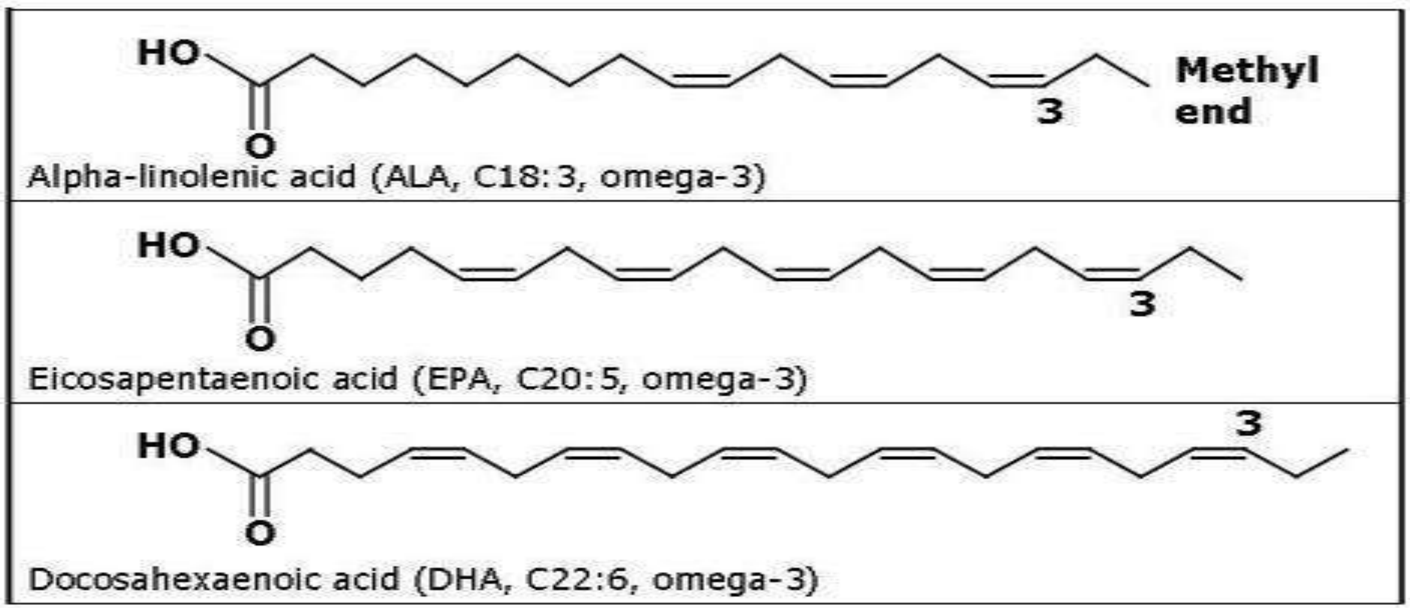
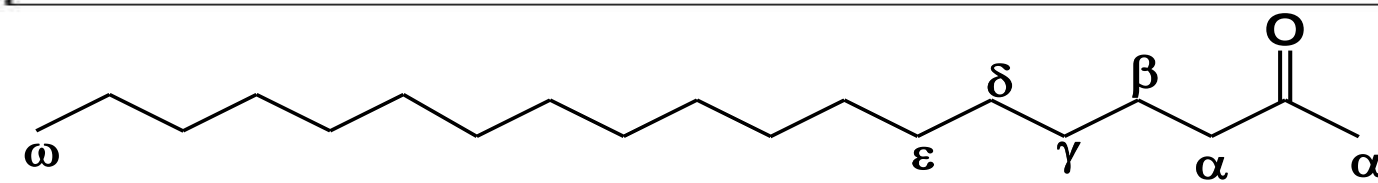
$\alpha-$Carbonyl Condensation Reactions

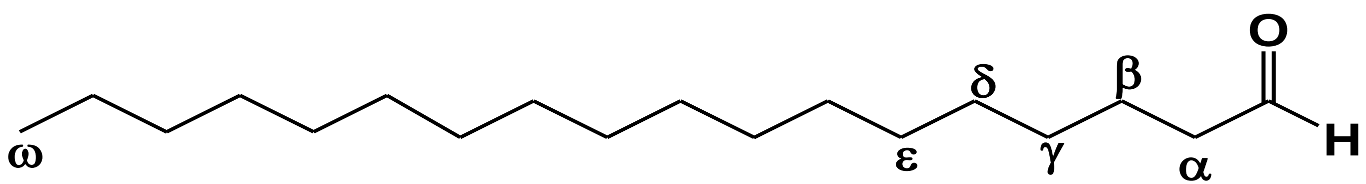
What does α, β, …..ω …..etc mean?

Letter	Upper case	Lower-case	Letter	Upper-case	Lower-case
alpha	Α	α	nu	Ν	ν
beta	Β	β	xi	Ξ	ξ
gamma	Γ	γ	omicron	Ο	ο
delta	Δ	δ	pi	Π	π
epsilon	Ε	ε	rho	Ρ	ρ
zeta	Ζ	ζ	sigma	Σ	σ
eta	Η	η	tau	Τ	τ
theta	Θ	θ	upsilon	Υ	υ
iota	Ι	ι	phi	Φ	φ
kappa	Κ	κ	chi	Χ	χ
lambda	Λ	λ	psi	Ψ	ψ
mu	Μ	μ	omega	Ω	ω

We will focus on α Hydrogen that shows a significant acidity.

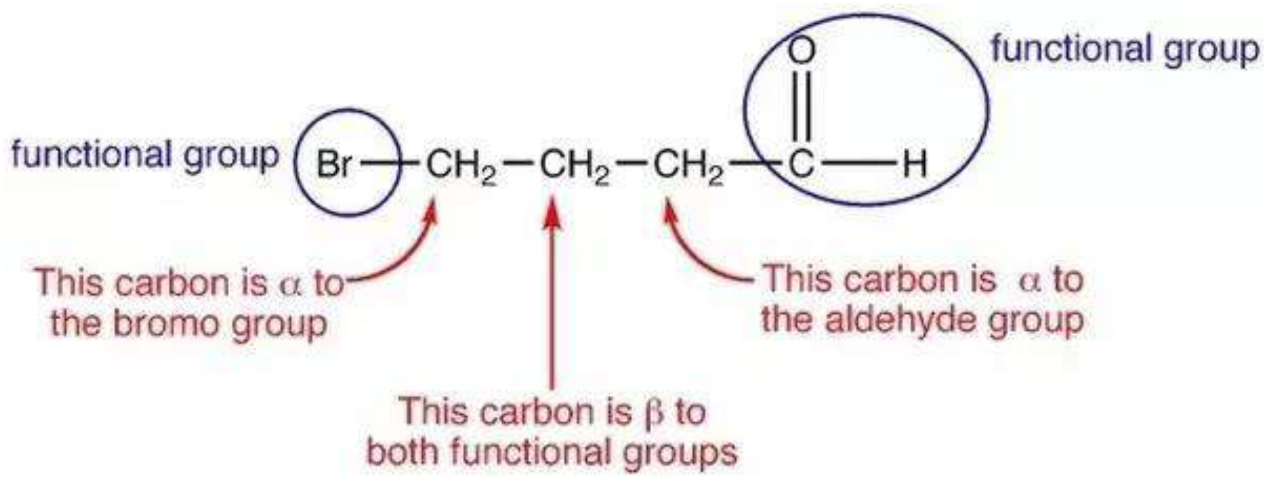


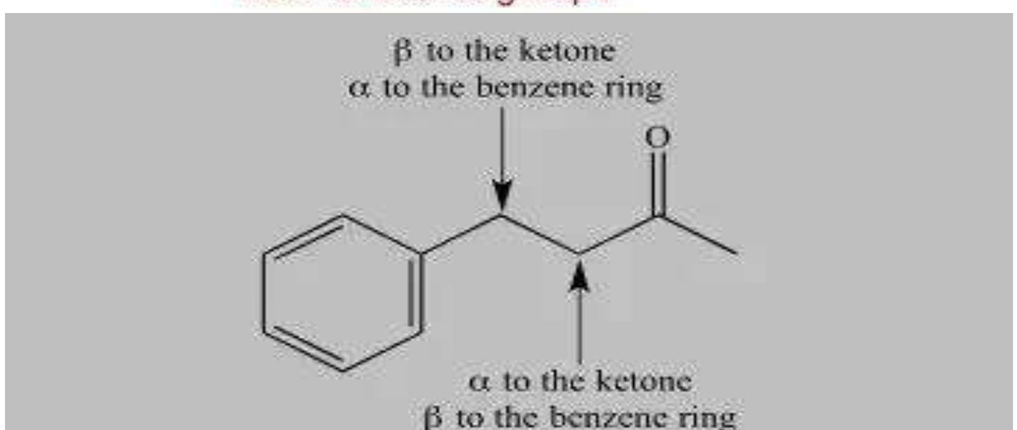




What is α-hydrogen?

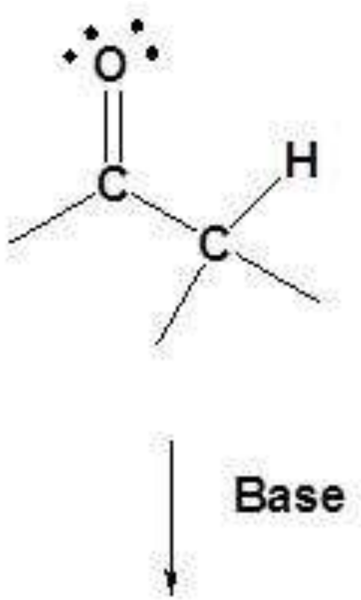
α-hydrogens are those hydrogen atoms which are attached to the alpha carbon and alpha carbon is that carbon which is attached to the functional group.



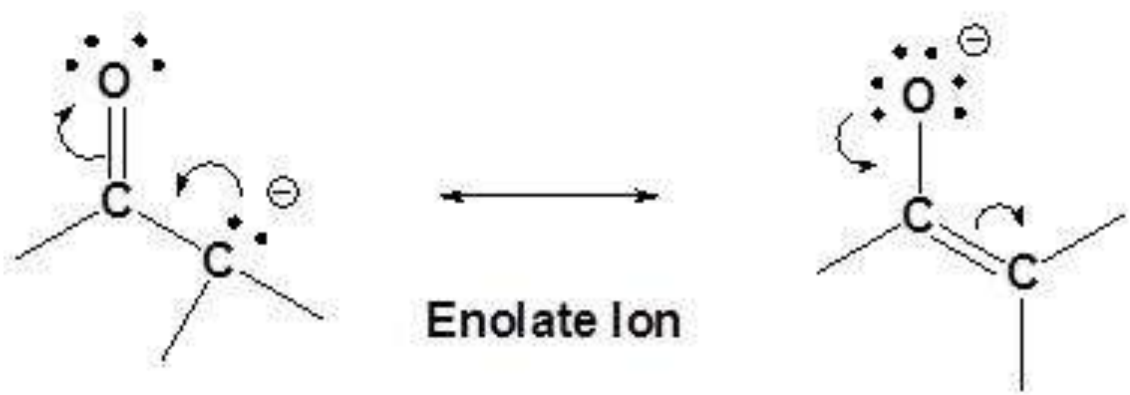


An alpha carbon can also be a beta carbon, depending upon the reference point.

Why α hydrogen has a significant acidity?

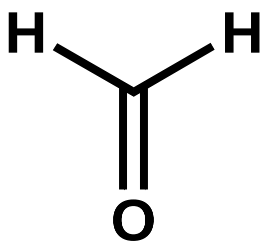


Why α hydrogen has a significant acidity?



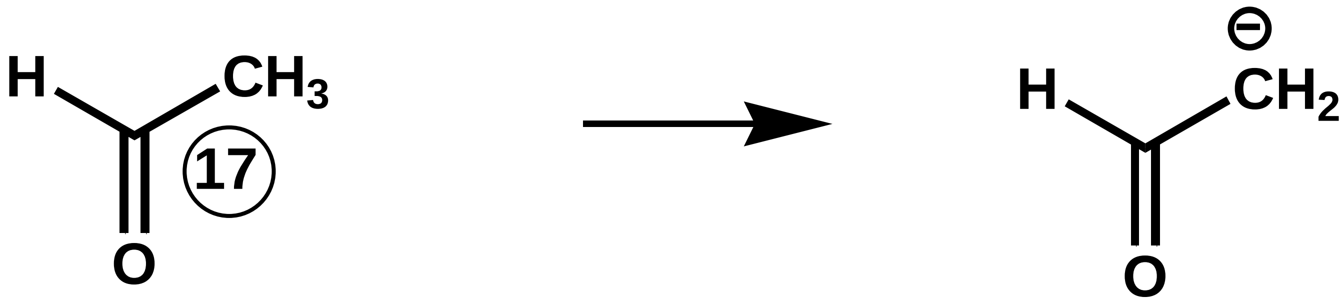
Both I and M effect cause this sort of acidity!!!

