

Chap 11. Carbonyl Alpha-Substitution Reactions and Condensation Reactions

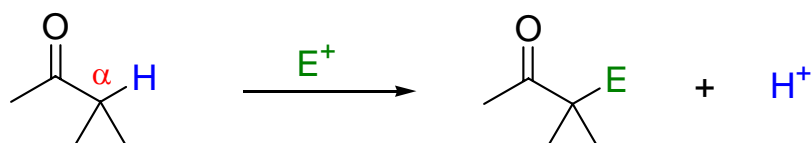
Four fundamental reactions of carbonyl compounds

1) Nucleophilic addition (aldehydes and ketones)

2) Nucleophilic acyl substitution (carboxylic acid derivatives)

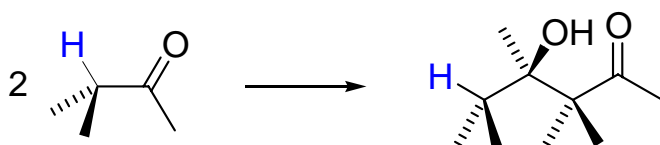
3) The alpha-substitution

Reactions occur at the position next to the carbonyl group—the alpha position—and result in the substitution of an α hydrogen atom by some other electrophilic group, E^+ :

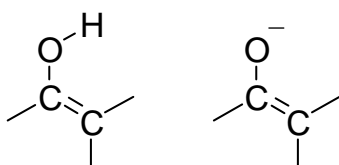


4) The carbonyl condensation

Reactions take place when two carbonyl compounds react with each other in such a way that the α carbon of one partner becomes bonded to the carbonyl carbon of the second partner.



The key feature of the reactions (3, 4) is that they take place through the formation of either **enol** or **enolate ion** intermediates.

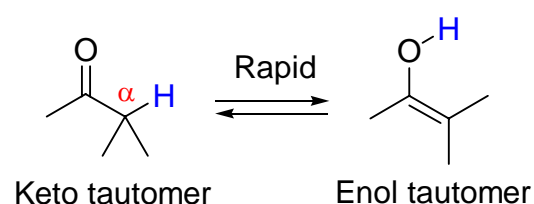


11.1 Keto-Enol Tautomerism

The interconversion between the keto and enol forms of carbonyl compounds is a special kind of isomerism called **tautomerism**.

In Greek, tauto means “the same,” and meros means “part.”

The interconversion of **tautomers** involves **the movement of atoms (H)**, so they are different from resonance forms.

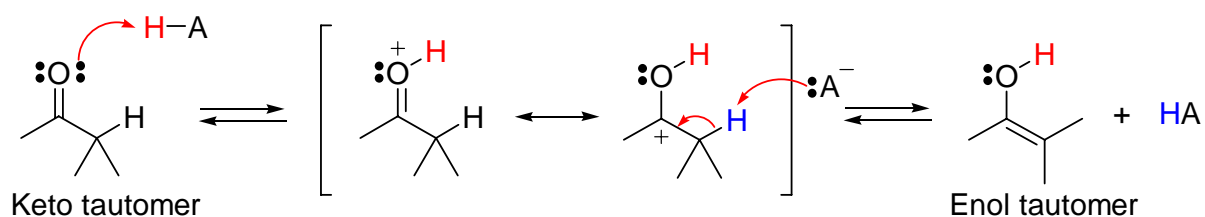


Most carbonyl compounds exist almost entirely in the keto form at equilibrium.

