9.9: MIXED CLAISEN CONDENSATIONS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate a mixed Claisen condensation.
2. identify the structural features that should be present in the two esters if a mixed Claisen condensation is to be successful.
3. determine whether a given pair of esters is likely to produce a good yield of a single product when subjected to a mixed Claisen condensation.
4. identify the product formed when a given pair of esters is used in a mixed Claisen condensation.
5. identify the esters that should be used to produce a given β-keto ester by a mixed Claisen condensation.
6. write an equation to illustrate the formation of a β-diketone through a mixed Claisen-type condensation between an ester and a ketone.
7. identify the β-diketone formed as the result of a mixed Claisen-type condensation between a given ester and a given ketone.
8. identify the reagents necessary to synthesize a given β-diketone by a mixed Claisen-type condensation between an ester and a ketone.
9. write detailed mechanisms for mixed Claisen reactions and reactions that are related to the mixed Claisen reaction, including those in which both reacting moieties are present in the same compound.

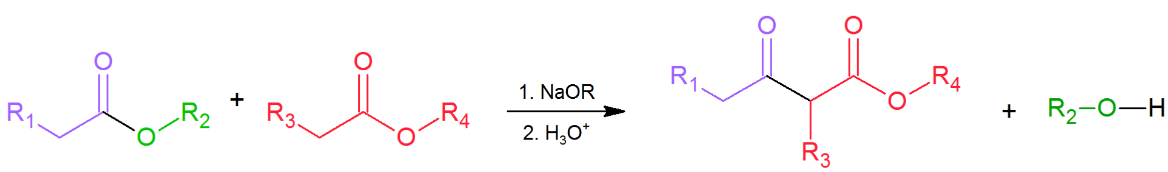
STUDY NOTES

Just as we can react together two different aldehydes or ketones in a mixed aldol condensation, so can we react together two different esters in a mixed (or “crossed”) Claisen condensation. Again, by carefully selecting our substrates we can obtain a good yield of the desired product and minimize the number of possible by-products. Note that even if we replace one of the esters with a ketone, the reaction is still referred to as Claisen condensation. The important thing to realize as you study these reactions is that they all take place by essentially the same mechanism—attack by an enolate anion on a carbonyl group.

CROSSED CLAISEN CONDENSATION

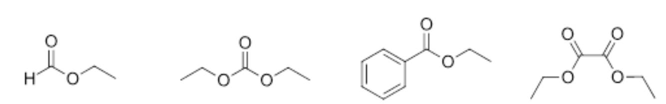
Claisen condensations between different ester reactants are called **Crossed Claisen** reactions. Crossed Claisen reactions in which both reactants can serve as Claisen donors and Claisen acceptors generally give complex mixtures which are difficult to separate.

General Reaction



ester ester β keto-ester alcohol

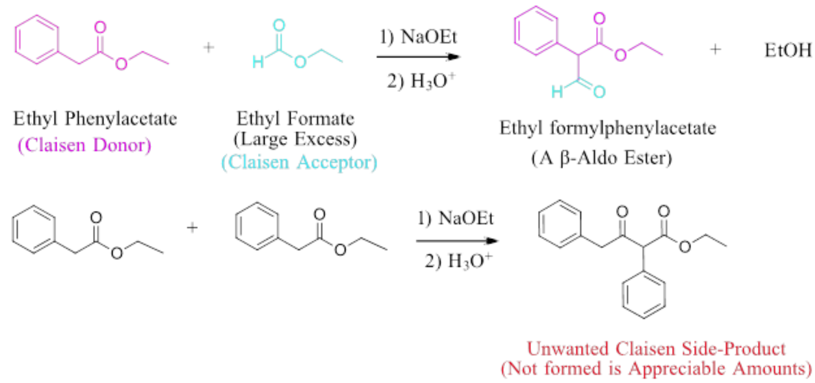
To avoid complex mixtures most Crossed Claisen reactions are usually not successful unless one of the two esters has no alpha-hydrogens as in the following examples.



Ethyl Formate Diethyl Carbonate Ethyl Benzoate Diethyl Oxalate

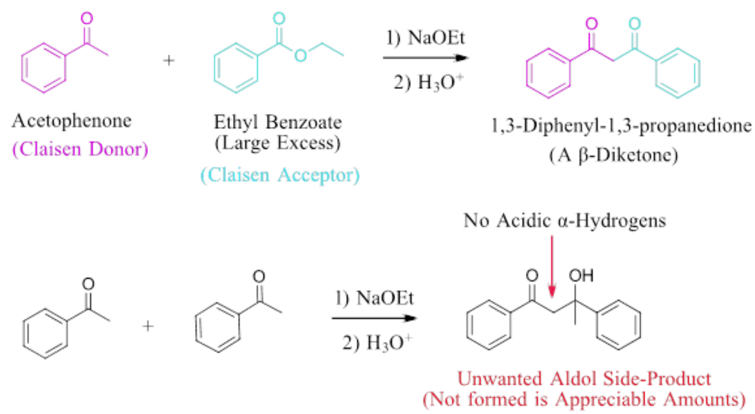
This forces the ester with alpha-hydrogens to be the Claisen donor (enolate) and the ester without alpha-hydrogens to be the Claisen acceptor (electrophile). Even with this differentiation, it is possible for the ester with alpha-hydrogens to undergo a Claisen Condensation with itself to produce an unwanted side-product. This is typically partially prevented by using the ester without alpha-hydrogens in a large excess.

