

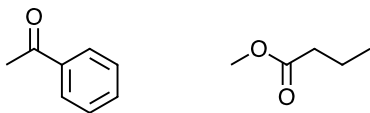
Objective 13. Apply nucleophilic addition and elimination concepts to enols and enolates reactions (aldol and Claisen condensations)

Skills: Draw structure, ID structural features and reactive sites (alpha C, beta C, LG, etc.), ID Nu⁻ and E⁺, use curved arrows to show bonds breaking and forming, show delocalized electrons with resonance structures.

Key ideas: new type of alpha C. Enolate = Nu⁻ and can react like any other Nu⁻. E.g., in substitution, Nu addn.

Practice problems solutions:

1. Consider the ketone and ester below.



a. Circle the alpha carbon(s). Box the beta carbon(s).

b. The pK_a of an alpha carbon is between 16-20 for an RCHO or RCOR and > 20 for an ester. NaOH, NaOEt, and LDA are commonly used bases that reacts at the H bonded to the alpha carbon. LDA is the strongest base of the three.

(i) Write a chemical equation that represents the reaction between the acetophenone (the ketone shown above) and LDA. Will a lot of enolate ion be produced or a little? In other words, does equilibrium favor products or reactants?

(ii) Write a chemical equation that represents the reaction between the acetophenone and NaOEt. Will a lot of enolate ion be produced or a little? In other words, does equilibrium favor products or reactants?

Answers:

a. the alpha carbon is the carbon adjacent to the carbonyl carbon. (Another type of alpha carbon.)

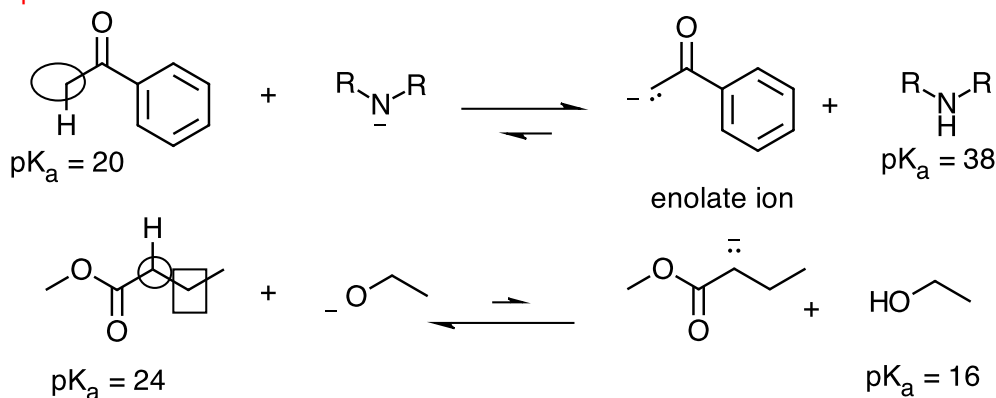
Each compound has one alpha C.

The beta carbon is the carbon adjacent to the alpha carbon. (Another type of beta carbon.)

Acetophenone does not have a beta carbon. Methyl butanoate (the ester) has one beta carbon.

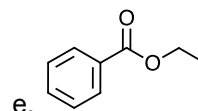
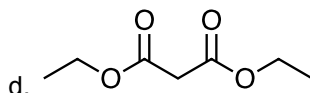
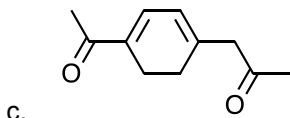
(i) A lot of enolate ion is formed. LDA is a very strong base and will remove the H on the alpha C. Equilibrium favors products.

(ii) A little enolate ion is formed. C₂H₅O⁻ is not a strong enough base to remove the H on the alpha C in the ester. Equilibrium favors reactants.



