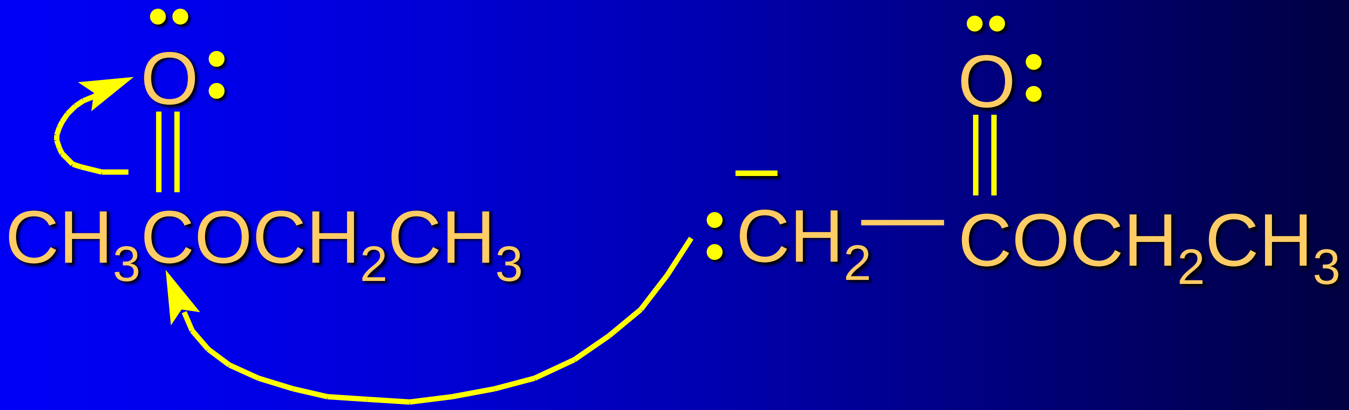
Lecture 21

The Claisen Condensation



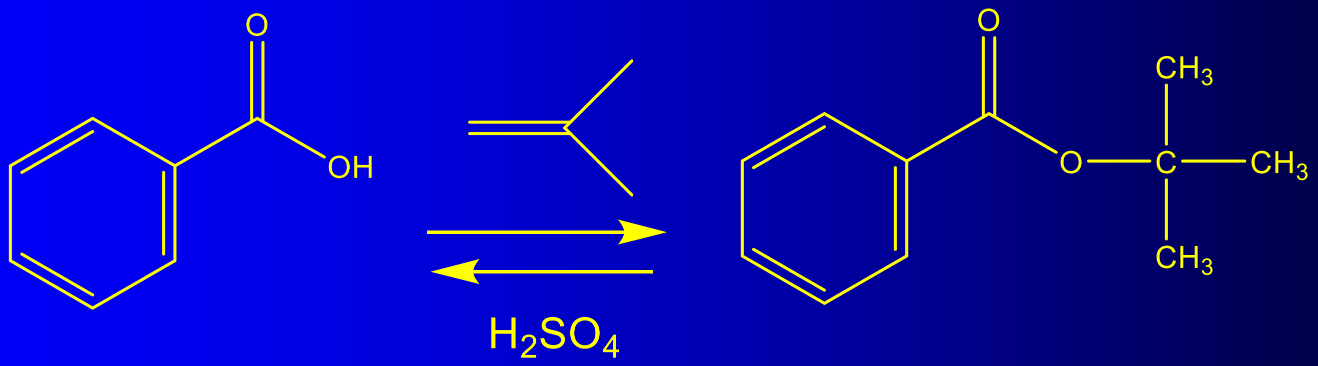
$$CH_3\overset{\overset{\ddot{O}:}{\|}}{C}OCH_2CH_3 \qquad :\overset{-}{C}H_2 — \overset{\overset{\ddot{O}:}{\|}}{C}OCH_2CH_3$$

April 9, 2019

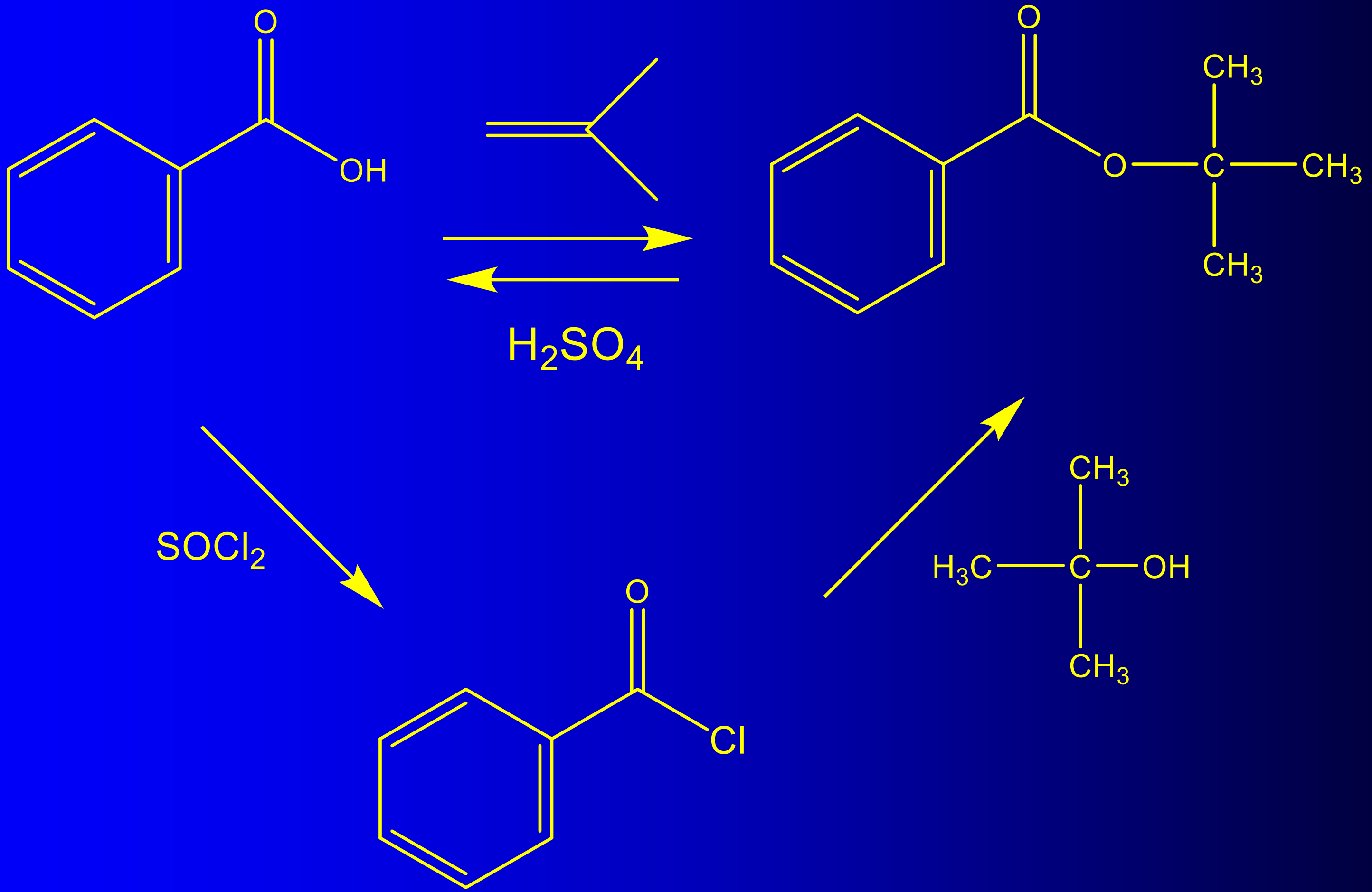
Exam III - Wed April 24

- PAI 3.02
- 7-9 PM
- Covers thru 4/18
- Homework
- Hydrolysis
- Reactions
- Synthesis
- Get an A!!!

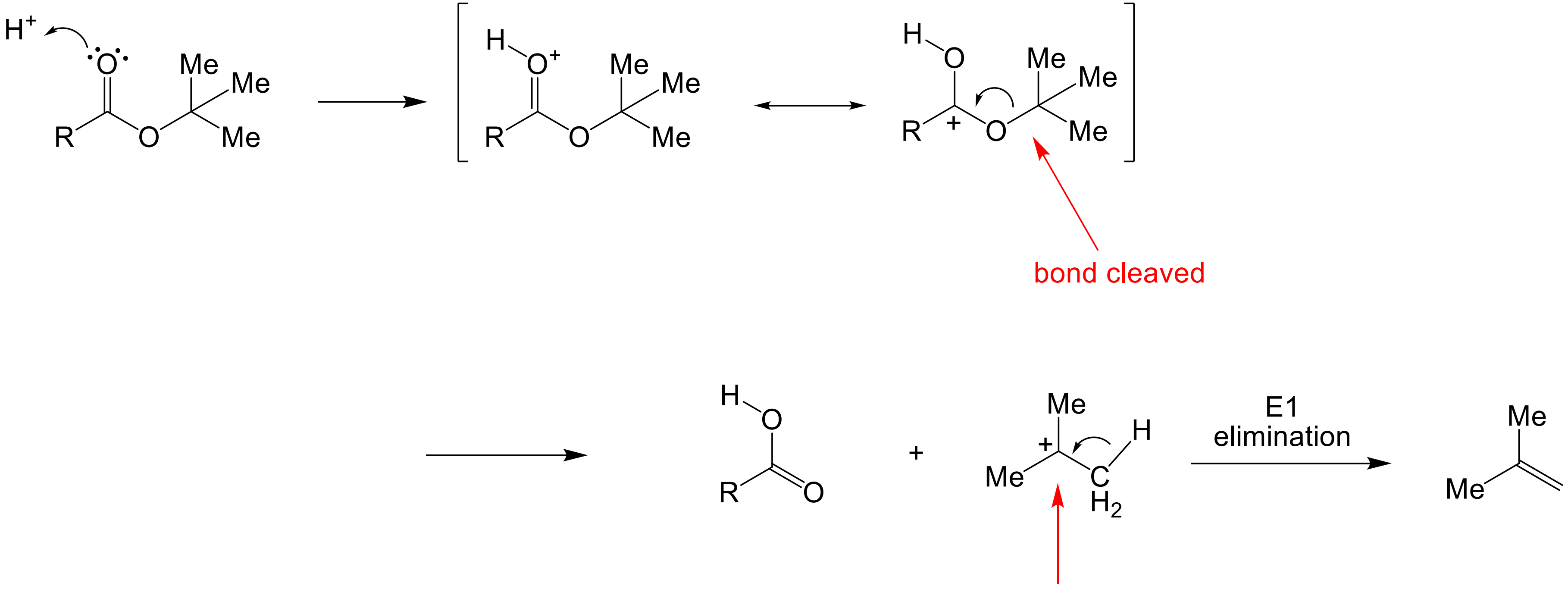
t-Butyl esters



t-Butyl esters



t-Butyl ester hydrolysis

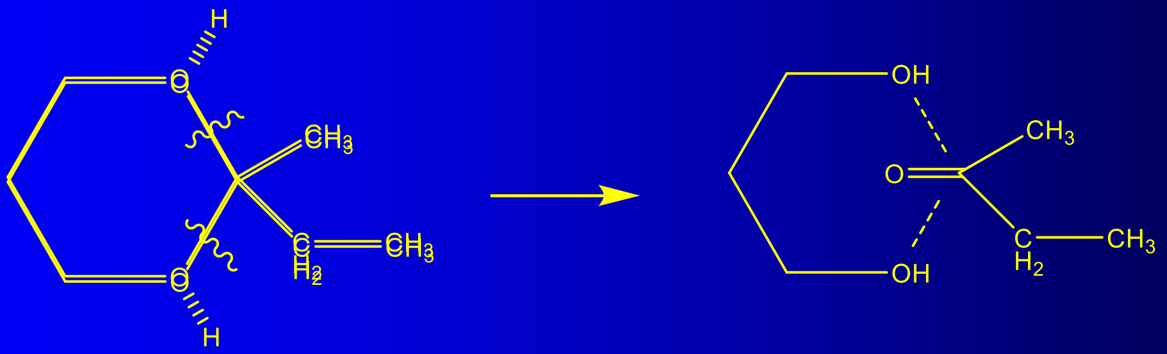


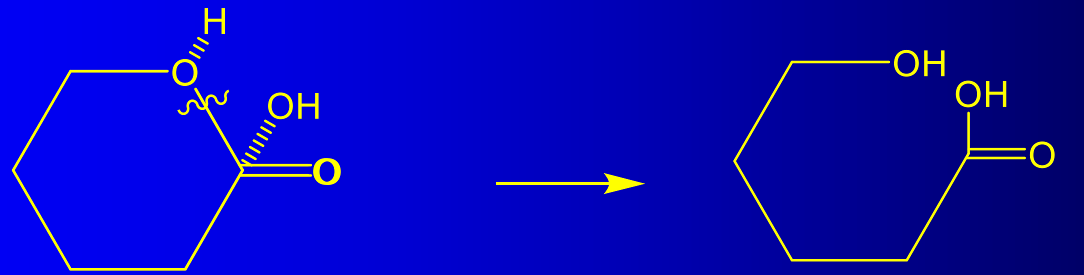
bond cleaved

Relatively stable
tertiary carbocation

Note which bond is broken in this hydrolysis !!

