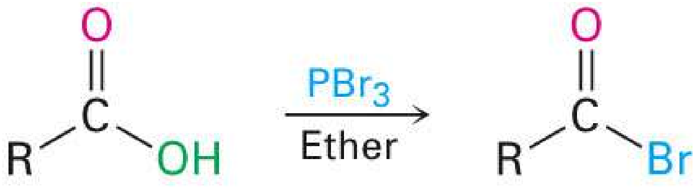
일곱째주

Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution Reactions (2)

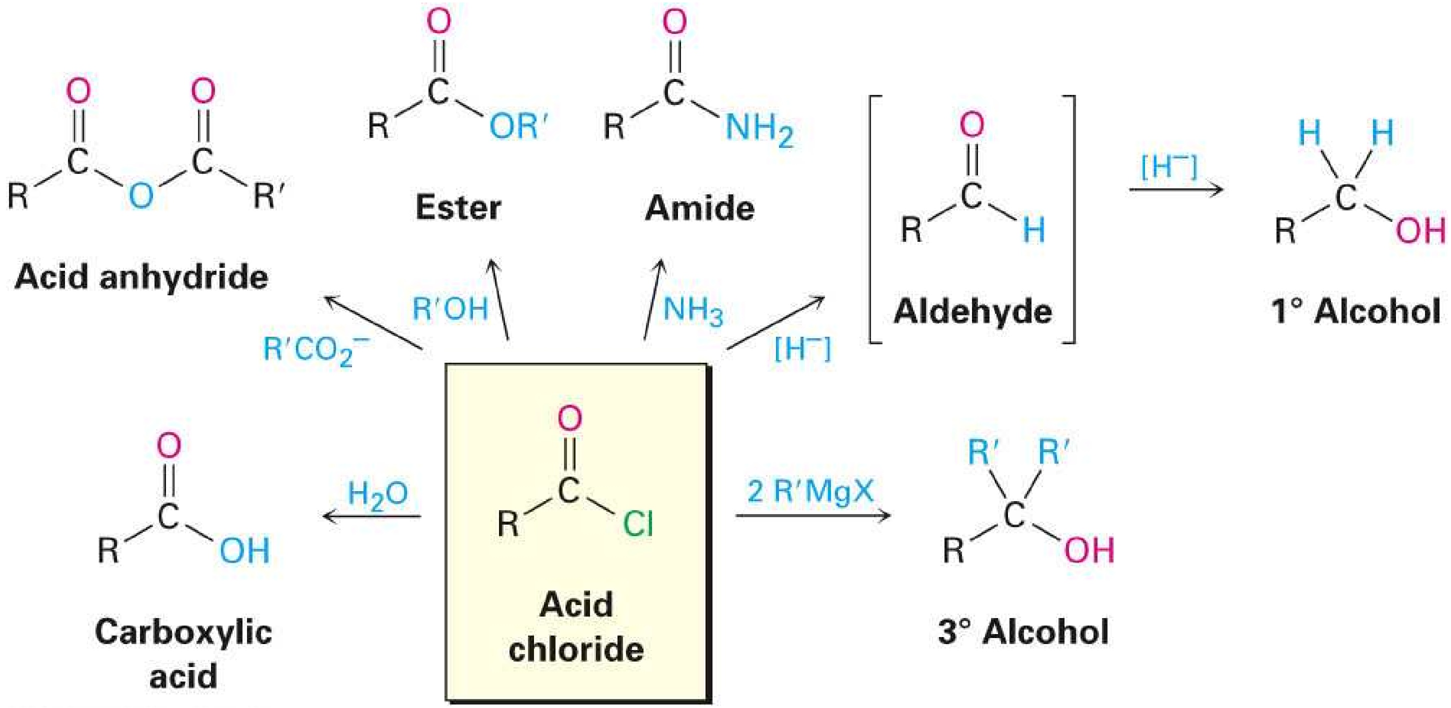
Chemistry of Acid Halides

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



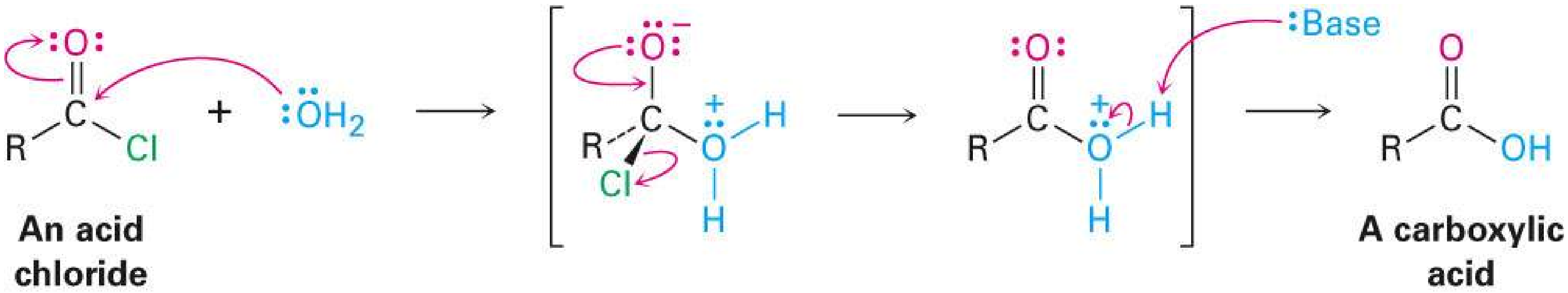
Acid Halide의 반응

- Nucleophilic acyl substitution
- Halogen replaced by —OH, by —OR, or by —NH_2
- Reduction yields a primary alcohol
- Grignard reagent yields a tertiary alcohol



