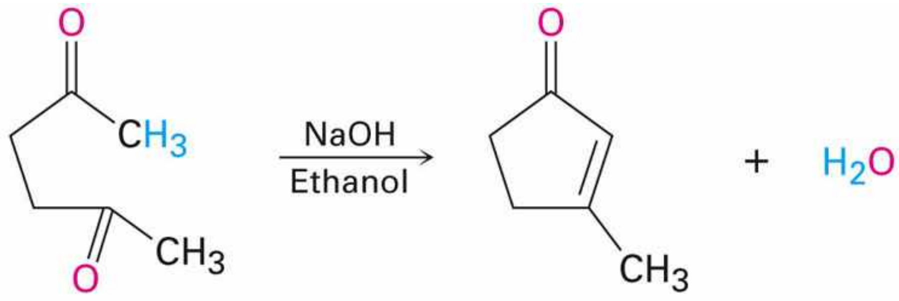
열한번째주

Carbonyl Condensation Reactions (2)

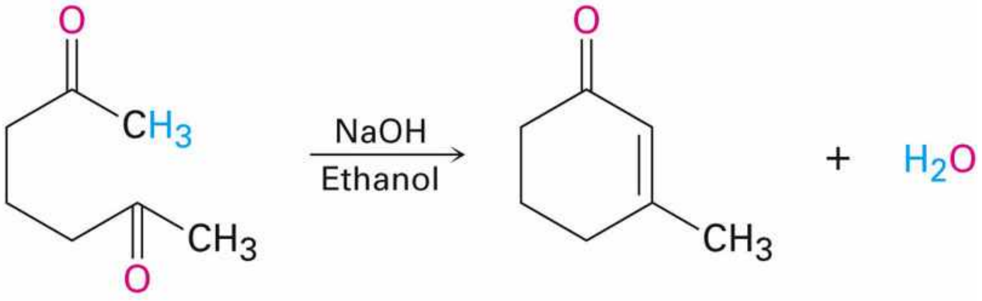
Intramolecular Aldol Reactions

- Treatment of certain *di*carbonyl compounds with base produces cyclic products by intramolecular reaction



2,5-Hexanedione
(a 1,4-diketone)

