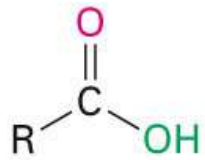
여섯째주

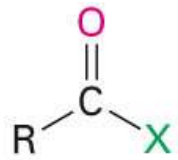
Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution Reactions (1)

Carboxylic Compounds

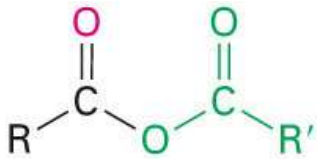
- Acyl group bonded to X, an electronegative atom or leaving group
- Includes: X = halide (acid halides), acyloxy (anhydrides), alkoxy (esters), amine (amides), thiolate (thioesters), phosphate (acyl phosphates)



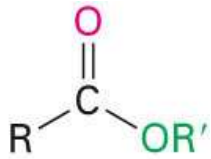
Carboxylic acid



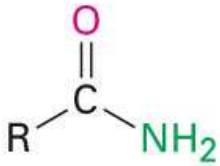
Acid halide
(X = Cl, Br)



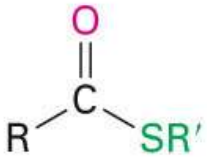
Acid anhydride



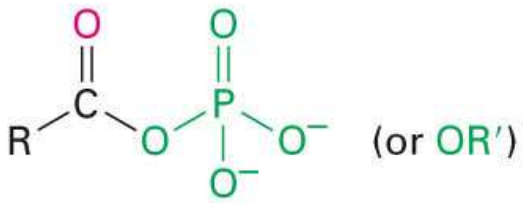
Ester



Amide



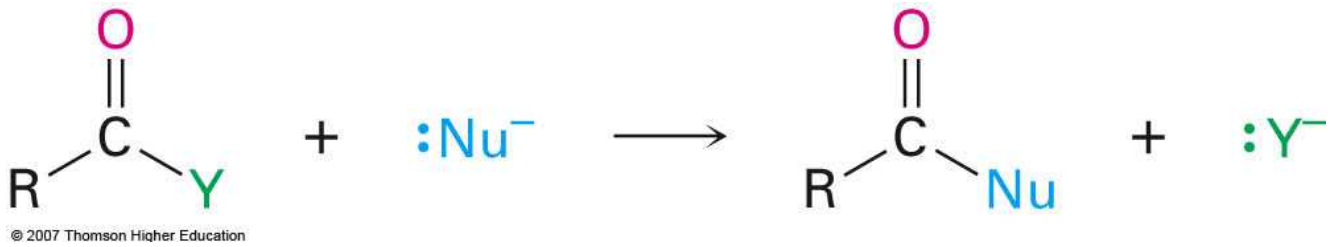
Thioester



Acyl phosphate

일반적인 반응 형태

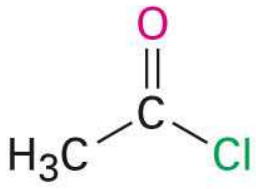
- **Nucleophilic acyl substitution**



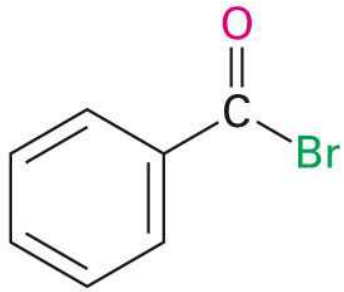
- Carboxylic acids are among the most widespread of molecules.
- A study of them and their primary reaction "**nucleophilic acyl substitution**" is fundamental to understanding organic chemistry

Carboxylic Acid Derivatives의 명명

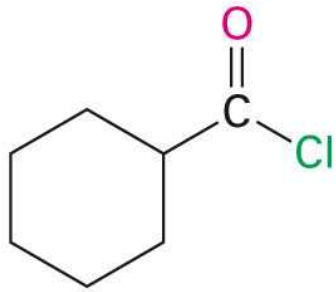
- Acid Halides, RCOX
  - Derived from the carboxylic acid name by replacing the -*ic acid* ending with -*yl* or the -*carboxylic acid* ending with –*carbonyl* and specifying the halide



Acetyl chloride



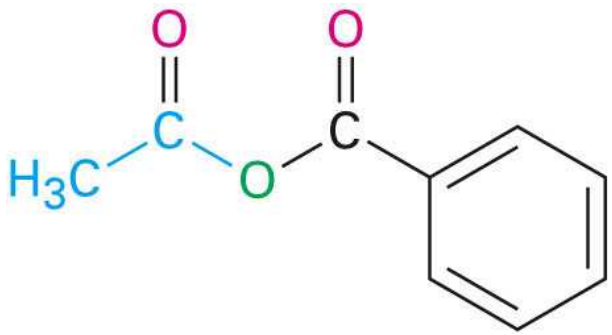
Benzoyl bromide



Cyclohexanecarbonyl chloride

Acid Anhydrides, RCO_2COR'의 명명

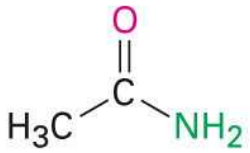
- If symmetrical replace "*acid*" with "*anhydride*" based on the related carboxylic acid
- From substituted monocarboxylic acids: use *bis*- ahead of the acid name
- Unsymmetrical anhydrides— cite the two acids alphabetically



