2 - ALDEHYDES, KETONES AND DERIVATIVES

Carbonyl chemistry is one of the most important areas of organic chemistry. You have been introduced to the chemistry of carboxylic acids in CHEM*2700, and in this course we will focus on aldehydes and ketones. Hence the compounds that we will study in this chapter will possess a carbonyl group which has either hydrogens or carbons attached to it.

![Carbonyl group, Ketone (R≠H), Aldehyde](image)

The reactivity of aldehydes and ketones is based on two important reactions of them. These species are prone to nucleophilic attack at the carbonyl carbon and one can make a nucleophile on a carbon α to the carbonyl group.

![Nucleophilic Attack](image)

This chapter will first demonstrate some synthetic routes to aldehydes and ketones, and then will describe some of their vast chemistry based on the two principal modes of reaction shown above.

1. Synthetic Routes to Aldehydes and Ketones (SF/SFS 16.4, 16.5)

One of the main methods for the preparation of aldehydes and ketones is oxidation of an alcohol as shown in a general sense below.

![Oxidation](image)

The following are some popular routes to aldehydes and ketones and of course include oxidation of an alcohol. Most should be familiar to you.
a) Aldehydes

\[
\text{primary alcohol} \quad \xrightarrow{\text{PCC, } \text{CH}_2\text{Cl}_2} \quad \text{aldehyde, 75%}
\]

\[
PCC = \begin{array}{c}
\text{pyridinium chlorochromate}
\end{array}
\]

b) Aldehydes and Ketones

\[
\text{menthol} \quad \xrightarrow{\text{O}_3, \text{CH}_2\text{Cl}_2, -78 \, ^\circ\text{C}} \quad \xrightarrow{\text{Zn, HOAc}} \quad \text{menthone, 84}\%
\]

c) Ketones

\[
\text{Grignard chemistry followed by oxidation}
\]
2. Acidity and Enolization of Aldehydes and Ketones (SF/SFS 18.1-18.2 and SF 3.5-3.7; SFS 3.5-3.6)

As stated, one of the origins of the reactivity of aldehydes and ketones is their inherent acidity, which is based on the electronic properties of the carbonyl group. The carbonyl group is an electron-withdrawing group by both induction and resonance. So, hydrogens α to the group possess increased acidity simply due to their proximity and the incipient anion can be stabilized through π-resonance with the carbonyl group.

There is a geometric requirement for facile proton removal in this chemistry. The C-H bond that holds the removable hydrogen must be aligned with the π-orbitals of the C=O π-bond. The required conformation is trivial to achieve in a freely rotating system, but may not be accessible in cyclic or constrained molecules. Without the proper orbital overlap, then the π-resonance stabilization of the anion is not possible. The result is that the acidity of the α hydrogen is greatly reduced.
Bases suitable for deprotonation of an aldehyde or ketone must meet two principal requirements:

a) The base must be strong enough to remove the hydrogen. In this regard, any base whose conjugate acid has a $pK_a$ greater than 20 will be suitable. Sometimes a weaker base will work, but the reaction must proceed under equilibrium deprotonation conditions.

b) The base has to perform selective attack at hydrogen and cannot have properties that will promote nucleophilic attack at the carbonyl carbon. A sterically hindered base usually provides the desired chemoselectivity. LDA, lithium diisopropylamide ([Me₂HC]₂N-Li⁺) is often the base of choice.

The resonance stabilized anion that results from these deprotonation reactions is called an enolate, which means that it is the anion of an acid called an enol.

These species are of course interconvertible through the transfer of one proton. As we will see shortly, the enolate and the enol can be functionalized at the $\alpha$-carbon. Hence one can use an enol or an enolate for derivatizing the compound next to its carbonyl group.

Enols can be generated through a reversible acid catalyzed reaction.

The methods of forming enols and enolates are fully reversible. So the carbonyl compound can be regenerated from an enol by simply adding acid and isolating the substrate (except in specialized instances). Attempted isolation of the enol from acid solution will provide the aldehyde or ketone.
Mechanistically, regeneration of the carbonyl compound can be the reverse of enolate formation, or may involve the enol.

Under these conditions, the keto form of the compound is regenerated upon isolation. The equilibrium between enol and keto shown above is called tautomerism, since the compounds are tautomers of one another. The carbonyl compound is usually the thermodynamically favoured form, based on the carbonyl bond strength, but there are exceptions to this rule. A number of equilibrium constants have been determined for keto-enol tautomerism. They are calculated as shown, and are of course dependent on the medium in which the measurement is made. If the substrate is neat, the tautomer ratio depends on the origin of the material.

\[ K_{eq} = \frac{[\text{enol}]}{[\text{keto}]} \]

The \( K_{eq} \) (keto-enol) for acetone in water is \( 1.5 \times 10^{-7} \). It should be noted that despite the fact that the ratio can significantly favor the keto form, reactions selective for the enol form can still take place, as we shall see.

