



CARBOXYLIC ACID DERIVATIVES



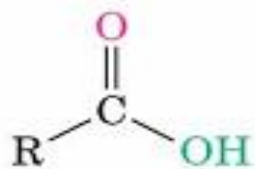
Objectives

- **Nomenclature**
- **Structures of the functional groups**
- **Physical properties**
- **Preparation of acyl halides and reactions**
- **Preparation of acid anhydrides and reactions**
- **Preparation of esters and their reactions**
- **Preparation of amides and their reactions**

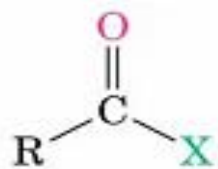
Introduction

Acyl group bonded to Y, an electronegative atom or leaving group

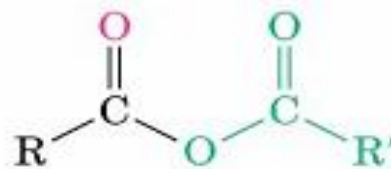
Includes: Y = halide (acid halides), acyloxy (anhydrides), alkoxy (esters), amine (amides), thiolate (thioesters), phosphate (acyl phosphates)



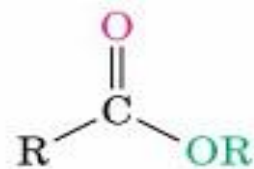
Carboxylic acid



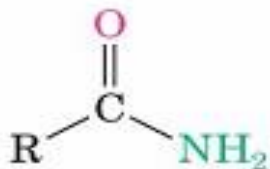
Acid halide
(X = Cl, Br)



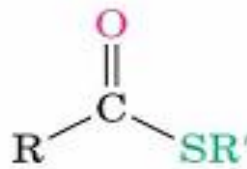
Acid anhydride



Ester



Amide



Thioester



Acyl phosphate

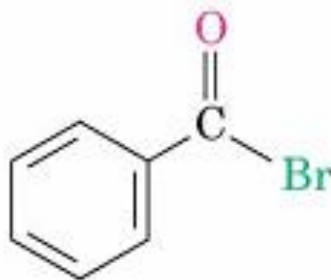
Naming Carboxylic Acid Derivatives

Acid Halides, RCOX

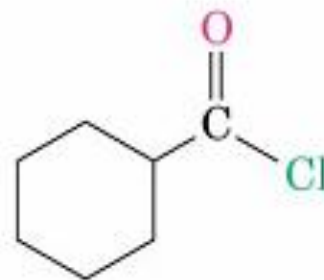
Derived from the carboxylic acid name by replacing the *-ic acid* ending with *-yl* or the *-carboxylic acid* ending with *-carbonyl* and specifying the halide



Acetyl chloride
(from acetic acid)



Benzoyl bromide
(from benzoic acid)



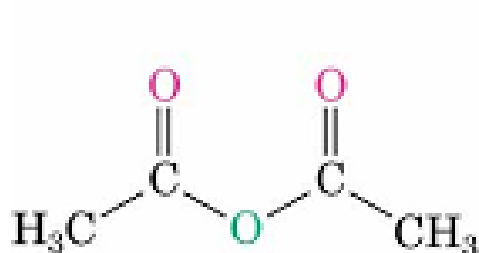
Cyclohexanecarbonyl chloride
(from cyclohexanecarboxylic acid)

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

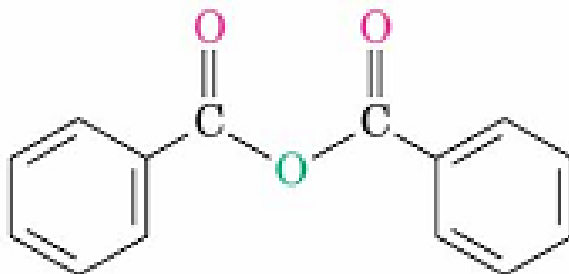
If symmetrical replace "*acid*" with "*anhydride*" based on the related carboxylic acid (for symmetrical anhydrides)

From substituted monocarboxylic acids: use *bis-* ahead of the acid name

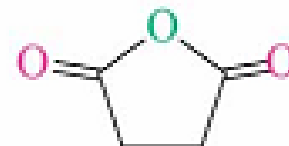
Unsymmetrical anhydrides— cite the two acids alphabetically



Acetic anhydride



Benzoic anhydride



Succinic anhydride

Naming Amides, RCONH_2

With unsubstituted —NH_2 group. replace *-oic acid* or *-ic acid* with *-amide*, or by replacing the *-carboxylic acid* ending with *-carboxamide*

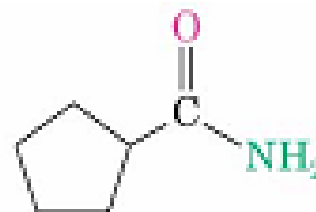
If the N is further substituted, identify the substituent groups (preceded by "N") and then the parent amide



Acetamide
(from acetic acid)



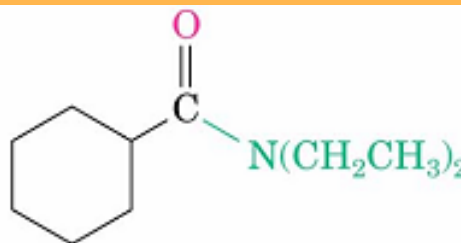
Hexanamide
(from hexanoic acid)



Cyclopentanecarboxamide
(from cyclopentanecarboxylic acid)



N-Methylpropanamide



N,N-Diethylcyclohexanecarboxamide

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

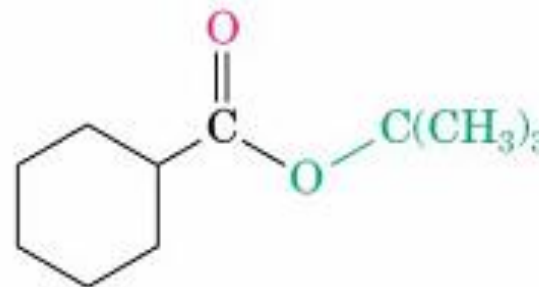
Name R' and then, after a space, the carboxylic acid (RCOOH), with the “-*ic acid*” ending replaced by “-*ate*”



Ethyl acetate
(the ethyl ester of
acetic acid)


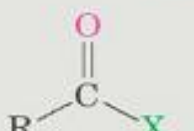
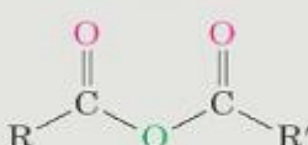
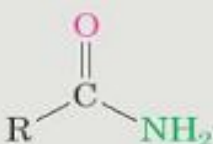
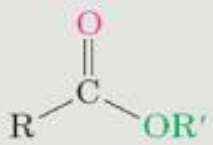


Dimethyl malonate
(the dimethyl ester of
malonic acid)

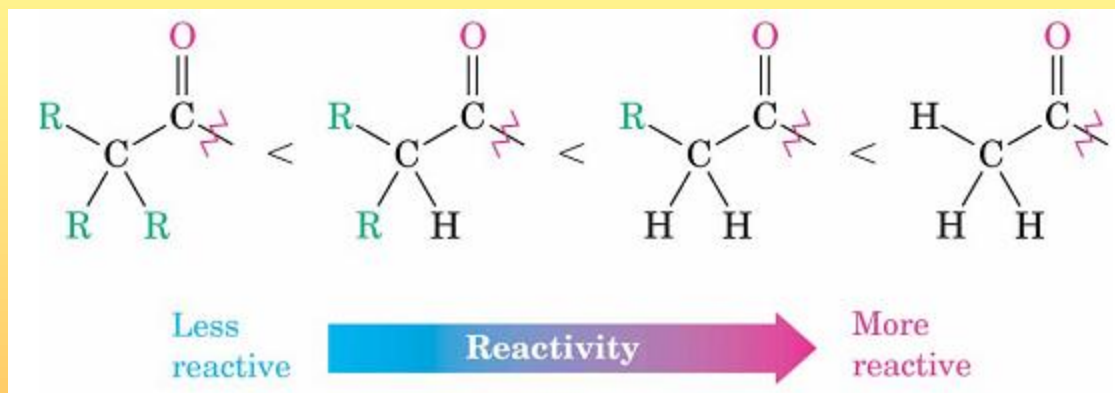


***tert*-Butyl**cyclohexanecarboxylate
(the *tert*-butyl ester of
cyclohexanecarboxylic acid)

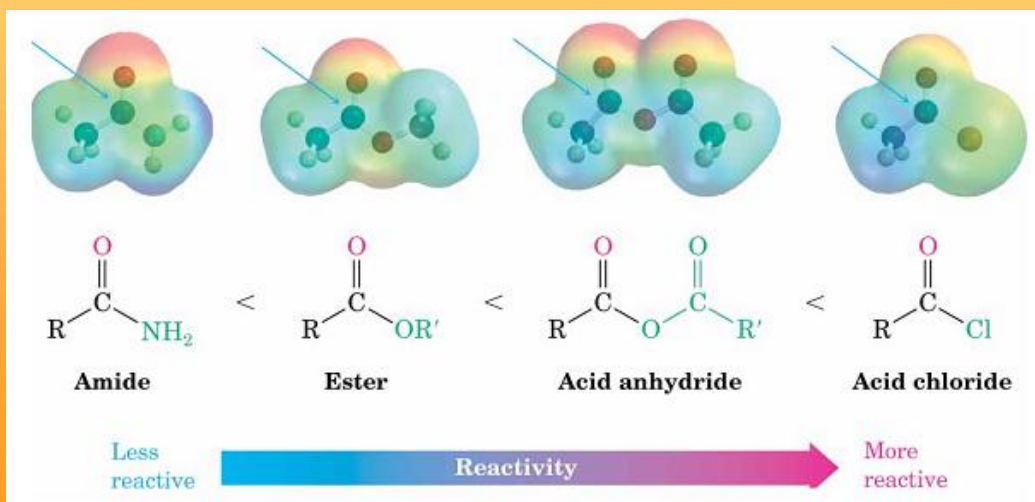
Summary of nomenclature

Nomenclature of Carboxylic Acid Derivatives		
Functional group	Structure	Name ending
Carboxylic acid		<i>-ic acid</i> (-carboxylic acid)
Acid halide		<i>-yl halide</i> (-carbonyl halide)
Acid anhydride		<i>anhydride</i>
Amide		<i>-amide</i> (-carboxamide)
Ester		<i>-ate</i> (-carboxylate)

