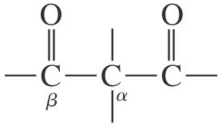
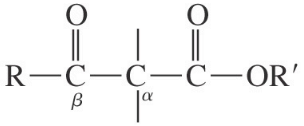
Azido Deribatuak(b)
Konposatu β-Dikarbonilodunak

♦ Sarrera

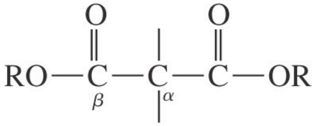
- Bi karbonilo talde hirugarren karbono batez bananduak



The **β-dicarbonyl system**

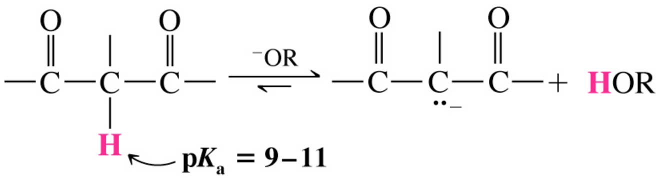


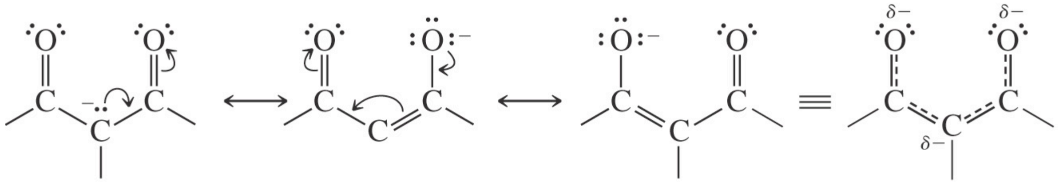
A **β-keto ester** (Section 19.2)



A **malonic ester** (Section 19.4)

- Tarteko karbonoan (Cα) dauden hidrogenoak azidoak dira (pK_a = 9-10)
  - ★ Enolatoa egonkortua dago erresonantziz bi aldeetatik

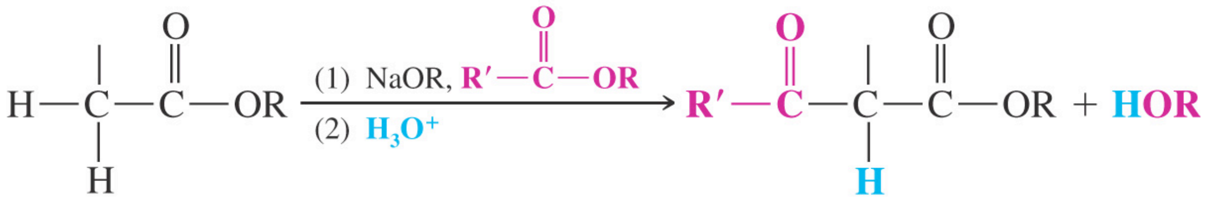




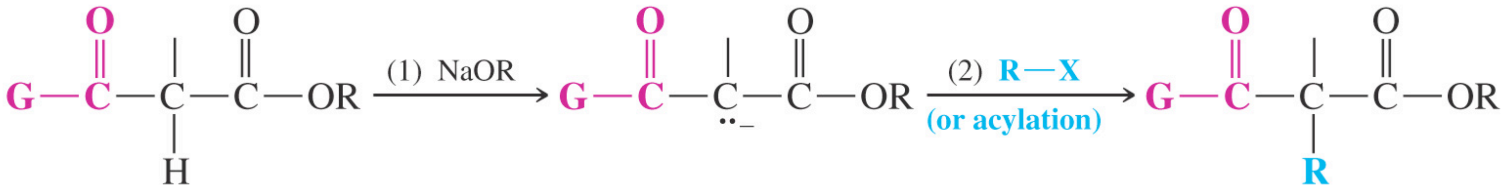
Contributing resonance structures

Resonance hybrid

- **Konposatu β–dikarbonilodunak bi esterren arteko Claisen-en kondentsazioz lor daitezke**

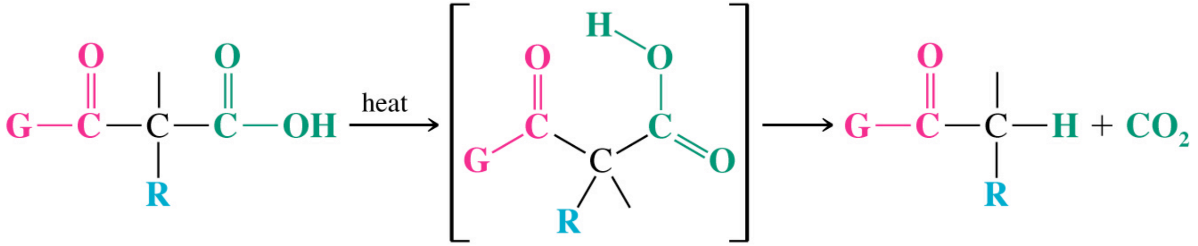


- **Konposatu β-dikarbonilodunak sintesi *azetilazetikoan* eta *malonikoan* erabiltzen dira**



Acetoacetic ester synthesis, $G = CH_3$
Malonic ester synthesis, $G = RO$

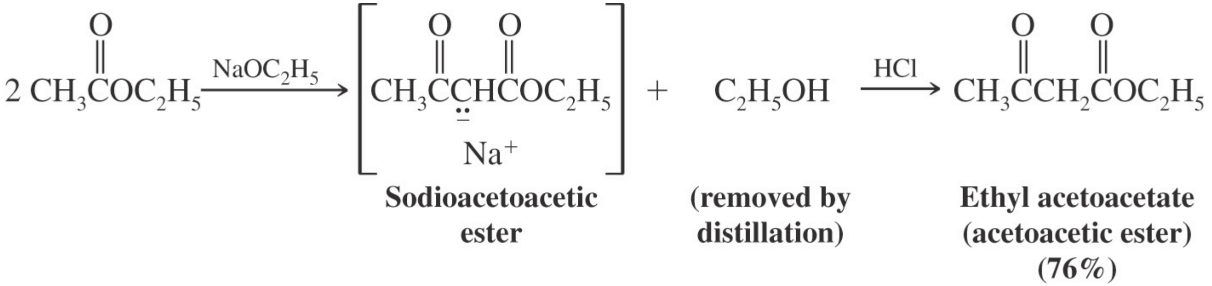
- **Sintesi *azetilazetikoan* eta *malonikoan* azken urratsa dekarboxilazioa da**



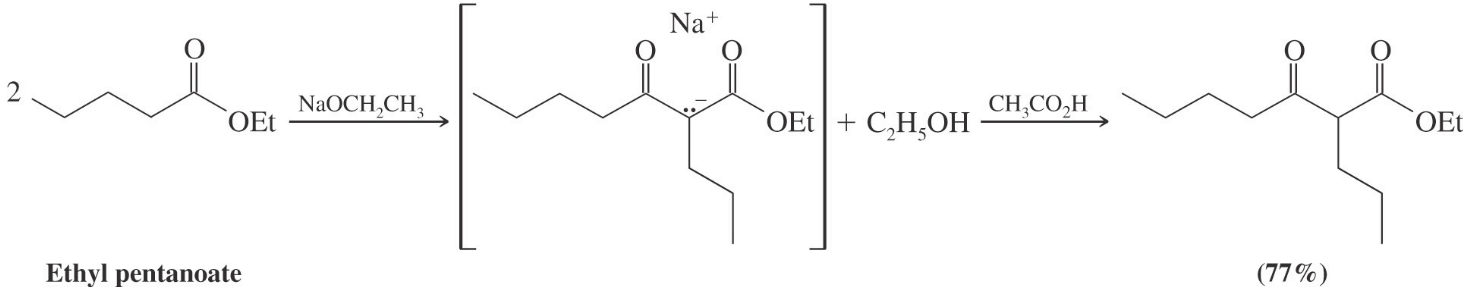
(Section 18.10)

♦ Claisen-en Kondentsazioa: β-Zeto Esterren Sintesia

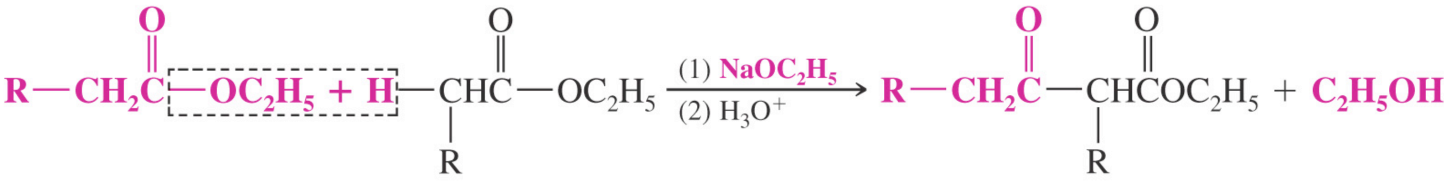
- ➡ Etil azetatoak sodio etoxidoarekin ester azetoazetikoa ematen du



- ➡ Antzeko adibide bat ethyl pentanoatoarekin



- Orotara, ester batek hidrogenoa galtzen du eta besteak etoxido taldea



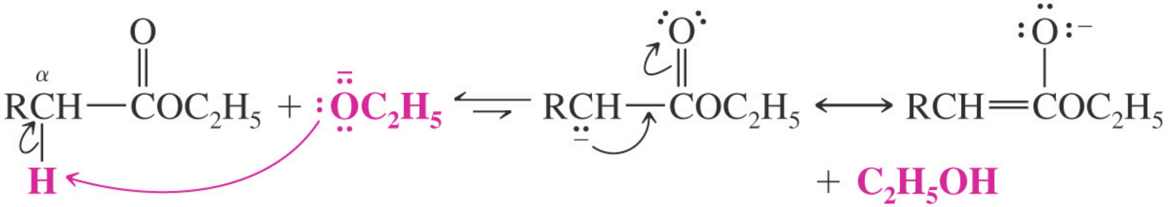
$$R-CH_2\overset{O}{\overset{\|}{C}}-OC_2H_5 + H-\underset{R}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow[(2)\ H_3O^+]{(1)\ NaOC_2H_5} R-CH_2\overset{O}{\overset{\|}{C}}-\underset{R}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}OC_2H_5 + C_2H_5OH$$