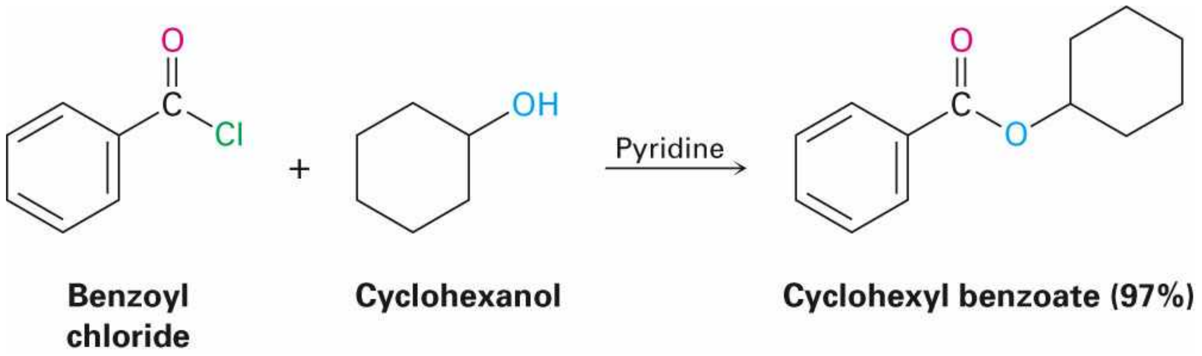
Hydrolysis: Acid Halides into Acids

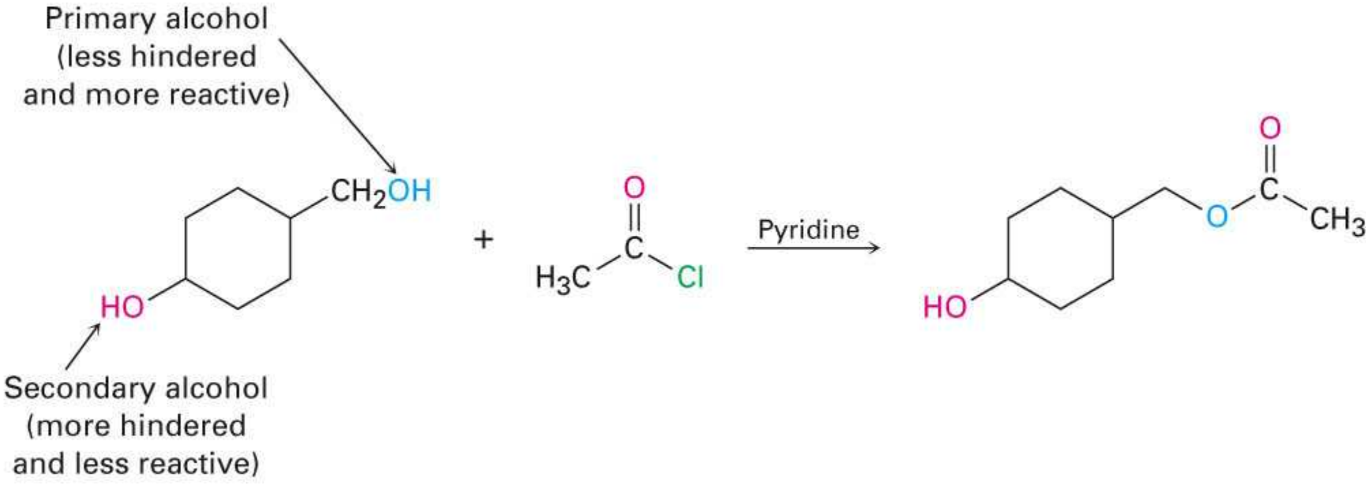
- Acid chlorides react with water to yield carboxylic acids
- HCl is generated during the hydrolysis: a base is added to remove the HCl



Conversion of Acid Halides to Esters

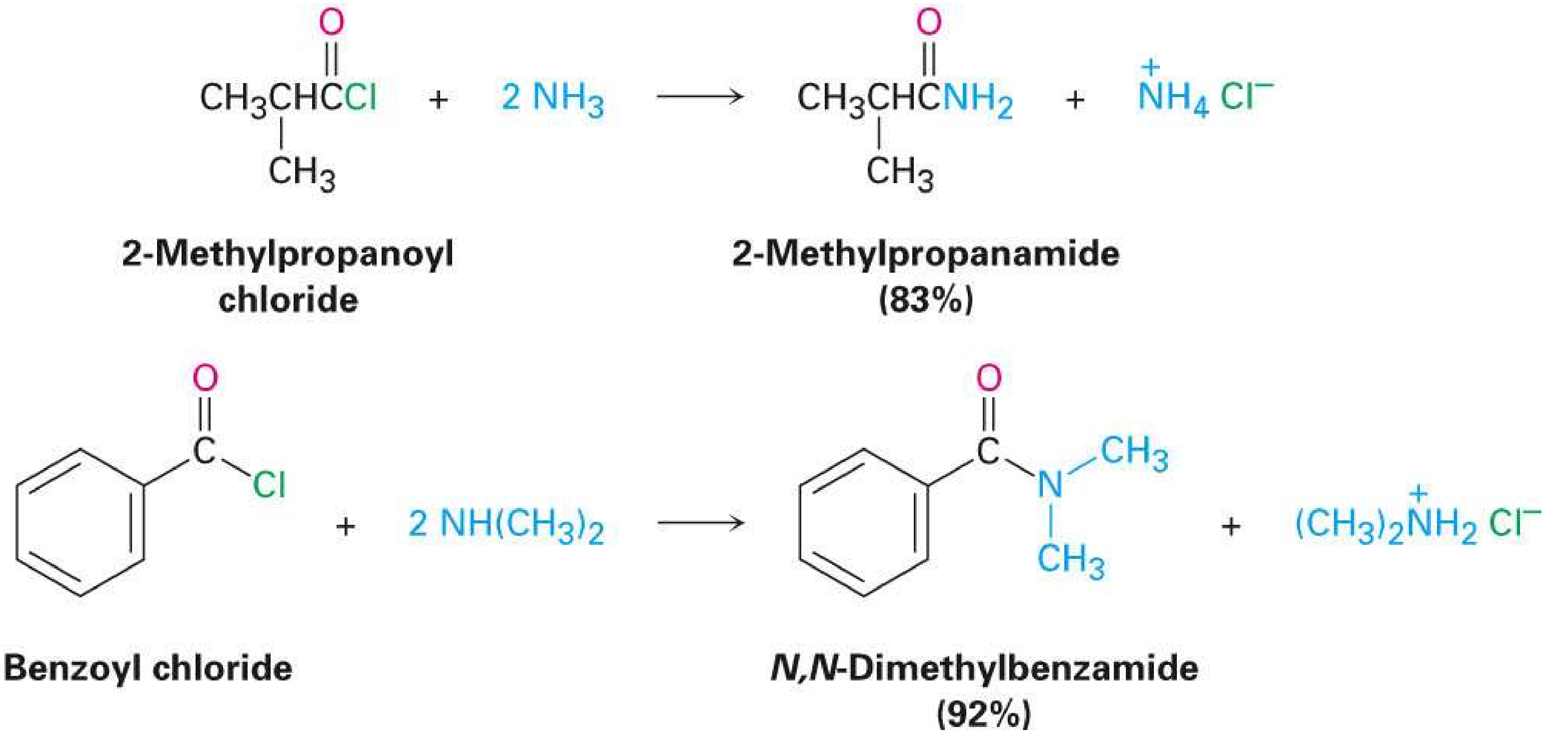
- Esters are produced in the reaction of acid chlorides with alcohols in the presence of pyridine or NaOH. This is called **Alcoholysis**
- The reaction is better with less steric bulk





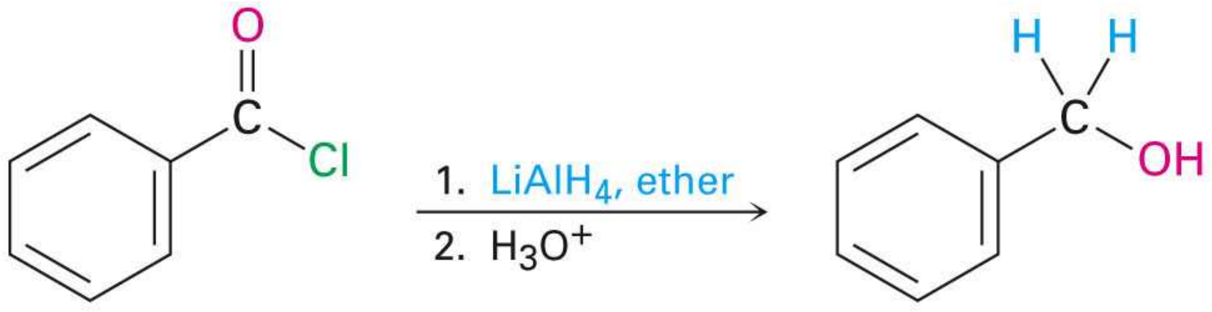
Aminolysis:Acid Halides into Amides

- 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: Acid Chlorides into Alcohols

- $LiAlH_4$ reduces acid chlorides to yield aldehydes and then primary alcohols

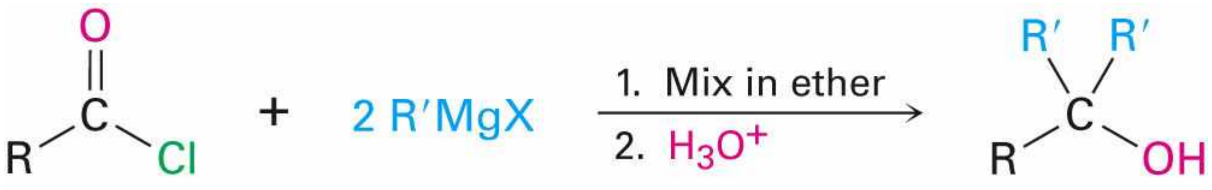


Benzoyl chloride

Benzyl alcohol (96%)

