

Organic Chemistry-4
Semester-4, CBCS
Course: CEMA CC-4-8-TH

Course taught by: Kaushik Basu, Department of Chemistry, SPCMC, Kolkata
email: chiralkaushik@gmail.com

Recommended texts:

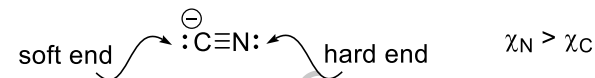
1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588,
2. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719

Organonitrogen Chemistry

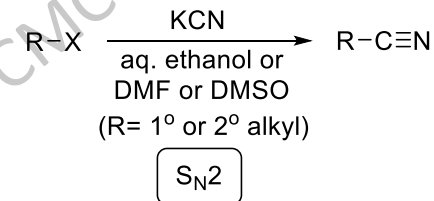
Chemistry of organocyanides (also known as nitriles):

Synthesis of organocyanides:

A] Nucleophilic substitution with cyanide ion: Cyanide ion is an ambident nucleophile:



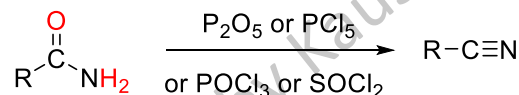
When reacted with alkyl halides R-X, where R is amenable to nucleophilic displacement, the product is a mixture of organocyanides and isocyanides. The product ratio can be made to favour the organocyanide by choosing potassium cyanide as the source of CN⁻. The reaction is generally carried out in aq. ethanolic solution but using polar, protic solvents such as DMF or DMSO improves the yield.



Failure in case of tertiary alkyl halides where elimination ensues.

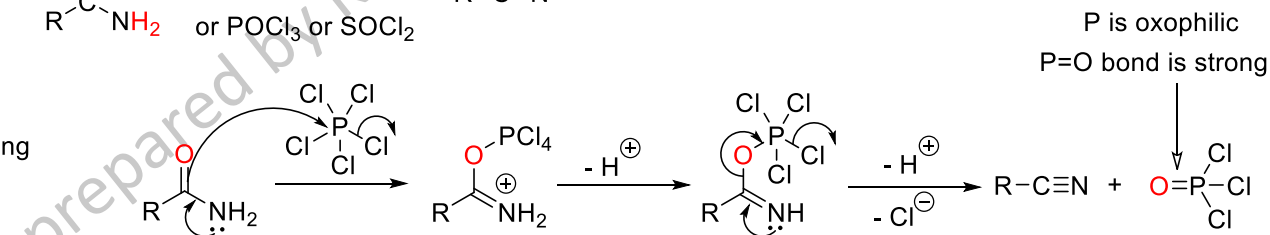
B] Dehydration of amides and aldoximes:

Amides can be dehydrated in variety of manners:

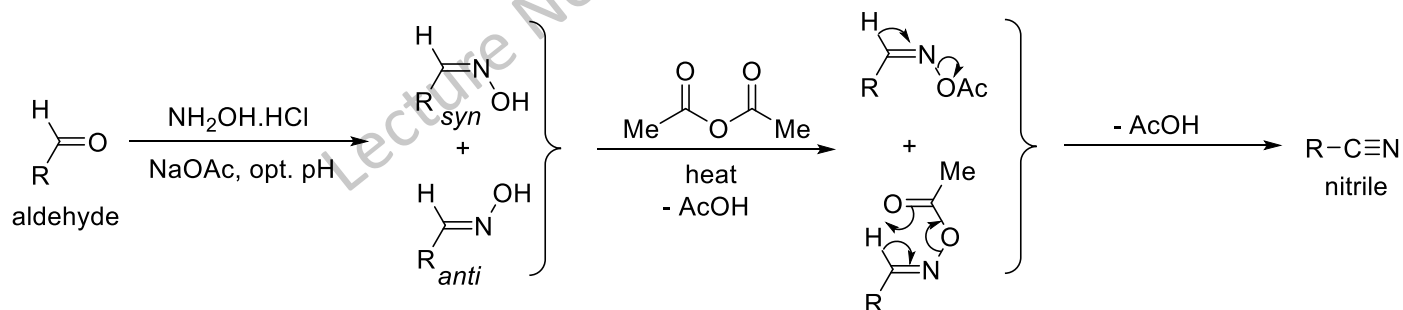


Concentrated sulphuric acid is unsuitable here as the cyanide produced is hydrolysed in that medium.

A representative mechanism of this dehydration using PCl₅ is outlined:



Aldoximes offer cyanide when treated under Beckmann reaction condition:



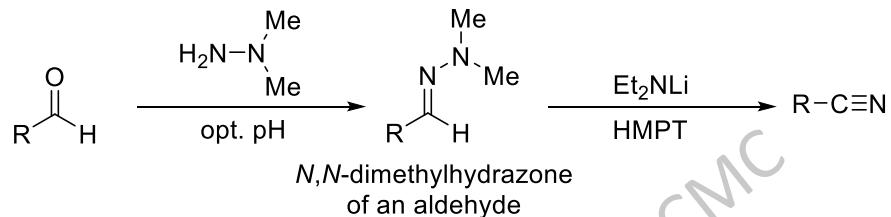
Use of strong acid is not encouraged as it might induce the hydrolysis of the product cyanide or the aldoxime itself.

Organonitrogen Chemistry

Chemistry of organocyanides (also known as nitriles):

Synthesis of organocyanides (contd.):

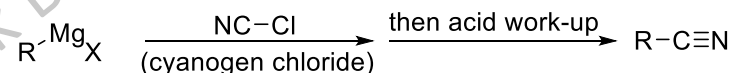
C] Treatment of a suitable hydrazone with a base:



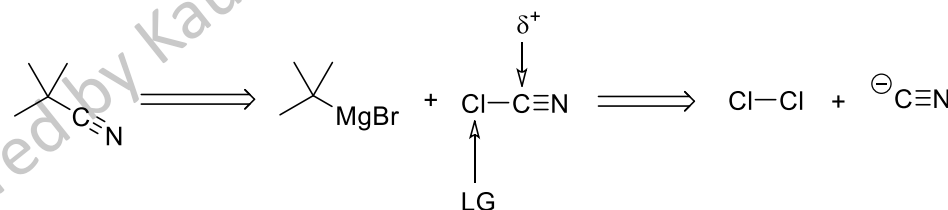
D] From Grignard reagent:

In Grignard reagent the R part is nucleophilic, so we need to have a source of cyanide where the cyanide carbon is electrophilic and carries a good LG.

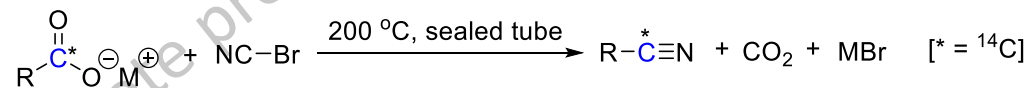
Such a reagent is cyanogen chloride, produced by oxidizing sodium cyanide with chlorine:



This is the best technique for preparing tertiary alkyl cyanides which are difficult to prepare otherwise:

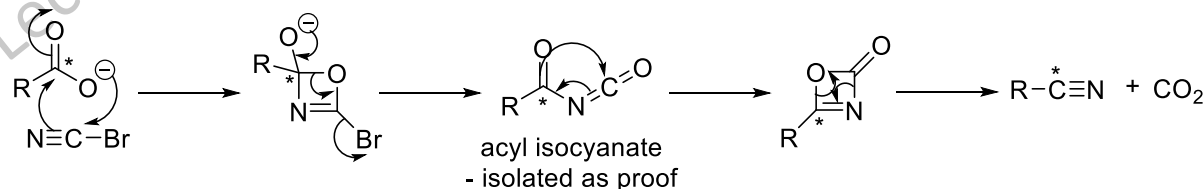


E] From carboxylate salts:



This labelling study indicates that the C-N bond cleavage takes place during the reaction course.

A plausible mechanism for this rather unusual transformation is outlined below:



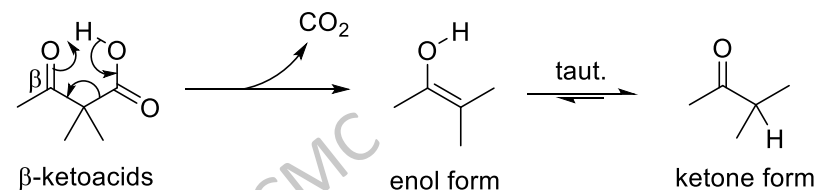
Organonitrogen Chemistry

Chemistry of organocyanides (also known as nitriles):

Synthesis of organocyanides (contd.):

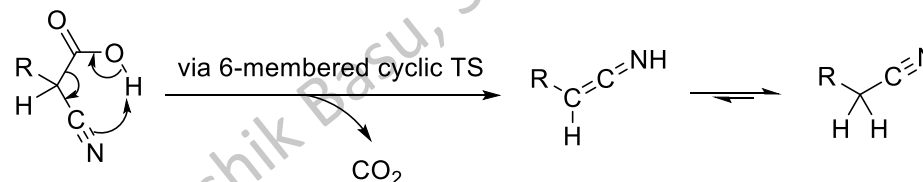
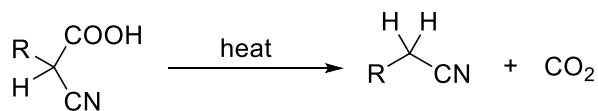
F] Decarboxylation of α -cyanocarboxylic acid:

Recall the decarboxylation of β -keto carboxylic acids, i.e. EAA and DEM derivatives:

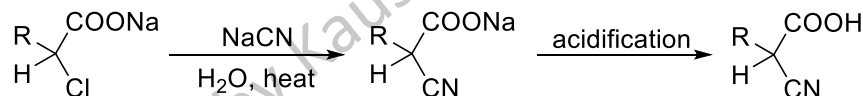


Similarly, α -cyanocarboxylic acids decarboxylate, eventually affording cyanides:

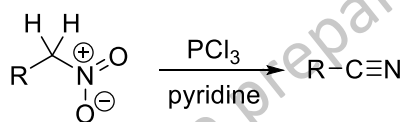
Mechanism is pretty similar to such decarboxylations that we have seen already:



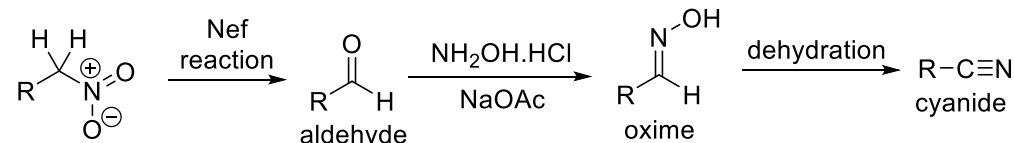
The α -cyanocarboxylic acids are derived from α -halocarboxylic acid salts (why salts?):



