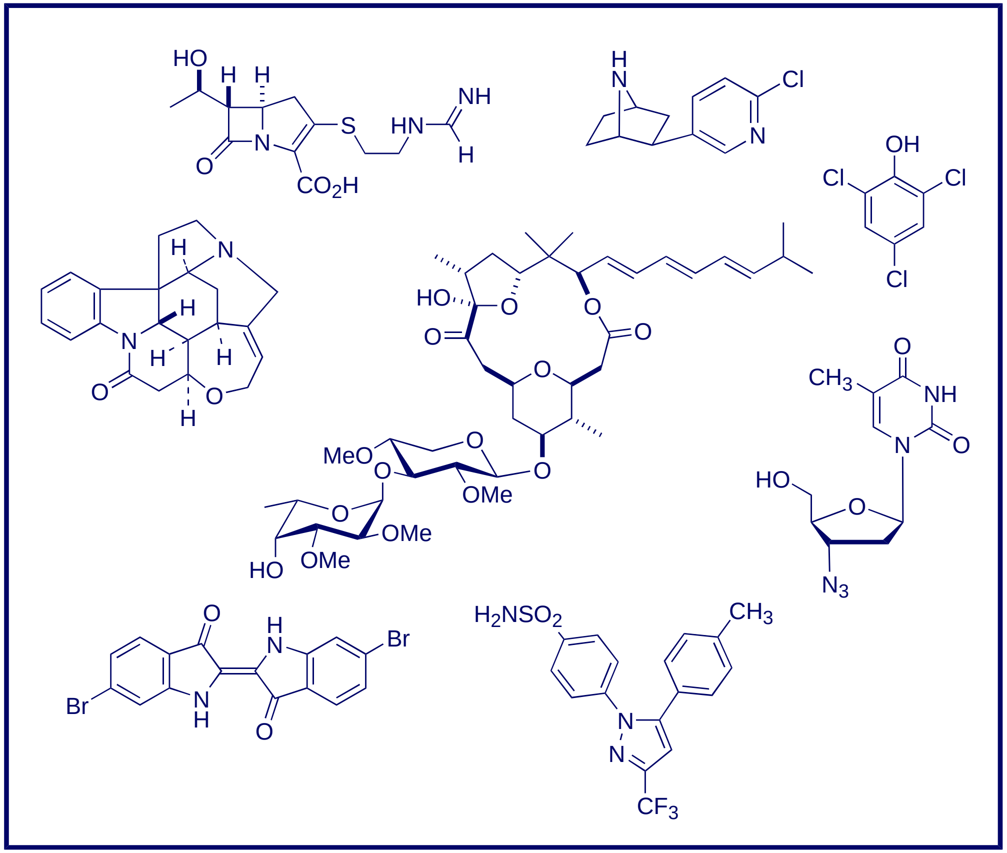
Chem 234 Organic Chemistry II

Professor Duncan J. Wardrop

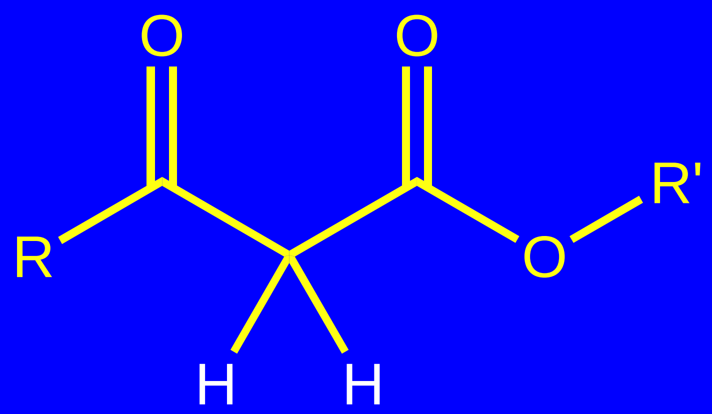


Spring 2004

University of Illinois at Chicago

Chapter 21
Ester Enolates

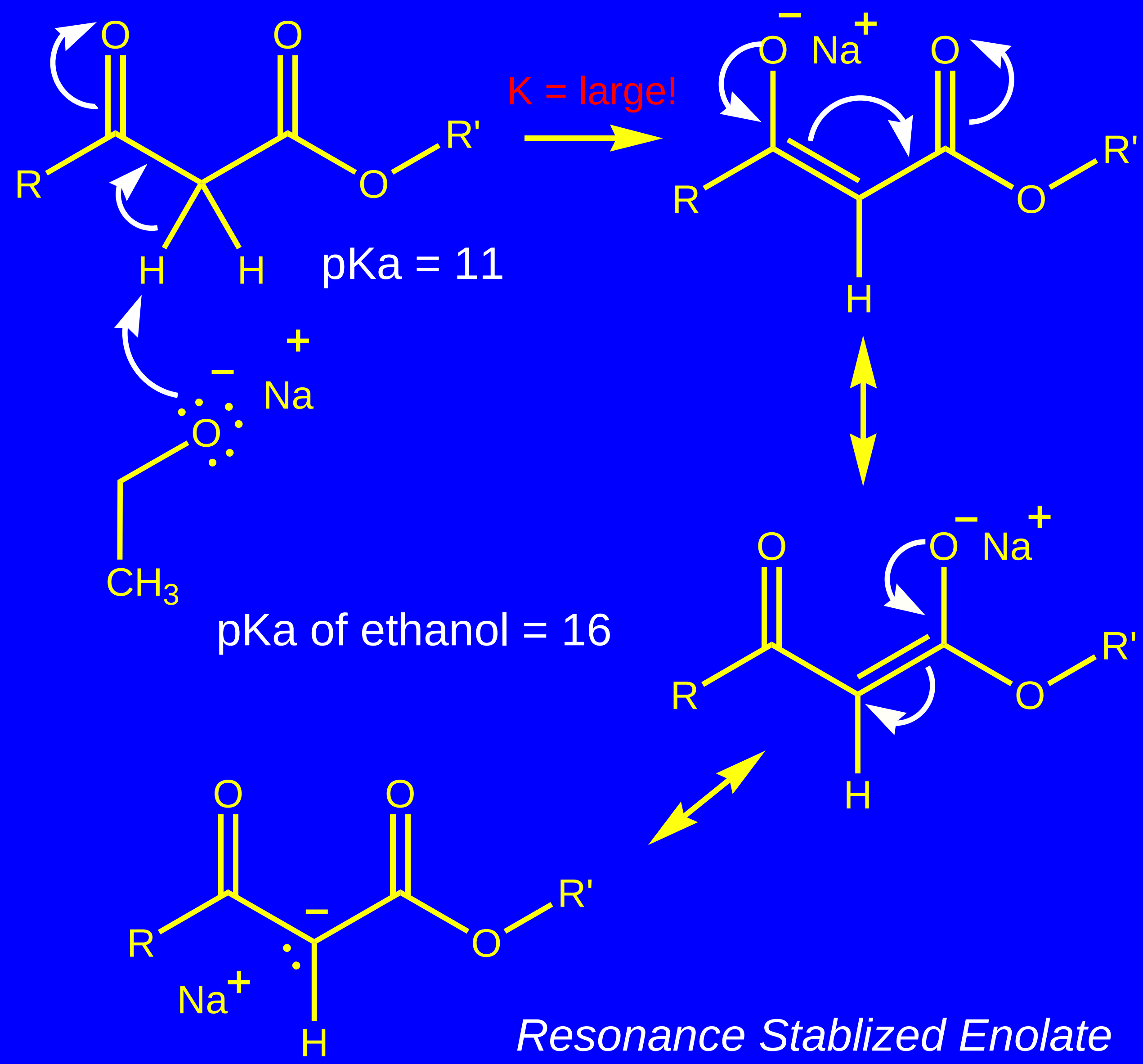
Preparation of β-Keto Esters



Acidic Protons!

The hydrogen atoms at the alpha position of a β–keto ester are relatively acidic and can be deprotonated with alkoxide bases to form the corresponding enolate anion

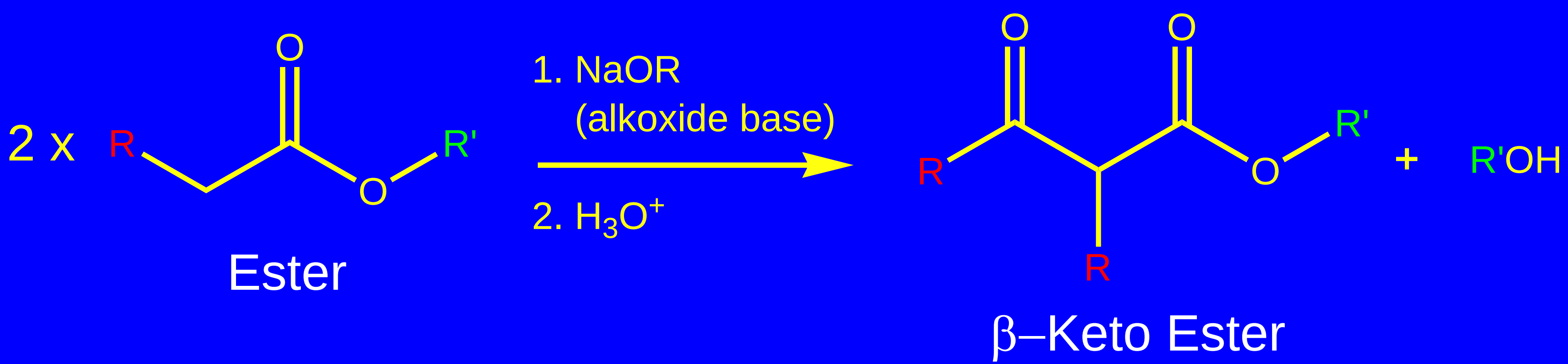
Deprotonation of β-Keto Esters



21.1

The Claisen Condensation

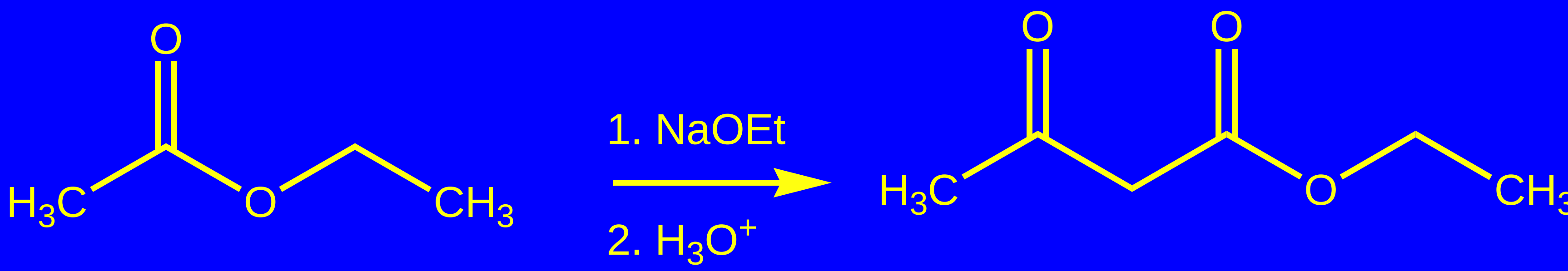
The Claisen Condensation



1. β-Keto esters are made by the reaction shown, which is called the Claisen condensation.

2. Ethyl esters are typically used, with sodium ethoxide as the base.

The Claisen Condensation - Example 1

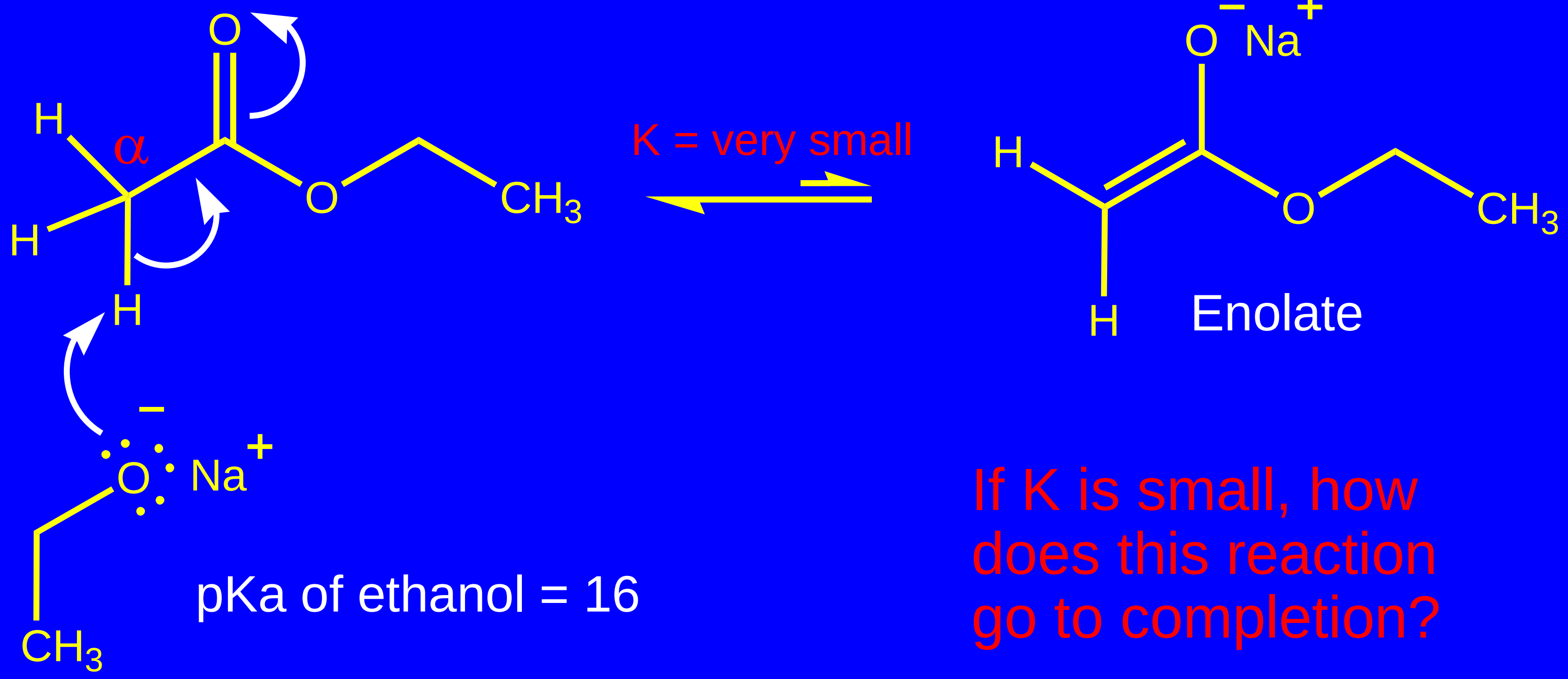


Ethyl Acetate

Ethyl Acetoacetate

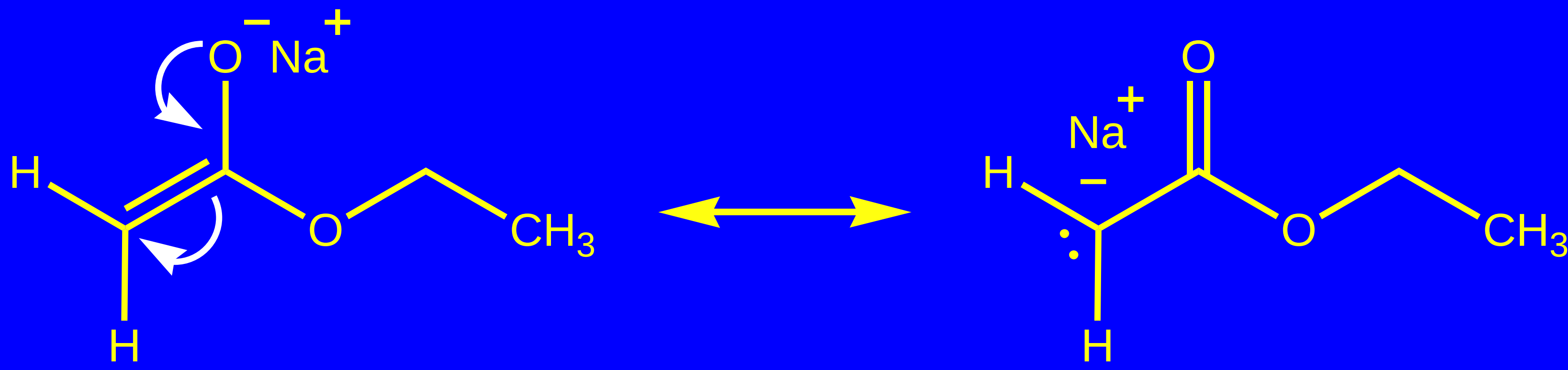
The Claisen Condensation - Mechanism
Step 1 - Deprotonation

pKa of esters ~ 24



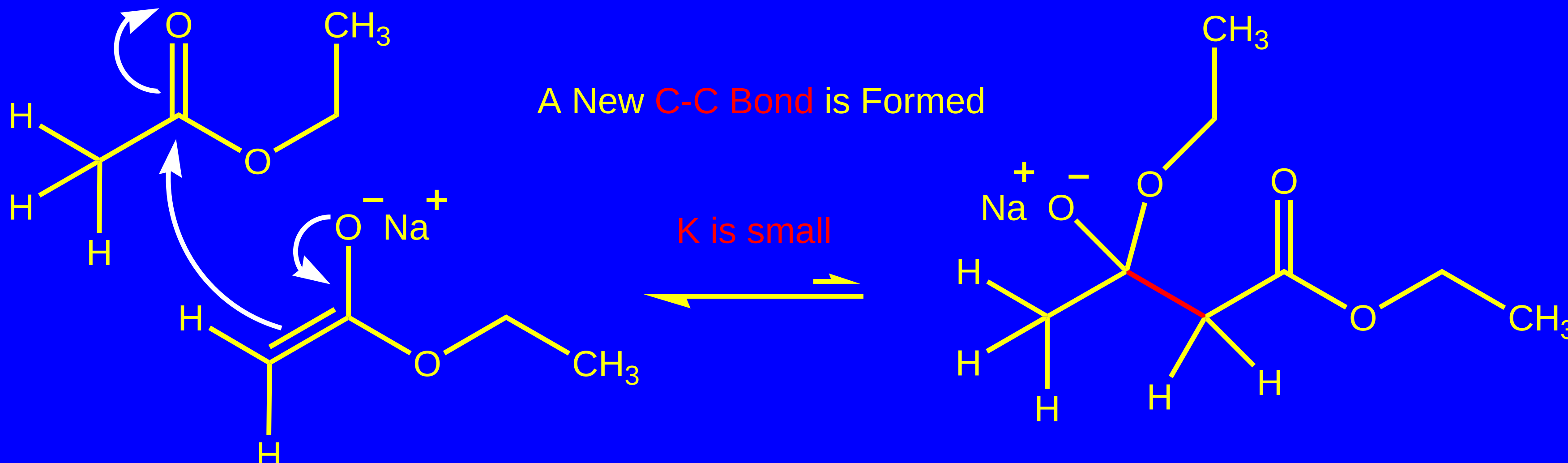
If K is small, how does this reaction go to completion?

The Claisen Condensation - Mechanism
Step 1 - Deprotonation Generates an Ester Enolate



Anion produced is stabilized by electron delocalization; it is the enolate of an ester.

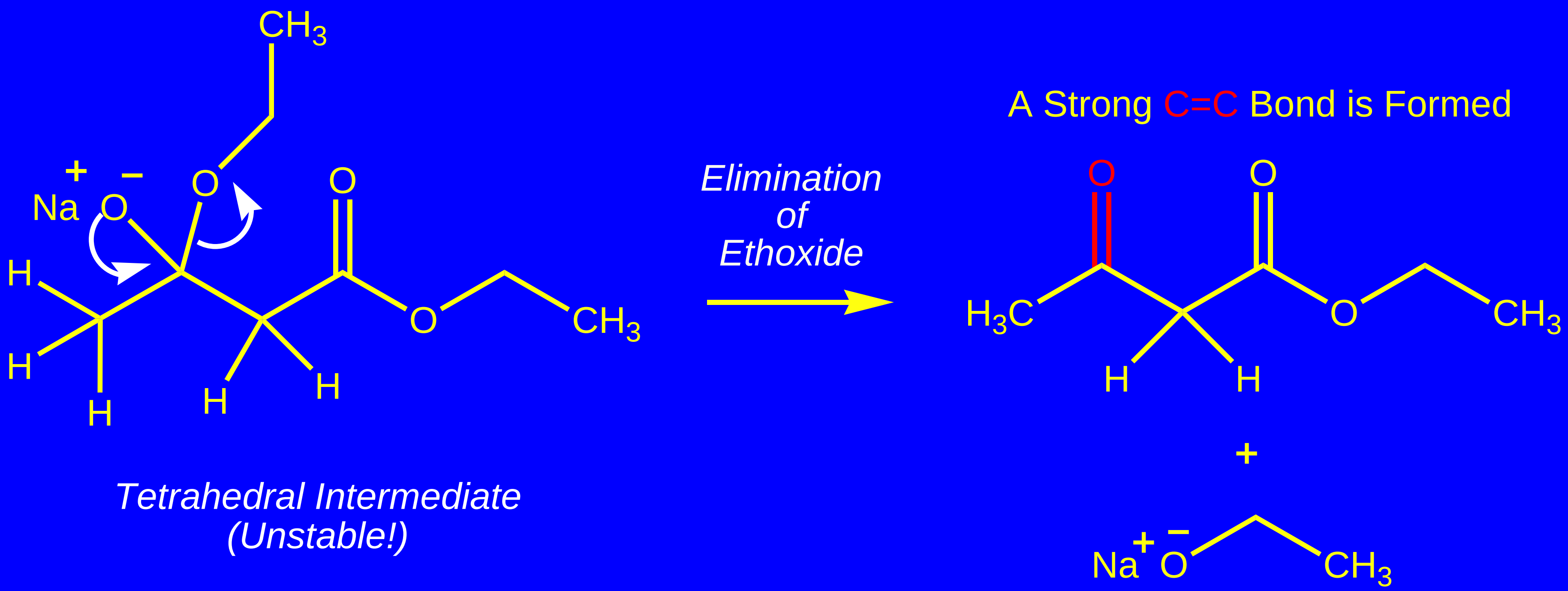
The Claisen Condensation - Mechanism
Step 2 - Nucleophilic Addition & Formation of Tetrahedral Intermediate



Tetrahedral Intermediate
(Unstable!)

If K is small, how does the Claisen condensation reaction go to completion?