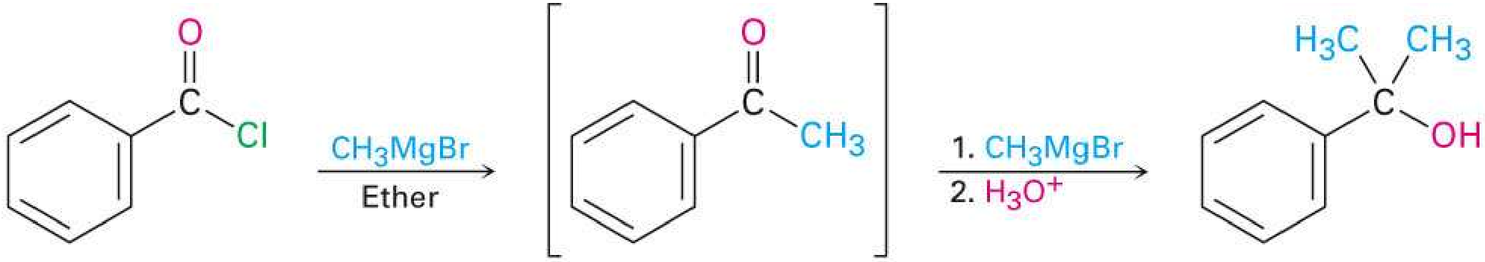
Reaction of Acid Chlorides with Organometallic Reagents

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



Acid chloride

3° Alcohol



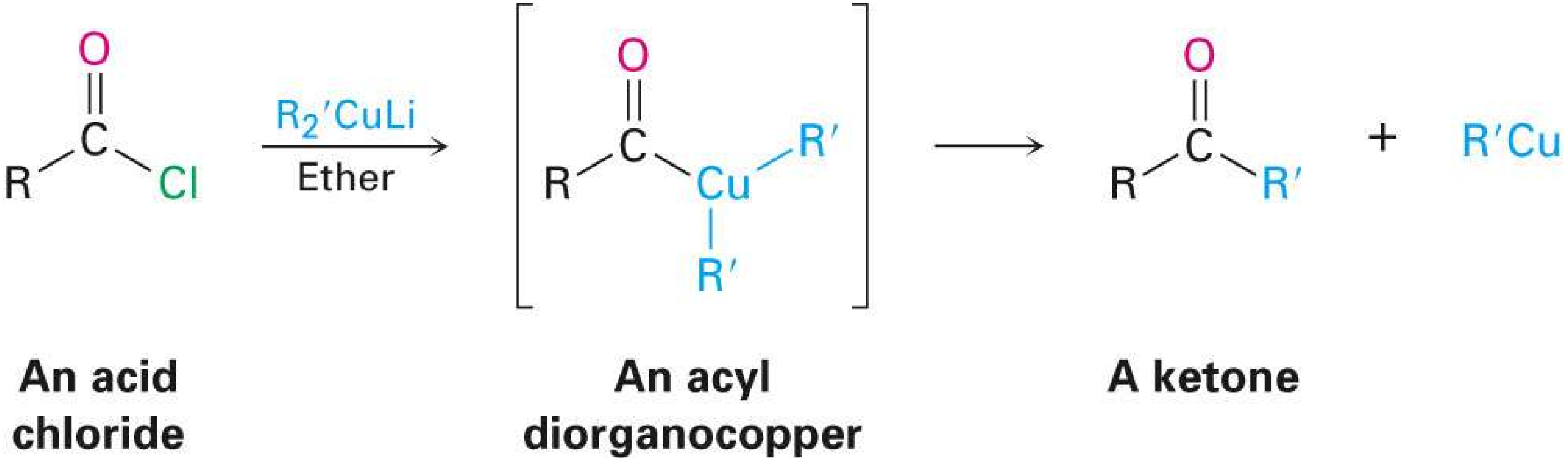
Benzoyl chloride

Acetophenone
(NOT isolated)

2-Phenyl-2-propanol
(92%)

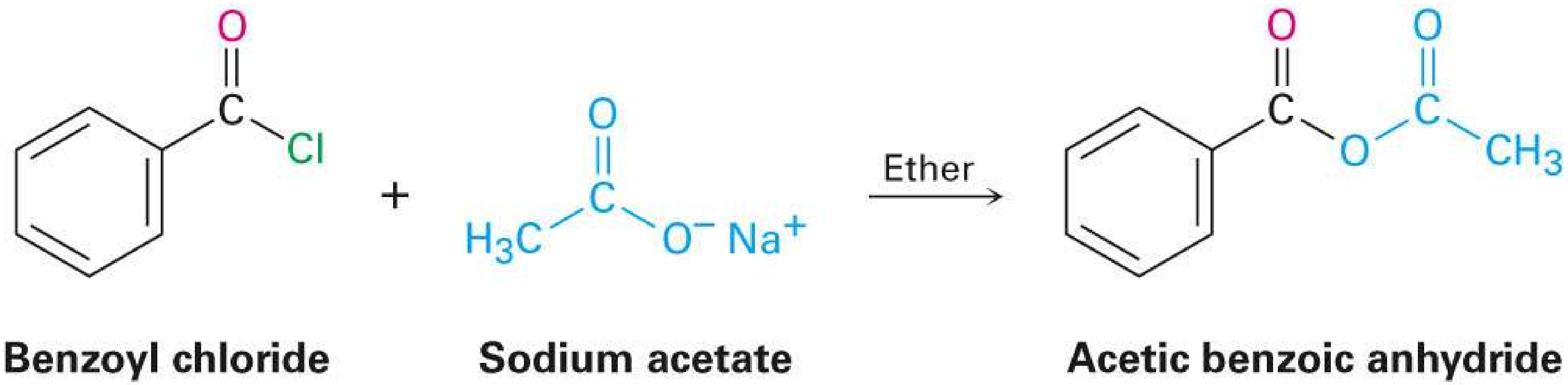
Formation of Ketones from Acid Chlorides

- Reaction of an acid chloride with a lithium diorganocopper (Gilman) reagent, $Li^+ R_2Cu^-$
- Addition produces an acyl diorganocopper intermediate, followed by loss of R′Cu and formation of the ketone



