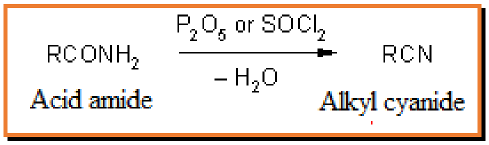
Alkyl Nitrile and Alkyl Isonitrile

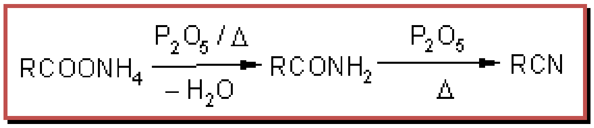
❖ Preparation

1. From acid amides:

Alkyl or aryl cyanides may be prepared by dehydration of acid amide using phosphorus pentoxide (P_2O_5) or thionylchloride ($SOCl_2$)

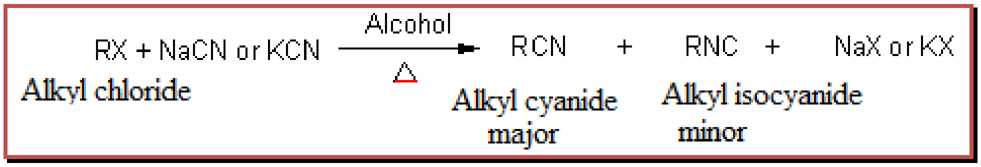


In the above reaction, you may also use ammonium salts of carboxylic acids $RCOONH_4$ in place of amides.



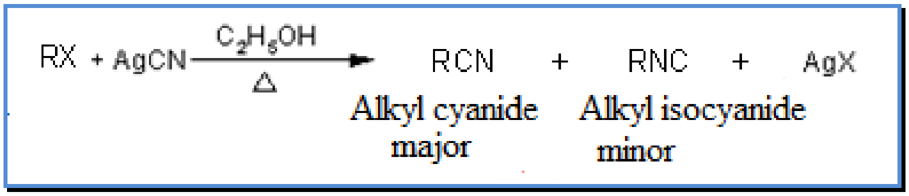
The major advantage of this method is that pure cyanide is obtained without any contamination with isocyanide.

2. From alkyl halides:



The cyanide ion (- C ≡ N :) is ambident in nature; has an unshared pair of electrons on both carbon as well as nitrogen. Hence the alkyl group may attach either through carbon or through nitrogen giving cyanides or isocyanides respectively. When NaCN or KCN is used then substitution reaction takes place through S_N2 pathway and gives alkyl cyanide as major product.

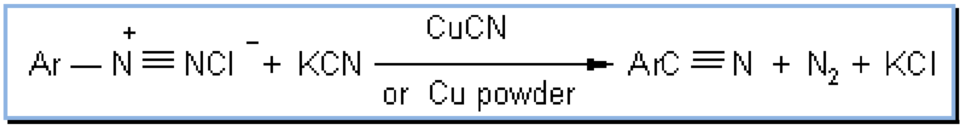
But alkyl isocyanides are the major product when silver cyanide is used in place of NaCN or KCN.



The above method cannot be used for aryl cyanides or aryl isocyanides as aryl halides do not easily undergo nucleophilic substitution reactions.

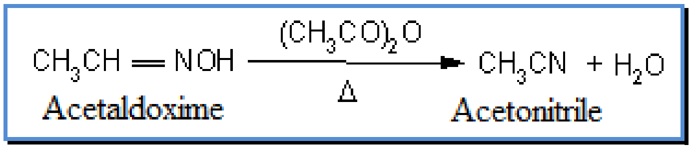
3. From aromatic diazonium salts:

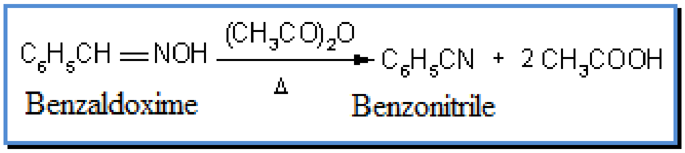
Aryl diazonium salts react with a mixture of copper (I) cyanide or copper powder and sodium or potassium cyanide to give aryl cyanides with loss of nitrogen. The above reaction is a special case of Sandmeyer or Gattermann reaction. Alkane diazonium salts being very unstable even at low temperature, this method cannot be used for the preparation of alkyl cyanides.



