ALKAYL CYANIDES (NITRILES) AND ISOCYANIDES

Parent compound of nitriles in hydrocyanic acid (HCN). It was isolated by Scheele in 1782 by the acid hydrolysis of a glycoside known as 'Amygdalin'. Hydrolysis of amygdalin produced benzaldehyde, glucose, and hydrocyanic acid, which is also known as Prussic acid.

$$\underset{\text{Amygdalin}}{C_{20}H_{27}O_{11}N} + 2H_2O \longrightarrow \underset{\text{Hydrocyanic acid}}{HCN} + \underset{\text{Benzaldehyde}}{C_6H_5CHO} + \underset{\text{Glucose}}{2C_6H_{12}O_6}$$

HCN is also formed when sodium cyanide is heated with concentrated sulphuric acid.

$$NaCN + H_2SO_4 \longrightarrow HCN + NaHSO_4$$

In industry, HCN is obtained from a mixture of ammonia, oxygen and methane. This mixture is passed over platinum-sodium catalyst at 1000°C.

$$2NH_3 + 3O_2 + 2CH_4 \longrightarrow 2HCN + 6H_2O$$

Properties and Reactions of HCN:

Hydrogen cyanide is a highly poisonous gas. It boils at 26°C and is soluble in water, alcohol and ether. It is a weak acid.

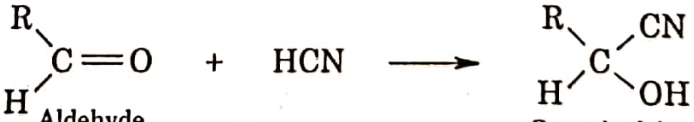
(i) HCN undergoes hydrolysis when warmed with dilute acid. Initial product is formamide, which gives ammonium formate as the final product.

$$HCN + H_2O \longrightarrow \underset{\text{Formanide}}{HCONH_2} \longrightarrow \underset{\text{Ammonium formate}}{HCOONH_4}$$

(ii) HCN forms methylamine when reduced with metallic zinc and concentrated hydrochloric acid.

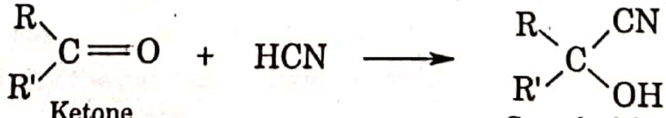
$$HCN \xrightarrow{Zn\,/\,HCl} \underset{\text{Methylamine}}{CH_3NH_2}$$

(iii) HCN forms cyanohydrin with carbonyl compounds in presence of small amount of alkali like NaOH or KOH.



Aldehyde

Cyanohydrin



Ketone

Cyanohydrin

HCN is largely used in the synthesis of organic compounds. Very dilute aqueous solution of HCN has medicinal application.

Nature and Reactions of Cyanide ION (CN^-):

Replacement of hydrogen atom from HCN by an alkyl or aryl group results in the formation of two classes of compounds. In nitriles, alkyl group is attached to the carbon atom of the CN part (R–CN) and in isocyanides, the group remains attached to the nitrogen atom (R–NC).

Alkyl nitriles are formed when an alkyl halide is treated with an aqueous solution of ionic cyanides like potassium or sodium cyanide.

Isocyanides are formed as predominant product when alkyl halides are treated with aqueous silver cyanide solution.

$$\text{R–X} + \text{KCN} \longrightarrow \text{R–CN (nitrile)}$$
$$\text{R–X} + \text{AgCN} \longrightarrow \text{R–NC (iscyanide)}$$

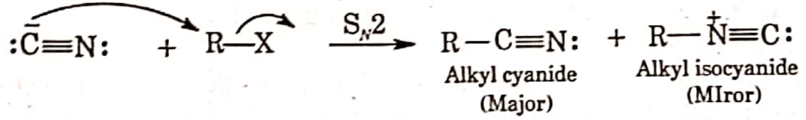
Formation of different compounds under different reaction conditions suggests that CN^- reacts in different manner when the reaction conditions are changed.

The Lewis structure of cyanide ion can be represented as "$:\bar{C}{\equiv}N:$" and in this form both carbon and nitrogen atoms bear lone pair of electrons.