“Trick” for Predicting Products

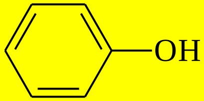
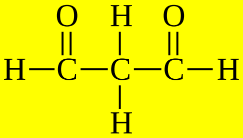
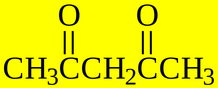
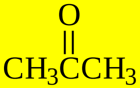




Recall our discussion of the acidity of protons α to carbonyls

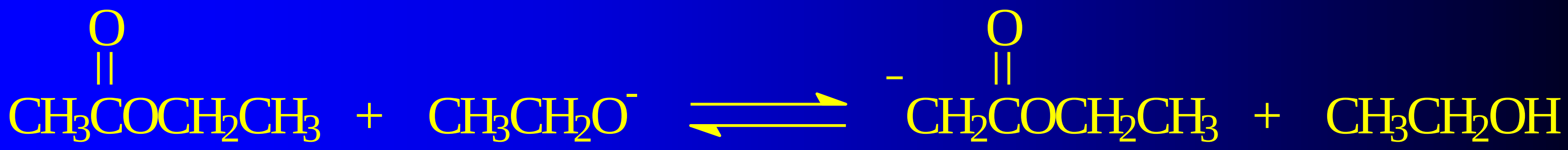
- The anion is stabilized by resonance
- The better the stabilization, the more acidic the a proton
- Acidity of a protons on“normal” aldehydes and ketones is about that of alcohols and less than water…pKa ~ 18-20
- Some are far more acidic, i.e. β-dicarbonyl compounds that have quite low pKa’s

Recall the pKa of some acids and some α protons

CH_3CO_2H	**4.75**
HF	**3.45**
HCl	**-9.0!!**
	**10**
 $\mathrm{H{-}\overset{O}{\overset{\Vert}{C}}{-}\underset{H}{\overset{H}{C}}{-}\overset{O}{\overset{\Vert}{C}}{-}H}$	**5.0**
CH_3OH	**16**
 $\mathrm{CH_3\overset{O}{\overset{\Vert}{C}}CH_2\overset{O}{\overset{\Vert}{C}}CH_3}$	**10**
 $\mathrm{CH_3\overset{O}{\overset{\Vert}{C}}CH_3}$	**20**
CH_3CH_3	**50**

Some Acid Base Chemistry

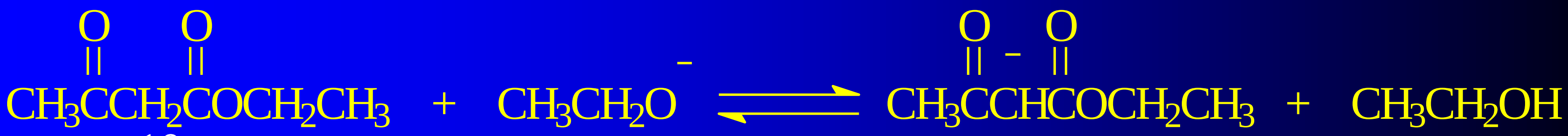
$$2\ CH_3CH_2OH + 2Na \longrightarrow H_2 + 2\ CH_3CH_2O^-\ Na^+$$



$$CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3 + CH_3CH_2O^- \rightleftharpoons {}^-CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3 + CH_3CH_2OH$$

pKa 25

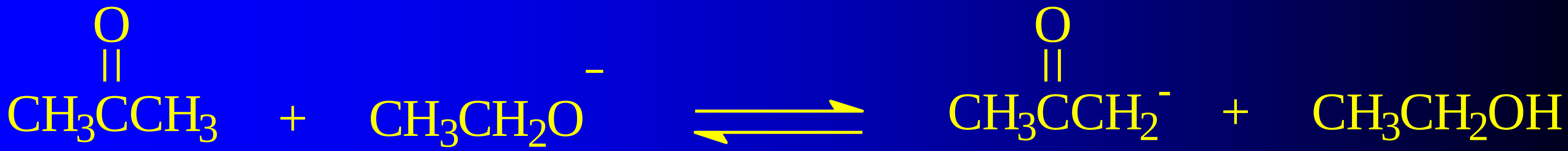
pKa 16



$$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3 + CH_3CH_2O^- \rightleftharpoons CH_3\overset{\overset{O}{\|}}{C}\overset{-}{C}H\overset{\overset{O}{\|}}{C}OCH_2CH_3 + CH_3CH_2OH$$

10

16



$$CH_3\overset{\overset{O}{\|}}{C}CH_3 + CH_3CH_2O^- \rightleftharpoons CH_3\overset{\overset{O}{\|}}{C}CH_2^- + CH_3CH_2OH$$

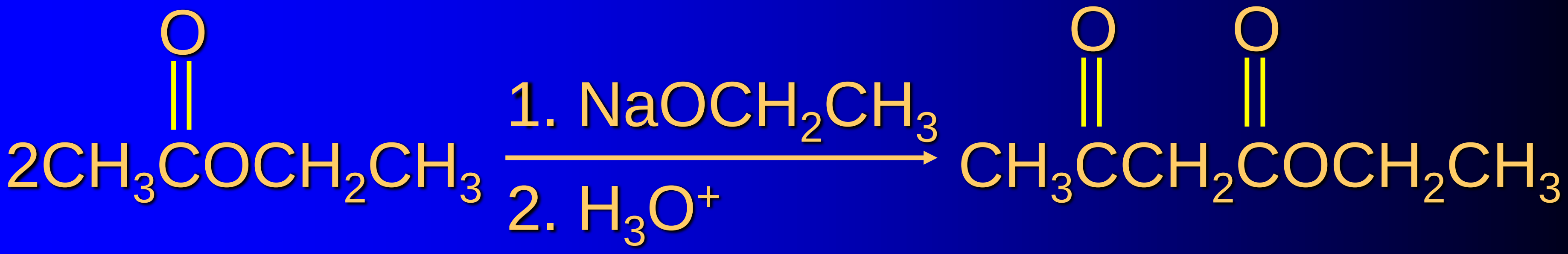
20

16

Which way do the equilibria lie?

- **Rainer Ludwig Claisen** (1851-1930): Born in Köln and studied chemistry at Bonn, and briefly at Göttingen. He earned his doctorate at Bonn under August Kekulé (1829-1896).

Classical Claisen Condensation

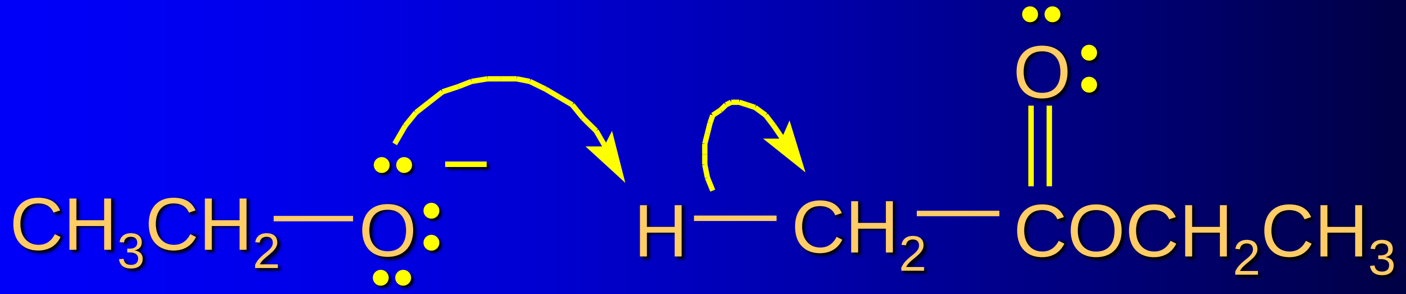


$$2CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3} CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3$$

- Two moles of ethyl acetate condense to give *ethyl acetoacetate or (acetoacetic ester)*

Mechanism

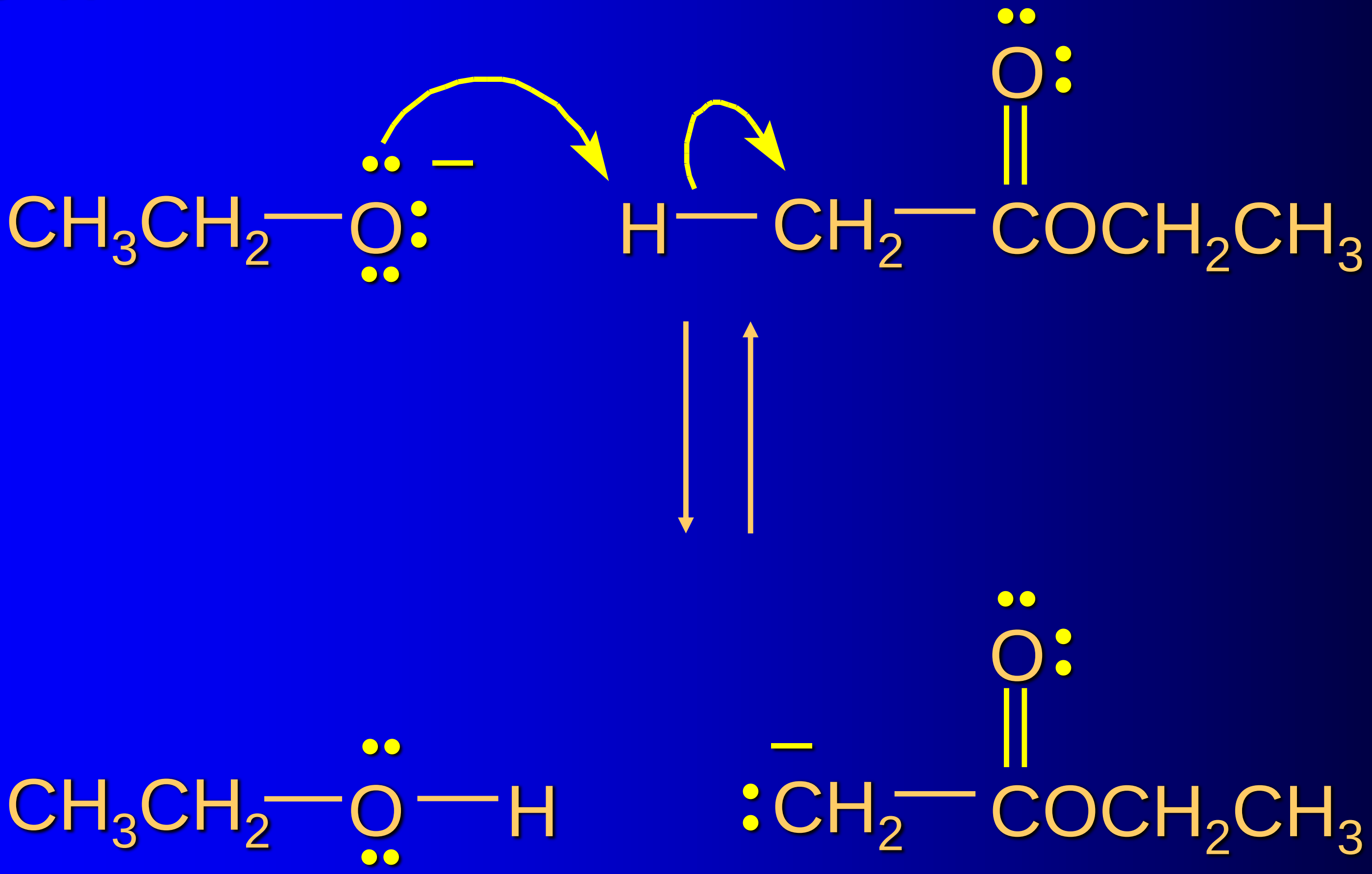
Step 1:



$$CH_3CH_2-\ddot{\underset{..}{O}}:^{-} \qquad H-CH_2-\overset{\overset{\Large O}{\|}}{C}OCH_2CH_3$$

Mechanism

Step 1:



$$CH_3CH_2-\ddot{\underset{..}{O}}:^{-} \quad H-CH_2-\overset{\overset{\ddot{O}:}{\|}}{C}OCH_2CH_3$$

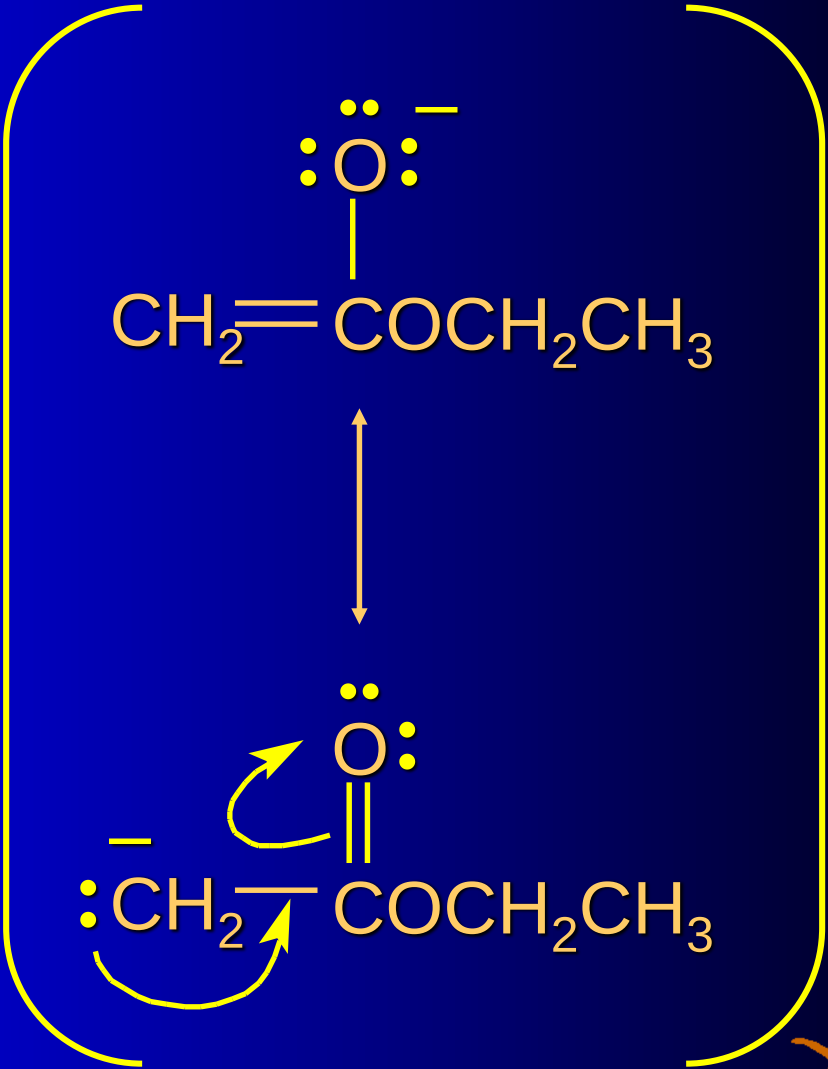
$$\rightleftharpoons$$

$$CH_3CH_2-\ddot{\underset{..}{O}}-H \quad :\overset{-}{C}H_2-\overset{\overset{\ddot{O}:}{\|}}{C}OCH_2CH_3$$