3-Methyl-2-cyclopentenone

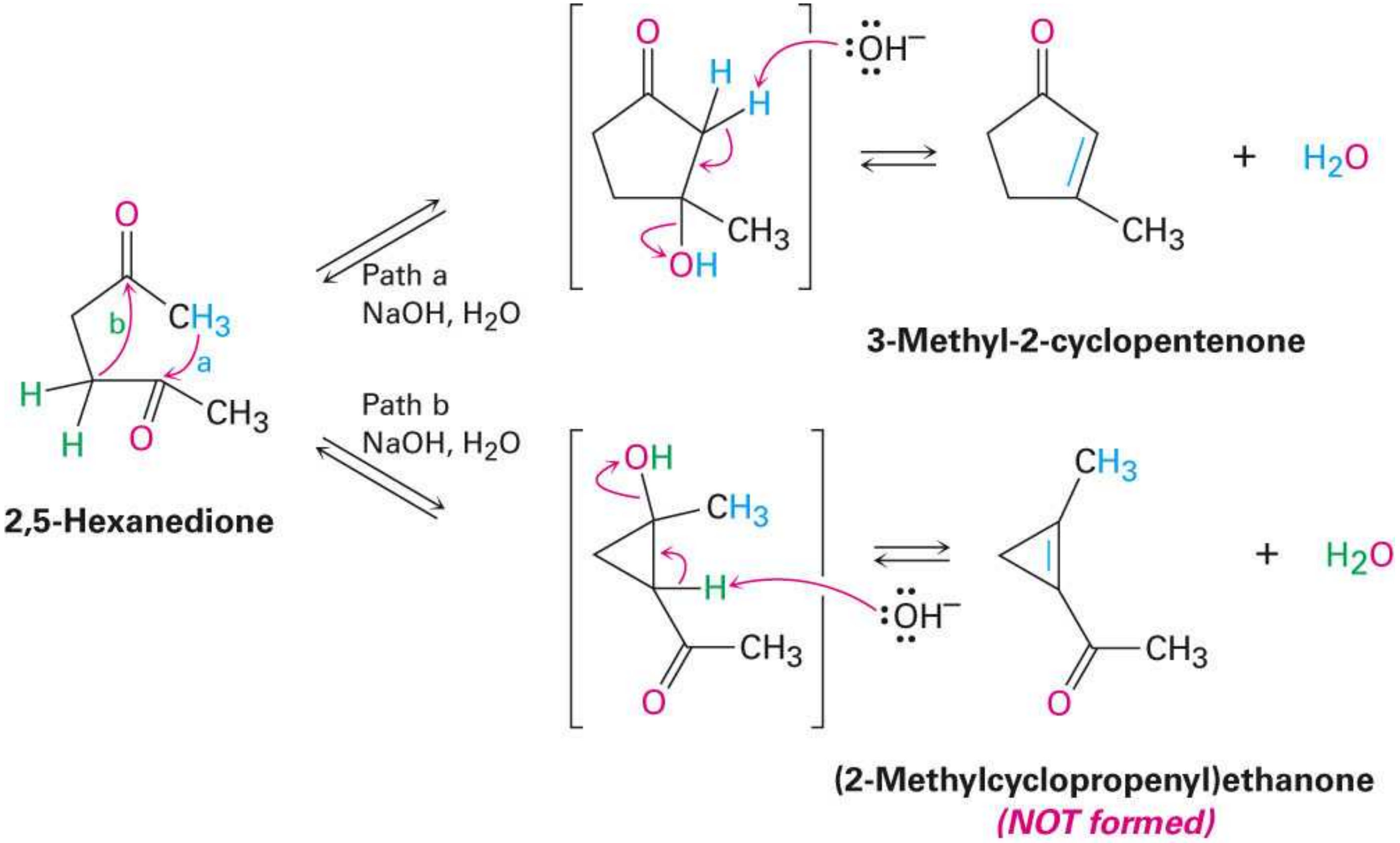


2,6-Heptanedione
(a 1,5-diketone)

3-Methyl-2-cyclohexenone

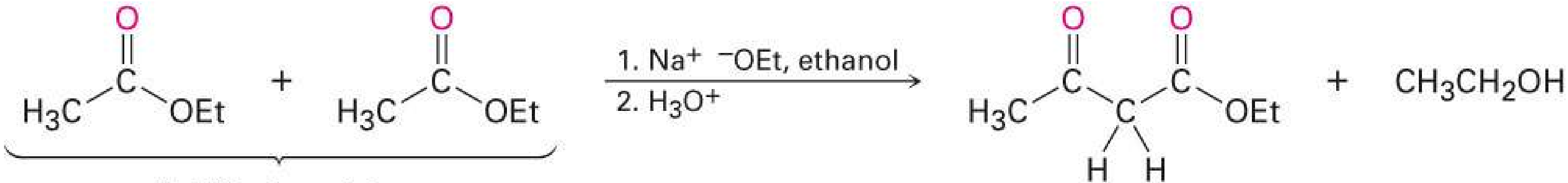
Mechanism of Intramolecular Aldol Reactions

- Both the nucleophilic carbonyl anion donor and the electrophilic carbonyl acceptor are now in the same molecule.
- The least strained product is formed because the reaction is reversible



Claisen Condensation Reaction

- Reaction of an ester having an α hydrogen with 1 equivalent of a base to yield a β-keto ester



2 Ethyl acetate

**Ethyl acetoacetate,
a β-keto ester (75%)**

Mechanism of the Claisen Condensation

- Similar to aldol condensation: nucleophilic acyl substitution of an ester enolate ion on the carbonyl group of a second ester molecule

