STUDIES ON NOVEL METHODOLOGIES FOR THE SYNTHESIS OF PRECURSOR OF BIOACTIVE COMPOUNDS

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in

CHEMISTRY

By

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(M.Sc. in Chemistry)

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June, 2021

Dedicated
to
My Beloved
Parents

DECLARATION

I declare that the thesis entitled "**STUDIES ON NOVEL METHODOLOGIES FOR THE SYNTHESIS OF PRECURSOR OF BIOACTIVE COMPOUNDS**" has been prepared by me under the guidance of Dr. Pranab Ghosh, Professor of Chemistry, Head of Department, University of North Bengal. No element of this thesis has formed the origin for the award of any degree or fellowship earlier.

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CERTIFICATE

I certify that **Mr. Hridoydip Ranjan Dasgupta** has prepared the thesis entitled **"STUDIES ON NOVEL METHODOLOGIES FOR THE SYNTHESIS OF PRECURSOR OF BIOACTIVE COMPOUNDS"**, for the award of Ph.D. Degree of the University of North Bengal, under my guidance. **She** has carried out the research work at the Department of Chemistry, University of North **Bengal**. No part of this thesis has formed the basis for the award of any degree or fellowship **previously**.

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ABSTRACT

The research work incorporated in this thesis entitled "**STUDIES ON NOVEL METHODOLOGIES FOR THE SYNTHESIS OF PRECURSOR OF BIOACTIVE COMPOUNDS**" is mainly focused on the development of efficient and environment benign methodologies for the new and efficient methodologies to synthesize synthons of bioactive compounds. The entire work depicted in this thesis has been divided into five chapters.

In the beginning, **Chapter I** deals with a brief idea about bioactive compound. The area of application of Bioactive compounds are wide such as: plant science, modern pharmacology, geo-medicine, agrochemicals, cosmetics, food industry, nano-bio-science... etc. Thus it is a very promising area in full development, which has resulted in research works more and more numerous, designed to diversify the resources of bioactive compounds and improve their salvage pathways or synthesis. At first we need to prepare the synthon of such bioactive compound. As their natural availability is not so promising, henceforth we feel to pursue our research interest to synthesize the precursor of bioactive compounds in a novel way.

In **Chapter II**, chemo selective reduction of a wide range of aromatic nitro compound has been performed by using inexpensive Zn powder and $CuSO_4$ system in water medium at room temperature. This system has high tolerance to other highly reducible groups present in nitro substance along with high conversation and selectivity. This chemo-selective reduction also provides a facile root for the synthesis of other industrially important fine chemicals or biologically important compounds where other highly reducible groups are present in close proximity to the targeted nitro groups.

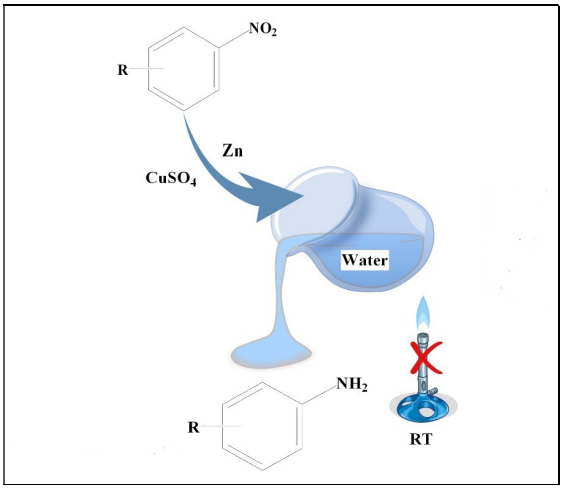

Figure: Graphical abstract of chapter I

In **Chapter III**, Small amount of Zn dust and $NaHSO_3$ is utilized to efficiently synthesize benzimidazole derivatives via one pot reductive cyclocondensation process in water medium at 100°C temperature. Very good to excellent yields in reasonably short reaction times, high atom economy and usage of readily available starting material, operational simplicity and easy workup are the fundamental features of this protocol.

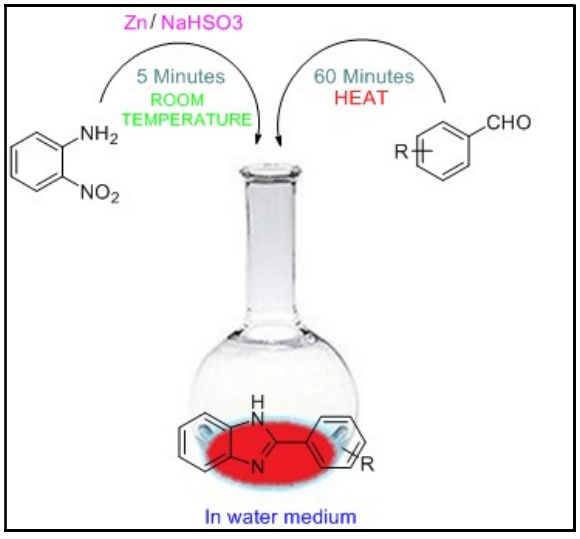

Figure: Graphical abstract of chapter II

In **Chapter IV**, an efficient catalytic system for the synthesis of Pyrazine derivatives using an extract of onion at room temperature is discussed. A very good to excellent

yields in reasonably short reaction time, high atom economy, usage of readily available starting material, operational simplicity and easy workup are the fundamental features of this protocol. The versatility of our method is determined by synthesizing a large number of pyrazine derivatives with (85-96%) good yield.

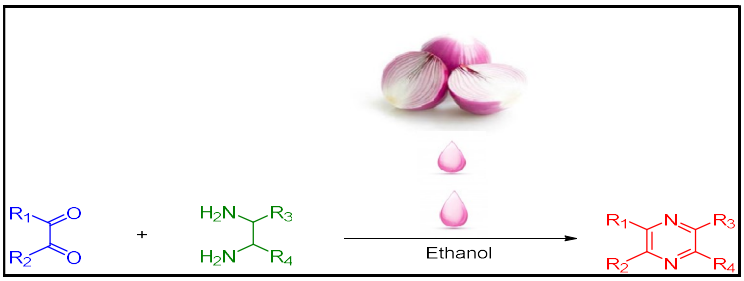

Figure: Graphical abstract of chapter III

At last, in **Chapter V**, on observing the usefulness of imidazole ring as a starting material for the synthesis of wide range of nitrogen containing physiologically active natural as well as synthetic compounds and limitations to synthesize the important moiety, we felt necessity to investigate the synthesis of same imidazole derivatives from same starting materials with different reagents by solid as well as in liquid phase and comparing the processes to know which one are the better path or which one we should follow.

PREFACE

Bioactive compounds have broad periphery of applications: plant science, modern pharmacology, geo-medicine, agrochemicals, cosmetics, food industry, nano-bio-science... etc. Bioactive compounds contain chemicals that are found in small quantities in plants. As their natural availability is not so hopeful, researchers feel to prepare such compounds in a synthetic manner. The thesis starts with Chapter I, discussed a brief idea about bioactive compound, its sources, examples with importance, synthons of some bioactive compounds and some method to synthesize it. Chapter II, deals with novel approach towards chemoselective reduction of nitro to amine. Chapter III, describes one pot reductive synthesis of benzimidazole derivatives from 2-nitro aniline and aromatic aldehydes by using $Zn/NaHSO_3$ in water medium Chapter IV deals with onion extract mediated novel synthesis of pyrazine. At last, Chapter V describes solid phase *vs*. solution phase synthesis of trisubstituted imidazoles.

Acknowledgement

*First, foremost, I would like to express my heartfelt gratitude to **Almighty God**, for his showers of blessings by providing me the strength, patience and required courage throughout my research work after all the challenges and difficulties.*

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*I am highly obliged to **Prof. A. Misra Sir**, HEAD, Department of Chemistry, N.B.U. It was a great privilege and honor to study under **Prof. M. N. Roy Sir, Prof. B. Basu Sir, Dr. Pinaki Bandhyapadhay Sir, Prof. A. K. Nanda Sir, Prof. B. D Sir, Prof. A. K. Panda Sir, Dr. S. Das Sir, Prof. B. Sinha Sir** during my post graduation. Their motivation deeply inspired me to do my research work. I also sincerely express my deep sense of gratitude to the other **faculty members** and the **non-teaching staffs** of the Department of Chemistry, N.B.U for their cordial support during my research period.*

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*I am extremely grateful to my parents, **Mrs. Munmun Sengupta** and **Mr. Subir Ranjan Dasgupta** for their love, caring, understanding, encouragement, belief and sacrifices for educating me. They are my source of energy, motivation and patience. Also I express my thanks to my elder brother **Mr. Joydip Ranjan Dasgupta** for his active support. I would like to convey my heartfelt thanks to my entire family and my in-laws, my friends for their moral support throughout my research period.*

I am extremely thankful to my wife, ***Mrs. Ananya Das*** *for her sincere, unprecedented cooperation and moral support throughout my life and during this work.*

There are so ***many others like all my fellow research mates*** *whom I may have inadvertently left out and I sincerely thank all of them for their help.*

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ABBREVIATION

Å	Angstrom
acac	Acetylacetonate
AcOH	Acetic acid
^{o}C	Degree Celsius
Cm	Centimeter
Cy	Cyclohexyl
d	Doublet
DCE	1, 2-Dichloroethane
DME	1, 2–Dimethoxyethane
DMF	*N, N*–Dimethylformamide
DMSO	Dimethyl sulfoxide
Dppe	1, 2-Bis(diphenylphosphino)ethane
Dppf	1, 1-Bis(diphenylphosphino)ferrocene
Equiv.	Equivalent
EtOH	Ethanol
FT-IR	Fouriertransforminfraredspectroscopy
g	Gram/Grams
h	Hour/Hours
HRMS	High-resolution mass spectroscopy
m	Multiplet
m	Meta
MHz	Mega hertz
min.	Minute/Minutes
mL	Milliliter
mmol	Millimole
Mole%	Mole percent
mp	Melting point
MW	Microwave

nm	Nanometer
NMR	Nuclear magnetic resonance
o	ortho
p	para
PEG	Polyethylene glycol
Phen	Phenyl
RT	Room temperature
s	Singlet
SEM	Scanning electron microscope
t	Triplet
t-BuOCl	*tert*-butyl hypochlorite
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TfOH	Triflic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography

CHAPTER-1

BRIEF IDEA ABOUT BIOACTIVE COMPOUNDS AND SYNTHETIC APPROACHES OF ITS PRECURSOR

I.1. Introduction

Bioactive compounds are experiencing a flourishing interest in broad periphery of applications: plant science, modern pharmacology, geo-medicine, agrochemicals, cosmetics, food industry, nano-bio-science... etc. Though the range of bioactive compounds is wide, the definition of bioactive compounds remains ambiguous and dim. **What is a bioactive compound?** To answer this question, we will, firstly, discuss different definitions collected, to redraft a definition from the various concepts discussed.

The term "bioactive" is built by two words: 'bio' and 'active'. In etymology: 'bio' from the Greek "bios" refers life and 'active' from the Latin "activus" means dynamic, full of energy, with energy [1-3], or involves an activity [4]. This activity presents all the phenomena such as a form of life, a functioning or a process [5]. Simply a bioactive compound is a substance that has a biological activity [6]. In medical vocabulary, a bioactive substance is a substance having an impact on [7] or causes a reaction [8], or triggers a response in [9] the living tissue.

Generally bioactive compounds are non-essential, because same compound (or molecule) cannot play two physiological roles simultaneously in the same organism: one, nutritional (energetic metabolism and development), and other: bioactive (non-nutritional). This suggestion is aiming the contrast between two completely unlike processes: the first, which requires the degradation of the compound or molecule to liberate the essential energy for the functioning of the organism along with its maturing and the second, which requires the interaction of the compound (or molecule) in its integrality with one or more components of the living tissue. Therefore, a bioactive compound is a compound which has the capability to interact with one or more component(s) of the living tissue. So it comes back from itself and without need to mention it after, this interaction (bioactivity) can disclose whatever the source of bioactive compound: food and non-food, integrated into an essential nutrient or not.

I.2. Sources of Bioactive compounds

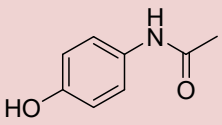
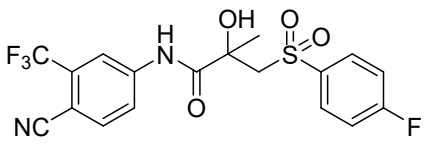
Bioactive compounds contain chemicals that are found in small amount in plants [in general] and certain foods (such as vegetables, fruits, nuts, oils and whole grains); they have actions in the body that can promote good health [10]. Typical bioactive plant compounds are produced as secondary metabolites that are not requisite for the daily functioning of the plant (such as growth) [11], but play an

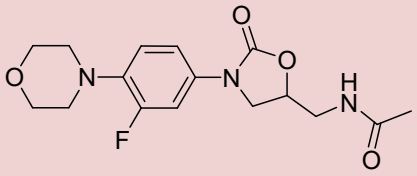
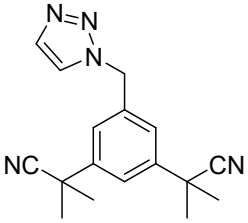
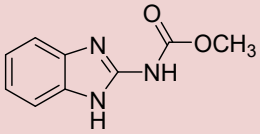
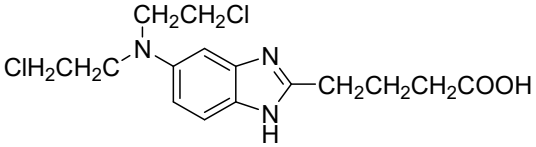
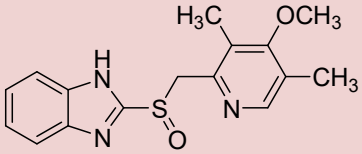
important role in the competition, defense, attraction and signaling [12]. Bioactive compounds in the plants can be explained, then, as secondary plant metabolites eliciting pharmacological or toxicological effects in humans and animals [11]. Thus, plants are not the solitary source of bioactive substances. These substances are also found in other living organisms and microorganisms, such as bacteria [13-18] mushroom [18-23] and in some groups of animals [24-28]. What is said about the terrestrial (micro-) organisms, also applies to marine (micro-) organisms. These, produce too, potentially useful substances as bioactive secondary metabolites [16-18, 24, 29-33]. It should be noted that in addition to natural bioactive substances [34, 35] the ability to synthesize a wide variety of bioactive molecules began in the early twentieth century, despite the development of pharmaceutical chemistry [36] and the emergence of new tools for chemical synthesis [37], thereby adding synthetic source of bioactive molecules. Thus a bioactive compound may be of natural or synthetic origin. This is a very encouraging area in full development, which has resulted in research works more and more numerous, designed to diversify the resources of bioactive compounds and improve their salvage pathways or synthesis.

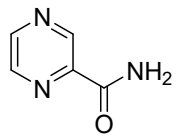
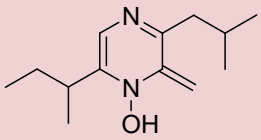
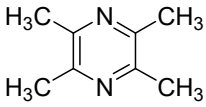
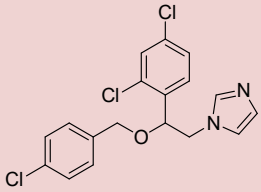
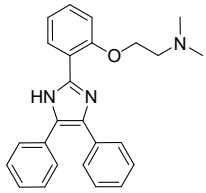
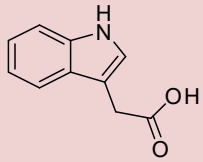
I.3. Bioactive compounds and their activity

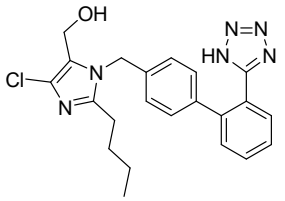
Some bioactive compounds along with their application in living tissue are shown below.

Table I.1. Examples of some bioactive compound and their bioactivity.

Sl. No.	Examples of bioactive compounds	Bioactivity
1.	Paracetamol 	Analgesic, Antipyretic
2.	Bicalutamide 	Anticancer(Prostate)

3.	Linezolide 	Antibiotic
4.	Anastrazole 	Breast-cancer treatment
5.	Carbendazim 	Fungicide
6.	Imet 3393 or Bendamustine 	Anti-cancer
7.	Omeprazole 	Treatment of GERD

8.	Pyrazinamide 	Antitubarcular
9.	Aspergillic acid 	Fungal antibiotic
10.	Ligustrazine 	Pulmonary heart disease
11.	Econazole 	Anti-fungal
12.	Trifenagrel 	Platelet aggregation inhibitor
13.	Auxine 	Plant growth regulator

14.	Losertan		Anti-hypertensive

I.4. Precursors of bioactive compounds

In chemistry, a precursor is a compound that participates in a chemical reaction that produces another compound. Simply we can say a compound from which another is formed. Therefore, precursor of bioactive compound means that a compound from which we can derive bioactive compounds. Some examples of such important precursors are shown below:

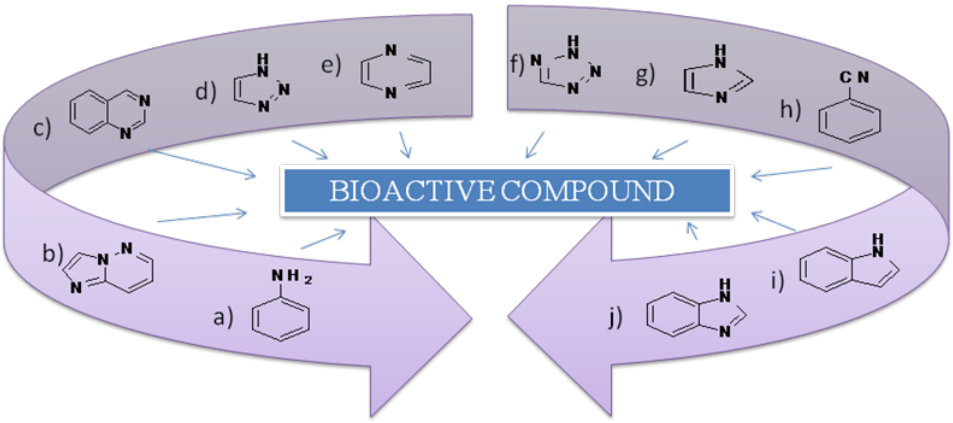


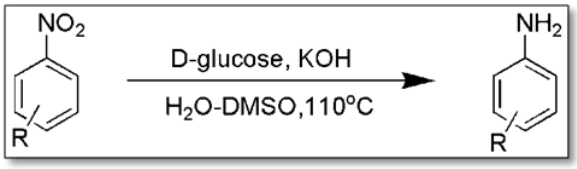
Figure I.1. Some examples of precursor of bioactive compounds. a) Aniline, b) Pyrazolopyrimidine, c) Quinazoline, d) Triazole, e) Pyrazine, f) Tetrazine, g) Imidazole, h) Nitrile, i) Indole, j) Benzimidazole.

I.5. Some synthetic approaches towards the precursor of bioactive compounds

As their natural availability is not so promising, researchers feel to prepare such compounds in a synthetic manner. After studying literature we came to know that there are large number of synthetic procedures are present by which we can prepare synthons of bioactive compounds. Some synthetic paths are shown below.

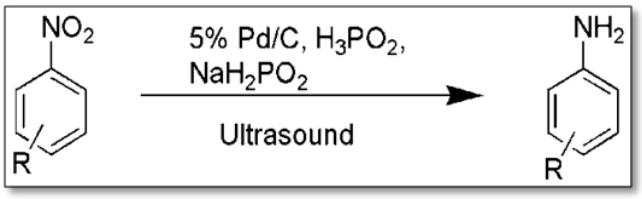
I.5.A. Synthesis of aniline

a) In 2013 M. Kumar *et al.* [38] reported reduction of aryl nitro to corresponding amine by D-glucose and KOH in water-DMSO medium at 110°C.



Scheme I.1. Reduction of aryl nitro using D-glucose-KOH.

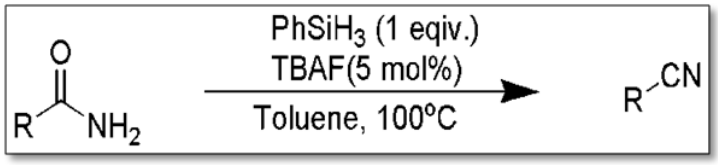
b) In the same year M. Baron *et al.* [39] reported aryl amine synthesis from aryl nitro by in-situ hydrogen generation.



Scheme I.2. Reduction of aryl nitro by in-situ hydrogen generation.

I.5.B. Synthesis of nitrile

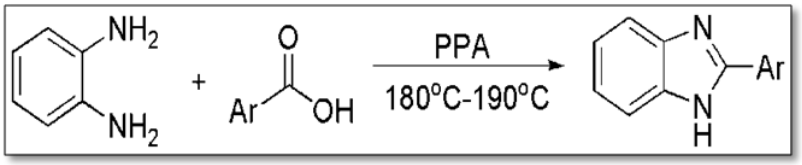
a) M. Beller *et al.* [40] converted aliphatic/aromatic amides into nitriles using catalytic amount of tetra-butyl ammonium fluoride (TBAF) and silanes.



Scheme I.3. Synthesis of nitrile using tetra-butyl ammonium fluoride (TBAF) and silanes.

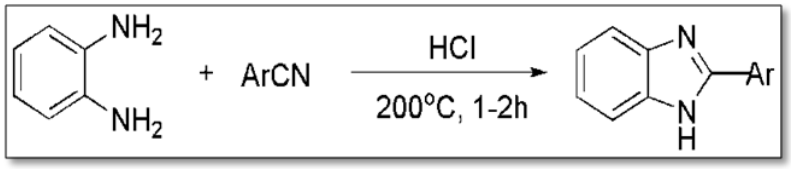
I.5.C. Synthesis of benzimidazole

a) In the presence of catalyst polyphosphate ester (PPA) at 180-190ºC, Maleki *et al*. [41], condensed *o*-phenylenediamine with aromatic carboxylic acid and got 2-arybenzimidazole.



Scheme I.4. Synthesis of 2-arybenzimidazole using catalyst polyphosphate ester (PPA).

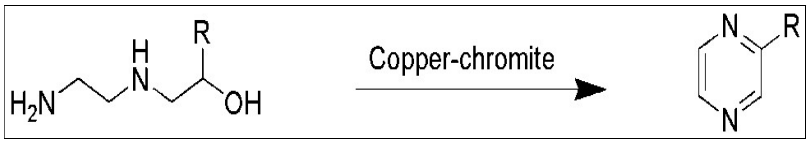
b) Hollies and Wagner obtained 2-substituted benzimidazole by the reaction of o-phenylenediamine with the substituted nitrile at 200 ºC for 1 to 2 h [42].



Scheme I.5. Synthesis of 2-substituted benzimidazole by o-phenylenediamine with substituted nitrile.

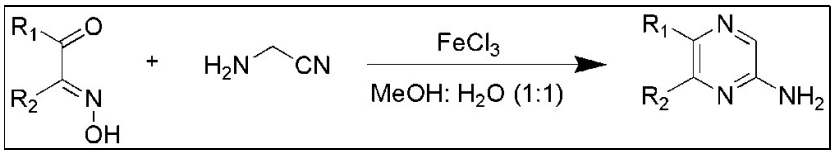
I.5.D. Synthesis of pyrazine

a) In 1990, Lee *et al.* [43] patented (U.S. Patent No. 4,966,970, 1990) the synthesis of pyrazine using copper-chromite catalyst (Scheme I.6). The catalytic reaction was carried out by adding copper-chromite catalyst to diamine compound at 300-450°C for 1-3 hours.



Scheme I.6. Synthesis of pyrazine using copper chromite.

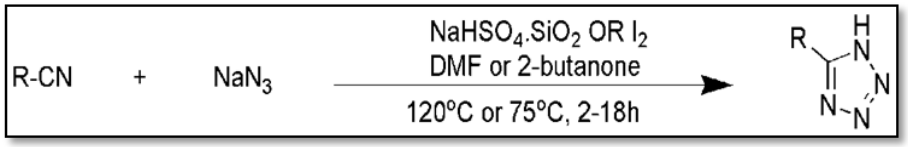
b) In year 2002, Itoh *et al.* [44] reported the reaction between isonitroso-acetophenone and aminoacetonitrile in the presence of one equivalent of $FeCl_3$ to give *N*-oxide pyrazine and subsequent hydrogenation with 10% of Pd-C to afford 55-80% pyrazine (Scheme I. 7).



Scheme I.7. Catalytic formation of pyrazine using $FeCl_3$.

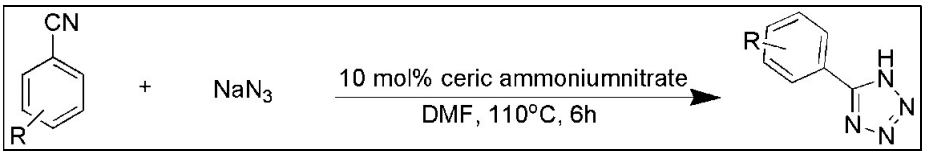
I.5.E. Synthesis of tetrazole

a) In 2009, R. Narender *et al.* [45] reported synthesis of 5-substituted 1*H*-tetrazoles using iodine or silica-supported sodium hydrogen sulfate. Here wide array of nitriles including aliphatic, aromatic, hetero nitriles as well as chloroalkyl nitriles are converted to corresponding tetrazoles with outstanding yield (Scheme I.8).



Scheme I.8. Synthesis of 5-substituted 1H-tetrazoles using iodine or silica-supported sodium hydrogen sulfate.

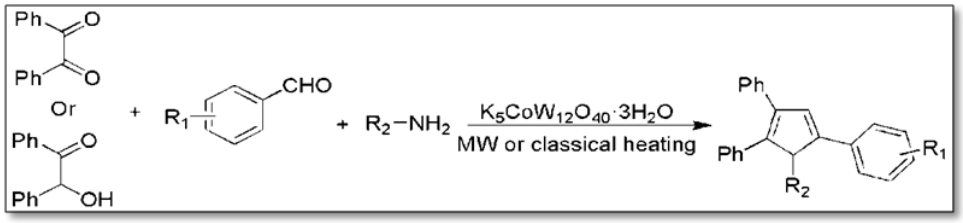
b) In 2014, S. K. Awasthi *et al.* [46] reported conversion of nitriles to 5-substituted 1H-tetrazoles using cerric ammoniumnitrate ($(NH_4)_2Ce(NO_3)_6$)as eco-friendly catalyst (Scheme I.9).



Scheme I.9. Synthesis of 5-substituted 1H-tetrazoles using $(NH_4)_2Ce(NO_3)_6$.

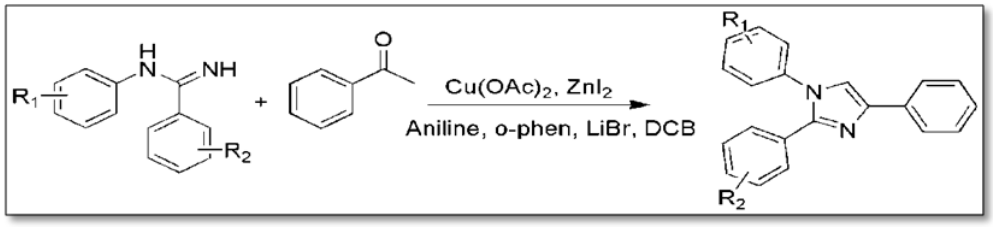
I.5.F. Synthesis of imidazole

a) In 2007, L. Nagarapu *et.al.* [47] reported potassium dodecatugstocobaltate trihydrate ($K_5CoW_{12}O_{40}\cdot 3H_2O$) catalyzed one-pot synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles under conventional heating and microwave irradiation.



Scheme I.10. Potassium dodecatugstocobaltate trihydrate catalyzed synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles.

b) Bao-Hua Chen *et al.* [48] have reported copper and zinc co-catalyzed efficient synthetic approach to imidazoles from amidines and arylketone via oxidative coupling of (sp^3) C-H bond and N-H bond (Scheme I.11).



Scheme I.11. Copper and zinc co-catalyzed synthetic approach to imidazoles from amidines and arylketone.

I.6. Conclusion

Above synthetic procedure draw our interest to synthesize different precursors of bioactive compound in a more convenient way as the processes have large number of limitations, such as-

- Use of organic hazardous solvents

- High temperature
- Difficult reaction setup
- Use of non available reagents
- Use of corrosive chemical
- Time consuming process

In one word the processes are not environmental friendly. Henceforth, to minimize the drawback of these processes I feel to pursue my research interest to synthesize the precursor of bioactive compounds in a novel way.

I.7. References

References are given in BIBLIOGRAPHY under Chapter I.

CHAPTER-2

A NOVEL APPROACH TOWARDS CHEMOSELECTIVE REDUCTION OF NITRO TO AMINE

II.1. Amines

By replacing one or more hydrogen atoms of ammonia molecule by alkyl/aryl group(s) we get an important class of organic compounds called amine. According to the nature of substituents on nitrogen, amines can be classified as aliphatic amines and aromatic amines. Amines, alkyl and aryl alike, are organized into three subcategories, primary (1°) amines, secondary (2°) amines, tertiary (3°) amines based on the number of carbon atoms adjacent to the nitrogen (Figure II.1).

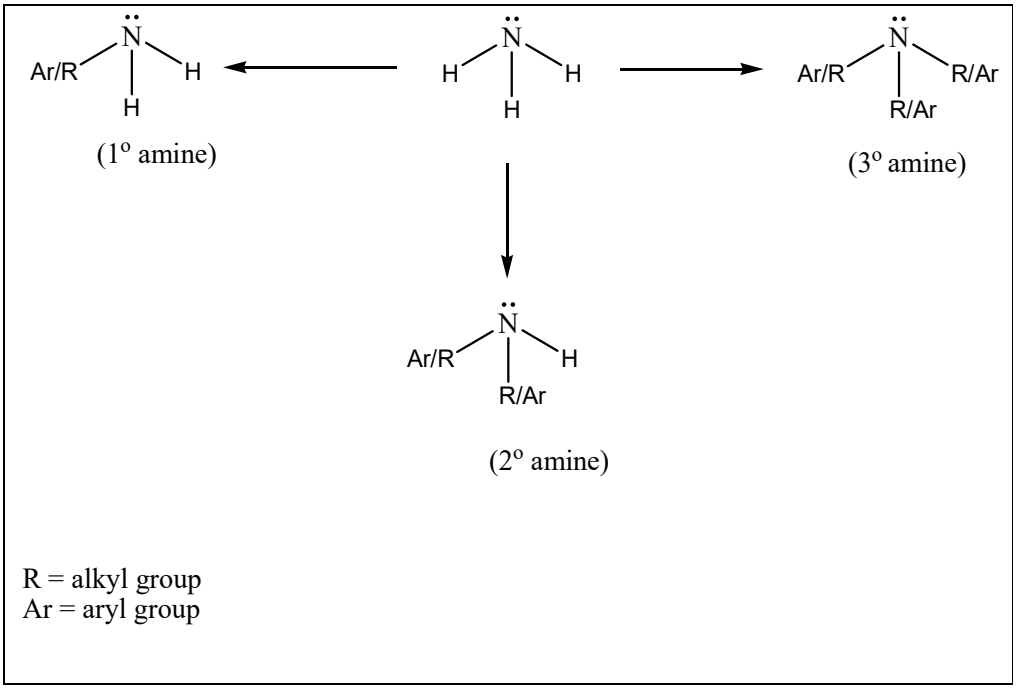


Figure II.1. Different types of amine.

II.2. Importance of aromatic amines

Aromatic amines represent a category of chemical agents of considerable importance as witnessed by their widespread use as intermediates in the manufacture of drugs, pesticides, plastics, as antioxidants in the preparation of rubber for the manufacture of tires and cables and as curing agents in the preparation of various plastics. In addition, they are widely used as intermediates in the synthesis of several nitrogen-containing biologically active compounds, agrochemicals, dyes, polymers, etc [1]. They are the precursors for many synthetically important intermediates like amides, imines, azo compounds, isocyanates and diazonium salts which could be converted to various other functional groups [2].

Anilines also form many pharmaceutical compounds. Paracetamol[3] 1a is a widely used analgesic and antipyretic. Bicalutamide[4] 1b is a non-steroidal antiandrogen administered orally for the treatment of prostate cancer and hirsutism. Nilutamide[5] 1c is used in the treatment of advanced-stage prostate cancer. Erlotinib[6] 1d is used in the treatment of non-small cell lung cancer and pancreatic cancer. Linezolid[7] 1e, a synthetic antibiotic for multi drug resistant Gram-positive bacteria. Fosamprenavir[8] 1f, is an anti-HIV drug and pro-drug of amprenavir. They all are the derivatives of aminophenol or aniline.

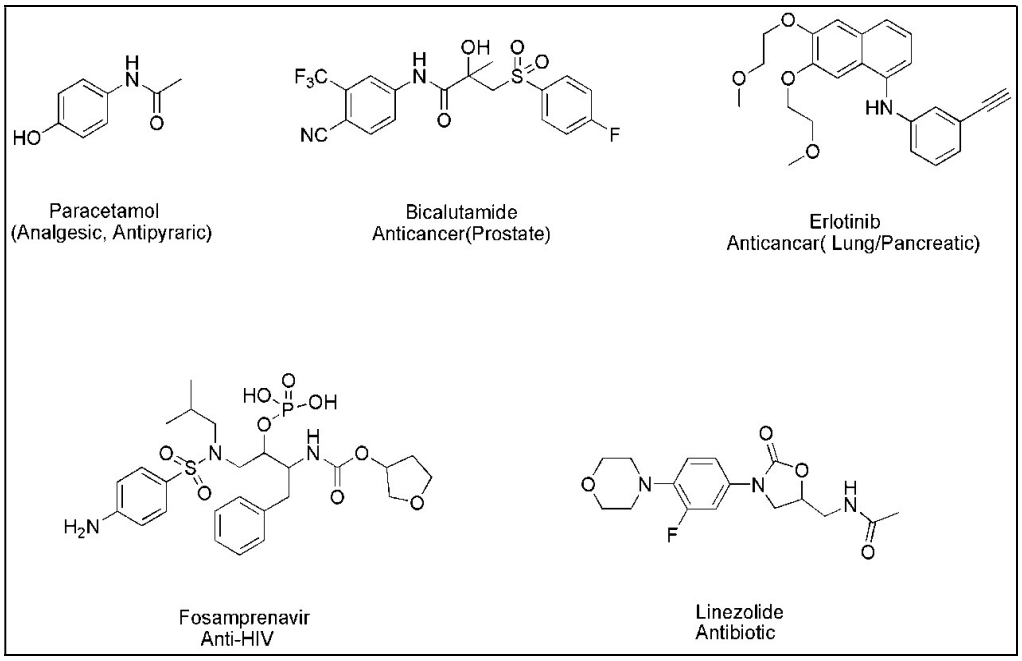
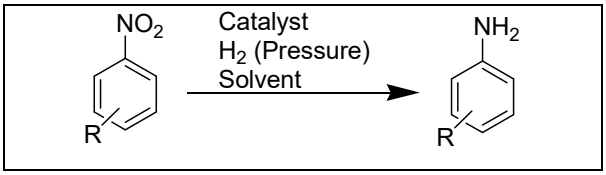


Figure II.2. Some pharmaceutical compounds derived from aniline.

II.3. Synthesis of Aromatic Amines

The importance of aryl amines as raw materials for various applications has spurred extensive research in developing economic processes for the reduction of nitroarenes. Here we compile some recent progresses and achievements for reduction of nitroarenes to arylamines.

II.3.A. Hydrogen gas



Scheme II.1. Reduction of nitroarenes using hydrogen gas.

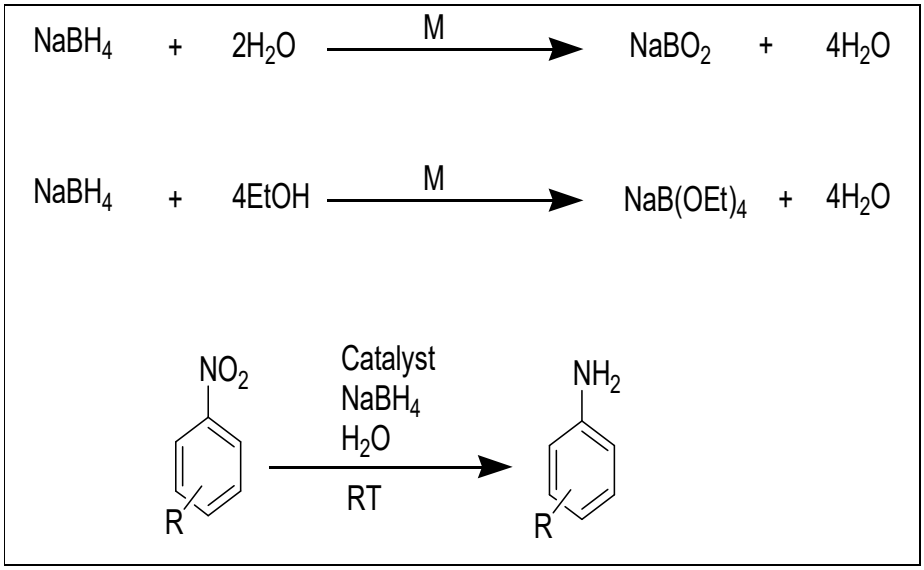
Table II.1. Reduction methodologies using hydrogen gas.

Entry	Catalysts	H_2-pressure (atm)	Solvent, Conditions	References
1	Pd/Fe_3O_4	1	EtOH/THF, RT	[9]
2	Pt-Ionic liquid	10	90°C	[10]
3	$Au\text{-}TiO_2$	9	Toluene,100°C	[11]
4	$Ni\text{-}SiO_2$	20-30	EtOH, 110°C	[12]
5	Ru-Reduced grapheme oxide	20	EtOH/H2O, 110°C	[13]

Catalytic hydrogenation is routinely employed in industry and in research laboratories, but it has the distinct disadvantage of the requirement of special equipment to handle high-pressure and inflammable H_2. Also a large amount of hydrogen is wasted and is usually lost to the atmosphere after the reaction is over.

II.3.B. By $NaBH_4$

$NaBH_4$ used for reduction of nitro to amine functionality with formation of non-toxic sodium borate as a by-product (Scheme II. 2).



Scheme II.2. Reduction of nitroarenes using $NaBH_4$.

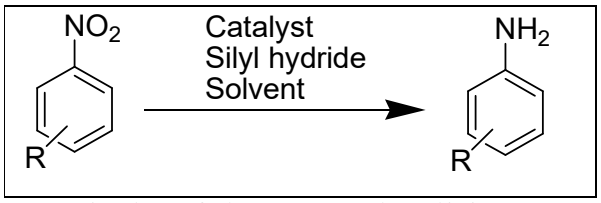
Table II.2. Reduction methodologies using $NaBH_4$

Entry	Catalyst	References
1	Au-graphene hydrogel	[14]
2	Cu NPs	[15]
3	Co_3S_4	[16]
4	Au-Fe_3O_4 nanocatalyst	[17]
5	Ag quantum clastures	[18]

Though $NaBH_4$ mediated reductions are safer to handle compared to catalytic hydrogenations, however they have the problem of workup to extract the product from the aqueous reaction medium. Also excess of $NaBH_4$ is required to complete the reduction process. In addition, metal reacting with $NaBH_4$ generates hydrogen, which needs to be taken care of when large-scale reductions are to be carried out. Also in most of the above cases the selectivity problem was not addressed; rather, the work centered on making NPs and demonstrating the usefulness of the NPs for catalytic processes.

II.3.C. Silyl hydrides

Nitro reduction with silyl hydrides proceeds through the nitroso and hydroxylamines route; the exact mechanism for this reduction process is not clear. It may take place via metalcatalyzed hydrosilylation or via hydrogenation with evolved hydrogen gas (Scheme II. 3).



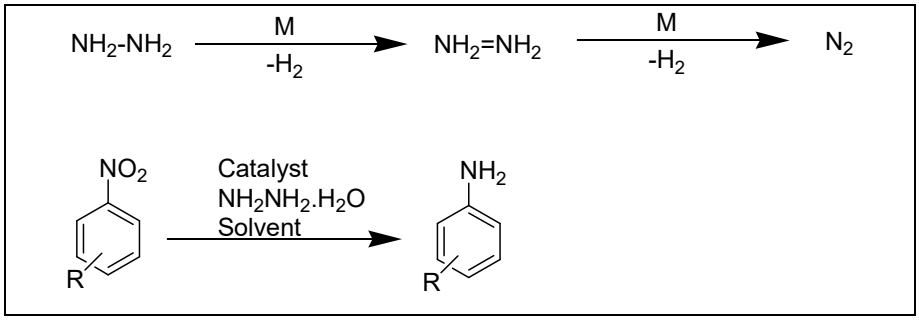
Scheme II. 3. Reduction of nitroarenes using silyl reagents.

Table II.3. Reduction methodologies using Silyl reagents.

Entry	Catalyst	Silanes (equivalent)	Solvent, Condition	References
1	$Pd(OAc)_2$	PMHS(4)/KF	THF/H_2O, RT	[19]
2	$Fe(acac)_3$	TMDS(4)	THF, 60°C	[20]
3	Au-Fe_3O_4	TMDS (4-10)	EtOH, RT	[21]

Again like $NaBH_4$-mediated reductions, the problem of work up, scaling up and use of excess reducing agent cannot be avoided for this system. However, the selectivity in the reduction process looks to be promising and further developments are expected.

II.3.D. Hydrazine hydrate



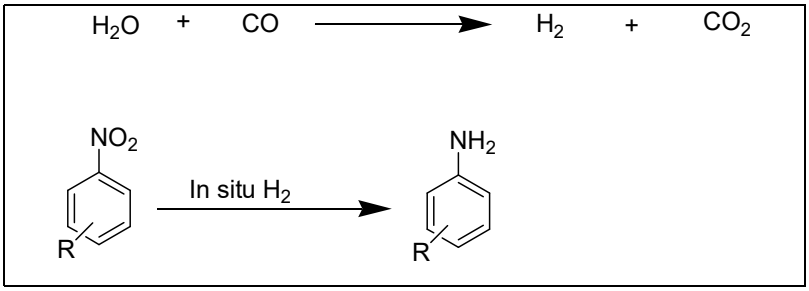
Scheme II.4. Reduction of nitroarenes using hydrazine.

Table II.4. Reduction methodologies using hydrazine.

Entry	Catalyst	Solvent, Conditions	References
1	Pd-C nanospheres	$EtOH/H_2O$, 80°C	[22]
2	Graphene-Fe_3O_4	70°C	[23]
3	MoS_2	Toluene, 60-80°C	[24]
4	PVP-Stabilysed Ni or Co	H_2O, RT	[25]

Hydrazine hydrate-mediated reductions are much cleaner than the hydride processes as the byproducts are nitrogen and hydrogen. However, selectivity in the presence of carbon– carbon double bond, triple bond and aldehyde may be difficult to achieve, although it has been claimed in some instances.