pKa’s values for some mono carbonyl compounds

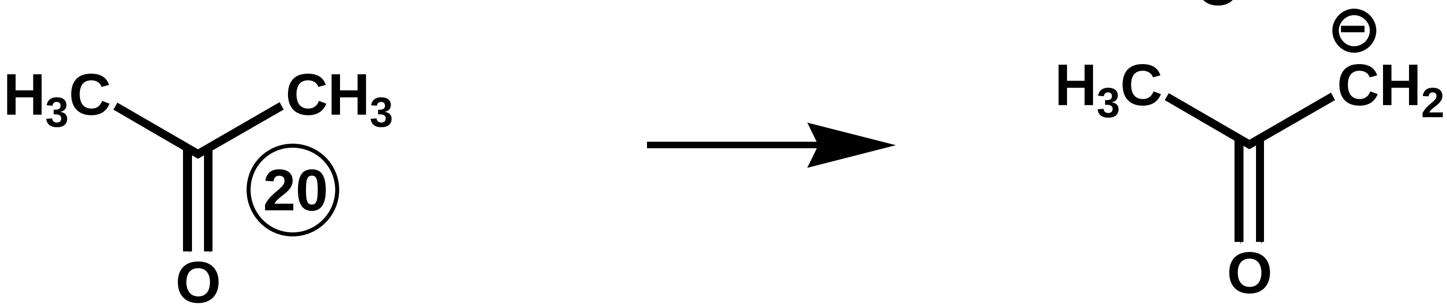


Has no alpha hydrogen

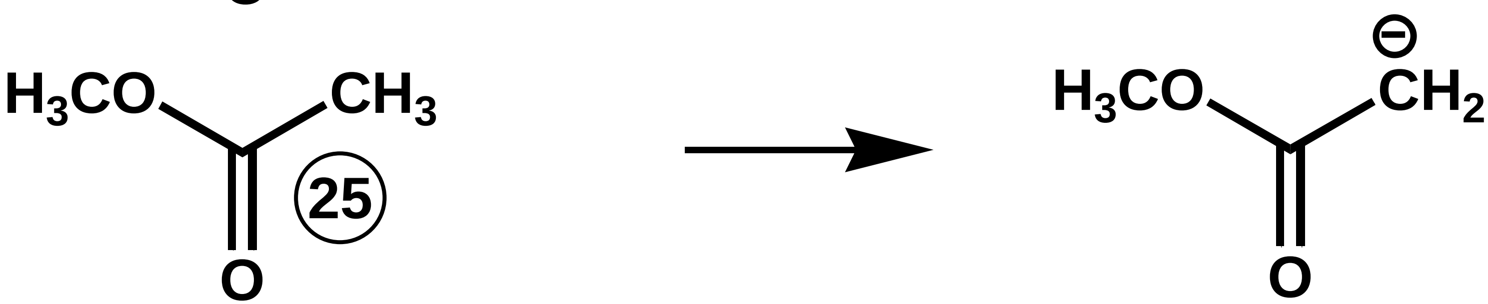
pKa



pKa

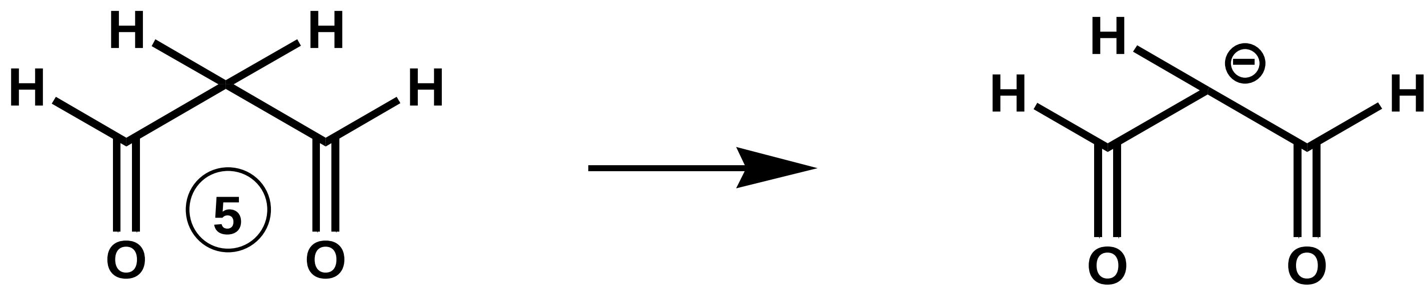


pKa

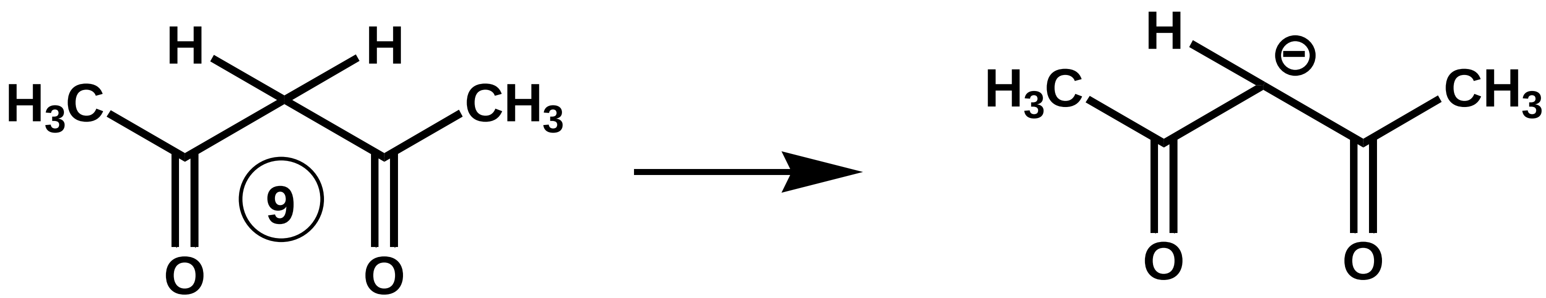


pKa's values for some di- carbonyl compounds

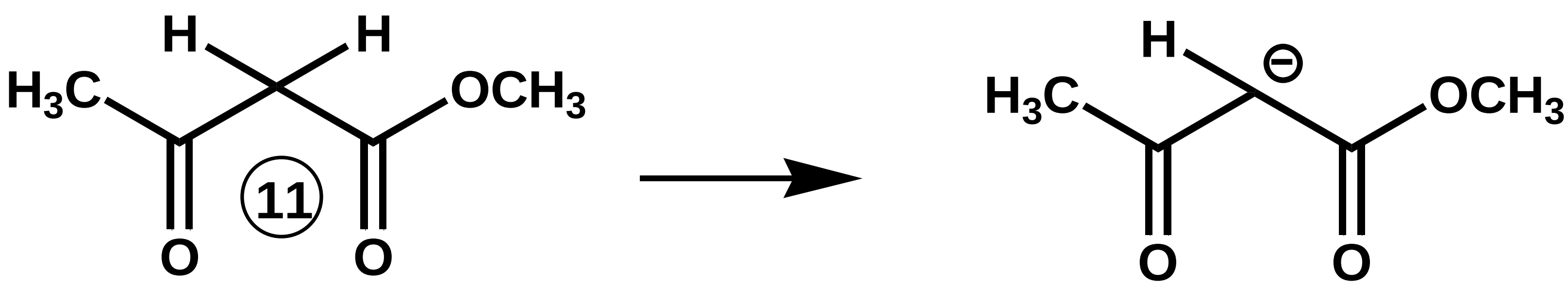
pKa 5



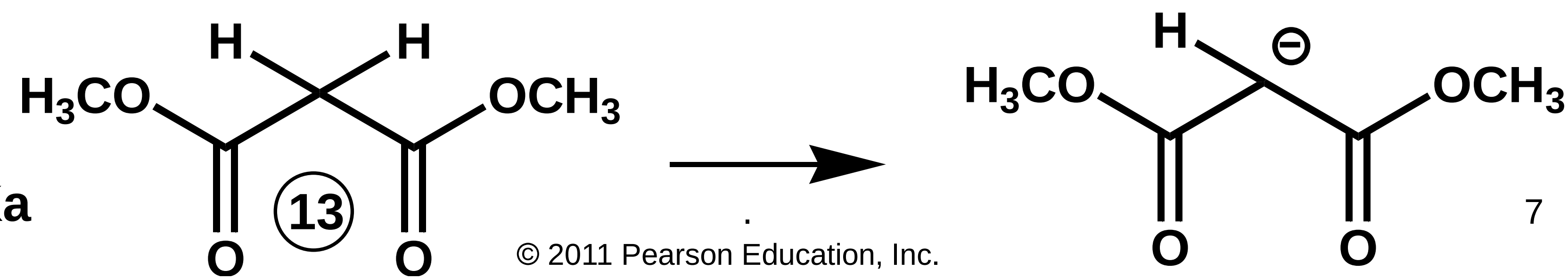
pKa 9



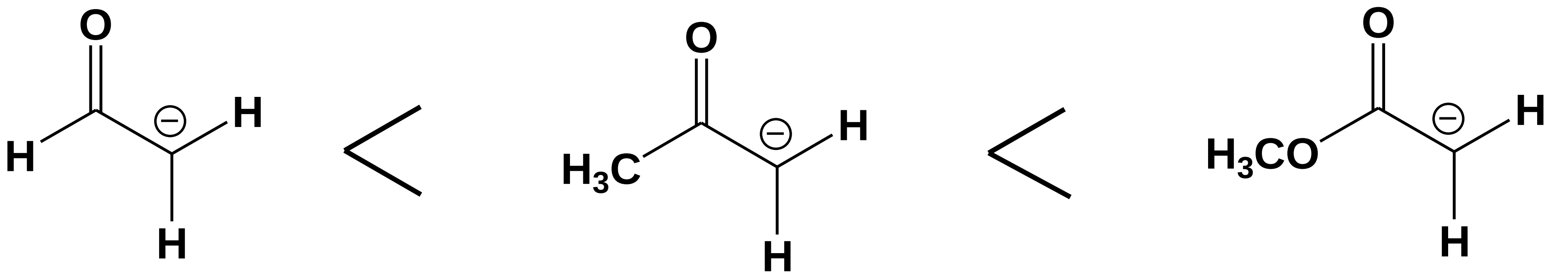
pKa 11



pKa 13

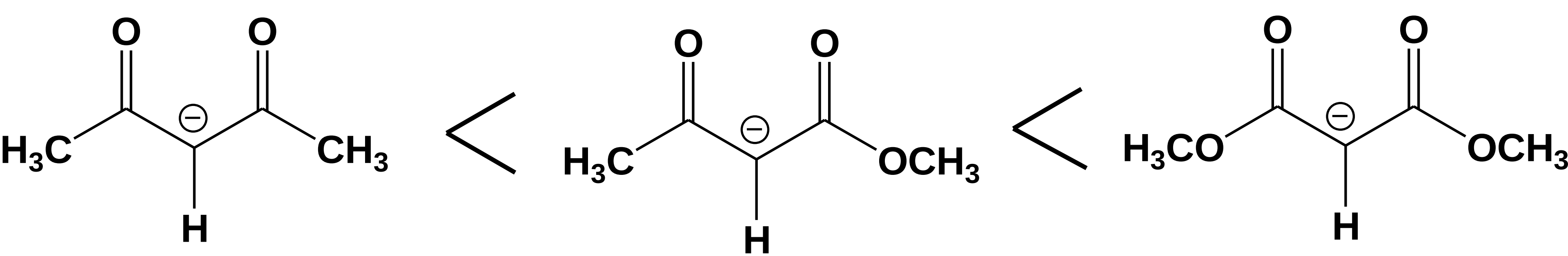


The stronger the acid; the weaker the conjugated base {Each strong acid is accompanied with weak conjugated base}



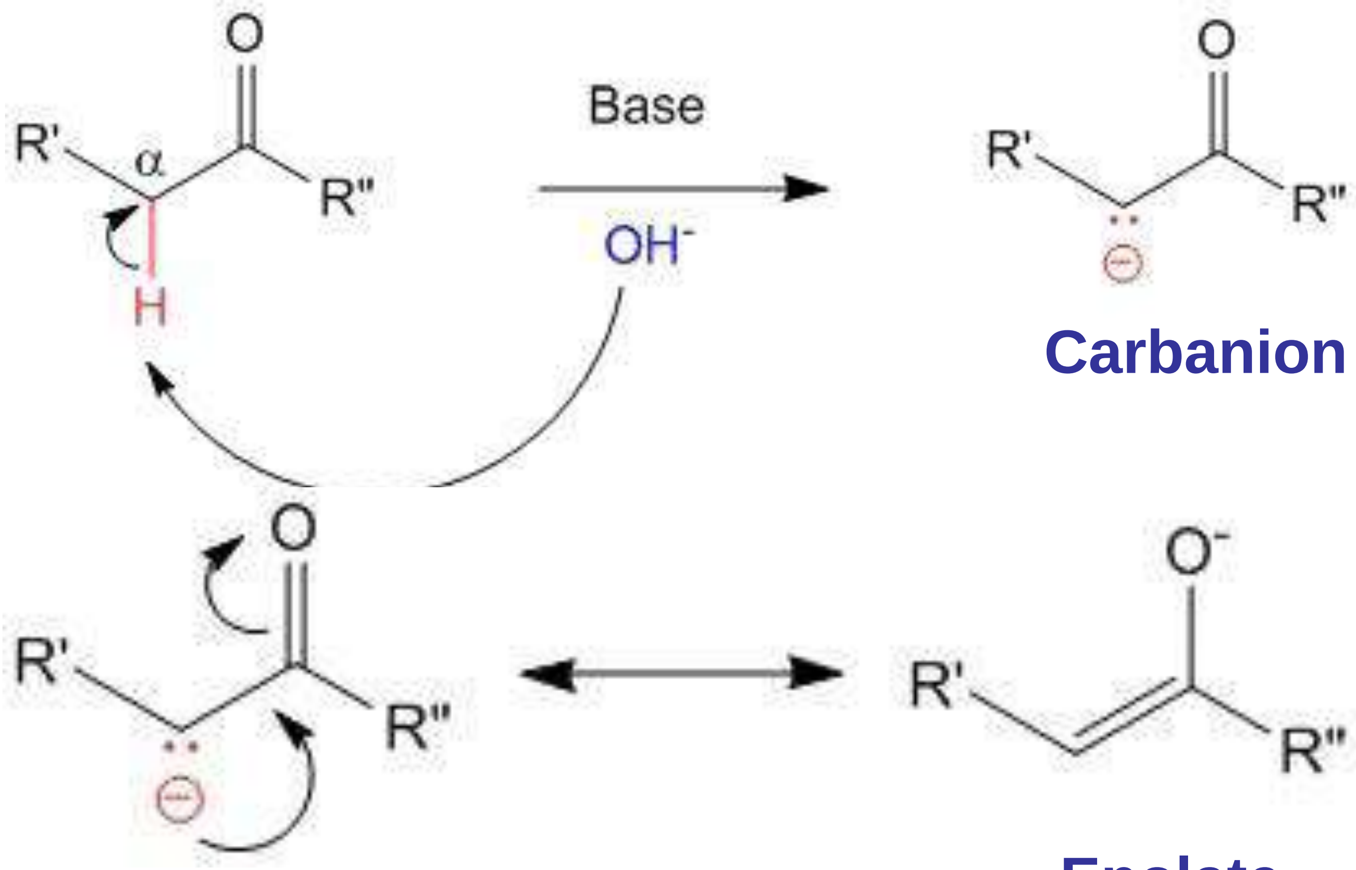
weakest conjugated base

strongest conjugated base

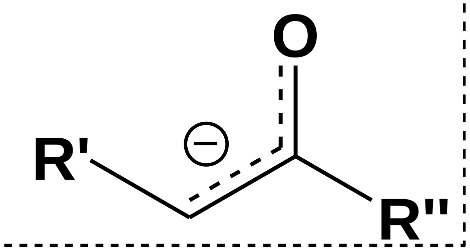


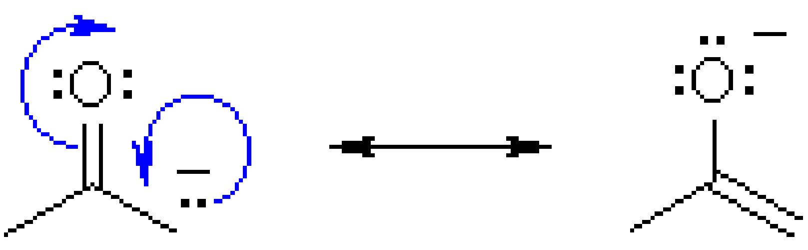
weakest conjugated base

strongest conjugated base

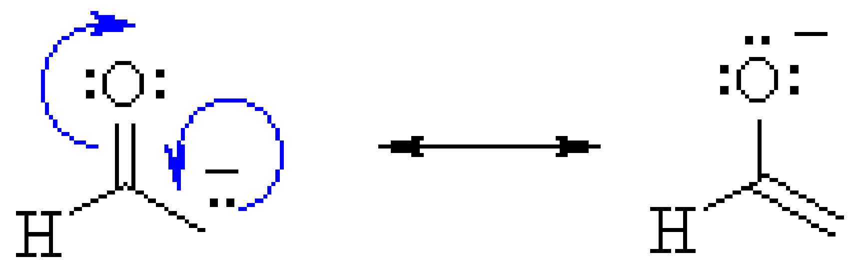


Carbanion resonates to the corresponding enolate and vice versa





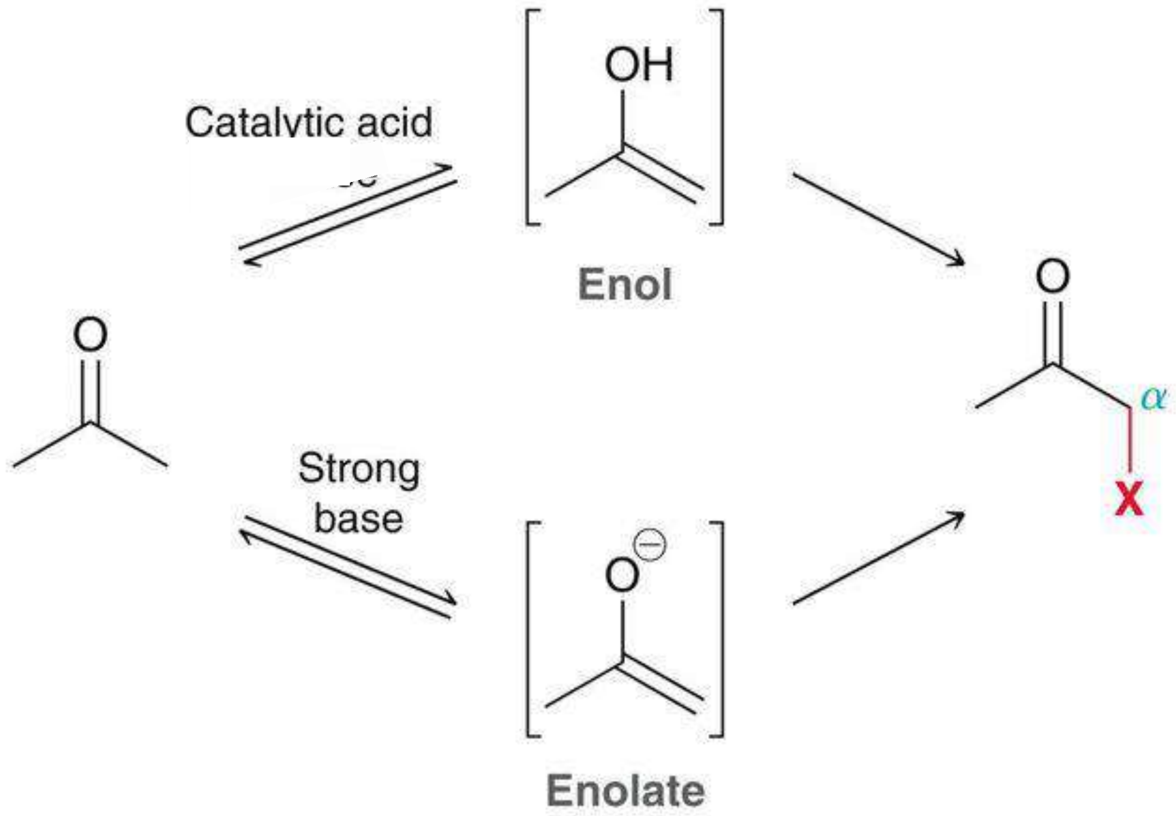
ketone system



aldehyde system

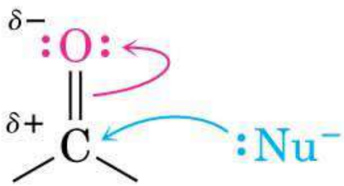
Introduction Alpha Carbon Chemistry: Enols and Enolates

- The reactions we will explore proceed though either an enol or an enolate intermediate

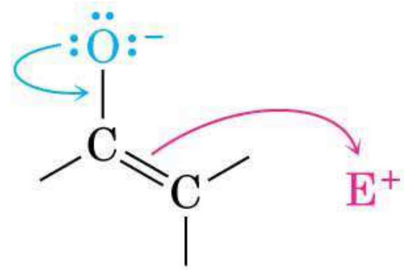


Condensation Reactions

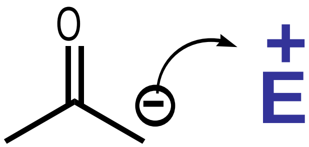
- Carbonyl compounds are *both* the electrophile and nucleophile in carbonyl condensation reactions



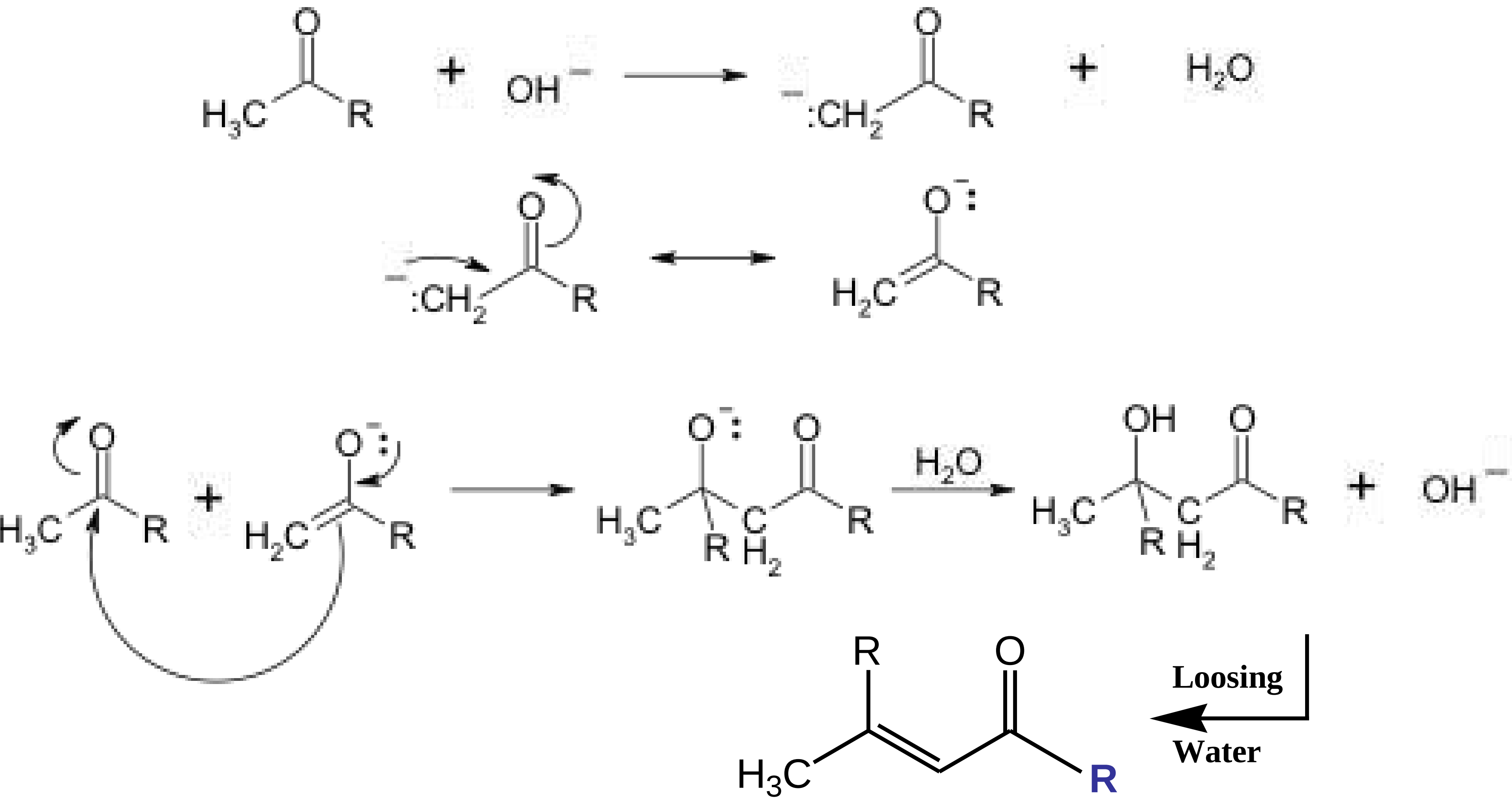
Electrophilic carbonyl group is attacked by nucleophiles



