Chapter 18
Alddehydes and Ketones
Reaction at the $\alpha$-carbon of carbonyl compounds

The Acidity of the $\alpha$ Hydrogens of Carbonyl Compounds: Enolate Anions

- Hydrogens on carbons $\alpha$ to carbonyls are unusually acidic.
- The resulting anion is stabilized by resonance to the carbonyl.

The enolate anion can be protonated at the carbon or the oxygen.
- The resultant enol and keto forms of the carbonyl are formed reversibly and are interconvertible.

Keto and Enol Tautomers
- Enol-keto tautomers are constitutional isomers that are easily interconverted by a trace of acid or base.
- Most aldehydes and ketones exist primarily in the keto form because of the greater strength of the carbon-oxygen double bond relative to the carbon-carbon double bond.
**p-Dicarbonyl compounds exist primarily in the enol form**

The enol is more stable because it has a conjugated σ system and because of stabilization of the enol through hydrogen bonding.

![Resonance stabilization of the enol form]

**Mechanism for Base- and Acid-catalyzed enolization**

**First – abstraction of the β-hydrogen**

**First – protonation of the oxygen from the carbonyl group**

**Reactions via Enols and enolates - Racemization**

Consequences of the keto-enol equilibration is the racemization of the chiral carbonyl compounds into racemic mixture in the basic or acidic conditions since enols are achiral intermediates.

**Halogenation of Ketones**

Ketones can be halogenated at the α position in the presence of acid or base and X₂. Base-promoted halogenation occurs via an enolate.

1. **Step 1**
   - Enolate formation

2. **Step 2**
   - Halogenation reaction
Acid-catalyzed halogenation proceeds via the enol.

Important

Overall effect α-substitution: Replacement of proton with electrophile.

Haloform Reaction

Reaction of methyl ketones with X₂ in the presence of base results in multiple halogenation at the methyl carbon.

Haloform Reaction

When methyl ketones react with X₂ in aqueous hydroxide the reaction gives a carboxylate anion (carboxylic acids) and a haloform (CX₃H).

α-Halo Carboxylic Acids: The Hell-Volhard-Zelinski reaction

Carboxylic acids with α-hydrogens react with bromine or chlorine to give α-halo carboxylic acids.

How does the reaction occur?
### Formation of Lithium Enolates

Enolates can be conveniently generated by treatment of ketones with strong bases such as LDA.

\[ \text{Ketone} + \text{LDA} \rightarrow \text{Enolate} \]

Since base employed is a weaker base than the enolate, this is not a very good approach.

This is a good method since base employed is a stronger base than the enolate.

### Preparation of LDA

- **Lithium diisopropylamide (LDA or Li(NiPr)_2)**

### Regioselective Formation of Enolate Anions

Unsymmetrical ketones can form two different enolates.

- **The thermodynamic enolate** is the most stable enolate, i.e., the one with the more highly substituted double bond.
  - A weak base favors the thermodynamic enolate because an equilibrium between the enolates is established.

- **The kinetic enolate** is the enolate formed fastest and is usually the enolate with the least substituted double bond.
  - A strong, sterically hindered base such as lithium diisopropylamide favors formation of the kinetic enolate.

### Direct Alkylation of Ketones via Lithium Enolates

Enolates can also be alkylated with primary alkyl, benzyl, and allylic halides via an S_N2 reaction.

Unsymmetrical ketones can be alkylated at the least substituted position if LDA is used to form the kinetic enolate.
**Direct Alkylation of Esters**

Enolates generated from esters (α-carbanions) can also be alkylated with primary alkyl halides via an S_N2 reaction.

- **β-Dicarbonyl compounds** have two carbonyl groups separated by a carbon.
  - Protons on the α-carbon of β-dicarbonyl compounds are acidic ($pK_a = 9-10$).
  - Recall that protons for ketones on the α-carbon have $pK_a = 18-20$.
  - This unusually low acidity for organic compounds can be explained by resonance stabilization of the corresponding enolate by two carbonyl groups.

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**Acidity of organic compounds (pKa's) (Page 111)**

- Alkanes and alkenes R-H 45 (40-50)
- Terminal alkynes RC≡CH 25
- α-H of carbonyls (-CO-CH) 20
- Alcohols ROH 16 (3° = 18)
- β-dicarbonyls RCO-CH₂-COR 10
- Phenol C₆H₅OH 10
- Carboxylic acids RCOOH 5

**Comparisons:** water = 15.7, NH₃ and H₂ about 35

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**The Acetoacetic Ester Synthesis:**

**Synthesis of Methyl Ketones (Substituted Acetones)**

- **Alkylation**
  - Alkylation of the enolate derived from acetoacetic ester is called the acetoacetic ester synthesis.
  - This is an S_N2 reaction with the ethyl acetoacetate enolate acting as the nucleophile.
  - Please note that contrary to ketones the sodium ethoxide is a sufficient base to generate enolates from β-Dicarbonyl compounds.