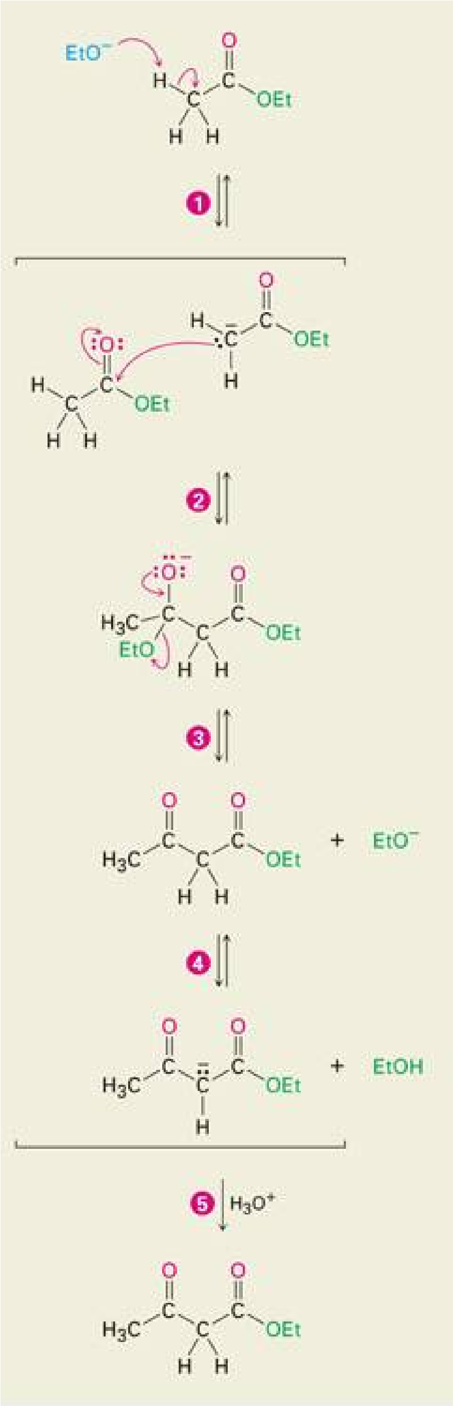
1. Base abstracts an acidic alpha hydrogen atom from an ester molecule, yielding an ester enolate ion.

2. The enolate ion adds in a nucleophilic addition reaction to second ester molecule, giving a tetrahedral alkoxide intermediate.

3. The tetrahedral intermediate expels ethoxide ion to yield a new carbonyl compound, ethyl acetoacetate.

4. But, ethoxide ion is a strong enough base to deprotonate ethyl acetoacetate, shifting the equilibrium and driving the overall reaction to completion.

5. Protonation of athe enolate ion by addition of aqueous acid in a separate step yields the final β-keto ester product.



Features of the Claisen Condensation

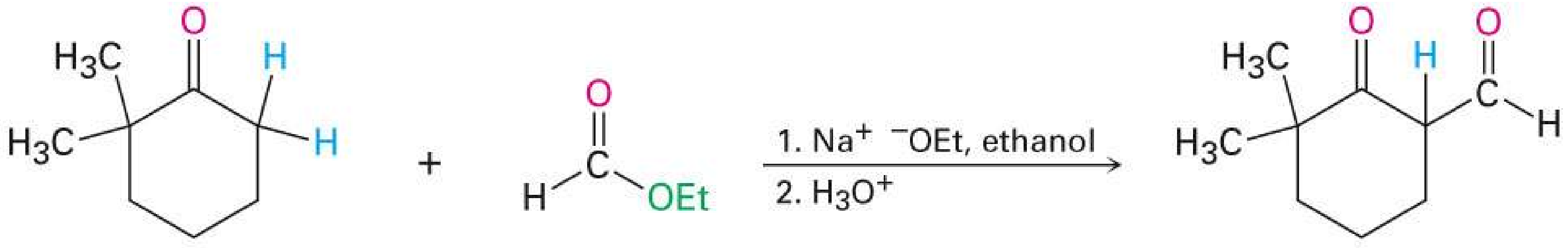
- If the starting ester has more than one acidic a hydrogen, the product β-keto ester has a doubly activated proton that can be abstracted by base
- Requires a full equivalent of base rather than a catalytic amount
- The deprotonation drives the reaction to the product

Mixed Claisen Condensations

- Successful when one of the two esters acts as the electrophilic acceptor in reactions with other ester anions to give mixed β-keto esters

Esters and Ketones

- Reactions between esters and ketones, resulting in β-diketones
- Best when the ester component has no α hydrogens and can't act as the nucleophilic donor



2,2-Dimethylcyclohexanone
(donor)

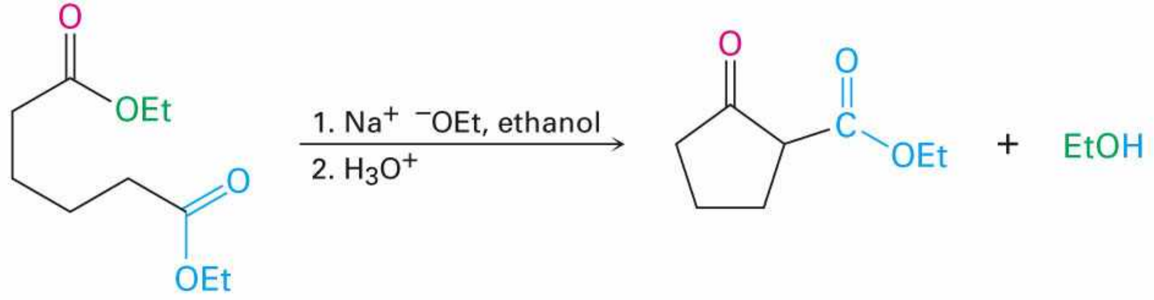
Ethyl formate
(acceptor)

