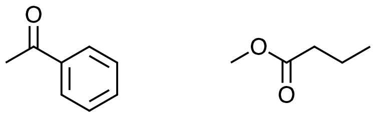
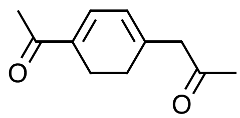
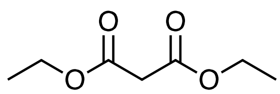
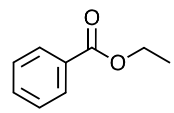
Objective 13. Apply nucleophilic addition and elimination concepts to enols and enolates reactions (aldol and Claisen condensations)

1. Consider the ketone and ester below.



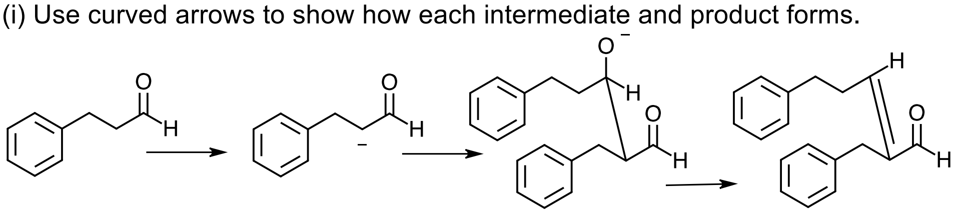
a. Circle the alpha carbon(s). Box the beta carbon(s).
b. The pK_a of an alpha carbon is between 16-20 for an RCHO or RCOR and > 20 for an ester. NaOH, NaOEt, and LDA are commonly used bases that reacts at the H bonded to the alpha carbon. LDA is the strongest base of the three.
(i) Write a chemical 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?
(i) 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?

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.

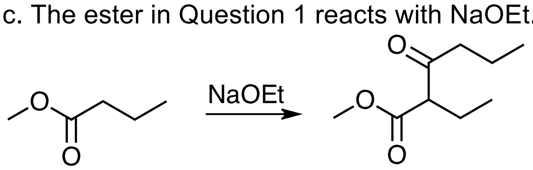
c. 
d. 
e. 

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.

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.



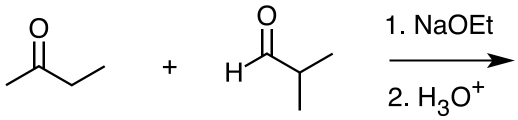
(ii) Circle the bond in the product that formed between the enolate and aldehyde.
b. The ketone (acetophenone) from Question 1 reacts with NaOEt. Use curved arrows to show how each intermediate and product forms.
c. The ester in Question 1 reacts with NaOEt. Use curved arrows to show how each intermediate and product forms.



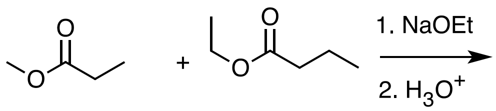
c. Mixed aldol-Claisen reactions: The ketone (acetophenone) in Question 1 reacts with the ester in Question 1 in the presence of NaOH. Draw the structure of the possible products.

4. Predict the product of each reaction.

a.

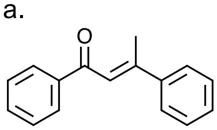


b.

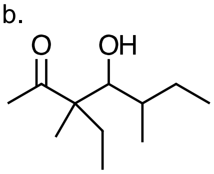


5. Synthesis: Draw the structure of the reactants to make each compound. State the reaction conditions.

a.

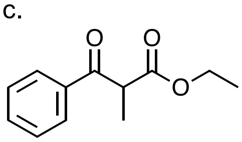


b.



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

c.



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