**Comparisons:**

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CH₃C(=O)CH₂-COCH₃ + NaOEt → CH₃C(=O)CH₂-COCH₂-CH₃ + Na⁺ Et⁻
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**Enolates of β-Dicarbonyl compounds**

- β-Dicarbonyl compounds have two carbonyl groups separated by a carbon.
- Protons on the α-carbon of β-dicarbonyl compounds are acidic ($pK_a = 9-10$).
- Recall that protons for ketones on the α-carbon have $pK_a = 18-20$.
  - This unusually low acidity for organic compounds can be explained by resonance stabilization of the corresponding enolate by two carbonyl groups.
Hydrolysis of the ester and heating of the resultant β-ketoacid causes decarboxylation. The product is a substituted acetone derivative (methyl ketones).

Specific example of the application of ethyl acetoacetate towards synthesis of monosubstituted acetone (methyl ketones):

1. $\text{NaOEt/EtOH}$
2. $\text{H}_{2}\text{O}$

Ethyl acetoacetate (acetonaacetic acid)

Ethyl butyroacetoacetate (alkyl ketones)

2-Heptanone (52-61% overall from ethyl acetoacetate)

A second alkylation can be performed. A stronger base such as potassium tert-butoxide must be used to deprotonate the monoalkyl ester.

Example: Application of Acetoacetic ester towards synthesis of the $\alpha$-(di)substituted methyl ketones (acetones)

Home take message:

Ethyl acetoacetate ion is the synthetic equivalent of Acetone enolate.

A mono-substituted acetone

A di-substituted acetone
If α-halo esters are used to alkylate the acetoacetic ester enolate, γ-keto acids are obtained (see review Problem 18.8)

Acylation of Ethyl Acetoacetate anion

Acetoacetic ester anion (enolate) can also be acylated with acyl halides or anhydrides to produce β-diketones. The reaction is carried out in aprotic solvents such as DMF or DMSO because these will not destroy the acylating reagents.

The Malonic Ester Synthesis:

Synthesis of Substituted Acetic Acids

(1) Alkylation of diethylmalonate, (2) hydrolysis of the diester to the β-dicarboxylic acid, and (3) decarboxylation steps can be used to synthesize mono- and disubstituted acetic acids. The mechanism is analogous to that for the acetoacetic ester synthesis.

In step 1 the stabilized anion is formed.

In step 2 the anion is mono- or dialkylated using \( S_N 2 \) reactions with primary alkyl halides.
In step 3 the mono- or dialkylated product is hydrolyzed and decarboxylated.

Home take message:
- Diethyl malonate anion is the synthetic equivalent of acetic acid dianion.

The Application of the Malonic Ester in Organic Synthesis

Malonic Ester can be applied towards synthesis of 3-, 4-, 5-, and 6-membered rings. For example terminal dihalides can react to form rings by alkylation of one molar equivalent of malonate. The resulting haloalkylmalonic ester can undergo internal alkylation via $S_2$ reaction.

Reactions of Other Active Hydrogen Compounds
- Compounds in which the hydrogen atoms of a methylene (-CH$_2$-) group are made acidic by two attached electron-withdrawing groups are called active hydrogen compounds or active methylene compounds.
- A variety of electron-withdrawing groups can produce enhanced $\alpha$ hydrogen acidity.
For example, deprotonation of ethyl cyanoacetate forms a resonance-stabilized anion, which can then undergo alkylation even with secondary alkyl halides.

Enamines have a nucleophilic carbon and are the equivalent of ketone and aldehyde enolates. The nitrogen of enamines is also nucleophilic.

Enamines can be acylated and alkylated. C-Acylation leads to β-diketones. N-Acylated products are formed, but they are unstable and act as acylating agents themselves (intramolecular acylation!).

Synthesis of Enamines: Stork Enamine Reactions

- Aldehydes and ketones react with secondary amines to form enamines (see Section 16.8C).
- The reaction is catalyzed by acid.
- Removal of water drives enamine formation to completion.
- Cyclic amines are often used.

Lack of hydrogen on nitrogen atom excludes formation of imine and therefore enamine is formed.

N-(N-Cytrilethoxy)pyrroline (an enamine)
Alkylation of enamines can lead to some N-alkylation. Similarly to the N-acylated product discussed on the previous slide, the N-alkylated product can also be converted to the C-alkylated product by heating.