(R may also be H)

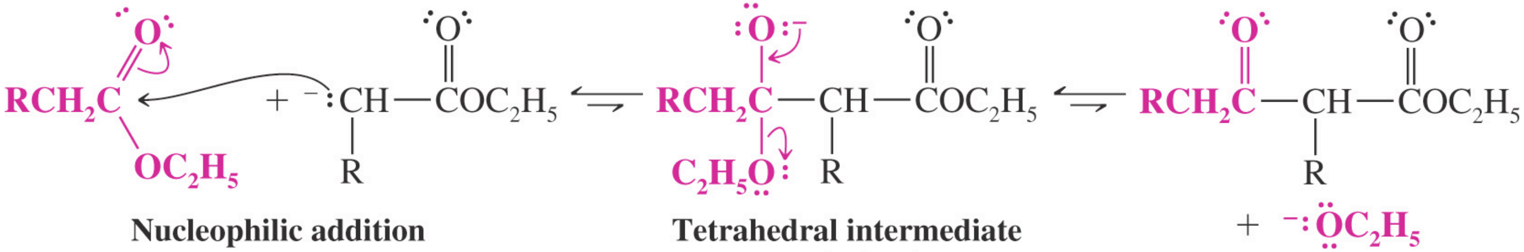
A β-keto ester

- Erreakziobidea adizio nukleozalea-eliminazioa da

Step 1



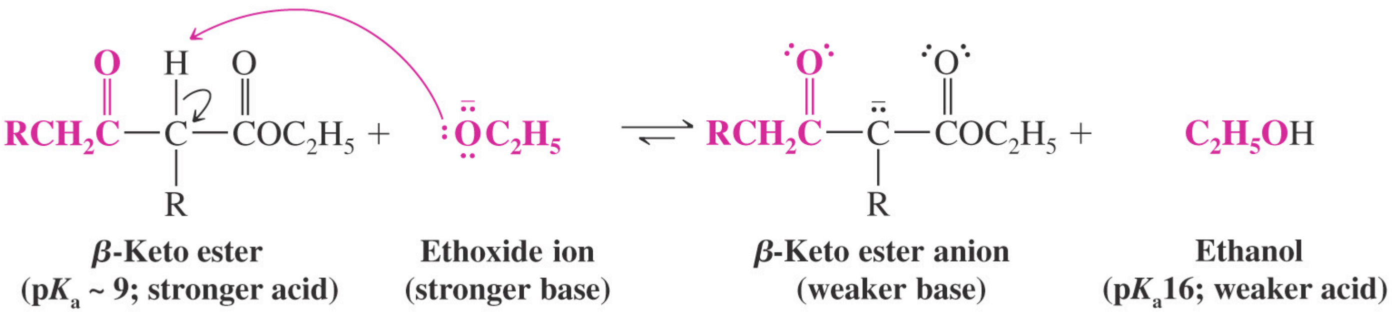
Step 2



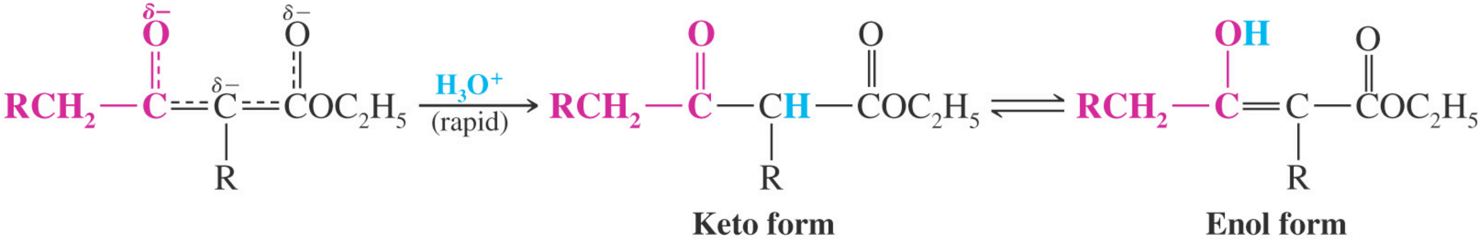
Nucleophilic addition

Tetrahedral intermediate and elimination

Step 3



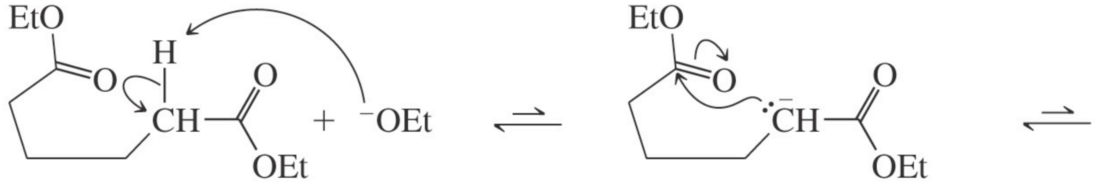
Step 4



$$RCH_2-C(=O)-CH(R)-COOC_2H_5 \rightleftharpoons RCH_2-C(OH)=C(R)-COOC_2H_5$$

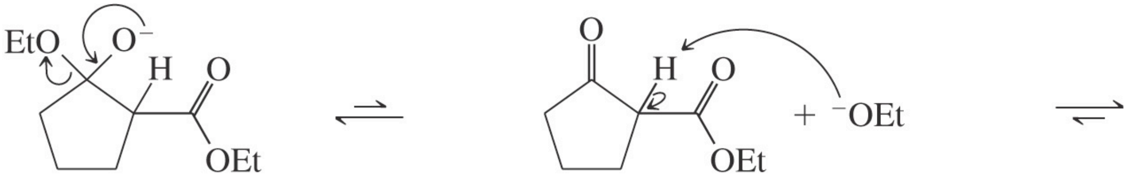
- **Alkoxidoaren eta esterraren alkil taldeak berdinak izan behar dute**
  - ★ **Desberdinak badira, transesterifikazioa eman daiteke (nahasteak)**
- **α-Karbonoan Hidrogeno bakarra duten esterrak ezin dute Claise-en erreakzioa eman (ikusi erreakziobidearen 3. urratsa)**

- **Dieckmann-en kondentsazioa Claisen-en erreakzioaren bertsio intramolekularra da**
  - ★ **Modu honetara 5eko eta 6ko eraztunak soilik lor daitezke**



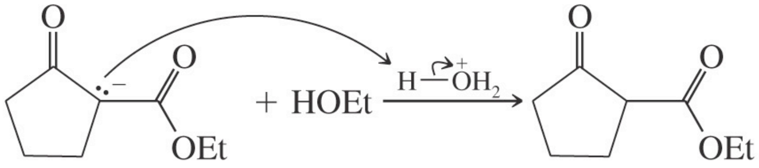
Ethoxide anion removes an α hydrogen.

The enolate anion attacks the carbonyl group at the other end of the chain.



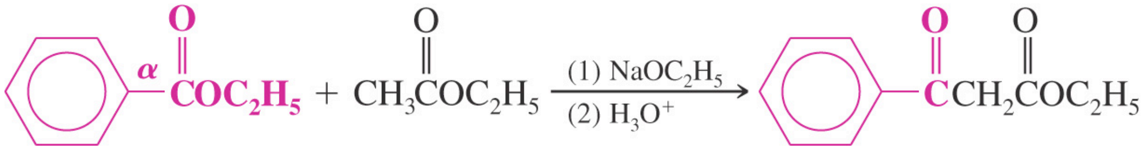
An ethoxide anion is expelled.

The ethoxide anion removes the acidic hydrogen located between two carbonyl groups. This favorable equilibrium drives the reaction.



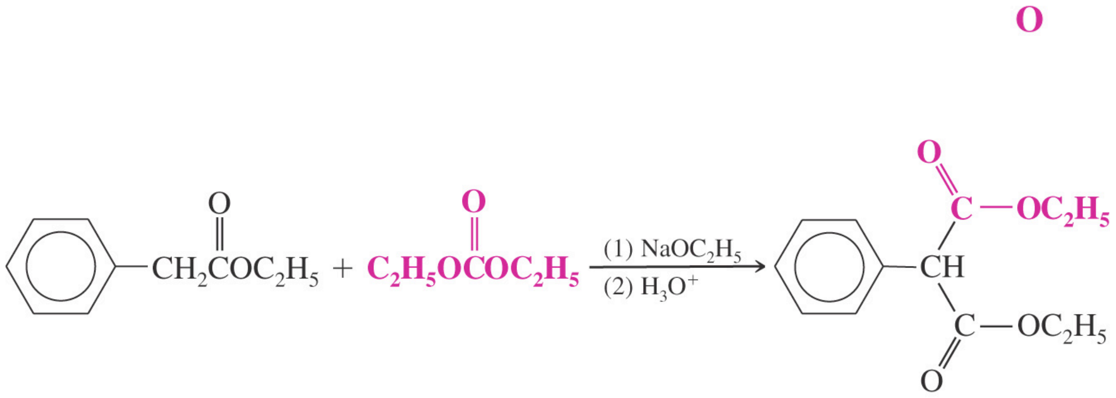
Addition of aqueous acid rapidly protonates the anion, giving the final product.

