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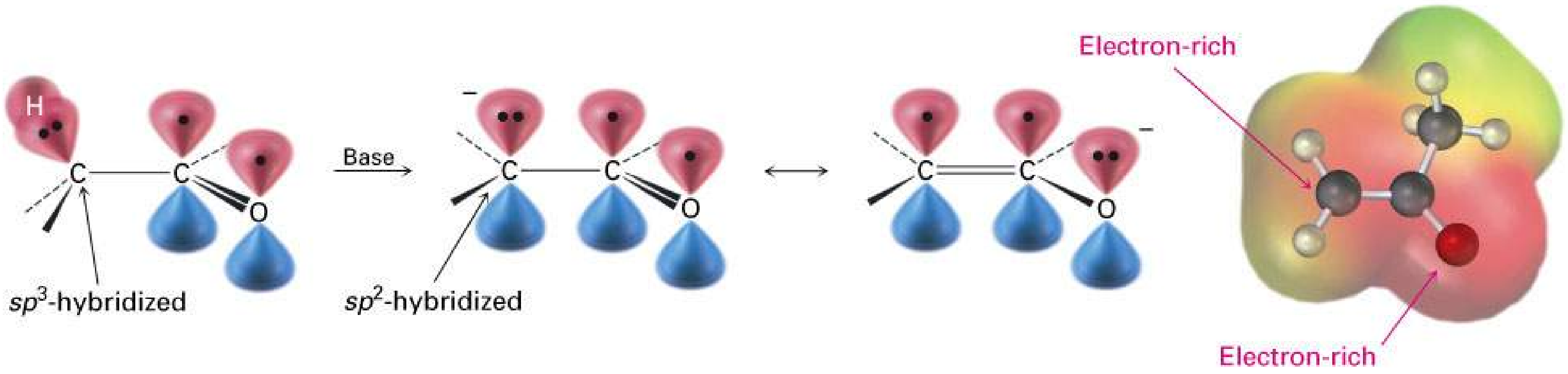
Carbonyl Alpha-Substitution Reactions (2)

Acidity of Alpha Hydrogen Atoms

Enolate Ion Formation

- Carbonyl compounds can act as weak acids (pK_a of acetone = 19.3; pK_a of ethane = 60)
- The conjugate base of a ketone or aldehyde is an enolate ion - the negative charge is delocalized onto oxygen



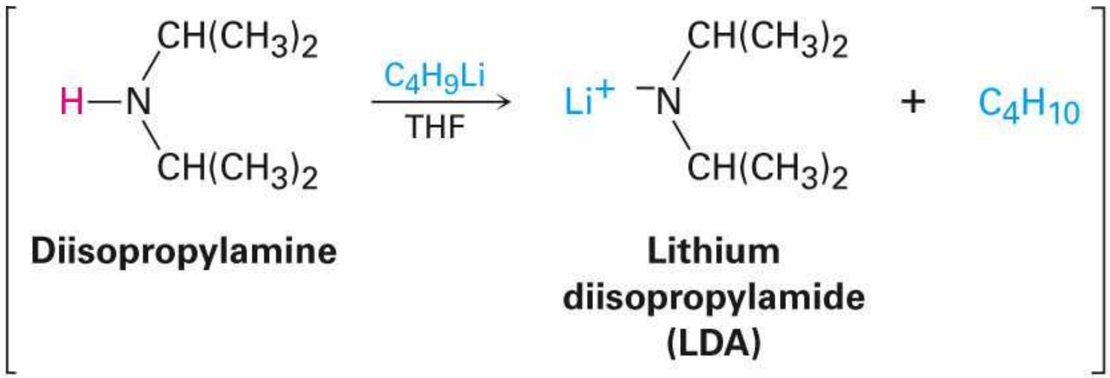
Reagents for Enolate Formation

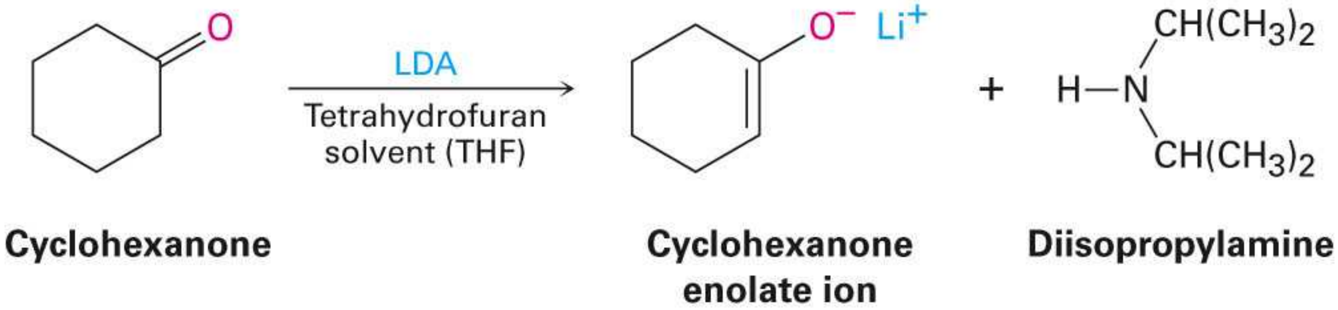
- Ketones are weaker acids than the OH of alcohols so a more powerful base than an alkoxide is needed to form the enolate

- Sodium hydride (NaH) or lithium diisopropylamide $[\mathrm{LiN}(i\text{-}\mathrm{C}_3\mathrm{H}_7)_2]$ are strong enough to form the enolate

Lithium Diisopropylamide (LDA)

