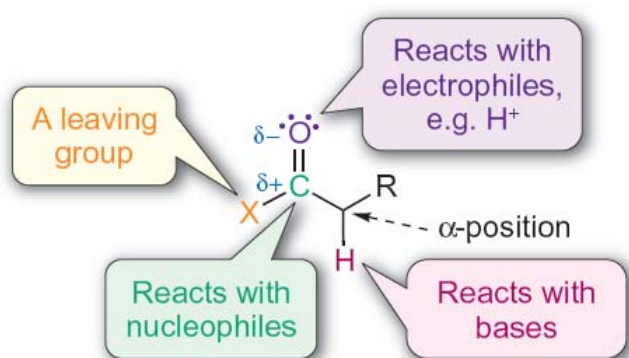


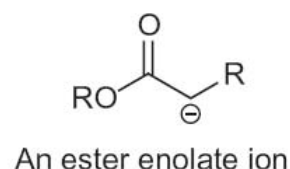
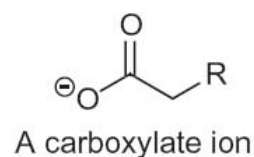
# Carboxylic acids and derivatives: nucleophilic acyl substitution and $\alpha$ -substitution reactions

## 24.1 Structure and reactions of carboxylic acids and derivatives

- Carboxylic acids and carboxylic acid derivatives (acyl chlorides, acid anhydrides, esters, and amides) have a C=O bond linked to an electronegative oxygen, nitrogen, or halogen atom.
- The C=O bond is polar and the electrons are attracted to the oxygen atom—the oxygen atom reacts with electrophiles and the carbon atom reacts with nucleophiles.
- Deprotonation of a carboxylic acid forms a carboxylate ion, whereas deprotonation of an ester forms an ester enolate ion ( $H^+$  is lost from the  $\alpha$ -position).



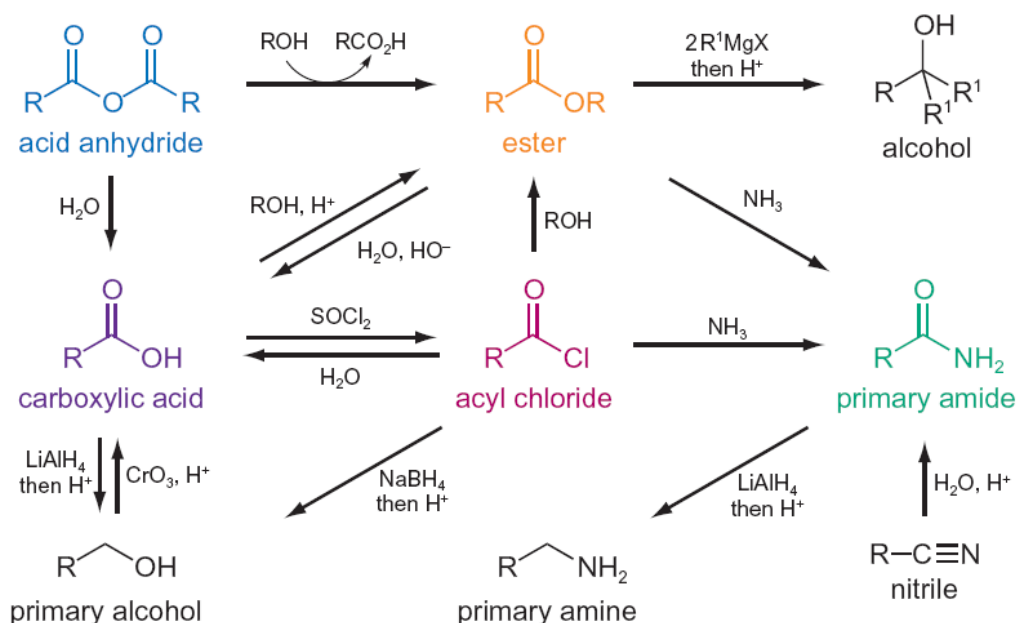
X = OH (carboxylic acid); Cl (acyl chloride);  
OCOR (acid anhydride); OR (ester);  
NH<sub>2</sub>, NHR, or NR<sub>2</sub> (amide)



