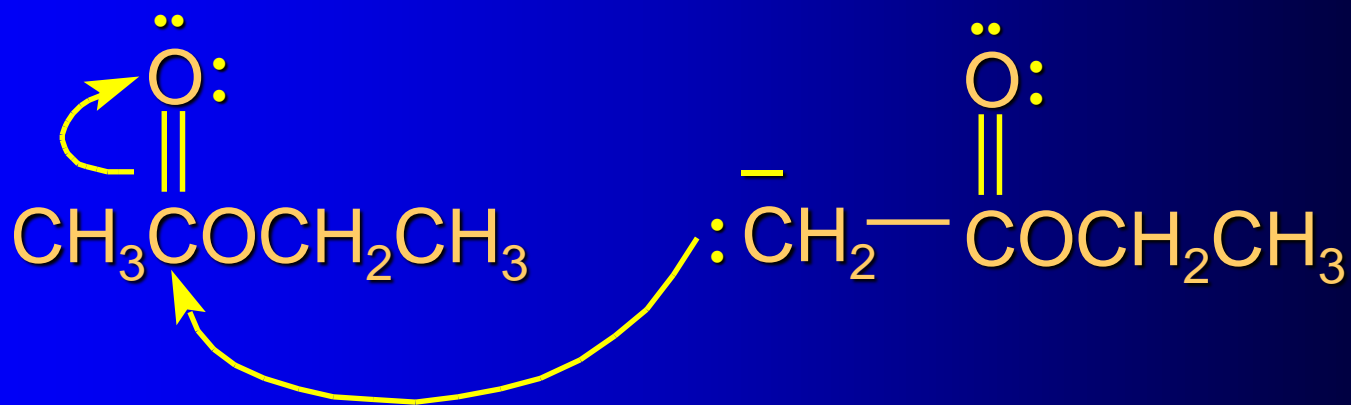


Lecture 19

The Claisen Condensation



Exam Tomorrow Evening!!

Review tonight
5PM -6PM
Welch 1.316



Some “loose ends” before we go on

- Spectroscopy of acid derivatives
- A selective reduction for your tool box



Reduction of Acid Derivatives

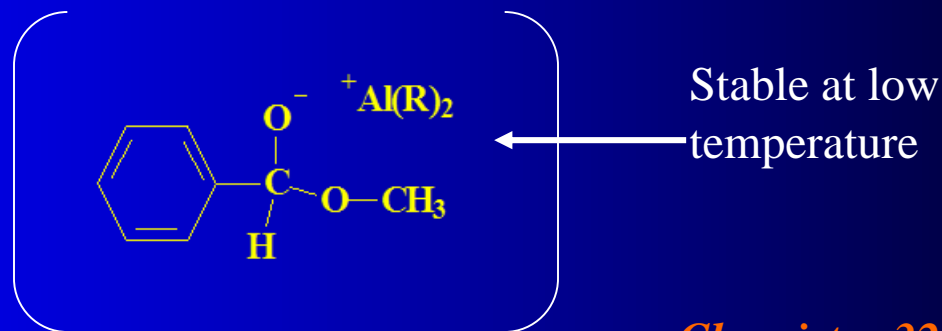
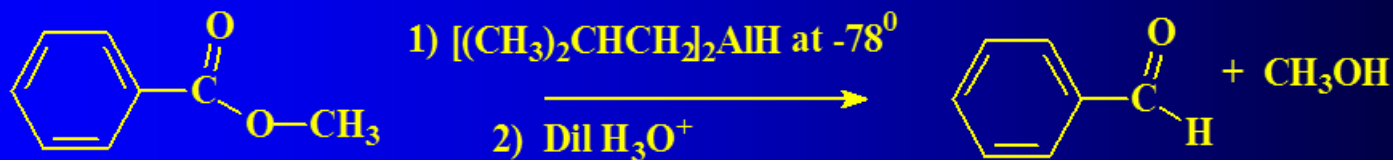
- Acids (page 679-681)
- Esters (page 738-739)
- Please work through the example on 738
- Amides (page 739-742)
- Nitriles (page 742)
- Selective reductions with NaBH_4



DIBALH

Diisobutylaluminum hydride (DIBALH) at -78°C selectively reduces esters to aldehydes

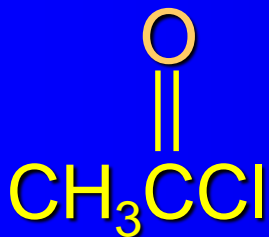
- at -78°C , the tetrahedral intermediate does not collapse and it is not until hydrolysis in aqueous acid that the carbonyl group of the aldehyde is liberated



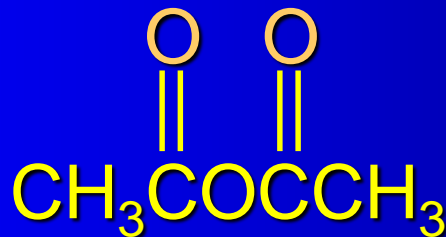
Infrared Spectroscopy

C=O stretching frequency depends on whether the compound is an acyl chloride, anhydride, ester, or amide.

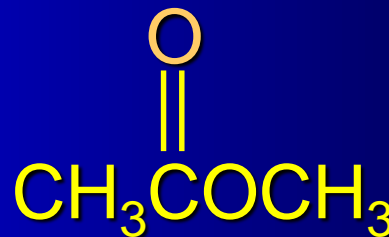
C=O stretching frequency ν



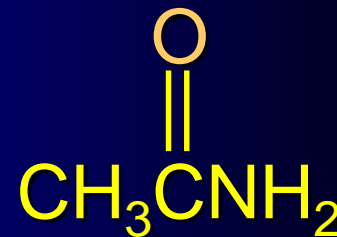
1822 cm^{-1}



1748
and
1815 cm^{-1}



1736 cm^{-1}



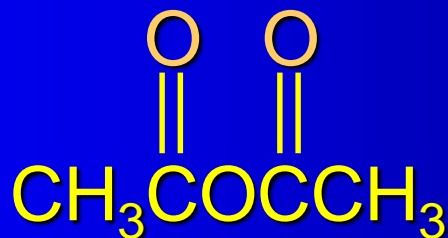
1694 cm^{-1}



Infrared Spectroscopy

Anhydrides have two peaks due to C=O stretching. One from symmetrical stretching of the C=O and the other from an antisymmetrical stretch.

C=O stretching frequency ν



1748 and 1815 cm⁻¹



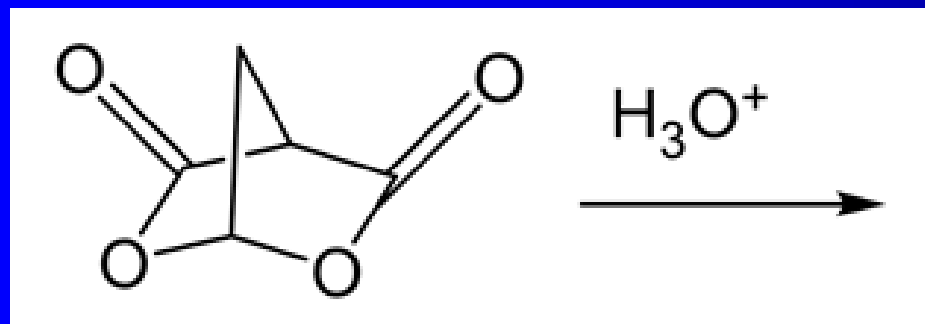
Infrared Spectroscopy

Nitriles are readily identified by absorption due to carbon-nitrogen triple bond stretching that is “all alone” in the

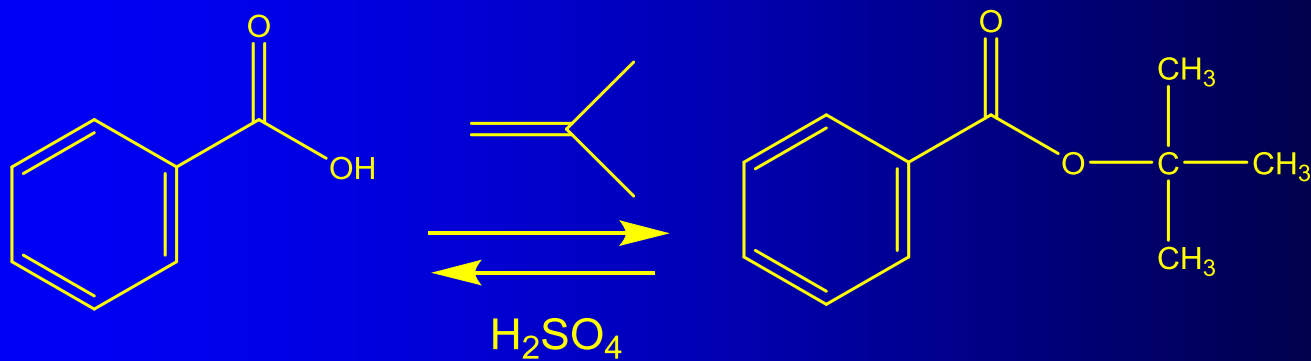
2210-2260 cm^{-1} region.



