Organic Chemistry III

Mohammad Jafarzadeh

Faculty of Chemistry, Razi University

Organic Chemistry, *Structure and Function* **(7th edition)**

By *P. Vollhardt* and *N. Schore*, Elsevier, 2014

23-2 β-Dicarbonyl compounds as synthetic Intermediates

This section will show that the corresponding anions are readily alkylated and that 3-ketoesters are hydrolyzed to the corresponding acids, which can be decarboxylated to give ketones or new carboxylic acids.

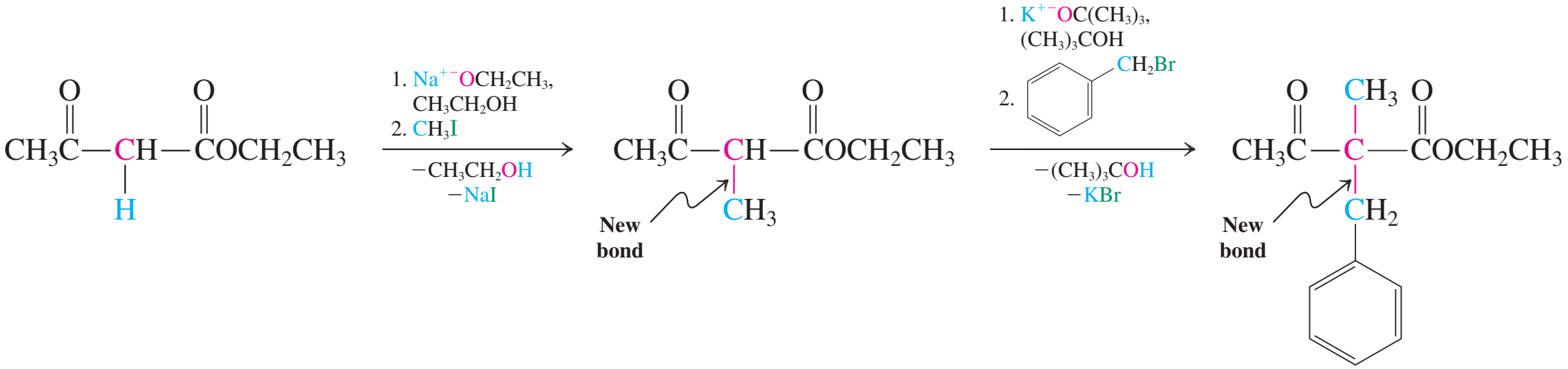
β-Dicarbonyl anions are nucleophilic

The unusually high acidity of the methylene hydrogens of **β**-ketocarbonyl compounds can be used to synthetic advantage. Their unusually low pK_a values allow alkoxide bases to remove a proton from this methylene group essentially quantitatively, giving an enolate ion that may be alkylated to produce substituted derivatives.

For example, treatment of ethyl 3-oxobutanoate (ethyl acetoacetate) with $NaOCH_2CH_3$ effects complete deprotonation to the enolate, which reacts via the S_N2 mechanism with iodomethane to afford the methylated derivative.

The remaining acidic hydrogen at this position can be abstracted with the somewhat stronger base $KOC(CH_3)_3$. The resulting anion may undergo another S_N2 alkylation with benzyl bromide to yield the doubly substituted product.

β-Ketoester Alkylations



Ethyl 3-oxobutanoate (Ethyl acetoacetate)

65%

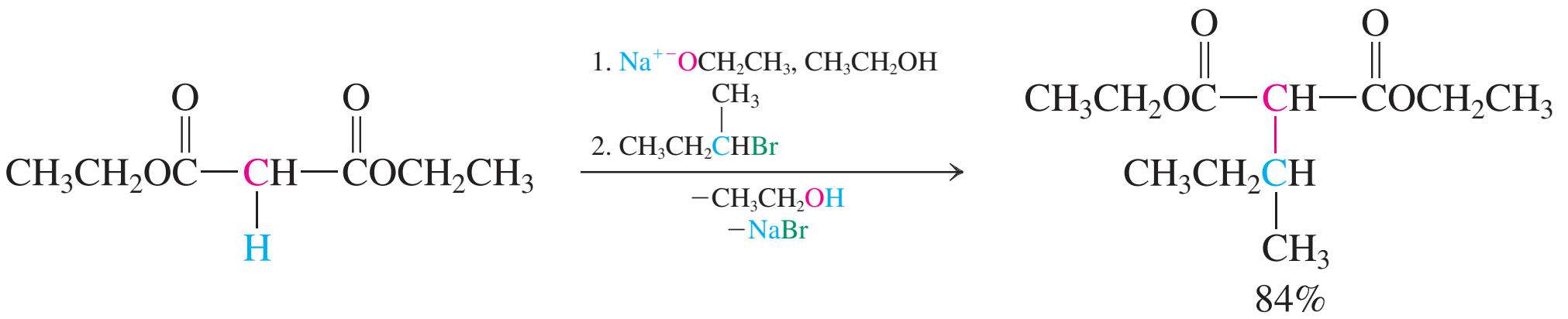
Ethyl 2-methyl-3-oxobutanoate

77%

Ethyl 2-methyl-2-(phenylmethyl)-3-oxobutanoate

These alkylations provide synthetic access to 2,2-disubstituted **β**-ketoesters, which cannot be prepared directly by means of the Claisen condensation.

Other **β**-dicarbonyl compounds undergo similar reactions.



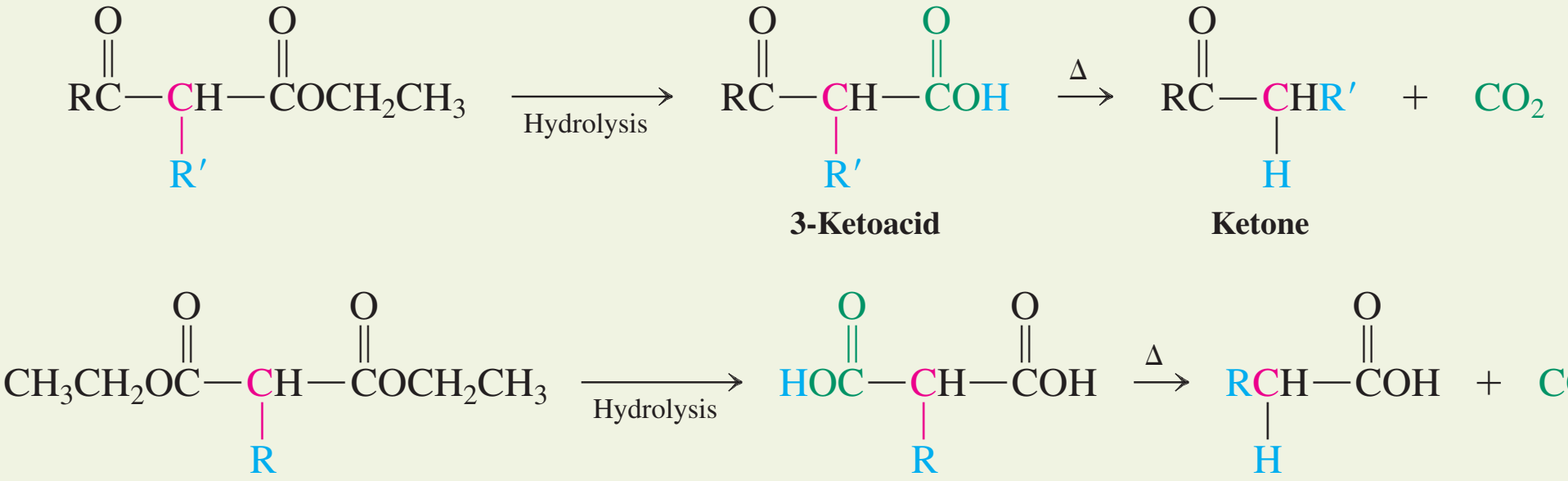
Diethyl propanedioate (Diethyl malonate)

Diethyl 2-(1-methylpropyl)propanedioate

3-Ketoacids readily undergo decarboxylation

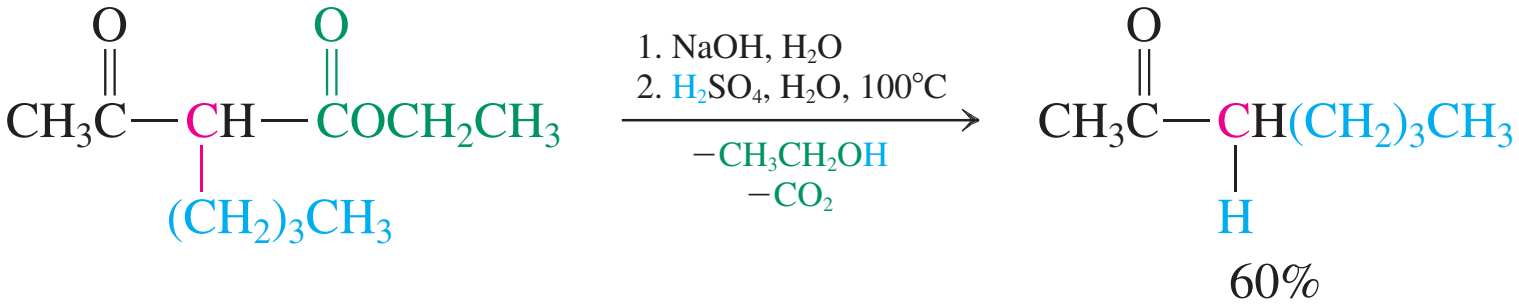
Hydrolysis of 3-ketoesters furnishes 3-ketoacids, which in turn readily undergo decarboxylation under mild conditions. The products contain the alkyl groups introduced in prior alkylation steps.

Formation and Decarboxylation of 3-Ketoacids

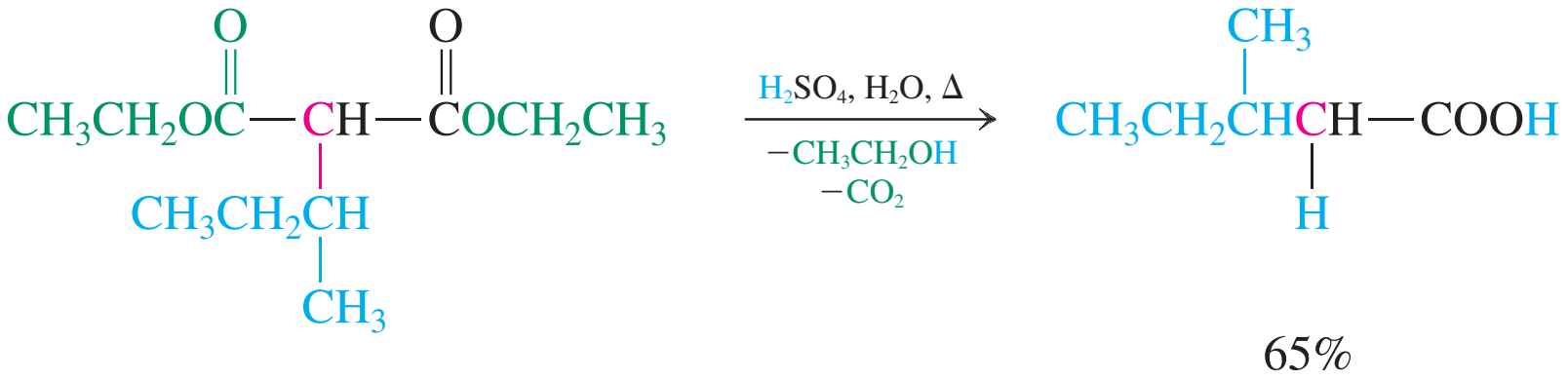


Note that only carboxylic acids with a second carbonyl group in the 3- or **β**-position are structurally capable of reacting in this way.

Carboxylic acids lacking a **β**-carbonyl function do not decarboxylate, regardless of the presence of C=O groups elsewhere in the molecule.



Ethyl 2-butyl-3-oxobutanoate — **2-Heptanone**



Diethyl 2-(1-methylpropyl)propanedioate — **3-Methylpentanoic acid**

Decarboxylation, or loss of CO_2, is not a typical reaction of carboxylic acids under ordinary conditions. However, **β**-ketoacids are unusually prone to decarboxylation for two reasons:

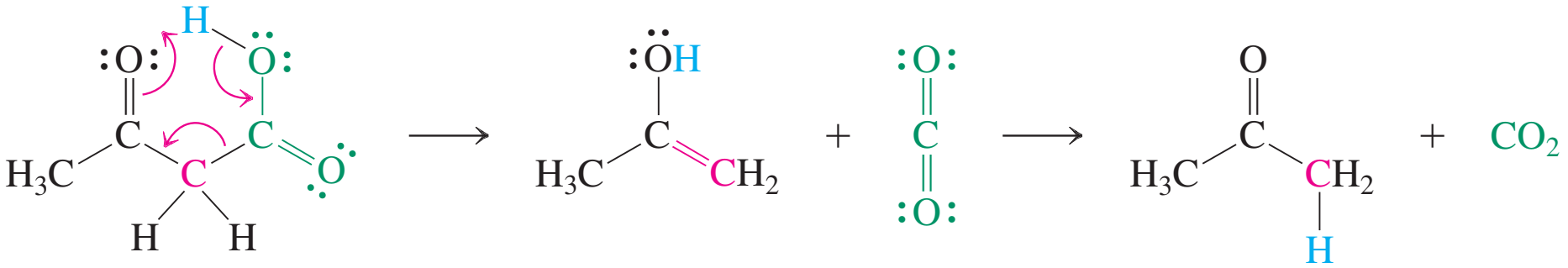
(i) the Lewis basic oxygen of the 3-keto function is ideally positioned to bond with the carboxy hydrogen by means of a cyclic six-atom transition state.

(ii) this transition state has aromatic character, because three electron pairs shift around the cyclic six-atom array.

The species formed in decarboxylation are CO_2 and an enol, which tautomerizes rapidly to the final ketone product.

Loss of CO_2 occurs readily only from the neutral carboxylic acid. If the ester is hydrolyzed with base, acid must be added to protonate the resulting carboxylate salt.

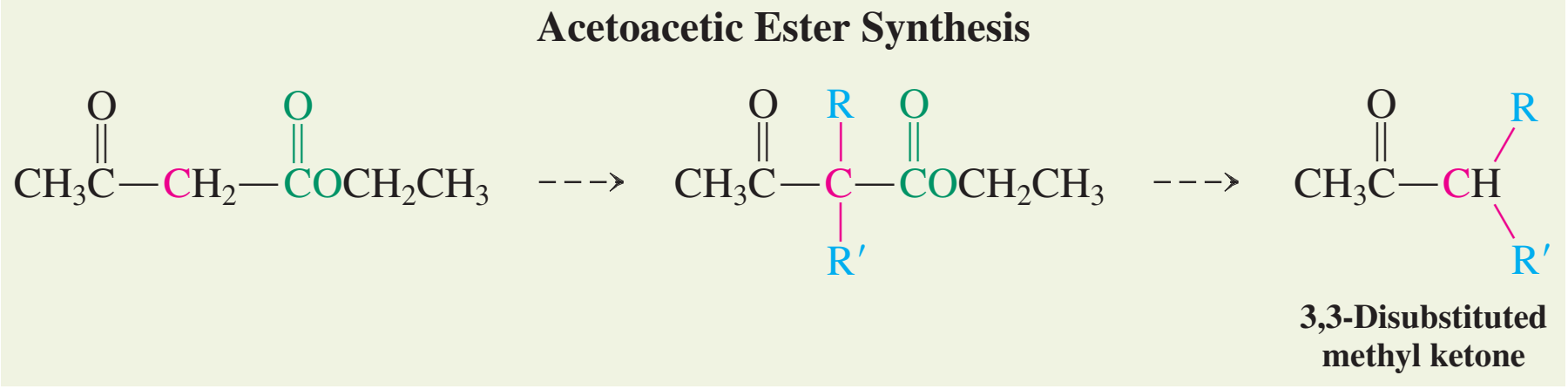
Mechanism of Decarboxylation of 3-Ketoacids



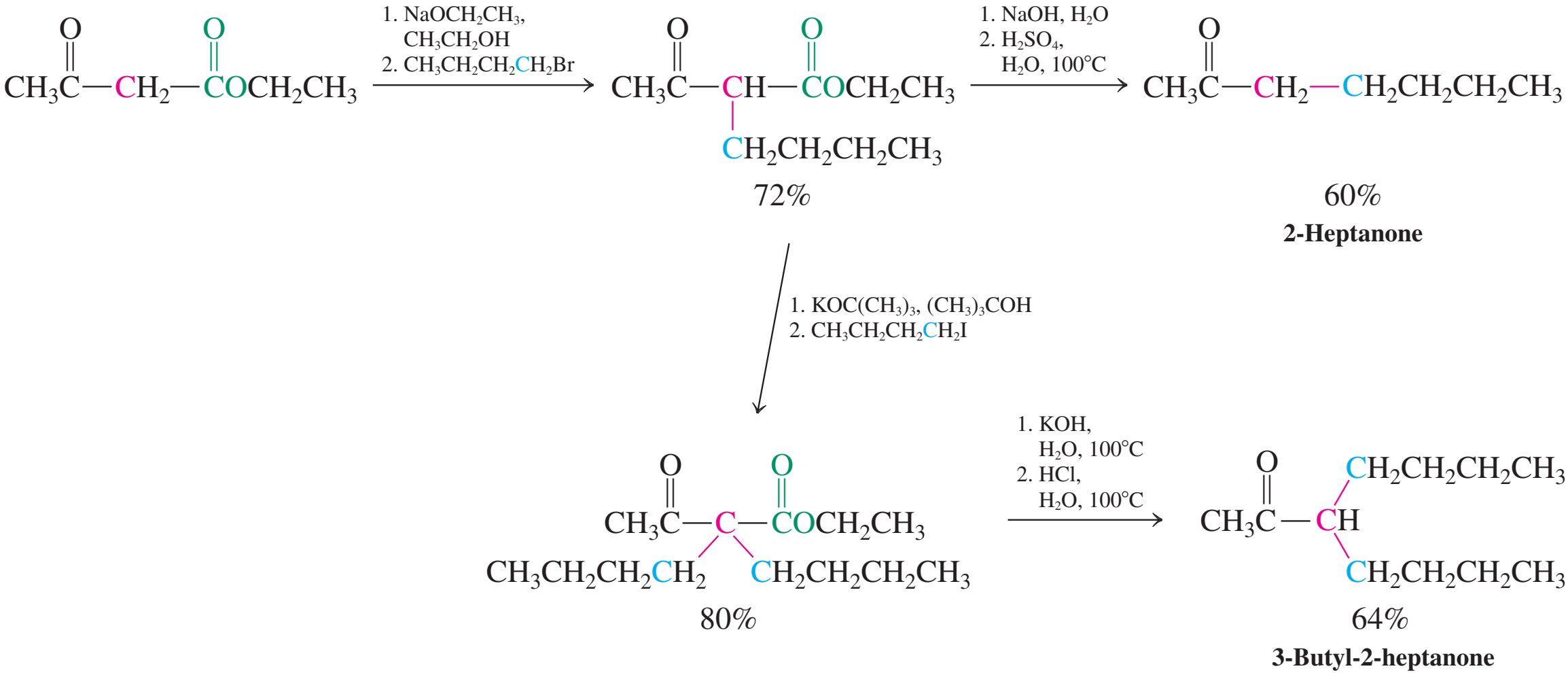
The acetoacetic ester synthesis leads to methyl ketones

The combination of alkylation followed by ester hydrolysis and finally decarboxylation allows ethyl 3-oxobutanoate (ethyl acetoacetate) to be converted ultimately into 3-substituted or 3,3-disubstituted methyl ketones. This strategy is called the acetoacetic ester synthesis.

Methyl ketones with either one or two substituent groups on C3 can be synthesized by using the acetoacetic sequence.



Syntheses of Substituted Methyl Ketones



The malonic ester synthesis furnishes carboxylic acids

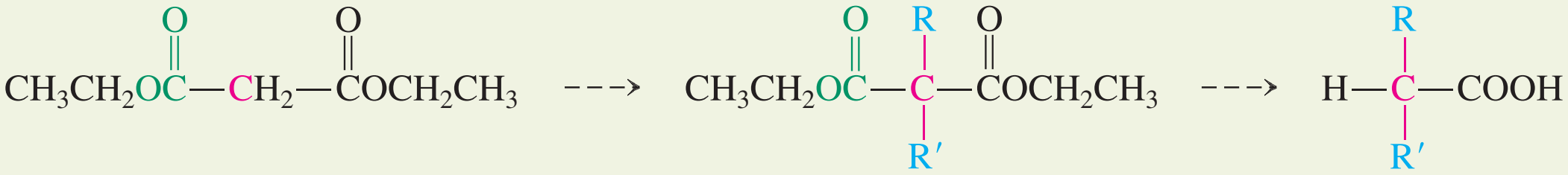
Diethyl propanedioate (malonic ester) is the starting material for preparing 2-alkylated and 2,2-dialkylated acetic acids, a method called the malonic ester synthesis.

Like the acetoacetic ester route to ketones, the malonic ester synthesis can lead to carboxylic acids with either one or two substituents at C2.

The rules and limitations governing S_N2 reactions apply to the alkylation steps. Thus, tertiary haloalkanes exposed to **β**-dicarbonyl anions give mainly elimination products.

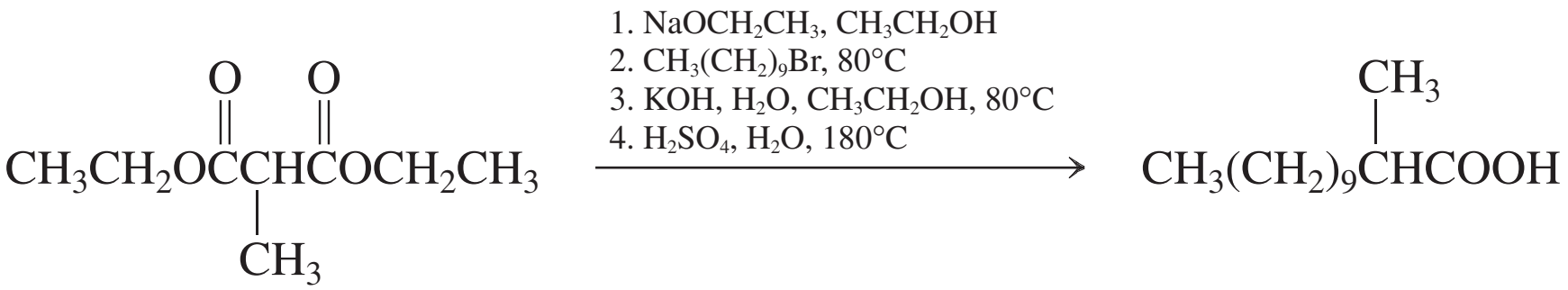
However, the anions can successfully attack acyl halides, ***α***-bromoesters, ***α***-bromoketones, and oxacyclopropanes.

Malonic Ester Synthesis



2,2-Dialkylated acetic acid

Synthesis of a 2,2-Dialkylated Acetic Acid



Diethyl 2-methylpropanedioate (Diethyl methylmalonate)

74%

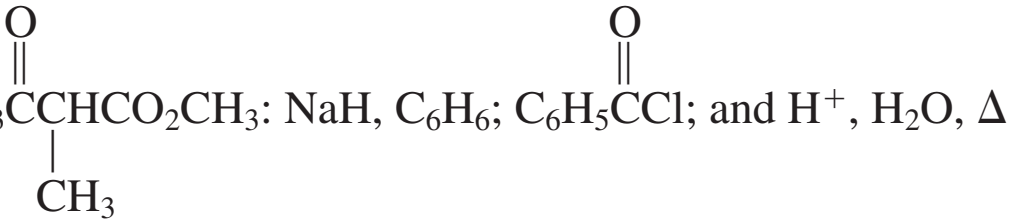
2-Methyldodecanoic acid

Exercise 23-14

The first-mentioned compound in each of the following parts is treated with the subsequent series of reagents. Give the final products. (Note: The choice of the conditions for the last step(s), either direct acid-catalyzed hydrolysis–decarboxylation or stoichiometric base hydrolysis–acidification– decarboxylation, are arbitrary.)

(a) $CH_3CH_2O_2C(CH_2)_5CO_2CH_2CH_3$: $NaOCH_2CH_3$; $CH_3(CH_2)_3I$; NaOH; and H^+, H_2O, Δ

(b) $CH_3CH_2O_2CCH_2CO_2CH_2CH_3$: $NaOCH_2CH_3$; CH_3I; KOH; and H^+, H_2O, Δ

(c) 

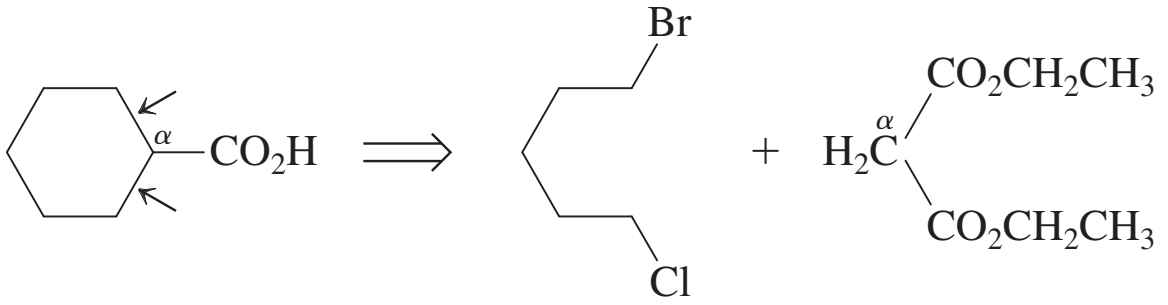
(d) 

(e) $CH_3CH_2CH(CO_2CH_2CH_3)_2$: $NaOCH_2CH_3$; $BrCH_2CO_2CH_2CH_3$; and H^+, H_2O, Δ

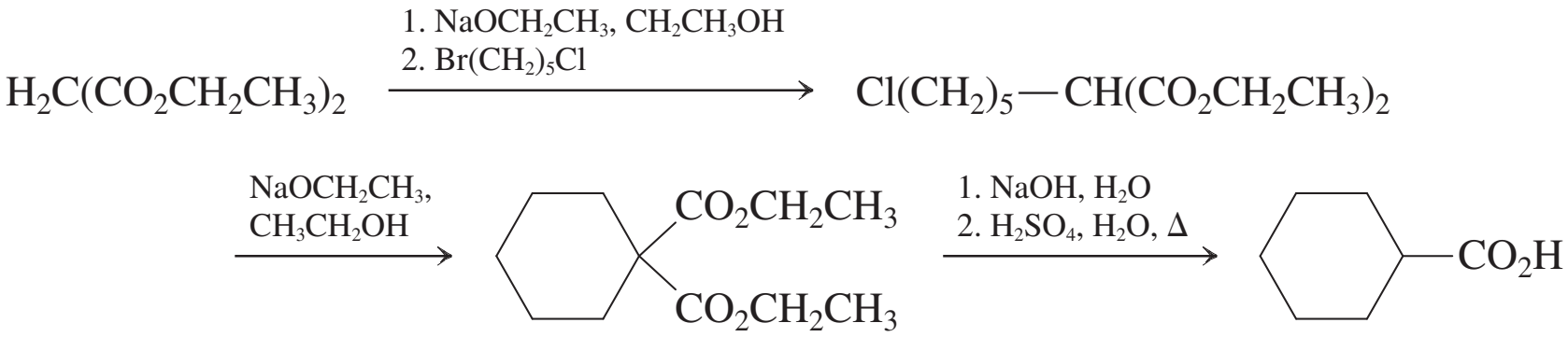
(f) 

Solved Exercise 23-15

Propose a synthesis of cyclohexanecarboxylic acid from diethyl propanedioate (malonate), $CH_2(CO_2CH_2CH_3)_2$, and 1-bromo-5-chloropentane, $Br(CH_2)_5Cl$.



Cyclohexane-carboxylic acid | **1-Bromo-5-chloropentane** | **Diethyl propanedioate (Diethyl malonate)**



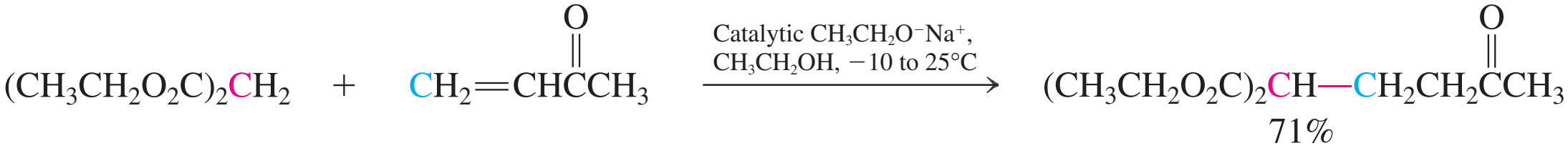
23-3 β-Dicarbonyl anion chemistry: Michael additions

Reaction of the stabilized anions derived from **β**-dicarbonyl compounds and related analogs with ***α***,**β**-unsaturated carbonyl compounds leads to 1,4-additions. This transformation, an example of Michael addition, is base catalyzed and works with ***α***,**β**-unsaturated ketones, aldehydes, nitriles, and carboxylic acid derivatives, all of which are termed **Michael acceptors**.

Why do stabilized anions undergo 1,4- rather than 1,2-addition to Michael acceptors?

1,2-Addition occurs, but is reversible with relatively stable anionic nucleophiles, because it leads to a relatively high-energy alkoxide. Conjugate addition is favored thermodynamically because it produces a resonance-stabilized enolate ion.

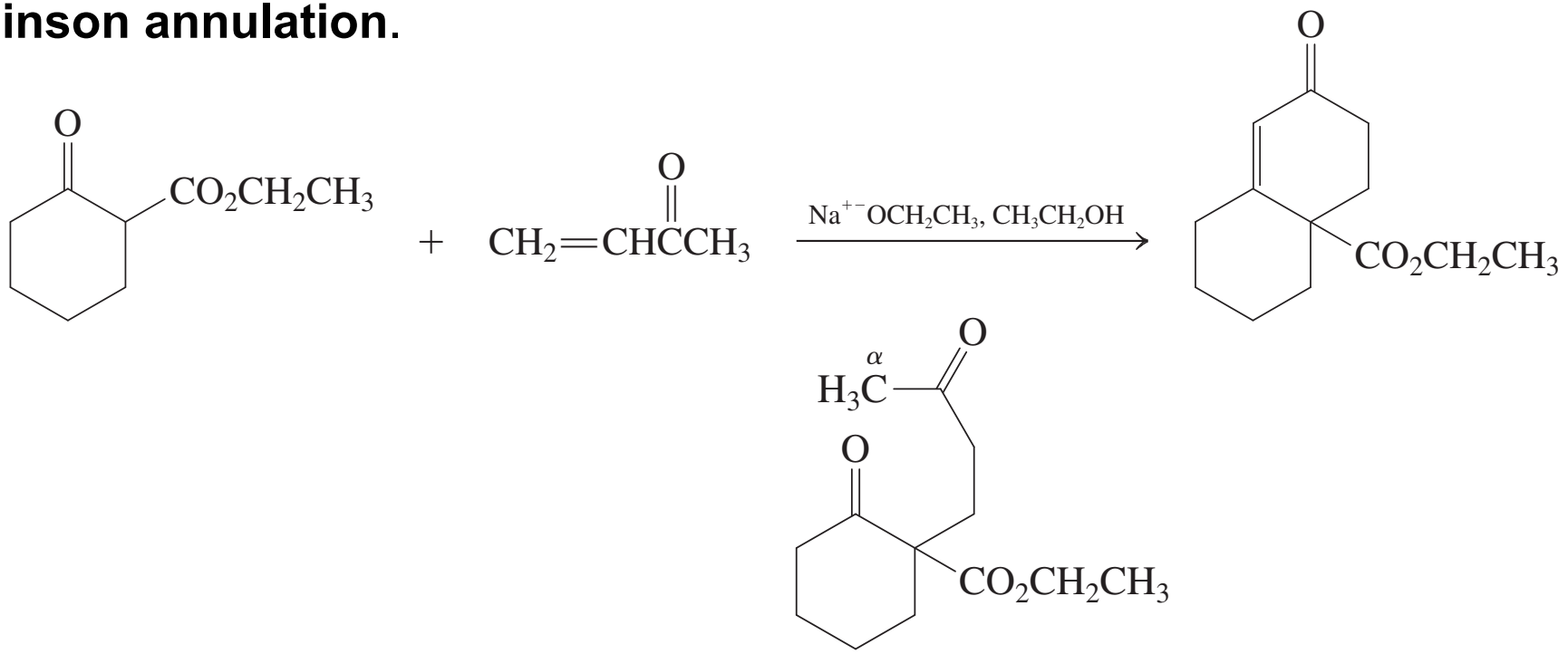
Michael Addition



The following reaction is a useful application of Michael addition of anions of **β**-ketoesters to ***α***,**β**-unsaturated ketones. The addition gives initially the diketone.

Deprotonation of the ***α***-methyl group in the side chain gives an enolate that is perfectly positioned to react with the carbonyl carbon of the cyclohexanone ring. This **intramolecular** aldol condensation forms a second six-membered ring.

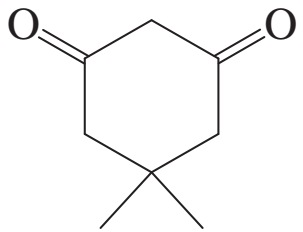
The synthesis of six-membered rings by *Michael addition* followed by *aldol condensation* is called **Robinson annulation**.

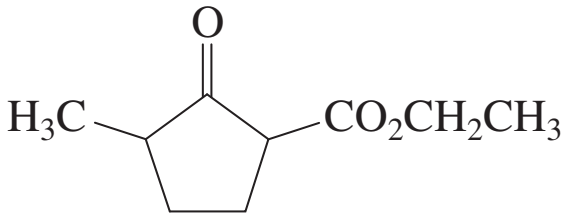


Exercise 23-18

Give the products of the following Michael additions [base in square brackets].

(a) $CH_3CH_2CH(CO_2CH_2CH_3)_2$ + $CH_2{=}CHCH{=}O$ $[Na^{+-}OCH_2CH_3]$

(b)  + $CH_2{=}CHC{\equiv}N$ $[Na^{+-}OCH_3]$

(c)  + $CH_3CH{=}CHCO_2CH_2CH_3$ $[K^{+-}OCH_2CH_3]$

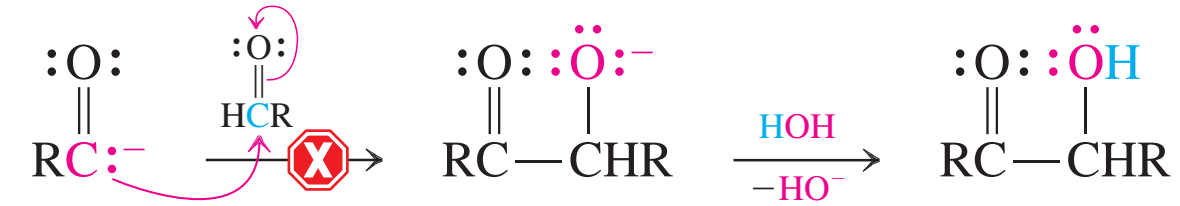
23-4 Acyl anion equivalents: Preparation of *α*-hydroxyketones

We have no way of making a direct connection between two carbonyl carbon atoms, because both are electrophilic: Neither can serve as a nucleophilic electron source to attack the other.

One may imagine a hypothetical carbonyl-derived nucleophilic species, such as an acyl anion, which might add to an aldehyde or ketone to give an ***α***-hydroxyketone, as follows.

Unfortunately, acyl anions are high-energy species and cannot be generated readily for synthetic applications.

A Plausible (but Unfeasible) Synthesis of *α*-Hydroxyketones



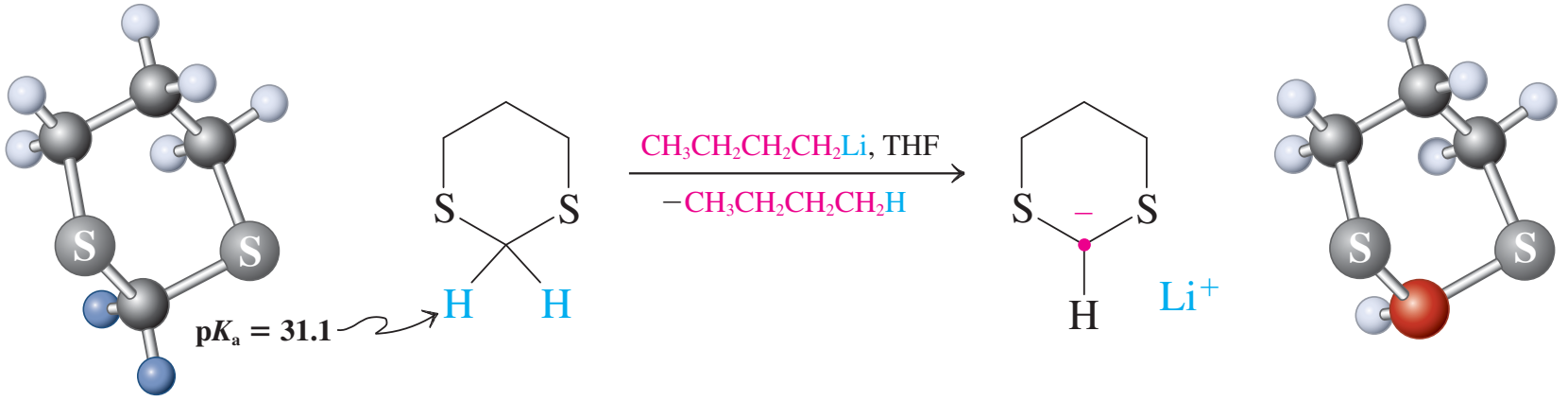
Acyl anion (cannot be made)

Chemists have explored the construction of chemical species containing negatively charged carbon atoms that can undergo addition reactions and later be transformed into carbonyl groups. These special nucleophiles are called **masked acyl anions** or **acyl anion equivalents**.

Cyclic thioacetals are masked acyl anion precursors

Cyclic thioacetals are formed by the reaction of dithiols with aldehydes and ketones. The hydrogens on the carbon positioned between the two sulfur atoms in thioacetals are acidic enough (pK_a ≃ 31) to be removed by suitably strong bases, such as alkyllithiums. The negative charge in the conjugate base is stabilized inductively by the highly polarizable sulfur atoms.

Deprotonation of 1,3-Dithiacyclohexane, a Cyclic Thioacetal, by Butylithium



1,3-Dithiacyclohexane

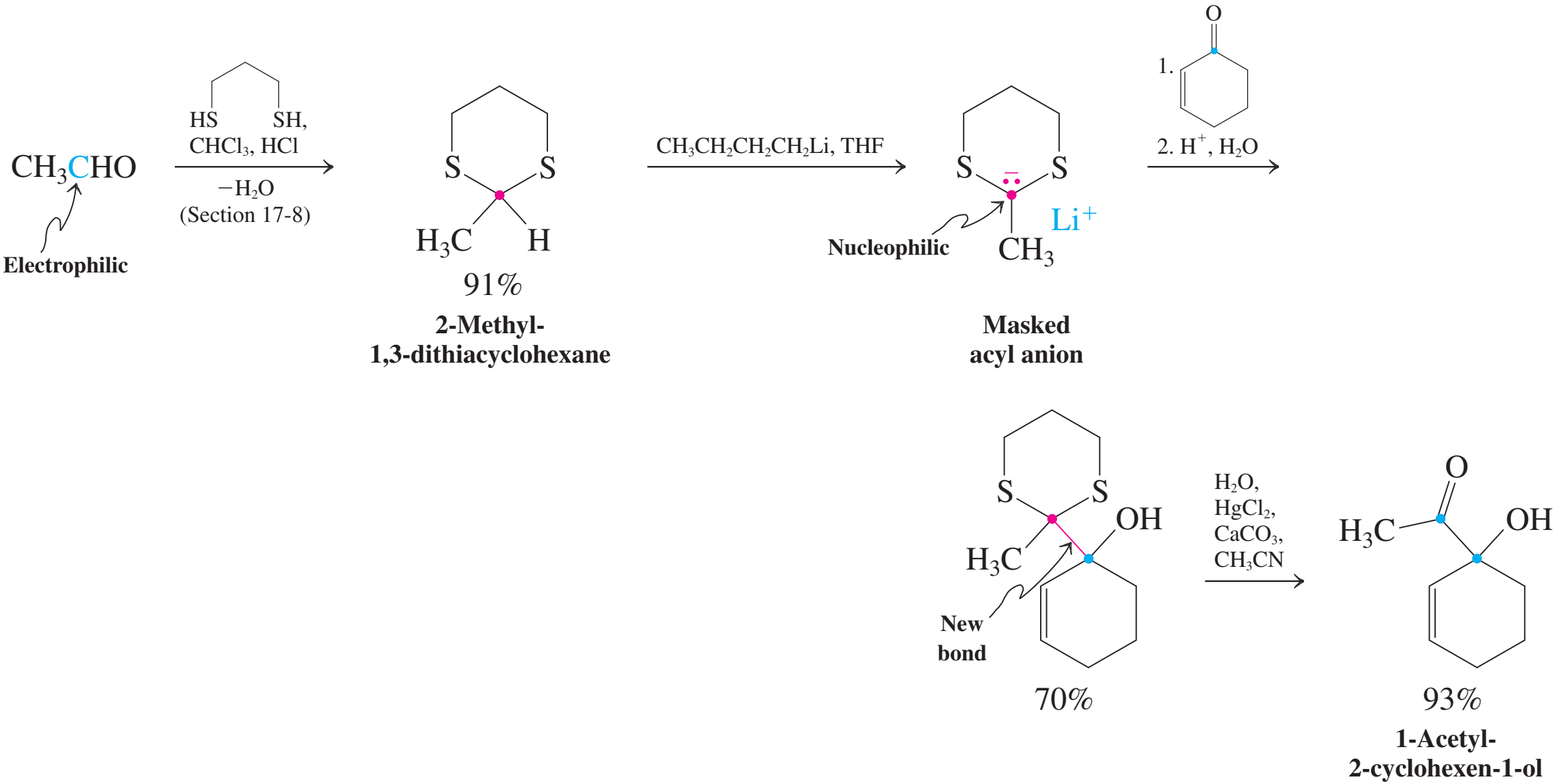
The anion of 1,3-dithiacyclohexane (also known as a 1,3-dithiane) is nucleophilic and add to aldehydes and ketones, furnishing alcohols with an adjacent thioacetal group.

Deprotonation gives the masked acyl anion, which adds to the carbonyl group of 2-cyclohexenone to give an alcohol.

Finally, hydrolysis of the thioacetal regenerates the original electrophilic carbonyl group, now as part of an ***α***-hydroxyketone product.

The sequence therefore employs the reversal of the polarization of this carbon atom to form the carbon–carbon bond.

Reagents exhibiting reverse polarization greatly increase the strategies available to chemists in planning syntheses, for example, conversion of a haloalkane into an organometallic (e.g., Grignard) reagent reverses the polarity of the functionalized carbon from electrophilic ($^{\delta+}$C–X$^{\delta-}$) to nucleophilic ($^{\delta-}$C–M$^{\delta+}$).

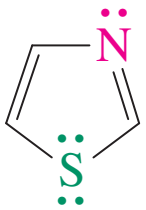

CH3CHO
Electrophilic
HS SH,
CHCl3, HCl
−H2O
(Section 17-8)
S S
H3C H
91%
2-Methyl-
1,3-dithiacyclohexane
CH3CH2CH2CH2Li, THF
Nucleophilic
S S
Li+
CH3
Masked
acyl anion
1.
O
2. H+, H2O
S S
OH
H3C
New
bond
70%
H2O,
HgCl2,
CaCO3,
CH3CN
O
H3C
OH
93%
1-Acetyl-
2-cyclohexen-1-ol

Thiazolium salts catalyze aldehyde coupling

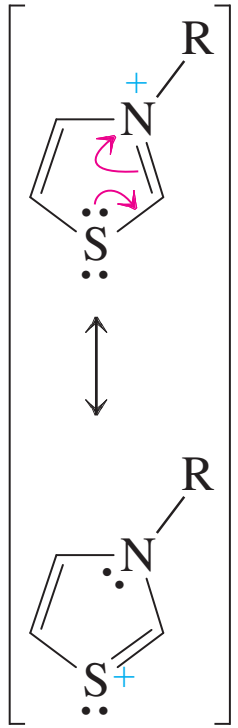
Masked acyl anions feature as reactive intermediates in the dimerization of aldehydes to ***α***-hydroxyketones catalyzed by thiazolium salts.

Thiazole is a heteroaromatic compound containing sulfur and nitrogen.

The salts are derived from thiazoles by alkylation at nitrogen and contain a resonance-stabilized positive charge.



Thiazole

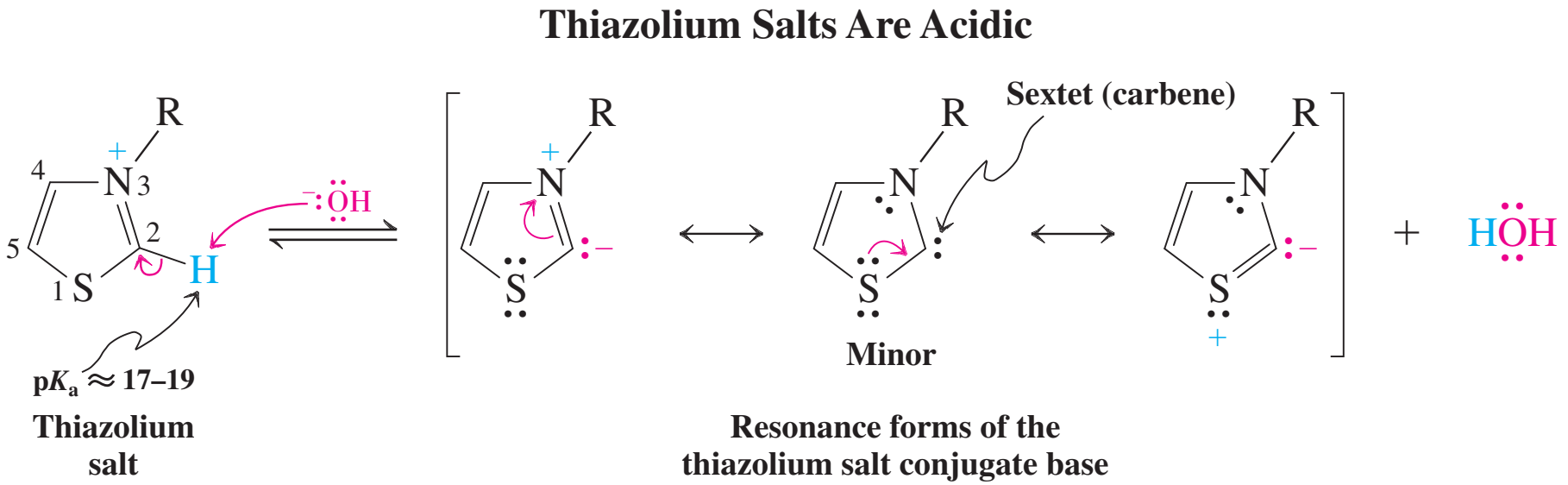


Thiazolium salt

The thiazolium ion has an unusual feature: a relatively acidic proton located between the two heteroatoms (at C2).

The corresponding carbanion is stabilized inductively by the adjacent positive charge that is distributed over both heteroatoms by resonance.

The charge-neutral carbene form is a minor contributor to the resonance hybrid.

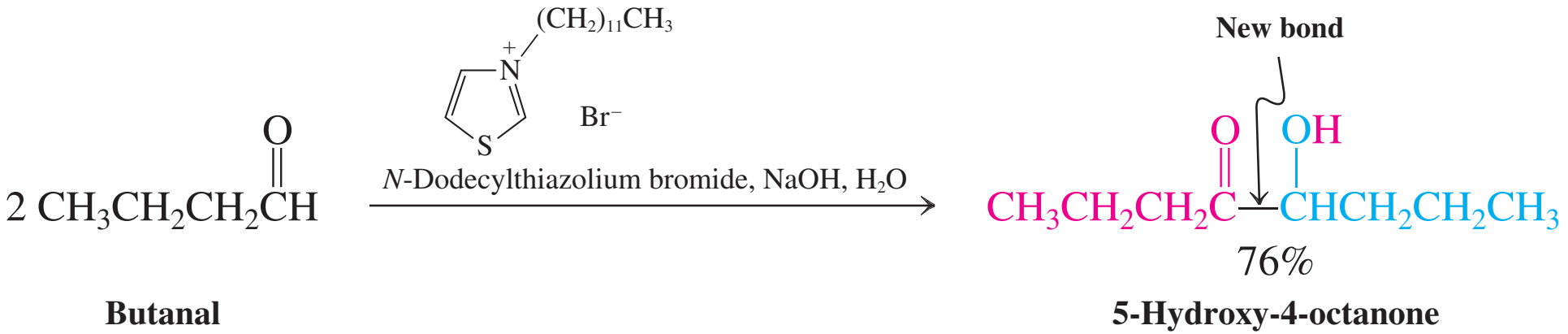


In the presence of thiazolium salts, aldehydes undergo conversion into ***α***-hydroxyketones. An example of this process is the conversion of two molecules of butanal into 5-hydroxy-4-octanone.

The catalyst is *N*-dodecylthiazolium bromide, which contains a long-chain alkyl substituent to improve its solubility in organic solvents.

The mechanism of this reaction begins with reversible addition of C2 in the deprotonated thiazolium salt to the carbonyl function of an aldehyde.

