Pharmaceutical Organic Chemistry **BP202TP**

CARBONYL COMPOUNDS

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- ***General Methods of Preparation***
- ***Nucleophilic Addition to the Carbonyl Group***
- ***Cyanohydrins of Aldehydes and Ketones***
- ***The Nucleophilic Approach: Bürgi-Dunitz Trajectory***

General Methods of Preparation

1. *By Oxidation/Dehydrogenation of Alcohols*
2. *By Oxidation of 1,2-Alkanediols*
3. *By Heating of Calcium Salt of Monocarboxylic Acid*
4. *By Ozonolysis of Suitable Alkenes*
5. *By Hydration of Alkynes under Suitable Conditions*
6. *By Rosenmund's Reduction*
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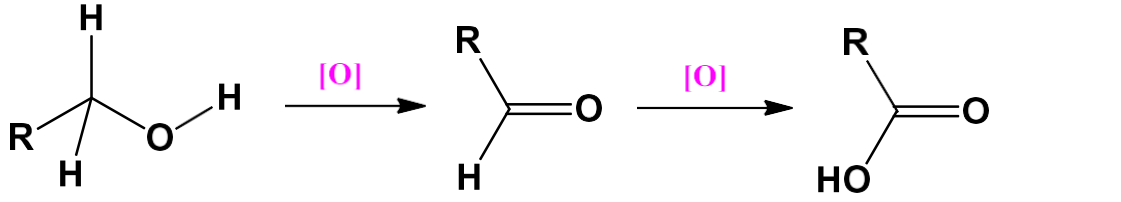
***Many suitable methods are available for the synthesis of aldehydes and ketones. Only a few of them are mentioned here. Other methods and the detailed discussion on these synthetic routes will be made at the appropriate sections of Organic Chemistry.*

Oxidation/Dehydrogenation of Alcohols

- The oxidation of an alcohol involves the loss of one or more hydrogens (***α***-hydrogens) from the carbon bearing the –OH group. The nature of product that is formed depends upon how many of these ***α***-hydrogens the alcohol contains, that is, upon whether the alcohol is ***primary***, ***secondary***, or ***tertiary***.

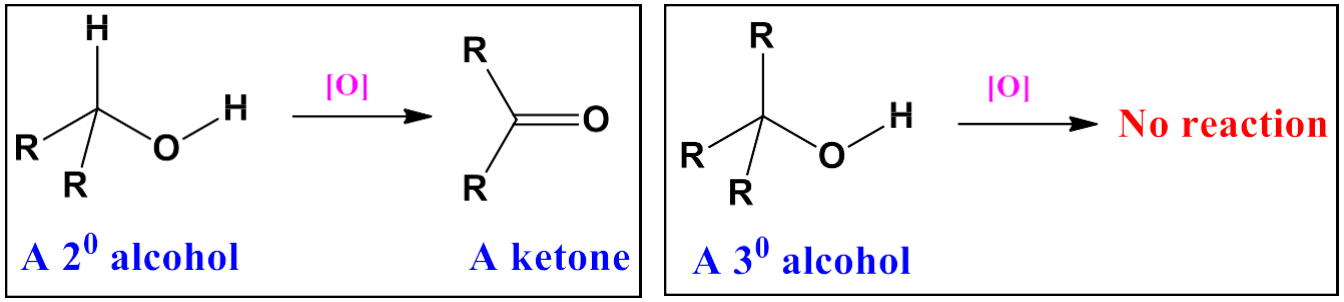
- A ***primary*** alcohol contains two ***α***-hydrogens, and can either lose one of them to form an aldehyde, or both of them to form a carboxylic acid. Both aldehyde and the acid contain the same number of carbon atoms as the original alcohols.



A 1^0 alcohol **An aldehyde** **A carboxylic acid**

Oxidation/Dehydrogenation of Alcohols

- A ***secondary*** alcohol can lose its only ***α***-hydrogen to form a ***ketone***. A ***tertiary*** alcohol contains no ***α***-hydrogen and is not oxidised under normal condition. An acidic oxidising agents can, however, dehydrate the alcohol to an alkene and then oxidise this.



- **Aldehydes:** An aldehyde is obtained by the partial oxidation of a ***primary*** alcohol. *t*-Butyl chromate (prepared by adding chromium trioxide to *t*-butanol) oxidises ***primary*** alcohols to aldehyde quantitatively.

$$\text{R-CH}_2\text{OH} \xrightarrow[\text{Me}_3\text{COH}]{\text{CrO}_3} \text{R-CHO}$$

Oxidation/Dehydrogenation of Alcohols

- A ***primary*** alcohol is dehydrogenated to an ***aldehyde*** when the alcohol vapour is passed over copper at 300 °C.

$$R\text{-}CH_2OH \xrightarrow[300\ ^oC]{Cu} R\text{-}CHO$$

- **Ketones:** A ***secondary alcohol*** *is* oxidised to a ketone by aluminium *t*-butoxide [$(Me_3CO)_3Al$] in presence of a ketone other than the product (**Oppenauer Oxidation**).

$$3\ R^1CH(OH)R^2 + (Me_3CO)_3Al \xrightarrow[Me_2CO]{reflux} 3\ R^1COR^2 + 3\ Me_3COH + (Me_2CHO)_3Al$$

- A ***secondary*** alcohol is dehydrogenated to a ***ketone*** when the alcohol vapour is passed over copper at 300 °C.

$$R_2CHOH \xrightarrow[300\ ^oC]{Cu} R_2CO$$

Oxidation of 1,2-Alkanediols

- Oxidation of 1,2-diols with lead tetraacetate or periodic acid results in a fission of the carbon-carbon bond to give aldehydes and/or ketones. The nature of the product formed depends on the nature of the diol used.

