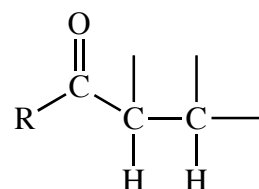


Lecture Notes
Chem 51C
S. King

Chapter 23 Substitution Reactions of Carbonyl Compounds at the α -Carbon

I. Acidity of α -Hydrogens

The hydrogen atoms bound to the carbon adjacent to a carbonyl carbon of an aldehyde, ketone, or ester, are acidic enough to be removed by a strong base. Once deprotonated, the carbanion generated is stabilized by delocalization of the (-) charge to the oxygen atom of the carbonyl.



compare acidities:

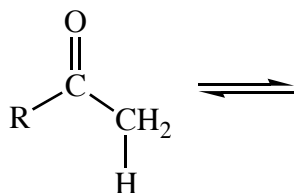
alcohols, H_2O > aldehydes & ketones > esters $\approx \text{HC}\equiv\text{CCH}_3$

Q. Why is the α -hydrogen of a carbonyl compound so much more acidic than the typical H bound to carbon?

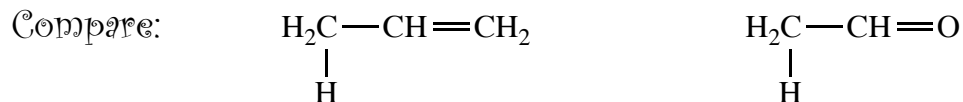
A. Three reasons:

1. The carbonyl is strongly electron withdrawing.

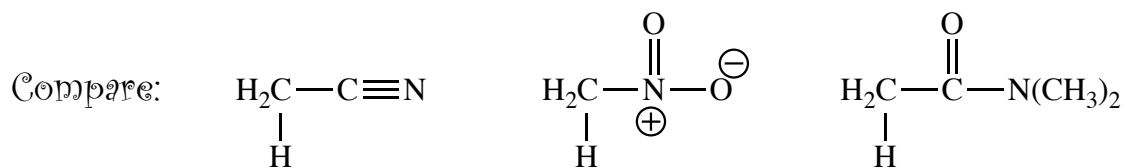
2. Loss of the α -hydrogen gives a resonance-stabilized anion.



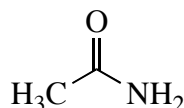
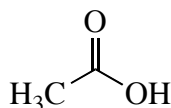
3. The negative charge of the enolate is delocalized onto oxygen, an electronegative element.



Nitroalkanes, nitriles and *N,N*-disubstituted amides also have unusually acidic α -hydrogens. In each of these, electrons left behind when the proton is removed can be delocalized onto an atom that is more electronegative than carbon.

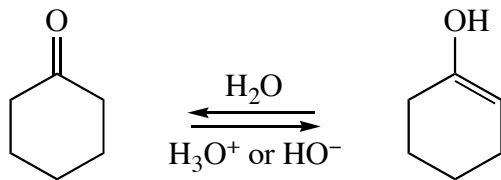


☞ **Remember:** Treatment of carboxylic acids and 1° & 2° amides with base *does not* result in removal of the α -hydrogen. *Why?* Their O–H, and N–H hydrogens are far more acidic (*review acidity of carbonyl compounds in chapter 19*).



II. Enolization of Carbonyl Compounds

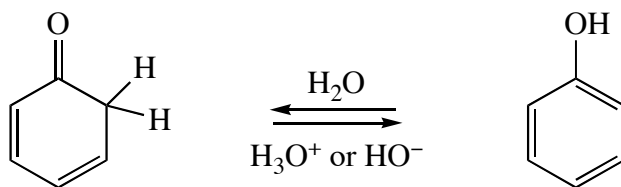
Carbonyl compounds with α -hydrogens are in equilibrium with vinylic alcohol isomers called enols. The two isomers that interconvert are called *tautomers*.