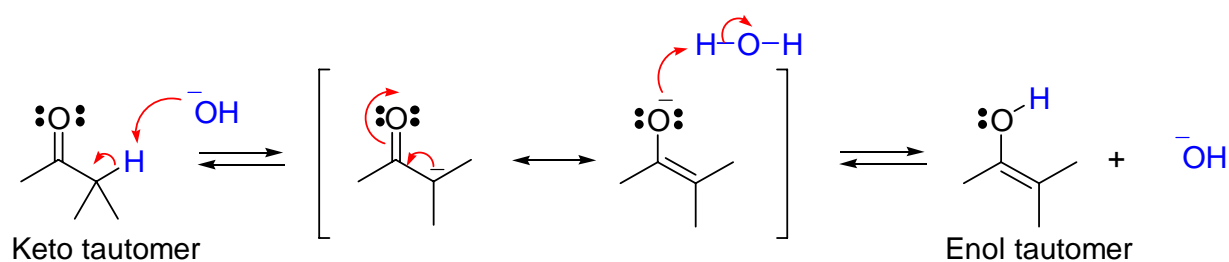


Mechanism of keto-enol tautomerism

Acid catalysis

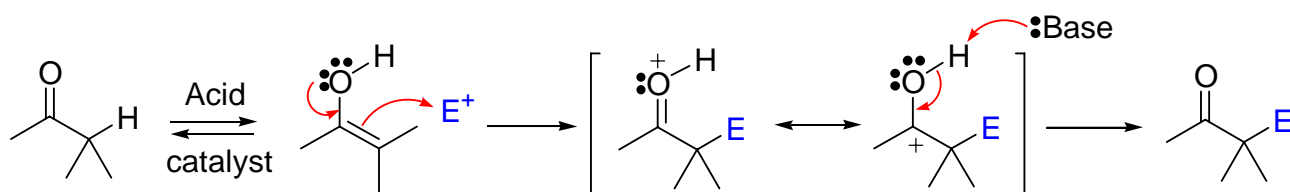
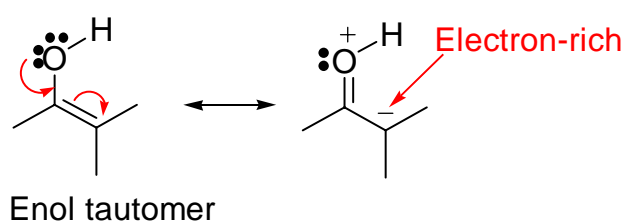


Base catalysis



11.2 Reactivity of Enols: The Mechanism of Alpha-Substitution Reactions

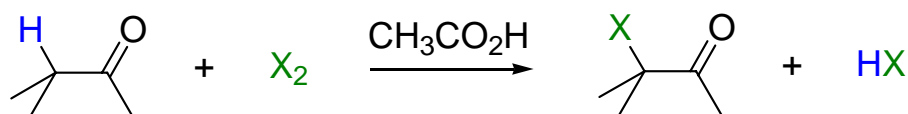
Since their double bonds are electron-rich, enols behave as nucleophiles and react with electrophiles in the same way as alkenes do.



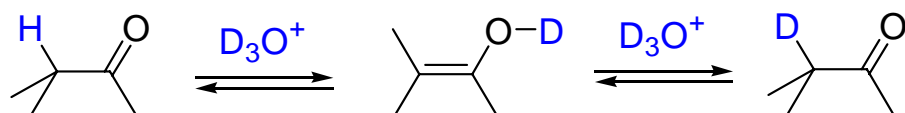
The addition step is the same as that of alkene but the intermediate cation loses the $-OH$ proton to regenerate a carbonyl compound. The net result of the reaction is α substitution.

11.3 Alpha Halogenation of Aldehydes and Ketones

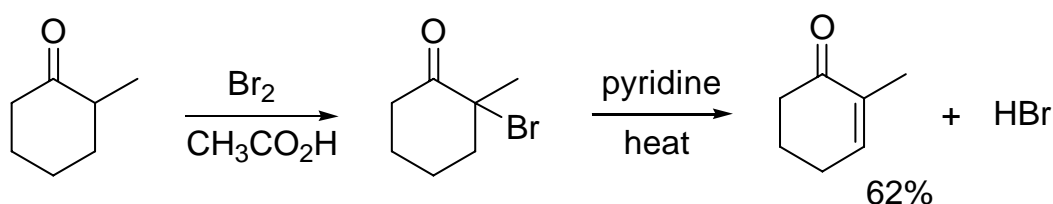
Aldehydes and ketones are halogenated at their α positions by reaction with Cl_2 , Br_2 , or I_2 in acidic solution.