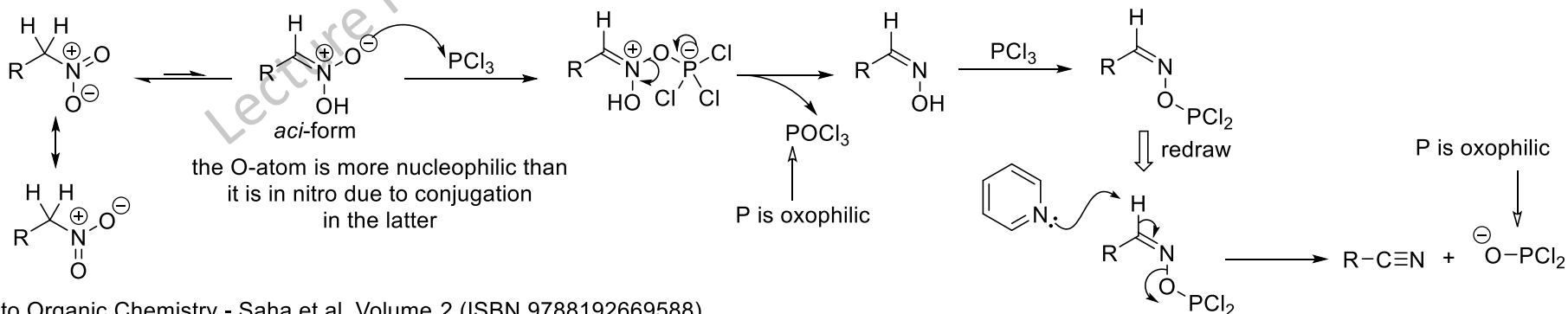
G] From compounds containing the nitromethyl group:



Indirect method:



A plausible mechanism is outlined below:



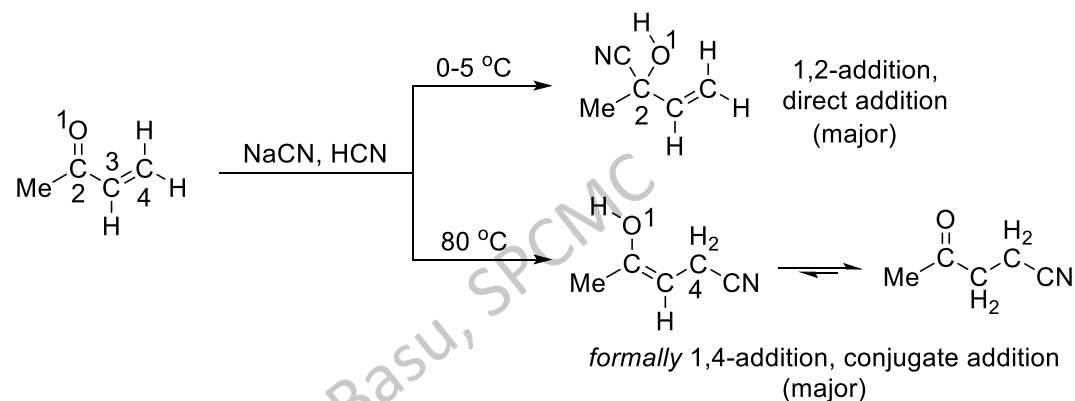
Organonitrogen Chemistry

Chemistry of organocyanides (also known as nitriles):

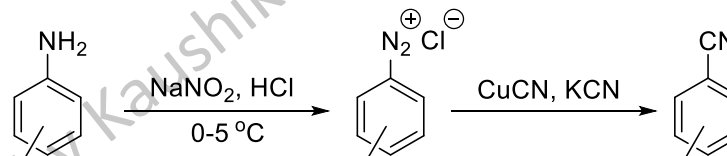
Synthesis of organocyanides (contd.):

H] Nucleophilic addition reactions:

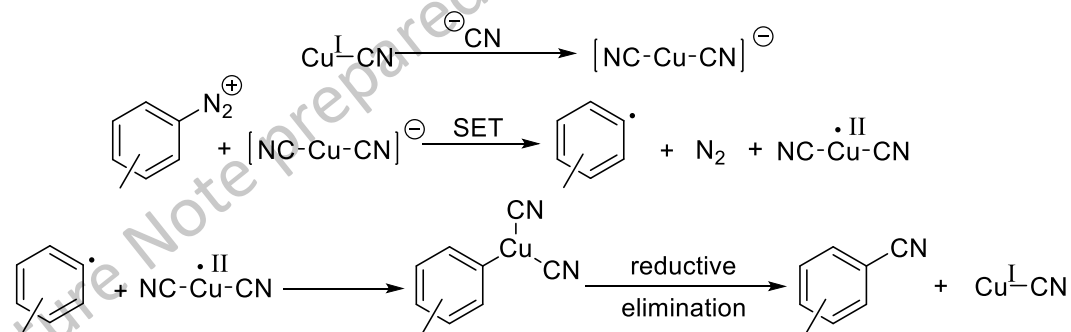
Alkenes are generally unreactive towards HCN addition but C=C conjugated with EWG can undergo such an addition, as we have seen previously.



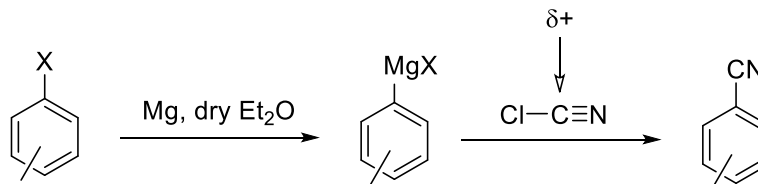
I] Aromatic cyanides are best prepared by Sandmeyer reaction:



The reaction is believed to proceed in a free radical pathway:



The cyanogen chloride route is also useful:



T. Sandmeyer
(1854-1922)

Organonitrogen Chemistry

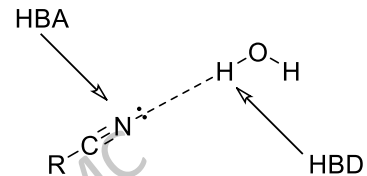
Chemistry of organocyanides (also known as nitriles):

Reaction of cyanides:

A] Lower molecular weight cyanides are water-soluble, can form H-bonds with water.

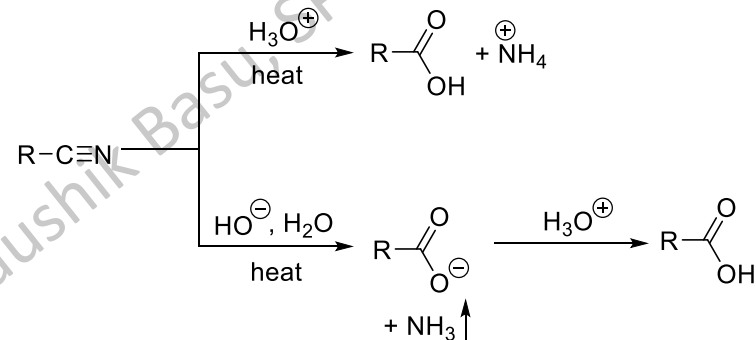
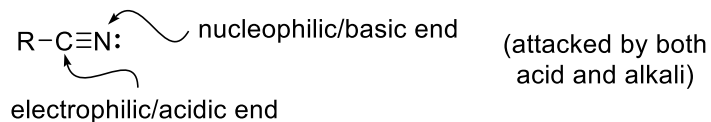
As the size of R increases, the water solubility drops.

Organocyanides are relatively volatile because Ar/R-CN cannot form H-bonding among themselves.

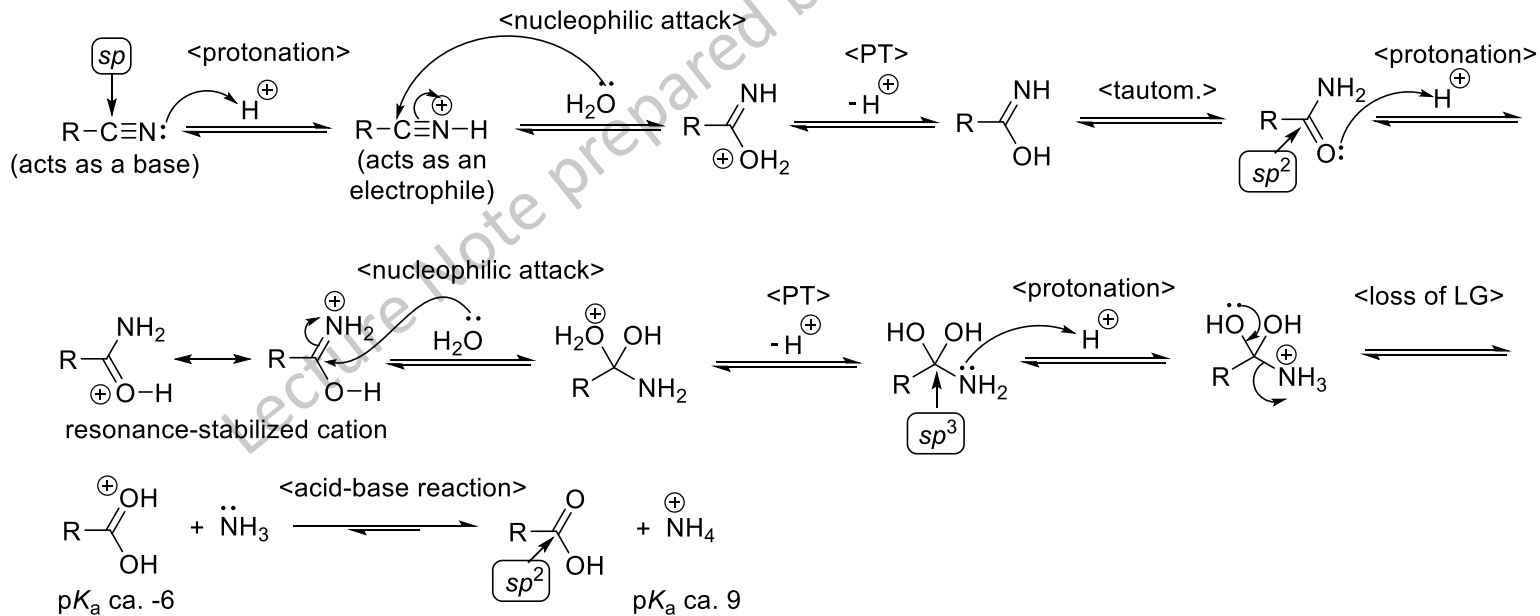


B] Hydrolysis:

Alkyl or aryl cyanides can be hydrolysed in *either acid or base medium* to the corresponding carboxylic acids, or their salt, as the case may be:



The mechanism of hydrolysis under acidic condition:

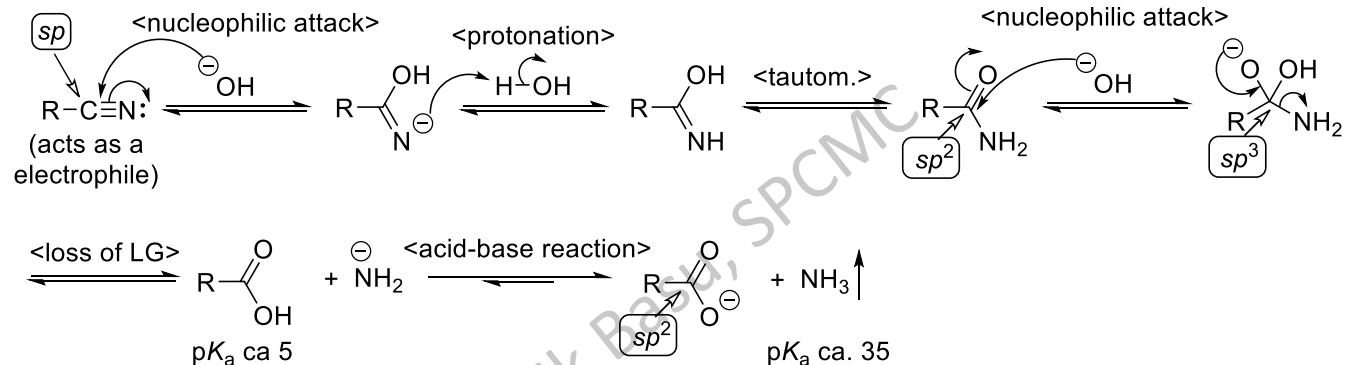


Organonitrogen Chemistry

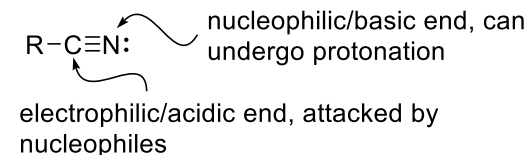
Chemistry of organocyanides (also known as nitriles):

Reaction of cyanides:

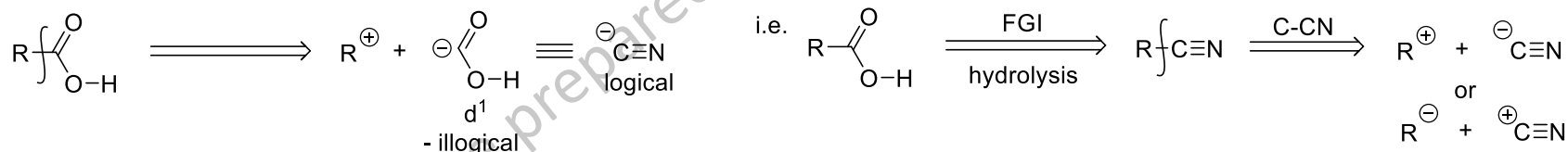
The mechanism of hydrolysis under basic condition:



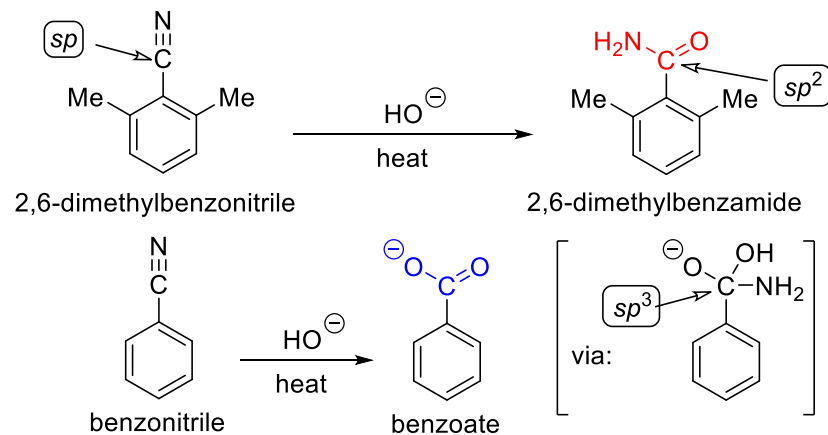
Point to note that alkyl or aryl cyanides are susceptible to hydrolysis in both acidic as well as basic medium because they contain both electrophilic as well as nucleophilic centres within the same structure:



Hydrolysis of cyanides is thus a valuable technique for synthesis of carboxylic acids:



Hydrolysis in either acid or base medium entails a change in hybridisation of the cyanide carbon from sp to sp^2 to sp^3 and finally to sp^2 . So sterically hindered systems such as 2,6-dimethylbenzonitrile do not allow complete hydrolysis and stops the reaction at the amide stage:



Recall that *ortho*-disubstitution permits change of hybridisation on the reaction site from sp to sp^2 but not sp^2 to sp^3 , as was seen for esterification of mesitoic acid (A_{AC1} , revise!). Phenylcyanide, on the other hand, is smoothly converted to the benzoate salt when heated with alkali, a reaction that you have done yourself while in Sem-2. No steric hindrance such as that seen in the 2,6-dimethylated analogue is present here, so full hydrolysis ensured.

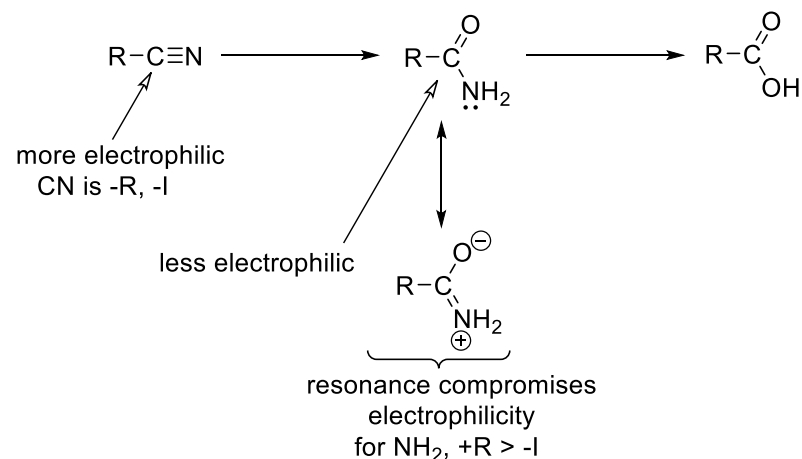
Organonitrogen Chemistry

Chemistry of organocyanides (also known as nitriles):

Reaction of cyanides:

B] Hydrolysis (contd.)

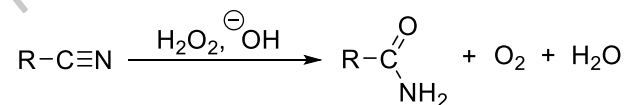
Let us take a closer look at the hydrolysis of cyanide:



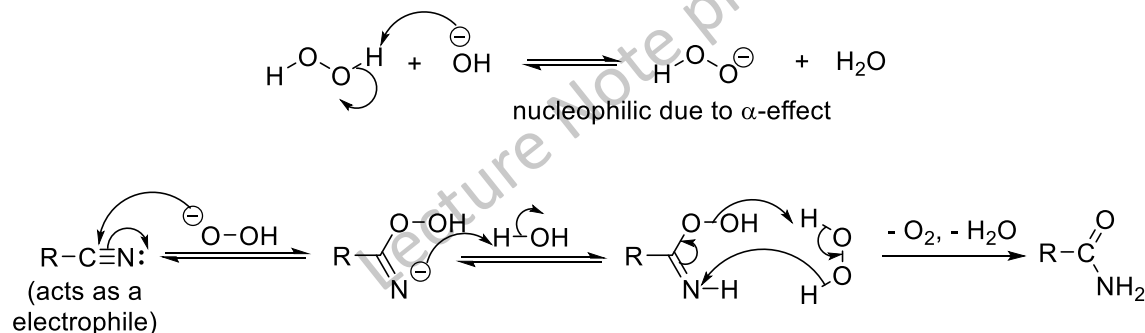
So, theoretically, the reaction can be stopped at the amide stage for every organocyanide, if we can set up the appropriate condition.

Several methods are available:

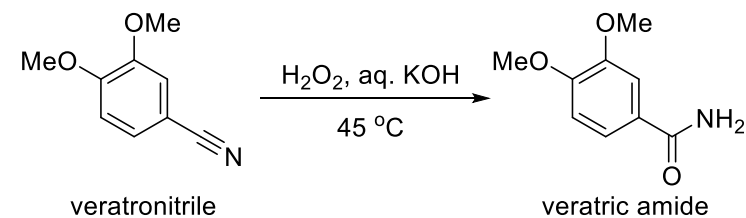
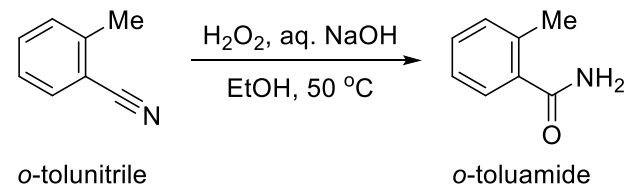
- RCN dissolved in concentrated sulphuric acid in cold condition, and water is continuously poured into it,
- shaking RCN with concentrated HCl,
- using alkaline hydrogen peroxide:



A plausible mechanism for this partial hydrolysis is outlined below:



Examples:



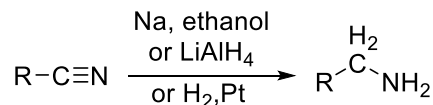
Organonitrogen Chemistry

Chemistry of organocyanides (also known as nitriles):