A *β*-keto aldehyde
(91%)

Intramolecular Claisen Condensations

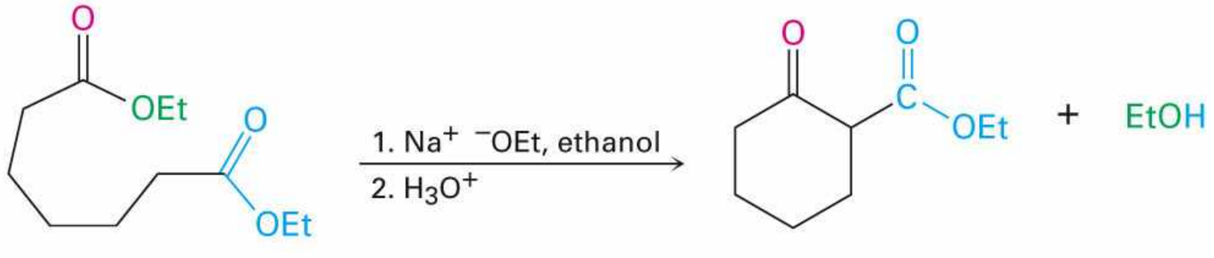
Dieckmann Cyclization

- Intramolecular Claisen condensation
- Best with 1,6-diesters (product: 5-membered β-ketoester) and 1,7-diesters (product: 6-membered β-ketoester)



Diethyl hexanedioate
(a 1,6-diester)

Ethyl 2-oxocyclopentanecarboxylate
(82%)



Diethyl heptanedioate
(a 1,7-diester)

Ethyl 2-oxocyclohexanecarboxylate

Mechanism of the Dieckmann Cyclization

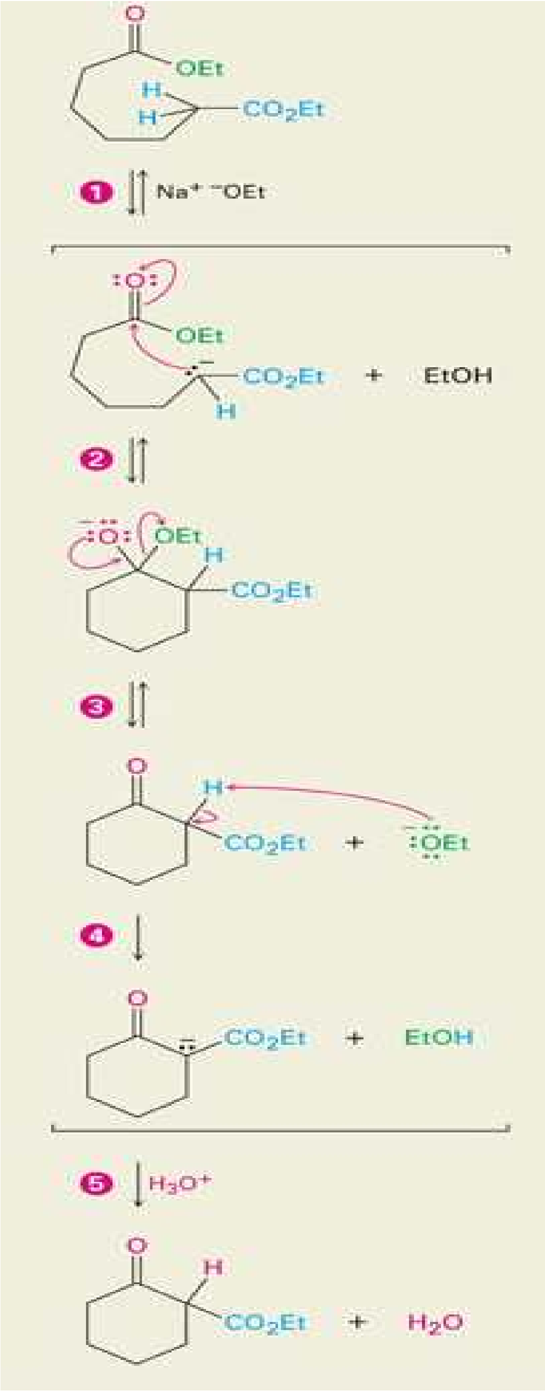
1. Base abstracts an acidic alpha hydrogen atom from an ester molecule, yielding an ester enolate ion.

