METHODOLOGICAL APPROACH ON CARBON-HETERO BOND FORMATION REACTION

A Thesis submitted to the University of North Bengal

For the Award of
Doctor of Philosophy
in
Chemistry

By

Suvodip Mukherjee

Guide

Prof. Pranab Ghosh

Department of Chemistry
University of North Bengal

June-2022

Dedicated
To
My Beloved Parents,
Mayuri
&
Family Members

DECLARATION

I declare that the thesis entitled "**METHODOLOGICAL APPROACH ON CARBON-HETERO BOND FORMATION REACTION**", has been prepared by me under the guidance of Prof. Pranab Ghosh, Professor of Chemistry, University of North Bengal. No element of this thesis has formed the origin for the award of any degree or fellowship earlier.

Suvodip Mukherjee

Suvodip Mukherjee

Department of Chemistry

University of North Bengal

Darjeeling-734013

West Bengal

India

Date: 14.06.2022

UNIVERSITY OF NORTH BENGAL

Accredited by NAAC with grade "A"

Prof. P. Ghosh
Department of Chemistry
University of North Bengal
Darjeeling – 734013, India

समानो मन्त्र समितिः समानी

Ph: +91 3532776381 (off)
+91 9474441468 (M)
Fax: +91 3532699001
Email: pizy12@yahoo.com

CERTIFICATE

I certify that **Mr. Suvodip Mukherjee** has prepared the thesis entitled **"METHODOLOGICAL APPROACH ON CARBON-HETERO BOND FORMATION REACTION"**, for the award of Ph.D. Degree of the University of North Bengal, under my guidance. He 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.

Prof. Pranab Ghosh
Department of Chemistry
University of North Bengal
Darjeeling - 734013
West Bengal, India

Date: 14.06.2022

Curiginal

Document Information

Analyzed document	Suvodip Mukherjee_Chemistry.pdf (D139506658)
Submitted	2022-06-07T10:06:00.0000000
Submitted by	University of North Bengal
Submitter email	nbuplg@nbu.ac.in
Similarity	8%
Analysis address	nbuplg.nbu@analysis.urkund.com

Sources included in the report

W	URL: https://www.organic-chemistry.org/synthesis/C1N/amines/reductiveamination.shtm Fetched: 2020-01-28T18:29:10.1130000	4
W	URL: https://s-space.snu.ac.kr/bitstream/10371/167844/1/000000159153.pdf Fetched: 2022-06-07T10:06:49.3870000	19
W	URL: https://pdfs.semanticscholar.org/ef01/c0300ad0be806ac2b9b6031f675a464de250.pdf Fetched: 2022-06-07T10:06:38.4200000	10

Suvodip Mukherjee
14.06.2022

14.06.2022

Department of Chemistry
University of North Bengal
Darjeeling - 734013, India

ACKNOWLEDGEMENT

This work would not have been possible without the help of many persons who were a constant source of inspiration and support. I would like to take this privilege to thank those persons.

First of all, I would like to express my sincere gratitude to my honorable supervisor Prof. Pranab Ghosh, Professor, University of North Bengal, Darjeeling, for his active guidance and supervision, valuable advice and constant encouragement and motivation following which this work has come to life.

I express my sincere gratitude Prof. B. Sinha, HOD, Department of Chemistry, NBU. I feel pride to have acquainted with all non-teaching staffs that always stood beside me for constant support and spent a lot of their valuable time to motivate me in my darker hours.

I would like to thank my past and present labmates, Bijeta di, Gyan da, Tandra di, Hridoy da, Rabindra da, Puja di, Bittu da, Debashis da, Manishita di, Kumaresh, Biswajit, Aminul, Sourav, Sharmistha, Subhankar,Koushik, Dina Bandhu da, Saikat and others for their active co–operation throughout my research period.

I would also like to convey my special thanks to Prasun da, Pranesh, da, Ananya di, Sudip, Soumik, Gautam for their constant help and support.

The story will remain incomplete if I fail to express my thanks to the Lab no.107, Dept. of Chemistry, NBU where I have done my research work with my laptop where I have made the draft of my thesis.

I am thankful to University of North Bengal for providing the infrastructural facilities.

Finally, this work would not have been possible without the blessings of my beloved parents Shri. Tapan Mukherjee and Smt. Chhandana Mukherjee and by very close friend smt. Mayuri Mukherjee who's always stood by my side and also my lovable dog DOGO.

I would also take this opportunity to express my sincere apologies for any mistake on my part or any word or behaviour of mine that may have hurt anyone working with me.

Finally, despite best of my efforts and sincerity I might have committed some unintentional errors and mistakes in my thesis. Suggestions and criticisms from learned professors will be thankfully accepted.

Thank you.

Suvodip Mukherjee

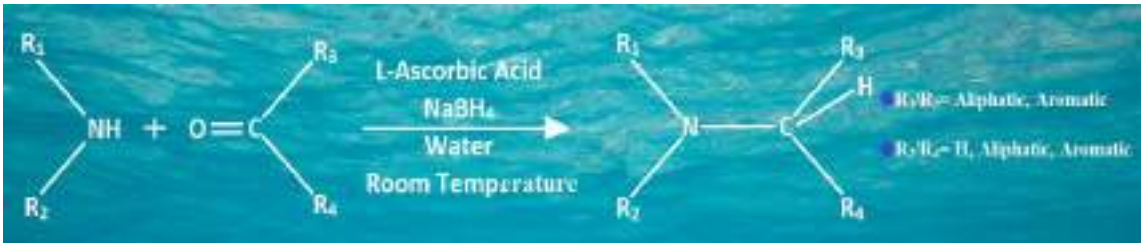
14.06.2022

Suvodip Mukherjee.

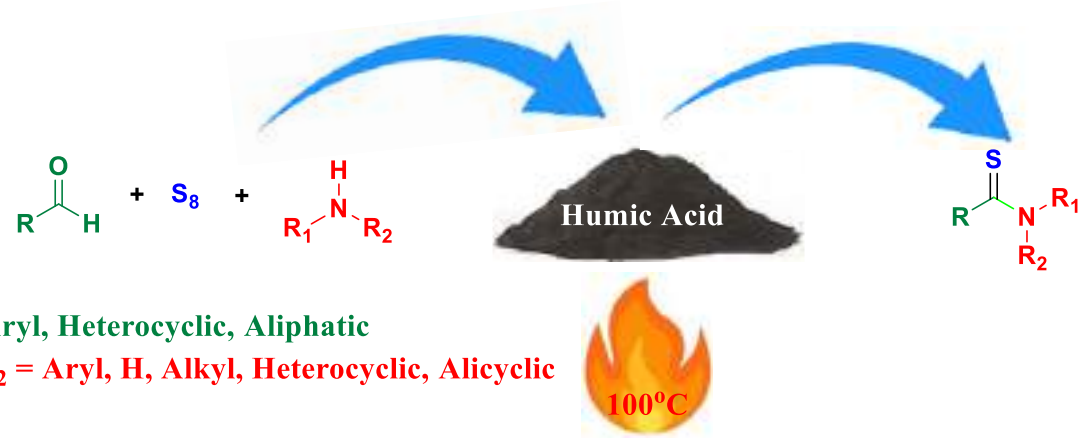
ABSTRACT

Beginning from the summer days of 2017, it took nearly five long years to finish the research work incorporated in this thesis entitled "**METHODOLOGICAL APPROACH ON CARBON-HETERO BOND FORMATION REACTION**". The work is mainly focused on development of efficient and environment benign methodologies for carbon-hereto bond formation reactions. The entire work depicted in this thesis has been divided into five chapters. In the beginning, **Chapter I** deals with a brief review on carbon-hetero bond formation reactions. Carbon-hetero bonder compounds has been extensively used in the designing of various pharmaceutically significant compounds. Apart from this, they are considered to be powerful starting materials for the construction of naturally occurring biological active compounds like amino acids, glycosides, naturally occurring heterocyclic compounds etc.

In **Chapter II** a novel, biomimetic concept for the direct reductive amination of aldehyde and ketones has been developed which uses largely available, low cost and harmless L- ascorbic acid as sustainable, versatile, non-toxic catalyst and $NaBH_4$ as a reductant. Described herein is a one-pot conversion of effortlessly accessible primary and secondary amines to biologically active higher degree amines in water at room temperature. The mild condition, environmentally benign by-products and broad scope of makes this transformation very useful.

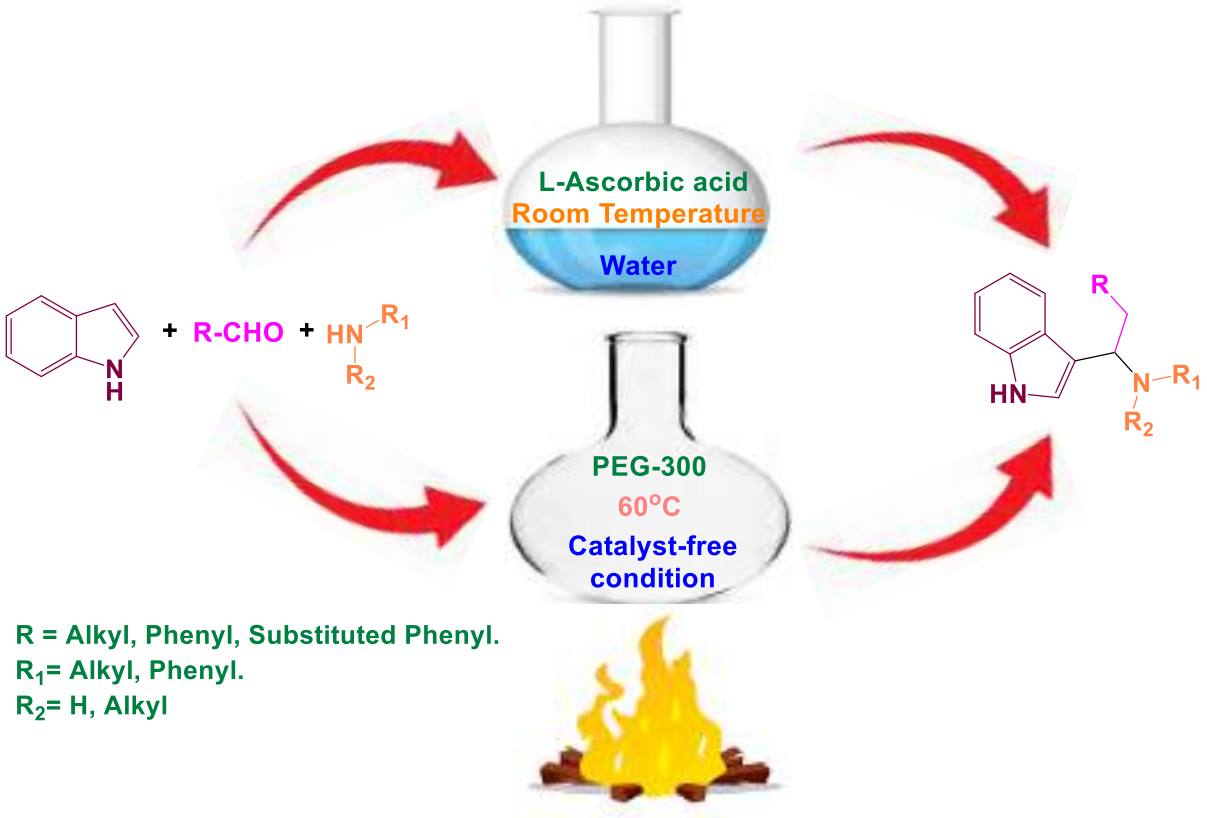


In **Chapter III** an environmentally sustainable, green synthesis of thioamide through MCR (multi component reaction) of aldehyde, amine and sulfur catalyzed by humic acid in solvent-free condition at 100 °C. The key features of this protocol are use of humic acid, a greener, easily recyclable, easily available and almost unexplored catalyst and circumvention of noxious solvents that amplify the scope of the reaction. The proposed protocol also possess tolerance to aromatic as well as aliphatic aldehydes and amines comprising variety electron donating and withdrawing functional groups.



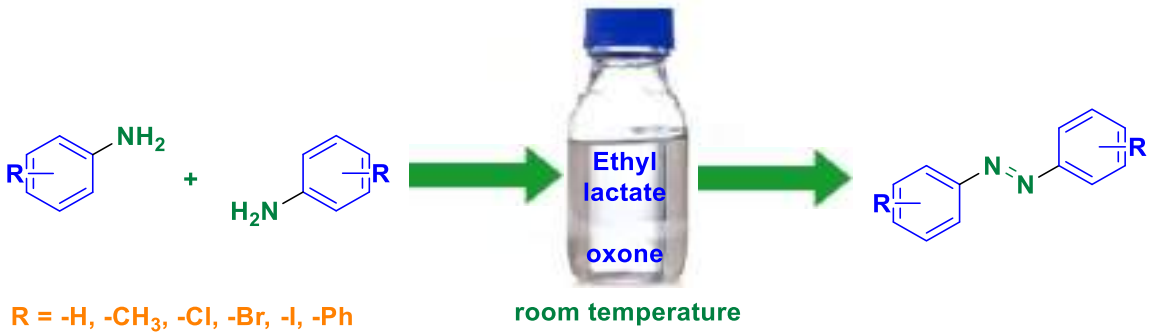
R = Aryl, Heterocyclic, Aliphatic
R_1, R_2 = Aryl, H, Alkyl, Heterocyclic, Alicyclic

In **Chapter IV** heterocyclic molecules based on indole are valuable and important structural unit that are present in numerous biologically active natural products, agrochemicals and pharmaceuticals. In this paper a facile one-pot three component coupling of indoles, aldehydes and amines has been attained in a metal-free, economical and eco-friendly L-ascorbic acid in water medium and an alternate route has been also developed by using PEG-300 in a catalyst-free condition at 60 °C. The salient features of this process are the operational simplicity of the method, mild reaction conditions, shorter reaction time, good yield of desired product and low-cost of acid catalyst and further catalyst-free condition.



R = Alkyl, Phenyl, Substituted Phenyl.
R_1= Alkyl, Phenyl.
R_2= H, Alkyl

In **Chapter V** inexpensive, environmental benign catalyst Ethyl lactate was used in synthesis of verities of azobenzene. Oxone was utilized as the oxidant and ethanol as the solvent in this protocol. The methodology proceeds without the use of toxic metal catalyst and avoids harsh reaction conditions. A green methodology is thus reported with synthesis of good yield of the product.



PREFACE

Carbon-hetero bond consisting group has been extensively used in the designing of various pharmaceutically significant compounds. These molecules also have their significant influence in the field of agrochemical industries as well. Apart from this, they are considered to be powerful starting materials for the construction of naturally occurring biological active compounds like amino acids, glycosides, naturally occurring heterocyclic compounds etc.

The present work describes methodologies for construction of various carbon-hetero bonds. The thesis starts with Chapter I, deals with a brief review on carbon-hetero bond formation reactions. Carbon-hetero functional group has been extensively used in the designing of various pharmaceutically significant compounds. Chapter II deals with a one pot conversion of effortlessly accessible primary and secondary amines to biologically active higher degree amines in water at room temperature. Chapter III describes green synthesis of thioamide through MCR (multi component reaction) of aldehyde, amine and sulfur catalyzed by Humic acid in solvent-free condition at100 ^{o}C. Chapter IV describes a facile one pot three component coupling of indoles, aldehydes and amines has been attained in a metal-free, economical and eco-friendly L-ascorbic acid in water medium and an alternate route has been also developed by using PEG-300 in a catalyst-free condition at 60 ^{o}C. Finally, at last Chapter V describes the synthesis of azobenzenes using Ethyl lactate as an efficient catalyst.

TABLE OF CONTENTS

CHAPTER I

Carbon hetero bond formation reactions and a brief overview

CHAPTER II

Room temperature direct reductive amination of carbonyl compounds by L-ascorbic acid–$NaBH_4$ in water

CHAPTER III

Humic acid catalyzed solvent-free green protocol for synthesis of thioamide

CHAPTER IV

Greener one-pot synthesis of 3-substituted indoles using L-ascorbic acid in water as green eco-friendly catalyst and alternatively using PEG-300 in catalyst-free condition

CHAPTER V

Ethyl lactate mediated transition metal-free efficient synthesis of azobenzenes

LIST OF TABLES

LIST OF SCHEMES

LIST OF FIGURES

LIST OF APPENDICES

APPENDIX A

List of Research Publications

1. "Room Temperature Direct Reductive Amination of Carbonyl compounds by L-ascorbic Acid – NaBH4 in Water." **Suvodip Mukherjee**, Gyan Chandra Pariyar, Bijeta Mitra, Pranab Ghosh*, Communicated to *Chemistry select* on April,**2022** with manuscript number: slct.202201022

2. "Humic acid catalyzed solvent-free green protocol for synthesis of thioamide." **Suvodip Mukherjee**, Gyan Chandra Pariyar, Bijeta Mitra, Pranab Ghosh*, Communicated to *Chemistry select* on June,**2022** with manuscript number: slct.202202168

3. "Greener One pot Synthesis of 3-Substituted Indoles using L-Ascorbic acid in water as green eco-friendly catalyst and alternatively using PEG-300 in catalyst -free condition". **Suvodip Mukherjee,** Gyan Chandra Pariyar, Pranab Ghosh*, (Communication under process.)

4. "Ethyl lactate mediated transition metal -free efficient synthesis of azobenzenes" Gyan Chandra Pariyar, Tandra Kundu, Bijeta Mitra, **Suvodip Mukherjee**, Pranab Ghosh*, *Chemistry Select*, **2020**, 5, 9781 –9786

5. "Organo-cu (ii) catalyst: an efficient synthesis of Substituted n-heterocycles via double Condensation/ tandem oxidationcyclization/elimination-cyclization reactions From easily accessible precursors", Bittu Saha, Bijeta Mitra, **Suvodip Mukherjee**, Raju Subba, Dhiraj Brahmin, Biswajit Sinha, Pranab Ghosh*, *RASAYAN J. Chem*., **2021**, 14, 2406-2412.

6. "Onion extract catalyzed novel synthesis of pyrazine." Hridoydip Ranjan Dasgupta, Suvodip Mukherjee, Pranab Ghosh*, *Asian journal of gren chemistry*, **2021**, 5, 235-247.

7. "Ascorbic Acid as an Efficient Organocatalyst for the Synthesis of 2-Substituted-2,3-dihydroquinazolin-4(1*H*) one and 2-Substituted Quinazolin-4(3H)-one in Water." Gyan Chandra Pariyar, Bijeta Mitra, **Suvodip Mukherjee**, Prof. Pranab Ghosh*, *Chemistry Select*, **2020,** 5, 104-108.

8. "A novel approach towards chemoselective reduction of nitro to amine." Hridoydip Ranjan Dasgupta, **Suvodip Mukherjee**, Pranab Ghosh*, *Tetrahedron Letters*, **2019**, 60, 151208.

9. "One pot three-component synthesis of 5-substituted 1*H*-tetrazole from aldehyde assisted by $(NH_4)_2Ce(SO_4)_4.2H_2O$, an efficient reusable catalyst." Bijeta Mitra, **Suvodip Mukherjee**, Gyan Chandra Pariyar, Pranab Ghosh*, *Tetrahedron Letters*, **2018**, 59, 1385-1389.

APPENDIX B

Poster Presentations

1. "**Novel protocol for one-pot three component synthesis of Dyhydroquinazolin-4(1*H*)-one**" by **Suvodip Mukherjee**, Gyan Chandra Pariyar, Pranab Ghosh* in the International Seminar on "Frontiers in Chemistry 2020" organized by DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH BENGAL, India, March, 2020.

2. "**A metal -free approach to Direct Reductive amination of Carbonyl Compounds in Water**", by **Suvodip Mukherjee** and Pranab Ghosh* in the International Seminar on "RECENT TRENDS IN CHEMISTRY (RTC-2019)" organized by DEPARTMENT OF CHEMISTRY, P.D WOMEN'S COLLEGE, JALPAIGURI, WEST BENGAL in association with INDIAN CHEMICAL SOCIETY, KOLKATA, January, 2019.

ABBREVIATION

Å	Angstrom
acac	Acetylacetonate
AcOH	Acetic acid
BDMS	Bromodimethylsulfonium bromide
BiNPs	Bismuth nanoparticles
br	Broad
cm	Centimeter
Cy	Cyclohexyl
d	Doublet
DCE	1,2-Dichloroethane
DMAP	4-Dimethylaminopyridine
DME	1,2–Dimethoxyethane
DMEDA	1,2-Dimethylethylenediamine
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	Fourier-transform infrared spectroscopy
g	gram/grams
h	hour/hours
HRMS	High-resolution mass spectroscopy
IBS	4-(1-imidazolium)-butane sulfonate
LDA	Lithium diisopropylamide
m	Multiplet
MHz	Mega hertz
min	minute/minutes
mL	millilitre
mmol	millimole
mol%	mole percent

MS	Molecular sieve
MW	microwave
NCTS	*N*-Cyano-*N*-phenyl-p-toluenesulfonamide
NHPI	*N*-Hydrophthalimide
nm	Nanometer
NMR	Nuclear magnetic resonance
°C	Degree Celsius
PMA	Phosphomolybdic acid
PC	Phosphatidylcholine
PEG	Polyethylene glycol
Phen	Phenyl
PMHS	Polymethylhydrosiloxane
RT	Room temperature
s	Singlet
SPhos	Alkyl 2-(trimethylsilyl)ethyl sulfoxides
t	Triplet
TBAF	Tetra-n-butylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBHP	*tert*-Butyl hydroperoxide
TBT	Tributyltin
t-BuOCl	*tert*-butyl hypochlorite
TCT	2,4,6-trichloro-1,3,5-triazine
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TfOH	Triflic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine

Chapter I

Carbon hetero bond formation reactions and a brief overview

I.A. Introduction to carbon-hetero bond

The major function of many organic compounds is often derived from the presence of heteroatoms in their structure. Presence of atoms like nitrogen, oxygen, phosphorous, sulfur etc. often amplifies the applicability of organic compounds for biological, agrochemical as well as vast field of chemistry. For instance, most of the major pharmaceuticals often consist of C-O, C-N or C-S bond and almost all natural products also have the same. Another advantage of these C-Heterocyclic ring formation in organic compounds is that, they can bind with metals or metal ions by complex formation and form stable compounds which have vast array of application in organic and even inorganic field. An easy example of such is chlorophyll and hemoglobin which are stabilized by the presence of nitrogen ligand. These compounds are also treated as a strong precursor for synthesis of many biological product which occur in nature like glycosides, amino acids etc. The applicability of these compound can be seen in many available drugs in current market.

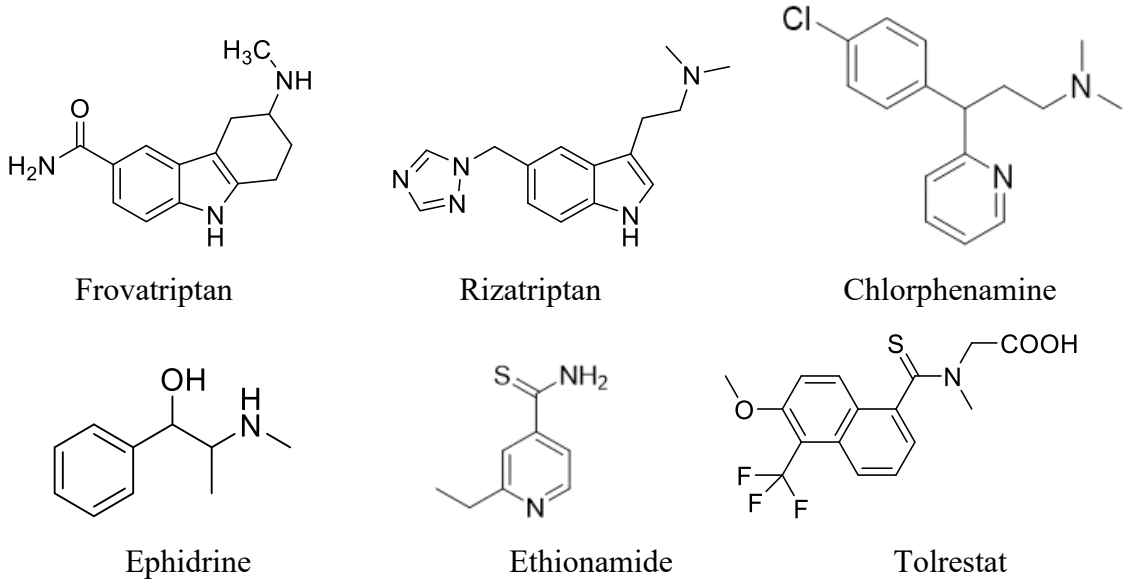


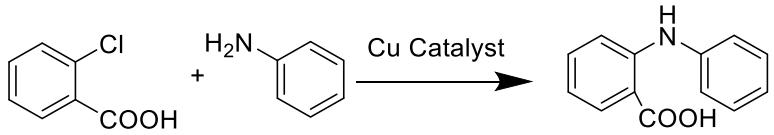
Figure I.1. Biologically active C-Hetero bonded compounds.

Various methodologies have been discovered for the synthesis of C-hetero compound synthesis reactions. Here we represent a brief review of the prominent work on formation of various C-hetero compound formation reactions.

I.A.1. C-N bond formation reaction

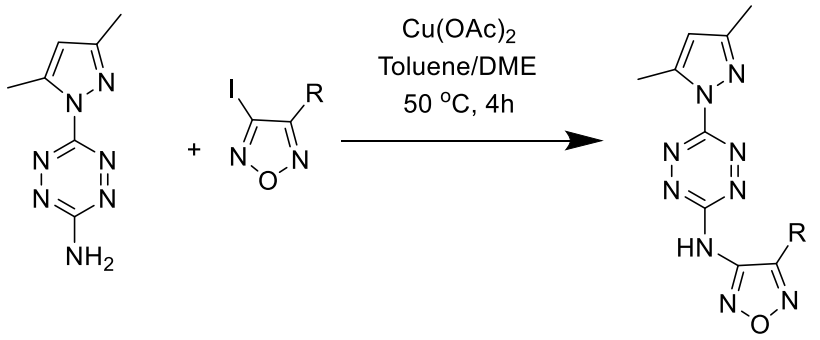
Compounds having C-N bond like, amines, enamines. Isocyanides, azides, imines, amides, lactums, carbamates, imides, thioamides, thioureas, amidines, sulfonamides, cyanamides, guanidines, urea and its derivatives, hydrazones, isocyanatesaziridines, nitro compounds and their derivatives etc. are extremely important today in organic and overall chemical fields. In recent years notable advantages have been found where other transition metals and even metal-

free conditions are also used. Metal catalyzed synthesis of C-N coupling reaction was used by Ullmann (Scheme I.1) and Goldberg in 1903[1,2]. They have used Cu as catalyst for C-N bond formation.



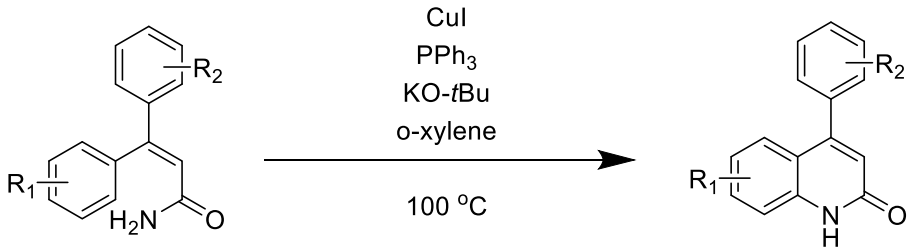
Scheme I.1. Synthesis of diphenyl amine by Cu catalyst.

In present time M. Yu. Antipin *et al.* developed a robust method for the coupling of a variety of furazanyl iodides with 1,2,4,5-tetrazines[3] (Scheme I.2) where they have employed $Cu(OAc)_2$ as catalyst at 50°C. Here electron-deficient nitrogen-rich heterocyclic iodides were coupled with electron-deficient nitrogen-rich heterocyclic amines to yield tetrazine.



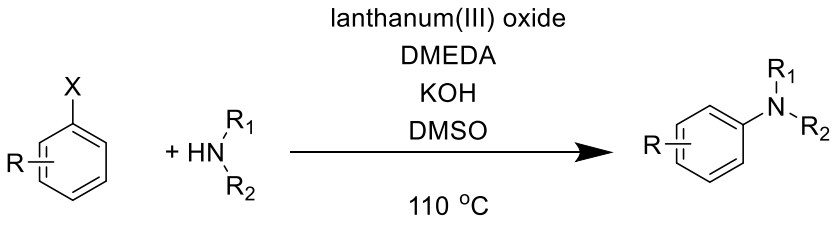
Scheme I.2. Coupling reaction of furazanyl iodides with 5-tetrazinylamines by $Cu(OAc)_2$.

A. Goggiamani *et al.* developed another Cu catalyzed protocol for construction of 2-quinolines based on an intramolecular C-N bond forming process[4] (Scheme I.3) . They produced good yield by using CuI and PPh_3 in presence of KO-*t*Bu at 100 °C in *o*-xylene.



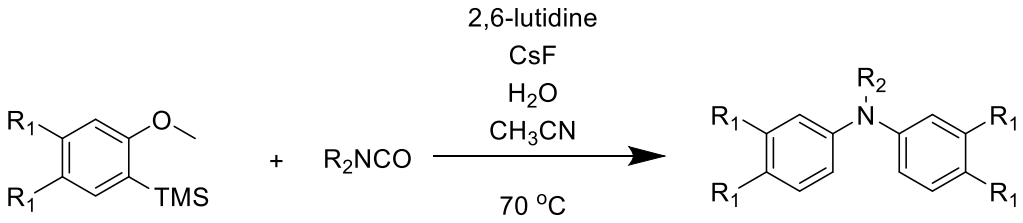
Scheme I.3. Synthesis of 2-quinolones by CuI in PPh_3 and KO-*t*Bu.

Other transition metals than Cu are also employed successfully for C-N bond formation reaction. Recently aryl halides are coupled with aromatic and heteroaromatic amines by Y. V. D. Nageswar *et al.* using lanthanum(III) oxide, DMEDA and KOH as base in DMSO[5] (Scheme I.4). It has been noticed that electron donating and withdrawing groups on iodobenzene and nitrogen nucleophile have no significant effect on the product yield of the C–N cross-coupled product.



Scheme I.4. Synthesis of *N*-arylated derivatives by lanthanum(III) oxide.

Nowadays, metal-free approach for a particular bond formation is of huge interest. Following that trend C-N bond formation has also been successfully done in metal-free condition. Coupling of isocyanates and benzynes have been discovered by J.C. Hsieh *et al.*[6]. Substituted ortho-(trimethylsilyl)phenyl triflate was reacted with different isocyanates in CsF as base in CH_3CN at 70 °C which produced corresponding substituted diphenylamine (Scheme I.5). This protocol tolerates various functional groups on both sides.

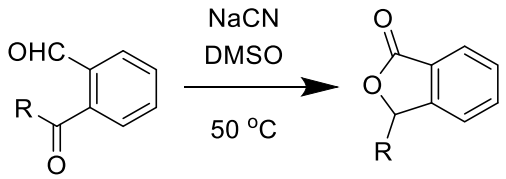


Scheme I.5. Coupling reaction of isocyanates 116 and benzynes by CsF.

I.A.2. C-O bond formation reaction

Bond formation between C-O bear huge importance in organic chemistry and vast list of publications are present on this specific topic. Large array of produccs can be synthesized following this bond formation between C-O like ethers, epoxides, lactols, carboxylic acids, lactones, carbonate derivatives, imino ethers, thiocarbamates, hemiacetals, esters, isoureas, thionoesters, nitrites and many more.

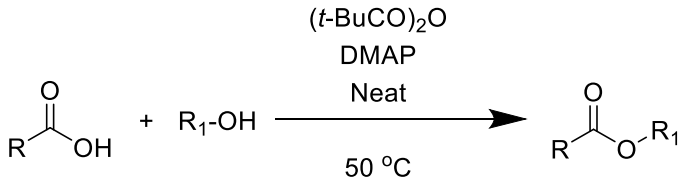
H.G. Schmalz *et al.* reported recently facile conversion of 2-formyl-arylketones into 3-substituted phthalides in presence of NaCN in DMSO at 50 °C[7]. This reqction is explored in a Cannizarro-Tishchenko-type reaction under nucleophile catalysis (NaCN) or under photochemical conditions (Scheme I.6).



Scheme I.6. Synthesis of 3-substituted phthalides in NaCN and DMSO.

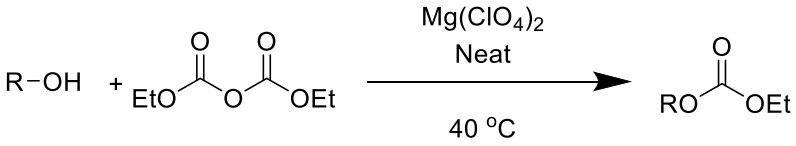
K. Ishihara *et al.* explored esterification by only a 0.05−2 mol % of DMAP with alcohol and carboxylic acids[8] of various types to produce good yield of products (Scheme I.7). The process

has been done under auxiliary base- and solvent-free conditions to give the corresponding esters. Further they have recycled the polystyrene supported DMAP several times and reused.



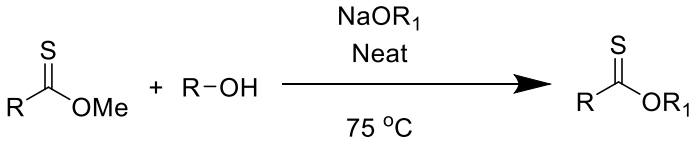
Scheme I. 7. Synthesis of ester in DMAP in neat condition.

Aryl or alkyl carbonates are another important group formed by C-O bond formation reactions. L. Sambri *et al.* reported an easy conversion of alcohol to aryl and alkyl carbonates[9] by using $Mg(ClO_4)_2$ in solvent-free condition in presence of 1,3-dicarbonyl compound (Scheme I.8). Versatile products have been achieved by this reaction process in good yield.



Scheme I.8. Synthesis of aryl and alkyl ethyl carbonates by $Mg(ClO_4)_2$ in solvent-free condition.

A recent advancement of thionoesters in very good yields is reported by C.M. Friesen *et al.* in alcohol as solvent in various sodium alkoxides[10]. This process produces excellent yield while methanol by product is simultaneously separated from the reaction mixture (Scheme I.9). Benzyl and alkyl thionobenzoates and thionoheterobenzoates were competently prepared using numerous alcohols.

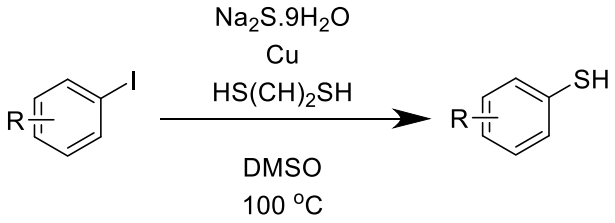


Scheme I.9. Transesterification of Thionoesters in presence of sodium alkoxide in neat condition.

I.A.3. C-S bond formation reaction

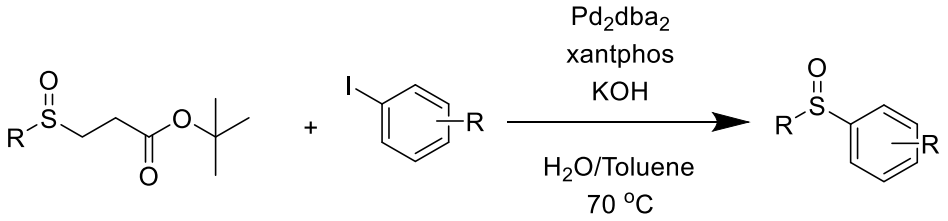
Vast array of compounds which has huge importance in organic chemistry bear C-S bond in their structures such as, thiophenols, thioesters, sulfides, sulfoxides, sulfones, sulfonic acids, sulfonamides, sulfanamides, thiosulfonates, isothioureas, thiocyanates etc. Therefore, for synthesis of those important compounds thorough study of C-S bond formation reactions are purely of interest.

Y. Liu *et al.* reported conversion of iodoarenes into thiophenol by easily available Na_2S, 1,2-Ethanedithiol in DMSO at 100 ^oC[11]. Copper is used as catalyst in this process and any iodine derivative can produce very good yield in this process (Scheme I.10).



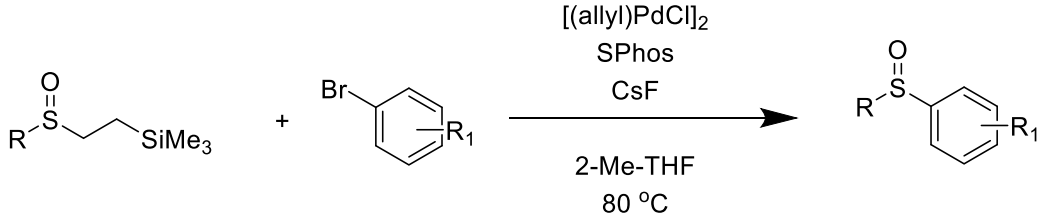
Scheme I.10. Synthesis of thioamides by Cu as catalyst in DMSO.

Another important compound is aryl sulphoxide investigated by G. Poli *et al.* Paladium is used as catalyst in this case and arylation of sulfenate anions produced from β-sulfinyl esters is generated under basic biphasic conditions in this reaction[12]. This reaction gives a simple, mild, efficient route to aryl sulfoxides in excellent yields (Scheme I.11).



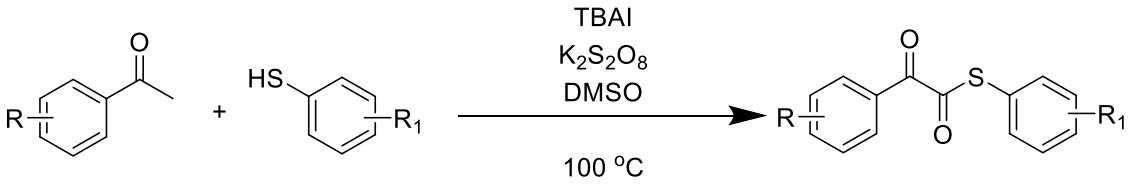
Scheme I.11. Synthesis of aryl sulfoxides catalyzed by Pd.

P.J. Walsh *et al.* reported mild preparation of aryl sulfones in Pd catalyzed condition using alkyl 2-(trimethylsilyl)ethyl sulfoxides in CsF and 2-Me-THF at 80 ^oC[13]. The success of this process lies within the use of mild reaction condition sue to base sensitivity of the reactants, intermediated and products its often difficult to achieve good yield. This protocol however furnishes high yield with various derivatives of the reactants (Scheme I.12).



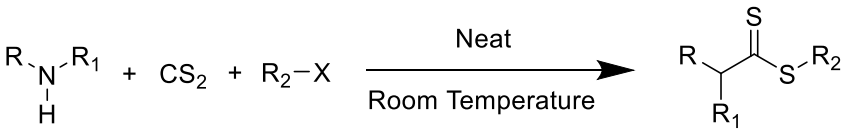
Scheme I.12. Synthesis of sulphones in Pd catalyzed THF medium.

In recent development of C-S bond formation F. Yu *et al.* reported metal-free thioester formation from methyl ketones in presence of TBAI[14]. DMSO is used as solvent in this protocol and the reaction is done at 100 ^oC. This reaction offers large scale production option for thioesters and it has broad functional group tolerance (Scheme I.13).



Scheme I..13. Synthesis of α-ketothioesters in metal-free condition.

Added, in metal-free approach for C-S bond formation M. R. Saidi *et al.* reported a mild and efficient method for synthesis of dithiocarbamates in neat condition at room temperature[15] by amines, carbon disulphide and aryl and alkyl halides with high yield of products. Catalyst-free process at room temperature and without using any solvent makes this process green and sustainable too (Scheme I.14).

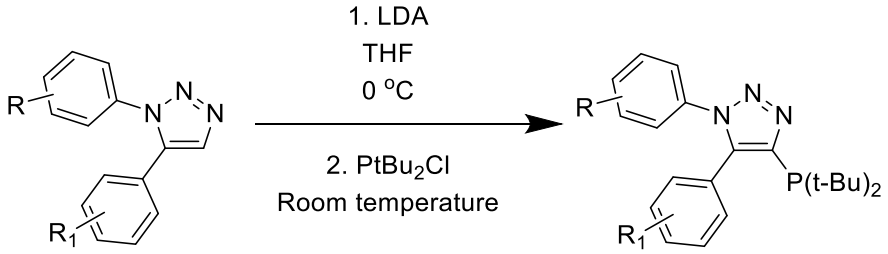


Scheme I.14. Synthesis of dithiocarbamates in solvent-free condition at room temperature.

I.A.4. C-P bond formation reaction

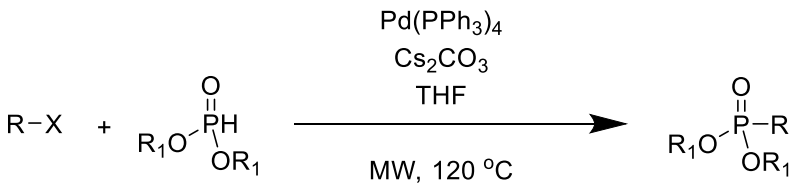
Various compounds with C-P hetero bond also have utmost importance in organic chemistry like phosphines, phosphine oxides, phosphonates, thiophosphines, phosphinates and its acid derivatives, thiophosphonates and its derivatives etc.

Monophosphine ligands are an important class of ligands and X. Zhang *et al.* proposed preparation of triazole based monophosphine ligands via cycloaddition[16]. These ligands complexing with Pd provides a very efficient catalyst for Suzuki-Miyaura coupling and also applicable in amination reactions of aryl chlorides (Scheme I.15).



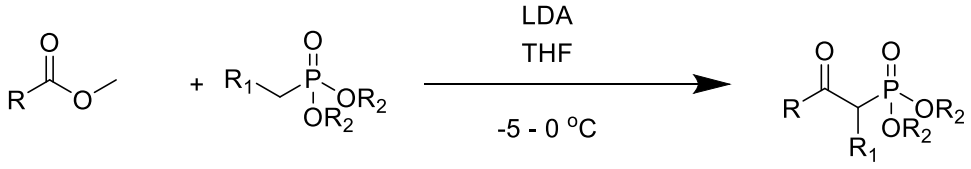
Scheme I.15. Synthesis of Triazole-based monophosphine ligands by cycloaddition.

J. Stawinski *et al.* reported production of phosphonates using palladium catalyst, $Pd(PPh_3)_4$[17]. They reported a cross coupling reaction between aryl and vinyl halides at 120 °C under microwave irradiation with various H-phosphonate diesters (Scheme I.16). The reaction occurs within 10 minutes with retention in configuration.



Scheme I.16. Synthesis of phosphonates by Pd catalyzed reaction under MW irradiation.

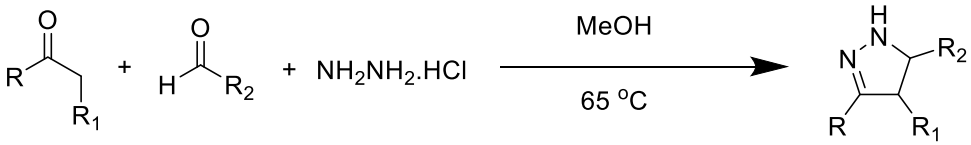
Another advancement of C-P bond formation reaction has been reported by J. Y. L. Chung *et al.* for synthesis of β-Ketophosphonates by condensation of esters and phosphonates[18]. The reaction is catalyzed by Lithium diisopropylamide and temperature requirement is 0 °C (Scheme I.17). This protocol provides prominent yield of the product with promise of easy operation and large scalability.



Scheme I.17. Synthesis of β-Ketophosphonates by LDA.

I.A.5. Synthesis of pyrazolines

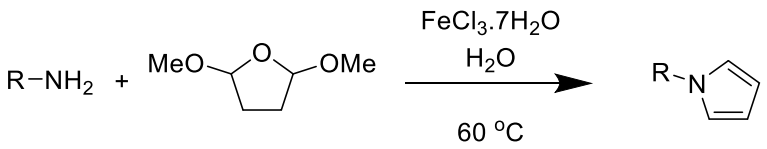
In recent years, heterocyclic motif formation by C-N bond formation have also gained lots of interest among chemists. Such a heterocycle formation is reported by R. Faessler *et al.* for the formation of substituted pyrazoles in a one -pot three component synthesis from ketones, aldehydes and hydzine monochloride[19]. This reported protocol readily produces desired pyrazoles under metal-free condition in MeOH as solvent at 65 °C. A variety of pyrazoles can be obtained with good yield by this process (Scheme I.18).



Scheme 1.18. One -pot synthesis of pyrazoles in metal-free condition in MeOH.