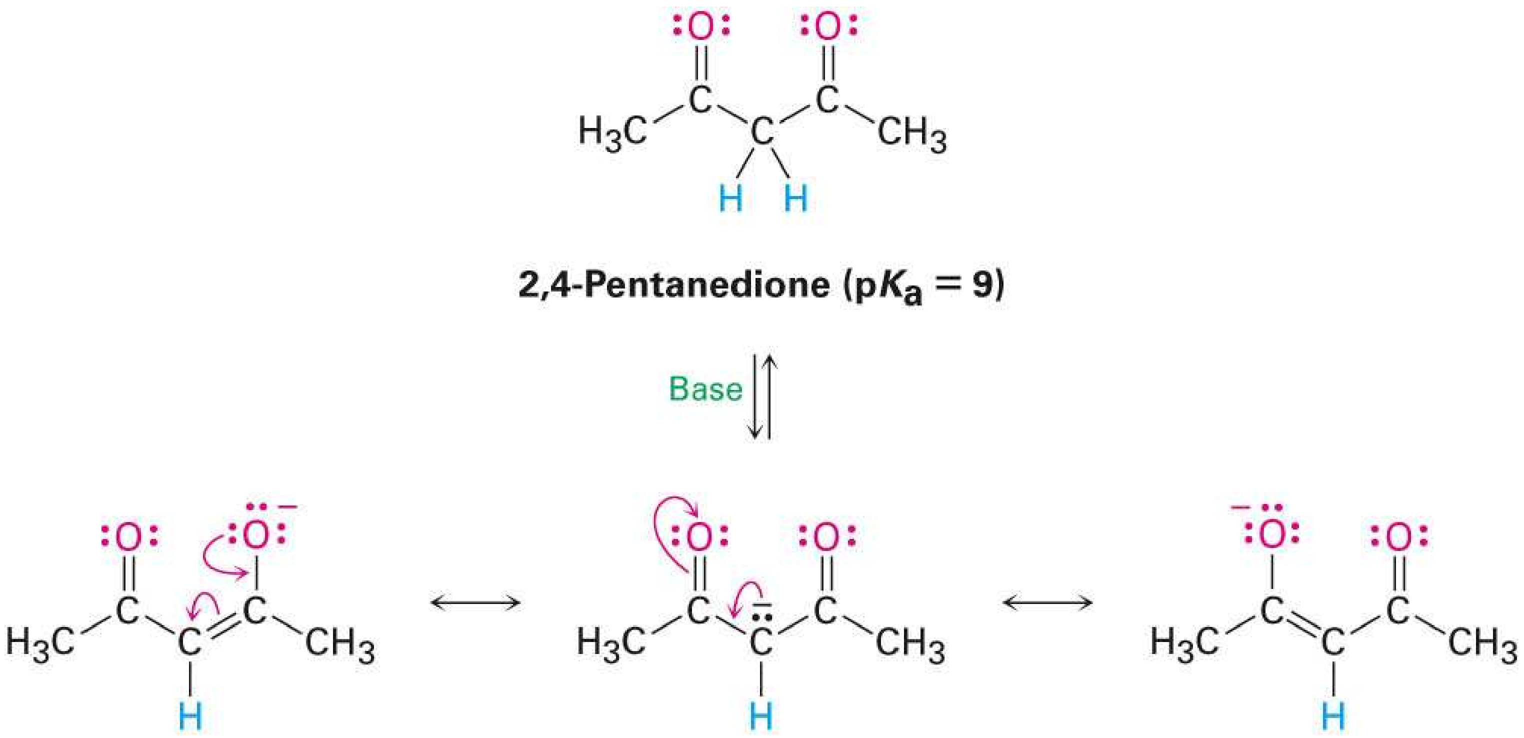
- LDA is from butyllithium (BuLi) and diisopropylamine (pK_a ≈ 40)
- Soluble in organic solvents and effective at low temperature with many compounds
- Not nucleophilic