The relative acidity of the hydrogens next to the carbonyl groups of aldehyde or ketones has both advantages and disadvantages. For one advantage, the acidity allows for deuterium incorporation into the molecule. The protocol involves simple addition of the carbonyl compound to \( D_2O \) containing a trace amount of acid or base. Any hydrogens in the \( \alpha \)-position that can adopt the required conformation for enol or enolate formation will become fully deuterated, given sufficient time.

Another consequence of enol formation, having negative and positive implications, is the ease with which chiral \( \alpha \)-carbons can invert their stereochemistry. Hence if you have taken the time to make an important, optically pure product possessing stereochemistry at the \( \alpha \)-carbon, exposure to acid or bases may racemize the material (SF/SFS 18.3A). For example, optically active 3-phenyl-2-butanone in basic ethanol (r.t.) racemizes within minutes.
There are instances of advantageous isomerism of \( \alpha \)-carbon, through their planar form.

In the anionic form, the \( \alpha \)-carbon is planar and in theory can be protonated from either face. However, the configuration of the \( \beta \)-carbon which bears the methyl group is a constant and that substituent creates a bias in the reprotonation reaction. The allyl and methyl substituents prefer to be trans to one another for steric reasons and trans isomer is produced in >95% yield under these thermodynamic conditions.
3. Halogenation of Ketones and Aldehydes  (SF/SFS 18.3B-18.3D)

The following general reaction is the topic of this section.

\[
\text{H}_{\text{C=O}} + X_2 \xrightarrow{\text{acid or base}} \text{X}_{\text{C=O}}
\]

As noted, halogenation of these carbonyl compounds may proceed under acidic or basic conditions. Under either of these conditions, the mechanism for generation of the enol or enolate is the same as previous. The reactive compound then attacks the halogen rather than any other electrophile such as a proton.

Rate studies have shown that initial rates of the halogenation are independent of halogen concentration. This is interpreted to mean that introduction of halogen into the substrate is not rate determining. Furthermore, experiments have shown that the rate is dependent on concentration of carbonyl compound and acid (or base). From this evidence, it is generally believed that enol or enolate formation is rate determining.

\[
\begin{align*}
\text{Cl}_2, H^+ & \quad \text{70 °C} \\
85\%
\end{align*}
\]
Sometimes as shown below, the reaction is *autocatalytic*. That is, it is very slow until some halogenation occurs which produces acid as a byproduct. The rate of halogenation then accelerates due to the presence of acid. Hence the term autocatalytic, since the reaction provides the means to promote itself.

\[
\text{CH}_3\text{CO} + \text{Br}_2 \xrightarrow{\text{MeOH}} \text{CH}_3\text{COBr} + \text{HBr}
\]

70%

Under basic conditions, multiple halogenation is often a problem and therefore basic conditions are not recommended if one is striving for only the monohalogenated product. Note that this reactive character can be used to one’s advantage, as shown below. For the introduction of only one halogen, the reaction is usually performed under acidic conditions since introduction of one halogen into the molecule slows further reaction. *For synthetic efficiency, monohalogenation reaction must be performed under acidic conditions.*

Multiple halogenation of methyl ketones provides chemistry that has been used as a functional group identification technique, although spectroscopic methods are now more popular. Multiple halogenation of methyl ketones leads to the haloform reaction and iodine is the more common halogen employed (iodoform reaction). The mechanism involves triple iodination of the methyl group of the ketone under basic conditions.

```
H
O
H+
```

```text
In the halogenated form, the electron withdrawing nature of the halogen retards the initial step of enol formatic and hence slows the introduction of more halogens.
```

```
Base
I_2
\text{RCH}_2\text{O} + 2I_2 \rightarrow \text{RCH}_2\text{I} + 2I_2
```

Then, hydroxide attacks at the carbonyl group to make a tetrahedral intermediate which expels \(-\text{Cl}_3\).
Interaction with the solvent provides the products: iodoform and carboxylate. \( \text{Cl}_3^- \) is a good leaving group in this case because the three electronegative halogens help to stabilize the negative charge on the carbon atom. The electronegativity also accounts for the multiple halogenation at a single site. Once one halogen is introduced, the remaining hydrogens on that same carbon atom have enhanced acidity.