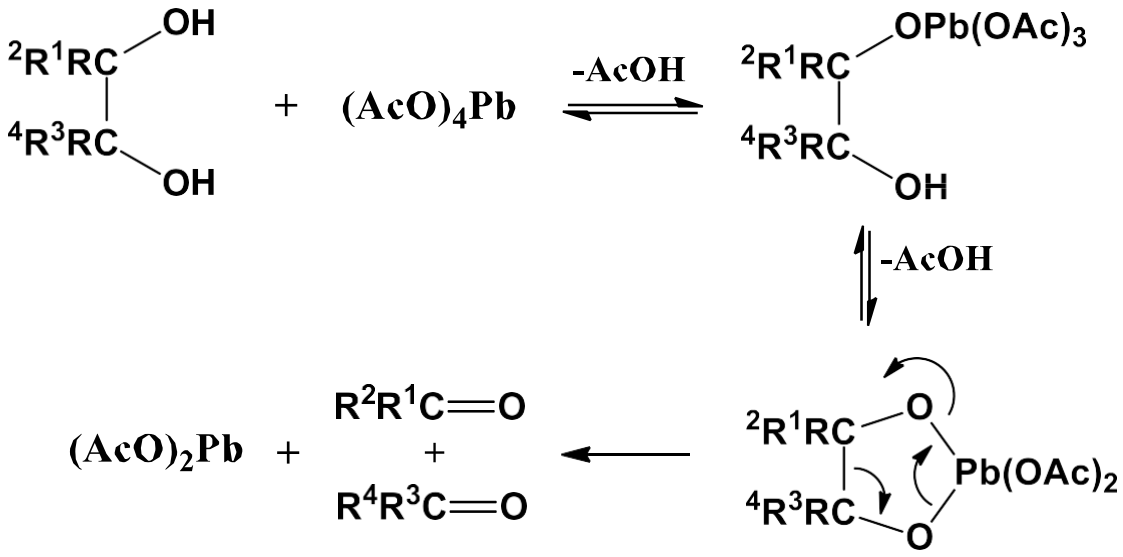
- Oxidation of 1,2-diols occurs more rapidly with ***cis***-glycols than with the ***trans***-isomers, and this has been interpreted as evidence for the formation of ***cyclic intermediate***.

- The fact that ***trans***-isomers are oxidised suggests that the reaction proceeds through a ***non-cyclic intermediate*** for these compounds. The non-cyclic ester could be formed in the first step.

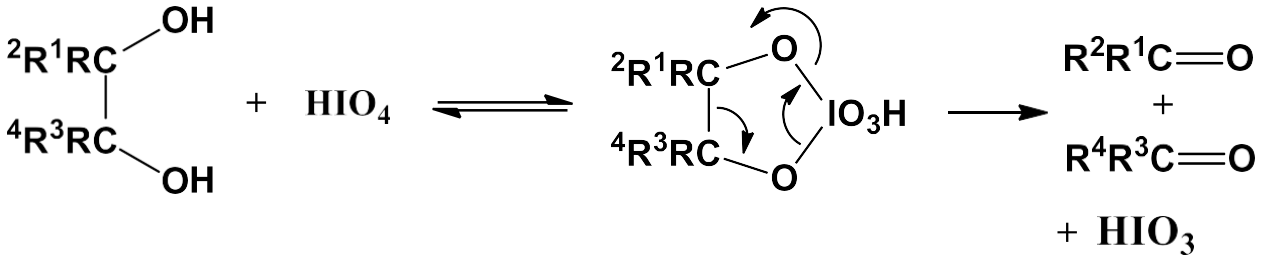
- These oxidations are subject to steric hindrance. The ***slow*** step for glycol oxidation is the fission of the ***cyclic intermediate***, whereas that for pinacol is the formation of the this ***intermediate***.

Oxidation of 1,2-Alkanediols

Oxidation with Lead tetraacetate



Oxidation with Periodic acid



If $R^2 = R^4 = H$: The products are Aldehydes, R^1CHO and R^3CHO

If R^2 and R^4 = Any alkyl group: The products are Ketones

Heating of Calcium Salt of Monocarboxylic Acid

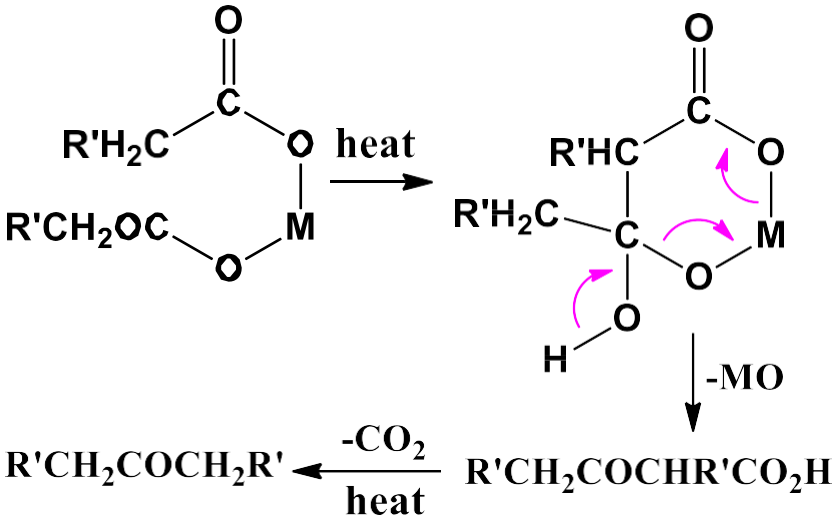
- **Aldehydes:** An aldehyde is obtained by heating a mixture of the calcium salts of formic acid and any one of its homologues depending upon the nature of the desired aldehyde:

$$(RCO_2)_2Ca + (HCO_2)_2Ca \xrightarrow{heat} 2\,RCHO + 2\,CaCO_3$$

- **Ketones:** A ketone is obtained by heating the calcium salt of any monocarboxylic acid other than formic acid :

$$(RCO_2)_2Ca \xrightarrow{heat} R_2CO + CaCO_3$$

- The mechanism of this reaction occurs via the formation of an aldol and a *β*-keto acid. No aldol formation is possible unless the acid contains an α-hydrogen atom (M = metal).