Nucleophilic enolate ion attacks electrophiles

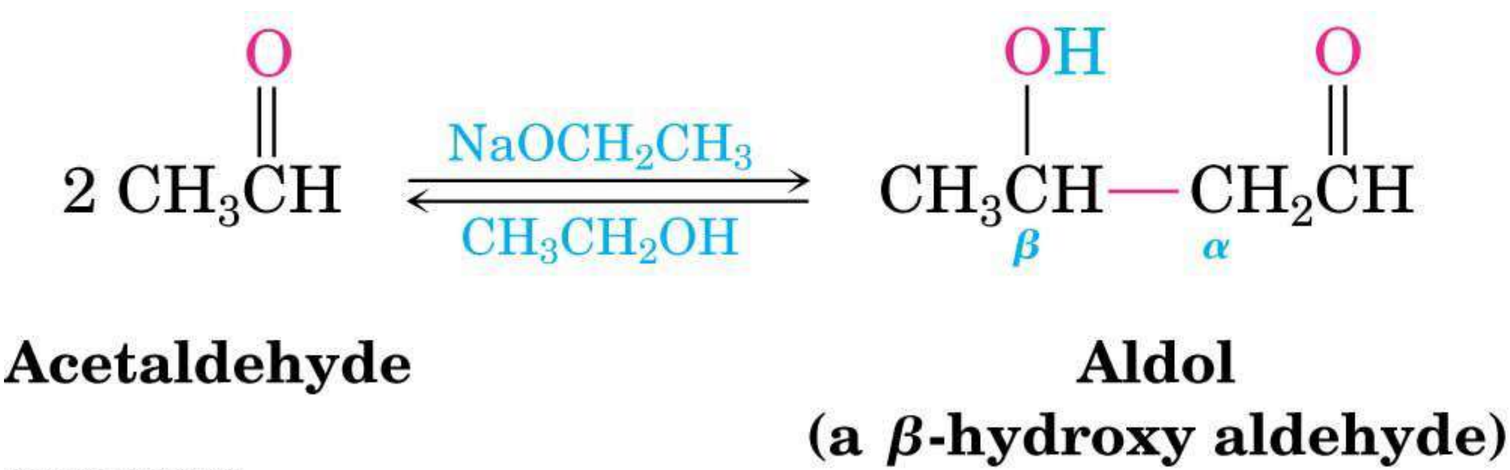


General reaction of aldol condensation



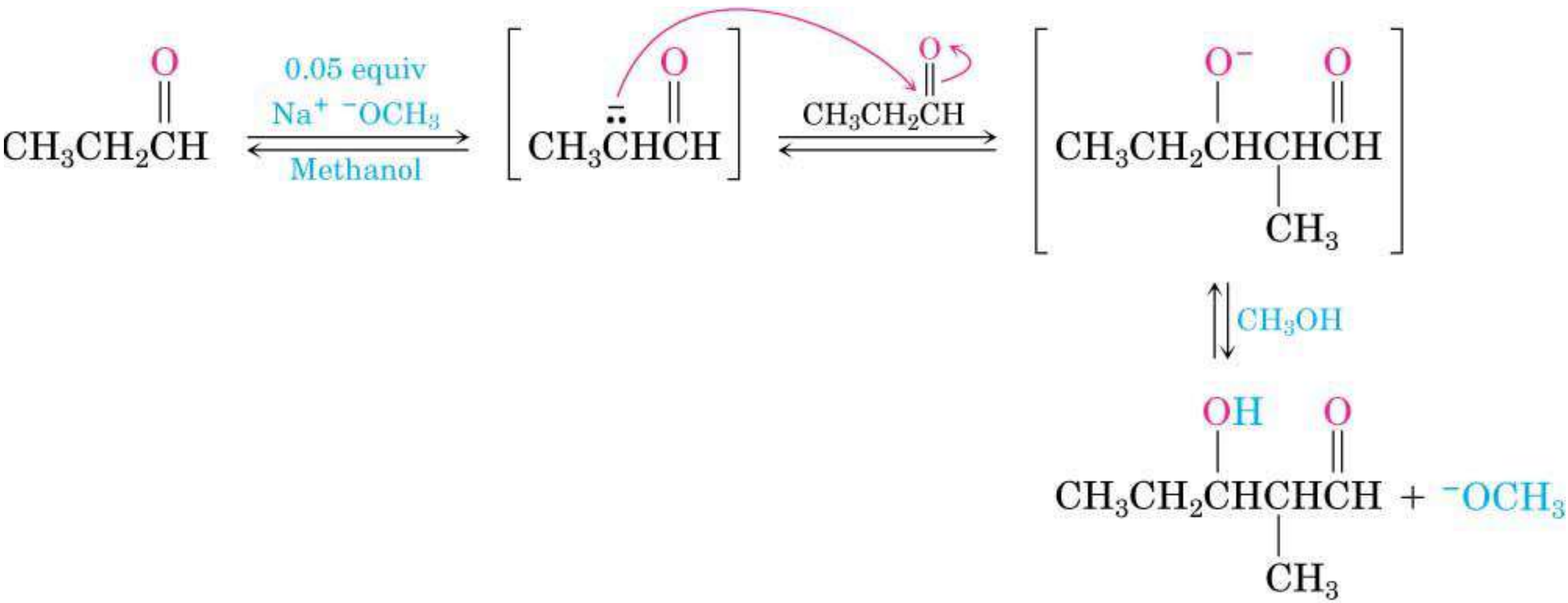
Condensations of Aldehydes and Ketones: The Aldol Reaction

- Acetaldehyde reacts in basic solution (NaOEt, NaOH) with another molecule of acetaldhyde
- The β-hydroxy aldehyde product is *aldol* (*ald*ehyde + alcoh*ol*)
- This is a general reaction of aldehydes and ketones
- The aldol product loses water molecule affording α,β-unsaturated aldehyde or ketone



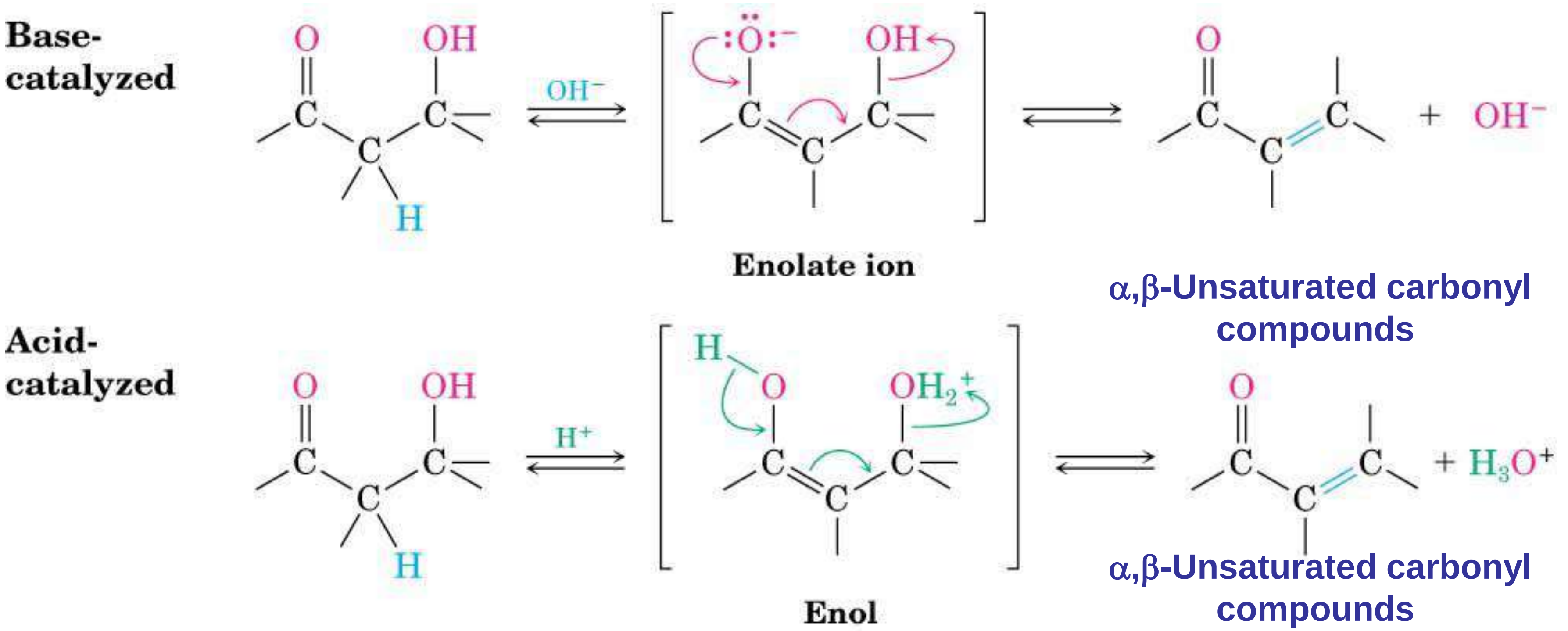
Conditions for Condensations

- A small amount of base is used to generate a small amount of enolate in the presence of unreacted carbonyl compound
- After the condensation, the basic catalyst is regenerated



Dehydration of β-Hydoxy Ketones and Aldehydes

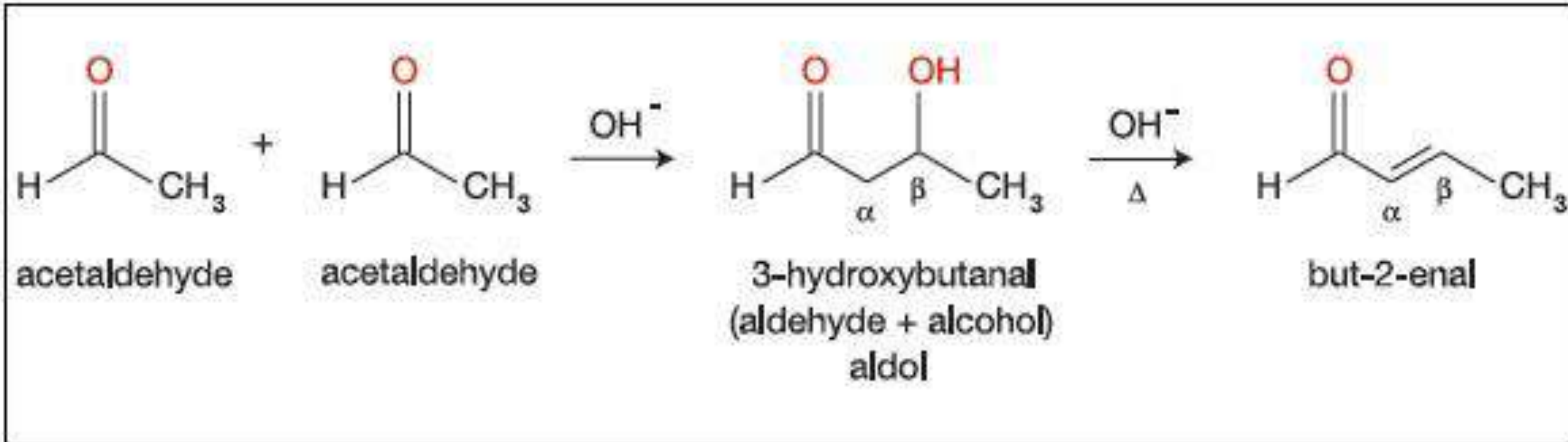
- The α hydrogen is removed by a base, yielding an enolate ion that expels the –OH leaving group
- Under *acidic* conditions the —OH group is protonated and water is expelled

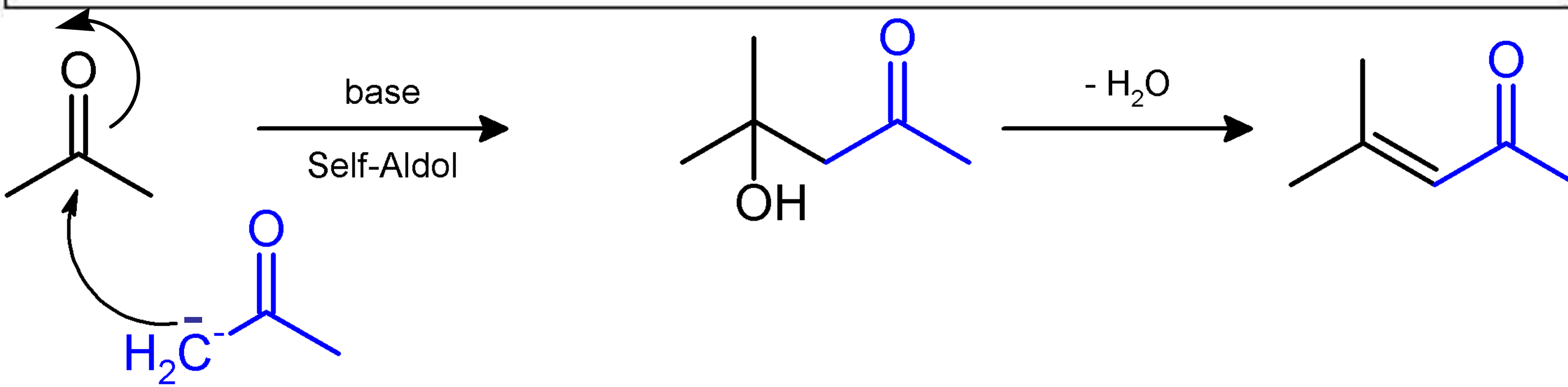


α,β-Unsaturated carbonyl compounds

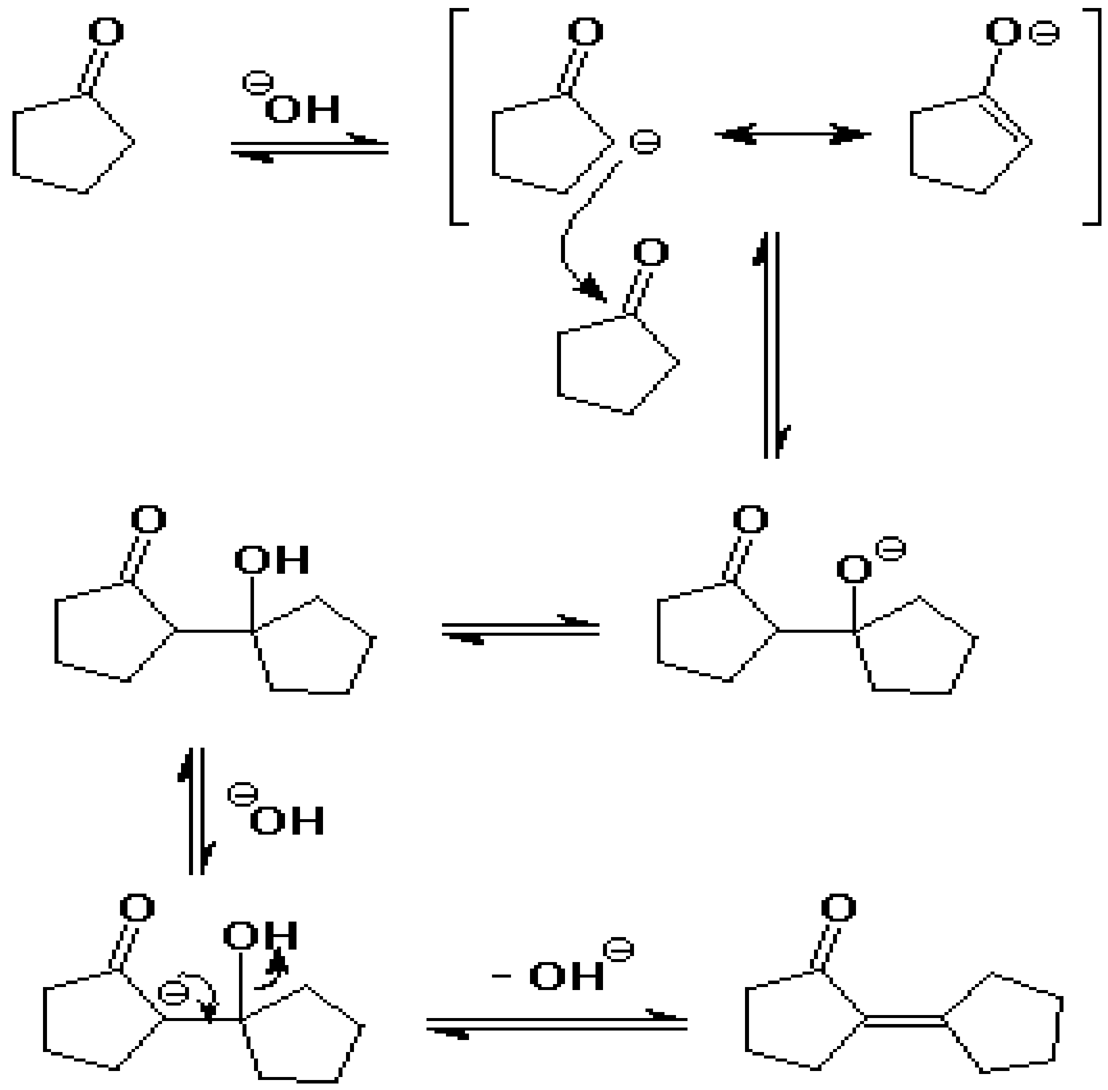
α,β-Unsaturated carbonyl compounds

Self aldol condensation
“ The same aldehyde or the same ketone reacts with itself.



