CHEM 4113 ORGANIC CHEMISTRY II LECTURE NOTES
CHAPTER 22

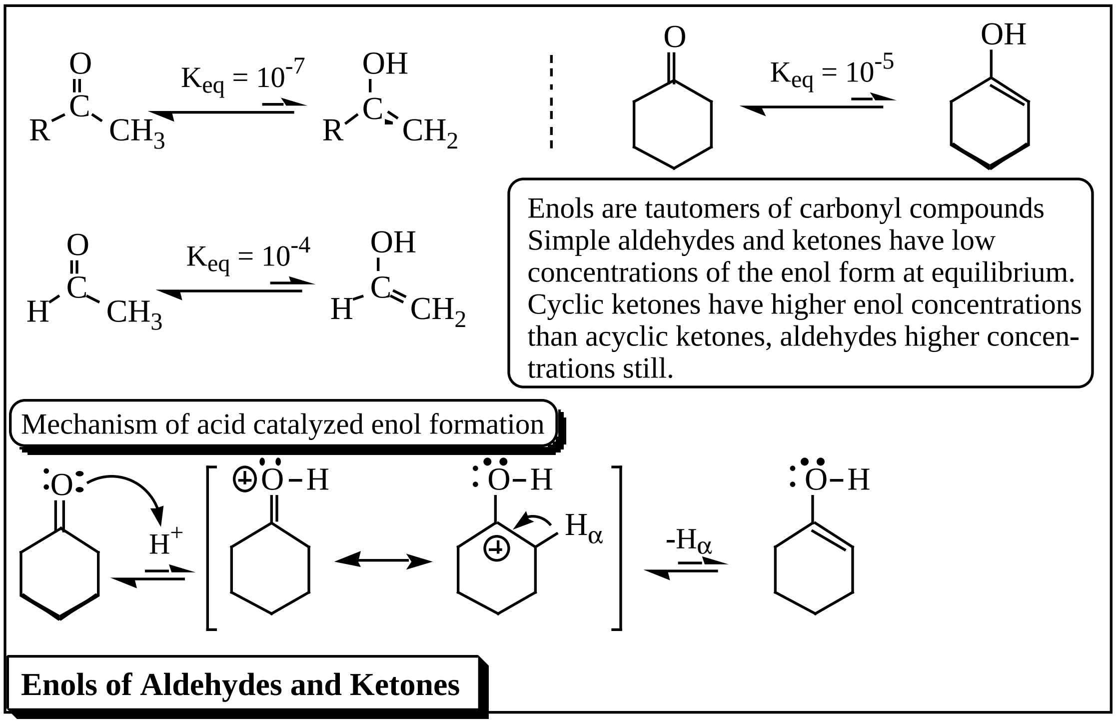
1. Introduction

The carbonyl group greatly increases the reactivity of the hydrogens on the carbons α to the carbonyl. Thus, carbonyl compounds, especially aldehydes, esters and ketones, are able to undergo alpha substitution reactions. These substitution reactions occur via the formation of two key intermediates: enols and enolate ions. Carbonyl compounds form enols under acidic conditions, and enolates when treated with a base.

2. Alpha Substitution of Enols

Carbonyl compounds that have hydrogen atoms on their α carbons are rapidly inter convertible with they enol forms when treated with acid. Enols are tautomers (structural isomers related by the shift of a hydrogen and one π bond). Most carbonyl compounds exist almost exclusively as the keto form, however the enol form is always present, albeit in low concentrations. The rate at which the keto-enol inter convert is relatively slow unless catalyzed by H^+, which greatly accelerates the process. However the addition of H^+ does nothing to shift the equilibrium, it is only a catalyst.

One class of carbonyl with a high percentage of enol present at equilibrium is the 1,3-dicarbonyl compounds (or ß-dicarbonyl compounds). The enol form of a 1,3-dicarbonyl compound has stabilizing resonance conjugation between one carbonyl and the enol form of the other.



Enols are tautomers of carbonyl compounds Simple aldehydes and ketones have low concentrations of the enol form at equilibrium. Cyclic ketones have higher enol concentrations than acyclic ketones, aldehydes higher concentrations still.

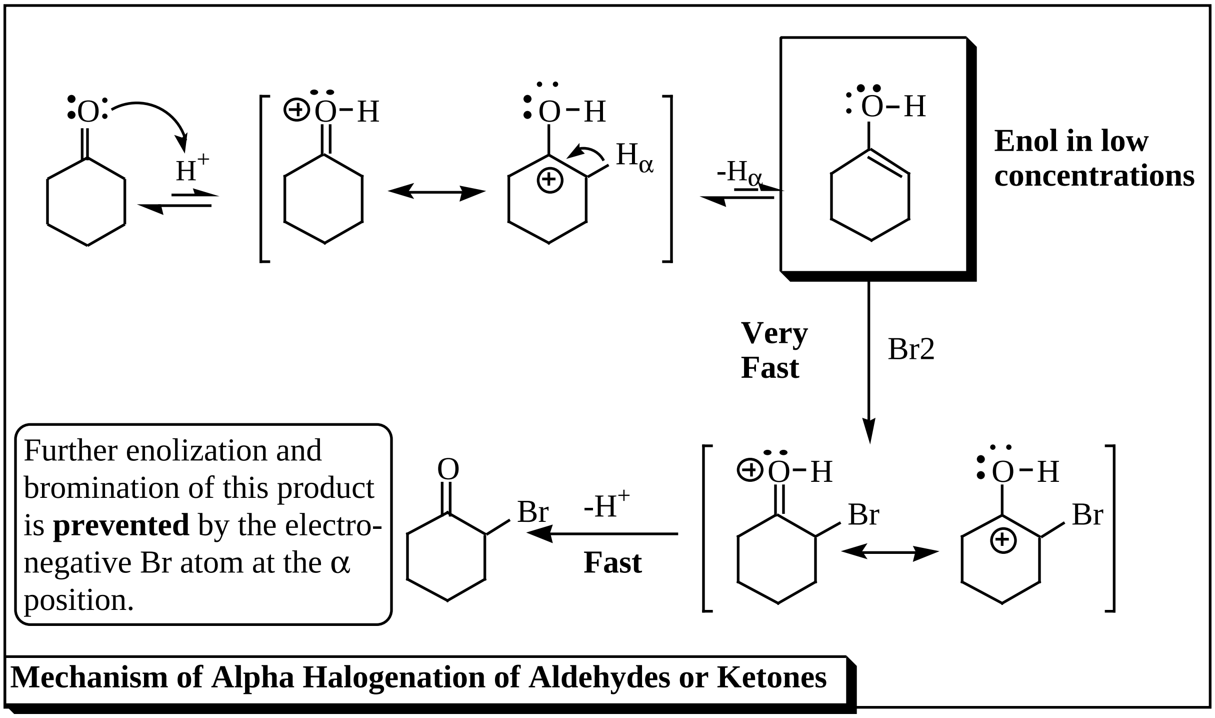
Mechanism of acid catalyzed enol formation

