Synthesis and Characterization of Compounds Derived From 2-Cyanopyridine

Submitted by

Vijendra Kumar Fulwa
Roll No. 07612202

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati – 781 039

Dedicated to

My Family Members

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India, under the guidance of Dr. V. Manivannan.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

Vijendra 15/06/2012

Vijendra Kumar Fulwa

June, 2012.
Guwahati

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Vijendra Kumar Fulwa has been working under my supervision since July, 2007 as a regular registered Ph. D. student. I am forwarding his thesis entitled "**Synthesis and Characterization of Compounds Derived From 2-Cyanopyridine**" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

V. Manivannan

June, 2012.
Guwahati

Dr. V. Manivannan
Supervisor
15/06/2012

ACKNOWLEDGMENT

I wish to express my sincere thanks to my supervisor, Dr. V. Manivannan for his guidance, encouragement, inspiration and creative and scientific ideas which helped me to enhance my knowledge. I am also thankful to him for giving me freedom to pursue my own interests and I find myself privileged to have worked under his kind guidance.

I would like to acknowledge my sincere gratitude to all my doctoral committee members for their insightful advices and valuable suggestions. I would also like to thank all faculty members of Department of Chemistry of IIT Guwahati for their motivation, encouragement.

I wish to acknowledge my sincere gratitude to IIT Guwahati for financial support and all the facilities that were made available to me. I also thank Central Instrument Facility of the institute for providing the Instrument facility and DST for providing the X-ray facility.

I am thankful to Mr. Babulal Das (for Single Crystal XRD) of Department of Chemistry and all the non-teaching staff of Department of Chemistry for their help during my Ph.D. tenure.

I would like to thanks all of friends and group members.

Finally, my Ph. D. endeavor could not be completed without the endless love, unending support, tolerance and blessings from my family. They are the main soul and inspiration for each and every step that I achieve in my life.

And, I thank God for being there for me in a way no one else can.

Vijendra Kumar Fulwa

ABBREVIATIONS

a	Unit cell dimension a
b	Unit cell dimension b
c	Unit cell dimension c
α	Interfacial angle α in a unit cell
β	Interfacial angle β in a unit cell
γ	Interfacial angle γ in a unit cell
Z	Unit cell formula units
λ	Wave length
ν	Wave number
μ	Absorption coefficient
ε	Molar extinction coefficient
τ	Geometric parameter applicable for five-coordinate structures as an index of trigonality between trigonal bipyramidal and rectangular pyramidal
μ_{eff}	Effective Magnetic moment
H	Applied magnetic field
g	Lande splitting factor
A	Hyperfine splitting constant
IR	Infrared
NMR	Nuclear magnetic resonance
ORTEP	Oak ridge thermal ellipsoid program
ppm	Parts per million
TLC	Thin layer chromatography

Contents

Preface

The Ph. D. thesis entitled as "**Synthesis and Characterization of Compounds Derived From 2-Cyanopyridine**" has been divided in to six chapters. A summary of the contents of the Thesis Chapters is described here.

Chapter 1 summarizes the literature reports that use 2-cyanopyridine, specifically, for the synthesis of heterocycles has been reviewed.

Chapter 2 describes the synthesis and characterization of copper(II) coordination polymers using two amidoximes *viz*., pyridine-2-amidoxime and pyrazine-2-amidoxime. In addition a linear trinuclear complex synthesized using the latter has been described.

Chapter 3 describes the synthesis of 2,4,5-tris(pyridyl)imidazoles and *N*-(3-(pyridyl)imidazo[1,5-*a*]pyridine)picolinamidines using 2-cyanopyridine and picolylamines. Plausible mechanism for the formation of these compounds is proposed.

Chapter 4 describes the reaction of 2-cyanopyridine, hydrazine hydrate and pyridinecarboxaldehydes. The products isolated include 3,5-di(2-pyridyl)-1,2,4-triazole 1-(3-(2-pyridyl)-5-(pyridyl)-1,2,4-triazolyl)-3-(pyridyl)imidazo[1,5-*a*]pyridine and 1-((pyridyl)methanimine)-3-(pyridyl)imidazo[1,5-*a*]pyridine

Chapter 5 describes the synthesis and characterization of 3-substituted imidazo[1,5-*a*]pyridines having *N*-picolinamidin-2-yl group at 1-position. This was achieved by reacting one equivalent of an aldehyde and two equivalents of 2-cyanopyridine.

The molecular structures of compounds described in Chapter 3–5, were elucidated using ^{1}H, ^{13}C NMR and ESI mass spectra as well as single crystal X-ray diffraction methods.

Chapter 6 describes the reaction of amidines and diamidines derived using 2-cyanopyridine and amines such as 2-picolylamine and benzylamine. The compounds isolated include species containing bis(2-pyridylcarbonyl)amide ion and 2-phenyl-4,6-di(2′-pyridyl)-1,3,5-triazine.

Finally, I have taken utmost care to bring out this Thesis free from errors and it is my sole responsibility for any error that might have crept in.

Vijendra Kumar Fulwa

Chapter 1

Introduction, Materials, Instrumentation and Methods

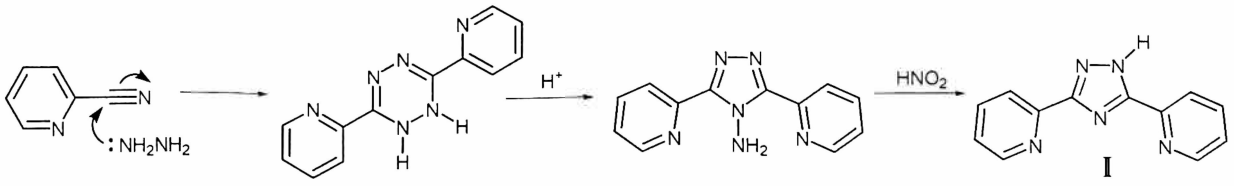
1.1. Introduction

Organonitriles are important compounds and are crucial for the synthesis of many heterocyclic compounds.[1] The nitrile function is susceptible to addition of nucleophiles[1] or electrophiles[2] or asymmetric dipolar cycloaddition.[3] Using such reactivity novel C–C, C–N, C–O, and C–S bonds can be created. 2-Cyanopyridine in particular has been used for generation of various kinds of heterocyclic rings that include: 1,2,4-triazole, tetrazole, 1,2,4-oxadiazole, 1,2,4-oxadiazoline, imidazoline, imidazole, pyrimidine, isoquinoline, imidazo[1,5-*a*]pyridine, pyrazine, desferrithiocin, pyridine, pyrazole, 1,2,4-triazine and 2-oxazoline. In this Chapter use of 2-cyanopyridine (**1**) in particular, for the synthesis of heterocycles and reactions that occur at nitrile function of **1** have been reviewed.

1.2. Synthesis of Heterocycles

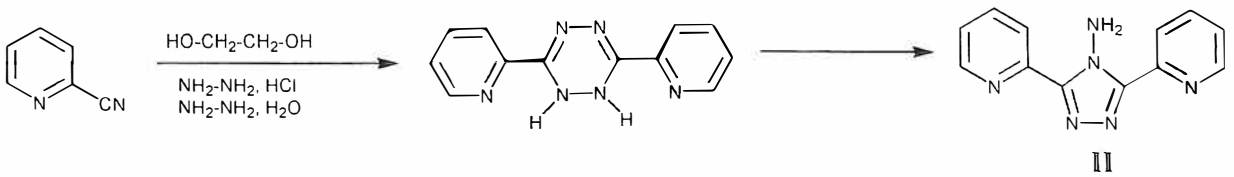
1.2.1. 1,2,4-Triazole

The 1,2,4-triazole nucleus is an important structural motif present in a large number of functionalized molecules. The 3,5-di(2′-pyridyl)-1,2,4-triazole (**I**) was prepared from **1** by reacting with hydrazine followed by acidification to yield 3,5-di(2′-pyridyl)-4-amino-1,2,4-triazole (**II**) and then deamination of **II** with nitrous acid.[4]



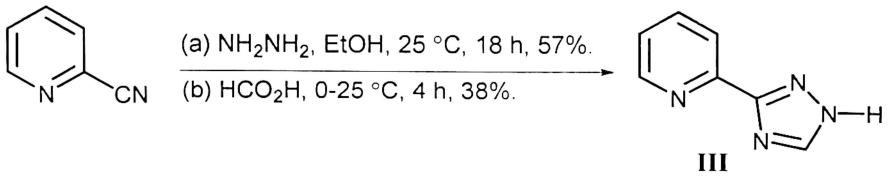
J. Org. Chem. **1965**, *30*, 318–319.

A number of symmetrically 3,5-disubstituted 4-amino-1,2,4-triazoles were prepared by the reaction of aromatic nitriles on hydrazine dihydrochloride in the presence of an excess of hydrazine hydrate in ethylene glycol under microwave irradiation, including 3,5-di(2′-pyridyl)-4-amino-1,2,4-triazole (**II**).[5]



Tetrahedron Lett. **2000**, *41*, 1539–1541.

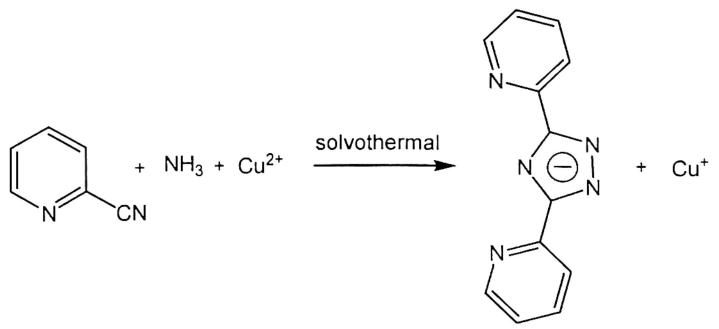
A series of 3,5-di(2′-pyridyl)-1,2,4-triazole derivatives were examined for their *in vivo* activity in lowering the serum uric acid levels in rats. In particular, 3-(3′-cyano-4′-pyridyl)-5-(4″-pyridyl)-1,2,4-triazole was found to be one of the most potent FYX-051-*a* xanthine oxidoreductase inhibitor for the treatment of hyperuricemia.[6a] The compound 3-(2′-pyridyl)-1,2,4-triazole (**III**) was synthesized, evaluated for mGlu5 receptor antagonist activity and found to have very weak activity.[6b]



III

J. Med. Chem. **2004**, *47*, 4645–4648.

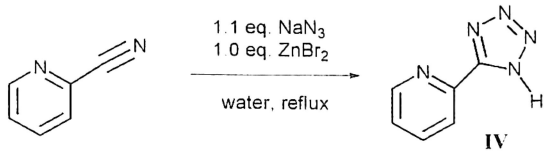
Reaction of organonitriles, ammonia, and Cu(II) salts yielded Cu(I) and 3,5-disubstituted 1,2,4-triazolates under solvothermal conditions. Using **1**, copper(I) salt of 3,5-di(2′-pyridyl)-1,2,4-triazolate ion was obtained.[7]



J. Am. Chem. Soc. **2005**, *127*, 5495–5506.

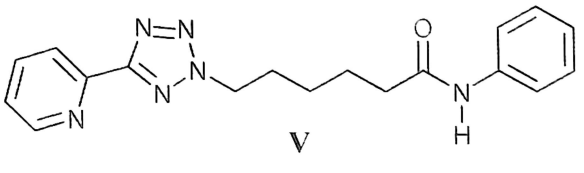
1.2.2. 1*H*-Tetrazole

The 5-substituted 1*H*-tetrazoles are nitrogen-rich compounds and conventional synthesis of them is via [3+2] cycloaddition of azide salt with corresponding nitriles.[8] Sharpless[9] reported an innovative and safe procedure by reacting sodium azide with nitriles in water using Zn(II) salts. Using **1**, 2-(1*H*-tetrazol-5-yl)pyridine (**IV**) was synthesized. This reaction was optimized using a continuous flow synthesis technology.[10] CoY zeolite is also useful as a catalyst for the reaction of sodium azide with nitriles.[11] The following tetrazole (**V**) was evaluated for matrix metalloproteinases (MMPs) inhibitor activity but found to be non-effective.[12]



IV

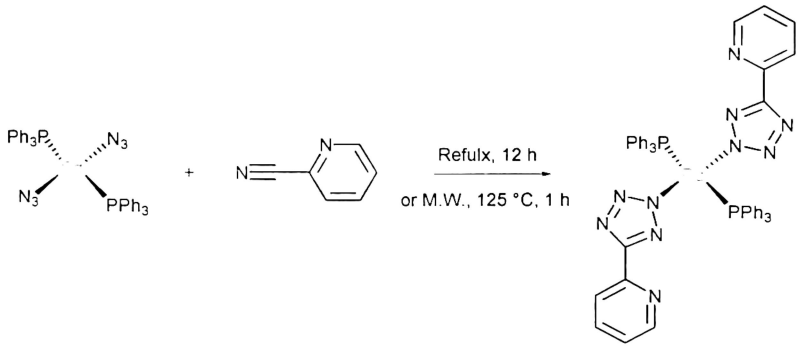
J. Org. Chem. **2001**, *66*, 7945–7950.



V

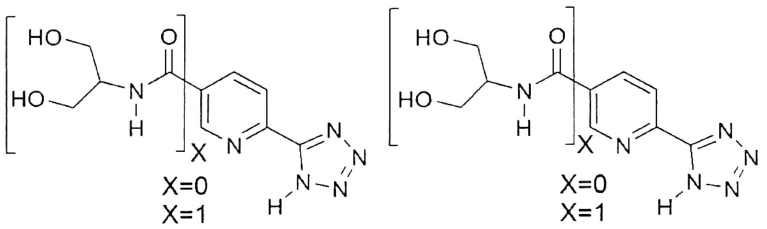
Bioorg. Med. Chem. Lett. **2007**, *17*, 6864–6870.

The palladium bound azide ion in *trans*-$Pd(N_3)_2(PPh_3)_2$ on reaction with **1** produced *trans*-$Pd(\mathbf{L})_2(PPh_3)_2$ wherein **L** is [**IV**$^-$].[13]



J. Organomet. Chem. **2011**, *696*, 3513–3520.

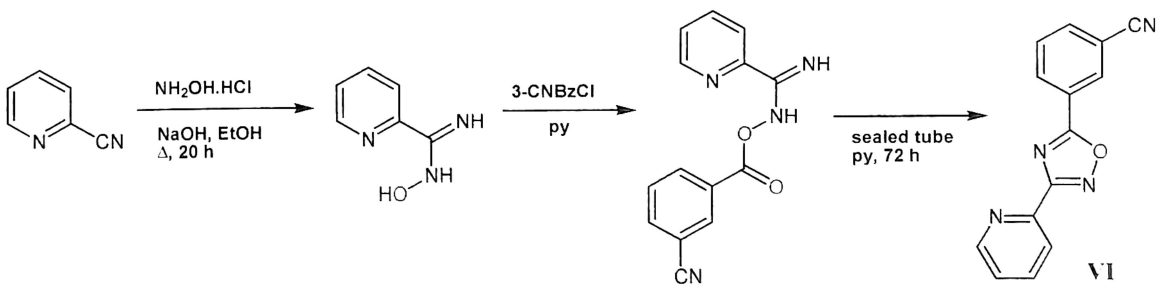
Synthesis of following tetrazole ligands from **1** and preparation of water-soluble Ln(III) and Zn (II) was reported. The Gd derivatives have been shown to have great potential as high-relaxivity, low-osmolarity MRI contrast agents.[14]



Chem. Commun. **2004**, *15*, 1770–1771.

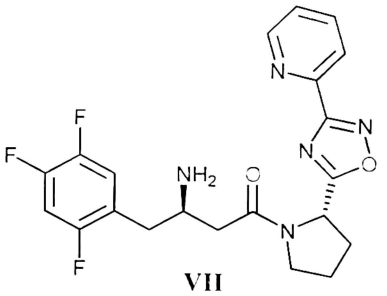
1.2.3. 1,2,4-Oxadiazole

The 1,2,4-oxadiazole scaffold is a class of heterocycles commonly found in biologically active molecules. The compound 5-(3′-cyanophenyl)-3-(2″-pyridyl)-1,2,4-oxadiazole (**VI**) has been found to be active as metabotropic glutamate subtype 5 (mGlu5) receptor antagonist. It has been synthesized by reacting **1** with hydroxylamine to give the amidoxime, followed by cyclization of the *O*-acyl amidoxime formed from the reaction of amidoxime with an acyl chloride.[15]



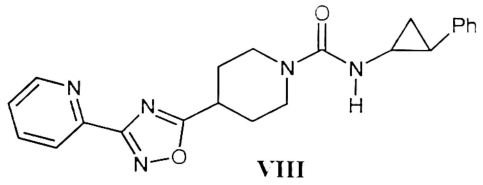
J. Org. Chem. **2008**, *73*, 7219–7223.

A 2-pyridyl containing 1,2,4-oxadiazole (**VII**) was evaluated for selective DDP-4 inhibitor properties.[16] The soluble epoxide hydrolase (sEH) inhibitor property of another 2-pyridyl containing 1,2,4-oxadiazole (**VIII**) was also determined.[17]



VII

Bioorg. Med. Chem. Lett. **2009**, *19*, 6340–6345.

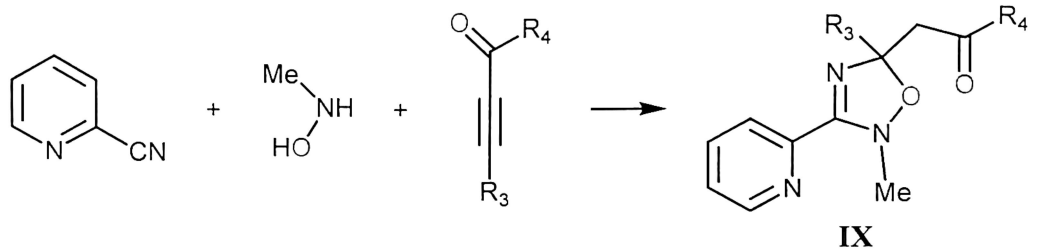


VIII

J. Med. Chem. **2009**, *52*, 5009–5012.

1.2.4. 1,2,4-Oxadiazoline

The 2,3,5-substituted 1,2,4-oxadiazolines were prepared in "*one pot*" by the reaction of amidoximes (formed *in situ*) with electron-deficient alkynes.[18] Compounds **IX** (R_3 = COOEt; H; Me and R_4 = OEt; R_3 = Et and R_4 = Me) were obtained from **1**.

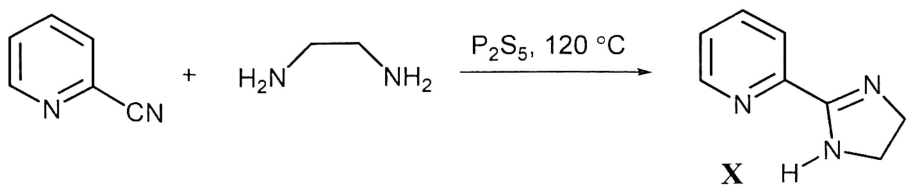


IX

Org. Lett. **2005**, *7*, 1391–1393.

1.2.5. Imidazoline

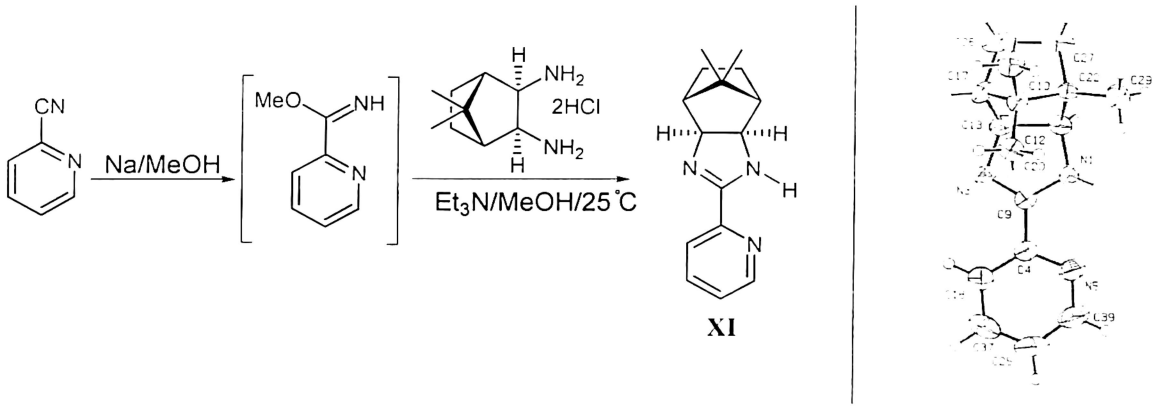
Reaction of **1** with ethylenediamine (**EDA**) in presence of P_2S_5 at 120°C afforded 2-(2′-pyridyl)-4,5-dihydro-1*H*-imidazole (**X**). This imidazoline along with many others were evaluated *in vitro* as imidazoline sites and α-adrenergic (α_1 and α_2) receptor ligands.[19]



X

Bioorg. Med. Chem. **2001**, *9*, 585–592.

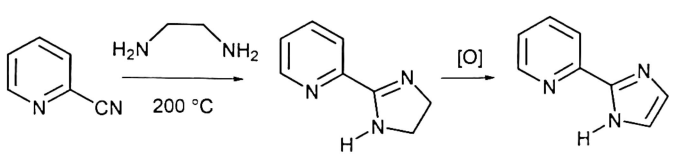
The synthesis of 2-(2′-pyridyl)-4,5-dihydro-1*H*-imidazole (**XI**) from **1** and **EDA** using sulfur as a catalyst in microwave, is reported to have advantages such as: short reaction times, high yields and the ability of large scale reactions.[20] This reaction was also studied using various copper(II) catalyst, out of which cupric indole-3-acetate [Cu(**IAA**)$_2$] was found to be most efficient.[21] The camphor-annulated imidazoline was synthesized from **1** and from this the copper(II)-catalyzed Henry reaction product was isolated.[22]



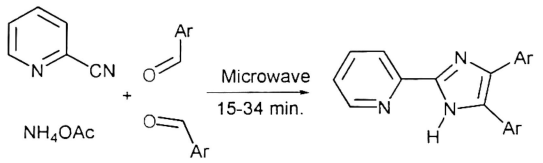
Tetrahedron Lett. **2009**, *50*, 3042–3045.

1.2.6. Imidazole

The imidazole ring system is an important function in biology, chemistry as well as in pharmaceutical, veterinary and agrochemical products.[23-26] These compounds are generally prepared through the conversion of the corresponding nitrile into the imidazoline followed by oxidation to the desired imidazole.[27] There are several methods for the synthesis of 2-imidazolines by the reaction of **EDA** with nitriles using different reaction conditions as noted previously in Section 1.1.5.[19–22]

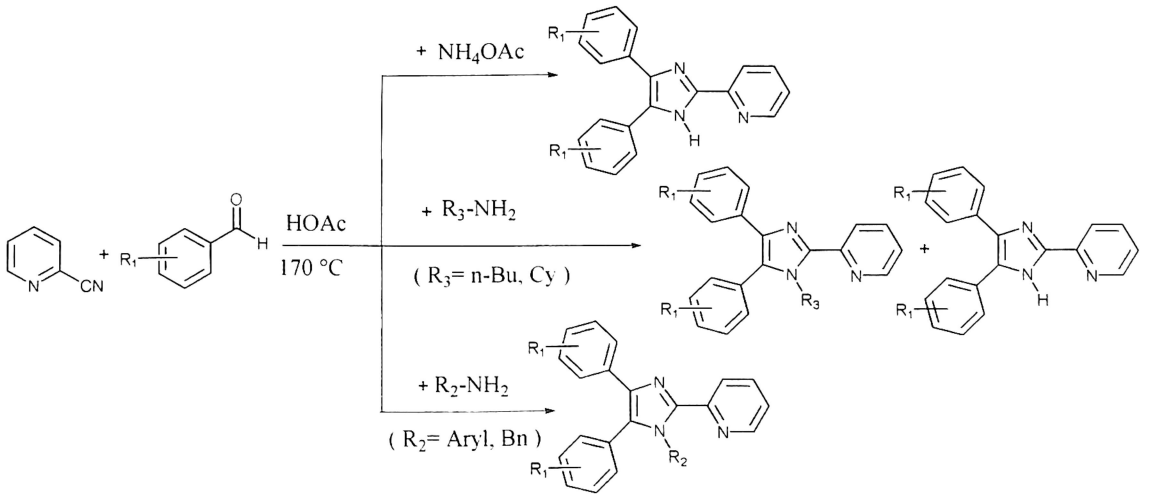


Tetrahedron, **2007**, *64*, 645–651.



J. Org. Chem. **2009**, *24*, 9486–9489.

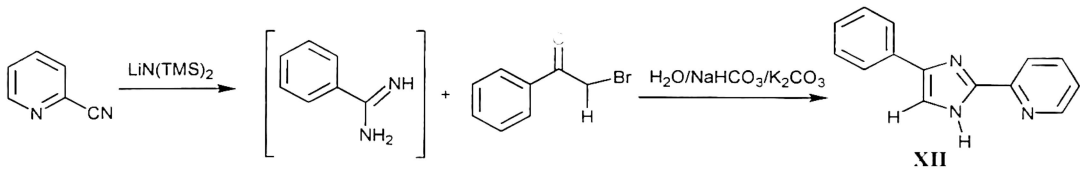
Recently, the various *poly*-substituted 2-(2′-pyridyl)imidazoles were synthesized from **1**, corresponding aromatic aldehydes (16 examples) and NH_4OAc/primary amine (11 examples) in the solvent of acetic acid at 170 °C or by heating in microwave.[28]



J. Comb. Chem. **2010**, *12*, 829–835.

The compound 2-(2′-pyridyl)-4-phenyl-1*H*-imidazole (**XII**) was synthesized from the reaction of amidine {obtained by reacting **1** with $LiN(TMS)_2$} with $PhCOCH_2Br$ in the

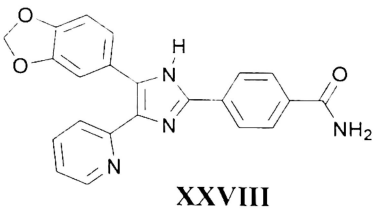
$H_2O/NaHCO_3/K_2CO_3$. This 2-(2′-pyridyl)-4-phenyl-1*H*-imidazole was shown to have potent *in vitro* activity at the NPY5 receptor.[29]



XII

Bioorg. Med. Chem. Lett. **2003**, *13*, 3593–3596.

1,2,4-trisubstituted-imidazole containing a 2-pyridyl ring (**XXVIII**) prepared using **1**, showed moderate ALK5 inhibition activity as well as cytotoxicity.[30]

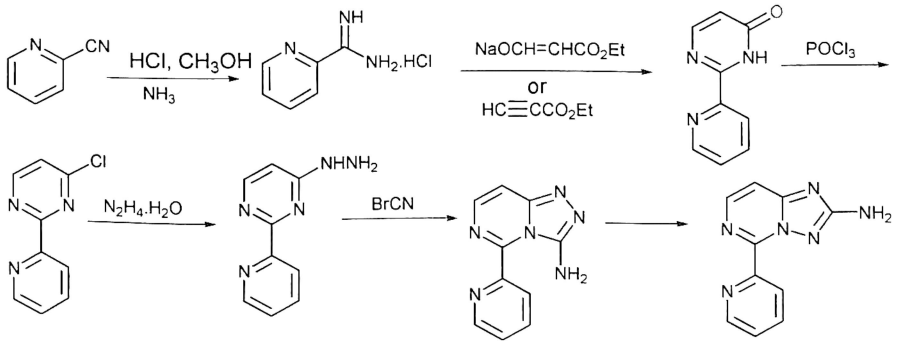


XXVIII

Bioorg. Med. Chem. Lett. **2009**, *19*, 4868–4872.

1.2.7. Pyrimidine

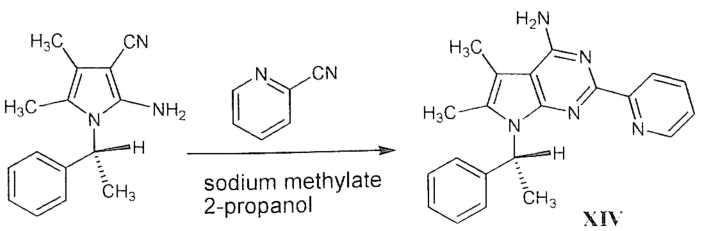
Pyrimidines are important nitrogen heterocycles as they are the integral part of nucleic acids. Many 5-substituted aminotriazolo[1,5-*c*]pyrimidines were synthesized and studied for their utility as antiasthma agent. The 2-pyridyl compound (**XIII**) synthesized starting from **1**, however did not show such activity.[31]



XIII

J. Med. Chem. **1990**, *33*, 1230–1241.

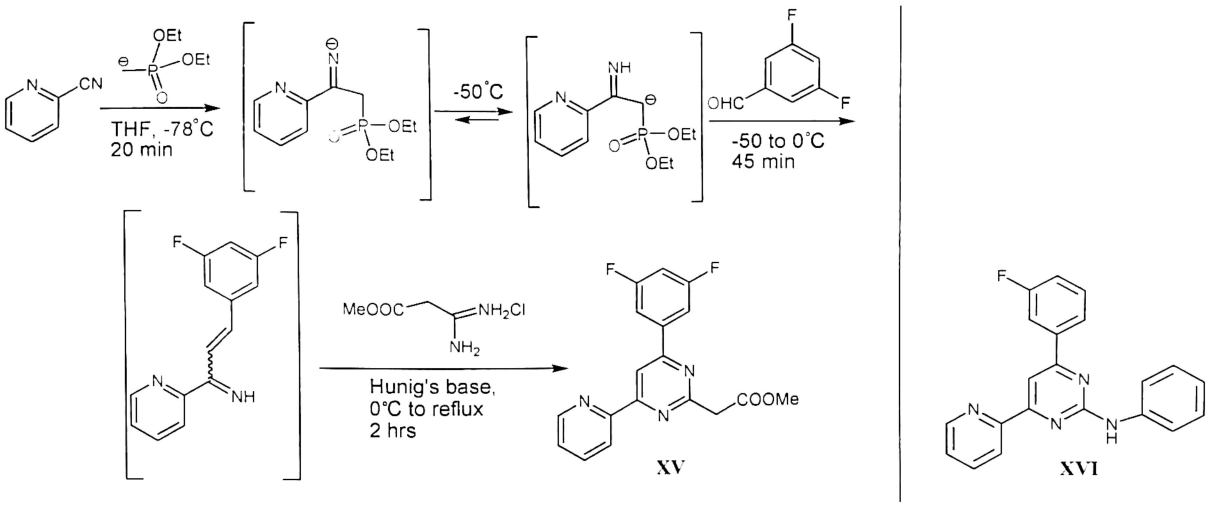
A 5,6-dimethylpyrrolo[2,3-*d*]pyrimidine-4-amine (**XIV**) was made from **1** and sodium methylate in 2-propanol was studied for A_1 and A_3 adenosine receptor antagonists activity.[32]



XIV

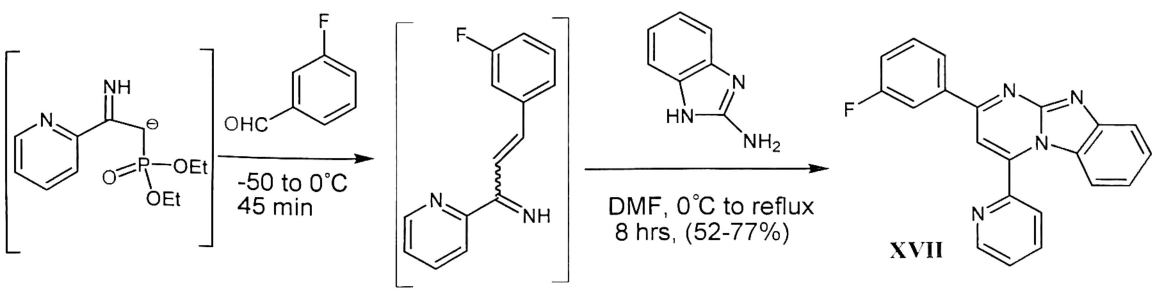
J. Med. Chem. **2000**, *43*, 4636–4646.

Two 2-pyridyl ring containing pyrimidines (**XV** and **XVI**) were synthesized from *in situ* generated α,β-unsaturated imines and the corresponding amidine or guanidine derivatives in a convenient "*one pot*" procedure by the reaction sequence shown below using appropriate substrates:[33]



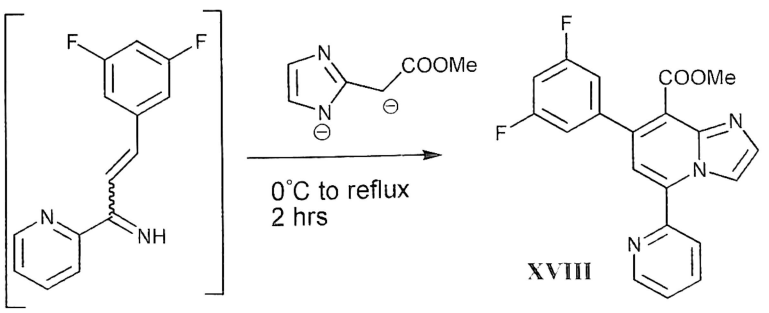
Tetrahedron Lett. **2005**, *46*, 1663–1665.

A convenient regioselective "*one pot*" approach to imidazo[1,2-*a*]pyrimidine derivatives were also reported from *in situ* generated α,β-unsaturated imines and amino heterocycles. This reaction is general with respect to all three components, namely (i) nitrile (**XVII** from **1**), (ii) aldehyde, and (iii) amino heterocycle reagents.[34]



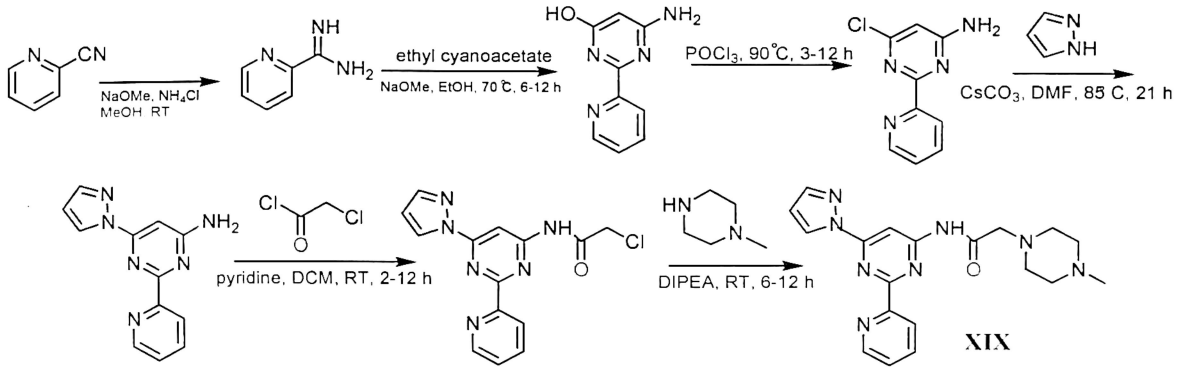
Tetrahedron Lett. **2006**, *47*, 2611–2614.

A series of 5,7,8-polysubstituted imidazo[1,2-*a*]pyridines (**XVIII** from **1**), were synthesized regioselectively from *in situ* generated α,β-unsaturated imines and dianions derived from methyl azolyl acetates.[35]



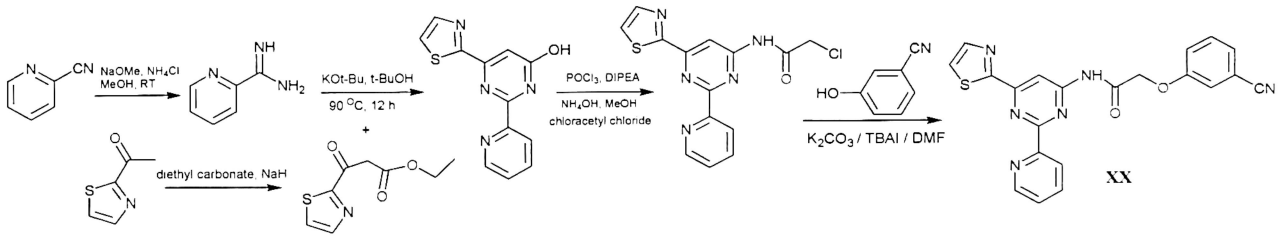
Tetrahedron Lett. **2006**, *47*, 2941–2944.

A series of potent and selective A_{2A} receptor antagonists with excellent aqueous solubility (**XIX** from **1**), were synthesized and it was found that many compounds showed good activity but the 2-pyridyl analog did not.[36]



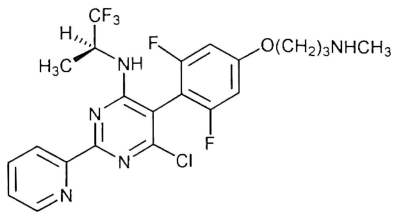
J. Med. Chem. **2008**, *51*, 1719–1729.

In a similar study the pyrimidine based adenosine A_{2A} antagonists were synthesized (**XX** from **1**), and activity was evaluated.[37]

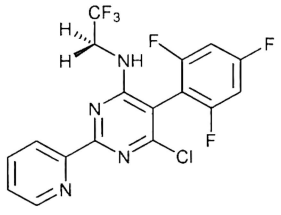


Bioorg. Med. Chem. Lett. **2008**, *18*, 1269–1273.

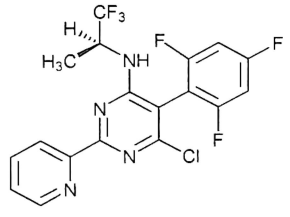
The synthesis and SAR of a series of 6-chloro-4-fluoroalkylamino-2-heteroaryl-5-(substituted)phenylpyrimidines as anti-cancer agents were reported and three 2-pyridyl ring containing compounds (**XXI–XXIII**) synthesized using **1** showed weak inhibition of COLO 205 cell proliferation.[38]



XXI



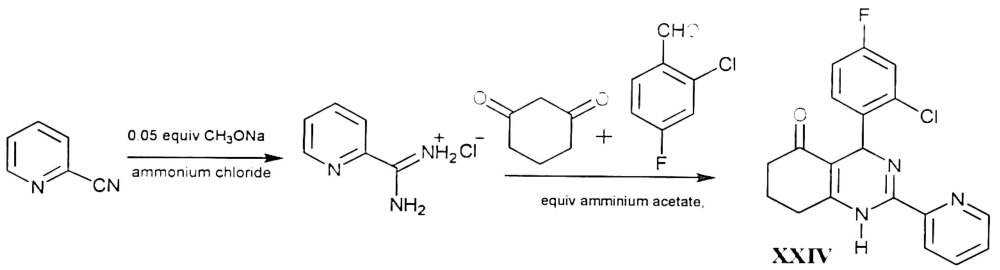
XXII



XXIII

Bioorg. Med. Chem. **2009**, *17*, 111–118.

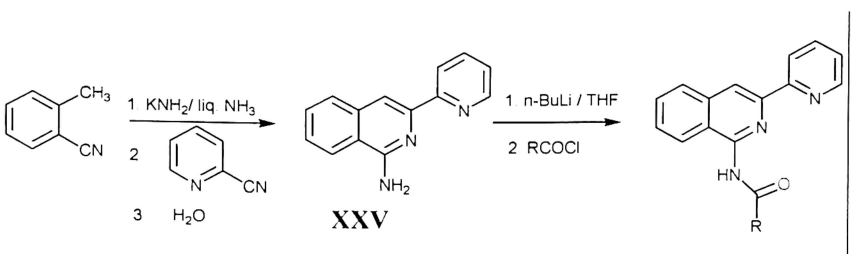
A series of 2,4-diaryl-4,6,7,8-tetrahydroquinazolin-5(1*H*)-one derivatives were designed and synthesized, as potent inhibitors of HBV capsid assembly. These compounds arose from efforts to rigidify an earlier series of heteroaryldihydropyrimidines (HAPs), and the compound **XXIV** derived from **1** showed potent inhibition of HBV capsid assembly.[39]



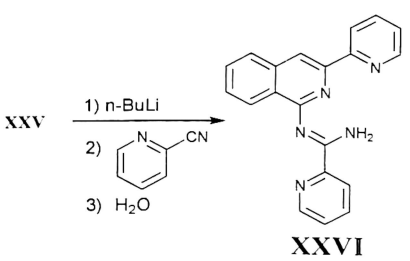
Bioorg. Med. Chem. Lett. **2010**, *20*, 299–301.

1.2.8. Isoquinoline

The synthesis (using **1**) and antimycoplasmal activity of both aliphatic and aromatic amides derived from l-amino-3-(2′-pyridyl)isoquinoline (**XXV**) was reported. The most active compounds appeared to be as active as Tylosin, an antimycoplasmal therapeutic that is used in veterinary practice, in the presence of a small nontoxic amount of copper. Furthermore, it was found that antimycoplasmal activity depends on the hydrophobic fragmental value of the amide residue. A quantitative SAR established the optimal hydrophobic fragmental value of the amide residue to be 0.30.[40]



J. Med. Chem. **1988**, *31*, 716–22.

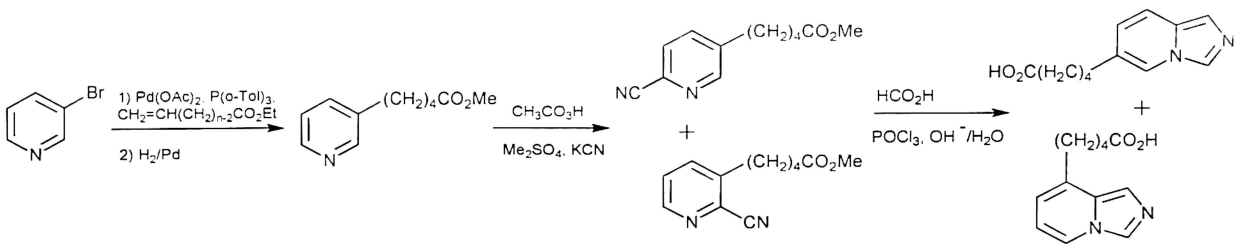


J. Med. Chem. **1989**, *32*, 487–493.

In a similar manner, antimycoplasmal activity of a series of aromatic amidines derived from **XXV** was reported. In the presence of 40 μM copper the most active compounds showed growth inhibition of ***Mycoplasma gallisepticum*** in the nanomolar range. These compounds are 3 times as active as tylosin. In the presence of copper, amidines derived from **XXV** are 2-3 times more active than the corresponding amides. Furthermore it was established that for these compounds too, the presence of a 2,2'-bipyridyl moiety is a necessary prerequisite for antimycoplasmal activity. As for the amides, antimycoplasmal activity of amidines is dependent on the hydrophobic fragmental value of the aromatic nucleus of the amidine moiety.[41]

1.2.9. Imidazo[1,5-*a*]pyridine

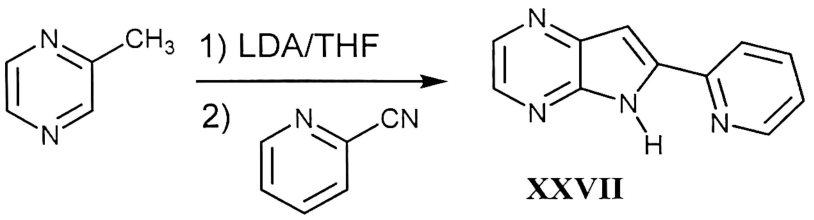
A series of imidazo[1,5-*a*]pyridines were synthesized from 5-substituted 2-cyanopyridines and the SAR profiles as well as potency and specificity of thromboxane A2 synthetase inhibitor activity was reported.[42]



J. Med. Chem. **1985**, *28*, 164–170.

1.2.10. Pyrazine

Cyclin-dependent kinases (CDKs) regulate the cell cycle, apoptosis, neuronal functions, transcription, and exocytosis. In this respect, 6-(2'-pyridyl)[5*H*]pyrrolo[2,3-*b*]pyrazine (**XXVII**) was synthesized as a novel potent CDK inhibitory scaffold.[43]

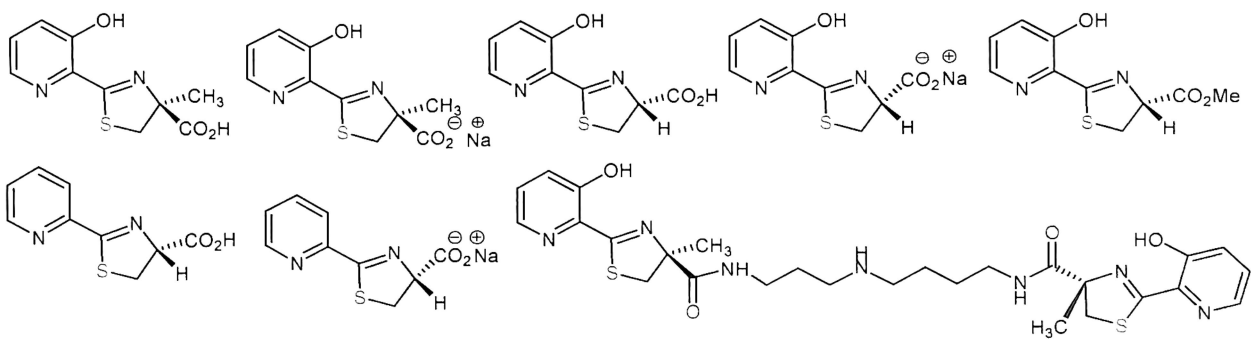


XXVII

J. Med. Chem. **2003**, *46*, 222–236.

1.2.11. Desferrithiocin

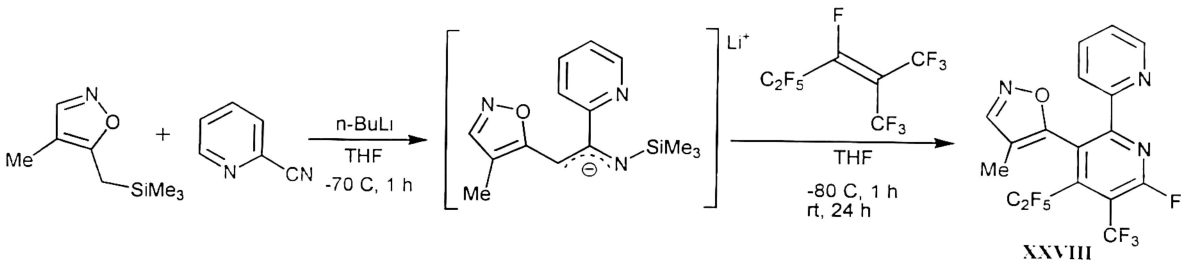
Desferrithiocins containing a 2-pyridyl ring at a thiazoline ring were synthesized from **1** or 3-hydroxy-2-cyanopyridine. These were evaluated for their ability to promote iron clearance.[44]



J. Med. Chem. **1991**, *34*, 2072–2078.

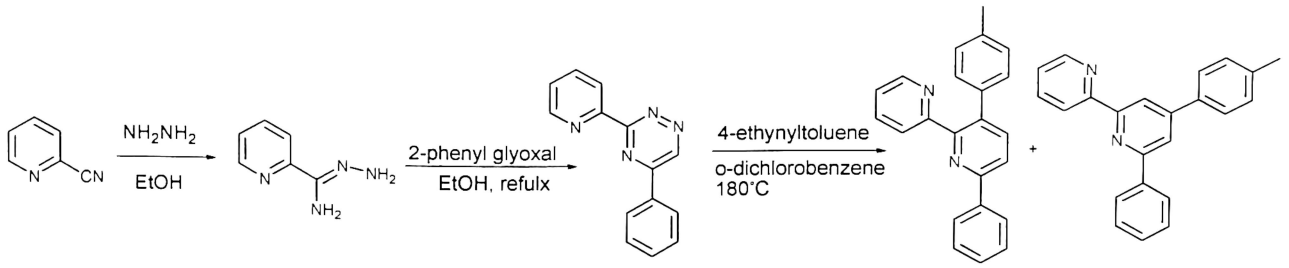
1.2.12. Pyridine

2-Cyanopyridine readily add silane having isoxazolyl group to form the 1-azaallyl anion, which further reacted with fluorine-substituted alkene yielding fluorine-containing pentasubstituted pyridine (**XXVIII**) derivative.[45]



J. Org. Chem. **2007**, *72*, 5878–5881.

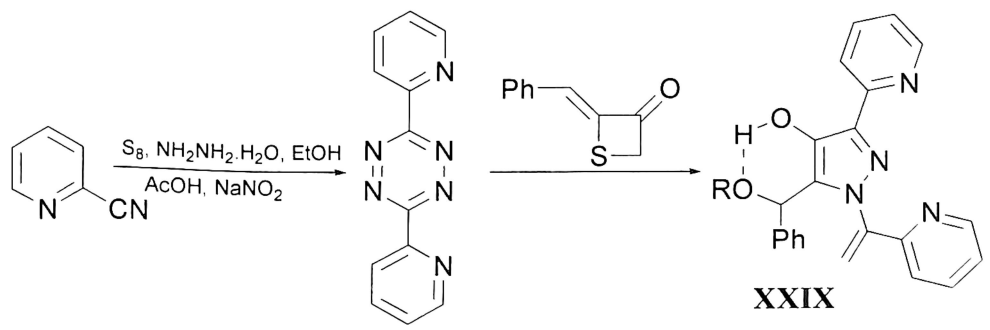
2-Cyanopyridine has been used for the synthesis of some 2,2′-bipyridine derivatives.[46]



Tetrahedron Lett. **2007**, *48,* 8069–8073.

1.2.13. Pyrazole

2-Cyanopyradine on treatment with ethanolic sulfur and hydrazine afforded the dihydrotetrazine which was oxidized to 3,6-di(2′-pyridyl)[1,2,4,5]tetrazine by sodium nitrite in acetic acid. 3,6-di(2′-pyridyl)[1,2,4,5]tetrazine was used for the synthesis of fully substituted pyrazole (**XXIX**).[47]

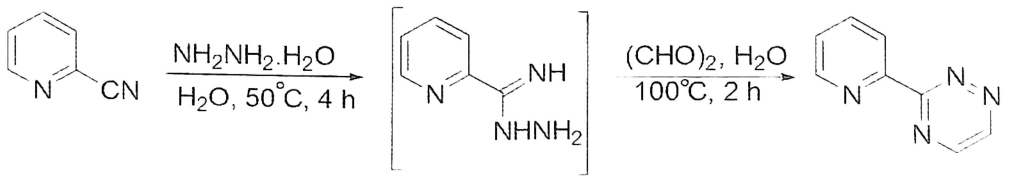


XXIX

J. Org. Chem. **2005**, *70*, 8468–8471.

1.2.14. 1,2,4-Triazine

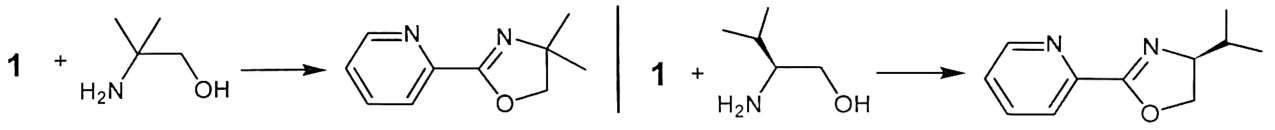
Reaction of **1** with hydrazine hydrate yielded 3-(2′-pyridyl)amidrazone which reacted with $(CHO)_2$ yielding of 3-(2′-pyridyl)-1,2,4-triazine.[48]



Chem. Lett. **2005**, *34*, 836–837.

1.2.15. 2-Oxazoline

Natural kaolinitic clay has been used to promote the conversion of **1** to 2-oxazoline by refluxing with eight equivalents of 1,2-aminoalcohol.[549]

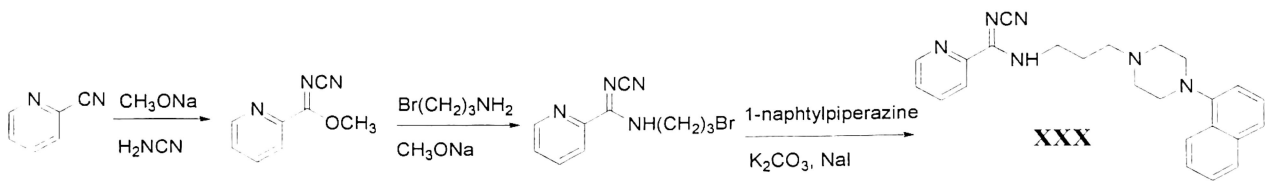


Tetrahedron Lett. **1998**, *39*, 459–462.

1.3. Reactions

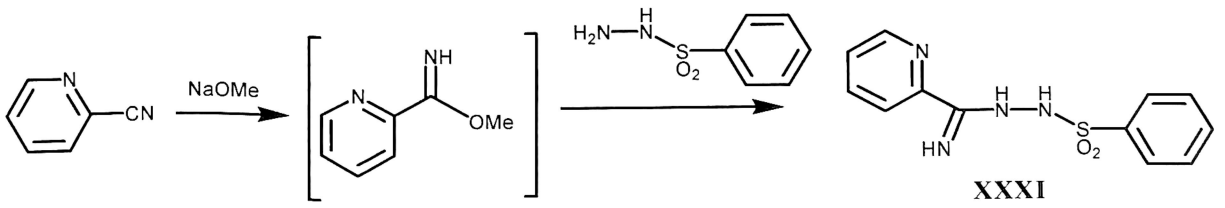
1.3.1. Amidine

The *N*′-cyano-*N*-(3-(4-(naphthalen-1-yl)piperazin-1-yl)propyl)picolinamidine (**XXX**) was synthesized using **1** and its use as serotoninergic ligands with an antiproliferative activity on PC3 cells was studied. Compound **XXX** showed high *in vitro* affinity and selectivity toward 5-HT1A receptor and induced, after 96 h of treatment, a dose-dependent growth inhibition of PC3 cells with IC_{50} value at 23.75 μM.[50]



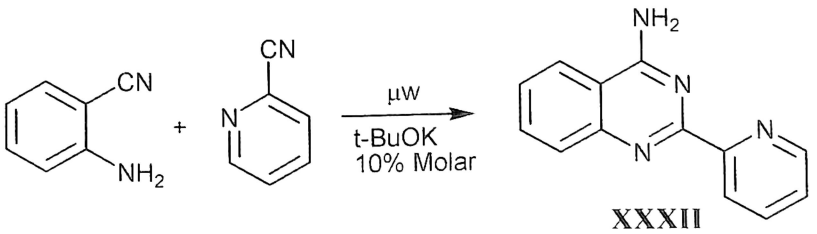
Eur. J. Med. Chem. **1999,** *34*, 2206–2216.

Condensation of **1** with sulfonylhydrazides in the presence of sodium methoxide produced the amidine (**XXXI**) which exhibited good anti-inflammatory activity.[51]



Bioorg. Med. Chem. **2006**, *14*, 4657–4663.

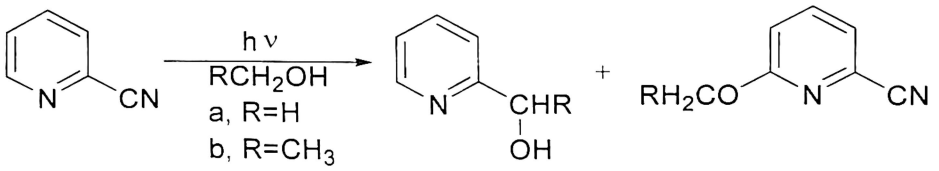
2-Cyanopyridine reacted with anthranilonitrile in a domestic microwave oven affording the corresponding 2-(2′-pyridyl)-4-aminoquinazoline (**XXXII**) in good yields.[52]



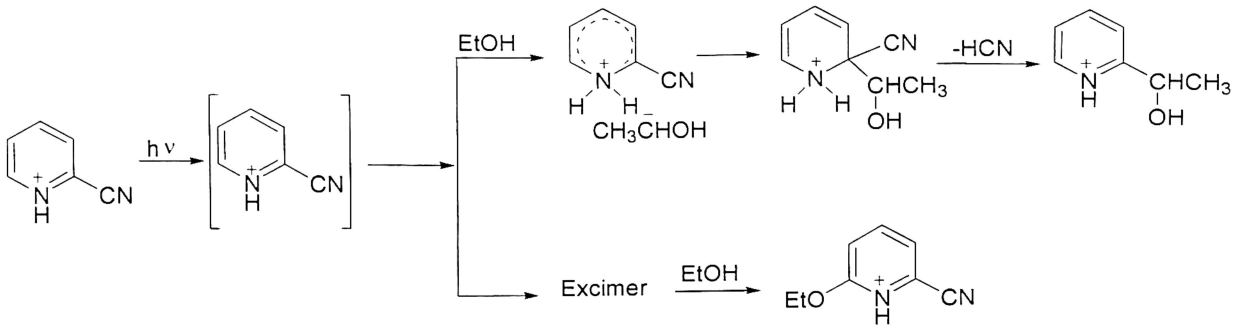
Tetrahedron Lett. 2000, *41*, 2215–2217.

1.3.2. *α*-Hydroxyalkylation

The UV irradiation of **1** in methanol and in ethanol, led to the replacement of the cyano group by the hydroxyalkyl group as well as replacement of the ring hydrogen group by the alkyl group.[53]



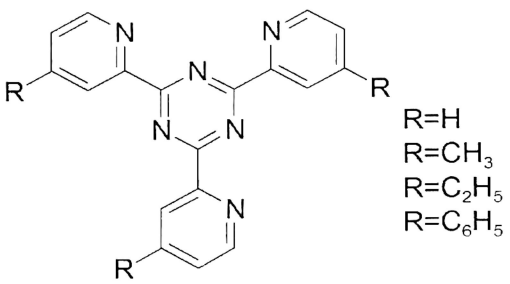
The mechanism is as follows:



Bull. Chem. Soc. Jpn. **1982,** *55*, 2906–2910.

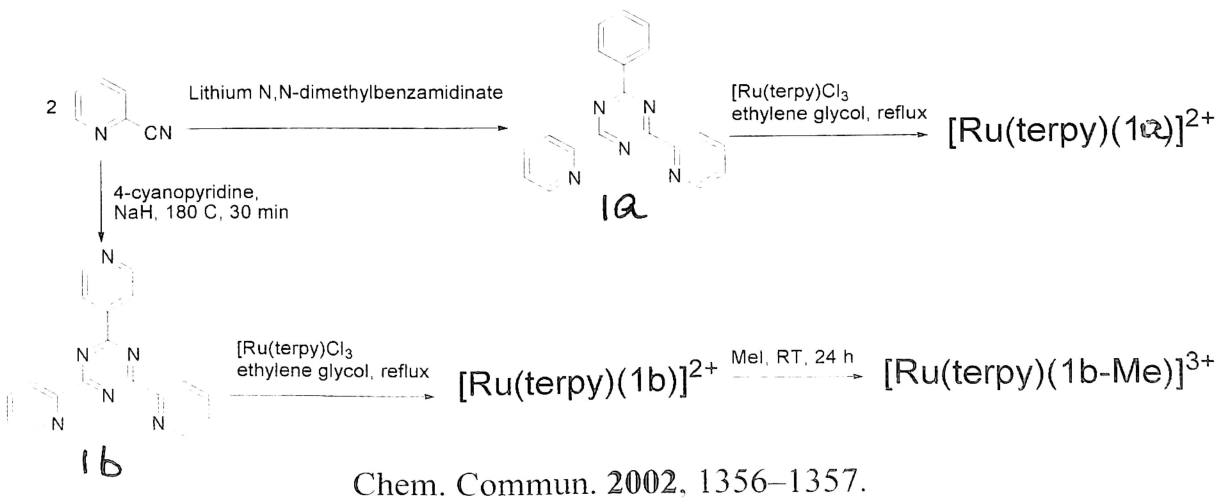
1.3.3. Cyclization

In presence of small amounts of NaH, on heating at 160–165°C for 5 h in nitrogen atmosphere, **1** afforded 2,4,6-tris(2′-pyridyl)-1,3,5-triazine.[54]



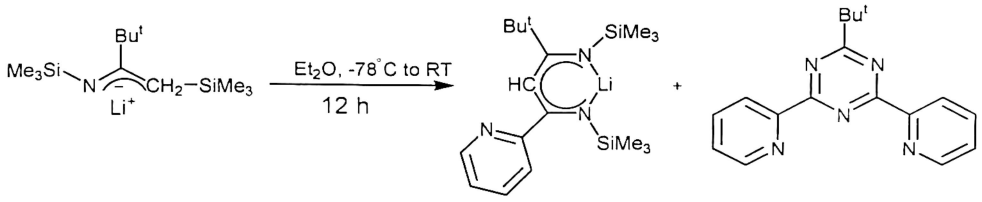
J. Am. Chem. Soc. **1959**, *81*, 904–906.

Using **1**, two 1,3,5-substituted triazines were prepared.[55]



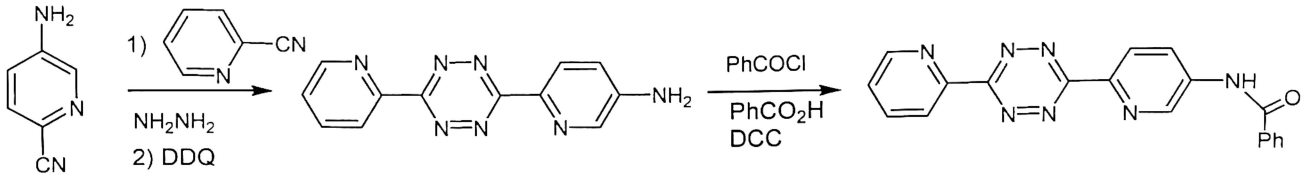
Chem. Commun. **2002**, 1356–1357.

Reaction of **1** with bis(trimethylsilyl)methyl lithium reagent Li[CH(SiMe$_3$)$_2$] afforded β-diketiminatolithiums and yielded 2,4,-bis(2′-pyridyl)-6-tertbutyl-1,3,5-triazine *via* 1-azaallyllithium intermediate.[56]



J. Organomet. Chem. **2002**, *655*, 89–95.

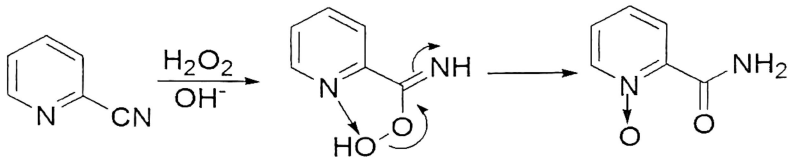
Unsymmetrical tetrazine was prepared from the reaction of hydrazine with 5-amino-2-cyanopyridine and **1**.[57]



J. Am. Chem. Soc. **2008**, *130*, 13518–13519.

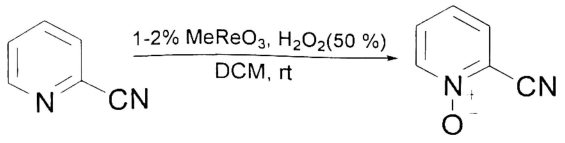
1.3.4. Oxidation

On oxidation with H_2O_2 at pH 7.5–8, **1** afforded amide N-oxide.[58]

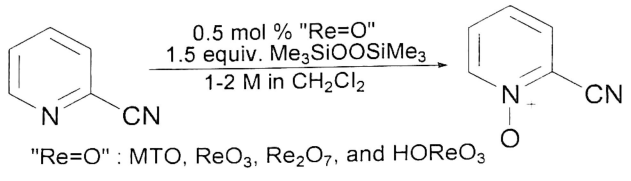


J. Org. Chem. **1961**, *26*, 668–670.

The N-oxide of **1** was synthesized by the reaction with MTO and H_2O_2,[59] as well as using MTO/ReO_3/Re_2O_7/$HOReO_3$ and bis(trimethylsilyl)peroxide.[60]



J. Am. Chem. Soc. **2009**, *131*, 3291–3306.

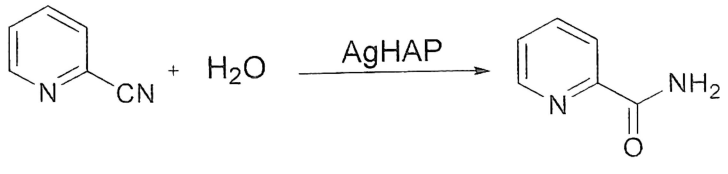


Tetrahedron Lett. **1998**, *39*, 761–764.

1.3.5. Hydration

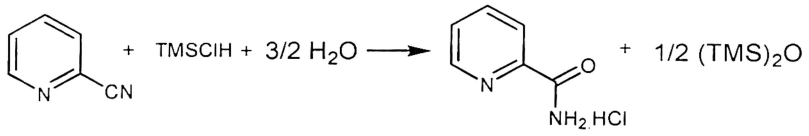
Hydration of nitrile to amide including **1** was achieved by several ways. They are by:

(a) using hydroxyapatite-supported silver nanoparticles (AgHAP) in water.[61]



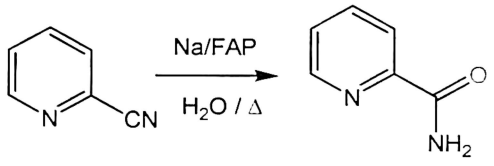
Chem. Commun. **2009**, *22*, 3258–3260.

(b) hydrogen halide generated by the hydrolysis of trimethylsilylhalides.[62]



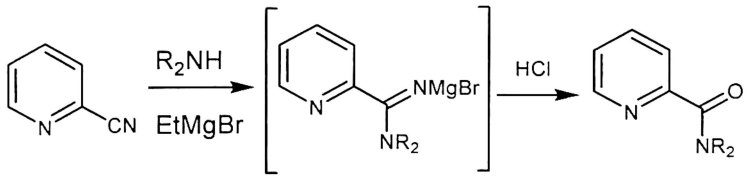
Tetrahedron Lett. **1998**, *39*, 3005–3006.

(c) using sodium nitrate modified synthetic fluorapatite in water.[63]



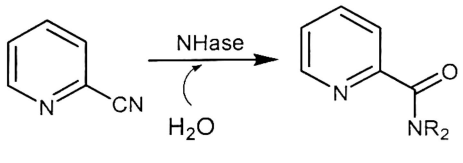
Tetrahedron Lett. **2003,** *44,* 4031–4033.

(d) reacting with magnesium amides to produce carboxamides.[64]



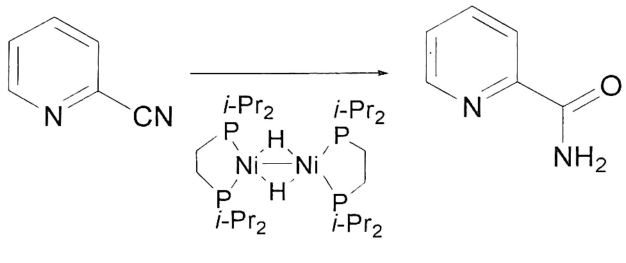
Tetrahedron Lett. **2006**, *47*, 505–506.

(e) using the nitrile hydratase enzyme from *Rhodopseudomonas palustris* CGA009.[65]



Tetrahedron Lett. **2010**, *51*, 1639–1641.

(f) homogeneous catalytic method using 0.5 mol% of [(dippe)Ni(μ-H)]$_2$ as catalyst precursor under heating at 100 °C.[66]



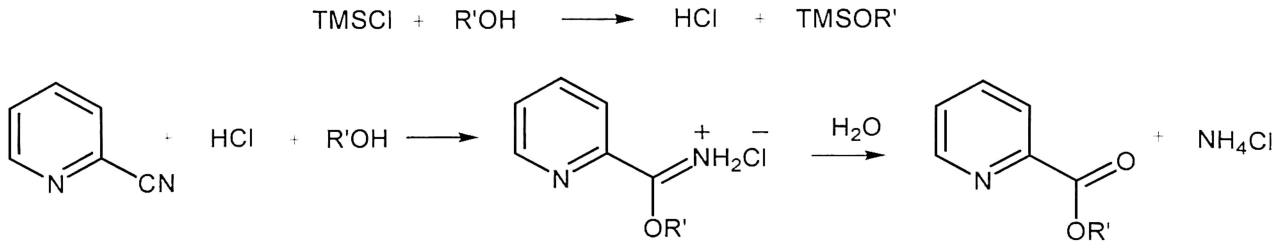
Inorganica Chimica Acta **2010**, *363*, 1092–1096.

Hydrolysis of **1** to picolinamide was reported to be accelerated 100-300 fold, as compared with spontaneous hydrolysis, in the presence of a complex formed from Cu(I1) ion and (S)-l-benzyl-2-[(ethylamino)methyl]pyrrolidine at 30 °C and pH 6-9.5 in H_2O. The rate enhancement was attributed to the intramolecular attack of coordinated hydroxide ion at the cyano group of the coordinated **1**. No picolinic acid was detected in the reaction mixture. But the copper(II)-catalyzed 2-cyanopyridine

hydrolysis in the presence of *(S)*-1-benzyl-2-[((2-hydroxyethyl)amino)methyl]-pyrrolidine produced about 30-60% of picolinic acid, along with picolinamide. The formation of picolinamide and of picolinic acid followed different pathways, the latter being a typical consecutive two-stage type reaction with a buildup of an intermediate complex. The hydrolysis of **1** to picolinic acid is considered to result from the initial nucleophilic attack of the coordinated hydroxyethyl group at the cyano group of the coordinated cyanopyridine with the formation of an intermediate coordinated imino ester, which is in turn slowly hydrolyzed further to picolinic acid.[67]

1.3.5. Ester

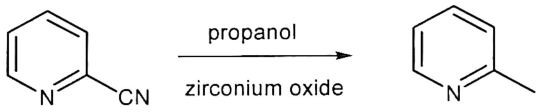
Several nitriles including **1** were converted to esters by reaction with alcohol and trimethylchlorosilane at 50°C. Plausible reaction pathway is:[68]



Tetrahedron Lett. **1998**, *39*, 9455–9456.

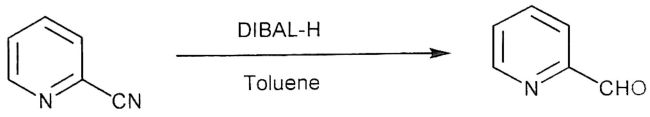
1.3.7. Reduction

Vapor phase reduction of **1** using propanol over hydrated zirconium oxide yielded 2-picoline. This is reported to proceed *via* pyridyl carbinol and pyridyl carbocation.[69]



Chem. Lett. **1990**, *2*, 311–314.

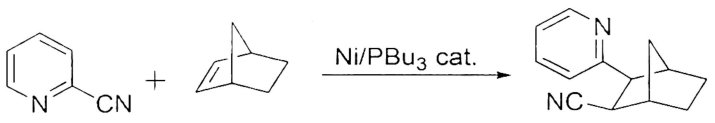
Using continuous flow technology, **1** has been reduced with diisobutylaluminium hydride (DIBAL-H) to pyridine-2-carboxaldehyde.[70]



Tetrahedron Lett. **2011**, *52*, 6058–6060.

1.3.8. Addition to a double bond

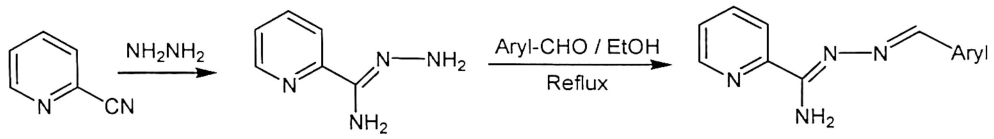
2-Cyanopyridine added to norbornene under nickel catalyst to give (2R*,3S*)-3-(2′-pyridyl)-2-cyanobicyclo[2.2.1]-heptane.[71]



Chem. Lett. **2006**, *35*, 790–791.

1.3.9. Amidrazone

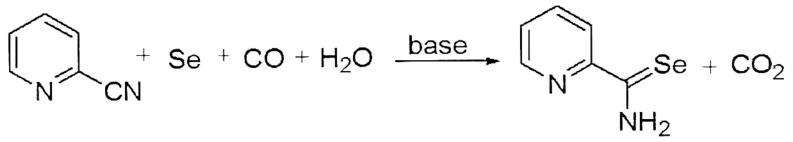
Preparation of phenolic *N*1-benzylidene–pyridinecarboxamidrazones and their evaluation for antimycobacterial activity were reported. These compounds show a pronounced selectivity for Gram-positive bacteria over Gram-negative micro-organisms. In addition, this compound is active against various drug-resistant Gram-positive bacteria.[72]



Bioorg. Med. Chem. Lett. **2006**, 16, 879–883.

1.3.10. Selenocarboxamide

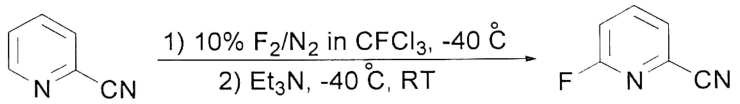
Pyridine-2-selenocarboxamide was prepared from **1** by reaction with selenium, carbon monoxide and water.[73]



J. Org. Chem. **1985**, *50*, 384–386.

1.3.11 Ring fluorination

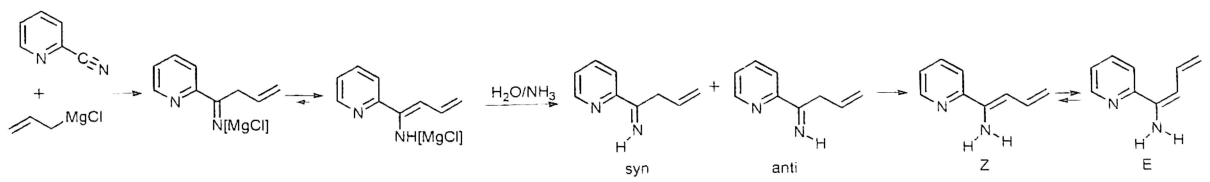
6-Fluoro-2-cyanopyridine was prepared by the reaction of **1** with 10% F_2/N_2 in $CFCl_3$ at –40 °C followed by treatment with excess base such as triethylamine.[74]



J. Org. Chem. **1989**, *54*, 1726–1731.

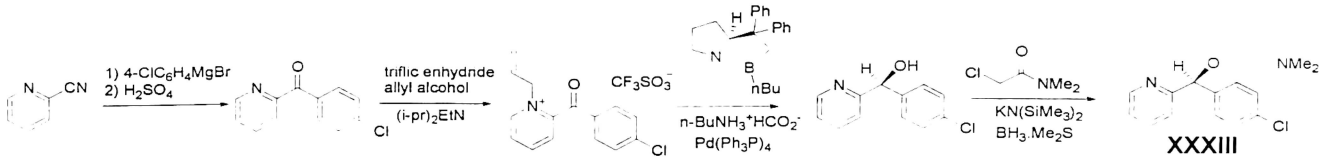
1.3.12 With Grignard reagent

Addition of allylmagnesium chloride to **1** followed by hydrolysis by H_2O, NH_3 and CH_3OH was reported. Controlled hydrolysis with ammonia yielded enamine product.[75]



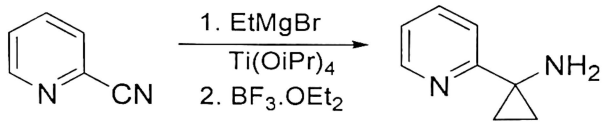
J. Org. Chem. **1995**, *60*, 5284–5290.

(*S*)-Carbinoxamine (**XXXIII**) is therapeutically important histamine H_1 antagonist and **1** is useful as the starting compound for its synthesis as shown below:[76]



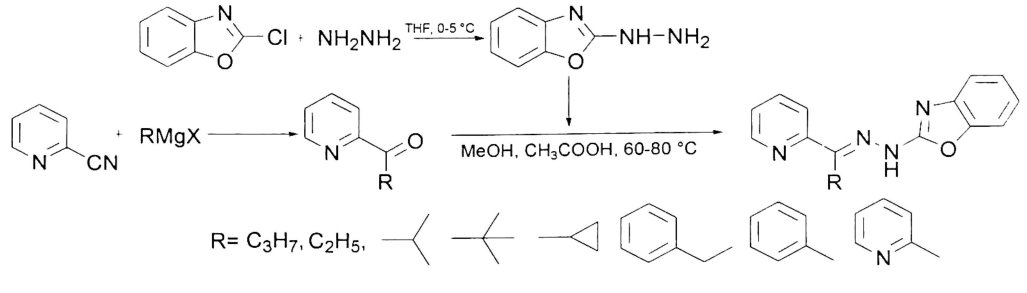
Tetrahedron Lett. **1996**, *37*, 5675–5678.

Addition of ethylmagnesium bromide to **1** afforded 1-(2′-pyridyl)cyclopropylamine.[77]



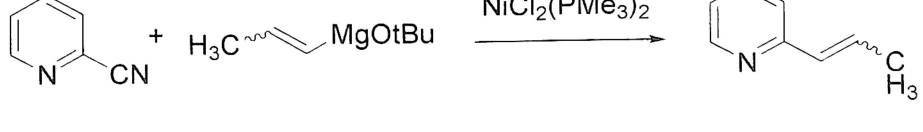
J. Org. Chem. **2002**, *67*, 3965–3968.

The alkyl-2-pyridinyl ketones were synthesized by treating **1** with the corresponding alkylmagnesium halide. Synthesis, SAR, and antitumor studies of 2-benzoxazolyl hydrazones derived by reacting equimolar amounts of 2-hydrazinobenzoxazole with the appropriate alkyl-2-pyridyl ketone in methanol containing traces of glacial acetic acid was reported.[78]



J. Med. Chem. **2006,** *49,* 6343–6350.

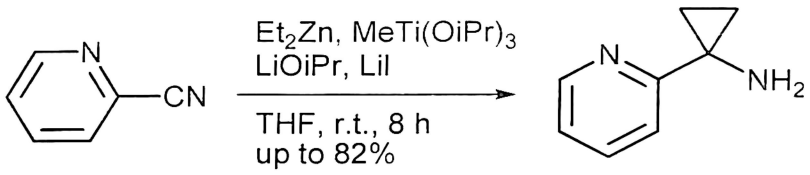
The nickel catalyzed cross-coupling of alkenyl Grignard reagents with **1** afforded the corresponding alkenes *via* activation of the C–CN bond. To prevent direct addition of nucleophile to the nitrile group, the reactivity of the Grignard reagent was modulated by reaction with either LiO*t*-Bu or PhSLi prior to cross-coupling. The optimum catalyst was determined to be $NiCl_2(PMe_3)_2$.[79]



Tetrahedron Lett. **2003**, *44*, 1907–1910

1.3.13. With diethylzinc

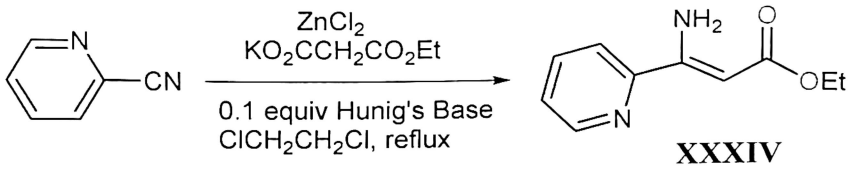
Compound **1** afforded 1-(2′-pyridyl)cyclopropylamine by reaction with diethylzinc, and methyltitanium triisopropoxide.[80]



Org. Lett. **2003**, *5*, 753–755.

1.3.14. Decarboxylative Blaise reaction

In a decarboxylative Blaise reaction, **1** reacted with potassium ethylmalonate in presence of zinc chloride and a catalytic amount of Hünig's base, provided (*Z*)-3-amino-3-pyridin-2-yl-acrylic acid ethyl ester (**XXXIV**).[81]

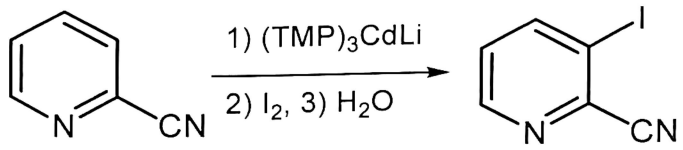


XXXIV

J. Org. Chem. **2007**, *72*, 10261–10263.

1.3.15 Ring iodination

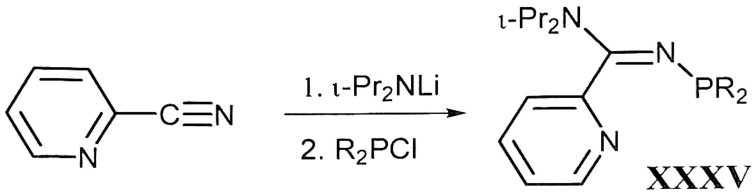
The 3-iodo derivative was achieved by direct ring iodination using iodine and (2,2,6,6-tetramethylpiperidino)$_3$CdLi in tetrahydrofuran at room temperature.[82]



J. Org. Chem. **2010**, *75*, 839–847.

1.3.16. *N*-Phosphanylamidine

The *N*-phosphanylamidines (**XXXV**) were synthesized by successive addition of lithiumdiisopropylamide (LDA) and R_2PCl (R = Ph and ^{i}Pr) at –78 °C.[83]

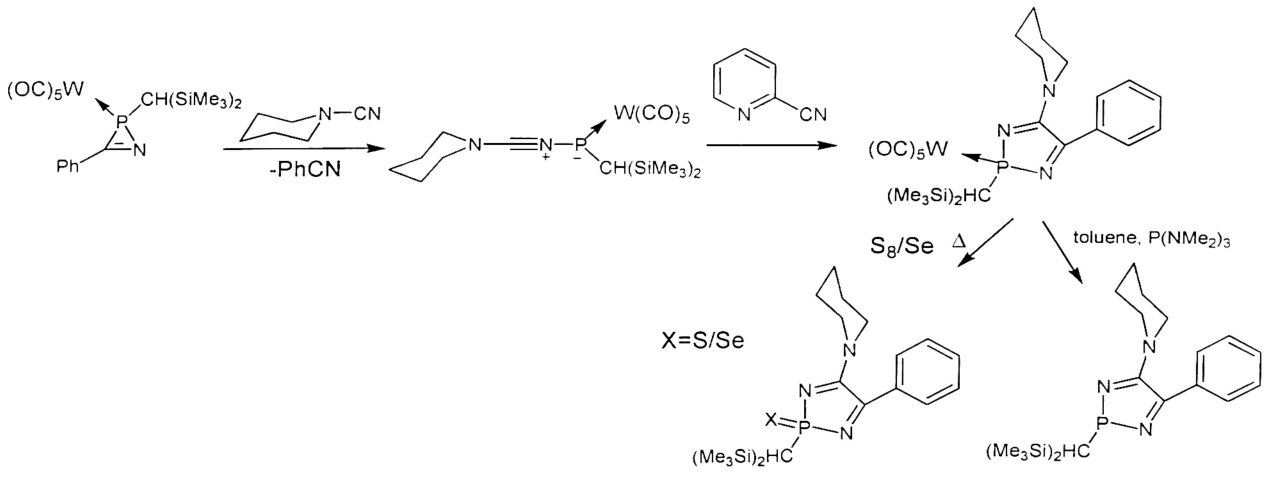


XXXV

J. Organomet. Chem. **2011**, *696*, 897–904.

1.3.17. Diazaphosphole

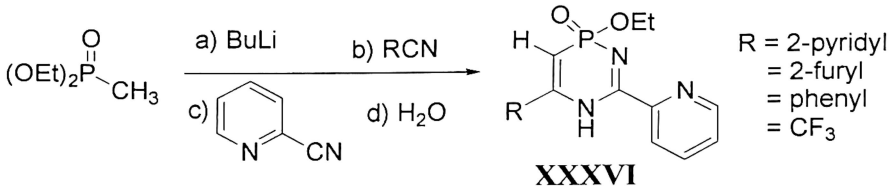
Thermal ring opening of 2*H*-azaphosphirene tungsten complex in the presence of 2-piperidino carbonitrile and **1** furnished selectively the 2*H*-1,3,2-diazaphosphole tungsten complex. The corresponding P^V=S and P^V=Se were obtained by oxidative decomplex-ation using elemental sulfur and selenium. Deselenization was achieved with $P(NMe_2)_3$.[84]



J. Organomet. Chem. **2003**, *682*, 212–217.

1.3.18. Diazaphosphinine

Synthesis of phosphorus-containing pyrimidine analogues such as 4,6-disubstituted-2-ethoxy-2,5-dihydro-1,5,2-diazaphosphinine 2-oxide (**XXXVI**) from primary enamine phosphonates and nitriles were achieved in "*one pot*" reaction of phosphonate with butyllithium followed by the addition of excess of nitriles.[85]

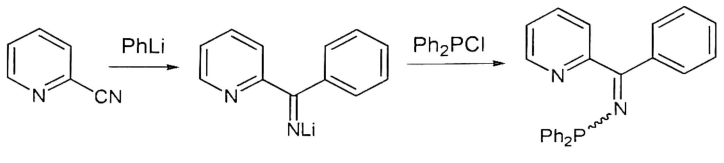


XXXVI

Tetrahedron Lett. **2002**, *43*, 5917–5919; Tetrahedron **2005**, *61*, 1087–1094.

1.3.19. Diphenylphosphino-imine

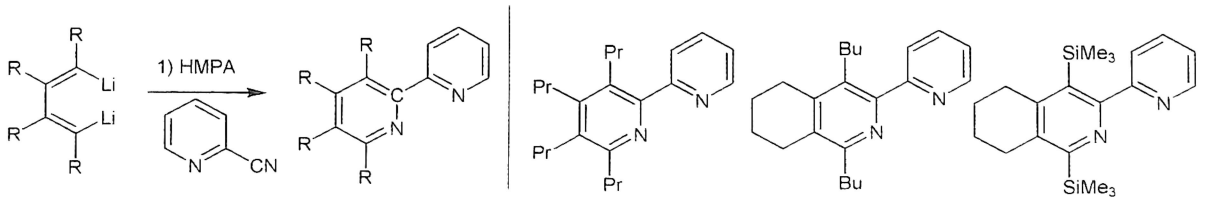
In a simple "*one pot*" procedure, P–N-chelating ligand diphenylphosphino(phenyl-2-pyridinyl-methylene)amine has been synthesized by reacting **1** with PhLi and Ph_2PCl.[86]



J. Organomet. Chem. **2005**, *690*, 5264–5281.

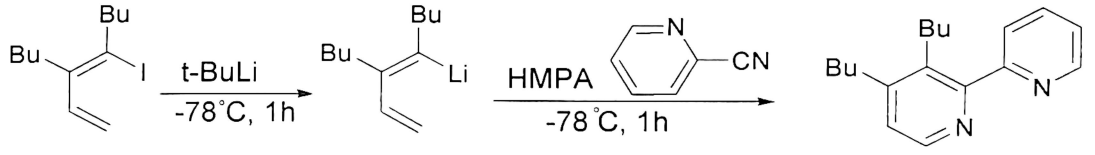
1.3.20. With alkyl lithium

The reaction **1** with dilithio compounds in HMPA afforded 2,2′-bipyridine derivatives.[87]



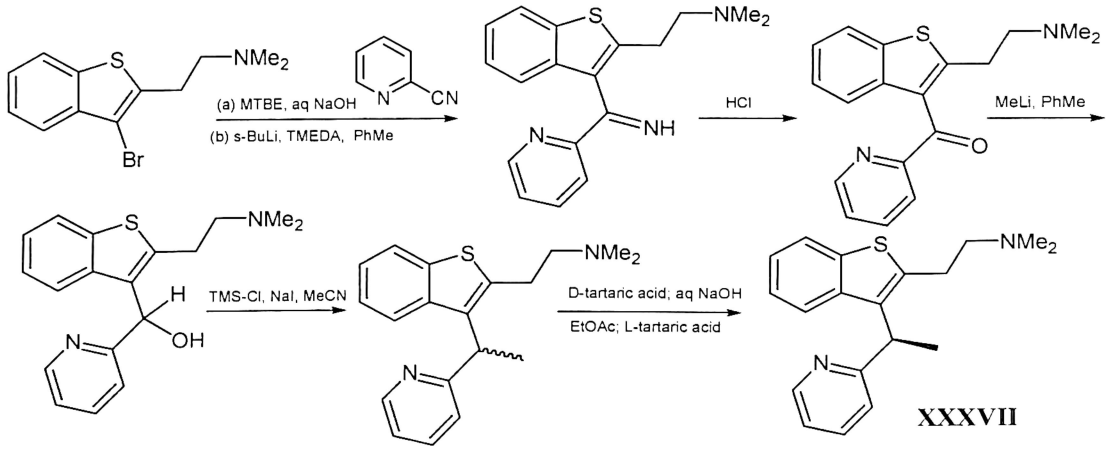
J. Am. Chem. Soc. **2002**, *124*, 6238–6239.

Lithiation of 1,2-dibutyl monoiodobutadiene with ^{t}BuLi afforded 1,2-dibutyl 1-lithio-1,3-butadiene, which on reaction with HMPA and **1** afforded 2,2′-(3,4-dibutyl)bipyridine.[88]



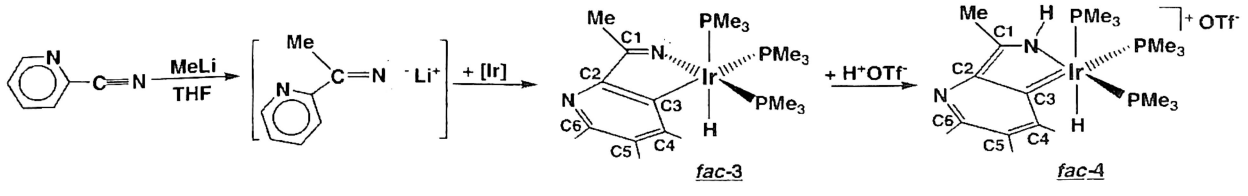
J. Org. Chem. **2006**, *71*, 8565–8571.

NBI-75043 (**XXXVII**) is a highly selective and potent H1 antagonist that was under evaluation for safety and efficacy in the treatment of insomnia. The scale up synthesis of using **XXXVII** using **1** has been reported.[89]



Org. Process Res. Dev. **2008**, *12*, 929–939.

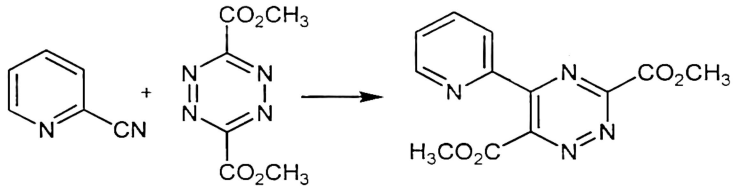
Treatment of **1** with methyllithium produced *N*-lithiated imine reagents, which, when reacted with (η^2-cyclooctene)(Cl)Ir(PMe_3)$_3$, generated fused iridaazacycles *via* ortho-metalation. Monoprotonation of these iridaazacycles using triflic acid produces fused iridapyrrole derivatives.[90]



Organometallics **2008,** *27*, 5744–5747.

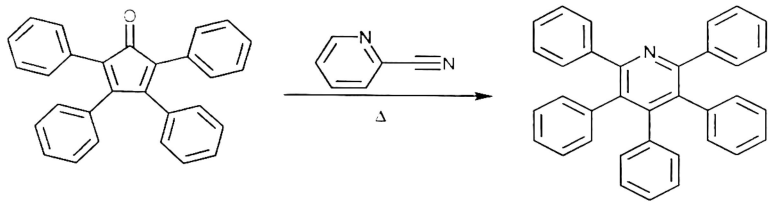
1.3.21. Diels Alder Reaction

Compound **1** acted as dienophile to undergo Diels-Alder reaction with dimethyl-1,2,4,5-tetrazine-3,6-dicarboxylate to form the product dimethyl-5-(2-pyridyl)-1,2,4-triazine-3,6-dicarboxylate.[91]



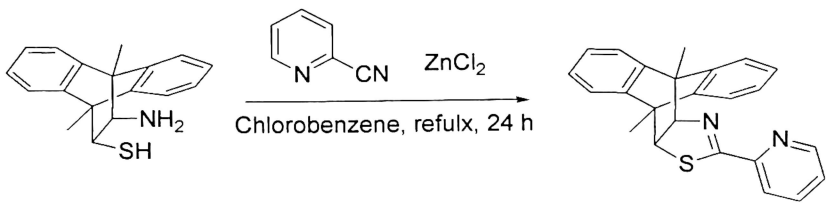
J. Am. Chem. Soc. **1985**, *107*, 5745–5754.

Diels–Alder [4+2] cycloaddition with tetra(phenyl)cyclopenta-2,4-dien-1-one afforded 2-(2′-pyridyl)-3,4,5,6-tetraphenylpyridine as the product.[92]



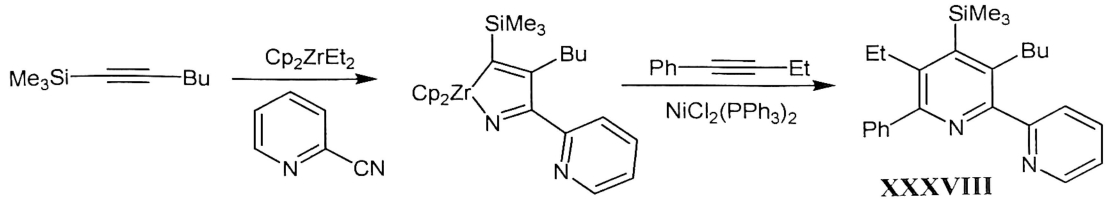
Dalton Trans. **2008**, *2*, 283–290.

Roofed *cis*-2-aminothiol was obtained from the chiral 2-thiazolidinone by hydrolytic ring cleavage with $Ba(OH)_2$ in ethanol. The *cis*-2-aminothiol underwent Diels–Alder reaction with **1** in presence of $ZnCl_2$ to yield new roofed pyridylthiazoline ligand.[93]



Tetrahedron Lett. **2005**, *46*, 4019–4022.

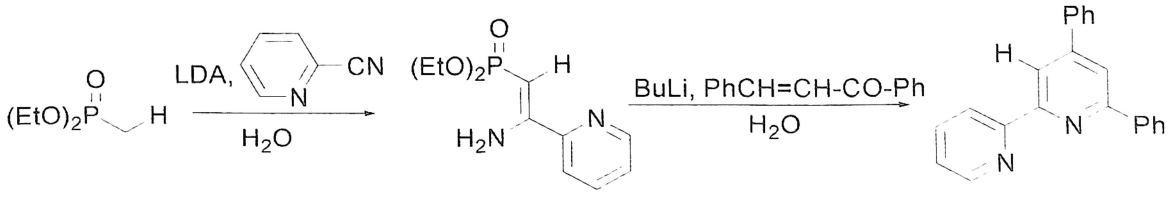
The compound 2,2′-[3-butyl-5-ethyl-6-phenyl-4-(trimethylsilyl)]bipyridine (**XXXVIII**) was synthesized by the following method:[94]



J. Am. Chem. Soc. **2002**, *124*, 5059–5067.

1.3.22. With *β*-enaminophosphonate

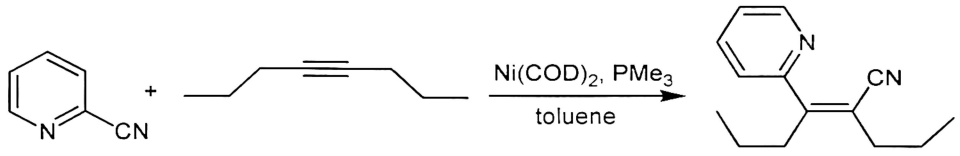
In a general method, *β*-enaminophosphonate obtained from phosphonates by reaction with LDA and **1** was converted to tetrasubstituted pyridines by the addition of BuLi and *α*,*β*-unsturated ketone to *β*-enaminophosphonate.[95]



Tetrahedron Lett. **1996**, *37*, 4577–4580.

1.3.23. Acylcyanation

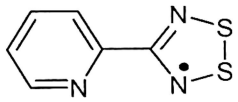
Reaction of **1** on reaction with 4-octyne in the presence of $Ni(COD)_2$ (10 mol%), PMe_3 (20 mol%) in toluene at 100 °C afforded (*Z*)-3-(2′-pyridyl)-2-propyl-2-hexenenitrile.[96]



Tetrahedron **2006**, *62*, 7567–7576.

1.3.24. Dithiadiazolyl radical

The 4-(2′-pyridyl)-1,2,3,5-dithiadiazolyl radical (**XXXIX**) was synthesized in a three step process. Firstly preparation of 2-(2′-pyridyl)-*N*,*N*,*N*.-tris(trimethylsilyl)amidine by the reaction of **1** with $LiN(TMS)_2{\cdot}Et_2O$ and chlorotrimethylsilane. Resulting amidine was converted to [4-(2′-pyridyl)-1,2,3,5-dithiadiazolyl] chloride by stirring with excess sulfur monochloride, which on treatment with triphenylantimony afforded the 4-(2′-pyridyl)-1,2,3,5-dithiadiazolyl radical as a solid product.[97]

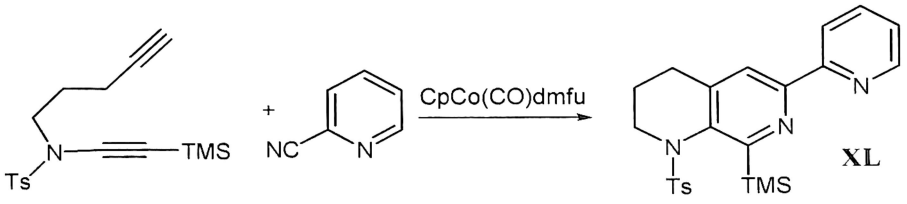


XXXIX

J. Am. Chem. Soc. **2004**, *126*, 9942–9943.

1.3.25. [2+2+2] Cycloaddition

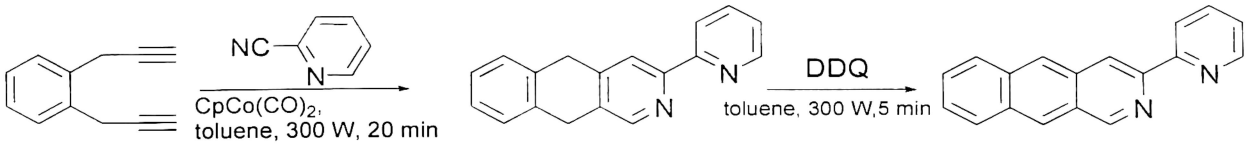
Bimolecular cobalt-catalyzed [2+2+2] cycloaddition between yne-ynamides and **1** afforded (**XL**).[98]



XL

Org. Lett. **2011**, *13*, 2030–2033.

The compound 5,10-dihydro-3-(2′-pyridyl)benzo[*g*]isoquinoline (**XLI**) was prepared by the reaction of 1,2-diethynylbenzene with **1** using $(\eta^5\text{-}C_5H_5)Co(CO)_2$ as catalyst *via* a [2+2+2] cyclotrimerization reaction by heating in microwave which on oxidation with DDQ afforded the 3-(2′-pyridyl)benzo[*g*]isoquinoline.[99]

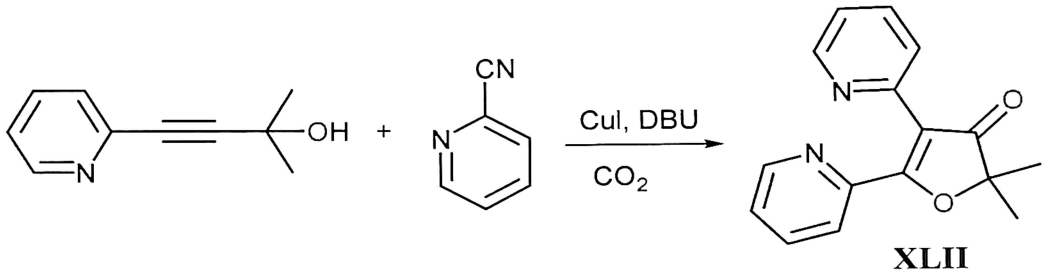


XLI

Org. Lett. **2008**, *10*, 4661–4664.

1.3.26. Furanone

A novel carbon dioxide triggered and copper-catalyzed domino reaction for the efficient synthesis of highly substituted 3(2*H*)-furanone (**XLII**) from **1** and propargylic alcohol has been reported. Carbon dioxide is a prerequisite for achieving the present catalytic transformation, and one of the oxygen atoms of carbon dioxide is incorporated into the 3(2*H*)-furanone. Copper salts play dual roles of activating both the propargylic alcohols and **1**.[100]

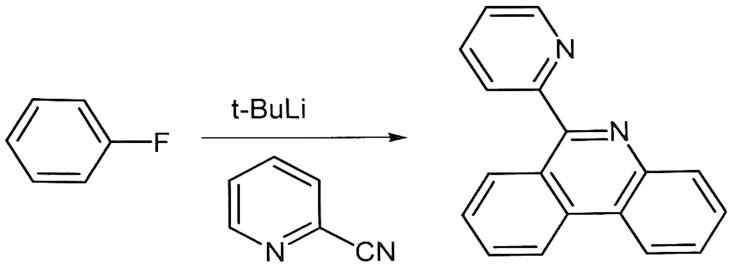


XLII

Org. Lett. **2011,** *13*, 5520–5523.

1.3.27. With 1,2-benzyne

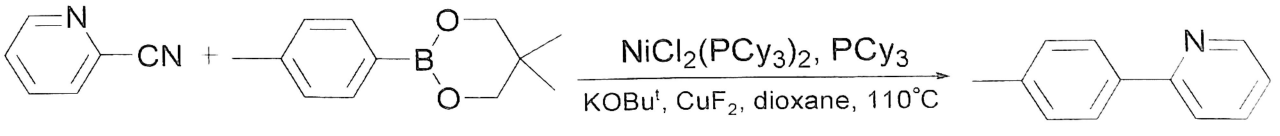
In one-pot, *t*-BuLi-induced synthesis of 6-(2′-pyridyl)phenanthridine from fluorobenzene and **1** *via* 1,2-benzyne was reported.[101]



Org. Lett. **2002**, *4*, 2687–2690.

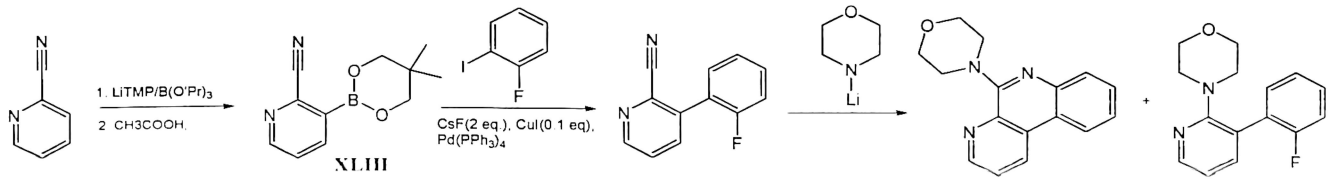
1.3.28. Suzuki-Miyaura cross coupling

Suzuki-Miyaura cross coupling (through C–CN bond cleavage) between 4-tolylboronic ester and **1** using $NiCl_2(PCy_3)_2$ has also been reported.[102]



Org. Lett. **2009**, *11*, 3374–3377.

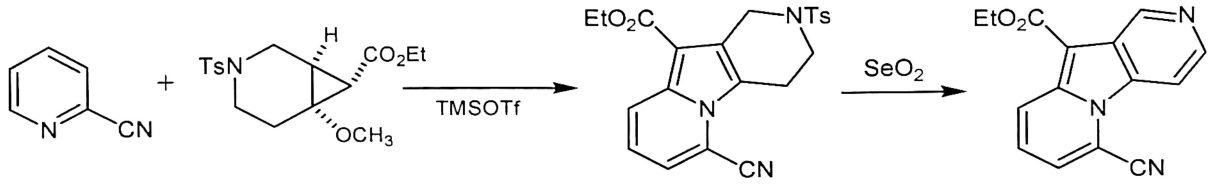
The boronic ester 3-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)picolinonitrile (**XLIII**) was prepared from **1**. This **XLIII** was used for the synthesis of biaryls via Suzuki–Miyaura cross-coupling by adding CuI and CsF.[103]



Tetrahedron **2005**, *61*, 9955–9960.

1.3.29. [3+2] Dipolar cycloaddition

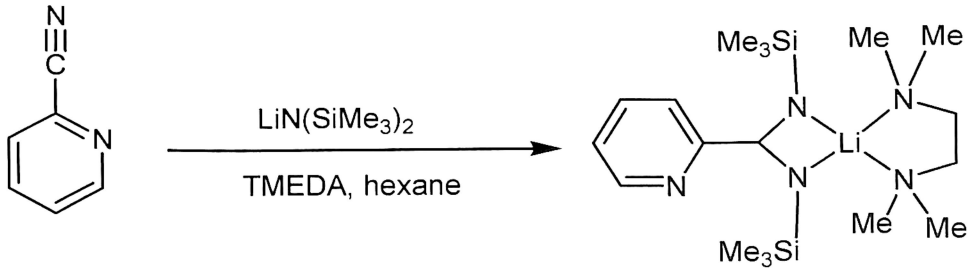
The synthesis of 5-azaindole derivative by a [3+2] dipolar cycloaddition between **1** and a 3,4-cyclopropanopiperidine followed by SeO_2 oxidation was reported.[104]



Org. Lett. **2010**, *12*, 3168–3171.

1.3.30. Lithium amidinate

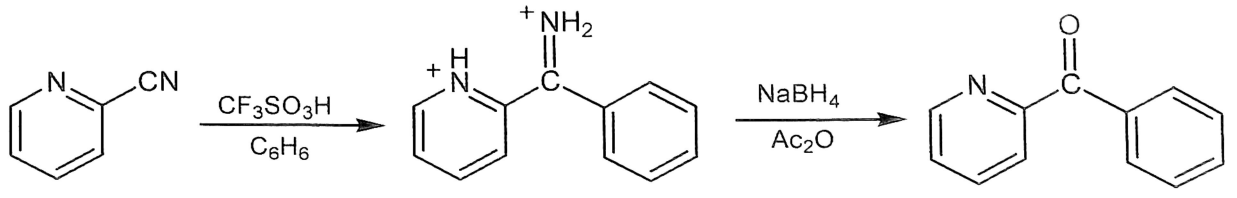
The *N*,*N*′ bis(trimethylsilyl)lithium amidinate was synthesized from the reaction of lithium amides with **1** or organolithium compounds with carbodiimides.[105]



Organometallics **2008,** *27*, 1869–1877.

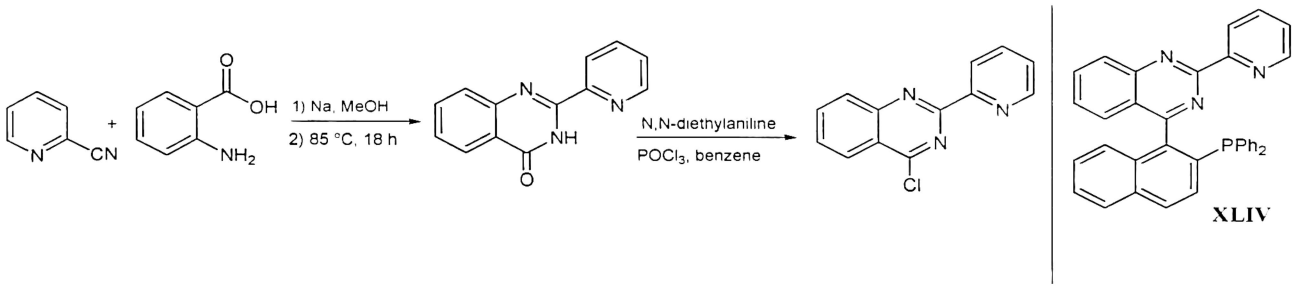
1.3.31. Houben-Hoesch reaction

Superacid-promoted Houben-Hoesch reaction of **1** afforded phenyl(2-pyridyl)ketone.[106]



Tetrahedron **2011**, *67*, 4494–4497.

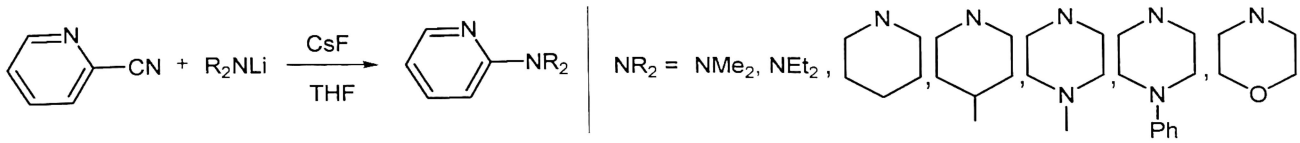
Compound **1** was used for the synthesis and resolution of axially chiral quinazoline-containing phosphinamine ligands, 2-(2′-pyridyl)quinazolinap (**XLIV**), as the final product in a multi-step synthesis.[107]



Tetrahedron **2005**, *61*, 9808–9821.

1.3.32. Displacement of cyanide

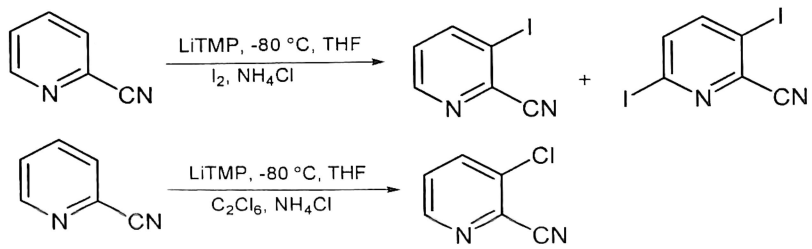
The direct reaction of **1** with lithium amides afforded good yields of the corresponding aminopyridines *via* displacement of cyanide group. Addition of CsF accelerated the reaction and lead to significantly higher yields.[108]



Tetrahedron Lett. **2004**, *45*, 2667–2669.

1.3.33. Ortholithiation

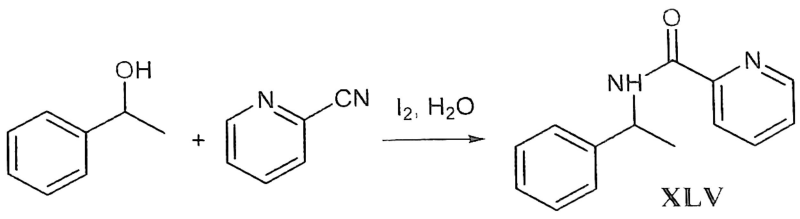
Orthолithiation of **1** using two equivalents of 2,2,6,6-tetramethylpiperidide (LiTMP) and trapping the lithio intermediate with I_2 or C_2Cl_6 as electrophiles yielded ortho-substituted-2-cyanopyridine.[109]



Tetrahedron Lett. **2005**, *46*, 135–137.

1.3.34. Ritter reaction

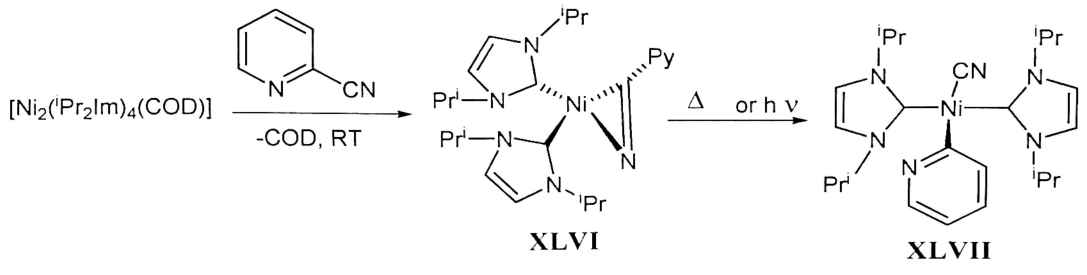
Iodine catalyzed Ritter reaction with **1** and 1-phenylethanol, gave the amide **XLV**.[110]



Tetrahedron Lett. **2010**, *51*, 2813–2819.

1.3.35. η^2-Coordination

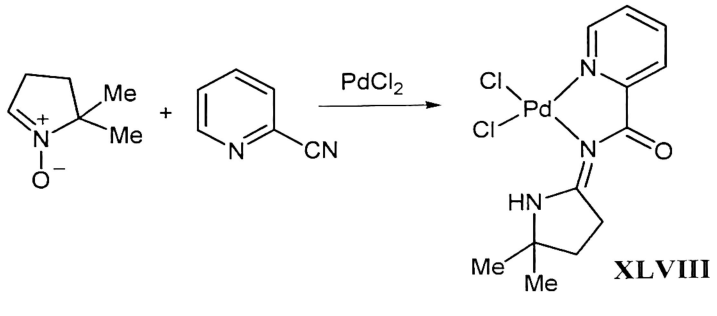
The reaction of the nickel complex $[Ni_2(iPr_2Im)_4(COD)]$ with **1** smoothly and irreversibly proceeded *via* η^2-coordinated **1** as intermediate **XLVI** which formed *trans* **XLVII** either on heating or photolysis.[111]



Dalton Trans. **2007**, *20*, 1993–2002.

1.3.36. [2+3] Cycloaddition

The [2+3] cycloaddition of the pyrrolin *N*-oxide with **1** in the presence of $PdCl_2$ at room temperature in acetone gave the ketoimine palladium(II) complex **XLVIII** containing the (*E*)-*N*-(5,5-dimethylpyrrolidin-2-ylidene)picolinamide ligand.[112]



Dalton Trans. **2009**, *16*, 3074–3084.

NOTE: The ORTEP diagram in Section 1.2.3. and the Scheme involving iridium metal in Section 1.3.20. were adopted from the original article.

1.4. Materials

$Cu(NO_3)_2 \cdot 3H_2O$, $CuCl_2 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$, $Fe(NO_3)_3 \cdot 9H_2O$, $Na_2CO_3 \cdot H_2O$, hydroxylamine hydrochloride, 2–hydroxybenzaldehyde, benzaldehyde, 4-methoxy-benzaldehyde, 2-naphthaldehyde, 9-anthracenaldehyde, hydrazine hydrate, ammonium acetate, polyethylene glycol (PEG) 400, anhydrous $MgSO_4$, silica gel GF (< 0.02 mm), KOH, KSCN, and $NaBH_4$ were purchased from Merck India. 2-Cyanopyridine, 2-picolylamine, 3-picolylamine, 4-picolylamine, 2-pyridinecarboxaldehyde, 3-pyridinecarboxaldehyde, 4-pyridinecarboxaldehyde, 4-methylbenzaldehyde, 2-thiophenecarboxaldehyde, 2-bromobenzaldehyde, 1-pyrenecarboxaldehyde, pyrazinecarbonitrile, aluminum oxide (activated, basic, 58Å), $CDCl_3$, and KBr were

purchased from M/S Aldrich, USA. All the chemicals and solvents were of reagent grade and were used as received without further purifications.

1.5. Instrumentation and Methods

UV–Vis spectra were recorded using a Perkin–Elmer Lambda 25 UV–Vis spectrometer for solutions obtained by dissolving a calculated amount of the sample in an appropriate solvent. A Perkin–Elmer Spectrum One FT–IR spectrometer (KBr disc in the range 4000–250 cm^{-1}), has been used to record IR for air dried samples. ^{1}H NMR analysis were recorded in a Varian Mercury plus 400 MHz NMR Spectrometer and the chemical shifts were recorded in parts per million (*ppm*) on the scale using tetramethylsilane (TMS) as a reference. Perkin–Elmer Series II CHNS/O Analyzer 2400 was used obtaining for elemental analysis of samples. JEOL JES FA-200 X-band EPR spectrometer fitted with a quartz dewar for measurements at liquid nitrogen temperature was used for recording the EPR spectra, which was calibrated with Mn marker. Waters Q-TOF premier mass spectrometer is used for recording the mass spectra. Lakshore VSM Setup has been used for measurement of room temperature magnetic susceptibility data and the moment gain is calibrated using Ni standard which has magnetization of 6.92 emu / gm at 5 KOe.

1.5.2. X-Ray Crystallography

X-ray crystallographic data were collected using Bruker SMART APEX–CCD diffractometer with Mo Kα radiation (λ = 0.71073 Å). The intensity data were corrected for Lorentz and polarization effects and empirical absorption corrections was applied using SAINT program [113–114] All the structures were solved by direct methods using SHELXS–97.[115] Non-hydrogen atoms located from the difference Fourier maps were refined anisotropically by full-matrix least-squares on F^2, using SHELXL–97.[115] The hydrogen atoms were included in the calculated positions and refined isotropically using a riding model.

1.6. References

1. (a) Boyd, G. V. *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1991; Vol. 2. (b) Kukushkin, V. Y. Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771–1802.
2. Gridnev, I. D.; Gridneva, N. A. *Usp. Khim. (Russ. Chem. Rev.)* **1995**, *64*, 1091.
3. (a) Karlsson, S.; Hogberg, H.-E. *Org. Prep. Proced. Int.* **2001**, *33*, 103–172. (b) Raimondi, L.; Benaglia, M. *Eur. J. Org. Chem.* **2001**, 1033–1043. (c) De March, P.; Figueredo, M.; Font, J. *Heterocycles* **1999**, *50*, 1213–1226. (d) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449–1458. (e) Gothelf, K. V.; Jensen, K. B.; Jørgensen, K. A. *Sci. Prog.* **1999**, *82*, 327–350. (f) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–890.
4. Geldard, J. F.; Lions, F. *J. Org. Chem.* **1965**, *30*, 318–319.
5. Bentiss, F.; Lagrenée, M.; Barbry, D. *Tetrahedron Letters*, **2000**, *41*, 1539–1541.
6. (a) Sato, T.; Ashizawa, N.; Matsumoto, K.; Iwanaga, T.; Nakamura, H.; Inoue, T.; Nagata, O. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6225–6229. (b) Roppe, J.; Smith, N. D.; Huang, D.; Tehrani, L.; Wang, B.; Anderson, J.; Brodkin, J.; Chung, J.; Jiang, X.; King, C.; Munoz, B.; Varney, M. A.; Prasit, P.; Cosford, N. D. P. *J. Med. Chem.* **2004**, *47*, 4645–4648.
7. Zhang, J.-P.; Lin, Y.-Y.; Huang, X.-C.; Chen, X.-M. *J. Am. Chem. Soc.* **2005**, *127*, 5495–5506.
8. Hantzsch, A.;Vagt, A. *Justus Liebigs Ann.Chem.* **1901**, *314*, 339–369.
9. Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945– 7950.
10. Palde, P. B.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3525–3528.
11. Rama, V.; Kanagaraj, K.; Pitchumani. K. *J. Org. Chem.* **2011**, *76*, 9090–9095.
12. Hayashi, R.; Jin, X.; Cook, G. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6864–6870.
13. Lasri, J.; Rodriguez, M. J. F.; Guedes da Silva, M. F. C.; Smolenski, P.; Kopylovich, M. N.; Frausto da Silva, J. J. R.; Pombeiro, A. J. L. *J. Organomet. Chem.* **2011**, *696*, 3513–3520.
14. Facchetti, A.; Abbotto, A.; Beverina, L.; Bradamante, S.; Mariani, P.; Stern, C. L.; Marks, T. J.; Vacca, A.; Pagani, G. A. *Chem. Commun.*, **2004**, *15*, 1770–1771.
15. Grant, D.; Dahl, R.; Cosford, N. D. P. *J. Org. Chem.* **2008**, *73*, 7219–7223.

16. Nordhoff, S.; Bulat, S.; Cerezo-Gálvez, S.; Hill, O.; Hoffmann-Enger, B.; López-Canet, M.; Rosenbaum, C.; Rummey, C.; Thiemann, M.; Matassa, V. G.; Edwards, P. J.; Feurer, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6340–6345.
17. Shen, H. C.; Ding, F.-X.; Wang, S.; Deng, Q.; Zhang, X.; Chen, Y.; Zhou, G.; Xu, S.; Chen, H.-S.; Tong, X.; Tong, V.; Mitra, K.; Kumar, S.; Tsai, C.; Stevenson, A. S.; Pai, L.-Y.; Alonso-Galicia, M.; Chen, X.; Soisson, S. M.; Roy, S.; Zhang, B.; Tata, J. R.; Berger, J. P.; Colletti, S. L. *J. Med. Chem.* **2009**, *52*, 5009–5012.
18. Naidu, B. N.; Sorenson, M. E. *Org. Lett.* **2005**, *7*, 1391–1393.
19. Anastassiadou, M.; Danoun, S.; Crane, L.; Mouysset, G. B.; Payard, M.; Caignard, D.-H.; Rettori, M.-C.; Renard, P. *Bioorg. Med. Chem.* **2001**, *9*, 585–592.
20. Mirkhani, V.; Moghadam, M.; Tangestaninejada, S.; Kargar, H. *Tetrahedron Lett.* **2006**, *47*, 2129–2132.
21. Zhang, J.; Wang, X.; Yang, M.; Wan, K.; Yin, B.; Wang, Y.; Li,J.; Shi, Z. *Tetrahedron Lett.* **2011**, *52*, 1578–1582.
22. Bureš, F.; Kulhánek, J.; Růžička, A. *Tetrahedron Lett.* **2009**, *50*, 3042–3045.
23. Grimmett, M. R. *In Comprehensive Heterocyclic Chemistry II:* Katritzky, A. R.; Ress, C. W.; Scriven, E. F. V. Eds.; Pergamon Press: Oxford, 1996: Vol. 3, pp 77–220.
24. (a) Grimmett, M. R. *Imidazole and Benzimidazole Synthesis*; Academic Press: New York, 1997 and references therein. (b) Grimmett, M. R. *Adv. Heterocycl. Chem.* **1970**, *12*, 103–183.
25. Novelli, A.; De Santis, A. *Tetrahedron Lett.* **1967**, *8*, 265–269.
26. Huang, N. Xi. Q.; Liu, L. *In Comprehensive Heterocyclic Chemistry III:* Katritzky, A.; Ramsden, C.; Scriven, E.; Taylor, R. Eds. Elsevier, 2008: Vol 4, pp 143–364.
27. Voss, M. E.; Beer, C. M.; Mitchell, S. A.; Blomgren, P. A.; Zhichkin, P. E. *Tetrahedron,* **2007**, *64*, 645–651.
28. (a) Jiang, B.; Wang, X.; Shi, F.; Tu, S. J.; Ai, T.; Ballew, A.; Li, G. *J. Org. Chem.* **2009**, *24*, 9486–9489. (b) Wu, X. J.; R, Jiang.; Xu, X. P.; Su, X. M.; Ji, S. J. *J. Comb. Chem.* **2010**, *12*, 829–835.
29. Elliott, R. L.; Oliver, R. M.; Laflamme, J. A.; Gillaspy, M. L.; Hammond, M.; Hank, R. F.; Maurer, T. S.; Baker, D. L.; DaSilva-jardine, P. A.; Stevenson, R. W.; Mack, C. M.; Cassella, J. V. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3593–3596.

30. Li, X.; Wang, L.; Long, L.; Xiao, J.; Hu, Y.; Li, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4868–4872.

31. Medwid, J. B.; Paul, R.; Baker, J. S.; Brockman, J. A.; Du, M. T.; Hallett, W. A.; Hanifin, J. W.; Hardy, R. A.; Tarrant, J. M. E.; Torley L. W.; Wrenn, S. *J. Med. Chem.* **1990**, *33*, 1230–1241.

32. Hess, S.; Muller, C. E.; Frobenius, W.; Reith, U.; Klotz, K. N.; Eger, K. *J. Med. Chem.* **2000**, *43*, 4636–4646.

33. Kiselyov, A. S. *Tetrahedron Lett.* **2005**, *46*, 1663–1665.

34. Kiselyov, A. S.; Smith, L. *Tetrahedron Lett.* **2006**, *47*, 2611–2614.

35. Kiselyov, A. S. *Tetrahedron Lett.* **2006**, *47*, 2941–2944.

36. Slee, D. H.; Chen, Y.;Zhang, X.; Moorjani, M.; Lanier, M. C.; Lin, E.; Rueter, J. K.; Williams, J. P.; Lechner, S. M.; Markison, S.; Malany, S.; Santos, M.; Gross, R. S.; Joswig, T.; Jalani, K.; Sai, Y.; Zuo, Z.; Yang, C.; Castro-Palomino, J. C.; Crespo, M. I.; Prat, M.; Gual, S.; Diaz, J. L.; Saunders, J. *J. Med. Chem.*, **2008**, *51*, 1719–1729.

37. (a) Moorjani, M.; Zhang, X.; Yang, C.; Lin, E.; Rueter, J. K.; Gross. R.S.; Lanier, M. C.; Tellew, J. E.; Williams, J. P.; Lechner, S. M.; Malany, S.; Santos, M.; Ekhlassi, P.; Castro-Palomino, J. C.; Crespo, M. I.; Prat, M.; Gual, S.; D´ıaz, J. L.; Saunders, J.; Slee, D. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1269–1273. (b) Zhang, X.; Rueter, J. K.; Yongsheng, C.; Moorjani, M.; Lanier, M. C.; Lin, E.; Gross. R.S.; Tellew, J. E.; Williams, J. P.; Lechner, S. M.; Markison, S.; Joswig, T.; Malany, S.; Santos, M.; Castro-Palomino, J. C.; Crespo, M. I.; Prat, M.; Gual, S.; Díaz, J. L.; Saunders, J.; Slee, D. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1778–1783.

38. Zhang, N.; Ayral-Kaloustian, S.; Nguyen, T.; Hernandez, R.; Lucas, J.; Discafani, C.; Beyer, C. *Bioorg. Med. Chem.* **2009**, *17*, 111–118.

39. Zhu, X.; Zhao, G.; Zhou, X.; Xu, X.; Xia, G.; Zheng, Z.; Wang, L.; Yang, X.; Li, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 299–301.

40. De Zwart, M. A. H.; Van der Goot, H.; Timmerman, H. *J. Med. Chem.* **1988**, *31*, 716–722.

41. De Zwart, M. A. H.; Van der Goot, H.; Timmerman, H. *J. Med. Chem.* **1989**, *32*, 487–494.

42. Ford, N. F., Browne, L. J., Campbell, T., Gemenden, C., Goldstein, R., Gude, C., Wasley, W. F. *J. Med. Chem.* **1985**, *28*, 164–170.

43. Mettey, Y.; Gompel, M.; Thomas, V.; Garnier, M.; Leost, M.; Picot, I. C.; Noble, M.; Endicott, J.; Vierfond, J.-M.; Meijer, L. *J. Med. Chem.* **2003,** *46,* 222–236.
44. Bergeron, R. J.; Wiegand, J.; Dionis, J. B.; Karmakka, M. E.; Frei, J.; Tencer, A. H.; Peter, H. H. *J. Med. Chem.* **1991,** *34,* 2072–2078.
45. Suzuki, H.; Sakai, N.; Iwahara, R.; Fujiwaka, T.; Satoh, M.; Kakehi, A.; Konakahara, T. *J. Org. Chem.* **2007**, *72*, 5878–5881.
46. Diring, S.; Retailleau, P.; Ziesse, R. *Tetrahedron Lett.* **2007**, *48,* 8069–8073.
47. Suen, Y. F.; Hope, H.; Nantz, M. H.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2005**, *70*, 8468–8471.
48. Shintou, T.; Ikeuchi, F.; Kuwabara, H.; Umihara, K.; Itoh, I. *Chem. Lett.* **2005**, *34*, 836–837.
49. Jnaneshwara, G. K.; Deshpande, V. H.; Lalithambika, M.; Ravindranathan, T.; Bedekar, A.V. *Tetrahedron Lett.* **1998**, *39,* 459–462.
50. Fiorino, F.; Magli, E.; Perissutti, E.; Severino, B.; Frecentese, F.; Esposito, A.; De Angelis, F.; Incisivo, G. M.; Massarelli, P.; Nencini, C.; Gennaro, E. D.; Budillon, A.; Cintio, A. D.; Santagada, V.; Caliendo, G. *Eur. J. Med. Chem.* **1999,** *34,* 2206–2216.
51. (a) Sondhi, S. M.; Dinodia, M.; Kumar, A. *Bioorg. Med. Chem.* **2006**, *14*, 4657–4663. (b) Sondhi, S. M.; Rani, R.; Roy, P. Agrawal, S. K.; Saxena, A. K. *Eur. J. Med. Chem.* **2010**, *45*, 902–908.
52. Seijas, J. A.; Vázquez-Tato M. P.; Martínez. M. M. *Tetrahedron Lett.*, **2000**, *41*, 2215–2217.
53. Sugimori, A.; Furihata, T.; Mikayama, S.; Yoshida, M.; Nakanishi, Y. *Bull. Chem. Soc. Jpn.* **1982,** *55*, 2906–2910.
54. Case, F. H.; Koft, E. *J. Am. Chem. Soc.* **1959**, *81*, 904–906.
55. Polson, M. I. J.; Taylor, N. J.; Hanan, G. S. *Chem. Commun.*, **2002**, 1356–1357.
56. Chen, X.; Dub, C.; Guo, J. P.; Wei, X. H.; Liu D. S. *J. Organomet. Chem.* **2002**, *655*, 89–95.
57. Blackman, M. L.; Royzen, M.; Fox, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 13518–13519.
58. Payne, G. B. *J. Org. Chem.* **1961**, *26*, 668–670.
59. Campeau, L. C.; Stuart, D. R.; Leclerc, J. P.; Laperle, M. B.; Villemure, E.; Sun, H. Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291–3306.

60. Coperet, C.; Adolfsson, H.; Chiang, J. P.; Yudin, A. K.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 761–764.

61. Mitsudome, T.; Mikami, Y.; Mori, H.; Arita, S.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Chem. Commun.*, **2009**, *22*, 3258–3260.

62. Basu, M. K.; Luo, F. T. *Tetrahedron Lett.*, **1998**, *39*, 3005–3006.

63. Solhy, A.; Smahi, A.; Badaoui, H. E.; Elaabar, B.; Amoukal, A.; Tikad, A.; Sebtia, S.; Macquarrieb, D. J. *Tetrahedron Lett.* **2003,** *44*, 4031–4033.

64. Bhattacharya, A.; Plata, R. E.; Villarreal, V.; Muramulla, S.; Wu, J. *Tetrahedron Lett.*, **2006**, *47*, 505–506.

65. Black, G. W.; Gregson, T.; McPake C. B.; Perry, J. J.; Zhang M. *Tetrahedron Lett.*, **2010**, *51*, 1639–1641.

66. Crisóstomo, C.; Crestani, M. G.; García, J. J. *Inorganica Chimica Acta* **2010**, *363*, 1092–1096.

67. Belokon, Y. N.; Tararov, V. I.; Savel'eva, T. F.; Vitt, S. V.; Paskonova, E. A.; Dotdayev, S. C.; Borisov, Y. A.; Struchkov, Y. T.; Batasanov, A. S.; Belikov, V. M. *Inorg. Chem.* **1988**, *27*, 4046–4052.

68. Luo, F. T.; Jeevanandam, A. *Tetrahedron Lett.*, **1998**, *39*, 9455–9456.

69. Takahashi, K.; Shibagaki, M.; Matsushita, H. *Chem. Lett.* **1990**, *2*, 311–314.

70. Muñoz, J. D. M.; Alcázar, J.; Hoz, A. D. L.; Díaz-Ortiz, A. *Tetrahedron Lett.* **2011**, *52*, 6058–6060.

71. Nakao, Y.; Yada, A.; Satoh, J.; Ebata, S.; Oda, S.; Hiyama, T. *Chem. Lett.* **2006**, *35*, 790–791.

72. Rathbone, D. L.; Parker, K. J.; Coleman, M. D.; Lambert, P. A.; Billington, D. C. *Bioorg. Med. Chem. Lett.* **2006**, 16, 879–883.

73. Ogawa, A.; Miyake, J.; Karasaki, Y.; Murai, S.; Sonoda, N. *J. Org. Chem.* **1985**, *50*, 384–386.

74. Umemoto, T.; Tomizawa G. *J. Org. Chem.* **1989**, *54*, 1726–1731.

75. Erker, G.; Riedel, M.; Koch, S.; Jodicke, T.; Wiirthwein, E. U. *J. Org. Chem.* **1995**, *60*, 5284–5290.

76. Corey, E. J.; Helal, C. J. *Tetrahedron Lett.*, **1996**, *37*, 5675–5678.

77. Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2002**, *67*, 3965–3968.

78. Easmon, J.; Pürstinger, G.; Thies, K. S.; Heinisch, G.; Hofmann, J. *J. Med. Chem.* **2006,** *49*, 6343–6350.

79. Miller, J. A.; Dankwardt, J. W. *Tetrahedron Lett.* **2003**, *44*, 1907–1910.

80. Wiedemann, S.; Frank, D.; Winsel, H.; de Meijere, A. *Org. Lett.* **2003**, *5*, 753–755.

81. (a) Lee, J. H.; Choi, B. S.; Chang, J. H.; Lee, H. B.; Yoon, J. Y.; Lee, J.; Shin, H. *J. Org. Chem.* **2007**, *72*, 10261–10263. (b) Tasnádi, G.; Forró, E.; Fülöp, F. *Tetrahedron: Asymmetry* **2009**, *20*, 1771–1777.

82. Ababsa, G. B.; Ely, S. C. S.; Hesse, S.; Nassar, E.; Chevallier, F.; Nguyen, T. T.; Derdour, A.; Mongin, F. *J. Org. Chem.* **2010**, *75*, 839–847.

83. Maura, R.; Steele, J.; Vendier, L.; Arquier, D.; Bastin, S.; Urrutigoïty, M.; Kalck, P.; Igau, A. *J. Organomet. Chem.* **2011**, *696*, 897–904.

84. Khan, A. A.; Neumann, C.; Wismach, C.; Jones, P. G.; Streubel, R. *J. Organomet. Chem.* **2003**, *682*, 212–217.

85. (a) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; López de Munain, R. *Tetrahedron Lett.* **2002**, *43,* 5917–5919. (b) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Munain, R. L. D.; Oyarzabal, J.; Ezpeleta, J. M. *Tetrahedron* **2005**, *61,* 1087–1094.

86. Dyer, P. W.; Fawcett, J.; Hanton, M. J. *J. Organomet. Chem.* **2005**, *690*, 5264–5281.

87. Chen, J.; Song, Q.; Wang, C.; Xi, Z. *J. Am. Chem. Soc.* **2002**, *124*, 6238–6239.

88. Wang, C.; Wang, Z.; Liu, L.; Wang, C.; Liu, G.; Xi, Z. *J. Org. Chem.* **2006**, *71*, 8565–8571.

89. Gross, T. D.; Chou, S.; Bonneville, D.; Gross, R. S.; Wang, P.; Campopiano, O.; Ouellette, M. A.; Zook, S. E.; Reddy, J. P.; Moree, W. J.; Jovic, F.; Chopade, S. *Org. Process Res. Dev.* **2008**, *12*, 929–939.

90. Bleeke, J. R.; Putprasert, P.; Thananatthanachon T.; Rath, N. P. *Organometallics* **2008,** *27*, 5744–5747.

91. Boger, D. L.; Panek J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745–5754.

92. Ollagnier, C. M. A.; Perera, S. D.; Fitchett C. M.; Draper S. M. *Dalton Trans.*, **2008**, *2*, 283–290.

93. Yamakuchi, M.; Matsunaga, H.; Tokuda, R.; Ishizuka, T.; Nakajima, M.; Kunieda, T. *Tetrahedron Lett.* **2005**, *46,* 4019–4022.

94. Takahashi, T.; Tsai, F. Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059–5067.

95. Pnlacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J. *Tetrahedron Lett.* **1996**, *37*, 4577–4580.

96. Nakao, Y.; Oda, S.; Yada A.; Hiyama, T. *Tetrahedron* **2006**, *62*, 7567–7576.
97. Hearns, N. G. R.; Preuss, K. E.; Richardson, J. F.; Salamon, S. B. *J. Am. Chem. Soc*. **2004**, *126*, 9942–9943.
98. Garcia, P.; Evanno, Y.; George, P.; Sevrin, M.; Ricci, G.; Malacria, M.; Aubert, C.; Gandon, V. *Org. Lett.*, **2011,** *13*, 2030–2033.
99. Zou, Y.; Young, D. D.; Montanez, A. C.; Deiters, A. *Org. Lett*. **2008**, *10*, 4661–4664.
100. Qi, C.; Jiang, H.; Huang, L.; Yuan, G.; Ren, Y. *Org. Lett.* **2011,** *13,* 5520–5523.
101. Pawlas, J.; Begtrup, M. *Org. Lett*. **2002**, *4*, 2687–2690.
102. Yu, D. G.; Yu, M.; Guan, B. T.; Li, B. J.; Zheng, Y.; Wu, Z. H.; Shi, Z. J. *Org. Lett*. **2009**, *11*, 3374–3377.
103. Hansen, H. M.; Lysén, M.; Begtrup M.; Kristensen, J. L. *Tetrahedron* **2005**, *61,* 9955–9960.
104. Abd Rabo Moustafa M. M.; Pagenkopf, B. L. *Org. Lett*. **2010**, *12*, 3168–3171.
105. Aharonovich, S.; Kapon, M.; Botoshanski, M.; Eisen, M. S. *Organometallics* **2008,** *27*, 1869–1877.
106. Raja, E. K.; Klumpp D. A. *Tetrahedron* **2011**, *67,* 4494–4497.
107. Flanagan, S. P.; Goddard, R.; Guiry P. J. *Tetrahedron* **2005**, *61,* 9808–9821.
108. Penney, J. M. *Tetrahedron Lett.* **2004**, *45,* 2667–2669.
109. Cailly, T.; Fabis, F.; Lemaıˆtre, S.; Bouillon, A.; Rault, S. *Tetrahedron Lett.* **2005**, *46,* 135–137.
110. Theerthagiri, P.; Lalitha, A.; Arunachalam, P. N. *Tetrahedron Lett.* **2010**, *51,* 2813–2819.
111. Schaub, T.; Döring, C.; Radius, U. *Dalton Trans.* **2007**, *20*, 1993–2002.
112. Kopylovich, M. N.; Lasri, J.; Guedes da Silva, M. F. C.; Pombeiro, A. J. L. *Dalton Trans.* **2009**, *16*, 3074–3084.
113. Sheldrick, G. M.; SADABS, 1996, based on the method described in: Blessing, R. H.; *Acta Crystallogr*. **1995**, *A51*, 33–38.
114. SMART and SAINT, Siemens Analytical X-ray Instruments Inc., Madison, WI, 1996.
115. Sheldrick, G. M.; *Acta Crystallogr*. **2008**, *A64*, 112–122.

Chapter 2

Molecular Structures of Some Metal Amidoximes

Abstract: Two new 1D-coordination polymers having the molecular formulae $[Cu(\mathbf{L1H})(NCS)_2]_n$ (**1**), $[Cu(\mathbf{L2H})(NCS)_2]_n$ (**2**) were synthesized using **L1H**/**L2H**, $CuCl_2 \cdot 2H_2O$ and KSCN (**L1H** = pyridine-2-amidoxime; **L2H** = pyrazineamidoxime). A linear homo trinuclear complex of formula $[Fe_3(\mathbf{L2})_6]$ (**3**) was synthesized using **L2H** and $Fe(NO_3)_3 \cdot 9H_2O$. The molecular structures **1**–**3** were established using single crystal X-ray crystallography.

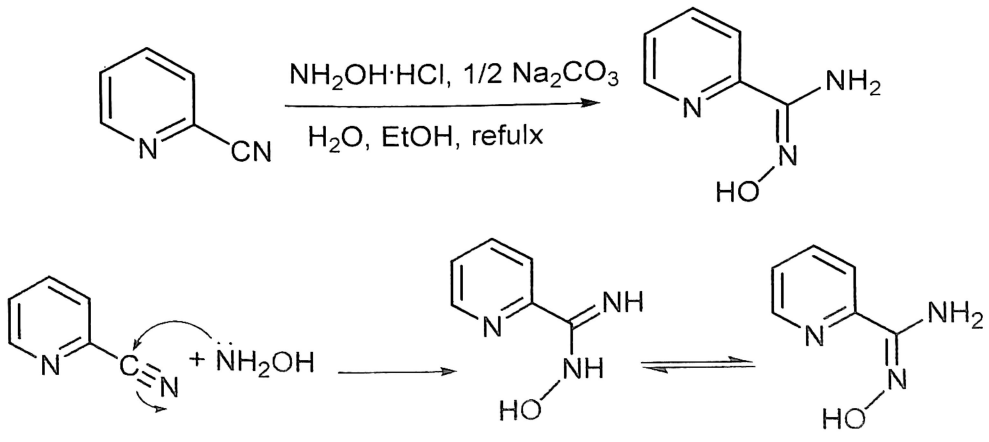
2.1. Introduction

Amidoximes {(R)C(NH_2)NOH} can be considered as oxime of an amide[1] and pyridine ring based amidoxime was reported about 55 year ago[2]. Amidoximes are good ligand and are known to coordinate in different fashions.[3–8] The presence of the amine functionality is special due to its coordination capability, potential for deprotonation and to impart different electronic properties. Also it can potentially involve in hydrogen bonding effect that can alter the coordination behaviour of this ligand in comparison with that of the oxime (Py)C(R)NOH (R=H, Me, Ph, etc.) ligands. Its 2-pyridyl, oxime and amino functionalities provide a rich potential for cluster formation as well. In addition, amidoxime have found numerous technological applications such as, single-molecule magnets (SMMs),[9] corrosion inhibition, stabilizing polymeric coating for chemical electronic micro sensors, uranium recovery from seawater.[10] Amidoxime, especially those carrying arylsulfonyl and pyridyl, were reported to have shown significant biological activities, like hypoglycaemic, analgesics, pesticides, herbicides and antihypertensic.[10]

2.2. Results and discussion

2.2.1. Synthesis

Pyridine-2-amidoxime (**L1H**) was synthesized by adopting the reported procedures which involve the reaction of hydroxylamine with 2-cyanopyridine. In this reaction, hydroxylamine-N acts as a nucleophile, which attacks the carbon atom of nitrile function present in 2-cyanopyridine (Scheme 1). The ligands **L1H** and **L2H** (pyrazineamidoxime) were prepared and using them, complexes **1–3** were synthesized. Amidoximes having pyridine ring (or closely related rings) have been used as ligands, to prepare metal complexes in view of their interesting magnetic properties.[11]



Scheme 1. Synthesis of **L1H**.

2.2.2. Molecular Structures

The molecular structures of **1–3** were established using the single crystal X-ray diffraction methods. The crystallographic data and refinement parameters are listed in Table 1. Complex **1** and **2** crystallized in the $P2_1/c$ and $C2/c$ space groups respectively. In both complexes, the bivalent copper is bound by one **L1H/L2H** ligand and two thiocyanate ions. Thiocyanate ion is an ambidentate ligand which can coordinate either through nitrogen or sulphur ends. In **1–2**, one of the two thiocyanate ions is linked with Cu(II) ion by the nitrogen end. The other thiocyanate ion bridges (by simultaneously coordinating through nitrogen and sulphur ends) two copper(II) ions leading to a 1D-coordination polymeric chain. Each of the copper(II) centres has a distorted square pyramidal geometry as inferred from the τ value of 0.008 (in **1**) and 0.07 (in **2**).[12] In both complexes, the Cu–N_{TA} bond is shorter than Cu–N_{TB} bond by ~0.028(4) Å (N_{TA} = terminal thiocyanate-N; N_{TB} = bridging thiocyanate-N; N_A = amidoxime-N; N_P = pyridyl-N) and Cu–N_A bond is shorter than the Cu–N_P bond by ~0.035(3)Å (in **1**), ~0.074(3)Å (in **2**). Overall the trend Cu–N_{TA} < Cu–N_{TB} ~ Cu–N_A < Cu–N_P is present. The sulphur atom of the bridging thiocyanate ion occupies the axial site of the square pyramid and has a long Cu–S bond. The non-bonded Cu···Cu distance is 5.759(1) Å in **1** and 5.878(1) Å in **2**.

The ORTEP picture showing coordination geometry in **1**, is displayed in Figure 1 and a perspective view of 1D coordination polymer in Figure 2. The ORTEP picture showing coordination geometry in **2**, is displayed in Figure 3 and a perspective view of 1D coordination polymer in Figure 4.

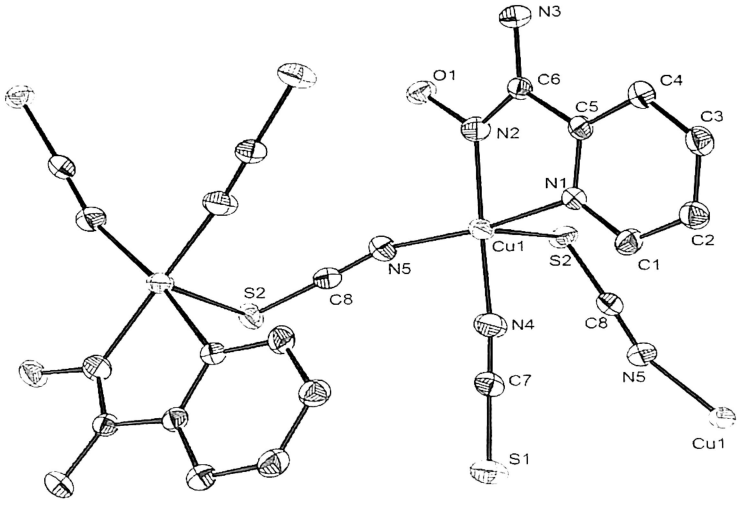


Figure 1. ORTEP (30% probability) diagram of **1**. All the hydrogen atoms were omitted for clarity.

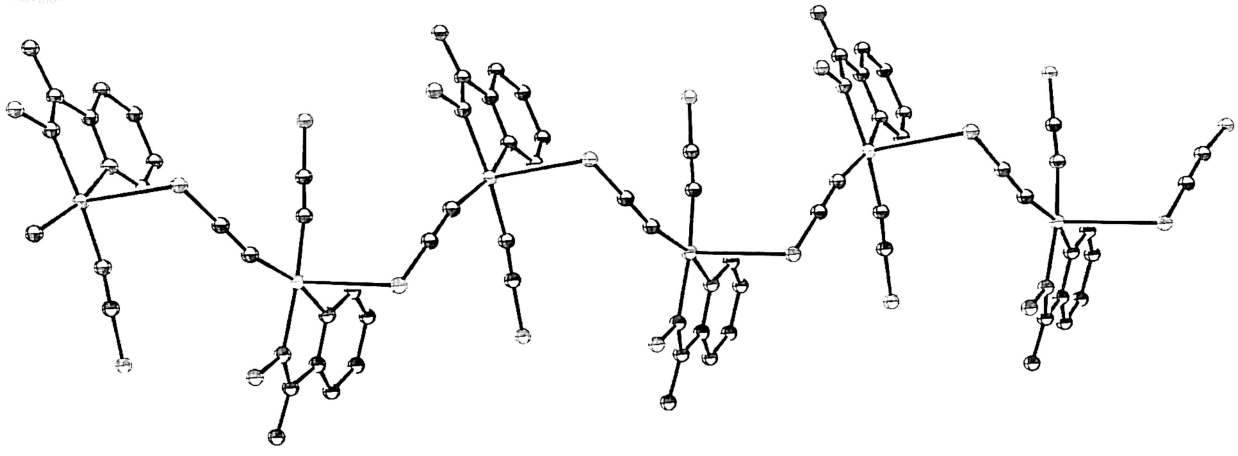


Figure 2. The 1D coordination polymeric chain in **1**.

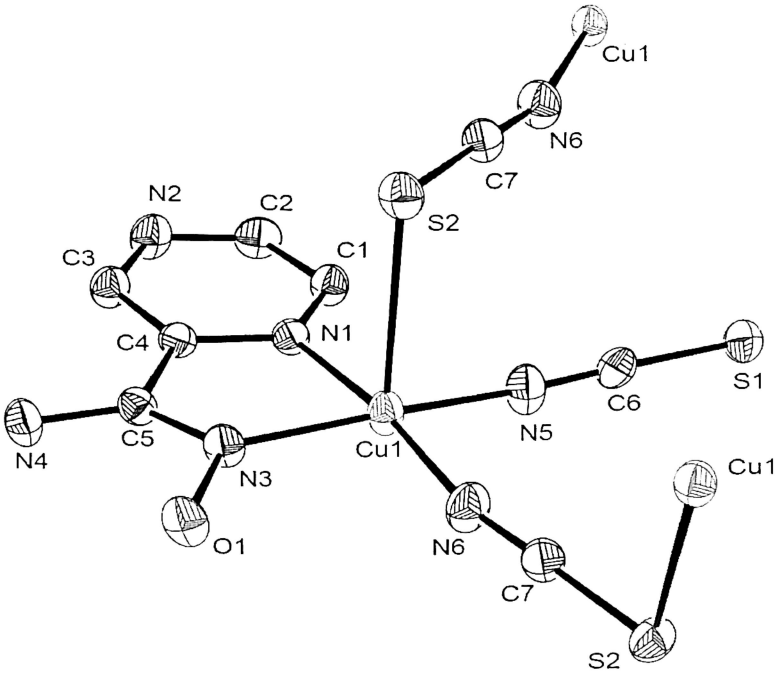


Figure 3. ORTEP (30% probability) diagram of **2**. All the hydrogen atoms were omitted for clarity.

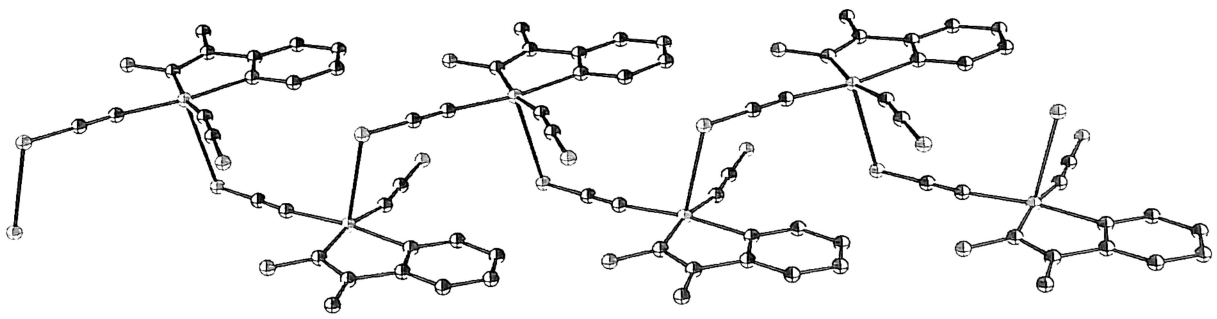


Figure 4. The 1D coordination polymeric chain in **2**.

Table 1. Crystallographic data and refinement parameters **1**–**3**.

	1	**2**	**3**
Formula	$C_8H_7N_5OS_2Cu$	$C_7H_6N_6OS_2Cu$	$C_{30}H_{36}N_{24}O_6Fe_3$
Mol. wt.	316.85	317.84	996.30
Cryst. color, habit	Green, needle	Blue, block	Red, block
T, K	298(2)	298(2)	298(2)
Cryst. syst.	Monoclinic	Monoclinic	Rhombohedral
Space group	$P2_1/c$	$C2/c$	$R\bar{3}$
a, Å	6.6510(18)	12.8602(11)	12.9046(9)
b, Å	19.346(4)	9.0926(7)	12.9046(9)
c, Å	10.447(2)	19.2938(13)	31.2081(12)
α ,deg	90.00	90.00	90.00
β, deg	121.046(14)	92.868(5)	90.00
γ ,deg	90.00	90.00	120.00
V, Å^3	1151.7(4)	2253.2(3)	4500.8(5)
Z	1	6	1
*D*calcd, g cm^{-3}	1.788	2.213	1.116
μ, mm^{-1}	2.246	3.148	0.778
GOF[a] on F^2	1.075	1.020	1.031
F(000)	609	1490	1495
Reflection collected	2639	2734	2296
Unique reflections	2403	1883	2143
R_1[b], wR_2[c] ($I \geq 2\sigma(I)$)	0.0419, 0.1177	0.0501, 0.1299	0.0738, 0.1843
R_1[b], wR_2[c] (all data)	0.0512, 0.1221	0.0770, 0.1431	0.0811, 0.1898

[a]GOF (Goodness-of-fit) = $[\sum[w(F_0^2 - F_c^2)^2] / M - N]^{1/2}$ (M =number of reflections, N = number of parameters refined). [b] $R_1 = \sum \| F_0 | - | Fc \| / \sum | F_0 |$. [c]$wR_2 = [\sum[w(F_0^2 - F_c^2)^2] / \sum[w(F_0^2)^2]]$.

Compound **3** crystallized in *R*-3 space group and have two types of Fe(II) centers *viz*., terminal and central. The two terminal bivalent ions are surrounded by three mono-anionic $\mathbf{L2}^-$ species. Since the two donor nitrogen atoms N_A and N_P in $\mathbf{L2}^-$ are different the tris-chelate can exist in two geometrical isomeric forms *viz*., *facial* and *meridional*. In this case, the two terminal Fe(II) ions are *facially* coordinated and this makes the three oximato-O atoms suitably dispositioned such that the *tris*-chelate $[Fe(\mathbf{L2})_3]^-$ again act as a tridentate ligand towards another metal center. This concept has been

Table 2. Selected bond distance (Å) and angles (°) in **1** and **2**.

	1		**2**
Cu1–N4	1.925(4)	Cu1–N5	1.923(4)
Cu1–N5	1.953(4)	Cu1–N6	1.953(3)
Cu1–N2	1.965(3)	Cu1–N3	1.957(3)
Cu1–N1	2.001(3)	Cu1–N1	2.031(3)
Cu1–S2	2.8030(13)	Cu1–S2	2.864(1)
N4–Cu1–N5	91.24(16)	N5–Cu1–N6	91.35(16)
N4–Cu1–N2	166.78(15)	N5–Cu1–N3	168.04(15)
N5–Cu1–N2	95.55(15)	N6–Cu1–N3	95.73(14)
N4–Cu1–N1	92.27(14)	N5–Cu1–N1	93.22(14)
N5–Cu1–N1	166.32(14)	N6–Cu1–N1	172.36(14)
N2–Cu1–N1	78.58(13)	N3–Cu1–N1	78.77(13)
N4–Cu1–S2	97.52(13)	N6–Cu1–S2	100.5(1)
N5–Cu1–S2	99.14(12)	N5–Cu1–S2	92.9(1)
N2–Cu1–S2	92.59(10)	N3–Cu1–S2	95.3(1)
N1–Cu1–S2	93.51(9)	N1–Cu1–S2	85.1(1)

widely used for the synthesis of homo- and hetero- trinuclear complexes.[13] Hence the complex can be formulated as a $Fe^{II}Fe^{II}Fe^{II}$ trinuclear cluster. The non-bonded Fe···Fe distance is 3.533(1) Å. The Fe···Fe···Fe axis coincides with the C_3 rotational axis of symmetry, hence is exactly linear and a perspective view of **3** is shown in Figure 5. All the three iron atoms are *hexa*-coordinated and have a distorted octahedral geometry. The two terminal iron centers has a $Fe(N_AN_P)_3$ coordination environment while the central iron has a FeO_6 environment. Since a $Fe(AB)_3$ type complex can exist in two optical isomeric (Δ and Λ) forms, the terminal $Fe(N_AN_P)_3$ coordination complex formed from $[Fe(\mathbf{L2})_3]^-$ should also in principle exit in two enantiomeric forms. In $Fe_3\mathbf{L2}_6$, the formulation is $[Fe(\mathbf{L2})_3]_2Fe$ and since the center of symmetry lies at the central iron atom, the two terminal $[Fe(\mathbf{L2})_3]^-$ complexes have the opposite chirality and overall molecule is achiral. The Fe–N_A bonds are shorter than the Fe–N_P bonds by 0.018(3) Å and Fe–N bonds are shorter than the Fe–O bonds by 0.083(3)–0.101(3) Å. The bond length values are consistent with the low-spin nature of the two terminal Fe(II) centers and high-spin nature of the central Fe(II) ion.[14] It is pertinent to note that the room temperature magnetic moment value of 4.64 B.M. per molecule is consistent with the presence of four unpaired electrons, which can be due to the high-spin nature of iron(II)

ion at center and low-spin diamagnetic iron(II) at two termini of the trinuclear species. The non-bonded $N_P \cdots N_P$, $N_A \cdots N_A$ and O···O distances are respectively 2.841(8), 2.692(7) and 2.904(7) Å. The chelate bite angle is 80.25(14)° and the N_A–Fe–N_A angles are smaller than the N_P–Fe–N_P angles.

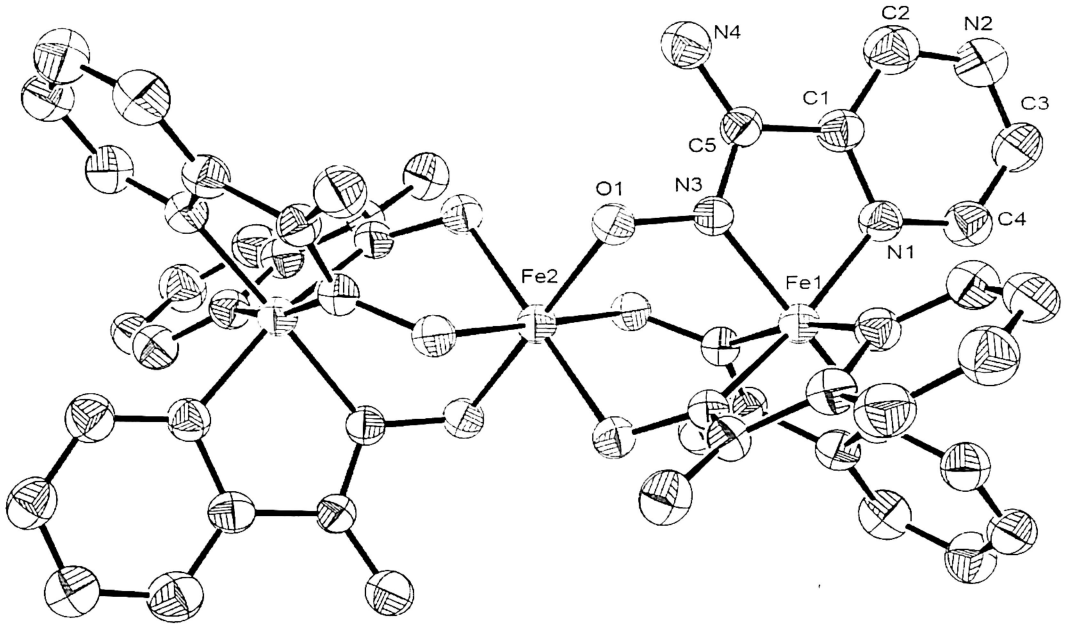


Figure 5. ORTEP (30% probability) diagram of **3**. All the hydrogen atoms were omitted for clarity. Selected bond distances (Å) and angles (°): Fe1–N1, 1.938(3); Fe1–N3, 1.920(3); Fe2–O1, 2.021(3); N3–Fe1–N3, 88.98(13); N3–Fe1–N1, 80.25(14); N3–Fe1–N1, 97.65(14); N3–Fe1–N1, 167.21(14); N1–Fe1–N1, 94.27(14), O1–Fe2–O1, 88.19(11); O1–Fe2–O1, 91.81(11); O1–Fe2–O1, 180.0.

2.3. Conclusion

In summary, two known amidoximes were synthesized from respective nitrile compounds using hydroxylamine as the nucleophile. Using them, two new copper(II) coordination polymers and a linear trinuclear iron cluster have been synthesized. The copper(II) complexes are penta-coordinated having a distorted square pyramidal geometry and form a thiocyanate ion bridged 1D coordination polymers. The iron complex is exactly linear and C_3-axis coincides with Fe···Fe···Fe axis. The central iron has a FeO_6 coordination environment while the two terminal irons have FeN_6 environment. Use of hydroxylamine as a nucleophile in the synthesis of amidoximes, has inspired to study the reaction of other potential nucleophiles with 2-cyanopyridine and the results are discussed in the next three Chapters.

2.4 Experimental Section

Ligands **L1H** was prepared by using the reported procedures.[2] In a typical method, a solution of hydroxylamine hydrochloride (2.1 g, 0.030 mol) and sodium carbonate monohydrate (1.9 g, 0.015 mol) in of water (10 mL) was heated to 60°C. The 2-cyanopyridine (3.0 g 0.029 mol) was added in one portion, followed by sufficient ethyl alcohol (7 mL). The temperature of the mixture was raised to 85°C and maintained for 2 hr. The alcohol was removed under reduced pressure and on cooling **L1H** precipitated as white crystalline solid was filtered, washed with ice-cold water, and dried in a vacuum desiccator over calcium chloride. Yield 3.7 g. 93%.

By following the same procedure and using pyrazinecarbonitrile, **L2H** was obtained.

2.4.1. Synthesis

{Cu(L1H)(NCS)$_2$}$_n$ (1): To 45 mg (0.26 mmol) of $CuCl_2 \cdot 2H_2O$ dissolved in 20 mL of methanol, 51 mg (0.52 mmol) of KSCN was added and stirred for 10 min. Then 36 mg of (0.26 mmol) **L1H** was added and stirred for another 1 h. The reaction mixture was left undisturbed and the green needle shaped crystals deposited after a week was collected by filtration after washing with ice-cold methanol and dried in desiccators. Yield 70 mg (83%). IR (KBr, cm^{-1}): 3421(s), 3188(b), 2762(m), 2130(s), 2093(s), 1664(s), 1610(s), 1585(m), 1493(m), 1422(s), 1390(s), 1294(m), 1175(m), 1157(m), 1095(m), 1040(s), 834(m), 812(m), 790(s), 748(m), 687(m), 664(s), 610(m), 523(m), 479(m). *Anal.* Calc. for $C_8H_7N_5OS_2Cu$: C, 30.33; H, 2.23; N, 22.10%. Found: C, 30.17; H, 2.18; N, 22.02%. UV–Vis [λ_{max}, nm (ε, $M^{-1}cm^{-1}$), CH_3OH solution]: 698(98); 377(1025). EPR (CH_3OH solution, 298 K): $g = 2.131$, $A = 82$ G. μ_{eff}, 1.86 B. M.

{Cu(L2H)(NCS)$_2$}$_n$ (2): To 40 mg (0.23 mmol) of $CuCl_2 \cdot 2H_2O$ dissolved in 20 mL of water, 46 mg (0.46 mol) of KSCN was added and stirred for 10 min. Then 32 mg of (0.23 mmol) **L2H** was added and stirred for 1 h. The reaction mixture was left undisturbed and after 10 days, blue block shaped crystals deposited were collected by filtration after washing with ice-cold methanol. Yield 60 mg (80%).IR (KBr, cm^{-1}): 3409(s), 3309(m), 3138(b), 2727(m), 2120(s), 2100(s), 1660(s), 1602(m), 1492(m), 1442(m), 1399(s), 1297(m), 1196(m), 1174(s), 1110(m), 1047(s), 932(m), 856(s), 816(m), 718(m), 683(m), 626(s), 536(s), 477(m). *Anal.* Calc. for $C_7H_6N_6OS_2Cu$: C, 26.45; H, 1.90; N, 26.44%. Found: C, 26.29; H, 1.88; N, 26.32%. UV–Vis [λ_{max}, nm (ε,

$M^{-1}cm^{-1}$). CH_3OH solution]: 708(2); 398(348); 320(930); 259(2560); 212(3995). EPR (CH_3OH solution, 298 K): g = 2.133, A = 100 G. μ_{eff}, 1.94 B. M.

{Fe_3(L2)$_6$} (**3**): To 80 mg (0.57 mol) of **L2H** dissolved in 30 mL of methanol, 58 mg (0.57 mmol) of triethylamine was added followed by 116 mg (0.28 mmol) of $Fe(NO_3)_3.9H_2O$. After stirring the reaction mixture for 2 h, **3** precipitated as brown solid was filtered and dried in desiccators. From the filtrate reddish brown block shaped crystal obtained after few days was used for diffraction studies. Yield, 120 mg (41%). IR (KBr, cm^{-1}): 3281(b), 2928(m), 2738(m), 2676(s), 2491(m), 1621(s), 1471(s), 1432(m), 1384(s), 1170(s), 1120(s), 1069(m), 1052(m), 1032(s), 859(m), 825(m), 762(m), 729(s), 642(s), 535(m), 475(s). *Anal.* Calc. for $C_{30}H_{36}N_{24}O_6Fe_3$: C, 36.17; H, 3.64; N, 33.74%. Found: C, 36.01; H, 3.58; N, 33.57%. UV–Vis [λ_{max}, nm (ε, $M^{-1}cm^{-1}$), CH_3OH solution]: 599(2280); 368(2880); 295(4160); 257(7260); 213(10860). EPR (CH_3OH solution, 298 K): no signal. μ_{eff}/Fe (298 K), 1.54 B. M and μ_{eff} (per molecule, 298 K), 4.64 B.M.

2.5. References

1. Katritzky, A. R.; Huang, L.; Chahar, M.; Sakhuja, R.; Hall, C. D. *Chem. Rev.* **2012**, *112*, 1633–1649.
2. Bernasek, E. *J. Org. Chem.* **1957**, *22*, 1263.
3. Pearse, G. A.; Raithby, P. R.; Hay, C. M.; Lewis, J. *Polyhedron* **1989**, *8*, 301–304.
4. Pearse, G. A.; Raithby, P. R.; Hay, C. M.; Lewis, J. *Polyhedron* **1989**, *8*, 305–310.
5. Nasakkala, M.; Saarinem, H.; Korvenranta, J.; Oranrua, M. *Acta Crystallogr. Sect. C*, **1989**, *45*, 1514–1517.
6. Cullen, D. L.; Liugafelten, E. C. *Inorg. Chem.* **1970**, *9*, 1865–1877.
7. Pearse, G. A.; Raithby, P. R.; Maughan, M. M. J. *Polyhedron*, **1994**, *13*, 553–558.
8. Pearse, G. A.; Pfluger, C. E. *Inorg. Chim. Acta* **1994**, *227*, 171–174.
9. (a) Milios, C. J.; Inglis, R.; Vinslava, A.; Bagai, R.; Wernsdorfer, W.; Parsons, S.; Perlepes, S. P.; Christou, G.; Brechin, E. K. *J. Am. Chem. Soc.* **2007**, *129*, 12505–12511. (b) Milios, C. J.; Vinslava, A.; Wernsdorfer, W.; Moggach, S.; Parsons, S.; Perlepes, S. P.; Christou, G.; Brechin, E. K. *J. Am. Chem. Soc.* **2007**, *129*, 2754–2755. (c) Milios, C. J.; Vinslava, A.; Wernsdorfer, W.; Prescimone, A.; Wood, P. A.; Parsons, S.; Perlepes, S. P.; Christou, G.; Brechin, E. K. *J. Am. Chem. Soc.* **2007**, *129*, 6547–6561. (d) Milos, C. J.; Prescimone, A.; Mishra, A.; Parasons, S.; Wernsdorfer, W.; Christou, G.; Perlepes, S. P.; Brechin, E. K. *Chem. Commun.*

2007, 153–155. (e) Papatriantafyllopoulou, C.; Aromi, G.; Tasiopoulos, A. J.; Nastopoulos, V.; Raptopoulou, C. P.; Teat, S. J.; Escuer, A.; Perlepes, S. P. *Eur. J. Inorg. Chem.* **2007**, 2761–2774. (f) Stamtatos, T. C.; Albiol, D. F.; Lee. S.-C.; Stoumpos, C. C.; Raptopoulou, C. P.; Terzis, A.; Wernsdorfer, W.; Hill, S. O.; Perlepes, S. P.; Christou, G. *J. Am. Chem. Soc.* **2007**, *129*, 9484–9499.

10. Nicolaides, D. N.; Varella, E. A. "The chemistry of amidoximes in the chemistry of acid derivatives", eds. S. Patai, **1992**, Vol. 2, Suppl. B., John Wiley & Sons Ltd.
11. (a) An, G. Y.; Ji, C. M.; Cui, A. L.; Kou, H. Z. *Inorg. Chem.* **2011**, *50*, 1079–1083. (b) Papatriantafyllopoulou, C.; Jones, L. F.; Nguyen, T. D.; Salvador, N. M.; Silva, L. C.; Almeida Paz, F. A.; Rocha, J.; Evangelisti, M.; Brechin, E. K.; Perlepes, S. P. *Dalton Trans.* **2008**, 3153–3155. (c) Bovenzi, B. A.; Pearse, G. A. *Dalton Trans.* **1997**, 2793–2797. (d) Ji, C. M.; Yang, H. J.; Zhao, C. C.; Tangoulis, V.; Cui, A. L.; Kou, H. Z. *Cryst. Growth Des.* **2009**. *9*, 4607–4609. (e) Gole, B.; Chakrabarty, R.; Mukherjee, S.; Song, Y.; Mukherjee, P. S. *Dalton Trans.* **2010**, *39*, 9766–9778.
12. Addison, A. W.; Rao, T. N.; Reedijk, J.; Van Rijn, J.; Verschor, G. C. *J. Chem. Soc. Dalton Trans.* **1984**, 1349–1356.
13. (a) Chakravorty, A. *Coord. Chem. Rev.* **1974**, *13*, 1–46. (b) Chaudhuri, P. *Coord. Chem. Rev.* **2003**, *243*, 143–190. (c) Kukushkin, V. Y.; Tudela, D.; Pombeiro, A. J. L. *Coord. Chem. Rev.* **1996**, *156*, 333–362. (d) Kukushkin, V. Y.; Pombeiro, A. J. L. *Coord. Chem. Rev.* **1999**, *181*, 147–175. (e) Smith, A. G.; Tasker, P. A.; White, D. J. *Coord. Chem. Rev.* **2003**, *241*, 61–85.
14. Pal, S.; Melton, T.; Mukherjee, R.; Chakravarty A. R.; Thomas, M.; Falvello, L. R.; Chakravorty, A. *Inorg. Chem.* **1985**, *24*, 1250–1257.

Chapter 3

Novel Synthesis of 2,4-Bis(2-pyridyl)-5-(pyridyl)imidazoles and Formation of *N*-(3-(Pyridyl)imidazo[1,5-*a*]pyridine)picolinamidines: Nitrogen Rich Ligands*

Abstract: Heating a neat 1:2 mixture of 2-picolylamine and 2-cyanopyridine followed by treatment of the resultant red gummy substance with aqueous KOH resulted in the isolation of 2,4,5-tris(2-pyridyl)imidazole (**1a**) as the major product and *N*-(3-(2-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine (**2a**) in small amounts. Similarly, using 3-picolylamine, 2,4,-bis(2-pyridyl)-5-(3-pyridyl)imidazole (**1b**) and *N*-(3-(3-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine (**2b**) were isolated, by using 4-picolylamine, 2,4,-bis(2-pyridyl)-5-(4-pyridyl)imidazole (**1c**) and *N*-(3-(4-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine (**2c**) were isolated. The plausible mechanism of the formation of **1a-c** and **2a-c** is delineated.

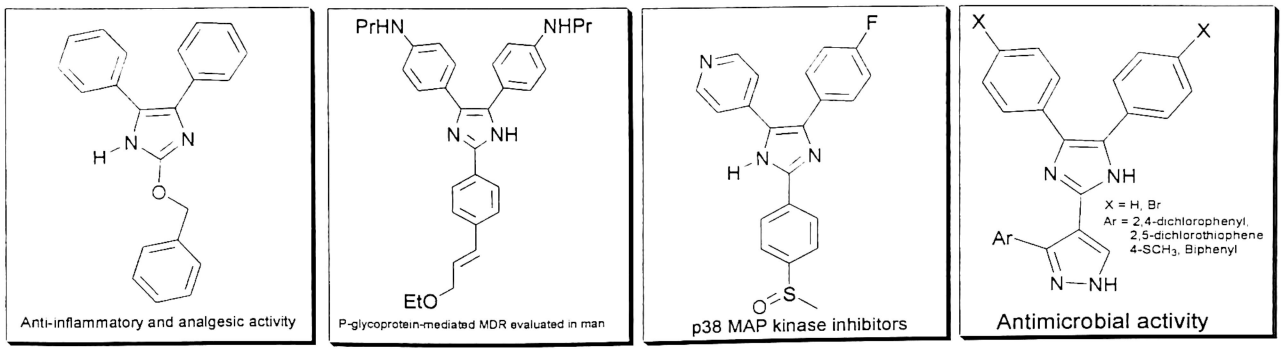
---

*This work has been published in:

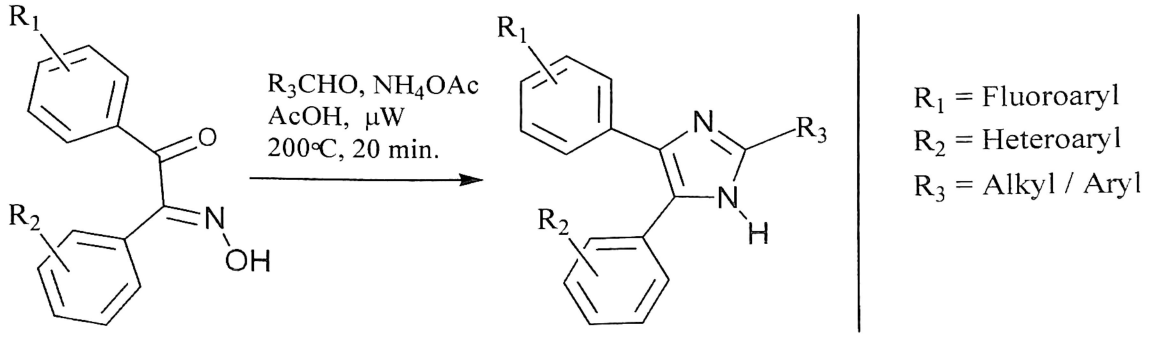
Fulwa, V. K.; Sahu, R.; Jena, H. S.; Manivannan, V. *Tetrahedron Lett.* **2009**, *50*, 6264–6267.

3.1. Introduction

The imidazole ring system is an important function in biology, chemistry as well as in pharmaceutical, veterinary and agrochemical products.[1–4] They are useful ligands in coordination chemistry and synthesis of the compounds containing the imidazole ring is an important area of scientific investigation.[1–3]



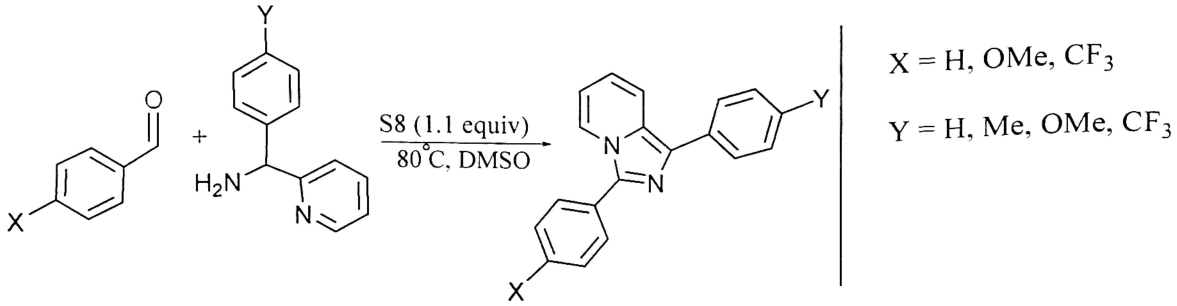
Multicomponent reaction (MCR) methods involving the isocyanides as one of the components for the synthesis of imidazole derivatives has been reviewed.[5] The synthesis of the 1,2,4-trisubstituted imidazole by palladium-catalyzed cyclization of *O*-pentafluorobenzoylamidoximes is reported.[6] Addition reaction of imidazoliumylides to electron-deficient imines is an useful method for the synthesis of 2-(α-substituted-amidoalkyl)imidazoles.[7] An efficient, mild *one-pot* method for preparing polysubstituted imidazoles from aryl-substituted tosylmethylisocyanide (TosMIC) reagents and *in situ* generated imines[8] as well as a new synthetic approach for the synthesis of chiral imidazoles using thio-Ugi reaction[9] have been reported. The synthesis of annulated terpene-imidazole[10], a microwave assisted organic synthesis (MAOS) method for the synthesis of 2,4,5-triaryl-imidazole[11a] as well as synthesis and p38 MAP kinase inhibitor property[11b] have been described.



Org. Lett. **2004**, *6*, 2473–2475.

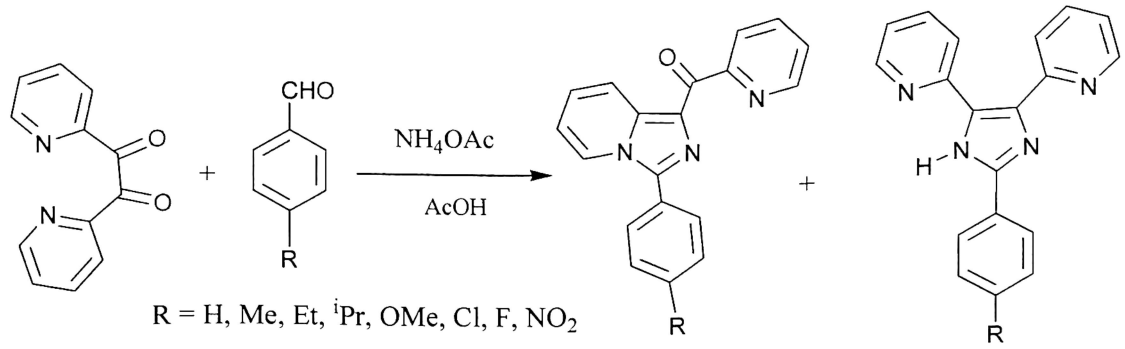
It is known that hydroxylamine readily act as a nucleophile towards 2-cyanopyridine yielding 2-pyridylamidoxime.[12] In the previous Chapter, two such amidoximes were

synthesized as a part of evaluating their coordination chemistry, has inspired to study the reaction of 2-cyanopyridine with other nucleophiles. This Chapter describes one such reaction involving picolylamines as nucleophile which lead to a facile formation of 2,4-bis(2-pyridyl)-5-(pyridyl)imidazoles (**1a-1c**) in a simple three component method. In addition the details of other minor product, *N*-(3-(pyridyl)imidazo[1,5-*a*]pyridine)picolinamidines (**2a-2c**) formed in this reaction are described.



J. Org. Chem. **2009**, *74*, 3566–3568.

The synthesis of compounds containing the imidazo[1,5-*a*]pyridine ring is another general area of research.[13,14] Formation of the varying amounts of 2,4,5-trisubstituted imidazole and imidazo[1,5-*a*]pyridine ring systems from 2,2'-pyridil, aromatic aldehyde, ammonium acetate and acetic acid is relevant to mention.[13]

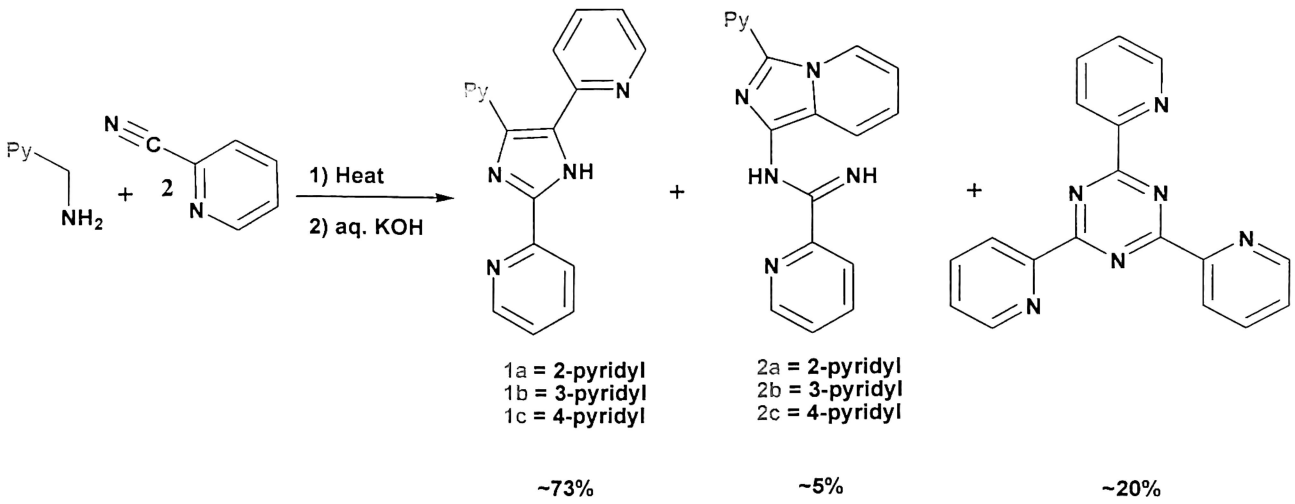


J. Org. Chem. **2003**, *68*, 5415–5418.

3.2 Results and Discussion

Heating a neat 1:2 mixture of 2-picolylamine and 2-cyanopyridine at 100 °C, followed by treatment of the resultant red gummy substance with alkali resulted in the formation of 2,4,5-tris(2-pyridyl)imidazole (**1a**) and *N*-(3-(2-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine (**2a**) (Scheme 1). From the alkaline solution, **2a** and 2,4,6-tris(2-pyridyl)1,3,5-triazine (**3**) which precipitated were separated by filtration, while **1a** remained dissolved in the solution. On adjusting the pH of the aqueous solution to 7-8, **1a** separated as a yellow gel-like substance, which afforded yellow crystals from the ether medium. Since the formation of the triazine ring from cyanopyridines is already

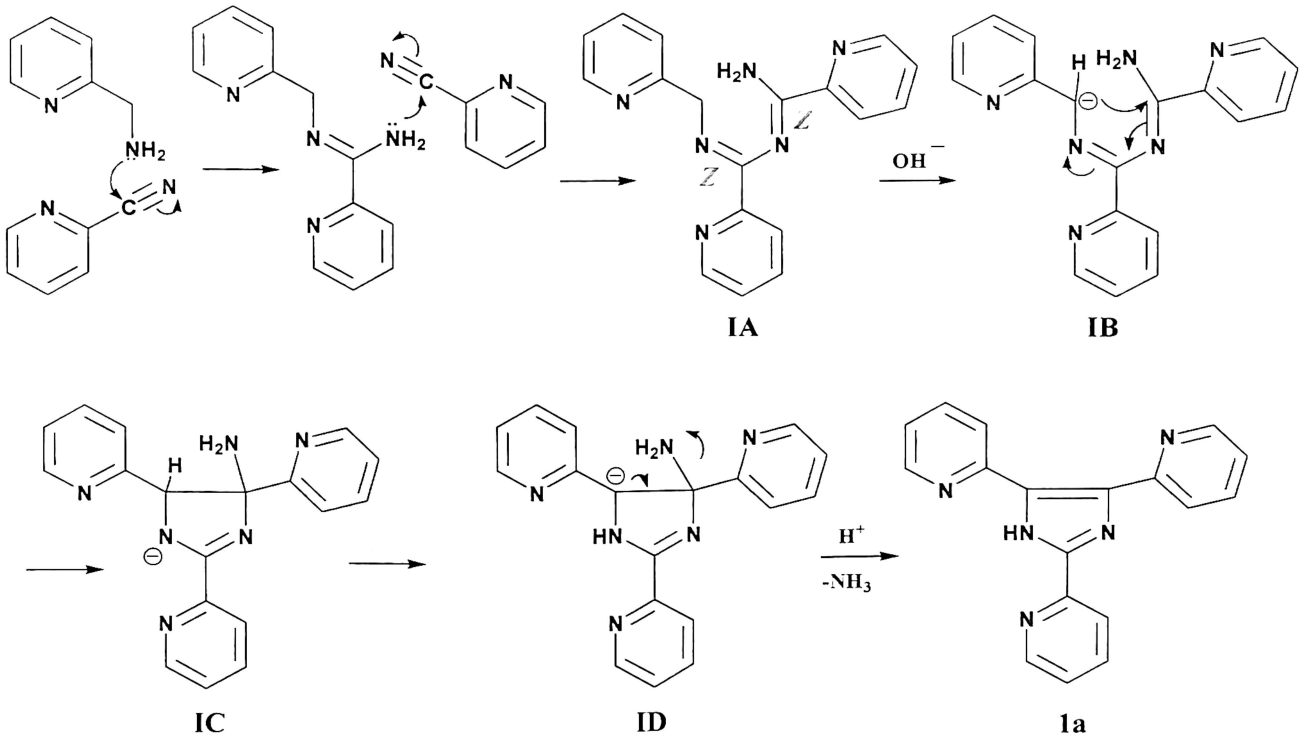
well established.[15] discussion is limited only to **1a** and **2a**. Formation of these two compounds is believed to involve the presence of intermediate adduct **IA** and **IIA** (in Scheme 2 and 3) which may be present in major and minor quantities, respectively. In addition **3** could have formed at this stage. In the aqueous solution of KOH, **IA** and **IIA** respectively leads to the generation of the imidazole nucleus and to the imidazo[1,5-*a*]pyridine ring systems.



Scheme 1: Synthesis of **1a-c** and **2a-c**. Legend inside the scheme is for substituent Py.

The plausible intermediates involved in the formation of **1a** are depicted in Scheme 2. One molecule of 2-cyanopyridine forming adduct with 2-picolylamine leading to an amidine, which in turn form an adduct with another molecule of 2-cyanopyridine through the $-NH_2$ nitrogen atom of the amidine function. One of the methylene hydrogen atoms in **IA** is removed by the base to generate **IB**; then the negative charge attacks the carbon atom of amidine function that leads to formation of the five-membered central ring in **IC**. The proton shift occurs in **IC** that leads to **ID**, from which elimination of one molecule of NH_3 occurs, resulting in formation of **1a** as the final product. Presence of strong ammonia stench in the reaction mixture is consistent with its evolution noted in the final step. It is pertinent to note that a low-yielding method of preparation of **1a** by the reduction of 2-cyanopyridine with sodium borohydride was described earlier.[16]

The ^1H and ^{13}C NMR spectra of **1a** are consistent with the structure. The ESI mass spectrum shows a characteristic M^++H peak at m/z = 300. The single crystal X-ray structure (Table 1) was established and a perspective view of **1a** is shown in Figure 1.



Scheme 2. Plausible mechanism for the formation of **1a**.

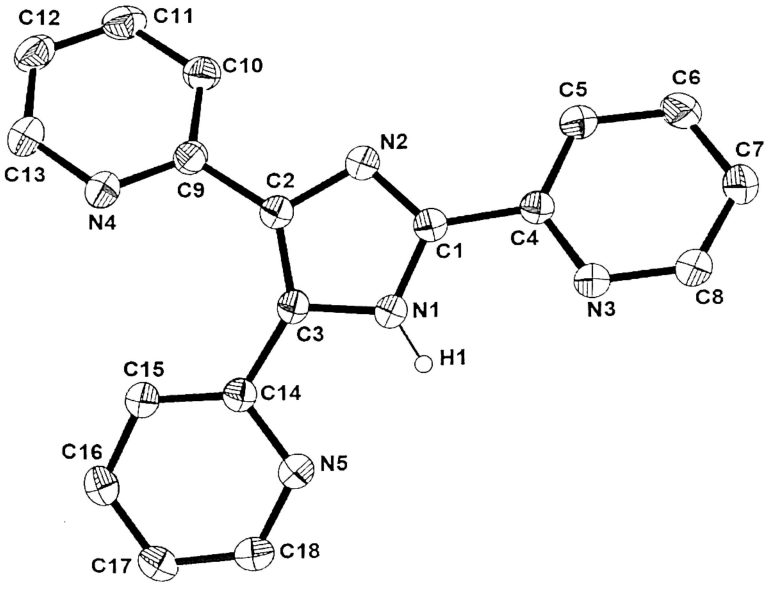
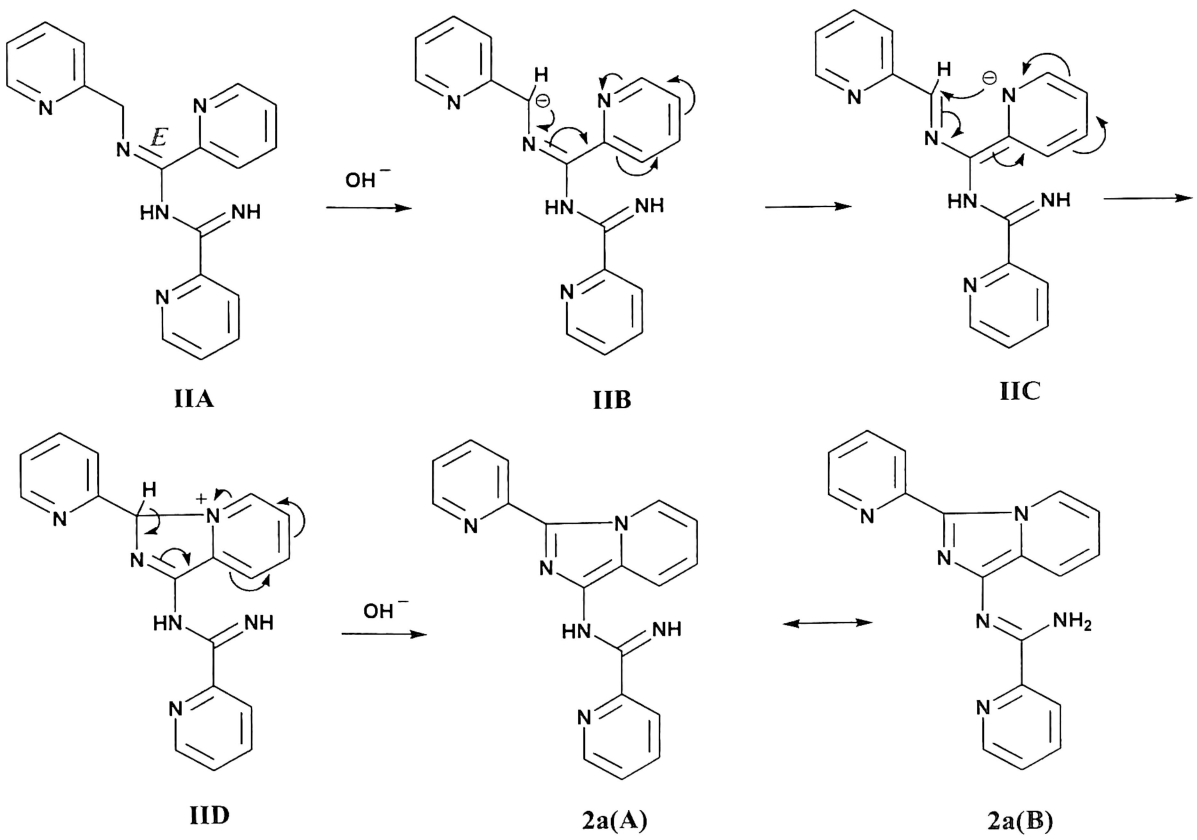


Figure 1. ORTEP (30% probability) diagram of **1a**. All the hydrogen atoms except H1 were omitted for clarity. Selected distances, Å: N1–C1 1.3462(16), N1–C3 1.3702(16), N2–C1 1.3256(15), N2–C2 1.3832 (15), C1–C2 1.3434(15).

Formation of small quantities of **2a** is interesting, which has separated as solid from the basic reaction mixture. Pure fibrous solids of **2a** were obtained after chromatographic separation on basic alumina using 3:7 ethyl acetate-hexane mixtures. Probable intermediates involved are represented in Scheme 3. The intermediate **IIA** (*E*)

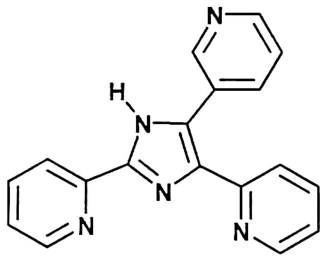
is geometrical isomer of **IA** (*Z*) with respect to –N=C< group attached to the methylene group and hence the 2-pyridyl ring instead of amidine group is in the vicinity of methylene group. Abstraction of a proton from the methylene group generates a negative charge which is delocalized into the 2-pyridyl ring as shown in **IIB**. This leads to the concentration of electron density on the nitrogen atom of 2-pyridyl ring, **IIC**. The resultant negative charge on the nitrogen atom attacks the sp^2 carbon and generates the fused five-membered ring in **IID**. The proton abstraction by a base in **IID** leads to formation of **2a** that contain the imidazo[1,5-*a*]pyridine nucleus, which could exist in two tautomeric forms **2a(A)** and **2a(B)**. The ^{1}H NMR spectrum show two broad signals for the NH protons and therefore is consistent with the **2a(A)** form. Two distinct triplets at δ = 6.81, 6.85 *ppm* in the ^{1}H NMR and presence of M^++H peak at *m/z* = 315 in the ESI mass spectra of **2a** are characteristic.[17]



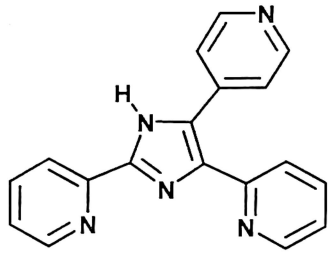
Scheme 3. Plausible mechanism for the formation of **2a**.

Under the same experimental conditions and using the same quantities of respective reagents, the reaction proceeded very well with 3- and 4-picolylamines. The products isolated using 3-picolylamine are 2,4,-bis(2-pyridyl)-5-(3-pyridyl)imidazole (**1b**) and *N*-(3-(3-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine (**2b**). With 4-picolylamine, 2,4,-bis(2-pyridyl)-5-(4-pyridyl)imidazole (**1c**) and *N*-(3-(4-pyridyl)imidazo[1,5-

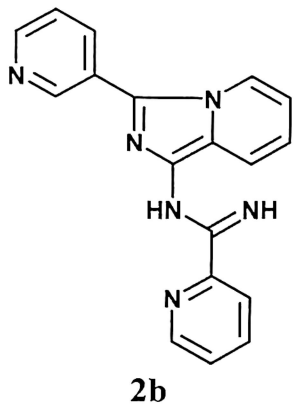
a]pyridine)picolinamidine (**2c**) were isolated in similar yields. The ^{1}H, ^{13}C NMR and ESI mass spectra of **1b**, **1c**, **2b** and **2c** are in accordance with the structures.



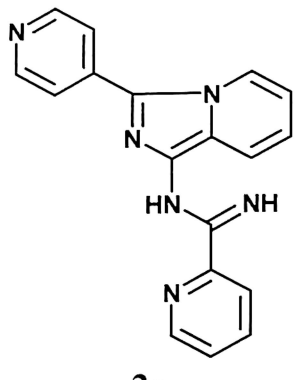
1b



1c



2b



2c

In conclusion, this chapter describes an efficient and simple three-component method for the synthesis of 2,4-bis(2-pyridyl)-5-(pyridyl)imidazoles (**1a-1c**) and the formation of *N*-(3-(pyridyl)imidazo[1,5-*a*]pyridine)picolinamidines (**2a-2c**) in small amounts as minor product. This method could provide insights towards the synthesis of derivatives of imidazole as well as substituted imidazo[1,5-*a*]pyridine nucleus.

3.3. Synthesis

2-Picolylamine (1 g, 9.26 mmol) and 2-cyanopyridine (1.93 g, 18.6 mmol) were heated at 100 °C in an oil-bath for 12h. The resultant red gummy oil was suspended in 30 mL of water, KOH (3.11 g, 55.6 mmol) was added and stirred for 12h. The yellow solid obtained was filtered, washed with water and dried in vacuum over fused $CaCl_2$. The dry solid was subjected to chromatographic separation using basic alumina column. Firstly compound **2a** was eluted with ethyl acetate-hexane (3:7) mixture and the yellow fibrous solid of **2a** was obtained after removal of the solvents. Yield: 150 mg (5%). Then tris(2-pyridyl)triazine (3) was eluted using methanol Yield: 390 mg (20%). The filtrate had a strong ammonia smell, the pH of which was adjusted to 7-8 using 5 M HCl. **1a** separated as yellow gel-like substance and was separated from the aqueous solution by decantation. The gel on crystallization from ether afforded single-

crystals suitable for X-ray diffraction studies. Yield 1.42 g. The decanted aqueous solution was extracted with ether affording another crop of **1a**. Yield: 600 mg, which was recrystallized from ether. Combined yield of **1a**: 73%.

3.4. References and Notes

1. Grimmett, M. R. *In Comprehensive Heterocyclic Chemistry II:* Katritzky, A. R.; Ress, C. W.; Scriven, E. F. V. Eds.; Pergamon Press: Oxford, 1996: Vol. 3, pp 77–220.
2. (a) Grimmett, M. R. *Imidazole and Benzimidazole Synthesis*; Academic Press: New York, 1997 and references therein. (b) Grimmett, M. R. *Adv. Heterocycl. Chem.* **1970**, *12*, 103–183.
3. Novelli, A.; De Santis, A. *Tetrahedron Lett.* **1967**, *8*, 265–269.
4. Huang, N.; Xi. Q.; Liu, L. *In Comprehensive Heterocyclic Chemistry III:* Katritzky, A.; Ramsden, C.; Scriven, E.; Taylor, R. Eds. Elsevier, 2008: Vol 4, pp 143–364.
5. (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17-89. (b) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210.
6. Zaman, S.; Mitsuru, K.; Abell, A. D. *Org. Lett.* **2005**, *7*, 609–611.
7. Zificsak, C. A.; Hlasta, D. J. *Tetrahedron Lett.* **2005**, *46*, 4789–4792.
8. (a) Sisko, J.; Mellinger, M. *Pure Appl. Chem.* **2002**, *74*, 1349-1357. (b) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516–1524. (c) Sisko, J. *J. Org. Chem.* **1998**, *63*, 4529–4531.
9. Gulevich, A. V.; Balenkova, E. S.; Nenajdenko, V. G. *J. Org. Chem.* **2007**, *72*, 7878–7885.
10. Kulhánek, J.; Bureš, F.; Šimon, P.; Schweizer, W. B. *Tetrahedron: Asymmetry* **2008**, *19*, 2462–2469.
11. (a) Sparks, R. B.; Combs, A. P. *Org. Lett.* **2004**, *6*, 2473–2475. (b) Boehm, J. C.; Smietana, J. M.; Sorenson, M. E.; Garigipati, R. S.; Gallagher, T. F.; Sheldrake, P. L; Bradbeer, J.; Badger, A. M.; Laydon, J. T.; Lee, J. C.; Hillegass, L. M.; Griswold, D. E.; Breton, J. J.; Chabot-Fletcher, M. C.; Adams, J. L. *J. Med. Chem.* **1996**, *39*, 3929–3937.
12. Bernasek, E. *J. Org. Chem.* **1957**, *22*, 1263.
13. Wang, J.; Mason, R.; VanDerveer, D.; Feng, K.; Bu, X. R. *J. Org. Chem.* **2003**, *68*, 5415–5418.

14. (a) Shibahara, F.; Sugiura, R.; Yamaguchi, E.; Kitagawa, A.; Murai, T. *J. Org. Chem.* **2009**, *74*, 3566–3568. (b) Salassa, L.; Garino, C.; Albertino, A.; Volpi, G.; Nervi, C.; Gobetto, R.; Hardcastle, K. I. *Organometallics* **2008**, *27*, 1427–1435. (c) Shibahara, F.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *Org. Lett.* **2006**, *8*, 5621–5624. (d) Wang, J.; Dyers, L.; Mason, R. Jr.; Amoyaw, P. Jr.; Bu, X. R. *J. Org. Chem.* **2005**, *70*, 2353–2356. (e) Katritzky, A. R.; Qiu, G. *J. Org. Chem.* **2001**, *66*, 2862–2864. (f) Sasaki, K.; Tsurumori, A.; Hirota, T. *J. Chem. Soc. Perkin Trans. 1*, **1998**, 3851–3856. (g) Krapcho, A. P.; Powell, J. R. *Tetrahedron Lett.* **1986**, *27*, 3713–3714.

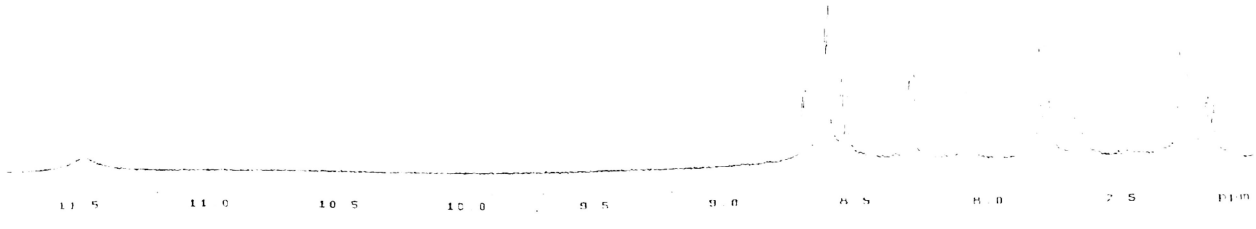
15. Case, F. H.; Koft, E. *J. Am. Chem. Soc.* **1959**, *81*, 905–906.

16. Yamada, S.; Kuramoto, M.; Kikugawa, Y. *Tetrahedron Lett.* **1969**, *10*, 3101–3104.

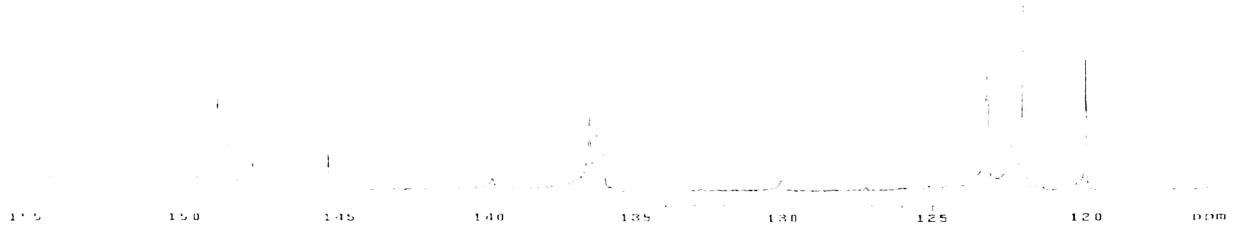
17. Only a very weakly diffracting crystals of Ni(II) complexes of **2a** could be obtained and from the data, only the structure of **2a** could be ascertained.

3.5. Spectral data

2,4,5-tris(2-pyridyl)imidazole (**1a**): mp. 144 °C; ESI-MS: *m/z* calcd. for $C_{18}H_{13}N_5^+$ 299.117 found (M^++H) 300.114. 400 MHz ^{1}H NMR (δ (*J*, Hz), CDCl3): 11.4 (1NH, s), 8.69 (1H, d, 4.8), 8.61 (2H, d, 4.4), 8.54 (1H, d, 8.0), 8.29 (1H, d, 8.0), 8.09 (1H, d, 7.6), 7.80 (2H, dd, 7.5), 7.65 (1H, t, 7.6), 7.27 (2H, dd, 4.8), 7.17 (1H, t, 6.2). 100 MHz 13C NMR (δ, $CDCl_3$): 148.9, 148.7, 148.4, 147.8, 145.3, 136.6, 136.4, 136.1, 123.2, 122.4, 122.0, 120.0. FTIR (KBr, cm^{-1}): 3439, 3053, 1586, 1566, 1530, 1478, 1452, 1435, 1422, 1387, 1291, 1274, 1250, 1212, 1151, 1119, 1075, 1042, 993, 980, 968, 897, 800, 789, 776, 737, 716, 696, 658, 626, 605, 552, 507, 486, 413, 400.

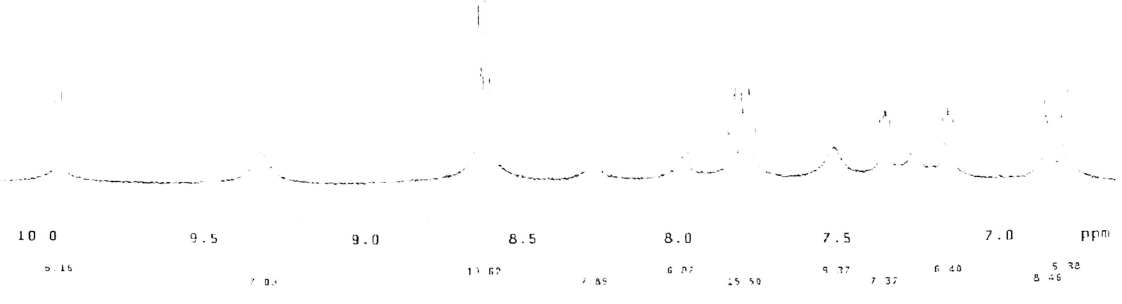


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2,4,5-tris(2-pyridyl)imidazole (**1a**).

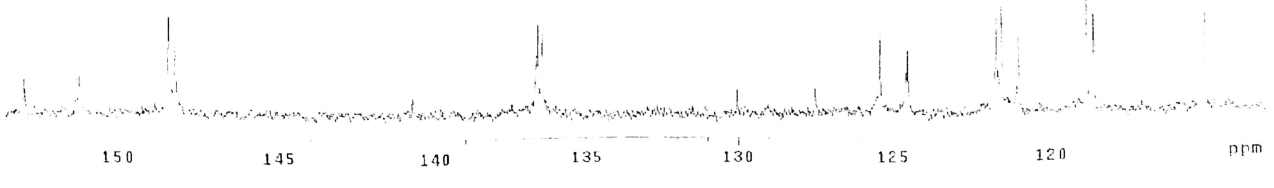


^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 2,4,5-tris(2-pyridyl)imidazole (**1a**).

***N*-(3-(2-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine** (**2a**): mp. 186 °C. ESI-MS: *m/z* calcd. for $C_{18}H_{14}N_6^+$ 314.128 found (M^++H) 315.135. R_f = 0.66. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 9.94 (1H, d, 7.2), 9.32 (1NH, s), 8.63 (3H, m), 8.28 (1H, d, 8.0), 7.99 (1H, d, 8.8), 7.80 (2H, qu, 8.0), 7.51 (1NH, s), 7.35 (1H, t, 5.6), 7.15 (1H, t, 5.6), 6.85 (1H, t, 7.6), 6.81 (1H, t, 6.4). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 152.9, 151.3, 151.2, 148.4, 148.2, 140.7, 136.6, 136.5, 130.0, 127.5, 125.4, 124.5, 121.7, 121.6, 121.0, 118.9, 118.7, 115.2. FTIR (KBr, cm^{-1}): 3366, 3250, 3058, 1689, 1621, 1587, 1563, 1542, 1495, 1469, 1454, 1429, 1397, 1252, 1190, 1137, 1090, 1048, 995, 879, 816, 785, 747, 730, 700, 685, 622, 594, 460, 421, 404. Anal. calcd. for $C_{18}H_{14}N_6$: C, 68.78; H, 4.49; N, 26.74%. Found: C, 68.71; H, 4.44; N, 26.68%.



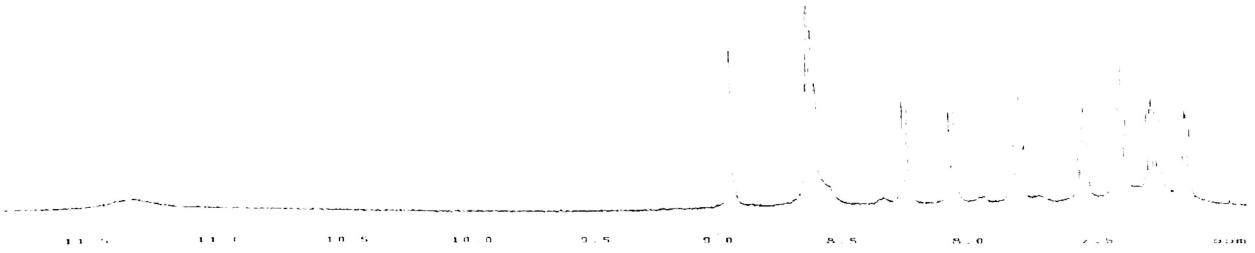
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-(3-(2-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine (**2a**).



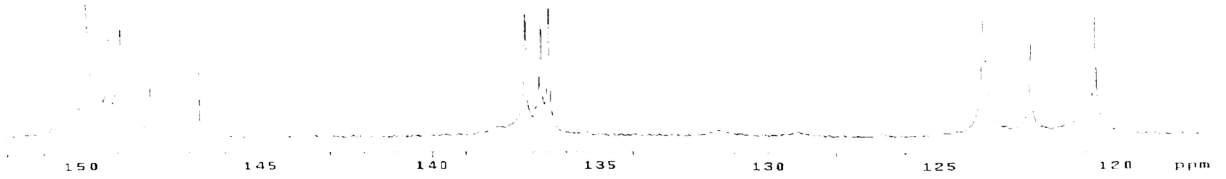
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of *N*-(3-(2-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine (**2a**).

2,4,-bis(2-pyridyl)-5-(3-pyridyl)imidazole (**1b**): Yield: 2.05 g, 75% mp. 193 °C; ESI-MS: *m/z* calcd. for $C_{18}H_{13}N_5^+$ 299.117 found (M^++H) 300.124. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 11.3 (1NH, s), 8.95 (1H, s), 8.63 (3H, m), 8.25 (1H, d, 8.0), 8.07

(1H, d, 8.0), 7.80 (1H, t, 7.8), 7.55 (1H, t, 7.8), 7.41 (2H, m), 7.30 (1H, t, 6.2), 7.16 (1H, t, 6.2). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 149.9, 149.2, 148.9, 148.1, 146.7, 137.2, 136.7, 136.5, 123.7, 122.4, 120.6. FTIR (KBr, cm^{-1}): 3458, 1641, 1625, 1590, 1562, 1530, 1502, 1472, 1438, 1389, 1321, 1302, 1254, 1181, 1140, 1097, 1029, 955, 797, 727, 702, 624. Anal. calcd. for $C_{18}H_{13}N_5$: C, 72.23; H, 4.38; N, 23.40%. Found: C, 72.15; H, 4.36; N, 23.36%.

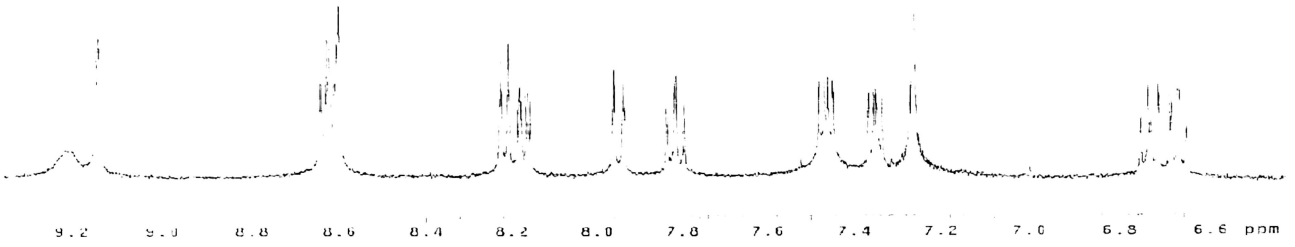


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2,4,-bis(2-pyridyl)-5-(3-pyridyl)imidazole (**1b**).

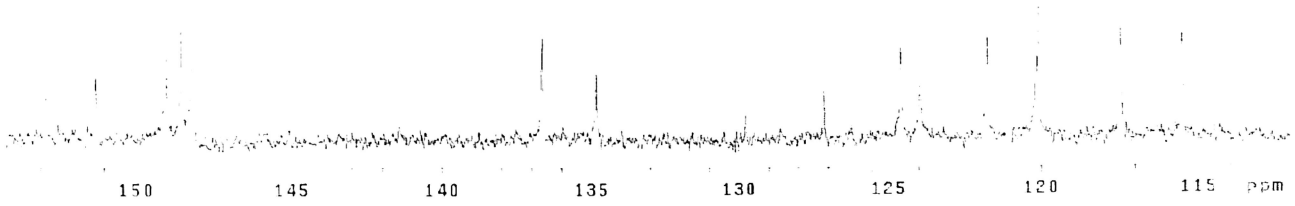


^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 2,4,-bis(2-pyridyl)-5-(3-pyridyl)imidazole (**1b**).

***N*-(3-(3-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine (2b)**: Yield: 150 mg, 5% mp. 195 °C; ESI-MS: *m/z* calcd. for $C_{18}H_{14}N_6^+$ 314.128 found (M^++H) 315.135. R_f = 0.64. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 9.21 (1NH, s), 9.14 (1H, s), 8.63 (2H, m), 8.22 (1H, d, 8.0), 8.17 (1H, d, 12.0), 7.95 (1H, d, 11.2), 7.82 (1H, t, 8.8), 7.46 (2H, dd, 7.0), 7.35 (1H, t, 6.6), 6.74 (1H, t, 8.0), 6.67 (1H, t, 7.6). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 152.8, 151.3, 149.0, 148.6, 148.2, 141.4, 136.6, 134.8, 129.8, 127.1, 126.2, 124.6, 123.9, 121.7, 120.1, 120.0, 117.4, 115.5. FTIR (KBr, cm^{-1}): 3414, 3052, 2853, 1651, 1589, 1562, 1489, 1469, 1447, 1427, 1393, 1289, 1263, 1185, 1137, 1090, 1084, 1046, 1025, 995, 967, 847, 790, 743, 719, 700, 621, 500. Anal. calcd. for $C_{18}H_{14}N_6$: C, 68.78; H, 4.49; N, 26.74%. Found: C, 68.68; H, 4.42; N, 26.70%.



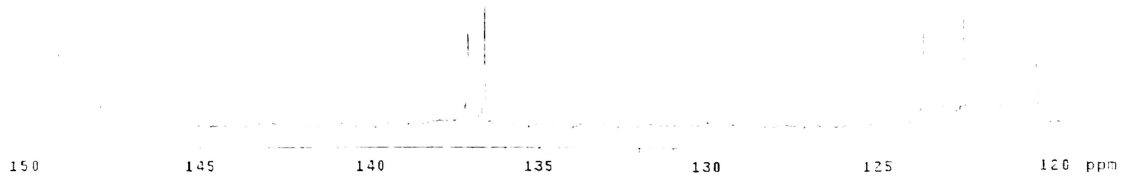
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-(3-(3-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine (**2b**).



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of *N*-(3-(3-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine (**2b**).

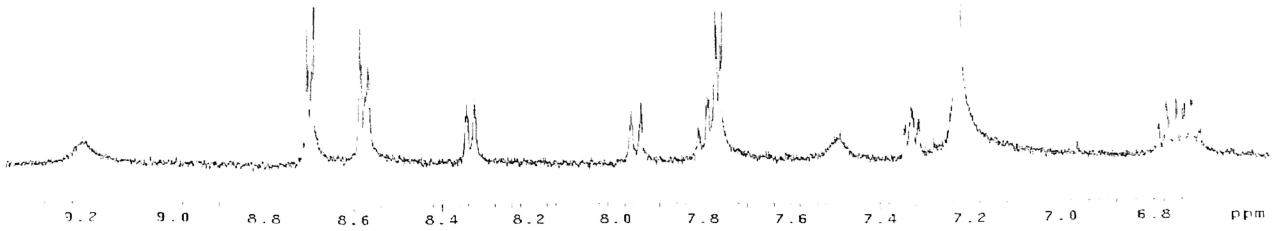
2,4,-bis(2-pyridyl)-5-(4-pyridyl)imidazole (**1c**): Yield: 2.02 g, 73% mp. 196 °C; ESI-MS: *m/z* calcd. for $C_{18}H_{13}N_5^+$ 299.117 found (M^++H) 300.123. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 11.41 (1NH, s), 8.66 (2H, m), 8.59 (2H, d, 4.0), 8.25 (1H, d, 8.0), 7.81 (1H, t, 7.2), 7.68 (2H, d, 5.2), 7.60 (1H, t, 7.4), 7.53 (1H, d, 7.6), 7.30 (1H, t, 7.6), 7.20 (1H, t, 6.0). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 149.8, 149.7, 149.0, 147.9, 146.8, 137.1, 136.6, 124.0, 123.0, 122.5, 121.5, 120.5. FTIR (KBr, cm^{-1}): 3498, 3218, 1644, 1608, 1574, 1567, 1496, 1471, 1447, 1418, 1398, 1332, 1320, 1293, 1272, 1246, 1218, 1143, 1105, 1090, 1049, 1001, 994, 917, 822, 807, 790, 764, 754, 738, 720, 705, 683, 666, 632, 612, 547, 520, 498, 459. Anal. calcd. for $C_{18}H_{13}N_5$: C, 72.23; H, 4.38; N, 23.40%. Found: C, 72.17; H, 4.33; N, 23.34%.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2,4,-bis(2-pyridyl)-5-(4-pyridyl)imidazole (**1c**).

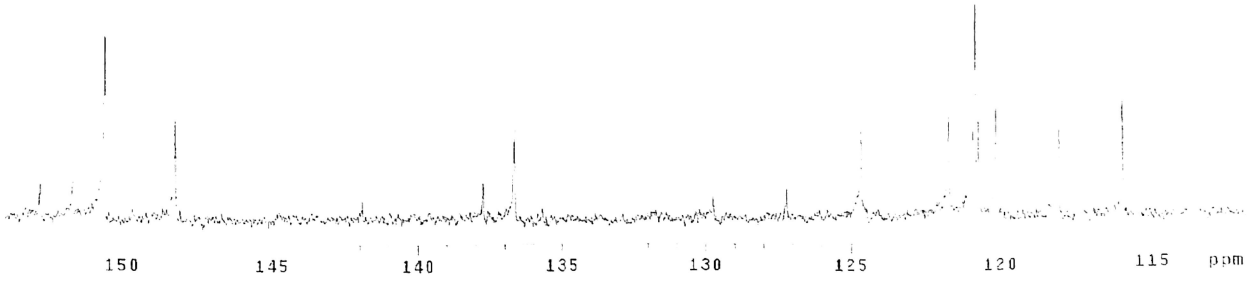


^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 2,4,-bis(2-pyridyl)-5-(4-pyridyl)imidazole (**1c**).

***N*-(3-(4-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine (2c)**: Yield: 135 mg, 4.5% mp. 183 °C; ESI-MS: *m/z* calcd. for $C_{18}H_{14}N_6^+$ 314.13 found (M^++H) 315.14. R_f = 0.60. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 9.19 (1NH, s), 8.70 (2H, d, 6.0), 8.57 (2H, d, 8.8), 8.34 (1H, d, 7.2), 7.95 (1H, d, 10.0), 7.77 (3H, m), 7.48 (1NH, s), 7.34 (1H, t, 6.8), 6.79 (1H, t, 8.0), 6.74 (1H, t, 6.8). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 152.7, 151.6, 150.6, 148.2, 141.9, 137.7, 136.6, 129.7, 127.2, 124.7, 121.7, 120.8, 120.7, 120.1, 118.0, 116.0. FTIR (KBr, cm^{-1}): 3438, 3305, 1643, 1624, 1598, 1564, 1527, 1497, 1472, 1454, 1325, 1289, 1247, 1218, 1182, 1112, 998, 961, 815, 800, 724, 703, 658, 507, 484. Anal. calcd. for $C_{18}H_{14}N_6$: C, 68.78; H, 4.49; N, 26.74%. Found: C, 68.70; H, 4.40; N, 26.65%.



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-(3-(4-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine (**2c**).



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of *N*-(3-(4-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine (**2c**).

Table 1. Crystallographic data of 2,4,5-tris(2-pyridyl)imidazole (**1a**):

Formula	$C_{18}H_{13}N_5$
Formula weight	299.33
T (K)	296(2)
Crystal system	Monoclinic
Space group	$P2_1/c$
a (Å)	16.3582(6)
b (Å)	11.5830(4)
c (Å)	7.6079(3)
α (°)	90.00
β (°)	92.996(2)
γ (°)	90.00
V (Å^3)	1439.55(9)
Z	4
D_{calc} (g cm^{-3})	1.381
μ (mm^{-1})	0.87
F (000)	624
R_{int}	0.0336
Goodness-of-fit[a] on F^2	1.042
R_1[b], wR_2[c] ($I \geq 2\sigma(I)$)	0.0425, 0.1030
R_1[b], wR_2[c] (all data)	0.0628, 0.1140

[a] GOF = $[\sum[w(F_0^2 - F_c^2)^2] / M - N]^{1/2}$ (M = number of reflections, N = number of parameters refined).
[b] $R_1 = \sum ||F_0| - |F_c|| / \sum |F_0|$.
[c] $wR_2 = [\sum[w(F_0^2 - F_c^2)^2] / \sum[w(F_0^2)^2]]^{1/2}$.

Chapter 4

Synthesis of Some 1,3-Disubstituted Imidazo[1,5-*a*]pyridines Using 2-Cyanopyridine*

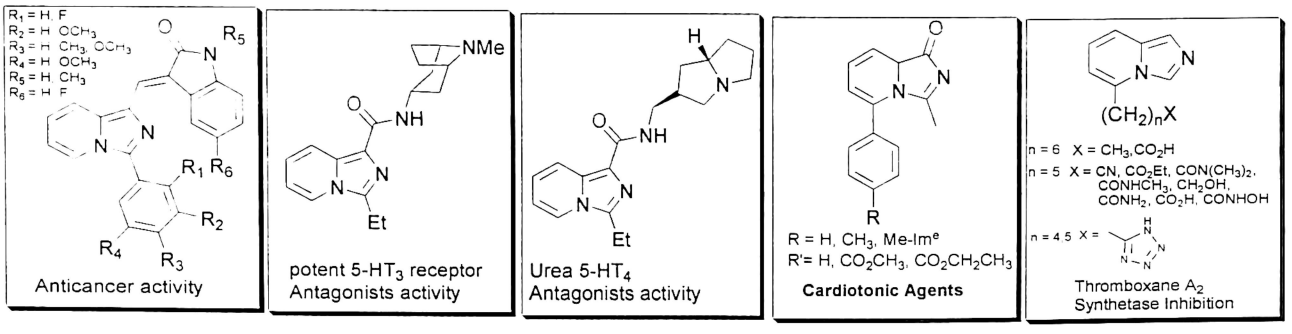
Abstract: Heating 2-cyanopyridine and hydrazine hydrate at 100 °C and reheating the resultant liquid with pyridine-2-carboxaldehyde yielded a red semi-solid. On adding aqueous KOH, a mixture of 1-(3,5-bis(2-pyridyl)-1,2,4-triazolyl)-3-(2-pyridyl)imidazo-[1,5-*a*]pyridine (**2a**) and 1-((2-pyridyl)methanimine)-3-(2-pyridyl)imidazo[1,5-*a*]pyridine (**2b**) precipitated and from the filtrate 3,5-bis(2-pyridyl)-1,2,4-triazole (**1**) was isolated. Similar compounds were obtained from two other pyridinecarboxaldehydes.

*This work has been published in:

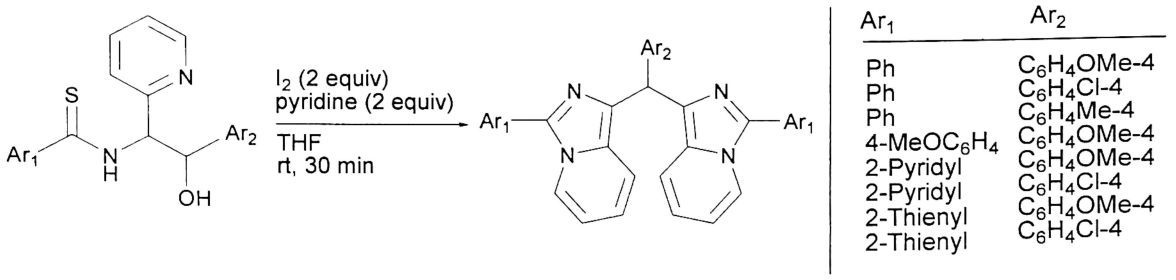
Fulwa, V. K.; Manivannan, V. *Tetrahedron Lett.* **2012**, *53*, 2420–2423.

4.1. Introduction

Imidazo[1.5-*a*]pyridine is a class of fused bicyclic 5:6 system having two nitrogen atoms among which one lie at the bridgehead 4-position and other at the 2-position of the five-membered ring.[1]

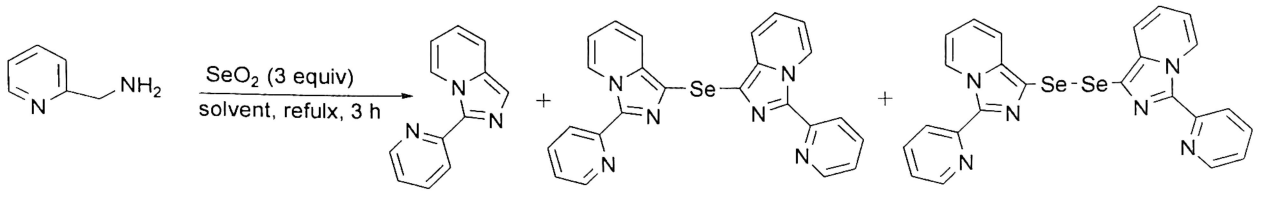


This class of compounds are shown to be active as thromboxane A_2 synthetase inhibitors[2a] and ionotropic agents.[2b]



Chem. Commun. **2009**, 7009–7011.

The synthesis of imidazo[1,5-*a*]pyridine having different substituents at pyridine[2,3] and at 3– and/or 1– positions of the imidazole[4] rings have been reported.



Chem. Lett. **2011**, *40*, 449–451.

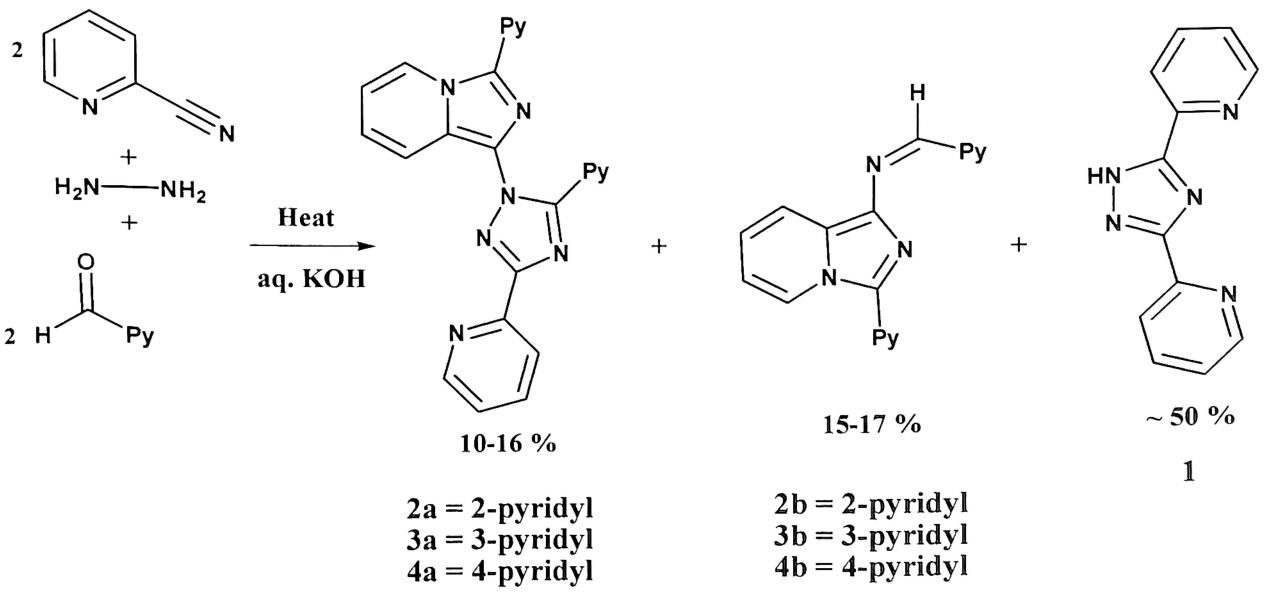
The carbon at 3– or 1– position have also been utilized to serve as a carbene under suitable conditions.[5] Chapter 3 described the formation of imidazo[1,5-*a*]pyridine nucleus from the reaction between 2-cyanopyridine and 2-picolylamine.

As noted in Chapter 1, Section 1.3.9., the product of reaction of 2-cyanopyridine and hydrazine is amidrazone. This Chapter describes the results of examination of the reaction of 2-cyanopyridine with hydrazine and pyridine-carboxaldehydes.

4.2 Results and Discussion

A neat 2:1 mixture of 2-cyanopyridine and hydrazine hydrate on heating in an oil bath at 100 °C for 12h produced a thick red liquid, to which pyridine-2-carboxaldehyde was added and reheated at 100 °C for another 6h. The resultant red semi-solid was suspended in water and KOH was added, which yielded a precipitate containing a mixture of **2a** and **2b**. They were separated on a basic alumina column and **1** was isolated from the filtrate by adjusting the pH of the solution to 7-8 using 5M HCl. This is shown in Scheme 1.

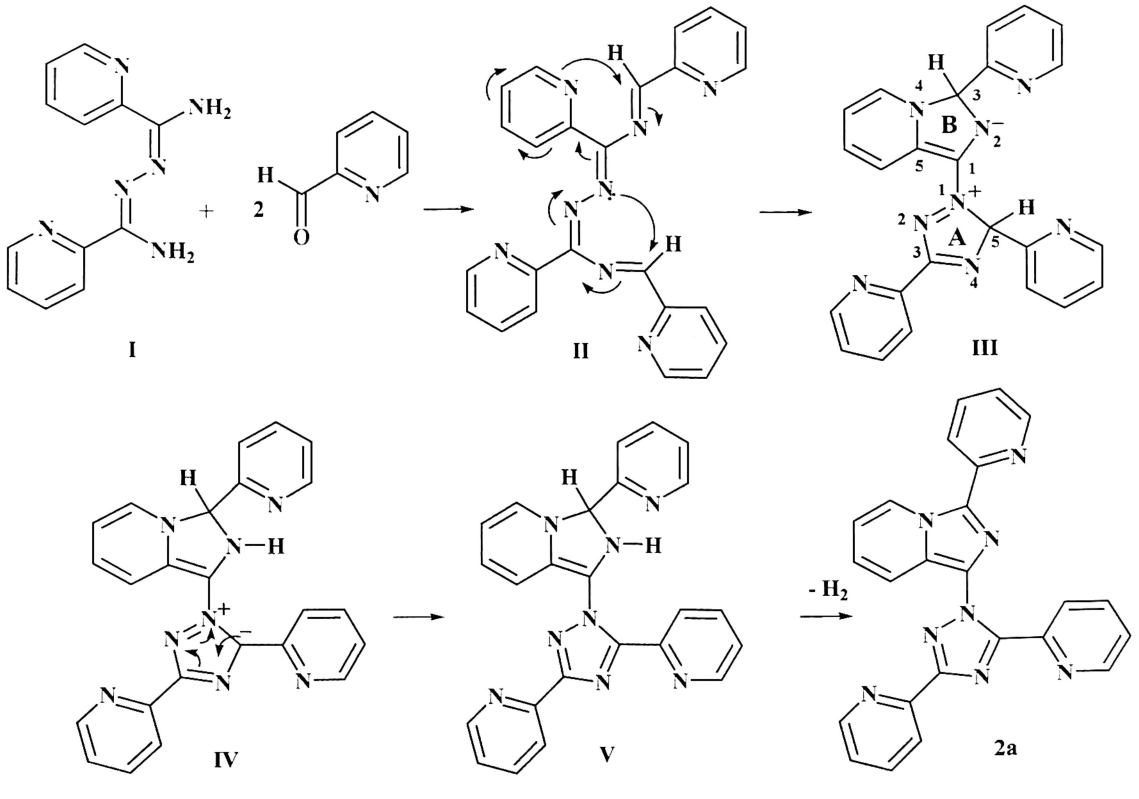
By using pyridine-3-carboxaldehyde, 1-(3-(2-pyridyl)-5-(3-pyridyl)-1,2,4-triazolyl)-3-(3-pyridyl)imidazo[1,5-*a*]pyridine (**3a**) and 1-((3-pyridyl)methanimine)-3-(3-pyridyl)imidazo[1,5-*a*]pyridine (**3b**) along with **1** and using pyridine-4-carboxaldehyde, 1-(3-(2-pyridyl)-5-(4-pyridyl)-1,2,4-triazolyl)-3-(4-pyridyl)imidazo-[1,5-*a*]pyridine (**4a**) and 1-((4-pyridyl)-methanimine)-3-(4-pyridyl)imidazo[1,5-*a*]pyridine (**4b**) along with **1** were isolated. The compounds **2a-4a** and **2b-4b** were characterized by ^{1}H and ^{13}C NMR, IR as well as mass spectroscopic methods. The molecular structures of **2a** and **4b** were also established using single crystal X-ray (Table 1) diffraction methods.



Scheme 1. Synthesis of **2a–4a**, **2b–4b**. Legend inside the scheme is for substituent Py.

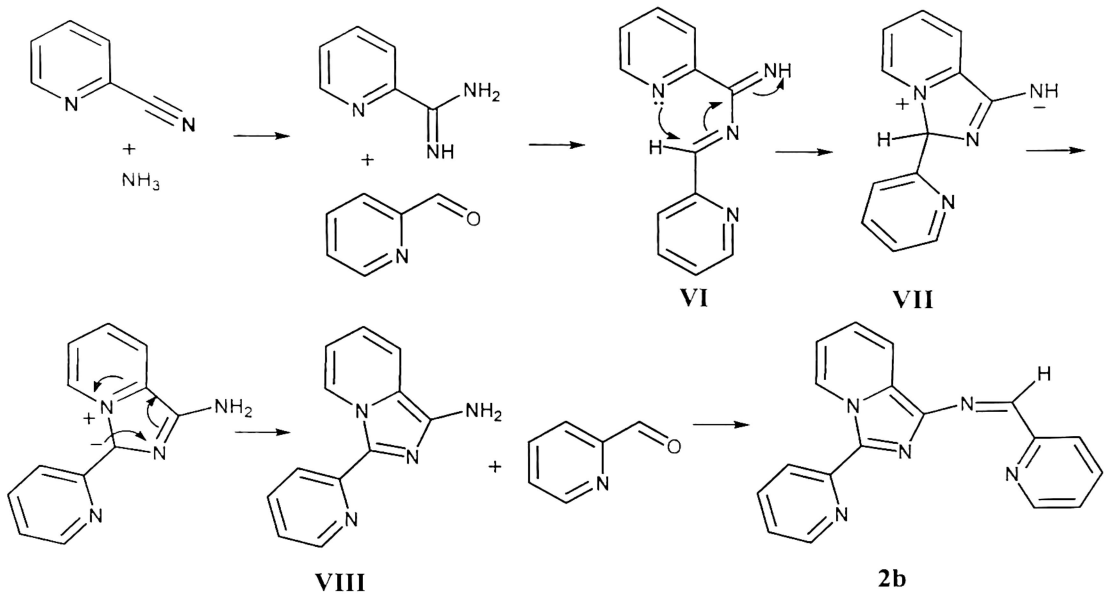
A plausible mechanism for the formation **2a** has been shown in Scheme 2. The intermediate **I** having two amine functions, formed on heating 2-cyanopyridine and hydrazine hydrate could condense with two molecules of pyridine-2-carboxaldehyde yielding intermediate **II**. The lone-pair of electron on the nitrogen atom could attack the

aldimine carbon atom, subsequent migration of the π-electron cloud will lead to formation of rings **A** and **B** which are respectively linked through 1– and 1–positions, as shown in intermediate **III**. A proton shift from C5 of ring **A** to N2 of ring **B**, then migration of the resultant negative charge on C5 to N1 of ring **A** forming the 1,2,4-triazole ring as in intermediate **V**. Removal of a hydrogen molecule from ring **B** will lead to the imidazo[1,5-*a*]pyridine nucleus. These 1,2,4-triazole and imidazo[1,5-*a*]pyridine nuclei are uniquely linked through 1– and 1– positions, respectively.



Scheme 2. A plausible mechanism for the formation of **2a**.

A plausible mechanism for the formation **2b** has been given in Scheme 3. Hydrazine is known to generate ammonia on heating, which could combine with 2-cyanopyridine to form the 2-picolinamidine. The 2-picolinamidine will condense with pyridine-2-carboxaldehyde to form the intermediate **VI**. The lone pair of electron on the pyridine ring could attack carbon atom of the imine group, which will lead to generation of the fused five-membered ring as in **VII**. The proton shift followed by migration of the negative charge will lead to formation of the imidazo[1,5-*a*]pyridine nucleus having a free amino group which could readily condense further with another molecule of pyridine-2-carbaxaldehyde to form the product **2b**. Synthesis[6a] of 3,5-di(2-pyridyl)-1,2,4-triazole and also its formation under solvothermal conditions[6b] has been reported.



Scheme 3. A plausible mechanism for the formation of **2b**.

Compounds **2a–4a** show a characteristic M^++H peak at *m/z* = 417 which is consistent with the molecular mass calculated for the formula $C_{24}H_{16}N_8$. Two distinct triplets in the range δ = 6.80–7.00 *ppm* in the ^{1}H NMR is characteristic of the fused pyridine ring present in imidazo[1,5-*a*]pyridine ring. The single crystal X-ray structure of **2a**·H_2O has been determined and a perspective view of **2a** is shown in Figure 1. The compound crystallized in the *P*-1 space group. The imidazo[1,5-*a*]pyridine ring is planar and the 2-pyridyl group attached at the 3- position is also coplanar with the imidazo[1,5-*a*]pyridine ring. The 1,2,4-triazole ring attached at 1-position of the imidazo[1,5-*a*]pyridine ring is twisted with each other as evident from the dihedral angle of 61.5° between planes of N4N5C19N6C13 and C6N2C11C12N3. Within the two five-membered rings the bond parameters lie within the normal range. The triazole ring makes a dihedral angle of 26.6° and 39.9° with 2-pyridyl rings containing the atoms C20C21C22C23C24N8 and C14C15C16C17C18N7, respectively.

Synthesis of **2b** from pyridine-2-carbaldehyde and NH_4OAc by heating at 100 °C in DMSO was reported by Bureš *etal* and its spectral details are also available.[7] Compounds **3b-4b** show a characteristic M^++H peak at *m/z* = 300 which is consistent with the molecular mass calculated for the formula $C_{18}H_{13}N_5$. Two distinct triplets in the range δ = 6.70–7.00 *ppm* in the ^{1}H NMR is characteristic of the fused pyridine ring of imidazo[1,5-*a*]pyridine nucleus. The imine proton is observed in the range δ = 9.20–9.40 as singlet peak. The single crystal X-ray structure of **4b** has been determined and a perspective view is shown in Figure 2. The compound crystallized in the $P2_1/c$ space

group. The imidazo[1,5-*a*]pyridine and attached 2-pyridyl ring are nearly coplanar with each other.

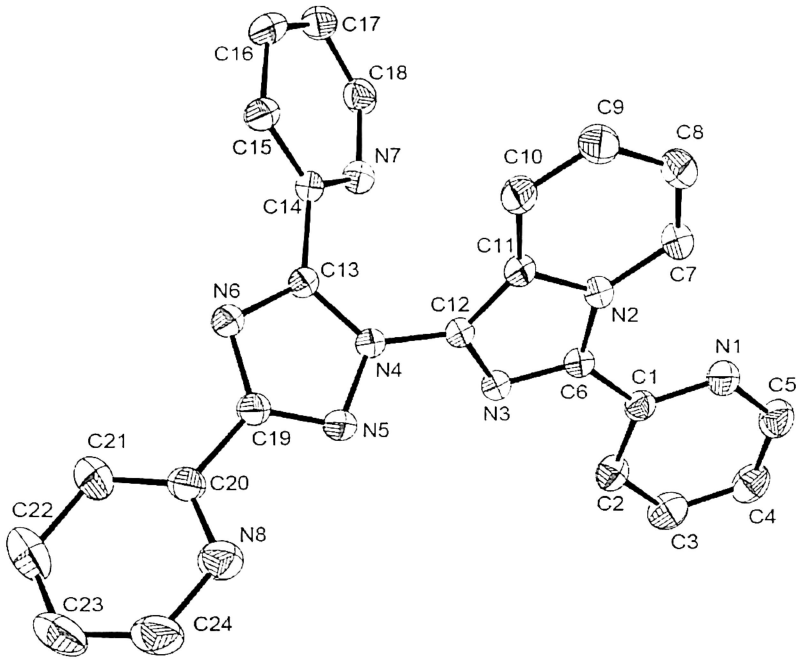


Figure 1.ORTEP (30% probability) diagram of **2a**. Hydrogen atoms are omitted for clarity. Selected distances, Å: N2–C6 1.385(2), N2–C11 1.394(2), C11–C12 1.377(2), N3–C12 1.341 (2), N3–C6 1.329(2), N4–C12 1.417(2), N4–C13 1.349(2), N6–C13 1.325(2), N6–C19 1.365 (2), N5–C19 1.313(2), N4–N5 1.3691(19).

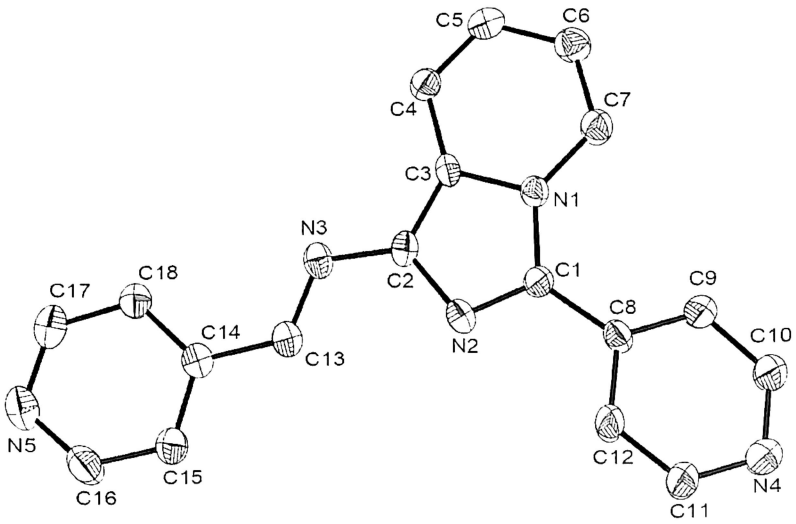
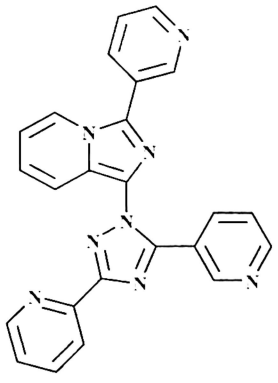
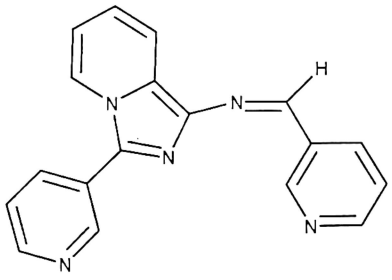


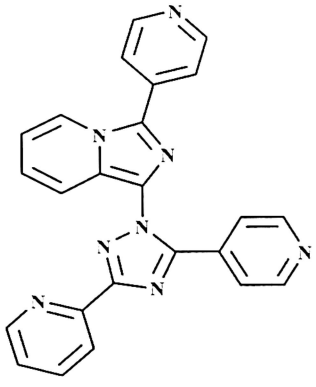
Figure 2.ORTEP (30% probability) diagram of **4b**. Hydrogen atoms are omitted for clarity. Selected distances, Å: N1–C1 1.377(7), N1–C3 1.403(7), C3–C2 1.382(9), N2–C2 1.371(7), N2–C1 1.313(8), N3–C2 1.390(8), N3–C13 1.287(7).



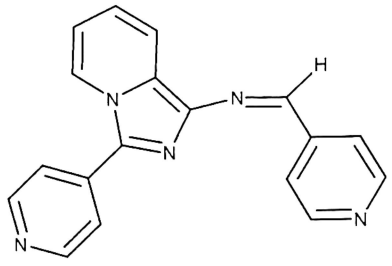
3a



3b



4a



4b

4.3. Conclusion

In conclusion, this Chapter describes the reaction of 2-cyanopyridine, hydrazine hydrate and pyridine-carboxaldehydes. The products isolated include two 1,3-disubstituted imidazo[1,5-*a*]pyridine compounds and 3,5-bis(2-pyridyl)-1,2,4-triazole.

4.4. Synthesis

A mixture of hydrazine hydrate (0.250 g, 5.0 mmol) and 2-cyanopyridine (1.04 g, 10.0 mmol) was heated at 100 °C in an oil-bath for 12h. The mixture was cooled and then 2-pyridinecarboxaldehyde (1.07 g, 10.0 mmol) was added and reheated at 100°C in an oil-bath for another 6h. The resultant red gummy oil was suspended in 30 mL of water, solid KOH (0.56 g, 10.0 mmol) was added and stirred for 5h. The yellow solid obtained was filtered, washed with water and dried in vacuum over fused $CaCl_2$. The dry solid was subjected to chromatographic separation using basic alumina column. Firstly compound 1-((2-pyridyl)methanimine)-3-(2-pyridyl)imidazo[1,5-*a*]pyridine (**2b**) was eluted with ethyl acetate-hexane (3:7) mixture and the yellow fibrous solid of **2b** was obtained after removal of the solvents. Yield of **2b**: 150 mg (17%). Then 1-(3,5-bis(2-pyridyl)-1,2,4-triazolyl)-3-(2-pyridyl)imidazo[1,5-*a*]pyridine (**2a**) was eluted using dichloromethane Yield of **2a**: 390 mg (10%). The filtrate had a strong ammonia

smell, the pH of which was adjusted to 7-8 using 5 M HCl. The aqueous solution was extracted with ether (3 × 50 mL) and 3,5-bis(2-pyridyl)-1,2,4-triazole (**1**) was obtained as yellow solid after evaporating the ether. Yield of **1**: 1.42 g (52%).

4.5. References

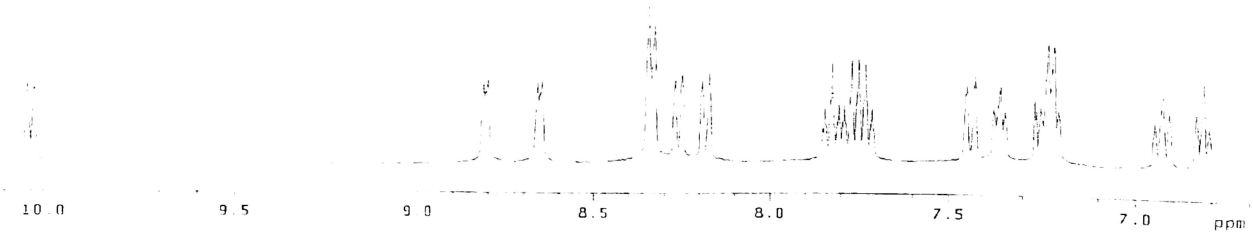
1. Couty, F., Evano, G. In Comprehensive Heterocyclic Chemistry III; Katritzky, A. R., Ramsden, C. A., Eric, F.V. AAA., Taylor, R. J. K., Eds.; Elsevier Ltd.: 2008; Vol. 11, pp 435–443.
2. (a) Ford, N. F.; Browne, L. J.; Campbell, T.; Gemenden, C.; Goldstein, R.; Gude, C.; Wasley, J. W. F. J. *Med. Chem.* **1985**, *28*, 164–170. (b) Davey, D.; Erhardt, P. W.; Lumma, W. C., Jr.; Wiggins, J.; Sullivan, M.; Pang, D.; Cantor, E. *J. Med. Chem.* **1987**, *30*, 1337–1342.
3. (a) Browne, L. J.; Gude, C.; Rodriguez, H.; Steele, R. E. *J. Med. Chem.* **1991**, *34*, 725–736. (b) Davey, D. D. *J. Org. Chem.* **1987**, *52*, 1863–1867.
4. (a) Alcarazo, M.; Roseblade, S. J.; Cowley, A. R.; Fernández, R.; Brown, J. M.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3290–3291. (b) Fürstner, A.; Alcarazo, M.; Krause, H.; Lehmann, C. W. *J. Am. Chem. Soc.* **2007**, *129*, 12676–12677. (c) Roseblade, S. J.; Ros, A.; Monge, D.; Alcarazo, M.; Álvarez, E.; Lassaletta, J. M.; Fernández, R. *Organometallics* **2007**, *26*, 2570–2578. (d) Nonnenmacher, M.; Kunz, D.; Rominger, F.; Oeser, T. *J. Organomet. Chem.* **2007**, *692*, 2554–2563. (e) Cheng, Y.; Peng, J.-H.; Li, J.-Q. *J. Org. Chem.* **2010**, *75*, 2382–2388.
5. (a) Bower, J. D.; Ramage, G. R. *J. Chem. Soc.* **1955**, 2834–2837. (b) Palacios, F.; Alonso, C.; Rubiales, G. *Tetrahedron* **1995**, *51*, 3683. (b) Krapcho, A. P.; Powell, J. R. *Tetrahedron Lett.* **1986**, *27*, 3713–3714. (c) Sasaki, K.; Tsurumori, A.; Hirota, T. *J. Chem. Soc. Perkin Trans.1* **1998**, 3851–3856. (d) Katritzky, A. R.; Qiu, G. *J. Org. Chem.* **2001**, *66*, 2862–2864. (e) Bluhm, M. E.; Ciesielski, M.; Görls, H.; Döring, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 2962–2965. (f) Wang, J.; Mason, R.; VanDerveer, D.; Feng, K.; Bu, X. R.; *J. Org. Chem.* **2003**, *68*, 5415–5418. (g) Wang, J.; Dyers, Jr. L.; Mason, Jr. R.; Amoyaw, P.; Bu, X. R. *J. Org. Chem.* **2005**, *70*, 2353–2356. (h) Kim, D.; Wang, L.; Hale, J. J.; Lynch, C. L.; Budhu, R. J.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Hrin, R. C.; Carver, G.; Carella, A.; Henry, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.*

2005. *15*. 2129–2134. (i) Shibahara, F.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *Org. Lett.* **2006**, *8*, 5621–5624. (j) Shibahara, F.; Sugiura, R.; Yamaguchi, E.; Kitagawa, A.; Murai, T. *J. Org. Chem.* **2009**, *74*, 3566–3568. (k) Crawforth, J. M.; Paoletti, M. *Tetrahedron Lett.* **2009**, *50*, 4916–4918. (l) Shibahara, F.; Yamaguchi, E.; Kitagawa, A.; Imai, A.; Murai, T. *Tetrahedron* **2009**, *65*, 5062–5073. (m) Tahara, S.; Shibahara, F.; Maruyama, T.; Murai, T. *Chem. Commun.* **2009**, 7009–7011. (n) Arvapalli, V. S.; Chen, G.; Kosarev, S.; Tan, M. E.; Xie, D.; Yet, L. *Tetrahedron Lett.* **2010**, *51*, 284–286. (o) Zhang, A.; Zheng, X.; Fan, J.; Shen, W. *Tetrahedron Lett.* **2010**, *51*, 828–831. (p) Niyomura, O.; Yamaguchi, Y.; Tamura, S.; Minoura, M.; Okamoto, Y. *Chem. Lett.* **2011**, *40*, 449–451. (q) Huang, C.; Giokaris, A.; Gevorgyan, V. *Chem. Lett.* **2011**, *40*, 1053–1054. (r) Yamaguchi, E.; Shibahara, F.; Murai, T. *Chem. Lett.* **2011**, *40*, 939–940.

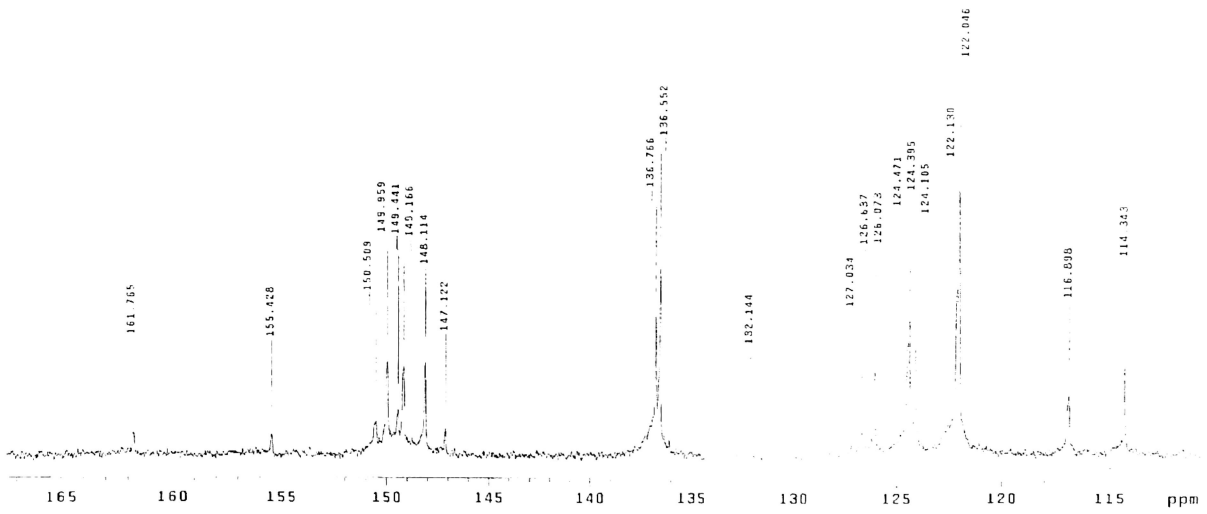
6. (a) Geldard, J. F.; Lions, F. *J. Org. Chem.* **1965**, *30*, 318–319. (b) Cheng, L; Zhang, W.; Ye, B.; Lin, J.; Chen, X. *Inorg. Chem.* **2007**, *46*, 1135–1143.
7. Kulhánek, J.; Bureš, F.; Šimon, P.; Schweizer, W. B. *Tetrahedron: Asymmetry* **2008**, *19*, 2462–2469.

4.6. Spectral data

1-(3,5-bis(2-pyridyl)-1,2,4-triazolyl)-3-(2-pyridyl)imidazo[1,5-*a*]pyridine (2a): mp. 210 °C; ESI-Mass: calcd. for $C_{24}H_{16}N_8^+$ 416.150 found (M^++H) 417.13. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 10.04 (1H, d, 7.6), 8.81 (1H, d, 4.8), 8.66 (1H, d, 4.8), 8.34 (2H, d, 7.2), 8.27 (1H, d, 7.6), 8.19 (1H, d, 8.4), 7.78 (3H, m), 7.45 (1H, d, 8.8), 7.36 (1H, t, 6.8), 7.24 (2H, m), 6.94 (1H, t, 7.2), 6.83 (1H, t, 7.2). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 161.8, 155.4, 150.5, 150.0, 149.4, 149.2, 148.1, 147.1, 136.8, 136.6, 132.1, 127.0, 126.6, 126.1, 124.5, 124.4, 124.1, 122.1, 122.0, 116.9, 114.3. Selected FTIR (KBr, cm^{-1}): 1639, 1589, 1505, 1473, 1417, 1385, 1359, 1160, 1091, 1014, 996, 952, 790, 742, 713, 695. Anal. calcd. for $C_{24}H_{16}N_8$: C, 69.22; H, 3.87; N, 26.91%. Found: C, 69.03; H, 3.79; N, 26.75%.

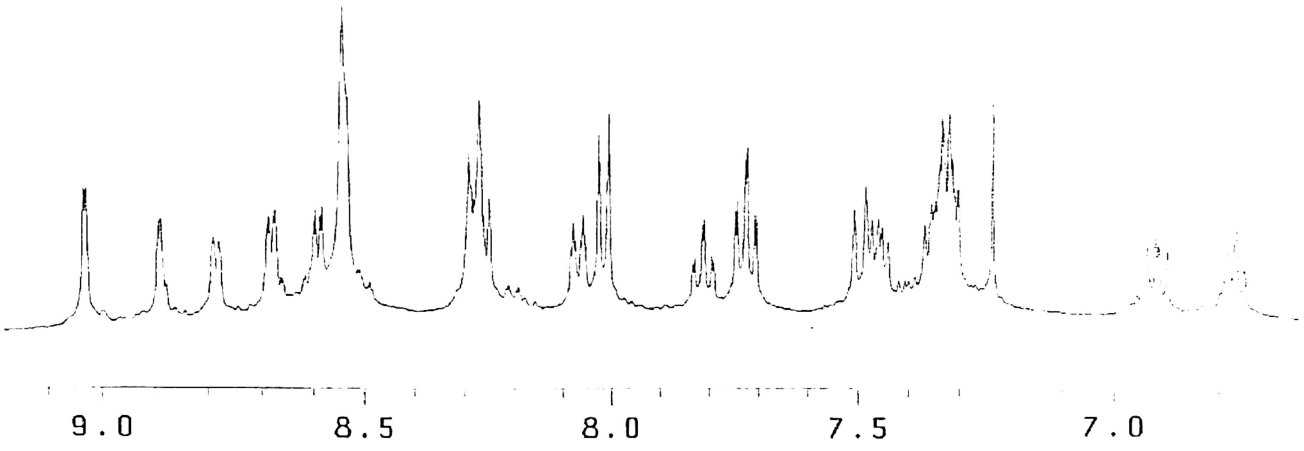


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 1-(3,5-bis(2-pyridyl)-1,2,4-triazolyl)-3-(2-pyridyl)imidazo[1,5-*a*]pyridine (**2a**).

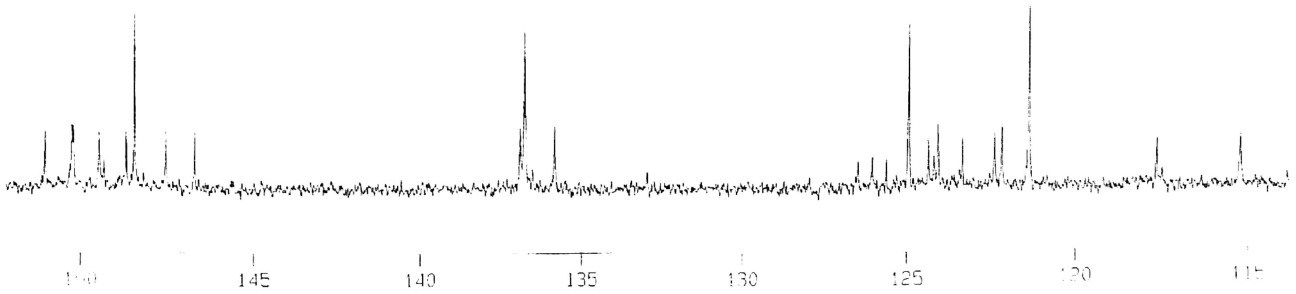


^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 1-(3,5-bis(2-pyridyl)-1,2,4-triazolyl)-3-(2-pyridyl)imidazo[1,5-*a*]pyridine (**2a**).

1-(3-(2-pyridyl)-5-(3-pyridyl)-1,2,4-triazolyl)-3-(3-pyridyl)imidazo[1,5-*a*]pyridine (**3a**): Yield: 625 mg (16%). mp. 215°C; ESI-Mass: calcd. for $C_{24}H_{16}N_8^+$ 416.150 found (M^++H) 417.17. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 9.06 (1H, s), 8.93 (1H, s), 8.82 (1H, d, 4.0), 8.71 (1H, d, 6.8), 8.62 (1H, d, 6.4), 8.30 (3H, m), 8.10 (1H, d, 7.6), 7.84 (1H, t, 7.6), 7.54 (1H, d, 9.2), 7.49 (1H, t, 4.8), 7.37 (2H, m), 6.95 (1H, t, 6.4), 6.80 (1H, t, 6.4). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 151.0, 150.3, 150.2, 149.4, 149.3, 148.7, 147.5, 146.7, 136.9, 136.5, 135.8, 126.5, 126.0, 125.6, 124.9, 124.3, 124.2, 124.1, 123.3, 122.4, 122.2, 121.4, 117.6, 115.2. Selected FTIR (KBr, cm^{-1}): 1636, 1580, 1557, 1523, 1510, 1465, 1424, 1363, 1306,1224, 1146, 977, 945, 808, 743, 702, 692. Anal. calcd. for $C_{24}H_{16}N_8$: C, 69.22; H, 3.87; N, 26.91%. Found: C, 68.96; H, 3.74; N, 26.76%.

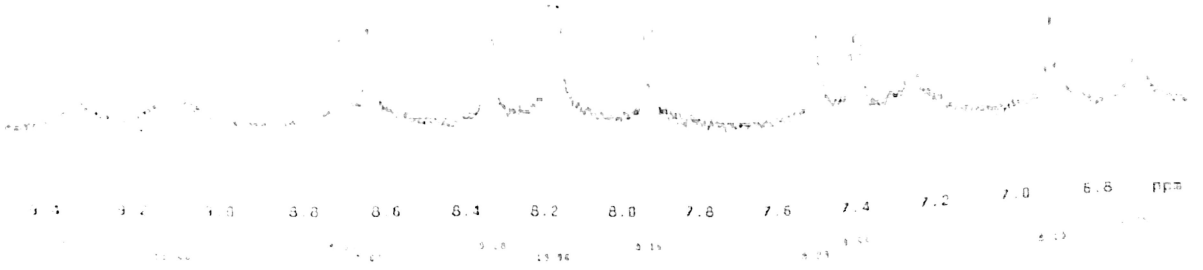


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 1-(3-(2-pyridyl)-5-(3-pyridyl)-1,2,4-triazolyl)-3-(3-pyridyl)imidazo[1,5-*a*]pyridine (**3a**).

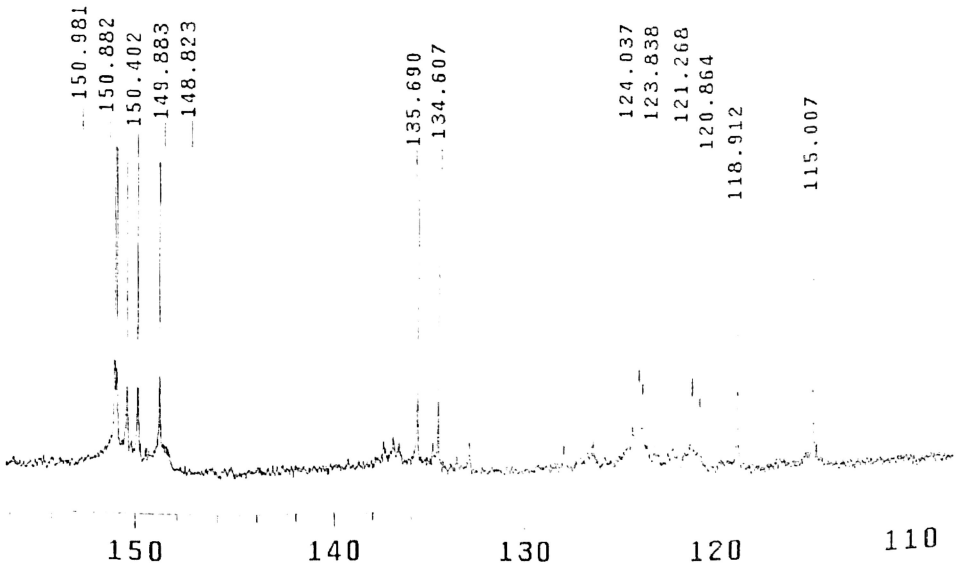


^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 1-(3-(2-pyridyl)-5-(3-pyridyl)-1,2,4-triazolyl)-3-(3-pyridyl)imidazo[1,5-*a*]pyridine (**3a**).

1-((3-pyridyl)methanimine)-3-(3-pyridyl)imidazo[1,5-*a*]pyridine (**3b**): Yield: 130 mg (15%). mp. 190°C; ESI-Mass: calcd. for $C_{18}H_{13}N_5^+$ 300 found (M^++H) 300.10. R_f = 0.25 (3:7 ethylacetate-hexane). 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 9.33 (1H, s), 9.12 (2H, s), 8.70 (1H, d, 7.0), 8.64 (1H, d, 7.0), 8.34 (1H, d, 8.0), 8.20 (2H, m), 8.03 (1H, d, 9.6), 7.50 (1H, t, 8.0), 7.40 (1H, t, 8.0), 7.02 (1H, t, 8.8), 6.70 (1H, t, 6.4). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 151.0, 150.9, 150.4, 149.9, 148.8, 135.7, 134.6, 124.0, 123.8, 121.3, 120.9, 118.9, 115.0. Selected FTIR (KBr, cm^{-1}): 1633, 1591, 1513, 1479, 1417, 1356, 1301, 1242, 1189, 1177, 1128, 1026, 956, 824, 804, 747, 732, 713, 698. Anal. calcd. for $C_{18}H_{13}N_5$: C, 72.23; H, 4.38; N, 23.40%. Found: C, 71.90; H, 4.28; N, 23.22%.



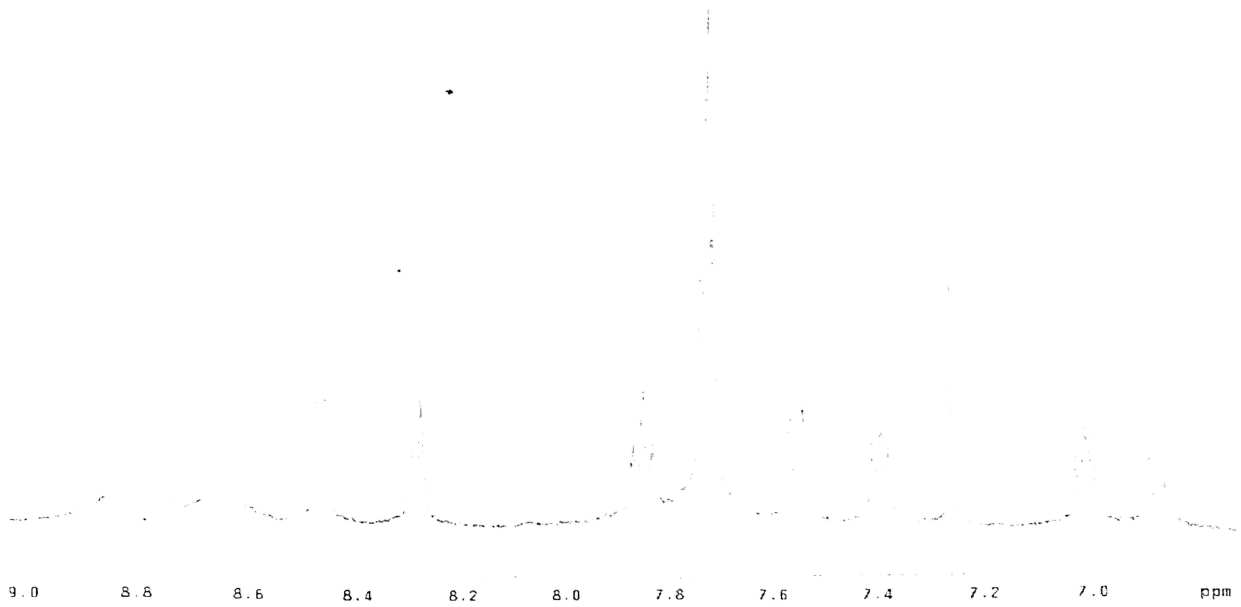
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 1-((3-pyridyl)methanimine)-3-(3-pyridyl)imidazo[1,5-*a*]pyridine (**3b**).



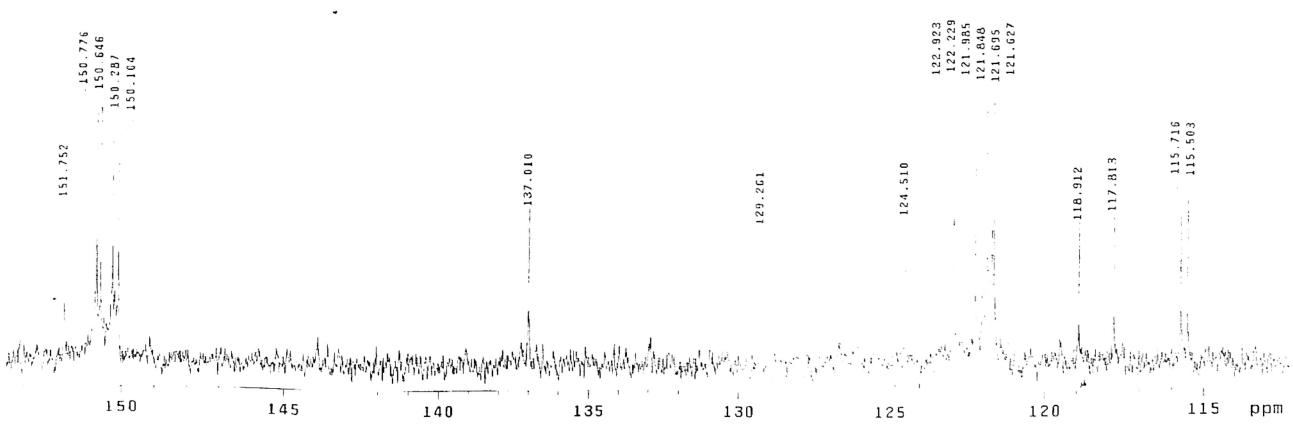
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 1-((3-pyridyl)methanimine)-3-(3-pyridyl)imidazo[1,5-*a*]pyridine (**3b**).

1-(3-(2-pyridyl)-5-(4-pyridyl)-1,2,4-triazolyl)-3-(4-pyridyl)imidazo[1,5-*a*]pyridine (**4a**): Yield: 500 mg (13%). mp. 220°C; ESI-Mass: calcd. for $C_{24}H_{16}N_8^+$ 416.150 found (M^++H) 417.10. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 8.81 (3H, m), 8.65 (2H, m), 8.47 (1H, d, 7.2), 8.29 (1H, d, 8.0), 7.86 (1H, t, 6.4), 7.73 (4H, m), 7.56 (1H, d, 9.2), 7.41 (1H, t, 5.2), 7.02 (1H, t, 9.2), 6.89 (1H, t, 7.2). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 152.0, 151.0, 150.8, 150.5, 150.2, 137.5, 137.1, 124.6, 123.0, 122.7, 122.3, 121.9, 121.7, 119.1, 117.9, 115.8. Selected FTIR (KBr, cm^{-1}): 1634, 1603, 1455, 1415, 1384,

1216, 1198, 1124, 1094, 1002, 743, 729, 719, 693. Anal. calcd. for $C_{24}H_{16}N_8$: C, 69.22; H, 3.87; N, 26.91%. Found: C, 69.09; H, 3.81; N, 26.82%.



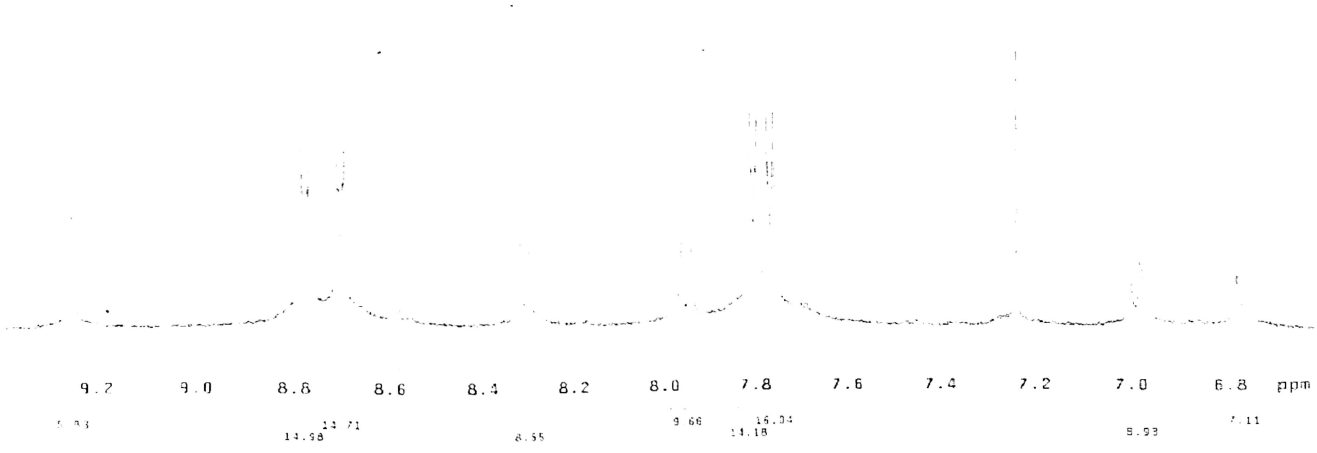
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 1-(3-(2-pyridyl)-5-(4-pyridyl)-1,2,4-triazolyl)-3-(4-pyridyl)imidazo[1,5-*a*]pyridine (**4a**).



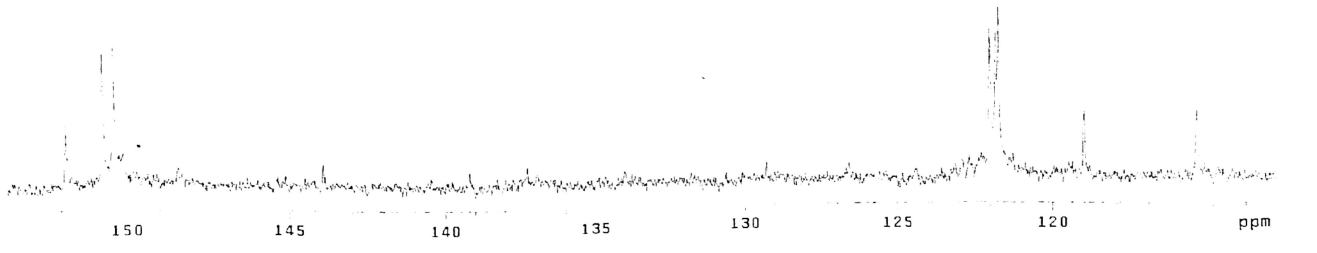
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 1-(3-(2-pyridyl)-5-(4-pyridyl)-1,2,4-triazolyl)-3-(4-pyridyl)imidazo[1,5-*a*]pyridine (**4a**).

1-((4-pyridyl)methanimine)-3-(4-pyridyl)imidazo[1,5-*a*]pyridine (**4b**): Yield: 130 mg (15%).mp. 180°C; ESI-Mass: calcd. for $C_{18}H_{13}N_5^+$ 300 found (M^++H) 300.16. R_f = 0.71 (1:1 ethylacetate-hexane). 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 9.25 (1H, s), 8.76 (2H, d, 6.4), 8.70 (2H, d, 6.0), 8.31 (1H, d, 7.2), 7.95 (1H, d, 9.2), 7.81 (2H, d, 6.0), 7.77 (2H, d, 6.0), 6.98 (1H, t, 6.0), 6.77 (1H, t, 7.2). 100 MHz ^{13}C NMR (δ,

$CDCl_3$): 151.9, 150.7, 150.4, 143.9, 122.9, 122.7, 122.0, 121.8, 121.7, 119.0, 115.5. Selected FTIR (KBr, cm^{-1}): 1628, 1595, 1492, 1411, 1301, 1251, 1177, 1138, 987, 841, 756, 737, 693, 547, 523. Anal. calcd. for $C_{18}H_{13}N_5$: C, 72.23; H, 4.38; N, 23.40%. Found: C, 72.04; H, 4.31; N, 23.33%.



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 1-((4-pyridyl)methanimine)-3-(4-pyridyl)imidazo[1,5-*a*]pyridine **(4b)**.



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 1-((4-pyridyl)methanimine)-3-(4-pyridyl)imidazo[1,5-*a*]pyridine **(4b)**.

Table 1. Crystallographic data **2a** and **4b**.

	2a	**4b**
Formula	$C_{24}H_{18}N_8O$	$C_{18}H_{13}N_5$
Formula weight	434.45	299.33
T (K)	296(2)	296(2)
Crystal system	Triclinic	Monoclinic
Space group	*P*–1	$P2_1/c$
a (Å)	8.4452(3)	9.3301(12)
b (Å)	9.2304(3)	4.7326(8)
c (Å)	14.4128(5)	32.194(4)
α (°)	74.361(2)	90.00
β (°)	74.632(2)	95.529(9)
γ (°)	84.530(2)	90.00
V (Å^3)	1042.89(6)	1414.9(3)
Z	2	4
D_{calc} (g cm^{-3})	1.377	1.405
μ (mm^{-1})	0.91	0.89
F (000)	448	624
R_{int}	0.0263	0.0691
Goodness-of-fit[a] on F^2	1.041	1.000
R_1[b], wR_2[c] ($I \geq 2\sigma(I)$)	0.0471, 0.1408	0.0704, 0.1916
R_1[b], wR_2[c] (all data)	0.0572, 0.1486	0.0864, 0.2083

[a] GOF = $[\sum[w(F_0^2 - F_c^2)^2] / M - N]^{1/2}$ (M = number of reflections, N = number of parameters refined).
[b] $R_1 = \sum ||F_0| - |F_c|| / \sum |F_0|$.
[c] $wR_2 = [\sum[w(F_0^2 - F_c^2)^2] / \sum[w(F_0^2)^2]]^{1/2}$.

Chapter 5

Synthesis of 3-Substituted Imidazo[1,5-*a*]pyridines Having 1-(*N*-Picolinamidin-2-yl) group*

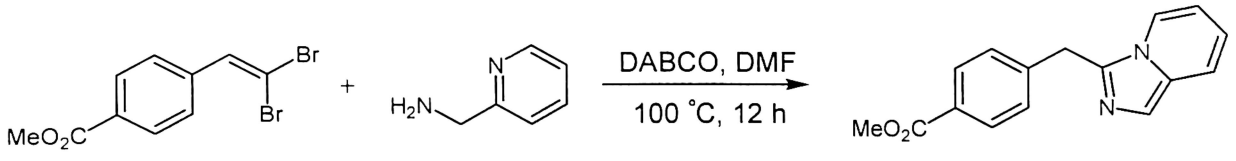
Abstract: The 3-substituted imidazo[1,5-*a*]pyridine compounds having 1-(*N*-picolinamidin-2-yl) group (**1a-1h**) were synthesized by heating one equivalent of an aldehyde (8 examples), two equivalents of 2-cyanopyridine and ammonium acetate in PEG-400. By heating two equivalents of the aldehyde and one equivalent of 2-cyanopyridine under the same experimental conditions, 2,4,5-trisubstituted imidazoles (**2a-2c**) were isolated. All the reported compounds were thoroughly characterized and the molecular structures of **1a** and **2b** were established by single crystal X-ray diffraction studies.

*This work has been published in:

Fulwa, V. K.; Manivannan, V. *Tetrahedron*, **2012**, *68*, 3927–3931.

5.1. Introduction

Imidazo[1,5-*a*]pyridine is a class of fused bicyclic 5:6 system having two nitrogen atoms.[1] Some of its derivatives are shown to be active as thromboxane A_2 synthetase inhibitors[2] and positive ionotropic agents.[3] The *de novo* synthesis of imidazo[1,5-*a*]pyridine nucleus having different substituents at pyridine[2–5] and at 3– and/or 1–positions of the imidazole[6–24] rings have been reported. This nucleus is generally generated from imines or methylamines derived from di-2-pyridyl ketone and 2-aminomethylpyridine or 2-cyanopyridine.



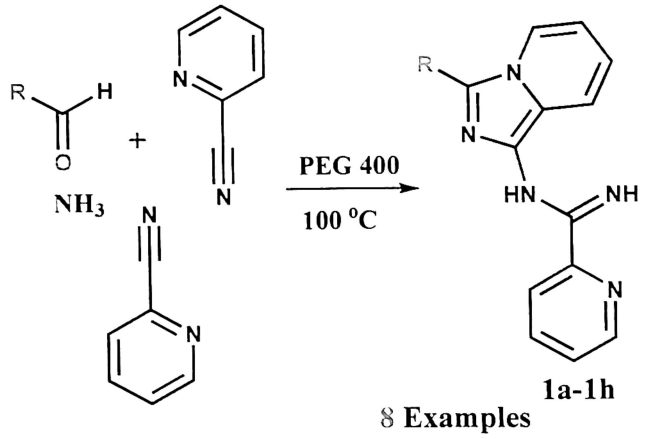
Tetrahedron Lett. **2010**, *51*, 828–831.

Synthesis of some 2,4,5-trisubstituted imidazoles and formation of imidazo[1,5-*a*]pyridine nucleus from a reaction between 2-cyanopyridine and picolylamines has been discussed in Chapter 2. This reaction is limited to *N*-(3-(2-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidines and they were obtained in low yields as minor product along with 2,4,6-tris(2-pyridyl)1,3,5-triazine, hence required further chromatographic separation. As its continuation, the reaction of 2-cyanopyridine with some aldehydes in presence of ammonium acetate has been examined. This reaction afforded 3-substituted imidazo[1,5-*a*]pyridine compounds having 1-(*N*-picolinamidin-2-yl) group, as clean unique product in good yields and the results are described here.

5.2. Results and Discussion

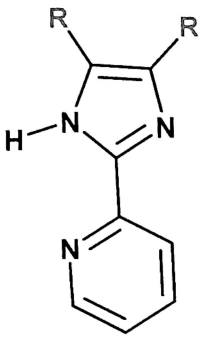
Heating a mixture of one equivalent of an aldehyde and two equivalents of 2-cyanopyridine along with ammonium acetate (as a source of free ammonia) in PEG-400 at 100 °C, yielded a viscous liquid which on pouring into water precipitated the product (Scheme 1) as solid. Thorough characterization of the solid confirmed the presence of 1,3-disubstitued imidazo[1,5-*a*]pyridine nucleus in which the 3–substitutent arise from the aldehyde and 1–substitutent arise from the 2-cyanopyridine (Scheme 1). It is important to note that one equivalent of 2-cyanopyridine is required to form the imidazo[1,5-*a*]pyridine nucleus while the second equivalent becomes part of amidine group. Attempts to isolate the 1–amino substituted imidazo[1,5-*a*]pyridine by using a 1:1 equivalent of the reactants (attempted only in the case of salicylaldehyde with 2-

cyanopyridine) could not succeed and led to 2,4,5-trisubstituted imidazole compound (*vide infra*).



Scheme 1. Synthesis of 3-substituted imidazo[1,5-*a*]pyridine compounds having 1-(*N*-picolinamidin-2-yl) group.

However, under the same experimental conditions performing the reaction with two equivalent of an aldehyde and one equivalent of 2-cyanopyridine yielded 2,4,5-trisubstitued imidazole compounds. In this case, the 4– and 5– substituents arise from the aldehyde group while that at 2– position arise from the nitrile reactant (Scheme 2). It is pertinent to note that the synthesis of 2,4,5-trisubstitued imidazole from 2:1 mixture of an aldehyde and 2-cyanopyridine has been reported by heating in microwave[25] and as well as by using various ratios[26] in hot acetic acid. Here the synthetic details of **2a–2c** have been provided and their spectroscopic data were identical.



2a, R = 2-hydroxyphenyl
2b, R = phenyl
2c, R = 2-thienyl

Scheme 2. General structure of compound **2**.

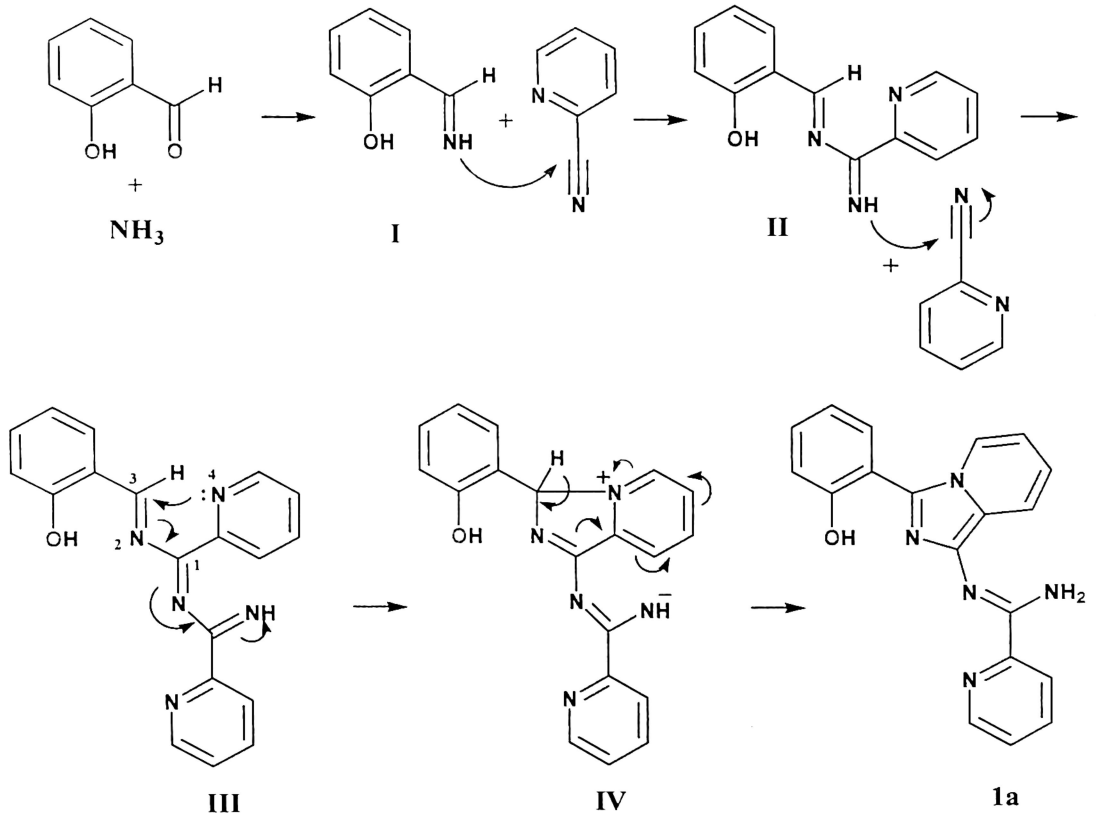
Hence by having control over stoichiometric ratio of aldehyde and 2-cyanopyridine, imidazo[1,5-*a*]pyridine or imidazole nuclei can be generated in PEG-400. To explore the scope of this reaction, eight aldehydes have been used for the synthesis of

imidazo[1.5-*a*]pyridine compounds. With aldehydes having heterocyclic or aromatic rings. the reaction afforded the expected products in very good yields. But only to test the use of PEG-400 for synthesis of imidazoles, three aldehydes were employed, in which their yields were good (Table 1) and has not examined any further.

Table 1: Synthesis of 3-substituted imidazo[1,5-*a*]pyridine compounds having 1-(*N*-picolinamidin-2-yl) group and 2,4,5-trisubstitued imidazole compounds.

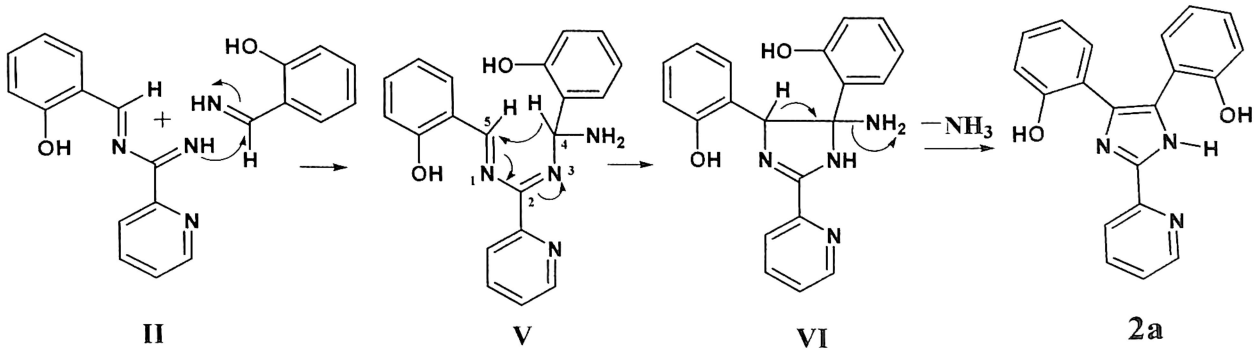
Entry	R group	Product	Yield (%)
1	2-Hydroxyphenyl	1a	83
2	Phenyl	1b	80
3	2-Thienyl	1c	65
4	4-Methoxyphenyl	1d	75
5	2-Pyrenyl	1e	82
6	9-Anthracenyl	1f	70
7	4-Methylphenyl	1g	78
8	2-Bromophenyl	1h	60
9	2-Hydroxyphenyl	2a	65
10	Phenyl	2b	70
11	2-Thienyl	2c	60

A plausible mechanism for the formation of **1a** is shown in Scheme 3. Salicylaldehyde is known to form an imine (**I**) with ammonia which can react further with 2-cyanopyridine to form an amidine (**II**). The amidine nitrogen of intermediate **II** can attack the carbon atom of another molecule of 2-cyanopyridine to form the diamidine intermediate **III**. The lone pair of electron on nitrogen atom–4 can attack carbon–3 of the diamidine group resulting in the formation of the fused five membered rings in **IV**. Subsequent proton removal and delocalization of the negative charge will lead to the final product **1a**.



Scheme 3. Plausible mechanism for the formation of **1a**.

A plausible mechanism for the formation of **2a** is shown in Scheme 4. The amidine nitrogen in **II** can attack the carbon atom of another molecule of imine (**I**) to generate the intermediate **V**. Attack by C(4)–H bond pair of electron on carbon–5 lead to formation of the sigma bond between them. This results in the generation of five-membered ring as in **VI**. Elimination of one molecule of ammonia will yield the final product **2a** that contain the imidazole ring.



Scheme 4. A plausible mechanism for the formation of **2a**.

All the compounds have been thoroughly characterized using various techniques. ^{1}H and ^{13}C NMR spectra of **1a-1h** are consistent with the expected structures. Characteristically, compounds **1a**, **1b**, **1d–1h** exhibit two distinct triplet at δ = 6.5–7.0

ppm in their ^{1}H NMR spectra for the fused pyridine ring of imidazo[1,5-*a*]pyridine nucleus, but **1c** exhibit a multiplet at $\delta = 6.7$ *ppm*. The molecular ion M$^+$+H peak in the HRMS/ESI-MS of **1a-1h**, were found at respective *m/z* values with good agreement. The molecular structure of **1a** has been determined by single crystal X-ray diffraction method (Table 2) which reveals the presence of 3-(2-hydroxyphenyl) substituted imidazo[1,5-*a*]pyridine compound having 1-(*N*-picolinamidin-2-yl) group. The molecular structure **2b** has also been determined (Table 2) and perspective views of **1a** and **2b** are shown in Figures 1 and 2, respectively.

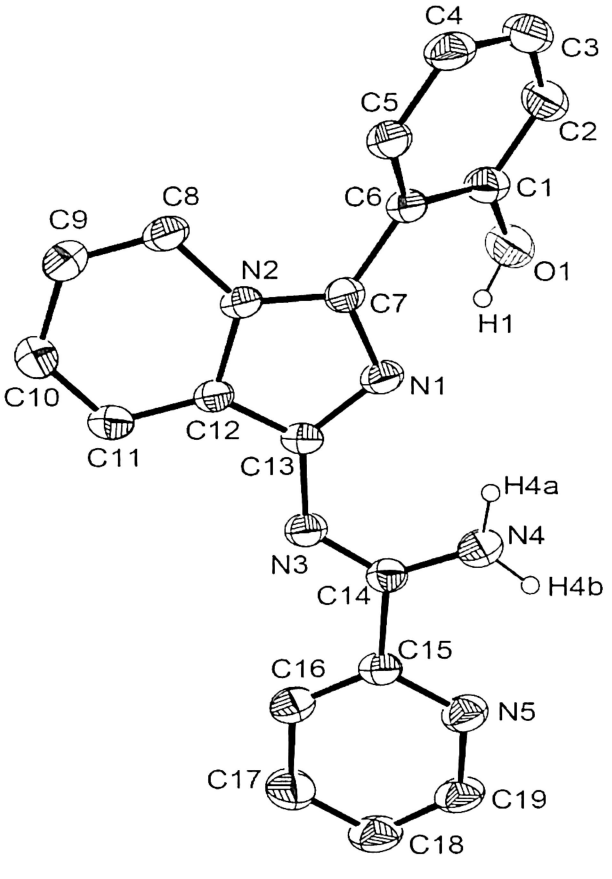


Figure 1. ORTEP (30% probability ellipsoids) plot of **1a**. Hydrogen atoms in the aromatic rings are omitted for clarity. Selected distances (Å): N2–C7 1.369(3), N2–C8 1.390(3), C8–C9 1.338(3), C10–C9 1.421(3), C11–C10 1.348(3), C12–C11 1.397(3), N2–C12 1.405(3), C12–C13 1.380(3), N1–C13 1.378(3), N1–C7 1.344(3), N3–C13 1.391(3), N3–C14 1.291(3), N4–C14 1.344(3).

5.3. Conclusion

In conclusion, this Chapter describes a simple and efficient method for the synthesis of 3-substituted 1-(*N*-2-picolinamidinyl)imidazo[1,5-*a*]pyridine by reacting an aldehyde and 2-cyanopyridine in 1:2 ratio with ammonium acetate in PEG-400 at 100

°C. On the other hand, 2,4,5-trisubstituted imidazoles were obtained by reacting an aldehyde and 2-cyanopyridine in 2:1 ratio under the same experimental conditions. This method can be useful for the synthesis of different imidazo[1,5-*a*]pyridines and 2,4,5-trisubstituted imidazoles using PEG as solvent.

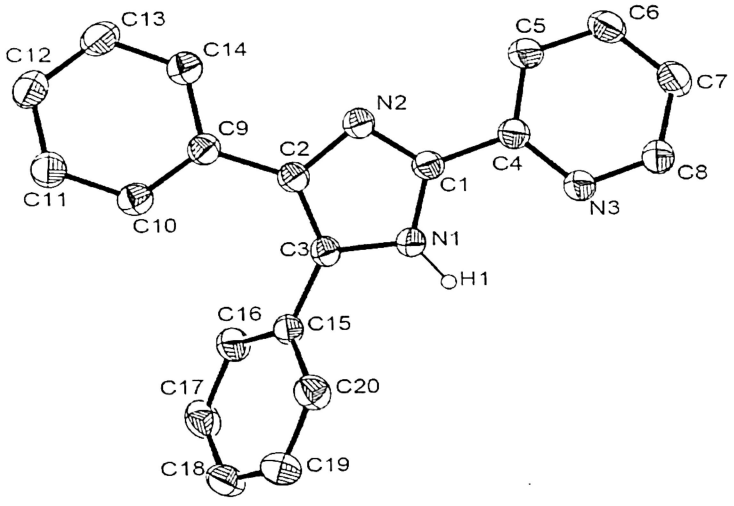


Figure 2. ORTEP (30% probability ellipsoids) plot of **2b**. Hydrogen atoms in the aromatic rings are omitted for clarity. Selected distances (Å): N1–C1 1.3620(18), N2–C1 1.3180(19), N2–C2 1.384(2), C2–C3 1.387(2), N1–C3 1.374(2).

5.4. Synthesis

***N*-(3-(2-Hydroxyphenyl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (1a)**: A mixture of salicylaldehyde (0.500 g, 4.13 mmol), 2-cyanopyridine (0.860 g, 8.26 mmol) and ammonium acetate (0.636 g, 8.26 mmol) in PEG-400 (2.0 g) was heated at 100 °C in an oil-bath for 12h. The mixture was cooled and then added to water (50 mL) with stirring. After stirring for 1h, the greenish-yellow precipitate was filtered washed with water and dried in vacuum over P_4O_{10} and recrystallized from dichloromethane. Crystals suitable for X-ray studies were obtained by slow evaporation of dichloromethane solution of **1a**. Yield: 1.13 g (83%). Compounds **1b–1h** were synthesized by adopting the same procedure described for **1a**, using 8.26 mmol of 2-cyanopyridine.

2-(2-Pyridyl)-4,5-bis(2-hydroxyphenyl)imidazole (2a): A mixture of salicylaldehyde (1.0 g, 8.26 mmol), 2-cyanopyridine (0.430 g, 4.13 mmol) and ammonium acetate (1.27 g, 16.52 mmol) in PEG-400 (2.0 g) was heated at 100 °C in an

oil-bath for 12h. The mixture was cooled and then added to water (50 mL) with stirring. After stirring for 1h, the yellow precipitate was filtered washed with water, dried in vacuum over P_4O_{10} and recrystallized from dichloromethane. Yield of **2a**: 0.89 g (65%).Compounds 2-(2-pyridyl)-4,5-bis(phenyl)imidazole (**2b**) and 2-(2-pyridyl)-4,5-bis(2-thienyl)imidazole (**2c**) were synthesized by adopting the same procedure described for **2a**.

5.5. References

1. Couty, F., Evano, G. In Comprehensive Heterocyclic Chemistry III; Katritzky, A. R.; Ramsden, C. A.; Eric, F.V. AAA.; Taylor, R. J. K. Eds. Elsevier Ltd.: 2008; Vol. 11, pp 435–443.
2. Ford, N. F.; Browne, L. J.; Campbell, T.; Gemenden, C.; Goldstein, R.; Gude, C.; Wasley, J. W. F. J. *Med. Chem.* **1985**, *28*, 164–170.
3. Davey, D.; Erhardt, P. W.; Lumma, W. C., Jr.; Wiggins, J.; Sullivan, M.; Pang, D.; Cantor, E. *J. Med. Chem.* **1987**, *30*, 1337–1342.
4. Browne, L. J.; Gude, C.; Rodriguez, H.; Steele, R. E. *J. Med. Chem.* **1991**, *34*, 725–736.
5. Davey, D. D. *J. Org. Chem.* **1987**, *52*, 1863–1867.
6. Bower, J. D.; Ramage, G. R. *J. Chem. Soc.* **1955**, 2834–2837.
7. Palacios, F.; Alonso, C.; Rubiales, G. *Tetrahedron* **1995**, *51*, 3683–3690.
8. Krapcho, A. P.; Powell, J. R. *Tetrahedron Lett.* **1986**, *27*, 3713–3714.
9. Sasaki, K.; Tsurumori, A.; Hirota, T. *J. Chem. Soc. Perkin Trans.1* **1998**, 3851–3856.
10. Katritzky, A. R.; Qiu, G. *J. Org. Chem.* **2001**, *66*, 2862–2864.
11. Bluhm, M. E.; Ciesielski, M.; Görls, H.; Döring, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 2962–2965.
12. Wang, J.; Mason, R.; VanDerveer, D.; Feng, K.; Bu, X. R.; *J. Org. Chem.* **2003**, *68*, 5415–5418.
13. Wang, J.; Dyers, Jr. L.; Mason, Jr. R.; Amoyaw, P.; Bu, X. R. *J. Org. Chem.* **2005**, *70*, 2353–2356.
14. Kim, D.; Wang, L.; Hale, J. J.; Lynch, C. L.; Budhu, R. J.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Hrin, R. C.; Carver, G.; Carella, A.; Henry, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129–2134.

15. Shibahara, F.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *Org. Lett.* **2006**, *8*, 5621–5624.

16. Shibahara, F.; Sugiura, R.; Yamaguchi, E.; Kitagawa, A.; Murai, T. *J. Org. Chem.* **2009**, *74*, 3566–3568.

17. Crawforth, J. M.; Paoletti, M. *Tetrahedron Lett.* **2009**, *50*, 4916–4918.

18. Shibahara, F.; Yamaguchi, E.; Kitagawa, A.; Imai, A.; Murai, T. *Tetrahedron* **2009**, *65*, 5062–5073.

19. Tahara, S.; Shibahara, F.; Maruyama, T.; Murai, T. *Chem. Commun.* **2009**, 7009–7011.

20. Arvapalli, V. S.; Chen, G.; Kosarev, S.; Tan, M. E.; Xie, D.; Yet, L. *Tetrahedron Lett.* **2010**, *51*, 284–286.

21. Zhang, A.; Zheng, X.; Fan, J.; Shen, W. *Tetrahedron Lett.* **2010**, *51*, 828–831.

22. Niyomura, O.; Yamaguchi, Y.; Tamura, S.; Minoura, M.; Okamoto, Y. *Chem. Lett.* **2011**, *40*, 449–451.

23. Huang, C.; Giokaris, A.; Gevorgyan, V. *Chem. Lett.* **2011**, *40*, 1053–1054.

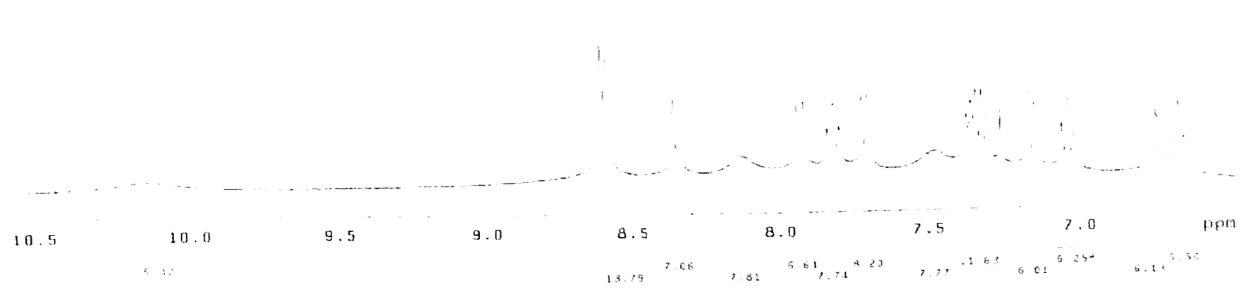
24. Yamaguchi, E.; Shibahara, F.; Murai, T. *Chem. Lett.* **2011**, *40*, 939–940.

25. Jiang, B.; Wang,X.; Shi, F.; Tu, S. J.; Ai, T.; Ballew, A.; Li, G. *J. Org. Chem.* **2009**, *74*, 9486–9489.

26. Wu, X.; Jiang, R.; Xu, X.; Su, X.; Lu, W.; Ji, S. *J. Comb. Chem.* **2010**, *12*, 829–835.

5.6. Spectral data

***N*-(3-(2-Hydroxyphenyl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (1a)**: mp. 198 °C; HRMS-Mass: calcd. for $C_{19}H_{15}N_5O^+$ 329.1277 found (M^++H) 330.1288. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 10.10 (1H, s), 8.60 (2H, d, 7.2), 8.35 (1H, d, 7.2), 8.13 (1H, s), 7.93 (1H, d, 8.8), 7.82 (1H, t, 8.8), 7.71 (1H, d, 7.6), 7.50 (1H, s), 7.34 (2H, m), 7.16 (1H, d, 9.2), 7.04 (1H, t, 8.8), 6.75 (1H, t, 6.4), 6.68(1H, t, 6.0). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 155.5, 152.5, 150.7, 148.2, 138.7, 136.6, 130.2, 130.0, 125.4, 125.0, 125.0, 121.7, 121.0, 120.0, 120.0, 118.0, 117.5, 115.5, 115.0. FTIR (KBr, cm^{-1}): 3080, 3046, 1625, 1580, 1563, 1533, 1508, 1467, 1436, 1396, 1369, 1314, 1283, 1249, 1230, 1158, 1140, 1089, 1039, 994, 957, 870, 826, 796, 770, 747, 731, 703, 689, 656, 488, 470. Anal. calcd. for $C_{19}H_{15}N_5O$: C, 69.29; H, 4.59; N, 21.26%. Found: C, 69.20; H, 4.54; N, 21.19%.

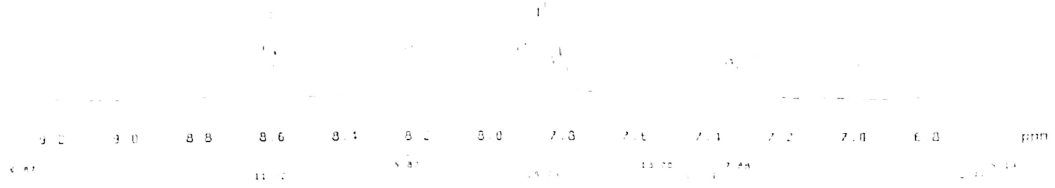


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-(3-(2-hydroxyphenyl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1a**).

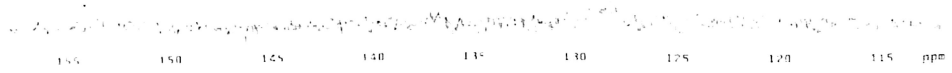
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of *N*-(3-(2-hydroxyphenyl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1a**).

***N*-(3-PhenylH-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (1b)**: Yield: 1.03 g (80%). mp. 188°C; HRMS-Mass: calcd. for $C_{19}H_{15}N_5^+$ 313.1327 found (M^++H) 314.1328. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 9.30 (1H, s), 8.60 (2H, t, 8), 8.22 (1H, d, 7.2), 7.85 (4H, m), 7.53 (2H, t, 8.0), 7.42 (2H, t, 7.2), 7.33 (1H, t, 7.6), 6.78 (1H, t, 6.4), 6.60 (1H, t, 7.2). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 153.0, 151.0, 148.1, 141.0, 136.4, 133.0, 131.0, 129.1, 128.3, 127.8, 125.5, 124.3, 122.0, 120.5, 120.0, 117.0, 115.0. FTIR (KBr, cm^{-1}): 3048, 1620, 1584, 1563, 1531, 1515, 1506, 1468,

1415, 1380, 1324, 1307, 1252, 1235, 1177, 1156, 1137, 1077, 1044, 996, 954, 816, 795, 761, 775, 736, 707, 660, 623, 599, 571, 493, 475. Anal. calcd. for $C_{19}H_{15}N_5$: C, 72.83; H, 4.82; N, 22.35%. Found: C, 72.75; H, 4.80; N, 22.32%.

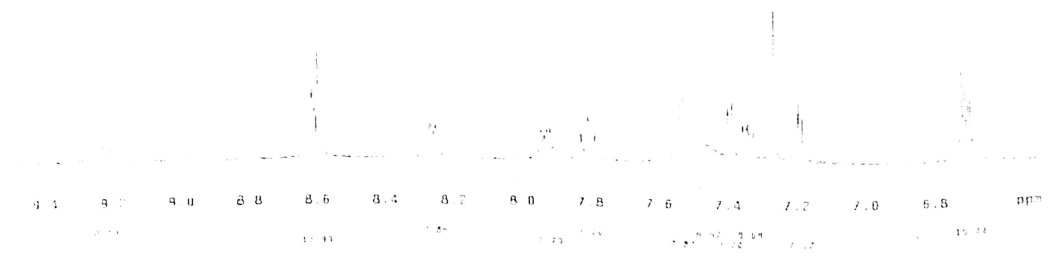


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-(3-phenylH-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1b**).



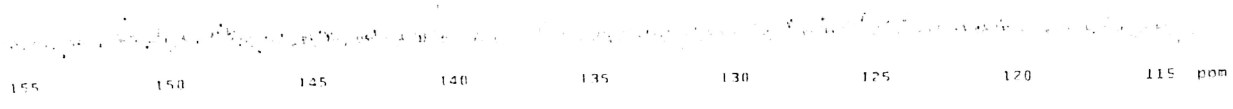
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of *N*-(3-phenylH-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1b**).

***N*-(3-(Thiophen-2-yl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine** (**1c**): Yield: 0.86 g (65%). mp. 170°C; HRMS-Mass: calcd. for $C_{17}H_{13}N_5S^+$ 319.0892 found (M^++H) 320.0893. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 9.23 (1H, s), 8.60 (2H, m), 8.26 (1H, d, 8.4), 7.92 (1H, t, 8.0), 7.80 (1H, t, 7.6), 7.50 (1H, d, 4.4), 7.50 (1H, s), 7.40 (1H, d, 6), 7.34 (1H, t, 6.4), 7.20 (1H, t, 3.2), 6.70 (2H, m). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 153.0, 151.0, 148.2, 148.1, 140.6, 136.4, 133.0, 128.0, 126.0, 125.2, 124.4, 124.0, 121.6, 121.0, 120.0, 117.0, 115.2. FTIR (KBr, cm^{-1}): 1635, 1619, 1591, 1562, 1530,



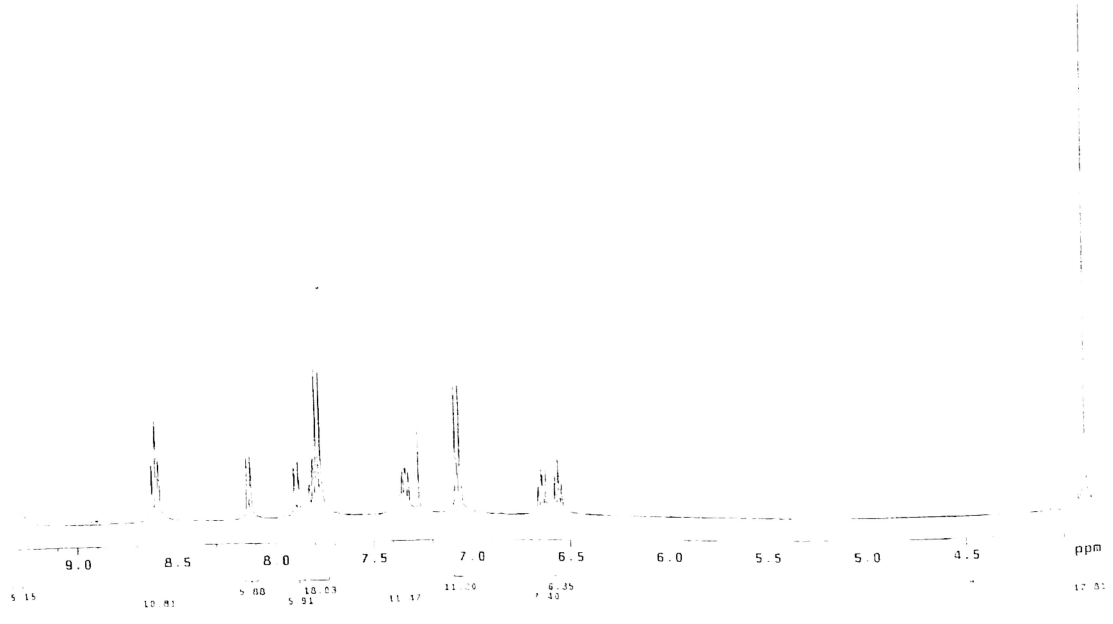
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-(3-(thiophen-2-yl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1c**).

1497, 1472, 1447, 1410, 1391, 1320, 1300, 1245, 1146, 1097, 1048, 1030, 997, 908, 843, 797, 742, 729, 714, 684, 648, 625, 572, 523, 489. Anal. calcd. for $C_{17}H_{13}N_5S$: C, 63.93; H, 4.10; N, 21.93%. Found: C, 63.88; H, 4.08; N, 21.85.%



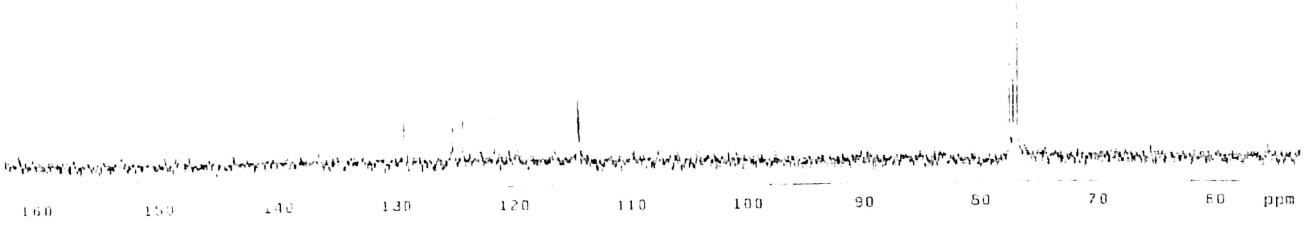
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of *N*-(3-(thiophen-2-yl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1c**).

***N*-(3-(4-Methoxyphenyl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (1d)**: Yield: 1.06 g (75%). mp. 165°C; HRMS-Mass: calcd. for $C_{20}H_{17}N_5O^+$ 343.1433, found 344.1576 (M^++H) . 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 9.30 (1H, s), 8.60(2H, d, 8.8), 8.13 (1H, d, 7.2), 7.90 (1H, d, 9.2), 7.80 (3H, m), 7.38 (1H, s), 7.32 (1H, t, 7.2), 7.06 (2H, d, 8.4), 6.63 (1H, t, 9.2), 6.65 (1H, t, 11.2), 3.09 (3H, s). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 159.8, 153.0, 150.70, 150.64, 148.1, 136.5, 133.0, 129.3, 125.2, 124.3, 123.2, 121.6, 120.4, 119.7, 116.5, 114.5, 114.4, 55.6. FTIR (KBr, cm^{-1}): 1636, 1625, 1584, 1562, 1523, 1470, 1382, 1312, 1284, 1247, 1235, 1186, 1176, 1135, 1111, 1049,



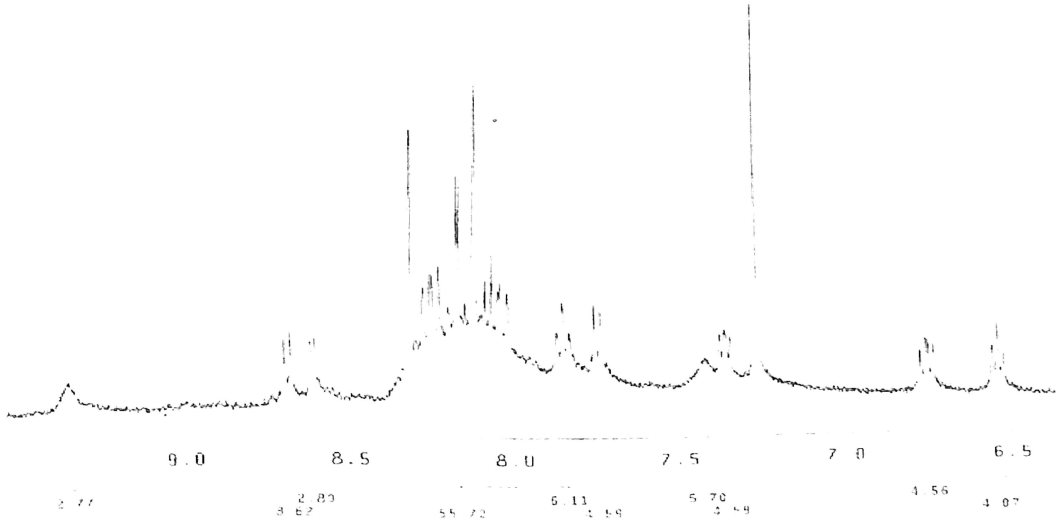
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-(3-(4-methoxyphenyl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1d**).

1036, 1017, 994, 954, 838, 802, 749, 723, 707, 681, 616, 579, 501, 486, 446, 429. Anal. calcd. for $C_{20}H_{17}N_5O$: C, 69.96; H, 4.99; N, 20.40%. Found: C, 69.82; H, 4.93; N, 20.33%.

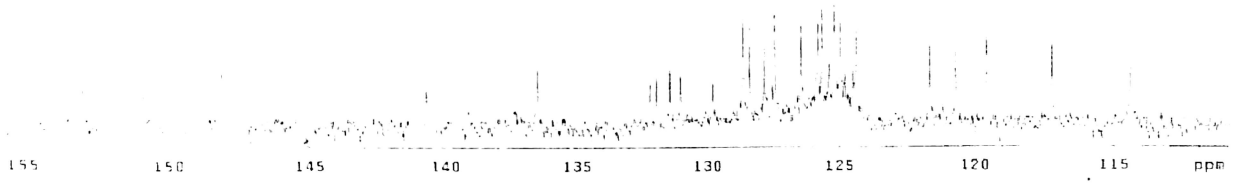


^{13}C NMR (100 MHz, $CDCl_3$) spectrum of *N*-(3-(4-methoxyphenyl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1d**).

***N*-(3-(Pyren-2-yl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine** (**1e**): Yield: 1.48 g (82%). mp. 214°C; HRMS-Mass: calcd. for $C_{29}H_{19}N_5^+$ 437.1640, found (M^++H) 438.1929. 400 MHz ^1H NMR (δ (*J*, Hz), $CDCl_3$): 9.35 (1H, s), 8.70(1H, d, 8.0), 8.60 (1H, d, 4.8), 8.20 (10H, m), 7.85 (1H, t, 7.6), 7.70 (1H, d, 7.6), 7.42 (1H, s), 7.40 (1H, t, 5.6), 6.76 (1H, t, 6.4), 6.55 (1H, t, 7.2). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 153.0, 151.0, 148.1, 141.0, 136.5, 132.2, 132.0, 131.4, 131.0, 131.0, 129.0, 128.4, 128.0, 127.4, 126.4, 126.0, 125.6, 125.4, 125.1, 125.0, 124.7, 124.5, 124.3, 122.0, 121.0, 119.5, 117.2, 114.4. FTIR (KBr, cm^{-1}): 1619, 1586, 1563, 1532, 1500, 1467, 1443, 1385, 1316, 1253, 1179, 1141, 1096, 1064, 994, 950, 847, 832, 801, 746, 729, 715, 682, 642. Anal. calcd. for $C_{29}H_{19}N_5$: C, 79.60; H, 4.38; N, 16.01%. Found: C, 79.42; H, 4.28; N, 15.94%.

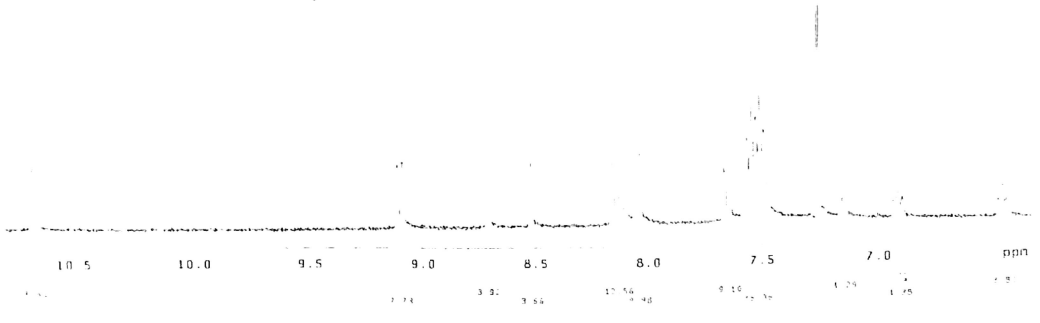


^1H NMR (400 MHz, $CDCl_3$) spectrum of *N*-(3-(pyren-2-yl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1e**).

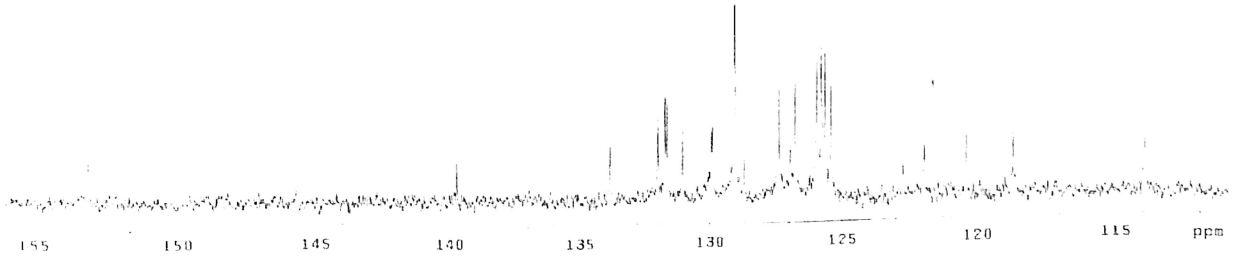


^{13}C NMR (100 MHz, $CDCl_3$) spectrum of *N*-(3-(pyren-2-yl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1e**).

***N*-(3-(Anthracen-9-yl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine** (**1f**): Yield: 1.19 g (70%). mp. 240°C; HRMS-Mass: calcd. for $C_{27}H_{19}N_5^+$ 413.1640 found (M^++H) 414.1781. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 10.70 (1H, s), 9.10 (2H, d, 8.8), 8.70 (1H, s), 8.52 (1H, s), 8.13 (3H, m), 8.05 (2H, d, 8.0), 7.70 (2H, d, 8.4), 7.54 (4H, m), 7.15 (1H, d, 6.8), 7.00 (1H, t, 6.4), 6.50 (1H, t, 6.8). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 153.1, 140.0, 134.0, 132.0, 132.0, 132.0, 131.0, 130.0, 130.0, 129.0, 129.0, 127.3, 127.0, 127.0, 126.0, 126.0, 126.0, 125.4, 123.0, 122.0, 120.4, 118.6, 114.0. FTIR (KBr, cm^{-1}): 3048, 1621, 1550, 1505, 1441, 1365, 1314, 1294, 1230, 1134, 1096, 1051, 1014,



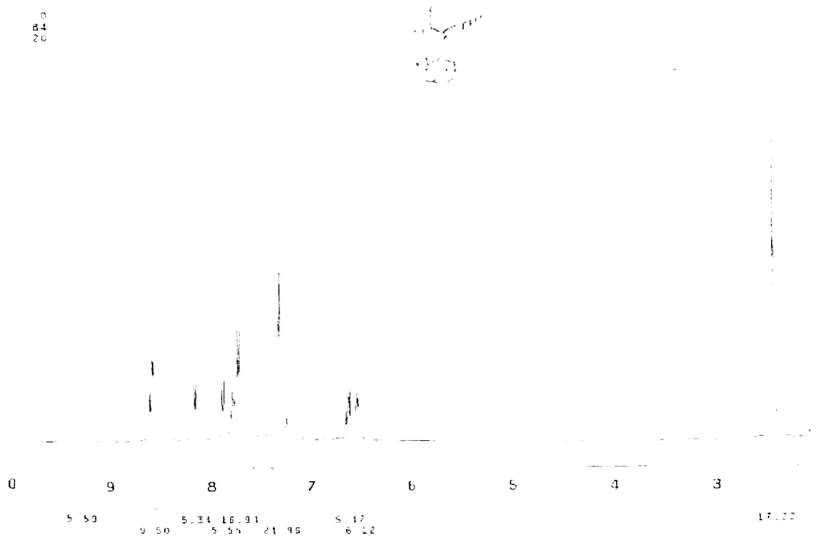
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-(3-(anthracen-9-yl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1f**).



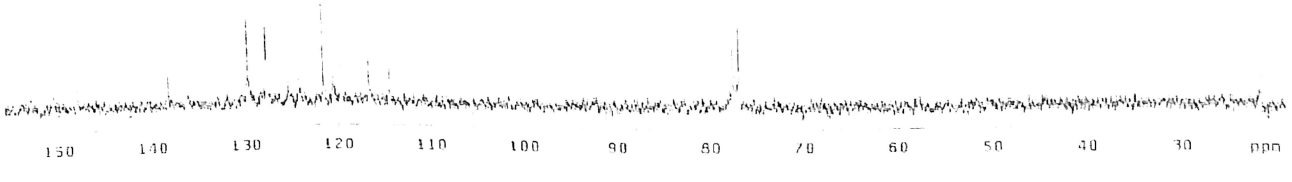
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of *N*-(3-(anthracen-9-yl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1f**).

990, 955, 914, 888, 849, 787, 760, 728, 707, 590, 571, 538, 512. Anal. calcd. for $C_{27}H_{19}N_5$: C, 78.43; H, 4.63; N, 16.94%. Found: C, 78.30; H, 4.57; N, 16.91%.

***N*-(3-*p*-TolylH-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (1g)**: Yield: 1.05 g (78%). mp. 164°C; HRMS-Mass: calcd. for $C_{20}H_{17}N_5^+$ 327.1484 found (M^++H) 328.1643. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 9.30 (1H, s), 8.60 (2H, m), 8.16 (1H, d, 10.8), 7.90 (1H, d, 8.4), 7.79 (1H, t, 12.0), 7.73 (2H, d, 8.0), 7.33 (4H, m), 6.64 (1H, t, 6.4), 6.55 (1H, t, 6.8), 2.43 (3H, s). 100 MHz ^{13}C NMR (δ, $CDCl_3$):153.0, 150.6, 148.0, 140.4, 138.2, 136.4, 133.0, 130.0, 128.0, 128.0, 125.3, 124.2, 121.5, 120.4, 119.6, 116.5, 114.4, 21.5. FTIR (KBr, cm^{-1}):3423, 3278, 3054, 2994, 2912, 2851, 1633, 1621, 1587, 1559, 1523, 1504, 1469, 1446, 1388, 1311, 1297, 1251, 1185, 1135, 1108, 1033, 995, 954, 824, 801, 748, 727, 714, 626, 577, 503. Anal. calcd. for $C_{20}H_{17}N_5$: C, 73.37; H, 5.23; N, 21.39%. Found: C, 73.25; H, 5.20; N, 21.32%.

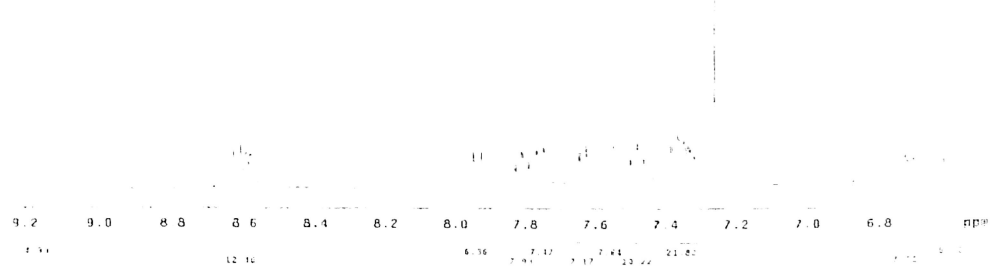


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-(3-*p*-tolylH-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1g**).

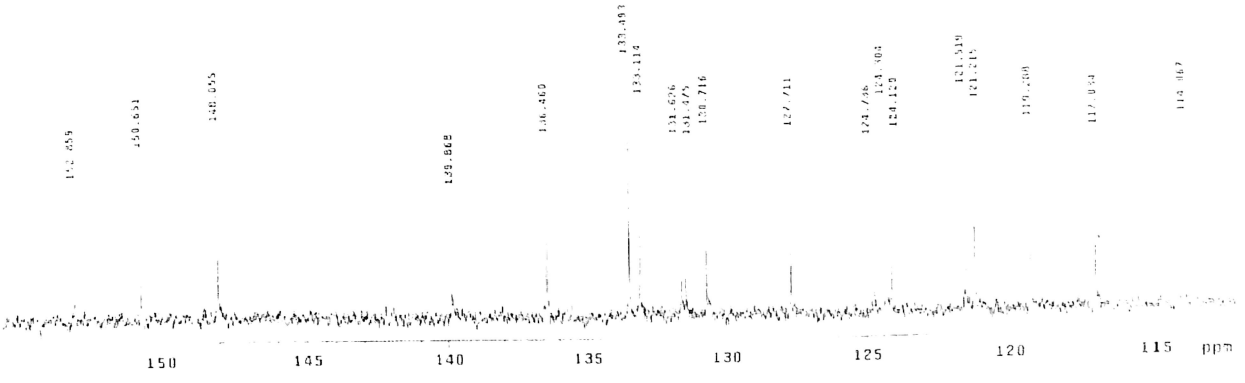


^{13}C NMR (100 MHz, $CDCl_3$) spectrum of *N*-(3-*p*-tolylH-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1g**).

***N*-(3-(2-Bromophenyl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine** (**1h**): Yield: 0.97 g (60%). mp. 174°C; HRMS-Mass: calcd. for $C_{19}H_{14}BrN_5^+$ 391.0433 found (M^++^{23}Na) 414.0693. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 9.20 (1H, s), 8.60 (2H, m), 7.94 (1H, d, 8.8), 7.81 (1H, t, 7.6), 7.76 (1H, d, 8.4), 7.64 (1H, d, 7.6), 7.57 (1H, d, 7.2), 7.48 (1H, t, 7.6), 7.36 (3H, m), 6.73 (1H, t, 6.4), 6.61 (1H, t, 7.2). 100 MHz ^{13}C NMR (δ, $CDCl_3$):153.0, 151.0, 148.0, 140.0, 136.5, 133.5, 133.1, 131.6, 131.5, 131.0, 128.0, 125.0, 124.3, 124.2, 121.5, 121.2, 119.3, 117.0, 114.0. FTIR (KBr, cm^{-1}): 3459, 3324, 3192, 2976, 2919, 1618, 1587, 1562, 1504, 1428, 1370, 1295, 1266, 1248, 1204, 1180, 1135, 1059, 992, 891, 812, 796, 752, 732, 694, 640, 570, 524, 456. Anal. calcd. for $C_{19}H_{14}BrN_5$: C, 58.18; H, 3.60; N, 17.85%. Found: C, 58.05; H, 3.52; N, 17.76%.



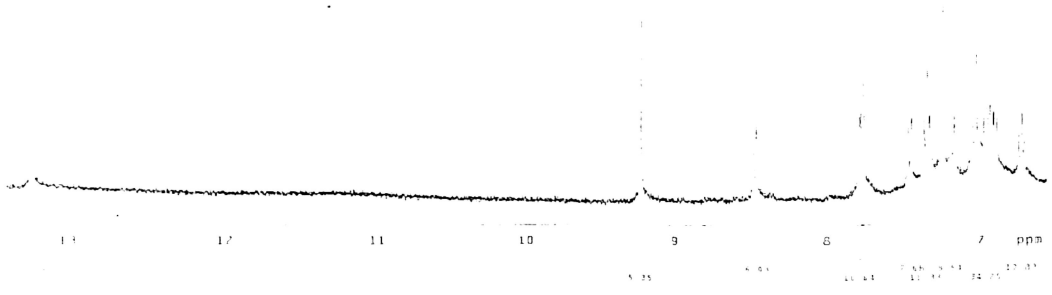
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-(3-(2-bromophenyl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1h**).



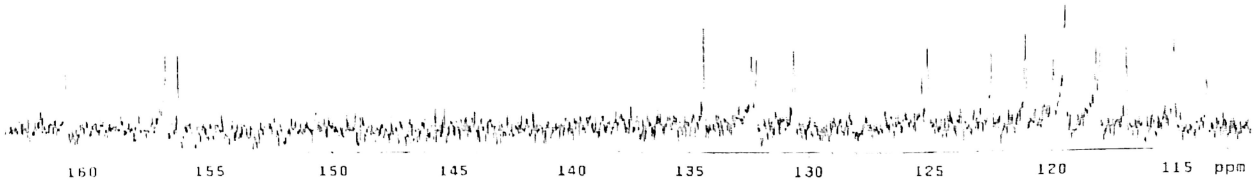
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of *N*-(3-(2-bromophenyl)H-imidazo[1,5-*a*]pyridin-1-yl)picolinamidine (**1h**).

2-(2-Pyridyl)-4,5-bis(2-hydroxyphenyl)imidazole (**2a**): mp. 198°C; HRMS-Mass: calcd. for $C_{19}H_{15}N_5O^+$ 329.1277 found (M^++H) 330.1288. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 10.10 (1H, s), 8.60 (2H, d, 7.2), 8.35 (1H, d, 7.2), 8.13 (1H, s), 7.93 (1H, d, 8.8), 7.82 (1H, t, 8.8), 7.71 (1H, d, 7.6), 7.50 (1H, s), 7.34 (2H, m), 7.16 (1H, d, 9.2),

7.04 (1H, t, 8.8), 6.75 (1H, t, 6.4), 6.68(1H, t, 6.0). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 155.5, 152.5, 150.7, 148.2, 138.7, 136.6, 130.2, 130.0, 125.4, 125.0, 125.0, 121.7, 121.0, 120.0, 120.0, 118.0, 117.5, 115.5, 115.0.

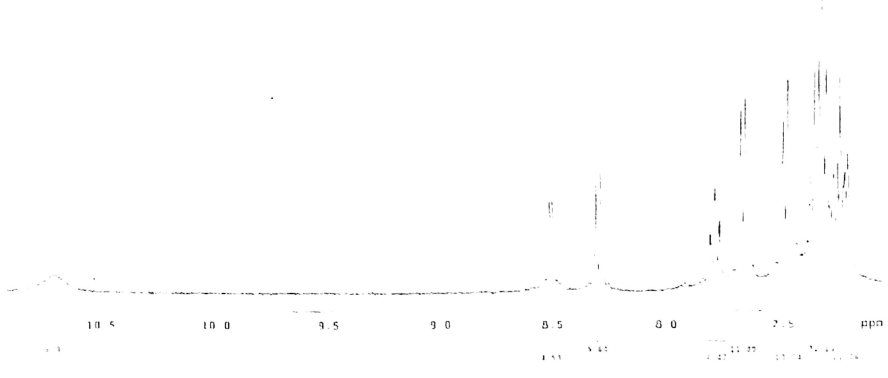


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2-(2-pyridyl)-4,5-bis(2-hydroxyphenyl)imidazole (**2a**).

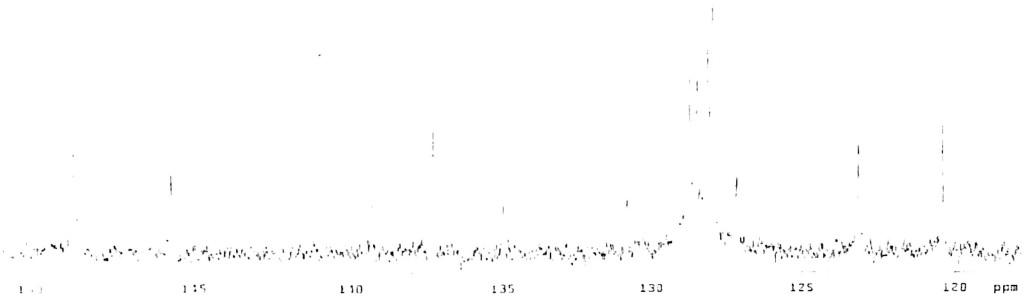


^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 2-(2-pyridyl)-4,5-bis(2-hydroxyphenyl)imidazole (**2a**).

2-(2-pyridyl)-4,5-bis(phenyl)imidazole (2b): mp. 188°C; HRMS-Mass: calcd. for $C_{19}H_{15}N_5^+$ 313.1327 found (M^++H) 314.1328. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 9.30 (1H, s), 8.60 (2H, t, 8), 8.22 (1H, d, 7.2), 7.85 (4H, m), 7.53 (2H, t, 8.0), 7.42 (2H, t, 7.2), 7.33 (1H, d, 7.6), 6.78 (1H, t, 6.4), 6.60 (1H, t, 7.2). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 153.0, 151.0, 148.1, 141.0, 136.4, 133.0, 131.0, 129.1, 128.3, 127.8, 125.5, 124.3, 122.0, 120.5, 120.0, 117.0, 115.0.

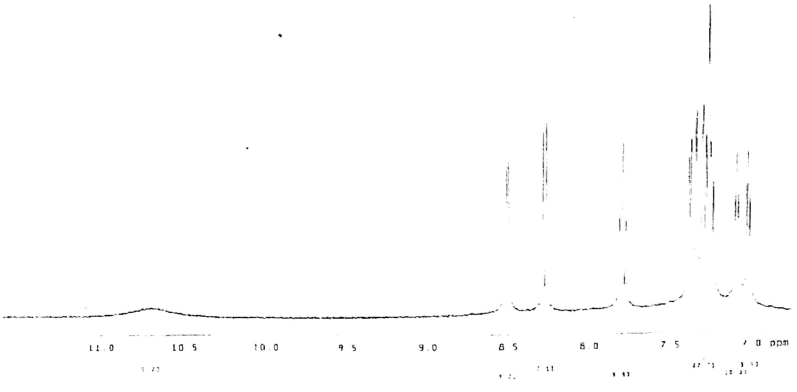


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2-(2-pyridyl)-4,5-bis(phenyl)imidazole (**2b**).

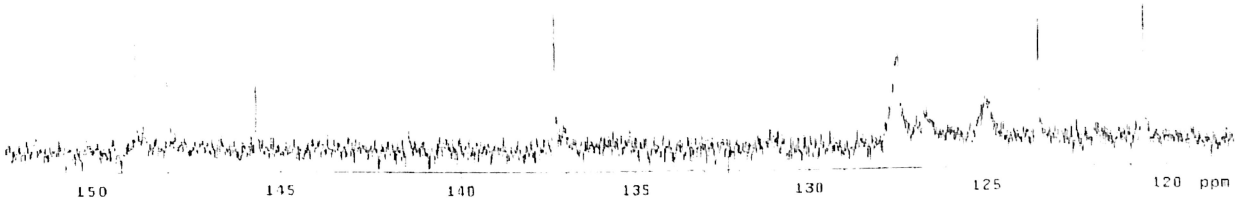


^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 2-(2-pyridyl)-4,5-bis(phenyl)imidazole (**2b**).

2-(2-pyridyl)-4,5-bis(2-thienyl)imidazole (**2c**): mp. 170°C; HRMS-Mass: calcd. for $C_{17}H_{13}N_5S^+$ 319.0892 found (M^++H)320.0893. 400 MHz ^1H NMR (δ (*J*, Hz), $CDCl_3$): 9.23 (1H, s), 8.60 (2H, m), 8.26 (1H, d, 8.4), 7.92 (1H, t, 8.0), 7.80 (1H, t, 7.6), 7.50 (1H, d, 4.4), 7.50 (1H, s), 7.40 (1H, d, 6), 7.34 (1H, t, 6.4), 7.20 (1H, t, 3.2), 6.70 (2H, m). 100 MHz ^{13}C NMR (δ, $CDCl_3$): 153.0, 151.0, 148.1, 140.6, 136.4, 133.0, 128.0, 126.0, 125.2, 124.4, 124.0, 121.6, 121.0, 120.0, 117.0, 115.2.



^1H NMR (400 MHz, $CDCl_3$) spectrum of 2-(2-pyridyl)-4,5-bis(2-thienyl)imidazole (**2c**).



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 2-(2-pyridyl)-4,5-bis(2-thienyl)imidazole (**2c**).

Table 1. Crystallographic data for **1a** and **2b**.

	1a	**2b**
Formula	$C_{19}H_{15}N_5O$	$C_{20}H_{14}N_3$
Formula weight	329.34	296.34
T (K)	296(2)	296(2)
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$C2/c$
a (Å)	8.9812(7)	23.5453(12)
b (Å)	12.1712(11)	11.1287(7)
c (Å)	15.0575(13)	13.0794(7)
α (°)	90.00	90.00
β (°)	100.863(6)	116.320(5)
γ (°)	90.00	90.00
V (Å^3)	1616.5(2)	3071.9 (3)
Z	4	8
D_{calc} (g cm^{-3})	1.345	1.282
μ (mm^{-1})	0.88	0.77
F (000)	680	1240
R_{int}	0.0487	0.0598
Goodness-of-fit (GOF)[a] on F^2	1.045	1.009
R_1[b], wR_2[c] ($I \geq 2\sigma(I)$)	0.0399, 0.1030	0.0423, 0.1037
R_1[b], wR_2[c] (all data)	0.0487, 0.1104	0.0598, 0.1150

[a] $GOF = [\sum[w(F_0^2 - F_c^2)^2] / M - N]^{1/2}$ (M = number of reflections, N = number of parameters refined).
[b] $R_1 = \sum ||F_0| - |F_c|| / \sum |F_0|$.
[c] $wR_2 = [\sum[w(F_0^2 - F_c^2)^2] / \sum[w(F_0^2)^2]]^{1/2}$.

Chapter 6

Reaction of Amidines and Diamidines Derived From 2-Cyanopyridine With Copper(II) Salts

Abstract: In air, methanolic solution of *N*'-((2-pyridyl)methyl)picolinamidine (**L3**) or *N*'-(((2-pyridyl)methylimino)(2-pyridyl)methyl)picolinamidine (**L4**), on stirring with one equivalent of $Cu(OAc)_2 \cdot H_2O$, afforded $[Cu(\mathbf{L5})(OAc)(H_2O)] \cdot H_2O$ (**1**) {**L5** = bis(2-pyridylcarbonyl)amide ion} in good yields. The complex $[Cu(\mathbf{L6})(H_2O)_3](NO_3)_2 \cdot 3H_2O$ (**2**) {**L6** = 2-phenyl-4,6-di(2′-pyridyl)-1,3,5-triazine} was isolated by stirring *N*'-((benzylimino)(2-pyridyl)methyl)picolinamidine (**L7**) and $Cu(NO_3)_2 \cdot 3H_2O$ in methanol. The reaction of *N*'-benzylpicolinamidine (**L8**) with $Cu(NO_3)_2 \cdot 3H_2O$ afforded a complex of composition $[Cu(\mathbf{L8})_2(H_2O)(NO_3)]NO_3$ (**3**). The molecular structures of **1**–**3** were determined by single crystal X-ray diffraction method.

6.1. Introduction

Amidines are addition compounds formed by the nucleophilic attack of an amine group at the carbon atom of an organonitrile.[1] Various routes of synthesis of amidines derived from 2-cyanopyridine has been reviewed in Chapter 1.

An attempt has been made to isolate the diamidines derived using 2-picolylamine and benzylamine. In this Chapter, results of reaction of these two diamidines with copper(II) salts are described. In addition, the reaction product of amidine (derived using 2-picolylamine and benzylamine) with copper(II) salts are also described

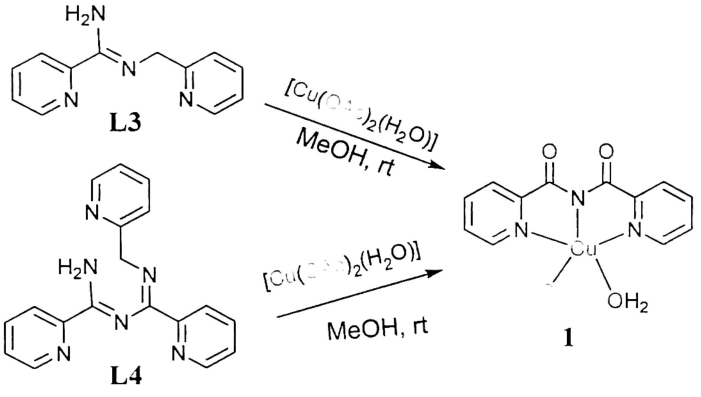
6.2. Results and Discussion

The amidines, *N*'-((2-pyridyl)methyl)picolinamidine (**L3**) and *N*'-benzylpicolinamidine (**L8**), are reported to be formed on reacting a 1:1 mixture of 2-cyanopyridine and appropriate amine.[2] Since the diamidine *N*'-(((2-pyridyl)methylimino)(2-pyridyl)methyl)picolinamidine (**L4**) is crucial in the formation of imidazole and imidazo[1,5-*a*]pyridines as discussed in Chapter 2, an attempt has been made to isolate the diamidines derived using 2-picolylamine and benzylamine. But both diamidines **L4** and *N*'-((benzylimino)(2-pyridyl)methyl)picolinamidine (**L7**) {formed from benzylamine} could not be isolated in their pure forms. While **L4** converted to 2,4,5-tris(2-pyridyl)imidazole and *N*-(3-(2-pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine, **L7** converted to amidine **L8** on eluting them through alumina column. Hence, reaction of **L4** and **L7** with copper(II) salts was examined.

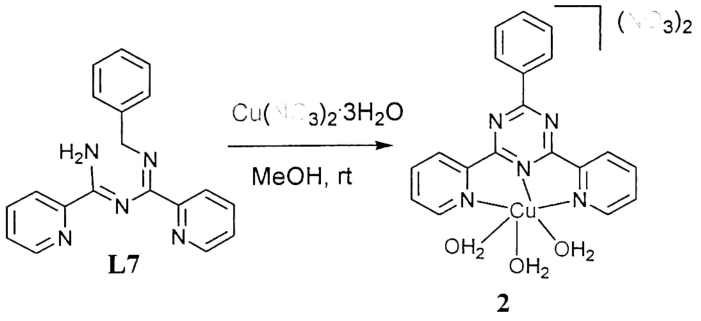
On stirring in air, **L3** or **L4** and $Cu(OAc)_2 \cdot H_2O$, in methanol afforded the complex of composition $[Cu(\mathbf{L5})(OAc)(H_2O)] \cdot H_2O$ (**1**) {**L5** = bis(2-pyridylcarbonyl)amide ion}. In the case of reaction of **L3** with copper(II) acetate, hydrolysis of $-NH_2$ group and oxidation of the methylene function has occurred. Similarly reaction of **L4** with copper(II) acetate, resulted in hydrolysis of ((2-pyridyl)methylimino)picolinamidine group and oxidation of the methylene function (Scheme 1).

The complex $[Cu(\mathbf{L6})(H_2O)_3](NO_3)_2 \cdot 3H_2O$ (**2**) {**L6** = 2-phenyl-4,6-di(2-pyridyl)-1,3,5-triazine, which is useful ligand for designing multinuclear metal complexes[3, 4]} was isolated by stirring **L7** and $Cu(NO_3)_2 \cdot 3H_2O$ (Scheme 2) in methanol. Oxidation of the methylene group followed by condensation of the resultant carbonyl function with amidine is the essential step in formation of the triazine ring. Reaction of **L8** with $Cu(NO_3)_2 \cdot 3H_2O$ afforded a complex having composition $[Cu(\mathbf{L8})_2(H_2O)(NO_3)]$

$NO_3 \cdot H_2O$ (**3**). The molecular structures of **1**–**3** have been confirmed by single crystal X-ray diffraction methods.

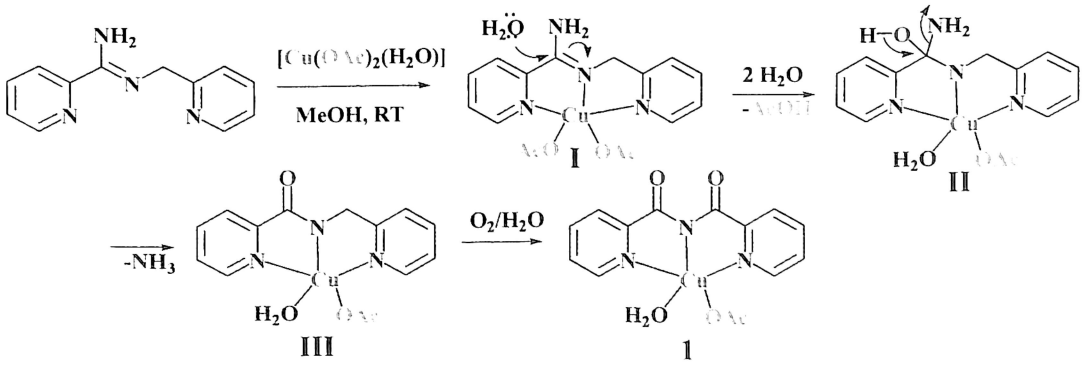


Scheme 1. Reaction of **L3** and **L4** with $Cu(OAc)_2 \cdot H_2O$.



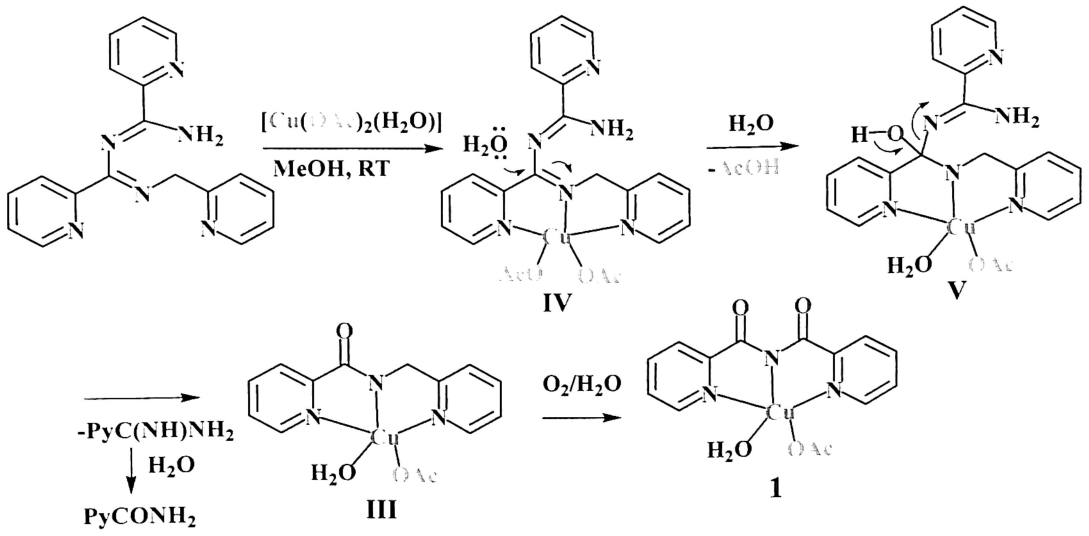
Scheme 2. Reaction of **L7** with $Cu(NO_3)_2 \cdot 3H_2O$.

A plausible mechanism for the conversion of **L3** to **1** is shown in Scheme 3. Coordination of one molecule of **L3** at the copper atom to form **I** in which copper(II) ion is bound by a neutral tridentate ligand **L3** and two acetate ions. Attack by a water molecule at the C=N bond will allow the negative charge to reside on the resultant amide-N atom. This will also lead to the replacement of the coordinated acetate ion by a water molecule as shown in **II**. Elimination of ammonia molecule from tetrahedral carbon lead to intermediate **III** that contain *N*-(2-picolyl)picolinamide moiety. Oxidation of methylene group (attached by a 2-pyridyl and an amide/imine function is know in only few cases[5]) will lead to the final product **1**.



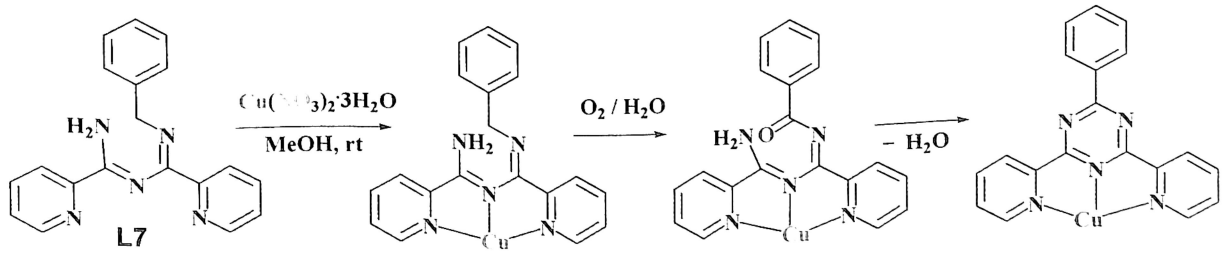
Scheme 3. A plausible mechanism for the formation of **1** from **L3**.

A plausible mechanism for the conversion of **L4** to **1** is shown in Scheme 4. Coordination of one molecule of **L4** at the copper atom to form **IV** in which copper(II) ion is bound by a neutral tridentate ligand **L4** and two acetate ions. Attack by a water molecule at the C=N bond will allow the negative charge to reside on the resultant amide-N atom. This will also lead to the replacement of the coordinated acetate ion by a water molecule as shown in **V**. Elimination of picolinamidine molecule from tetrahedral carbon lead to intermediate **III** which will lead to the final product **1**, as noted earlier.



Scheme 4. A plausible mechanism for the formation of **1** from **L4**.

A plausible mechanism for the conversion of **L7** to **2** is shown in Scheme 3. Coordination of **L7** as tridentate ligand to a copper(II) center (other coligands and overall charge on the molecule are not shown) followed by oxidation of the methylene group and condensation of resultant carbonyl function with amidine $-NH_2$ group are the essential steps in the formation of the final product containing $[Cu(\mathbf{L6})(H_2O)_3]^+$ ion. It is pertinent to note that **L6** has been synthesized by reacting the amidinide salt (obtained *in situ* from benzonitrile and lithium dimethylamide) with two equivalents of 2-cyanopyridine.[5]



Scheme 5. A plausible mechanism for the formation of [Cu(**L6**)] unit from **L7** (Other coligands and overall charge on the molecule are not shown).

6.3. Molecular Structures

The molecular structures of **1–3** were established by single crystal X-ray diffraction methods and the crystal data are listed in Table 1. The crystallographic and bond parameters of **1** (prepared by the procedure reported here) are identical to that reported for **1** prepared from other three routes *viz.*, by reacting $Cu(OAc)_2 \cdot H_2O$ with (*i*) 2,4,6-tris(2-pyridyl)-1,3,5-triazine[6] (*ii*) 2-picolylamine[5c] and (*iii*) *N*-(2-pyridylmethyl)-pyridine-2-carbaldimine.[5b] Hence its structural details are not elaborated further but a perspective view is shown in Figure 1.

Compound **2** crystallized in *C*2/*c* space group and the asymmetric unit consists of half molecule of $[Cu(\mathbf{L6})(H_2O)_3]$ unit (in which the C_2-axis passes through the atoms O1Cu1N2C7C8C11), one nitrate ion and 1.5 molecules of water. Hence the overall formula $[Cu(\mathbf{L6})(H_2O)_3](NO_3)_2 \cdot 3H_2O$ is consistent. A perspective view of the $[Cu(\mathbf{L6})(H_2O)_3]$ unit is shown in Figure 2 and selected bond parameters are listed in Table 2. The copper(II) ion is *hexa*-coordinated and is bound by the meridionally coordinating end-cap tridentate **L6** ligand and three water molecules. Hence the copper(II) ion has a distorted octahedral geometry and the Cu–N_T distance is shorter than Cu–N_P {N_T = triazine–N; N_P = pyridyl–N} by 0.023(3) Å. The Cu–O1 bond is shorter than Cu–O2 by 0.412(5) Å and is expected from Jahn-Teller distortions. The bond parameters within **L6** molecule are comparable with reported values of triazine complexes.[4, 7] The room temperature magnetic moment value of 1.82 B.M. is consistent with the presence of one electron and d^9 electronic configurations. The room temperature EPR spectrum in methanol solution exhibited a four line spectrum at g_{av} = 2.126 having A_{av} = 96 G.

Compound **3** crystallized in *P*1 space group, a perspective view of the $[Cu(\mathbf{L8})_2(H_2O)(NO_3)]$ unit is shown in Figure 3 and selected bond parameters are listed in Table 3. The **L8** act as a bidentate ligand, bind through the nitrogen atoms of pyridine ring and $-NH_2$ group. Two of the ligands are bound to copper atom in the square plane and span *trans* positions. The two axial sites are occupied by water molecule and a nitrate ion. Hence, the overall coordination stereochemistry around copper(II) center is *trans-trans-trans*-$(N_P)_2(N_A)_2(O_WO_N)$ {N_A = amidine–N; O_W = water–O; O_N = nitrate–O} and has a distorted octahedral geometry. The room temperature magnetic moment value of 1.69 B.M. is consistent with the presence of

one electron and d^9 electronic configurations. The room temperature EPR spectrum in methanol solution exhibited a four line spectrum at $g_{av} = 2.129$ having $A_{av} = 63$ G.

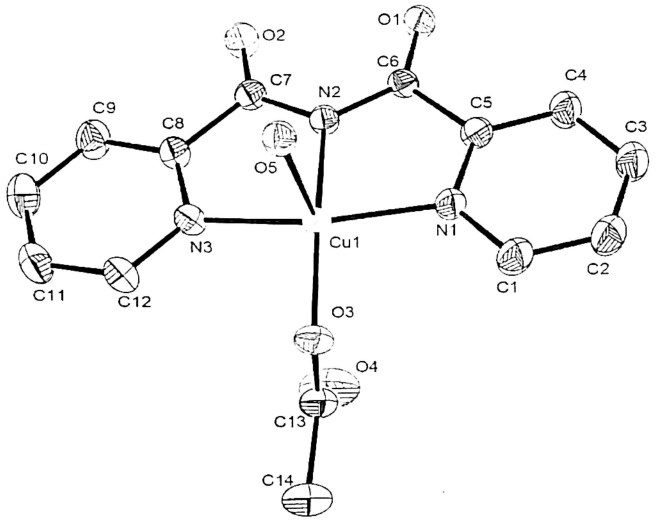


Figure 1. ORTEP (30% probability ellipsoids) diagram of **1** (Hydrogen atoms are omitted for clarity).

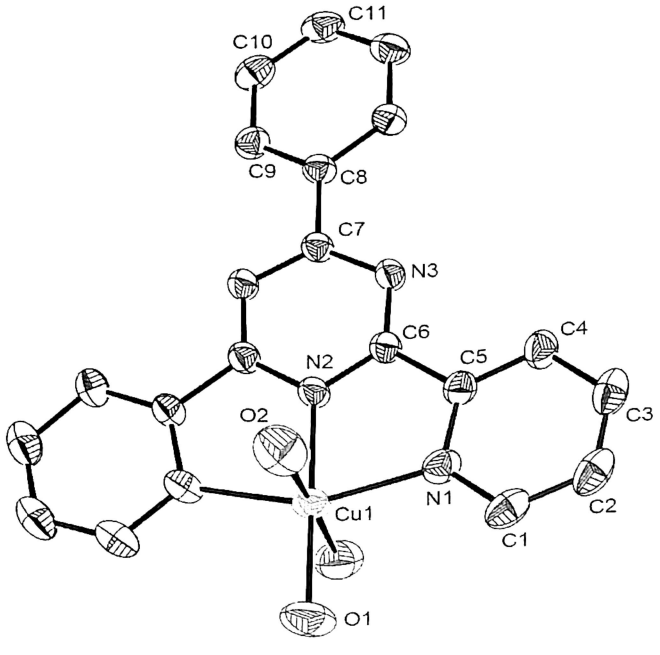


Figure 2. ORTEP (30% probability ellipsoids) diagram [Cu(**L6**)$(H_2O)_3$] unit in **2** (Hydrogen atoms are omitted for clarity).

6.4. Conclusion

In summary, the amidine and diamidine formed between 2-cyanopyridine and 2-picolylamine reacted with copper(II) acetate and converted to bis(2-pyridylcarbonyl)amide species. This reaction involve hydrolysis of $-NH_2$ group (in **L3**) or ((2-pyridyl)methylimino)picolinamidine group (in **L4**) and oxidation of the

methylene function. The diamidine (formed between 2-cyanopyridine and benzylamine) reacted with $Cu(NO_3)_2 \cdot 3H_2O$ and converted to 2-phenyl-4,6-di(2-pyridyl)[1,3,5]triazine that remain bound to copper(II) center. The amidine **L8** formed a complex **3** without any conversion.

Table 1. Summary of crystal data and refinement parameters for **1–3**.

	1	**2**	**3**
Formula	$C_{14}H_{15}CuN_3O_6$	$C_{19}H_{25}CuN_7O_{12}$	$C_{26}H_{28}CuN_8O_7$
Mol. wt.	384.83	606.99	628.10
Cryst. color, habit	Blue block	Green block	Green plate
T, K	298(2)	298(2)	298(2)
Cryst. syst.	Triclinic	Monoclinic	Triclinic
Space group	*P*-1	*C*2/c	*P*1
a, Å	7.4059(6)	14.3960(5)	8.0245(5)
b, Å	8.6237(7)	14.8390(5)	8.9863(5)
c, Å	13.0042(11)	12.0413(4)	11.2548(7)
α ,deg	74.671(5)	90.00	96.712(2)
β, deg	84.883(6)	98.601(2)	105.920(3)
γ ,deg	81.143(5)	90.00	107.681(3)
V, Å^3	790.41(11)	2543.36(15)	725.63(8)
Z	1	4	2
*D*calcd, g cm^{-3}	1.547	1.316	2.059
μ, mm^{-1}	1.412	0.894	0.0522
F(000)	363	1036	456
Reflection collected	3625	3014	3564
Unique reflections	3624	1941	1984
GOF[a] on F^2	1.039	1.044	1.011
R_1[b], wR_2[c] *($I \geq 2\sigma(I)$)*	0.0347, 0.1124	0.0560, 0.1687	0.0524, 0.1171
R_1[b], wR_2[c] (all data)	0.0348, 0.1124	0.0881, 0.1929	0.0879, 0.1272

[a] GOF(Goodness-of-fit) = $[\sum[w(F_0^2 - F_c^2)^2] / M - N]^{1/2}$ (M =number of reflections, N = number of parameters refined). [b] $R_1 = \sum \| F_0 | - | Fc \| / \sum | F_0 |$. [c] $wR_2 = [\sum[w(F_0^2 - F_c^2)^2] / \sum[w(F_0^2)^2]]$.

Table 2. Selected bond distances (Å) and angles (°) in **2**.

Cu1–N1	2.093(3)	N1–Cu1–N2	78.68(8)
Cu1–N2	1.916(3)	N1–Cu1–O1	101.32(8)
Cu1–O1	1.948(4)	N1–Cu1–N1	157.37(15)
Cu1–O2	2.360(5)	N1–Cu1–O2	89.89(14)
N1–C1	1.329(5)	N1–Cu1–O2	90.92(15)
N1–C5	1.355(4)	N2–Cu1–O1	180.00(1)
N2–C6	1.333(3)	N2–Cu1–O2	92.05(13)
N3–C6	1.318(4)	O1–Cu1–O2	87.95(13)
N3–C7	1.350(3)	O2–Cu1–O2	175.9(3)
		C1–N1–Cu1	129.0(3)
		C5–N1–Cu1	113.6(2)
		C6–N2–Cu1	120.96(18)

Table 3. Selected bond distances (Å) and angles (°) in **3**.

Cu1–N1	1.980(7)	N1–Cu1–N2	81.2(3)
Cu1–N2	1.915(8)	N1–Cu1–N5	97.4(3)
Cu1–N4	2.008(6)	N1–Cu1–N4	176.8(4)
Cu1–N5	1.992(7)	N2–Cu1–N4	99.2(3)
Cu1–O1	2.392(12)	N2–Cu1–N5	176.7(5)
Cu1–O2	2.60(2)	N4–Cu1–N5	82.0(3)
N2–C6	1.312(9)	N1–Cu1–O1	88.1(4)
N3–C6	1.281(13)	N2–Cu1–O1	92.3(4)
N3–C7	1.420(17)	N4–Cu1–O1	95.0(4)
N5–C19	1.233(10)	N5–Cu1–O1	90.6(4)
N6–C19	1.346(13)	N1–Cu1–O2	98.9(4)
N6–C20	1.500(14)	N2–Cu1–O2	87.3(4)
		N4–Cu1–O2	78.1(4)
		N5–Cu1–O2	90.0(4)
		O1–Cu1–O2	172.8(4)
		N3–C6–N2	126.2(10)
		N3–C6–C5	120.0(7)
		N2–C6–C5	113.7(8)
		N3–C7–C8	115.5(12)
		N5–C19–N6	121.1(9)
		N5–C19–C18	119.3(8)
		N6–C19–C18	119.5(6)
		N6–C20–C21	110.5(9)

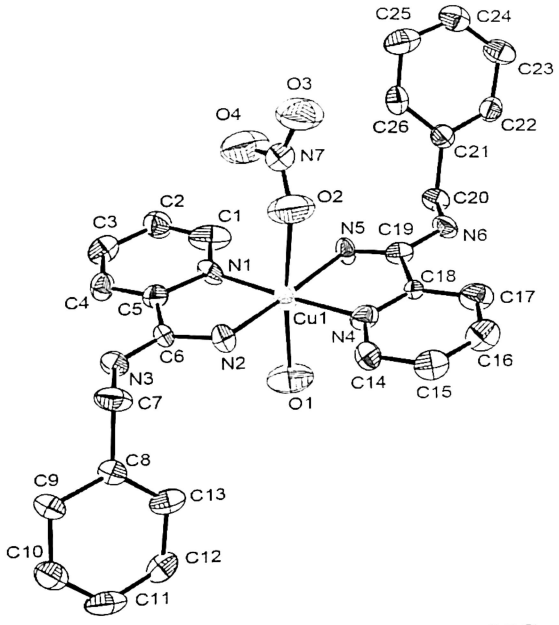


Figure 3. ORTEP (30% probability ellipsoids) diagram of [Cu(**L8**)$_2$(H_2O)(NO_3)] unit in **3** (Hydrogen atoms are omitted for clarity).

6.5. Experimental Section

6.5.1. Synthesis

***N'*-((2-Pyridyl)methyl)picolinamidine (L3)**: A neat mixture of 2-picolylamine (0.500 g, 4.63 mmol) and 2-cyanopyridine (0.480 g, 4.63 mmol) were heated at 100°C in oil bath for 12 h. The mixture was cooled, loaded on basic alumina column and **L3** was eluted with ethylacetate-hexane (1:5) mixture. Yield 0.900 g (92%). ESI-Mass: calcd. for $C_{12}H_{12}N_4^+$ 212.11 found (M^++H) 213.04. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 8.60 (1H, d, 4.8), 8.40 (1H, d, 4.8), 7.74 (1H, t, 7.6), 7.60 (1H, d, 8.0), 7.50 (1H, t, 7.6), 7.40 (1H, t, 6.0), 7.14 (1H, d, 8.0), 7.02 (1H, t, 4.8), 3.80 (2H, s), 2.16 (2H, s). FTIR (KBr, cm^{-1}): 3438(b), 1634(s), 1563(m), 1480(m), 1437(m), 1382(m), 1289(s), 1251(s), 1215(s), 1149(s), 1091(s), 1045(s), 997(s), 793(s), 745(s), 691(m), 628(m).

***N'*-(((2-Pyridyl)methylimino)(2-pyridyl)methyl)picolinamidine (L4)**: A neat mixture of 2-picolylamine (0.500 g, 4.63 mmol) and 2-cyanopyridine (0.960 g, 9.26 mmol) were heated at 100°C in oil bath for 12 h. The resultant red gummy substance was triturated with hexane, dried in *vacuo* and was used further for reaction with copper(II) acetate. Attempts to isolate **L4** by purification on a alumina or silica column failed and while doing so, **L4** converted to 2,4,5-tris(2-pyridyl)imidazole and *N*-(3-(2-

pyridyl)imidazo[1,5-*a*]pyridine)picolinamidine. Hence its spectroscopic data could not be obtained.

***N'*-((Benzylimino)(2-pyridyl)methyl)picolinamidine (L7)**: A neat mixture of benzylamine (0.500 g, 4.67 mmol) and 2-cyanopyridine (0.970 g, 9.34 mmol) were heated at 100°C in oil bath for 24 h. The resultant red gummy substance was triturated with hexane, dried in *vacuo* and was used further for reaction with copper(II) nitrate. Our attempts to isolate **L7** by purification on alumina or silica column failed and while doing so, **L7** converted to *N'*-benzylpicolinamidine. Hence its spectroscopic data could not be obtained.

***N'*-Benzylpicolinamidine (L8)**: A neat mixture of benzylamine (0.500 g, 4.67 mmol) and 2-cyanopyridine (0.485 g, 4.67 mmol) were heated at 100°C in oil bath for 24 h. The mixture was cooled, loaded on basic alumina column and **L8** was eluted with ethylacetate-hexane (1:5) mixture. Yield 0.900 g (92%). ESI-Mass: calcd. for $C_{13}H_{13}N_3^+$ 211.11 found (M^++H) 212.32. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 8.51 (1H, d, 6.0), 8.24 (1H, d, 8.0), 7.80 (1H, t, 7.6), 7.70 (1H, t, 7.6), 7.40 (5H, m), 4.65 (2H, s), 4.50 (2H, s). FTIR (KBr, cm^{-1}): 3059(s), 2862(m), 1645(m), 1588(m), 1524(s), 1492(m), 1466(m), 1429(s), 1361(s), 1286(m), 1250(s), 1204(s), 1156(s), 1091(m), 1070(s), 1044(s), 996(s), 902(m), 802(m), 779(m), 736(s), 698(s), 622(s), 546(m).

[Cu(L5)(OAc)(H_2O)]·H_2O (1): In air, a mixture of **L3** (0.500g, 2.36 mmol) and $Cu(OAc)_2·H_2O$ (0.470g, 2.36 mmol) in 80 mL methanol was stirred for 6 h. The solution was left undisturbed and crystals of **1** deposited after one week was collected and washed with ice-cold methanol. Yield 0.640 g (70%).

Alternatively on stirring a mixture of **L4** (0.500g, 1.58 mmol) and $Cu(OAc)_2·H_2O$ (0.320g, 1.58 mmol) in 80 mL methanol for 6 h, also deposited crystals of **1** after one week, which was collected and washed with ice-cold methanol. Yield 0.40 g (65%). IR (KBr, cm^{-1}): 1716(s), 1637(s), 1602(s), 1566(s), 1445(m), 1410(s), 1360(s), 1289(m), 1154(m), 1094(m), 1045(s), 1024(s), 801(m), 760(s), 701(s), 650(m), 630(m). All the spectroscopic characteristics **1** are same as that reported previously and hence the data are not listed here.

[Cu(L6)(H_2O)](NO_3)$_2$·$3H_2O$ (2): A mixture of **L7** (0.500 g, 1.59 mmol) and $Cu(NO_3)_2·3H_2O$ (0.380 g, 1.59 mmol) in 100 mL of methanol was stirred in air for 6 h. The mixture was allowed to stand for a week and the crystals of **2** deposited were

collected by filtration and washed with ice-cold methanol. Yield 0.57 g (65%). IR (KBr, cm^{-1}): 1579(s), 1563(s), 1537(s), 1495(m), 1479(m), 1384(s), 1301(m), 1262(m), 1155(m), 1096(m), 1068(m), 1038(m), 1013(s), 824(m), 766(s), 665(s). Anal. Calcd. for $C_{19}H_{25}N_7O_{12}Cu$: C, 37.60; H, 4.15; N, 16.15%. Found C, 37.41; H, 4.10; N, 16.08%. UV–Vis [λ_{max}, nm (ε, $M^{-1}cm^{-1}$), CH_3OH solution]: 680(54); 370(560); 271(21870). EPR (CH_3OH solution, 298 K): g = 2.126, A = 96 G. μ_{eff}, 1.82 B. M.

$[Cu(L8)_2(H_2O)(NO_3)](NO_3)\cdot H_2O$ (3): A mixture of **L8** (0.500 g, 2.37 mmol) and $Cu(NO_3)_2\cdot 3H_2O$ (0.570 g, 2.37 mmol) in 100 mL of methanol was stirred in air for 6 h. The mixture was allowed to stand for a week and the crystals of **3** deposited were collected by filtration and washed with ice-cold methanol. Yield 1.05 g (72%). IR (KBr, cm^{-1}): 3085(s), 1633(s), 1604(s), 1563(m), 1478(m), 1384(s), 1273(m), 1238(m), 1111(m), 1080(m), 1055(m), 1036(m), 1024(s), 969,(m) 918(m), 827(m), 801(m), 756(s), 697(s), 604(m), 541(b). Anal. Calcd. for $C_{26}H_{28}N_8O_7Cu$: C, 49.72; H, 4.49; N, 17.84%. Found C, 49.61; H, 4.45; N, 17.68%. UV–Vis [λ_{max}, nm (ε, $M^{-1}cm^{-1}$), CH_3OH solution]: 661(69); 360(184); 271(10340). EPR (CH_3OH solution, 298 K): g = 2.129, A = 63 G. μ_{eff}, 1.69 B. M.

6.6. References

1. (a) Boyd, G. V. *The Chemistry of Amidines and Imidates*; Patai, S.; Rappoport, Z. Eds. Wiley: Chichester, 1991; Vol. 2. (b) Kukushkin, V. Y. Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771–1802.
2. (a) Fiorino, F.; Magli, E.; Perissutti, E.; Severino, B.; Frecentese, F.; Esposito, A.; De Angelis, F.; Incisivo, G. M.; Massarelli, P.; Nencini, C.; Gennaro, E. D.; Budillon, A.; Cintio, A. D.; Santagada, V.; Caliendo, G. *Eur. J. Med. Chem.* **1999**, *34*, 2206–2216. (b) Seijas, J. A.; Vázquez-Tato M. P.; Martínez. M. M. *Tetrahedron Lett.* **2000**, *41*, 2215–2217. (c) Sondhi, S. M.; Dinodia, M.; Kumar, A. *Bioorg. Med. Chem.* **2006**, *14*, 4657–4663. (d) Sondhi, S. M.; Rani, R.; Roy, P. Agrawal, S. K.; Saxena, A. K. *Eur. J. Med. Chem.* **2010**, *45*, 902–908.
3. (a) Paul, P.; Tyagi, B.; Bhadbhade, M. M.; Suresh, E. *J. Chem. Soc. Dalton Trans.* **1997**, 2273–2277. (b) Paul, P.; Tyagi, B.; Bilakhiya, A. K.; Bhadbhade, M. M.; Suresh, E. *J. Chem. Soc. Dalton Trans.* **1999**, 2009–2014. (c) Granifo, J. *Polyhedron* **1999**, *18*, 1061–1066. (d) Cotton, S. A.; Franckevicius, V.; Fawcett, J. *Polyhedron* **2002**, *21*, 2055–2061. (e) Majumder, A.; Pilet, G.; Rodriguez, M. T. G.; Mitra, S. *Polyhedron* **2006**, *25*, 2550–2558. (f) Cooke, M. W.; Hanan, G.

S.; Loiseau, F.; Campagna, S.; Watanabe, M.; Tanaka, Y. *J. Am. Chem. Soc.* **2007**, *129*, 10479–10488. (g) Medlycott, E. A.; Hanan, G. S. *Chem. Commun.* **2007**, 4884–4886. (h) Medlycott, E. A.; Udachin, K. A.; Hanan, G. S. *J. Chem. Soc. Dalton Trans.* **2007**, 430–438. (i) Medlycott, E. A.; Hanan, G. S.; Abedin, T. S. M.; Thompson, L. K. *Polyhedron* **2008**, *27*, 493–501. (j) Bolink, H. J.; Coronado, E.; Costa, R. D.; Gaviña, P.; Ortí, E.; Tatay, S. *Inorg. Chem* **2009**, *48*, 3907–3909. (k) Santoni, M. P.; Hanan, G. S.; Hasenknopf, B.; Proust, A.; Nastasi, F.; Serronic, S.; Campagna, S. *Chem. Commun.* **2011**, *47*, 3586–3588.

4. Polson M. I. J.; Medlycott, E. A.; Hanan, G. S.; Mikelsons, L.; Taylor, N. J.; Watanabe, M.; Tanak, Y.; Loiseau, F.; Passalacqua, R.; Campagna, S. *Chem. Eur. J.* **2004**, *10*, 3640–3648.

5. (a) Rowland, J. M.; Olmstead, M. M.; Mascharak, P. K. *Inorg. Chem.* **2002**, *41*, 2754 –2760. (b) Padhi, S. K.; Manivannan, V. *Inorg. Chem.* **2006**, *45*, 7994–7996. (c) Sahu, R.; Padhi, S. K.; Jena, H. S.; Manivannan, V. *Inorg. Chim. Acta* **2010**, *363*, 1448–1454. (d) Sahu, R.; Fulwa, V. K.; Jena, H. S.; Manivannan, V. *Polyhedron* **2012**, *50*, 9–12.

6. Folgado, J. V.; Martínez-Tamayo, E.; Beltran-Porter, A.; Beltrán-Porter, D. *Polyhedron* **1989**, *8*, 1077–1083.

7. (a) Nastasi, F.; Loiseau, F.; Campagna, S.; Medlycott, E. A.; Santoni, M.-P.; Hanan, G. S. *Can. J. Chem.* **2009**, *87*, 254–263. (b) Medlycott, E. A.; Theobald, I.; Hanan, G. S. *Eur. J. Inorg. Chem.* **2005**, 1223–1226. (c) Polson, M. I. J.; Taylor, N. J.; Hanan, G. S. *Chem. Commun.* **2002**, 1356–1357.

Conclusion and Future Perspectives

This thesis describes novel synthetic strategies for the synthesis of *N*-heterocycles using 2-cyanopyridine. Methods have been designed for the synthesis of 2,4,5-trisubstituted imidazoles and 1,3-disubstituted imidazo[1,5-*a*]pyridines.

In future, I believe that these synthetic strategies will be applicable for the synthesis of new *N*-heterocycles and serve as valuable additions in the modern synthetic organic synthesis. Further, the compounds prepared by these methods will be useful classes of compounds for evaluating their biological activities. In addition, these compounds will be useful for studying their transition metal chemistries.

List of Publications

1. Synthesis of 3-substituted imidazo[1,5-*a*]pyridines having 1-(*N*-picolinamidin-2-yl) group.
   Fulwa, V. K.; Manivannan, V. *Tetrahedron*, **2012**, *68*, 3927–3931.

2. Synthesis of some 1,3-disubstituted imidazo[1,5-*a*]pyridines using 2-cyanopyridine.
   Fulwa, V. K.; Manivannan, V. *Tetrahedron Lett.* **2012**, *53*, 2420–2423.

3. Novel synthesis of 2,4-bis(2-pyridyl)-5-(pyridyl)imidazoles and formation of *N*-(3-(pyridyl)imidazo[1,5-*a*]pyridine)picolinamidines: nitrogen-rich ligands.
   Fulwa, V. K.; Sahu, R.; Jena, H. S.; Manivannan, V. *Tetrahedron Lett.* **2009**, *50*, 6264–6267.

4. Copper(II) acetate mediated conversion of *ortho* aminomethyl substituted isoquinolines to bis(isoquinolylcarbonyl)amides.
   Sahu, R.; **Fulwa, V. K.**; Jena, H. S.; Manivannan, V. *Polyhedron* **2012**, *50*, 9–12.