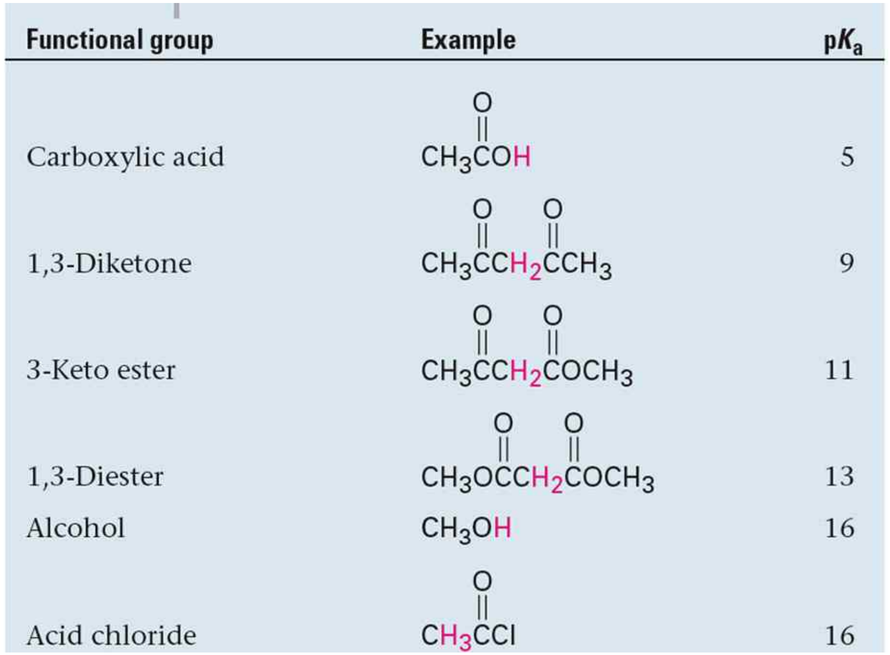


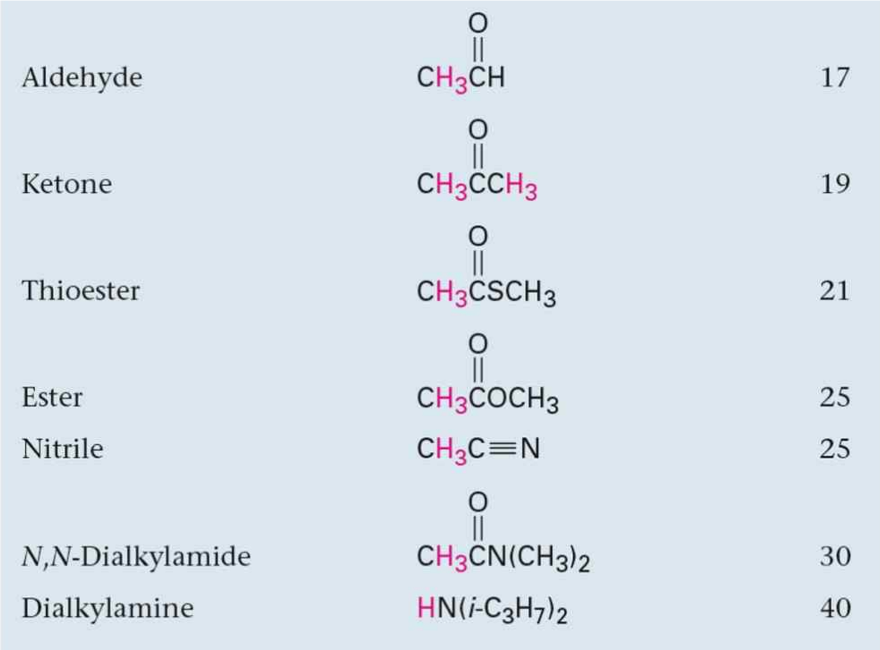
β-Dicarbonyls Are More Acidic

- When a hydrogen atom is flanked by two carbonyl groups, its acidity is enhanced
- Negative charge of enolate delocalizes over both carbonyl groups



Acidities of Organic Compounds

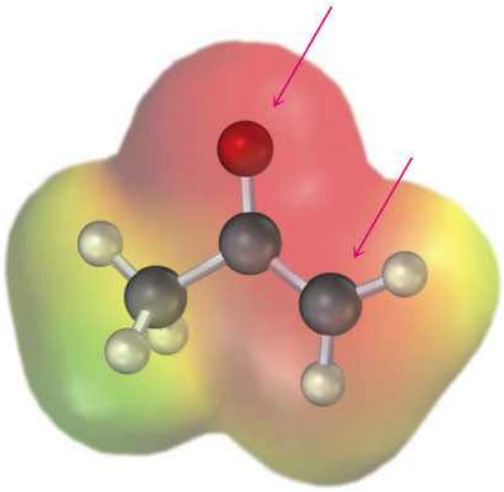


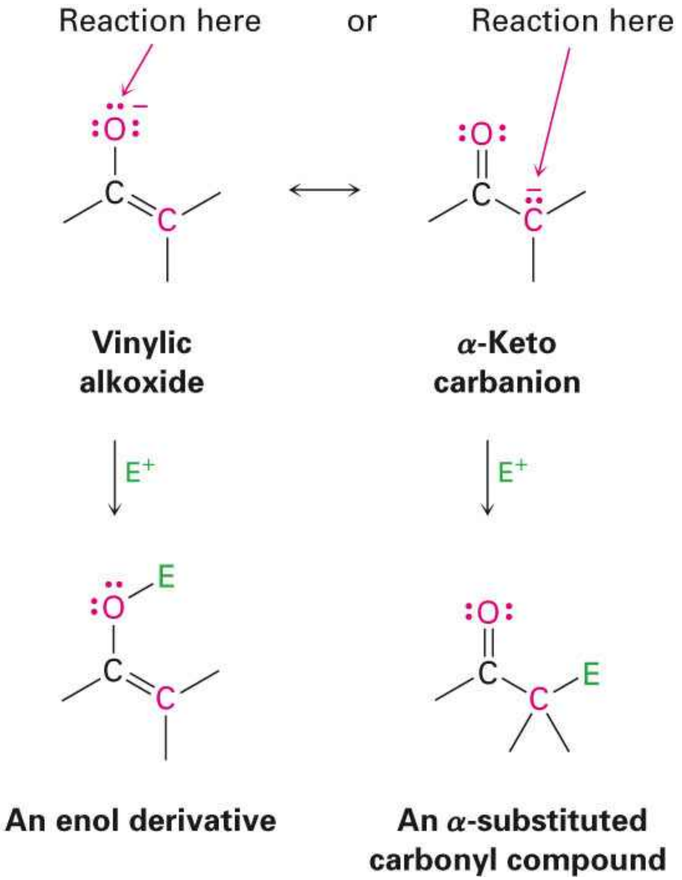


Functional group	Example	pK_a
Carboxylic acid	$CH_3\overset{O}{\overset{\Vert}{C}}OH$	5
1,3-Diketone	$CH_3\overset{O}{\overset{\Vert}{C}}CH_2\overset{O}{\overset{\Vert}{C}}CH_3$	9
3-Keto ester	$CH_3\overset{O}{\overset{\Vert}{C}}CH_2\overset{O}{\overset{\Vert}{C}}OCH_3$	11
1,3-Diester	$CH_3O\overset{O}{\overset{\Vert}{C}}CH_2\overset{O}{\overset{\Vert}{C}}OCH_3$	13
Alcohol	CH_3OH	16
Acid chloride	$CH_3\overset{O}{\overset{\Vert}{C}}Cl$	16
Aldehyde	$CH_3\overset{O}{\overset{\Vert}{C}}H$	17
Ketone	$CH_3\overset{O}{\overset{\Vert}{C}}CH_3$	19
Thioester	$CH_3\overset{O}{\overset{\Vert}{C}}SCH_3$	21
Ester	$CH_3\overset{O}{\overset{\Vert}{C}}OCH_3$	25
Nitrile	$CH_3C\equiv N$	25
N,*N*-Dialkylamide	$CH_3\overset{O}{\overset{\Vert}{C}}N(CH_3)_2$	30
Dialkylamine	$HN(i\text{-}C_3H_7)_2$	40