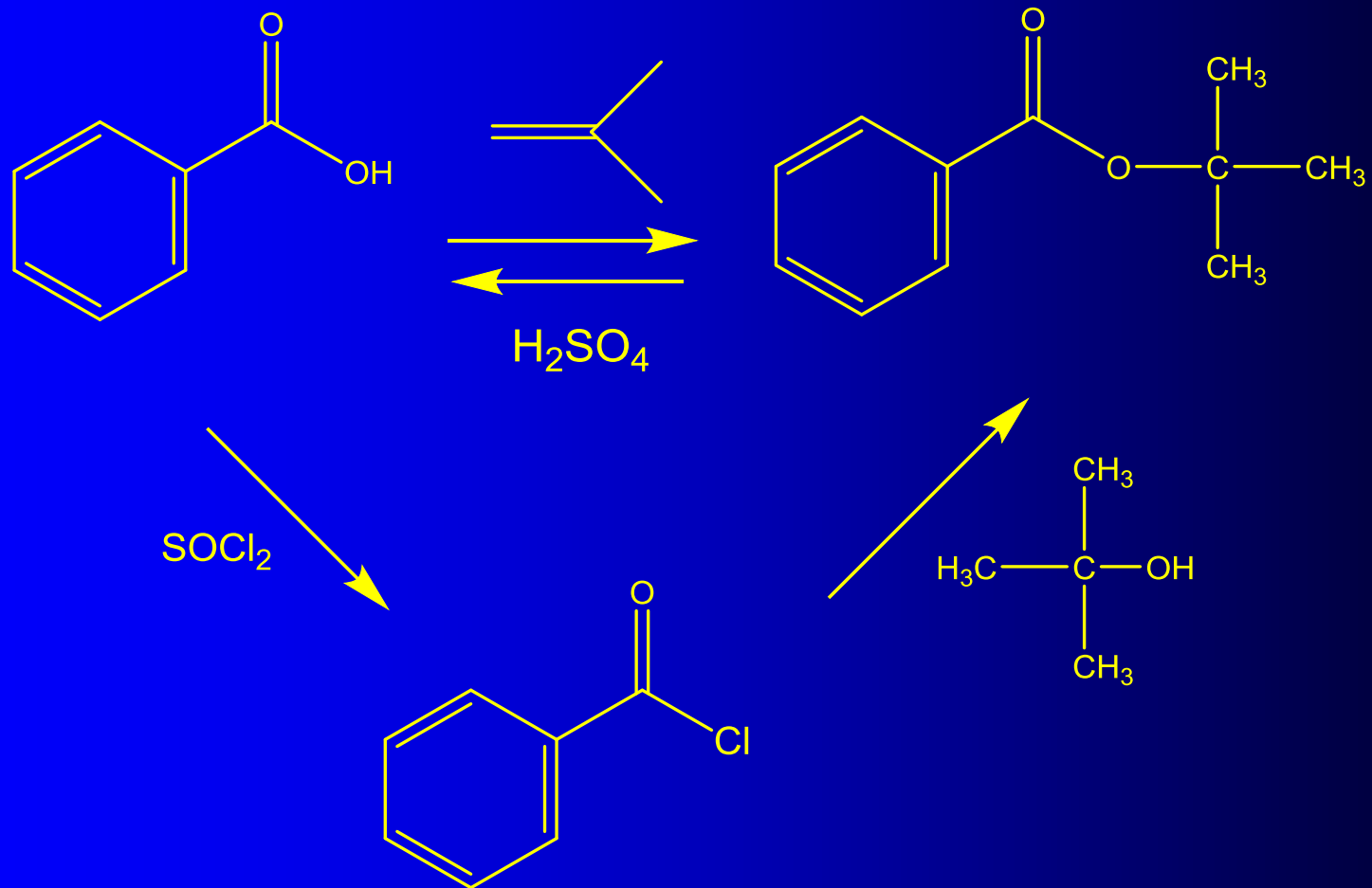
Hydrolysis and Decarboxylation



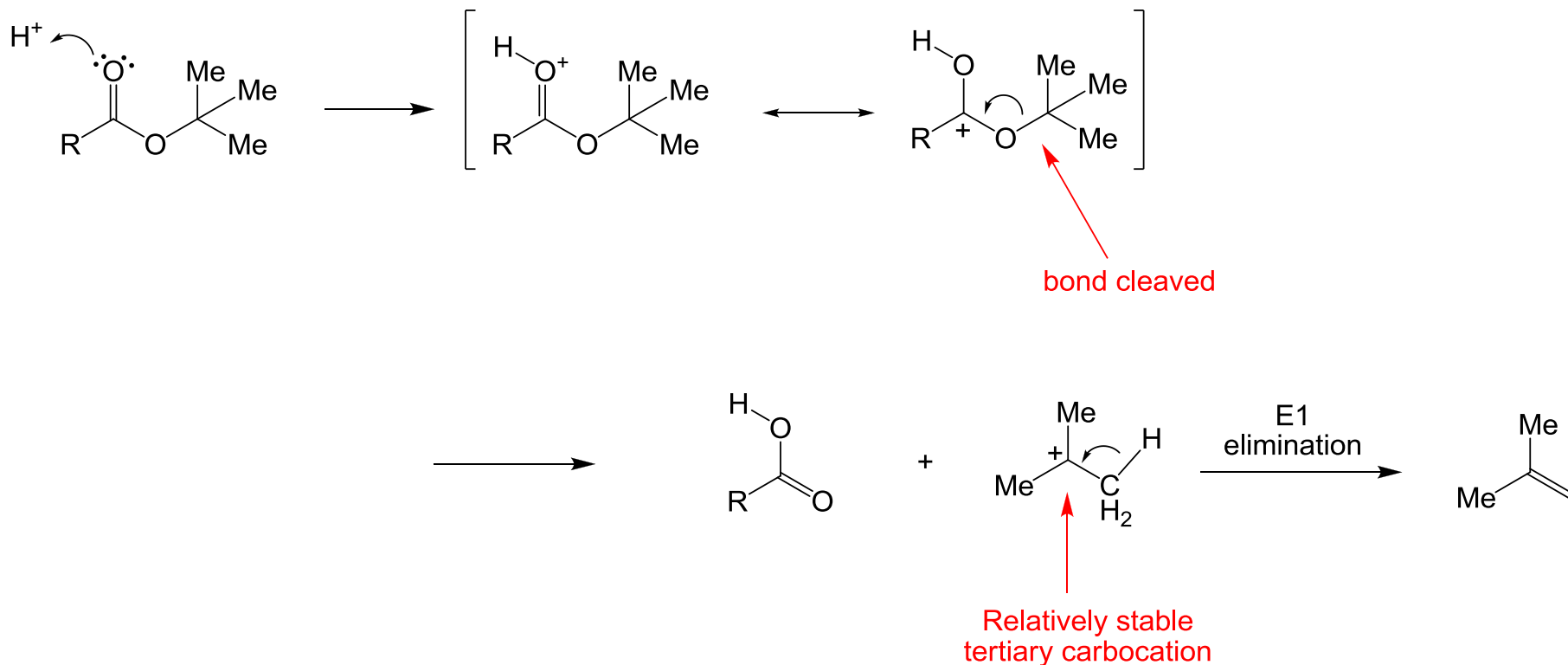
t-Butyl esters



t-Butyl esters



t-Butyl ester hydrolysis



Note which bond is broken in this hydrolysis !!



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 α proton
- Acidity of α protons on “normal” aldehydes and ketones is about that of alcohols and less than water...pKa \sim 18-20
- Some are far more acidic, i.e. β -dicarbonyl compounds that have quite low pKa's

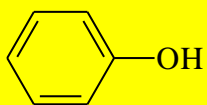


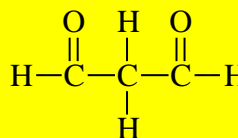
pKa of some acids and some α protons

$\text{CH}_3\text{CO}_2\text{H}$ 4.75

HF 3.45

HCl -9.0!!

 10

 5.0

CH_3OH 16 ←

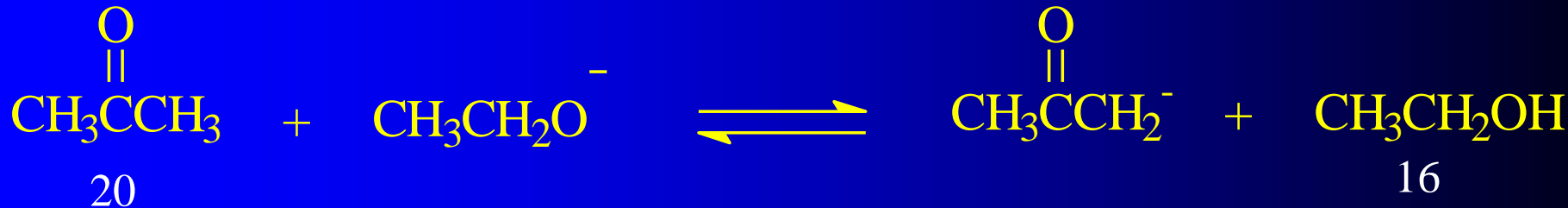
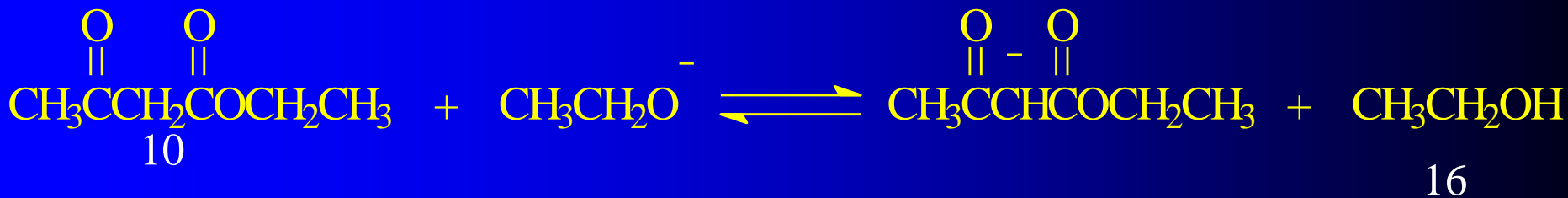
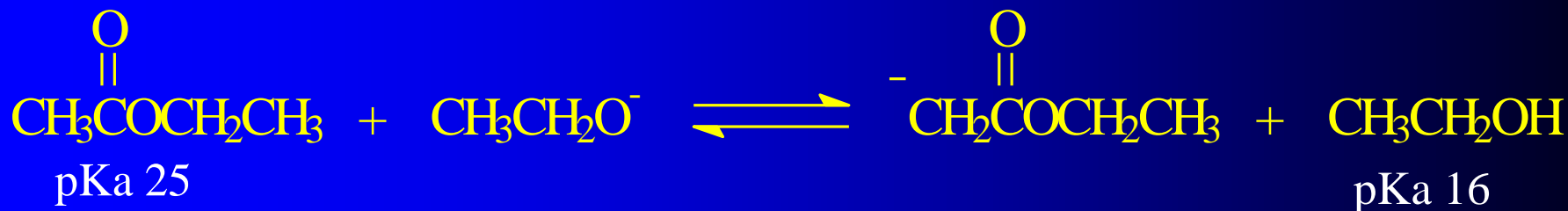
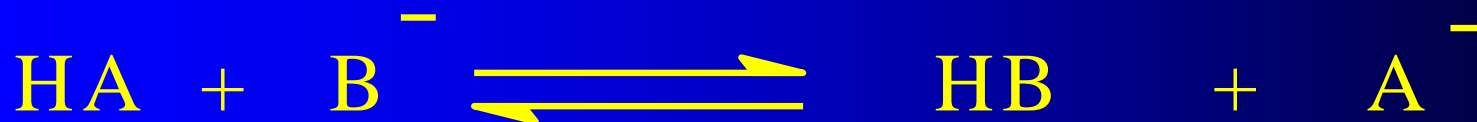
 10 ←

 20 ←

CH_3CH_3 50

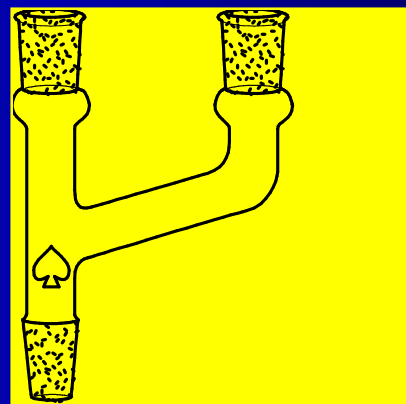


Some Acid Base Chemistry



Which way do the equilibria lie?

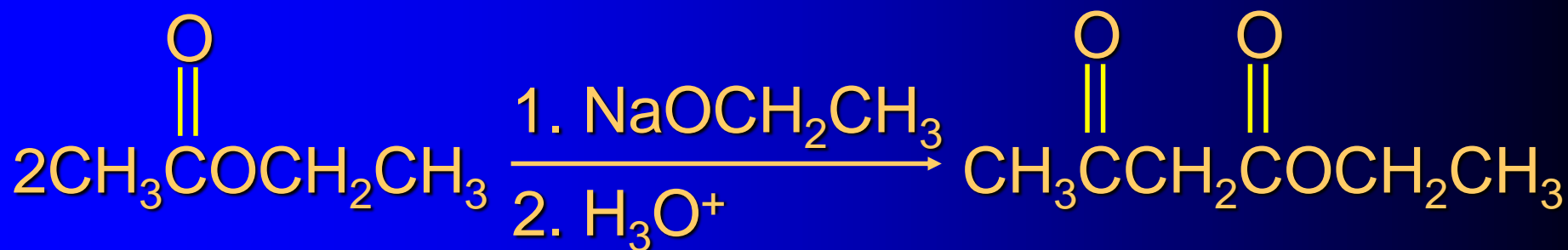




- **Rainer Ludwig Claisen** (1851-1930): Born in Köln and studied chemistry at Bonn, and briefly at Göttingen. He earned his doctorate at Bonn under August Kekulé (1829-1896).



Classical Claisen Condensation

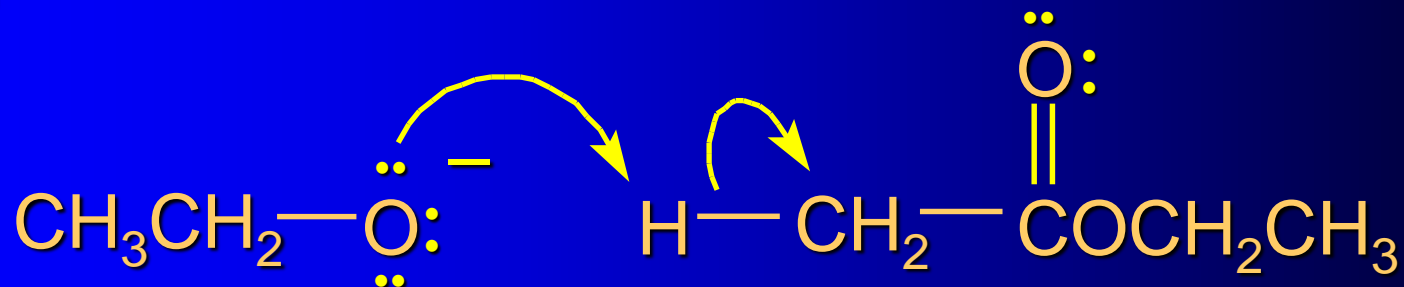


- Two moles of ethyl acetate condense to give *ethyl acetoacetate* or (*acetoacetic ester*)



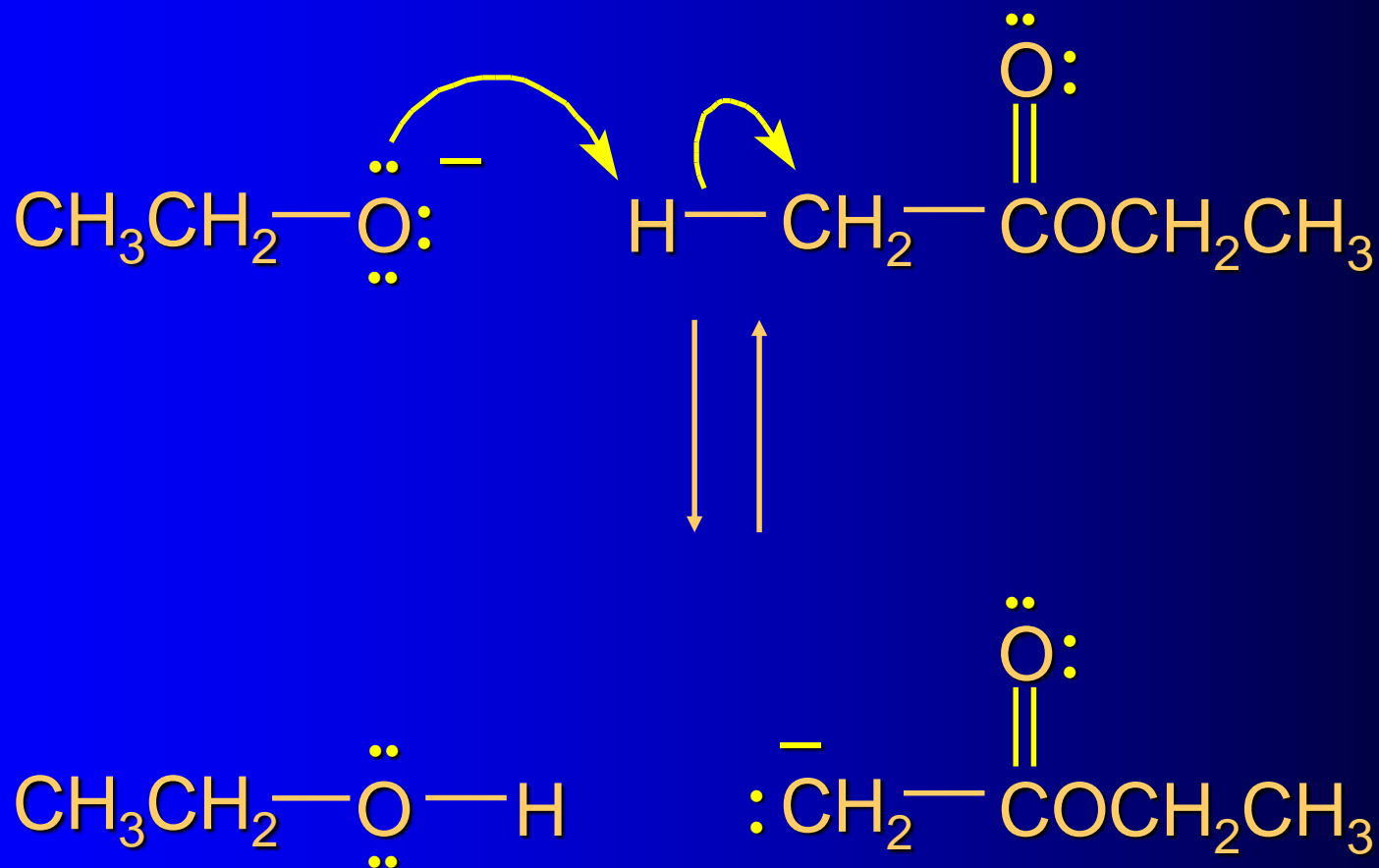
Mechanism

Step 1:



Mechanism

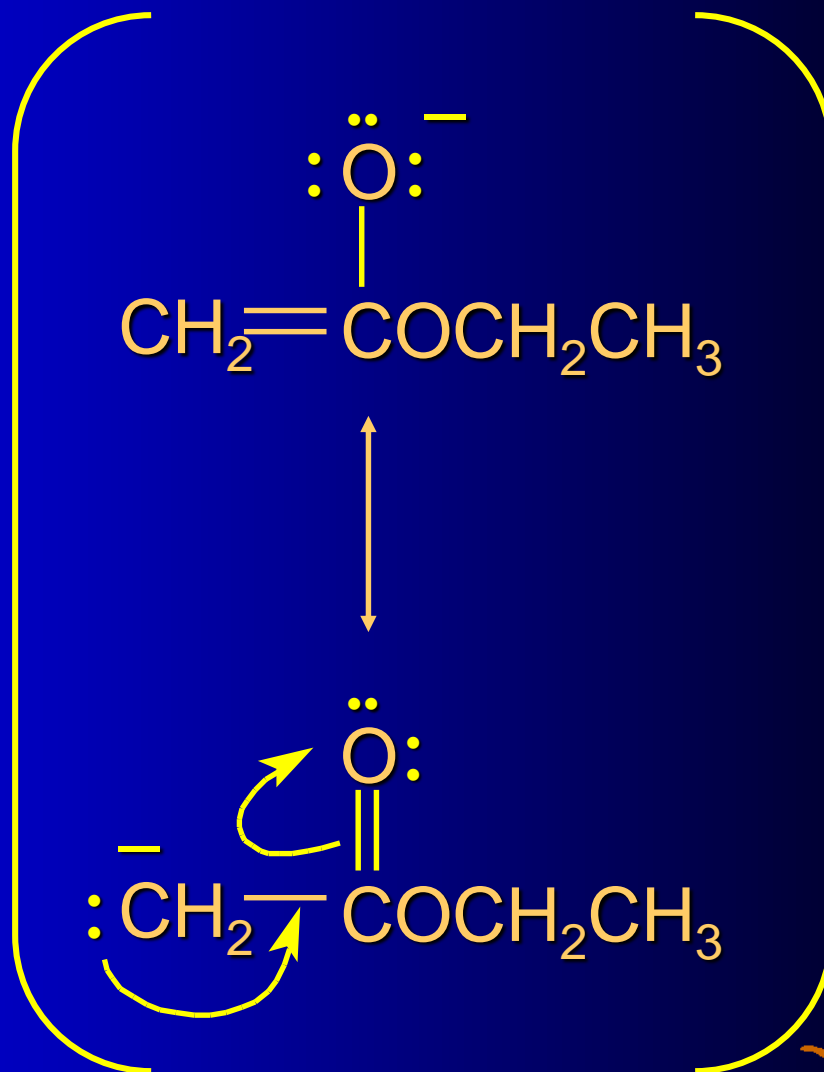
Step 1:



Mechanism

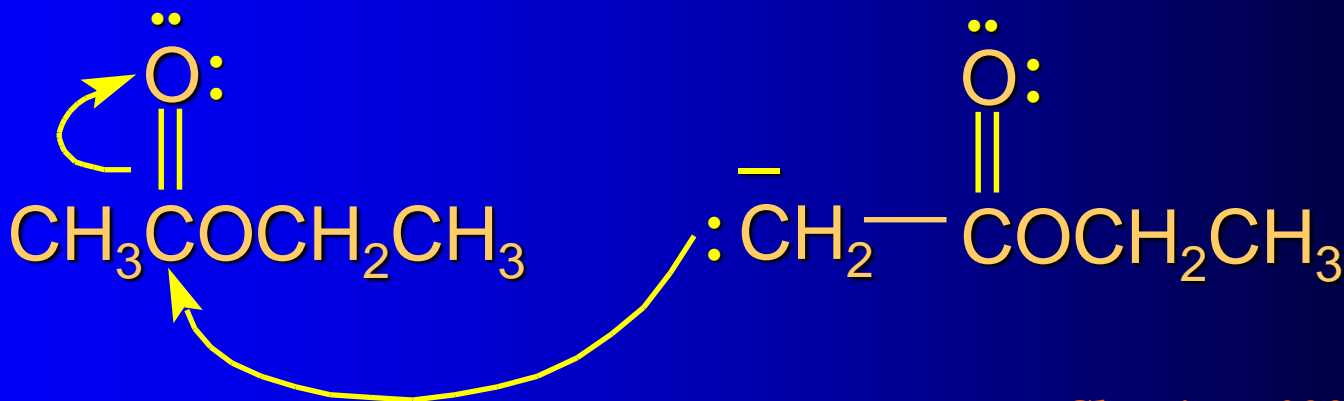
Step 1:

- The enolate anion is stabilized by resonance



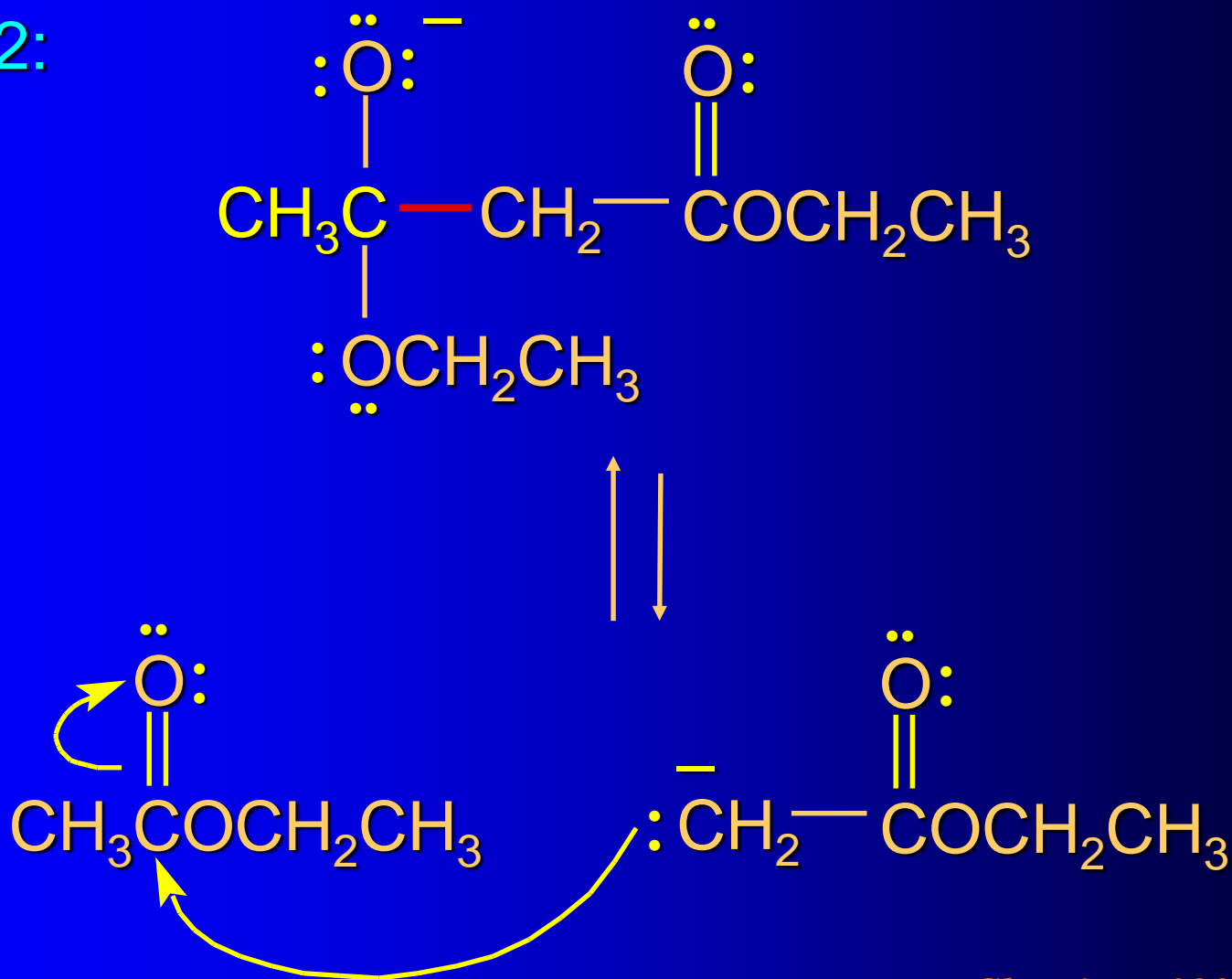
Mechanism

Step 2: Nucleophilic acyl substitution



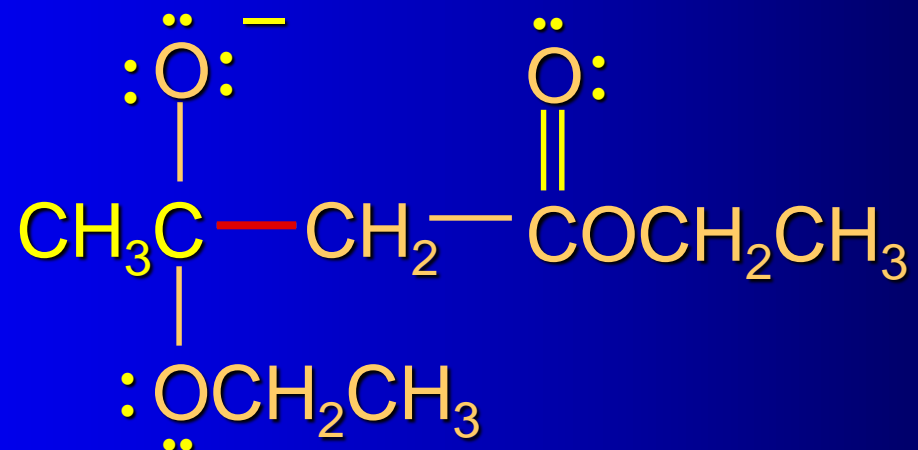
Mechanism

Step 2:



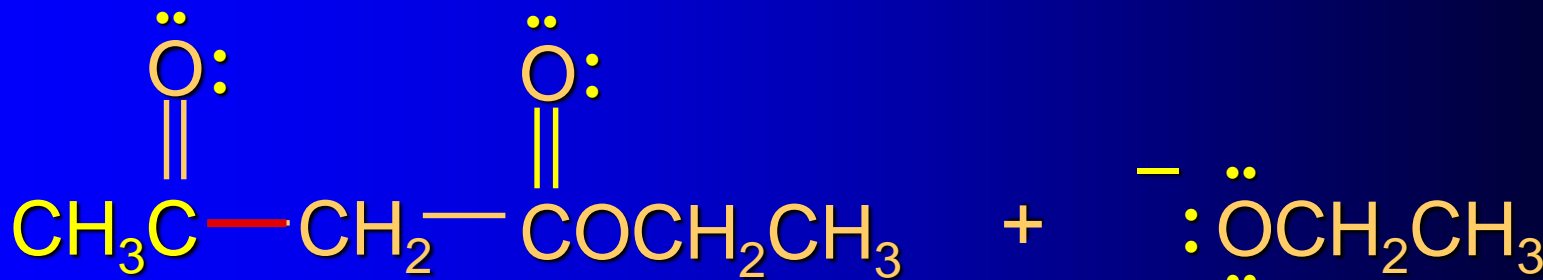
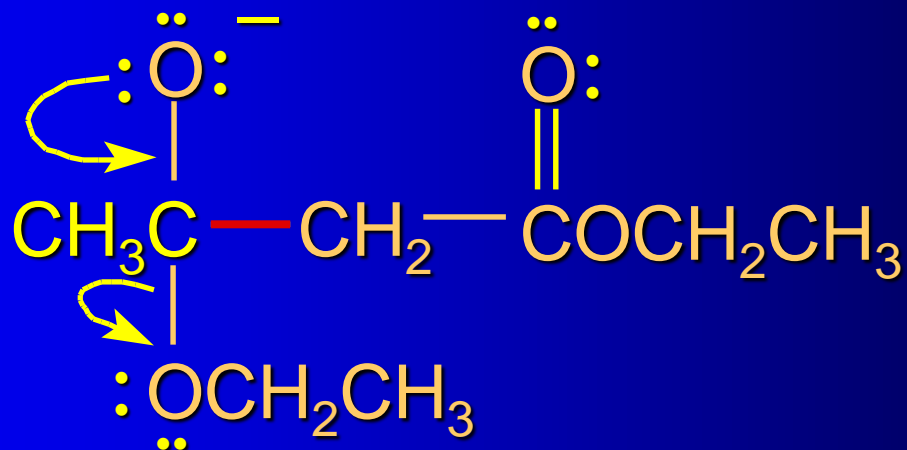
Mechanism

Step 2:



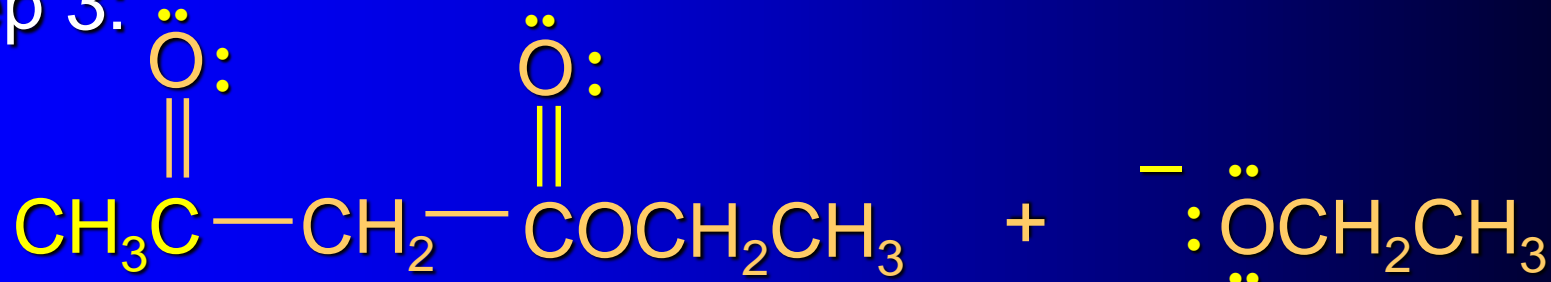
Mechanism

Step 3:



Mechanism

Step 3:

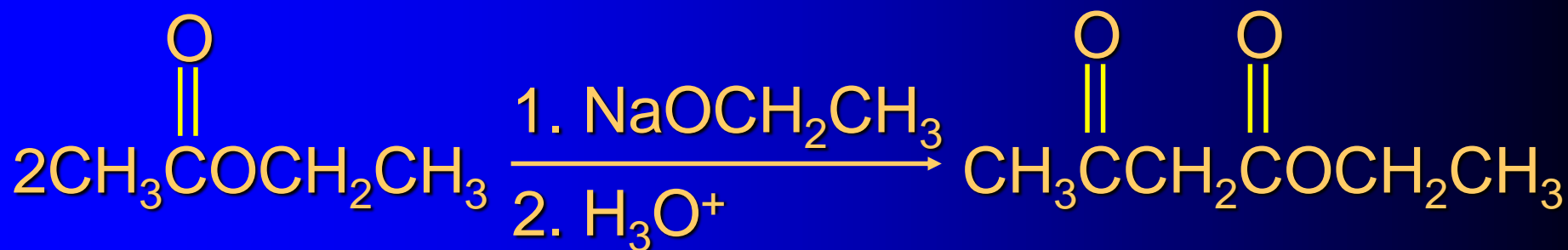


- The product is ethyl acetoacetate.
- However, were nothing else to happen, the yield of ethyl acetoacetate would be small because the equilibrium constant for its formation is small.
- Something else does happen. Ethoxide abstracts a proton from the CH₂ group to give a stabilized anion. The equilibrium constant for this acid-base reaction is very favorable.



