Acyl Substitution

- Carboxylic acid derivatives have an acyl carbon bonded to a group —Y that can leave
- A tetrahedral intermediate is formed and the leaving group is expelled to generate a new carbonyl compound, leading to substitution



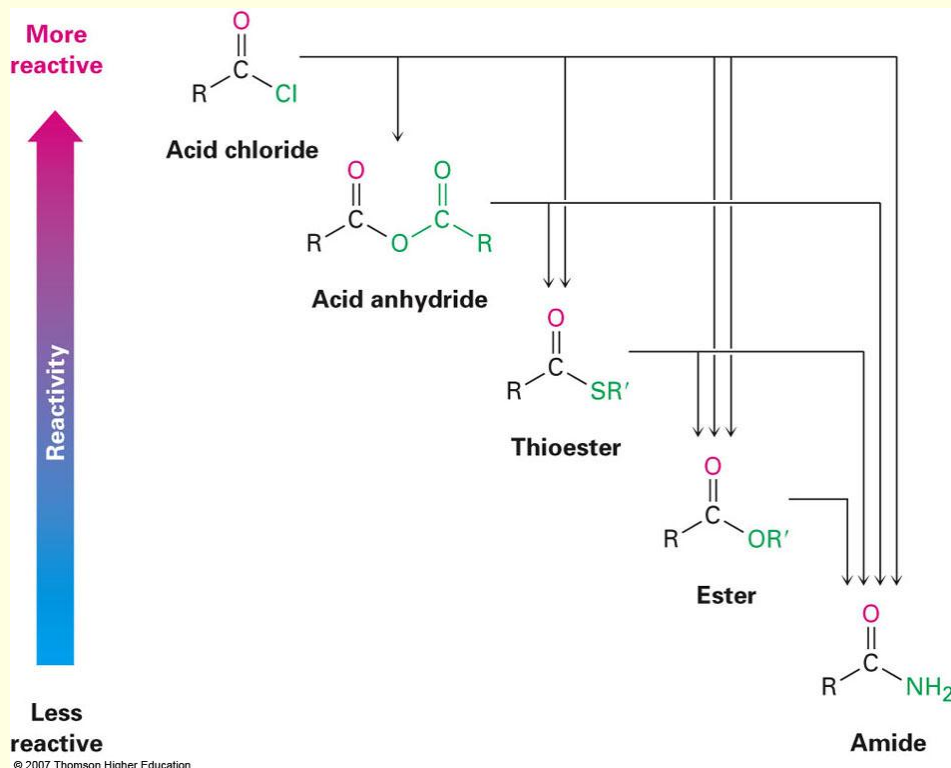
Relative Reactivity of Carboxylic Acid Derivatives

- Nucleophiles react more readily with unhindered carbonyl groups
- More electrophilic carbonyl groups are more reactive to addition (acyl halides are most reactive, amides are least)
- The intermediate with the best leaving group decomposes fastest



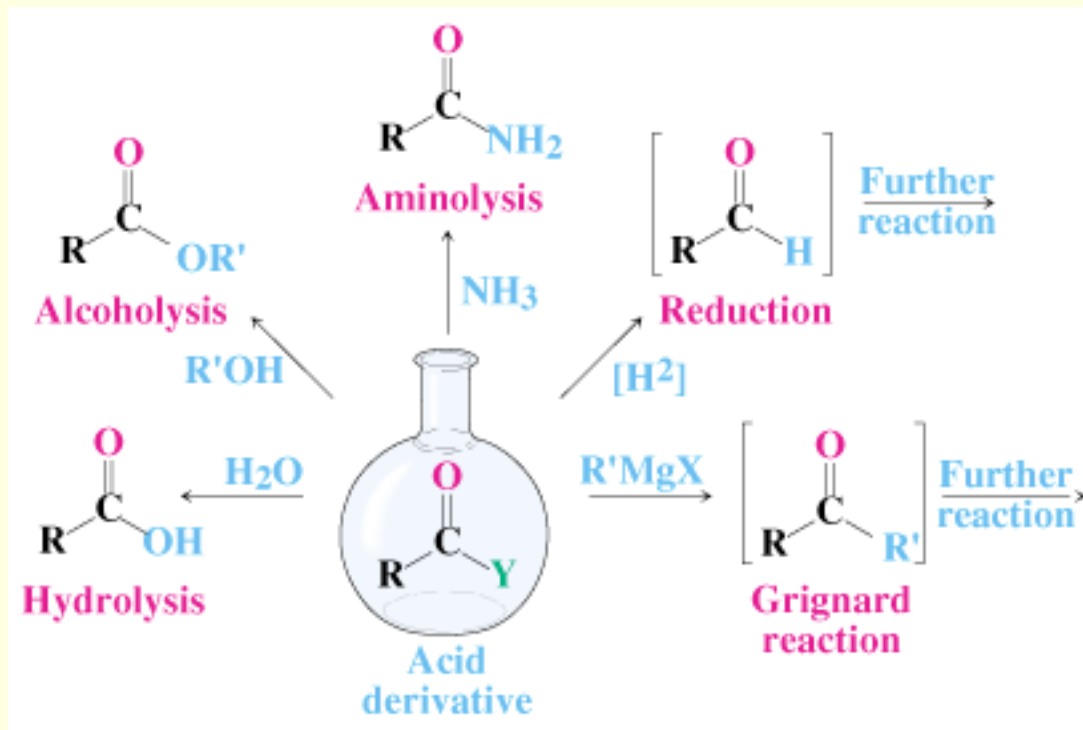
Substitution in Synthesis

- We can readily convert a more reactive acid derivative into a less reactive one
- Reactions in the opposite sense are possible but require more complex approaches



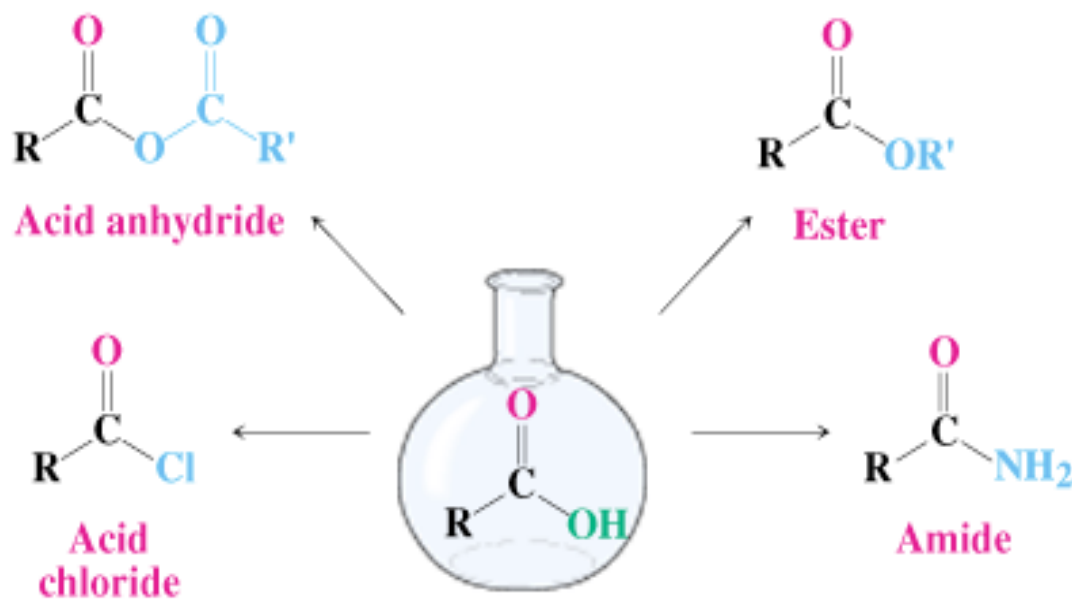
General Reactions of Carboxylic Acid Derivatives

- water ⌚
carboxylic acid
- alcohols ⌚
esters
- ammonia or an amine ⌚
an amide
- hydride source ⌚
an aldehyde or an alcohol
- Grignard reagent ⌚
a ketone or an alcohol



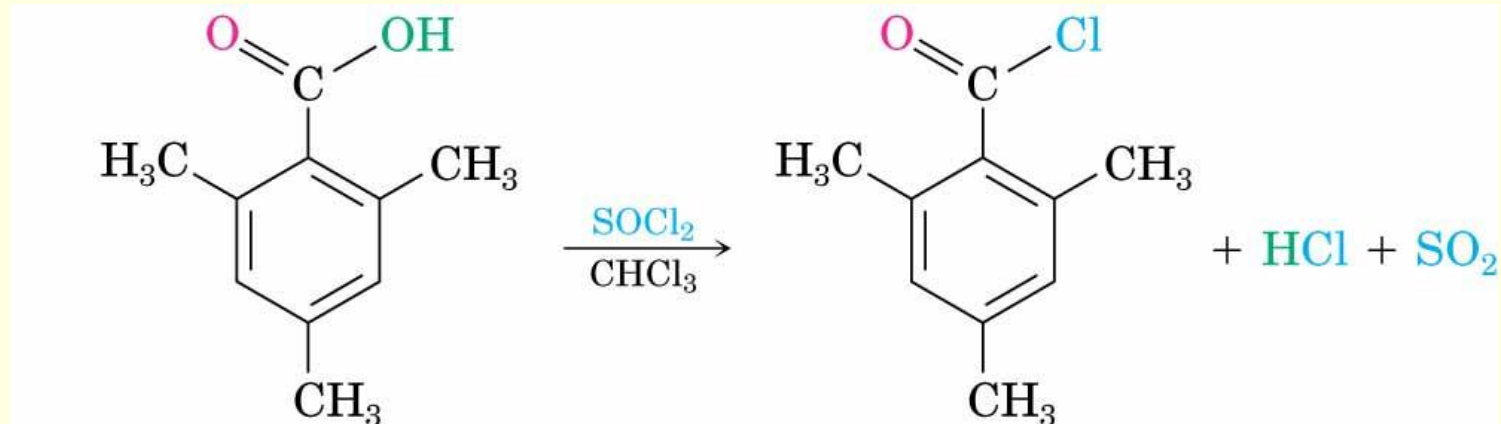
21.3 Nucleophilic Acyl Substitution Reactions of Carboxylic Acids

- Must enhance reactivity
- Convert —OH into a better leaving group
- Specific reagents can produce acid chlorides, anhydrides, esters, amides



Conversion of Carboxylic Acids into Acid Chlorides

- Reaction with thionyl chloride, SOCl_2



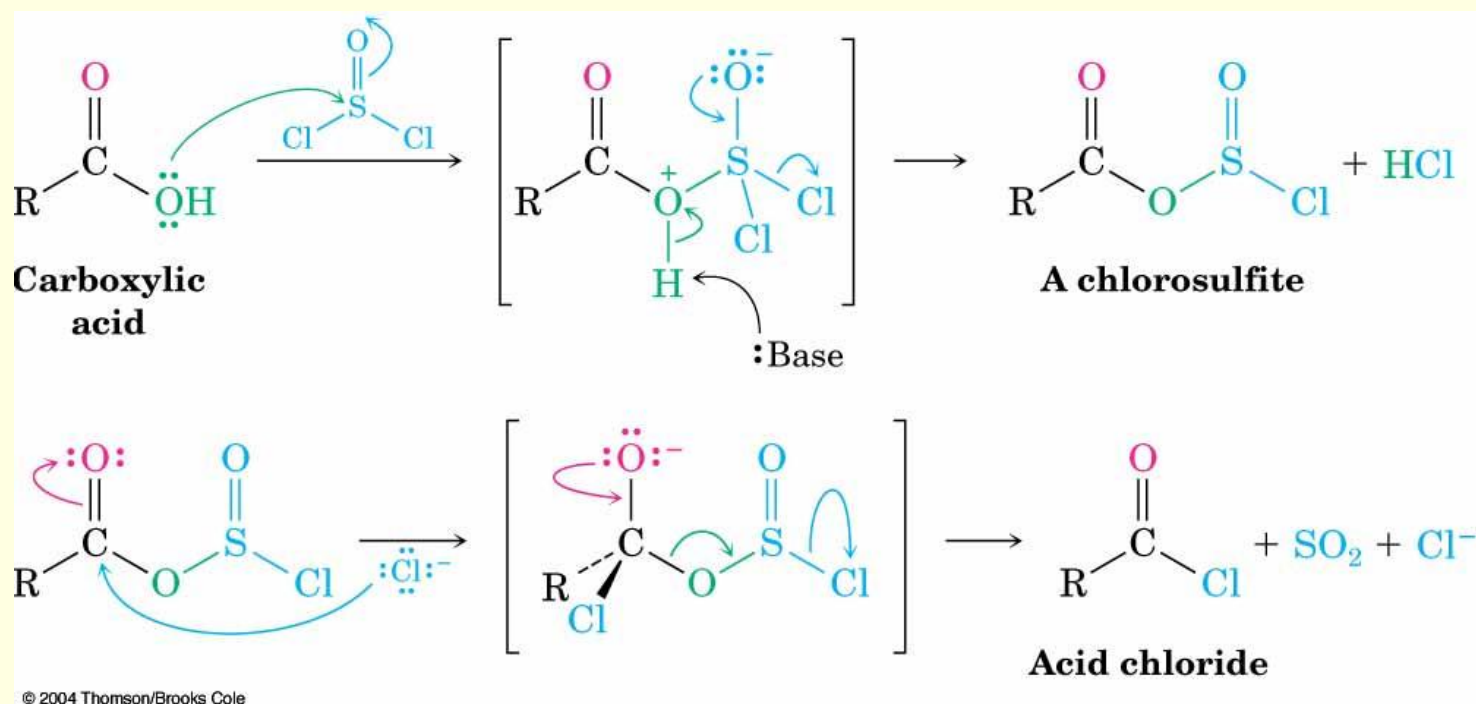
2,4,6-Trimethylbenzoic acid

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

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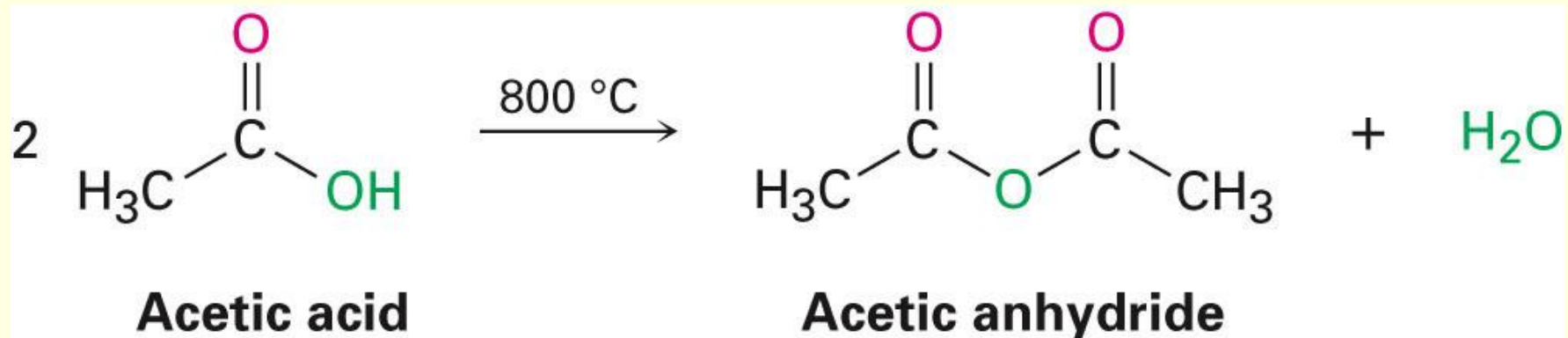
Mechanism of Thionyl Chloride Reaction