Ozonolysis of Suitable Alkenes

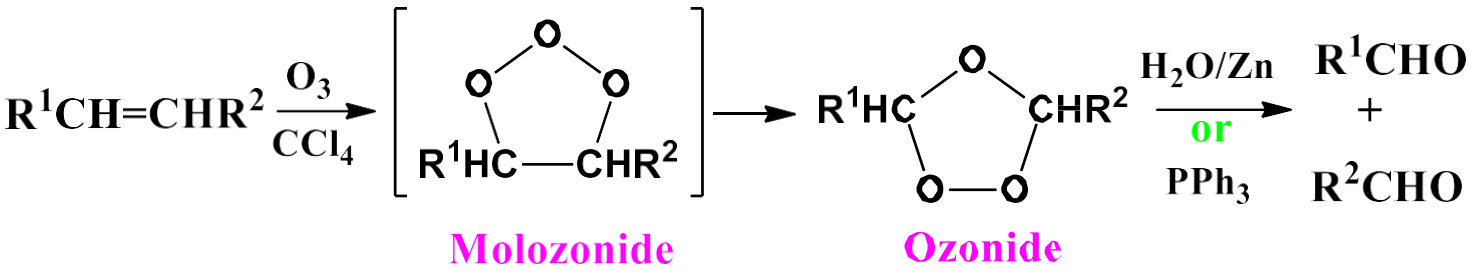
- Alkenes add on ozone to form ozonides. The molozonide is formed first, and this then rearranges to the ozonide. The ozonides on hydrolysis or by reduction under suitable conditions give the corresponding aldehydes and/or ketones.

- The complete process of preparing the ozonide and decomposing it (and identifying the products formed) is known as ozonolysis. This method is used to determine the position of a double bond in any olefinic compound.

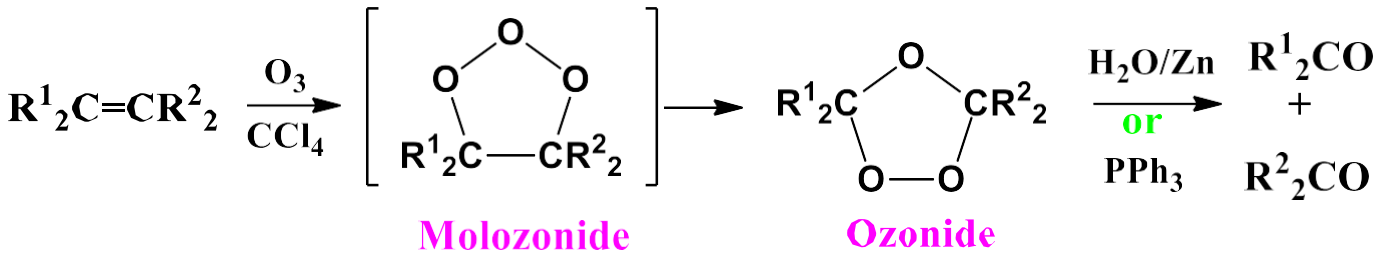
- The ozonide is prepared by dissolving the olefinic compound in a solvent that is unaffected by ozone, e.g., chloroform, carbon tetrachloride, glacial acetic acid, light petrol, etc., and a stream of ozonised oxygen is passed through.

Ozonolysis of Suitable Alkenes

- **Aldehydes:** An aldehyde is obtained by the ozonolysis of an alkene of the type $R^1CH=CHR^2$.

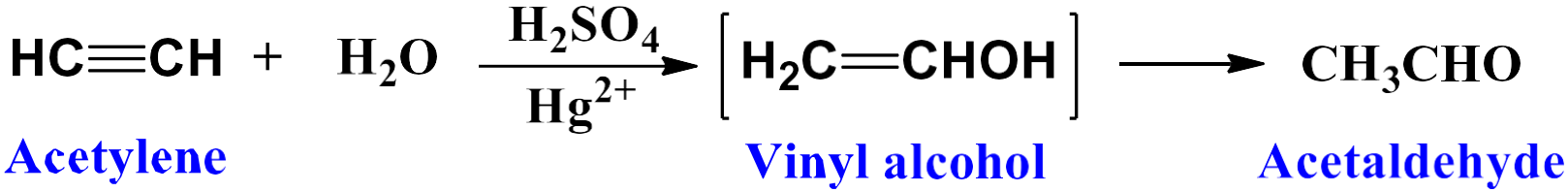


- **Ketones:** A ketone is obtained by the ozonolysis of an alkene of the type $R^1_2C=CR^2_2$.