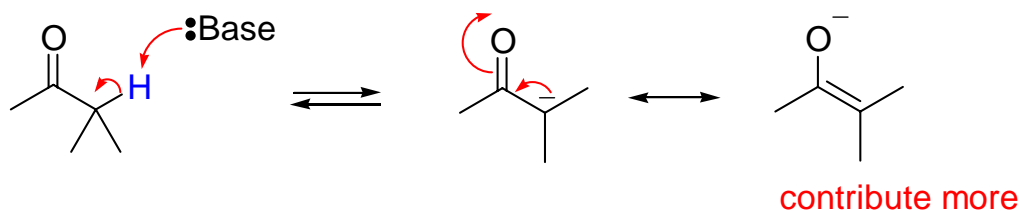
Deuterium-hydrogen exchange



Preparation of α,β -unsaturated ketones from α -bromo ketones



11.4 Acidity of Alpha Hydrogen Atoms: Enolate Ion Formation



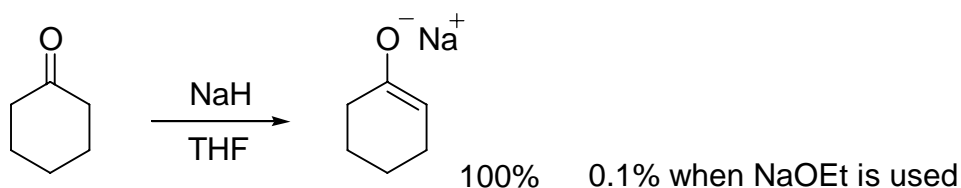
An enolate ion

Why are carbonyl compounds weakly acidic? (The presence of the carbonyl group increases the acidity of the neighboring C–H by a factor of 10^{30})

The enolate ion is stabilized by resonance, and the negative charge is shared by the electronegative oxygen and the α carbon.

Carbonyl compounds ($pK_a = 20$) are more acidic than alkanes (50) for the same reason that carboxylic acids (5) are more acidic than alcohols (16).

Strong bases are needed to form enolate ions.

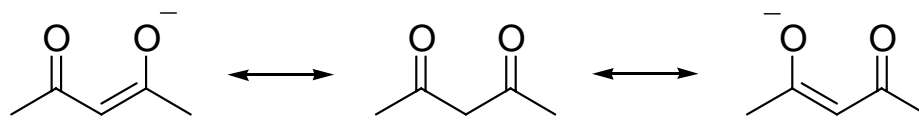


compound	pK _a	compound	pK _a	compound	pK _a
CH ₃ CO ₂ H	5		19		40
	9		20		41
	9		~23		43
CH ₃ NO ₂	10		~24		44
	11	CH ₃ CO ₂ H	~24		52
	13	CH ₃ -C≡C-H	25	Substituent effects	
CH ₃ OH	16	CH ₃ CN	~25	R	(+)1~2
EtOH	18		~30	X	(-)1~2
<i>t</i> -BuOH	19	Ph ₃ CH	~40	=	(-)5~7
			~40	Ph-	(-)5~7
				S	(-)3~5

anion stabilizing effect



The enolate ions derived from the β-dicarbonyl compounds are stabilized by sharing of the negative charge onto two neighboring carbonyl oxygens.



11.5 Reactivity of Enolate Ions

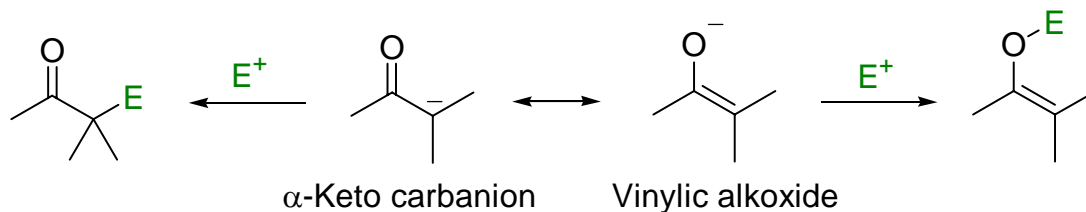
Enols vs. Enolate Ions

1. Pure enols can't be isolated but are generated only as transient intermediates in low concentration.
2. Enols are neutral and are not reactive.

3. Stable solutions of pure enolate ions are easily prepared by treatment with a strong base.
4. Enolate ions have a negative charge that makes them much better nucleophiles.