- Nucleophilic acyl substitution pathway
- Carboxylic acid is converted into a *chlorosulfite* which then reacts with chloride



Conversion of Carboxylic Acids into Acid Anhydrides

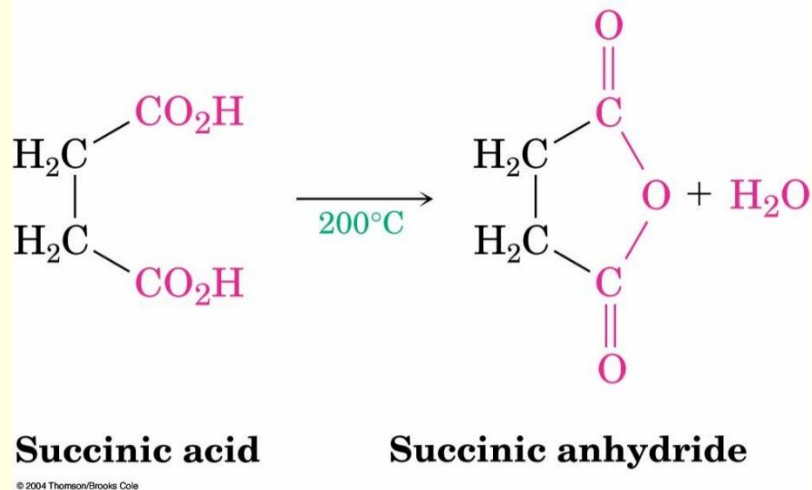
- Acid anhydrides can be derived from two molecules of carboxylic acid by strong heating to remove water



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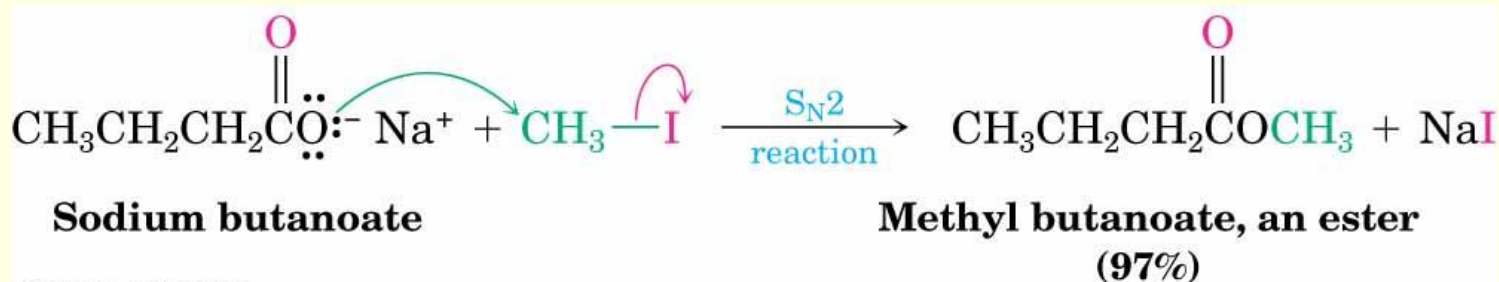
Conversion of Carboxylic Acids into Acid Anhydrides

- Heat cyclic dicarboxylic acids that can form five- or six-membered rings
- Acyclic anhydrides are not generally formed this way - they are usually made from acid chlorides and carboxylic acids



Conversion of Carboxylic Acids into Esters

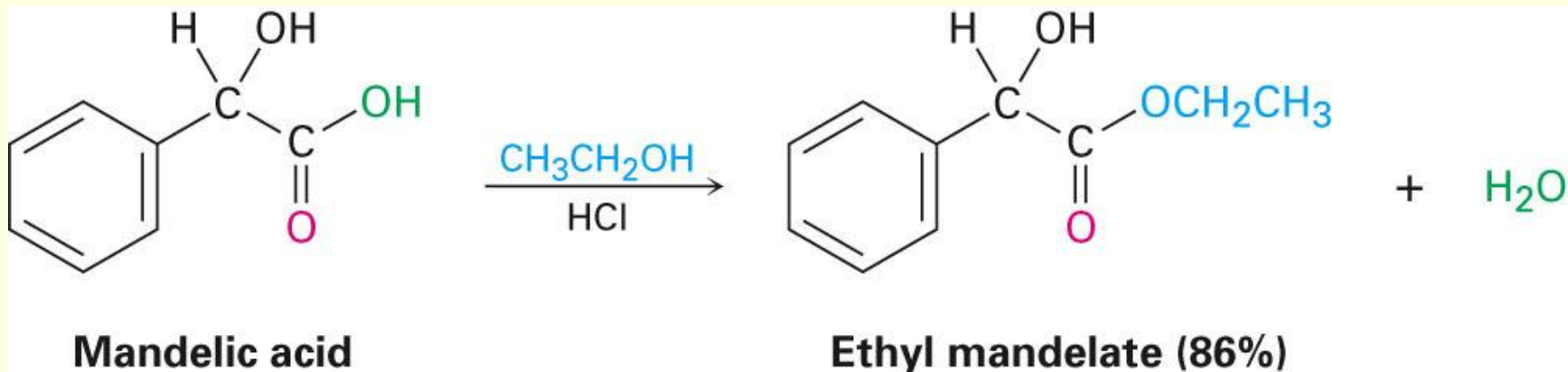
- Methods include reaction of a carboxylate anion with a primary alkyl halide



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Fischer Esterification

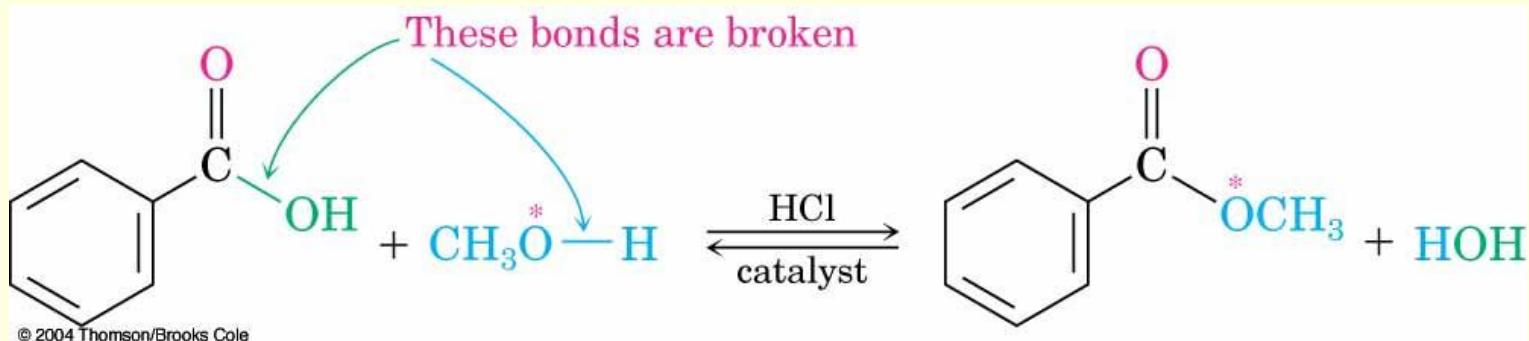
- Heating a carboxylic acid in an alcohol solvent containing a small amount of strong acid produces an ester from the alcohol and acid



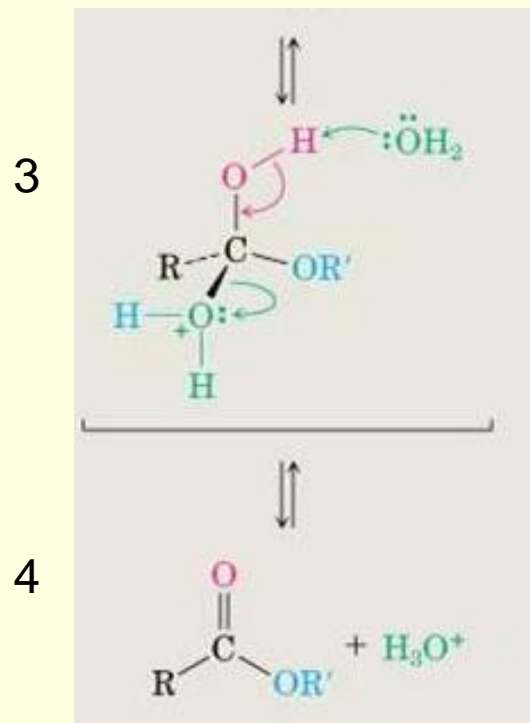
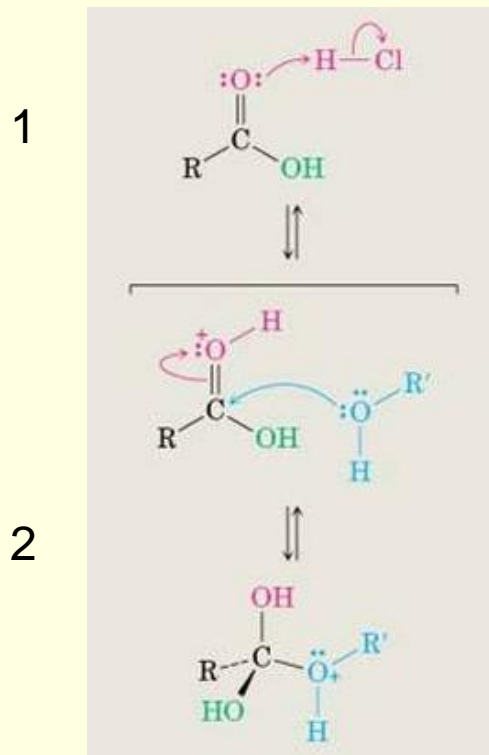
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Mechanism of the Fischer Esterification

- The reaction is an acid-catalyzed, nucleophilic acyl substitution of a carboxylic acid
- When ^{18}O -labeled methanol reacts with benzoic acid, the methyl benzoate produced is ^{18}O -labeled but the water produced is unlabeled



Fischer Esterification: Detailed Mechanism



- 1 Protonation of the carbonyl oxygen activates the carboxylic acid . . .
- 2 . . . toward nucleophilic attack by alcohol, yielding a tetrahedral intermediate.
- 3 Transfer of a proton from one oxygen atom to another yields a second tetrahedral intermediate and converts the OH group into a good leaving group.
- 4 Loss of a proton and expulsion of H₂O regenerates the acid catalyst and gives the ester product.