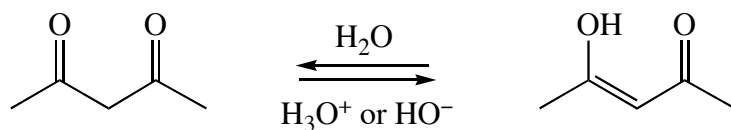
Most ketones and aldehydes are considerably more stable than the corresponding enols:

Keto Form		Enol form	% Enol @ equilibrium
	\rightleftharpoons		6.0×10^{-5}
	\rightleftharpoons		6.0×10^{-7}
	\rightleftharpoons		1.0×10^{-6}
	\rightleftharpoons		4.0×10^{-5}

There are exceptions, however:



The enols of **β -dicarbonyls** are also relatively stable:



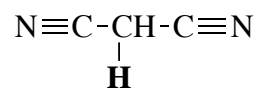
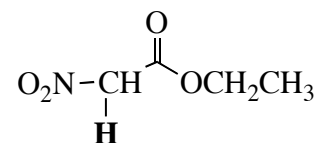
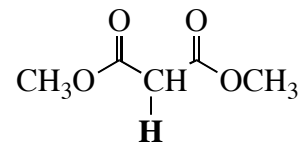
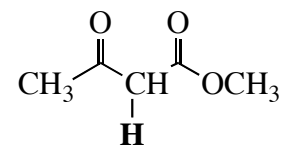
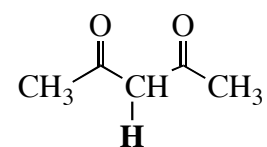
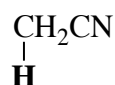
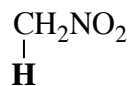
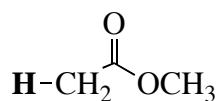
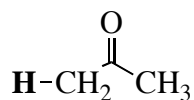
Two factors that contribute to the stabilization of **β -dicarbonyls**:

- Conjugation of the carbonyl group with the enol double bond.
- Stable H-bonded 6-membered ring structure of the enol form.

Q: What determines the percentage of enol form present at equilibrium?

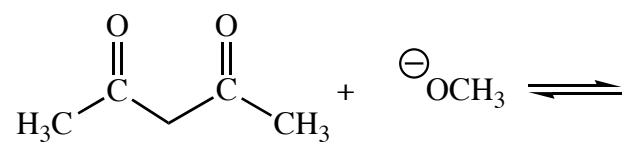
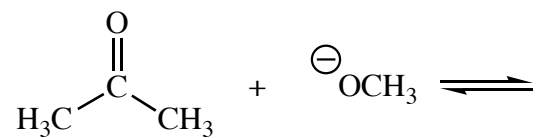
A: The % of enol at equilibrium depends on the structure of the carbonyl compound, which determines the acidity of the α -hydrogens. The *more* resonance stabilization, the *greater* the % of enol at equilibrium.

☛ *The acidity or pK_a can be correlated to the extent of keto-enol tautomerization at equilibrium:*



- Ability of groups to stabilize an enolate anion:
- A methylene group that is α to two carbonyl, nitro, or cyano groups is called an **active methylene group**. The hydrogens of an active methylene group are easily removed by bases such as alkoxide because the resulting conjugate base is highly stabilized by resonance.

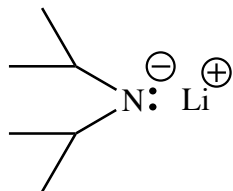
Compare:



Q: How would you completely deprotonate acetone?

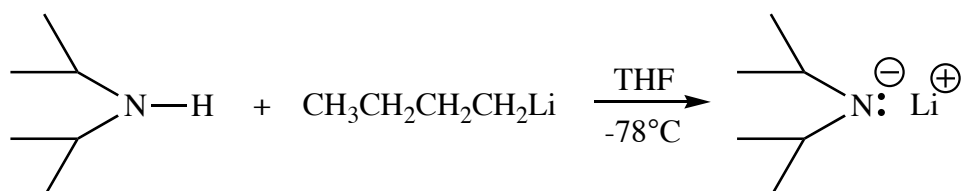
A:

The formation of an enolate is an acid-base equilibrium, so the stronger the base, the more enolate that forms. The most common base used to completely deprotonate a simple aldehyde or ketone is LDA:

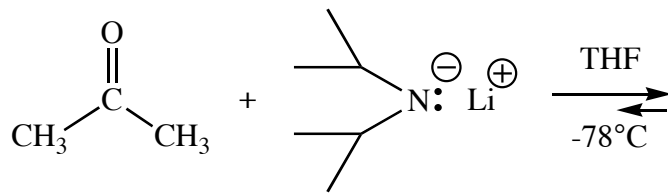


LDA (lithium diisopropyl amide)

Synthesis of LDA:



Typical reaction:



Why LDA?

