CHAPTER - II

Synthesis of α-Aminonitriles Using Sodium Hydrogen Sulphate On Silica Gel And Polyvinyl Pyridine Hydrochloride

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Synthesis of α–Aminonitriles using silica supported sodium hydrogen sulphate/polyvinyl pyridine hydrochloride as a catalyst.

2.1 Introduction:

Amino acids act as building blocks of cellular structures in all living organisms from simple unicellular algae to mutlicellular complex organism like human being.[1] Properties of the matters can be studied only when we have optimum quantity of material. Thus, it is mandatory that one must synthesize it at least on laboratory scale. Considering organic synthesis, this advancement is still contained by basic parameters like cost, economy, simplicity of handling operations etc. Thus, synthesis of existing molecules using new synthetic route is still a challenging field in research arena.

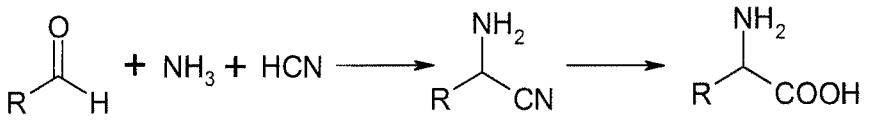
For the synthesis of any organic molecule, one step, one pot method is undoubtedly an ideal method as it minimizes steps of isolation and purification of intermediates involved. The penultimate step in approach by multistep protocol towards the synthesis of a target molecule is the synthesis of precursor, 'the molecule which can directly be converted to target molecule'.

α–Aminonitriles are the precursors for the α–amino acids and as they are also employed in the synthesis of medicinally important heterocyclic compounds[2] such as imidazoles,[3a] thiadiazoles,[3b] natural products , etc.

2.2 Historical Perspective:

Adolph Strecker (1822 – 1871) first reported his work on the reaction of acetaldehyde and ammonia with hydrogen cyanide in 1850. The intermediate was

hydrolyzed to afford alanine, the first synthetically prepared α–amino acid.[4] Its name was derived from the nature of its starting materials. Emil Erlenmeyer in 1875 showed that the intermediate resulted in this reaction was probably an α–aminonitrile. Thus, hydrolysis of α-aminonitriles becomes a general method for the synthesis of α-aminoacids. (Scheme-1) In 1880, John Tiemann (1848–1899), altered the synthetic protocol by reversing the order of addition and showed that the cyanohydrins of carbonyl compound react with ammonia to produce same intermediate aminonitrile with improved yields. Zelinskii Stadnikov further modified the reaction conditions by use of potassium or sodium cyanide instead of hydrogen cyanide and by use of ammonium salts for aldehydes that exhibited reduced reactivity. The Knoevenagel–Buchener modification makes use of bisulfite adducts of aldehyde to improve the reactivity and provide access to the desired product.



Scheme: 1

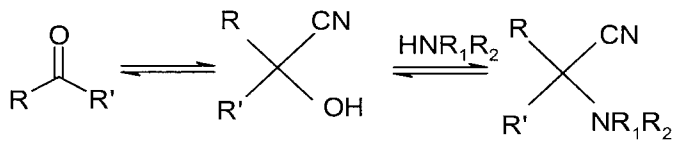
2.3 Methods of Synthesis:

The α–Aminonitriles are routinely synthesized using the strecker reaction which involves the nucleophilic addition of cyanide ion to imine. Originally strecker reaction was associated with two main drawbacks viz. the use of volatile and toxic hydrocyanic acid as well as poor yields. Owing to the high toxicity of hydrogen cyanide, the improvements were mainly focused on the change in the cyanide ion source and it was realized that amongst various cyanide ion sources such as HCN, NaCN, KCN, TMSCN, tri-butyltin cyanide, diethyl phosphono cyanidate, acetone cyanohydrin, [5ab] etc. trimethylsilyl cyanide is safer and more

easily handled reagent compared to other reagents and most of protocols reported during the last decade involves the use of trimethylsilyl cyanide as a cyanide ion source.

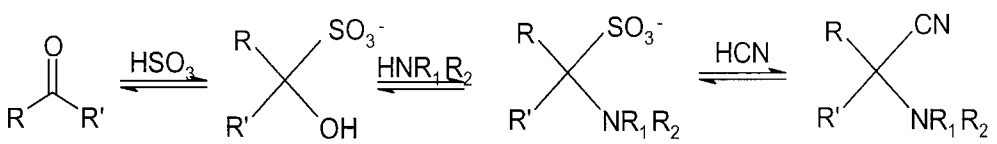
The other improvements in strecker reaction were as regards,

a) Change in the order of mixing the reagents. (Scheme 2) i.e. synthesis of a cyanohydrins followed by the attack of an amine. [5b]



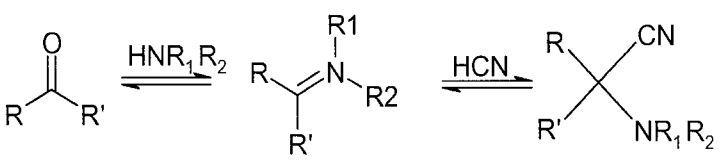
Scheme 2

b) Conversion of aldehydes having low reactivity to corresponding bisulfite adducts of more reactivity followed by sequential addition of an amine cyanide ion equivalent. (Scheme 3)



Scheme 3

c) Use of ammonium or alkyl ammonium salts in excess for preparation of sec – aminonitriles and carrying out the reaction in water. (Scheme 4)



Scheme 4

Irrespective of the pathways involved in the synthesis of α–aminonitriles they are generally prepared by one pot, three component condensation between an aldehyde, amine and a cyanide ion source in the presence of an acid catalyst.

The use of Lewis acid [6] as catalyst is one of the keys of performing this reaction efficiently. However, the main drawbacks for the choice of Lewis acids being their ability to undergo decomposition in the presence of nitrogen containing substrates. Despite this fact, owing to greater catalytic efficiency, a variety of Lewis acids such as chlorides of Gd[7a], Ce[7b], Co[7c], In[7d], Ru[7e], Ni[7f], Bi[7g], bromide of Li[7h], nitrates of Lanthanum[7a], triflates of Ga[8a], Cu[8b], V[8c], Pr[8d], Sc[8e], trimethyl silyl[8f] and perchlorates of Li[9a] and Fe[9b] have been shown to be effective catalysts for this synthesis.

In recent years, an efficient method for addition of TMSCN to various aldehydes and ketones has been described using Fe $(CP)_2$ PF_6 as a catalyst under solvent free condition[10], while cyanuric acid[11] and bis (dialkyl amino) cyanoboranes have reported in this aminative cyanation[12] reaction.

Diethyl phosphonocyanidate (DEPC) was introduced as a cyanide ion source in the synthesis of α–aminonitriles by Shioiri et al[13]. The main advantage of this process was that, the α–aminonitriles were derived also from ketones. Heydari et al.[14] have reported the use of lithium perchlorate diethyl ether (LDPE) for the synthesis of optically active α–aminonitriles.

Some microbial carbohydrates like α–cyclosophorohexadearose and succinoglycan monomers[15], polymer supported catalyst like PVP – SO_2 complex[16], polyethylene glycol[17] are used as catalyst in strecker transformation.

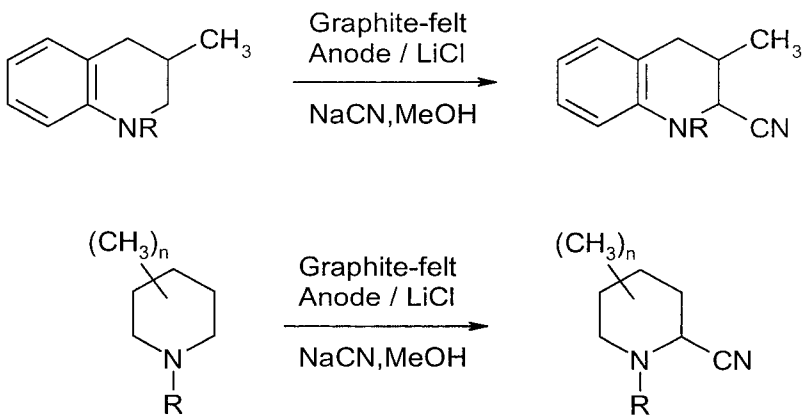
Like Lewis acids, Bronsted acids have also been demonstrated as useful catalyst in the synthesis of α–Aminonitriles. Thus the use of reusable heterogeneous solid acid catalyst like Montmorillonite KSF, silica sulphuric acid, sulfamic acid was demonstrated by Yadav et al[18], Chen et al[19], Heydari et al[20]. as well as Li et al[21] respectively. Bromodimethyl sulfonium bromide[22], guanidine

hydro chloride[23] were used as catalyst, as they serve as indirect source of Bronsted acid viz HBr/HCl.

Due to acidic and redox properties, heteropoly compounds like $H_{14}[NaP_5W_{30}O_{110}]$, Preyssler's heteropoly acid[24] and polyoxometalates like $K_5CoW_{12}O_{40}.3H_2O$ have been demonstrated as useful catalyst in the synthesis of α–Aminonitriles.

Although many acid catalysts have been reported for the synthesis of α–aminonitriles, seldom we found reports on base catalyzed strecker synthesis. In this context, use of triethylamine as a base catalyst reported by Sudalai et al.[8b] is noteworthy. Apart from these methods the use of cyclic dipeptides [25] have also been found useful to catalyze this transformation.

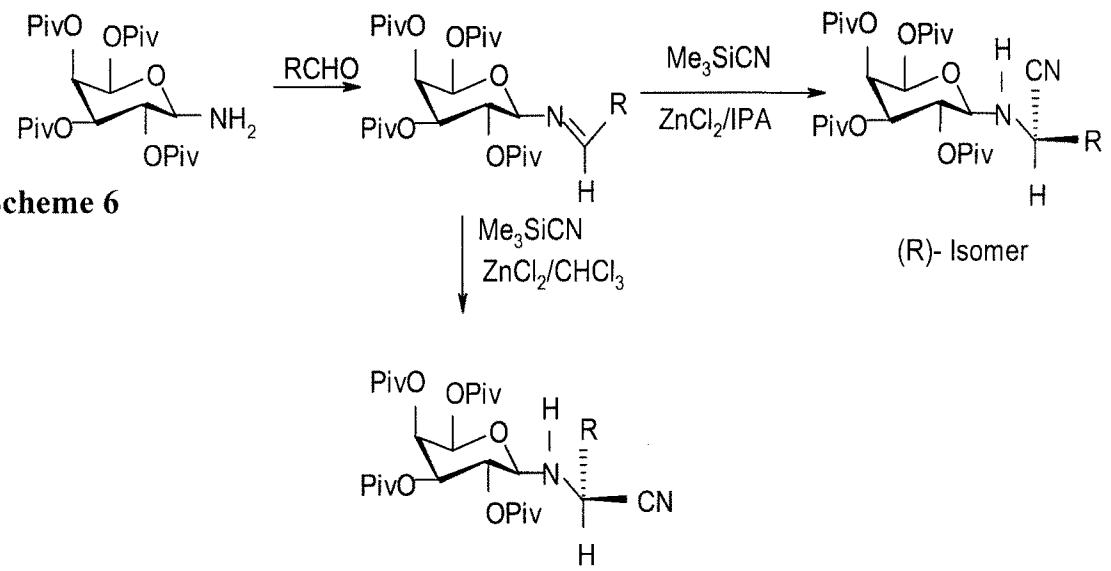
A smart synthesis of α–aminonitriles using electro chemical methods has been investigated by Hurvois et al.[26] recently. In one case methanolic solution of N–substituted tetrahydroquinolines and N – phenyl piperidines in the presence of sodium cyanide and lithium acetate were found to undergo anodic cyanation at a graphite electrode to provide corresponding α– aminonitrile. (Scheme 5)



Scheme 5

2.4 Asymmetric Strecker Reaction:

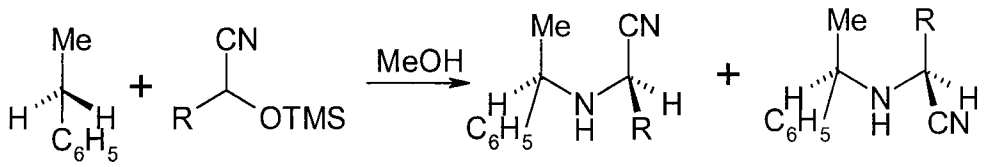
Asymmetric strecker reaction employing chiral amine auxiliaries have been extensively reviewed in recent past. [27] Kunz et al[28a, b] described the use of β-1-amino-tetra-o-pivaloyl-D-galatose auxiliary as a chiral ammonia equivalent. (Scheme 6)



Scheme 6

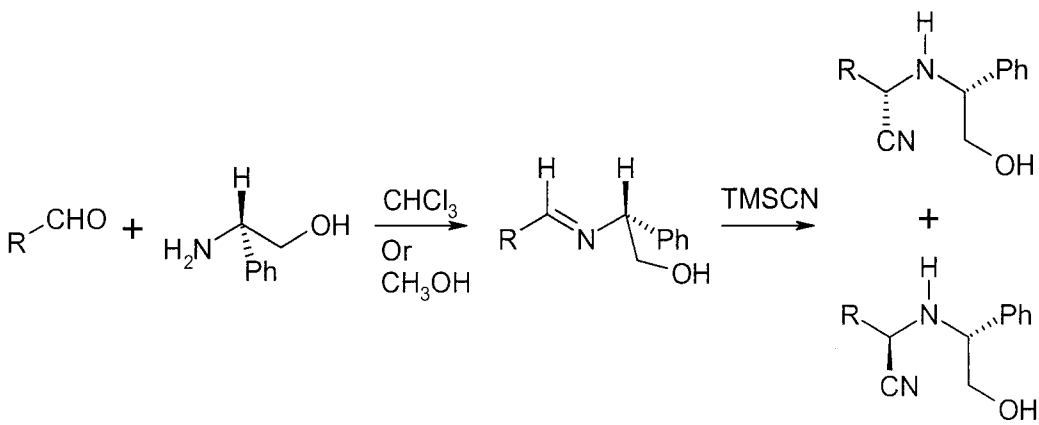
Scheme 6

Mai et al. [29] have reported asymmetric synthesis of α–aminonitriles by reaction of α–trimethyl silyloxynitriles essentially prepared by the reaction between aldehyde and TMSCN with optically active α–benzyl methylamine in methanol. The ratio of diasteromers (RR: RS) was established through ^{1}H NMR integration of α–proton. (Scheme 7)



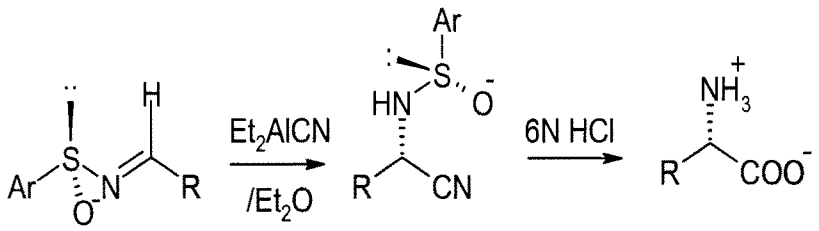
Scheme 7

A diastereoselective synthesis of α–aminonitriles has been reported by chakraborty et al.[30] using α–phenylglycinol as a chiral auxiliary. This modified method allows large scale preparation of α–aminonitriles. (Scheme 8)



Scheme 8

Davis et al[31] has employed enantiomerically pure sulfinimines as chiral ammonia imine equivalent in a wide variety of asymmetric transformations, one of these being an asymmetric version of Strecker reaction. [32a,b] (Scheme 9)



Scheme 9

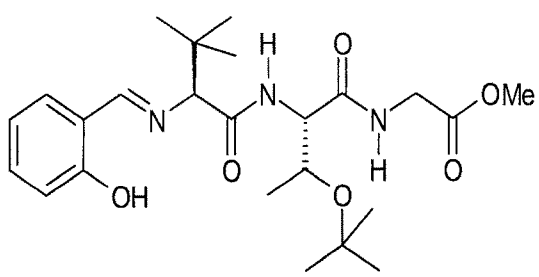
2.5 Catalytic Asymmetric Strecker Reaction:

It is well known that many processes are catalyzed using chiral Schiff base metal complexes with excellent levels of asymmetric induction.

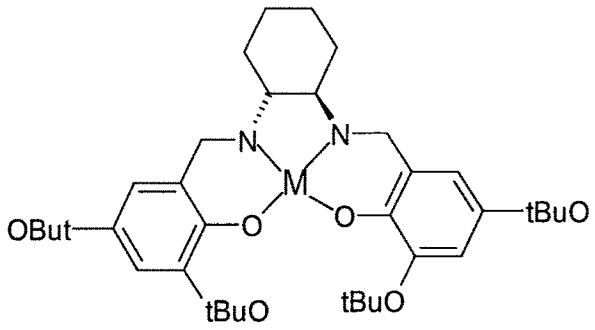
Hoveyda et al.[33] disclosed that the metal isopropoxide complexes of the tripeptide Schiff base promoted TMSCN addition to imines. The optimal reaction conditions were found upon using the titanium complex in toluene containing IPA with benzhydryl imines to afford the corresponding aminonitriles with high enantiomeric purities. (ee, 85 > 99%)

Jacobsen et al[34] have showed the use of (salen) Al(III) complex as a chiral metal complex for enantioselective addition of cyanide ion to imines in the synthesis of α–aminonitriles.

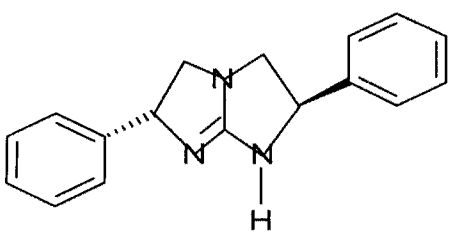
The use of C_2–symmetric bicyclic guanidine derivative cyclic dipeptide as a catalyst was demonstrated by Corey[35] and Lipton[36]respectively. (Scheme10)

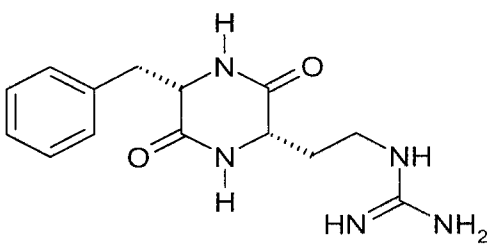


(a)

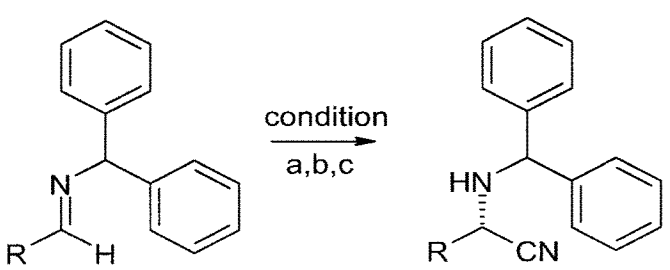


(b)





(c) (d)



a) Catalyst a (10 mol %), Ti(oiPr)4 (10 mol %), TMSCN in toluene

b) Catalyst b (5 mol%), TMSCN in toluene at 70°C for 15 hr

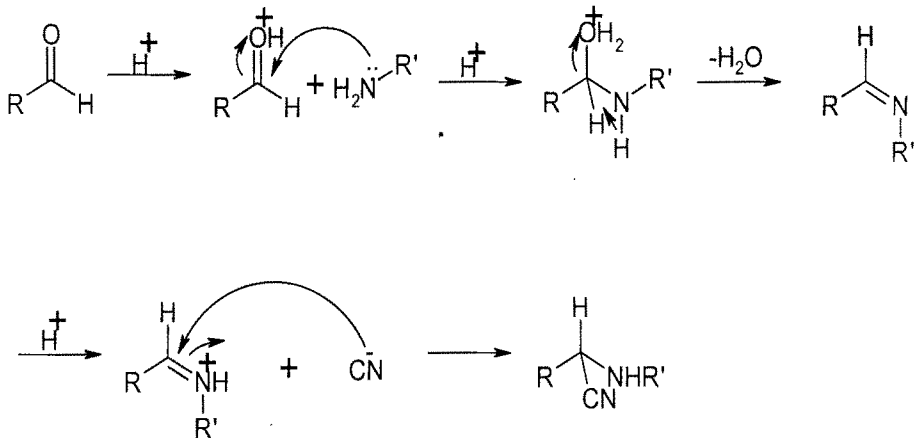
c) Catalyst c or d (10 mol %) 2 eq. HCN toluene or MeOH at -40°C

Scheme 10

2.6 Mechanism of Strecker Reaction:

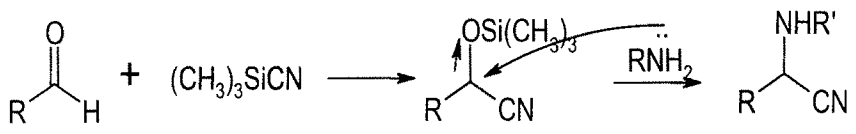
The reaction is routinely carried out as a one pot three component condensation between an aldehyde, amine and a cyanide ion source. Such a condensation is believed to proceed in two different ways.

(a) In the first approach cyanide ion is believed to attack nucleophilically to the protonated aldimines. (Scheme 11)



Scheme 11

(b) In second approach the reaction between aldehyde and trimethylsilyl cyanide is believed to yield trimethyl silyloxynitrile as an intermediate which is then attacked by an amine. (Scheme 12)



Scheme 12

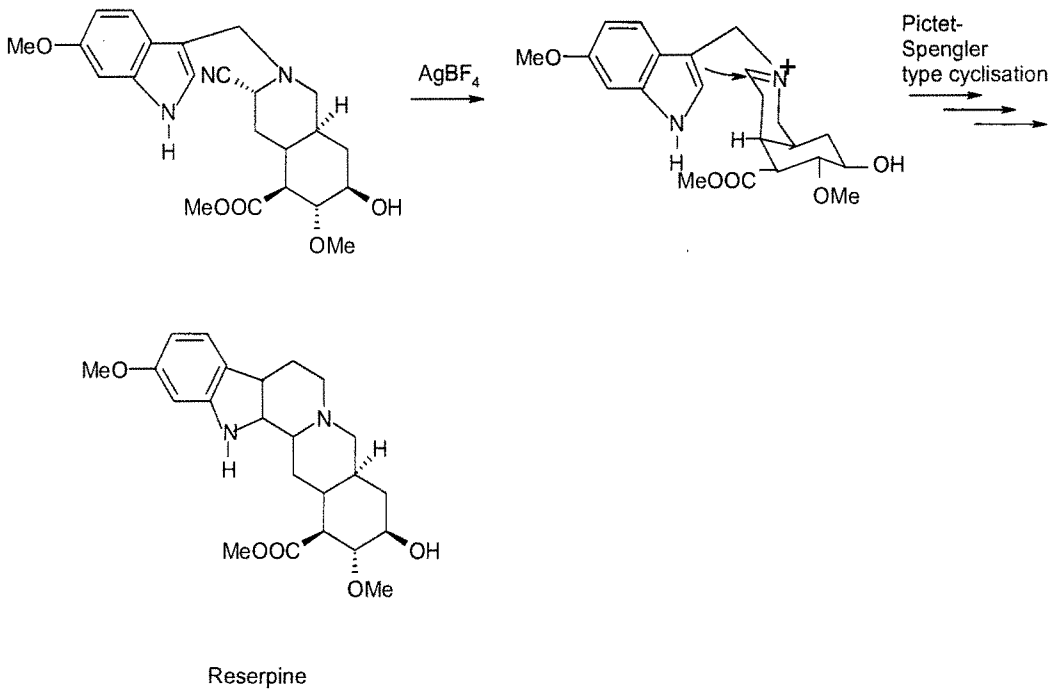
Irrespective of approach greater reactivity was observed for the carbonyl compound bearing electron donating group rather than electron withdrawing group, while aldehydes furnish higher yields than ketones. In fact, cyanoamination of ketones proceeds only under drastic conditions.

2.7 Applications of α–aminonitriles:

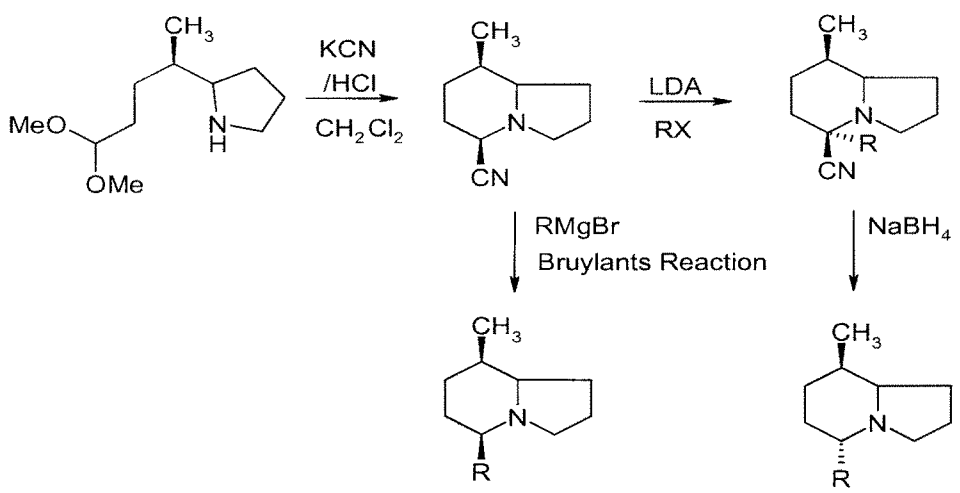
Applications of α-aminonitriles is truly a matter of an independent review article and that not being the objective of the present thesis, we have summarized in following few paragraphs only important applications of α-aminonitriles.

(1) The relatively high stability of α–aminonitriles and their ability to undergo cyanide ion loss under very mild condition to generate iminium ions has lead to their application towards the synthesis of many natural products and important building blocks. Stork et al[37] have disclosed synthesis of reserpine. The α–aminonitrile intermediate synthesized here is capable of acting as a masked iminium ion. The addition of either silver fluoroborate or dilute HCl had the effect of breaking up the tight ion pair to generate the free iminium ion species. subsequent ring closure takes place with nucleophilic attack of indole system to give pentacyclic indologuinolizidine bearing the configuration corresponding to reserpine. (Scheme 13)

(2) The dual reactivity of the α–aminonitrile group has regularly been employed in the synthesis of bicyclic alkaloids. A good example of this is Polniaszek's synthesis of indolzidine alkaloids.[38] In this case highly facile and selective substitution of the cyano group *via* an intermediate iminium ion is possible by either hydride or carbanionic species. (Scheme 14)

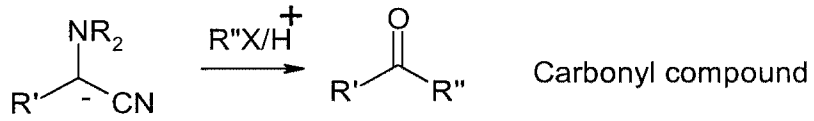


Scheme 13

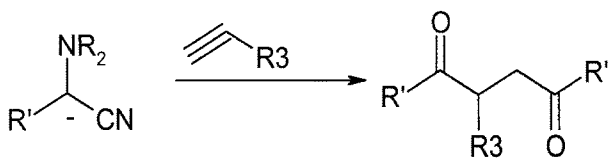


Scheme 14

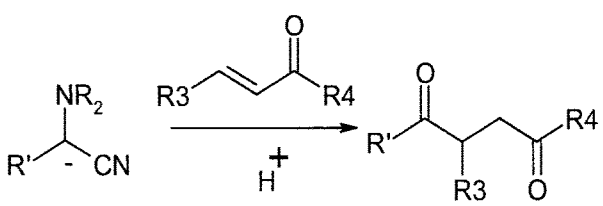
3) The use of metallated α–aminonitriles as acyl anion equivalents opens up the possibility for asymmetric synthesis. In this way it is possible to carry out asymmetric nucleophilic acylation reactions at prochiral electrophillic centers as in 1, 2 additions to aldehydes and 1, 4 additions to α, β–unsaturated carbonyl compounds. [39] (Scheme 15)



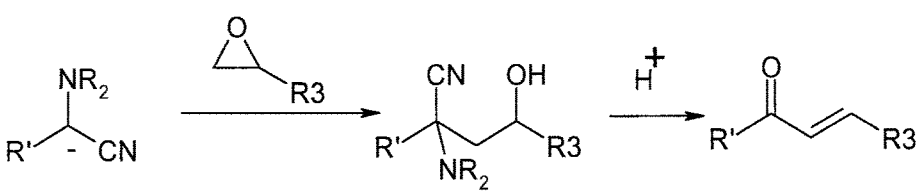
Carbonyl compound



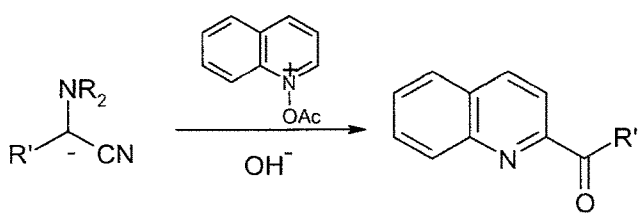
1,4 dicarbonyl compound



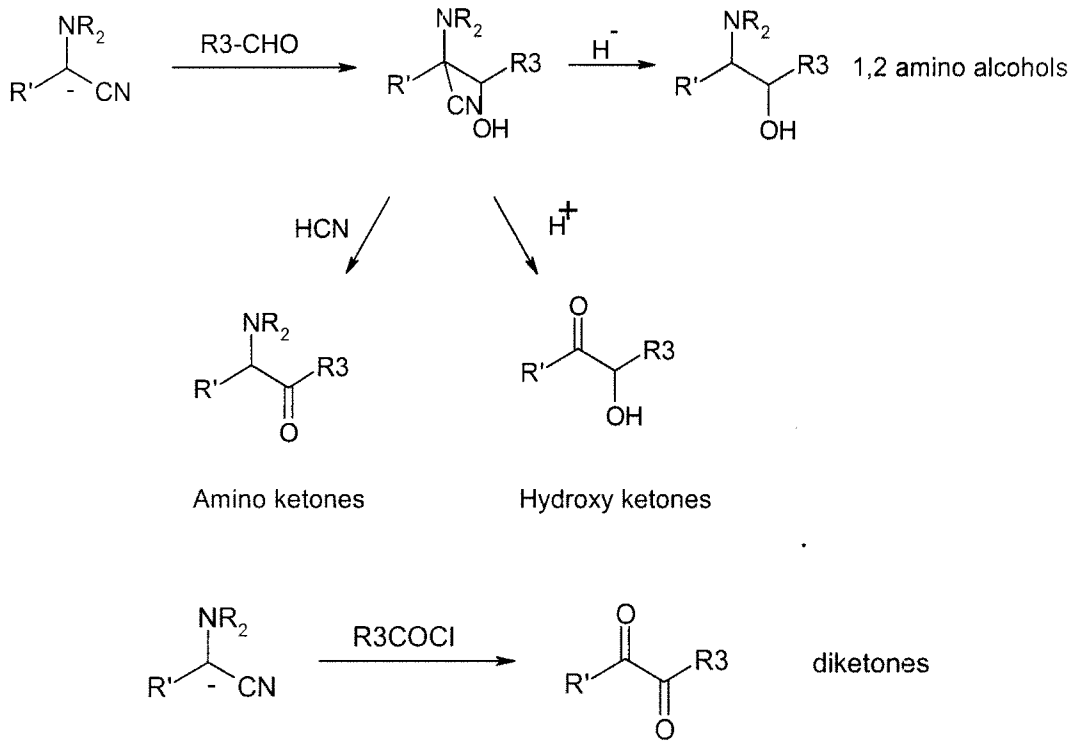
1,4-dicarbonyl compound



Unsaturated Carbonyl compound



Aroyl quinolines



Scheme 15

4) Biological Activity: At present time the biological and biochemical properties of α–aminonitriles have been studied quite widely. Amino acetonitrile is known to inhibit different enzymes, dimethylase, Nitrilase,etc. It also has an effect on contraction of muscles and mechanical properties of bones.[39]

After this literature survey, in view of the importance of α-aminonitriles as precursors to α-aminoacids and a few heterocyclic compounds and due to an ongoing work in our laboratory regarding the development of ecobenign and practically simple protocols for the synthesis of biologically important molecules, it was decided to develop a simple protocol for the synthesis of α-aminonitriles using a simple, reusable and inexpensive heterogeneous solid acid catalyst.

With an objective to develop environmentally friendly methods that obviate the need for potentially toxic metal based catalysts in organic transformations, during the past two decades, there has been a remarkable increase in the interest

towards the development of new synthetic methodologies employing various non–conventional acid / base catalysts. One particularly useful mode of catalysis is heterogeneous catalysis and catalytic transformations using solid heterogeneous catalyst have received considerable attention within the synthetic organic chemistry community.[39]

During the development of these new methods attention is mainly focused on the versatile properties of solid heterogeneous catalysts like easy recovery, reusability, environmental friendliness with respective to corrosiveness, safety, less waste, cost effective etc. Though heterogeneous catalysts offer several advantages their use must be done with great care taking into account the economic viability. The heterogeneous catalyst must exhibit activities and selective comparable or even superior to existing homogeneous route. Meeting their requirements our attention got focused on sodium hydrogen sulfate as a heterogeneous solid acid catalyst as well as polyvinyl pyridine hydrochloride as none of these catalysts have so far been explored in the synthesis of α-aminonitriles.

In the following article we have taken a very brief account of the synthesis as well as applications of silica gel supported sodium hydrogen sulphate in various organic transformations and to our delight since the discovery of PVP. HCl,[40] there are no reports on the applicability of this catalyst in multicomponent reactions.

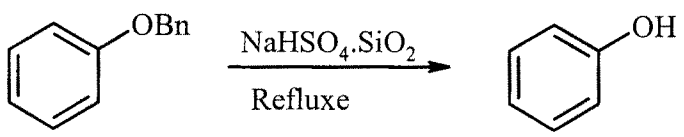
2.8 Brief account on silica gel supported sodium hydrogen sulphate as a solid acid catalyst:

Historically the sodium hydrogen sulfate on silica gel catalyst was prepared by Breton [41] from inexpensive, readily available and non-toxic bench top reagents i.e. $NaHSO_4$ and silica gel (SiO_2) (finer than 200 mesh) and latter on its

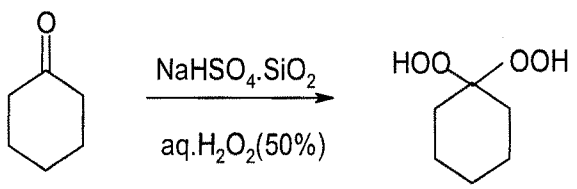
applications in various organic transformations were explored by many workers. This catalyst is less expensive, highly reactive, eco-friendly and easy to handle. It can be conveniently removed from the reaction mixture by simple filtration.

Literature survey for the applications of silica gel supported $NaHSO_4$ revealed that this catalyst has been used to catalyze many organic transformations like debenzylation of aromatic benzyl ethers[42] (Scheme 16), synthesis of aryl-14H-diebenzo [a,b] xanthenes by condensation of 2-naphthol and aryl aldehydes[43], synthesis of 4(3H)–quinazolinones[44], synthesis of β–acetylamino ketones[45], synthesis of gem-dihydroperoxides from ketones[46] (Scheme 17), synthesis of 1-carbamato-alkyl-2-naphthol derivatives[47] (Scheme 18), α-bromination of carbonyl compounds[48] (Scheme 19), stereoselective synthesis of (Z) and (E) allyl bromides, [49] (Scheme 20) etc.

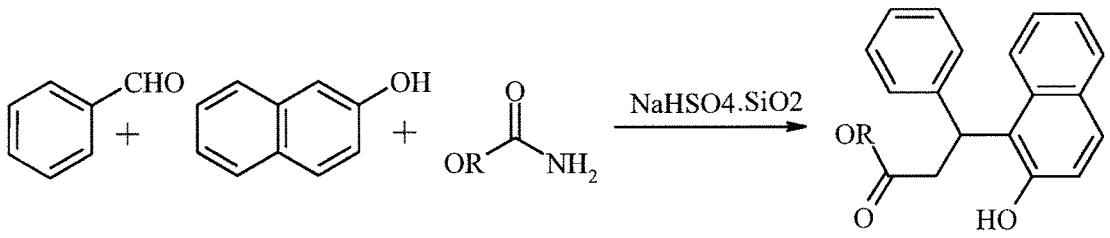
Das et al.[50] as well as Breton et al.[41] have reported the chemoselective acetylation of alcohols (Scheme 21) and amines while Ramu et al[51] have reported the use of $NaHSO_4.SiO_2$ in conversion of 4-hydroxy benzyl alcohols to 4-hydroxybenzyl ethers and thio ethers. Das et al.[52] have also reported the use of $NaHSO_4.SiO_2$ for deprotection of different protecting groups like TBDMS ethers, trityl ether[53], and monomethoxy methyl ethers[54] and phenyl esters[55] (Scheme 22).



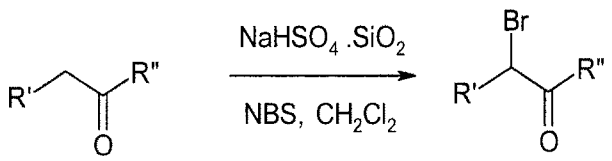
Scheme 16



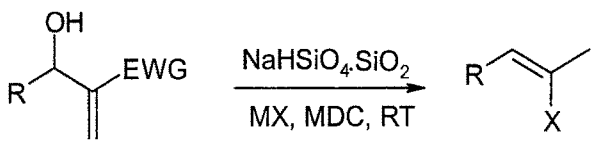
Scheme 17



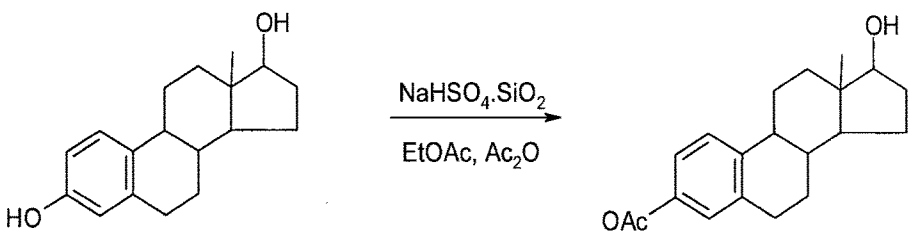
Scheme 18



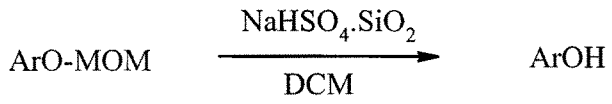
Scheme 19

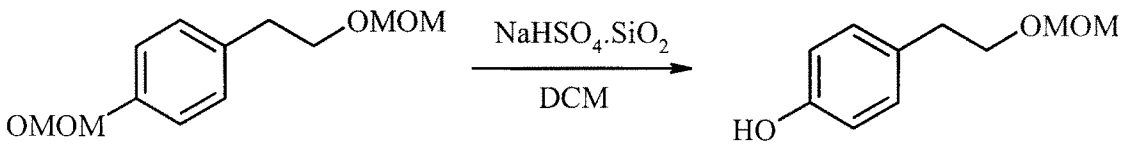


Scheme 20



Scheme 21





Scheme 22

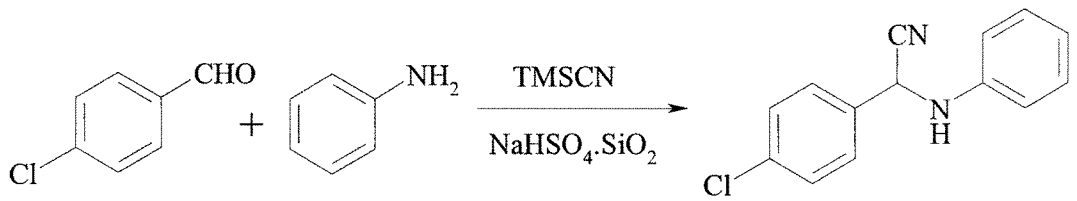
2.9 Summary:

The silica supported sodium hydrogen sulphate works under heterogeneous conditions and the catalyst can be conveniently removed by simple filtration. Thus it can easily be handled and removed from the reaction mixture. The catalyst can easily be prepared from inexpensive starting materials and it is non-toxic so we can conclude that sodium hydrogen sulphate catalyst can be explored for it's synthetic utility in important organic transformations that includes the synthesis of α-aminonitrile.

In recent years, the use of polymer based and reusable catalysts are gaining importance as they can also possess the well documented advantages of conventional inorganic support based solid acid catalysts. In this context our attention was focused on another easy to prepare and easy to handle catalyst *viz* polyvinyl pyridine hydrochloride. Basically it can also work as a reusable Bronsted acid catalyst. Since its introduction there are no reports on the use of this catalyst in any multicomponent reactions there exists a scope for exploration of PVP.HCl in the synthesis of α-aminonitriles.

2.9 Present Work:

We first planned to test the efficiency of sodium hydrogen sulphate as a catalyst in one pot three component synthesis of 2-(N-anilino)-2-4-chlorophenyl-acetonitrile as a model compound using 4-chloro benzaldehyde, aniline and TMSCN as substrates. (Scheme 23)



Scheme 23

Thus, to a mixture of 4-chlrobenzaldehyde (2 mmol), aniline (2 mmol) and trimethylsilyl cyanide (2.2 mmol) was added sodium hydrogen sulphate (200 mg) and the reaction mixture was stirred at ambient temperature. TLC examination indicated the formation of a new product at the expense of starting materials. On completion of the reaction, (TLC) the reaction mixture was diluted with chloroform and filtered. The filter was washed with chloroform and the combined filtrate was concentrated which yielded a white solid. It was purified by passing through a short column of silica gel to afford the pure compound. It was characterized by spectral methods. IR spectrum **(Fig.1)** clearly showed a band at 3330 cm^{-1} for –NH stretching and a weak band at 2252 cm^{-1} for the nitrile function. ^{1}H-NMR spectrum of the same compound showed a doublet at δ 4.03 (J = 6 Hz) for –NH proton, a doublet at δ 5.35 for benzylic methine proton (J = 6 Hz), a doublet at δ 6.68 for two aromatic protons *ortho* to –NH (J = 6 Hz), a triplet at δ 6.85 due to one aromatic proton *para* to –NH (J = 6 Hz), a distorted triplet at δ 7.20 due to aromatic protons *meta* to –NH (J = 6 Hz), a doublet at δ 7.34 due to two aromatic protons *ortho* to chlorine and a doublet at δ 7.47 due to aromatic

protons *meta* to chlorine (J = 6 Hz). The appearance of a band at 2238 cm^{-1} in IR spectrum and two doublets at δ 4.03 and 5.35 in the ^{1}H-NMR spectrum clearly indicated the formation of desired product viz. 2-(N-anilino)-2-4-chlorophenyl-acetonitrile.

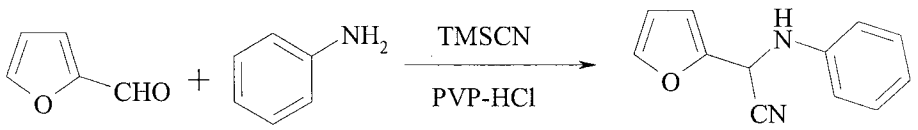
Encouraged with this success, in the preparation of α–aminonitrile using sodium hydrogen sulphate on silica gel as an effective catalyst, the attention was focused on the optimization of the reaction conditions with respect to the amount of catalyst essential for optimum conversion as well as towards the choice and essentiality of the solvent in this one pot synthesis using the same substrates. The results of these studies summarized in **Table-I** clearly reveal the essentiality of 200 mg of sodium hydrogen sulfate on silica gel as catalyst while the use of either protic or non-protic polar solvents *viz.* ethanol or methylene chloride did not show any appreciable effect on the time essential for this conversion. Infact, the reaction proceeds smoothly in absence of any added solvent. Thus the protocol developed, not alone offered the advantage of use of cheaper, easy to handle and non toxic catalyst but it was advantageous from environmental view point.

Table-I Effect of amount of $NaHSO_4.Sio_2$ and solvent on the yield of α-aminonitrile.

Entry	Catalyst amount (mg)	Solvent	Time (h)	Yield (%)
1.	50	-	3	25
2.	100	-	3	45
3.	150	-	3	70
4.	200	-	3	93
5.	250	-	3	95
6.	200	CH_2Cl_2	3	93
7.	200	EtOH	4	91
8.	200	CH_3CN	3	91

Reaction conditions: 4-Chlorobenzaldehyde (2 mmol), Aniline (2 mmol), Trimethylsilyl cyanide (2.2 mmol), catalyst, solvent, RT

After this initial success, the synthesis of another α–aminonitrile was planned using polyvinyl pyridine hydrochloride as another heterogeneous catalyst. The catalyst was prepared according to procedure reported in the literature. This time instead of using conventional aromatic aldehyde, furfuraldehyde was chosen as a model heteroaromatic aldehyde as the substrate. Accordingly, to a stirred mixture of furfuraldehyde (2 mmol) aniline (2 mmol) and TMSCN (2.2 mmol) was added polyvinyl pyridine hydrochloride (200 mg, 20 meq. of H^+) and the reaction mixture was stirred at ambient temperature. (Scheme 24)



Scheme 24

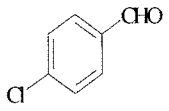
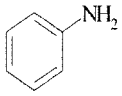
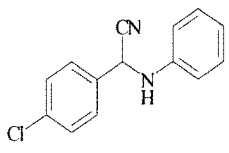
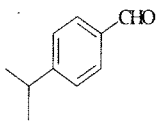
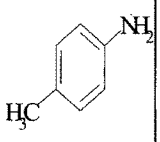
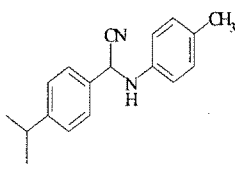
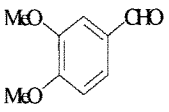
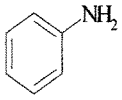
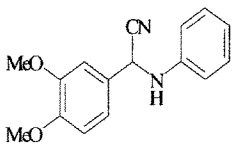
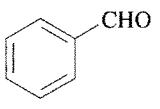
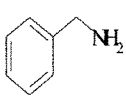
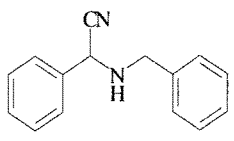
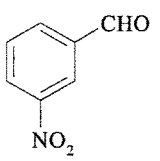
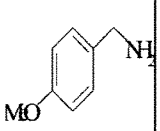
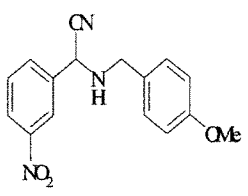
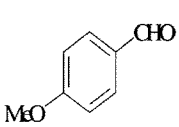
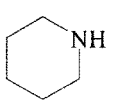
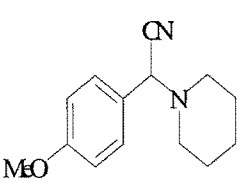
The reaction was monitored by TLC and it went to completion within two hours. Work-up of the reaction mixture as described earlier followed by short column chromatography furnished white crystalline solid whose melting point was in good agreement with that of reported in literature. Even then the structure was confirmed by IR as well as ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum exhibited characteristic broad singlet at δ 4.13 (**NH**), a doublet at δ 5.44 due to benzylic methine proton while protons from heterocyclic ring were observed at δ 6.41 (J = 3 Hz), 6.57 (J = 4 Hz) and 7.46 (J = 3 Hz). Optimization of the reaction conditions as regards the quantity of this catalyst was again carried out as described earlier which showed that the reaction proceeds with more than 90 % conversion with the use of 200 mg of PVP.HCL as catalyst again under solvent-free conditions.

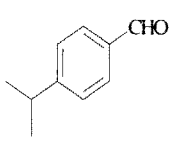
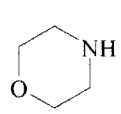
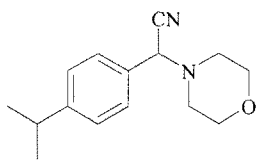
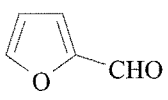
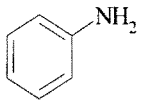
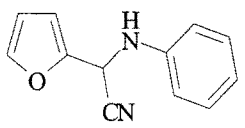
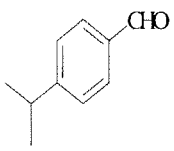
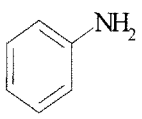
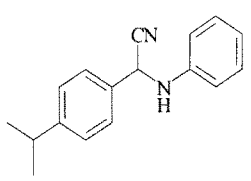
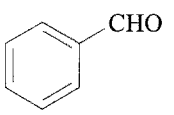
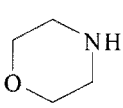
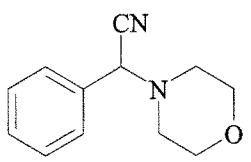
Under the optimized reaction conditions as regards the choice of both the catalysts, in a view to prove the generality of the protocol, a variety of aromatic aldehydes possessing electron donating as well as electron withdrawing groups as well as a few heteroaromatic aldehydes were reacted with various primary aromatic, benzylic and secondary heterocyclic amines with trimethylsilylcyanide. The results of this study are summarized in **Table II**. In all the cases, respective α-aminonitrile was obtained in excellent yield. All the synthesized α–aminonitriles were characterized by various spectral methods.

IR spectrum **(Fig. 2)** of 2-(N-4-methylphenyl)-2-4 isopropylphenyl acetonitrile, resulted by reaction between 4-isopropyl benzaldehyde, p-toluidine and TMSCN using both the catalysts exhibited two bands at 3364, 3334 cm^{-1} for secondary –NH and a weak band at 2233 cm^{-1} for – CN function. ^{1}H NMR spectrum **(Fig. 3)** was in perfect agreement with the expected structure. It exhibited a doublet at δ 1.26 (J = 6.9 Hz) and a septet at δ 2.93 (J = 6.9 Hz) characteristics for the presence of isopropyl methyl group and methine protons. It also exhibited a singlet at δ 2.27 for aromatic methyl group while benzylic methine proton appeared as a singlet at δ 5.33. In aromatic region four doublets (J = 8.2 Hz, each) we are observed each corresponding to two aromatic protons and typically exhibiting AA' BB' pattern.

^{13}C NMR spectrum of the same compound **(Fig. 4)** exhibited the signals at δ 20.37 (Ar-**C**H_3), 24.12 (**C**$H_3)_2$, 34.1 [-**C**H$(CH_3)_2$] , 50.56 (-**C**-CN), 118.78 (-**C**N) proving the structure of the compound an ambigiousing. GCMS of this compound **(Fig. 5)** was recorded to confirm purity of sample and to have the mass spectrum. It exhibited a weak molecular ion peak at m/z = 264, a strong peak at 237 due to $(M\text{-}CN)^+$ ion and a weak peak at 222 due to $(M\text{-}CN\text{-}CH_3)^+$ ion.

Table II: Synthesis of α- aminonitriles using $NaHSO_4.SiO_2$/PVP-HCl as catalyst

Sr. No.	Aldehyde	Amine	α –aminonitrile	Cata. A Time (h)	Cata. A Yield (%)	Cata. B Time (h)	Cata. B Yield (%)
1.				3	92	2.5	90
2.				2.5	88	2	90
3.				3	82	3	80
4.				4	80	3.5	82
5.				3.5	75	3.5	78
6.				2.5	87	3	93

7.				3 78	3 81
8.				2.5 86	2 87
9.				2.5 90	2.5 88
10				3 81	3 78

A: Reaction carried out using $NaHSO_4.SiO_2$ as a catalyst

B: Reaction carried out using PVP.HCl as a catalyst

Thus, by using $NaHSO_4$ on silica gel as well as polyvinyl pyridine hydrochloride as heterogeneous catalysts we could synthesized range of α-aminonitriles starting from a variety of aldehydes and amines with TMSCN as a source of cyanide ion.

The attention was then focused on the choice of benzyl amine in place of substituted anilines. A model reaction between benzaldehyde, benzyl amine and TMSCN was although sluggish it furnished the expected α-aminonitrile *viz.* 2-(N-benzylamino)-2-phenyl acetonitrile in excellent yield in four hours. The ^1H NMR spectrum **(Fig. 6)** interestingly exhibited two sets of doublets (an AB quartet) for

the benzylic methylene protons. In addition –NH proton appeared as broad singlet at δ 2.05 while benzylic methine proton appeared as a slightly broad singlet at δ 4.72 ppm.

In the initial trial with benzyl amine as amine equivalent corresponding α-aminonitrile was obtained in slightly longer time hence it was then planned to test the feasibility of other aldehydes in reaction with benzyl amine or substituted benzyl amine. The reaction between 3,4-dimethoxy benzaldehyde, benzyl amine and TMSCN was equally sluggish in the presence of both the catalysts but it didn't go to completion. The TLC examination indicated only 80% conversion. The modification of reaction conditions as regard the amount of catalyst and the increasing time was not found to be beneficial for the driving of reaction to completion. The workup of the reaction mixture as reported earlier followed by careful separation of the product by column chromatography furnished 2-(N-benzylamino)-2-(3,4 dimethoxy phenyl) acetonitrile. ^{1}H NMR spectrum **(Fig. 7)** exhibited two merged singlets at δ 3.90 and 3.92 for aromatic methoxyl groups and a broad singlet at δ 4.79 for benzylic methyl protons. The other signals in the spectrum were in accordance with the expected structure. In this spectrum characteristic AB quartet of benzylic methylene protons possible due to the presence of chiral center was not observed hence the structure was further proved by ^{13} C NMR. The spectrum **(Fig. 8)** in the aliphatic region exhibited a strong signal at δ 55.95 due to two methoxy carbons and at 64.88 due to benzylic methyl carbon.

The reaction between 4-methoxy benzyl amine (electron rich, more basic benzyl amine) and m-Nitrobenzaldehyde was also successful but as expected the reaction didn't go to completion and the conversion was ≈ 75%. The ^{1}H NMR of the resultant product **(Fig. 9)** exhibited a singlet at δ 3.81 due to methoxyl protons an AB quartet at δ 3.98 and a singlet at δ 4.86 for benzylic methine proton. The signal assignment to various aromatic protons could very easily be made from proton ^{1}H-NMR spectrum. In this spectrum two doublets (J = 7.5 Hz each) due to

protons *ortho* to and *meta* to methoxy group were observed at δ 6.90 and δ 7.33, respectively. A triplet at δ 7.61 (J = 7.8 Hz) was due to the proton *meta* to $-NO_2$ group. Two more doublets (J = 6.9 Hz, each) at δ 7.92 and δ 8.24 were due to the protons *para* to and *ortho* $-NO_2$ group. While the remaining aromatic protons *ortho* to $-NO_2$ was observed the broad singlet at δ 8.44.

It was then planned to test the feasibility of these two catalysts for the reaction between aldehydes, heterocyclic amines such as morpholine, pyrrolidone, piperidines and TMSCN as cyanide ion source. Interestingly the reaction between morpholine as well as piperidines was successful to furnish the desired products in excellent yields while the reaction with pyrrolidone surprisingly didn't go to completion. The product of reaction between anisaldehyde, piperidines and TMSCN was a yellowish oil which in it's ^1H NMR spectrum **(Fig. 10)** exhibited a diffused multiplet between δ 1.47 to δ 1.61 for six protons from piperidines ring while the remaining four protons α to nitrogen appear as diffused triplet (J = 4.2 Hz) at δ 2.49. The proton due to methoxy group and due to benzylic methine proton as expected exhibited singlets δ 3.82 and δ 4.76, respectively. The aromatic protons again exhibited two doublets at δ 6.91 and δ 7.44. ^{13}C NMR spectrum in non aromatic region exhibited the signals at δ 23.98, δ 25.78, δ 50.79, δ 55.33, δ 62.41. Among these signals at δ 23.98, 25.78, 50.97 appeared inverted in DEPT scan of the spectrum **(Fig. 12)** indicating those being due to methylene group carbons.

It was then planned to test the feasibility of ketone as the source of carbonyl compound. However, using both $NaHSO_4.SiO_2$ as well as PVP-HCl as catalysts, ketones failed to furnish respective α–aminonitriles and this is in tune with the fact of the lower reactivity of ketones than aldehydes in formation of imines, the intermediates necessary in the synthesis of α–aminonitriles by one-pot, three component condensation protocol.

The principle advantage regarding the use of heterogeneous solid acid catalysts in organic transformations is their reusability. Both, $NaHSO_4$. SiO_2 as well

as PVP. HCl being insoluble in common organic solvents like methylene chloride, THF, ethyl alcohol, ethyl acetate, etc. upon completion of the reaction, the resultant product was isolated using chloroform while the catalyst recovered after drying was used in the synthesis of the same or different aminonitriles. It was observed that the catalyst can be reused for the successive runs without any appreciable change in its activity.

2.10 Conclusion:

In summary, we have developed a mild, practically simple, efficient and environmentally benign protocol for the synthesis of α–aminonitriles by using sodium hydrogen sulphate as well as polyvinyl pyridine hydrochloride as less inexpensive and reusable solid acid catalyst at ambient temperature.

2.11 Experimental :

2.11.1 *General*

Sodium hydrogen sulphate on silica gel was prepared according to the reported procedure. [39] Aldehydes (E Merck, Lancaster and SD fine chemicals), amines (SD fine chemicals and SRL) and TMSCN (Lancaster) were used as received. IR spectra were recorded on Perkin-Elmer FT-IR-783 spectro-photometer while NMR spectra were recorded on Bruker AC-200 or avance-300 (200MHz or 300MHz) spectrometer in $CDCl_3$ using TMS as an internal standard and δ values are expressed in ppm. Melting points recorded are uncorrected.

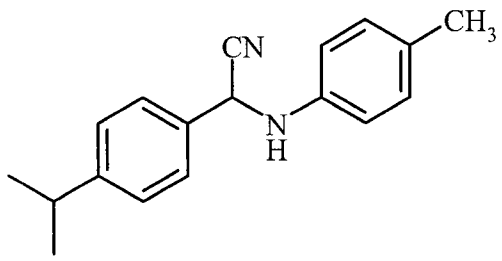
2.11.2 *Experimental Procedure*

A mixture of an aldehyde (2mmol), aniline (2mmol), TMSCN (2.2mmol) and $NaHSO_4$ (0. 2 g) or polyvinyl pyridine (0. 2 g) was stirred at room temperature for an appropriate time (Table II). On completion of reaction (TLC), chloroform was added and the reaction mixture was filtered. The catalyst was washed with chloroform (2 X 10 ml). From the combined filtrate chloroform was removed under vacuum and the crude product obtained was purified by column chromatography on silica gel to afford pure α–aminonitriles. which was characterized by spectral methods.

All the compounds were characterized by spectral methods and the spectral data of the resultant α–aminonitriles has been summarized below.

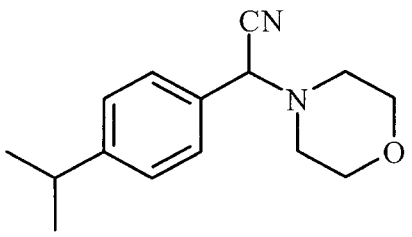
2.12 Spectral Data:

2-(N-4-Methylphenyl (4-isopropyl phenyl) acetonitrile



White solid, mp. 72-74°c; **IR** (KBr): 3364, 3334, 2233, 1524, 1320, 1130, 805 cm^{-1}; **^{1}H NMR:** δ 1.22 (6H, d, *J* =7 Hz), 2.26(3H, s), 2.96 (1H, septet), 4.0 (1H, bs), 5.38 (1H, s), 6.65 (2H, d, *J* = 8 Hz), 7.03 (2H, d, *J* = 8 Hz), 7.30 (2H, d, *J* = 8 Hz).

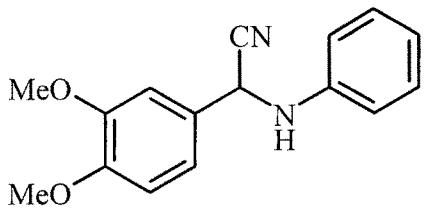
2-(N-Morpholino)-2-(4-isopropyl phenyl) acetonitrile



IR: 2930, 1511, 1454, 1248, 1116, 1064, 829 cm^{-1}; **^{1}H NMR:** δ 1.21 (6H, d, *J* =7 Hz), 2.58(2H, s), 2.95 (1H, septet), 3.65 (2H, s), 4.78 (1H, s), 7.23 (2H, d, *J* = 8 Hz), 7.4 (2H, d, *J* = 8 Hz)

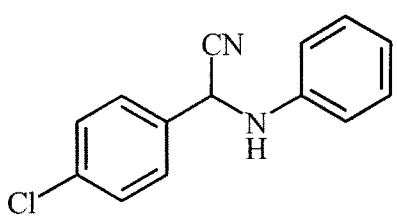
MS: m/z = 245 (M^++1)

2-(N-Anilino)-2-(3,4-dimethoxy phenyl) acetonitrile



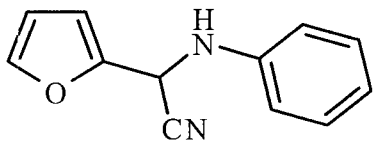
IR: 3419, 3020, 2966, 2236, 1607, 1504, 1373, 929 cm-1; **^{1}H NMR:** δ 3.91 (1H, s), 3.95(6H, s), 5.37 (1H, brs), 6.77(2H, d, J = 8 Hz), 6.92 (1H, t, J = 8 Hz), 7.06-7.15 (2H, m), 7.26 (1H, d), 7.41 (2H, d, J = 8 Hz) **^{13}C NMR:** δ 49.70, 55.80, 108.66, 110.98, 113.84, 118.23, 119.44, 119.82, 125.96, 128.86, 129.25, 144.52, 149.45.

2-(N-Anilino)-2-4-chlorophenyl acetonitrile



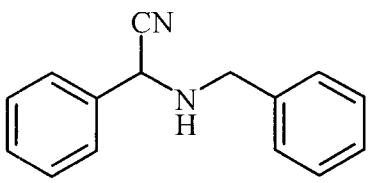
Mp 109-110°c; **IR:** 3330, 2924, 2854, 2252, 1603, 1502, 1385, 1218, 1094, 770 cm-1; **1H NMR:** δ 4.03 (1H, d, J = 8 Hz), 5.33 (1H, d, J = 6Hz), 6.69 (2H, d, J = 7 Hz), 6.87(1H, t, J = 7 Hz), 7.22 (2H, t, J = 7 Hz), 7.37 (2H, d, J = 7 Hz), 7.48 (2H, d, J = 7 Hz), **13C NMR**: δ 49.60, 114.36, 117.63, 128.61, 129.53, 132.58, 132.64, 144.41

2-(N-Anilino)-2-furylacetonitrile



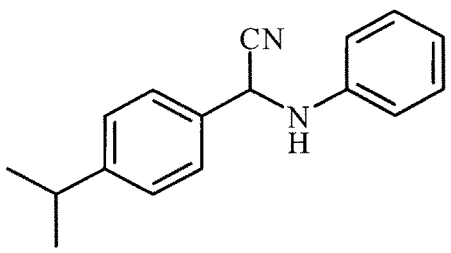
Mp 67-69°c; **IR**: 3393, 3020, 2236 (weak), 1738, 1603, 1523, 1424, 1217, 1018, 770, 670 cm-1; **1H NMR**: δ 4.13 (1H, brs), 5.44 (1H, d, J = 6 Hz), 6.41 (1H, d, J = 3Hz), 6.57 (1H, d, J = 4 Hz), 6.72 (2H, d, J = 8 Hz), 6.88 (1H, t, J = 8 Hz), 7.25 (2H, d, J = 8 Hz), 7.46 (1H, d, J = 3 Hz)

2-(N-benzylamino)-2-phenyl acetonitrile



IR: 3397, 3020,2229, 1661, 1531, 1261, 1216, 1095, 759, 669 cm^{-1}; **^{1}H NMR:** δ 2.18 (1H, brs), 3.94 (2H, AB quartet), 4.71 (1H, s,), 7.19-7.82 (10H, m); **^{13}C NMR:** δ 14.32, 31.20, 48.53, 54.92, 120.36, 127.63, 128.91, 129.36, 135.70

2-(N-Anilino)-2-4-isopropylphenyl acetonitrile



IR: 3420, 3020, 2966, 2236(weak), 1607, 1504, 1373, 1219, 929, 757 cm^{-1}; **^{1}H NMR:** δ 1.31 (6H, d *J* = 8 Hz), 2.99 (1H, septet, J = 8 Hz), 5.41 (1H, s,), 6.81 (2H, d, J = 8 Hz); 6.93 (1H, t), 7.27-7.37 (4H, m), 7.31 (2H, d, J =8 Hz), 7.37 (1H, s), 7.55 (2H, d)

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