Organic Chemistry, *Fourth Edition*

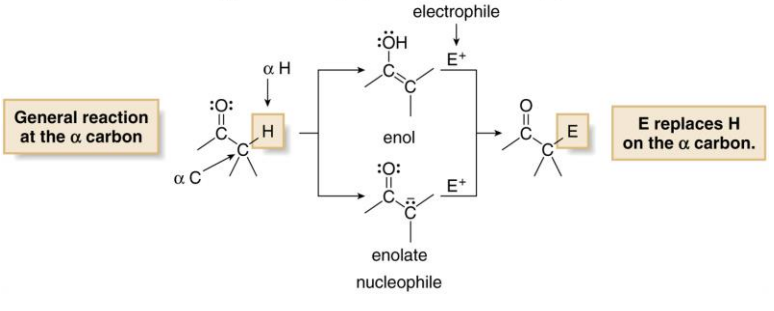
Janice Gorzynski Smith
University of Hawai'i

Chapter 23
Lecture Outline

Prepared by Layne A. Morsch
The University of Illinois - Springfield

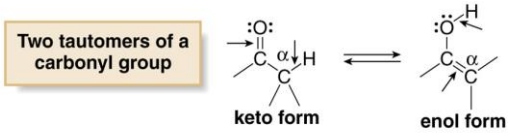
Reactions α to Carbonyl Groups

- **Carbonyl compounds can undergo reactions at the carbon that is α to the carbonyl group.**
- **These reactions proceed by way of enols and enolates.**
- **The reaction results in the substitution of the electrophile E^+ for hydrogen.**



Keto-Enol Tautomers

- **Enol and keto forms are tautomers of the carbonyl group that differ in the position of the double bond and a proton.**
- **These constitutional isomers are in equilibrium with each other.**

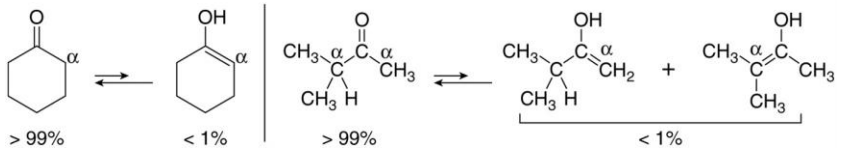


- A keto tautomer has a C = O and an additional C – H bond.
- An enol tautomer has an O – H group bonded to a C = C.

3

Equilibrium of Keto-Enol Tautomers

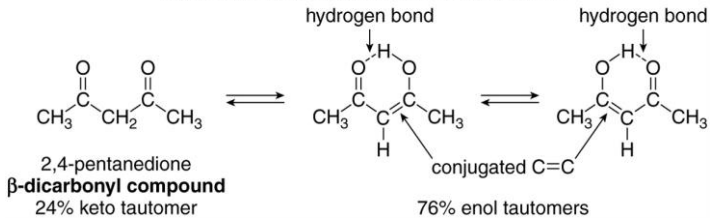
- **Equilibrium favors the keto form for most carbonyl compounds largely because the C=O is much stronger than a C=C.**
- **For simple carbonyl compounds, <1% of the enol is present at equilibrium.**
- **With unsymmetrical ketones, two different enols are possible, yet they still total <1%.**



4

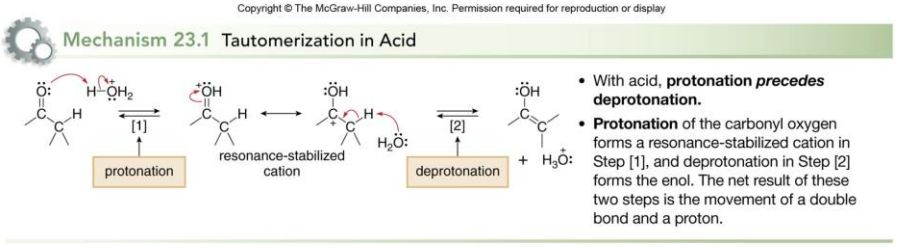
1,3-Dicarbonyl Compounds

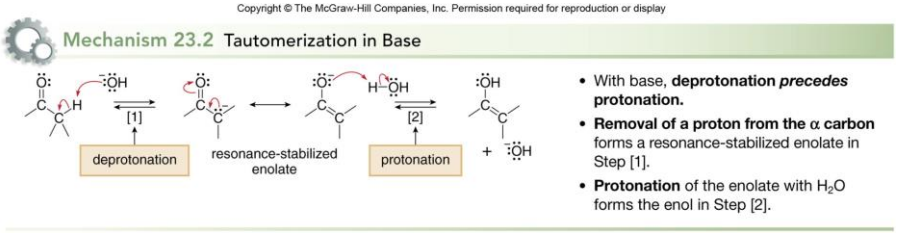
- **With compounds containing two carbonyl groups separated by a single carbon (called β-dicarbonyl or 1,3-dicarbonyl compounds), the concentration of the enol form sometimes exceeds the concentration of the keto form.**



- **Two factors stabilize the enol of β-dicarbonyl compounds: conjugation and intramolecular hydrogen bonding.**
- **The latter is especially stabilizing when a six-membered ring is formed, as in this case.**

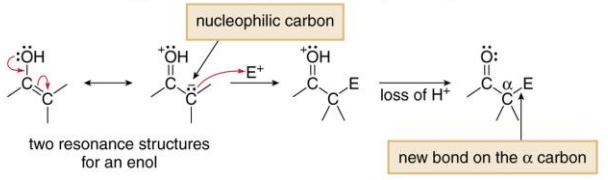
Tautomerization Catalyzed by Acids and Bases





Enol Structures

- **Enols are more electron rich than alkenes because the OH group has a powerful electron-donating resonance effect.**
- **This causes them to be quite reactive toward electrophiles.**
- **A resonance structure can be drawn that places a negative charge on one of the carbon atoms, making this carbon nucleophilic.**
- **The nucleophilic carbon can react with an electrophile to form a new bond to carbon.**

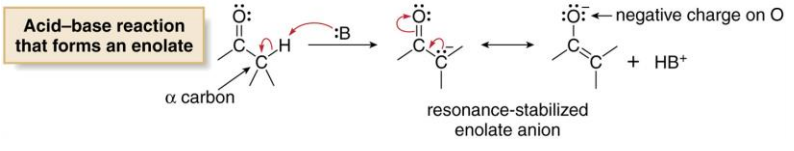


- Reaction of an enol with an electrophile E^+ forms a new C – E bond on the α carbon. The net result is substitution of H by E on the α carbon.