Thus, CN^- anion can participate in a nucleophilic reaction either through its carbon atom or nitrogen atom. Such an anion in which there is more than one reactive centre is generally known as '*Ambident anion*'. In this case CN^- ion is an ambident nucleophile.

$$\underset{\text{I}}{:\bar{C}{\equiv}\ddot{N}} \longleftrightarrow \underset{\text{II}}{:C{=}\bar{N}:}$$

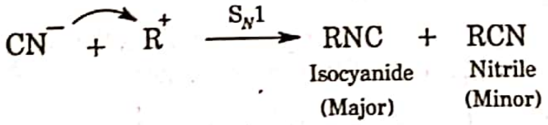
Of these two canonical forms, I is more contributing because it has greater number of covalent bonds. So far as *nucleophilicity* of the two ends are concerned, carbon-end is more nucleophilic because of larger size and lesser electronegativity of the carbon atom (see Chapter 3), compared to nitrogen. The lone pair of electrons on the carbon atom is more polarisable. Therefore, when CN^- reacts in a S_N2 type substitution then the carbon end takes part in the reaction to produce alkyl cyanide as the major compound.



$$:\bar{C}{\equiv}N: + R{-}X \xrightarrow{S_N2} \underset{\substack{\text{Alkyl cyanide}\\ \text{(Major)}}}{R{-}C{\equiv}N:} + \underset{\substack{\text{Alkyl isocyanide}\\ \text{(MIror)}}}{R{-}\overset{+}{N}{\equiv}C:}$$

When reaction of alkyl halide is carried out with AgCN, then Ag^+ ion acts as Lewis acid to react with alkyl halide to form a carbocation (R^+). This carbocation then reacts with nitrogen end of the CN^- to form isocyanide as the major product. The reaction is S_N1 substitution. In S_N1 substitution, an ambident nucleophile reacts more effectively with its less polarisable but more electron rich end.

$$\text{RX} + \text{AgCN} \longrightarrow \overset{+}{R} + CN^- + \text{AgX}\downarrow$$



$$CN^- + \overset{+}{R} \xrightarrow{S_N1} \underset{\substack{\text{Isocyanide}\\ \text{(Major)}}}{\text{RNC}} + \underset{\substack{\text{Nitrile}\\ \text{(Minor)}}}{\text{RCN}}$$

ALKYL CYANIDES OR NITRILES

Alkyl cyanides are also known as carbonitriles. They are represented by the general formula $C_nH_{2n+1}CN$, n = number of carbon atoms.

Nomenclature:

These are usually named as derivatives of HCN.

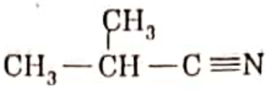
$H{-}C{\equiv}N$	$CH_3{-}C{\equiv}N$	$CH_3{-}CH_2{-}C{\equiv}N$
Hydrogen cyanide	Methyl cyanide	Ethyl cyanide

When these are named as nitriles, the names of the acids, which are formed as hydrolysed products, are taken as the root names. 'ic' part of the name of the acid is replaced by 'onitrile'.

$CH_3{-}C{\equiv}N$

Acetonitirle

(Hydrolysed product is acetic acid)



$CH_3{-}\overset{CH_3}{\overset{|}{C}H}{-}C{\equiv}N$

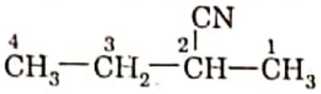
Isobutyronitrile

(Hydrolysed product is isobutyric acid)

According to IUPAC system, name of the corresponding hydrocarbon is taken as the root name. Carbon atom of CN group is included in deciding the name of the hydrocarbon. The name ends with the word 'nitrile'. There should not be any space between the name of the alkane and the word 'nitrile' (see Chapter 1)

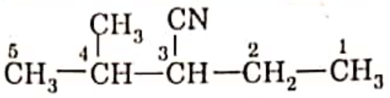
CH_3CN	CH_3CH_2CN	$CH_3CH_2CH_2CN$
Ethanenitrile	Propanenitrile	Butanenitrile

When the –CN group is considered as prefix, then it is called 'cyano' group.



$\overset{4}{C}H_3{-}\overset{3}{C}H_2{-}\overset{CN}{\overset{2|}{C}H}{-}\overset{1}{C}H_3$

2-cyanobutane



$\overset{5}{C}H_3{-}\overset{CH_3}{\overset{4|}{C}H}{-}\overset{CN}{\overset{3|}{C}H}{-}\overset{2}{C}H_2{-}\overset{1}{C}H_3$

3-cyano-2-methylpentane

GENERAL METHODS OF PREPARATION

(1) From alkyl halides:

Alkyl halides form nitriles when warmed with an ethanolic-aqueous solution of potassium cyanide or sodium cyanide.

$$R{-}X + KCN \longrightarrow R{-}CN + KCl$$

$$\underset{\text{Methyl chloride}}{CH_3Cl} + KCN \longrightarrow \underset{\text{Methyl cyanide (Ethanenitrile)}}{CH_3CN} + KCl$$

$CH_3{-}\overset{CH_3}{\overset{|}{C}H}{-}Cl + NaCN \longrightarrow CH_3{-}\overset{CH_3}{\overset{|}{C}H}{-}CN + NaCl$

Isopropyl chloride Isopropyl cyanide (Propane-2-nitrile)

Tertiary cyanides cannot be prepared by this method because tertiary halides readily decompose into alkenes and hydrogen halides when subjected to heat.