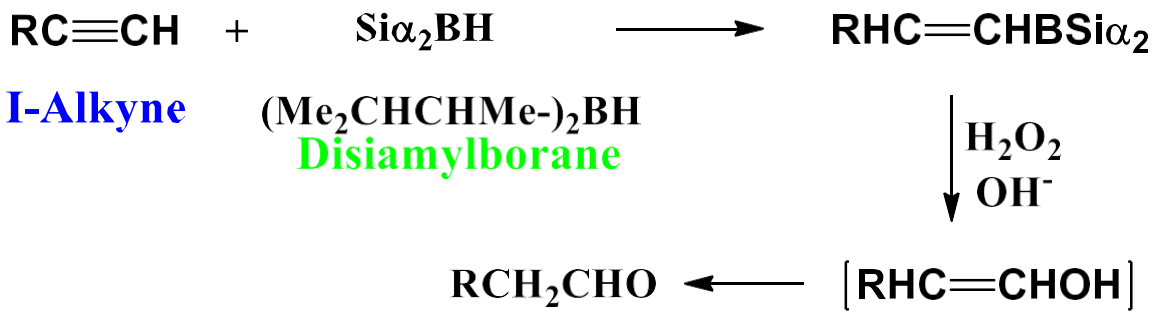


Hydration of Alkynes under Suitable Condition

- **Aldehydes:** When passed into dilute sulphuric acid at 60 °C in the presence of mercuric sulphate as catalyst, acetylene adds on one molecule of water to form acetaldehyde. The reaction takes place via the formation of vinyl alcohol as an intermediate.

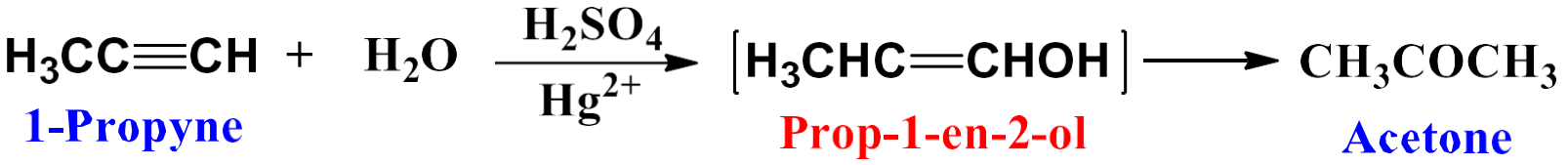


- On the other hand, higher aldehydes are obtained when 1-alkynes undergo hydroboration with disiamylborane followed by oxidation with hydrogen peroxide under alkaline condition.

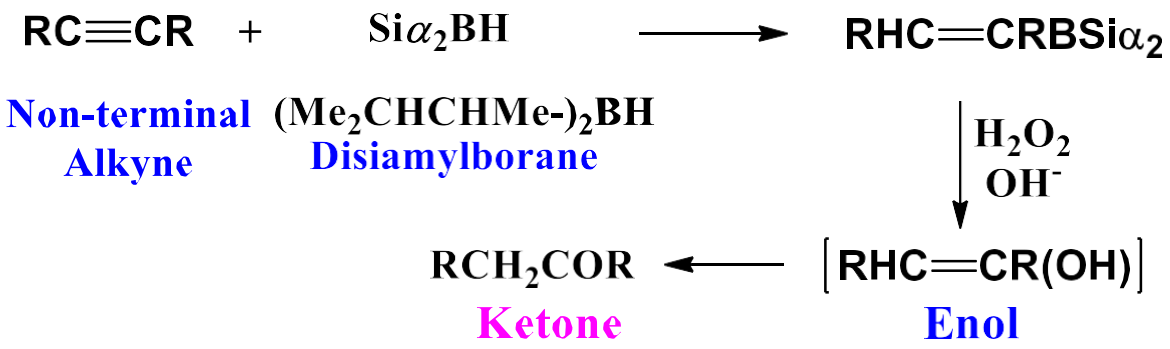


Hydration of Alkynes under Suitable Condition

- **Ketones:** When passed into dilute sulphuric acid at 60 °C in the presence of mercuric sulphate as catalyst, 1-propyne adds on one molecule of water to form acetone. The reaction takes place via the formation of an enol as intermediate.



- On the other hand, higher ketones are obtained when non-terminal alkynes undergo hydroboration with disiamylborane followed by oxidation with hydrogen peroxide under alkaline condition.



Rosenmund's Reduction

- **Aldehydes:** By the reduction of an acid halide with hydrogen in boiling xylene using a palladium catalyst supported on barium sulphate.

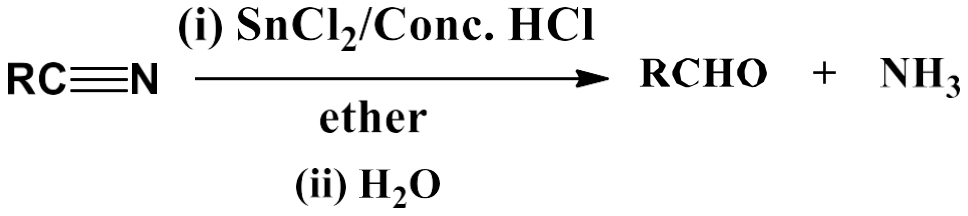
$$RCOCl + H_2 \xrightarrow[BaSO_4]{Pd} RCHO + HCl$$

- Aldehydes are more readily reduced than the acid chlorides, and therefore one would except to obtain the alcohol as the final product. It is the barium sulphate that prevents the aldehyde from being reduced, acting as a poison to the palladium catalyst in the reaction. Generally, when the Rosenmund reduction is carried out, a small amount of quinoline and sulphur is added; these are very effective in poisoning the catalyst in the aldehyde reduction.

- **Ketones:** There is no analogous method for the preparation of ketones.