Acidic workup affords the carboxylic acid if desired as opposed to the carboxylate. The iodoform is a bright yellow precipitate that serves as a useful indicator. If a compound is suspected of being a methyl ketone, simply add excess hydroxide and I\(_2\) and look for a yellow precipitate for confirmation of the suspected structure. The reaction can also be synthetically useful in that it can be used to achieve the overall conversion of methyl ketone to carboxylic acid.
4. Alkylation Reactions and Enamines (SF 16.8C, 18.4A-B, 18.9; SFS 16.8D, 18.4A-B, 18.9)

Generating an enolate from a ketone or aldehyde and quenching it with an alkylating agent affords a method for the synthesis of compounds bearing an alkyl substituent next to the carbonyl group. Simple reactions can occur in some cases.

\[
\begin{align*}
\text{O} & \quad \text{EtO} \\
\text{EtO} & \quad \text{O}^{\mathrm{Li}^+} \\
\text{LDA} & \quad \text{cold} \\
\text{MeI} & \quad \text{warm to r.t.}
\end{align*}
\]

\[
\begin{align*}
\text{EtO} & \quad \text{O}^{\mathrm{Li}^+} \\
\text{EtO} & \quad \text{Me} \\
\text{HN(}i\text{Pr}_2 & \quad \text{93%}
\end{align*}
\]

(SF/SFS 18.4A-B)

5-methyl-3-hexen-2-one \[\rightarrow\] 5-methyl-2-pentenoic acid

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{O} & \quad \text{+ CHCl}_3 \\
\text{1. Cl}_2/\text{NaOH} & \quad \\
\text{2. HCl/H}_2\text{O} & \quad \\
\text{chloroform} & \quad \\
\end{align*}
\]

5-methyl-3-hexen-2-one \[\rightarrow\] 5-methyl-2-pentenoic acid
There can be problems associated with this simple approach. One is that there are two sites for deprotonation when the compound bears $\alpha$-hydrogens on either side of the carbonyl group. There can also be a problem with multiple alkylations, depending on the substrate and reaction conditions. For this reason, other methods to achieve simple efficient alkylation have been developed.

One useful method for overcoming some of the difficulties involves the chemistry of enamines. As their name indicates enamines contain a double bond (ene) and an amine and the name is applied to systems where the two are in conjugation.

\[
\text{enamine} \quad \leftrightarrow \quad \text{imine}
\]

Gilbert Stork of Columbia University developed the chemistry shown here and it still bears his name. Enamines are prepared by condensing a secondary amine with a ketone or an aldehyde. If the amine is a primary amine the result is an imine, which is actually the more thermodynamically stable form of an imine/enamine tautomeric equilibrium (SF 16.8C; SFS 16.8D).

The following mechanism accounts for the enamine formation.
Water must be driven from the reaction vessel in order to force the equilibrium reaction to completion. This is usually achieved through the use of a Dean Stark apparatus:

Evaporated compounds condense, fall into graduated tube and separate. Water stays on lower layer and never return to the flask while the benzene (or toluene) rises to the level where it runs back into the reaction vessel.
As shown above the enamine has nucleophilicity at carbon and it is this atom that is preferentially functionalized in a simple $S_N2$ reaction.

![Chemical structure diagram](image)

usually $X = -\text{CH}_2\text{CH}_2\text{-} \quad$ (pyrrolidine)
$-\text{CH}_2\text{CH}_2\text{CH}_2\text{-} \quad$ (piperidine)
$-\text{CH}_2\text{OCH}_2\text{-} \quad$ (morpholine)

In this reaction the $\beta$-carbon of the enamine ($\alpha$-carbon of the ketone) bears the new substituent. To remove the nitrogen auxiliary and recover the new ketone, the iminium salt is hydrolyzed under aqueous acid conditions. The amine is lost in the acidic medium and can be recycled if desired. This method is preferred over simple deprotonation and alkylation since it minimizes double or multiple alkylation. The reaction occurs best with reactive halo compounds such as methyl iodide, benzyl halides, allyl halides, $\alpha$-halocarbonyl compounds and acyl halides. Below is an example of the overall reaction sequence.

$$\begin{align*}
\text{CH}_3\text{CH}2\text{C} & \quad \text{pyrrolidine, H}^+ \\
\text{BrCH}_2\text{CH}_3 & 2. \text{BrCH}_2\text{CH}_3 \\
\text{H}^+, \text{H}_2\text{O} & 3. \text{H}^+, \text{H}_2\text{O}
\end{align*}$$

67%
Other examples:

5. The Aldol Condensation (SF/SFS 19.4-19.6)

To this point we have examined the reactions of enols and enolates with a number of reactive electrophiles. One can also react them with the very substrates that provide enols and enolates: CARBONYL COMPOUNDS. Under the proper conditions the carbonyl group is sufficiently reactive to accept electron density from an enol or enolate. The archetypal example in many texts is the base catalyzed reaction of two molecules of acetaldehyde. The name aldol originates from the presence of an aldehyde and an alcohol in the product molecule. This name is used even if ketones are involved in the chemistry.