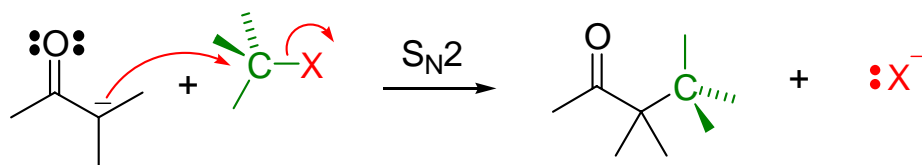
The resonance hybrid enolate ions

α -keto carbanions or vinyl alkoxides – enolate ions can react with electrophiles either on oxygen or on carbon.



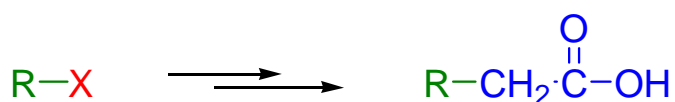
11.6 Alkylation of Enolate Ions

The nucleophilic enolate ion reacts with the electrophilic alkyl halide in an S_N2 reaction, displacing the halide ion.

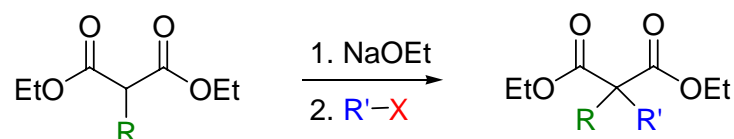
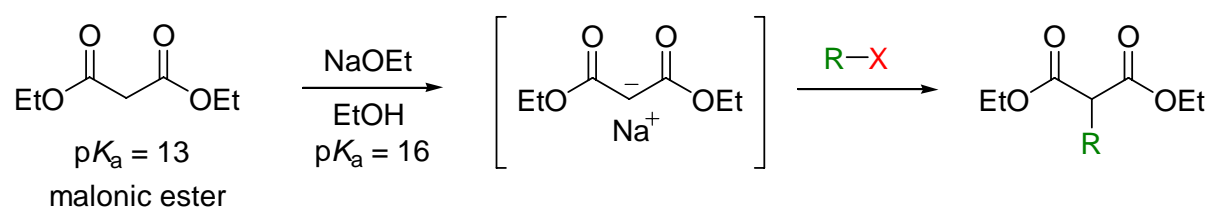


Alkylations are successful only when a primary alkyl halide or methyl halide is used. The leaving group X can be chloride, bromide, or iodide.

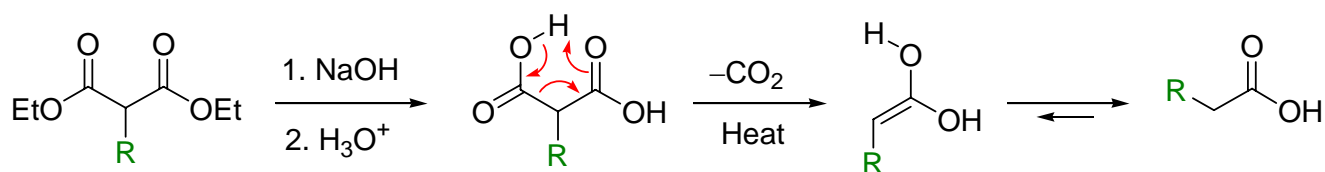
Malonic ester synthesis – for preparing a substituted acetic acid from an alkyl halide.