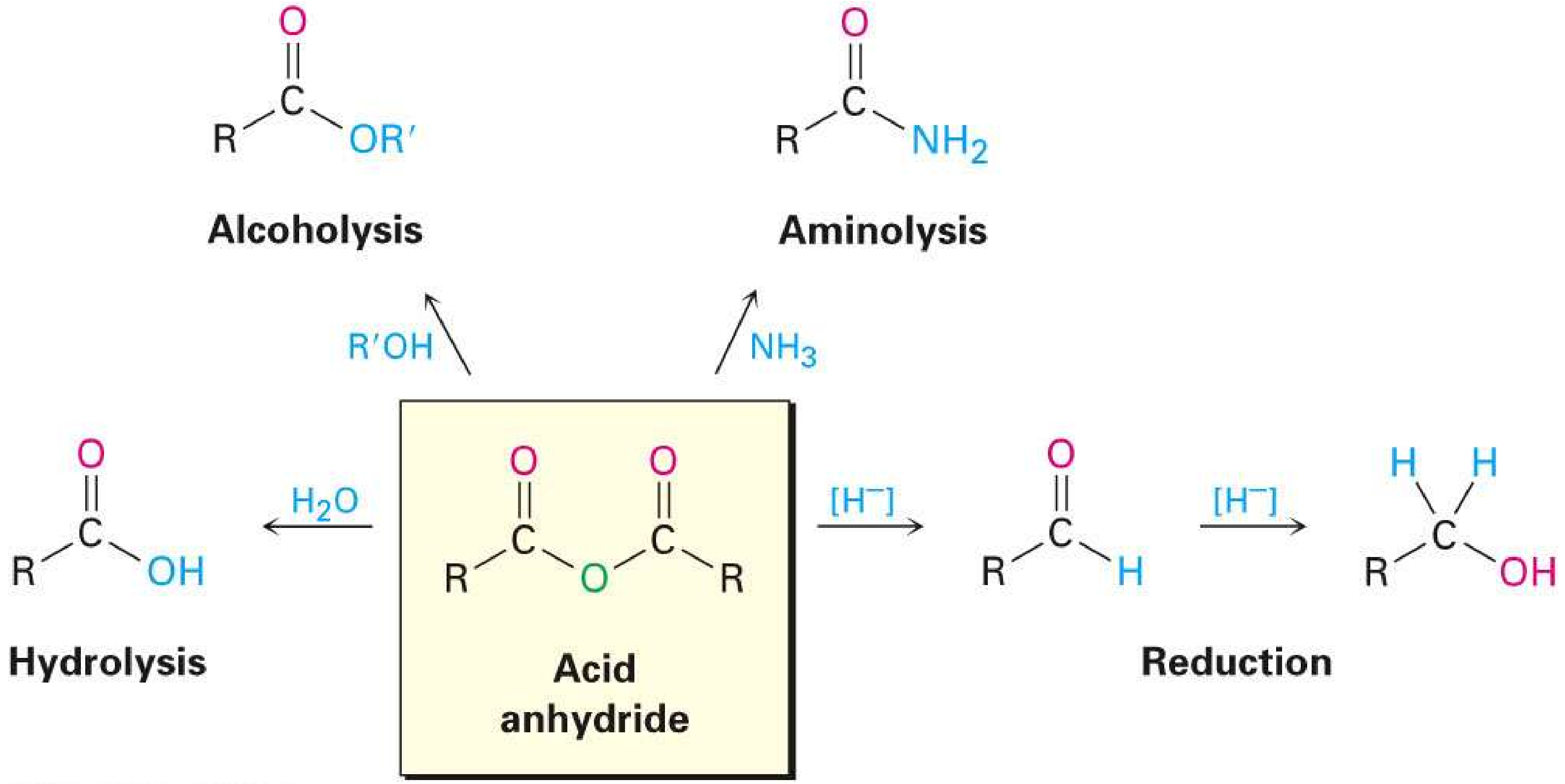
Acid Anhydrides

- Prepared by nucleophilic acyl substitution of a carboxylate with an acid chloride



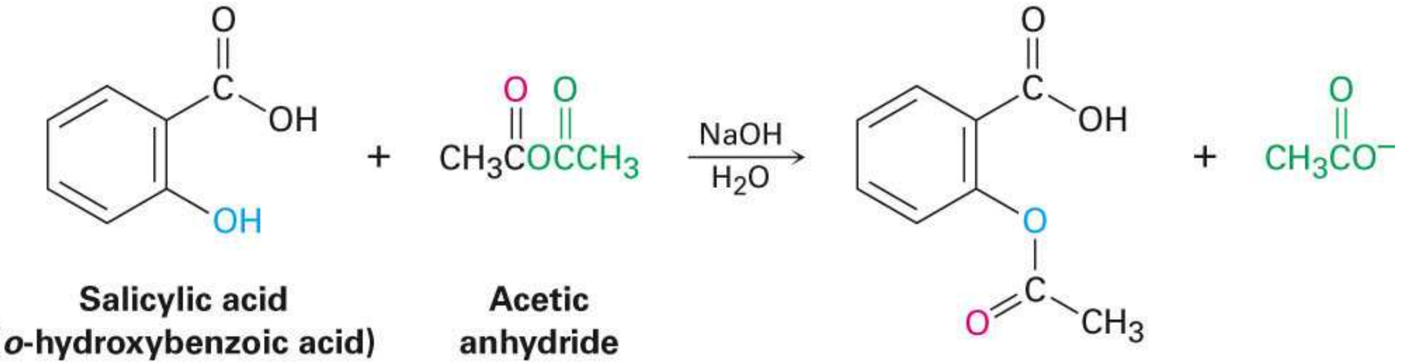
Acid Anhydrides의 반응

- Similar to acid chlorides in reactivity

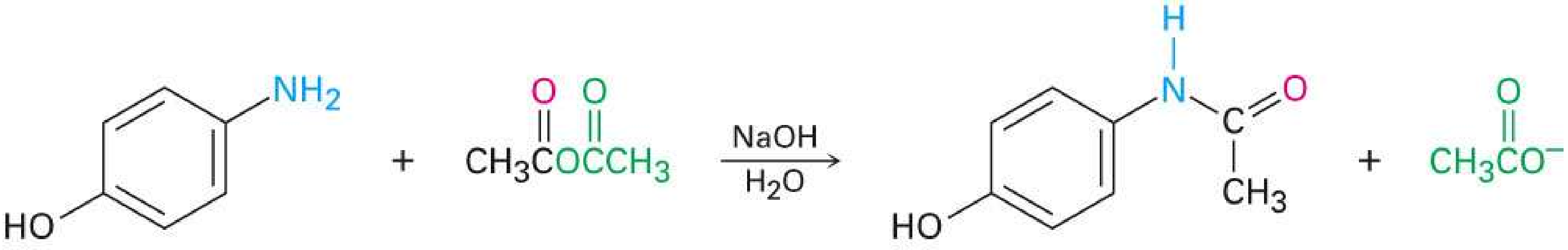


Acetylation

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



Salicylic acid (*o*-hydroxybenzoic acid) + **Acetic anhydride** → **Aspirin (an ester)**



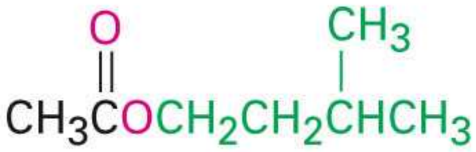
***p*-Hydroxyaniline** + **Acetic anhydride** → **Acetaminophen**

Esters

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

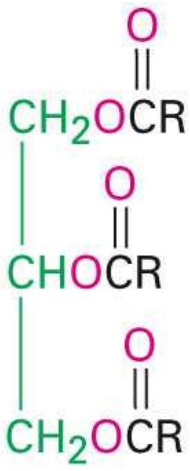
$$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3$$

Methyl butanoate
(from pineapples)



$$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_3$$

Isopentyl acetate
(from bananas)