Reactivity of Enolate Ions

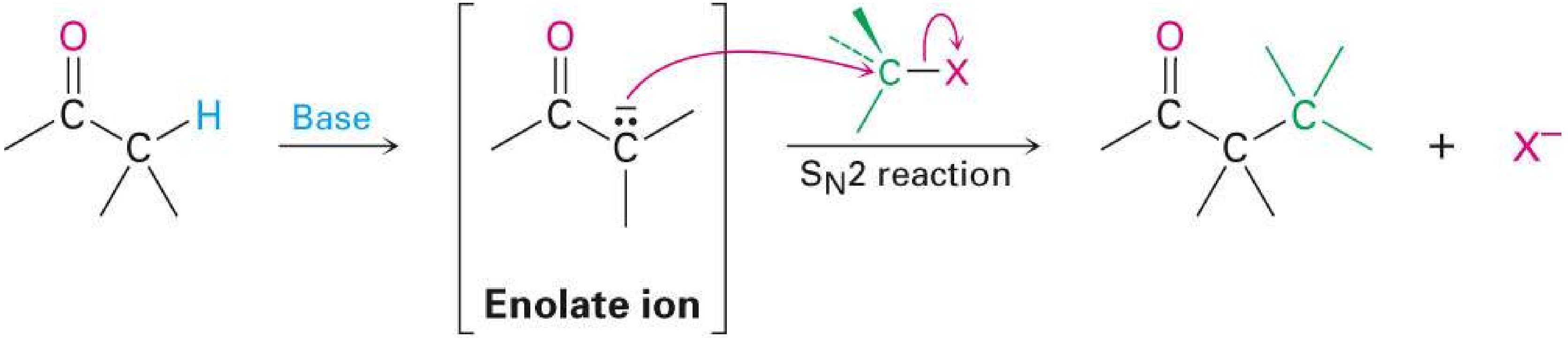
- The carbon atom of an enolate ion is electron-rich and highly reactive toward electrophiles (enols are not as reactive)
- Reaction on oxygen yields an enol derivative
- Reaction on carbon yields an α-substituted carbonyl compound





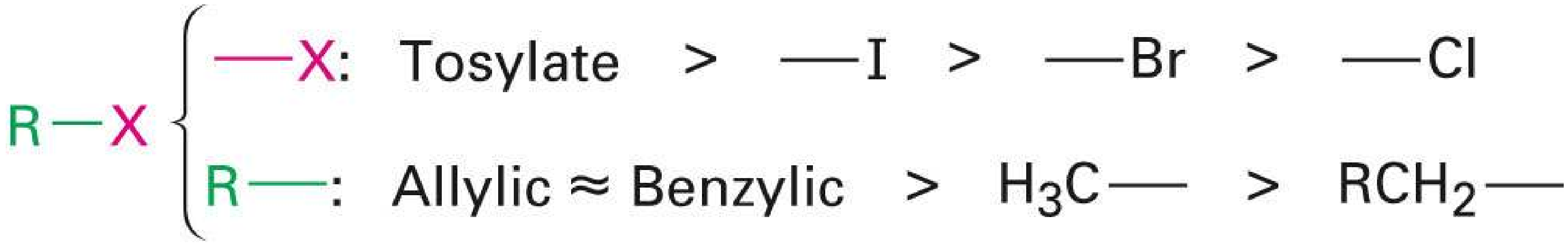
Alkylation of Enolate Ions

- Base-promoted reaction occurs through an enolate ion intermediate



Constraints on Enolate Alkylation

- S_N2 reaction:, the leaving group X can be chloride, bromide, iodide, or tosylate.
- R should be primary or methyl and preferably should be allylic or benzylic.
- Secondary halides react poorly, and tertiary halides don't react at all because of competing elimination.



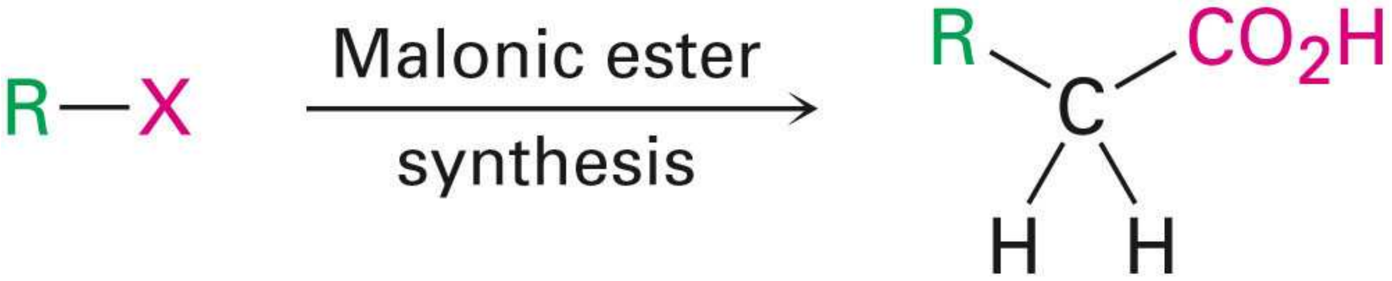
R—X

—X: Tosylate > —I > —Br > —Cl

R—: Allylic ≈ Benzylic > H_3C— > RCH_2—

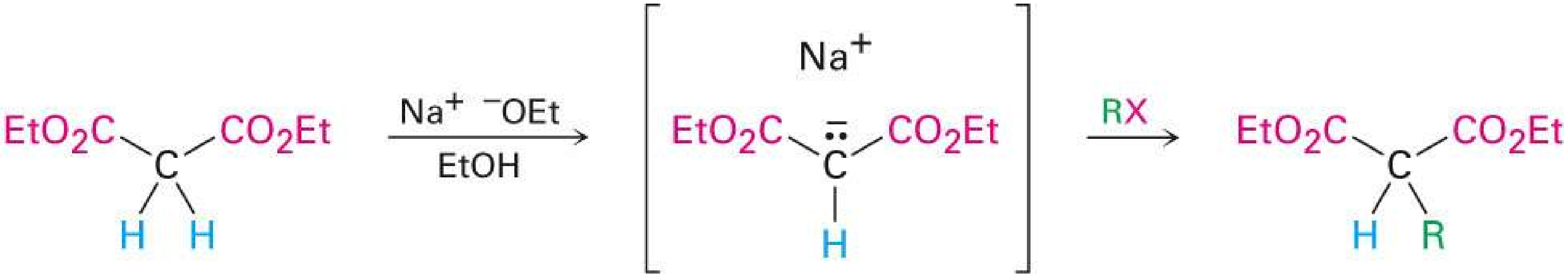
The Malonic Ester Synthesis

- For preparing a carboxylic acid from an alkyl halide while lengthening the carbon chain by two atoms