Classical Claisen Condensation

An excellent path to β -keto esters

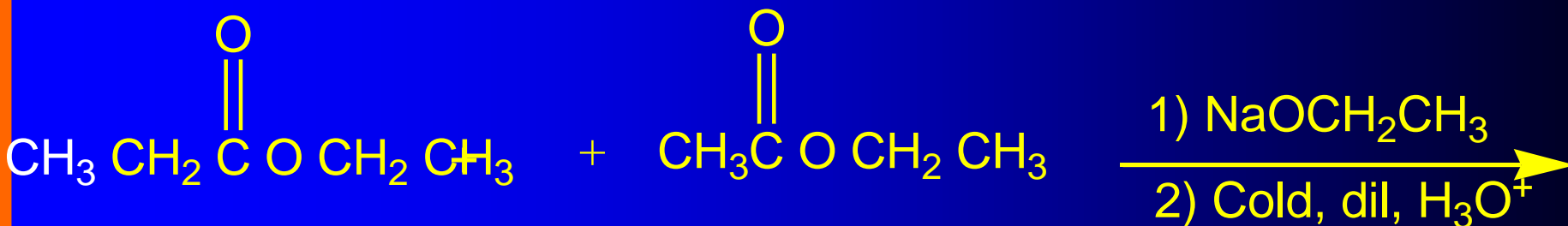


- Two moles of ethyl acetate condense to give ethyl 3-oxobutanoate or ... *ethyl acetoacetate aka acetoacetic ester*



Crossed Claisen Condensation

- What is wrong with this?



No No No...it gives a mixture of products, a big fat mess!!



Crossed Claisen Condensation

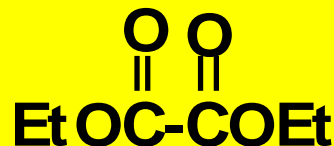
Crossed reactions can work if one does it carefully and one of the reactants does not have an alpha hydrogen such as:



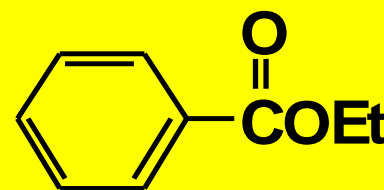
**Ethyl
formate**



**Diethyl
carbonate**



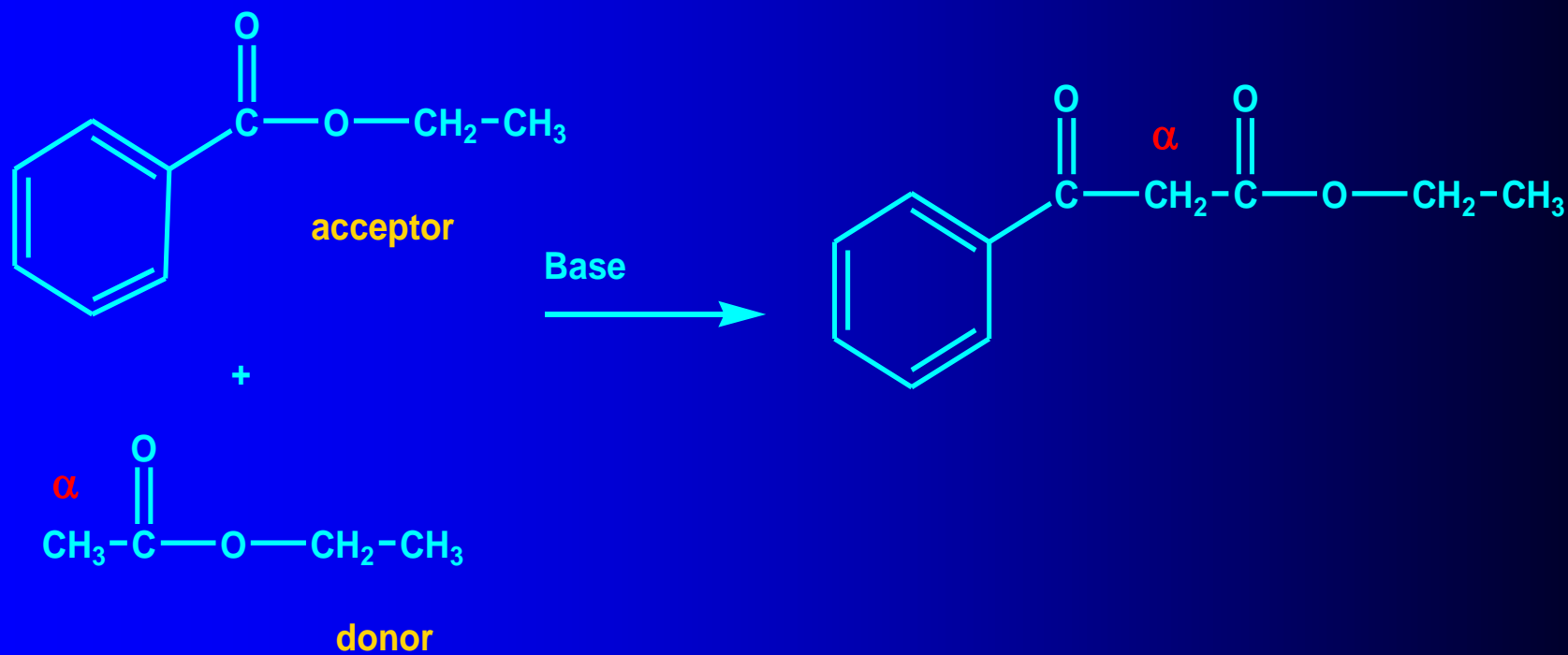
**Diethyl ethanedioate
(Diethyl oxalate)**



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?

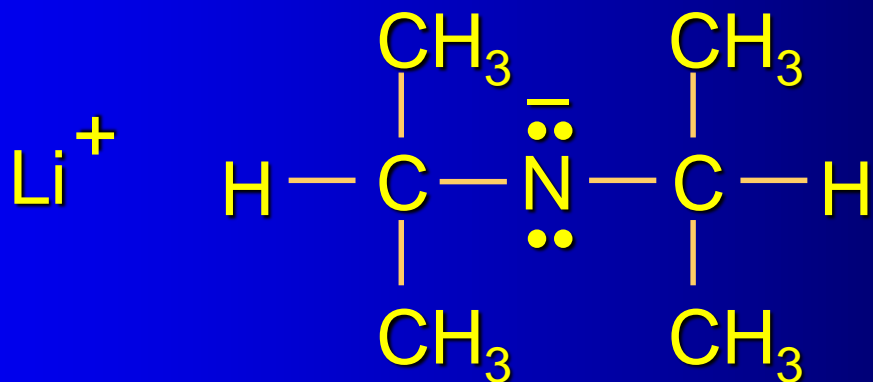


Deprotonation of Simple Esters

- Ethyl acetoacetate ($pK_a \sim 11$) 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)

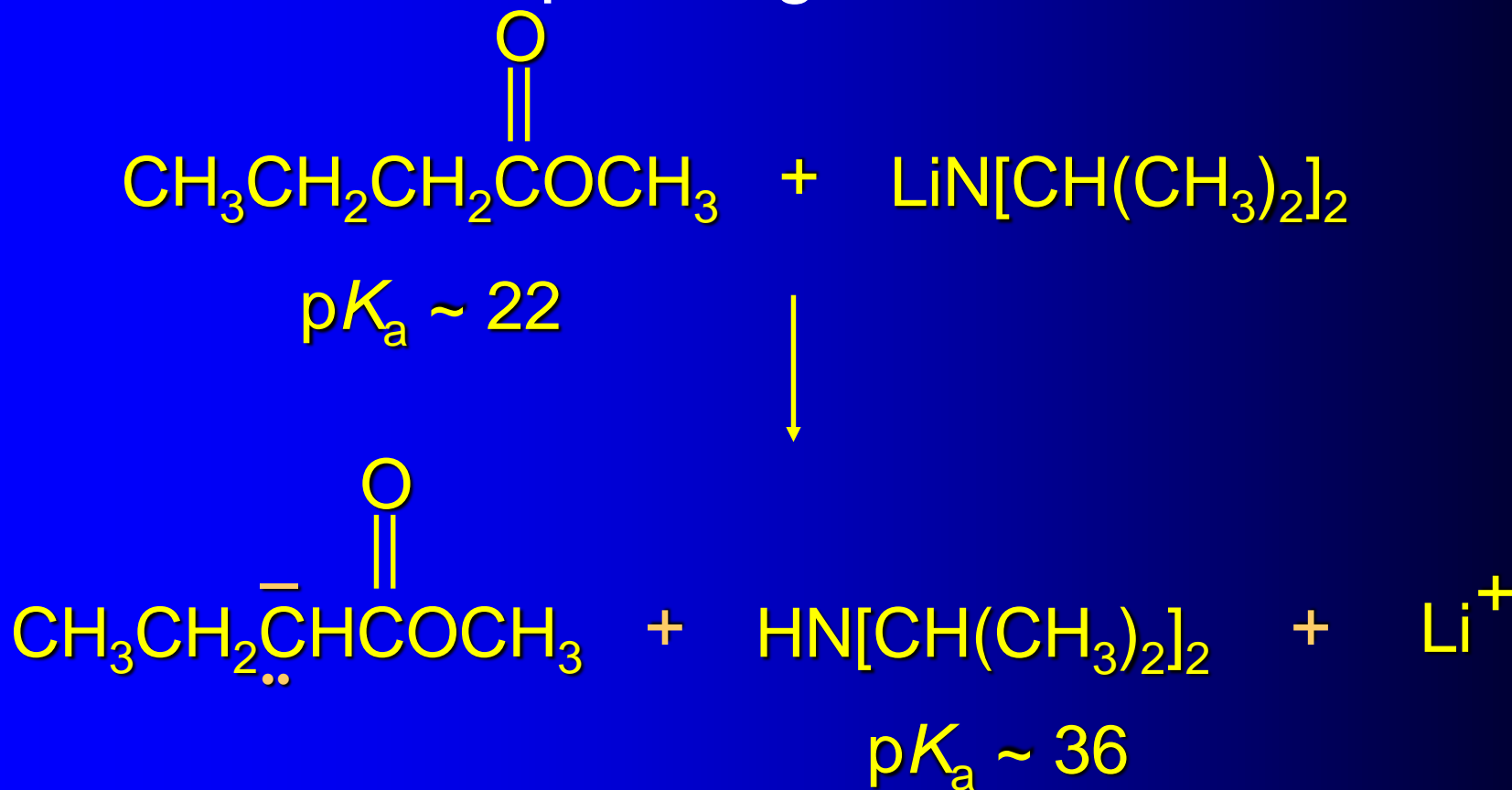


- LDA is a strong base (just as NaNH_2 is a very strong base). $\text{pK}_a \sim 36$
- Because it is so sterically hindered, LDA does not add to carbonyl groups.