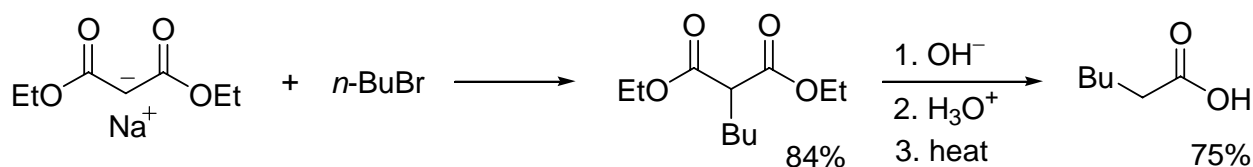
Alkylation



Hydrolysis and decarboxylation

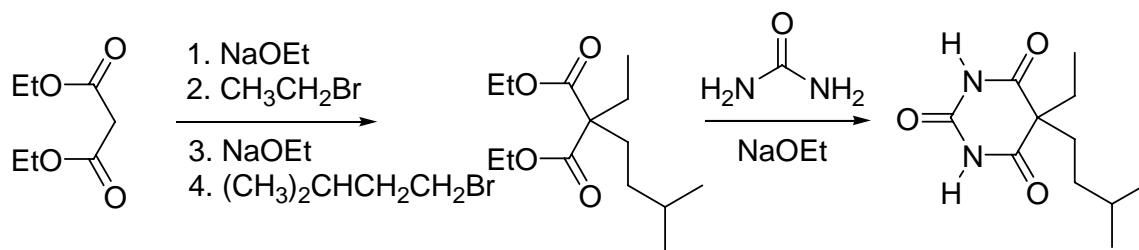


Example



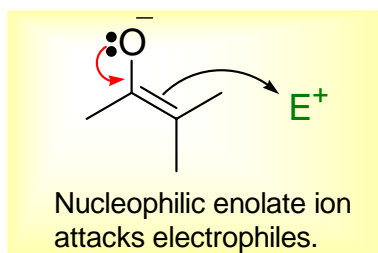
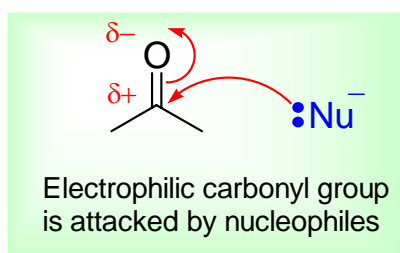
11.7 Enolate Alkylation and the Dawn of Modern Medicine

The Synthesis of Barbiturates (a potent sedative) in early 1900s.



11.8 Carbonyl Condensation Reactions

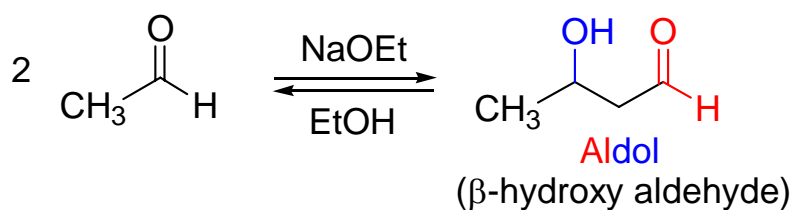
Carbonyl compounds can behave as either electrophiles or nucleophiles.



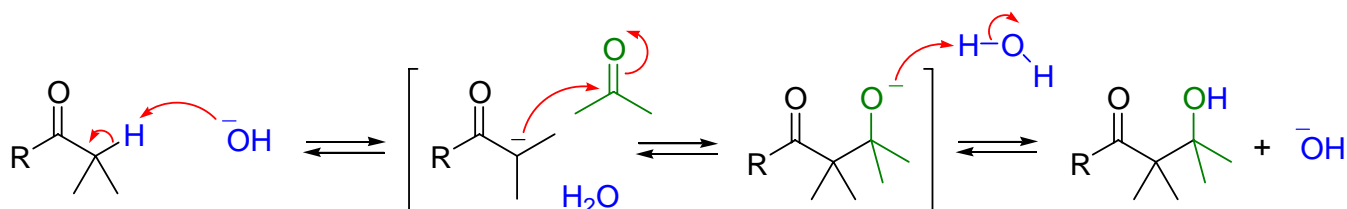
Carbonyl condensation reactions take place between two carbonyl partners and involve a combination of nucleophilic addition and α -substitution steps. One partner is converted into an enolate ion and undergoes an α -substitution reaction, while the other partner undergoes a nucleophilic addition reaction.

11.9 Condensations of Aldehydes and Ketones: The Aldol Reaction

A rapid and reversible condensation of aldehyde under a base catalyst in an alcohol solvent to produce **β -hydroxy aldehyde (aldol)**.