2. Intramolecular nucleophilic addition of the ester enolate ion to the carbonyl group of the second ester at the other end of the chain then tives a cyclic tetrahedral intermediate.

3. Loss of alkoxide ion from the tetrahedral intermediate forms a cyclic β-keto ester.

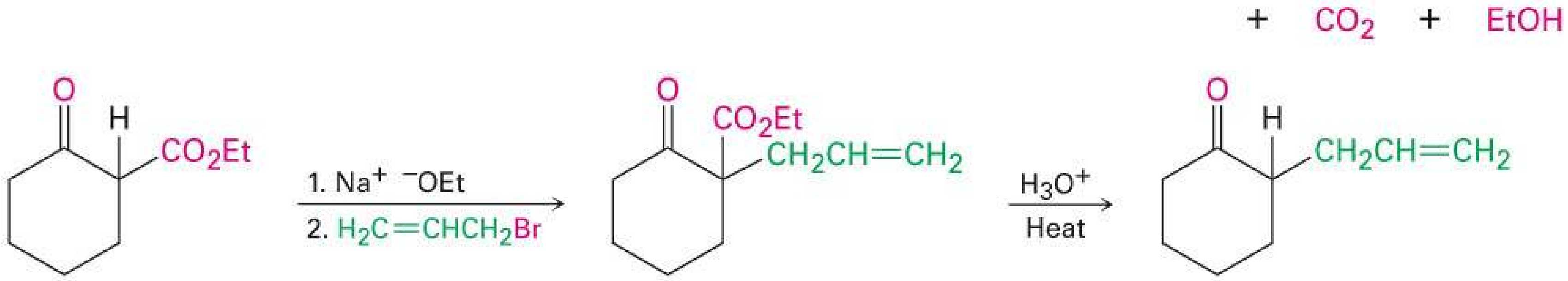
4. Deprotonation of the acidic β-keto ester gives an enolate ion…

5. … which is protonated by addition of aqueous acid at the end of the reaction to generate the neutral β-keto ester product.



Alkylation of Dieckmann Product

- The cyclic β-keto ester can be further alkylated and decarboxylated as in the acetoacetic ester synthesis

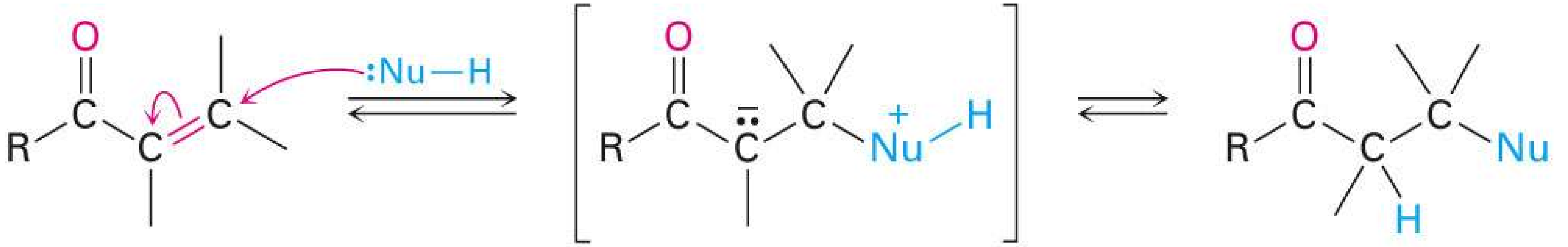


Ethyl 2-oxocyclohexanecarboxylate

2-Allylcyclohexanone (83%)