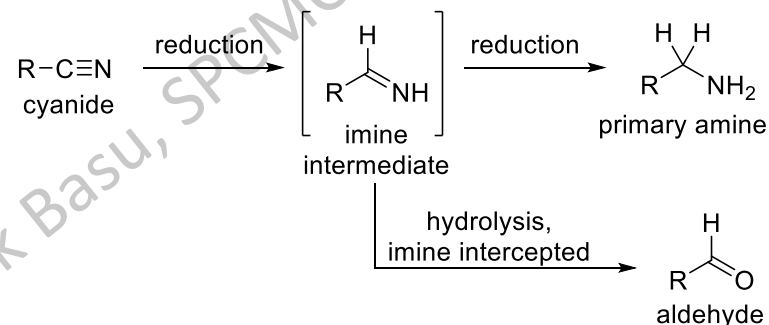
Reaction of cyanides:

C] Reduction of cyanide:

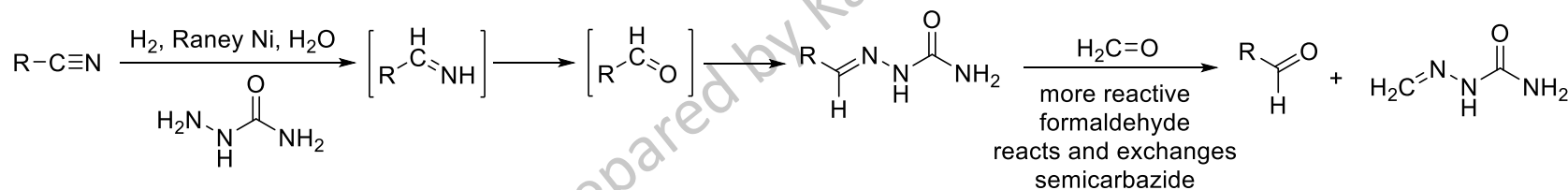
Important method to obtain primary amines:



We have seen this reaction previously while discussing synthesis of primary amine. This reduction involves the intermediacy of an imine, which, if hydrolysed, would give access to an aldehyde.

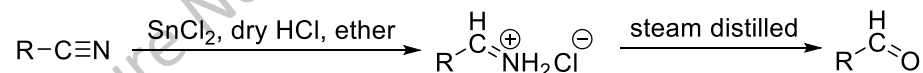


This is done by carrying out the catalytic reduction in presence of water which hydrolyses the imine that is captured in situ by semicarbazide in form of a semicarbazone to protect from further reductions. Final deprotection reveals the target aldehyde:

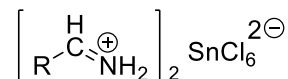


Other general methods for conversion of RCN to RCHO is available:

i) Stephen's reduction:



Ether is saturated with dry hydrogen chloride, SnCl₂ is suspended in it, then the RCN is added, followed by 1 hour stirring and then steam distillation is done. The imine hydrochloride actually forms a complex:



H. Stephen
(1889-1965)

Organonitrogen Chemistry

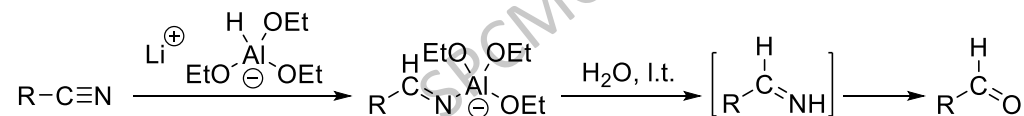
Chemistry of organocyanides (also known as nitriles):

Reaction of cyanides:

C] Reduction of cyanide: General methods for conversion of RCN to RCHO (contd.):

ii) Reduction with lithium triethoxyaluminumhydride, Li[AlH(OEt)₃] (LTEAH):

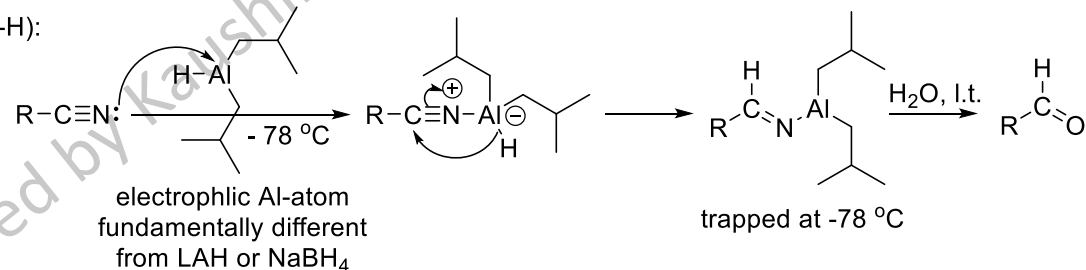
Normally, LAH reduction converts RCN to RCH₂NH₂, but with the modified reagent lithium triethoxyaluminumhydride, at low temperature, the reaction may be arrested, so that aqueous work-up may afford the aldehyde.



Recall that with the increasing number of alkoxy groups, the reducing ability of the alkoxy aluminium hydride decreases (you might want to think why this is so considering the fact that the same substitution increases the reducing capacity of borohydride reagents).

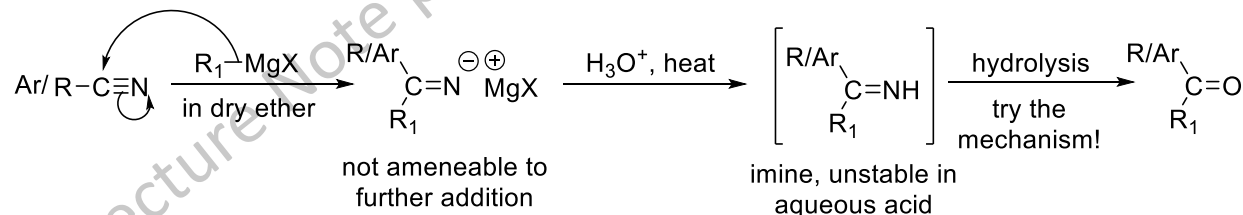
iii) Reduction with diisobutylaluminium hydride (DIBAL/DIBAL-H):

The Al-atom of DIBAL is a Lewis acid, so the reduction is fundamentally different from those by LAH or borohydrides:

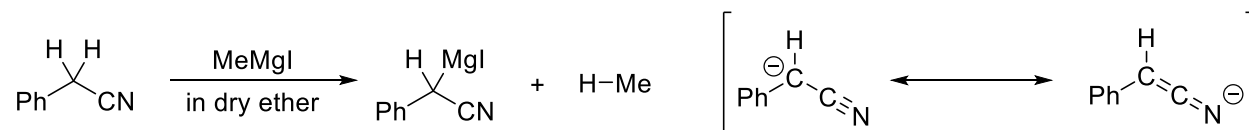


D] Reaction with Grignard reagents:

A general method for ketone synthesis:



However, the GR can act as a base if the organocyanide contains a highly acidic C-H bond, e.g.



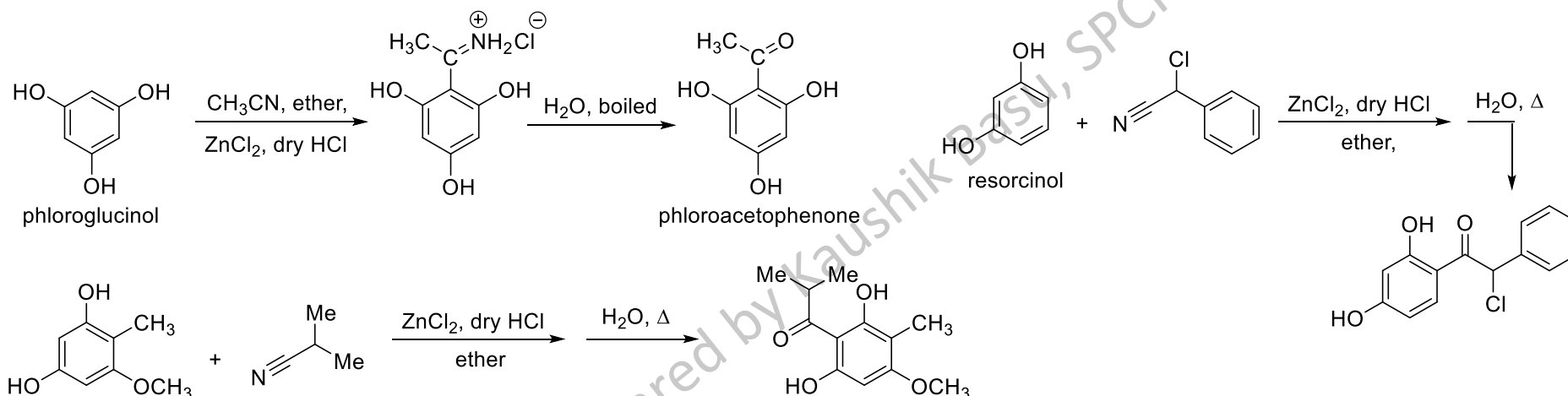
Organonitrogen Chemistry

Chemistry of organocyanides (also known as nitriles):

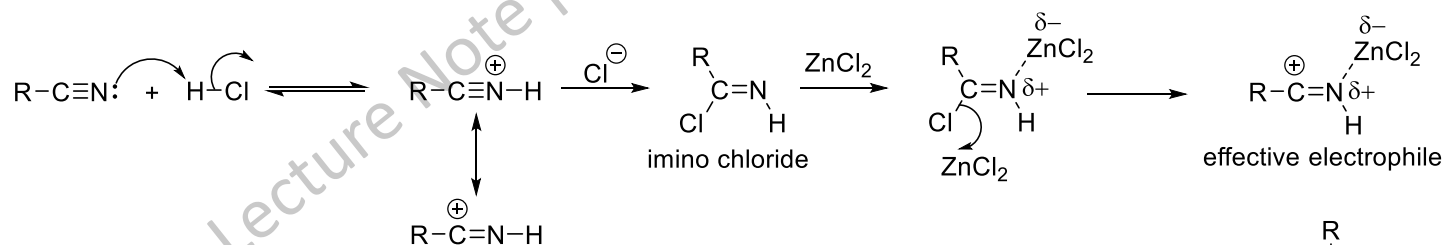
Reaction of cyanides:

E] Reaction with activated aromatic rings:

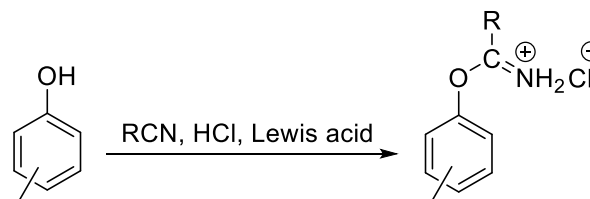
An extension of the reaction of organocyanides with Grignards is the Houben-Hoesch synthesis, where an activated aromatic ring is made to react with a Lewis acid-activated alkyl cyanide in an aromatic electrophilic substitution, giving access to an aromatic ketone:



The electrophile for Houben-Hoesch Reaction is generated from the cyano compound in acidic medium in the following way:



The reaction occurs only with very highly activated aromatic compounds such as di- and polyhydric phenols. Monohydric phenols react mainly at oxygen to give imido-esters:

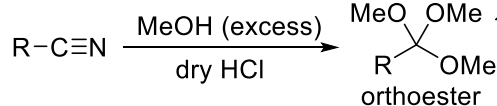


Organonitrogen Chemistry

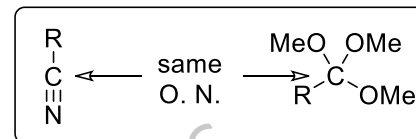
Chemistry of organocyanides (also known as nitriles):

Reaction of cyanides:

E] Reaction with alcohol:



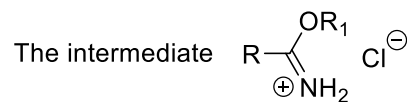
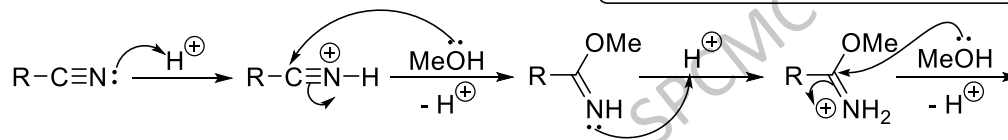
useful reactants for ketone synthesis
from Grignards



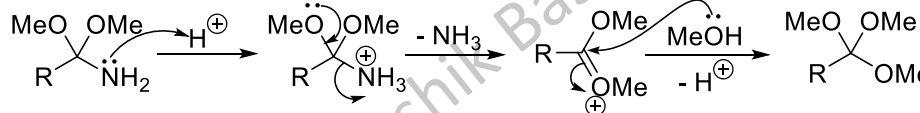
Adolf Pinner

A. Pinner
(1842-1909)

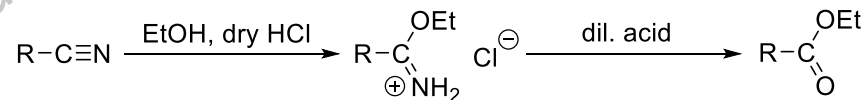
This is called the Pinner reaction and it proceeds in the following way:



is known as the Pinner salt.



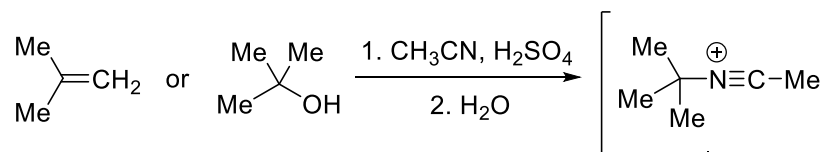
It can react with various nucleophiles to afford different products, e.g. if a limited amount of alcohol is used, and then worked up with dilute acid, we will get an ester.



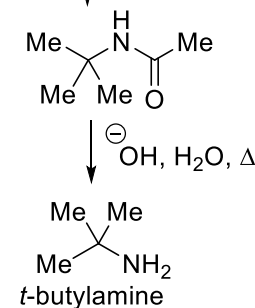
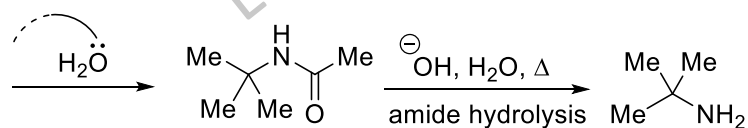
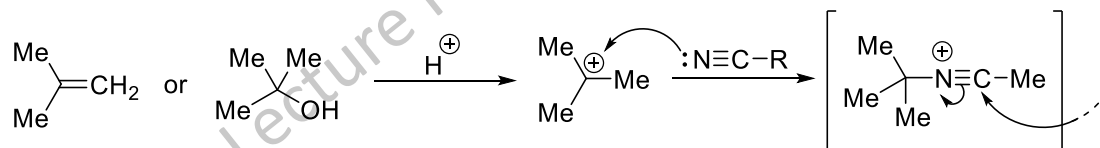
This is a useful technique to convert -CN to COOR.

F] Ritter reaction/amidation:

Reaction of cyanides with highly electrophilic carbocations, an efficient technique for synthesis of *tert.* alkylamines.:



The mechanism:



Organonitrogen Chemistry

Chemistry of organocyanides (also known as nitriles):

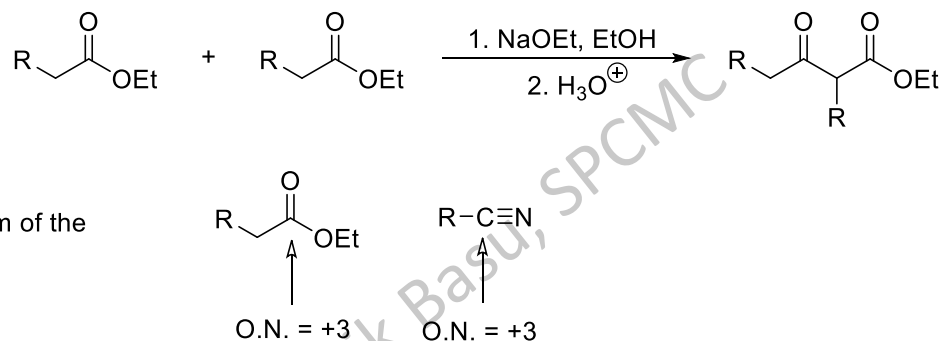
Reaction of cyanides:

G] Thorpe nitrile condensation:

Recall the Claisen ester condensation:

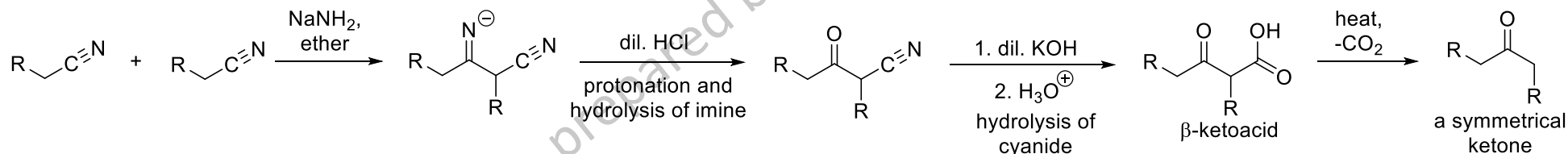
This takes place through nucleophilic substitution by an enolate derived from one of the ester molecules onto the ester group of the other.

Note carefully that the oxidation number of the carbon atom of the ester carbonyl is same to that of the cyanide group:

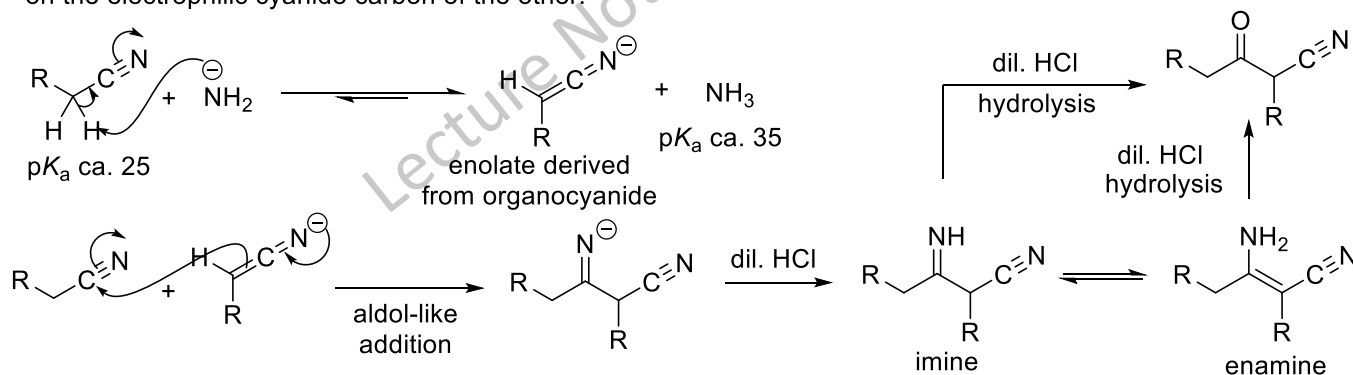


If we take a look at the hydrolysis reaction of cyanides and esters, certain similarities also emerge. So we can say that *cyanides are carboxylic acid derivative mimics*.

Considering this aspect, a Claisen condensation-like reaction from cyanides is entirely expected and we have Thorpe nitrile condensation:



The anion derived from one of the alkyl cyanides makes a nucleophilic attack on the electrophilic cyanide carbon of the other:



The rest of the synthesis is pretty straight-forward.

[This enamine is isolated if the condensation is done with *t*-BuOK/*t*-BuOH, the alcohol then acts as the proton source.]



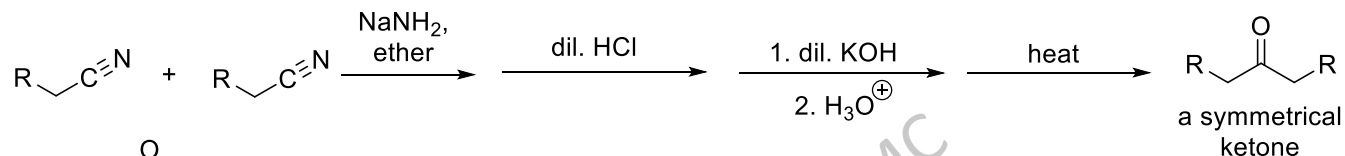
J. F. Thorpe
(1872-1940)

Organonitrogen Chemistry

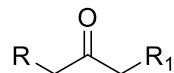
Chemistry of organocyanides (also known as nitriles):

Reaction of cyanides:

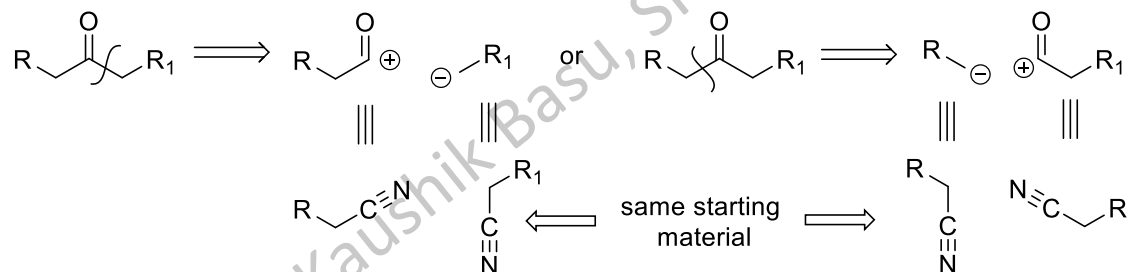
G] Thorpe nitrile condensation (contd.):



If we need an unsymmetrical ketone like:

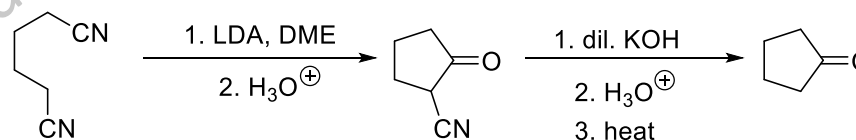


we may consider the following disconnection:



Therefore, we need a cross-aldol-type condensation here.