(2) From Amides and Aldoximes:

When amides and aldoximes are heated with phosphorus pentoxide or acetic anhydride, alkyl cyanides are formed by the loss of a molecule of water.

$$\underset{\text{Acetamide}}{CH_3CH_2CONH_2} \longrightarrow \underset{\text{Ethyl cyanide}}{CH_3CH_2CN} + H_2O$$

$$\underset{\text{Acetaldehydeoxime}}{CH_3CH{=}NOH} \longrightarrow \underset{\text{Methyl cyanide}}{CH_3CN} + H_2O$$

Amides of high molecular weights form cyanides and water when simply heated.

(3) From Grignard reagents:

Grignard reagents and cyanogen chloride react to form alkyl cyanides. This is one of the most important methods for the preparation of tertiary cyanides.

$$\underset{\text{t-Butyl magnesium bromide}}{(CH_3)_3C{-}MgBr} + Cl{-}CN \longrightarrow \underset{\text{t-butyl cyanide}}{(CH_3)_3C{-}CN} + MgBrCl$$

Properties:

Alkyl cyanides are stable and neutral compounds. They are sweet-smelling and non-poisonous. Lower members are liquid under normal conditions and are soluble in water due to the formation of hydrogen bonds with water molecules.

Alkyl cyanides cannot become associated due to its inability to form intermolecular hydrogen bonds. Due to this reason, alkyl cyanides are more volatile than carboxylic acids of similar molecular weights. For example, formic acid (mol. wt. 46) boils at 100.5°C while methyl cyanide (mol. wt. 41) boils at 82°C.

On the other hand, alkyl cyanides are high-boiling than that of alcohols of similar molecular weights. This may be due to greater polar character of alkyl cyanide molecules. Electrostatic forces of attraction between molecules of alkyl cyanides are greater than that in alcohol molecules. Thus CH_3CH_2OH (mol. wt. 46) boils at 78.2ºC while CH_3CN (mol. wt. 41) boils at 82ºC.

Reactions:

(1) Hydrolysis:

Alkyl cyanides can be hydrolysed by both dilute acid and dilute alkali. The final product is a carboxylic acid. Amide has been isolated as an intermediate compound.

$$R{-}C\equiv N \xrightarrow{HCl} R{-}COOH\ ; \qquad RC\equiv N \xrightarrow{NaOH} R{-}COONa$$

$$\underset{\text{Methyl cyanide}}{CH_3{-}C\equiv N} + H_2O \xrightarrow{HCl} \underset{\text{Acetamide}}{[CH_3CONH_2]} \longrightarrow \underset{\text{Acetic acid}}{CH_3COOH} + NH_4^+\text{ salt}$$

$$\underset{\text{Ethyl cyanide}}{CH_3{-}CH_2{-}C\equiv N} + H_2O \xrightarrow{NaOH} \underset{\text{Propoinamide}}{[CH_3CH_2CONH_2]} \longrightarrow \underset{\text{Sodium propionate}}{CH_3CH_2COONa} + NH_3$$

Acid, RCOOH reacts immediately with the alkali to form the corresponding sodium or potassium salt (as the case may be) and remain in the aqueous medium. Acidification of the aqueous solution liberates the free acid.

(2) Reaction with alcohols:

Alkyl cyanides react with alcohol to forms esters. For example, when an alcoholic solution of methyl cyanide is warmed with concentrated sulphuric or hydrochloric acid, ethyl acetate is formed.

$$\underset{\text{Methyl cyanide}}{CH_3CN} + C_2H_5OH + H_2O \longrightarrow \underset{\text{Ethyl acetate}}{CH_3COOC_2H_5} + NH_4^+\text{ salt}$$

(3) Reduction:

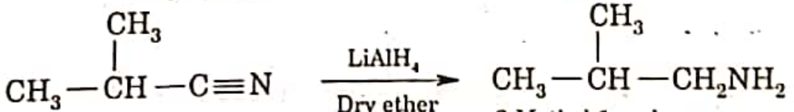
(i) When alkyl cyanides are reduced with stannous chloride and concentrated hydrochloric acid, aldehydes are formed. The reaction is known as Stephen's reaction (see Chapter 10).

$$\underset{\text{Methyl cyanide}}{CH_3{-}C\equiv N} \xrightarrow{SnCl_2\,/\,\text{conc. HCl}} \underset{\text{Aldimine stannichloride}}{[CH_3{-}CH{=}NH]_2^+\,SnCl_6^{2-}} \xrightarrow{H_2O} \underset{\text{Acetaldehyde}}{CH_3{-}CHO}$$