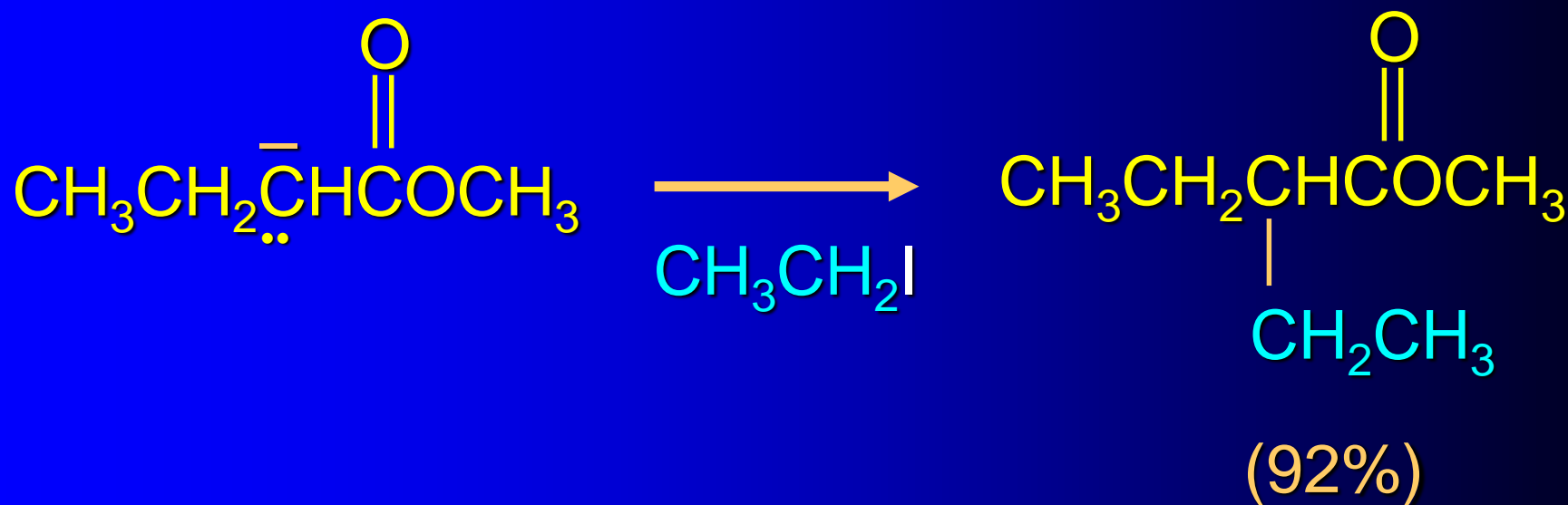
Lithium diisopropylamide (LDA)

- LDA converts simple esters quantitatively to the corresponding enolate.



Lithium diisopropylamide (LDA)

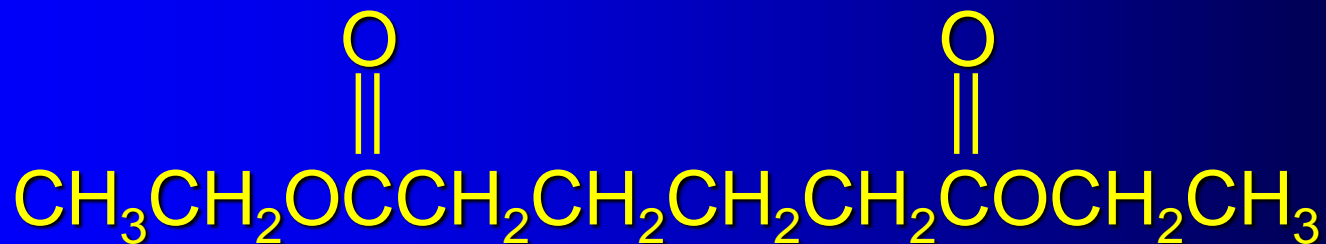
- Enolates generated from esters and LDA can be alkylated.



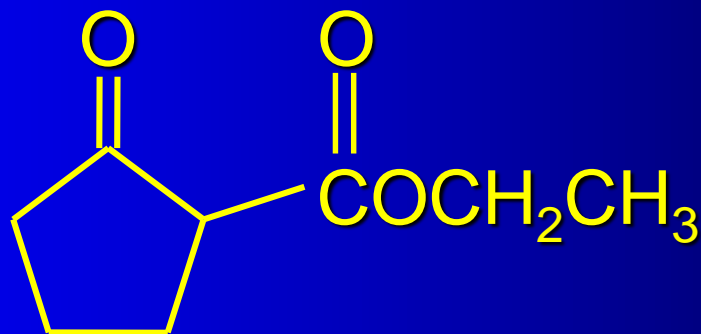
Intramolecular Claisen Condensation: The Dieckmann Reaction



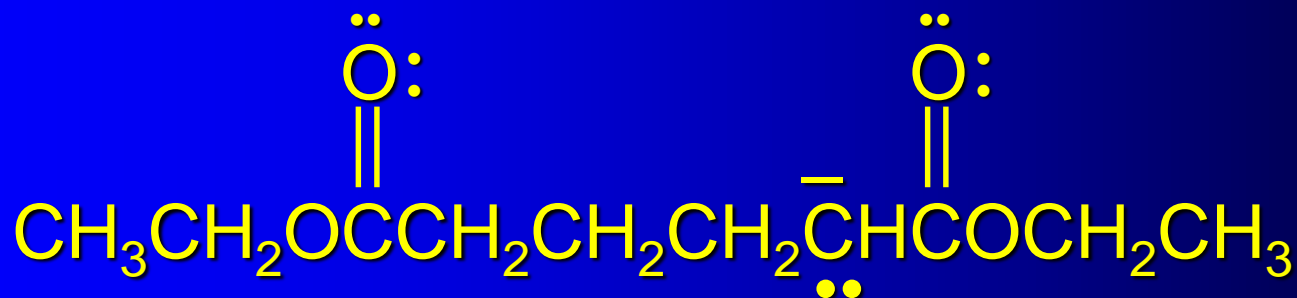
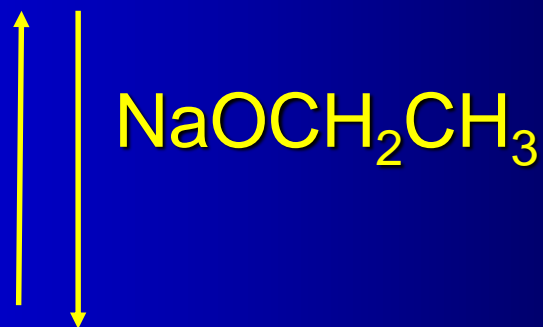
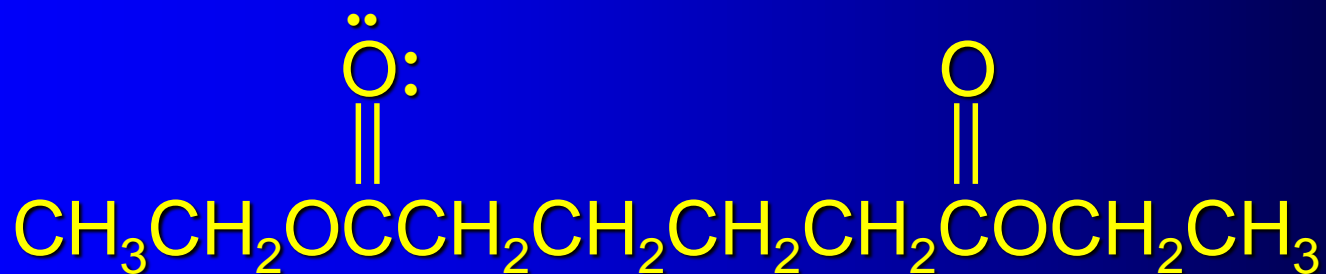
Example



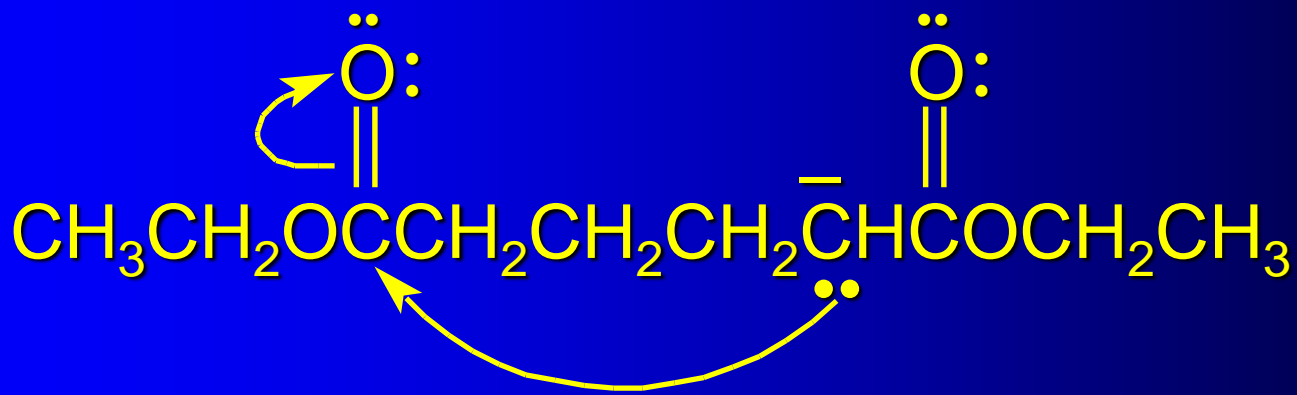
1. $\text{NaOCH}_2\text{CH}_3$
2. H_3O^+