Relative Reactivity of Carboxylic Acid Derivatives



Nucleophiles react more readily with unhindered carbonyl groups



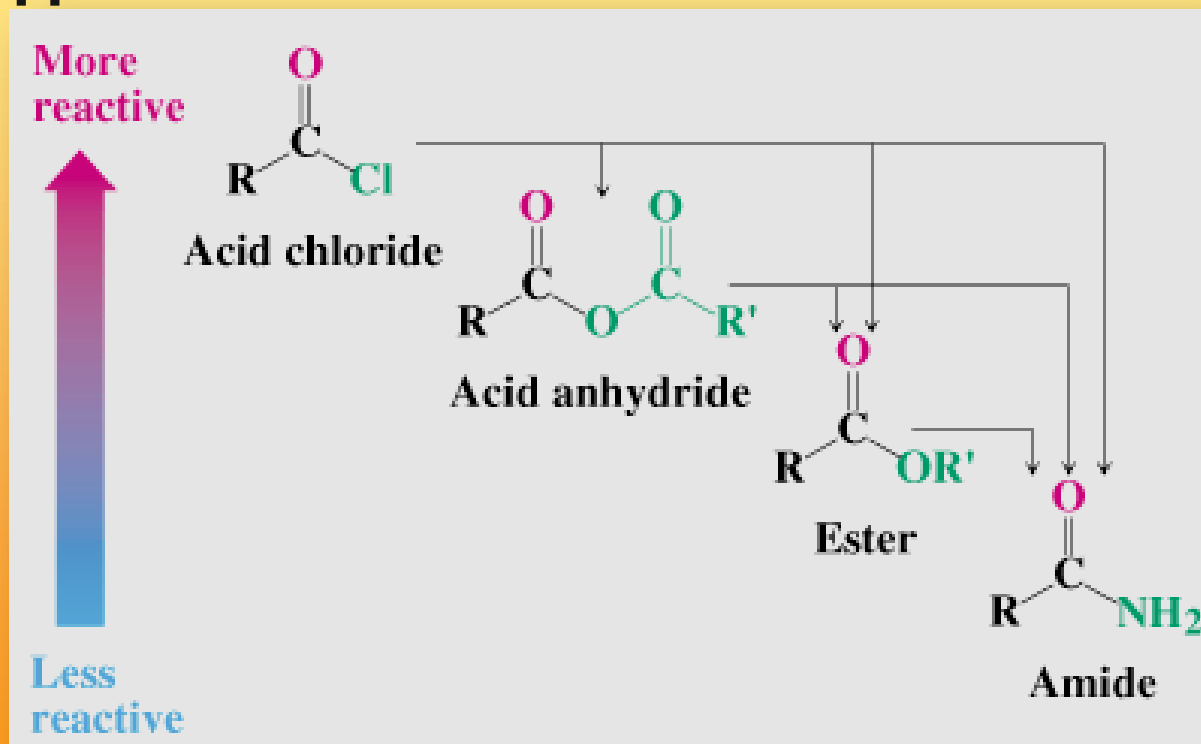
More electrophilic carbonyl groups are more reactive to addition (acyl halides are most reactive, amides are least)

The intermediate with the best leaving group decomposes fastest

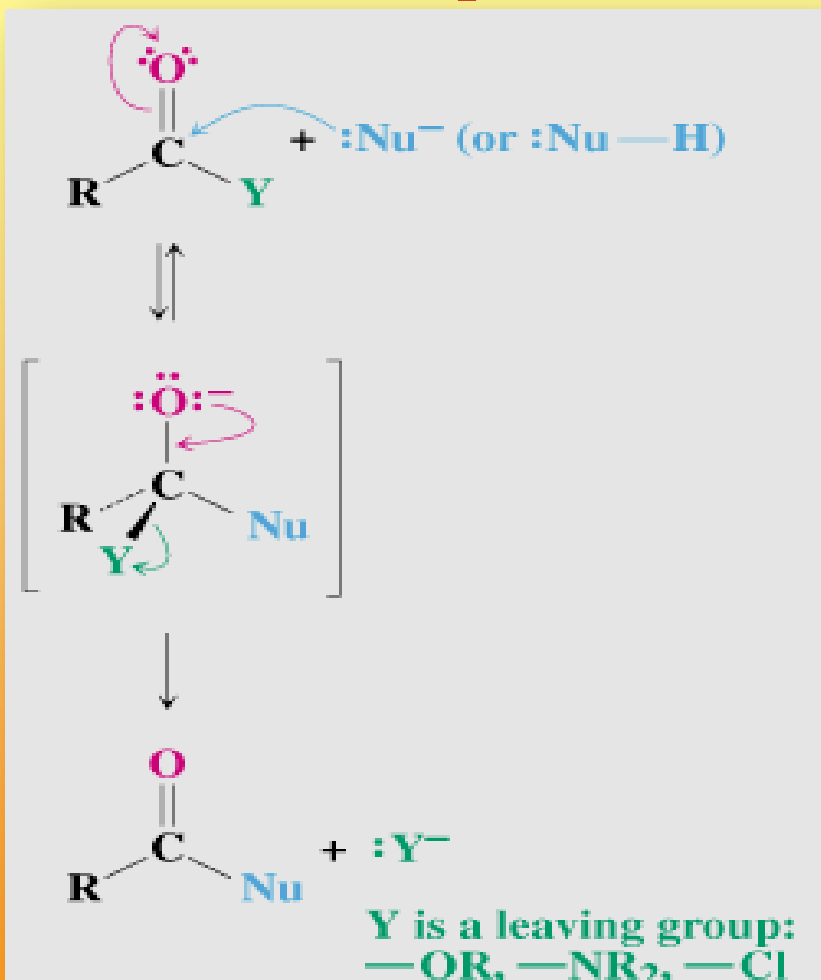
Substitution in Synthesis

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



Nucleophilic Acyl Substitution



Carboxylic acid derivatives have an acyl carbon bonded to a group $-\text{Y}$ that can leave

A tetrahedral intermediate is formed and the leaving group is expelled to generate a new carbonyl compound, leading to substitution

General Reactions of Carboxylic Acid Derivatives

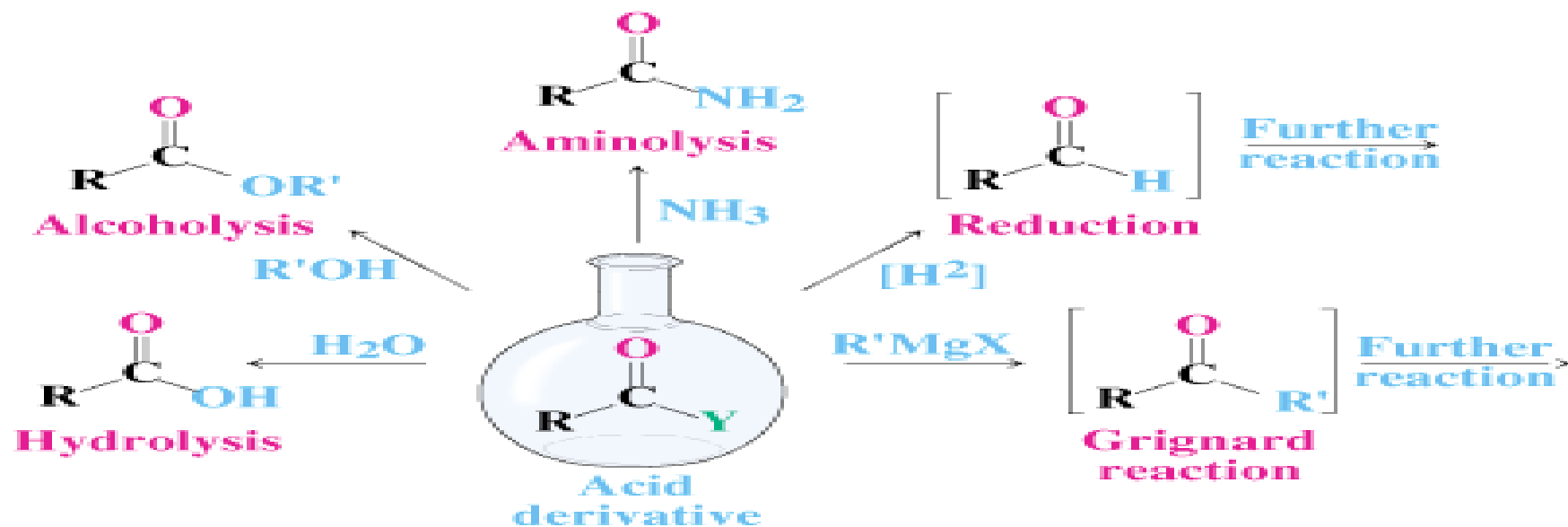
With water \rightarrow carboxylic acid

With alcohols \rightarrow esters

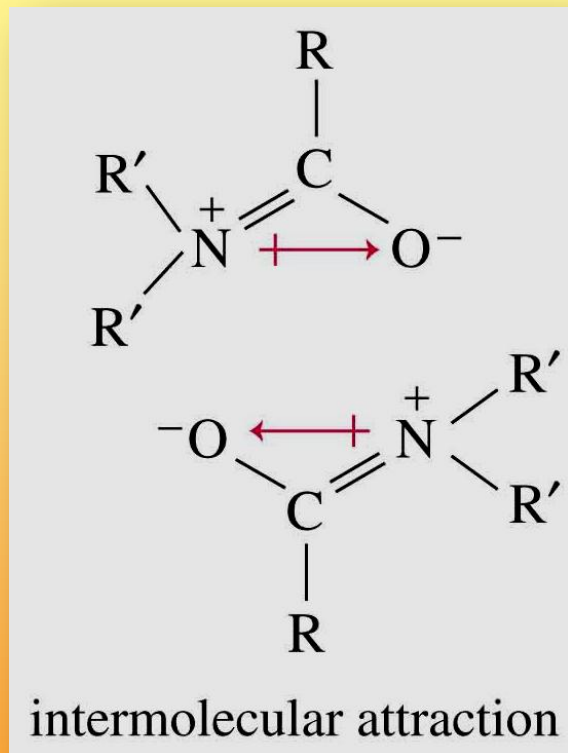
With ammonia or an amine \rightarrow an amide

With hydride source \rightarrow an aldehyde or an alcohol

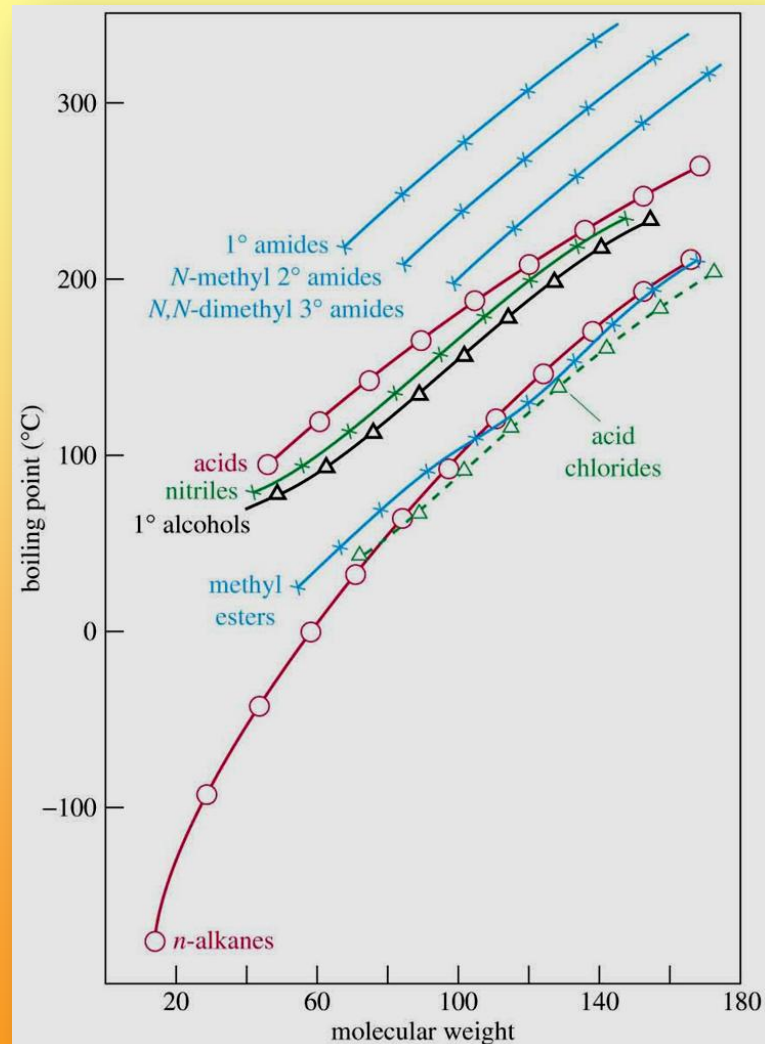
With Grignard reagent \rightarrow a ketone or an alcohol



Boiling Points



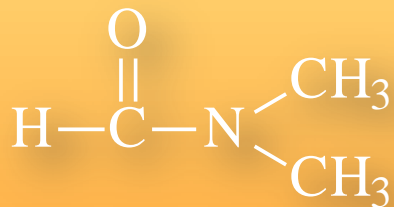
Even 3° amides have strong attractions.