Formation of Enolate and Alkylation

- Malonic ester (diethyl propanedioate) is easily converted into its enolate ion by reaction with sodium ethoxide in ethanol
- The enolate is a good nucleophile that reacts rapidly with an alkyl halide to give an a-substituted malonic ester



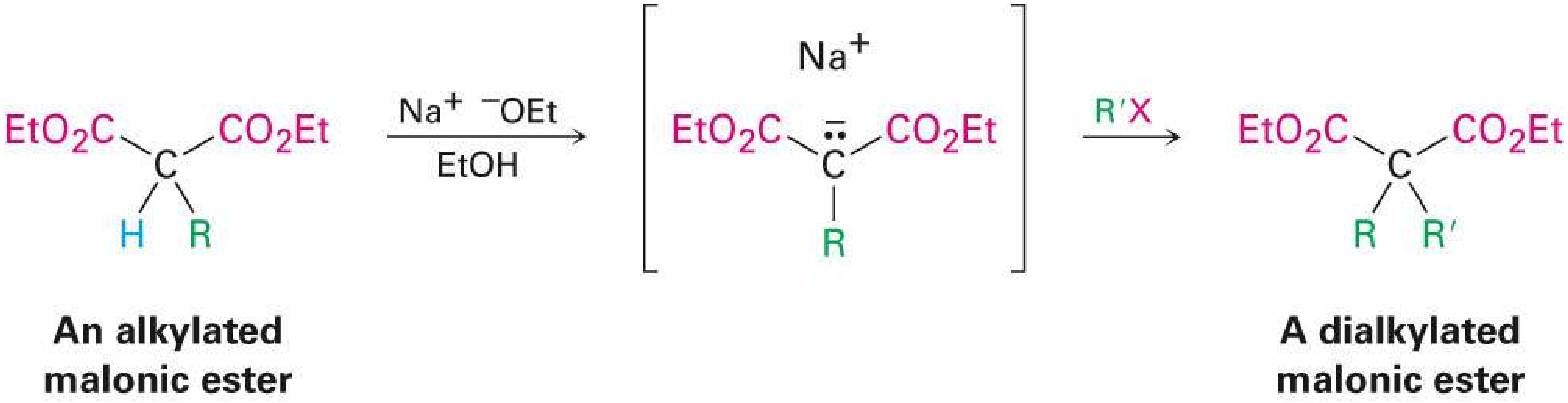
Diethyl propanedioate (malonic ester)

Sodio malonic ester

An alkylated malonic ester

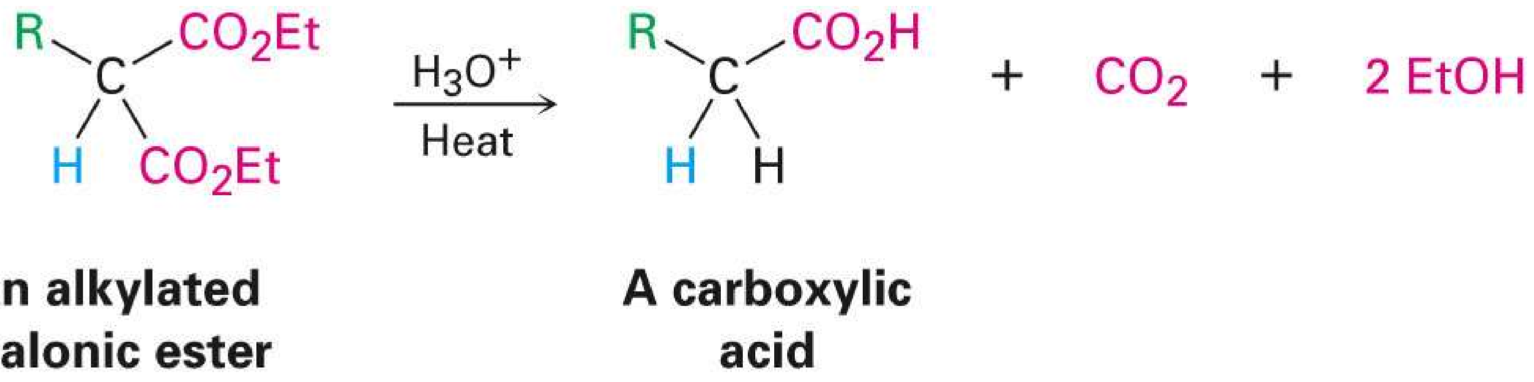
Dialkylation

- The product has an acidic α-hydrogen, allowing the alkylation process to be repeated