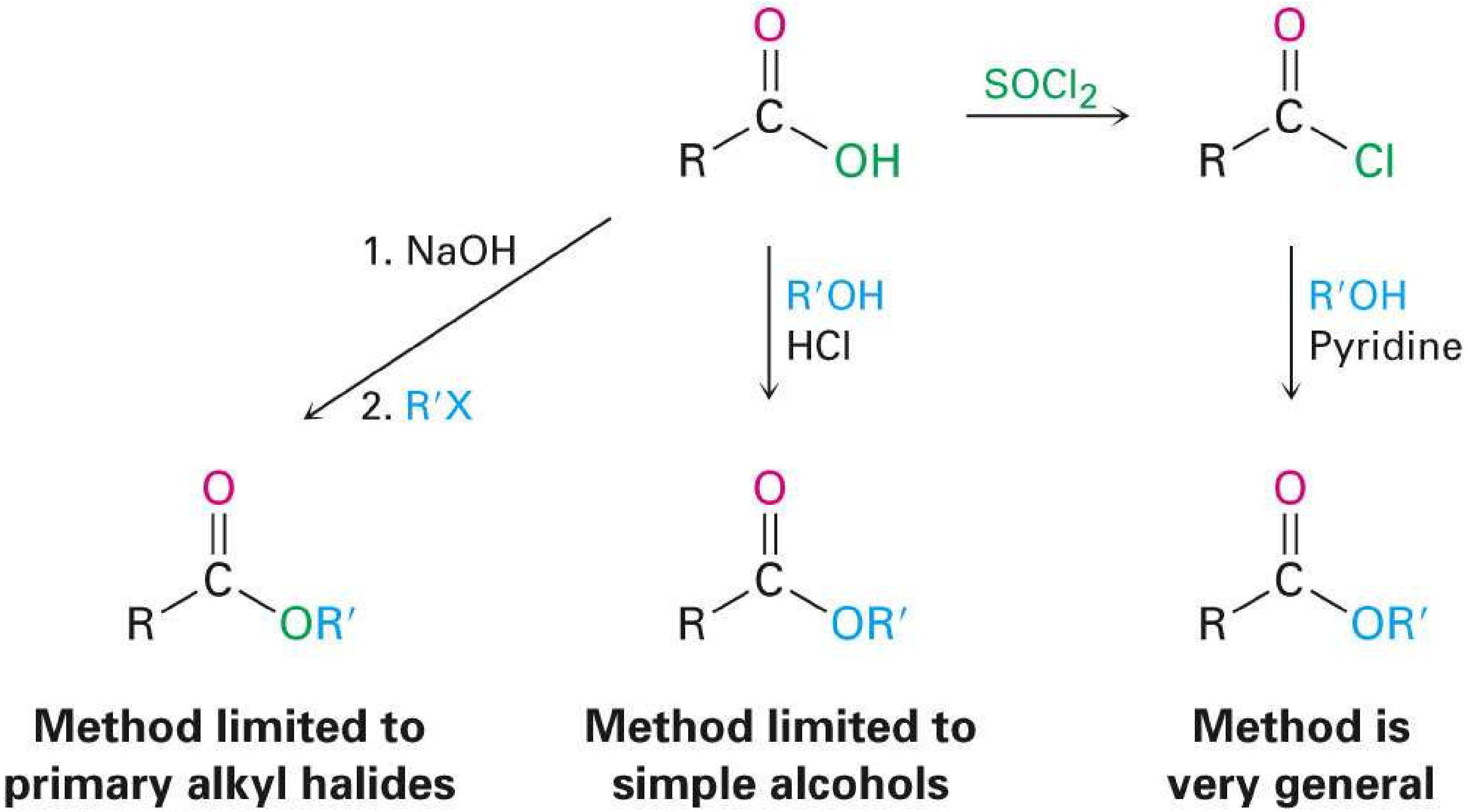


$$\begin{array}{l} CH_2O\overset{O}{\overset{\|}{C}}R \\ | \\ CHO\overset{O}{\overset{\|}{C}}R \\ | \\ CH_2O\overset{O}{\overset{\|}{C}}R \end{array}$$

A fat
(R = C_{11-17} chains)

Esters

- Esters are usually prepared from carboxylic acids



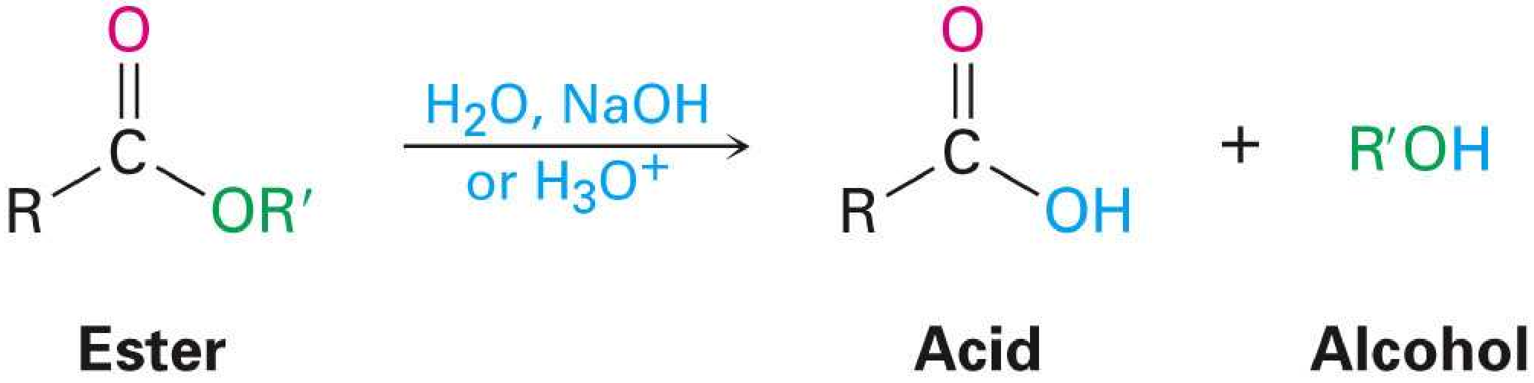
Reactions of Esters

- Less reactive toward nucleophiles than are acid chlorides or anhydrides

- Cyclic esters are called lactones and react similarly to acyclic esters

Hydrolysis: Esters into Carboxylic Acids

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



Ester Hydrolysis 기전

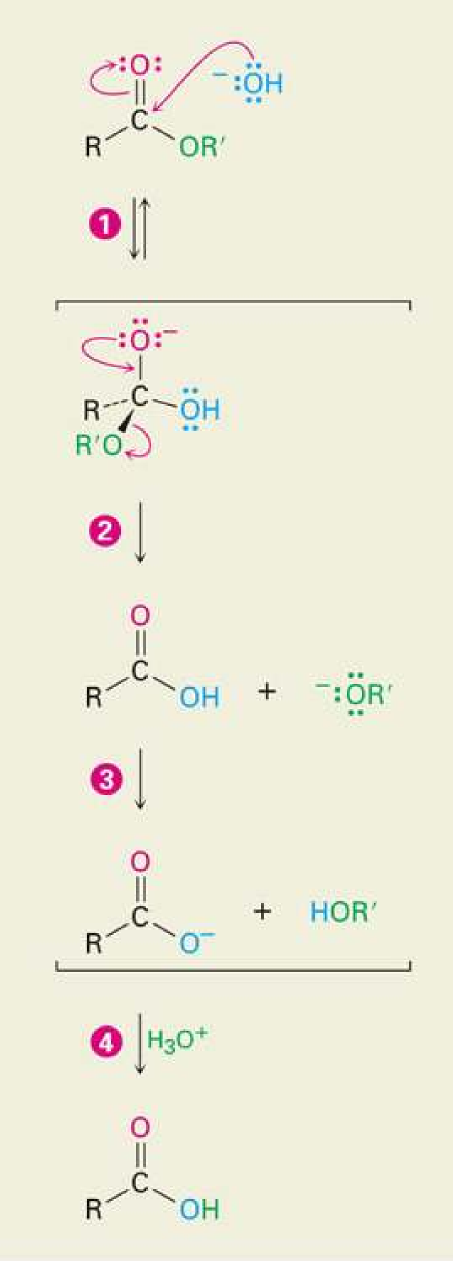
- Hydroxide catalysis via an addition intermediate

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

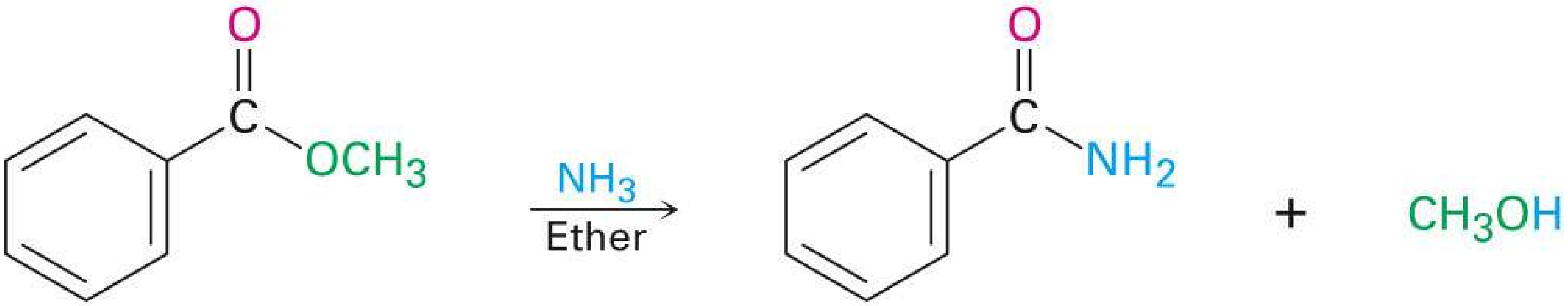
3. Alkoxide ion abstracts the acidic proton from the carboxylic acid and yields a carboxylate ion.