- **Claisen-en Cross-Kondentsazioa**
  - ➡ **Erabilgarria da esterretako batek hidrogenorik ez duenean Cα-n**



Ethyl benzoate
(no α hydrogen)

Ethyl benzoylacetate
(60%)

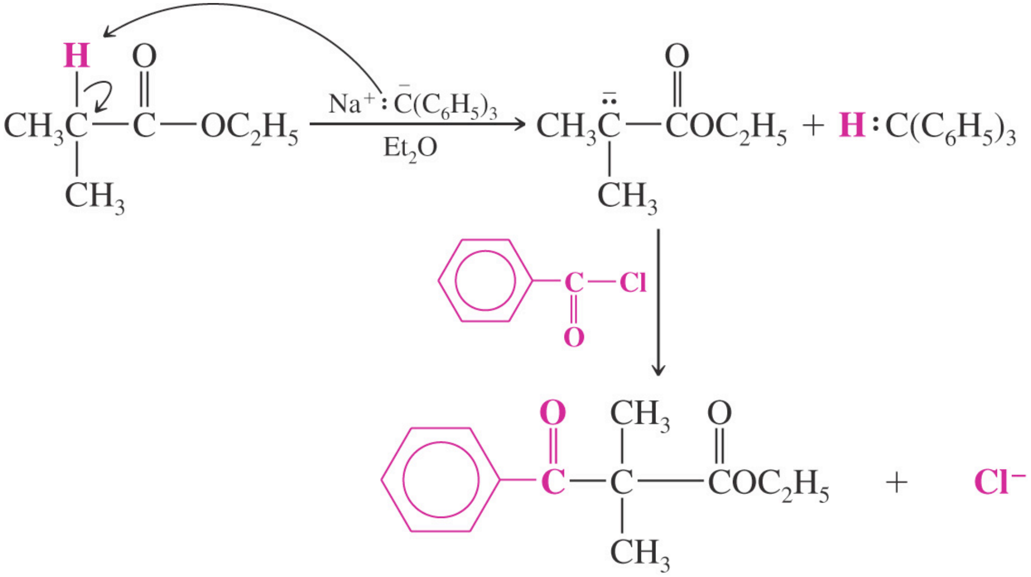


Ethyl phenylacetate

Diethyl carbonate
(no α carbon)

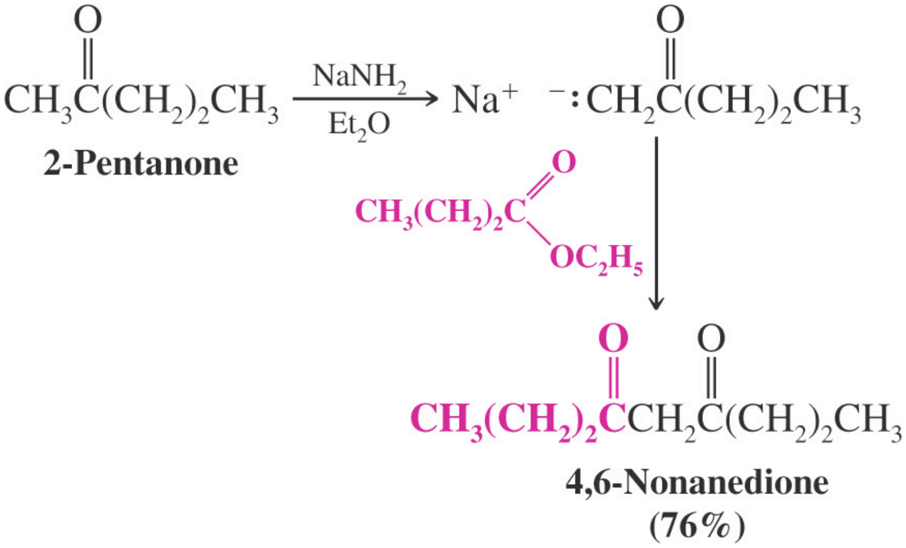
Diethyl phenylmalonate
(65%)

- α-Posizioan hidrogeno bakar bat duten esterrek ere eman dezakete Claisen-en kondentsazioa baldin eta base sendo bat eta azilatzaile bezela azido kloruro bat erabiltzen badira



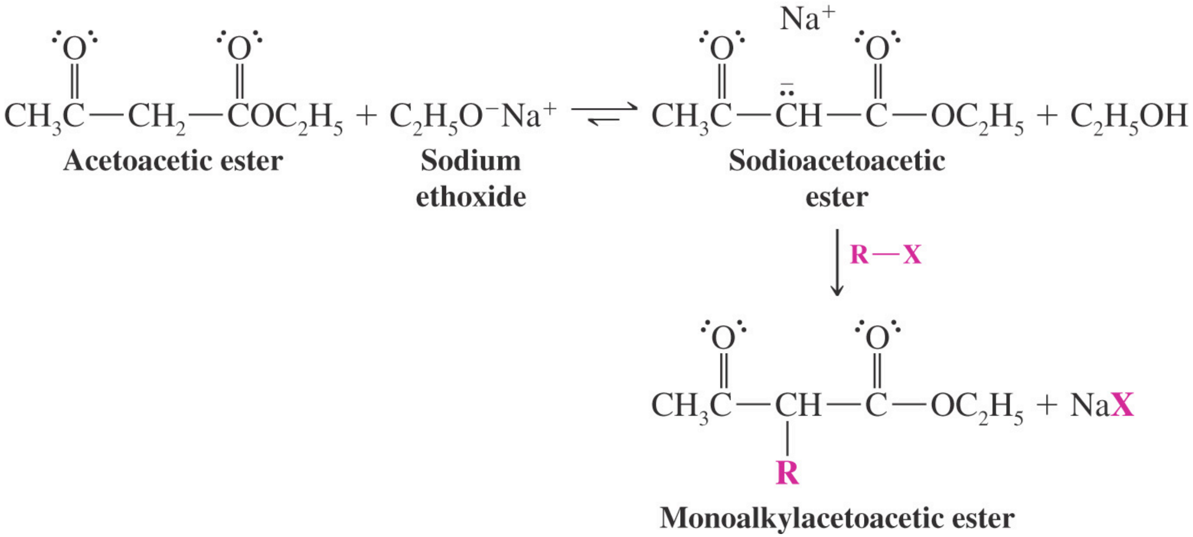
Ethyl 2,2-dimethyl-3-oxo-3-phenylpropanoate

- **Beste Karbanioien Azilazioa**
  - ➡ **Zetonen enolatoak ere azila daitezke konposatu β-dikarbonilodunak emanez**

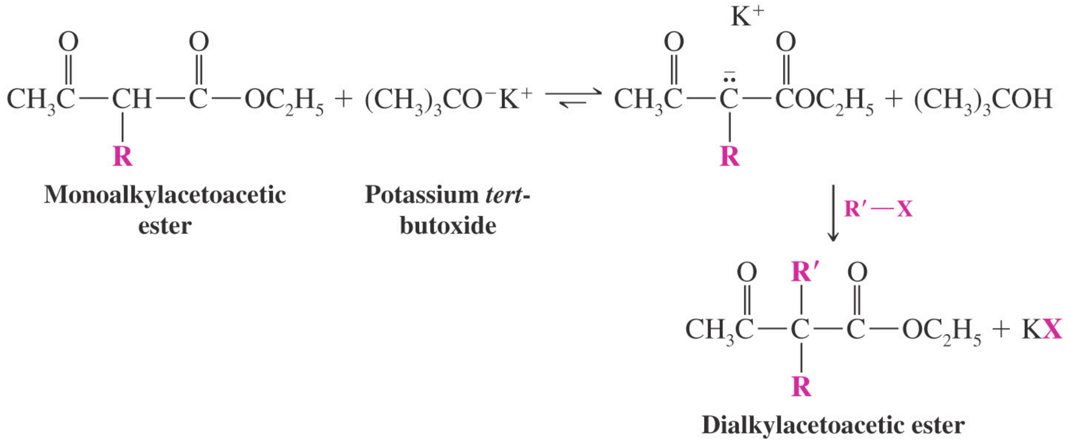


♦ Sintesi Azetoazetikoa: Metil Zetonen Lorpena

- **Lehen urratsa: Ester azetoazetiko baten alkilazioa**



- **Bigarren alkilazio bat ere eman daiteke, orain base sendoagoa erabiliz (*tert*-butoxidoa)**



$$CH_3\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{CH}-\overset{\overset{O}{\|}}{C}-OC_2H_5 + (CH_3)_3CO^-K^+ \rightleftharpoons CH_3\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{\overset{K^+}{\ddot{\bar{C}}}}-\overset{\overset{O}{\|}}{C}OC_2H_5 + (CH_3)_3COH$$