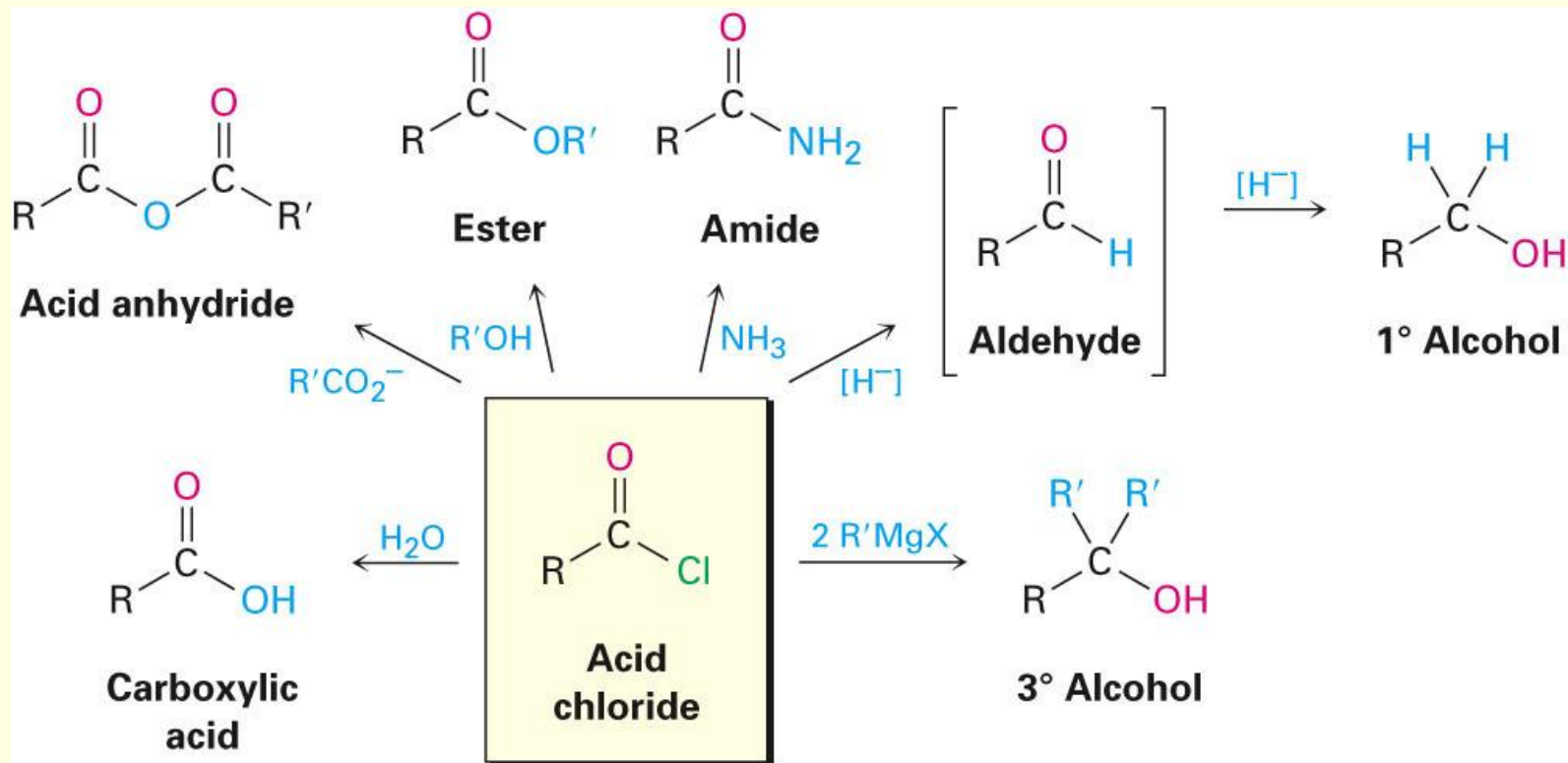
21.4 Chemistry of Acid Halides

- Acid chlorides are prepared from carboxylic acids by reaction with SOCl_2
- Reaction of a carboxylic acid with PBr_3 yields the acid bromide



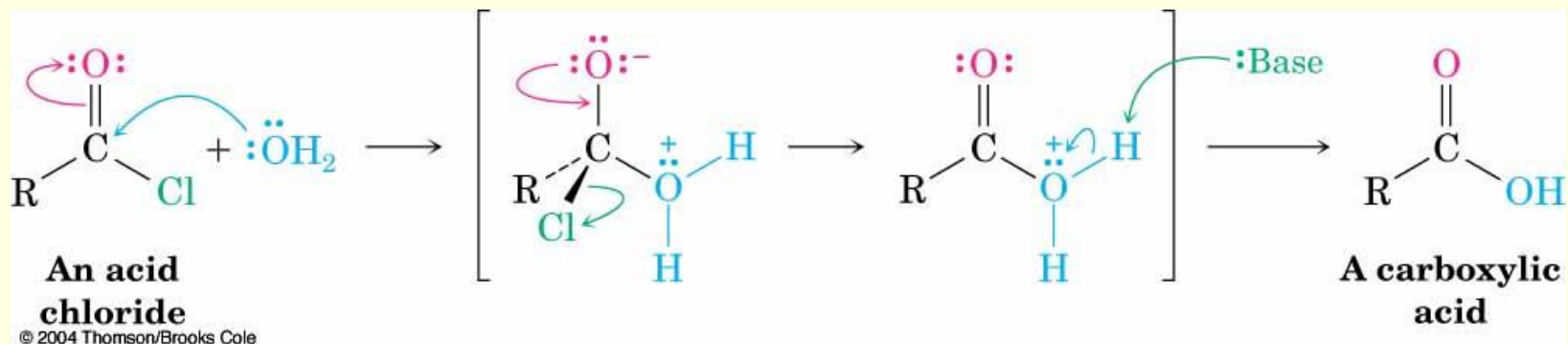
Reactions of Acid Halides

- Nucleophilic acyl substitution
- Halogen replaced by —OH, by —OR, or by —NH₂
- Reduction yields a primary alcohol



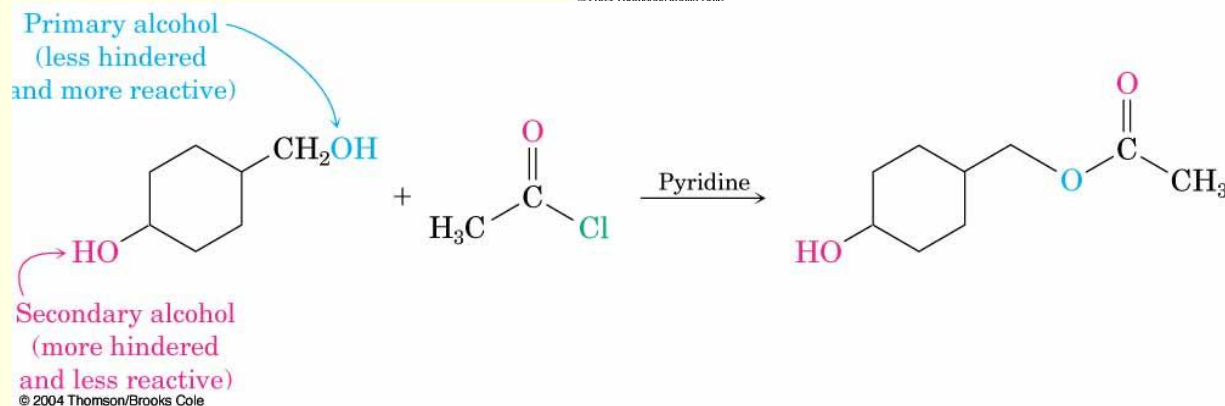
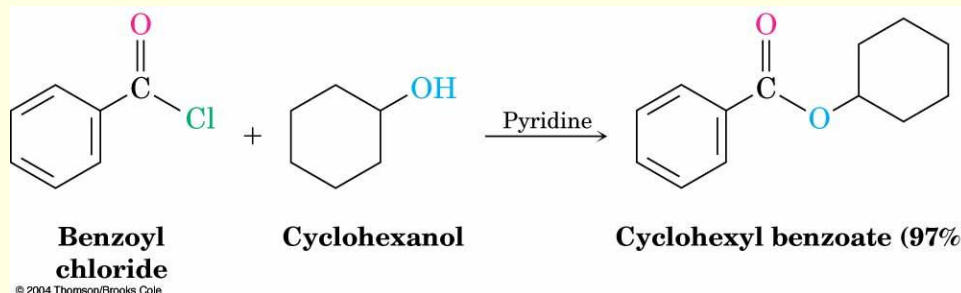
Hydrolysis: Conversion of Acid Halides into Acids

- Acid chlorides react with water to yield carboxylic acids
- HCl is generated during the hydrolysis: a base is added to remove the HCl



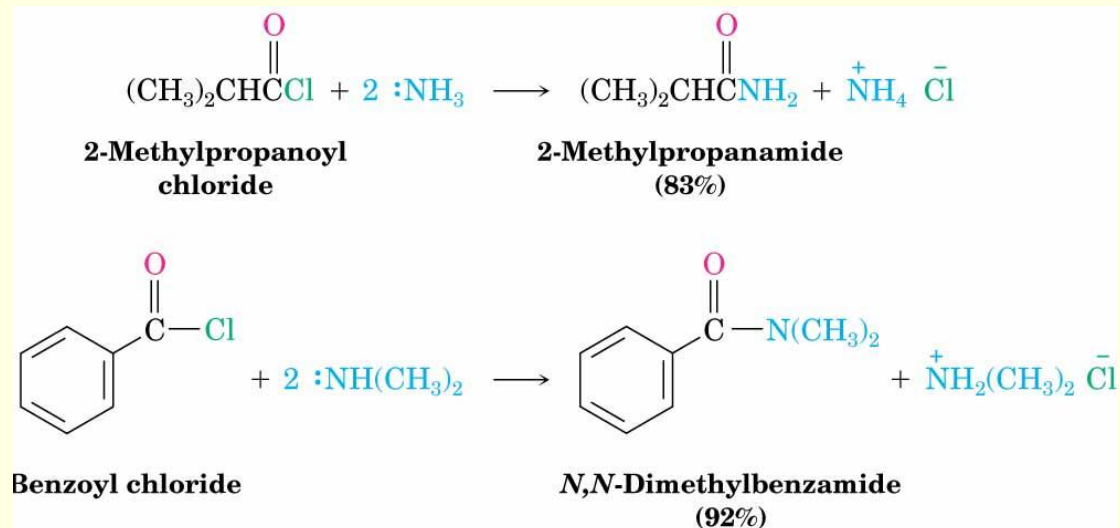
Conversion of Acid Halides to Esters

- Esters are produced in the reaction of acid chlorides react with alcohols in the presence of pyridine or NaOH. This is called **Alcoholysis**.
- The reaction is better with less steric bulk



Aminolysis: Conversion of Acid Halides into Amides

- Amides result from the reaction of acid chlorides with NH_3 , primary (RNH_2) and secondary amines (R_2NH)
- The reaction with tertiary amines (R_3N) gives an unstable species that cannot be isolated
- HCl is neutralized by the amine or an added base

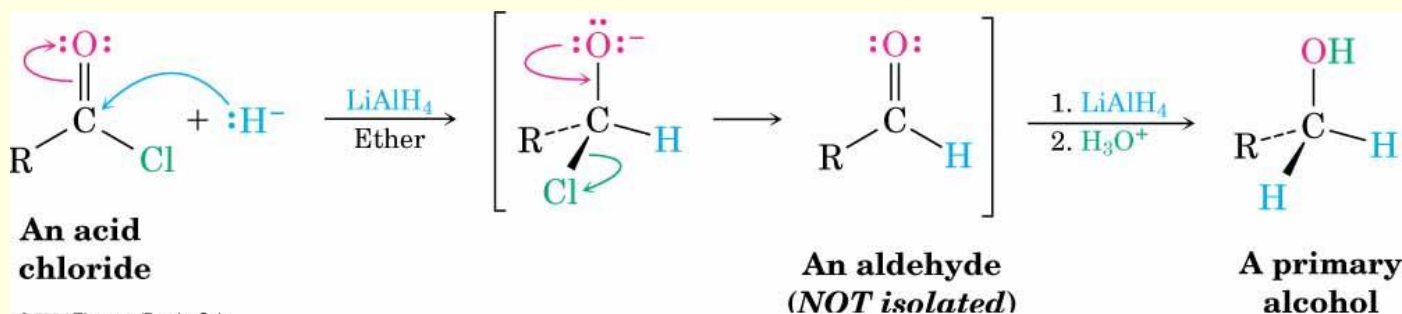


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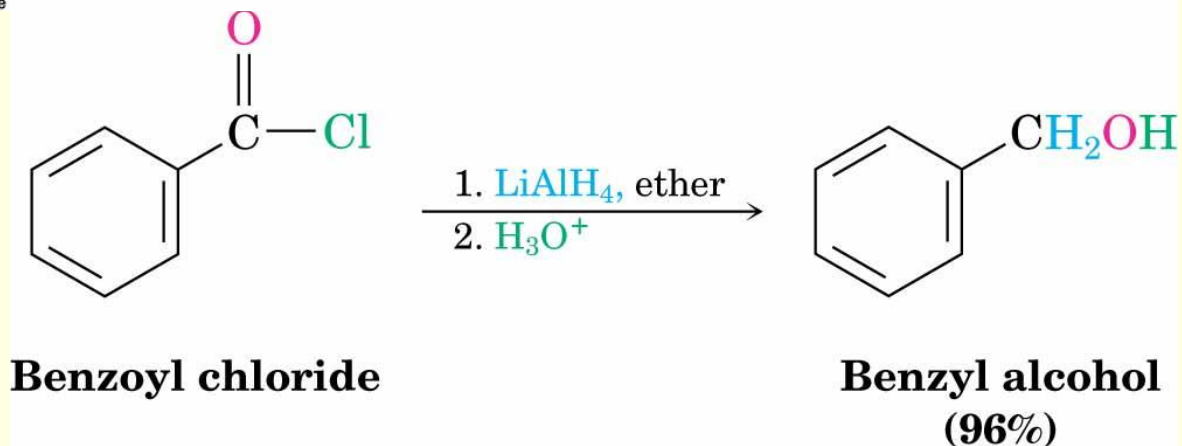
Based on McMurry, Organic Chemistry, Chapter 21, 6th edition, (c) 2003
.....Dr.Mohanad Al-Hachamii

