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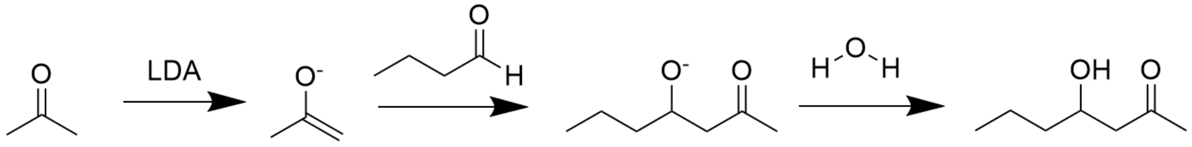
Chem 51C
Professor Van Vranken
https://sites.uci.edu/ochemtutors/

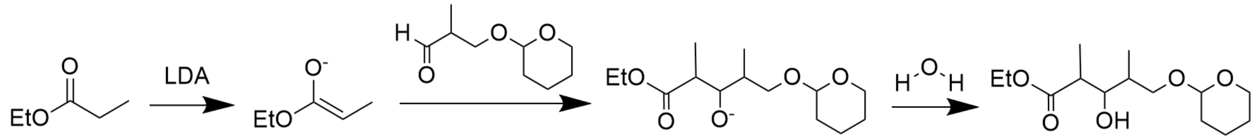
Week 8 Worksheet KEY

1. Draw the product formed in each directed aldol reaction. [Smith 6e 22.32]

a.



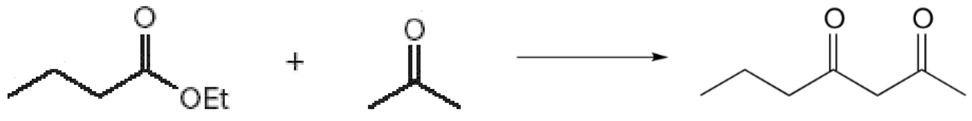
b.



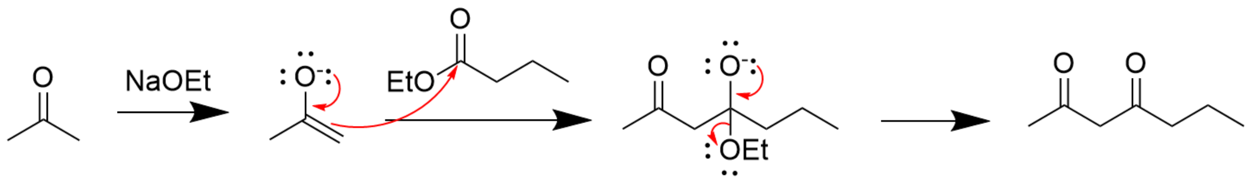
In both A and B, the enolate is formed first, which allows greater control of the subsequent carbonyl attack. A general pattern for the aldol reaction is to form the enolate on the first molecule, attack the carbonyl of a second molecule, then neutralize with water.

2. Draw the product formed from a Claisen reaction with the given starting materials using NaOEt (1 equivalent), EtOH. [Smith 6e 22.40]

a.

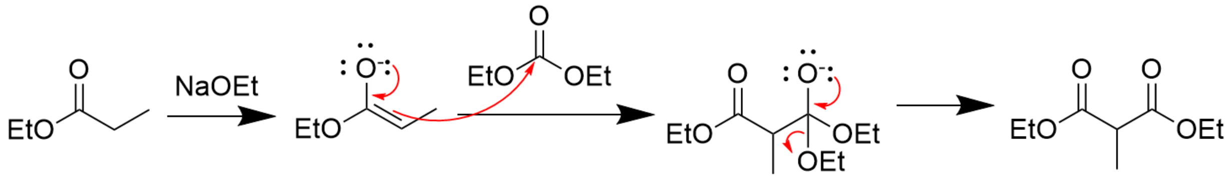


In this case, both molecules have α-hydrogens that can be removed, so there are two possible enolates. However, only one of them will lead to a Claisen reaction, which is the enolate formed by deprotonation of acetone. We can also check this intuition against standard pKas of α-H's: ketone α-H's have pKas around 20, while ester α-H's have pKas around 25, so acetone will be deprotonated 5 orders of magnitude more preferable than the ester. An arrow-pushing mechanism is shown below to illustrate the nature of the $^{-}$OEt leaving group:



b.

Considering this pair of molecules, only one of them has an α-H, so it is clear that the left molecule will form an enolate and attack the right molecule, displacing $^{-}$OEt. A more intricate mechanism is shown below:

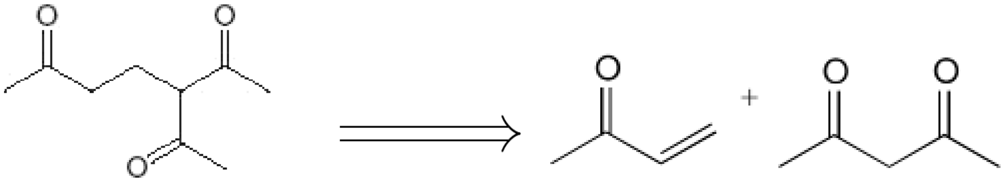


c.