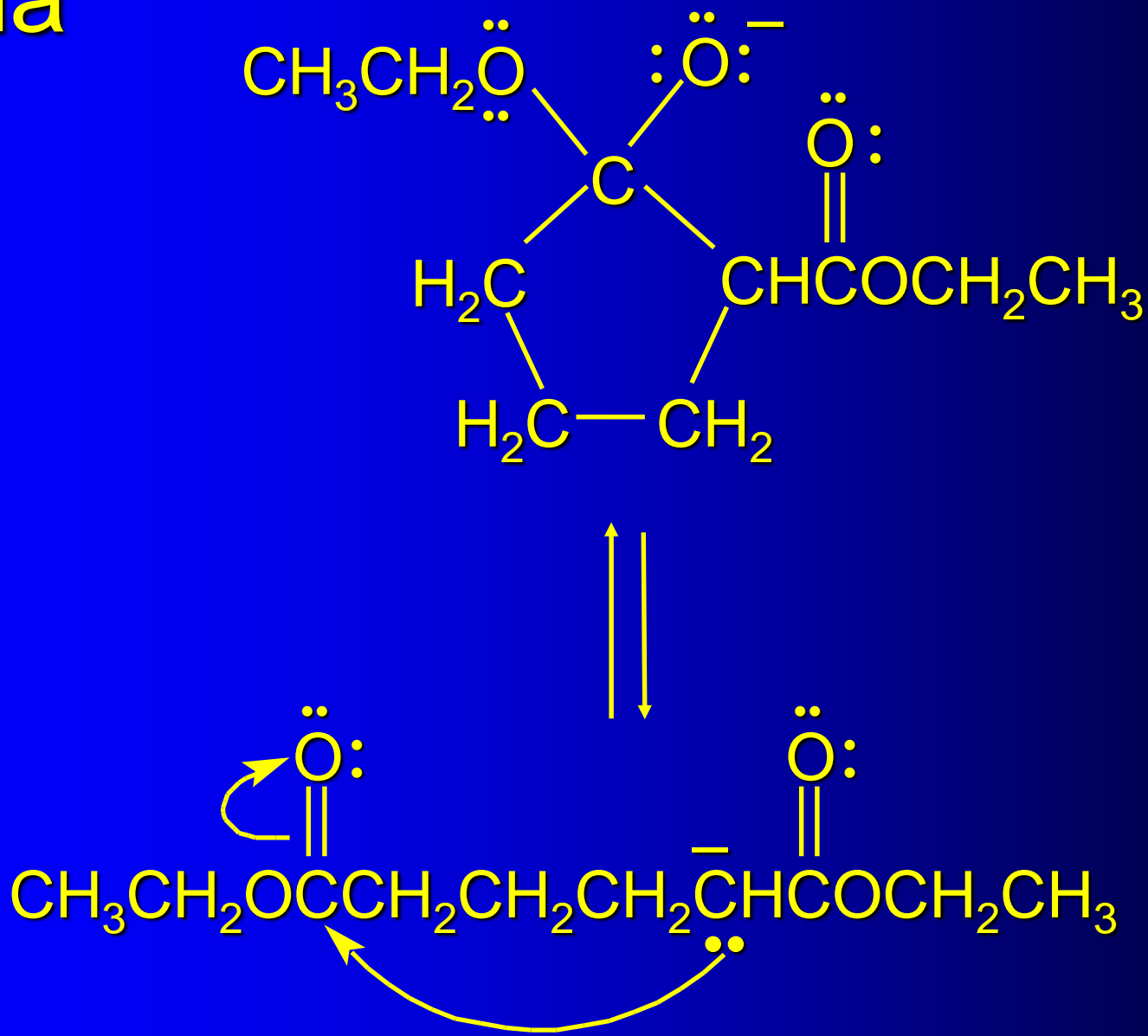
via



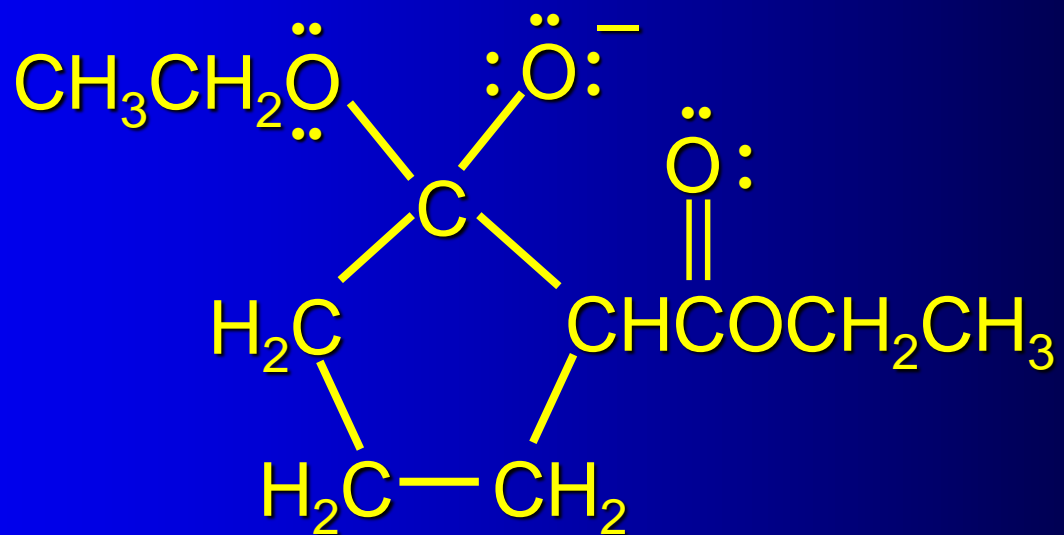
via



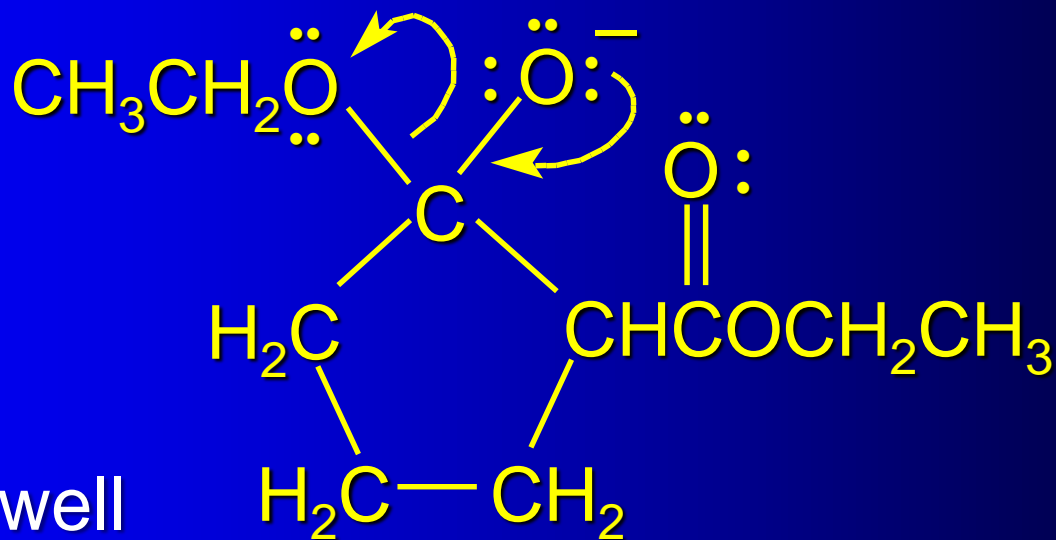
via



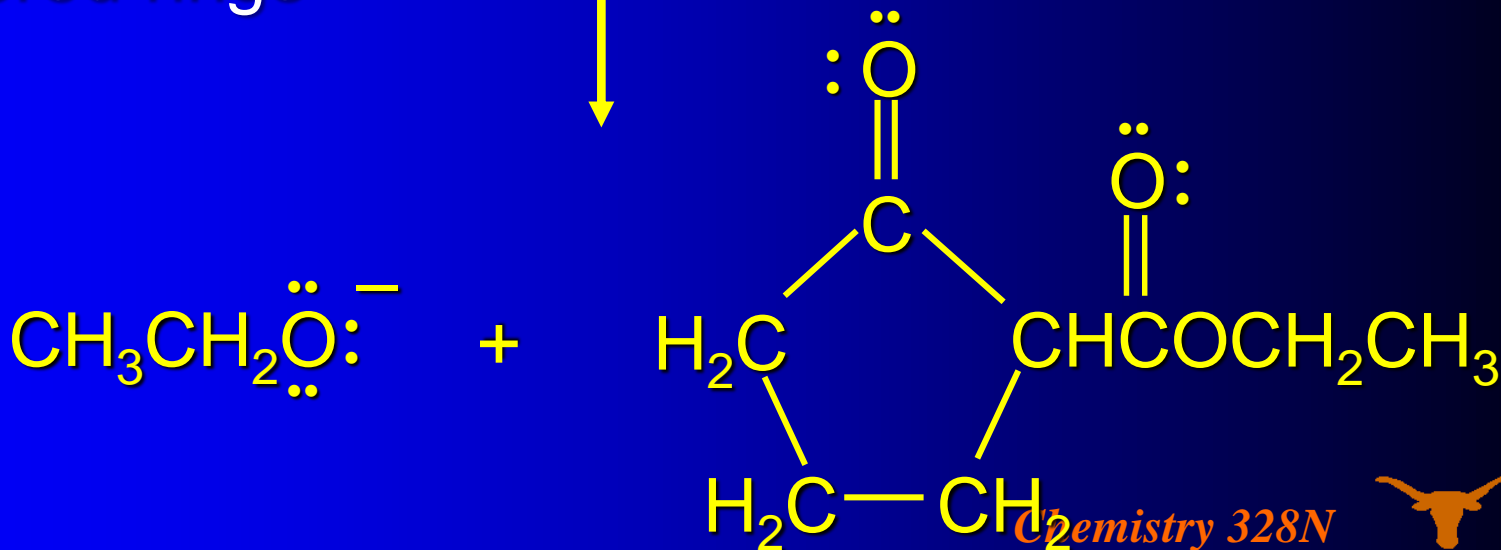
via



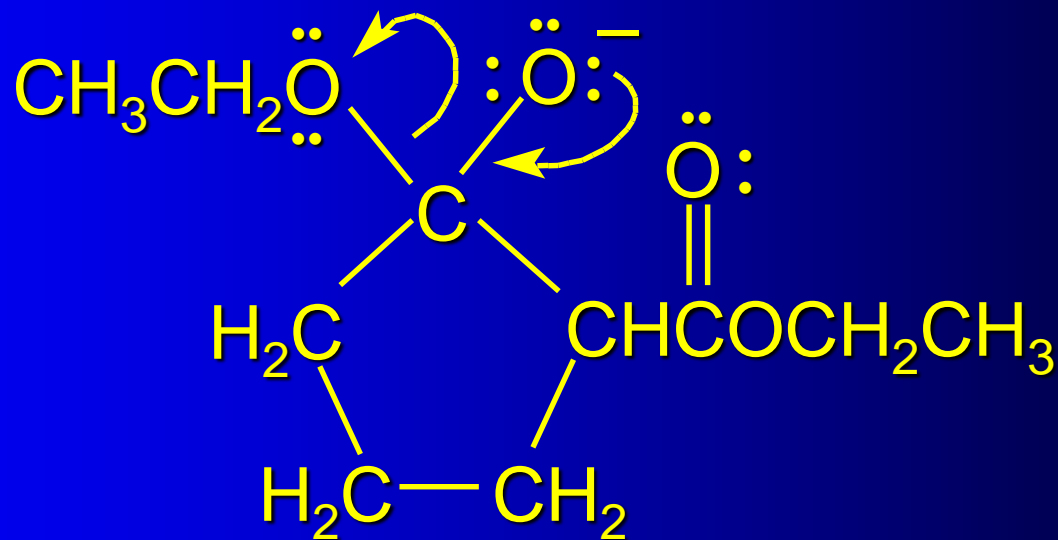
via



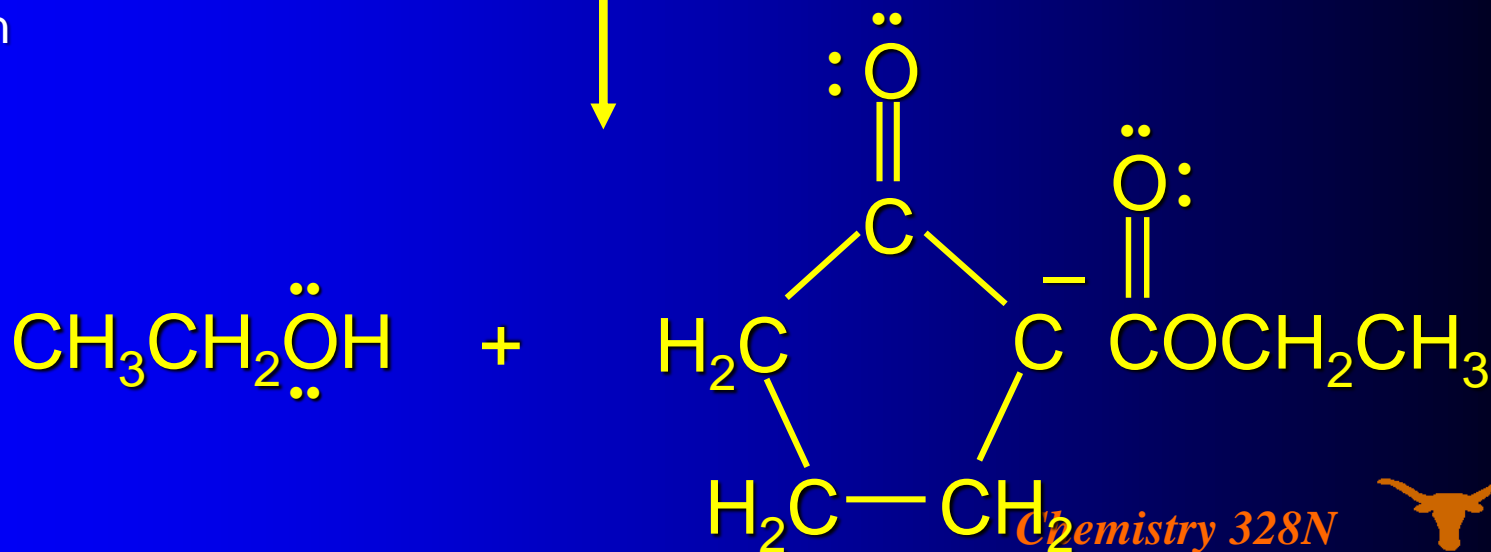
This works well
for 5 and 6
membered rings