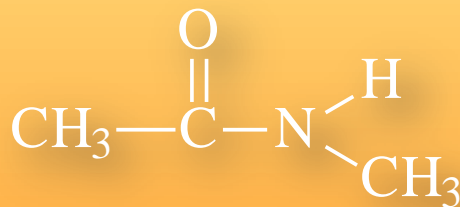
Melting Points

Amides have very high melting points.

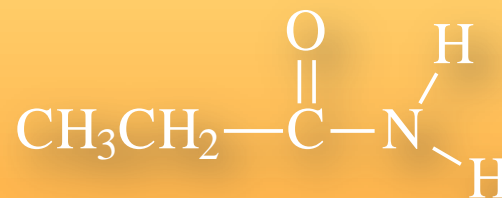
Melting points increase with increasing number of N-H bonds.



m.p. -61°C



m.p. 28°C



m.p. 79°C



Solubility

Acid chlorides and anhydrides are too reactive to be used with water or alcohol.

Esters, 3° amides, and nitriles are good polar aprotic solvents.

Solvents commonly used in organic reactions:

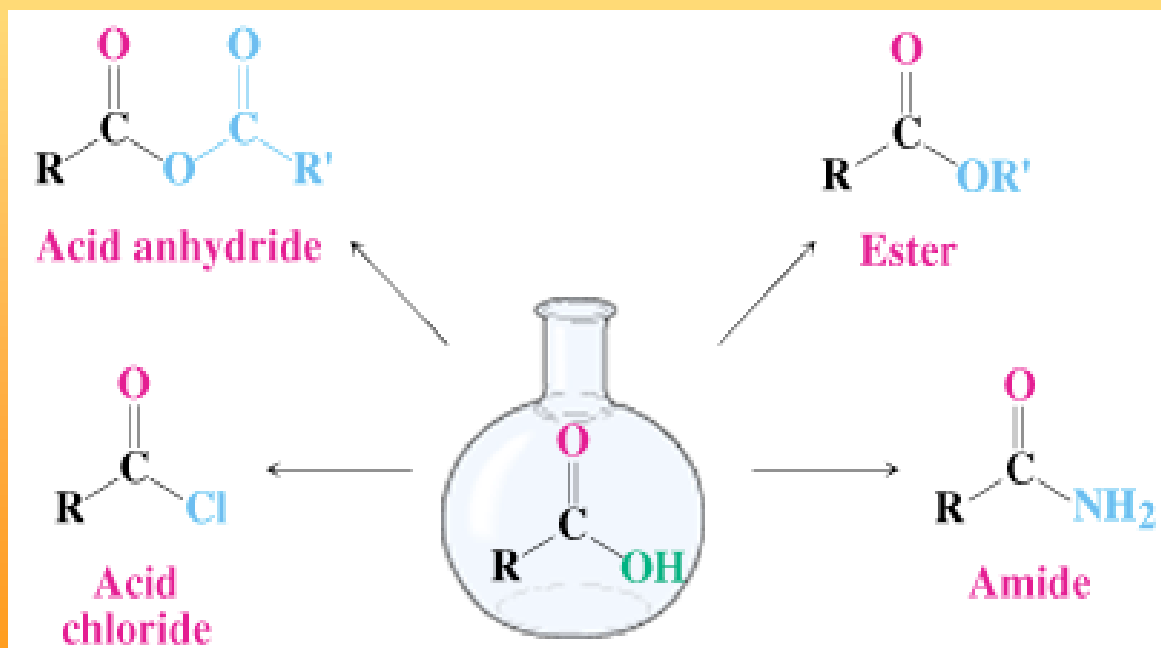
- Ethyl acetate
- Dimethylformamide (DMF)
- Acetonitrile

Preparation of acid derivatives

Must enhance reactivity

Convert —OH into a better leaving group

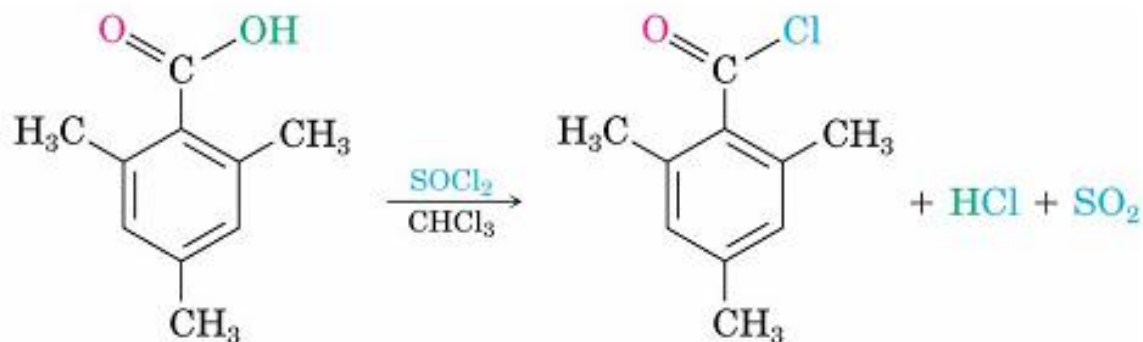
Specific reagents can produce acid chlorides, anhydrides, esters, amides



From carboxylic acids into acid Chlorides

Reaction with thionyl chloride, SOCl_2 .

Reaction with PBr_3 .



2,4,6-Trimethylbenzoic acid

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



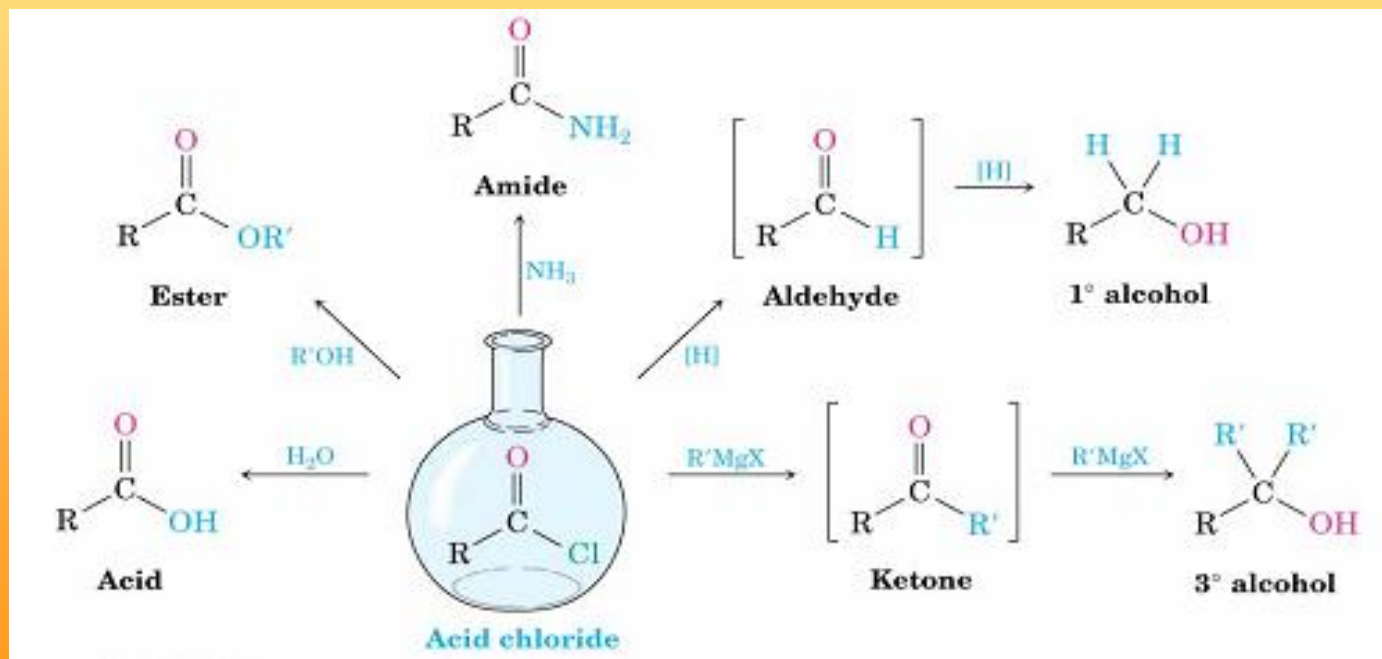
Reactions of Acid Halides

Nucleophilic acyl substitution

Halogen replaced by —OH , by —OR , or by —NH_2

Reduction yields a primary alcohol

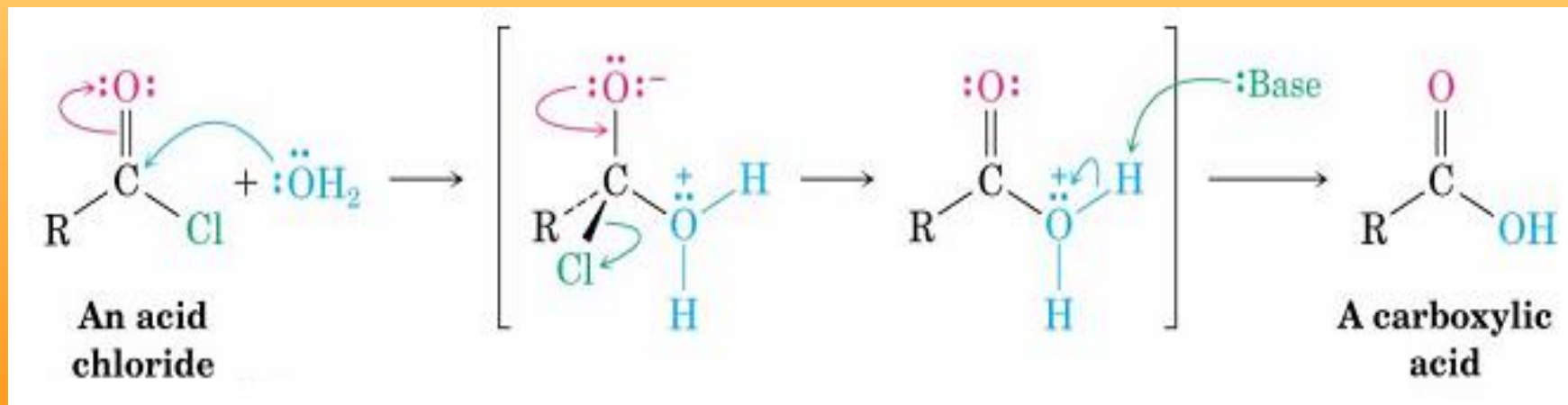
Grignard reagent yields a tertiary alcohol