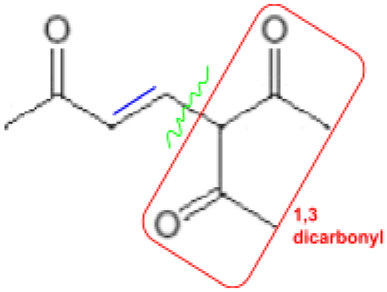
This pair of molecules follows the same pattern as before, where only one has an α-H; in this case, it is the left ester. Don't be fooled by the H on the right molecule; this is not an α-H, and is ineligible for deprotonation in this situation! Mechanistically, this will follow the same pattern as before: the enolate formed by the left molecule will attack the carbonyl on the right, and $^-$OEt will subsequently be displaced, leaving the final product shown above.

3. What starting materials are needed to prepare each compound using a Michael reaction? [Smith 6e 22.44]

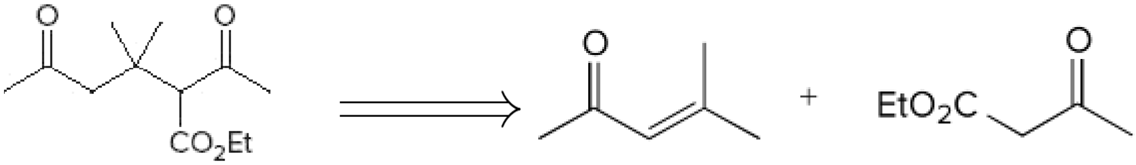
a.



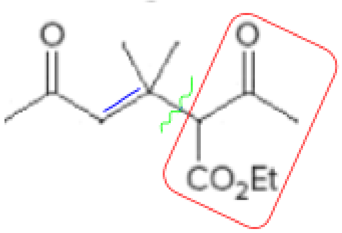
The Michael reaction involves a good enolate that attacks an α-β unsaturated carbonyl (i.e. a carbonyl conjugated with a double-bond) to generate a new C-C bond. A general strategy for identifying which portion should be the enolate and which should be the α-β unsaturated carbonyl is to locate a 1,3 dicarbonyl – this will serve as the enolate-forming compound. Then, cleave the bond connecting this segment to the rest of the molecule, which will clearly indicate the two starting compounds.



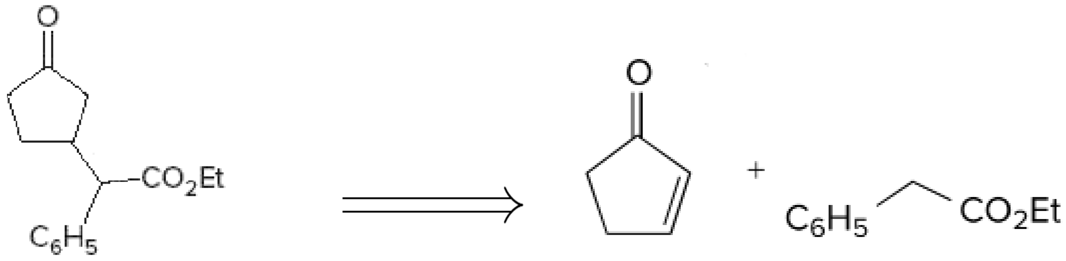
b.



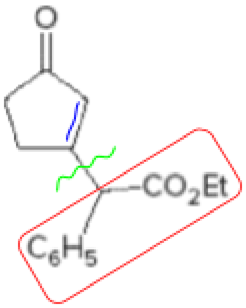
The same strategy can be employed here. The 1,3 dicarbonyl is circled in red; the bond to be cleaved is shown in green, and the location we should put the double bond to form the α-β unsaturated carbonyl is shown in blue.



c.

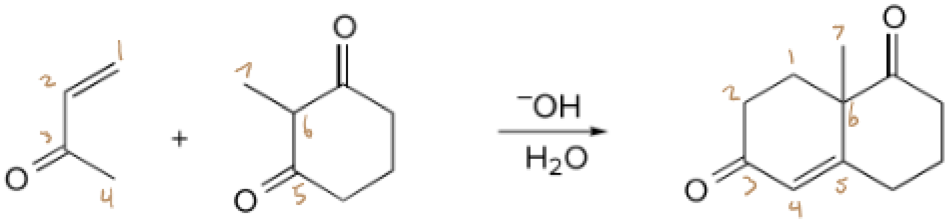


This molecule does not have a suitable 1,3 dicarbonyl portion we can isolate. However, we can still identify a portion that will form a good enolate, and based on that we can find the α-β unsaturated carbonyl.