A. Mechanism of Keto-Enol Tautomerization

- 1. Base Catalyzed:** Step 1: loss of proton from α -carbon
 Step 2: protonation of carbonyl

- ◆ For most simple ketones, the keto form is more stable than the enol form. Nevertheless the enol is a crucial intermediate in a variety of reactions with ketones & aldehydes.
- ◆ The enolate ion is a powerful nucleophile.

- 2. Acid Catalyzed:** Step 1: protonation of carbonyl
Step 2: loss of proton from α -carbon

- ◆ An enol has an electron-rich double bond. When electrons from this double bond attack an electrophile, the resulting cation is stabilized through resonance with the oxygen atom.

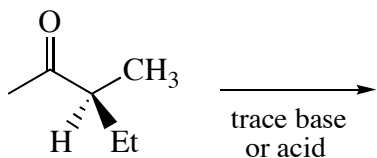
III. Reactions at the α -Carbon

Enols and enolates are nucleophilic, and therefore, react with electrophiles such as halogens, alkyl halides, and other carbonyl groups.

↳ in base	↳ in acid
enolate ion is the nucleophile	enol is the nucleophile

A. Racemization

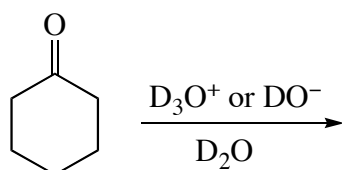
Because the formation of enols, and the reverse reaction, conversion of enols into carbonyl compounds is catalyzed by both acids and bases, when a ketone or aldehyde with a chiral α -carbon is allowed to sit in solution with a trace of acid or base, racemization occurs.



Mechanism (base catalyzed):

B. Deuterium Exchange

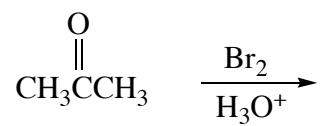
α -Hydrogens can also be exchanged for deuteriums by a similar process in either acid or base.



Mechanism (acid catalyzed):

C. α -Halogenation

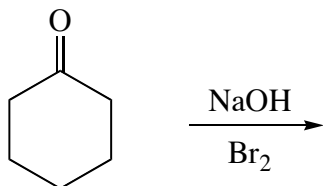
1. Acid catalyzed Halogenation of Aldehydes and Ketones



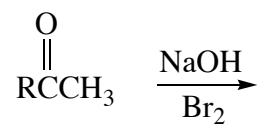
Mechanism: *In acid, an enol is the reactive intermediate*

2. Base-Promoted Halogenation of Aldehydes and Ketones:

In the base-promoted reaction, *all* enolizable H's are substituted with halogens.



If a methyl ketone is used:



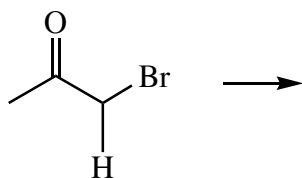
Mechanism: *In base, an enolate ion is the reactive intermediate.*

➤ When iodine & NaOH are used in this reaction, it is called an iodoform reaction. In the presence of a methyl ketone, a yellow precipitate (CHI_3) forms. This is a chemical test for the presence of a methyl ketone.

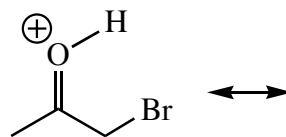
Q: Why is multiple halogenation seen with base-promoted halogenation, but only monohalogenation with acid-catalyzed halogenation?

A: Compare:

in base:

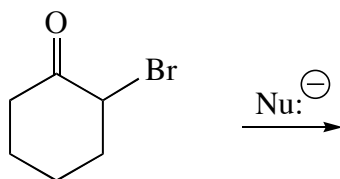


in acid:

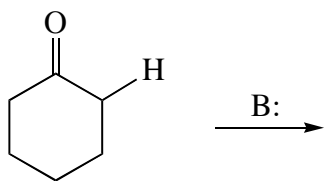


D. α - Halogenated Carbonyl Compounds in Synthesis

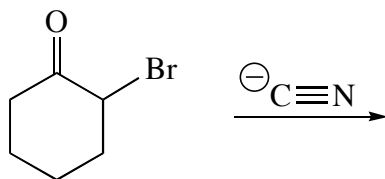
When the α -position is halogenated, it becomes electrophilic, and can therefore be attacked by nucleophiles.