Mechanism

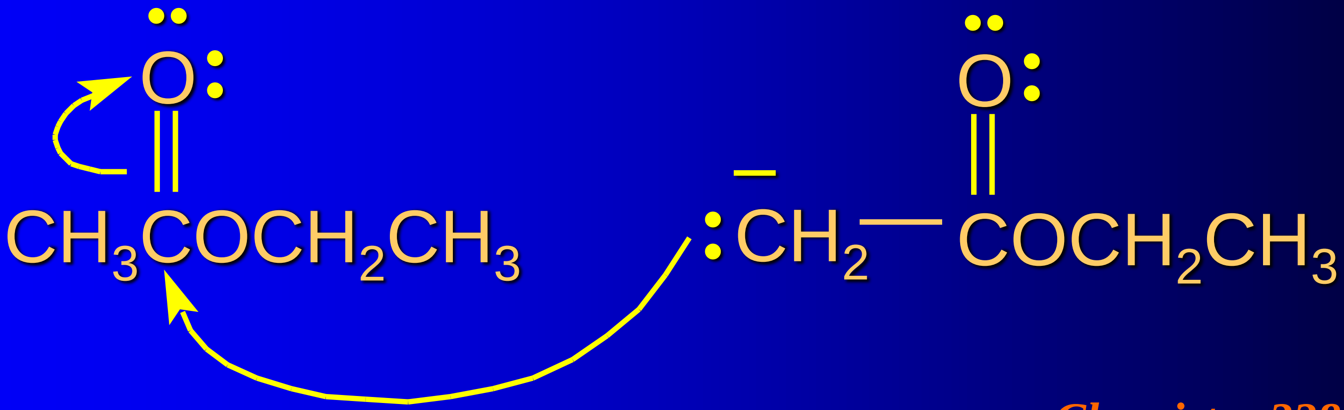
Step 1:

- The enolate anion is stabilized by resonance



Mechanism

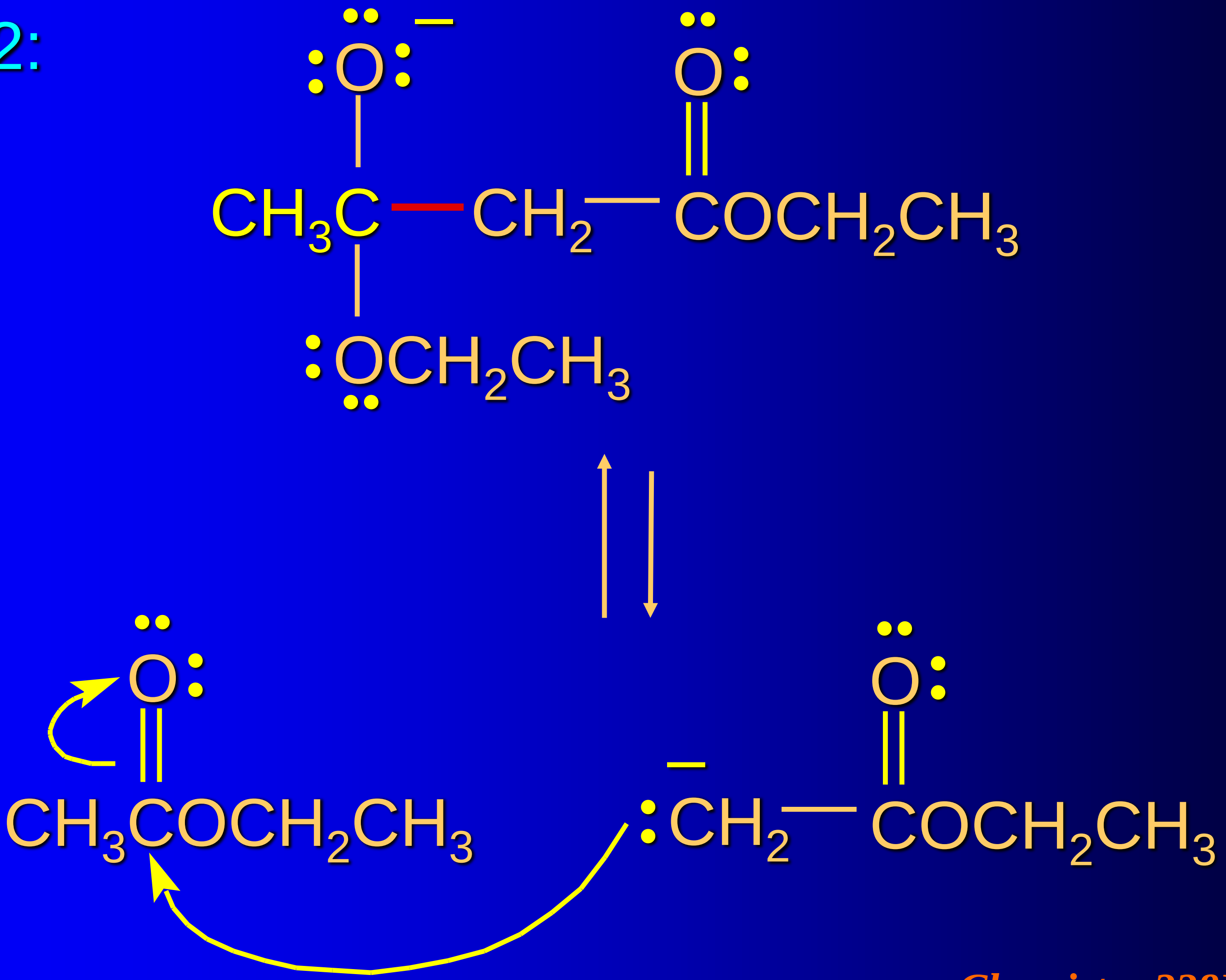
Step 2: Nucleophilic acyl substitution



$$CH_3\overset{\overset{\displaystyle \ddot{O}:}{\|}}{C}OCH_2CH_3 \qquad :\overset{-}{C}H_2-\overset{\overset{\displaystyle \ddot{O}:}{\|}}{C}OCH_2CH_3$$

Mechanism

Step 2:



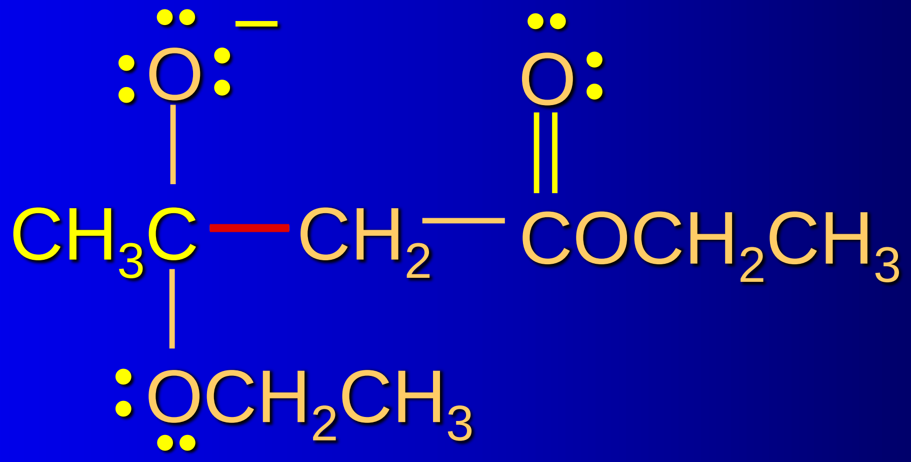
$$CH_3\overset{\overset{O^-}{|}}{\underset{\underset{OCH_2CH_3}{|}}{C}}-CH_2-\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

$$\rightleftharpoons$$

$$CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3 \quad {}^-:CH_2-\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

Mechanism

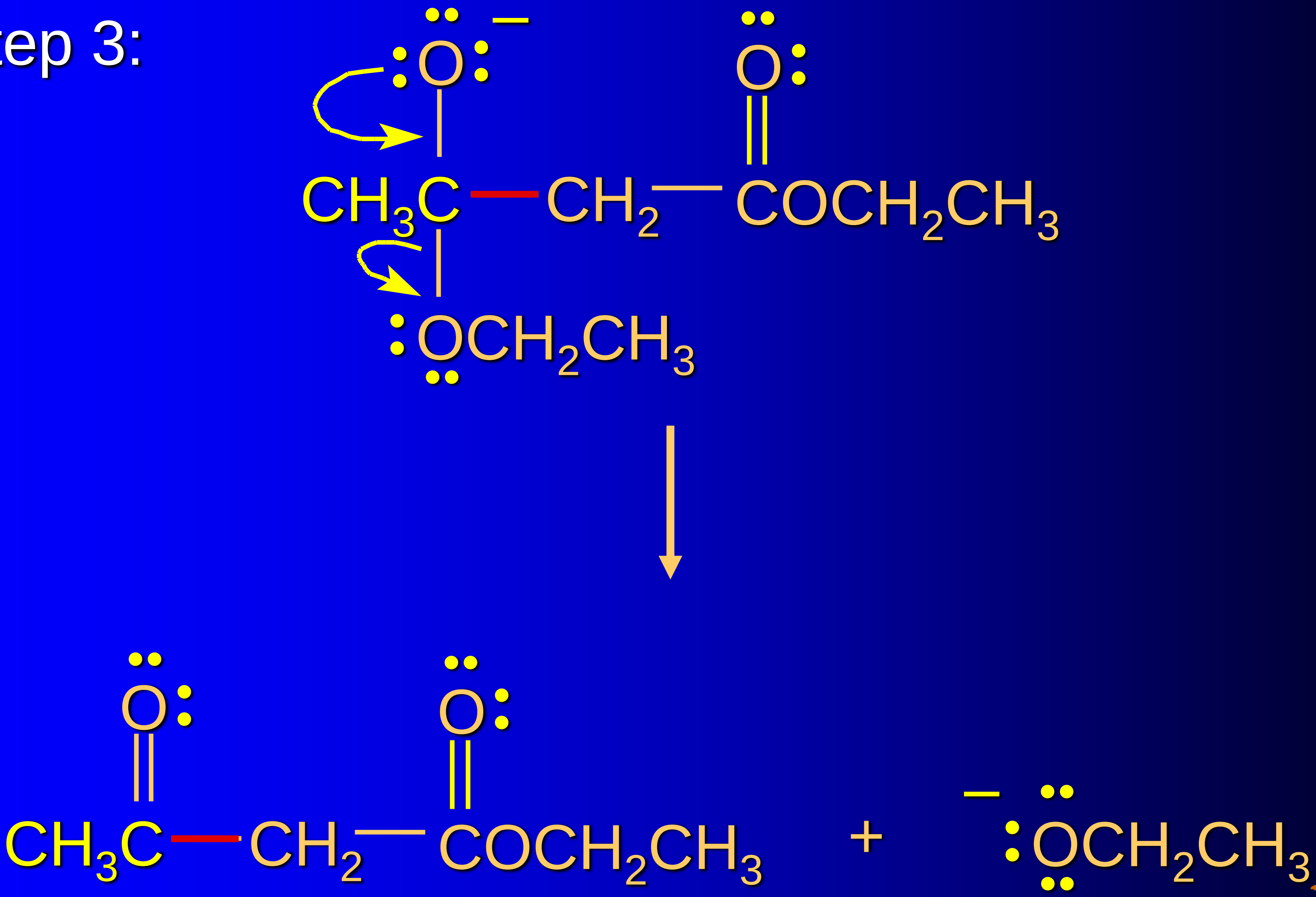
Step 2:



$$CH_3\overset{\overset{:\ddot{O}:^{-}}{|}}{\underset{\underset{:\ddot{O}CH_2CH_3}{|}}{C}}-CH_2-\overset{\overset{\ddot{O}:}{\|}}{C}OCH_2CH_3$$

Mechanism

Step 3:



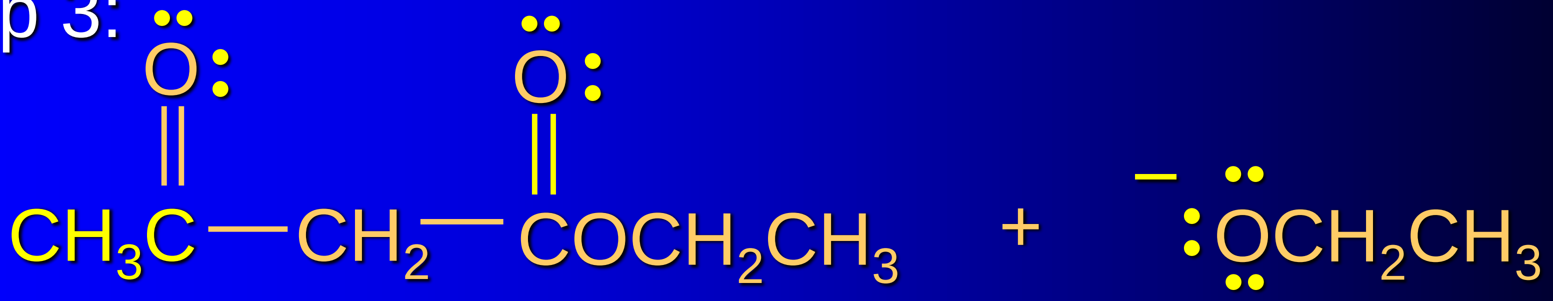
$$\mathrm{CH_3\overset{\overset{\ddot{O}:^{-}}{|}}{\underset{\underset{:\ddot{O}CH_2CH_3}{|}}{C}}-CH_2-\overset{\overset{\ddot{O}:}{\|}}{C}OCH_2CH_3}$$

$$\downarrow$$

$$\mathrm{CH_3\overset{\overset{\ddot{O}:}{\|}}{C}-CH_2-\overset{\overset{\ddot{O}:}{\|}}{C}OCH_2CH_3 \; + \; {}^{-}:\ddot{O}CH_2CH_3}$$

Mechanism

Step 3:

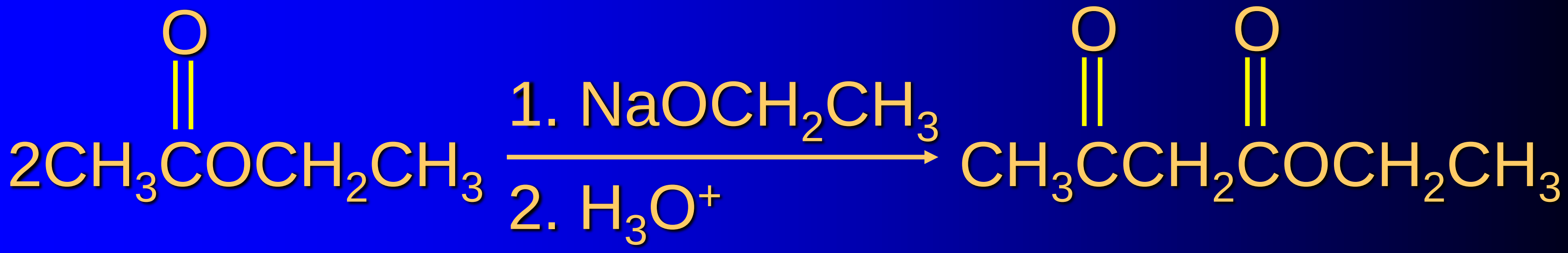


$$CH_3\overset{\overset{\ddot{O}:}{\|}}{C}-CH_2-\overset{\overset{\ddot{O}:}{\|}}{C}OCH_2CH_3 + {}^{-}:\ddot{O}CH_2CH_3$$

- The product is ethyl acetoacetate.
- However, were nothing else to happen, the yield of ethyl acetoacetate would be small because the equilibrium constant for its formation is small.
- Something else **<u>does</u>** happen. Ethoxide abstracts a proton from the CH_2 group to give a stabilized anion. The equilibrium constant for this acid-base reaction is very favorable.

Classical Claisen Condensation

An excellent path to β-keto esters

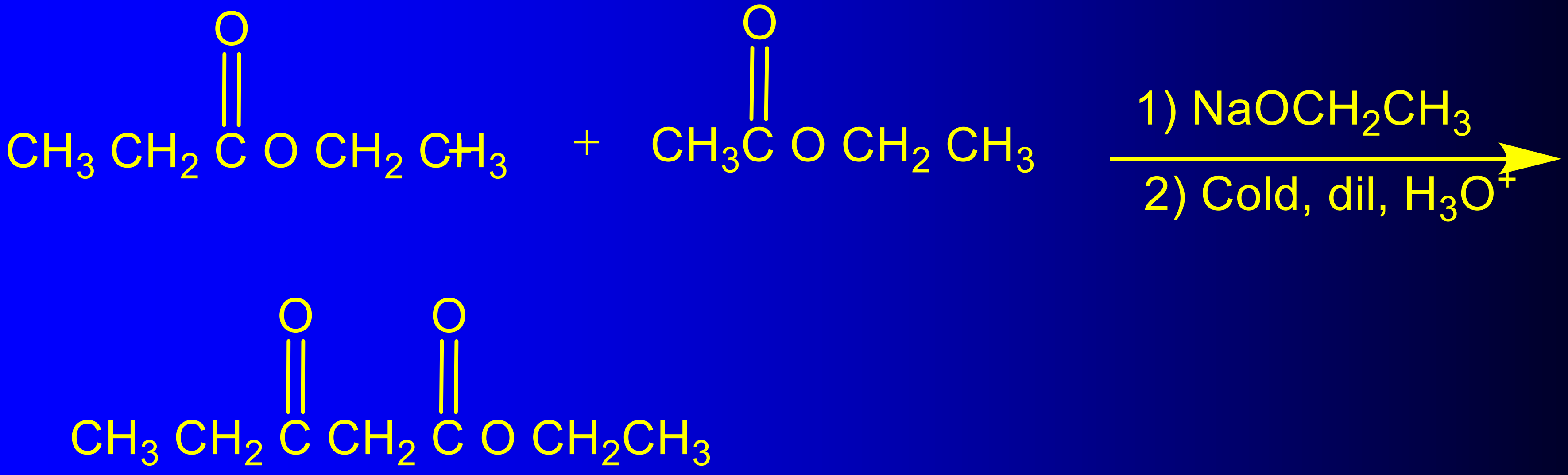


$$2CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3} CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

- Two moles of ethyl acetate condense to give ethyl 3-oxobutanoate or … *ethyl acetoacetate aka acetoacetic ester*

Crossed Claisen Condensation

- What is wrong with this?



$$CH_3CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3 + CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3 \xrightarrow[\text{2) Cold, dil, } H_3O^+]{\text{1) } NaOCH_2CH_3}$$

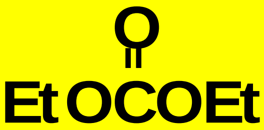
$$CH_3CH_2\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

Crossed Claisen Condensation

Crossed reactions can work if one does it carefully and one of the reactants does not have an alpha hydrogen such as:

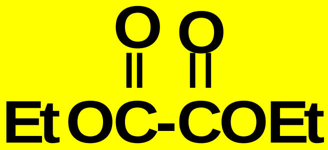
$$H\overset{\overset{O}{\|}}{C}OEt$$

Ethyl formate



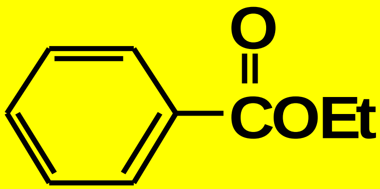
$$EtO\overset{\overset{O}{\|}}{C}OEt$$

Diethyl carbonate



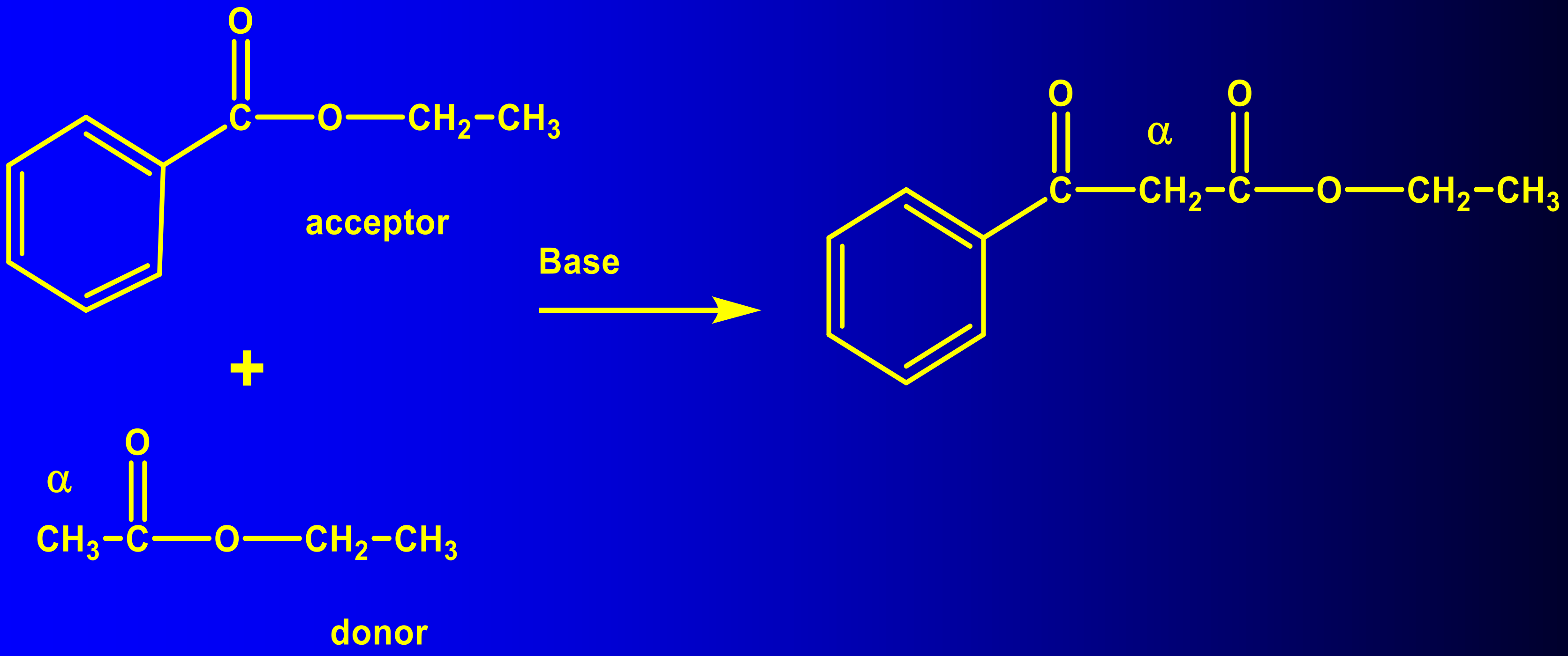
$$EtO\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}OEt$$

Diethyl ethanedioate (Diethyl oxalate)



Ethyl benzoate

Crossed Claisen Condensation -- An Example



Crossed Claisen Condensation

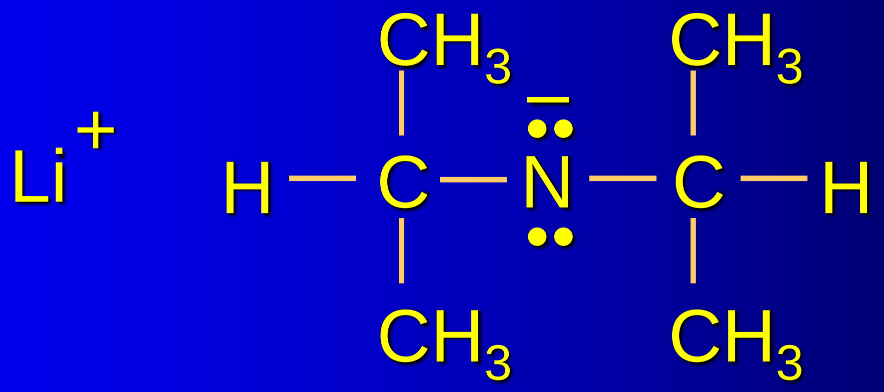
- Crossed Claisen condensations between two different esters, each with α-hydrogens, give bad mixtures. They are not useful and will not be accepted as legitimate answers in our class

- You can do this if you use one component with no α-hydrogen *and* if you run the reaction properly
  - How would YOU run the reaction??
  - What sequence of additions?
  - What stoichiometry?
  - What base?

Deprotonation of Simple Esters

- Ethyl acetoacetate (pKa ~11) is “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.
- Do there exist bases strong enough to completely deprotonate simple esters, giving ester enolates quantitatively?