Stephen's Reduction

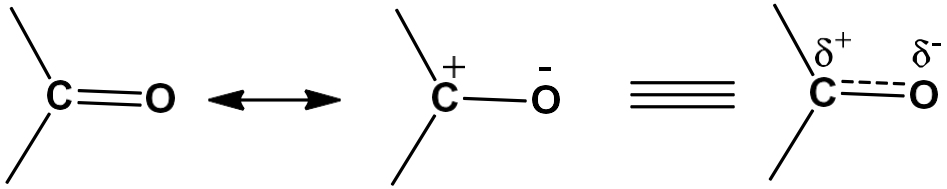
- **Aldehydes:** An alkyl cyanide is dissolved in ether or in ethyl acetate and reduced with stannous chloride and concentrated hydrochloric acid, and then steam distilled. Stephen's process proceeds via the iminochloride or aldimine hydrochloride (which is present as the stannichloride)



- **Ketones:** There is no analogous method for the preparation of ketones.

Nucleophilic Addition to the Carbonyl Group

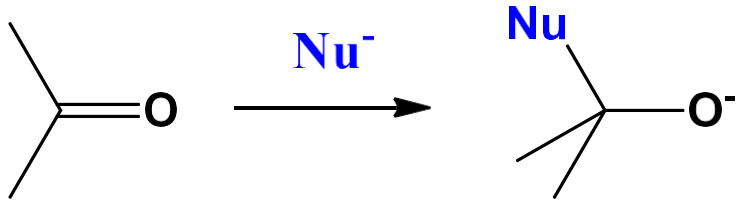
- Carbonyl group contains two types of bonds, the C=O double bond is shorter than a typical C–O single bond, and also over twice as strong. The polarized C=O bond gives the carbon atom some degree of positive charge, and this charge attracts negatively charged nucleophiles (like cyanide) and encourages reaction.



- The polarization of the antibonding **π*** orbital towards carbon is important, because, when the carbonyl group reacts with a nucleophile, electrons move from the ***HOMO*** of the nucleophile into the ***LUMO*** of the electrophile, i.e., to the **π*** orbital of the C=O bond. The greater coefficient of the π* orbital at carbon means a better ***HOMO–LUMO*** interaction, so this is where the nucleophile attacks.

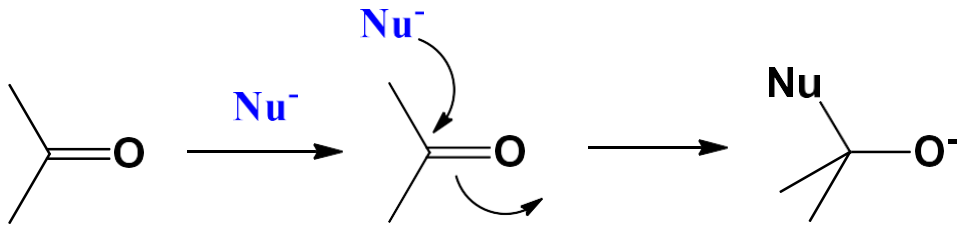
Nucleophilic Addition to the Carbonyl Group

- As the nucleophile, Nu^-, approaches the carbonyl carbon atom, the electron pair in its ***HOMO*** starts to interact with the ***LUMO*** (antibonding **π***) to form a new **σ** bond. Since the electrons enter the antibonding **π*** of the carbonyl group, the **π** bond is broken, leaving only the C–O **σ** bond intact.

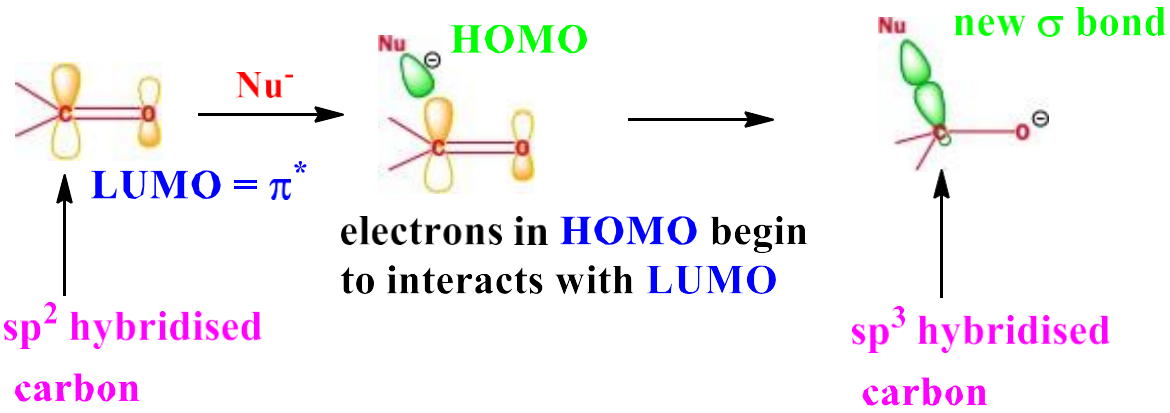


- The electrons in the **π** bond move off on to the electronegative oxygen, which ends up with the negative charge that started on the nucleophile. The ***HOMO-LUMO*** interaction involved in the addition reaction is shown in **Figure 1**. During this transformation, the trigonal, planar sp^2 hybridized carbon atom of the carbonyl group changes to a tetrahedral, sp^3 hybridized state in the product.

Nucleophilic Addition to the Carbonyl Group



Orbitals involved



While at the same time ....