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



Aminolysis of Esters

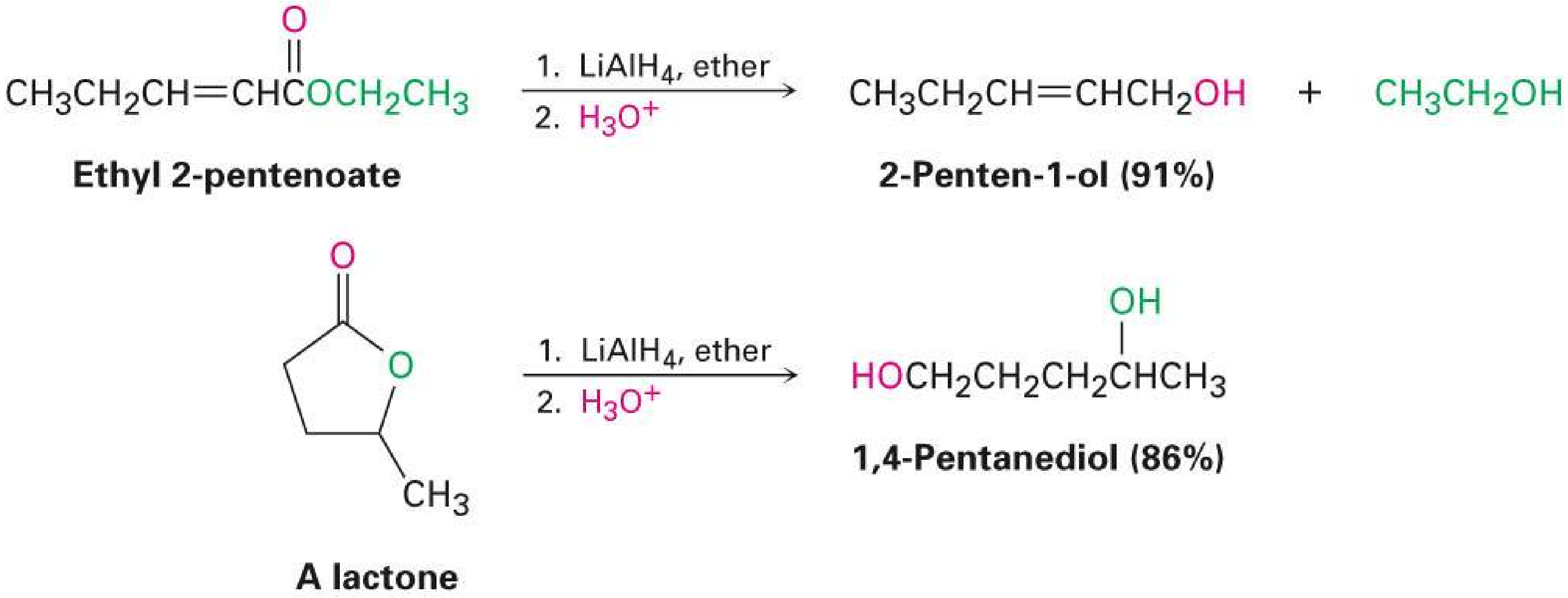
- Ammonia reacts with esters to form amides



Methyl benzoate **Benzamide**

Reduction: Esters into Alcohols

- Reaction with $LiAlH_4$ yields primary alcohols



$$CH_3CH_2CH{=}CH\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[\text{2. } H_3O^+]{\text{1. } LiAlH_4\text{, ether}} CH_3CH_2CH{=}CHCH_2OH + CH_3CH_2OH$$

Ethyl 2-pentenoate

2-Penten-1-ol (91%)

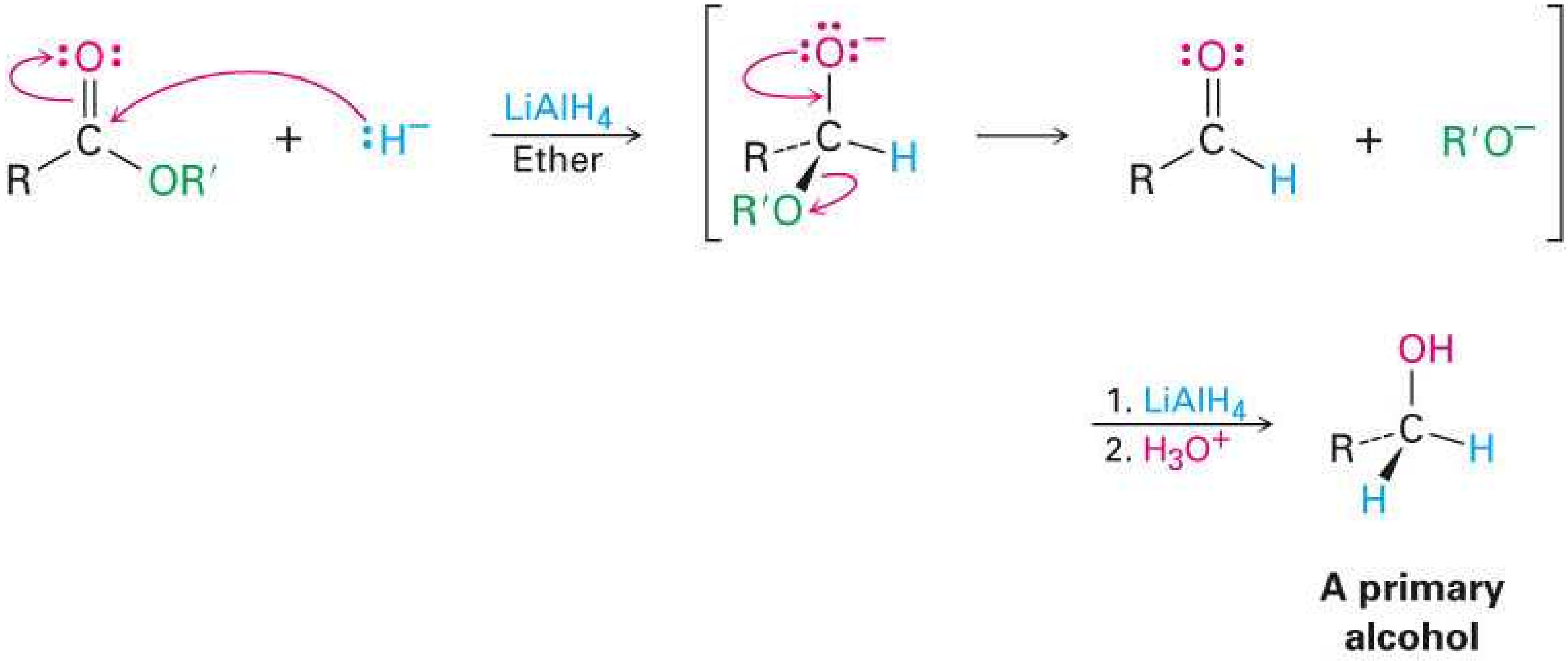
$$\xrightarrow[\text{2. } H_3O^+]{\text{1. } LiAlH_4\text{, ether}} HOCH_2CH_2CH_2\overset{OH}{\overset{|}{C}}HCH_3$$

A lactone

1,4-Pentanediol (86%)