The mechanism for the reaction is straightforward and is the basis of many other reactions yet to be introduced in this chapter. It begins with the reversible generation of
an enolate. The enolate then reacts as indicated. Note that all the steps are reversible and sometimes aldol condensations are difficult to complete because of a propensity to revert to starting materials.

Sometimes the aldol product will lose water spontaneously to afford a double bond. The conjugation of the double bond with the carbonyl group is the driving force in the dehydration. This can often be achieved simply by heating the reaction mixture during or after the bond forming process. Sometimes making the solution acidic will achieve the same purpose. The term condensation arises from the loss-of-water step. In synthetic chemistry, condensation means: the loss of water or its equivalent. Sometimes when the equilibrium constant for aldol formation is small, the reaction can still be driven by pushing the product through to the dehydrated product, the formation of which proceeds efficiently and is less reversible.

Basic conditions:
Acidic conditions:

The whole aldol condensation can also be performed under acidic conditions, where an enol rather than an enolate is the nucleophile. The acid initially induces enol formation by the means shown earlier in this chapter. This enol is a weak nucleophile and will only undergo aldol chemistry when the electron accepting carbonyl group has been protonated.

Mechanism for acidic aldol reaction with loss of water:
It is very difficult to isolate the true aldol product under acidic conditions. The reactions usually carries through to the unsaturated material.

Both ketones and aldehydes can undergo the aldol condensation. Aldehydes are more reactive since nucleophilic attack at the ketone carbonyl is more sterically hindered. Also, the extra electron donating substituent makes the ketone less electrophilic.

Aldol condensations as shown above with two molecules of acetaldehyde are the simplest possible examples. Complications quickly arise when two different aldehydes are used, or when ketones with two sets of \( \alpha \)-hydrogens are employed. For instance with two different aldehydes, four products are available. The list includes two compounds from self condensation and two different products from a crossed aldol reaction.

Selectivity can be achieved by choosing one reactant that does not have \( \alpha \)-hydrogens.
Sometimes, when there is a large number of α-hydrogens in the systems, it may be possible to selectively generate a particular enolate and then quench that enolate with another carbonyl compound. Such a protocol requires a method for preparation of specific enolates. The use of LDA is recommended in these circumstances. Recall that treatment of an aldehyde or ketone with LDA is a reliable method for the complete and irreversible formation of a lithium enolate. With asymmetric ketones, LDA will remove a proton from the least sterically hindered position, to afford the kinetic enolate. This is generally believed to be the best method for carrying out crossed aldol condensations.

If a given substrate possesses two carbonyl groups, it is possible for the compound to undergo an intramolecular aldol condensation. This form of the reaction is only suitable for the synthesis of 5, 6, and 7 membered rings. There are some rules that can be applied at this stage. One is a reminder that aldehydes are more electrophilic than ketones. The other is that 5 membered rings will form more readily than 7-membered rings while 6-membered rings are the best. Recall that aldol condensations are reversible and there is opportunity to form the most thermodynamically stable product. Intramolecular aldol condensations will virtually always proceed through with loss of water to form the a,b-unsaturated ketone or aldehyde. When deciding the product of this cyclization, an important step in the analysis is determining when water can be readily lost from the aldol. If not, aldol formation often reverses itself.

1Of the two possible enolates formed from a ketone such as methyl ethyl ketone, the one with the least substituents on the double bond of the enolate is termed the kinetic enolate. The kinetic enolate is formed by deprotonation of the least hindered site. Deprotonation from the more hindered site (which can be achieved under different conditions) gives the thermodynamic enolate, which is more stable because it has more substituents around the double bond form of the enolate. See SF/SFS 18.4.
Before we leave the aldol condensation, the role of the carbonyl group in this chemistry should be emphasized. The polarity and resonance ability of the carbonyl group enhances the acidity of the hydrogens α to it, allowing for the formation of enolates. That creates the nucleophilic component of the two reactants. For the electrophilic component the carbonyl group is polarized such that the carbon can accept attack by a nucleophile and the oxygen can hold the negative charge.

6. Other Related Condensation Reactions

Whereas the Aldol condensation involves the reaction of an enolate of an aldehyde or ketone with another aldehyde or ketone, the Claisen Condensation (SF/SFS 19.2) involves the reaction of an enolate of an ester and a carboxylic acid derivative, usually another ester. One can view the initial steps of the Claisen condensation as analogous to ketone chemistry. Enolates of esters are less acidic than enolates of ketones or aldehydes and can therefore undergo chemistry with less reactive compounds. The archetypal example in this condensation involves the reaction of two molecules of ethyl acetate induced by ethoxide ion. The mechanism of the reaction is shown below.
Although the scheme above shows the β-ketoester as the product, it should be realized that under the reaction conditions, the material actually rests as the deprotonated form until acted upon by the addition of acid which returns the hydrogen. That is, the Claisen reaction mixture must be quenched with acid before isolation of the product. Acetic acid or aq. ammonium chloride are often employed.

Note that anions derived from the β-ketoester have two carbonyl groups available for conjugation. Hence the pK\textsubscript{a} of the β-ketoester is much lower than that of a simple ketone or ester, since anion stabilization is offer by both of these carbonyl groups in a single molecule. Hence, the β-ketoester is readily deprotonated by ethoxide.
The deprotonation step as shown above is key to the completion of the reaction. The β-ketoester anion is essentially inert and furthermore, in anionic form, the species is captured and frozen and cannot succumb to the reversibility of the reaction. The overall reaction only works well when there are 2 or 3 hydrogens on the starting ester. The β-ketoester drawn above is known by the common name of ethyl acetoacetate and hence the self-condensation of esters is sometimes known as the *acetoacetate ester condensation*.

Example:

\[
\begin{align*}
\text{2 MeO}^- \text{Na}^+ & \quad \text{1. MeO}^- \text{Na}^+ \quad \text{2. H}^+ \\
\text{MeO}^- \text{Na}^+ \quad \text{H}^+ & \quad \text{MeO}^- \text{Na}^+ \\
\end{align*}
\]

Crossed Claisen condensations are possible when one of the esters does not possess α-hydrogens, much like the ideal situation for crossed aldol reactions.
Note that in each of the three examples above, one of the reacting esters does not contain $\alpha$-hydrogens. Carbonate esters which also lack $\alpha$-hydrogens will successfully partake in crossed Claisen reactions.

Another reaction that simplifies potentially complicated reactions is the Reformatsky reaction. It begins with an $\alpha$-halo ester* and uses metallic zinc to establish an ester enolate. In this reaction, the halo ester and zinc are mixed together to create a solution containing a zinc enolate, to which the ketone or aldehyde is added.

As with aldol condensations, the product of Reformatsky reactions can be readily converted to the unsaturated material by treatment with acid. This achieves the dehydration process.

* $\alpha$-Halo esters can be prepared by the Hell-Volhard-Zelinski reaction whereby a carboxylic acid is treated with molecular halogen and elemental phosphorus and then water. See SF/SFS 18.3D for details of this preparation. The acid can then simply be esterified.
If two ester groups are in the same molecule and are separated by 4 or 5 carbon atoms, then one can achieve an intramolecular Claisen condensation. This reaction is called the Dieckmann (SF/SFS 19.2A) condensation. Again there is an archetypal system that exemplifies the reaction.
As with the Claisen condensation, the equilibrium is frozen at the desired product by deprotonation of the acidic hydrogen between the carbonyl groups. The Dieckmann condensation is only useful for 5 and 6 membered rings.

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{EtO}^- \quad \text{H}^+ \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} & \quad \text{HCO}_2\text{Et}
\end{align*}
\]

A form of the **Claisen Condensation** is very prevalent in biological systems: it is vital to the construction of many naturally occurring and biologically important chemicals. In this case the carboxylic acid being attacked is a thiolester (textbooks will tell you thioester), and the sulfur and the remainder of coenzyme A is lost in a potentially reversible step. The nucleophile is not exactly the enolate of an ester, but one that bears an extra -CO\(_2\)\(^-\) unit. The release of CO\(_2\), concurrent with nucleophilic attack, assists the Claisen Condensation over its kinetic barrier.

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{H} & \quad \text{O} & \quad \text{H} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{CH}_2 & \quad \text{S} & \quad \text{CoA} \\
\text{H}_3\text{C} & \quad \text{CH}_2 & \quad \text{S} & \quad \text{CoA} \\
\text{reduce, dehydrate,} & \quad \text{reduce} & \quad \text{CH}_3\text{CH}_2\text{CH}_2 & \quad \text{S} & \quad \text{CoA} \\
\text{more repetitions} & \quad \text{steroidal hormone} & \quad \text{bile acids} & \quad \text{terpenes}
\end{align*}
\]
7. Synthetic Applications of Condensation Reactions

a) Acetoacetic Ester Synthesis (SF/SFS 18.6)

This synthesis, named after the starting material employed is a valuable means of preparing substituted acetones (methyl ketones). The approach utilizes two key qualities of the starting material, MeC(O)CH₂CO₂Et. One is that the compound possess a CH₂ group with low acidity that can be readily functionalized. The other is that the ester can be converted to an acid which is then completely removed.

The general equation for the overall transformation is as follows, where R = a non-hydrogen group and R' may be hydrogen or another group.

\[
\begin{align*}
\text{Acetoacetic Ester} & \quad \text{RO}^+ M^+ \quad \text{RX} \\
\text{Reagent} & \quad \text{Acetone Product} \\
\end{align*}
\]

In detail, the first reaction is similar to those you have seen before. One of the acidic hydrogens of the dicarbonyl compound is easily deprotonated by an alkoxide and the anion is captured at carbon by addition of an electrophile. Such chemistry will lead to a mono-substituted acetone. One can repeat the chemistry and introduce a second electrophile and the result would eventually be a di-substituted acetone.
The next step is alkaline hydrolysis of the ethyl ester, a process called saponification. The solution is quenched with acid to allow for the isolation of the $\beta$-keto acid.

\[
\text{O} \quad \text{1. } \text{NaOH, H}_2\text{O} \quad \text{O} \\
\text{H} \quad \text{2. } \text{HCl, H}_2\text{O} \\
\text{R'}
\]

The last step in the overall transformation has its origin in the structure of the $\beta$-keto acid. $\beta$-Carbonyl carboxylic acids often adopt a conformation where the acid hydrogen can hydrogen bond in an intramolecular sense with the other carbonyl group. The hydrogen bonding interaction is idealized by the fact that the system forms a six-membered ring.

The hydrogen bonded arrangement allows the $\beta$-carbonyl carboxylic acids to undergo a thermally induced decarboxylation reaction. The arrows in the diagram below help to assign the re-positioning of the electrons. Only when the system form a 6-membered cyclic form is the decarboxylation facilitated, as indicated by the arrows.

The decarboxylation is effected by heating the substrate at 100 °C. The immediate product of the carboxylation is actually an enol but upon isolation, the material tautomerizes to the ketone.
The same chemistry takes place if the target molecule is a di-substituted acetone. The only difference is that after the introduction of the first alkyl group and before the saponification, the substrate is deprotonated again and quenched again with another electrophile. Once the introduction of two groups between the carbonyl is complete then the conversion to acid and subsequent decarboxylation can proceed.

Some examples:
Sometimes the acid and thermolysis treatments can be addressed simultaneously:

1. NaOH, H₂O
2. H₂O, H₂SO₄, heat

1. NaOEt, EtOH
2. CH₃CH₂CH₂CH₂Br

1. NaOH, H₂O
2. H₂O, H₂SO₄, heat

1. NaOEt
2. MeI
The same chemistry can be performed on a wide range of β-keto esters.

\[
\begin{align*}
\text{O} & \quad \text{H} & \quad \text{CO}_2\text{Et} \\
\text{1. NaOEt, EtOH} & \quad \text{2. excess } \text{Br(CH}_2\text{)}_3\text{Br} \\
\text{1. saponification} & \quad \text{2. } \text{H}^+ & \quad \text{3. heat} \\
\text{O} & \quad \text{H} & \quad \text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \\
60\% & \\
\end{align*}
\]

b) Malonic Ester Synthesis (SF/SFS 18.7)

The steps required in the malonic ester synthesis are analogous to those of the acetoacetic ester synthesis. One difference is the starting material, changing the methyl ketone to an ethyl ester creates a difference in the product: a substituted acetic acid derivative is obtained rather than a methyl ketone.

Starting material:

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{H} & \quad \text{R} & \quad \text{O} \\
\end{align*}
\]

Final product:

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{R} \\
\text{H} & \quad \text{O} & \quad \text{R} \\
\end{align*}
\]
Overall reaction of malonate synthesis

Diethyl malonate is the usual starting material. The anion of it is quenched with an electrophile. The product, also a malonate, is hydrolyzed to a diacid, which is then thermally decarboxylated. The result is the monosubstituted acetic acid. Disubstituted acetic acids are also available and can be obtained by following the same protocol as for disubstituted acetones. Diethyl malonate is slightly less acidic than acetyl acetone, with a pK$_a$ of 13.3, but the same chemistry can take place anyway.

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* 1,3-Propanedioic acid is commonly known as malonic acid and so diesters are known as malonates.
Clearly, the prominent structural feature in the acetoacetic esters and the malonates is the methylene group surrounded by two electron stabilizing functionalities. Although there is a detailed presentation here of the chemistry of the systems with two esters and with a ketone and an ester, other functional groups may also be present. Indeed, a number of groups can serve the role of electron withdrawing groups in the general structure $Z$-$\text{CH}_2$-$Z'$ (SF/SFS 18.8). Typical ones include of course esters and ketones, but one may also encounter other carbonyl containing compounds as well as nitriles, nitro compounds and sulfur or phosphorus containing groups. The final step of thermal decarboxylation is not always possible. Indeed, sometimes one wishes to maintain both of the groups in the molecule. Furthermore, there may be other methods for removing the particular functional groups once they have served their role.
c) Robinson Annulation (SF/SFS 19.7B)

Before introducing the chemistry and overall value associated with the Robinson Annulation, it is important to introduce a very important reaction known as the Michael Addition (SF/SF 19.7A).

The Michael addition was originally defined as the addition of a malonate to the β position of an α,β-unsaturated ketone, ester or nitrile. This strict definition has subsided and a Michael addition is now defined as the addition of any nucleophile to the β position of an alkene bearing one or more electron withdrawing groups.

Below are some examples using nucleophiles that have recently been introduced to you. Other carbon nucleophiles can be used in this chemistry as can amines, alcohols and sulfur nucleophiles.

### Examples

<table>
<thead>
<tr>
<th>Nucleophiles:</th>
<th>Michael Acceptors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-diketones, β-keto esters, dialkyl cuprates, enamines, β-keto nitriles, α-nitro ketones amines, alcohols, thiols</td>
<td>conjugated aldehydes, conjugated ketones, conjugated esters, conjugated amides, conjugated nitriles, conjugated nitro compounds</td>
</tr>
</tbody>
</table>

Note that the product of these reaction possesses two strong electron withdrawing groups and may well contain one or two carbonyl groups. The Robinson annulation begins with a Michael addition and is completed by an intramolecular aldol condensation.

In general, there are other materials that can participate in Michael additions (but not necessarily the full Robinson annulation).
Mechanism of Michael addition:

Using the example in the mechanism above, where R = CH₃, exposure of that material to base (usually from the original Michael addition reaction mixture), provides a means for the intramolecular aldol reaction. In this particular case, the anion of the methyl group may attack one of two equivalent ketone groups. In many cases there is a lone ketone and the reaction works perfectly well. From this point the regular aldol and its dehydration occur.
The thermodynamics of the reaction make the formation of 6 membered ring most favorable. Hence the Robinson annulation is ideal for the formation of cyclohexenones including those fused to other rings.

Overall, as stated, the Robinson annelation involves, first a Michael addition and then an aldol condensation.

Some examples:

\[
\text{Cyclohexene} + \text{Methyl vinyl ketone (MVK)} \rightarrow \text{Cyclohexenone}
\]
More, general examples of the annulation.

\[
\text{MeO} + \text{O} + \text{O} + \text{ethyl vinyl ketone} \quad \overset{\text{NaOMe, MeOH}}{\longrightarrow} \quad \overset{\text{Michael addition product}}{\downarrow} \quad \overset{\text{Robinson annulation product}}{\downarrow}
\]
d) Other Conjugate Additions (SF/SFS 19.7)

As you know, a number of nucleophiles add to the carbonyl carbon of aldehydes and ketones. The presence of a conjugated double bond creates an additional electrophilic site, and above it was shown that stabilized carbon anions will perform Michael additions on these substrates. Simple carbon nucleophiles such as Grignards will still attack at the C=O group. Organolithium reagents can attack at either electrophilic site and are not synthetically useful for this chemistry. Organocuprate reagents attack in a conjugate fashion and are easily generated using Grignard reagents in the presence of Cul.

A number of other nucleophiles are also useful in conjugate addition reactions. The list includes amines (RNH₂, RR'NH), alcohols (ROH), thiols (RSH) and HCN (prepared via KCN/H⁺). The addition of a nitrile is particularly synthetically useful since it can be converted to a carboxylic acid by hydrolysis.
A significant example of a Michael addition has recently been found in nature.

The Michael reaction is critical to the operation of a rather promising anticancer drug, calicheamicin. In the first step in its operation the trisulfide bond is broken (1). The nucleophilic sulfide then adds in Michael fashion to give enolate 2. This addition changes the shape of the molecule, bringing the ends of the two acetylenes closer together. A cyclization occurs to give a di-radical (3), and this diradical abstracts hydrogen from the cancer cell's DNA, killing it. Calicheamicin depends on the change of shape. Before the Michael reaction, the ends of the two acetylenes are too far apart to cyclize. They are freed to do so when the sulfur adds to the a,b unsaturated carbonyl.

