A New Avenue for the Synthesis of Some Biologically Active Isatin Derivatives

THESIS SUBMITTED IN PARTIAL FULFILLMENT FOR THE AWARD OF DEGREE

DOCTOR OF PHILOSOPHY

By

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I, *"Suresh Kumar Maury"*, certify that the work embodied in this thesis is my own bonafide work and carried out by me under the supervision of *"Dr.(Mrs.) Sundaram Singh"* from *"July, 2017 to October, 2022"*, at the "Department of Chemistry", Indian Institute of Technology (B.H.U.), 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 on websites and have not included them in this thesis and have not cited as my work.

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ACKNOWLEDGEMENT

I give honor to God, the creator and sustainer of life, for blessing me to be able to pursue and complete this milestone. I thank God for giving me much knowledge, wisdom, and health to complete this work on time.

Foremost, I would like to thank my Research Supervisor, **Dr. (Mrs.) Sundaram Singh,** for her wide experience, unrivaled knowledge of chemistry, learned guidance, stimulating discussion, and unstinting moral support, which helped me immensely in completing this work in time. I thank her for putting up with my shortcomings and helping me to improve and overcome the same. Particularly, in the final stages, she has sustained me with her paternal care and thoughtful advice.

I am thankful to Head **Prof. Y.C. Sharma** of the Department and **Prof. Dhanesh Tiwary,** former Head of the Department of Chemistry, Indian Institute of Technology (Banaras Hindu University), for providing necessary lab facilities and a pleasant working atmosphere in the Department.

I would also like to thank my RPEC members, **Dr. Jeyakumar Kandasamy,** Department of Chemistry, Indian Institute of Technology (Banaras Hindu University), **Prof. Vandana Srivastava**, (Internal subject expert), Department of Chemistry, Indian Institute of Technology (Banaras Hindu University), and **Dr. Abha Mishra** (External subject expert), Department of Biochemical Engineering, Indian Institute of Technology (Banaras Hindu University), for their valuable suggestions throughout this work.

I'm highly indebted to Department of Chemistry for IR and CIFC, Indian Institute of Technology (BHU), for providing an NMR Spectroscopy facility.

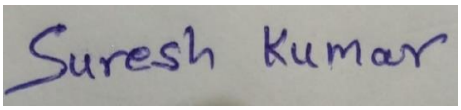
I also wish to thank all the non-teaching staff of the Department of Chemistry, Indian Institute of Technology (BHU), for their cooperation and timely help.

I would also like to thank my friends **Shivchand, Dipendra, Vishal, Vimlesh,** and **Mangal** for their affection, prayer, and support in my research work.

My warm sense of gratitude is due to my lab members, **Dhirendra Kumar, Savita Kumari, Arsala Kamal, Himanshu Kumar Singh, Ambuj Kumar Kushwaha,** and **Kavita,** for their help and cooperation at every step of the research work.

I take this opportunity to register my sincere thanks to the Department of Chemistry, Indian Institute of Technology (BHU), for a Research Fellowship and valuable pecuniary support.

Last but not least, I thank all my well-wishers whose names I may have failed to mention here unintentionally. Thanks to all of you for being there for me when times were the toughest.



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List of Notations, Symbols and Abbreviations

Notations	Abbreviations
%	Percentage
<	Less than
>	More than
°	Degree
Å	Angstrom
Ac	Acetyl
Ac_2O	Acetic anhydride
AcOH	Acetic acid
brs	Broad singlet
Obser.	Observed
Calc.	Calculated
©	Copyright
$CHCl_3$	Chloroform
$CDCl_3$	Deuterated chloroform
cm	Centimeter
J	Coupling constant
DMF	Dimethylformamide
DMSO-d^6	Deuterated dimethyl sulfoxide
D_2O	Deuterated water
^oC	Degree Celsius
d	Doublet
DMAP	4-Dimethylaminopyridine
DCE	Dichloroethane
DCM	Dichloromethane
CH_3CN	Acetonitrile
K_2CO_3	Potassium carbonate
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
ddt	Doublet of doublet of triplet

DMSO	Dimethyl sulfoxide
dq	Doublet of quartet
dt	Doublet of triplet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DABCO	1,4-Diazabicyclo[2.2.2]octane
equiv.	Equivalent
EtOH	Ethanol
EtOAc	Ethyl acetate
equiv.	Equivalent
g	Gram; Gravitational force
h	Hour
Hz	Hertz
IR	Infra-Red
m	Multiplet
MeOH	Methanol
mg	Milligram
MHz	Megahertz
min	Minute
mL	Milliliter
mm	Millimeter
mmol	Millimole
µm	Micrometer
M.p.	Melting point
nm	Nanometer
NMR	Nuclear Magnetic Resonance
n-BuLi	*n*-Butyllithium
KOH	Potassium hydroxide
pH	Potential of hydrogen
ppm	Parts per million
RT	Room temperature
s	Singlet
NMP	N-Methyl-2-pyrrolidone
t-Bu	Tertiary butyl
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TMS	Tetramethylsilane

