Green Synthesis of Imidazopyridines

Project work to the Central University of Punjab

For the award of

Master of Science

In

Chemistry

By

Nikhil Das Mehar

Supervisor

Dr. Rakesh Kumar

Department of Chemical Sciences

School of Basic & Applied Sciences

Central University of Punjab, Bathinda, Punjab-151001

May 2018

DECLARATION

I declare that the thesis entitled "**Green Synthesis of Imidazopyridines"** has been prepared by me under the guidance of **Dr. Rakesh Kumar**, Assistant Professor, Department of chemical Sciences, School of Basic & Applied Sciences, Central University of Punjab. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

Nikhil Das Mehar

Department of chemical Sciences

School of Basic & Applied Sciences

Central University of Punjab, Bathinda

Punjab-151001

Date:

CERTIFICATE

I certify that Nikhil Das Mehar has prepared his thesis entitled "**Green Synthesis of Imidazopyridines"** for the award of MSc. Chemistry of the Central University of Punjab, under my guidance. He has carried out this work at the Department of Chemical Sciences, School of Basic & Applied Sciences,Central University of Punjab.

Dr. Rakesh Kumar

Assistant Professor

Department of Chemical Sciences

School of Basic & Applied Sciences

Central University of Punjab

Bathinda-151001

Date:

ABSTRACT

Green synthesis of imidazopyridine

Name of student: Nikhil Das Mehar

Registration number: 16mscchm10

Degree for which submitted: M.Sc. Chemical Science

Name of supervisor: Rakesh Kumar

Name of Center: Department of Chemical Sciences

Name of school: School of Basic & Applied Sciences

A green synthesis of imidazopyridineusing environmentally friendly ionic liquids have been explored. The role of imidazolium based ionic liquids was evaluated. It was found that alkyl side chain of ionic liquid play an important role for product formation. The best optimized condition includes the use of ionic liquid [hmim]Br. Even the reaction was found to proceed under water. This is of significant importanceas solvent waste and their disposal is one of the major challenges faced by chemical industries.

Nikhil Das Mehar **Dr. Rakesh Kumar**

(Assistant Professor)

Dedicated to my beloved family

ACKNOWLEDGEMENT

This project is the end of my journey in obtaining my M.Sc. I have not travelled in a vacuum in this journey. This project has been kept on track and been seen through to completion with the support and encouragement of numerous people including my well-wishers, my friends, and colleagues. At the end of my project, it is a pleasant task to express my thanks to all those who contributed in many ways to the success of this study and made it an unforgettable experience for me.

I would like to pay my sincere thanks to honorable Vice Chancellor **Prof. R.K. Kohli** for providing me the entire infrastructure for my research work.

I am extremely indebted to our Dean Academic affairs **Prof. P. Ramarao** and H.O.D **Dr.Rajesh Kumar**, Associate Professor, Centre for Chemical Sciences, School of Basic and Applied Sciences, for providing necessary infrastructure and resources to accomplish my research work for his valuable advice, constructive criticism and his extensive discussions around my work.

At this moment of accomplishment, first of all, I pay honor to my supervisor **Dr.Rakesh Kumar**, Assistant Professor, Department of Chemical Sciences, School of Basic and Applied Sciences. This work would not have been possible without his guidance, support and encouragement. Under his guidance, I successfully overcome my difficulties and learned a lot. I can't forget his hard times. Despite of his busy schedule, he used to review my project progress, give his valuable suggestions and made corrections. I would like to thank **Dr. Rajendra Singh Dhayal,**Assistant Professor, **Dr. J.N. Babu**, Assistant Professor, **Dr. K. K. Haldar**, Assistant Professor, Department of Chemical Sciences, **Dr. Biplab banerji** Assistant Professor, Department of Chemical Sciences for their help and support.

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Table of Content

List of Tables

Table of Figures

List of Appendices

List of Abbreviations

Sr. No.	Full Form	Abbreviation
1	Dichloromethane	DCM
2	Dichloroethane	DCE
3	Dimethylformamide	DMF
4	Dimethylsulphoxide	DMSO
5	Excited state intramolecular proton transfer	ESIPT
6	Fourier-transform infrared spectroscopy	FTIR
7	Gas chromatography–mass spectrometry	GCMS
8	Hour	hr
19	Ionic liquids	ILs
10	Microwave	MW
11	*N*-Methyl-2-pyrrolidine	NMP
12	Tetrahydrofuran	THF
13	Tetramethylethylenediamine	TMEDA
14	*p*- Tolunesulphonic acid	PTSA
15	Thin layer chromatography	TLC
16	Ultra-violet	UV
17	X-ray diffraction	XRD

CHAPTER 1

INTRODUCTION

1.1 Heterocyclic compounds:

Heterocycles are organic compounds containing heteroatom such as nitrogen, sulfur and oxygen in the ring. Heterocycles are considered as backbone for pharmaceutical compounds, drug molecules, natural products, dyes etc. Heterocycles possess various biological activities such as antifungal, analgesic, anti-inflammatory, antibacterial, anticancer and cardiovascular activities (Dua, Shrivastava, Sonwane, & Srivastava, 2011). These constitute an important part of agrochemicals also. Since last two decades, 70% of agrochemicals introduced in market are constituted of the heterocyclic compounds. Some of the major commercial products having heterocycles in their structure are fungicides like azoxystrobin, neonicotinoid insecticide imidacloiprid etc. (Kondo et al., 2012).According to 2014 statistics, out of the 25 best-selling drugs, 12 are heterocycles (mostly nitrogen containing).

1.2 Nitrogen containing heterocycles:

The nitrogen containing heterocycles are well known for their biological importance. They are present in nucleic acids, vitamins, proteins and other biologically important molecular systems. Some of the bicyclic *N*-containing heterocycles are indole, purines, isoindole, indolizine, quinoline, isoquinoline, imidazopyridine etc. Various *N*-containing heterocyclic drugs are losartan, olmesartondasetron (imidazole containing), telmisartan, esomeprazole, pantoprazole, candesartan **(**benzimidazole containing), Atrovastatin, sunitinib, Fluvastatin, Rosuvastitn, nitrofurantoin, pitavastatin (pyrrole containing) 5-fluoroflucytosine, floxuridine, Lopinavir, Lamivudine, zidovudine, minoxidil (pyrimidines containing), difenacoum, flocoumafen, coumatetralyl (Deiters & Martin, 2004).

1.3 Imidazopyridine:

Imidazopyridine is an important nitrogen containing heterocyclic compound finding huge research interest of synthetic chemists due to their availability in many pharmaceutical drugs. There are many synthetic strategies for Imidazopyridine and 2-aminopyridine is common starting materials among most of them (Ostrovskii, Koldobskii, & Trifonov III, 2008) (Figure 1).

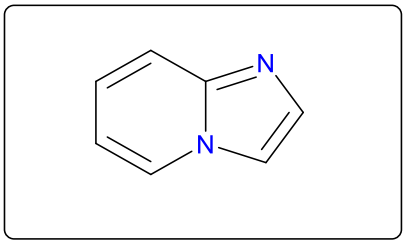


Figure-1 Imidazo[1,2-a]pyridine

1.4 Importance:

Imidazopyridine and their derivatives show a wide range of biological activities such as antifungal, anti-inflammatory, antitumour, antiviral, antibacterial, antiprotozoals, antipyretics, analgesic, antiapoptotic, hypnoselective, and anxioselective, hinder for β-amyloid formation, (Rupert et al., 2003), (Hranjec et al., 2007). Imidazopyridine also present in many drugs molecules such as zolmidine **(1)** used to treatment of peptic ulcer), alpidem **(2)** anxiolytic agents) (Langer, 1990) (Almirante et al., 1965), mindronic acid **(3)** for treatment of ostereophoresis), Olprinone **(4)** cardiotonic agents) Necopidem **(5),** zolpidem (used to treatment in the insomnia), structure mention in (Figure-2) (zushige, Ueda, Yukiiri, & Suzuki, 2002).

Structure of imidazopyridine as drugs:

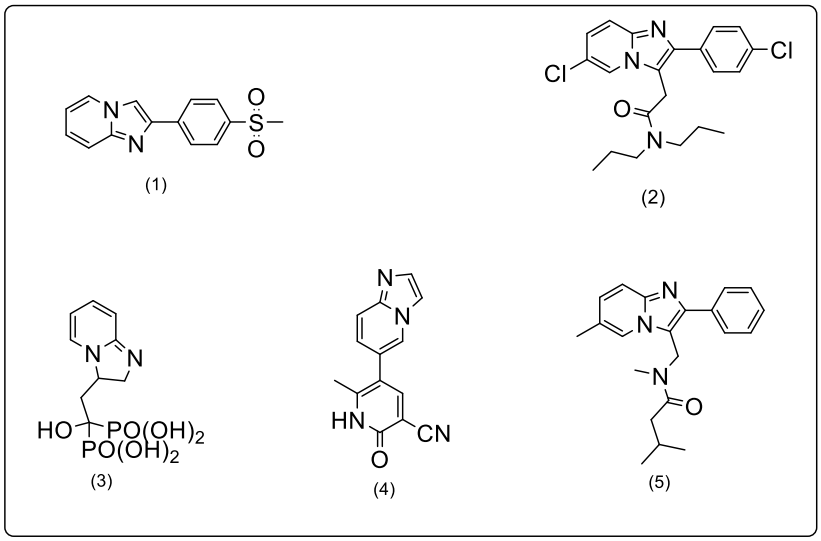


Figure 2: Structure of common imidazopyridine based drugs, zolmidine (1) alpidem (2) mindronic acid (3) olprinone (4) and necopidem (5).

1.5 Methods for synthesis of imidazopyridine:

There are diversified strategies for the synthesis of imidazopyridine, each one having their own peculiar characteristic features. Some of these are - condensation, multicomponent, oxidative coupling, tandem reaction, amino-oxygenation, hydro-amination reaction etc. Condensation reaction is conventional strategy for the synthesis of Imidazo[1,2-a]pyridine. It include the reaction of α-haloketone and 2-amino pyridine (Zhu, Chen, Liu, Ding, & Wu, 2009) via a condensation reaction.

Tandem strategies: Tandem reaction is a chemical process that composed of at least two succeeding reactions**,** designing in such a way that product of first reaction act as a reactant of next one. Synthesis of imidazopyridine using Morita–Baylish-Hilman acetate of nitroalkene followed by attack of 2-aminopyridine (Nair, Mobin, & Namboothiri, 2012).

Multicomponent strategy: It is a synthetic strategy in which more than two reactants come together in a single step to give an efficient product. This is the type of reaction that reduces time and is atom-economical. A multicomponent reaction between 2-aminopyridine, aldehyde and alkyne can lead to the synthesis of imidazopyridines.

Oxidative coupling: It is the synthesis of imidazopyridine from the readily available alkene, alkynes, ketones, nitrolefins and diones treating with 2-aminopyridine. In this strategy, an oxidation of an unsaturated moieties take place (Donohoe, Kabeshov, Rathi, & Smith, 2012).

In recent years, designing of reaction in such a way that produce minimum waste and increase the efficiency of the reaction (Reactions, 2005), (Kappe & Zhu, 2005) (Santra, Mitra, Bagdi, Majee, & Hajra, 2014) has received huge attention.

1.6 Ionic liquids (ILs) - Ionic liquid are a salt of poorly coordinated ions. These solvent are liquid below 100 °C or evenly at room temperature (Wasserscheid & Keim, 2000). The formation of stable crystal structure is prevented by one organic component and delocalized charge on cation. The properties such as- melting point, viscosity and their solubility is decided by cations, organic component and substituent present on it (Holbrey et al., 2008). Due to this these are considered as designer solvents (Seddon, 1995). Both polar and non-polar compounds can be dissolved in

ionic liquids (ILs). Thus, ILs are of potentials to carry out the reaction under benign condition, separation of the product is easy (sometime product may form layer above the ILs). Volatile product can be distilled, because ILs is having negligible vapor pressure. Various methylimidazolium and pyridinium based ionic liquids have been explored for a number of organic reactions (Farmer & Welton, 2002).

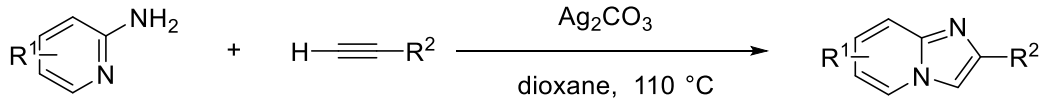
Chapter 2

Review of Literature

2 Review of literature:

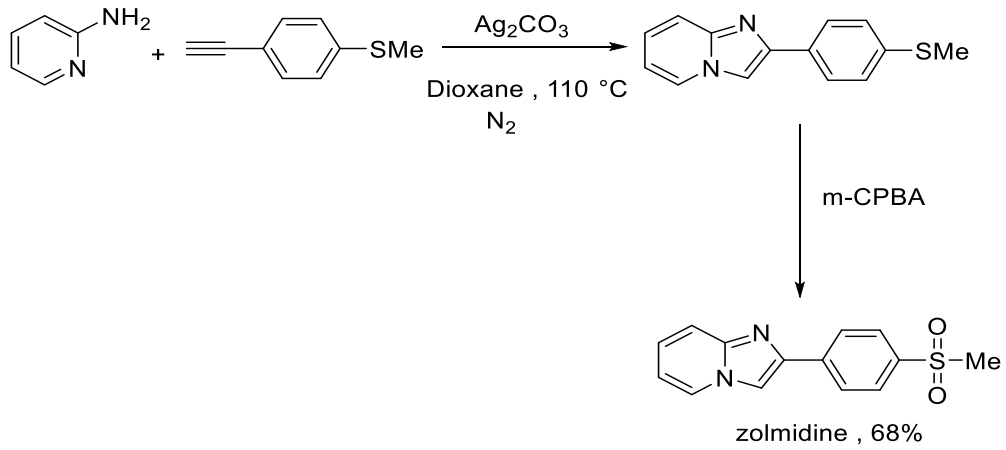
Imidazopyridine: Among all the bicyclic *N*-containing heterocycle, imidazopyridine find an important position due to their broad range of application. As also discussed earlier, imidazopyridines show a variety of biological activities like- antifungal, anti-inflammatory, antitumour, antiviral, antibacterial, antiprotozoals, antipyretics, analgesic, antiapoptotic, hypnoselective, and anxioselective, hinder for β-amyloid formation. They are present in various synthetic drugs such as zolmidine, zolpidem, alpidem, olprinone, mindronic acid etc.

Chuan He *et al***.** demonstrated the synthesis of 2-arylimidazo [1,2-a]pyridine (Scheme 2.1) with the help basic commercially available starting materials such as pyridine and terminal alkynes. They used silver mediated reaction through C-H/N-H oxidative cross coupling/cyclization (He et al. 2012). The reaction was tested under the catalysts of Cu(I) Iron(III) and silver(I) salts, wherein, silver(I) catalyst proved better. The best transformation obtained *via* using 2 equivalents of Ag_2CO_3 in dioxane, at 110 °C. Other acidic or basic additives (e.g. KOAc, NaOAc, K_2CO_3, $CsCO_3$, DBU, HOAc and HOPiv) were also screened but did not improve the efficiency of reaction.



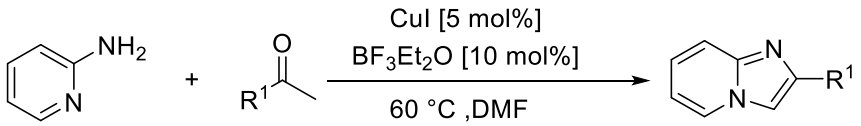
Scheme 2.1 Oxidative cross coupling between 2-aminopyridineand terminal alkyne

Antiulcer drug zolmidine (Scheme 2.11) was also prepared by Ag mediated reaction of 2-aminopyridine and 4-ethynylphenylmethylsulfane (Tang, Furuya, & Ritter, 2010).



Scheme 2.11 Synthesis of drug zolmidine (anti-ulcer).

The simple and efficient strategy for the synthesis of imidazo [1,2-a]pyridine via reaction of 2-aminopyridine with ketone. This transition metal catalyzed reaction results in the simultaneous C-H activation and C-N bond formation through the loss of water and hydrogen gases. A model copper catalyzed reaction between 2-aminopyridine (5mmol) and acetophenone (7.5 mmol) at 60° C have been reported using BF_3Et_2O as additive in solvent DMF (Chandra Mohan, Reddy Donthiri, Nageswara Rao, & Adimurthy, 2013).



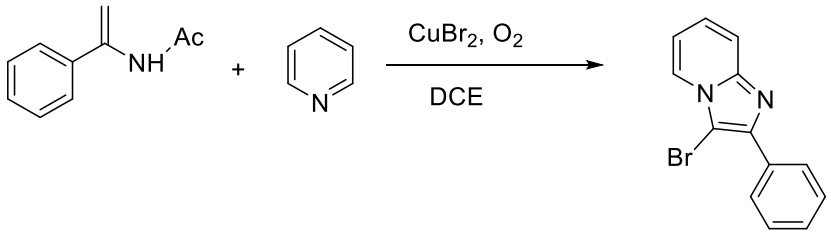
Scheme 2.2 Synthesis of imidazo[1,2-a]pyridine.

In contemporary organic synthesis reaction which is efficient, atom economical and environmental friendly is preferred (Nicolaou, Edmonds, & Bulger, 2006). As we discussed earlier that addition of nucleophile to α,β- unsaturated compound taken place easily via Michael type of addition.

Sougata Santra *et al*. demonstrated the imidazopyridine synthesis through one pot cascade reaction of nitroolefins and 2-aminopyridine in presence of Iron(III) catalyst (Santra, Bagdi, Majee, & Hajra, 2013). The reaction mechanism goes through Michael type addition trail by intramolecular cyclization and in situ denitration (Scheme 2.3).

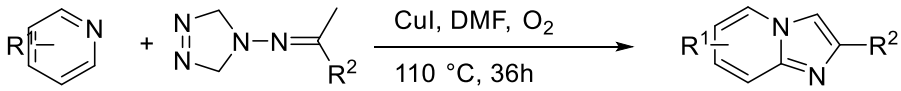
Scheme 2.3 One pot cascade reaction synthesis of imidazo [1,2-a]pyridine.

Xiaoqiang Zho *et al*. reported aerobic oxidative synthesis of 3-Bromo-imidazo[1,2-a]pyridines under copper catalysis with the help of pyridines and enamides (Zhou et al., 2015). The transformation is compatible with various functional group and a series of 3-Bromo-imidazo[1,2-a]pyridines was obtained under normal conditions. The higher yield given by solvent DCE, $CuBr_2$ is comparatively better than CuBr. The oxidants TBHP, DTBP, $K_2S_2O_8$ and oxygen was evaluated, oxygen found good ability among them. The best condition include the use of $CuBr_2$, solvent dichloroethane at 70 °C using $CuBr_2$ under aerobic conditions (Zhou et al., 2015) (Scheme 2.4).



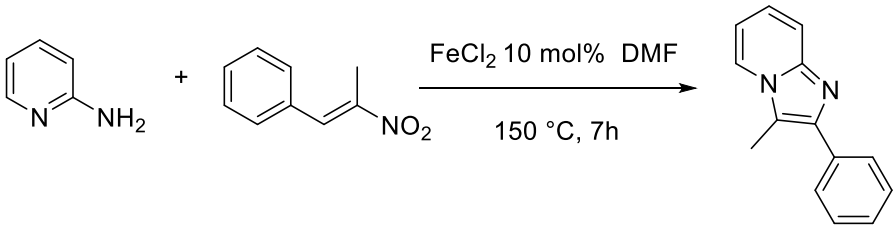
Scheme 2.4 Oxidative synthesis of 3-bromoimidazo[1,2-a]pyridine.

Jipan Yu, *et al*. reported the synthesis of imidazopyridine *via* copper catalyzed aerobic C-H functionalization of substituted of pyridine with *N*-(alkylidine)-4-H1,2,4-trazol-4-amines. This reaction goes through the breaking of N-N bond of *N*-(alkylidine)-4-H1,2,4-trazol-4-amines followed by the activation of aryl C-H bond of substituted pyridine. The optimization condition was CuI (10 mol %), DMF as solvent at 110 °C, oxygen as oxidant, varying the temperature lead to decrease the reaction yield. It was found that pyridine with electron donating group having higher yield than electron withdrawing. *N*-(alkylidine)-4-H1,2,4-trazol-4-amines having electron withdrawing group provide higher yield than neutral or electron donating groups (Scheme2.5).



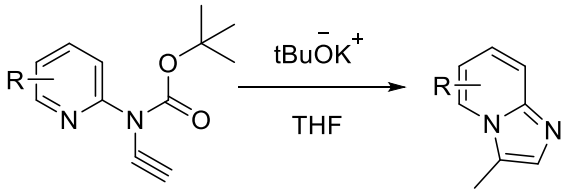
Scheme 2.5 C-H functionalization of substituted pyridine.

HaoYan, *et al*. reported the Iron(II) catalyzed, synthesis 3-methyl-2arylimidazo[1,2-a]pyridine. The reaction was carried out between 2-aminopyridines and nitroolefins. Reaction was started with CuI at 150 °C for 7 h to provide 30% yield of 3-methyl-2arylimidazo[1,2-a]pyridine. Different copper salt used but there is no significant increase in yield. On employing the Iron(II) salt, the product yield enhanced significantly. Lowering the temperature (130 °C) decreased the yield. Electron withdrawing groups were having higher yield as compared to electron donating group. Also, the substituents at fourth position of aminopyridine were having higher yield as comparison to other similarly substituted position. Also electron withdrawing group (chloro, bromo, cyano) on aromatic ring of nitrololfine were having higher yield than electron donating(methyl or methoxy) (Yan et al., 2012) (Scheme 2.6).



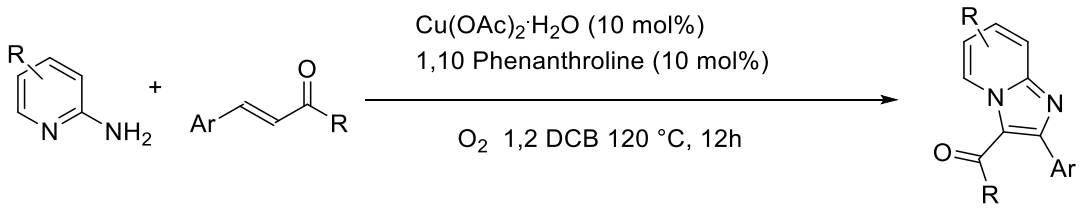
Scheme 2.6 Iron(II) catalyzed synthesis 3-methyl-2arylimidazo [1,2-a]pyridine.

Suren Hasinec, *et al*. reported the synthesis of imidazopyridine *via* base mediated cyclization of *N*-propargylaminopyridine. The reaction was employed using excess of base at room temperature. The stereochemistry of substituents was found to affect the cyclization process. Various reaction parameters were investigated, wherein, solvent THF and tBuOk base at room temperature proved better (Husinec, Markovic, Petkovic, Nasufovic, & Savic, 2011) (Scheme 2.7).



Scheme 2.7 Cyclization of N-propargyl aminopyridine.

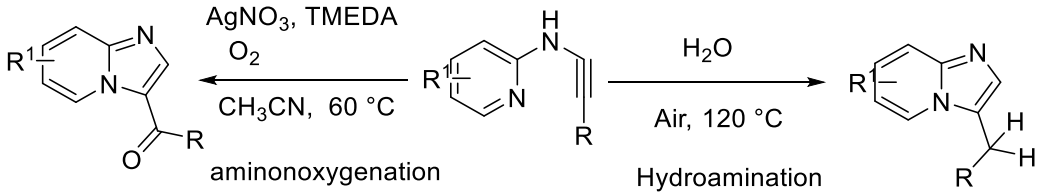
Kamarul Monir *et al***.** describe the synthesis of 3-aroylimidazo[1,2-a]pyridine via copper catalyzed aerobic oxidative coupling of chalcone and 2-aminopyridine through C-H amination (Scheme 2.8). The reaction proceeds *via* tandem Michel type addition trailed by intramolecular C-H amination. The reaction between 2-aminopyridine and 1,3-diphenylpropenonone when carried using 10 mol% of $Cu(OAc)_2.H_2O$ in 1,2-DCB under air yield 52% of desired product. Various ligands were screened such as bipyridine, DMEDA, TEMEDA, 1,10-phenanthroline and 8-hydroxy quinoline. The best result was obtained with 1,10-phenanthroline (64% yield). Various solvents were used (DMSO, DMF etc.) but not effective as compared to 1,2 DCB. Among various screened copper salts such as CuBr, $CuBr_2$, CuCl, $CuCl_2$ and $Cu(Otf)_2$,$Cu(OAc)_2{\cdot}H_2O$, $Cu(OAc)_2{\cdot}H_2O$ was most effective one (Monir, Kumar Bagdi, Mishra, Majee, & Hajra, 2014).



Scheme 2.8 Synthesis of 3-Aroylimidazo[1,2-a]pyridine via oxidative coupling.

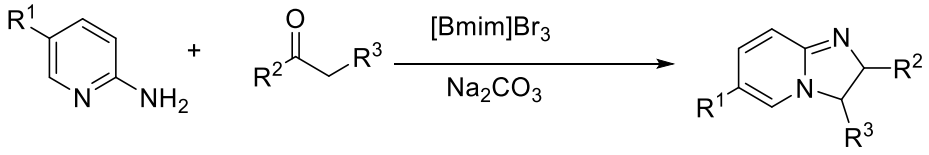
Darapaneni Chandra *et al.* describe the synthesis of imidazo [1,2-a]pyridine through silver mediated aminooxygenation using acetonitrile as a solvent (Scheme 2.9). Various silver salts were screened where in the best result were obtained when (2 mol%) of $AgNO_3$ along with 10 mol% of TMEDA in acetonitrile were temperature. An example for the formation of 8-(benzyloxy)imidazo[1,2-a]pyridine-3-carbaldyhde, confirmed by single crystal XRD techniques has been disclosed. It was found that *N*-

(prop-2-yn-1-yl)pyridine-2-amines were easily converted to methylimidazo[1,2-a]pyridine without using any catalyst under water medium. (Chandra Mohan, Nageswara Rao, & Adimurthy, 2013).



Scheme 2.9. Synthesis of imidazopyridine derivative by aminooxygenation and hydroamination.

Zhang-Geo *et al.* described the one pot synthesis of 2-phenylimidazo [1,2-a-α]pyridine with the help of acetophenone in ionic liquid [Bmim]Br_3 and 2-aminopyridine in solvent free condition (Scheme 2.10). The process was carried out in the presence of base, Na_2CO_3 providing good yield in the range of 72%-89% (Le, Xie, & Xu, 2012).



Scheme 2.10 One pot synthesis of 2-phenylimidazo[1,2-a-α]pyridine via ionic liquid.

Chapter 3

Objectives

3.1: Objectives:

The main objectives of project are:

1: Review of literature on synthesis of imidazopyridine via different strategies.

2: Green synthesis of imidazopyridine.

Chapter 4

Material and Methods

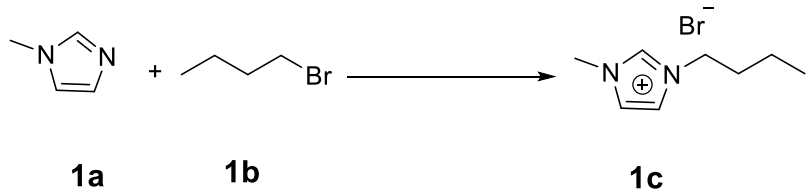
4.1 Materials and methods:

All the chemicals (reagents & solvents) were purchased from the commercial sources (Sigma Aldrich, Himedia) and used as received.

1) For thin layer chromatography, pre-coated TLC plates (0.2 mm silica gel 60 F-254-Merck) were used. Column chromatography was performed using silica gel (60-120 mesh) spectrochem as an adsorbent.
2) For weighing purposes, sartorious analytical balance (BSA224S-CW) was used, during the reaction JSGW heating mantle, stirrer, heater, and ILMVAC Rodist digital rotary evaporator, etc were used.
3) FT-IR spectrum was carried out on GC-MS, Tensor-27 spectrometer.
4) Mass analysis was carried out on GC-MS (Gas Chromatography-Mass spectrometry).
5) NMR analysis was carried out on 400 MHz NMR- Spectrometer.

4.2 Procedure for the Synthesis of 1-butyl-3-methylimidazolium Bromide ([bmim]Br) (1c)

N-methylimidazole (**1a**, 0.3 mol) and butyl bromide (**1b**,1.2 eq) were taken in 100 ml round bottom refluxed for 24 h at 70 °C (Kärkkäinen & Peuhkurinen, 2007). The mixture was washed with diethyl ether to remove the excess butyl bromide. The ionic liquid (**1c)** was obtained; it was dried on rotavapor under reduced pressure (Scheme 4.1).



Scheme 4.1 Synthesis of 1-butyl-3-methylimidazolium bromide.

Light yellow viscous oily liquid

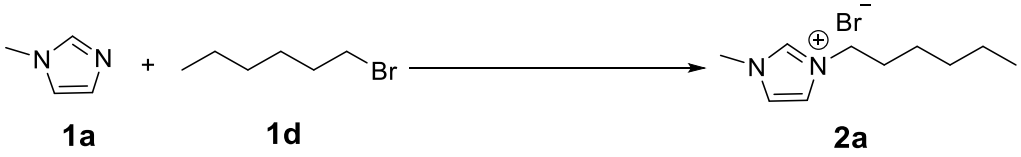
Yield - 70%

Molecular formula- $C_8H_{15}BrN_2$

Molecular weight: 219.122 g/mol.

4.3 procedure for Synthesis of 1-hexyl-3-methylimidazolium Bromide ([hmim]Br):

N-methylimidazole (**1a,** 0.2 mol) and 1-bromohexane (**1d,** 1.2 eq.) were taken in 100 ml round bottom flask for 24 h at 70 °C in refluxed condition. The solution was washed with diethyl ether to remove excess hexyl bromide and obtained Ionic liquid (**2a)** was further vacuum evaporated (Scheme 4.2) (Javadian et al., 2013).



Scheme 4.2 Synthesis of 1-hexyl-3-methylimidazolium Bromide.

Dark brown viscous liquid

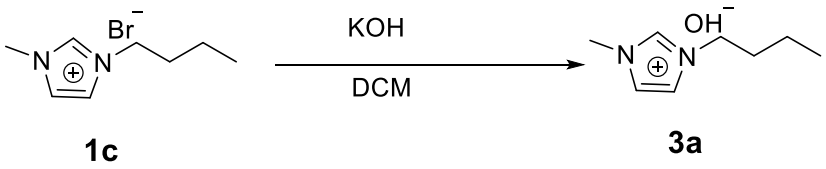
Yield - 72%

Molecular formula- $C_{10}H_{19}BrN_2$

Molecular weight- 247.18 g/mol

4.4 Procedure for Synthesis of 1-butyl-3-methylimidazolium Hydroxide ([bmim]OH):

[bmim]Br (**1c** 40 mmol) and KOH (1.0 eq.) were taken in 100 ml round bottom flask, followed by the addition of 20 ml DCM. The reaction was stirred for 10 h at room temperature and the reaction mixture was filtered to remove any precipitated KBr. The solution was then evaporated on rotary-evaporator under reduced pressure at 60 °C For purification, the resulting viscous liquid **(3a)** was washed with ether and then dried using rotavapor (Scheme 4.3) (A. Hajipour & Rafiee, 2009).



Scheme 4.3 Synthesis of 1-butyl-3-methylimidazolium Hydroxide (**3a**).

Reddish Brown viscous liquid

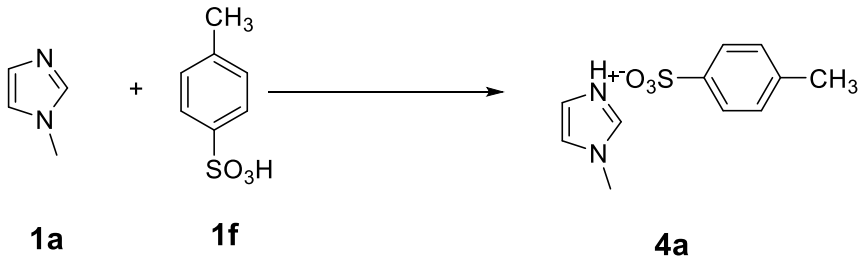
Yield- 69%

Molecular formula- $C_8H_{16}N_2O$

Molecular weight- 156.225 g/mol

4.5 Procedure for the synthesis of 1-methylimidazolium *p*-tolunesulphonic acid:

N-Methylimidazole (**1a**, 5 g) was added in a flask equipped with a magnetic stirrer and cooled in an ice water bath followed by addition of *p*-toluene sulfonic acid (**1f**, 10.5 g) and 1 ml water. The mixture was stirred for an additional period of 2 h. Water in the crude product was evaporated at 70 °C to afford a viscous liquid (**4a**) (Scheme 4.4) (A. R. Hajipour & Rafiee, 2010).



1a **1f** **4a**

Scheme 4.4 Synthesis of 1-butyl-3-methylimidazolium-*p*-toluenesulfonic acid **(4a)**.

White solid

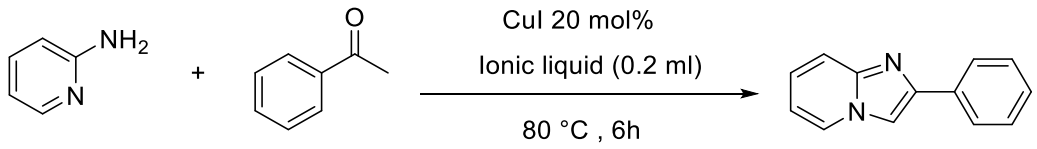
Yield- 68%

Molecular formula-$C_{11}H_{14}N_2SO_3$

Molecular weight- 254.30 g/mol

4.6 Screening of different ionic liquids for the synthesis of imidazo[1,2-a]pyridine: (6c)

Firstly, we tried the synthesis of imidazopyridine in the presence of various synthetically prepared ionic liquids such as [bmim]Br, [hmim]Br, [bmim]OH, [Hmim]*p*TSA. The reaction was carried out using 2-aminopyridine (**6a**, 1.2 eq), acetophenone (**6b**, 50 mg, 0.416 mmol), CuI (20 mol%) as a catalyst in the presence of ionic liquid (0.2 ml) at 80 °C for 6 h (scheme 4.5).



6a **6b** **6c**

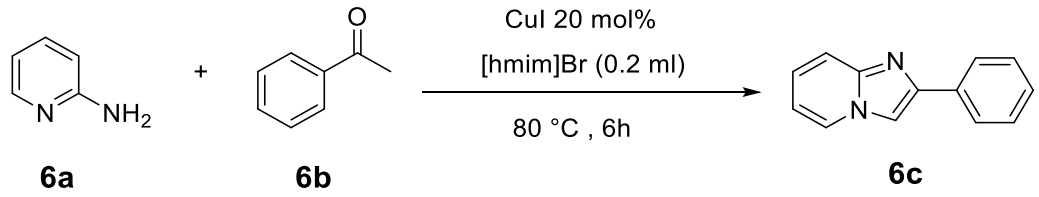
Scheme 4.5 Synthesis of imidazo[1,2-a]pyridine **(6c)**

The progress of reaction was checked regularly by using the pre-coated TLC under the UV lamp. After completion of the reaction, the work-up was done by ethyl acetate and water to separate out the inorganic and organic part. Organic layer was passed through sodium sulfate to remove the moisture. The product was isolated in all cases.

The yield of the product obtained by using various ionic liquids was observed and compared. Out of all used ionic liquids, the best yield of product was obtained using [hmim]Br ionic liquid. The result of optimization of the reaction conditions are summarized in result and discussion chapter.

4.7 Representative procedure for the synthesis of Imidazo[1,2-a]pyridine:

The reaction of 2-aminopyridine (**6a,** 46.98 mg, 1.2 eq) and acetophenone (**6b,** 0.416 mmol) was carried out using ionic liquid [hmim]Br (0.2 ml) along with copper iodide (0.2 eq, 15.84 mg) at 80 °C for 6 h. The progress of reaction was checked regularly by using the pre-coated TLC under the UV lamp. After completion of the reaction, the work-up was done by ethyl acetate and water to separate out the inorganic and organic part. Organic layer was passed through sodium sulfate to remove the moisture. The product was isolated through column chromatography in 75% yield (Scheme 4.6).



6a **6b** **6c**

Scheme 4.6 Synthesis of 2-phenylimidazo[1,2-a]pyridine using ionic liquid [hmim]Br

Characterization-^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09 (1H, d, j = 8 Hz), 7.94 (1H, d, j = 4Hz), 7.84 (1H, s), 7.62 (1H, d, j = 8Hz), 7.43 (1H, t, j_1 =4Hz, j_2=8Hz), 7.32 (1H,d, j_1= 8Hg, j_2= 8Hz), 7.15 (1H, t, j_1= 8Hg, j_2= 8Hz), 6.75 (1H, t, , j_1= 8Hz, j_2= 4Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.86, 145.77, 133.82, 128.82, 120.07, 126.11, 125.68, 124.76, 117.64, 112.52, 108.21.

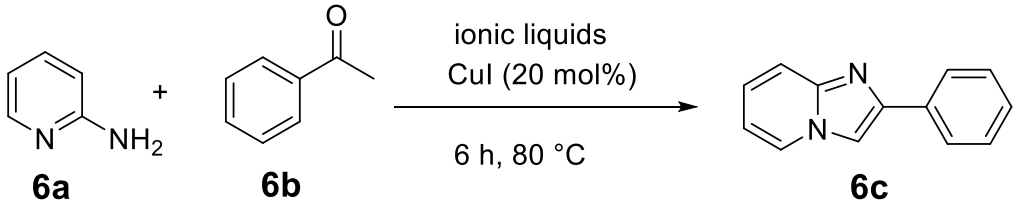
Same procedure was applied for the synthesis of other imidazopyridines.

Chapter 5

Result and Discussion

Since last few decades, imidazopyridine scaffold has attracted significant attention due to its pharmaceutical potential. Thus, the chemists are more interested in developing new alternatives for the synthesis of imidazopyridine. Various synthetic strategies involving multicomponent reactions, amino-oxygenation, hydro-amination etc. have been explored for the synthesis of imidazopyridines. Also, the search for the benign synthesis of imidazopyridine utilizing various principle of green chemistry is on rise. In this context, we have tried to explore the synthesis of imidazopyridine using benign solvents such as ionic liquid and water. Ionic liquids are considered as effective catalysts as well as solvents in wide range of conventional acid/base catalyzed reactions. Here in this report, we used room temperature ionic liquids for the synthesis of imidazopyridine. In particular, imidazolium based ionic liquids have been screened (Table 1).

Table 1: Screening of ionic liquids for synthesis of 2-phenylimidazo[1,2-a]pyridine.

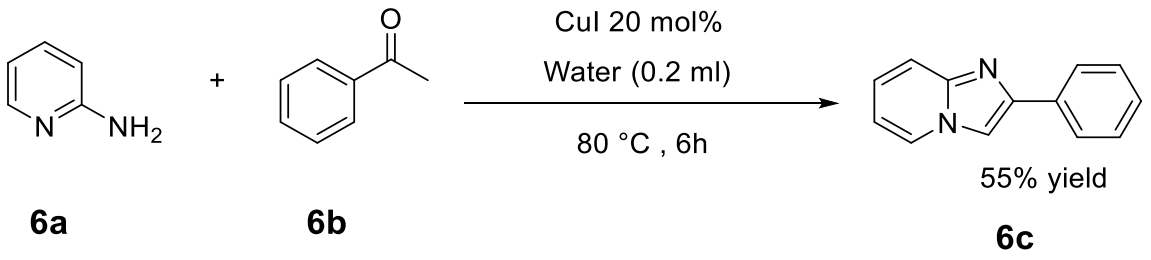


Entry	Ionic liquid	Yield (%)[b]
1	1-butyl-3-methylimidazolium bromide	48%
2	1-hexyl-3-methylimidazolium bromide	75%
3	1-methylimidazolium *p*-toluenesulfonic acid	35%
4	1-butyl-3-methylimidazolium hydroxide	28%

[a] reaction condition: 2-aminopyridine (1.2 eq), acetophenone (50 mg, 0.416 mmol), 0.2 ml ionic liquid,
[b] yield determined by column chromatography.

The reaction was carried out using 2-aminopyridine (**6a**, 1.2eq), acetophenone (**6b**, 0.416 mmol), CuI (20 mol%) as a catalyst in the presence of ionic liquid (0.2 ml) at 80 °C for 6 h (Table 1). Thus, using ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br), product (**6c)** was obtained in 48% yield (Table 1, entry 1). However, on increasing the alkyl chain of ionic liquid i.e. 1-hexyl-3-methylimidazolium bromide ([hmim]Br), the yield of the product increased up to 75% (Table 1, entry 2). Acidic ionic liquid 1-methylimidazolium*p*-toluenesulfonic acid ([Hmim]*P*TSA) provided only 35% yield of product (Table 1, entry 3). On the other side basic ionic liquid 1-butyl-3-methylimidazolium hydroxide ([bmim]OH) provided inferior yield of 28% as compared to acidic ionic liquid [Hmim]PTSA (Table 1, entry 4).

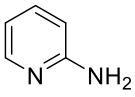
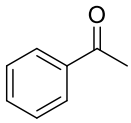
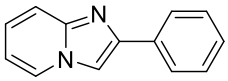
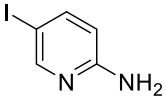
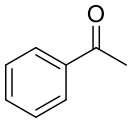
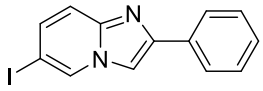
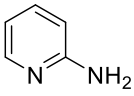
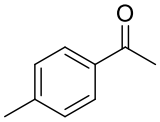
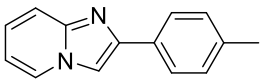
Even reaction under water (Scheme 5.2) provided the desired product in 55% yield under same reaction conditions. This result is of significant importance as solvent waste and their disposal is one of the major challenges faced by chemical industries.



Scheme 5.2 Synthesis of 2-phenylimdazo[1,2-a]pyridine.

By changing the various substituents on 2-aminopyridine and on acetophenone, we synthesized various imidazopyridine derivatives using [hmim]Br as listed in Table 2.

Table 2: Various substrate for synthesis of imidazo[1,2-a]pyridine derivatives[a]

Entry	2-aminopyridine	Acetophenone	Product	Time	yield
1				6h	75%
2				6h	68%
3				6h	60%

[a] Reaction condtiton: 2-aminopyridine (1.2 eq), acetophenone (0.416 mmol), [hmim]Br (0.2 ml) CuI (20 mol%)
[b] yield determined by column chromatography.

Conclusion:

In conclusion, we have explored a Cu-catalyzed synthesis of 2-phenylimidazo [1,2-a]pyridine from 2-aminopyridine and acetophenone using green ionic liquids. The present method, using ionic liquids has many advantages such as easy product isolation, avoiding toxic solvent and simplicity of methodology. Even the reaction was found to proceed under water. This has significant importance as solvent waste and their disposal is one of the major challenges faced by chemical industries.

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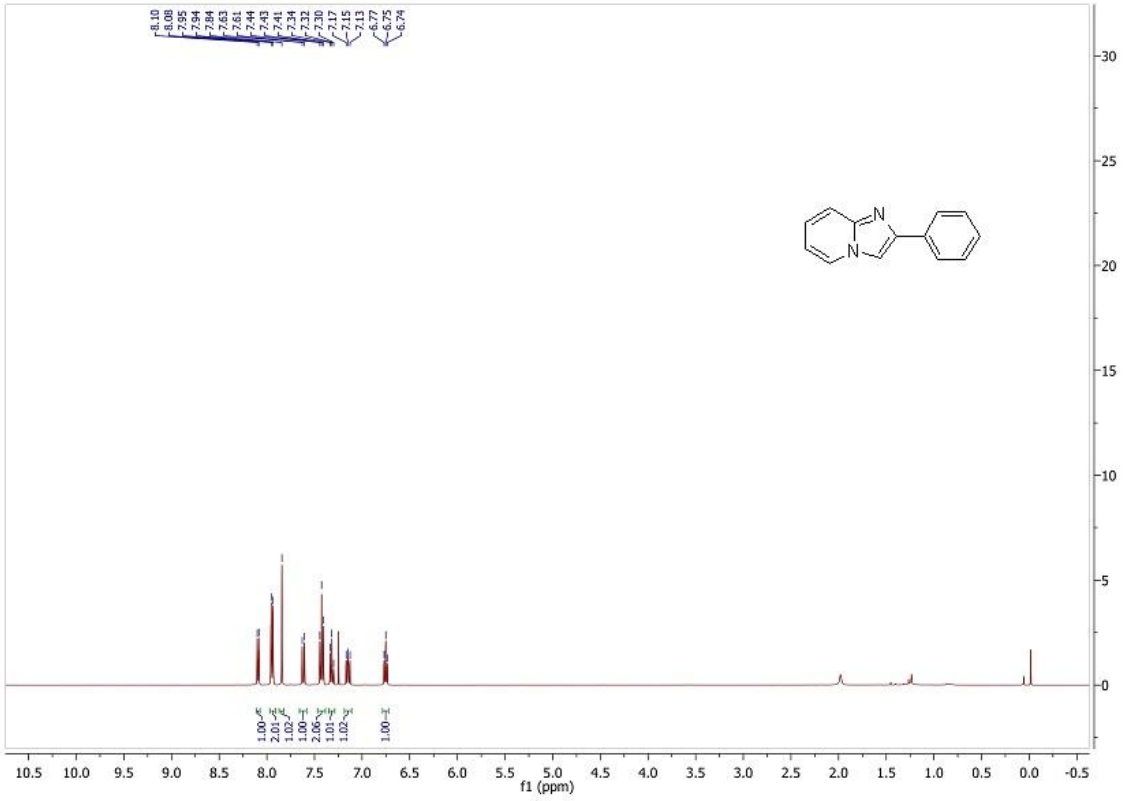
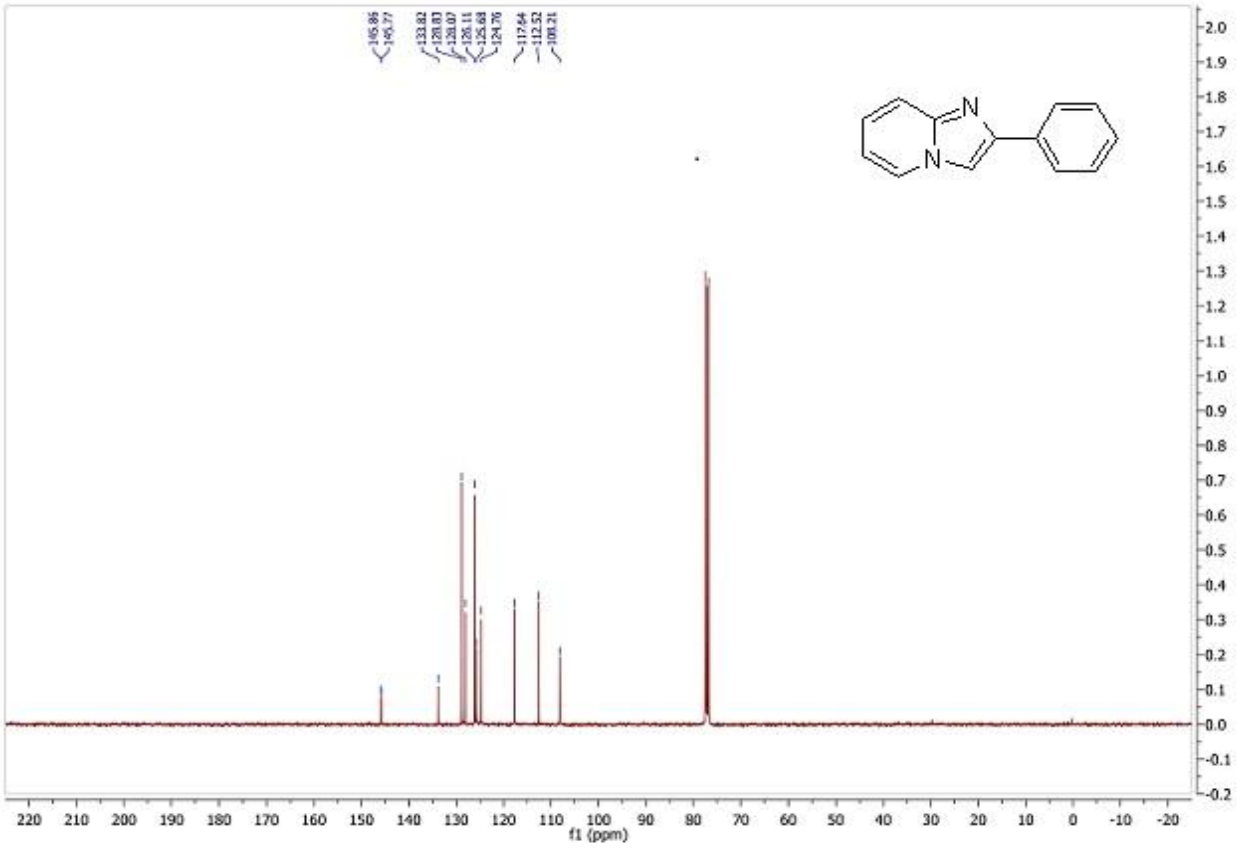
Appendix-

^{1}H NMR in $CDCl_3$ of 2-phenylimidazo[1,2-a]pyridine.



^{13}C NMR in $CDCl_3$ of 2-phenylimidazo[1,2-a]pyridine.



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4

1.1 Heterocyclic compounds: Heterocycles are organic compounds containing heteroatom such as nitrogen, sulfur and oxygen in the ring. Heterocycles are considered as backbone for pharmaceutical compounds, drug molecules, natural products, dyes etc. Heterocycles possess various biological activities such as antifungal, analgesic, anti-inflammatory, antibacterial, anticancer and cardiovascular activities (Dua, Shrivastava, Sonwane, & Srivastava, 2011). These constitute an important part of agrochemicals also. Since last two decades, 70% of agrochemicals introduced in market are constituted of the heterocyclic compounds. Some of the major commercial products having heterocycles in their structure are fungicides like azoxystrobin, neonicotinoid insecticide imidacloiprid etc. (Kondo et al., 2012).According to 2014 statistics, out of the 25 best-selling drugs, 12 are heterocycles (mostly nitrogen containing). 1.2 Nitrogen containing heterocycles: The nitrogen containing heterocycles are well known for their biological importance. They are present in nucleic acids, vitamins, proteins and other biologically important molecular systems. Some of the bicyclic N-containing heterocycles are indole, purines, isoindole, indolizine, quinoline, isoquinoline, imidazopyridine etc. Various N-containing heterocyclic drugs are losartan, olmesartondasetron (imidazole containing), telmisartan, esomeprazole, pantoprazole, candesartan (benzimidazole containing), Atrovastatin, sunitinib, Fluvastatin, Rosuvastitn, nitrofurantoin, pitavastatin (pyrrole containing) 5-fluoroflucytosine, floxuridine, Lopinavir, Lamivudine, zidovudine, minoxidil (pyrimidines containing), difenacoum, flocoumafen, coumatetralyl (Deiters & Martin, 2004). 1.3 Imidazopyridine: Imidazopyridine is an important nitrogen containing heterocyclic compound finding huge research interest of synthetic chemists due to their availability in many pharmaceutical drugs. There are many synthetic strategies for Imidazopyridine and 2-aminopyridine is common starting materials among most of them (Ostrovskii, Koldobskii, & Trifonov III, 2008) (Figure 1).

Figure-1 Imidazo[1,2-a]pyridine 1.4 Importance: Imidazopyridine and their derivatives show a wide range of biological activities such as antifungal, anti-inflammatory, antitumour, antiviral, antibacterial, antiprotozoals, antipyretics, analgesic, antiapoptotic, hypnoselective, and anxioselective, hinder for β-amyloid formation, (Rupert et al., 2003), (Hranjec et al., 2007). Imidazopyridine also present in many drugs molecules such as zolmidine (1) used to treatment of peptic ulcer), alpidem (2) anxiolytic agents) (Langer, 1990) (Almirante et al., 1965), mindronic acid (3) for treatment of ostereophoresis), Olprinone (4) cardiotonic agents) Necopidem (5), zolpidem (used to treatment in the insomnia), structure mention in (Figure-2) (zushige, Ueda, Yukiiri, & Suzuki, 2002). Structure of imidazopyridine as drugs:

Figure 2: Structure of common imidazopyridine based drugs, zolmidine (1) alpidem (2) mindronic acid (3) olprinone (4) and necopidem (5). 1.5 Methods for synthesis of imidazopyridine: There are diversified strategies for the synthesis of imidazopyridine, each one having their own peculiar characteristic features. Some of these are - condensation, multicomponent, oxidative coupling, tandem reaction, amino-oxygenation, hydro-amination reaction etc. Condensation reaction is conventional strategy for the synthesis of Imidazo[1,2-a]pyridine. It include the reaction of α-haloketone and 2-amino pyridine (Zhu, Chen, Liu, Ding, & Wu, 2009) via a condensation reaction. Tandem strategies: Tandem reaction is a chemical process that composed of at least two succeeding reactions, designing in such a way that product of first reaction act as a reactant of next one. Synthesis of imidazopyridine using

Morita–Baylish-Hilman acetate of nitroalkene followed by attack of 2-aminopyridine (Nair, Mobin, & Namboothiri, 2012). Multicomponent strategy: It is a synthetic strategy in which more than two reactants come together in a single step to give an efficient product. This is the type of reaction that reduces time and is atom-economical. A multicomponent reaction between 2-aminopyridine, aldehyde and alkyne can lead to the synthesis of imidazopyridines. Oxidative coupling: It is the synthesis of imidazopyridine from the readily available alkene, alkynes, ketones, nitrolefins and diones treating with 2-aminopyridine. In this strategy, an oxidation of an unsaturated moieties take place (Donohoe, Kabeshov, Rathi, & Smith, 2012). In recent years, designing of reaction in such a way that produce minimum waste and increase the efficiency of the reaction (Reactions, 2005), (Kappe & Zhu, 2005) (Santra, Mitra, Bagdi, Majee, & Hajra, 2014) has received huge attention. 1.6 Ionic liquids (ILs) - Ionic liquid are a salt of poorly coordinated ions. These solvent are liquid below 100 °C or evenly at room temperature (Wasserscheid & Keim, 2000). The formation of stable crystal structure is prevented by one organic component and delocalized charge on cation. The properties such as- melting point, viscosity and their solubility is decided by cations, organic component and substituent present on it (Holbrey et al., 2008). Due to this these are considered as designer solvents (Seddon, 1995). Both polar and non-polar compounds can be dissolved in ionic liquids (ILs). Thus, ILs are of potentials to carry out the reaction under benign condition, separation of the product is easy (sometime product may form layer above the ILs). Volatile product can be distilled, because ILs is having negligible vapor pressure. Various methylimidazolium and pyridinium based ionic liquids have been explored for a number of organic reactions (Farmer & Welton, 2002).

Chapter 2 Review of Literature

2 Review of literature: Imidazopyridine: Among all the bicyclic N-containing heterocycle, imidazopyridine find an important position due to their broad range of application. As also discussed earlier, imidazopyridines show a variety of biological activities like- antifungal, anti-inflammatory, antitumour, antiviral, antibacterial, antiprotozoals, antipyretics, analgesic, antiapoptotic, hypnoselective, and anxioselective, hinder for β-amyloid formation. They are present in various synthetic drugs such as zolmidine, zolpidem, alpidem, olprinone, mindronic acid etc. Chuan He et al. demonstrated the synthesis of 2-arylimidazo [1,2-a]pyridine (Scheme 2.1) with the help basic commercially available starting materials such as pyridine and terminal alkynes. They used silver mediated reaction through C-H/N-H oxidative cross coupling/cyclization (He et al. 2012). The reaction was tested under the catalysts of Cu(I) Iron (III) and silver(I) salts, wherein, silver(I) catalyst proved better. The best transformation obtained via using 2 equivalents of Ag_2CO_3 in dioxane, at 110 °C. Other acidic or basic additives (e.g. KOAc, NaOAc, K_2CO_3, $CsCO_3$, DBU, HOAc and HOPiv) were also screened but did not improve the efficiency of reaction.

Scheme 2.1 Oxidative cross coupling between 2-aminopyridineand terminal alkyne Antiulcer drug zolmidine (Scheme 2.11) was also prepared by Ag mediated reaction of 2-aminopyridine and 4-ethynylphenylmethylsulfane (Tang, Furuya, & Ritter, 2010).

Scheme 2.11 Synthesis of drug zolmidine (anti-ulcer). The simple and efficient strategy for the synthesis of imidazo [1,2-a]pyridine via reaction of 2-aminopyridine with ketone. This transition metal catalyzed reaction results in the simultaneous C-H activation and C-N bond formation through the loss of water and hydrogen gases. A model copper catalyzed reaction between 2-aminopyridine (5mmol) and acetophenone (7.5 mmol) at 60° C have been reported using BF3Et2O as additive in solvent DMF (Chandra Mohan, Reddy Donthiri, Nageswara Rao, & Adimurthy, 2013).

Scheme 2.2 Synthesis of imidazo[1,2-a]pyridine. In contemporary organic synthesis reaction which is efficient, atom economical and environmental friendly is preferred (Nicolaou, Edmonds, & Bulger, 2006). As we discussed earlier that addition of nucleophile to α,β-unsaturated compound taken place easily via Michael type of addition. Sougata Santra et al. demonstrated the imidazopyridine synthesis through one pot cascade reaction of nitroolefins and 2-aminopyridine in presence of Iron(III) catalyst (Santra, Bagdi, Majee, & Hajra, 2013). The reaction mechanism goes through Michael type addition trail by intramolecular cyclization and in situ denitration (Scheme 2.3).

Scheme 2.3 One pot cascade reaction synthesis of imidazo [1,2-a]pyridine. Xiaoqiang Zho et al. reported aerobic oxidative synthesis of 3-Bromo-imidazo[1,2-a]pyridines under copper catalysis with the help of pyridines and enamides (Zhou et al., 2015). The transformation is compatible with various functional group and a series of 3-Bromo-imidazo[1,2-a]pyridines was obtained under normal conditions. The higher yield given by solvent DCE, CuBr2 is comparatively better than CuBr. The oxidants TBHP, DTBP, K2S2O8 and oxygen was evaluated, oxygen found good ability among them. The best condition include the use of CuBr2, solvent dichloroethane at 70 °C using CuBr2 under aerobic conditions (Zhou et al., 2015) (Scheme 2.4).

Scheme 2.4 Oxidative synthesis of 3-bromoimidazo[1,2-a]pyridine. Jipan Yu, et al. reported the synthesis of imidazopyridine via copper catalyzed aerobic C-H functionalization of substituted of pyridine with N-(alkylidine)-4-H1,2,4-trazol-4-amines. This reaction goes through the breaking of N-N bond of N-(alkylidine)-4-H1,2,4-trazol-4-amines followed by the activation of aryl C-H bond of substituted pyridine. The optimization condition was CuI (10 mol %), DMF as solvent at 110 °C, oxygen as oxidant, varying the temperature lead to decrease the reaction yield. It was found that pyridine with electron donating group having higher yield than electron withdrawing. N-(alkylidine)-4-H1,2,4-trazol-4-amines having electron withdrawing group provide higher yield than neutral or electron donating groups (Scheme2.5).

Scheme 2.5 C-H functionalization of substituted pyridine. HaoYan, et al. reported the Iron(II) catalyzed, synthesis 3-methyl-2arylimidazo[1,2-a]pyridine. The reaction was carried out between 2-aminopyridines and nitroolefins. Reaction was started with CuI at 150 °C for 7 h to provide 30% yield of 3-methyl-2arylimidazo[1,2-a]pyridine. Different copper salt used but there is no significant increase in yield. On employing the Iron(II) salt, the product yield enhanced significantly. Lowering the temperature (130 °C) decreased the yield. Electron withdrawing groups were having higher yield as compared to electron donating group. Also, the substituents at fourth position of aminopyridine were having higher yield as comparison to other similarly substituted position. Also electron withdrawing group (chloro, bromo, cyano)

on aromatic ring of nitrololfine were having higher yield than electron donating(methyl or methoxy) (Yan et al., 2012) (Scheme 2.6).

Scheme 2.6 Iron(II) catalyzed synthesis 3-methyl-2arylimidazo [1,2-a]pyridine. Suren Hasinec, et al. reported the synthesis of imidazopyridine via base mediated cyclization of N-propargylaminopyridine. The reaction was employed using excess of base at room temperature. The stereochemistry of substituents was found to affect the cyclization process. Various reaction parameters were investigated, wherein, solvent THF and tBuOk base at room temperature proved better (Husinec, Markovic, Petkovic, Nasufovic, & Savic, 2011) (Scheme 2.7).

Scheme 2.7 Cyclization of N-propargyl aminopyridine. Kamarul Monir et al. describe the synthesis of 3-aroylimidazo[1,2-a]pyridine via copper catalyzed aerobic oxidative coupling of chalcone and 2-aminopyridine through C-H amination (Scheme 2.8). The reaction proceeds via tandem Michel type addition trailed by intramolecular C-H amination. The reaction between 2-aminopyridine and 1,3-diphenylpropenonone when carried using 10 mol% of Cu(OAc)2.H2O in 1,2-DCB under air yield 52% of desired product. Various ligands were screened such as bipyridine, DMEDA, TEMEDA, 1,10-phenanthroline and 8-hydroxy quinoline. The best result was obtained with 1,10-phenanthroline (64% yield). Various solvents were used (DMSO, DMF etc.) but not effective as compared to 1,2 DCB. Among various screened copper salts such as CuBr, CuBr2, CuCl, CuCl2 and Cu(Otf)2 ,Cu(OAc)2.H2O, Cu(OAc)2.H2O was most effective one (Monir, Kumar Bagdi, Mishra, Majee, & Hajra, 2014).

Scheme 2.8 Synthesis of 3-Aroylimidazo[1,2-a]pyridine via oxidative coupling.

Darapaneni Chandra et al. describe the synthesis of imidazo [1,2-a]pyridine through silver mediated aminooxygenation using acetonitrile as a solvent (Scheme 2.9). Various silver salts were screened where in the best result were obtained when (2 mol%) of AgNO3 along with 10 mol% of TMEDA in acetonitrile were temperature. An example for the formation of 8-(benzyloxy)imidazo[1,2-a]pyridine-3-carbaldyhde, confirmed by single crystal XRD techniques has been disclosed. It was found that N-(prop-2-yn-1-yl)pyridine-2-amines were easily converted to methylimidazo[1,2-a]pyridine without using any catalyst under water medium. (Chandra Mohan, Nageswara Rao, & Adimurthy, 2013). Scheme 2.9. Synthesis of imidazopyridine derivative by aminooxygenation and hydroamination. Zhang-Geo et al. described the one pot synthesis of 2-phenylimidazo [1,2-a-α]pyridine with the help of acetophenone in ionic liquid [Bmim]Br3 and 2-aminopyridine in solvent free condition (Scheme 2.10). The process was carried out in the presence of base, Na2CO3 providing good yield in the range of 72%-89% (Le, Xie, & Xu, 2012).

Scheme 2.10 One pot synthesis of 2-phenylimidazo[1,2-a-α]pyridine via ionic liquid.

Chapter 3 Objectives

3.1: Objectives: The main objectives of project are: 1: Review of literature on synthesis of imidazopyridine via different strategies. 2: Green synthesis of imidazopyridine.

Chapter 4 Material and Methods

4.1 Materials and methods: All the chemicals (reagents & solvents) were purchased from the commercial sources (Sigma Aldrich, Himedia) and used as received. 1) For thin layer chromatography, pre-coated TLC plates (0.2 mm silica gel 60 F-254-Merck) were used. Column chromatography was performed using silica gel (60-120 mesh) spectrochem as an adsorbent. 2) For weighing purposes, sartorious analytical balance (BSA224S-CW) was used, during the reaction JSGW heating mantle, stirrer, heater, and ILMVAC Rodist digital rotary evaporator, etc were used. 3) FT-IR spectrum was carried out on GC-MS, Tensor-27 spectrometer. 4) Mass analysis was carried out on GC-MS (Gas Chromatography-Mass spectrometry). 5) NMR analysis was carried out on 400 MHz NMR- Spectrometer.

4.2 Procedure for the Synthesis of 1-butyl-3-methylimidazolium Bromide ([bmim]Br) (1c) N-methylimidazole (1a, 0.3 mol) and butyl bromide (1b,1.2 eq) were taken in 100 ml round bottom refluxed for 24 h at 70 °C (Kärkkäinen & Peuhkurinen, 2007). The mixture was washed with diethyl ether to remove the excess butyl bromide. The ionic liquid (1c) was obtained; it was dried on rotavapor under reduced pressure (Scheme 4.1).

Scheme 4.1 Synthesis of 1-butyl-3-methylimidazolium bromide. Light yellow viscous oily liquid Yield - 70% Molecular formula- C8H15BrN2 Molecular weight: 219.122 g/mol. 4.3 procedure for Synthesis of 1-hexyl-3-methylimidazolium Bromide ([hmim]Br): N-methylimidazole (1a, 0.2 mol) and 1-bromohexane (1d, 1.2 eq.) were taken in 100 ml round bottom flask for 24 h at 70 ° C in refluxed condition. The solution was washed with diethyl ether to remove excess hexyl bromide and obtained Ionic liquid (2a) was further vacuum evaporated (Scheme 4.2) (Javadian et al., 2013).

Scheme 4.2 Synthesis of 1-hexyl-3-methylimidazolium Bromide. Dark brown viscous liquid Yield - 72% Molecular formula- C10H19BrN2 Molecular weight- 247.18 g/mol

4.4 Procedure for Synthesis of 1-butyl-3-methylimidazolium Hydroxide ([bmim]OH): [bmim]Br (1c 40 mmol) and KOH (1.0 eq.) were taken in 100 ml round bottom flask, followed by the addition of 20 ml DCM.

The reaction was stirred for 10 h at room temperature and the reaction mixture was

filtered to remove any precipitated KBr. The solution was then evaporated on rotary-evaporator under reduced pressure at 60 °C For purification, the resulting viscous liquid (3a) was washed with ether and then dried using rotavapor (Scheme 4.3) (A. Hajipour & Rafiee, 2009).

Scheme 4.3 Synthesis of 1-butyl-3-methylimidazolium Hydroxide (3a). Reddish Brown viscous

liquid Yield- 69%

Molecular formula- C8H16N2O Molecular weight- 156.225 g/mol

4.5

Procedure for the synthesis of 1-methylimidazolium p-tolunesulphonic acid: N-Methylimidazole (1a, 5 g) was added in a flask equipped with a magnetic stirrer and cooled in an ice water bath followed by addition of p-toluene sulfonic acid (1f, 10.5 g) and 1 ml water. The mixture was stirred for an additional period of 2 h. Water in the crude product was evaporated at 70 oC to afford a viscous liquid (4a) (Scheme 4.4) (A. R. Hajipour & Rafiee, 2010).

Scheme 4.4 Synthesis of 1-butyl-3-methylimidazolium-p-toluenesulfonic acid (4

0: http://doras.dcu.ie/17467/ 75%

a).

White solid Yield- 68% Molecular formula-C11H14N2SO3 Molecular weight- 254.30 g/mol

4.6

Screening of different ionic liquids for the synthesis of imidazo[1,2-a]pyridine: (6c) Firstly, we tried the synthesis of imidazopyridine in the presence of various synthetically prepared ionic liquids such as [bmim]Br, [hmim]Br, [bmim]OH, [Hmim]pTSA. The reaction was carried out using 2-aminopyridine (6a, 1.2 eq), acetophenone (6b, 50 mg, 0.416 mmol), CuI (20 mol%) as a catalyst in the presence of ionic liquid (0.2 ml) at 80 °C for 6 h (scheme 4.5).

Scheme 4.5 Synthesis of imidazo[1,2-a]pyridine (6c)

The progress of reaction was checked regularly by using the pre-coated TLC under the UV lamp. After completion of the reaction, the work-up was done by ethyl acetate and water to separate out the inorganic and organic part. Organic layer was passed through sodium sulfate to remove the moisture. The product was isolated in all cases. The yield of the product obtained by using various ionic liquids was observed and compared. Out of all used ionic liquids, the best yield of product was obtained using [hmim]Br ionic liquid. The result of optimization of the reaction conditions are summarized in result and discussion chapter. 4.7 Representative procedure for the synthesis of Imidazo[1,2-a]pyridine: The reaction of 2-aminopyridine (6a, 46.98 mg, 1.2 eq) and acetophenone (6b, 0.416 mmol) was carried out using ionic liquid [hmim]Br (0.2 ml) along with copper iodide (0.2 eq, 15.84 mg) at 80 °C for 6 h. The progress of reaction was checked regularly by using the pre-coated TLC under the UV lamp. After completion of the reaction, the work-up was done by ethyl acetate and water to separate out the inorganic and organic part. Organic layer was passed through sodium sulfate to remove the moisture. The product was isolated through column chromatography in 75% yield (Scheme 4.6).

Scheme 4.6 Synthesis of 2-phenylimidazo[1,2-a]pyridine using ionic liquid [hmim]Br Characterization-1

H NMR (400 MHz, CDCl3) δ = 8.09 (1

H, d,

j = 8 Hz), 7.94 (1H, d, j = 4Hz), 7.84 (1H, s), 7.62 (1H, d, j = 8Hz), 7.43 (1

H,

t, j1 =4Hz, j2=8Hz), 7.32 (1H,d, j1= 8Hg,

j2= 8Hz), 7.15 (1H, t, j1= 8Hg, j2= 8Hz), 6.75 (1H, t, , j1= 8Hz, j2= 4Hz). 13

C NMR (100

MHz,

CDCl3)

δ = 145.86, 145.77, 133.82, 128.82, 120.07, 126.11, 125.68, 124.76, 117.64, 112.52, 108.21.

Same procedure was applied for the synthesis of other imidazopyridines.

Chapter 5 Result and Discussion

Since last few decades, imidazopyridine scaffold has attracted significant attention due to its pharmaceutical potential. Thus, the chemists are more interested in developing new alternatives for the synthesis of imidazopyridine. Various synthetic strategies involving multicomponent reactions, amino-oxygenation, hydro-amination etc. have been explored for the synthesis of imidazopyridines. Also, the search for the benign synthesis of imidazopyridine utilizing various principle of green chemistry is on rise. In this context, we have tried to explore the synthesis of imidazopyridine using benign solvents such as ionic liquid and water. Ionic liquids are considered as effective catalysts as well as solvents in wide range of conventional acid/base catalyzed reactions. Here in this report, we used room temperature ionic liquids for the synthesis of imidazopyridine. In particular, imidazolium based ionic liquids have been screened (Table 1).

Table 1: Screening of ionic liquids for synthesis of 2-phenylimidazo[1,2-a]pyridine.

The reaction was carried out using 2-aminopyridine (6a, 1.2eq), acetophenone (6b, 0.416 mmol), CuI (20 mol%) as a catalyst in the presence of ionic liquid (0.2 ml) at 80 °C for 6 h (Table 1). Thus, using ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br), product (6c) was obtained in 48% yield (Table 1, entry 1). However, on increasing the alkyl chain of ionic liquid i.e. 1-hexyl-3-methylimidazolium bromide ([hmim]Br), the yield of the product increased up to 75% (Table 1, entry 2). Acidic ionic liquid 1-methylimidazoliump-toluenesulfonic acid ([Hmim] PTSA) provided only 35% yield of product (Table 1, entry 3). On the other side basic ionic liquid 1-butyl-3-methylimidazolium hydroxide ([bmim]OH) provided inferior yield of 28% as

compared to acidic ionic liquid [Hmim]PTSA (Table 1, entry 4). Even reaction under water (Scheme 5.2) provided the desired product in 55% yield under same reaction conditions. This result is of significant importance as solvent waste and their disposal is one of the major challenges faced by chemical industries.

Scheme 5.2 Synthesis of 2-phenylimdazo[1,2-a]pyridine.

By changing the various substituents on 2-aminopyridine and on acetophenone, we synthesized various imidazopyridine derivatives using [hmim]Br as listed in Table 2.

Table 2: Various substrate for synthesis of imidazo[1,2-a]pyridine derivatives[a]

Conclusion: In conclusion, we have explored a Cu-catalyzed synthesis of 2-phenylimidazo [1,2-a]pyridine from 2-aminopyridine and acetophenone using green ionic liquids. The present method, using ionic liquids has many advantages such as easy product isolation, avoiding toxic solvent and simplicity of methodology. Even the reaction was found to proceed under water. This has significant importance as solvent waste and their disposal is one of the major challenges faced by chemical industries.

31

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0: http://doras.dcu.ie/17470/ 71%	0: http://doras.dcu.ie/17470/ 71%
The reaction was stirred for 10 h at room temperature and the reaction mixture was	The reaction was allowed to continue without stirring for 2.5 h at room temperature and then the reaction mixture was
1: http://doras.dcu.ie/17470/ 100%	**1: http://doras.dcu.ie/17470/ 100%**
Molecular formula- C8H16N2O Molecular weight- 156.225 g/mol 4.5	Molecular formula: C 23 H 36 N 2 O 8 Molecular weight: 500.61 g/mol 1

Instances from: http://doras.dcu.ie/17467/

2: http://doras.dcu.ie/17467/ 75%

a).

White solid Yield- 68% Molecular formula-C11H14N2SO3 Molecular weight- 254.30 g/mol

4.6

2: http://doras.dcu.ie/17467/ 75%

a off white solid in 97 % yield (9.86 g, 28.1 mmol) Molecular formula: C 16 H 25 N 5 O 4 Molecular weight: 351.4 g/mol

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3: http://repositori.urv.cat/fourrepopublic/search/item/TDX:1432
56%

H NMR (400 MHz, CDCl3) δ = 8.09 (1

H, d,

j = 8 Hz), 7.94 (1H, d, j = 4Hz), 7.84 (1H, s), 7.62 (1H, d, j = 8Hz), 7.43 (1

H,

t, j1 =4Hz, j2=8Hz), 7.32 (1H,d, j1= 8Hg,

j2= 8Hz), 7.15 (1H, t, j1= 8Hg, j2= 8Hz), 6.75 (1H, t, , j1= 8Hz, j2= 4Hz). 13

C NMR (100

MHz,

CDCl3)

3: http://repositori.urv.cat/fourrepopublic/search/item/TDX:1432
56%

H NMR (400 MHz, CDCl 3) ? 7.24-7.21 (2H, m), 7.17-7.10 (4H, m), 6.95 (2H, d, J = 8.35 Hz), 6.74 (1H, t, J = 7.2 Hz), 5.31 (1H, t, J = 7.1 Hz), 3.64-3.52 (2H, m), 3.60 (3H, s), 3.04 (1H, ddd, J 1 = 16.1 Hz, J 2 = 9.0 Hz, J 3 = 5.6 Hz), 2.96 (1H, dd, J 1 = 14.9 Hz, J 2 =7.1 Hz), 2.79 (1H, dt, J d = 16.1 Hz, J t = 4.9 Hz), 2.66 (1H, dd, J 1 = 15.0 Hz, J 2 = 7.0 Hz); 13 C NMR (100 MHz, CDCl 3) ? 171.9, 148.8, 137.4, 134.6, 129.3, 128.8, 127.0, 126.7, 126.1, 118.1, 114.6, 56.3, 51.7, 41.5, 41.3, 27.0;