(ii) Alkyl cyanides give the corresponding primary amines when reduced with sodium/alcohol, lithium aluminium hydride or hydrogen in presence of nickel.

$$\underset{\text{cyanide}}{R{-}C\equiv N} \longrightarrow \underset{\text{Amine}}{R{-}CH_2NH_2}$$

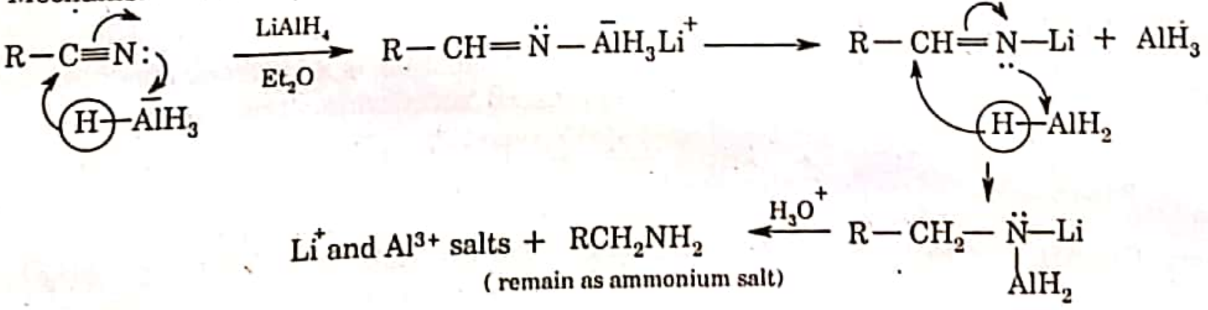
$$\underset{\text{Methyl cyanide}}{CH_3{-}C\equiv N} \longrightarrow \underset{\text{Ethylamine}}{CH_3{-}CH_2{-}NH_2}$$



$$\underset{\text{Isopropyl cyanide}}{CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{C}H}{-}C\equiv N} \xrightarrow[\text{Dry ether}]{LiAlH_4} \underset{\text{3-Methyl-1-amino propane}}{CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{C}H}{-}CH_2NH_2}$$

(IUPAC. 3-Methylpropanenitrile)

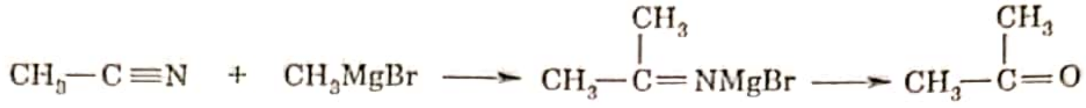
Mechanism of $LiAlH_4$ reduction of alkyl cyanide to a primary amine can be shown as follows.



It is to be noted that hydrolysis and reduction products of alkyl cyanides prove that -CN group in alkyl cyanides is linked to the alkyl group through the carbon atom and not through the nitrogen atom.

(4) Reaction with Grignard reagents:

Alkyl cyanides react with Grignard reagents to form ketones.

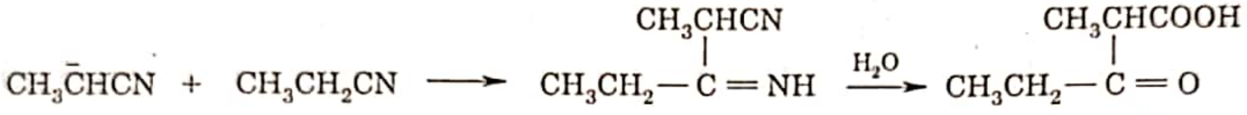


$$\underset{\text{Alkyl cyanide}}{CH_3-C\equiv N} + \underset{\text{Grignard reagent}}{CH_3MgBr} \longrightarrow \underset{\text{Addition compound}}{CH_3-\overset{\overset{CH_3}{|}}{C}=NMgBr} \longrightarrow \underset{\text{Ketone}}{CH_3-\overset{\overset{CH_3}{|}}{C}=O}$$

(5) Condensation reactions:

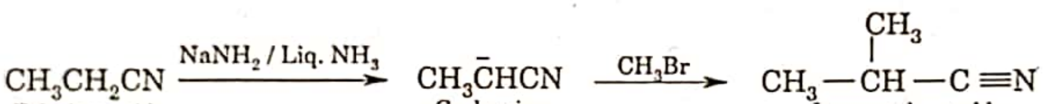
Alkyl cyanides containing α-H atoms undergo aldol-type condensation reactions. Due to –I effect of –CN group, and hyperconjugative resonance, α-H atoms of alkyl cyanides are considerably acidic and can be easily taken up by a strong base or highly electropositive metals like sodium and potassium and a carbanion is generated. This anion then reacts with another molecule of alkyl cyanide to form condensation product. The condensation product on hydrolysis produces a β-keto acid

$$CH_3CH_2CN \xrightarrow{Na\ /\ Ether} \underset{\text{Carbanion}}{CH_3\overset{-}{C}HCN}$$



$$CH_3\overset{-}{C}HCN + CH_3CH_2CN \longrightarrow \underset{\text{Condensation product}}{CH_3CH_2-\overset{\overset{CH_3CHCN}{|}}{C}=NH} \xrightarrow{H_2O} \underset{\beta\text{-Keto acid}}{CH_3CH_2-\overset{\overset{CH_3CHCOOH}{|}}{C}=O}$$

Carbanion from alkyl cyanides can also function as a good nucleophile and reacts with alkyl halides to form substituted products.



$$\underset{\text{Ethyl cyanide}}{CH_3CH_2CN} \xrightarrow{NaNH_2\ /\ Liq.\ NH_3} \underset{\text{Carbanion}}{CH_3\overset{-}{C}HCN} \xrightarrow{CH_3Br} \underset{\text{Isopropyl cyanide}}{CH_3-\overset{\overset{CH_3}{|}}{CH}-C\equiv N}$$

ALKYL ISOCYANIDES

Alkyl isocyanides are also called carbylamines. These are isomeric to alkyl cyanides and their general formula is $C_nH_{2n+1}NC$, where n=number of carbon atoms.

GENERAL METHODS OF PREPARATION:

(1) From alkyl halides:

Alkyl halides give alkyl isocyanides when warmed with aqueous-ethanolic silver cyanide (AgCN) solution. The term 'isonitrile' cannot be used because it is not an accepted IUPAC name.

$$RX + AgCN \longrightarrow RNC + AgX$$

$$\underset{\text{Methyl iodide}}{CH_3I} + AgCN \longrightarrow \underset{\text{Methyl isocyanide}}{CH_3NC} + AgI$$

$$\underset{\text{Ethyl bromide}}{CH_3CH_2Br} + AgCN \longrightarrow \underset{\text{Ethyl isocyanide}}{CH_3CH_2NC} + AgBr$$

(2) From primary amines:

Primary amines give isocyanides when reacted with chloroform and strong alkali like sodium hydroxide or potassium hydroxide. The reaction is called '*carbylamine* 'reaction.

$$\underset{\text{Primary amine}}{RNH_2} + CHCl_3 + 3KOH \longrightarrow \underset{\text{Alkyl isocyanide}}{R-\overset{+}{N}\equiv\overset{-}{C}:} + 3KCl + 3H_2O$$

$$CH_3NH_2 + CHCl_3 + 3KOH \longrightarrow \underset{\text{Methyl isocyanide}}{CH_3-\overset{+}{N}\equiv\overset{-}{C}:} + 3KCl + 3H_2O$$

Properties:

Isocyanides of low molecular weights are poisonous liquids with a obnoxious smell. They are low boiling compared to the isomeric alkyl cyanides. Alkyl isocyanides are insoluble in water because hydrogen bonds with water molecules are not possible due to the absence of lone pair of electrons on nitrogen.

The functional group –NC is actually $-\overset{+}{N}\equiv\overset{-}{C}:$ a lone pair of electrons of nitrogen has been donated to carbon to form a co-ordinate covalence. Carbon atom contains a pair of electrons and that is why alkyl isocyanides can take part in many reactions as a strong reducing agent.

Reactions:

(1) Hydrolysis:

Alkyl isocyanides can be hydrolysed by dilute acids only. Hydrolysed products are primary amine and formic acid. Dlute alkali has no action on alkyl isocyanides.

$$R\text{–}N^+\equiv C^- \xrightarrow{\text{dil. HCl}} R\text{–}NH_2 + HCOOH$$

$$\underset{\text{Methyl isocyanide}}{CH_3\text{–}N^+\equiv C^-} \xrightarrow{\text{dil. HCl}} \underset{\text{Methylamine}}{CH_3\text{–}NH_2} + HCOOH$$

(2) Reducing character:

Alkyl isocyanides are strong reducing agents. They can reduce mercuric oxide into elemental mercury. Isocyanides are oxidised to isocyanates.

$$\underset{\text{Methyl isocyanide}}{CH_3\text{–}N^+\equiv C^-:} + HgO \longrightarrow \underset{\text{Methyl isocyanate}}{CH_3\text{–}N=C=O} + Hg$$

Alkyl isocyanides combine directly with elemental sulphur to form isothiocyanates.

$$\underset{\text{Methyl isocyanide}}{CH_3\text{–}N^+\equiv C^-:} + S \longrightarrow \underset{\text{Methyl isothiocyanate}}{CH_3\text{–}N=C=S}$$

(3) Rearrangement reaction:

On prolonged heating alkyl isocyanides rearrange to alkyl cyanides.