TFA	Trifluoroacetic acid
UV	Ultraviolet
XRD	X-ray Diffraction
HRMS	High-resolution mass spectrometry
MWI	Microwave irradiation
MCR	Multicomponent reactions
NMR	Nuclear magnetic resonance
α	Alpha
β	Beta
γ	Gamma
δ	Chemical shift
[ox]	Oxidation
R_f	Refractive Index
o	Ortho
m	Meta
p	Para
H_2O_2	Hydrogen peroxide
H_2SO_4	Sulfuric acid
Et_3N	Triethylamine
$Sc(OTf)_3$	Scandium triflate
$Cu(OTf)_2$	Copper (II) trifluoromethanesulfonate
$Yb(OTf)_3$	Ytterbium (III) trifluoromethanesulfonate
TBHP	*tert*–Butylhydroperoxide
BHT	Butylatedhydroxytoluene
$LiAlH_4$	Lithium aluminium hydride
$ZnCl_2$	Zinc chloride
$KMnO_4$	Potassium permanganate
$K_2S_2O_8$	Potassium persulfate
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxidanyl
ZnO	Zinc oxide
CH_3COOH	Acetic acid
p-TSA	*p*-Toluenesulfonic acid
NH_2SO_3H	Sulfamic acid

TiO_2	Titanium dioxide
CuCl	Copper (I) chloride
$AlCl_3$	Aluminium chloride
$NaBH_4$	Sodium borohydride
DTBP	Di-*tert*-butyl peroxide
et al.	et alia, Latin for “and others”
i.e.	that is
e.g.	Example
equiv.	Equivalents

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General Experimental Considerations

All the chemicals were procured from Aldrich, USA and E. Merck, Germany and were used as received. The solvents were purchased from Merck, India and Ranbaxy, India and were purified before its use. The preparation and particulars of the substrates employed for the work undertaken are given in their respective chapters. **Melting points** were measured using Stuart Melting point apparatus SPM10 in open capillary tubes and are uncorrected. **Infrared (IR)** spectra were recorded on Perkin-Elmer FT-IR-5300 spectrophotometer (ν_{max} expressed in cm^{-1}). The **^{1}H** (500 MHz) and **^{13}C** (126 MHz) **NMR** spectra were run on a Bruker Advance 500 MHz FT-NMR at 500 MHz spectrometers. Chemical shifts are given in δ ppm, using tetramethylsilane (TMS) as an internal standard. **HRMS** (m/z) were recorded in an electron ionization or electrospray ionization (ESI) mode on Water-Q-TOF premier-HAB213 and Sciex X500RQTOF instruments. The **elemental microanalyses** were performed on Exeter Analytical Inc Model, CE-440 elemental analyzer.

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. Merck silica gel (100-200 mesh) was used for column chromatography (approximately 15-20 g per 1 g of the crude product).

Preface

A central objective in synthetic organic chemistry has been to develop a greener and more economically competitive processes for the efficient synthesis of biologically active compounds with potential application in the pharmaceutical and related industries.

Isatin and its derivatives represent an important class of 'privileged structures' capable of serving as ligands for a wide range of biological targets. Due to this reason, in past few decades, isatin and its derivatives have been used extensively as key intermediate in organic synthesis.

The content of the thesis have been divided into five chapters.

Chapter 1 gives an overview of the chemistry of isatin, it starts from short introduction followed by methods of synthesis and after that chemical reactivity of isatin. In this section, reduction, oxidation, electrophilic aromatic substitution, N-substitution and reactivity of the carbonyl group of isatin are briefly covered. After that, synthesis of isatin based spiro-fused heterocyclic scaffolds and at least, recent application of isatin in organic synthesis have been briefly included. The actual investigation and findings are presented in the subsequent four chapters.

Chapter 2 deals with a facile and efficient multicomponent synthesis of benzodiazepine ring via the reaction of isatin, diphenylamine, and 1,3-diketone under ultrasound irradiation in water. **Chapter 3** gives an account for a grinding induced catalyst-free, multicomponent synthesis of indoloindole pyrimidine from isatin, barbituric acid and enaminone under ethanol as a solvent at room temperature.

Chapter 4 investigates of a facile and ecologically friendly one-pot multicomponent synthesis of biologically active spiro [indoline-3, 4'-quinoline] derivatives via oxidative coupling of indole with enaminone and malononitrile under EtOH: H_2O (4:1) as a solvent. **Chapter 5** describes a facile, efficient and environment friendly , easy work, short reaction time approach for the synthesis of Spiro[Indoline-3,4'-Quinoline] via one pot, four component reaction of amine, dimedone, isatin , and malononitrile using DABCO in the presence of ethanol at 80^{o}C.