I.A.6. Synthesis of pyrroles

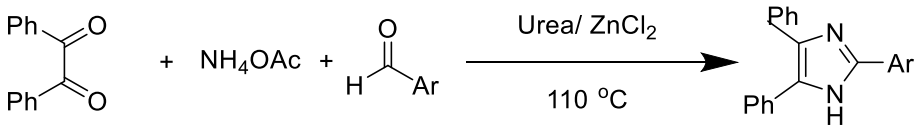
Pyrroles are generally prepared by conversional Paal-Knorr pyrrole condensation. Recently, M. R. Saidi *et al.* reported an efficient method[20] for *N*-substituted pyrrole synthesis by condensation of 2,5-dimethoxytetrahydrofuran with several amines, sulfonamines in water in the presence of a catalytic quantity of iron(III) chloride. This reaction is done in mild reaction condition at 60 °C (Scheme I.19).



Scheme I.19. *N*-substituted pyrroles in the presence of a catalytic amount of iron(III) chloride.

I.A.7. Synthesis of imidazoles

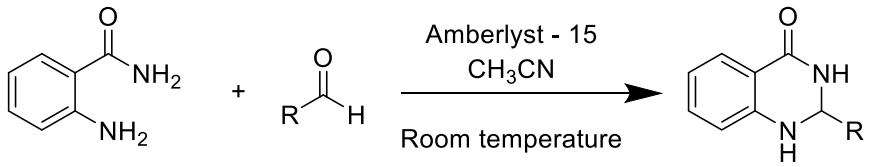
C. Ochoa-Puentes *et al.* reported an easy and efficient method for the preparation of imidazole from dicarbonyl compound along with ammonium acetate and organic aldehyde[21]. Mild reaction condition is used as only $ZnCl_2$/ Urea is employed as catalyst at 110 °C. The reaction completes within 30 minutes adds advantage to the protocol (Scheme I.20).



Scheme I.20. Synthesis of imidazoles from dicarbonyl compounds in urea/$ZnCl_2$.

I.A.8. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

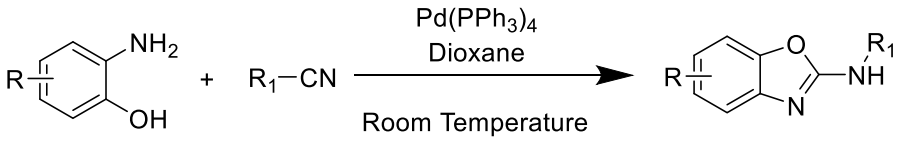
Quinazolinone is one of the most important heterocycles having C-N bond. An advancement of the study has been done by P. V. N. S. Murthy *et al.* reported green and efficient synthesis of 2,3-dihydro quinazolin-4(1*H*)-ones using Amberlyst-15 as a catalyst at room temperature[22]. A number of dihydro quinazolinone derivatives have been synthesized successfully from aldehyde and 2-aminobenzamide. Acetonitrile has been used as solvent in this reaction (Scheme I.21).



Scheme I.21. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones catalyzed by Amberlyst-15.

I.A.9. Synthesis of 2-aminobenzoxazoles

2-aminobenzoxazoles exhibit C-N as well as C-O bond formation reaction. B. Liu *et al.* reported efficient method of preparation of palladium catalyzed 2-aminobenzoxazoles. Isocyanides with *o*-amino phenols in aerobic condition at room temperature[23]. The scope of this reaction is also explored by them for synthesis of other *N*-hetero systems (Scheme I.22).



Scheme I.22. Synthesis of 2-aminobenzoxazoles catalyzed by palladium.

I.B. Conclusion

In this chapter we have observed immense importance of carbon- hetero bond formation reaction in present day chemical, biological and pharmaceutical advancements. Moreover, any bioactive natural product also has C-hetero bond present in its structure. We have also observed cyclisation of various precursors into heterocyclic compounds to yield important parts of bioactive motif. The scope in this topic is definitely huge and we have tried to explore the same. In many cases we have observed use of toxic metals, costly catalysts, hazardous reaction conditions for synthesis of C-hetero bonds. Further solvents also play an important role in making the protocol hazardous and economically unfavourable. Therefore, we felt necessary to step towards greener, cost effective, environmentally sustainable catalyst and solvent mediated formation of C-hetero bonds in a straightforward approach.

I.C. References

References are given in BIBLIOGRAPHY under Chapter I.

Chapter II

Room Temperature Direct Reductive Amination of Carbonyl compounds by L-ascorbic acid – $NaBH_4$ in Water

II.A. Introduction

Amines are functional groups containing basic nitrogen atom. As the nitrogen bears a lone pair of electrons, it is a lewis base. Amines are previously prepared from ammonia where one or more hydrogen atoms are replaces by alkyl or aryl groups. Presence of hydrogen bond influences the property of primary and secondary amines significantly but tertiary amines do not have any influence of hydrogen. Due to that amine shows good solubility in water owing to hydrogen bonding, though amines with larger substituents are lipophilic in nature. Amines are ubiquitous in biological field as they are structural units of amino acids. For instance, a decaying fish smells of trimethyl amine as a result of breakdown in amino acids present in it. Neurotransmitters like norepinephrine, epinephrine, serotonin, dopamine and histamine are amines.

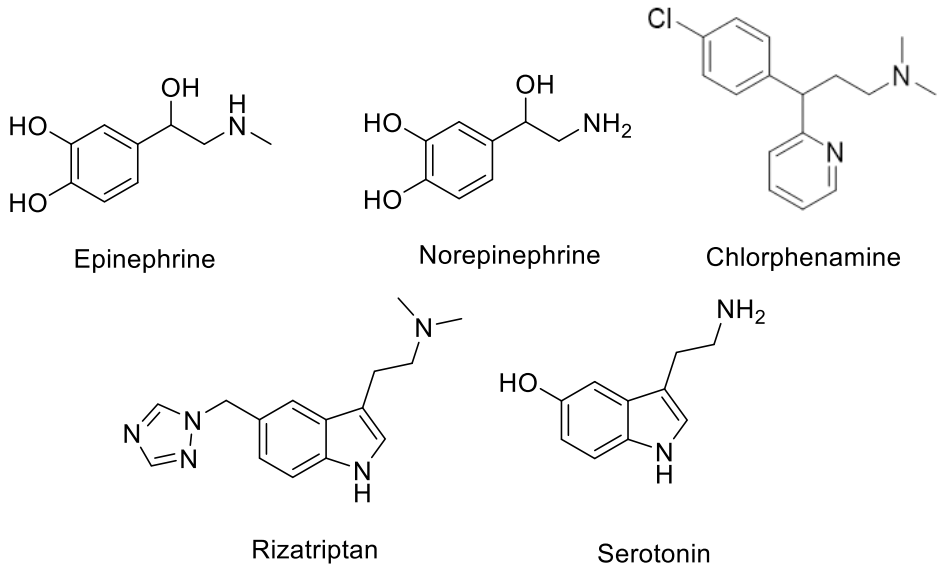


Figure II.1. Neurotransmitters containing amines.

Most common positively charged moieties in proteins are protonated amino groups ($-NH_3^+$). Specially in amino acids like lysine. Further, the anionic polymer of DNA is also bound to different amine containing proteins. Primary amines are also used majorly as starting material of many azo dyes such as Methyl orange, Ponceau, Direct brown 138, Sunset yellow FCF etc. Around the world approximately 40-42% drugs contain amine functional groups it their structure. A few examples are, opiate analgesics like codeine, morphine and heroin are tertiary amines. Amoxapine, nortriptyline and desipramine are secondary amines and tricyclic antidepressants. Ephedrine and phenylephrine are amine hydrochlorides and are applied as decongestants. Chlorpromazine is a tranquilizer that sedates but without inducing sleep. Chlorpheniramine is an antihistamine that aids to discharge allergic conditions due to cold, insect bites, hay fever, itchy skin and stings.

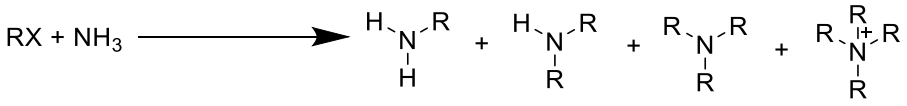
In natural gas industry, to remove CO_2 and H_2S in refining process various amines are employed such as, Aqueous monoethanolamine (MEA), diglycolamine (DGA), diisopropanolamine (DIPA) diethanolamine (DEA) and methyldiethanolamine (MDEA). Amines also posess the ability to reduce greenhouse gasses from the environment. This type of gas treatment by amines are also known as amine scrubbing, gas sweetening and acid gas removal.

Dimethylethylamine, cyclohexylamine, a variety of diamines such as 4,4-diaminodicyclohexylmethane and multifunctional amines like triethylenetetramine tetraethylenepentamine are often used as epoxy resin curing agents. The lone pair electrons present on nitrogen in amine attacks the outermost carbon in oxirane ring of the epoxy resin that relieves stress on the epoxide and leads to the reaction.

Though amines are easily handleable compounds, low molecular weight amines are often slightly toxic in nature whereas complex members of the class like heroin or strychnine can also be extremely bioactive in nature.

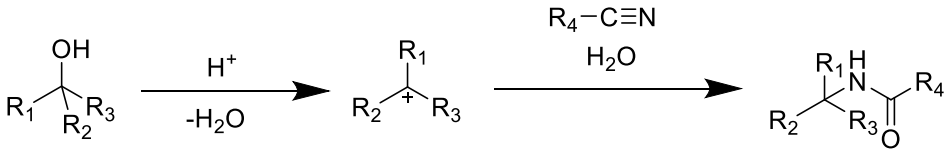
II.B. Background and objectives

In large scale alkyl amines are prepared by amination of alcohols by ammonia. In laboratory another facile route is formation of amines by alkylation of ammonia by haloalkanes (Scheme II.1). But in such reactions a major drawback is formation of mixture of primary, secondary and tertiary amines as a product along with ammonium salt formation. Use of excess ammonia often elevates the yield of primary amine formation but lacks in formation of secondary and tertiary amines in the process. Further, the reaction is not completely -free of unwanted byproducts. Also following the route, a huge amount of ammonia is often wasted considering the reaction requirements.



Scheme II.1. Preparation of amines by amination of alkyl halides.

To overcome the hurdles another method is suggested in Ritter's reaction[1] in which disubstituted alkenes reacts with HCN in a strong acid catalyzed condition (Scheme II.2). This method is also employed industrially for production of mainly tertiary amines. Clearly this reaction lacks in ease of handling of the reactants and definitely a hazardous alternative.

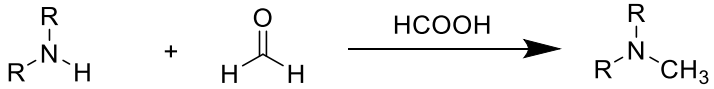


Scheme II.2. Synthesis of amine from cyanide in presence of strong acid.

Hydroamination has also been practiced as an alternate catalyzed by zeolite based solid acids. Many reductive routes have also been explored like hydrogenation using hydrogen and nickel as catalyst. *N*-containing functional groups from which amines have been prepared are azides, imines, oximes, amides, nitriles and nitro groups. But these protocols suffer from functional group sensitivity as it reduces other functional groups too. Further use of metal is always a limitation towards green synthetic approach. $LiAlH_4$ is also commonly applied for reduction purpose.

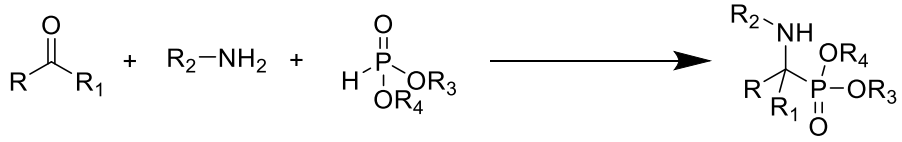
II.B.1. Specialized methods for synthesis of substituted amines

Many advancements have been reported for synthesis of amines and their derivatives. W. Eschweiler *et al.* reported in 1905 preparation of amines from aldehyde using formic acid as catalyst[2]. This simple reaction allows the synthesis of tertiary methyl amines from secondary amines by treating it with formaldehyde (Scheme II.3). In this reaction the formate ion is utilised as hydride donor for the reduction of iminium ion formed. So overall it can be termed as reductive amination too. By this process formation of quaternary salts of amines is not possible.



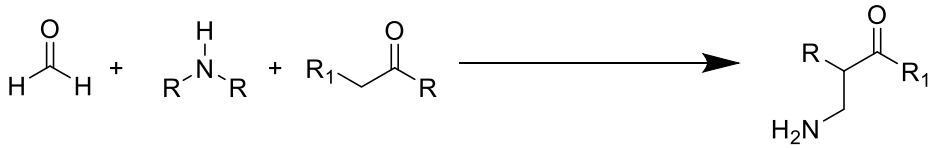
Scheme II.3. Synthesis of amine from formaldehyde and secondary amines catalyzed by formic acid.

The Kabachnik-Fields Reaction shows vast importance in drug discovery research for the formation of peptidomimetic compounds. In this reaction carbonyl compound couples with amine and a hydrophosphoryl compound which leads to the formation of α-aminophosphonates[3]. Initially very few aldehydes were successfully used in this method for preparation of respective α-aminophosphonates. But advancement of this reaction now permits use of various carbonyl compound even sterically hindered carbonyl compounds can be used as starting materials (Scheme II.4).



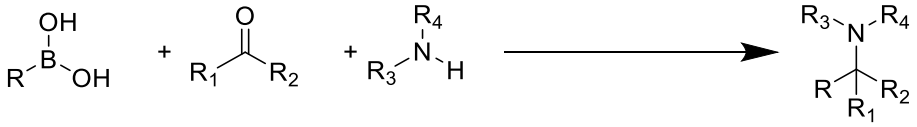
Scheme II.4. Synthesis of α-aminophosphonates by condensation of carbonyl, amine and hydrophosphoryl compound.

Another multi component condensation of aldehyde having no alpha hydrogens with primary and secondary amine and another enolizable carbonyl compound produces aminomethylated corresponding products (Scheme II.5). This reaction is well known as Mannich reaction[4] and in this reaction the iminium derivative of the aldehyde acts as the acceptor. Mannich reaction is vastly involved in many biosynthetic pathways mainly for alkaloids.



Scheme II.5. Multicomponent condensation to produce aminomethylated products.

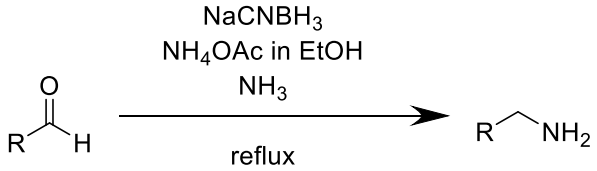
An advancement of previous process is known as Petasis reaction or also known as Boronic Acid Mannich Reaction[5]. In this multicomponent reaction, amines and their derivatives are prepared via reaction of imine with organic ligands of boronic acids, where boronic acid acts as a nucleophile (Scheme II.6). The role of boronic acid is very much similar to the role of enolizable carbonyl compound in mannich reaction.



Scheme II.6. Multicomponent synthesis of amine and its derivatives by boronic acid.

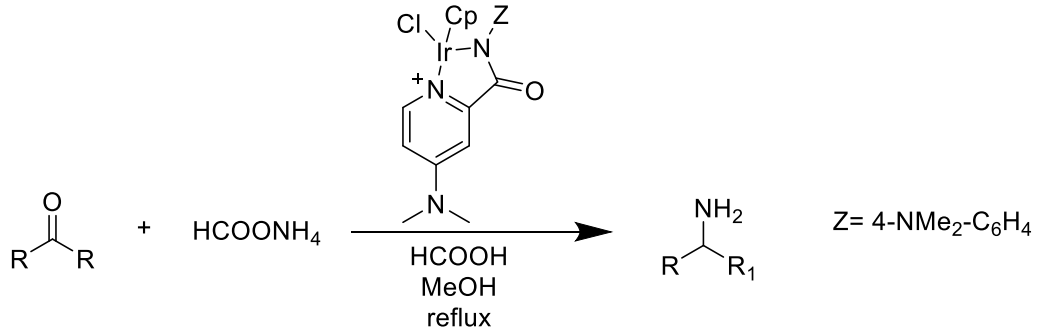
II.B.2. Modern approach towards reductive amination

M. S. M. Timmer *et al.* reported metal hydride ammonia mediated reductive amination of aldehydes[6]. In this reaction primary amines are selectively prepared without forming any unwanted byproducts such as secondary and tertiary amines. This protocol is applicable on a range of aldehydes, even on in situ formed aldehydes produced by Vasella reaction[7].



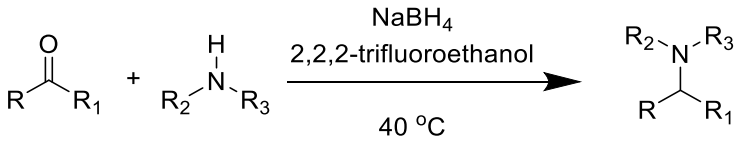
Scheme II.7. Synthesis of primary amines in metal hydride/ammonia.

M. Watanabe *et al.* reported another facile method recently for synthesis of primary amines from ketones by direct reductive amination[8]. The reaction is catalyzed by Cp*Ir complexes bearing a 2-picolinamide moiety. In this reaction ammonium formate acts as both nitrogen and hydrogen source (Scheme II.8).



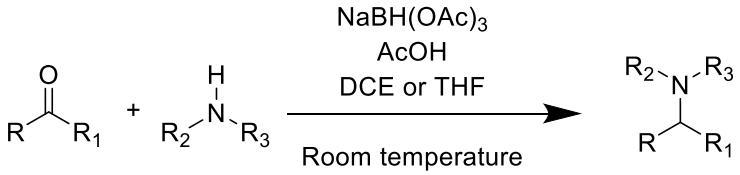
Scheme II.8. Synthesis of primary amine by Cp-Ir complex from ketones.

S. Khaksar *et al.* reported alternative way of synthesis of substituted amine by a mild and convenient procedure[9]. This method starts with primary and secondary amines and ketones to produce *N*,*N*-dimethyl tertiary amines. Sodium borohydride is used as reducing agent without use of any catalyst in 2,2,2-trifluoroethanol at 40 ^{o}C (Scheme II.9). An advantage of this method is the reusability of the solvent.



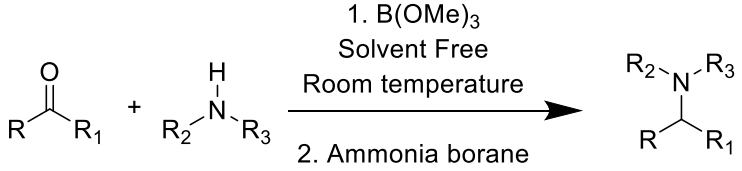
Scheme II.9. Synthesis of tertiary amine from primary and secondary amines by sodium borohydride in 2,2,2-trifluoroethanol.

Sodium triacetoxyborohydride has also been employed as selective reducing agent for reductive amination of various aldehydes and ketones by R. D. Shah *et al.*[10]. 1,2-Dichloroethane (DCE) is used as solvent in this reaction. But this reaction also shows prominent result with tetrahydrofuran and even acetonitrile (Scheme II.10). In special cases of ketones as reactants, acetic acid can be used as catalyst too. This reaction has a huge functional group tolerance such as nitro, cyano and even unsaturation of C-C bond.



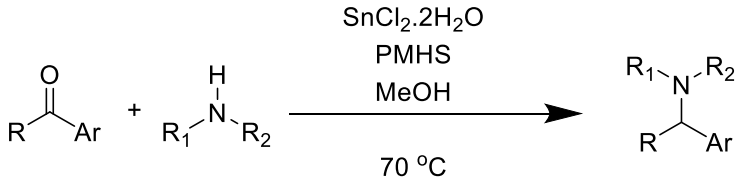
Scheme II.10. Synthesis of substituted amines by Sodium triacetoxyborohydride.

A very recent study on reductive amination successfully achieves the desired product in a solvent -free condition by using trimethyl borate as catalyst. This reaction was reported by A. Singh *et al.*[11] (Scheme II.11). This reductive amination process successfully converts aromatic and aliphatic aldehydes and ketones into aliphatic and aromatic substituted amines respectively in which borane itself acts as reductant as well. The only drawback of this process being its time requirement which is up to 36 hours.



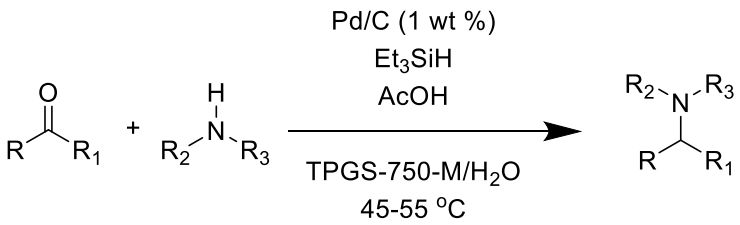
Scheme II.11. Synthesis of substituted amines in solvent -free condition by trimethyl borate.

N. Kumar *et al.* developed Chemoselective reductive amination process using stannous chloride as catalyst in presence of polymethylhydrosiloxane as reductant[12]. Methanol is used as solvent in this reaction and the reaction is optimized at 70 ºC (Scheme II.12). Various aromatic carbonyl compounds produce respective secondary and tertiary amines in good yield in this process.



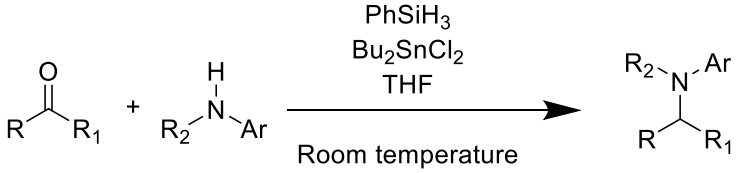
Scheme II.12. Synthesis of substituted amines by stannous chloride.

Another very recent exploration of reductive amination has been reported by B. H. Lipshutz *et al.*[13].This reaction is mediated by hydrophobic cores of nanomicelles, an environmentally benign surfactant TPGS-750-M, in water. A broad range of aldehydes, ketones with amines undergo this protocol under mild condition. Presence of 0.20 mol % Pd/C and triethylsilane is required for satisfactory yield of desired product of secondary and tertiary amines (Scheme II.13). The use of TPGS-750-M makes this protocol costly which can be a downside of this methodology.



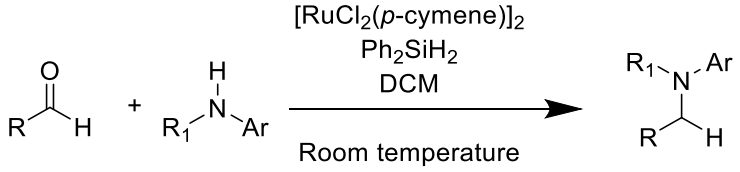
Scheme II.13. Synthesis of substituted amines by hydrophobic cores of nanomicelles in water.

W. Xiao *et al.* developed dibutyltin dichloride catalyzed direct reductive amination of aldehydes and ketones[14]. Phenylsilane is used as reductant in this case in presence of THF as solvent. The reaction produces good yield of desired product even at room temperature (Scheme II.14). Anilines and dialkyl amines give good product yield in this reaction but an exception for monoalkylamines is a boundary of the reaction. Further this reaction reveals a time requirement of up to 24 hours which is another limitation of this methodology.



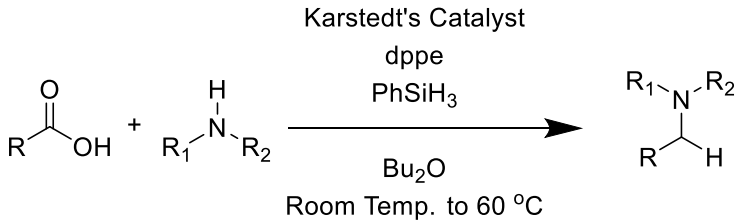
Scheme II.14. Direct reductive amination of aldehydes and ketones in the presence of phenylsilane.

Reductive amination using $[RuCl_2(p\text{-cymene})]_2/Ph_2SiH_2$ catalytic system has been introduced by L. Chen *et al.*[15]. Aldehydes with various substituted anilines produced good yield of desired product in this reaction protocol. DCM is used as solvent at room temperature for this protocol (Scheme II.15). Secondary as well as tertiary amines has been successfully synthesized by this reaction. In terms of functional group tolerance this reaction exhibits wide range of functional groups tolerance such as, CN, NO_2, COOMe, F, Cl, OMe, Me, Br, alkyl and furyl. The only notable drawback is difficulty to produce $[RuCl_2(p\text{-cymene})]_2/Ph_2SiH_2$ catalytic system in economic condition.



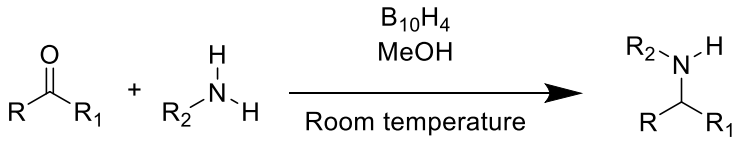
Scheme II.15. Synthesis of secondary and tertiary amines in $[RuCl_2(p\text{-cymene})]_2/Ph_2SiH_2$ catalytic system.

Another route of *N*-alkyl amine formation is suggested by M. Beller *et al.* This methodology starts with carboxylic acid in presence of silanes, 1,2-Bis(diphenylphosphino)ethane (dppe) and Karstedt's catalyst [16]. The hydride source as silane enables C-N bond construction in an efficient and mild way in this reaction (Scheme II.16). A wide range of alkylated secondary and tertiary amine can be achieved by this reaction process. Some notable amines like bioactive compound Cinacalcet HCl and fluoroalkyl-substituted anilines has been successfully prepared by this process.



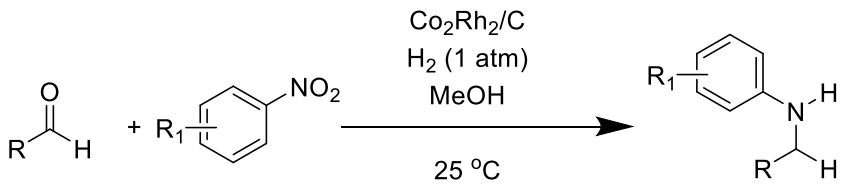
Scheme II.16. Synthesis of alkylated secondary and tertiary amines using Karstedt's catalyst and silanes.

An easy and efficient reductive amination of carbonyls with amines is reported by C. M. Yoon *et al.* using decaborane in methanol[17]. Room temperature is maintained during the process under nitrogen atmosphere to control high reactivity of decaborane (Scheme II.17). Another limitation of the reaction is inability to produce tertiary amines.



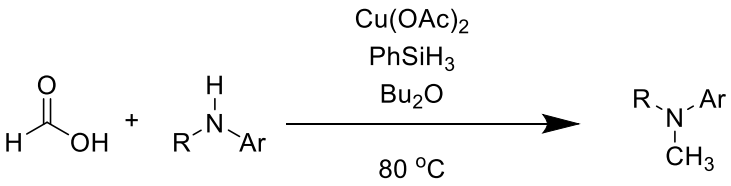
Scheme II.17. Synthesis of secondary amines using decaborane in methanol.

A distinct methodology for synthesis of substituted amines by reductive amination is reported by Y. K. Chung *et al.* using Cobalt-rhodium heterobimetallic nanoparticles[18]. Aromatic nitro compounds are used as precursor of desired substituted amines and the nitro compounds are reacted with aldehydes under mild condition at 25 °C. 1 atm of H_2 pressure is required throughout the reaction for reduction purpose. Reusability of catalyst and gram scale production of substituted amines are two major highlights of this reaction methodology (Scheme II.18). But use of metal catalyst and costly reaction setup can be considered as limitation of the process.



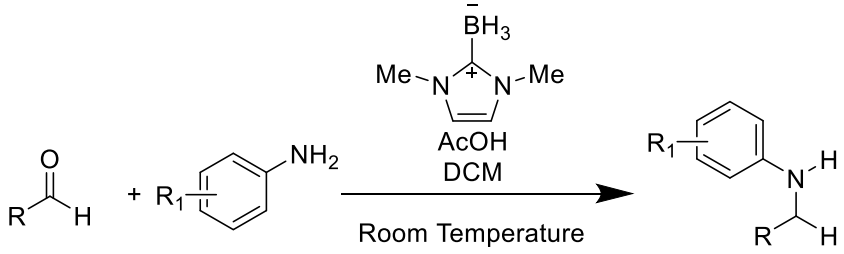
Scheme II.18. Synthesis of secondary amines using Cobalt-rhodium heterobimetallic nanoparticles.

Another copper catalyzed protocol for reductive methylation was formulated by L.N. He *et al.*[19]. By this protocol amines and imines were successfully condensed with formic acid in presence of phenyl silane as reducing agent to produce corresponding substituted amines. Bu_2O is applied as solvent at 80 °C. Copper acetate is used as catalyst in this method (Scheme II.19). Use of metal catalyst is a drawback in this case.



Scheme II.19. Synthesis of methylated anilines catalyzed by copper in presence of phenyl silane.

D. P. Curran *et al.* proposed reductive amination by *N*-heterocyclic carbene boranes (NHC-boranes)[20]. Carbene boranes like diMe-Imd-BH_3 are one of the most nucleophilic classes of neutral hydride donors. Definitely this heterocycle is yet to be explored to its full potential. Highly electron poor bonds like C=N and C=C provide hydrogenation products in addition with stable borylated products. Various aldehydes with aniline produce corresponding substituted amines in this process. Difficulty in catalyst preparation can be a drawback in this process.



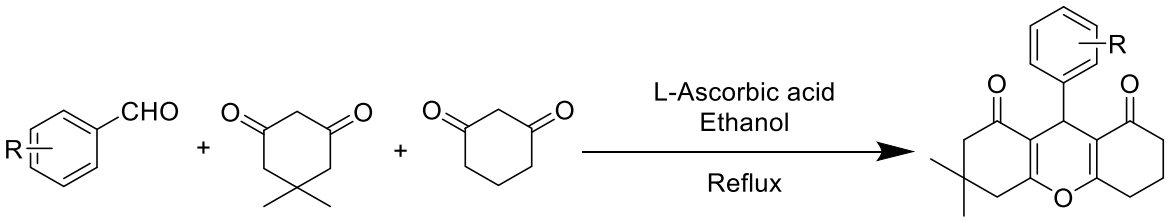
Scheme II.20. Synthesis of substituted anilines using diMe-Imd-BH_3.

II.B.3. Background of L-ascorbic acid in organic synthesis

In recent times organo catalyts mediated reaction have gained ample interest due to its greener approach towards synthesis of organic compounds as a substitute to metal catalysts. The superiority of organ catalysts over metal catalysts lies within their inexpensiveness, ease of

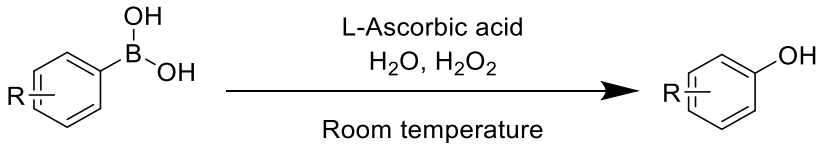
availability, environmental sustainability, easy handling, nontoxic nature[21]. L-ascorbic acid is known to mankind for a very long time as vitamin-C. L-ascorbic has exceptional medicinal values to cure numerous diseases. However, application of L-ascorbic acid as organo catalyst was very little explored up to later part of twentieth century. After that period of time L-ascorbic acid has been proven to be effective organo catalyst for modelling synthetic route to many biologically significant compounds and chemotherapeutic agents.

In 2014 E.H Chung *et al.* synthesis of 3,4,6,7- tetrahydro-3,3-dimethyl-9-phenyl-2*H*-xanthene-1,8(5*H*,9*H*)-diones with ascorbic acid as catalyst in ethanol[22]. The reaction takes place in reflux condition and reported good yields of desired xanthene dione derivatives (Scheme II.21).



Scheme II.21. Synthesis of 3,4,6,7-tetrahydro-3,3-dimethyl-9-phenyl- 2*H*-xanthene-1,8(5*H*,9*H*)-diones catalyzed by ascorbic acid.

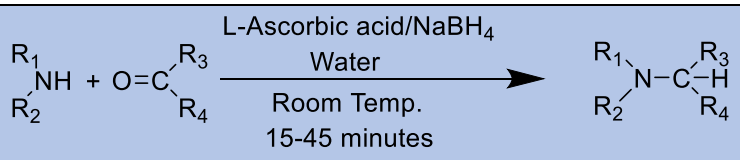
Another prominent organic synthesis of phenol derivatives reported by U. Bora *et al.* catalyzed by L-ascorbic acid in water and hydrogen peroxide[23]. Aryl boronic acids were used as precursor for the reaction and good yield of corresponding phenols were reported at room temperature (Scheme II.22).



Scheme II.22. Synthesis of phenols from aryl boronic acid by using ascorbic acid.

II.C. Present Work

Here we are reporting a novel, biomimetic concept for the direct reductive amination of aldehyde and ketones is developed which uses largely available, low cost and harmless L-ascorbic acid as sustainable, versatile, non-toxic catalyst and $NaBH_4$ as a reductant. Described herein is a one -pot conversion of effortlessly accessible primary and secondary amines to biologically active higher degree amines in water at room temperature. The mild condition, environmentally benign by-products and broad scope of makes this transformation very useful.



1 **2** **3**

Scheme II.23. Direct reductive amination in L-ascorbic acid and water at room temperature.

II.C.1 Result and discussion

Preliminary study was carried out to study the feasibility and reaction conditions of the imine reduction and direct reductive amination. $NaBH_4$ is selected as reducing agent over other available options due to its ability to rapidly reduce the imine to corresponding desired amine. The obstructing possibility is the $NaBH_4$ with water produces a low hydrogen yield due to pH stabilization of reaction medium, which is caused by formation of strongly basic metaborate ions. The addition of L-ascorbic acid delays the formation of the metaborate ions by shifting the pH of the reaction medium to lower values which eventually increases the H-Yield[24]. In order to establish superiority of L-ascorbic acid over other reducing agents we attempted various catalyst or reductant couples like PTSA/$NaBH_4$ (Table II.1, entry 1), H_3BO_3/ $NaBH_4$ (Table II.1, entry 2), Ph-COOH/$NaBH_4$ (Table II.1, entry 4), CH_3COOH/ $NaBH_4$ (Table II.1, entry 5). Among these PTSA/$NaBH_4$ (Table II.1, entry 1) and H_3BO_3/$NaBH_4$ (Table II.1, entry 2) shows prominent yield but L-ascorbic acid/$NaBH_4$ (Table II.1, entry 3) reducing couple proves to be the best couple in terms of yield. We also tried to carry out the scheme solely employing L-ascorbic acid and $NaBH_4$ but failed to generate any desired product. This suggests the enhancement in catalytic activity of L-ascorbic acid/$NaBH_4$ (Table II.1, entry 3) couple as reducing agent.

Table II.1. [a]Optimization of the reducing agent for direct reductive amination for the synthesis of *N*-benzylaniline

Entry	Reductant	Yield [%][b]
1	PTSA/$NaBH_4$	95%
2	H_3BO_3/ $NaBH_4$	92%
3	**L-ascorbic acid/$NaBH_4$**	**97%**
4	Ph-COOH/ $NaBH_4$	60%
5	CH_3COOH/ $NaBH_4$	50%
6	L-ascorbic acid	-
7	$NaBH_4$	-

The bold signifies most optimized condition.

[a] Reaction of Benzaldehyde (1 mmol), aniline (1 mmol) in presence of reducing agent and 5 ml of water as solvent at room temperature.

[b] Isolated yield

Our investigation for direct reductive amination of carbonyls and primary and secondary amines by L-ascorbic acid/$NaBH_4$ has been tested initially in neat condition (Table II.2, entry 8). Dissatisfied by the % yield in neat condition, we tried with various other solvents like methanol (Table II.2, entry 1), ethanol (Table II.2, entry 2), acetonitrile (Table II.2, entry 3), water (Table II.2, entry 6), glycerol (Table II.2, entry 4), PEG-300 (Table II.2, entry 5). Even mixtures of water/ethanol (1:1) (Table II.2, entry 7) was also tested. From our observation, water and acetonitrile both shows prominent results. Among all the other solvents water (Table II.2, entry 6) is the cheapest, non-flammable, non-toxic and environmentally benign solvent. Further, reaction in water eliminates the additional efforts of preparing anhydrous substances before use. So, water is selected as our suitable catalyst for its superiority over other organic solvents.

Table II.2. [a]Optimization of solvent for direct reductive amination for the synthesis of *N*-benzylaniline.

Entry	Solvent[b]	Yield [%][c]
1	CH_3OH	80%
2	C_2H_5OH	85%
3	Acetonitrile	98%
4	Glycerol	30%
5	PEG-300	45%
6	**H_2O**	**97%**
7	H_2O+ C_2H_5OH (1:1)	90%
8	Neat	~20%

The bold signifies most optimized condition.

[a] Reaction of Benzaldehyde (1 mmol), aniline (1 mmol) in presence of reducing agent at room temperature.

[b] 5 ml of solvent is taken

[c] Isolated yield

Room temperature is maintained during the reaction. This not only simplifies the reaction conditions but also terminates the reducing probability of aldehydes. After knowing the important role played by L-ascorbic acid/$NaBH_4$ couple we examined the optimum amount required for the direct reductive amination process. We started with 0.5 mmol of each L-ascorbic acid/$NaBH_4$ (1:1) (Table II.3, entry 1) reducing couple but failed to generate desired

significant yield. After several attempts 3 mmol of L-ascorbic acid/$NaBH_4$ in 1:2 (Table II.3, entry 3) ratio provided 97% yield, which is the highest among the other results.

Table II.3: [a]Optimization of amount of catalyst for direct reductive amination for the synthesis of *N*-benzylaniline.

Entry	L-ascorbic acid (mmol)	$NaBH_4$ (mmol)	Yield [%][b]
1	0.5	0.5	40%
2	1	1	80%
3	**1**	**2**	**97%**
4	2	1	75%
5	2	2	95%

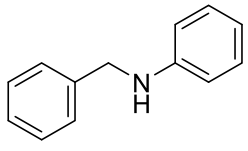
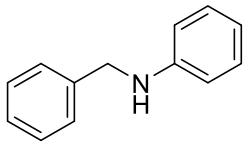
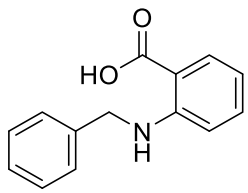
The bold signifies most optimized condition.

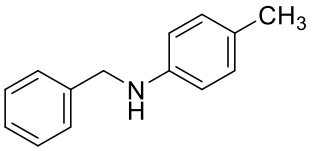
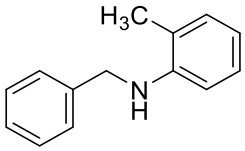
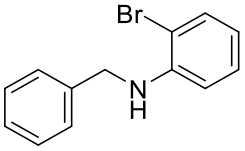
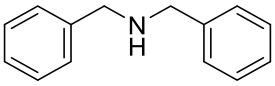
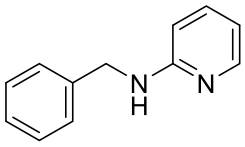
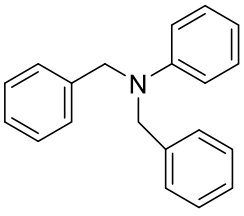
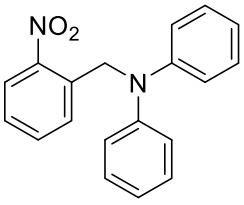
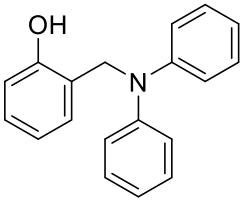
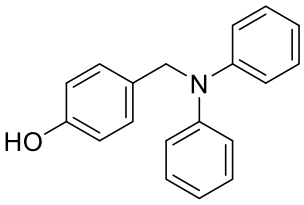
[a] Reaction of Benzaldehyde (1 mmol), aniline (1 mmol) in presence of reducing agent at room temperature.

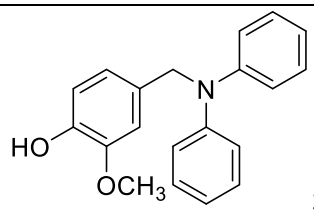
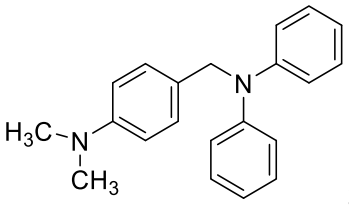
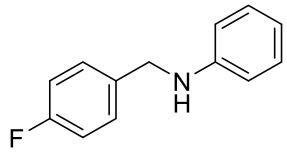
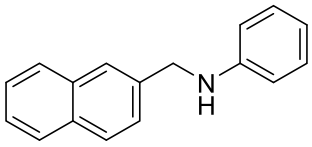
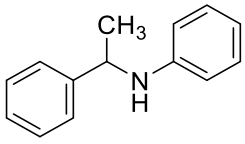
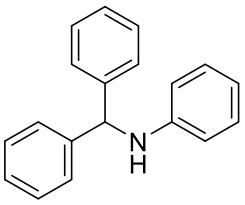
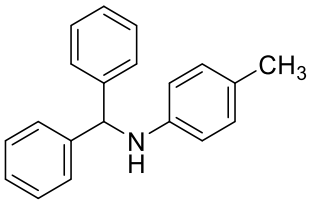
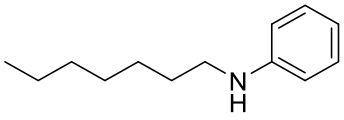
[b] Isolated yield

After achieving the optimum condition for the reaction, we then started to explore the reaction with various aldehydes and amines. The aldehydes (entry 3a-3p) and amines used were aromatic (entry 3a-3p) (containing electron withdrawing and electron donating groups) and aliphatic (entry 3t) both. Aromatic amine and aldehydes produce better result in the reaction (entry 3a – 3s). Electron withdrawing groups present in amines results in slightly lower yield whereas electron withdrawing group present in aldehyde escalates the yield. This is probably due to the increase in positive character of the carbonyl carbon atom. We further investigated the protocol exploring ketones (entry 3q - 3s) and the received yield was very satisfying.

Table II.4: [a]Synthesis of *N*-benzylaniline derivatives.

Entry	Product	Yield (%)[b]
1	 3a	97
2	 3b	82
3	 3c	84

4	 3d	92
5	 3e	93
6	 3f	88
7	 3g	83
8	 3h	86
9	 3i	82
10	 3j	85
11	 3k	87
12	 3l	88

13	 3m	75
14	 3n	92
15	 3o	89
16	 3p	65
17	 3q	85
18	 3r	83
19	 3s	90
20	 3t	72

[a]Reaction conditions: Aldehyde/ ketone (1.0 mmol), amine (1.0 mmol), in presence of reducing agent in water as the solvent (5 mL), at room temperature.

[b]Isolated yield of product measured by column chromatography.

Lower yield observed in some cases may be due to presence of electron withdrawing groups (entry 3b, entry 3c, entry 3j) or steric hindrance between the phenyl rings present in close vicinity (entry 3i, entry 3m, entry 3r). Presence of larger rings like naphthalene (entry 3p)

decreases the yield considerably. Also, the scheme produced less yield with aliphatic aldehydes like heptanal (entry 3t). Heterocyclic products also have shown promising yield (entry 3h).

II.D. Conclusion

In conclusion we have developed a simple, relevant, benign and eco-friendly facile strategy for the direct reductive amination using L-ascorbic acid and $NaBH_4$ without any transition metal catalysts. Use of water as solvent further enhances the advantage of the protocol. Replacement of expensive and toxic metal catalysts by environment friendly L-ascorbic acid is the highlight of this protocol. Further achievement of good yield with ketones and production of 3° amines in less reaction time and at room temperature has added further advantages to this protocol. Therefore, we expect this protocol to achieve wide application in natural product synthesis and in pharmaceutical industry.

II.E. Experimental

II.E.1. General Information

^{1}H 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.E.2. General procedure for the Direct reductive amination

A mixture of Carbonyl (1 mmol) and amine (1 mmol) in the presence of L-ascorbic acid (1 mmol) and $NaBH_4$ (2 mmol) was stirred at room temperature in water as solvent (5 ml). After completion of the reaction (observed by TLC), the reaction mixture was cooled down to room temperature. The solution was poured into 100 ml water and extracted with ethyl acetate, and washed several times with water. The organic mixture was dried over anhydrous Na_2SO_4, concentrated and the residue was purified by column chromatography on silica gel 60-120 mesh using petroleum ether/ ethyl acetate as eluent to afford the pure product. All products were characterized by ^{1}H NMR and ^{13}C NMR.

II.E.3. Spectroscopy data

1. *N*-benzylaniline [25] (Table II.4, entry 3a) (97% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.22 (br s, 1H), 4.35 (s, 2H), 6.67 (d, *J*= 7.9 Hz, 2H),6.75 (t, *J*= 7.3 Hz, 1H), 7.20 (t, *J*= 7.9 Hz, 2H), 7.26 - 7.47 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 48.4, 112.9, 117.7, 127.2, 127.5, 128.6, 129. 2, 139.3, 147.9 ppm.