Lithium diisopropylamide (LDA)

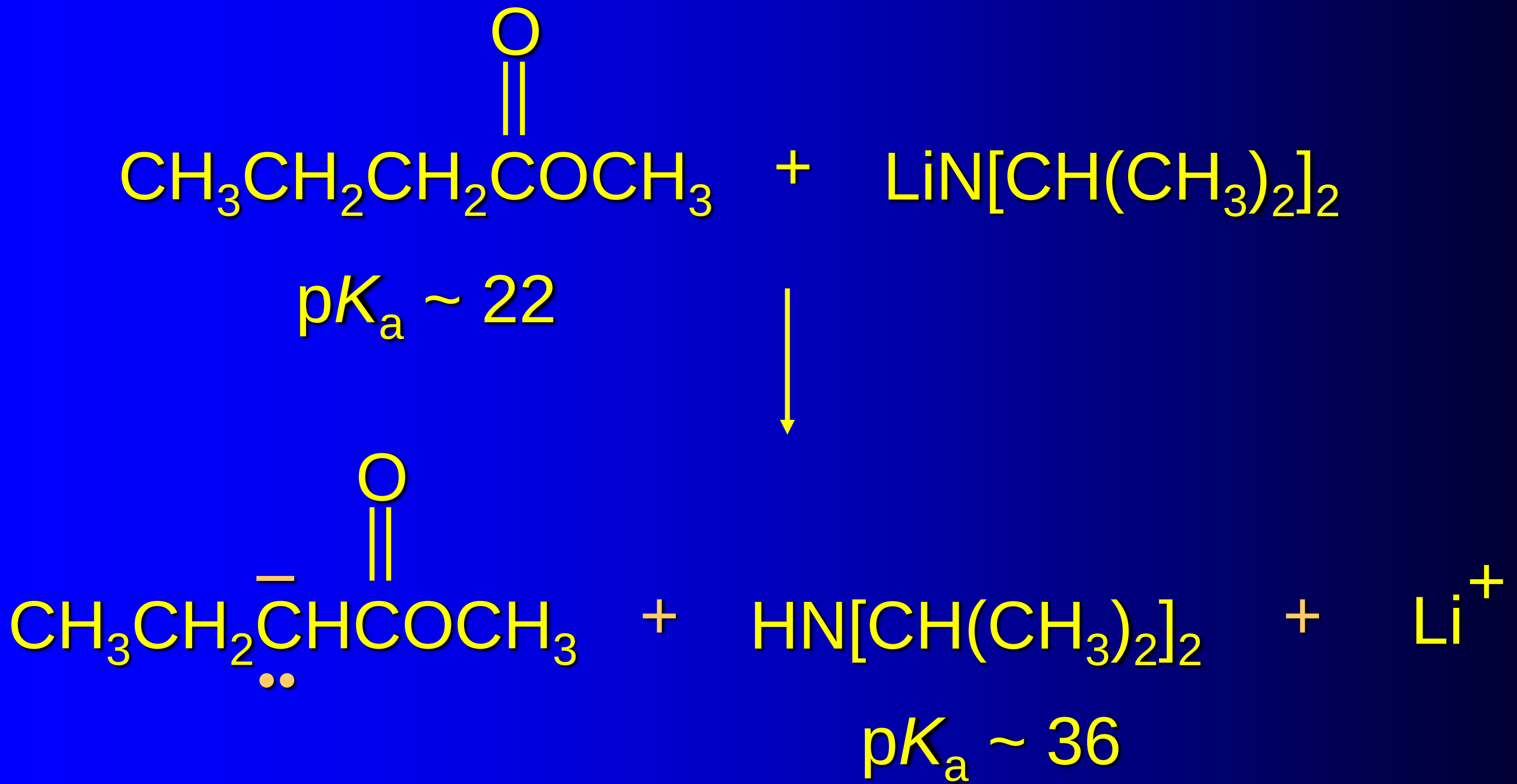


$$\mathrm{Li}^+ \quad \mathrm{H}-\underset{\mathrm{CH_3}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\overset{-}{\underset{\cdot\cdot}{\ddot{\mathrm{N}}}}-\underset{\mathrm{CH_3}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{H}$$

- LDA is a strong base (just as $NaNH_2$ is a very strong base). pKa ~36
- Because it is so sterically hindered, LDA does not add to carbonyl groups.

Lithium diisopropylamide (LDA)

- LDA converts simple esters quantitatively to the corresponding enolate.



$$CH_3CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}OCH_3 \quad + \quad LiN[CH(CH_3)_2]_2$$

pK_a ~ 22

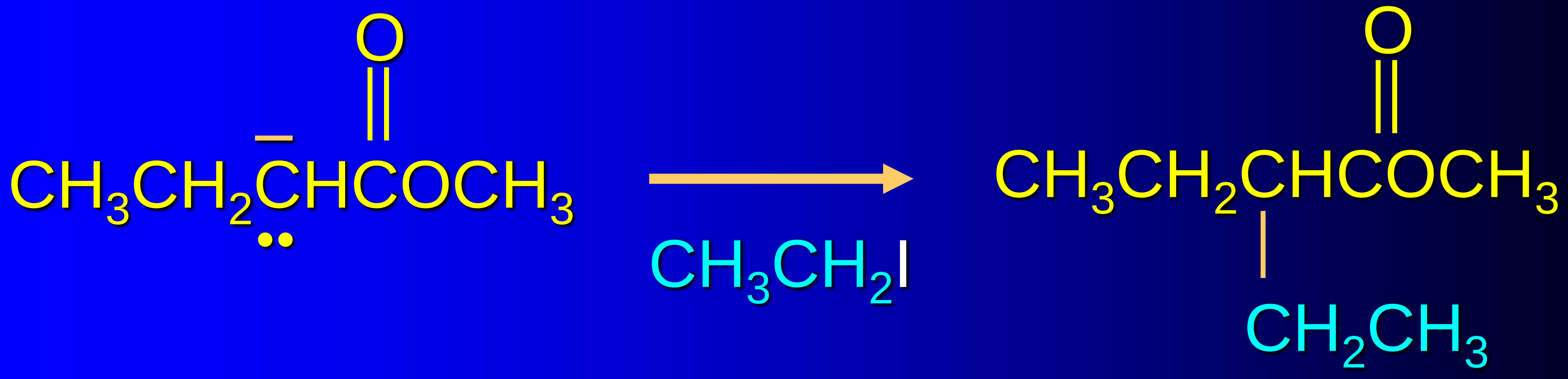
$$\Big\downarrow$$

$$CH_3CH_2\underset{\bullet\bullet}{\overset{-}{C}}H\overset{\overset{\displaystyle O}{\|}}{C}OCH_3 \quad + \quad HN[CH(CH_3)_2]_2 \quad + \quad Li^+$$

pK_a ~ 36

Lithium diisopropylamide (LDA)

- Enolates generated from esters and LDA can be alkylated.



$$CH_3CH_2\underset{\cdot\cdot}{\overset{-}{C}}H\overset{\overset{O}{\|}}{C}OCH_3 \xrightarrow[CH_3CH_2I]{} CH_3CH_2\underset{\underset{CH_2CH_3}{|}}{C}H\overset{\overset{O}{\|}}{C}OCH_3$$

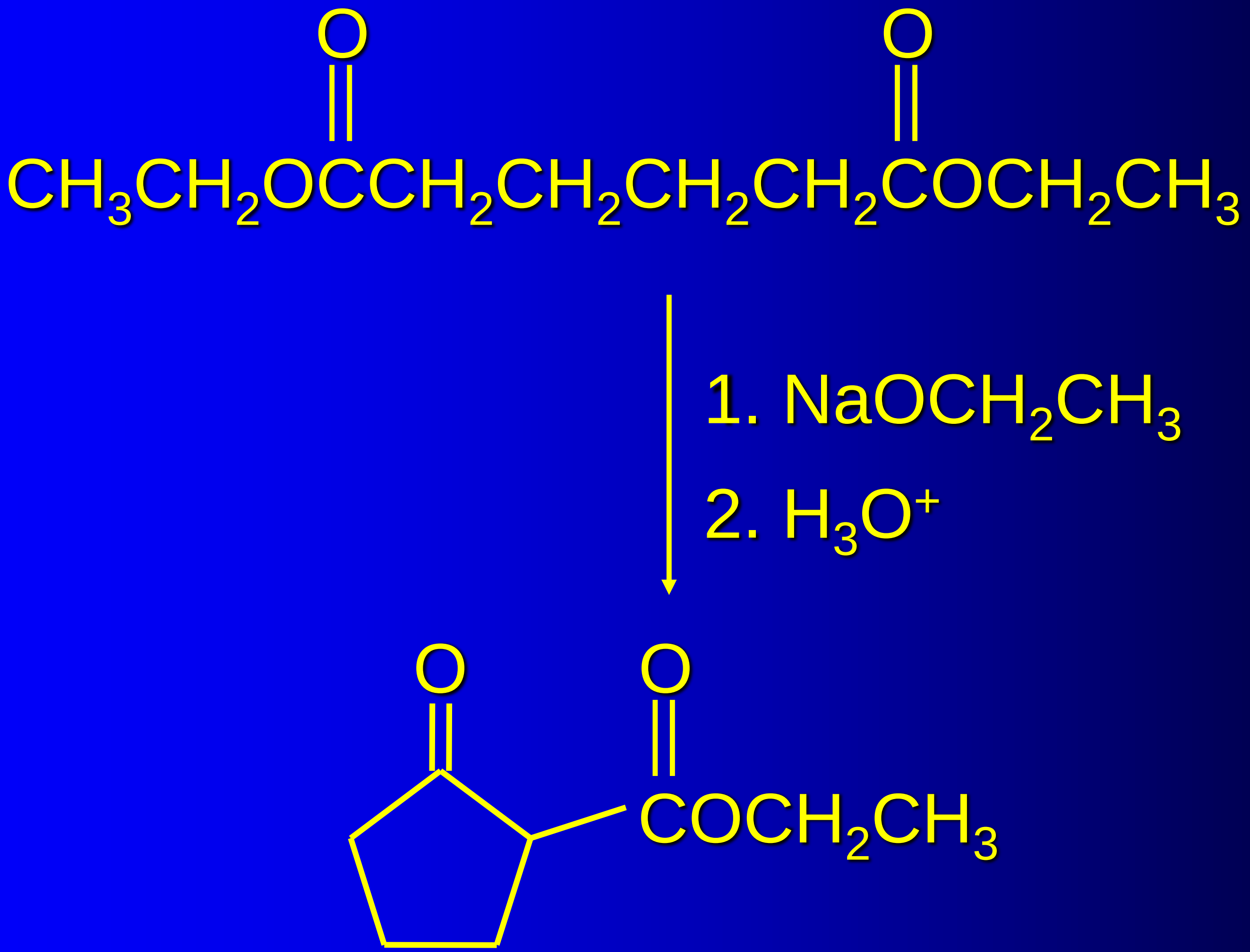
(92%)

Intramolecular Claisen Condensation: The Dieckmann Reaction

Walter Dieckmann

1869 –1925

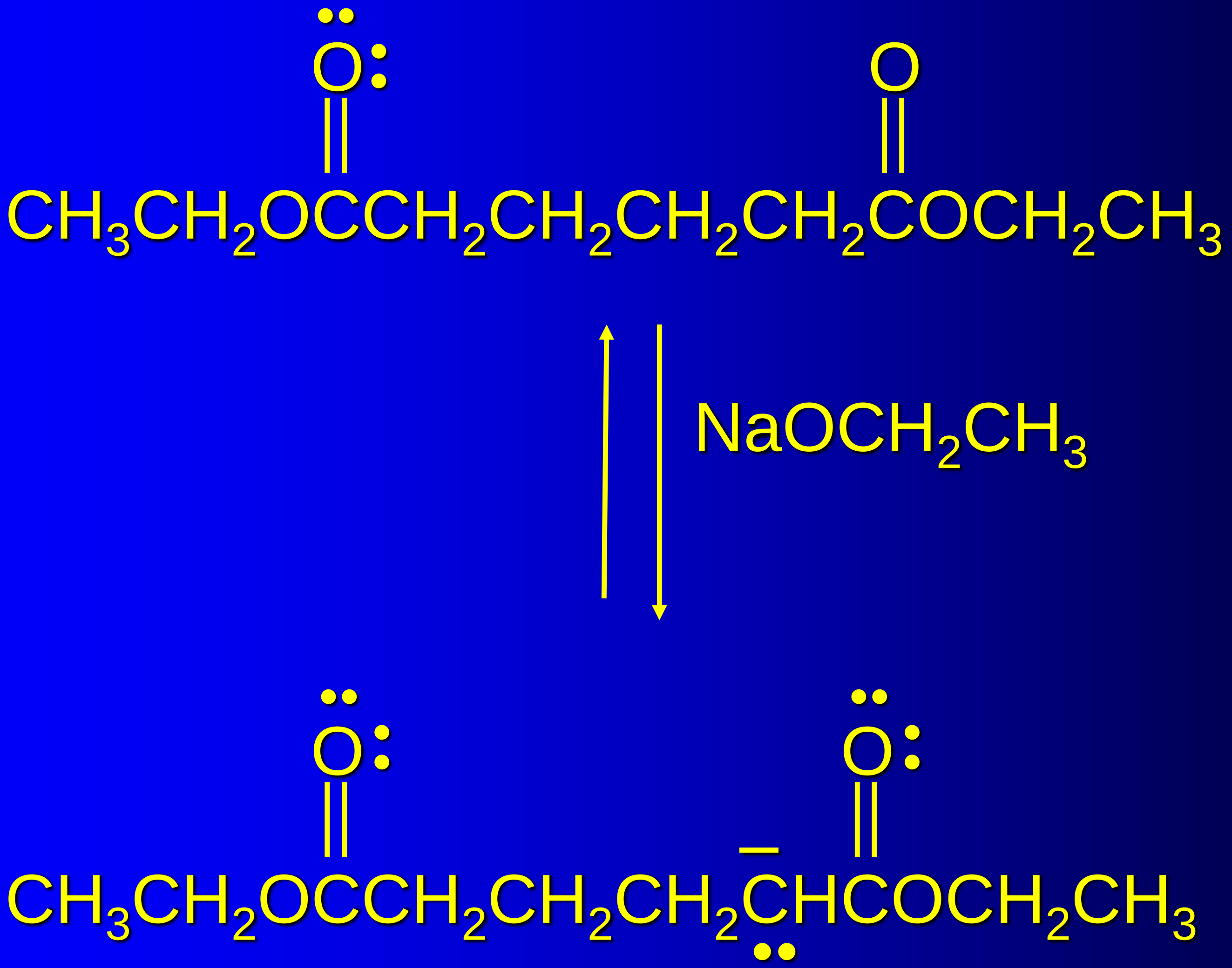
Example



$$CH_3CH_2O\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH_2CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}OCH_2CH_3$$

