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ACKNOWLEDGEMENTS

By the grace and blessings of almighty God, finally a day has come to acknowledge those who directly or indirectly contributed in completion of this doctoral thesis which was a far big dream when I started my journey. The success and outcome of this thesis required a lot of guidance and assistance from many people around me and I am extremely privilege to have this all along the completion of my Ph.D. First of all, I thank Lord Shree Ganesha and Maa Saraswati for letting me through all the difficulties. I have experienced Your guidance and blessings day by day. I will keep on trusting You for my future.

I respect and thank Prof. Anil Kumar, for providing me an excellent opportunity to do the CSIR-project work in BITS Pilani, and opening a whole new phase of research life for me. I would like to express my sincere gratitude to him for supervising me as his Ph.D student with all support and guidance, which made me complete the tiring journey with absolute smoothness. I am extremely thankful to him for his invaluable guidance, endless patience, outstanding motivation, amazing enthusiasm, and immense knowledge throughout my Ph.D study for research. His inspiring hard work and constant encouragement, and moral support have helped me to evolve as an optimistic and enthusiastic researcher.

I am thankful to the members of my Doctoral Advisory Committee, Prof. Dalip Kumar and Prof. Rajeev Sakhuja for their great cooperation during my Ph.D. At the onset, their valuable suggestion for refining my proposal and seminar had a great impact to begin my research. I acknowledge them for continuous suggestions and corrections for improving my thesis without any time limits.

I express my thankfulness to Prof. Souvik Bhattacharyya (Vice-Chancellor), Prof. Ashok Kumar Sarkar (Director), Mr. Ernest Samuel Ratnakumar J (Registrar), Prof. S. Krishnaswamy (Dean Admin), Prof. S. Krishnaswamy (Dean, A-GSR), Prof. Jitendra Panwar (Assoc. Dean, A-GSR) and Dr. Hemant R. Jadhav (Ex. Assoc. Dean, A-GSR), Birla Institute of Technology & Science, Pilani (BITS Pilani) for giving me the opportunity to pursue my doctoral studies by providing necessary facilities. I overwhelmingly acknowledge the office staff of A-GSR, whose secretarial assistance helped me in submitting the various evaluation documents in time.

I highly appreciate the cooperation and affection extended by all the respected faculty members of the Department of Chemistry, BITS Pilani, which has made my stay here very productive. I owe my sincere thanks to Prof. I. R. Laskar (Convener, DRC), and previous DRC conveners Prof. R K Roy, Prof. Ajay Sah, and Prof. Saumi Ray along with other members of DRC. I would like to extent my sincere acknowledgements to Head, Department of Chemistry during my Ph.D work, Prof. S. K. Saha, Prof. Anil Kumar, Prof. Bharti Khungar, and Prof. Saumi Ray for helping me and providing me appropriate research facility. I specially thank Ms. Pusplata Das for her kind support and access to general chemicals and equipment whenever I needed. My sincere thanks to all the staff of library, BITS Pilani for their help rendered while utilizing the library services. I acknowledge UGC, New Delhi for providing me research fellowship during the tenure of my Ph.D. In addition DST-FIST is also deeply acknowledged for providing instrumentation facilities in department.

The great inspirational and enjoyable atmosphere along with the achievements made in Lab 3145 is one of the most memorable things in my life. My sincere thanks to seniors Dr. Kameswara Rao, Dr. Manoj Kumar Muthyala, Dr. Kasiviswanadharaju Pericherla, Dr. Ganesh M. Shelke, Dr. Sunita Choudhary, Dr Poonam, Dr. Pankaj Nehra, and Dr. Pinku for their friendly gesture and guidance. I am really fortunate and blessed to meet a wonderful bunch of friends as well as group members Mr. Hitesh, Mr. Shiv and Mr. Nitesh whose untiring and continued support in last five year is beyond the word to express. Those tea breaks and unending discussions over all kinds of personal or professional issues made my days in BITS Pilani very smooth and tranquil. My sincere thanks to other group members: Dr. Hemant Joshi and Dr. Om Prakash Singh Patel for all the valuable helps regarding research; Mr. Vikki Narayan Shinde and Ms. Sonam for being enjoyable and assisting juniors; Ms saroj and Ms. Vaishali. I feel really happy to have Ms. Sonam Sharma, Ms. Moyna Das, Ms. Santosh Kumari, Mr. Manish Mehra and Mr. Devesh Aggarwal as incredibly cooperative and cheerful friends in the department. Words come short to thank number of people here in

the department of chemistry: (Dr. Mukund Tantak, Dr. Mir Nisar, Dr. Abdul Shakoor, Mr. Anoop Singh, Mr. Vishal, Ms. Susheela, Ms. Sunita, Mr. Santosh Khandagale, Mr. Roshan Nazir, Mr. Vimal and Mr.Venkataramana Reddy) for their continuous support and charming company during the whole thesis work.