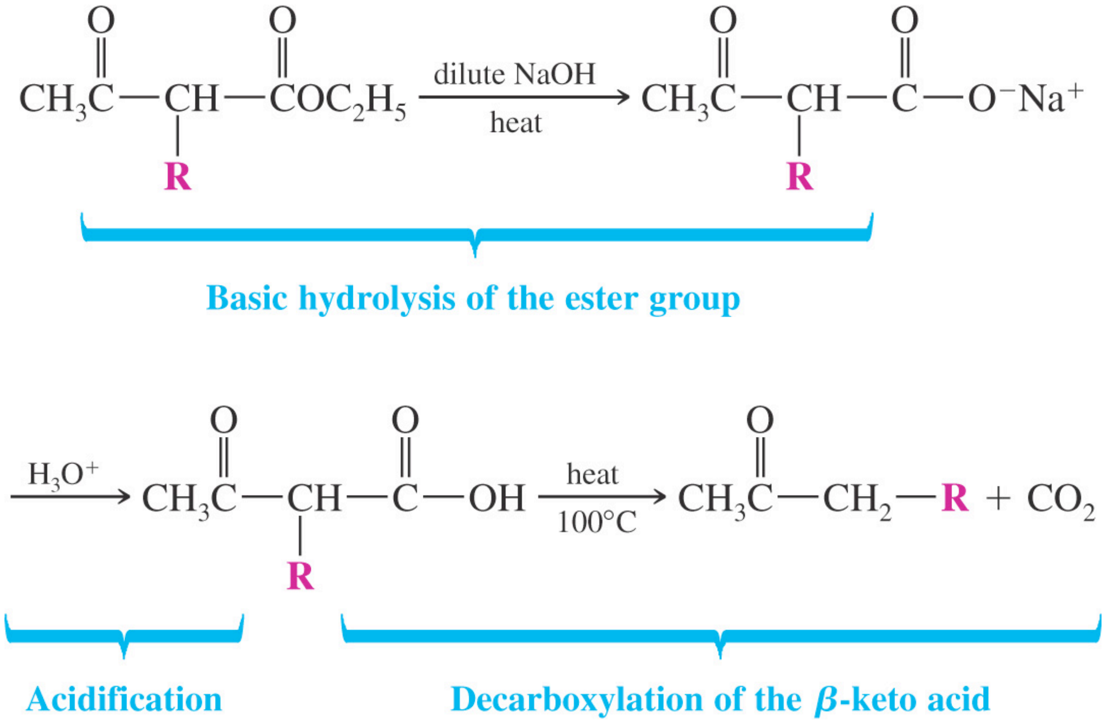
Monoalkylacetoacetic ester

Potassium *tert*-butoxide

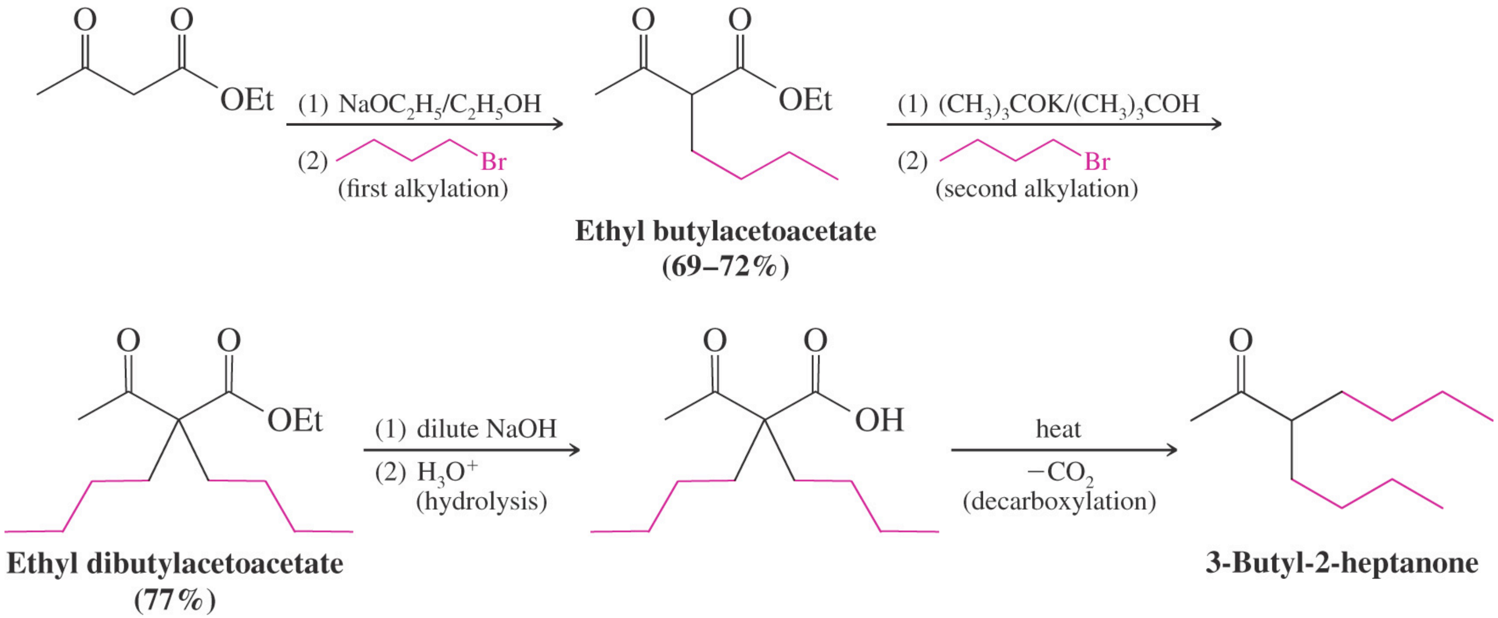
$$\xrightarrow{R'-X} CH_3\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{\overset{\overset{R'}{|}}{C}}-\overset{\overset{O}{\|}}{C}-OC_2H_5 + KX$$

Dialkylacetoacetic ester

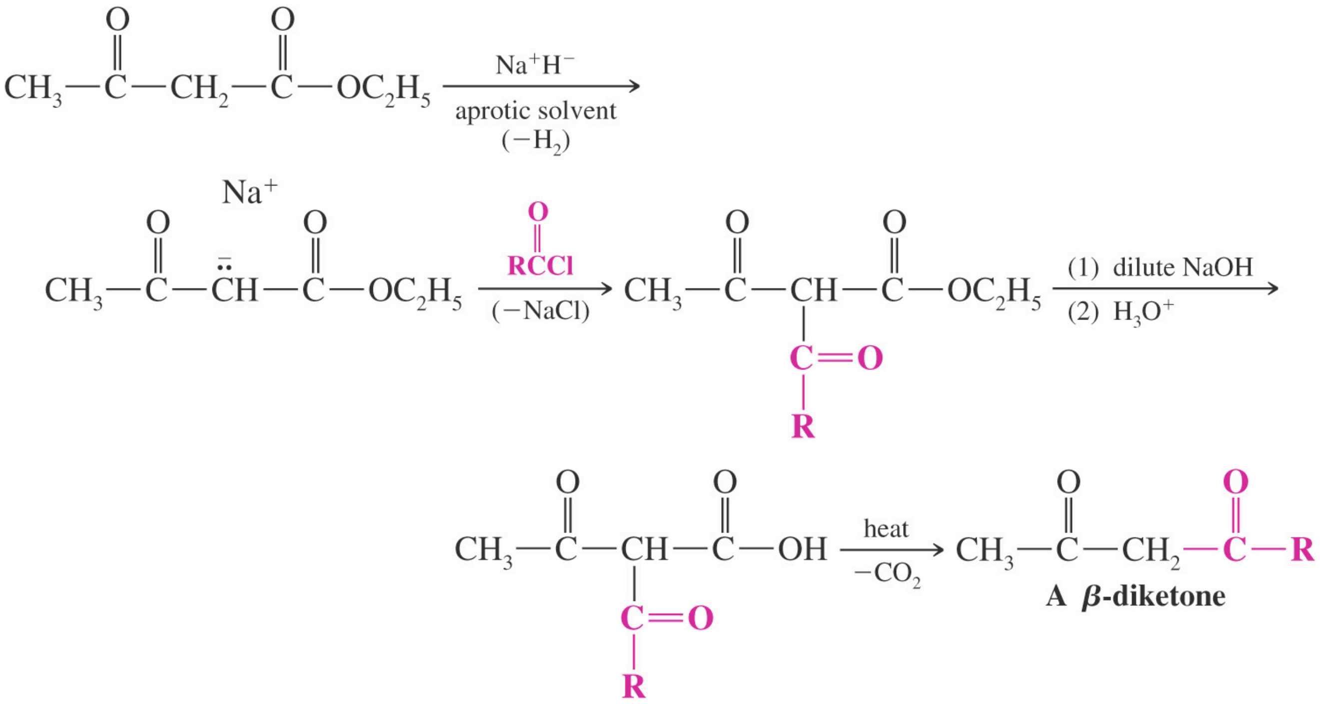
- **Esterraren hidrolisiak ematen duen β-zetoazidoa deskarboxilatu daiteke**
  - ★ **Produktua azetona ordezkatu bat da**



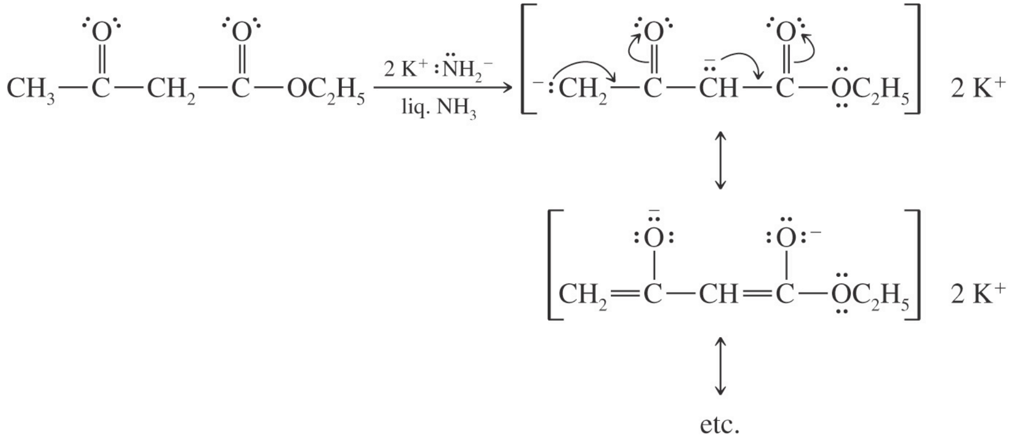
➡ Adibidea:


O
O
OEt
(1) NaOC2H5/C2H5OH
(2) Br
(first alkylation)
O
O
OEt
Ethyl butylacetoacetate
(69–72%)
(1) (CH3)3COK/(CH3)3COH
(2) Br
(second alkylation)
O
O
OEt
Ethyl dibutylacetoacetate
(77%)
(1) dilute NaOH
(2) H3O+
(hydrolysis)
O
O
OH
heat
−CO2
(decarboxylation)
O
3-Butyl-2-heptanone