Thorpe nitrile condensation can be done with dinitriles where an intramolecular condensation leads to a cyclisation:

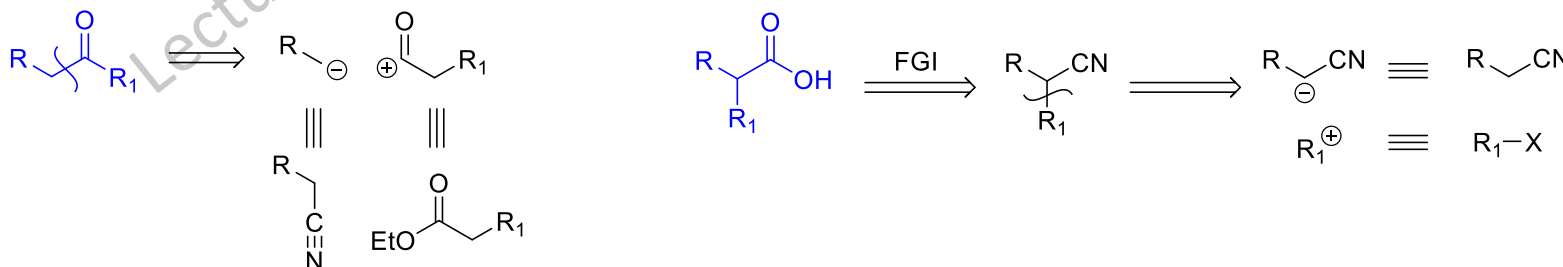


This variant is closely similar to Dieckmann condensation.

It is also known as the Thorpe-Ziegler reaction (after Karl Zeigler)

This concept can be extended further. The carbanion derived from alkyl cyanide can be made to react with other electrophiles, e.g. esters and alkyl halides. Subsequent hydrolysis of the cyanide group will reveal the carboxylic acid, which, in suitable cases can be knocked off.

Consider the following **target molecules**:



Organonitrogen Chemistry

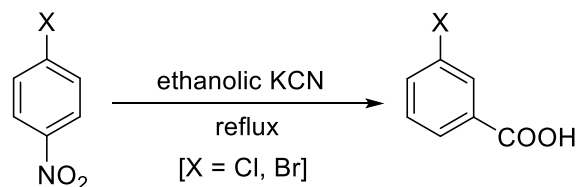
Chemistry of organocyanides (also known as nitriles):

Reaction of cyanides:

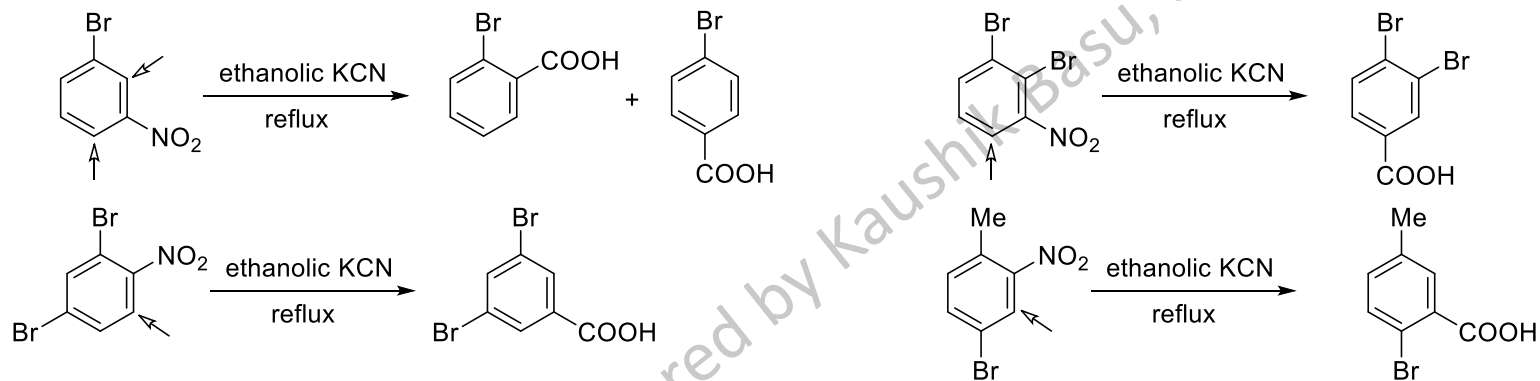
G] von Richter reaction:

A curious aromatic nucleophilic substitution reaction:

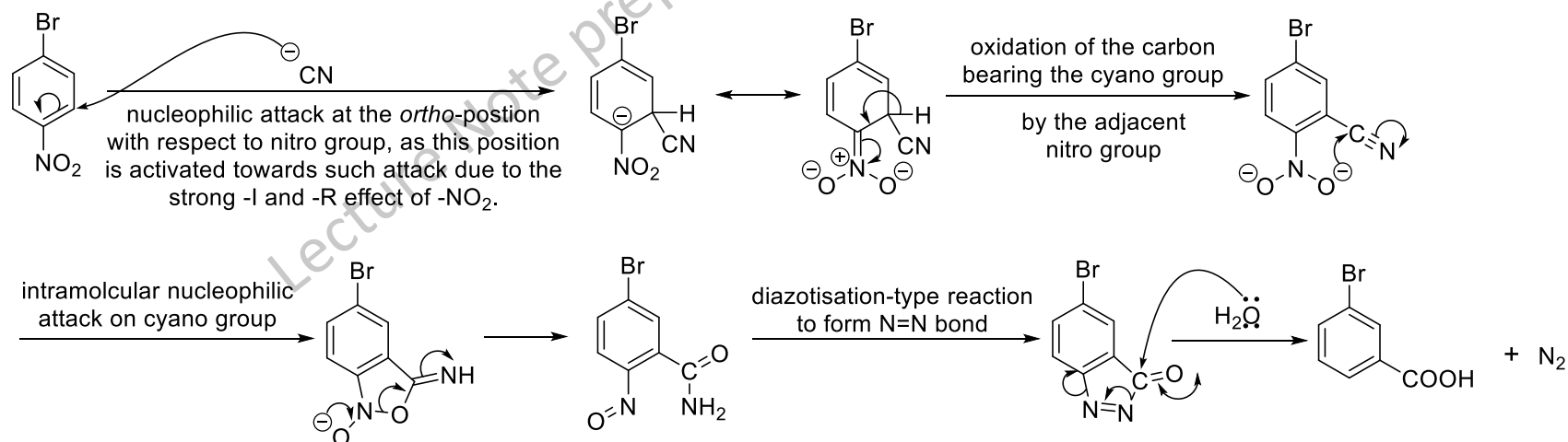
This reaction is known as von Richter reaction.



Carboxylation *o*- to position occupied by the nitro group in the starting material. An example of *cine* substitution



A plausible mechanism is outlined below:



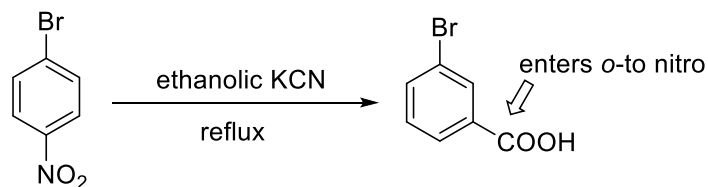
V. von Richter
(1841-91)

Organonitrogen Chemistry

Chemistry of organocyanides (also known as nitriles):

Reaction of cyanides:

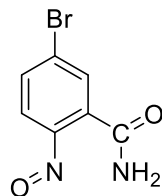
G] von Richter reaction:



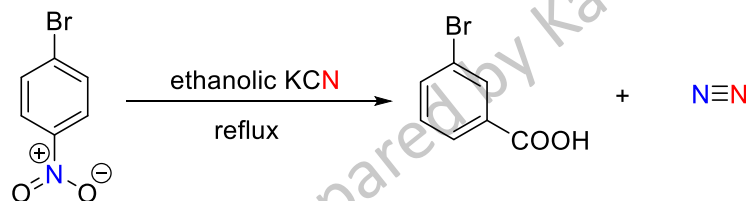
One of the early examples of *cine*-substitution where the entering group takes up a position adjacent to the one vacated by the leaving group

Proof of mechanism for von Richter reaction:

a) The following intermediate has been isolated:

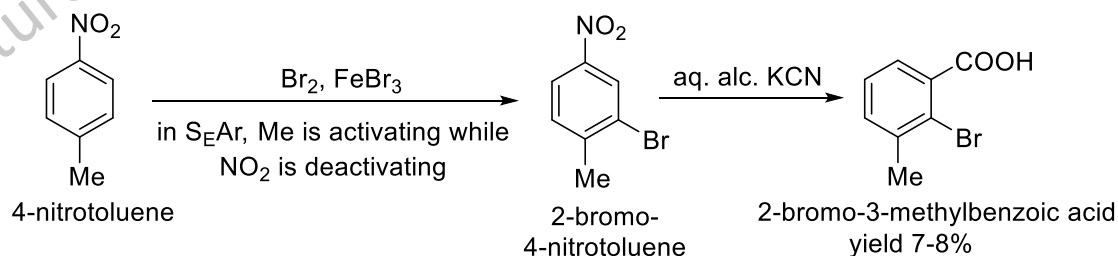


b) Of the two nitrogen atoms of N_2 - one comes from nitro group and another from ^-CN - this has been confirmed through isotope labelling studies.



c) When using other aromatic cyanides in the reaction medium, it is found that those are not hydrolyzed under this reaction condition. So it cannot be a simple substitution by cyanide and subsequent hydrolysis.

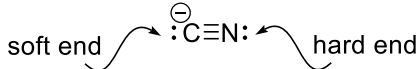
Using von Richter reaction in the preparation 2-bromo-3-methylbenzoic acid:



Organonitrogen Chemistry

Chemistry of organoisocyanides (also known as isonitriles, carbylamines):

Synthesis of isocyanides:

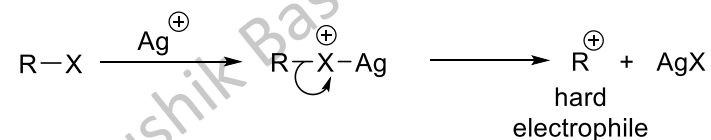
A] Nucleophilic substitution with cyanide ion: Cyanide ion is an ambident nucleophile: 

When reacted with alkyl halides R-X, where R is susceptible to nucleophilic displacement, the product is a mixture of organocyanides and isocyanides.

The product ratio can be made to favour the isocyanide by choosing silver cyanide as the source of CN^- . The reaction is generally carried out in aq. ethanolic solution:

$$\text{R-X} \xrightarrow[\text{aq. ethanol}]{\text{AgCN}} \text{R-N}\equiv\text{C}^{\ominus}$$

It was *earlier believed* that when R-X is treated with AgCN, we should have the following situation:

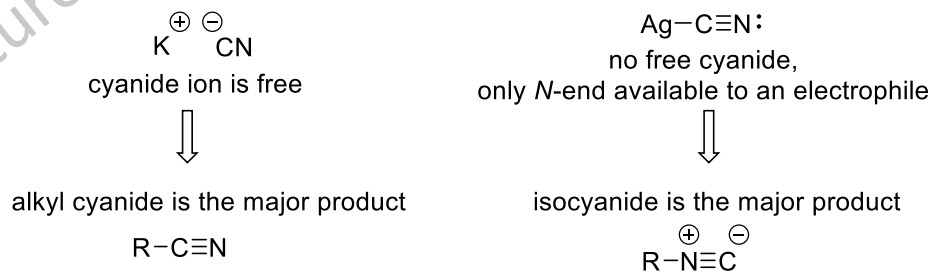


In this case, the extent of '+' charge over 'R' is significant to consider it to be a hard electrophile. Thus *via* a hard-hard interaction between R-X and the nitrogen end of cyanide through $\text{S}_{\text{N}}1$ -type reaction we get R-NC, an alkyl isocyanide as the major product.

However, this explanation depends upon the attack by the free cyanide ion (of AgCN) which appears to be ambiguous because it is now known that AgCN has much less ionic character than KCN.

Since Ag^+ is a soft acid, it remains attached with the carbon centre of cyanide ion and there is also some scope of a *back bonding* between the filled d-orbital of the silver ion and the vacant π^* orbital of the cyano group.

As a result, AgCN has significant covalent nature and subsequently when it is used to react with R-X, only the nitrogen end is available to attach itself with the electrophilic carbon centre of the alkyl halide. This, of course, leads to the alkyl isocyanide, R-NC.



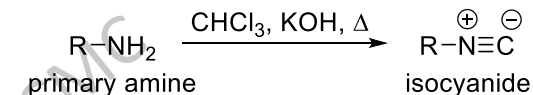
Organonitrogen Chemistry

Chemistry of organoisocyanides (also known as isonitriles, carbylamines):

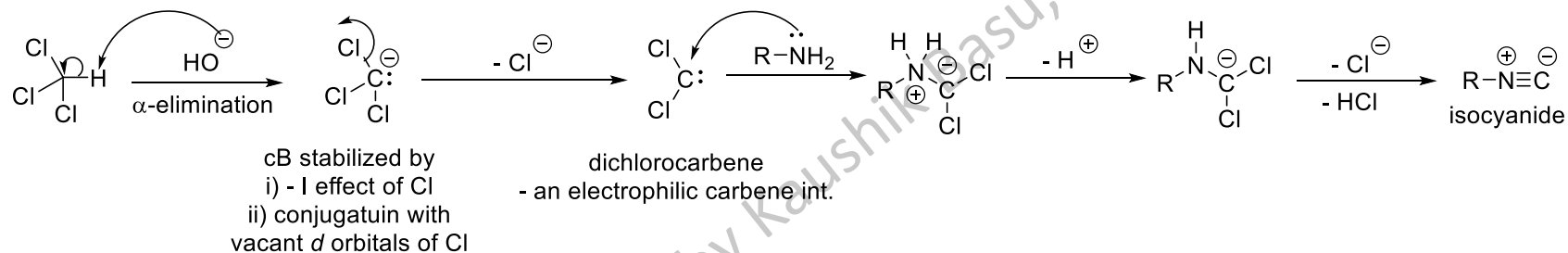
Synthesis of isocyanides:

B] Carbylamine reaction:

A diagnostic test to detect the presence of a primary amines is Hofmann's carbylamine test where the amine is treated with chloroform in alkaline medium to produce the vile-smelling isocyanides (aka carbylamines)



The reaction proceeds via the *in situ* formation of strongly electrophilic dichlorocarbene intermediate:



Recall that the dipole moment of isocyanides are typically less than that of corresponding cyanides and consequently, the isocyanides are more volatile;

	$\text{R}-\text{C}\equiv\text{N}^{\oplus}\text{C}^{\ominus}$	$\text{R}-\text{N}^{\oplus}\text{C}^{\ominus}$	$\begin{array}{c} \xrightarrow{\mu_{\sigma}} \\ \text{R}-\text{C}\equiv\text{N}^{\oplus} \\ \xleftarrow{\mu_{\pi}} \end{array}$	$\begin{array}{c} \xrightarrow{\mu_{\pi}} \\ \text{R}-\text{N}^{\oplus}=\text{C}^{\ominus} \\ \xleftarrow{\mu_{\sigma}} \end{array}$
d.m. (D):	~ 4	~ 3	$\text{R}-\text{C}\equiv\text{N}^{\oplus} \longleftrightarrow \text{R}-\text{C}^{\oplus}=\text{N}^{\ominus}$	$\text{R}-\text{N}^{\oplus}=\text{C}^{\ominus} \longleftrightarrow \text{R}-\text{N}^{\ominus}=\text{C}^{\oplus}$
B.P. (°C):			The two moments augment each other, overall moment higher	The two moments oppose each other, overall moment lower
(for R = Me)	82	60		
(for R = Et)	97	77		
(for R = Ph)	190	165		
(for R = CH ₂ Ph)	234	106		

Dipole-dipole interaction b/w alkyl cyanides are higher than in isocyanide.

Due to this larger intermolecular association the b.p. of alkyl cyanides are generally greater than that of isocyanides.

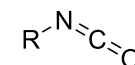
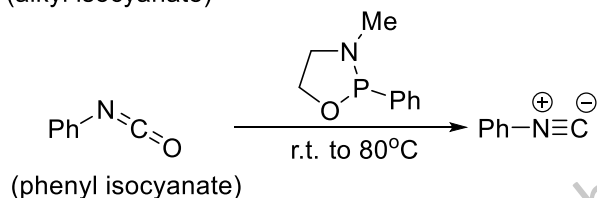
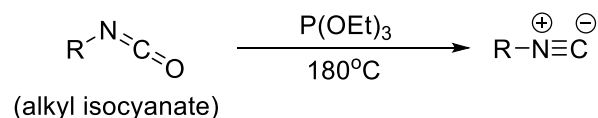
Organonitrogen Chemistry

Chemistry of organoisonitrides (also known as isonitriles, carbylamines):

Synthesis of isocyanides:

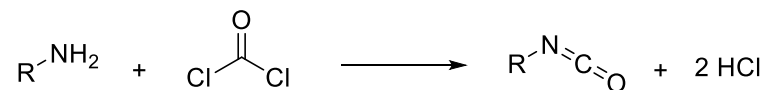
C] Deoxygenation of isocyanates:

The oxygen atom of isocyanates can be stripped off to access isocyanide compounds. Recall in this connection that P-O bond is exceptionally strong. You might want to recap also where you have seen this very concept in action earlier.



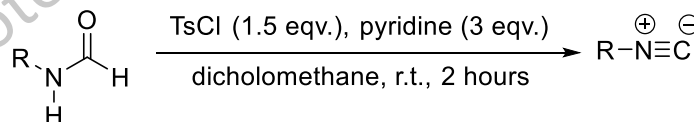
We have encountered isocyanate as an intermediate in our studies related to rearrangement reactions where a group migrates from C to e-deficient N

It is generally prepared using various reagents from primary amines, e.g.

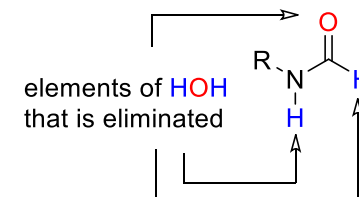
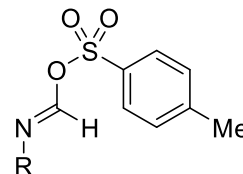


D] Dehydration of *N*-alkylformamides:

This is one of the most modern and widely accepted technique for accessing isocyanides. The dehydration is generally effected with an acylating or a tosylating agent and a base, e.g.



The reaction possibly proceeds via formation of the *O*-tosylated derivative:



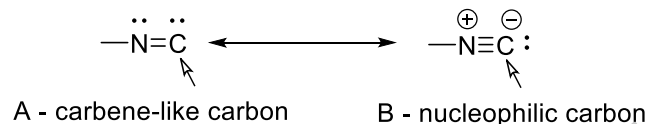
Can you propose a plausible mechanism for this dehydration? And while you are at it, please also think of a suitable synthesis of the starting *N*-alkylformamide.

Organonitrogen Chemistry

Chemistry of organoisonitrides (also known as isonitriles, carbylamines):

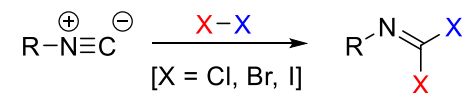
Reactions:

The isocyano group is unique in being the only stable functional group incorporating bivalent carbon. In valence bond terms it can be viewed as the resonance hybrid of the following two canonical forms A and B, the former indicating its bivalent carbenic character and latter its potential as a nucleophilic reagent. It follows that the reactivity of the isocyano group (and hence of isocyanide) is dominated by a desire to regain the stable covalent state and a tendency to undergo insertion rather than addition, and electrophilic rather than nucleophilic attack.

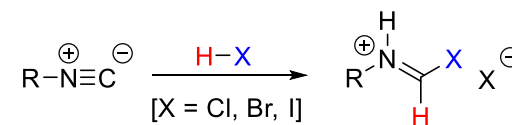


A] Reactions with electrophiles:

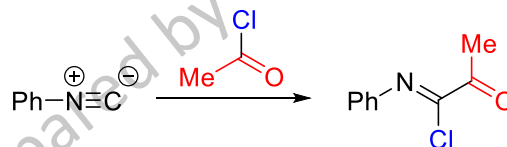
Isocyanides react violently with halogens (Cl_2 , Br_2 , I_2) at ambient temp. but these reactions can be controlled at low temp. to afford the corresponding iminocarbonyl halides.



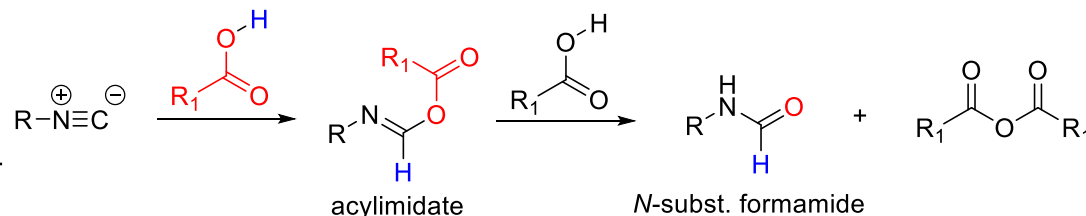
The reaction of organocyanides with anhydrous hydrogen halides (HCl , HBr , HI) are likewise vigorous but can be controlled at -15 degrees to afford formidoyl halides as hydrochloride salts.



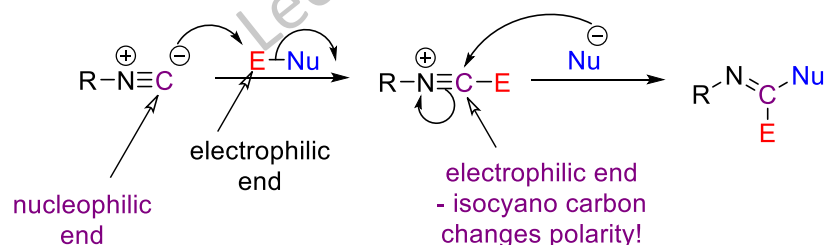
Isocyanides are found to react with acid chlorides to form α -ketoimidoyl chlorides:



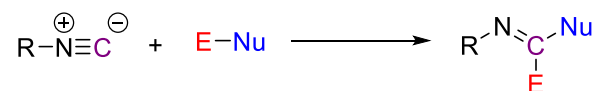
The reaction of carboxylic acids with isocyanides to give anhydrides and the corresponding formamide can be rationalized by the intermediacy of an acylimidate, which, being a potential acylating agent will react with further carboxylic acid to give the observed product.



In all cases, the initial addition reaction proceeds in the following way:



Notice that the isocyanide is "inserted" into the E-Nu bond in each case - a testament to the carbene-like character of the isocyano carbon:



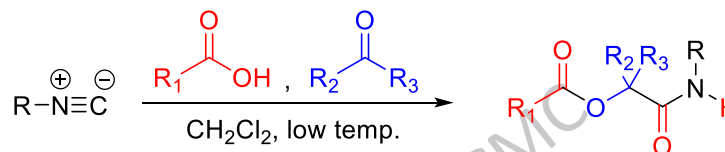
Organonitrogen Chemistry

Chemistry of organoisonitrides (also known as isonitriles, carbylamines):

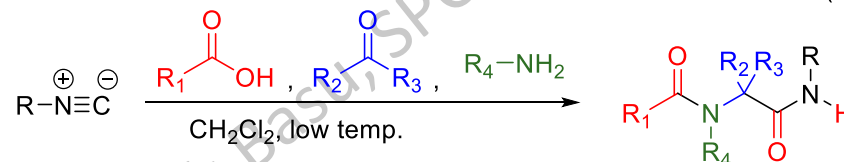
Reactions:

A] Reactions with electrophiles (contd.):

Isonitriles combine with aldehydes/ketones and carboxylic acid in a three-component reaction to afford an α -hydroxycarboxamide (Passerini reaction):



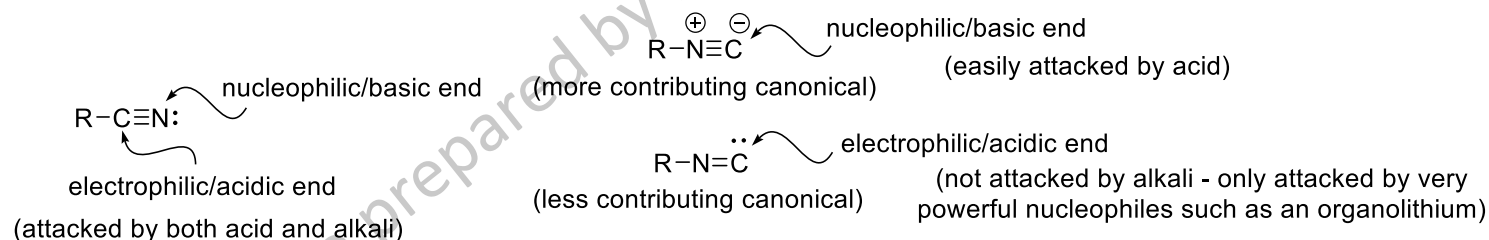
The ability of isocyanides to act as the "linchpin" of such multi-centre condensations is further demonstrated in their reaction with amines, carbonyl compounds and carboxylic acids under mild conditions to afford excellent yields of α -amino acid derivatives (Ugi reaction):



I. K. Ugi
(1930-2005)

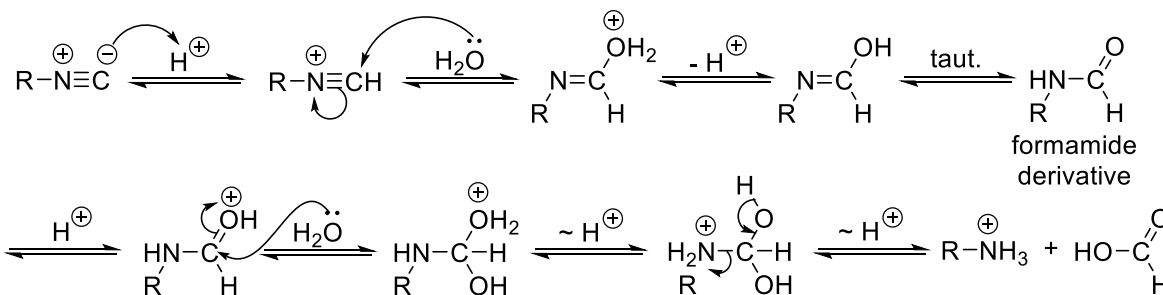
B] Hydrolysis:

Unlike organocyanides that have both an electrophilic/acidic and a nucleophilic/basic centre within the same structure, the more contributing canonical form of isocyanides contains only a nucleophilic/basic centre:



So, expectedly, isocyanides are prone to acidic hydrolysis but resist alkaline medium. The acid hydrolysis is rapid and affords an amine salt and formic acid.

The mechanism is outlined below:



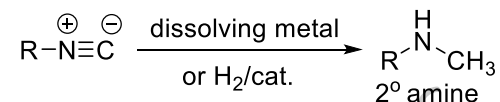
The lack of hydrolytic reactions in alkaline medium for isocyanide is a *distinguishing feature* for this class of compounds from organocyanides.

Organonitrogen Chemistry

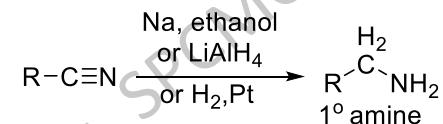
Chemistry of organoisocyanides (also known as isonitriles, carbylamines):

Reactions:

B] Reduction: A secondary amine results when isocyanide is reduced with dissolving metals or subjected to catalytic hydrogenation.

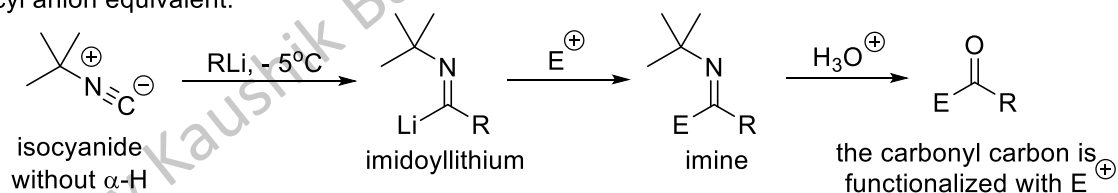


Contrast this observation with the catalytic reduction of cyanides that afford a primary amine. So this is another way to distinguish between the two classes of compounds.



C] Reaction with organolithium: generation of imidoyllithium - an acyl anion equivalent:

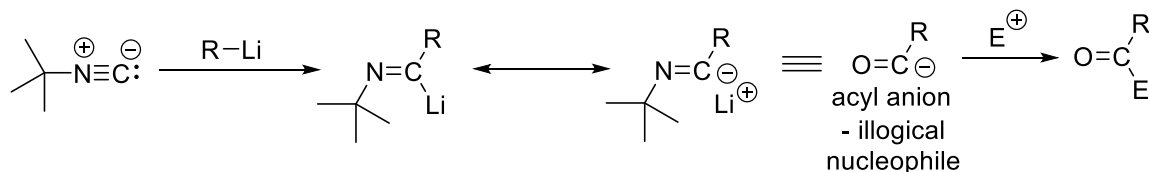
Isonitriles which do not contain any α -H undergo nucleophilic addition with organolithiums to afford lithioimines (also known as imidoyllithiums or lithium aldimines) which are susceptible to electrophilic attack and generates imine derivatives upon reaction with various electrophiles. These can be hydrolysed to corresponding carbonyl compounds.



Note carefully that both the metal and the alkyl part of the alkyllithium reagent adds to the carbon atom of isocyanide.

very similar to the *insertion* reactions seen for carbenes

The anion generated from addition of the organolithium to the isocyanide is an *acyl anion equivalent*. The same acyl anion is obtainable by reacting organolithium with carbon monoxide,



A variety of electrophiles may be used here to combine with the imidoyllithium to access a number of carbonyl-based compounds such as aldehydes, ketones, α -ketoacids, α -ketoesters α -hydroxyketones and β -hydroxyketones.