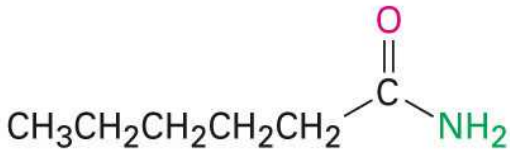
Acetic benzoic anhydride

Amides, $RCONH_2$의 명명

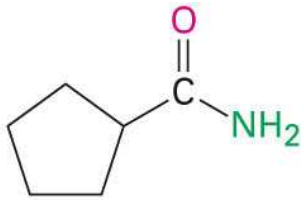
- With unsubstituted —NH_2 group. replace -*oic acid* or -*ic acid* with -*amide*, or by replacing the -*carboxylic acid* ending with –*carboxamide*
- If the N is further substituted, identify the substituent groups (preceded by “N”) and then the parent amide



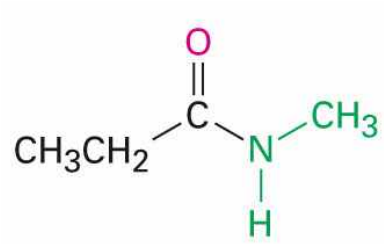
Acetamide



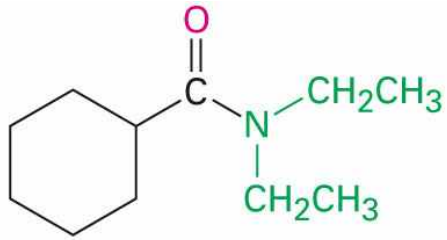
Hexanamide



Cyclopentane-carboxamide



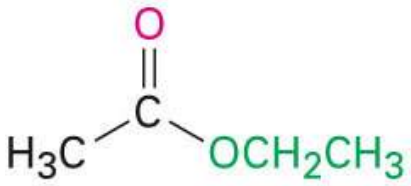
***N*-Methylpropanamide**



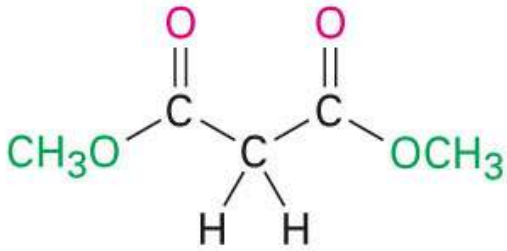
***N,N*-Diethylcyclohexanecarboxamide**

Esters, RCO_2R' 의 명명

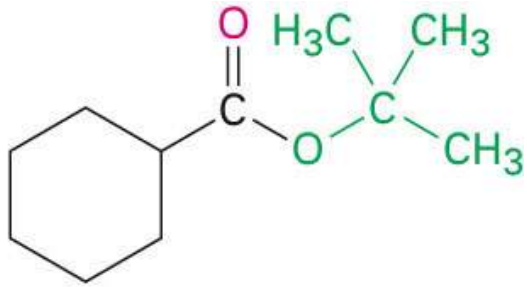
- Name R' and then, after a space, the carboxylic acid (RCOOH), with the "-*ic acid*" ending replaced by "-*ate*"



Ethyl acetate

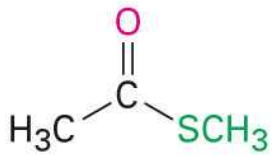


Dimethyl malonate

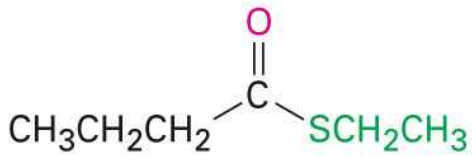


***tert*-Butyl cyclohexane-carboxylate**

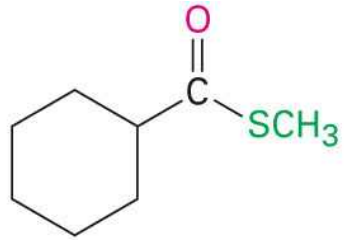
Thioester와 Phosphoester의 명명



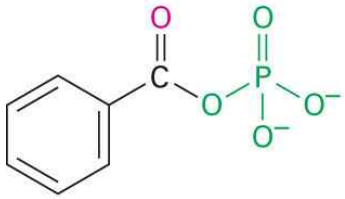
Methyl thioacetate



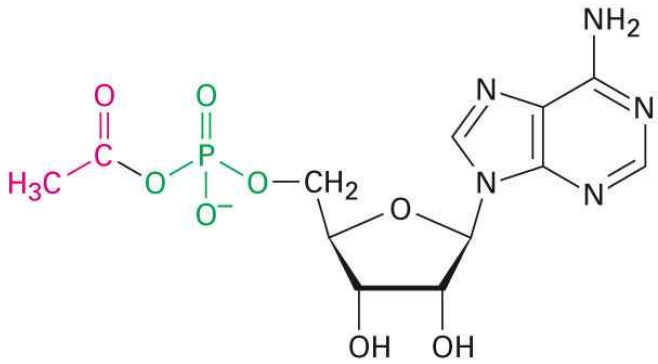
Ethyl butanethioate



Methyl cyclohexane-carbothioate

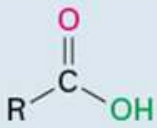
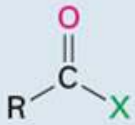
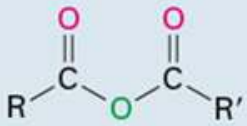
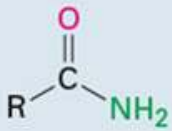
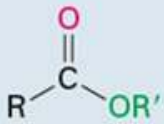
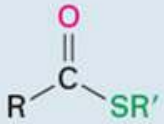
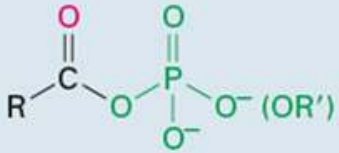


Benzoyl phosphate



Acetyl adenosyl phosphate

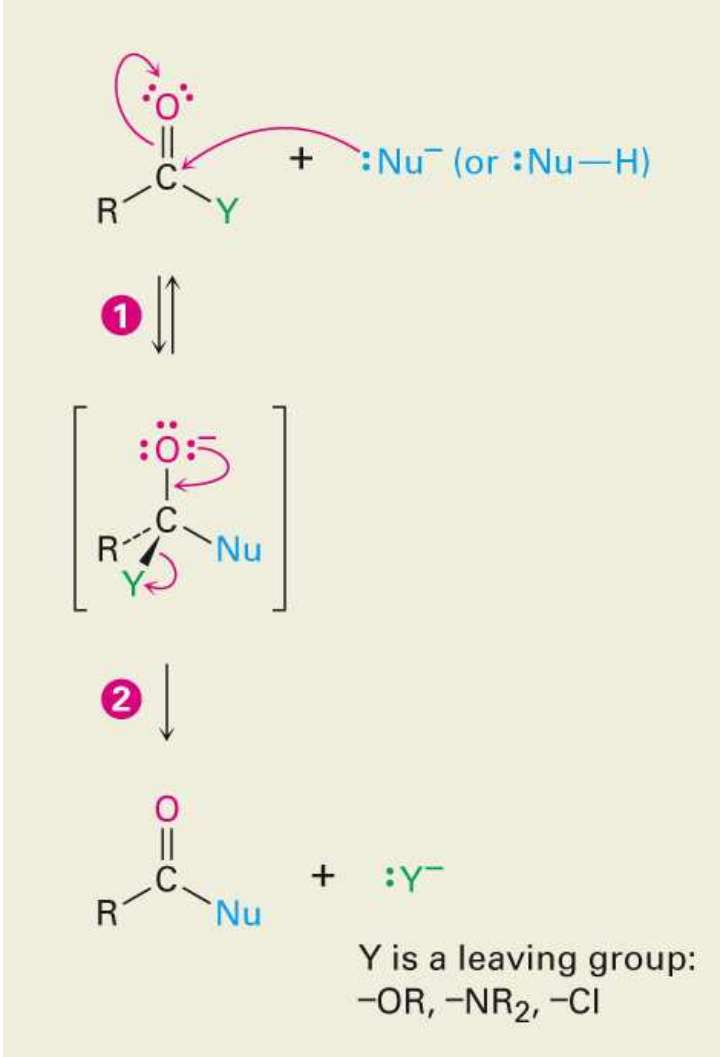
Carboxylic Acid 유도체의 명명

Functional group	Structure	Name ending
Carboxylic acid		*-ic acid (-carboxylic acid)*
Acid halide		*-oyl halide (-carbonyl halide)*
Acid anhydride		*anhydride*
Amide		*-amide (-carboxamide)*
Ester		*-ate (-carboxylate)*
Thioester		*-thioate (-carbothioate)*
Acyl phosphate		*-yl phosphate*

Nucleophilic Acyl Substitution

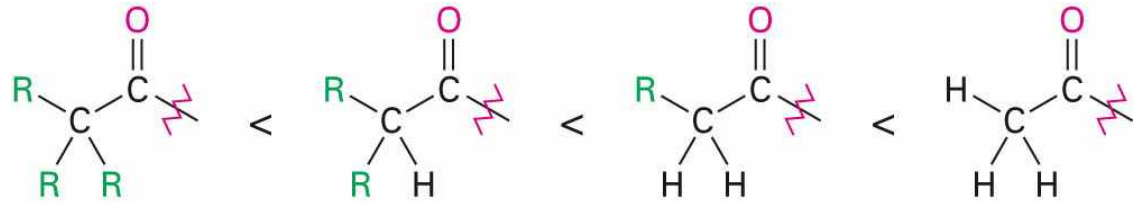
- Carboxylic acid derivatives have an acyl carbon bonded to a group —Y that can leave