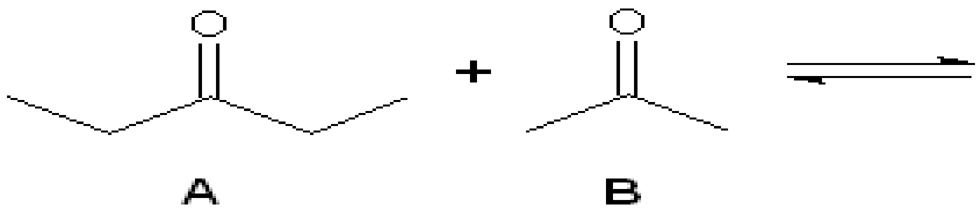


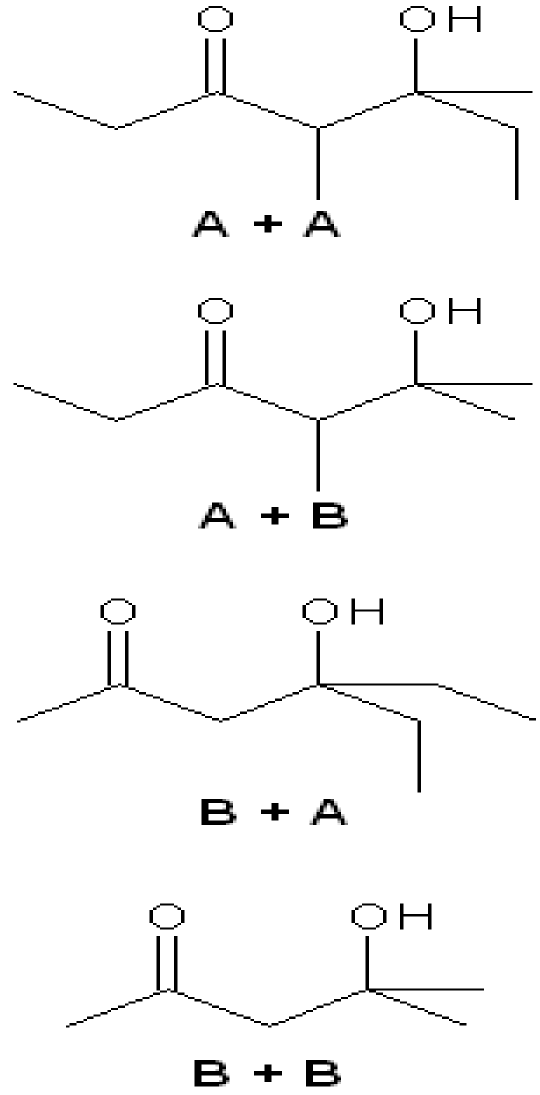
Cyclopentanone self condensation

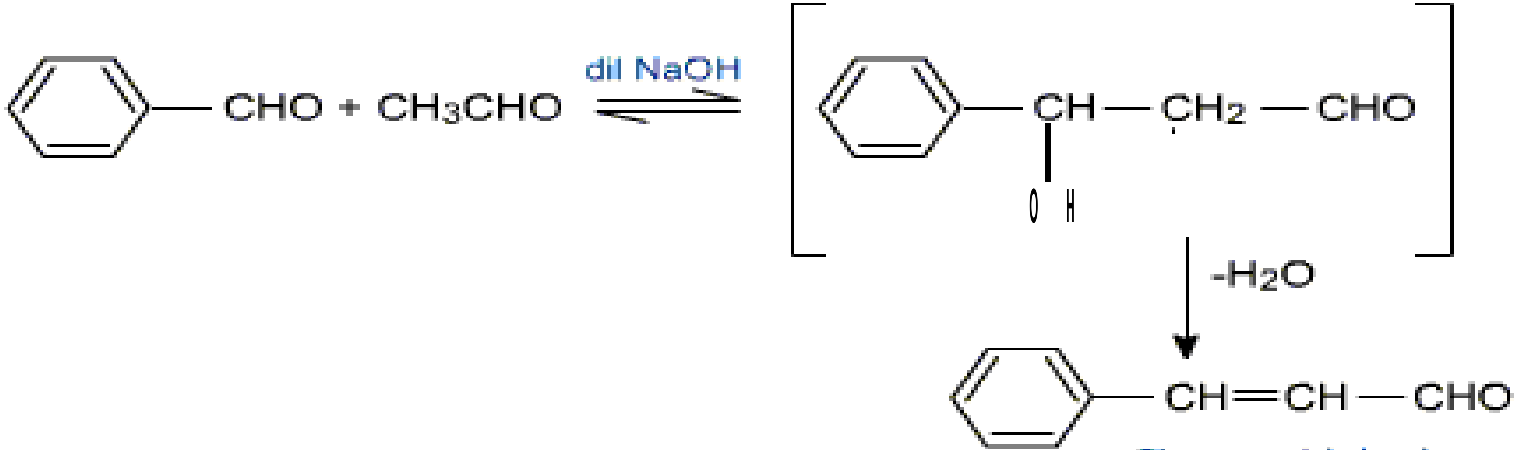


Mixed Aldol Reactions:-

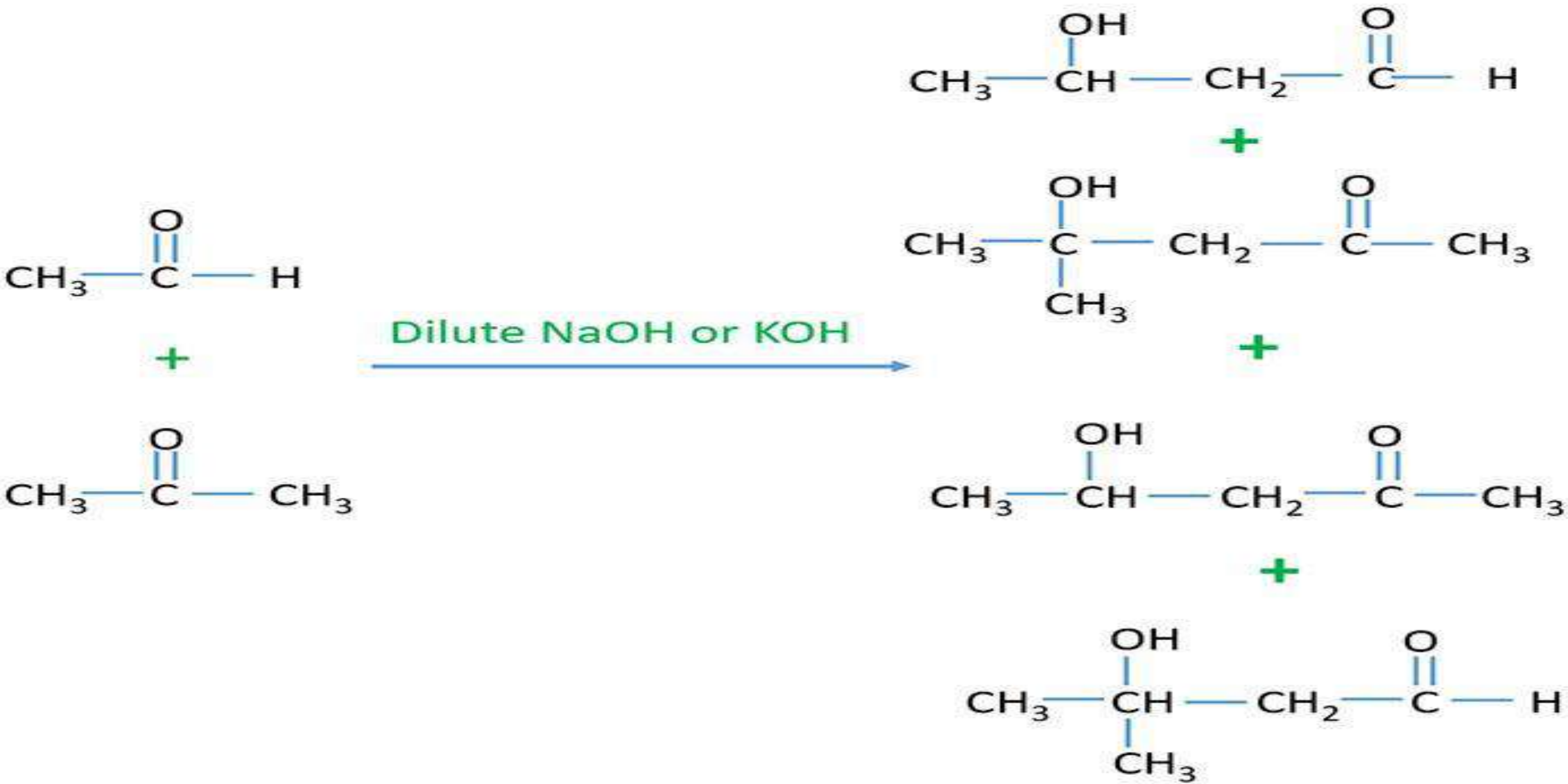
it could be:-
1] aldehyde(a) + aldehyde (b)
2] ketone (a) + ketone (b)
3] aldehyde + ketone

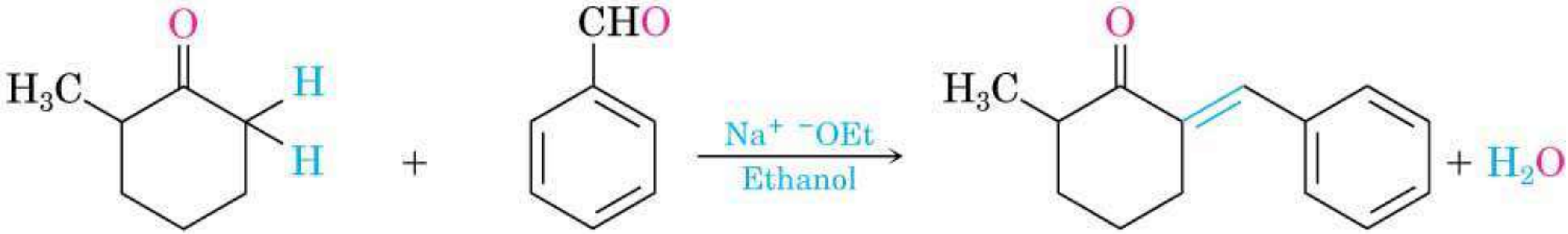




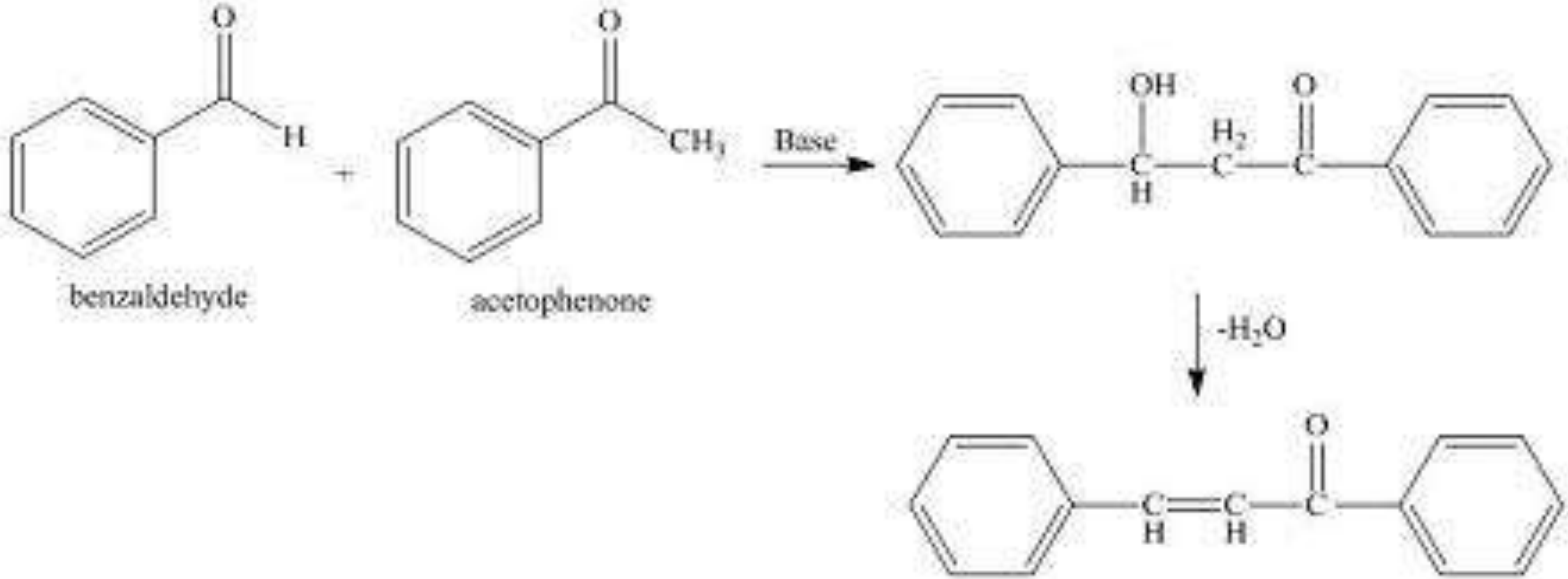


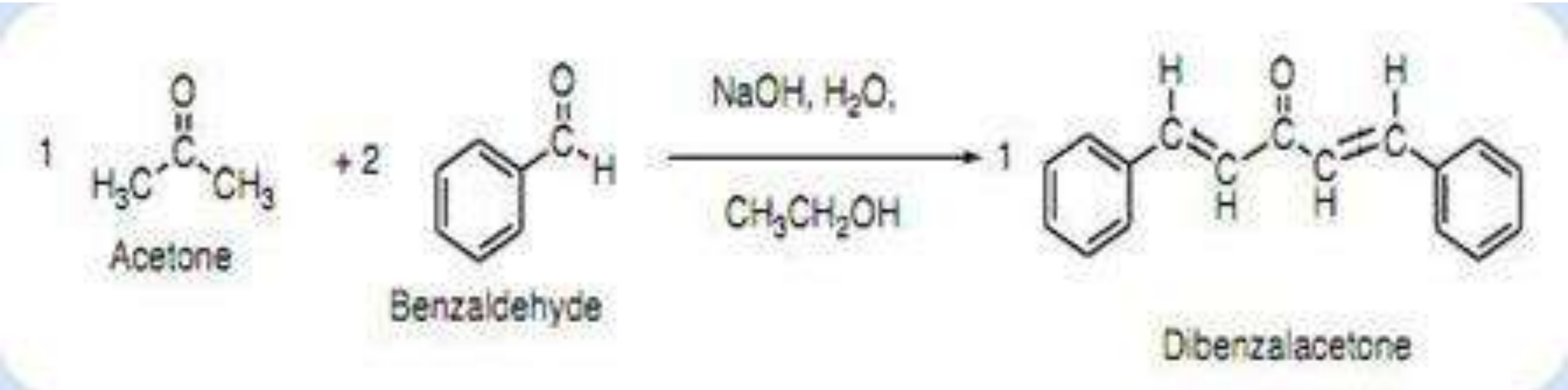
Cinnameldehyde
or
3-phenylprop-2-enal

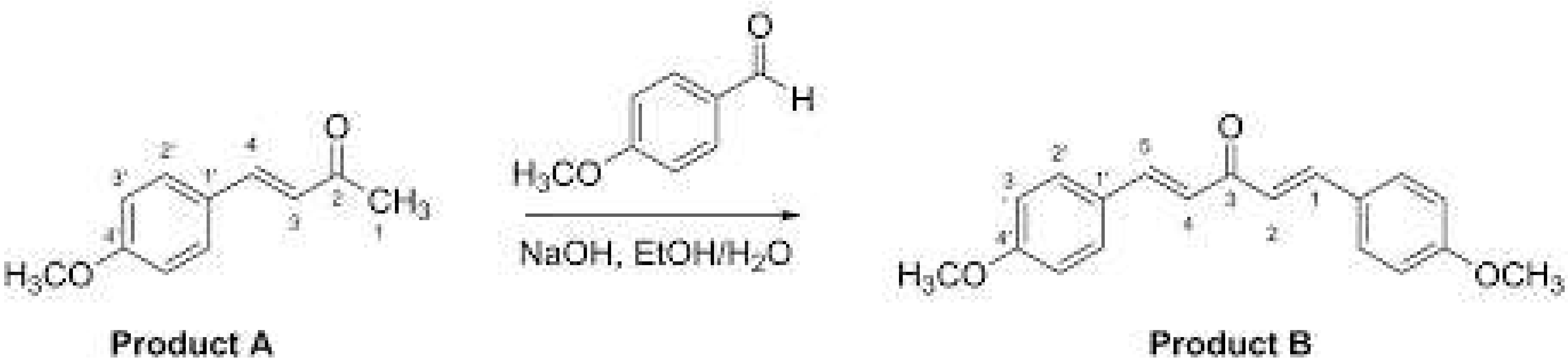




2-Methylcyclohexanone (donor) **Benzaldehyde (acceptor)** **78%**

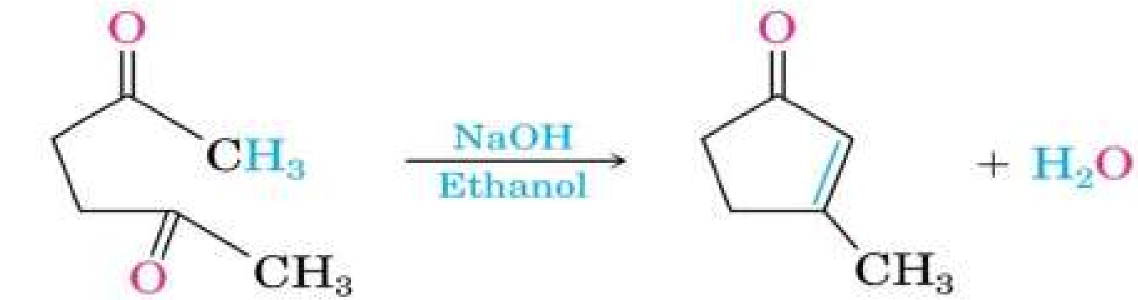


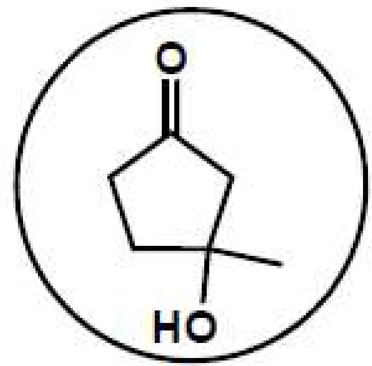

1
Acetone
+ 2
Benzaldehyde
NaOH, H₂O,
CH₃CH₂OH
1
Dibenzalacetone


NaOH, EtOH/H₂O
Product A
Product B

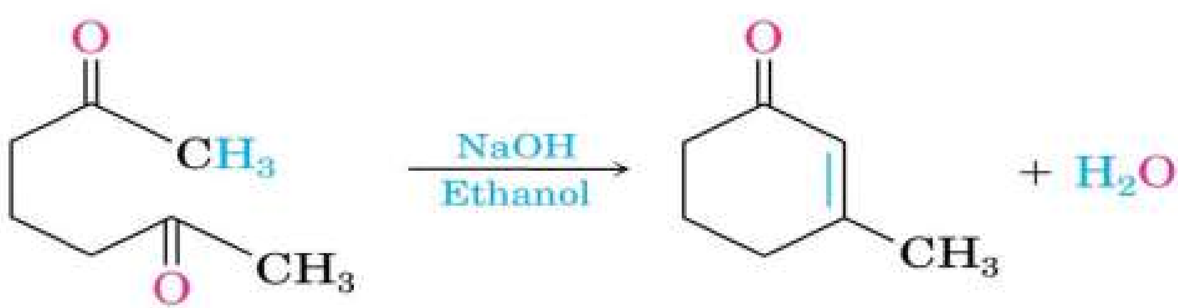
Intramolecular Aldol Reactions

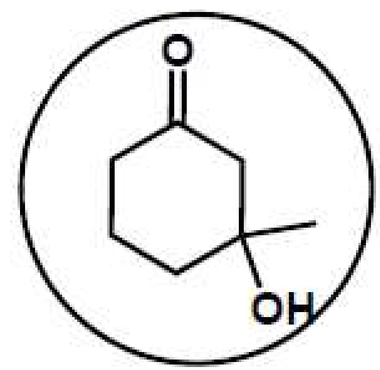
- Treatment of certain *di*carbonyl compounds with base produces cyclic products by intramolecular reaction





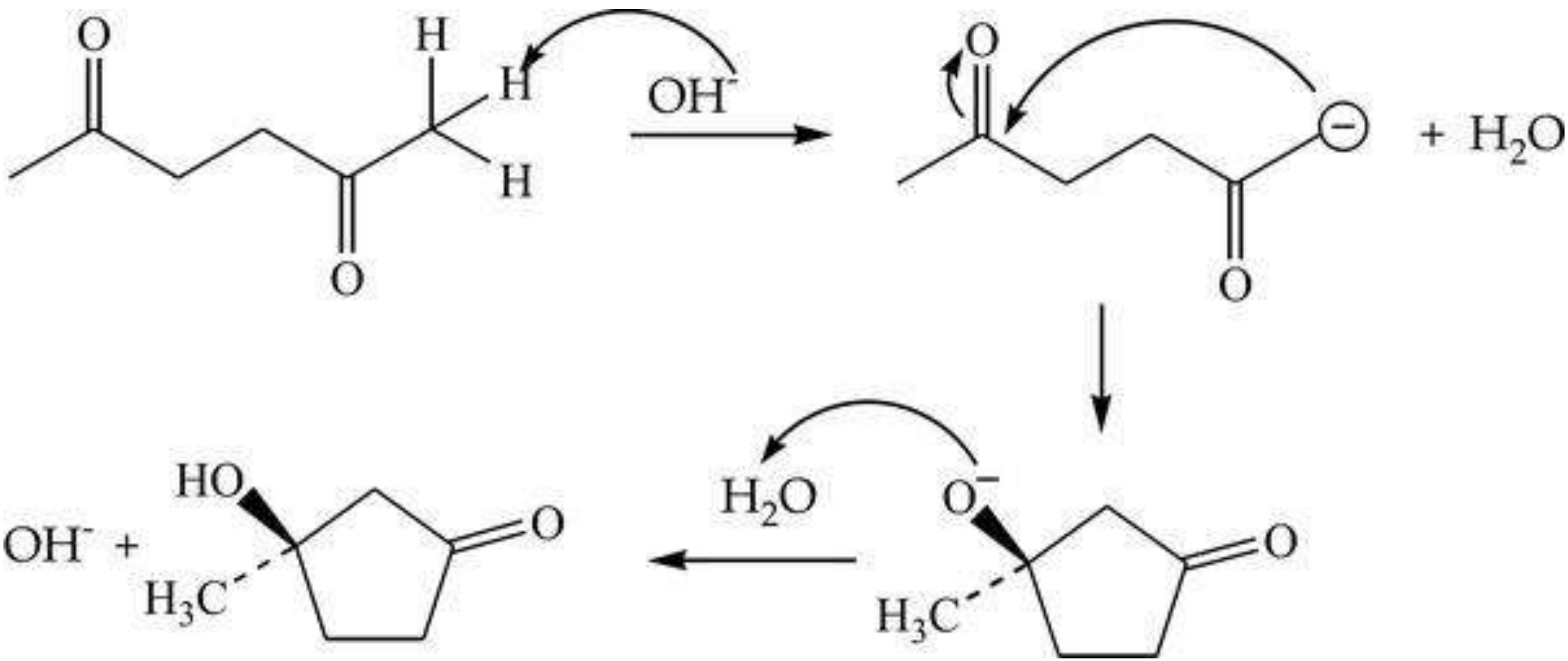
2,5-Hexanedione (a 1,4-diketone) **3-Methyl-2-cyclopentenone**