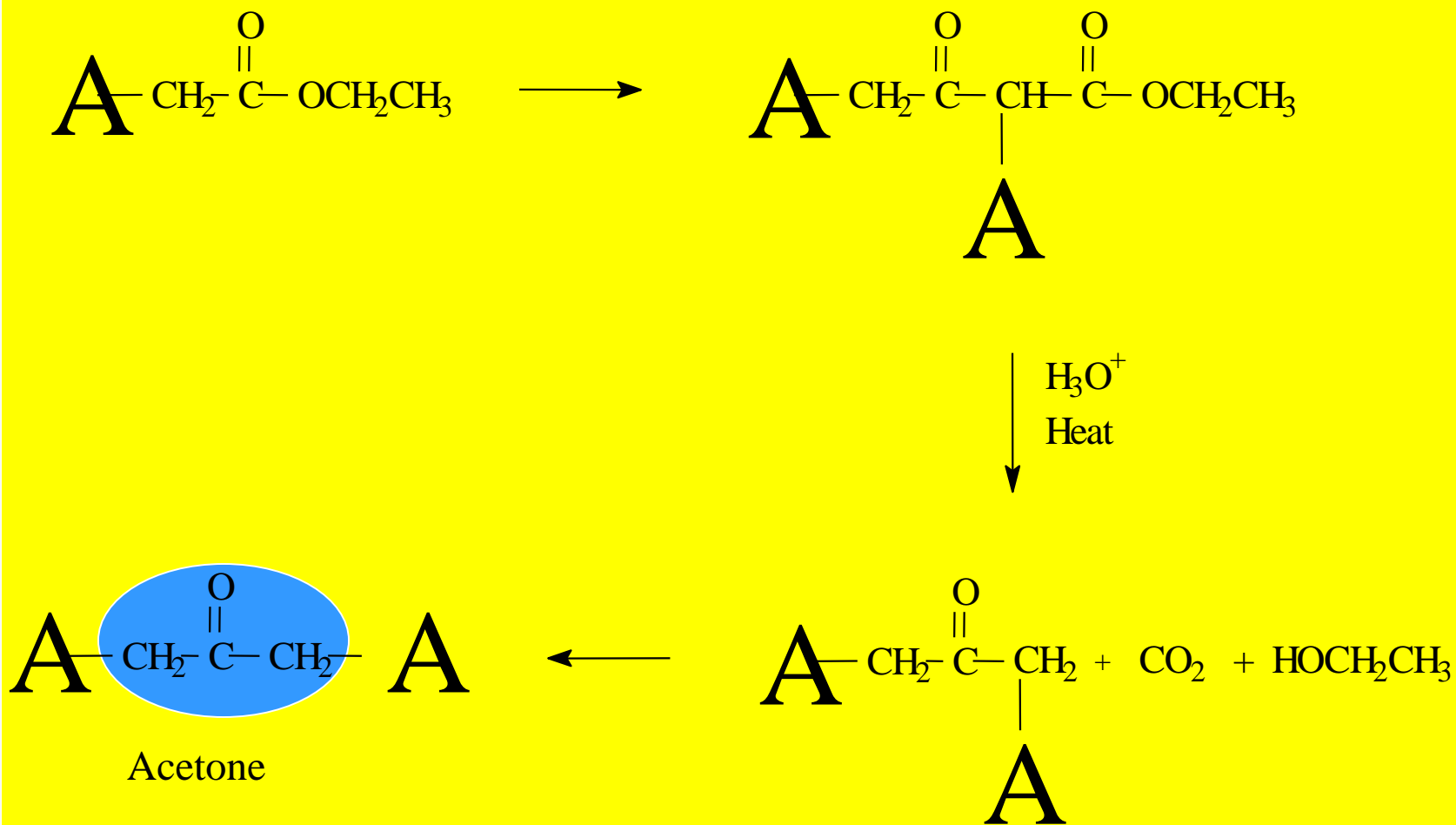
via



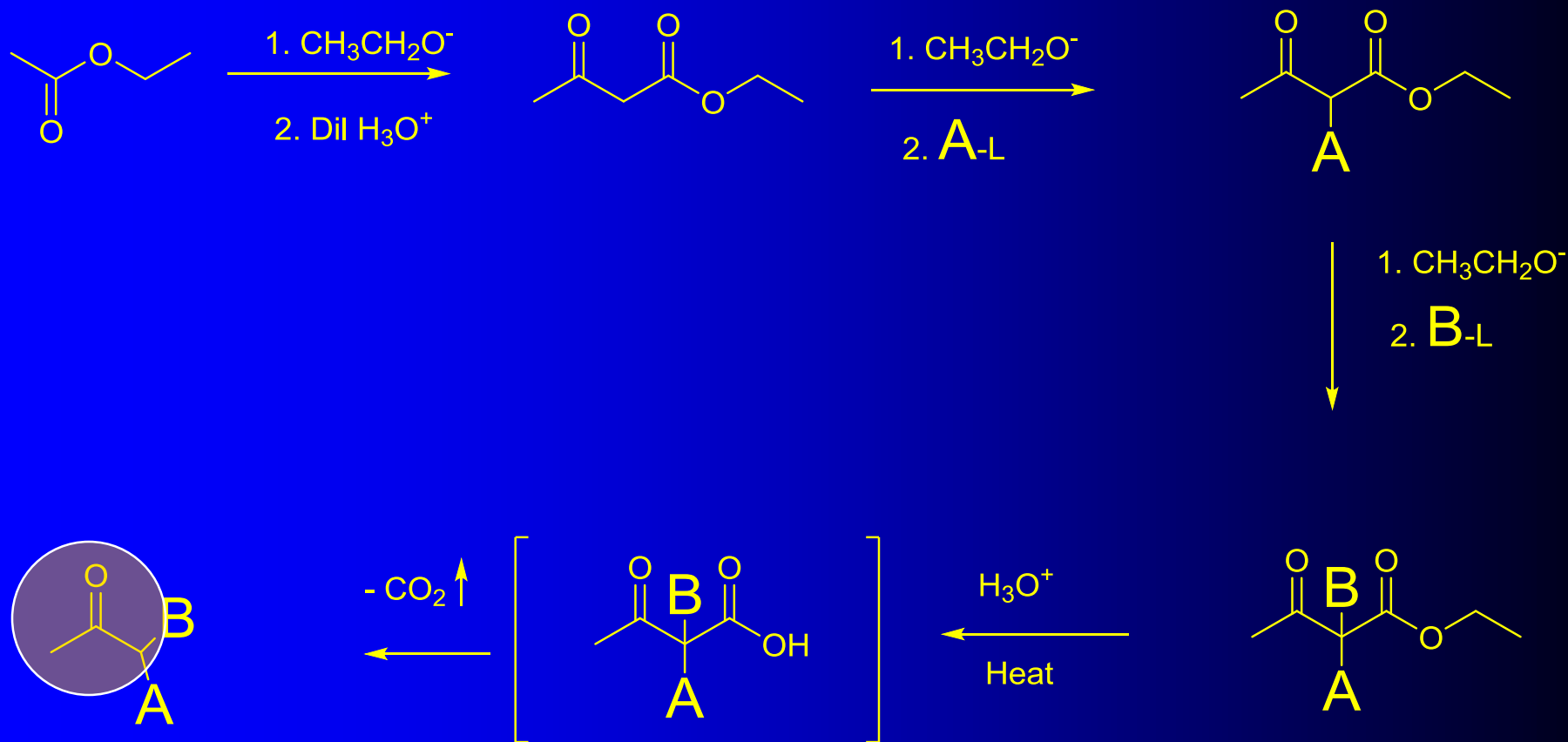
The product is the stable
carbanion prior to
acidification



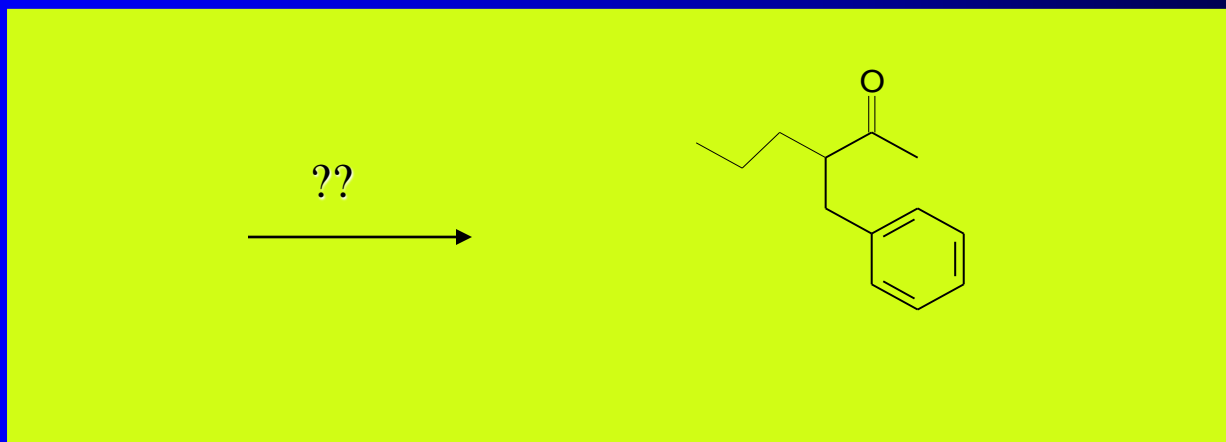
A versatile synthesis of β -ketoesters and symmetrically substituted acetones



Alkylation of Acetoacetic Ester gives unsymmetrically substituted acetone



Acetoacetic Ester Synthesis



Ketone Synthesis

Let's work another example together