2. Use curved arrows to show how each compound below reacts with NaOEt to form an enolate ion or ester enolate ion. Include resonance structures. Are the resonance structures equivalent? If not, identify the major contributor.

a and b. The ketone and ester compounds in Question 1.



f. Compare Compounds from (d) and (e). Which compound is the stronger acid? (Hint: look at the stability of the enolate.)

g. The enolate ion and ester enolate ion are nucleophiles. Which one is stronger?

h. (i) The enolate ion from part (c) reacts with HBr. Use curved arrows to show how this reaction occurs. Draw the structure of the major product.

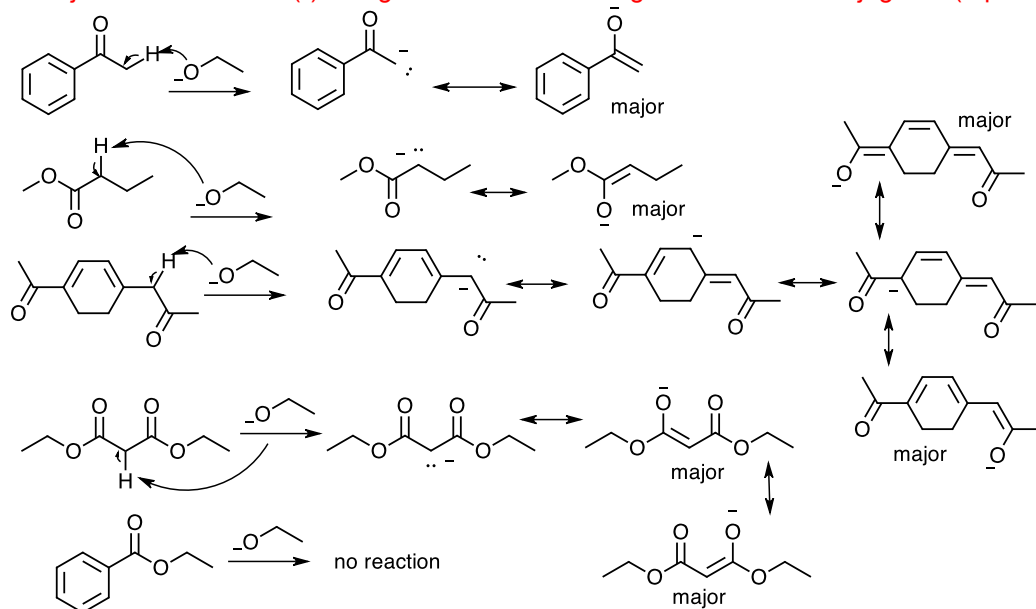
(ii) The ester in part (d) is diethyl malonate, which is used in the "malonic ester synthesis." (We see this one again in Objective 14.) The ester enolate ion from part (d) reacts with ethyl bromide. Draw the structure of the product of this reaction. What is the reaction type? Is there a competing reaction?

(iii) The enolate ion from part (a) reacts with Br_2 . Use curved arrows to show how this reaction occurs. Draw the structure of the product.

Answers:

a-e.

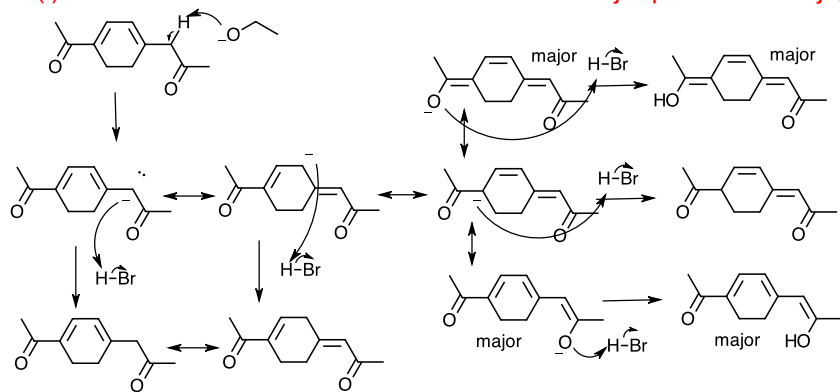
c. Major contributor has (-) charge on more electronegative O and is conjugated (4 pi bonds).