2. *N*-benzyl-2-nitroaniline (Table II.4, entry 3b) (82% yield). ^{1}H NMR (300MHz, $CDCl_3$) : δ = 4.32 (s, 2H), 6.81 (br s, 1H), 7.08 (t, *J*= 7.5Hz, 1H), 7.31-7.46 (m, 6H), 7.67 (t, *J*= 7.5 Hz, 1H), 8.20 (d, *J*= 7.5 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.0, 114.4, 118.0, 125.9, 126.7, 126.9, 128.5, 131.7, 135.6, 139.9, 146.7 ppm.

3. 2-(Benzylamino)benzoic acid (Table II.4, entry 3c) (84% yield). ^{1}H NMR (300MHz, $CDCl_3$) : δ = 4.32 (s, 2H), 6.92 (br s, 1H), 7.03 (d, 1H, *J* = 7.5 Hz), 7.29- 7.38 (m, 5H, *J* = 7.3Hz), 7.53 (t, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 7.5Hz, 1H), 13.11 (br s, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.1, 107.4, 113.4, 117.0, 126.7, 126.8, 126.9, 128.5, 128.6, 131.1, 139.9, 150.1, 169.3 ppm.

4. *N*-benzyl-4-methylaniline (Table II.4, entry 3d) (93% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.32 (s, 3H), 4.02 (br s, 1H), 4.36 (s, 2H) 6.47 -6.57 (m, 2H), 6.60 (d, *J* = 6.9 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 7.28 - 7.45 (m, 5H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.6, 48.4, 110.0, 113.1, 113.7, 118.6, 127.2, 127.5, 128.6, 129.1, 129.7, 139.0, 139.5, 148.2 ppm.

5. *N*-benzyl-2-methylaniline[25] (Table II.4, entry 3e) (93% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.16 (s, 3H), 3.96 (br s, 1H), 4.37 (s, 2H), 6.62 (d, *J* = 7.9 Hz, 1H), 6.68 (t, *J* = 7.3 Hz, 1H), 7.09 (dd, *J* = 15.1, 7.5 Hz, 2H), 7.28 (t, *J* = 7.0 Hz, 1H), 7.31 - 7.41 (m, 4H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.5, 48.4, 110.1, 117.3, 122.0, 127.2, 127.3, 127.6, 128.6, 130.1, 139.4, 145.9 ppm.

6. *N*-benzyl-2-bromoaniline[26] (Table II.4, entry 3f) (88% yield): H^1 NMR ($CDCl_3$, 300 MHz) δ= 7.43-7.39 (m, 1H), 7.33-7.23 (m, 5H), 7.12-7.06 (m, 1H), 6.58-6.51 (m, 2H), 4.64 (br, 1H), 4.34 (s, 2H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz) δ=144.9, 138.8, 132.5, 128.8, 128.6, 127.4, 127.3, 118.1, 111.7, 109.8, 48.1 ppm.

7. *N*-(phenylmethyl)-benzenemethanamine (Table II.4, entry 3g) (83% yield): H^1 NMR ($CDCl_3$, 300 MHz) δ= 3.76 (s, 2H), 5.01 (br s, 1H), 7.29-7.61 (m, 10H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 57.8, 127.0, 127.9, 128.5, 140.2 ppm.

8. *N*-benzylpyridin-2-amine (Table II.4, entry 3h) (86% yield): H^1 NMR ($CDCl_3$, 300 MHz) δ= 4.35 (s,1H), 6.41-6.58 (m, 1H), 6.93 (br s, 1H), 7.13 – 7.42 (m, 5H), 7.86-7.98 (m, 2H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 46.4, 106.5, 126.7, 126.9, 128.5, 138.3, 139.9, 148.1, 158.5 ppm.

9. *N, N*-dibenzylaniline[27] (Table II.4, entry 3i) (82% yield): ^{1}H NMR (400MHz, $CDCl_3$): δ 7.15-7.34 (m, 12H), δ 6.68-6.74 (m, 3H), δ 4.65 (s, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ= 149.15, 138.57, 129.20, 128.61, 126.85, 126.62, 116.68, 112.41, 54.15 ppm.

10. *N*-(2-nitrobenzyl)-*N*-phenylaniline (Table II.4, entry 3j) (85% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.20 (s, 2H), 7.06-7.21 (m, 2H), 7.33- 7.61 (m, 10H), 7.72-7.87 (m, 1H), 7.99 (d, *J* = 7.3 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 52.4, 119.1, 121.9, 124.7, 126.1, 127.6, 129.6, 131.2, 142.6, 149.1 ppm.

11. 2-((diphenylamino)methyl)phenol (Table II.4, entry 3k) (87% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.17 (s, 2H), 6.73-6.83 (m, 2H), 7.06-7.11 (m, 4H), 7.33-7.67 (m, 8H), 10.12 (br s, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 50.8, 115.7, 119.1,121.1, 121.9, 128.1, 128.3, 128.9, 129.6, 149.1, 156.6 ppm.

12. 4-((diphenylamino)methyl)phenol (Table II.4, entry 3l) (88% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.29 (s, 2H), 6.71 (d, *J*= 7.4 Hz, 2H), 6.95 (d, *J*= 7.5 Hz, 2H), 7.06-7.10 (m, 2H), 7.33 – 7.40 (m, 8H), 9.06 (br s, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 57.0, 115.7, 119.1, 121.9, 129.6, 130.7, 130.9, 149.1, 156.5 ppm.

13. 4-((diphenylamino)methyl)-2-methoxyphenol (Table II.4, entry 3m) (75% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.77 (s, 3H), 4.28 (s, 2H), 6.63 (d, *J*= 7.3Hz, 1H), 6.81 (t, *J* = 7.4Hz, 2H), 7.06 (t, *J*= 6.9 Hz, 2H), 7.31- 7.47 (m, 8H), 9.92 (br s, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 56.1, 57.3, 109.6, 115.4, 119.1, 121.9, 123.2, 129.6, 135.2, 146.7, 147.3, 149.1 ppm.

14. 4-((diphenylamino)methyl)-*N*,*N*-dimethylaniline (Table II.4, entry 3n) (92% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.02 (s, 6H), 4.20 (s 2H), 6.71 (d, *J* = 6.9, 2H), 7.03-7.12 (m, 4H), 7.33 – 7.47 (m, 8H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 41.3, 57.0, 112.3, 119.1, 121.9, 127.6, 127.8, 129.8, 148.7, 149.1 ppm.

15. *N*-(4-fluorobenzyl)benzenamine[26] (Table II.4, entry 3o) (92% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ= 7.31-7.26 (m, 2H), 7.18-7.12 (m, 2H), 7.03-6.96 (m, 2H), 6.73-6.68 (m, 1H), 6.60-6.57 (m, 2H), 4.24 (s, 2H) 3.84 (br, 1H) ppm.

^{13}C NMR ($CDCl_3$, 75MHz) δ= 163.8, 160.6, 148.2, 135.5, 129.5, 129.2, 129.1, 117.9, 115.7, 115.4, 113.1, 47.6 ppm.

16. *N*-(naphthalen-2-ylmethyl)aniline[27] (Table II.4, entry 3p) (65% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ= 7.72 (m, 4H),7.38 (m, 3H), 7.08 (m, 2H), 6.63 (d, *J* = 9.0 Hz, 1H), 6.57 (d, *J*=10.3 Hz, 2H), 4.39 (d, *J* = 6.7 Hz, 2H), 4.21 (br s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 148.59, 137.36, 133.90, 133.17, 129.69, 128.77, 128.16, 128.10, 126.55, 126.31, 126.13, 126.12, 118.03, 113.34, 48.90.

17. *N*-(1-phenylethyl)aniline[28] (Table II.4, entry 3q) (85% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ= 1.54 (d, *J* = 6.8 Hz, 3H), 4.19 (br s, 1H), 4.51 (q, *J* = 6.7 Hz, 1H), 6.55 (dd, *J*= 8.7, 0.9 Hz, 2H), 6.67 (tt, *J*= 7.3, 1.0 Hz, 1H), 7.11 (dd, *J*= 8.5, 7.3 Hz, 2H), 7.20- 7.28 (m, 1H), 7.29-7.43 (m, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.9, 53.4, 113.4, 117.3, 125.8, 126.9, 128.6, 129.1, 145.1, 147.1 ppm.

18. *N*-benzhydrylaniline[29] (Table II.4, entry 3r) (83% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.20 (br, 1H), 5.48 (s, 1H), 6.51-6.52 (m, 2H), 6.67 (s, 1H), 7.07-7.09 (m, 2H), 7.22-7.24 (m, 2H), 7.29-7.33 (m, 8H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.1, 113.6, 117.7, 127.4, 127.5, 128.9, 129.2, 143.0, 147.4 ppm.

19. *N*-benzhydryl-4-methylaniline[29] (Table II.4, entry 3s) (90% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 (s, 3H), 4.11 (br, 1H), 5.47 (s, 1H), 6.45-6.47 (m, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 7.21-7.25 (m, 2H), 7.28-7.32 (m, 4H), 7.36 (d, *J* = 7.6 Hz, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 63.4, 113.7, 126.8, 127.4, 127.5, 128.8, 129.7, 143.2, 145.2 ppm.

20. *N*-heptylaniline[30] (Table II.4, entry 3s) (72% yield): ^{1}H NMR (300MHz, $CDCl_3$): δ = 7.08 (t, *J* = 6.79 Hz, 2H), 6.60 (t, *J* = 6.04 Hz, 1H), 6.51 - 6.49 (m, 2H), 3.40 (br s, 1H), 3.06 (t, *J* = 6.79 Hz, 2H), 1.63 - 1.54 (m, 2H), 1.40 - 1.22 (m, 8H), 0.91 - 0.87 (m, 3H) ppm.

^{13}C NMR (75MHz, $CDCl_3$): δ = 148.4, 129.1, 116.9, 112.5, 43.9, 31.7, 29.5, 29.0, 27.0, 22.5, 14.0 ppm.

II.E.4. Scanned copies of ^{1}H and ^{13}C NMR of the derivatives

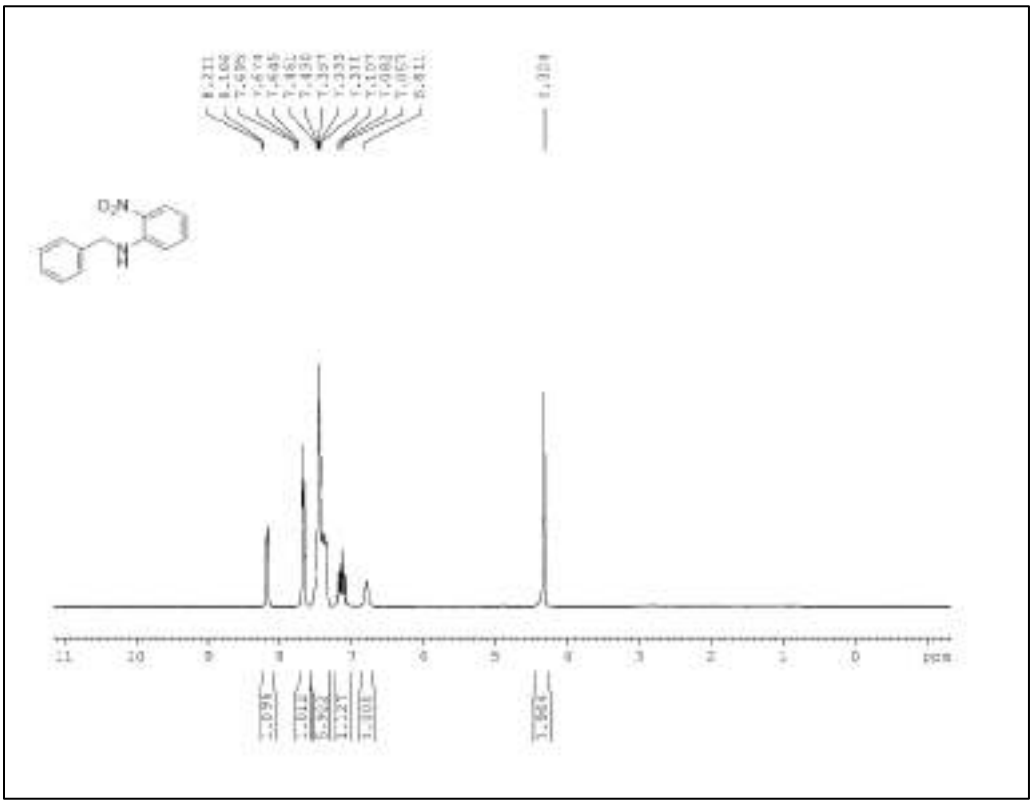


Figure II.2. Scan copy of ^{1}H NMR of *N*-benzyl-2-nitroaniline.

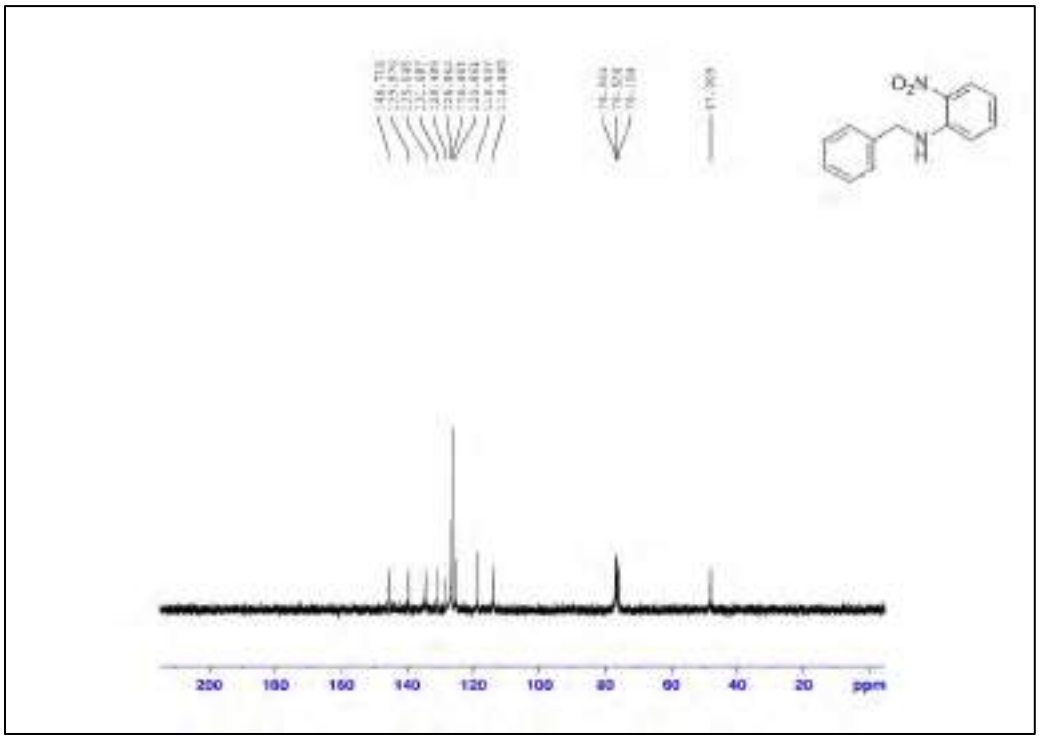


Figure II.3. Scan copy of ^{13}C NMR of *N*-benzyl-2-nitroaniline.

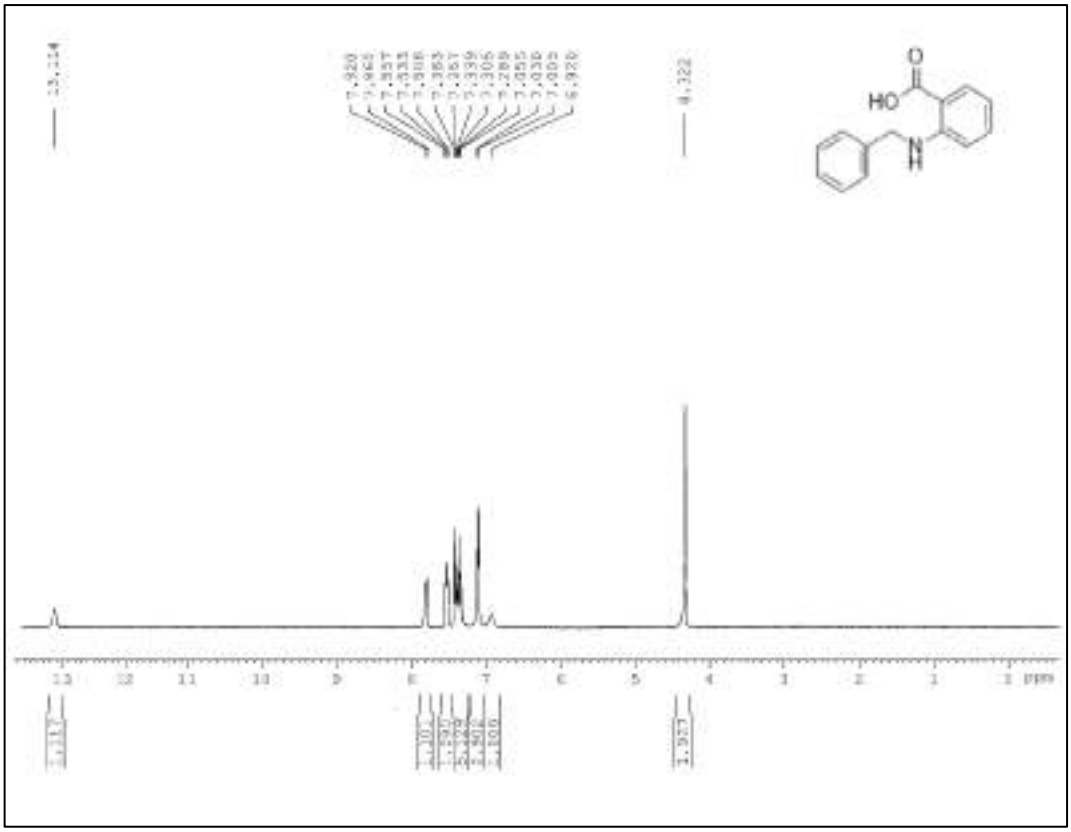


Figure II.4. Scan copy of ^{1}H NMR of 2-(Benzylamino)benzoic acid.

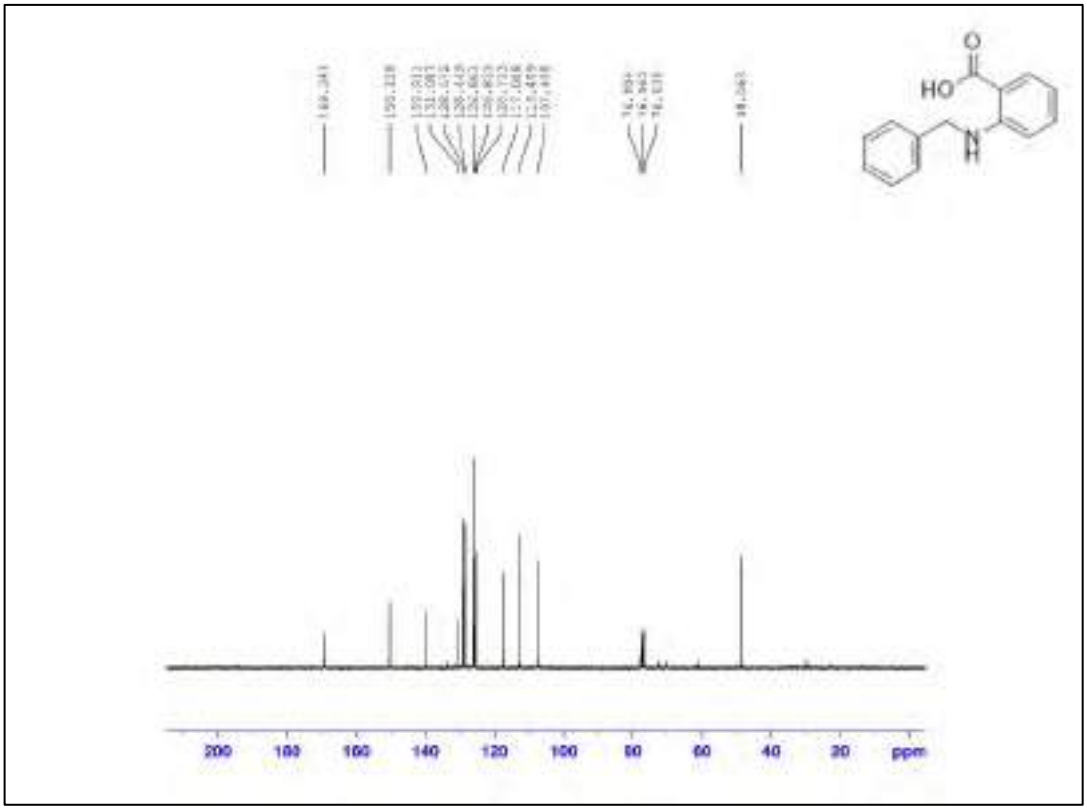


Figure II.5. Scan copy of ^{13}C NMR of 2-(Benzylamino)benzoic acid.

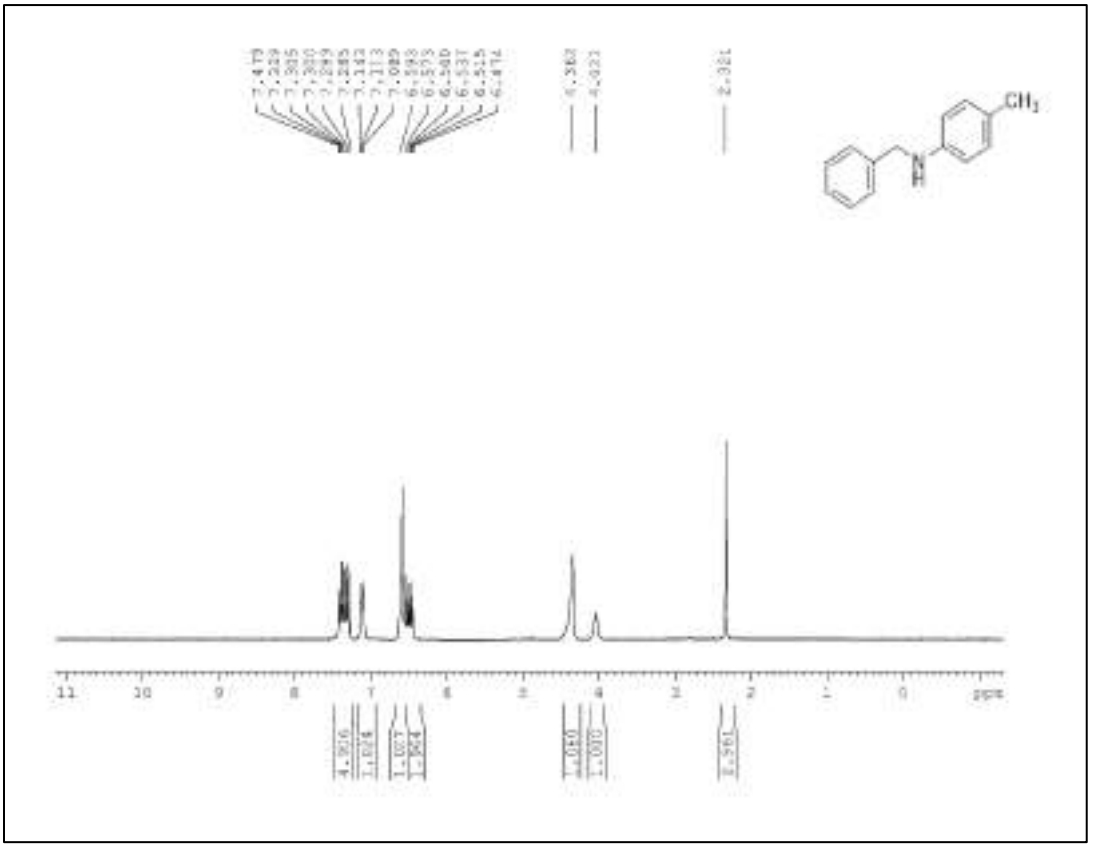


Figure II.6. Scan copy of ^{1}H NMR of *N*-benzyl-4-methylaniline.

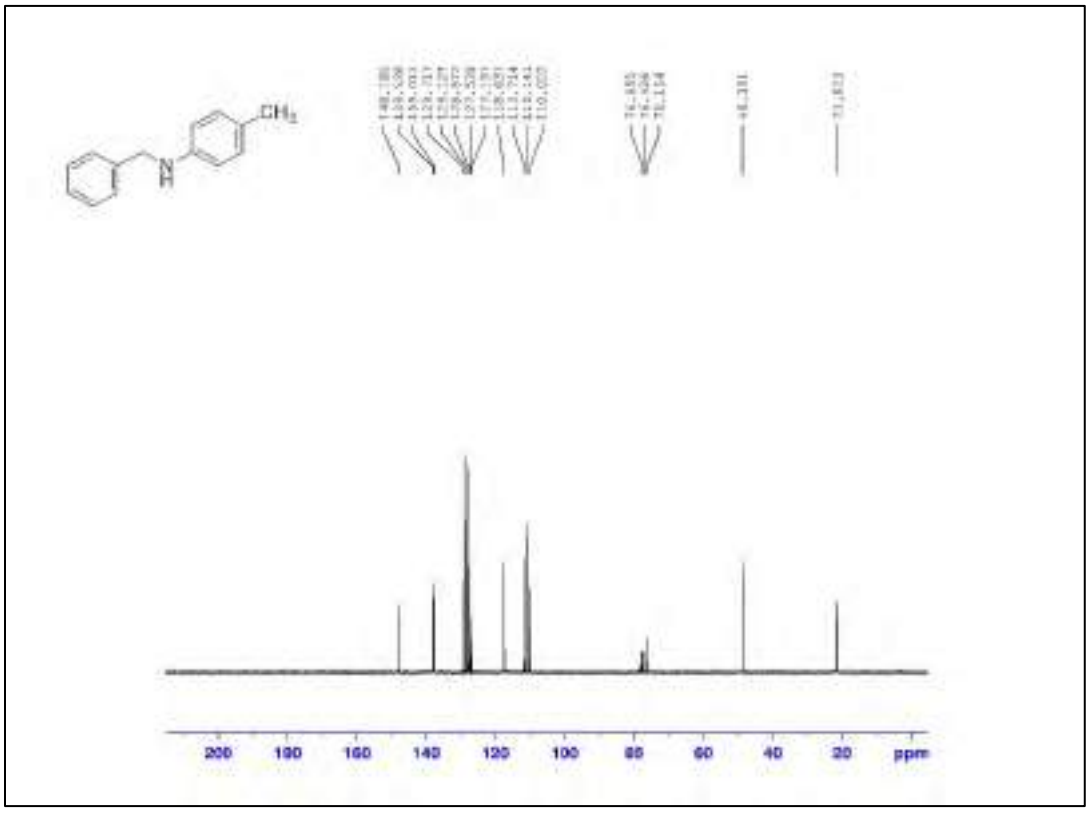


Figure II.7. Scan copy of ^{13}C NMR of *N*-benzyl-4-methylaniline.

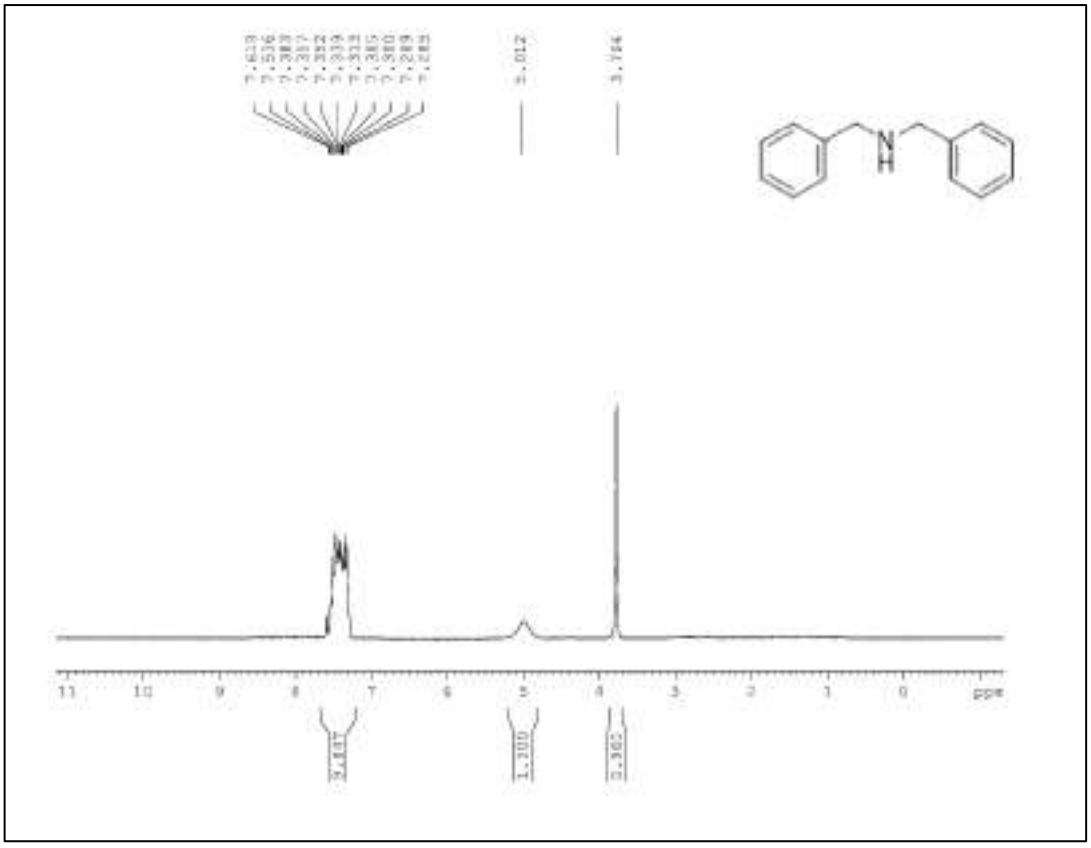


Figure II.8. Scan copy of ^{1}H NMR of *N*-(phenylmethyl)-benzenemethanamine.

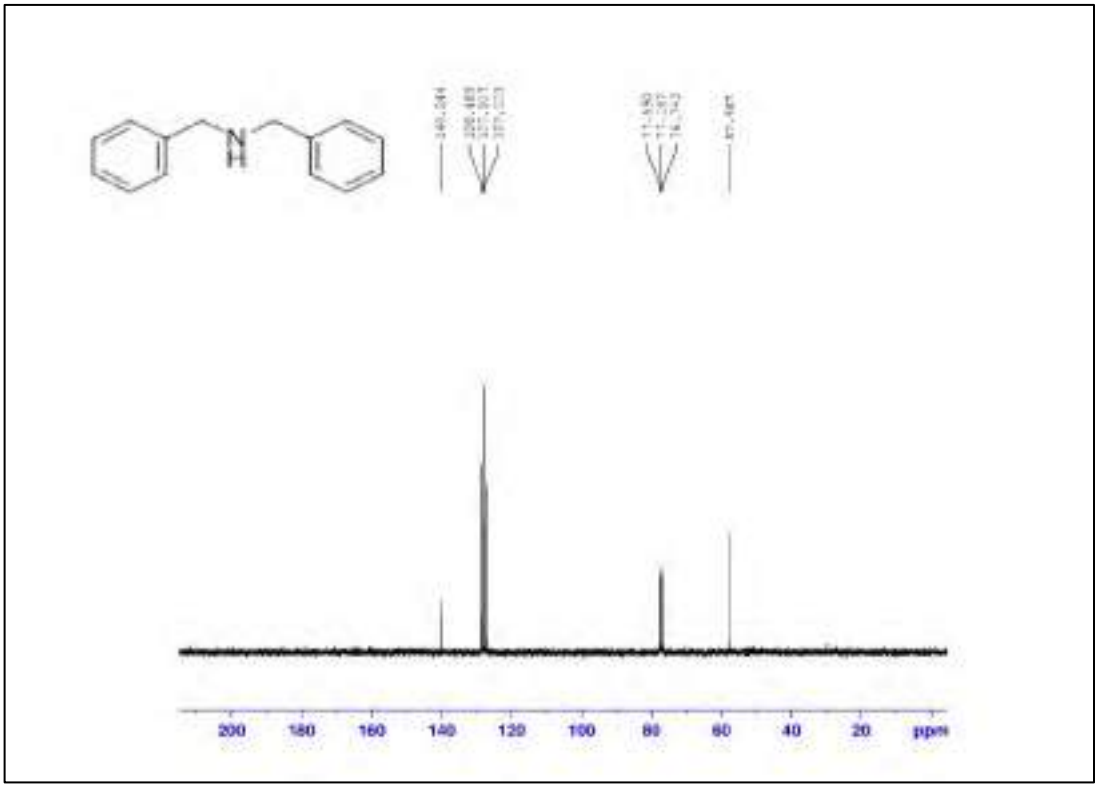


Figure II.9. Scan copy of ^{13}C NMR of *N*-(phenylmethyl)-benzenemethanamine.

II.F. Reference

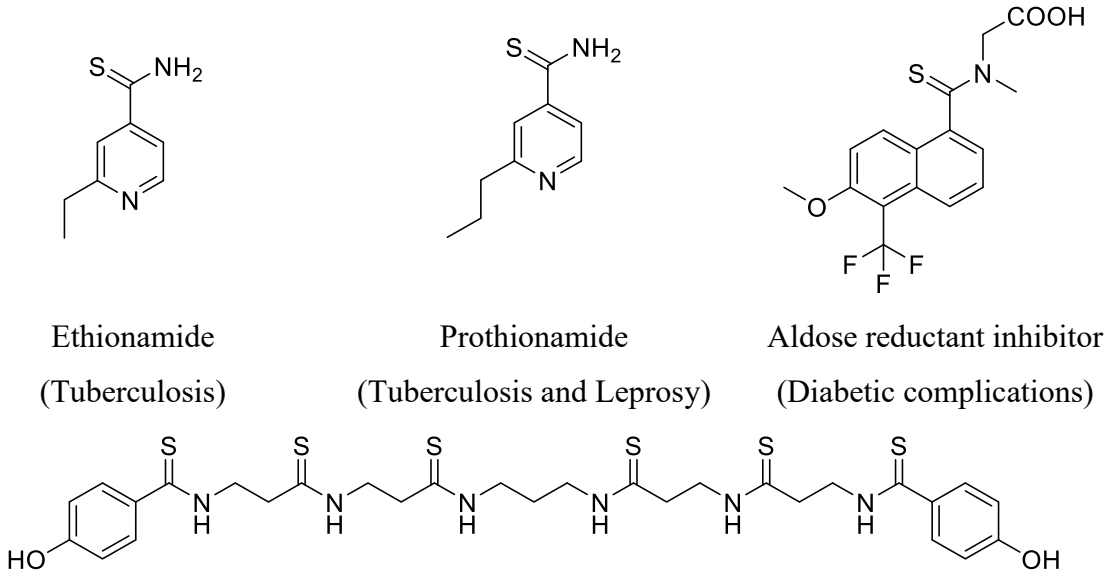
References are given in BIBLOGRAPHY under Chapter II.

Chapter III

Humic acid catalyzed solvent-free green protocol for synthesis of thioamide

III.A. Introduction

Thioamides were first introduced in the year 1815 by Gay-Lussak and later by Berzelius in 1843 by conversion of amides to its thio analogs is the basis of thioamide formations. Thioamide derivatives have been explored from long time in synthesis of various important thio-heterocyclic compounds like thiazoles[1-3], tetrazoles[1], thiazolins[4], thiazolinones[4]. These bioactive thio heterocycles have huge range of applicability in the field of various important medicinal and pharmateutical applications. P-glycoprotein, a modulators of the ATP binding cassette transporters[5]; closthioamide, a polythioamide antibiotics[6]; *N*-cyclohexylethyl-ETASV, an inhibitor of the PSD-95-NMDA receptor interaction[7]; antithyroid drugs[8]; these examples amplify the application of bioactive thio-compounds in medicinal and ptherapeutic field and a few such derivatives are presented in Figure III.1 as well.



Ethionamide (Tuberculosis)

Prothionamide (Tuberculosis and Leprosy)

Aldose reductant inhibitor (Diabetic complications)

Closthioamide (Polythioamide antibiotic)

Figure III.1. Few Biologically active compounds having thioamide moiety.

Thioamide derivatives are also widely used as grease additives, vulcanization agents, plastic pigments, petroleum products[9], as ligands for estrogen receptors[10], as aldose reductase inhibitors[11], as fungistatic molecules[12] etc.

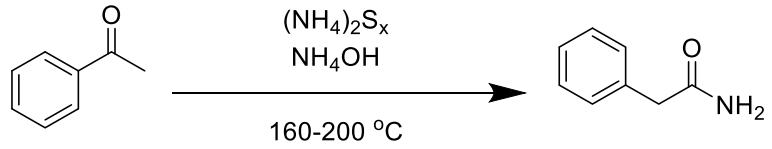
III.B. Background and Objectives

For synthesis of thioamides, various methods have been developed previously. Precursors like amines, nitriles, amides, oximes, carboxylic acids, carbonyls, and thiols have been employed for such synthesis. The most conventional method for synthesis of thioamide is use of Lawesson's reagent[13]. Moreover, thioamide have been synthesized by reaction of formamide

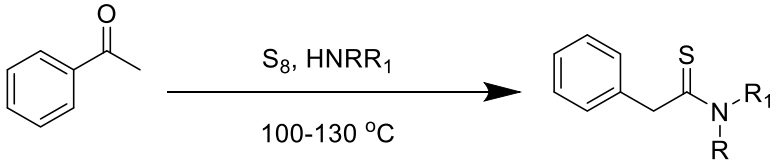
with aldehyde in sodium sulphide and presence of water[14], copper (II) catalyzed oxidation of thiols in presence of compounds like 1,5,7-triazabicyclo[4.4.0]dec-5-ene[15] and oxidative coupling of primary amine with sulphur[16]. Owing to use of expensive metal catalysts, noxious solvents, harsh reaction condition, longer reaction time etc. these protocols need advancement from the green chemistry standpoint to make the process environmentally sustainable.

III.B.1. Specialized methods for synthesis of thioamides

In 1887 Conrad Willgerodt first described formation of amides from ketones by treating it with ammonium hydroxide, and ammonium polysulfide at 160-200 °C temperature[17] (Scheme III.1). In 1923 Karl Kindler modified the scheme using secondary amines in presence of sulfur at 100-130 °C to yield thioamides successfully[18] (Scheme III.2).

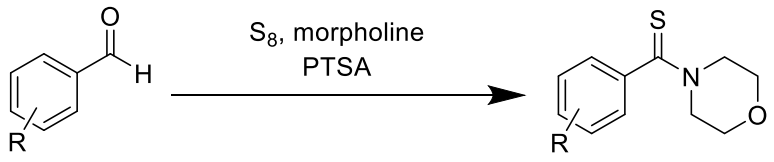


Scheme III.1. Synthesis of amides by Willgerodt reaction.



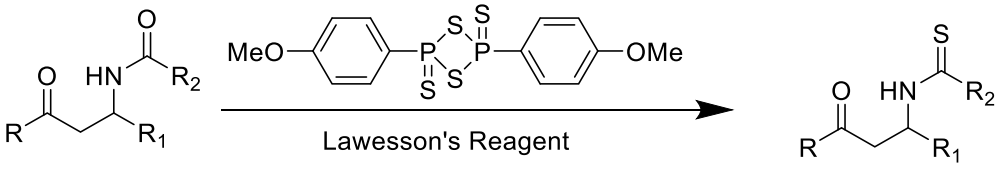
Scheme III.2. Synthesis of thioamides by Kindler modification.

The Willgerodt–Kindler reaction is not widely used nowadays in organic syntheses is due to the disadvantage that this process produces low yield and provides complex reaction mixtures. In late 1970's Kul'ganek *et al.* reported preparation of thioamides using morpholine in PTSA as catalyst[19]. By this reaction aldehyde derivatives could also be converted into thioamides for the first time. Further, dialdehydes like *o-,m-,p-* pthalaldehydes undergo this reaction too (Scheme III.3). The major drawback of this reaction is use of PTSA which is hazardous strong acid.



Scheme III.3. Synthesis of thioamides using PTSA.

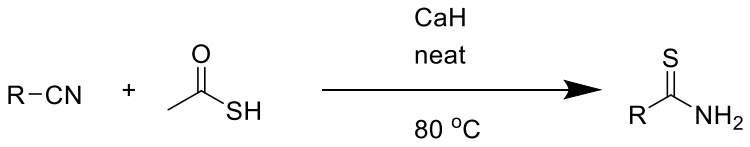
Another notable method is developed by using Lawesson's reagent. Lawesson's reagent was first prepared in 1956 while doing a systematic study of the reactions of arenes with P_4S_{10}[20]. One such example is Nishio et al. investigated the thionation reactions of beta-hydroxy amides which resulted in the formation of unsaturated thioamide[21] (Scheme III.4).



Scheme III.4. Synthesis of thioamide by Lawesson's reagent.

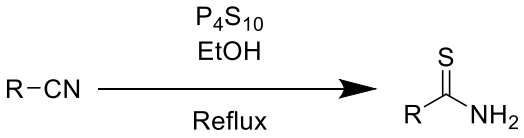
III.B.2. Modern approach towards thioamide synthesis

P. N. Arunachalam *et al.* developed modern method for synthesis of thioamide from aliphatic and aromatic nitriles[22]. Thioacetic acid is used in this reaction with presence of calcium hydride to produce corresponding thioamide in good to excellent yield (Scheme III.5). A major drawback of this reaction is haloaryl nitriles do not undergo this method under given condition. And use of nitrile as precursor always makes the method harmful to handle and limits its scalability.



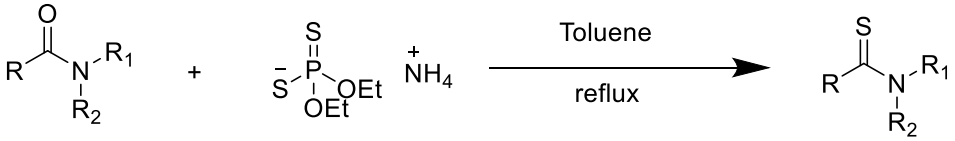
Scheme III.5. Synthesis of thioamide by thioacetic acid and calcium hydride.

Another efficient method of synthesis of thioamide from nitrile is reported by D. Elhamifar *et al.*[23] Aliphatic and aromatic nitriles undergo this reaction with good yield of corresponding product. In this reaction phosphorus pentasulfide is used in ethanol under reflux condition (Scheme III.6). It is a rapid, high yielding process but the drawback lies within nitrile precursor.



Scheme III.6. Synthesis of thioamide using phosphorus pentasulfide

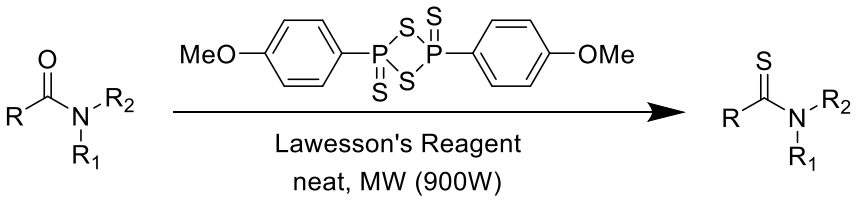
Thionation of amide can be used as another route for synthesis of thioamides and that is reported by L. Malekzadeh *et al.* in 2011. Wide range of aromatic and aliphatic amides are converted into thioamides using ammonium phosphorodithioate[24]. Toluene is used as solvent under reflux condition (Scheme III.7). This reaction can take up to 10 hours in specific cases.



Scheme III.7. Synthesis of thioamide using ammonium phosphorodithioate

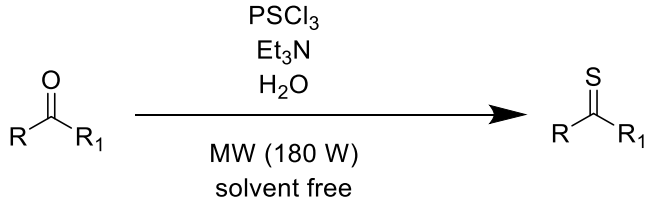
Microwave irradiated method for conversion of amides to thioamides is reported by D. Kumar *et al.* using Lawesson's reagent[25]. The reaction is performed in solvent-free condition in an

open vessel and product obtained in 2-4 minutes (Scheme III.8). Excess of reagent is required for this process annthe method is not very cost effective.



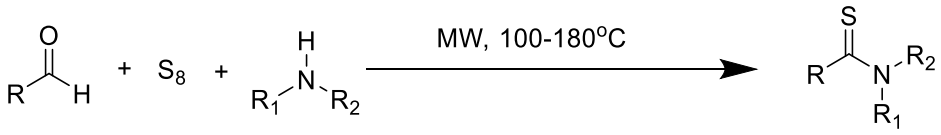
Scheme III.8. Microwave assisted synthesis of thioamide using Lawesson's reagent.