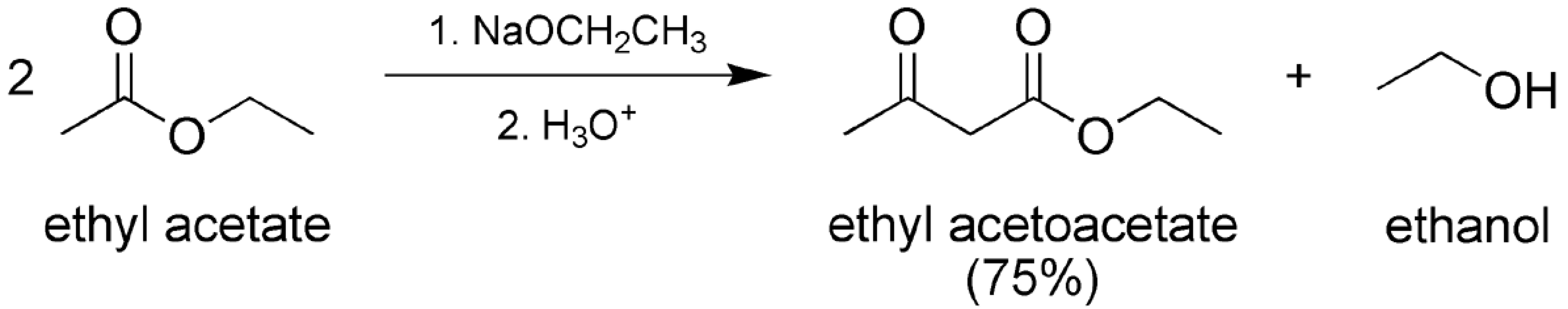
2,6-Heptanedione (a 1,5-diketone) **3-Methyl-2-cyclohexenone**

Mechanism of Intramolecular Aldol Reactions
‘’cyclization is expected’’



The Claisen Condensation Reaction
”Self ester condensation”

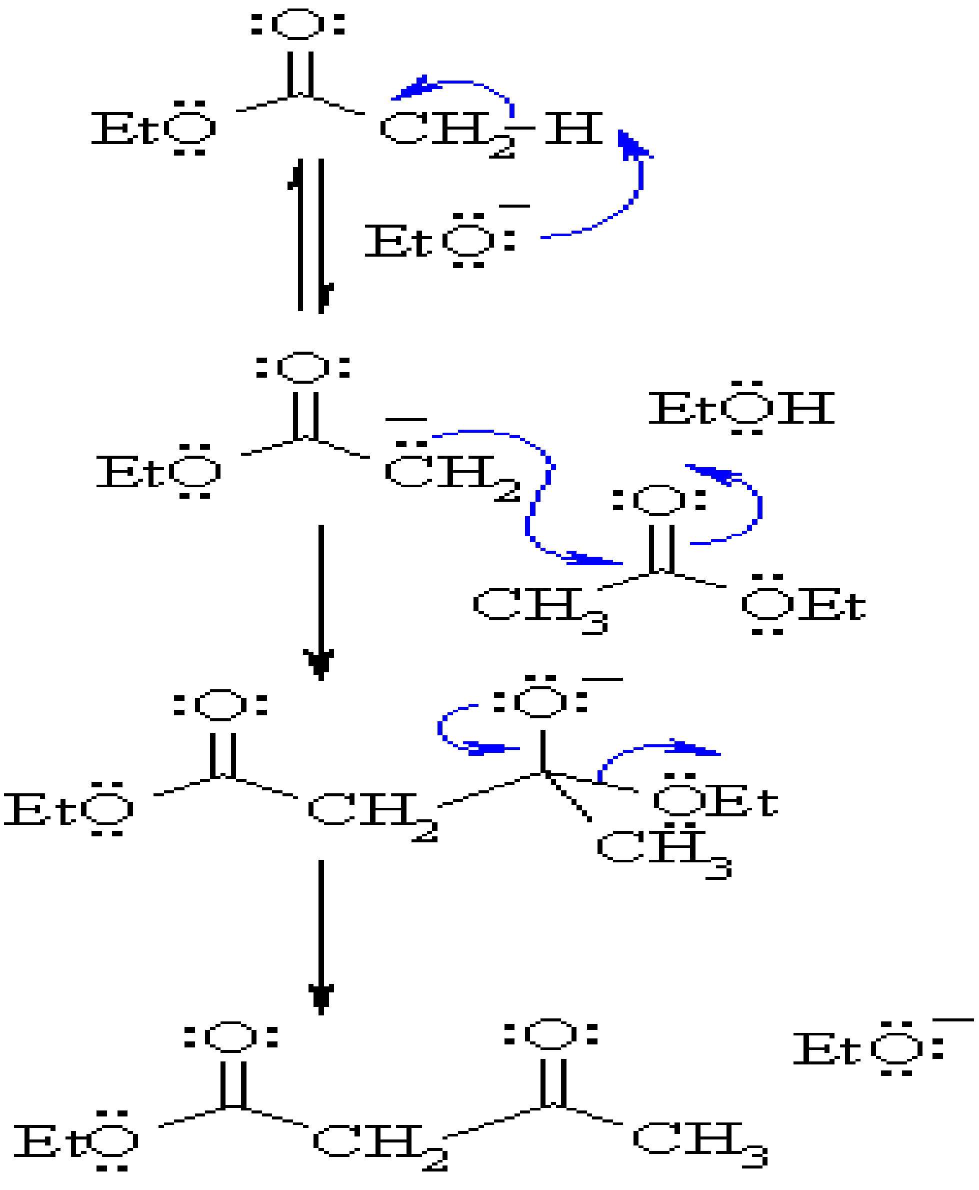
- Reaction of the same ester having an α hydrogen with 1 equivalent of a base to yield **a β-keto ester**



1] Can NaOH be used as a base to abstract the acidic proton as in the case of aldehydes and ketones?

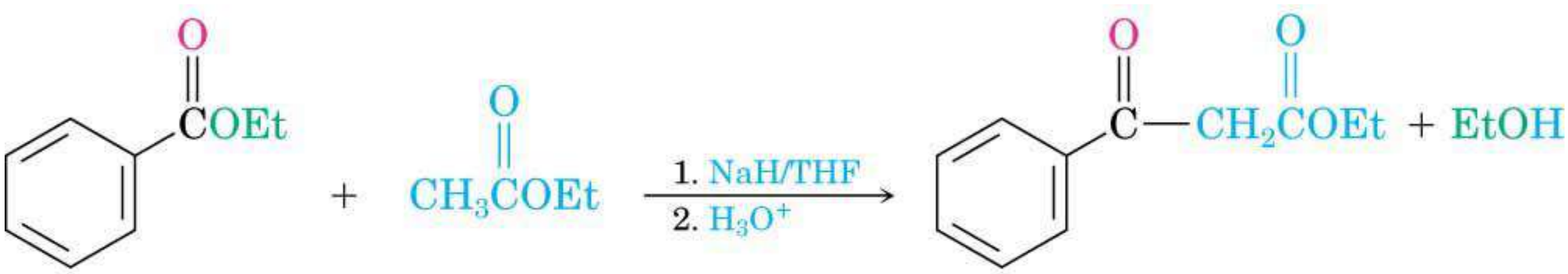
2] From product functionality viewpoint; notice the difference between aldehydes and ketone condensation and the ester condensation!!!!

Mechanism of the Claisen Condensation



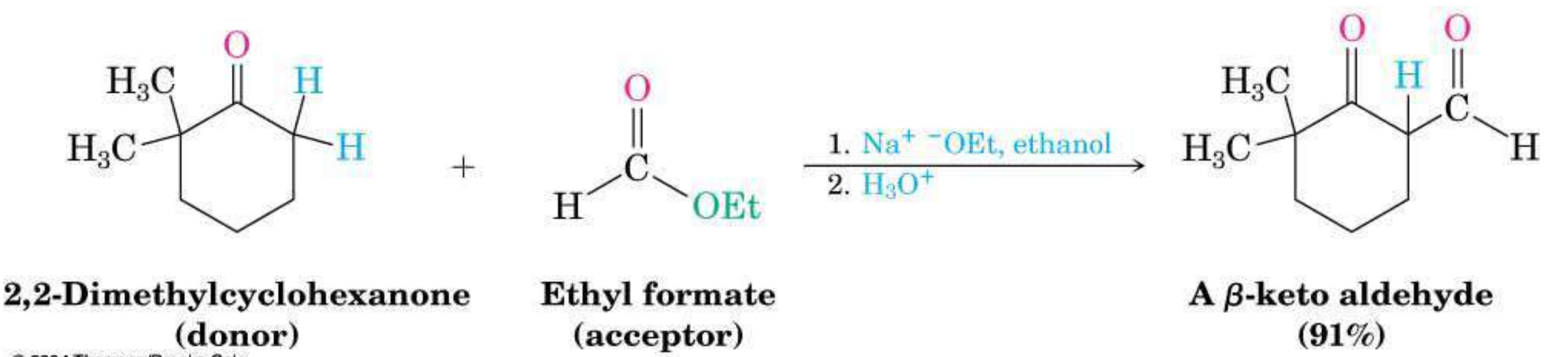
Mixed Claisen Condensations

- Successful when one of the two ester act as the electrophilic acceptor in reactions with other ester anions (has an alpha hydrogen) to give mixed β-keto esters



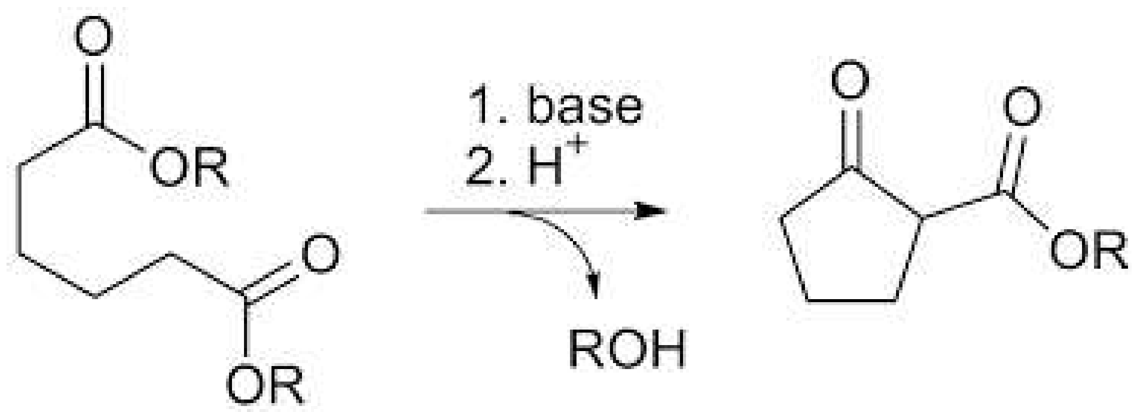
Esters and Ketones

- Reactions between esters and ketones, resulting in β-diketones
- Best when the ester component has no α hydrogens and can't act as the nucleophilic donor

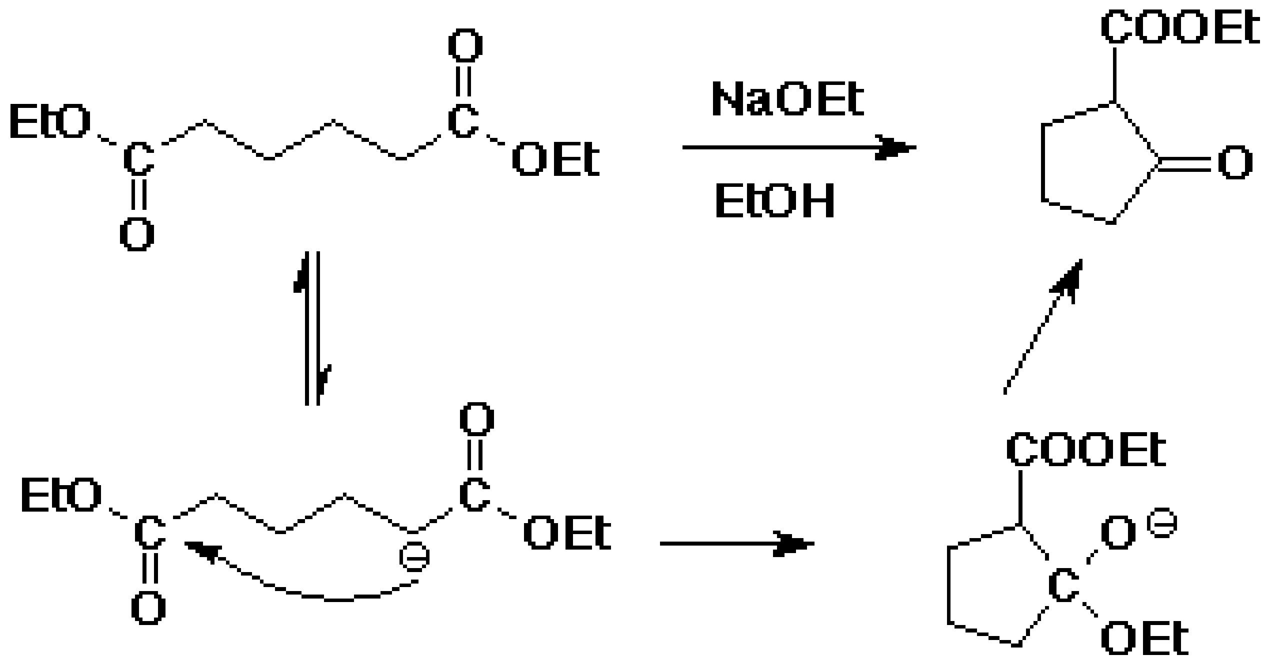


Intramolecular Claisen Condensations:
“ Dieckmann Cyclization”

- Intramolecular Claisen condensation
- Best with 1,6-diesters (product: 5-membered β-ketoester) and 1,7-diesters (product: 6-membered β-ketoester)

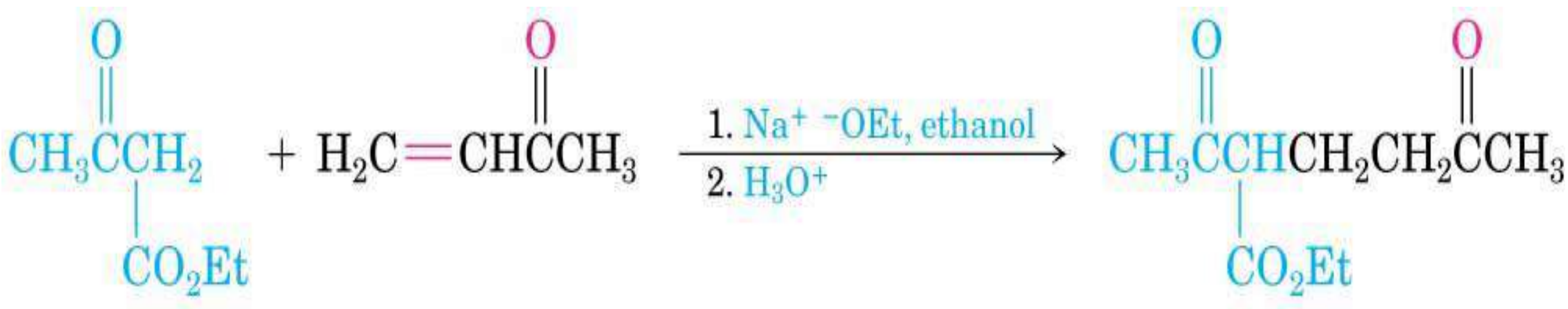


Mechanism of the Dieckmann Cyclization



Michael Reaction

is the nucleophilic addition of a carbanion or another nucleophile to an α,β-unsaturated carbonyl compound.

