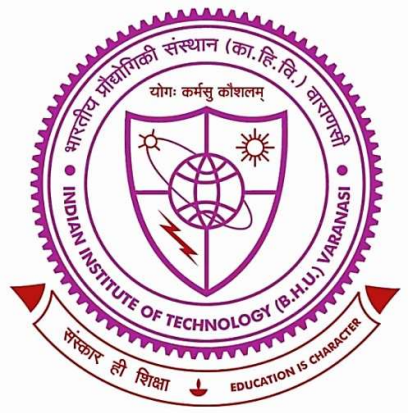
Synthesis and Applications of *N*-Activated Amides in Different Organic Transformations



Thesis submitted in partial fulfilment for the

Award of Degree

Doctor of Philosophy

by

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Dedicated to my beloved

Grandfather (Baba)

Shri Chandrika Singh

CERTIFICATE

It is certified that the work contained in the thesis titled **"Synthesis and Application of *N*-Activated Amides in different Organic Transformations"** by **Ms. Shweta Singh** has been carried out under my supervision and that this work has not been submitted elsewhere for a degree.

It is further certified that the student has fulfilled all the requirements of Comprehensive Examination, Candidacy and SOTA for the award of Ph.D. Degree.

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DECLARATION BY THE CANDIDATE

I, ***Ms. Shweta Singh***, certify that the work embodied in this thesis is my own bonafide work and carried out by me under the supervision of "***Dr. Jeyakumar Kandasamy***" from "***July-2018***" to "***October-2022***," at the ***Department of Chemistry***, ***Indian Institute of Technology (BHU), Varanasi***. The matter embodied in this thesis has not been submitted for the award of any other degree/diploma. I declare that I have faithfully acknowledged and given credits to the research workers wherever their works have been cited in my work in this thesis. I further declare that I have not willfully copied any other's work, paragraphs, text, data, results, etc., reported in journals, books, magazines, reports dissertations, theses, etc., or available at websites and have not included them in this thesis and have not cited as my own work.

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Place: Varanasi.

(***Ms. Shweta Singh***)

CERTIFICATE BY THE SUPERVISOR

It is certified that the above statement made by the student is correct to the best of my/our knowledge.

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ACKNOWLEDGEMENTS

I would like to express my truthful appreciation and heartful thanks to all the persons around me intended for their valuable advice, critics, commitment and encouragement that made my journey conceivable.

Initially, I "***Ms. Shweta Singh***" would like to express my deep sense of gratitude to my mentor, guide and supervisor "**Dr. Jeyakumar Kandasamy"**, Department of Chemistry, Indian Institute of Technology (Banaras Hindu University), Varanasi, for all support, suggestions, ideas, time and energy. His incredible knowledge and experience have encouraged me in all the time of my academic research and daily life.

I would like to thank my RPEC members, "**Prof. Vandana srivastava**", Department of Chemistry, IIT (BHU), Varanasi and "**Dr. Gyan Prakash Modi**", Department of Pharmaceutical Engineering and Technology, IIT (BHU), Varanasi for their valuable suggestions, constant guidance and kind encouragement during my research work.

My sincere thanks to the former Head, "**Prof. Dhanesh Tiwary**" Department of Chemistry, IIT (BHU), Varanasi, and the present head "**Prof. Yogesh Chandra Sharma**" as well as all the faculty members of the Department of Chemistry IIT (BHU) for their kind support and for extending all required facilities to carry out my research work smoothly.

I gratefully acknowledge the facilities provided by **CIFC-IIT (BHU),** Varanasi for **NMR** facilities for doing characterization of samples and **Pondicherry University** for **HRMS** facilities.

I am grateful and indebted to **IIT (BHU)** for providing me financial support during my research work.

I would like to express my deepest affection to my father "**Rajesh Singh**", mother, "**Snehlata singh**", and sister "**Shalini Singh**" brother "**Akash singh**" for their love, concern, continuous moral support and encouragement which enabled me to perform my liabilities.

I would like to extend my sincere thanks to "**Prof. Vinod kumar tiwari**", Department of Chemistry, Banaras Hindu University, Varanasi, for his encouragement throughout my research.

My special thanks to my loving seniors "**Dr. Priyanka Chaudhary**" and "**Dr. Varsha Tiwari**," my roommate, labmate and moreover my friend "**Dr. Sadaf Azeez**" and who stood there for me always.

I am thankful to all my lab members "**Dr. Kunj Bihari Mishra**", "**Dr. Surabhi Gupta**", "**Dr. Adesh Kumar Singh**", "**Dr. Sureshbabu Popuri**", "**Dr. Siddharth Baranwal**", "**Dr. Rapally Venkatesh**", "**Mr. Kanaujiya Vimlesh Kumar**", "**Ms. Aswathi CN**" and "**Mr. Nitin Kumar**" for their kind co-operation and friendly environment during the entire period of my research. Special thanks to project staff member "**Ashish Kumar Maurya**" in our laboratory for his support during my research.

I am deeply grateful and indebted to my supporter and friend "**Madhav"** who kept me encouraged and motivated during the lowest times of my research.

Some special words of gratitude go to all my friends who have always been a major source of support when things would get a bit discouraging. Thank you guys for always being there for me.

It will be endless to list each and every friend, relative and well-wisher of mine who has directly or indirectly wished for my success in all endeavors. I thank one and all.

Date: 14/11/2022

(Ms. Shweta Singh)

Research Scholar

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LIST OF NOTATIONS, SYMBOLS ANDABBREVIATIONS

Notations	Abbreviations
%	Percentage
<	Less than
>	More than
°	Degree
°C	Degree Celsius
©	Copyright
Å	Angstrom
1,10-Phen.	1, 10-phenanthroline
2,2-Bipy	2,2-Bipyridine
Ac	Acetyl group
Ac_2O	Acetic anhydride
AIBN	Azobisisobutyronitrile
AcOH	Acetic acid
Aq.	Aqueous
atm.	Atmosphere
brs	Broad Singlet
Bn	Benzyl
Bz	Benzoyl group
Calc.	Calculated
calcd	Calculated
$CHCl_3$	Chloroform
cm	Centimeter
$CDCl_3$	Deuterated Chloroform
CD_3OD	Methanol-d_4
c	Concentration
cc	Column chromatography
CSA	Camphorsulfonic acid
COSY	^1H-^1H Correlation Spectroscopy
D_2O	Deuterated water
DCE	1,2-Dichloroethane
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarization transfer
d	Doublet

dd	Doublet of doublet
ddd	Doublet of doublet of doublet
ddt	Doublet of doublet of triplet
dq	dq
dt	Doublet of triplet
DNA	Deoxyribonucleic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
Dppe	1,2-Bis(diphenylphosphino)ethane
EDG	Electron donating group
EWG	Electron withdrawing group
equiv.	Equivalent
EtOH	Ethanol
EtOAc	Ethyl acetate
Et_3N	Triethylamine
ESI	Electrospray ionization
g	Gram; Gravitational force
GC-MS	Gas Chromatography Mass Spectrometry
h	Hour
HRMS	High Resolution Mass Spectrometry
HPLC	High-performance liquid chromatography
Hz	Hertz
HSQC	Heteronuclear single quantum coherence spectroscopy
i-Pr	*Iso*-propyl
IR	Infra Red
J	Coupling constant
KI	Potassium iodide
KOH	Potassium hydroxide
LG	Leaving group
lit.	Literature
m	Multiplet
m/z	Mass to charge ratio
MeOH	Methanol
mg	Milligram
MHz	Megahertz
min	Minute
mL	Milliliter
mm	Millimeter
mmol	Milli Mole
µm	Micrometer
m.p.	Melting Point

MOM	Methoxymethyl
MS	Molecular sieve
MeOD	Dutereted methanol
nm	Nanometer
NaCl	Sodium chloride
NMR	Nuclear Magnetic Resonance
n-BuLi	*n*-Butyllithium
NMP	N-Methyl-2-pyrrolidone
nr	Not reported
nd	Not determined
NBS	N-Bromosuccinimide
NIS	N-Iodosuccinimide
NCS	N-Chlorosuccinimide
NOESY	Nuclear Overhauser Effect Spectroscopy
Obser.	Observed
PDC	Pyridinium dichromate
PG	Protectin group
pH	Potential of hydrogen
ppm	Parts per million
Py	Pyridine
PTSA	*p*-Toluenesulfonic acid
Pd-C	Palladiun on carbon
Quant.	Quantitative
RT	Room Temperature
RNA	Ribonucleic acid
R*f*	Retardation Factor
s	Singlet
t-Bu	Tertiary butyl
TBN	*tert*-Butyl nitrite
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TMS	Tetramethylsilane
TMEDA	Tetramethylethylenediamine
TBAI	Tetran-n-Butyl Ammonium Iodide
TBAF	Tetran-n-Butyl Ammonium Fluoride
TBAB	Tetran-n-Butyl Ammonium Bromide
TBS	*tert*-Butyldimethylsilyl
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl

TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
t	Triplet
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TsCl	4-Toluenesulfonyl chloride
UV	Ultraviolet
XRD	X-ray diffraction
α	Alpha
β	Beta
δ	Chemical shift
δ	Delta
[ox]	Oxidation
[α]	Specific rotation
i.e.	that is
o	Ortho
m	Meta
p	Para

GENERAL EXPERIMENTAL CONSIDERATIONS

All the reactions were carried out in oven dried glasswares. Starting materials were prepared using modified literature procedures and modified procedures as described in the experimental sections. Solvents, Chemicals were purchased from commercial sources (Aldrich, Alfa Aesar, SD fine and Avra) and used without further purifications, unless otherwise stated. **Melting points** of products were measured Staurt SMP10 melting point apparatus using in open capillary tubes. **FT-IR** for the products were recorded on ALPHA BRUKER Eco-ATR fitted out on ZnSe ATR crystal in the range of 500-3000 cm^{-1}. **^{1}HNMR** and **^{13}C NMR** spectra were recorded on Bruker Avance 500 MHz NMR spectrometer using deuterated solvents. Chemical shifts are given in ppm, using tetramethylsilane (TMS) as an internal standard. **Mass spectra (HRMS)** were measured on water's Quattro Micro V 4.1. Electronic absorption spectra were recorded on Shimadzu UV-2450 spectrophotometer. **Optical rotation** was measured using JASCO-2000 polarimeter. **Thin layer chromatography (TLC)** was performed using pre-coated plates obtained from E. Merck (TLC silica gel 60 F254). The TLCs were visualized in UV Chamber with 254 nm wavelength lamp, then further analyzed by charring in stain solution (5% H_2SO_4 in MeOH) and also sometimes in iodine chamber. **Column chromatography** was performed on silica gel (60-120 or 100-200 mesh) using different eluents. Optical rotation for all compounds has been performed using Jasco P-2000 polarimeter. **IR spectra** of the new compounds have been recorded using PerkinElmer instrument. **HPLC analysis** was performed on Agilent LC/192168254.11. C-8 Reverse phase column was used for the analysis with solvent acetonitrile:water = 70:30. Flow rate was maintained 1mL/minute. 10 Micro litre sample was injected for each analysis. The details of other fine chemicals, reaction conditions, substrate preparation etc. are given in respective chapters.

PREFACE

Amides are one of the most fundamental functional groups omnipresent in chemistry, biology, and materials science. Their widespread presence in Nature (e. g. in proteins, peptides, alkaloids, hormones and innumerous natural products) makes them essential structures to be explored. They are proven to be potential drugs such as paracetamol (analgesic), penicillin G (antibiotic), isoniazid (antituberculous agent), moreover, 25% of existing drugs and 33% of new drug candidates contain amide framework in their structures. Fertilizers like urea, herbicides such as alachlor and nylon which is an important polymer, are amides..

In this context, the thesis entitled **"Synthesis and Application of *N*-Activated Amides in different Organic Transformations"** has focused on the development of methodologies involving *N*-activated amides as starting materials for various organic transformations. **Chapter 1** will provide a general introduction to amides and their biological and synthetic importance. **Chapter 2** will introduce diversification of α–ketoamides via transamidation reactions with alkyl and benzyl amines at room temperature. **Chapter 3** will elaborate the synthesis of *N*-Aryl *α*–ketoamides, *α*–ketoesters, *α*–ketothioesters and their applications in quinoxalinone preparation. **Chapter 4** will describe the synthesis of acyl hydrazides from amides and hydrazine hydrate under metal free conditions at room temperature. **Chapter 5**, will present the synthesis of 1,3-dicarbonyl compounds using *N*-Cbz amides as an acyl source under transition metal-free conditions at room temperature. Finally, the **Chapter 6** will summarize and conclude the total thesis work.