Throughout my studies and Ph.D research, my close friends have been extremely supportive. In particular, I would like to thank my best friend Ms. Kalpna Rajput for her encouragements and cheering me up all the time. I express my gratitude to my lovely ladies of favorite Chitter Chatter group Ms. Prerna, Ms. Aditi, Ms. Anita, Ms. Shweta, Ms. Akanksha, Ms. Isha, Ms. Elizabeth, Ms. Jensy, Ms. Apporva and Ms. Ranjitha. I could not imagine my stay in BITS Pilani without the constant love, support and compassion provided by all of you.

I deeply acknowledge my best friend and my soul mate, who always has stood with me in every ups and downs, my beloved husband Mr. Purshottam Sharma. I feel lucky to have extremely understanding, loving and gentle life partner who considers my achievements as his happiness. His calming aura and inspirational outlook for our life helped me to overcome all the frustration and to keep things in perspective. Completion of this thesis in anticipated time would have been difficult for me without his constant encouragement and support.

This acknowledgement will be incomplete without mentioning the most basic energy source of my life: my parents and siblings. I have an amazing and unique family in many ways. A special acknowledgement is dedicated to my father, Mr. Rukmagat Pandey for understanding and providing me the wings to fly high in life. I am indebted to my mother, Mrs. Rooma Pandey for loving me unconditionally, believing and encouraging me. Their vision, ethical principles, moral support, endless patience and eternal inspiration to face any situation in life have guided me to the successful completion of this work and it will be continue for the rest of my life for any kind of problems. It feels great to have a bunch of siblings Ms. Pavitra, Ms. Reeta, Ms. Priyanka and Master Krishna Pandey who always have celebrated my success as their own which gave me immense pleasure to achieve the best in my life. Their support has been unconditional all these years; they have given up many things for me to be a Ph.D; they have cherished with me every great moment and supported me whenever I needed it. They have sincerely encouraged and motivated me throughout my research work and lifted me uphill this phase of life and I have strong feeling and confidence that they will be always there for me. Words and this limited space do not seem adequate enough to express my indebtedness to my venerable parents and siblings. The acknowledgement of their contribution has been indelibly imprinted on my mind.

I deeply acknowledge the new family in my life for believing and assisting me in pursuing my dream. My father-in-law, Mr. S C Sharma and mother-in-law, Mrs. Kanta Sharma, have always supported me and motivated me to work hard. Their confidence to achieve something great and support to get that greatness will be always with me. I also sincerely acknowledge my brother-in-law Mr. Ankit Sharma for well wishes.

At last, I would acknowledge my inner self for consciously celebrating the best in me. I firmly believe that the motivation from people around us can do nothing if we don't have a fire within ourselves. My enthusiasm and joy in pursuing this degree helped me to overcome all the negativities around me. When ratio of failure to success was high, I stood firm and motivated to suppress all the pessimisms and shine bright. The completion of this thesis would be impossible without my passion to get success and zeal to move forward in any situation.

Khima Pandey

ABSTRACT

Among various onium salts, the pyridinium salt is an important heterocyclic motif which is widely present in a range of biologically active compounds as well as show applicability in the diverse fields of synthetic and material chemistry. On the other hand, imidazo[1,2-*a*]pyridines and amides represent significant class of compounds with extensive biological, medicinal and optoelectronic applications. The synthesis and functionalization of imidazo[1,2-*a*]pyridine with novel methods is desired both from economic and environmental point of view. The current thesis entitled "**Synthesis of Functionalized Imidazo[1,2-*a*]pyridines and Amides using Pyridinium Salts**" focuses on synthesis of functionalized imidazo[1,2-*a*]pyridines and amide derivatives from pyridinium salts *via* C–C and C-X (X = N, O, S) bond formation strategy using transition-metal catalysts as well as transition metal-free conditions. In this thesis, imidazolium-supported 2-chloropyridinium triflate has been synthesized and used for amide bond formation and further 2-amino-functionalized pyridinium salts were utilized to synthesize imidazo[1,2-*a*]pyridines *via* C-X (X = N, O, S) bond formation in presence of iodine, base or palladium/copper as catalyst. A brief outline of the work presented in the thesis is given below.

The first chapter of the thesis deals with the recent literature survey on the application of pyridinium salts as reagents and as efficient reactive partner for the synthesis of aza-fused heterocycles. Initially, importance of pyridinium salts and synthetic protocols to access pyridinium salts are discussed. Next, application of pyridinium salts in the synthesis of pyrazolopyridine, indolizine and imidazopyridines were discussed concisely. At last the application of pyridinium salts as efficient reagent in different organic transformation was summarized.

The second chapter of the thesis describes the synthesis and application of imidazolium-supported 2-chloro pyridinium salt as an efficient condensation reagent for synthesis of amides. The synthesised reagent was fully characterised using NMR, IR and mass spectroscopic technique and subsequently utilized for the synthesis of library of amides. All synthesized product were characterized using IR and NMR technique. The reaction conditions are benign, required shorter reaction time and furnished good yields of amides with a variety of substrates. The evasion of column chromatography, regeneration and reuse of the reagents are salient features of the methodology.