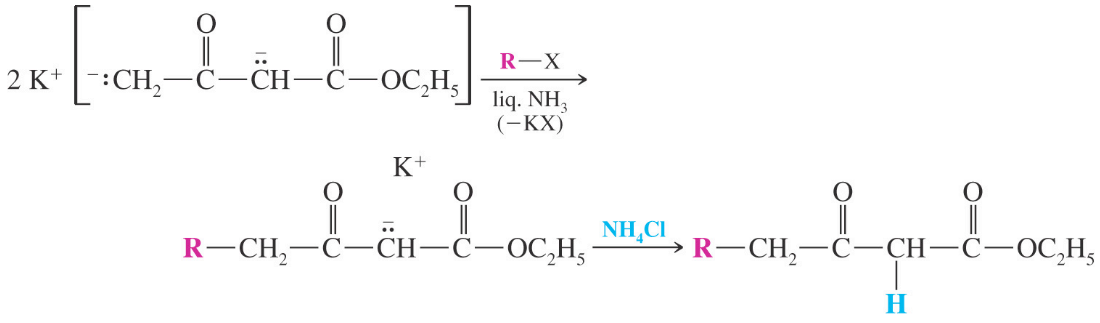
- **Azilazioa**
  - **Ester azetoazetikoaren anioia azilatua ere izan daiteke**
    - ★ **Orain DMF eta DMSO bezelako disolbatzaile aprotikoak erabili behar ditugu, alkoholak azilatuak izango lirateke**



- **Ester Azetoazetikoaren Dianioia: Muturreko Karbonoaren Alkilazioa**
  - ➡ **Dianioia sortzeko base sendo baten bi baliokide behar ditugu**

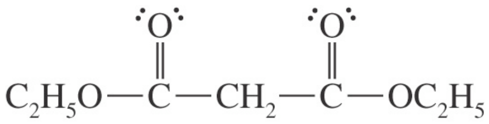


  - ➡ **Alkilazioa lehenik muturreko karbonoan ematen da**



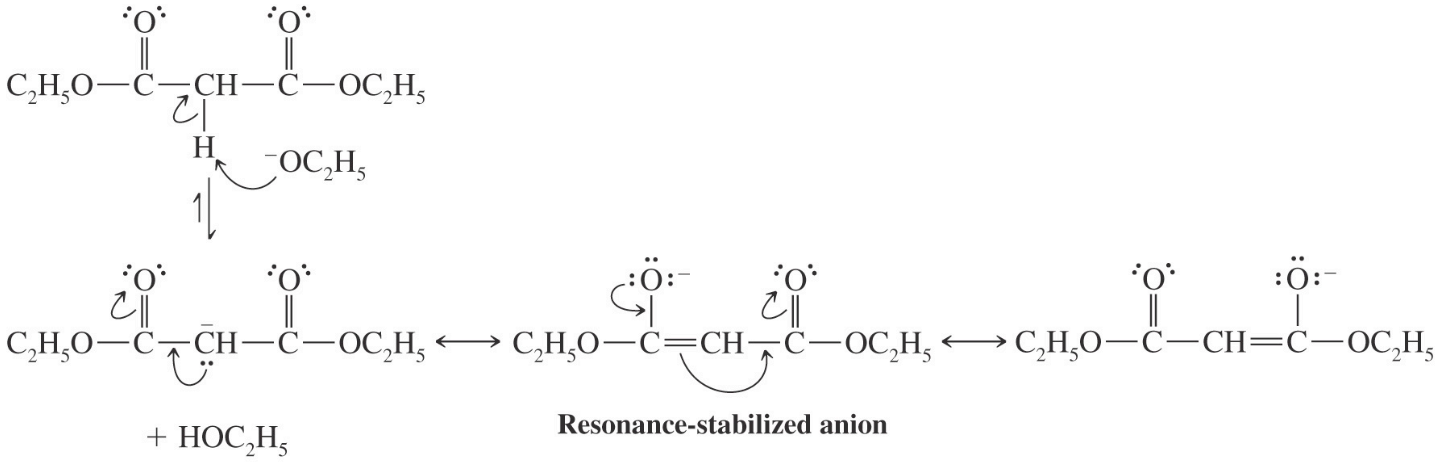
♦ Sintesi Malonikoa: Azido Azetikoen Sintesia

- ➡ **Aurrekoan bezelako urratsak: alkilazioa, hidrolisia, dekarboxilazioa**



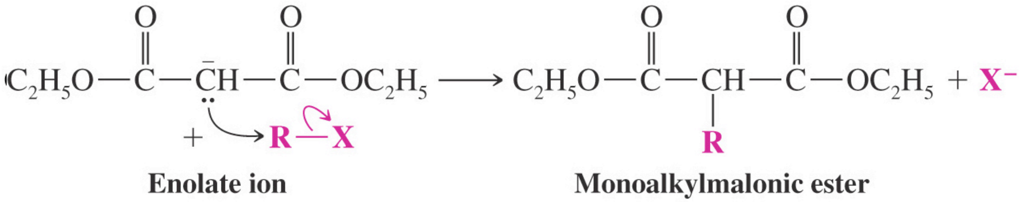
$$C_2H_5O-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5$$

Diethyl malonate
(a *β*-dicarboxylic acid ester)



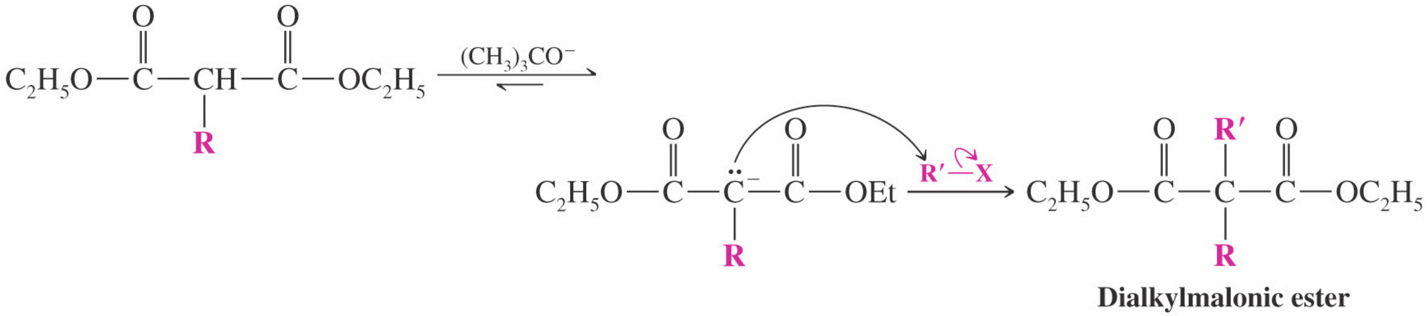
➡ 2. Urratsean anioia mono- edo dialilatu egiten da (*S_N2* erreakzioa*)*

Step 2 This enolate anion can be alkylated in an S_N2 reaction,



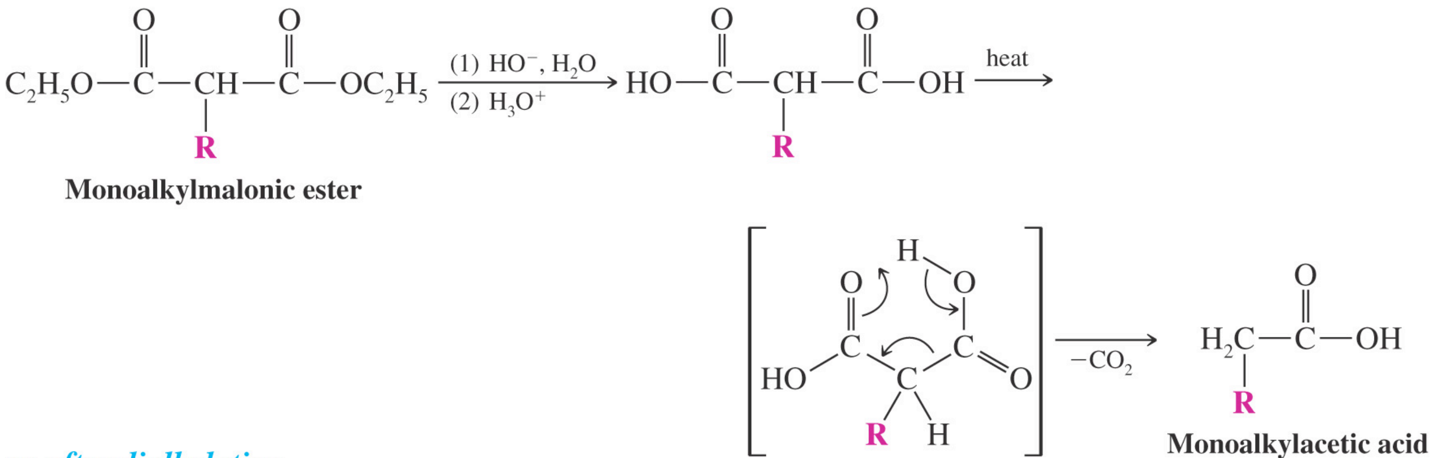
$$C_2H_5O-C(=O)-\overset{-}{C}H-C(=O)-OC_2H_5 + R-X \longrightarrow C_2H_5O-C(=O)-CH(R)-C(=O)-OC_2H_5 + X^-$$

and the product can be alkylated again if our synthesis requires it:

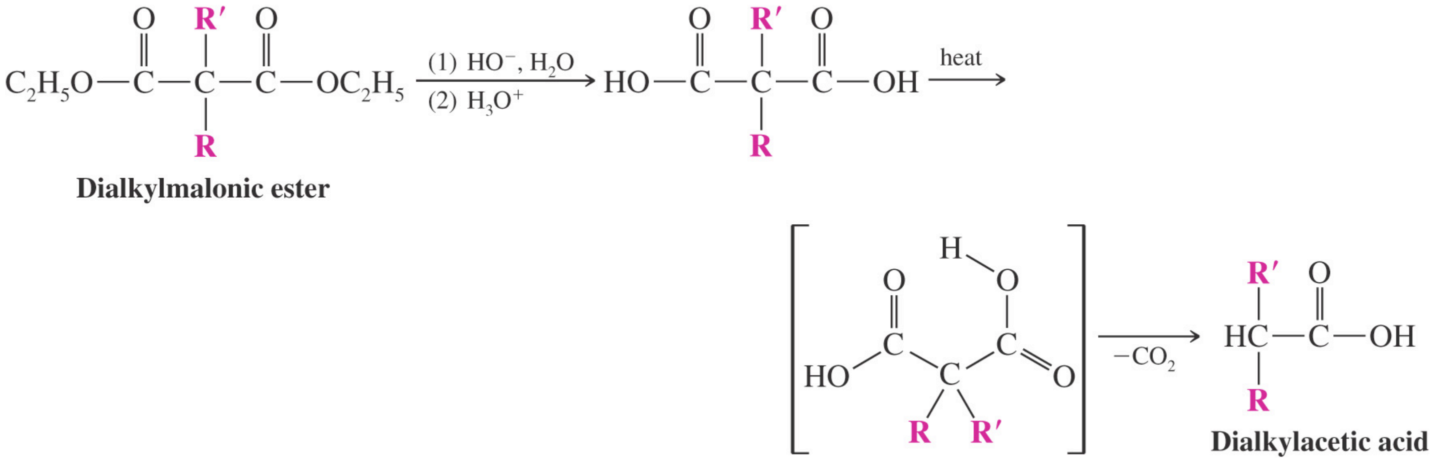


$$C_2H_5O-C(=O)-CH(R)-C(=O)-OC_2H_5 \xrightleftharpoons{(CH_3)_3CO^-} C_2H_5O-C(=O)-\overset{-}{C}(R)-C(=O)-OEt \xrightarrow{R'-X} C_2H_5O-C(=O)-C(R)(R')-C(=O)-OC_2H_5$$

➡ 3. Urratsean: Hidrolisia eta deskarboxilazioa

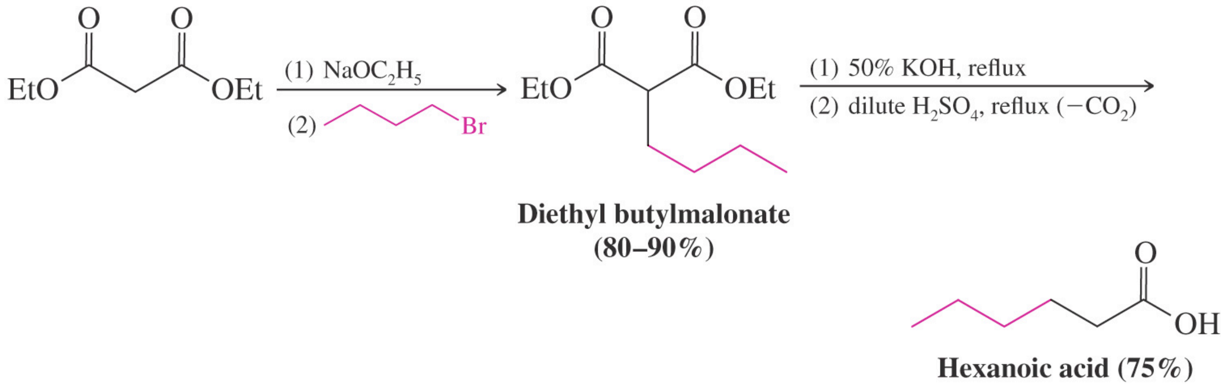


or after dialkylation,

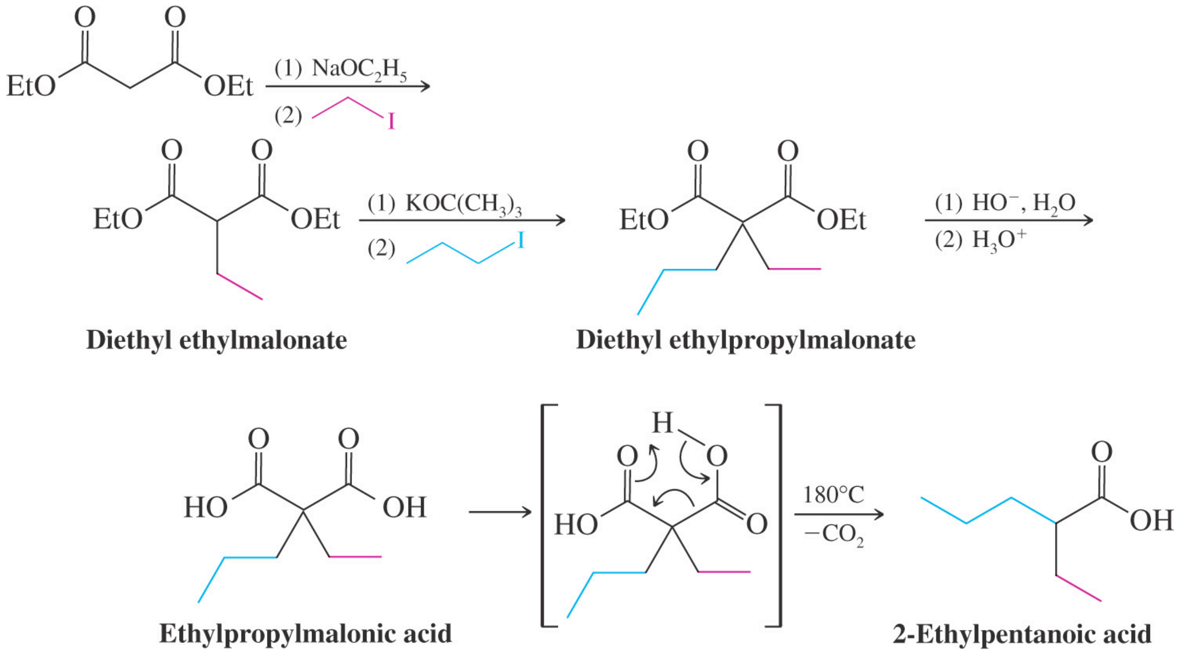


➡ Adibideak

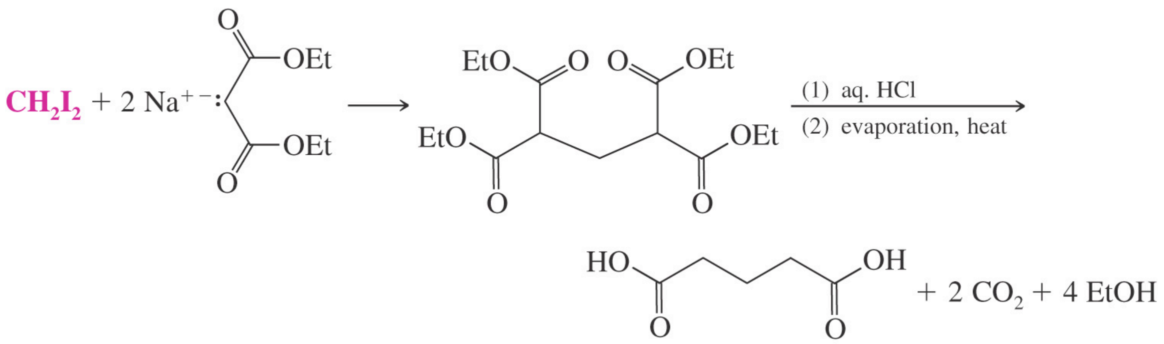
A Malonic Ester Synthesis of Hexanoic Acid



A Malonic Ester Synthesis of 2-Ethylpentanoic Acid

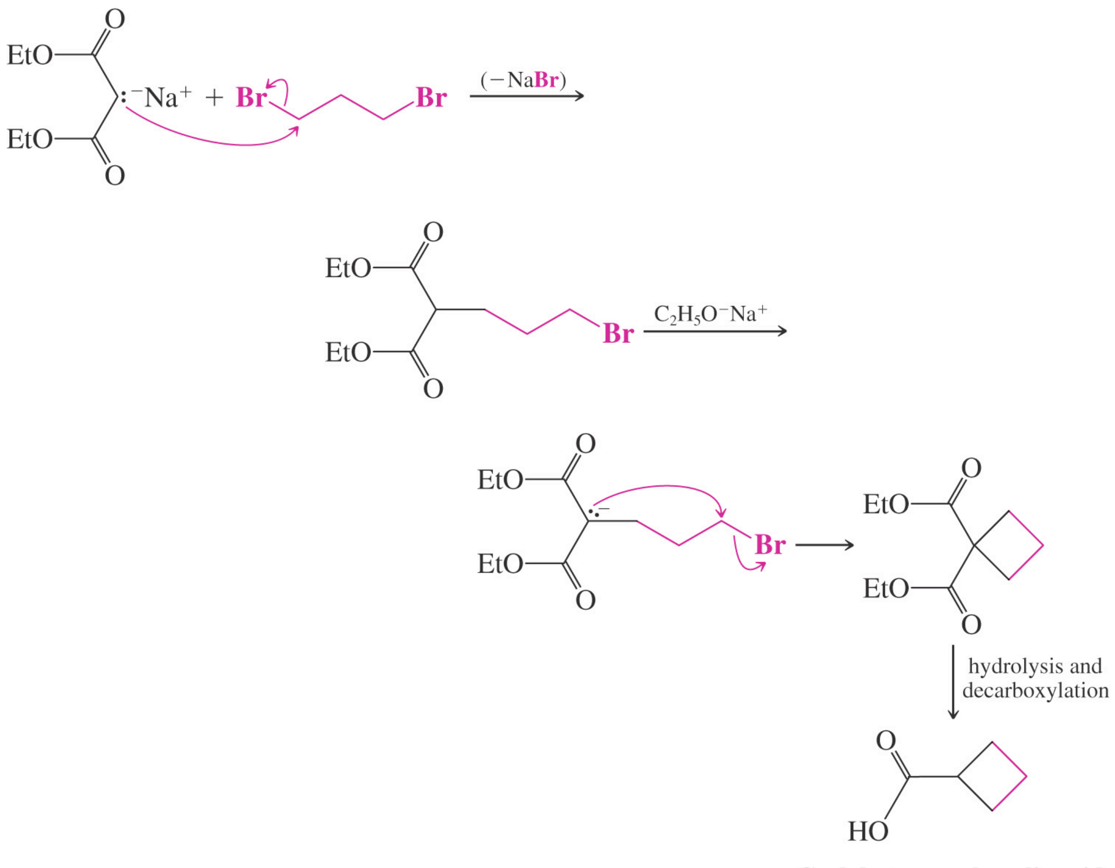


➡ Azido dikarboxilikoen lorpena dihaluroak erabiliz



Glutaric acid
(80% from tetraester)

