Chapter IV

β-Cyclodextrin: A supramolecular catalyst for metal-free approach towards the synthesis of 2-amino-4,6-diphenylnicotinonitrile

IV.1. Introduction

Pyridine is a six-membered aromatic heterocyclic compound with molecular formula C_5H_5N. Its structure is related to benzene ring where one methine (=CH-) group is replaced by N. The pyridine motif is very essential scaffold due to its occurrence in natural products, biological and medicinal chemistry (Figure IV.1).

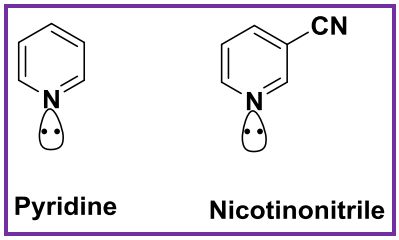


Figure IV.1. Structure of pyridine moieties

Nicotinonitrile is an organic compound with molecular formula C_5H_4NCN named 3-cyanopyridine. Among the pyridine ring systems, 2-aminonicotinonitrile derivatives have achieved elevated synthetic attention as an imperative heterocyclic molecule due to its existence as bio-active species such as IKK-β inhibitors,[1] potent inhibitor of HIV-1 integrase,[2] A2A adenosine receptor antagonist[3] and also in antitubercular,[4] anticancer, anticardiovascular[5] and antimicrobial activity (Figure IV.2**)**.[6] Pyridines are also valuable in materials and surfaces,[7] organocatalysis,[8] supramolecular structures[9] and coordination chemistry.[10] Also, these compounds serve as useful intermediates for the preparation of a diversity of heterocyclic compounds.[11]

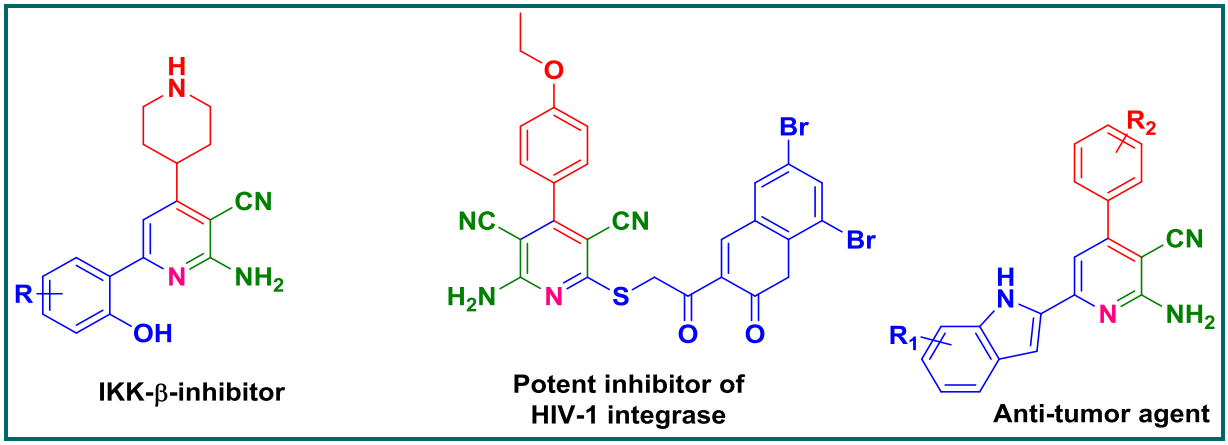


Figure IV.2. Biologically potent molecule having nicotinonitrile moiety

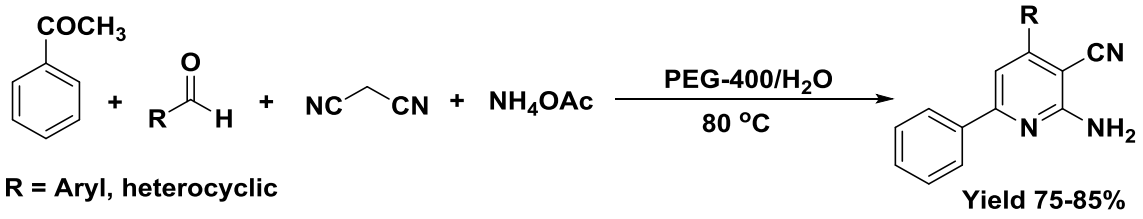
IV.2. Background and Objectives

In past decades, for the production of diverse array of heterocyclic molecules and making the synthetic route simpler, one-pot multi-component organic synthesis has an imperative role in the field of chemistry. Three or sometimes more starting materials coalesce together in the same pot to construct the target molecule exclusively in multi-component synthesis without separating intermediate which aid to reduce the reaction time, solvent waste, energy consumption and therefore have the great compensation over the multistep procedure.[12]

Many diverse protocols have been reported for synthesis of this derivative such as use of ionic liquid, ultrasound irradiation, Lewis acid catalysts, Fe_3O_4, graphene oxide and so on. Although several methods for preparation of 2-amino-4,6-diphenylnicotinonitrile are well documented in literature, but most of them have few drawbacks such as use of hazardous solvents like benzene or toluene, very high temperature, multiple step pathway, long reaction times with low yields, use of transition metal which leads to metal contamination at the end of reaction and harsh reaction conditions which are not environmentally friendly. Some of the protocols for synthesis of pyridine derivatives are given below.

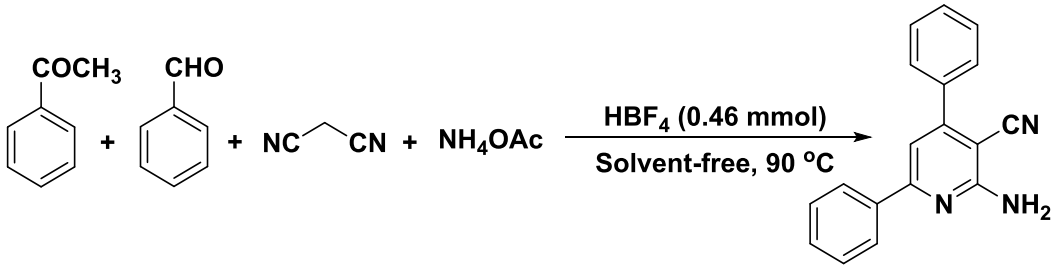
IV.2.1. One-pot four-component synthesis of 2-amino-3-cyanopyridine

In 2017, P. Balaswamy *et al.* reported a greener protocol for synthesis of 2-amino-3-cyanopyridines through one-pot multi-component synthesis using PEG-400 as phase transfer catalyst under aqueous condition with recyclability of solvent (Scheme IV.1).[13]



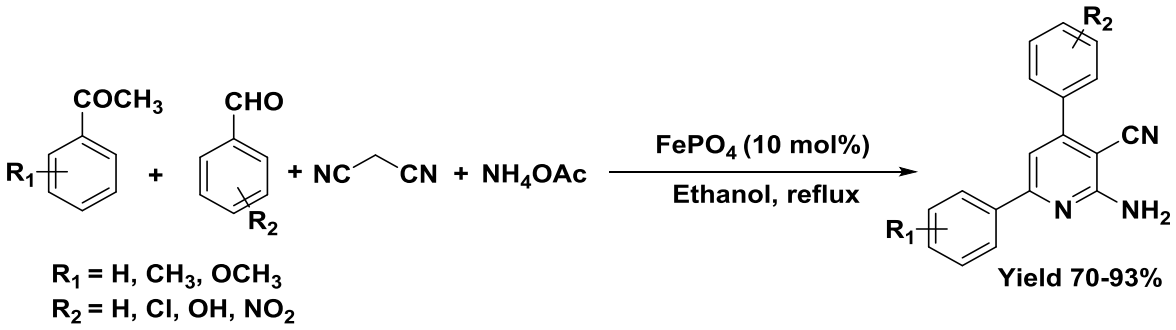
Scheme IV.1. PEG-400: Metal-free synthesis of 2-amino-3-cyanopyridine in water

Another protocol was developed using HBF_4 as an oxidizing catalyst by M. A. Zolfigol *et al.* in 2017 under solvent-free condition (Scheme IV.2).[14] The recommended mechanism is supported by experimental and theoretical studies. The theoretical study shows that the intermediate isomers with 5R- and 5S- chiral positions have suitable structures for the aromatization through an anomeric based oxidation in the final step of the mechanistic pathway.



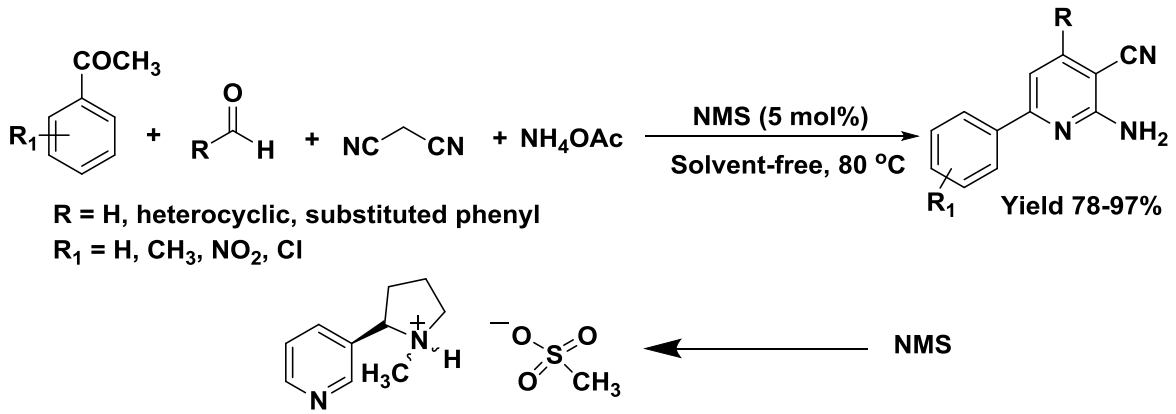
Scheme IV.2. HBF_4: An oxidizing catalyst for synthesis of pyridine derivatives

In 2015, M. Zadpour *et al.* demonstrated a methodology in presence of green and reusable heterogeneous catalysts $FePO_4$ to afford the corresponding 4,6-disubstituted 2-aminopyridine-3-carbonitriles (Scheme IV.3).[15]



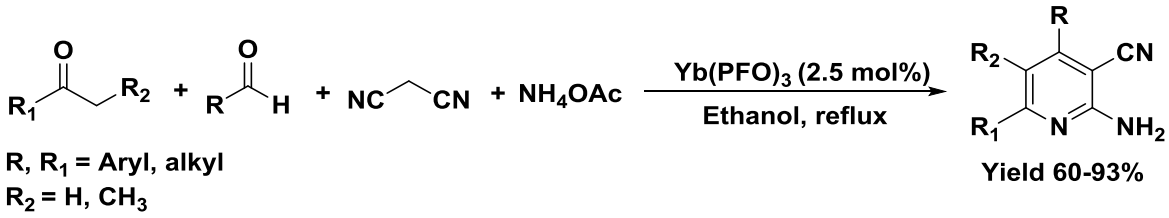
Scheme IV.3. Synthesis of pyridine derivative in presence of heterogeneous catalyst $FePO_4$

Modifying the same work, F. Tamaddon *et al.* prepared an ionic liquid from nicotine and methane sulfonic acid named nicotinum methane sulfonate with dual activity of acid and base functional groups in 2018. This recyclable protic ionic liquid was reported to have performed the catalytic activity for this methodology very well under solvent-free condition (Scheme IV.4).[16]



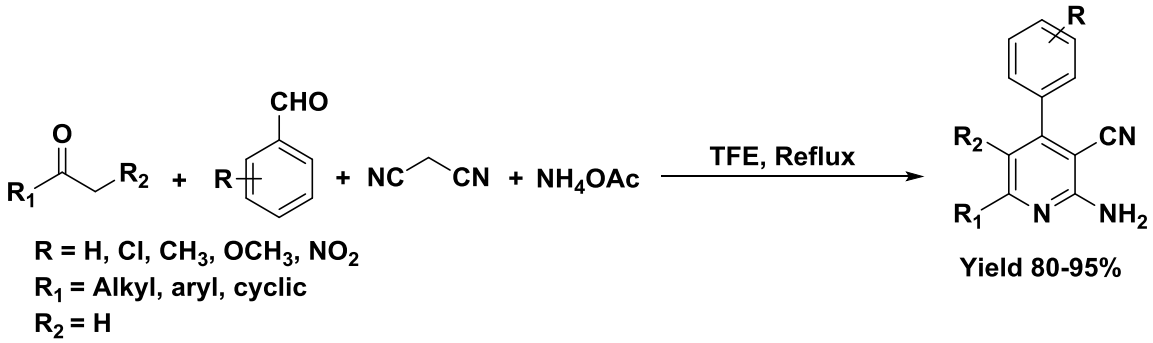
Scheme IV.4. NMS: A protic ionic liquid for synthesis of 2-aminonicotinonitriles

In 2011, J. Tang *et al.* reported a simple procedure *via* one-pot reaction catalyzed by ytterbium perfluorooctanoate [$Yb(PFO)_3$] with good substrate tolerance using ethanol as a solvent (Scheme. IV.5).[17]



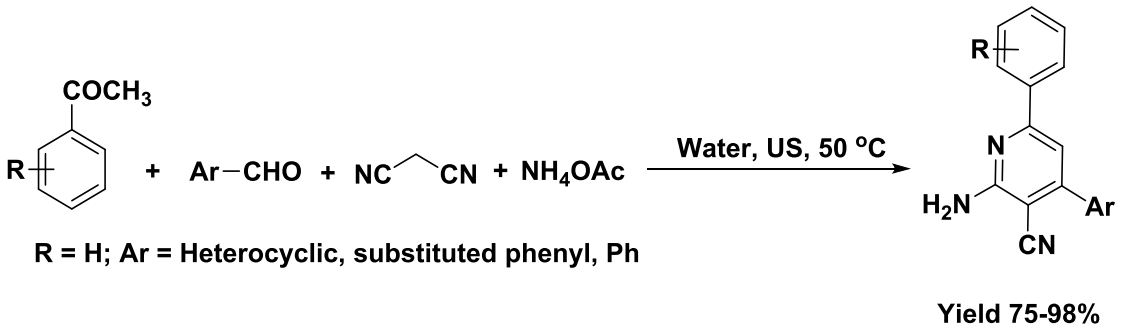
Scheme IV.5. [$Yb(PFO)_3$] promoted synthesis of 2-amino-3-cyanopyridine

S. Khaksar *et al.* promoted trifluoroethanol (TFE) as an efficient and recyclable medium to afford the corresponding 2-amino-3-cyanopyridine derivatives in 2012. The solvent was reported to be readily separated from reaction products and recovered for direct reuse (Scheme IV.6).[18]



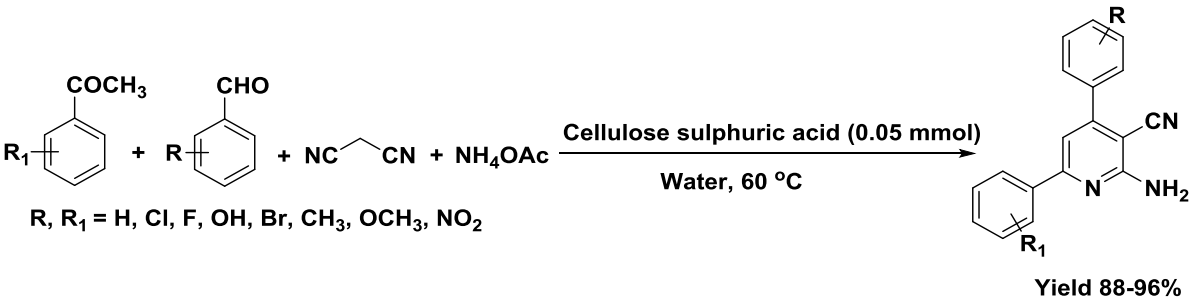
Scheme IV.6. Trifluoroethanol mediated synthesis of 2-aminonicotinonitriles

In 2012, J. Safari *et al.* described a convenient approach towards this synthesis in water under ultrasound irradiation without the need of transition metal or base catalyst. Environment friendly synthesis is the prominent features of this sonocatalyzed procedure (Scheme IV.7).[19]



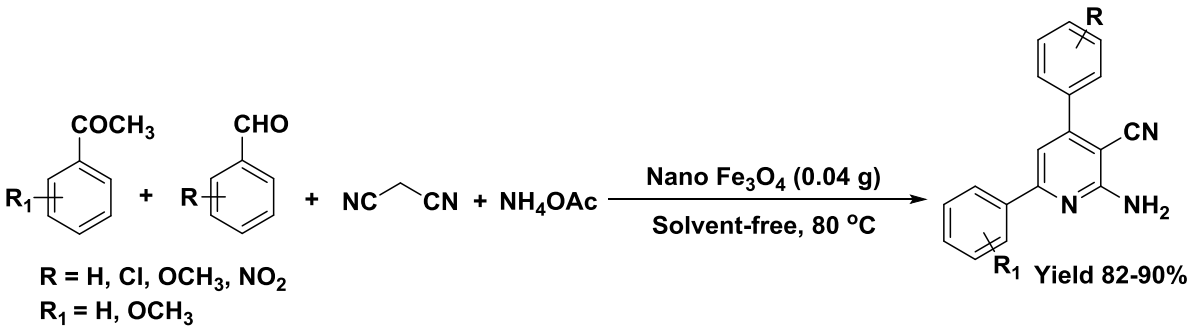
Scheme IV.7. Ultrasound-promoted method for designing nicotinonitriles in water

S. S. Mansoor *et al.* designed a heterogeneous reusable catalyst named cellulose-sulphuric acid from cellulose powder and chlorosulfonic acid in 2014. Then they utilized this catalyst for the synthesis of nicotinonitriles in water and were reported to have an excellent yield (Scheme IV.8).[20]



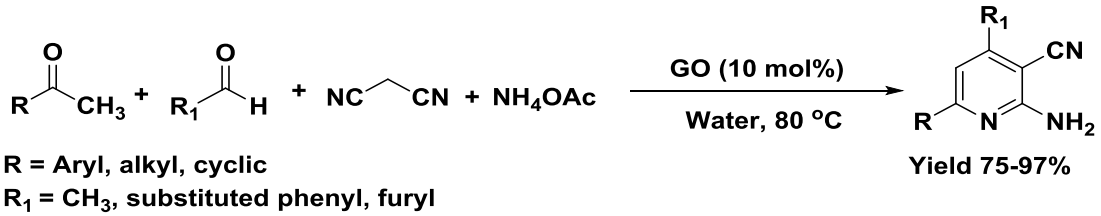
Scheme IV.8. Cellulose sulfuric acid: An efficient catalyst for preparation of 2-amino-3-cyanopyridine in water

Nano Fe_3O_4 with high surface area and recyclability was developed by M. M. Heravi *et al.* in 2015 and it was utilized for the synthesis of 2-amino-3-cyanopyridine derivative through one-pot multi-component method (Scheme IV.9).[21]



Scheme IV.9. Nano Fe_3O_4 catalysed synthesis of 2-amino-3-cyanopyridine

D. Khalili *et al.* in 2016 demonstrated a protocol using heterogeneous carbocatalyst graphene oxide in water. The graphene oxide catalyst was published to be effective and most of its activity was preserved after being reused for five times (Scheme IV.10).[22]

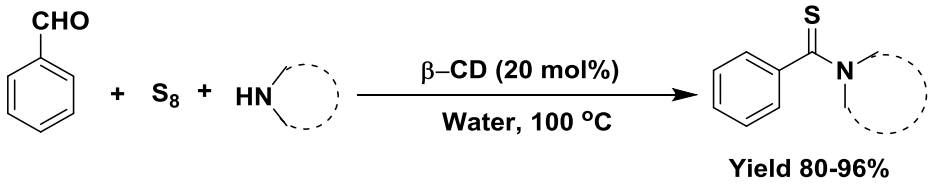


Scheme IV.10. Graphene oxide: A carbocatalyst mediated synthesis of 2-amino nicotinonitriles in water

IV.2.2. β-Cyclodextrin mediated organic synthesis

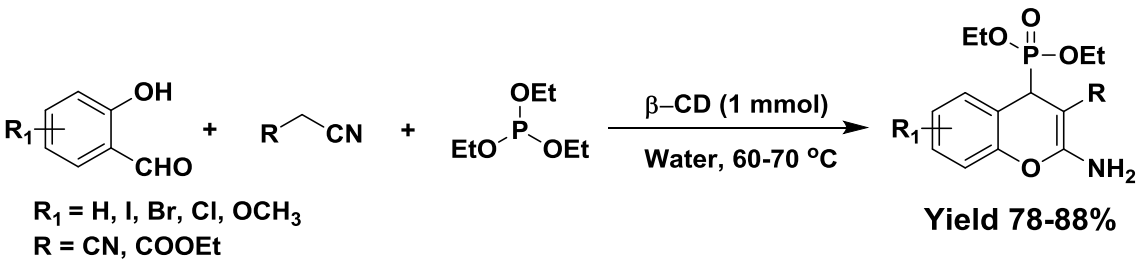
With the advancement of supramolecular chemistry and homogeneous catalysis, supramolecular catalyst has been emerging as an important tool in synthesis of organic heterocyclic compounds.[23] Among the array of supramolecular hosts, cyclodextrins (CDs) is one of an important enzyme models.[24-29] Being cyclic oligosaccharides, cyclodextrins possess hydrophobic cavities which enable them to bind with substrates selectively due to which they are able to catalyze chemical reactions ensuring high selectivity.[30-33] During the course of the reaction, CDs are able to reversible host-guest complex with the substrates *via* non-covalent bonding thus forming a complex which is responsible for the alteration of product distribution during organic reactions. The characteristics shown are due to the development of geometrical constrains developed in guest molecules as it gets included inside the cavity of CDs. β-Cyclodextrin uses its hydrophobic cavity in order to encapsulate biologically active molecules from its aqueous solution which eventually enhances the bioavailability and stability of drug molecules. These properties have made CDs as an important asset in pharmaceutical industries. Besides, CDs are easily recyclable, cheaper and non-toxic.[34-35] Reactions reported in literature utilizing β-cyclodextrin are exemplified below.

In 2018, Y. A. Tayade *et al.* published a protocol for synthesis of thioamide derivatives in water *via* a one-pot three-component reaction between substituted aldehydes, sulfur powder and secondary amines by using recyclable catalyst β-cyclodextrin (Scheme IV.11).[36]



Scheme IV.11. β-Cyclodextrin catalysed synthesis of thioamide derivatives

Various 2-amino-4*H*-chromen-4-yl phosphonate derivatives were synthesized in water medium utilizing β-cyclodextrin as a polymeric and recyclable catalyst by condensation of salicylaldehyde, malononitrile or ethylcyanoacetate and triethyl phosphite by S. N. Murthy *et al.* (Scheme IV.12).[37]

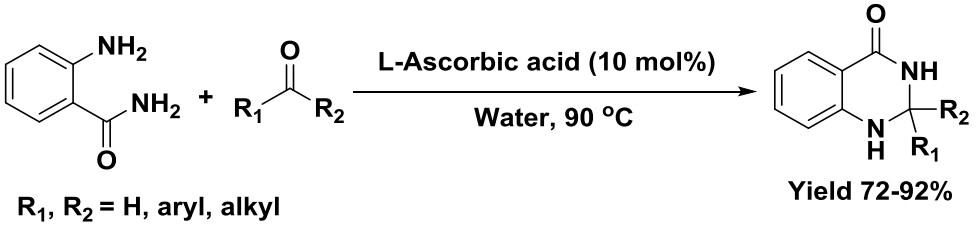


Scheme IV.12. One-pot synthesis of 2-amino-4*H*-chromen-4-yl phosphonate derivatives using β-cyclodextrin in water

IV.2.3. Water as green reaction medium

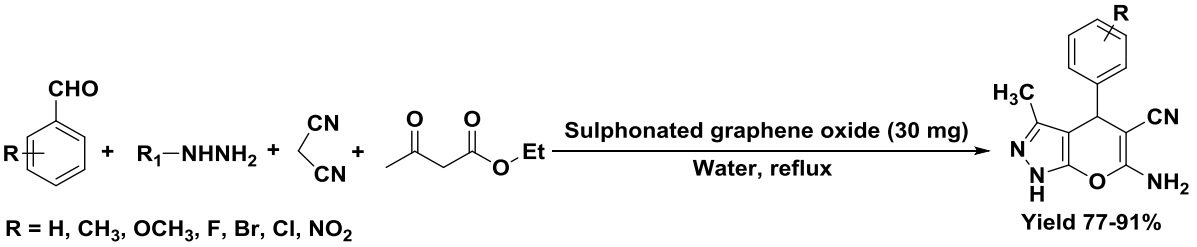
In organic transformation, a major apprehension has been focused on solvents. Pyrophoric property and hazardous nature of solvent with high volatility and poor recovery are the major drawbacks. These disadvantages can be removed by using any green solvent which is good for the environment. Water as a reaction medium is highly advantageous and few methodologies reported in literature are discussed below.

In 2020, G. C. Pariyar *et al.* demonstrated a straightforward protocol for synthesis of diverse array of 2,3-dihydroquinazolin-4(1*H*)-ones using 2-aminobenzamide and various aldehydes or ketones in presence of ascorbic acid as catalyst in water medium (Scheme IV.13).[38]



Scheme IV.13. Water mediated synthesis of 2,3-dihydroquinazolin-4(1*H*)-one

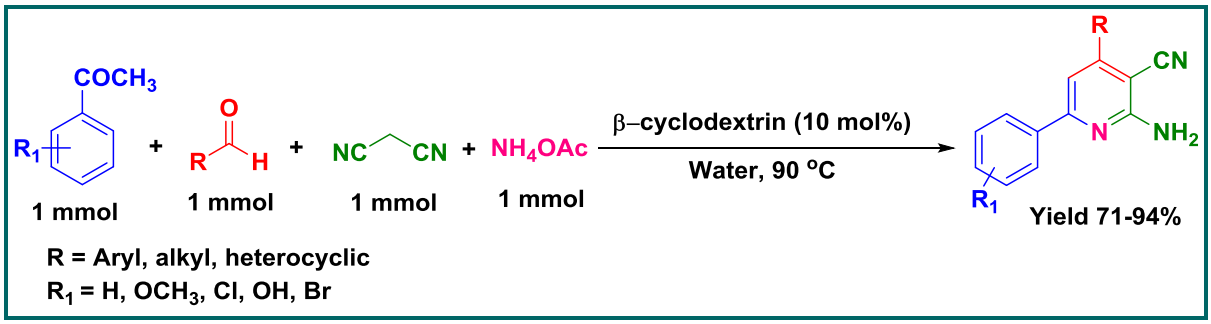
In 2020, P. Basak *et al.* reported a water mediated methodology towards furnishing functionalised 6-Amino-3-methyl-4-phenyl-1,4-[2,3-*c*]pyrazole-5-carbonitriles utilizing a new class of heterogeneous carbocatalyst, sulfonated graphene oxide. The prepared SGO was characterised by FE-SEM, HR-TEM, FT-IR and was recyclable up to 5th run without significant drop in its catalytic activity (Scheme IV.14).[39]



Scheme IV.14. Sulfonated graphene oxide catalyzed synthesis of pyrano[2,3- *c*]pyrazole in water

IV.3. Present work: Result and Discussion

So, keeping all those factors discussed in mind, we have utilized the environmentally benign supramolecular catalyst β-cyclodextrin as a promoter for metal-free one-pot four-component synthesis of nicotinonitriles using aldehyde and acetophenone as two main precursors in water medium (Scheme IV. 15).



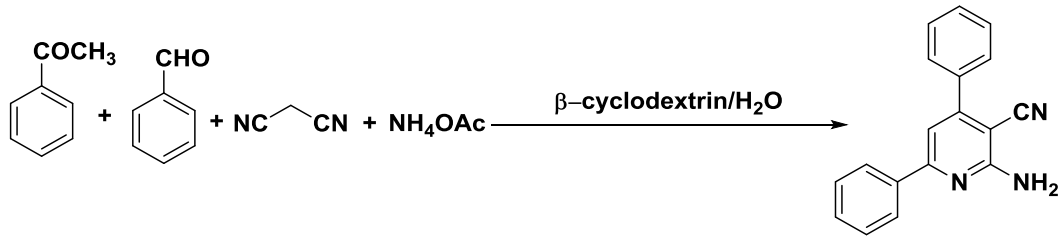
Scheme IV.15. One-pot four-component synthesis of 2-amino-4,6-diphenylnicotinonitriles

IV.3.1. Optimization of the reaction conditions

To begin our study, we have taken benzaldehyde, acetophenone, malononitrile and ammonium acetate as a model reaction in water medium. For optimization of reaction conditions, parameter such as temperature, time and amount of catalyst were reported to have an influence on the reaction and it was monitored by TLC. Since β-cyclodextrin is soluble in water through its hydrophilic part compared to any other organic solvent, we performed all reactions in water. The experimental results are summarized in Table IV.1. Initially, the reaction was performed at 90 ^{o}C with 30 mol% of catalyst for 8 h, 88% product was then formed (Table IV.1, entry 1). Then we started to reduce the amount of the catalyst (Table IV.1, entry 2, 3), when only 10 mol% of catalyst was used the yield was almost comparable with the yield of 30 mol% of catalyst (Table IV.1, entry 3). The same observation was seen in case of optimization of time. By decreasing the time to 2 h, yield was still 84% (Table IV.1, entry 4). Further decrease in the temperature (Table IV.1, entry 8, 9) and time (Table IV.1,

entry 5), decreased the yield of the desired product. In absence of catalyst, no product was formed and only intermediates were formed which was concluded by monitoring TLC (Table IV.1, entry 7). From this it can be concluded that the reaction is catalyzed by β-cyclodextrin and water is mandatory to carry out the conversion.

Table IV.1. [a]Optimisation of reaction parameter for 2-amino-4,6-diphenylnicotinonitriles



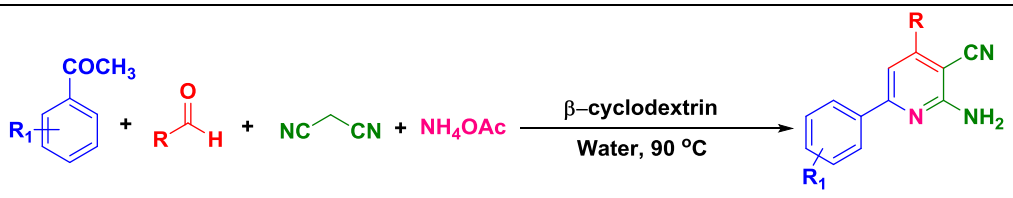
Entry	Loading of catalyst (mol%)	Temperature (^{o}C)	Time (h)	[b]Yield (%)
1	30	90	8	88
2	20	90	8	86
3	10	90	8	86
4	**10**	**90**	**2**	**84**
5	10	90	1	74
6	5	90	8	72
7	-	90	12	-
8	10	50	2	73
9	10	Room temperature	12	68

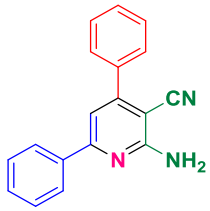
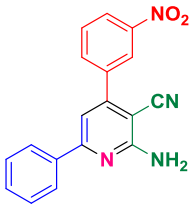
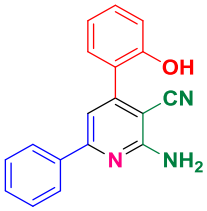
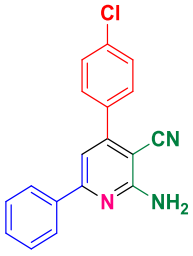
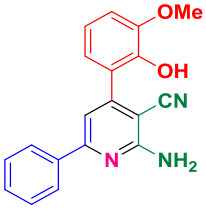
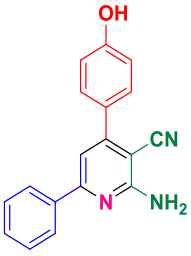
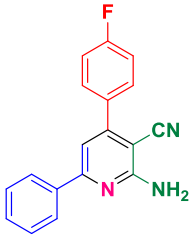
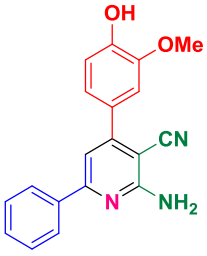
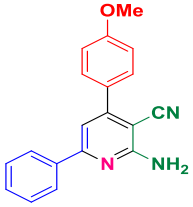
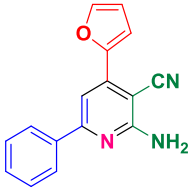
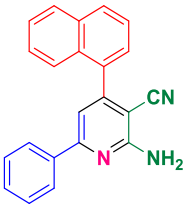
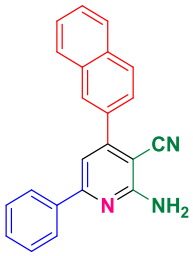
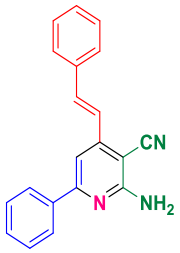
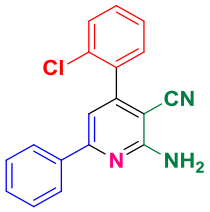
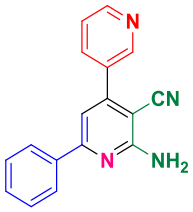
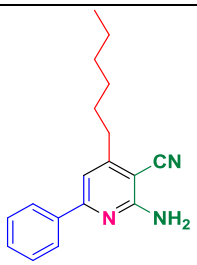
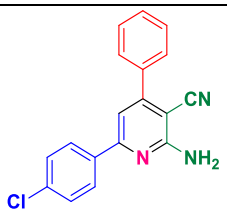
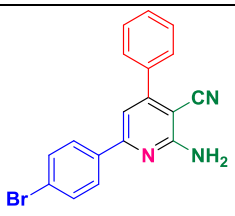
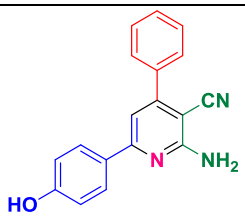
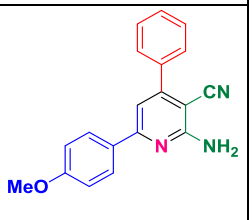
The bold significance represents the most optimized protocol/conditions;

[a]Reaction of Benzaldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol) and ammonium acetate (1 mmol);

[b]Isolated yield of product by column chromatography.

Table IV.2. [a]Synthesis of some diversified 2-amino-4,6-diphenylnicotinonitriles



 **2a, 85%**	 **2b, 90%**	 **2c, 94%**	 **2d, 92%**	 **2e, 91%**
 **2f, 82%**	 **2g, 91%**	 **2h, 75%**	 **2i, 88%**	 **2j, 84%**
 **2k, 79%**	 **2l, 71%**	 **2m, 83%**	 **2n, 91%**	 **2o, 81%**
 **2p, 90%**	 **2q, 82%**	 **2r, 76%**	 **2s, 84%**	 **2t, 86%**

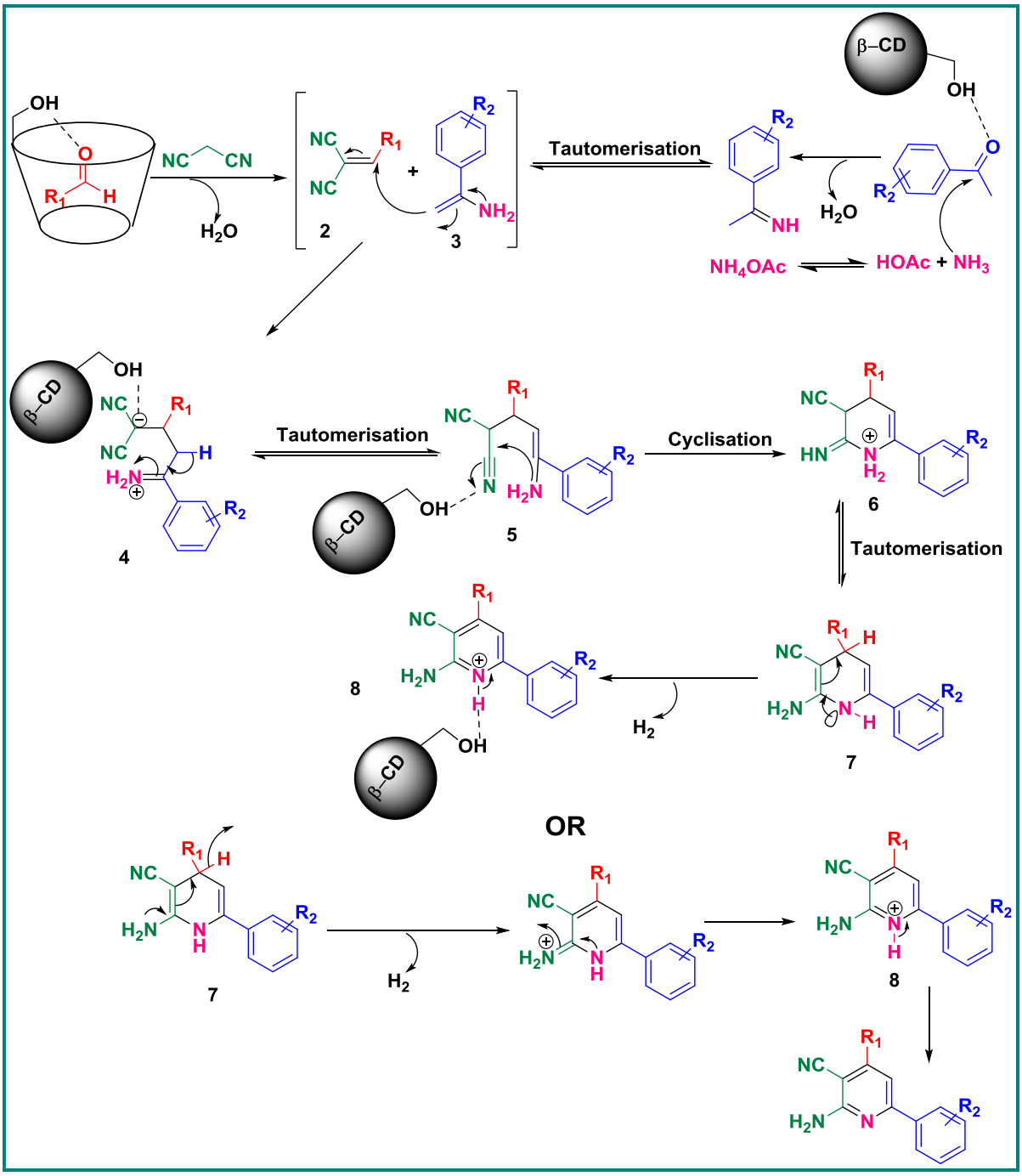
[a]Reaction condition: Aldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol) and ammonium acetate (1 mmol) in presence of β-CD (10 mol%) in water were mixed and strirred at 90 ^{o}C for 2 h.

Subsequently, the scope and efficiency of the reagent were explored under the optimized reaction conditions for the condensation of different acetophenone with a broad range of structurally diverse aldehydes to furnish the related products. The structural diversity of

reactants is displayed in Table IV.2. The reactants containing not only phenyl groups bearing either electron withdrawing substituents, such as chloro, bromo and nitro groups, but also those having electron-donating substituents, such as methyl and methoxy groups and also heterocyclic, aliphatic were well tolerated under the reaction conditions, affording the final products in moderate to good yields (Table IV.2, entries 2-20). Electronic effects were also noticed in the reaction process. Aldehyde having electron withdrawing group give a better performance than electron donating group whereas when hydroxyl group was present at 2-position, it gave better result may be due to H-bonding whereas when hydroxyl group was present at 4-position yield was moderate. Due to steric factor, aldehyde having 2-naphthyl moiety gave better result than aldehyde having 1-naphthyl moiety.

IV.3.2. Mechanism

A plausible mechanism has been discussed in Scheme IV.16. It is assumed that β-CD with its seven free primary –OH groups synergistically behaves as an efficient host and supramolecular catalyst. β-CD, our potential catalysts simultaneously activate both the arylaldehyde and acetophenone derivative as active electrophile species. The reaction of malononitrile and ammonium acetate with these two activated electrophiles generates the corresponding intermediates **2** and **3** respectively. Afterwards, the reaction between these two intermediates will produce the corresponding intermediate **4**. A sequence of tautomerization, cyclization and again tautomerization generates the intermediate **7** which possesses structure having lone pair on nitrogen sharing electrons from both ─NH_2 and ─NH functional groups through C═C double bonds in the presence of the described catalyst and yields the desired products.



Scheme IV.16. Plausible mechanism for formation of the pyridine motif

IV.4. Conclusion

In conclusion, we have developed a straightforward, robust and eco-friendly facile strategy for synthesis of 2-amino-4,6-diphenylnicotinonitriles using a bio-based supramolecule, β-cyclodextrin in water without using any additional catalyst or metal salt for these protocol that further enhances the advantage of the protocol. Replacement of toxic and expensive metal

catalyst by environment friendly and inexpensive solvent is the novelty of this protocol. This environmentally benign protocol is expected to achieve wide applications in the pharmaceutical industry and natural product synthesis.

IV.5. Experimental Section

IV.5.1. General Information

All the compounds were purchased from commercial suppliers and used without further purification. All the products were purified by column chromatography on silica gel (60-120 mesh, SRL, India). For TLC, Merck plates coated with silica gel 60, F_{254} were used. ^{1}H NMR and ^{13}C NMR were recorded using 400 MHz, 300 MHz and 100 MHz, 75 MHz respectively on Bruker AV 400 NMR spectrometer and Bruker AV 300 NMR spectrometer using TMS as internal standard. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad) and m (multiplet).

IV.5.2. General procedure for the synthesis of 2-amino-4,6-disubstituted nicotinonitriles

To a mixture of aldehydes (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol) and ammonium acetate (1 mmol) in a round-bottom flask, β-cyclodextrin (10 mol%) and water were added. The resulting mixture was stirred at 90 °C for 2 h in open air. The reaction progress was monitored using TLC with a mixture of ethyl acetate and n-hexane as the eluent system. After completion of the reaction, the mixture was quenched to room temperature and was extracted with ethyl acetate twice (2×20 mL). Combined extracts were washed with distilled water, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by passing through a column packed with silica gel. The products obtained were known compounds and identified by melting point, ^{1}H and ^{13}C NMR spectroscopy.

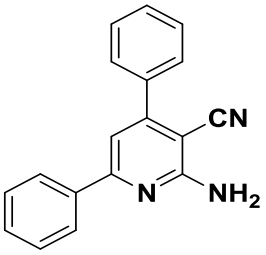
IV.5.3. Characterization data of various nicotinonitile derivatives

2-Amino-4,6-diphenylpyridine-3-carbonitrile (Table IV.2, entry 2a)

Pale yellow solid; M.P.: 208-210 ^{o}C;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 5.48 (s, 2H), 6.98 (d, J = 7.8 Hz, 2H), 7.20 (s, 1H), 7.40-7.47 (m, 3H), 7.68-7.82 (m, 3H), 8.14-8.26 (m, 2H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 88.4, 110.0, 114.2, 117.8, 127.8, 129.4, 129.9, 130.3, 130.5, 138.1, 155.6, 158.8, 160.7, 161.9.

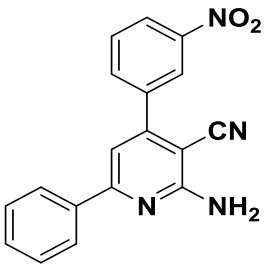


2-Amino-4-(3-nitrophenyl)-6-phenylnicotinonitrile (Table IV.2, entry 2b)

Dark brown solid; M.P.: 251-253 ^{o}C;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 6.28 (s, 2H), 7.35 (s, 1H), 7.45-8.20 (m, 7H), 8.15 (d, J = 7.2 Hz, 1H), 8.42 (s, 1H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 85.8, 110.6, 116.9, 120.4, 128.6, 129.3, 130.6, 133.4, 136.7, 138.5, 148.0, 156.5, 158.9, 162.8.

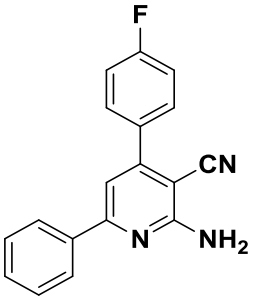


2-Amino-4-(4-fluorophenyl)-6-phenylnicotinonitrile (Table IV.2, entry 2g)

Yellow solid; M.P.: 148-150 ^{o}C;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 6.88 (s, 2H), 7.19 (s, 1H), 7.41 (t, J = 7.8 Hz, 2H), 7.46-7.52 (m, 3H), 7.69-7.72 (m, 2H), 8.16-8.20 (m, 2H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 88.9, 109.2, 115.6, 117.9, 127.2, 128.6, 130.1, 130.9, 133.3, 138.7, 154.8, 163.8.

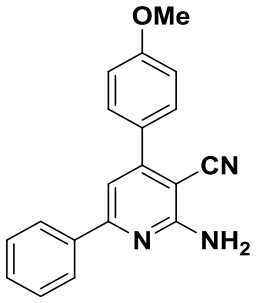


2-Amino-4-(4-methoxyphenyl)-6-phenylnicotinonitrile (Table IV.2, entry 2i)

Yellow solid; M.P.: 192-195 ^{o}C;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.64 (s, 3H), 7.06 (d, J = 7.8 Hz, 2H), 7.20 (s, 1H), 7.42-7.68 (m, 3H), 7.65 (d, J = 7.8 Hz, 2H), 7.88 (d, J = 7.2 Hz, 2H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 55.6, 86.9, 109.5, 114.6, 117.8, 127.7, 129.1, 129.5, 130.3, 130.5, 138.1, 154.9, 158.9, 160.8, 161.4.

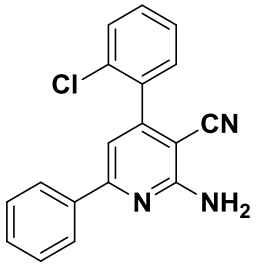


2-Amino-4-(2-chlorophenyl)-6-phenylnicotinonitrile (Table IV.2, entry 2n)

White solid; M.P.: 194-197 ^{o}C;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 6.12 (s, 2H), 7.18 (s, 1H), 7.45-7.58 (m, 5H), 7.66 (d, J = 7.2 Hz, 2H), 8.21-8.34 (m, 2H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 88.4, 109.7, 116.1, 125.2, 127.5, 128.7, 129.7, 130.2, 130.9, 131.2, 136.6, 137.9, 153.0, 158.5, 160.1.

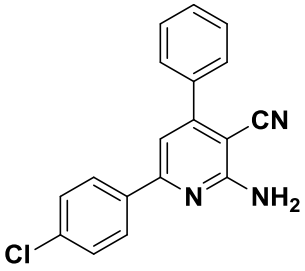


2-Amino-4-phenyl-6-(4-chlorophenyl)nicotinonitrile (Table IV.2, entry 2q)

Yellow solid;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 5.68 (s, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.21 (s, 1H), 7.56-7.59 (m, 3H), 7.69 (d, J = 8.4 Hz, 3H), 8.24-8.29 (m, 2H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 86.9, 111.5, 115.6, 117.8, 127.3, 128.6, 129.5, 130.3, 131.6, 138.1, 154.9, 158.9, 160.8, 161.4.

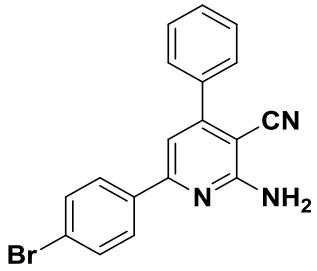


2-Amino-4-phenyl-6-(4-bromophenyl)nicotinonitrile (Table IV.2, entry 2r)

Yellow solid;

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 6.98 (s, 2H,), 7.16 (s, 1H), 7.28 (d, J = 7.8 Hz, 2H), 7.60-7.65 (m, 3H), 7.79 (d, J = 7.8 Hz, 2H), 8.12-8.20 (m, 2H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 87.2, 108.9, 113.9, 117.8, 127.3, 129.1, 129.5, 130.3, 130.8, 138.0, 153.9, 159.4, 161.0, 162.1.

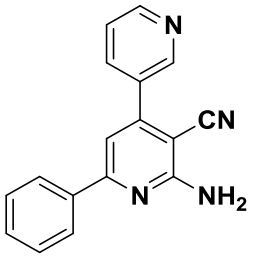


2'-amino-6'-phenyl-[3,4'-bipyridine]-3'-carbonitrile (Table IV.2, entry 2o)

Yellow solid;

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.29 (s, 2H), 7.53-7.70 (m, 5H), 8.15 (d, J = 7.6 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.45 (s, 1H), 9.03 (brs, 1H), 9.19 (brs, 1H);

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 94.8, 95.1, 116.3, 119.0, 127.7, 129.1, 130.0, 136.7, 137.7, 146.9, 149.1, 150.6, 154.5.



IV.5.4. Scanned copies of ^{1}H and ^{13}C NMR spectra of 2'-amino-6'-phenyl-[3,4'-bipyridine]-3'-carbonitrile

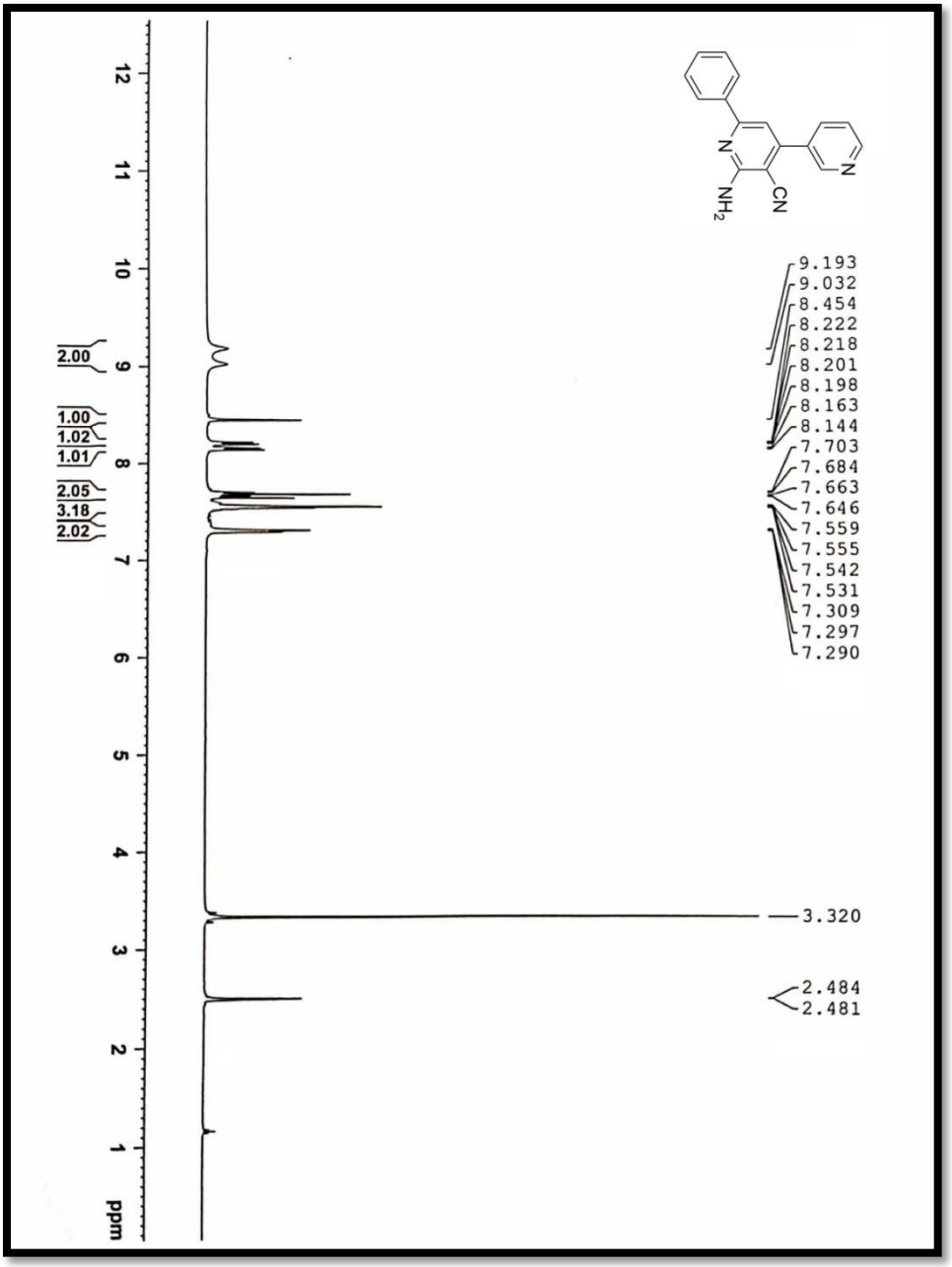


Figure IV.3. Scanned copy of ^{1}H NMR of 2'-amino-6'-phenyl-[3,4'-bipyridine]-3'-carbonitrile

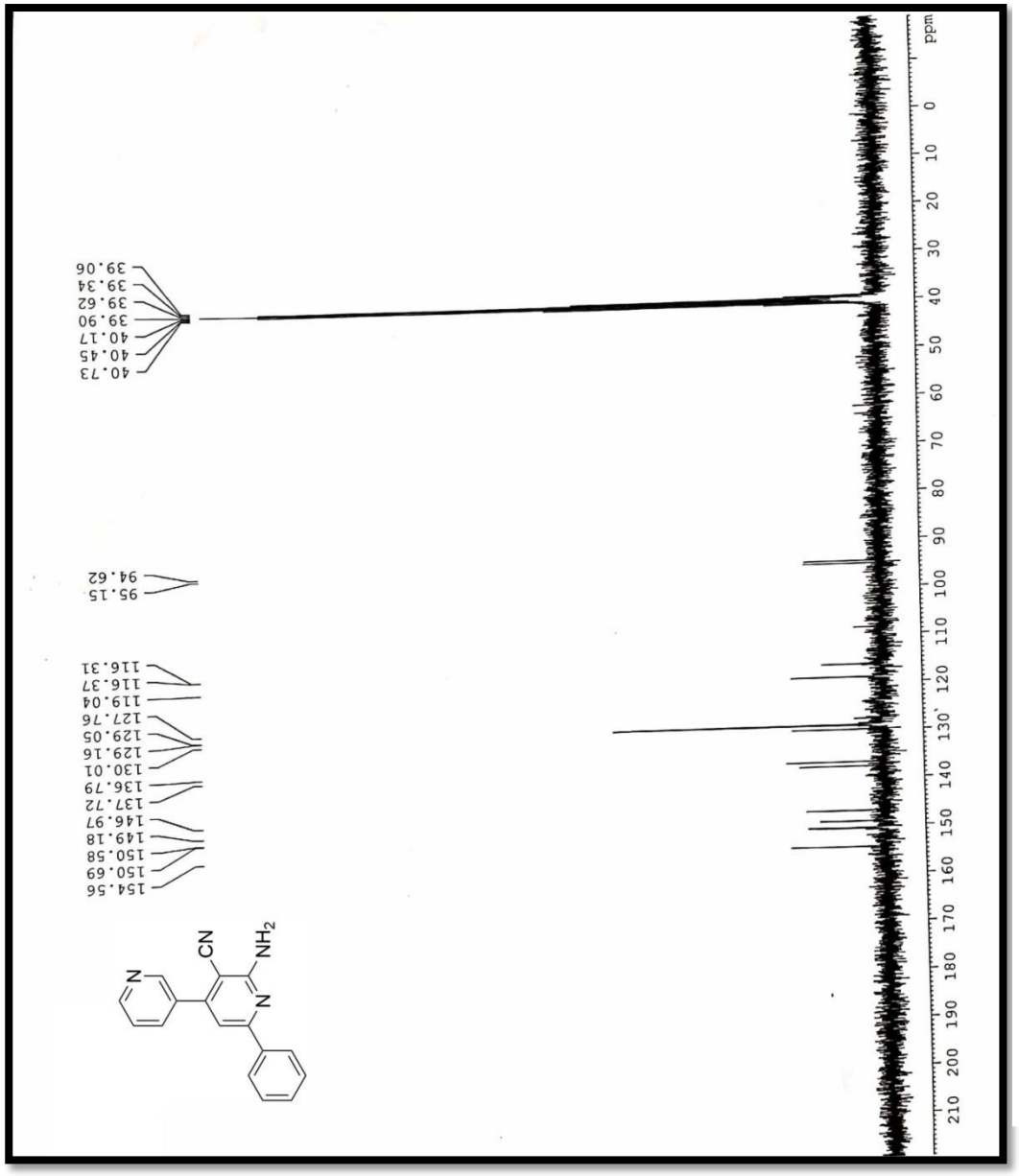


Figure IV.4. Scanned copy of ^{13}C NMR of 2'-amino-6'-phenyl-[3,4'-bipyridine]-3'-carbonitrile

IV.6. References

References are given in BIBLIOGRAPHY under Chapter IV (page 175-177).