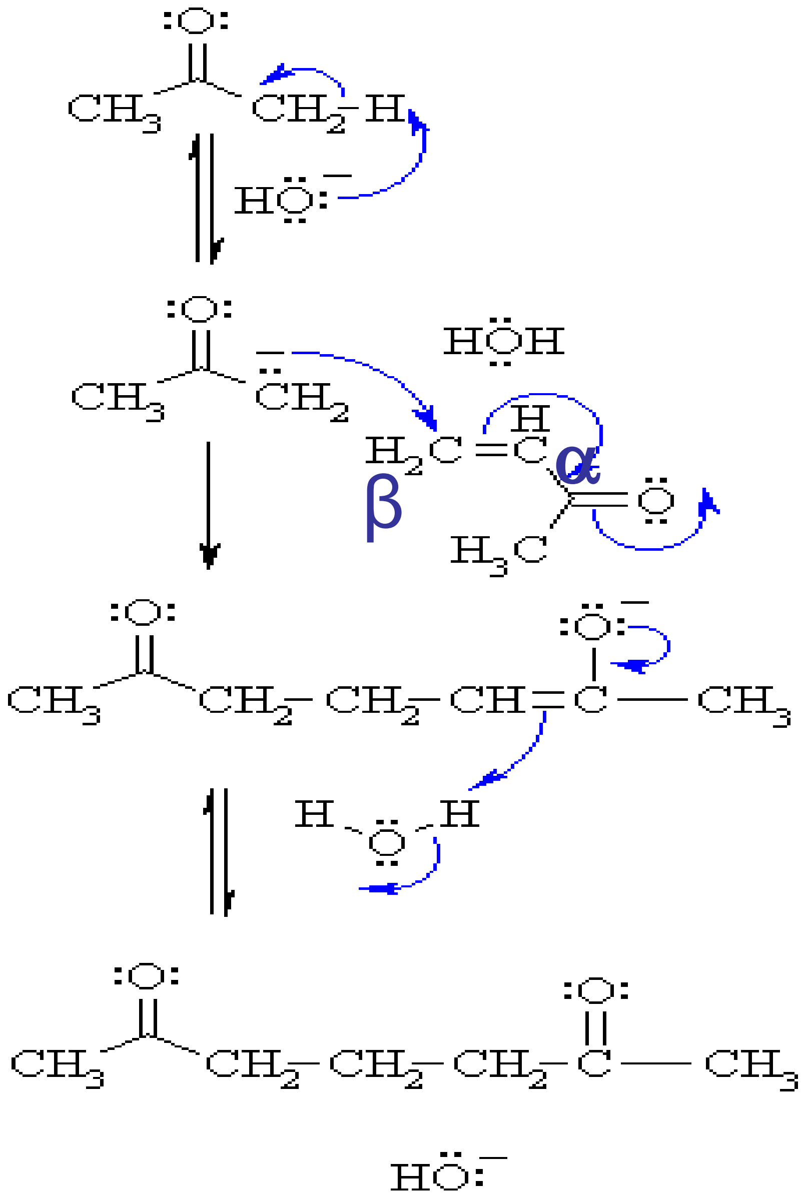


Ethyl acetoacetate

3-Buten-2-one

94%

Mechanism of the Michael Reaction

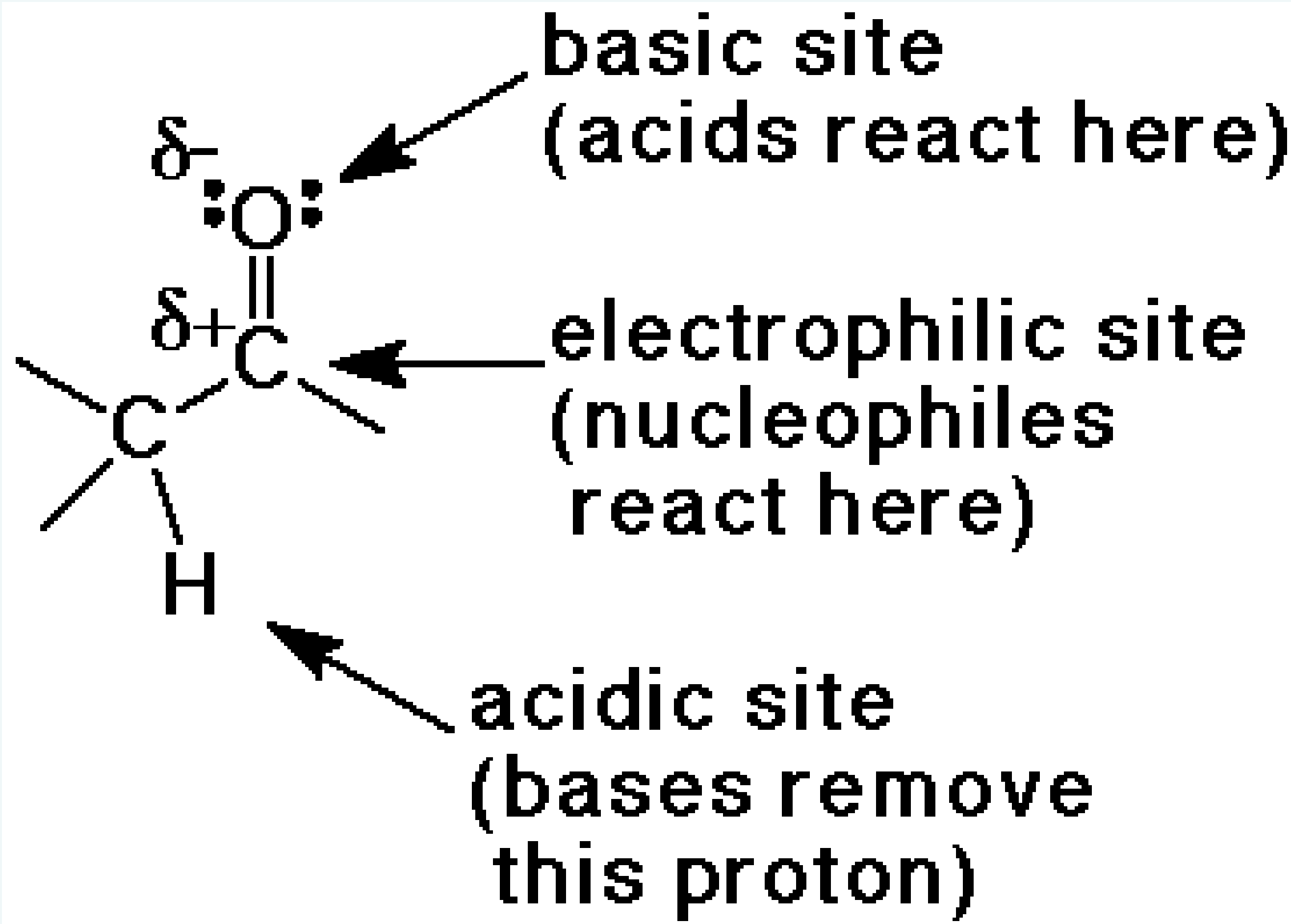


Simply it is Nucleophilic addition of a enolate ion donor to the β carbon of an α,β-unsaturated carbonyl acceptor.

©

α-Carbonyl Substitution

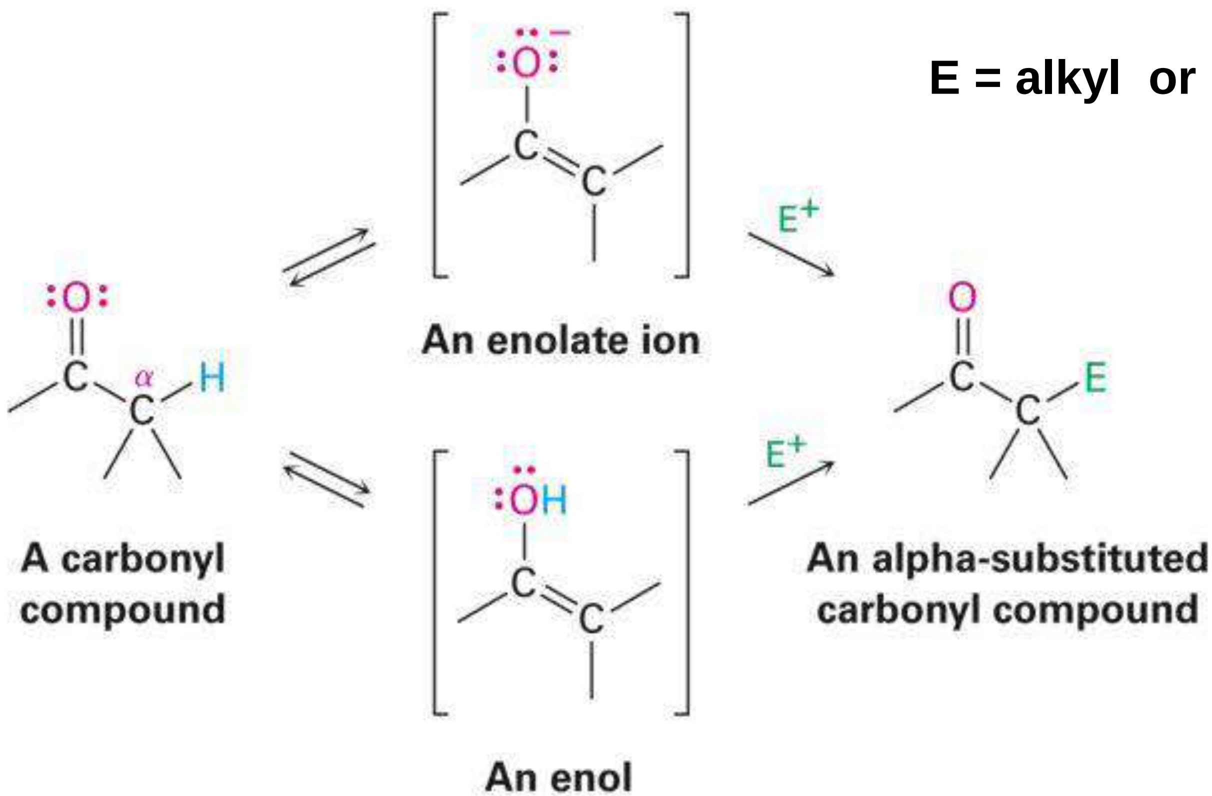
Reactive Sites of the Carbonyl Group



The α Position

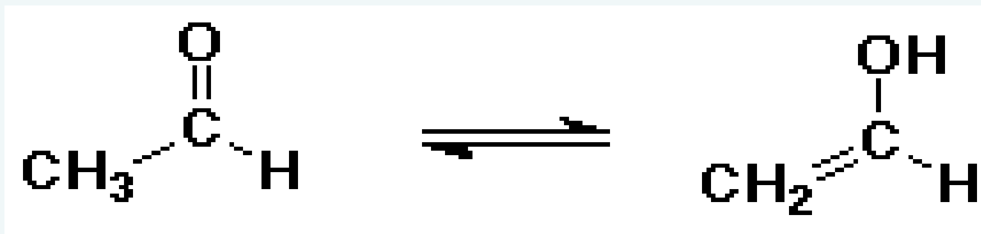
- The carbon next to the carbonyl group is designated as being in the α position
- Electrophilic substitution occurs at this position through either an *enolate or enol ion*

E = alkyl or Halogen

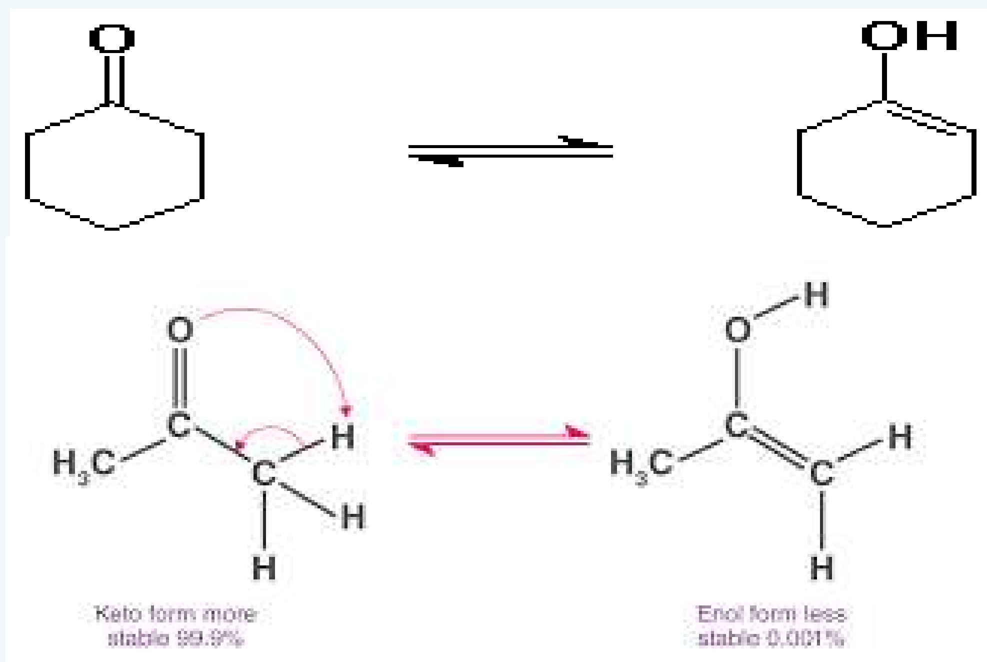


Enols

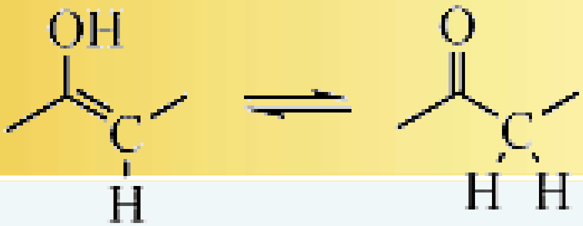
Tautomers - constitutional isomers that are easily interconverted enol structure vs. carbonyl (keto) structure differs by location of one H and double bond.