➡ C2-tik C5-era bitarteko dihaluroak: azido dikarboxiliko zizklikoen lorpena



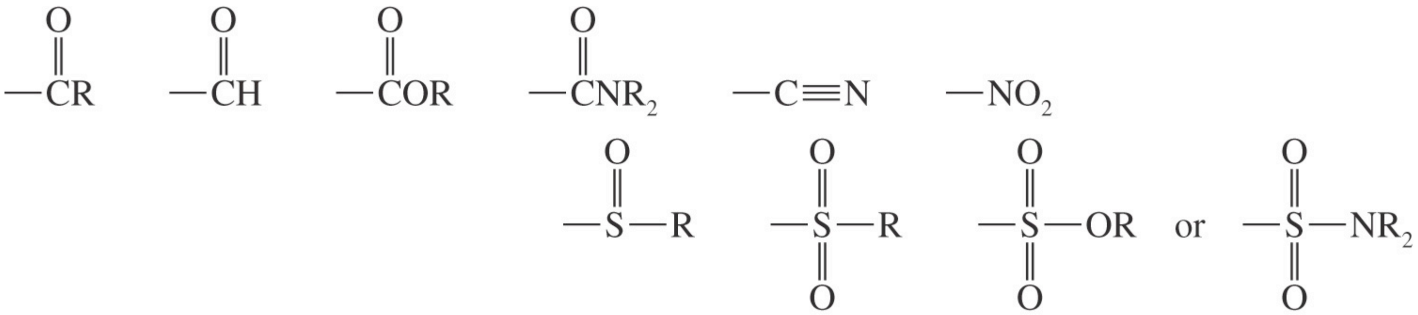
Cyclobutanecarboxylic acid

♦ Beste Metileno Aktibo Batzuk

➨ (-CH_2-) Taldea bi talde elektroi-erakarlez inguraturik dagoenean

$Z-CH_2-Z'$

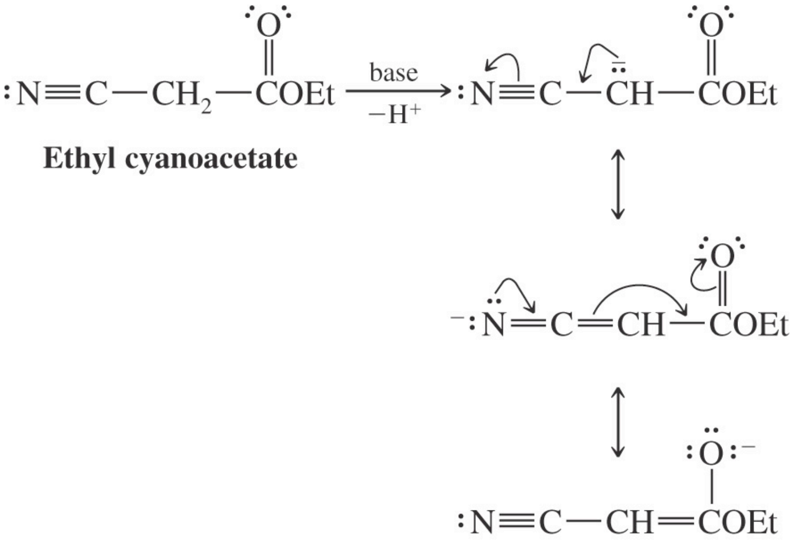
Active hydrogen compound
(Z and Z′ are electron-withdrawing groups.)



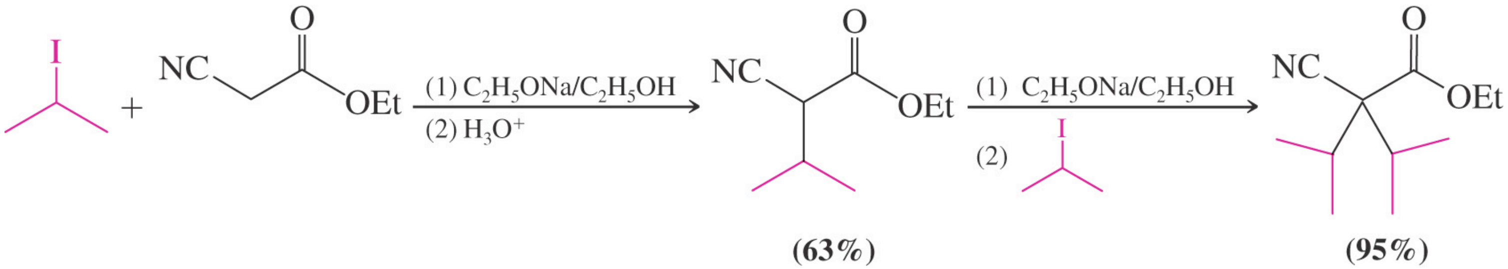
$$-\overset{O}{\overset{\|}{C}}R \quad -\overset{O}{\overset{\|}{C}}H \quad -\overset{O}{\overset{\|}{C}}OR \quad -\overset{O}{\overset{\|}{C}}NR_2 \quad -C\equiv N \quad -NO_2$$

$$-\overset{O}{\overset{\|}{S}}-R \quad -\underset{\underset{O}{\|}}{\overset{O}{\overset{\|}{S}}}-R \quad -\underset{\underset{O}{\|}}{\overset{O}{\overset{\|}{S}}}-OR \text{ or } -\underset{\underset{O}{\|}}{\overset{O}{\overset{\|}{S}}}-NR_2$$

➡ Adibidea: Etil zianoazetatoaren alkilazioa

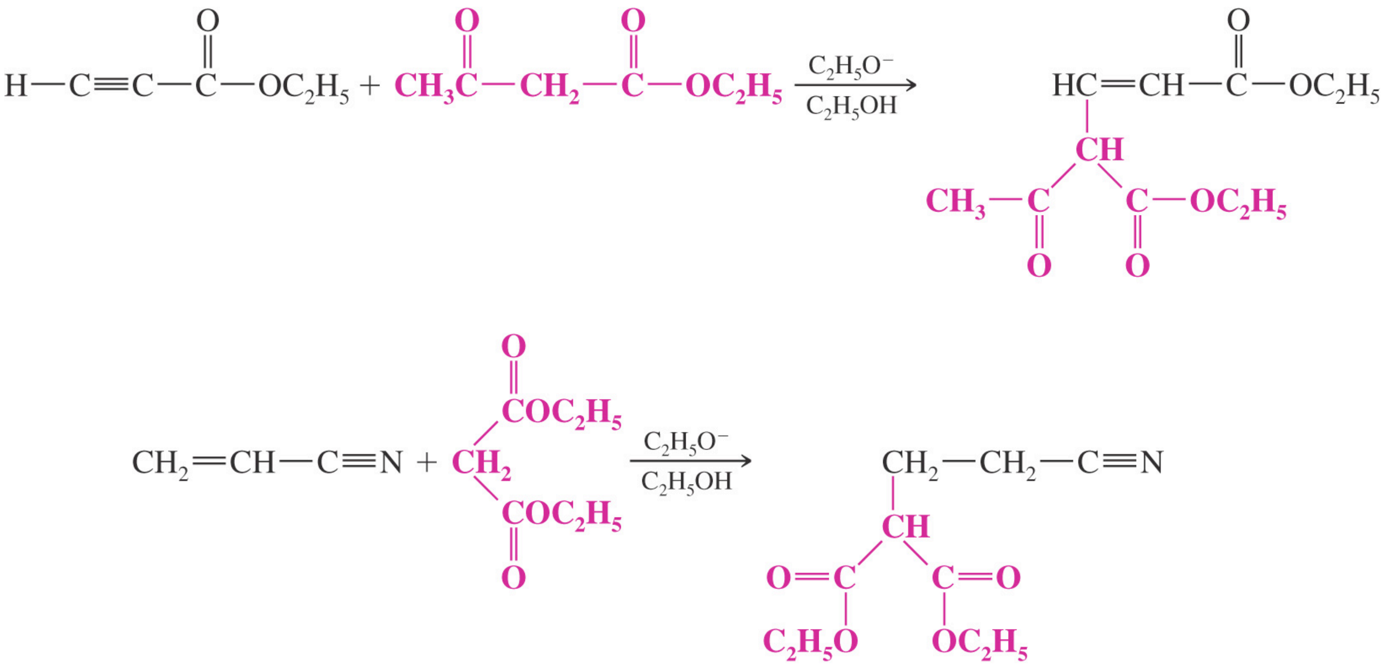


Ethyl cyanoacetate

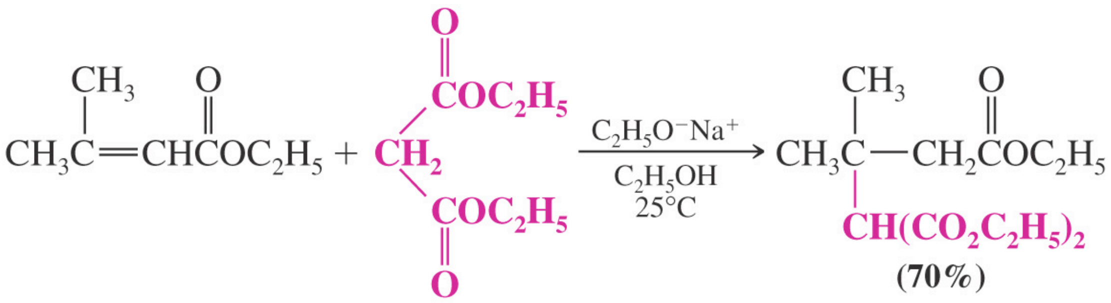


♦ Michael-en Adizioak

- ➡ **Metileno aktibo baten (hau da, enolato baten) adizio konjokatua konposatu karbonilodun α,β-asegabe batengan**
- ➡ **Beste hainbat konposatu α,β-asegabeek ere eman dezaketena**