Enols of Aldehydes and Ketones

a. Alpha Halogenation of Aldehydes and Ketones (Halogenation in Acidic Solution)

Aldehydes and ketones are rapidly halogenated at the alpha position by reaction with chlorine, bromine or iodine in the presence of an acid (often glacial acetic acid is used as the solvent). The rate is independent of the halogen concentration; this means that the slow step (rate determining step) is the enolization process. The enol, once formed (in low concentrations) reacts rapidly with the halogenating agent to afford product. The halogenation is essentially irreversible, the equilibrium greatly favoring product. This removal of the enol cause the keto to tautomerize in order to maintain equilibrium; this to reacts with the halogen to form product. **Halogenation in acidic solution**

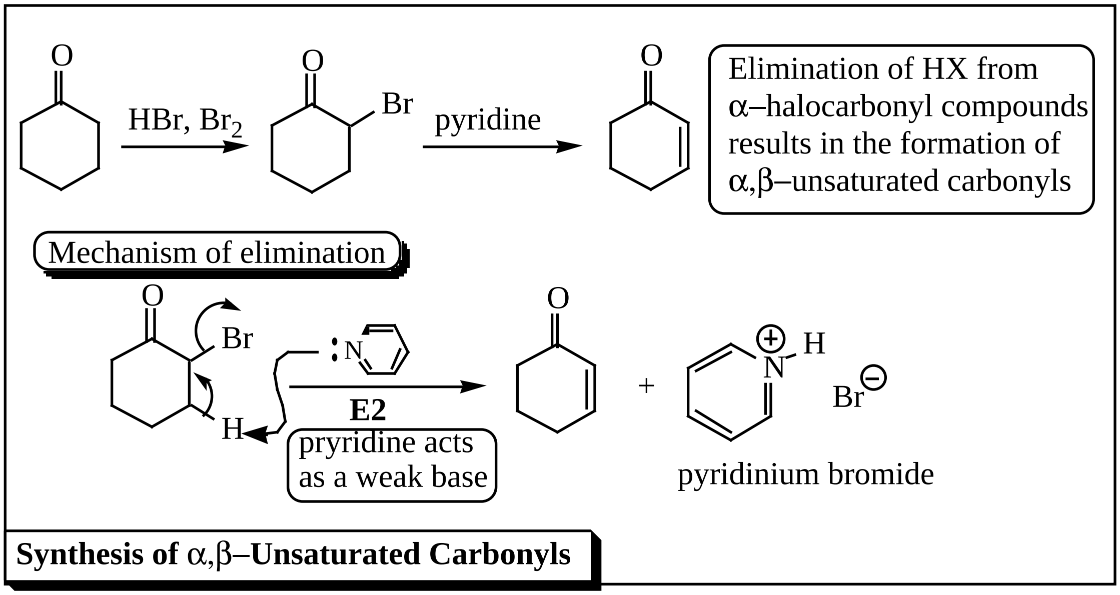
proceeds cleanly to the mono-halogenation carbonyl product. The inductive effect of the halogen retards further enolization of the α-haloketone or aldehyde.



Further enolization and bromination of this product is **prevented** by the electro-negative Br atom at the α position.

Mechanism of Alpha Halogenation of Aldehydes or Ketones

Alpha halo ketones and aldehydes are useful in organic synthesis because they can be dehydrohalogenated by base to give α,β–unsaturated carbonyl compounds. The reaction occurs by an E2 mechanism will give high yields even with a weak base such as pyridine.