7

Formation of Enolates

- **Enolates are formed when a base removes a proton on a carbon that is α to a carbonyl group.**
- **The C–H bond on the α carbon is more acidic (pK_a is ~20) than most other sp^3 hybridized C–H bonds, because the resulting enolate is resonance stabilized.**



- **Though considerably more acidic than most C–H bonds in alkanes and alkenes, the α carbon is still less acidic than O–H bonds in alcohols or carboxylic acids.**

8

Table 23.1 A Comparison of pK_a Values

Compound	pK_a	Conjugate base	Structural features of the conjugate base
CH_3CH_3	50	$CH_3\ddot{C}H_2$	• The conjugate base has a (–) charge on C, but is not resonance stabilized.
$CH_2{=}CHCH_3$	43	$CH_2{=}CH{-}\ddot{C}H_2 \longleftrightarrow \ddot{C}H_2{-}CH{=}CH_2$	• The conjugate base has a (–) charge on C, and is resonance stabilized.
$(CH_3)_2C{=}O$	19.2		• **The conjugate base has two resonance structures, one of which has a (–) charge on O.**
CH_3CH_2OH	16	$CH_3CH_2\ddot{O}:^-$	• The conjugate base has a (–) charge on O, but is not resonance stabilized.
CH_3CO_2H	4.8		• The conjugate base has two resonance structures, both of which have a (–) charge on O.

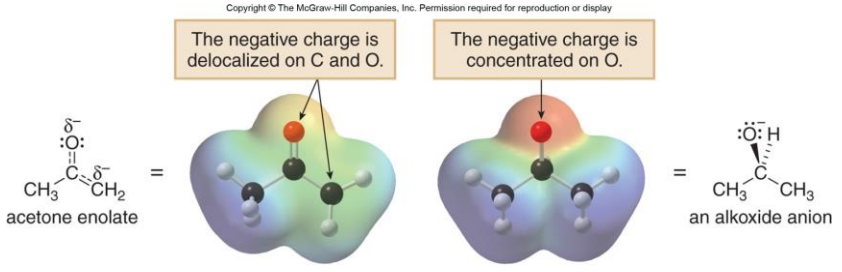
Increasing acidity
Increasing stability of the conjugate base

- **Resonance stabilization of the conjugate base increases acidity.**
  - $CH_2{=}CHCH_3$ is more acidic than $CH_3CH_2CH_3$.
  - CH_3COOH is more acidic than CH_3CH_2OH.
- **Placing a negative charge on O in the conjugate base increases acidity.**
  - CH_3CH_2OH is more acidic than $CH_3CH_2CH_3$.
  - CH_3COCH_3 is more acidic than $CH_2{=}CHCH_3$.
  - CH_3COOH (with two O atoms) is more acidic than CH_3COCH_3.

9

Electron Density of Enolates and Alkoxides

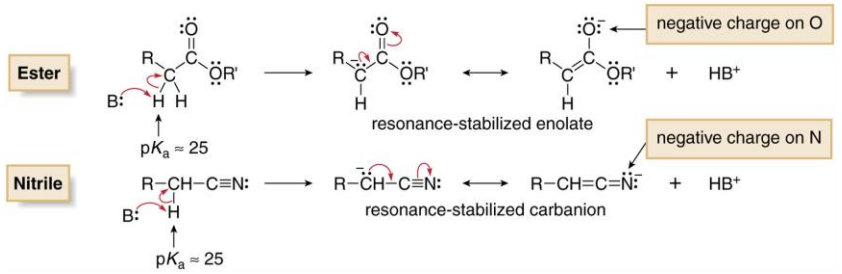
- **The acetone enolate is resonance stabilized.**
  - **The negative charge is delocalized on the oxygen and carbon atoms.**
- **The alkoxide anion is not resonance stabilized.**
  - **The negative charge is concentrated on the oxygen atom only.**



10

Enolates from Esters, Amides, and Nitriles

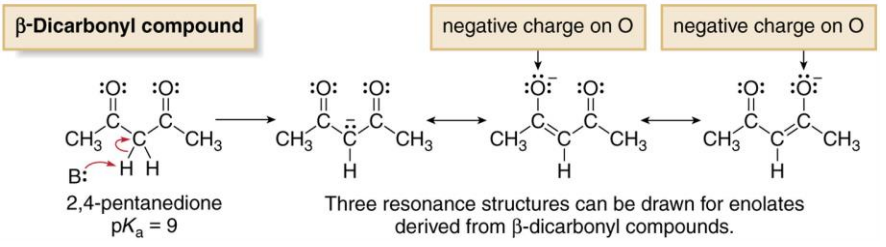
- **Enolates can be formed from esters and 3° amides as well, although α hydrogens from these compounds are somewhat less acidic.**
- **Nitriles also have acidic protons on the carbon adjacent to the cyano group.**



11

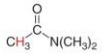
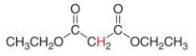
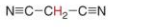
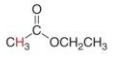
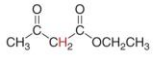
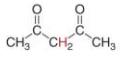
β-Dicarbonyl Compounds

- **The protons on the carbon between the two carbonyl groups of a β-dicarbonyl compound are especially acidic because resonance delocalizes the negative charge on two different oxygen atoms.**



12

Table 23.2 pK_a Values for Some Carbonyl Compounds and Nitriles

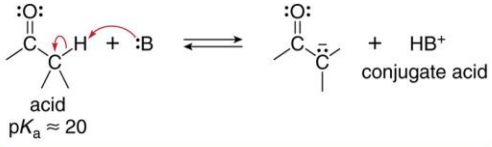
Compound type	Example	pK_a	Compound type	Example	pK_a
[1] Amide		30	[6] 1,3-Diester		13.3
[2] Nitrile		25	[7] 1,3-Dinitrile		11
[3] Ester		25	[8] β-Keto ester		10.7
[4] Ketone		19.2	[9] β-Diketone		9
[5] Aldehyde		17			

13

Equilibrium of Enolate Formation

- **The formation of an enolate is an acid–base equilibrium, so the stronger the base, the more enolate that forms.**

Enolate formation—An acid–base equilibrium



Stronger bases drive the equilibrium to the right.