Hydrolysis: Conversion of Acid Halides into Acids

Acid chlorides react with water to yield carboxylic acids

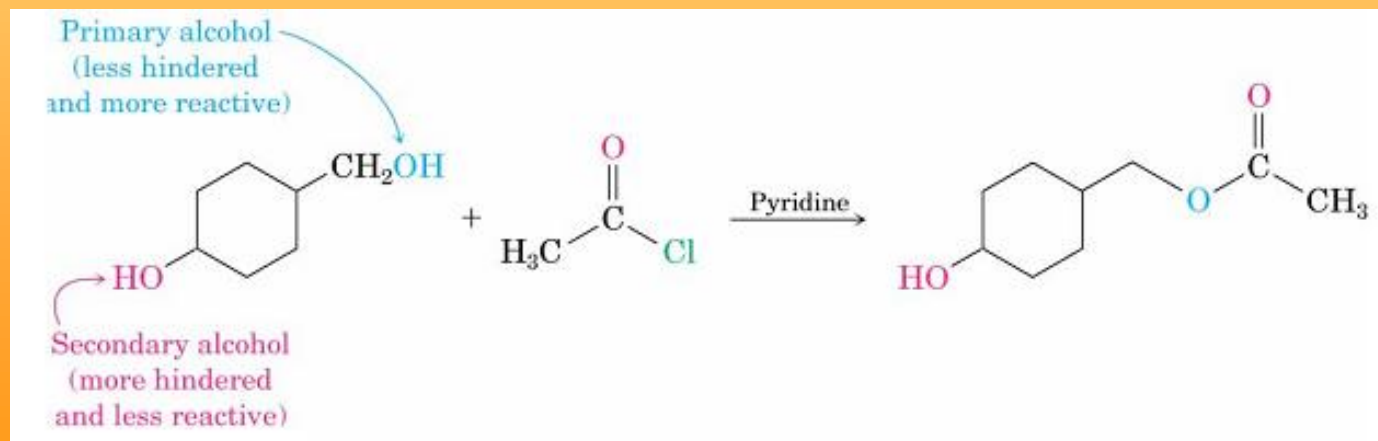
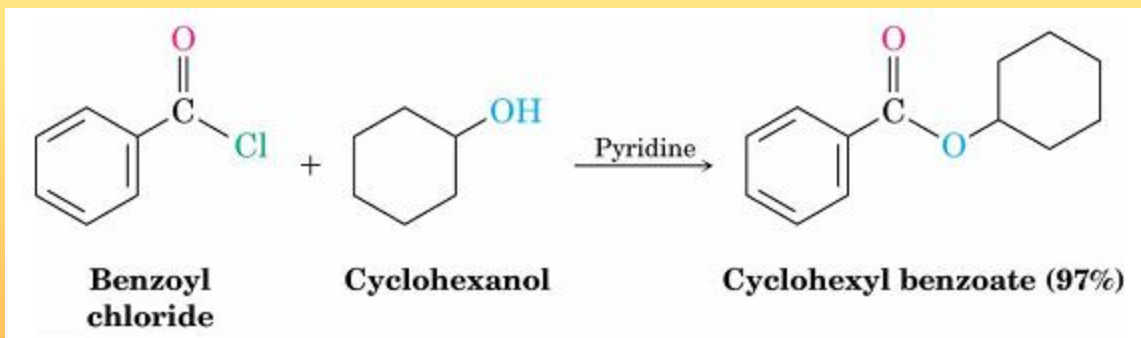
HCl is generated during the hydrolysis: a base is added to remove the HCl



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

The reaction is better with less steric bulk

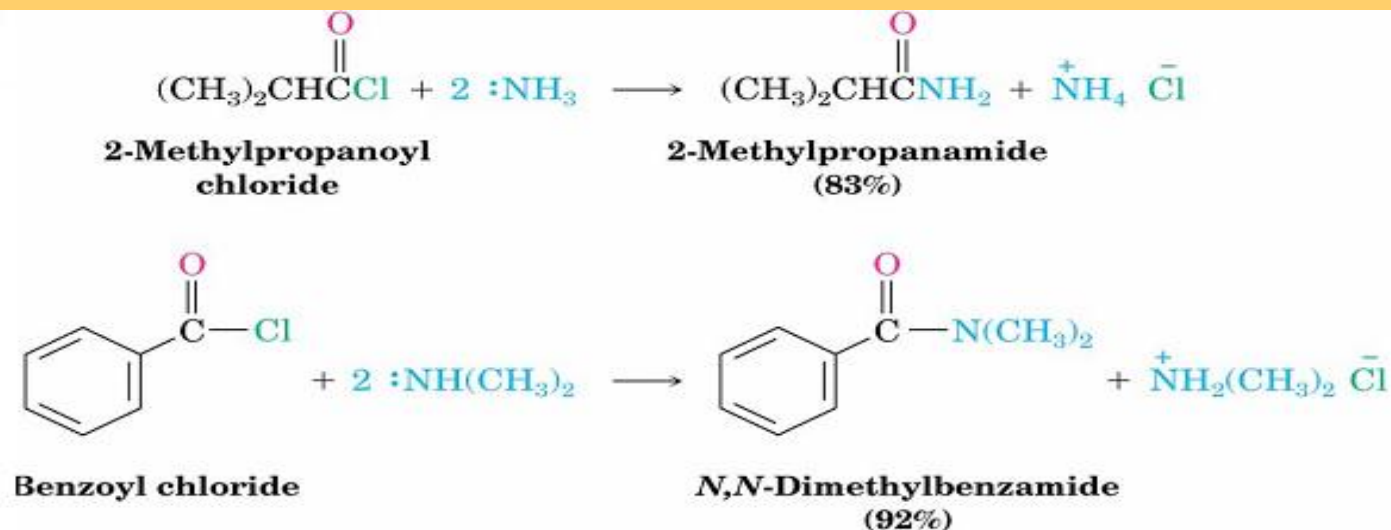


Aminolysis: Conversion of Acid Halides into Amides

Amides result from the reaction of acid chlorides with NH_3 , primary (RNH_2) and secondary amines (R_2NH)

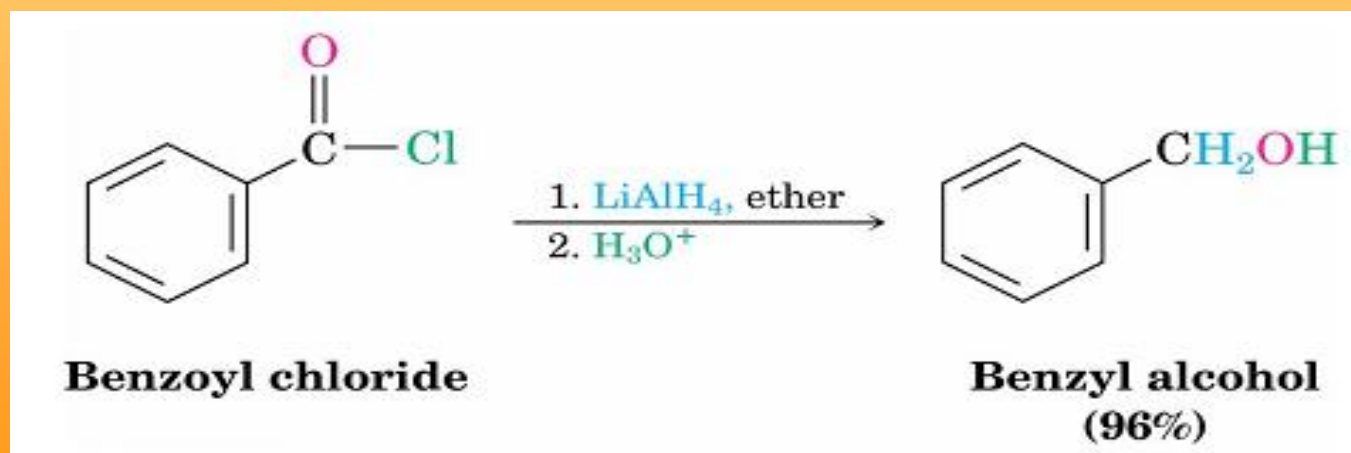
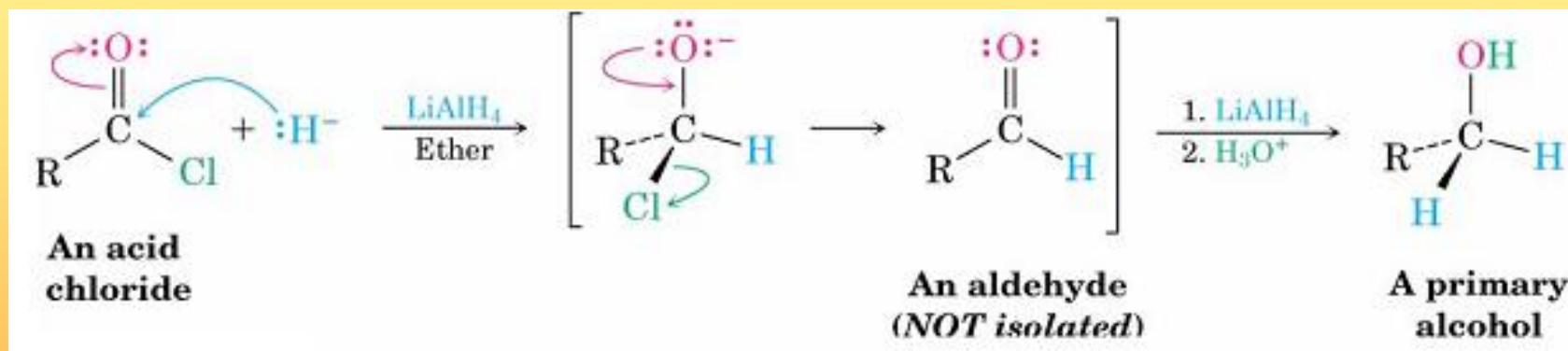
The reaction with tertiary amines (R_3N) gives an unstable species that cannot be isolated