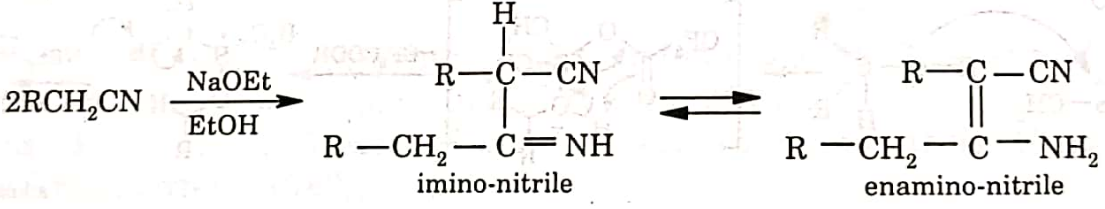
$$\underset{\text{Methyl isocyanide}}{CH_3\text{–}N^+\equiv C^-:} \longrightarrow \underset{\text{Methyl cyanide}}{CH_3\text{–}C\equiv N:}$$

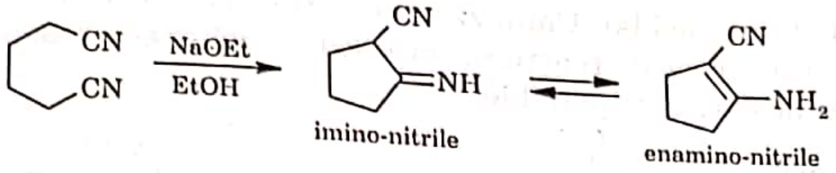
Difference between Alkyl cyanides and Alkyl isocyanide:

Alkyl cyanide	Alkyl isocyanide
(i) Structure is RCN	(i) Structure is RNC
(ii) Undergoes hydrolysis by both dilute acids. $RC\equiv N + 2H_2O \rightarrow RCOOH + NH_3$	(ii) Undergoes hydrolysis by acids only to form primary amine and formic acid. $RN\equiv C + 2H_2O \rightarrow RNH_2 + HCOOH$
(iii) Can be reduced to primary amine by hydrogen and metals like Ni, Pt.	(iii) Can be reduced by hydrogen in presence of Ni, Pt to produce a secondary amine with one CH_3 group with nitrogen. $RNC + 4[H] \rightarrow RNHCH_3$
(iv) Have no reducing properties.	(iv) Have strong reducing properties, reduces. Reduces mercuric oxide to metallic mercury. $RN\equiv C + HgO \rightarrow RNCO + Hg$.
(v) Soluble in water due to the formation of hydrogen bonds with water molecules.	(v) Insoluble in water due to inability to form hydrogen bonds with water molecules.
(vi) Usually sweet smelling and are not very poisonous.	(vi) Have obnoxious smell and are poisonous.

THORPE-ZIEGLER REACTION

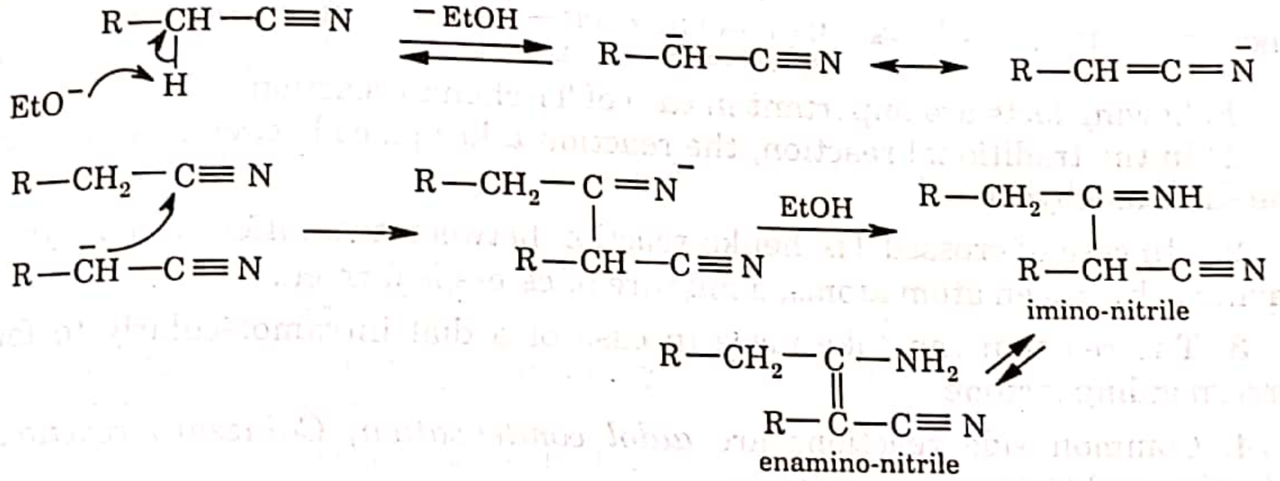
Nitrile molecules having α-hydrogen atoms undergo base catalysed aldol type condensation to form imino-nitrile. This reaction reaction can be carried out intramolecularly as well as intermoleculary. The reaction as a whole is called Thrope-Ziegler reaction.