- **The extent of an acid–base reaction can be predicted by comparing the pK_a of the starting acid with the pK_a of the conjugate acid formed.**
- **The equilibrium favors the side with the weaker acid.**
- **Common bases used to form enolates are $^-$OH, $^-$OR, $^-$H and dialkylamides ($^-NR_2$).**

14

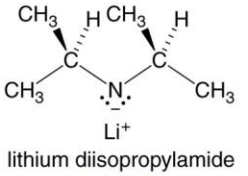
Table 23.3 Enolate Formation with Various Bases: $RCOCH_3$ ($pK_a \approx 20$) + B: → $RCOCH_2^-$ + HB^+

	Base (B:)	Conjugate acid (HB^+)	pK_a of HB^+	% Enolate
[1]	$Na^+ {}^-OH$	H_2O	15.7	< 1%
[2]	$Na^+ {}^-OCH_2CH_3$	CH_3CH_2OH	16	< 1%
[3]	$K^+ {}^-OC(CH_3)_3$	$(CH_3)_3COH$	18	1–10% (depending on the carbonyl compound)
[4]	Na^+H^-	H_2	35	100%
[5]	$Li^+ {}^-N[CH(CH_3)_2]_2$	$HN[CH(CH_3)_2]_2$	40	100%

15

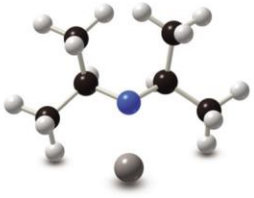
LDA—A Strong Nonnucleophilic Base

- **To form an enolate in essentially 100% yield, a much stronger base such as lithium diisopropylamide, $Li^+ {}^-N[CH(CH_3)_2]_2$, abbreviated LDA, is used.**
- **LDA is a strong nonnucleophilic base.**



lithium diisopropylamide

LDA

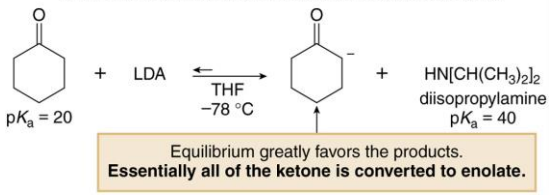


The N atom is too crowded to be a nucleophile.

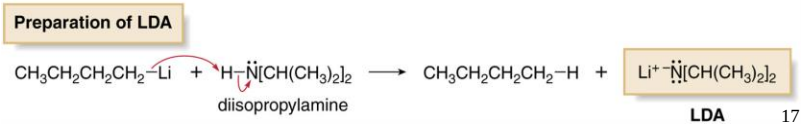
16

Preparation and Use of LDA

- **LDA quickly deprotonates essentially all of the carbonyl starting material, even at –78°C, to form the enolate product.**
- **THF is the typical solvent for these reactions.**



- **LDA can be prepared by deprotonating diisopropylamine with an organolithium reagent such as butyllithium, and then used immediately in a reaction.**



17

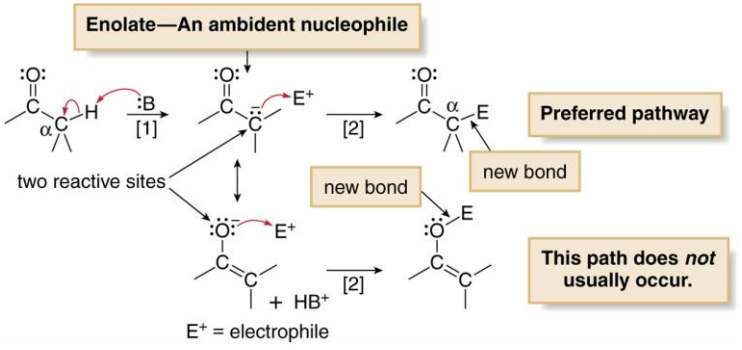
Chemistry of Enolates

- **Enolates are nucleophiles, and as such, they react with many electrophiles.**
- **Since an enolate is resonance stabilized, it has two reactive sites—the carbon and oxygen atoms that bear the negative charge.**
- **A nucleophile with two reaction sites is called an ambident nucleophile.**
- **In theory, each of these atoms could react with an electrophile to form two different products, one with a new bond to carbon, and one with a new bond to oxygen.**

18

Reactive Site of Enolates

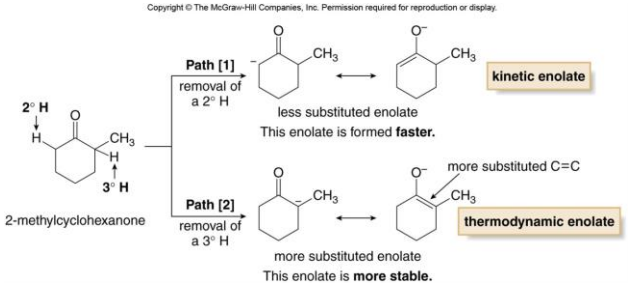
- **Enolates usually react with electrophiles on the α carbon, because this site is more nucleophilic.**
- **Since enolates usually react with carbon, the resonance structure that places the negative charge on oxygen will often be omitted in multistep mechanisms.**



19

Enolates of Unsymmetrical Carbonyl Compounds

- **When an unsymmetrical carbonyl compound like 2-methylcyclohexanone is treated with base, two enolates are possible.**



- **Path [1] occurs more quickly because it results in removal of the less hindered 2° H, forming the kinetic enolate.**
- **Path [2] results in formation of the more stable (thermodynamic) enolate, which predominates at equilibrium.**

20

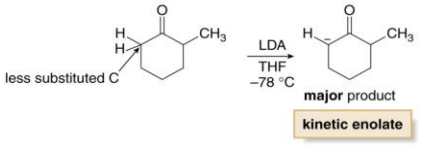
Formation of Kinetic Enolates

- It is possible to regioselectively form one or the other enolate by the proper use of reaction conditions, because the base, solvent and reaction temperature all affect the identity of the enolate formed.
- The kinetic enolate forms more quickly, so mild reaction conditions favor it over slower processes with higher energies of activation.
- The kinetic enolate is the less stable enolate, so it must not be allowed to equilibrate to the more stable thermodynamic enolate.

21

Conditions that Favor Kinetic Enolates

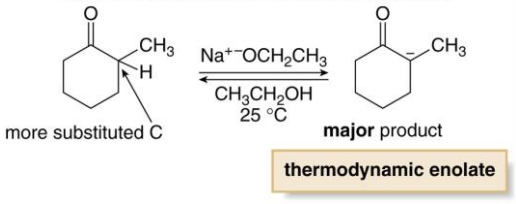
- A strong nonnucleophilic base—a strong base ensures that the enolate is formed rapidly.
  - A bulky base like LDA removes the more accessible proton on the less substituted carbon much more quickly than a more hindered proton.
- Polar aprotic solvent—the solvent must be polar to dissolve the polar starting materials and intermediates.
  - It must be aprotic so that it does not protonate any enolate that is formed.
- Low temperature—the temperature must be low (−78°C) to prevent the kinetic enolate from equilibrating to the thermodynamic enolate.