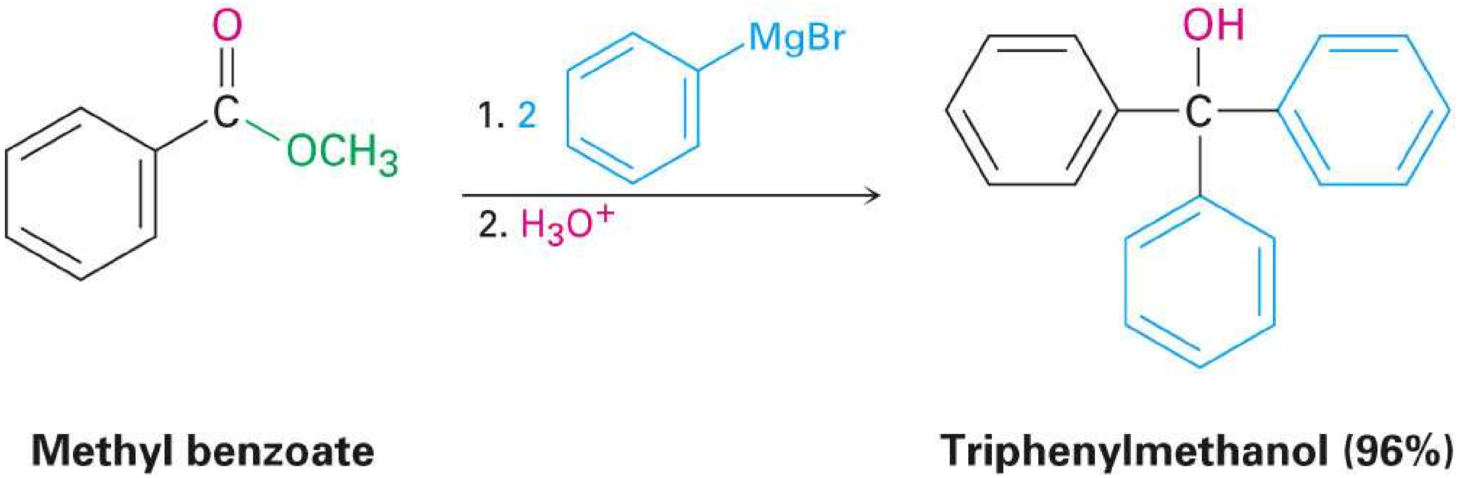
Mechanism of Reduction of Esters

- 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



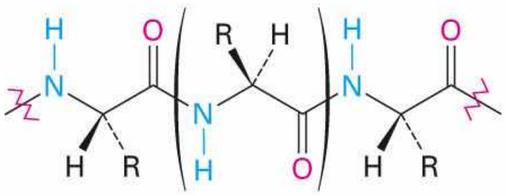
Reaction of Esters with Grignard Reagents

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

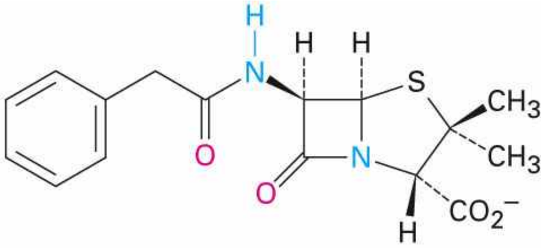


Amides

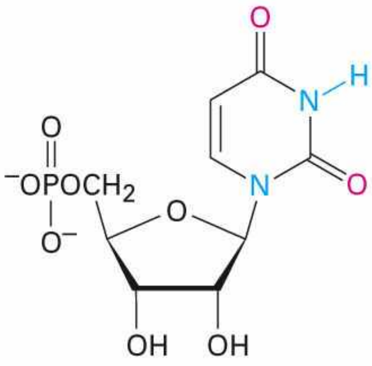
- Amides are abundant in all living organisms…proteins, nucleic acids, and other pharmaceuticals have amid functional groups



A protein segment



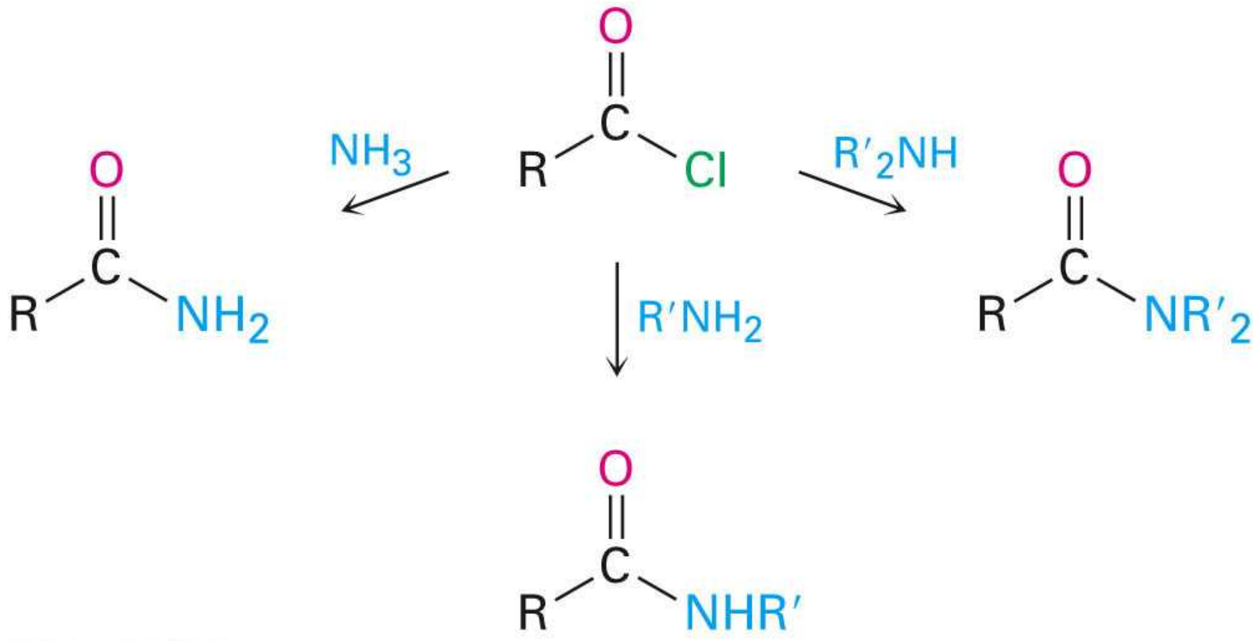
Benzylpenicillin (penicillin G)



Uridine 5′-phosphate (a ribonucleotide)