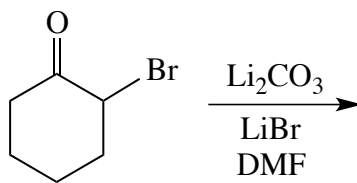
compare with:



Now we can incorporate both *electrophiles* and *nucleophiles* into the α -position!

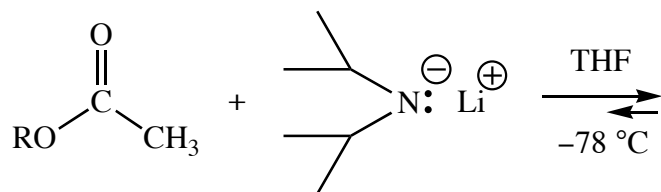


A-halo ketones can also be converted into α,β -unsaturated ketones:



IV. Direct Alkylation of Enolate Ions

General Reaction:



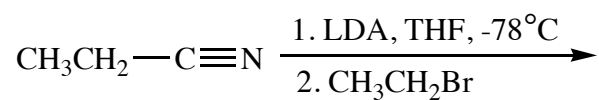
- This is an S_N2 reaction and is subject to the same considerations as the S_N2 reaction:

1° Alkyl halides or tosylates (*AKA: alkylating agents*) work great!

2° Alkyl halides or tosylates: Not great.

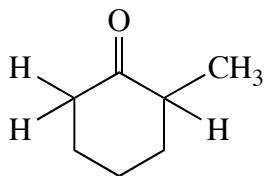
3° Alkyl halides: Doesn't work at all.

◆ **This reaction works well for esters and nitriles:**



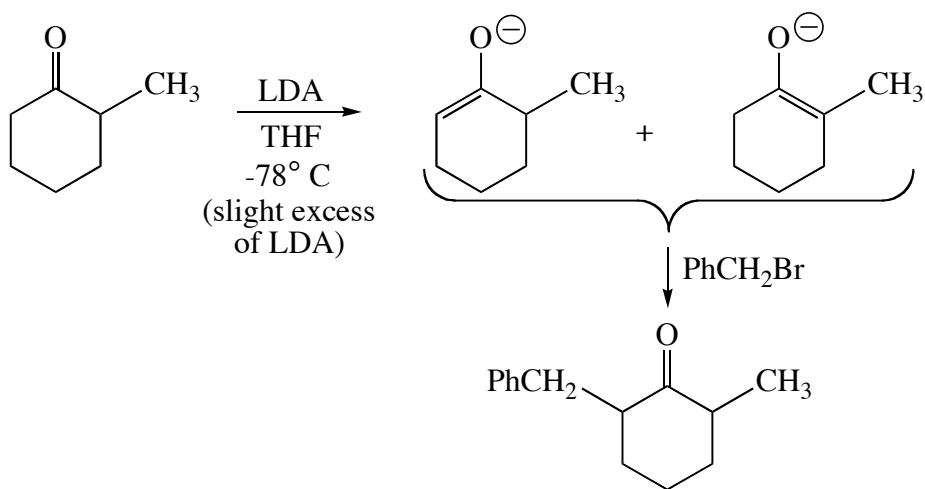
◆ **The enolates of ketones can also react with alkyl halides, but the reaction is more complicated:**