Overall Reaction:

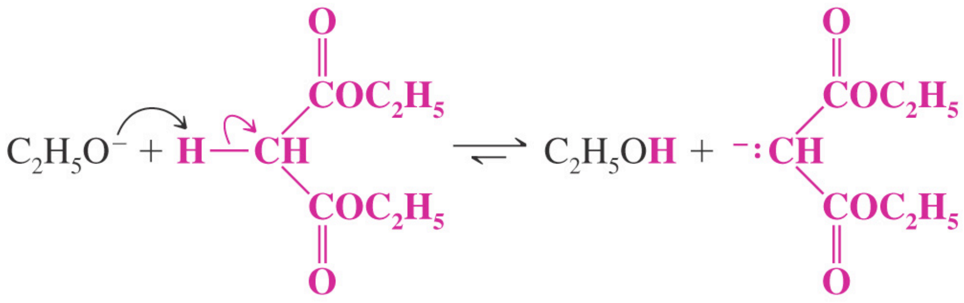


$$\mathrm{CH_3\overset{\overset{CH_3}{|}}{C}{=}CH\overset{\overset{O}{\|}}{C}OC_2H_5 + CH_2\left(\overset{\overset{O}{\|}}{C}OC_2H_5\right)_2 \xrightarrow[\substack{C_2H_5OH\\ 25^\circ C}]{C_2H_5O^-Na^+} CH_3\underset{\underset{CH(CO_2C_2H_5)_2}{|}}{\overset{\overset{CH_3}{|}}{C}}{-}CH_2\overset{\overset{O}{\|}}{C}OC_2H_5}$$

(70%)

Mechanism:

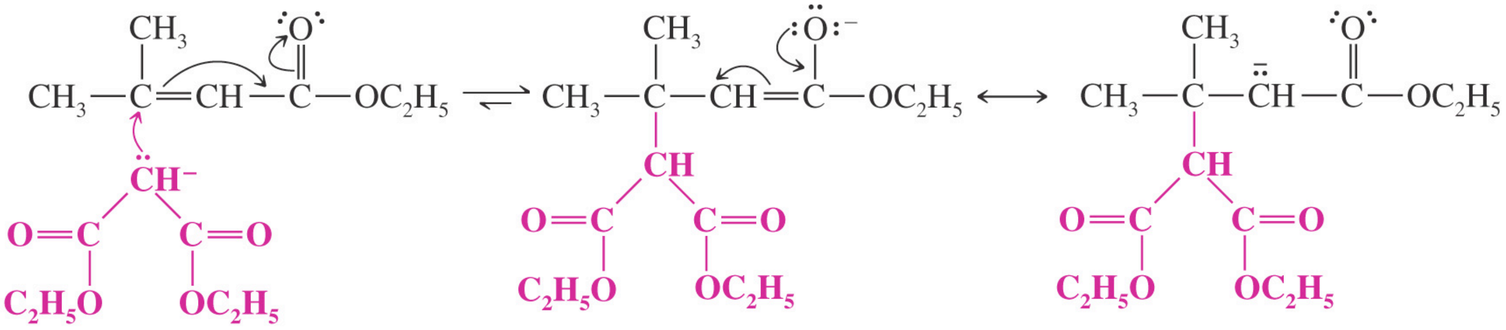
Step 1



$$\mathrm{C_2H_5O^- + H{-}CH\left(\overset{\overset{O}{\|}}{C}OC_2H_5\right)_2 \rightleftharpoons C_2H_5OH + {}^{-}{:}CH\left(\overset{\overset{O}{\|}}{C}OC_2H_5\right)_2}$$

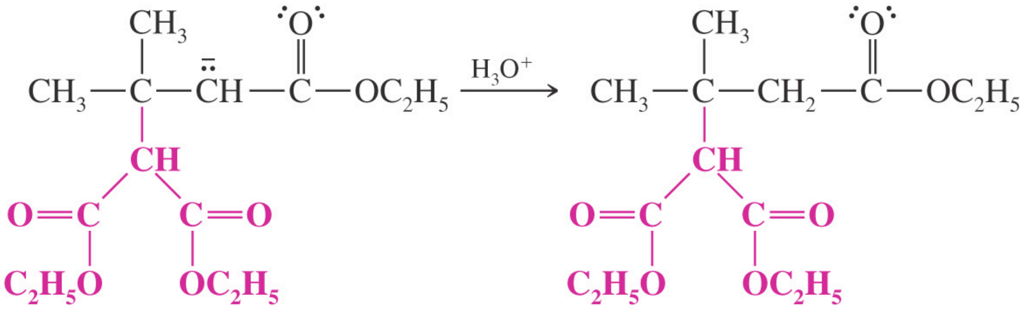
An alkoxide anion removes a proton to form the anion of the active methylene compound.

Step 2



Conjugate addition of the anion to the α,β-unsaturated ester leads to a new enolate anion.

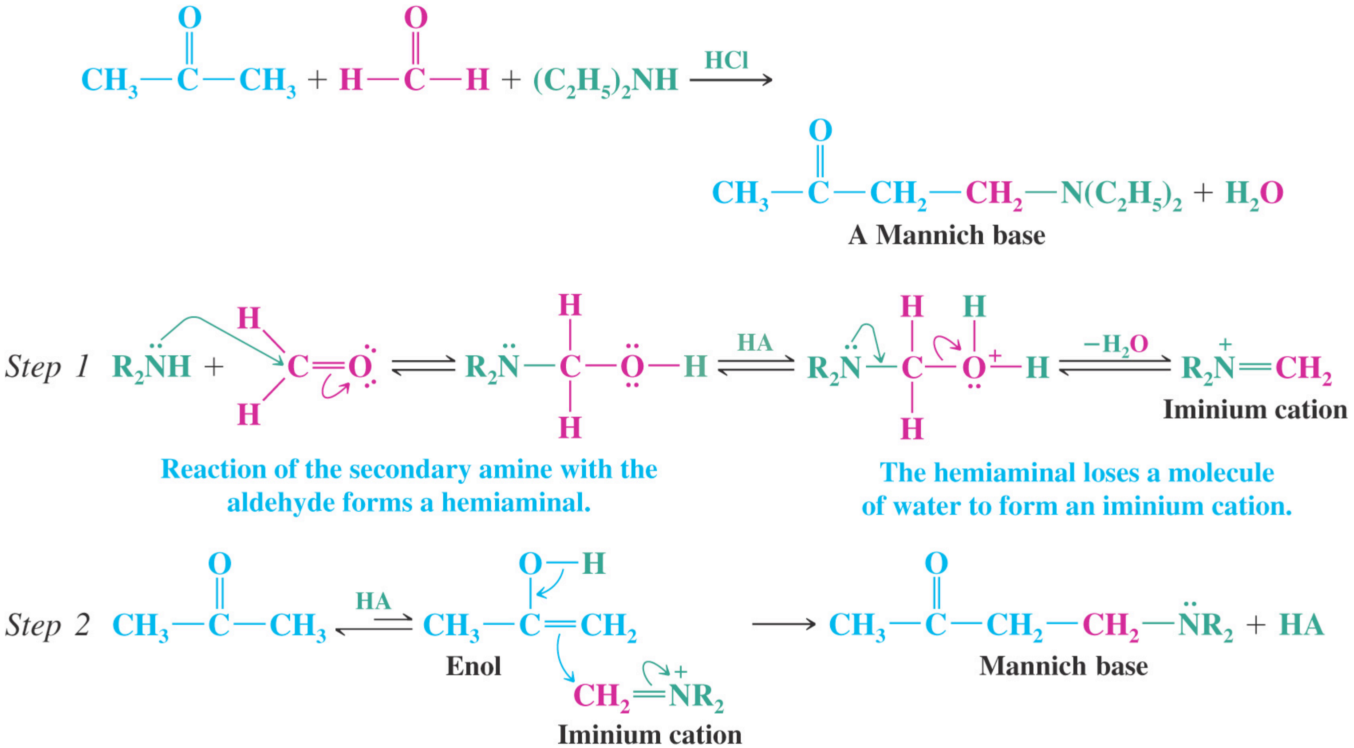
Step 3



The enolate anion is protonated by an acid during the workup of the reaction.

♦ Mannich-en Erreakzioa

- ➡ **Enol bat osa dezaketen konposatuek ematen dutena formaldehidoaren iminekin (edo iminio ioiekin)**
  - ★ **Formaldehidok iminak eman ditzake amina 1°-ekin eta iminio ioiak amina 2°-ekin**



Reaction of the secondary amine with the aldehyde forms a hemiaminal.

The hemiaminal loses a molecule of water to form an iminium cation.

The enol form of the active hydrogen compound reacts with the iminium cation to form a β-aminocarbonyl compound (a Mannich base).