Another microwave assisted method is reported by R. Tank *et al.* from carbonyl compounds. They used $PSCl_3/H_2O/Et_3N$ system for thioamide formation[26]. Along with thioamides this method is also capable of forming other products like thiolactams, thioketones, thioxanthones and thioacridone. The process is reported under solvent-free condition at 70-100 ºC and completion time is within 6 minutes (Scheme III.9).



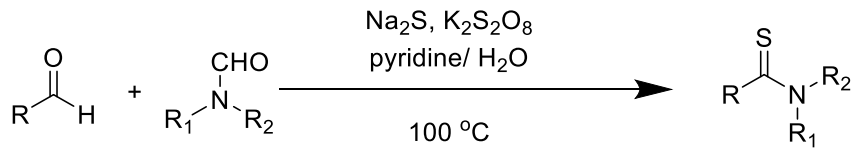
Scheme III.9. Synthesis of thioamide with microwave assistance using $PSCl_3/H_2O/Et_3N$ system.

A microwave assisted three component thioamide synthesis is reported by C. O. Kappe *et al.* in Kindler type reaction[27]. Aldehydes, amines and elemental sulfur were reacted using 1-methyl-2-pyrrolidone as solvent at 110-180 ºC. Good yield of products obtained within 20 minutes (Scheme III.10).



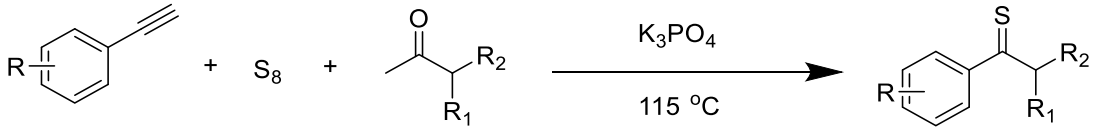
Scheme III.10. Synthesis of thioamide by three component synthesis using microwave irradiation.

In recent time, a very effective synthetic method for thioamide synthesis is reported by X. Jiang *et al*. from aldehydes[28]. *N*-substituted formamides are reacted with aldehydes using sodium sulphide in water and pyridine medium at 100 ºC to yield corresponding thioamide (Scheme III.11). Modifications of bioactive molecules are also represented in this article. Requirement of up to 24-hour time of completion for the reaction is a limitation of this process.



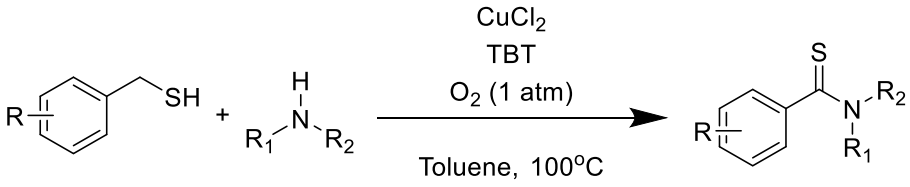
Scheme III.11. Synthesis of thioamide from *N*-substituted formamides using sodium sulphide.

Another recent advancement towards thioamide synthesis is reported by L. Liu *et al.*[29]. Starting with aromatic alkyne the reported transition metal-free cleavage of C-C triple bond in presence of amide and sulfur to yield thioamide (Scheme III.12). Wide substrate scope is reported by the author and the method is suitable for some internal aromatic alkynes and acetamides. Though time requirement of 20 hours is a limitation of the process at 115 °C.



Scheme III.12. Synthesis of thioamide from aromatic alkynes.

A substitute route for synthesis of thioamides from thiols is reported by H.Y. Jang *et al.*[30] Thiols are used as starting material to bypass the use of elemental sulfur in this case. As a catalyst Cu(II) salt is used in presence of tributyltin (TBT) (Scheme III.13). O_2 is supplied in 1 atm pressure during the reaction at 100 °C in toluene medium. Use of metal catalyst, up to 18 hour reaction time and requirement of O_2 during the reaction makes the reaction hazardous and non-economical.



Scheme III.13. Synthesis of thioamides from thiols using Cu(II) salt and tributyltin.

III.B.3. Background of Humic acid in organic synthesis

Now a days, to construct a protocol environmentally sustainable and greener, substitution of these detrimental catalysts and solvents are desirable in drug chemistry and in organic synthesis too. As a greener alternative catalyst, biodegradable high molecular weight materials are getting noteworthy attention due to their ease of handling, low toxicity and easily separable, recoverable also reusable nature in many cases. Among these alternates, humic acid is rarely explored polymer that has potential to manifest extraordinary catalytic activity owing to the presence of functional groups like carboxyl (-COOH) and hydroxyl (=CH-OH) in its structure (Figure III.2).

Humic acid is mostly obtained from the biodegradation of deceased organic materials available as soil, coal, peat, upland streams, dystrophic lakes and well water. From a green standpoint humic acid is non-toxic, inexpensive, easily accessible, environmentally benign, organo catalyst which is reported in very limited articles.

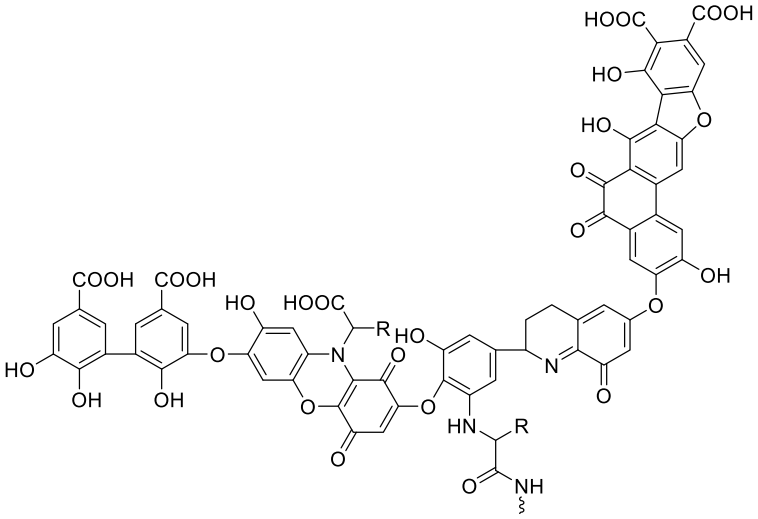
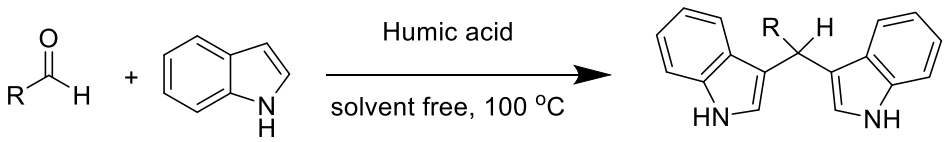


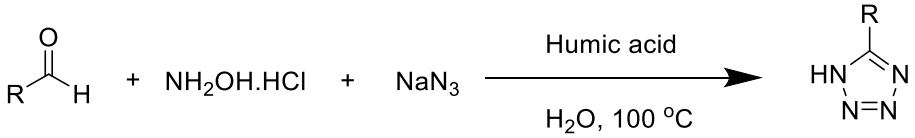
Figure III.2. Structure of Humic acid.

In 2020, P. Ghosh *et al.* reported a facile synthesis of Bis(indolyl)methanes, Bis(pyrazolyl) methanes, Bis-coumarins and Bis-lawsones catalyzed by humic acid in solvent-free condition[31] (Scheme III.14). Some of the major advantages they achieved in this method over other conventional methods are, no hazardous solvents required, toxic metal catalysts-free, no harsh reaction conditions, low catalyst loading, good yield and excellent functional group tolerance.



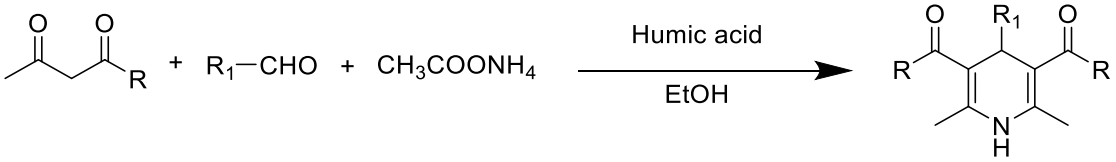
Scheme III.14. Synthesis of some diversified bis(indolyl)methane from aldehydes.

Another application of humic acid as organocatalyst is reported by X. Wang *et al.* in 2020[32]. They synthesized 5-substituted 1*H*-tetrazoles in water using humic acid as catalyst. Aldehydes, hydroxyamine hydrochloride and sodium azide are used as starting material in water (Scheme III.15).



Scheme III.15. Humic acid catalyzed one-pot three-component synthesis of 5-substituted 1*H*-tetrazoles.

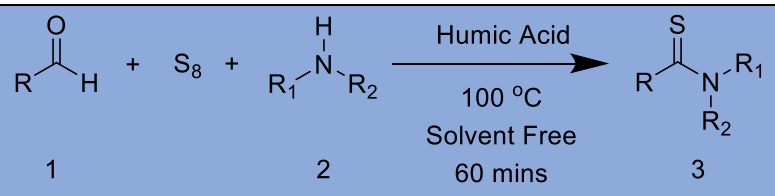
In 2017, W. Yongqiu *et al.* reported Synthesis of 1,4-Dihydropyridine compounds catalyzed by humic acid[33]. Synthesis of 1,4-dihydropyridine compounds is reported through Hantzsch reaction in this article. Aldehydes, ammonium acetate and ethyl acetoacetate or methyl acetoacetate are used as starting material to achieve desired product in this reaction (Scheme III. 16). Various aldehydes and diketones are employed in the process with excellent yield of corresponding product. Ethanol is used as greener solvent for this protocol.



Scheme III.16. Synthesis 1,4-dihydropyridine compounds with humic acid.

III.C. Present work

Here we are reporting an environmentally sustainable, green synthesis of thioamide through MCR of aldehyde, amine and sulfur catalyzed by humic acid in solvent -free condition at 100°C. The key features of this protocol is use of humic acid, a greener, easily recyclable, easily available and almost unexplored catalyst and circumvention of noxious solvents that amplify the scope of the reaction. The proposed protocol also possess tolerance to aromatic as well as aliphatic aldehydes and amines comprising variety electron donating and withdrawing functional groups.



R = Aryl, Heterocyclic, Aliphatic

R_1, R_2 = Aryl, H, Alkyl, Heterocyclic, Alicyclic

Scheme III.17. Synthesis of thioamides from aldehydes and amines.

III.C.1. Result and discussion

To perpetuate the optimum condition for our continuing effort on humic acid catalyzed green synthetic methodology we started with benzaldehyde, pyrrolidine and sulfur as a model reaction. While optimizing we found that time and temperature has significant effect on the reaction. The temperature effect was investigated at ambient, 80 °C and 100 °C (Table III.1). Though at room temperature no yield of desired product was reported (Table III.1, entry 7) but gradually increase in temperature upto 100 °C (Table III.1, entry 9) shows notable increase in the yield. We examined with various solvents and in solvent -free condition, none of the

solvents appear to be advantageous than solvent -free condition. Hence 100 ºC and solvent -free condition is chosen as best for our Humic acid catalyzed reaction condition (Table III.1).

Table III.1. [a]Optimization of time, temperature and solvent for synthesis of thioamide.

Entry	Solvent	Temperature (ºC)	Time (min)	Yield [%][b]
1	Ethanol	Reflux	180	-
2	Methanol	Reflux	180	-
3	Water	Reflux	180	Trace
4	Ethylene glycol	100	180	Trace
5	Solvent -free	100	180	93
6	Solvent -free	80	180	72
7	Solvent -free	RT	180	46
8	Solvent -free	100	120	92
9	**Solvent -free**	**100**	**60**	**91**

The bold signifies most optimized condition.

[a] Reaction of Reaction of Benzaldehyde (1 mmol), pyrolidine (1 mmol) and sulphur (1.25 mmol) in presence of Humic acid catalyst.

[b] Isolated yield

Now, to optimize the amount of sulfur we started with 0.25 mmol (Table III.2, entry 1) of sulfur, where we did not achieve desired yield. Upon increasing the the amount of sulfur to 1.25 mmol (Table III.2, entry 4) and 1.50 mmol (Table III.2, entry 5) respectively the yield of desired thioamide also increased but was almost the same for both the cases. The amount of catalyst loading was also optimized and 15 mg (Table III.2, entry 7) was found to be the best for our scheme (Table III.2).

Table III.2. [a]Optimization of amount of catalyst and amount of sulfur for synthesis of thioamide.

Entry	Catalyst Loading (mg)	Sulfur (mmol)	Yield [%][b]
1	50	0.25	52
2	50	0.50	68
3	50	1.00	83
4	50	1.25	91
5	50	1.50	93
6	25	1.25	92
7	**15**	**1.25**	**91**

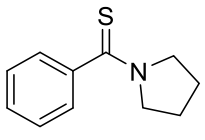
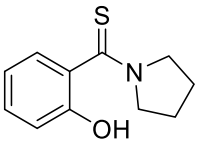
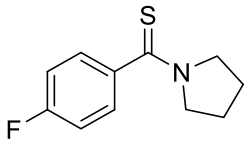
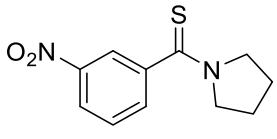
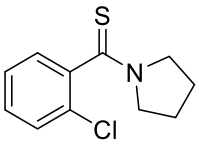
The bold signifies most optimized condition.

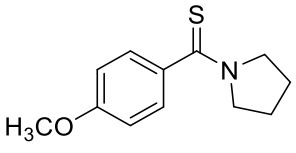
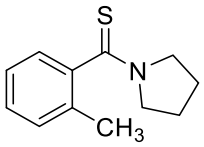
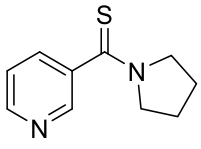
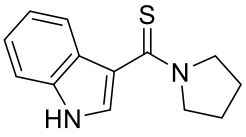
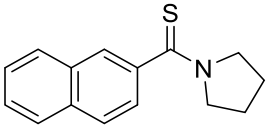
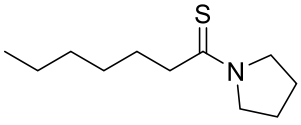
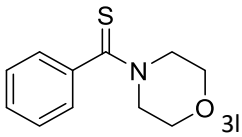
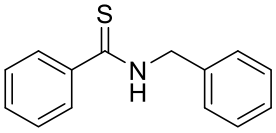
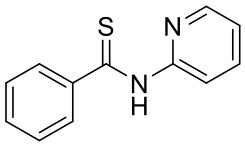
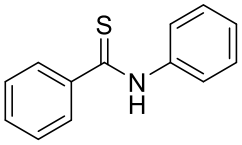
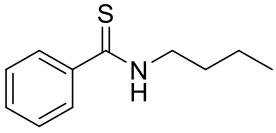
[a] Reaction of Reaction of Benzaldehyde (1 mmol), pyrolidine (1 mmol) and sulphur (1.25 mmol) in presence of humic acid catalyst.

[b] Isolated yield

Afterwards, the efficiency of the reagents was investigated under optimized reaction condition for condensation of pyrrolidine with broad range of aldehydes to produce the desired products. The reaction was successful for phenyl group in benzaldehyde (Table III.3, entry 3a-3k) bearing electron withdrawing substituents like nitro, chloro and fluoro groups (Table III.3, entry 3c, 3d, 3e) as well as electron donating groups such as methoxy, hydroxy and methyl groups (Table III.3, entry 3b, 3f, 3g). Aliphatic and heterocyclic aldehydes (Table III.3, entry 3h, 3i, 3k) also produce moderate to good yield under optimized condition. The applicability of the protocol was also examined over vast range of amines having pyridine, benzyl, alicyclic, aromatic motif (Table III.3, entry 3l-3p) which successfully produced respective desired thioamide in good yield (Table III.3).

Table III.3. [a]Synthesis of some diversified thioamides derivatives under solvent-free condition catalyzed by Humic acid.

Entry	Product	Yield[%][b]
1	 3a	91
2	 3b	82
3	 3c	90
4	 3d	83
5	 3e	76

6	 3f	90
7	 3g	82
8	 3h	76
9	 3i	73
10	 3j	78
11	 3k	80
12	 3l	86
13	 3m	67
14	 3n	64
15	 3o	60
16	 3p	78

[a]Reaction condition: Aldehyde (1 mmol), pyrrolidine (1 mmol) and sulphur (1. 25 mmol) in presence of 15 mg humic acid in solvent -free condition at 100 °C for 60 min;
[b]Isolated yield of product by column chromatography.

III.C.2. Catalyst recovery

The catalyst recovery and reusability were investigated by four cycles counting the use of fresh catalyst for the preparation of phenyl(pyrrolidin-1-yl)methanethione (Table III.3, entry 3a) by the reaction of Aldehyde (1 mmol), pyrrolidine (1 mmol) and sulphur (1. 25 mmol) in presence of 15 mg humic acid in solvent -free condition at 100 °C for 60 min. After the completion of the 1st run, ethyl acetate was added to the reaction mixture (5 mL). The catalyst was easily recovered from the reaction mixture by simple filtration. It was washed with ethyl acetate (3×5 mL) several times and then dried before being used for the next run. After every cycle, the catalyst was almost quantitatively recovered with slight loss in amount up to fourth run. But on fifth cycle, notable decrease in yield and recovery of catalyst was observed.

III.D. Conclusion

In conclusion, we have established a, environmentally benign, upfront and simplistic strategy for the synthesis of functionalized thioamide derivatives under solvent--free condition using humic acid without using any metal catalyst. Absence of any solvent further improves the advantage of the protocol. Catalyst can be recovered by simple filtration which makes these protocols more attractive in the field of green organic synthesis. Replacement of toxic and expensive metal catalyst by environment friendly and inexpensive humic acid is the uniqueness of this protocol which may be helpful in the medicinal as well as industrial chemistry.

III.E. Experimental

III.E.1. General Information

^{1}H NMR, ^{19}F NMR and ^{13}C NMR were recorded using 400 MHz, 376 MHz and 100 MHz Bruker Avance FT-NMR Spectrometer using TMS as internal standard. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad), q (quartet) and m (multiplet).

III.E.2. General procedure

In our general procedure, a mixture of aldehyde (1 mmol), amine (1 mmol) and sulphur (1.25 mmol) in presence of 15 mg humic acid in solvent -free condition at 100°C for 60 min in a 50 mL round-bottom flask using a magnetic stirring bar under open air for 30-60 min and the progress of the reaction was monitored on the TLC. After completion of the reaction the reaction mixture was cooled, then the solution was poured into 100 mL water and extract with ethyl acetate, washed several times with water. The combined organic mixture was dried over

anhydrous Na_2SO_4, concentrated and the residue was purified by column chromatography on silica gel 60–120 mesh using petroleum ether/ethyl acetate as eluent to afford the pure product. All compounds were analyzed by NMR techniques.

III.E.3. Spectroscopy data

1. Phenyl(pyrrolidin-1-yl)methanethione: (Table III.3, entry 3a)

Yellow solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.91-2.11 (m, 4H), 3.46 (t, *J* = 6.6 Hz, 2H), 3.98 (t, *J* = 6.6 Hz, 2H), 7.27-7.40 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.67, 26.49, 52.42, 53.81, 125.63, 128.30, 128.72, 143.98, 197.22.

2. (4-fluorophenyl)(pyrrolidin-1-yl)methanethione: (Table III.3, entry 3c)

Brown solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.90 (s, 2H), 2.00 (d, *J*= 4.8 Hz, 2H), 3.40 (d, *J* = 3.6 Hz, 2H), 3.87 (s, 2H), 6.95-7.31 (m, 4H).

^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm): -112.20 (s, 1F).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.72, 26.60, 53.74, 54.03, 115.16, 115.38, 127.95, 128.04. 140.12, 140.15, 161.50, 163.98, 195.95.

3. (3-nitrophenyl)(pyrrolidin-1-yl)methanethione: (Table III.3, entry 3d)

Brown solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.00-2.19 (m, 1H), 3.58 (t, *J* = 6.6 Hz, 2H), 3.89 (t, *J* = 6.6 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 7.0 Hz, 1H), 8.09-8.14 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 23.15, 26.31, 52.97, 53.87, 121.64, 122.70, 127.56, 130.56, 145.35, 146.78, 193.26.

4. (4-methoxyphenyl)(pyrrolidin-1-yl)methanethione: (Table III.3, entry 3f)

Yellow solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.80-1.95 (m, 4H), 3.40 (t, *J* = 4.8 Hz, 2H), 3.67 (s, 3H), 3.81 (t, *J* = 6.0 Hz, 2H), 6.71-6.74 (m, 2H), 7.23-7.26 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.73, 26.61, 53.83, 54.11, 55.47, 55.60, 113.05, 113.41, 113.72, 127.50, 127.80, 128.08, 132.09, 136.48, 160.06, 196.82.

5. (pyrrolidin-1-yl)(o-tolyl)methanethione: (Table III.3, entry 3h)

Brown liquid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.89-2.03 (m, 2H), 2.18 (s, 3H), 3.26 (t, *J* =5.8 Hz, 1H), 3.28 (t, *J* = 6.0 Hz, 1H), 7.04-7.27 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm):17.98, 25.45, 25.87, 51.36, 52.09, 122.58, 126.83, 127.99, 131.56, 143.95, 197.87.

6. (1*H*-indol-3-yl)(pyrrolidin-1-yl)methanethione: (Table III.3, entry 3i)

Brown solid;

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.78-1.95 (m, 4H), 3.71 (t, *J* = 5.8 Hz, 2H), 3.83 (t, *J* = 6.6 Hz, 2H), 7.01-7.14 (m, 2H), 7.47 (d, *J* = 5.8 Hz, 1H), 7.67 (d, *J* = 5.7 Hz, 1H), 7.93 (d, *J* = 5.8 Hz, 1H), 10.98 (s, 1H);

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 23.75, 27.45, 52.93, 113.85, 117.68, 121.08, 121.78, 123.75, 124.72, 127.44, 135.79, 191.07.

7. (naphthalen-3-yl)(pyrrolidin-1-yl)methanethione: (Table III.3, entry 3j)

Yellow solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.72-2.01 (m, 4H), 3.48 (t, *J* = 6.0 Hz, 2H), 3.89 (t, *J* = 6.0 Hz, 2H), 7.35-7.41 (m, 5H), 7.69 (t, *J* = 5.9 Hz, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 22.88, 25.87, 53.24, 53.67, 121.66, 123.32, 125.96, 126.34, 126.93, 128.65, 128.91, 131.36, 135.37, 140.46, 198.01.

8. Morpholino(phenyl)methanethione:[34] (Table III.3, entry 3l)

Yellow solid;

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.64-3.63 (m, 4H), 3.90 (t, *J* = 4.6 Hz, 2H), 4.46 (t, *J* = 4.8 Hz, 2H), 7.38-7.27 (m, 5H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 49.17, 52.20, 65.65, 65.94, 125.78, 128.22, 128.47, 142.35, 161.83, 198.66.

9. *N*-benzylbenzothioamide: (Table III.3, entry 3m)

Brown liquid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.79 (s, 2H), 7.13-7.37 (m, 8H), 7.59 (d, *J* = 5.4 Hz, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 48.47, 124.87, 126.99, 127.22, 128.13, 129.46, 131.78, 134.62, 138.37, 197.93.

10. *N*-butylbenzothioamide: (Table III.3, entry 3p)

Yellow solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.03 (t, 3H), 1.36 (q, 2H), 1.57-1.65 (m, 2H), 3.61-3.77 (m, 2H), 7.25-7.63 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm):11.86, 20.35, 27.76, 45.07, 124.29, 126.85, 130.12, 142.49, 197.91

III.E.4. Scanned copies of ^{1}H and ^{13}C NMR of the derivatives

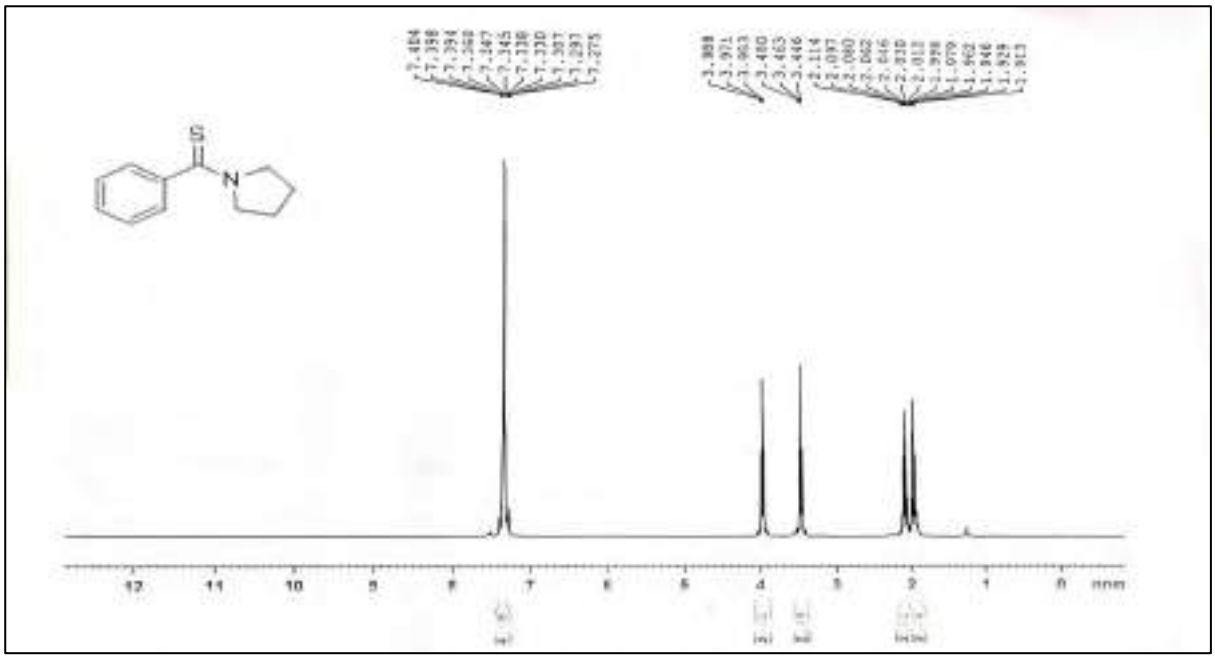


Figure III.3. Scan copy of ^{1}H NMR of Phenyl(pyrrolidin-1-yl)methanethione.

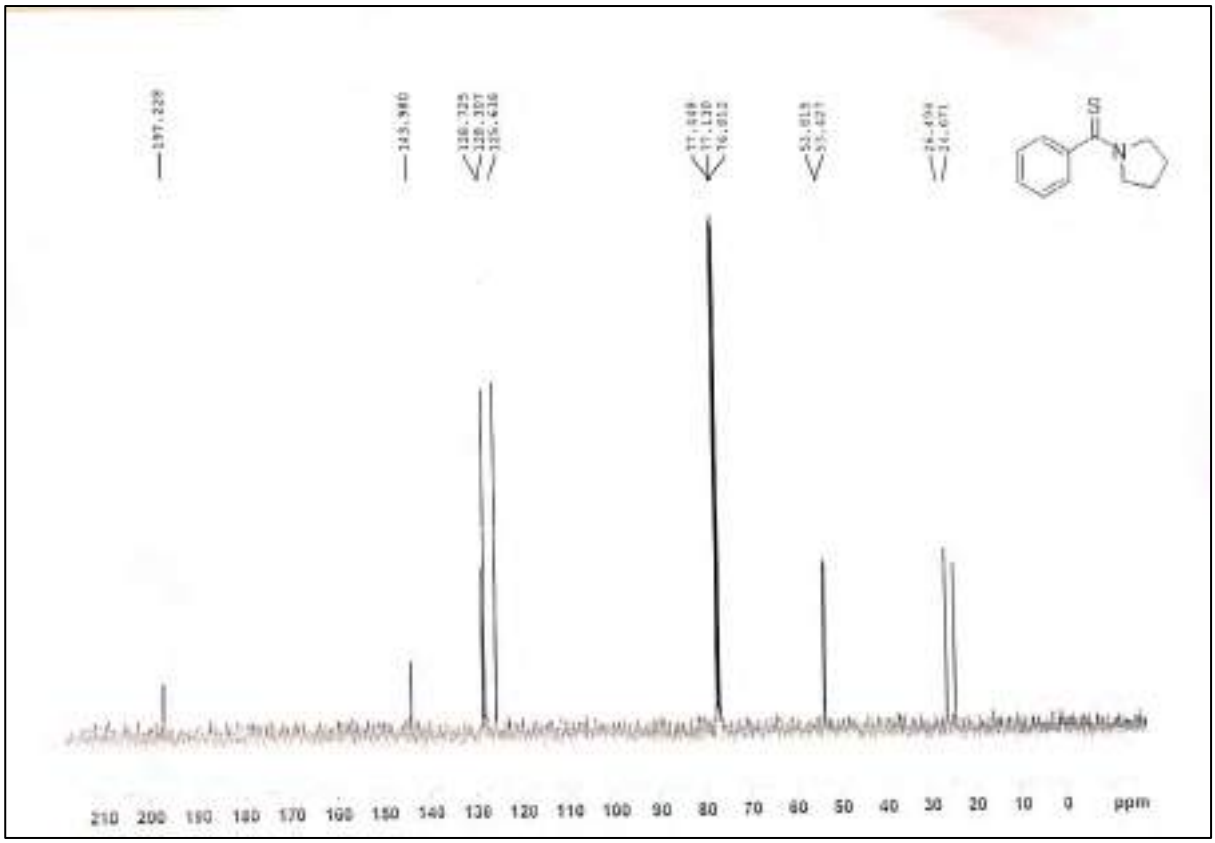


Figure III.4. Scan copy of ^{13}C NMR of Phenyl(pyrrolidin-1-yl)methanethione.

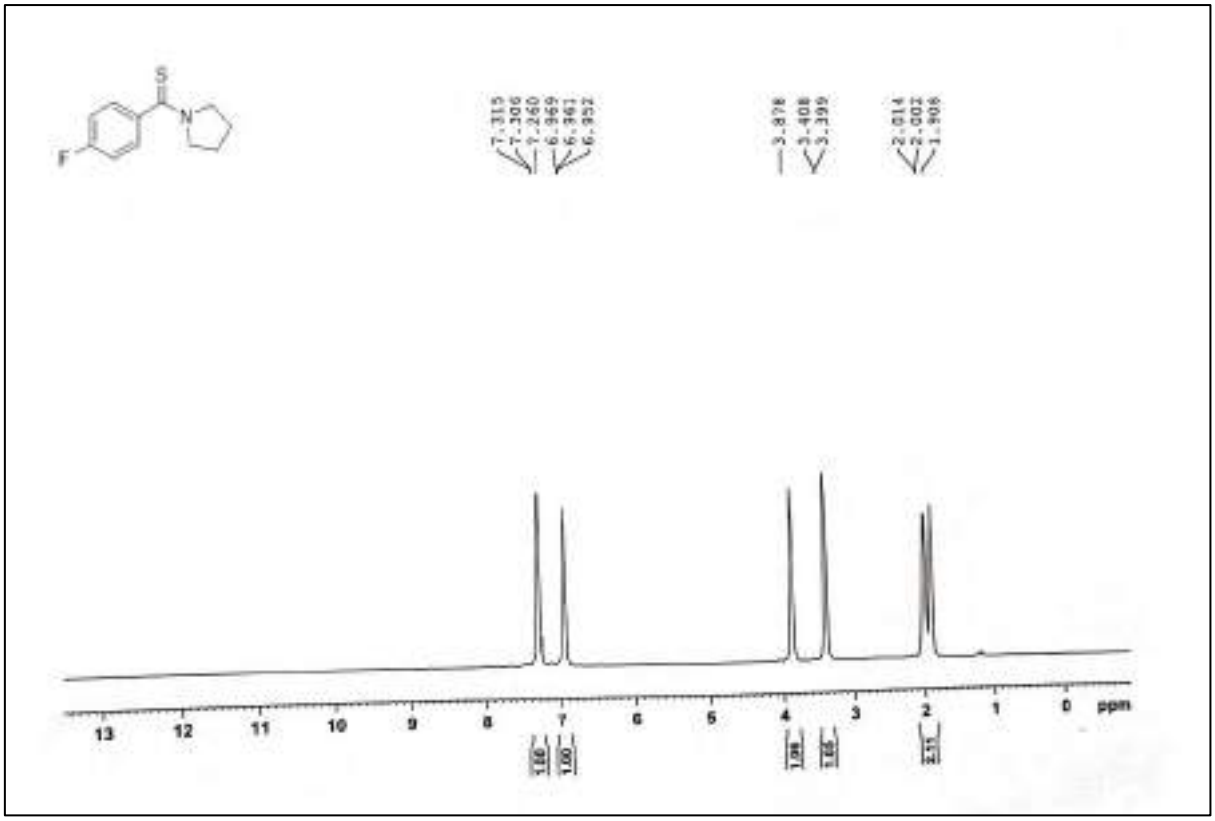


Figure III.5. Scan copy of ^{1}H NMR of (4-fluorophenyl)(pyrrolidin-1-yl)methanethione.

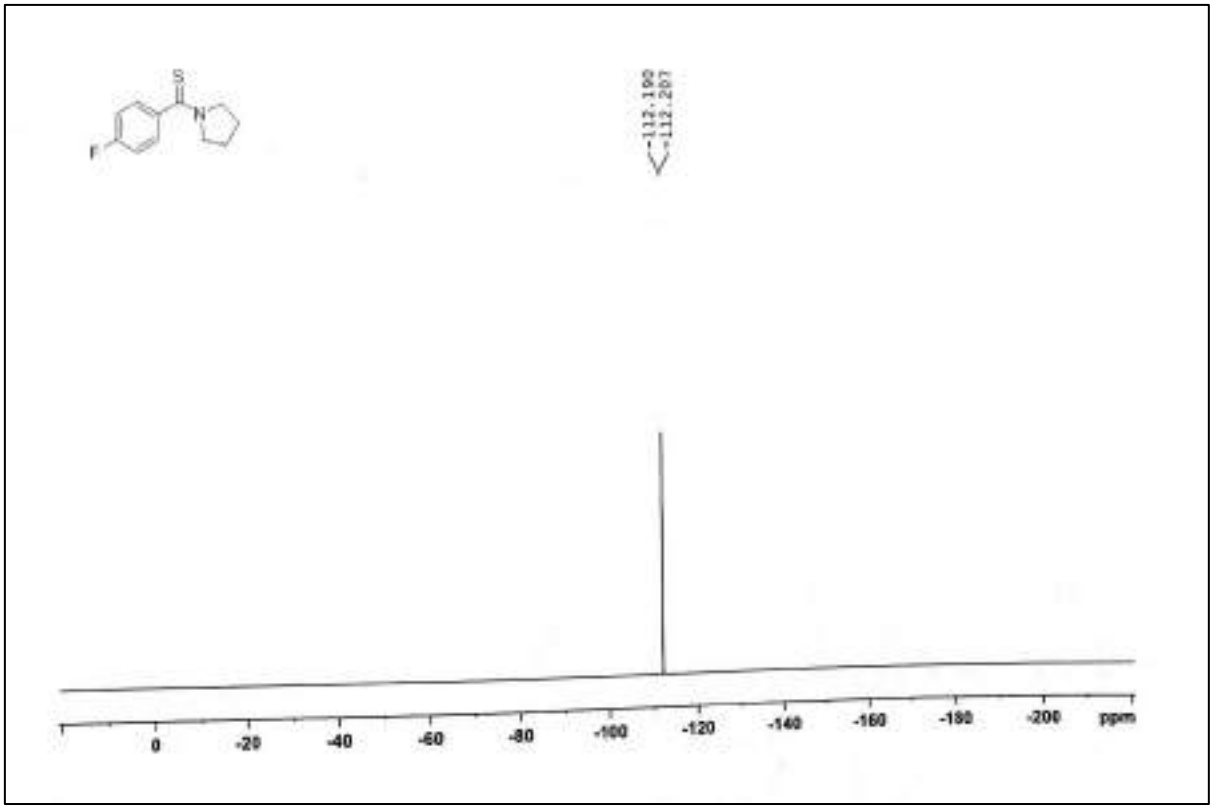


Figure III.6. Scan copy of ^{19}F NMR of (4-fluorophenyl)(pyrrolidin-1-yl)methanethione.

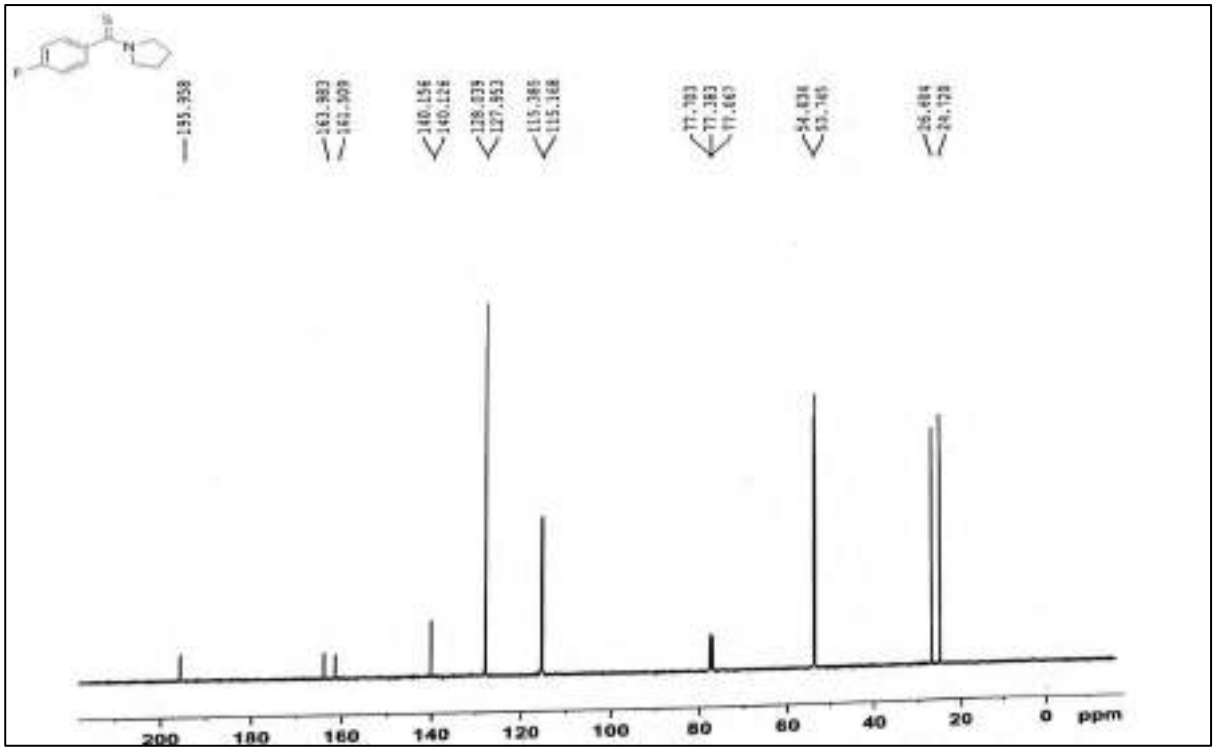


Figure III.7. Scan copy of ^{13}C NMR of (4-fluorophenyl)(pyrrolidin-1-yl)methane.

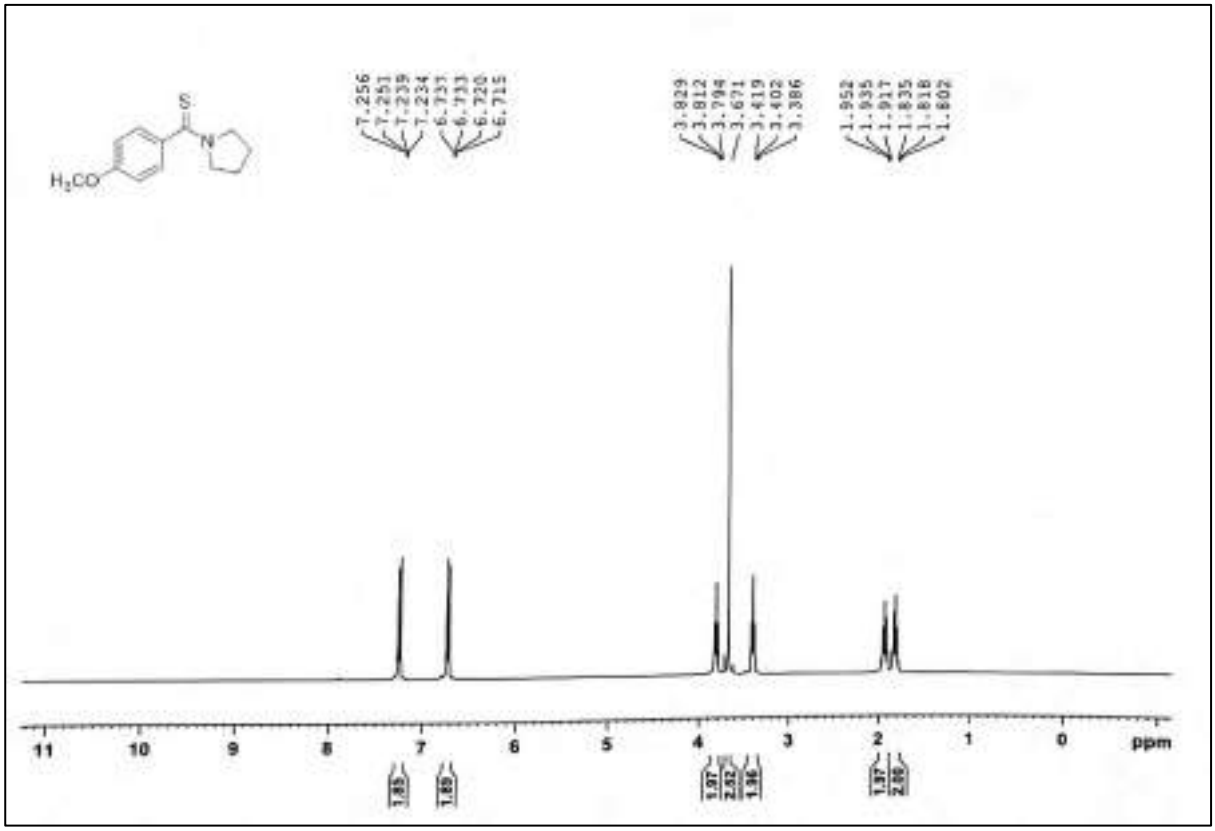


Figure III.8. Scan copy of ^{1}H NMR of (4-methoxyphenyl)(pyrrolidin-1-yl)methanethione.

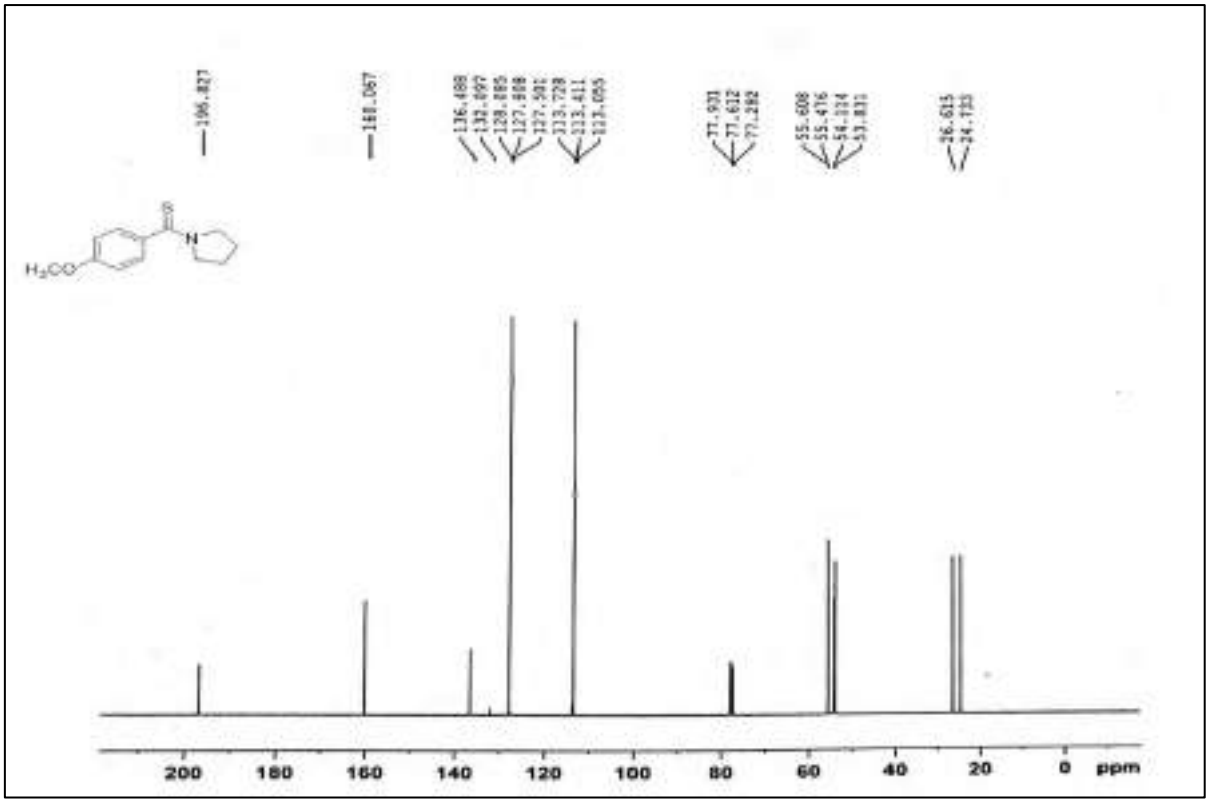


Figure III.9. Scan copy of ^{13}C NMR of (4-methoxyphenyl)(pyrrolidin-1-yl)methanethione.