Problem: *There are two sides where the enolate can form:*



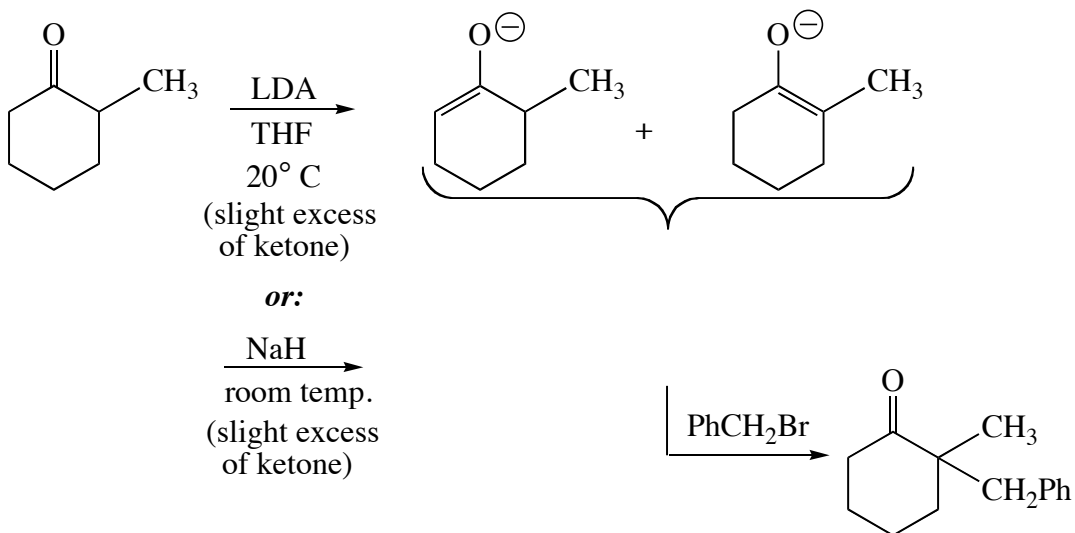
By adjusting the conditions, it is possible to establish either *kinetic or thermodynamic control*.

To favor kinetic enolate: Ideal conditions for kinetic control of enolate formation are those in which deprotonation is rapid, quantitative, and irreversible (*strong base, aprotic solvent, no excess ketone, low temp.*)



To favor thermodynamic enolate:

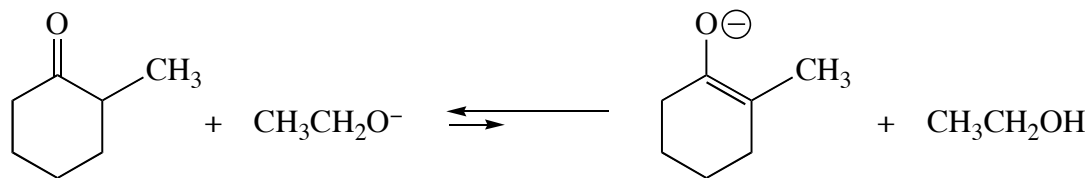
Ideal conditions for thermodynamic control of enolate formation are those in which the enolates can be interconverted rapidly so that equilibrium can be established (*strong base, protic solvent or slight excess ketone, warmer temp.*) The product composition will reflect the relative thermodynamic stability of the enolates (*most stable enolate will predominate.*)



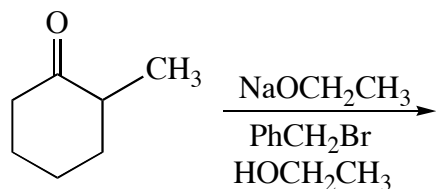
How is this equilibrating?

*** Book uses $\text{NaOCH}_2\text{CH}_3$ in $\text{CH}_3\text{CH}_2\text{OH}$ to form the thermodynamic enolate. This doesn't work well! *Why?*

NaOEt is not strong enough to quantitatively remove the alpha hydrogen!



So, the alkyl halide has to be present when the enolate forms:



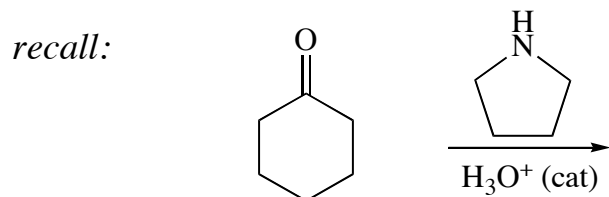
Competing reactions:

1. Alkyl halide reacts with $\text{CH}_3\text{CH}_2\text{O}^-$
2. Aldol reaction (*Chapter 24*)
3. Reaction with kinetic enolate

V. Alternatives to Direct Alkylation of Enolate Ions

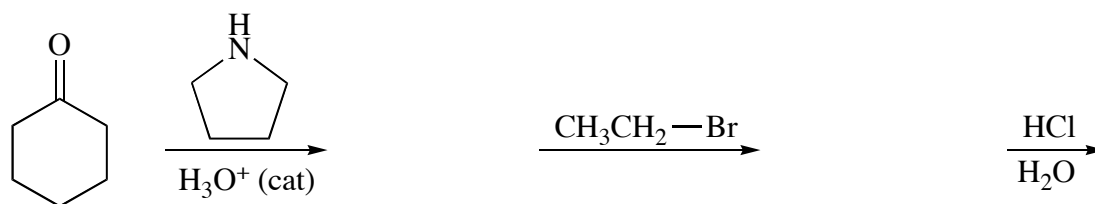
Fortunately, there are other ways to alkylate ketones that work better!