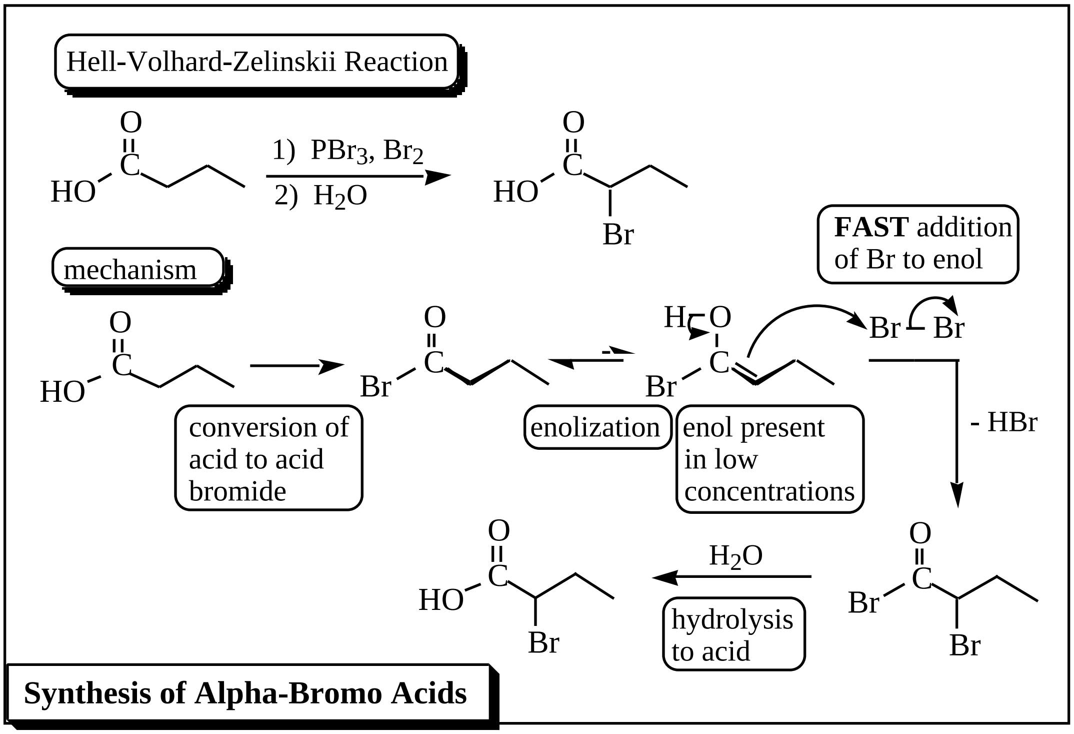


Elimination of HX from α–halocarbonyl compounds results in the formation of α,β–unsaturated carbonyls

Synthesis of α,β–Unsaturated Carbonyls

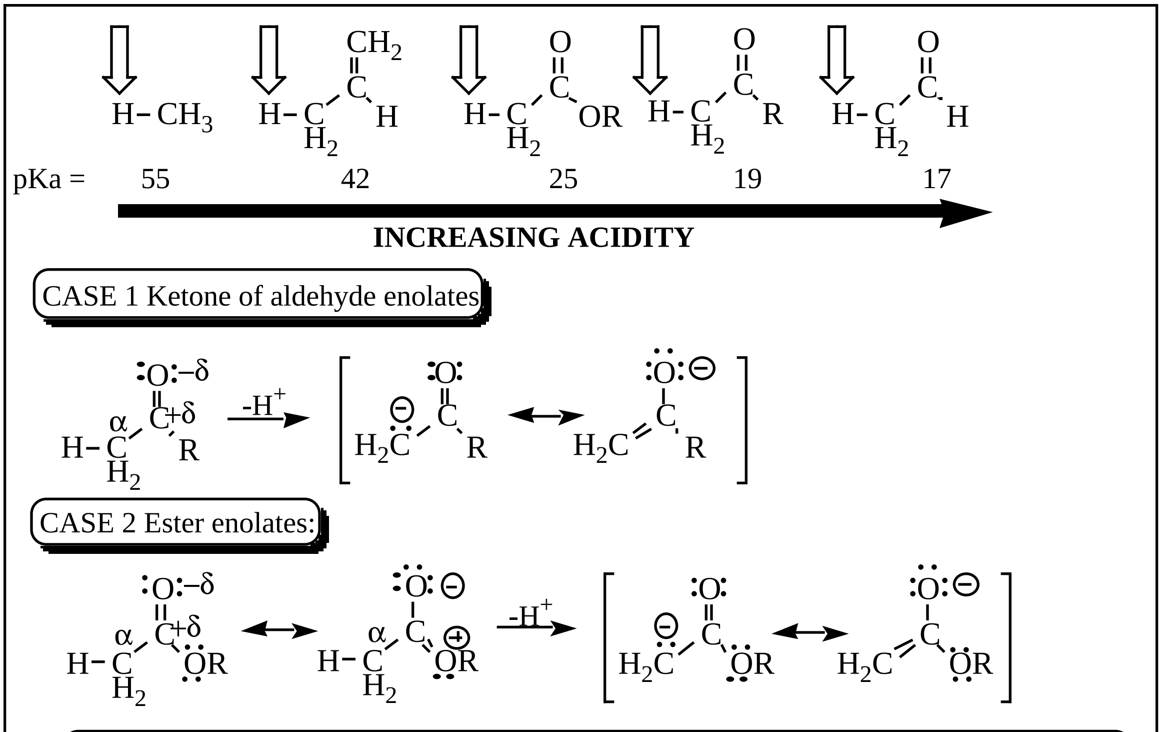
b. Alpha Bromination of Carboxylic Acids (Hell-Volhard-Zelenski Reaction)

Direct halogenation of carbonyl compounds is limited to aldehydes and ketones since the equilibrium enol content of esters, amides and carboxylic acids is very low (too low for halogenation to take place). Carboxylic acid can be brominate by a mixture of PBr_3 and Br_2 in a process called the Hell-Volhard-Zelinski reaction. The first step in the HVZ reaction is conversion of the acid into the acid bromide derivative by the action of PBr_3. The HBr released in this step catalyzes the enolization of the acid bromide and the enol reacts rapidly with Br_2. Hydrolysis of the α–bromo acid bromide with water forms the α–bromo acid.



Synthesis of Alpha-Bromo Acids

3. Acidity of α–Hydrogen atoms - Enolate Formation



The partial charge on the carbonyl weakens the C-H bond on the carbon. Esters have an important resonanceform that neutralizes the amount of positive charge at the carbonyl carbon; **this is why esters are less acidic than either ketones or aldehydes**.

Resonance and Electronic Effects in Enolates

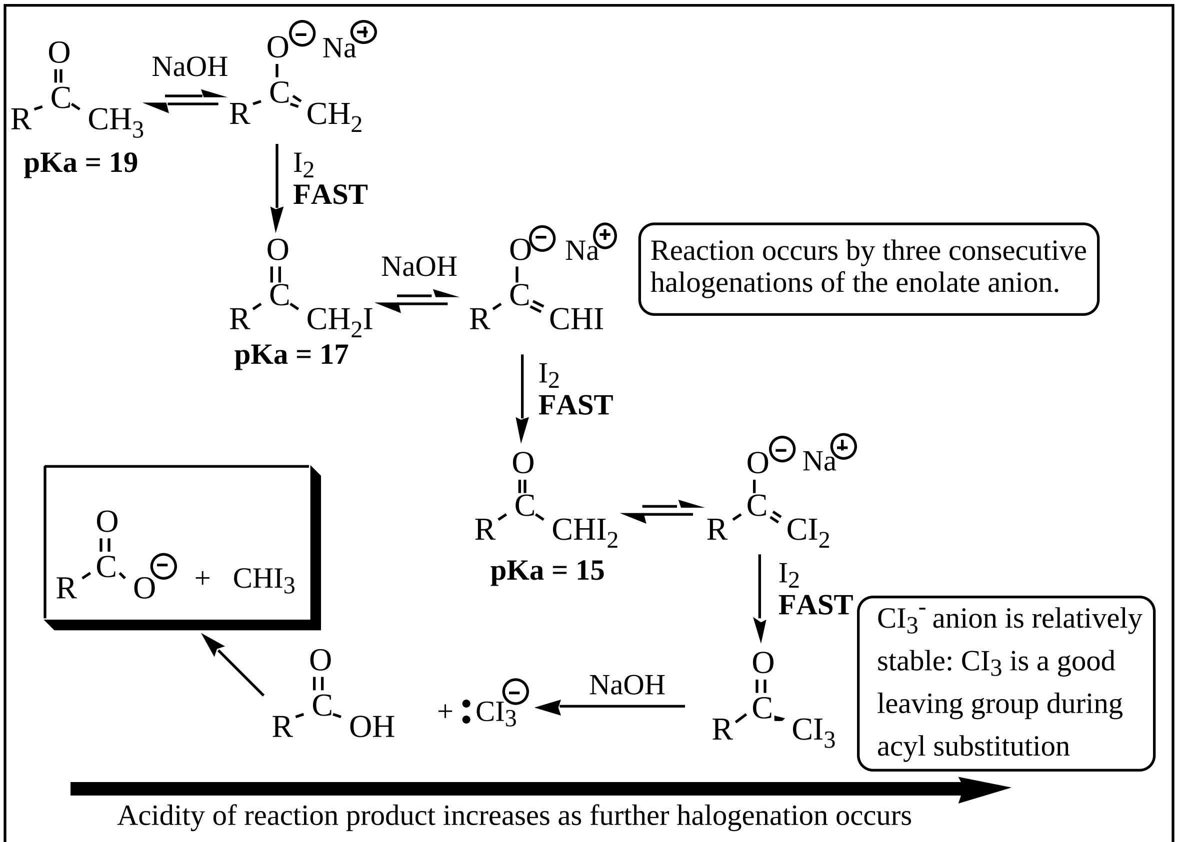
Alpha hydrogen atoms of carbonyl compounds are acidic and can be abstracted by strong bases to yield enolate anions. Two factors are important in determining the acidity of α–protons of carbonyl compounds. The **first factor** relates to the inductive effect of the carbonyl group which withdraws electron density from the adjacent C-H bonds. Any substitution of the carbonyl group which increases the partial positive charge on the carbon of the carbonyl will increase the acidity of the α–protons(decreases the pKa). Also, any substitution of the carbonyl which slightly decreases the positive charge will decrease the acidity of the C-H bond. This is why aldehydes are slightly more acidic than ketones (the alkyl group of the ketone is electron donating by hyperconjugation). A more dramatic example of this effect is seen in esters where resonance donation of the lone pair electrons of the alkoxy group partly neutralizes the positive charge of the carbonyl carbon, making the C-H bond less acidic than in a ketone. **The factor which most determines the acidity of carbonyl compounds is the resonance stabilization afforded to the product enolate anion**.

Enolate anions are highly reactive as nucleophiles because of their negative charge.

a. Halogenation of Aldehydes and Ketones in Basic Solution

While halogenation of carbonyl compounds under acidic conditions is easily controlled to stop at the mono-halo stage, this is not the case when the reaction is done in basic solution. The reason for this difference is that the initially produced mono-halo ketone or aldehyde is more acidic (because of the inductive effect of the halogen) than the original compound. Thus, the enolate anion of this new product is more likely to form (are present in higher concentrations) than the parent carbonyl compound. The more abundant enolates then undergo preferential reaction with the halogenating agent. **The reaction proceeds rapidly to the trihalo product**. When all the acidic protons have been replaced by halogens(especially iodine atoms), **the trihalomethyl group has acquired enough electron-withdrawing groups to facilitate breaking a carbon-carbon bond**.

In the case of a triiodomethyl group, the addition of water or dilute aqueous acid is able to hydrolyze the compound, leading to the formation of an acid and iodoform.



Reaction occurs by three consecutive halogenations of the enolate anion.

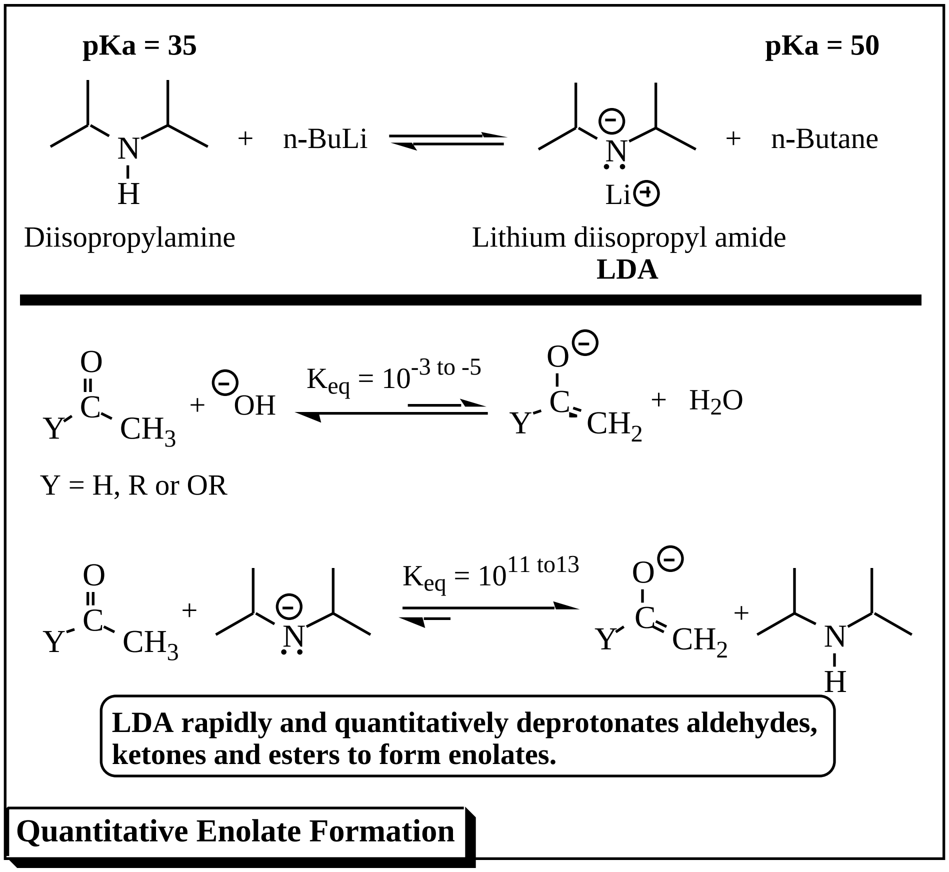
CI_3^- anion is relatively stable: CI_3 is a good leaving group during acyl substitution

Acidity of reaction product increases as further halogenation occurs

The Iodoform Reaction: Halogenation of Methyl Ketones in Base.

b. Direct Alkylation of Enolates Derived from Aldehydes, Ketones and Esters

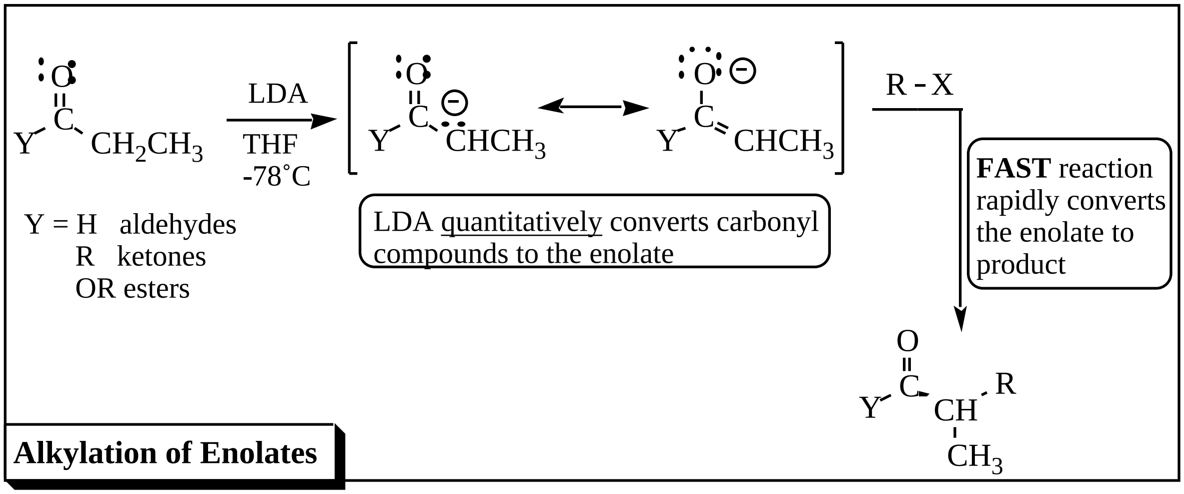
Simple aldehydes (pKa=17), Ketones (pKa=19) and esters (pKa=25) don not form high concentrations of enolates when treated with relatively weak bases like hydroxide and alkoxides (pKa of water, alcohols ~16-18). To effect carbon alkylation of these enolates, and to avoid Aldol and Claisen condensation reactions (chapter 23), it is necessary to use very strong bases such as sodium hydride (NaH) and Sodium amide ($NaNH_2$). A useful addition to these reagents is Lithium Diisopropyl Amide (**LDA**) which rapidly and quantitatively deprotonates aldehydes, ketones and esters at temperatures as low as -78˚C. The relative bulk of LDA allows us to selectively remove the least hindered acidic α–proton. After the highly nucleophilic enolate has been formed it can be treated with electrophiles and various α–substituted carbonyl compounds can be formed.



LDA rapidly and quantitatively deprotonates aldehydes, ketones and esters to form enolates.

Quantitative Enolate Formation

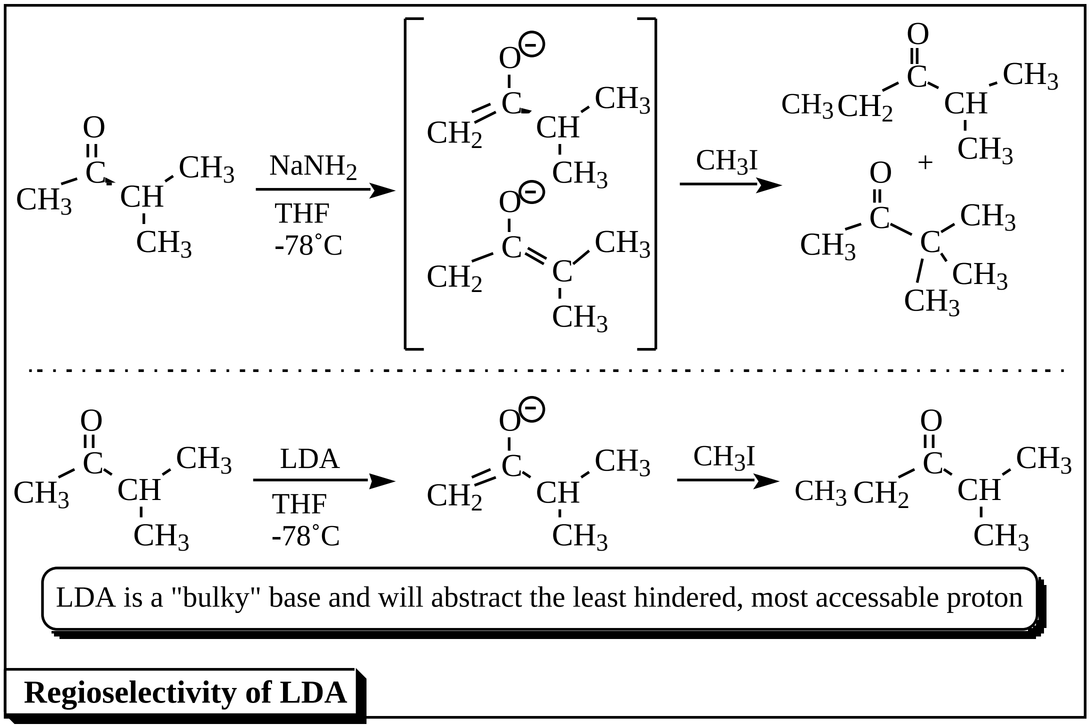
Treatment of an enolate with an alkyl halide will result in alkylation at the α–position with formation of a new C-C bond. This reaction proceeds smoothly when R is a primary or unhindered secondary alkyl halide.



LDA quantitatively converts carbonyl compounds to the enolate

FAST reaction rapidly converts the enolate to product

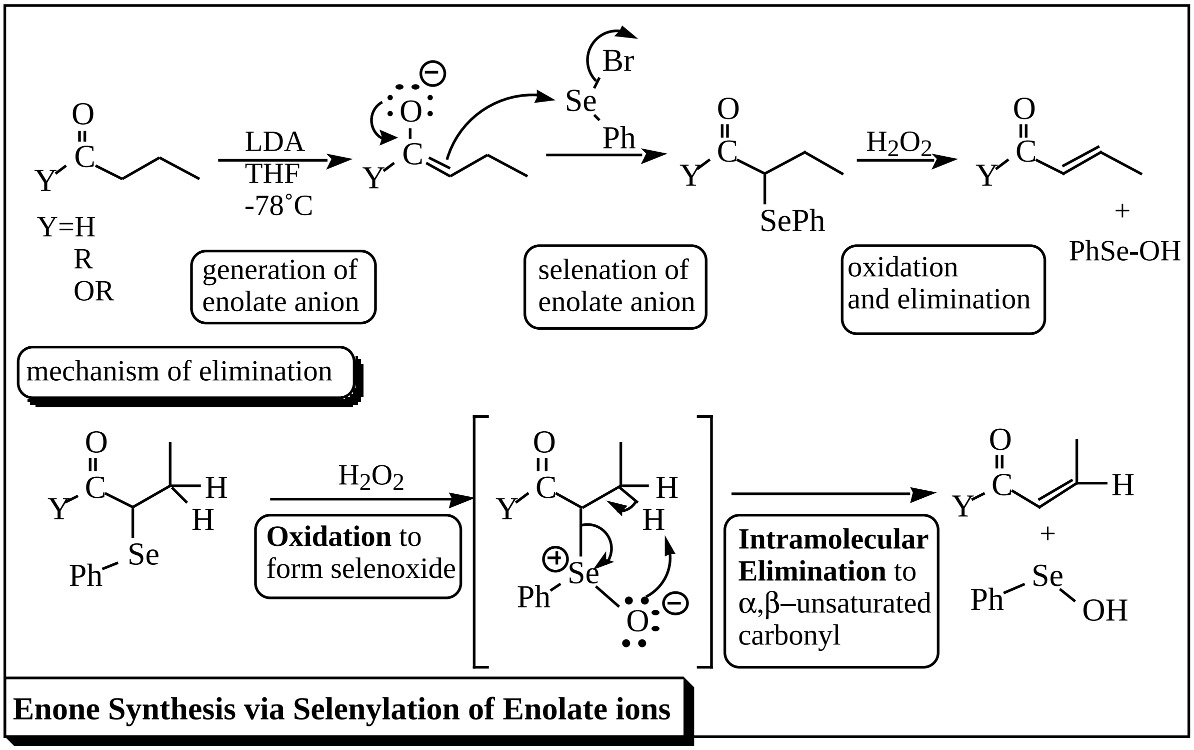
Alkylation of Enolates



LDA is a "bulky" base and will abstract the least hindered, most accessable proton

Regioselectivity of LDA

Enolates react with benzeneseleneyl bromide to yield α–phenylselenenylated products, which in turn give α,β–unsaturated carbonyl compounds when treated with H_2O_2.



generation of enolate anion

selenation of enolate anion

oxidation and elimination

mechanism of elimination

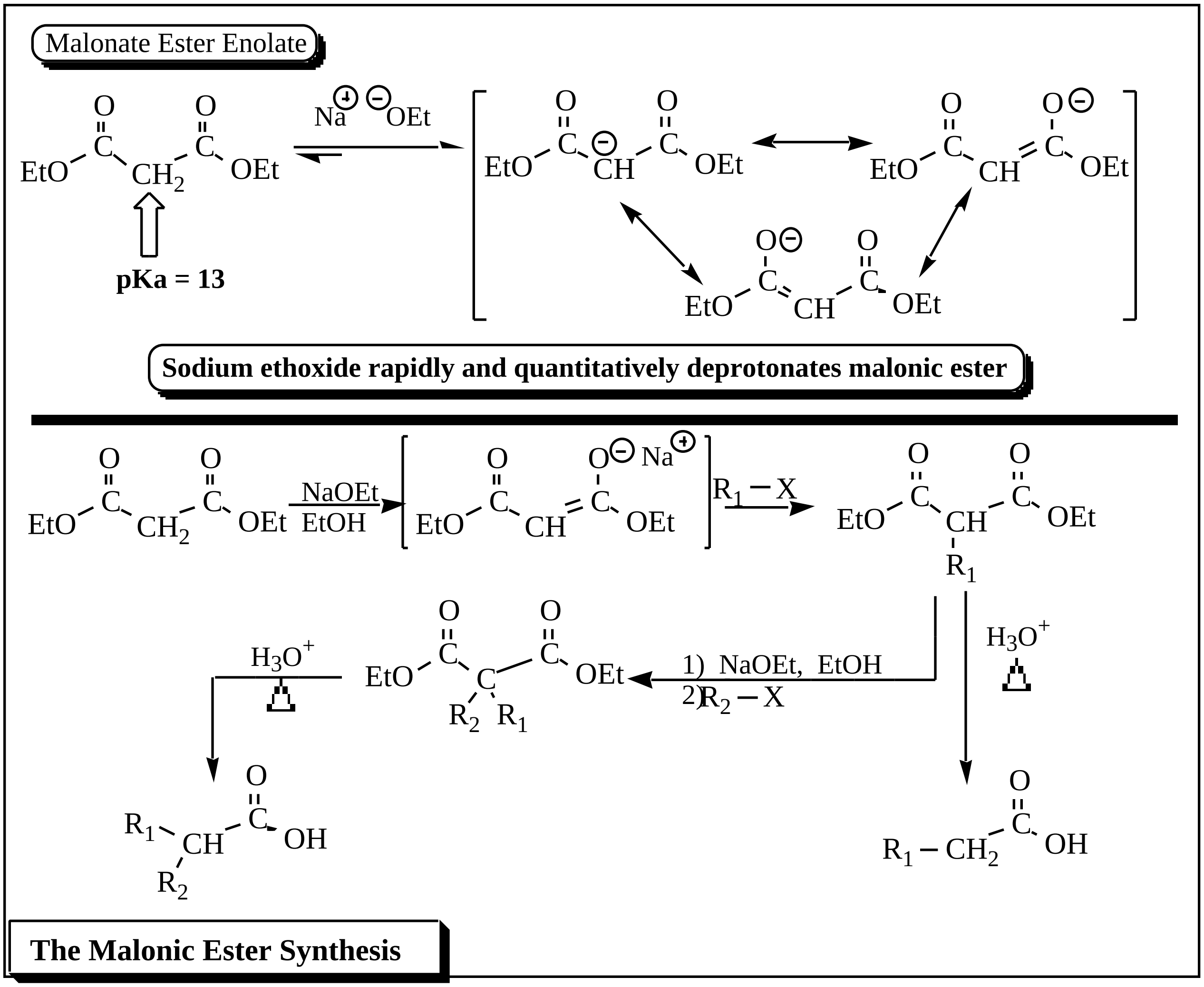
Oxidation to form selenoxide

Intramolecular Elimination to α,β–unsaturated carbonyl

Enone Synthesis via Selenylation of Enolate ions

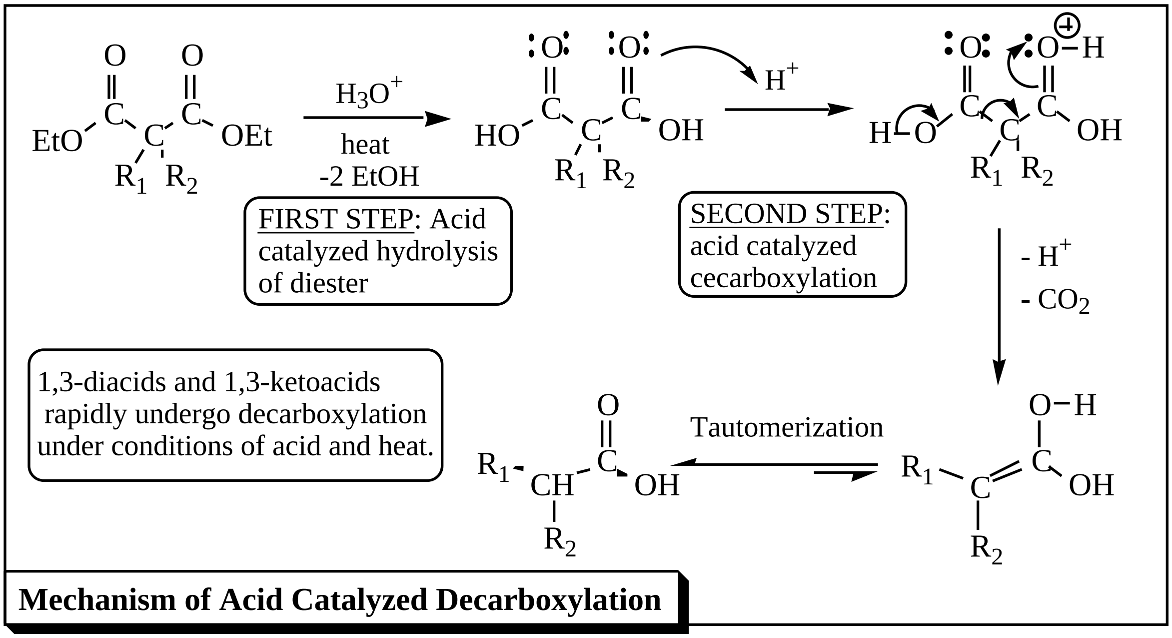
c. <u>Malonic Ester Synthesis and Acetoacetic Ester Synthesis</u>

The malonic ester synthesis involves alkylation of diethyl malonate with one or two alkyl halides, provides a method for preparing mono or dialkylated acetic acid derivatives. The two ester groups of malonic ester activate the central methylene toward deprotonation since the enolate derived from deprotonation of malonic ester can be more extensively delocalized than in a simple ester. The methylene hydrogens of malonic ester are highly acidic (pKa = 13). Thus alkoxide anions derived form alcohols (pKa= 16-18) will rapidly and quantitatively carry out the deprotonation to form the enolate. The enolate so produced may be sequentially alkylated with alkyl halides via the SN2 reaction. Acid catalyzed hydrolysis of the two ester moieties, followed by acid catalyzed decarboxylation at elevated temperature affords the substituted acetic acid derivative.


Malonate Ester Enolate

Sodium ethoxide rapidly and quantitatively deprotonates malonic ester

The Malonic Ester Synthesis

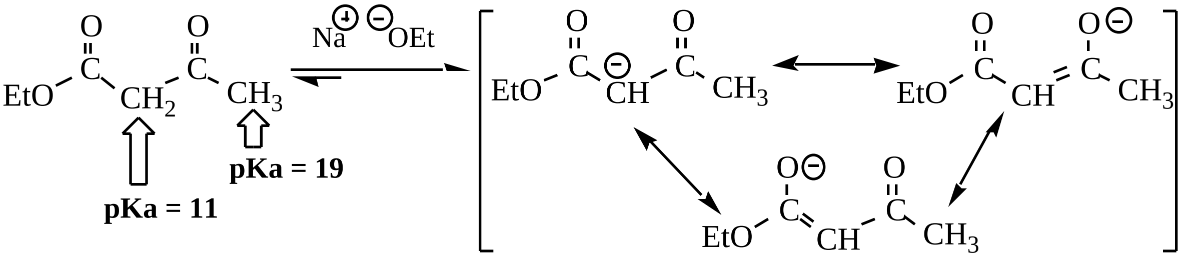

FIRST STEP: Acid catalyzed hydrolysis of diester

SECOND STEP: acid catalyzed cecarboxylation

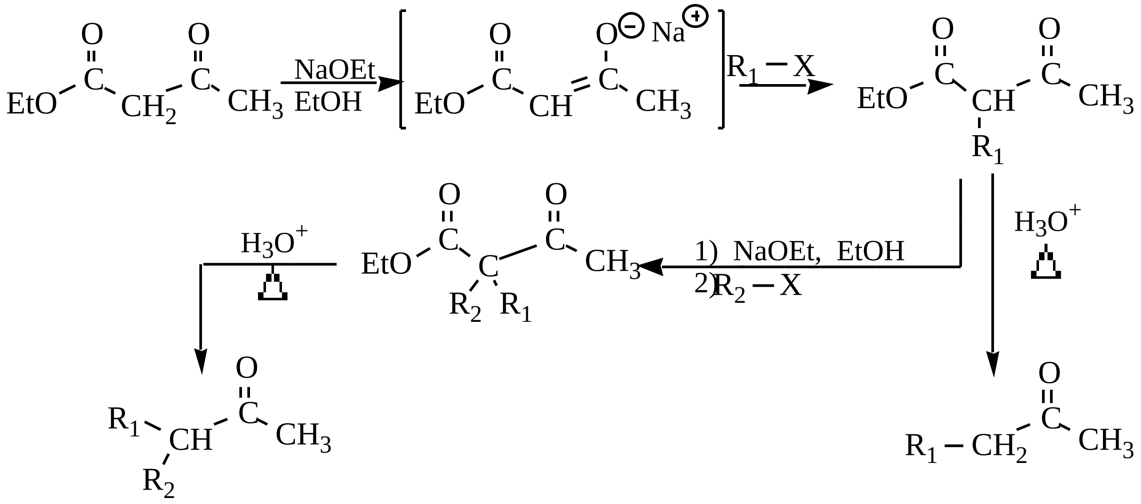
1,3-diacids and 1,3-ketoacids rapidly undergo decarboxylation under conditions of acid and heat.

Mechanism of Acid Catalyzed Decarboxylation

Acetoacetic ester enolate



Sodium ethoxide rapidly and quantitatively deprotonates acetoacetic ester



The AcetoaceticEster Synthesis