III.F. Reference

References are given in BIBLOGRAPHY under Chapter III.

Chapter IV

Greener One-pot Synthesis of 3-Substituted Indoles using L-Ascorbic acid in water as green eco-friendly catalyst and alternatively using PEG-300 in catalyst-free condition

IV.A. Introduction

Structural motif of Indole has been familiar universally as a privileged structure in chemistry of medicinal field due to presence of heterocyclic scaffold in plentiful therapeutic agents and natural products. This demonstrates wide range of biological[1-5] and pharmacological properties[6-12] such as antioxidative, antibacterial, anticancer, antimicrobial and insecticidal activities, and an array of derivatives of indole have been also used as antibiotics in pharmaceuticals[13-14]. Indole nucleus[15] is present in a number of drugs available in market currently. Most of these drugs belong to 3-substituted indole family, as an important intermediate for chemical synthesis.

Drugs like Frovatriptan, Sumatriptan, Zolmitriptan and Rizatriptan are utilized as anti-migraine headaches[16-18] is made of 3-substituted indole as main structural unit. Whereas azolylbenzyl indole is used as a breast cancer inhibitor[19] and bis-indole is used as HIV-1 integrase inhibitor[20] (Figure IV.1).

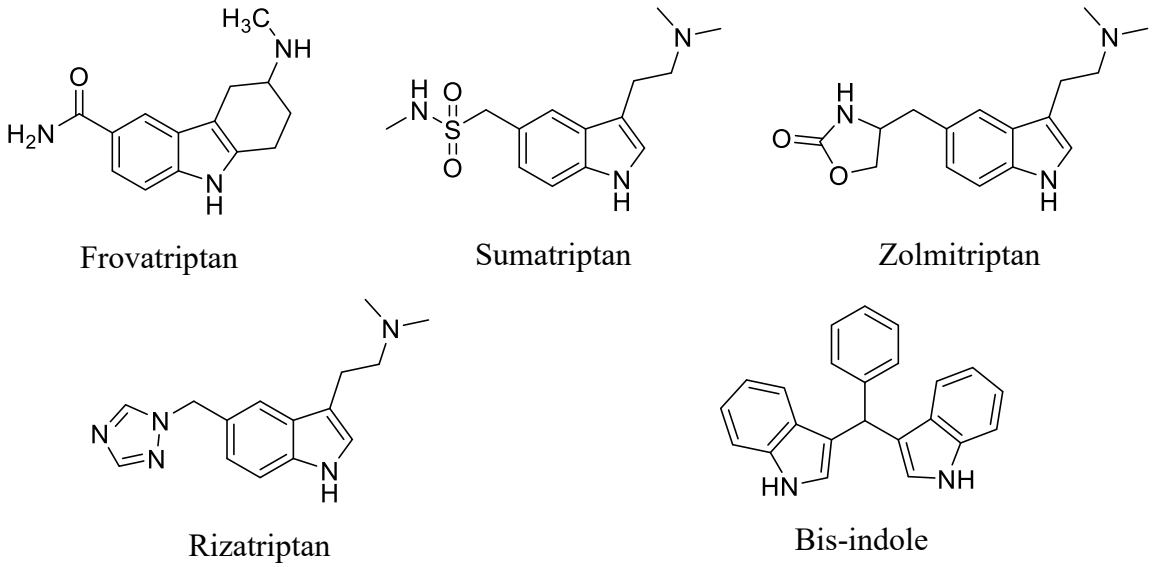


Figure IV.1. Biologically active 3-substituted indoles.

IV.B. Background and objectives

Indole is also addressed as benzopyrrole containing benzenoid nucleus and has ten π-electrons and hence aromatic in nature. Therefore, electrophilic substitutions occur readily as pi ring cloud is present over it. Regioselective functionalization of indole ring at the 3-position can be carried out exploiting a Friedel–Crafts process. For this process use of electron poor alkenes activated by bronsted or lewis acid is widely used[21]. There are various ways to perform the alkylation of indolyl compounds, with the main modifications lying in the nature of the electrophile utilized. Among the different methods 1,2-addition of arenes to carbonyl compounds, Micheal type condensation between Arenes and electron deficit C=C bonds,

opening of ring of epoxides and aziridines are some of the established methods. Transition metal catalyzed allylic substitution known as Tsuji-Trost reaction is also applicable[22]. A few substitutions of indole core is represented in Figure IV.2.

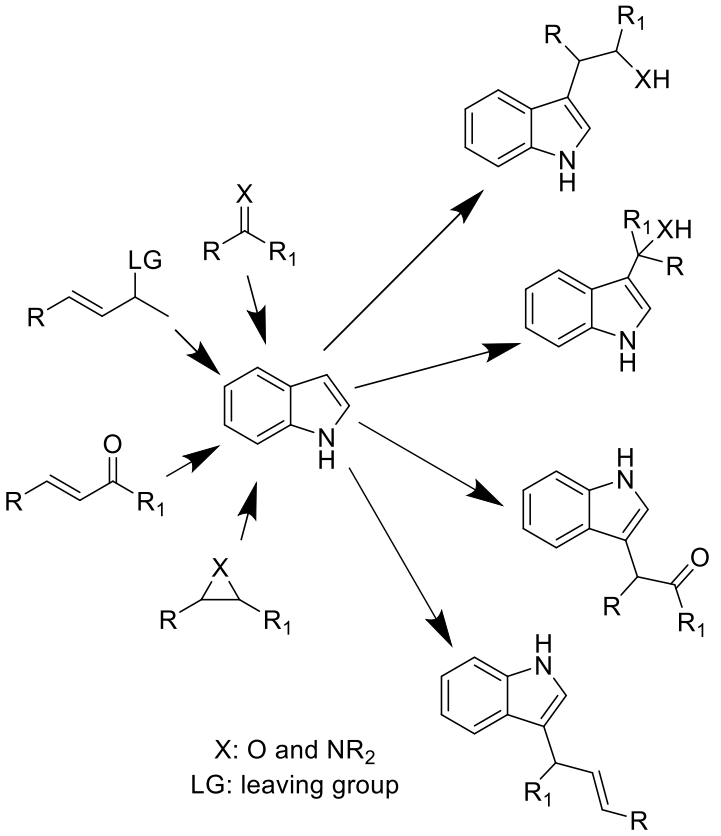
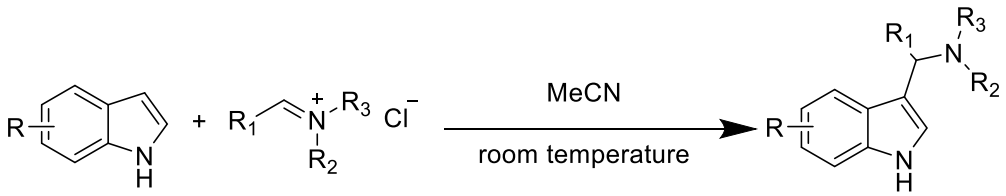


Figure IV.2. Different approaches for the Friedel–Crafts alkylation of indoles.

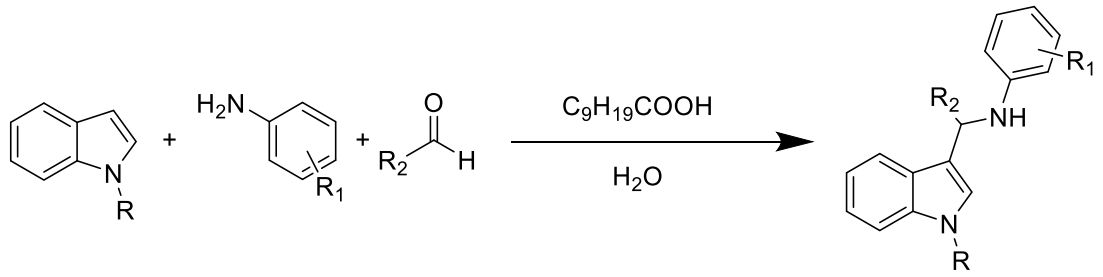
IV.B.1. Specialized methods for synthesis of 3-substituted amino indoles

Many advancements have been reported for synthesis of 3-substituted amines and their derivatives. In 1996, Nikolaus Risch *et al.* had synthesized 3-amino alkylated indoles[23-25] using indole and the iminium salt of the aromatic aldehyde in a Mannich based reaction (Scheme IV.1). Acetonitrile has been used as solvent in this process at room temperature. Various indoles; like *N*-methyl, *N*-benzyl, 1*H*, *N,N*-dimethylaniline, indoles are employed for this method with good yield. Se of toxic acetonitrile is a limitation of this process and reaction time reported up to 48 hours in some cases.



Scheme IV.1. 3-substituted amino indole synthesis using acetonitrile.

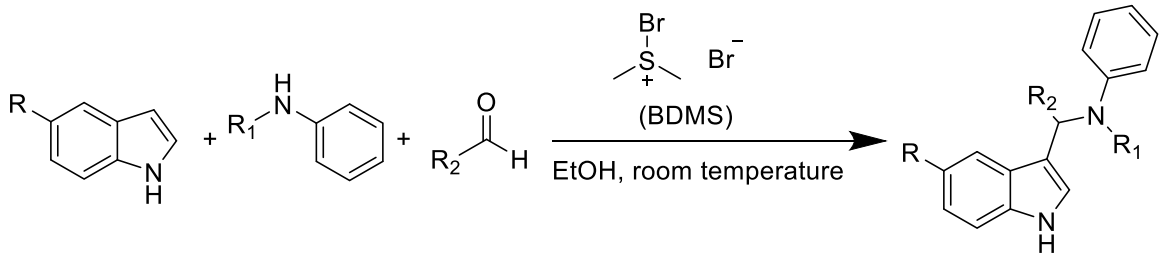
Later Kobayashi *et. al.* reported synthesis of 3-substituted indole derivatives by using Aza Friedel Craft's reactions. This process is catalyzed by carboxylic acid and developed by reactiong aldehyde, primary amines and indoles in water. But the reaction had only employed *o*-anisidine depicting it has substrate limitations[26] (Scheme IV.2).



Scheme IV.2. Synthetic Scheme of 3-Substituted Indoles using carboxylic acid.

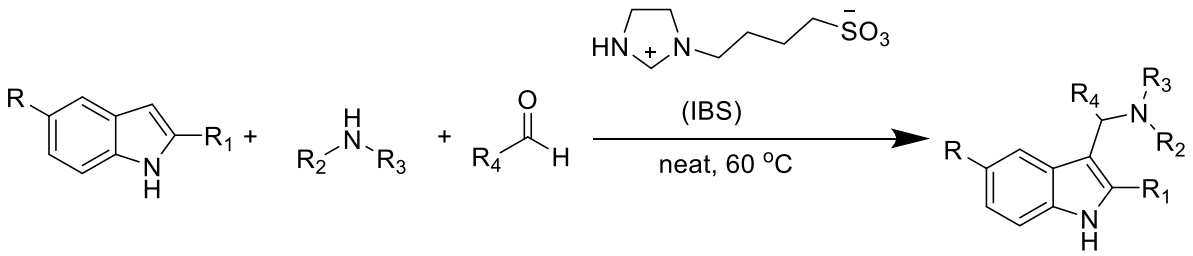
IV.B.2. Modern approach towards 3-substituted amino indoles

In 2010, S. Yadav *et al.* reported a facile synthesis of 3-substituted indoles via multi-component synthesis of substituted indoles, aldehydes and substituted amines[27]. In this method bromodimethylsulfonium bromide (BDMS) is used as catalyst in ethanol medium at room temperature (Scheme IV.3).



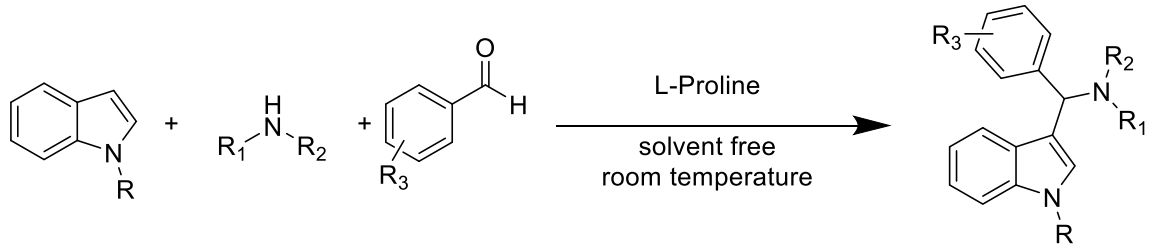
Scheme IV.3. Synthesis of 3-aminoalkylated indoles using bromodimethylsulfonium bromide.

Another multicomponent reaction for synthesis of 3-amino indole is reported by A. Hajra *et al.*[28]. In the three-component coupling they have used indole, aldehyde and amines. Catalytic amount of zwitterionic-type molten salt, 4-(1-imidazolium)-butane sulfonate (IBS) is used for the reaction under solvent-free condition at 60 ºC temperature (Scheme IV.4).



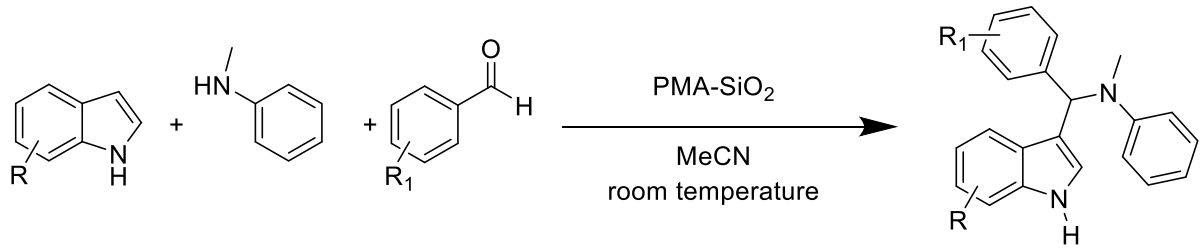
Scheme IV.4. Synthesis of 3-aminoalkylated indoles using 4-(1-imidazolium)-butane sulfonate.

L-proline is also employed as catalyst for synthesis of 3-amino alkylated indoles by M. Kumar *et al.*[29]. The reaction progressed through multi-component mannich type reaction. Secondary amines, aldehydes and indoles are condensed in a solvent -free reaction condition at room temperature. Several aldehydes with electron releasing and withdrawing groups produce good yield of corresponding 3-amino alkylated indole in this reaction condition (Scheme IV.5).



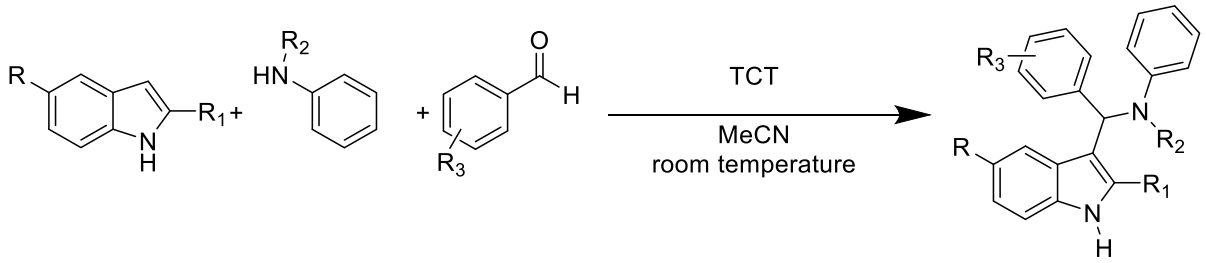
Scheme IV.5. Synthesis of 3-amino alkylated indole by L-proline.

J.S. Yadav *et al.* reported another multi-component one-pot synthesis of 3-substituted indoles[30]. Solid supported phosphomolybdic acid (PMA) with silica (SiO_2) is used as catalyst. The reaction is performed in acetonitrile as solvent and at room temperature to yield desired 3-substituted indoles with various aldehydes and amines in good yield (Scheme IV.6).



Scheme IV.6. Synthesis of 3-amino alkylated indole using PMA-SiO_2.

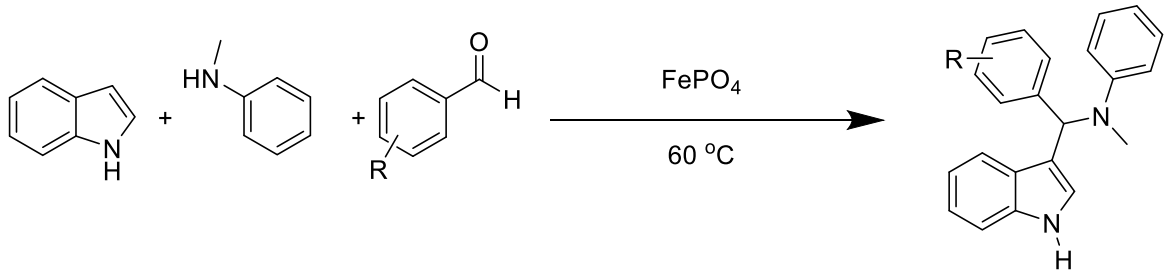
Another interesting method for formation of 3-amino alkylated indole is described by K. Damodar *et al.*[31]. In this reaction multi-component condensation of substituted indole, aldehydes and amines is attempted using 2,4,6-trichloro-1,3,5-triazine (TCT) as catalyst (Scheme IV.7). Acetonitrile is used as solvent for the process at room temperature. This method is applicable for various aldehydes and ketones.



Scheme IV.7. Synthesis of 3-[(*N*-Alkylanilino)(aryl)methyl]indoles Using TCT.

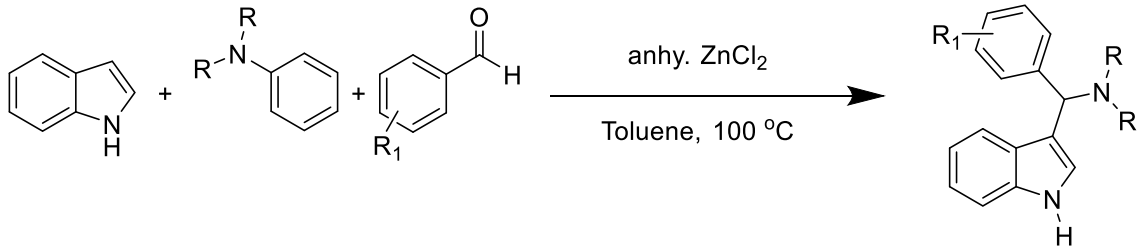
In recent time, F.K. Behbahani *et al.* reported a multi-component one-pot synthesis of 3-amino alkyl indoles[32]. Iron (III) phosphate is used as catalyst in this process at 60 ºC by combination

of aromatic aldehydes, *N*-methyl aniline and indole as precursor (Scheme IV.8). No solvent is used in this method of 3-amino alkylated indole preparation.



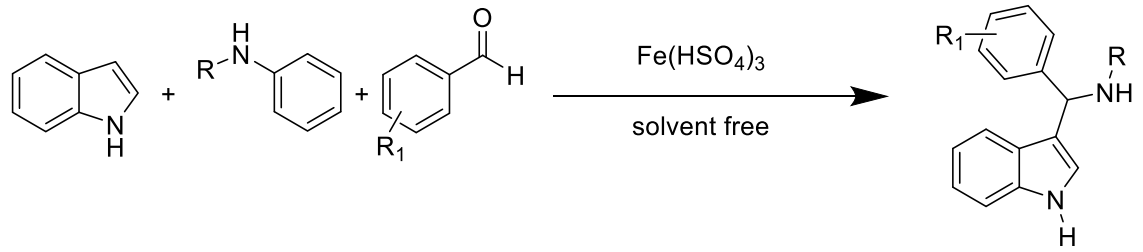
Scheme IV.8. Three-component synthesis of 3-aminoalkylindoles using iron (III) phosphate.

Ganesan *et al.* reported another one-pot synthesis of 3-arylmethyl and diarylmethyl indoles via multi-component synthesis[33]. The reaction is mediated by anhydrous $ZnCl_2$ in toluene at 100 °C temperature (Scheme IV.9). The reaction takes up to 5 hours in some cases.



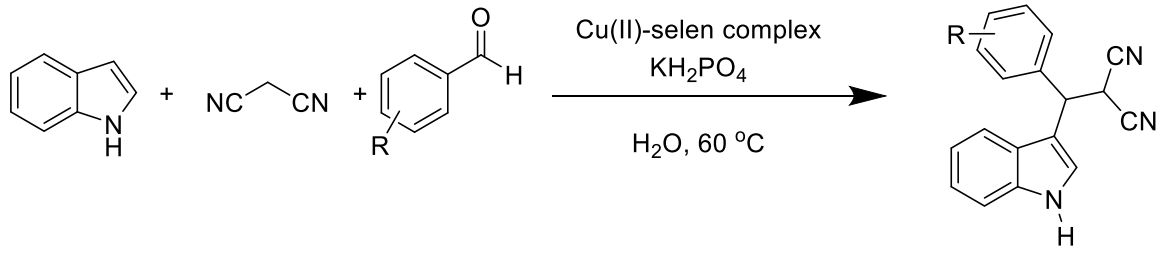
Scheme IV.9. Synthesis of 3-arylmethylindole using $ZnCl_2$.

M. Gholizadeh *et al.* reported one-pot method for synthesis of *tert*-indolylmethane amine derivatives[34]. In this multi-component coupling between aldehyde, *N*-alkyl aniline and indole is catalyzed by $Fe(HSO_4)_3$ in solvent -free condition at 45 °C temperature (Scheme IV.10). The metal catalyst has reusability property up to six times. Reaction time is up to 2.5 hours in ideal cases.



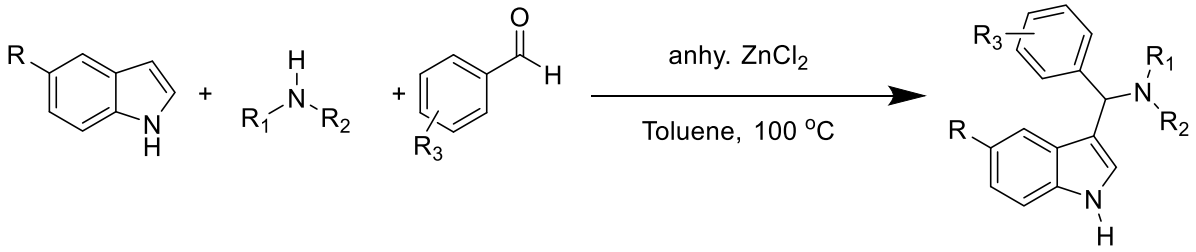
Scheme IV.10. Solvent-free synthesis of 3-substituted indole derivatives by $Fe(HSO_4)_3$.

An interesting effort towards synthesis of 3-indole derivatives is reported by X. Zhou *et al.* in water[35]. Copper acetate combining with sulfonato salen complex successfully yielded desired 3-substituted indole product in good yield from indole, aldehyde, and malononitrile (Scheme IV.11). Weak acid KH_2PO_4 is beneficial for the increase in yield of the reaction.



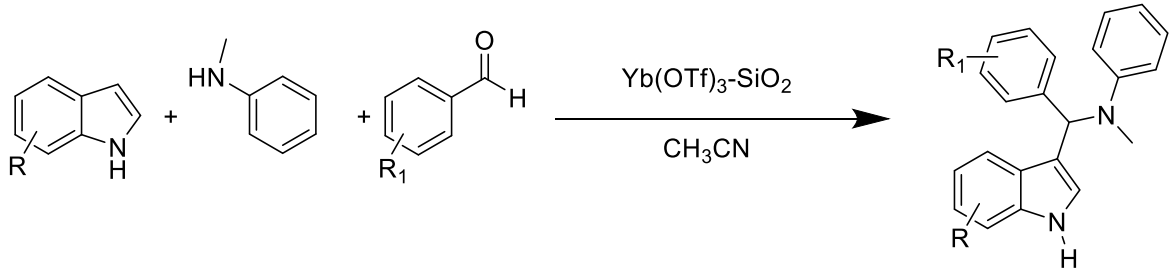
Scheme IV.11. Synthesis of 3-indole derivatives by copper sulfonato salen catalyst.

A. Kumar *et al.* reported an unique micelle promoted multicomponent synthesis of 3-amino alkylated indoles via a Mannich-type reaction[36]. In this reaction secondary amines, aldehydes and indoles combine to form desired 3-amino alkyl indoles (Scheme IV.12). The advantage of using micelle is it stabilizes the intermediate iminium ions, which eventually undergo to give 3-amino alkylated indole. SDS is used as surfactant at 80 °C for the reaction.



Scheme IV.12. Micelle promoted multicomponent synthesis of 3-amino alkylated indoles.

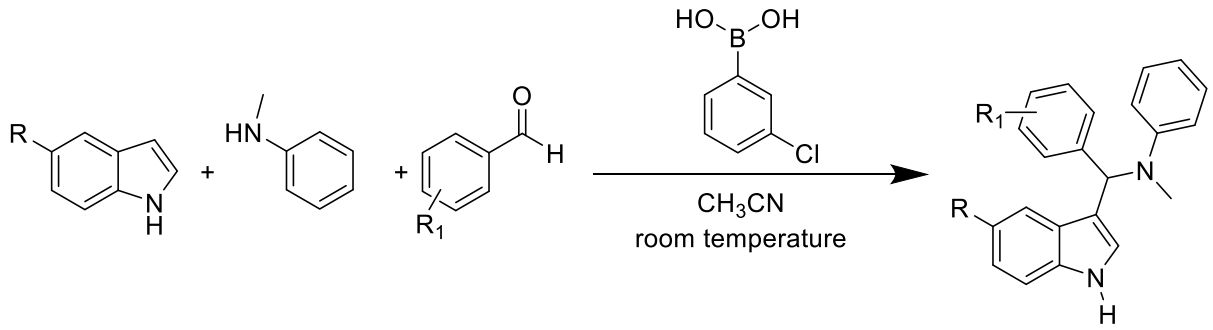
In an effort of finding anticancer and src kinase inhibitory activities of 3-substituted indoles A. Kumar *et al.* reported one-pot synthesis of 3-substituted indoles by multi-component condensation catalyzed by $Yb(OTf)_3$–SiO_2[37]. Acetonitrile is used as solvent in the reaction at room temperature for up to 2 hours (Scheme IV.13). All the synthesized compounds were estimated for inhibition of cell proliferation of human ovarian adenocarcinoma (SK-OV-3), human colon carcinoma (HT-29) and c-Src kinase activity.



Scheme IV.13. Synthesis of 3-substituted indoles by one-pot three-component coupling using $Yb(OTf)_3$–SiO_2.

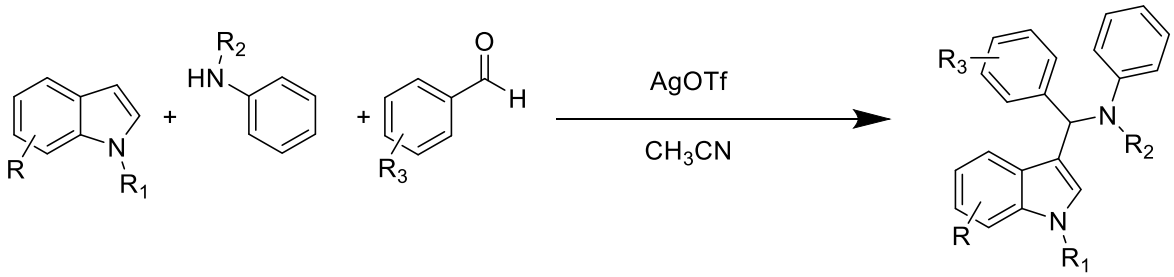
S.R. Bhusare *et al.* reported another one-pot three component synthesis of 3-aminoalkylated indoles[38]. 3-chlorophenylboronic acid is used as organo catalyst in this reaction in acetonitrile at room temperature in this method (Scheme IV.14). Three components indoles, aromatic

aldehydes and *N*-methyl aniline forms corresponding 3-aminoalkylated indoles in good yield in this method.



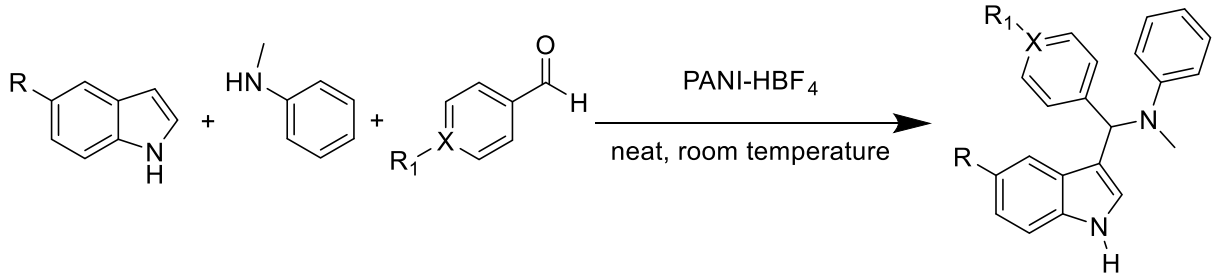
Scheme IV.14. Synthesis of 3-aminoalkylated indoles using 3-chlorophenylboronic acid.

A. Kumar *et al.* advanced their study for synthesis of 3-aminoalkylated indoles using Silver triflate as catalyst[39]. In this method they used acetonitrile as solvent too (Scheme IV.15). One-pot multi-component coupling of aldehydes, *N*-methylanilines, and indoles produced good yield of corresponding product. Further, 3-aminoalkylated indoles was examined for their antibacterial activities against Gram-negative and Gram-positive bacteria respectively.



Scheme IV.15. Synthesis of 3-aminoalkylated indoles using silver triflate.

S. Palaniappan *et al.* reported synthesis of multi-component synthesis of 3-substituted amino methyl indoles under solvent-free conditions[40] (Scheme IV.16). Polyaniline salt is used as polymer-based catalyst in this process and this three-component synthesis yields desired product in good yield even at room temperature. Reusability of the polymer catalyst is also explored in this reaction.



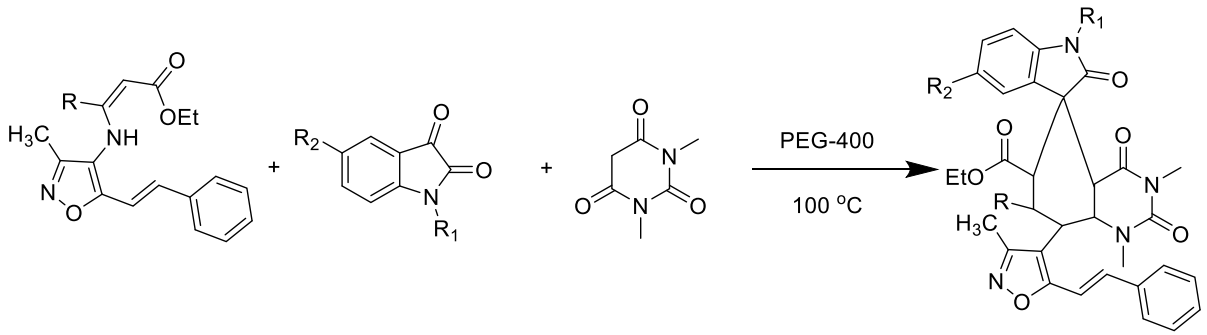
Scheme IV.16. Three-component one-pot synthesis of 3-substituted amino methyl indoles using PANI-HBF_4.

IV.B.3. Background of PEG 300 in organic synthesis

In organic synthesis, a major concern is with solvents due to wide range of environmental hazards caused by them. Major disadvantages incorporate their volatile nature, pyrophoric property and less recoverability. Develop solvent -free protocols was attempted in many cases, which to some extent have been successful for a few reactions[41]. However, solvent plays a significant role in organic transformations by providing homogeneous phase to the reactants and enhancing the molecular interactions. To solve the critical concerns and developing efficient catalyst systems, utilizing PEG as reaction medium is highly looked-for in terms of environmentally benign condition as well as atom economy.

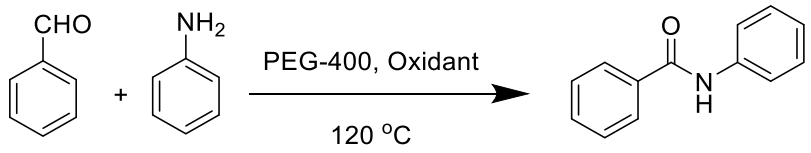
Meanwhile, water as a green solvent has also been well cited for many years. Though, the practical utilization is limited because of the hydrophobic nature of organic compounds and the sensitivity of various catalysts to moisture. Now a day, an alternate reaction media polyethylene glycol (PEG)[42] is more popular, due to their attractive properties like non-toxicity, bio-compatibility and bio-degradability. Moreover, PEG is considered as a high boiling, environmentally benign, inexpensive, easily separable, safe, recyclable, bio-degradable, non-flammable solvent.

PEG mediated synthesis is getting notable appreciation in recent times. P.K. Pittala *et al.* reported one-pot synthesis of isoxazole substituted spirooxindole derivatives in PEG-400 medium[43] (Scheme IV.17). This method is advantageous as it is a toxic metal -free synthesis which elevates its scope. Excellent yield of product is reported by this method for synthesis of various functionalized isoxazoles.



Scheme IV.17. PEG-400 facilitated synthesis of substituted spirooxindole derivatives.

Z.C. Shang *et al.* reported recently oxidative amidation with aldehyde and amines in a one-pot synthesis[44]. PEG-400 is used as catalyst as well as reaction medium at 120°C temperature. *N*-substituted amides are produced in good yield in this method (Scheme IV.18).

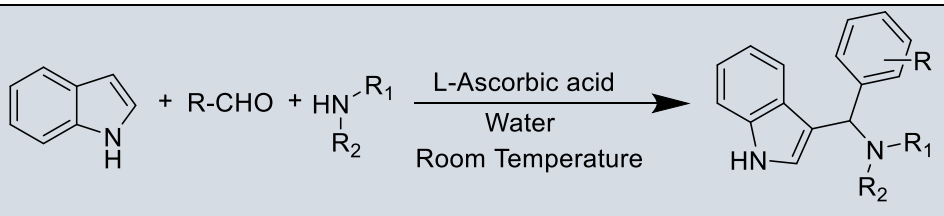


Scheme IV.18. Synthesis of *N*-substituted amide in PEG-400/oxidant system.

IV.C. Present Work

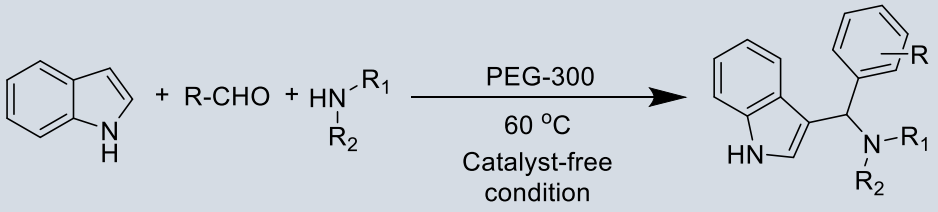
Our strategy for synthesis of 3-amino alkylated indoles involves a multi-component mannich type reaction[20] in metal -free condition. L-ascorbic acid has been proven to be a very useful mild and economical reagent in our previous findings of synthesis of 2-Substituted-2,3-dihydroquinazolin-4(1*H*) one and 2-Substituted Quinazolin-4(3*H*)-one in water[21] and synthesis of substituted 1*H*-tetrazoles from organic nitrile precursors. Therefore, we continued our study for synthesis of 3-amino indole with L-ascorbic acid in water which produced good yield (Scheme 1). According to green chemistry, water is considered as an economic and environmentally benign solvent. Though, water is a poor solvent for organic synthesis mainly due to poor solubility of reactants in it, still we observed sizable yield of product while observing our scheme in water as solvent and that is worth exploring. Further we extended the scope of the reaction with PEG-300 taking inspiration from success of various sustainable organic synthesis[22].PEG-300, a bio-degradable solvent which itself acted as a catalyst produced 3-amino indole in considerable amount (Scheme 2). It is well known that PEG is less basic than other hydroxylic solvents such as water, ethanol or methanol, ethers. Thus, it results in the hydrogen atoms of PEG being more positive (acidic) to activate electron rich carbonyl oxygen. The oxygen atom of PEG may activate acidic proton to initiate the iminium ion formation and then attacking of indole on iminium ion, followed by proton abstraction from indole moiety to yield the final product.

Herein we report synthesis of 3-amino alkylated indoles involving a multi-component mannich type reaction by L-ascorbic acid and water at room temperature. Also, we are reporting an alternate approach for synthesis of 3-amino indole in PEG-300 at 60 °C temperature under catalyst-free condition.



1 2 3 4

Scheme IV.19. L-Ascorbic acid catalysed multi-component synthesis of the 3-amino indole in water.



1 2 3 4

Scheme IV.20. Multi-component synthesis of the 3-amino indole in PEG-300 without any catalyst.

Where, R = Alkyl, Phenyl, Substituted phenyl. R_1= Alkyl, Phenyl. R_2= H, Alkyl.

IV.C.1. Result and discussion

We started our investigation with mild acid, L-ascorbic acid for formation of initial iminium ion by nucleophilic attack of substituted amine on substituted aldehyde which further trapped by indole to provide 3-amino alkyl indoles. Stronger bronsted acids like PTSA (Table IV.1, entry 1), TFA (Table IV.1, entry 2) produces large amount of bis-indole as by product. None of the silica supported acids viz., SiO_2-Cl (Table IV.1, entry 4), $HClO_4$-SiO_2 (Table IV.1, entry 3) etc. too were found to be efficient to yield desired compound. We also turned our attention to organo catalysts like amino acids due to their inexpensiveness and recyclability for various organic reactions. Basic amino acids like L-histidine (Table IV.1, entry 5) and L-lysine (Table IV.1, entry 6) were found ineffective to form the desired product. But acidic amino acids like L-aspartic acid (Table IV.1, entry 7) and L-glutamic acid (Table IV.1, entry 8) were found to be delivering 3-amino indoles but in poor yield. L-proline (Table IV.1, entry 9) provided better yield of our desired product in ethanol but still fails to meet the yield achieved by L-Ascorbic acid in water medium (Table IV.1, entry 10).

Table IV.1. [a]Optimization of acid catalysts for synthesis of 3-amino indole.

Entry	Acid Catalyst	[b]Yield(%)
1	PTSA	20
2	TFA	17

3	$HClO_4$-SiO_2	Trace
4	SiO_2-Cl	Trace
5	L-histidine	-
6	L-lysine	-
7	L-aspartic acid	32
8	L-glutamic acid	35
9	L-proline	62
10	**L-ascorbic acid**	**88**

The bold signifies most optimized condition.

[a] Reaction of Indole (1 mmol), 4-methoxybenzaldehyde (1.2 mmol) and aniline (1.2 mmol) in presence of acid catalyst and 5 ml of water as solvent at room temperature.

[b] Isolated yield

We also tried various mild solvents with L-ascorbic acid like ethanol (Table IV.2, entry 3,4), methanol (Table IV.2, entry 1, entry 2), DCM (Table IV.2, entry 12), Benzene (Table IV.2, entry 5), DMF (Table IV.2, entry 6), DMSO (Table IV.2, entry 7), THF (Table IV.2, entry 8) and in solvent-free condition too (Table IV.2, entry 10). Ethanol (Table IV.2, entry 4) and methanol (Table IV.2, entry 2) produces very close yield of 3-amino indoles compared to water (Table IV.2, entry 11). But considering its availability and economical advantage over the other solvents, water is selected as most competent solvent with L-Ascorbic acid (Table IV.2).

Table IV.2. [a]Optimization of solvent and time for synthesis of 3-amino indole.

Entry	Solvents	Time (hours)	Yield[%][b]
1	MeOH	10	82
2	MeOH	3	80
3	EtOH	10	86
4	EtOH	3	83
5	Benzene	10	56
6	DMF	10	45
7	DMSO	10	67
8	THF	10	Trace
9	Water	10	92
10	Solvent -free	10	26
11	**Water**	**3**	**88**
12	DCM	10	Trace

The bold signifies most optimized condition.

[a] Reaction of Indole (1 mmol), 4-methoxybenzaldehyde (1.2 mmol) and aniline (1.2 mmol) in presence of L-Ascorbic acid and 5 ml of solvent at room temperature.

[b] Isolated yield

We have developed an alternate approach to this 3-amino indole formation as well using PEG-300 only in a catalyst-free condition (Table IV.3, entry 8). This reaction opportunity is explored using various catalyst -free conditions using DMSO (Table IV.3, entry 1), DMF (Table IV.3, entry 2), CH_3CN (Table IV.3, entry 6), Toluene (Table IV.3, entry 3), EtOH (Table IV.3, entry 5), Water (Table IV.3, entry 4), PEG-600 (Table IV.3, entry 10, entry 11), Glycerol (Table IV.3, entry 12, entry 13) and PEG-300 (Table IV.3, entry 8, entry 9). Among all these solvents PEG-600 (Table IV.3, entry 10) produced middling yield but a higher temperature requirement is a drawback. Glycerol (Table IV.3, entry 12) also shown considerable yield but PEG-300 (Table IV.3, entry 8) produced the best yield among all the solvents (Table IV.3).

Table IV.3. [a]Optimization of solvent and temperature for synthesis of 3-amino indole under catalyst-free condition

Entry	Solvent	Temp (^oC)	Yield[%][b]
1	DMSO	120	30
2	DMF	120	25
3	Toluene	110	33
4	Water	reflux	53
5	EtOH	reflux	50
6	CH_3CN	70	26
7	PEG-300	120	89
8	**PEG-300**	**60**	**86**
9	PEG-300	RT	68
10	PEG 600	120	78
11	PEG 600	60	60
12	Glycerol	120	72
13	Glycerol	60	66

The bold signifies most optimized condition.

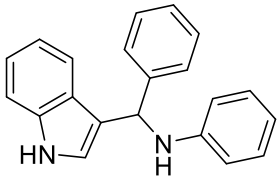
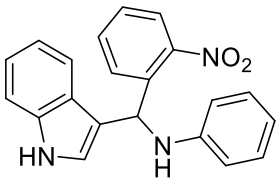
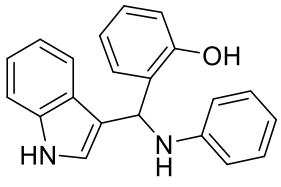
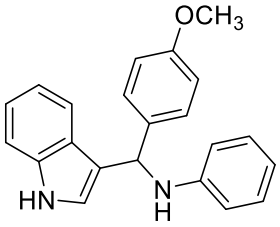
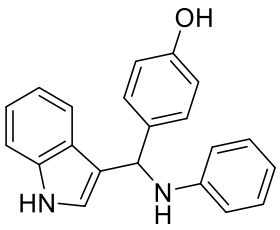
[a] Reaction of Indole (1 mmol), 4-methoxybenzaldehyde (1.2 mmol) and aniline (1.2 mmol) in presence of 5 ml of solvent at various temperature under catalyst-free condition for 3 hours.

