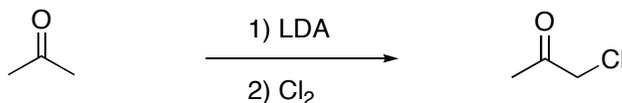
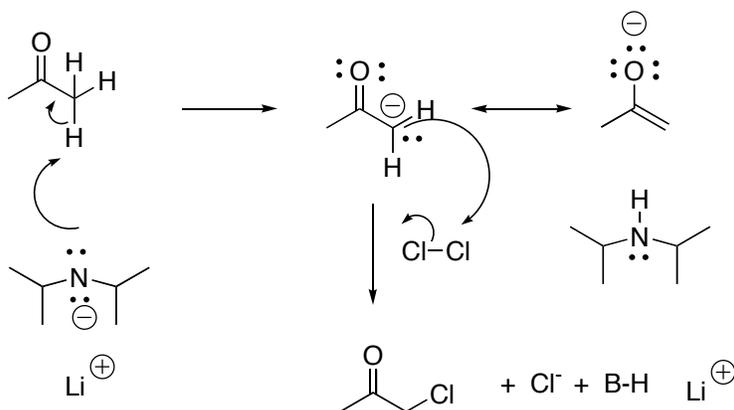


From last class, we looked at the formation of chloroacetone (tear gas) from acetone using lithium diisopropyl amide (LDA) and chlorine gas (Cl_2) as shown below.



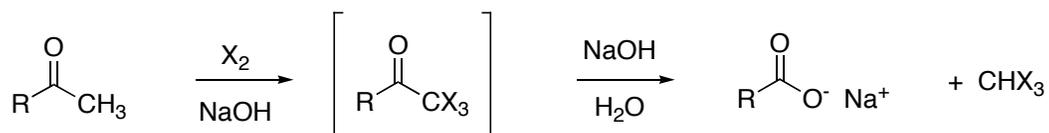
In this reaction, chlorine is the electrophile that reacts with the nucleophilic enolate. The first step of the reaction is the formation of the enolate with lithium diisopropyl amide (LDA) (also depicted as $:\text{B}^-$ in some cases below). LDA is a strong, bulky base, which will remove the alpha hydrogen to produce the resonance stabilized enolate anion. In the second step, the enolate attacks the weak Cl-Cl bond to form the halo ketone and the chloride anion. The Cl-Cl bond is susceptible to attack because the two electronegative chlorines pull electrons out of the bond making it electron poor and weak.



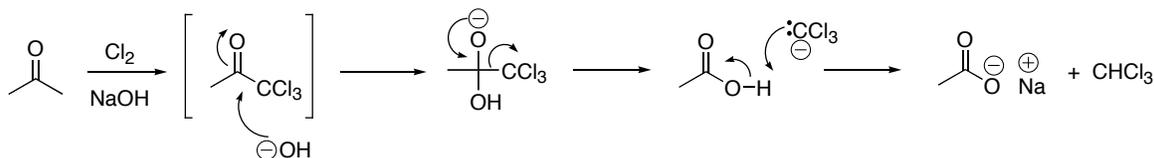
In the above example, the addition of chlorine makes the alpha hydrogens of the product (chloroacetone) even more acidic due to the electron withdrawing effect of the chlorine. Side reactions, including multiple chlorinations are possible.

The Haloform Reaction

A problem with doing the above reaction under basic conditions using sodium hydroxide is the side reaction called the haloform reaction. The haloform reaction converts a methyl ketone into a carboxylic acid salt plus a haloform (chloroform, CHCl_3 ; bromoform, CHBr_3 ; or iodoform, CHI_3) and is the qualitative test for methyl ketones. A sample of an unknown structure, which may be a methyl ketone) is dissolved in THF or ether, and dilute solutions of aqueous NaOH and I_2 are added. Formation of a yellow precipitate of solid iodoform signals a positive test and indicates that the sample is a methyl ketone as shown below in the general example.