II.3.E. In situ hydrogen generation:



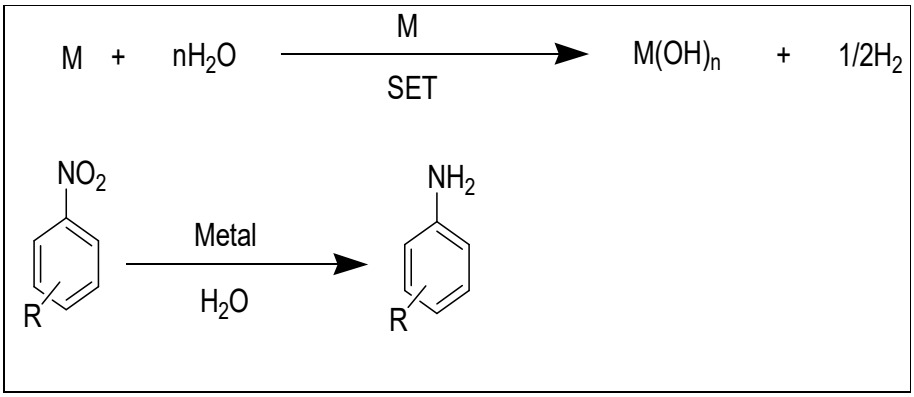
Scheme II.5. Reduction of nitroarenes by In situ hydrogen generation.

Table II.5. Reduction methodologies by In situ hydrogen generation.

Entry	Reagents(equivalents)	Solvent, Conditions	References
1	HCOOH(excess)	HTP water, 300°C	[26]
2	5% Pd/C, H_3PO_2(1), NaH_2PO_2(3)	Ultrasound	[27]
3	CeY zeolite, HCOOH or HCOONH4(1.6)	Microwave, 140°C	[28]

Milder conditions and stoichiometric use of decomposing reagents and simplified workup procedures are required to make these methods popular.

II.3.F. Direct metal



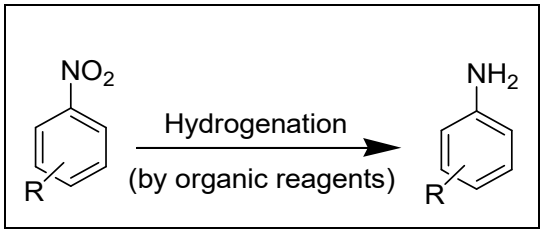
Scheme II.6. Reduction of nitroarenes by using metal.

Table II.6. Reduction methodologies using direct metal.

Entry	Metal reagent (equivalent)	Solvent	References
1	Fe NPs (3)	H_2O, RT	[29]
2	Te(3)	H_2O, 275°C	[30]
3	Zn,CO_2(1atm)	H_2O, ultrasound	[31]

Metal reductions as such are very selective in reducing the nitro functionality, but stoichiometric requirement of metals makes these processes unattractive.

II.3.G. Organic reducing agents



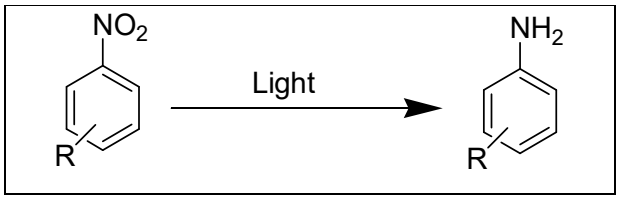
Scheme II.7. Reduction of nitroarenes by using organic reducing agents.

Table II.7. Reduction methodologies using non- classical reagents.

Entry	Reagents (equivalent)	Solvent, Conditions	References
1	D-Glucose(2), KOH(4)	H_2O: DMSO, 110°C	[32]
2	Pinacol(4), $MoO_2Cl_2(dmf)_2$	Toluene, MW, 150°C	[33]
3	Polymer- bound palladium, K_3PO_4(1.5), cyclohexanol	DMF, 110°C	[34]

Transfer hydrogenations using sustainable materials under mild conditions may go a long way in meeting the future demands of such reduction processes.

II.3.H. Light- Induced Photocatalysis



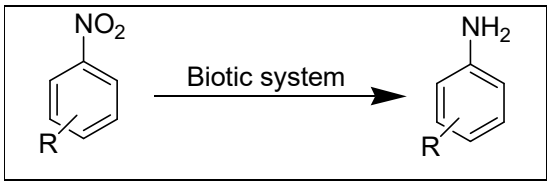
Scheme II.8. Reduction of nitroarenes by using light.

Table II.8. Reduction methodologies using light sources.

Entry	Reagents	Solvent, Conditions	References
1	Ru-dye-TiO_2, TEOA, 530nm	MeCN, RT	[35]
2	$PbBiO_2Br$, 440nm, TEOA	MeCN, RT	[36]
3	CdS nanowires, reduced graphine oxide, >420 nm, $HCOONH_4$	H_2O, RT	[37]

Direct sunlight-mediated photochemical reductions on a large scale particularly for environmental cleaning will be of great help in the future.

II.3.I. Biotic reduction



Scheme II.9. Reduction of nitroarenes by using biotic system.

Table II.9. Reduction methodologies using natural sources.

Entry	Natural sources	Conditions	References
1	Cattle tick Boophilus microplus, spider Nephila plumipes	In vivo	[38]
2	Plant cells from grapes (Vitis vinifera L.)	H2O, 25°C	[39]
3	Biocatalyzed cathode	Glucose, 25°C	[40]

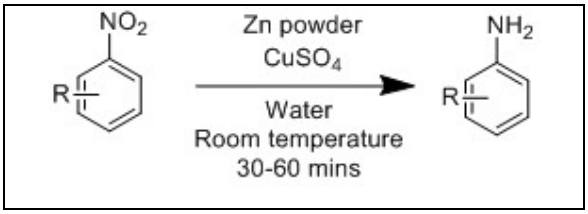
Enzymatic reductions have shown great promise, and sustained research in this field is required for future developments.

Cost-effective green alternatives of transfer hydrogenation, enzymatic and photochemical reduction methods are the ones where more progress is expected. The market potential for a new industrial application is also very high due to the demand of the final reduction product, aniline. Vastly employed method for the preparation of substituted aromatic amines is reduction of corresponding nitro substrates. But

selective reduction of a functional group in presence of other functional group which is also reducible is often a very difficult task. [41] By accepting the challenge to make difficult task to facile path, I tried and took a small step to convert aryl nitro to aryl amine.

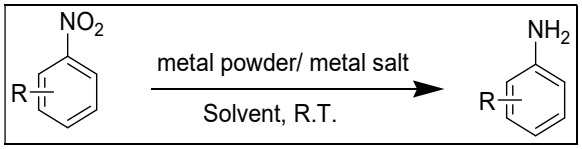
II.4. Present Work

Aromatic nitro compounds were reduced in good yield to the corresponding amino compounds under mild conditions in the presence of low cost and easily available metal and metal salt Zn and $CuSO_4$ respectively in water, with single product. The compound obtained were monitored by TLC and separated by column chromatography. The general scheme and reaction are shown in Scheme II.10.



Scheme II.10. Conversion of aryl nitro to aryl amine.

II.4.A. Results and discussion



Scheme II.11. Plan for Conversion of aryl nitro to aryl amine.

Table II.10. [a]Optimization of the reaction condition for reduction of Nitroarenes to the corresponding Anilines.

Entry	Metal/Metal salt	Solvent	Time (min.)	Temperature (^{0}C)	[b]Yield (%)
1	Fe/$CuSO_4$	Nil	180	R.T	Nil
2	Zn	H_2O	180	R.T	Nil
3	Fe	H_2O	180	R.T	Nil
4	$CuSO_4$	H_2O	180	R.T	Nil
5	Fe/$CuSO_4$	H_2O	180	R.T	68
6	Fe/$CuSO_4$	H_2O+EtOH	180	R.T	60

7	Fe/ $CuSO_4$	EtOH	180	R.T	56
8	Cu/$CuSO_4$	H_2O	180	R.T	65
9	Zn/$CuSO_4$	H_2O	180	R.T	95
10	Zn/$FeSO_4$	H_2O	180	R.T	80
11	Zn/$ZnSO_4$	H_2O	180	R.T	76
12	Zn/$NiSO_4$	H_2O	180	R.T	72
13	Zn/$CuSO_4$	H_2O	120	R.T	95
14	**Zn/$CuSO_4$**	**H_2O**	**60**	**R.T**	**94**
15	Zn/$CuSO_4$	H_2O	30	R.T	70
16	Zn/$CuCl_2$	H_2O	60	R.T	84
17	Zn/$Cu(OAc)_2$	H_2O	60	R.T	72
18	Zn/$CuBr_2$	H_2O	60	R.T	66
19	Zn/$CuSO_4$	H_2O	60	60	89
20	Zn/$CuSO_4$	H_2O	60	80	87

[a]Reaction of o-nitrobenzaldehyde (1mmol), Zn (3mmol), $CuSO_4$ (3mmol) in water on magnetic stirrer. [b]Isolated yield.

Table II.11. [a]Optimization of amount of Zn and $CuSO_4$.

Entry	**Zn (mmol)**	**$CuSO_4$ (mmol)**	**Time (min)**	**[b]Yield (%)**
1	1	1	60	54
2	2	2	60	67
3	**3**	**3**	**60**	**94**
4	4	4	60	95

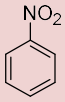
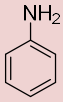
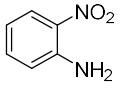
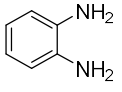
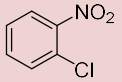
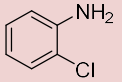
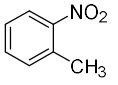
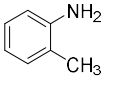
[a]Reaction of o-nitrobenzaldehyde (1mmol), Zn (1-4 mmol), $CuSO_4$ (1-4 mmol) in water on magnetic stirrer. [b]Isolated yield.

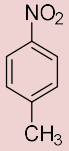
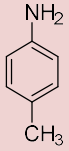
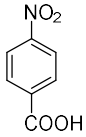
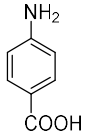
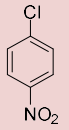
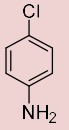
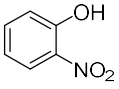
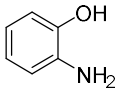
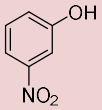
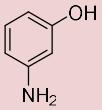
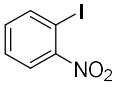
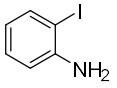
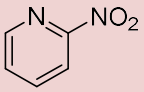
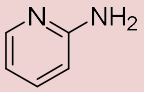
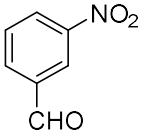
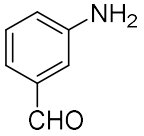
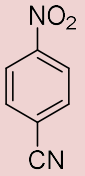
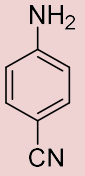
We found that both metal and additive were necessary for this reduction process (Table II.10, entries 3, 4, 5). Compared with $CuSO_4$, other additives were inferior in terms of yield of product and reaction time. Entry 5, 8, 9 (Table II.10) implies that here Zn metal play a vital role for nitro reduction. Electro chemical series

also support our result. The reduction potential of applied metal and additive is as follows, $E^0_{Zn2+/Zn}$=- 0.76, $E^0_{Fe2+/Fe}$=-0.44 and $E^0_{Cu2+/Cu}$=+0.34, which clearly indicates the reduction potential difference between Zn and Cu is higher, which facilitate the transfer of electrons in the process than the other couples. This concept is in accordance with our observed results (Table II.10). But entry 11 also suggests that acidic nature of metal salts is indebted for reduction and reduction potential difference between metals amplify the potency of the process. Entries 9 to 14 implies that if we lower the time from 180 minutes to 60 minutes the yield of the product more or less same, but when we were tried to decrease the time from 60 minutes to 30 minutes then product's yield decreases remarkably. Now we were tried to optimize temperature. With the help of entries 14, 19, 20 we observed that if we increase the temperature yield of the product decreases. So with respect to time, temperature, metal/metal salt entry 14 is the optimized condition. Further we optimized the amount of Zn and $CuSO_4$ required (Table II.11). We started our optimization with 1 mmol each. The yield was considerable but low. As the amount of reagents has been increased we reached our optimum yield at 3 mmol Zn and 3 mmol $CuSO_4$. No further increase in yield has been observed with increasing reagents. Considering the above mentioned points, under atmospheric pressure, 60 minutes of reaction time and room temperature is finalized as the optimum condition for this reaction (Table II.10).

This procedure is followed for all of the reactions listed in Table II. 12.

Table II. 12. [a]Zn and $CuSO_4$ mediated reduction to amines.

Entry	Reactant	Product	Time (min)	[b]Yield (%)
1			50	90
2			30	85
3			30	85
4			30	95

5			30	92
6			40	80
7			30	93
8			30	93
9			30	94
10			40	93
11			50	87
12			60	89
13			50	92

[a]Reaction of nitro compound (1mmol), Zn (3 mmol), $CuSO_4$ (3 mmol) in water at room temperature for different time intervals on magnetic stirrer.

[b]Isolated yields

On the basis of the Table II.10, reduction of other nitroarenes was carried out by using Zn/CuSO4 in water without any organic solvent at room temperature under atmospheric pressure (Table II. 11). Several substituted aromatic nitro compounds were subjected to this procedure to produce the corresponding aromatic amines. The results are presented in Table II. 11. 2-chloro, 2-iodo and 4-chloro nitro benzene (Table II. 11, entries 3, 5, 8) were cleanly reduced to the corresponding anilines

without any dehalogenation which was often encountered with several procedures such as hydrogenation. Acid, aldehyde, nitrile functionality present in aromatic ring remained unaffected during reduction of the corresponding nitro benzene by this process (Table II. 11, entries 6, 12, 13). These results demonstrate that we can employ this technique to nitroarenes containing reduction-sensitive substituents. The reaction took place smoothly and chemoselectively to produce corresponding anilines in moderate to high yields.

II.4.B. Probable Mechanism

The pentahydrated copper (II) sulphate (blue vitriol) exothermically dissolves in aqueous solution to gives hexaaqua complex $[Cu(H_2O)_6]^{2+}$, which has octahedral molecular geometry (Wikipedia). Because the central Cu^{2+} ion is positively charged, it polarizes the O−H bonds towards oxygen, which makes the hydrogens more acidic. Therefore, the ion acts as a weak Brønsted acid, with a pKa of approximately 8 (J. Phys. Chem. A, 2015, 119 (12), pp 2926–2939). Therefore with the help of H^+ ion generated by the aqueous Cu (II) ion and electrons released by zinc metal (in acidic medium) aromatic nitro group smoothly converted to aromatic amine by successive steps.

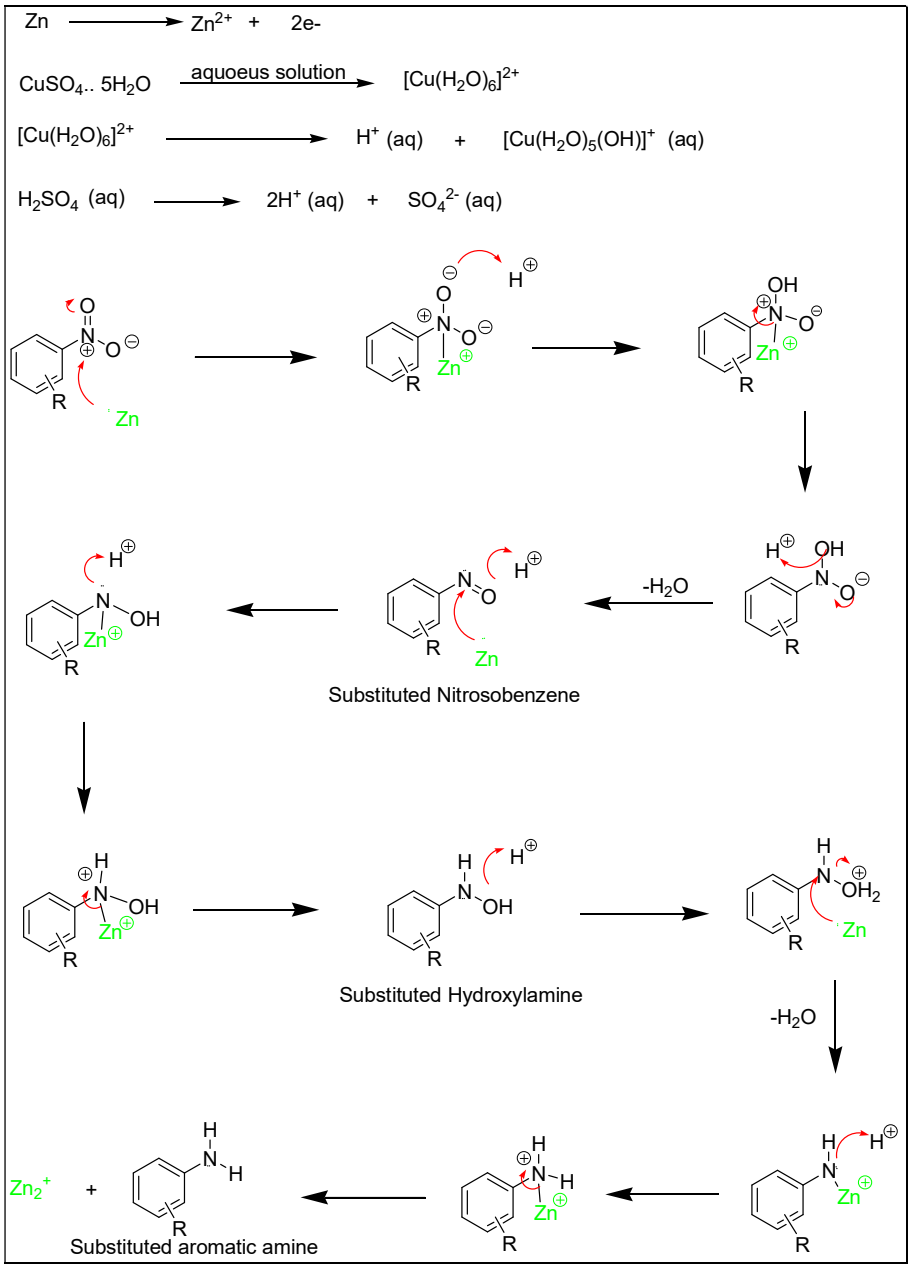


Figure II.3. Probable mechanism of conversion of aryl nitro to aryl amine.

II.5. Conclusion

For reduction of nitroarenes leading to aromatic amines with Zn metal, methods employing Zn/HCl[42], Zn/aq. NaOH/EtOH[43], Zn/NH_3[44], Zn/$CaCl_2$/EtOH[45], Zn/near-critical water[46], Zn/Ru-complex/H_2O/KOH[47], Zn/ether/H_2O[48], Zn/CO_2/H_2O[49], Zn/SiO_2-PEG[50] had been reported. However, since the conventional methods required organic solvents and/or drastic conditions using an irritant reagent such as NH_3, corrosive reagents HCl, NaOH, it is difficult to contend

that these methods are environmentally harmonious. On the other hand, the reaction time is prolonged for Zn/NH_3 (24h), Zn/Ru-complex/H_2O/KOH (16h), Zn/ether/H_2O (5-11h).In addition, some special apparatus and high temperature is required for some processes. To overcome these hurdles, we have introduced our scheme using Zn metal, $CuSO_4$ and water at room temperature. The greatest advantage of our method compared with other methods is easy handling, cost effective, environmentally benign.

II.6. Experimental

II.6.A. General Information

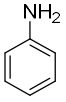
^{1}H NMR and ^{13}C NMR were recorded using 300 MHz Bruker Avance FT-NMR Spectrometer using TMS as internal. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad) and m (multiplet).

II.6.B. General Procedure for the synthesis of aryl amines from nitro compounds

A mixture of nitro compound (1 mmol), Zn powder (3 mmol), $CuSO_4$ (3 mmol) in 5 mL water at room temperature was stirred on a magnetic stirrer. The progress of the reaction was monitored by TLC. After completion of the reaction, the metallic part was filtered off. The filtrate was was poured into 100 mL water and extracted with ethyl acetate, washed several times with water. Evaporation of solvent followed by column chromatography over basic alumina using petroleum ether/ethyl acetate (3:1) as eluent toafford the pure aryl amines. The spectroscopic data (IR, 1HNMR, 13CNMR) of this compound are in good agreement with those reported.

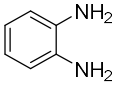
II.6.C. Spectroscopy data of synthesized amine derivatives

Aniline



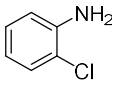
Brown liquid, ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) 3.52 (s, 2H), 6.65 (d, *J* = 8.5 Hz, 2H), 6.77 (t, *J* = 8.5 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 2H).

1, 2-phenylenediamine



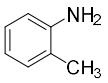
Brown solid, m.p = 101-103 ^{o}C, ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) 3.37 (s, 4H), 6.77 (s, 4H).

2-chloroaniline



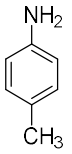
Pale yellow liquid, ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) 4.06 (s, 2H), 6.72 (t, *J* = 8.1 Hz, 1H), 6.80 (d, *J* = 7.8Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H).

o-toluidine



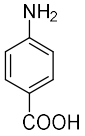
Pale yellow liquid, ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) 2.23 (s, 3H), 3.54 (s, 2H), 6.69 (d, *J* = 7.8Hz, 1H), 6.75 (t, *J* = 8.1 Hz, 1H), 7.08 (t, *J* = 8.5 Hz, 2H).

p-toluidine



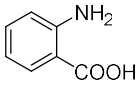
Grey solid, m.p = 42-44 ^{o}C, ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) 2.32 (s, 3H), 3.61 (br, s, 2H), 6.76 (d, *J*= 8Hz, 2H), 7.12 (d, *J* = 8Hz, 2H).

p-aminobenzoicacid



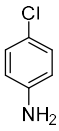
Grey solid, m.p = 183-185 ^{o}C, ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) = 7.91 (d, *J* = 8.56, 2H), 6.65 (d, *J* = 8.56, 2H)

o-aminobenzoic acid



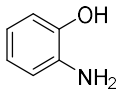
Light yellow solid, m.p = 144-146

p-chloroaniline



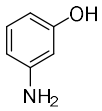
Pale yellow solid, m.p = 70-72 ^{o}C) ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) 3.68 (br, s, 2H), 6.67 (d, *J*= , 2H) , 7.17 (d, *J*= , 2H),

o-hydroxyaniline



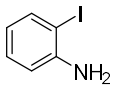
(White solid, m.p = 173-175 ^{o}C)

m-hydroxyaniline



(White solid, m.p = 118-120 ^{o}C)

o-iodoaniline



(White solid, m.p = 57-59 ^{o}C) ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) 4.09 (br, s,2H), 6.58 (t, *J* = , 1H), 6.80 (d, *J* = , 1H), 7.19 (t, *J* = , 1H), 7.78 (d, *J*= , 1H).

II.6.D. Scan copy of ^{1}H NMR of aniline derivatives

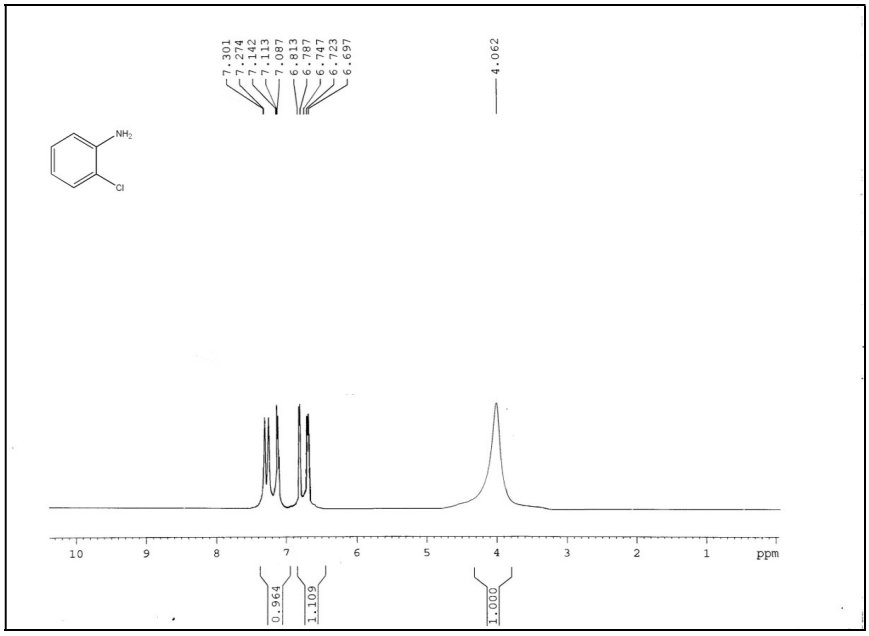


Figure II. 4. ^{1}H NMR of 2-chloroaniline.

II.7. References

References are given in BIBLIOGRAPHY.

CHAPTER-3

ONE POT REDUCTIVE SYNTHESIS OF BENZIMIDAZOLE DERIVATIVES FROM 2-NITRO ANILINE AND AROMATIC ALDEHYDES

III.1. Benzimidazole

The benzo derivative of imidazole is referred to as benzimidazole (Bansal, 2002) having chemical formula $C_7H_6N_2$. Although benzimidazole is the commonest name of the parent compound of the series, other names such as 1*H*-Benzo[d]imidazole and 1*H*-1, 3-benzimidiazole (Figure III.1) are often used. Benzimidazole ring exists in two equivalent tautomeric forms (Figure III.2). It is an important heterocyclic aromatic organic compound. Among heterocyclic pharmacophores, this bicyclic ring system is quite common. It is a vital Pharmacophore and privileged structure, owing to their extensive recurrence in bioactive compounds. In spite of great interest in ligands and structural chemistry of benzimidazole, medicinal chemistry, biological activities, development and synthesis of novel molecules with therapeutic values are the leading attractiveness in this field [1].

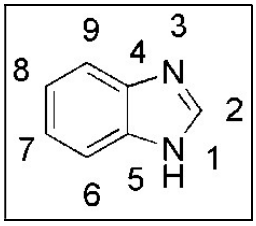


Figure III.1. 1*H*-1, 3-benzimidiazole.

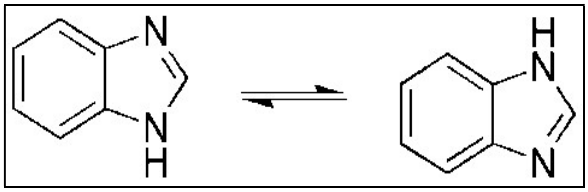


Figure III.2. Equivalent tautomeric forms of benzimidazole.

Benzimidazole is whitish solid having characteristic odor with the melting point 172 ^{o}C and boiling point 360 ^{o}C. It is freely soluble in alcohol, sparingly soluble in ether, practically insoluble in benzene, petroleum ether but soluble in aqueous solutions of acids and strong alkalis [2].

III. 2. Natural occurrences

The benzimidazole nucleus does not appear to occur very widespread in nature. The 5, 6-di methyl-1-(α-D-ribofuranosyl)benzimidazole ring system was discovered in 1948 as an integral part of the structure of vitamin B12 [3] (Figure III.3).

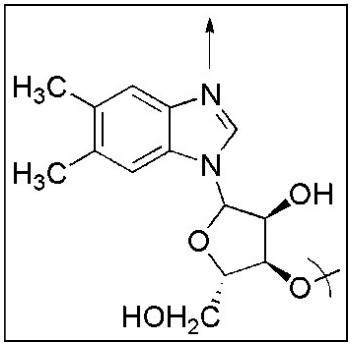


Figure III.3. 5, 6-di methyl-1-(α-D-ribofuranosyl)benzimidazole ring system in vitamin B12.

III.3. Medicinal and biological activities of benzimidazole derivatives

The early 1950s was a significant period to unlock the biological importance of benzimidazole-containing structures [4, 5, 6] and the closely-related purines (Figure III.4). Subsequently pharmaceutical, veterinary and agrochemical products were discovered including thiabendazole, cimetidine, azomycin, metronidazole, misonidazole, and chlotrimazole, antihistamines, astemizole and the anti-ulcerative omeprazole) [7]. These biological activities include anti-cancer [8], bactericidal [9], fungicidal [10-11], analgesic [12] anti-viral properties [13] and some have cardiovascular applications [14] while some derivatives have been synthesized and evaluated for inhibition of HIV-1 infectivity [15]. Most recently, the anti-protozoal activity of substituted 2-trifluoro benzimidazole has been reported [16]. It was also suggested that the benzimidazole derivatives may selectively and irreversibly inhibit the absorption of glucose by helminths and produce degenerative changes in the intestinal tract of nematodes and in the absorptive cells of cystodes. Thus benzimidazole-based drugs exhibit a wide range of different biological activities, as a result of changing the groups on the core structure, as shown below (Figure III.5).

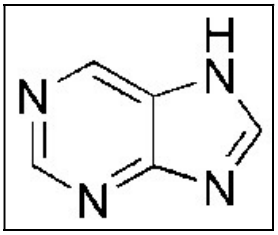


Figure III. 4. Purine ring

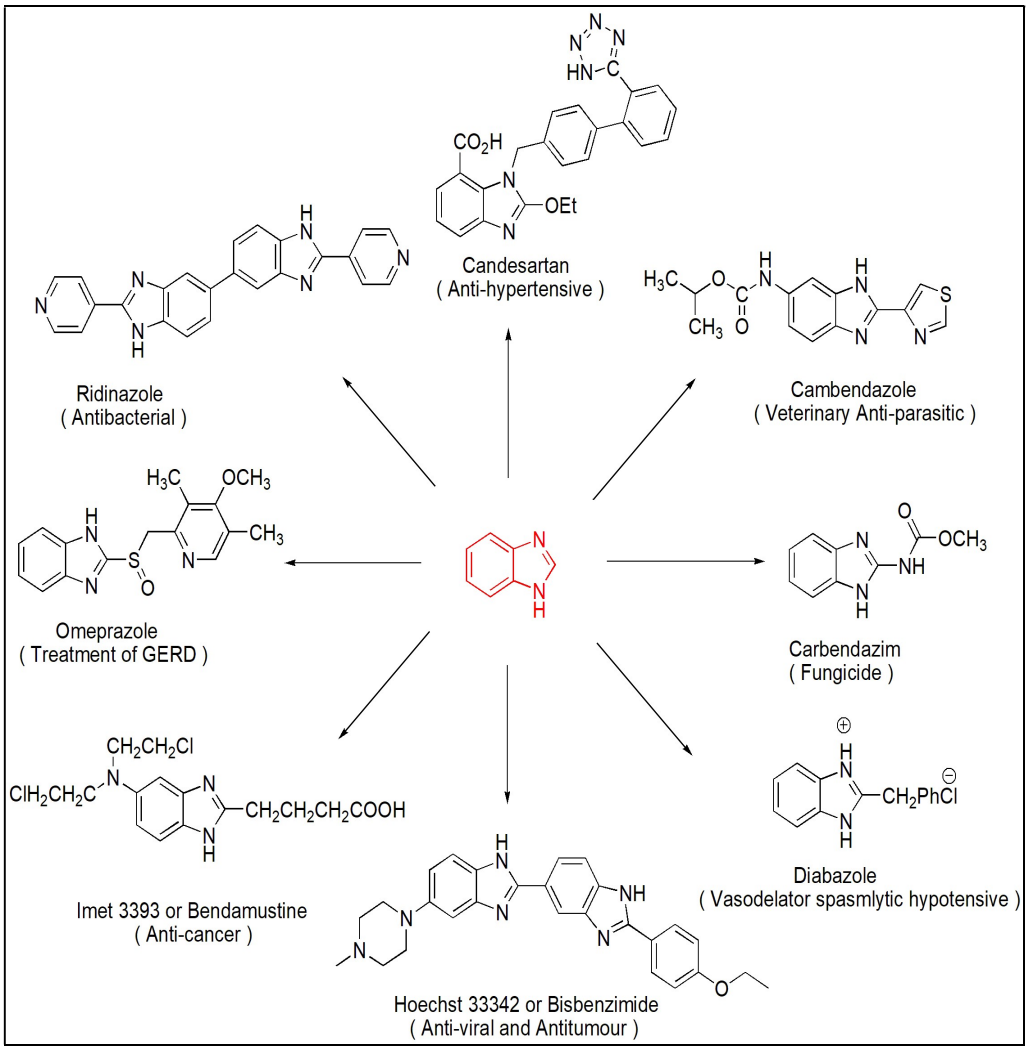
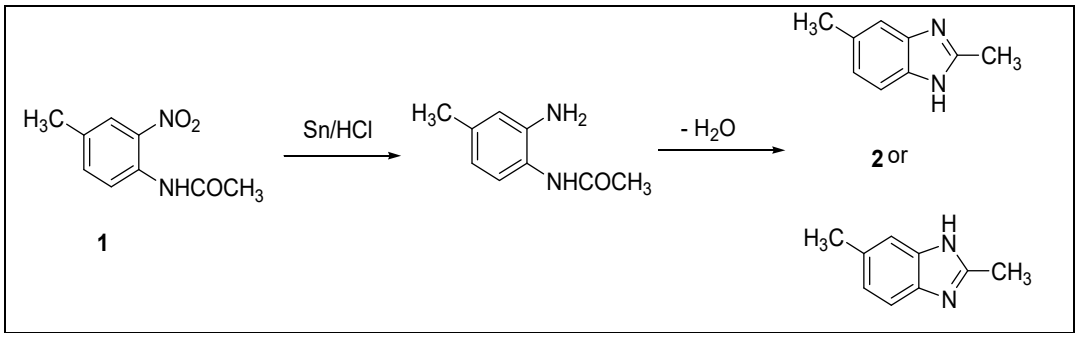


Figure III.5. Varity of drugs containing benzimidazole ring.

III.4. Memoir of foremost synthesis of Benzoimidazole derivatives

In 1872, first benzimidazole was prepared by Hoebrecker [17], who obtained 2, 5-dimethylbenzimidazole (2) by the reduction and dehydration of 2-nitro-4-methylacetanilide (1) (Scheme III.1).

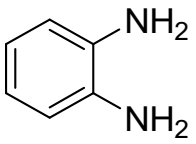


Scheme III.1. Hoebrecker method for synthesis of benzimidazole derivatives.

III.5. Synthesis of Benzoimidazole derivatives

Literature unveiled that, there has been a lot of work done in last few years to synthesize benzimidazoles ring. This indicated clearly the worth of benzimidazoles ring for a Chemist, a Researcher or an Industrialist. To amplify the scope of synthesis of benzimidazole ring, researchers were used various paths. Here a number of different synthetic methods for benzimidazoles have been grouped according to the starting material.

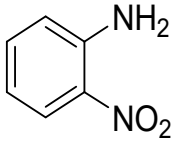
A. From-



+

- Aliphatic / Aromatic carboxylic acid
- Acid chloride
- Aldehydes
- Ketones
- Nitrile
- Ester
- Acid anhydrides
- Urea
- Lactone

B. From-



+

- Aryl aldehydes
- Carboxylic acid
- Alcohol
- Activated methyl group

C. Through C-H functionalization-

D. Through C-X functionalization-

E. Miscellaneous work

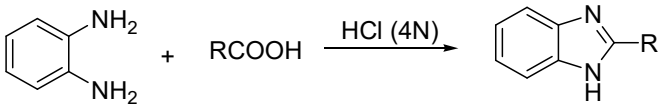
F. Green Protocols

III.5.A.i. By the reaction with Aliphatic / Aromatic carboxylic acid

The prevalent laboratory method for preparation benzimidazoles is Phillip's method [18], involves the condensation of o-diaminobenzenes with carboxylic acids or its derivatives (Scheme III.2), including heating the reagents together in the presence of concentrated hydrochloric acid. E. Wundt et al [19] and Von Niemantowski et al [20] also walked in a similar path.

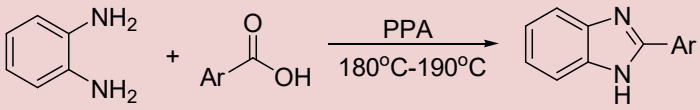
In the presence of catalyst polyphosphate ester (PPA) at 180-190ºC, Maleki *et al*., condensed *o*-phenylenediamine with aromatic carboxylic acid and got 77% yield of 2-arybenzimidazole (Scheme III.3)[21]. Room temperature is also sufficient to synthesize 2-substituted benzimidazole derivatives and gives about 83% yield, which was proven by Venkateswarlu *et al*., from the reaction of o-phenylenediamine and substituted benzoic acid in the presence of lanthanum chloride in acetonitrile (Scheme III.4). [22]

Scheme III.2



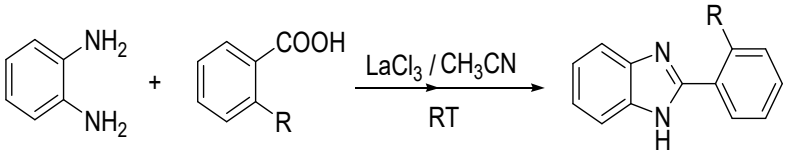
Phillip's method.

Scheme III.3



Synthesis of 2-arybenzimidazole using polyphosphate ester (PPA) as a catalyst.

Scheme III.4



Synthesis of 2-substituted benzimidazole derivatives in the presence of lanthanum chloride and acetonitrile.

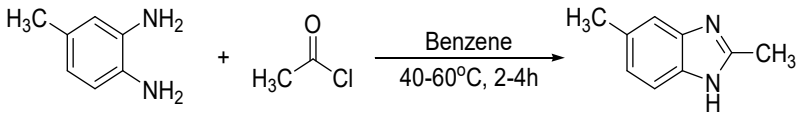
III.5.A.ii. By the reaction with acid chloride

Most reactions between o-phenylenediamines and acid chlorides to give benzimidazoles have been carried out with aroyl chlorides. Since benzimidazoles have no grouping in the l-position may undergo acylation with acid chlorides leads to benzimidazoles or monoacylated or diacylated o-phenylenediamines, depending upon experimental conditions.

Acetyl chloride with 5-methyl-1, 2- diaminophenyl in benzene medium have been condensed by Benguer *et al*. at 40 to 60 ºC for 2 to 3 h it gives 2,6-dimethyl benzimidazole with 71% yield (Scheme III.5) [23].

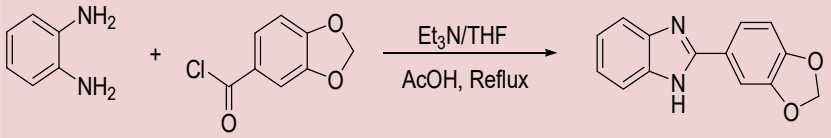
A novel antitumor agent, 2-phenyl-(3, 4-methylenedioxy)benzimidazol Kadri *et al.* had synthesized from *o*-phenylenediamine and 1,3-benzodioxole-5-carbonyl chloride, by stirring at 0°C in triethylamine and THF for 1 h. The residue got from the reaction was refluxed with acetic acid for 12 h to obtain the desired product in 46-59% yield (Scheme III.6) [24].

Scheme III.5



Synthesis of 2,6-dimethyl benzimidazole from acetyl chloride with 5-methyl-1, 2- diaminophenyl in benzene medium.

Scheme III.6



Synthesis of 2-phenyl-(3, 4-methylenedioxy)benzimidazol from *o*-phenylenediamine and 1,3-benzodioxole-5-carbonyl chloride in Et_3N/THF.

III.5.A.iii. By the reaction with aldehydes

The condensation of phenylenediamines with aldehydes is achieved by various reported conditions. Since an oxidation is involved, the reaction is best carried out under oxidative conditions. This oxidation may be brought about by the air or, more

conveniently, by the use of other oxidizing agents. Smith, Rao and Ratnam *et al*., reported synthesis of 2-aryl benzimidazole from o-phenylenediamine and aryl aldehydes, in the presence of the oxidising agents like- cupric acetate, mercuric oxide, chlorine, lead tetraacetate, manganese dioxide, Nickel peroxide at room temperature. This eco-friendly method gives about 85% yield. (Scheme III.7)[25].

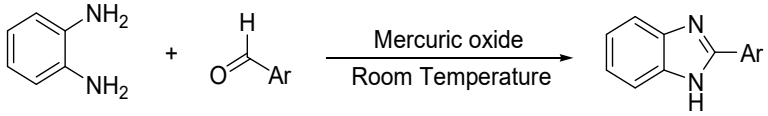
In the presence of silica phenyl sulfonic acid as a solid, heterogeneous catalyst Veisi *et al*., synthesized 2-aryl-benzimidazole by reacting *o*-phenylenediamine and aromatic aldehyde in water, gives 67% yield of 2-aryl –benzimidazole.(Scheme III.8**)** [26].

Varala *et al*., used L-proline to synthesized 2-aryl-5-alkyl-benzimidazoles by the condensation of o-phenylenediamine with aromatic aldehydes in chloroform medium to get a yield of 72-95% at ambient temperature (Scheme III.9**)** [27].

With the help of heterogeneous catalyst Amberlite IR-120 (strongly acidic cation exchange resin), Sharma *et al.,* synthesized 2, 5-substituted-benzimidazoles by the reacting 4-substituted-o-phenylenediamine with the substituted aldehydes, the media is ethanol and water solution (2:1). This method gives a 72% yield. The catalyst is recyclable without loss of activity (Scheme III.10**)** [28].

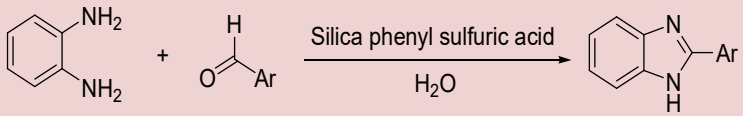
With a good yield of 81%, Ravi *et al.,* selectively synthesized 1,2,4,5-tetrasubstituted benzimidazoles by using 4,5- substituted o-phenylenediamine and substituted aldehydes at room temperature in presence of Zn-proline, a water-soluble and recyclable Lewis acid catalyst (Scheme III.11**)** [29].

Scheme III.7



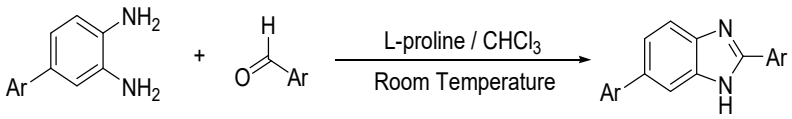
Synthesis of 2-aryl benzimidazole using oxidising agents.

Scheme III.8



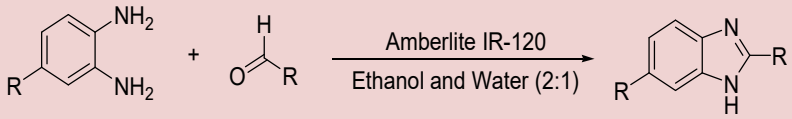
Using silica phenyl sulfonic acid synthesis of 2-aryl - benzimidazole in water medium.

Scheme III.9



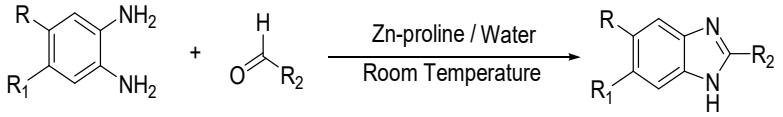
L-proline mediated synthesis of 2-aryl-5-alkyl-benzimidazoles.

