NATIONAL OPEN UNIVERSITY OF NIGERIA

SCHOOL OF SCIENCE AND TECHNOLOGY

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Course Developer/Writer: Adeniran, Oluremi Isola

Department of Chemistry

Faculty of Science

University of Abuja, Abuja, Nigeria.

MODULE 1 Oxidation Reactions

UNIT 1 Oxidation reactions

Contents

1.0 Introduction

Oxidation as defined in ionic and free radical reactions, is a process by which an element undergoes a net loss of electrons. The concept as applied to organic covalent compounds, where elements share electrons rather than losing or gaining them is the same, but it's often simplified and narrowed down to make it easier to recognize this process. Therefore it must be kept in mind that, while the following definition in this unit is grossly simplified, it serves the goal of quickly identifying oxidation process in many organic reactions.

2.0 Objectives

At the end of this unit, students should be able to:
i. Define oxidation reaction
ii. Recognize oxidation in organic reactions
iii. List some oxidizing reagents

3.0 Main content

3.1 Definitions

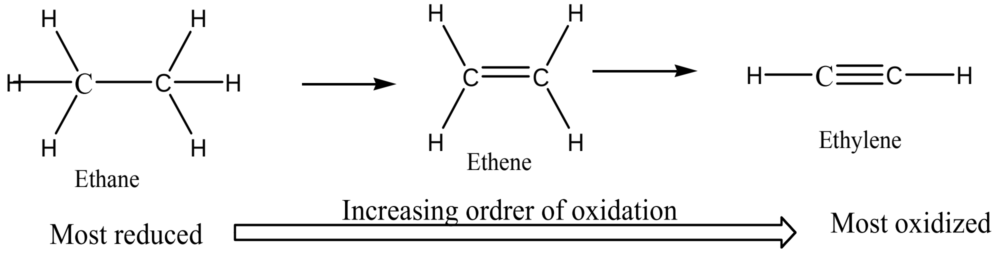
Oxidation in inorganic chemistry is considered as a loss of electrons. For inorganic ions, as when Fe^{2+} is oxidized to Fe^{3+}, this concept works well. Since most organic compounds are uncharged, electron gain or loss is not apparent. Organic chemists tend to think of oxidation as the result of adding an oxidizing agent such as O_2, F_2, Cl_2, and Br_2.

In reference to organic molecules therefore, ***oxidation*** is broadly defined as ***either the removal of hydrogen or the replacement of a hydrogen atom attached to a carbon atom with another more electronegative element, most frequently oxygen.***

This definition is illustrated by the following examples: (i) successive dehydrogenation of ethane and (ii) oxidative series of transformation of methane.

(i) Successive (oxidative) dehydrogenation of ethane

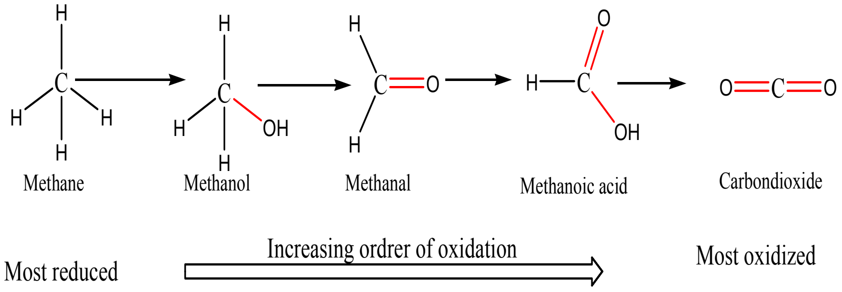
When in an organic compound a carbon atom loses a bond to hydrogen and forms a new bond to a heteroatom (or to another carbon), the compound is said to have been dehydrogenated, or oxidized. The loss of **C-H** bonds to form new **C-C** bonds in successive dehydrogenation (removal of hydrogen) of ethane to ethylene is oxidation.



Note: The greater the bond multiplicity the more oxidized the molecule i.e. single bond < double bond < triple bond. In this series of two-carbon system each of the two carbon atoms loses a C-H bond and gains a C-C bond in a stepwise manner, and thus is oxidized.

(ii) Oxidative transformation of methane.

Redox reactions in organic chemistry mostly deal with a small set of very identifiable functional group transformations. Familiarity with the idea of 'oxidation states' as applied to organic functional groups is therefore essential. Familiar functional groups can be arranged in order of increasing or decreasing oxidation state by comparing the relative number of bonds to hydrogen atoms. Consider a series of single carbon compounds as an example. The degree of oxidation increases as you move methane, with four carbon-hydrogen (C-H) bonds, is highly reduced. Following in the sequence is methanol (three carbon-hydrogen bonds, one carbon-oxygen bond), followed by methanal, methanoic acid, and finally carbon dioxide at the highly oxidized end of the group.



Note: The more the **C-O** bonds or the less the less the **C-H** bonds, the more oxidized the molecule.

You can now understand by considering the illustrations above that oxidation of a Carbon atom in an organic compound involves one or more of the following changes: (i) an increase in the multiple bond order of the Carbon atom (ii) addition of Oxygen to a Carbon atom (iii) replacement of an Hydrogen on a Carbon atom by a more electronegative element especially Oxygen.

In section 3.3, the pattern adopted to illustrate oxidation in organic chemistry is conversion of one functional group to another by oxidation. This choice is with an intention of conveying a general sense of the application of oxidation in organic synthesis. This includes transformations of alcohols to carbonyls, alkenes to epoxides or diols, and alkenes to carbonyl compounds (oxidative cleavage).

SAQ I-1: *Give a precise definition of oxidation as applied to organic chemistry.*

3.2 Oxidizing Reagents

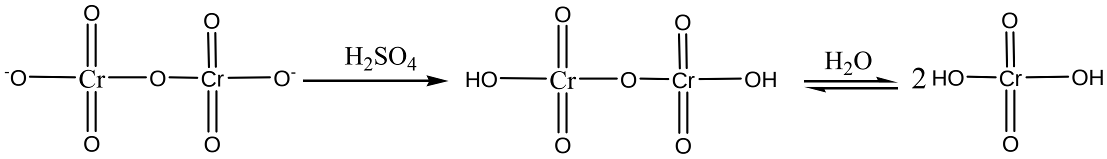
Several examples of oxidizing agents (reagents) exist. This section presents some of these reagents, a simple method of preparation and some applications of each in functional group transformation.

Chromic Acid (H_2CrO_4)

(a) Preparation

This reagent is prepared by reacting sodium or potassium dichromate with sulphuric acid as shown in below:

$$\underset{\text{Dichromate ion}}{Cr_2O_7^{2-}} \xrightarrow{H_2SO_4} H_2Cr_2O_7 \overset{H_2O}{\rightleftharpoons} \underset{\text{Chromic acid}}{2\,H_2CrO_4}$$

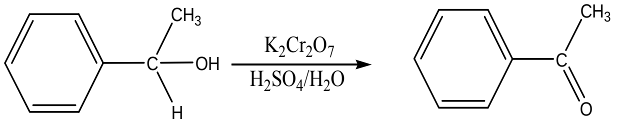


Dichromate ion

Chromic acid

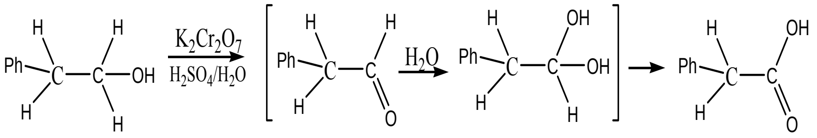
(b) Application in functional group transformation:

(i) Oxidation of secondary alcohols to ketones:



2° Alcohol Ketone

(ii) Oxidation of primary alcohols to carboxylic acids. The alcohol is first oxidized to an aldehyde. Under the reaction conditions, a molecule of water adds to the carbonyl group to form a hydrate which is subsequently oxidized to the carboxylic acid.



Pyridinium Chlorochromate (PCC) – $C_5H_5NH[CrO_3Cl]$

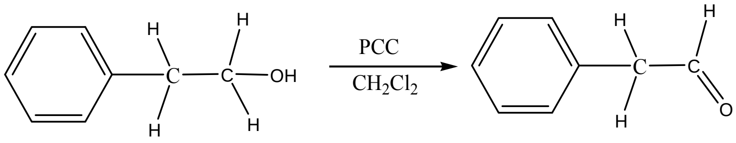
(a) Preparation

The original preparation, involves the reaction of pyridine with chromium trioxide and concentrated hydrochloric acid:

$$C_5H_5N + HCl + CrO_3 \rightarrow [C_5H_5NH][CrO_3Cl]$$

(b) Application in functional group transformation:

With pyridinium chlorochromate the oxidation of primary alcohols can be stopped at aldehydes. In order to prevent aldehydes from further oxidation, it is necessary to maintain anhydrous condition (avoid the addition of water to the carbonyl group). PCC was developed as a non-aqueous alternative to chromic acid. PCC therefore offered the advantage of the selective oxidation of alcohols to aldehydes. Using this reagent, 2-phenylethanol may be oxidized to phenyl acetaldehyde without subsequent oxidation to phenylacetic acid:



2-phenylethanol phenyl acetaldehyde

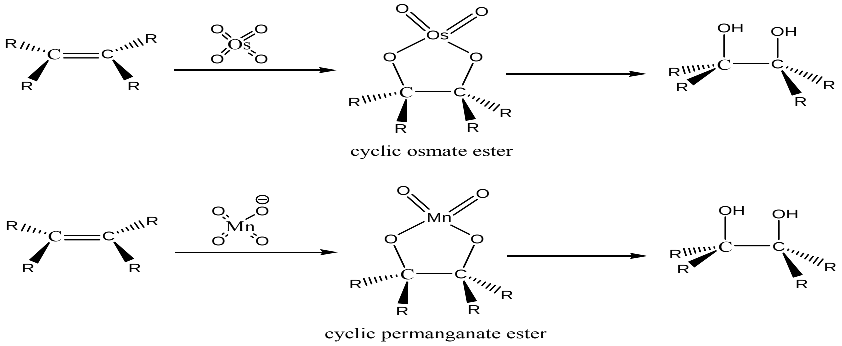
Potassium permanganate ($KMnO_4$) and Osmium tetroxide (OsO_4)

(a) Preparation

Dissolve 3.3 g of reagent grade potassium permanganate ($KMnO_4$) in 1 L of deionized water and heat on a steam bath for two hrs. Cover and allow the solution to stand for 24 hrs. Filter through a fine porosity sintered glass crucible. Store the solution in a glass-stoppered, amber-colored bottle. Avoid exposure to direct sunlight; cover the neck of the bottle with a small beaker as a protection against dust. If manganese dioxide precipitates on standing, refilter before use.

(b) Application in functional group transformation:

Osmium tetroxide (OsO4), or potassium permanganate (KMnO4) in aqueous base, reacts with alkenes to yield 1,2-diols. These reagents are used to convert alkenes into the corresponding 1,2-diols (glycols) by a stereospecific process called ***syn hydroxylation or syn addition*** of two OH groups because they involve the formation of intermediate cyclic inorganic "esters" that decompose to the diol in subsequent steps as shown in the following illustrations. The reaction is thought to involve the formation of an intermediate cyclic permanganate ester which is readily hydrolysed under the reaction conditions to yield the 1,2-diol. A cyclic osmate ester is generated with OsO_4.



Osmium tetraoxide gives excellent yields of 1,2-diols, but it is toxic (it causes blindness) and expensive. Potassium permanganate is inexpensive and safer to use, but it gives much lower yields of diols. This is partly because it can cleave the C-C bond of the diol as we describe in a subsequent section.

Since aqueous $KMnO_4$ is purple, this reaction is often used as a qualitative test for the presence of an alkene: a dilute solution of permanganate is added to a sample of the unknown compound; if the color is discharged, the test is taken as positive. The formation of a grey-black precipitate of manganese dioxide confirms the analysis.

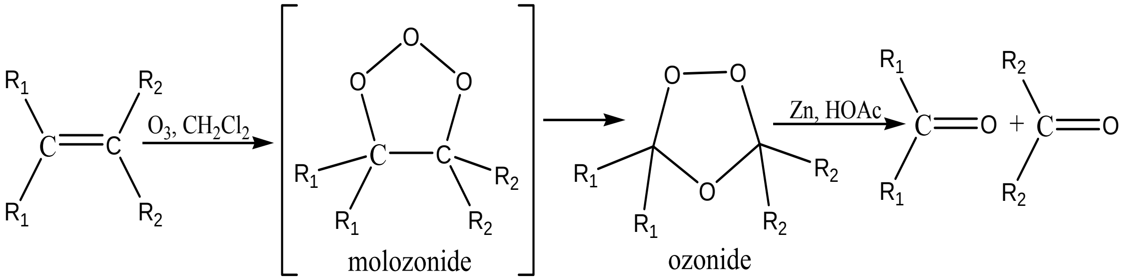
Ozone (O_3)

(a) Preparation

Ozone, O_3, is an allotrope of oxygen. It is a highly reactive molecule that is generated by passing a stream of oxygen over a high voltage electric discharge. It is possible to smell ozone in the atmosphere after a lightning storm if the lightning has struck nearby.

(b) Application in functional group transformation:

The reaction between ozone (O_3) and an alkene involves direct addition of O_3 across the double bond to give an unstable intermediate that decomposes to an ***ozonide*** intermediate in a process called ***ozonolysis***, an alkene is treated with ozone to produce intermediates called ***ozonides*** which are reduced directly, generally with zinc metal in acetic acid, to yield aldehydes or ketones, depending on the substituents attached to the double bond of the initial alkene.



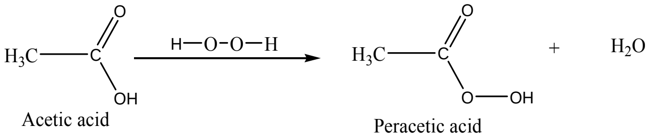
Note that an aromatic ring is resistant to ozone. The value of ozonolysis lies in the structural insight it affords a chemist who is trying to determine the identity of an unknown compound.

Peroxy-acids or Peracids (RCO_3H)

A number of peracids having the general formula, RCO3H have been used for the oxidation of organic compounds. Some of the common peracids are: peracetic acid (CH_3CO_3H), perbenzoic acid ($PhCO_3H$), trifluoroacetic acid (CF_3CO_3H) and *m*-chloroperbenzoic acid (*m*-$ClC_6H_4CO_3H$).

(a) Preparation

Peroxycarboxylic acids (or peracids) are usually prepared *in situ*by the reactions of carboxylic acids with hydrogen peroxide (H_2O_2) as shown for peracetic acid.



Acetic acid

Peracetic acid

Most peroxy-acids are rather unstable and generally have to be prepared freshly before use. Performic and peracetic acids, for example, are often prepared *in situ*, and not isolated, by action of hydrogen peroxide on the carboxylic acid. Epoxidation with peroxy-acids are highly stereoselective and take place by cis addition to the double bond of the alkene.

(b) Application in functional group transformation

(i) Oxidation of alkenes

Oxidation of alkenes with peroxy-acids gives rise to epoxides (oxiranes) or to trans-1,2-diols, depending on the experimental condition. A number of peroxy-acids have been used in the past, including perbenzoic, performic and peracetic acid, but these have now been largely superseded, for the formation of epoxides at any rate, by *m*-chloroperbenzoic acid; it is commercially available and is an excellent reagent for the epoxidation of alkenes. It is more stable than the peroxy-acids and has even been used at an elevated temperature (90°C) to effect the epoxidation of unreactive alkenes.

(ii) Oxidation of ketones

On oxidation with peroxy-acids, ketones are converted into esters or lactones. This reaction was discovered in 1899 by Baeyer and Villiger. Better yields are obtained with organic peroxy-acids such as perbenzoic acid, peracetic acid and trifluoroperacetic acid; although in practice nowadays most reactions are effected with *m*-chloroperbenzoic acid. This is more stable than the other acids, which usually have to be prepared immediately before use, and is commercially available. The reaction occurs under mild conditions and has been widely used both in degradative work and in synthesis. It is applicable to open chain and cyclic ketones and to aromatic ketones, and has been used to prepare a variety of steroidal and terpenoid lactones, as well as medium and large ring lactones which are otherwise difficult to obtain. It also provides a route to alcohols from ketones, through hydrolysis of esters formed, and of hydroxyl-acids from cyclic ketones by way of the lactones; lithium aluminium hydride reduction of the lactones gives diols with a defined disposition of the two hydroxyl groups.

SAQ I-2: *What does PCC stand for? Show the structure.*

4.0 Conclusion

This unit treated the definition of oxidation reactions, explained oxidation in organic reactions, and discussed the composition and applications of some oxidizing reagents.

5.0 Summary

Oxidation of a Carbon atom in an organic compound involves one or more of the following changes: (i) an increase in the multiple bond order of the carbon (ii) addition of oxygen to a carbon (iii) replacement of an hydrogen on a carbon by oxygen. These criteria can be combined in the statement that "oxidation of organic molecules involves an increase in the multiple bond order, a gain in oxygen and/or loss of hydrogen".

6.0 Tutor-Marked Assignment

1. What product is formed when cyclopentene is reacted with osmium tetroxide followed by treatment with basic hydrogen peroxide?
2. What functional groups result from the reaction of 2-methylcyclopentene with (a) ozone followed by reaction with dimethyl sulphide and (b) KMnO4 in acid with heating?
3. Which of the following reactions is oxidation: (a) formation of 1,2-diiodoethane from ethene (ethylene), (b) formation of ethane from ethene, and (c) formation of ethanol from ethene?

7.0 References/further reading

(1) Daniel R. Bloch. *Organic Chemistry Demystified*. McGraw-Hill, New York **2006**.

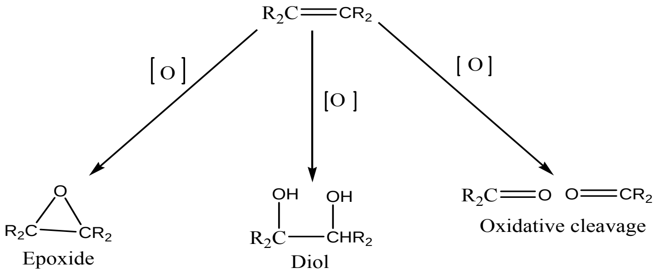
(2) Richard S. Monson. *Advanced Organic Synthesis Methods and Techniques*. United Kingdom Edition, published by ACADEMIC PRESS, INC. (LONDON) LTD. Berkeley Square House, London WlX 6BA, **1971**.

Unit 2 Transformation of Alkenes to epoxides, diols and carbonyl compounds

Contents

1.0 Introduction

There are a variety of oxidation reactions in which C=C bonds add oxygen or are cleaved to oxygenated products. When oxygen adds to C=C bonds, the products are epoxides or 1,2-diols. Some of the most important reactions of alkenes involve oxidation. When we speak of oxidation, we usually mean reactions that form carbon-oxygen bonds. (Halogens are oxidizing agents, and the addition of a halogen molecule across a double bond is formally an oxidation as well.) Oxidations are particularly important because many common functional groups contain oxygen, and alkene oxidations are some of the best methods for introducing oxygen into organic molecules. We will consider methods for epoxidation, hydroxylation, and oxidative cleavage of alkene double bonds.



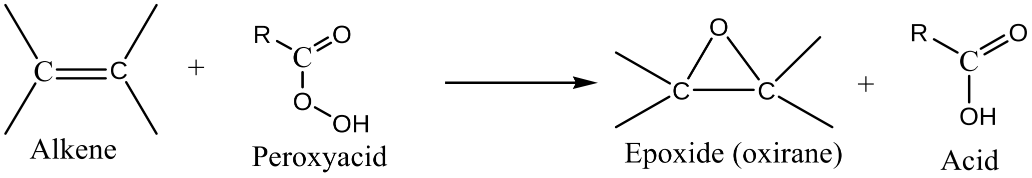
2.0 Objectives

At the end of this unit, students should be able to:
i. Discuss conversion of alkenes to epoxides
ii. Recognize oxidation in organic reactions
iii. List some oxidizing reagents
iv. Describe how functional group transformation can be achieved by oxidation

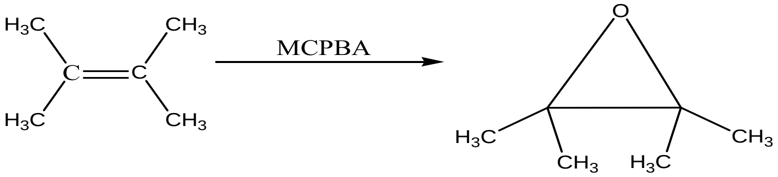
3.0 Main content

3.1 Conversion of alkenes to epoxides (epoxidation*)*

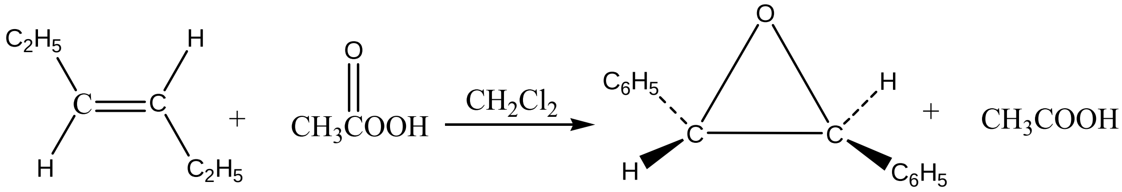
An epoxide is three-membered cyclic ether, also called an oxirane or oxacyclopropane. Epoxides are valuable synthetic intermediates used for converting alkenes to a variety of other functional groups. An alkene is converted to an epoxide by a peroxyacid, a carboxylic acid that has an extra oxygen atom in a -O-O- (peroxy) linkage.



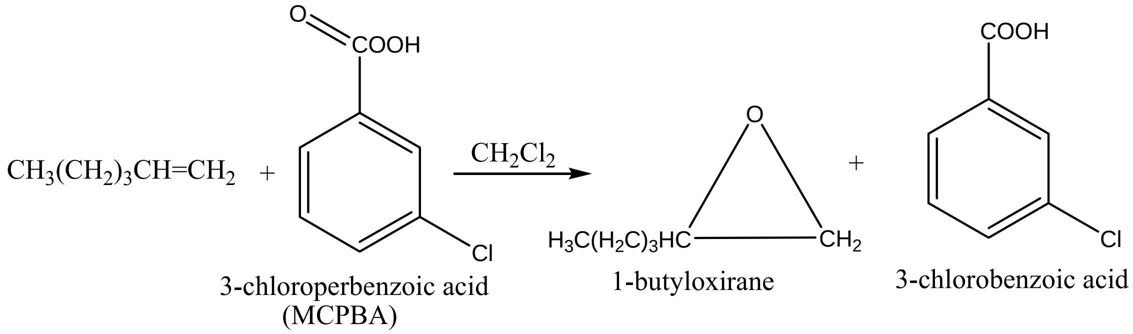
The epoxidation of an alkene is clearly an oxidation, since an oxygen atom is added. Peroxyacids are highly selective oxidizing agents. A peroxyacid epoxidizes an alkene by a concerted electrophilic reaction where several bonds are broken and several others are formed at the same time. Starting with the alkene and the peroxyacid, a one-step reaction gives the epoxide and the acid directly, without any intermediates. The reaction mechanism is a single step (concerted) transfer of an oxygen atom to the C=C. For example, using peroxycarboxylic acids such as *m*-chloroperbenzoic acid (MCPBA), perbenzoic acid, or peracetic acid, 2,3-dimethyl-2-butene is converted to the corresponding epoxide.



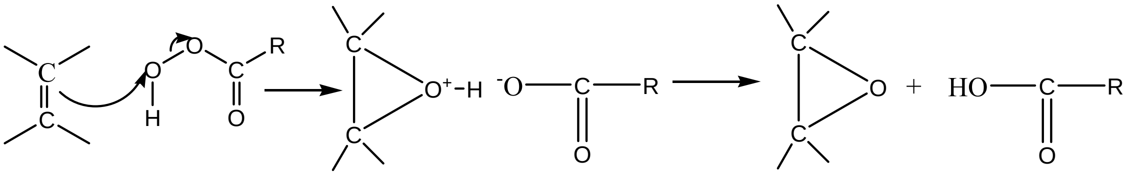
Trans-3-hexene can also be oxidized by peracetic acid as in the following equation.



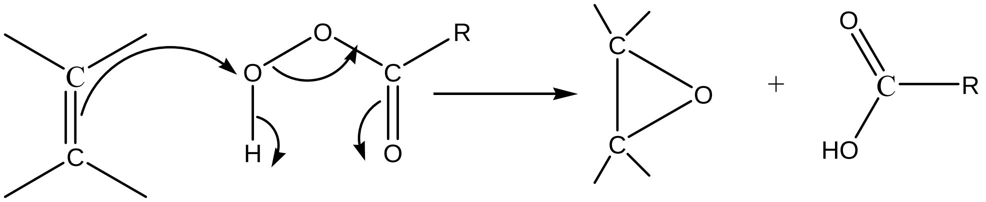
Like hydrogen peroxide, H_2O_2, peroxycarboxylic acids are oxidizing agents and are often used for that purpose. Peroxycarboxylic acids are generally unstable and must be stored in the cold or, preferably, be prepared as needed. An important exception is 3-chloroperoxybenzoic acid, an exceptionally stable crystalline solid now available commercially. This reagent provides a simple and convenient one-step route to epoxides.



The mechanism of the reaction can be represented as a displacement reaction on an electrophilic oxygen by a nucleophilic alkene.

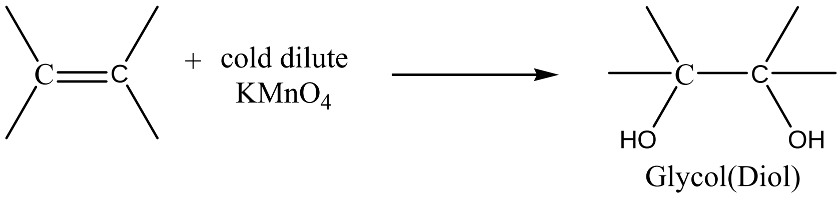


The reaction may actually take place in a single step

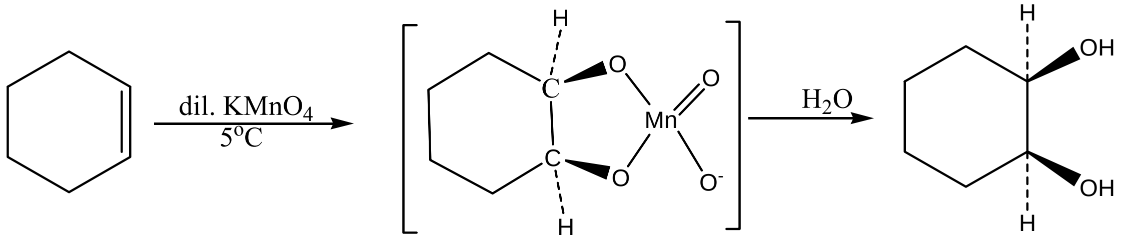


3.2 Conversion of alkenes to syn-1,2-diols (hydroxylation)

Alkenes are oxidized readily by potassium permanganate, $KMnO_4$, but the products depend on the reaction conditions. Cold dilute potassium permanganate reacts with double bonds to give vicinal diols, which are commonly called glycols.

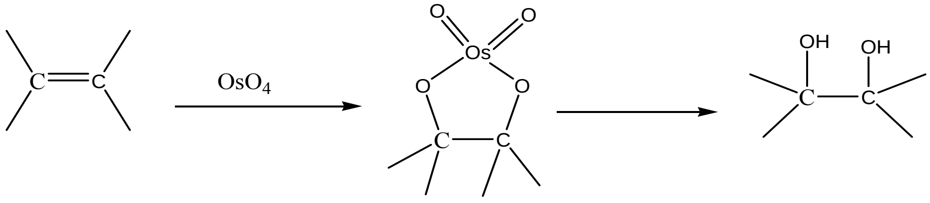


Reaction conditions need to be carefully controlled. Yields are variable and usually low. The reaction occurs with *syn* addition and is thought to involve an intermediate cyclic manganate ester that is rapidly hydrolyzed.



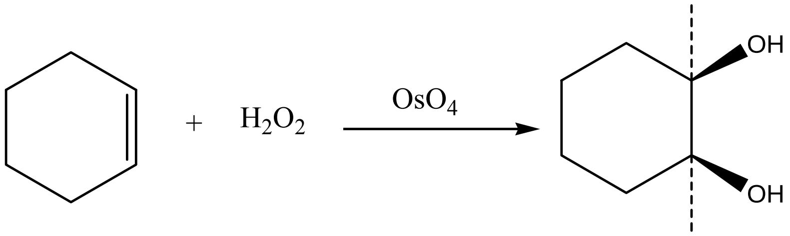
Cis-1,2-cyclohexane diol

The same overall reaction can be accomplished with osmium tetroxide, which forms isolable cyclic esters with alkenes.

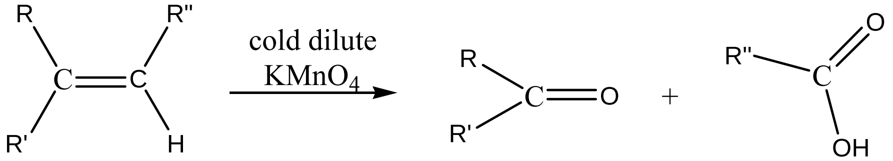


cyclic osmate ester

The cis-diol can be isolated from the osmate ester with H_2S, but a more convenient (and less expensive) procedure involves the combination of hydrogen peroxide with a catalytic amount of osmium tetroxide. The osmate ester is formed but is converted by the peroxide to the cis-diol. Osmium tetroxide is constantly regenerated, so that only a small amount need be used.



When more concentrated solutions of potassium permanganate are used in the oxidation of alkenes, the initially formed glycol is oxidized further. The product is a mixture of ketones or carboxylic acids, depending on the extent of substitution of the double bond.



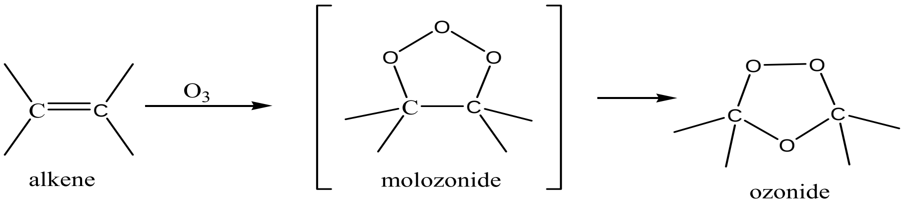
$$HCR{=}CH_2 \xrightarrow{KMnO_4} RCOOH + CO_2$$

This is not a common reaction in organic synthesis because the yields are usually low. Oxidative cleavage of the double bond can generally be accomplished in better yield by reaction with ozone.

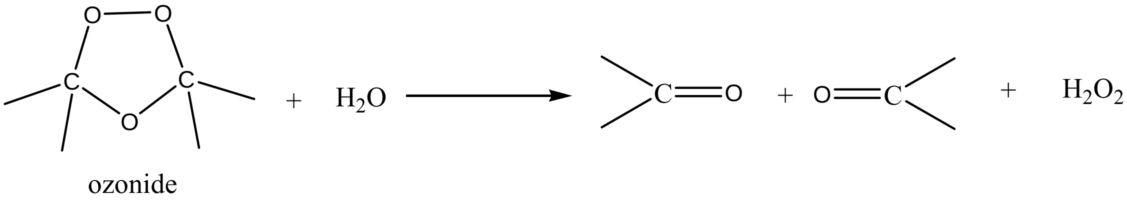
SAQ I-3: *What product is formed when cyclopentene is reacted with osmium tetroxide followed by treatment with basic hydrogen peroxide?*

3.3 Ozonolysis of alkenes (oxidative cleavage)

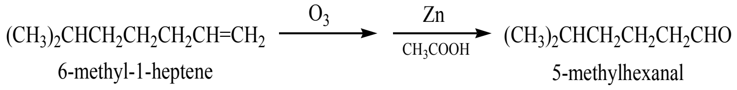
Reactions of alkenes with ozone are normally carried out by passing ozone-containing air through a solution of the alkene in an inert solvent at low temperatures (usually-80^{o}C). Reaction is rapid and completion of reaction is determined by testing the effluent gas with potassium iodide. Unreacted ozone, reacts to give iodine. Suitable solvents for ozonisations include methylene chloride, alcohol and ethylacetate. The first formed addition product, the molonozonide, rearranges rapidly, even at low temperatures, to the ozonide structure:



In some cases polymeric structures are obtained. Some ozonides, especially the polymeric structures, decompose with explosive violence on heating; hence, the ozonides are generally not isolated but are decomposed directly to desired products. Hydrolysis with water occurs readily to give carbonyl compounds and hydrogen peroxide.



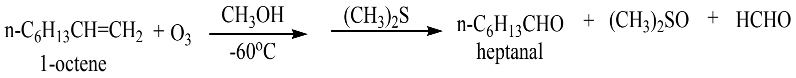
Aldehydes are oxidized by hydrogen peroxide to carboxylic acids. Hence, reductions are often used in decomposing the ozonides. Such conditions include zinc dust and acetic acid, catalytic hydrogenation, and dimethyl sulphide.



$$(CH_3)_2CHCH_2CH_2CH_2CH{=}CH_2 \xrightarrow{O_3} \xrightarrow[CH_3COOH]{Zn} (CH_3)_2CHCH_2CH_2CH_2CHO$$

6-methyl-1-heptene

5-methylhexanal

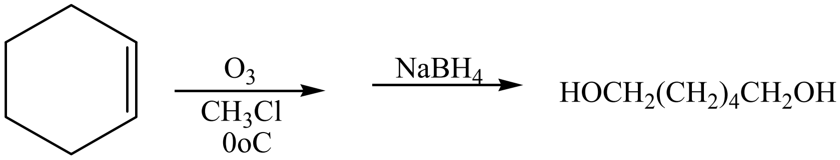


$$n\text{-}C_6H_{13}CH{=}CH_2 + O_3 \xrightarrow[-60^{o}C]{CH_3OH} \xrightarrow{(CH_3)_2S} n\text{-}C_6H_{13}CHO + (CH_3)_2SO + HCHO$$

1-octene

heptanal

Treatment of the ozonide with sodium borohydride gives the corresponding alcohols.



$$\xrightarrow[CH_3Cl,\ 0oC]{O_3} \xrightarrow{NaBH_4} HOCH_2(CH_2)_4CH_2OH$$

cyclohexene

1,6-hexanediol

SAQ I-4: *(1) Explain the following terms: (i) hydroxylation (ii) oxidative*

(iii) cleavage (iv) epoxidation of alkenes.

(2) Ozone reacts with tetrasubstituted alkenes to give --------

(a) aldehydes (b) ketones (c) aldehydes and ketones

(d) acids. Choose the correct option.

4.0 Conclusion

This unit discussed methods for epoxidation, hydroxylation, and oxidative cleavage of alkene double bonds and how this functional group can be transformed by oxidation.

5.0 Summary

- Peroxyacids are good oxidizing agents, donating oxygen atoms to other molecules. Peracids break the π bond in an alkene forming a three-membered ring, called an epoxide or an oxirane. The oxygen atom bonds to an alkene in a *syn* manner. Epoxide compounds are very reactive cyclic ethers.
- Two common methods for converting alkenes into alcohols containing two alcohol (OH) groups on adjacent carbon atoms are: (i) oxidation with potassium permanganate ($KMnO_4$) under mild, basic conditions to give molecules called dialcohols, 1,2-diols, vicinal diols, or glycols and (ii) osmium tetroxide (OsO_4) in an inert solvent. Both reactions for making diols involve a cyclic intermediate. The cyclic structure necessarily attaches to both oxygen atoms on the same side of the alkene molecule. This is called syn addition giving a *cis*-1,2-diol.

- Ozone reacts with an alkene to initially form a cyclic ozonide. In a subsequent step the ozonide is reduced with dimethyl sulfide $(CH_3)_2S$ to a carbonyl-containing (C=O) compound. Ozone is a very reactive molecule (an oxidizing agent) and is able to break the σ and π bonds in alkenes and alkynes, but it does not break isolated C-C single σ bonds.

6.0 Tutor-Marked Assignment

1. What product is formed when cyclopentene is reacted with osmium tetroxide followed by treatment with basic hydrogen peroxide?
2. What functional groups result from the reaction of 2-methylcyclopentene with (a) ozone followed by reaction with dimethyl sulphide and (b) KMnO4 in acid with heating?
3. Which of the following reactions is oxidation: (a) formation of 1,2-diiodoethane from ethene (ethylene), (b) formation of ethane from ethene, and (c) formation of ethanol from ethene?

7.0 References/further reading

(1) Daniel R. Bloch. *Organic Chemistry Demystified*. McGraw-Hill, New York **2006**.

(2) Richard S. Monson. *Advanced Organic Synthesis Methods and Techniques*. United Kingdom Edition, published by ACADEMIC PRESS, INC. (LONDON) LTD. Berkeley Square House, London WlX 6BA, **1971**.

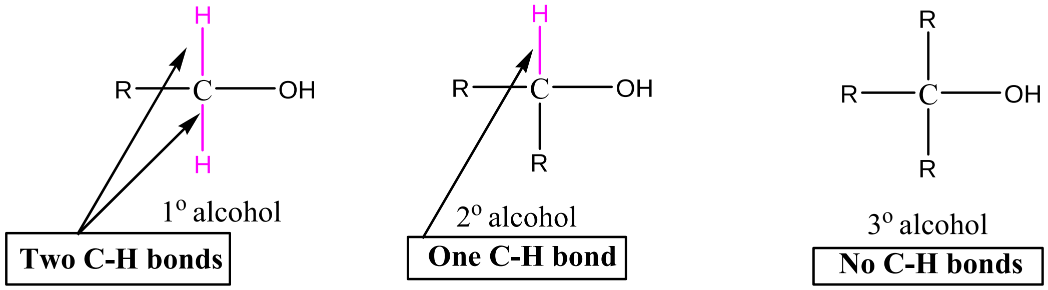
Unit 3 Transformation of alcohols to carbonyls

Contents

1.0 Introduction

Primary and secondary alcohols are easily oxidized by a variety of reagents, including chromium reagents, permanganate, nitric acid, and even household bleach (NaOCl, sodium hypochlorite). The choice of reagent depends on the amount and value of the alcohol. We use cheap oxidants for large-scale oxidations of simple, inexpensive alcohols. We use the most effective and selective reagents, regardless of cost, for delicate and valuable alcohols. In this unit, we study only the oxidants that have the widest range of uses and the best selectivity.

Alcohols are oxidized to a variety of carbonyl compounds. Primary alcohols are oxidized to either aldehydes or carboxylic acids by replacing one or two C-H bonds by C-O bonds. Secondary alcohols are oxidized to ketones by replacing the only C-H bond in the molecule by a C-O bond. Tertiary alcohols do not have H atom on the carbon atom bearing the OH functional group hence they are not easily oxidized.



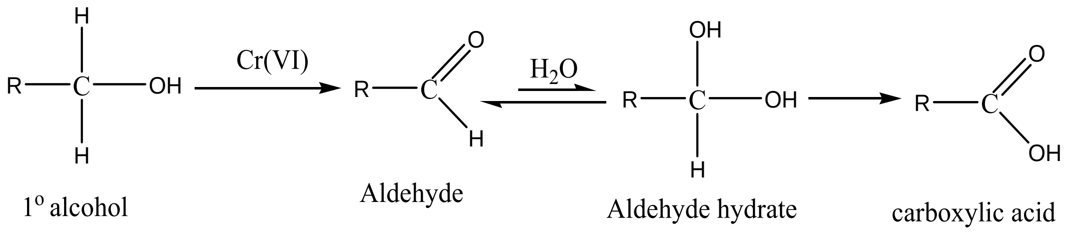
2.0 Objectives

At the end of this unit, students should be able to:
i. Describe stages involved in oxidation of primary alcohols
ii. Give products of oxidation of secondary alcohols
iii. Explain why tertiary alcohols are not oxidized

3.0 Main content

3.1 Oxidation of primary alcohols

Primary alcohols can be oxidized to either aldehydes or further to carboxylic acids depending on the reaction conditions. In aqueous media, the carboxylic acid is usually the major product. The direct oxidation of primary alcohols to carboxylic acids normally proceeds through the corresponding aldehyde, which is transformed via an aldehyde hydrate by reacting with water before it can be further oxidized to the carboxylic acid.

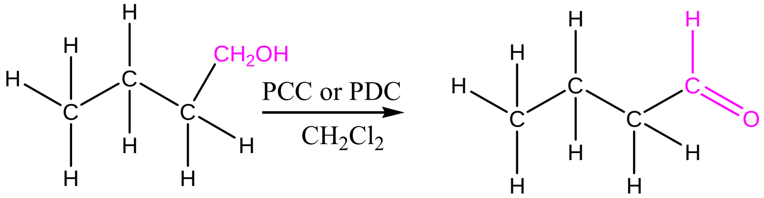


Obtaining the aldehyde is often difficult; since most oxidizing agents are strong enough to oxidize primary alcohols also oxidize aldehydes. Chromic acid generally oxidizes a primary alcohol all the way to the carboxylic acid. Aldehydes formed from oxidation of primary alcohols using Cr(VI) reagents are usually further oxidized to carboxylic acids; this 'over-oxidation' is a practical problem. We can prevent this by distilling the intermediate aldehyde from the reaction mixture as it forms before it is oxidized further. This method is only successful for aldehydes of sufficiently low molecular weight. In this way, 1- butanol gives butanal in 50% yield.

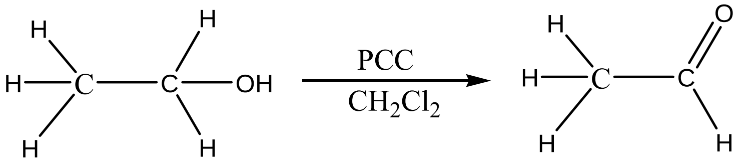
$$\underset{\text{1-Butanol}}{CH_3CH_2CH_2CH_2OH} + H_2Cr_2O_7 \longrightarrow \underset{\text{Butanal}}{CH_3CH_2CH_2CHO}$$

Only aldehydes that boil significantly below 100°C can be conveniently prepared in this manner. Since this effectively limits the method to the production of few aldehydes, it is not an important synthetic method. Other special oxidants have developed that helped to circumvent this problem. By using modified Cr(VI) reagents that is described in the paragraph following.

A common reagent that selectively oxidizes a primary alcohol to an aldehyde (and no further) is pyridinium chlorochromate, (PCC) or pyridinium dichromate (PDC). These reagents, (PCC) or (PDC), which are used in dichloromethane, allow the oxidation to be stopped at the intermediate aldehyde.



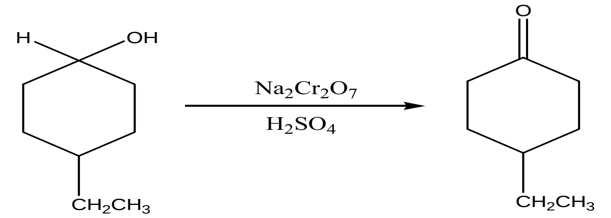
If you used ethanol as a typical primary alcohol, you would produce the aldehyde ethanal, (CH_3CHO).



Ethanol Ethanal

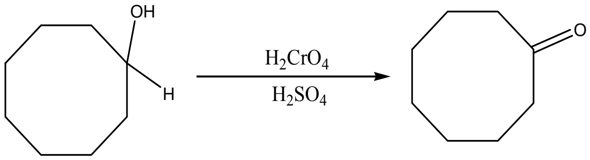
3.2 Oxidation of secondary alcohols

Since ketones are more stable to general oxidation than aldehydes, chromic acid oxidations are more important for secondary alcohols. In one common procedure a 20% excess of sodium dichromate is added to an aqueous mixture of the alcohol and a stoichiometric amount of acid.



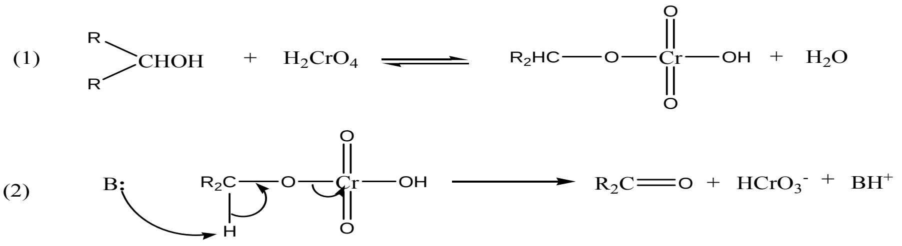
4 - Ethylcyclohexanol 4 - Ethylcyclohexanonone

An especially convenient oxidizing agent is Jones reagent, a solution of chromic acid in dilute sulphuric acid. The secondary alcohol in acetone solution is "titrated" with the reagent with stiring at 15-20°C. Oxidation is rapid and efficient. The green chromic salts separate from the reaction mixture as a heavy sludge; the supernatant liquid consists mainly of an acetone solution of the product ketone.

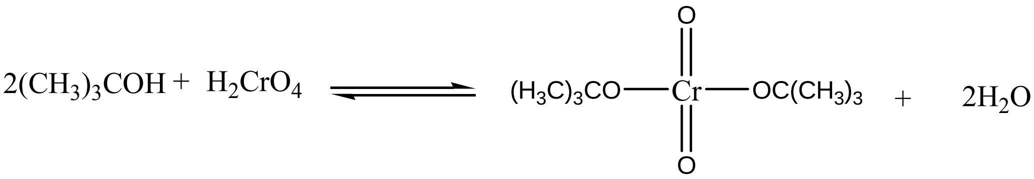


Cyclooctanol Cyclooctanone

Chromic (VI) oxidations are known to proceed by way of a chromate ester of the alcohol. If the alcohol has one or more hydrogen attached to the carbinol position, a base-catalyzed elimination occurs, yielding the aldehyde or ketone and a chromium (iv) species. The overall effect of these two consecutive reactions is oxidation of the alcoholand reduction of the chromium.



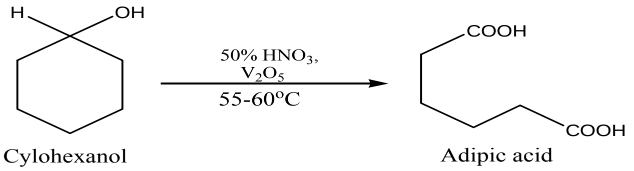
Under conditions such as these, tertiary alcohols do not generally react, although under proper conditions the chromate ester can be isolated.



$$2(CH_3)_3COH + H_2CrO_4 \rightleftharpoons (H_3C)_3CO-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{Cr}}-OC(CH_3)_3 + 2H_2O$$

Since there is no carbinol proton to eliminate in the case of a tertiary alcohol, such esters are stable. If the chromate ester is treated with excess water, simple hydrolysis occurs with regeneration of the tertiary alcohol and chromic acid.

More vigorous oxidizing conditions result in cleavage of C-C bonds. Aqueous nitric acid is such a reagent. Oxidation all the way to carboxylic acid is the normal result. Such oxidations appear to proceed by way of the intermediate ketone, which undergoes further oxidation.



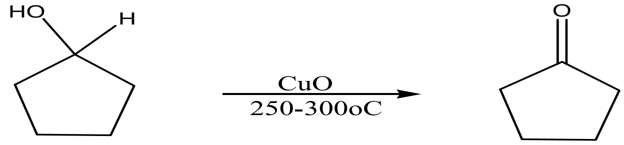
Nitric acid may also be used as an oxidant for primary alcohols; again the product is a carboxylic acid.

$$ClCH_2CH_2CH_2OH \xrightarrow[25\text{-}30^oC]{71\%\ HNO_3} ClCH_2CH_2COOH$$

Instead of oxidation, direct dehydrogenation can be accomplished with various catalysts and conditions. The reaction is of industrial interest but is not much used in the laboratory because of the specialized equipment and conditions required. Catalysts include copper metal, copper chromite, or copper-chromium oxides prepared in special ways. Examples of dehydrogenation are:

$$CH_3CH_2CH_2CH_2OH \xrightarrow[300\text{-}345^oC]{\text{Cu-Cr oxide on celite}} CH_3CH_2CH_2CHO$$

n-Butyl alcohol Butyraldehyde



Cyclopentanol Cyclopentanone

3.3 Oxidation of tertiary alcohols

Tertiary alcohols are not oxidised by acidified sodium or potassium dichromate (VI) solution. There is no reaction whatsoever. If you look at what is happening with primary and secondary alcohols, you will see that the oxidising agent is removing the hydrogen from the -OH group, and hydrogen from the carbon atom attached to the -OH. Tertiary alcohols don't have a hydrogen atom attached to that carbon. You need to be able to remove those two particular hydrogen atoms in order to set up the carbon-oxygen double bond.

4.0 Conclusion

The unit described oxidation of different classes of alcohols with a discussion of the possible functional group transformations of each class.

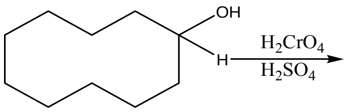
5.0 Summary

- *Primary alcohols* are oxidized to carboxylic acids in acidic solutions of dichromate ($Cr_2O_7^{2-}$) or basic solutions of permanganate (MnO_4^-). The 1° alcohol is first oxidized to an aldehyde, which is rapidly oxidized to a carboxylic acid.
- *Secondary alcohols* are oxidized to ketones in acidic solutions of dichromate or basic solutions of permanganate.
- *Tertiary alcohols* do not react with dichromate or permanganate. Oxidation of 3° alcohols would require cleavage of a carbon–carbon bond. Carbon–carbon bond cleavage does not occur under conditions used to oxidize 1° and 2° alcohols.
- Primary alcohols can be oxidized to aldehydes (and not to acids) by reaction with *pyridinium chlorochromate* (*PCC*) in anhydrous solvents.

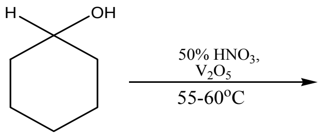
6.0 Tutor-Marked Assignment

1. What product is formed when:
   (a) CH_3CH_2OH reacts with acidic dichromate ($Cr_2O_7^{2-}$)?
   (b) CH_3CH_2OH reacts with pyridinium chlorochromate (PCC)?
2. Give the product of each of the following reactions:

(a)



(b)



7.0 References/further reading

(1) Daniel R. Bloch. *Organic Chemistry Demystified*. McGraw-Hill, New York **2006**.

(2) Richard S. Monson. *Advanced Organic Synthesis Methods and Techniques*. United Kingdom Edition, published by ACADEMIC PRESS, INC. (LONDON) LTD. Berkeley Square House, London WlX 6BA, **1971**.

Unit 4 Transformation of arenes (Benzene and other Aromatic Hydrocarbons)

Contents

1.0 Introduction

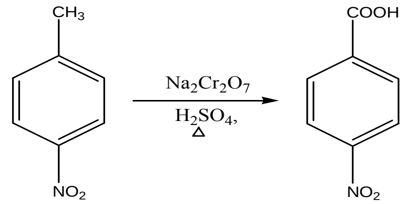
The benzene ring is rather stable to oxidizing agents, and under appropriate conditions side-chain alkyl groups are oxidized instead.

2.0 Objectives

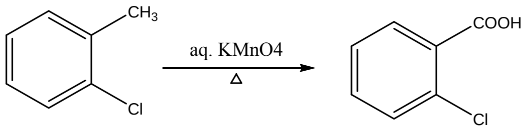
At the end of this unit, students should be able to:
i. Discuss oxidation of the alkylbenzenes
ii. Mention some industrially important reactions of the arenes

3.0 Main content

Sodium dichromate in aqueous sulphuric acid or acetic acid is a common laboratory procedure, but aqueous nitric acid and potassium permanganate have also been used.

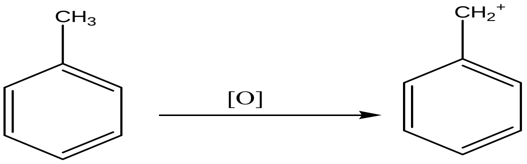


p-Nitrotoluene p-Nitrobenzoic acid

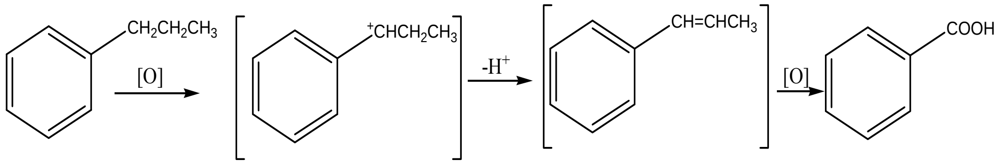


o-Chlorotoluene o-Chlorobenzoic acid

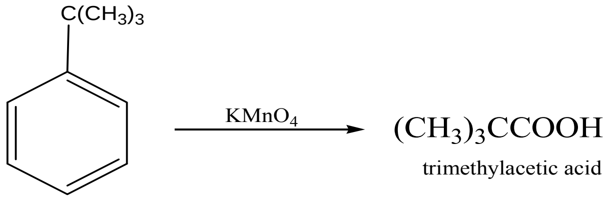
The detailed reaction mechanisms by which these oxidations occur are complex. They involve numerous intermediates including chromate and permanganate esters, but they also appear to involve an intermediate benzyl cation.



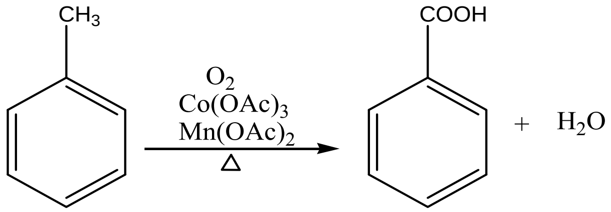
As we have seen, this carbocation is relatively stable because of conjugation of the positive charge with the benzene ring. Reaction with water yields benzyl alcohol, which can oxidize further. Larger side chains can also be oxidized completely so long as there is one benzylic hydrogen for the initial oxidation. Cleavage reactions of larger side chains probably involve the formation of an intermediate alkene.



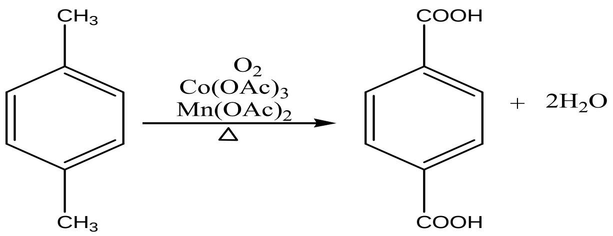
The more extensive oxidation required in these reactions often results in lower yields so that they are not as useful for laboratory preparation as they are for structural identification. When there is no benzylic hydrogen, the side chain resists oxidation. For example, vigorous conditions are required for the oxidation of *t*-butylbenzene, and the product is trimethylacetic acid, the product of oxidation of the benzene ring.



Oxidation of the side-chain methyl groups is an important industrial route to aromatic carboxylic acids. The most important oxidizing agent for such reactions is air.



An important industrial reaction of this general type is the oxidation of *p*-xylene to the dicarboxylic acid.



4.0 Conclusion

In this unit you have learnt that the C-H bond transformation is a capable and sustainable requirement of organic transformations. It also has some fundamental features in organic molecules for a convenient and proficient benzylic C-H Oxidation of alkyl and cycloalkyl arenes.

5.0 Summary

Benzene rings do not react with strong oxidants. However, the benzene ring can activate the benzylic position of alkylbenzene toward oxidation with strong oxidants such as $KMnO_4$ and $Na_2Cr_2O_7$ to give benzoic acids.

6.0 Tutor-Marked Assignment

1. Show with the aid of equation the oxidation of *p*-xylene to the dicarboxylic acid.
2. What product is formed when *t*-butylbenzene is oxidized under vigorous conditions? Give reasons for the observed product.
3. Give the structure of benzylic cation.

7.0 References/further reading

(1) Daniel R. Bloch. *Organic Chemistry Demystified*. McGraw-Hill, New York **2006**.

(2) Richard S. Monson. *Advanced Organic Synthesis Methods and Techniques*. United Kingdom Edition, published by ACADEMIC PRESS, INC. (LONDON) LTD. Berkeley Square House, London WlX 6BA, **1971**.

MODULE 2 Reduction Reactions

UNIT 1 Catalytic hydrogenation

Contents

1.0 Introduction

The reverse of each oxidation reaction in the previous sections is a reduction reaction. The characteristics of reduction reactions are opposite to those of oxidation reactions. As a result, organic molecules *lose* oxygen and/or *gain* hydrogen in reduction reactions.

2.0 Objectives

At the end of this unit, students should be able to
i. Define reduction reaction
ii. Recognize reduction in organic reactions
iii. Explain types of reduction reactions.

3.0 Main Content

3.1 Definitions

Reduction is any chemical reaction involving gaining of electrons. It can still be defined in the sense of addition of hydrogen to an unsaturated group such as carbon-carbon double bond, a carbonyl group or an aromatic nucleus, or addition of hydrogen with concomitant fission of a bond between two atoms, as in the reduction of a disulphide to a thiol or of an alkyl halide to a hydrocarbon.

Reductions are generally effected either chemically or by catalytic hydrogenation, which is by the addition of molecular hydrogen to compounds under the influence of catalyst. Each method has its advantages. In many reductions either method may be used equally well. Complete reduction of an unsaturated compound can generally be achieved without undue difficulty, but the aim is often selective reduction of one group in a molecule in the presence of other unsaturated groups. Both catalytic and chemical methods of reduction offer considerable scope in this direction, and the method of choice in a particular case will often depend on the selectivity required and on the stereochemistry of the desired product.

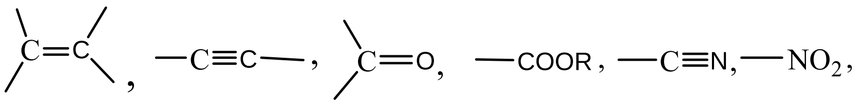
3.2 Types of Reduction Reactions

3.2.1 Catalytic hydrogenation

Of many methods available for reduction of organic compounds catalytic hydrogenation is one of the convenient. Reaction is easily effected simply by stirring or shaking the substrate with the catalyst in a suitable solvent, or without a solvent if the substance being reduced is a liquid, in an atmosphere of hydrogen in an apparatus which is arranged so that the uptake of hydrogen can be measured. At the end of the reaction the catalyst is filtered off and the product is recovered from the filtrate, often in a high state of purity. The method is easily adapted for work on a micro scale, or on a large, even industrial, scale. In many cases reaction proceeds smoothly at or near room temperature and at atmospheric or slightly elevated pressure. In other cases high temperature (100-200°C) and pressure (100-300 atmosphere) are necessary, requiring special high pressure equipment.

Catalytic hydrogenation may result simply in the addition of hydrogen to one or more unsaturated groups in the molecule or it may be accompanied by fission of a bond between atoms. The latter process is known as hydrogenolysis.

Most of the common unsaturated groups in organic chemistry, such as



and aromatic and heterocyclic nuclei can be reduced catalytically under appropriate conditions, although they are not all reduced with equal ease.

Many different catalysts have been used for catalytic hydrogenations; they are mainly finely divided metals, metallic oxides or sulphides. The most commonly used in the laboratory are the platinum metals (platinum, palladium and to a lesser extent rhodium and ruthenium), nickel and copper chromate. The catalysts are not specific and with the exception of copper chromite may be used for a variety of different reductions.

For hydrogenation at high pressure the most common catalysts are Raney nickel and copper chromite. Raney nickel is a porous, finely divided nickel obtained by treating a powdered nickel-aluminium alloy with sodium hydroxide. It is generally used at high temperatures and pressures, but with the more active catalysts many reactions can be effected at atmospheric pressure and normal temperature. Nearly all unsaturated groups can be reduced with Raney nickel but it is most frequently used for reduction of aromatic rings and hydrogenolysis of sulphur compounds.

Many hydrogenations proceed satisfactorily under a wide range of conditions, but where a selective reduction is wanted, conditions may be more critical. The choice for catalyst for hydrogenation is governed by the activity and selectivity required. Selectivity is a property of the metal, but it also depends to some extent on the activity of the catalyst and on the reaction conditions. In general, the more active the catalyst the less discriminating it is in its action, and for greatest selectivity reactions should be run with the least active catalyst and under the mildest possible conditions consistent with a reasonable rate of reaction.

3.2.2 Reduction by Hydride-Transfer Reagents

A number of metal hydrides have been employed as reducing agents in organic chemistry, but the most commonly used are lithium aluminium hydride and sodium borohydride, both of which are commercially available. Another useful reagent is borane.

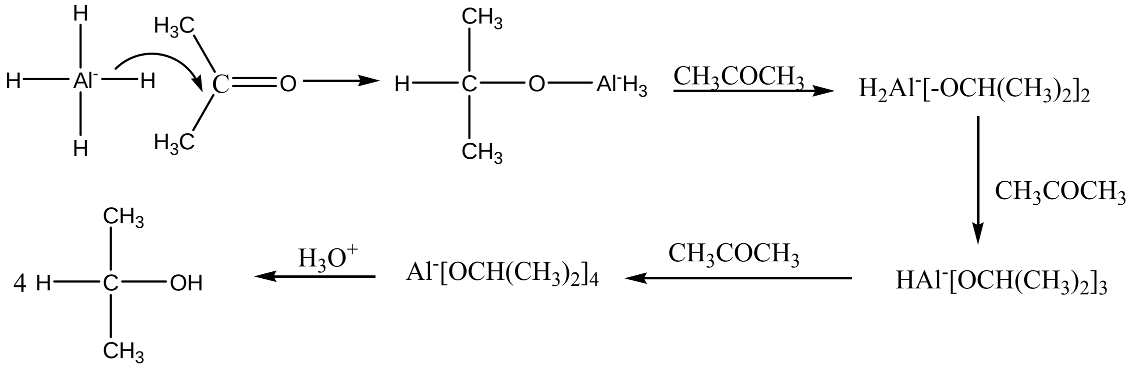
The anions of the two complex hydrides can be regarded as derived from lithium or sodium hydride and either aluminium hydride or borane.

$$\mathrm{LiH} \quad + \quad \mathrm{AlH_3} \longrightarrow \mathrm{Li^+AlH_4^-}$$

$$\mathrm{NaH} \quad + \quad \mathrm{BH_3} \longrightarrow \mathrm{Na^+BH_4^-}$$

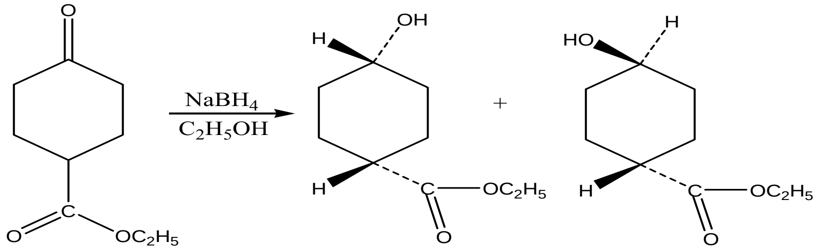
The anions are nucleophilic reagents and as such they normally attack polarised multiple bonds such as C=O or C≡N by transfer of hydride ion to the more positive atom. They do not usually reduce isolated carbon-carbon double or triple bonds.

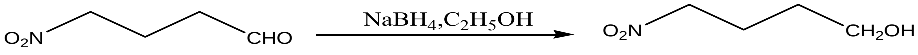
With both reagents all four hydrogen atoms may be used for reduction being transferred in a stepwise manner as illustrated below for the reduction of a ketone with lithium aluminium hydride.



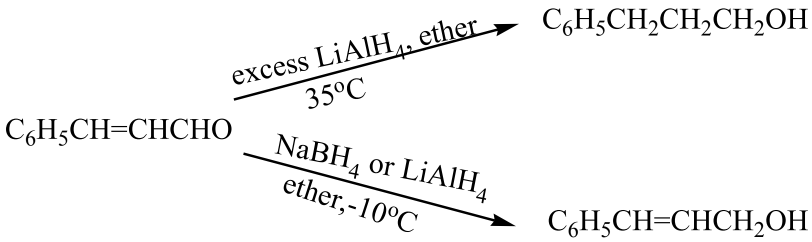
There is evidence that in borohydride reductions a more complex path may be followed. For reduction with lithium aluminium hydride (but not with sodium borohydride) each successive transfer of hydride ion takes place more slowly than the one before, and this has been exploited for the preparation of modified reagents which are less reactive and more selective than lithium aluminium hydride itself by replacement of two or three of the hydrogen atoms of the anion by alkoxy groups.

Lithium aluminium hydride is a more powerful reducing agent than sodium boriohydride and reduces most of the commonly encountered organic functional groups. It reacts readily with water and other compounds which contain active hydrogen atoms and must be used under anhydrous conditions in a non-hydroxylic solvent; ether and tetrahydrofuran are commonly employed. Sodium borohydride reacts slowly with water and most alcohols at room temperature and reductions with this reagent are often effected in ethanol solution. Being less reactive than lithium aluminium hydride, it is more discriminating in its action. At room temperature in ethanol it readily reduces aldehydes and ketones but it does not generally attack esters or amides and it is normally possible to reduce aldehydes and ketones selectively with sodium borohydride in the presence of a variety of other functional groups. Some typical examples are shown below:





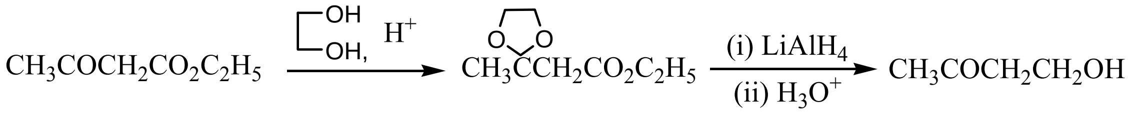
Lithium borohydride is also sometimes used. It is a more powerful reducing agent than sodium borohydride and selective in its action but it has the advantage that it is soluble in ether and tetrahdrofuran. An exception to the general rule that carbon-carbon double bonds are not attacked by hydride reducing agents is found in the reduction of β-aryl-αβ-unsaturated carbonyl compounds with lithium aluminium hydride, where the carbon-carbon double bond is often reduced as well as the carbonyl group. Even in these cases, however, selective reduction of the carbonyl group can generally be achieved by working at low temperatures or by using sodium borohydride or aluminium hydride as reducing agent.



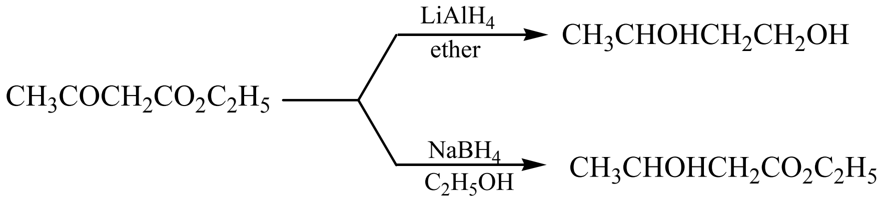
$$C_6H_5CH{=}CHCHO \xrightarrow[35^{o}C]{\text{excess LiAlH}_4\text{, ether}} C_6H_5CH_2CH_2CH_2OH$$

$$C_6H_5CH{=}CHCHO \xrightarrow[\text{ether,-}10^{o}C]{\text{NaBH}_4\text{ or LiAlH}_4} C_6H_5CH{=}CHCH_2OH$$

Lithium aluminium hydride and sodium borohydride have probably found their most widespread use in the reduction of carbonyl compounds. Aldehydes, ketones, carboxylic acids, esters and lactones can all be reduced smoothly to the corresponding alcohols under mild conditions. Reaction with lithium aluminium hydride is the method of choice for the reduction of carboxylic acids to primary alcohols. Substituted amides are converted into amines or aldehydes, depending on the experimental conditions. To effect selective reduction of the ester, the keto group of ethylacetoacetate for example, must be protected as its acetal, and the ester reduced with lithium aluminium hydride. Mild acid hydrolysis then regenerates the ketone to give the β-keto-alcohol.



Note that on reduction of ethyl acetoacetate with lithium aluminium hydride both the ester and ketone functional groups are reduced to afford 1,3-butandiol, however, only the keto group is reduced with the milder sodium borohydride to give ethyl-3-hydroxybutanoate.



3.2.3 *Reduction by dissolving metals*

Chemical methods of reduction are of two main types: those which take place by addition of electrons to the unsaturated compound followed or accompanied by transfer of protons; and those which take place by addition of hydride ion followed in a separate step by protonation.

Reductions which follow the first path are generally effected by a metal, the source of the electrons, and a proton donor which may be water, an alcohol or an acid. They can result either in the addition of hydrogen atoms to a multiple bond or in fission of a single bond between atoms, usually, in practice, a single bond between carbon and a heteroatom. In these reactions an electron is transferred from the metal surface (or from the metal in solution) to the organic molecule being reduced, giving, in the case of addition to a multiple bond, an anion radical, which in many cases is immediately protonated. The resulting radical subsequently takes up another electron from the metal to form an anion which may be protonated immediately or remain as the anion until work-up. In the absence of a proton source dimerization or polymerization of the anion-radical may take place. In some cases a second electron may be added to the anion-radical to form a di-anion, or two anions in the case of fission reactions.

The metals commonly employed in these reductions include the alkali metals, calcium, zinc, magnesium, tin and iron. The alkali metals are often used in solution in liquid ammonia or as suspensions in inert solvents such as ether or toluene, frequently with addition of an alcohol or water to act as a proton source. Many reductions are also effected by direct addition of sodium or, particularly, zinc, tin, or iron, to a solution of the compound being reduced in a hydroxylic solvent such as ethanol, acetic acid or an aqueous mineral acid.

4.0 Conclusion

The unit described different methods of achieving reduction in organic chemistry. These include catalytic hydrogenation, reduction by hydride-transfer reagents and reduction by dissolving metals.

5.0 Summary

In reference to organic molecules, reduction is a process by which a carbon atom gains bonds to less electronegative elements, most commonly hydrogen. It is obvious from this unit that reductive processes are important in organic synthesis.

6.0 Tutor-Marked Assignment

(1) Give five examples of metals that can be used in organic reduction reactions

(2) Show the product obtained when $CH_3COCH_2COOC_2H_5$ is reacted separately with (i) $NaBH_4$ and (ii) $LiAlH_4$.

(3) Mention two catalysts used commonly in hydrogenation of unsaturated organic compounds

7.0 References/further reading

(1) Daniel R. Bloch. *Organic Chemistry Demystified*. McGraw-Hill, New York **2006**.

(2) Richard S. Monson. *Advanced Organic Synthesis Methods and Techniques*. United Kingdom Edition, published by ACADEMIC PRESS, INC. (LONDON) LTD. Berkeley Square House, London WlX 6BA, **1971**.

Unit 2 Reduction of functional groups

Contents

1.0 Introduction

The reverse of each oxidation reaction in the previous sections is a reduction reaction. The characteristics of reduction reactions are opposite to those of oxidation reactions. As a result, organic molecules *lose* oxygen and/or *gain* hydrogen in reduction reactions.

2.0 Objectives

At the end of this unit, students should be able to:

i Describe conversion of functional groups by reduction
ii. Give appropriate reagents for specific functional group transformation
iii Mention some named reduction reactions
iv Explain the mechanism of these named reactions

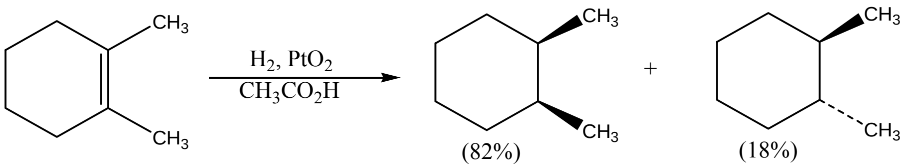
3.0 Main Content

3.1 Reduction of Functional groups

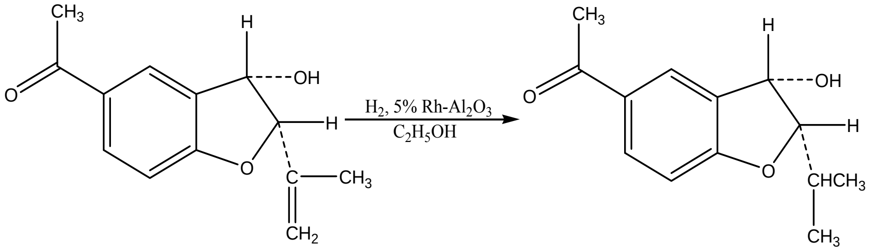
3.1.1 Reduction of Alkenes

Hydrogenation of carbon-carbon double bonds takes place easily and in most cases can be effected under mild conditions. Only a few highly hindered alkenes are resistant to hydrogenation and even these can generally be reduced under more vigorous conditions. Platinum and palladium are the most frequently used catalysts. Both are very active and the preference is determined by the nature of other functional groups in the molecule and by the degree of selectivity required; platinum usually brings about a more exhaustive reduction Raney nickel may also be in some cases.

Thus cinnamyl alcohol is reduced to the dihydro compound with Raney nickel in ethanol at 20^oC, and 1,2-dimethyl-cyclohexane with hydrogen and platinum oxide in acetic acid is converted mainly into cis-1,2-dimethylcyclohexane.



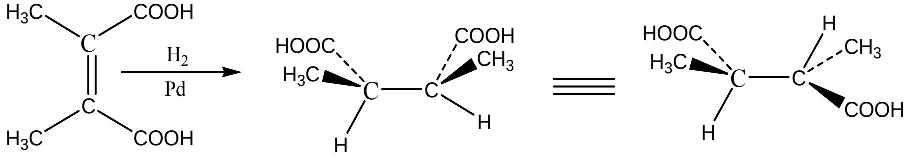
Rhodium and ruthenium catalysts have not been much used in hydrogenation of alkenes, but they sometimes show useful selective properties. Rhodium is particularly useful for hydrogenation of alkenes when concomitant hydrogenolysis of an oxygen function is to be avoided. Thus, the plant toxin, toxol, on hydrogenation over rhodium-alumina in ethanol was smoothly converted into the dihydro compound;



With platinum and palladium catalysts, on the other hand, extensive hydrogenolysis took place and a mixture of products was formed.

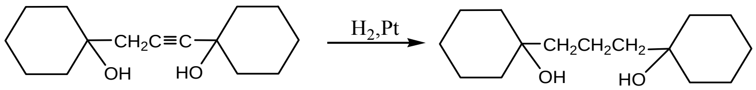
The ease of reduction of an alkene decreases with the degree of substitution of the double bond, and this sometimes allows selective reduction of one double bond in a molecule which contains several. Selective reduction of carbon-carbon double bonds in compounds containing other unsaturated groups can usually be accomplished, except in the presence of triple bonds, aromatic nitro groups and acyl halides

The detailed reaction mechanism is complex and involves various types of metal-carbon bonds. Since the two hydrogens are added to the double bond from the surface of the metal, they are normally both added to the same face of the double bond. This type of addition is referred to as ***syn***, just as the addition of two “pieces” of a reagent to opposite faces of a double bond is called ***anti***, addition. In the case of catalytic hydrogenation the alkene molecule is adsorbed to the catalyst surface with one face of the double bond coordinated to the surface; the two hydrogens are both added to this face.

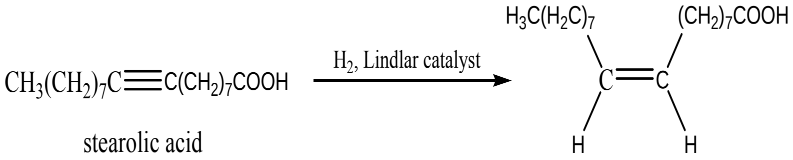


3.3.2 *Reduction of Alkynes*

Catalytic hydrogenation of alkynes takes place in a stepwise manner, and like alkene and alkane can be isolated. Complete reduction of the alkynes to the saturated compound is easily accomplished over platinum, palladium, or Raney nickel. A complication which sometimes arises, particularly with platinum catalysts, is the hydrogenolysis of propargylic (saturated C-atom adjacent to a triple bond) hydroxyl groups.



More useful from a synthetic point of view is the partial hydrogenation of alkynes to Z-alkenes. This reaction can be effected in high yield with a palladium-calcium carbonate catalyst which has been partially deactivated by addition of lead acetate (Lindlar's catalyst) or quinoline. It is aided by the fact that the more electrophilic acetylenic compounds are adsorbed on the electron-rich catalyst surface more strongly than the corresponding alkenes. An important feature of these reductions is their high stereo selectivity. In most cases the product consists very largely of the thermodynamically less stable Z-alkene, and partial catalytic hydrogenation of alkynes provides one of the most convenient routes to Z-1,2-disubstituted alkenes. Thus stearolic acid on reduction over Lindlar's catalyst in ethyl acetate solution affords a product containing 95% of oleic acid.



stearolic acid

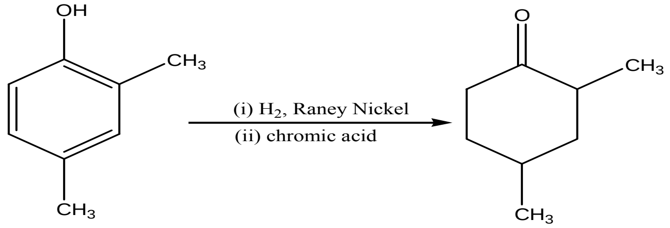
oleic acid

Partial reduction of alkynes with Lindlar's catalyst has been invaluable in the synthesis of carotenoids and many other natural products with Z-distributed double bonds.

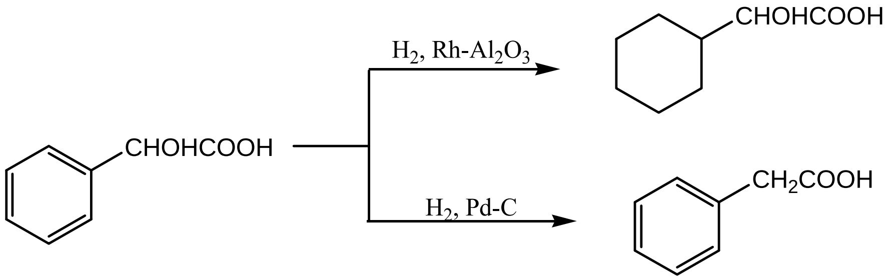
3.3.3 *Reduction of Aromatic Compounds*

Reduction of aromatic rings by catalytic hydrogenation is more difficult than those of most other functional groups, and selective reduction is not easy. The commonest catalysts are platinum and rhodium, which can be used at ordinary temperatures, and Raney nickel or ruthenium which require high temperatures and pressures.

Benzene itself can be reduced to cyclohexane with platinum oxide in acetic acid solution. Derivatives of benzene such as benzoic acid, phenol or aniline are reduced more easily. For large scale work the most convenient method is hydrogenation over Raney nickel at 150-200°C and 100-200atm. hydrogenation of phenols, followed by oxidation of the resulting cyclohexanol is a convenient method for the large-scale preparation of substituted cyclohexanones.



Reduction of benzene derivatives carrying oxygen or nitrogen functions in benzylic positions is complicated by the easy hydrogenolysis of such groups, particularly over palladium catalysts. Preferential reduction of the benzene ring in these compounds is best achieved with ruthenium, or preferably with rhodium, catalysts which can be used under mild conditions. Thus mandelic acid is readily converted into hexahydromandelic acid over rhodium-alumina in methanol solution, whereas, with palladium, hydrogenolysis to phenylacetic acid is the main reaction.



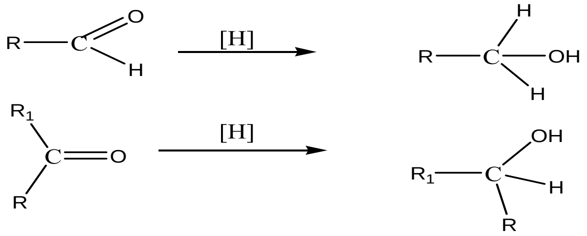
With polycyclic aromatic compounds it is often possible, by varying the conditions, to obtain either partially or completely reduced products. Thus naphthalene can be converted into tetrahydro or decahydro compound over Raney nickel depending on the temperature. With anthracene and phenanthrene the 9,10-dihydro compounds are obtained by hydrogenation over copper chromite, although in general, aromatic rings are not reduced with this catalyst. To obtain more fully hydrogenated compounds more active catalysts must be used.

3.3.4 Reduction of Aldehydes and ketones

Reduction of ketones or aldehydes transforms their C=O groups to alcohol groups (ROH), or to CH_2 groups.

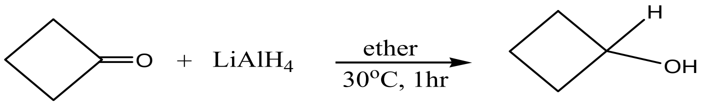
3.3.4.1 Converversion of C=O group to OH

Aldehydes and ketones are easily reduced to the corresponding primary and secondary alcohols, respectively.



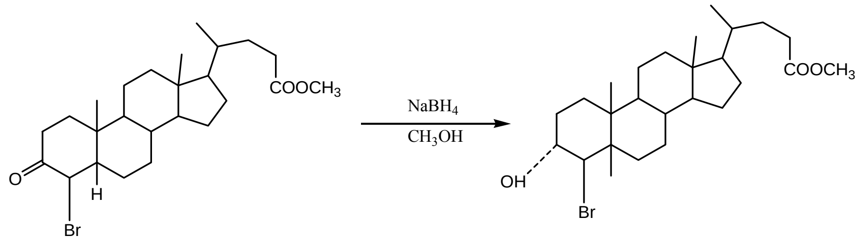
Many different reducing agents may be used. For laboratory applications the complex metal hydrides are particularly effective. Lithium aluminium hydride ($LiAlH_4$) is a powerful reducing agent that has been used for this purpose.

Reactions with LiAlH4 are normally carried out by adding an ether solution of the aldehyde or ketone to an ether solution of $LiAlH_4$. Reduction is rapid even at -78°C (dry ice temperature). At the end of the reaction the alcohol is present as a mixture of lithium and aluminium salts and must be liberated by hydrolysis.



The reagent also reduces many other oxygen- and nitrogen- containing functional groups. The chief disadvantage of the reagent is its cost, which renders it useful only for fairly small-scale laboratory applications, and the hazards involved in handling it.

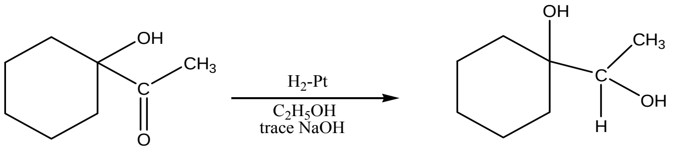
Sodium borohydride, $NaBH_4$, offers certain advantages. This hydride is much less reactive than $LiAlH_4$ and is consequently more selective. Of the functional groups that are reduced by $LiAlH_4$, only aldehydes and ketones are reduced at a reasonable rate by $NaBH_4$. The reagent is moderately stable in aqueous and in alcoholic solution, especially at basic pH. The example below illustrates the selectivity that may be achieved with the reagent.

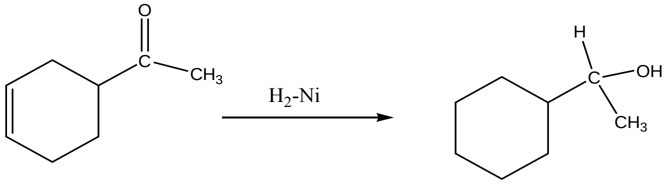


The carbonyl group is reduced rapidly and quantitatively by diborane in ether or THF. The initial product is the ester of boric acid and an alcohol, a trialkyl borate. This material is rapidly hydrolysed upon treatment with water.

$$(CH_3)_2CHCHO + B_2H_6 \longrightarrow [(CH_3)_2CHCH_2O]_3B \xrightarrow{H_2O} (CH_3)_2CHCH_2OH$$

Aldehydes and ketones may also be reduced to alcohols by hydrogen gas in the presence of a metal catalyst (catalytic hydrogenation). The chief advantages of this method are that it is relatively simple to accomplish and usually affords quantitative yield of product because no complicated work-up procedure is required. However, it suffers from the disadvantages that many of the catalysts used (Pd, Pt, Ru, Rh) are relatively expensive and that other functional groups (C=C, -C≡C-, NO_2, -C≡N) also react.

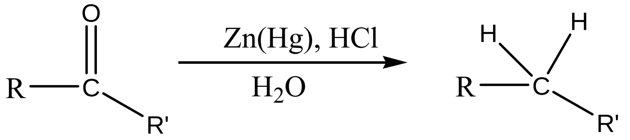




3.3.4.2 Converversion of C=O group to CH_2

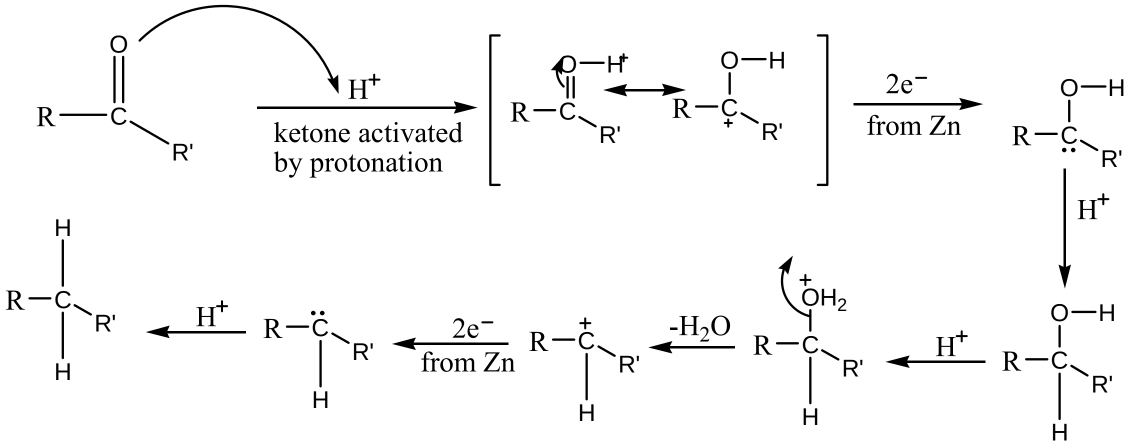
Complete reduction to the alkane (CH_2) is not possible using either metal-hydride reduction or catalytic hydrogenation of aldehydes and ketones. These processes will stop at the alcohol oxidation state. We can convert the C=O group of ketones and aldehydes into a CH_2 group by the **Clemmensen reduction** or the **Wolff-Kishner reaction**.

Clemmensen Reduction: We carry out this reaction by treating an aldehyde or ketone with **zinc amalgam** (Zn treated with mercury metal (Hg) in aqueous HCl). Because this reaction uses aqueous HCl, it is not useful for compounds that are sensitive to acid. (In those cases we can use the reaction described in the next section.) A plausible reaction mechanism for the reduction is as shown below.



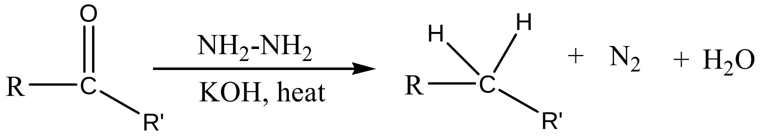
[Clemmenssen reduction]

Mechanism:



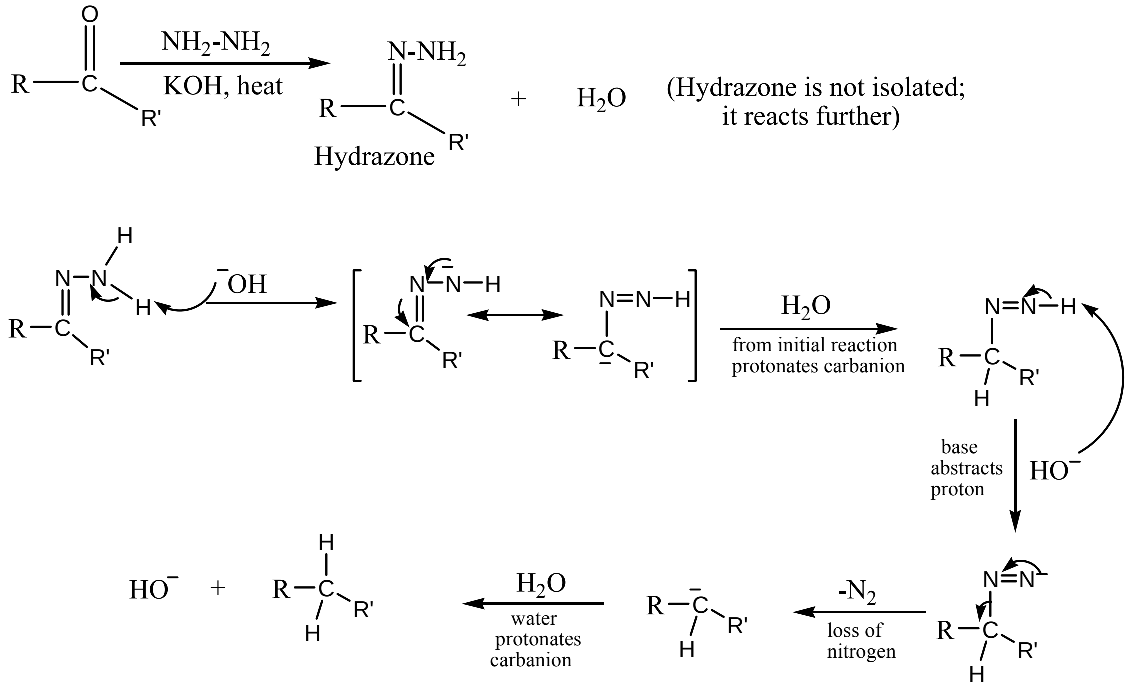
Mechanism of Clemmensen reduction of carbonyls

Wolff-Kishner Reaction: The mechanism of *Wolff-Kishner reaction* involves nucleophilic addition of hydrazine to the C=O group to form the intermediate hydrazone. This intermediate reacts further with H_2O in the reaction mixture to form N_2 and the final organic product. Because the reaction medium is basic, we can use the *Wolff-Kishner reaction* with compounds sensitive to the acidic conditions of the *Clemmensen reduction*.



[Wolff-Kishner reduction]

Mechanism:



Mechanism of Wolff-Kishner reduction of carbonyls

One drawback of the Wolff-Kishner reaction is that it involves the use of strong base (KOH) at elevated temperatures, conditions which may affect other base sensitive functional groups within the molecule.

4.0 Conclusion

In this unit you have learnt that most of the reduction techniques, despite their differences in mechanism and reagents, accomplish the same or similar functional group changes. The unit described types of reduction, with a discussion of applicable functional group transformations and correlates each type of reduction with its relative utility in organic synthesis.

5.0 Summary

In reference to organic molecules, reduction is a process by which a carbon atom gains bonds to less electronegative elements, most commonly hydrogen. It is obvious from this unit that reductive processes are important in organic synthesis.

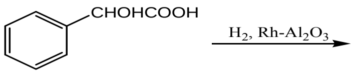
6.0 Tutor-Marked Assignment

Predict the product(s) in each of the following reactions:

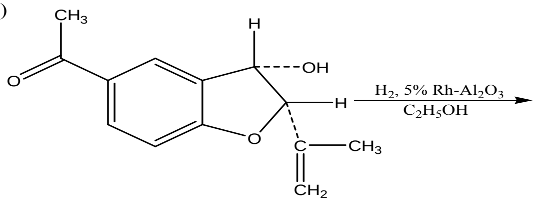
(i) $CH_3(CH_2)_7C\equiv C(CH_2)_7COOH \xrightarrow{H_2,\ \text{Lindlar catalyst}}$

stearolic acid

(ii)



(iii)



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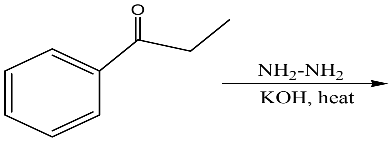
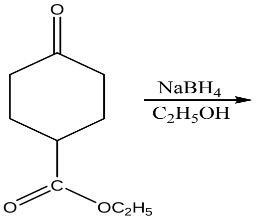


(v) $C_6H_5CH{=}CHCHO \xrightarrow[\text{ether},\,-10^{o}C]{NaBH_4 \text{ or } LiAlH_4}$

(vi)



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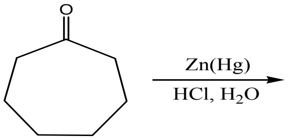


7.0 References/Further Reading

(1) Carey, F. A.; Sundberg, R. J. In Advanced Organic Chemistry Part B, Springer: New York, **2007**.
(2) Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, New York, **1999**.
(3) Hudlicky´, M. *Reductions in Organic Chemistry*, Ellis Horwood Ltd., Chichester **1984**.

Unit 3 Acetylenes

Contents

1.0 Introduction

Alkynes are compounds that contain carbon-carbon triple bonds. The general formula for an acyclic, mono-alkyne is C_nH_{2n-2}. There are two main classifications of alkynes: terminal (RC≡CH) and internal (RC≡CR). The alkyne group is very reactive and few molecules with a triple bond are found in nature. Acetylene (HC≡CH) is the most widely used alkyne and is probably best known for its use in oxyacetylene torches.

2.0 Objectives

At the end of this unit, students should be able to:

i. Describe the nature of the bond in acetylenes
ii. Discuss the acidity of alkynes
iii. Explain how acetylenes can be prepared
iv. Give details of various methods of synthesis of alkynes

3.0 Main Content

3.1 Nature of –C≡C−H Bond

The simplest member of the alkyne family is acetylene, C_2H_2. It is a linear molecule, all four atoms lying along a single line. Both carbon-hydrogen and carbon-carbon bonds are cylindrically symmetrical about a line joining the nuclei, and are therefore σ-bonds. The carbon-carbon "triple bond" is made up of one strong σ-bond and two weaker π-bonds.

The triple bond (−C≡C−) is drawn with three identical lines suggesting all three bonds are identical. This is not the case however; as one bond is a σ bond and the other two bonds are π bonds. Each carbon atom in a triple bond is sp hybridized according to hybrid atomic orbital theory. The alkyne carbon atom has two sp orbitals that are 180^o apart, which minimizes repulsion between electrons in these two orbitals. Each carbon atom also has two unhybridized p orbitals. The p orbitals on one carbon atom (p_x and p_z) are in a common plane and perpendicular to each other. Two sp orbitals, one from each carbon atom, overlap to form a σ bond. The two p orbitals on one carbon atom overlap with the two p orbitals on the adjacent carbon atom to form two π bonds. The overlapping p orbitals must be in the same plane for maximum overlap and bond strength.

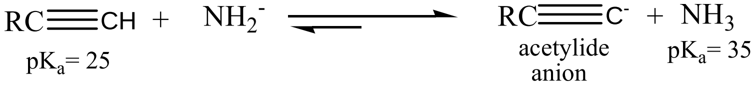
SAQ I-5: *Why isn't an alkyne bond three times as strong as a single bond?*

3.2 Acidity of Alkynes

Very strong bases (such as sodium amide) deprotonate terminal acetylenes to form carbanions called acetylide ions (or alkynide ions). Hydroxide ion and alkoxide ions are not strong enough bases to deprotonate alkynes. Internal alkynes do not have acetylenic protons, so they do not react.

$$CH_3CH_2{-}C{\equiv}C{-}H + NaNH_2 \longrightarrow CH_3CH_2{-}C{\equiv}C{:}^- Na^+ + NH_3$$

The hydrogens in terminal alkynes are relatively acidic; acetylene itself has a pK_a of about 25. It is a far weaker acid than water (pK_a 15.7) or the alcohols pK_a (16-19), but is much more acidic than ammonia (pK_a 35). Amide ion in liquid ammonia converts acetylene and other terminal alkynes into the corresponding carbons. Terminal alkynes act as acids in the presence of a strong base. The amide anion, $^-NH_2$, the conjugate base of ammonia (pK_a = 35), is a strong enough base to completely remove a proton from a terminal alkyne. The following equation shows this reaction and the corresponding pK_a values. This is an acid-base reaction where RC≡CH is the acid on the left side of the equilibrium expression and ammonia, NH_3, is the conjugate acid on the right side of the expression. In acid-base reactions, the rule is a survival of the weakest. Since ammonia is a weaker acid (pK_a = 35) than the alkyne (pK_a = 25), the reaction is shifted strongly to the right. The larger the pK_a value, the weaker the acid. The conjugate base of this reaction is the acetylide anion, RC≡C−.



$$RC{\equiv}CH + NH_2^- \rightleftharpoons RC{\equiv}C^- + NH_3$$

This reaction does not occur with alkenes or alkanes. Ethylene has a pK_a of about 44 and methane has a pK_a of about 50.

Electrons in s-orbitals are held, on the average, closer to the nucleus than they are in p-orbitals. This increased electrostatic attraction means that s-electrons have lower energy and greater stability than p-electrons. In general, the greater the amount of s-orbital in a hybrid orbital containing a pair of electrons, the less basic is that pair of electrons. Lower basicity corresponds to higher acidity of the conjugate acid.

Alkynes are quantitatively deprotonated by alkyllithium compounds.

$$CH_3(CH_2)_3C\equiv CH + n\text{-}C_4H_9Li \longrightarrow CH_3(CH_2)_3C\equiv CLi + n\text{-}C_4H_{10}$$

The foregoing transformation is simply an acid-base reaction, with 1-hexyne being the acid and n-buthyllithium being the base. Terminal alkynes give insoluble salts with a number of heavy metal cations such as Ag^+ and Cu^+. The formation of the salts serves as a useful chemical diagnosis for the $RC\equiv CH$ function, but many of these salts are explosively sensitive when dry and should always be kept moist.

3.3 Preparation of Alkynes

Acetylene or ethyne is the most important member of this series, and it may be prepared by any of the following methods.

1) By the action of water on calcium carbide

$$CaC_2 + 2H_2O \longrightarrow HC\equiv CH + Ca(OH)_2$$

This method of preparation is used industrially.

2) By the action of ethanolic potassium hydroxide on ethylene dibromide.
In principle, a triple bond can be introduced into a molecule by elimination of two molecules of HX from either a germinal (twin), or a vicinal (near) dihalide.

$$BrCH_2CH_2Br + KOH \xrightarrow{\text{ethanol}} H_2C{=}CHBr + KBr + H_2O$$

$$H_2C{=}CHBr + KOH \xrightarrow{\text{ethanol}} HC\equiv CH + KBr + H_2O$$

3.4 Synthesis of Alkynes

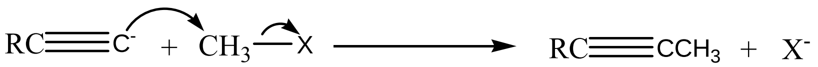
Two different approaches are commonly used for the synthesis of alkynes. In the first, an appropriate electrophile undergoes nucleophilic attack by an acetylide ion. The electrophile may be an unhindered primary alkyl halide (undergoes S_N2), or it may be a carbonyl compound (undergoes addition to give an alcohol). Either reaction joins two fragments and gives a product with a lengthened carbon skeleton. This approach is used in many laboratory syntheses of alkynes.

The second approach forms the triple bond by a double dehydrohalogenation of a dihalide. This reaction does not enlarge the carbon skeleton. Isomerization of the triple bond may occur (see Section 9-8), so dehydrohalogenation is useful only when the desired product has the triple bond in a thermodynamically favoured position.

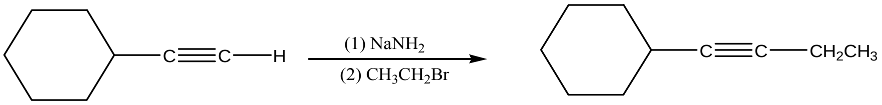
3.4.1 Alkylation Reaction (Synthetic application)

Organic chemistry includes the study of synthesizing molecules that are not readily available from natural sources. The acetylide anion is a useful synthetic reagent. These anions are strong bases and good nucleophiles. They have a nonbonding electron pair they are willing to share with an electrophile. Acetylide anions react readily with methyl compounds (CH_3X) and primary alkyl compounds (RCH_2X)

where X is a good leaving group like a halide or tosylate anion. An example of this reaction is shown in the equation following. The C−X bond is polar when the X atom/group is more electronegative than C. Bond polarity makes C partially positive and electrophilic. The reaction shown below is called a *nucleophilic substitution reaction*. The X group is replaced (substituted) with the acetylide group.



Alkylation via an acetylide anion. (X^- = Cl^-, Br^-, I^- or tosylate)



Typical reaction conditions for formation of alkynes involve the use of molten KOH, solid KOH moistened with alcohol, or concentrated alcoholic KOH solutions at temperatures of 100-200°C. In practice, these conditions are so drastic that the method is only useful for the preparation of certain kind of alkynes. Under these highly basic conditions the triple bond can migrate along a chain.

$$CH_3CH_2C\equiv CH \underset{\Delta}{\overset{\text{alcohol KOH}}{\rightleftharpoons}} CH_3CH_2C\equiv CCH_3$$

Disubstituted alkynes are thermodynamically more stable than terminal alkynes (because of the preference for s-character in C-C bonds). Consequently these conditions may be used only where such rearrangement is not possible.

Sodium amide is an effective strong base that is used in generating an acetylide anion for synthesis of acetylenes. A nucleophilic substitution reaction is a convenient way of making larger molecules containing an alkyne function. The equation below shows a reaction scheme starting with acetylene.

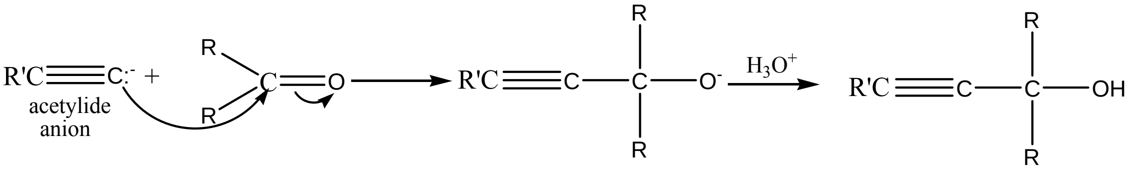
$$HC\equiv CH \xrightarrow[\text{2. RX}]{\text{1. } NH_2^-} RC\equiv CH \xrightarrow[\text{2. R'X}]{\text{1. } NH_2^-} RC\equiv CR'$$

In the first step, a proton is removed from acetylene by the amide anion ($^-NH_2$). The resulting acetylide anion reacts with a primary alkyl halide to give a terminal alkyne. In the next step, amide anion is again used to remove the remaining acetylenic proton. The resulting acetylide anion reacts with another alkyl halide molecule to give a disubstituted internal alkyne. Only methyl and primary alkyl halide reagents can be used in these reactions. Secondary and tertiary alkyl halide compounds tend to give elimination reactions (alkene formation), not substitution reactions.

3.4.2 Addition of Acetylide Ions to Carbonyl Groups

Like other carbanions, acetylide ions are strong nucleophiles and strong bases. In addition to displacing halide ions in S_N2 reactions, they can add to carbonyl (C = O) groups. Because oxygen is more electronegative than carbon, the C = O double bond is polarized. The oxygen atom has a partial negative charge balanced by an equal amount of positive charge on the carbon atom.

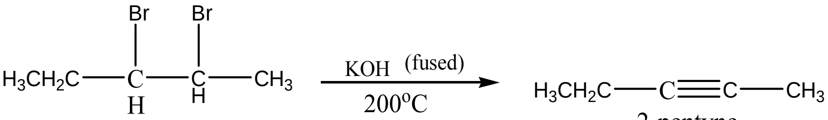
An acetylide ion can serve as the nucleophile in the nucleophilic addition to a carbonyl group. The acetylide ion adds to the carbonyl group to form an alkoxide ion; addition of dilute acid (in a separate step) protonates the alkoxide to give the alcohol.



3.4.3 Synthesis of Alkynes by Elimination Reactions

In some cases, we can generate a carbon-carbon triple bond by eliminating two moleculesof HX from a dihalide. Dehydrohalogenation of a geminal or vicinal dihalide gives a vinyl halide. Under strongly basic conditions, a second dehydrohalogenation may occur to form an alkyne.

Conditions for Elimination: We have already seen many examples of dehydrohalogenation of alkyl halides. The second step is new, however, because it involves dehydrohalogenation of a vinyl halide to give an alkyne. This second dehydrohalogenation occurs only under extremely basic conditions for example, fused (molten) KOH or alcoholic KOH in a sealed tube, usually heated to temperatures close to 200°C. Sodium amide is also used for the double dehydrohalogenation. Since the amide ion ($^{-}$:NH_2) is a much stronger base than hydroxide, the amide reaction takes place at a lower temperature. The following reactions are carefully chosen to form products that do not rearrange (see below).



$$H_3CH_2C-\underset{H}{\overset{Br}{C}}-\underset{H}{\overset{Br}{C}}-CH_3 \xrightarrow[200^{o}C]{KOH\ (fused)} H_3CH_2C-C\equiv C-CH_3$$

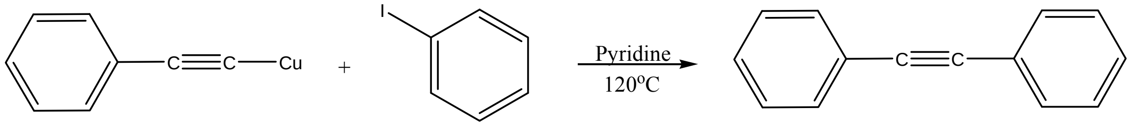
2,3-dibromopentane 2-pentyne

$$CH_3CH_2CH_2CH_2CHCl_2 \xrightarrow[(2)\ H_2O]{(1)\ NaNH_2,\ 150^{o}C} H_3CH_2CH_2CC\equiv CH$$

1,1-dichloropetane 1-pentyne

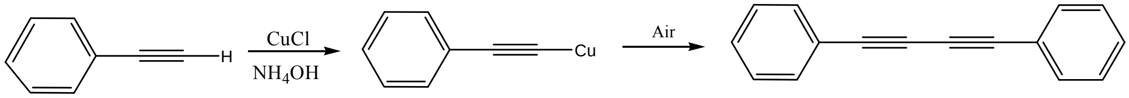
3.5 Coupling Reactions.

Carbon-carbon and carbon-heteroatom bonds are found in many compounds that exhibit important biological, pharmaceutical and materials properties. Due to the importance of these bonds, there has been a need to develop mild and general methods for their synthesis. Classically, the synthesis of these bonds involved nucleophilic aromatic substitution reactions, which required the use of electron-deficient aryl halides or N_2 as a leaving group. The discovery of transition-metal mediated reactions for the synthesis of carbon-carbon and carbon-heteroatom bonds was an important discovery for synthetic chemists. Cuprous acetylides undergo oxidative coupling to aryl halides in the Castro-Stephens Coupling.



Castro-Stevens coupling reaction

The Glaser coupling involves the oxidative coupling of a terminal acetylene to produce a diacetylene.



3.0 Conclusion

Hydrocarbons that contain a carbon–carbon triple bond are called alkynes. Noncyclic alkynes have the molecular formula C_nH_{2n-2}. Acetylene (HC≡CH) is the simplest alkyne. We call compounds that have their triple bond at the end of a carbon-carbon chain (RC≡CH) mono-substituted or terminal alkynes. Di-substituted alkynes (RC≡CR) are said to have internal triple bonds. Alkynes have four electrons in their π bonding system, two in each π bond. They are willing to share these electrons with electrophiles (a species that wants electrons). Thus alkynes are nucleophilic. They seek positively charged or electron-deficient species.

5.0 Summary

You have seen in this chapter that a carbon–carbon triple bond is a functional group, reacting with many of the same reagents that react with the double bonds of alkenes. The most distinctive aspect of the chemistry of acetylene and terminal alkynes is their acidity. As a class, compounds of the type RC≡CH are the most acidic of all simple hydrocarbons. The structural reasons for this property, as well as the ways in which it is used to advantage in chemical synthesis, are important elements discussed in this chapter.

6.0 Tutor-Marked Assignment

1. Show how to synthesize 3-decyne from acetylene and any necessary alkyl halides.
2. Propose a mechanism to show how 2-pentyne reacts with sodium amide to give 1-pentyne.
3. (Z)-9-Tricosene [(Z)-$CH_3(CH_2)_7CH{=}CH(CH_2)_{12}CH_3$] is the sex pheromone of the female housefly. Synthetic (Z)-9-tricosene is used as bait to lure male flies to traps that contain insecticide. Using acetylene and alcohols of your choice as starting materials, along with any necessary inorganic reagents, show how you could prepare (Z)-9-tricosene.

7.0 References/Further Reading

(1) Wade L. G. *Organic Chemistry.* Sixth edition, Pearson Education, Inc **2006**.

(2) R.H.Petrucci, W.S.Harwood and F.G.Herring "*General Chemistry*", 8th edn. (Prentice-Hall **2002**).

MODULE 3 Some named reactions

Unit 1 Aldol and Aldol-type Reactions

Contents

1.0 Introduction

In an "aldol addition" reaction an enol or enolate of an aldehyde or ketone reacts with a second aldehyde or ketone forming a new carbon-carbon bond. This makes the aldol reaction an important reaction for organic synthesis. Originally, the aldol reaction used ethanal and therefore the product contained both an **ald**ehyde and an alcoh**ol** functional group; thus it became known as the **aldol** reaction.

2.0 Objectives

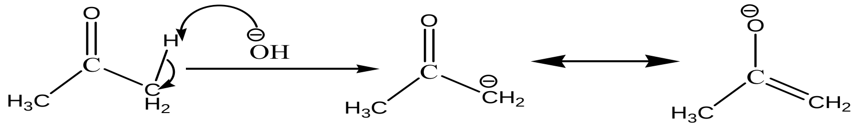
At the end of this unit, students should be able to:
i. Explain the mechanism of the Aldol condensation
ii. Discuss some Aldol-type reactions
iii. State the applications and limitations of each of these reactions
iv. Give the synthetic applications of this type of reaction.

3.0 Main Content

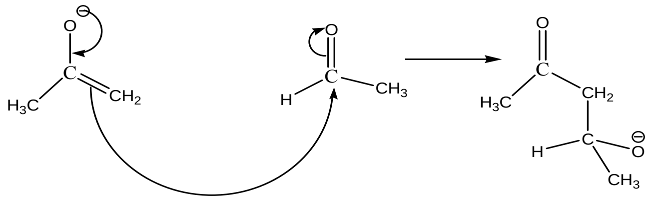
3.1 Mechanism of Aldol Condensation

Methylene groups that are α to the carbonyl function are acidic. They can therefore be abstracted by a base, usually NaOH, Na_2CO_3, *t*-amine, or *n*-BuLi. This generates a nucleophilic species which attacks the carbonyl group of another carbonyl compound. The carbonyl compounds that may be involved include the following: (a) Aldehyde + aldehyde (b) aldehyde + ketone and (c) ketone + ketone. In the above cases the aldehyde may be the same or different or the ketones may be the same or different. When they are different it is called mixed aldol condensation. The product of aldol condensation is a β-hydroxycarbonyl hence the name ***aldol.*** It is an important reaction in organic chemistry because on dehydration of the aldol it gives an α,β-unsaturated carbonyl compound.

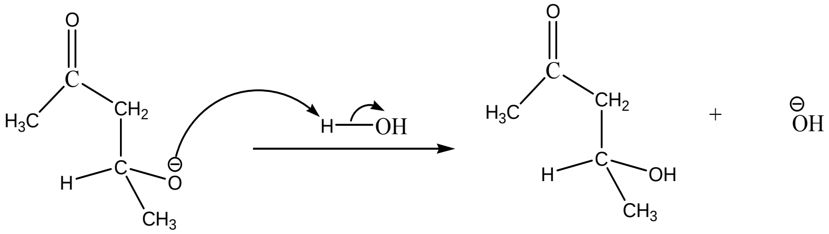
First, the base deprotonates a hydrogen adjacent to the carbonyl:



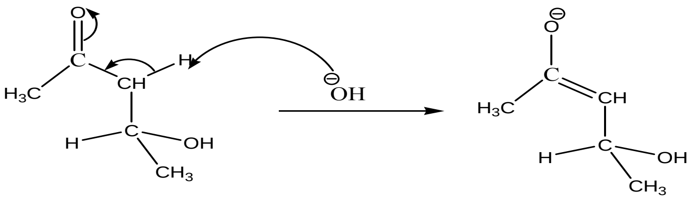
This resonance-stabilized enolate acts as a nucleophile on the aldehyde



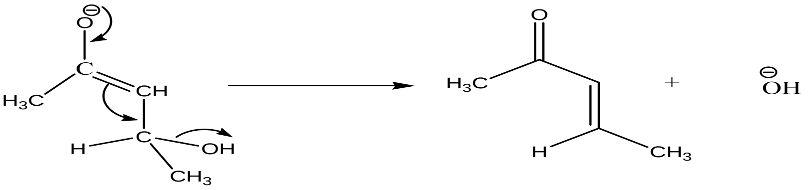
The alkoxide is then protonated to regenerate the hydroxide base:



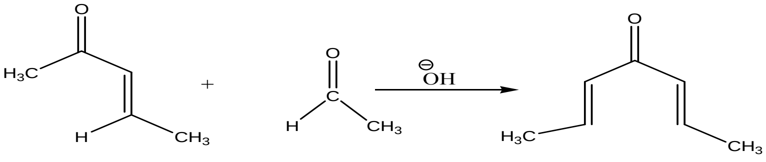
The base then deprotononates the α-carbon again to form an enolate:



The enolate then forms an α,β-unsaturated carbonyl with the loss of hydroxide.



If the initial carbonyl has another α-proton to depronpremonate, then the entire process can happen again and result in the addition of 2 aldehydes

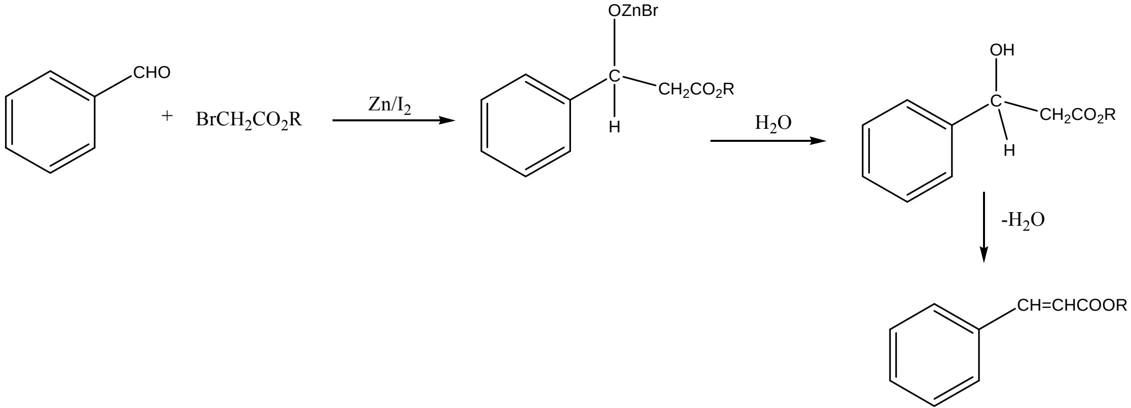


3.2 Aldol-type Condensation reactions

The above is the general aldol condensation reaction. There are other aldol-like reactions which are very important in organic synthesis. They include reactions such as Reformatsky reaction and Perkin reaction.

3.2.1 Reformatsky Reaction

The Reformatsky reaction is an organic reaction which condenses aldehydes (or ketones), with α-halo esters, using metallic zinc to form β-hydroxy-esters. This on dehydration gives an α,β-unsaturated ester which can be hydrolysed to the corresponding carboxylic acid. If applied to an aromatic aldehyde it leads to formation of cinnamic acid derivatives.



Cinnamate

<u>Mechanism of the Reformatsky Reaction</u>

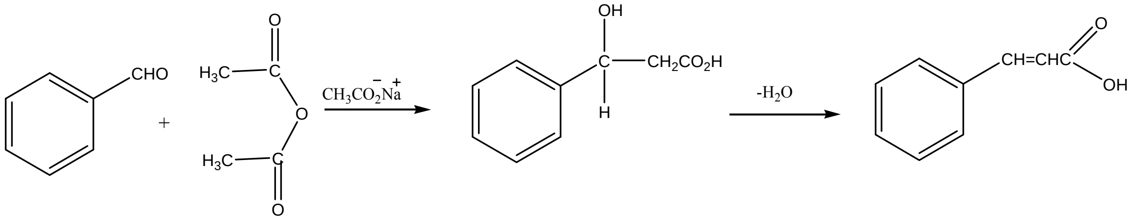
Organozinc compounds are prepared from α-halogenesters in the same manner as Grignard reagents. This reaction is possible due to the stability of esters against organozincs. Due to the very low basicity of zinc enolates, there is hardly any competition from proton transfer, and the scope of carbonyl addition partners is quite broad. In presence of ketones or aldehydes, the organozinc compounds react as the nucleophilic partner in an addition to give β-hydroxy esters.

An ester-stabilized organozinc reagent compared to organolithiums and organomagnesium halides (Grignard reagents), the organozinc halide reagents used in the Reformatsky reaction are relatively stable, and many are available commercially.

3.2.2 Perkin Reaction

The Perkin reaction is an organic reaction developed by William Henry Perkin that can be used to make cinnamic acids i.e. α-β-unsaturated aromatic acid by the aldol condensation of aromatic aldehydes and acid anhydrides in the presence of an alkali salt of the acid. The

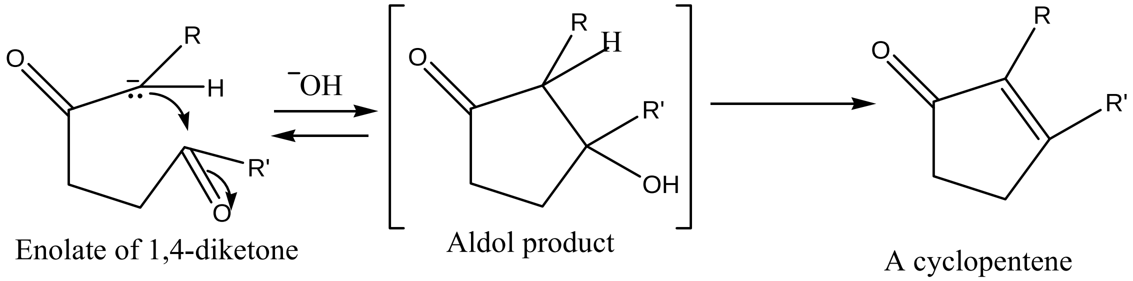
Perkin condensation is a very useful organic reaction which provides a way to add two carbon atoms to the side chain of an aromatic ring. The mechanism of the Perkin reaction is complex. It involves the attack of the enolate anion of the acetic anhydride on the aromatic aldehyde. A series of rearrangement follows, with the overall effect of forming a carbon–carbon double bond (loss of water) and hydrolyzing the anhydride function. Usually the trans-isomer forms preferentially because it is more stable.



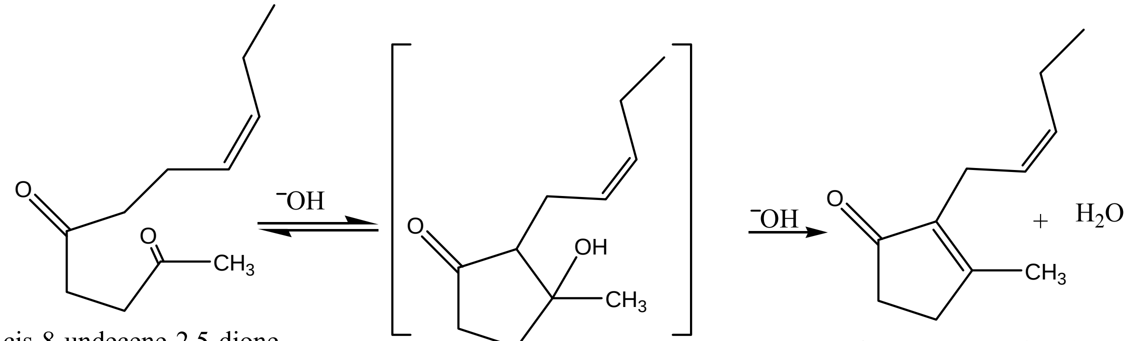
Note: This reaction is only applicable to aromatic aldehydes.

3.3 Synthetic Application: Aldol Cyclization

Intramolecular aldol reactions of diketones are often useful for making five- and six-membered rings. Aldol cyclizations of rings larger than six and smaller than five are less common because larger and smaller rings are less favoured by their energy and entropy. The following reactions show how a 1,4-diketone can condense and dehydrate to give a cyclopentenone and how a 1,5-diketone gives a cyclohexenone.



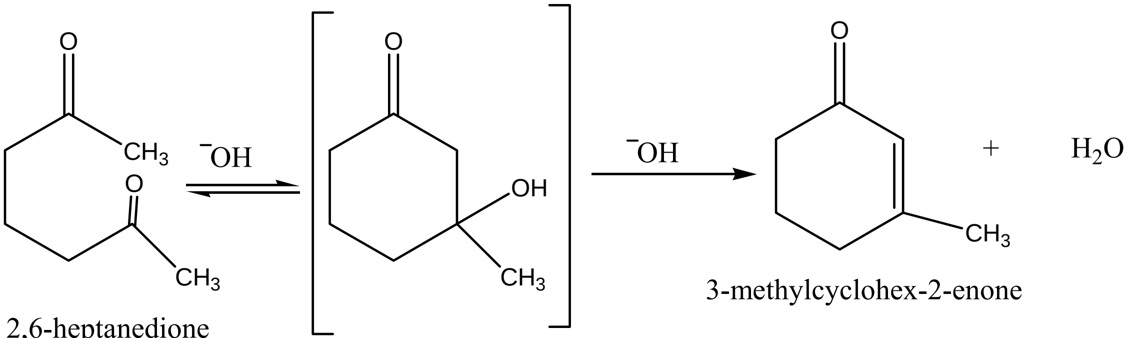
Examples:



cis-8-undecene-2,5-dione

aldol product

cis-jasmone (a perfume)



2,6-heptanedione
(a 1,5-diketone)

aldol product

3-methylcyclohex-2-enone

4.0 Conclusion

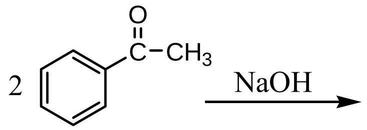
In this unit you have learnt the mechanism for synthesis of an α,β-unsaturated carbonyl compounds. The unit described other reactions that utilize the mechanism of Aldol condensation to obtain compounds like α,β-unsaturated aromatic acid and α,β-unsaturated esters.

5.0 Summary

Condensation reactions are molecular transformations that join together two molecules to produce a larger molecule and also a smaller molecule (usually water, hence the name condensation). Aldol reactions join two carbonyl containing molecules together forming a new carbon-carbon bond between the alpha carbon of one molecule and the carbon of the carbonyl of the second molecule. This forms a beta hydroxyl carbonyl compound. If this product undergoes a subsequent dehydration, then an aldol condensation reaction has taken place. Condensation reactions are a convenient way to synthesize a functionalized larger molecule from smaller starting reagents. Condensation reactions are often utilized in the manufacture of pharmaceuticals, coatings and plastics.

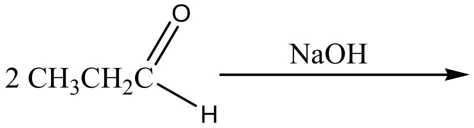
6.0 Tutor-Marked Assignment

(1) Predict the product of the aldol condensation of acetophenone:



Acetophenone

(2) Predict the product of the aldol reaction shown. (Hint: No water is produced).



(3) Predict the major products of the following base-catalyzed aldol condensations with dehydration. (a) benzophenone (PhCOPh) + propionaldehyde
(b) 2,2-dimethylpropanal + acetophenone

7.0 References/Further reading

(1) Weissermel, K, Arpe, H.-J., *Industrial Organic Chemistry*, 3rd Completely Revised Edition, VCH, New York, **1997.**

(2) Wade, L. G. *Organic Chemistry (6th ed.)*. Upper Saddle River, New Jersey: Prentice Hall **2005**. pp. 1056–66. ISBN 0-13-236731-9.

Unit 2 Wittig Synthesis of C=C bond

Contents

1.0 Introduction

The Wittig reaction is the overall substitution of a C=O bond with a C=C bond. It allows one to selectively prepare alkenes in a manner unmatched by any other methodology. The starting materials are an alkyl halide and an aldehyde or ketone. It is a reaction between a cabonyl compound (aldehyde or ketone only) and a species known as a phosphonium ylide. An ylide is a species with a positive and negative charge on adjacent atoms. A phosphonium ylide carries its positive charge on phosphorus.

The reaction of a phosphorus ylide with an aldehyde or ketone, as first described in 1953 by Wittig and Geissler, is probably the most widely recognized method for carbonyl olefination. This so-called Wittig reaction has a number of advantages over other olefination methods; in particular, it occurs with total positional selectivity (that is, an alkene always directly replaces a carbonyl group). By comparison, a number of other carbonyl olefination reactions often occur with double-bond rearrangement. In addition, the factors that influence E- and Z-stereoselectivity are well understood and can be readily controlled through careful selection of the phosphorus reagent and reaction conditions. A wide variety of phosphorus reagents are known to participate in Wittig reactions and the exact nature of these species is commonly used to divide the Wittig reaction into three main groups, namely the ‘‘classic’’ Wittig reaction of phosphonium ylides, the Horner–Wadsworth–Emmons reaction of phosphonate anions, and the Horner–Wittig reaction of phosphine oxide anions. Each of these reaction types has its own distinct advantages and limitations, and these must be taken into account when selecting the appropriate method for a desired synthesis.

2.0 Objectives

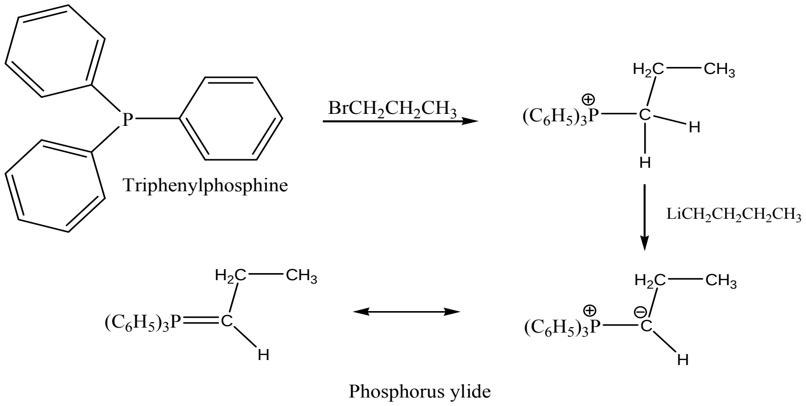
At the end of this unit, students should be able to:
i. Explain methods of preparation of phosphorus ylides
ii. Discuss the mechanism and stereochemistry of Wittig reaction
iii. Describe the Horner-Wadsworth-Emmons (HWE) reaction
iv. Give some synthetic applications of the Wittig reaction
v. List some advantages of the Wittig reacion

3.0 Main Content

3.1 Preparation of reagents (ylides)

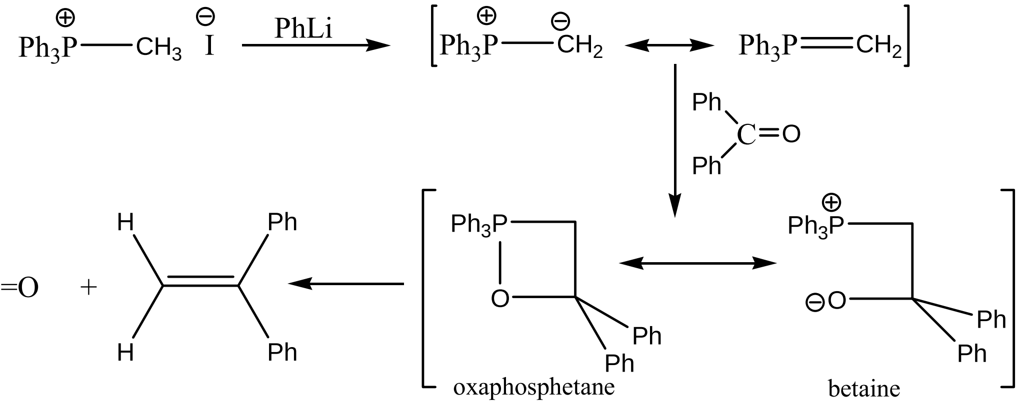
Ylides are prepared from alkyl halides by a two-stage process.
The first step is a nucleophilic substitution whereby an alkyl halide is allowed to react with a phosphine (triphenylphosphine) to give a four coordinate phosphine cation.

In the second step, the phosphonium salt is suspended in a solvent such as diethyl ether or tetrahydrofuran (THF) and treated with a strong base (like *n*-butyl lithium) in order to remove a proton from the carbon bonded to phosphorus to give a neutral compound called a phosphorous ylide. The negatively charged carbon of the ylide can act as a nucleophile and attacks the carbon of the aldehyde or ketone.

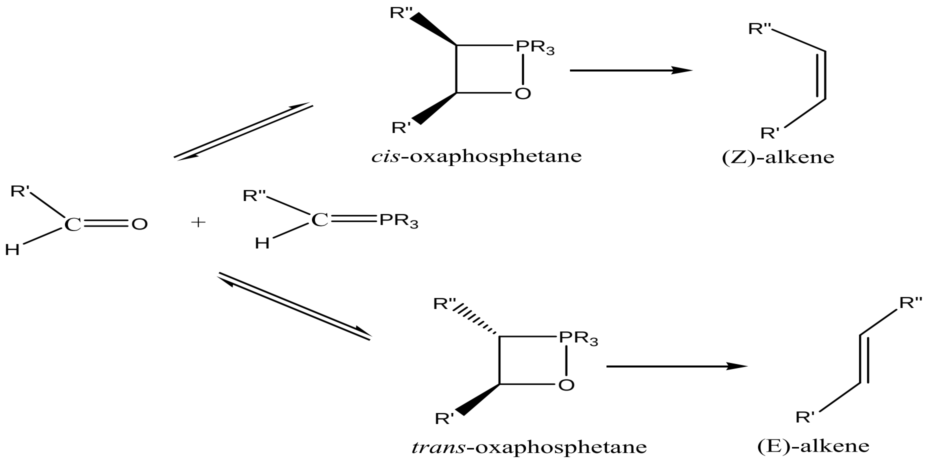


3.2 Mechanism and Stereochemistry of the Wittig reaction

The mechanism of the Wittig reaction has long been considered to involve two intermediate species, a diionic betaine and an oxaphosphetane, as shown in the scheme below.



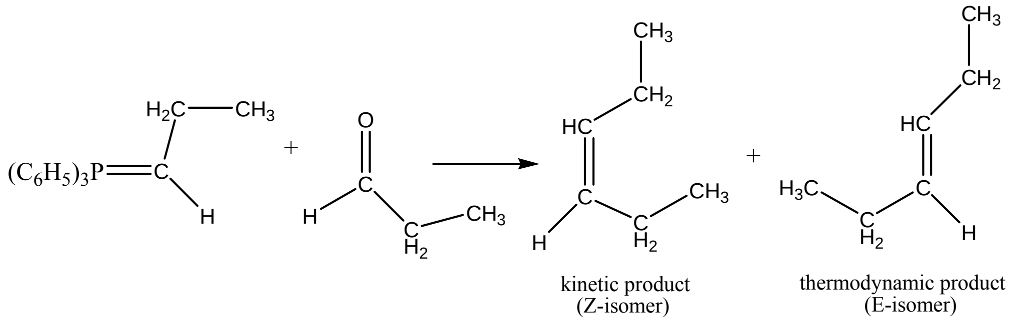
However, there has been much debate as to which of these two species plays the most important mechanistic role and also as to how each influences the stereochemical outcome under different reaction conditions. For many years, it was generally accepted that the betaine is the more important intermediate; however, recent low temperature ^{31}P NMR studies suggest that this may not be the case. This supposition is further supported by recent calculations that reveal that oxaphosphetanes are of lower energy than the corresponding betaines. As such, the currently accepted mechanism for the Wittig reaction is as shown in the scheme that follows.



The phosphine is very big and there is a major steric factor governing the stereochemistry of the addition. The remarkable thing is that for simple compounds, the reaction is Z selective. The reaction is under kinetic control.

The first step of the reaction between the ylide and the carbonyl involves the formation of an intermediate called a betaine. The carbonyl approaches the ylide carbon turned at a 90° angle with respect to the Carbon-Phosphorus bond. This path is the best path in terms of sterics and is also consistent with a detailed molecular orbital analysis of the problem. Once the betaine is formed the oxygen atom can swing over and form a new covalent bond to the phosphorous atom. Phosphorous likes to form five bonds and forms very strong bonds to oxygen in particular. The result of this new bond is a four membered ring compound called a oxaphosphetane.

When the oxaphosphatane forms the stereochemistry of the substituents turns out to be cis. This is due to the chosen path of the carbonyl when the betaine was formed. This means that the favoured final alkene product will be the Z isomer.

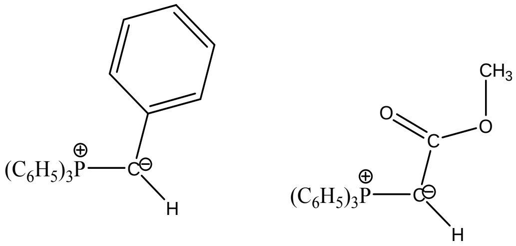


The Z isomer is not the thermodynamic product, it is the kinetic product. The key to a good yield of the kinetic Z isomer is to minimize anything that would equilibrate the betaine and thus the subsequent oxaphosphetane ring. Carrying out the reaction at low temperature helps, so does minimizing extraneous salts that would help stabilize the charged intermediates.

But what if one wanted the thermodynamic product, the E isomer? Then one would want to intentionally isomerize the betaine to lead to the more stable product. A method for doing this has been discovered by a chemist named Schlosser. It involves the addition of a mole of strong base, usually phenyl lithium, to the betaine. The added PhLi deprotonates the betaine and leads to an isomerization. The E-alkene is the final result. The Wittig reaction works very well with aldehydes. It can also be used with ketones, but the stereochemistry control is not as good.

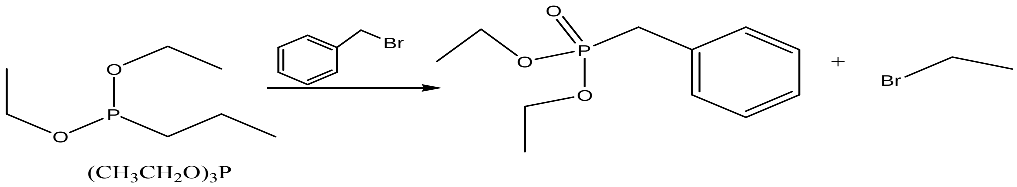
3.2.1 The Horner-Wadsworth-Emmons (HWE) Reaction

One limitation of the Wittig reaction is that phosphorous ylides that contain stabilizing groups next to the negatively charged carbon are not reactive enough to undergo the desired reaction with a carbonyl.

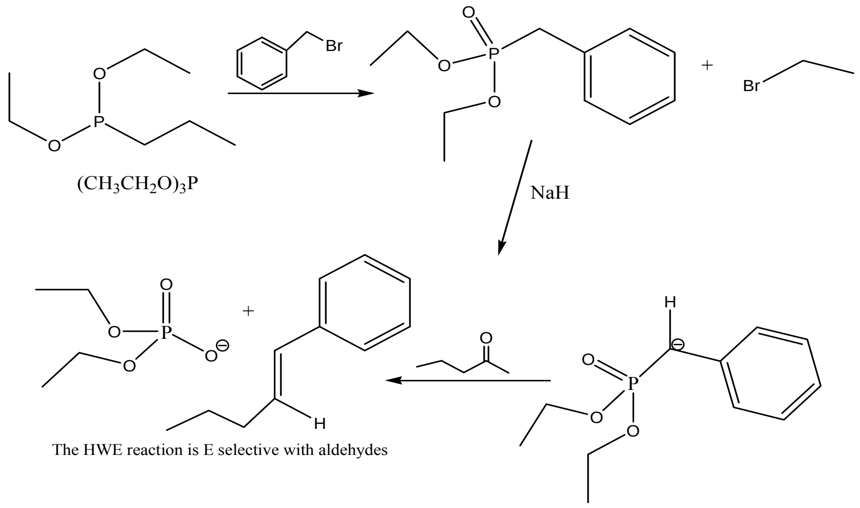


Examples of ylides with stabilizing groups

The stabilizing groups can spread out the negative charge via resonance and thus reduce the nucleophilicity of the carbon atom. The way around the problem is to use a more reactive phosphorous compound to form the ylide. The most popular method is the Horner-Wadsworth-Emmons (HWE) reaction, which starts with triethyl phosphate to form a phosphonate ester.

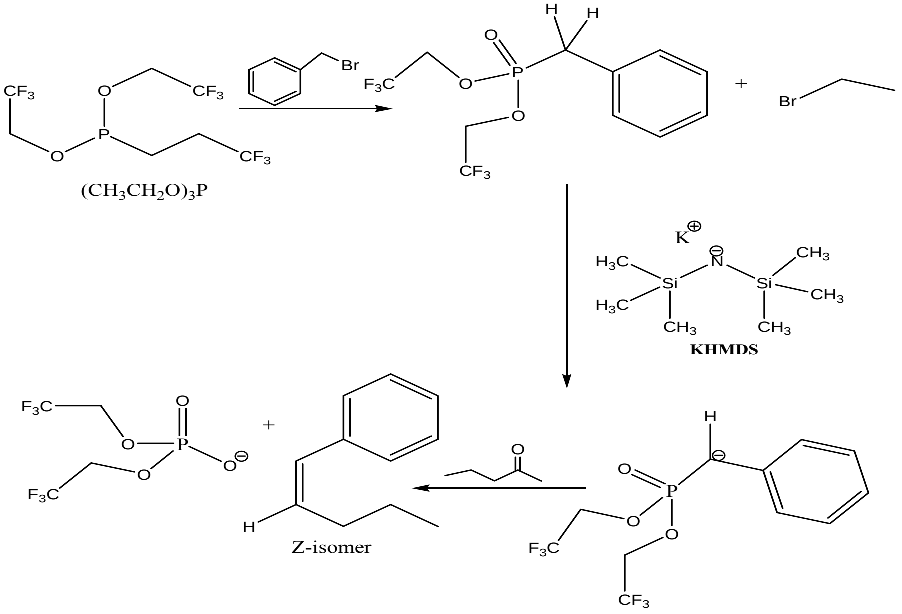


The phophonate ester products will react with a base such as NaH to give ylides reactive enough to carry out the reaction



Horner-Wadsworth-Emmons (HWE) modification

The reaction is slow enough that it gives the thermodynamic E isomer. But what if we wanted the Z isomer of a alkene derived from a stabilized ylide? People have worked on that problem as well. A chemist named Still found that if you added electron withdrawing CF_3 groups to the phosphite you would get a more reactive ylide. The more reactive ylide reacts faster and once again the reacton is under kinetic control. The Z isomer is the result.

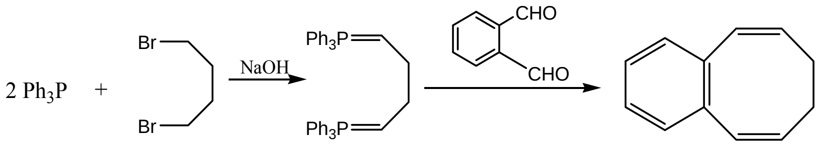


The Still-HWE reaction is Z selective with aldehydes

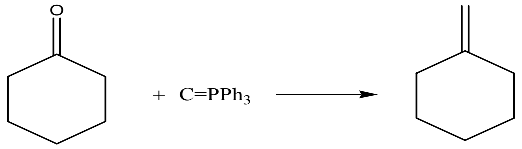
The Still-HWE procedure involves the use of a special base, potassium hexamethyldisilamide (KHMDS). Ketones are difficult to react with stabilized ylides and the stereochemical selectivity is poor.

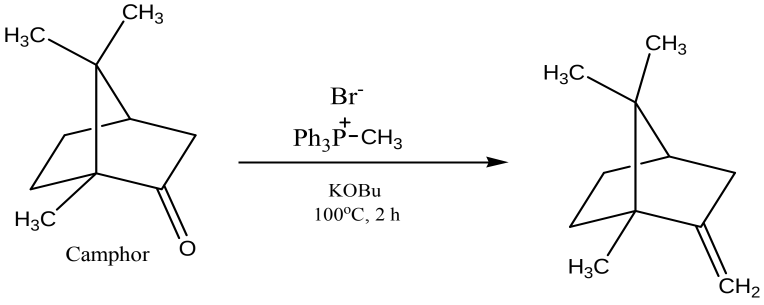
All of this sounds wonderful and it is, but one must realize that all of this is highly variable. None of the reactions listed here are perfect and mixtures of isomers are the norm. In most cases one can predict the predominant product stereochemistry, but in most cases one will have to be prepared for a surprise.

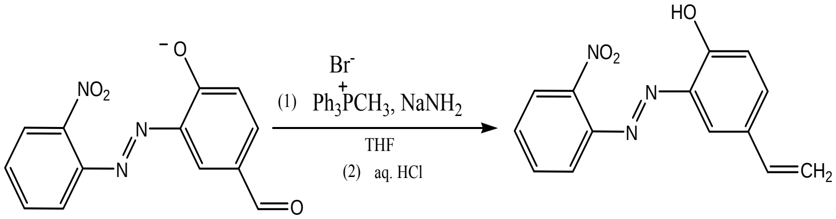
3.3 Synthetic applications



1,2-benzo-1,3,7-octatriene







SAQ II-1: What product results when the ylide of triphenylphosphine and methyl bromide is reacted with acetone?

3.4 Advantages of Wittig reaction over other methods

This Wittig reaction has a number of advantages over other olefination methods:

(1) It is more convenient than its rival, the Reformatsky reaction and has been used to synthesize hitherto unknown compounds.

(2) The position of the carbon-carbon double (C=C) bond is certain. In particular, it occurs with total positional selectivity (that is, an alkene always directly replaces a carbonyl group). By comparison, a number of other carbonyl olefination reactions often occur with double-bond rearrangement.

(3) The stereochemistry of the products can be controlled. The factors that influence E- and Z-stereoselectivity are well understood and can be readily controlled through careful selection of the phosphorus reagent and reaction conditions.
(4) The yield generally is greater than in Reformatsky.
(5) It can take place in the presence of ester group.

4.0 Conclusion

In this unit, you have learnt about a very effective synthetic method for preparing alkenes. The Wittig reaction (and its variants) is a predictable and reliable method for the synthesis of a wide range of alkenes, often with high E- or Z-stereoselectivity. Also in the unit, it has been shown that a judicious selection of the type of phosphorus reagent, carbonyl compound, and reaction conditions can be used to produce a desired compound with high E- or Z-selectivity.

5.0 Summary

Wittig reaction involves a reaction between a phosphorus ylide and an aldehyde or ketone. Ylides are prepared from alkyl halides by a two-stage process. The first step is a nucleophilic substitution. Triphenylphosphine is the nucleophile. In the second step, the phosphonium salt is treated with a strong base in order to remove a proton from the carbon bonded to phosphorus. Typical strong bases include organolithium reagents (RLi), and the conjugate base of dimethyl sulfoxide as its sodium salt [$NaCH_2S(O)CH_3$].

The Wittig reaction normally gives both cis- and trans- isomers; the cis-isomer predominates if the reaction is fast while the trans-isomer predominates if the reaction is slow. Studies have shown, however, that use of non-polar solvents and introduction of PhLi can improve the yield of the trans isomer while the use of polar solvent such as DMF, introduction of Li-salts and use of reactive ylides can lead predominantly to cis-isomers.

6.0 Tutor-Marked Assignments

(1) Explain how the phosphorous ylide is formed to initiate a Wittig reaction. Illustrate your answer with appropriate chemical structures.
(2) Discuss the two possible intermediate species involved in the mechanism of Wittig reaction.
(3) What do you understand by the Horner-Wadsworth-Emmons (HWE) reaction?

7.0 References/Further reading

(1) W. Carruthers, Some Modern Methods of Organic Synthesis, Cambridge University Press, Cambridge, UK, **1971**.
(2) B. J. Walker, in Organophosphorus Reagents in Organic Synthesis (Ed.:J. I. G. Cadogan), Academic Press, London, **1979**.

Unit 3 Diels-Alder Reaction

Contents

1.0 Introduction

One of the most powerful tools for the formation of cyclic molecules is the Diels-Alder reaction. The reaction generally involves the combination of a diene with a "dienophile". There are surprisingly few limitations on the character of either fragment, although the presence of electron withdrawing substituents on the dienophile enhances the reaction rate. The number of examples of this reaction that have been studied is vast, and the procedures given here are typical.

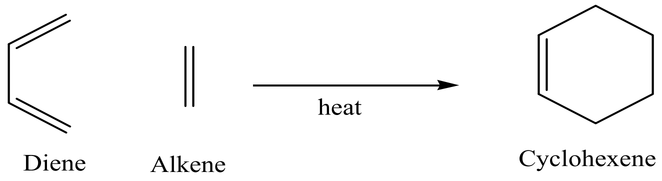
2.0 Objectives

At the end of this unit, students should be able to:
i. Describe the Diels-Alder reaction
ii. Show the mechanism involved in the reaction
iii. Give examples of dienes and dienophiles
iv. Present some applications of the reaction in synthesis

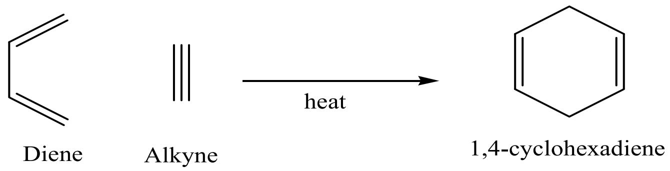
3.0 Main Content

3.1 Reaction mechanism

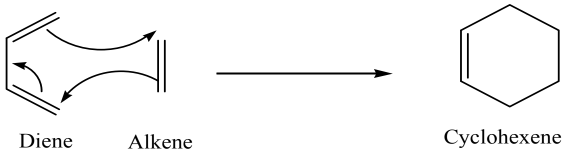
The Diels-Alder reaction is a conjugate addition reaction of a ***conjugated* diene** to an alkene (the ***dienophile***) to produce a cyclohexene. The simplest example is the reaction of 1,3-butadiene with ethene to form cyclohexene:



The analogous reaction of 1,3-butadiene with ethyne to form 1,4-cyclohexadiene is also known:



Since the reaction forms a cyclic product, via a cyclic transition state, it can also be described as a "***cycloaddition***". The reaction is a concerted process:

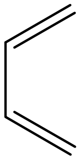


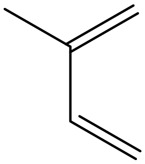
Due to the high degree of regio- and stereoselectivity (due to the concerted mechanism), the Diels-Alder reaction is a very powerful reaction and is widely used in synthetic organic chemistry.

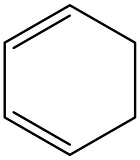
3.2 Dienes and Dienophiles

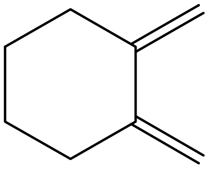
The reaction is usually thermodynamically favourable due to the conversion of 2 π-bonds into 2 new stronger σ-bonds. The two reactions shown above require harsh reaction conditions, but the normal Diels-Alder reaction is favoured by electron withdrawing groups on the electrophilic dienophile and by electron donating groups on the nucleophilic diene. Some common examples of the components are shown below:

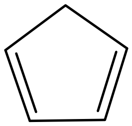
3.2.1 Examples of Dienes



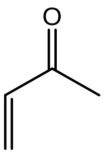


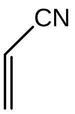


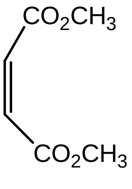


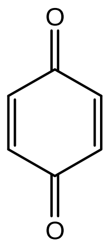


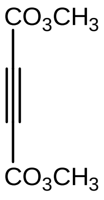
3.2.2 Examples of dienophiles

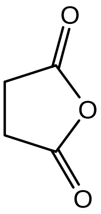


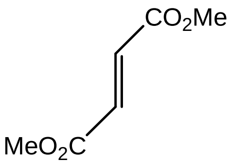






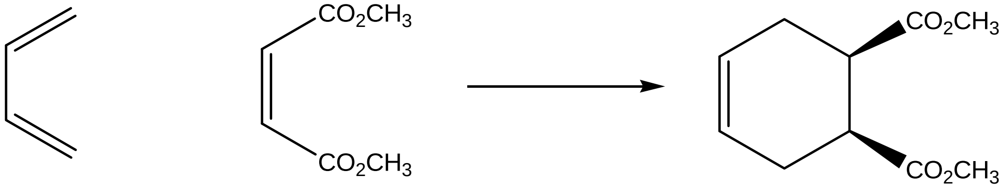




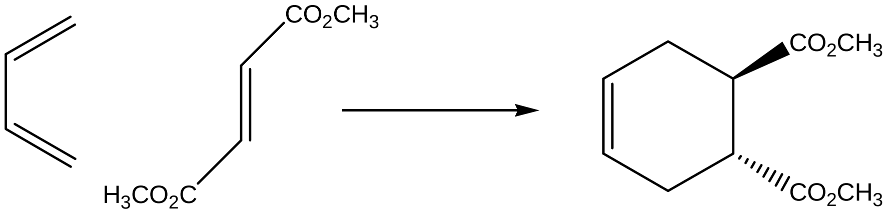


3.3 Stereoselectivity

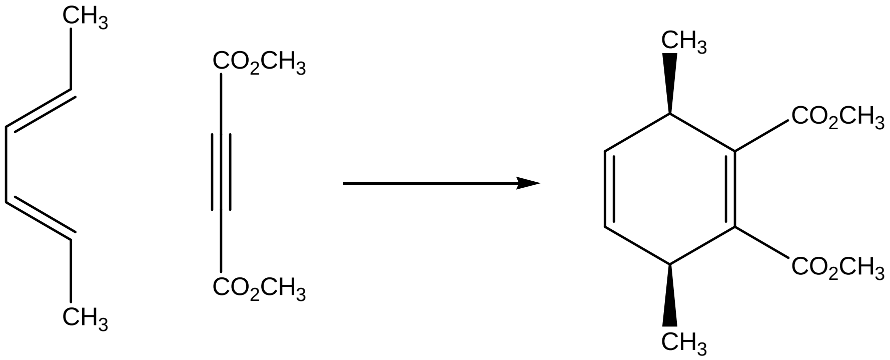
The Diels-Alder reaction is stereospecific with respect to both the diene and the dienophile. Addition is ***syn*** on both components (bonds form from same species at the same time). This is illustrated by the examples below:



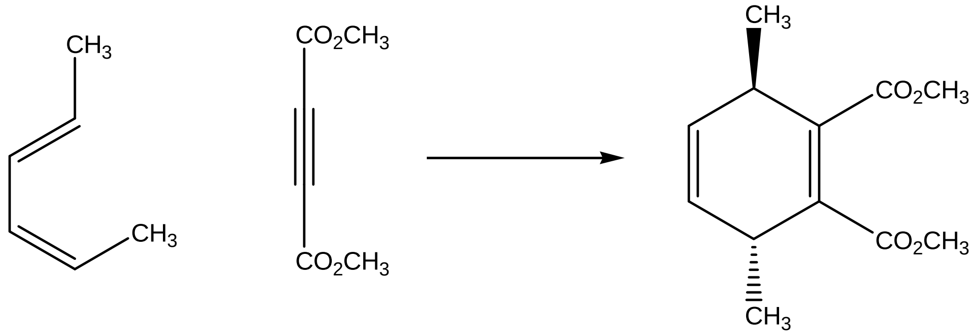
A *cis*-dienophile gives *cis*-substituents in the product as shown by the two ester groups in the product above. On the other hand, a *trans*-dienophile gives *trans*-substituents in the product as illustrated by the two ester groups in the product below:



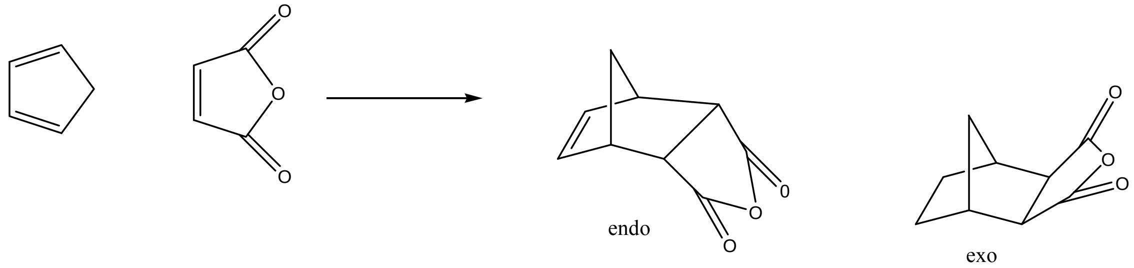
If the diene substituents have the same stereochemistry (in the illustration that follows they are both E), then both diene substituents end up on the same face of the product. Consider the two methyl groups in the reaction product that follows:



If the diene substituents have opposite stereochemistry (as in the illustration that follows one is E and one Z), then the diene substituents end up on opposite faces of the product (look at the two methyl groups in the product)

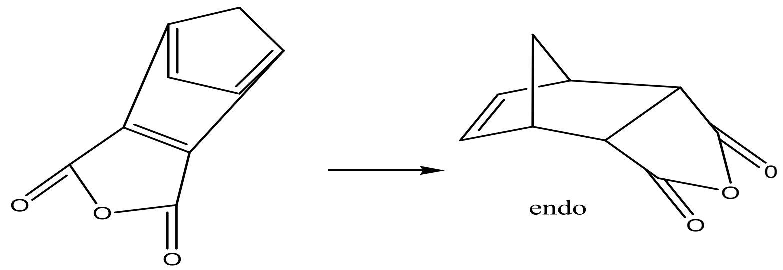


Cyclic dienes can give stereoisomeric products depending on whether the dienophile lies under or away from the diene in the transition state. The endo product is usually the major product (due to kinetic control).



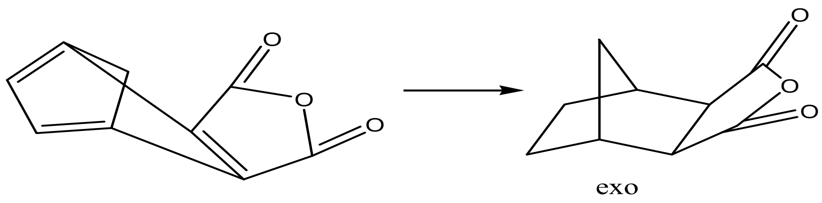
Diene and dienophile aligned directly over each other gives the endo product

(dienophile under or in = endo)



Diene and dienophile staggered with respect to each other gives the exo product

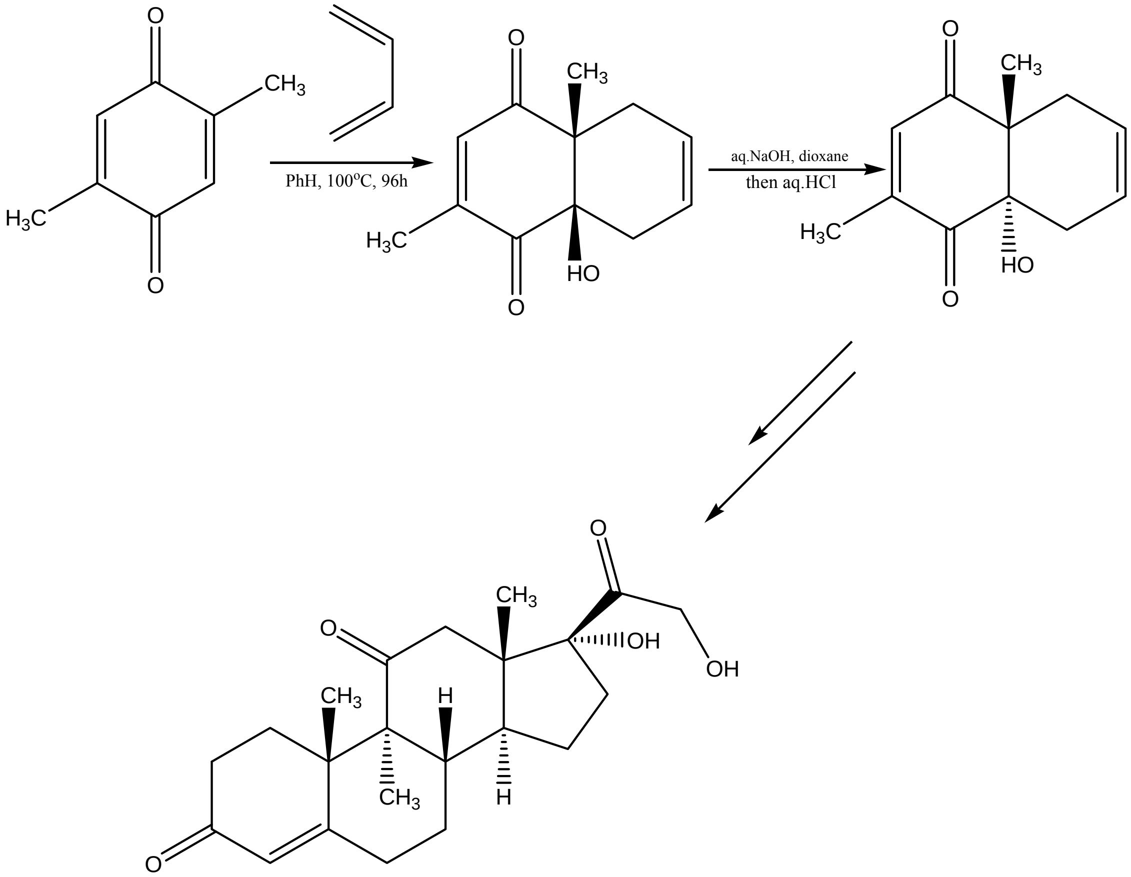
(dienophile exposed or out = exo)



3.4 Synthetic applications

(i) *Synthesis of steroids*

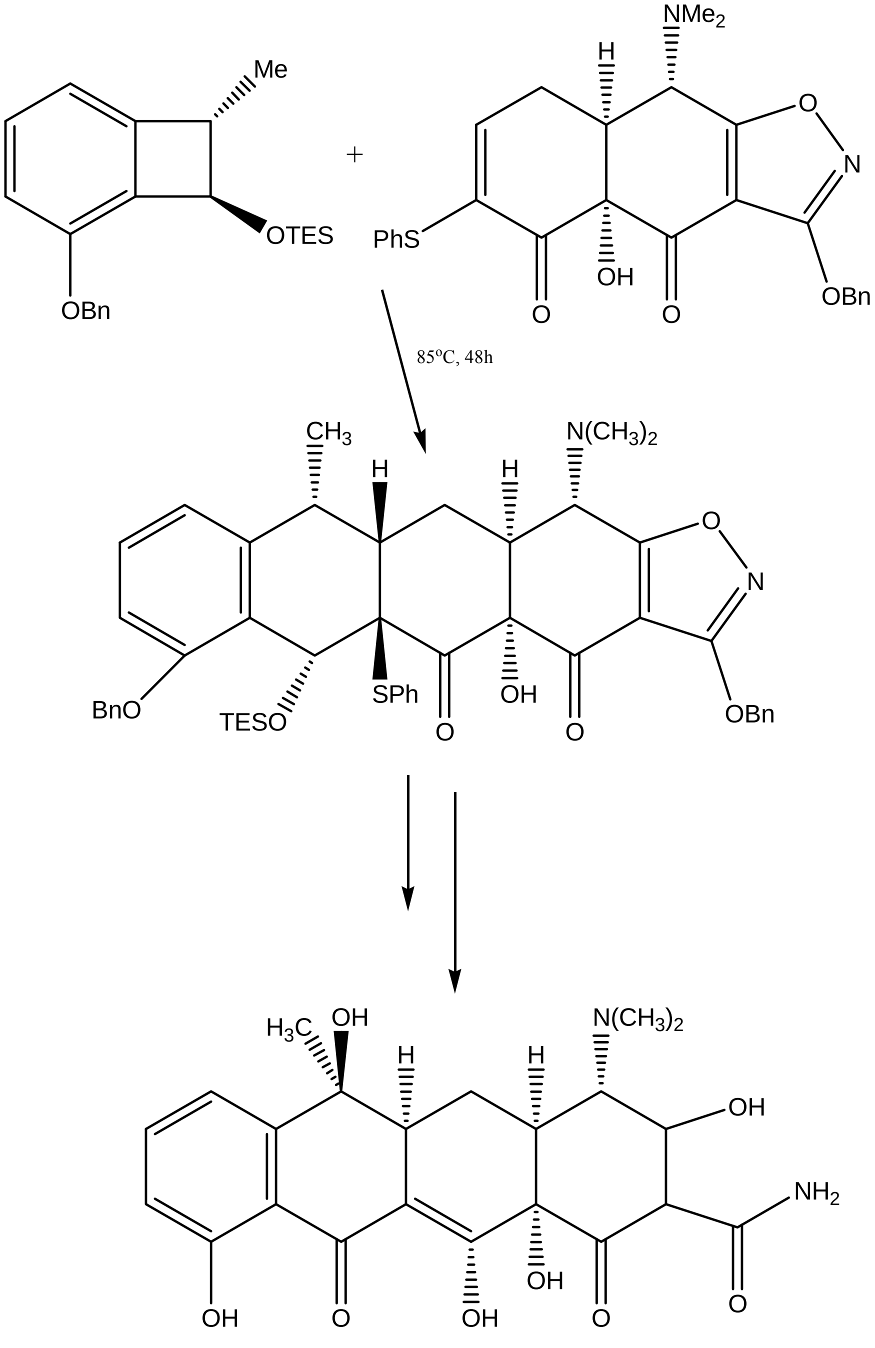
One of the earliest and most important examples of the Diels–Alder reaction in total synthesis was in syntheses of the steroids cortisone and cholesterol.



Cortisone

(ii) *Synthesis of tetracycline*

Synthesis of the linear tetracyclic core of the antibiotic was achieved with a Diels–Alder reaction. Thermally initiated, conrotatory opening of the benzocyclobutene generated the o-quinodimethane, which reacted intermolecularly to give the tetracycline skeleton.



(-)-Tetracycline

4.0 Conclusion

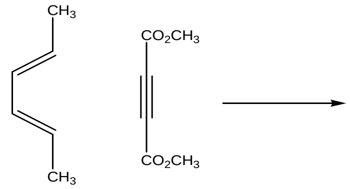
In this unit, you have learnt about the Diels-Alder reaction, the mechanism involved in the reaction, examples of dienes and dienophiles and some applications of the reaction in synthesis.

5.0 Summary

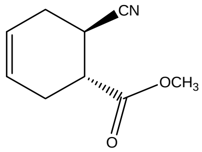
A Diels-Alder reaction is a [4+2]-cycloaddition. A [4+2]-cycloaddition is a reaction in which a compound containing four π electrons reacts with a compound containing two π electrons to form a new cyclic compound. Dienes containing electron-releasing groups (usually alkyl groups) react faster, especially with dienophiles that contain electron-withdrawing groups (almost always groups that contain electronegative atoms). The opposite combination also gives relatively fast reactions, but the starting materials are unusual.

6.0 Tutor-Marked Assignment

(1) What is the major product of the following reactions?



(2) Give the reactants (including stereochemistry) that would give the following Diels-Alder product.



7.0 References/Further Reading

(1) Vollhardt, K. Peter C., and Neil E. Schore. *Organic Chemistry: Structure and Function*. New York: W.H. Freeman and Company, **2007**.
(2) Carey, Francis. *Advanced Organic Chemistry*. 5th ed. Springer, **2007**.