Reduction: Conversion of Acid Chlorides into Alcohols

- LiAlH₄ reduces acid chlorides to yield aldehydes and then primary alcohols



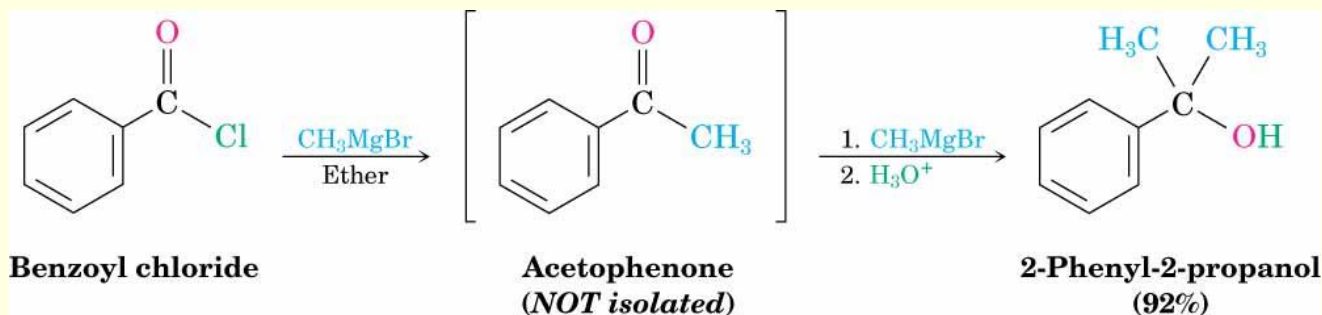
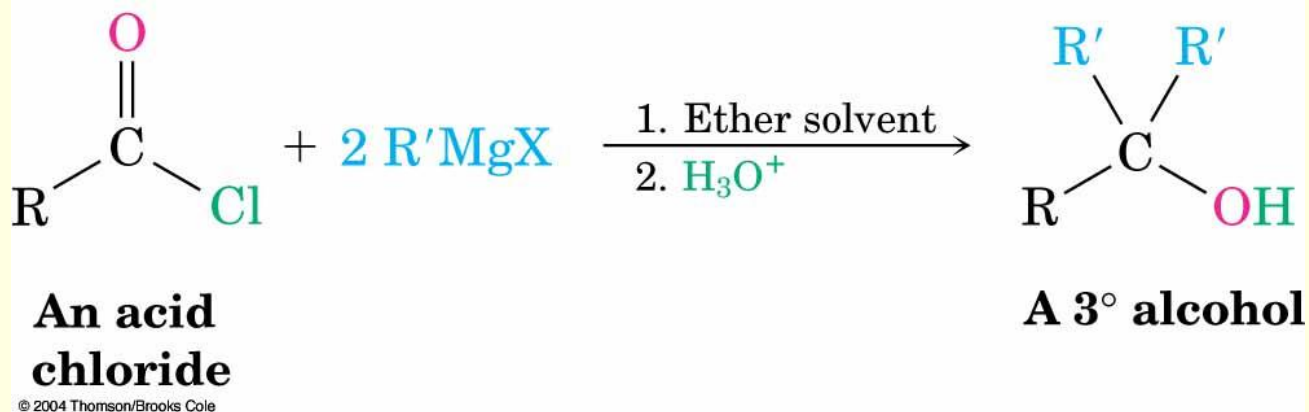
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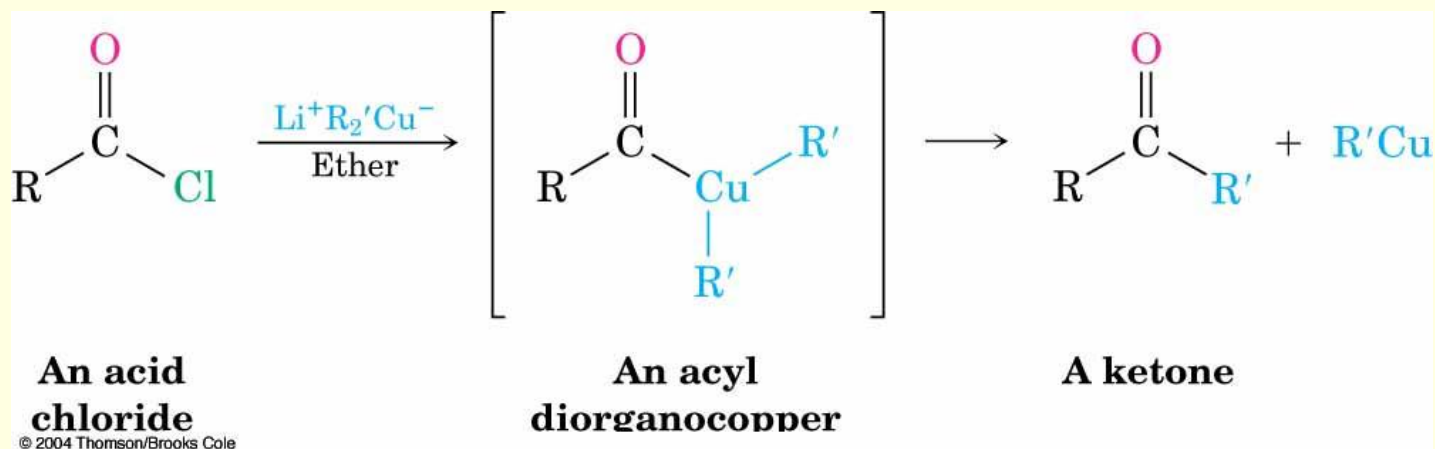
Reaction of Acid Chlorides with Organometallic Reagents

- Grignard reagents react with acid chlorides to yield tertiary alcohols in which two of the substituents are the same



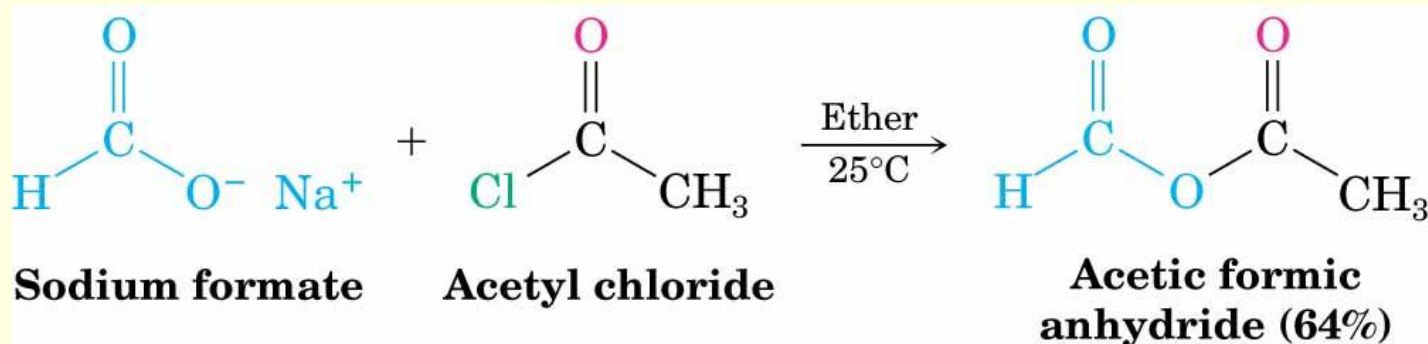
Formation of Ketones from Acid Chlorides

- Reaction of an acid chloride with a lithium diorganocopper (Gilman) reagent, $\text{Li}^+ \text{R}_2\text{Cu}^-$
- Addition produces an acyl diorganocopper intermediate, followed by loss of $\text{R}'\text{Cu}$ and formation of the ketone

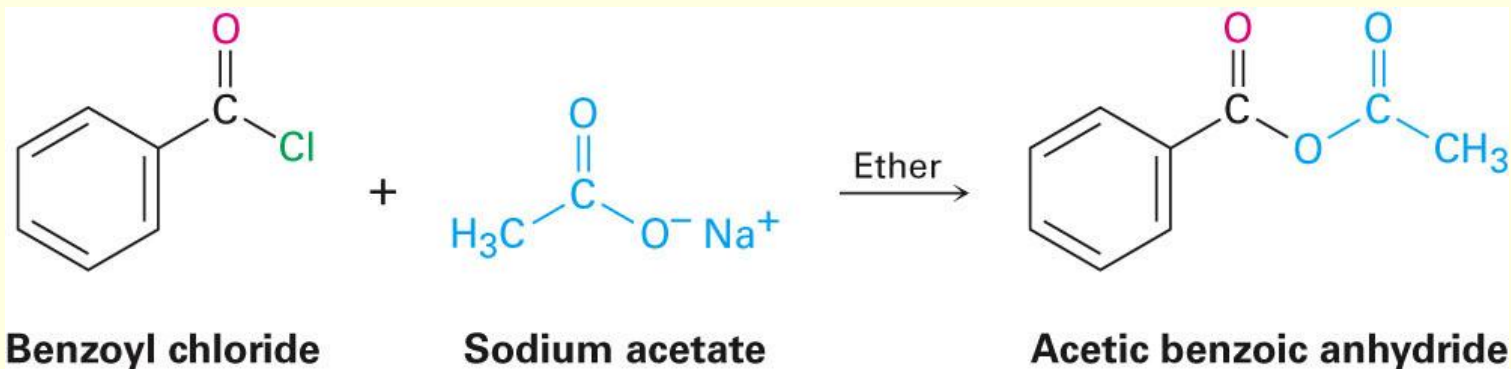


21.5 Chemistry of Acid Anhydrides

- Prepared by nucleophilic of a carboxylate with an acid chloride



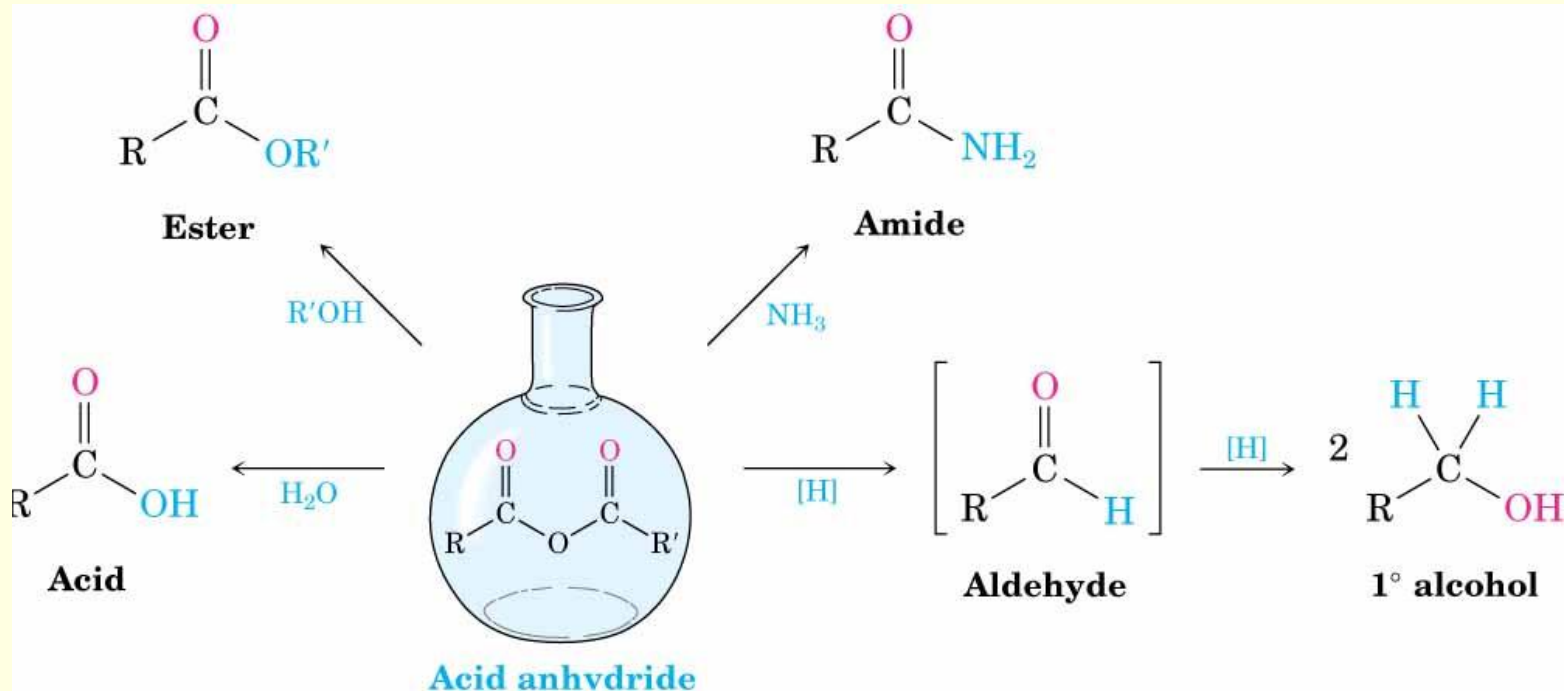
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Reactions of Acid Anhydrides

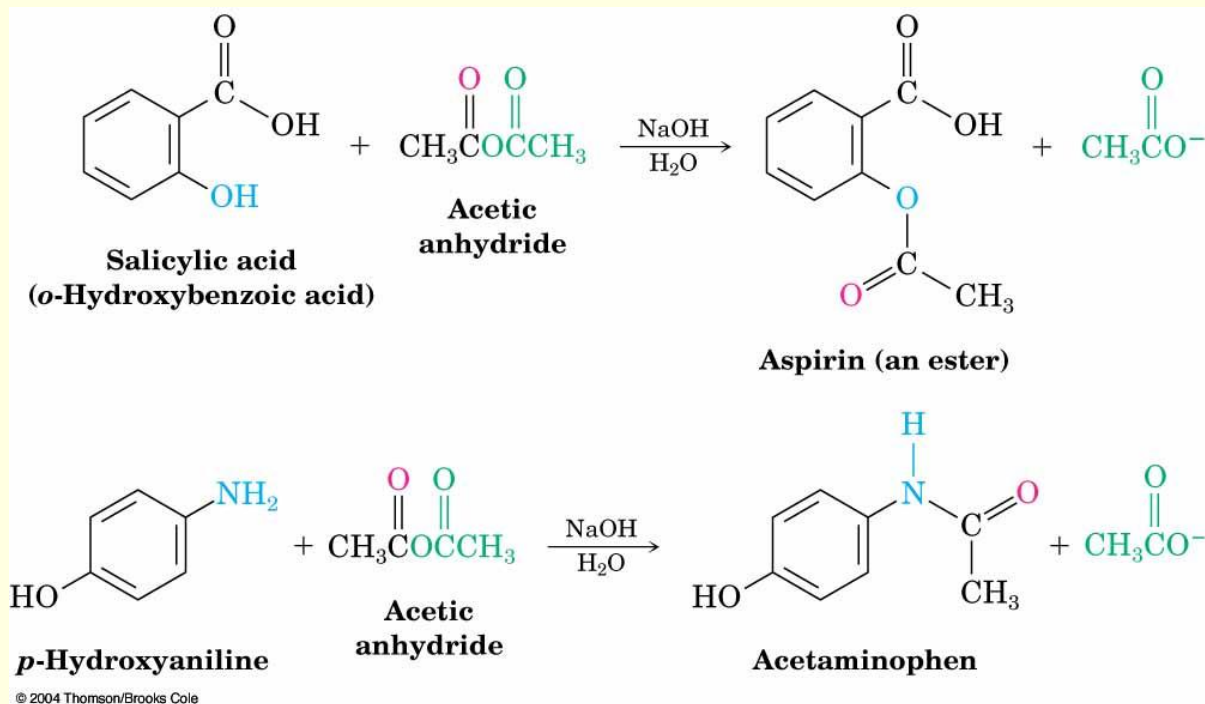
- Similar to acid chlorides in reactivity



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Acetylation

- Acetic anhydride forms acetate esters from alcohols and *N*-substituted acetamides from amines



21.6 Chemistry of Esters

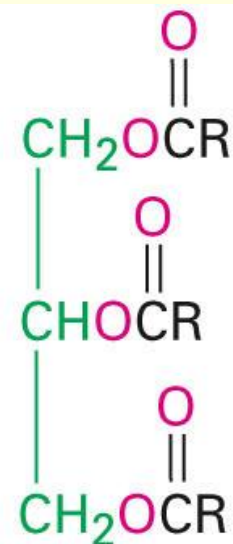
- Many esters are pleasant-smelling liquids: fragrant odors of fruits and flowers
- Also present in fats and vegetable oils



Methyl butanoate
(from pineapples)



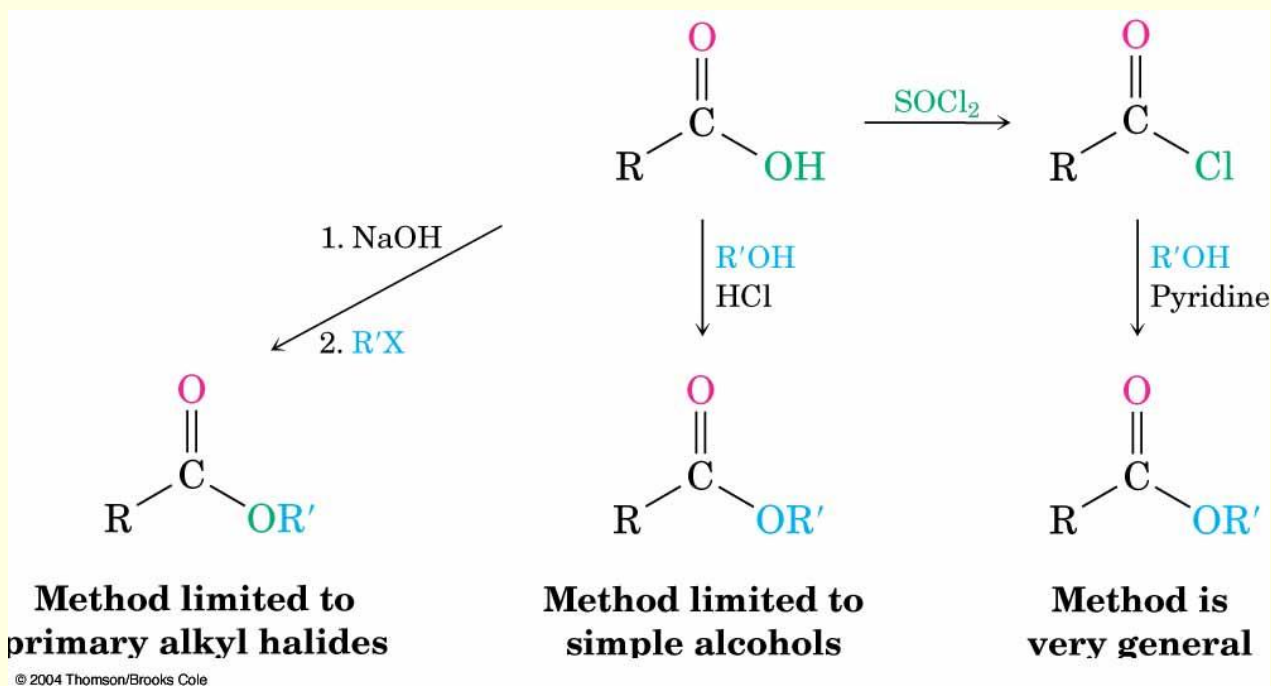
Isopentyl acetate
(from bananas)



A fat
(R = C₁₁₋₁₇ chains)

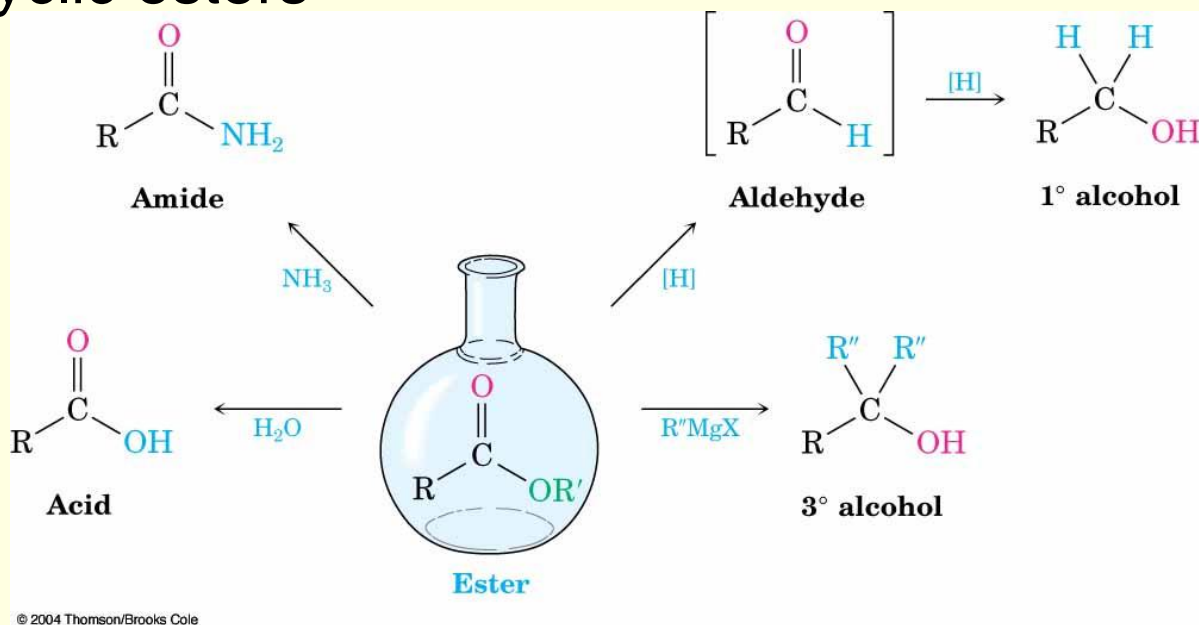
Preparation of Esters

- Esters are usually prepared from carboxylic acids



Reactions of Esters

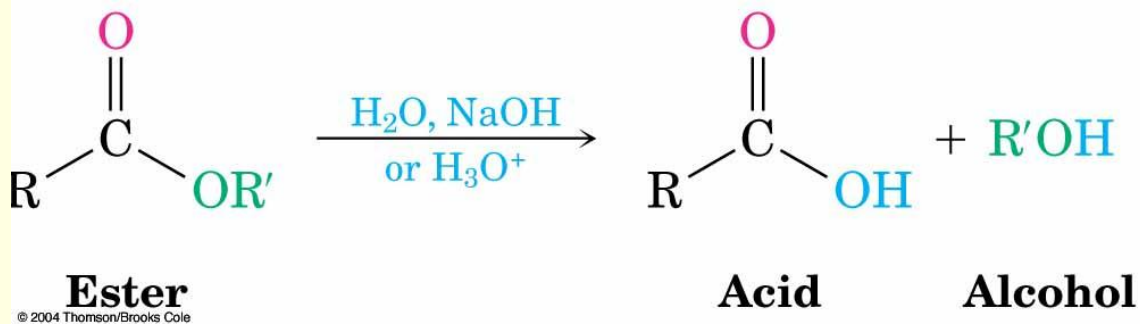
- Less reactive toward nucleophiles than are acid chlorides or anhydrides
- Cyclic esters are called lactones and react similarly to acyclic esters



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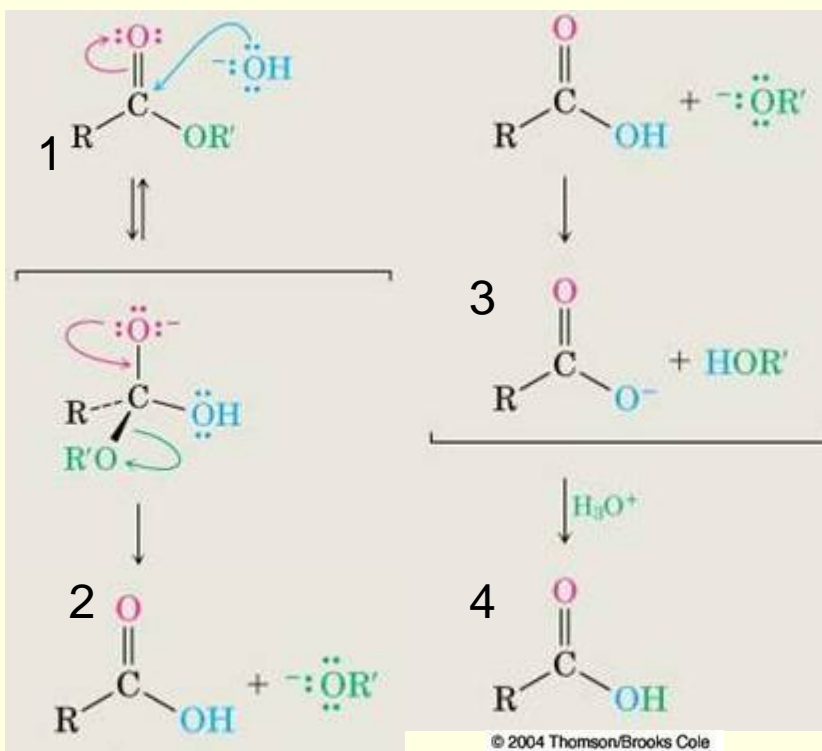
Hydrolysis: Conversion of Esters into Carboxylic Acids

- An ester is hydrolyzed by aqueous base or aqueous acid to yield a carboxylic acid plus an alcohol



Mechanism of Ester Hydrolysis

Hydroxide catalysis via an addition intermediate



1 Nucleophilic addition of hydroxide ion to the ester carbonyl group gives the usual tetrahedral alkoxide intermediate.

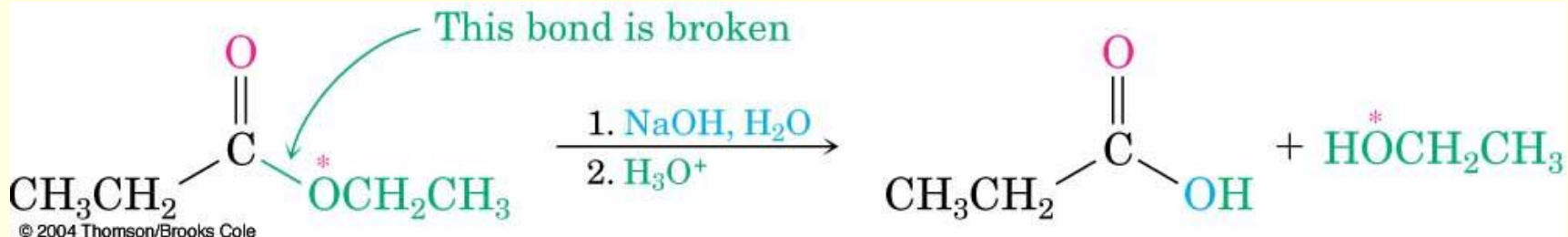
2 Elimination of alkoxide ion then generates the carboxylic acid.

3 Alkoxide ion abstracts the acidic proton from the carboxylic acid and yields a carboxylate ion.

4 Protonation of the carboxylate ion by addition of aqueous mineral acid in a separate step then gives the free carboxylic acid.

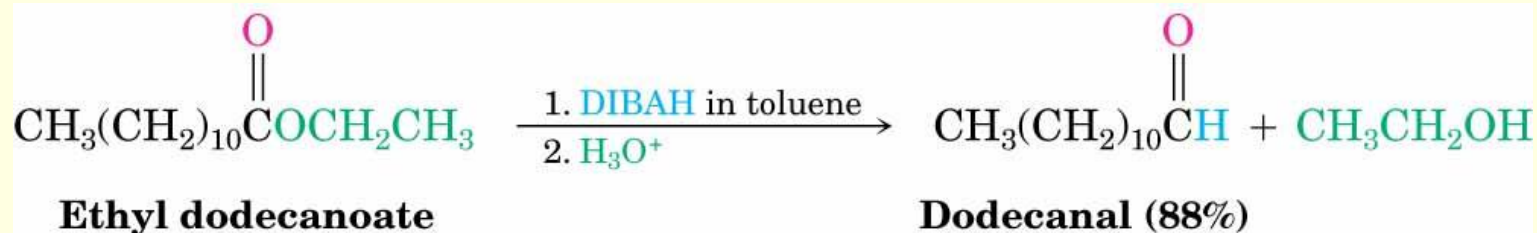
Evidence from Isotope Labelling

- ^{18}O in the ether-like oxygen in ester winds 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



Acid Catalyzed Ester Hydrolysis

- The usual pathway is the reverse of the Fischer esterification

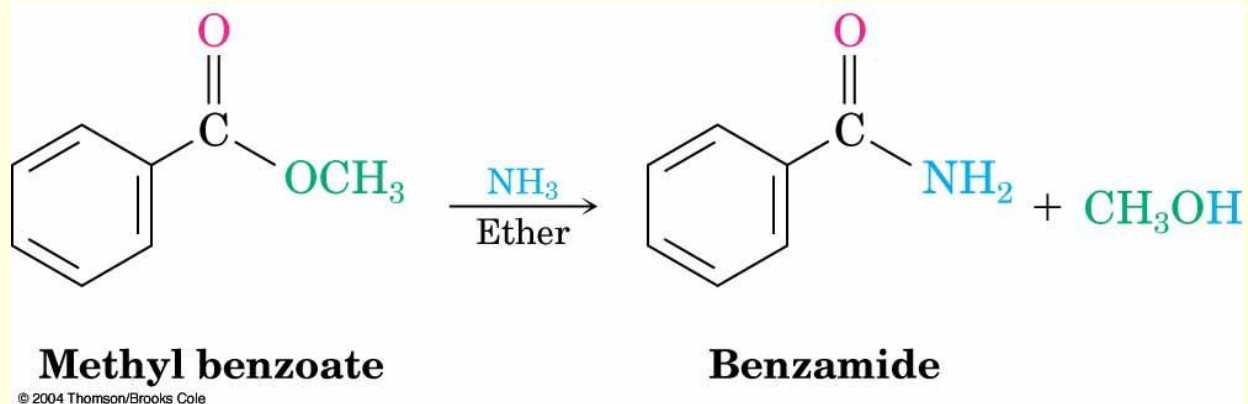


where DIBAH = $[(\text{CH}_3)_2\text{CHCH}_2]_2\text{AlH}$

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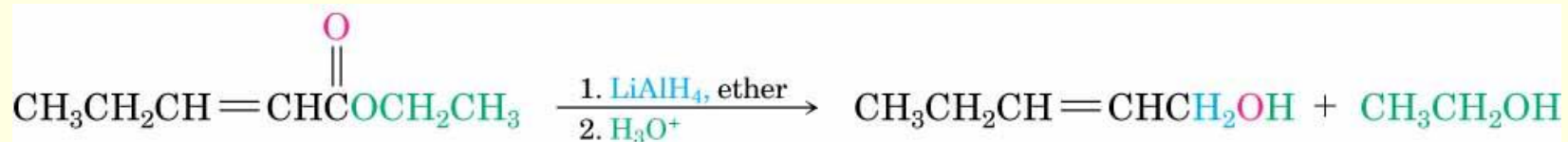
Aminolysis of Esters

- Ammonia reacts with esters to form amides



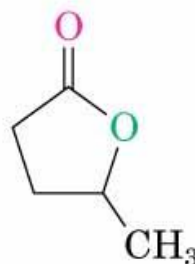
Reduction: Conversion of Esters into Alcohols

- Reaction with LiAlH_4 yields primary alcohols



Ethyl 2-pentenoate

2-Penten-1-ol (91%)



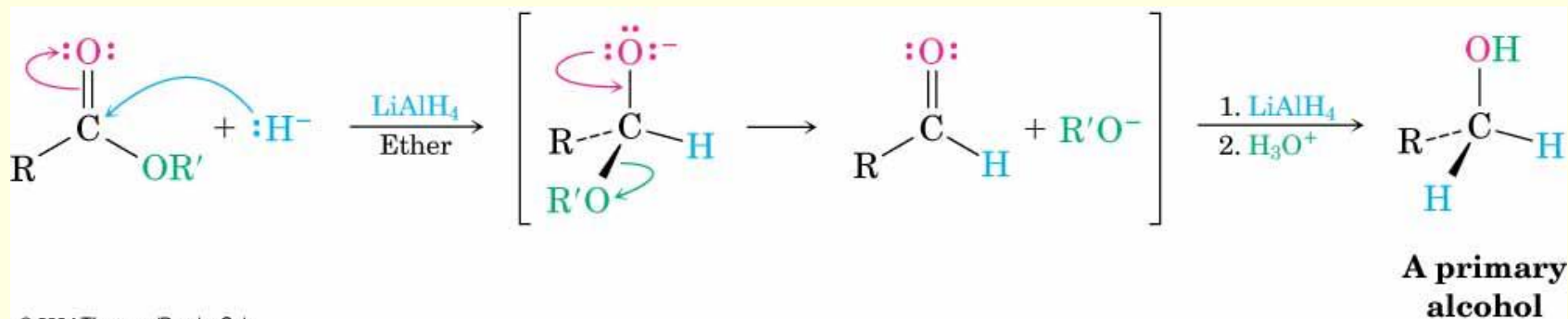
1,4-Pentanediol (86%)

A lactone

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Mechanism of Reduction of Esters

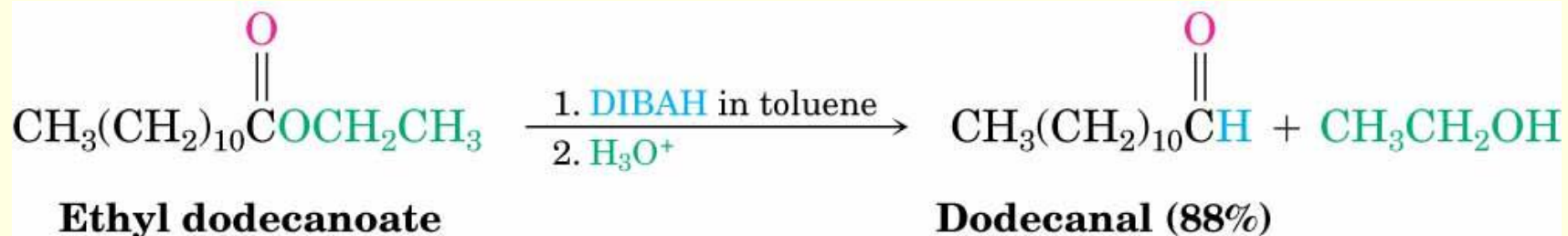
- Hydride ion adds to the carbonyl group, followed by elimination of alkoxide ion to yield an aldehyde
- Reduction of the aldehyde gives the primary alcohol



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Partial Reduction to Aldehydes

- Use one equivalent of diisobutylaluminum hydride (DIBAH = $((\text{CH}_3)_2\text{CHCH}_2)_2\text{AlH}$) instead of LiAlH_4
- Low temperature to avoid further reduction to the alcohol

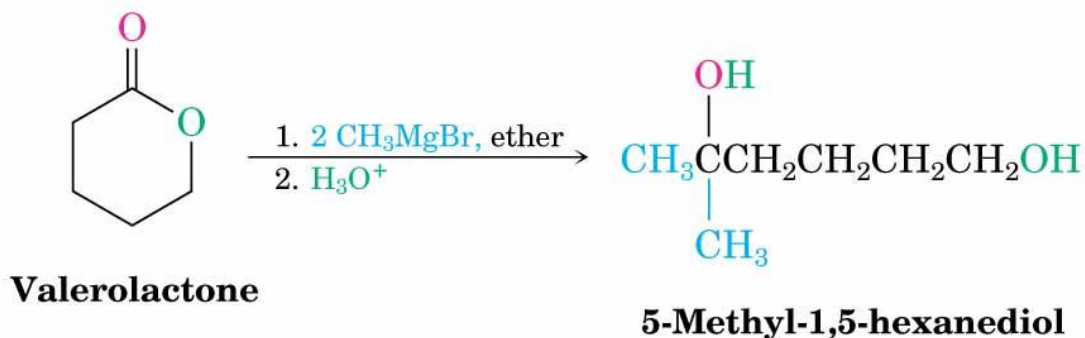
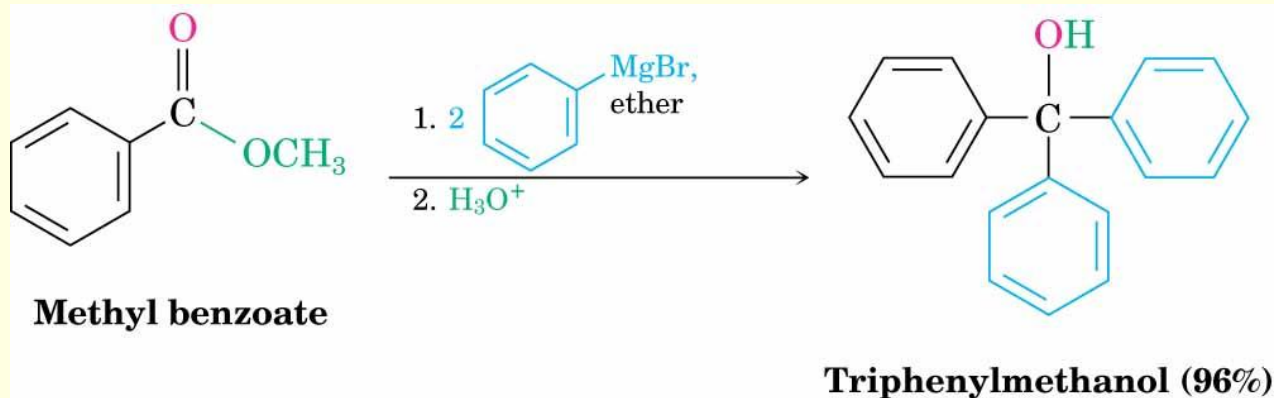


where $\text{DIBAH} = [(\text{CH}_3)_2\text{CHCH}_2]_2\text{AlH}$

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Reaction of Esters with Grignard Reagents

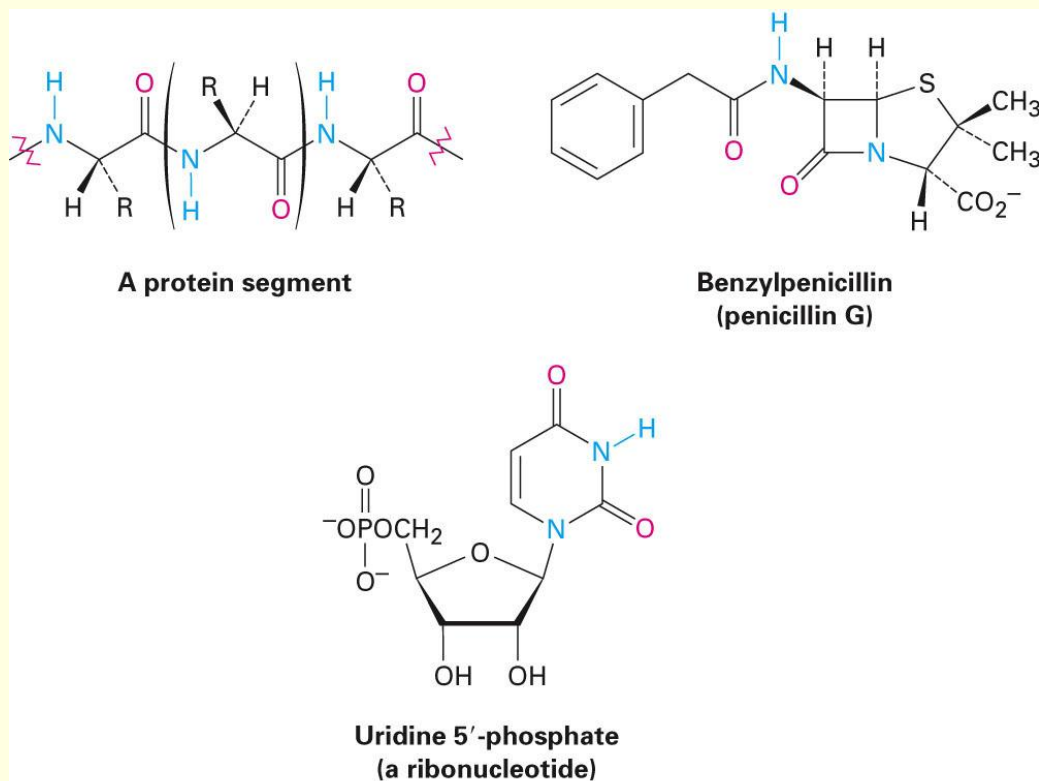
- React with 2 equivalents of a Grignard reagent to yield a tertiary alcohol



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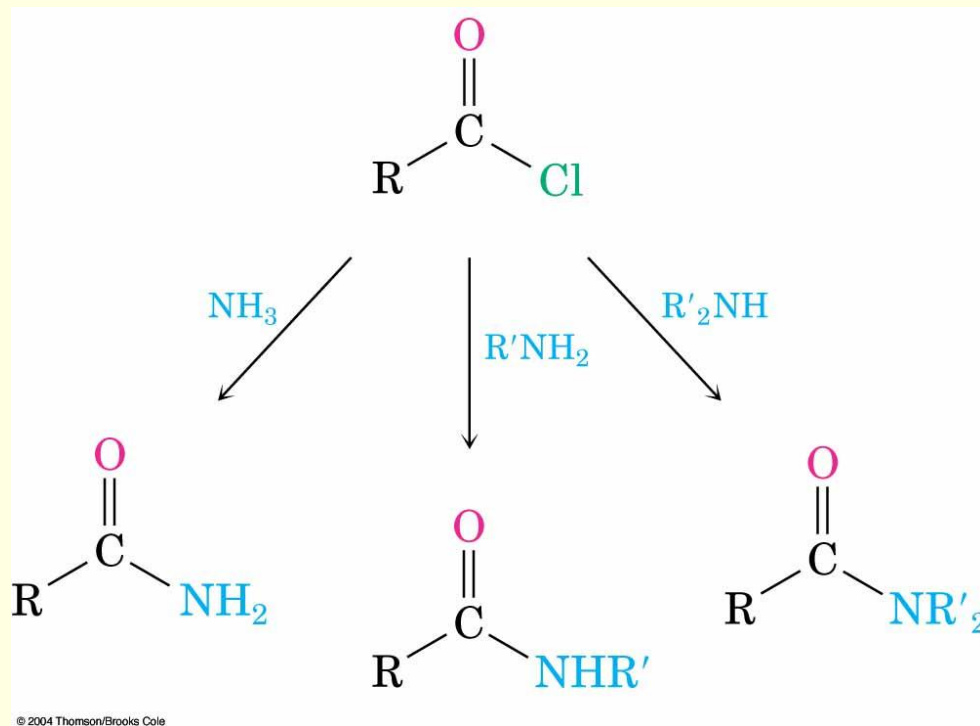
21.7 Chemistry of Amides

- Amides are abundant in all living organisms...proteins, nucleic acids, and other pharmaceuticals have amid functional groups



21.7 Chemistry of Amides

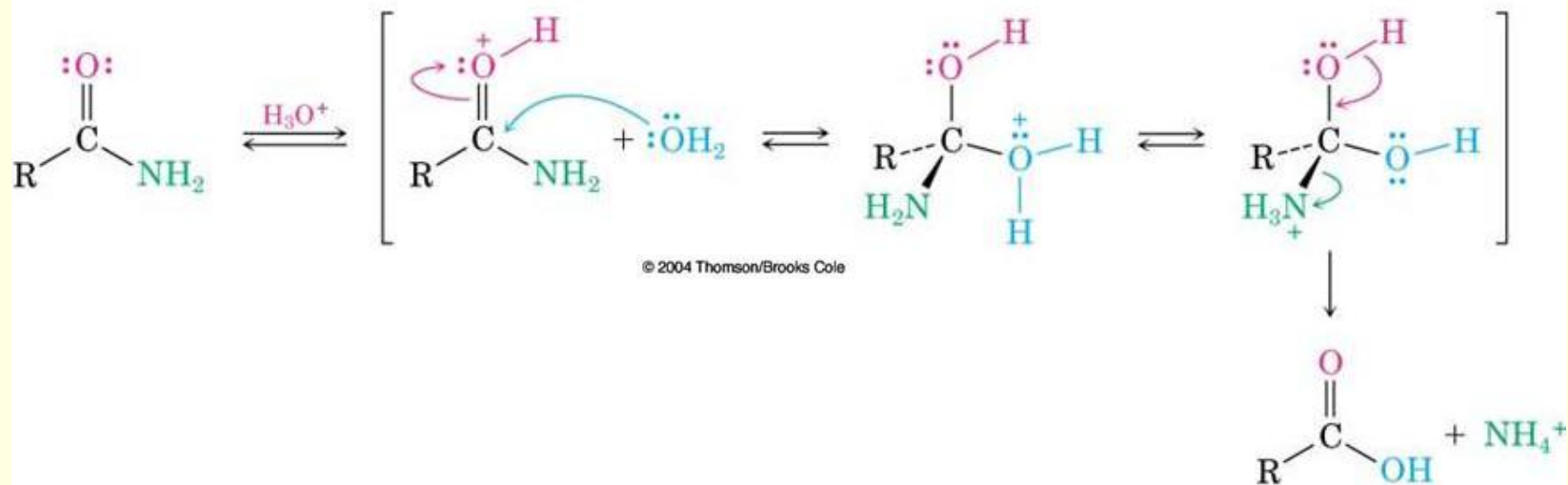
- Prepared by reaction of an acid chloride with ammonia, monosubstituted amines, or disubstituted amines



Reactions of Amides

- Heating in either aqueous acid or aqueous base produces a carboxylic acid and amine
- Acidic hydrolysis by nucleophilic addition of water to the protonated amide, followed by loss of ammonia

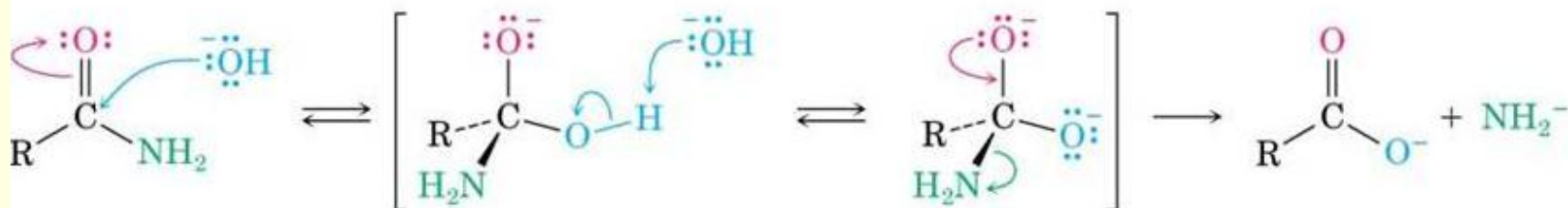
Acidic hydrolysis



Basic Hydrolysis of Amides

- Addition of hydroxide and loss of amide ion

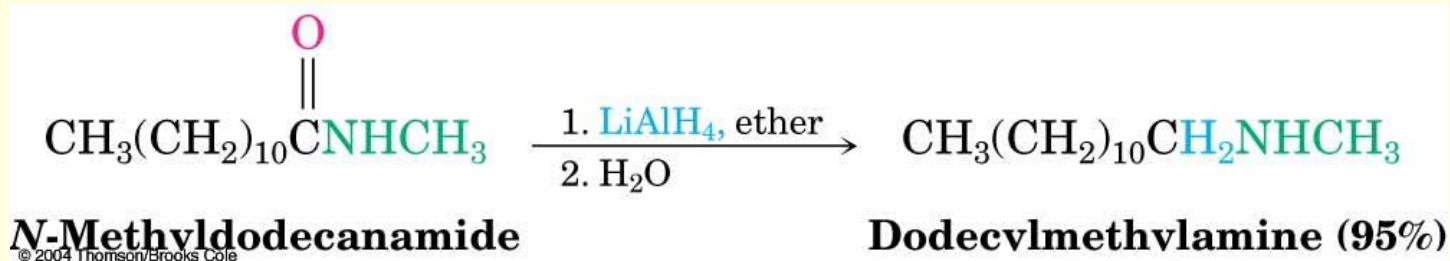
Basic hydrolysis



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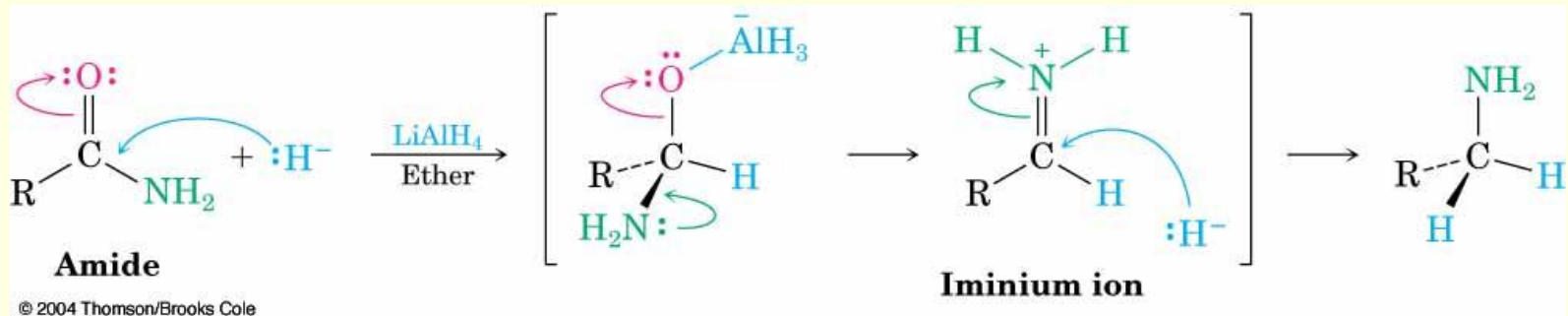
Reduction: Conversion of Amides into Amines

- Reduced by LiAlH_4 to an amine rather than an alcohol
- Converts $\text{C}=\text{O} \rightarrow \text{CH}_2$



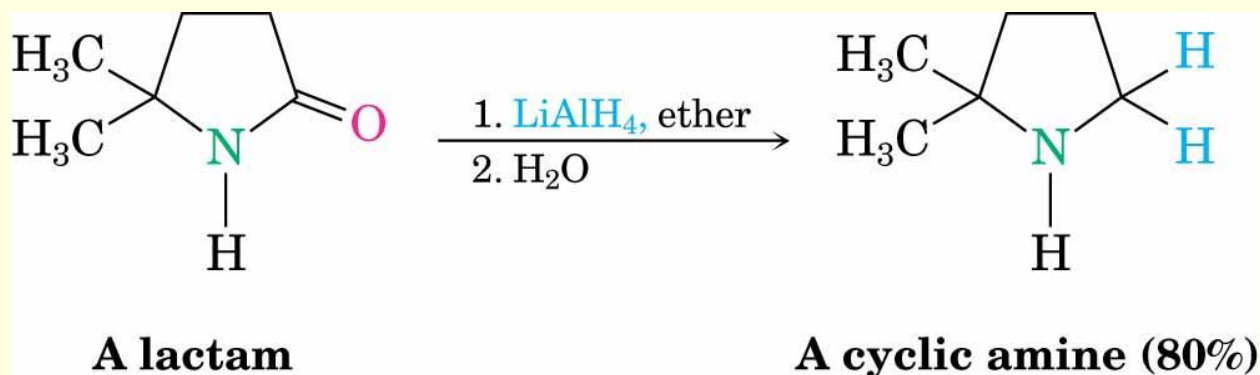
Mechanism of Reduction

- Addition of hydride to carbonyl group
- Loss of the oxygen as an aluminate anion to give an iminium ion intermediate which is reduced to the amine



Uses of Reduction of Amides

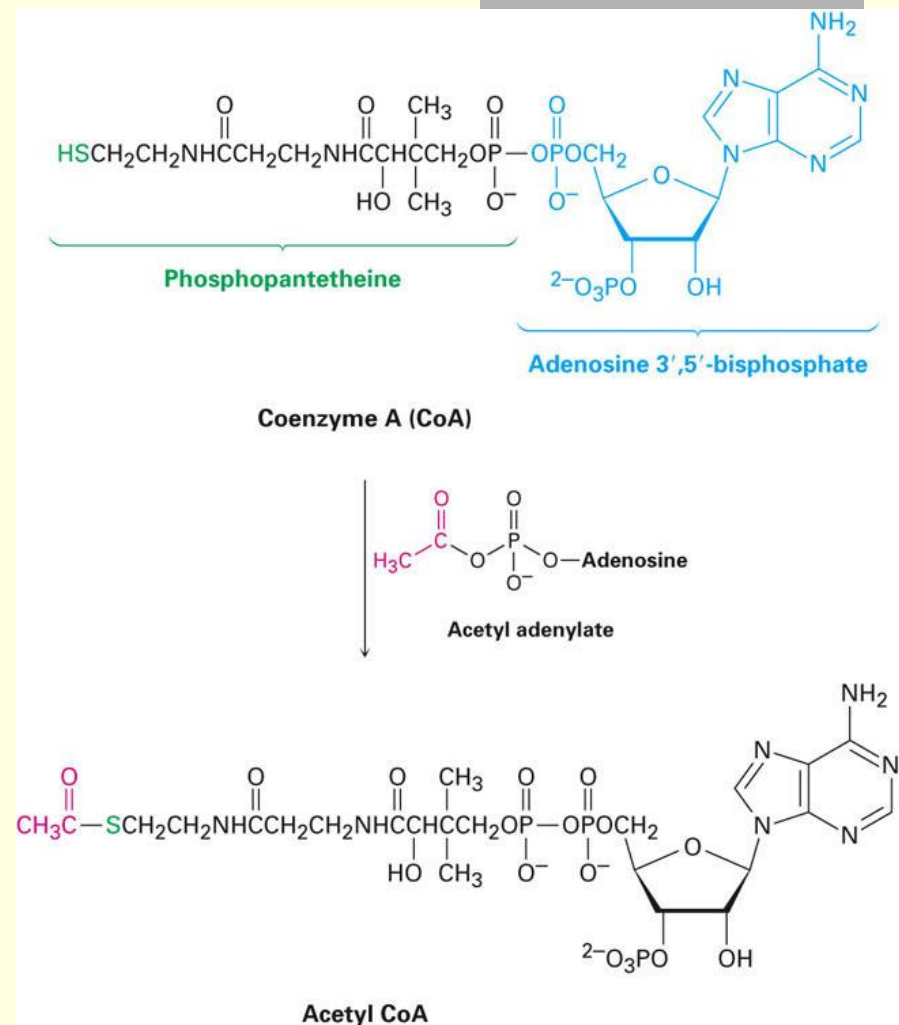
- Works with cyclic and acyclic
- Good route to cyclic amines



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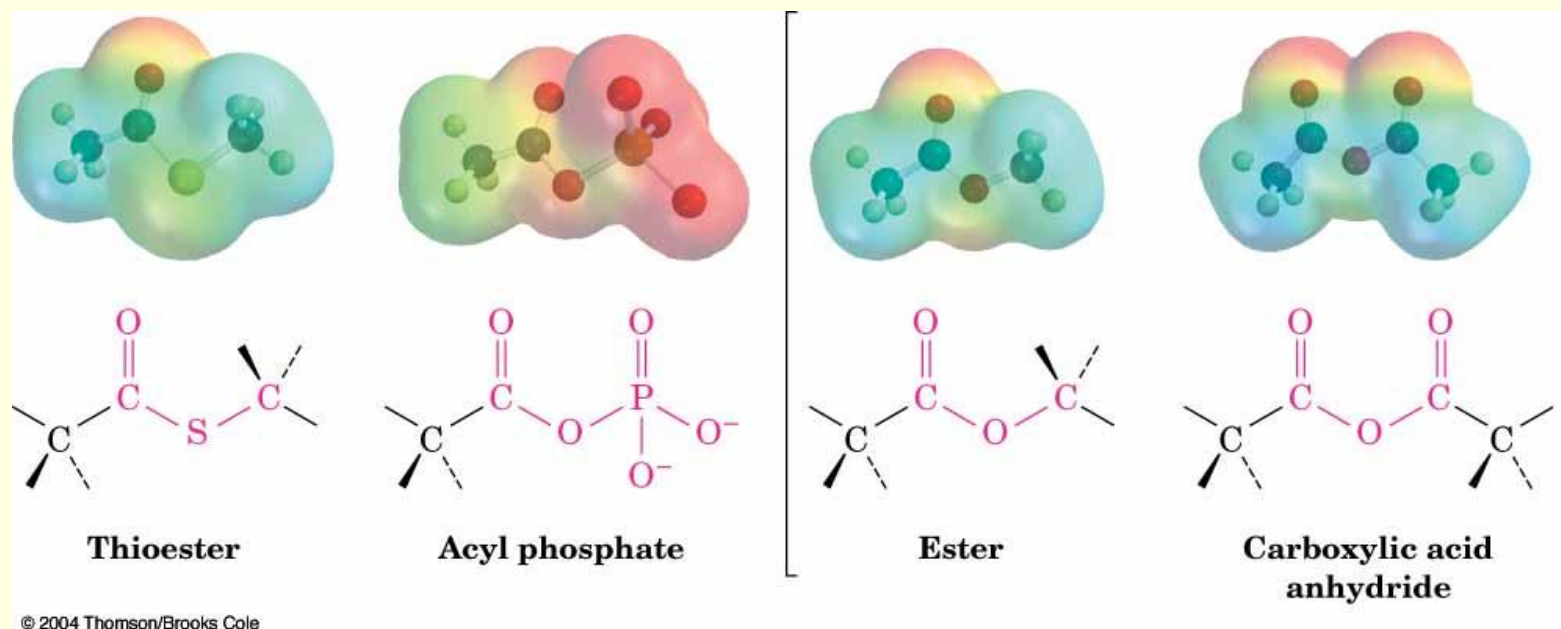
21.8 Chemistry of Thioesters and Acyl Phosphates: Biological Carboxylic Acid Derivatives

- Nucleophilic carboxyl substitution in nature often involves a thioester or acyl phosphate
- Acetyl CoA's are most common thioesters in nature



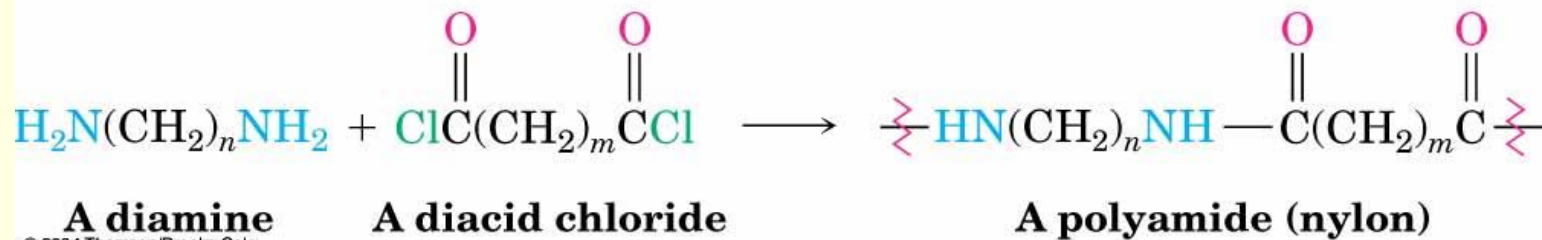
21.8 Thioesters and Acyl Phosphates: Biological Carboxylic Acid Derivatives

- These have unique binding properties and are readily activated by enzymes

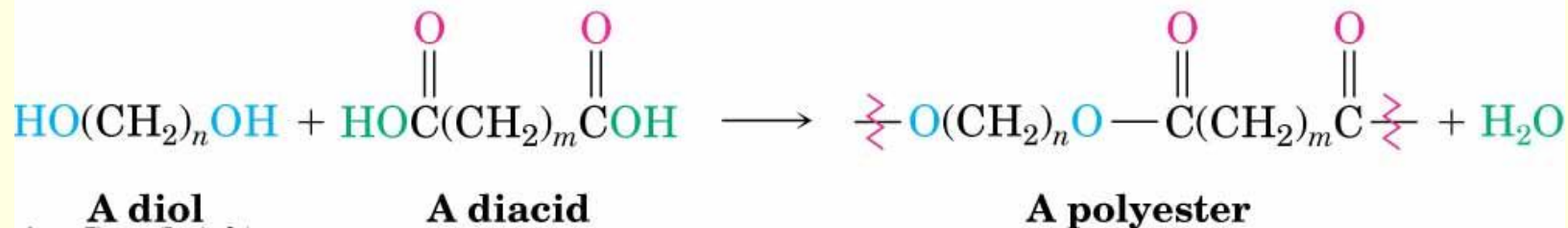


21.9 Polyamides and Polyesters: Step-Growth Polymers

- Reactions occur in distinct linear steps, not as chain reactions
- Reaction of a diamine and a diacid chloride gives an ongoing cycle that produces a polyamide
- A diol with a diacid leads to a polyester



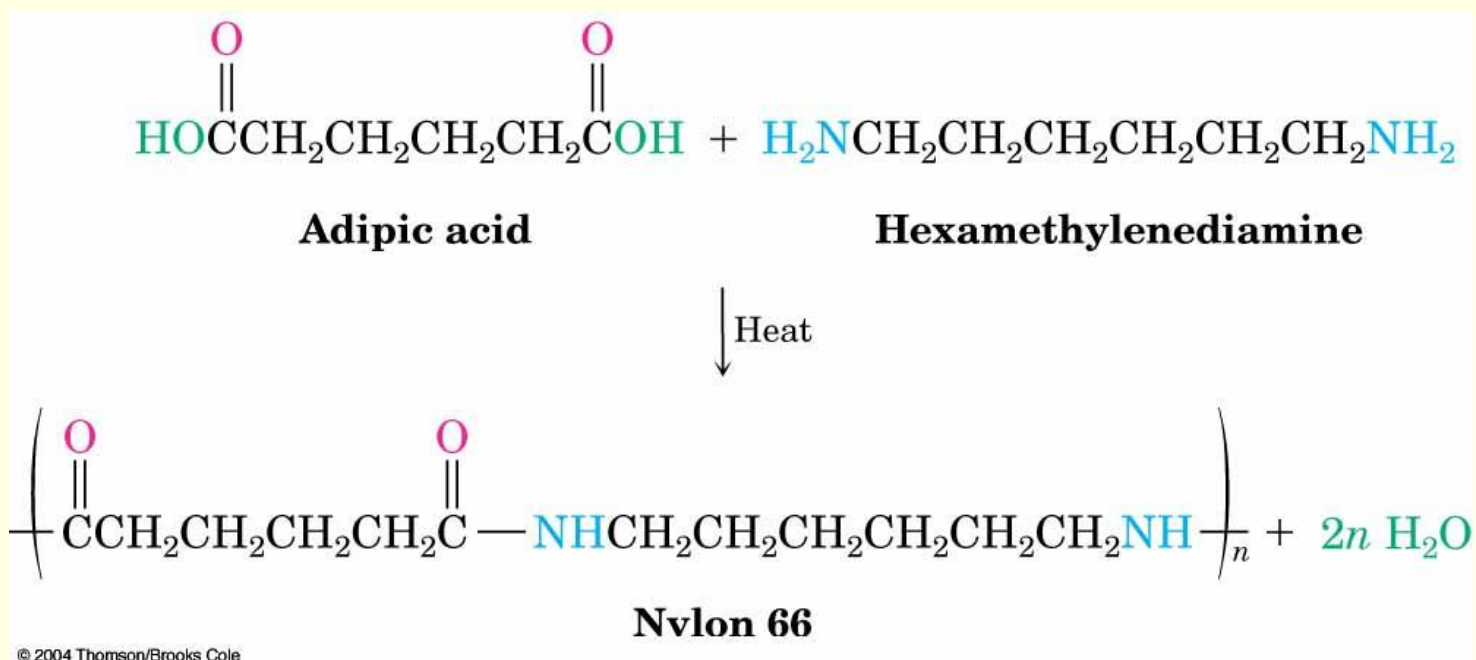
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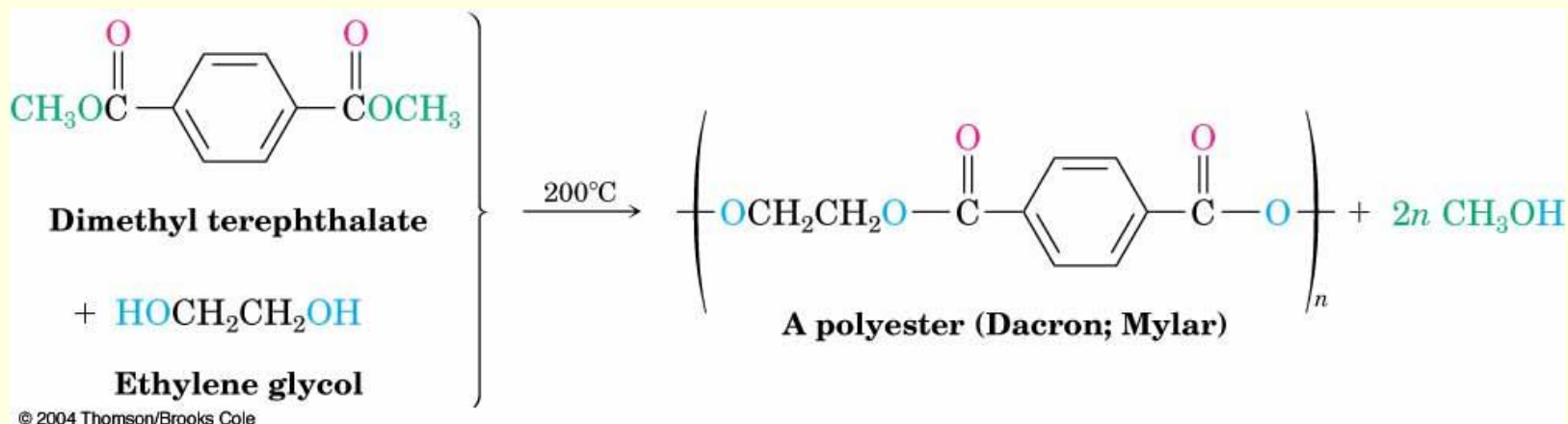
Polyamides (Nylons)

- Heating a diamine with a diacid produces a polyamide called Nylon[®]
- Nylon 66[®] is from adipic acid and hexamethylenediamine at 280°C



Polyesters

- The polyester from dimethyl terephthalate and ethylene glycol is called Dacron[®] and Mylar[®] to make fibers

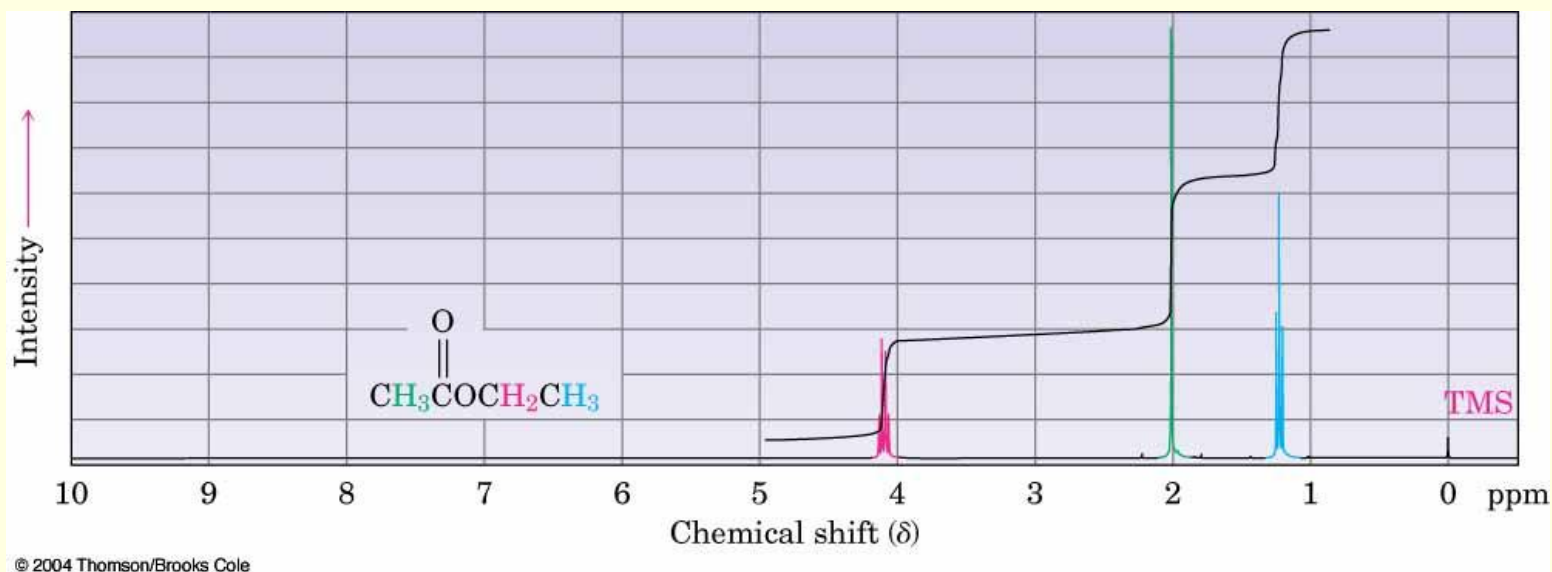


21.10 Spectroscopy of Carboxylic Acid Derivatives

- Infrared Spectroscopy
 - Acid chlorides absorb near 1800 cm^{-1}
 - Acid anhydrides absorb at 1820 cm^{-1} and also at 1760 cm^{-1}
 - Esters absorb at 1735 cm^{-1} , higher than aldehydes or ketones
 - Amides absorb near the low end of the carbonyl region

Nuclear Magnetic Resonance Spectroscopy

- Hydrogens on the carbon next to a C=O are near $\delta 2$ in the ^1H NMR spectrum.
- All acid derivatives absorb in the same range so NMR does not distinguish them from each other



^{13}C NMR

- ^{13}C NMR is useful for determining the presence or absence of a carbonyl group in a molecule of unknown structure
- Carbonyl carbon atoms of the various acid derivatives absorb from $\delta 160$ to $\delta 180$

Table 21.4 ^{13}C NMR Absorptions in Some Carbonyl Compounds

Compound	Absorption (δ)	Compound	Absorption (δ)
Acetic acid	177.3	Acetic anhydride	166.9
Ethyl acetate	170.7	Acetone	205.6
Acetyl chloride	170.3	Acetaldehyde	201.0
Acetamide	172.6		

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