1. $NaOCH_2CH_3$
2. H_3O^+

via

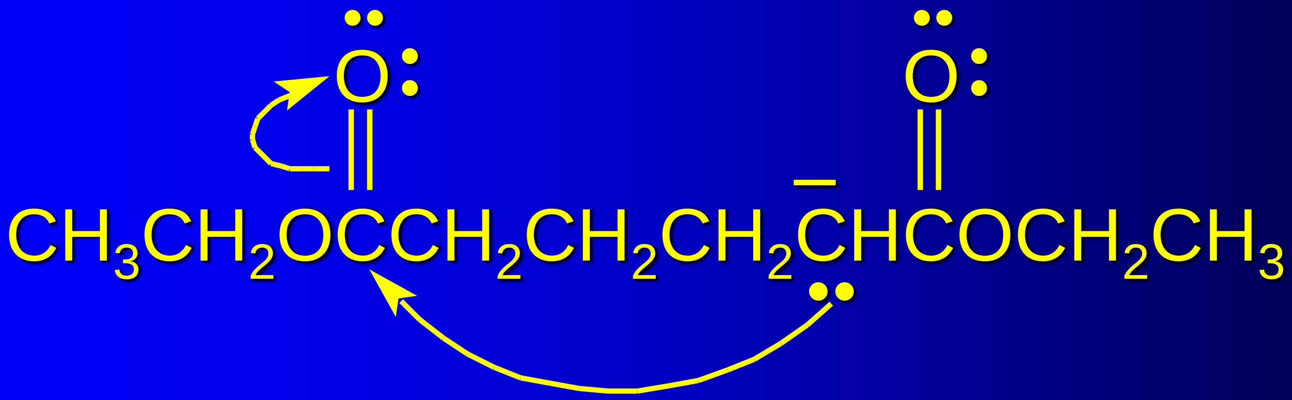


$$CH_3CH_2O\overset{\overset{\ddot{O}:}{\|}}{C}CH_2CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

$$\downarrow\uparrow \; NaOCH_2CH_3$$

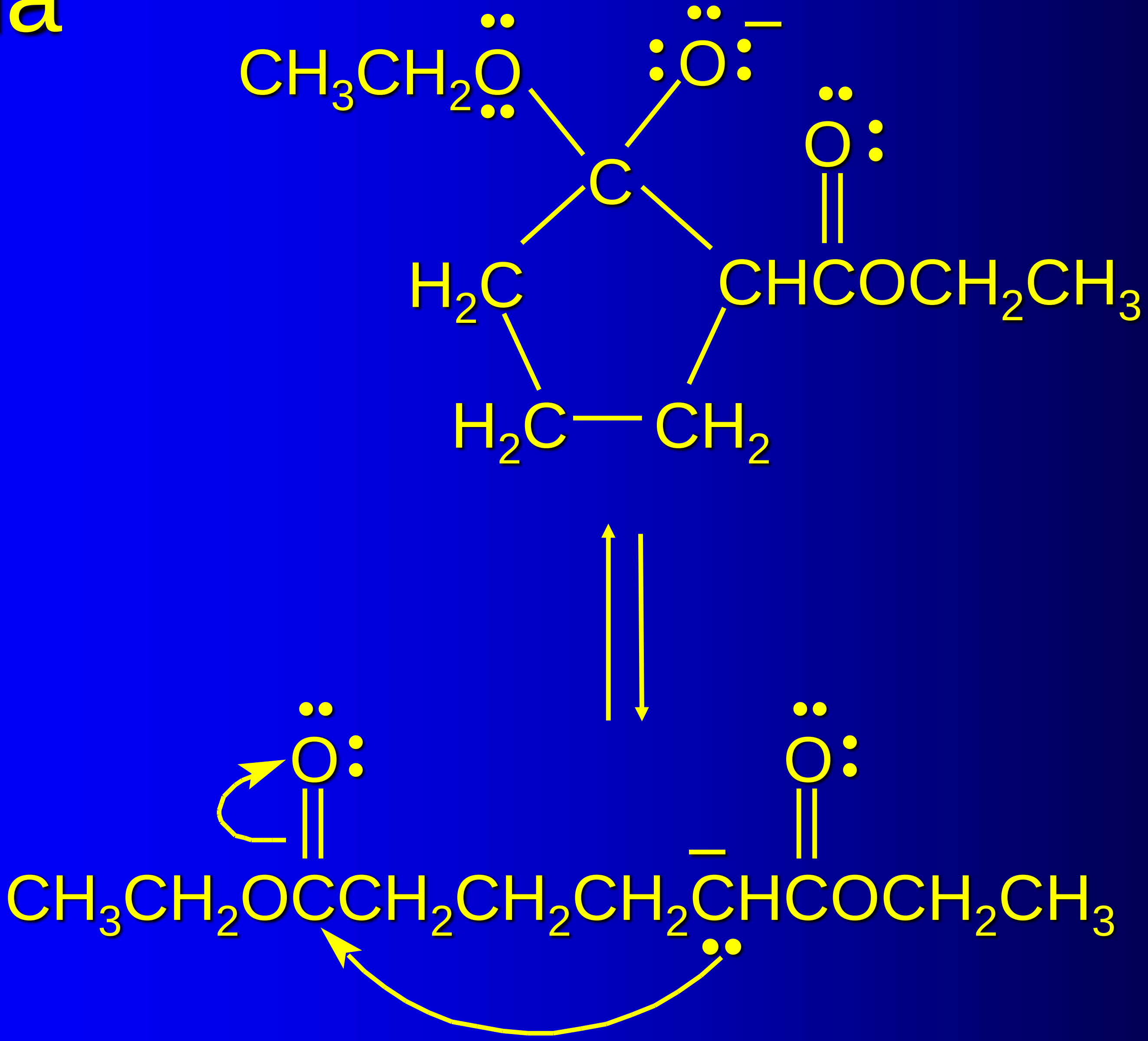
$$CH_3CH_2O\overset{\overset{\ddot{O}:}{\|}}{C}CH_2CH_2CH_2\overset{-}{\underset{\cdot\cdot}{C}}H\overset{\overset{\ddot{O}:}{\|}}{C}OCH_2CH_3$$

via



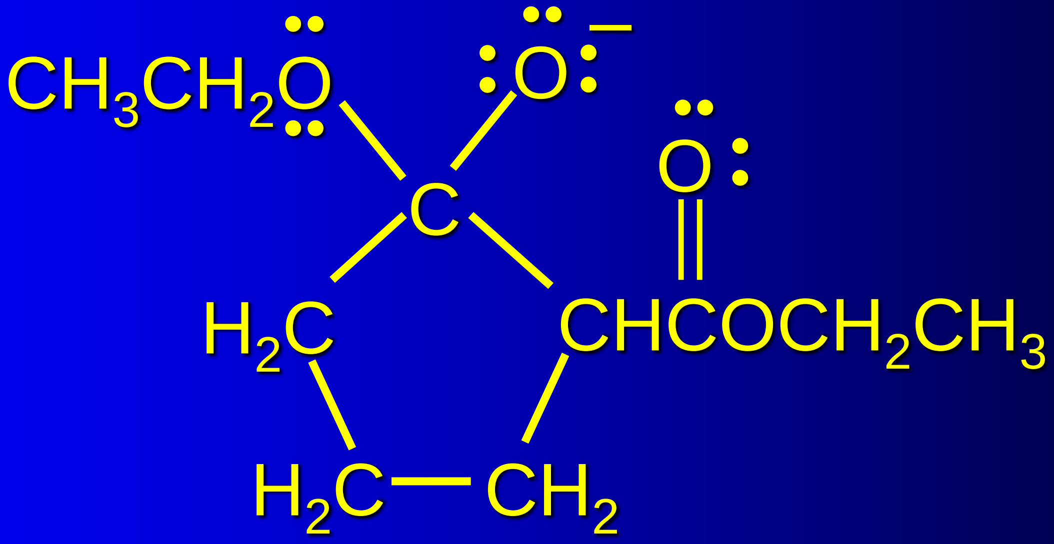
$CH_3CH_2O\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2\overset{-}{C}H\overset{\overset{O}{\|}}{C}OCH_2CH_3$

via

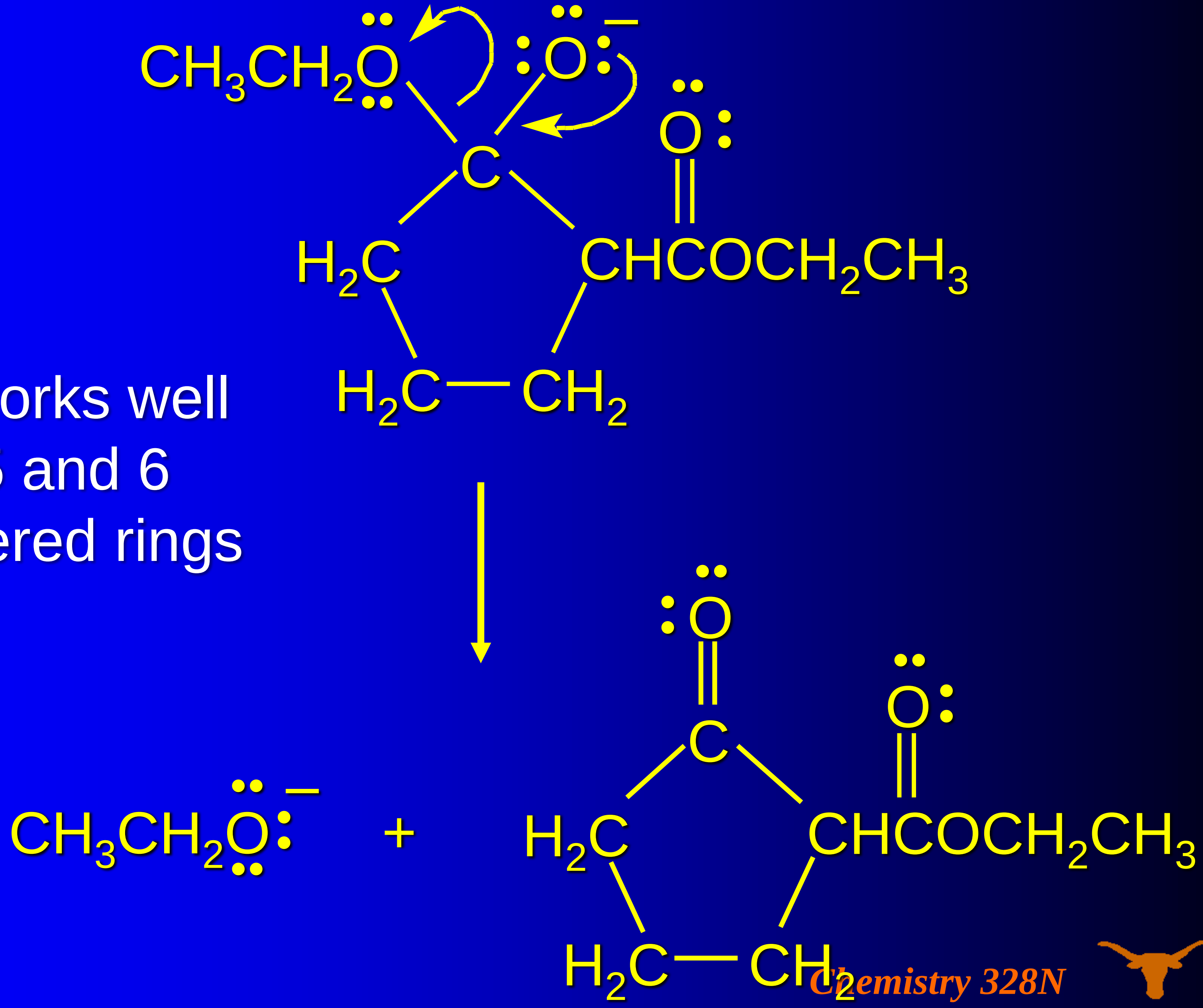


$$CH_3CH_2O\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2\overset{-}{C}H\overset{O}{\overset{\|}{C}}OCH_2CH_3$$

via

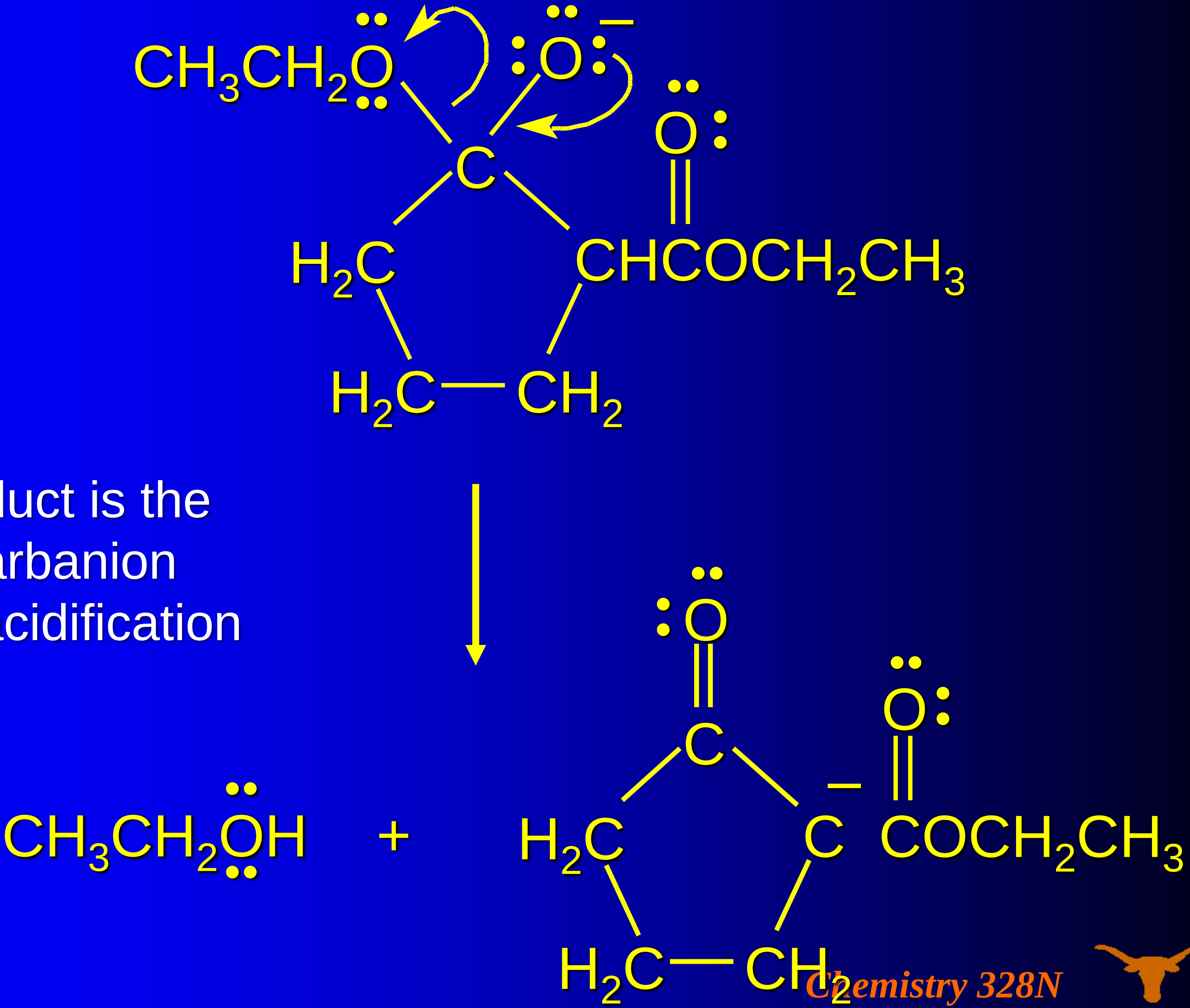


via



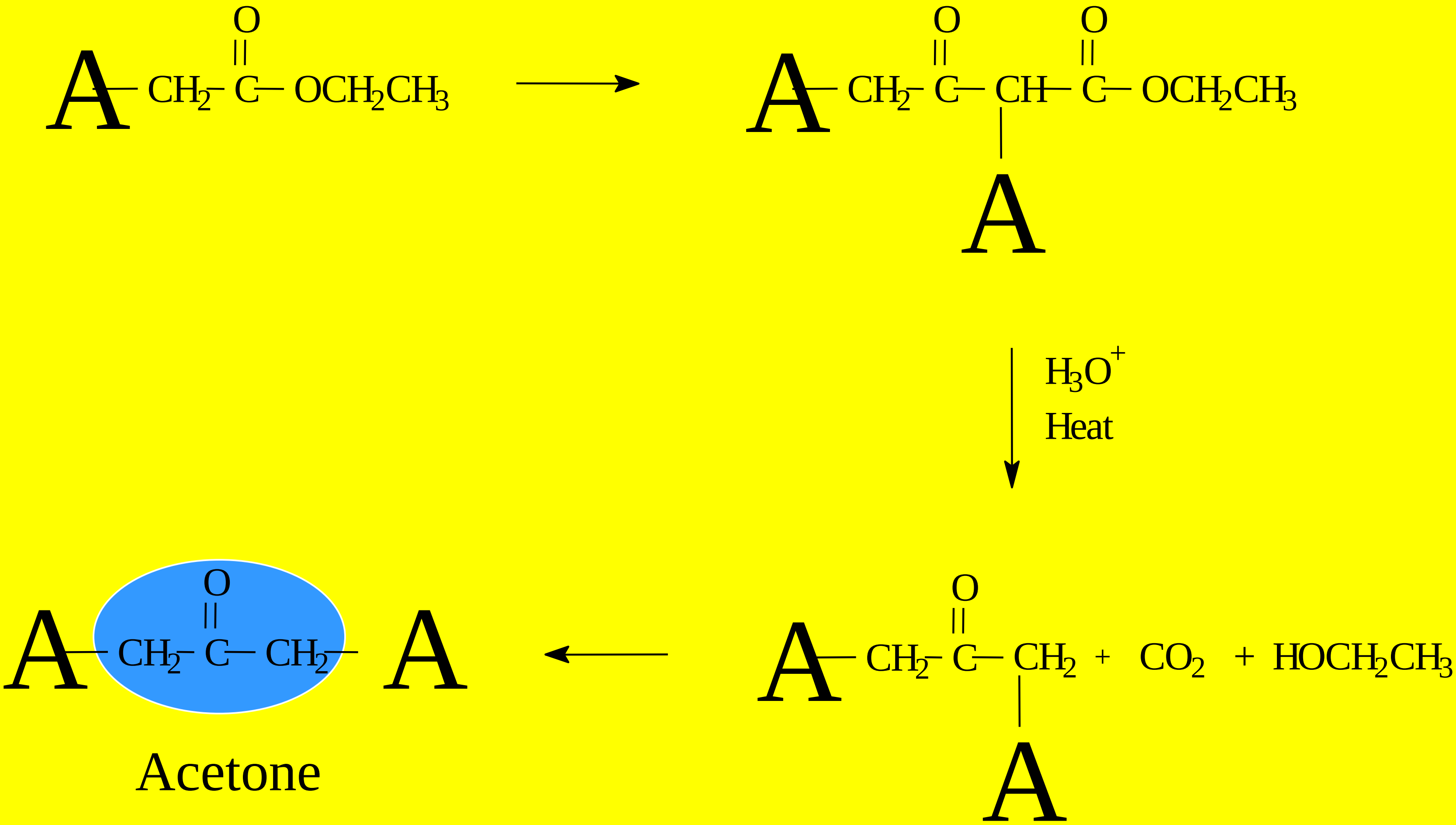
This works well for 5 and 6 membered rings

via



The product is the stable carbanion prior to acidification

A versatile synthesis of β-ketoesters and *symmetrically* substituted acetones



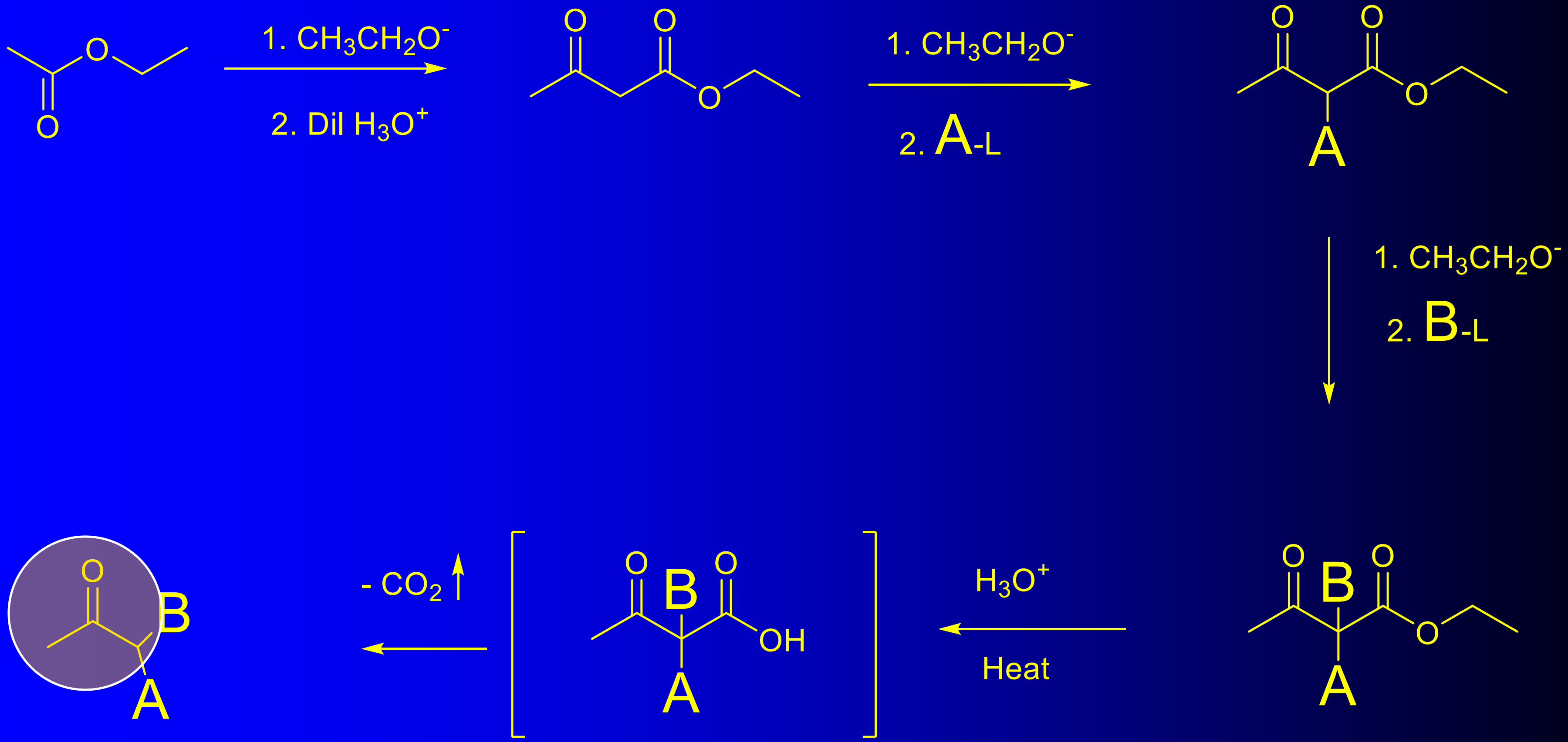
$$A-CH_2-\overset{O}{\overset{\|}{C}}-OCH_2CH_3 \longrightarrow A-CH_2-\overset{O}{\overset{\|}{C}}-\underset{A}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-OCH_2CH_3$$

$$\Big\downarrow \begin{array}{l} H_3O^+ \\ \text{Heat} \end{array}$$

$$A-CH_2-\overset{O}{\overset{\|}{C}}-CH_2-A \longleftarrow A-CH_2-\overset{O}{\overset{\|}{C}}-\underset{A}{\underset{|}{CH_2}} + CO_2 + HOCH_2CH_3$$

Acetone

Alkylation of Acetoacetic Ester gives <u>*unsymmetrically*</u> substituted acetone



1. $CH_3CH_2O^-$
2. Dil H_3O^+

1. $CH_3CH_2O^-$
2. A-L

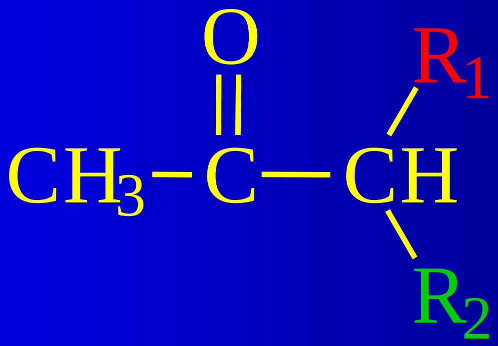
1. $CH_3CH_2O^-$
2. B-L

H_3O^+

Heat

$- CO_2 \uparrow$

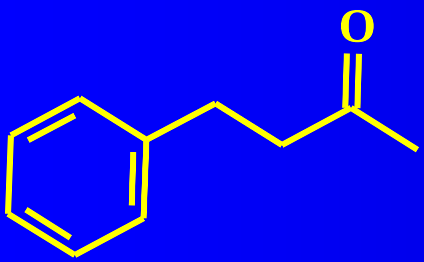
Acetoacetic Ester Synthesis

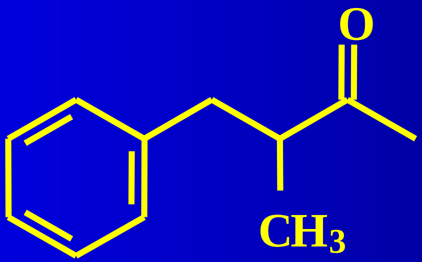


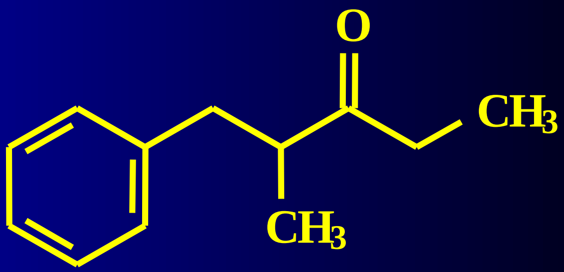
$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{R_2}{\overset{R_1}{CH}}$$