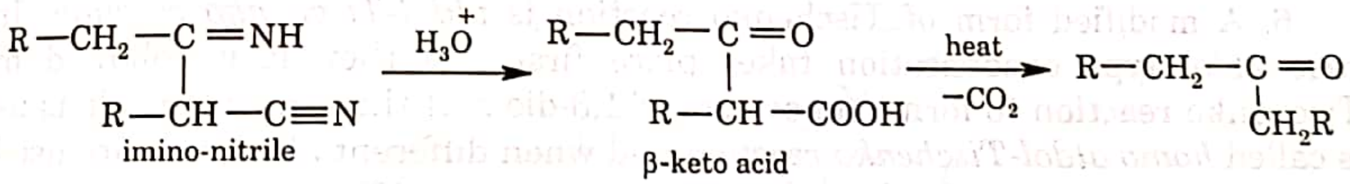


Mechanism:

The mechanism of Thorpe-Zeigler reaction is analogous to base catalysed aldol condensation. α-Hydrogen atoms of a nitrile are acidic and can be abstracted by a strong base to generate a carbanion, which is resonance stabilized. The carbanion, as a good nucleophile attacks the elctrophilic carbon of the –CN group. A condensation product is formed, called imino-nitrile which tautomerises to enamino-nitrile.



It is to be noted here that imino-nitrile can be hydrolysed to a β-keto acid. Subsequent decarboxylation produces a carbonyl compound.



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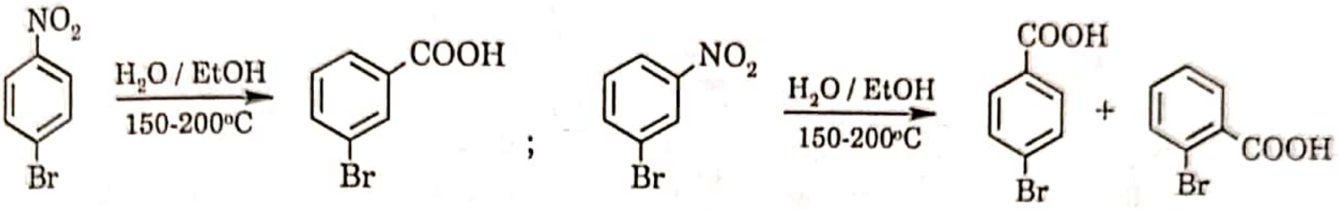
2. Zeigler, K. *Ann.* **1933**, 94, 504.
3. Schefer, J. P., Bloomfield, J. J. *Org. React.* **1967**, 15, 1 (Review)

von RICHTER REARRANGEMENT

When *meta*- and *para*-nitrohalobenzenes are treated with aqueous–alcoholic potassium cyanide solution above 150 °C then loss of nitro group takes place along with the introduction of a carboxylic group ortho to the departing nitro group. This reaction is called von Richter reaction.



Following facts are to be noted in case of von Richter reaction.

1. The reaction is usually carried out with *meta*- and *para*-nitrohalobenzenes. *Ortho*-nitrohalobenzenes are relactant to react, perhaps due to steric hindrance during the reaction steps.

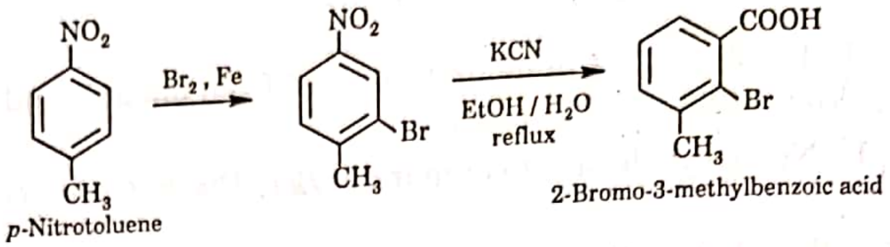
2. The position taken by the incoming -COOH group is not the same as that vacated by the -NO$_2$ group but take a position *ortho*- to the original position of the nitro group in the substrate molecule.