The third chapter of the thesis describes a simple and highly efficient protocol for the chemoselective synthesis of carbonyl-functionalized imidazo[1,2-*a*]pyridines *via* iodine-mediated 5-*exo*-*dig* type intramolecular cyclization of 2-amino-1-propargylpyridinium bromides in the presence of a 1N NaOH. Variously substituted imidazo[1,2-*a*]pyridine derivatives were obtained in good to excellent yields (45-89%). Additionally, direct access to 2-methylimidazo[1,2-*a*]pyridines from pyridinium salts was carried

out in presence of base through intramolecular hydroamination reaction. A facile and greener approach combined with good to excellent yields of products are advantages of the protocol.

The forth chapter of the thesis deals with the tandem intermolecular cyclisation of 2-aminopyridinum salts and 2-bromocarbaldehydes for the synthesis of chromone/pyrano-fused imidazo[1,2-*a*]pyridines. A direct one-pot tandem synthesis of chromeno-annulated imidazo[1,2-*a*]pyridines is accomplished by the reaction of 2-amino-1-(2-ethoxy-2-oxoethyl)pyridinium salts with 2-bromoarylaldehydes using $Pd(TFA)_2$ as a catalyst and $Cu(OAc)_2$ as an oxidant. The overall scheme comprises tandem base-mediated amidation and Knoevenagel condensation, followed by palladium-catalyzed Wacker type oxidation and intramolecular C−O coupling reaction. The method is simple, tolerates different functional groups to generate 33 examples of desired products with moderate to good yields (28-77%).

The fifth chapter of the thesis deals with the KOH-mediated cross-dehydrogenative $C(sp^3)$-S bond formation between 2-aminopyridinium salt and thiols to access 3-sulfenylimidazo[1,2-*a*]pyridin-2-ol derivatives in acetonitrile at 30 °C. The reaction afforded 29 examples of differently substituted 2-hydroxy-3-sulfenylimidazo[1,2-*a*]pyridine derivatives in 56-95% yields. The reaction is believed to proceed through intramolecular amidation followed by cross-dehydrogenative $C(sp^3)$-S coupling reaction.

The simultaneous inclusion of hydroxy functionality in the molecule give added advantages for further functionalization and generation of complex scaffolds. The hydroxyl group was further utilized to access 2-aryl-3-sulfenylimidazo[1,2-*a*]pyridines.

Finally, in the **sixth chapter** of the thesis, a summary of the thesis work is presented along with future scope of the research work.

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LIST OF ABBREVIATIONS / SYMBOLS

Abbreviation/Symbol	Description
α	Alpha
β	Beta
γ	Gamma
°C	Degree centigrade
Å	Angstrom
AcOH	Acetic acid
ACN	Acetonitrile
Ar	Aryl
Aq	Aqueous
BHT	Butylated hydroxytoluene
[Bmim][BF_4]	1-Butyl-3-methylimidazolium tetrafluoroborate
Bn	Benzyl
t-BuOK	Potassium *tert*-butoxide
Cat.	Catalytic
^{13}C	Carbon-13
CDC	Cross-dehydrogenative coupling
m-CPBA	*meta*-Chloroperoxybenzoic acid
d	Doublet
dd	Doublet of doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane

DCM	Dichloromethane
DPE	1,1-Diphenylethylene
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO-d_6	Deuterated dimethylsulfoxide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
[emim][BF_4]	1-Ethyl-3-methylimidazolium tetrafluoroborate
ESI-MS	Electron Spray Ionization Mass Spectrometry
ESI-TOF	Electron Spray Ionization-Time of Flight
EtOAc	Ethyl acetate
EtOH	Ethanol
equiv.	Equivalent
g	Gram
h	Hours
HFIP	Hexafluoroisopropanol
HRMS	High Resolution Mass Spectra
HTIB	[Hydroxy(tosyloxy)iodo]benzene
IBD	Iodobenzene diacetate
IBX	2-Iodoxybenzoic acid
ILs	Ionic liquids
IR	Infra-red
Hz	Hertz

IP	Imidazo[1,2-*a*]pyridines
J	Coupling constant
KOAc	Potassium acetate
Lit.	Literature
MP	Melting point
m	Multiplet
MHz	Mega hertz
min	Minutes
mmol	Millimole
MW	Microwave
N_2	Nitrogen
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
O_2	Oxygen
PEG400	Polyethylene Glycol400
1, 10-Phen	1,10-Phenanthroline
PIDA	Phenyl iodonium diacetate
PIFA	(Bis(trifluoroacetoxy)iodo)benzene
PivOH	Pivalic acid
ppm	Parts per million
%	Percentage
rt	Room temperature
S	Singlet

SET	Single electron transfer
t	Triplet
TEA	Triethyl amine
TFA	Trifluoroacetic acid
TBAB	Tetrabutylammonium bromide
TBHP	*tert*-Butyl hydroperoxide
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMDEA	Tetramethylethylenediamine
TMS	Tetramethylsilane
TMSCl	Trimethylsilyl chloride
-OTf	Triflouromethanesulfonate
-OTs	*p*-Toluenesulfonyl