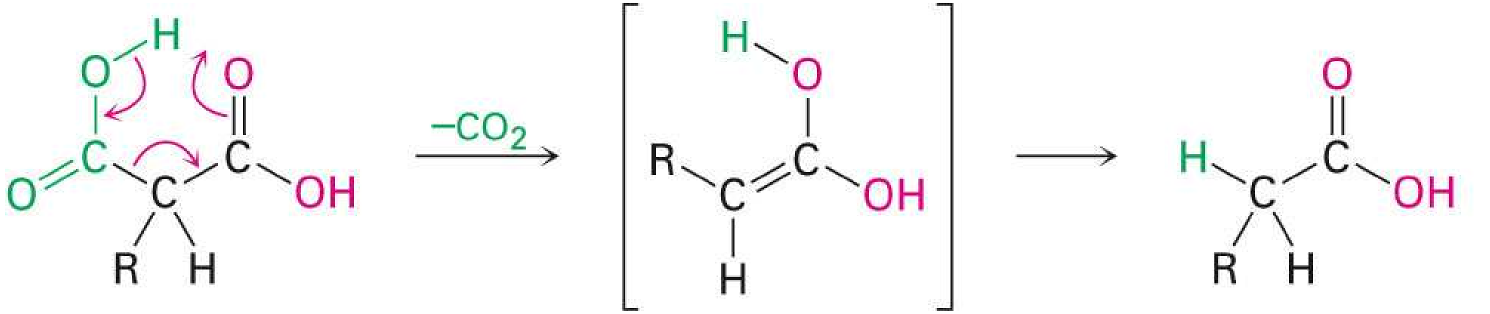
Hydrolysis and Decarboxylation

- The malonic ester derivative hydrolyzes in acid and loses CO_2 ("decarboxylation") to yield a substituted monoacid

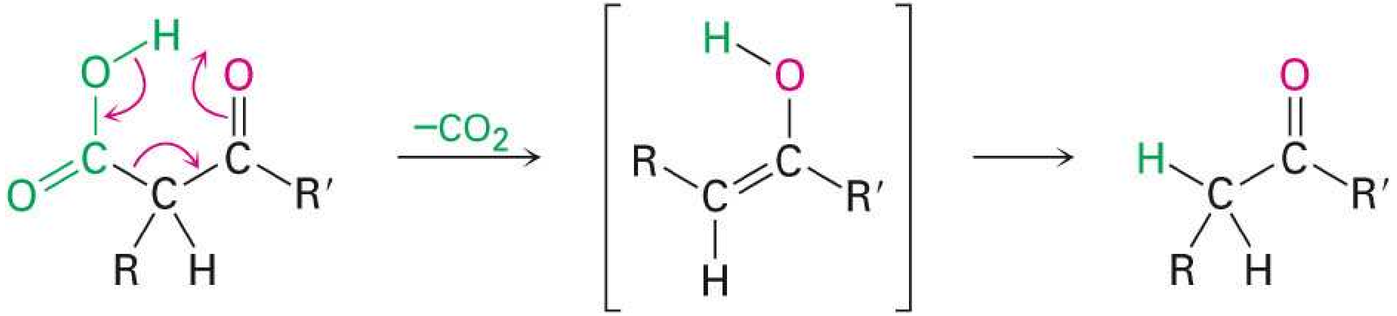


Decarboxylation of β-Ketoacids

- Decarboxylation requires a carbonyl group two atoms away from the —CO_2H



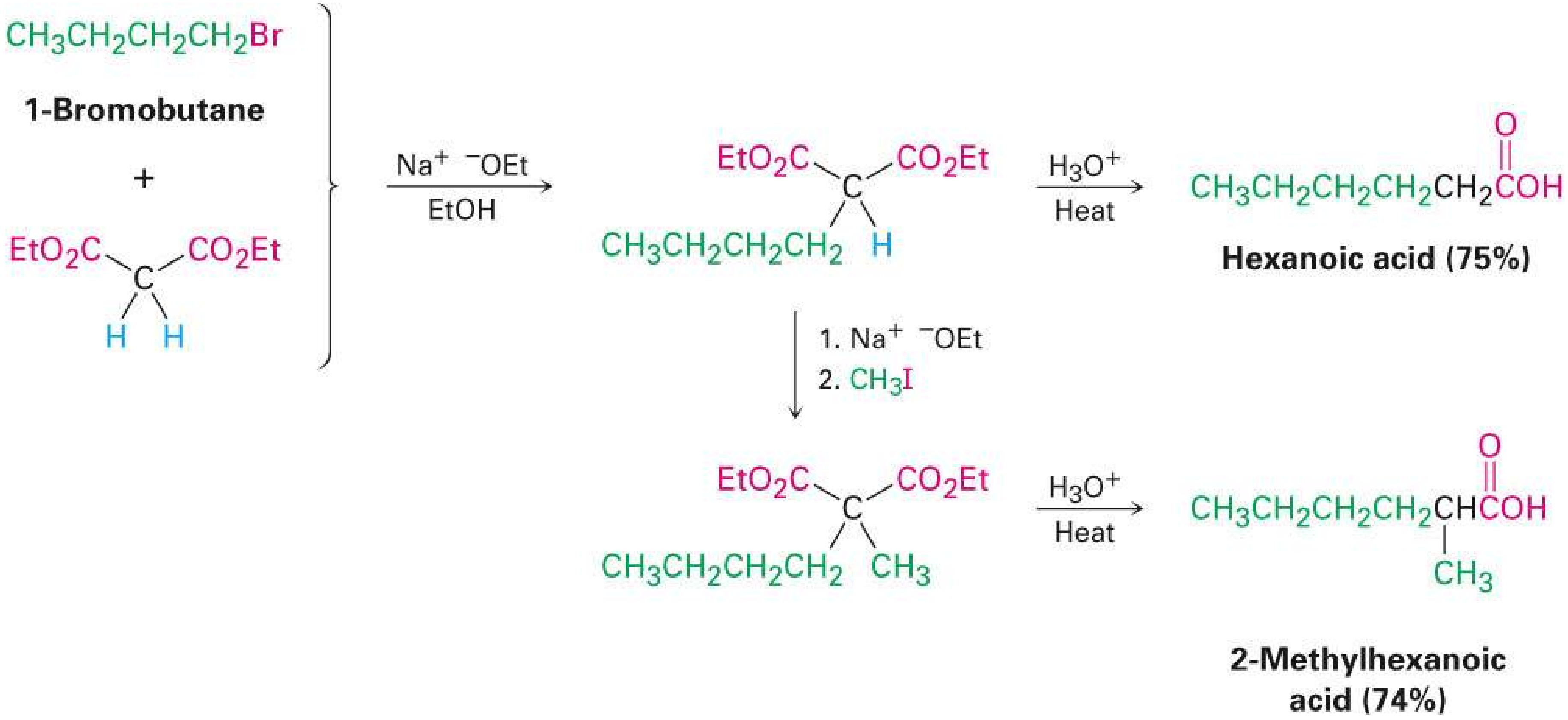
A diacid **An acid enol** **A carboxylic acid**