The Claisen Condensation - Mechanism
Step 3 - Collapse of Tetrahedral Intermediate, Elimination of Ethoxide & Formation of Product



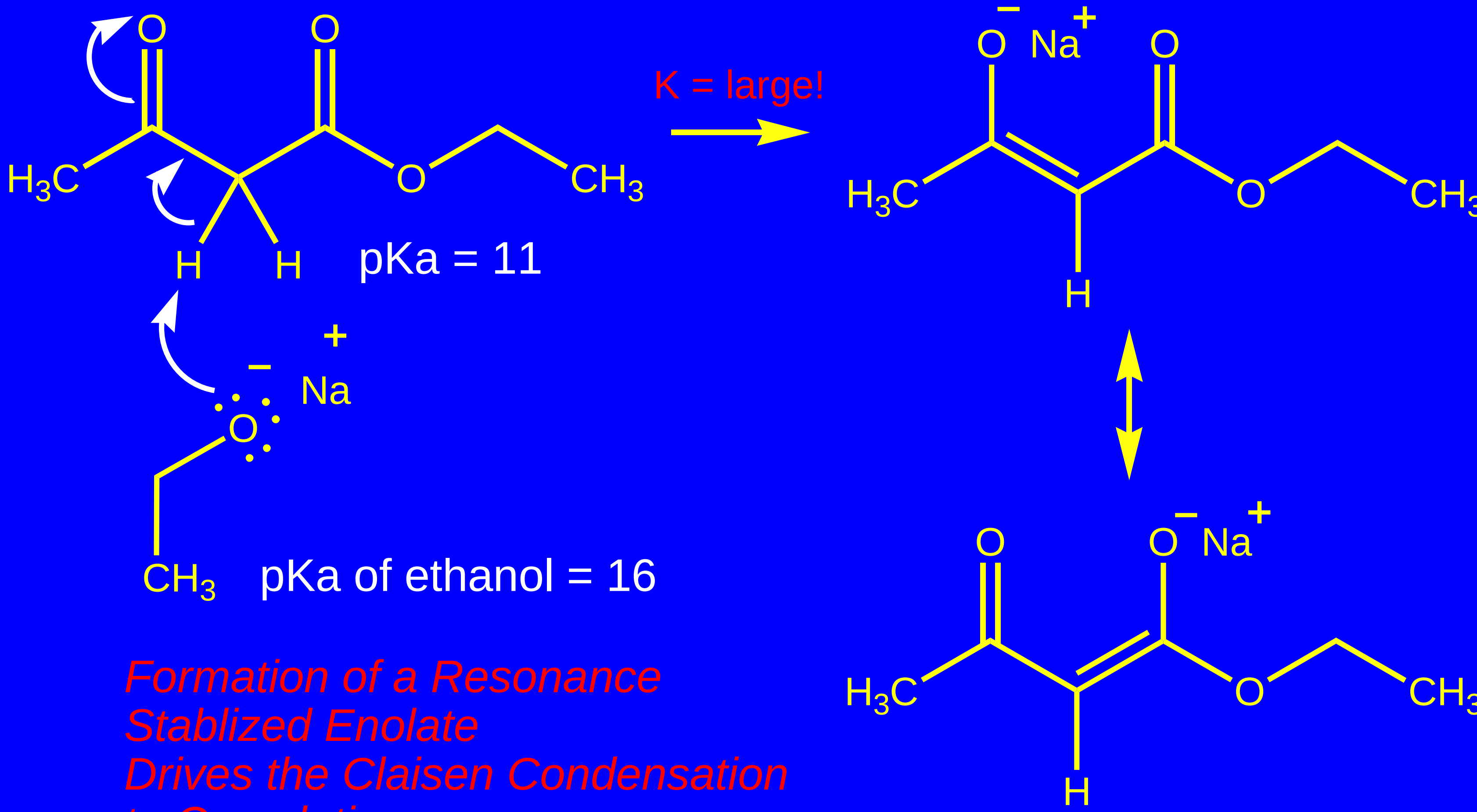
The Claisen Condensation - Mechanism
Step 3 - What About that Small Equilibrium Constant?

1. The product at this point is ethyl acetoacetate.

2. However, were nothing else to happen, the yield of ethyl acetoacetate would be small because the equilibrium constant for its formation is small.

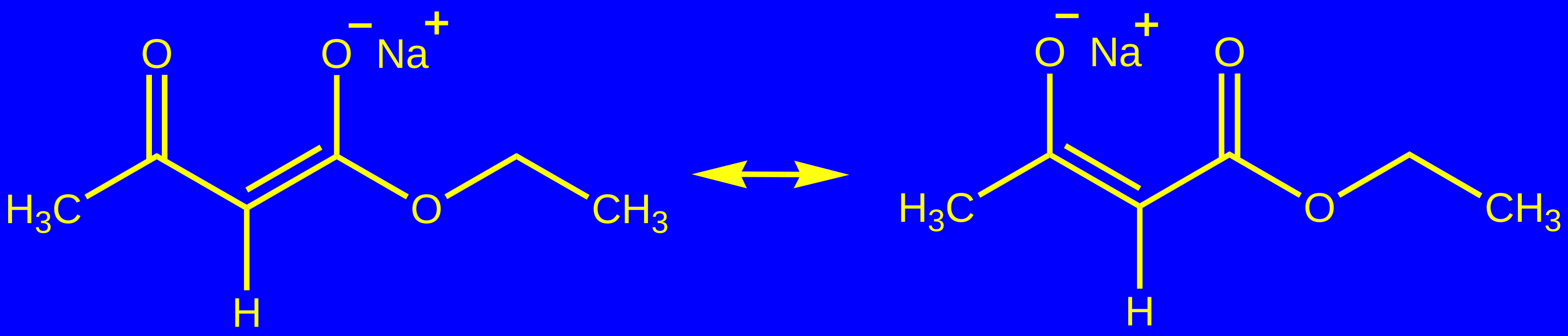
3. Something else does happen. Ethoxide abstracts a proton from the CH_2 group to give a stabilized anion. The equilibrium constant for this reaction is favorable.

The Claisen Condensation - Mechanism
Step 4 - Deprotonation of the β-Keto Ester Product



Formation of a Resonance Stablized Enolate Drives the Claisen Condensation to Completion

The Claisen Condensation - Mechanism
Step 5 - Addition of Acid to Protonate Enolate

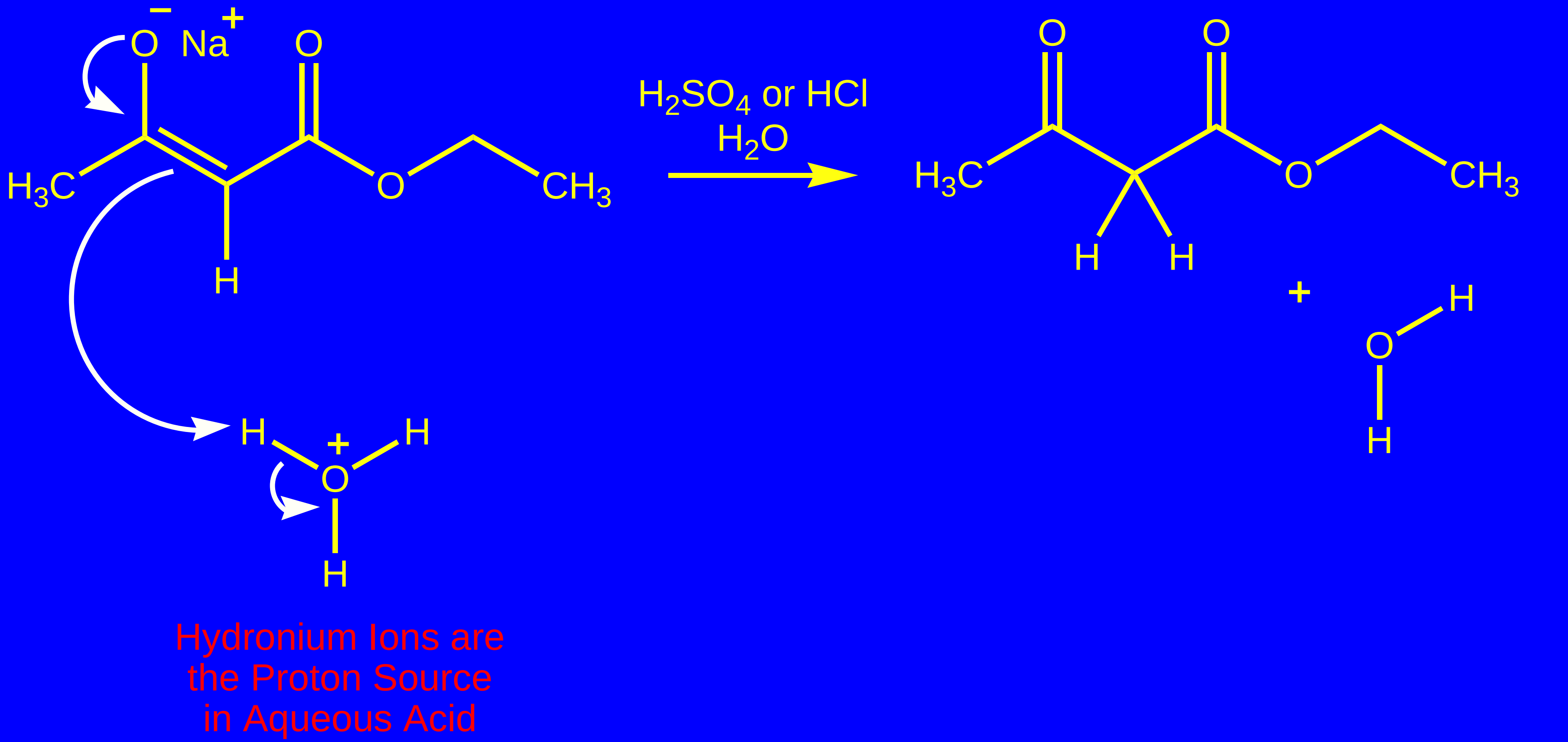


Claisen condensations are one-pot, two-step processes:

1. Condensation of two esters, under basic conditions.

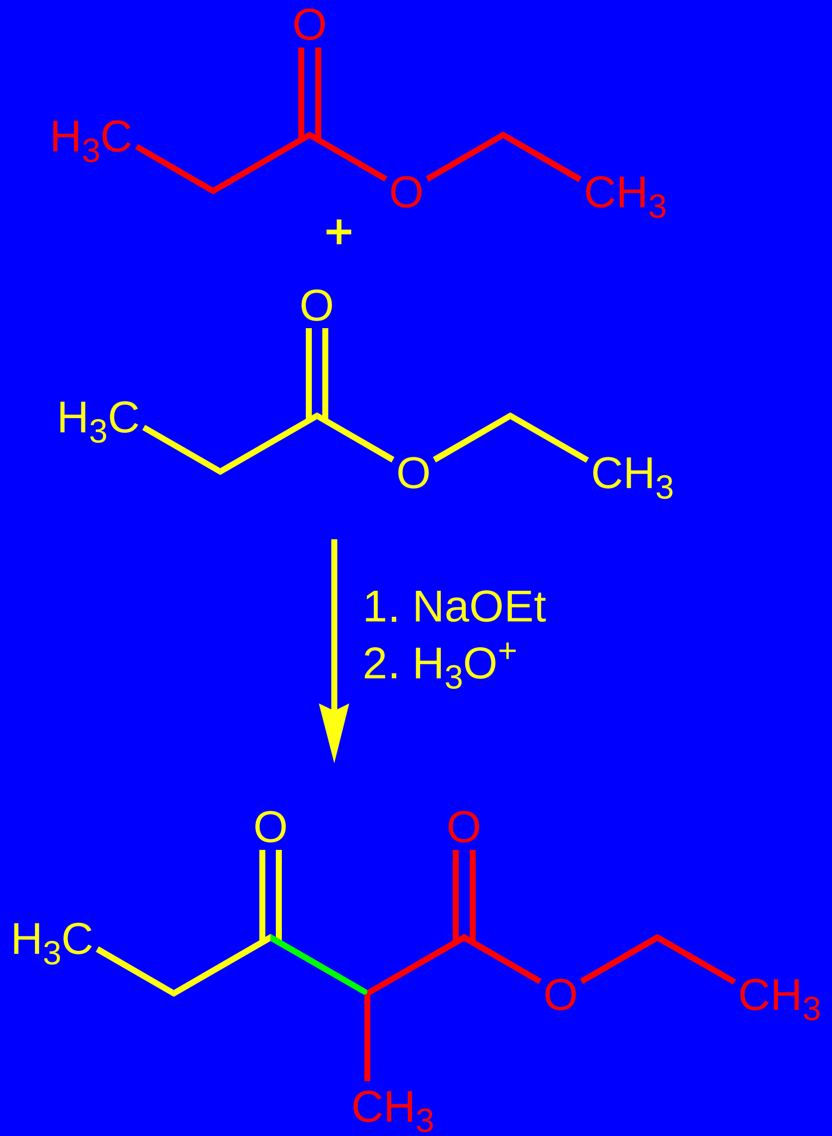
2. Protonation of the β-keto ester enolate generated in the first step.

The Claisen Condensation - Mechanism
Step 5 - Protonation of β-Keto Ester Enolate



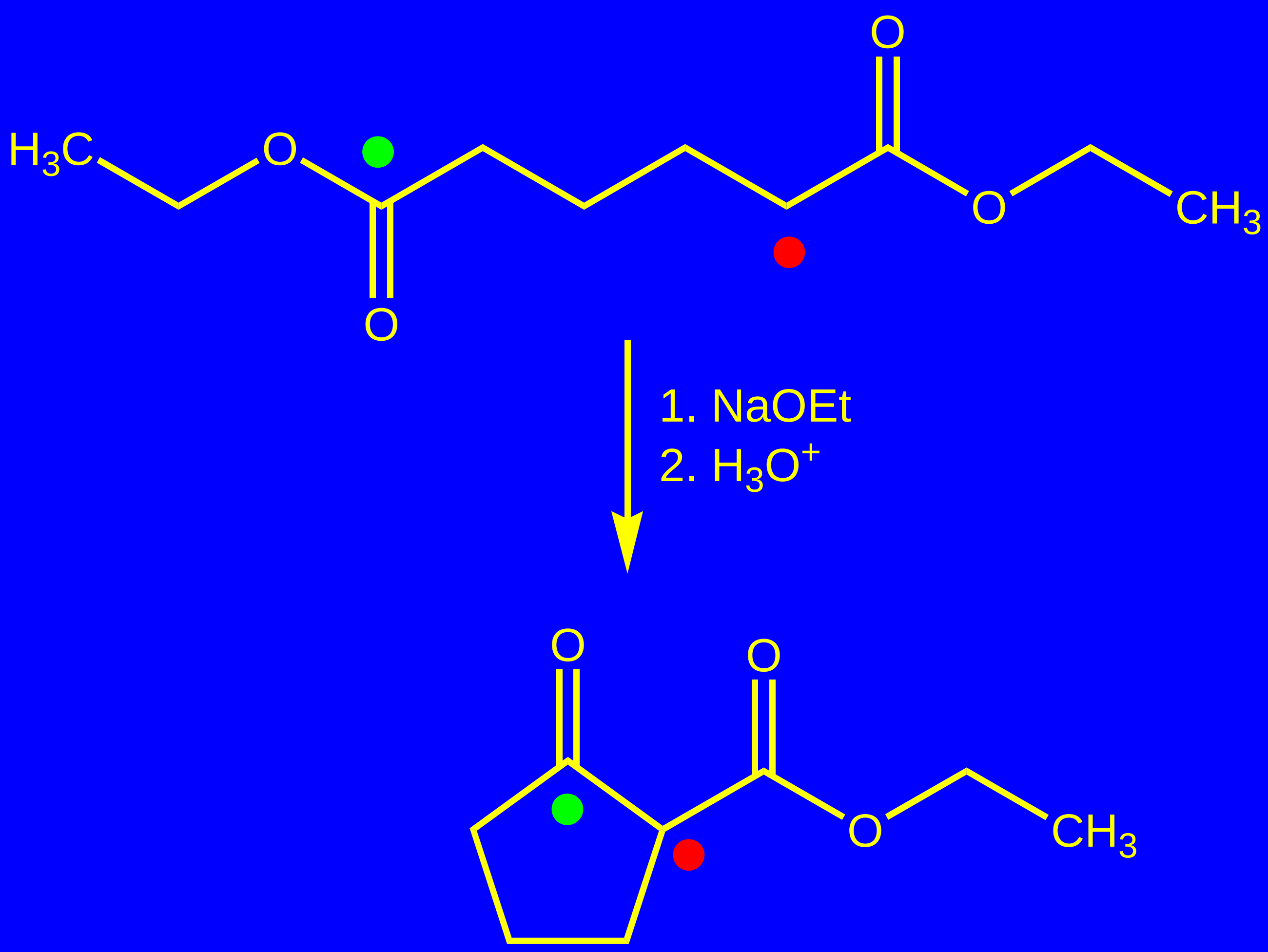
The Claisen Condensation - Example 2

Reaction involves bond formation between the α-carbon atom of one ethyl propionate molecule and the carbonyl carbon of the other. A new C-C bond is formed

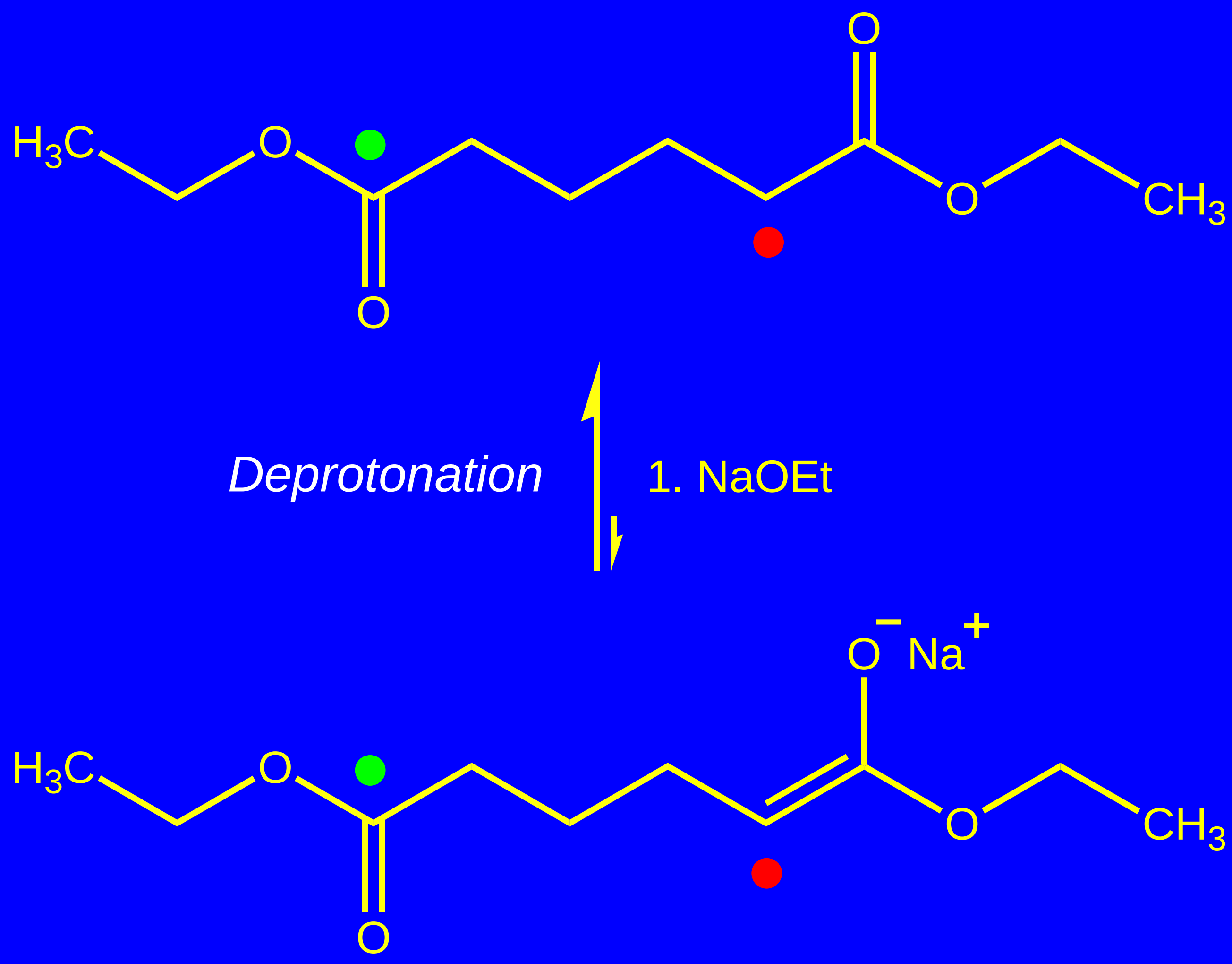


21.2
Intramolecular Claisen Condensation:
The Dieckmann Reaction

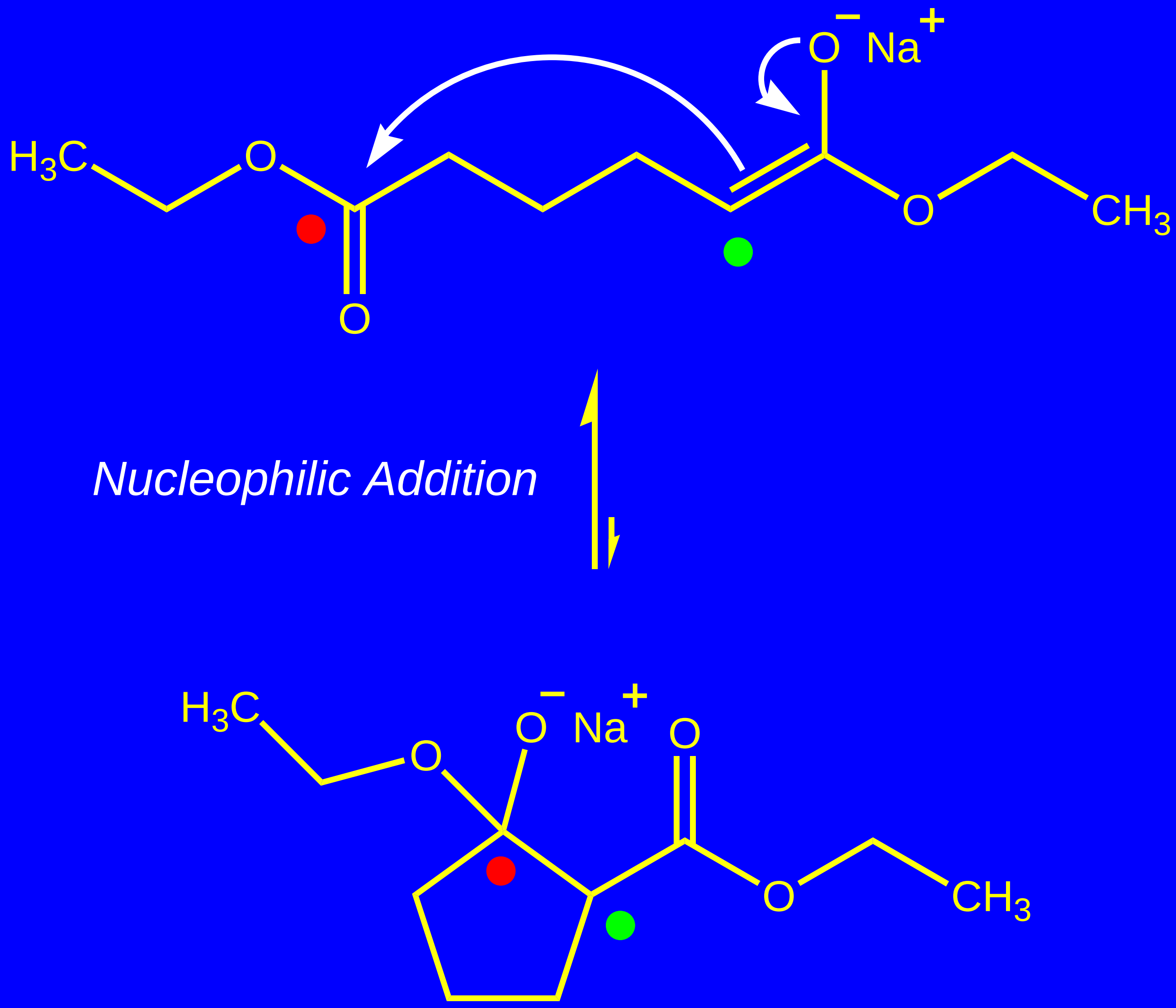
The Dieckmann Reaction - An Intramolecular Claisen Condensation of a 1,*n*-Diester