R = series of sugar moieties

dead cancer cells + DNA

+ dead cancer cells

DNA
8. The Wittig Olefination of Aldehydes and Ketones

The most popular method for the conversion of aldehydes and ketone to alkenes is the Wittig Reaction. Generally speaking it involves the reaction of a carbonyl compound with a phosphorus ylide. The result is an alkene and a phosphine oxide.

\[
\text{R''}_3\text{P}^+\text{C}^+\text{R} \quad \xrightarrow{\text{ylide}} \quad \text{R''}_3\text{P}^-\text{O}^- + \text{C}^+\text{R} \\
\text{R''}_3\text{P} = \text{O}
\]

A specific procedure is usually required to prepare the Wittig reagent. First one treats the halogen in an alkyl halide with a phosphine, usually triphenylphosphine. The result is an alkyltriphenylphosphonium salt. The salt is then treated with a strong base, usually butyllithium in order to generate the ylide.

[Diagram showing the reaction]

Deprotonation of the phosphonium salt may also be achieved using alkoxides or NaH. Some ylides are stable. Most often the ylide is prepared in the flask and then is brought together with the carbonyl compound. Under these circumstances, the carbon anion portion of the ylide attacks the carbonyl group. The result is a phosphonium betaine, which readily closes to a cyclic isomer, an oxaphosphetane. To conclude the synthesis, the oxaphosphetane fragments to make the alkene and triphenylphosphine oxide. One of the driving forces of the reaction is the formation of the strong P=O bond.

* An ylide was originally defined as a compound that possesses a carbon anion directly beside a heteroatomic cation, where the formation of a multiple bond is usually not possible. The definition has eased in recent years and now encompasses any compound bearing adjacent positive and negative charges in situations where a formal multiple bond may or may not be possible. Other popular methods for olefination may involve silicon or sulfur atoms rather than a phosphorus atom.
The Wittig reaction can be carried out in the presence of ether, ester, halogen and other multiple bond functionalities. It often affords a mixture of geometric isomers about the double bond, although sometimes the reaction is selective.

Some examples:

\[
\begin{align*}
\text{O} & \quad + \quad \text{Ph}_3\text{P}^+\text{CH(\text{CH}_2\text{)}_3\text{CH}_3} & \rightarrow & \quad =\text{CH(\text{CH}_2\text{)}_3\text{CH}_3} & + & \quad \text{Ph}_3\text{P}=\text{O} \\
\text{PhCH}_2\text{H} & \quad + \quad \text{Ph}_3\text{P}^+\text{CHCH}_3 & \rightarrow & \quad =\text{CHCH}_3 & + & \quad \text{Ph}_3\text{P}=\text{O} \\
& & & \text{87:13} = \text{Z:E} \\
\text{PhCH}_2\text{H} & \quad + \quad \text{Ph}_3\text{P}^+\text{CH(\text{CH}_2\text{)}_3\text{CH}_3} & \rightarrow & \quad \text{PhCH}_2\text{CHCH}_3 & + & \quad \text{Ph}_3\text{P}=\text{O} \\
& & & \text{E isomer only}
\end{align*}
\]
\[
\text{PPh}_3 X^- + \text{PPh}_3 \rightarrow \text{MeOC(O)Me}
\]

\[
\text{HO}^-, \text{H}_2\text{O (saponification)}
\]

\[
\text{Vitamin A}_1
\]

\[
\text{H}^+ \text{PPh}_3 \rightleftharpoons \text{Bu}^- \text{Li}^+ + \text{CHO}
\]

\[
\text{H}^+ \text{PPh}_3 + \text{Ph}_3\text{P=CHCO} \rightarrow \text{H}^+ \text{PPh}_3 + \text{Bu}^- \text{Li}^+ + \text{CHO}
\]

\[
\text{H}^+ \text{PPh}_3 + \text{Ph}_3\text{P=CHCO} \rightarrow \text{H}^+ \text{PPh}_3 + \text{Bu}^- \text{Li}^+ + \text{CHO}
\]
9. Reductive Conversion of C=O to CH₂

A final important transformation of aldehydes and ketones is their conversion to methylene groups. The following two reagent systems are observed routinely with ketones and occasionally aldehydes. The Wolff-Kishner approach (SFS 15.9, 16.8C) utilizes $\text{H}_2\text{NNH}_2$/high boiling solvent/NaOH/heat while the Clemmensen reduction (SF/SFS 15.9) involves refluxing the ketone in hydrochloric acid with a zinc amalgam [Zn(Hg)]. Clearly the Wolff-Kishner protocol is best for substrates that are not base sensitive while the Clemmensen procedure is preferred when there are no acid sensitive functionalities in the ketone. Each of these procedures are part of the family of reductions known as deoxygenations.

$$\text{MeO}$$  $\text{H}_2\text{NNH}_2, \text{NaOH}$  $\text{HCl, Zn(Hg)}$  $\text{heat}$

Both methods are particularly effective in tandem with electrophilic aromatic acylation reactions.