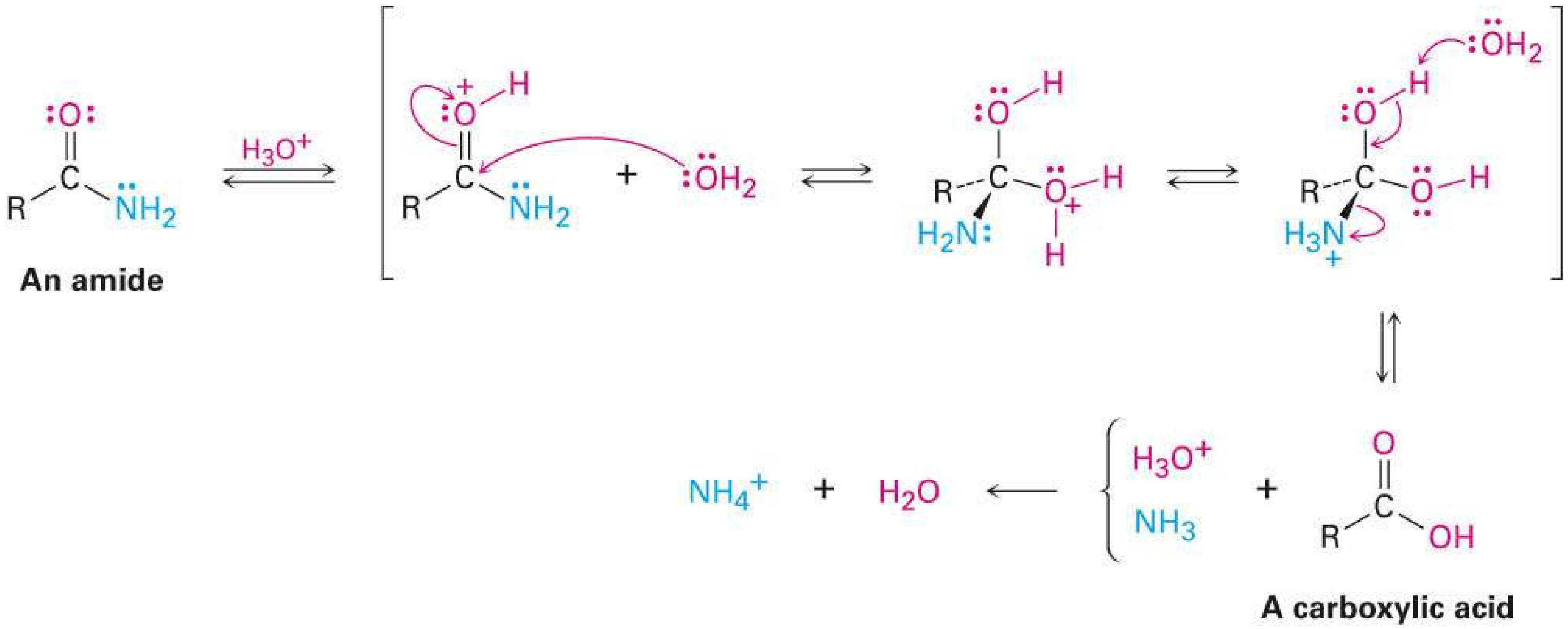
Preparation of Amides

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



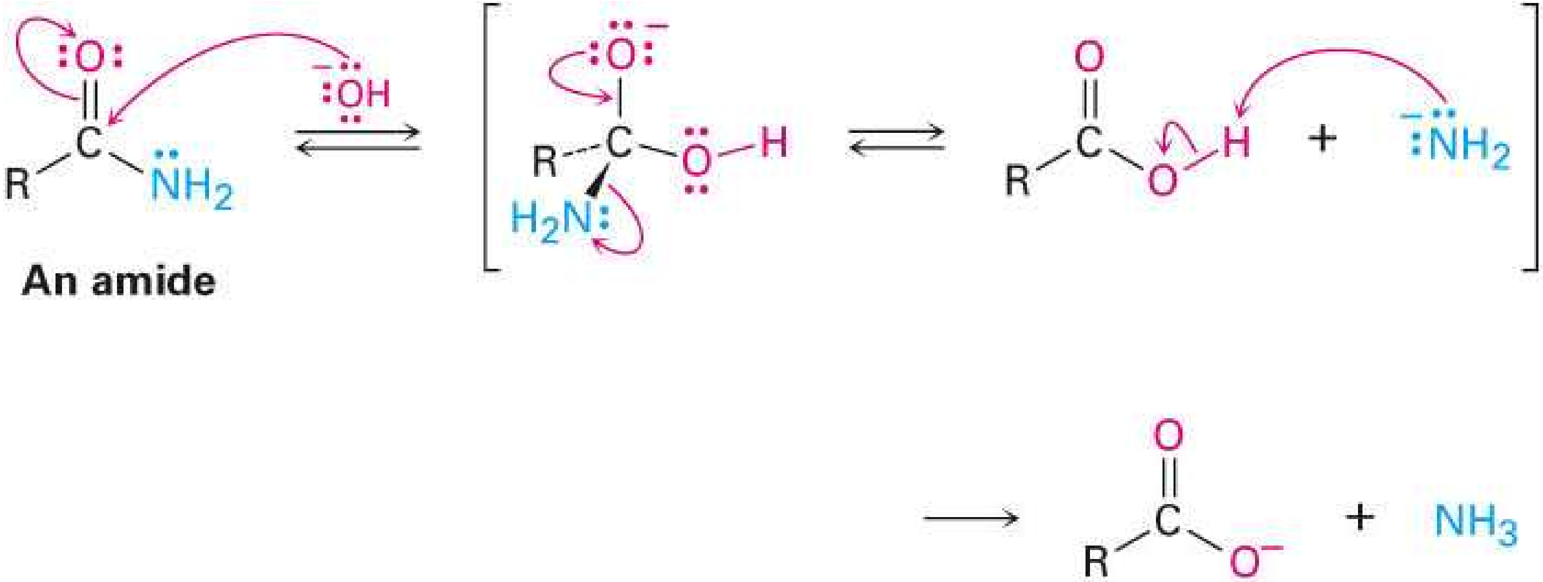
Reactions of Amides

- 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



Basic Hydrolysis of Amides

- Addition of hydroxide and loss of amide ion

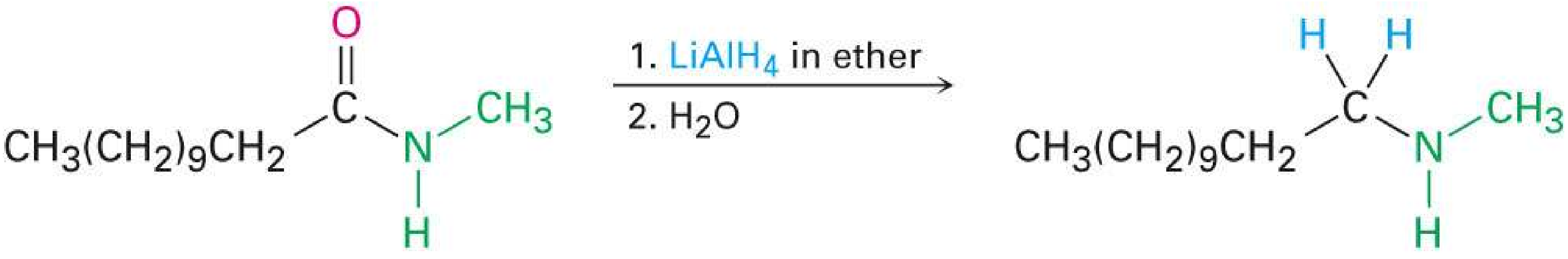


An amide

A carboxylate ion

Reduction: Amides into Amines

- Reduced by $LiAlH_4$ to an amine rather than an alcohol
- Converts C=O → CH_2

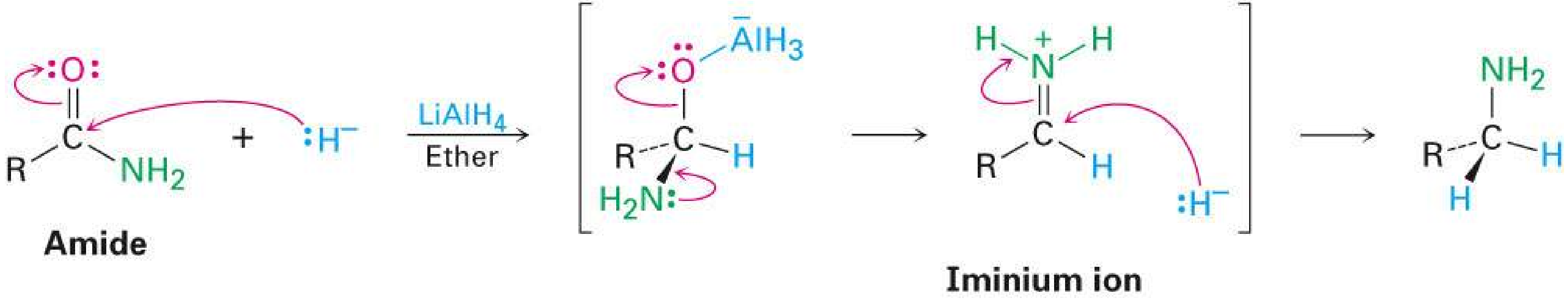


***N*-Methyldodecanamide**

Dodecylmethylamine (95%)

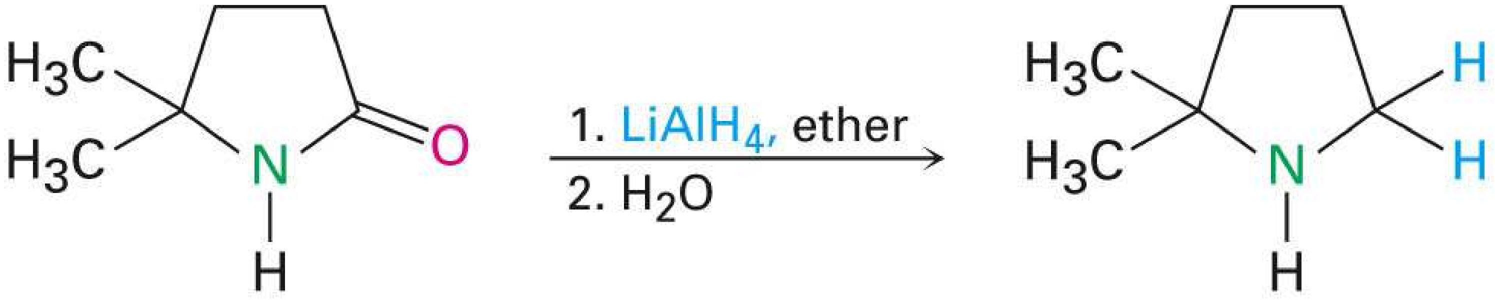
Mechanism of Reduction

- 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



A lactam

A cyclic amine (80%)