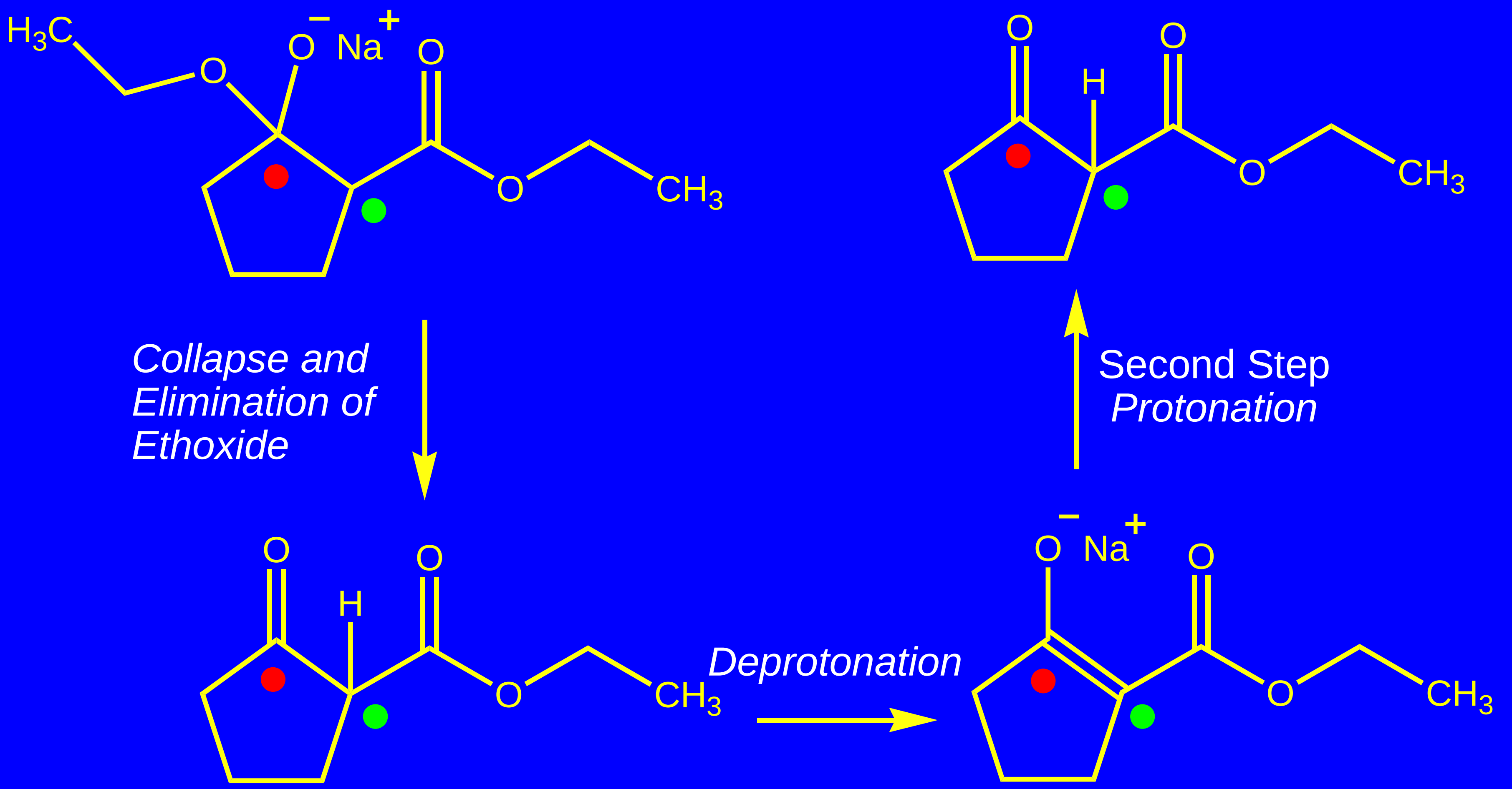
Mechanism of the Dieckmann Reaction
Step 1 - Deprotonation



Mechanism of the Dieckmann Reaction
Step 2 - Intramolecular Nucleophilic Addition



Mechanism of the Dieckmann Reaction
Steps 2, 3 & 4 - Collapse, Deprotonation & Reprotonation



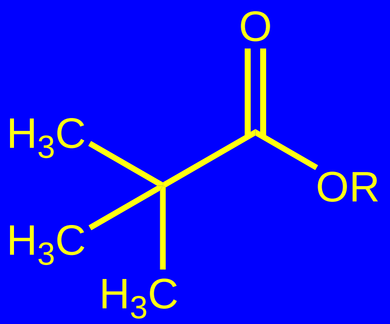
21.3
Mixed Claisen Condensations

The Mixed Claisen Condensation Reaction

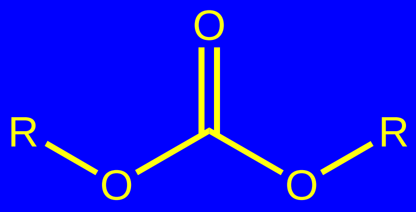
As with mixed aldol condensations, mixed Claisen condensations are best carried out when the reaction mixture contains one compound that can form an enolate and another that cannot.

Esters that Cannot Form Enolates are Good Substrates for the Claisen Condensation

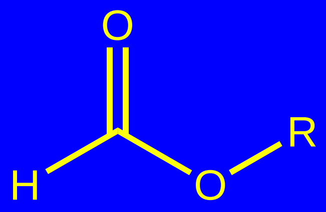
Aromatic Acid Esters
(benzoates)



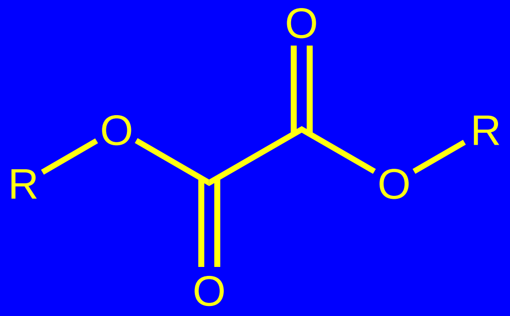
Esters with no Alpha Protons
(pivaloates)



Carbonic Acid Esters
(carbonates)

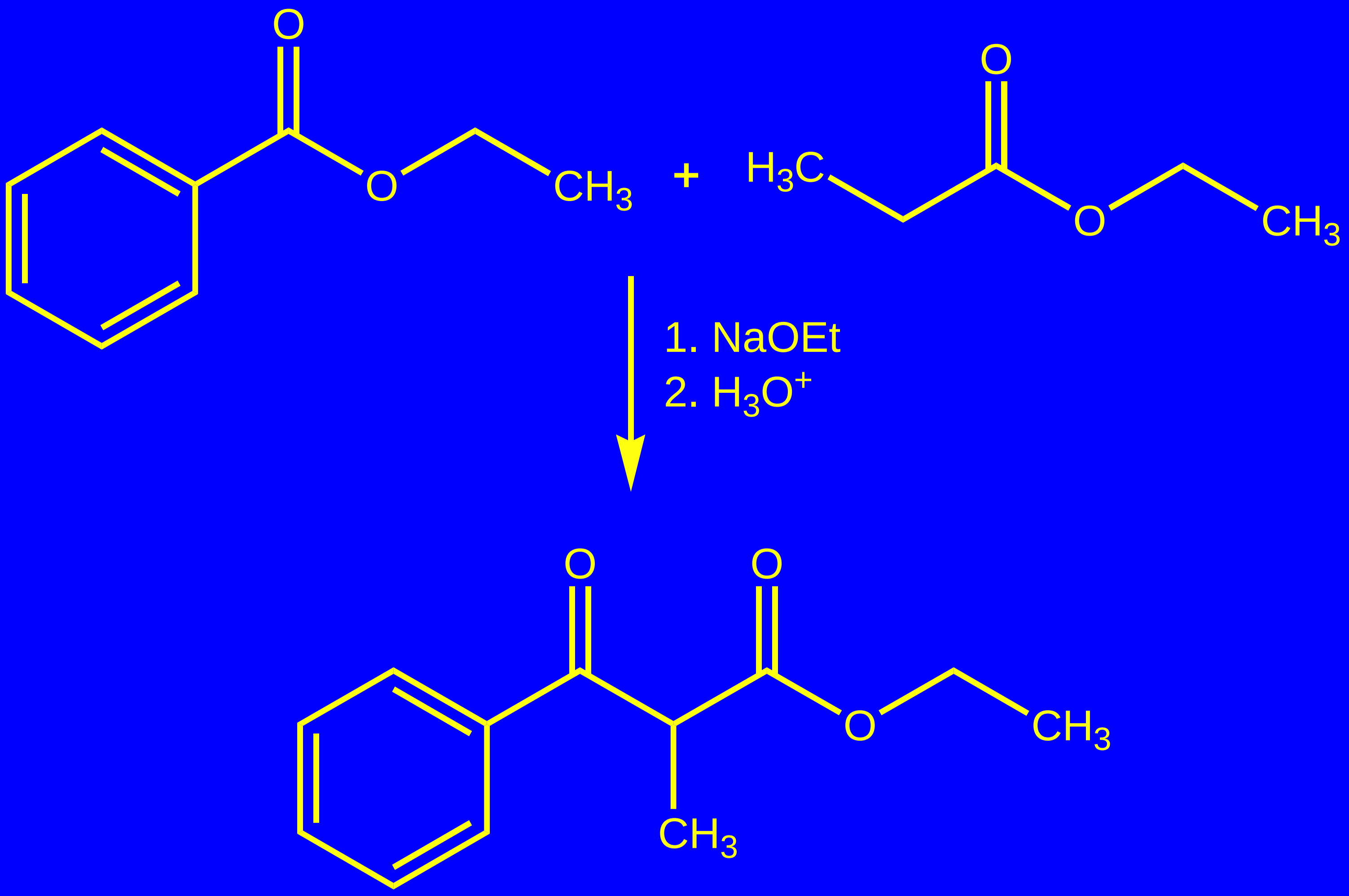


Formic Acid Esters
(formates)



Oxalic Acid Esters
(oxalates)

The Mixed Claisen Condensation Reaction - Example



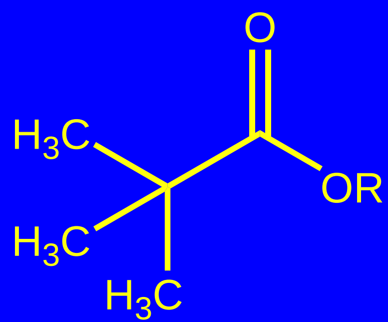
21.4

Acylation of Ketones with Esters

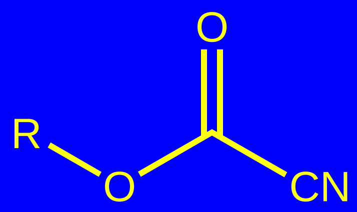
Acylation of Ketones with Esters

Esters that cannot form an enolate can be used to acylate ketone enolates.

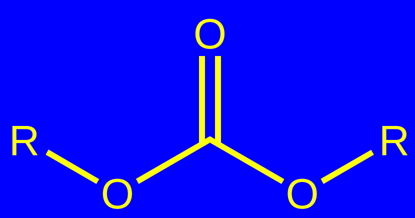
Aromatic Acid Esters
(benzoates)



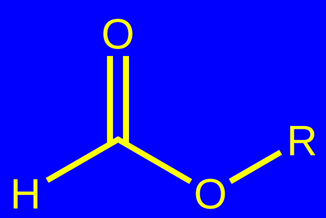
Esters with no Alpha Protons
(pivaloates)



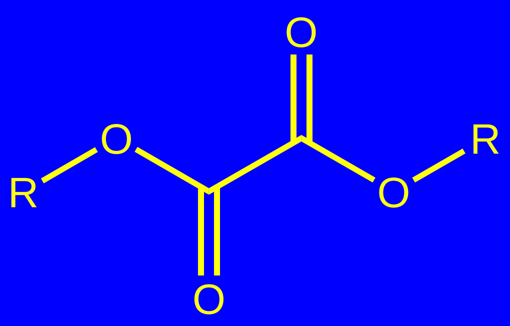
Acyl Cyanides



Carbonic Acid Esters
(carbonates)

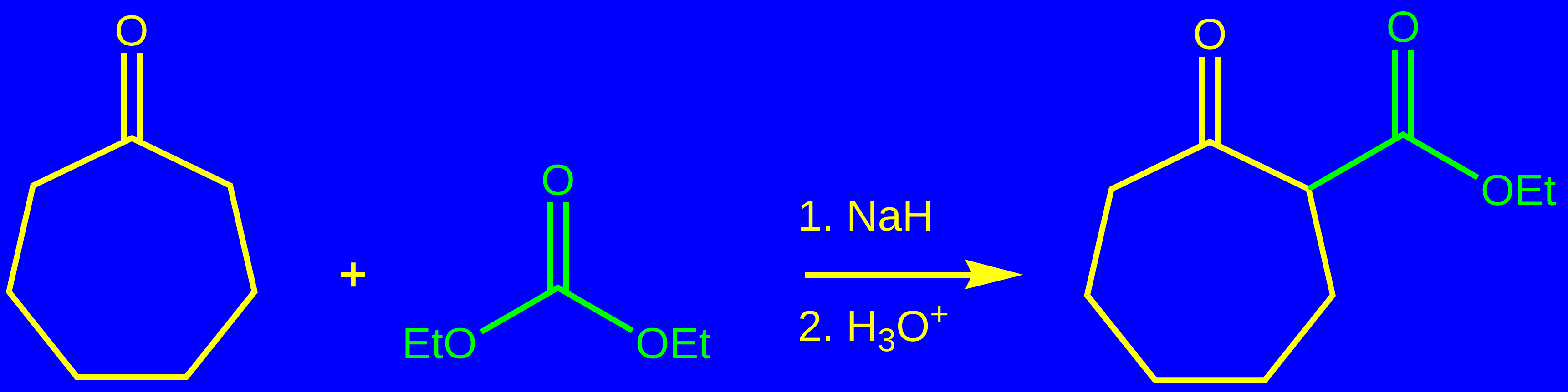


Formic Acid Esters
(formates)

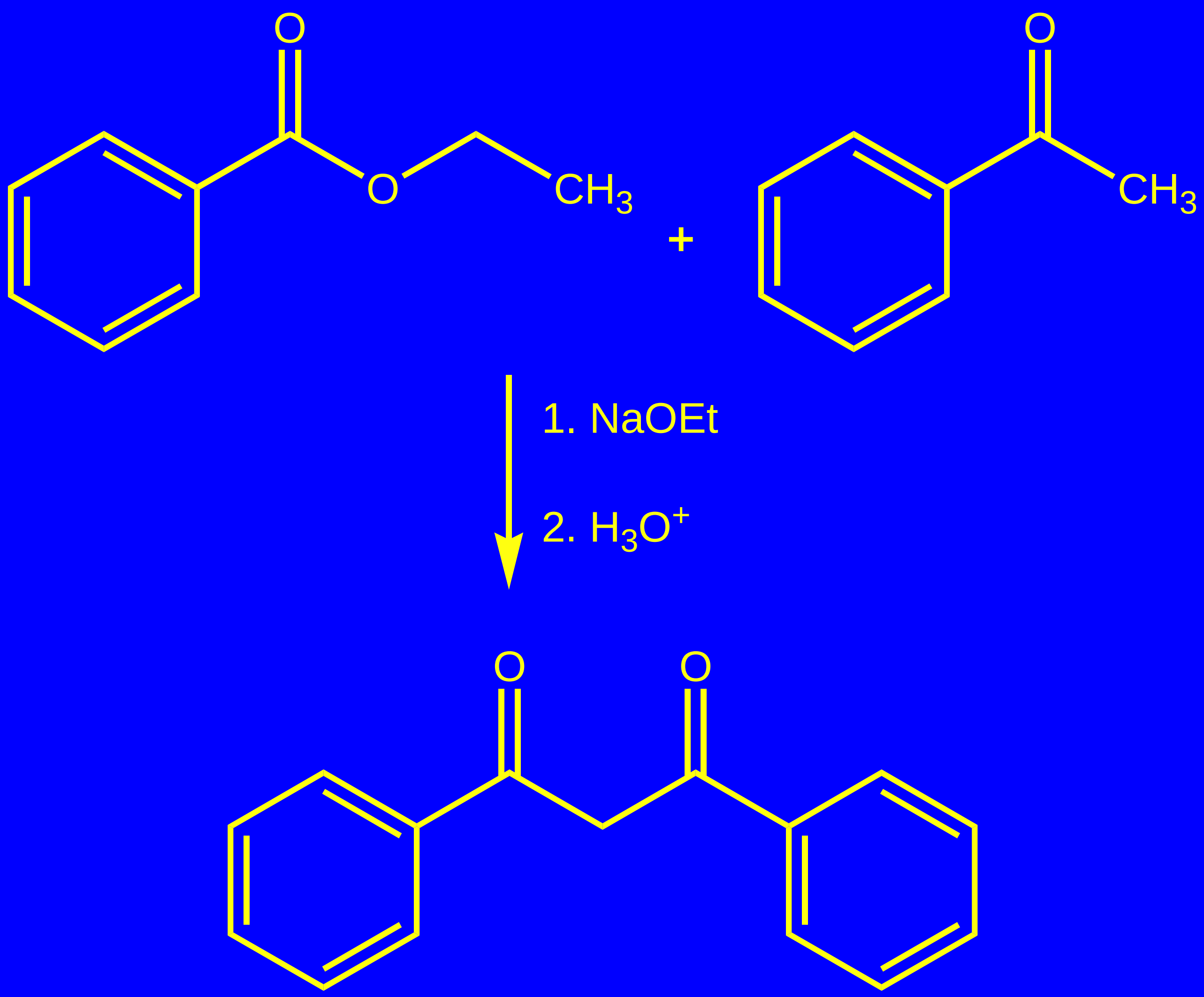


Oxalic Acid Esters
(oxalates)

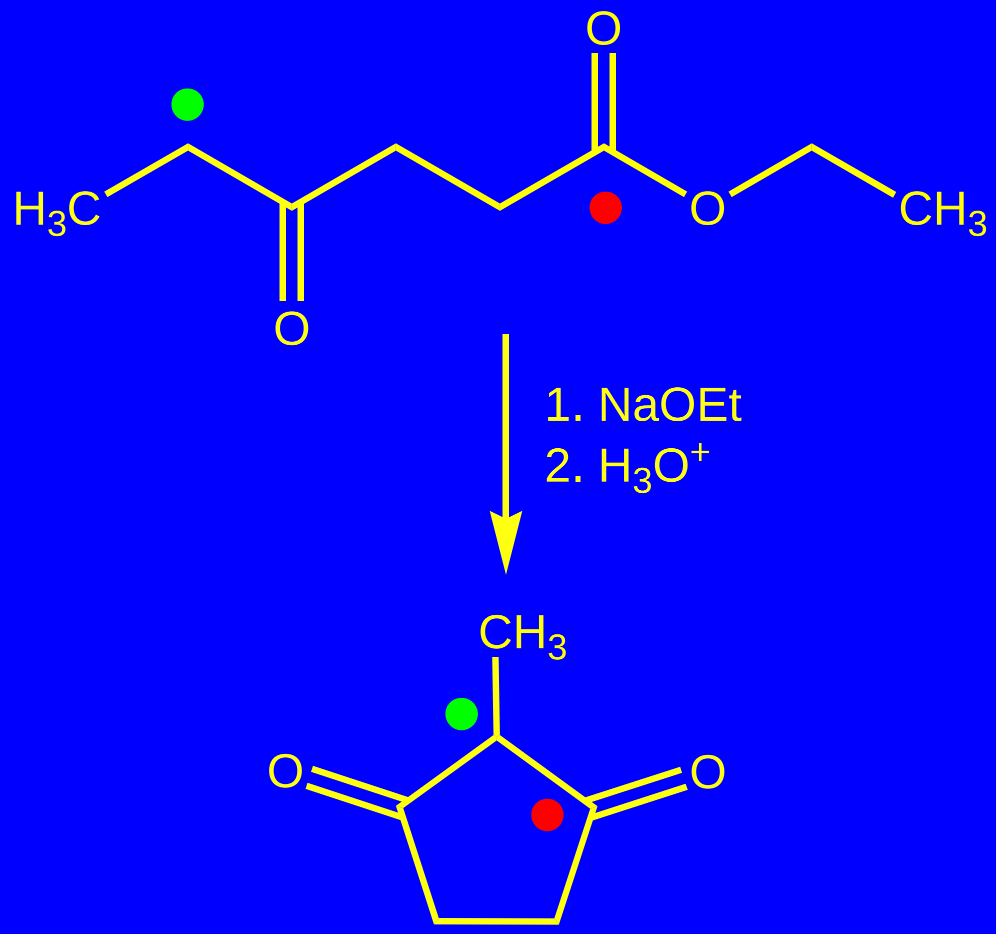
Acylation of Ketones with Esters - Example 1



Acylation of Ketones with Esters - Example 2



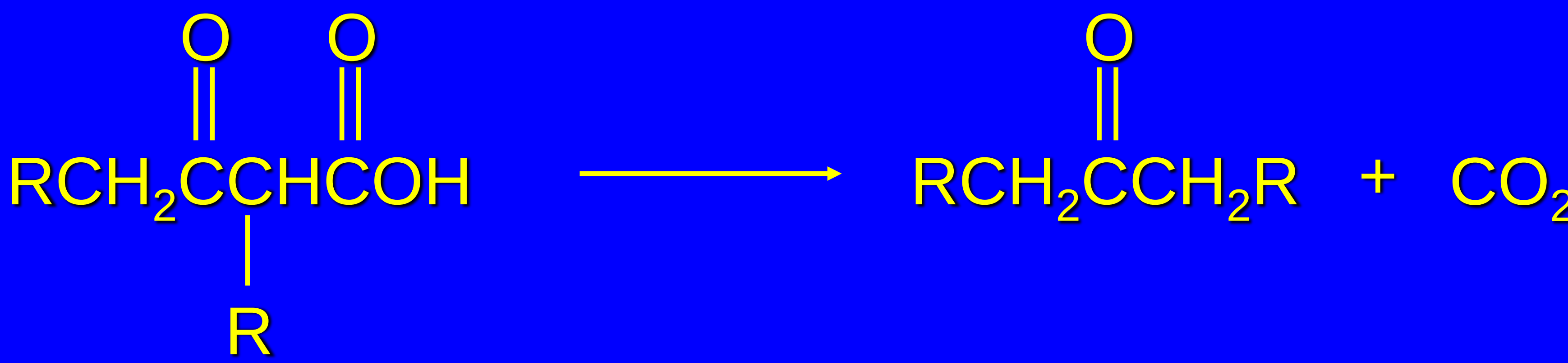
Acylation of Ketones with Esters - Example 3



21.5

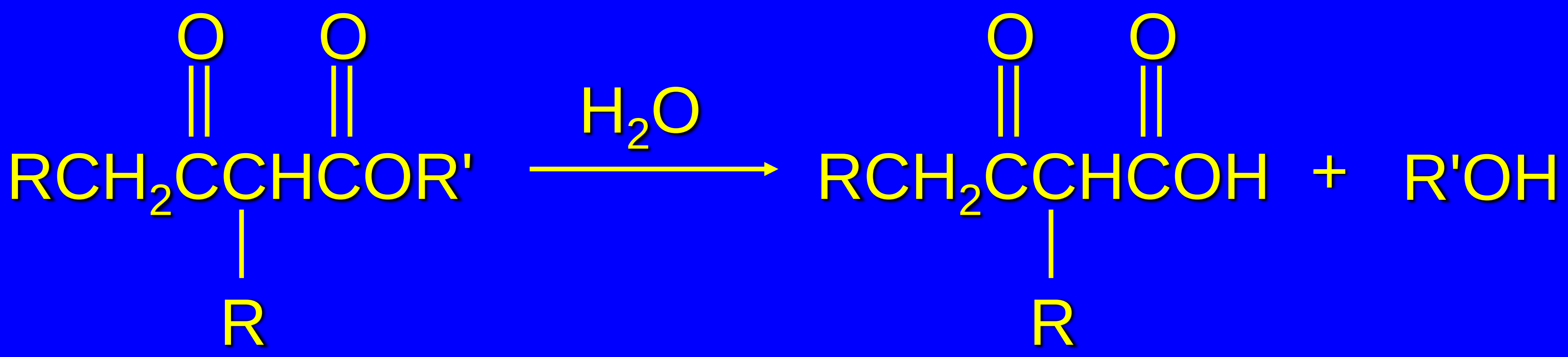
Ketone Synthesis via β-Keto Esters

The β-Keto Ester Synthesis of Ketones - Part 1



β-Keto acids decarboxylate readily to give ketones (Section 19.17).