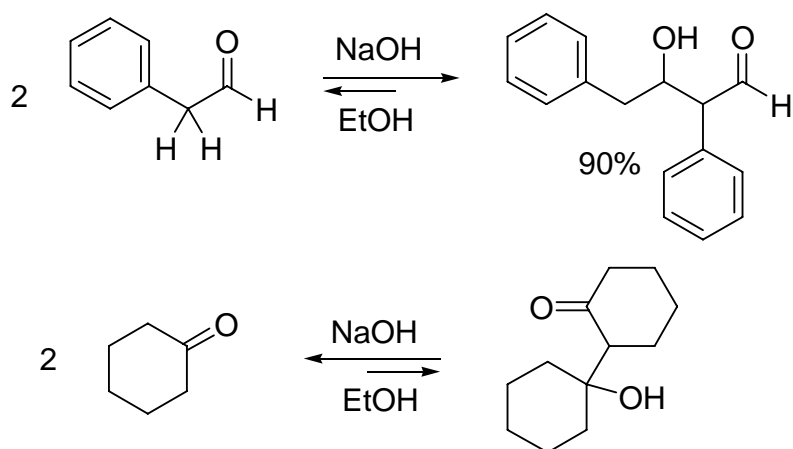


Mechanism



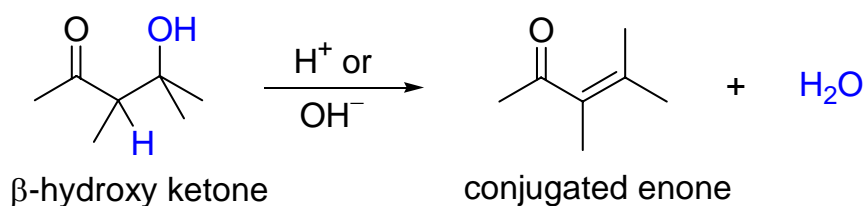
Aldol reaction is a general reaction of all aldehydes and ketones with **α hydrogen atoms**. If the aldehyde or ketone does not have an α hydrogen atom, aldol condensation can't occur.

The position of the aldol equilibrium depends both on reaction conditions and on substrate structure.



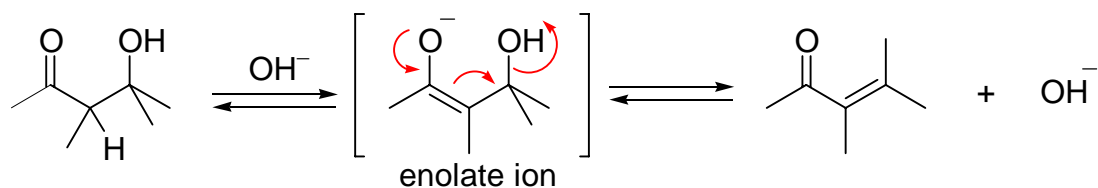
11.10 Dehydration of Aldol Products: Synthesis of Enones

The β-hydroxy ketones and aldehydes are easily dehydrated to yield conjugated (α,β-unsaturated) enones.