HCl is neutralized by the amine or an added base



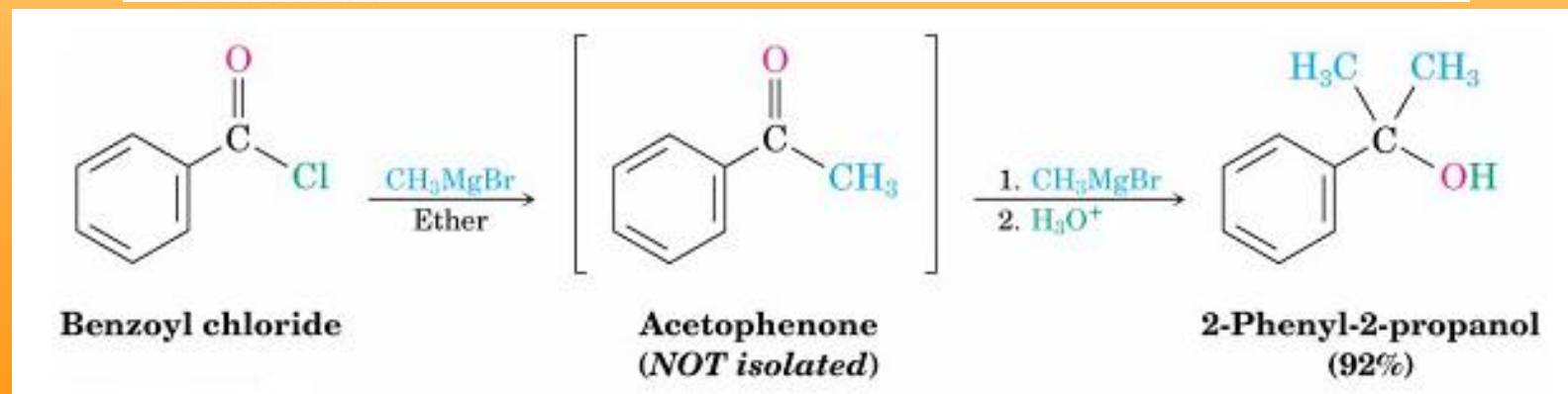
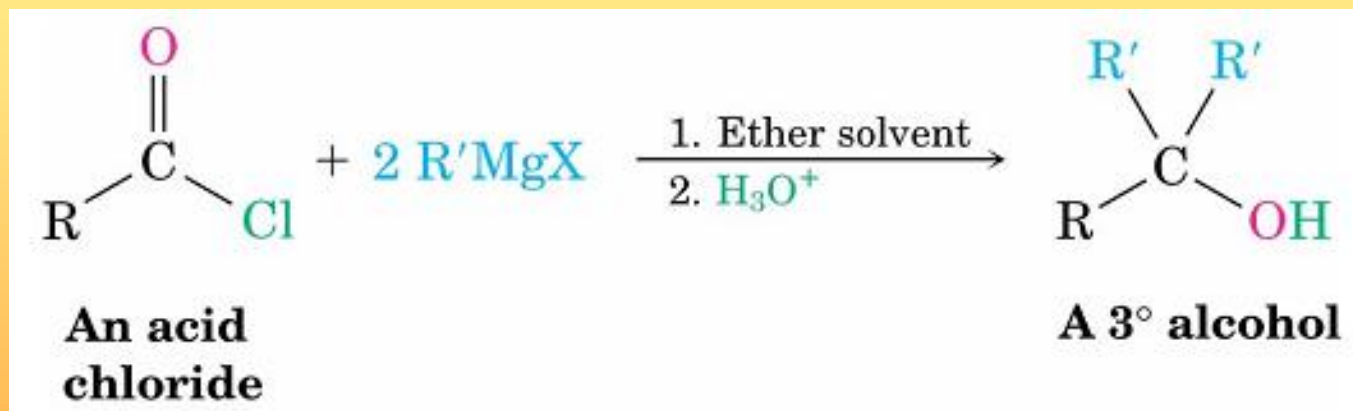
Reduction: Conversion of Acid Chlorides into Alcohols

LiAlH_4 reduces acid chlorides to yield aldehydes and then primary alcohols



Reaction of Acid Chlorides with Organometallic Reagents

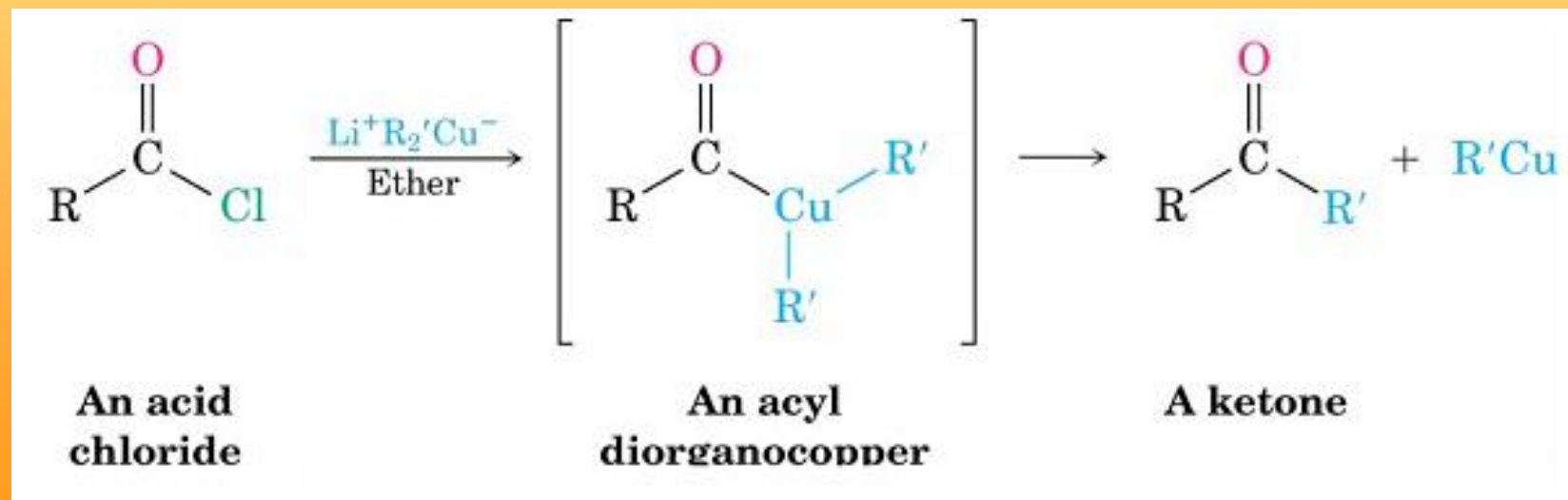
Grignard reagents react with acid chlorides to yield tertiary alcohols in which two of the substituents are the same



Formation of Ketones from Acid Chlorides

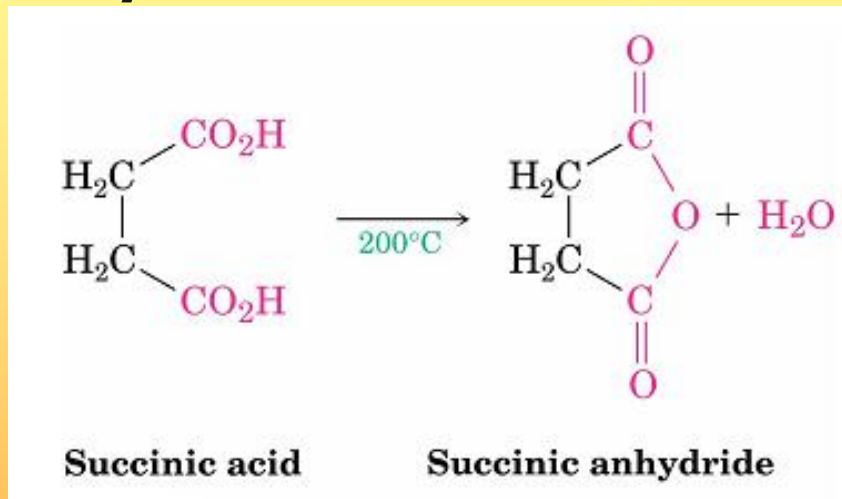
Reaction of an acid chloride with a lithium diorganocupper (Gilman) reagent, $\text{Li}^+ \text{R}_2\text{Cu}^-$

Addition produces an acyl diorganocupper intermediate, followed by loss of $\text{R}'\text{Cu}$ and formation of the ketone

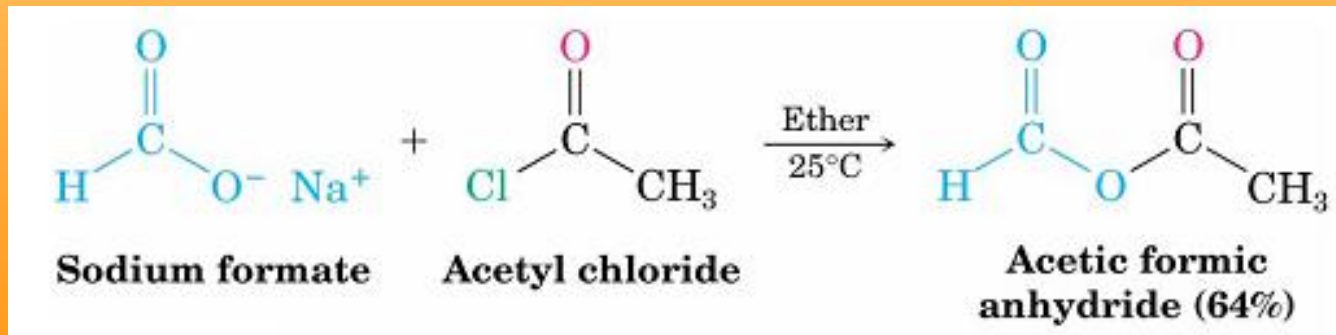


Preparation of acid anhydrides

Heat cyclic dicarboxylic acids that can form five- or six-membered rings



from acid chlorides and carboxylic acids



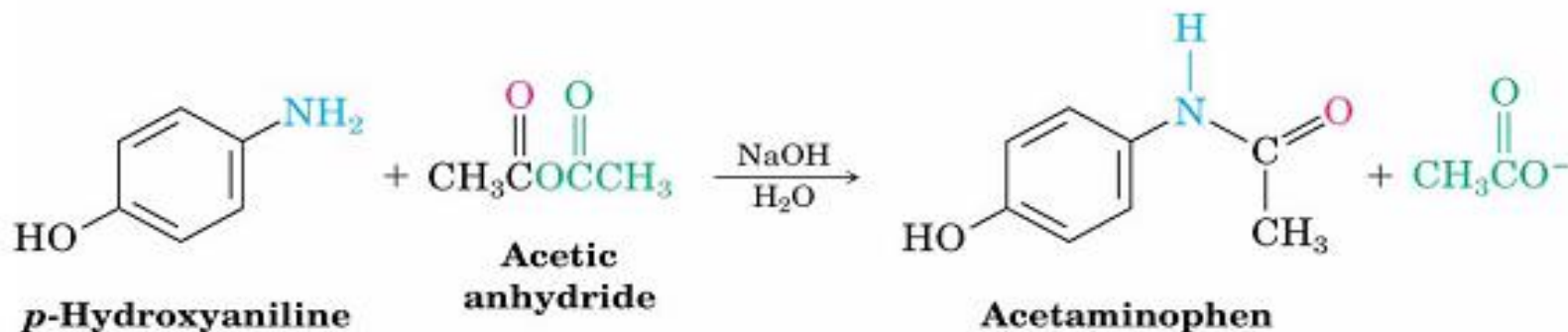
Reactions of Acid Anhydrides

Similar to acid chlorides in reactivity



Acetylation

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



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)



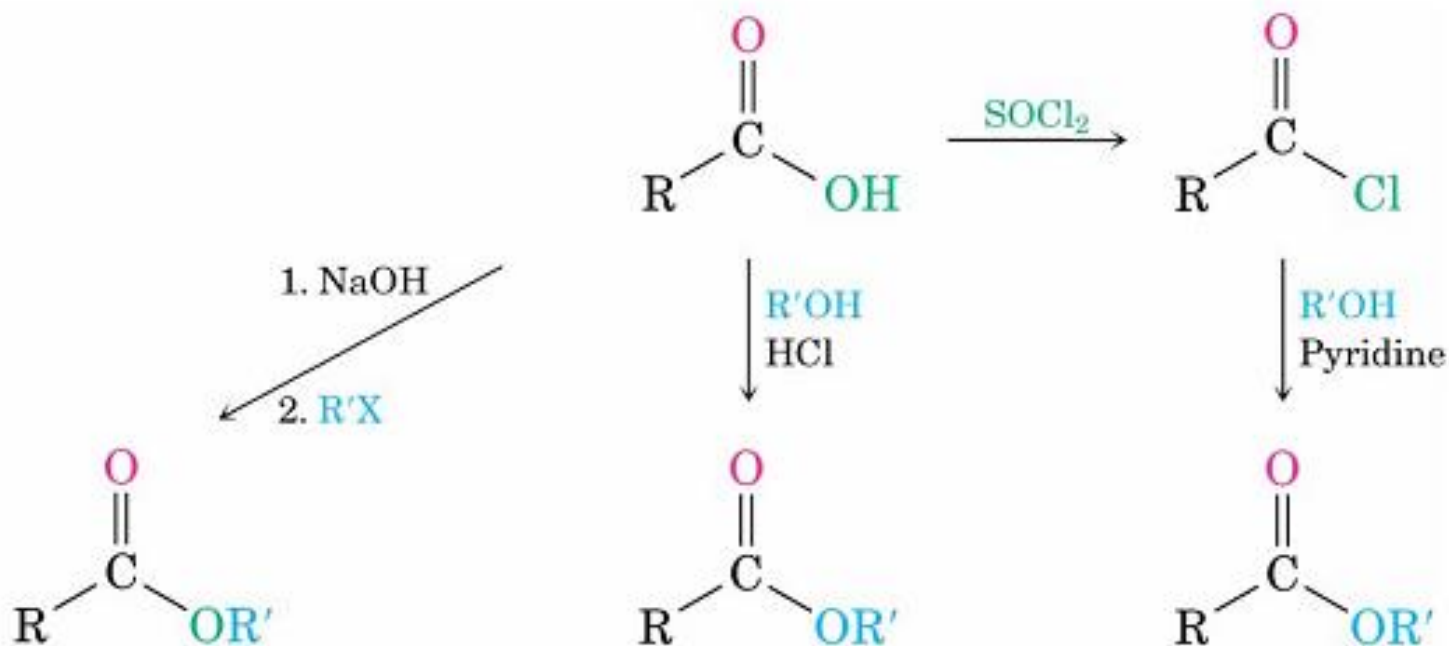
Isopentyl acetate
(from bananas)



A fat
(R = C₁₁₋₁₇ chains)

Preparation of Esters

Esters are usually prepared from carboxylic acids



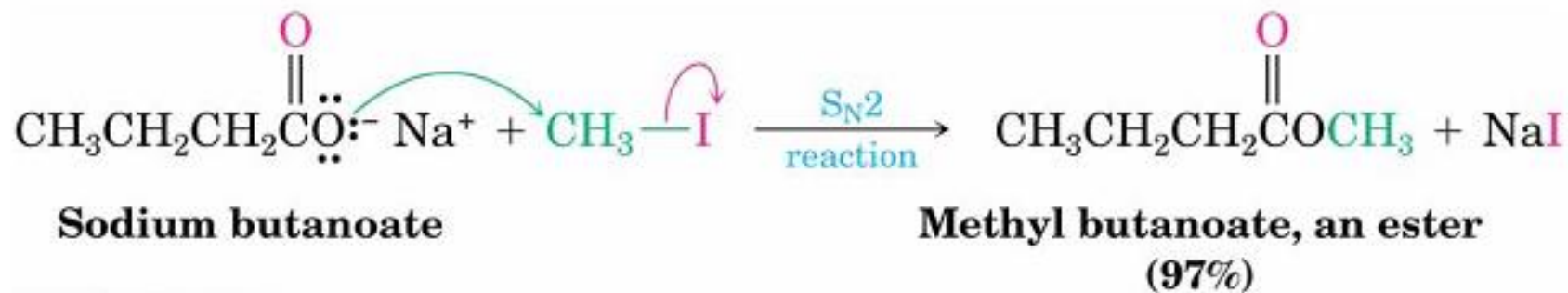
Method limited to
primary alkyl halides

Method limited to
simple alcohols

Method is
very general

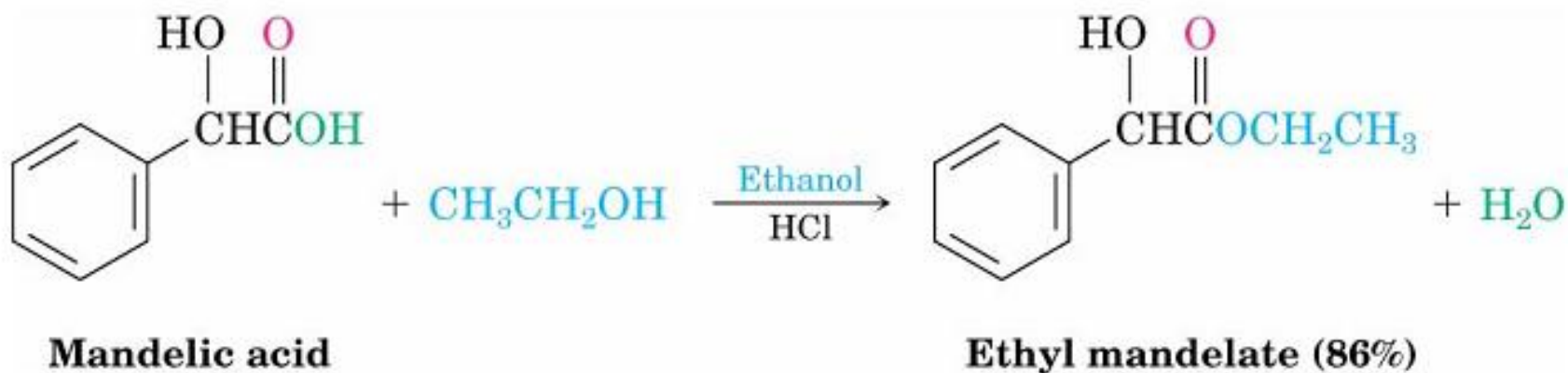
Preparation of esters

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

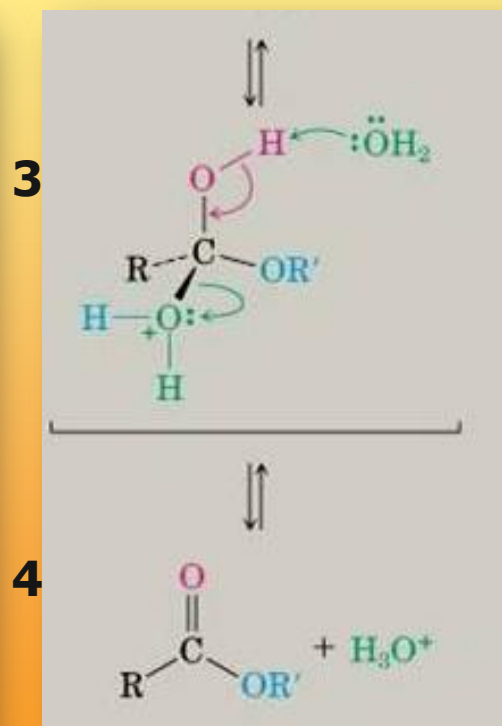
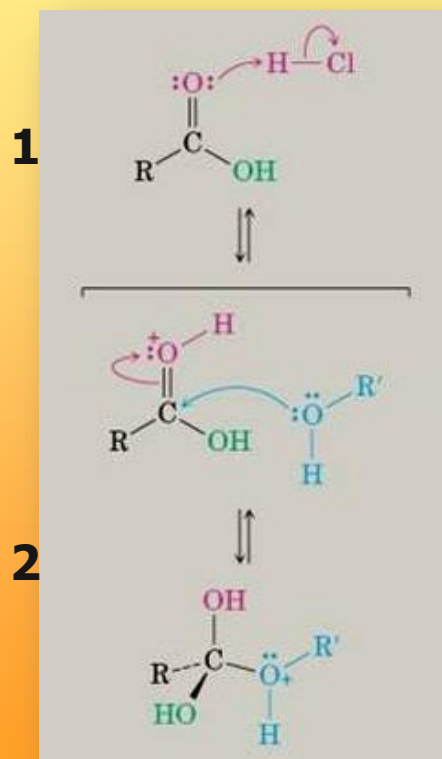


Fischer Esterification

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



Fischer Esterification: Detailed Mechanism

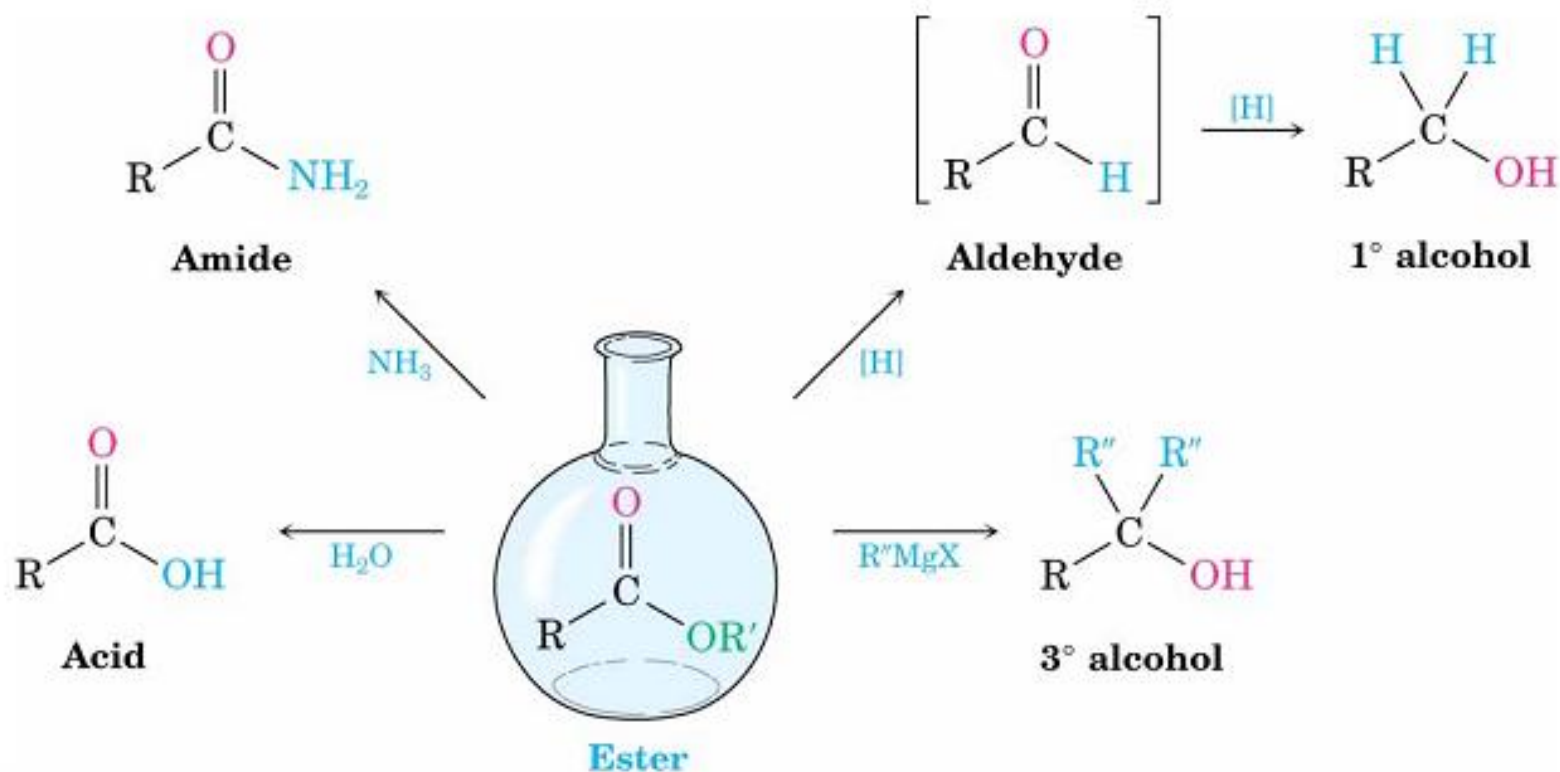


1. Protonation of carbonyl oxygen activates the carboxylic acid.
2. Towards nucleophilic attack by alcohol, yielding a tetrahedral intermediate.
3. Transfer a proton from one oxygen atom to another yields a second tetrahedral intermediate and converts the —OH group into a good leaving group.
5. Loss of a proton and expulsion of a H_2O regenerates the acid catalyst and gives the ester product.

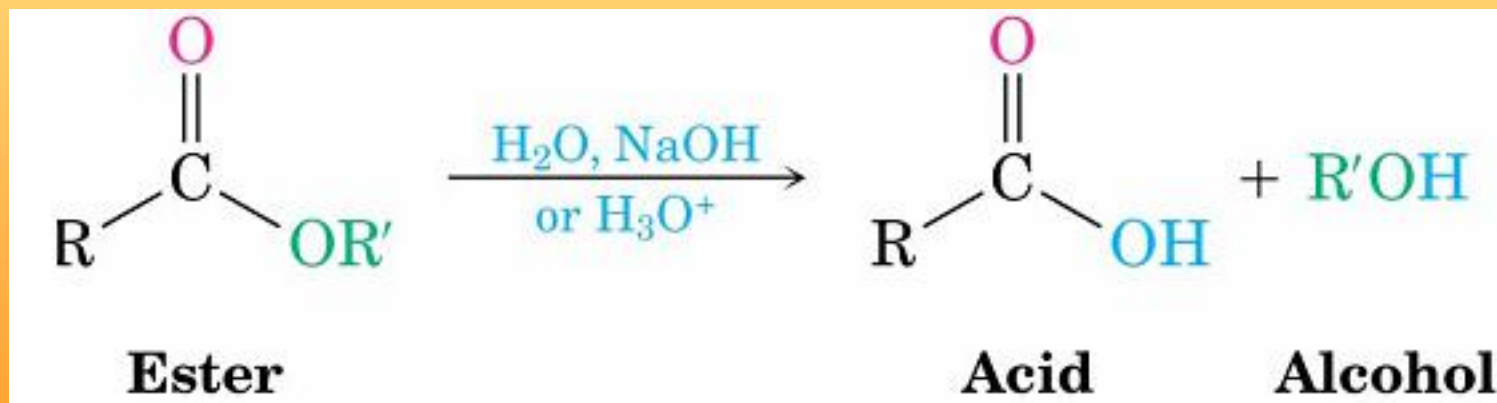
Reactions of Esters

Less reactive toward nucleophiles than are acid chlorides or anhydrides

Cyclic esters are called lactones and react similarly to acyclic esters



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



Acid Catalyzed Ester Hydrolysis

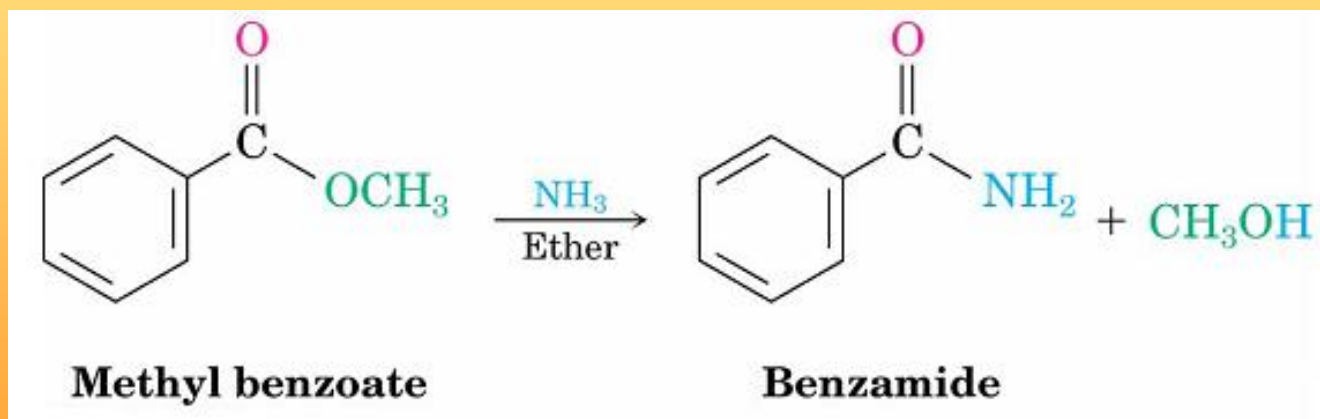
The usual pathway is the reverse of the Fischer esterification



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

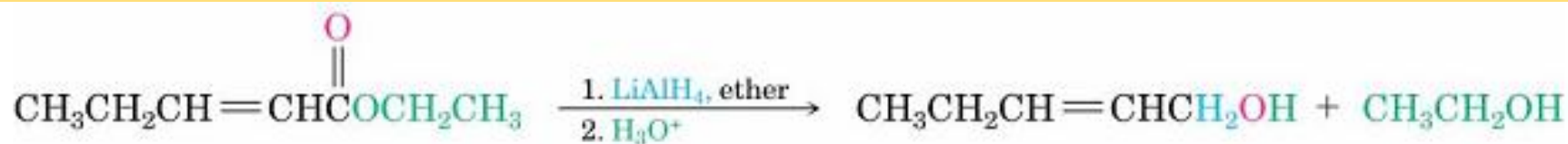
Aminolysis of Esters

Ammonia reacts with esters to form amides



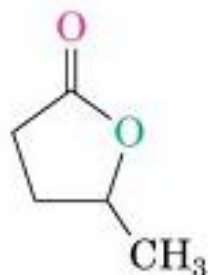
Reduction: Conversion of Esters into Alcohols

Reaction with LiAlH_4 yields primary alcohols



Ethyl 2-pentenoate

2-Penten-1-ol (91%)



A lactone

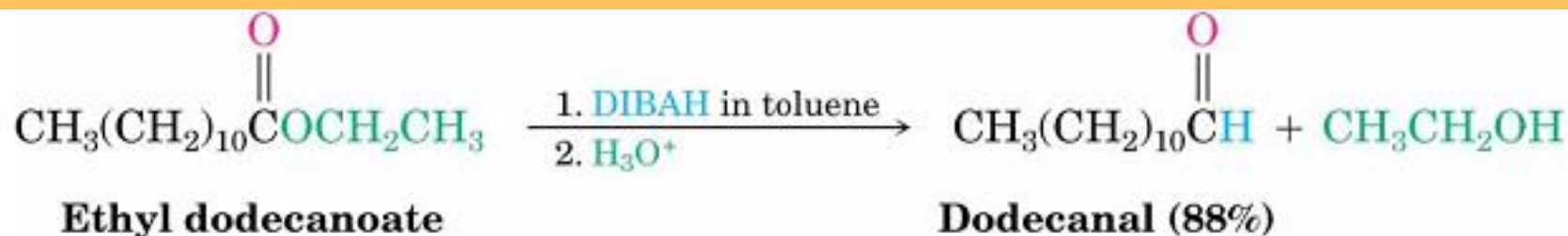


1,4-Pentanediol (86%)

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

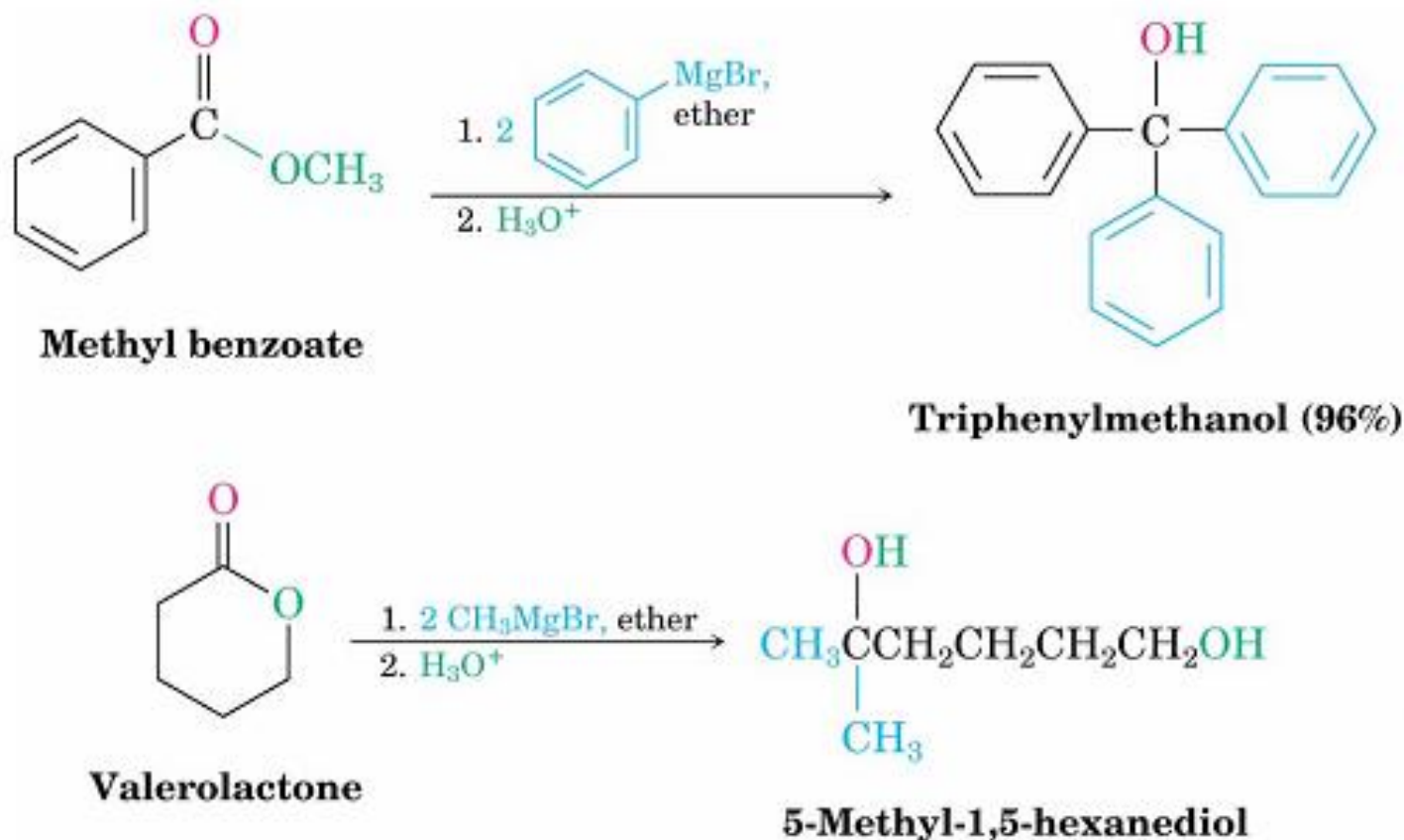
Low temperature to avoid further reduction to the alcohol