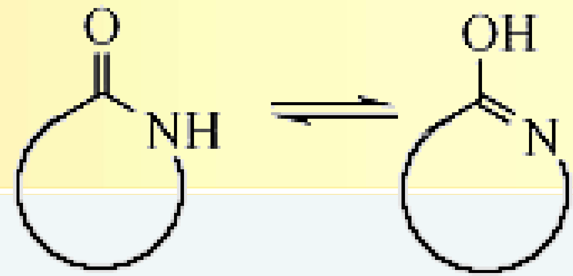
Keto form **Enolform**



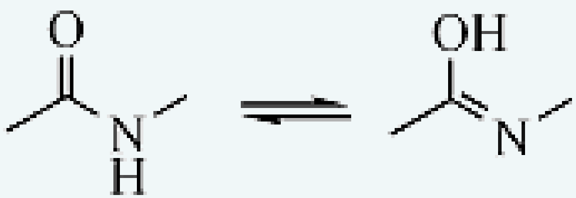
Enol form Keto form



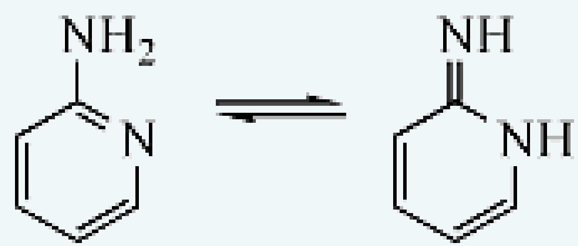
Lactam form Lactim form

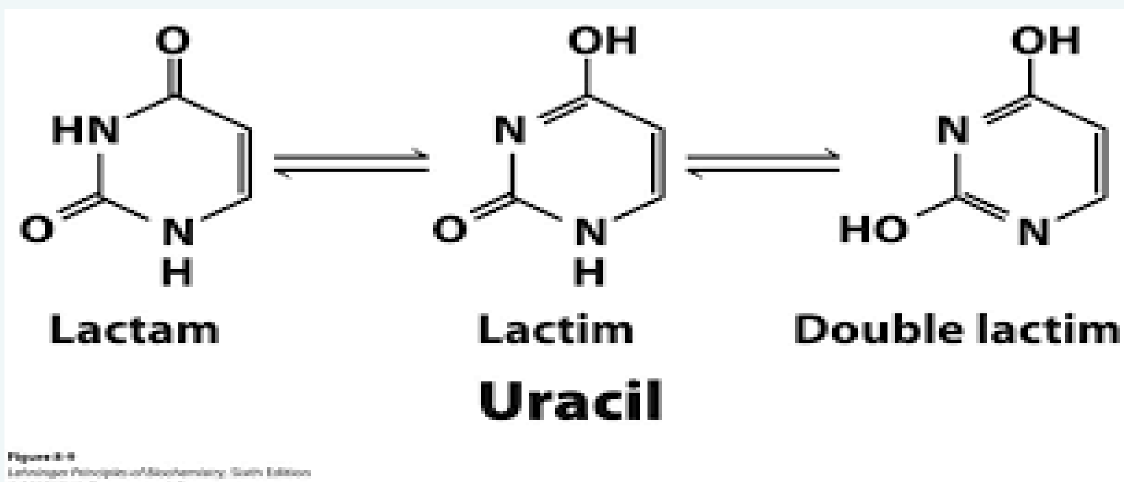


Amide form Imidic acid form

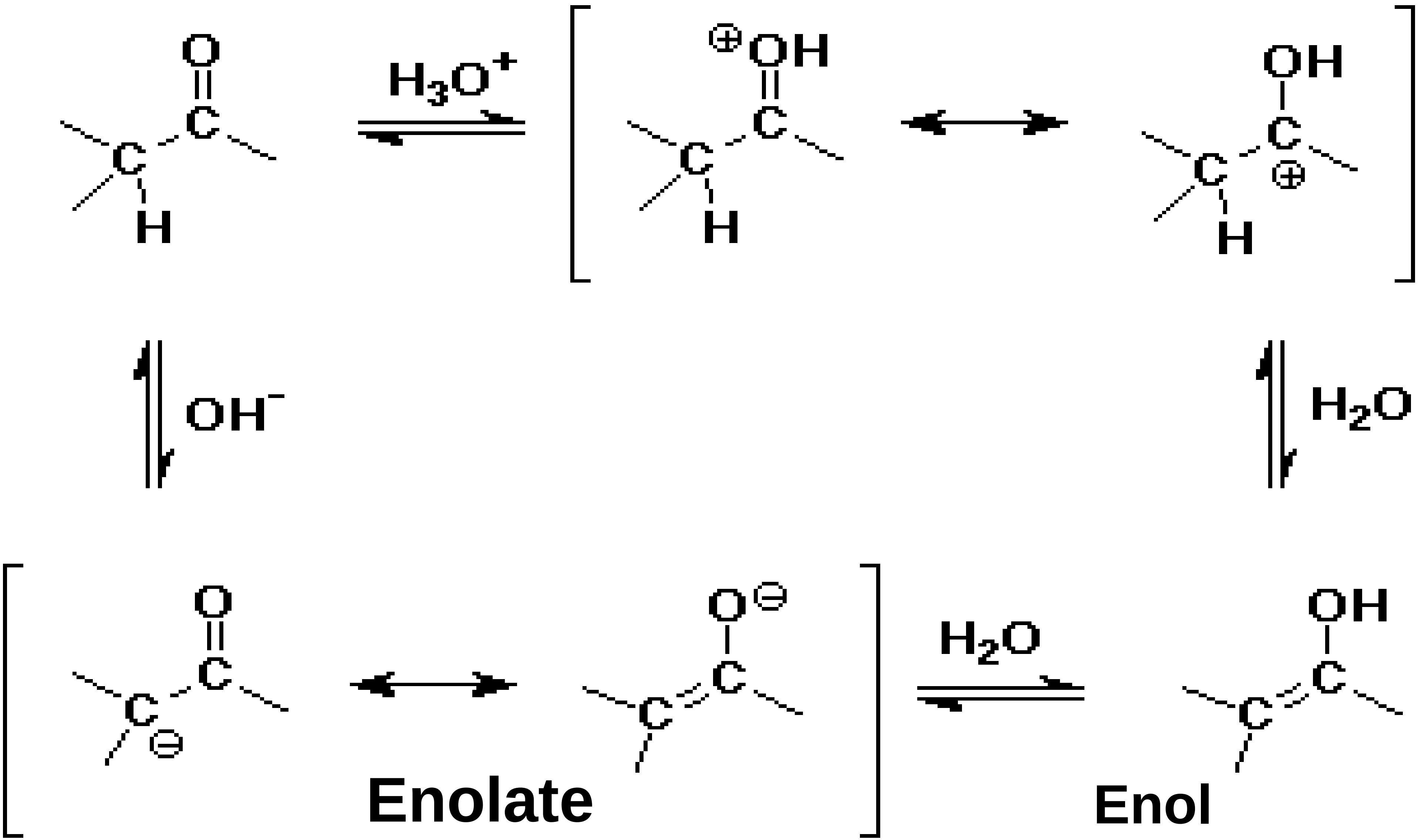


Amine form Imine form



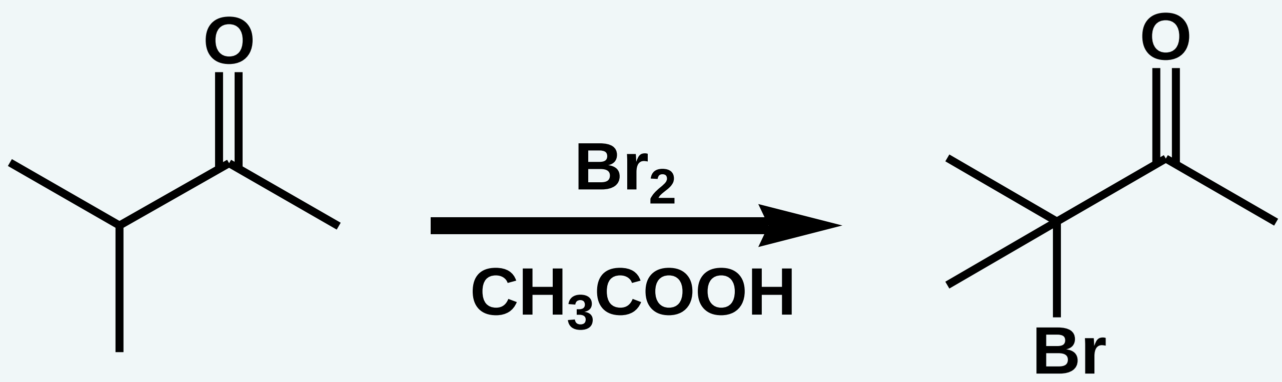


Acid- and Base-Catalyzed Enolization

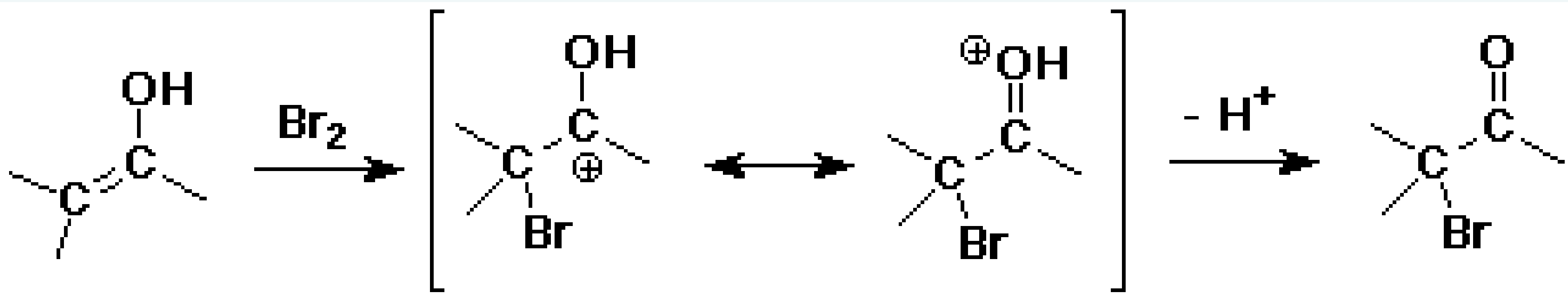


Alpha-Substitution on Enols

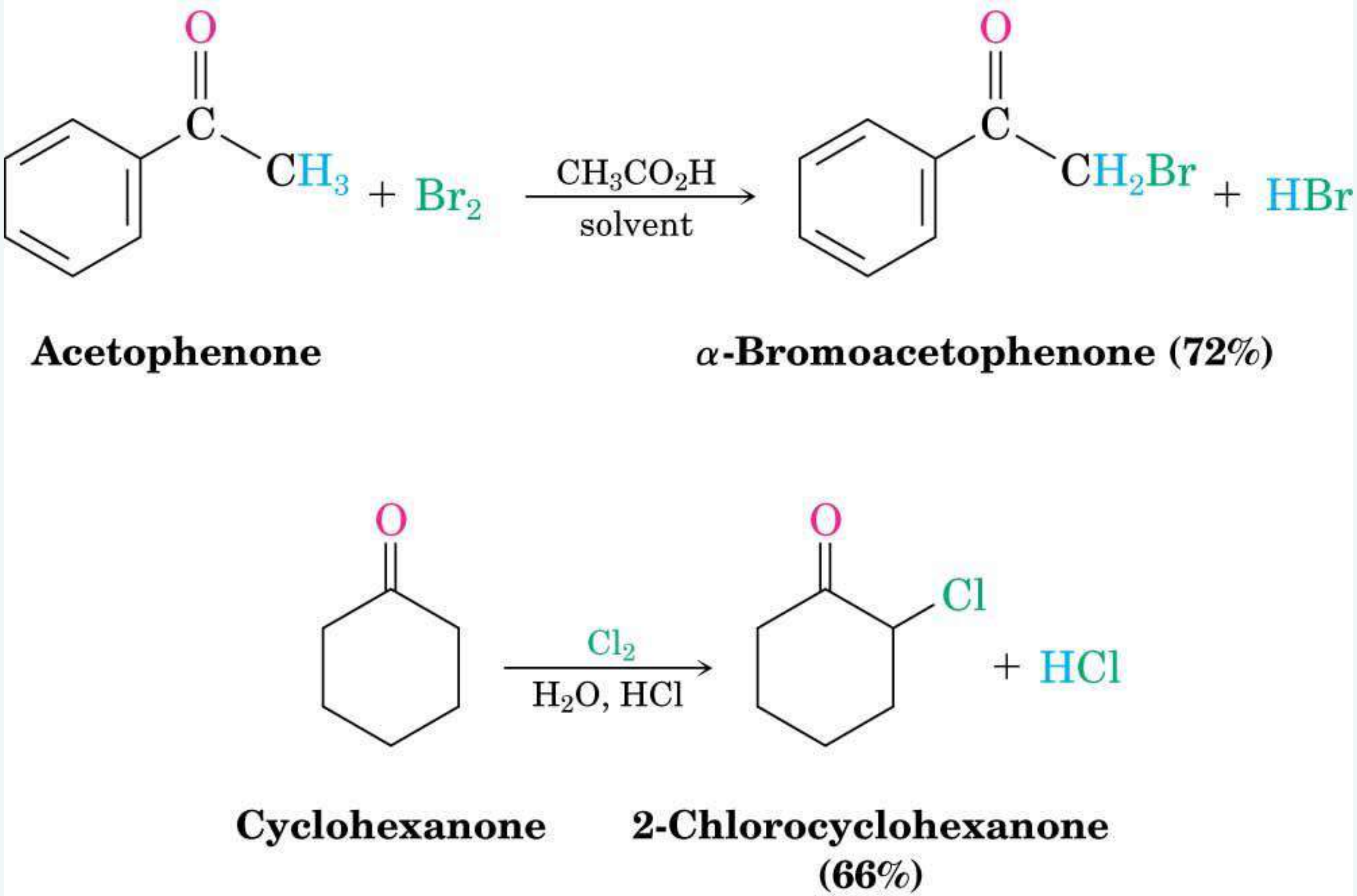
I] α-Halogenation of aldehydes and ketones



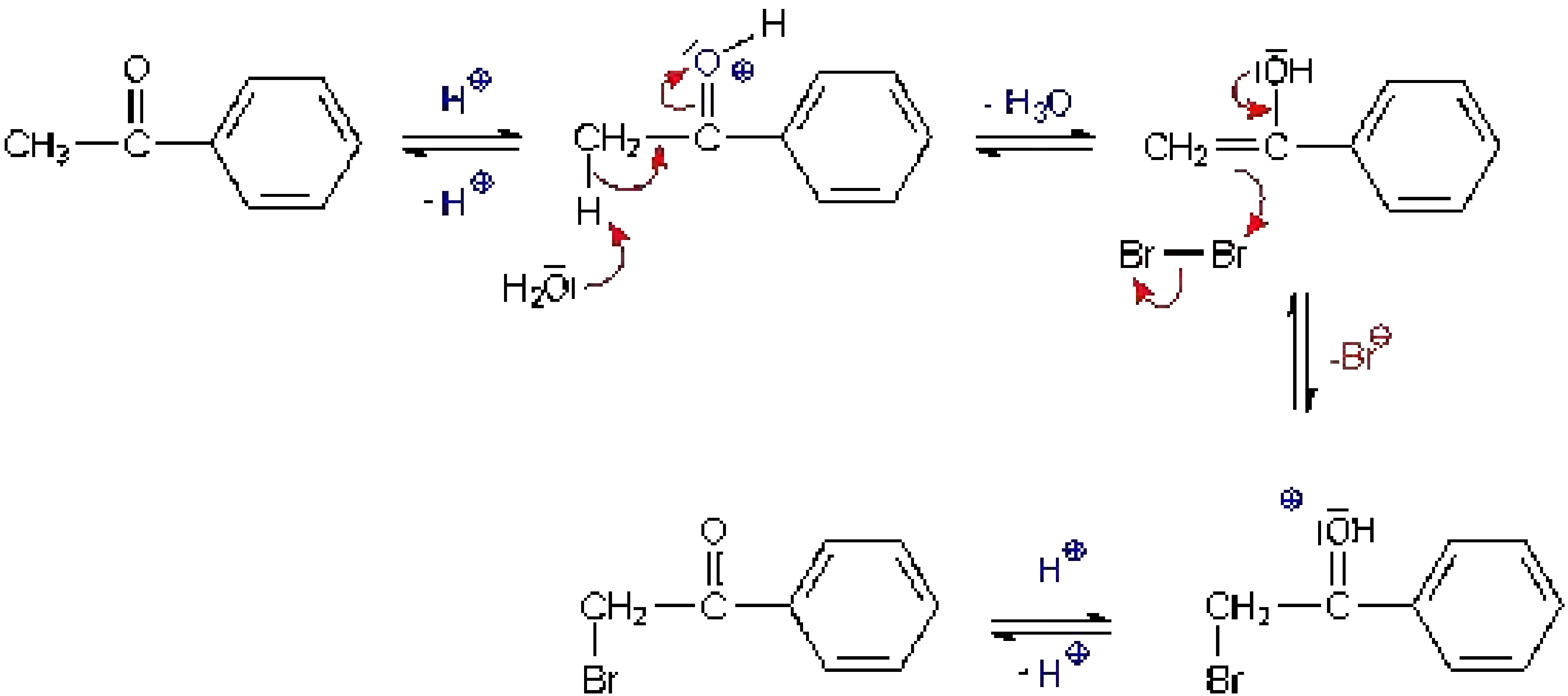
Mechanism



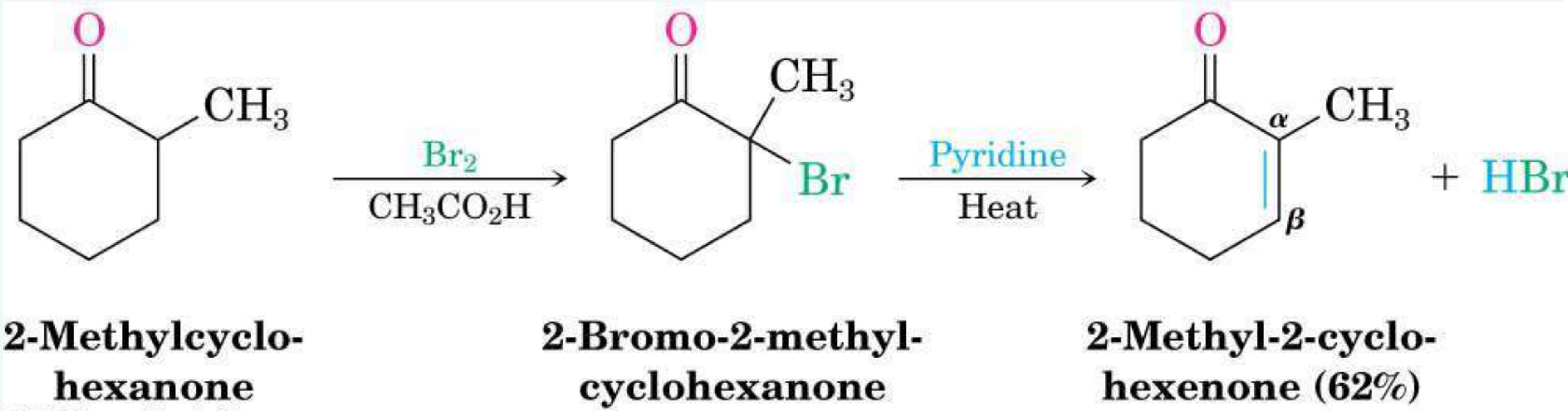
Aldehydes and ketones can be halogenated at their α positions by reaction with Cl_2, Br_2, or I_2 in acidic solution



Mechanism of aldehydes or ketones Electrophilic Substitution

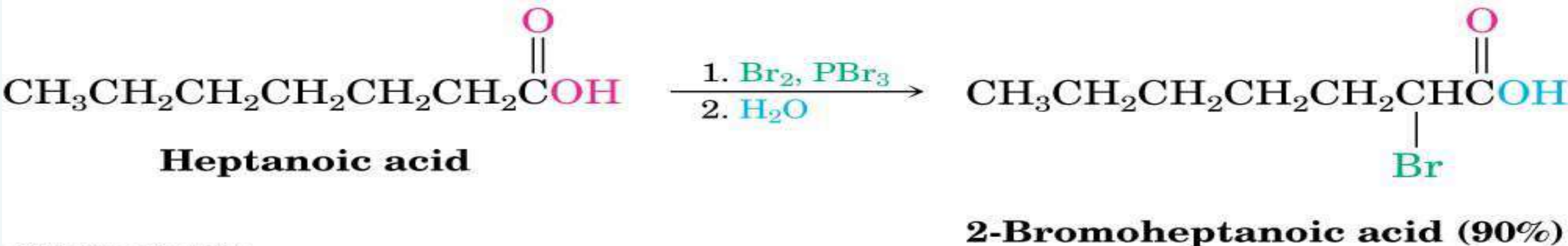


α-Bromo ketones can be dehydrobrominated by base treatment to yield α,β-unsaturated ketones

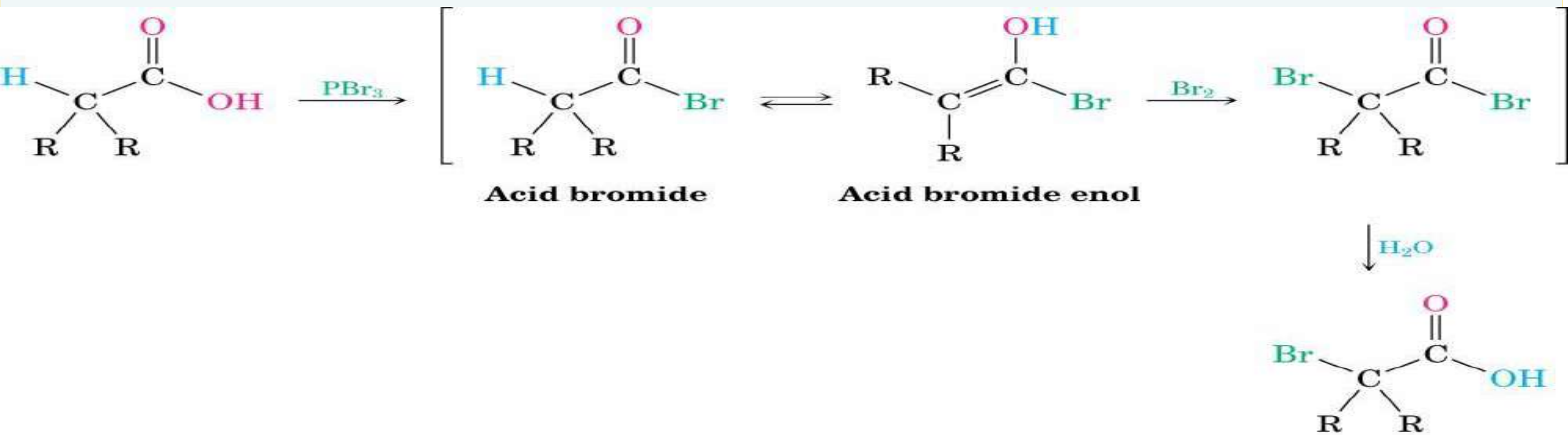


II] Alpha Halogenation of Carboxylic Acids: The Hell–Volhard–Zelinskii Reaction

- Carboxylic acids do not react with Br_2 (Unlike aldehydes and ketones)
- They are brominated by a mixture of Br_2 and PBr_3

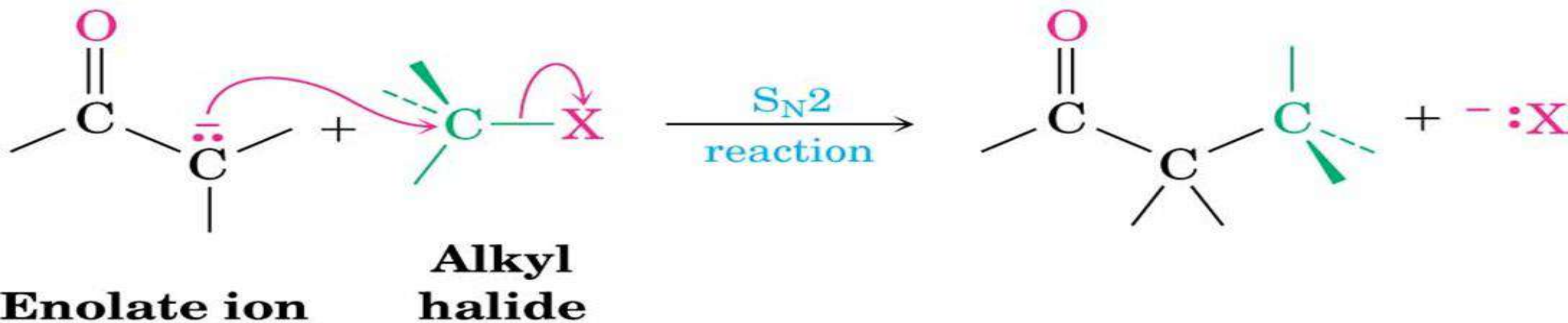


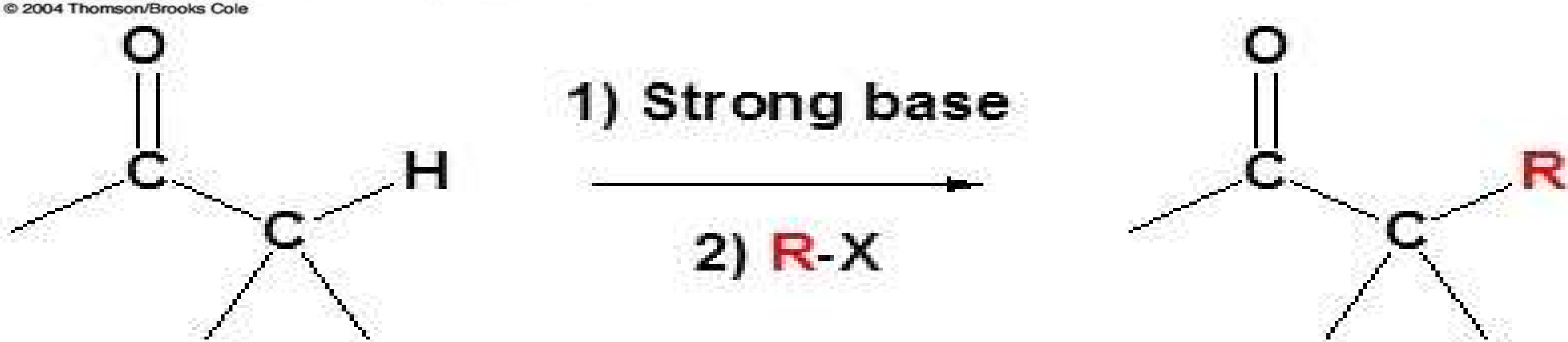
Mechanism of H.V.Z



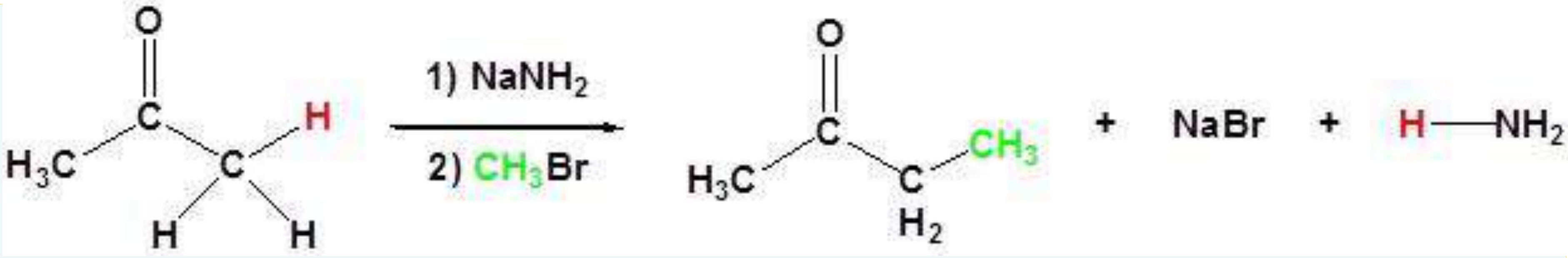
III] Alkylation of alpha ketone or aldehyde

- **Sodium hydride (NaH) or lithium diisopropylamide [LiN(*i*-$C_3H_7)_2$] LDA and $NaNH_2$ are strong enough to form the enolate.**
- **Alkylation at alpha position can be achieved when such enolate react with alkyl halides.**