Aldehyde Coupling

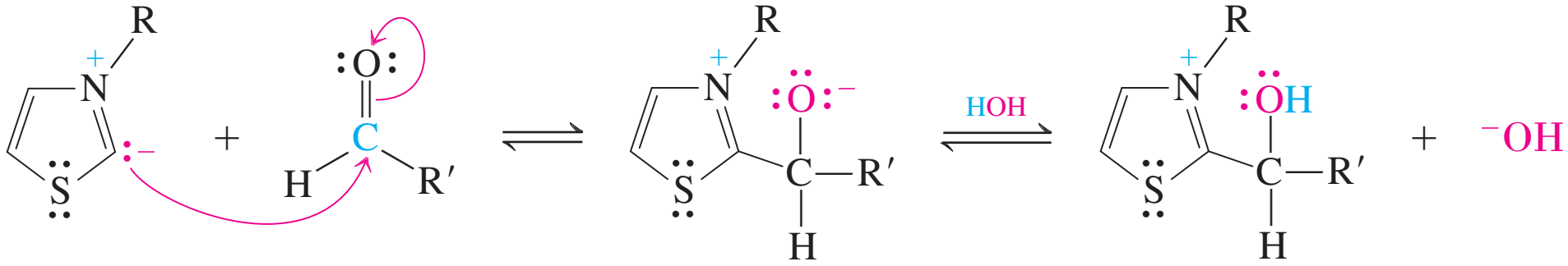


Butanal **5-Hydroxy-4-octanone**

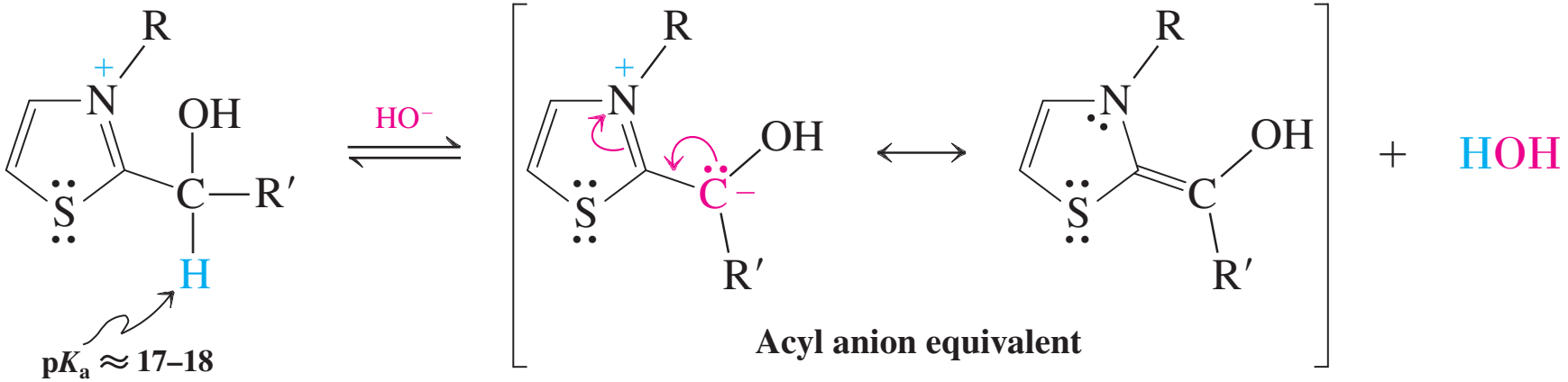
Mechanism of Thiazolium Salt Catalysis in Aldehyde Coupling

Step 1. Deprotonation of thiazolium salt

Step 2. Nucleophilic attack by catalyst

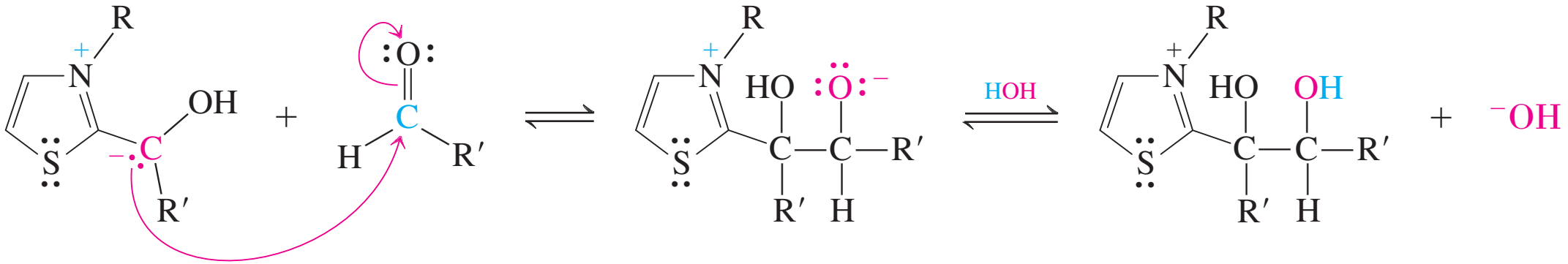


Step 3. Masked acyl anion formation

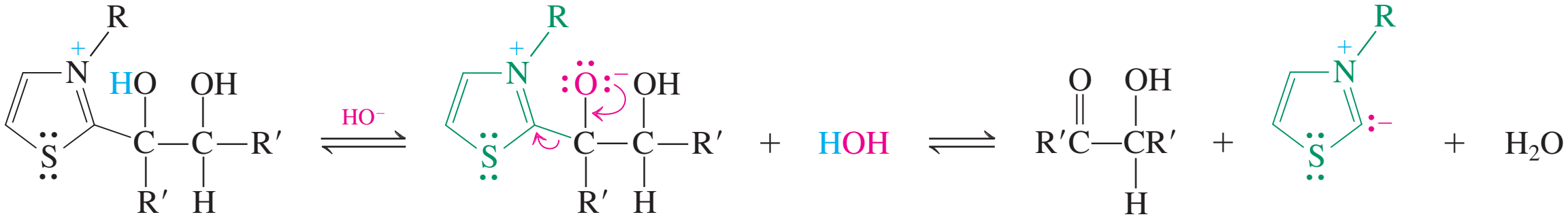


$pK_a \approx 17–18$

Step 4. Nucleophilic attack on second aldehyde



Step 5. Liberation of α-hydroxyketone



The product alcohol of step 2 contains a thiazolium unit as a substituent. This group is electron withdrawing and increases the acidity of the adjacent proton. Deprotonation leads to an unusually stable masked acyl anion.

Nucleophilic attack by this anion on another molecule of aldehyde, followed by loss of the thiazolium substituent, liberates the ***α***-hydroxyketone. The thiazolium moiety thus released may initiate another catalytic cycle.

This process represents another example of **organocatalysis**—catalysis utilizing exclusively organic species.

Comparison of the thiazolium method for synthesis of ***α***-hydroxyketones with the use of dithiacyclohexane anions is instructive.

Thiazolium salts have the advantage in that they are needed in only *catalytic amounts*. However, their use is limited to the synthesis of molecules R–CO–CHOH–R in which the two R groups are identical.

The dithiacyclohexane method is more versatile and can be used to prepare a much wider variety of substituted ***α***-hydroxyketones.

Exercise 23-24

Which of the following compounds can be prepared by using thiazolium ion catalysts, and which are accessible only from 1,3-dithiacyclohexane anions? Formulate syntheses of at least two of these substances, one by each route.