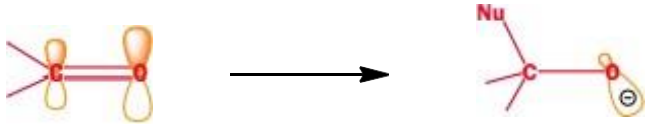
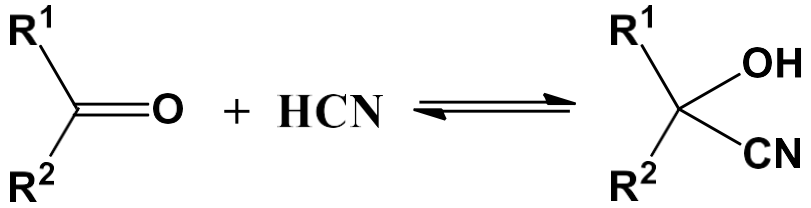


Figure 1: HOMO–LUMO interaction involved in the addition reaction

Cyanohydrins of Aldehydes and Ketones

- Aldehydes and ketones add on hydrogen cyanide to form cyanohydrins.



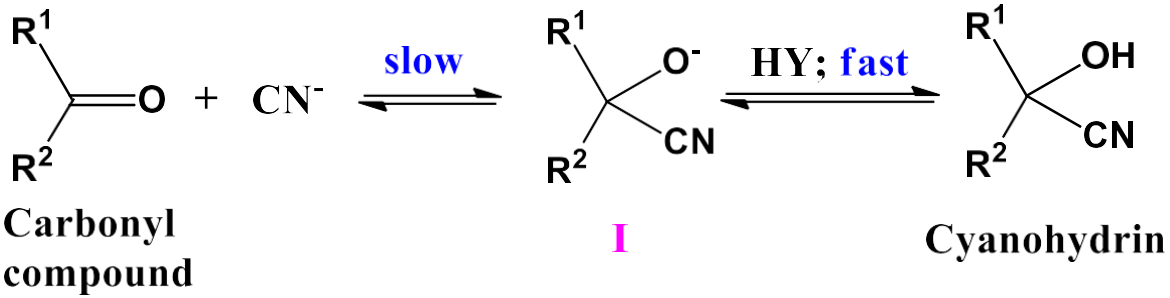
- HCN (**p*Ka*** = 9.21) is a weak acid, and produces lower concentration of cyanide ion on ionisation. The reaction is thus slow. Consequently, the reaction requires base-catalysis in order to convert HCN into the more nucleophilic cyanide ion (CN^-). The reaction obeys the following rate law:

$$\textbf{Rate} = k[R^1R^2C{=}O][CN^-]$$

- The addition of HCN to carbonyl compounds is accelerated by bases and retarded by acids. Therefore, cyanohydrin is formed when the carbonyl compound is treated with sodium cyanide and dilute HCl or H_2SO_4.

Cyanohydrins of Aldehydes and Ketones

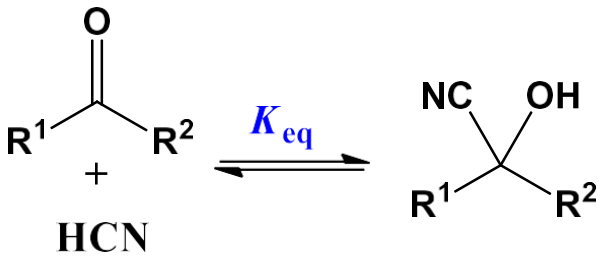
- The addition of CN^- is reversible, and tends to lie over in favour of the starting materials unless a proton donor is present: thus pulls the reaction over to the right as the equilibrium involving the cyanohydrin is more favourable than that involving the intermediate anion (I).



- Attack by cyanide ion is ***slow*** (rate-limiting), while proton transfer from HCN or a protic solvent, H_2O), is ***fas***t. The effect of the structure of the carbonyl compound on the position of equilibrium in cyanohydrin formation is shown in **Table 1**.

Cyanohydrins of Aldehydes and Ketones

Some equilibrium constants



aldehyde or ketone	K_{eq}
Acetaldehyde	too large
Benzaldehyde	210
p-Nitrobenzaldehyde	1430
p-Methoxybenzaldehyde	32
Ethyl methyl ketone	38
Acetophenone	0.77

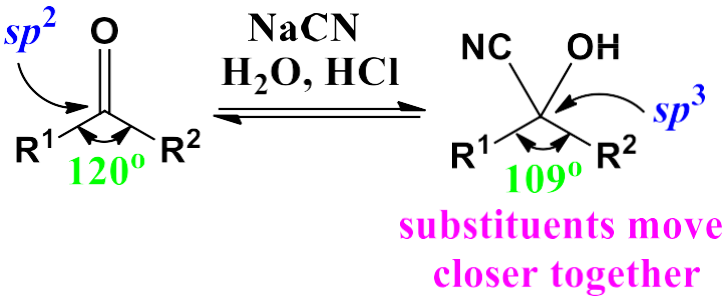
Table 1: Formation constants of cyanohydrins

- These data provide a measure of the "carbonyl character" of a particular carbonyl compound. The greater the cyanohydrin formation constant (K_{eq}), the more reactive is the carbonyl compound and the more carbonyl character it possesses. Thus, acetaldehyde is strongly carbonyl-like in character; benzaldehyde, ethyl methyl ketone, and acetophenone are somewhat less carbonyl-like.

Cyanohydrins of Aldehydes and Ketones

- Cyanohydrin formation is therefore an equilibrium between starting materials and products. The equilibrium is more favourable for aldehyde cyanohydrins than for ketone cyanohydrins, and the reason is the size of the groups attached to the carbonyl carbon atom.

- As the carbonyl carbon atom changes from ***sp*²** to ***sp*³**, its bond angles change from about 120° to about 109° - in other words, the substituents it carries move closer together.



- This reduction in bond angle is not a problem for aldehydes, because one of the substituents is a small hydrogen atom, but for ketones, especially ones that carry larger alkyl groups, this effect can disfavour the addition reaction.

