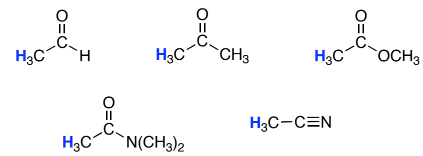
Chapter 21: Ester Enolates

21.1: Ester α Hydrogens and Their pK_a's. The α-protons of esters are less acidic that ketones and aldehydes.

Typical pK_a's of carbonyl compounds (α-protons):

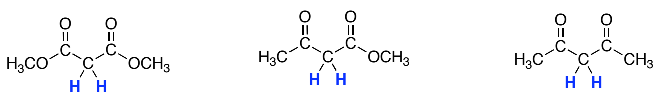
aldehydes	17
ketones	19
esters	24
amides	30
nitriles	25



Acidity of 1,3-dicarbonyl compounds

ester
pK_a= 24

ketone
pK_a= 19



1,3-diester
pK_a= 13

1,3-keto ester
pK_a= 11

1,3-diketone
pK_a= 9

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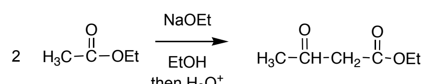
21.2: The Claisen Condensation Reaction. Base-promoted condensation of two esters to give a β-keto-ester product



Ethyl acetate

Ethyl 3-oxobutanoate
(Ethyl acetoacetate)

Mechanism (Fig. 21.1, page 884-5) is a nucleophilic acyl substitution of an ester by an ester enolate and is related to the mechanism of the aldol condensation.

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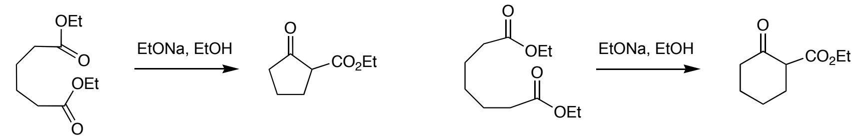
21.3: Intramolecular Claisen Condensation: The Dieckmann Cyclization.

Dieckmann Cyclization works best with 1,6-diesters, to give a 5-membered cyclic β-keto ester product, and 1,7-diesters to give 6-membered cyclic β-keto ester product.



Mechanism: same as the Claisen Condensation

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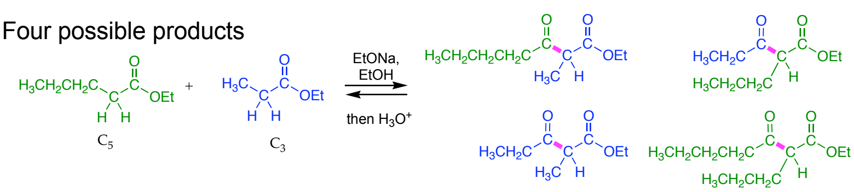
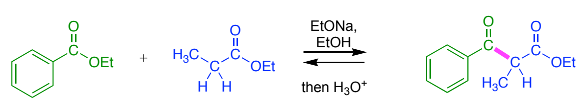
21.4: Mixed Claisen Condensations.

Similar restrictions as the mixed aldol condensation.

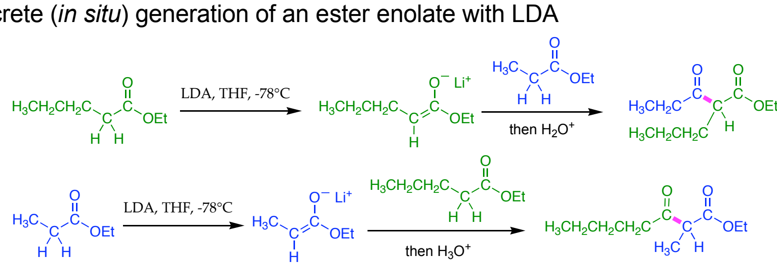
Four possible products



Esters with no α-protons can only act as the electrophile



Discrete (*in situ*) generation of an ester enolate with LDA



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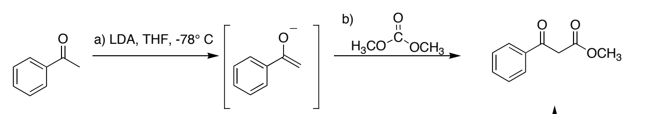
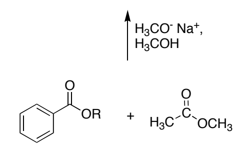
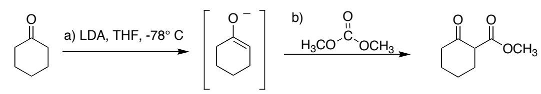
21.5: Acylation of Ketones with Esters. An alternative to the Claisen condensations and Dieckmann cyclization.

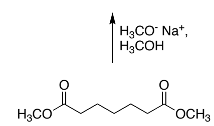


Equivalent to a mixed Claisen condensation

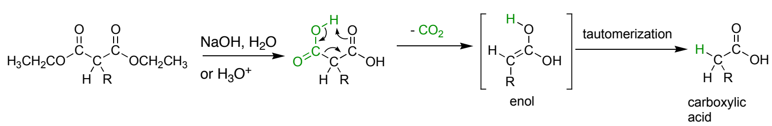


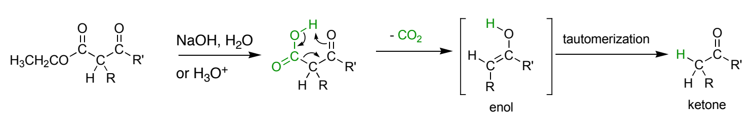


Equivalent to a Dieckmann cyclization

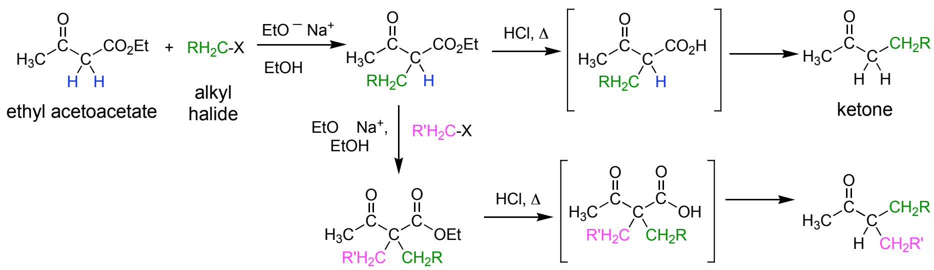


21.6: Ketone Synthesis via β-Keto Esters. The β-keto ester products of a Claisen condensation or Dieckmann cyclization can be hydrolyzed to the β-keto acid and decarboxylated to the ketone.





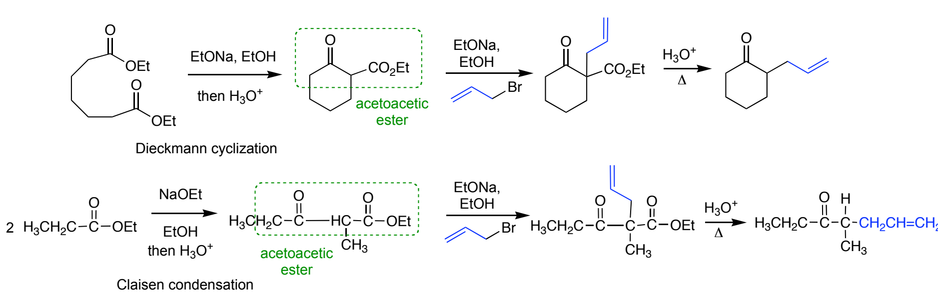
21.7: Acetoacetic Ester Synthesis. The anion of ethyl acetoacetate can be alkylated using an alkyl halide (S_N2). The product, a β-keto ester, is then hydrolyzed to the β-keto acid and decarboxylated to the ketone.



An acetoacetic ester can undergo one or two alkylations to give an α-substituted or α-disubstituted acetoacetic ester

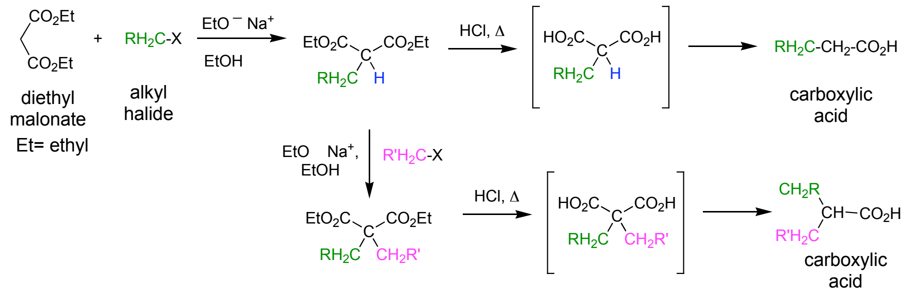
The enolates of acetoacetic esters are synthetic equivalents to ketone enolates

β-Keto esters other than ethyl acetoacetate may be used. The products of a Claisen condensation or Dieckmann cyclization are acetoacetic esters (β-keto esters)



21.8: The Malonic Acid Synthesis.

overall reaction



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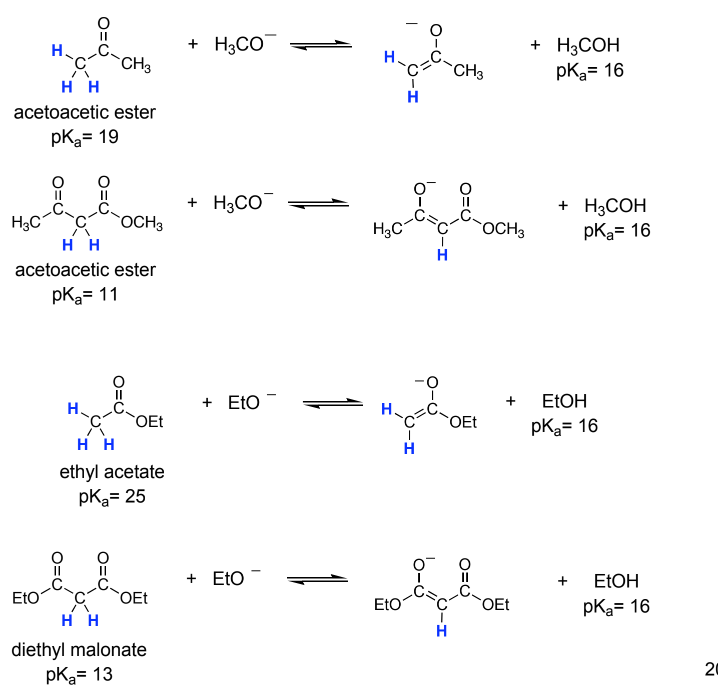

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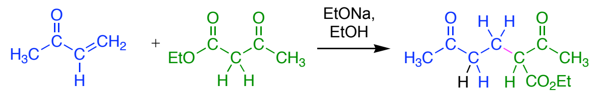
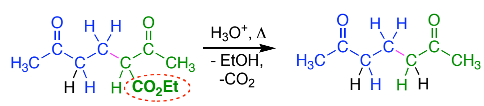
Summary:
Malonic ester synthesis: equivalent to the alkylation of a carboxylic (acetic) acid enolate
Acetoacetic ester synthesis: equivalent to the alkylation of an ketone (acetone) enolate

21.9: Michael Addition of Stablized Anions. Enolates of malonic and acetoacetic esters undergo Michael (1,4-) addition to α,β-unsaturated ketones.



This Michael addition product can be decarboxylated



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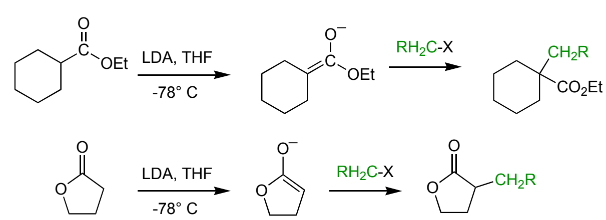
21.10: Reactions of LDA-Generated Ester Enolates. Ester enolates can be generated with LDA in THF rapidly and quantitatively. The resulting enolates can undergo carbonyl addition reactions with other esters, aldehydes, ketones or alkylation reactions with alkyl halides or tosylates.



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