Ketone Synthesis

Let’s work another example together

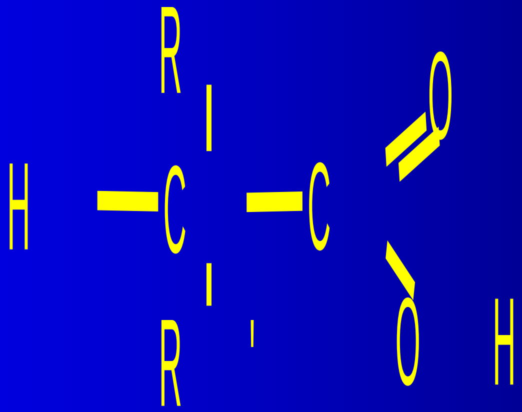




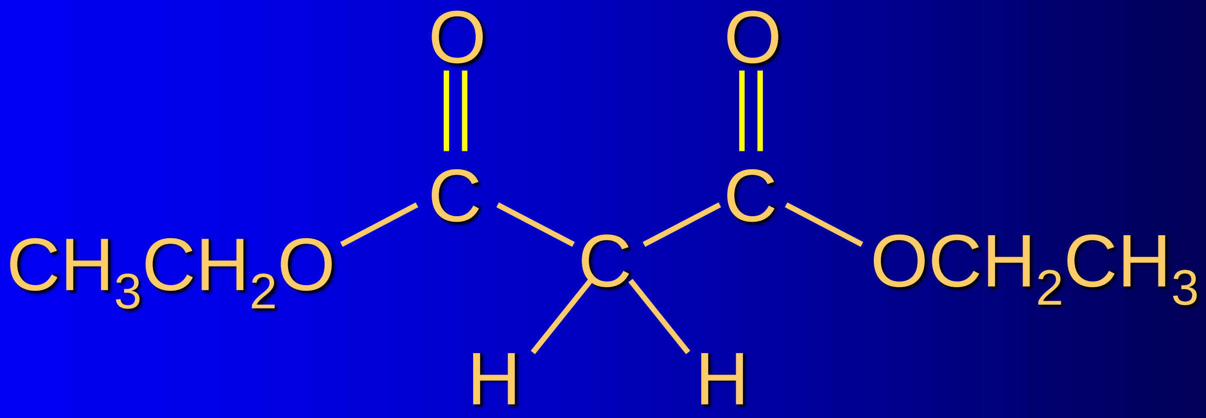


The Malonic Ester Synthesis

Versatile Synthesis of Carboxylic acids

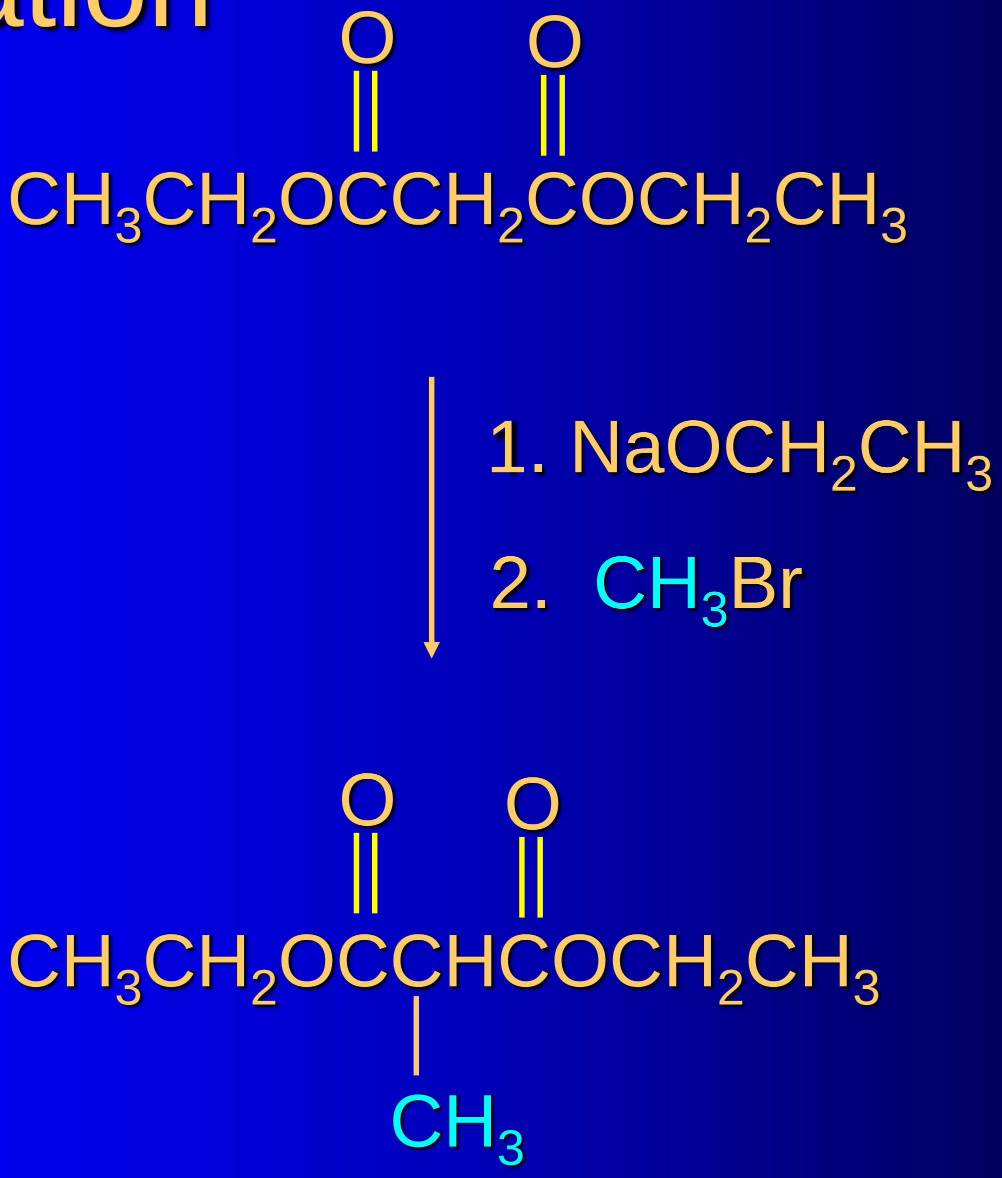


Malonic Ester



- *Malonic ester* is another name for *diethyl malonate*.
- The "malonic ester synthesis" uses diethyl malonate as a reactant for the preparation of carboxylic acids.

Dialkylation

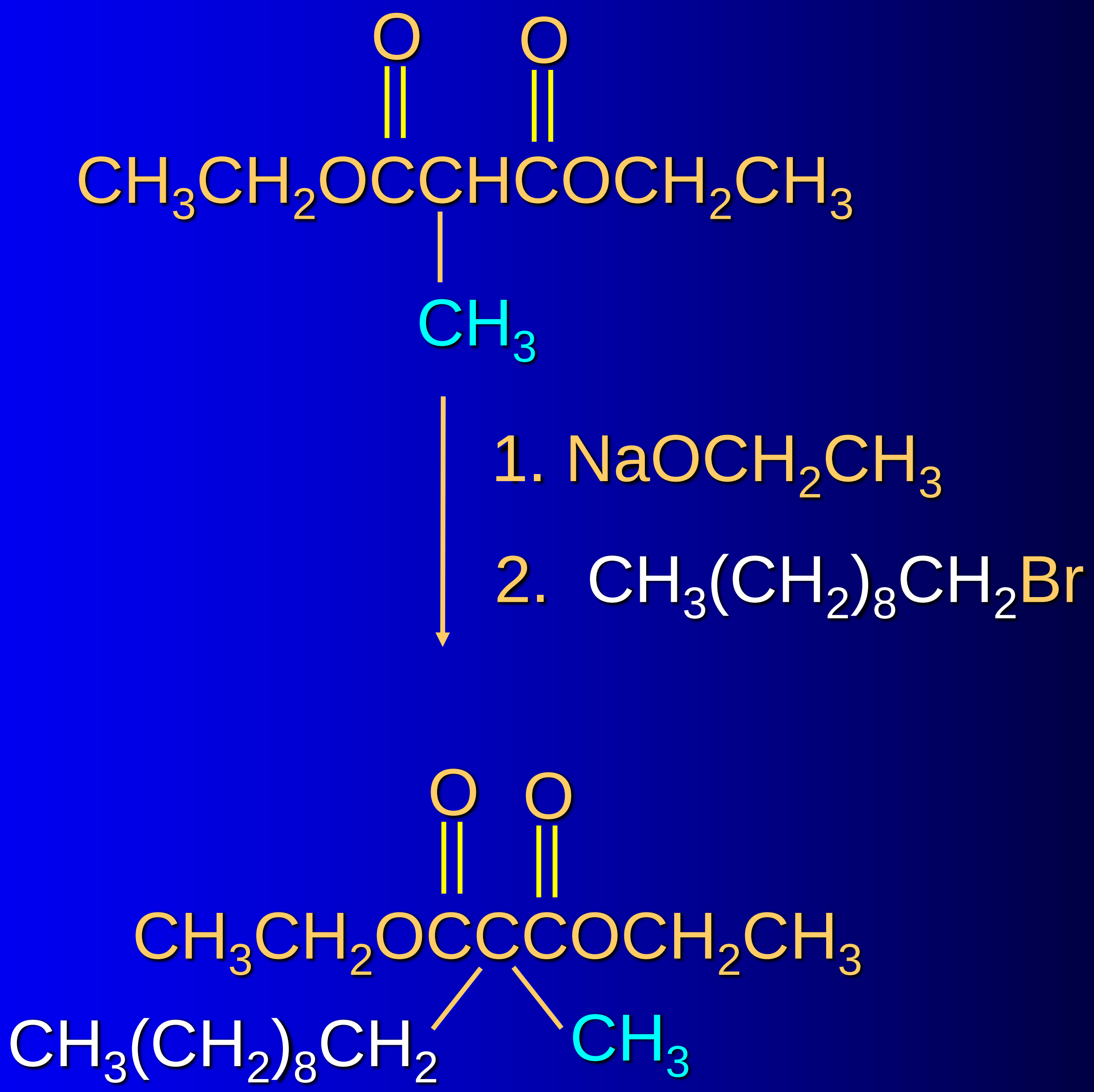


$$CH_3CH_2O\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3$$

1. $NaOCH_2CH_3$

2. CH_3Br

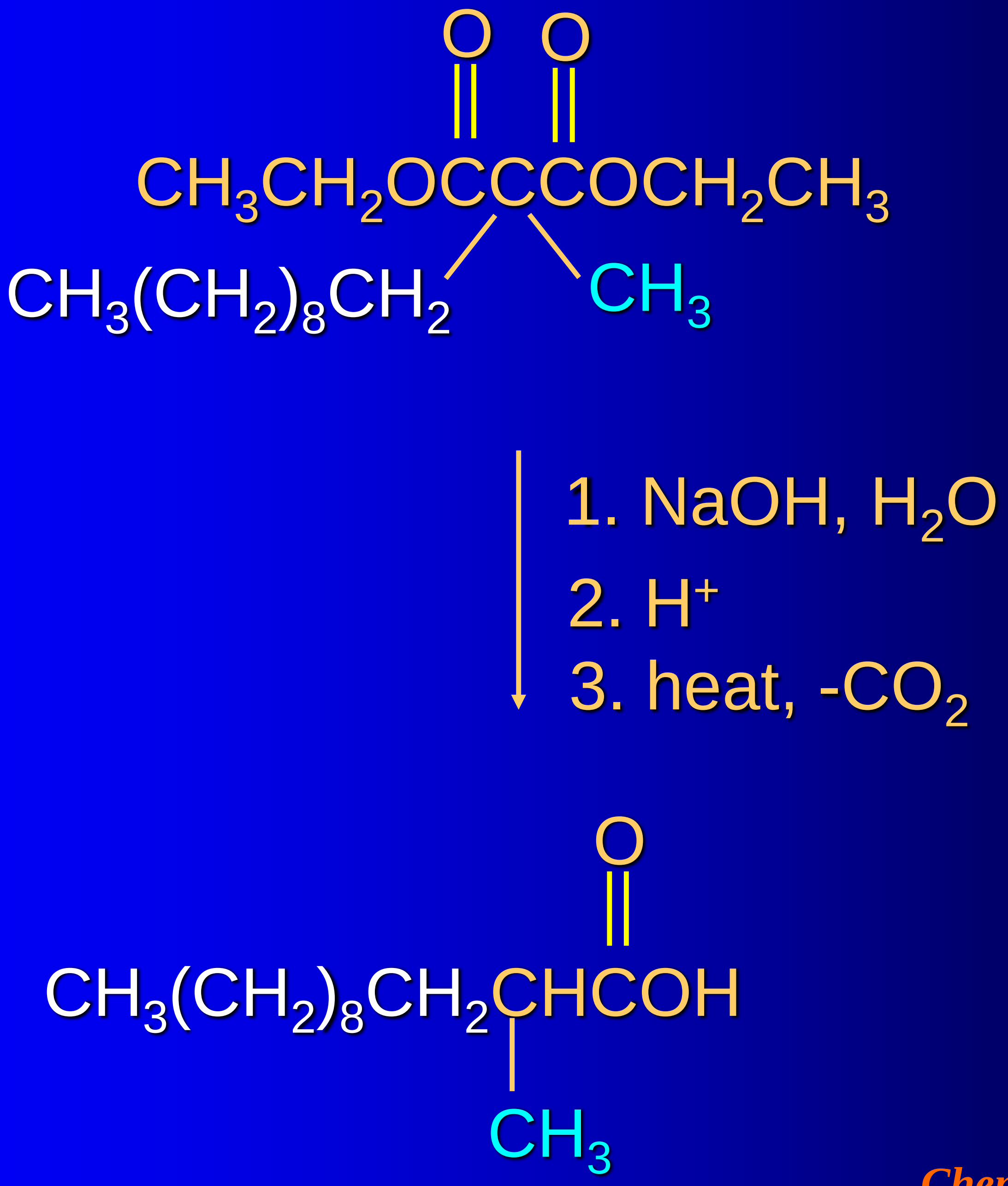
$$CH_3CH_2O\overset{O}{\overset{\|}{C}}\underset{\underset{CH_3}{|}}{C}H\overset{O}{\overset{\|}{C}}OCH_2CH_3$$



$$CH_3CH_2O\overset{O}{\overset{\|}{C}}\underset{\underset{CH_3}{|}}{C}H\overset{O}{\overset{\|}{C}}OCH_2CH_3$$

$$\Bigg\downarrow \begin{array}{l} 1.\ NaOCH_2CH_3 \\ 2.\ CH_3(CH_2)_8CH_2Br \end{array}$$

$$CH_3CH_2O\overset{O}{\overset{\|}{C}}\underset{CH_3(CH_2)_8CH_2\diagup\ \diagdown CH_3}{C}\overset{O}{\overset{\|}{C}}OCH_2CH_3$$



$$CH_3CH_2O\overset{\overset{O}{\|}}{C}\underset{CH_3(CH_2)_8CH_2\ \ \ \ CH_3}{C}\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

1. NaOH, H_2O
2. H^+
3. heat, $-CO_2$

$$CH_3(CH_2)_8CH_2\underset{\underset{CH_3}{|}}{CH}\overset{\overset{O}{\|}}{C}OH$$

Malonic Ester Synthesis