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

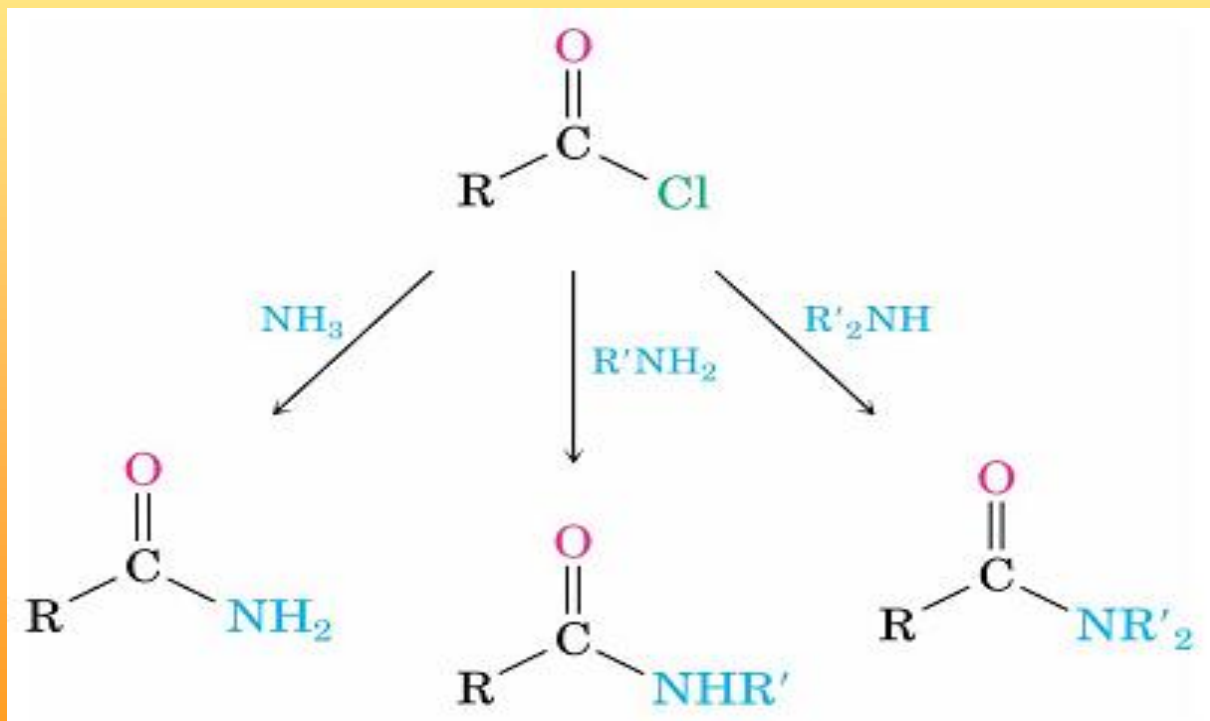
Reaction of Esters with Grignard Reagents

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



Chemistry of Amides

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

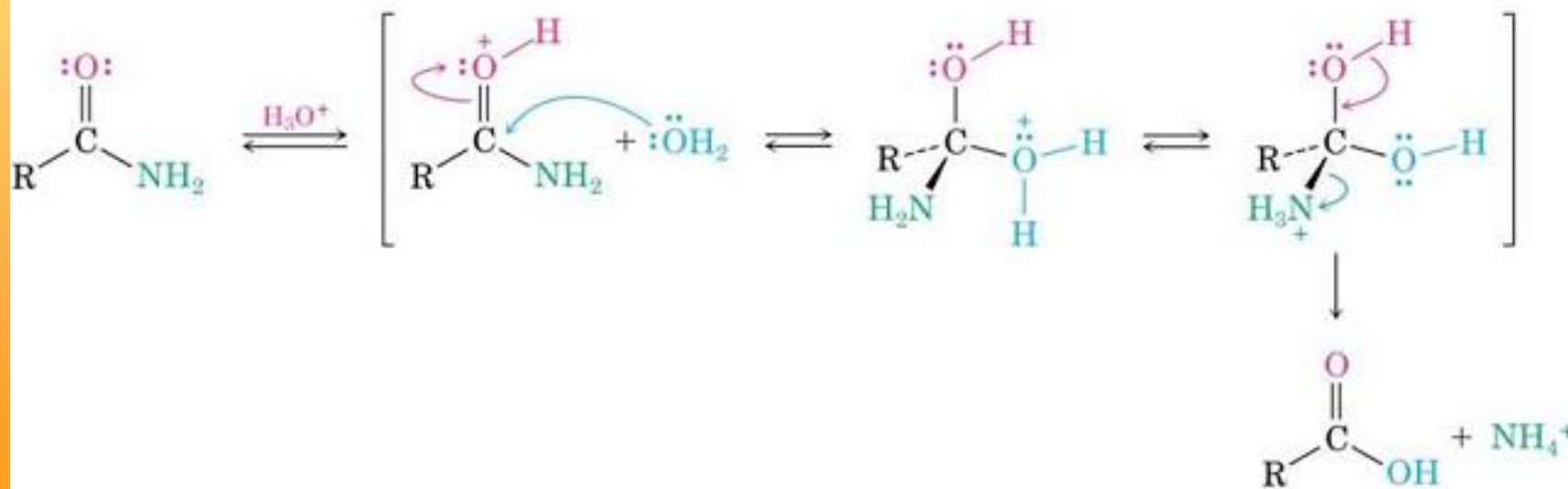


Reactions of Amides

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.

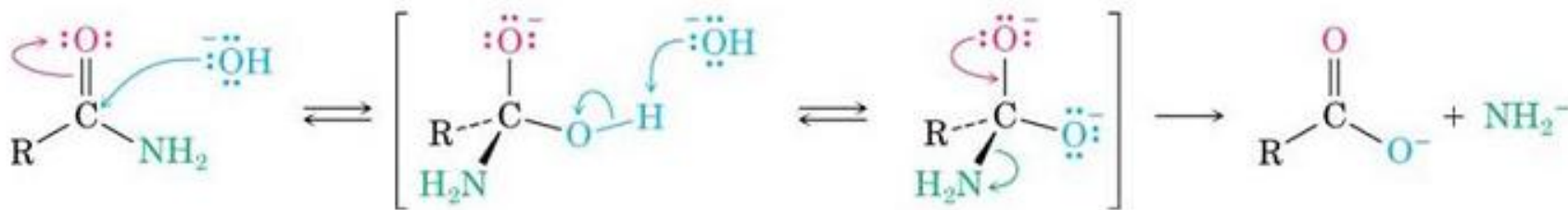
Acidic hydrolysis



Basic hydrolysis of amides

Addition of hydroxide and loss of amide ion

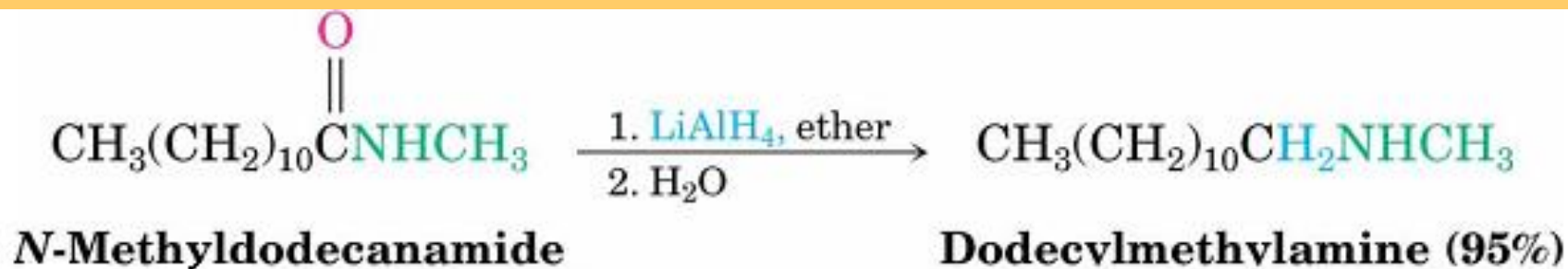
Basic hydrolysis



Reduction: Conversion of Amides into Amines

Reduced by LiAlH_4 to an amine rather than an alcohol

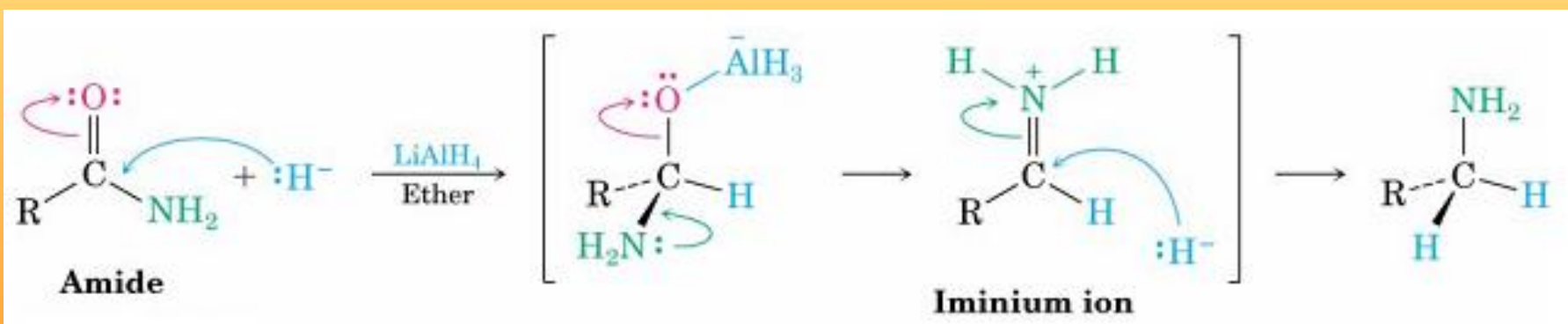
Converts $\text{C}=\text{O} \rightarrow \text{CH}_2$



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





Thanks...