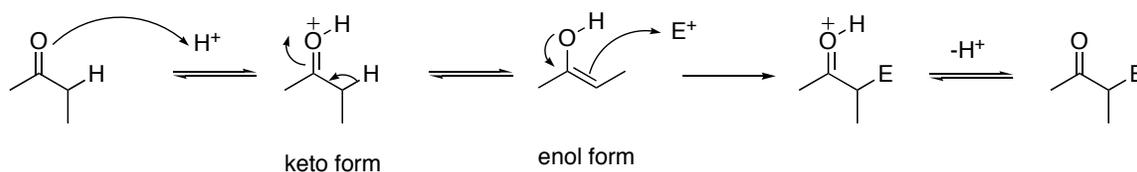


When acetone is reacted with excess Cl_2 and aqueous NaOH , multiple chlorinations occur to form trichloroacetone as shown before. This is then followed by attack of the hydroxide ion on the carbonyl to form a tetrahedral intermediate. This intermediate then displaces the CCl_3 group by donation of a lone pair of electrons from the oxygen to reform the carbonyl. The CCl_3 group leaves as a stabilized anion because the three electron withdrawing chlorine atoms are capable of stabilizing the negative charge. Proton transfer then lead to the products.

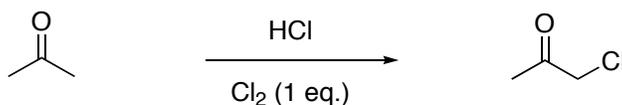


Enol Formation

Enols behave as nucleophiles and react with electrophiles in much the same way as enolates. The main difference between the two is that enols are formed under acidic conditions and enolates under basic conditions. The general mechanism of enol formation is shown below. Protonation of the carbonyl oxygen makes the alpha proton more acidic and deprotonation occurs to form the enol. The enol and keto forms are tautomers (interconverting structural isomers). An electron pair from the enol oxygen reforms the double bond and attacks an electrophile, forming a new carbon-electrophile bond. Loss of a proton from the oxygen yields a neutral alpha-substitution product as the carbonyl is reformed.

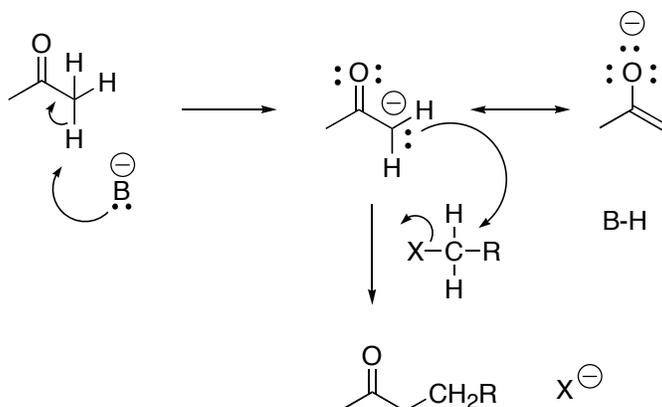


An example is the chlorination of acetone under acidic conditions. Monochlorination is hard to control under basic conditions and there is the competing haloform reaction (see above). Under acidic conditions, this is easy to do with 1 molar equivalent (1 eq.) of chlorine gas.



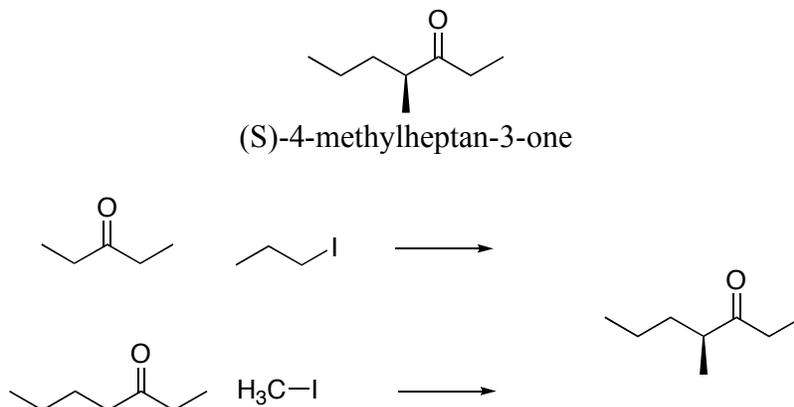
Enolate Alkylation Reactions

An important reaction of enolate ions is their alkylation by treatment with an alkyl halide. The alkylation reaction is useful because it forms a new C-C bond. Alkylation occurs when a nucleophilic enolate ion reacts with the electrophilic alkyl halide in an S_N2 reaction and displaces the leaving group by back-side attack as shown in the general mechanism below.

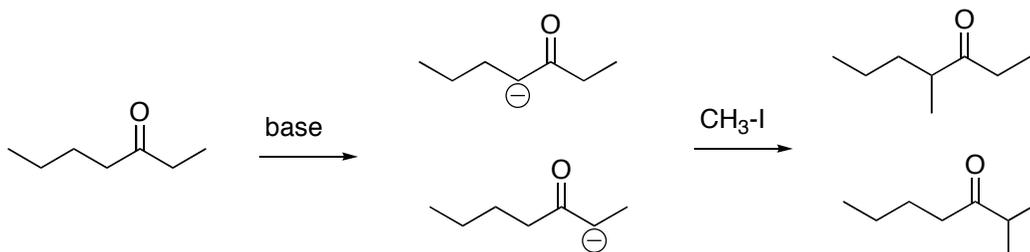


Alkylation reactions are subject to all the rules that affect all S_N2 reactions. The leaving group X in the alkylating agent can be chloride, bromide, iodide, or tosylate. The alkyl group R must be primary and preferably allylic or benzylic. Secondary halides react poorly, and tertiary don't react at all because of competing E2 elimination. Vinylic and aryl halides are also unreactive, because S_N2 attack is sterically prevented.

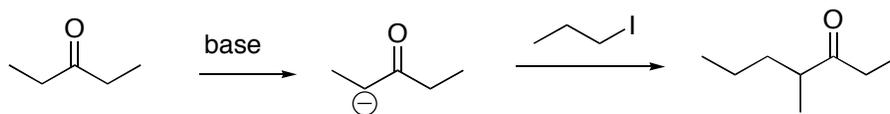
The below example is the ant alarm pheromone (S)-4-methylheptan-3-one. This compound is synthesized using an alkylation reaction of an enolate. There are two possible enolates that can be used in this reaction. The first possibility is the use of the enolate of 3-pentanone and reaction with 1-iodopropane. The second possibility is the use of the enolate of 3-heptanone and reaction with methyl iodide.



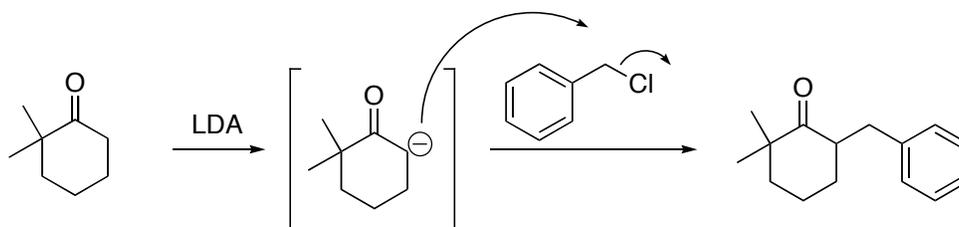
The alkylation of 3-heptanone with methyl iodide is a poor choice for this synthesis. Upon enolate formation of 3-heptanone, two possible enolates can be formed because the molecule is unsymmetrical. Therefore, alkylation can occur at the 2 and 4 positions of 3-heptanone.



The alkylation of 3-pentanone with 1-iodopropane is the best choice because upon enolate formation, there is only one enolate formed because the molecule is symmetrical. In this reaction is important to know that the alkylation product is racemic (1:1 mixture of enantiomers) because there is no stereochemical control.

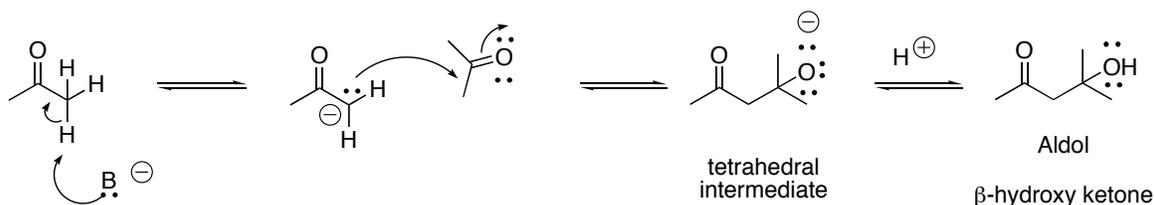


An example is the alkylation of 2,2-dimethylcyclohexanone with LDA and benzyl chloride to give the benzyl substituted product shown below. The enolate undergoes an S_N2 attack of the methylene bearing the chloride to give the final product.

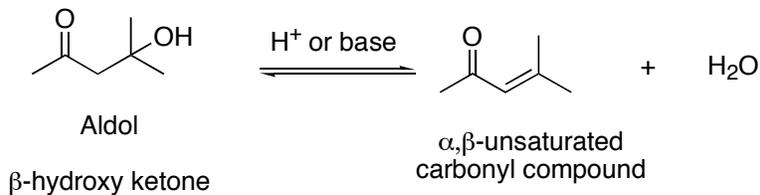


Aldol Formation

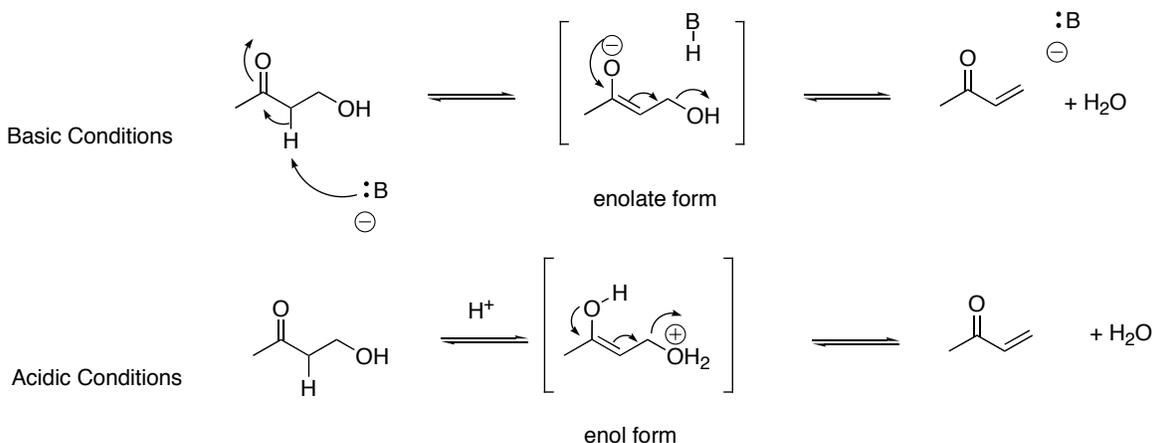
The base induced aldol formation is a general reaction for ketones and aldehydes with alpha hydrogen atoms. If the ketone or aldehyde does not have alpha hydrogens, the aldol reaction cannot occur. Aldol condensations are typical carbonyl condensations. They occur by nucleophilic addition of the enolate ion of the donor molecule to the carbonyl group of the acceptor molecule, yielding a tetrahedral intermediate that is protonated to give the aldol product (a β -hydroxy carbonyl compound). This reaction is completely reversible, and can revert to the starting materials in the presence of base.



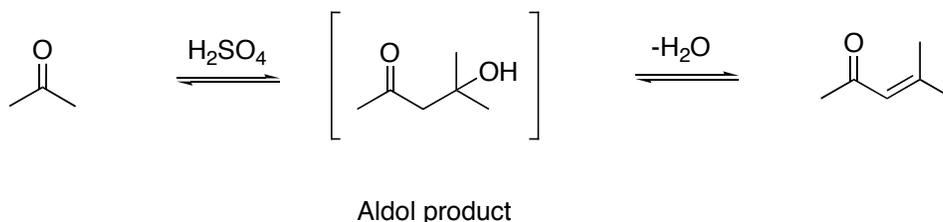
The β -hydroxy ketones and β -hydroxy aldehydes formed in the aldol process can easily be dehydrated ($-\text{H}_2\text{O}$) to yield conjugated enones called α,β -unsaturated carbonyl compounds with the application of heat with acid or base.



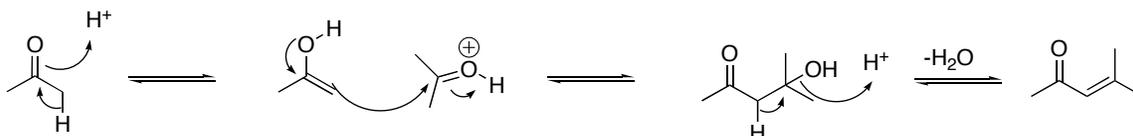
Most alcohols are resistant to dehydration with acid or base but a hydroxyl group beta to a carbonyl compound is different. Under basic conditions, the acidic alpha hydrogen is abstracted, yielding the enolate ion (or enol under acidic conditions) that expels the $-OH$ leaving group as water (a proton is abstracted from the medium or the protonated base). Under acidic conditions, an enol is formed, the OH group is protonated first and water is expelled in a similar fashion as above.



An example is the aldol condensation of acetone under acidic conditions. In this reaction, an intermediate aldol product is formed, followed by dehydration to the α,β -unsaturated carbonyl compound 4-methylpent-3-ene-2-one (also known as mesityl oxide).

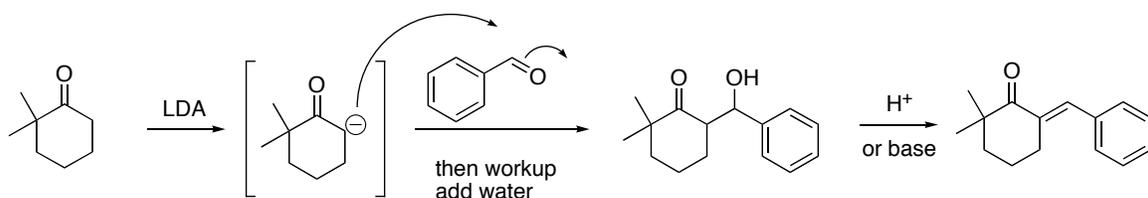


The first step of the mechanism involves the formation of the enol under acidic conditions. The enol then attacks a protonated acetone molecule to form the tetrahedral intermediate aldol product. This aldol product then dehydrates to give the final product.



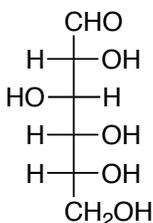
Until now we have only considered symmetrical aldol reaction, in which the two carbonyl components have been the same. A mixed (crossed) aldol reaction involves an aldol reaction between two different carbonyl partners. In principle, a mixed aldol reaction between two similar ketone and aldehyde components can lead to a mixture of four possible products including the self condensed products and the two mixed products. On the other hand, mixed aldol reaction can lead cleanly to a single product if one of the carbonyl compounds is much more reactive or contains no alpha hydrogen's and therefore cannot form an enolate ion to become the donor. The electrophile does have to contain a reactive carbonyl group that is a good acceptor of nucleophiles.

An example is the aldol condensation of 2,2-dimethylcyclohexanone with benzaldehyde in which only a single compound is formed to yield the dehydrated product as shown below.



Carbohydrates (also known as sugars or saccharides) – See Handout

Approximately 0.02% of the sun's energy is used on this planet for photosynthesis in which organisms convert carbon dioxide (CO_2) and water (H_2O) to D-glucose ($\text{C}_6\text{H}_{12}\text{O}_6$) and oxygen (O_2). About 4×10^{11} tons of carbon dioxide are converted to glucose annually by plants, and glucose (in bound form) is one of the most abundant compounds on the planet. Learn the structure of D-glucose shown below.



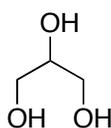
Glucose (also called dextrose)

Carbohydrates occur in every living organism. The sugar in starch in food, and the cellulose in wood, paper, and cotton, are carbohydrates. Modified carbohydrates form

part of the coating in living cells, other carbohydrates are found in the DNA that carried genetic information, and still others are used in medicine.

The term carbohydrate is used to refer to a broad class of polyhydroxylated aldehydes and ketones commonly called sugars. Carbohydrates are also known as saccharides.

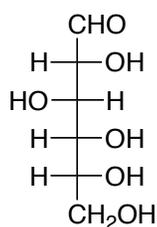
The general formula for a carbohydrate is approximated as $C_NH_{2N}O_N$. The number of carbons in the carbohydrate chain is also given special nomenclature. A three carbon carbohydrate, such as glycerol, is called triose, a 4 carbon carbohydrate is called a tetrose, a 5 carbon carbohydrate is called a pentose, and a 6 carbon carbohydrate is called a hexose. Know the structure of glycerol.



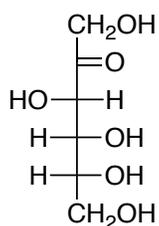
Glycerol

(a triose)

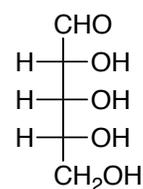
Carbohydrates can further be classified as either aldoses or ketoses. The -ose suffix is used to identify the carbohydrate, and the aldo- and keto- prefixes identify the nature of the carbonyl group. For example, glucose is an aldohexose, a six carbon aldehyde sugar; fructose is a ketohexose, a six carbon keto sugar; and ribose is an aldopentose, a five carbon aldehyde sugar. The most commonly occurring sugars are either aldopentoses or aldohexoses.



Glucose
(an aldohexose)



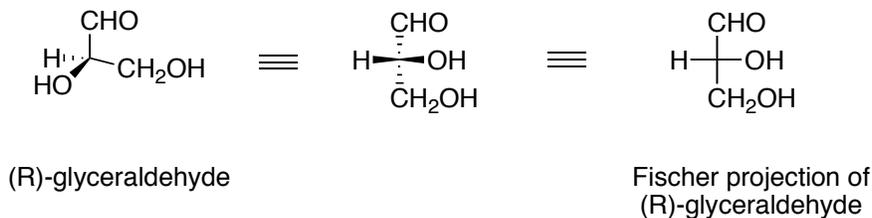
Fructose
(a ketohexose)



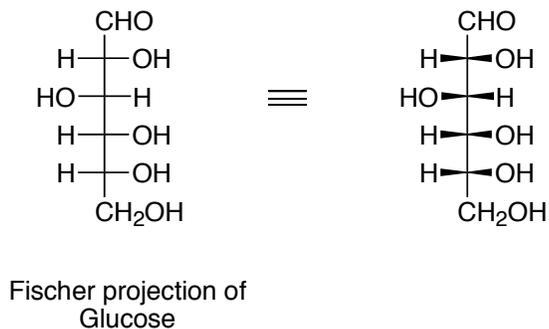
Ribose
(an aldopentose)

Configuration of Sugars: Fischer Projections

Since all of the sugars have stereogenic centers, Fischer projections depict the stereogenic centers on a flat page surface. A Fischer projection is represented by two crossed lines, in which the horizontal line represents bonds coming out of the page, and the vertical lines represent bonds going into the page. By convention, the carbonyl is placed at or near the top of the Fischer projection. Shown below is the Fischer projection of (R)-glyceraldehyde.

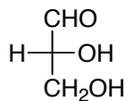


Another example is the Fischer projection of glucose. Glucose has four stereogenic centers stacked on top of one another, with the carbonyl placed near the top.

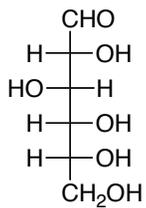


D,L Configuration of Sugars

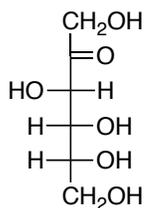
Glyceraldehyde has only one stereogenic center and therefore has two enantiomers (mirror image) forms. A D-sugar is defined as one that has R configuration at the highest numbered stereogenic center. L-sugars are those that have S-configuration at the highest numbered stereogenic center (see handout).



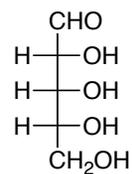
D-Glyceraldehyde



D-Glucose



D-Fructose



D-Ribose