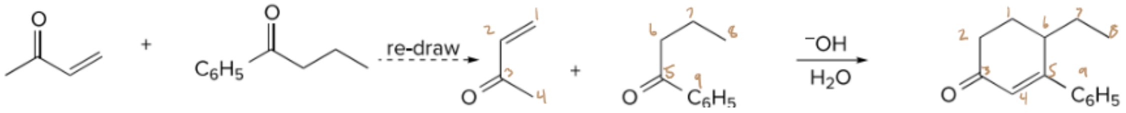


4. Draw the product of each Robinson annulation from the given starting materials using $^{-}$OH in H_2O solution.

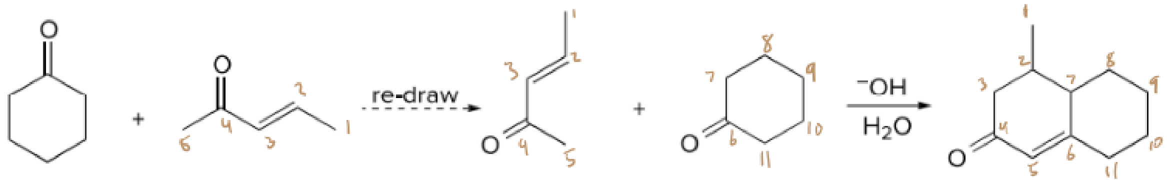
a.



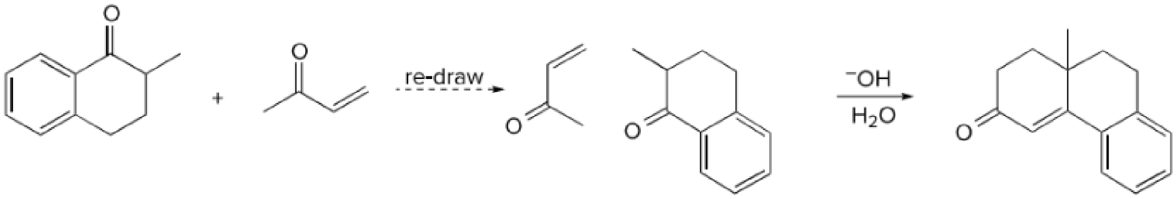
b.



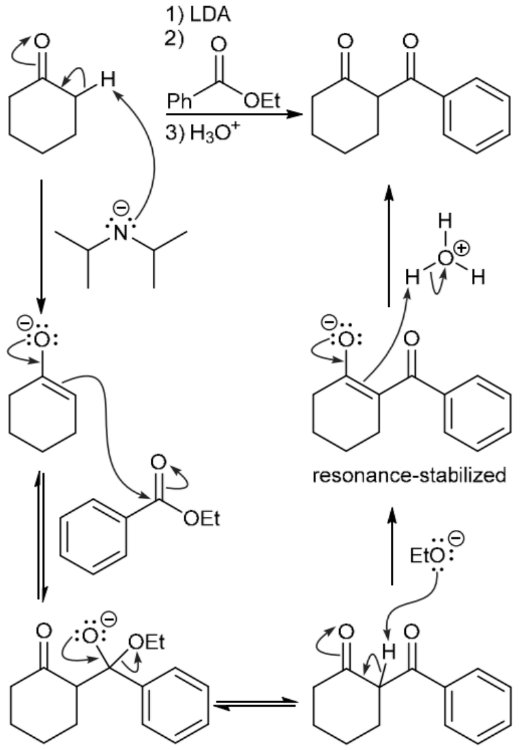
c.



d.

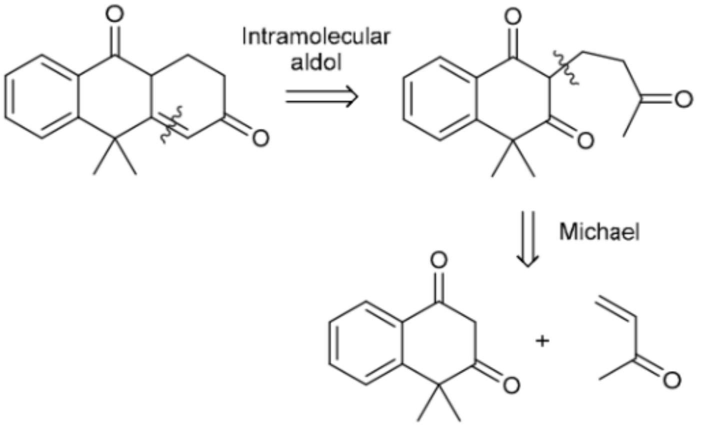


5. Draw a mechanism for this Claisen-like reaction. Why is the acid source required after the reaction is complete?



LDA is a strong sterically hindered base and irreversibly deprotonates the cyclohexanone at the α position to give an enolate. The ketone is symmetrical so deprotonation can occur at either α carbon, leading to the same enolate ion. When treated with the ester, the enolate ion attacks the ester to give a tetrahedral intermediate, reforming the carbonyl group by expelling ethoxide. The resulting compound is then deprotonated to provide a stabilized enolate. The formation of this resonance-stabilized anion is a driving force of this reaction. <u>After the reaction, the acid is required to protonate this anion!</u>

6. Identify reactants and reagents that can be used to make the following compound with a Robinson annulation reaction:



A Robinson annulation comprises of a Michael reaction followed by an intramolecular aldol condensation. The retrosynthetic analysis was drawn above to determine the starting materials necessary to prepare the desired product via a Robinson annulation.