4. From aldoximes:

Dehydration of aldoximes with phosphorus pentoxide (P_2O_5) or acetic anhydride gives alkyl or aryl cyanide.





5. Using Grignard reagents:

Cyanogen chloide can be treated with Grignard reagent to give alkyl cyanides. Tertiary alkyl cyanides can be prepared easily by this method.

$$\boxed{RMgX + CNCl \xrightarrow[\text{ether}]{\text{Dry}} RCN + MgXCl}$$

$$\boxed{CH_3MgBr + Cl-CN \xrightarrow[\text{ether}]{\text{Dry}} CH_3CN + MgBrCl}$$

6. From primary amines:

The carbylamine reaction can be used to prepare alkyl and aryl isocyanides. A mixture of primary amine can be heated with chloroform and alcoholic potassium hydroxide solution.

$$\boxed{RNH_2 + CHCl_3 + 3\,KOH\,(alc) \xrightarrow{\Delta} RN \equiv C + 3\,KCl + 3\,H_2O}$$

$$\boxed{C_6H_5NH_2 + CHCl_3 + 3\,KOH\,(alc) \xrightarrow{\Delta} C_6H_5N \equiv C + 3\,KCl + 3H_2O}$$

A major disadvantage of this method is that it cannot be used to prepare alkyl cyanides.

❖ Reaction

A. Hydrolysis of cyanide:

Cyanides are easily hydrolyzed under acidic as well as basic conditions to give acid amides. Acid amides undergo further hydrolysis to carboxylic acids and ammonia. Using mild conditions, the reaction can be stopped at the amide stage.

Under acidic condition:

$$\boxed{RCN + H_2O \xrightarrow{H^+} RCONH_2}$$

$$\boxed{RCONH_2 + H_2O \xrightarrow{H^+} RCOOH + NH_3}$$

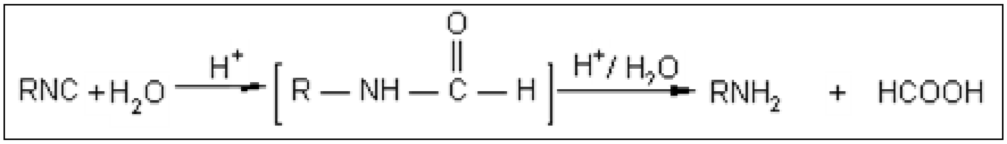
Under basic condition:

$$\boxed{RCN + H_2O \xrightarrow{OH^-} RCONH_2}$$

$$RCONH_2 \xrightarrow{OH^-} RCOONa + NH_3$$

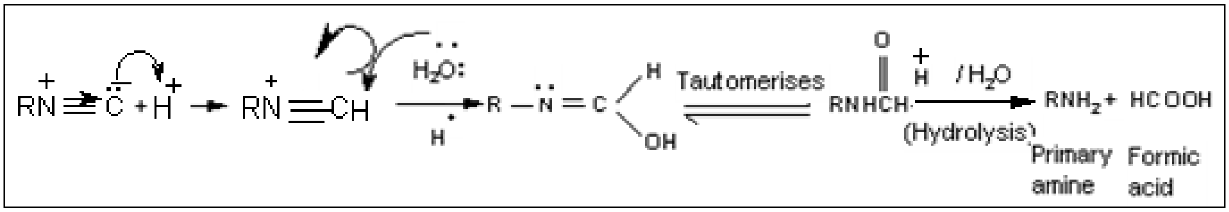
B. Hydrolysis of isocyanide:

Isocyanides are hydrolyzed by dilute mineral acids to give primary amine and formic acid. Isocyanides are not hydrolyzed by base. Because the negative charge present on carbon atom in isocyanides initially attracts electrophiles (H^+) but repels nucleophiles (OH^-). When a proton gets attracted to negatively charged carbon atom, the tendency of this carbon atom to attract a nucleophile increases due to presence of positive charge on the N atom and hydrolysis is facilitated as shown below.



$$RNC + H_2O \xrightarrow{H^+} \left[R - NH - \overset{\overset{O}{\|}}{C} - H \right] \xrightarrow{H^+/H_2O} RNH_2 + HCOOH$$

Mechanism:



C. Reduction (Complete reduction and Partial reduction)

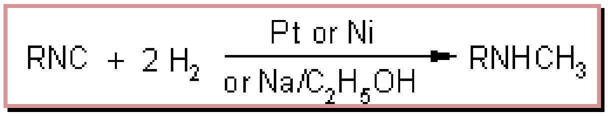
Complete Reduction of cyanide:

Alkyl cyanides can be completely reduced either catalytically by hydrogen or chemically by lithium aluminium hydride to give the corresponding primary amine.

$$RCN + 2H_2 \xrightarrow{\text{Pt or Ni}} RCH_2NH_2$$

Complete Reduction of isocyanide:

Isocyanides on reduction give N- methyl amines i.e. secondary amine.

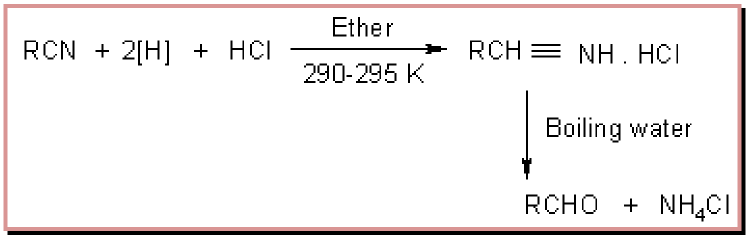


$$RNC + 2H_2 \xrightarrow[\text{or } Na/C_2H_5OH]{\text{Pt or Ni}} RNHCH_3$$

Partial reduction:

On reducing the solution of a nitrile in ether with hydrogen chloride gas and stannous chloride at room temperature, a precipitate of amine hydrochloride is formed which on hydrolysis with boiling water gives aldehydes.

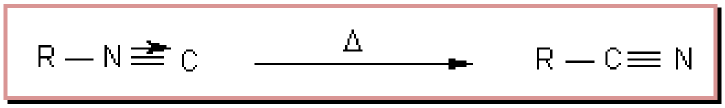
$$SnCl_2 + 2HCl \longrightarrow SnCl_4 + 2[H]$$



$$RCN + 2[H] + HCl \xrightarrow[\text{290-295 K}]{\text{Ether}} RCH{\equiv}NH\,.\,HCl \xrightarrow{\text{Boiling water}} RCHO + NH_4Cl$$

D. Isomerisation:

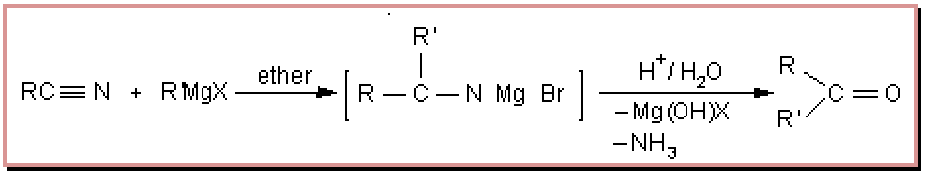
Cyanides are formed by rearrangement of isocyanides by heating them for a long time.



$$R-N\equiv C \xrightarrow{\Delta} R-C\equiv N$$

E. Reaction with Grignard reagent:

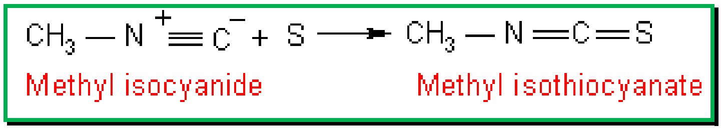
Grignard reagent reacts with nitriles to give ketones