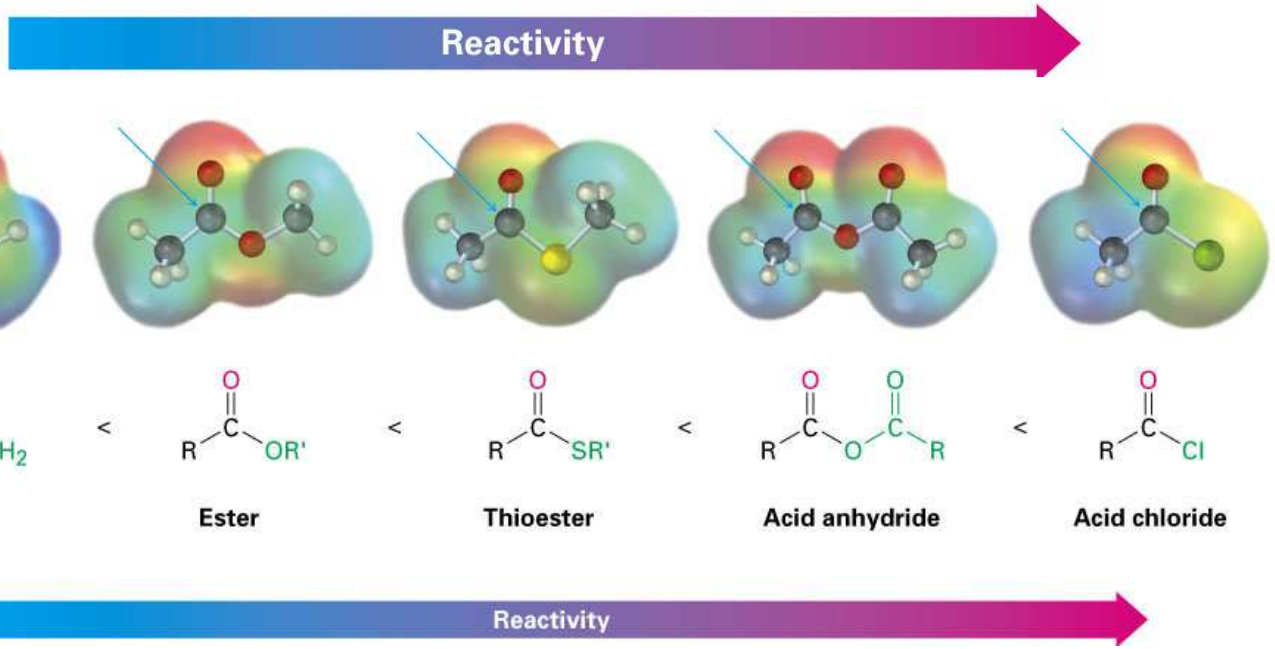
- A tetrahedral intermediate is formed and the leaving group is expelled to generate a new carbonyl compound, leading to substitution



Carboxylic Acid유도체의 상대적 반응성

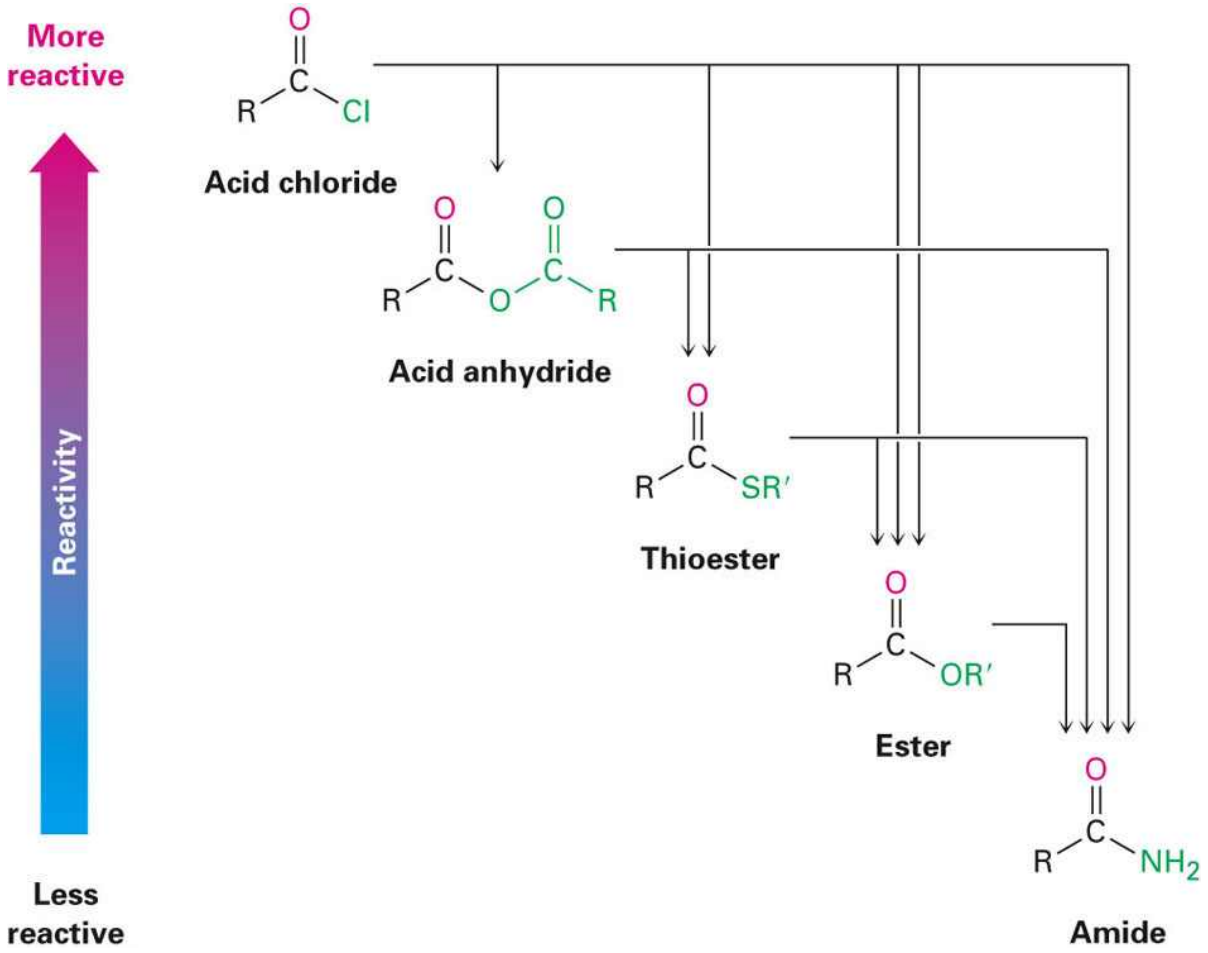
- Nucleophiles react more readily with unhindered carbonyl groups
- More electrophilic carbonyl groups are more reactive to addition (acyl halides are most reactive, amides are least)
- The intermediate with the best leaving group decomposes fastest



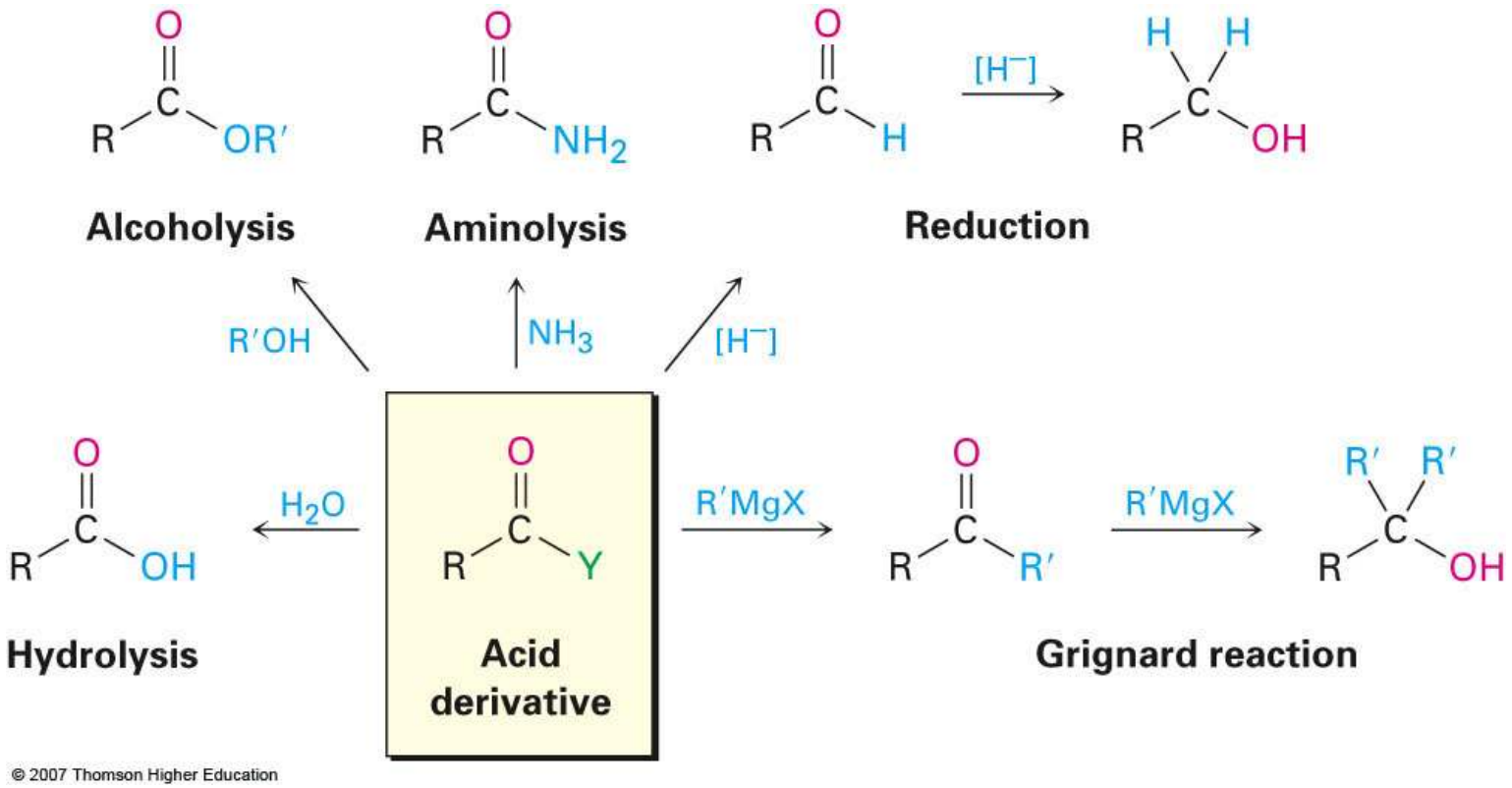


Substitution in Synthesis

- 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



Carboxylic Acid Derivatives의 일반적 반응성



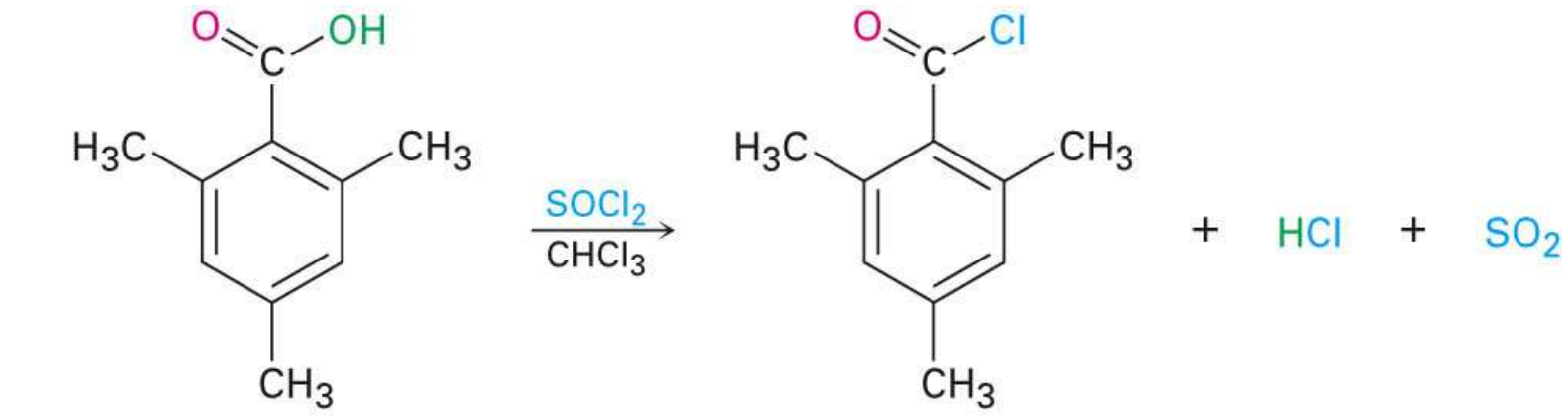
- water : carboxylic acid
- alcohols : esters
- ammonia or an amine : an amide
- hydride source : an aldehyde or an alcohol
- Grignard reagent : a ketone or an alcohol

Nucleophilic Acyl Substitution Reactions

- 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, $SOCl_2$

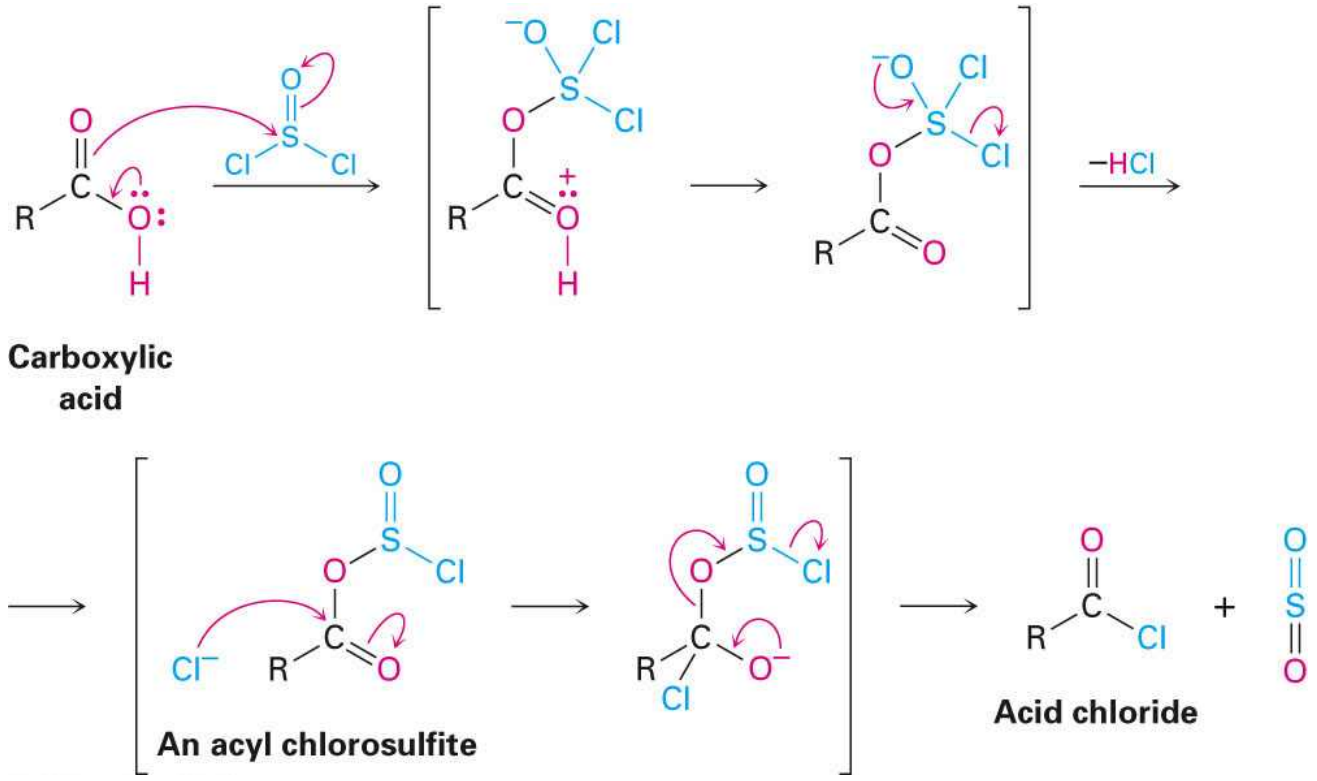


2,4,6-Trimethylbenzoic acid

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

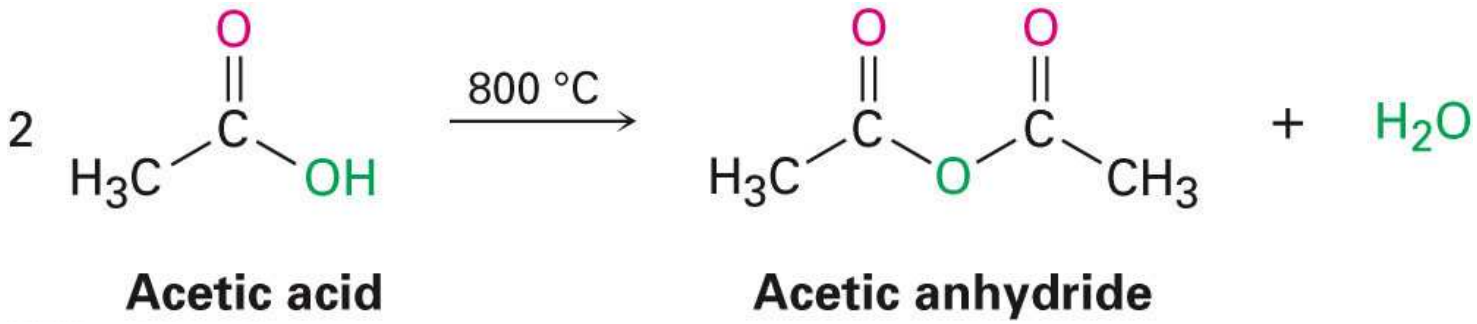
Thionyl Chloride Reaction 기전

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



Carboxylic Acids into Acid Anhydrides

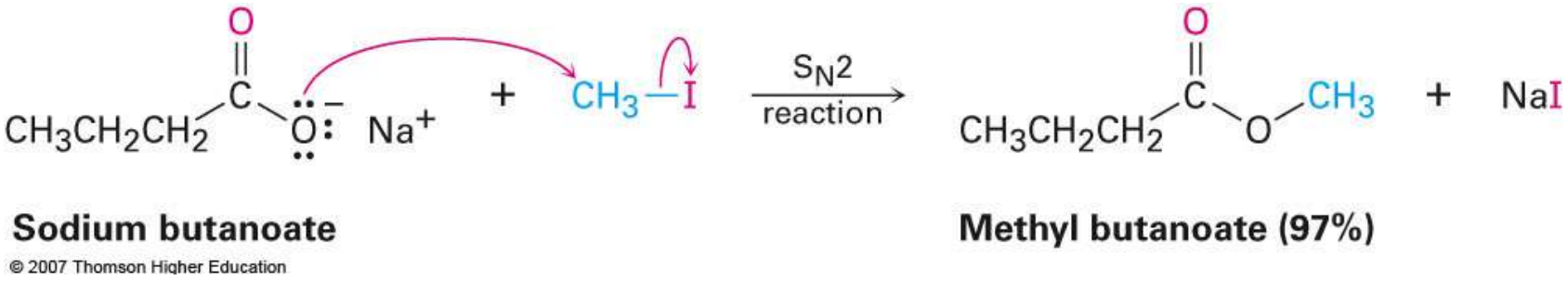
- Acid anhydrides can be derived from two molecules of carboxylic acid by strong heating to remove water



Acetic acid **Acetic anhydride**

Carboxylic Acids into Esters

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

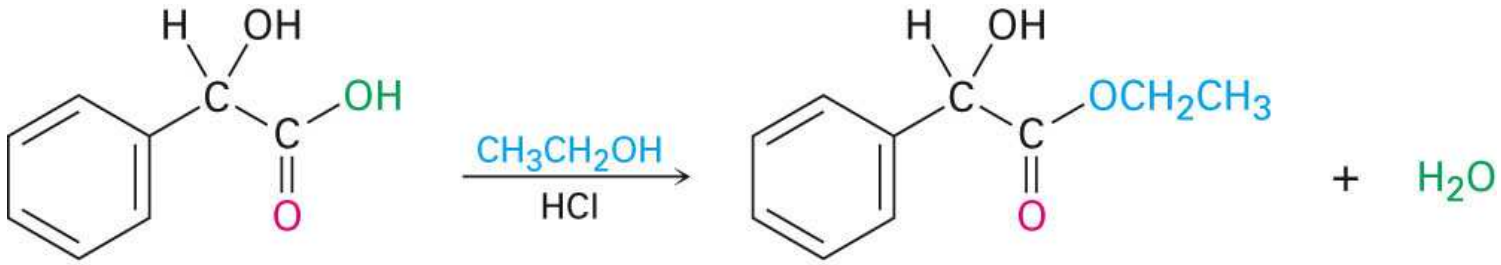


Sodium butanoate

Methyl butanoate (97%)

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



Mandelic acid **Ethyl mandelate (86%)**

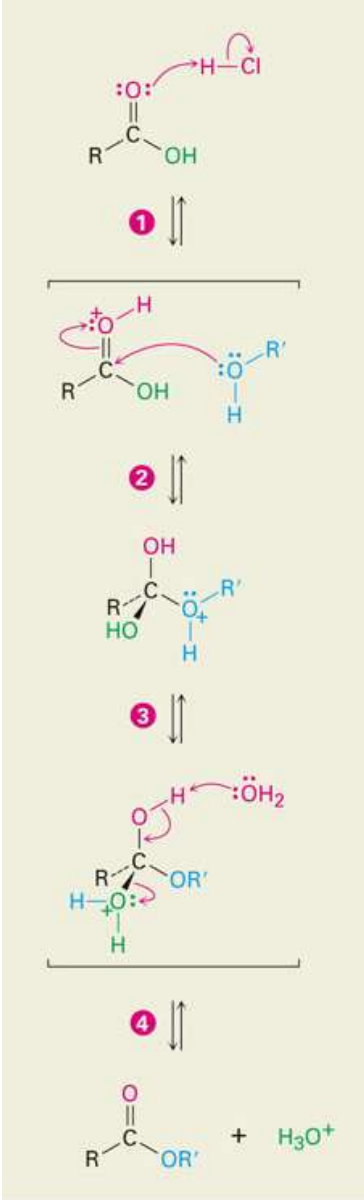
Fischer Esterification 반응 기전

1. Protonation of the carboxylic oxygen activates the carboxylic acid

2. Toward nucleophilic attack by alcohol, yielding a tetrahedral intermediate

3. Transfer of a proton from one oxygen atom ato another yields a second tetrahedral intermediate and converts the OH group into a good leaving group.

4. Loss of a proton and expulson of H2O regenerates the acid catalyst and gives the ester product.



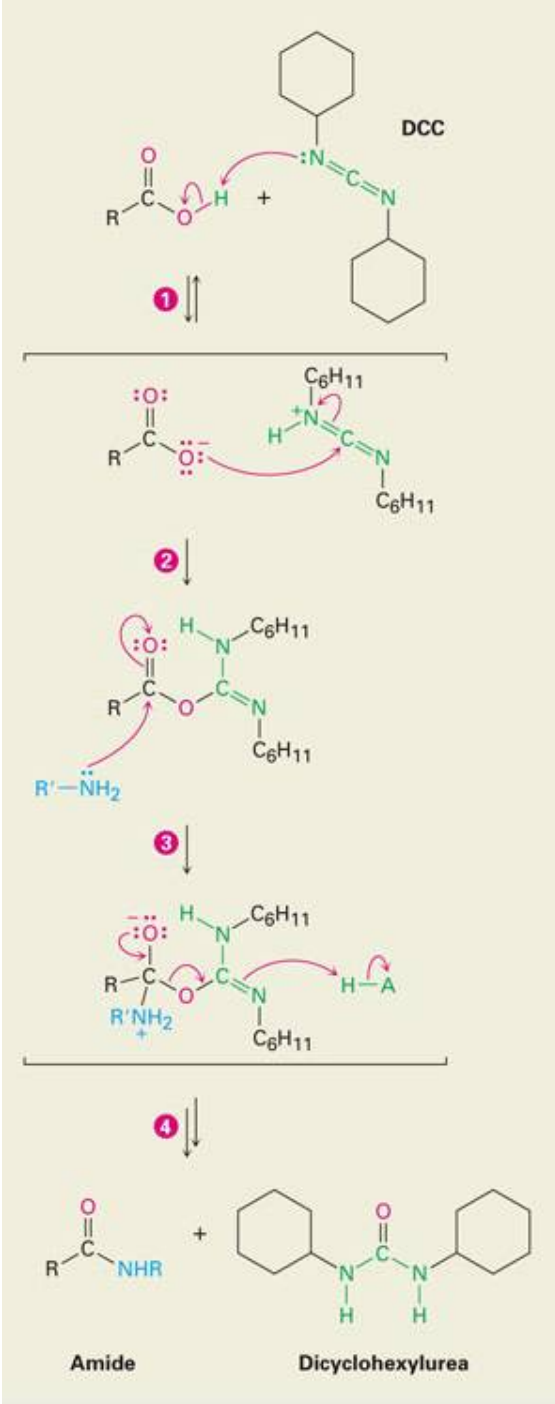
Carboxylic Acids into Amides

1. Dicyclohexylcarbidiimide is first protonated by the carboxylic acid to make it a better acceptor.

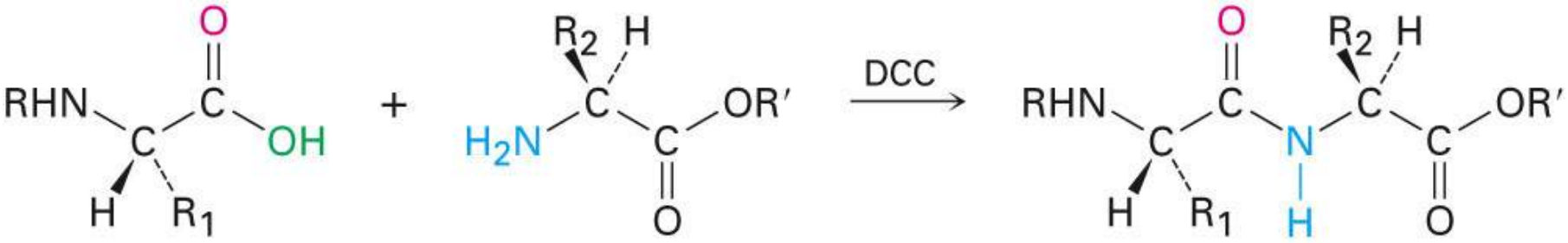
2. The carboxylate then adds to the protonated carbodiimide to yield a reactive acylating agent.

3. Nucleophilic attack of the amine on the acylating agent gives a tetrahedral intermediate.

4. The intermediate loses dicyclohexylurea and gives the amide.



Peptide Synthesis



Amino acid 1 **Amino acid 2** **A dipeptide**

Conversion of Carboxylic Acids into Alcohol