Conjugate Carbonyl Additions: The Michael Reaction

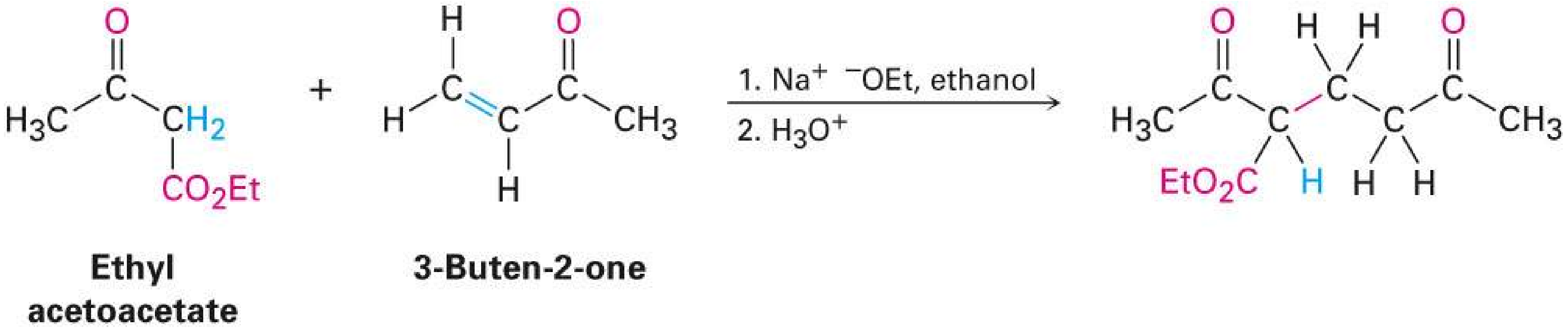
- Enolates can add as nucleophiles to α,β-unsaturated aldehydes and ketones to give the conjugate addition product



Conjugate addition product

Best Conditions for the Michael Reaction

- When a particularly stable enolate ion
- Example: Enolate from a β-keto ester or other 1,3-dicarbonyl compound adding to an unhindered α,β-unsaturated ketone



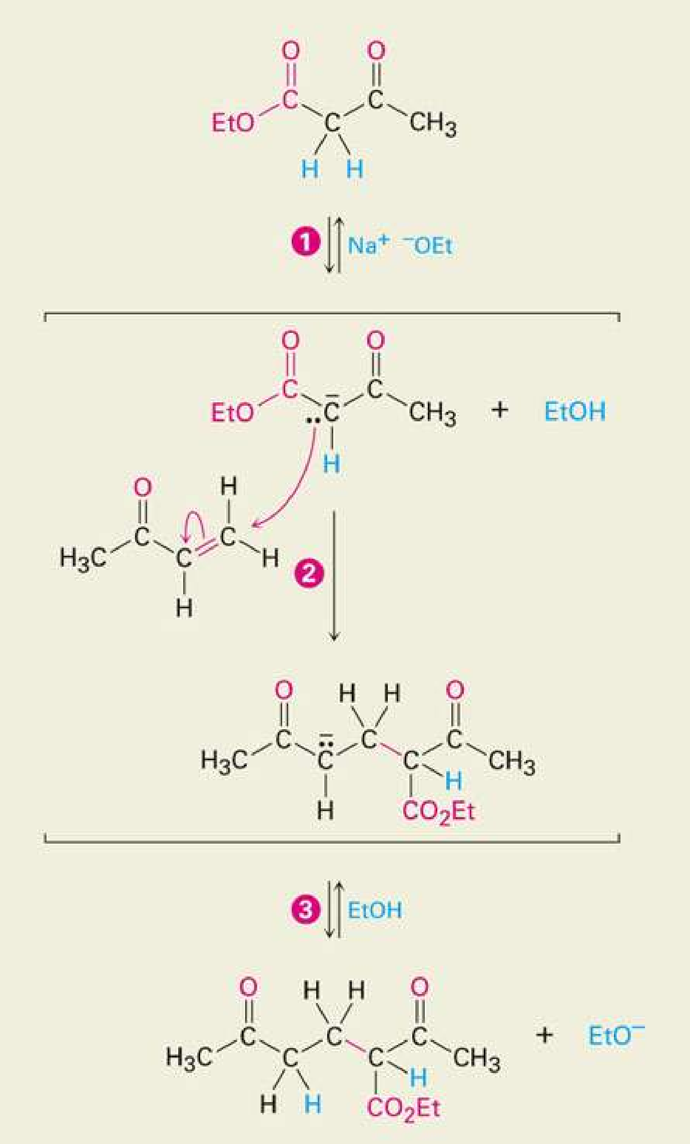
Mechanism of the Michael Reaction

- Nucleophilic addition of a enolate ion donor to the β carbon of an α,β-unsaturated carbonyl acceptor

1. The base catalyst removes an acidic alpha proton from the starting β-keto ester to generate a stabilized enolate ion nucleophile.

2. The nucleophile adds to the β-unsaturated ketone electrophile in a Michael reacton to generate a new enolate as product.

3. The enolate product abstracts an acidic proton, either from solvent or from starting keto ester to yield the final addition product



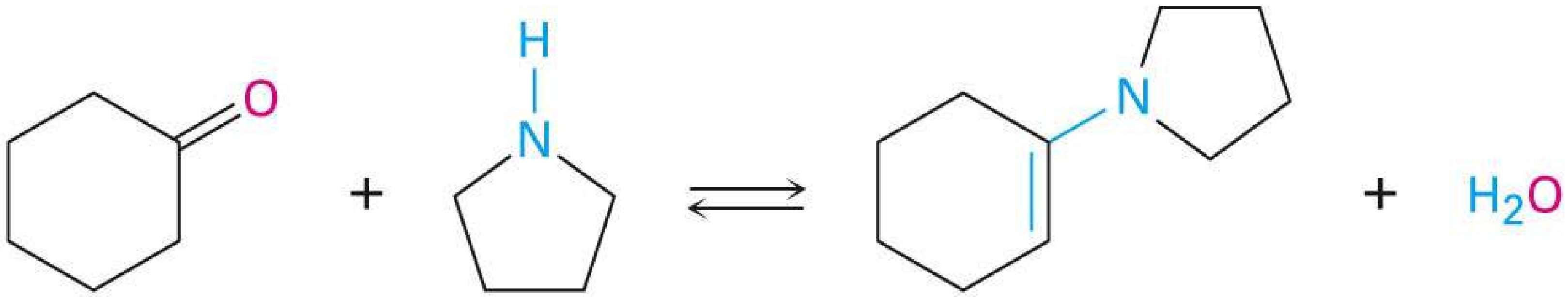
Generality of the Michael Reaction

- Occurs with a variety of α,β-unsaturated carbonyl compounds (aldehydes, esters, nitriles, amides, and nitro compounds)
- Donors include β-diketones, β-keto esters, malonic esters, β-keto nitriles, and nitro compounds

Carbonyl Condensations with Enamines:

The Stork Reaction

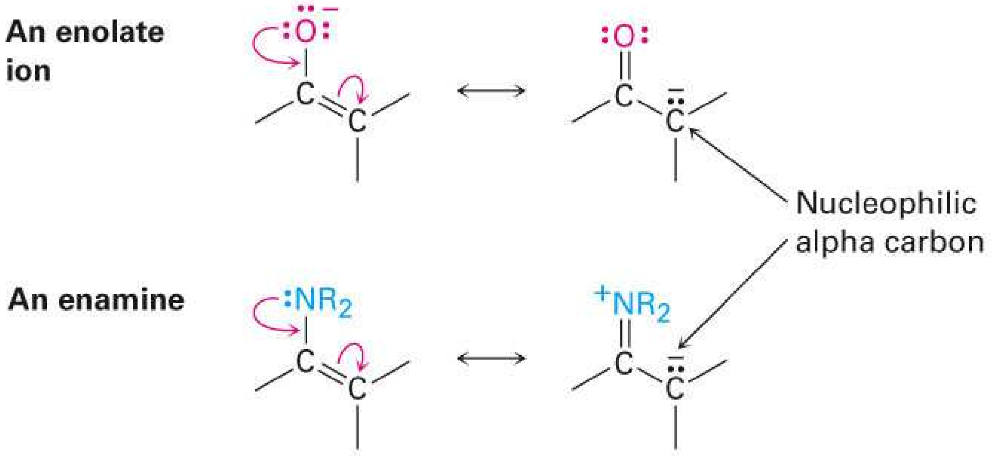
- Enamines are equivalent to enolates in their reactions and can be used to accomplish the transformations under milder conditions
- Enamines are prepared from a ketone and a secondary amine