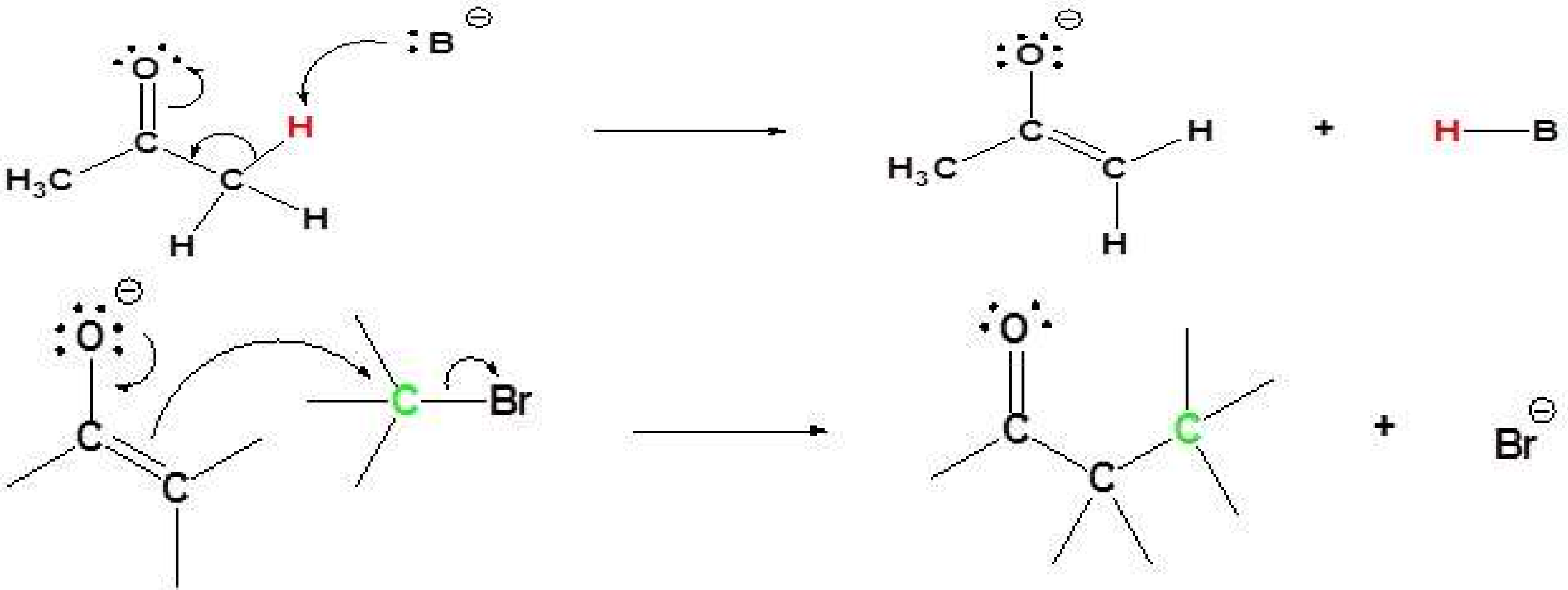




Examples

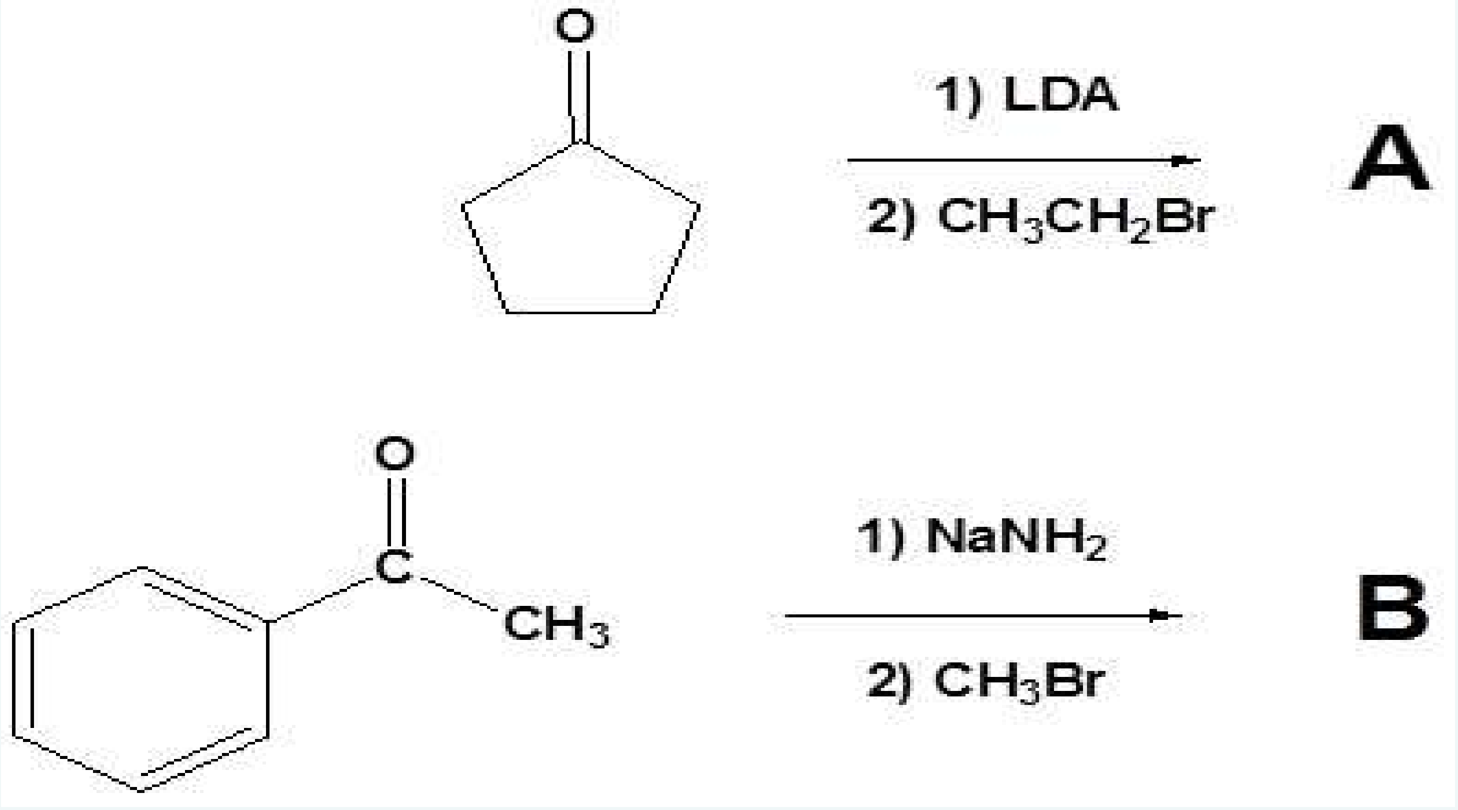


Mechanism of ketone or aldehyde alkylation



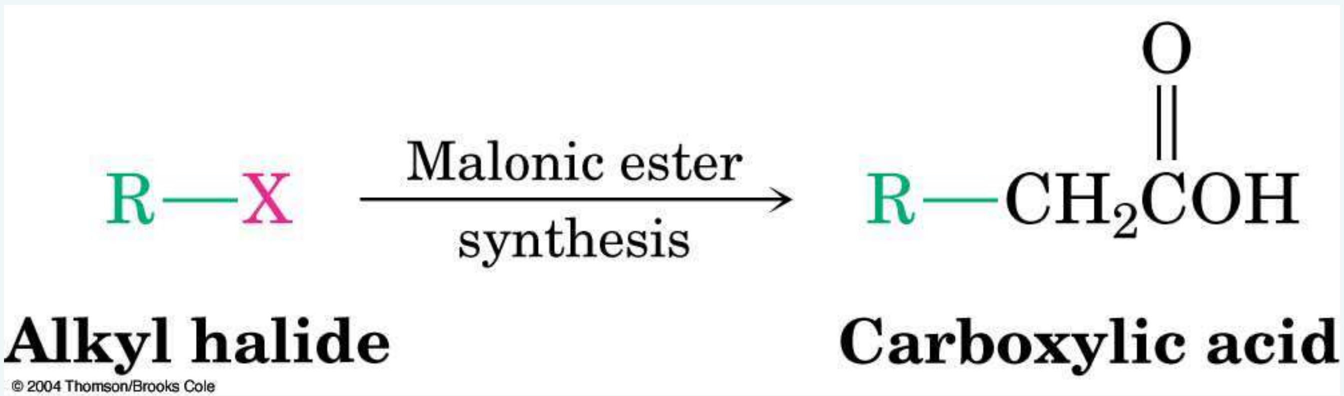
1- How to convert acetone to pentane?

2- Write the structure of the product for the following reactions.

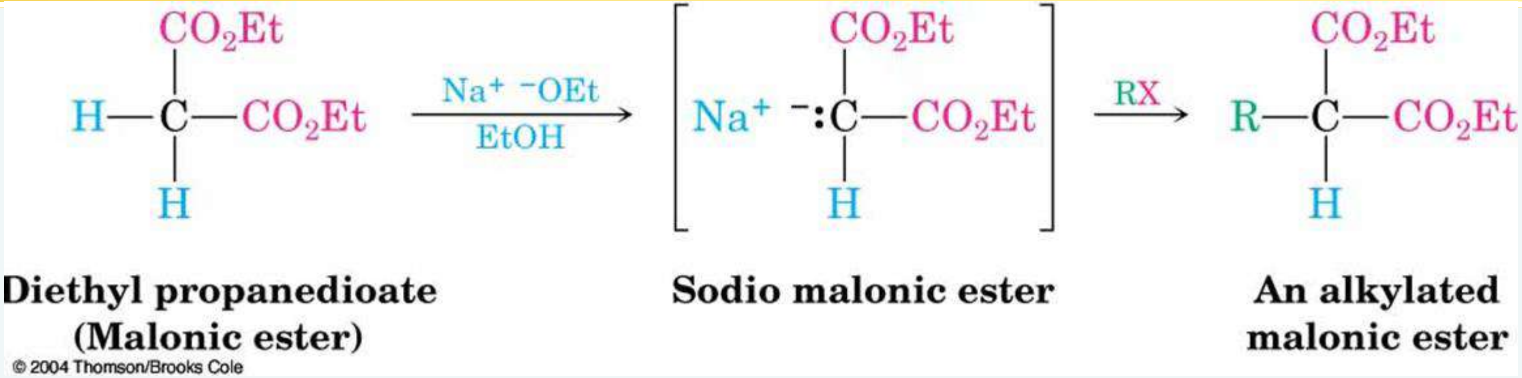


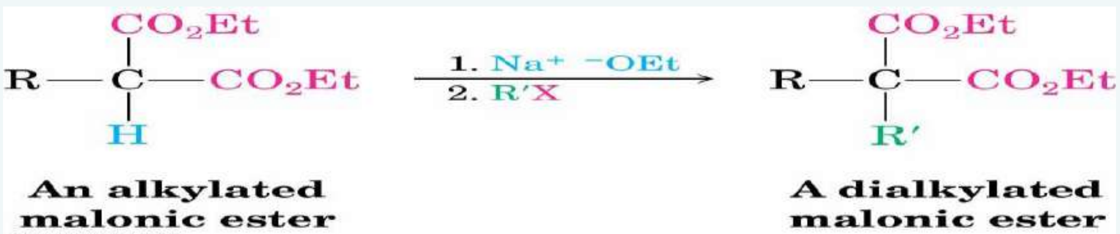
The Malonic Ester Synthesis

- **For preparing a carboxylic acid from an alkyl halide while lengthening the carbon chain by two atoms**

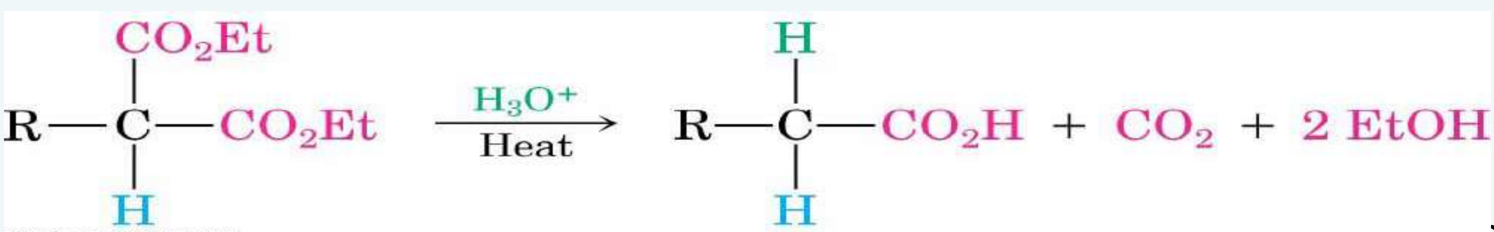


Mono and Di alkylation of malonic ester



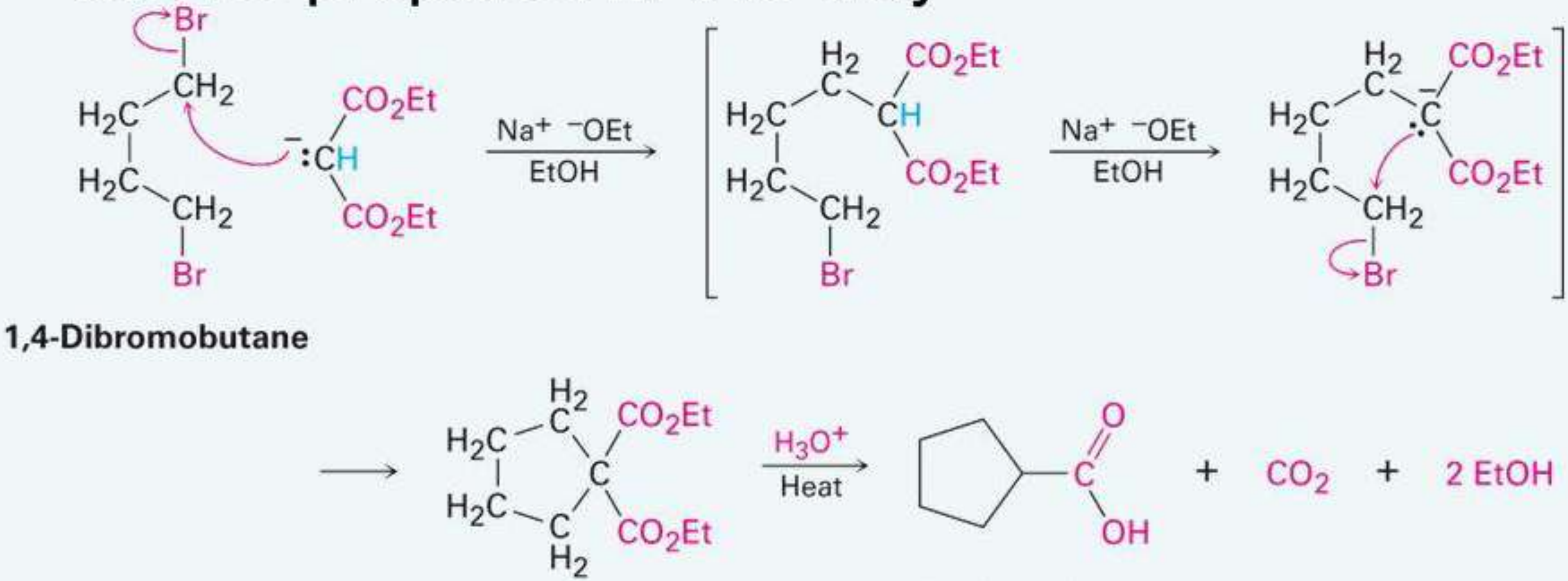


The malonic ester derivative hydrolyzes in acid and loses CO_2 (decarboxylation) to yield a substituted monoacid



Preparation of Cycloalkane Carboxylic Acids

- 1,4-dibromobutane reacts twice, giving a cyclic product
- Three-, four-, five-, and six-membered rings can be prepared in this way

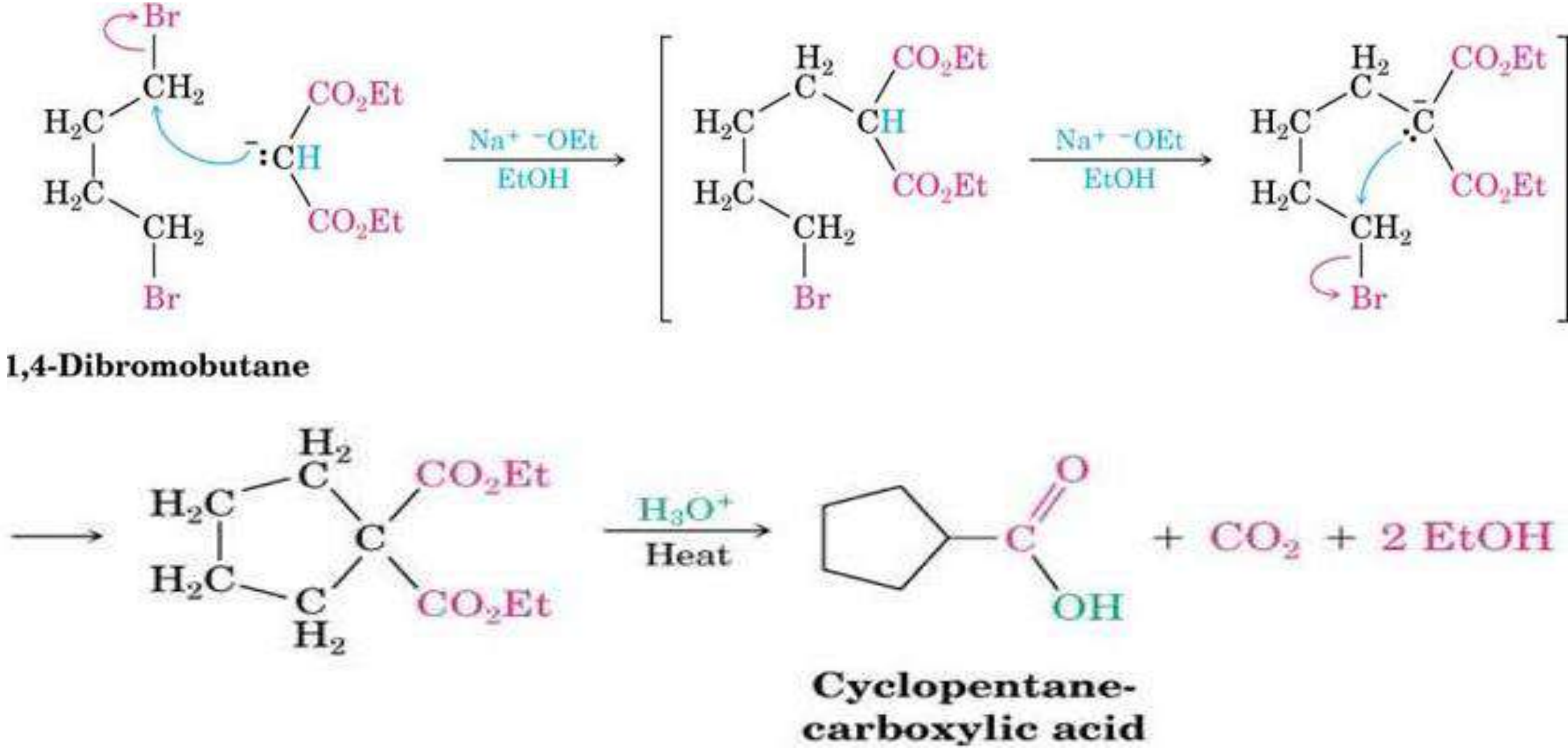


1,4-Dibromobutane

Cyclopentane-carboxylic acid

Preparation Cycloalkane Carboxylic Acids

a] 1,4-dibromobutane reacts twice, giving a cyclic product
b] Three-, four-, five-, and six-membered rings can be prepared in this way



Starting with methane; how can you prepare cycloheptane carboxylic acid??