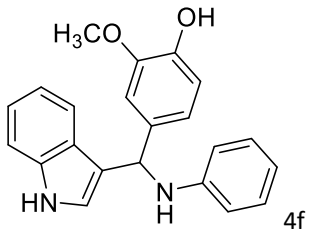
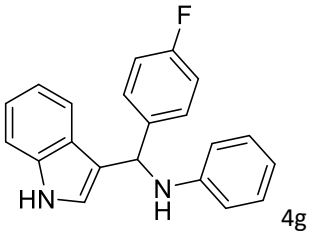
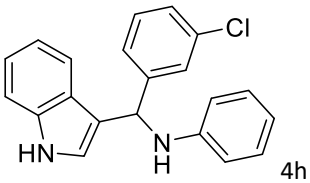
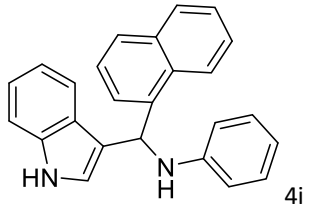
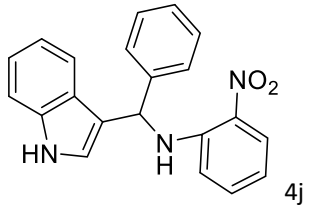
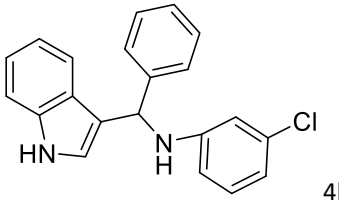
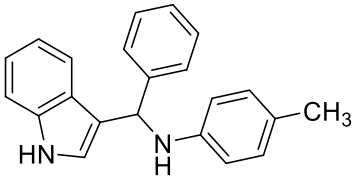
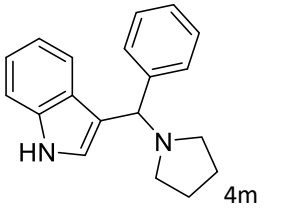
[b] Isolated yield

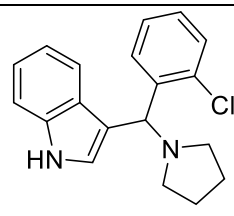
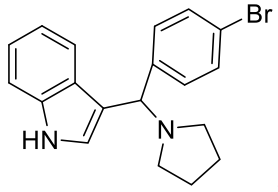
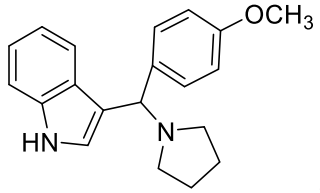
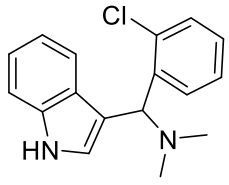
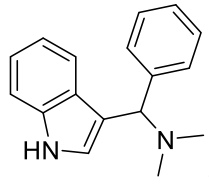
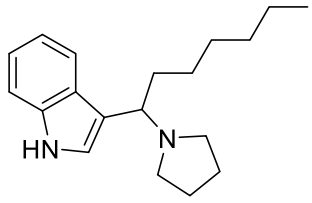
Generally, the 3-aminoalkylation reaction occurs at the C3 position of the indole ring. But when the C3 position is covered by a group, the reaction did not proceed to C2 position. In free C3 indoles the reaction proceeded smoothly with aromatic aldehydes, anilines and secondary

amines containing different functional groups as alkoxy, hydroxy, nitro, bromo, fluoro, chloro, alkyl. Aromatic aldehydes and aniline containing electron donating group produces good yield (Table IV.4, entry 4c, 4d, 4e, 4h, 4k, 4l, 4o, 4p), whereas electron deficit aromatic aldehydes also provided considerable yield but lesser in amount (Table IV.4, entry 4b, 4j). Presence of naphthalene group in aldehyde also yields satisfactory result (Table IV.4, entry 4i). Further the reaction was not very successful under same condition with aliphatic aldehydes (Table IV.4, entry 4s) and unsuccessful with *N*,*N*-diphenylamine. The prospect of this reaction is demonstrated with respect to various aromatic aldehydes and amines and the results are presented in Table IV.4.

Table IV.4. [a]Synthesis of 3-amino indole under catalyst-free condition.

Entry	Product	Yield[%] (With L-Ascorbic acid/water)[b]	Yield[%] (With PEG-300)[c]
1	 4a	86	84
2	 4b	76	72
3	 4c	85	81
4	 4d	88	86
5	 4e	87	83

6	 4f	81	77
7	 4g	82	76
8	 4h	84	82
9	 4i	77	71
10	 4j	78	73
11	 4k	84	75
12	 4l	86	85
13	 4m	83	81

14	 4n	82	78
15	 4o	85	83
16	 4p	86	85
17	 4q	72	75
18	 4r	78	75
19	 4s	58	52

[a]Reaction conditions: indole (1 mmol), aldehyde (1.2 mmol) and amine (1.2 mmol) in presence of [b]L-Ascorbic acid in water as the solvent (5 mL) and in presence of [c]PEG-300 (5 mL) at room temperature. Isolated yield of product measured by column chromatography.

IV.D. Conclusion

In conclusion we have developed a simple, relevant, benign and eco-friendly facile strategy for synthesis of 3-amino indole and its derivatives using L-ascorbic acid and water (Scheme IV.19). Use of water as solvent further enhances the advantage of the protocol. Replacement of expensive and toxic metal catalysts by environment friendly L-ascorbic acid is the highlight of this protocol. Further achievement of good yield and production of 3-amino indoles and its derivatives in less reaction time and at room temperature has added further advantages to this protocol. Alternatively, we extended the scope with catalyst -free condition using only PEG-

300. It provides higher environmental compatibility and sustainability factors as it is a catalyst -free greener process. Therefore, we expect this protocol to achieve wide application in natural product synthesis and in pharmaceutical industry.

IV.E. Experimental

IV.E.1. General Information

All the compounds were purchased from commercial suppliers and used without further purification. All the products were purified by column chromatography on silica gels (60−120 mesh, SRL, India). For TLC, Merck plates coated with silica gel 60, F_{254} were used. ^{1}H NMR and ^{13}C NMR were recorded using 400 MHz, 300 MHz and 100 MHz, 75 MHz respectively on Bruker AV 400 and 300 NMR spectrometer using TMS as internal standard.

IV.E.2. General Procedure

In a typical experiment, the aldehyde (1.2 mmol), amine (1.2 mmol), indole (1 mmol) and L-ascorbic acid (1 mmol) and 5 mL of water were placed in a 25 ml round-bottom flask. The reaction mixture was stirred at room temperature until the reaction was complete (monitored by TLC). After completion the reaction mixture was diluted with water and extracted with ethyl acetate, dried over sodium sulphate and evaporated under vacuum to give the crude product, which was purified by silica gel (60-120 mesh) column chromatography to afford the corresponding product. All products were characterized by ^{1}H NMR and ^{13}C NMR.

IV.E.3. Spectroscopy data

1. *N*-((1*H*-indol-3-yl)(phenyl)methyl)aniline: (Table IV.4, entry 4a)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.82 (s, 1H), 6.45 (s, 2H), 6.96 (t, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.15-7.24 (m, 5H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.55 (s, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 39.7, 110.7, 118.8, 119.1, 119.5, 121.5, 123.2, 125.7, 126.6, 127.8, 128.3, 136.2, 143.6, 147.0.

2. *N*-((1*H*-indol-3-yl)(4-methoxyphenyl)methyl)aniline: (Table IV.4, entry 4d)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.80 (s, 3H), 5.87 (s, 1H), 6.53 (s, 2H), 6.85 (d, *J*=6.0 Hz, 2H), 7.07 (t, *J*= 5.4 Hz, 2H), 7.13-7.44 (m, 6H), 7.45 (d, *J*= 6 Hz, 2H), 7.65 (s, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 29.3, 38.9, 54.8, 55.1, 110.7, 113.2, 113.5, 114.6, 118.8, 119.5, 119.6, 121.5, 121.9, 123.3, 126.6, 129.1, 129.3, 130.8, 133.6, 133.8, 135.9, 136.2, 157.4.

3. 4-((1*H*-indol-3-yl)(phenylamino)methyl)-2-methoxyphenol: (Table IV.4, entry 4f)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.86 (s, 3H), 5.77 (s, 1H), 6.52 (s, 2H), 6.78 (d, *J*= 8 Hz, 2H), 6.84 (s, 1H), 6.97 (t, *J*= 7.6 Hz, 2H), 7.12 (t, *J*= 7.6 Hz, 2H), 7.26 (d, *J*= 8.4 Hz, 2H), 7.37 (d, *J* = 8 Hz, 2H), 7.83 (s, 2H), 10.73 (s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 39.4, 55.4, 110.7, 110.8, 111.1, 113.6, 118.7, 118.9, 119.3, 119.4, 120.2, 120.8, 121.4, 121.6, 121.8, 122.2, 123.2, 126.6, 135.8, 136.3, 143.3, 145.9.

4. 3-(phenyl(pyrrolidin-1-yl)methyl)-1*H*-indole: (Table IV.4, entry 4m)[45]

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.75 (s, 4H), 2.51 (d, *J*=6.5 Hz, 4H), 4.59 (s, 1H), 7.04-7.15(m, 4H), 7.21-7.26 (m, 3H), 7.54 (d, *J*=7.2Hz, 2H), 7.82 (d, *J*=7.5 Hz, 1H), 8.10 (br, s, 1H);

^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 144.41, 136.08, 128.16, 127.69, 126.53, 122.0, 121.79, 119.73, 119.39, 119.30, 111.01, 67.97, 53.68, 23.51.

5. 3-((2-chlorophenyl)(pyrrolidin-1-yl)methyl)-1*H*-indole (Table IV.4, entry 4n)[45]

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.72 (s, 4H), 2.53 (d, *J*=3.2 Hz, 4H), 5.15 (s, 1H), 6.98-7.23 (m, 7H), 7.93(d, *J*=7.2 Hz, 2H), 8.07 (br, s, 1H);

^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 141.25, 135.89, 132.81, 129.40, 129.33, 127.39, 126.83, 126.42, 122.83, 121.74, 119.73, 119.33, 117.75, 111.05, 62.89, 53.41, 23.47;

6. 3-((4-bromophenyl)(pyrrolidin-1-yl)methyl)-1*H*-indole (Table IV.4, entry 4o)[46]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.06, (br s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.19–7.14 (m, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 4.56 (s, 1H), 2.51 (d, *J* = 8.0 Hz, 4H), 1.77 (s, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 143.82, 136.43, 131.59, 129.72, 126.56, 122.33, 120.47, 119.97, 119.80, 119.21, 111.46, 67.63, 53.94, 23.83.

7. 3-((4-methoxyphenyl)(pyrrolidin-1-yl)methyl)-1*H*-indole (Table IV.4, entry 4p)[46]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.02 (br s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 2H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 4.55 (s, 1H), 3.74 (s, 3H), 2.56–2.46 (m, 4H), 1.76 (s, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 158.53, 137.03, 136.47, 129.07, 126.84, 122.14, 120.10, 120.05, 119.62, 113.84, 111.36, 67.61, 55.48, 54.00, 23.86.

8. 1-(2-chlorophenyl)-1-(1*H*-indol-3-yl)-*N*,*N*-dimethylmethanamine (Table IV.4, entry 4q)[45]

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.27 (s, 6H), 5.05 (s, 1H), 7.03-7.26 (m, 7H), 7.87(br, s, 2H), 8.19 (br, s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 137.32, 136.89, 133.97, 132.19, 130.41, 130.30, 128.35, 127.71, 127.00, 122.13, 121.14, 120.14, 115.97, 113.48, 73.71, 41.64.

9. 1-(1*H*-indol-3-yl)-*N*,*N*-dimethyl-1-phenylmethanamine (Table IV.4, entry 4q)[47]

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.70 (s, 6H), 4.98 (s, 1H), 6.59-6.74 (m, 2H), 6.83-6.85 (m, 3H), 6.94- 7.03 (m, 4H), 7.20 (s, 1H), 7.42 (d, *J* = 6.8 Hz, 1H);

^{13}C, NMR (50 MHz, $CDCl_3$) δ (ppm): 137.32, 136.43, 129.61, 129.24, 128.77, 128.12, 127.00, 122.13, 121.15, 120.14, 115.35, 113.49, 74.28, 41.64.

IV.E.4. Scanned copies of ^{1}H and ^{13}C NMR

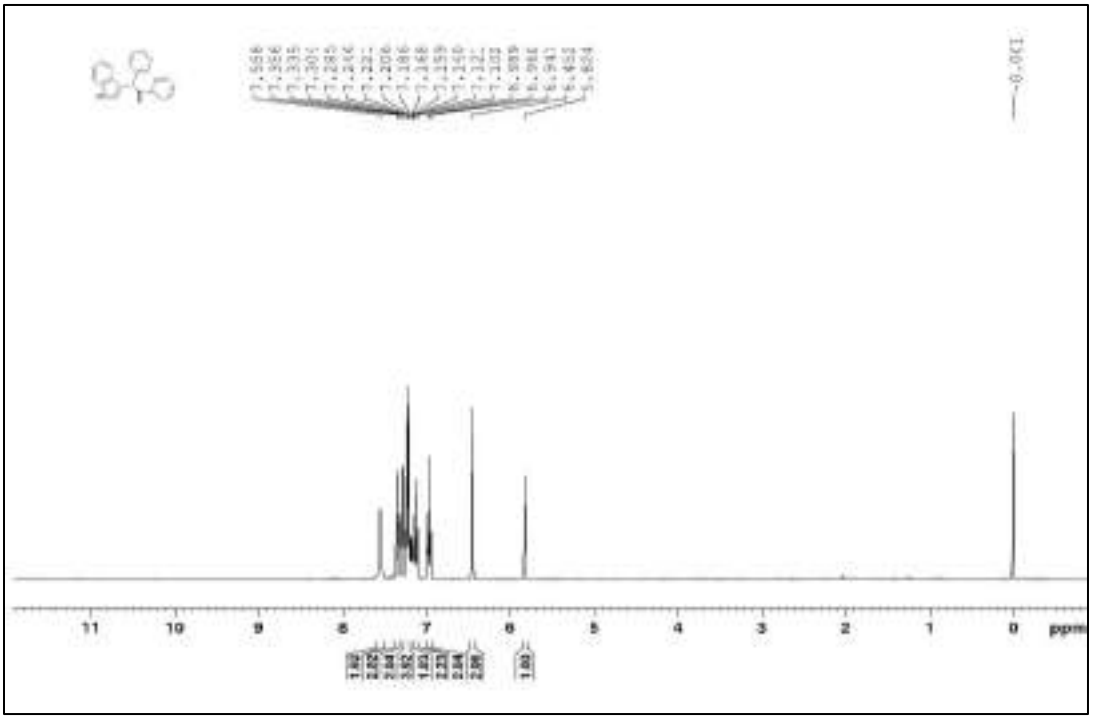


Figure IV.3. Scan copy of ^{1}H NMR of *N*-((1*H*-indol-3-yl)(phenyl)methyl)aniline.

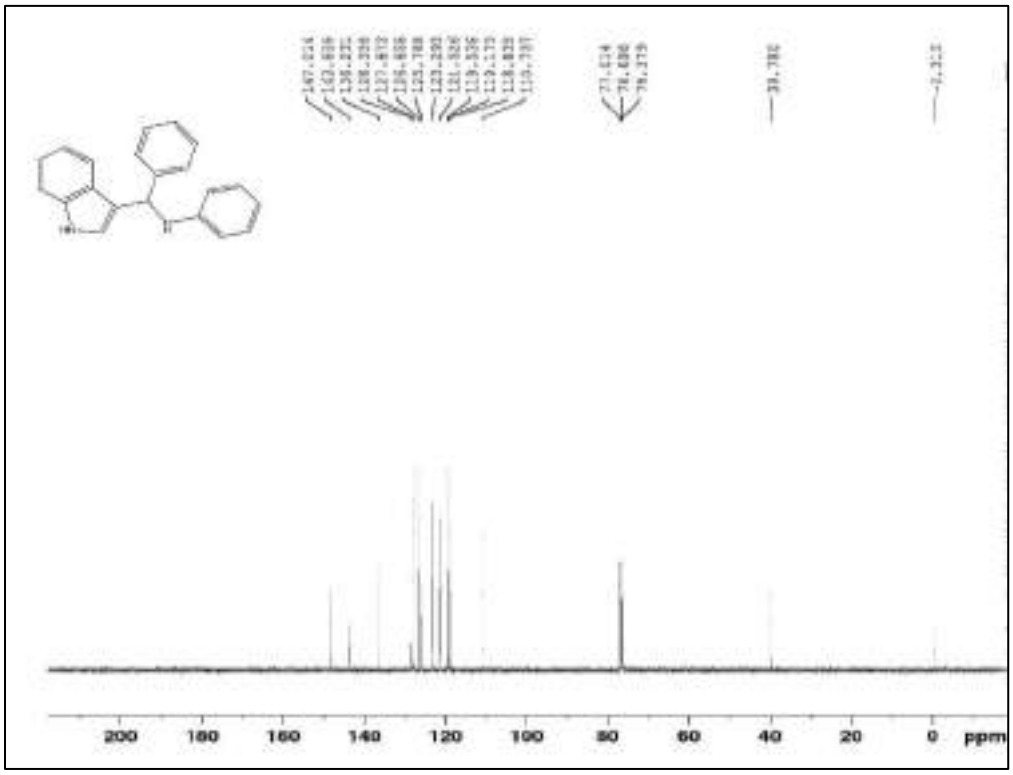


Figure IV.4. Scan copy of ^{13}C NMR of *N*-((1*H*-indol-3-yl)(phenyl)methyl)aniline.

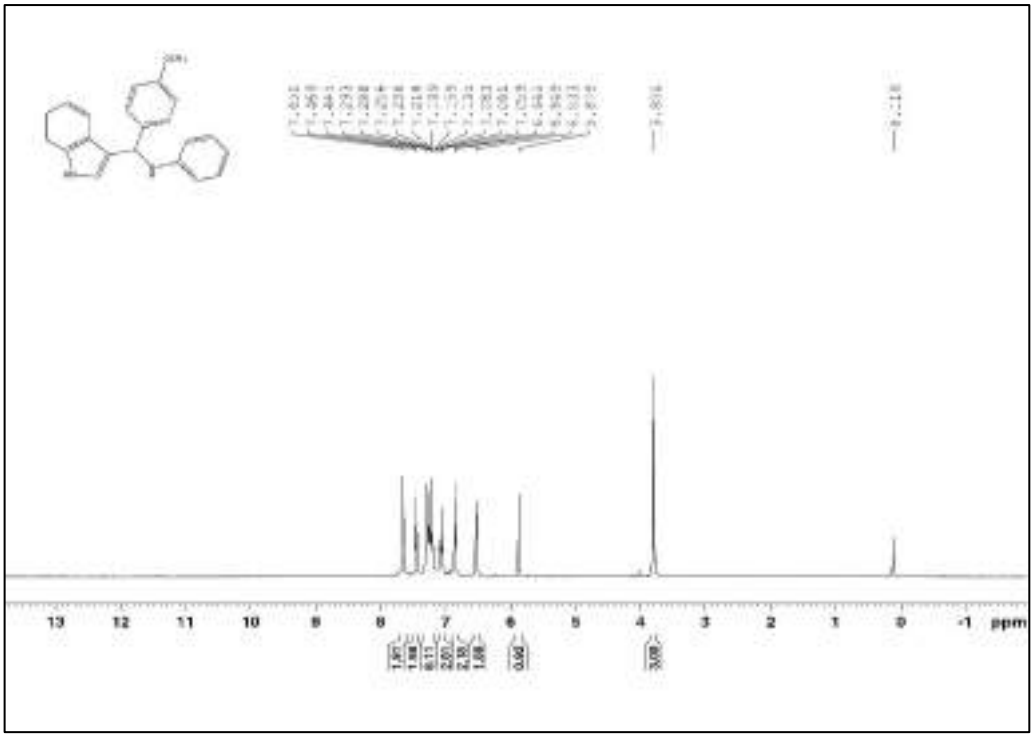


Figure IV.5. Scan copy of ^{1}H NMR of *N*-((1*H*-indol-3-yl)(4-methoxyphenyl)methyl)aniline.

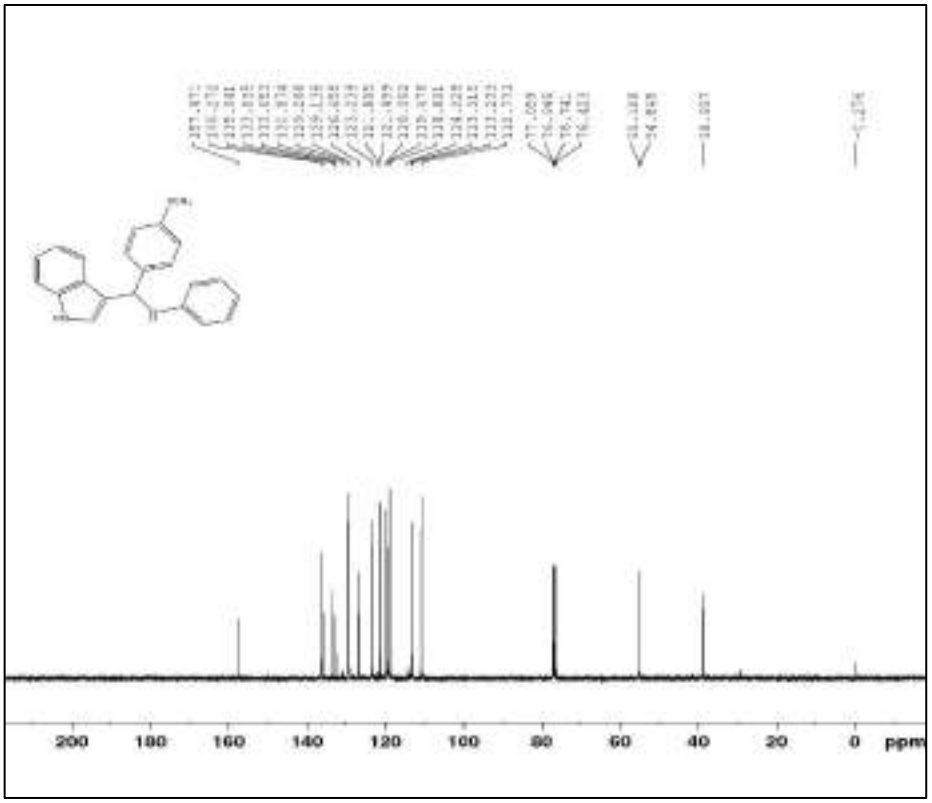


Figure IV.6. Scan copy of ^{13}C NMR of *N*-((1*H*-indol-3-yl)(4-methoxyphenyl)methyl)aniline.

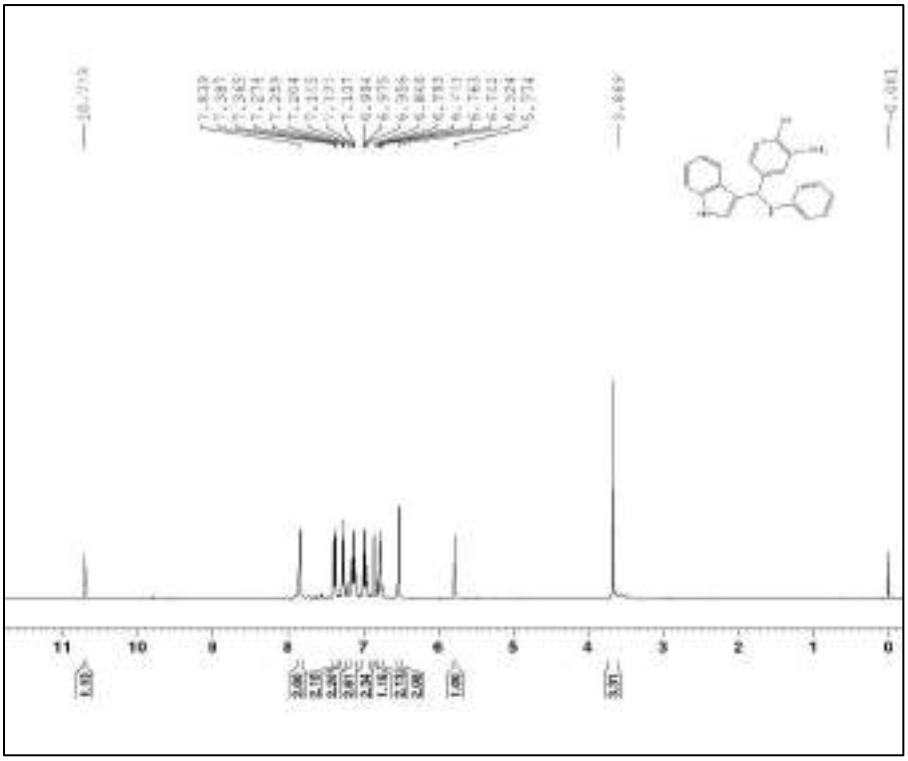


Figure IV.7. Scan copy of ^{1}H NMR of 4-((1*H*-indol-3-yl)(phenylamino)methyl)-2-methoxyphenol.

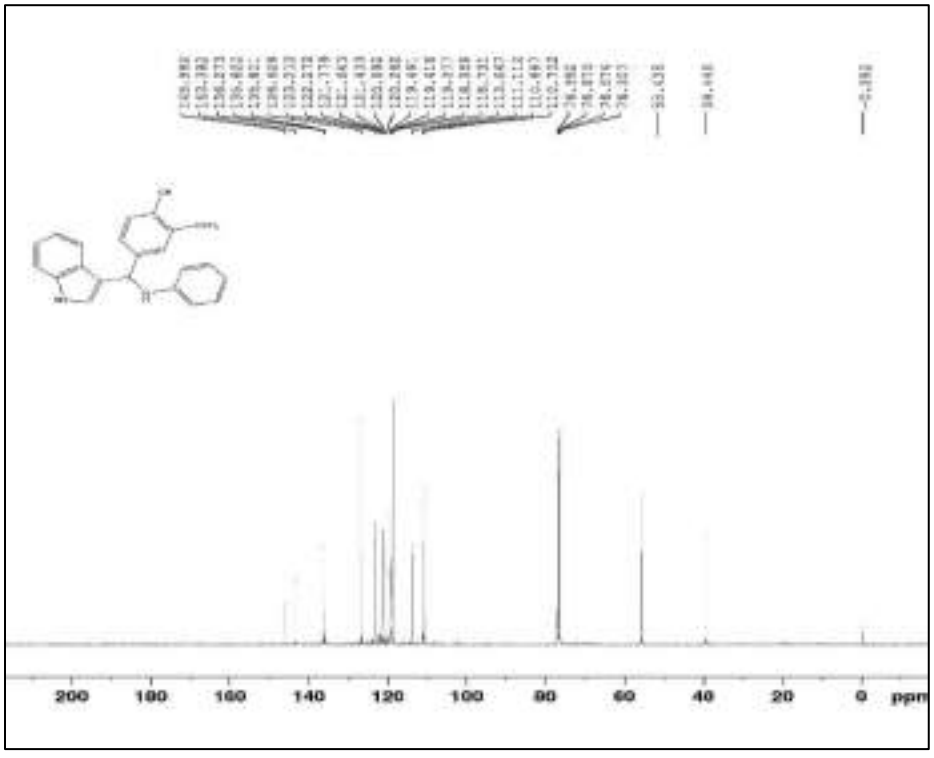


Figure IV.8. Scan copy of ^{13}C NMR of 4-((1*H*-indol-3-yl)(phenylamino)methyl)-2-methoxyphenol.

IV.F. Reference

References are given in BIBLOGRAPHY under Chapter IV.

Chapter V

Ethyl lactate mediated transition metal-free efficient synthesis of azobenzenes

V.A. Introduction

For a long period, aromatic azo compound has gained considerable amount of consideration among the chemists. The main motive behind this is the tremendous collection of application these motif promises in the field of indicators, food additives, organic dyes and therapeutic agents (Figure V.1)[1-4]. Moreover, due to their outstanding photochemical properties, these compounds have been widely used as smart polymers[5-7], liquid crystals[8], photochromic ligands in optochemical genetics[9-10] and photo switches in biological systems[11-14]. By C-H activation, azo compounds have been lately reported to be used for production of valued compounds like *o*-alkoxyazobenzenes[15], indole derivatives[16] and *o*-acylazobenzenes[17-20]. They are also used in the production of proactive glass and filters.

Azobenzenes are the group of chemical compounds having two phenyl rings coupled through N=N double bond. Azobenzene occurs in two geometrical isomeric forms, *trans* and *cis*-azobenzene. *Cis*-azobenzene is nonplanner but *trans*-azobenzene is planer in structure. The N-N distance in *cis*-azobenzene and *trans*-azobenzene are 1.251Å and 1.189Å respectively. The *cis*-azobenzene is less stable than *trans*-azobenzene by about 50 KJ/mol. *Cis* form can be changed into the *trans* isomer by using an suitable wavelength (visible blue light> 400 nm) of light whereas different wavelength (UV at 300-400nm) can convert *trans* isomer back to *cis* form (Figure V.2).

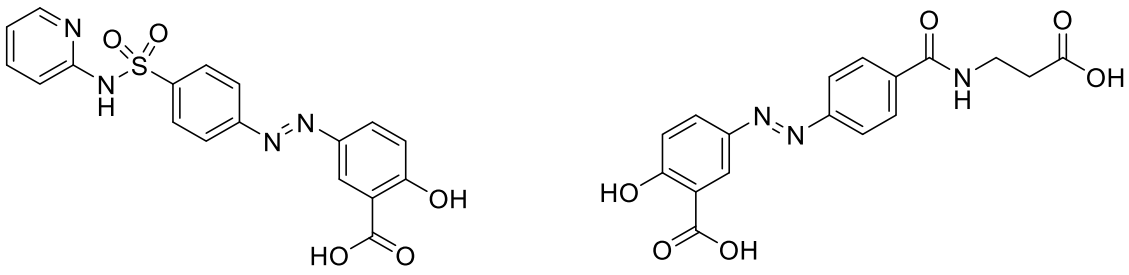


Figure V.1. Biologically active compounds having azo moiety.

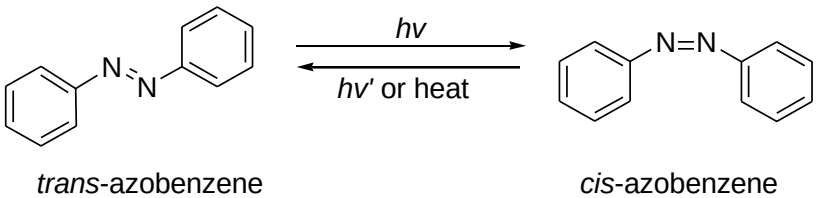


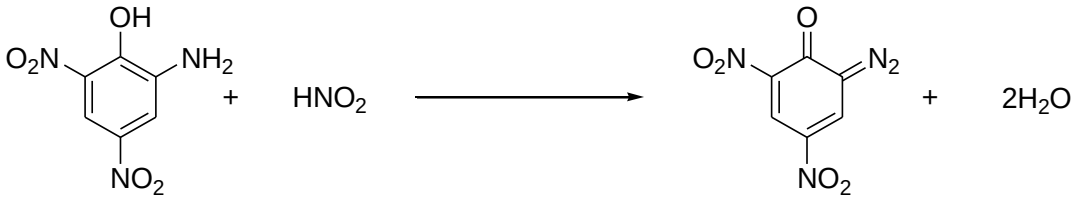
Figure V.2. Interconversion of *cis*-azobenzene and *trans*-azobenzene.

V.B. Background and objectives

From literature review, it has been documented that a number of approaches have been described so far for the production of azo compounds and their derivatives. Amid the few are Wallach reaction, Mills reaction, reduction of azobenzenes, oxidation of amines, opening of quinine acetals, reaction of quinine acetals with arylhydrazines, dehydrogenation of arylhydrazines, thermolysis of azides, metal catalyzed coupling of arylhydrazines, triazene rearrangements, oxidation of amines, opening of benzotriazoles and dimerization of diazonium salts. Comparing all these methods, the easiest methodology is the one step route in the synthesis of azocompounds by oxidation of amines. Literature survey shows that the synthesis of azo-compounds by oxidation of amines have been achieved by a number of catalysts[21-28].

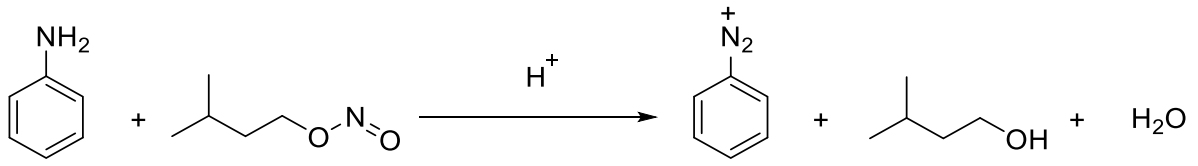
V.B.1. Classical method for Synthesis of azobenzenes

In 1858, Peter Griess *et al.* reported the first preparation of aromatic azo compounds[29-30]. In this reaction the diazotization of *o*-aminophenol using nitric acid and arsenous acid is produced. Nitrous acid was theoretically to be generated within the reaction mixture by the reaction of nitric acid and arsenous acid that converts *o*-aminophenol to the corresponding azo-compound (Scheme V.1).



Scheme V.1. Griess method for synthesis of diazo-compound.

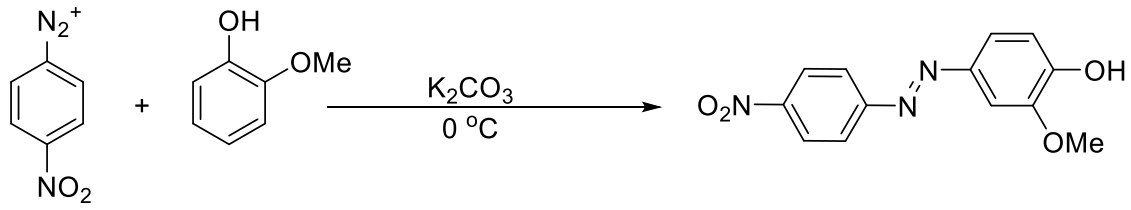
Later Knoevenagel *et al.* modified Griess's method by employing nitrite esters[31]. Transformation was more effective in this method in preparing azo-compounds in acidic medium (Scheme V.2). Using this method, he was able to convert aniline to corresponding diazo-benzene.



Scheme V.2. Knoevenagel reaction for synthesis of diazo-benzene.

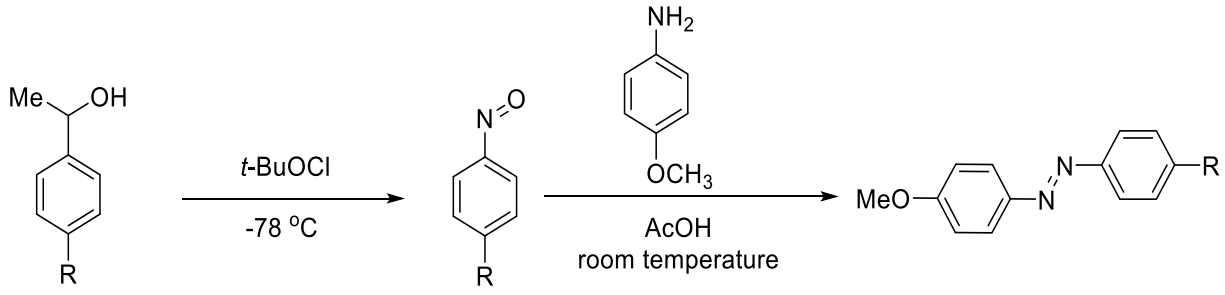
V.B.2. Modern approaches for synthesis of diazo compounds

Common azobenzenes are usually synthesized using azo coupling reaction method. The method includes diazotization of aromatic primary amines in very low temperature and at that point reacting with electron rich aromatic nucleophiles. Shorter reaction time and excellent yield are the main advantages of this method. K. Haghbeen *et al.* reported high yield of azo compound by reacting diazonium salt and phenol at 0 °C using base like K_2CO_3[32] (Scheme V.3). Diazonium salts are regarded as weak electrophiles and hence react with electron rich species like substituted arenes with electron donating groups such as amine or hydroxyl to form azobezenes. Usually, reaction takes place at the para position to the electron donating group but when the para position is already occupied, the substitution takes place at the the ortho position.



Scheme V.3. Azo coupling reaction for synthesis of azobenzenes by K_2CO_3

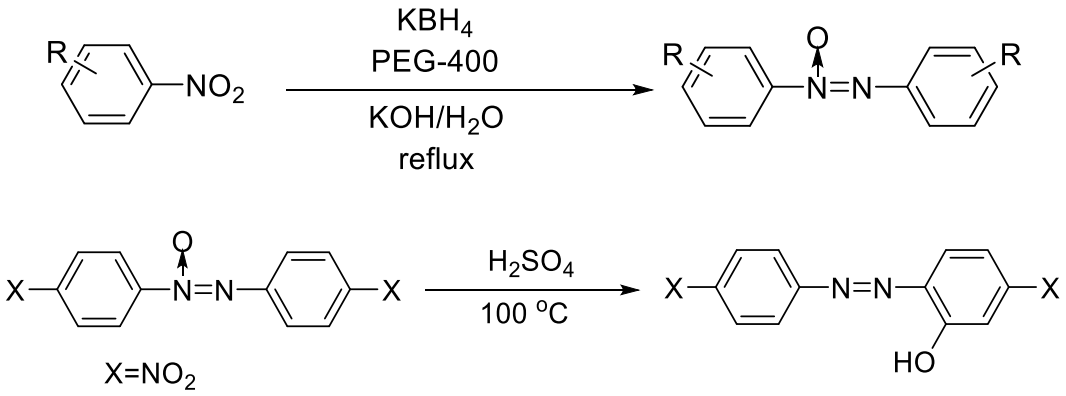
In a multistep reaction T.J. Marks *et al.* reported the synthesis of azobenzene by the reaction between aromatic nitroso compounds and aniline derivatives in presence of glacial acetic acid[33]. Previously, nitroso derivatives were arranged by oxidation of aromatic methylhydroxylamine by *tert*-butyl hypochlorite. The oxidation reaction needed to be carried out at very low temperature (-78 °C) and high dilution is required as it is a very fast reaction and often overoxidation takes place along with the oxidation of nitrosobenzene to nitrobenzene (Scheme V.4).



Scheme V.4. Synthesis of azobenzenes using *tert*-butyl hypochlorite

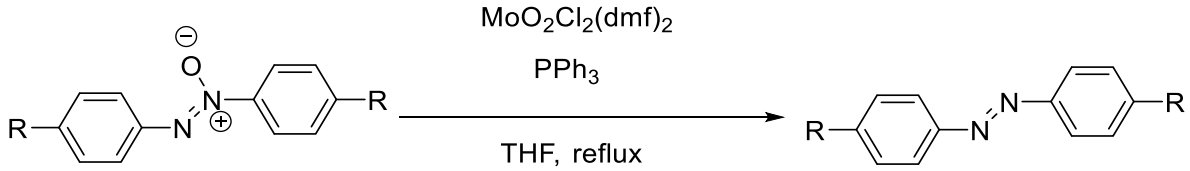
In 1880, O. Wallach discovered the process for convertion of aromatic azoxy compound into azo compound using strong acids[34]. Recently, Y. Lu *et al.* have extended the reduction of nitrobenzenes into corresponding azoxybenzene with potassium borohydride as the reducing

agent and water as medium[35] (Scheme V.5). PEG-400 was employed as the phase transfer catalyst in this reaction. The electron-withdrawing groups generally accelerate the reaction whereas the electronic- releasing group slows down the reaction to various degrees.



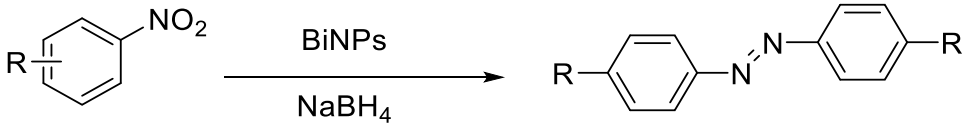
Scheme V.5. Synthesis of azobenzenes from nitro compounds by Wallach reaction by KBH_4/PEG-400 system.

Recently, F.J. Arnáiz *et al.* reported the conversion of azoxybenzene to azobenzene in good yield[36]. Tertiary phosphines are used as reducing agent in this reaction (Scheme V.6). The reaction was performed using dichlorodioxomolybdenum (VI) as catalyst in THF medium.



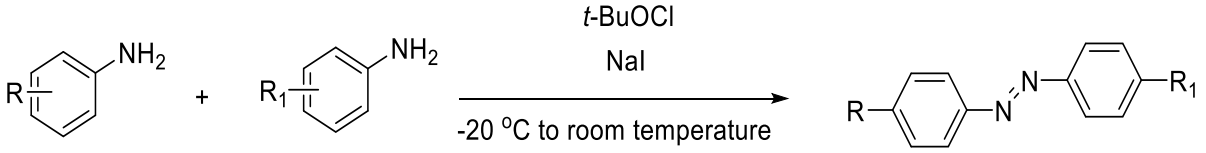
Scheme V.6. Reduction of azoxybenzene by tertiary phosphines for synthesis of azobenzenes using molybdenum (VI) catalyst.

A number of reducing agents have been used so far using suitable of nitrobenzene for the synthesis of symmetrical aromatic azo compounds. Recently, Z. Wang *et al.* reported transformation of nitrobenzene to azobenzenes by bismuth nanoparticles as catalyst[37]. The conversion was done under environmentally benign conditions with good yield of the product. Also, the catalyst was recoverable and reused without losing much of its efficiency (Scheme V.7).



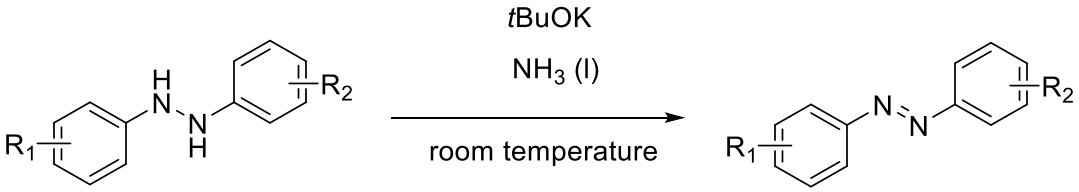
Scheme V.7. Synthesis of azobenzenes by reductive coupling of aromatic nitro derivatives using bismuth nanoparticles.

T.W. McIntyre *et al*. reported synthetic method for preparation of azobenzenes by electrolytic oxidation of aromatic amines[38]. However, the procedure was not efficient as the yield obtained by them was low. Numerous protocols have been published after that which assured improvement of this synthesis using several reaction conditions, various oxidizing agents and a wide range of catalysts. Recently, S. Minakata *et al.* reported development of cost-efficient and facile method for oxidative dimerization of azobenzenes from aromatic amines using *tert*-butyl hypochlorite (*t*-BuOCl) and NaI as catalyst[39] (Scheme V.8). Main advantage of this protocol is the synthesis of unsymmetrical azobenzenes as well.



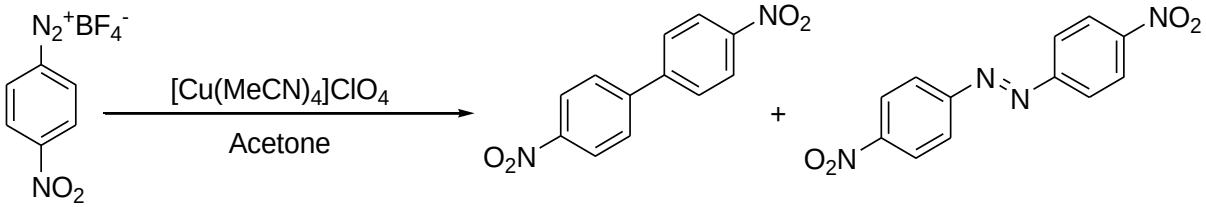
Scheme V.8. Oxidation of anilines for synthesis of azobenzenes by *tert*-butyl hypochlorite.

M. Hashimoto *et al.* have reported approach for dehydrogenation of *N*,*N*-diarylhydrazines by using potassium *tert*-butoxide in liquid ammonia[40]. High competence of the methodology and very short reaction time was one of the main features of this synthesis (Scheme V.9). The scope is further extended by the synthesis of diazirines.



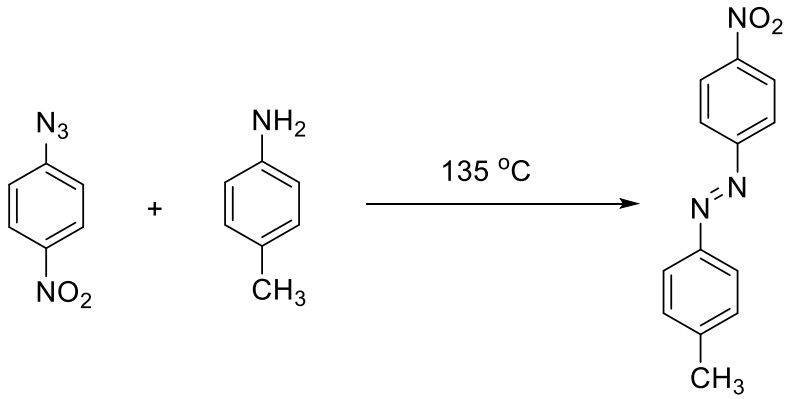
Scheme V.9. Synthesis of azobenzenes by *tert*-butoxide in liquid ammonia.

Dimerization of diazonium salts in presence of copper and acid is known as Gatterman's method or copper (I) salts moves to the formation of azobenzene. The reaction is highly delicate towards the nature of the aromatic group present. Due to C-C coupling, in presence of electron-withdrawing group, biaryl is the main product whereas in presence of electron-donating group, azobenzene governs as the main product (Scheme V.10).