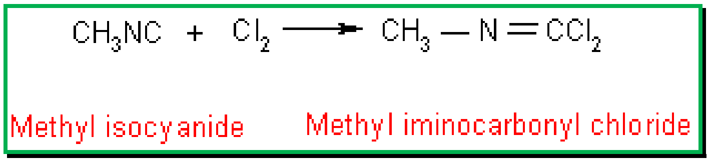
$$RC\equiv N + R'MgX \xrightarrow{\text{ether}} \left[R-\overset{R'}{\overset{|}{C}}-N\ Mg\ Br\right] \xrightarrow[\substack{-Mg(OH)X \\ -NH_3}]{H^+/H_2O} \begin{matrix}R \\ R'\end{matrix}\!\!>C=O$$

F. Addition reactions:

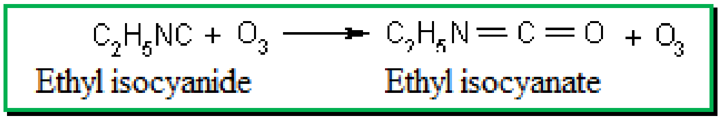
Addition products are formally reaction of isocyanides with sulphur, halogens, ozone, etc. cyanides do not undergo these reaction



$$CH_3-\overset{+}{N}\equiv\overset{-}{C} + S \longrightarrow CH_3-N=C=S$$

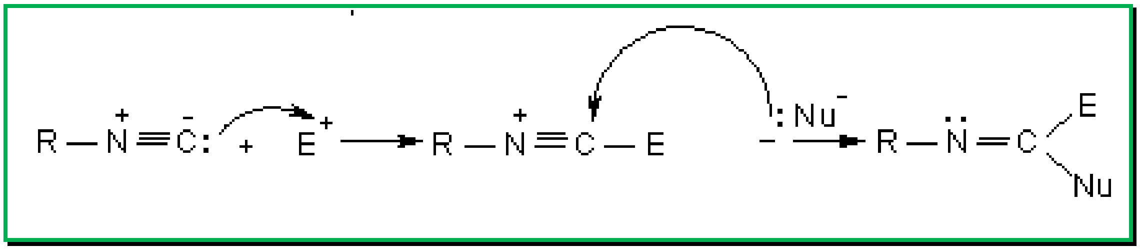


$$CH_3NC + Cl_2 \longrightarrow CH_3-N=CCl_2$$



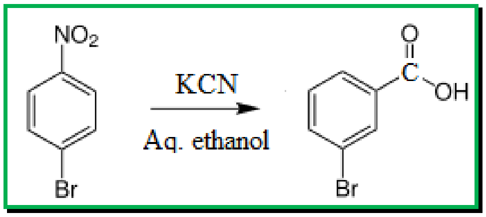
$$C_2H_5NC + O_3 \longrightarrow C_2H_5N=C=O + O_3$$

In usual addition reactions, the electronhile and nucleophile add to two different atoms of the unsaturated system but in isocyanides, the mechanism of addition reactions is different as electrophile and nucleophile add to the same carbon atom. The negative charge on carbon atom accepts an electrophile to form species in which the positive charge on nitrogen atom gets neutralised by the addition of the nucleophile to the carbon atom.