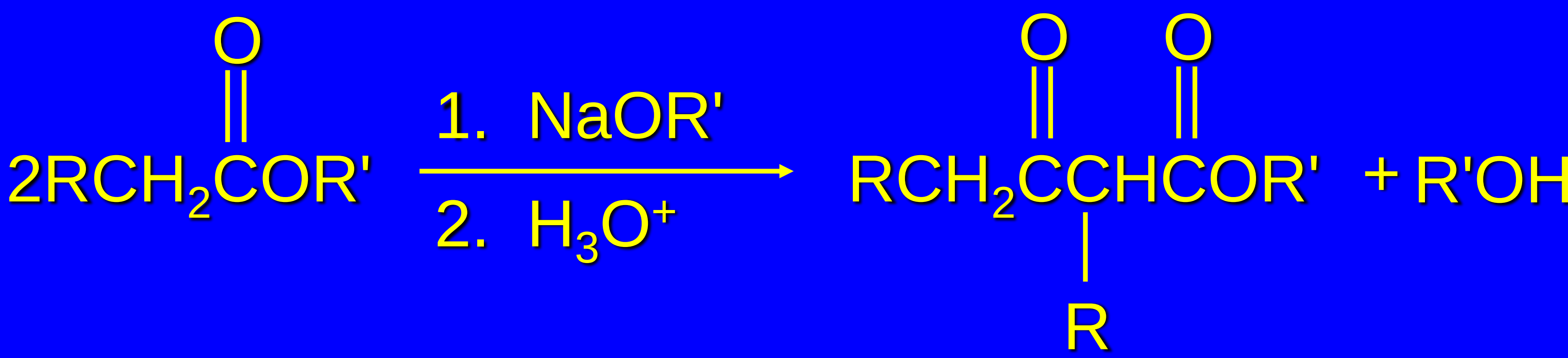
The β-Keto Ester Synthesis of Ketones - Part 2



β-Keto acids decarboxylate readily to give ketones (Section 19.17).

β-Keto acids are available by hydrolysis of β-keto esters.

The β-Keto Ester Synthesis of Ketones - Part 3

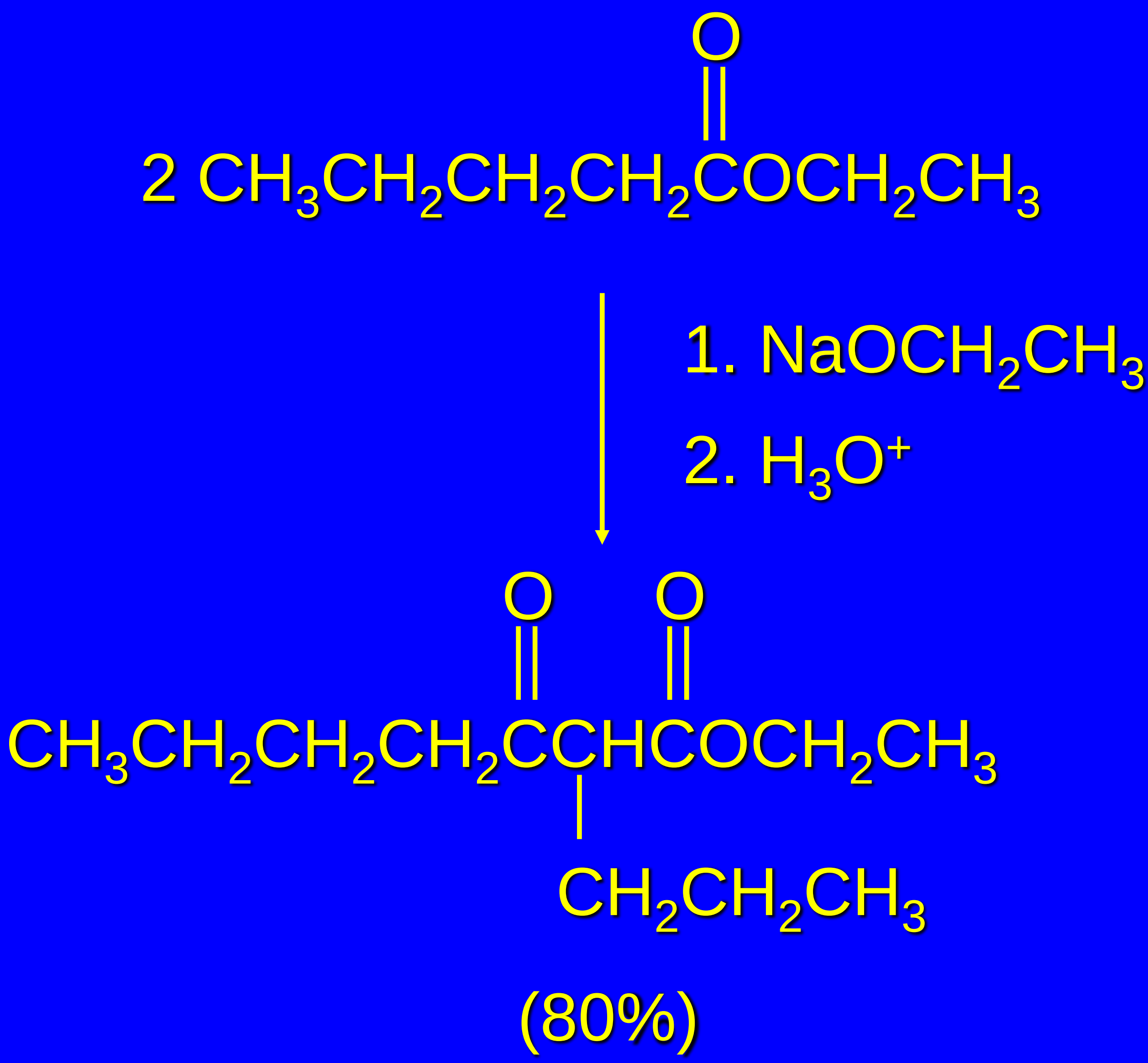


β-Keto acids decarboxylate readily to give ketones (Section 19.17).

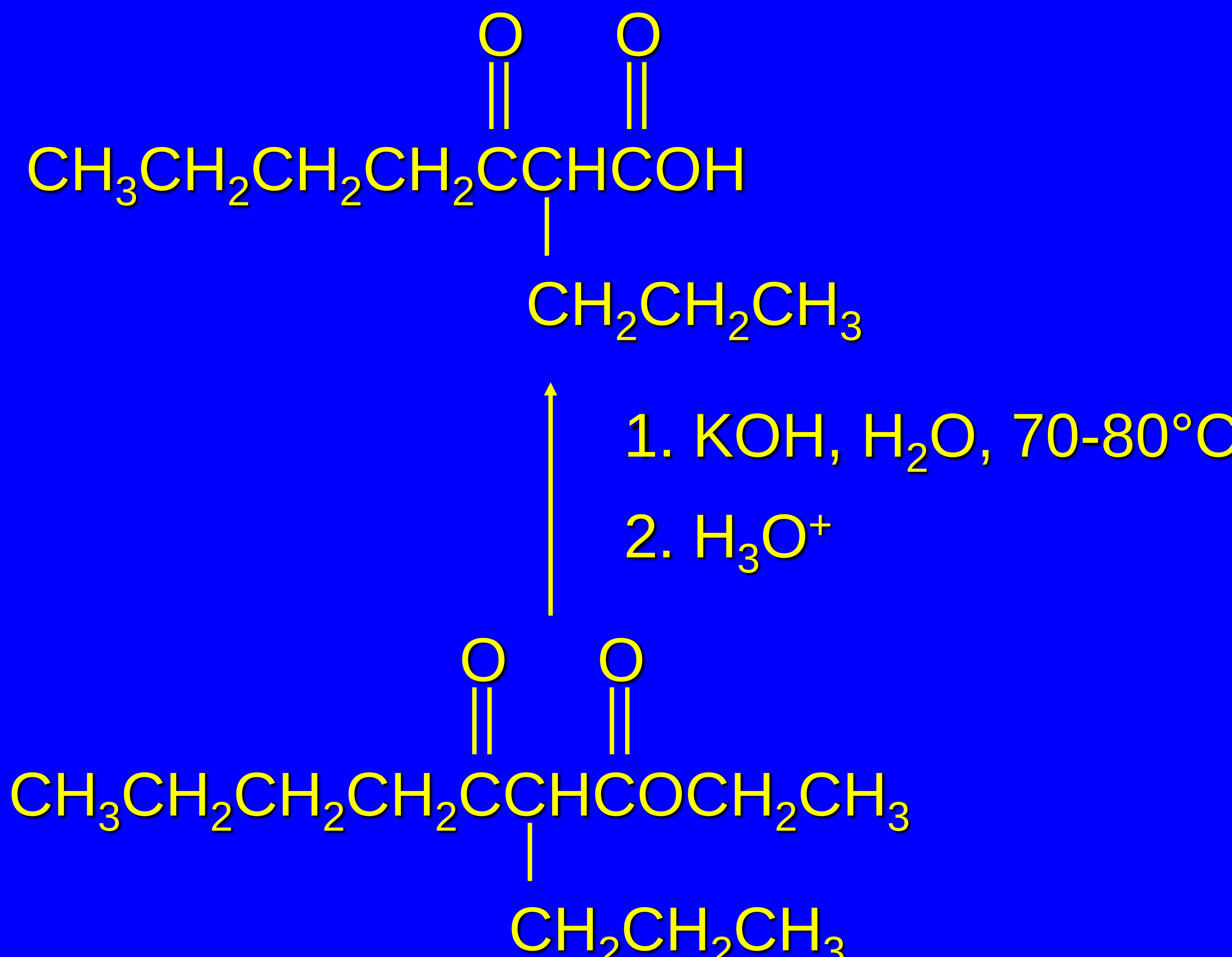
β-Keto acids are available by hydrolysis of β-keto esters.

β-Keto esters can be prepared by the Claisen condensation.

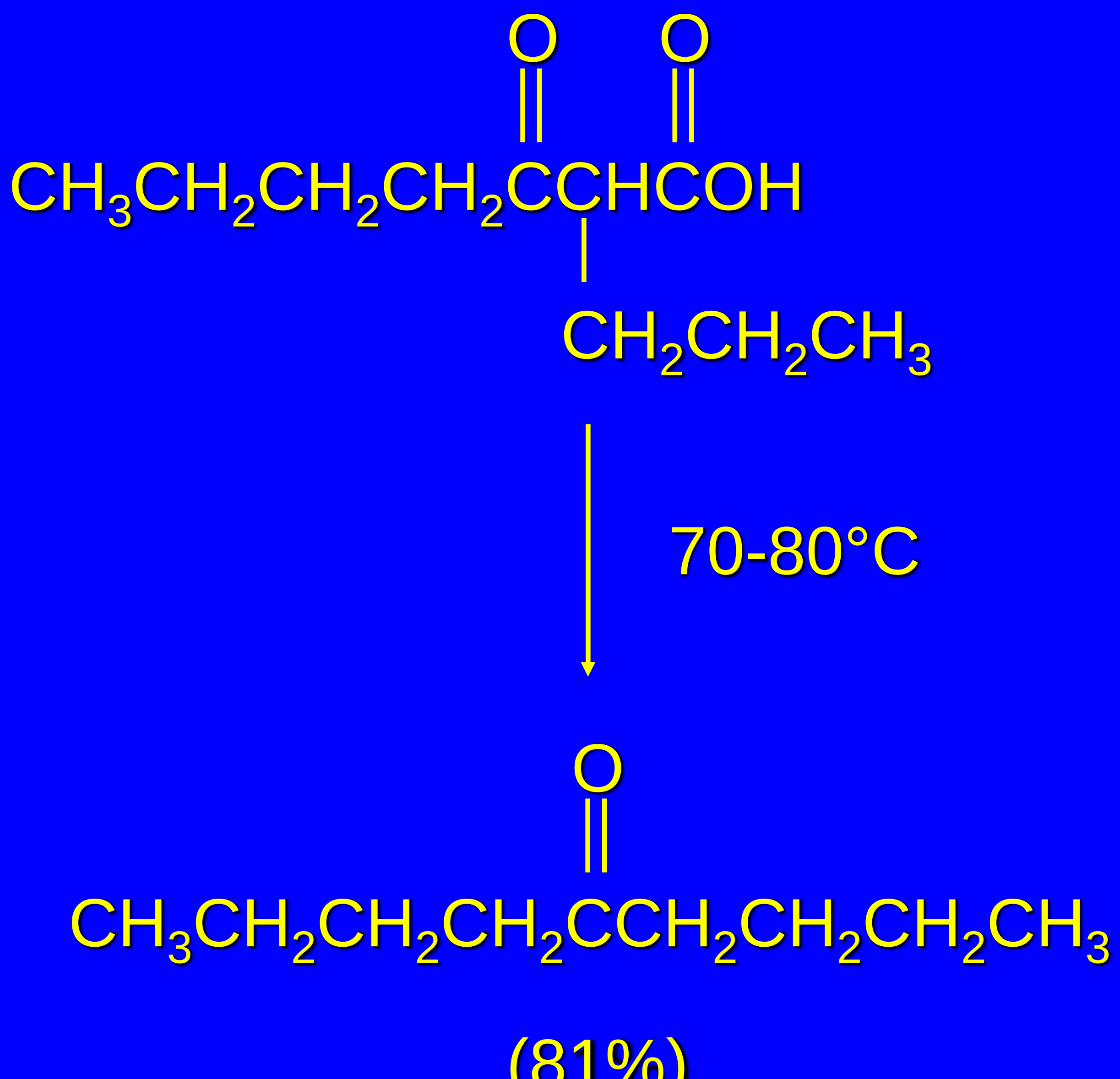
The β-Keto Ester Synthesis of Ketones - Example 1



The β-Keto Ester Synthesis of Ketones - Example 2



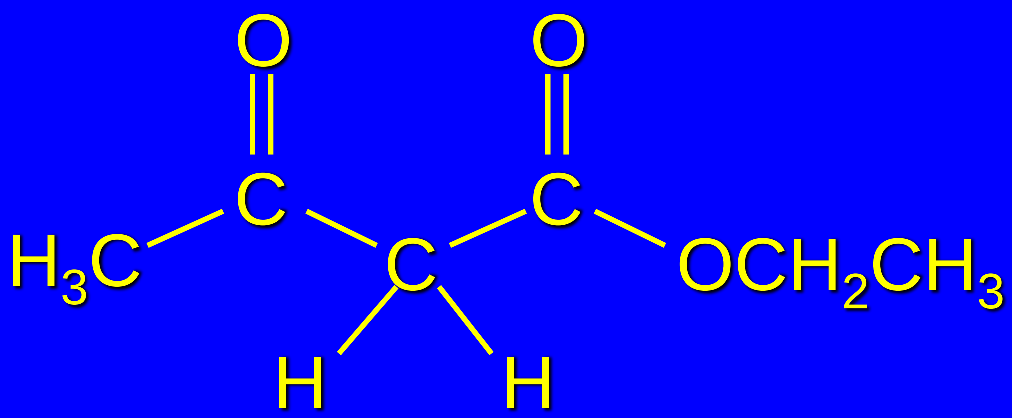
The β-Keto Ester Synthesis of Ketones - Example 3



21.6

The Acetoacetic Ester Synthesis

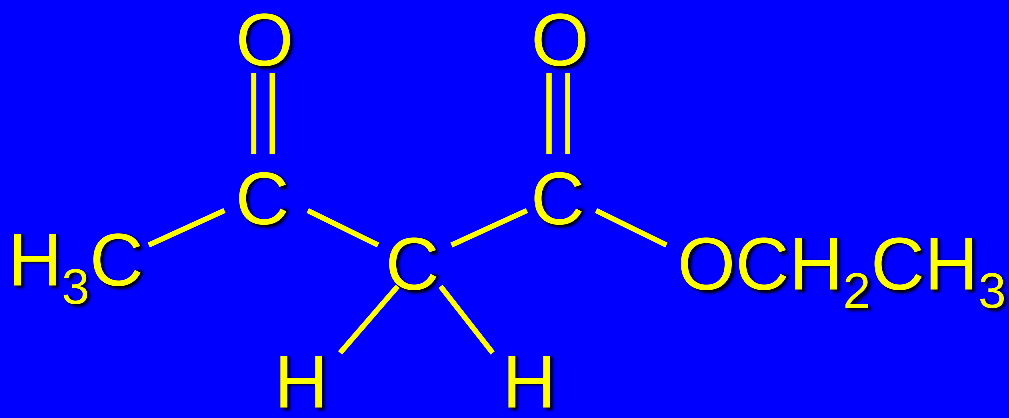
Acetoacetate Esters



Acetoacetic ester is another name for *ethyl acetoacetate*.

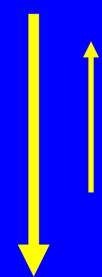
The "acetoacetic ester synthesis" uses acetoacetic ester as a reactant for the preparation of ketones.

Ethyl Acetoacetate is Deprotonated by Sodium Ethoxide

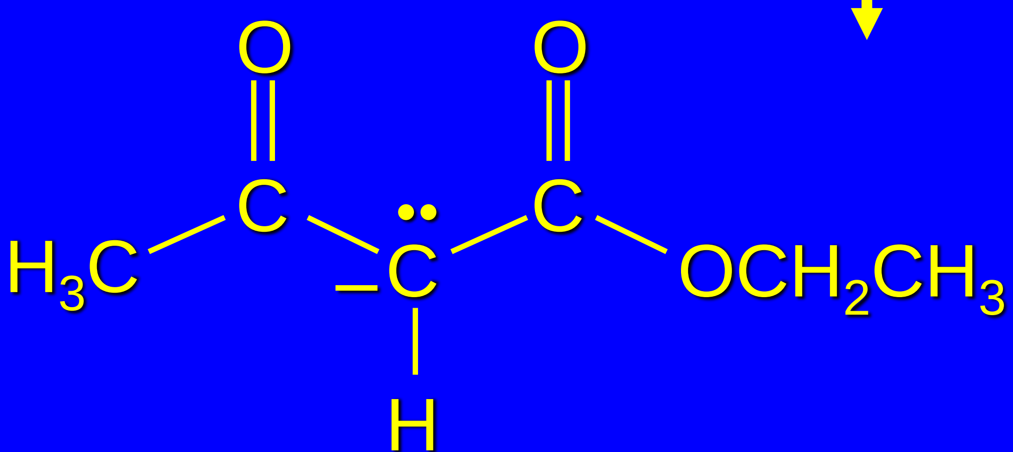


pK_a ~ 11

+ $CH_3CH_2O^-$



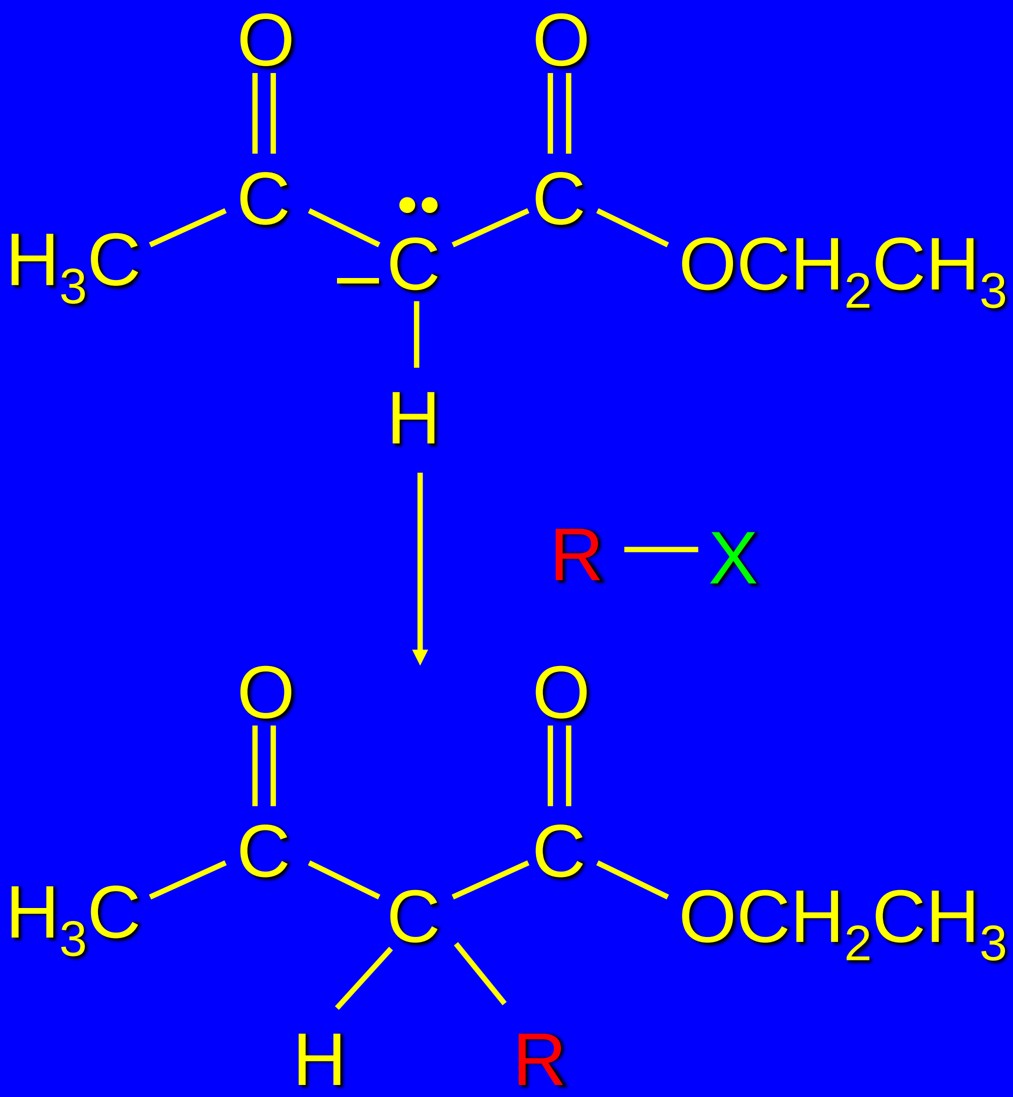
Ethyl acetoacetate can be converted readily to its anion with bases such as sodium ethoxide.



+ CH_3CH_2OH

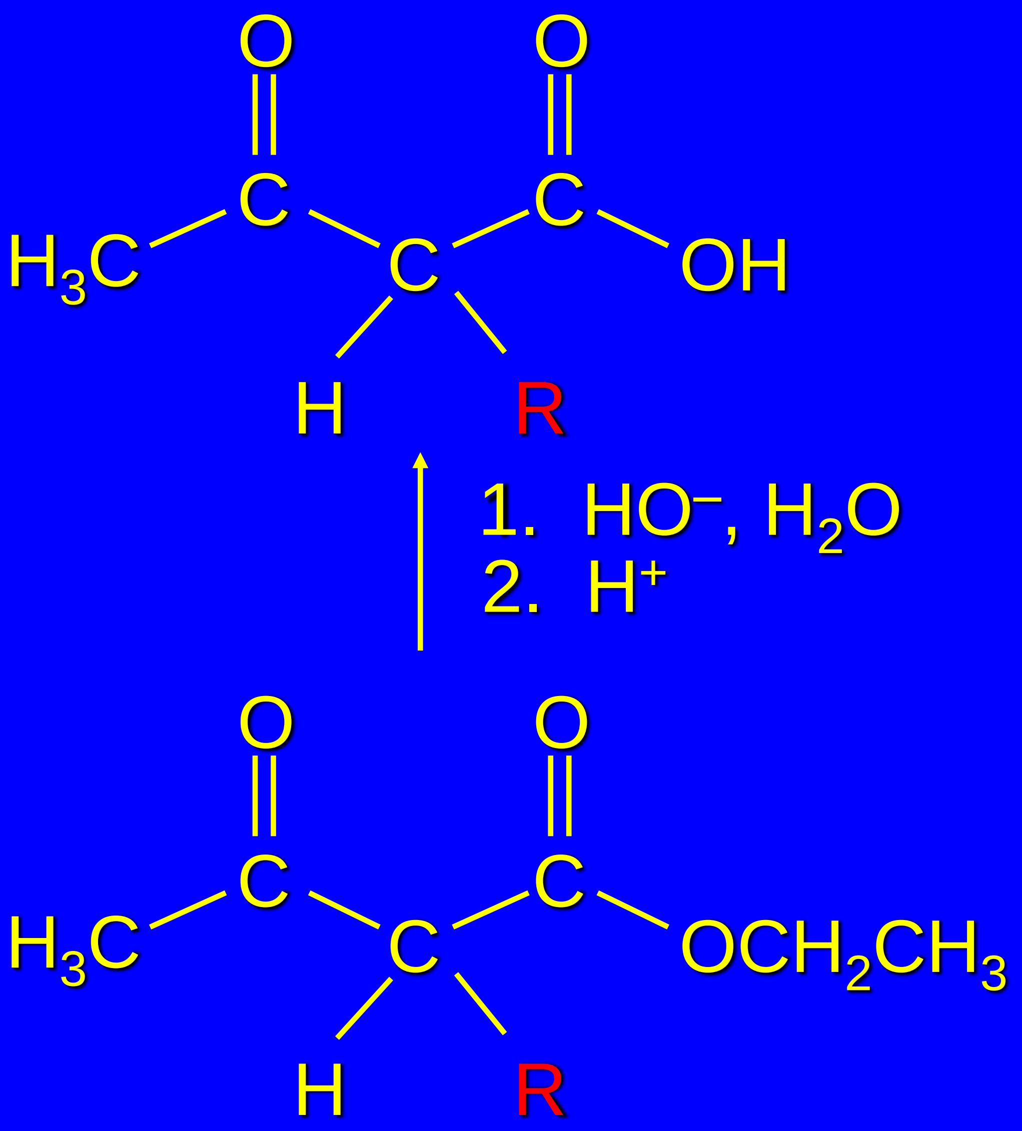
pK_a ~ 16

Alkylation of Ethyl Acetoacetate



The anion of ethyl acetoacetate can be alkylated using an alkyl halide (S_N2: primary and secondary alkyl halides work best; tertiary alkyl halides undergo elimination).

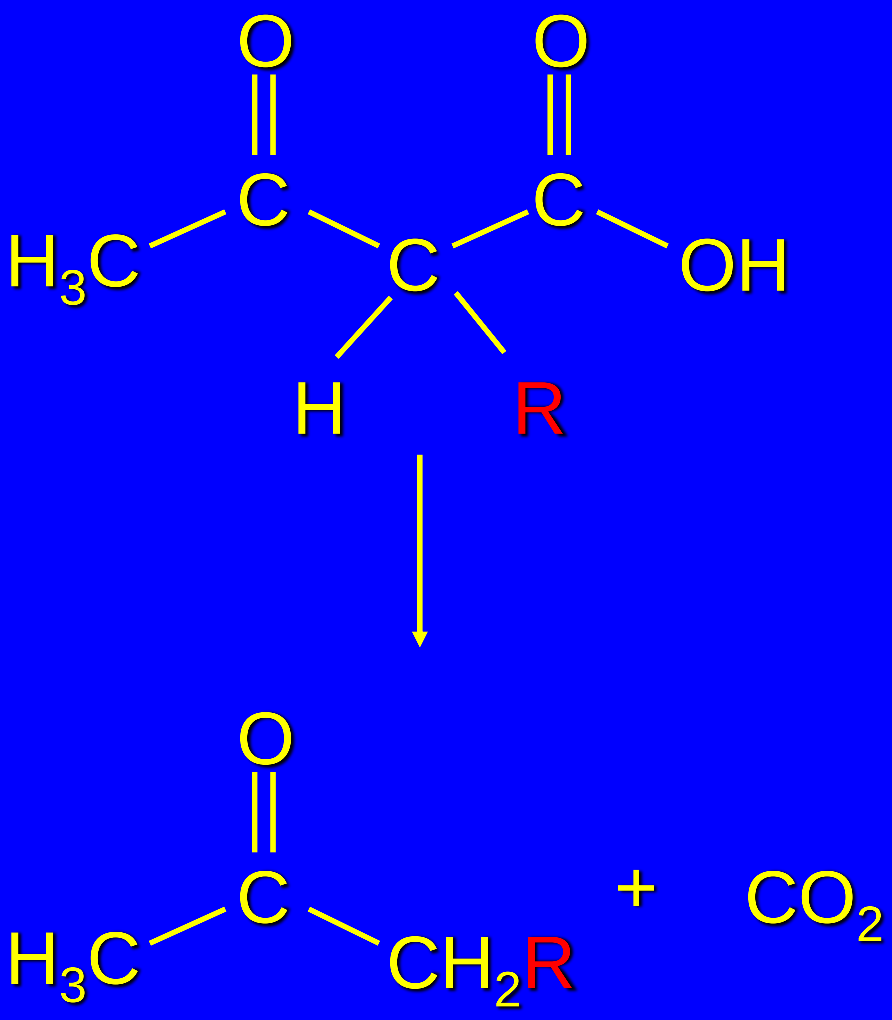
Conversion to Ketone



Saponification and acidification convert the alkylated derivative to the corresponding β-keto acid.

The β-keto acid then undergoes decarboxylation to form a ketone.

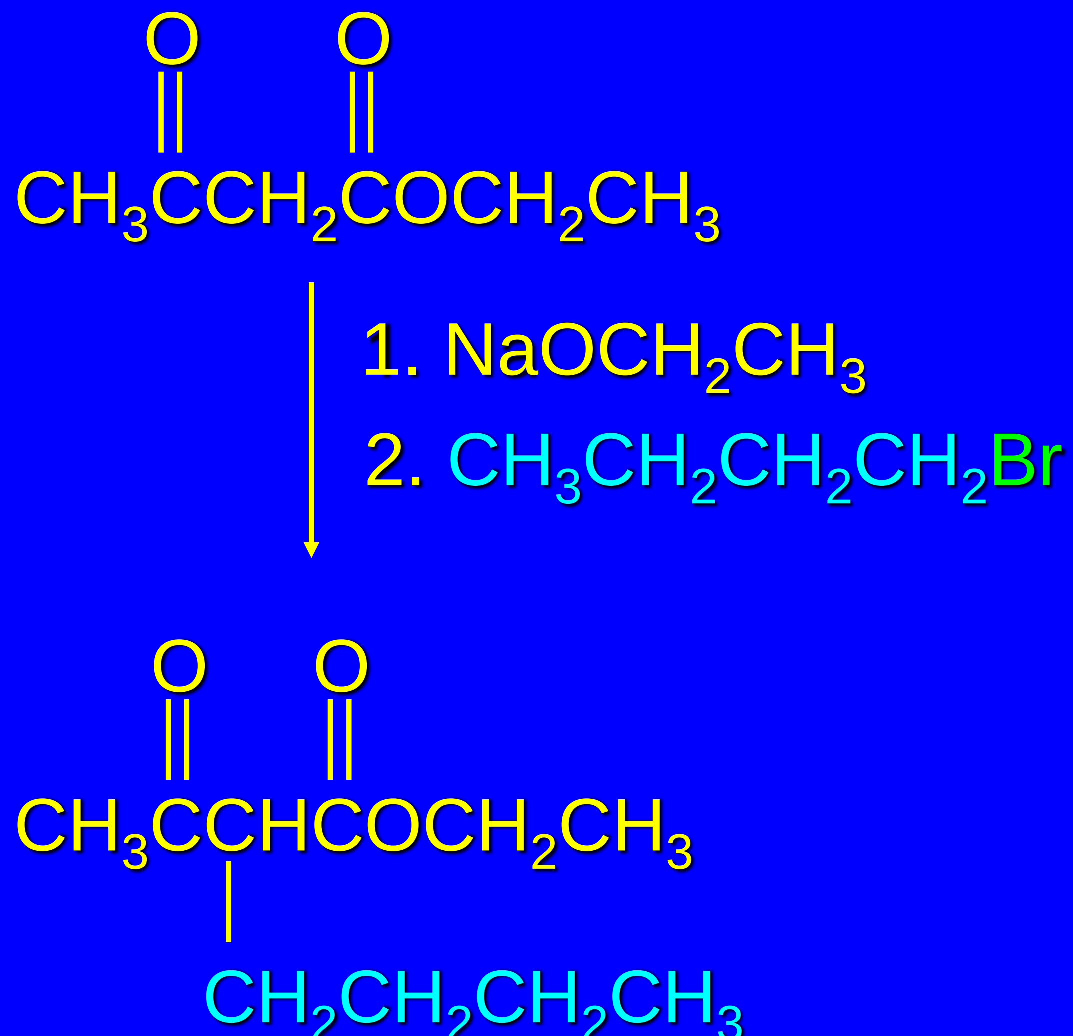
Conversion to Ketone



Saponification and acidification convert the alkylated derivative to the corresponding β-keto acid.

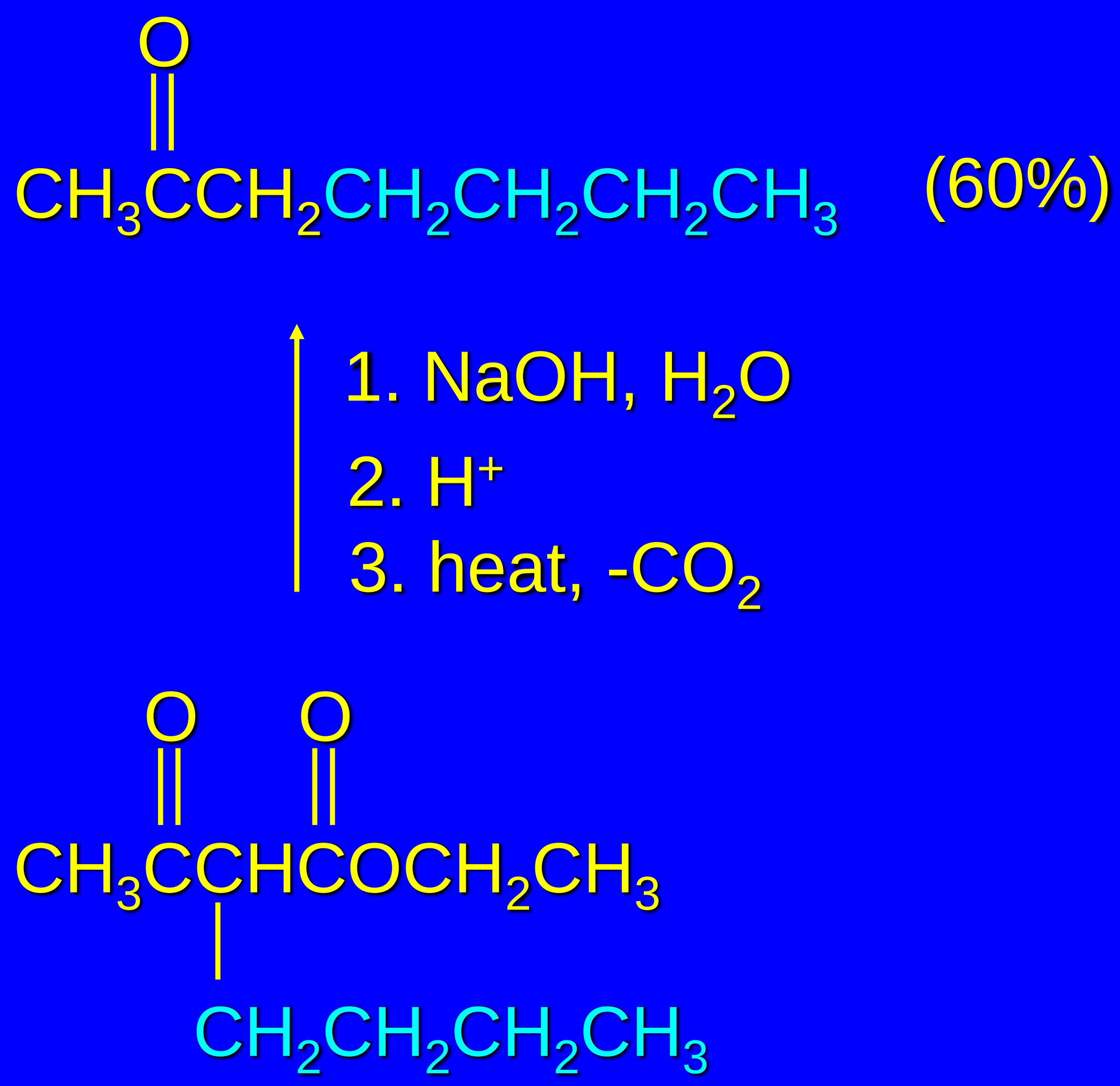
The β-keto acid then undergoes decarboxylation to form a ketone.

Example


O O
CH3CCH2COCH2CH3
1. NaOCH2CH3
2. CH3CH2CH2CH2Br
O O
CH3CCHCOCH2CH3
CH2CH2CH2CH3

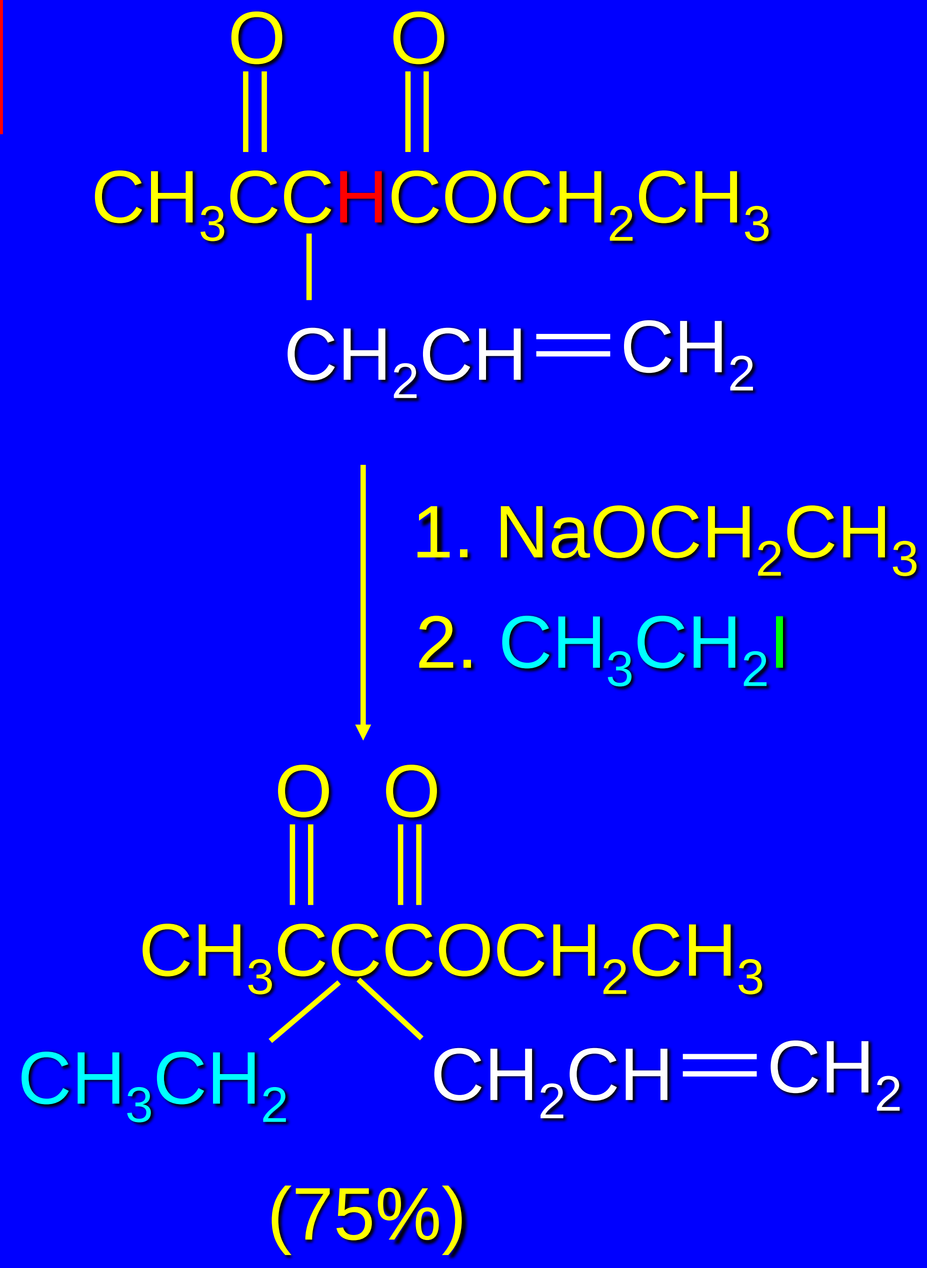
(70%)

Example

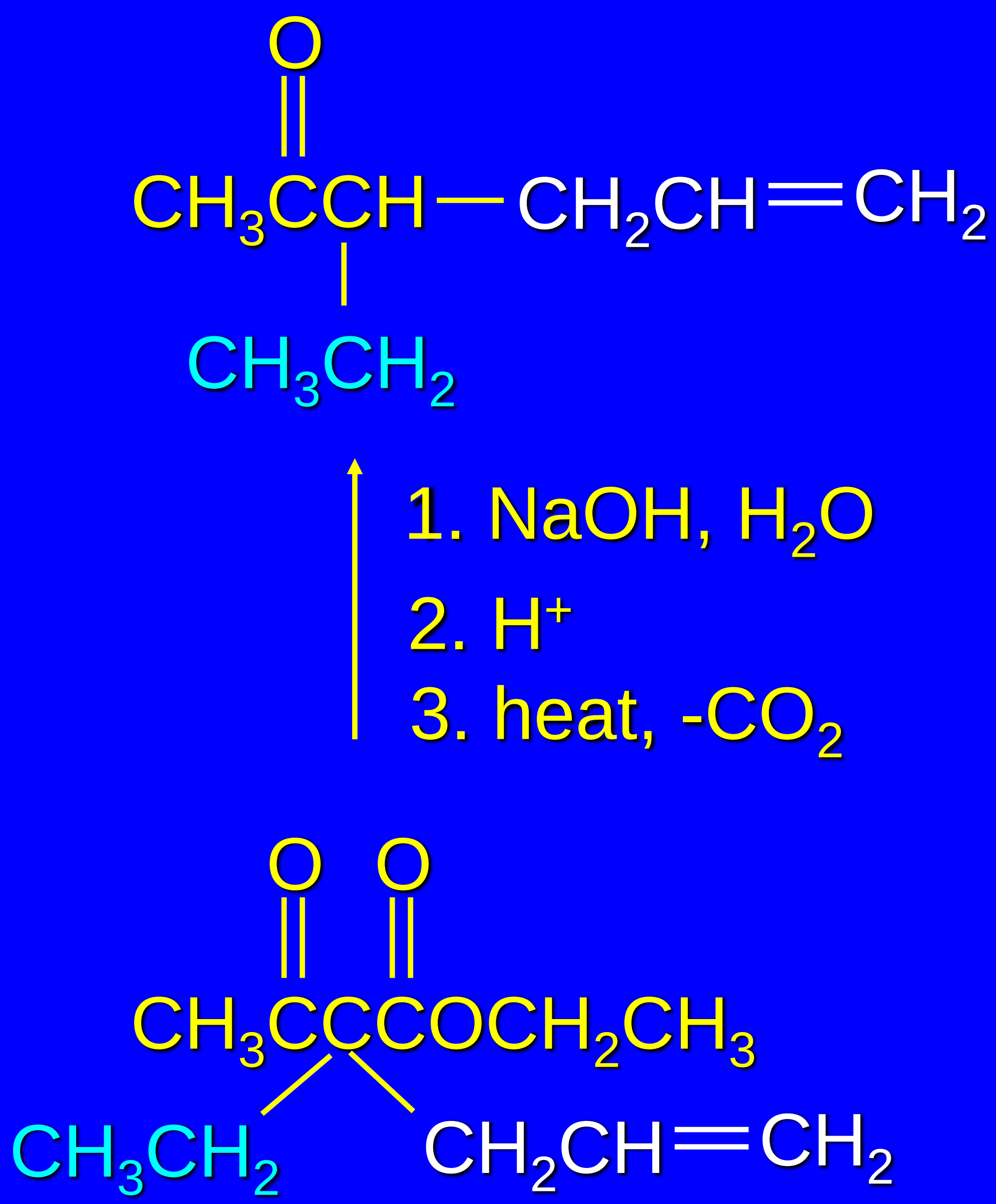


O
CH3CCH2CH2CH2CH2CH3
(60%)
1. NaOH, H2O
2. H+
3. heat, -CO2
O O
CH3CCHCOCH2CH3
CH2CH2CH2CH3

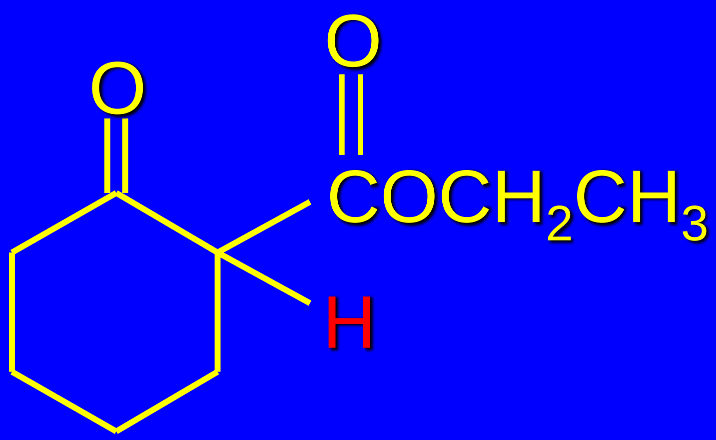
Example: Dialkylation



Example: Dialkylation

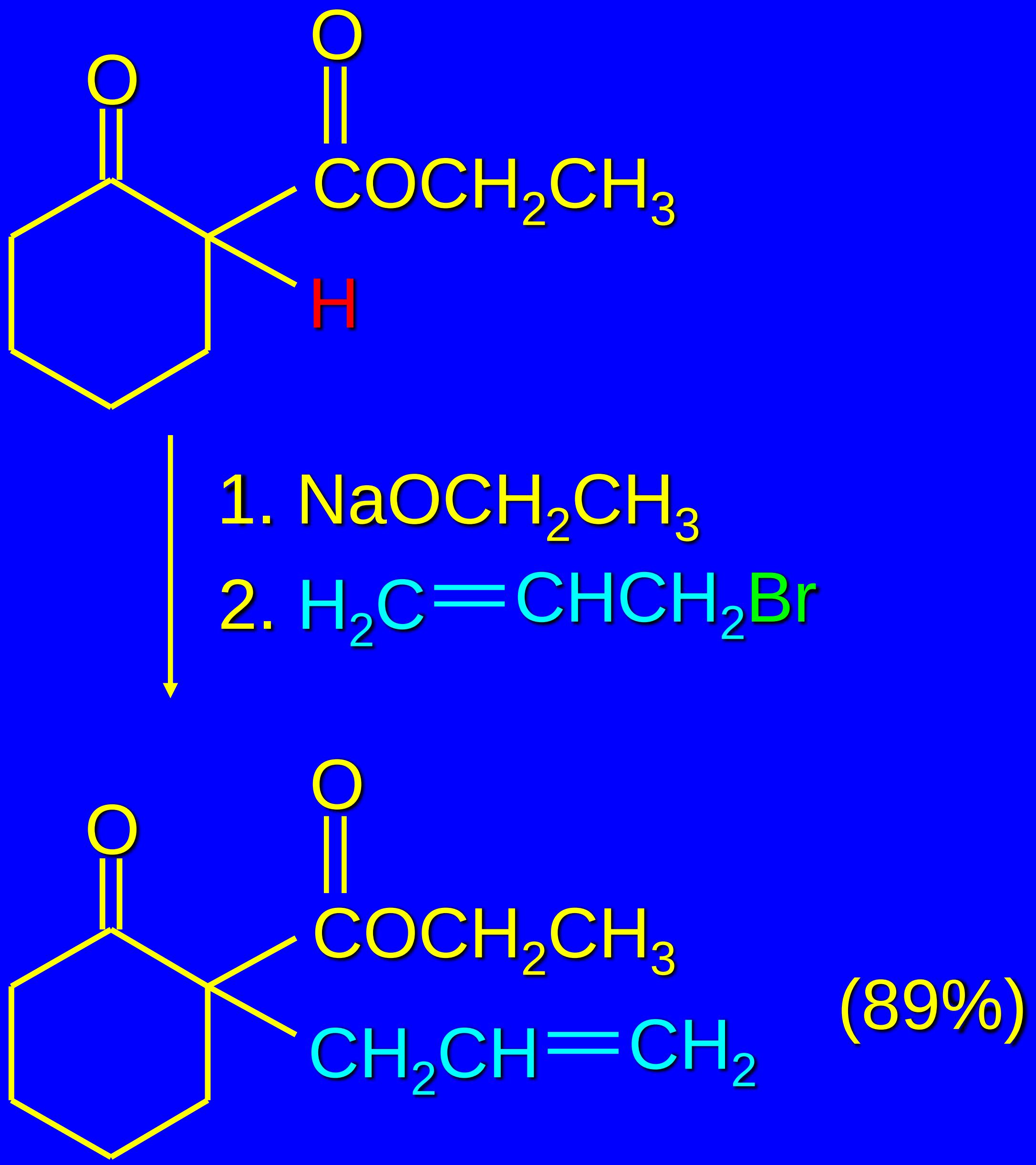


Another Example

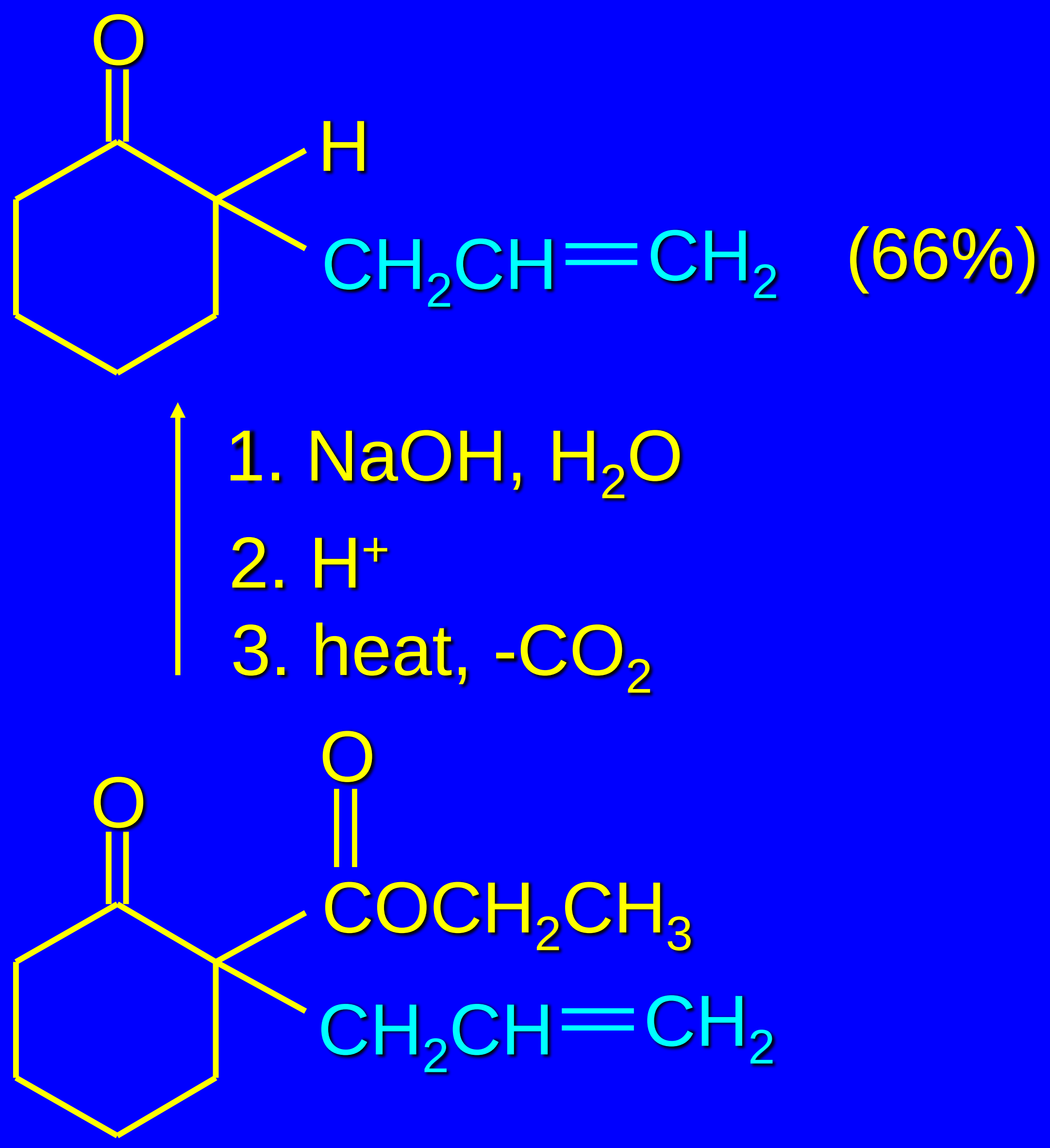


β-Keto esters other than ethyl acetoacetate may be used.

Another Example



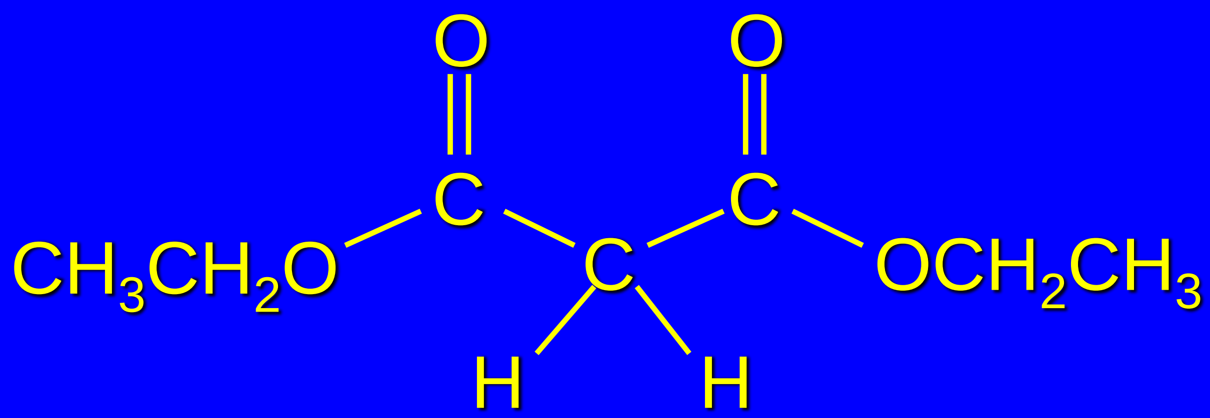
Another Example



21.7

The Malonic Ester Synthesis

Malonic Ester

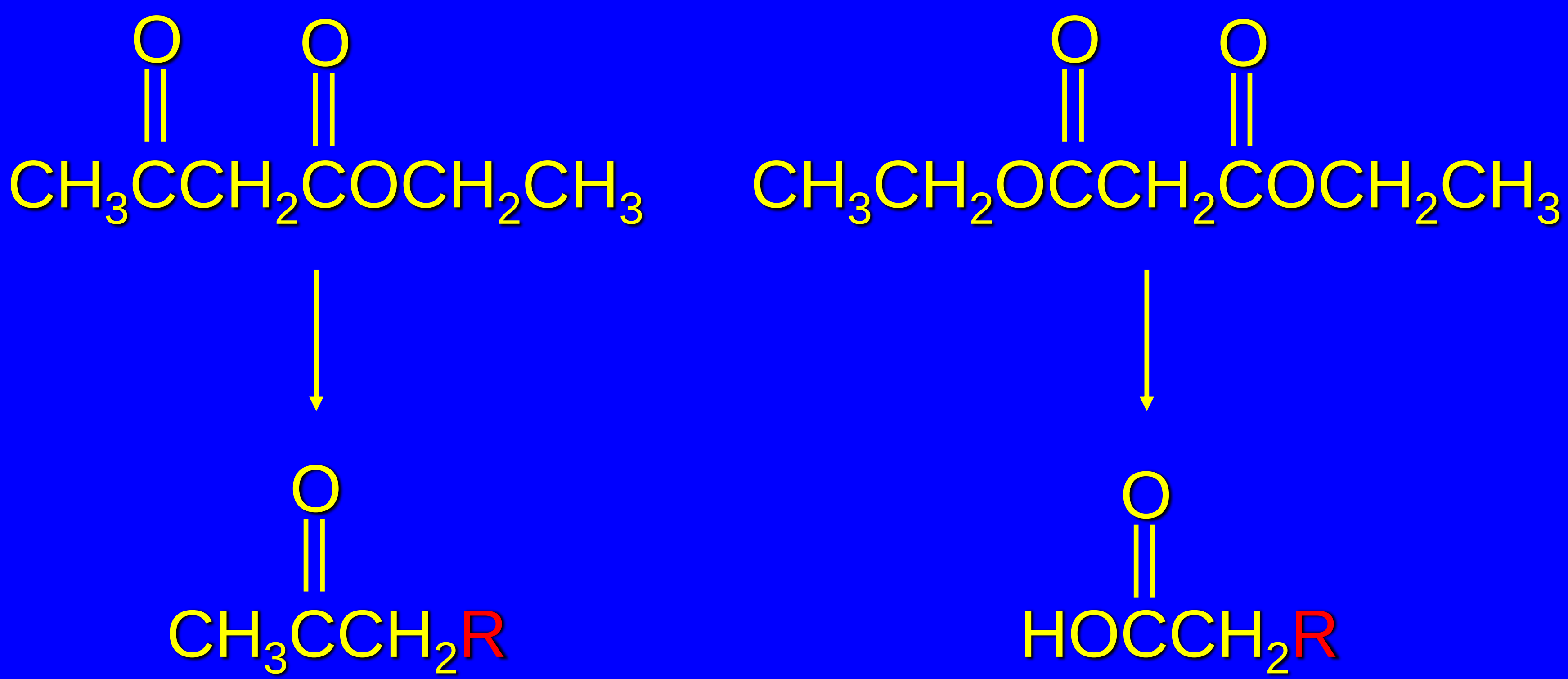


Malonic ester is another name for *diethyl malonate*.

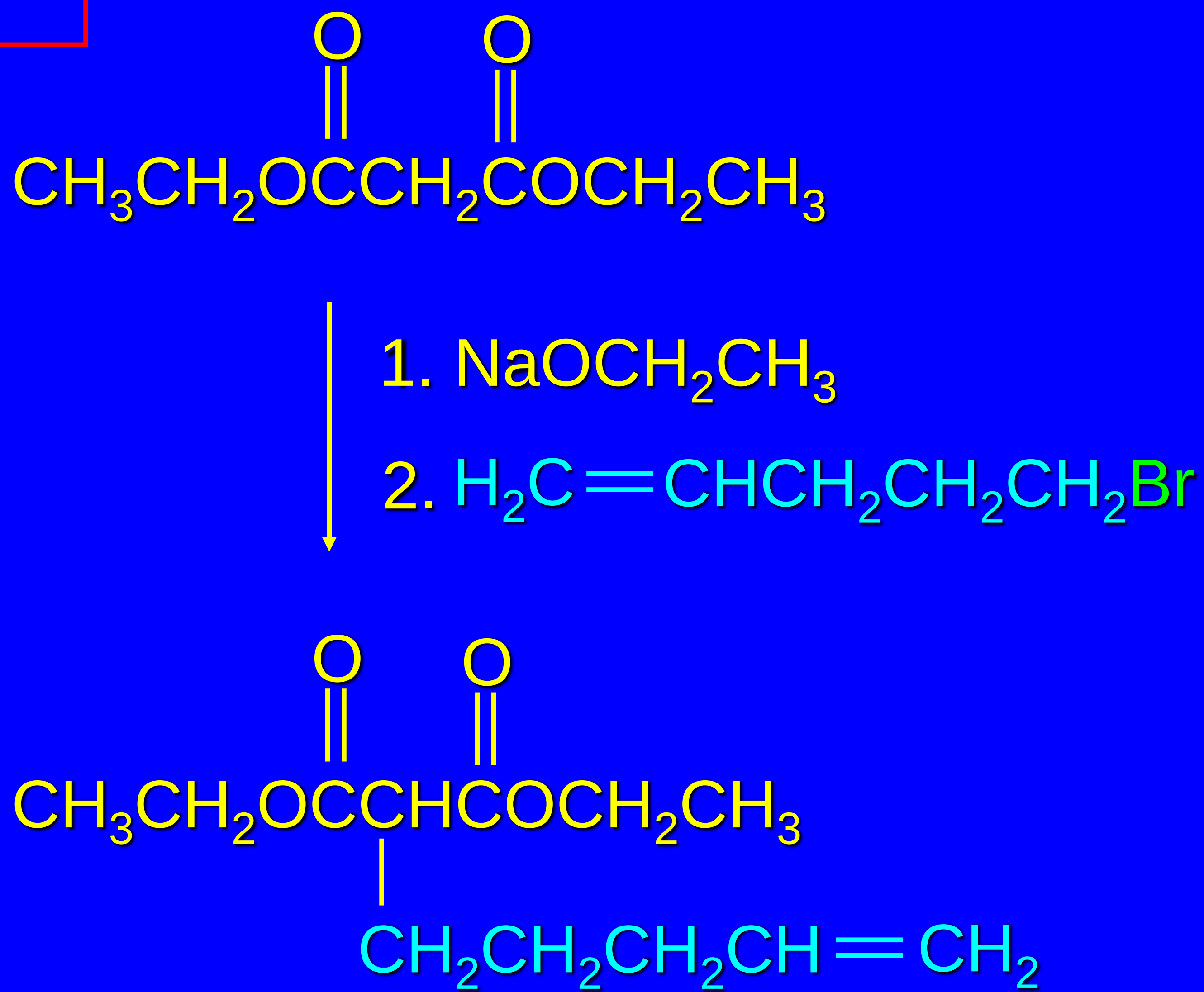
The "malonic ester synthesis" uses diethyl malonate as a reactant for the preparation of carboxylic acids.

An Analogy

The same procedure by which ethyl acetoacetate is used to prepare ketones converts diethyl malonate to carboxylic acids.



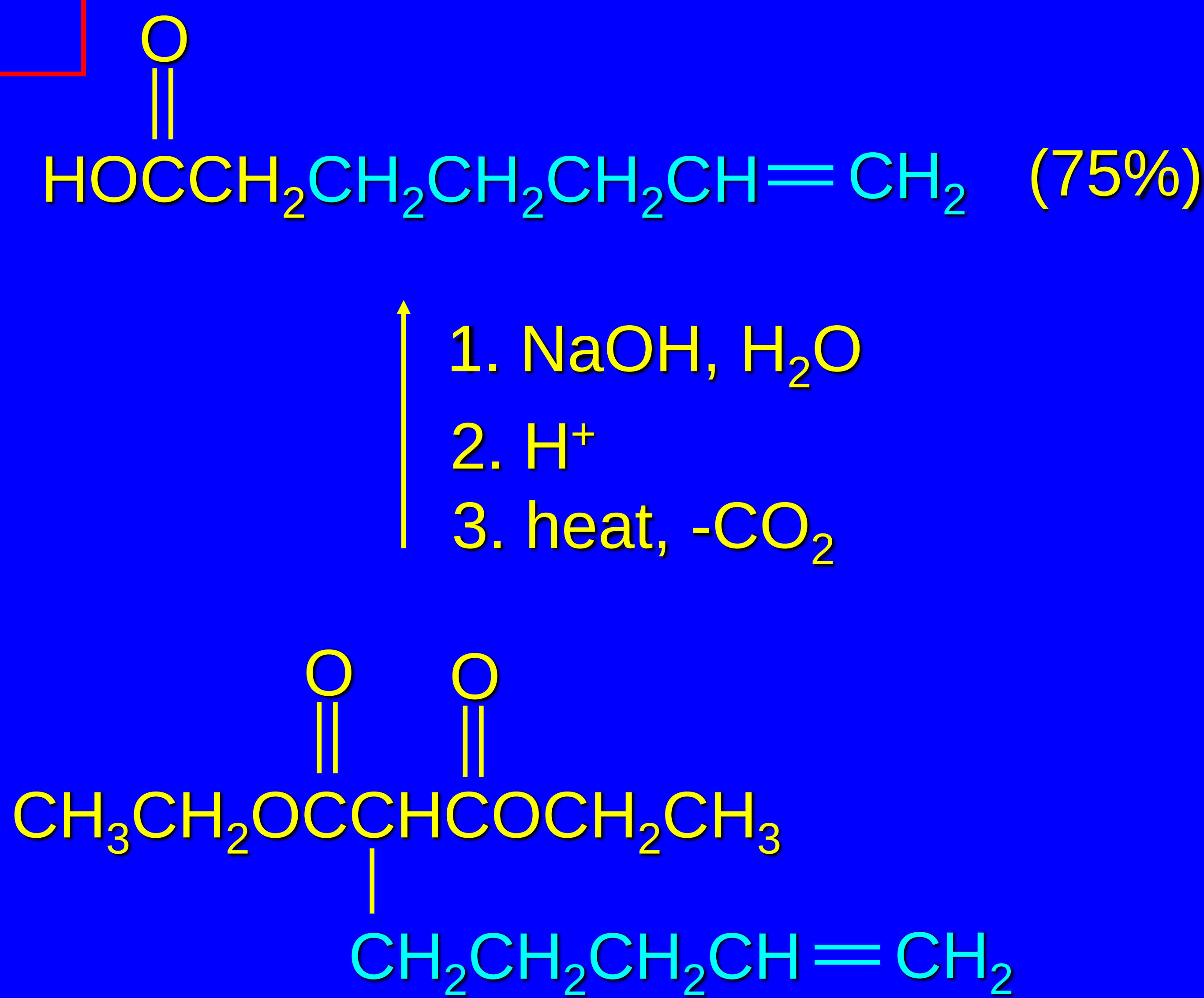
Example



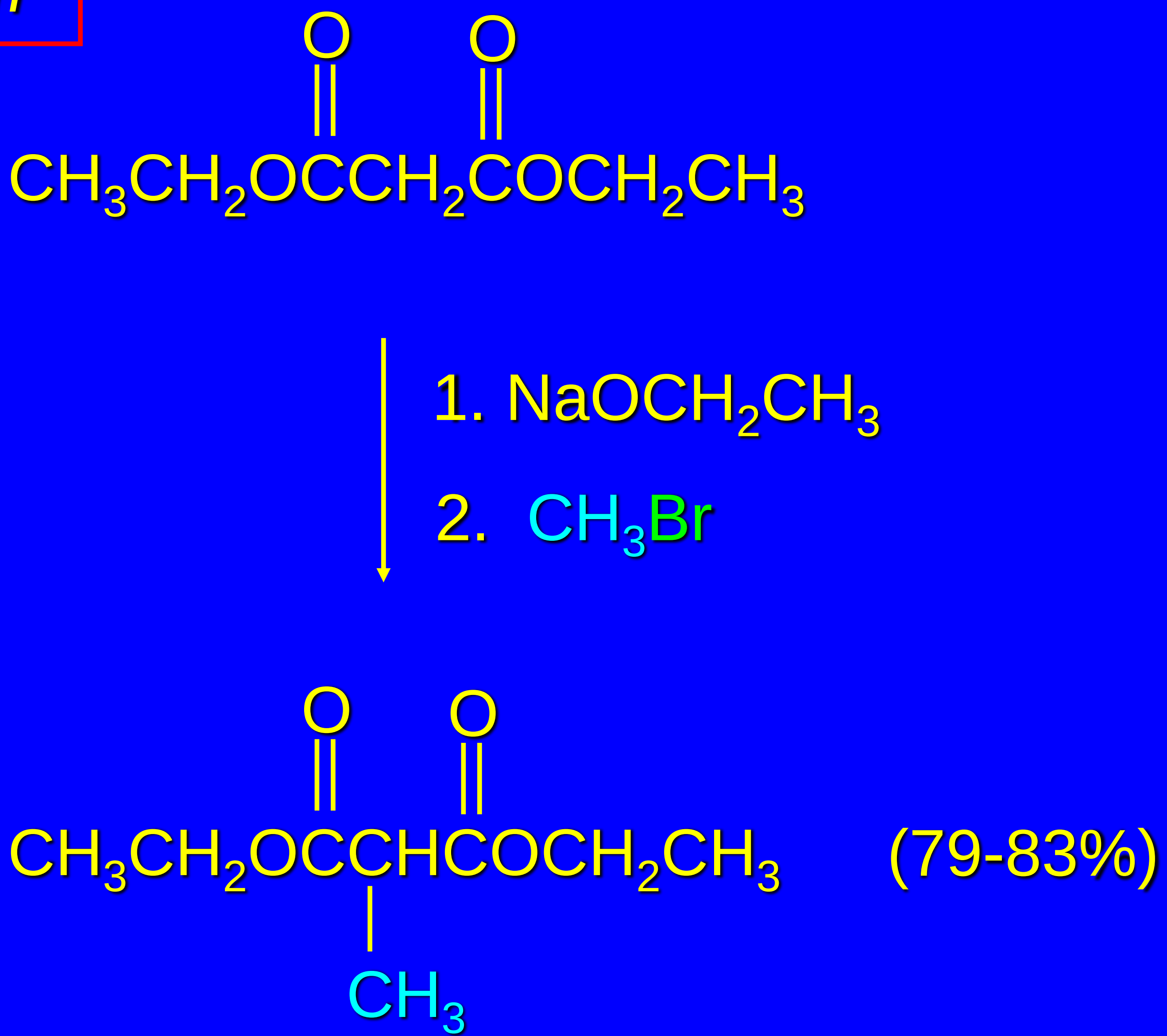
CH3CH2OCCH2COCH2CH3
1. NaOCH2CH3
2. H2C═CHCH2CH2CH2Br
CH3CH2OCCHCOCH2CH3
CH2CH2CH2CH═CH2

(85%)

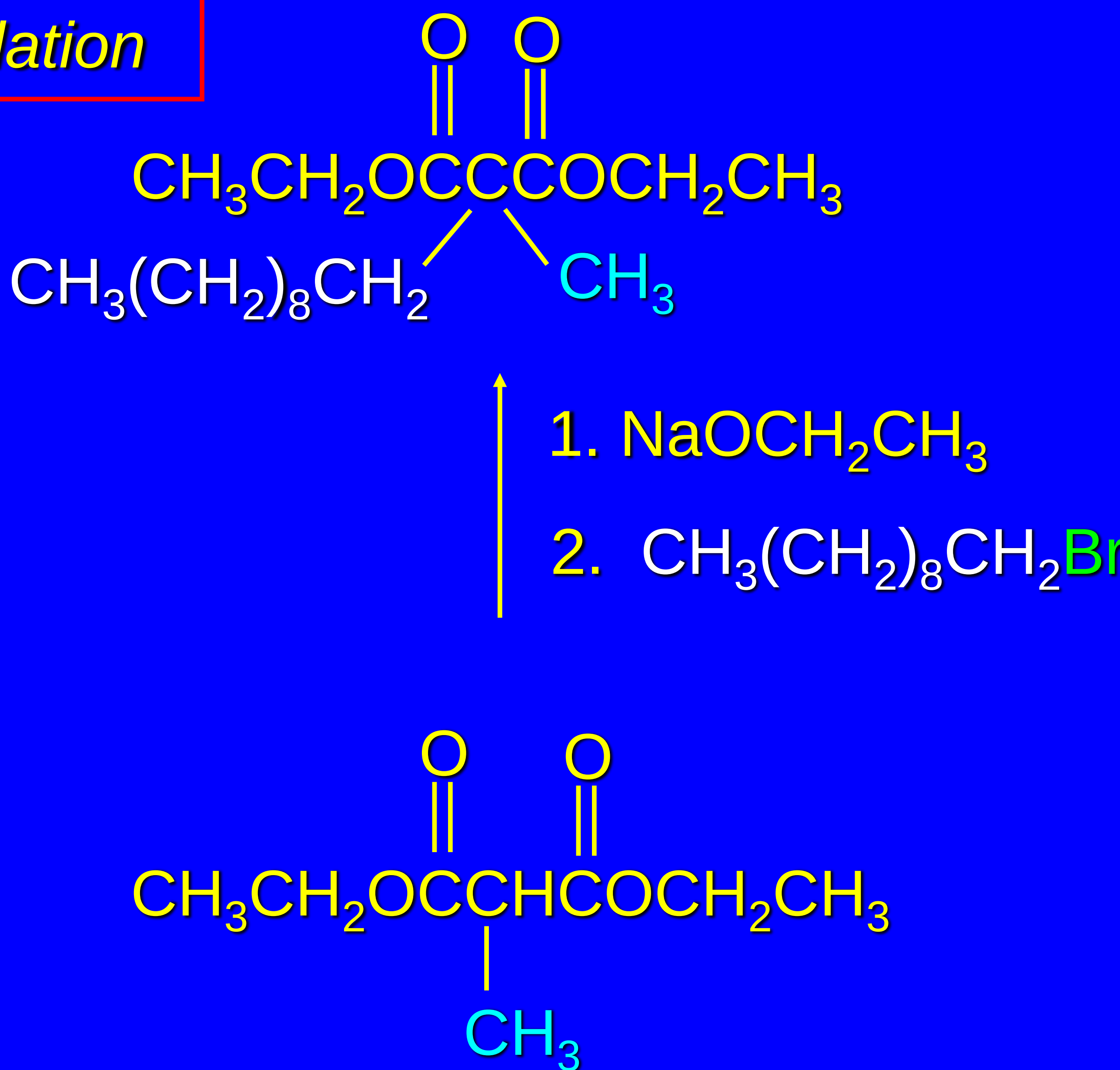
Example


HOCCH2CH2CH2CH2CH=CH2
(75%)
1. NaOH, H2O
2. H+
3. heat, -CO2
CH3CH2OCCHCOCH2CH3
CH2CH2CH2CH=CH2

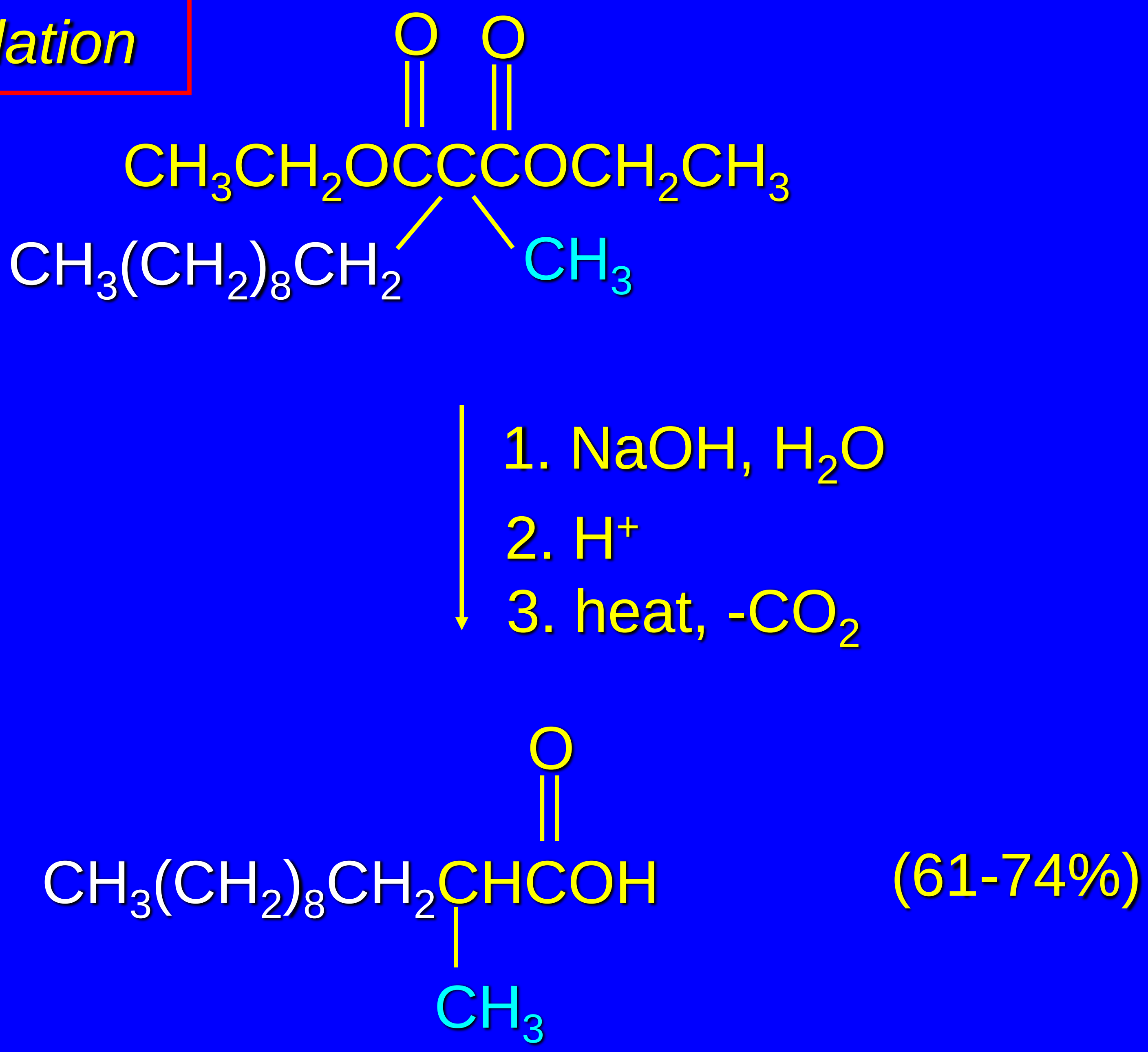
Dialkylation



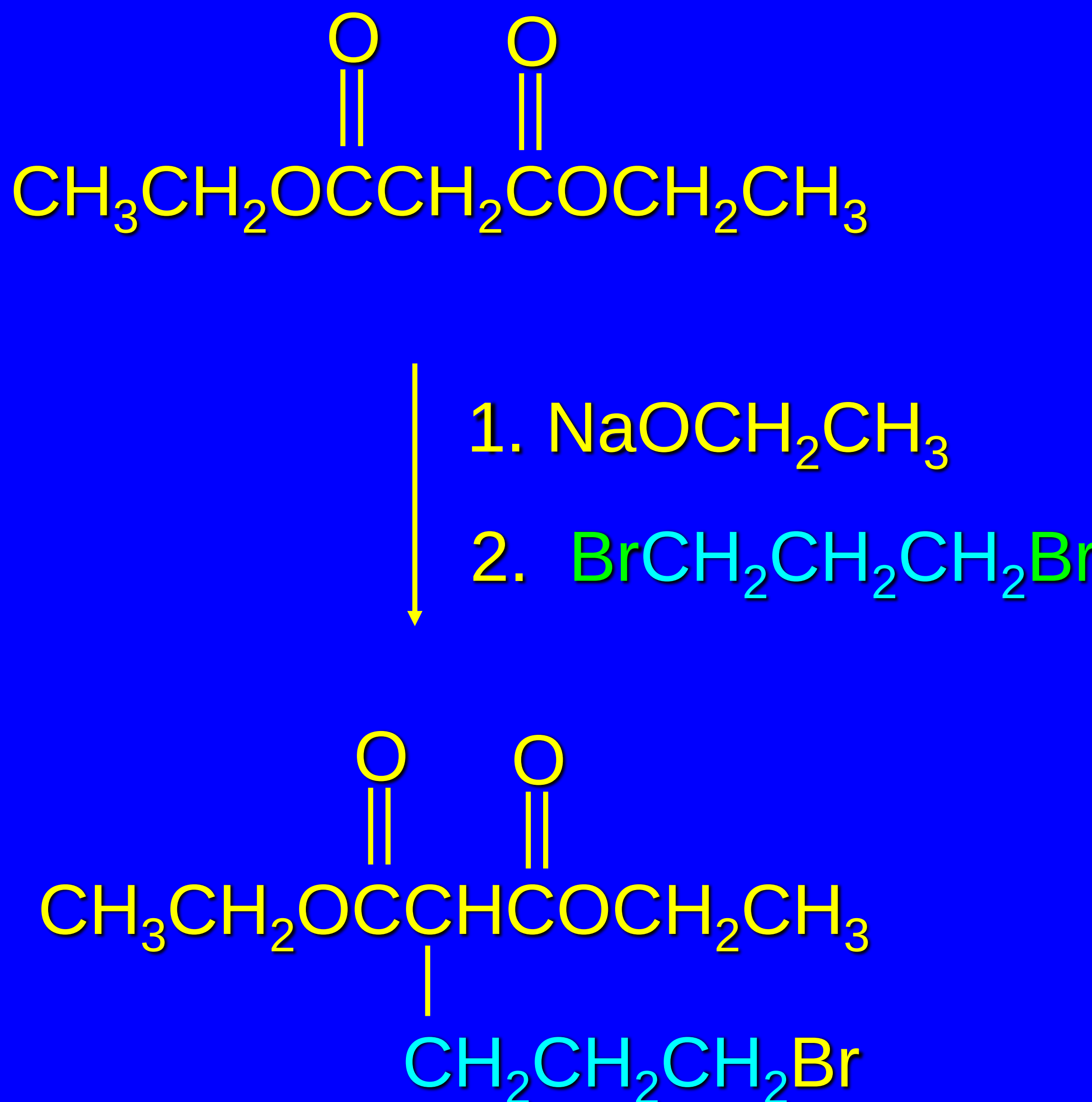
Dialkylation



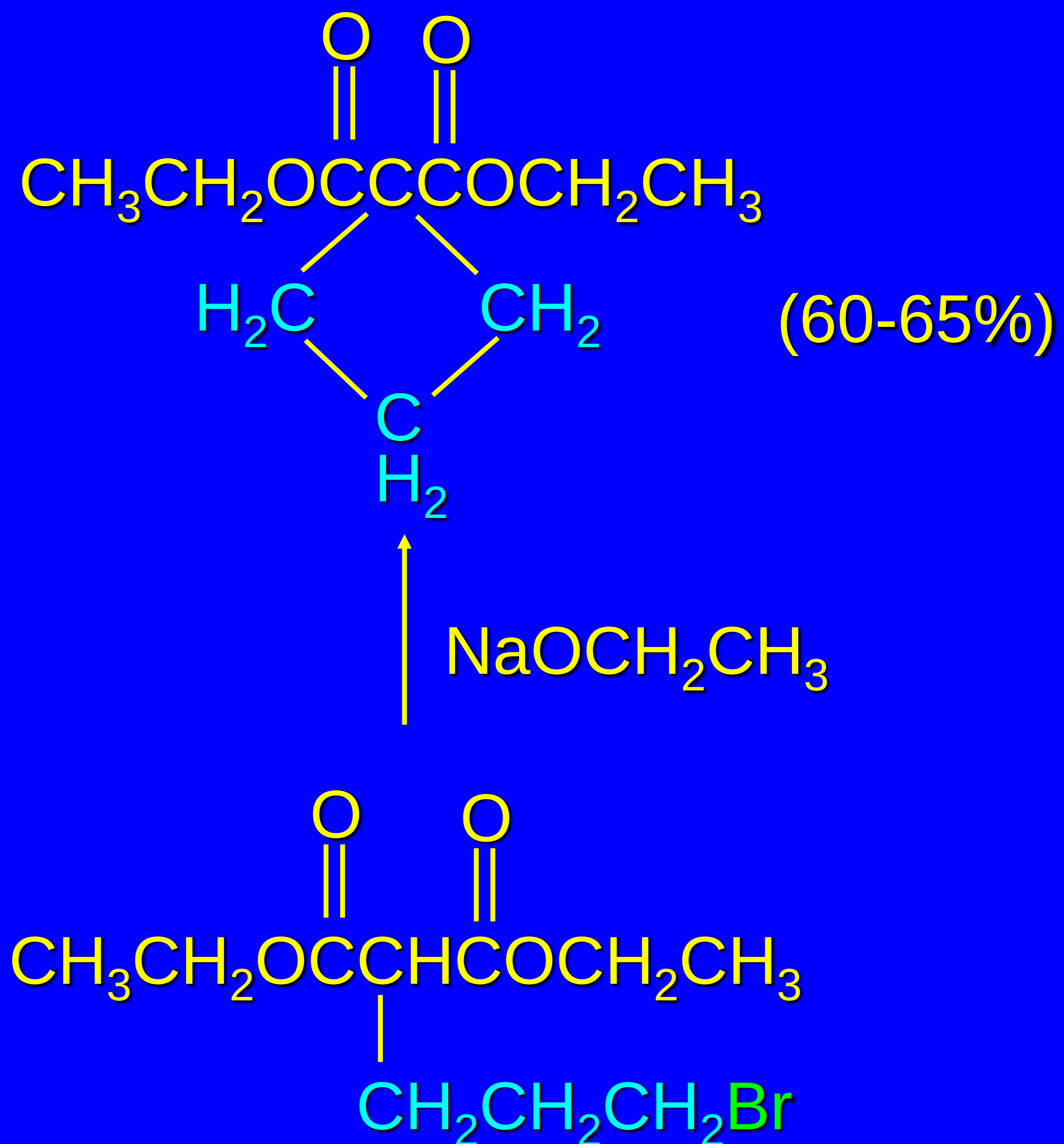
Dialkylation



Another Example

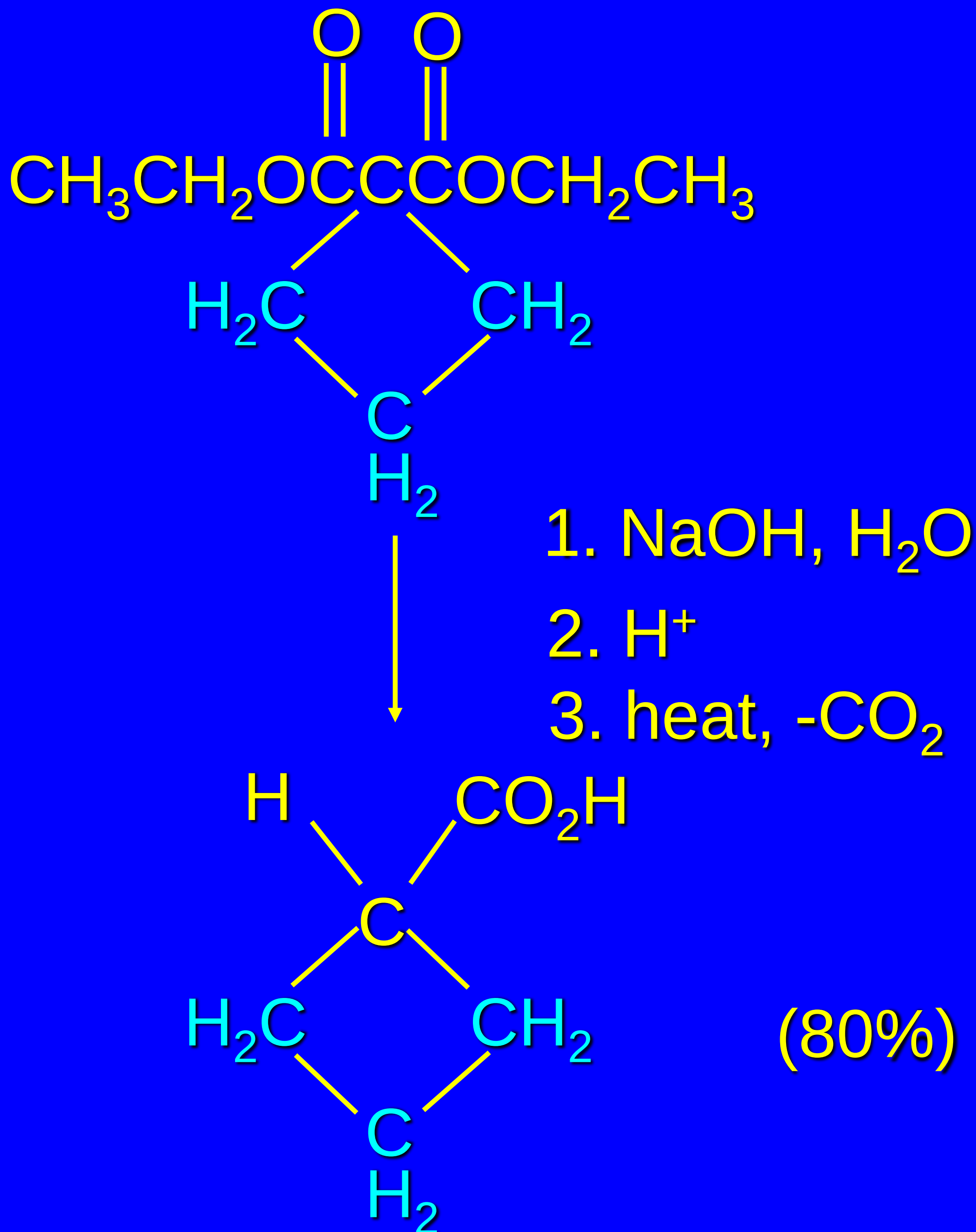


Another Example



This product is not isolated, but cyclizes in the presence of sodium ethoxide.

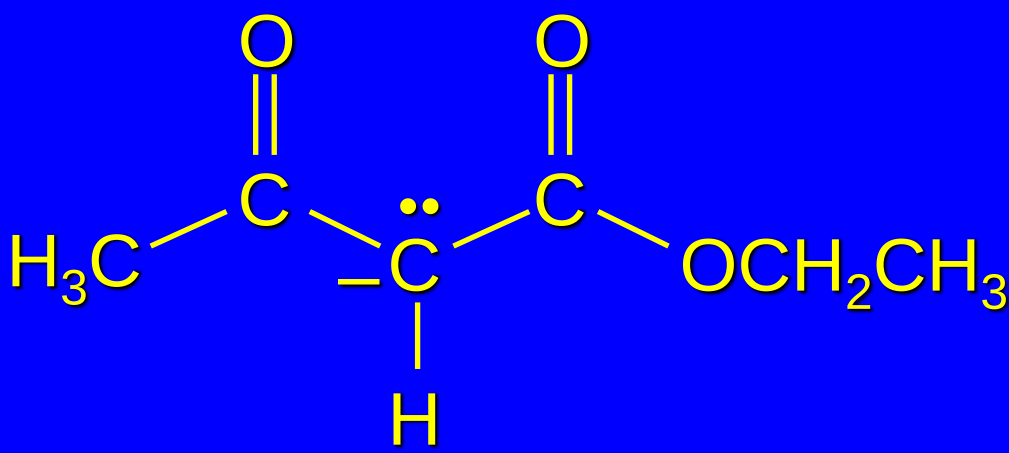
Another Example

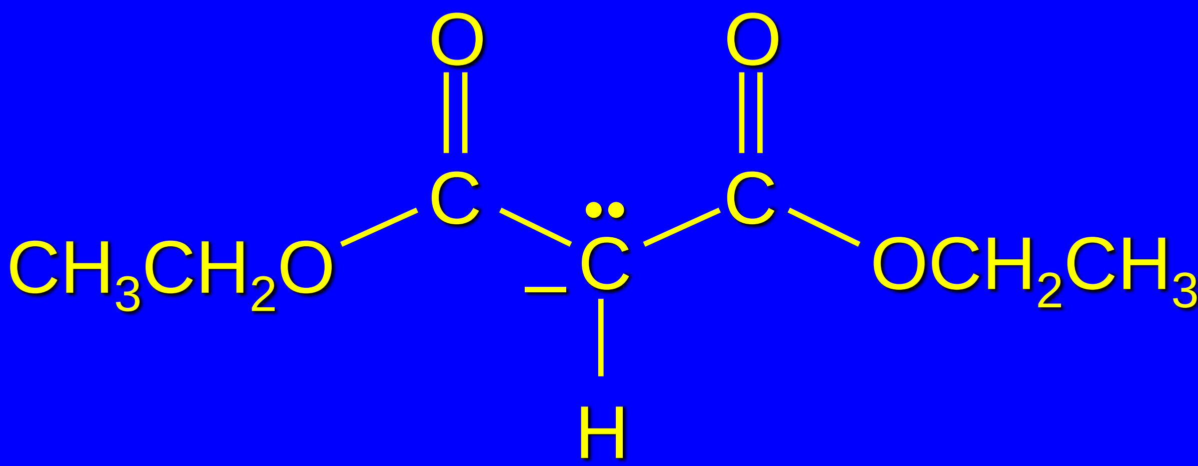


21.9

Michael Additions of Stabilized Anions

Stabilized Anions

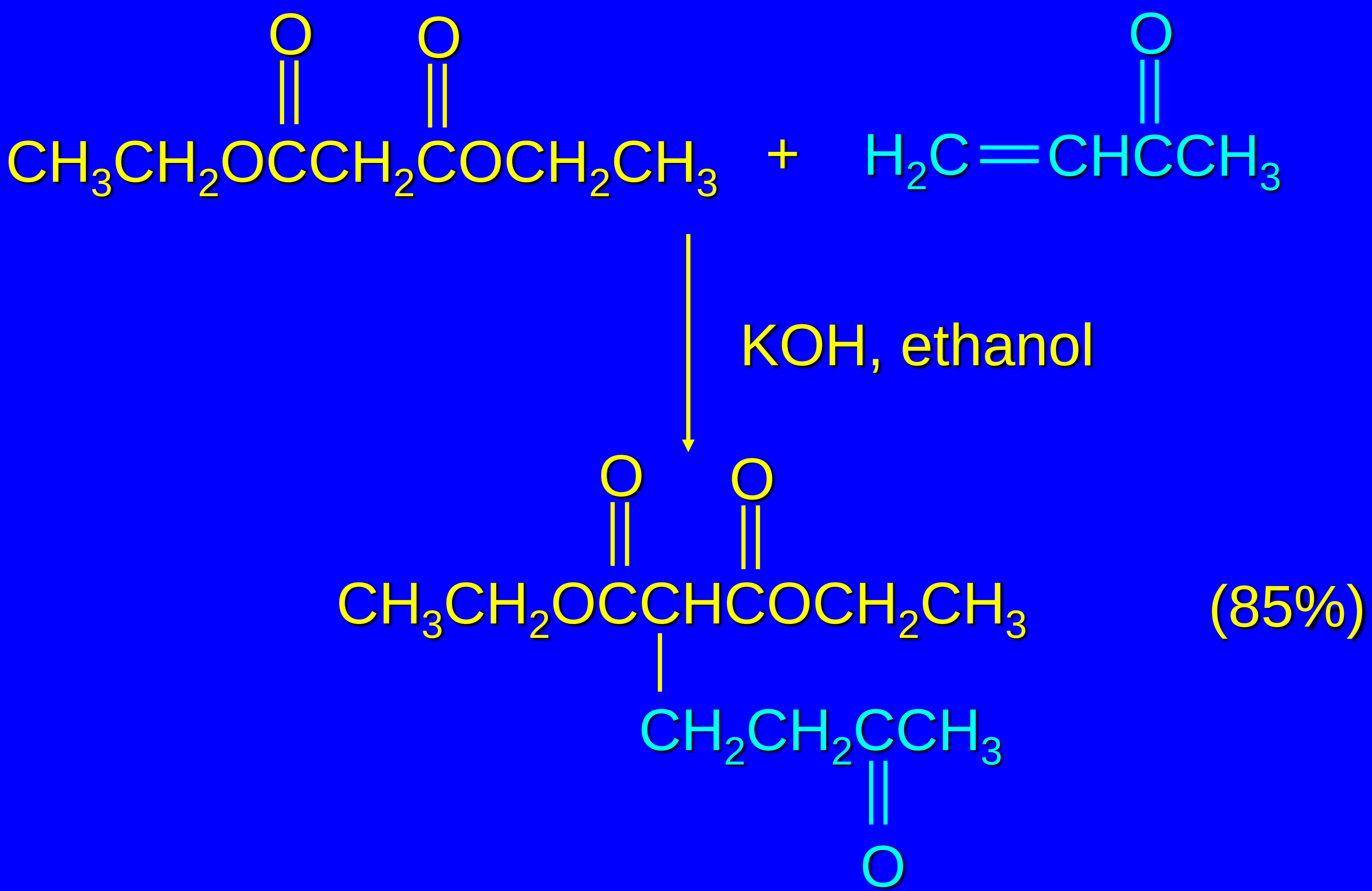




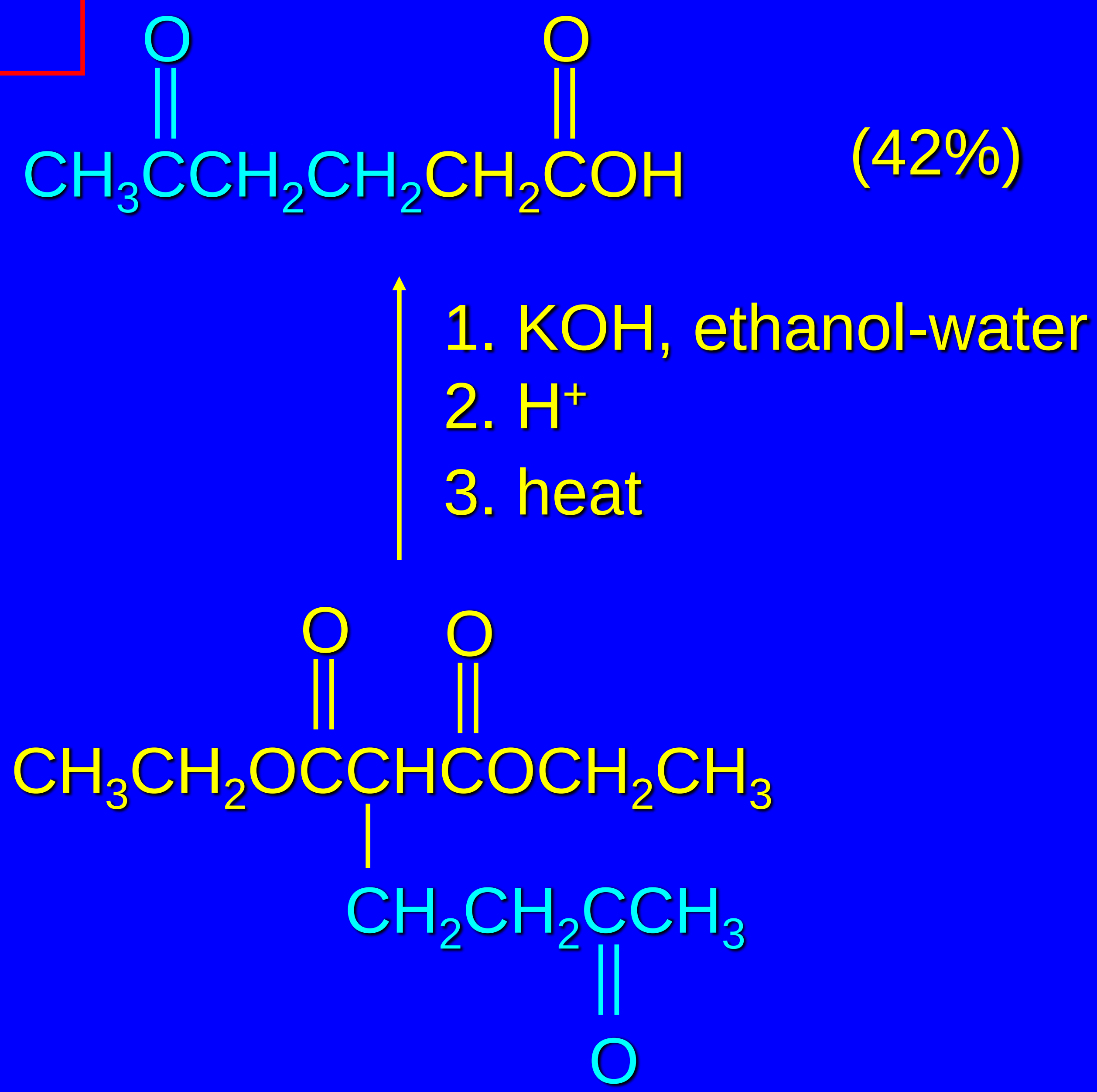
The anions derived by deprotonation of β-keto esters and diethyl malonate are weak bases.

Weak bases react with α,β-unsaturated carbonyl compounds by conjugate addition.

Example


CH3CH2OCCH2COCH2CH3
+
H2C═CHCCH3
KOH, ethanol
CH3CH2OCCHCOCH2CH3
CH2CH2CCH3
(85%)

Example


O
O
CH3CCH2CH2CH2COH
(42%)
1. KOH, ethanol-water
2. H+
3. heat
O
O
CH3CH2OCCHCOCH2CH3
CH2CH2CCH3
O

21.10

α-Deprotonation of Carbonyl Compounds by Lithium Dialkylamides

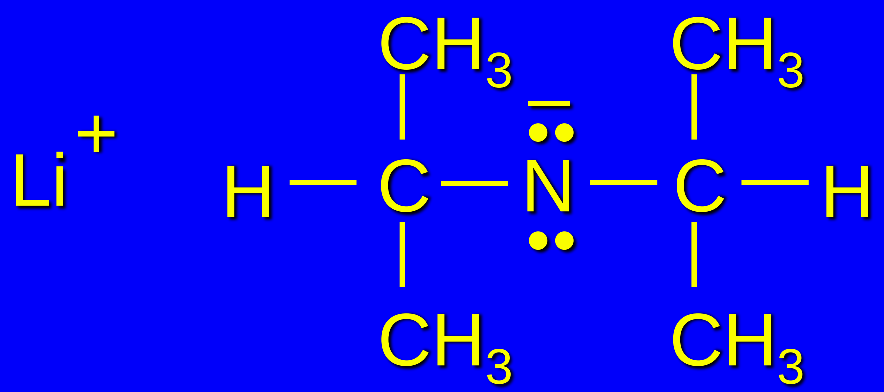
Deprotonation of Simple Esters

Ethyl acetoacetate (pKa ~11) and diethyl malonate (pKa ~13) are completely deprotonated by alkoxide bases.

Simple esters (such as ethyl acetate) are not completely deprotonated, the enolate reacts with the original ester, and Claisen condensation occurs.

Are there bases strong enough to completely deprotonate simple esters, giving ester enolates quantitatively?

Lithium diisopropylamide

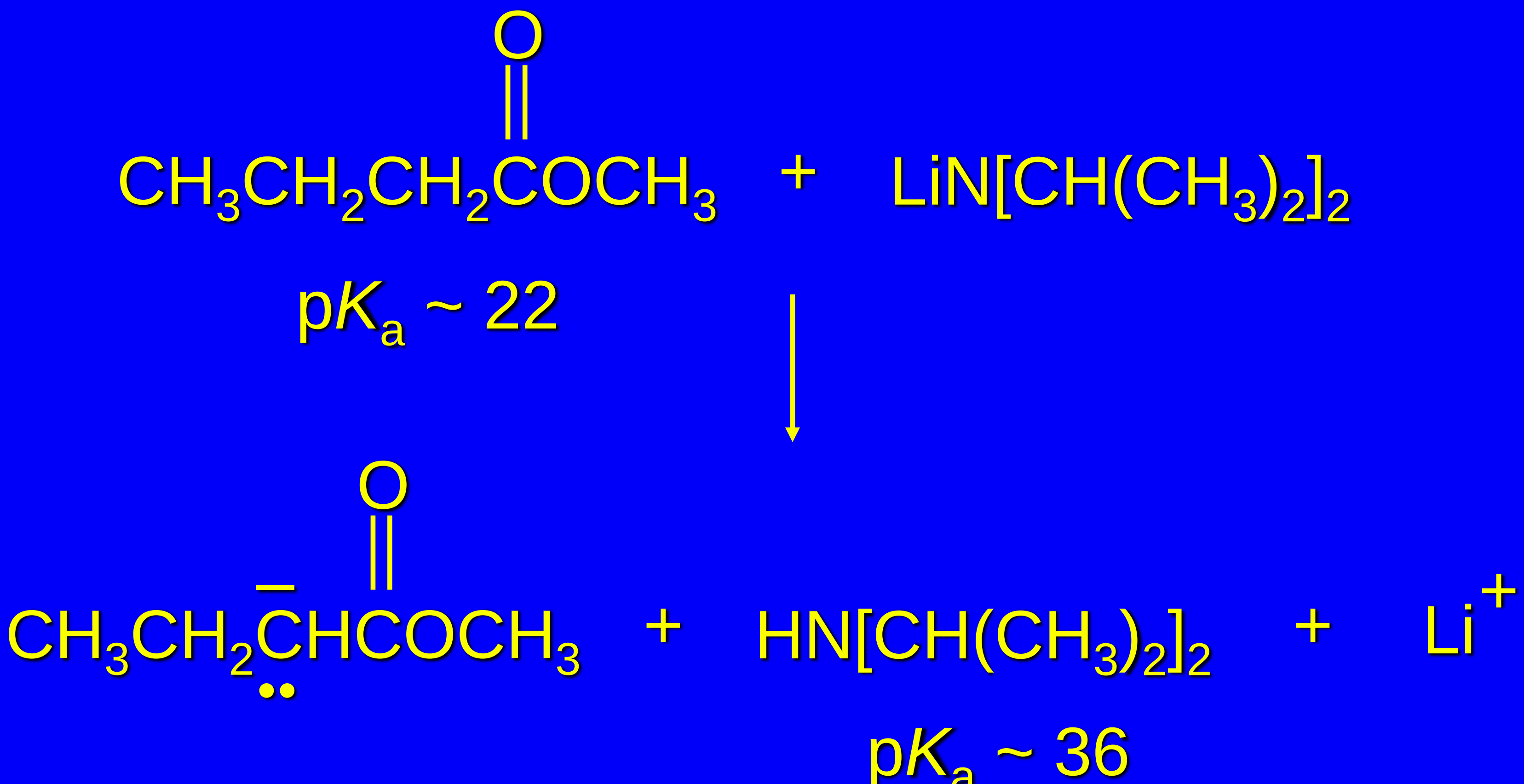


Lithium dialkylamides are strong bases (just as $NaNH_2$ is a very strong base).

Lithium diisopropylamide is a strong base, but because it is sterically hindered, does not add to carbonyl groups.

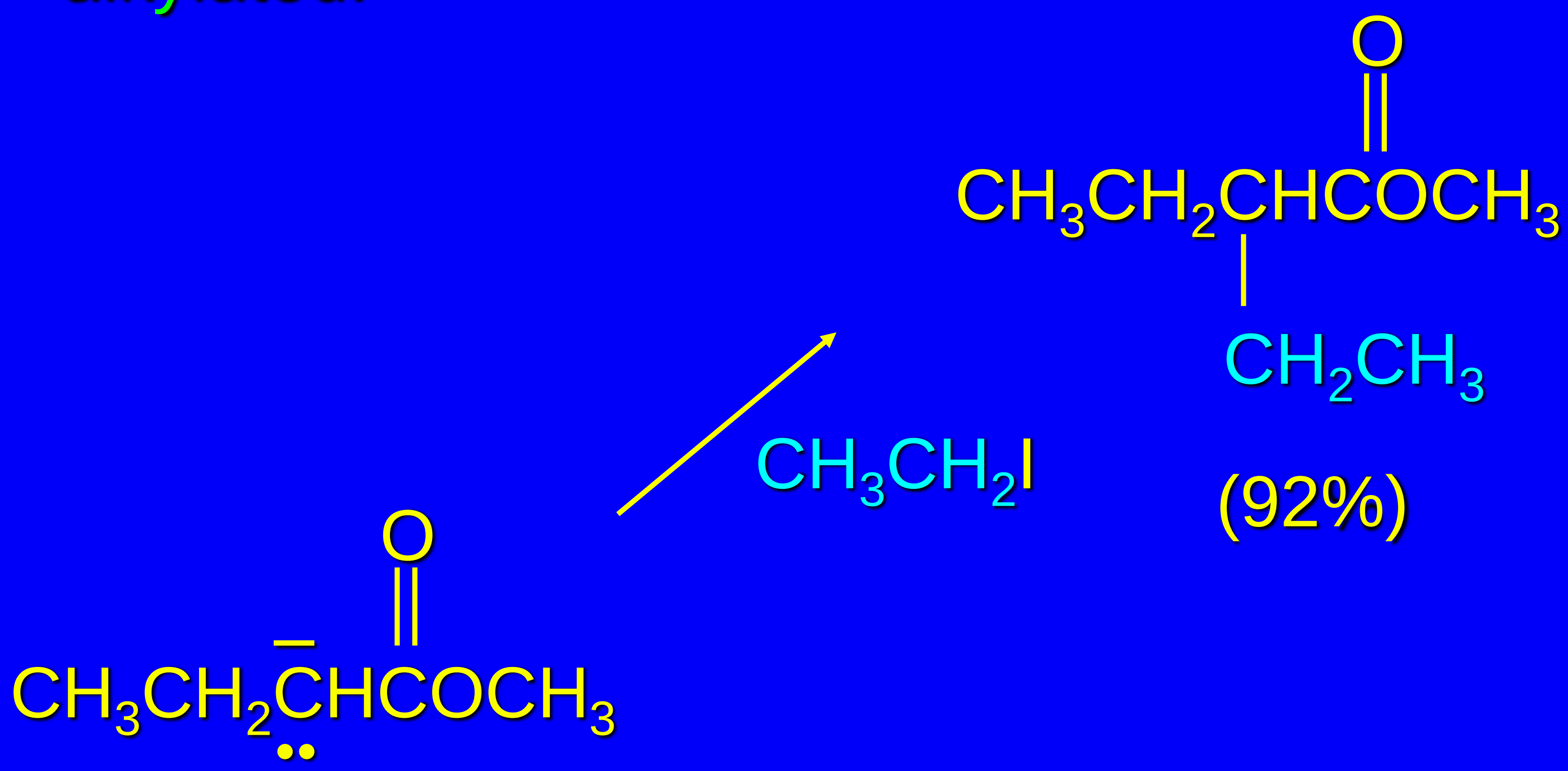
Lithium diisopropylamide (LDA)

Lithium diisopropylamide converts simple esters to the corresponding enolate.



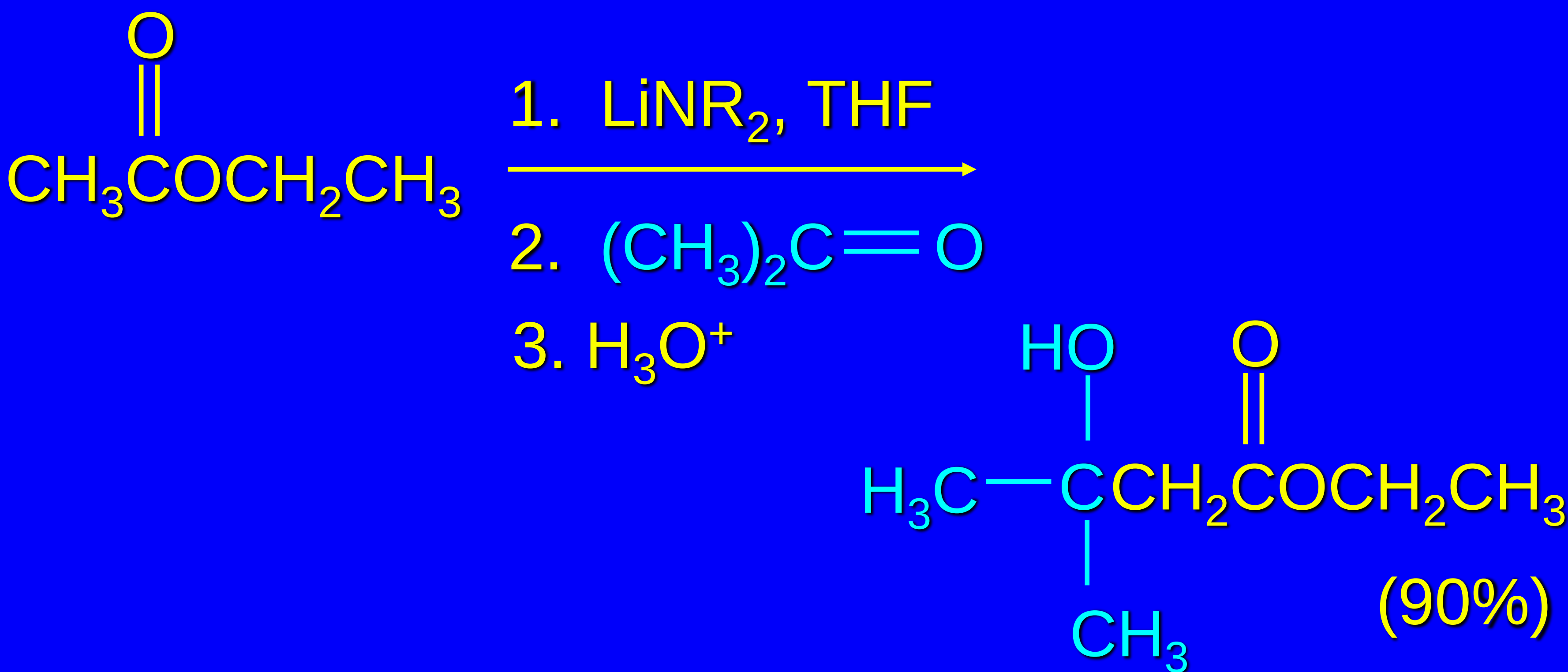
Lithium diisopropylamide (LDA)

Enolates generated from esters and LDA can be alkylated.



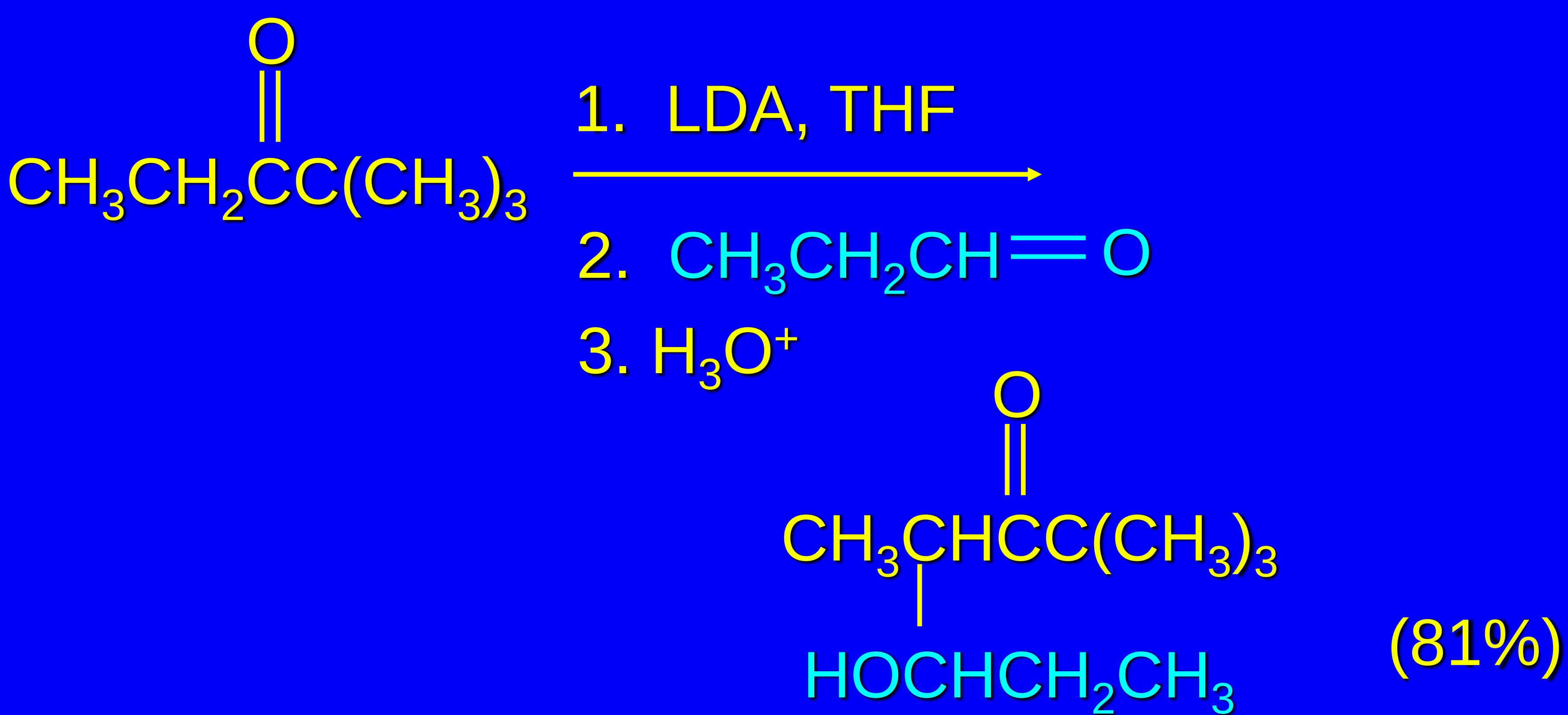
Aldol addition of ester enolates

Ester enolates undergo aldol addition to aldehydes and ketones.



Ketone Enolates

Lithium diisopropylamide converts ketones quantitatively to their enolates.



Information & Suggested Problems

Sample Midterm Exam Posted on Website

Office Hour: Today, 3.30 P.M., SES 4446

Next Week: Tuesday, 3.30 P.M., SES 4446