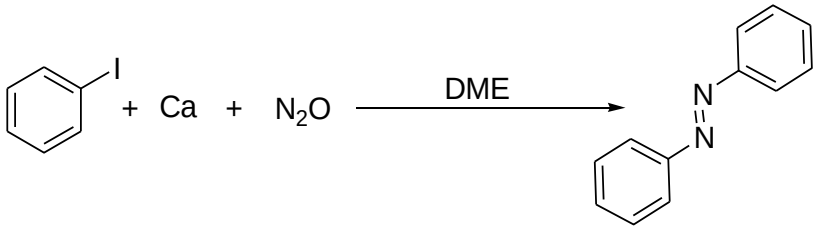
Scheme V.10. Dimerization reaction of diazonium salts for synthesis of azobenzenes using Cu (I) salt

Aromatic azides can be heated in presence of aniline to yield unsymmetrical azo compounds. However, the yield obtained in such reactions are often low. Also, the azides are explosive in nature and are difficult to handle. Such a reaction is reported by J. March *et al.*[41]. In this reaction azide condenses with aniline and its derivatives to yield corresponding azo compounds at 135 ^{o}C (Scheme V.11). Very long reaction time up to 48 hours is a drawback of this method.



Scheme V.11. Synthesis of azobenzenes by thermolysis of azides.

Aromatic calcium derivatives act as a good starting material for the synthesis of azobenzenes. T.P. Hanusa *et al.* have reported the synthesis of azobenzene in excellent yield by reacting iodobenzene with nitrous oxide and metallic calcium in presence of dimethoxethane[42]. Though the yield became low when the reaction is performed in presence of organolithium compounds (Scheme V.12). Phenylcalcium iodide was assumed to be generated by the reaction of iodobenzene and calcium.

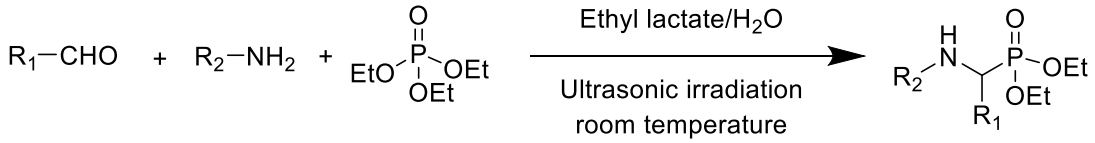


Scheme V.12. Synthesis of azobenzenes by dimethoxethane.

V.B.3. Background of Ethyl lactate in organic synthesis

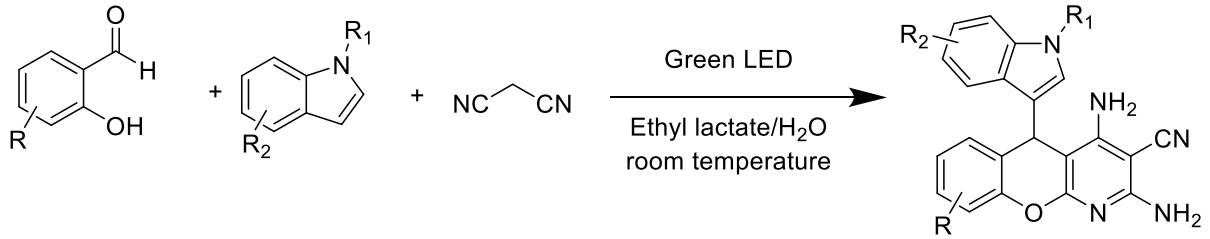
Ethyl lactate can be smoothly produced by fermentation of biomass raw materials[43]. As it is non-toxic, it has been permitted by European Food Safety Authorities and Food and Drug Administration (EFSA) for the use as pharmaceutical additives and food additives[44]. It also has been profitably engaged in the extraction of many bioactive compounds and diverse food such as polyphenols[45], carotenoids[46], caffeine[47], amino acids[48].

Ethyl lactate has effectively been employed as a green solvent in a number of prominent organic reactions. Recently, Z.H. Zhang *et al.* reported an efficient one-pot synthesis of α-aminophosphonates [49]. This reaction is done in metal -free condition in aqueous ethyl lactate medium. This reaction is a one-pot three-component reaction of wide range of aldehydes, amines and triethyl phosphate under ultrasonic irradiation conditions at room temperature (Scheme V.13).



Scheme V.13. Synthesis of α-aminophosphonates in aqueous ethyl lactate medium.

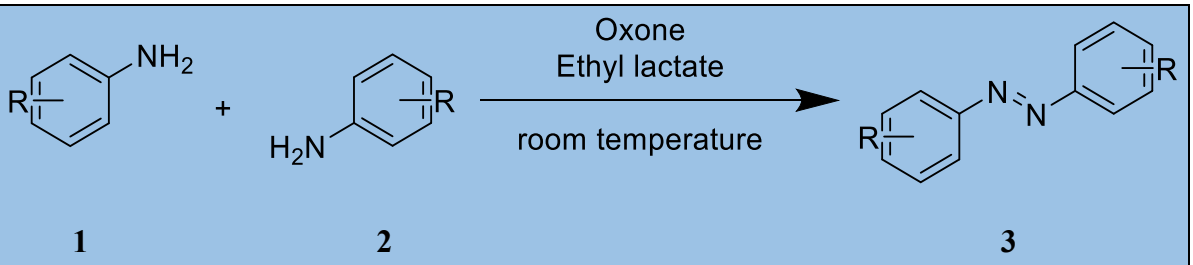
Another recent organic synthesis of 5-substituted indole chromeno[2,3]-bipyridines is reported by Z.H. Zhang *et al.*[50]. This innovative approach is catalyzed by green LED light in Ethyl lactate and water medium (Scheme V.14). It is described as a pseudo four-component one-pot reaction of salicylaldehydes, indole and malononitrile and good yield of corresponding pyridine derivatives are reported.



Scheme V.14. Synthesis of 5-substituted indole chromeno[2,3]-bipyridines by ethyl lactate/H_2O system.

V.C. Present Work

During the development of our research work, with an goal to develop a new procedure for our synthesis, we found that easily available, environmental benevolent and cost-effective solvent ethyl lactate can be explored as an excellent and effective mediator in the synthesis of azobenzenes from amines without using any additional catalyst. In our work, we report ethyl lactate as a green and efficient solvent for the synthesis of symmetric azobenzenes at room temperature (Scheme V.15). During the synthesis of symmetric azobenzenes, oxone accomplished the role of an oxidizing agent.



1 **2** **3**

Scheme V.15. Synthesis of azobenzene from amines by ethyl lactate at room temperature.

V.C.1. Result and discussion

To standardize the reaction protocol, aniline was taken as the starting material and the progress of the reaction was monitored by TLC. The reaction was first carried out by taking 1 mmol of aniline and 0.5 mmol of oxone under neat condition for 12 hours when only trace amount of the product was obtained (Table V.1, entry 1). Now with the same reaction conditions, different solvents were used to monitor the reaction. Water only furnished trace amount of the product (Table V.1, entry 2). However, with chloro- form the reaction gave encouraging yield of 50% (Table V.1, entry 3). PEG 400 further increased the yield to 74% (Table V.1, entry 4). Toluene and ethanol gave 55% and 59% of the yield respectively (Table V.1, entry 5, 6). However slightly fewer yields of 40% was obtained with methanol (Table V.1, entry 7). We then decided to use ethyl lactate as the solvent and we were excited to find the yield increased to 78% (Table V.1, entry 11). We also used the solution of ethyl lactate/H_2O at different ratios but yield remained almost the same (Table V.1, entry 10, 11, 12). Now with the solvent being optimized, we increased the amount of oxone to 1.0 mmol but here we were surprised to find that yield decreased considerably to 62% (Table V.1, entry 13). It may be due to the oxidation of aniline to nitrobenzene before undergoing coupling reaction. While reducing the amount of oxone to 0.25 mmol reduced the yield to 38% (Table V.1, entry 14). We further investigated the reaction by increasing the time to 24 hours which did not give any significant increase in the yield of the product (Table V.1, entry 15). However, decreasing the time to 6 hours decreased the yield to 60%. Increasing the temperature of the reaction to 90° C also showed a large decrease in the yield (Table V.1, entry 16). The decrease of yield to 35% may be due to the oxidation of aniline to nitrobenzene at high temperature. Hence finally we report that the optimal reaction condition is 1 mmol of aniline and 0.5 mmol of oxone in ethyl lactate for 12 hours.

Table V.1. [a]Optimization of reaction condition for symmetric azobenzene.

Entry	Oxone (mmol)	Solvent	Time (h)	Yield (%)[b]
1	0.5	Neat	12	Trace

2	0.5	Water	12	Trace
3	0.5	$CHCl_3$	12	50
4	0.5	PEG-400	12	74
5	0.5	Toluene	12	55
6	0.5	EtOH	12	59
7	0.5	MeOH	12	40
8	0.5	Ethyl lactate/H_2O (2:1)	12	76
9	0.5	Ethyl lactate/H_2O (1:1)	12	75
10	0.5	Ethyl lactate/H_2O (1:2)	12	73
11	0.5	Ethyl lactate	12	78
12	1.0	Ethyl lactate	12	62
13	0.25	Ethyl lactate	12	38
14	0.5	Ethyl lactate	24	78
15	0.5	Ethyl lactate	06	60
16	0.5	Ethyl lactate	12	35[c]

The bold significance represents the optimized protocol/conditions.

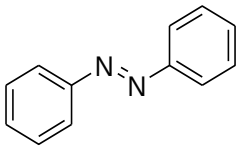
[a]Reaction of aniline (1 mmol).

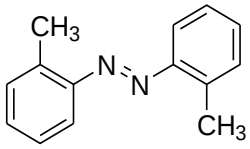
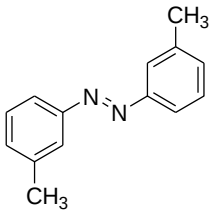
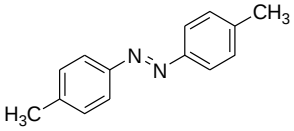
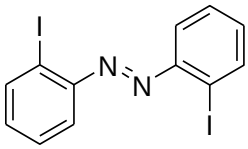
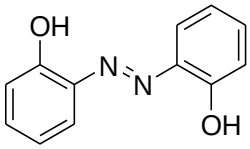
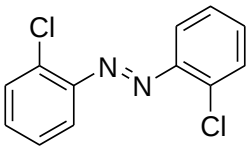
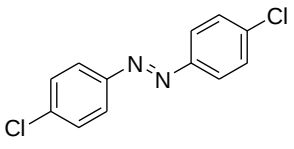
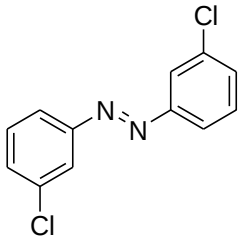
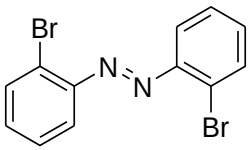
[b]Isolated yield of product by column chromatography.

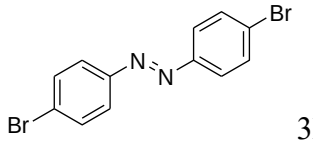
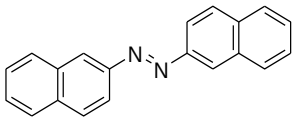
[c]Reaction carried out at 90° C.

A number of amines have been employed in the synthesis of symmetric azobenzenes in our methodology. As evidence from table 2, good yield of different products has been obtained all at room temperature. The procedure has been generalized for a range of amines having electron-donating, electron-withdrawing groups on benzene ring as well as naphthyl rings. Better results were obtained for amines having electron-donating effect compare to those having electron withdrawing effect. It may be due to the electron density on nitrogen atom making them more nucleophilic. It was also observed that ortho-product gave fewer yields than the other products. This may be due to steric factors at the ortho positions.

Table V.2. [a]Ethyl lactate mediated synthesis of symmetric azobenzenes.

Entry	Product	Yield (%)[b]
1	 3a	78

2	 3b	73
3	 3c	78
4	 3d	77
5	 3e	55
6	 3f	68
7	 3g	61
8	 3h	64
9	 3i	65
10	 3j	57

11	 3k	59
12	 3l	79

[a]Reaction conditions: Aniline (1 mmol), oxone (0.5 mmol) in ethyl lactate for 12 h at room temperature.

[b]Isolated yield of product by column chromatography.

V.D. Conclusion

In conclusion, we have developed an environmentally benign protocol for the single-step facile synthesis of symmetric azobenzenes from amines by using ethyl lactate as a solvent without the use of any catalyst. The reaction protocol includes the use of an inexpensive and non-toxic green solvent and gives excellent yield of the desired products with simple and easy reaction conditions and workup process.

V.E. Experimental

V.E.1. General Information

^{1}H NMR and ^{13}C NMR were recorded using 300 MHz, 400 MHz and 75 MHz, 100 MHz respectively on Bruker AV 300 NMR spectrometer and Bruker AV 400 NMR spectrometer using TMS as internal standard. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad) and m (multiplet).

V.E.2. General procedure for the synthesis of symmetric azobenzenes from amines

Aniline (1 mmol) and oxone (0.5 mmol) were mixed and stirred in ethyl lactate (1 mL) at room temperature for 12 hours. After completion of the reaction (observed on TLC), the reaction mixture was cooled down to room temperature. Then the solution was poured into 100 mL water and extract with ethyl acetate, washed several times with water. The combined organic mixture was dried over anhydrous Na_2SO_4, concentrated and the residue was purified by column chromatography on silica gel 60–120 mesh using petroleum ether as eluent to afford the pure solid product. All the products were characterized by ^{1}H NMR and ^{13}C NMR.

V.E.3. Spectroscopy data

1. (*E*)-Azobenzene (Table V.2, entry 3a)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.93 (d, *J*=7.2, 4H), 7.54-7.49 (m, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):152.62, 131.00, 129.10, 122.84.

2. (*E*)-4,4′-Dimethylazobenzene (Table V.2, entry 3d)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.71 (d, *J* = 8.4 Hz, 4H), 7.19 (d, *J* = 8.1 Hz, 4H), 2.32 (s, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):150.82, 141.22, 129.73, 122.75, 21.50.

3. (*E*)-2,2′-Dimethylazobenzene (Table V.2, entry 3b)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.74 (s, 4H), 7.43 (t, *J*=7.8, 2H), 7.20 (t, *J*=7.2, 4H), 2.28 (s, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 149.46, 142.78, 131.23, 128.62, 121.56, 18.48.

4. (*E*)-3,3′-Dichloroazobenzene (Table V.2, entry 3i)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):7.42 (s, 1H), 7.37 (s, 1H), 7.31 (d, *J* = 7.8, 1H), 7.11(d, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 2H), 6.60-6.51 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):143.87, 134.18, 131.38, 129.27, 124.78, 119.98.

5. (*E*)-2,2′-Diiodoazobenzene (Table V.2, entry 3e)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.52 (d, *J* = 7.8 Hz, 2H), 7.17 (t, *J* = 7.8 Hz, 3H), 6.61 (d, *J* = 7.8 Hz, 2H), 6.36 (t, *J* = 7.2 Hz, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):146.83, 139.04, 129.44, 120.06, 114.87, 84.37.

6. (*E*)-2,2′-Dihydroxyazobenzene (Table V.2, entry 3f)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.13 (d, *J* = 8.4 Hz, 2H), 7.77 (t, *J* = 8.1 Hz, 2H), 7.30-7.40 (m, 2H), 6.93-7.09 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):152.35, 150.88, 133.35, 131.90, 126.27, 122.64, 118.92.

7. (*E*)-1,2-di(2-naphthyl)diazene (Table V.2, entry 3l)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.04 (s, 1H), 8.79 (s, 1H), 8.38 (d, *J*=1.8 Hz, 1H), 8.00-7.75 (m, 7H), 7.51 (t, *J*=3.9, 2H), 7.44 (t, *J*=3.6, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 141.59, 134.59, 133.71, 132.53, 129.65, 128.85, 127.84, 126.51, 124.92, 119.54.

V.E.4. Scanned copies of ^{1}H and ^{13}C NMR of the derivatives

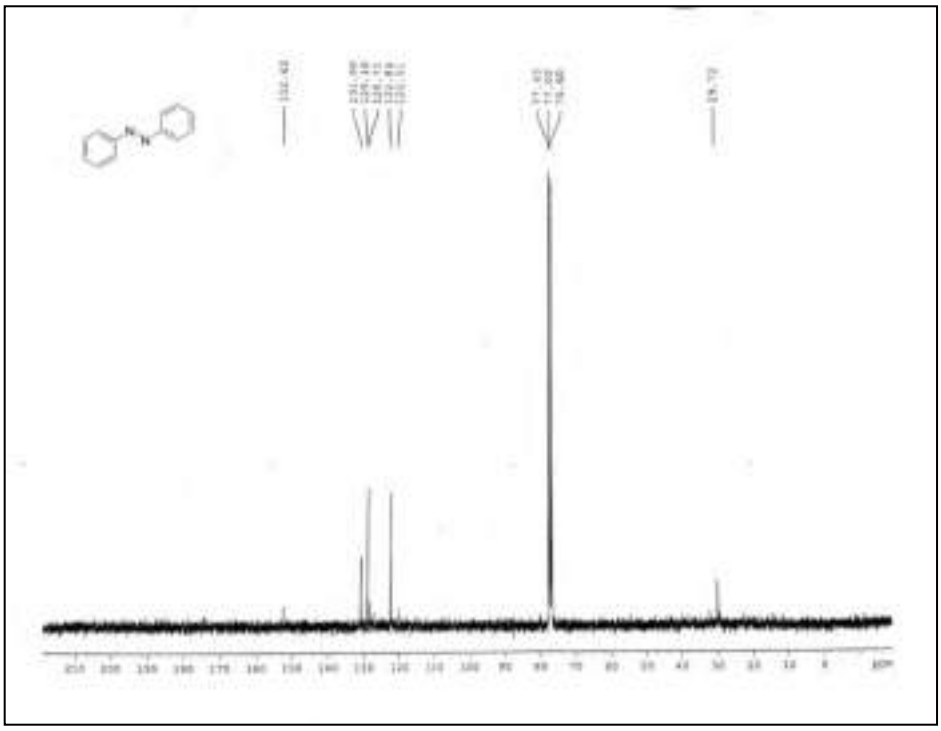


Figure V.3. Scan copy of ^{13}C NMR of (*E*)-Azobenzene.

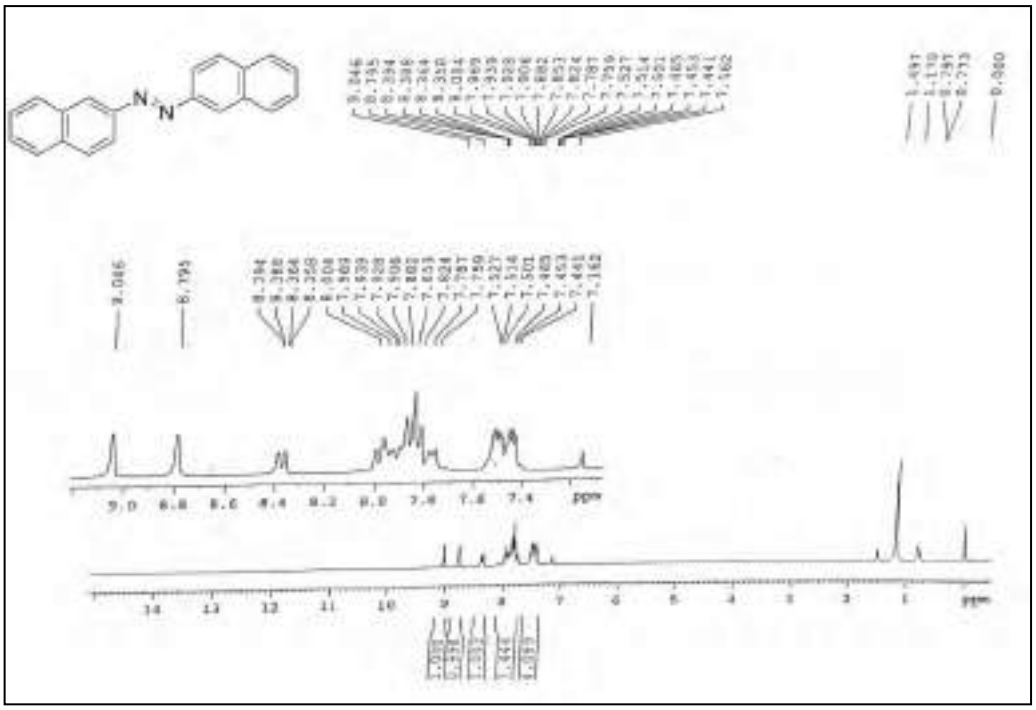


Figure V.4. Scan copy of ^{1}H NMR copy of (*E*)-2,2'-Azonaphthalene.

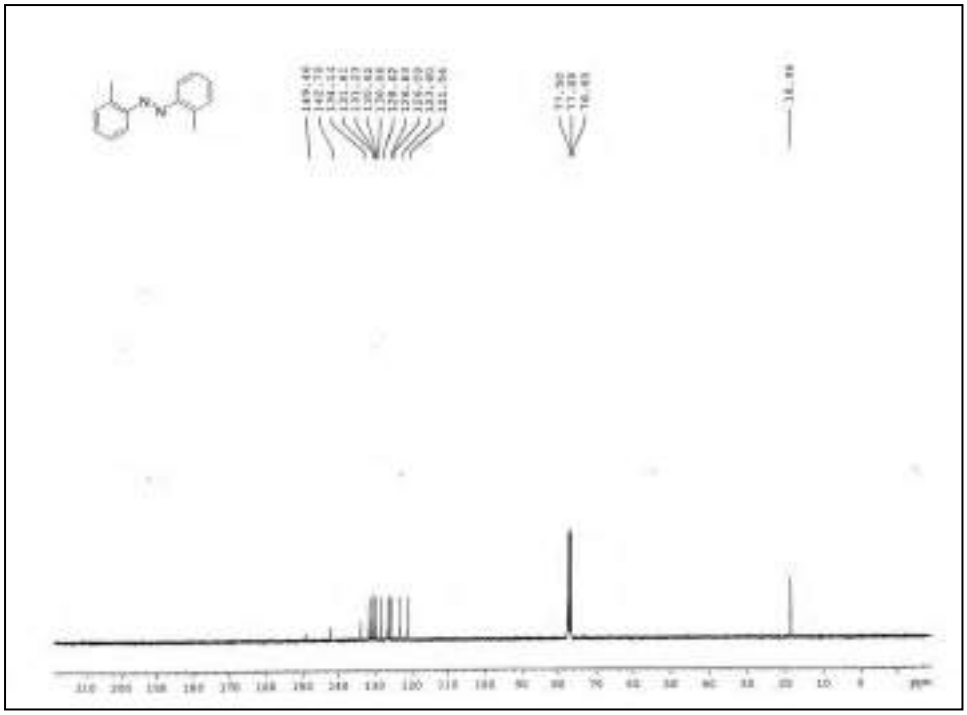


Figure V.5. Scan copy of ^{13}C NMR of (*E*)-2,2′-Dimethylazobenzene.

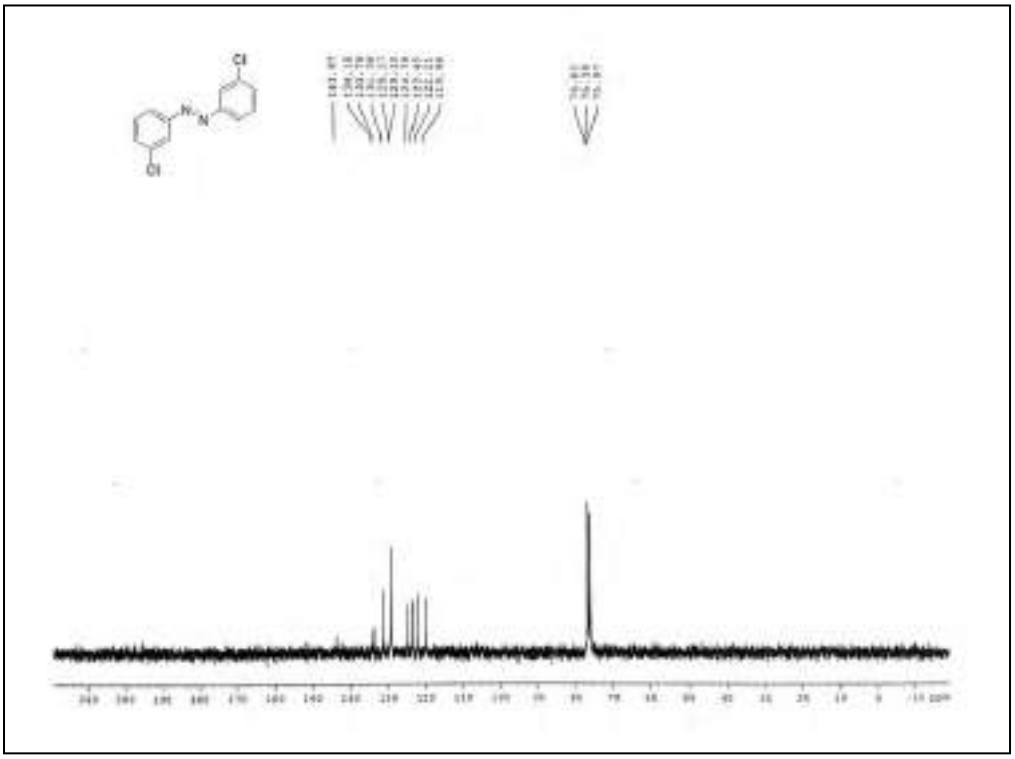


Figure V.6. Scan copy of ^{13}C NMR of (*E*)-3,3′-Dichloroazobenzene.

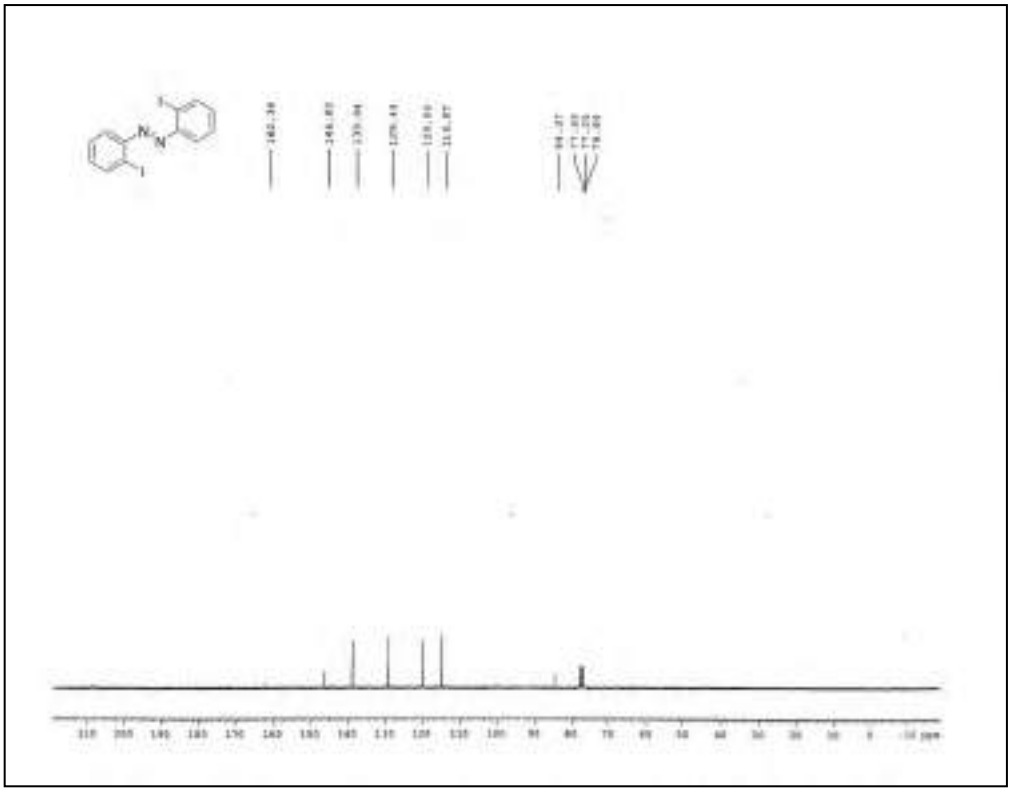


Figure V.7. Scan copy of ^{13}C NMR of (*E*)-2,2′-Diiodoazobenzene.

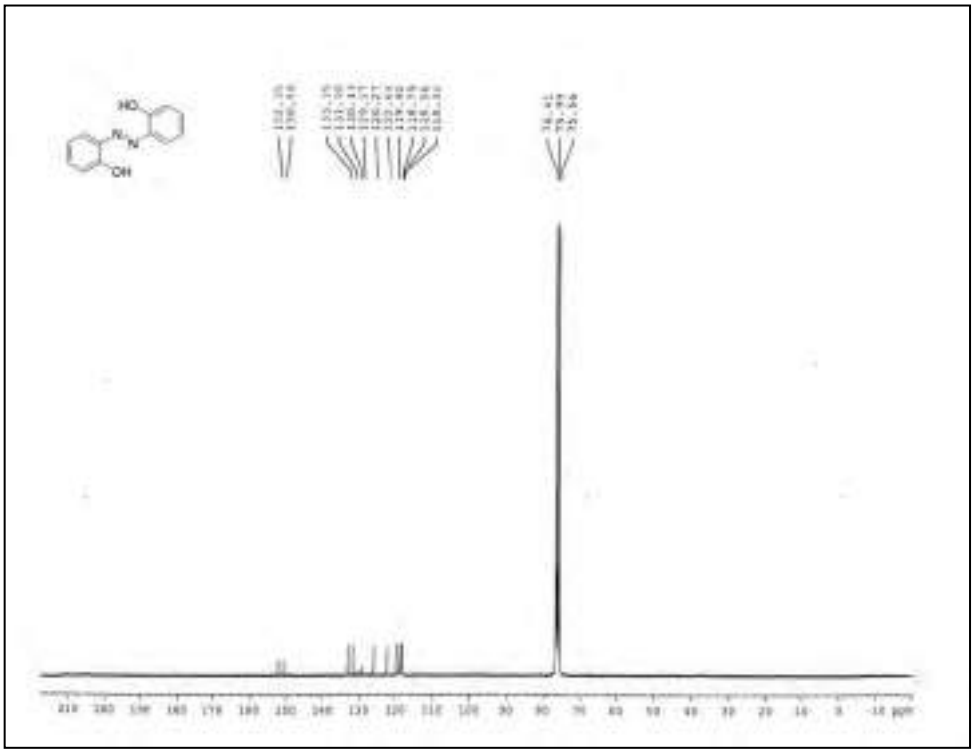


Figure V.8. Scan copy of ^{13}C NMR of (*E*)-2,2′-Dihydroxyazobenzene.

V.F. Reference

References are given in BIBLOGRAPHY under Chapter V.

BIBLIOGRAPHY

I. E. References

1. F. Ullmann, *Ber. Dtsch. Chem. Ges*., **1903**, 36, 2382–2384.

2. I. Goldberg, *Ber. Dtsch. Chem. Ges*., **1906**, 39, 1691–1692.

3. A. B. Sheremetev, N. V. Palysaeva, M. I. Struchkova, K. Yu. Suponitsky, M. Yu. *Antipin*, *Eur. J. Org. Chem*., **2012**, 2266–2272.

4. R. Berrino, S. Cacchi, G. Fabrizi, A. Goggiamani, *J. Org. Chem*., **2012**, 77, 2537–2542.

5. S. N. Murthy, B. Madhav, V. P. Reddy, Y. V. D. Nageswar, *Adv. Synth. Catal*., **2010**, 352, 3241–3245.

6. Y.H. Lee, Y.C. Chen, J.C. Hsieh, *Eur. J. Org. Chem*., **2012**, 247–250.

7. D. C. Gerbino, D. Augner, N. Slavoy, H.G. Schmalz, *Org. Lett*., **2012**, 14, 2338-2341.

8. A. Sakakura, K. Kawajiri, T. Ohkubo, Y. Kosugi, K. Ishihara, *J. Am. Chem. Soc*., **2007**, 129, 14775-14779.

9. G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, E. Marcantoni, P. Melchiorre, P. Palazzi, L. Sambri, *Eur. J. Org. Chem*., **2006**, 4429-4434.

10. J. J. Newton, R. Britton, C. M. Friesen, *J. Org. Chem*., **2018**, 83, 12784-12792.

11. H. Xue, B. Jing, S. Liu, Y. Chae, Y. Liu, *Synlett,* **2017**, 28, 2272-2276.

12. G. Maitro, S. Vogel, G. Prestat, D. Madec, G. Poli, *Org. Lett.*, **2006**, *8*, 5951-5954.

13. T. Jia, M. Zhang, H. Jiang, C. Y. Wang, P. J. Walsh, *J. Am. Chem. Soc*., **2015**, 137, 13887-13893.

14. B. Hu, Pan Zhou, Q. Zhang, Y. Wang, S. Zhao, L. Lu, S. Yan, F. Yu, *J. Org. Chem*., **2018**, 83, 14978-14986.

15. N. Azizi, F. Aryanasab, M. R. Saidi, *Org. Lett.*, **2006**, *8*, 5275-5277.

16. D. Liu, W. Gao, Q. Dai, X. Zhang, *Org. Lett*., **2005**, 7, 4907-4910.

17. M. Kalek, A. Ziadi, J. Stawinski, *Org. Lett*., **2008,** 10, 4637-4640.

18. K. M. Maloney, J. Y. L. Chung, *J. Org. Chem*., **2009**, 74, 7574-7576.

19. V. Lellek, C.-y. Chen, W. Yang, J. Liu, X. Ji, R. Faessler, *Synlett*, **2018**, *29*, 1071-1075.

20. N. Azizi, A. Khajeh-Amiri, H. Ghafuri, M. Bolourtchian, M. R. Saidi, *Synlett*, **2009**, 2245-2248.

21. N. L. Higuera, D. Peña-Solórzano, C. Ochoa-Puentes, *Synlett*, **2019**, *30*, 225-229.

22. P.V.N.S. Murthy, D. Rambabu, G.R. Krishna, C.M. Reddy, K.R.S. Prasad, M.V.B. Rao, M. Pal, *Tetrahedron Lett*., **2012**, 53, 863–867.

23. B. Liu, M. Yin, H. Gao, W. Wu, H. Jiang, *J. Org. Chem*., **2013**, 78, 3009-3020.

II. E. References

1. J.J. Ritter, P.P. Minieri, *Journal of the American Chemical Society*, **1948**, 70**,** 4045–4048.

2. W. Eschweiler, *Eur. J.I.C*., **1905**, 38, 880-882.

3. M.I. Kabachnik T.Y. Medved, *Dokl. Akad. Nauk SSSR*., **1952**, 83, 689–692.

4. C. Mannich, W. Krösche, *Archiv der Pharmazie*, **1912**, 250, 647–667.

5. N.A. Petasis, I. Akritopoulou, *Tetrahedron Lett*., **1993**, 34, 583–586.

6. E. M. Dangerfield, C. H. Plunkett, A.L. Win-Mason, B. L. Stocker, M. S. M. Timmer, J. *Org. Chem*., **2010**, 75, 5470-5477.

7. P. Cintas, *activated metals in organic synthesis*, **1993**, 1, 8.

8. K. Tanaka, T. Miki, K. Murata, A. Yamaguchi, Y. Kayaki, S. Kuwata, T. Ikariya, M. Watanabe, *J. Org. Chem*., **2019**, 84, 10962-10977.

9. M. Taibakhsh, R. Hosseinzadeh, H. Alinezhad, S. Ghahari, A. Heydari, S. Khaksar, *Synthesis*, **2011**, 490-496.

10. A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem*., **1996**, 61, 3849-3862.

11. P. V. Ramachandran, S. Choudhary, A. Singh, *J. Org. Chem*., **2021**, 86, 4274-4280.

12. O. S. Nayal, V. Bhatt, S. Sharma, N. Kumar, *J. Org. Chem*., **2015**, 80, 5912-5918.

13. R. R. Thakore, B. S. Takale, G. Casotti, E. S. Gao, H. S. Jin, B. H. Lipshutz, *Org. Lett*., **2020**, 22, 6324-6329.

14. R. Apodaca, W. Xiao, *Org. Lett*., **2001**, 3, 1745-1748.

15. B. Li, J. Zheng, W. Zeng, Y. Li, L. Chen, *Synthesis*, **2017**, 49, 1349-1355.

16. I. Sorribes, K. Jung, M. Beller, *J. Am. Chem. Soc*., **2014**, 136, 14314-14319.

17. J. W. Bae, S. H. Lee, Y. J. Cho, C. M. Yoon, *J. Chem. Soc., Perkin Trans*., **2000**, 145-146.

18. I. Choi, S. Chun, Y. K. Chung, *J. Org. Chem*., **2017**, 82, 12771-12777.

19. C. Qiao, X.F. Liu, X. Liu, L.N. He, *Org. Lett*., **2017**, 19, 1490-1493.

20. M. Horn, H. Mayr, E. Lacôte, E. Merling, J. Deaner, S. Well, T. McFadden, D. P. Curran, *Org. Lett.,* **2012**, 14, 82-85.

21. R.J. Shaikh, *Catal.*, **2014**, 1–35.

22. A.A. Napoleon, F.R.N. Khan, E.D. Jeong, E.H. Chung, *Tetrahedron Lett.,* **2014**, 55, 5656 –5659.

23. S.K. Das, P. Bhattacharjee, U. Bora, *ChemistrySelect*, **2018**, 3, 2131 – 2134.

24. A. Shokrolahi, A. Zali, M.H. Keshavarz, *Green Chem. Lett. and Reviews*, **2011**, 4, 195-203.

25. Q. Zhang, S. Li, M. Zhu, Y. Liu, H. He, Y. Cao, *Green Chem*., **2016**, 18, 2507-2513.

26. M. Zhang, H. Yang, Y. Zhang, C. Zhu, W. Li, Y. Cheng, H. Hua; *Chem. Commun*., **2011**, 47, 6605-6607.

27. Y. Zhang, X. Qi, X. Cui, F. Shi, Y. Deng, *Tetrahedron Lett.,* **2011**, 52, 1334-1338.

28. D. Menche, J. Hassfeld, J. Li, G. Menche, A. Ritter, S. Rudolph, *Org. Lett*., **2006**, 8, 741-744.

29. A. Yu,Y. Wu, B. Cheng, K. Wei, J. Li, *Advanced Synthesis & Catalysis*, **2009,** 351, 767-771.

30. K. Swapna, A. V. Kumar, V. P. Reddy, K. R. Rao, *J. Org. Chem*. **2009**, 74, 7514–7517.

31. J. R. Miecznikowski, R. H. Crabtree, *Polyhedron*, **2004**, 23, 2857–2872.

III. E. References

1. Y. Suzuki, M. Iwata, R. Yazaki, N. Kumagai, M. Shibasaki, *J. Org. Chem*., **2012**, 77, 4496-4500.

2. P. S. Chaudhari, S. P. Pathare, K. G. Akamanchi, *J. Org. Chem*., **2012**, **77**, 3716-3723.

3. T. Murai, F. Hori,T. Maruyama, *Org. Lett.*, **2011**, **13**, 1718-1721.

4. N. K. Downer, Y. A. Jackson, *Org. Biomol. Chem*., **2004**, **2**, 3039-3043.

5. S. P. Ebert, B. Wetzel, R. L. Myette, G. Conseil, S. P. C. Cole, G. A. Sawada, T. W. Loo, M. C. Bartlett, D. M. Clarke, M. R. Detty, *J. Med. Chem*., **2012**, 55, 4683-4699.

6. T. Lincke, S. Behnken, K. Ishida, M. Roth, C. Hertweck, *Angew. Chem. Int. Ed*., **2010**, 49, 2011-2013.

7. A. Bach, J. N. N. Eildal, N. Stuhr-Hansen, R. Deeskamp, M. Gottschalk, S. W. Pedersen, A. S. Kristensen, K. Stromgaard, *J. Med. Chem*., **2011**, **54**, 1333-1346.

8. E. J. Petersson, J. M. Goldberg, R. F. Wissner, *Phys. Chem. Chem. Phys*., **2014**, 16, 6827-6837.

9. R. N. Hurd, G. DeLamate, *Chem. Rev*., **1961**, 61, 45-86.

10. S. R. Stauffer, J. Sun, B. S. Katzenellenbogen, J. A. Katzenellenbogen, *Bioorg. Med. Chem*., **2000**, 8, 1293-1316.

11. K. Sestanj, F. Bellini, S. Fung, N. Abraham, A. Treasurywala, L. Humber, N. Simard-Duquesne, D. Dvornik, *J. Med. Chem*., **1984**, 27, 255-256.

12. J. Matysiak, A. Niewiadomy, G. Macik-Niewiadomy, T. Korniłłowicz, *Eur. J. Med. Chem.*, **2000**, 35, 393-404.

13. S. Coats, J. S. Link, D. Hlasta, *Org. Lett*., **2003**, 5, 721-724.

14. J. Wei, Y. Li, X. Jiang, *Org. Lett*., **2016**, 18, 340-343.

15. X. Wang, M. Ji, S. Lim, H. Y. Jang, *J. Org. Chem*., **2014**, 79, 7256-7260.

16. B. Kurpil, B. Kumru, T. Heil, M. Antonietti and A. Savateev, *Green Chem*., **2018**, 20, 838-842.

17. C. Willgerodt, *Ber. Dtsch. Chem. Ges*., **1887**, 20, 2467-2470.

18. K. Kindler, *Liebigs Ann. Chem*., **1923**, 413, 187-230.

19. V. V. Kulganek, L. A. Yanovskaya, *Bull. Acad. Sci. USSR, Div. Chem. Sci*., **1979**, 28, 2402-2403.

20. H. Z. Lecher, R. A. Greenwood, K. C. Whitehouse, T. H. Chao, *J. Am. Chem. Soc.* **1956**, 78, 5018-5022.

21. T. Nishio, M. Orib, *Helvetica Chimica Acta*, **2001**, 84, 2347-2354.

22. K. A. Mahammed, V. P. Jayashankara, N. P. Rai, K. M. Raju, P. N. Arunachalam, *Synlett,* **2009**, 2338-2340.

23. B. Kaboudin, D. Elhamifar, *Synthesis*, **2006**, 224-226.

24. B. Kaboudin, L. Malekzadeh, *Synlett*, **2011**, 2807-2810.

25. R. S. Varma, D. Kumar, *Org. Lett*., **1999**, 1, 697-700.

26, U. Pathak, L. K. Pandey, R. Tank, *J. Org. Chem*., **2008**, 73, 2890-2893.

27. O. I. Zubruyev, N. Stiasni, C. O. Kappe, *J. Comb. Chem*., **2003**, 5, 145-148.

28. J. Wei, Y. Li, X. Jiang, *Org. Lett.*, **2016**, *18*, 340-343.

29. K. Xu, Z. Li, F. Cheng, Z. Zuo, T. Wang, M. Wang, L. Liu, *Org. Lett*., **2018**, 20, 2228-2231.

30. X. Wang, M. Ji, S. Lim, H.Y. Jang, *J. Org. Chem*., **2014**, 79, 7258-7260.

31. B. Mitra, P. Ghosh, *Chemistry Select*, **2021**, 6, 68– 81.

32. H. Wang, Y. Wang, Y. Han, W. Zhao, X. Wang, *RSC Adv*., **2020**, 10, 784-789.

33. Z. Wei, J. Li, Z. Wang, P. Li, Y. Wang, Chin. *J. Org. Chem*. **2017**, 37,1835-1838.

34. M. Papa, I. Chiarotto, M. Feroci, *Chemistry Select*, **2017**, 2, 3207–3210

IV. E. References

1. R. J. Sundberg, *Indoles, Academic Press: London*, **1996.**

2. D. J. Faulkner, *Nat. Prod. Rep*., **1999**, 16, 155.

3. M. Lounasmaa, A. Tolvanen, *Nat. Prod. Rep*., **2000**, 17, 175.

4. A. Rahman, A. Basha, *Indole Alkaloids; Harwood Academic Publishers Amsterdam*, **1998**, 141.

5. W. Gul, M. T. Hamann, *Life Sci*., **2005**, 78, 442–453.

6. J. S. Bindra, *The Alkaloids (Ed: R. H. F. Manske), Academic Press, New York*, **1973**, 14, 84-119.

7. R. J. Sundberg, *The Chemistry of Indoles, Academic Press, New York*, **1970**.

8. R. K. Brown, *Indoles (Ed.: W. J. Houlihan), Wiley-Interscience, New York*, **1972**.

9. W. Hong, I. C. Paterson, J. Li, Z. Chang, T. Xiaoli, H. Yang, O. Yifan, Y. Yang, K. Sargit, F. N. Yun, H. Wang, *J. Antibiot*., **2017**, 70, 832–844.

10. N. Vidhya Lakshmi, P. Thirumurugan, K. M. Noorulla, T. P. Paramasivan, *Bioorg. Med. Chem. Lett*., **2010**, 20, 5054–5061.

11. C. Ting Cai, K. Tian, X. Qin Li, L. Zhang, Y. Yuan Gan, J. Meng, S. Qun Wu, J. Lin Wan, Yang Xu, G. Ping Ouyang, Z. Chao Wang, *Chem. Pap*., **2019**, 73, 17–25.