A β-keto acid **An enol** **A ketone**

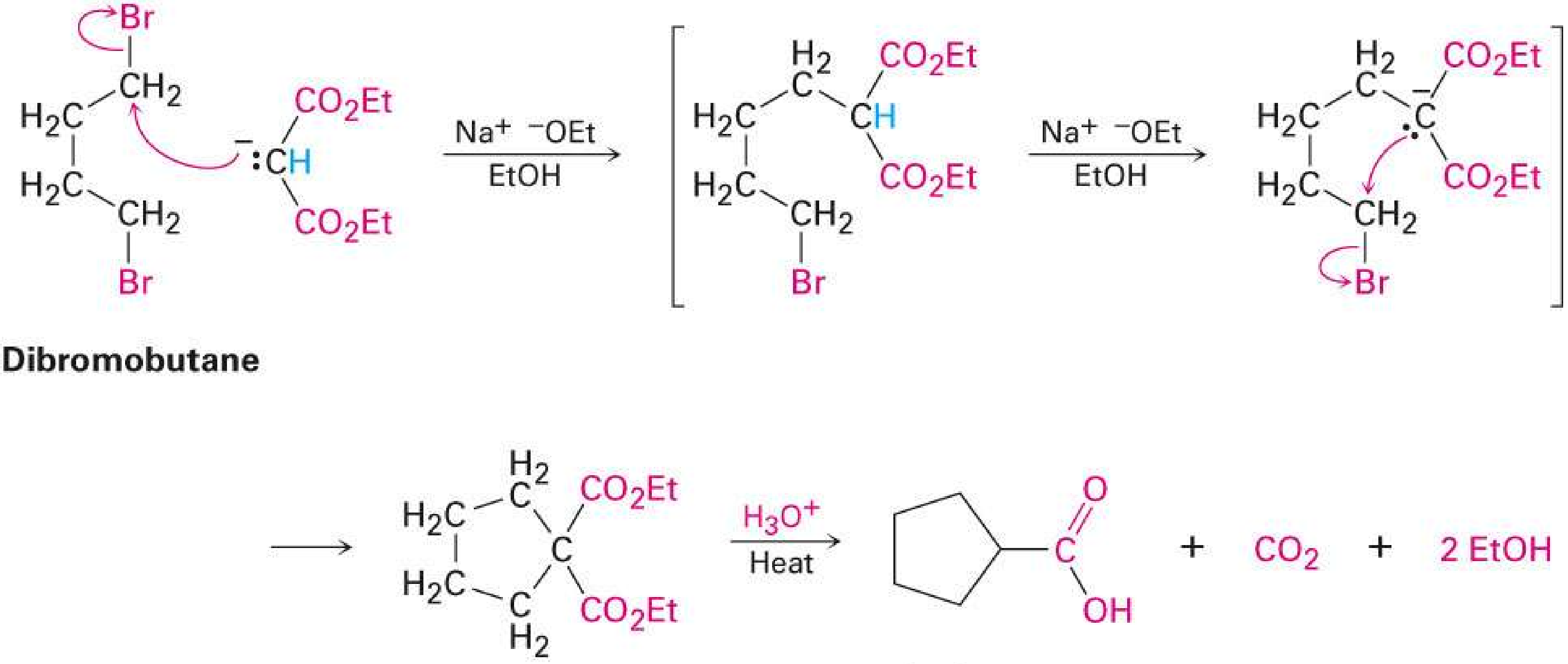
Overall Conversion

- The malonic ester synthesis converts an alkyl halide into a carboxylic acid while lengthening the carbon chain by two atoms



Preparation Cycloalkane Carboxylic Acids

- 1,4-dibromobutane reacts twice, giving a cyclic product
- Three-, four-, five-, and six-membered rings can be prepared in this way