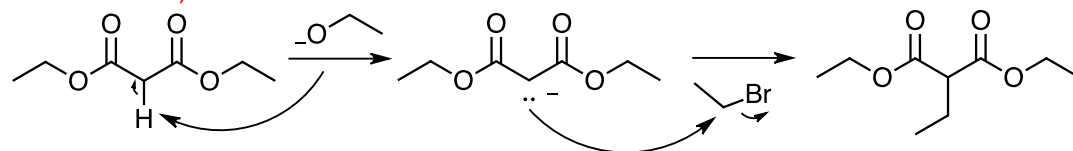
f. Compound from (d) is the stronger acid because pK_a is approximately 9 to 11 (see diketone $\text{pK}_a = 11$ and β -keto ester $\text{pK}_a = 11$) and stable conjugate base ((-) charge and pi electrons are delocalized over 5 atoms).

g. The ester enolate ion is a stronger base (nucleophile) than the enolate ion. According to pK_a table, conjugate acid of the enolate ion is 20; conjugate acid of the ester enolate ion is 24.

h. (i) enolate ion + HBr is an acid-base reaction. Major product is conjugated.



(ii) This reaction is a substitution reaction (from Chem 12A). Competing reaction is elimination to form pi bond ($\text{H}_2\text{C}=\text{CH}_2$ in this reaction).

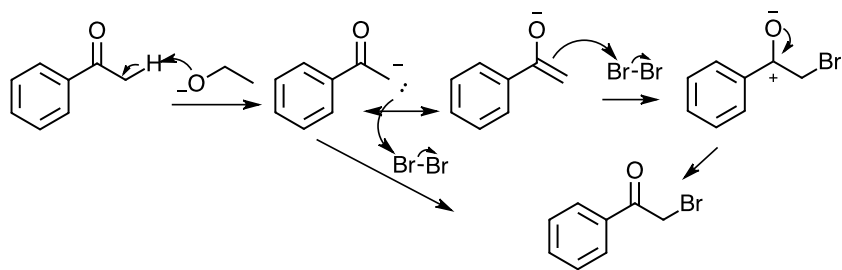


(iii) This reaction is an alpha halogenation reaction – see

[https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Supplemental_Modules_\(Organic_Chemistry\)/Reactions/Reactivity_of_Alpha_Hydrogens/Alpha_Halogenation](https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Supplemental_Modules_(Organic_Chemistry)/Reactions/Reactivity_of_Alpha_Hydrogens/Alpha_Halogenation)

$\text{Br}-\text{Br}$ behaves like an electrophile (see Electrophilic addition reaction from Chem 12A).

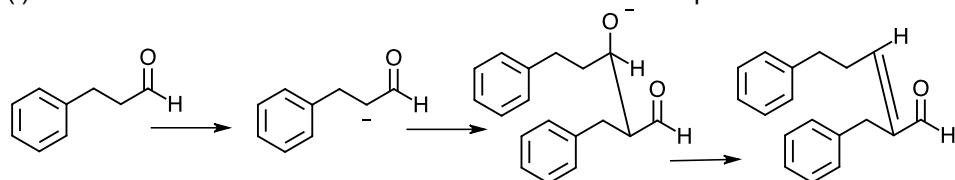
Nucleophilic enolate ion reacts with electrophilic $\text{Br}-\text{Br}$.



3. Aldol and Claisen condensations.

a. The compound below reacts with NaOEt. The enolate ion reacts with the aldehyde reactant. The enolate is the nucleophile and the carbonyl carbon is the electrophile. The difference between this reaction and the reactions from Question 2h is the electrophile. (Note: NaOEt is used to get a mixture of the aldehyde and enolate ion. If you use LDA, the product is almost all enolate ion and there is no aldehyde to react with the enolate.)