Cyanohydrins of Aldehydes and Ketones

- The difference in equilibrium constant for acetaldehyde and ethyl methyl ketone, for example, is primarily due to steric influences. The ethyl group is very much more space filling than is a hydrogen atom, a bond forming collision between the carbonyl group and the cyanide ion requires more energy. This reduces the rate of the forward reaction.

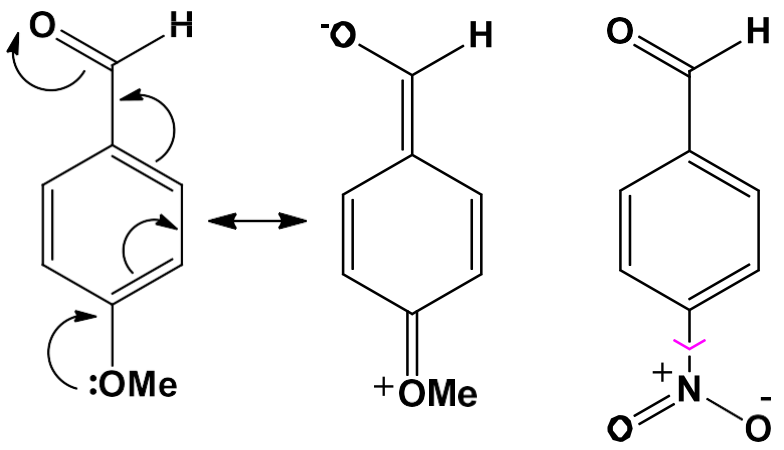
- The difference between ethyl methyl ketone and acetophenone, on the other hand, is only partly to be ascribed to steric factors and must also involve an electronic factor.

- Acetophenone carries a phenyl group attached to the carbonyl group, and this allows the electron deficiency at the carbonyl carbon to be delocalised into the aromatic ring. Therefore, the electron deficiency, hence electrophilic character at the carbonyl carbon reduces.

Cyanohydrins of Aldehydes and Ketones

- Changes in the ***para*** substituent can have little effect on the aldehyde group through steric interaction, but may have a strong influence via electronic transmission through the benzene ring. For instance, *p*-methoxybenzaldehyde (methoxyl group is electron-releasing via the resonance-electronic route; **+R > -I**) has a lower cyanohydrin formation constant than benzaldehyde.

- While *p*-nitrobenzaldehyde (nitro group is electron-withdrawing via the resonance-electronic route as well as via the inductive route; **-R and -I**) has a higher cyanohydrin formation constant.



- Similarly, highly hindered ketones, such as di-*t*-butyl ketone ($Me_3CCOCMe_3$), benzophenone, etc., do not react at all.

Cyanohydrins of Aldehydes and Ketones

- Cyanohydrin formation involves a carbonyl compound and sodium cyanide in the presence of an acid, which protonates the resulting alkoxide to give cyanohydrin. The mechanism (**Figure 2**) shows the reaction of a general aldehyde.

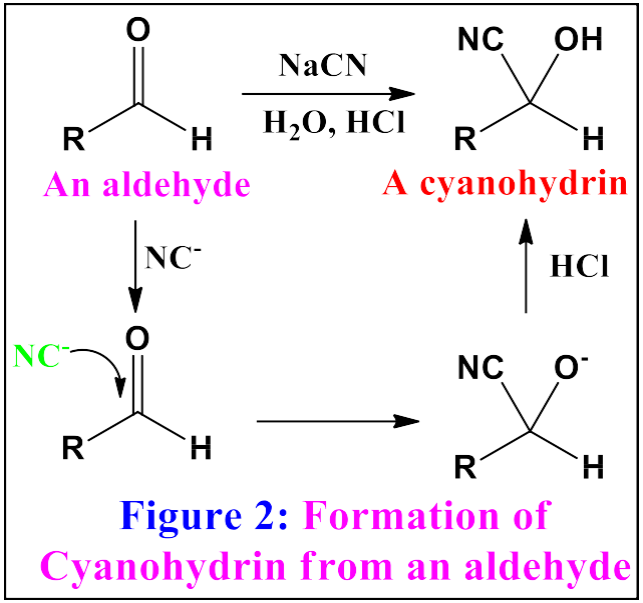


Figure 2: Formation of Cyanohydrin from an aldehyde

- Cyanohydrin formation is reversible, therefore on dissolving a cyanohydrin in water can give back the starting aldehyde or ketone, and aqueous base usually decomposes cyanohydrins completely to the starting carbonyl compound as shown in **Figure 3**. This occurs readily as cyanide is a good *leaving group*.