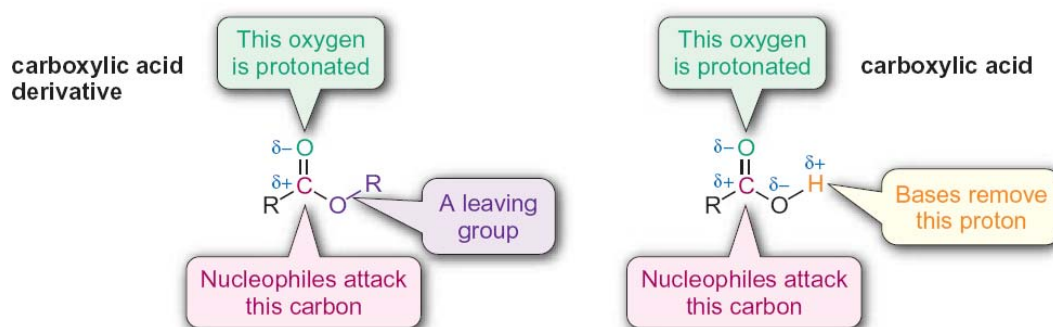
- Carboxylic acids undergo a limited number of nucleophilic substitution reactions—many nucleophiles act as bases and deprotonate the carboxylic acid, rather than attack the C=O bond.
- Carboxylic acid derivatives undergo nucleophilic acyl substitution reactions,  $\alpha$ -substitution reactions, and carbonyl–carbonyl condensation reactions.
- In a nucleophilic acyl substitution reaction the Cl, OCOR, OR, or NR<sub>2</sub> group bonded to C=O acts as the leaving group. (Aldehydes and ketones do not undergo nucleophilic acyl substitution reactions because the R and/or H groups bonded to C=O are very poor leaving groups.)
- The order of reactivity of carboxylic acid derivatives in nucleophilic acyl substitutions is: acyl chloride > acid anhydride > ester > amide.
- The order of reactivity of carbonyl compounds towards nucleophiles is: acyl chloride > acid anhydride > aldehyde > ketone > ester > amide.

## 24.2 Nucleophilic acyl substitution reactions

- Acyl chlorides (RCOCl), acid anhydrides (RCO<sub>2</sub>COR), esters (RCO<sub>2</sub>R), and amides (RCONH<sub>2</sub>) are called carboxylic acid derivatives because they can be prepared from a carboxylic acid (RCO<sub>2</sub>H).
- Carboxylic acids and derivatives are useful compounds in synthesis because they can be converted into various functional groups. To convert one carboxylic acid derivative into another requires a nucleophilic acyl substitution reaction.

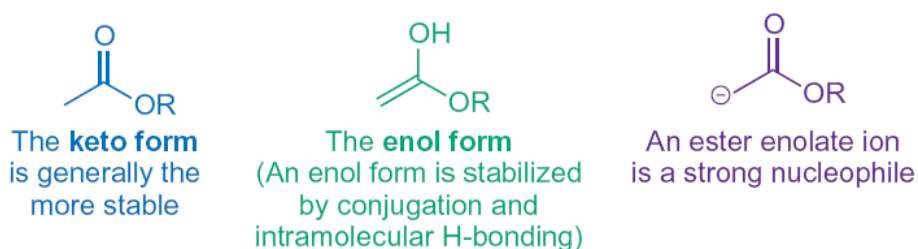


- Protonation of the C=O bond in a carboxylic acid or derivative converts it into a stronger electrophile, which reacts more rapidly with nucleophiles.

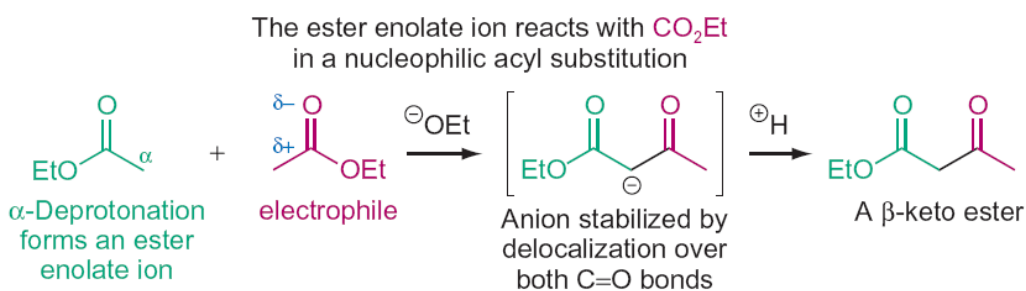


### 24.3 $\alpha$ -Substitution and carbonyl–carbonyl condensation reactions

- For carboxylic acids and derivatives, the keto form is usually more stable than the enol form. The enol form and, particularly the enolate ion, are good nucleophiles that react with electrophiles in  $\alpha$ -substitution reactions.

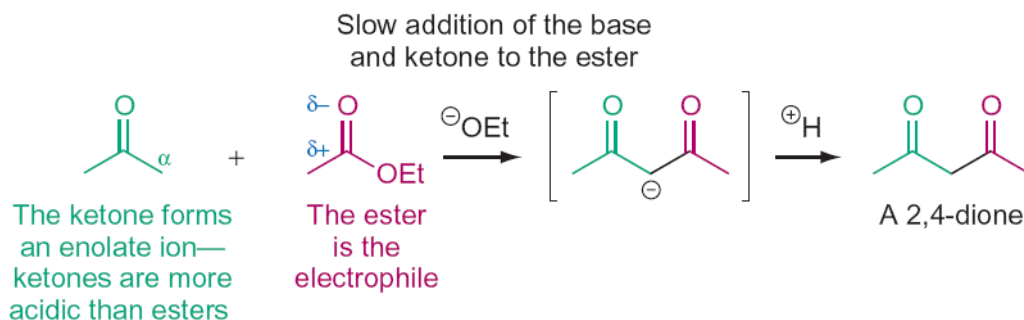


- $\alpha$ -Bromination of carboxylic acids using a mixture of  $\text{PBr}_3$  and  $\text{Br}_2$  is called the Hell–Volhard–Zelinsky (HVZ) reaction.
- Reaction of two molecules of the *same* ester to form a  $\beta$ -keto ester is called a Claisen condensation.

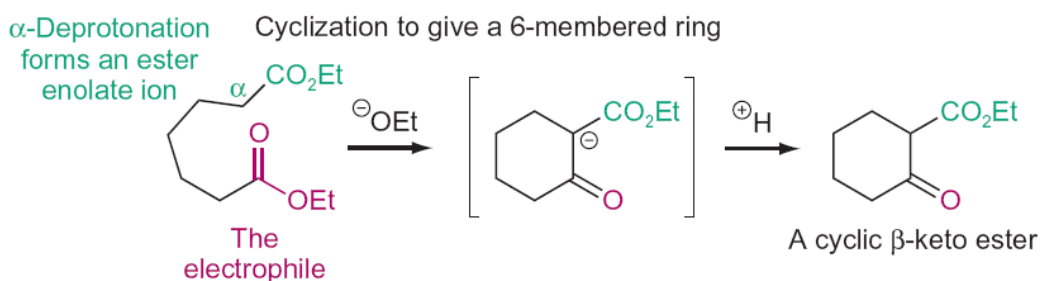


- Reactions of two *different* ester molecules are called crossed (mixed) Claisen condensations.

- Related condensation reactions take place between an ester and an aldehyde or ketone.



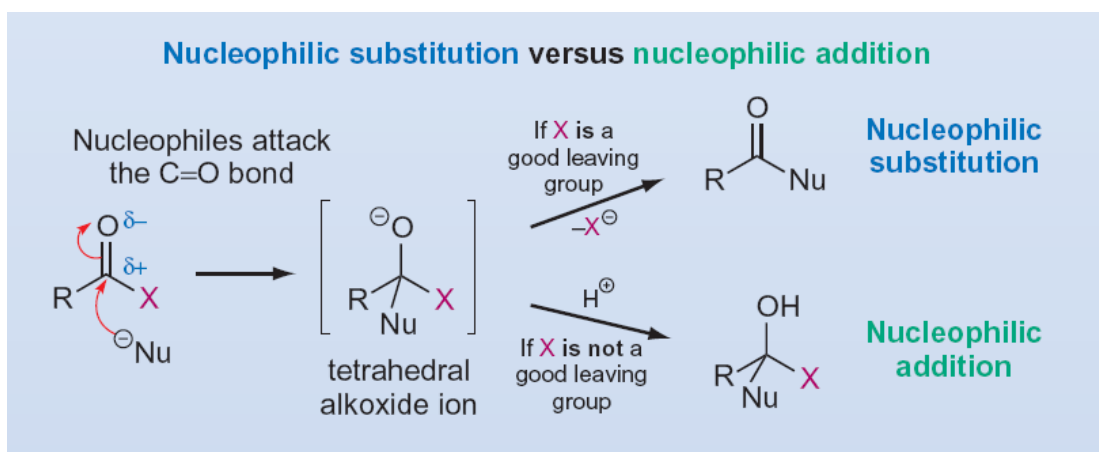
- When a molecule containing two ester groups reacts with itself, this is called an intramolecular Claisen condensation or a Dieckmann reaction.



## Learning outcomes

By the end of this chapter you should be able to do the following.

- Recognize carboxylic acids, acyl chlorides, acid anhydrides, esters, and amides.
- Understand how carboxylic acids and derivatives react with nucleophiles,  $H^+$ , or a base.
- Draw a general mechanism for a nucleophilic acyl substitution reaction and explain why carboxylic acid derivatives react with nucleophiles in substitution reactions rather than addition reactions.



- Explain why carboxylic acid derivatives are not equally reactive to nucleophiles.
- Draw a general mechanism for an  $\alpha$ -substitution reaction and a carbonyl-carbonyl condensation reaction of a carboxylic acid derivative.
- Draw mechanisms of nucleophilic acyl substitution reactions of carboxylic acids using the following reagents: ROH,  $H^+$  (catalyst);  $SOCl_2$ ;  $NH_3$  (heat).
- Draw mechanisms of nucleophilic acyl substitution reactions of acyl chlorides using the following reagents:  $H_2O$ ; ROH;  $NaBH_4$  then  $H^+$ ;  $NH_3$  (two equivalents);  $RMgX$  (two equivalents) then  $H^+$ .
- Draw mechanisms of nucleophilic acyl substitution reactions of acid anhydrides using the following reagents:  $H_2O$ ; ROH;  $LiAlH_4$  then  $H^+$ ;  $NH_3$  (two equivalents).
- Draw mechanisms of nucleophilic acyl substitution reactions of esters using the following reagents:  $H_2O$ ,  $H^+$ ;  $H_2O$ ,  $HO^-$  then  $H^+$ ;  $LiAlH_4$  then  $H^+$ ;  $NH_3$ ;  $RMgX$  (two equivalents) then  $H^+$ .
- Draw mechanisms of nucleophilic acyl substitution reactions of amides using the following reagents:  $H_2O$ ,  $H^+$  (heat).
- Understand how nitriles are hydrolysed to form carboxylic acids.
- Discuss keto-enol tautomerism in carboxylic acid derivatives and understand the factors that influence the stability of keto and enol forms.
- Draw the mechanism of  $\alpha$ -bromination of a carboxylic acid using  $PBr_3$  and  $Br_2$ .
- Explain why esters are less acidic than aldehydes or ketones.

- Draw mechanisms for Claisen condensations, crossed (mixed) Claisen condensations, and intramolecular Claisen condensations (Dieckmann reactions).
- Predict the structure of a product derived from a nucleophilic acyl substitution, an  $\alpha$ -substitution, or a carbonyl–carbonyl condensation reaction of a carboxylic acid derivative.
- Propose reagents for converting a carboxylic acid derivative into a product derived from a nucleophilic acyl substitution, an  $\alpha$ -substitution, or a carbonyl–carbonyl condensation reaction.