Scheme III.10



Synthesis of 2, 5-substituted-benzimidazoles using amberlite IR-120 in ethanol and water solution (2:1).

Scheme III.11

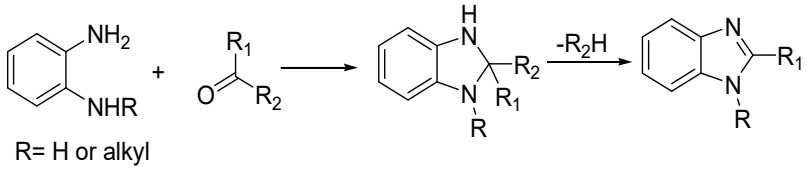


Selective synthesis of 1, 2, 4, 5-tetrasubstituted benzimidazoles at room temperature by using Zn-proline.

III.5.A.iv. By the reaction with ketones

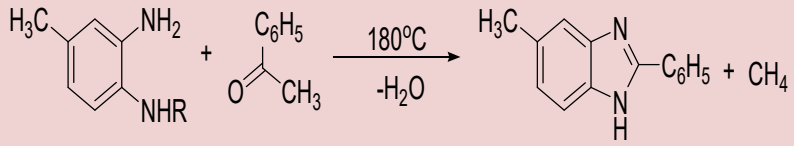
Elderfield and Kreysa, investigated the reaction of o-phenylenediamines with a number of ketones.(Scheme III.12). *o*-Phenylenediamine reacts with ketones to form 2- disubstituted benzimidazolines, these decompose under the influence of heat with the formation of a 2-substituted benzimidazole and a hydrocarbon. The decomposition of unsymmetrically substituted benzimidazoline may lead to formation of two different benzimidazoles depending upon whether the substituent R_1 or the substituent R_2 is eliminated preferentially. By heating 3, 4-diaminotoluene with acetophenone at 180^{o}C for some time Ladenburg and Rugheimer have obtained 2-phenyl-5 (or 6)-methylbenzimidazole. Here the methyl group eliminated preferentially (Scheme III.13).

Scheme III.12



Synthesis of di-substituted benzimidazole from ketone.

Scheme III.13

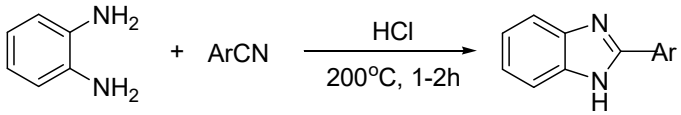


Synthesis of 2-phenyl-5-methylbenzimidazole by 3,4-diaminotoluene with acetophenone.

III.5.A.v. By the reaction with nitrile

Hollies and Wagner obtained 2-substituted benzimidazole by the reaction of o-phenylenediamine with the substituted nitrile at 200 ºC for 1 to 2 h and gives 77% yield (Scheme III.14) [30].

Scheme III.14

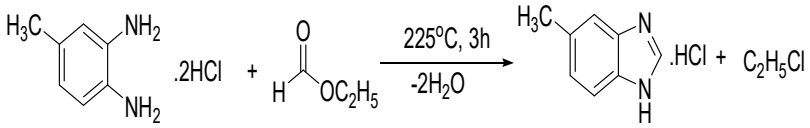


Synthesis of 2-substituted benzimidazole by *o*-phenylenediamine with substituted nitrile.

III.5.A.vi. By the reaction with ester

Reaction of o-phenylenediamines with esters also gives benzimidazoles. Von Niementowski first investigated the reaction of esters and o-phenylenediamines to give benzimidazoles. Equimolecular amounts of 3,4-diaminotoluene dihydrochloride and ethyl formate when heated in a sealed tube for 3 h at 225 °C give 84% of 5(or 6)-methylbenzimidazole hydrochloride [31] (Scheme III.15). The product is not further alkylated by the ethyl chloride formed. Ethyl acetate under the same conditions gives only a poor yield of 2, 5(or 2,6)-dimethylbenzimidazole, and poor yields of benzimidazoles would probably be obtained from esters of acids of higher molecular weight.

Scheme III.15

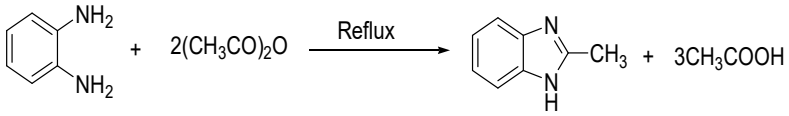


Synthesis of 5(or 6)-methylbenzimidazole by 3,4-diaminotoluene dihydrochloride and ethyl formate.

III.5.A.vii. By the reaction with acid anhydrides

Literature survey has revealed that depending on the conditions acid anhydrides and *o*-phenylenediamines will lead to benzimidazoles or to N, N-diacylphenylenediamines. It was formerly thought that o-phenylenediamine yields benzimidazoles with acids and diacyl derivatives with acid anhydrides; however, this was shown to be incorrect. Time appears to be a decisive factor and if the refluxing is continued long enough benzimidazoles may be obtained, usually in good yields. *o*-Phenylenediamines when reflux for several hours with acetic anhydride is completely converted to 2-methylbenzimidazole [31] (Scheme III.16).

Scheme III.16

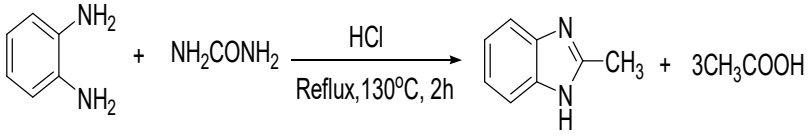


Synthesis of 2-methylbenzimidazole from o-Phenylenediamines and acetic anhydride.

III.5.A.viii. By the reaction with urea

By refuxing o-phenylenediamine and urea in amyl alcohol solution until the evolution of ammonia ceased, Mistry and Guha have obtained a 95% yield of 2(3H)-benzimidazolone. [31] On refluxing o-phenylenediamine with urea in the presence of hydrochloric acid at 130 ºC for 2 h gives a 78% yield of benzimidazole (Scheme III.17) [32] .

Scheme III.17

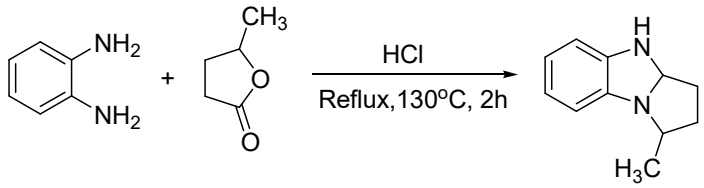


Synthesis of benzimidazole by o-phenylenediamine and urea.

III.5.A.ix. By the reaction with lactone

On refluxing Valerolactone (5-methyldihydrofuran-2(3H)-one) with o-phenyllenediamine at 130 ºC for 1 to 2 h in the presence hydrochloric acid gives 76% yield of 1,2-(1- methyltrimethylene) benzimidazole (Scheme III.18) [33] .

Scheme III.18



Synthesis of 1, 2-(1- methyltrimethylene) benzimidazole by *o*-phenyllenediamine and Valerolactone.

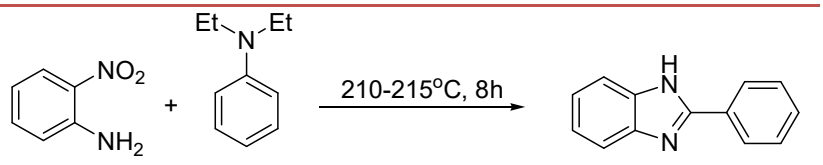
III.5.B.i. By the reaction with aldehydes

2-Nitroanilines were also used for one pot synthesis of 2- arylbenzimidazoles under different reaction conditions. Nishioka et al. have obtained of 2-phenylbenzimidazole (3) from 2-nitro aniline (23) and N, N-diethylaniline (24) by heating them at 210-215°C for 8h (Scheme III.19) [34]. one-pot reduction triggered heterocyclization of 2- nitroanilines (23) or 1,2-dinitroarenes to 2-phenylbenzimidazoles (3) in excellent yield when refluxed in presence of indium/AcOH in ethyl acetate, (Scheme III.20) [35].

The reductive cyclization of o-nitroarylamine with aldehyde using sodium dithionite ($Na_2S_2O_4$) have been reported by Oda et al. The reaction was accelerated by addition of H_2O for the one-Pot Synthesis of N-1- and C-2-substituted benzimidazole [36].

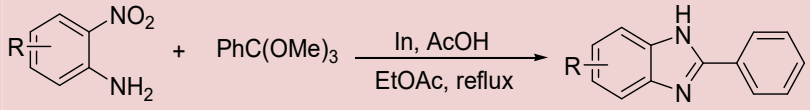
M. P. Surpur et al., reported one-pot synthesis of benzimidazoles from o-nitroanilines under microwaves via a reductive cyclization by using $Na_2S_2O_4$ in water-DMF medium and it took only 2 minutes to produce 65-92% product. (Scheme III.21) [37].

Scheme III.19



Synthesis of 2-phenylbenzimidazole from 2-nitro aniline and N,N-diethylaniline

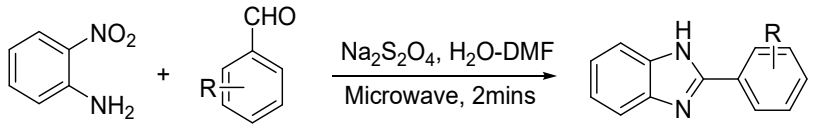
Scheme III.20



R= Me, OMe, Br, I

Heterocyclization of 2- nitroanilines or 1, 2-dinitroarenes to 2-phenylbenzimidazoles.

Scheme III.21

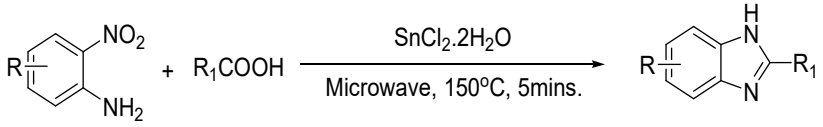


Synthesis of benzimidazoles from o-nitroanilines under microwaves.

III.5.B.ii. By the reaction with carboxylic acids

David S. VanVliet et al. have reported that by using stannous chloride and microwave irradiation of 2-nitroaniline with various carboxylice acids gives 2-substituted benzimidazoles. (scheme III.22) [38].

Scheme III.22

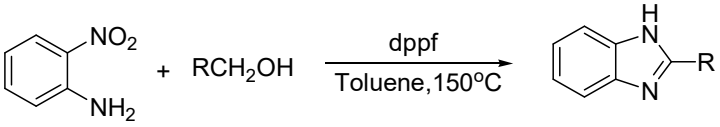


Synthesis of 2-substituted benzimidazoles by using stannous chloride and microwave irradiation.

III.5.B.iii. By the reaction with alcohols

Iron-catalyzed heterocyclizations from 2- nitroanilines and benzylic alcohols in the presence of dppf [1, 10- bis(diphenylphosphino)-ferrocene] at 150 °C to form benzimidazoles using hydrogen transfer reaction have been reported by Haihong Huang et al. [39]. (Scheme III.23).

Scheme III.23

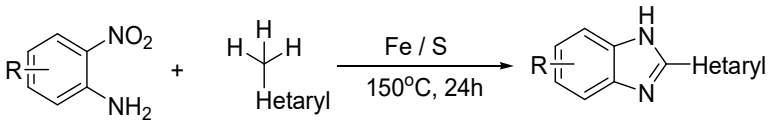


Benzimidazole synthesis 2- nitroanilines and benzylic alcohols in the presence of dppf.

III. 5. B. iv. By the reaction with active methyl group:

Direct coupling of 2-nitroaniline and the methyl group bearing a 2, 4-picolyl or 2-benzimidazolyl substituent providing 2-hetarylbenzimidazoles. The reaction employs a catalytic amount of iron sulfide generated in situ from the elements under solvent-free conditions (scheme III.24) [40].

Scheme III.24

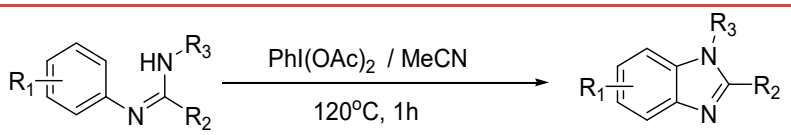


Synthesis of 2-hetarylbenzimidazoles from 2-nitroaniline and the methyl group.

III.5.C. Through C-H functionalisation:

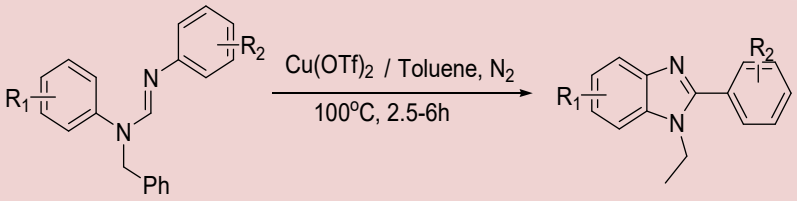
From literature I came to know that there are few routes to derivatives of benzimidazoles from C-H bond functionalization. Ya-Qiu Long et al. [41]. presented the TEMPO promoted synthesis of multisubstituted benzimidazoles via metal-free oxidative C-N coupling between the sp3 C-H and free N−H of readily available N-benzyl/alkyl-1, 2- phenylenediamines. The same group have also reported that iodine (III) promoted metal free selective oxidative annulations of aryl amidines for the synthesis of multisubstituted benzimidazoles through C(sp2)−N bond formation in polar solvent (Scheme III.25) [42]. Tharmalingam Punniyamurthy et al. shown the copper (II)-mediated synthesis of 2-aryl-N-benzylbenzimidazoles from N-benzyl bisarylhydrazones via C-H functionalization (Scheme III.26) [43].

Scheme III.25



Multisubstituted benzimidazoles synthesis through C(sp2)−N bond formation.

Scheme III.26

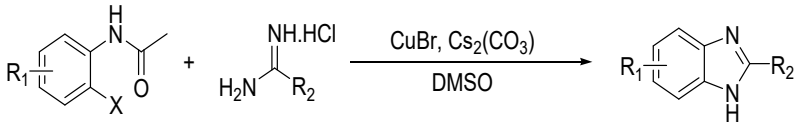


Copper (II)-mediated synthesis of 2-aryl-N-benzylbenzimidazoles from N-benzyl bisarylhydrazones via C-H functionalization.

III.5.D. Through C-X functionalisation

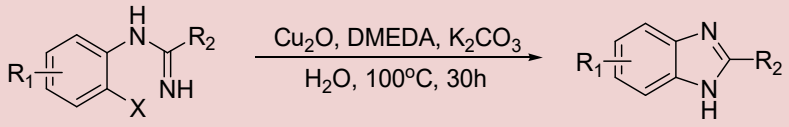
A well known transition metal catalyzed C-X functionalization for the organic transformations are in CuBr catalyzed synthesis of 2-substituted benzimidazoles from *o*-haloacetanilide derivatives and amidine hydrochloride under ligand free conditions (Scheme III.27),[44]. CuI/L-Proline catalyzed synthesis of substituted benzimidazoles by coupling of aqueous ammonia with 2-iodoacetanilides, [45] CuI catalyzed synthesis of N-substituted benzimidazoles [46]. Cu_2O in combination with a simple diamine derivative (DMEDA) catalyzed synthesis organic chemistry. There are few numbers of literature report where the transition metals play excellent catalytic role for the synthesis of substituted benzimidazoles by C-X bond activation such as, palladium catalyzed synthesis of benzimidazoles using aryl amination chemistry, [47] of substituted benzimidazoles by intramolecular N-arylation in water (Scheme III.28), [48] palladium catalyzed synthesis of substituted benzimidazoles from N-(o-halophenyl)-imidoyl chlorides and the corresponding imidates using variety of N-nucleophiles. [49] Recently, Carsten Bolm et al. have reported KOH/DMSO mediated transition metal free synthesis of benzimidazoles by intramolecular N-arylation of amidine, [50] copper or palladium catalyzed the formation of 2-aminobenzimidazoles through intramolecular C-N bond formation between an aryl halide and a guanidine moiety[51].

Scheme III.27



CuBr catalyzed synthesis of 2-substituted benzimidazoles.

Scheme III.28



X= Cl, Br, I

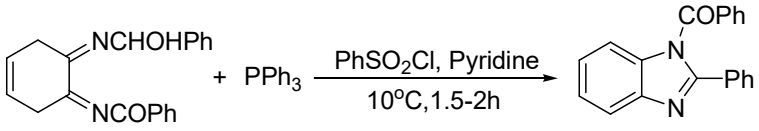
Synthesis of benzimidazoles by intramolecular N-arylation.

III. 5. E Miscellaneous work:

Some miscellaneous works are also presented here:

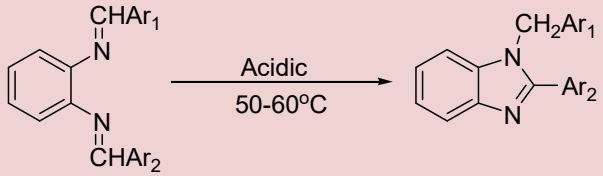
Scheme III.29

R. S. Kumar *et al.*[52]



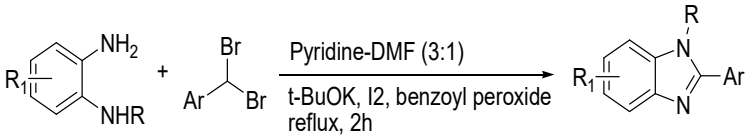
Scheme III.30

Dianils *et al.*[53]



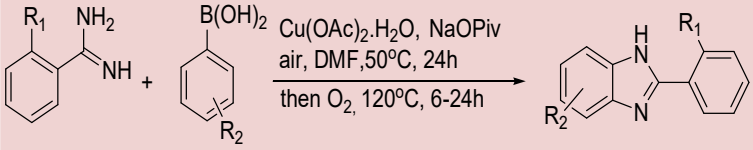
Scheme III.31

Kanchugarakoppal S. Rangappa *et al.*[54]



Scheme III.32

Jieping Zhu *et al.*[55]

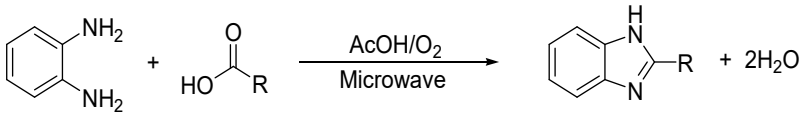


III. 5. F. Green Approaches

E-factor or environmental factor was also present in researcher's mind during their work. As for example, in 2010 Davood Azarifar *et al*., got 2-substituted-benzimidazole with 77% yield by the reaction of o- phenylenediamine with a carboxylic acid using microwaves. This method is promoted to green chemistry and avoided using of hazardous solvents (Scheme III.33) [56]. Kabeer A. Shaikh et al., 2012 have been efficiently synthesized Benzimidazoles in high yields by treatment of 1, 2- diamine with aldehydes using the metal coordinate complex K4[Fe(CN)6] as a catalysis. The method was carried out under solvent free condition via oxidation of carbon-nitrogen bond which is green, mild and inexpensive process (Scheme III.34) [57]. M. Rekha et al., studied catalytic activity of alumina, zirconia, manganese oxide/alumina, and manganese oxide/zirconia in the condensation reaction between *o*-phenylenediamine and an aldehyde or a ketone to synthesise 2-substituted benzimidazoles and 1, 5-disubstituted benzodiazepines respectively and found to be simple and economical (Scheme III.35) [58]. In the presence of polyethyleneglycol-400

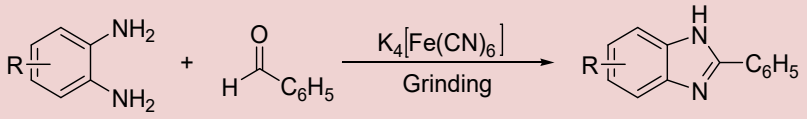
(PEG-400) Mita D. Khunt *et al*., refluxed o-phenylenediamine with substituted aldehydes for 1.5 to 2 h gives 76% yield of 2-substituted-benzimidazole. PEG is a green and eco-friendly solvent (Scheme III.36) [59].

Scheme III.33



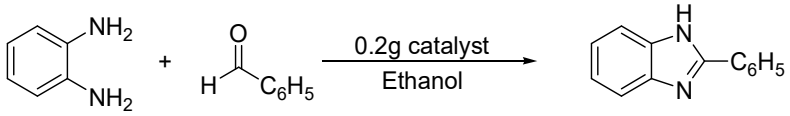
Synthesis of 2-substituted-benzimidazole from *o*-phenylenediamine with a carboxylic acid using microwaves.

Scheme III.34



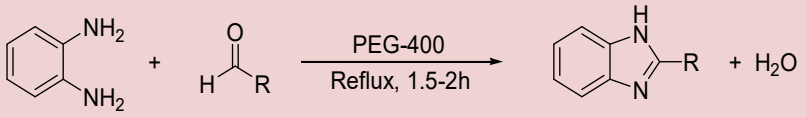
Synthesis of benzimidazoles by 1, 2- diamine with aldehydes using the metal coordinate complex as a catalyst.

Scheme III.35



M. Rekha et al. synthesis of 2-substituted benzimidazoles from *o*-phenylenediamine and an aldehyde or a ketone.

Scheme III.36



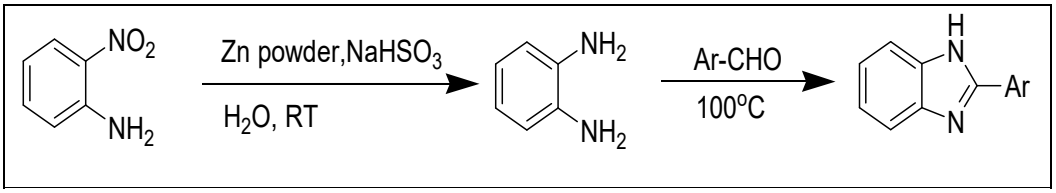
Synthesis of 2-substituted-benzimidazole using PEG-400.

From the above discussion it is clear that one of the most important precursors of medicinal and biological ring is benzimidazole, which can be synthesized in various ways. Different researchers from different countries tried a lot to search the best path to synthesize it. Till now many are working on it. I am also searching a route to avoid hazardous, expensive chemicals, time consuming method and organic solvent to provide a scheme to synthesize the privileged ring.

III. 6. Present Work

We report a simple and mild one-pot method for the synthesis of 2-substituted benzimidazoles (Scheme III.37) from 2-nitroanilines and aromatic aldehyde via reductive cyclocondensation process with the help of suitable metal, Zn and metal salt

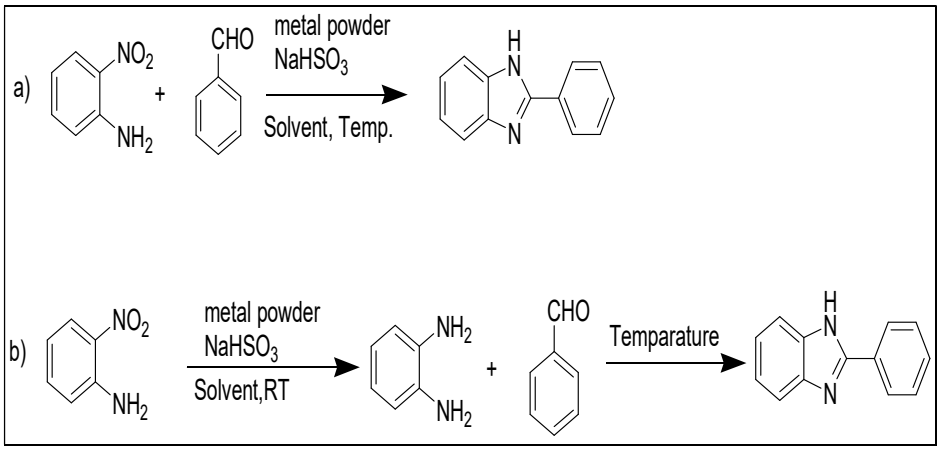
$NaHSO_3$ at 100°C in water. $NaHSO_3$ is a non-hazardous, easily available, inexpensive weakly acidic species having pKa value 6.97 which helps to trigger the reaction in the presence of Zn. Adduct formation ability of it with the aldehydes, may help cyclocondensation in the present protocol. Key features of this draft are very good to excellent yields in reasonably short reaction times, high atom economy, and use of readily available starting material, operational simplicity and easy workup process.



Scheme III.37. General scheme for the synthesis of benzimidazole derivatives.

III.6.A. Results and discussion

For screening the reaction, 2-nitroaniline and benzaldehyde was selected as model substrates for intended transfiguration. Initially we performed the reaction of *o*-nitroaniline with benzaldehyde in water at room temperature for 1h on a magnetic stirrer in presence of the combination of Fe powder and sodium bisulphite. The reaction yielded only the diamine (*o*-phenylenediamine). The yield of diamine decreases with a rise in temperature and benzimidazole was undetected (Table III.1, scheme III.38a). The scheme was also tried (Scheme III.38a) without using $NaHSO_3$ (Table III.1, entry 4), but it failed to produce the diamine even at a trace amount. Thus, it is obvious that, as a hydrogen ion's source $NaHSO_3$ plays a vital role to reduce nitro to amine.



Scheme III.38. Two different plans for the synthesis of benzimidazole derivatives.

Table III.1. [a]Reaction (Scheme-2a) condition optimization.

Entry	Time (h)	Temperature (^oC)	Additive (3 mmol)	Yield of diamine	Yield of Benzimidazole
1	1	RT	$NaHSO_3$	70	Nil
2	1	60	$NaHSO_3$	44	Nil
3	1	80	$NaHSO_3$	25	Nil
4	1	RT	-	Nil	Nil

[a]Reaction of *o*-nitrobenzaldehyde (1 mmol), Fe (3mmol), in water on magnetic stirrer.

With this experimental data we followed our scheme III.38b. In this process *o*-nitroaniline was reduced to 1, 2-diamine with Zn and $NaHSO_3$ in presence of water at room temperature and the process was completed within 5 minutes. It was followed by the addition of benzaldehyde with continuous stirring at 100 ^oC. As a solvent, water was first screened (Scheme III.38b, Table III.2, entry 4), and very surprisingly no product was isolated in its absence (Table III.2, entry 5). Further, being the most easily available and most significantly its green nature has really enriched the objective of the present investigation.

The presence of metal is the necessary requirement for the initial reduction of the nitro compound (Table III.2, entry 8) and in comparison to Fe and Cu, Zn is estimable in terms of yield of the product and the time of completion of reaction (Table III.2, entries 4, 6, 7). We also tried the scheme at different temperature; finally at 100 ^oC temperature the desired product, benzimidazole was isolated as a single compound (Table III.2, entry 7). Further we optimized the amount of Zn and $NaHSO_3$ required (Table III.3). Further investigation towards the optimization of the process revealed that a 3 mmol Zn and 6 mmol $NaHSO_3$, (Table III.3) under atmospheric pressure at 100^oC yielded the best result to produce the desired benzimidazole in 1h (compared with Table III.2, entries 7, 14, 15)

Table III. 2. [a]Reaction (**Scheme III. 38b**) conditions optimization.

Entry	Metal	Solvent	Time(min.)	Temperature(^{o}C)	Yield (%)[b]
1	Fe	DMF	60	100	68
2	Fe	DMSO	60	100	60
3	Fe	Toluene	60	100	56
4	Fe	H_2O	60	100	80
5	Fe	-	60	100	Nil
6	Cu	H_2O	60	100	75
7	Zn	H_2O	60	100	94
8	-	H_2O	60	100	Nil
9	Zn	H_2O	60	RT	Nil
10	Zn	H_2O	60	80	50
11	Zn	H_2O	60	60	Nil
12	Zn	H_2O	60	40	Nil
13	Zn	H_2O	90	100	95
14	Zn	H_2O	45	100	87
15	Zn	H_2O	120	100	94

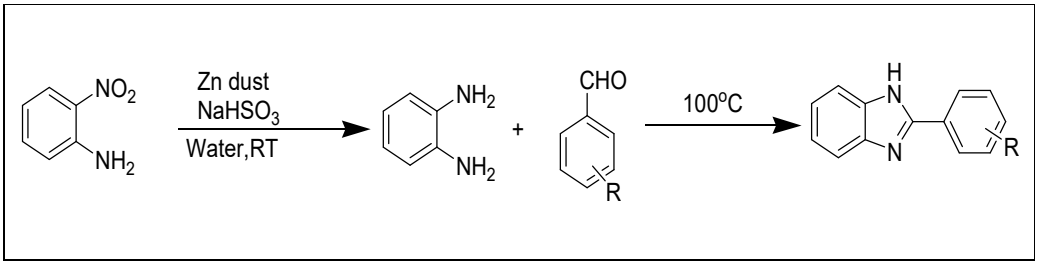
[a]Reaction of o-nitrobenzaldehyde (1 mmol), Zn (3mmol), $NaHSO_3$ (6 mmol) in water on magnetic stirrer. [b]Isolated yield of benzimidazole.

Table III. 3. [a]Optimization of amount of Zn and $NaHSO_3$.

Entry	Zn (mmol)	$NaHSO_3$ (mmol)	Time (min)	Yield (%)[b]
1	3	3	60	54
2	3	4	60	62
3	3	5	60	82
4	3	6	60	94
5	3	7	60	94
6	2	6	60	75

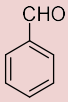
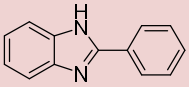
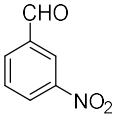
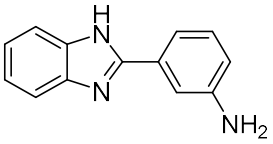
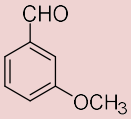
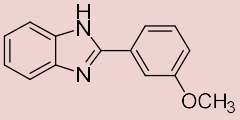
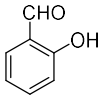
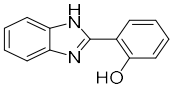
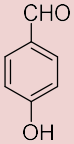
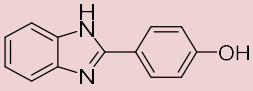
[a]Reaction of *o*-nitrobenzaldehyde (1mmol), Zn (2-3 mmol), $NaHSO_3$ (4-7 mmol) in water on magnetic stirrer at 100^{o}C. [b]Isolated yield.

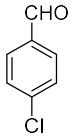
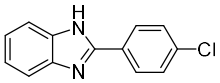
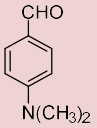
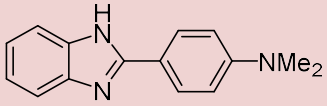
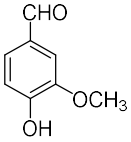
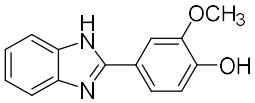
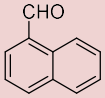
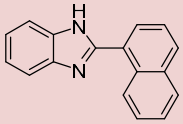
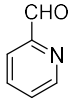
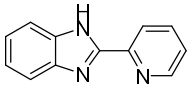
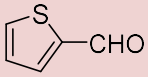
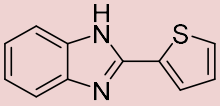
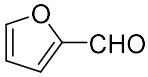
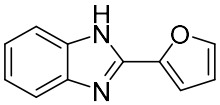
Now the optimized procedure is followed for all of the reactions listed in Table III.4. Staggering part of our reaction is chemoselective reduction of nitro to amine. We really enthralled and exhilarated on observing Table III.4 entry 3, 4, 5, 6, 7, 8 that reducible groups remain intact after completion of the reaction. The reaction took place smoothly to produce corresponding benzimidazole in moderate to high yields (Table III.4).



Scheme III.39. Synthesis of benzimidazole derivatives with different aromatic aldehydes at optimum condition.

Table III.4. [a]Zn and $NaHSO_3$ mediated reduction to amines.

Entry	Reactant	Product	Time (min)	Yield (%)[b]
1			50	93
2			70	83
3			80	90
4			50	85
5			45	89

6			90	87
7			60	90
8			70	94
9			45	93
10			80	90
11			50	87
12			60	89

[a]Reaction of nitro compound (1mmol), Zn (3 mmol), $NaHSO_3$ (6 mmol) in water at 100 ^oC for different time intervals on magnetic stirrer. [b]Isolated yields.

III.6.B. Probable Mechanism

From the above observation we can propose a possible mechanism and tentative intermediates for the above developed protocol is shown below.

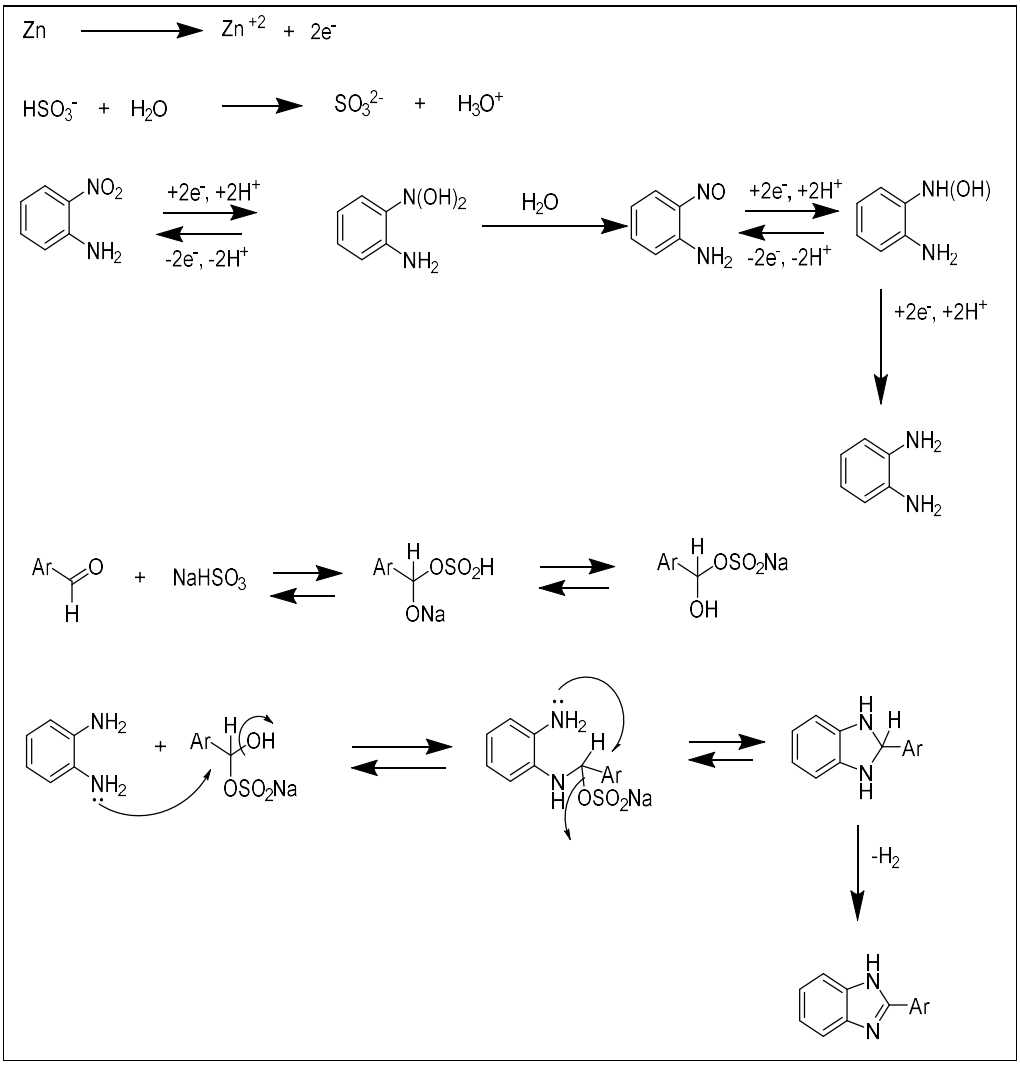


Figure III.6. Proposed mechanism for the synthesis of benzimidazole derivatives.

III.6.C. Conclusion

We have developed a novel and efficient protocol through one pot reductive cyclocondensation of 2-nitroaniline with aromatic aldehydes to benzimidazole with $Zn/NaHSO_3$ in water. The fascinating part of our method in comparison to the conventional methods is its simplicity, cost effectiveness, environmentally benign approach and a less time consuming process. We also earn that $Zn/NaHSO_3$ in water is also a better chemoselective reducing system to reduce nitro to amine. Thus, it

could potentially be complementary to the existing methods for the synthesis of biologically active benzimidazoles moiety.

III.6.D. Experimental

III.6.D.i. Chemicals

All the chemicals and solvents used in the study were purchased from commercial sources of Sigma Aldrich and SD Fine chemical company and were used without further purification unless stated. The organic solvents used were of analytical or spectroscopic grade. Before using, the solvents were dried and freshly distilled using the standard procedures whenever anhydrous solvents were required.

III.6.D.ii. General Information

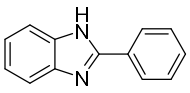
^{1}H NMR and ^{13}C NMR were recorded using 300 MHz Bruker Avance FT-NMR Spectrometer using TMS as internal. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad) and m (multiplet).

III.6.D.iii. General procedure for the synthesis of Benzimidazole derivatives from o-nitrianiline and benzaldehyde derivatives

In a round bottom flask 2-nitro aniline (1 mmol), Zn powder (3 mmol), $NaHSO_3$ (6 mmol) in 20 mL water at room temperature was stirred on a magnetic stirrer. After 10 minutes aromatic aldehyde added into it and at 100 ^{o}C temperature the mixture was stirred on a magnetic stirrer for 30 minutes. One cotton ball was present on the mouth of the round bottom flask during the process of reaction. The progress of the reaction was monitored by TLC. After completion of the reaction, the metallic part was filtered off. The filtrate was poured into 100 mL ice cold water and extracted with ethyl acetate, washed several times with water. After that we evaporate the solvent, subsequently column chromatography was done over basic alumina using petroleum ether/ethyl acetate (3:1) as eluent to afford the pure benzimidazole derivatives. The spectroscopic data (^{1}H NMR, ^{13}C NMR) of this compound are in good agreement with those reported.

III.6.D.iv. Spectroscopy data of synthesized benzimidazole derivatives

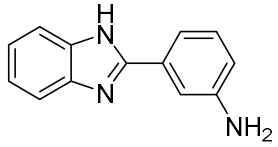
2-phenyl-1H-benzimidazole[1]



Pale yellow solid ($C_{13}H_{10}N_2$): Melting point: 292-295 ^{o}C. IR, KBr (cm^{-1}): 694, 1252, 1560, 3058; ^{1}H NMR (300 MHz), dmso-d^{6}, (ppm): δ, 7.19-7.22 (m, 2H), 7.46-7.61

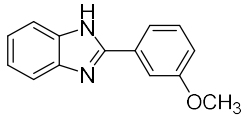
(m, 5H), 8.18-8.21 (m, 2H), 12.89 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 122.7, 126.9, 129.4, 130.3, 130.6, 151.63.

2-(3-amino phenyl)-1H-benzimidazole



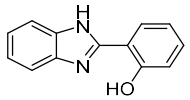
Light brown ($C_{13}H_{11}N_3$): Melting point: >290 ^{o}C. IR, KBr (cm^{-1}): 810, 1518.8, 1655.8, 3090.7, 3370.4; ^{1}H NMR (300 MHz), dmso-d^6, (ppm): δ, 4.02-4.07 (s,2H), 7.22-7.29 (m, 2H), 7.57(d, 1H, J=7.5Hz), 7.71 (d, 1H, J=7.5Hz), 7.80-7.86 (m, 1H), 8.29-8.32 (m, 1H), 8.60 (d, 1H, J=7.8Hz), 8.99-9.01 (m, 1H) 13.27 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 112.1, 119.7, 121.2, 122.6, 123.7, 124.6, 131.1, 132.1, 132.9, 135.5, 144.0, 148.8, 149.5.

2-(3-Methoxy phenyl)-1H-benzimidazole[1]



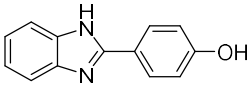
Yellow solid (C $_{14}$H $_{12}$N $_2$O): Melting point: 196-198^{o}C. IR, KBr (cm^{-1}): 830.30, 1655.8, 3067.6; ^{1}H NMR (300 MHz), dmso-d^6, (ppm): δ, 3.86 (s, 3H), 7.03-7.07 (m, 1H), 7.18-7.23 (m, 2H), 7.43-7.48 (m, 1H), 7.60 (s, 2H), 7.74-7.77 (m, 2H), 12.9 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 55.7, 111.8, 111.8, 116.3, 119.2, 122.5, 130.5, 131.9, 151.5, 160.1.

2-(2-Hydroxy phenyl)-1H-benzimidazole[1]



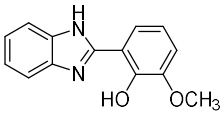
White solid ($C_{13}H_{10}N_2O$): Melting point: 238-240^{o}C. IR, KBr (cm^{-1}): 799, 1590, 3047.3, 3327.9; ^{1}H NMR (300 MHz), dmso-d^6, (ppm): δ, 6.99-7.06 (m, 2H), 7.28-7.41(m, 3H), 7.66 (br band, 2H), 8.06 (d, 1H, J=7.8Hz), 13.18 (s, 2H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 111.9, 113.0, 117.6, 118.4, 119.5, 122.9, 123.6, 126.6, 132.2, 152.1, 158.4.

2-(4-Hydroxy phenyl)-1H-benzimidazole[1]



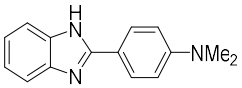
White solid ($C_{13}H_{10}N_2O$): Melting point: 253–255 ^oC. IR, KBr (cm^{-1}): 1565, 3360, 3570; ^1H NMR (300 MHz), dmso-d^6, (ppm): δ, 6.7-6.75 (m, 2H), 6.91-6.97 (m, 2H), 7.33 (s, 2H), 7.79-7.85 (m, 2H), 9.94 (s, 1H, -OH), 12.47 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6: δ, 111.6, 121.5, 122.1, 128.6, 152.2, 159.6.

2-(2-hydroxy-3-methoxy phenyl)-1H-benzimidazole[3]



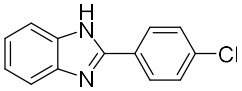
Light yellow ($C_{14}H_{12}N_2O_2$) IR, KBr (cm^{-1}): 743, 1422, 1593, 3067, 3336; ^1H NMR (300 MHz), dmso-d^6, (ppm): δ, 3.82 (s, 3H), 6.92-6.97 (m, 1H), 7.06-7.09 (m, 1H), 7.25-7.31 (m, 2H), 7.61-7.64 (m, 3H), 13.25 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 56.1, 112.9, 114.2, 117.9, 119.2, 123.3, 148.7, 149.0, 152.3.