22

Conditions that Favor Thermodynamic Enolates

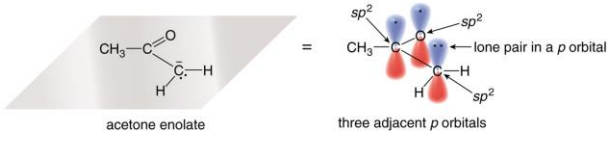
- **A thermodynamic enolate is formed with a strong base in a polar protic solvent at room temperature.**
- **A strong base—such as $Na^{+-}OCH_2CH_3$ or $K^{+-}OC(CH_3)_3$, yields both enolates, but in a protic solvent enolates can also be protonated to re-form the carbonyl starting material.**
- **At equilibrium, which can be attained by running the reaction at room temperature (25°), the lower energy intermediate always wins out so that the more stable, more substituted enolate is present in a higher concentration.**



Enolate Structure

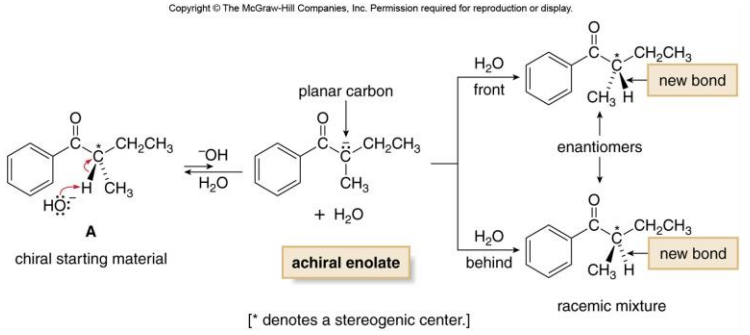
- **Recall that an enolate can be stabilized by the delocalization of electron density only if it possesses the proper geometry and hybridization.**
- **The electron pair on the carbon adjacent to the C=O must occupy a *p* orbital that overlaps with the two other *p* orbitals of the C=O, making an enolate conjugated.**
- **All three atoms of the enolate are sp^2 hybridized and trigonal planar.**

Figure 23.2
The hybridization and geometry of the acetone enolate $(CH_3COCH_2)^-$



Racemization at the α Carbon Atom

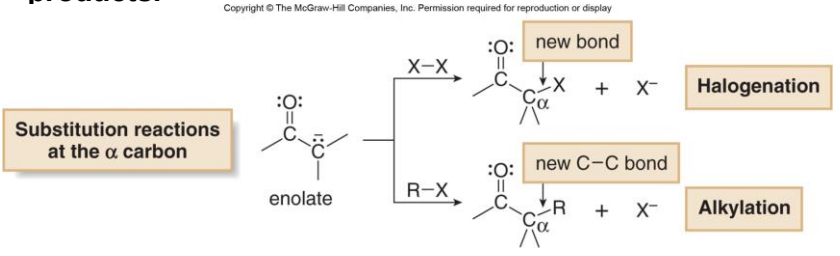
- **When the α carbon to the carbonyl is a stereogenic center, treatment with aqueous base leads to racemization by a two-step process:**
  - **deprotonation to form a planar enolate**
  - **protonation from either face to re-form a racemized carbonyl compound**



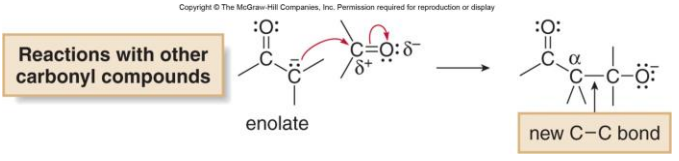
25

Reactions at the α Carbon

- **Enolates react with electrophiles to form substitution products.**



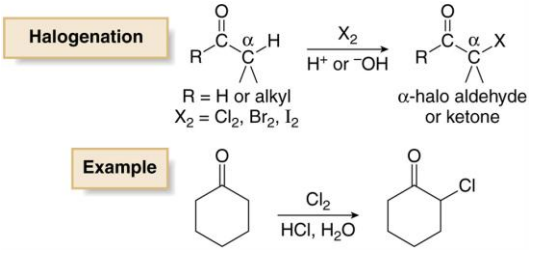
- **Enolates react with other carbonyl groups at the electrophilic carbon.**



26

Halogenation at the α Carbon

- **Treatment of a ketone or aldehyde with halogen and either acid or base results in substitution of X for H on the α carbon, forming an α-halo aldehyde or ketone.**

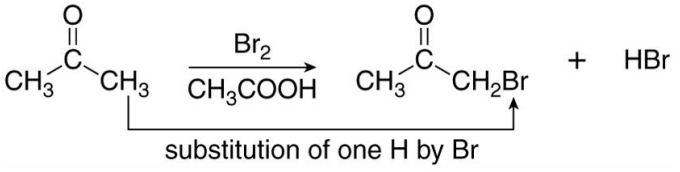


- **The mechanisms of halogenation in acid and base are somewhat different—reactions done in acid generally involve enol intermediates.**
- **Reactions done in base generally involve enolate intermediates.**

27

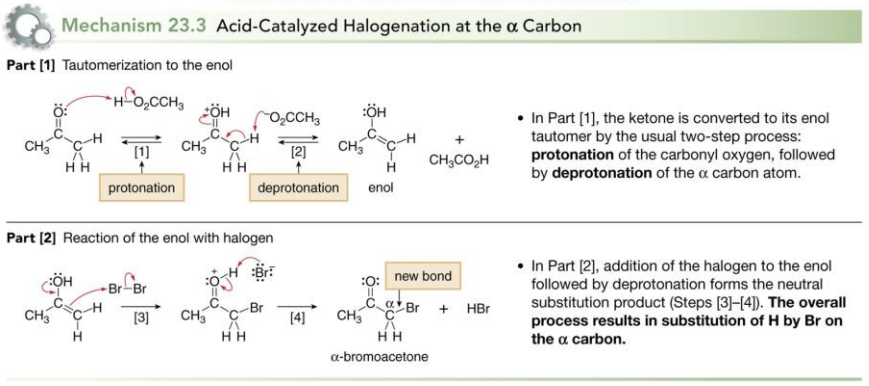
Acid-Catalyzed Halogenation

- **When halogenation is conducted in the presence of acid, the acid often used is acetic acid, which serves as both the solvent and the acid catalyst for the reaction.**



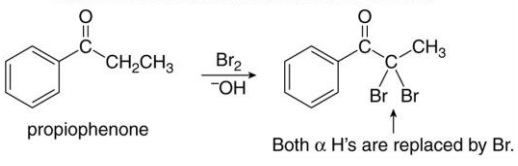
- **The mechanism of acid-catalyzed halogenation consists of two parts:**
  - **tautomerization of the carbonyl compound to the enol form**
  - **reaction of the enol with halogen**

28

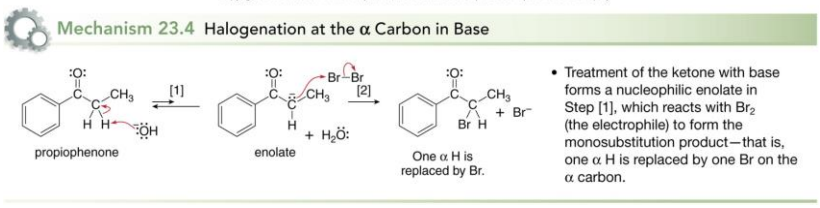


Halogenation at the α Carbon in Base

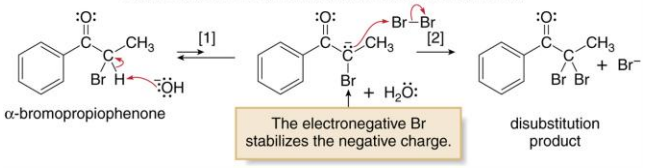
- **Halogenation in base is much less useful, because it is often difficult to stop the reaction after addition of just one halogen atom to the α carbon.**
- **For example, treatment of propiophenone with Br_2 and aqueous ^-OH yields a dibromoketone.**



- **The mechanism for introduction of each Br atom involves the same two steps:**
  - **deprotonation with base followed by**
  - **reaction with Br_2 to form a new C–Br bond**



- **Only a small amount of the enolate forms at equilibrium using $^-$OH as base, but the enolate is such a strong nucleophile that it readily reacts with Br_2, thus driving the equilibrium to the right.**
- **The same steps can be repeated to introduce a second bromine at the α carbon.**



31

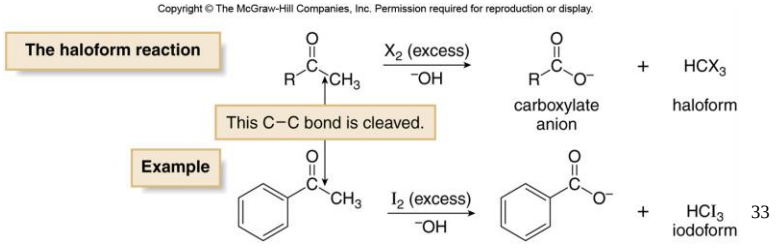
Haloform Reaction

- **The addition of one Br atom stabilizes the second enolate due to the electron-withdrawing inductive effect of Br.**
- **As a result, the α H of α-bromopropiophenone is more acidic than the α H atoms of propiophenone, making it easier to remove with base.**
- **Halogenation of a methyl ketone with excess halogen, called the haloform reaction, results in the cleavage of a C–C σ bond and formation of two products, a carboxylate anion and CHX_3 (commonly called haloform).**
- **The final cleavage step is actually a nucleophilic substitution, made possible by the fact that the tri-substituted CX_3 is now a good leaving group.**

32

Haloform Reaction

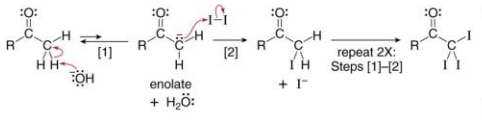
- **In the haloform reaction, the three H atoms of the CH_3 group are successively replaced by X to form an intermediate that is oxidatively cleaved with base.**
- **Methyl ketones form iodoform (CHI_3), a pale yellow solid that precipitates from the reaction mixture.**
- **This reaction is the basis of the iodoform test to detect methyl ketones.**
- **Methyl ketones give a positive iodoform test (appearance of a yellow solid) whereas other ketones give a negative iodoform test (no change in the reaction mixture).**



33

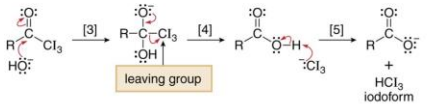
Mechanism 23.5 The Haloform Reaction

Part [1] The conversion of CH_3 to CI_3



- In Part [1], each of the three hydrogen atoms of the CH_3 group is replaced with iodine via the two-step mechanism previously discussed—that is, deprotonation followed by halogenation to form the substitution product.
- Steps [1] and [2] are then repeated twice more to form the triiodo substitution product.

Part [2] Oxidative cleavage with ^-OH

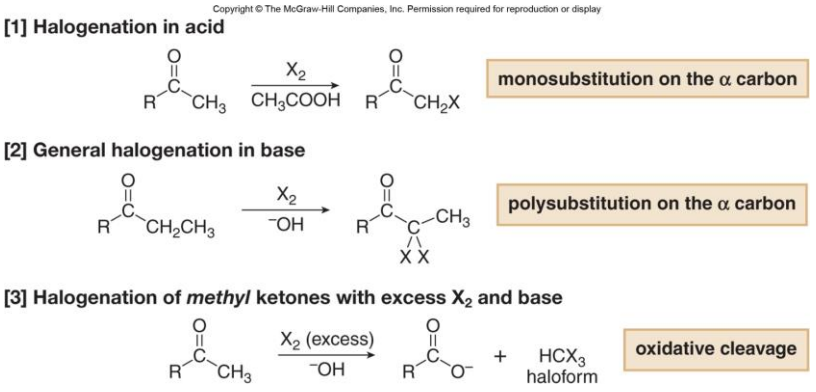


- In Step [3], ^-OH adds to the carbonyl group in a typical **nucleophilic addition** reaction of a ketone, but the three I atoms give this ketone a good leaving group, $^-CI_3$.
- **Elimination of $^-CI_3$ in Step [4] results in cleavage of a carbon–carbon bond,** and then in the last step, proton transfer forms the carboxylate anion and iodoform.

34

Halogenation Reactions at α Carbons

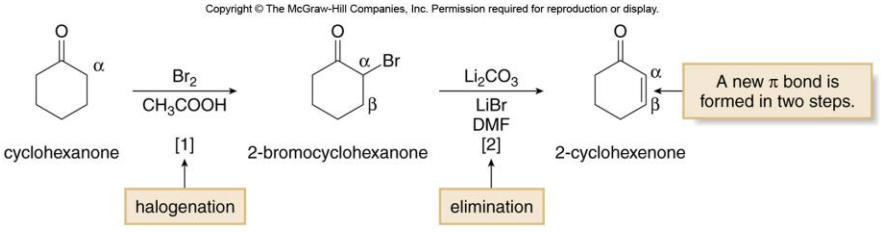
Figure 23.3



35

Elimination Reaction of α-Halo Carbonyls

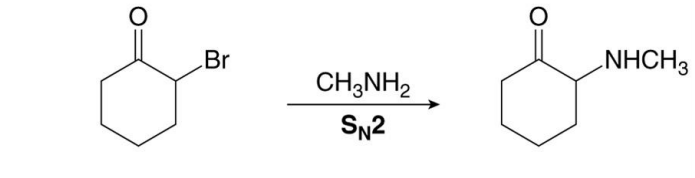
- **α-Halo carbonyl compounds undergo two useful reactions—elimination with base and substitution with nucleophiles.**
- **By a two step method involving elimination, a carbonyl compound such as cyclohexanone can be converted into an α,β-unsaturated carbonyl compound.**



36

Substitution Reaction of α-Halo Carbonyls

- **α-Halo carbonyl compounds also react with nucleophiles by S_N2 reactions.**
- **For example, reaction of 2-bromocyclo-hexanone with CH_3NH_2 affords the substitution product A.**

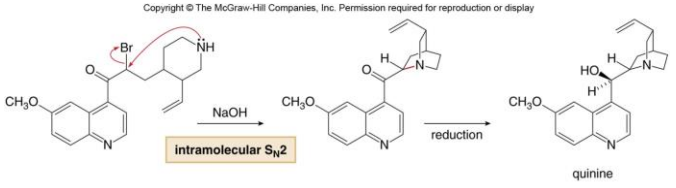


37

Intramolecular Nucleophilic Substitution

- **A related intramolecular nucleophilic substitution of an α-halo ketone was a key step in the synthesis of the antimalarial drug quinine, shown in Figure 23.4.**

Figure 23.4
Intramolecular nucleophilic substitution in the synthesis of quinine

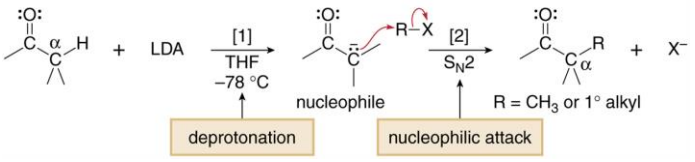


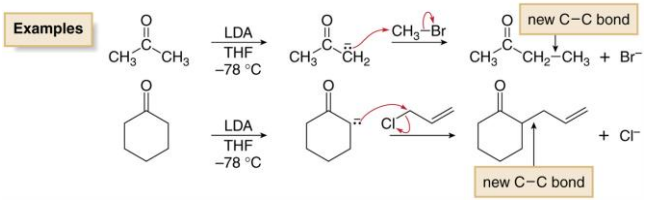
- Intramolecular S_N2 reaction of a nitrogen nucleophile with an α-halo ketone affords a compound that can be converted to quinine in a single step. The new C–N bond on the α carbon is labeled in red.

38

Direct Enolate Alkylation

- **Treatment of an aldehyde or ketone with base and an alkyl halide results in alkylation—the substitution of R for H on the α carbon atom.**

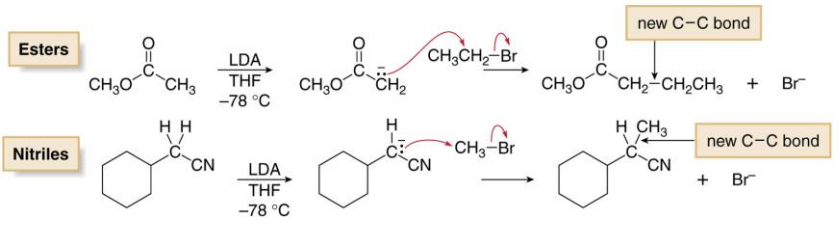




39

Enolate Addition with Esters and Nitriles

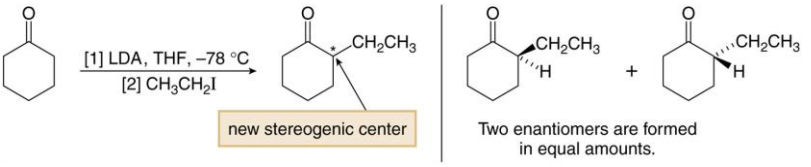
- **Since the second step is an S_N2 reaction, it only works well with unhindered methyl and 1° alkyl halides.**
- **Hindered alkyl halides and those with halogens bonded to *sp*^{2} hybridized carbons do not undergo substitution.**
- **Ester enolates and carbanions derived from nitriles are also alkylated under these conditions.**



40

Stereochemistry of Enolate Alkylation

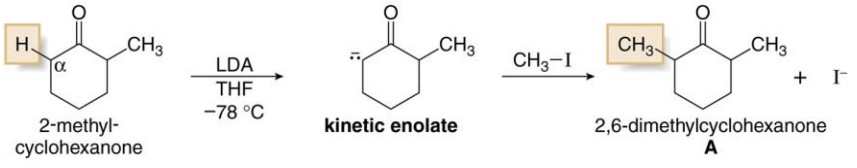
- **The stereochemistry of enolate alkylation follows the general rule governing stereochemistry of reactions: an achiral starting material yields an achiral or racemic product.**



41

Kinetic Product of Enolate Alkylation

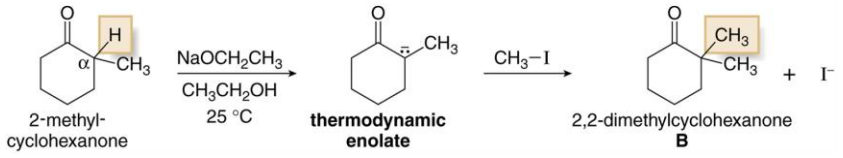
- **An unsymmetrical ketone can be regioselectively alkylated to yield either the kinetic or thermodynamic product.**
- **Treatment of 2-methylcyclohexanone with LDA in THF solution at –78°C gives the less substituted kinetic enolate.**
- **The enolate then reacts with CH_3I to form A.**



42

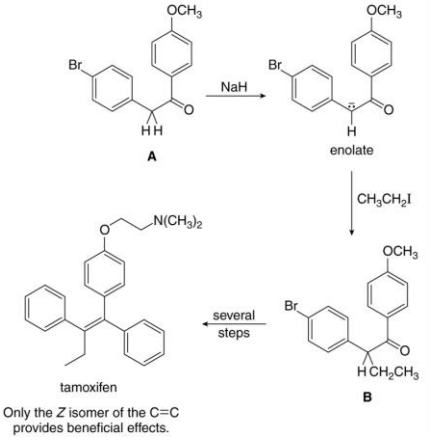
Thermodynamic Product of Enolate Alkylation

- **Treatment of that same ketone, 2-methylcyclohexanone, with $NaOCH_2CH_3$ in CH_3CH_2OH solution at room temperature forms the more substituted thermodynamic enolate.**
- **The enolate then reacts with CH_3I to form B.**



Application of Enolate Alkylation

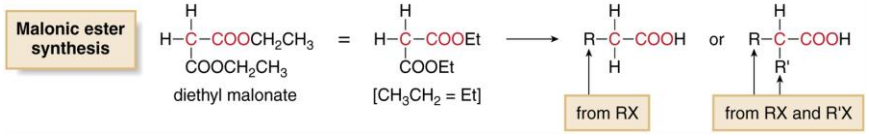
- **One step in the synthesis of tamoxifen, a potent anticancer drug, involves enolate formation and alkylation with CH_3CH_2I.**



Malonic Ester Synthesis

- **The malonic ester synthesis results in the preparation of carboxylic acids having two general structures:**

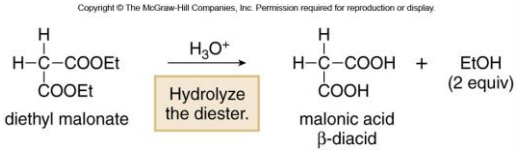
- **The malonic ester synthesis is a stepwise method for converting diethyl malonate into a carboxylic acid having one or two alkyl groups on the α carbon.**



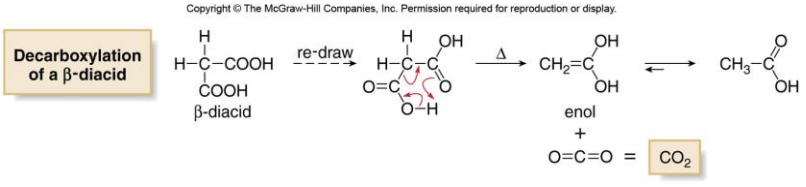
45

Decarboxylation of Malonic Esters

- **Heating diethyl malonate with acid and water hydrolyzes both esters to carboxy groups, forming a β-diacid (1,3-diacid).**



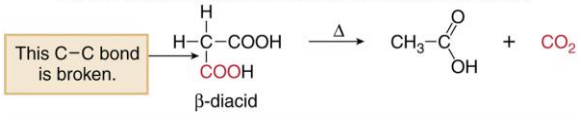
- **β-Diacids are unstable to heat and decarboxylate resulting in cleavage of a C–C bond and formation of a carboxylic acid.**



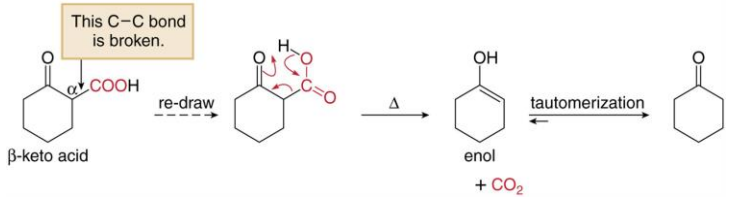
46

Decarboxylation Result

- **The net result of decarboxylation is cleavage of a C–C bond on the α carbon, with loss of CO_2.**
- **Decarboxylation occurs readily whenever a carboxy group (COOH) is bonded to the α carbon of another carbonyl group.**

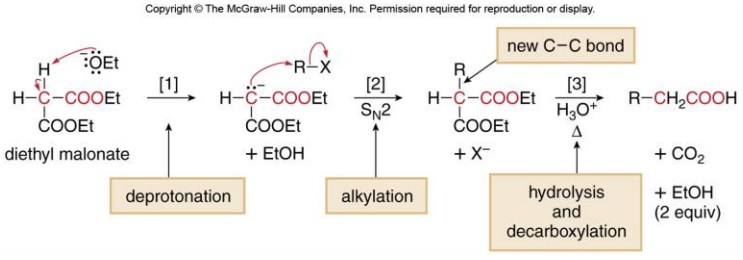


- **This can also occur with β-keto acids, forming a ketone.**



Path of Malonic Ester Synthesis

- **Thus, the malonic ester synthesis converts diethyl malonate to a carboxylic acid in three steps.**



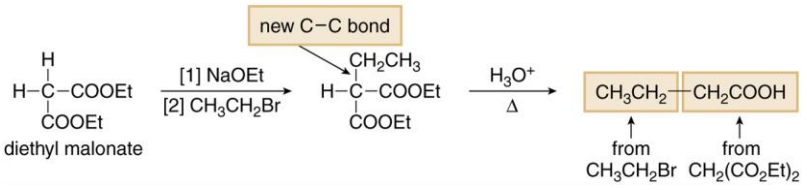
[1] Deprotonation – removing the acidic α proton.

[2] Alkylation – Nucleophilic enolate displaces halogen on an alkyl halide.

[3] Hydrolysis and decarboxylation – heating with aqueous acid causes loss of CO_2.

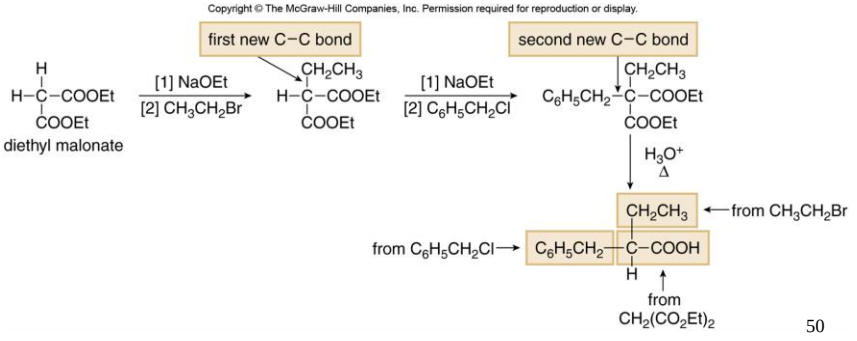
Example of Malonic Ester Synthesis

- **The synthesis of 2-butanoic acid ($CH_3CH_2CH_2COOH$) from diethyl malonate illustrates the basic process:**



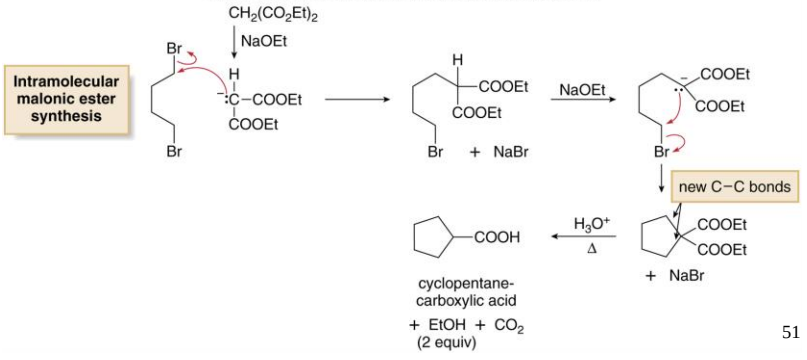
Repeated Malonic Ester Synthesis

- **If the first two steps of the reaction sequence are repeated prior to hydrolysis and decarboxylation, then a carboxylic acid having two new alkyl groups on the α carbon can be synthesized.**
- **This is illustrated in the synthesis of 2-benzylbutanoic acid [$CH_3CH_2CH(CH_2C_6H_5)COOH$] from diethyl malonate.**



Intramolecular Malonic Ester Synthesis

- **An intramolecular malonic ester synthesis can be used to form rings having three to six atoms, provided the appropriate dihalide is used as starting material.**
- **For example, cyclopentanecarboxylic acid can be prepared from diethyl malonate and 1,4-dibromobutane ($BrCH_2CH_2CH_2CH_2Br$) by the following sequence of reactions.**

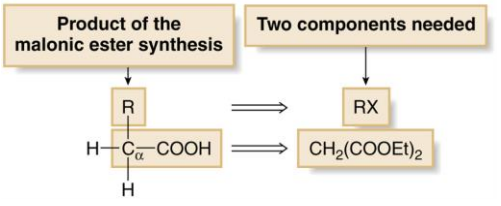


Retrosynthetic Analysis of Malonic Esters

- **To use the malonic ester synthesis, you must be able to determine what starting materials are needed to prepare a given compound—that is, you must work backwards in the retrosynthetic direction.**
- **This involves a two-step process:**

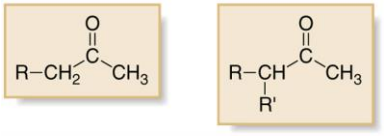
[1] Locate the α carbon to the COOH group, and identify all alkyl groups bonded to the α carbon.

[2] Break the molecule into two (or three) components: Each alkyl group bonded to the α carbon comes from an alkyl halide. The remainder of the molecule comes from $CH_2(COOEt)_2$.

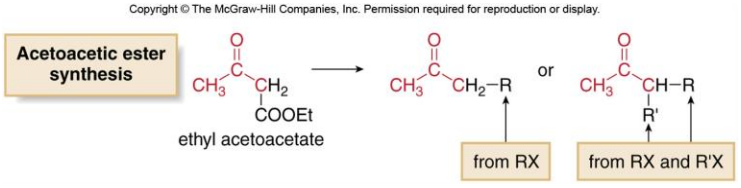


Acetoacetic Ester Synthesis

- **The acetoacetic ester synthesis results in the preparation of methyl ketones having two general structures:**



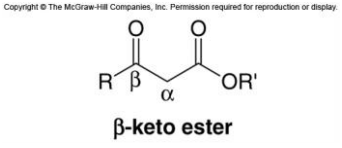
- **The acetoacetic ester synthesis is a stepwise method for converting ethyl acetoacetate into a ketone having one or two alkyl groups on the α carbon.**

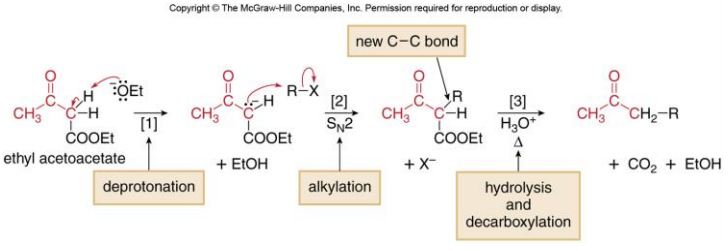


53

Outcome of Acetoacetic Ester Synthesis

- **The steps in acetoacetic ester synthesis are exactly the same as those in the malonic ester synthesis.**
- **Because the starting material is a β-ketoester, the final product is a ketone, not a carboxylic acid.**

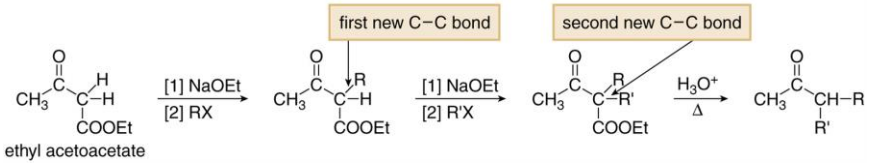




54

Repeated Acetoacetic Ester Synthesis

- **If the first two steps of the reaction sequence are repeated prior to hydrolysis and decarboxylation, then a ketone having two new alkyl groups on the α carbon can be synthesized.**

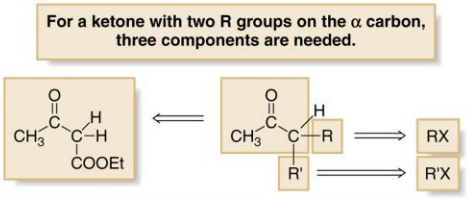


55

Retrosynthetic Analysis of Acetoacetic Esters

- **To determine what starting materials are needed to prepare a given ketone using the acetoacetic ester synthesis, you must again work in a retrosynthetic direction.**
- **This involves a two-step process:**

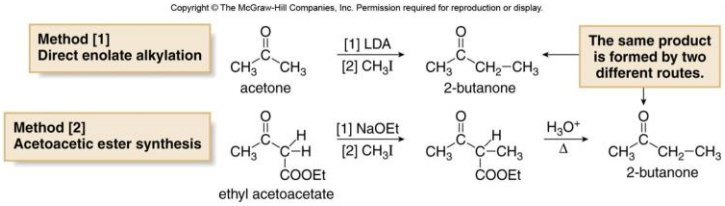
[1] Identify the alkyl groups bonded to the α carbon to the carbonyl group.
[2] Break the molecule into two (or three) components: Each alkyl group bonded to the α carbon comes from an alkyl halide. The remainder of the molecule comes from CH_3COCH_2COOEt.



56

Synthesis of Ketones

- **The acetoacetic ester synthesis and direct enolate alkylation are two different methods that can prepare similar ketones.**



- **Each method has its own advantages and disadvantages.**
- **The two step direct enolate alkylation usually requires a very strong base like LDA to be successful, whereas the acetoacetic ester synthesis utilizes NaOEt, which is prepared from cheaper starting materials.**
- **This cost factor makes the acetoacetic ester synthesis an attractive method, even though it involves more steps.**

57