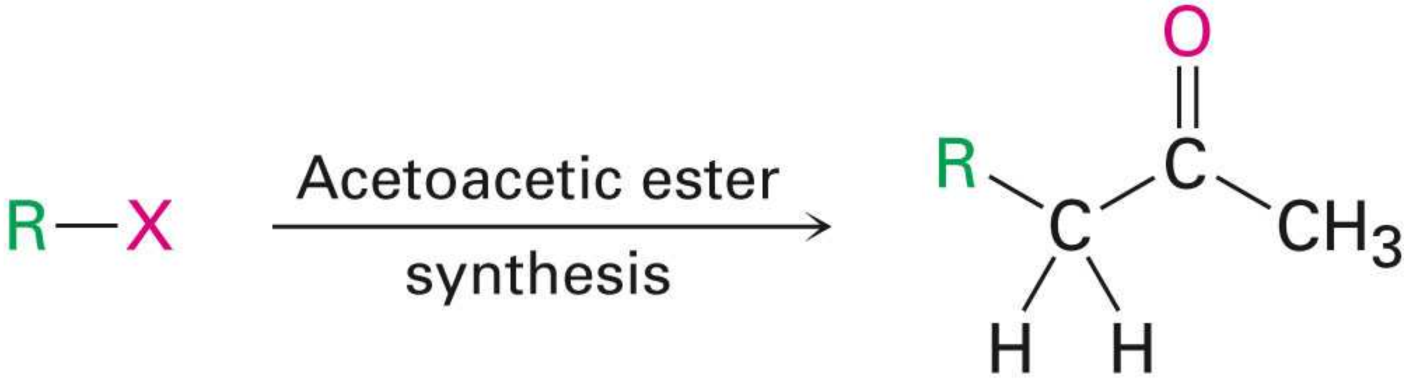


1,4-Dibromobutane

Cyclopentane-carboxylic acid

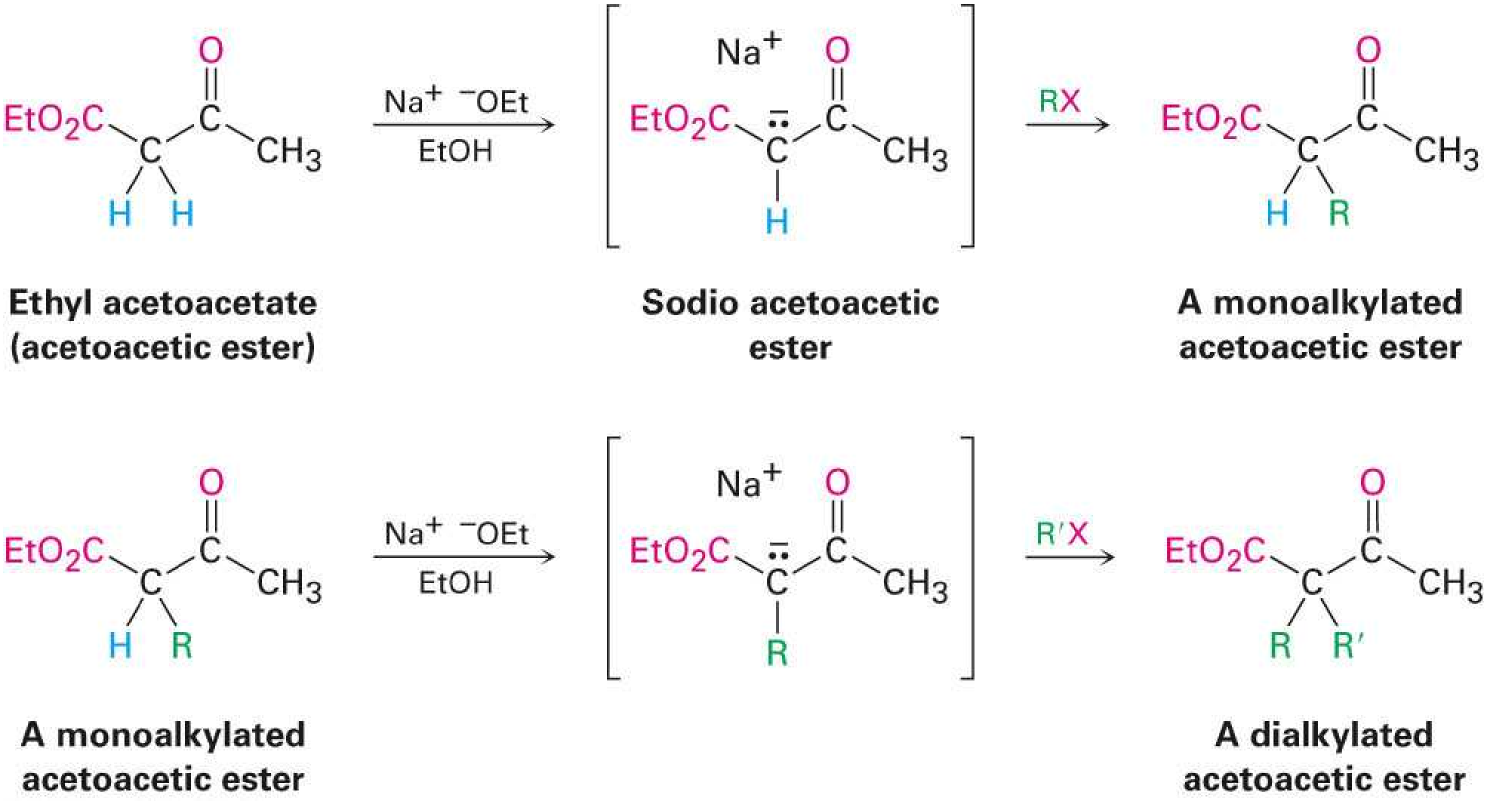
Acetoacetic Ester Synthesis

- Overall: converts an alkyl halide into a methyl ketone



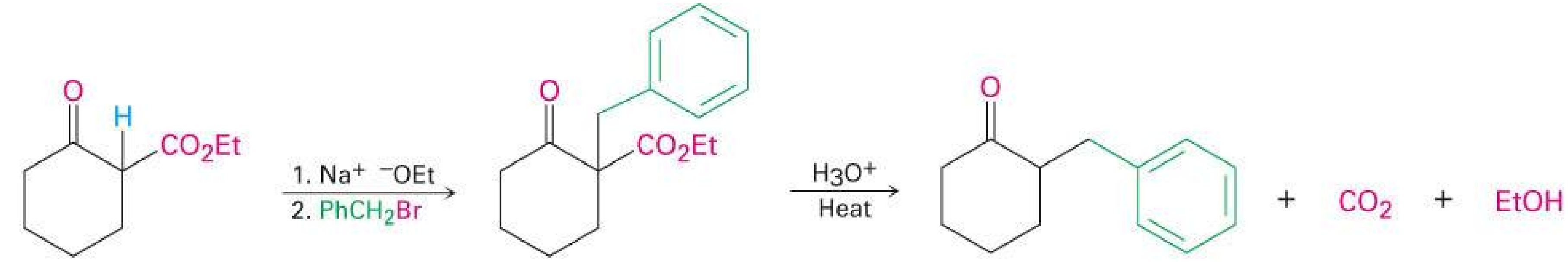
Acetoacetic Ester (Ethyl Acetoacetate)

- α carbon is flanked by two carbonyl groups, so it readily becomes an enolate ion
- This can be alkylated by an alkyl halide and also can react with a second alkyl halide



Generalization: β-Keto Esters

- The sequence: enolate ion formation, alkylation, hydrolysis/decarboxylation is applicable to b-keto esters in general
- Cyclic b-keto esters give 2-substituted cyclohexanones



Ethyl 2-oxocyclohexane-carboxylate
(a cyclic β-keto ester)

2-Benzylcyclohexanone
(77%)