3. Reactions can also be done without halogen substituents and also with alkyl substituted nitrobenzenes like *m*-nitrotoluene and *p*-nitrotoluene.

5. The reaction with *para*-hologenated nitrobenzene give *meta*-halogenated benzoic acid and *meta*-halogenated nitobenzenes give a mixture of *o*-halogenated benzoic acid and *p*-nitrobenzoic acid.

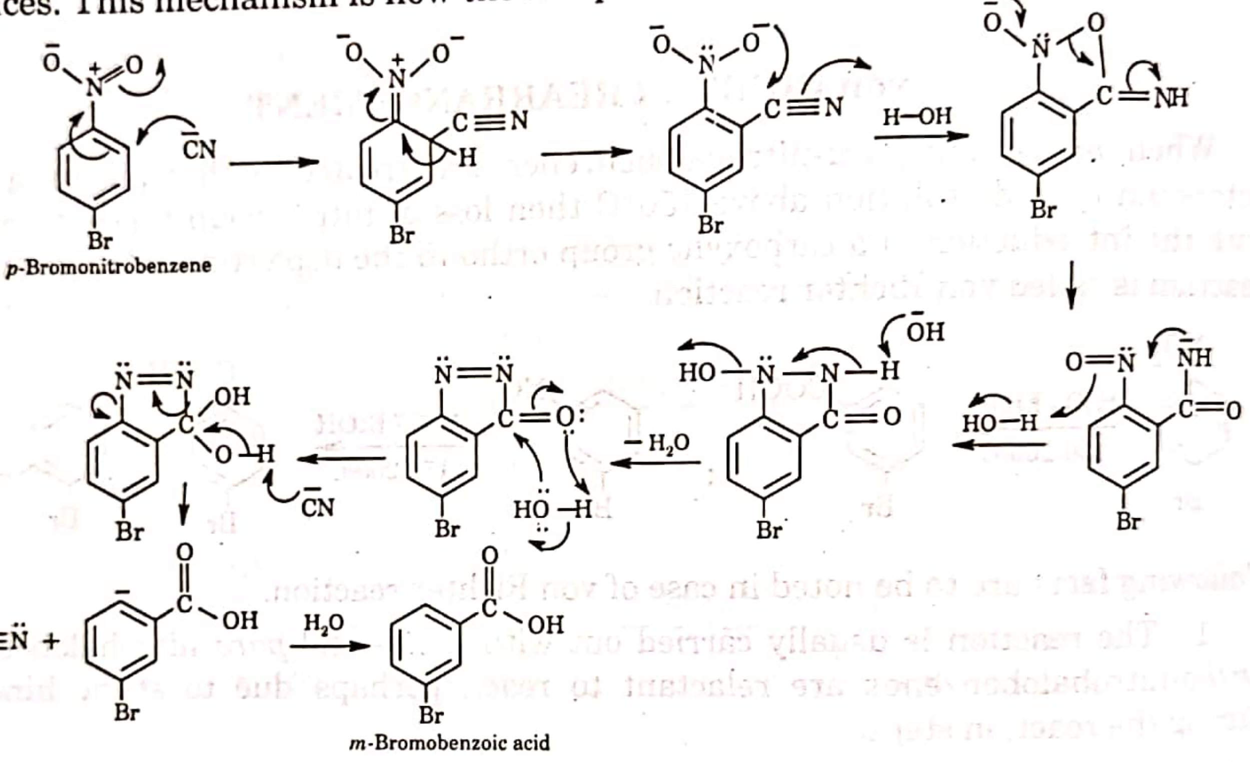
6. The reaction is usually carried out at an elevated temperature around 125 - 150°C.

7. von Richter reaction can be used to prepare certain substituted benzoic acids which are otherwise very difficult to prepare by normal aromatic substitution reactions. For example, *meta*-toluic acid, which is otherwise difficult to prepare, can be easily prepared from *p*-toluidine by von-Richter reaction. An example is the synthesis of 2-bromo-3-methylbenzoic acid from *p*-nitrotoluene.



Mechanism:

Several mechanisms were proposed for von-Richter reaction but the presently accepted mechanism was proposed by Rosenblum in 1960 based on definite chemical evidences. This mechanism is now the accepted one. Mechanism is given below.



In the proposed mechanism of Rosenbulm, one of the end products is molecular nitrogen. This has been detected as reaction product. Again when the $-NO_2$ group in nitrobenzene or halogen substituted nitrobenzene is labelled with ^{15}N, then the nitrogen obtained as product contains both ^{15}N and ^{14}N. This indicates that one of the nitrogens in N_2 molecule must have come from the nitro group, and the other from the cyano group in KCN. This corroborates the above mechanism.

References: