the α-hydrogens of an ester are weakly acidic and can be removed by a strong base. The product is an ester enolate.

$$-\overset{H}{\overset{|_{\alpha}}{\subset}}C\overset{O}{\overset{\text{base}}{\longleftarrow}}\left[-\overset{\Box}{\overset{\circ}{\subset}}C\overset{O}{\overset{\circ}{\subset}}C\overset{O}{\overset{\bullet}{\smile}}C\overset{\bullet}{\overset{\bullet}{\smile}}C\overset{O}{\overset{\bullet}{\smile}}C\overset{O}{\overset{\bullet}{\smile}}C\overset{O}{\overset{\bullet}{\smile}}C\overset{O}{\overset{\bullet}{\smile}}C\overset{O}{\overset{\bullet}{\smile}}C\overset{O}{\overset{\bullet}{\smile}}C\overset{O}{\overset{\bullet}{\smile}}C\overset{O}{\overset{\bullet}{\smile}}C\overset{O}{\overset{\bullet}{\smile}}C\overset{O}{\overset{\bullet}{\smile}}C\overset{\bullet}{\smile}C\overset$$

resonance contributors to an ester enolate

1

Common bases used for this purpose are sodium alkoxides (RO Na+). The ester enolate, once formed, can act as a carbon nucleophile and add to the carbonyl group of another ester molecule. This reaction is called the Claisen condensation. It is a way of making b-keto esters.

Treatment of ethyl acetate with sodium ethoxide in ethanol produces the β -keto ester, ethyl acetoacetate:

CH₃C — OCH₂CH₃ + H — CH₂ — C — OCH₂CH₃
$$\frac{1. \text{ NaOCH}_2\text{CH}_3}{\text{in ethanol}}$$
 ethyl acetate

O O O CH₃C — CH₂ — C — OCH₂CH₃ + CH₃CH₂OH ethyl acetoacetate (ethyl 3-oxobutanoate)

<u>つ</u>

The Claisen condensation takes place in three steps (Mechanism)

3

To complete the Claisen condensation, the solution is acidified, to regenerate the β -keto ester from its enolate anion

Step 1. CH₃C — OCH₂CH₃ + Na⁺ OCH₂CH₃
$$\Longrightarrow$$
 sodium ethoxide

O
Na⁺ CH₂COCH₂CH₃ + CH₃CH₂OH
ester enolate

Step 2. CH₃C — OCH₂CH₃ + CH₂COCH₂CH₃ \Longrightarrow

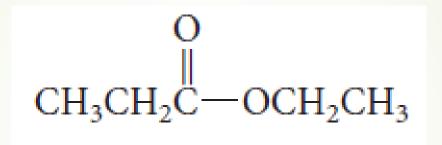
CH₃C — OCH₂CH₃ \Longrightarrow CH₃CCH₂COCH₂CH₃ + OCH₂CH₃

CH₂C — OCH₂CH₃ \Longrightarrow CH₃CCH₂COCH₂CH₃ + OCH₂CH₃

B-keto ester

O
O
CH₃C — CH₂COCH₂CH₃ + CH₃CH₂OH
enolate ion of a β-keto ester

Example: Identify the product of the Claisen condensation of ethyl propanoate



Solution The product is

$$CH_3CH_2C \overset{O}{\overset{\beta}{\overset{\alpha}{\subset}}} \overset{\alpha}{\overset{\beta}{\overset{\alpha}{\subset}}} H \overset{\parallel}{\overset{C}{\leftarrow}} COCH_2CH_3$$

The Claisen condensation, like the aldol condensation, is useful for making new carbon-carbon bonds. The resulting β -keto esters can be converted to a variety of useful products. For example, ethyl acetate can be converted to ethyl butanoate by the following sequence

$$\begin{array}{c} O & O \\ \parallel & \parallel \\ \text{CH}_3\text{CH} = \text{CHCOCH}_2\text{CH}_3 \xrightarrow{\text{H}_2} \text{CH}_3\text{CH}_2\text{CH}_2\text{COCH}_2\text{CH}_3 \\ \text{ethyl 2-butenoate} & \text{ethyl butanoate} \end{array}$$

6

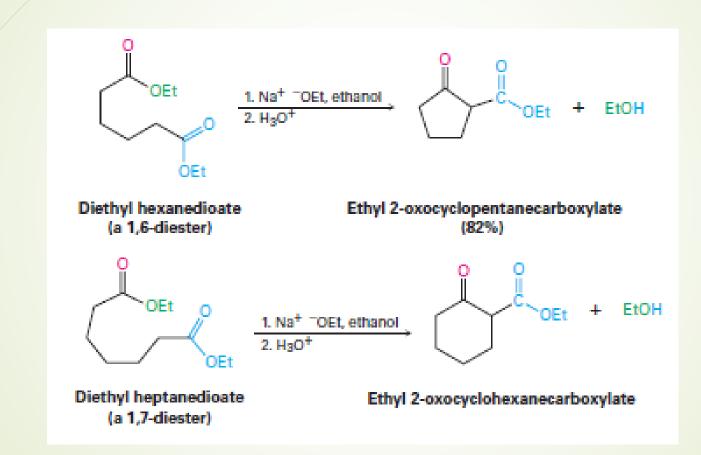
Mixed Claisen Condensations

The mixed Claisen condensation of two different esters

Mixed Claisen-like reactions can also be carried out between an ester and a ketone, resulting in the synthesis of a *b*-diketone.

Intramolecular Claisen Condensations: The Dieckmann Cyclization

Intramolecular Claisen condensations can be carried out with diesters



Dieckmann cyclization, the reaction works best on 1,6-diesters and 1,7-diesters. Intramolecular Claisen cyclization of a 1,6-diester gives a five-membered cyclic *b*-keto ester, and cyclization of a 1,7-diester gives a six-membered cyclic *b*-keto ester.

8

Mechanism of the Dieckmann cyclization of a 1,7-diester to yield a cyclic b-keto ester product.

- Base abstracts an acidic α proton from the carbon atom next to one of the ester groups, yielding an enolate ion.
- Intramolecular nucleophilic addition of the ester enolate ion to the carbonyl group of the second ester at the other end of the chain then gives a cyclic tetrahedral intermediate.
- Loss of alkoxide ion from the tetrahedral intermediate forms a cyclic β-keto ester.

Deprotonation of the acidic β-keto ester gives an enolate ion . . .

5 ... which is protonated by addition of aqueous acid at the end of the reaction to generate the neutral B-keto ester product.

Na+-OEs

2

3

4

5 H₂O+