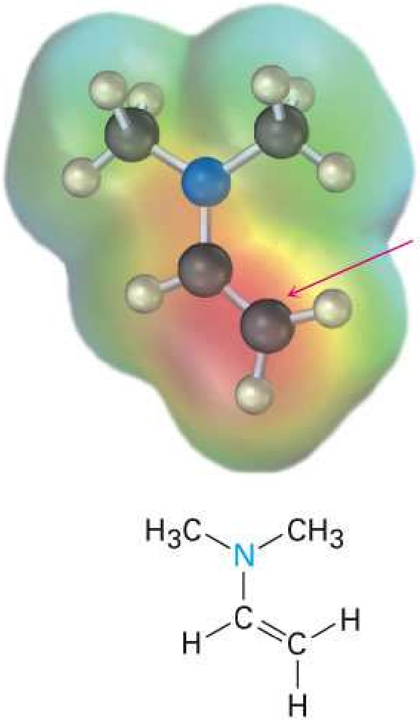


Cyclohexanone **Pyrrolidine** **1-Pyrrolidino-cyclohexene (87%)**

Enamines Are Nucleophilic

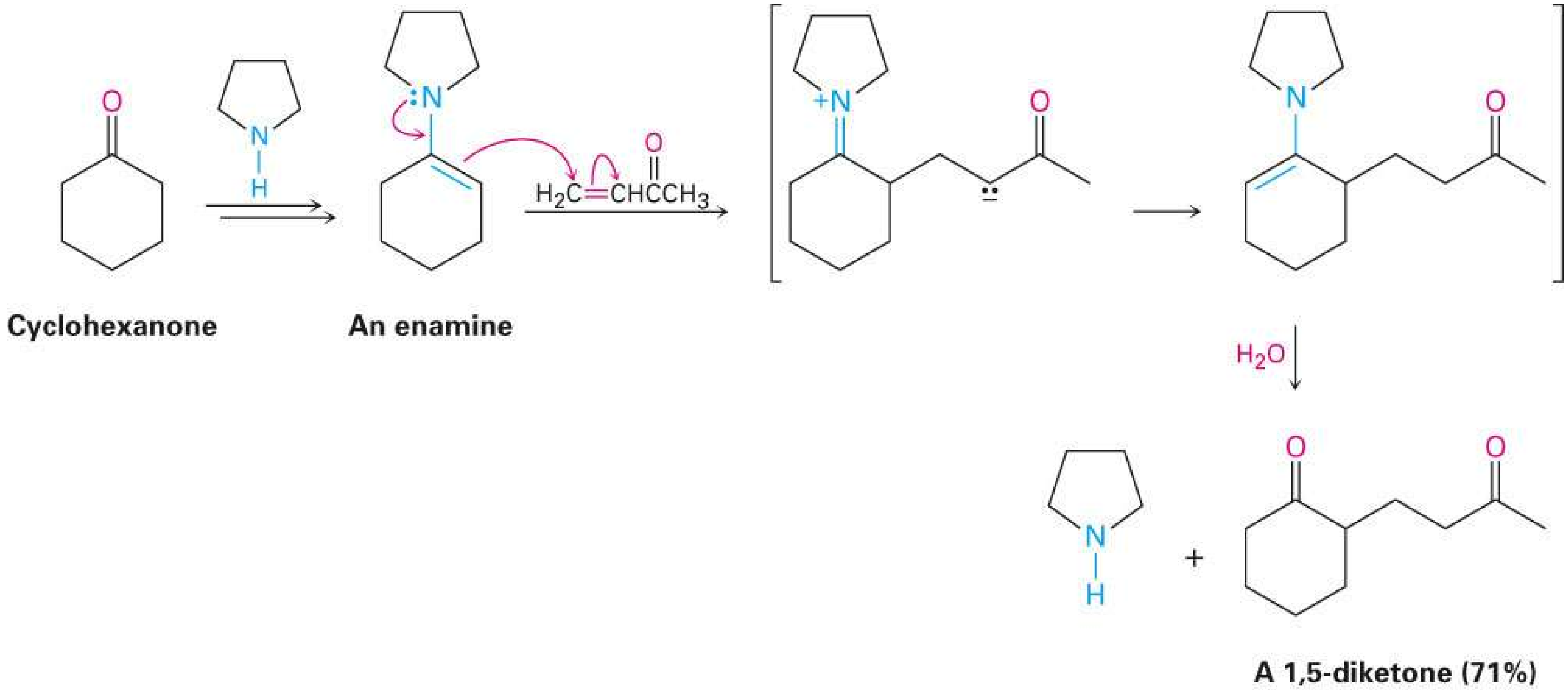
- Overlap of the nitrogen lone-pair orbital with the double-bond π orbitals increases electron density on the α carbon atom





Enamine Addition and Hydrolysis

- Enamine adds to an α,β-unsaturated carbonyl acceptor
- The product is hydrolyzed to a 1,5-dicarbonyl compound



Robinson Annulation Reaction

- A two-step process: combines a Michael reaction with an intramolecular aldol reaction
- The product is a substituted 2-cyclohexenone