2-(4-*N, N*-dimethyl phenyl)-1H-benzimidazole[1]



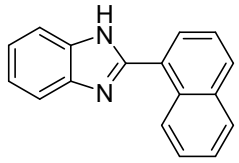
Yellow solid ($C_{15}H_{13}N_3$): Melting point: 277-279 ^oC. IR, KBr (cm^{-1}): 1459, 1518, 1605, 3391; ^1H NMR (300 MHz), dmso-d^6, (ppm): δ, 6.84 (2H, d, Ar, J = 7.8Hz), 7.43 (2H, m, Ar, J = 4Hz), 7.70 (2H, m, Ar, J = 4Hz), 8.21 (2H, d, Ar, J = 7.8 Hz), 15.2 (1H, s, NH); ^{13}C NMR (DMSO, 100 MHz)/δ ppm: 39.5, 107.8, 111.8, 113.2, 125.1, 129.1, 131.5, 149.8, 153.2.

2-(4-hydroxy, 3-methoxy phenyl)-1H-benzimidazole[2]



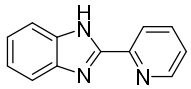
Colorless solid ($C_{13}H_9N_2Cl$): Melting point:290-292^oC IR, KBr (cm^{-1}): 754, 950, 1268, 1410, 1440, 3038; ^1H NMR (500 MHz), dmso-d^6, (ppm): δ, 7.20 (m, 2H), 7.49-7.64 (m, 4H), 8.15 (d, 2H), 12.9 (s, 1H, -NH); ^{13}C NMR (100 MHz), dmso-d^6, (ppm): δ, 111.1, 118.6, 121.9, 126.2, 128.6, 129.5, 130.0, 134.8, 143.5, 151.0.

2- (Napthyl-1yl)-1H-benzimidazole[3]



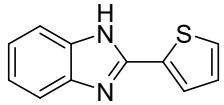
Pale yellow solid ($C_{17}H_{12}N_2$): Melting point: 196-198°C. IR, KBr (cm^{-1}): 774.4, 1560, 3057; ^{1}H NMR (300 MHz), dmso-d^6, (ppm): δ, 7.19-7.23 (m, 2H), 7.52-7.66 (m, 4H), 7.61(d, 1H, J= 6.6 Hz), 7.96-8.05 (m, 3H), 9.06 (d, 1H, J=8.1 Hz), 12.89 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 111.8, 119.5, 122.0, 123.1, 125.7, 126.8, 127.5, 127.9, 128.3, 128.8, 130.6, 130.9, 134.0, 134.9, 144.3, 151.8.

2-(Pyridin- 2yl)-1H-benzimidazole[2]



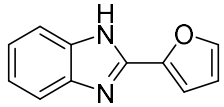
Yellow solid ($C_{12}H_9N_3$): Melting point: 240-242°C. IR, KBr (cm^{-1}): 926, 1275, 1410, 1444, 3041; ^{1}H NMR (500 MHz), dmso-d^6, (ppm): δ, 7.2 (d, 2H), 7.57 (m, 4H), 8.45 (d, 1H), 8.63 (d,1H), 9.3 (s, 2H), 13.0 (s, 1H, -NH); ^{13}C NMR (100 MHz), dmso-d^6, (ppm): δ, 112.3, 122.6, 124.6, 126.6, 134.3, 147.9, 149.3, 151.0.

2-(Thiophene-2yl)-1H-benzimidazole[4]



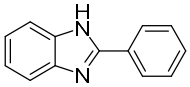
Pale yellow solid ($C_{11}H_8N_2S$): Melting point: >290°C. IR, (KBr) cm^{-1}: 743, 1423, 1571, 3051; ^{1}H NMR (300 MHz), dmso-d^6, (ppm): δ, 7.2-7.24 (m, 3H), 7.57(br band, 2H), 7.71 (d, 1H, J=0.9 Hz), 7.73 (d, 1H, J=0.9 Hz), 12.94 (s, 1H, -NH). ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 111.6, 119.0, 122.2, 122.9, 127.1, 128.7, 129.1, 134.1, 147.4.

2-(Furan-2-yl)-1H- benzimidazole[4]



Light yellow solid ($C_{11}H_8N_2O$): Melting point: 267- 270°C, IR, KBr (cm^{-1}): 738, 979, 1417, 1525, 1655, 3058; ^{1}H NMR (300 MHz), dmso-d^6, (ppm): δ, 6.71-6.76 (m, 1H), 7.18-7.22 (m, 3H), 7.54-7.57 (s, 2H), 7.93-7.97 (m, 1H), 12.94 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 110.9, 112.7, 122.7, 144.1, 145, 146.

III. 6. D. v. Scan copy of 1 H NMR and 13C NMR of benzimidazole derivatives



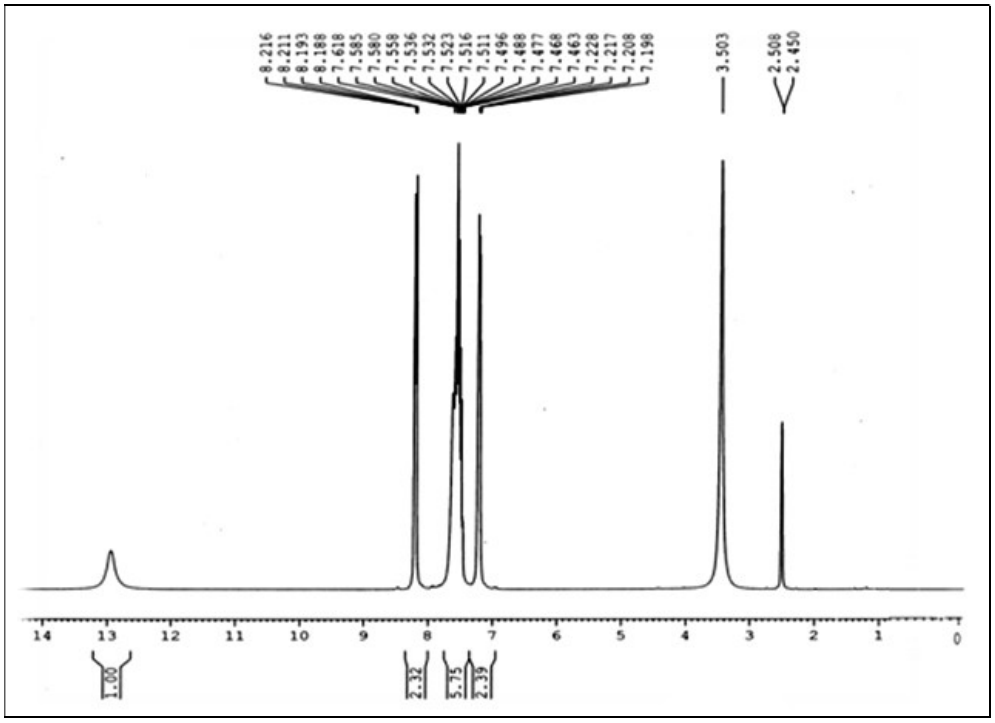


Figure III.7. [1]HNMR of 2-phenyl-1H-benzimidazole

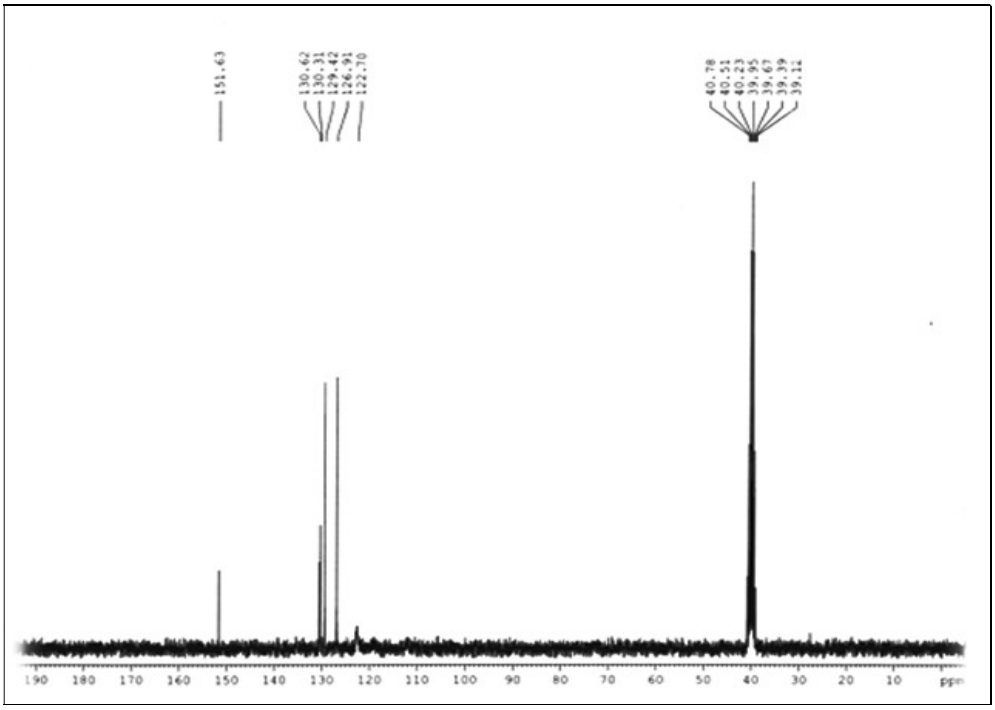
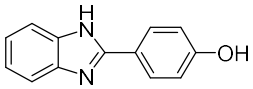


Figure III.8. [13]CNMR of 2-phenyl-1H-benzimidazole



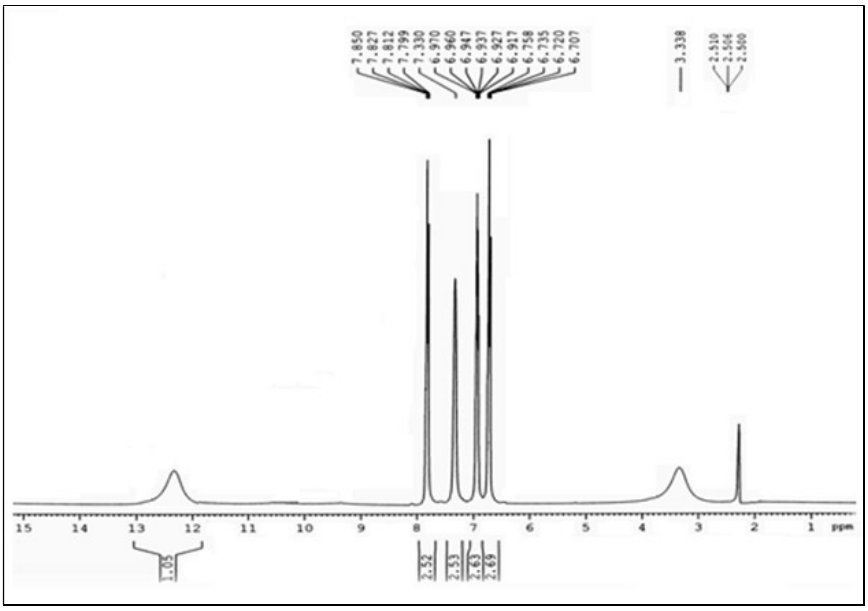


Figure III.9. [1]HNMR of 2-(4-Hydroxy phenyl)-1H-benzimidazole.

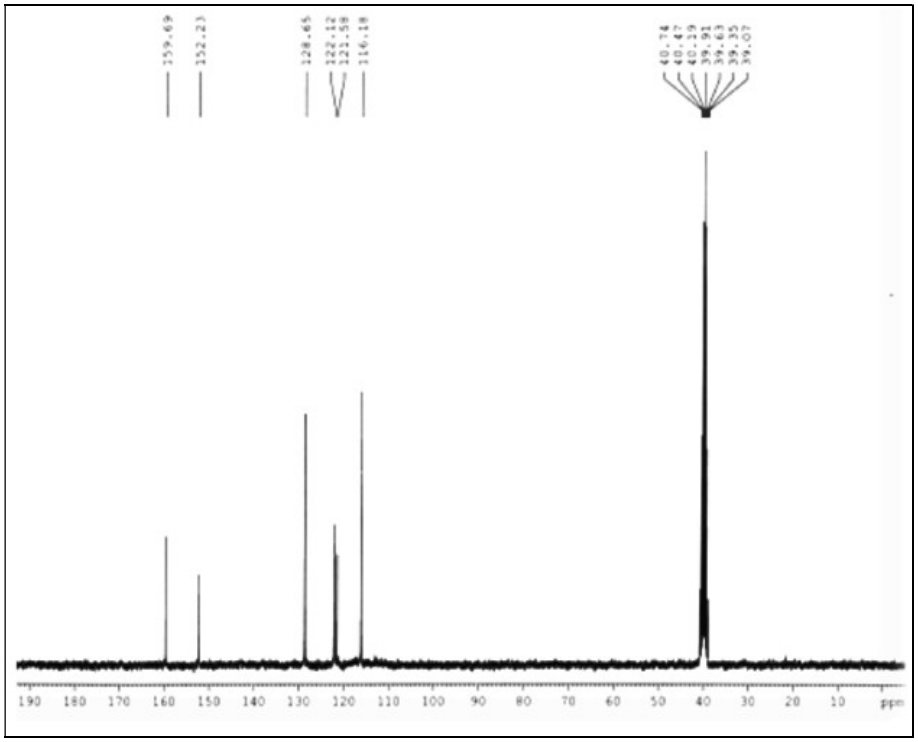
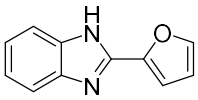


Figure III.10. [13]CNMR of 2-(4-Hydroxy phenyl)-1H-benzimidazole.



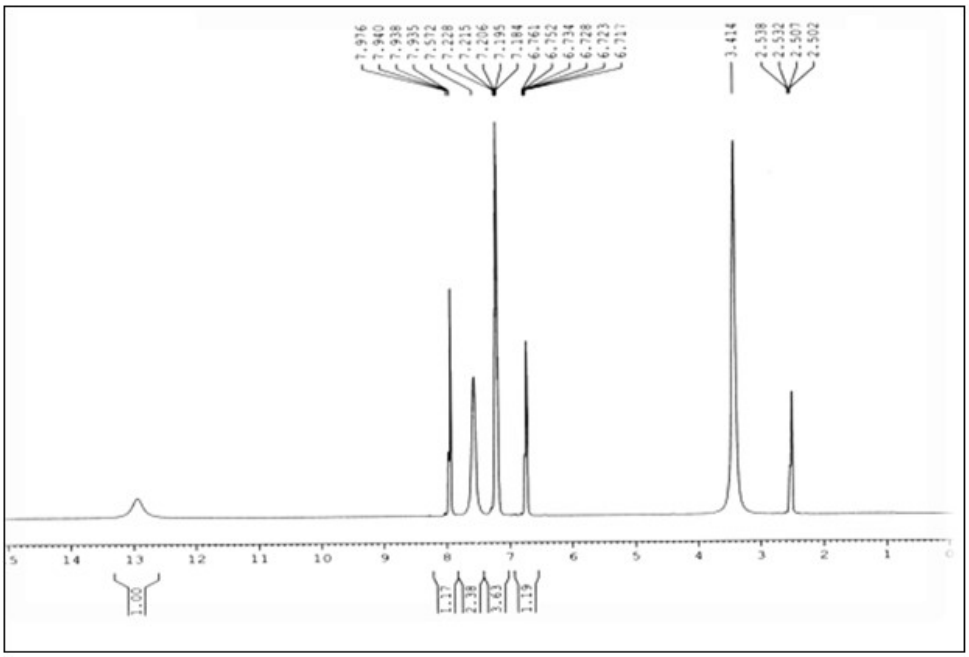


Figure III.11. [1]HNMR of 2-(Furan-2-yl)-1H- benzimidazole.

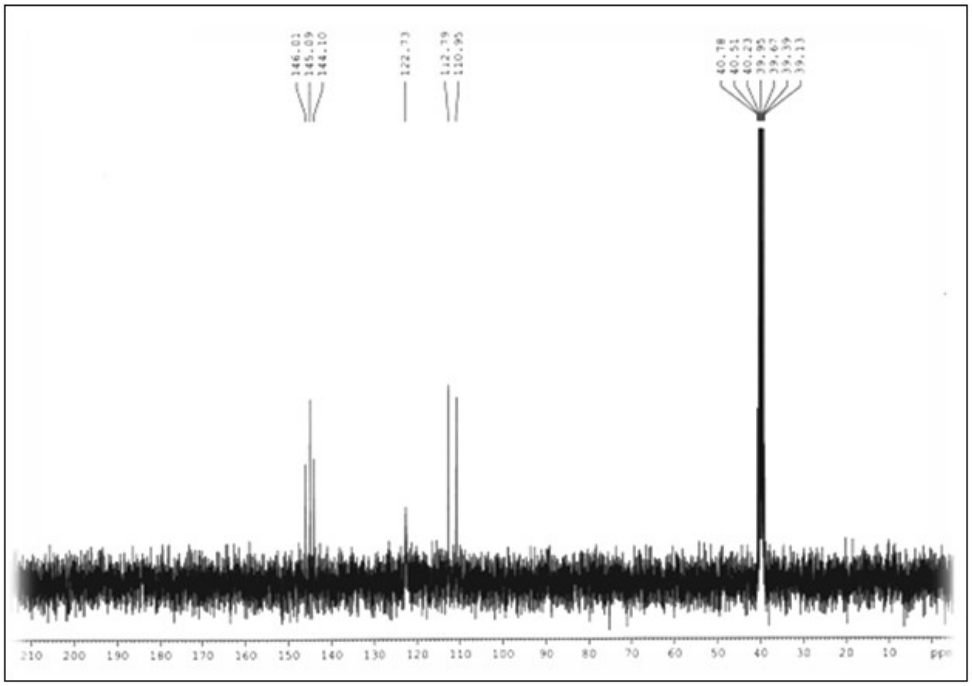


Figure III.12. [13]CNMR of 2-(Furan-2-yl)-1H- benzimidazole.

I.G. References

References are given in BIBLIOGRAPHY under Chapter III.

CHAPTER-4

ONION EXTRACT MEDIATED NOVEL SYNTHESIS OF PYRAZINE

IV.1. Pyrazine

Diazine is described as a compound with monocyclic aromatic ring having two nitrogen atoms with a molecular formula of $C_4H_4N_2$. The three isomers of diazine are pyridazine, pyrimidine and pyrazine (Figure IV.1). Pyrazine or more commonly known as 1,4- diazine, can be taken into consideration as aromatic in character and their chemistry has very little in common with benzene although their resonance energy is lower than benzene. Pyrazine display inductive resonance properties (Figure IV.2) and manifest the weakest basicity among diazine compounds, even weaker than pyridine. This is due to the electron withdrawing effect of nitrogen atoms that is positioned at *p*-position (Sato, 2014). The specific dissociation constant for pyrazine are pKa1= 0.65 and pKa2= - 5.78 (Dolezal & Zitko, 2015).

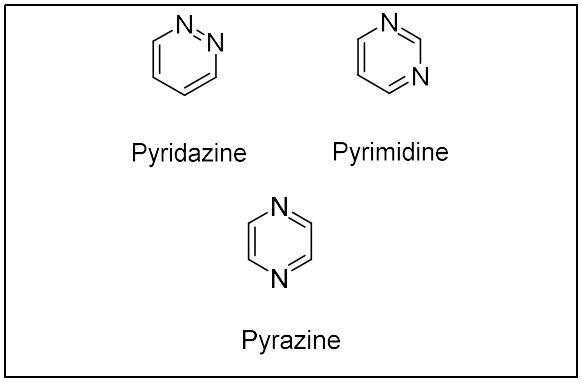


Figure IV.1. Three isomers of diazine.

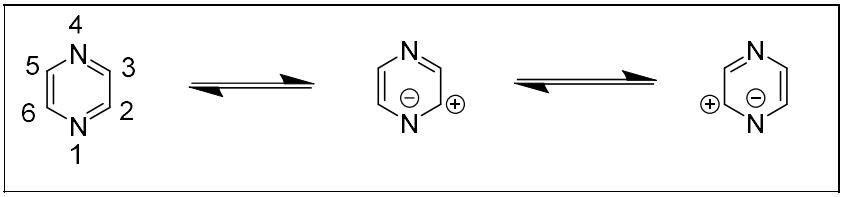


Figure IV.2. Inductive resonance property of pyrazine.

Pyrazine is stable, discoloured compound and its dipole moment is zero. The boiling point and the melting point of pyrazine are 116°C and 54°C respectively. Most of the lower homologues are liquids at room temperature which the lower members of the series are very soluble in water whereas several are miscible in all proportions. From an x-ray study, it was found that the ring is planar and the carbon-carbon distance is longer than benzene which is 1.40Å.

IV.2. Variety of application

Pyrazine is a momentous compound that have found manifold applications as pharmaceuticals. Pyrazines are exigent components of aroma fragrances [1], potential pharmacophore of a large number of biologically active substances [2-6], and widely used as agrochemicals [7-9]. Pyrazine derivatives are also used as relaxing cardiovascular and uterine smooth muscle, antithrombotic, anti-aggregation, COX-2 inhibiting, and analgesic effects [10], anticancer as well as anti-inflammatory activities [11].Some important derivatives are given bellow **(**Figure IV.3).

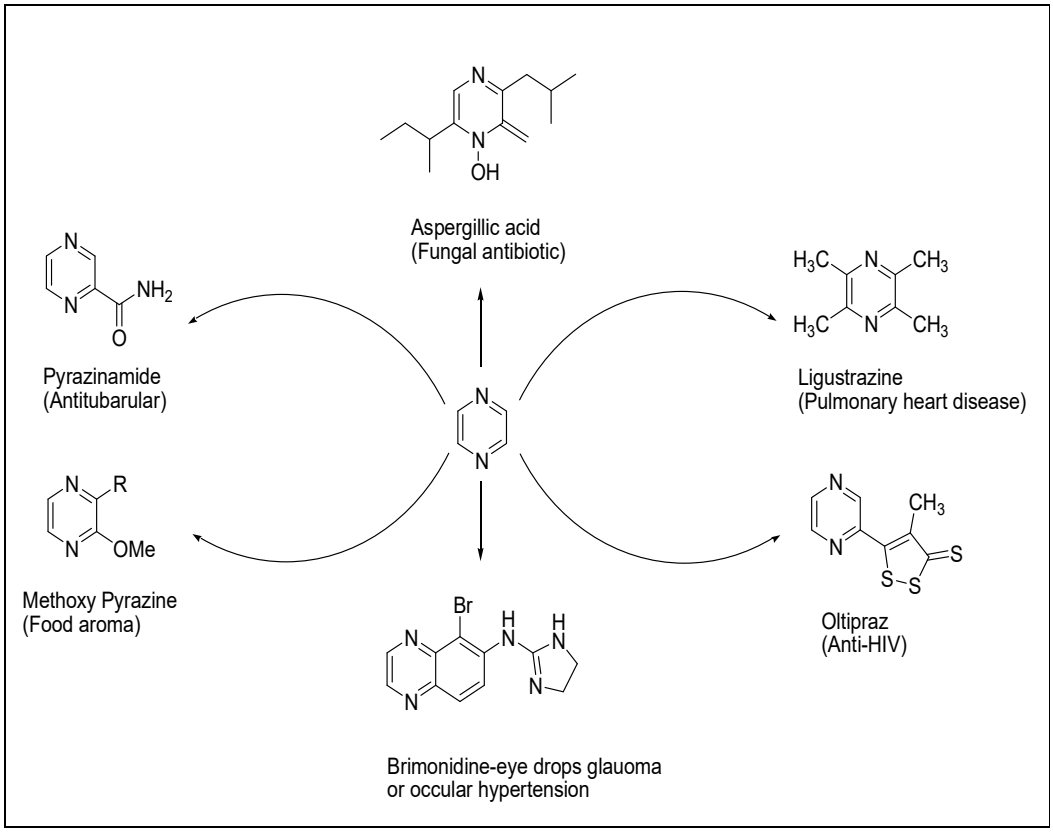


Figure IV.3. Examples of some bioactive Pyrazine derivatives.

They act as an odor signal to repel predators and effectively prevent vegetative tissue or immature fruit from being eaten [12] .That's why pyrazines find various applications as ingredients in pesticides, insecticides, dyes, and pharmaceutical compounds[13]. Pyrazines get attention from the food industry as important ingredients in raw and roasted foods. Especially alkylated pyrazines (Figure IV.4) are in the focus, as they have strong olfactory properties.

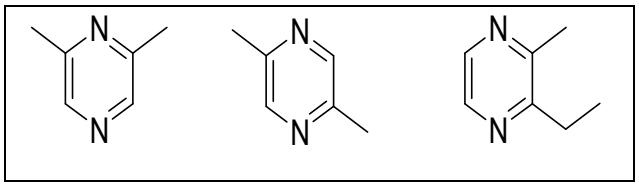


Figure IV.4. Some alkylated pyrazine used in food industries.

IV.3. Natural occurrences

Pyrazine are created naturally by living organisms such as plants [14], animals, insects[15], marine organisms as well as microorganisms[16]. Pyrazine compounds such as 2-methoxy-3-sec-butylpyrazine, 2-methoxy-3- iso-butylpyrazine, 2-methoxy-3-iso-propylpyrazine can be found in galbanum oil, beans, beetroot, lettuce, nasturtium and green pepper bell [17-18] .They can be extracted from potatoes, nuts, and coffee. Beside those compounds, pyrazine ring can be generally found in heat processed food as it is formed through Maillard reaction [19]. Allen and Lacey (1998) reported that 2-methoxy-3- isobutylpyrazine, 2-methoxy-3-secbutylpyrazine and 2-methoxy-3-isopropylpyrazine play significant role in the unique aroma of wine, especially the wine derived from grape. Apart from that, Woolfson and Rothschild (1990) reviewed that pyrazine acts as alerting pheromones, site markers, trail pheromones, repellent and escape pheromones for insects, bees as well as moths. Showalter et al. (2010) established that 2, 5-dimethyl-3(2-methylbutyl)pyrazine is the mandibular alarm pheromone excreted by fire ant Wasmannia auropunctata. Thus Pyrazine found ubiquitously in nature but only in relatively low content [20].

IV. 4. History of Pyrazine Synthesis

Laurent in 1844, first synthesized a new compound “amarone”, named by him. The “amarone” was prepared by dry distillation of α- phenyl-α-(benzylideneamino) acetonitrile, PhCH=NCHPhCN. It was later confirmed to be 2, 3, 5, 6-tetraphenylpyrazine in 1897 by Snape and Brooke (Figure IV. 5). [21]

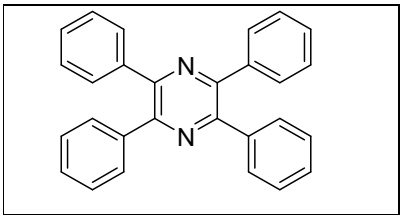


Figure IV. 5. 2, 3, 5, 6-tetraphenylpyrazine.

IV.5. Synthesis of Pyrazine

There are many synthetic viewpoints for the pyrazine ring and its derivatives. Ohtsuka et al.[22], Taylor and Dumas[23] synthesize pyrazine through cyclization process. In addition Büchi and Galindo[24] reported the regioselective formation of alkyl pyrazine via thermal electrocyclization aromatization path way. Beside this, Jones[25],Vogle and Taylor[26], Ohta et al.[27], Tazaki et al.[28], Zhang et al.[29] proposed condensation medthod to prepared pyrazine derivatives. Whereas Fukunaga and Begland[30] demonstrated that (4+2) cycloaddition also helpful to synthesize it. On the other hand Lee et al.[31], Itoh et al.[32], Richard[33], Park et al.[34], Latha et al.[35]tried their best to produce pyrazine derivatives by using metal catalyst.

Table IV.1. Some synthetic approachs of pyrazine derivatives.

Sl. No.	Reactants	Reagents /Catalyst	Solvent, Conditions	Product	Reported by (Year)
1	α-amino acid amides and 1,2-dicarbonyl	NaOH	MeOH	Pyrazine derivatives	Jones (1949)[25]
2	aminomalonamid amidine dihydrochloride and dry glyoxal bisulphate	dilute ammonium hydroxide	0-20°C	Pyrazine	Vogl and Taylor (1959)[26]
3	dicyanide with ammonia	-	MeOH	Pyrazine derivatives	Taylor and Dumas (1981)[23]
4	diiminosuccinonitrile with 1,2-dimethoxyethylene and ynamines	-	-	Pyrazine derivatives	Fukunaga and Begland (1984)[30]
5	diamine compound	copper-chromite catalyst	300-450°C	Pyrazine derivatives	Lee et al. (1990)[31]

6	allylamines and α-oximido carbonyl methyl chloroformate	potassium *tert*-butoxide	Toluene, 300°C	Pyrazine derivatives	Büchi and Galindo (1991)[24]
7	2,3- diamino-3-phenylthioacrylonitrile With glyoxal	m-chloroperbenzoic acid (MCPBA)	-	3-phenylthiopyrazinecarbonitrile	Tazaki *et al.* (1994)[28]
8	2,2-diethoxyacetophenone with 2,3- diamino-3-phenylthio-acrylonitrile	trifluoroacetic acid (TFA).	2-propanol, 22-24h	6-phenyl-3-phenylthio-pyrazinecarbonitrile	Zhang *et al.* (2001)[29]
9	isonitroso-acetophenone and aminoacetonitrile	$FeCl_3$, 10% Pd-C, H_2	MeOH, 50°C	Pyrazine derivatives	Itoh *et al.* 2002[32]
10	α-hydroxylketones and 1,2-diamino	MnO_2/ KOH-MeOH	CH_2Cl_2, Reflux, 90 mins.	Pyrazine derivatives	Richard (2003)[33]
11	propyleneglycol and ethylenediamine	CuO-ZnO-SiO2	360°C	2-methylpyrazine	Park *et al.* (2003)[34]
12	Two moles of ethylenediamine	copper oxide-copper chromite catalyst.	340-440°C	Pyrazine	Latha *et al.* (2007)[35]
13	1,2- diamine and 1,2-dicarbonyl	potassium *tert*-butoxide	RT, 6-8h	Pyrazine derivatives	Ghosh and Mandal (2012)[36]

14	*o*-phenylenediamine and benzil	*p*-toluenesulfonic acid (*p*-TSA) / ultrasonic wave	H_2O-EtOH	2,3-diphenylbenzopyrazine	Mahadik *et al.* (2014)[37]

IV.5.A. Formation of pyrazine through Maillard reaction

In addition to the previously mentioned methods, pyrazine can be synthesized by Louis-Camille Maillard (Nursten, 2005) or most commonly known as Maillard reaction[19]. The Maillard reaction is a non-enzymatic browning of food that involves condensation of carbonyl compound (reducing sugar) and amine (amino acid). Scalone et al. (2015) proposed that the general mechanism in producing pyrazine via the Maillard reaction starts with condensation of dicarbonyl compound (from degradation of reducing sugar) and amino acid. Strecker aldehyde and α-aminoketones were formed following decarboxylation of the condensed product through cyclic transition state. Then condensation of two molecules of α-aminoketones give dihydropyrazine. The dihydropyrazine could either go through oxidation to give pyrazine or deprotonation then combined with Strecker aldehyde to give another derivative of pyrazine (Scalone et al., 2015)[38].

IV.6. Importance of Onion

Common onion (Allium cepa L.) is one of the oldest cultivated plants, employ worldwide as both vegetable and flavouring. Onions are an important source of several phytonutrients as flavonoids, fructooligosaccharides (FOS), and thiosulfinates and other sulfur compounds, recognized as important elements of the Mediterranean diet [39]. The composition of the phytochemical may differ in accordance to geography, seasonal harvesting and processesing. Due to the presence of these phytochemicals, it has many applications in material chemistry [40–41] (Nanoparticle preparation) and medicinal field; including, anticancer, antiinflammatory, antiproliferative, reducing serum cholestereol, and blood pressure, immune stimulation, surgical scars, ability to modulate the detoxification system and free radical scavenging activity [42–50]. In fact, onions contain high levels of phenolic compounds, which have antioxidant properties besides beneficial effects against

different degenerative pathologies (cardiovascular and neurological diseases, dysfunctions based on oxidative stress) [51]. Flavonoids are the major phenolics in onions, which can be classified to different sub-group (flavones, flavanones, flavonols, isoflavones, flavanonols, flavanols, chalcones, and anthocyanins) on the basis of the degree of unsaturation and the degree of oxidation of the central ring. Flavonols are the most generous in onions, present as their glycosides, that is, quercetin and kaempferol [52, 53], in higher concentration (280–400mg/kg) than other vegetables (i.e., 100mg/kg in broccoli, 50mg/kg in apple) [54]. Anthocyanins, belonging to anthocyanidins, are mainly present in red onions (250mg/kg), besides having a composition rich inflavonols as yellow onions [55]. FOS represents another source of phytochemicals in onions bulbs. They are mostly inulin, kestose, nystose, and fructofuranosylnystose. The health benefits of these carbohydrates have been widely reported in the past years due to their prebiotic effect [56]. In onions, sulfur compounds are responsible for typical odour and flavour and are also active antimicrobial agents [57]; hence, onions may be used as natural preservatives to control microbial growth [57]. Furthermore, they have also protective effects against cardiovascular diseases.

IV.7. Organic synthesis catalyzed by onion extract

In the development of new synthetic and catalytic protocols in organic synthesis, the developments of environmentally benign and economical processes are highly demandable. One of the young catalysts is onion extract.

The precursors of sulfur-containing compounds in onion are S-alk(en)yl-L-cysteine sulfoxides (ACSOs, i.e., methiin, propiin, and isoalliin). 1-Propenyl-L-cysteine-sulphoxide (isoalliin, 1) is usually found in highest concentration and is responsible for the tearing and pungency associated with onions. When the onion is cut, the isoalliin (1) undergoes a series of rapid reactions. After the breakage of the tissue caused by cutting, enzyme Alliinase catalyzes the conversion of 1-propenylcysteine sulfoxide to (E)-1- propenesulfenic acid (2), which is then, rearranged to the volatile and highly reactive lachrymatory factor (LF) (Z)-propanethial S-oxide (5), which produces propionaldehyde (6), sulphuric acid (7) and hydrogen sulfide (8) [58]. Besides, onion extract contains water soluble phytochemicals- caffaeic acids, ferullic acid sinapinic acid, cyaniding, tannic acid and other organic acids. These factors responsible for the acidic nature of onion extract and make its pH 3.6 with the strength of 0.0034 N.

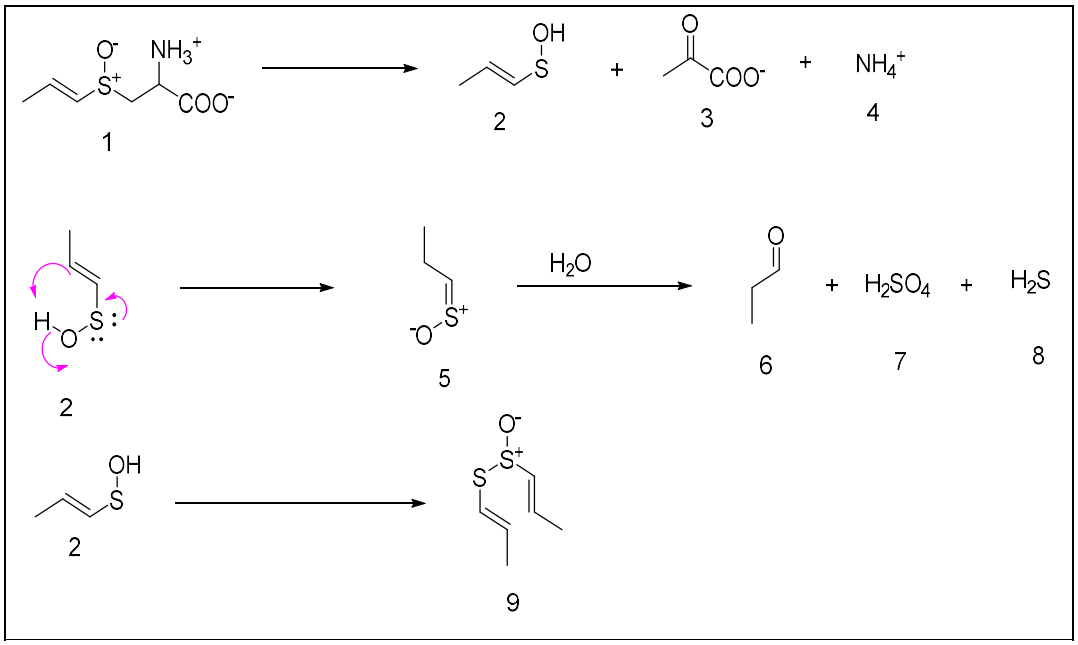
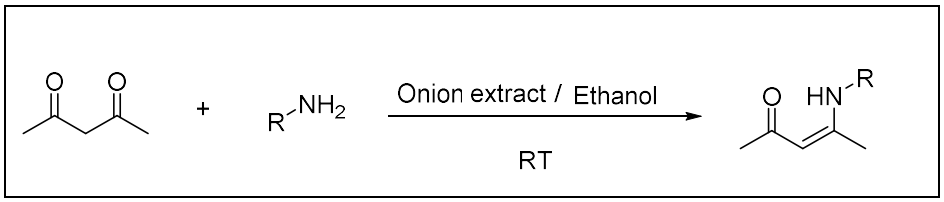


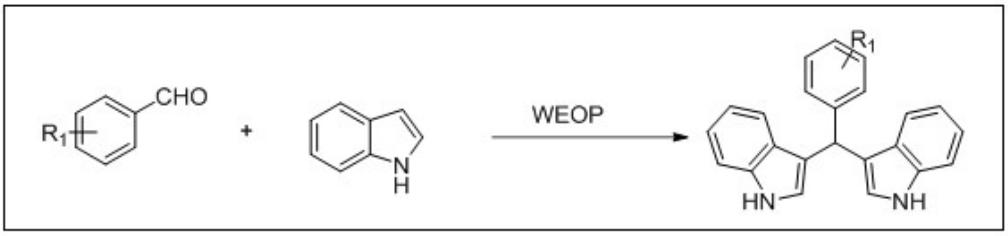
Figure IV.6. Pathway for the enzymatic synthesis of the lachrymatory factor propanethial-S-oxide (5) and for the spontaneous production of the flavour factor thiosulphinate (9), in onion. The lachrymatory factor propanethial-S-oxide (5) has two isomers, syn and anti. Both the isomers are formed, but the syn compound is formed preferentially.

Based on the above facts to avoid hazardous chemicals in recent years researchers utilized onion extract as a catalyst into some organic synthesis in different ways. In 2017, Kaliyan Prabakaran *et al.*[59] were reported the onion extract catalyzed method of synthesis of enaminones 3 and enaminoesters 5 from 1,3-dicarbonyl compounds and primary amines. The reaction was preceded smoothly in the presence of onion extract (0.01 mL) to afford enaminones and enaminoesters in good yields (Scheme IV.1).



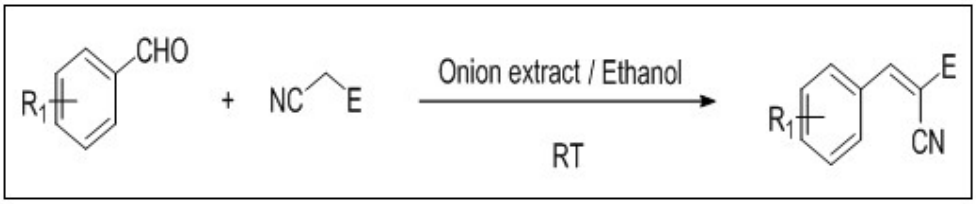
Scheme IV.1. General scheme for the synthesis of enaminone derivatives using onion extract. R = different functional groups.

In 2019, Poh Wai Chia *et al.*[60] demonstrated the synthesis of bisindolylmethanes (BIMs) using Water Extract of Onion Peel (WEOP) (Scheme IV.2).



Scheme IV.2. Synthetic route towards the preparation of bisindolylmethanes (BIMs) using WEOP. R_1 = different functional groups.

In 2019, again Kaliyan Prabakaran *et al*. [61] placed onion extract in a favourable light to catalyze Knoevenagel condensation reaction of active methylene compounds with various aldehydes such as aromatic, aliphatic, heterocyclic and α, β-unsaturated (Scheme IV.3).

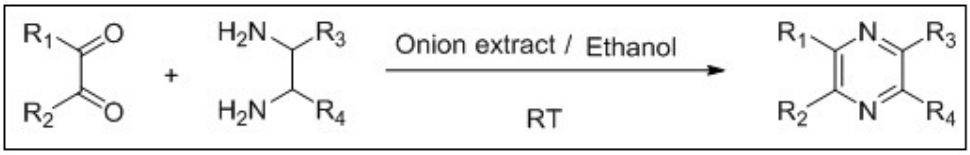


Scheme IV.3. General scheme for the synthesis of α-cyanoacrylonitriles and α-cyanoacrylates using onion extract.

Now, to explore the catalytic applicability of onion extract, worth of Pyrazine derivatives and to avoid the limitation of its synthesis, keeping these in mind, we report a simple and mild one-pot method for the synthesis of Pyrazine derivatives

IV.8. Present work

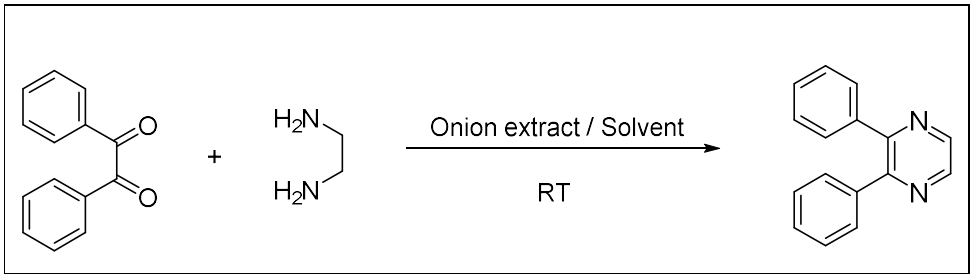
In the present work we report an efficient catalytic system for the synthesis of Pyrazine derivatives using extract of onion at room temperature is described. A very good to excellent yields in reasonably short reaction time, high atom economy, usage of readily available starting material, operational simplicity and easy workup are the fundamental features of this protocol.



Scheme IV.4. The general scheme and reaction for the synthesis of Pyrazine derivatives. R_1, R_2, R_3, R_4 are the different functional groups.

IV.8.A. Results and discussion

Our inaugural endeavor on this reaction, in order to earn a decent reaction condition, was made with the reaction of Benzil and Ethylenediamine in the attendance of onion extract under diversity of solvent systems for 45-90 minutes. It was found that, the method is efficient for all solvents with good yields. Here the greenest solvent, water could have been the first in this race, leaving every solvent behind, but its low ability to dissolve organic compounds did not allow him to do so (Table IV.2, entry 4). Our scheme also completes the reaction without solvent, though the yield is poor (Table IV.2, entry 5). After observing Table IV.2, we can conclude that EtOH is the superior for this novel purpose (Table IV.2, entry 3).



Scheme IV.5. Synthesis of Pyrazine derivatives from benzyl and ethylenediamine using onion extract.

Table IV.2. [a]Reaction conditions optimization by various solvents.