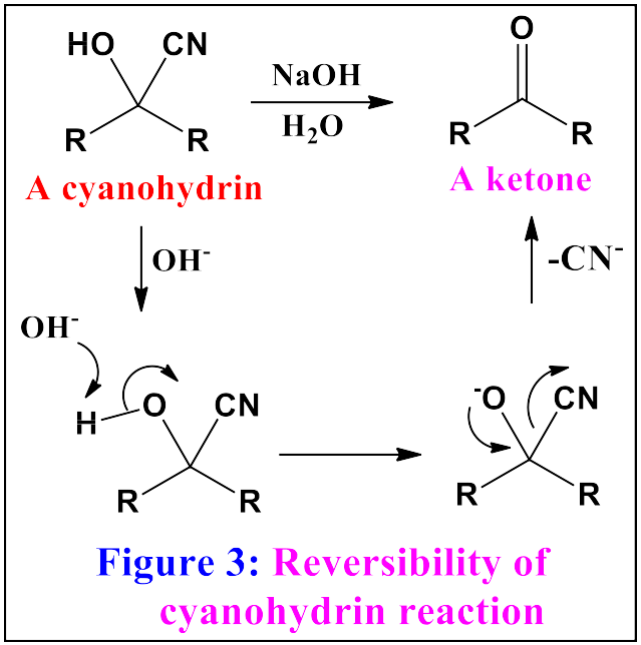


Figure 3: Reversibility of cyanohydrin reaction

Cyanohydrins of Aldehydes and Ketones

- Cyanide contains ***sp*** hybridized C and N atoms, and its ***HOMO*** is an ***sp*** orbital on carbon. The reaction is a typical nucleophilic addition reaction to a carbonyl group: the electron pair from the ***HOMO*** of the CN^- moves into the C=O ***π**** orbital (***LUMO*** of the electrophile); the electrons from the C=O ***π*** orbital move on to the oxygen atom. This interaction is shown in **Figure 4**.

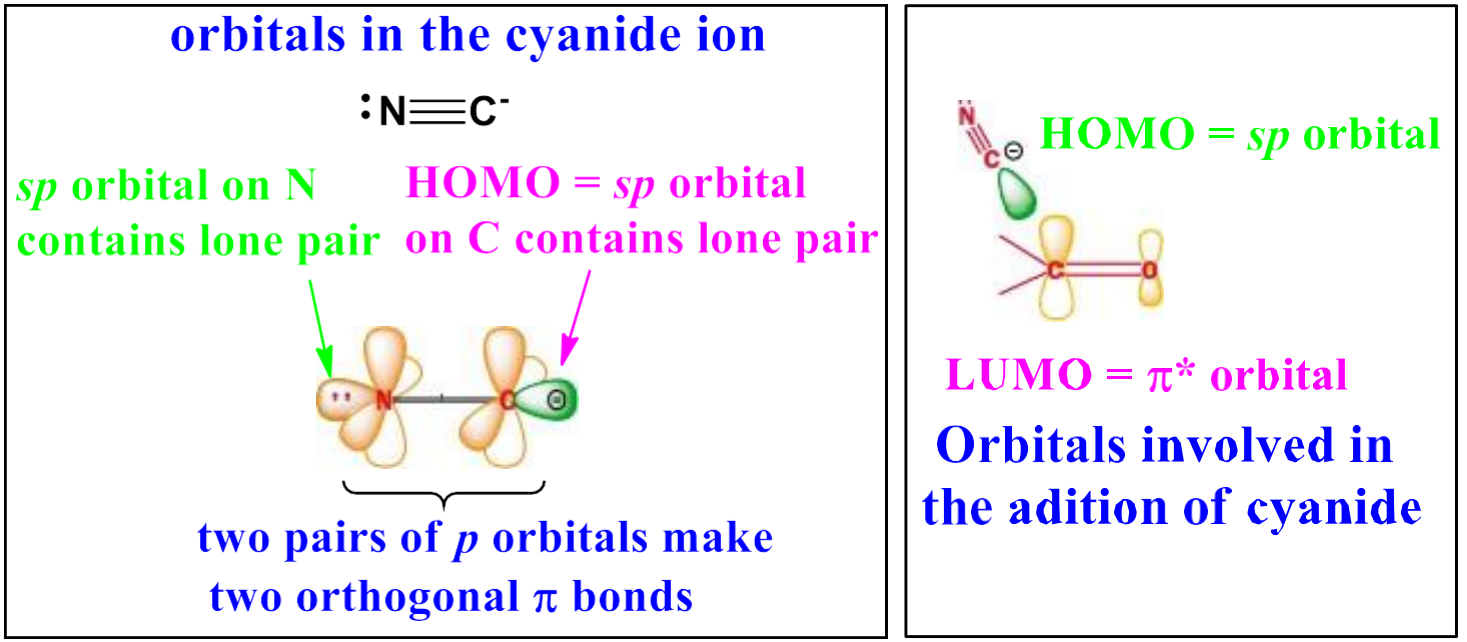


Figure 4: HOMO-LUMO interaction in nucleophilic addition to C=O

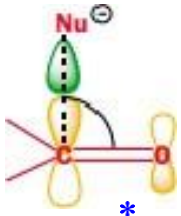
The Angle of Nucleophilic attack on Aldehydes and Ketones

- Not only do nucleophiles always attack carbonyl groups at carbon, but they also always approach from a particular angle. The nucleophiles attack not from a direction perpendicular to the plane of the carbonyl group but at about 107° to the C=O bond. This approach route is known as the **Bürgi-Dunitz trajectory**.

- The angle of attack can be thought as the result of a compromise between maximum orbital overlap of the ***HOMO*** of the nucleophile with π^* of C=O and minimum repulsion of the ***HOMO*** by the electron density in the carbonyl π bond.

- Any other portions of the molecule that get in the way of (or, that cause *steric hindrance* to) the **Bürgi-Dunitz trajectory** will greatly reduce the rate of addition and this is another reason why aldehydes are more reactive than ketones.

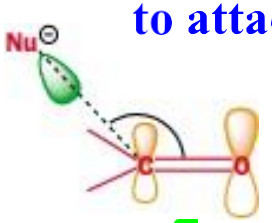
The Nucleophilic Approach: Bürgi-Dunitz Trajectory



π^*

maximum overlap with
π^* perpendicular
to C=O bond

repulsion from filled
π orbital forces nucleophile
to attack at obtuse angle



π

combined effect

nucleophile attacks
C=O at 107^o angle

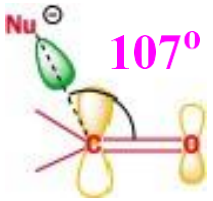


Figure 5: Approach of nucleophile to carbonyl carbon