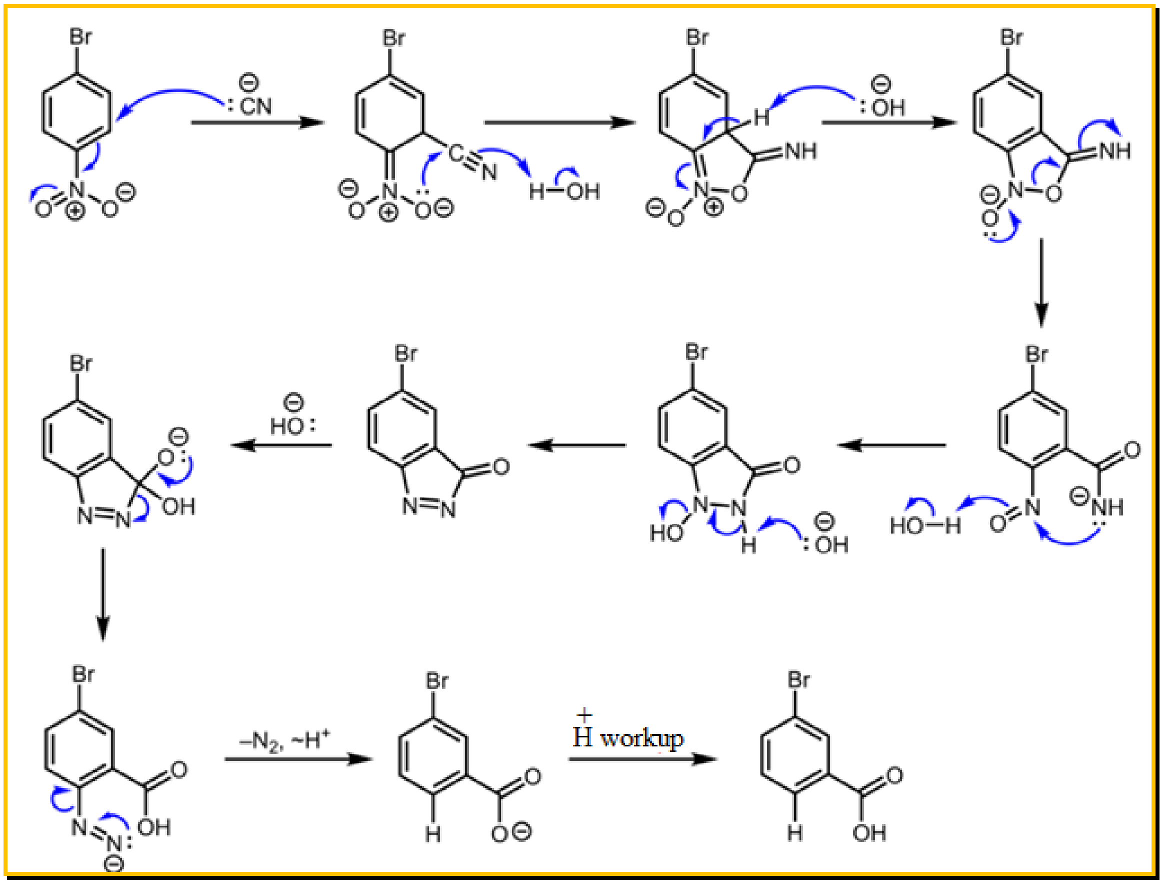


G. Von Ricter reaction:

The **von Richter reaction** is the reaction of aromatic nitro compounds with potassium cyanide in aqueous ethanol to give the product of *cine* substitution (ring substitution resulting in the entering group positioned adjacent to the previous location of the leaving group) by a carboxyl group. It is not generally synthetically useful due to the low chemical yield and formation of numerous side products.

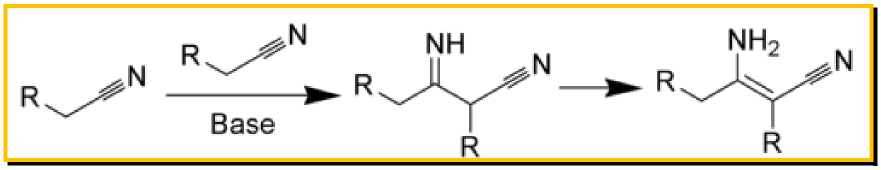


Mechanism:



H. Thorp condensation:

The Thorpe reaction is a chemical reaction described as a self-condensation of aliphatic nitriles catalyzed by base to form enamines.



Mechanism:

The Thorpe–Ziegler reaction or Ziegler method is the intramolecular modification with a dinitrile as a reactant and a cyclic ketone as the final reaction product after acidic hydrolysis. The reaction is conceptually related to the Dieckmann condensation.