A. Alkylation and Acylation of the α -Carbon *via* an Enamine Intermediate



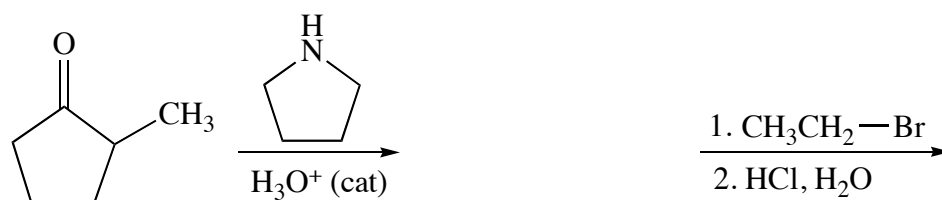
Enamines react with electrophiles in the same way that enolates do:

Typical reaction:



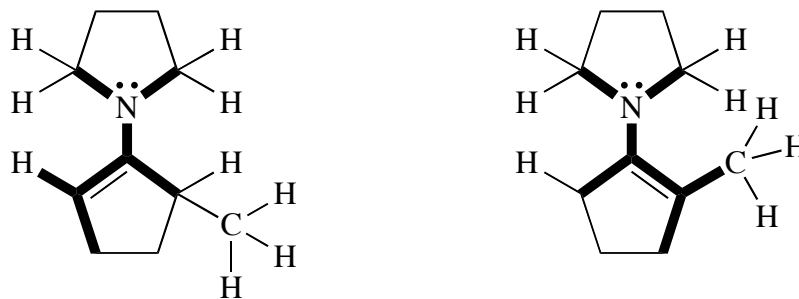
Advantages:

- Better yields
- Unsymmetrical ketones can be selectively alkylated at the least substituted side.
- Enamines can also be acylated.

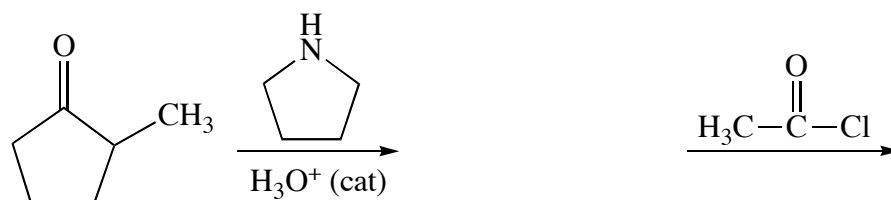


Q: Why does the enamine form on the least substituted side?

A: The less substituted enamine is more sterically favored. Conjugation between the N atom and the π -bond means that the bolded bonds must all be in the same plane.

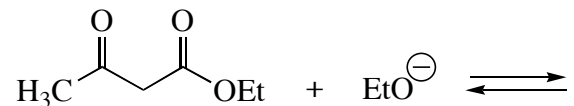


Another example:

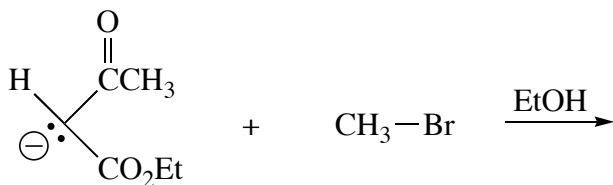


B. Alkylation of an Acetoacetic Ester

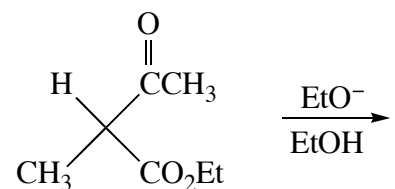
Unlike esters and ketones, the enolates of β -dicarbonyl compounds form completely with alkoxide bases such as sodium ethoxide.



The enolates of active methylene compounds are nucleophilic and react with alkyl halides and tosylates in typical $\text{S}_{\text{N}}2$ reactions to introduce alkyl groups to the α -position.



The process can be repeated by adding additional base and methyl bromide.