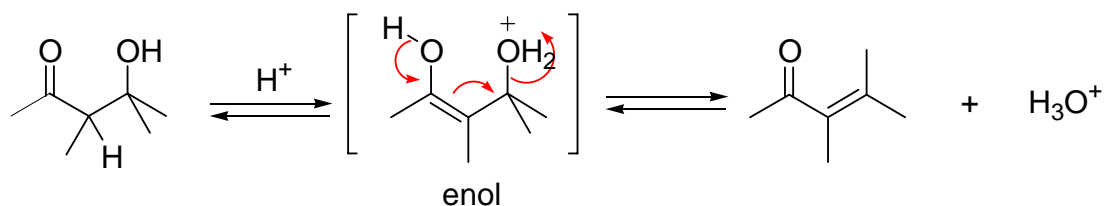


Mechanism

Base-catalyzed

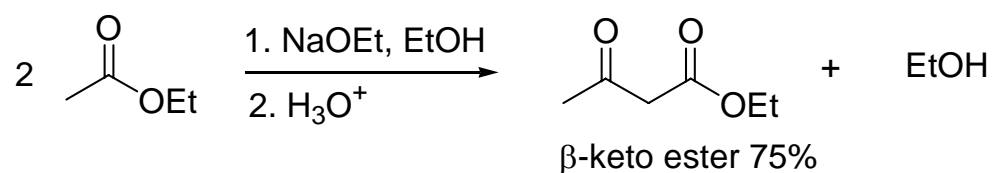


Acid-catalyzed



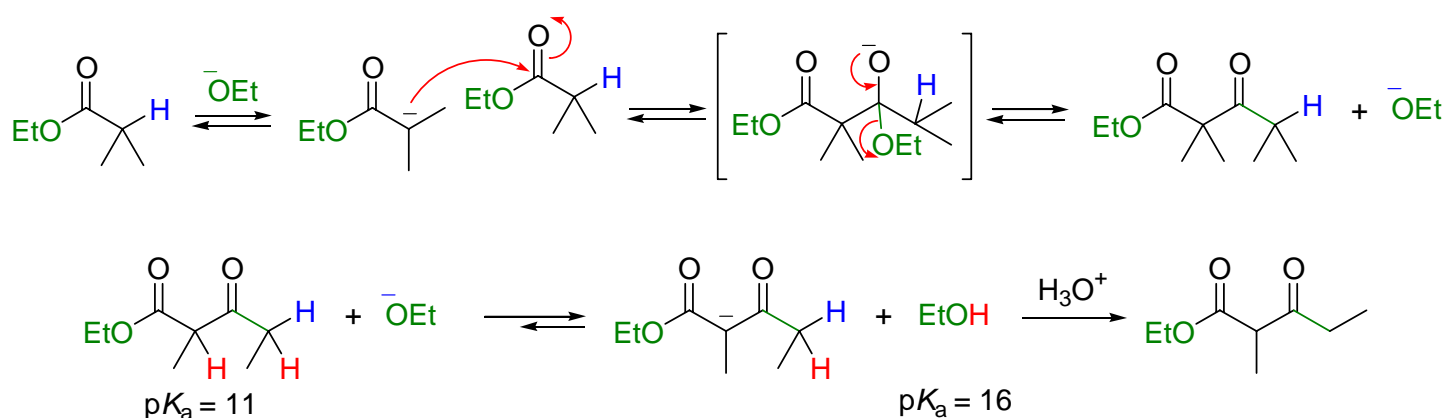
11.11 Condensation of Esters: The Claisen Condensation Reaction

A reversible condensation reaction of **an ester with an α hydrogen** under 1 equivalent of a base to yield a **β -keto ester product**.



Mechanism

Combination of α -substitution reaction and nucleophilic acyl substitution reaction of esters.

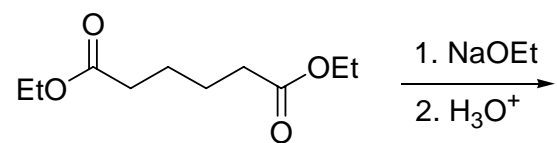


There should be at least two α hydrogens in esters for the Claisen condensation reaction.

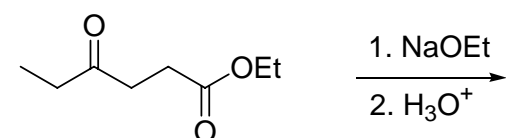
Homework

Draw the major product of the following reaction.

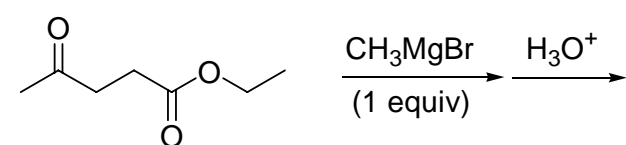
1.



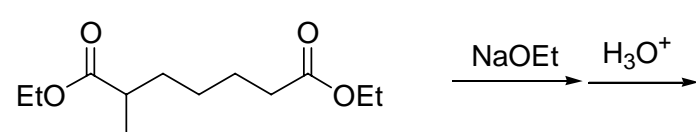
2.



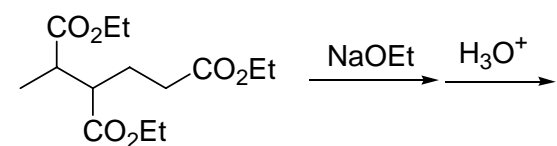
3.



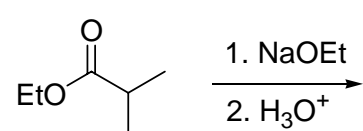
4.



5.



6.



Propose the best synthesis of the following product using any reagents with C5 or less.