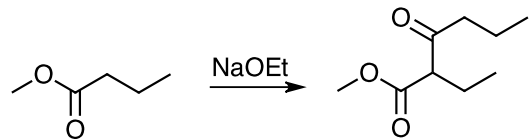
(i) Use curved arrows to show how each intermediate and product forms.



(ii) Circle the bond in the product that formed between the enolate and aldehyde. (Note: this will help you with the synthesis problems in Question 5.)

b. The ketone (acetophenone) from Question 1 reacts with NaOEt. Use curved arrows to show how each intermediate and product forms.

c. The ester in Question 1 reacts with NaOEt. Use curved arrows to show how each intermediate and product forms.



d. Mixed aldol-Claisen reactions: The ketone (acetophenone) in Question 1 reacts with the ester in Question 1 in the presence of NaOH. Draw the structure of the possible products.

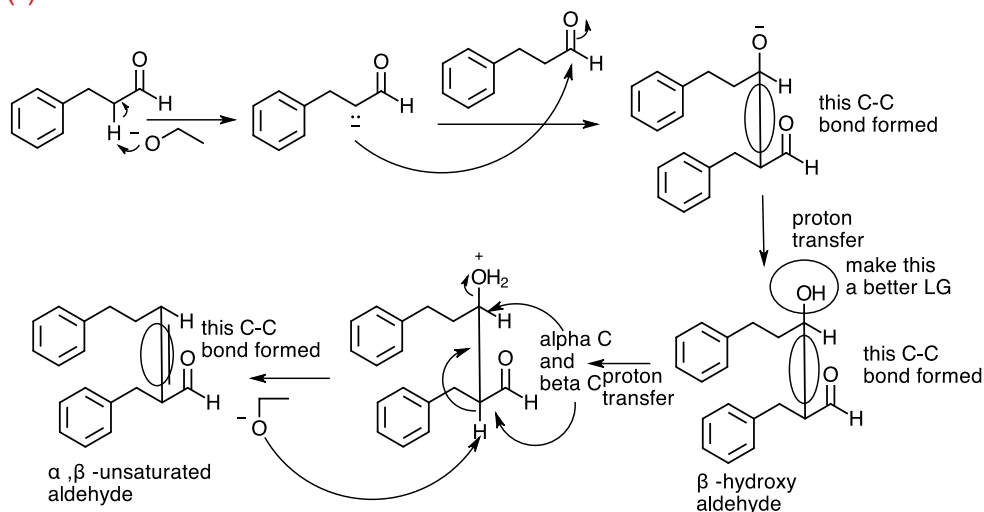
Answers:

a. (i) This is a nucleophilic addition reaction and elimination reaction.

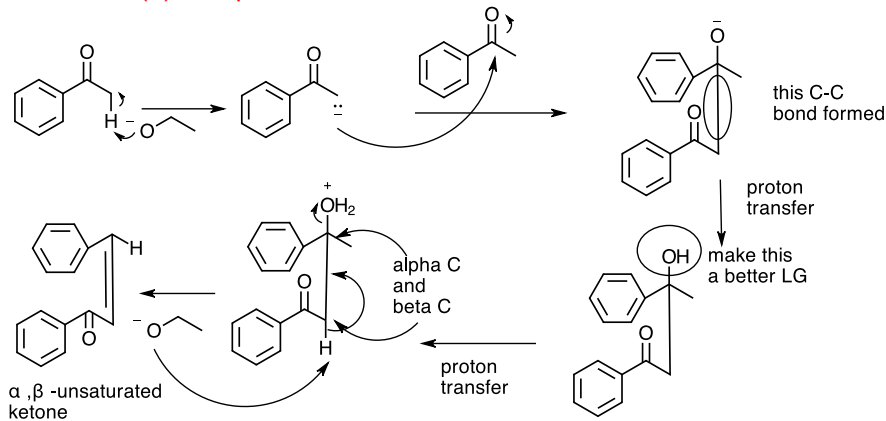
Nucleophilic addition reaction - the nucleophilic enolate ion reacts with the electrophilic carbonyl carbon to form a tetrahedral intermediate. One proton transfer forms -OH (beta-hydroxy aldehyde).

Elimination reaction - 2nd proton transfer forms a good leaving group. This leaving group is bonded to an alpha carbon (CHM 12A) that is bonded to a beta carbon that is bonded to an H. A nucleophile reacts at the H bonded to beta C, C=C pi bond forms, and leaving group leaves.

(ii)



b. Same as (a) except with ketone.

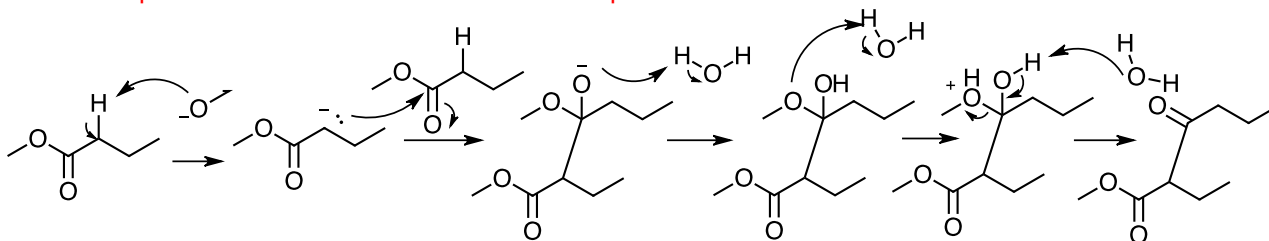


c. This is a nucleophilic acyl substitution reaction and elimination reaction.

The tetrahedral intermediate is the 2nd intermediate.

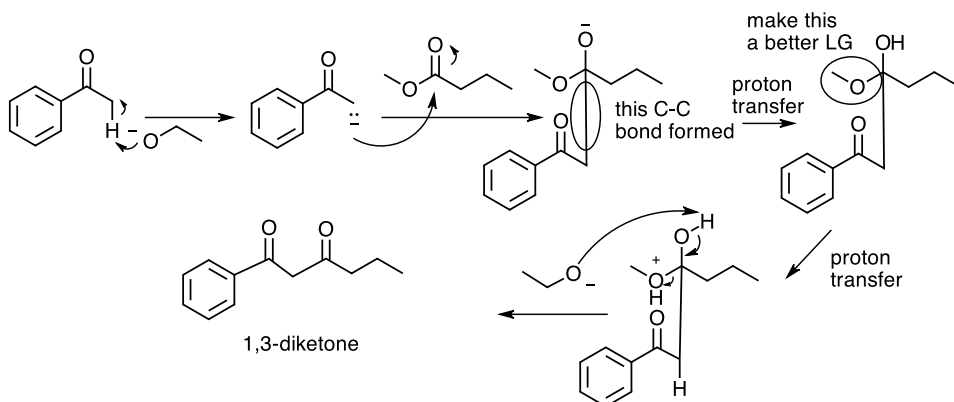
The leaving group is C_2H_5OH .

The last step is an elimination reaction that forms a pi bond.

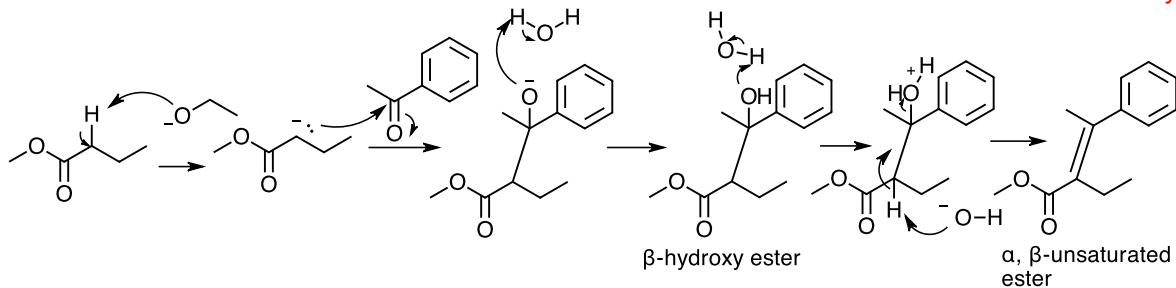


d. The ketone and the ester have alpha carbons. Two possible reactions produce two possible products.

The ketone can form an enolate ion. The enolate ion reacts with the ester at the carbonyl carbon.

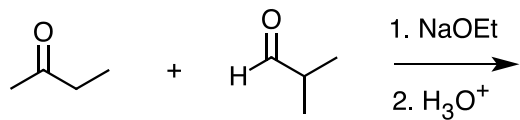


The ester can form an ester enolate ion. The ester enolate ion reacts with the ketone at the carbonyl carbon.

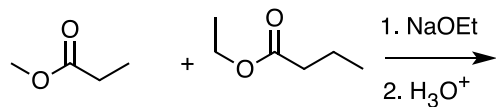


4. Predict the product of each reaction.

a.



b.



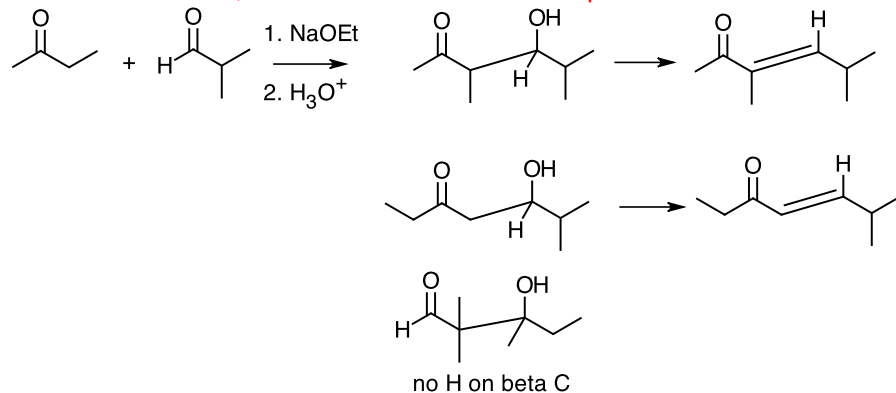
Answers:

a. The reactants have 3 alpha carbons so there are 3 possible products.

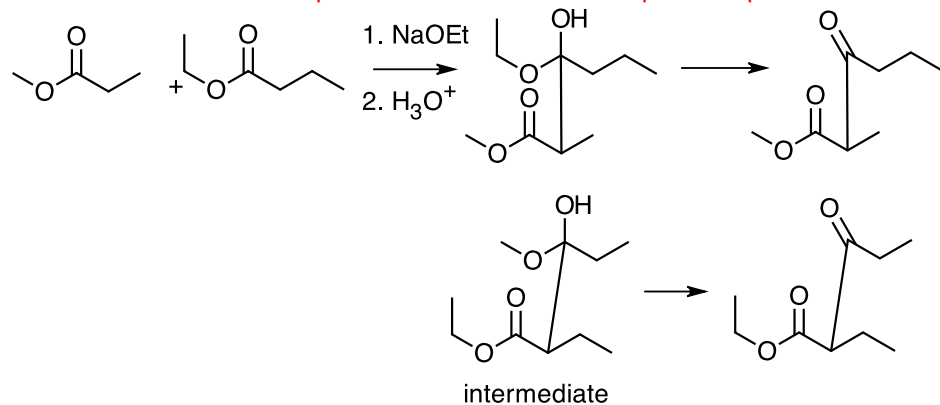
In each reaction, a β -hydroxy ketone forms.

In the first two reactions, there is a H bonded to a β carbon so an elimination reaction occurs to form a α, β -unsaturated ketone.

In the third reaction, there is not a H bonded to a β carbon.

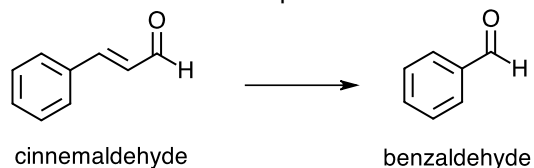


b. The reactants have 2 alpha carbons so there are 2 possible products.

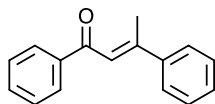


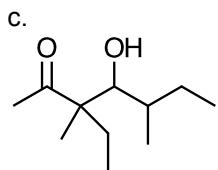
5. Synthesis: Draw the structure of the reactants to make each compound. State the reaction conditions.

a. Benzaldehyde (almond flavor) is produced from cinnamaldehyde (cinnamon flavor) in a retro-aldol reaction. Draw the structure of the second product.

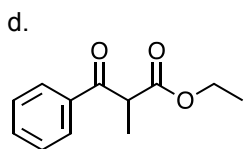


b.



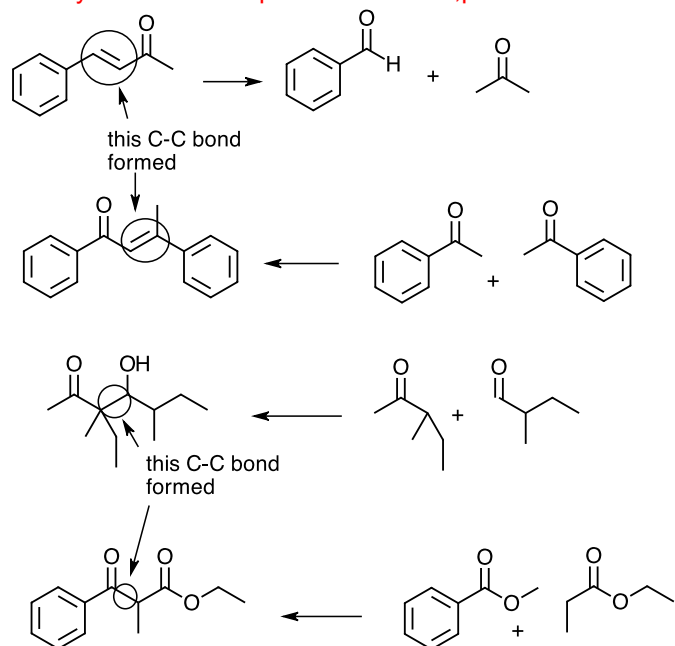


Why can't this compound form an α,β -unsaturated ketone?



Answers:

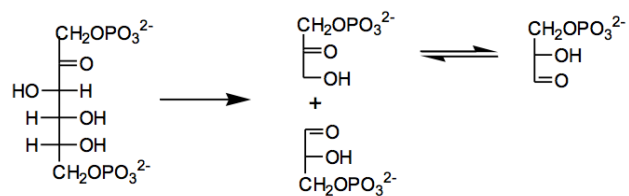
c. Why can't this compound form an α,β -unsaturated ketone? No H on beta carbon for elimination to occur.



6. The 4th step of glycolysis involves a retro (reverse) aldol condensation reaction. Use curved arrows to show how reactants form products. Identify the bond that breaks to form the aldehyde or ketone. Where is the enolate?

Glycolysis 4th step:

retro-Aldol condensation + keto-enol



c
Glycolysis may be a reaction for your Biology Reaction application project.
Instead of showing curved arrows, here is a description:

1. The reactant is a β -hydroxy ketone. ID the α and β carbons.
2. De-protonate the alcohol on the β carbon to form alkoxide ion.
3. The lone pair on the alkoxide ion forms a pi bond and the sigma bond between the α and β carbons break to form a carbanion on the α carbon (this is an enolate ion) and the aldehyde (2nd product on bottom).
4. The enolate ion is protonated to form the ketone (top product).