12. X. Zeng, S. Ji, S. Wang, *Tetrahedron*, **2005**, 43, 10235–10241.

13. C. Molina-Santiago, A. Daddaoua, S. Fillet, D. Estrella, R. Juan-Luis Ramos, *Environ. Microbiol.*, **2014**, 16, 1267–1281.

14. C. Ramesh, J. Banerjee, R. Pal, B. Das, *Adv. Synth. Catal*., **2003**, 345, 557–559.

15. T. R. Garbe, M. Kobayashi, N. Shimizu, N. Takesue, M. Ozawa, H. Yukawa, *J. Nat. Prod*., **2000**, 63, 596-598.

16. J. H.Wynne, W. M. Stalick, *J. Org. Chem*., **2002**, 67, 5850.

17. A. Kumar, S. Sharma, R. A. Maurya, *Tetrahedron Lett*., **2009**, 50, 5937–5940.

18. Z.-X. Wang, A. J. Kochanowska- Karamyan, M. T. Hamann, *Chem. Rev.,* **2010**, 110, 4489–4497.

19. M. P. Le´ze´, M. Le Borgne, P. Marchand, D. Loquet, M. Kogler, G. Le Baut, A. Palusczak, R. W. J. Hartmann, *J. Enzyme Inhib. Med. Chem*., **2004**, 19, 549-557.

20. R. Contractor, I. J. Samudio, Z. Estrov, D. Harris, J. A. McCubrey, S. H. Safe, M. Andreeff, M. Konopleva, *Cancer Res*., **2005**, 65, 2890-2898.

21. M. Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Synlett,* **200**5, 1199–1222.

22. B.M. Trost, M.L. Crawley, *Chem. Rev*., **2003**, 103, 2921-2944.

23. Z. X. Wang, H. L. Qin, *Green Chem*., **2004**, 6, 90-92.

24. C. L. Raston, J. L. Scott, *Green Chem*., **2000**, 2, 49-52.

25. K. Tanaka, T. Sugino, F. Toda, *Green Chem*., **2000**, 2, 303-304.

26. S. Shirakawa, S. Kobayashi, *Org. Lett*., **2006**, 8, 4939–4942.

27. K. D. Yadav, R. Patel, P. V. Srivastava, G. Watal, L. D. S. Yadav, *Tetrahedron Lett.*, **2010**, 51, 5701–5703

28. D. Kundu, A. K. Bagdi, A. Majee, A. Hajra, *Synlett*, **2011**, 8, 1165–1167.

29. A. Kumar, M. K. Gupta, M. Kumar, *Green Chem*., **2012**, 14, 290–295.

30. P. Srihari, V. K. Singh, D. C. Bhunia, J. S. Yadav, *Tetrahedron Lett*., **2009**, 50, 3763-3766.

31. B. Das, J. N. Kumar, A. S. Kumar, K. Damodar, *Synthesis*, **2010**, 6, 914-916.

32. S. Aghaalikhani, F. K. Behbahani, *Chemistry Select*, **2016**, 1, 5530–5532.

33. S. G. Subramaniapillai, A. Ganesan, *Tetrahedron Lett*., **2014**, 55, 694–698.

34. Md. Rahimizadeh, H. Eshghi, M. Mokaber-Esfahani, M. Gholizadeh, *J. Chin. Chem. Soc*., **2014**, 61, 1265-1269.

35. Y. Qu, F. Ke, L. Zhou, Z. Li, H. Xiang, D. Wu, X. Zhou, *Chem. Comm*. **2011**, 47, 3912–3914.

36. A. Kumar, M.K. Gupta, M. Kumar, D. Saxena, *RSC Adv*., **2013**, 3, 1673-1678.

37. V.K. Rao, B.S. Chhikara, A.N. Shirazi, R. Tiwari, K. Parang, A. Kumar, *Bioorg. & Med. Chem. Lett*., **2011**, 21, 3511-3514.

38. S.V. Goswami, P.B. Thorat, V.N. Kadam, S.A. Khiste, S.R. Bhusare, *Chinese Chem. Lett*., **2013**, 24, 422-424.

39. V.K. Rao, M.S. Rao, N. Jain, J. Panwar, A. Kumar, *Org Med Chem Lett*., **2011**, 10.

40. C.L. Devi, V.J. Rao, S. Palaniappan*, Synthetic Communications*, **2012**, 42, 1593-1603.

41. B. Majhi, D. Kundu, B.C. Ranu, *J. Org. Chem*., **2015**, 80, 7739–7745.

42. R.A. Sheldon, *Green Chem*., **2005**, 7, 267–278.

43. N.R. Modugu, P.K. Pittala, *New. J. Chem*., **2017**, 41, 14062- 14066.

44. J. Liang, J. Lv, J.Z.C. Shang, *Tetrahedron*, **2011**, 67, 8532-8535.

45. A. Kumar, M. K. Gupta, M. Kumar, *Green Chem*., **2012**, 14, 290-295.

46. U. C. Rajesh, R. Kholiya, V. S. Pavan, D. S. Rawat, *Tetrahedron Letters*, **2014**, 55, 2977–2981.

47. A. Kumar, M. K. Gupta, M. Kumar, D. Saxena, *RSC Adv*., **2013**, 3, 1673-1678.

V. E. References

1. K. Hunger, *Industrial Dyes. Chemistry, Properties, Applications, Wiley-VCH, Weinheim*, **2003**.

2. H. Zollinger, *Color Chemistry. Syntheses, Properties and Applications of Organic Dyes and Pigments, VCH, New York*, **1987**, 85;

3. P. F. Gordon, P. Gregory, *Organic Chemistry in Colour, Springer, New York*, **1983**, 95;

4. R. G. Anderson, G. Nickless, *Analyst*., **1967**, 92, 207-238.

5. C. J. Barrett, J.-I. Mamiya, K. G. Yager, T. Ikeda, *Soft Matter*, **2007**, 3, 1249-1261.

6. Y. Zhao, J. He, *Soft Matter*, **2009**, 5, 2686-2693.

7. G. S. Kumar, D. C. Neckers, *Chem. Rev*., **1989**, 89, 1915-1925.

8. Y. Ikeda, *J. Mater. Chem*., **2003**, 13, 2037-2057.

9. T. Fehrentz, M. Schçnberger, D. Trauner, *Angew. Chem*. **2011**,123, 12362-12390.

10. T. Fehrentz, M. Schçnberger, D. Trauner, *Angew. Chem. Int. Ed*., **2011**, 50, 12156-12182.

11. G. Kumar, D. Neckers, *Chem. Rev*., **1989**, 89, 1915-1925.

12. A. A. Beharry, G. A. Woolley, *Chem. Soc. Rev*., **2011**, 40, 4422-4437;
13. S. Ghose, A. Banthia, Z. Chen, *Tetrahedron*, **2005**, 61, 2889-2896.
14. H. D¨urr, H. Bouas-Laurent, *Photochromism: Molecules, Systems, Elsevier*, **2003**.
15. Z. Yin, X. Jiang, P. Sun, *J. Org. Chem*., **2013**, 78, 10002-10007.
16. H. Li, P. Li, L. Wang, *Org. Lett.*, **2013**, 15, 620-623.
17. H. Li, P. Li, H. Tan, L. Wang, *Chem.–Eur. J.,* **2013**, 19, 14432-14436.
18. Z.Y. Li, D.D. Li, G.-W. Wang, J. *Org. Chem.,* **2013**, 78, 10414-10420.
19. H. Song, D. Chen, C. Pi, X. Cui, Y. Wu, *J. Org. Chem*., **2014**, 79, 2955-2962.
20. F. Xiong, C. Qian, D. Lin, W. Zang, X. Lu, *Org. Lett*., **2013**, 15, 5444-5447.
21. E. Merino, *Chem. Soc. Rev*., **2011**, 40, 3835–3853;
22. K. Haghbeen, E. W. Tan, *J. Org. Chem*., **1998**, 63, 4503–4505;
23. H. H. Davey, R. D. Lee, T. J. Marks, *J. Org. Chem*., **1999**, 64, 4976–4979;
24. E. S. Bacon, D. H. Richardson, *J. Chem. Soc*., **1932**, 884–888;
25. H. S. Fry, *J. Am. Chem. Soc*. **1930**, 52, 1531–1536;
26. J. F. Vozza, *J. Org. Chem*. **1969**, 34, 3219–3220;
27. T. Yamada, *Bull. Chem. Soc*.,**1969**, 42, 3565–3571;
28. L. I. Smith, W. B. Irvine, *J. Am. Chem. Soc*. **1941**, 63, 1036–1043.
29. P. Griess, *Ann.,* **1860**, 113, 207-209.
30. H. Zollinger, *Azo, Diazo chemistry Aliphatic, Aromatic compounds*, **1961**, *13-14*, 308-309.
31. E. Knoevenagel, *Ber*., **1890**, 23, 2994-2997.
32. K. Haghbeen, E.W. Tan, *J. Org. Chem*., **1998**, 63, 4503-4505.
33. H.H. Davey, R.D. Lee, T.J.J. Marks, *Org. Chem*., **1999**, 64, 4976.
34. O. Wallach, E. Belli, *Chem. Ber.,* **1880**, *13*, 525
35. Y. Liu, B. Liu, A. Guo, Z. Dong, S. Jin, Y. Lu, *Molecules*, **2011**, 16, 3563-3568.
36. R. Sanz, J. Escribano, Y. Fernández, R. Aguado, M.R. Pedrosa, F.J. Arnáiz, *Synlett,* **2005**, 9, 1389–1392.
37. K. Pothula, L. Tang, Z. Zhaab, Z. Wang, *RSC Adv*., **2015**, 5, 83144-83148
38. S. Wawzonek, T.W. McIntyre, *J. Electrochem. Soc*., **1972**, 119, 1350.
39. Y. Takeda, S. Okumura, S. Minakata*, synthesis.*, **2013**, *45*, 1029–1033.
40. L. Wang, A. Ishida, Y. Hashidoko, M. Hashimoto, *Angew. Chem. Int. Ed*., **2016**, *55*, 1–5.
41. M.B. Smith, J. March, *Advanced Organic Chemistry*, John Wiley & Sons, *5th edn*, **2001**, 937.
42. M.L. Hays, T.P. Hanusa, *Tetrahedron Lett*., **1995**, 36, 2435-2436
43. C. S. M. Pereira, V. M. T. M. Silva, A. E. Rodrigues, *Green Chem*., **2011**, 13, 2658–2671.

44. D. Villanueva-Bermejo, G. Reglero, T. Fornari, *Trends Food Sci. Technol*. **2017**, 62, 1–12.
45. M. Lores, M. Pajaro, M. Alvarez-Casas, J. Dominguez, C. Garcia-Jares, *Talanta*., **2015**, 140, 134–142.
46. I. F. Strati, V. Oreopoulou, *Food Chem*. **2011**, 129, 747–752.
47. D. V. Bermejo, E. Ibanez, G. Reglero, T. Fornari, J. Supercrit. *Fluids* **2016**, 107, 507–512.
48. I. Kamalanathan, L. Canal, J. Hegarty, V. Najdanovic-Visak, *Fluid Phase Equilib*. **2018**, 462, 6–13.
49. L. Yang, J. Ping Wan, *Green Chem*., **2020**, 22, 3074-3078.
50. M. Zhang, M.N. Chen, Z.H. Zhang, *Adv. Syn. & cat*., **2019**, 361, 5182-5190.

INDEX

Reprint of Papers

Sustainable Chemistry

Ethyl lactate: An Efficient Green Mediator for Transition Metal Free Synthesis of Symmetric and Unsymmetric Azobenzenes

Gyan Chandra Pariyar,[a] Tandra Kundu,[b] Bijeta Mitra,[b] Suvodip Mukherjee,[b] and Pranab Ghosh*[b]

Ethyl lactate, a bio-based completely degradable green solvent has been explored as an efficient reaction medium for the synthesis of symmetric as well as unsymmetric azobenzenes using various amines. As an environment friendly solvent, ethyl lactate has been found to have an interesting effect in this methodology for the formation of azobenzenes without the use of any transitional metal catalysts at room temperature.

Introduction

With the growing concern regarding environmental health, green methodologies have received special weightage in the recent past. During organic synthesis, the reaction medium offers a fundamental role by not only facilitating the contact between the reactants but sometimes also varying the course of the reaction. Therefore, a reaction medium which is not only environmentally benign but also possesses exceptional functions and properties has always been welcomed with open hands in the field of green organic synthesis. Lately, ethyl lactate (EL), a biodegradable environment friendly biomass-derived solvent has received considerable interest over traditional solvents as an economically feasible green solvent. The motive behind is due to its distinctive properties such as fully bio-degradable, non-toxic, non-corrosive, non-ozone depleting, high stability and solubility with water and majority of organic compounds.[1]

EL can be effortlessly produced by fermentation of biomass raw materials.[2] Due to non-toxicity, it has been approved by European Food Safety Authorities and Food and Drug Administration for the use as food additives and pharmaceutical additives.[3] It also has been fruitfully engaged in the extraction of various bioactive compounds and diverse food such as carotenoids,[4] polyphenols,[5] amino acids[6] and caffeine.[7] Besides, it has successfully being employed as a green solvent in a number of effective organic reactions[8] for the preparation of significant compounds such as spirooxindole-pyran derivatives,[9] 1,4-benzothiazines,[10] bis(indolyl)methanes,[11] polyfunctionalized alkenes,[12] quinoxalines,[13] 4(3*H*)-quinazolinones,[14] 2-pyrazoline derivatives[15] and enaminones.[16]

For a long period, aromatic azo-compound has received considerable amount of interest among the chemists. The main reason behind this is the tremendous collection of application of these compound promises in the field of food additives, indicators, organic dyes and therapeutic agents (Figure 1).[17] Further, due to their exceptional photochemical response, these compounds have been extensively used as liquid crystals,[18] smart polymers,[19] photo switches in biological systems[20] and photo chromic ligands in optochemical genetics.[21] By C–H activation/functionalization, azo-derivatives have been recently reported to be used for synthesis of valuable compounds like *o*-alkoxyazobenzenes,[22] *o*-acylazobenzenes[23] and indole derivatives.[24] They are also used in the construction of filters and proactive glass.

From literature survey, it has been recognized that a number of methods have been reported so far for the synthesis of azo-compounds. Among the few are Mills reaction, Wallach reaction, oxidation of amines, reduction of azobenzenes, thermolysis of azides, opening of quinine acetals, reaction of quinine acetals with arylhydrazines, dehydrogenation of arylhydrazines, metal catalyzed coupling of arylhydrazines, triazene rearrangements, oxidation of amines, diamerization of diazonium salts and opening of benzotriazoles.[25] Comparing all these methods, the easiest methodology is the one step route in the synthesis of azo-compounds by oxidation of amines. Literature survey shows that the synthesis of azo-compounds by oxidation of amines have been achieved by a number of catalysts, which are gold nanoparticles immobilized on TiO_2, silver nanoparticles, nickel peroxide, MnO_2, $NaBO_3$, $BaMnO_4$, $AgMnO_4$, $Pb(OAc)_4$, Ag_2CO_3, $Ce(OH)_3O_2H$, $RuCl_3/H_2O_2$, *t*-BuOI, *t*-BuOCl, galvinoxyl/$K_3Fe(CN)_6$, KO_2, platinum and palladium nanowires and Cu(I)-diazinidinone.[26] A generalize scheme for the different processes so far reported in literature are drawn in Scheme 1.

Although most of the methodologies reported gave a good yield of the product, but still there are few disadvantages

[a] G. C. Pariyar
Department of Food Technology, University of North Bengal, Dist. Darjeeling, West Bengal, India.
[b] T. Kundu, B. Mitra, S. Mukherjee, Prof. P. Ghosh
Department of Chemistry, University of North Bengal, Dist. Darjeeling, West Bengal, India
Tel.: +91 (0353) 2776381
fax: +91 (0353) 2699001
E-mail address:
E-mail: pkg12@yahoo.com

Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.202002629

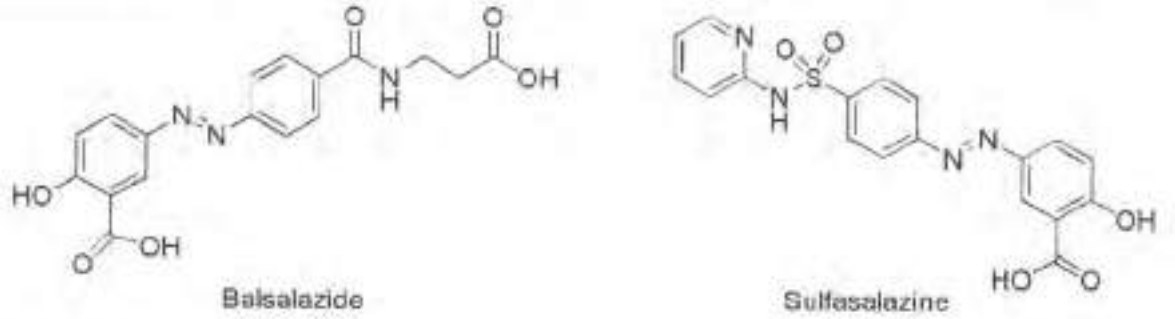
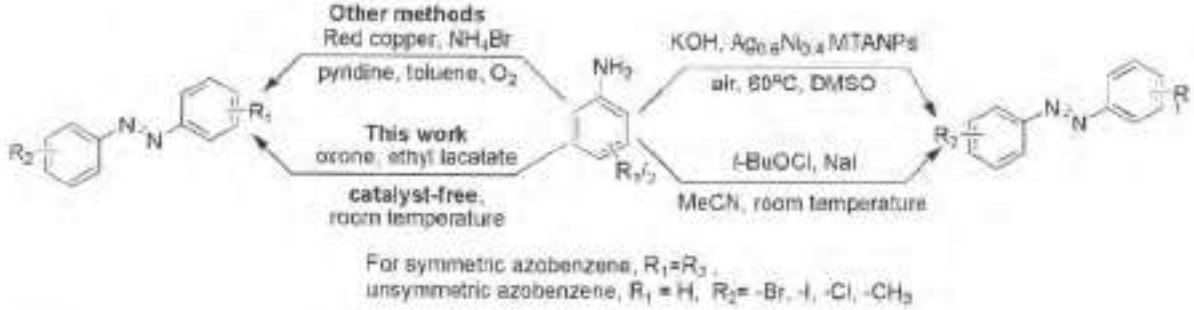


Figure 1. Biologically active molecules having azo-moiety



Scheme 1. Different processes of azobenzene synthesis

associated with them which includes use of environmental hazardous solvents, high temperature, use of expensive catalysts which may eventually led to metal contamination, use of transition metal catalysts, extended reaction time and tedious purification process. The formation of the by-products such as nitroso, nitro-, and azoxy-compounds depending on the catalysts and reaction conditions, is also one if the major concerns of these protocols during the oxidation of amines.[27]

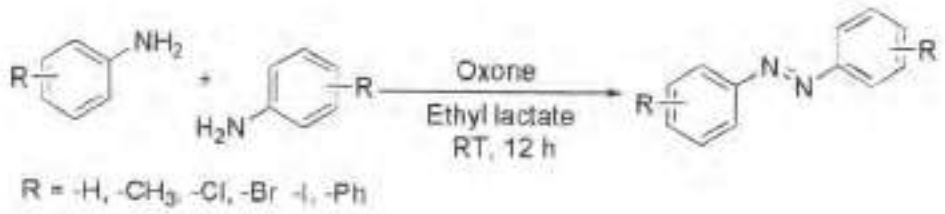
Hence, selection of methodology that will not only give a good yield of the product but also will minimize the formation of the by-products has been a challenge in the synthesis of azobenzenes by oxidation of amines. During the course of our research work, with an aim to develop a new methodology for our synthesis, we found that easily accessible, environmental benign and economical solvent ethyl lactate can be explored as an effective mediator in the synthesis of azobenzenes from amines without any additional catalyst.

Thus, in our work, we report ethyl lactate as an efficient, green solvent for the synthesis of both symmetric and unsymmetric azobenzenes at room temperature (Scheme 1, 2). During the synthesis of symmetric azobenzenes, oxone performed the role of an oxidant.

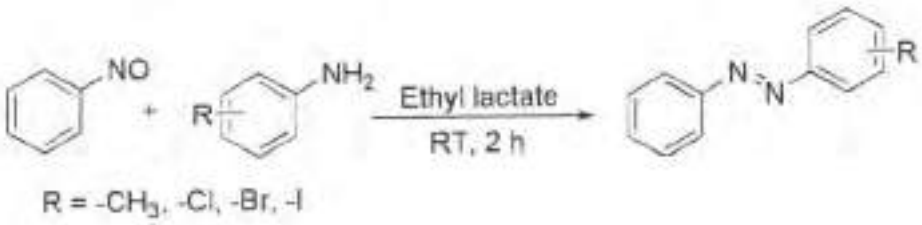
Result and discussion

i) Synthesis of symmetric azobenzenes

To standardize the reaction protocol, aniline was taken as the starting material and the progress of the reaction was monitored by TLC. The reaction was first carried out by taking 1 mmol of aniline and 0.5 mmol of oxone under neat condition for 12 hours when only trace amount of the product was obtained (Table 1, Entry 1). Now with the same reaction conditions, different solvents were used to monitor the reaction. Water only furnished trace amount of the product (Table 1, Entry 2). However, with chloro-

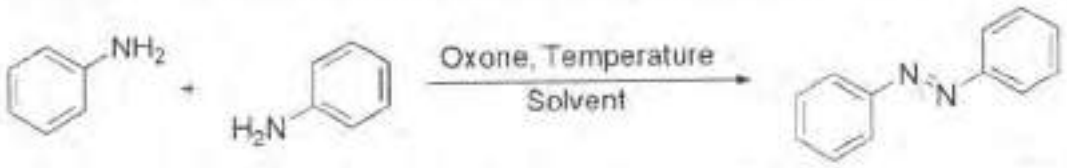


Scheme 2. Synthesis of symmetric azobenzene from amines



Scheme 3. Synthesis of unsymmetric azobenzene from amines

Table 1. Optimization of reaction condition for symmetric azobenzene[a]



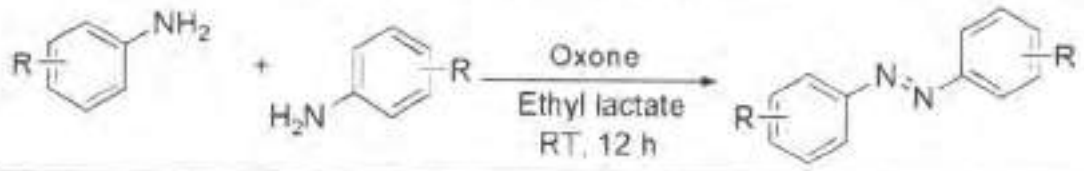
Entry	Oxone (mmol)	Solvent	Time (h)	Yield (%)[b]
1	0.5	Neat	12	Trace
2	0.5	Water	12	trace
3	0.5	$CHCl_3$	12	50
4	0.5	PEG 400	12	74
5	0.5	Toluene	12	55
6	0.5	EtOH	12	59
7	0.5	MeOH	12	40
8	0.5	EL/H_2O (2 : 1)	12	76
9	0.5	EL/H_2O (1 : 1)	12	75
10	0.5	EL/H_2O (1 : 2)	12	73
11	**0.5**	**EL**	**12**	**78**
12	1.0	EL	12	62
13	0.25	EL	12	38
14	0.3	EL	24	78
15	0.5	EL	06	60
16	0.5	EL	12	35[c]

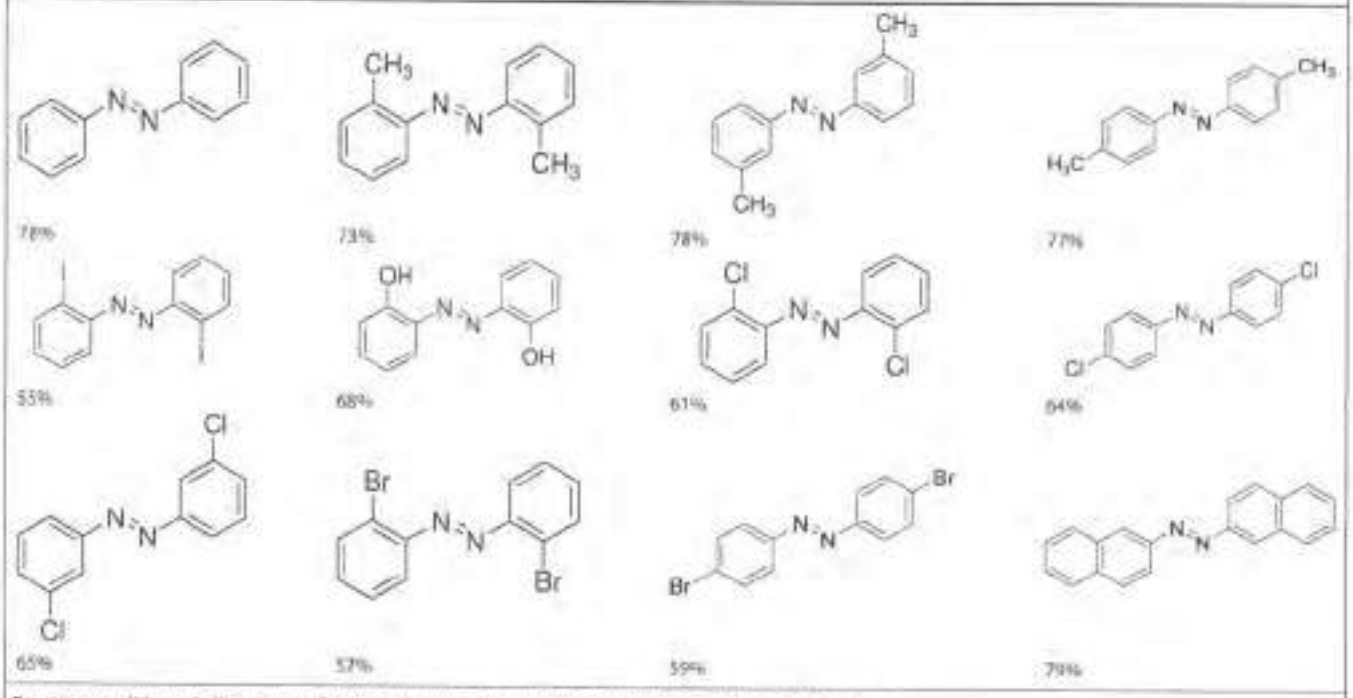
The bold significance represents the optimized protocol/conditions. [a]Reaction of aniline (1 mmol). [b]Isolated yield of product by column chromatography. [c]Reaction carried out at 90° C.

form the reaction gave encouraging yield of 50% (Table 1, Entry 3). PEG 400 further increased the yield to 74% (Table 1, Entry 4). Toluene and Ethanol gave 55% and 59% of the yield respectively (Table 1, Entry 5, 6). However slightly fewer yields of 40% was obtained with methanol (Table 1, Entry 7). We then decided to use ethyl lactate (EL) as the solvent and we were excited to find the yield increased to 78% (Table 1, Entry 11). We also used the solution of EL/H_2O at different ratios but yield remained almost the same (Table 1, Entry 10, 11, 12). Now with the solvent being optimized, we increased the amount of oxone to 1.0 mmol but here we were surprised to find that yield decreased considerably to 62% (Table 1, Entry 13). It may be due to the oxidation of aniline to nitrobenzene before undergoing coupling reaction. While reducing the amount of oxone to 0.25 mmol reduced the yield to 38% (Table 1, Entry 14). We further investigated the reaction by increasing the time to 24 hours which did not give any significant increase in the yield of the product (Table 1, Entry 15). However decreasing the time to 6 hours decreased the yield to 60%. Increasing the temperature of the reaction to 90° C also showed a large decrease in the yield (Table 1, Entry 16). The decrease of yield to 35% may be due to the oxidation of aniline to nitrobenzene at high temperature. Hence finally we report that the optimal reaction condition is 1 mmol of aniline and 0.5 mmol of oxone in ethyl lactate for 12 hours.

A number of amines have been employed in the synthesis of symmetric azobenzenes in our methodology. As evidence from table 2, good yield of different products has been obtained all at room temperature. The procedure has been generalized for a range of amines having electron-donating, electron-withdrawing groups on benzene ring as well as naphthyl rings. Better results were obtained for amines having electron-donating effect compare to those having electron-withdrawing effect. It may be due to the electron density on nitrogen atom making them more nucleophilic. It was also observed that ortho-product gave fewer yields than the other products. This may be due to steric factors at the ortho positions.

Table 2. Ethyl lactate mediated synthesis of symmetric azobenzenes





Reaction conditions: Aniline (1 mmol), oxone (0.5 mmol) in ethyl lactate for 12 h at Room Temperature.

ii) Synthesis of asymmetric azobenzenes

Using the same procedure for the synthesis of symmetric azobenzenes, we tried the synthesis of unsymmetric azobenzenes using 1 mmol of aniline, 1 mmol of *p*-toluidine and 0.5 mmol of oxone for 12 hours. However a mixture of different products was detected giving only trace amount of the desired product. We also tried stepwise process where first 1 mmol of aniline was reacted with 0.5 mmol of oxone for 30 min followed by addition of 1 mmol of p-toluidine. However, here also nitrobenzene is formed as the major product which may be due to oxidation of intermediate nitrosobenzene formed by oxone.

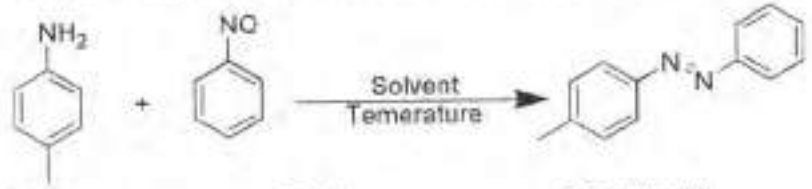
Therefore, we tried the reaction using *p*-toluidine and nitrosobenzene for 2 hours at room temperature. We were hopeful that the same solvent ethyl lactate that we used in the synthesis of symmetric azobenzenes might be applicable in this procedure and we were not surprised that it gave excellent yield of the desired product. We tried the reaction with a number of other solvents also but EL proved to be the best choice. No product was obtained when the reaction was carried out under neat condition (Table 3, Entry 1). As evident from Table 3, in water only trace amount of the product was obtained (Table 3, Entry 2). With ethanol, 47% of the yield was obtained (Table 3, Entry 3) and with DMF 32% was obtained (Table 3, Entry 4). As mentioned earlier, with EL, 83% of the product was isolated when carried out at room temperature for 2 hours (Table 3, Entry 5). With the increase of temperature to 80° C, the yield did not increase significantly (Table 3, Entry 6) which was also the case when the reaction was carried out for 6 hours (Table 3, Entry 7). However, decrease in the yield was observed when the reaction was carried for 1 hour (Table 3, Entry 8). So, finally we report the optimal reaction condition as 1 mmol of *p*-toluidine and 1 mmol of nitrosobenzene in 1 ml of ethyl lactate at room temperature for 2 h.

Amines having various substituents have been successfully converted into asymmetric azobenzene in good yields as depicted in Table 4. Various ortho- and para- substituted amines has been successfully converted into unsymmetric azobenzenes in good yield by our methodology. It is evident that ortho substituted amines gave fewer yields than the para substituted products. It may be due to the steric factor involved in ortho substituted products.

Mechanism

A plausible mechanism is given in Scheme 4. Oxone may have oxidized aniline either through radical mechanism or via electrophilic oxygen transfer with the subsequent generation of unstable nitrosobenzene. Electrophilic attack by the second molecule of aniline or other amines to nitrosobenzene,

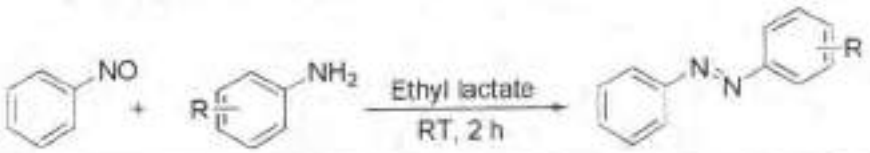
Table 3. Screening of the reaction conditions for synthesis of unsymmetric azobenzenes[a]

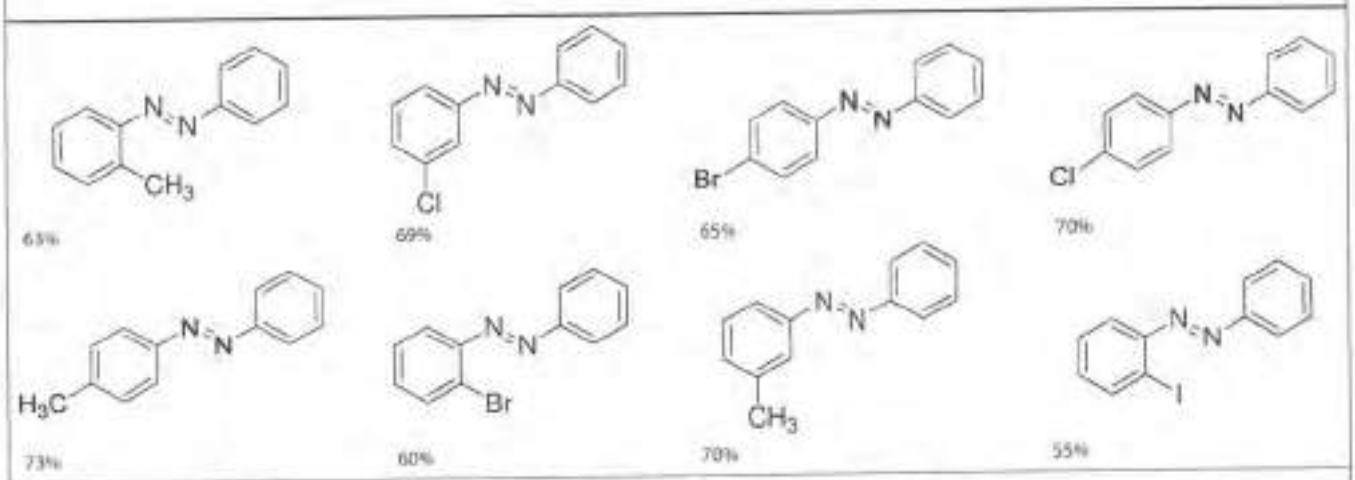


Entry	Solvent	Time (h)	Temperature (°C)	Yield (%)[b]
1	Neat	2	RT	Nil
2	Water	2	RT	Trace
3	Ethanol	2	RT	47
4	DMF	2	RT	32
5	**EL**	**2**	**RT**	**73**
6	EL	2	80	23
7	EL	6	RT	85
8	EL	1	RT	74

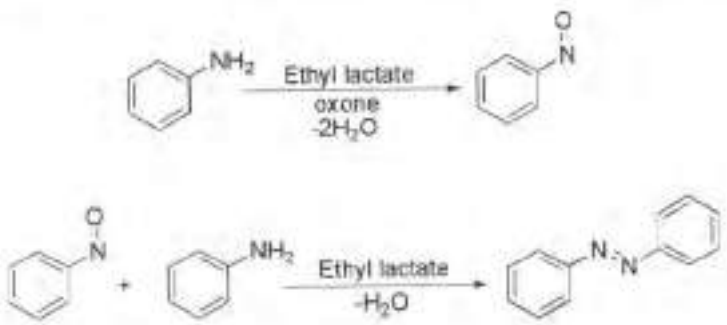
The bold significance represents the optimized protocol/conditions. [a]Reaction of amines(1 mmol) and nitrosobenzene (1 mmol). [b]Isolated yield of the products using column chromatography.

Table 4. Ethyl lactate mediated synthesis of unsymmetrical azobenzenes from nitrosobenzene





Reaction conditions: Nitrosobenzene (1 mmol), amines (1 mmol) in ethyl lactate for 2 h at room temperature.



Scheme 4. Plausible mechanism for azobenzene synthesis.

followed by dehydration led to the formation of *trans*-azobenzenes.

Conclusion

In conclusion, we have developed an environmentally benign protocol for the single-step facile synthesis of symmetric and unsymmetric azobenzenes from amines by using ethyl lactate as a solvent without the use of any catalyst. The reaction protocol includes the use of an inexpensive and non-toxic green solvent and gives excellent yield of the desired products with simple and easy reaction conditions and workup process.

Supporting Information Summary

All the experimental details for the synthesis of symmetric and unsymmetric azobenzenes, 13 C-NMR, and 1 H-NMR spectra have been summarized in the supporting information data.

Acknowledgement

One of the authors (B.M.) is thankful to CSIR, New Delhi for financial support.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Amines · Ethyl lactate · Nitrosobenzene · Room temperature · Azobenzenes

[1] a) S. Apanclo, R. Alcalde, *Green Chem.* **2009**, *11*, 65–78; b) C. S. M. Pereira, V. M. T. M. Silva, A. E. Rodrigues, *Green Chem.* **2011**, *13*, 2658–2671.
[2] *C. S. M. Pereira, V. M. T. M. Silva, A. E. Rodrigues, Green Chem.*, **2011**, *13*, 2658–2671.
[3] D. Villanueva-Bermejo, G. Reglero, T. Forman, *Trends Food Sci. Technol.* **2017**, *62*, 1–12.
[4] I. F. Strati, V. Oreopoulou, *Food Chem.* **2011**, *129*, 747–752.
[5] M. Lores, M. Pajaro, M. Alvarez-Casas, J. Dominguez, C. Garcia-Jares, *Talanta* **2015**, *140*, 134–142.
[6] L. Kamalanathan, L. Canal, J. Hegarty, V. Najdanovic-Visak, *Fluid Phase Equilib.* **2018**, *462*, 6–13.
[7] D. V. Bermejo, E. Ibanez, G. Reglero, T. Forman, *J. Supercrit. Fluids* **2016**, *107*, 507–512.
[8] a) L. Wei, X. Chen, Y. Liu, J. Wan, *Chin. J. Org. Chem.* **2016**, *36*, 954–961; b) M. Zhang, M. –N Chen, Z. –H Zhang, *Adv. Synth. Catal.* **2019**, *361*, 5182–5190; c) M. –N Chen, J. –Q Di, J. –M Li, L. –P Mo, Z. –H Zhang, *Tetrahedron* **2020**, *76*, 131059; d) Y. Han, J. –Q Di, A. –D Zhao, Z. –H Zhang, *Appl. Organomet. Chem.* **2019**, *33*, e5173; e) G. Gao, M. –N Chen, L. –P Mo, Z. –H Zhang, *Phosphorus Sulfur Silicon Relat. Elem.* **2019**, *194*, 528–532.
[9] M. Zhang, Q. Y. Fu, G. Gao, H. Y. He, Y. Zhang, Y. S. Wu, Z. H. Zhang, *ACS Sustainable Chem. Eng.* **2017**, *5*, 6175–6182.
[10] J. P. Wan, S. Cao, C. F. Hu, C. P. Wen, *Asian J. Org. Chem.* **2018**, *7*, 328–331.
[11] G. Gao, Y. Han, Z. H. Zhang, *Chemistryselect* **2017**, *2*, 11561–11564.
[12] J.-P. Wan, S. Zhong, L. Xie, X. Cao, Y. Liu, L. Wei, *Org. Lett.* **2016**, *18*, 584–587.
[13] S. Cao, S. Zhong, L. Xin, J.-P. Wan, C. Wen, *ChemCatChem* **2015**, *7*, 1478–1482.
[14] G. Shen, H. Zhou, P. Du, S. Liu, K. Zou, Y. Uozumi, *RSC Adv.* **2015**, *5*, 85646–85651.
[15] P. Bhat, G. Shridhar, S. Ladage, L. Ravishankar, *J. Chem. Sci.* **2017**, *129*, 1441–1448.
[16] Y. Gao, Y. Y. Liu, L. Wei, J. P. Wan, *Res. Chem. Intermed.* **2017**, *43*, 5547–5555.
[17] a) K. Hunger, *Industrial Dyes: Chemistry, Properties, Applications*, Wiley-VCH, Weinheim, **2003**; b) H. Zollinger, *Color Chemistry. Syntheses, Properties and Applications of Organic Dyes and Pigments*, VCH, New York, **1987**, p. 85; c) P. F. Gordon, P. Gregory, *Organic Chemistry in Colour*, Springer, New York, **1983**, p. 95; d) R. G. Anderson, G. Nickless, *Analyst*, **1967**, *92*, 207–238.
[18] T. Ikeda, *J. Mater. Chem.* **2003**, *13*, 2037–2057.
[19] a) C. J. Barrett, J.-I. Mamiya, K. G. Yager, T. Ikeda, *Soft Matter* **2007**, *3*, 1249–1261; b) G. S. Kumar, D.C. Neckers, *Chem. Rev.* **1989**, *89*, 1915–1925.
[20] a) G. Kumar, D. Neckers, *Chem. Rev.* **1989**, *89*, 1915–1925; b) A. A. Beharry, G. A. Woolley, *Chem. Soc. Rev.* **2011**, *40*, 4422–4437; c) S. Ghosh, A. Banthia, Z. Chen, *Tetrahedron*, **2005**, *61*, 2889–2896; d) H. Durr, H. Bouas-Laurent, *Photochromism: Molecules and Systems*, Elsevier, **2003**.
[21] T. Fehrentz, M. Schönberger, D. Trauner, *Angew. Chem. Int. Ed.* **2011**, *50*, 12156–12182.
[22] Z. Yin, X. Jiang, P. Sun, *J. Org. Chem.* **2013**, *78*, 10002–10007.
[23] a) H. Li, P. Li, H. Tan, L. Wang, *Chem.–Eur. J.* **2013**, *19*, 14432–14436; b) Z.-Y. Li, D.-D. Li, G.-W. Wang, *J. Org. Chem.* **2013**, *78*, 10414–10420; c) H. Song, D. Chen, C. Pi, X. Cui, Y. Wu, *J. Org. Chem.* **2014**, *79*, 2955–2962; d) F. Xiong, C. Qian, D. Lin, W. Zang, X. Liu, *Org. Lett.*, **2013**, *15*, 5444–5447.
[24] a) H. Li, P. Li, L. Wang, *Org. Lett.*, **2013**, *15*, 620–623; b) H. Wang, Y. Yu, X. Hong, Q. Tan, B. Xu, *J. Org. Chem.* **2014**, *79*, 3279–3288.
[25] a) E. Merino, *Chem. Soc. Rev.*, **2011**, *40*, 3835–3853; b) K. Haghbeen, E. W. Tan, *J. Org. Chem.*, **1998**, *63*, 4503–4505; c) H. H. Davey, R. D. Lee, T. J. Marks, *J. Org. Chem.*, **1999**, *64*, 4976–4979; d) E. S. Bacon, D. H. Richardson, *J. Chem. Soc.*, **1932**, 884–888; e) H. S. Fry, *J. Am. Chem. Soc.* **1930**, *52*, 1531–1536; f) J. F. Vozza, *J. Org. Chem.* **1969**, *34*, 3219–3220; g) T. Yamada, *Bull. Chem. Soc.*,**1969**, *42*, 3565–3571; h) L. I. Smith, W. B. Irvine, *J. Am. Chem. Soc.* **1941**, *63*, 1036–1043.
[26] a) S. Cai, H. Rong, X. Yu, X. Liu, D. Wang, W. He, *ACS Catal.* **2013**, *3*, 478–486; b) A. Grirrane, A. Corma, H. Garcia, *Science*, **2008**, *322*, 1661–1664; c) Y. Zhu, Y. Shi, *Org. Lett.* **2013**, *15*, 1942–1945; d) L. Hu, X. Cao, L. Chen, J. Zheng, J. Lu, X. Sun, H. Gu, *Chem. Commun.* **2012**, *48*, 3445–3447; e) M. Felizon, M. Gothier, R. Milcent, I. Papadakis, *Tetrahedron*, **1975**, *31*, 165–170; f) H. K. Hombrecher, K. Ludtke, *Tetrahedron* **1993**, *49*, 9489–9494; g) H. Firouzabadi, B. Vessal, M. Naderi, *Tetrahedron Lett.* **1982**, *23*, 1847–1850; h) G. Crank, M. I. H. Makin, *Aust. J. Chem.* **1984**, *37*, 845–855; i) E. Baer, A. L. Tosoni, *J. Am. Chem. Soc.* **1956**, *78*, 2857–2858; j) S. Okumura, C. H. Lin, Y. Takeda, S. Minakata, *J. Org. Chem.* **2013**, *78*, 12090–12105; k) Y. Takeda, S. Okumura, S. Minakata, *Angew. Chem., Int. Ed.* **2012**, *51*, 7804–7808; l) K. Nakagawa, T. Tsuji, *Chem. Pharm. Bull.* **1963**, *11*, 296–301; m) H. Firouzabadi, Z. Mostafavipoor, *Synth. Commun.* **1984**, *14*, 875–882; n) F. Habib, M. Zohreh, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 914–917.
[27] L. Lekha, K. K. Raja, G. Rajagopal, D. Easwaramoorthy, *J. Organomet. Chem.* **2014**, *753*, 72–80.

Submitted: July 1, 2020
Accepted: July 31, 2020