Example - no alpha hydrogens



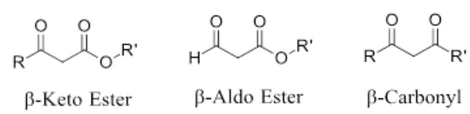
Another type of crossed Claisen condensation occurs when a ketone is reacted with an ester. The use of an ester without alpha-hydrogens is not necessary due to the greater reactivity of the ketone. The alpha-hydrogens of the ketone are much more acidic (pKa~20) than those of the ester (pKa~25). The alpha hydrogens of ketone will be preferably deprotonated to make it the enolate Claisen donor. The ester will therefore be the electrophilic Claisen acceptor and is likewise commonly used in a large excess. There is still a possibility of the ketone reacting with itself to form the product of an aldol reaction however the equilibrium is unfavorable. Also, the formation of the aldol product is reversible due to its lack of an acidic alpha hydrogen. The beta-diketone Claisen product can be irreversibly deprotonated due to its more acidic alpha-hydrogens, making it the reaction's main product.

Example - ester with ketone



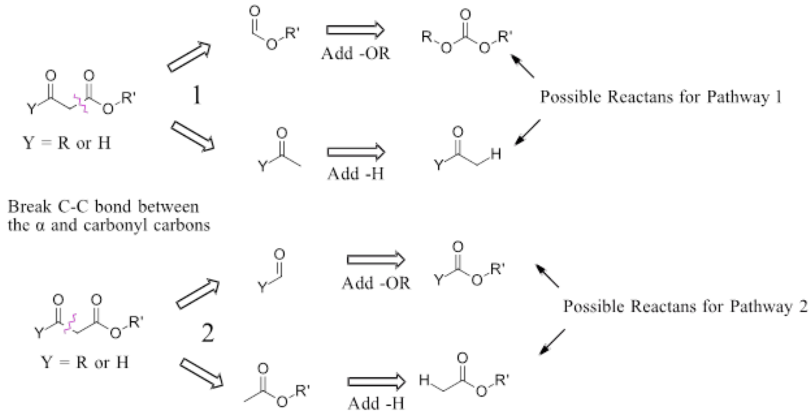
Planing a Synthesis using a Claisen or Crossed Claisen-like Reaction

A Claisen reaction should be considered for a synthesis pathway if the target molecule contains a beta-keto esters, a beta-aldo ester or a beta-dicarbonyl.



A beta-keto ester or a beta-aldo ester could possibly be made by a Claisen condensation of two esters. A beta-dicarbonyl could possibly be made by a Claisen-like condensation between a ketone and an ester. Here, the key bond cleavage is a C-C bond between one of the carbonyls and the alpha-carbon which lies between the carbonyl. In each of these situations there are two such C-C bonds so there will be two possible pathways to consider. After the C-C bond cleavage the fragment with the alpha-carbon will gain a hydrogen. The fragment with the bare carbonyl will gain an –OR group to become an ester. The –OR group added will be the same as any ester present in the target molecule. If none are present $–OCH_2CH_3$ is typically used.

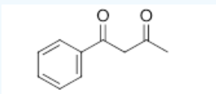
Analysis for Beta-Keto and Aldo Esters



A similar analysis can be performed on a 1,3-diketone and will be presented in the worked example below.

? WORKED EXAMPLE

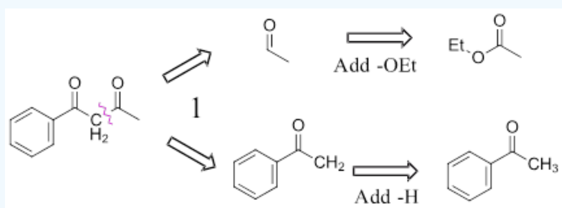
Show how the following molecule can be made using a Claisen-like condensation.



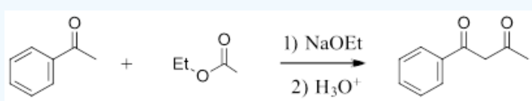
1-Phenyl-1,3-butanedione

Answer

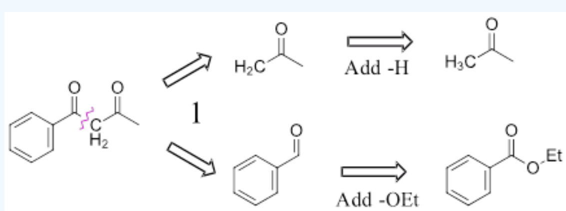
Pathway 1



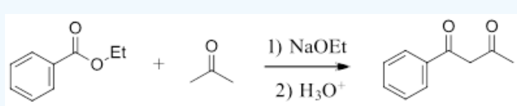
Solution 1



Pathway 2



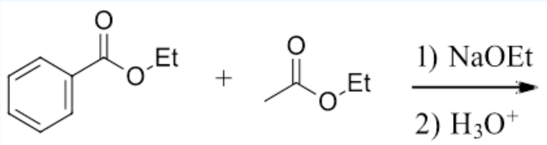
Solution 2



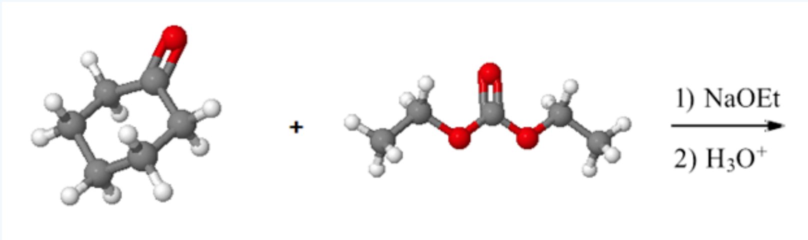
? EXERCISES 9.9.1

Draw the product of the following reactions:

a)

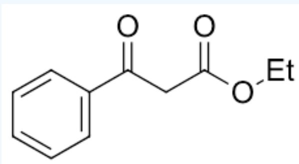


b)



Answers

a)



b)