Entry	Solvent (5 mL)	Time (min.)	Yield(%)[b]
1	DMF	60	68
2	DCM	60	86
3	EtOH	60	96
4	H_2O	60	80
5	-	60	75
6	Hexane	60	55
7	DMSO	60	84
8	Isopropanol	60	76
9	Acetonitrile	60	69
10	Toluene	60	50

[a]Reaction of Benzil (1 mmol) and ethylenediamine (1 mmol) catalysed by onion extract (2 ml) on magnetic stirrer at room temperature. [b]Isolated yield of Pyrazine.

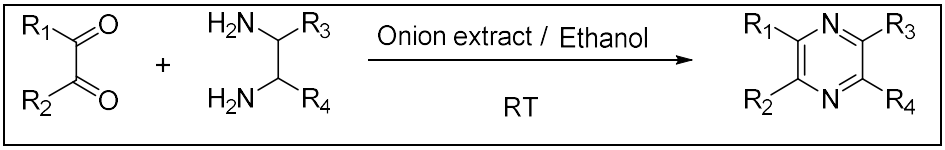
Next effort were undertaken to optimize the quantity of onion extract required to carry out the reaction. At first the substrates were stirred at room temperature for 120 minutes in the absence of onion extract, result rap out that onion extract play a key role to carry out the reaction (Table IV.3, entry 1), and also it was observed that minimum 0.2 mL onion extract and 60 minutes is sufficient enough to catalyze the reaction with better yield for desired product (Table IV.3, entry 6-10).

Table IV.3. [a]Reaction (Scheme-1) condition optimization.

Entry	Onion extract (mL)	Time(min.)	Yield (%)
1	0	120	Trace
2	1	120	97
3	0.8	120	97
4	0.6	120	97
5	0.4	120	96
6	0.2	120	96
7	0.1	120	95
8	0.2	90	96
9	0.2	60	96
10	0.2	45	92

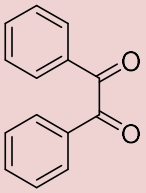
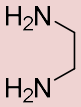
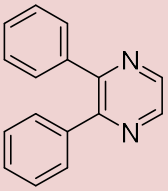
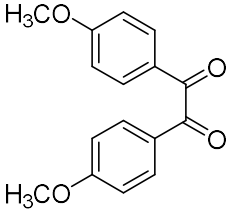
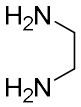
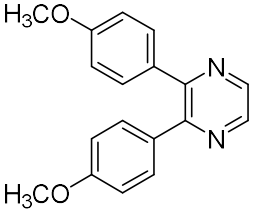
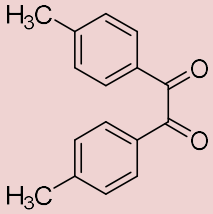
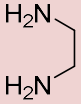
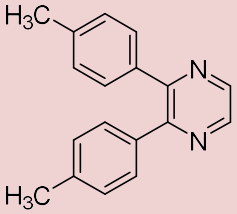
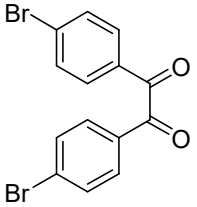
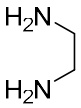
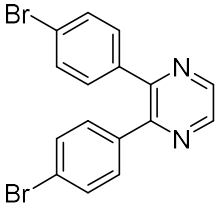
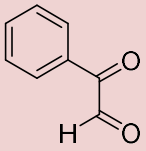
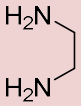
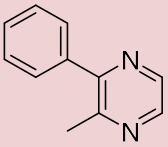
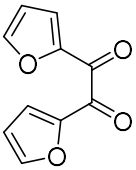
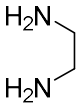
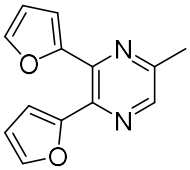
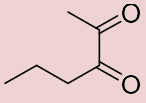
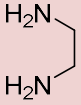
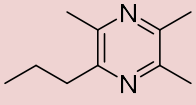
[a]Reaction of Benzil (1 mmol) and ethylenediamine (1 mmol) in EtOH (5 mL) on magnetic stirrer at room temperature.

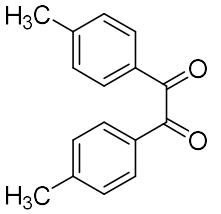
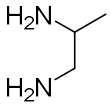
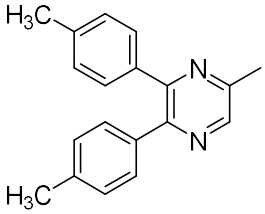
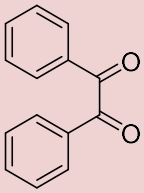
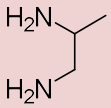
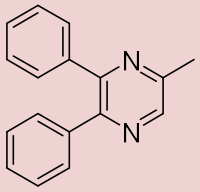
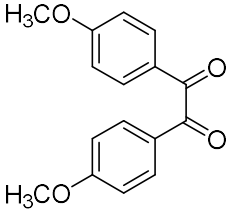
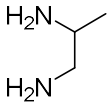
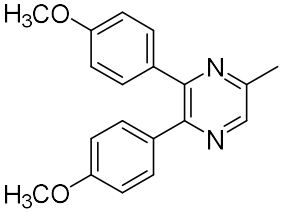
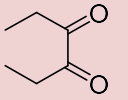
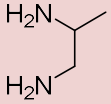
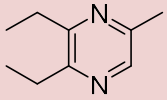
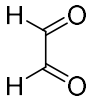
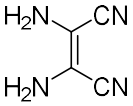
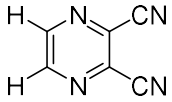
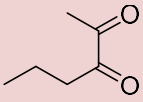
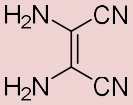
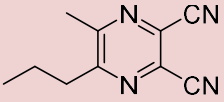
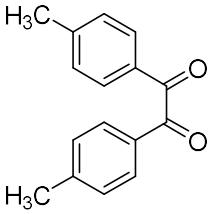
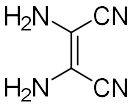
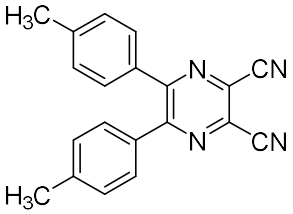
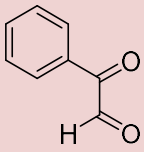
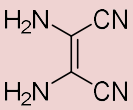
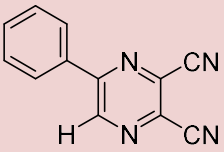
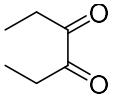
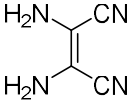
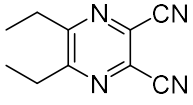
To widen the scope of our study, commercially available 1, 2-diketones and 1, 2-diamines are selected to synthesized corresponding products. As shown in Table 3, high yields were achieved for the synthesis of different Pyrazine derivatives within a reasonable time (Table IV.4, entry 1-15).

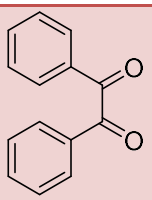
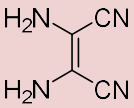
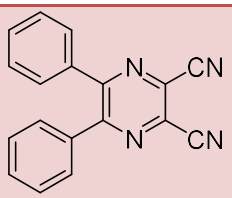


Scheme IV.6. The general scheme and reaction for the synthesis of Pyrazine derivatives using onion extract. R_1, R_2, R_3, R_4 are the different functional groups.

Table IV.4. Isolated yield and the catalytic synthesis of product.

Entry	Diketones	1,2-diamines	Product	Time (min)	Yield[b] (%)
1				60	96
2				70	94
3				80	96
4				50	92
5				45	89
6				60	89
7				50	90

8				50	94
9				90	96
10				70	95
11				70	93
12				60	89
13				45	85
14				50	87
15				80	89
16				70	86

17				45	88

[a]Reaction of Benzil (1 mmol) and ethylenediamine (1 mmol) in ethanol catalyzed by onion extract (0.2 ml) on magnetic stirrer. [b]Isolated yield of Pyeazine.

IV.8.B. Reusability of the catalyst and possible mechanism

The reusability study was examined for the onion extract catalyst (Figure IV.7). Our catalyst gave the desired product with good yield (96%-85%). The organic acids which are present in the onion extract were believed to serve as catalyst in the double condensation reaction and aromatization process to form Pyrazine derivatives.

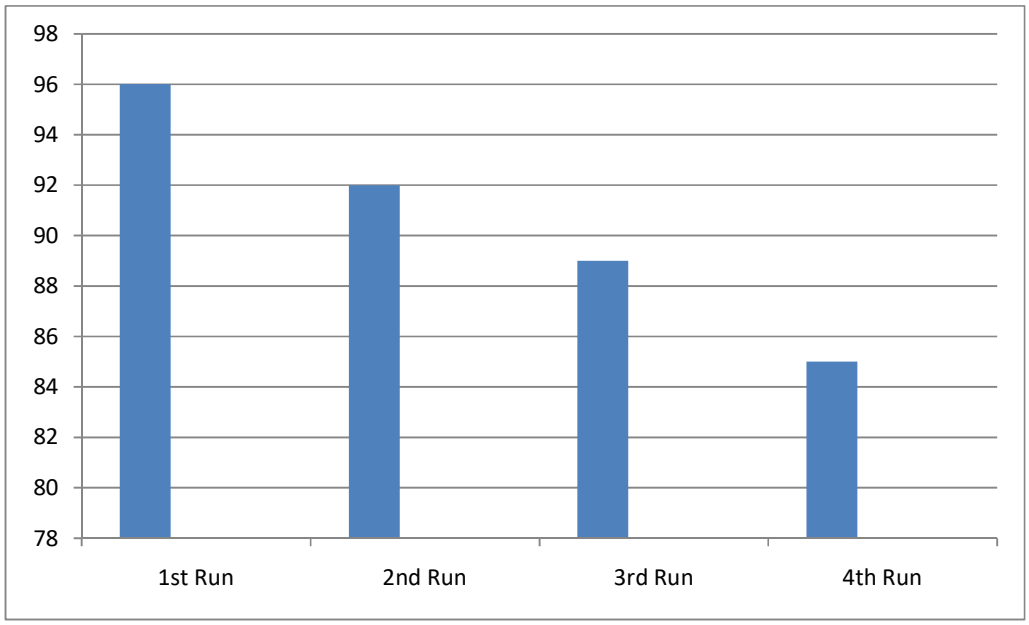


Figure IV.7. Reaction of Benzil (1 mmol) and ethylenediamine (1 mmol) in ethanol catalyzed by onion extract (0.2 ml) on magnetic stirrer. Recycling of our catalyst for synthesis of Pyrazine.

Literature report revealed that onion extract contain phenolic acids as major constituents along with other minor chemical constituents such as flavanols, flavones and anthocyanidines. The pH of the onion extract is found to be 3.6, which are due to the presence of water soluble phytochemicals- caffaeic acids, ferullic acid sinapinic acid, cyaniding, tannic acid and other organic acids. As they are water soluble that's

why we can easily collect the onion extract solution for our reusability purpose and we can also recover the acids after four successive usages. Therefore, we can propose the organic acids that are present in the onion extract served to protonate the oxygen atoms of the carbonyl groups of the diketone thereby faceiliting the nucleophilic attack by 1, 2-diamine promoting the synthesis of Pyrazine derivatives. From the above observation we can draw possible mechanism (**Figure IV.8**) and tentative intermediates in the synthesis of Pyrazine derivatives as follows.

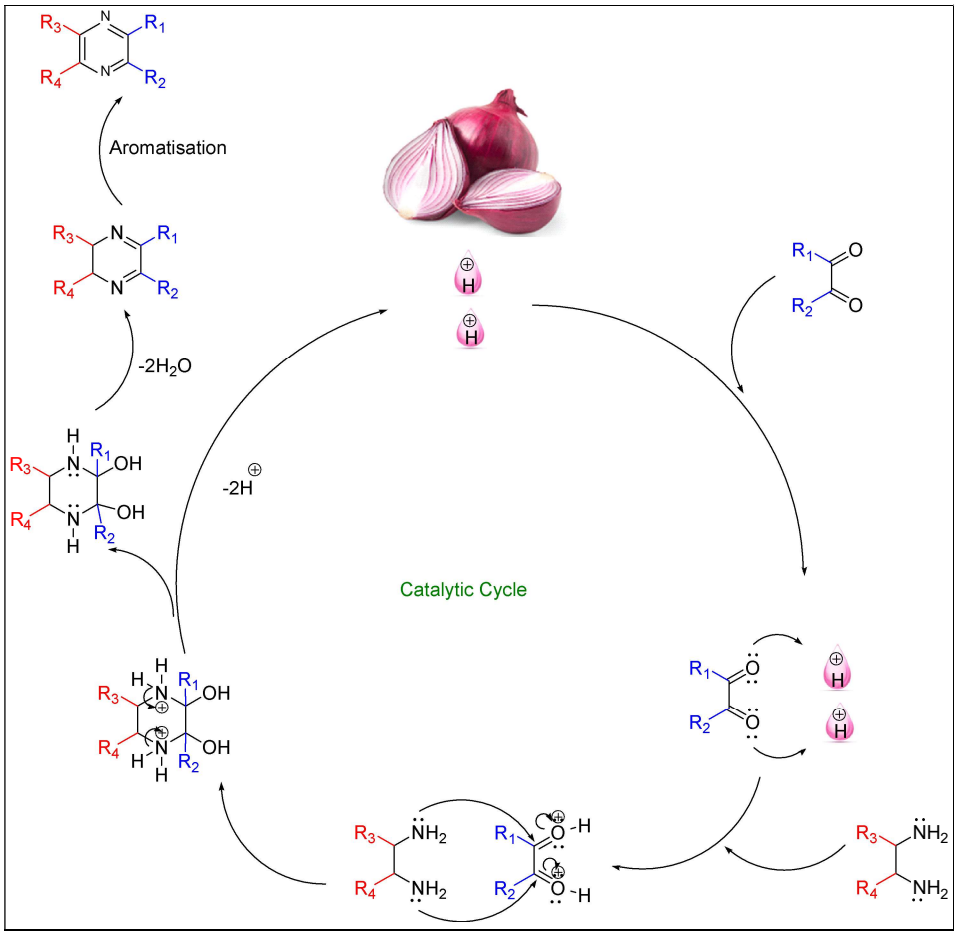


Figure IV.8. Possible mechanism and tentative intermediates in the synthesis of Pyrazine derivatives. R_1, R_2, R_3, R_4 are the different functional groups.

IV.8.C. Conclusion

In summary, we have achieved a simple and convenient procedure to synthesize Pyrazine derivatives in the presence of onion extract through condensation and aromatization from the easily available 1, 2-diketones and 1, 2- diamines. The current protocol offers many advantages including a simple and effective catalytic system, simple workup, benign reagents, cheap but good to excellent yields and the

reusability of the onion extract as a catalytic system. Further application of the onion extract in the synthesis of other bioactive heterocyclic compounds is currently ongoing in our laboratory and the results will be reported in due course.

IV.8.D. Experimental section

IV.8.D.i. General experimental detail

All the melting points were determined in an open capillary method; UV spectra were recorded in JASCO V-530 UV/VIS spectrophotometer; IR was recorded in Perkin-Elmer FT-IR spectrophotometer; and NMR was recorded in Bruker-Avance 300 MHz FT-NMR instrument using TMS as the internal standard. NMR spectra were recorded in $CDCl_3$. The entire chemicals were purchased from Merck, Fluka, SRL, and S.D. fine chemicals companies.

IV.8.D.ii. Preparation of Onion extract

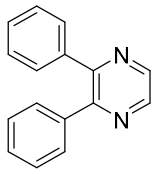
Onion was brought from local market and washed with water. Then squeezed the dry onion and filter it. The filtrate is onion extract and it is ready to use.

IV.8.D.iii. Representative Experimental Procedure for Reduction of Aromatic Nitro Compounds

In a round bottom flask Benzil (1 mmol), Ethylenediamine (1 mmol), Onion extract (0.2 mL) in 5 mL Ethanol at room temperature was stirred on a magnetic stirrer for 60 minutes. One cotton ball was present on the mouth of the round bottom flask during the process of reaction. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into 100 mL ice cold water and the product extracted with ethyl acetate, washed several times with water. Evaporation of solvent followed by column chromatography over basic alumina using petroleum ether/ethyl acetate (3:1) as eluent to afford the pure benzimidazole derivatives. The spectroscopic data (^{1}HNMR, ^{13}CNMR) of this compound are in good agreement with those reported.

IV. 8. E. Characterization of some representative compounds

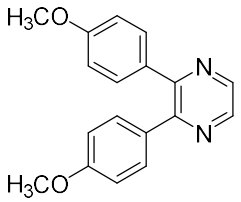
2, 3-diphenyl pyrazine



^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 7.14-7.25 (m, 5H, five aromatic hydrogen), 7.37-7.44 (m, 5H, five aromatic hydrogen), 8.52 (s, 2H, 2 aromatic hydrogen of the

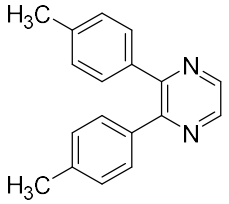
heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 128.1, 128.2, 128.5, 129.5, 138.5, 141.9 and 152.6.

2, 3-bis (4-methoxy phenyl) pyrazine



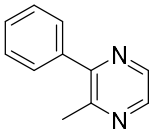
^1H NMR ($CDCl_3$, 300MHz): δ(ppm) 3.77 (s, 6H, 2-OCH3), 6.75-6.85 (m, 4H, four aromatic hydrogen), 7.33-7.43 (m, 4H, four aromatic hydrogen), 8.45 (s, 2H, two aromatic hydrogen of the heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 55.2, 113.7, 130. 9, 131.2, 141.4, 152.1 and 159.9.

2, 3-di p-tolyl pyrazine



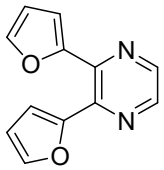
^1H NMR ($CDCl_3$, 300MHz): δ(ppm) 2.31 (s, 6H, 2-CH3); 7.04-7.12 (m, 3H, aromatic hydrogen), 7.27-7.46 (m, 5H, five aromatic hydrogen); 8.51 (s, 2H, two aromatic hydrogen of the heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 21.3, 129.0, 129.4, 135.8, 138.5, 141.7 and 152.6.

2-methyl-3-phenyl pyrazine



^1H NMR ($CDCl_3$, 300MHz): δ(ppm) 2.54 (s, 3H, -CH3), 7.46-7.59 (m, 5H, five aromatic hydrogen), 8.44 (d, 2H, J=2.4Hz). 13C NMR (CDCl3, 75MHz): δ(ppm) 23.1, 128.4, 128.7, 128.9, 138.5, 141.5, 142.1, 151.8 and 154.4.

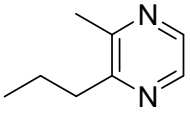
2, 3 di-(furan-2-yl)- pyrazine



^1H NMR ($CDCl_3$, 300MHz): δ 2.59 (s, 3H, -CH3), 6.56 (m, 4H, aromatic protons), 7.52 (m, 2H, aromatic protons), 8.37 (s, 1H, aromatic proton). ^{13}C NMR ($CDCl_3$,

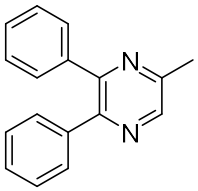
75MHz): δ(ppm) 21.3, 112.1, 112.7, 139.2, 140.8, 141.7, 143.4, 143.7, 150.5, 150.6, 151.2.

2-methyl-3-propylpyrazine



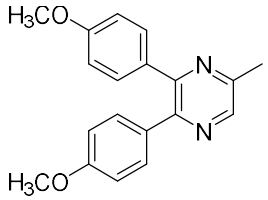
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 0.96-1.04 (m, 3H, - CH3), 1.70-1.82 (m, 2H,), 2.57 (s, 3H, -CH3), 2.79 (t, 2H, J=7.5Hz). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 14.0, 21.5, 21.7, 36.9, 141.1, 141.4, 152.3, 156.0.

2, 3-diphenyl-5-methylpyrazine



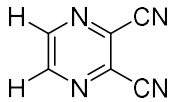
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 1.86 (s, 3H, -CH3), 6.63 (d, 10H, J=5.1Hz, ten aromatic hydrogen), 7.68 (s, 1H, one aromatic hydrogen of the heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 20.5, 127.4, 127.6, 128.7, 128.8, 137.8, 141.0, 148.8, 150.3, 150.7.

2, 3-bis (4-methoxy phenyl)-5-methylpyrazine



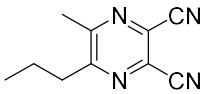
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 2.62 (s, 3H, -CH_3), 3.80 (s, 6H, 2-OCH_3), 6.82 (dd, 4H, J=1.8 Hz, four aromatic hydrogen), 7.38 (dd, 4H, J=1.8 Hz, four aromatic hydrogen), 8.39 (s, 1H, one aromatic hydrogen of the heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 21.2, 53.4, 55.2, 130.8, 130.9, 131.2, 131.4, 141.1, 149.0, 150.5, 150. 9, 159.8, 159.6.

Pyrazine-2, 3-dicarbonitrile



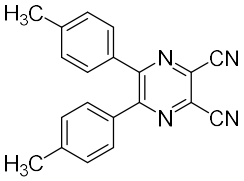
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 9.00 (s, 2H, aromatic protons). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 113.1, 133.84 (aromatic carbons), 147.5 (-CN).

5-methyl-6-propiopyrazine-2, 3-dicarbonitrile



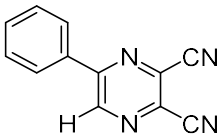
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 1.06 (t, 3H, J=7.2Hz); 1.78-1.88 (m, 2H); 2.75 (s, 2H, -CH_3); 2.94 (t, 2H, J=7.5 Hz). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 13.8, 20.4, 22.3, 36.9, 113.3, 113.4, 129.9, 130.4, 157.7, 161.2.

5, 6-dip-tolylpyrazine-2, 3-dicarbonitrile



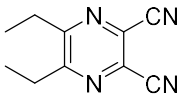
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 2.32 (m, 6H, 2 -CH_3), 6.99 (m, 4H, aromatic protons), 7.43 (m, 1H, aromatic proton), 7.94 (m, 3H, aromatic protons). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 21.6, 126.8, 128.6, 129.3, 130.0, 139.2, 144.0, 144.3, 193.3.

5-phenylpyrazine 2, 3-dicarbonitrile



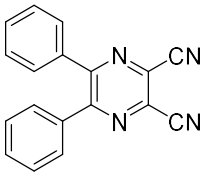
^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 7.61 (d, 3H, J7.5 Hz), 8.13 (d, 2H, J6.6Hz), 8.51 (s, 1H). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 128.0, 129.8, 130.8, 132.5, 133.0, 144.1, 154.8.

5, 6-diethylpyrazine-2, 3-dicarbonitrile



^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 1.39 (m, 6H), 1.97(m, 2H), 2.97 (m, 2H), ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 11.2, 19.8 (2-CH3); 25.1, 27.8 (2-CH2); 113.4, 130.2 (aromatic carbon); 161.3 (-CN).

5, 6-diphenyl pyrazine-2, 3-dicarbonitrile



^{1}H NMR ($CDCl_3$, 300MHz): δ(ppm) 7.16-7.30 (m, 5H, five aromatic hydrogen); 7.45 (t, 2H, J=7.3 Hz, two aromatic hydrogen); 7.57 (t, 1H, J=7.3 Hz, aromatic

hydrogen); 7.78 (d, 2H, J=7.2 Hz, aromatic hydrogen). ^{13}C NMR ($CDCl_3$, 75MHz): δ(ppm) 126.5, 127.5, 128.2, 128.4, 130.0, 132.4, 137.5, 143.8, 196.8 (carbon of nitrile group).

IV.8.F. Scane copy of 1H NMR, 13 C NMR ofsome pyrazine derivatives

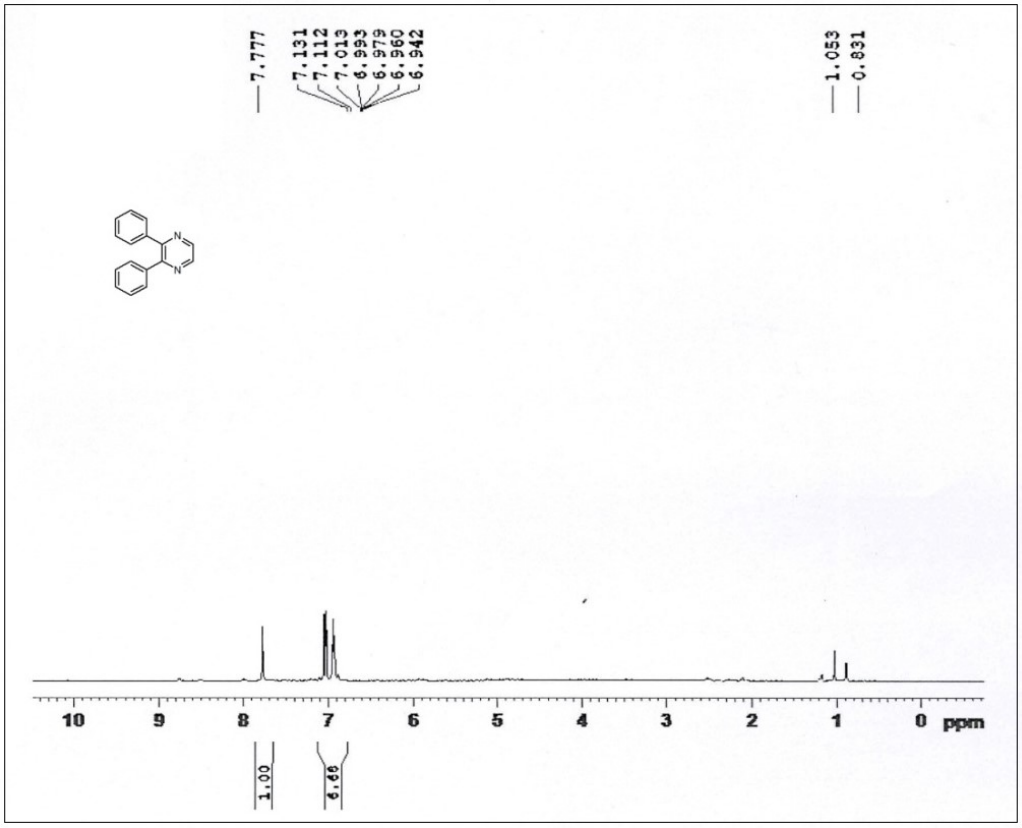


Figure IV.9. ^{1}HNMR of 2,3-diphenylpyrazine.

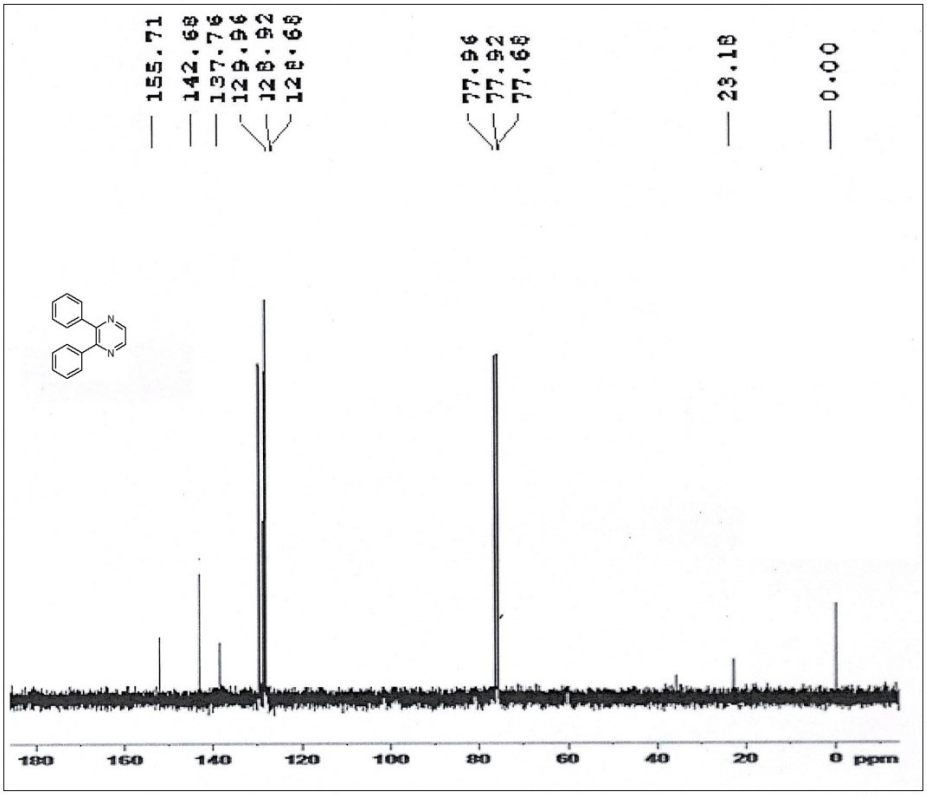


Figure IV.10. ^{13}C NMR of 2,3-diphenylpyrazine.

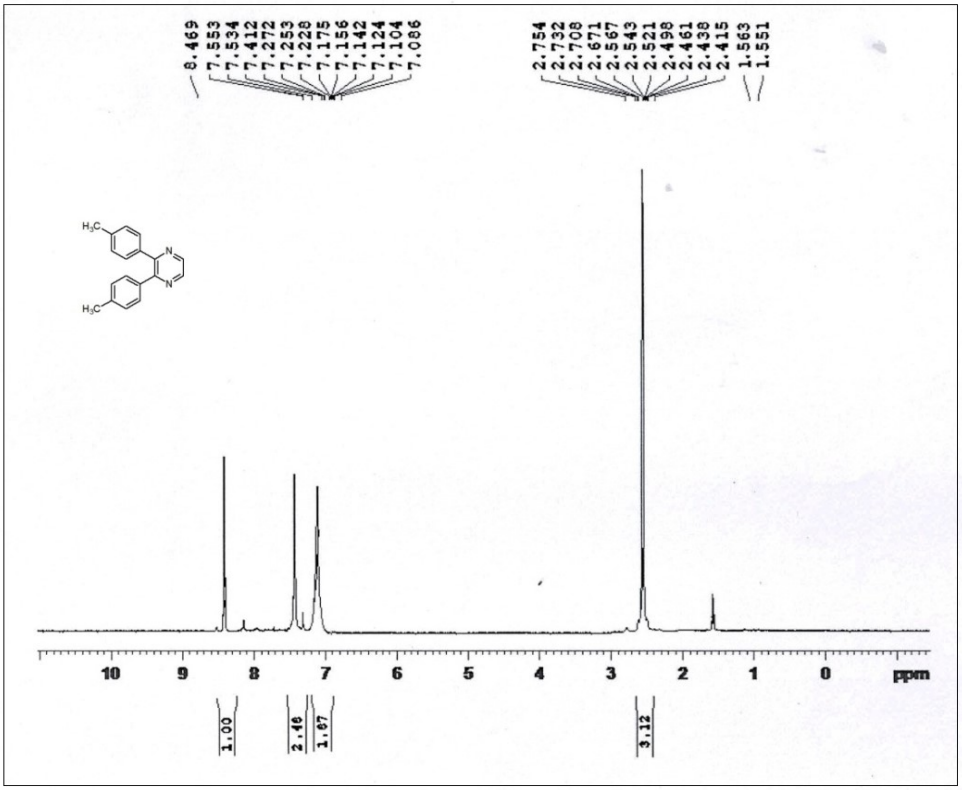


Figure IV.11. ^{1}HNMR of 2, 3-di p-tolyl pyrazine.

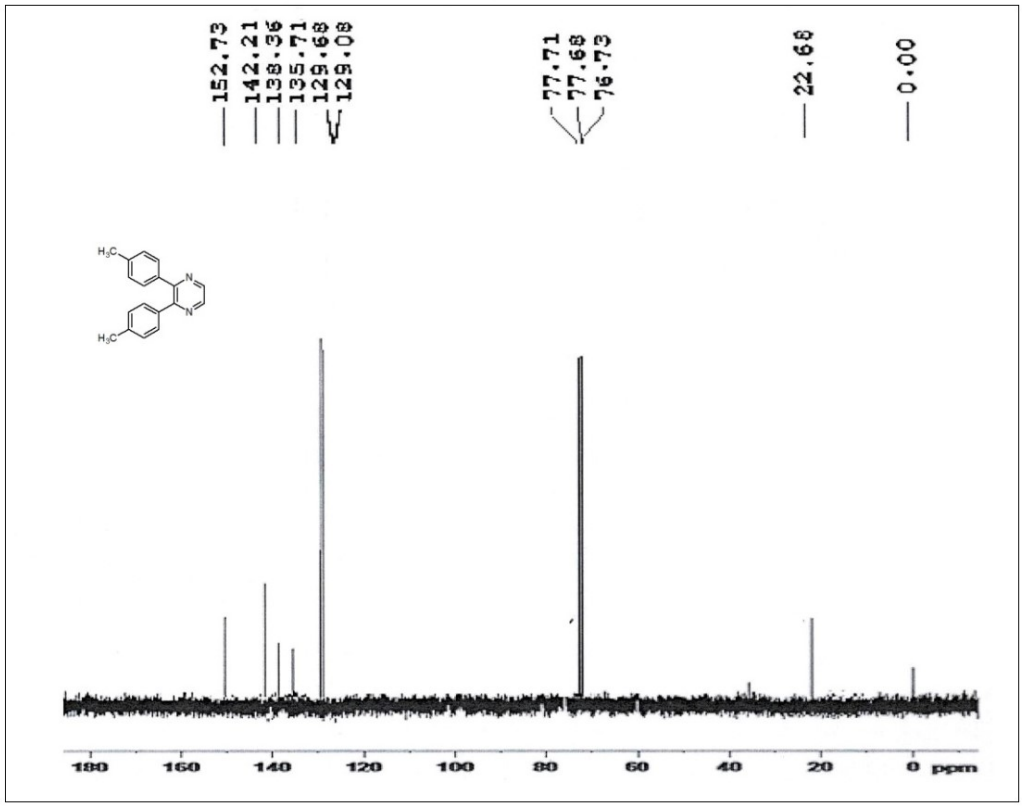


Figure IV.12. ^{13}C NMR of 2, 3-di p-tolyl pyrazine.

I.G. References

References are given in BIBLIOGRAPHY under Chapter IV.

CHAPTER-V

SOLID PHASE VS SOLUTION PHASE SYNTHESIS OF TRISUBSTITUTED IMIDAZOLES

V.1. Imidazole

Imidazole, colourless solid is an aromatic heterocyclic compound with the formula $C_3N_2H_4$. It is a planar 5-membered ring. It forms two equivalent tautomeric structures, as the proton can be placed on either of the two nitrogen atoms. The calculated dipole moment value of imidazole (3.61D) is an evidence of high polarity of the compound. It is highly aqueous soluble. The compound is categorized as aromatic because of the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the rest four atoms of the ring. The resonance structures of imidazole are shown below (Figure V.1).

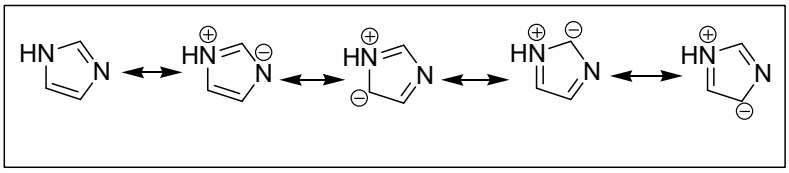


Figure V.1. Canonical form of Imidazole.

V.2. Biological importance of imidazole derivatives

Imidazole is associated with many essential biologically active molecules. The most important is the amino acid histidine (Figure V.2) which has an imidazole side chain. Histidine is present in various proteins as well as enzymes and plays a crucial part in the structure and binding functions of haemoglobin. Imidazole has become a vital part of numerous pharmaceuticals. Synthetic imidazoles are present in many antifungal, antiprotozoal, and antihypertensive drugs. It is present in the anticancer medication mercaptopurine, which combats leukemia by interfering with DNA activities.

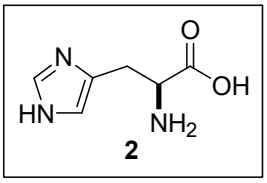


Figure V.2. Amino acid histidine**.**

Imidazoles belong to the class of azole antifungals, which includes eprosartan (1), econazole (2), trifenagrel (3), isoconazole (4), omoconazole (5), tioconazole (6) etc (Figure V.3).

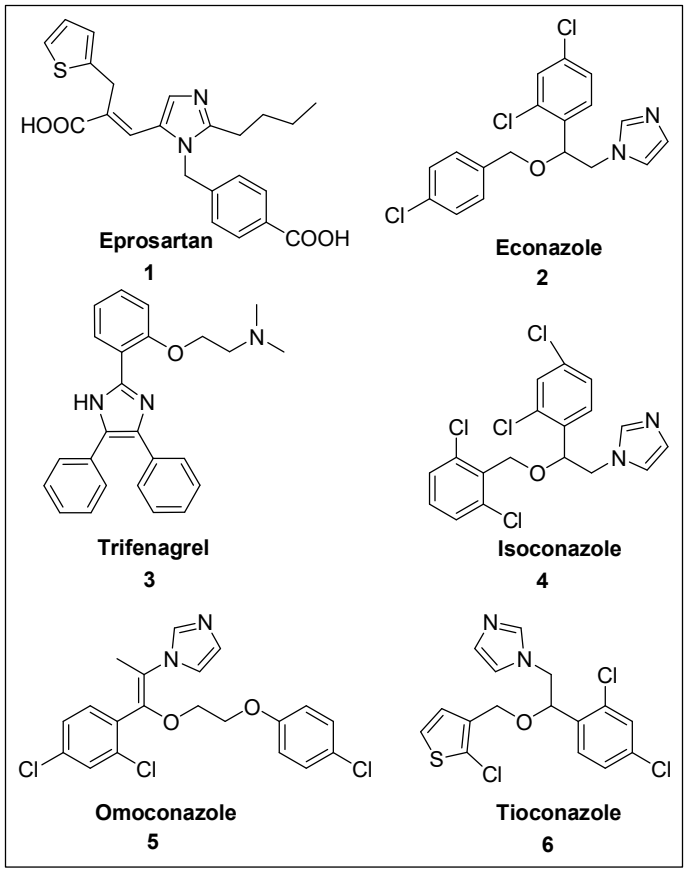


Figure V.3. Example of imidazole drugs.

Numerous imidazole derivatives have huge industrial and technological importance. Imidazole has been used widely as a corrosion inhibitor on certain transition metals, such as copper. The thermostable polybenzimidazole PBI contains imidazole fused to a benzene ring or linked to benzene, and serve as a fire retardant. Beside this imidazole is found in various compounds that are used for photography and electronics.

V.3. Application of imidazoles in organic synthesis

As imidazole moiety is associated with many bioactive useful organic compounds, it plays a useful starting material for the synthesis of wide range of nitrogen containing physiologically active natural and synthetic compounds (Figure V.4).[1] Owing to the presence of two nitrogen atom, the suitable derivatives of the imidazole act as important ligand to numerous transition metals which are useful for many organic transformations[2- 4] and sometimes used for the metal sensing fluorescence. It is very helpful organic counterpart for the synthesis of ionic liquids[5, 6].

Presently, imidazoles are also used as organo-catalyst for different organic transformation[7-10].

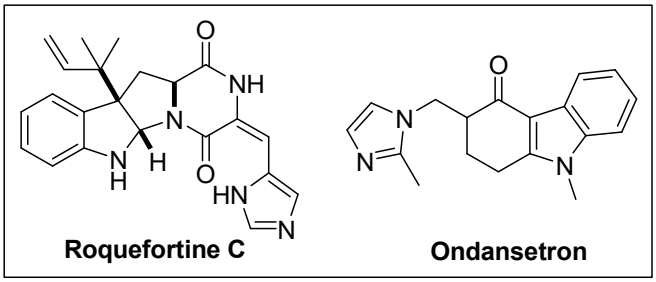
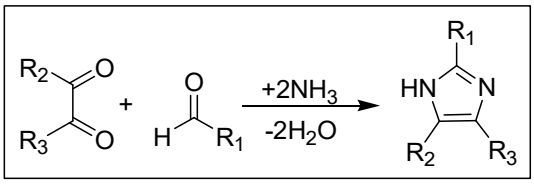


Figure V.4. Imidazole ring containing physiologically active compounds.

V.4. Synthetic approaches of imidazole derivatives

V.4. A. Classical methods for the preparation of imidazoles

In 1858, Heinrich Debus, first synthesized imidazole by the reaction of glyoxal and formaldehyde in ammonia to form imidazole but various imidazole derivatives had been discovered as early as the 1840s (Scheme V.1).[11]



Scheme V.1. Classical method for the synthesis of imidazoles.

V.4.B. Modern method for the synthesis of imidazoles

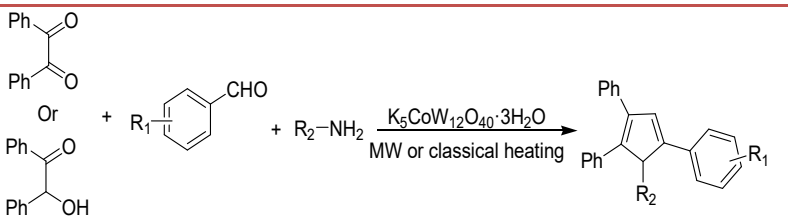
Literature review revealed that researchers have developed considerable synthetic protocols for the synthesis of tetrasubstituted imidazoles by four component condensation of benzil/ α-hydroxy ketone, aromatic aldehydes, primary amines in the presence of ammonium acetate such as synthesis of tetrasubstituted imidazoles catalyzed by zeolite HY and silica gel without any solvent under microwave irradiation,[12] potassium dodecatugstocobaltate trihydrate ($K_5CoW_{12}O_{40}\cdot 3H_2O$) catalyzed one-pot synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles under conventional heating and microwave irradiation (Scheme V.2),[13] Keggin-type heteropolyacids catalyzed four-component one-pot synthesis of tetrasubstituted imidazoles,[14] silica-supported boron trifluoride ($BF_3.SiO_2$) catalyzed one-pot synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles,[15] silica-bonded propylpiperazine-N-sulfamic acid catalyzed an efficient procedure for the preparation in chloroform,[16] 3-Methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulphate [$(CH_2)_4SO_3HMIM$] [HSO_4], a

Brønsted acidic ionic liquid catalyzed synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles using benzil, an aromatic aldehyde, and a primary amine in the presence of ammonium acetate under solvent-free condition,[17] trifluoroacetic acid (TFA) catalyzed synthesis of various tetrasubstituted imidazoles under microwave-irradiation and solvent-free conditions,[18] $HClO_4$–SiO_2 catalyzed one-pot, solvent-free synthesis of tetrasubstituted imidazoles.[19]

Scott E. Wolkenberg et al.[20] have reported the synthesis of alkyl-, aryl-, and heteroaryl-substituted imidazoles from 1, 2-diketones and aldehydes in the presence of NH_4OAc under microwave irradiation (Scheme V.3).

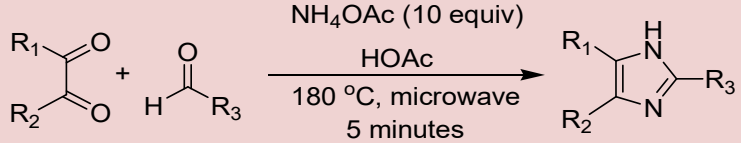
The reported synthetic routes to 2, 4, 5-trisubstituted imidazoles are multi component reaction between benzil or benzoin with aldehydes and ammonium acetate under diverse catalytic or reaction contions such as Cu(II) nitrate impregnated zeolite,[21] MoO_3/SiO_2 a recyclable solid acid,[22] silica-supported titanium tetrachloride under solvent-free conditions using conventional heating or microwave irradiation,[23] silica-sulfuric acid catalyzed synthesis in water,[24] L-proline (scheme V.4),[25] $InCl_3.3H_2O$,[26] $NiCl_2.6H_2O$, $ZrCl_4$,[27] supported into acidic alumina,[28] ceric (IV) ammonium nitrate in water medium under ultrasound at room temperature,[29] DABCO,[30] Fe_3O_4 nanoparticles,[31] bioglycerol-based recyclable carbon catalyst,[32] sulfated tin oxide.[33]

Scheme V.2



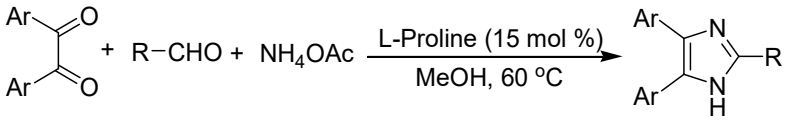
Potassium dodecatugstocobaltate trihydrate catalyzed synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles.

Scheme V.3



R= alkyl, aryl, heteroaryl

Synthesis of substituted imidazoles from 1, 2-diketones and aldehydes in the presence. of NH_4OAc under microwave irradiation.



Scheme.V.4

Synthesis of 2, 4, 5-trisubstituted imidazoles from benzil or benzoin with aldehydes and ammonium acetate in presence of L-Proline.

V.4.C. Miscellaneous approach for the synthesis of substituted imidazoles

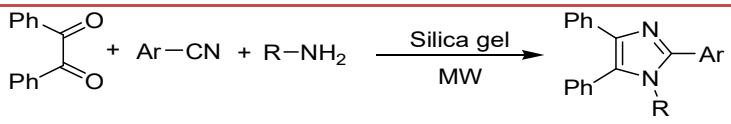
The literature survey reveals that the substituted derivatives of imidazole can also be prepared from the combination of 1, 2-diketo and non-carbonyl functions or carbonyl groups and other than 1, 2-diketo compounds. Saeed Balalaie et al.[34] have reported one-pot condensation of benzil, benzonitrile derivatives and primary amines on the surface of silica gel under solvent-free conditions and microwave irradiation[34] (SchemeV.5).

Andrew P. Combs et al.[35] reported microwave-assisted synthesis of 2, 4, 5-triaryl-imidazole directly from the keto-oxime. A catalyst free a convenient method for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles from readily available 2-azido acrylates and nitrones (Scheme V.6) was reported by Bao Hu et al.[36]. Transition metal catalyzed cycloaddition of suitable functional groups is also an alternative way for the construction of these derivatives. Yoshinori Yamamoto et al. [37] have reported the synthesis of imidazoles through the copper-catalyzed cross-cycloaddition between two different isocyanides. Bao-Hua Chen et al.[38] have reported copper catalyzed synthesis of substituted imidazoles via [3+2] cycloaddition (Scheme V.7).

Shun-Jun Ji et al.[39] have reported CuI/BF_3.Et_2O/O_2-mediated synthesis of substituted imidazoles from ketone and benzyl amines via C(sp^3)-H bond functionalization (Scheme V.8).

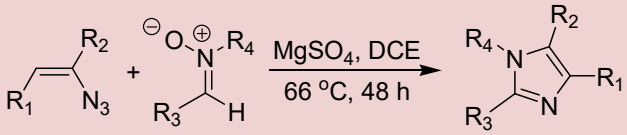
Bao-Hua Chen et al.[40] suggested copper and zinc co-catalyzed efficient synthetic approach to imidazoles from amidines and arylketone via oxidative coupling of (sp^3)C-H bond and N-H bond (Scheme.V.9**)**.

Scheme V.5



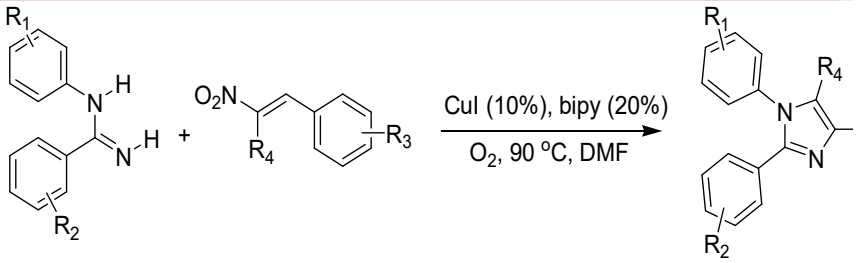
Synthesis of substituted derivatives of imidazole from multi component system in presence of silica gel under solvent-free conditions and microwave irradiation.

Scheme V.6



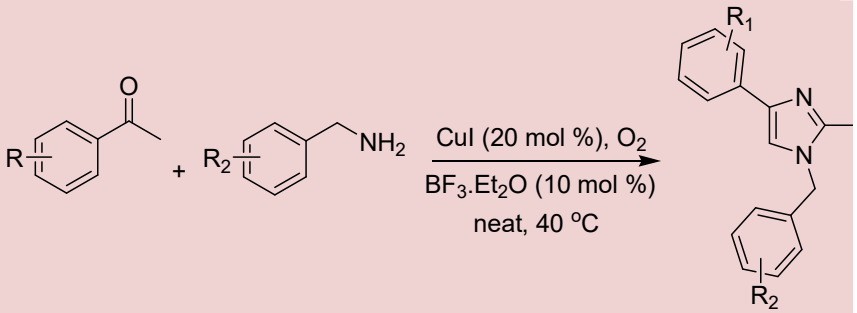
Synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles from 2-azido acrylates and nitrones.

Scheme V.7



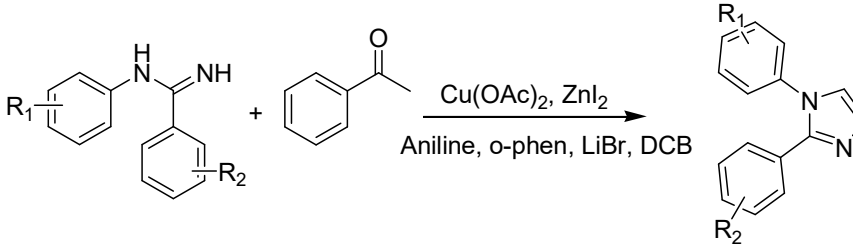
Copper catalyzed synthesis of substituted imidazoles

Scheme V.8



$CuI/BF_3.Et_2O/O_2$-mediated synthesis of substituted imidazoles from ketone and benzyl amines.

Scheme V.9



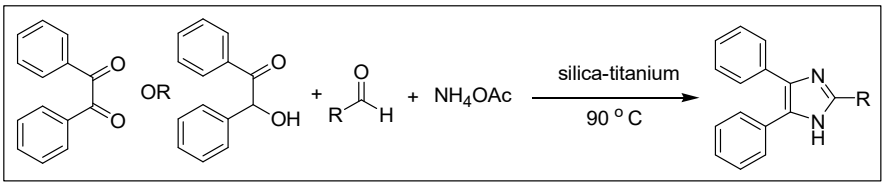
Copper and zinc co-catalyzed synthetic approach to imidazoles from amidines and arylketone

V.5. Conclusion

The numerous methodologies have been developed for the synthesis of substituted imidazoles using diverse catalytic system. Some catalytic processes are in solid phase and some are in solution phase. Researchers tried both the ways to get imidazole derivatives with good to better yield. After studding so many papers we come to the point that none of the process are best in term of reaction set-up, availability of reagent, reusability of catalyst, toxicity of reagent, nature benignity of solvent. On observing these limitations we felt necessity to investigate the synthesis same imidazole derivatives from same starting materials with different reagents by solid as well as in liquid phase and comparing the processes to know which one are the better path or which one we should follow?

V.6. Present Investigation-I

In the present work, we report one-pot synthesis of 2, 4, 5-trisubstituted imidazoles by multi-component reaction involving benzil/benzoin, aldehydes and NH_4OAc using a new and recyclable silica-titanium solid support under solvent free condition (Scheme V.10).



Scheme V.10. Synthesis of 2, 4, 5-trisubstituted imidazole under solvent free condition.

The demand of titanium based solid support or catalyst in the area of organic synthesis and transformation,[34] is continuously increasing. In order to find a possible applications and exploring the use of titanium based solid support into wide prospective, we report herein, one-pot synthesis of substituted imidazole on titanium incorporated silica solid support under solvent free condition.

V.6.A. Results and discussion

In our initial studies towards the development of new solid support for the synthesis these derivatives, $TiCl_3$ (0.25 mmol) and silica gel (silica gel HF 254) (1g) were added successively in methanol (10 ml). The mixture was allowed to stir on magnetic stirrer at 70-80 ^oC for 5 h and then allowed to cool at room temperature, evaporated the solvent on rotary evaporator. The dried titanium based solid support

was further activated by keeping in hot oven at 200 ^{o}C for 8 h and allowed to cool at room temperature and used for the desired transformation.

The model reaction comprising benzil (0.5 mmol), ortho hydroxy benzaldehyde (0.5 mmol) and ammonium acetate (2 mmol) on pure silica (1g) at room temperature gives no yield in 15 h, only starting material was recovered. Further gradual increase in reaction temperature up to 100 ^{o}C furnishes no significant yield (Table V.1).

Table V.1. Model reaction on pure silica[a].

Entry	Temp (^{o}C)	Time (h)	Yield (%)[b]
1	r.t	15	NR[c]
2	40	15	NR
3	60	10	NR
4	80	10	Trace
5	90	8	10-12
6	100	8	36

[a]Reaction of benzil (0.5 mmol), ortho hydroxy benzaldehyde (0.5 mmol) and ammonium acetate (2 mmol) in pure activated silica (1gm). [b]Isolated yield. [c]No reaction.

Only trace amount of the desired product was formed when the same reaction was carried out on titanium incorporated silica at room temperature (Table V.2). The gradual increase in temperature up to 90 ^{o}C found that the titanium-silica is catalyzing the reaction efficiently. The transformation is excellent at 90 ^{o}C (Table V.2.). It is clear from the (Table V.1) and (Table V.2) that the catalytic activity of the solid support is due to titanium incorporation. We attempted reusing the solid support to check its efficiency for the second reaction run and found no significant loss of its activity. For the reusability of solid support, the product was extracted from reaction mixture in ethyl acetate, washed the solid support by methanol (10x2 ml), several times by water and reactivated under vacuum at 200 ^{o}C for 8 h. The catalytic activity of used solid support was checked for five consecutive run and found almost equally active for all consecutive runs (Table V.3). The invariable catalytic activity after recycling indicates that no significant loss of titanium from solid support.

Table V.2. Optimization of temperature[a].

Entry	Temp (^{o}C)	Time (h)	Yield (%)[b]
1	r.t	4	Trace
2	40	4	18
3	60	4	38
4	70	4	57
5	80	4	76
6	90	4	92

[a]Reaction of benzil (0.5 mmol), orthohydroxy benzaldehyde (0.5mmol) and ammonium acetate (2 mmol) on titanium-silica solid support under solvent free condition. [b]Isolated yield.

Table V.3. Screening of catalyst recycling[a].

Entry	Time (h)	No. of runs	Yield (%)[b]
1	4	1	92
2	4	2	92
3	4	3	90
4	4	4	88
5	4	5	87

[a]Reaction of benzil (0.5 mmol), orthohydroxy benzaldehyde (0.5mmol) and ammonium acetate (2 mmol) on titanium-silica solid support at 90 ^{o}C under solvent free condition. [b]Isolated yield.

It is very clear from the SEM images, that the pure silica is converted into titanium-silica. The SEM images of pure silica (Figure V.5), freshly prepared titanium-silica (Figure V.6) and reused titanium-silica (Figure V.7- V.9) were compared for the conformation. The dissimilarities in surface morphology of pure silica and titanium-silica clearly indicate the incorporation of titanium in silica. The similar surface morphology of titanium-silica on recycling up to five consecutive runs also signify no loss of titanium from titanium-silica solid support.

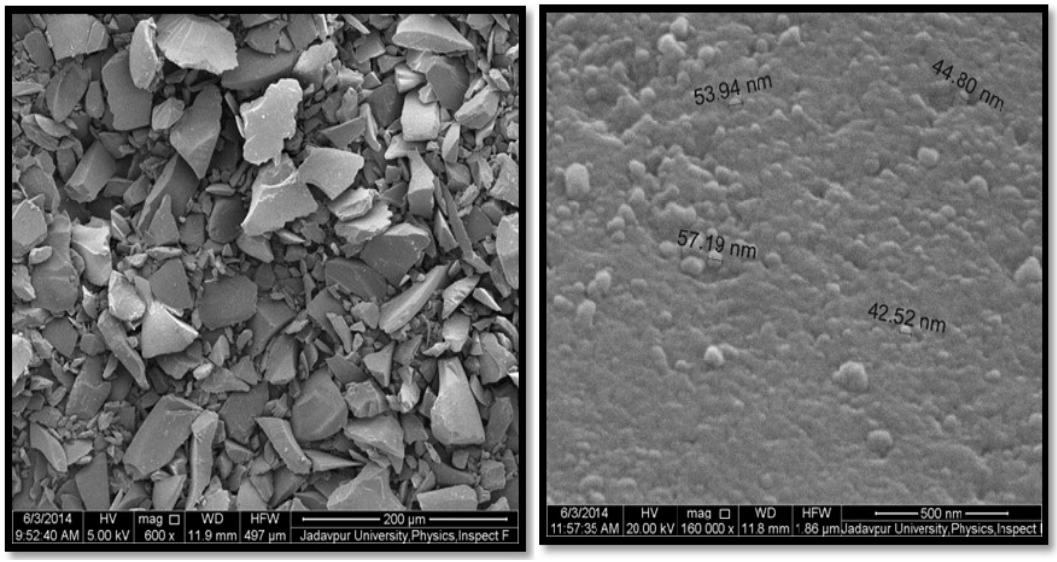


Figure V.5. SEM images of pure silica.

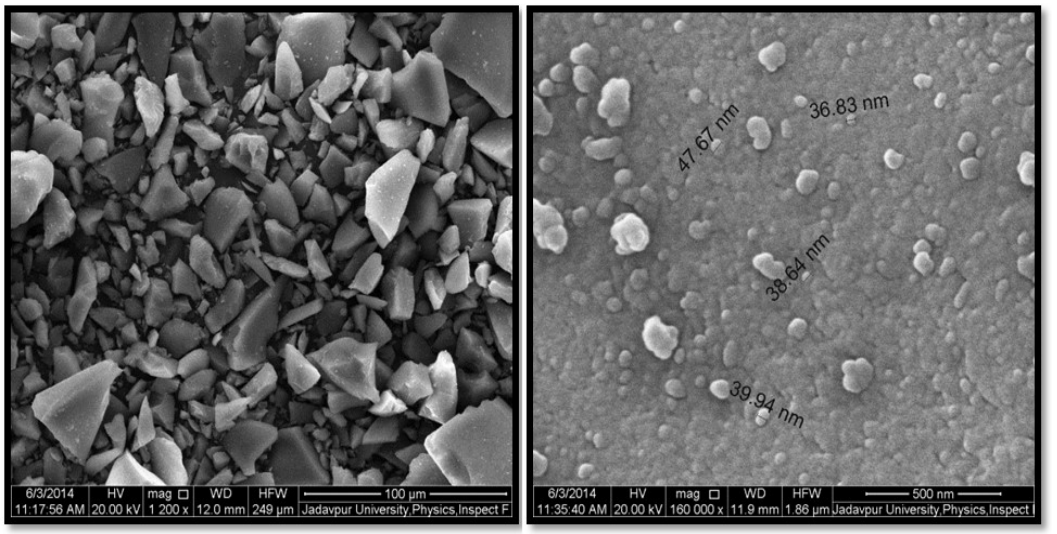


Figure V.6. SEM images of freshly prepared titanium-silica solid support.

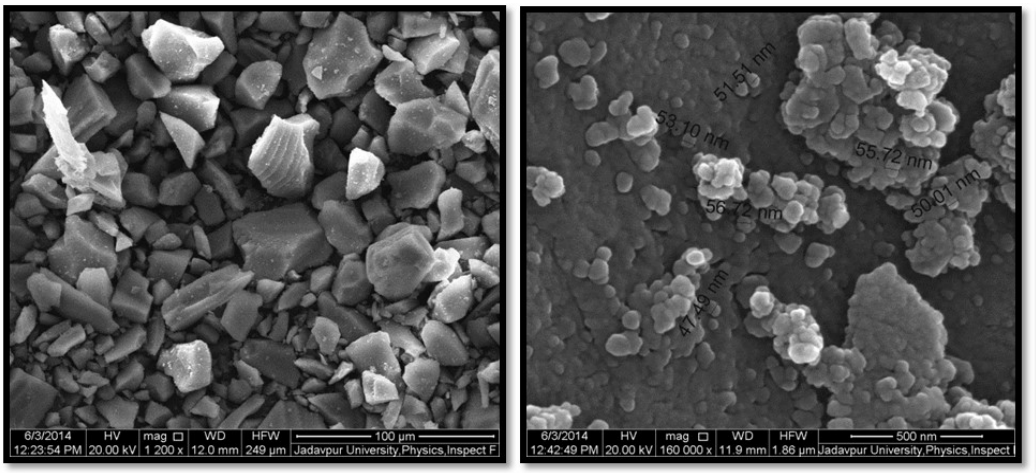


Figure V.7. SEM images of titanium-silica after first reaction run.

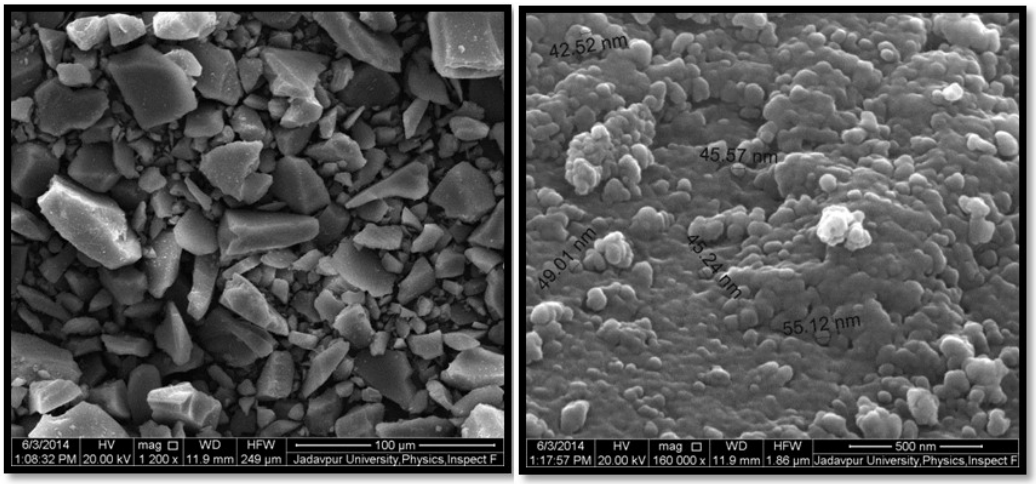


Figure V.8. SEM images of titanium-silica, after second reaction run.

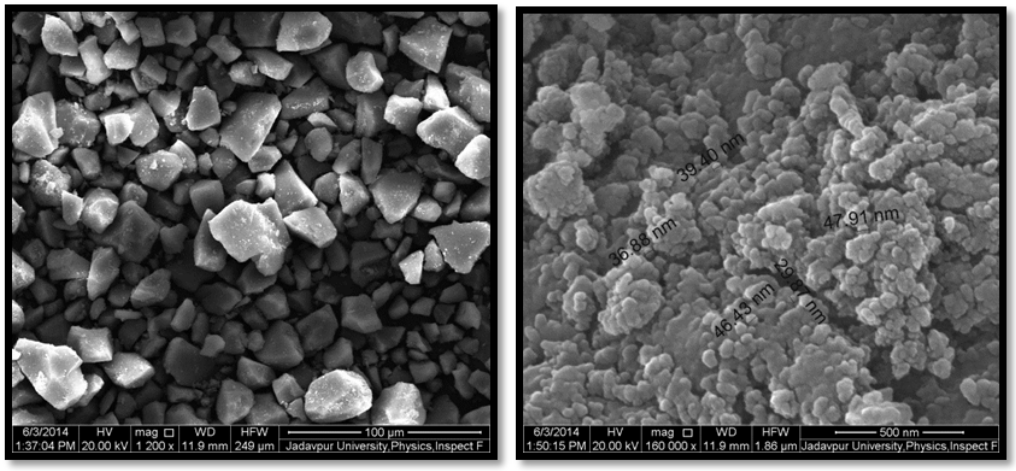
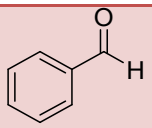
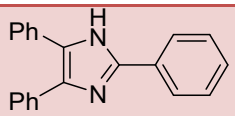
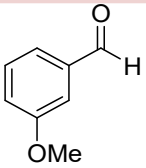
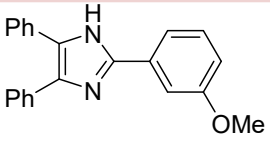
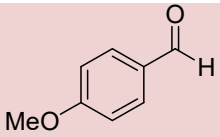
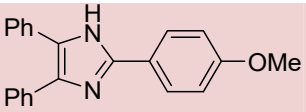
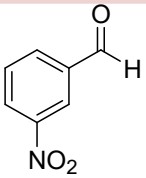
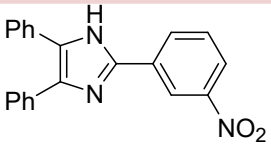
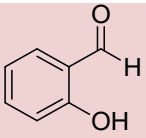
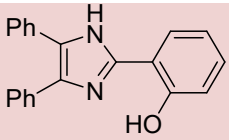
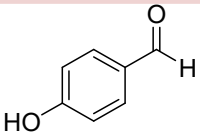
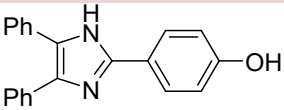
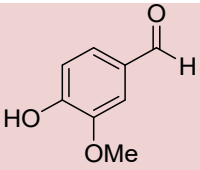
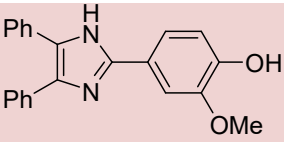
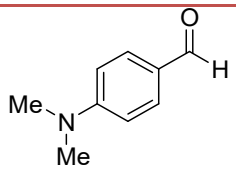
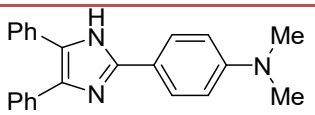
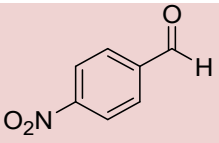
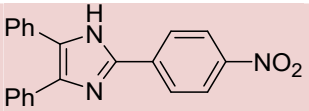
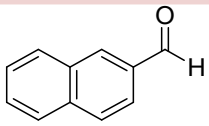
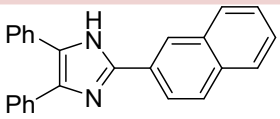
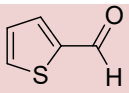
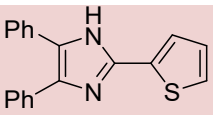


Figure V.9. SEM images of titanium-silica after fifth reaction run.

The general applicability of the solid support was examined by the synthesis of wide varieties of imidazole derivatives. The synthesis were carried out by taking benzil/benzoin (0.5 mmol), aldehyde (0.5 mmol) and NH_4OAc (2 mmol) on freshly prepared titanium-silica (1g) at 90 ^oC under solvent free condition. The results are summarized in (Table V.4).

Table V.4. Synthesis of 2, 4, 5-trisubstituted immidazole.

Entry	Aldehydes	Time	Trisubstituted	Yield(%)
1		4		94
2		5		91
3		5		90
4		4		93
5		4		92
6		5		87
7		6		84

8		6		89
9		4		90
10		4		89
11		4		74

[b]Isolated yield.

V.6.B. Reaction procedure and purification

V.6.B.i. Synthesis of 2, 4, 5- trisutituted imidazole

Benzil/benzoin (0.5 mmol), aldehyde (0.5 mmol) and ammonium acetate (2 mmol) were mixed intimately with titanium-silica (1.0 g). The mixture mixed intimately in motor and pestle. The resulting mixture was poured in round bottom flask (50 ml) and allowed to stir on magnetic stirrer at 90 ^{o}C for appropriate time (Table 5). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3x15 ml) washed several times with water. The combined organic mixture was dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography on silica gel 60-120 mesh using petroleum ether/ethyl acetate as eluent to afford pure compound.

V.6.B.ii. Preparation of titanium-silica solid support

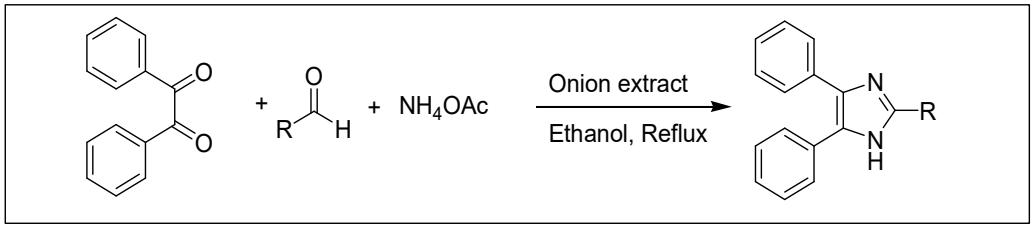
To a solution of $TiCl_3$ (0.25 mmol) in methanol (10 ml) at 70-80 ^{o}C, silica gel (1 g, 254 HF) was added. The mixture was allowed to stirrer at 70-80 ^{o}C for 5 h. The solvent was evaporated rotary evaporator and solid mass was kept in hot oven at 200 ^{o}C for 8 h and allowed to cool at room temperature and used for the desired transformation.

V.6.B.iii. Catalyst recycling

After the completion of the reaction, the catalyst was washed with methanol (2x25 ml) followed by washing with water (2x25 ml) and the solid mass was kept in hot oven at 200 ^{o}C for 8 h. The resulting recycled solid support was used for the reactions.

V.7. Present Investigation-II

We also investigate one-pot synthesis of 2, 4, 5-trisubstituted imidazoles by multi-component reaction involving benzil, aldehydes and NH_4OAc using small amount of onion extract with the help of verity of solvents (Scheme V.11).



Scheme V.11. Synthesis of 2, 4, 5-trisubstituted imidazole under solution phase.

V.7.A. Results and discussion

We had taken benzil (0.5 mmol), ortho hydroxy benzaldehyde (0.5 mmol) and ammonium acetate (2 mmol) for our model reaction.

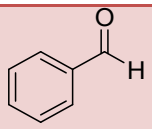
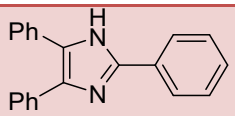
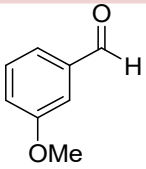
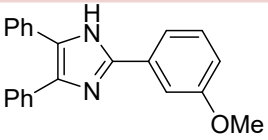
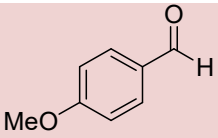
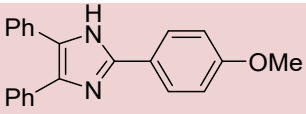
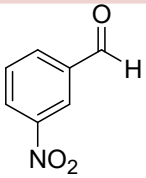
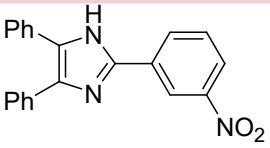
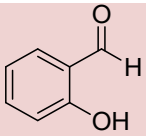
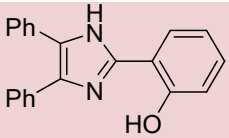
Table V.5. Optimisation table.

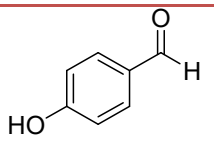
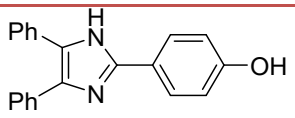
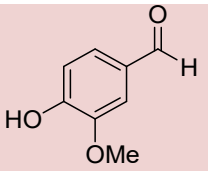
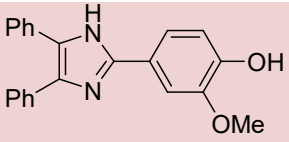
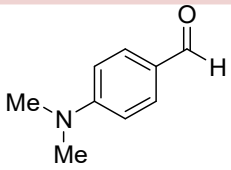
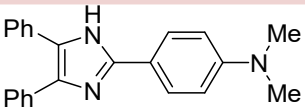
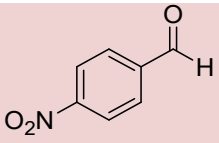
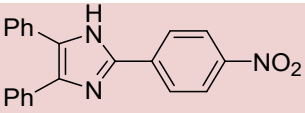
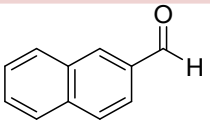
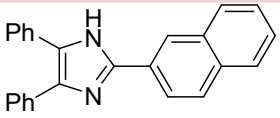
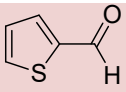
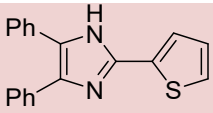
Entry	Solvent[b]	Temperature	Time	Onion extract	Yield[c] (%)
1	H_2O	RT	4h	1mL	Nil
2	EtOH	RT	4h	1mL	20
3	DMF	RT	4h	1mL	12
4.	DCM	RT	4h	1mL	9
5	EtOH	Reflux	4h	1mL	88
6	DMF	Reflux	4h	1mL	72
7	DCM	Reflux	4h	1mL	45
8	EtOH	Reflux	2h	1mL	87
9	EtOH	Reflux	1h	1mL	82
10	EtOH	Reflux	2h	2mL	86

[a]Reaction of benzil (0.5 mmol), ortho hydroxy benzaldehyde (0.5 mmol) and ammonium acetate (2 mmol) in pure activated silica (1gm).[b]Solvent (5mL). [c]Isolated yield.

At first we started our investigation by optimising solvent. As reported in Table V.5, we selected four different types of solvent according to their characteristics to interaction with solutes. We started with polar protic medium, such as ethanol and water; polar aprotic, such as N, N-dimethylformamide (DMF); nonpolar aprotic, such as dichloromethane (DCM). Table 1, entry 1 to 4 suggest us to avoid H_2O for this reaction. Thereafter we refluxed the reaction mixture with the rest three solvents. Entry 5, 6, 7 implies us; EtOH is superior to the other for this process. On decreasing reaction time 4 h to 2 h, yields almost same but if we further decrease the time 2h to 1h, yield of the product decreases subsequently. From entry 8, 9, 10 we can say that 1mL onion extract is enough for this purpose. Therefore Table V.5, entry 8 is optimised condition for this reaction. With the optimise condition we synthesised some tri-substituted imidazole derivatives shown in Table V.6.

Table V.6. Synthesis of 2, 4, 5-trisubstituted immidazole.

Entry	Aldehydes	Time	Trisubstituted	Yield(%)
1		4		86
2		5		83
3		5		81
4		4		78
5		4		87

6		5		85
7		6		76
8		6		80
9		4		81
10		4		73
11		4		75

[b]Isolated yield.

V.7.B. Experimental section

V.7.B.i. Preparation of Onion extract

Onion was brought from local market and washed with water. Then squeezed the dry onion and filter it. The filtrate is onion extract and it is ready to use.

V.7.B.ii. General procedure for synthesis of trisubstituted imidazole

A mixture of benzil (1 mmol), amine (1 mmol), aldehyde (1 mmol), ammonium acetate (5 mmol), and onion extract (1 mL) in ethanol (5 mL) was stirred under refluxing conditions for an appropriate time. After completion of the reaction (monitored by TLC), the mixture was poured into ice water, and the obtained solid

was separated by filtration. Pure products were obtained by recrystallization from ethanol.

V.8. Solid phase *vs.* solution phase synthesis

Thus we have synthesized tri-substituted imidazole with same reactants in both solid as well as liquid phase. Now the time comes for investigate to compare which path is better. In the following Table V.7 we summarized different factors which we noticed during two reactions parallelly for solid and liquid phase.

Table V.7. Comparing different conditions of solid phase and solution phase synthesis of tri- substituted imidazole.

Sl. No.	Conditions	Solid phase	Liquid phase
1	Solvent	-	EtOH
2	Temperature	90^{o}C	Reflux
3	Time	4h	2h
4	Preparation of catalyst	Required	Not required
5	Availability of reagents	Available	Available
6	Catalytic activity	Shown	-
7	Yield of product (%)	74-94	73-87

V.9. Conclusion

Thus we have developed two different paths to synthesize 2, 4, 5-trisustituted imidazole ring. In the first path solid surface help us to achieve desire product smoothly. On the other hand our second path made the process easy by solution phase. Above table may help us to choose the path to prepare tri-substituted imidazole. It is very difficult to choose the best path. Both processes have some benefits as well as drawbacks. In future if we want solvent free, catalytic activity and high yield of the product then we have to follow solid phase path but if we want less time consuming, less troublesome procedure then we will pursue our interest to liquid phase path.

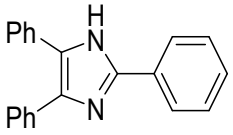
V.10. Spectroscopic measurements

IR spectra were recorded on KBr disc in the range 4000-400 on Shimadzu FT-IR 8300 Spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on 300 MHz Bruker Avance FT-NMR Spectrometer using TMS as internal standard. SEM images were taken in inspect F50 SEM, SE detector R580, emission current during analysis was

163.2 micro ampere. EDX were recorded in nano bruker, Xflash detector 410-M, bruker. Mass spectra were recorded on a JEOL-AccuTOF JMS-T100LC Mass Spectrometer.

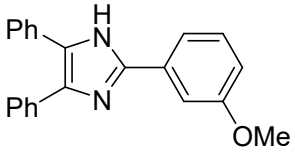
V.11. Spectroscopic data

2, 4, 5-Triphenyl-1*H*-imidazole



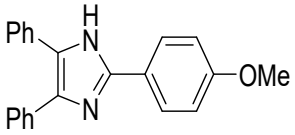
Mp 272-274 ^{o}C; IR (cm^{-1}, KBr): 689, 733, 1128, 1461, 1489, 3043. ^{1}H NMR (300 MHz, DMSO-d_6): δ(ppm) 7.71-7.96 (m, 13H) 8.52 (d, 2H, J=7.2Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ(ppm) 130.4, 132.4, 132.9, 133.4, 133.6, 133.8, 135.5, 150.7. m/z = 297 [M+1].

2-(3-Methoxyphenyl)-4, 5-diphenyl-1*H*-imidazole



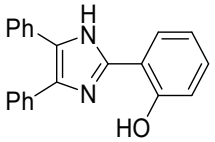
Mp 260-263 ^{o}C; IR (cm^{-1}, KBr): 1516, 1589, 3432. ^{1}H NMR (300 MHz, DMSO-d_6): δ(ppm) 3.84 (s, 3H), 6.83-7.76 (m, 14H), 12.61 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ(ppm) 55.6, 110.4, 113.9, 117.8, 127.6, 128.8, 129.1, 130.1, 131.9, 135.3, 137.4, 145.6, 159.4.

2-(4-Methoxyphenyl)-4, 5-diphenyl-1*H*-imidazole



Mp 227-229 ^{o}C; IR (cm^{-1}, KBr): 696, 763, 831, 1174, 1251, 1541, 1656, 3051. ^{1}H NMR (300 MHz, DMSO-d_6): δ(ppm) 3.82 (s, 3H), 7.05 (d, 2H, J=8.1Hz), 7.31-7.53 (m, 10H), 8.02 (d, 2H, J=8.1Hz), 12.51 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ(ppm) 55.6, 114.5, 123.4, 127.1, 127.5, 128.1, 128.8, 146, 159.8.

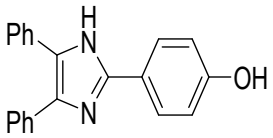
2-(2-Hydroxyphenyl)-4, 5-diphenyl-1*H*-imidazole



Mp 208-210 ^{o}C; IR (cm^{-1}, nujol): 723, 1261, 2923, 3186. ^{1}H NMR (300 MHz, DMSO-d_6): δ(ppm) 6.92-7 (m, 2H), 7.25-7.53 (m, 11H), 8.03-8.05 (d, 1H, J=7.5Hz),

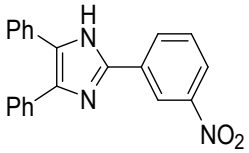
12.96 (s, 1H),13.04 (s, 1H) . ^{13}C NMR (75 MHz, DMSO-d_6): δ(ppm) 113.3, 117.3, 119.3, 125.4, 127.2, 127.5, 127.7, 128.8, 129, 129.2, 130.5, 130.7, 134, 134.5, 146.3, 157.1. m/z = 313 [M+1].

2-(4-Hydroxyphenyl)-4, 5-diphenyl-1*H*-imidazole



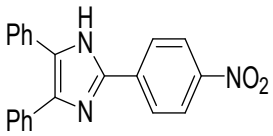
Mp 231-233 ^{o}C; IR (cm^{-1}, KBr): 1542, 1637, 3297, 3434. ^{1}H NMR (300 MHz, DMSO-d_6): δ(ppm) 5.93 (d, 1H, J=8.7Hz), 6.31-6.42 (m, 6H), 6.52-6.59 (m, 5H), 6.97 (d, 2H, J=8.3Hz), 8.81 (s, 1H) . ^{13}C NMR (75 MHz, DMSO-d_6): δ(ppm) 115.2, 120.9, 127.1, 127.7, 128.4, 145.8, 157.4.

2-(3-Nitrophenyl)-4, 5-diphenyl-1*H*-imidazole



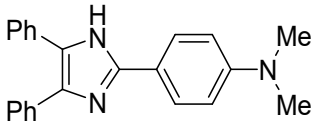
Mp 302-304 ^{o}C; IR (cm^{-1}, KBr): 1519, 1588, 1646, 3452. ^{1}H NMR (300 MHz, DMSO-d_6): δ(ppm) 7.65-7.29 (m, 12H), 7.94 (d, 1H, J=7.4Hz), 8.13 (d, 1H, J=7.5Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ(ppm) 126.7, 127.4, 127.9, 128.8, 129.9, 130.1.

2-(4-Nitrophenyl)-4, 5-diphenyl-1*H*-imidazole



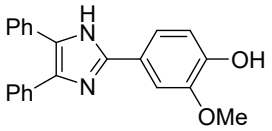
Mp 195-197 ^{o}C; IR (cm^{-1}, KBr): 1522, 1583, 1643, 3451. ^{1}H NMR (300 MHz, DMSO-d_6): δ(ppm) 7.25-8.43 (m, 14H), 12.59 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ(ppm) 123.2, 126.7, 126.9, 131.8, 147.3, 159.8.

2-(4-Dimethylaminophenyl)-4, 5-diphenyl-1*H*-imidazole



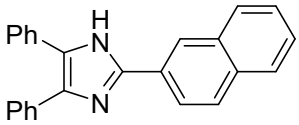
M.p.: 255-257 ^{o}C; IR (cm^{-1}, KBr): 723, 1305, 1610, 2854, 3170. ^{1}H NMR (300 MHz, DMSO-d_6): δ(ppm) 2.96 (s, 6H), 6.794 (d, 2H, J=8.7Hz), 7.27-7.38 (m, 6H), 7.48-7.51 (m, 4H),7.91 (d, 2H, J=8.4Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ(ppm) 40.3, 112.3, 118.1, 126.8, 127.4, 128.1, 128.8, 133.4, 146.8, 150.8. m/z = 340 [M+1].

2-(3-Methoxy-4-hydroxyphenyl)-4, 5-diphenyl-1*H*-imidazole



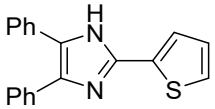
^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) 3.88 (s, 3H), 6.83-6.85 (m, 2H), 7.25-7.33 (m, 8H), 7.52-7.55 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) 56, 112, 112.8, 116, 118.8, 127.8, 128.6, 131.8, 145.4, 146.8, 148.6.

2-(2-Napthyl)-4, 5-diphenyl-1*H*-imidazole



Mp 269-272 ^{o}C; IR (cm^{-1}, KBr): 696, 750, 813, 912, 1110, 1411, 1450, 1500, 3047. ^{1}H NMR (300 MHz, DMSO-d_6): δ(ppm) 7.24-7.59 (m, 13H), 7.93-8.02 (m, 3H), 8.26 (dd, 1H, J=1.5, 8.4Hz), 8.61 (s, 1H), 12.89 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ(ppm) 123.9, 124.1, 126.8, 127.1, 127.2, 127.6, 128.2, 128.3, 128.5, 128.7, 128.8, 129, 129.1, 131.4, 133.1, 133.4, 135.5, 137.8, 145.1.

2-(2-Thienyl)-4, 5-diphenyl-1*H*-imidazole



Mp 262-264 ^{o}C; IR (cm^{-1}, KBr): 696, 765, 1493, 1593, 3047. ^{1}H NMR (300 MHz, DMSO-d_6): δ(ppm) 7.14-7.17 (m, 1H), 7.32-7.37 (m, 6H), 7.49-7.56 (m, 5H), 7.71 (d, 1H, J=3.6Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ(ppm) 124.8, 126.7, 128.2, 128.4, 128.9, 134.4, 142.

V.12. Supporting spectra

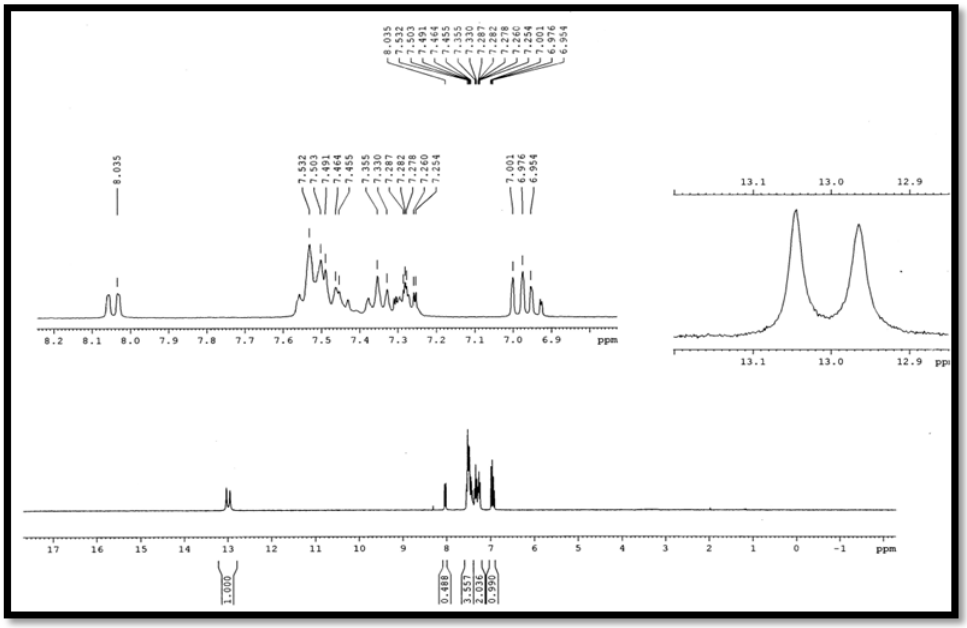


Figure V.10. ^{1}H NMR spectrum of 2-(2-Hydroxy-phenyl)-4, 5-diphenyl-1*H*-imidazole.

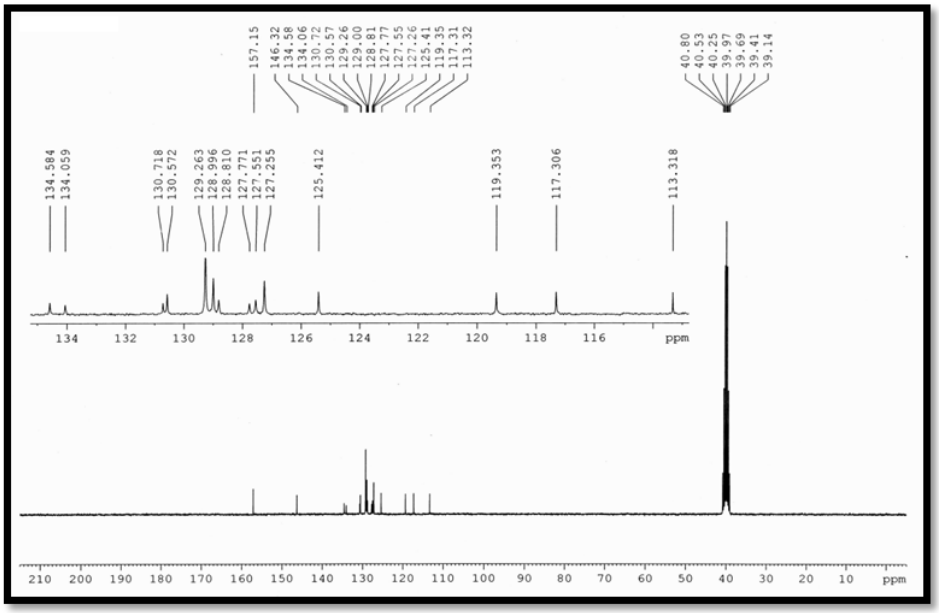


Figure V.11. ^{13}C NMR spectrum of 2-(2-Hydroxy-phenyl)-4,5-diphenyl-1*H*-imidazole.

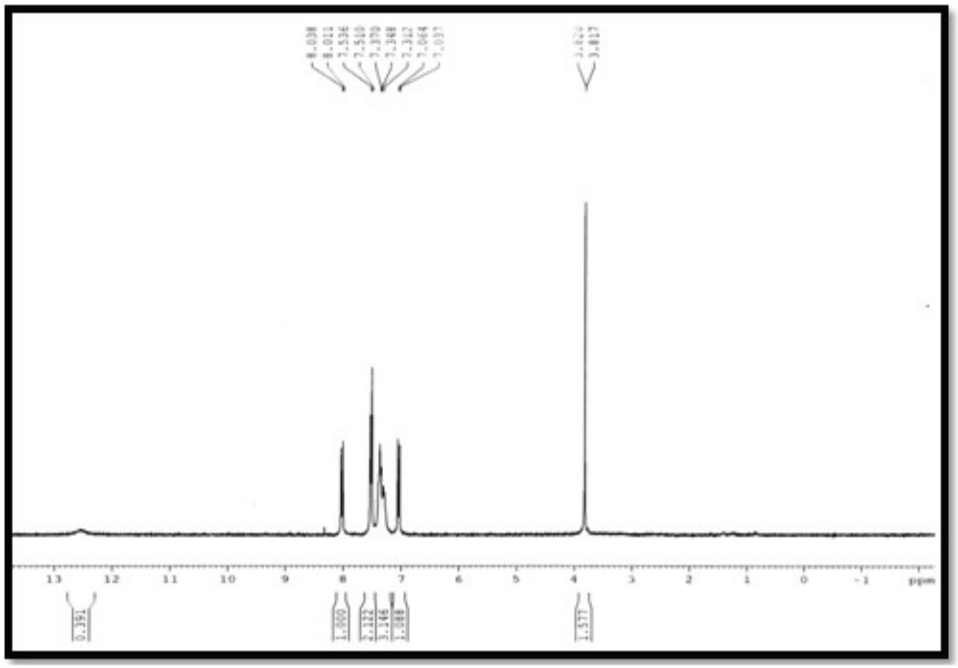


Figure V.12. ^{1}H NMR spectrum of 2-(4-Methoxy-phenyl)-4,5-diphenyl-1*H*-imidazole.

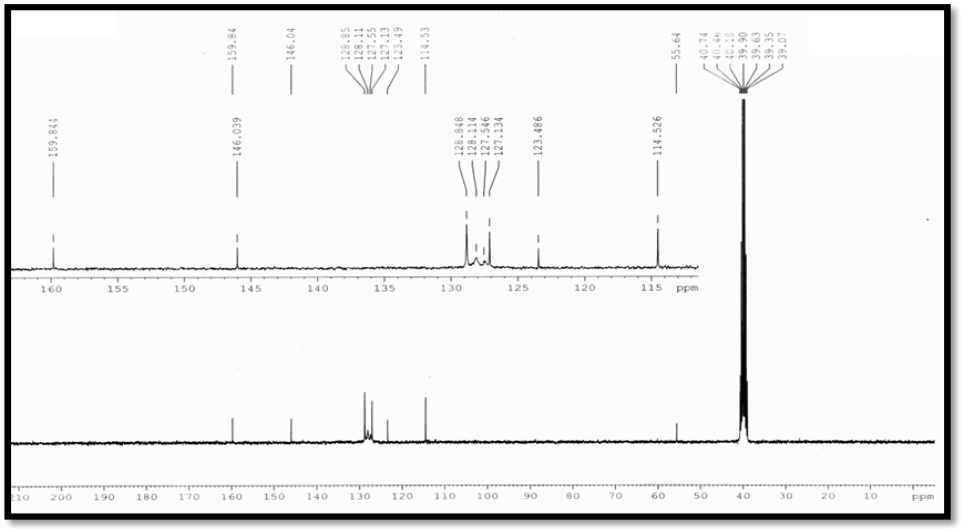


Figure V.13. ^{13}C NMR spectrum of 2-(4-Methoxy-phenyl)-4,5-diphenyl-1*H*-imidazole.

V.13. References

References are given in BIBLIOGRAPHY under Chapter V.

Concluding remarks

So the research work focused on 'STUDIES ON NOVEL METHODOLOGIES FOR THE SYNTHESIS OF PRECURSOR OF BIOACTIVE COMPOUNDS'. Chapter I constitute the introduction of the thesis it deals with a brief idea about bioactive compound and some synthetic roots of its precursor. Chapter II to Chapter V reveals new protocols to synthesis different precursor of bioactive compound with their physicochemical characterization.

In Chapter II, we performed reduction of aromatic nitro to corresponding amine. We have introduced Zn metal and $CuSO_4$ salt to reduce aryl nitro to aryl amine in presence of water as a hydrogen source and the reaction occurs smoothly at room temperature. The greatest advantage of our method compared with other methods is easy handling, cost effective, environmentally benign. In Chapter III, We have developed a novel and efficient protocol through one pot reductive cyclocondensation of 2-nitroaniline with aromatic aldehydes to benzimidazole with $Zn/NaHSO_3$ in water. The fascinating part of our method in comparison to the conventional methods is its simplicity, cost effectiveness, environmentally benign approach and a less time consuming process. In Chapter IV, we have achieved a simple and convenient procedure to synthesize Pyrazine derivatives in the presence of onion extract through condensation and aromatization from the easily available 1, 2-diketones and 1, 2-diamines. The current protocol offers many advantages including a simple and effective catalytic system, simple workup, benign reagents, cheap but good to excellent yields and the reusability of the onion extract as a catalytic system. In Chapter V, we synthesized same imidazole derivatives from same starting materials with different reagents by solid as well as in liquid phase. In solid phase we used a new and recyclable silica-titanium solid supported catalyst under solvent free condition. On the other hand in solution phase we used small amount of onion extract with the help of ethanol as a solvent.

Henceforth, we were succeeded to synthesize different precursor of bioactive compound in a novel way. But the major concerns regarding their synthesis are some process are not metal free, complicated purification process, separation process, all the process are not catalytic, gram scale experiments were not done. So, some works regarding these issues are underway in our laboratory. Hope we will shorten the limitations of our process to make it best.

APPENDIX I

List of Publications

- "A novel approach towards chemoselactive reduction of Nitro to Amine." **Hridoydip Ranjan Dasgupta**, Suvodip Mukherjee, Pranab Ghosh* *Tetrahedron Letter.* 2019, 60, 151028.

- "One pot reductive synthesis of Benzimidazole derivatives from 2-nitro aniline and aromatic aldehydes by using $Zn/NaHSO_3$ in water medium." **Hridoydip Ranjan Dasgupta**, Suvodip Mukherjee, Pranab Ghosh* *Prog. Chem. Biochem. Res.* 2021, 4(1), 57-67.

- $TiCl_3$-silica: A recyclable solid support for efficient synthesis of substituted imidazoles. ***Asian J. Nanosci. Mater.*** *2021,* 4**,** 31-45. Raju Subba, **Hridoydip Ranjan Dasgupta**, Bittu Saha, Abiral Tamang, Gyan Chandra Pariyar, Pranab Ghosh* *Asian J. Nanosci. Mater. 2021,* 4**,** 31-45.

- "Onion extract mediated novel synthesis of Pyrazine." Under revision in **Hridoydip Ranjan Dasgupta**, Suvodip Mukherjee, Pranab Ghosh* *Asian J. Green Chem*. Manuscript ID: AJGC-2012-1289.

- "Solid phase vs liquid phase synthesis of trisubstituted imidazoles." **Hridoydip Ranjan Dasgupta**, Raju Subba, Pranab Ghosh* (Manuscript under preparation).

APPENDIX II

Seminar, Symposium & Conventions Attended

- Frontiers in Chemistry 2015, organized by Department of Chemistry, University of North Bengal, Darjeeling, India on February 17th-18th 2015. (Presented a Poster)

- One day seminar on "Recent Trends on Chemistry and Biology Interface", organized by The Chemical Research Society of India NBU Local Chapter in collaboration with Department of Chemistry, University of North Bengal, August 28th , 2015.

- Science Academies' Lecture Workshop on "Recent Developments on the Theoretical and experimental aspects of advanced materials", organized by Department of Chemistry, University of North Bengal, September 18th -19th, 2015.

- 19th CRSI National Symposium in Chemistry, organized by Department of Chemistry, University of North Bengal, Darjeeling, India held from July 14th-16th, 2016.

- National Seminar on "Frontiers in Chemistry-2019", organized by Department of Chemistry, University of North Bengal, Darjeeling, India & CRSI North Bengal Local Chapter on May 22nd, 2019. (Presented a Poster).

- "One Day International Seminar (Virtual Mode) on Recent Trends in Chemistry-2020"

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A novel approach towards chemoselective reduction of nitro to amine

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ABSTRACT

Chemo selective reduction of a wide range of aromatic nitro compound has been performed by using inexpensive Zn powder and $CuSO_4$ system in water medium at room temperature. This system has high tolerance to other highly reducible groups present in nitro substance along with high conversation and selectivity. This chemo-selective reduction also provides a facile root for the synthesis of other industrially important fine chemicals or biologically important compounds where other highly reducible groups are present in close proximity to the targeted nitro groups.

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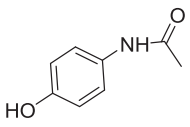
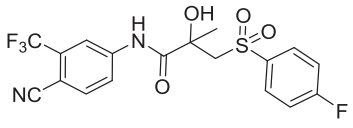
Introduction

Substituted aromatic amines are very important feedstock for synthesis of many significant fine chemicals like agrochemicals, dyes, biological active compounds, polymers and various other industrially important compounds [1]. Aromatic amines also form substructures of many pharmaceutical compounds. An acetyl derivative of *p*-aminophenol known as Paracetamol [2] 1a, a widely used analgesic and antipyretic. Bicalutamide [3] 1b has a *p*-cyano-*m*-trifluoroaniline component in its structure, is a non-steroidal antiandrogen administered orally for the treatment of prostate cancer and hirsutism.



Paracetamol 1a
(Analgesic,Antipyratic)



Bicalutamide 1b
Anticancer (Prostate)

Vastly employed method for the preparation of substituted aromatic amines is reduction of corresponding nitro substrates. But selective reduction of a functional group in presence of other functional group which is also reducible is often a very difficult task [4]. In general employing transition metal catalyst results in reduction of olefinic and halogeno functions than that of N–O bond. Moreover, traditional non-catalytic processes often produce large amount of waste and hence environmentally non-sustainable [5]. Catalytic hydrogenation is often a convenient and clean method but lacks selectivity [6]. Another alternative to catalytic hydrogenation, catalytic transfer of hydrogen is also introduced for reduction purpose in which hydrocarbons, alcohols, organic acids and their salts, hydrazine etc. were used as source of hydrogen with variety of metal based catalysts [7–11]. However, it's worth a note the main disadvantages to these procedures include the catalysts being incompatible to the acid-sensitive functional groups and requires higher reaction temperature, longer reaction time and suffers from low or mixed yield of products [12]. Recent successful attempt of reducing nitroarenes selectively by employing CO_2 gas at very high pressure resulting in-situ generation of carbonic acid, which further gets associated with reducing metals and performs the selective reduction process [13]. Nonetheless, the requirement of high CO_2 pressure in order to activate the reducing metal and generate carbonic acid, and high reaction temperature are the main drawbacks of the scheme. Another recent report worth mentioning is reduction of nitro compounds to corresponding amines selectively in presence of photo catalyst and Pd/CeO_2, CdS [14]. Despite the scheme shows high selectivity and considerable activity in presence of noble metals, costly noble metals are the major hurdles in this article. Recent communications on catalytic systems based on Co-Co_2B, Fe_2O_3, Co_2O_3 etc. show high activity and directs toward the development of more economical efforts [15–17]. But most of the contrivance uses harsh condition which is undesirable. Pure water has been employed as solvent by Poliakoff and Boix [18] using metallic reducing agents for selec-

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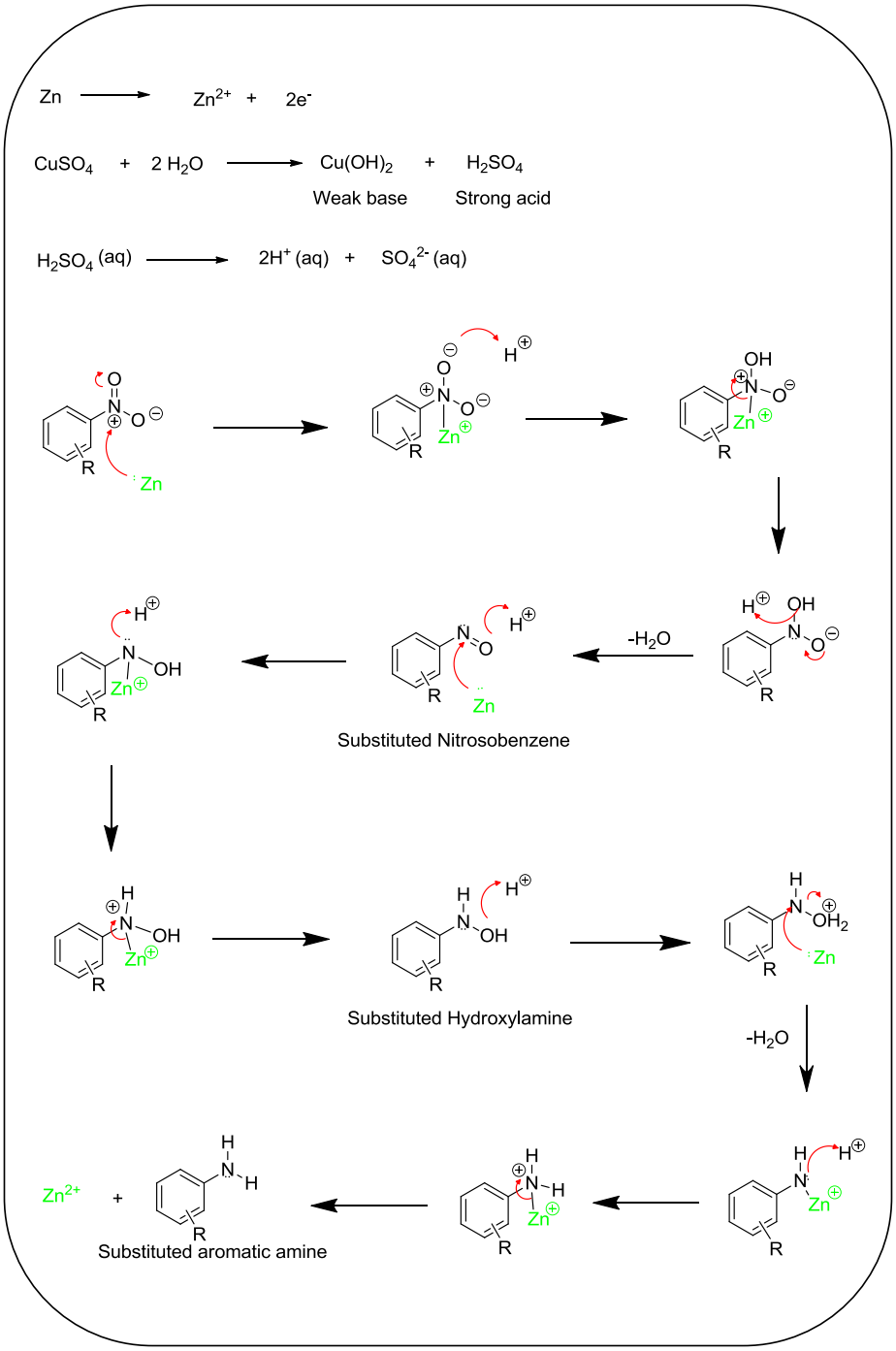
tive reduction of nitroarenes at 250 °C. With iron powder the yield reported is only 10% of substituted aniline under mentioned reaction condition. Modification has been done by Wang et al. [19] and iron powder has been replaced by nano-sized activated iron for direct and selective reduction of nitroarenes in water [20]. Though good yield has been achieved, the temperature requirement was still 210 °C. In addition to that preparation of nano-sized particle and maintaining the size requires extra effort and expense.

There exist very few reports on eco-friendly, inexpensive metal catalysts or reducing agents that can promote reduction of nitro groups selectively at room temperature. And needless to mention water based conversions are of critical importance in organic chemistry. Therefore, development of a cost effective, greener, easily achievable, less time consuming reaction scheme with non-hazardous reducing agents is highly desirable. Regarding this context our interest was solely on developing a new scheme using low cost, greener, metal-metal salt based reducing agent and to carry out the reaction on most easily available solvents like water and ethanol.

Herein, we report selective reduction of nitroarenes at room temperature in presence of non-hazardous, inexpensive and easily available metal salt like $CuSO_4$ and Zn metal in water solvent system within 30 min–60 min. (Scheme 1).



Scheme 1. Reduction of aryl nitro to corresponding amine.

Results and discussions

Aromatic nitro and substituted nitro compounds were reduced in good yield to the corresponding amino compounds under mild conditions in the presence of low cost and easily available metal and metal salt Zn and $CuSO_4$ respectively in water, with single product. The compound obtained were monitored by TLC and separated by column chromatography. The general scheme and reaction are shown in Scheme 1.

At first, we investigated the influences of solvents, additives, metals, time and temperature on the reduction of aromatic nitro to its corresponding amine (Scheme 1, Table 1). The reduction of selected model nitro substrate, *o*-nitrobenzaldehyde revealed that high conversion and selectivity could be achieved within 60 min in the presence of water. Entry 1 demonstrates that the reaction could not proceed in absence of solvent. From entry 1–7 (Table 1) we conclude that water is the superior solvent for the process, as in this process hydrogen ion is efficiently supplied by water. Further water is the most easily available and green solvent which enhances the cost effectiveness of our scheme.

We found that both metal and additive were necessary for this reduction process (Table 1, entries 3, 4, 5). Compared with that $CuSO_4$, other additives were inferior in terms of yield of product and reaction time. Entry 5, 8, 9 (Table 1) implies that here Zn metal play a vital role for nitro reduction. Electro chemical series also support our result. The reduction potential of applied metal and additive is as follows, $E^0_{Zn2+/Zn} = -0.76$, $E^0_{Fe2+/Fe} = -0.44$ and $E^0_{Cu2+/Cu} = +0.34$, which clearly indicates the reduction potential difference between Zn and Cu is higher, which facilitate the transfer of electrons in the process than the other couples. This concept is in accordance with our observed results (Table 1). But entry 11 also suggest that acidic nature of metal salts is indebted for reduction and reduction potential difference between metals amplify the potency of the process. Entries 9–14 implies that if we lower the time from 180 min to 60 min the yield of the product more or less same, but when we were tried to decrease the time from 60 min to 30 min then product's yield decreases remarkably. Now we were tried to optimize temperature. With the help of entries 14, 19, 20 we observed that if we increase the temperature yield of the product decreases. So with respect to time, temperature, metal/metal salt entry 14 is the optimized condition. Further we optimized the amount of Zn and $CuSO_4$ required (Table 2). We started our optimization with 1 mmol each. The yield was considerable but low. As the amount of reagents has been increased and we reached our maximum yield at 3 mmol Zn and 3 mmol $CuSO_4$. No further increase in yield has been observed with increasing reagents. Considering the above mentioned points, under atmospheric pressure, 60 min of reaction time and room temperature is finalized as the optimum condition for this reaction (Table 1).

Table 2
[a]Optimization of amount of Zn and $CuSO_4$.

Entry	Zn (mmol)	$CuSO_4$ (mmol)	Time (min)	[b]Yield (%)
1	1	1	60	54
2	2	2	60	67
3	3	3	60	94
4	4	4	60	95

[a] Reaction of *o*-nitrobenzaldehyde (1 mmol) in water on magnetic stirrer.
[b] Isolated yield.

This procedure is followed for all of the reactions listed in Table 3.

On the basis of the Table 1, reduction of other nitroarenes were carried out by using $Zn/CuSO_4$ in water without any organic solvent at room temperature under atmospheric pressure (Table 2). Aldehyde, halogens, nitrile, acid functionality present in aromatic ring remained unaffected during reduction of the corresponding nitro benzene by this process (entries). These results demonstrate that we can employ this technique to nitroarenes containing reduction-sensitive substituent. The reaction took place smoothly and chemoselectively to produce corresponding anilines in moderate to high yields (entries).

Plausible mechanism

A plausible mechanism has been shown in Fig 1. For the nitro reduction we need source of electron and hydrogen ion. From the mechanism we can see that in our reaction electrons are supplied by Zn metal and hydrogen ions are supplied by H_2O and here $CuSO_4$ increase the acidity of the medium which facilitate the reaction leading to the corresponding amine.

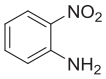
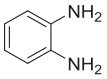
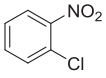
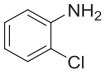
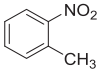
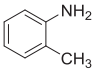
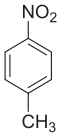
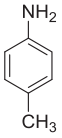
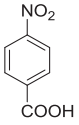
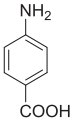
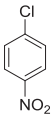
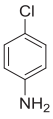
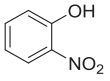
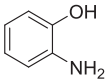
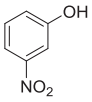
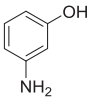
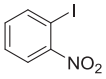
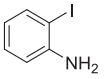
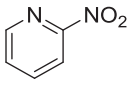
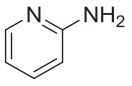
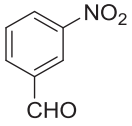
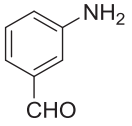
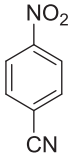
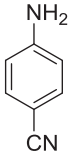
For reduction of nitroarenes leading to aromatic amines with Zn metal, methods employing Zn/HCl [21], Zn/aq. NaOH/EtOH [22],

Table1
[a]Optimizationof the reaction condition for reduction of Nitroarenes to the corresponding Anilines.

Entry	Metal/Metal salt	Solvent	Time (min)	Temperature (^{0}C)	[b]Yield (%)
1	$Fe/CuSO_4$	Nil	180	R.T	Nil
2	Zn	H_2O	180	R.T	Nil
3	Fe	H_2O	180	R.T	Nil
4	$CuSO_4$	H_2O	180	R.T	Nil
5	$Fe/CuSO_4$	H_2O	180	R.T	68
6	$Fe/CuSO_4$	H_2O + EtOH	180	R.T	60
7	Fe/ $CuSO_4$	EtOH	180	R.T	56
8	$Cu/CuSO_4$	H_2O	180	R.T	65
9	$Zn/CuSO_4$	H_2O	180	R.T	95
10	$Zn/FeSO_4$	H_2O	180	R.T	80
11	$Zn/ZnSO_4$	H_2O	180	R.T	76
12	$Zn/NiSO_4$	H_2O	180	R.T	72
13	$Zn/CuSO_4$	H_2O	120	R.T	95
14	$Zn/CuSO_4$	H_2O	60	R.T	94
15	$Zn/CuSO_4$	H_2O	30	R.T	70
16	$Zn/CuCl_2$	H_2O	60	R.T	84
17	$Zn/Cu(OAc)_2$	H_2O	60	R.T	72
18	$Zn/CuBr_2$	H_2O	60	R.T	66
19	$Zn/CuSO_4$	H_2O	60	60	89
20	$Zn/CuSO_4$	H_2O	60	80	87

[a] Reaction of *o*-nitrobenzaldehyde (1 mmol), Zn (3 mmol), $CuSO_4$ (3 mmol) in water on magnetic stirrer.
[b] Isolated yield.

Table 3
[a]Zn and $CuSO_4$ mediated reduction to amines.

Entry	Reactant	Product	Time (min)	[b]Yield (%)
1			50	90
2			30	85
3			30	85
4			30	95
5			30	92
6			40	80
7			30	93
8			30	93
9			30	94
10			40	93
11			50	87
12			60	89
13			50	92

[a] Reaction of nitro compound (1 mmol), Zn (3 mmol), $CuSO_4$ (3 mmol) in water at room temperature for different time intervals on magnetic stirrer.
[b] Isolated yields.

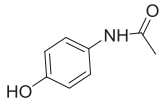


Fig. 1. Plausible mechanism for synthesis of amine from nitro derivative.

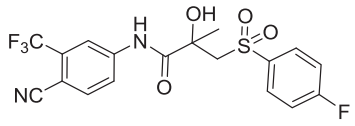


Fig. 1 (*continued*)

Zn/NH_3 [23], $Zn/CaCl_2/EtOH$ [24], Zn/near-critical water [25], Zn/Ru-complex/H_2O/KOH [26], Zn/ether/H_2O [27], $Zn/CO_2/H_2O$ [28], Zn/SiO_2-PEG [29] have been reported. However, since the conventional methods required organic solvents and/or drastic conditions using an irritant reagents such as NH_3, corrosive reagents HCl, NaOH, it is difficult to contend that these methods are environmentally harmonious. On the other hand, the reaction time is prolonged for Zn/NH_3 (24 h), Zn/Ru-complex/H_2O/KOH (16 h), Zn/ether/H_2O (5–11 h). In addition, some special apparatus and high temperature is required for some processes. To overcome these hurdles, we have introduced our scheme using Zn metal, $CuSO_4$ and water at room temperature. The greatest advantage of our method compared with other methods is easy handling, cost effective, environmentally benign.

All of this products are known compounds and were easily characterized by comparison of their spectra with those reported.

Experimental section

Representative experimental procedure for reduction of aromatic nitro compounds

A mixture of nitro compound (1 mmol), Zn powder (3 mmol), $CuSO_4$ (3 mmol) in 5 mL water at room temperature was stirred on a magnetic stirrer. The progress of the reaction was monitored by TLC. After completion of the reaction, the metallic part was filtered off. The filtrate was poured into 100 mL water and extracted with ethyl acetate, washed several times with water. Evaporation of solvent followed by column chromatography over basic alumina using petroleum ether/ethyl acetate (3:1) as eluent toafford the pure aryl amines ( ). The spectroscopic data (IR, ^1H NMR), of this compound are in good agreement with those reported.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151028.

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Original Research Article

One Pot Reductive Synthesis of Benzimidazole Derivatives from 2-Nitro Aniline and Aromatic Aldehydes Using Zn/$NaHSO_3$ in Water Medium

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KEYWORDS

2-nitroaniline,
one pot reaction,
Reductive cyclisation reaction,
Benzimidazole

ABSTRACT

Small amount of Zn dust and $NaHSO_3$ was utilized to efficiently synthesize benzimidazole derivatives via one pot reductive cyclocondensation process in water medium at 100°C temperature. Very good to excellent yields in reasonably short reaction times, high atom economy and usage of readily available starting material, operational simplicity and easy workup are the fundamental features of this protocol.

HIGHLIGHT

- One potreaction
- Chemoselective reductive cyclisation reaction.
- Aqueous medium.
- Shorter reaction time.
- Easy reaction set-up.
- Inexpensive, easily available reagent, easily separable by simple filtration.
- Mild reaction condition.

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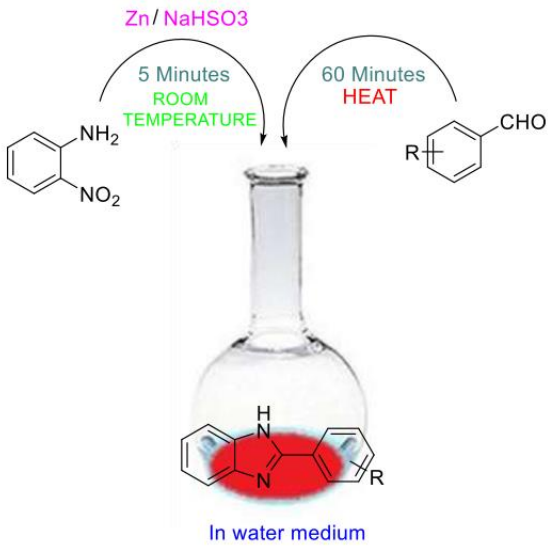
GRAPHICAL ABSTRACT



Introduction

Substituted benzimidazoles display beneficial biological properties such as antihypertensives, antivirals, antifungals, anticancers, and antihistaminics[1]. Furthermore, compounds belonging to this class have been employed as versatile building blocks of anthelmintics[2], proton pump inhibitors[3], and a host of pharmaceutical compounds [4]. A series of compounds with benzimidazole motifs have been used in the textile industry as wetting, emulsifying, foaming, or softening agents or as dispersants for use in dyeing.

As a consequence, a number of researchers have set their goal to synthesize benzimidazoles derivatives. Historically, the first benzimidazole was prepared in 1872 by Hoebrecker. To overcome the drawbacks of classical methods, the most common approaches to benzimidazoles are the combination of 1, 2-phenylinediamine with aldehyde [5-26], carboxylic acid [27-31] and ester [32-33] under different catalytic conditions.

Most of the protocols, however, suffer from drawbacks such as harsh reaction conditions, high temperature, strongly acidic / basic condition, prolonged reaction time, use of homogeneous catalyst, low yield and suffer from rapid loss of catalytic activity. Although the acceptable yield of benzimidazoles has been reported in most of the protocols where either toxic metal catalyst or costly reagents were used, people had to suffer handling tedious reaction conditions and work up process. To avoid these limitations, it is imperative to develop a high yielding greener, simple, cost effective and catalyst free efficient method for its synthesis with a broad range of substrate applicability.

Although 2-nitroaniline appears to be a potential precursor for a possible route to benzimidazole derivatives but except very few [34-36] reports, people have not yet explored its applicability.

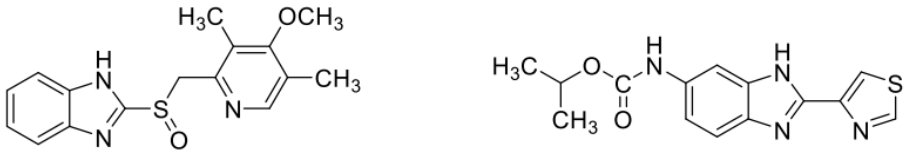
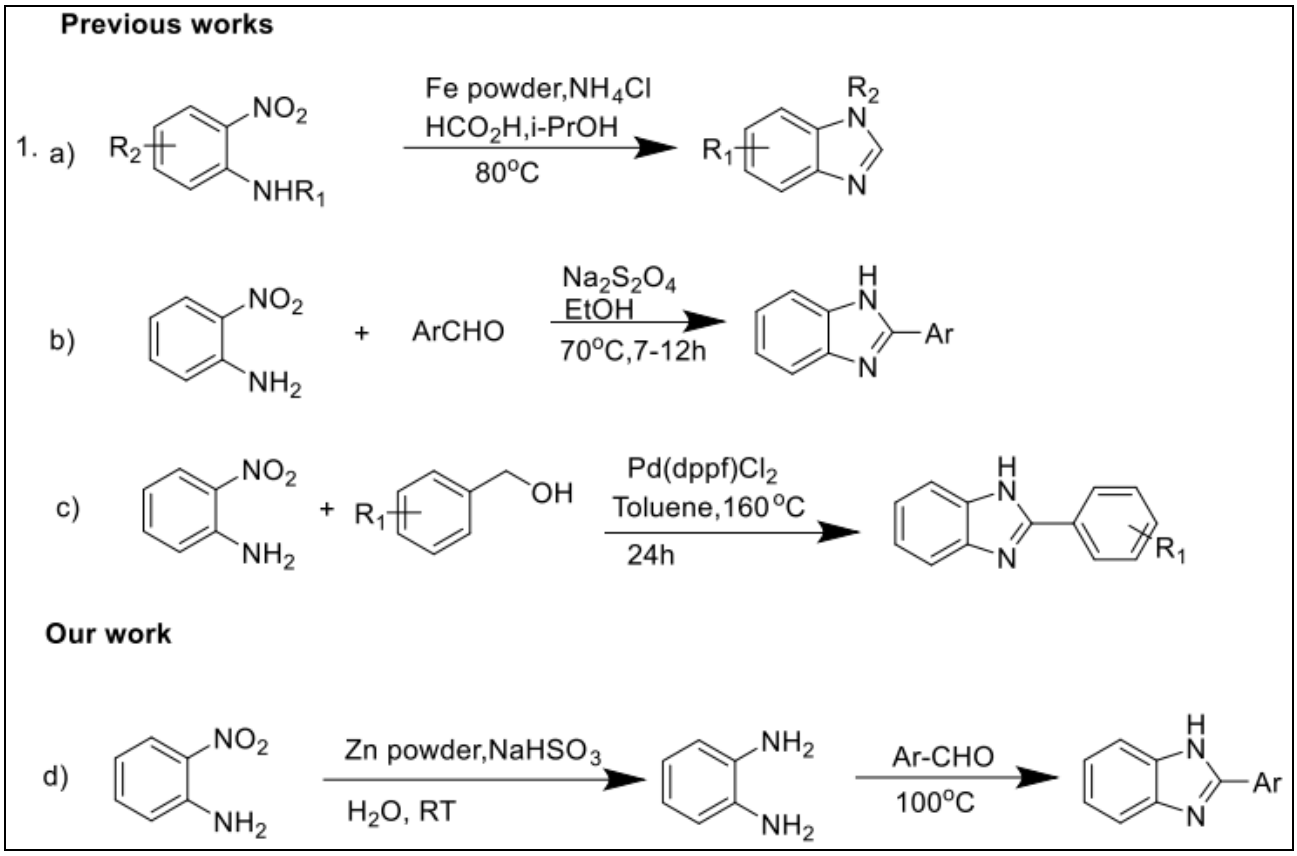


Figure 1: Examples of some bioactive benzimidazole derivatives

Based on the above reports, it seems necessary to develop an easy, cost-efficient and simple method for the preparation of these derivatives which meet the present demand for sustainable development. Keeping these issues in mind, we here reported a simple and mild one-pot method for the synthesis of 2-substituted benzimidazoles (scheme 1, d) from 2-nitroanilines by reductive cyclocondensation with a combination of suitable metal, Zn and metal salt $NaHSO_3$ at 100°C in water. $NaHSO_3$ is a non-hazardous, easily available, inexpensive weakly acidic species having pKa value 6.97, which helps to trigger the reaction in the presence of Zn. Its adduct formation ability with the aldehydes may contribute to cyclocondensation in the present protocol.



Scheme 1: Comparison of previous work and our work for the synthesis of benzimidazole derivatives.

Experimental Materials

Chemicals

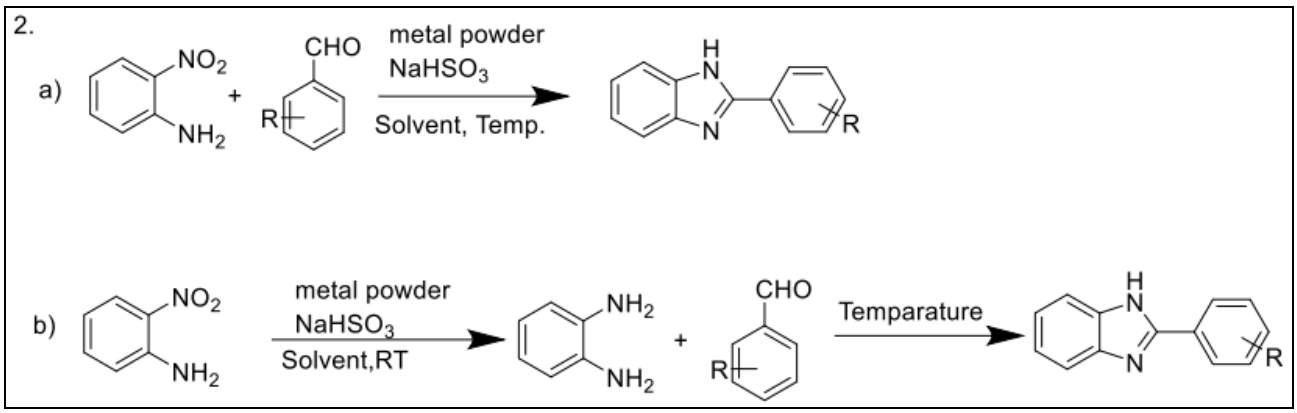
All the chemicals and solvents used in the study were purchased from commercial sources of Sigma Aldrich and SD Fine chemical company and were used without further purification unless stated. The organic solvents used were of analytical or spectroscopic grade. Before using, the solvents were dried and freshly distilled using the standard procedures whenever anhydrous solvents were required.

General Experimental Procedure

In a round bottom flask 2-nitro aniline (1 mmol), Zn powder (3 mmol), $NaHSO_3$ (6 mmol) in 20 mL water at room temperature was stirred on a magnetic stirrer. After 10 minutes, aromatic aldehyde was added into it and at 100 ^oC the mixture was stirred on a magnetic stirrer for 30 minutes. One cotton ball was present on the mouth of the round bottom flask during the process of reaction. The progress of the reaction was monitored by TLC. After completion of the reaction, the metallic part was filtered off. The filtrate was poured into 100 mL ice cold water, extracted with ethyl acetate, and washed several times with water. Evaporation of solvent followed column chromatography over basic alumina using petroleum ether/ethyl acetate (3:1) as eluent to afford the pure benzimidazole derivatives.

Results and Discussion

The general scheme and reaction are shown in scheme 2(a) and 2(b). The compound obtained were monitored by TLC and separated by column chromatography.



Scheme 2: Two different plan for the synthesis of benzimidazole derivatives.

Table1. [a]Reaction (Scheme-2a) condition optimization.

Entry	Time (min.)	Temperature (^oC)	Additive (3 mmol)	Yield of diamine	Yield of Benzimidazole
1	10	RT	$NaHSO_3$	70	Nil
2	10	60	$NaHSO_3$	44	Nil
3	10	80	$NaHSO_3$	25	Nil
4	10	RT	-	Nil	Nil

[a]Reaction of *o*-nitrobenzaldehyde (1 mmol), Fe (3mmol), in water on magnetic stirrer.

Table2. [a]Reaction (Scheme-2b) conditions optimization.

Entry	Metal	Solvent	Time(min.)	Temperature(°C)	Yield (%)[b]
1	Fe	DMF	60	100	68
2	Fe	DMSO	60	100	60
3	Fe	Toluene	60	100	56
4	Fe	H_2O	60	100	80
5	Fe	-	60	100	Nil
6	Cu	H_2O	60	100	75
7	Zn	H_2O	60	100	94
8	-	H_2O	60	100	Nil
9	Zn	H_2O	60	RT	Nil
10	Zn	H_2O	60	80	50
11	Zn	H_2O	60	60	Nil
12	Zn	H_2O	60	40	Nil
13	Zn	H_2O	90	100	95
14	Zn	H_2O	45	100	87
15	Zn	H_2O	120	100	94

[a]Reaction of o-nitrobenzaldehyde (1 mmol), Zn (3mmol), $NaHSO_3$ (6 mmol) in water on magnetic stirrer. [b]Isolated yield of benzimidazole

Table 3. [a]Optimization of amount of Zn and $NaHSO_3$

Entry	Zn (mmol)	$NaHSO_3$ (mmol)	Time (min)	Yield (%)[b]
1	3	3	60	54
2	3	4	60	62
3	3	5	60	82
4	3	6	60	94
5	3	7	60	94
6	2	6	60	75

[a]Reaction of *o*-nitrobenzaldehyde (1mmol), Zn (2-3 mmol), $NaHSO_3$ (4-7 mmol) in water on magnetic stirrer at 100°C. [b]Isolated yield.

To screen the reaction, 2-nitroaniline and benzaldehyde were selected as model substrates for intended transfiguration. Initially, we performed the reaction of *o*-nitroaniline with benzaldehyde in water at room temperature for 1h on a magnetic stirrer in presence of the combination of Fe powder and sodium bisulphite. The reaction yielded only the diamine (o-phenylenediamine). The yield of diamine decreases with a rise in temperature and benzimidazole was undetected (Table1, scheme-2a). It was also tried (scheme-2a) without using $NaHSO_3$ (Table 1, entry 4), but it failed to produce the diamine even at a trace amount. Thus, it is obvious that, as a hydrogen ion's source, $NaHSO_3$ plays a vital role to reduce nitro to amine. With this experimental data we followed our scheme 2b. In this process *o*-nitroaniline was reduced to 1, 2-diamine with Zn and $NaHSO_3$ in presence of water at room temperature and the process was completed within 5 minutes.

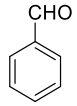
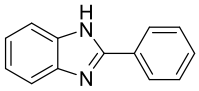
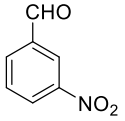
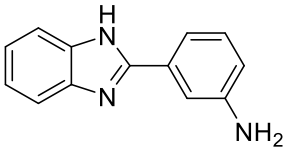
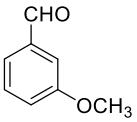
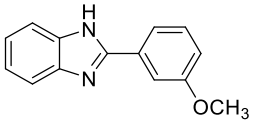
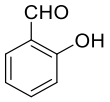
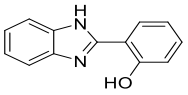
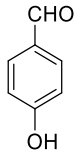
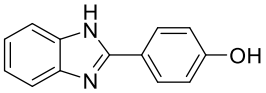
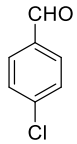
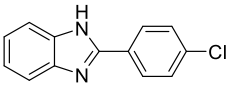
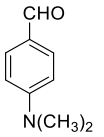
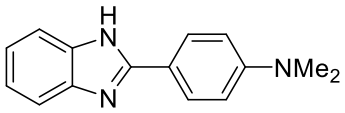
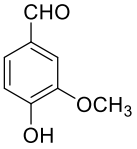
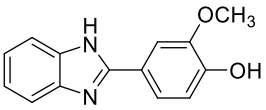
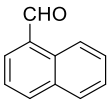
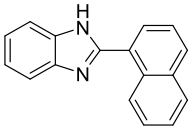
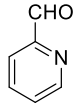
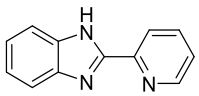
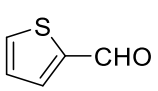
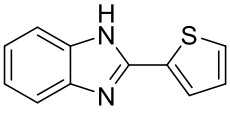
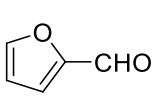
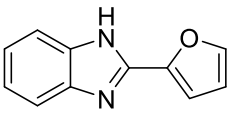
It was followed by the addition of benzaldehyde with continuous stirring at 100 ^oC. As a solvent, water was first screened (Scheme 2b, Table 2, entry 4), and very surprisingly no product was isolated in its absence (Table 2, entry 5). Further, as the most easily available and most significant, its green nature has really enriched the objective of the present investigation.

The presence of metal is the necessary requirement for the initial reduction of the nitro compound (Table 2, entry 8) and in comparison to Fe and Cu, Zn is estimable in terms of yield of the product and the time of completion of reaction (Table 2, entries 4, 6, 7). We also tried the scheme at different temperature; finally, at 100 ^oC temperature the desired product, i.e. benzimidazole, was isolated as a single compound (Table 2, entry 7). Further, we optimized the amount of Zn and $NaHSO_3$ required (Table 3).

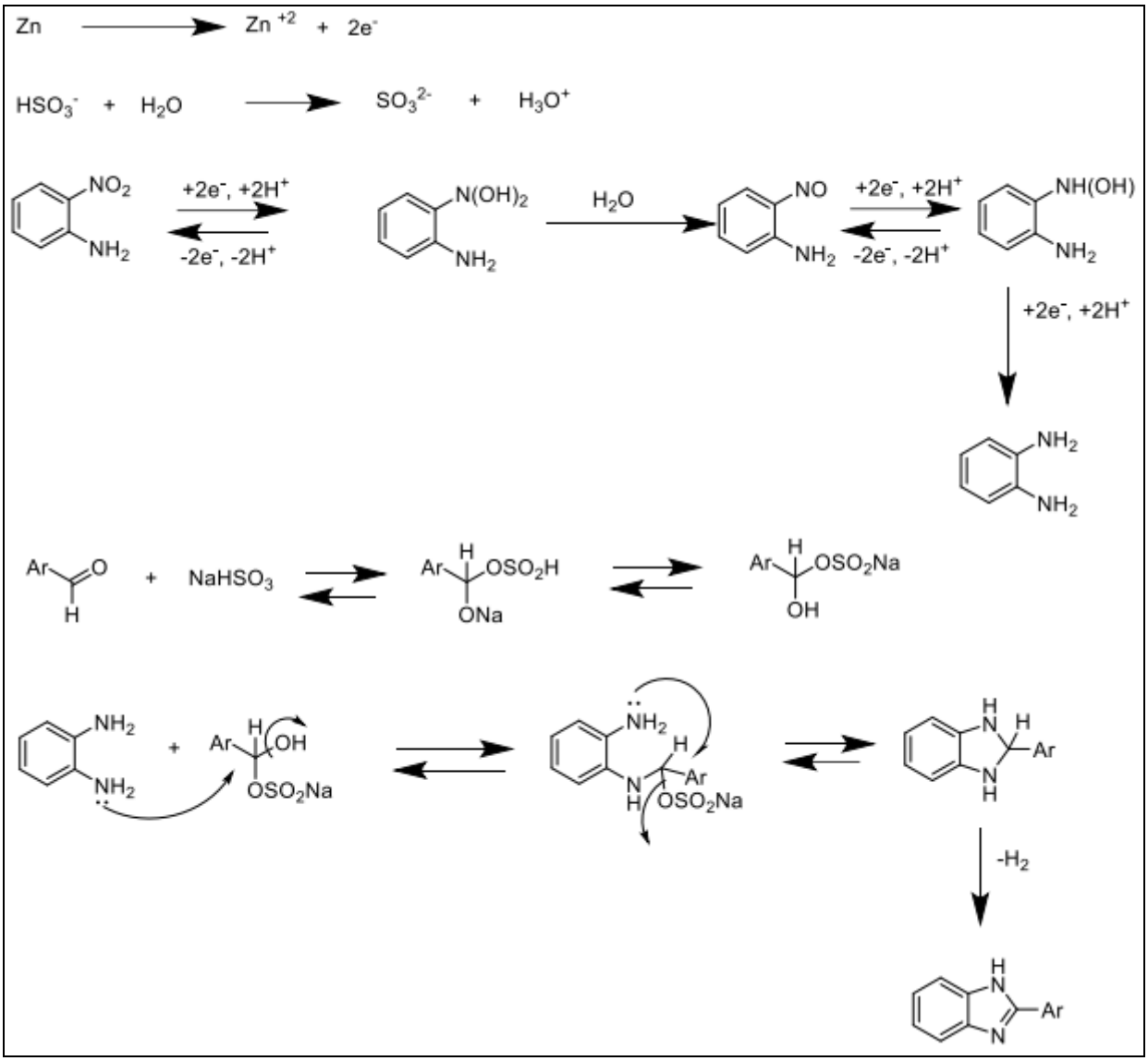
Further investigation towards the optimization of the process revealed that a 3 mmol Zn and 6 mmol $NaHSO_3$, (Table 3) under atmospheric pressure at 100^oC yielded the best result to produce the desired benzimidazole in 1h (compared with Table 2, entries 7, 14, 15). This procedure was followed for all of the reactions listed in Table (4). Staggering part of our reaction was chemoselective reduction of nitro to amine. We really enthralled and exhilarated on observing Table 4 entry 3, 4, 5, 6, 7, 8 that reducible groups remain intact after completion of the reaction. The reaction took place smoothly to produce corresponding benzimidazole in moderate to high yields.

From the above observation, we can propose a possible mechanism and tentative intermediates for the above developed protocol for the synthesis of benzimidazole as follows (scheme-3)

Table 4. [a]Zn and $NaHSO_3$ mediated reduction to amines

Entry	Reactant	Product	Time (min)	Yield (%)[b]	Melting point[c] (^oC)
1			50	93	289-290[37]
2			70	83	>290
3			80	90	200-202[37]
4			50	85	238-240[37]
5			45	89	254-255[37]
6			90	87	290-292[38]
7			60	90	277-279[37]
8			70	94	289
9			45	93	196-198[39]
10			80	90	240-242[38]
11			50	87	>290[40]
12			60	89	267-270[40]

[a]Reaction of nitro compound (1mmol), Zn (3 mmol), $NaHSO_3$ (6 mmol) in water at 100 ^oC for different time intervals on magnetic stirrer. [b]Isolated yields. [c]Melting points of the isolated compounds.



Scheme 3: Proposed mechanism for the synthesis of benzimidazole derivatives

Conclusion

We have developed a novel and efficient protocol through one pot reductive cyclocondensation of 2-nitroaniline with aromatic aldehydes to benzimidazole with $Zn/NaHSO_3$ in water. The fascinating part of our method in comparison to the conventional methods is its simplicity, cost effectiveness, environmentally benign approach and a less time consuming process. We also earn that $Zn/NaHSO_3$ in water is also a better chemoselective reducing system to reduce nitro to amine. Thus, it could potentially be complementary to follow the existing methods for the synthesis of biologically active benzimidazoles moiety.

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Original Resarch Article

Onion extract catalyzed novel synthesis of pyrazine

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Onion extract
One-pot method
High atom economy

ABSTRACT

An efficient catalytic system for analyzing Pyrazine derivatives using an extract of onion at room temperature is discussed in this research study. A very good to excellent yields in reasonably short reaction time, high atom economy, usage of readily available starting material, operational simplicity and easy workup are the fundamental features of this protocol. The versatility our method is determined by synthesizing a large number of pyrazine derivatives with (85-96%) good yield.

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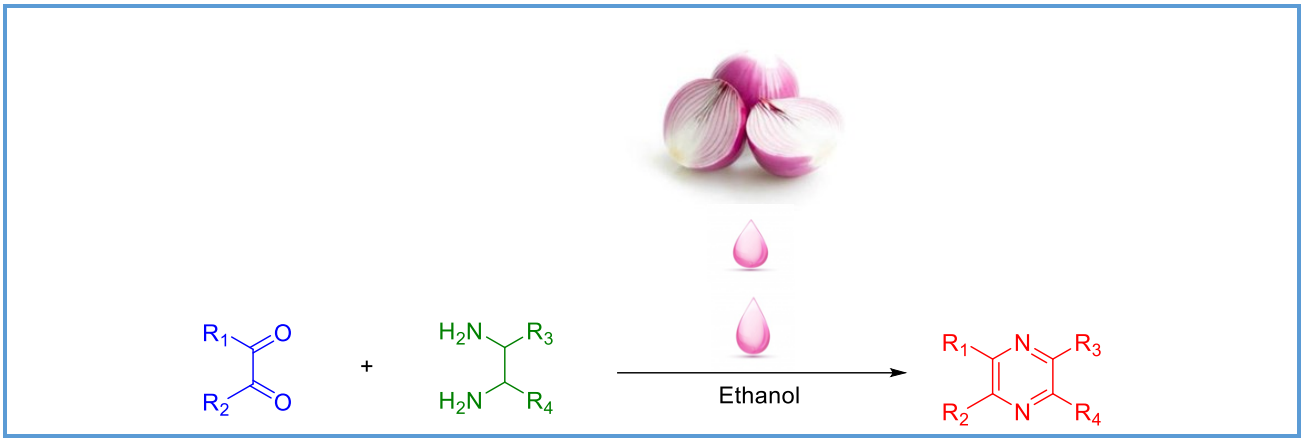
Graphical Abstract



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Introduction

Common onion (Allium cepa L.) is one of the oldest cultivated plants, utilized worldwide as both vegetable and flavoringsubstance. Onions are an important source of several phytonutrients as flavonoids, fructooligosaccharides (FOS), and thiosulfinates and other sulfur compounds, avowed as significant elements of the Mediterranean diet [1]. The composition of the phytochemical may vary in accordance to geography, seasonal harvesting and processesing. These phytochemicals are answerable for many applications in materialchemistry [2, 3] (nanoparticle preparation) and medicinal field including anticancer, antiinflammatory, antiproliferative, reducing serum cholestereol, and blood pressure, immunestimulation, surgical scars, ability to modulate the detoxification system and free radical scavenging activity [4–12] of onion. In fact, onions contain high levels of phenolic compounds, which have antioxidant properties besides beneficial effects against different degenerative pathologies (cardiovascular and neurological diseases, dysfunctions based on oxidative stress) [13]. Flavonoids which are the major phenolics in onions,can be classified in different subclasses (flavones, flavanones, flavonols, isoflavones, flavanonols, flavanols, chalcones, and anthocyanins), on the basis of the degree of unsaturation and the degree of oxidation of the central ring. Among different flavonoids, flavonols are the most abundant in onions, present as their glycosides, that is, quercetin and kaempferol [14, 15], in higher concentration (280–400 mg/kg) than other vegetables (i.e., 100 mg/kg in broccoli, 50 mg/kg in apple) [16]. Anthocyanins, belonging to anthocyanidins, are mainly present in red onions (250 mg/kg), besides having composition rich flavonoids as yellow onions [16]. On the other hand inulin, kestose, nystose, and fructofuranosylnystose are belongs to fructooligosaccharides(another source of phytochemicals in onions bulbs) and has health benefits due to their prebiotic effect [17]. Sulfur compounds which are present in onion, responsible for typical odor and flavor and are also active antimicrobial agents [18]. Therefore, onions may be used as natural preservatives to control microbial growth [19]. Furthermore, they have protective effects against the cardiovascular diseases.

The precursors of sulfur-containing compoundsin onion areS-alk(en)yl-L-cysteine sulfoxides (ACSOs, i.e., methiin, propiin, and isoalliin).1-Propenyl-L-cysteine-sulphoxide (isoalliin, 1) is usually found in highest concentration and is responsible for the tearing and pungency associated with onions. When the onion is cut, the isoalliin (1) undergoes a series of rapid reactions (Figure 1). After the breakage of the tissue caused by cutting, enzyme Alliinase catalyzes the conversion of 1-propenylcysteine sulfoxide to (E)-1- propenesulfenic acid (2), which is then, rearranged to the volatile and highly reactive lachrymatory factor (LF) (Z)-propanethial S-oxide (5), which produces propionaldehyde (6), sulphuric acid (7) and hydrogen sulfide (8) [20]. This transformation is shown in Figure 1. Owing to this consecutive transformation and presence of some organic acids, onion extract is acidic in nature, having pH 3.6 with the strength of 0.0034 N. So, we were interested to explore the effective application of onion extract as acid catalyst for condensation reactions.

Elsewhere Pyrazine is a remarkable compound that hasfoundmanifold applications in pharmaceuticals. Pyrazines are exigent components of aroma fragrances [21], potential pharmacophore of a large number of biologically active substances [22–26], and

widely used as agrochemicals [27–29]. Pyrazine derivatives are also utilized as relaxingcardiovascular and uterine smooth muscle, antithrombotic,anti-aggregation, COX-2 inhibiting, andanalgesic effects [30]. Among the various methods developed, pyrazine derivatives are synthesized by the reaction of diamines with diols in a vapor phasereaction in presence of granular alumina [31].

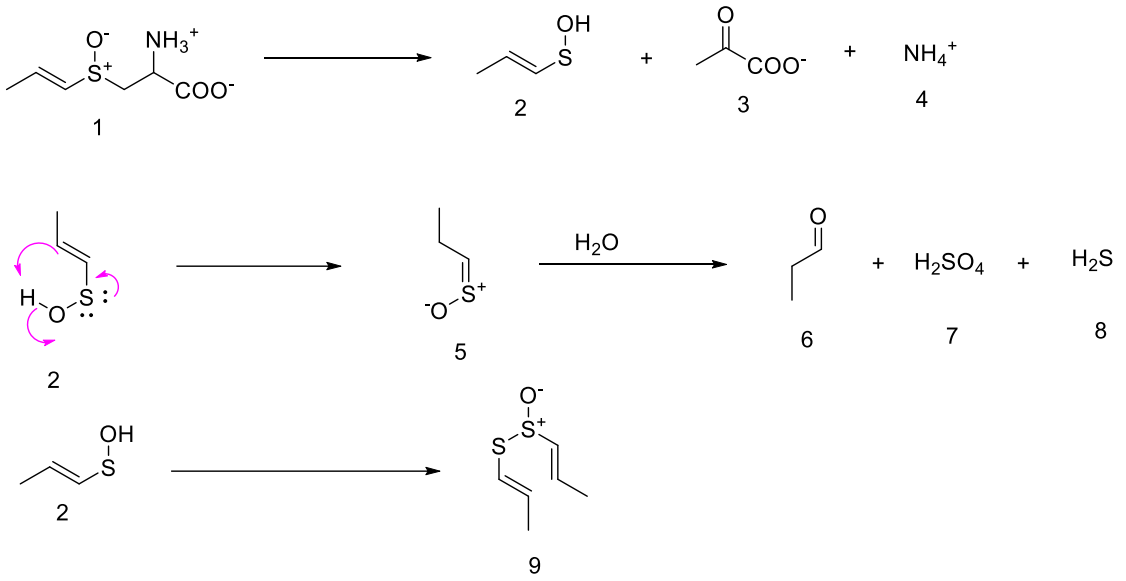
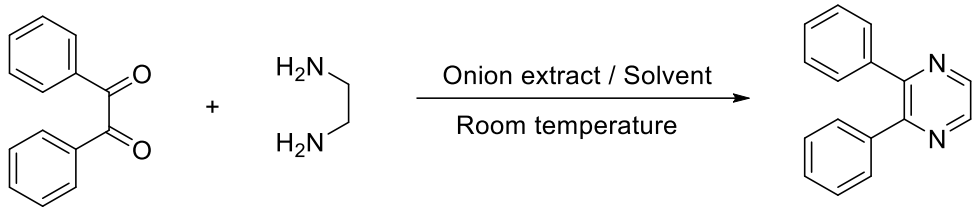


Figure 1. Pathway for the enzymatic synthesis of the lachrymatory factor propanethial-S-oxide (5) and for the spontaneous production of the flavour factor thiosulphinate (9), in onion. The lachrymatory factor propanethial-S-oxide (5) has two isomers, syn and anti. Both the isomers are formed, but the syn compound is formed preferentially

Catalyticsystems such as copper-chromium [32], copperzinc-chromium [33], zinc-phosphoric acid-manganese [34], and silver [35] are also patented as catalysts forthe preparation of 2-methylpyrazine from ethylenediamineand propylene glycol. Pyrazines are alsoobtained from condensation reaction of diamines and epoxides using copper-chromium catalyst [36], condensation reaction between alkanolamines [37], or cyclodehydrogenation of N-(-hydroxyalkyl) alkyldiamine [38] using the same catalysts. In the presence of a palladium catalyst, dehydrogenation of piperazines yields corresponding pyrazines in high yield [39]. Recently, synthesis of pyrazines from a-hydroxyketones and 1, 2-diamines via MnO_2 catalyzed tandem oxidation process under refluxing conditions has been reported. However, the yields are not encouraging and the loading of the catalyst was also high [40]. The method of bubbling oxygen under refluxing condition [41] suffers from scientific drawbacks. Strategically, direct condensation reaction of 1, 2-diketones with 1, 2-diamine [42] is the most straightforward as well as the classical route for the preparation of pyrazines. Although, a number of methods are reported in literature for the synthesis of pyrazine, none of them has been found to be effective due to the poor yield, harsh reaction condition, and tedious work-up procedures. Attempts to carryout dehydrogenation under a variety of milder and more convenient laboratory procedures were not successful. Although, some of them are apparently useful, most of them are

limited by long reaction time, low yields, and use of toxic solvents or heavy metals as the catalyst. Therefore, development of mild, efficient, and environmentally sound method for synthesizing pyrazines has been a major challenging contemporary in organic synthesis.

Now, to explore the catalytic applicability of onion extract, preciousness of Pyrazine derivatives in pharmaceutical industry and to avoid the limitation of its synthesis, keeping these in mind, the methodology reported in this work is simple, mild, economic, nontoxic, and one-pot for the synthesis of Pyrazine derivatives (Scheme 1).



Scheme 1. The general scheme and reaction for the synthesis of Pyrazine derivative

Experimental

Materials and methods

All the melting points were determined using an open capillary method; and nuclear magnetic resonance (NMR) spectroscopy was recorded using a Bruker-Avance 300 MHzFT-NMR instrument using TMS as the internalstandard. NMR spectra were recorded in $CDCl_3$. The entire chemicals were purchased from Merck, Fluka, SRL, and S.D. fine chemicals companies.

Preparation of onion extract

Onion was brought from local market and washed with water. Then the onion was dried, grinded and was stirred. The solution was filtered in Whatman grade 41 filter paper. The filtrate is onion extract and used as our reusable catalyst for the reaction.

Representative experimental procedure for reduction of aromatic nitro compounds

In a round bottom flask Benzil (1 mmol), Ethylenediamine (1 mmol), Onion extract (0.2 mL) in 5 mL Ethanol at room temperature was stirred on a magnetic stirrer for 60 min. One cotton ball was present on the mouth of the round bottom flask during the process of reaction. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into 100 mL ice cold water and the product extracted with ethyl acetate, washed several times with water. Evaporation of solvent followed by column chromatography over basic alumina using petroleum ether/ethyl acetate (3:1) as eluent to afford the pure benzimidazole derivatives. The spectroscopic data (^{1}H NMR, ^{13}C NMR) of this compound are in good agreement with those reported. All of these products are known compounds and were easily characterized by comparison of their spectra with those reported.

Characterization of some representative compounds

2, 3-Diphenyl pyrazine

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.14-7.25 (m, 5H, five aromatic hydrogen), 7.37-7.44 (m, 5H, five

aromatic hydrogen), 8.52 (s, 2H, 2 aromatic hydrogen of the heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 128.1, 128.2, 128.5, 129.5, 138.5, 141.9, 152.6.

2, 3-Bis (4-methoxy phenyl) pyrazine

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.77 (s, 6H, 2-OCH_3), 6.75-6.85 (m, 4H, four aromatic hydrogen), 7.33-7.43 (m, 4H, four aromatic hydrogen), 8.45 (s, 2H, two aromatic hydrogen of the heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.2, 113.7, 130. 9, 131.2, 141.4, 152.1, 159.9.

2, 3-Di p-tolyl pyrazine

^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.31 (s, 6H, 2-CH_3), 7.04-7.12 (m, 3H, aromatic hydrogen), 7.27-7.46 (m, 5H, five aromatic hydrogen), 8.51 (s, 2H, two aromatic hydrogen of the heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.3, 129.0, 129.4, 135.8, 138.5, 141.7, 152.6.

2-Methyl-3-phenyl pyrazine

^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.54 (s, 3H, -CH_3); 7.46-7.59 (m, 5H, five aromatic hydrogen), 8.44 (d, 2H, J2.4Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.1, 128.4, 128.7, 128.9, 138.5, 141.5, 142.1, 151.8, 154.4.

2, 3 Di-(furan-2-yl)-pyrazine

^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.59 (s, 3H, -CH_3), 6.56 (m, 4H, aromatic protons), 7.52 (m, 2H, aromatic protons), 8.37 (s, 1H, aromatic proton). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.3, 112.1, 112.7, 139.2, 140.8, 141.7, 143.4, 143.7, 150.5, 150.6, 151.2.

2-Methyl-3-propylpyrazine

^{1}H NMR ($CDCl_3$, 300M Hz): δ 0.96-1.04 (m, 3H, -CH_3); 1.70-1.82 (m, 2H,); 2.57 (s, 3H, -CH_3); 2.79 (t, 2H, J7.5Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0, 21.5, 21.7, 36.9, 141.1, 141.4, 152.3, 156.0.

2, 3-Diphenyl-5-methyl pyrazine

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.86 (s, 3H, -CH_3); 6.63 (d, 10H, J = 5.1 Hz, ten aromatic hydrogen), 7.68 (s, 1H, one aromatic hydrogen of the heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.5, 127.4, 127.6, 128.7, 128.8, 137.8, 141.0, 148.8, 150.3, 150.7.

2, 3-Bis (4-methoxy phenyl)-5-methyl pyrazine

^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.62 (s, 3H, -CH_3); 3.80 (s, 6H, 2-OCH_3); 6.82 (dd, 4H, J = 1.8 Hz, four aromatic hydrogen), 7.38 (dd, 4H, J = 1.8 Hz, four aromatic hydrogen), 8.39 (s, 1H, one aromatic hydrogen of the heterocyclic moiety). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.2, 53.4, 55.2, 130.8, 130.9, 131.2, 131.4, 141.1, 149.0, 150.5, 150. 9, 159.8, 159.6.

Pyrazine-2, 3-dicarbonitrile

^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.00 (s, 2H, aromatic protons). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 113.1, 133.84 (aromatic carbons); 147.5 (-CN).

5-Methyl-6-propiopyrazine-2, 3-dicarbonitrile

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.06 (t, 3H, J = 7.2Hz); 1.78-1.88 (m, 2H); 2.75 (s, 2H, -CH_3); 2.94 (t, 2H, J7.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8, 20.4, 22.3, 36.9, 113.3, 113.4, 129.9, 130.4, 157.7, 161.2.

5, 6-Dip-tolylpyrazine-2, 3-dicarbonitrile

^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.32 (m, 6H, 2 -CH_3), 6.99 (m, 4H, aromatic protons), 7.43 (m, 1H, aromatic proton), 7.94, (m, 3H, aromatic protons). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.6,

126.8, 128.6, 129.3, 130.0, 139.2, 144.0, 144.3, 193.3.

5-Phenylpyrazine 2, 3-dicarbonitrile

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61 (d, 3H, J = 7.5 Hz), 8.13 (d, 2H, J = 6.6Hz), 8.51 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 128.0, 129.8, 130.8, 132.5, 133.0, 144.1, 154.8.

5, 6-Diethylpyrazine-2, 3-dicarbonitrile

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.39 (m, 6H), 1.97 (m, 2H), 2.97 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.2, 19.8 (2-CH_3), 25.1, 27.8 (2-CH_2), 113.4, 130.2 (aromatic carbon), 161.3 (-CN).

5, 6-Diphenyl pyrazine-2, 3-dicarbonitrile

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.16-7.30 (m, 5H, five aromatic hydrogen), 7.45 (t, 2H, J = 7.3 Hz, two aromatic hydrogen), 7.57 (t, 1H, J = 7.3 Hz, aromatic hydrogen), 7.78 (d, 2H, J = 7.2 Hz, aromatic hydrogen). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 126.5, 127.5, 128.2, 128.4, 130.0, 132.4, 137.5, 143.8, 196.8 (carbon of nitrile group).

Results and Discussion

To pursue our interest through green protocol, we report herein the onion extract catalysed method of synthesis of Pyrazine derivatives from 1, 2-diketone and 1, 2-diamine. Therefore, our model substrates are Benzil and Ethylenediamine. The compound obtained were monitored by TLC and separated by the column chromatography.

At first, we investigate the influence of solvent on the conversion of 2, 3-diphenylpyrazine from Benzil and Ethylenediamine in the attendance of onion extract (Scheme 1, Table 1). It was found that, the method was efficient for all the solvents with good yields. Here the greenest solvent, water could have been the first in this race, leaving every solvent behind; however, its low ability to dissolve the organic compounds did not allow him to do so (Table 1, entry 4). Poor yield results in this reaction if we avoid to use solvent (Table 1, entry 5). As seen in Table 1, EtOH is the superior for this novel purpose (Table 1, entry 3).

Table 1. Reaction conditions optimization by various solvents[a]

Entry	Solvent (5 mL)	Time (min)
1	DMF	60
2	DCM	60
3	EtOH	60
4	H_2O	60
5	-	60
6	Hexane	60
7	DMSO	60
8	Isopropanol	60
9	Acetonitrile	60
10	Toluene	60
11	Acetone	60
12	$CHCl_3$	60
13	EtOH	90
14	EtOH	45

[a] Reaction of Benzil (1 mmol) and ethylenediamine (1 mmol) catalysed by onion extract (1 mL) on magnetic stirrer at room temperature

[b] Isolated yield of Pyrazine

Next efforts were undertaken to optimize the quantity of onion extract required to carry out the reaction. At first, the substrates were stirred at room temperature for 120 min in the absence of onion extract, result rap out that onion extract play a key role to carry out the reaction (Table 2, entry 1). In addition, it was observed that minimum 0.2 mL onion extract and 60 min is sufficient enough to catalyze the reaction with better yield for desired product (Table 2, entry 6-10).

To widen the scope of our study, commercially available 1,2-diketones and 1,2-diamines are selected to synthesized corresponding products. As can be seen in Table 3, high yields were achieved for the synthesis of different Pyrazine derivatives within a reasonable time (Table 3, entry 1-15).

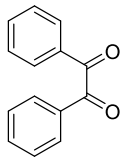
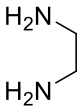
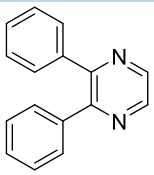
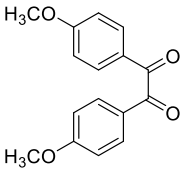
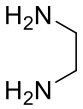
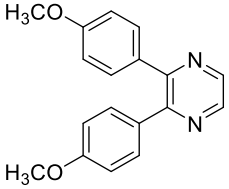
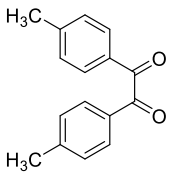
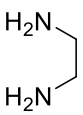
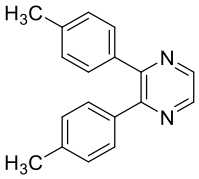
The reusability study was assessed for the onion extract catalyst (Figure 2). Our catalyst gave the desired product with good yield (96%-85%).

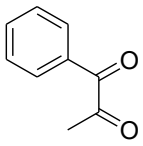
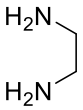
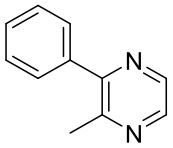
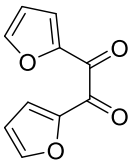
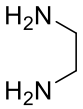
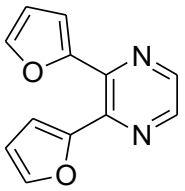
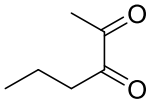
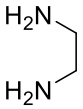
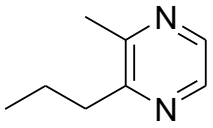
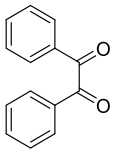
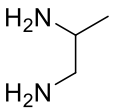
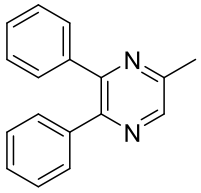
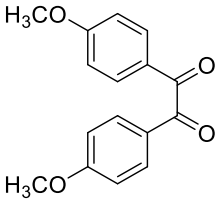
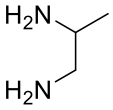
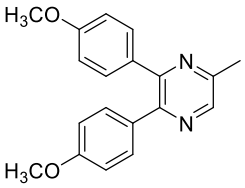
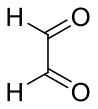
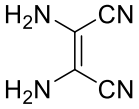
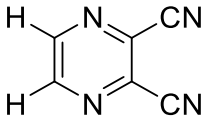
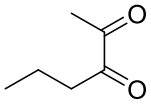
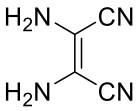
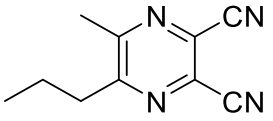
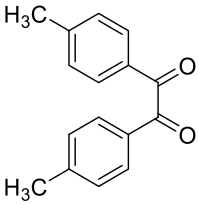
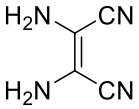
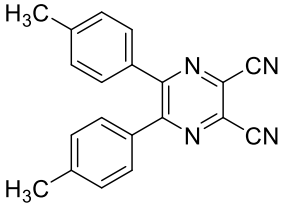
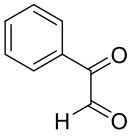
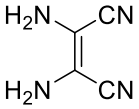
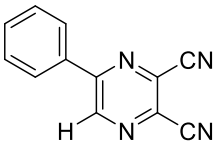
Table 2. Reaction condition optimization[a]

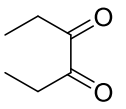
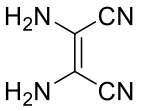
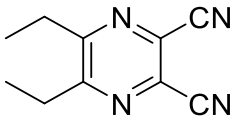
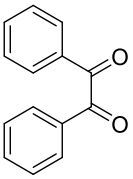
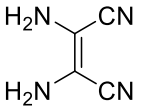
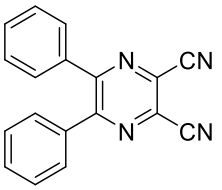
Entry	Onion extract (mL)	Time (min.)	Yield (%)
1	0	120	Trace
2	1	120	97
3	0.8	120	97
4	0.6	120	97
5	0.4	120	96
6	0.2	120	96
7	0.1	120	95
8	0.2	90	96
9	0.2	60	96
10	0.2	45	92

[a]Reactionof Benzil (1 mmol) and ethylenediamine (1 mmol) in EtOH (5 mL) on magnetic stirrer at room temperatur

Table 3. Isolated yield and the catalytic synthesis of product

Entry	1, 2-diketones	1,2-diamines	Product	Time (min)	Yield[b] (%)
1				60	96
2				70	94
3				80	96

4				45	89
5				60	89
6				50	90
7				90	96
8				70	95
9				60	89
10				45	85
11				50	87
12				80	89

13				70	86
16				45	88

[a] Reaction of Benzil (1 mmol) and ethylenediamine (1 mmol) in ethanolcatalyzed by onion extract (0.2 mL) on magnetic stirrer
[b] Isolated yield of Pyeazine

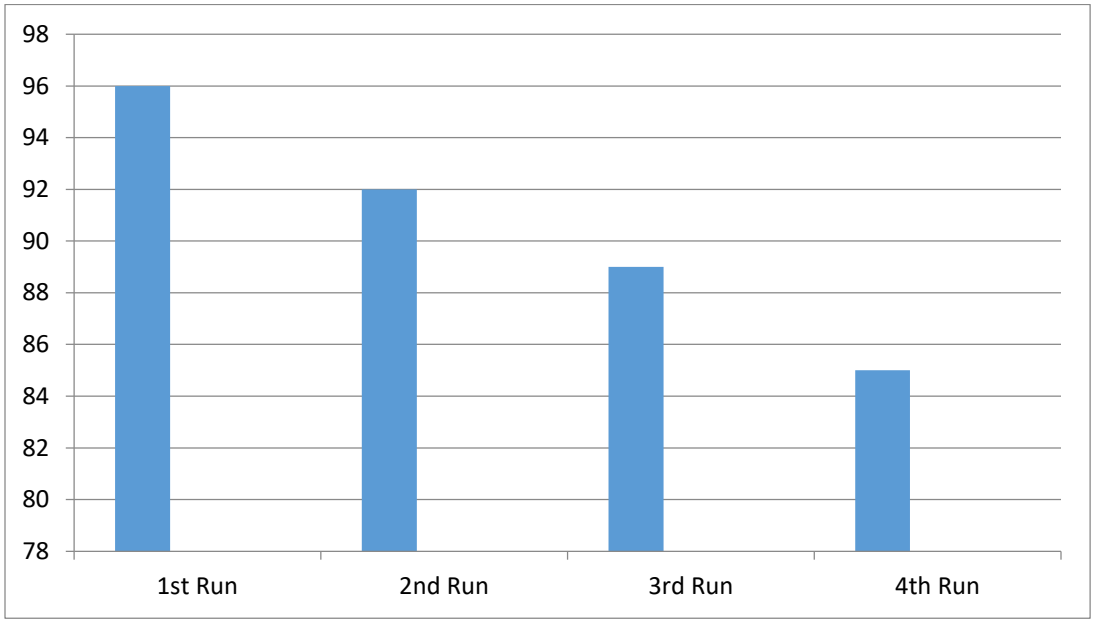
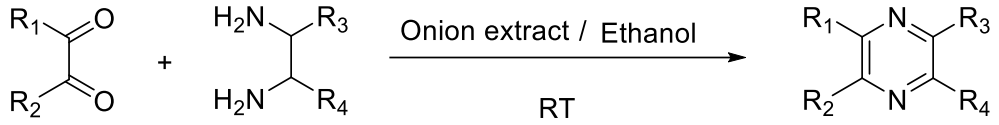


Figure 2. Reaction of Benzil (1 mmol) and ethylenediamine (1 mmol) in ethanol catalyzed by onion extract (0.2 mL) on magnetic stirrer. Recycling of our catalyst for synthesis of Pyrazine

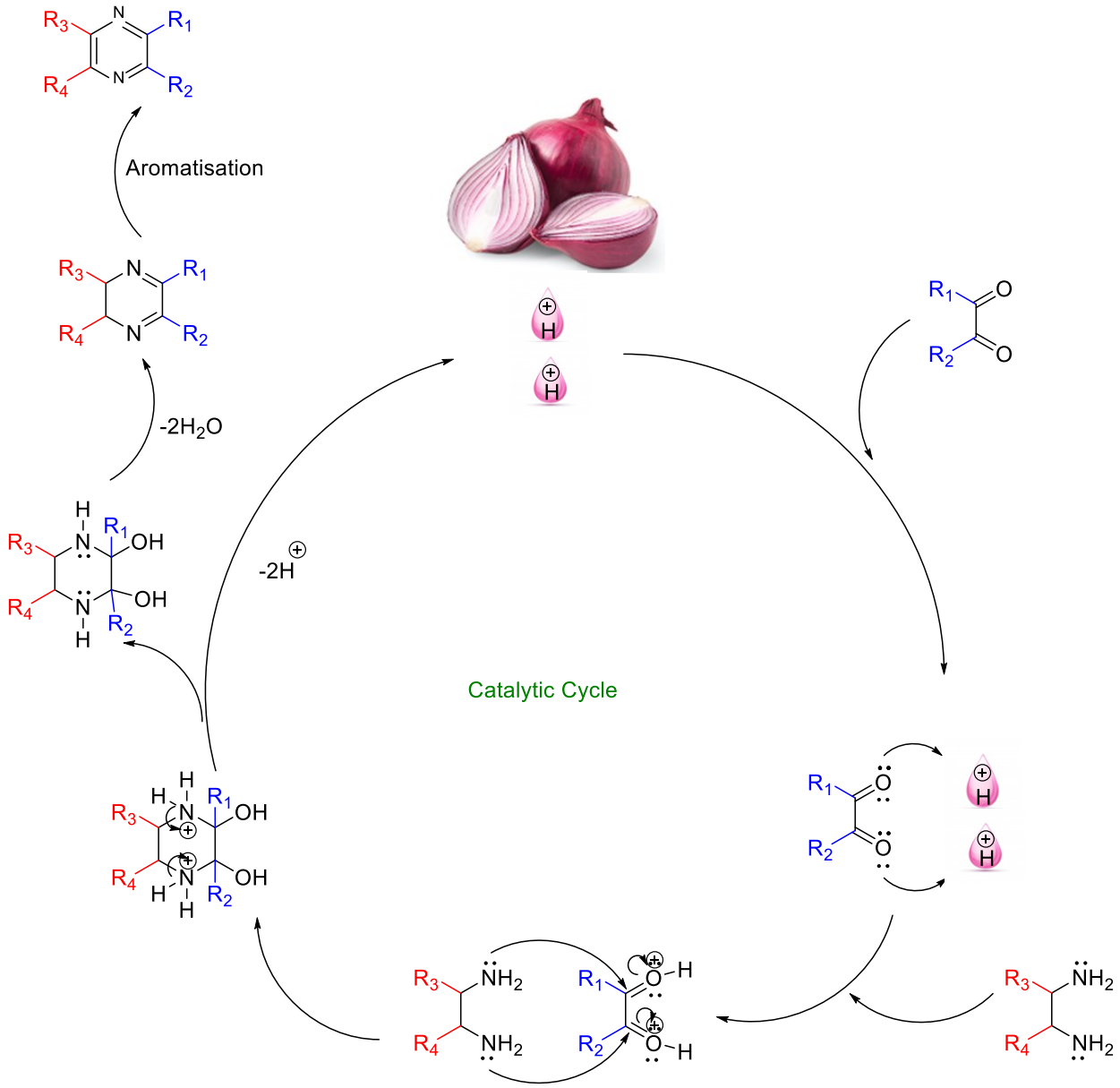
The organic acids which are present in the onion extract were believed to serve as catalyst in the double condensation reaction and aromatization process to form Pyrazine derivatives (Scheme 2).

It was reported that onion extract contains phenolic acids as major constituents along with other minor chemical constituents such as flavanols, flavones and anthocyanidines. The pH of the onion extract is found to be 3.6, which are owing to the presence of water soluble phytochemicals caffaeic acids, ferullic acid, sinapinic acid, cyaniding, tannic acid and other organic acids. As they are water soluble that's why we can easily collect the onion extract solution for our reusability purpose and we can also recover the acids after four successive usages. Therefore, we can propose the organic acids that are present in the onion extract served to protonate the oxygen atoms of the carbonyl groups of the diketone thereby faceiliting the nucleophilic attack by 1,2-diamine promoting the synthesis of Pyrazine derivatives.

From the above observation, we can draw possible mechanism and tentative intermediates for the synthesis of Pyrazine derivatives as follows (Scheme 3).



Scheme 2. Synthesis of pyrazine derivatives from various 1,2-diketones and 1,2-diamines at optimum condition. R_1, R_2, R_3, R_4 are the different functional group



Scheme 3. Possible mechanism and tentative intermediates in the synthesis of Pyrazine derivatives. R_1, R_2, R_3, R_4 are the different functional groups

To show the catalytic merit of the onion extract, the previous methods and their yields for synthesizing Pyrazines are summarized in Table 4. To date, many efficient catalytic system have been reported for this reaction, however, most of the previous methods encompassed the use of harsh condition, high temperature, expensive and non-recyclable catalysts for the synthesis of Pyrazine derivatives.The fascinating part of our method compared with other methods is easy handling, cost effective, environmentally benign and time consuming. We also earn that onion extract has also a better catalytic behavior for condensation reaction. Therefore, it could potentially be complementary to the existing methods for the synthesis of Pyrazine.

Table 4. Comparison of Synthesis of Pyrazine by different catalyst in different years

Entry	Year	Catalyst	Time (h)	Yield (%)	References
1	2002	$FeCl_3$, MeOH-H_20 (1:1), reflux	16 h	65-72	43
2	2003	$CuO/ZnO/SiO_2$ at 360 °C	350 h	87	44
3	2003	MnO_2, CH_2Cl_2, reflux, then 0.4 M KOH/MeOH	20 h	66	45
4	2007	Copper oxide/copper chromite catalysts at 340-440 °C	0.1 h	98-100	46
5	2012	MeOH/t-BuOK, Room temperature	6-8 h	74-88	47
6	2020	Onion extract, room temperature	60 minutes	85-96	Our work

Conclusions

In this work, we have developed a simple and convenient procedure to synthesize Pyrazine derivatives at the presence of onion extract through condensation and aromatization from the easily available 1, 2-diketones and 1, 2-diamines. The current protocol offers many advantages; benign reagents, simple workup process, good to excellent yields. In addition, easily available and the reusability of the onion extract as a catalyst increase the value of our work. Further application of the onion extract in the synthesis of other bioactive heterocyclic compounds is currently ongoing in our laboratory and the results will be reported in due course.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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