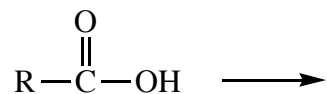


This is an $\text{S}_{\text{N}}2$ reaction:

- Best with methyl, primary, and primary allylic and primary benzylic substrates.
- 2° substrates:
- 3° substrates:

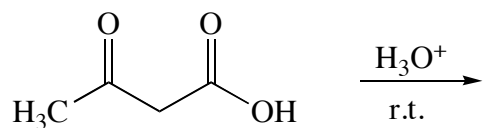
1. Decarboxylation of β -dicarbonyls

The loss of carbon dioxide from a carboxylic acid is called *Decarboxylation*.



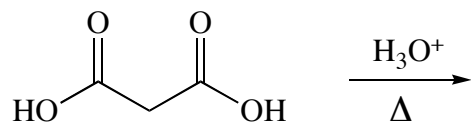
Certain carboxylic acids readily decarboxylate:

◆ β -Keto acids



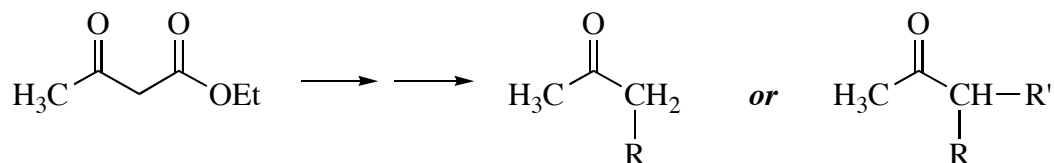
Mechanism:

◆ Malonic acids



2. Acetoacetic Ester Synthesis

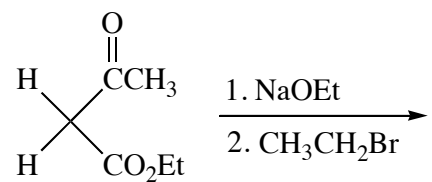
Acetoacetic esters are useful reagents for the preparation of methyl ketones of the type shown here:



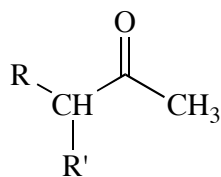
Strategy:

1. Alkylate acetoacetic ester
2. Hydrolyze ester
3. Decarboxylate

Example:

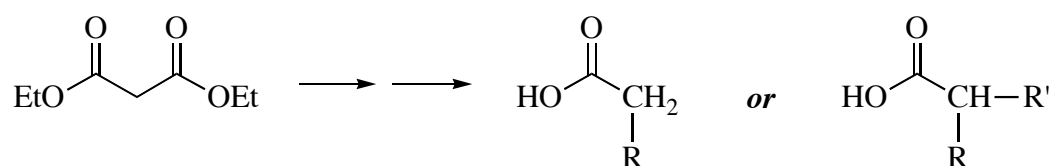


☛ **Retrosynthetic Analysis:**



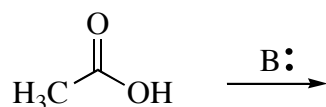
V. Alkylation of Acetic Acid: The Malonic Ester Synthesis

Diethylmalonate is a useful reagent for the preparation of substituted acetic acids:

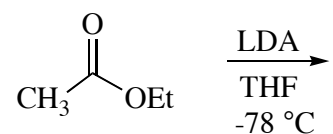


NOTE: *Carboxylic Acids cannot be alkylated in the alpha position directly!*

Why not?



We *can* alkylate the corresponding ester and saponify:



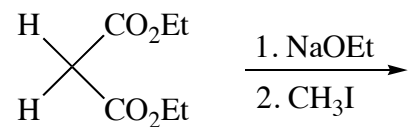
Drawbacks:

- more expensive
- requires inert atmosphere techniques
- better for small scale reactions
- enolate is a stronger base than a stabilized enolate, \therefore more E2

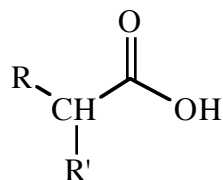
Conceptually malonic ester synthesis is similar to the acetoacetic ester synthesis:

1. Alkylate diethyl malonate
2. Hydrolyze both esters
3. Decarboxylate

Example:



☛ **Retrosynthetic Analysis:**



Example: Outline a malonic ester synthesis if the following carboxylic acid:

