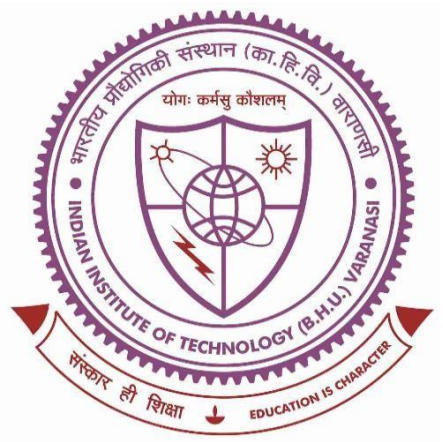
Green and Benign Strategies for Efficient Synthesis of Heterocyclic Compounds



Thesis submitted in partial fulfillment

for the Award of Degree

Doctor of Philosophy

By

Manjit Singh

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY

(BANARAS HINDU UNIVERSITY)

VARANASI – 221005

INDIA

Roll No: 19051006

Year: 2024


Dedicated
to
My Family

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It is certified that the work contained in the thesis titled **"Green and Benign Strategies for Efficient Synthesis of Heterocyclic Compounds"** by "Manjit 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, Candidacy and SOTA.

Manisha Malviya

Supervisor

Date: 08/04/24

(Dr. Manisha Malviya)

Department of Chemistry

Dr. MANISHA MALVIYA
DEPARTMENT OF CHEMISTRY
IIT (BHU), VARANASI
U.P.-221005

DECLARATION BY THE CANDIDATE

I, "**Manjit Singh**" certify that the work embodied in this thesis is my own Bonafide work and carried out by me under the supervision of "**Dr. Manisha Malviya**" from "July 2019" to "April 2024" at the "Department of Chemistry," Indian Institute of Technology, (Banaras Hindu University), 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, thesis, etc., or available at websites and have not included them in this thesis and have not cited as my own work.

Date: 08/04/2024

Manjit Singh
Signature of the Student

Place: Varanasi

"Manjit Singh"

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Department of Chemistry
भारतीय प्रौद्योगिकी संस्थान (का.हि.वि.वि.)
Indian Institute of Technology (B.H.U.)
वाराणसी–२२१००५ / Varanasi-221005

Manisha Malviya
Supervisor 08/04/24

(Dr. Manisha Malviya)

(Department of Chemistry)

Dr. MANISHA MALVIYA
DEPARTMENT OF CHEMISTRY
IIT (BHU), VARANASI
U.P.-221005

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Manjit Singh

CONTENTS

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List of Notation, Symbols and Abbreviations

Notation	Abbreviation
et al.	et alia, Latin for “and others
i.e.	That is
e.g.	Example
etc.	Et cetera, Latin for "and other similar things"
Fig.	Figure
mL	Milliliter
mg	Milligram
g	Gram
cm	Centimeter
Hz	Hertz
min	Minute
h	Hour
aq.	Aqueous
s^{-1}	Per Second
m.p.	Melting point
viz.	Namely
IR	Infrared
NMR	Nuclear magnetic resonance
TMS	Tetramethylsilane
Rf	Retardation Factor
HRMS	High resolution mass spectroscopy
MHz	Megahertz
rt	Room temperature
ppm	Parts per million
brs	Broad
Calc.	Calculated

Obser.	Observed
o	ortho
p	para
dil.	Diluted
approx.	Approximate
Equiv.	Equivalent
tert.	Tertiary
d	Doublet
m	Multiplet
q	Quartets
s	Singlet
t	Triplet
MW	Micro wave
m.f.	Molecular formula
V	Volume
vs.	Versus
sec	Second
CH_3CN	Acetonitrile
EtOAc	Ethyl acetate
OH	Hydroxy
I_2	Molecular iodine
TBN	*tert*- butyl nitrite
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
DMAP	4-Dimethylaminopyridine
Na_2SO_4	Sodium sulfate
TLC	Thin layer chromatography
D_2O	Deuterium oxide
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
MeOH	Methanol

DCE	Dichloroethane
DMF	N, N-Dimethyl formamide
DMSO	Dimethyl sulfoxide
THF	Tetrahydrofuran
PhMe	Toluene
Py	Pyridine
AgOTf	Silver trifluoro methane sulfonate
PPh_3	Triphenylphosphine
CuCl	Copper(I) chloride
$MgFe_2O_4$	Magnesium Ferrite
PTSA	*p*-Toluenesulfonic acid
NH_4Cl	Ammonium chloride
SiO_2	Silicon dioxide
$FeCl_3$	Iron (III) chloride
H_2SO_4	Sulphuric acid
$ZrCl_4$	Zirconium tetrachloride
$SOCl_2$	Thionyl chloride
NaNCS	Sodium thiocyanate
Fe_3O_4	Iron (II, III) oxide
VOCs	Volatile organic solvent
MCRs	Multi component reaction
MgO	Magnesium oxide
$InCl_3$	Indium (III) chloride
$PHI(OAC)_2$	(Diacetoxyiodo) benzene
A_COH	Acetic acid
NBS	N-Bromo succinimide

Symboles used

Symboles	Used
α	Alfa
β	Beta
γ	Gamma
°C	Degree Celsius
K	Kelvin
σ	Sigma
μ	Micro
△	Delta uppercase
©	Copyright
δ	Delta
>	Greater than
<	Less than
%	Percentage
Å	Angstrom
λ	Lambda
&	And
π	Pi
±	Either plus or minus

General Experimental Considerations

All solvents and chemicals were purchased from commercial sources (Sigma Aldrich, Alfa Aesar, and Avra) and used without further purifications, unless otherwise stated. **Thin-layer Chromatography** (**TLC**) was performed on glass plates (7.5 × 2.5 and 7.5 × 5.0 cm) coated with Merck silica gel GF 254 using various combinations of ethyl acetate and *n*-hexane as an eluent. Visualization of spots was accomplished either in **iodine chamber or by exposure to UV light**. The **column chromatography** was performed on silica-gel (60-120 mesh) using various combination of ethyl acetate and *n*-hexane eluents. **Melting points** of the products were measured through staurt SMP10 melting point apparatus (range 0 °C-300 °C) using an open capillary tube. **IR spectra** were recorded on Perkin-Elmer Spectrum 100 FT-IR spectrophotometer. **^{1}H** and **^{13}C NMR** spectra were recorded on Bruker Avance 500 MHz spectrometer in $CDCl_3$ and DMSO-*d6* as solvent and Tetramethylsilane (TMS) as an internal standard at 298 K, chemical shifts are given in ppm. **High resolution mass spectra** (**HRMS**) for all the compounds were measured on water's Quattro Micro V 4.1. **Ultrasonic irradiation** was performed using Sonics Vibra Cell Ultrasonic Processor Model VCX750 (Sonics & Materials, Inc.) with a fix power of 750 W and 20% amplitude and a tapered micro tip was used as ultrasonic probe operating at a frequency of 20 kHz. **Elemental analysis** was done by Eurovector EA3000 elemental analyzer.

Preface

Heterocyclic compounds are abundant in nature and they have important role in human life as they are present in vitamins, hormones, antibiotics and pigments. A vast number of nitrogen, oxygen and Sulphur containing heterocyclic compounds show biological activities and are used as key building blocks to develop compounds of biological or medicinal interest to organic chemists. Heterocyclic compounds are present in many biologically important moieties out of them some of the main scaffoldsare thiadiazols, coumarin, imidazo[1,2-a] pyridines and 4-*H* pyran. In this context, the thesis entitled "**Green and Benign Strategies for Efficient Synthesis of Heterocyclic Compounds**," will introduce various approaches for the synthesis of these heterocyclic compounds. **Chapter 1** will provide a general introduction and literature review of synthesis and applications of some main class of heterocyclic compounds. **Chapter 2** In this chapter, we have discussed a new synthetic method for the preparation of coumarin derivatives from *o*-cresols and active methylene compounds under metal and catalyst-free condition using beta-cyclodextrin as a green catalyst with the equimolar ratio of ethanol: water **(1:1)** reaction medium. **Chapter 3** is concerned with the development of novel, facile, efficient and scalable route for the synthesis of imidazo[1,2-a] pyridines. **Chapter 4** In this chapter, we have developed a facile, efficient and scalable protocol to successfully achieve the 6,7-dihydrobenzofuran-4(5H)-ones. **Chapter 5** Describes a completely eco-friendly and straightforward protocol for the biologically important synthesis of trisubstituted thiazole derivatives by the reaction of easily available starting materials barbituric acid, acetophenone and aryl thioamides in the presence $FeCl_3.6H_2O$ and O_2(Air) in DMF solvent.