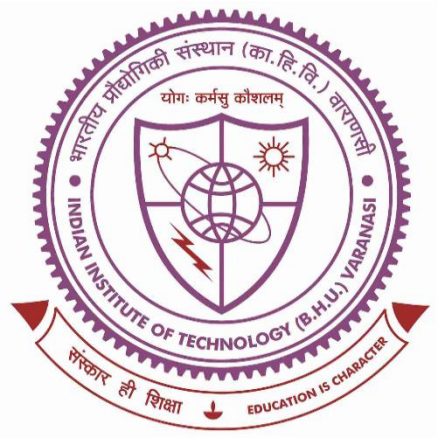
Green Approaches for the Synthesis of Some Biologically Relevant Heterocyclic Compounds



Thesis submitted in partial fulfillment

for the Award of Degree

Doctor of Philosophy

By

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DEPARTMENT OF CHEMISTRY

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Dedicated
to
My Family

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It is further certified that the student has fulfilled all the requirements of Comprehensive, Candidacy and SOTA.

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DECLARATION BY THE CANDIDATE

I, ***"Swati Chauhan"*** certify that the work embodied in this thesis is my own bonafide work and carried out by me under the supervision of ***"Prof. Vandana Srivastava"*** from ***"July 2015"*** to ***"August 2020"*** 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.

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Life is a race and in today's fast moving world, accomplishing a goal without the support of each other is a difficult task. Today, at the acme of my thesis, with heartiness, I greatfully remember many such individuals: as one flower makes no garland, this research would not have taken shape without their whole hearted encouragement and live involvement.

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With regards to numerous questions about my future academic endeavors from family and friends I shall answer in the words of ***Sir Winston Churchill***, “Now, this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.

I am indebted to **Indian Institute of Technology (BHU) Varanasi,** for providing financial support during my research work.

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Swati Chauhan

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List of Notations, Symbols and Abbreviations

Notation	Abbreviations
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 or rt	Room temperature
ppm	Part per million
brs	Broad

Calc.	Calculated
Obser.	Observed
o	ortho
p	para
dil.	Diluted
approx.	Approximate
Equiv.	Equivalent
tert.	Tertiary
MW	Microwave
US	Ultrasonicator
d	Doublet
m	Multiplet
q	Quartets
s	Singlet
t	Triplet
W	Watt
m.f.	Molecular formula
V	Volume
vs.	Versus
NR	No Reaction
sec	Second
CAN	Ceric ammonium nitrate
CH_3CN, MeCN	Acetonitrile
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
EtOAc	Ethyl acetate
OH	Hydroxy
H_2O	Water
I_2	Molecular iodine

TBHP	*tert*-Butyl hydrogen peroxide
TBN	*tert*- butyl nitrite
BHT	Butylated hydroxytoluene
KI	Potassium iodide
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
EtOH	Ethanol
$CHCl_3$	Chloroform
MeOH	Methanol
DCM, CH_2Cl_2	Dichloromethane
DCE	Dichloroethane
DMF	*N*,*N*-Dimethyl formamide
DMSO	Dimethylsulfoxide
THF	Tetrahydrofuran
EtOAc	Ethyl acetate
PhH	Benzene
PhMe	Toluene
Py	Pyridine
DABCO	1,4-diazabicyclo[2.2.2]octane
AgOTF	Silver trifluoromethanesulfonate
PPh_3	Triphenylphosphine
KBr	Potassium bormide
$AlCl_3$	Aluminium Chloride
K_2CO_3	Potassium Carbonate

NaOH	Sodium hydroxide
CuCl	Copper(I) chloride
$MgFe_2O_4$	Magnesium Ferrite
p-TSA	*p*-Toluenesulfonic acid
NH_4Cl	Ammonium chloride
SiO_2	Silicon dioxide
ZnO	Zinc oxide
$FeCl_3$	Iron(III) chloride
H_2SO_4	Sulphuric acid
$ZrCl_4$	Zirconium tetrachloride
MCM	Mesoporous material
$SOCl_2$	Thionyl chloride
NaNCS	Sodium thiocyanate
Br_2	Bromine
PIFA	(Bis(trifluoroacetoxy)iodo)benzene
TCT	Trichloroisocyanuric acid
DIPEA	*N, N*-Diisopropylethylamine
TEA	Triethylamine
HI	Hydrogen iodide
IBX	Iodoxybenzoic acid
BAIB	(Diacetoxyiodo)benzene
$CuSO_4$	Copper(II)sulfate
N_2O_4	Dinitrogen tetroxide
IAN	*iso*-Amyl nitrite
NBN	*n*-Butyl nitrite
H_2S	Hydrogen sulfide
CsF	Caesium fluoride
EDDA	Ethylenediammonium diacetate

TiO_2	Titanium dioxide
Fe_3O_4	Iron(II, III) oxide
PEG	Polyethylene glycol
Ag_2CO_3	Silver carbonate
VOCs	Volatile organic solvent
MCRs	Multi component reaction
$NiFe_2O_4$	Nickel ferrite
KF	Potassium fluoride
NBS	N-Bromosuccinimide
NaI	Sodium iodide
GO	Graphene oxide
Na_2CO_3	Sodium carbonate
MgO	Magnesium oxide
$NaHCO_3$	Sodium bicarbonate
$InCl_3$	Indium(III) chloride
$PHI(OAC)_2$	(Diacetoxyiodo)benzene
$ZrOCl_2.8\ H_2O$	Zirconyl chloride octahydrate
$H_3PW_{12}O_{40}$	Phosphotungstic acid
NPs	Nanoparticles
ACOH	Acetic acid
$P(4\text{-}VPH)ClO_4$	Poly(4-vinylpyridinium)perchlorate
ZrO_2	Zirconium dioxide
BDMS	Bromodimethylsulfonium Bromide
Cu@MNPs	Copper magnetic nanoparticles

Symboles used

Symboles	Full name
α	Alfa
β	Beta
γ	Gamma
°C	Degree Celsius
K	Kelvin
σ	Sigma
μ	mu
Δ	Delta Upercase
©	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 tubes. **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-d_6 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 moiety out of them some of the main scaffolds are thiadiazoles, coumarin, imidazo[1,2-a]pyridines and 4-*H* pyran. In this context, the thesis entitled "***Green Approaches for the Synthesis of Some Biologically Relevant 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** will describe synthesis of 1,2,4-thiadiazole and 1,2,4-selenadiazole by two different methods *i.e.* by *tert*-butyl nitrite and chloranil mediated dimerization of primary thioamides and selenoamides. **Chapter 3** will describe a facile and convenient approach for a practical synthesis of 3-functionalized coumarins under metal and catalyst-free condition using *tert*-butyl hydrogen peroxide. **Chapter 4** will describe a simple and efficient method for the synthesis of imidazo[1,2-a]pyridines in metal and solvent-free conditions using KI/TBHP catalytic system under grinding at room temperature. **Chapter 5** will explore a solar energy mediated green synthesis of tetrahydrobenzo[b]pyran derivatives by using organocatalyst L-ascorbic acid in aqueous mediated.

CHAPTER 1

Introduction

Overview of Some Main Class of Nitrogen, Oxygen and Sulphur Containing Heterocyclic Compounds

Chapter 1

Overview of Some Main Class of Nitrogen, Oxygen and Sulphur Containing Heterocyclic Compounds

Heterocyclic compounds are a class of cyclic organic compounds in which one or more of the carbon atoms inside the backbone of the molecule is changed apart from carbon. The most commonly found heteroatoms in heterocyclic compounds are nitrogen, oxygen and sulphur. Heterocyclic compounds are divided into different categories on the basis of total number of atoms in the cyclic structure they have like three, four, five, six, seven and eight membered and also fused types of heterocyclic compounds are known. Out of them nitrogen, oxygen and sulphur containing five, six membered and fused heterocyclic compounds maintained the curiosity of researchers throughout the decades of historical development of organic synthesis.

Five Membered Heterocyclic Compounds: Pyrrole, furan and thiophene are the important single heteroatom containing five membered heterocyclic compounds. The common five membered heterocyclic compounds having more than one heteroatoms are isoxazole, pyrazole, imidazole, azole, thiazole, thiadiazole, oxadiazole, triazene, etc. Heterocyclic compounds which are partially reduced are often referred to as dihydro or tetrahydro derivatives of the parent unsaturated compound (**Figure 1.1**).

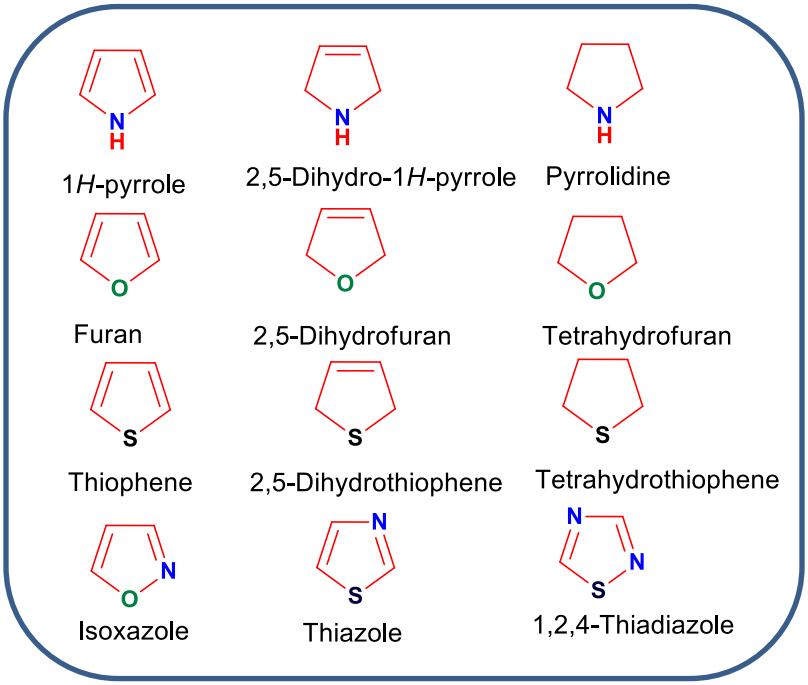


Figure 1.1: Some important five membered heterocyclic compounds.

Six Membered Heterocyclic Compounds: Pyridine, pyran and thiopyran are some common six membered heterocyclic compounds containing single heteroatom in the ring. The six membered heterocycles which comprises more than one heteroatoms are pyrazine, dioxane, dithine**,** oxazine, thiazine etc. Thiadiazine is a heterocyclic compound having two nitrogen atoms and one sulfur atom in six-membered ring skeleton and triazine also contains three nitrogen atoms in a six member ring (**Figure 1.2**).

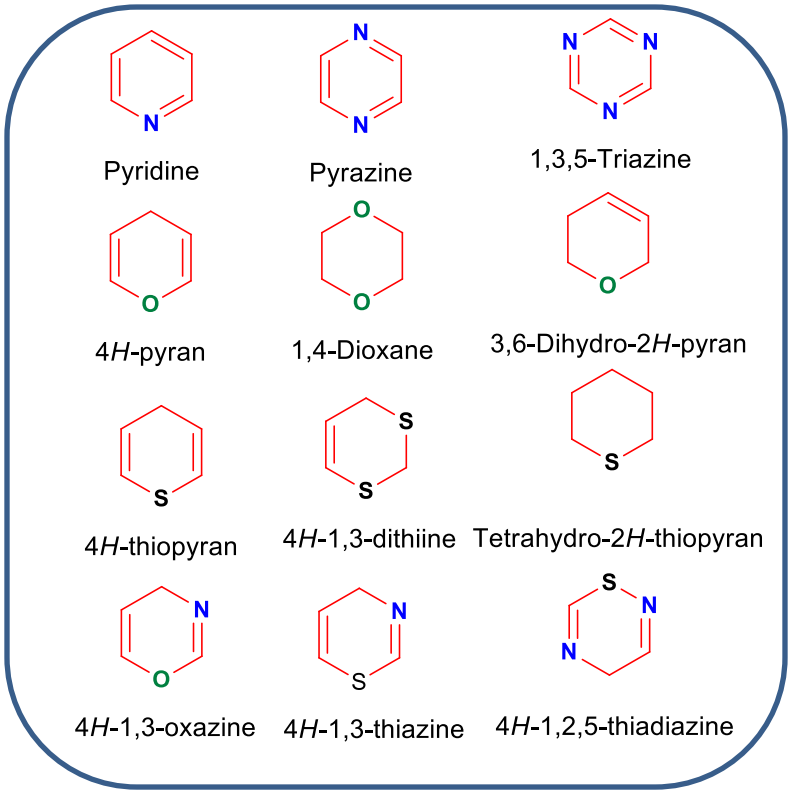


Figure 1.2: Some important six membered heterocyclic compounds.

Fused Heterocyclic Compounds: Fused heterocyclic ring structures are obtained by the fusion of one ring with other rings. Quinoline, 1*H*-indole, coumarin and benzothiophene are some important single heteroatom containing fused heterocyclic compounds. The common fused heterocyclic ring contains more than one heteroatoms such as imidazo[1,2-a]pyridine, benzothiazole, benzooxathiole and furopyran etc. Pyrazolooxazole is a heterocyclic compound holding one oxygen atom and three nitrogen atoms as share of the fused heterocyclic compound (**Figure 1.3**).

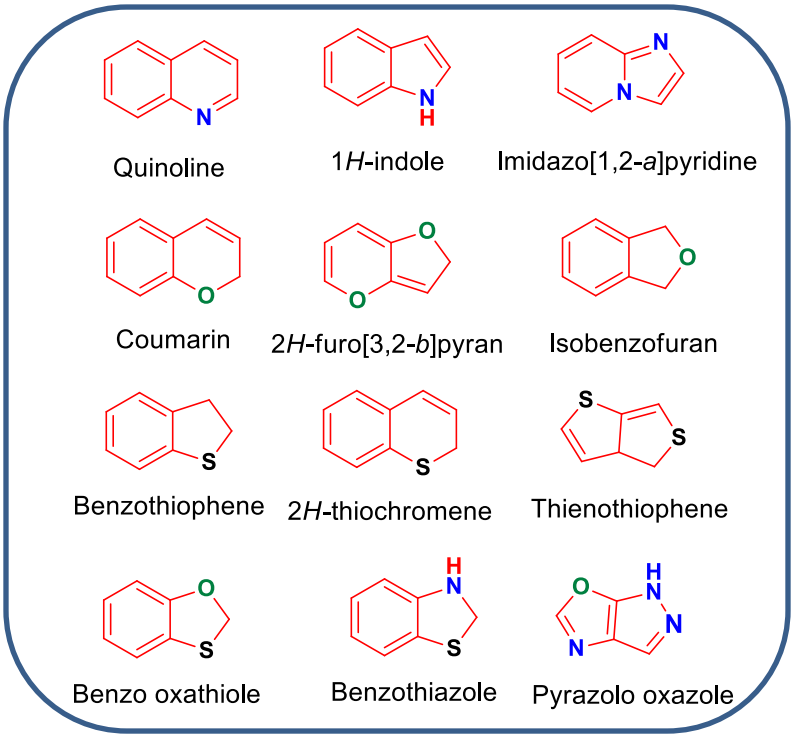


Figure 1.3: Some important fused heterocyclic compounds.

The chemical substances which comprise at least one heterocyclic moiety make them the most important class of compounds in organic chemistry. Heterocyclic compounds have attracted the attention of scientists over the years due to its vitality in human life and abundance in nature (Nagaraj et al. 2008) due to the fact that they are important structural subunits present in many herbal merchandise consisting of vitamins, hormones, antibiotics and pigments (Ju et al. 2006, Yadav et al. 2011). Thus, these derivatives have attracted considerable attention in the designing of biologically active molecules. Modern society depends on man-made heterocycles for many purposes together with drugs, pesticides,

dyes, plastics, cosmetics, solvents, antioxidants and vulcanization accelerators (Li et al. 2011, Martins et al. 2004) (**Figure 1.4**).

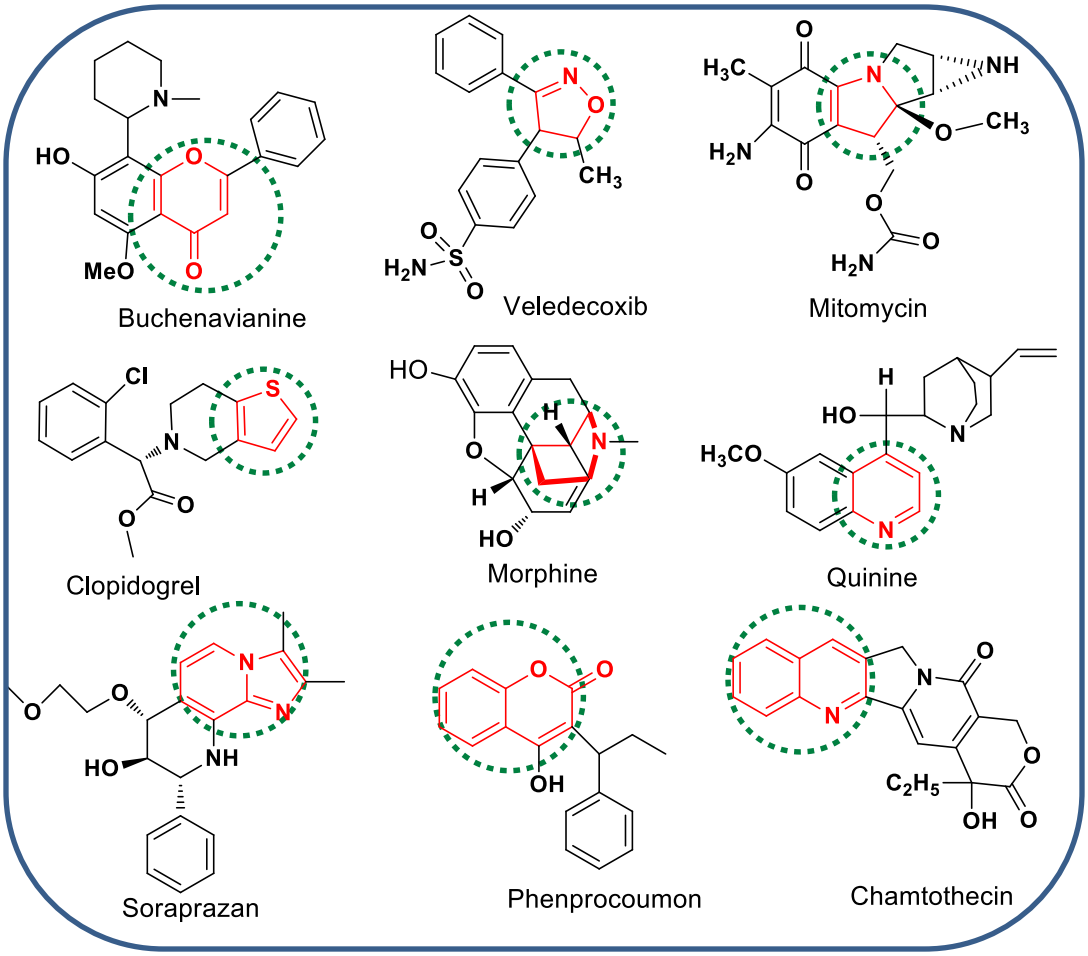


Figure 1.4: Some example of natural products and drugs containing different heterocyclic moieties.

Synthesis of heterocyclic skeleton with biologically ubiquitous functionalities is a lucrative aim for chemists. The five, six membered, fused heterocycles and related compounds have been the subject of major attraction for the researchers in the area of

synthetic organic chemistry. Therefore, chemists have been involved in extensive efforts to produce these heterocyclic compounds by rising new and effective synthetic transformation. Our main focus is on the study of 1,2,4-thiadiazole, coumarin, imidazo[1,2-a]pyridine and 4*H*-pyran scaffold.

1.1 Thiadiazole

Thiadiazoles are very important class of nitrogen and sulphur containing heterocyclic compounds. 1,2,3-thiadiazole, 1,2,5-thiadiazole, 1,2,4-thiadiazole and 1,3,4-thiadiazole are four isomeric forms of thiadiazole found in nature (Siddiqui et al. 2009). Out of them, we have focused on 1,2,4-thiadiazole. 1,2,4-Thiadiazole core structure are of great interest mainly because of their various biological activities and associated clinical applications (Iizawa et al. 1993, Donkor et al. 2000, Gurjar et al. 2014). They have diverse applications in different fields. A large number of synthetic 1,2,4-thiadiazole derivatives show wide range of biological activities such as thiadiazole KC 12291 which displayed the foremost proof of its cardioprotective activity (Hartmann et al. 1998), 6-(1,2,4-thiadiazol-5-yl)-3-amino pyridazine derivatives are recognized as unique angiogenesis inhibitors (Bongartz et al. 2002) and monocyclic 1,2,4-thiadiazoles have been found as useful insecticidal, herbicidal and fungicidal agents. Additionally, the properties of 1,2,4-thiadiazole as thioltrapping representatives has been reviewed recently (Tam et al. 2005) (**Figure 1.5**).

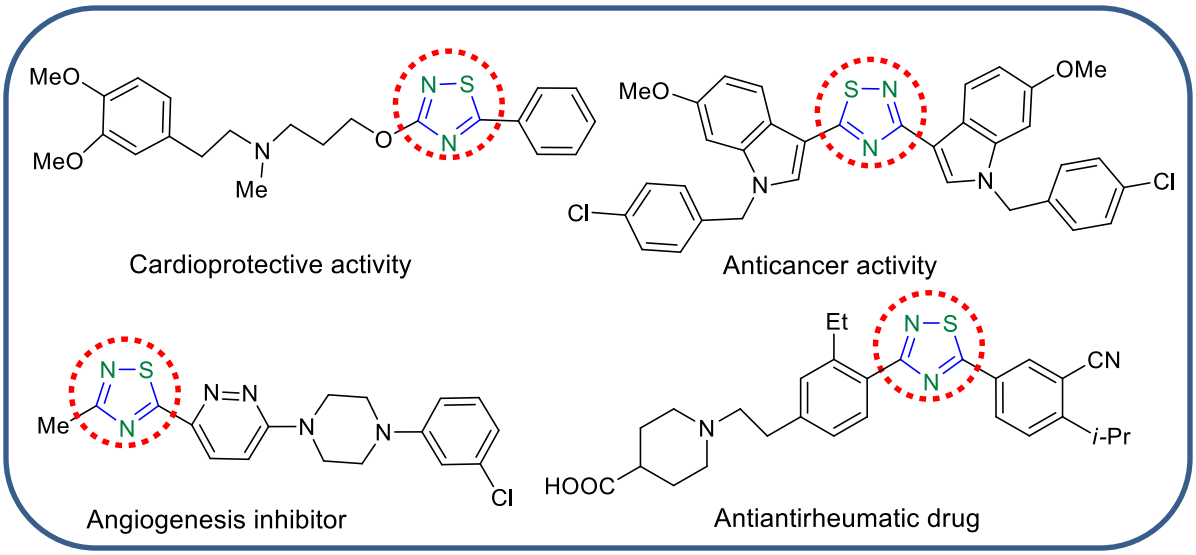
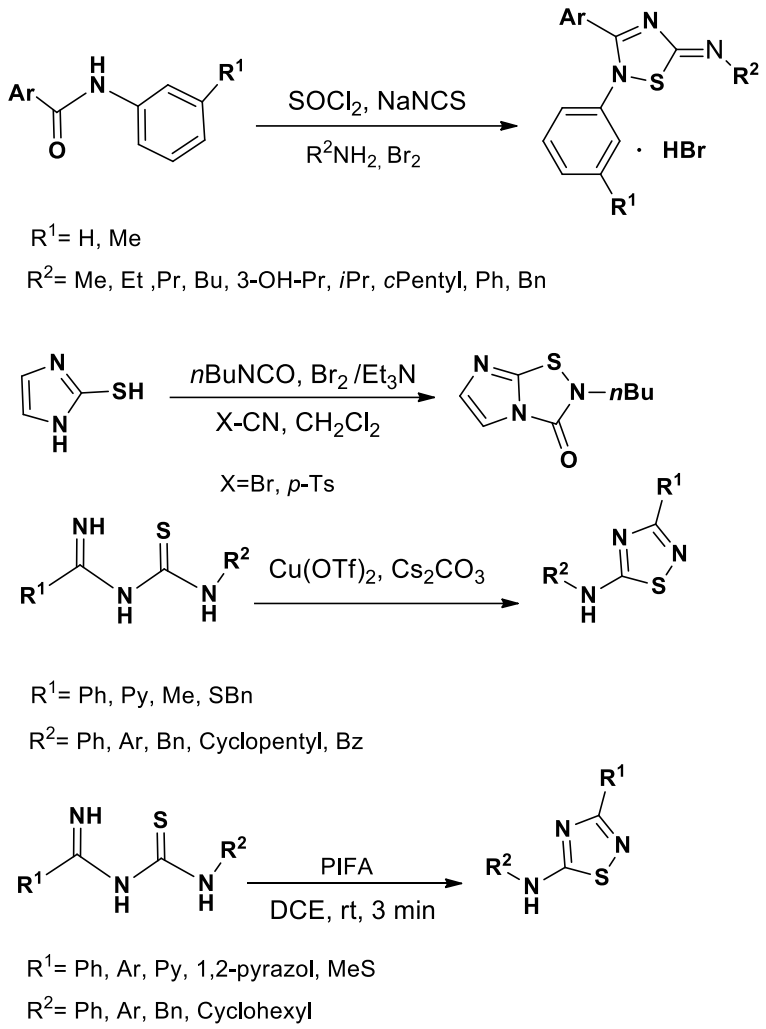


Figure 1.5: Some biological active compounds containing thiadiazole scaffold.

In this context, enormous efforts have been dedicated by chemists to establish many concise synthetic paths accessing thiadiazole framework. Synthesis of thiadiazole has been sub categorized in cyclization, dimerization and condensation reactions.

1.1.1 Synthesis of 1,2,4-Thiadiazoles by Cyclization

1,2,4-Thiadiazoles have been synthesized by cyclization of different starting materials in the presence of catalysts such as from benzamides in the presence of $SOCl_2$, NaNCS, RNH_2, Br_2 (Goblyos et al. 2005), from 2-mercaptoimidazole and *n*-butyl isocyanate via oxidative ring closure with Br_2 and triethylamine (Leung et al. 2005), from imidoylthioureas catalyzed by copper (Kim et al. 2014), imidoylthioureas mediated by phenyliodine(III) bis(trifluoroacetate) (PIFA) (Mariappan et al. 2016) (**Scheme 1.1**).

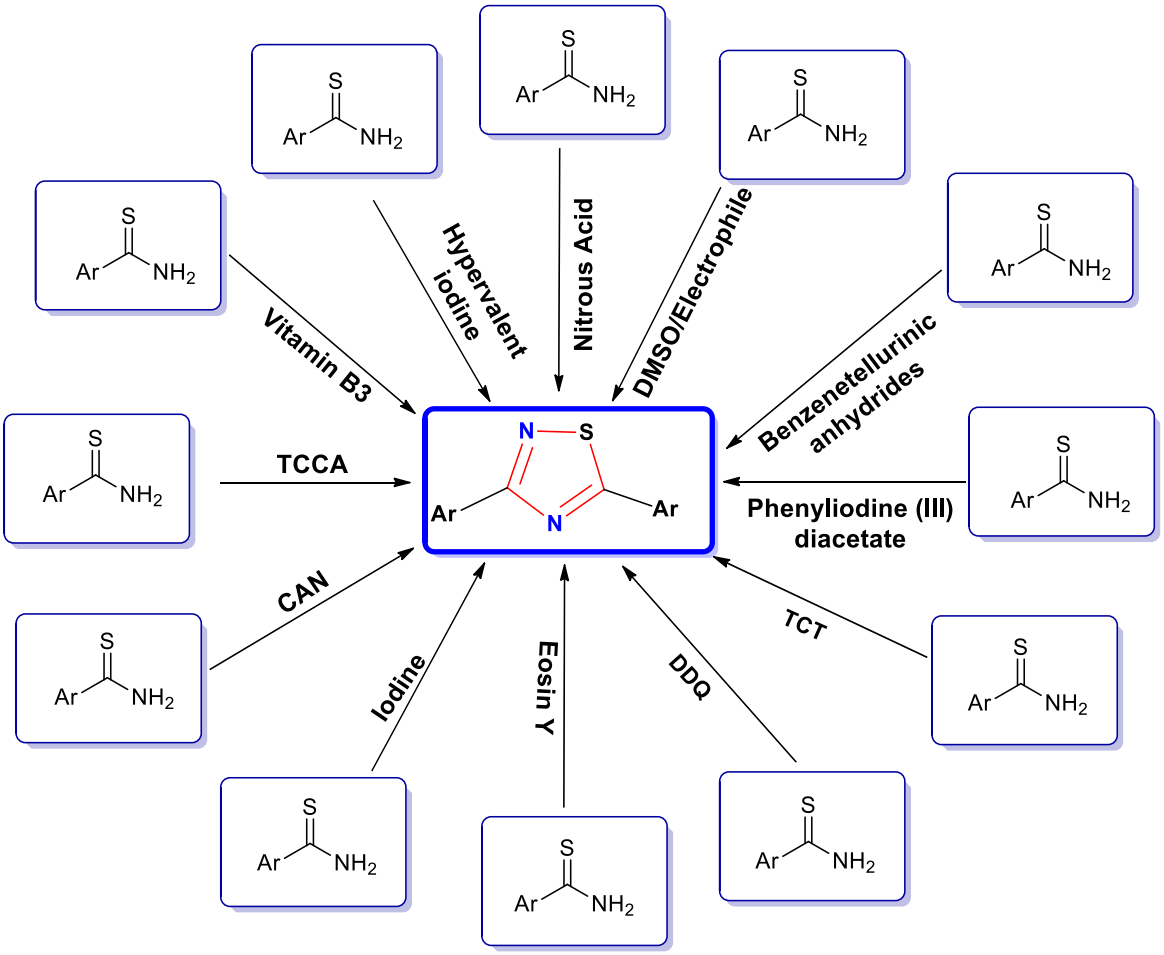


Scheme 1.1: Synthesis of 1,2,4-thiadiazoles by cyclization.

1.1.2 Synthesis of 1,2,4-Thiadiazoles by Dimerization of Thioamides

1,2,4-Thiadiazoles are also synthesized by dimerization of thioamides by using different oxidizing agents such as nitrous acid (Cronyn et al. 1952), DMSO/electrophile (Takikawa et al. 1985), benzene tellurinic mixed anhydrides

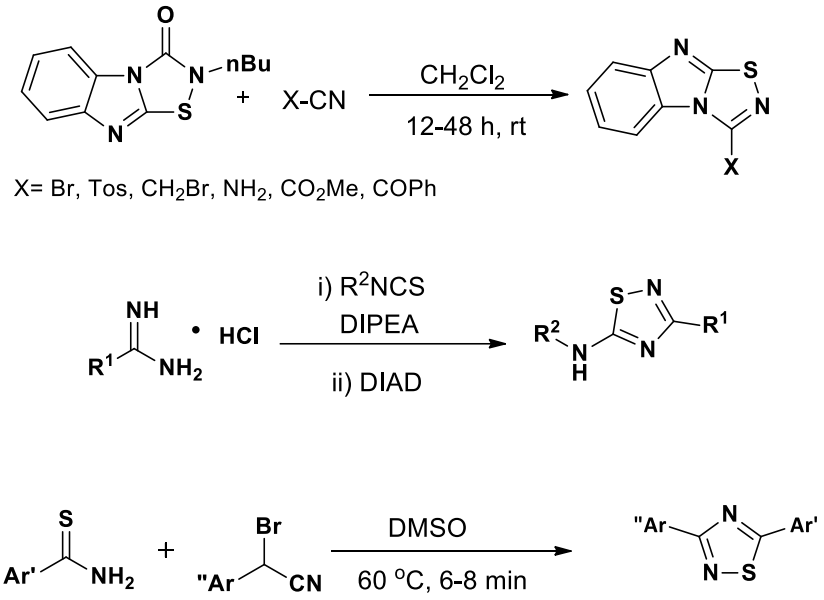
(Fukumoto et al. 1990), phenyliodine (III) diacetate (Yan et al. 2003), 2,4,6-trichloro-1,3,5-triazine (TCT) (Khosropour et al. 2010), 2,3-dichloro-5,6-dicyanobenzoquinone (Cheng et al. 2012), eosin Y in visible light (Srivastava et al. 2013), iodine (Zhao et al. 2014), ceric ammonium nitrate (Vanajatha et al. 2016), trichloroisocyanuric acid (TCCA) (Bose et al. 2017), organocatalytic approach by using vitamin B_3 (Putta et al. 2018), pseudo cyclic hypervalent iodine (Quarban et al. 2019) (**Scheme 1.2**).



Scheme 1.2: Synthesis of 1,2,4-thiadiazoles by dimerization of thiobenzamides.

1.1.3 Synthesis of 1,2,4-Thiadiazoles through Condensation Reactions

Another synthetic path to produce the useful 1,2,4-thiadiazole framework is through condensation or exchange reactions by using various precursors such as 1,2,4-thiadiazol-3(2*H*)one derivatives and substituted nitriles (e.g. cyanogen bromide or *p*-toluenesulfonyl cyanide) (Leung et al. 2005), from isothiocyanates, amidine hydrochlorides and *N*,*N*-diisopropylethylamine (DIPEA) followed by the addition of diisopropylazodicarboxylate (Wu et al. 2008), from benzothioamides with arylacetonitrile (Boeini et al. 2011) (**Scheme 1.3**).



Scheme 1.3: Synthesis of 1,2,4- thiadiazoles by condensation.

1.2 Coumarin

Coumarin compounds are important naturally occurring and synthetic oxygen containing heterocyclic compounds and it has benzopyrone framework. In 1820, Vogel isolated coumarin from tonka beans also known as coumarou in French (Gleye et al. 2003). This special benzopyrone structural moiety permits its derivatives to interact with a variety of enzymes and receptors in organisms through weak bond interactions and due to this property they are widely used in medicinal chemistry. Coumarins play an important role in numerous natural processes like plant physiology and also elaborate in the actions of plant growth hormones, growth regulators, control of respiration and photosynthesis (Vekariya et al. 2014). In the field of supramolecular chemistry which is important in pharmaceutical

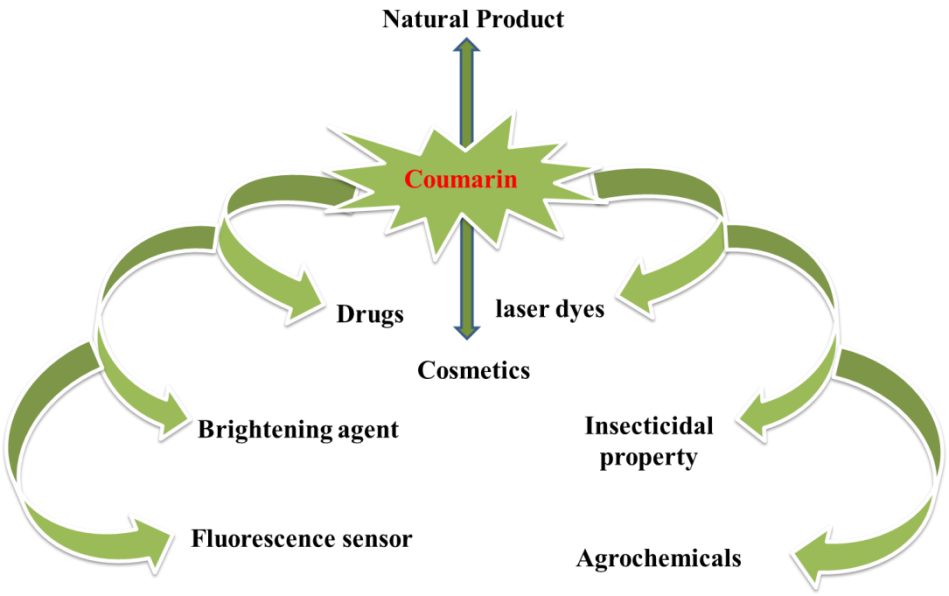


Figure 1.6: Applications of coumarin in different fields.

science, coumarin containing supramolecular medicine emerged as a new class of drugs in recent years. Coumarin has been investigated for a wide range of properties in different fields such as in fragrance & perfume, additive in food & cosmetics, laser dyes, agrochemicals, cosmetics, brightening agents, insecticides, fluorescence sensor and in drugs (Brahmachari et al. 2015) (**Figure 1.6**).

Figure 1.7 shows some coumarin containing biologically active natural products and drugs like Umbelliferone is used as sunscreen, Dicoumarol as anticoagulant drug, Seselin plays an important role as a metabolite, Calanolide A shows anti-tuberculosis activities, Chlorobiosin use as antibacterial and Lamellarin D shows cytotoxic activity against tumor cell lines.

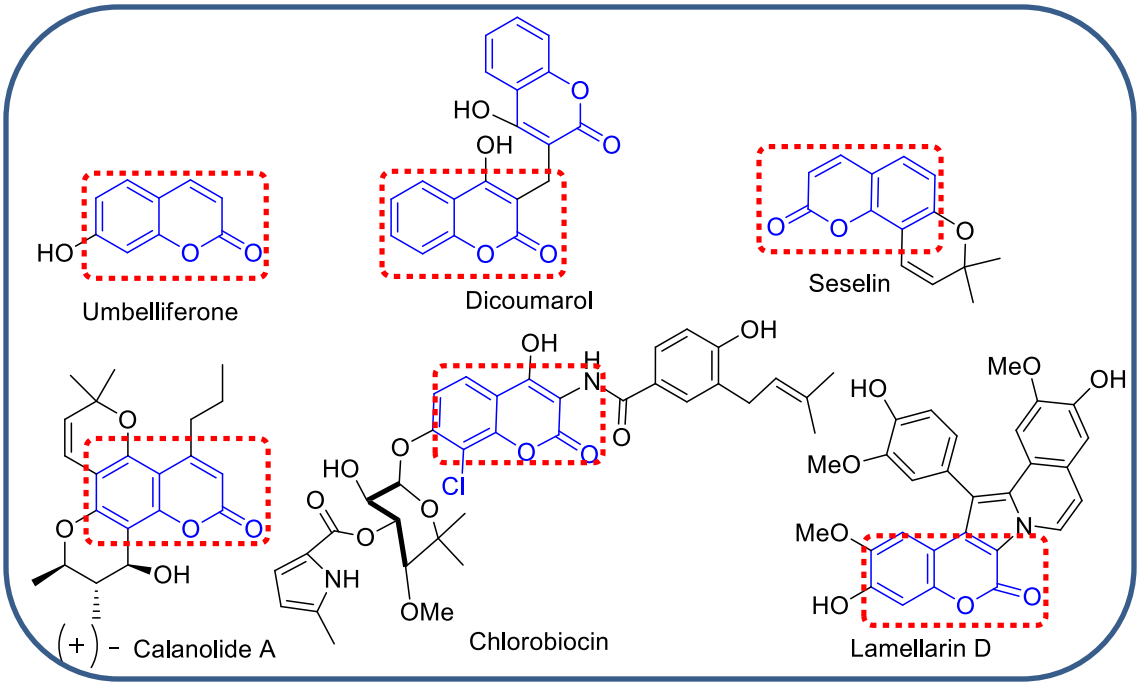
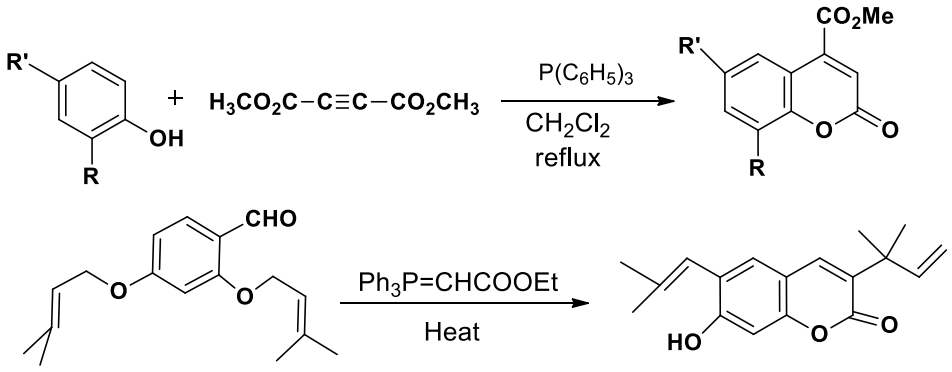


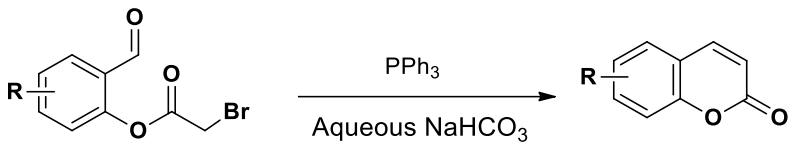
Figure 1.7: Coumarin containing biologically active compounds.

In view of the numerous applications in different fields, numerous natural coumarins are isolated from fungi, bacteria, plants and as well as obtained from chemical synthesis (Murray et al. 1991, Stefanachi et al. 2018). Synthesis of coumarin is always the subject of interest for the organic chemists. They have developed different methodologies for synthesis of this biologically important moiety. In literature, lots of methods have been described for the synthesis of coumarins by using different starting materials with different catalysts like Wittig reaction, Perkin reaction, Baylis-Hilmann reaction, Pechmann condensation and Knoevenagel condensation.

1.2.1 Wittig Reaction

Wittig reaction is tremendously used for C–C bond formation in the synthesis of natural products. Coumarins have been synthesized through Wittig reaction under different reaction conditions (Yavari et al. 1998, Patre et al. 2009, Belavagi et al. 2014) (**Scheme 1.4**).

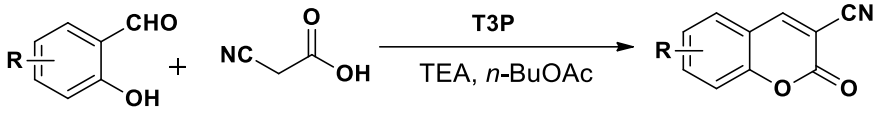




Scheme 1.4: Synthesis of coumarin by Wittig reaction.

1.2.2 Perkin Reaction

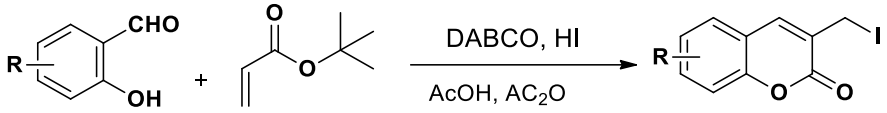
Perkin reaction is another method to synthesize coumarins. Augustine and co-workers described the synthesis of coumarins from salicylaldehyde and cyano acetic acid mediated by propylphosphonic anhydride (T3P) by Perkin reaction (Augustine et al. 2012) (**Scheme 1.5**).



Scheme 1.5: Synthesis of coumarin by Perkin reaction.

1.2.3 Baylis-Hilmann Reaction

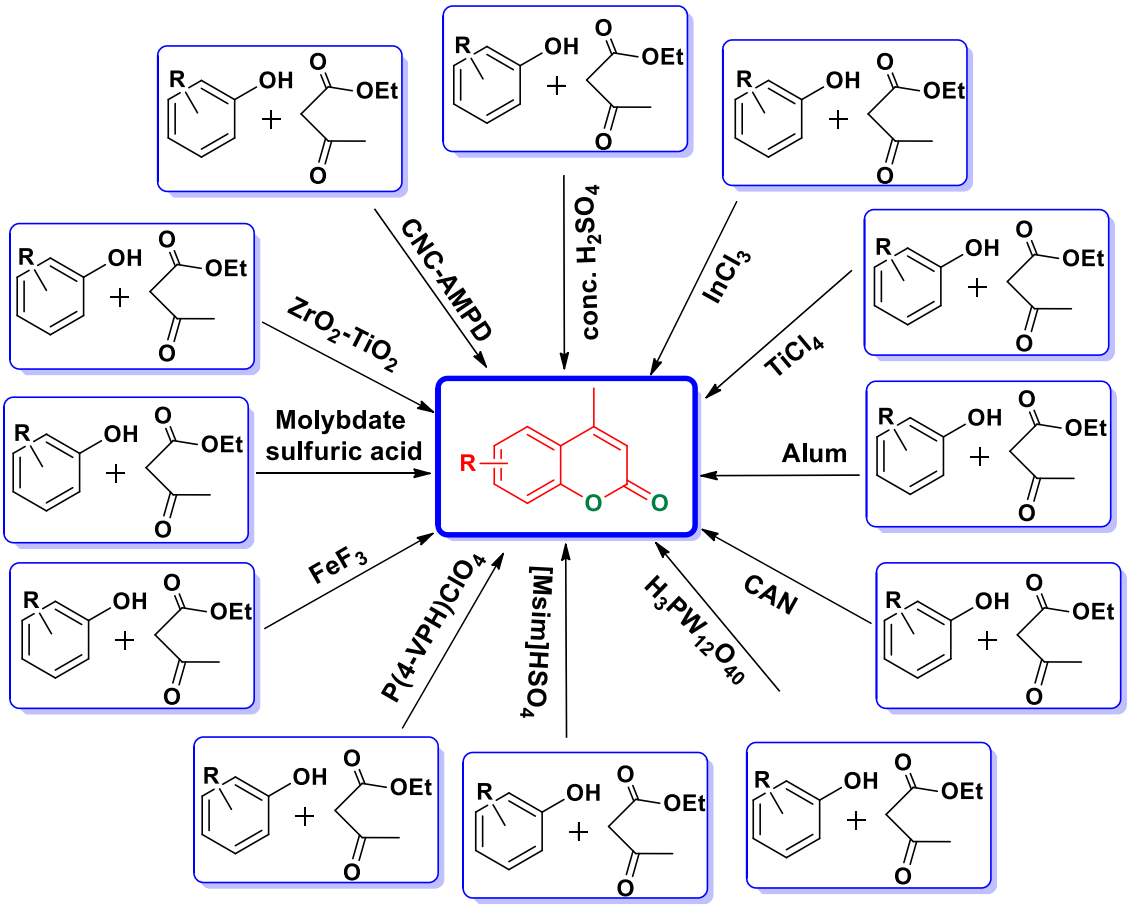
In Baylis-Hilmann methodology, coumarins are synthesized by the reaction of salicylaldehyde with *t*-butyl acrylate in the presence of DABCO, HI and acetic acid (Kaye et al. 2003) (**Scheme 1.6**).



Scheme 1.6: Synthesis of coumarin by Baylis-Hilmann reaction.

1.2.4 Pechmann Condensation

Traditionally coumarins have been synthesized over a decade by Pechmann reaction. In this protocol coumarins are synthesized by the reaction of phenol with β– keto esters or maleic acid in the presence of different catalysts such as conc. H_2SO_4 (Pechmann et al. 1884),

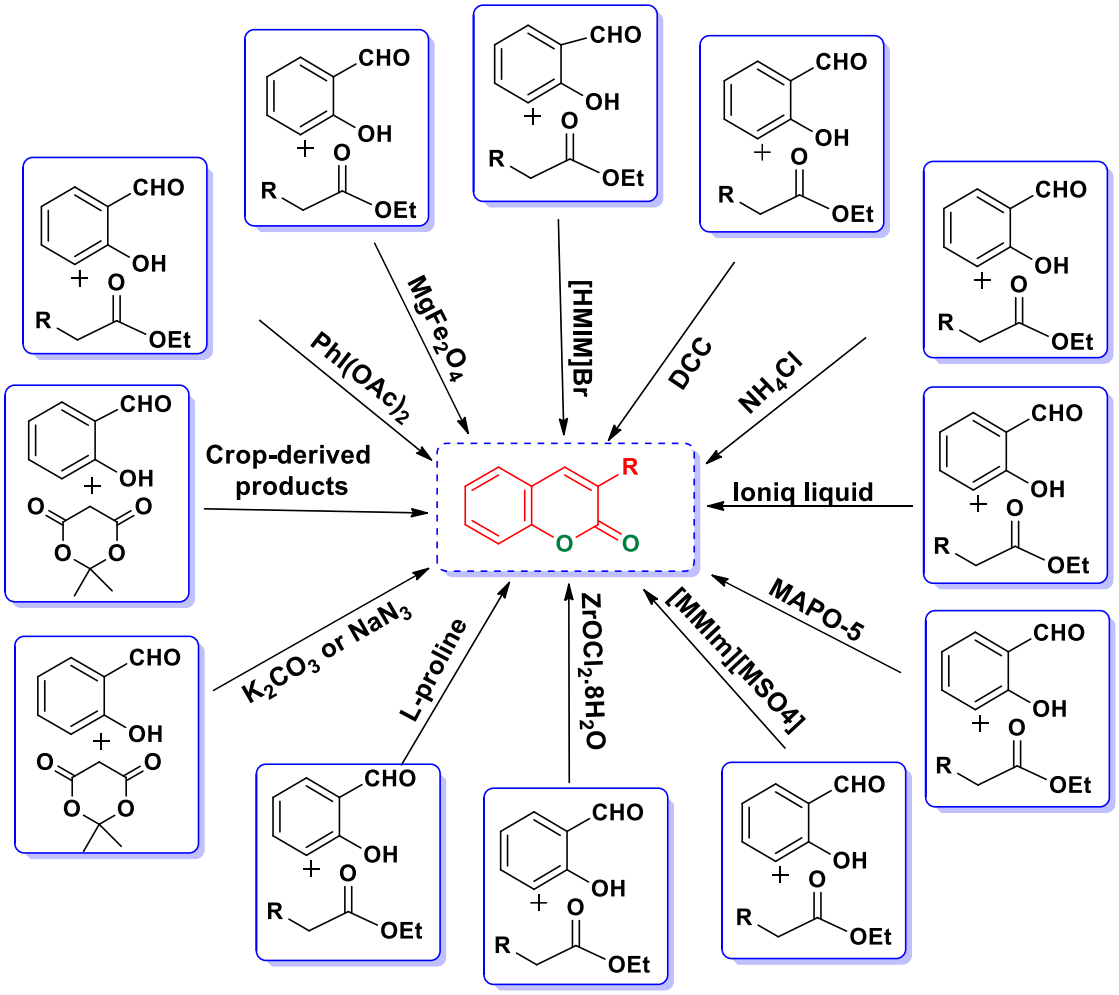


Scheme 1.7: Synthesis of coumarin by Pechmann reaction.

indium (III) chloride (Bose et al. 2002), $TiCl_4$ (Valizadeh et al. 2005), Alum (Dabiri et al. 2007), ceric ammonium nitrate (CAN) (Reddy et al. 2008), phosphotungstic acid (Keri et al. 2009), acidic ionic liquid (Khaligh et al. 2012), poly(4-vinylpyridinium)perchlorate (Khaligh et al. 2013), FeF_3 (Vahabi et al. 2014), molybdate sulfuric acid (Moradi et al. 2015), zirconia-based heterogeneous (Khan et al. 2016), cellulose nanocrystal supported palladium nanoparticles (Mirosanloo et al. 2018) (**Scheme 1.7**).

1.2.5 Knoevenagel Condensation

Knoevenagel condensation is most common process for the synthesis of coumarins. In this methodology coumarin have been synthesized by the reaction of *o*-hydroxybenzaldehydes *i.e.* salicylaldehyde derivatives and active methylene compounds in the presence of different catalyst such as DCC (Bonsignore et al. 1995), ammonium chloride (Valizadeh et al. 2001), ionic liquid (Ranu et al. 2006), Lewis acid metal ion-exchanged MAPO-5 molecular sieves (Gopalakrishnan et al. 2008), [MMIm][MSO4] containing proline (Verdia et al. 2011), $ZrOCl_2.8H_2O$ (Tasqeeruddin et al. 2013), L-proline (Srikrishna et al. 2014), K_2CO_3 or NaN_3 (Brahmachari et al. 2015), crop-derived products (Fiorito et al. 2016), $PhI(OAc)_2$ (Khan et al. 2017), $MgFe_2O_4$ nanocatalyst (Ghomi et al. 2018), [HMIM]Br, piperidene and AcOH (Dinparast et al. 2019) (**Scheme 1.8**).



Scheme 1.8: Synthesis of coumarin by Knoevenagel condensation.

1.3 Imidazo[1,2-a]pyridine

The imidazo[1,2-a]pyridine ring system was described by Chichibabin in 1925. Imidazo[1,2-a]pyridines are an important class of nitrogen ring junction heterocyclic compounds, in this imidazole moiety is fused with the pyridine ring.

Imidazo[1,2-a]pyridine is one of the imperative fused bicyclic 5–6 heterocycles with the applications ranging from medicinal and combinatorial chemistry to material chemistry. It is also known as a 'drug prejudice' framework due to its broad applications in pharmaceutical chemistry. Furthermore, this scaffold is beneficial in material science due to its unique structural features. These derivatives show a wide range of biological activities like antibacterial, antitumor, antifungal, antiviral, antipyretic, analgesic activities (Bagdi et al. 2015) **(Figure 1.8)**.

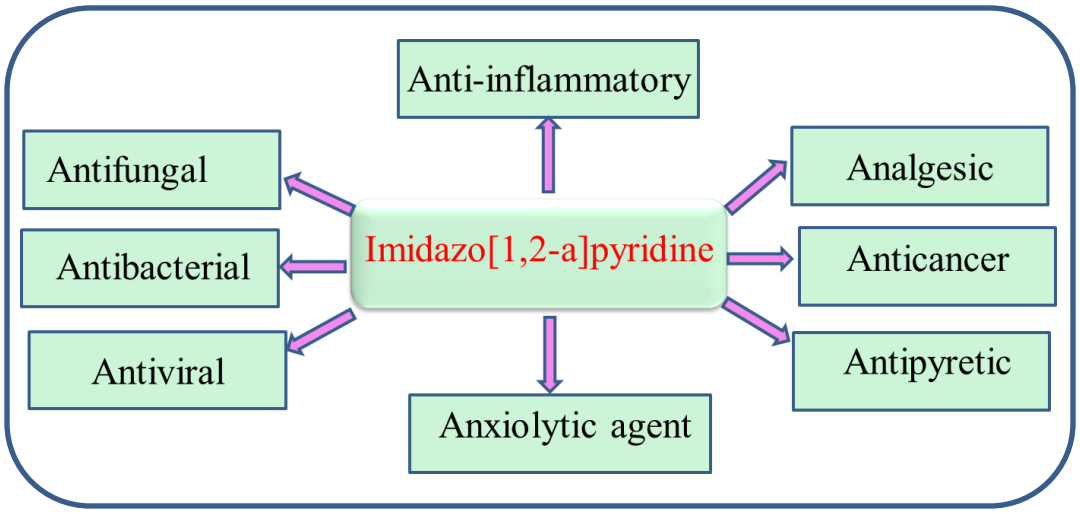


Figure 1.8: Biological activities of imidazo[1,2-a]pyridines.

Imidazo[1,2-a]pyridine moiety is present in many drugs and are used against various diseases **(Figure 1.9)**. Zolpidem was the first drug launched in the market as a hypnotic, Zolimidin as antiulcer, Saripidem is commercially available drug works as an anxiolytic

agent, Miroprofen an analgesic, GSK812397 as HIV infection and P13 K alpha inhibitor as an anti-cancer agent.

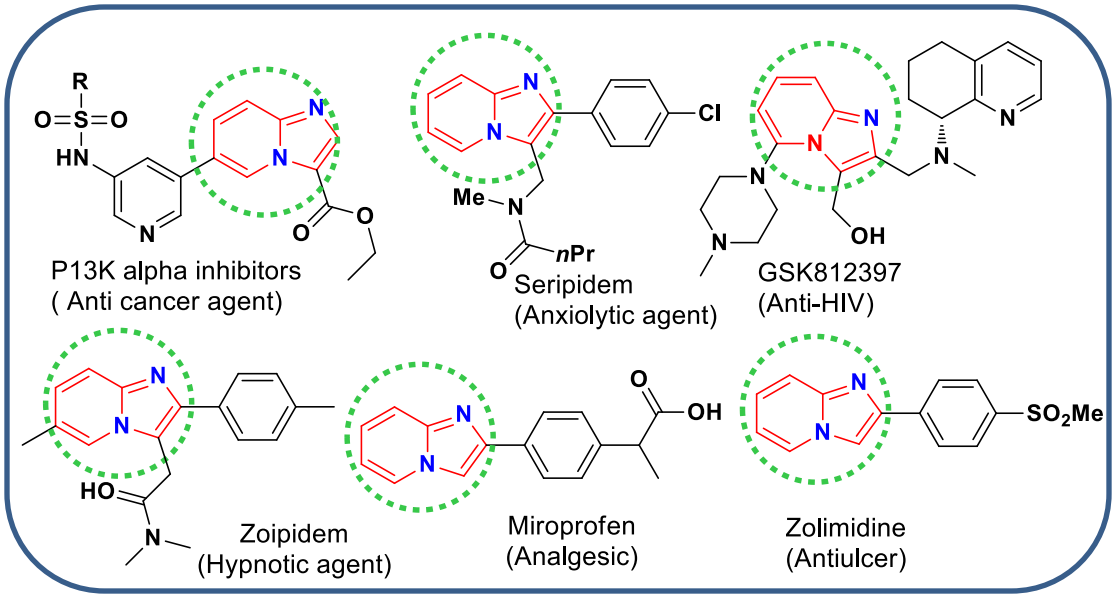


Figure 1.9: Imidazo[1,2-a]pyridine scaffold containing drugs.

Excited-state intramolecular proton transfer (ESIPT) property is observed in 2-substituted hydroxylphenyl imidazo[1,2-a]pyridines (**A**) in the majority of solvents which is responsible for strong, solid-state emission (Douhal et al. 1997). Imidazo[1,2-a]pyridines have established wide application as fluorescence sensors, laser dyes and also in molecular switches. Imidazo[1,2-a]pyridines (**B**) scaffold containing fluorescent dopamine D3 receptor ligands used as important probes for receptor visualization (Leopoldo et al. 2014).

In addition to this, metal complexes of imidazo[1,2-a]pyridine (**C**) are used in the area of electronic devices. Furthermore, 2-carbonyl-3-(pyridylamino)imidazo[1,2-a]pyridine (**D**) has been recognized as a luminous probe for mercury ion (Roopan et al. 2016) (**Figure 1.10**).

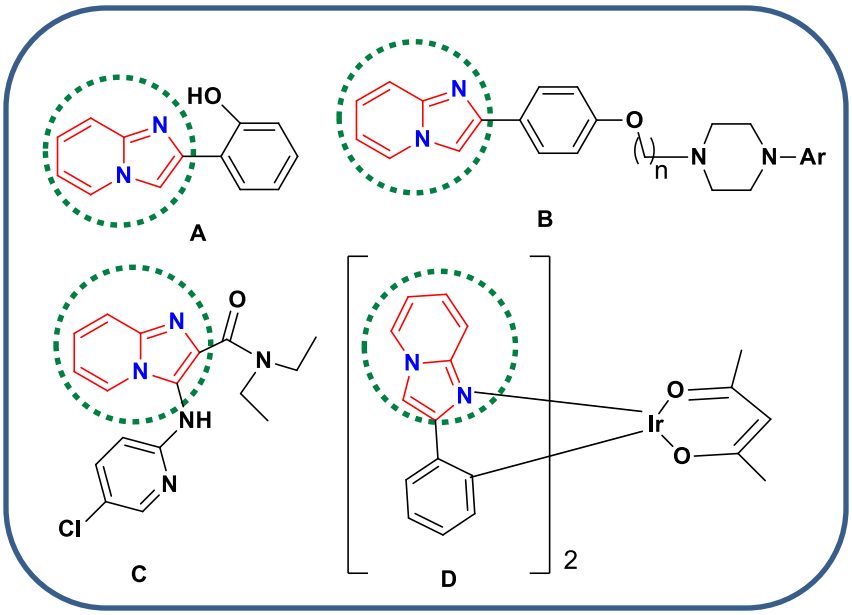


Figure 1.10: Material science application of imidazo[1,2-a]pyridine.

Due to its wide applicability in different branches of chemistry, it is desirable to synthesize this moiety from the readily available chemicals. Efforts have been focused to improve diverse synthetic approaches for the synthesis of imidazo[1,2-a]pyridines and numerous methods have been established. There are lots of methods described in literature for the synthesis of imidazo[1,2-a]pyridines and these methods can be categorized into multicomponent, tandem reaction, aminooxygenation, hydroamination, oxidative coupling

and condensation reaction. Different synthetic strategies of imidazo[1,2-a]pyridines by using various type of starting material is shown in **Figure 1.11**.

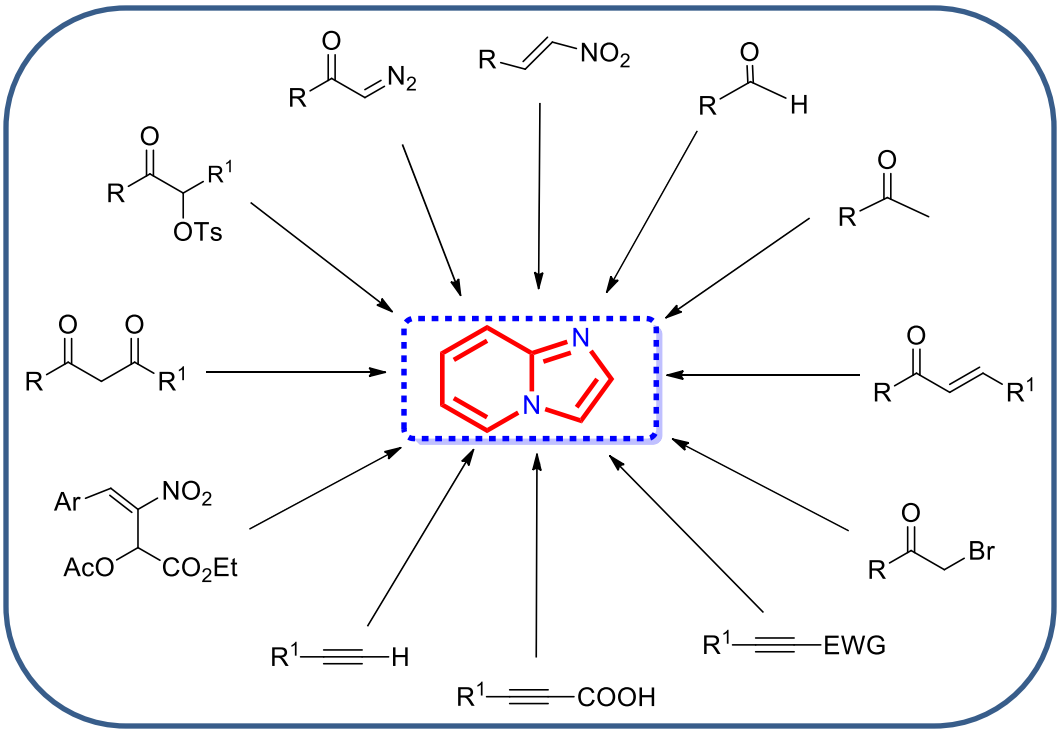
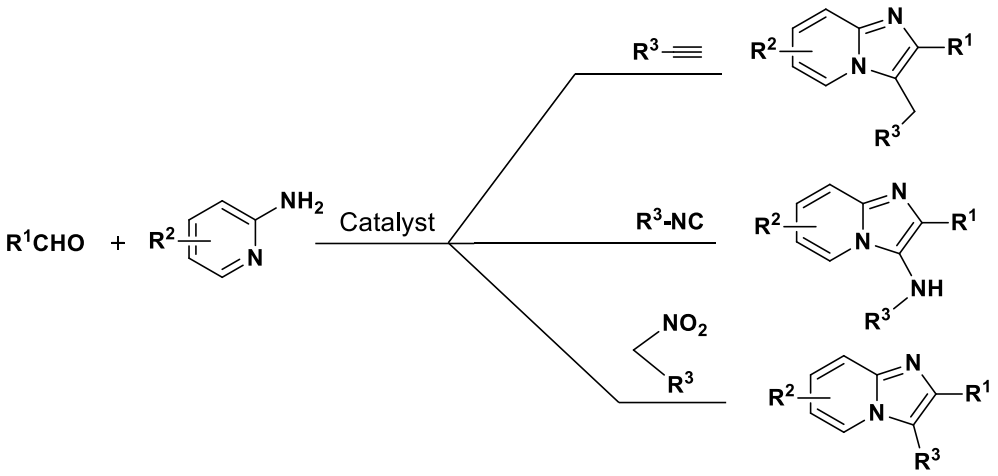


Figure 1.11: Synthesis of imidazo[1,2-a]pyridines by various starting material.

1.3.1 Multicomponent Approach

Imidazo[1,2-a]pyridines have been synthesized by the multicomponent approach through the reaction of 2-aminopyridine, aldehyde and cyanide or isocynide in the presence of various catalysts: scandium triflate (Schwerkoske et al. 2005), copper-catalyzed (Chernyak et al. 2010), K_2CO_3 (Adib et al. 2011), bromodimethylsulfonium bromide

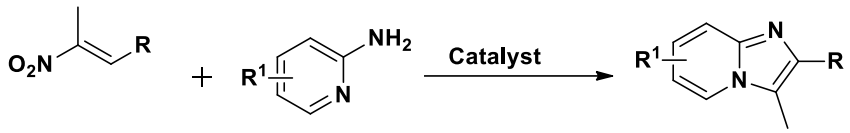
(BDMS) (Khan et al. 2012). Imidazo[1,2-a]pyridines were also achieved by the reaction of 2-aminopyridine, aldehyde and terminal alkyne catalyzed by $Cu(OTf)_3$ (Chernyak et al. 2010), $CuSO_4$ (Liu et al. 2010), nano-Fe_3O_4–$KHSO_4 \cdot SiO_2$ (Guntreddi et al. 2012) and from the reaction of 2-aminopyridine, aldehyde and nitro methane (Yan et al. 2014) (**Scheme 1.9)**.



Scheme 1.9: Synthesis of imidazo[1,2-a]pyridines by multicomponent approach.

1.3.2 Tandem Reaction

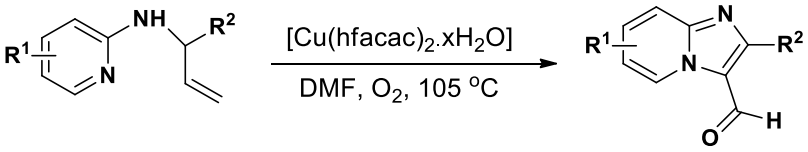
Imidazo[1,2-a]pyridines were synthesized by Tandem reaction of 2-aminopyridine with nitroalkenes in the presence of different catalyst such as iron (II) (Yan et al. 2012), iron (III) (Santra et al. 2013) (**Scheme 1.10)**.



Scheme 1.10: Synthesis of imidazo[1,2-a]pyridines by Tandem reaction.

1.3.3 Aminooxygenation

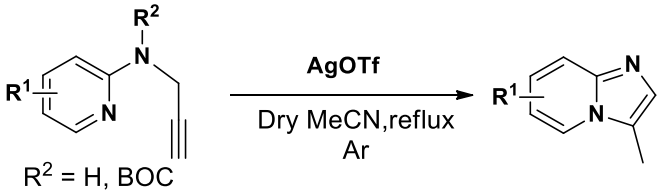
Imidazo[1,2-a]pyridines were also synthesized by copper-catalyzed intramolecular dehydrogenative aminooxygenation (Wang et al. 2011) (**Scheme 1.11)**.



Scheme 1.11: Synthesis of imidazo[1,2-a]pyridines by Aminooxygenation.

1.3.4 Hydroamination

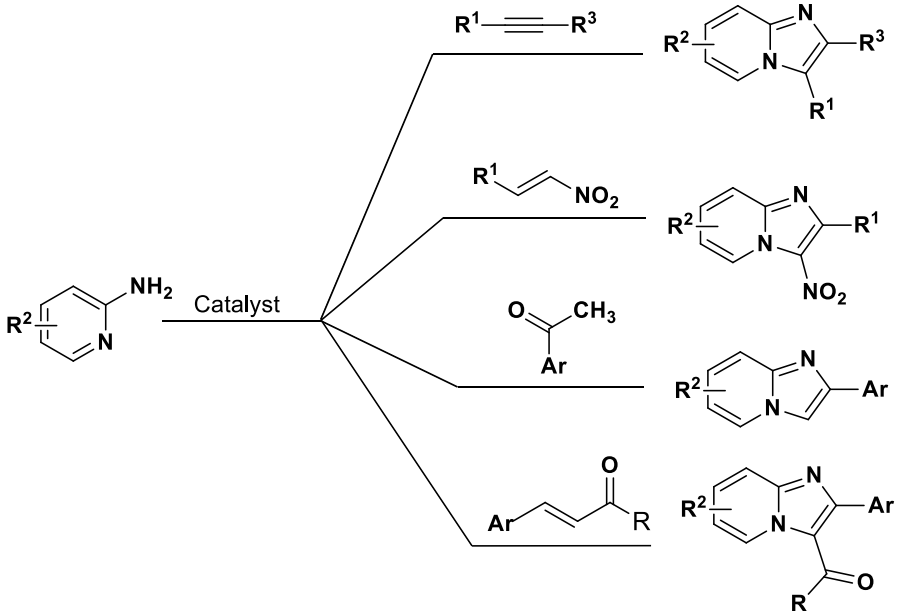
Chioua developed a method for the synthesis of 3-methylimidazo[1,2-a]pyridines through Ag-catalyzed cyclization of the N-(prop-2-yn-1-yl)pyridine-2-amines (Chioua et al. 2012) **(Scheme 1.12)**.



Scheme 1.12: Synthesis of imidazo[1,2-a]pyridines by Hydroamination.

1.3.5 Oxidative Coupling

Imidazo[1,2-a]pyridines were also synthesized by oxidative coupling of 2-aminopyridine with various substrates like alkynes (Zeng et al. 2012, He et al. 2012, Gao et al. 2013), nitroolefines (Yan et al. 2012), aryl methyl ketones (Chandra et al. 3013, Pericherla et al. 2013, Meng et al 2018), chalcones (Monir et al. 2014) etc. using different metal catalyst **(Scheme 1.13)**.

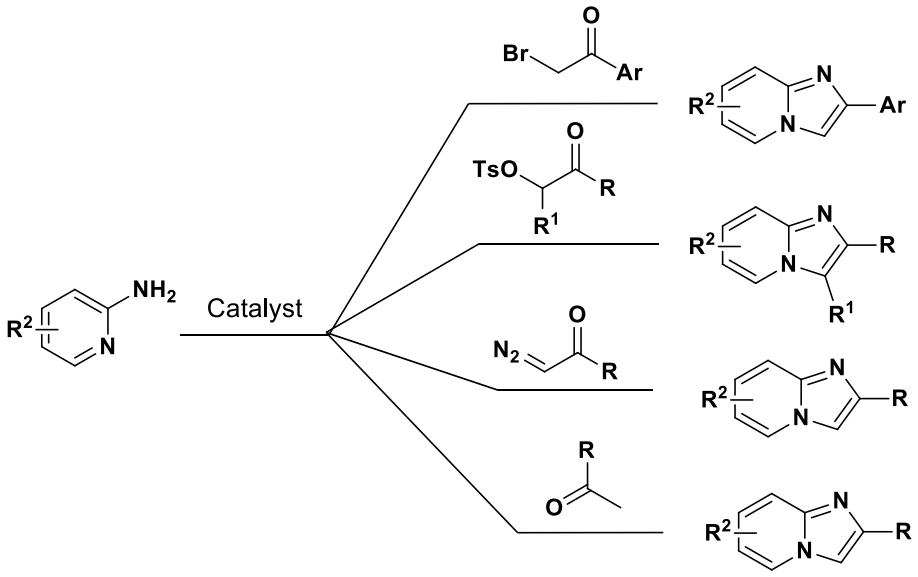


Scheme 1.13: Synthesis of imidazo[1,2-a]pyridines by oxidative coupling.

1.3.6 Condensation Reaction

Imidazo[1,2-a]pyridines were synthesized by the condensation of α-haloketones and 2-aminopyridines in the presence of different catalysts like neutral Al_2O_3 (Ponnala et al. 2005), $NaHCO_3$ (Hiebe et al. 2014), MgO (Patil et al. 2016), $NaHCO_3$ in eucalyptol

(Campos et al. 2019) and also in catalyst free condition (Burkholder et al. 2001, Zhu et al. 2009, Kong et al. 2016). Imidazo[1,2-a]pyridines were also synthesized by the reaction of 2-aminopyridine with different substrate such as α-tosyloxyketones catalyzed by $BPyBF_4$, Na_2CO_3 (Xie et al. 2002), α-diazoketones catalyzed by Cu (Yadav et al. 2007), methyl aryl ketones in the presence of different catalysts such as iodobenzene (Chang et al. 2010), I_2/NaOH (Stasyuk et al. 2012), graphene oxide (GO)/NaI (Kundu et al. 2015), iodine-ammonium acetate (Kour et al. 2016), NBS (Bhagat et al. 2017), I_2 in cyclohexane (Ghosh et al. 2018), HI (Feng et al. 2019), $FeCl_3/I_2$ (Ujwaldev et al. 2019) etc. (**Scheme 1.14**).



Scheme 1.14: Synthesis of imidazo[1,2-a]pyridines by condensation reaction.

1.4 4*H*-pyran

4*H*-pyran is oxygen containing heterocyclic compound which displays significant biological and pharmacological activities and also constitute a structural unit of a series of natural products. A number of 2-amino-4*H*-pyrans played imperative role in the discipline of drugs, photoactive materials, agrochemicals, cosmetics and pigment industries shown in Figure 1.12 (Fotouhi et al. 2007).

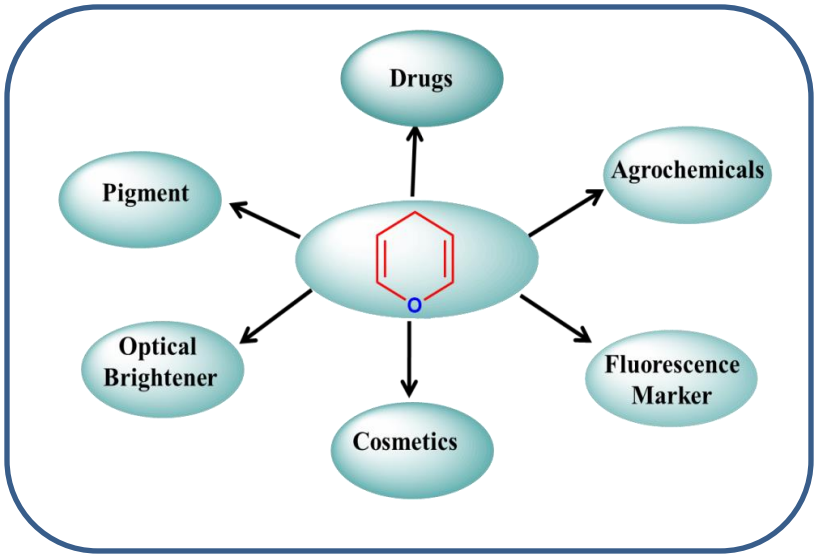


Figure 1.12: Applications of 4*H* -pyrans in different fields.

4*H*-pyrans are ubiquitous structural moiety in bioactive molecules due to their good biocompatibility. Mainly cyano functionality in 2-amino-4*H*-pyrans derivatives has an impending utility in the treatment of various diseases like cancer, rheumatoid, psoriasis (Azath et al. 2012) and also in the treatment of various neurodegenerative disease such as

alzheimer's disease, AIDS-associated dementia and down syndrome also for the treatment of schizophrenia and huntington's diseases (Thanaraj et al. 2019) (**Figure 1.13**).

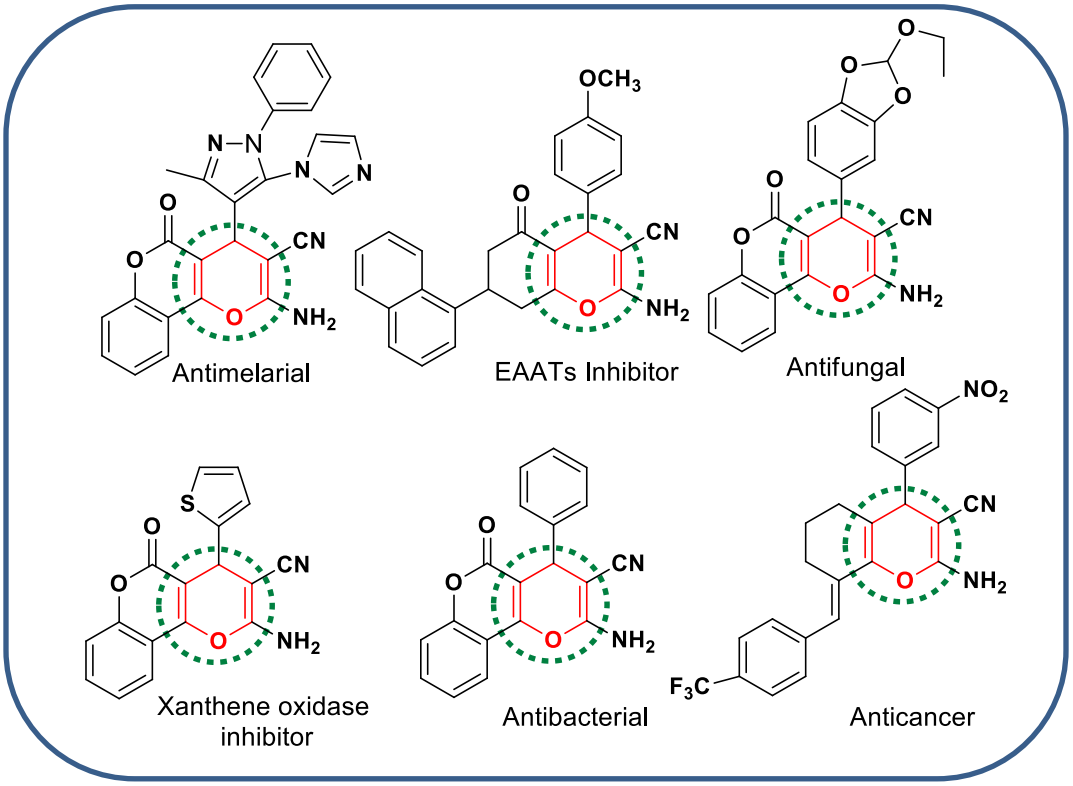
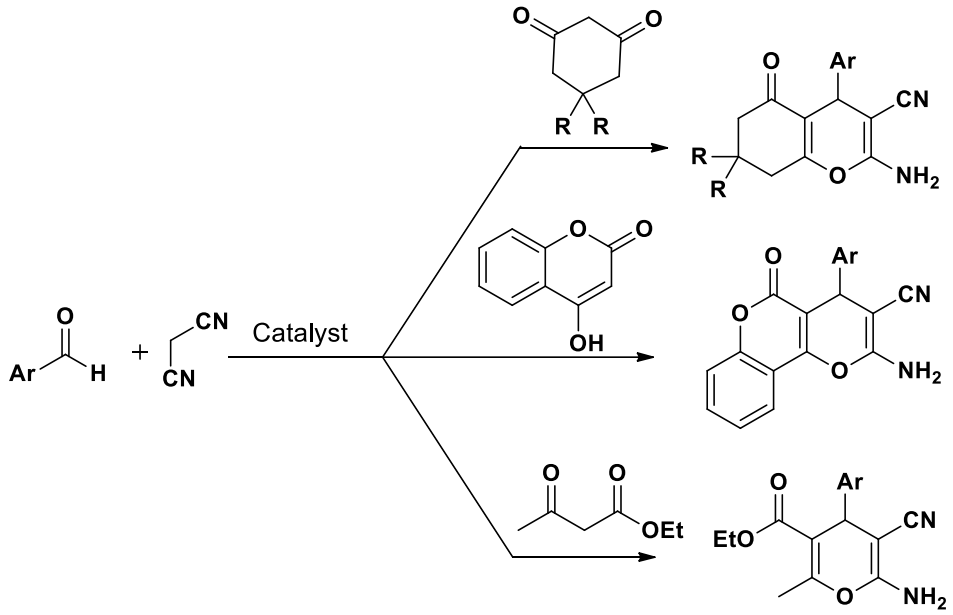


Figure 1.13: Drugs containing 4*H*-pyran moiety.

Considering the importance of these compounds, many methods have been reported for the synthesis of tetrahydro-4*H*-benzo[b]pyran derivatives. Out of the several approaches for the synthesis of 2-amino-4*H*-pyran, multicomponent reaction (MCR) is the most useful and preferred method for the construction of these heterocyclic compounds. The best protocol to synthesize 4*H*-pyrans is the Knoevenagel condensation-Michael cyclization

reaction by using aldehyde, carbonitrile and 1,3-dicarbonyl compound by one-pot multicomponent reaction.

Synthesis of 4*H*-pyran can be achieved by the reaction of benzaldehyde, malononitrile with different 1,3-dicarbonyl compounds in the presence of different catalyst such as triethyl amine (Elnagdi et al. 1989), ammonium acetate (Tu et al. 2002), KF-Al_2O_3 (Wang et al. 2003), S-proline (Balalaie et al. 2006), electrogenated base (Fotouhi et al. 2007), tetrabutylammonium bromide (Gurumurthi et al. 2009), per-6-amino-β-cyclodextrin (Azath et al. 2012), potassium tertiary butoxide (Rao et al. 2018), $TiO_2/H_{14}[NaP_5W_{30}O_{110}]$ (Azarifar et al. 2014), AuNPs@RGO-SH (Naeimi et al. 2017), $NiFe_2O_4$ nanoparticle-supported (Maleki et al. 2016), [pyridine-SO_3H]Cl (Sonyanaik et al. 2018),



Scheme 1.15: Common acid base catalyzed synthesis of 4*H*-pyran.

CuO-CNs (Thanaraj 2019), Cu@MNPs (Wanzheng et al. 2019). 4-*H* pyran can also be synthesized under catalyst free condition (Bandgar et al. 2007, Ponpandian et al. 2014, Elinson et al. 2015, Bakherad et al. 2019) (**Scheme 1.15**).

1.5 Objectives of Thesis Work

From this brief introduction, it is clear that heterocyclic compounds have found wide applications in various fields including organic synthesis, biochemistry, medicinal chemistry, material sciences and agriculture etc. Thus, our objective is to develop some efficient and greener methodology for synthesis of some biologically active heterocyclic compounds via conventional as well as non-conventional methods such as ultrasound, solar energy and grinding techniques which may make an encouraging contribution to the development of the green and clean chemistry.

The main focus of the current thesis work is aimed-

1. To investigate oxidative dimerization of primary thiobenzamides and selenamides into 1,2,4-thiadiazole and 1,2,4-selenadiazole by different methods under metal and catalyst-free condition using green oxidants TBN and Chloranil.

2. To develop a practical method for the synthesis of 3-functionalized coumarins by oxidative coupling of *o*-cresols and active methylene compounds under metal and catalyst-free condition in the presence of *tert*-butyl hydrogen peroxide (TBHP).

3. To explore a novel, facile, efficient and scalable route for the synthesis of imidazo[1,2-a]pyridines in solvent free conditions under grinding at room temperature using KI/TBHP.

4. To demonstrate a solar energy mediated environmentally benign, simple and efficient method for one pot multicomponent synthesis of tetrahydrobenzo[b]pyran using L-Ascorbic acid as a green biodegradable catalyst.

1.6 References

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CHAPTER 2

Synthesis of 1,2,4-Thiadiazoles and 1,2,4-Selenodiazoles by the Dimerization of Primary Thioamides and Selenoamides

Chapter 2

Synthesis of 1,2,4-Thiadiazoles and 1,2,4-Selenodiazoles by the Dimerization of Primary Thioamides and Selenoamides

2.1 Introduction

Sulfur and selenium based organic molecules received significant interest in different fields in the last few decades (Mugesh et al. 2001). 1,2,4-Thiadiazole is an important heterocyclic scaffold found in many drugs, bioactive molecules and natural products (Mayhoub et al. 2012, Li et al. 2013, Romagnoli et al. 2007, shen et al. 2007) (**Figure 2.1**). 1,2,4-Thiadiazoles are privileged building blocks in the synthesis of many bioactive molecules for the treatment of human leukemia (Romagnoli et al. 2007), as cathepsin B inhibitors (Leung et al. 2003), allosteric modulators (Van et al. 2004), factor XIIIa inhibitors (Leung et al. 2005), non-ATP competitive glycogen synthase kinase inhibitors (Martinez et al. 2002), dual 5-lipoxygenase and cyclooxygenase inhibitors (Unangst et al. 1992). In addition, thiadiazole scaffold containing molecules act as G-protein coupled receptors (Ana et al. 2000, Lanzafame et al. 2004, Kohara et al. 1996, Martinez et al. 2000), pesticides and fungicides (e.g. Etridiazole, **Figure 2.1**) (Leung et al. 2005). Therefore, over the decades interest has been maintained in the synthesis of organic compounds having thiadiazoles and selenodiazoles moiety for different fields (Dotsenko et al. 2013, Huang et al. 2003, shen et al. 2007, Pham et al. 2013).

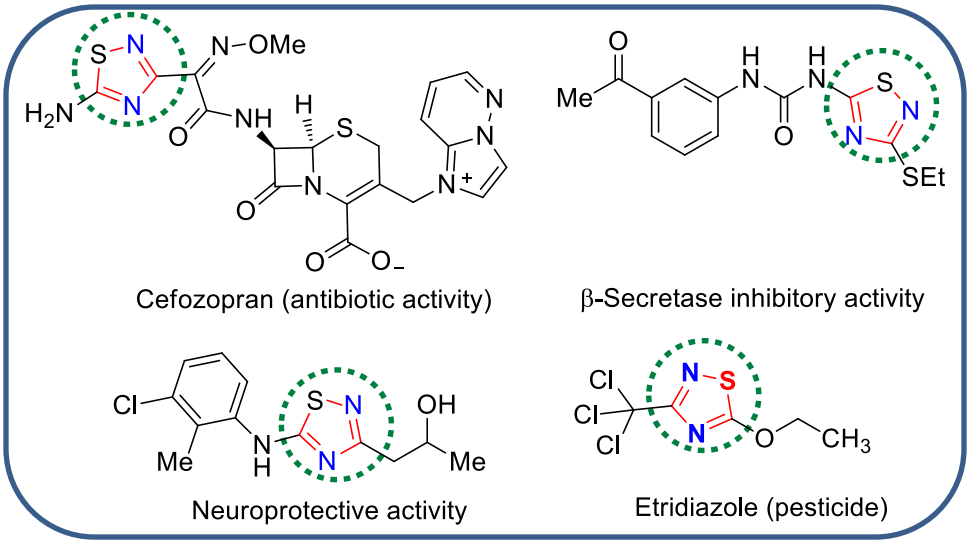
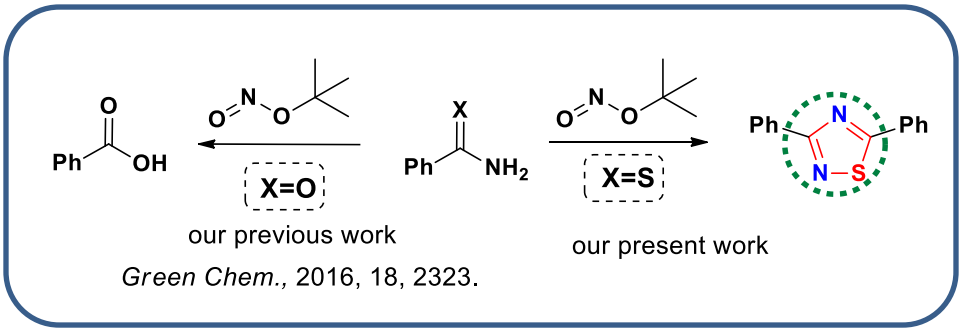


Figure 2.1: Biologically active thiadiazoles.

The simplest approach for the synthesis of 1,2,4-thiadiazoles involves the oxidative dimerization of primary thioamides. This transformation has been achieved using various metal and metal free oxidizing reagents such as ceric ammonium nitrate (CAN) (Vanajatha et al. 2016), 2-iodoxybenzoic acid (IBX) (Patil et al. 2009), bis-acetoxy iodobenzene (BAIB) (Cheng et al. 2002, Mamaeva et al. 2003), *N*-bromosuccinimide (NBS) (Xu et al. 2010), oxone (Yoshimura et al. 2014), nitrous acid (Cronyn et al. 1952), phosphovanadomolybdic acids (Yajima et al. 2014), pentyl pyrediniumtribromide (Zali et al. 2012) etc. However, many of these methods suffer from the use of excess reagents which produces large amounts of by-products, harsh reaction conditions, longer reaction time, tedious workup procedures etc. Therefore, finding a simple and efficient reagent for the dimerization of primary thioamides is of great interest.



Scheme 2.1: Reaction of *tert*-butyl nitrite with benzamide and thiobenzamide.

tert-Butyl nitrite (TBN) is an important synthetic reagent widely used for nitration reactions (Yan et al. 2013, Yan et al. 2014). For example, TBN has been explored for the nitration of phenols, azoarenes, arylboronic acids, acetanilides, sulfanilides etc. under mild reaction conditions (Barral et al. 2007, Marinescu et al. 2003, Zhang et al. 2011, Hao et al. 2015, Koley et al. 2009, Fisher et al. 2016, Majhi et al. 2014, Ji et al. 2015). In addition, TBN has also been explored as a radical initiator for the aerobic cleavage of benzylic carbon–carbon double bonds and triple bonds (Miao et al. 2011, Dutta et al. 2016). TBN is a green, inexpensive and commercially available reagent which can be easily handled and stored.

Our research group is mainly focused on developing simple, efficient and eco-friendly methods for organic transformations (Gupta et al. 2017, Gupta et al. 2017, Chaudhary et al. 2016, Chaudhary et al. 2016, Gupta et al. 2016). In pursuit of this, we have recently reported *N*-nitrosation of secondary amines using *tert*-butyl nitrite under solvent free conditions (Chaudhary et al. 2016). In the same report, we have also disclosed that primary

benzamides undergo hydrolysis to corresponding benzoic acids with *tert*-butyl nitrite in acetic acid (**Scheme 2.1**). In continuation of our previous work, here we would like to disclose an interesting outcome of the reaction between *tert*-butyl nitrite and primary thioamides. In fact, while attempting hydrolysis of thiobenzamide with *tert*-butyl nitrite in acetic acid, a significant amount of dimerized product was observed (**Scheme 2.1**) instead of hydrolysis. This observation spurred us to optimize the reaction condition for obtaining the dimerized product exclusively (**Table 2.1**).

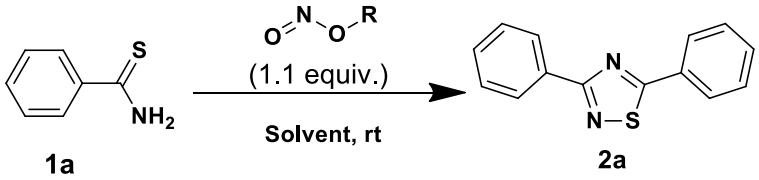
2.2 Results and Discussion

At the outset, the optimization of the dimerization reaction was investigated with thiobenzamide (**1a)** using 1.1 equiv. of TBN in various solvents at room temperature. In acetic acid, the dimerized product **2a** was obtained in 69% yield (**Table 2.1, entry 1**). Similarly, other polar protic solvents such as methanol, ethanol, *iso*-propanol, *tert*-butanol and water gave the desired product in 65-90% yield within the period of 30-60 min (**Table 2.1, entries 2-6**).

On the other hand, dimerization was achieved efficiently in various aprotic solvents such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, benzene and toluene in short span of time at room temperature (**Table 2.1, entries 7-12**). Among them, dichloromethane gave the desired product, i.e. 3,5-diphenyl-1,2,4-thiadiazole (**2a**) in 95% yield within 5 min (**Table 2.1, entry 7**). Further optimization was continued with other alkyl nitrites such as *iso*-amyl nitrite (IAN) and *n*-butyl nitrite (NBN) at room temperature.

Both the reagents gave the desired product in good yield but they require slightly longer time (*i.e.* 15 min) for completion of the reaction (**Table 2.1, entries 13 and 14**). Formation of model compound **2a** is confirmed by the ^{1}H & ^{13}C NMR spectroscopy (**Figure 2.2** and **2.3**).

Table 2.1: Optimization of dimerization of thiobenzamide[a]



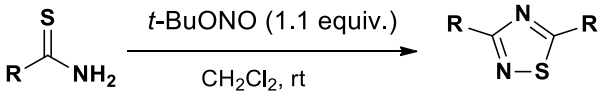
Entry	Solvent	Reagent	Time	Yield[b] (%)
1	CH_3COOH	TBN	30	69
2	CH_3OH	TBN	30	90
3	C_2H_5OH	TBN	40	89
4	*iso*-Propanol	TBN	40	85
5	*tert*-butanol	TBN	60	79
6	H_2O	TBN	60	65
7	CH_2Cl_2	TBN	5	95
8	$CHCl_3$	TBN	10	90
9	CH_3CN	TBN	15	89
10	THF	TBN	15	89
11	Benzene	TBN	15	70
12	Toluene	TBN	15	70
13	CH_2Cl_2	IAN[c]	15	93
14	CH_2Cl_2	NBN[d]	15	92

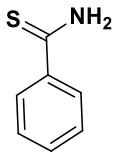
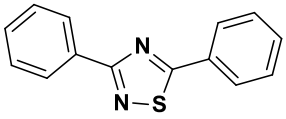
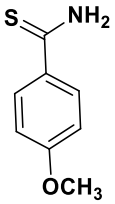
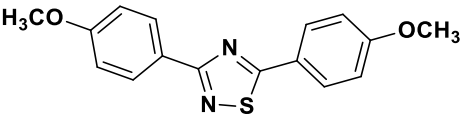
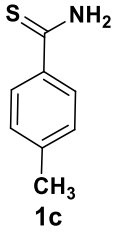
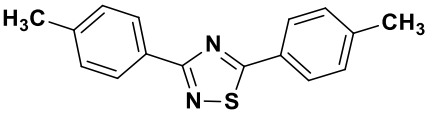
[a] **Reaction conditions**: Benzothioamide (1.0 mmol) and TBN were stirred in the respective solvents (2 mL) at room temperature, [b] Isolated yields, [c] IAN: *iso*-amyl nitrite, [d] NBN: *n*-butyl nitrite.

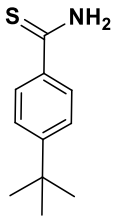
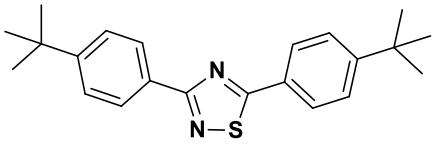
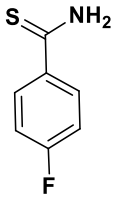
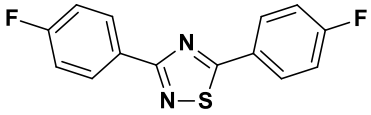
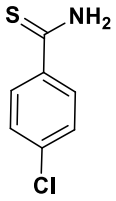
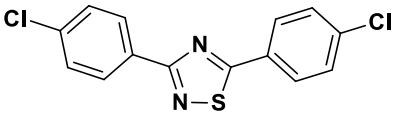
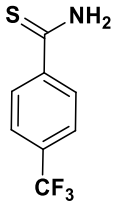
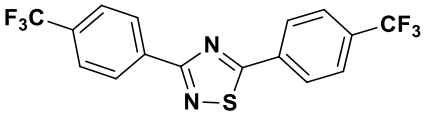
Having established the optimized condition, we examined the oxidative dimerization of various substituted thiobenzamides using *tert*-butyl nitrite in dichloromethane to explore the scope of substrates amenable to this method (**Table 2.2**). Electron donating groups such as methoxy (**1b**), methyl (**1c**) and *tert*-butyl substituted (**1d**) thiobenzamides were successfully dimerized to give product 3,5 bis(4-methoxyphenyl)-1,2,4-thiadiazole (**2b**), 3,5-dip-tolyl-1,2,4-thiadiazole (**2c**), 3,5-bis(4-*tert*-butylphenyl)-1,2,4-thiadiazole (**2d**) respectively, in excellent yields within 5 min (**Table 2.2**, **entries 2-4**). Similarly, dimerization of halogen substituted thiobenzamides such as 4-fluoro (**1e**) and chloro-thiobenzamides (**1f**) was successfully accomplished to obtain the desired products 3,5-bis(4-fluorophenyl)-1,2,4-thiadiazole (**2e**) and 3,5-bis(4-chlorophenyl)-1,2,4-thiadiazole (**2f**) (**Table 2.2, entries 5, 6**) in >89% yield.

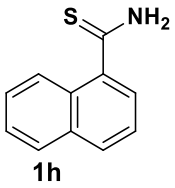
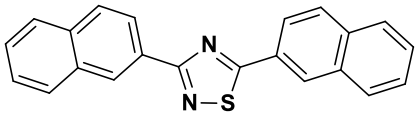
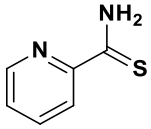
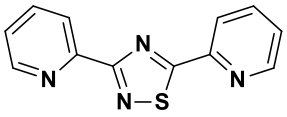
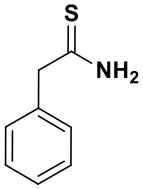
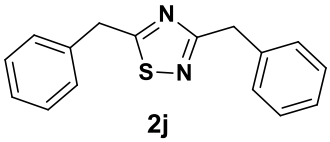
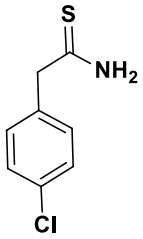
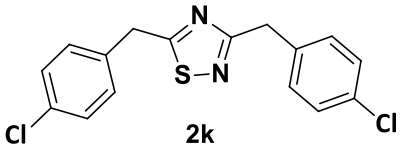
Further, the analogue possessing the strongly electron withdrawing trifluoromethyl (**1g**) group was subjected to the dimerization under optimized condition. To our delight, the substrate **1g** underwent dimerization smoothly and gave the desired product 3,5-bis(trifluoromethyl)phenyl-1,2,4-thiadiazole (**2g**) in 89% yield. However it requires 30 min (**Table 2.2, entry 7**). Likewise, 2-naphthyl thiobenzamide (**1h**) was successfully dimerized to 3,5-dinaphthyl 1,2,4-thiadiazoles (**2h**) in 82% yield (**Table 2.2, entry 8**).

Table 2.2: Dimerization of thioamides using *tert*-butyl nitrite[a]



Entry	Substrate	Product	Time (min)	Yield[b] (%)
1	 1a	 2a	5	95
2	 1b	 2b	5	94
3	 1c	 2c	5	92

4	 1d	 2d	5	83
5	 1e	 2e	15	89
6	 1f	 2f	15	90
7	 1g	 2g	30	89

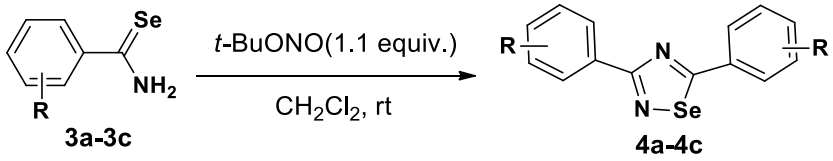
8	 1h	 2h	5	82
9	 1i	 2i	5	88
10	 1j	 2j	5	85
11	 1k	 2k	5	82

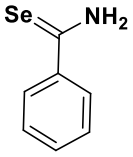
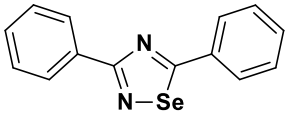
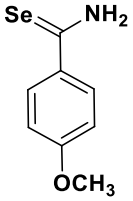
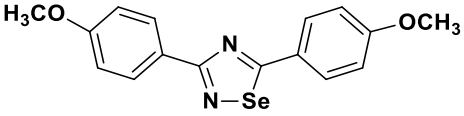
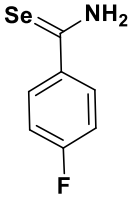
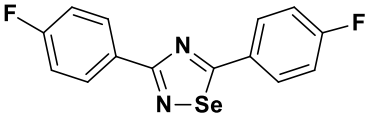
[a] **Reaction conditions:** Substrate (1.0 mmol) and *tert*-butyl nitrite (TBN) (1.1 equiv.) were stirred in dichloromethane (2 mL) at room temperature. [b] Isolated yields.

To our surprise, the optimized condition was also found to be suitable for the oxidative dimerization of heterocyclic thiobenzamide such as pyridine-2-carbothioamide (**1i**). The reaction proceeded smoothly to provide the 3,5-di(pyridin-2-yl)-1,2,4-thiadiazole (**2i**) in 88% yield within 5 minute (**Table 2.2, entry 9**). After the extensive study with thiobenzamides, oxidative dimerization of phenylethanethioamide *viz.* 2-phenylethanethioamide (**1j**) and 2-(4-chlorophenyl)ethanethioamide (**1k**) was investigated. The corresponding dimerized products, 3,5-dibenzyl-1,2,4-thiadiazole (**2j**) and 3,5-bis(4-chlorobenzyl-1,2,4-thiadiazole (**2k**) (**Table 2.2, entries 10 and 11**) were obtained in excellent yields demonstrating the broad scope of the current methodology.

Encouraged by the results obtained from dimerization of thioamides, we have attempted the oxidative dimerization of benzoselenoamide (**3a**) to 1,2,4-selenadiazole using *tert*-butyl nitrite (**Table 2.3**). For this study, differently substituted benzoselenoamides *viz.* benzoselenoamides (**3a**), 4-methoxybenzoselenoamide (**3b**) and 4-fluorobenzoselenoamide (**3c**) were prepared and subjected to dimerization under the optimized condition. To our delight, corresponding 3,5-disubstituted 1,2,4-selenadiazoles *viz*. 3,5-diphenyl-1,2,4–selenadiazole (**4a**), 3,5-bis(4-methoxyphenyl)-1,2,4-selenadiazole (**4b**) and 3,5-bis(4-fluorophenyl)-1,2,4-selenadiazole (**4c**) (**Table 3.3, entries 1-3**) were obtained in good yields within the period of 15-20 min which serves to extend the scope of the present methodology.

Table 2.3: Dimerization of benzoselenoamide using *ter*t-butyl nitrite[a]



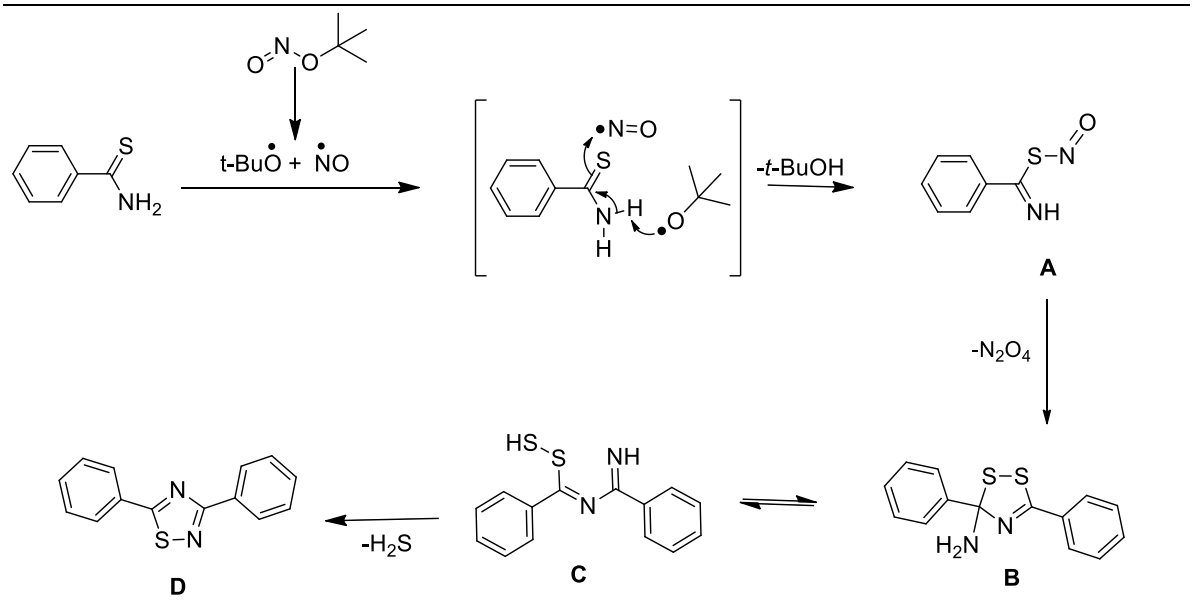
Entry	Substrate	Product	Time (min)	Yield[b] (%)
1	 3a	 4a	15	89
2	 3b	 4b	15	87
3	 3c	 4c	20	80

[a]**Reaction conditions:** Substrate (1.0 mmol) and *tert*-butyl nitrite (TBN) (1.1 equiv.) were stirred in dichloromethane (2 mL) at room temperature. [b] Isolated yields.

Overall, this practical metal-free approach shows good functional group tolerance while the desired products were obtained in excellent yields. ^{1}H & ^{13}C NMR spectra of 1,2,4-selenadiazole (**4a**) have been given in **Figure** 2.4 & 2.5.

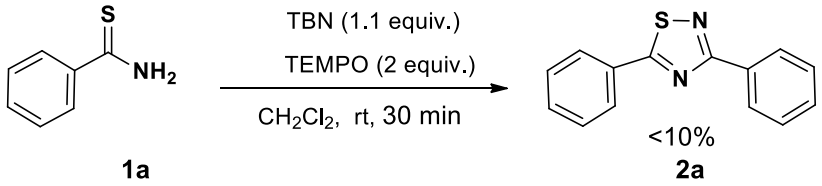
2.3 Mechanistic Studies and Control Experiment

A proposed mechanism for the TBN induced dimerization reaction is shown in **Scheme 2.2**. TBN undergoes radical dissociation to form *t*-butoxy and nitroso radicals which may react with thiobenzamide to form intermediate **A**. Further, this intermediate may undergo dimerization via elimination of dinitrogen tetroxide (N_2O_4) to form intermediate **B** which may be in equilibrium with intermediate **C**. Further, the intermediate **C** might release hydrogen sulfide (H_2S) to yield the desired product **D**.



Scheme 2.2: Proposed mechanism for the TBN induced dimerization reaction.

To support our mechanistic hypothesis, the dimerization reaction was carried out with a radical trapping reagent TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl). The experiment was performed with 2 equiv. of TEMPO under optimized conditions in dichloromethane at room temperature (**Scheme 2.3**). As expected, the dimerization process was inhibited by TEMPO with less than 10% of the desired product (*i.e.* 3,5-diphenyl-1,2,4-thiadiazole) observed.

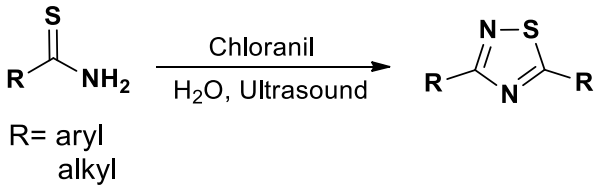


Scheme 2.3: Control experiment with TEMPO.

2.4 Development of another Methodology

Despite having many advantage of our previously reported method, there is still scope to developed another methodology for the synthesis of biologically important 1,2,4-thiadiazole moiety under environmentally benign condition. In the previous protocol, reaction has been performed in dichloromethane as a solvent but it is volatile organic solvent. Hence, in the continuation of our pervious method, we have developed another methodology for the synthesis of 1,2,4-thiadiazole derivatives in a greener way by replacing organic solvent to the greener solvent under non-conventional energy source. In

the present protocol, we have performed the reaction under ultrasound irradiation method in aqueous medium using chloranil as an oxidizing reagent (**Scheme 2.4**).



Scheme 2.4: Chloranil mediated synthesis of 1,2,4-thiadiazole derivatives.

The use of appropriate solvent in organic synthesis is also very important from the green chemistry point of view. In this regard the use of water as solvent has attracted great deal of interest in recent years. Water is the solvent of choice not only from an ecological point of view but also from an economic point of view because it is cheap, abundantly available, non-toxic and non-flammable and more selective than organic solvents. Water acts differently from other organic solvents in terms of its distinctive and unusual physical and chemical properties (Gawande et al. 2013, Lindstrom et al. 2008).

In this context, ultrasound assisted reactions have gained much attention because they offer several advantages such as milder reaction condition, higher reaction rate, excellent yield and low energy consumption. Many organic transformations have been successfully achieved with the help of ultrasound irradiation method as compared to conventional methods. The increasing requirement for environmentally clean technology that reduces production of waste source, long reaction time, high temperature and unsatisfactory yield prompt us to use the ultrasound irradiation method. Ultrasound wave improves the rate of

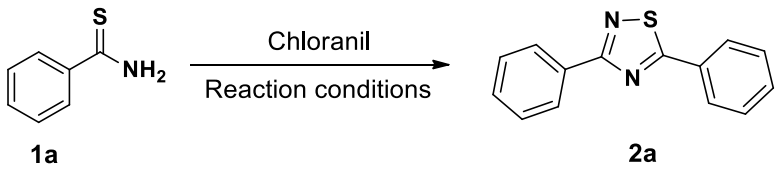
chemical reaction via the process of acoustic cavitation. Therefore, ultrasound assisted organic synthesis, as a green synthetic approach is considered as a powerful technique (Ghomi et al. 2018, Nishtala et al. 2017, Banerjee et al. 2017).

Chloranil is an expedient oxidant in organic chemistry and has extensive application in dehydrogenation reactions particularly suitable for aromatization of hydro aromatic substances (Jackman et al. 1960, Becker et al. 1974) and successful utilization in the synthesis of nitrogen (Landberg et al. 1975, Huisgen et al. 1962) and sulphur (Mcintosh et al. 1975, Tilak et al. 1964) containing heterocycles. Chloranil is used in selective oxidation of organic molecule by hydride abstraction mechanism (Wendlandt et al. 2015). It also undergoes facile nucleophilic displacement reaction with 1° and 2° amine leading to the formation of 2,5-bis amino derivatives and reaction proceed via one electron oxidation of amine (Foster et al. 1966). Chloranil is inexpensive, nontoxic and air stable which makes it easy to handle. The fascinating nature of water and beneficial effects of ultrasound technique encouraged us to undertake the synthesis of 1,2,4-thiadiazole derivatives without catalyst under benign conditions.

2.4.1 Optimization of Reaction Condition with Chloranil

The reaction conditions were first optimized using equimolar amounts of thiobenzamide (**1a**) as a test substrate and chloranil. The reaction was carried out in H_2O while stirring at room temperature for 3 h and yielded only 20% of product **2a**.

Table 2.4: Effect of reaction conditions on the yield of model compound **2a**[a]



1a **2a**

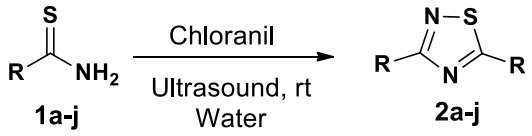
Entry	Reaction conditions	Solvent	Time	Yield[b] (%)
1	Stirring, rt	H_2O	3 h	20
2	Stirring, reflux	H_2O	3 h	40
3	50 °C	Solvent-free	3 h	50
4	80 °C	Solvent-free	3 h	70
5	120 °C	Solvent-free	3 h	70
6	**Ultrasound (US), rt**	**H_2O**	**3 min**	**95**
7	US, rt	MeCN	5 min	75
8	US, rt	THF	10 min	70
9	US, rt	EtOH	15 min	85
10	US, rt	1,4-Dioxane	12 min	65
11	US, rt	$CHCl_3$	8 min	78
12	US, rt	CH_2Cl_2	9 min	79
13	US, rt	DCE	7 min	82
14	US, rt	DMSO	10 min	78
15	US, rt	PhH	12 min	71
16	US, rt	PhMe	15 min	75

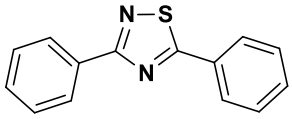
[a] **Reaction conditions**: Thiobenzamide (1.0 mmol), chloranil (1.1 mmol), solvent (3 mL).
[b] Isolated yield.

In the second run, the reaction mixture was refluxed for 3 h which gave low yield of the desired product (**Table 2.3, entry 2**). Further on heating the reaction mixture by conventional method at 50, 80 and 120 °C under solvent-free condition gave the desired product in 50–70% yield after 3 h (**Table 2.3, entries 3–5**). In order to improve the yield of the product, the reaction was performed under ultrasound irradiation at room temperature in H_2O. To our surprise, 95% yield was obtained in 3 min. To investigate the effect of solvents, the reaction was carried out in different polar and nonpolar solvents. Although the desired product was obtained in both polar (H_2O, MeCN, THF, EtOH, 1,4-dioxane, $CHCl_3$, CH_2Cl_2, DCE, DMSO) and nonpolar solvents (PhH, PhMe), H_2O was found to be the best solvent for the dimerization.

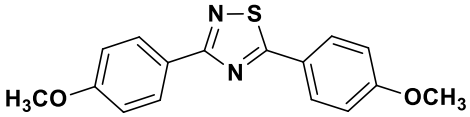
With optimized reaction conditions, the applicability of this methodology was examined with the different primary thiobenzamide derivatives and the results are summarized in Table 2.4. These reaction conditions with chloranil as oxidant show extensive functional group tolerance and prove to be a general method for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles. It was found that the reaction proceeds smoothly and provides an excellent yield of desired product *viz.* 3,5-bis(4-methoxyphenyl)-1,2,4-thiadiazole (**2b**), 3,5-dip-tolyl-1,2,4-thiadiazole (**2c**), 3,5-bis(4-*tert*-butylphenyl)-1,2,4-thiadiazole (**2d**), 3,5-bis(4-nitrophenyl)-1,2,4-thiadiazole (**2l**) within short period of time using thiobenzamide with electron-donating (methoxy **(1b)**, methyl (**1c**) and *tert*-butyl (**1d**) substituted or electron-withdrawing substituent (nitro) (**1l**).

Table 2.5: Synthesis of thiadiazoles derivatives **2a–j**[a]

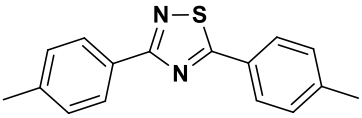




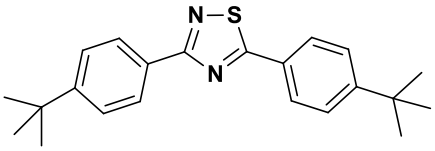
2a, 3 min, 95%[b]



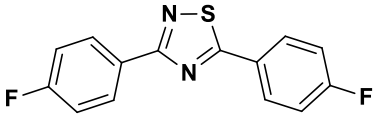
2b, 5 min, 94%



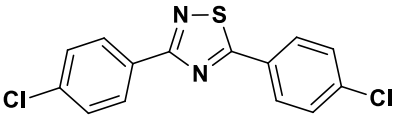
2c, 6 min, 95%



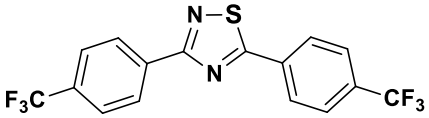
2d, 8 min, 89%



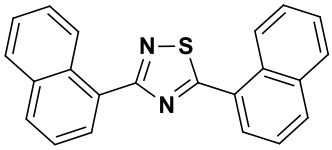
2e, 6 min, 90%



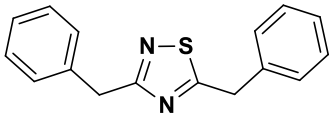
2f, 7 min, 88%



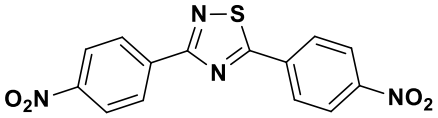
2g, 6 min, 91%



2h, 5 min, 87%



2j, 5 min, 87%



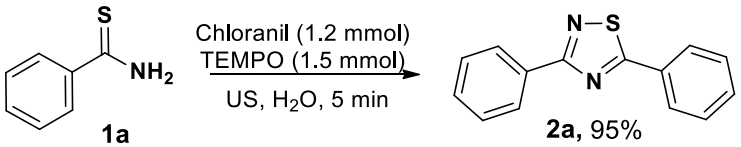
2l, 8 min, 94%

[a] **Reaction conditions:** substrate (1.0 mmol) and chloranil (1.1 mmol) were irradiated with ultrasound in H_2O (3 mL) at room temperature. [b]Isolated yield.

Interestingly, thiobenzamide bearing halogen substituents such as fluorine, chlorine, and trifluoro could also be reacted in efficient manner to obtain the desired products *viz*. products 3,5-bis(4-fluorophenyl)-1,2,4-thiadiazole (**2e**), 3,5 bis (4-chlorophenyl)-1,2,4-thiadiazole (**2f**) and 5-bis(trifluoromethyl)phenyl-1,2,4-thiadiazole (**2g**) in good yield. Likewise, naphthalene-1-carbothioamide (**1h**) was successfully transferred into 3,5-di(naphthalen-1-yl)-1,2,4-thiadiazole (**2h**) in 87% yield (**Table 2.5**) within few minutes. The results established that no significant electronic and steric effects of the substituents on the phenyl ring were observed. This reaction also gave good yield for 3,5-dibenzyl-1,2,4-thiadiazole (**2j)** (**Table 2.5**). The corresponding products were obtained in good yield which show the wide scope of current methodology.

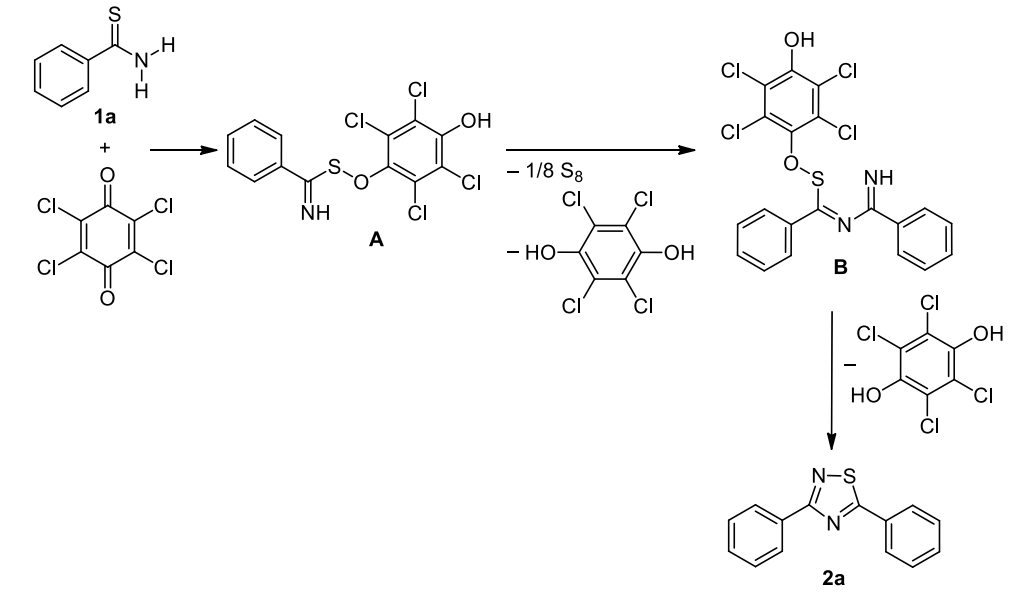
2.5 Mechanistic Studies and Control Experiment with TEMPO

A control experiment was performed using (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as radical trapping agent and it was observed that TEMPO does not quench the reaction. This shows that reaction does not proceed via radical intermediate and a nucleophilic pathway has been proposed (**Scheme 2.5**).



Scheme 2.5: Controlled experiment with TEMPO.

On the basis of product analysis, a mechanism for the chloranil-assisted dimerization of primary thiobenzamide is proposed in Scheme 2.6. Oxidative addition of thioamide **1a** to chloranil leads to intermediate **A** which dimerizes forming intermediate **B**. Product **2a** is formed after cyclization of intermediate **B**.



Scheme 2.6: Proposed mechanism for the chloranil-mediated synthesis of 1,2,4-thiadiazoles.

2.6 Experimental Section

2.6.1 Experimental procedure for the dimerization of benzothioamides using TBN

The primary thioamides (**1a**-**1k**) (1.0 mmol) was stirred in dichloromethane (2 mL) at room temperature to which 1.1 equiv. of *tert*-butyl nitrite (TBN) was added. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted

with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and subjected for silica gel (60-120 mesh) column chromatography purification (SiO_2: hexane–EtOAc) to obtain the desired products (**2a**-**2k**).

2.6.2 Experimental procedure for the dimerization of benzoselenoamide

The primary benzoselenoamides (**3a**-**3c**) (1.0 mmol) was stirred in dichloromethane (2 mL) at room temperature to which 1.1 equiv. of *tert*-butyl nitrite (TBN) was added. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and subjected for silica gel (60-120 mesh) column chromatography purification (SiO_2: hexane–EtOAc) to obtain the desired products (**4a**-**4c**).

2.6.3 Experimental procedure for control experiment with TEMPO

The thiobenzamide (**1a**) (1.0 mmol) and TEMPO (2.0 mmol) was stirred in dichloromethane (2 mL) at room temperature for 10 min to which 1.1 equiv. of *tert*-butyl nitrite (TBN) was added. The reaction was further stirred for 30 min and diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and subjected for silica gel (60-120 mesh) column chromatography purification (SiO_2: hexane–EtOAc) to obtain **2a**.

2.6.4 Experimental procedure for the dimerization of benzothioamides using chloranil

A flask was charged with primary thiobenzamide **1a–1l** (1.0 mmol) and chloranil (1.1 mmol) in H_2O (3 mL). The reaction mixture was irradiated with ultrasound at room temperature for appropriate time. The progress of reaction was monitored with TLC. After completion of the reaction, solvent was concentrated under reduced pressure and the obtained residue was subjected to silica gel column chromatography purification (hexane–EtOAc) to obtain the desired products.

2.7 Analytical Data

2.7.1 3,5- Diaryl -1,2,4- thiadiazoles (2a): The title compound was obtained as white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.59; (Yield: 226 mg (95%) in both TBN and chloranil); m.p. 90 °C; **IR** (neat) 3050, 2922, 1599, 1464, 1407, 1315, 1270, 1171, 751 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.32 (dd, 2H), 7.98 (dd, 2H), 7.48–7.40 (m, 6H); **^{13}C NMR** (125 MHz, CDCl3) δ (ppm): 188.1, 173.8, 132.8, 131.9, 130.7, 130.3, 129.2, 128.6, 128.3, 127.4.; **HRMS**: Calc. for $C_{14}H_{11}N_2S$ $[M+H]^+$: 239.0643, Obser: 239.0698.

2.7.2 3,5 Bis(4-methoxyphenyl)-1,2,4-thiadiazole (2b): The title compound was obtained as pale yellow solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); R_f = 0.60; (Yield: 280 mg (94%) in both TBN and chloranil); m.p. 138-140 °C; **IR** (neat) 2990, 2872, 1632, 1443, 1255, 1295, 1032, 835 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.24 (d, 2H), 7.91 (d, 2H), 6.93 (d, 4H), 3.81 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 187.3, 173.3, 162.4, 161.2, 129.8, 129.1, 126.0, 123.6, 114.5, 113.9, 55.4, 55.3; **HRMS**: Calc. for $C_{16}H_{15}N_2O_2S$ $[M+H]^+$: 299.0854, Obser: 299.0858.

2.7.3 3,5-Dip-tolyl-1,2,4-thiadiazole (2c): The title compound was obtained as white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.55; (Yield: 245mg (92%) in TBN, 253 mg (95%) in chloranil); m.p. 135-137 °C; **IR** (neat) 2962, 1915, 1402, 1317, 1011, 842, 735 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.20 (d, 2H), 7.86 (d, 2H), 7.24 (t, 4H), 2.36 (d, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 187.9, 173.7, 142.4, 140.4, 130.3, 129.9, 129.3, 128.2, 128.1, 127.4, 21.6, 21.5; **HRMS**: Calc. for $C_{16}H_{15}N_2S$ $[M+H]^+$: 267.0956, Obser: 267.0953.

2.7.4 3,5-Bis(4-*tert*-butylphenyl)-1,2,4-thiadiazole (2d): The title compound was obtained as white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.52; (Yield: 290 mg (83%) in TBN, 312 mg (89%) in chloranil); m.p. 91-93 °C; **IR** (neat) 2974, 2905, 1724, 1609, 1472, 1495, 1323, 1134, 835 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.34 (d, 1H), 8.00 (d, 1H), 7.61 (d, 1H), 7.55 (dd, 3H), 7.50 (d, 2H), 1.40 (s, 9H), 1.35 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 187.7, 173.7, 156.5, 155.4, 153.5, 131.9, 130.2, 128.0, 127.2, 126.1, 125.5, 35.2, 34.8, 31.2, 30.9; **HRMS**: Calc. for $C_{22}H_{27}N_2S$ $[M+H]^+$: 351.1895, Obser: 351.1904.

2.7.5 3,5-Bis(4-fluorophenyl)-1,2,4-thiadiazole (2e): The title compound was obtained as a white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.54; (Yield: 244 mg (89%) in TBN, 246 mg (90%) in chloranil); m.p. 185-187 °C; **IR** (neat) 2926, 2855, 1741, 1547, 1514, 1463, 1226, 835, 739 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.37 (dd, 2H), 8.05 (dd, 2H), 7.25–7.14 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 186.9, 172.7, 165.9, 163.9, 130.4, 129.6, 129.5, 129.0, 127.0, 116.6, 115.8; **HRMS**: Calc. for $C_{14}H_9F_2N_2S$ $[M+H]^+$: 275.0455, Obser: 275.0455.

2.7.6 3,5 Bis (4-chlorophenyl)-1,2,4-thiadiazole (2f): The title compound was obtained as a white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.55; (Yield: 276 mg (90%) in TBN, 270 mg (88%) in chloranil); m.p. 161-162 °C; **IR** (neat) 2925, 1741, 1464, 1424, 1091, 1013, 829, 738 cm-1; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.31 (d, 2H), 7.98 (d, 2H), 7.49 (dd, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 187.0, 172.8, 138.1, 136.5, 131.1, 129.6, 129.6, 128.9, 128.6; **HRMS**: Calc. for $C_{14}H_9Cl_2N_2S$ $[M+H]^+$: 306.9863, Obser: 306.9865.

2.7.7 3,5-Bis(trifluoromethyl)phenyl-1,2,4-thiadiazole (2g): The title compound was obtained as white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.56; (Yield: 332 mg (89%) in TBN, 340 mg (91%) in chloranil); m.p. 81 °C; **IR** (neat) 2927, 1742, 1469, 1319, 1268, 1128, 1063, 894

cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.52 (d, 1H), 8.19 (d, 1H), 7.80 (dd, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 186.9, 172.6, 135.5, 133.7, 132.3, 128.6, 127.9, 127.8, 126.4, 125.7, 124.6, 122.8; **HRMS**: Calc. for $C_{16}H_9F_6N_2S$ $[M+H]^+$: 375.0391, Obser: 375.0412.

2.7.8 3,5 Di(naphthalalen-1-yl)-1,2,4-thiadiazole (2h): The title compound was obtained as a white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.52; (Yield: 277 mg (82%) in TBN, 294 mg (87%) in chloranil); m.p. 120-121 °C; **IR** (neat) 3040, 2925, 2359, 1722, 1476, 1384, 1241, 1049, 795, 761 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 9.29 (d, 1H), 9.00 (d, 1H), 8.55 (dd, 1H), 8.27 (d, 1H), 8.10–8.05 (m, 4H), 7.99 (d, 1H), 7.93 (s, 1H), 7.71 (s, 1H), 7.63 (s, 1H), 7.54–7.50 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 186.8, 173.8, 134.0, 133.9, 133.1, 132.5, 131.0, 130.9, 130.1, 129.9, 129.8, 129.1, 128.5, 128.5, 128.5, 128.4, 127.9, 127.5, 127.1, 126.6, 126.3, 126.0, 125.1, 124.8; **HRMS**: Calc. for $C_{22}H_{15}N_2S$ $[M+H]^+$: 339.0956, Obser: 339.0965.

2.7.9 3,5-Di(pyridine-2-yl)-1,2,4-thiadiazole (2i): The title compound was obtained as a yellow solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10), R_f = 0.60; (Yield 211 mg (88%) in TBN); m.p. 134 °C; **IR** (neat) 2921, 2851, 1725, 1496, 1433, 1244, 1036, 896 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.71 (d, 2H), 8.53 (d, 2H), 7.85 (d, 2H), 7.49–7.44 (m, 2H); **^{13}C NMR** (125 MHz,

$CDCl_3$) δ (ppm): 196.0, 150.6, 149.4, 147.3, 141.2, 137.3, 134.8, 126.5, 126.3, 125.2, 120.6, 96.2; **HRMS**: Calc. for $C_{12}H_9N_4S$ $[M+H]^+$: 241.0548, Obser: 241.0556.

2.7.10 3,5-Dibenzyl-1,2,4-thiadiazole (2j): The title compound was obtained as yellow oil. The Residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5), R_f = 0.63; (Yield: 226 mg (85%) in TBN, 231 mg (87%) in chloranil); **IR** (neat) 3089, 1590, 1398, 1032, 832 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.41–7.39 (m, 2H), 7.36-7.33 (m, 6H), 7.29–7.26 (m, 2H), 4.38 (s, 2H), 4.33 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 192.2, 175.5, 137.1, 136.1, 129.0, 128.5, 127.7, 126.7, 39.2, 37.8; **HRMS**: Calc. for $C_{16}H_{15}N_2S$ $M+H]^+$: 267.0956, Obser: 267.0957.

2.7.11 3,5-Bis(4-chlorobenzyl-1,2,4-thiadiazole (2k): The title compound was obtained as yellow solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5), R_f = 0.60; (Yield 274 mg (82%) in TBN); m.p. 60-62 ^oC; **IR** (neat) 3034, 1542, 1322, 1101, 890 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.37 (s, 1H), 7.34–7.25 (m, 7H), 4.34 (s, 2H), 4.28 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 191.5, 175.2, 135.4, 134.4, 133.7, 132.7, 130.4, 130.3, 129.2, 128.7, 38.5, 37.0; **HRMS**: Calc. for $C_{16}H_{13}C_{l2}N_2S$ $[M+H]^+$: 335.0176, Obser: 335.0174.

2.7.12 3,5-Bis(4-nitrophenyl)-1,2,4-thiadiazole (2l): The title compound was obtained as yellow solid yellow solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5) R_f = 0.60; (Yield 309 mg (94%) in chloranil); m.p. 200–

201°C; **IR** (neat) 2924, 2853, 1602, 1536, 1470, 1351, 851, 716 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.58 (d, 2H); 8.43–8.37 (m, 4H); 8.25 (d, 2H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ (ppm): 186.5, 172.3, 150.0, 149.3, 137.8, 135.6, 129.5, 128.6, 124.9, 124.3.

2.7.13 3,5-Diphenyl-1,2,4–selenadiazole (4a): The title compound was obtained as a white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5), R_f = 0.65; (Yield 254 mg (89%) in TBN); m.p. 84-85 °C; **IR** (neat) 2852, 1482, 1333, 1240, 965cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.44 (d, 2H), 8.03 (d, 2H), 7.75–7.40 (m, 6H); **^{13}C NMR** (125MHz, $CDCl_3$) δ (ppm): 193.8, 174.4, 134.4, 134.1, 132.1, 130.1, 129.3, 128.8, 128.7, 128.3, 128.2. **HRMS**: Calc. for $C_{14}H_{11}N_2Se$ $[M+H]^+$: 287.0087, Obser: 287.0087.

2.7.14 3,5-Dip-methoxy-1,2,4-selenadiazole (4b): The title compound was obtained as a white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5), R_f = 0.67; (Yield 300 mg (87%) in TBN); m.p. 140 °C; **IR** (neat): 3033, 2942, 1606, 1511, 1485, 1352, 1176, 1152, 1090, 831 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.35 (d, 1H), 7.96 (d, 1H), 7.63–7.58 (m, 2H), 7.04–6.95 (m, 4H), 3.96 (s, 3H), 3.88 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 192.6, 162.8, 133.9, 130.3, 129.9, 119.2, 114.7, 114.5, 113.9, 103.9, 55.5; **HRMS**: Calc. for $C_{16}H_{15}O_2N_2Se$ $[M+H]^+$: 347.0299, Obser: 347.0314.

2.7.15 3,5-Bis (4-fluorophenyl)-1,2,4-selenadiazole (4c): The title compound was obtained as a white solid. The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5), R_f = 0.66; (Yield 256 mg (80%) in TBN); m.p. 171–172 ^oC; **IR** (neat): 1640, 1511, 1455, 1409, 1359, 1114, 950, 853cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.40 (dd, 2H), 8.02–7.99 (m, 2H), 7.19 (dt, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 192.4, 173.2, 165.9, 134.6, 130.8, 130.5, 130.4, 116.9, 116.7, 116.6, 116.4, 115.7, 115.5; **HRMS**: Calc. for $C_{14}H_9F_2N_2Se$ $[M+H]^+$: 322.9899, Obser: 322.9916.

2.8 Spectral Data of Synthesized Products

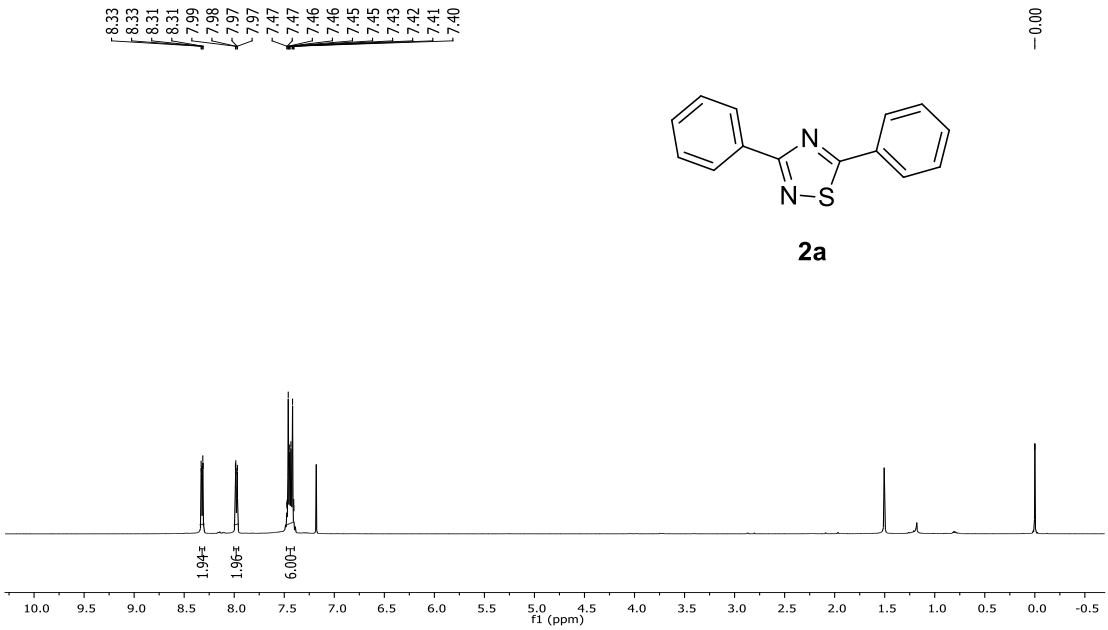


Figure 2.2: ^{1}H NMR of 1,2,4-thiadiazole (**2a**).

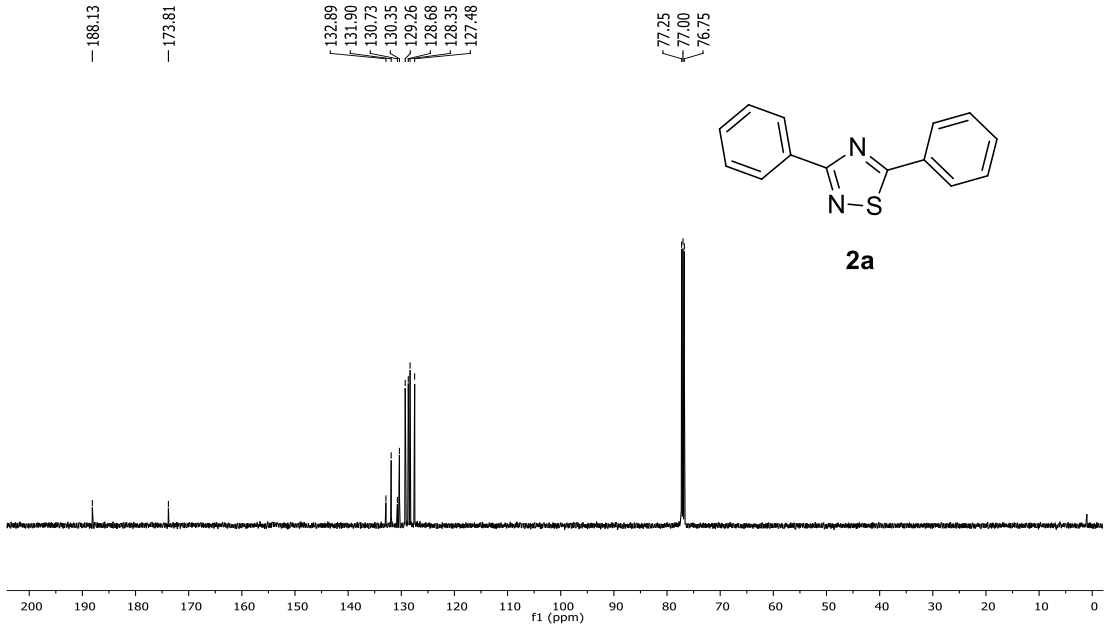


Figure 2.3: ^{13}C NMR of 1,2,4-thiadiazole (**2a**).

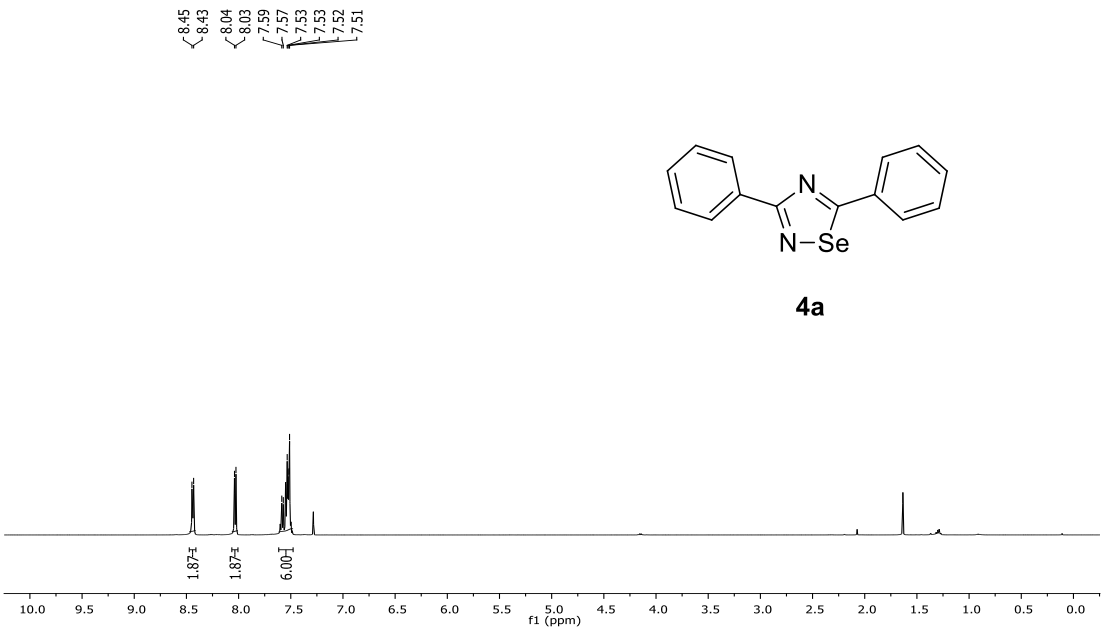


Figure 2.4: ^{1}H NMR of 1,2,4-selenadiazole (**4a**).

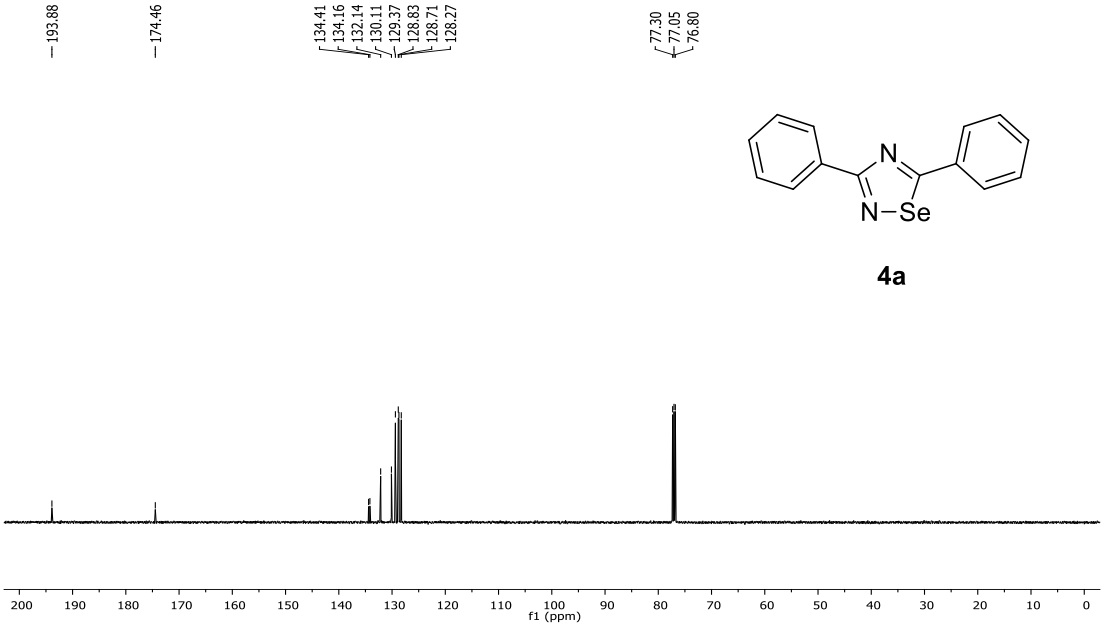


Figure 2.5: ^{13}C NMR of 1,2,4-selenadiazole (**4a**).

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CHAPTER 3

A Practical Synthesis of 3-Functionalized Coumarins from *o*-Cresols and Active Methylene Compounds under Metal and Catalyst-Free Conditions using *tert*-Butyl Hydrogen Peroxide

Chapter 3

A Practical Synthesis of 3-Functionalized Coumarins from *o*-Cresols and Active Methylene Compounds under Metal and Catalyst-Free Conditions using *tert*-Butyl Hydrogen Peroxide

3.1 Introduction

Coumarin scaffold is a well-regarded parent compound found in several natural products (Murray et al. 1989, Brahmachari et al. 2010) and bioactive molecules (Hoult et al. 1996). Coumarin derivatives possess a wide range of biological activities including antibacterial (Creaven et al. 2010), antifungal (Kayser et al. 1997), anti HIV (Bhavsar et al. 2011, Bedoya et al. 2005), antioxidant (Vazquez et al. 2013, Kontogiorgis et al. 2003), antimutagenic (Kontogiorgis et al. 2005), anticancer (Zhi et al. 2014, Wu et al. 2014), anti-inflammatory (Timonen et al. 2011, Melagraki et al. 2009), analgesic (Khode et al. 2009), antibiotic activities (Chimenti et al. 2006). Coumarin scaffold is also incorporated in insecticides (Moreira et al. 2007), fragrances & perfumes (Aslam et al. 2010), agrochemicals (Schonberg et al. 1954, Adronov et al. 2000) and additives in foods and cosmetics (Frosch et al. 2002, Brahmachari et al. 2015). Numerous carboxy coumarins are used as triplet oxygen sensitizers (Peroni et al. 2002) and fluorescent probes (Specht et al. 1982). Hence, coumarin is a very imperative building block for combinatorial library synthesis. **Figure 3.1** represents some biologically active compounds like Novobiocin, Hymechromone, Acenocoumaral, Ensaculin (KA 672), Batoprazine and Warfarin having coumarin moiety.

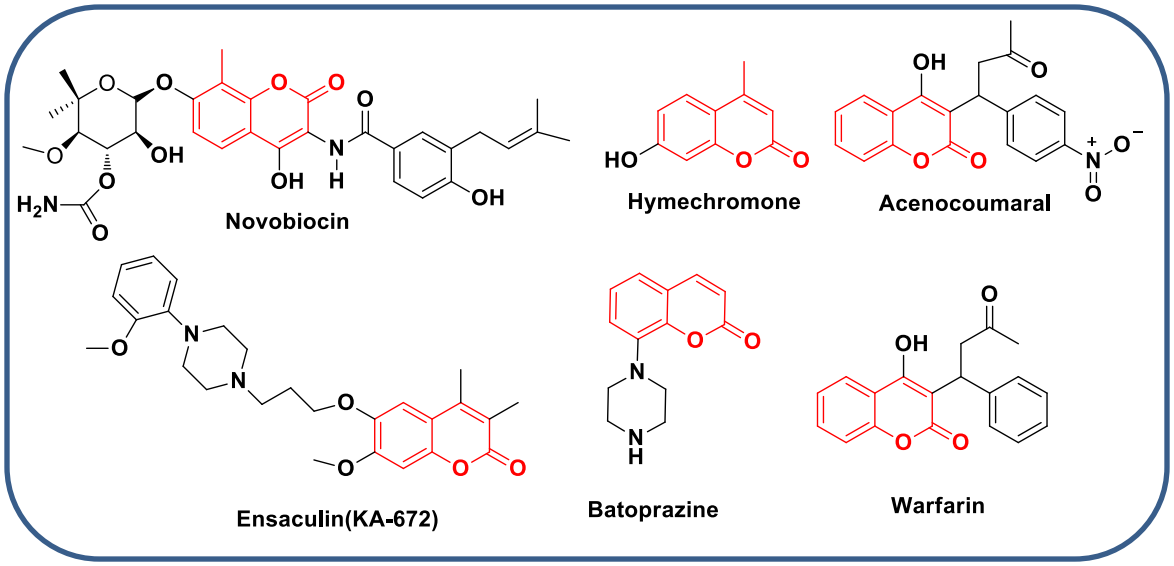


Figure 3.1: Biologically active molecules containing coumarin moiety.

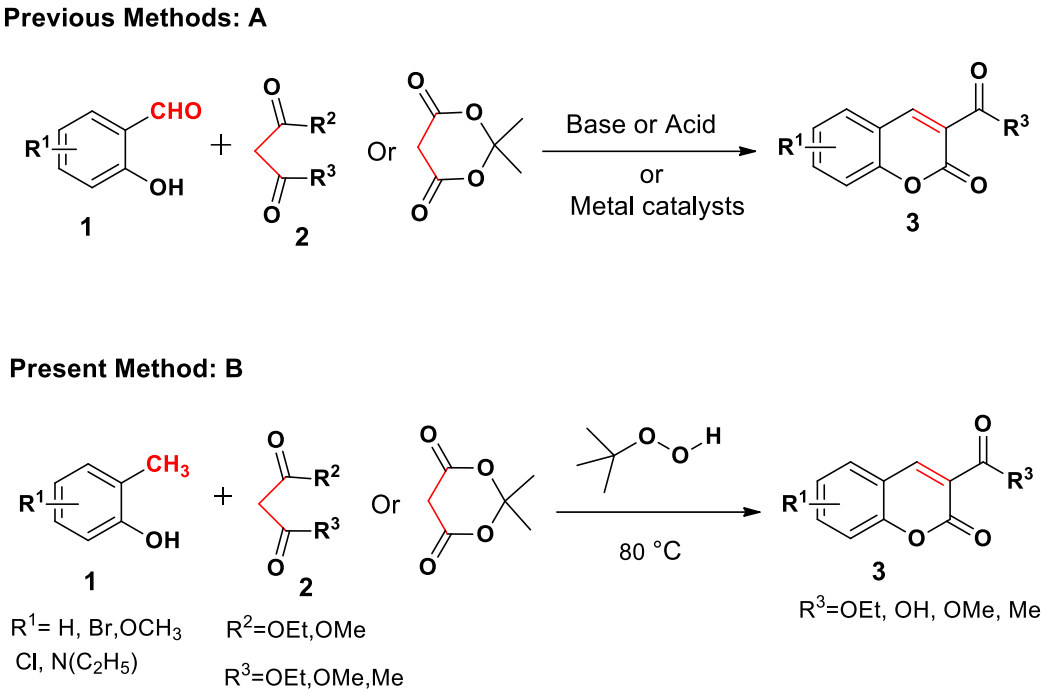
Synthesis of these oxygen containing heterocyclic compounds are usually executed by numerous methods such as von Pechmann (Pechmann et al. 1884), Perkin (Johnson et al. 2004), Wittig reaction (Yavari et al. 1998) and Baylis-Hilmann reaction (Kaye et al. 2003). Knoevenagel condensation is not only an alternative method but also an efficient method for the synthesis of 3-substituted coumarins from salicylaldehyde with active methylene compounds like meldrum acid, malonate esters, ethyl cyanoacetate (Jones et al. 2004) etc. Synthesis of 3-substituted coumarins via Knoevenagel condensation was achieved using different metal and metal-free catalyst like $ZrCl_4$ (Valizadeh et al. 2011), Mg-Al hydrotalcite (Bandgar et al. 1999), mesoporous molecular sieve MCM-41(Heravi et al. 2010), *p*-toluenesulfonic acid (Kumar et al. 2014), natural clay (Bandgar et al. 1999),

L-proline (Karade et al. 2007), NaOH (Zhang et al. 2004), piperidine (Volmajer et al. 2005), $MgFe_2O_4$ nanoparticles (Ghomi et al. 2018) (**Scheme 3.1, A**). However, most of these methods have their own merits and demerits.

Recently, the oxidative functionalization of methyl arenes has emerged as an efficient and alternative approach to access a wide range of functional groups including amides, esters, ketones, nitriles etc. (Vanjari et al. 2015, Zhou et al. 2009). Ready availability, high stability and easy handling are the major advantages of methyl arenes when compared to its aldehydes analogues. Despite the potential, so far no method has been developed for the oxidative synthesis of coumarins from the stable *ortho*-hydroxy methylarenes (*i.e. o*-cresols) via direct sp^3 C-H bond functionalization reactions with active methylene compounds.

As a well-known oxidant, *tert*-butyl hydrogen peroxide (TBHP) has found wide applications in several oxidation reactions to generate C–C, C–N, C–O, C–S and N–N bonds (Sun et al. 2018, Zheng et al. 2015, Guntreddi et al. 2014, Sun et al. 2016, Yuan et al. 2014, Jiang et al. 2019, Yu et al. 2016, Yang et al. 2017, Wu et al. 2017, Kumar et al. 2019, Li et al. 2017, Hill et al. 1983). TBHP has attracted much attention because of its easy availability, cost-effectiveness, easy handling, etc. In this context, we have recently explored the TBHP promoted transamidation reactions (Mishra et al. 2019). In continuation, here we report the synthesis of 3-functionalized coumarins from *o*-cresols and

active methylene compounds using *tert*-butyl hydrogen peroxide (TBHP) as an oxidant under solvent free condition (**Scheme 3.1, B**).



Scheme 3.1: Previous & present method for the synthesis of coumarin.

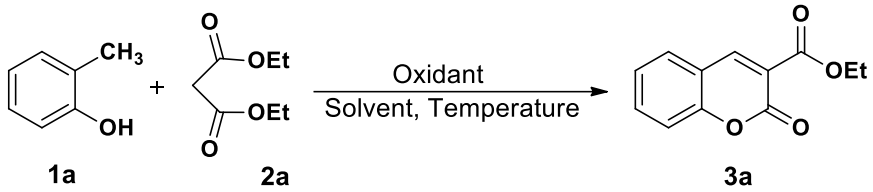
3.2 Results and Discussion

In order to optimize reaction conditions, *o*-cresol **1a** (1.0 mmol) and diethylmalonate **2a** (1.2 mmol) were chosen as the model substrates and subjected to the oxidative condensation reaction. The effect of different parameters including reaction medium, oxidant and its loading as well as temperature was examined on the model reaction. Initially, the condensation of *o*-cresol and diethylmalonate was performed using TBHP (5

equiv.) in different polar solvents like water, acetonitrile, 1,4-dioxane, dichloromethane, chloroform (**Table 3.1, entries 1-5**) and also in non-polar solvents like hexane, benzene (**Table 3.1, entries 6,7**) at its refluxed temperature. The reaction proceeded smoothly in all the solvents tested in this study and gave the desired product **3a** in 40-75% yield.

In order to improve the yield of the product in a greener way, we have switched to the solvent free condition. The model reaction was investigated under solvent free condition using TBHP (5 equiv.) as an oxidant at different temperatures. No product was obtained at room temperature (25 °C). Hence, the reaction was carried out at higher temperature 50-100 °C (**Table 3.1, entries 8-12**). At 50 and 70 °C, the desired product **3a** was obtained in 45, 70% yield while at 80 °C the reaction provides 91% yield (**Table 3.1, entry 11**). Any further increase in reaction temperature did not show significant change on reaction time and yield of the product (**Table 3.1, entry 12**). It is important to mention that the reaction temperature affect the yield of the product which is possibly due to the different rate of radical generation via thermal breakdown. Further, we have investigated the reaction progress by varying amount of TBHP from 2-6 equiv. (**Table 3.1, entries 11, 13-16**). The best result was obtained with 4 equiv. of TBHP (**Table 3.1, entry 14**) which provides the desired product in 91% yield within 2.5 h.

Table 3.1: Optimization of solvents, oxidants and temperature[a]



1a 2a 3a

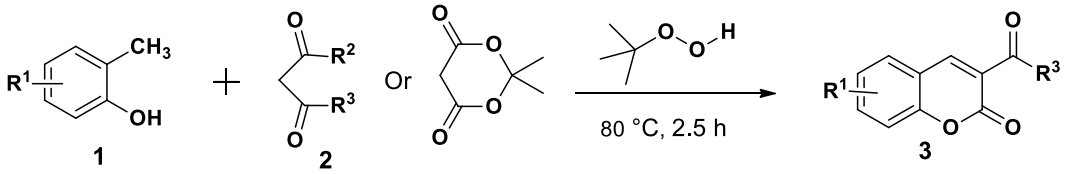
Entry	Solvent	Oxidant (Equiv.)	Temperature (°C)	Time (h)	Yield[b] (%)
1	Water	TBHP (5)	Reflux	5	75
2	Acetonitrile	TBHP (5)	Reflux	7	69
3	1,4-dioxane	TBHP (5)	Reflux	6	65
4	Dichloromethane	TBHP (5)	Reflux	5	40
5	Chloroform	TBHP (5)	Reflux	6	67
6	Hexane	TBHP (5)	Reflux	6	65
7	Benzene	TBHP (5)	Reflux	7	66
8	Solvent free[c]	TBHP (5)	rt	7	NR
9	Solvent free	TBHP (5)	50	6	45
10	Solvent free	TBHP (5)	70	4	70
11	Solvent free	TBHP(5)	80	2.5	91
12	Solvent free	TBHP (5)	100	2.5	91
13	Solvent free	TBHP (6)	80	2.5	91
14	**Solvent free**	**TBHP (4)**	**80**	**2.5**	**91**
15	Solvent free	TBHP (3)	80	2.5	50
16	Solvent free	TBHP (2)	80	2.5	20
17	Solvent free	CAN (4)	80	2.5	NR
18	Solvent free	Oxone (4)	80	2.5	NR
19	Solvent free	DDQ (4)	80	2.5	NR
20	Solvent free	Chloranil (4)	80	2.5	NR

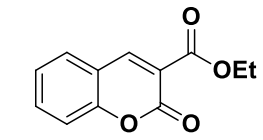
[a] **Reaction Condition:** *o*-cresol (1.0 mmol), diethylmalonate (1.2 mmol) and oxidizing agent. [b] Isolated yield. [c] No additional solvent.

The model reaction of *o*-cresol and diethylmalonate was also investigated with different organic/inorganic oxidizing agents such as ceric ammonium nitrate (CAN), oxone, DDQ and chloranil under solvent free condition at 80 °C (**Table 3.1, entries 17-20**), but not a trace of the product was obtained. Formation of model compound **3a** is confirmed by the ^{1}H & ^{13}C NMR spectroscopy (**Figure 3.2 and 3.3**).

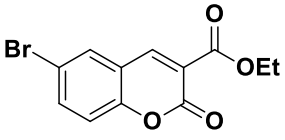
With these optimized conditions, the substrate scope of this methodology was explored with diethylmalonate and different substituted *o*-cresol. *o*-Cresol with different electron donating *viz.* ethyl 8-methoxy-2-oxo-2H-chromene-3-carboxylate (**3d**), ethyl 7-(diethylamino)-2-oxo-2H-chromene-3-carboxylate (**3e**) (**Table 3.2**, entries **3d** and **3e**) as well as electron withdrawing groups *viz.* ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (**3b**), ethyl 6-chloro-2-oxo-2H-chromene-3-carboxylate (**3c**), (**Table 3.2,** entries **3b** and **3c**) undergo subsequent transformation smoothly in good yields (87-90%).We have also tested the other active methylene compounds like dimethylmalonate, ethyl acetoacetate, meldrum acid. To our delight, these substrates participated efficiently in the oxidative coupling reaction and provided the desired products in good yields (**Table 3.2**, entries **3f-3s**) *viz.* 3-acetyl-2H-chromen-2-one (**3f**), 3-acetyl-6-bromo-2H-chromen-2-one (**3g**), 3-acetyl-6-chloro-2H-chromen-2-one (**3h**), 3-acetyl-8-methoxy-2H-chromen-2-one (**3i**), 3-acetyl-7-(diethylamino)-2H-chromen-2-one (**3j**), 2-oxo-2H-chromene-3-carboxylic acid (**3k**),

Table 3.2: TBHP mediated synthesis of coumarin under solvent free condition[a]

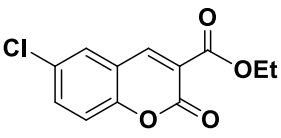




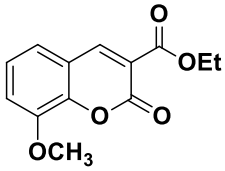
3a: 91%[b]



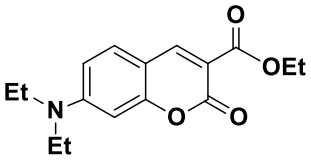
3b: 90%



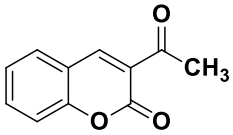
3c: 89%



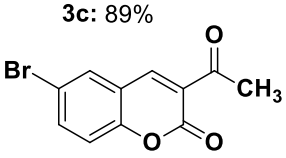
3d: 88%



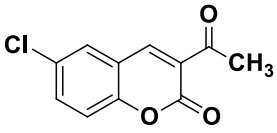
3e: 87%



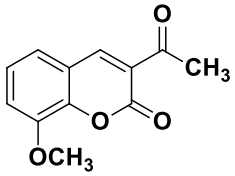
3f: 90%



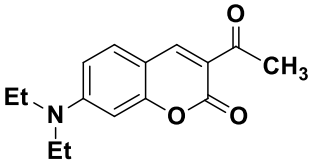
3g: 90%



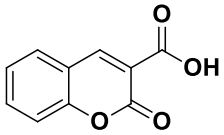
3h: 89%



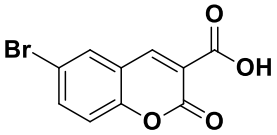
3i: 86%



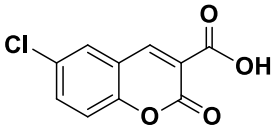
3j: 80%



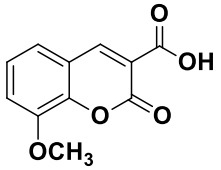
3k: 90%



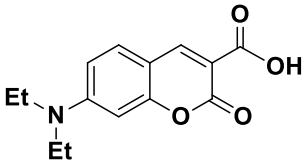
3l: 89%



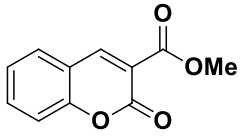
3m: 88%



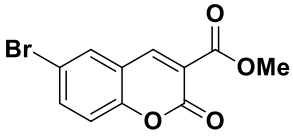
3n: 87%



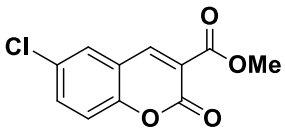
3o: 82%



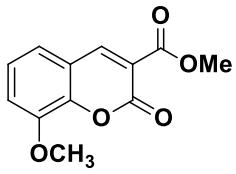
3p: 90%



3q: 89%



3r: 87%



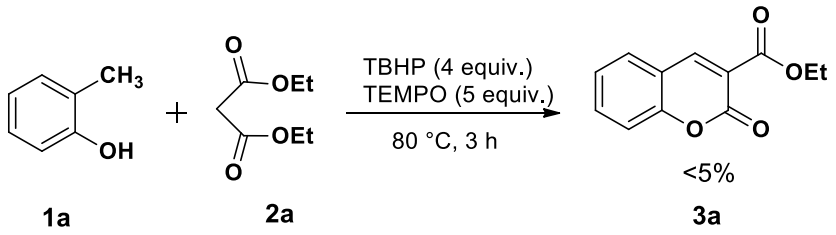
3s: 87%

[a]**Reaction conditions**: *o*-cresol derivatives (1.0 mmol), active methylene compounds (1.2 mmol), TBHP (4 equiv.) were heated at 80 °C. [b]Isolated yield

6-bromo-2-oxo-2H-chromene-3-carboxylic acid (**3l**), 6-chloro-2-oxo-2H-chromene-3-carboxylic acid (**3m**), 8-methoxy-2-oxo-2H-chromene-3-carboxylic acid (**3n**), 7-(diethylamino)-2-oxo-2H-chromene-3-carboxylic acid (**3o**), methyl 2-oxo-2H-chromene-3-carboxylate (**3p**), methyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (**3q**), methyl 6-chloro-2-oxo-2H-chromene-3-carboxylate (**3r**) and methyl 8-methoxy-2-oxo-2H-chromene-3-carboxylate (**3s**).

3.3 Mechanistic Study & Controlled Experiments

In order to establish the reaction mechanism, a controlled experiment was performed with radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (**Scheme 3.2**) under the same optimized reaction conditions with 5 equiv. of TEMPO, less than 5% of the desired product (**3a**) was obtained. This observation shows that the reaction proceeds through radical pathway.

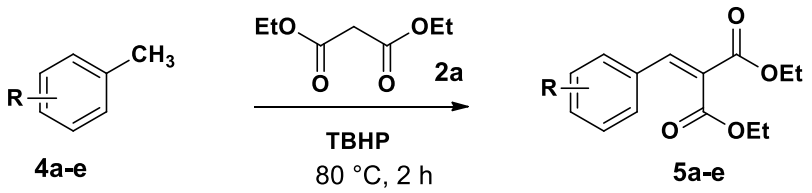


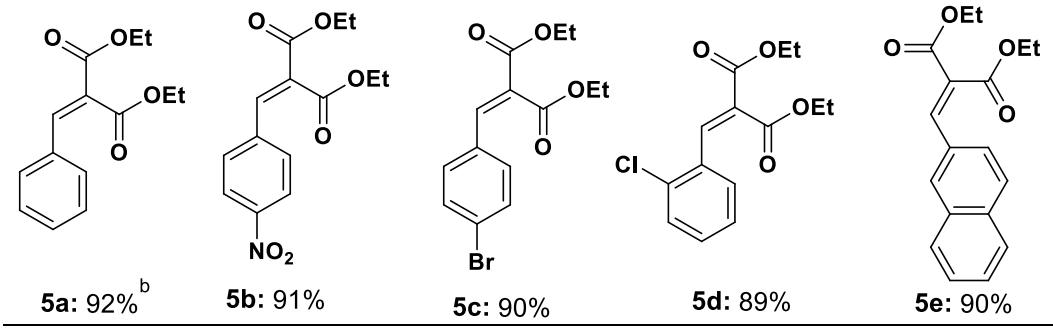
Scheme 3.2: Control experiment with TEMPO.

Next control reaction was performed between toluene (**4a**) and diethylmalonate (**2a**) in the presence of TBHP under optimized reaction conditions. The desired Knoevenagel

product **5a** was obtained in 92% yield. In fact, not only toluene but also many other methyl arenes underwent oxidative coupling with diethylmalonate (**2a**) and provided Knoevenagel products (**Table 3.3**, entries **5b**-**5e**) *viz.* diethyl 2-benzylidenemalonate (**5a**), diethyl 2-(4-nitrobenzylidene)malonate (**5b**), diethyl 2-(4-bromobenzylidene)malonate (**5c**), diethyl 2-(2-chlorobenzylidene)malonate (**5d**) and diethyl 2-(naphthalen-2-ylmethylene)malonate (**5e**) in good yields. It is clear from above observation that initially toluene oxidizes into benzaldehyde and then it reacts with diethylmalonate to give Knoevenagel product.

Table 3.3: Conversion of toluene derivatives into corresponding Knoevenagel products[a]

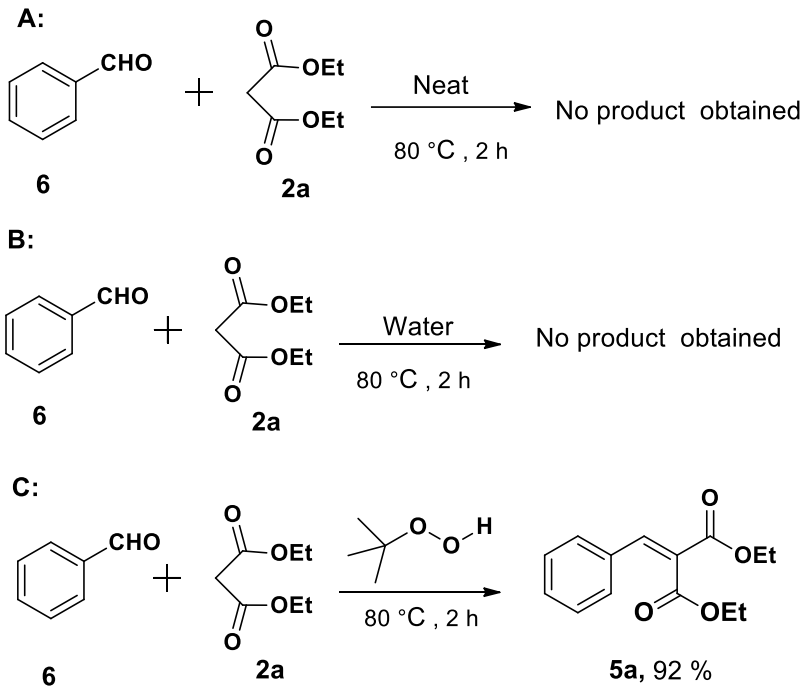




[a]**Reaction conditions**: Toluene derivative (1.0 mmol) active methylene (1.2 mmol) TBHP (4 equiv.) were heated at 80 °C. [b] Isolated yield**.**

To investigate the role of TBHP in Knoevenagel condensation of benzaldehyde (6) and diethylmalonate was performed in the absence of TBHP under solvent free condition at

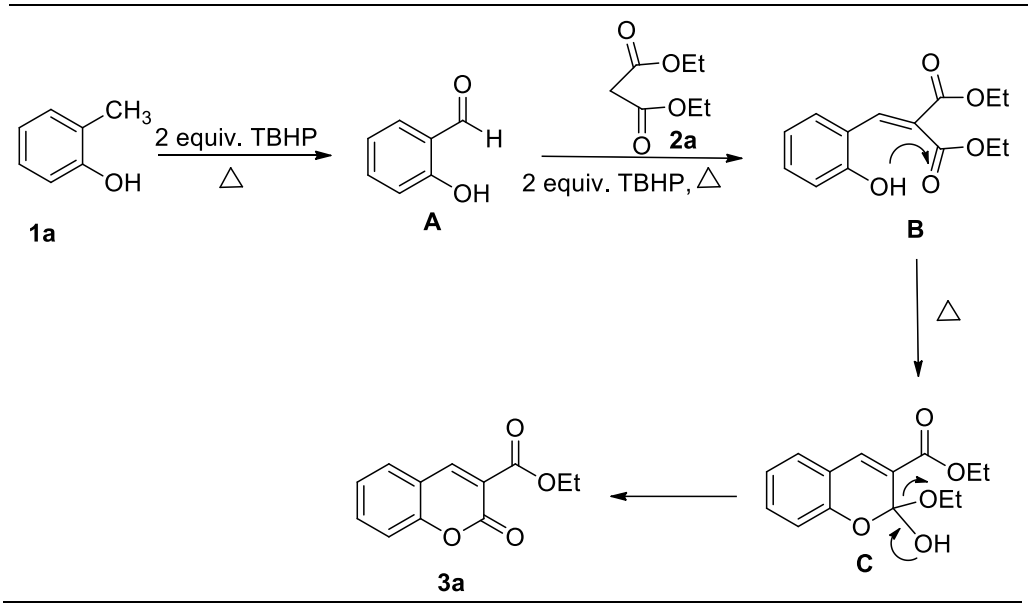
80 °C (**Scheme 3.2, A**). This reaction did not provide the desired product even after 2 h. Further, the reaction was performed only in water in the absence of TBHP to make sure that the reaction is not promoted by water. No product was obtained while starting material was remained as such (**Scheme 3.2, B**) which indicates that water did not take part in Knoevenagel condensation. However, when the same reaction was carried out in the presence of TBHP desired product was obtained in good yield (**Scheme 3.3, C**). These results indicate that TBHP took part not only in the oxidation of methyl arene to aldehyde but also in Knoevenagel condensation reaction.



Scheme 3.3: Controlled experiment with and without TBHP.

3.4 Plausible Reaction Mechanism

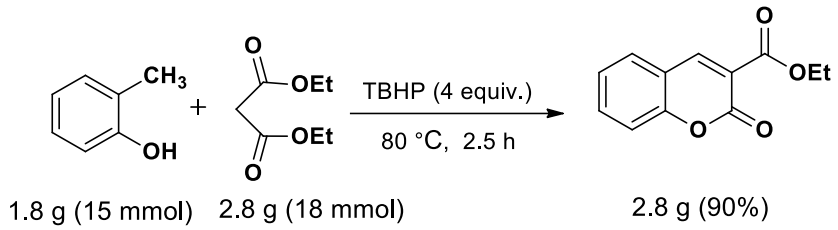
Based on the controlled experiments, a plausible reaction mechanism is proposed in Scheme **3.4.** In the presence of TBHP, *o*-cresol oxidizes to salicylaldehyde (**A**) (Rao et al. 2009, Rout et al. 2014) which reacts with active methylene compound (**2a**) giving the Knoevenagel product (**B**) which rearranges to give final product **3a**.



Scheme 3.4: Plausible reaction mechanism.

3.5 Scalability of the Protocol

To validate the prospective synthetic application of this process the synthesis of **3a** was carried out on gram scale *o*-cresol (**1a**) (1.8 g, 15.0 mmol), diethyl malonate (**2a**) (2.8 g, 18.0 mmol) and TBHP (4 equiv.), which gave the desired Product in good yield of 2.8 g (90%) under the optimum condition (**Scheme 3.5**).



Scheme 3.5: Gram scale synthesis of coumarin.

3.6 Experimental Section

3.6.1 General procedure for the synthesis of coumarin derivatives (3a-s)

o-Cresol (1.0 mmol), active methylene compound (1.2 mmol) and TBHP (70% aq., 4 equiv.) was stirred at 80 °C. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and subjected for silica gel (60-120 mesh) column chromatography purification (SiO_2: hexane/ethyl acetate) to obtain the pure desired products.

3.6.2 General procedure for the synthesis of 5a-e

Toluene (1.0 mmol), active methylene compound (1.2 mmol) and TBHP (70% aq., 4 equiv.) was stirred at 80 °C. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and

subjected for silica gel (60-120 mesh) column chromatography purification (SiO_2: hexane/ethyl acetate) to obtain the desired products.

3.6.3 Procedure for control experiment with TEMPO

o-Cresol (**1a**) (1.0 mmol), active methylene compound (1.2 mmol) and TEMPO (5.0 mmol) was stirred at 80 °C for 30 min to which 4 equiv. of *tert*-butyl hydrogen peroxide (TBHP) was added. The reaction was further stirred for 180 min and diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and subjected for silica gel (60-120 mesh) column chromatography purification (SiO_2: hexane:EtOAc) to obtain **3a**.

3.6.4 Gram-scale procedure for the synthesis of coumarin derivatives

o-Cresol (**1a**) (1.8 g, 15.0 mmol), diethyl malonate (**2a**) (2.8 g. 18.0 mmol) and TBHP (70% aq., 4 equiv.) was stirred at 80 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, it was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), the solvent was evaporated under vacuum and the product was purified by column chromatography on silica gel (60-120 mesh, hexane/ethyl acetate) gave the desired products (**3a**) in 90% yield (2.85 g).

3.7 Analytical Data

3.7.1 Ethyl 2-oxo-2H-chromene-3-carboxylate (3a): White crystalline solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 198 mg (91%); m.p. 90-91 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.46 (s, 1H), 7.57 (dd, 2H), 7.27 (t, 2H), 4.34 (q, 2H), 1.34 (t, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.1, 156.8, 155.2, 148.7, 134.4, 129.6, 124.9, 118.3, 117.9, 116.7, 62.0, 14.3; Anal. calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.00; H 4.59.

3.7.2 Ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (3b): White crystalline solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 266 mg (90%); m.p. 162-163 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 8.01 – 7.44 (m, 2H), 7.27 (d, 1H), 4.43 (q, 2H), 1.42 (t, , 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 162.7, 156.1, 154.0, 147.2, 137.0, 131.6, 119.5, 119.4, 118.6, 117.4, 62.3, 14.3; Anal. calcd for $C_{12}H_9BrO_4$: C, 48.51. H, 3.05; Found: C, 48.47; H, 3.03.

3.7.3 Ethyl 6-chloro-2-oxo-2H-chromene-3-carboxylate (3c): White crystalline solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 224 mg (89%); m.p. 174-176 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 7.59 (d, 2H), 7.33 (t, 1H), 4.42 (q, 2H), 1.41 (t, 3H); **^{13}C**

NMR (126 MHz, $CDCl_3$) δ (ppm): 162.7, 156.1, 153.5, 147.2, 134.2, 130.2, 128.5, 119.6, 118.9, 118.3, 62.3, 14.3; Anal. calcd for $C_{12}H_9ClO_4$: C, 57.05, H, 3.59; Found: C, 56.99, H, 3.57.

3.7.4 Ethyl 8-methoxy-2-oxo-2H-chromene-3-carboxylate (3d): Yellow crystalline solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 218 mg (88%); m.p. 89-90 ^oC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.43 (s, 1H), 7.19 (d, 1H), 7.11 (d, 1H), 7.10 (s, 1H), 4.33 (q, 2H), 3.90 (s, 3H), 1.34 (t, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.2, 156.2, 148.9, 147.1, 145.0, 124.8, 120.7, 118.5, 115.9, 62.1, 56.4, 14.3; Anal. calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.85; H, 4.85.

3.7.5 Ethyl 7-(diethylamino)-2-oxo-2H-chromene-3-carboxylate (3e): Yellowish solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (60:40); yield 251 mg (87%); m.p. 76 ^oC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.44 (s, 1H), 7.34 (d, 1H), 6.60 (dd, 1H), 6.43 (d, 1H), 3.89 (s, 2H), 3.43 (q, 4H), 1.22 (t, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 165.0, 158.5, 158.4, 153.0, 149.7, 131.2, 109.6, 108.3, 107.7, 96.6, 52.3, 45.1, 12.4; Anal. calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.37; H, 6.60; N, 4.81.

3.7.6. 3-Acetyl-2H-chromen-2-one (3f): Yellowish solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 169 (90%); m.p. 120-122 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 7.90 – 7.42 (m, 2H), 7.35 – 7.20 (m, 2H), 2.67 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 195.6, 159.4, 155.4, 147.6, 134.5, 130.3, 125.1, 124.6, 118.4, 116.8, 30.7; Anal. calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.29. Found: C, 70.16; H, 4.26.

3.7.7. 3-Acetyl-6-bromo-2H-chromen-2-one (3g): White solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 239 mg (90 %); m.p. 231-232 ^{o}C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 8.60 (s, 1H), 8.21 (s, 1H), 7.89 (d, 1H), 7.44 (d, 1H), 2.59 (s, 3H); **^{13}C NMR** (126 MHz, DMSO) δ (ppm): 195.4, 158.4, 154.1, 146.1, 137.1, 133.1, 125.9, 120.5, 118.8, 116.8, 30.4.; Anal. calcd for $C_{11}H_7BrO_3$: C, 49.47; H, 2.64. Found: C, 49.41; H, 2.62.

3.7.8 3-Acetyl-6-chloro-2H-chromen-2-one (3h): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 197 mg (89%); m.p. 210-211 ^{o}C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 8.59 (s, 1H), 8.06 (s, 1H), 7.77 (s, 1H), 7.50 (s, 1H), 2.57 (s, 3H); **^{13}C NMR** (126 MHz, DMSO) δ (ppm): 195.1, 158.1, 153.3, 145.8, 133.9, 129.6, 128.6, 125.5, 119.6, 118.2, 30.1; Anal. calcd for $C_{11}H_7ClO_3$: C, 59.35; H, 3.17. Found: C, 59.30; H, 3.13.

3.7.9 3-Acetyl-8-methoxy-2H-chromen-2-one (3i): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 187 mg (86%); m.p. 162-163 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.41 (s, 1H), 7.33 – 6.72 (m, 3H), 3.92 (s, 3H), 2.66 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 195.7, 158.8, 147.8, 147.1, 145.1, 124.9, 124.7, 121.4, 118.9, 115.9, 56.4, 30.7; Anal. calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.0; H, 4.59.

3.7.10 3-Acetyl-7-(diethylamino)-2H-chromen-2-one (3j): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (60:40); yield 207 mg (80%); m.p. 151-153 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.41 (s, 1H), 7.37 (d, 1H), 6.60 (d, 1H), 6.44 (s, 1H), 3.44 (dd, 4H), 2.65 (s, 3H), 1.22 (t, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 195.8, 161.0, 158.8, 153.1, 147.9, 132.0, 116.1, 109.9, 108.2, 96.6, 45.2, 30.7, 12.5; Anal. calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.42; H, 6.59; N, 5.35.

3.7.11 2-Oxo-2H-chromene-3-carboxylic acid (3k): Yellow crystalline solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); m.p. 189-190 °C; yield 171 mg (90%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 11.40 (s, 1H), 8.72 (s, 1H), 7.38 (dd, 2H), 7.06 – 6.95 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 164.8, 159.9, 133.6, 132.7, 119.8, 117.4, 117.3; Anal. calcd for $C_{10}H_6O_4$: C, 63.16; H, 3.18. Found: C, 63.09; H, 3.15.

3.7.12 6-Bromo-2-oxo-2H-chromene-3-carboxylic acid (3l): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 241 mg (89%); m.p. 197-199 °C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 11.14 (s, 1H), 8.94 (s, 1H), 7.90 (s, 1H), 7.54 (d, 1H), 6.95 (d, 1H); **^{13}C NMR** (126 MHz, DMSO) δ (ppm): 160.7, 159.9, 157.6, 142.1, 135.5, 132.0, 131.5, 131.0, 120.6, 118.95, 110.6; Anal. calcd for $C_{10}H_5BrO_4$: C, 44.64; H, 1.87. Found: C, 44.57; H, 1.84.

3.7.13 6-Chloro-2-oxo-2H-chromene-3-carboxylic acid (3m): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 197 mg (88%); m.p. 121-122 °C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 11.14 (s, 1H), 8.94 (s, 1H), 7.77 (s, 1H), 7.42 (d, 1H), 7.00 (d, 1H); **^{13}C NMR** (126 MHz, DMSO) δ (ppm): 164.1, 160.94, 157.3, 132.8, 128.7, 123.2, 120.0, 118.5; Anal. calcd for $C_{10}H_5ClO_4$: C, 53.48; H, 2.24. Found: C, 53.41; H, 2.22.

3.7.14 8-Methoxy-2-oxo-2H-chromene-3-carboxylic acid (3n): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 191 mg (87%); m.p. 218-220 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 11.56 (s, 1H), 8.69 (s, 1H), 7.00 (d, 2H), 6.92 (t, 1H), 3.93 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 164.9, 149.8, 148.4, 124.1, 119.5, 117.4, 115.2, 56.3; Anal. calcd for $C_{11}H_8O_5$: C, 60.00; H, 3.66. Found: C, 59.52; H, 3.63.

3.7.15 7-(Diethylamino)-2-oxo-2H-chromene-3-carboxylic acid (3o): Orange crystal; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (60:40); yield 214 mg (82%); m.p. 220-222 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 11.83 (s, 1H), 8.45 (s, 1H), 7.09 (d, 1H), 6.25 (d, 1H), 6.22 (s, 1H), 3.39 (q, 4H), 1.20 (t, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 161.5, 161.0, 151.3, 133.4, 107.0, 104.0, 97.9, 44.6, 12.8; Anal. calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.30; H, 5.76; N, 5.33.

3.7.16 Methyl 2-oxo-2H-chromene-3-carboxylate (3p): White solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 183 mg (90%); m.p. 116-117 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.53 (s, 1H), 7.63 – 7.58 (m, 2H), 7.31 (dd, 2H), 3.91 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.6, 156.7, 155.2, 149.2, 134.5, 129.6, 124.9, 117.8, 117.8, 116.7, 52.9; Anal. calcd for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 64.67; H, 3.93.

3.7.17 Methyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (3q): White solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 250 mg (89%); m.p. 183-184 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 7.73 (dd, 2H), 7.24 (d, 1H), 3.95 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.3, 156.0, 154.1, 147.6, 137.1, 131.7, 119.4, 119.2, 118.6, 117.5, 53.1; Anal. calcd for $C_{11}H_7BrO_4$: C, 46.67; H, 2.49. Found: C, 46.60, H, 2.47.

3.7.18 Methyl 6-chloro-2-oxo-2H-chromene-3-carboxylate (3r): White solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 207 mg (87%); m.p. 197-198 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 7.75 – 7.70 (m, 2H), 7.24 (d, 1H), 3.95 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.3, 156.0, 154.1, 147.6, 137.1, 131.7, 119.4, 119.2, 118.6, 117.5, 53.1; Anal. calcd for $C_{11}H_7ClO_4$: C, 55.37; H, 2.96. Found: C, 55.30; H, 2.94.

3.7.19 Methyl 8-methoxy-2-oxo-2H-chromene-3-carboxylate (3s): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 203 mg (87%); m.p. 123-124 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.50 (s, 1H), 7.26 – 7.21 (m, 1H), 7.17 (s, 1H), 7.15 (d, 1H), 3.94 (s, 3H), 3.91 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.6, 156.1, 149.3, 147.0, 144.8, 124.8, 120.6, 118.3, 118.0, 115.9, 56.3, 52.8; Anal. calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.47; H, 4.27.

3.7.20 Diethyl 2-benzylidenemalonate (5a): Yellow liquid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5); yield 92%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.73 (s, 1H), 7.44 (s, 2H), 7.38 (s, 2H), 4.33 (q, 2H), 4.29 (q, 2H), 1.33 (t, 3H), 1.28 (t, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 166.8, 164.2, 142.2, 133.0, 130.6, 129.5, 128.9, 126.4, 61.8, 61.7, 14.2, 13.9; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.68; H, 6.48.

3.7.21 Diethyl 2-(4-nitrobenzylidene)malonate (5b): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5): yield 91%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.64 (s, 1H), 7.50 (d, 2H), 7.31 (d, 2H), 4.31 (dd, 4H), 1.30 (dd, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 166.5, 164.0, 140.8, 132.1, 131.9, 130.9, 127.0, 125.1, 61.9, 61.8, 14.2, 14.0; Anal. calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.28; H, 5.13; N, 4.76.

3.7.22 Diethyl 2-(4-bromobenzylidene)malonate (5c): Yellow liquid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5); yield 90%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.24 – 8.21 (m, 2H), 7.75 (s, 1H), 7.60 (d, 2H), 4.33 (q, 4H), 1.34 (t, 3H), 1.28 (t, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 165.7, 163.4, 148.5, 139.3, 139.2, 130.1, 130.1, 124.0, 62.3, 62.2, 14.2, 14.0; Anal. calcd for $C_{14}H_{15}BrO_4$: C, 51.40; H, 4.62. Found: C, 51.32; H, 4.59.

3.7.23 Diethyl 2-(2-chlorobenzylidene)malonate (5d): Yellow liquid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5); yield 89%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.02 (s, 1H), 7.44 – 7.41 (m, 2H), 7.31 (t, 1H), 7.23 (d, 1H), 4.24(q, 2H), 4.32 (q, 2H), 1.34 (t, 3H)), 1.18 (t, 3H); ^{13}C **NMR** (126 MHz, $CDCl_3$) δ (ppm): 165.9, 163.7, 139.3, 134.7, 132.1, 131.2, 129.9, 129.3, 128.9, 126.9, 61.9, 61.7, 14.2, 13.9; Anal. calcd for $C_{14}H_{15}ClO_4$: C, 59.48; H, 5.35. Found: C, 59.40; H, 5.31.

3.7.24 Diethyl 2-(naphthalen-2-ylmethylene)malonate (5e): Brown liquid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5); yield 90%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.91 (s, 1H), 7.86 (s, 1H), 7.77 (t, 3H), 7.48 (dd, 2H), 4.34 (q, 2H), 4.29 (q, 2H), 1.31 (t, 3H), 1.26 (t, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 166.8, 164.2, 142.2, 134.1, 133.0, 130.9, 130.4, 128.7, 128.5, 127.7, 127.7, 126.8, 126.3, 125.3, 61.8, 61.7, 14.2, 14.0; Anal. calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.39; H, 6.05.

3.8 Spectral Data of Synthesized Products

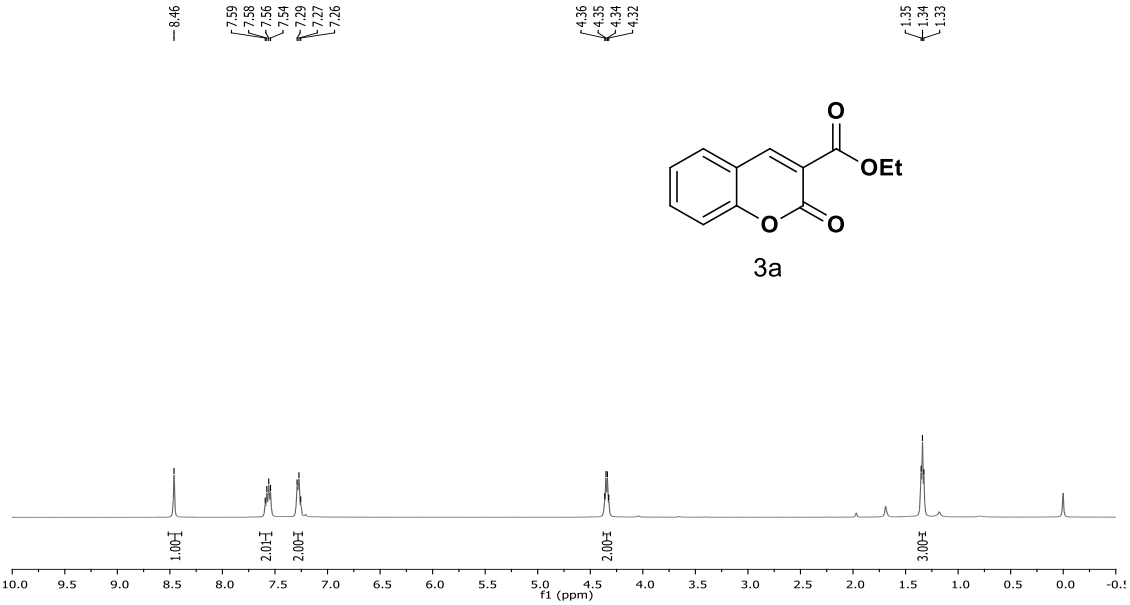


Figure 3.2: ^{1}H NMR spectrum of coumarin (**3a**).

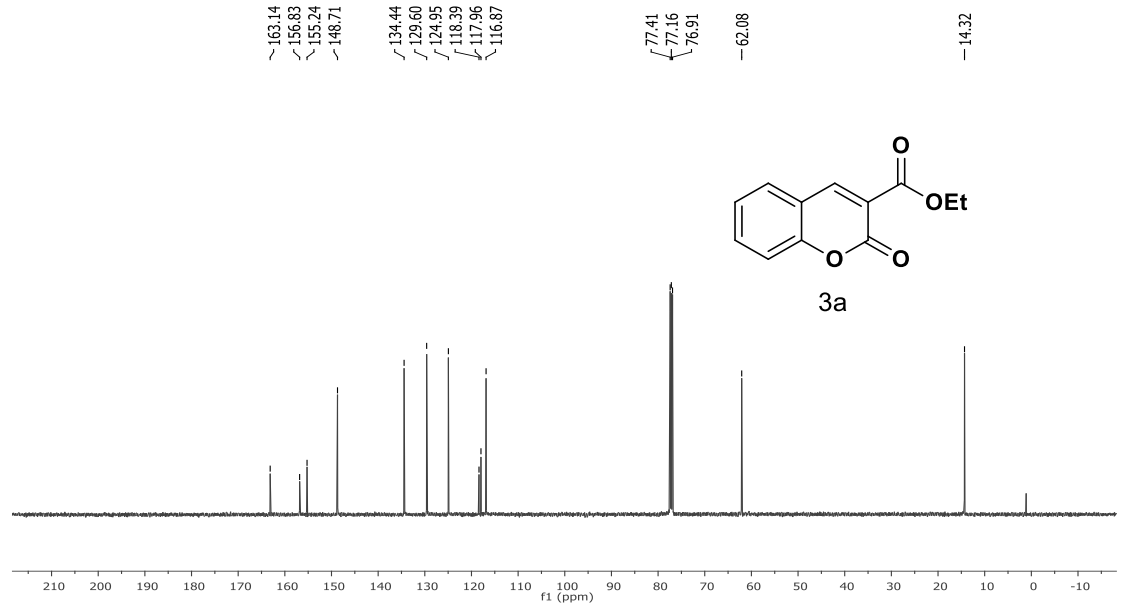


Figure 3.3: ^{13}C NMR spectrum of coumarin (**3a**).

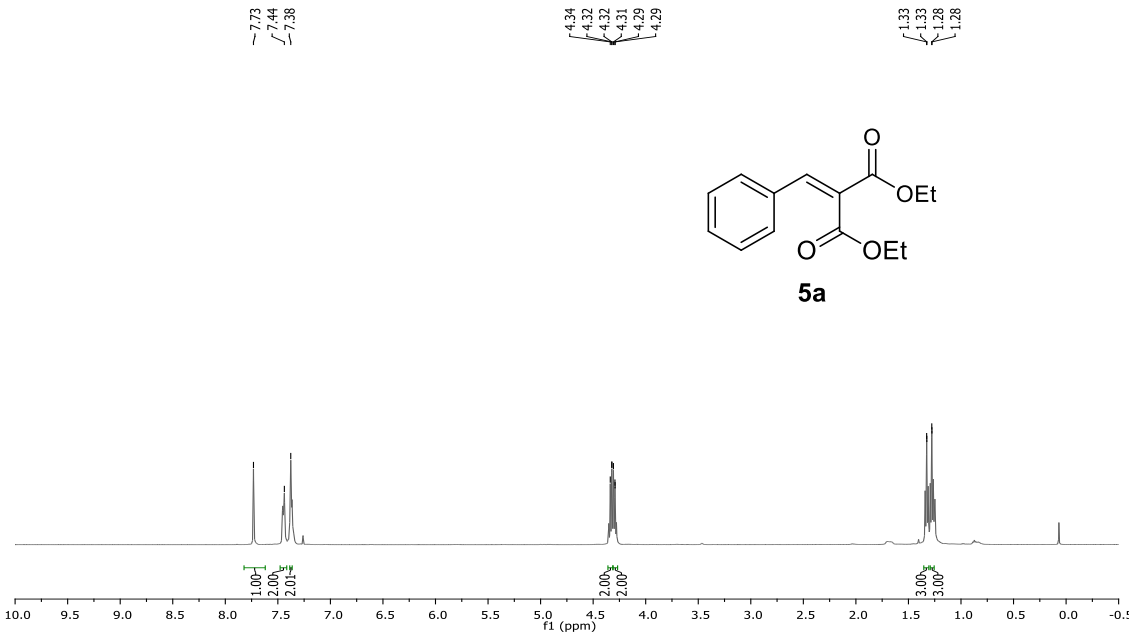


Figure 3.4: ^{1}H NMR spectrum of **5a**.

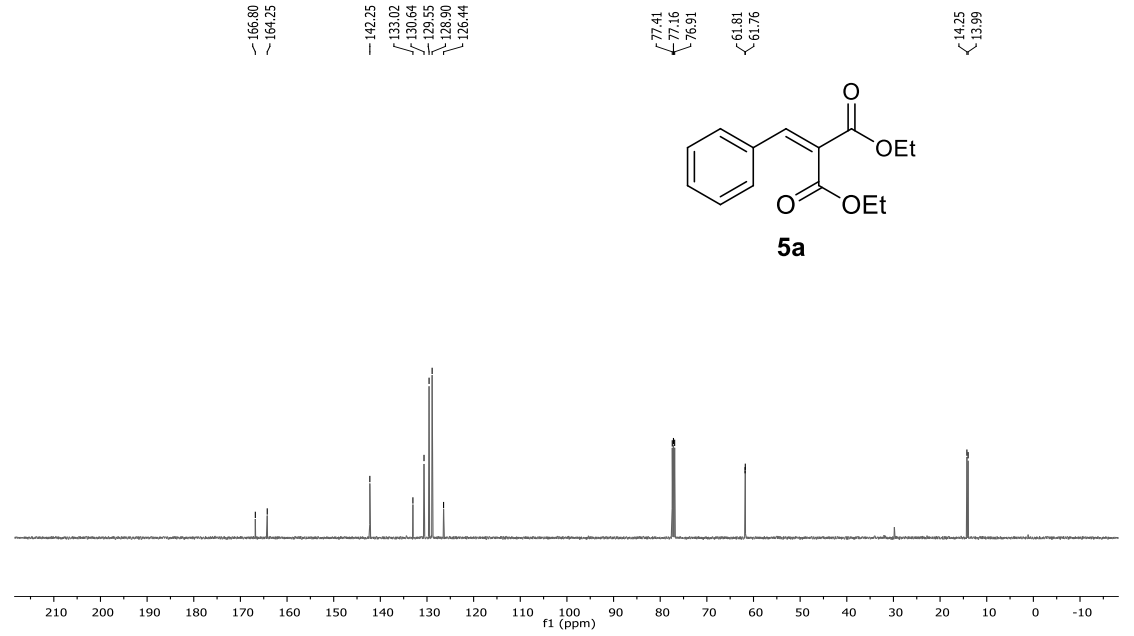


Figure 3.5: ^{13}C NMR spectrum of **5a**.

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CHAPTER 4

Development of a Scalable Route for the Synthesis of Imidazo[1,2-a]pyridines under Metal and Solvent Free Conditions

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4.1 Introduction

In the past decade, tremendous efforts have been made towards the synthesis of bioactive heterocyclic molecules and natural products through direct C–C, C–N, C–S and C–O etc. bonds construction by C–H bond functionalization (Pericherla et al. 2013, Chen et al. 2009, Dangel et al. 2002). Nitrogen containing bridgehead heterocyclic compounds like imidazo[1,2-a]pyridines and imidazo[2,1-b]thiazoles are the most imperative class of naturally occurring as well as synthetic compounds with several activities, present in numerous drugs and organic functional materials (Bhagat et al. 2017, Rupert et al. 2003). Out of these compounds, imidazo[1,2-a]pyridines have been extensively studied, presenting a remarkable spectrum of major biological activities such as antipyretic (Almirante et al. 1965), antiviral (Elhakmaoui et al. 1994), antiulcer (Starrett et al. 1989), anticancer (Hamdouchi et al. 1999), antibacterial (Byth et al. 2004) and anti-inflammatory (Lacerda et al. 2009) properties. It also function as nonpeptide B_2 receptor antagonists (Abe et al. 1998), GABA and benzodiazepine receptor agonists (Humphries et al. 2006). These heterocycles are also present in clinical important medicines such as anti-HIV drug (GSK812397) (Boggs et al. 2009), alpidem (Jain et al. 2004), olprinone (Mizushige et al.

2002), zolpidem (Humphries et al. 2006) and zolimidine (Almirante et al. 1965) (**Figure 4.1**).

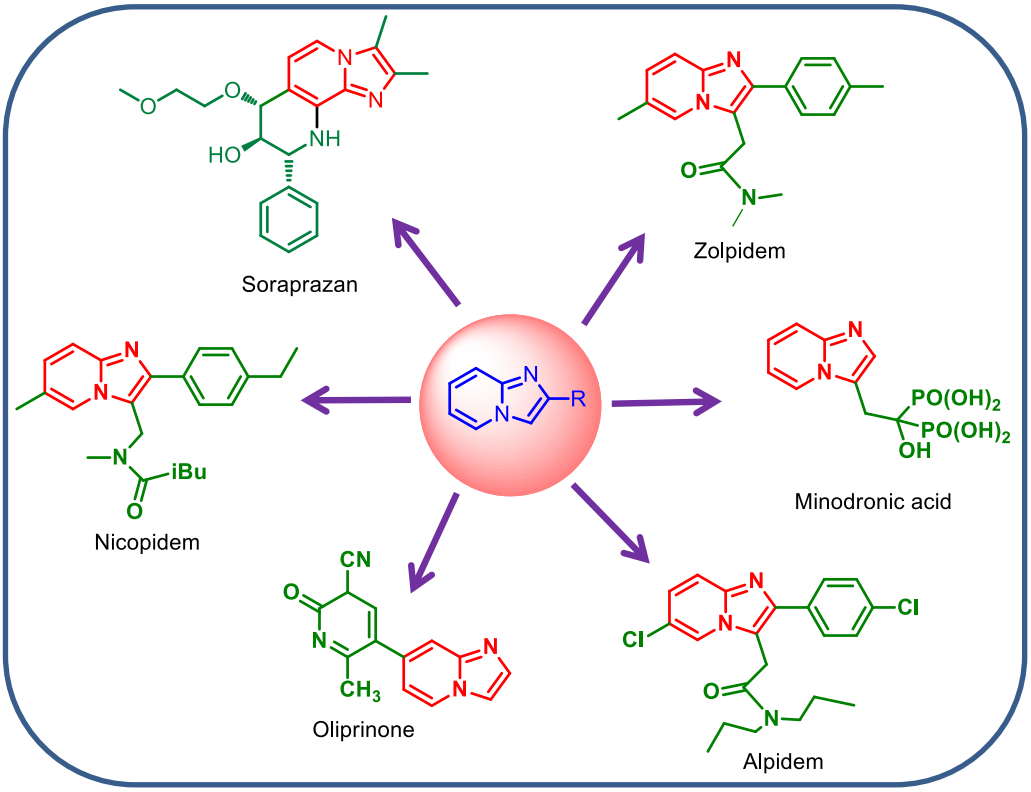


Figure 4.1: Drugs containing imidazo[1,2-a]pyridines moiety.

The usefulness of imidazo[1,2-a]pyridines has provoked great interest in the development of efficient methodologies to synthesize these bicyclic ring systems. Therefore, numerous methods have been established for the synthesis of imidazo[1,2-a]pyridines scaffold by the reaction of 2-aminopyridine with numerous substrates such as methyl aryl ketone (Meng et al. 2015), α-halo ketones (Zhu et al. 2009), alkynes derivatives (He et al. 2012) etc. These reactions generally perform in the presence of Lewis

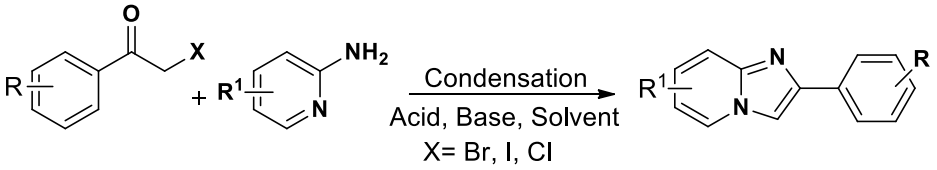
acid (Ge et al. 2013) or metal catalyst Cu (Cao et al. 2012, Pericherla et al. 2013), Fe (Santra et al. 2013), Zn (Liu et al. 2011), Ag (He et al. 2012) (**Scheme 4.1 A**). Stasyuk reported iodine mediated synthesis of imidazo[1,2-a]pyridine by the reaction of 2-aminopyridine and aryl methyl ketones in the presence of base (Stasyuk et al. 2012). Synthesis of imidazo[1,2-a]pyridine have been reported by multicomponent reaction of 2-aminopyridines, isonitriles and aldehydes also known as Groebke-Blackburn- Bienayme reaction (Palani et al. 2012, Masquelin et al. 2006, Khan et al. 2012, Chernyak et al. 2010, Lyon et al. 2004). These approaches are appropriate for a variety of substrates but have few shortcomings such as the use of metal catalyst, use of acid/base, low yield and tedious workup procedure.

Therefore, finding an eco-friendly, simple and practical approach for the synthesis of this important, pharmaceutically active scaffold from the readily available simple precursors is of great interest. Hence in the continuation of existing methods, we have developed a simple method for the synthesis of imidazo[1,2-a]pyridine by the C–H bond activation of methyl ketones, followed by the reaction with appropriate nucleophiles in the presence of KI/TBHP oxidative system under grinding condition (**Scheme 4.1, B**).

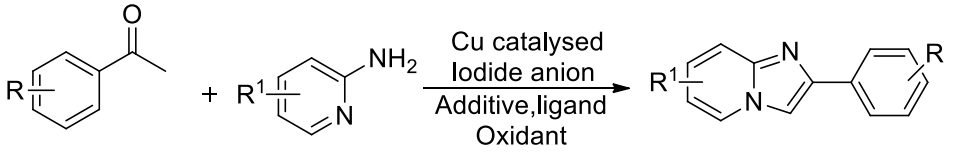
Potassium iodide is less toxic, cheaper and environment friendly as compared to molecular iodine. TBHP has attracted much attention because of their commercial availability inexpensive, easy handling, medium volatility and good solubility in common

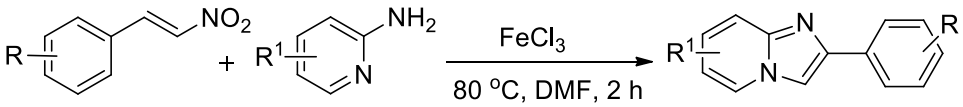
Previous Methods: A

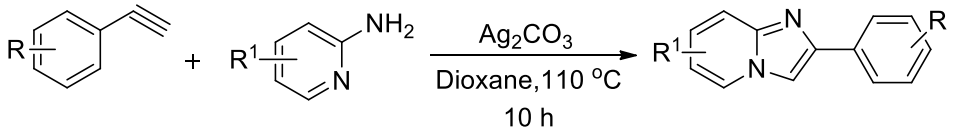
Traditional Method



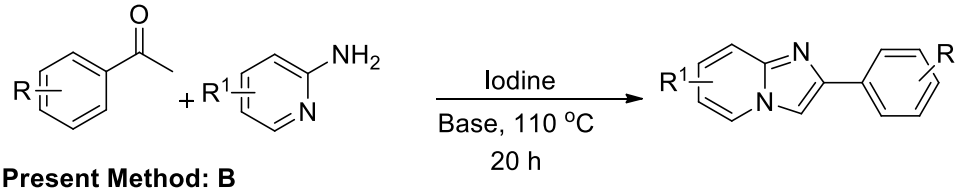
Metal catalysed synthesis:



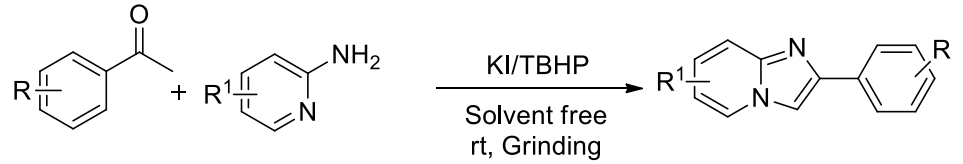




Metal free synthesis by using base:



Present Method: B



Scheme 4.1: Different approach for the synthesis of imidazo[1,2-a]pyridine.

solvents. The most important characteristic of this system (KI/TBHP) is that it has no metal and *tert*-butyl alcohol or water is the only by-product generated by this oxidant (Huang et al. 2014).This efficient catalytic system has attracted numerous chemists to synthesize many important compounds such as N-nitrosamines (Zhang et al. 2013), sulfonated oxindoles (Li et al. 2013), pyrrolo[2,1-a]isoquinolines (Huang et al. 2014), iodophenols (Reddy et al. 2010), polysubstituted furans (Li et al. 2016) and 2-aryl-2-oxazolines (Maheswari et al. 2014). In this context, here we report a simple and efficient KI/TBHP mediated synthesis of imidazo[1,2-a]pyridines from acetophenone derivatives and 2-amino pyridine derivatives for the first time.

Sustainable chemistry has become an important tool in the field of synthetic organic chemistry which comprises the synthesis of organic compounds in the absence of volatile organic solvent (VOCs) or in the solvent free condition. The avoidance of solvents in organic synthesis has become a major concern. Solvent-free, in solid state one-pot synthesis is effective toward organic conversion avoiding harmful volatile organic solvents (VOCs). Benefits associated without solvent or solid state synthesis are such as better worker's safety as well as favorable economics reaction conditions. Grindstone chemistry became an important tool in synthetic organic chemistry which reduces electrical energy consumption. The reactions under grinding are performed without solvent. In grinding methods, reaction starts with the transfer of the very small amount of mechanical energy which is generated

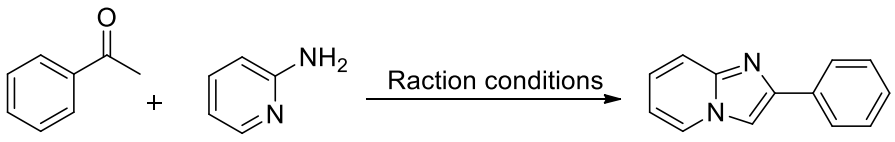
by grinding the reactants in a mortar and pestle and leads to the formation of the product. This solvent-free mechanically stimulated reaction helps in dropping the toxic waste by-products produced and therefore, becomes less damaging to the environment. Hence, we have chosen this technique because it is comparatively superior than existing methods since it has several advantages in terms of environmental impact, effectiveness, requires no special apparatus, cost of solvents & energy sources and easiness of the reaction protocol (Ando et al. 2011, Bose et al. 2004, Friscic et al. 2009, Yu et al. 2019, Nada et al. 2019, Wanyi et al. 2019).

4.2 Result and Discussion

Acetophenone (**1a**) and 2-aminopyridine (**2a**) was chosen as a model substrate with KI/TBHP for optimization of reaction conditions. The consequence of different parameters including solvents, reaction temperature, catalyst loading and reaction time was studied. The reaction performed in the presence of different polar (ethanol, methanol, water, DMSO, chloroform, 1,4-dioxane, THF) and non-polar solvents (toluene, benzene, xylene, hexane) under the stirring condition at room temperature and the results show that the reaction goes only in case of polar solvents with low yield. Out of all polar solvents, ethanol found the good in terms of product yield. In the case of non-polar solvents, no reaction occurs (**Table 4.1, entries 1-12**). Then to increase the product yield we turned our attention to the solvent-free condition at room temperature and the result shows that it gave

the 65% yield in 1h (**Table 4.1, entry 13**). After that the effect of temperature had been tested. By increasing temperature up to 80 ^{o}C under the stirring condition there is no considerable change in the product yield (**Table 4.1, entries 14, 15**). Grindstone chemistry that is useful for the synthesis of different compounds is considered as a green technique. Having this aspect in mind, reaction was performed under the grinding condition for a period in the presence of KI/TBHP. At first we have performed reaction for 5 min, gave the yield of 70% (**Table 4.1, entry 16**) and by increasing time to 8 min gave the yield of 80% (**Table 4.1, entry 17**). Surprisingly, we got the best result with 95% yield of product in 10 min (**Table 4.1, entry 18**). Further, on increasing time up to 15 min there is no considerable change in product yield (**Table 4.1, entry 19**). Further we optimized the amount of the catalyst and oxidant. We have started optimization of catalyst KI with 1 equiv. of TBHP, without KI no product was obtained (**Table 4.1, entry 20**). Next we increase the amount of KI by 0.2 equiv. we got 75% yield (**Table 4.1, entry 21**) of the product in 10 min. By increasing the amount of KI to 0.5 equiv. we got 95% yield in 10 min (**Table 4.1, entry 18**).

Table 4.1: Optimization of reaction condition for imidazo[1,2-a]pyridine[a]



1a **2a** **3aa**

Entry	Solvent	Catalyst/TBHP (Equiv.)	Reaction condition	Time (Min)	Yield[b] (%)
1	Ethanol	KI (0.5)/ 1	Stirring / rt	60	50
2	Methanol	KI (0.5)/ 1	Stirring / rt	60	50
3	Water	KI (0.5)/ 1	Stirring / rt	60	40
4	DMSO	KI (0.5)/ 1	Stirring / rt	60	20
5	1,4Dioxane	KI (0.5)/ 1	Stirring / rt	60	20
6	THF	KI (0.5)/ 1	Stirring / rt	60	15
7	Chloroform	KI (0.5)/ 1	Stirring / rt	60	10
8	DCM	KI (0.5)/ 1	Stirring / rt	60	12
9	Toluene	KI (0.5)/ 1	Stirring / rt	60	No reaction
10	Xylene	KI (0.5)/ 1	Stirring / rt	60	No reaction
11	Hexane	KI (0.5)/ 1	Stirring / rt	60	No reaction
12	Benzene	KI (0.5)/ 1	Stirring / rt	60	No reaction
13	Solvent free	KI (0.5)/ 1	Stirring/rt	60	65
14	Solvent free	KI (0.5)/ 1	50 ^{o}C	60	70
15	Solvent free	KI (0.5)/ 1	80 ^{o}C	60	70
16	Solvent free	KI (0.5)/ 1	Grinding/rt	5	70
17	Solvent free	KI (0.5)/ 1	Grinding/ rt	8	80
18	**Solvent free**	KI (0.5)/ 1	**Grinding/** rt	**10**	**95**
19	Solvent free	KI (0.5)/ 1	Grinding/ rt	15	96
20	Solvent free	KI (0.0)/1	Grinding/ rt	15	No reaction
21	Solvent free	KI (0.2)/1	Grinding/ rt	10	75
22	Solvent free	KI (1.0)/1	Grinding/ rt	15	95
23	Solvent free	KI (0.5)/0	Grinding/ rt	15	No reaction
24	Solvent free	KI (0.5)/ 2	Grinding/ rt	15	95
25	Solvent free	I_2 (0.5) /1	Grinding/ rt	25	80

[a] **Reaction Condition:** Acetophenone (1.0 mmol), 2-aminopyridine (1.2 mmol), KI and oxidant(TBHP)
[b] Isolated yield.

Further any increment in the amount of KI did not make any difference in the yield of the product (**Table 4.1, entry 22**). Next the amount of the oxidant TBHP was optimized with 0.5 equiv. of KI. First we performed reaction in the absence of TBHP no product was obtained (**Table 4.1, entry 23**) and the best result was obtained when the reaction performed with 1 equiv. of TBHP (**Table 4.1, entry 18**). Further any increment in the amount of TBHP did not affect the yield of product (**Table 4.1, entry 24**). These results show that the product was obtained only when the reaction was performed with the KI/TBHP catalytic system. We also performed reaction in the presence of iodine with TBHP and we got the 80% yield in 25 min (**Table 4.1, entry 25**). The results indicate that KI/TBHP found the best catalyst in the grinding protocol.

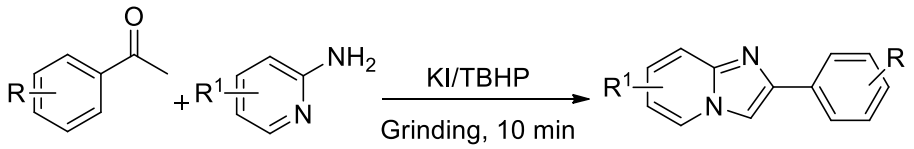
The results indicate that aryl methyl ketone (1.0 mmol), 2-amino pyridine (1.2 mmol) in the presence of KI/TBHP (0.5/1 equiv.) catalytic system under grinding was the optimum condition for the synthesis of imidazo[1,2-a]pyridine. Formation of model compound **3aa** is confirmed by the ^{1}H & ^{13}C NMR spectroscopy (**Figure 4.2 and 4.3**).

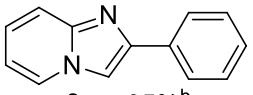
After optimization of reaction condition, the substrate scope has been examined for this transformation. Acetophenones with both the electron donating (methyl, methoxy) and electron withdrawing groups (nitro, fluoro, chloro, bromo) underwent the reation smoothly to give the desired products *viz.* 2-(p-tolyl)imidazo[1,2-a]pyridine (**3ba**), 2-(4-methoxyphenyl)imidazo [1,2-a]pyridine (**3ca**), 2-(3-nitrophenyl)imidazo[1,2-a]pyridine

(**3da**), 2-(4-chlorophenyl) imidazo[1,2-a]pyridine (**3ea**), 2-(4-bromophenyl)imidazo[1,2-a]pyridine (**3fa**), 2-(4-fluorophenyl)imidazo[1,2-a]pyridine (**3ga**) in good to excellent 90-95% yields (**Table 4.2**). 2-(Imidazo[1,2-a]pyridin-2-yl)phenol (**3ha**) which shows effectual excited state intramolecular proton transfer luminescence in the solid state was also fruitfully achieved under optimized reaction conditions with the yield of 89% (**Table 4.2**). It is worth mentioning that 2-(naphthalen-1-yl)imidazo[1,2-a]pyridine (**3la**) was obtained in good yield (**Table 4.2**). Further, to find the generality of the reaction, different heteroatom containing methyl ketones like 2-acetyl pyridine/2-acetyl thiophene were also explored and gave smoothly the corresponding products *viz.* 2-(pyridin-2-yl)imidazo[1,2-a]pyridine (**3ja**), 2-(thiophen-2-yl)imidazo[1,2-a]pyridine (**3ka**) in good yields (**Table 4.2**).

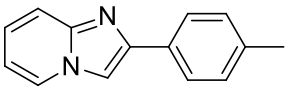
Having explored the scope of different acetophenones next we moved to investigate the scope of nucleophile *i.e.* 2-aminopyridine. To our satisfaction when alkyl and halogen substituted 2-aminopyridines were subjected to this reaction, gave the analogous products *viz.* 8-methyl-2-phenylimidazo[1,2-a]pyridine (**3ab**), 2-(4-methoxyphenyl)-8-methylimidazo[1,2-a]pyridine(**3cb**), 8-methyl-2-(3-nitrophenyl)imidazo[1,2-a]pyridine (**3db**), 2-(4-chlorophenyl)-8-methylimidazo[1,2-a]pyridine (**3eb**), 2-(4-bromophenyl)-8-methylimidazo[1,2-a]pyridine (**3fb**), 2-(4-fluorophenyl)-8-methylimidazo[1,2-a]pyridine (**3gb**), 2-(8-methylimidazo[1,2-a]pyridin-2-yl)phenol(**3hb**), 4-(8-methylimidazo[1,2-a]pyridin-2-yl)phenol (**3ib**),

Table 4.2: Substrate scope[a]

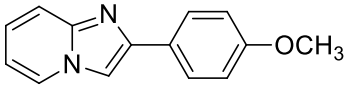




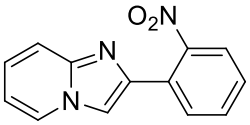
3aa: 95%[b]



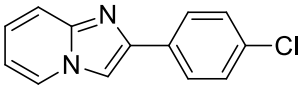
3ba: 93%



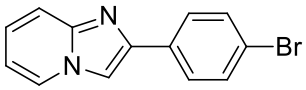
3ca: 94%



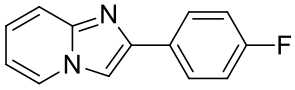
3da: 95%



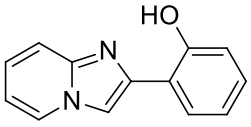
3ea: 92%



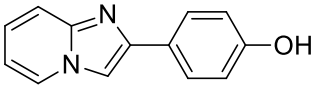
3fa: 90%



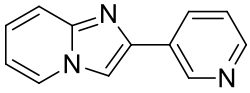
3ga: 94%



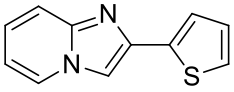
3ha: 89%



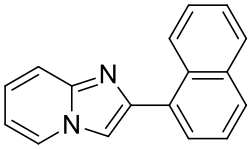
3ia: 88%



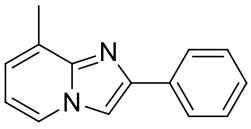
3ja: 85%



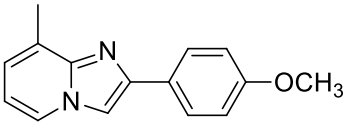
3ka: 92%



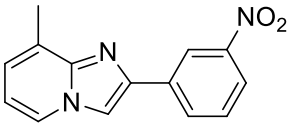
3la: 93%



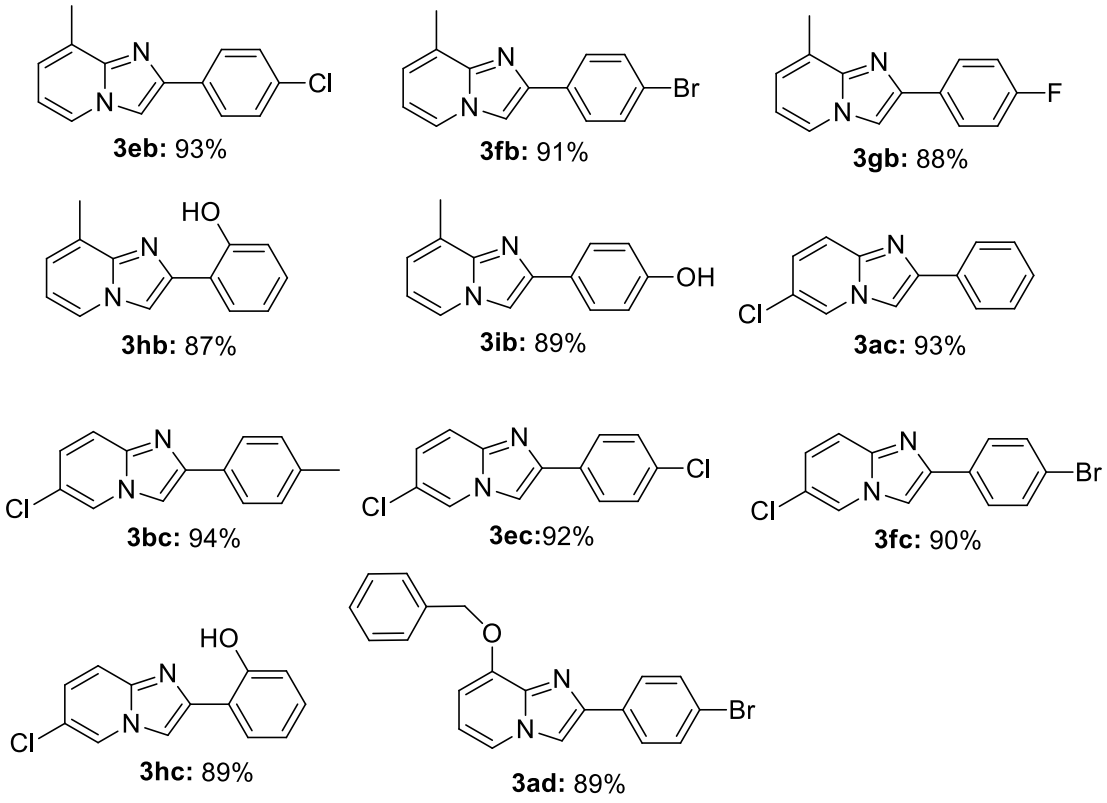
3ab: 91%



3cb:88%



3db:92%

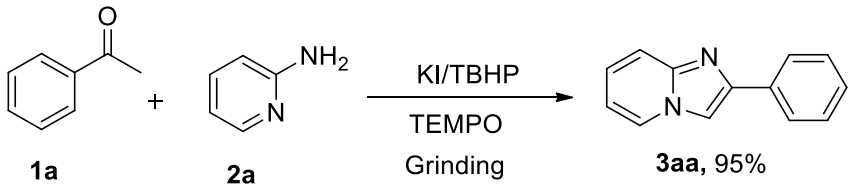


[a] **Reaction Condition:** Acetophenone (1.0 mmol), 2-aminopyridine (1.2 mmol), KI (0.5 equiv.) and oxidizing agent (1 equiv.). [b] Isolated yield.

6-chloro-2-phenylimidazo[1,2-a]pyridine (**3ac**), 6-chloro-2-(p-tolyl)imidazo[1,2-a]pyridine (**3bc**), 6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridine (**3ec**), 2-(4-bromophenyl)-6-chloroimidazo[1,2-a]pyridine (**3fc**), 2-(6-chloroimidazo[1,2-a]pyridin-2-yl)phenol (**3hc**), in good to excellent yield (**Table 4.2**). To our delight 2- aminopyridine containing benzyloxy substituent also gave the corresponding product *viz.* 8-(phenoxymethyl)-2-phenylimidazo[1,2-a]pyridine (**3ad**) in good yield. These results show that these nucleophiles did not affect the proficiency of the reaction (**Table 4.2**).

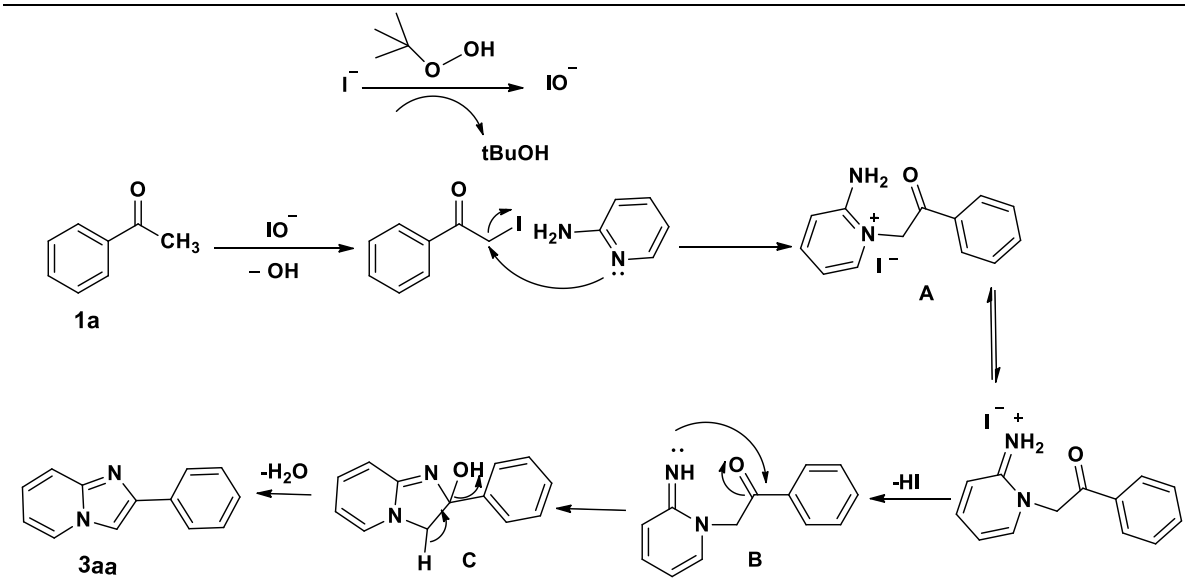
4.3 Plausible Reaction Mechanism

A control experiment has been conducted to explore the reaction mechanism (**Scheme 4.2**). The reaction was performed with radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) under optimized condition but it did not quench the reaction. It rules out the possibility of radical pathway of the reaction.



Scheme 4.2: Control experiment with TEMPO.

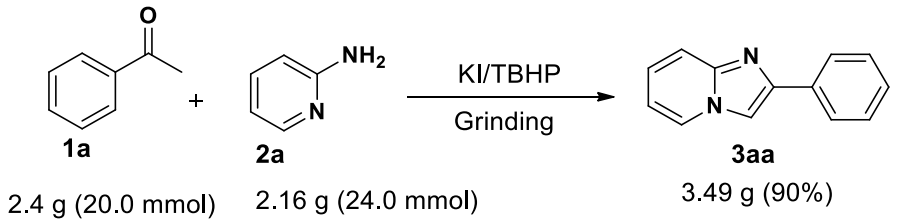
On the basis of literature reports and our observations, a plausible mechanism has been shown in **Scheme 4.3**. First, iodide is oxidized to hypoiodite by TBHP followed by the formation of iodoketone. This iodoketone produced the pyridinium salt (**A**) by the reaction of pyridyl nitrogen with the α-carbon of iodoketone. **A** undergoes deprotonation to give imine **B** which convert into tetrahydroimidazo[1,2-a]pyridin-2-ol (**C**) by intramolecular cyclization. Intermediate **C** then gives the final product, imidazo [1,2-a]pyridine (**3aa**) by the elimination of water.



Scheme 4.3: Plausible reaction mechanism.

4.4 Scalability of the Protocol

After developing this methodology, gram scalability have been demonstrated for this method. The reaction was performed with acetophenone (**1a**) **(**2.4 g, 20.0 mmol), 2-amino pyridine (**2a**) (2.16 g, 24.0 mmol) under optimized reaction conditions and it gave 90% (3.49 g) yield of the product (**3aa**) which is similar to the mmol scale synthesis. This indicates that our methodology is also effective for gram scale synthesis (**Scheme 4.4**).



Scheme 4.4: Gram scale synthesis of imidazo [1,2-a]pyridine.

4.5 Experimental Section

4.5.1 General procedure for the synthesis of products

A mixture of aryl methyl ketone (1.0 mmol), 2-amino pyridine (1.2 mmol), KI (0.5 equiv.) and TBHP (70% aq., 1 equiv.) were taken in mortar and ground continuously. The progress of the reaction was monitored by TLC. The syrup formed was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and subjected to silica gel (60-120 mesh) column chromatography purification (SiO_2: ethyl acetate/hexane) to obtain the pure desired products.

4.5.2 Procedure for gram scale synthesis

A mixture of acetophenone (20.0 mmol), 2-amino pyridine (24.0 mmol), KI (0.5 equiv.) and TBHP (70% aq., 1 equiv.) were added in mortar and ground continuously and the progress of the reaction was monitored by TLC. The obtained syrupy was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and subjected to silica gel (60-120 mesh) column chromatography purification (SiO_2: ethyl acetate/hexane) to obtain the pure desired products in 90% yield.

4.5.3 Procedure for control experiment with TEMPO

Acetophenone (**1a**) (1.0 mmol), 2-amino pyridine (**2a**) (1.2 mmol), KI (0.5 equiv.), TBHP (70% aq., 1 equiv.) and TEMPO (1.0 mmol) were taken in mortar and ground

continuously. Progress of the reaction was monitored by TLC. The formed syrup was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and subjected to silica gel (60-120 mesh) column chromatography purification (SiO_2:ethyl acetate/hexane) to obtain the pure desired product.

4.6 Analytical Data

4.6.1 2-Phenylimidazo[1,2-a]pyridine (3aa): White crystalline solid; yield 184 mg (95%); m.p. 135-136 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.11 (dt, 1H), 7.99 – 7.93 (m, 2H), 7.86 (s, 1H), 7.63 (dd, 1H), 7.48 – 7.39 (m, 2H), 7.37 – 7.29 (m, 1H), 7.20 – 7.13 (m, 1H), 6.77 (td, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 145.9, 145.8, 133.9, 128.8, 128.1, 126.1, 125.7, 124.7, 117.7, 112.5, 108.2.

4.6.2 2-(p-Tolyl)imidazo[1,2-a]pyridine (3ba): White solid; yield 193 mg (93%); m.p. 143-144 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.38 (d, 1H), 7.84 (d, 2H), 7.78 (s, 1H), 7.44 (d, 1H), 7.34 (dd, 1H), 7.27 (d, 2H), 2.41 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 146.5, 144.2, 138.3, 132.5, 130.5, 130.4, 129.6, 126.1, 118.5, 107.5, 21.4.

4.6.3 2-(4-Methoxyphenyl)imidazo[1,2-a]pyridine (3ca): White solid; yield 210 mg (94%); m.p. 138-139 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.09 (dd, 1H), 7.88 (d, 2H), 7.77 (s, 1H), 7.61 (d, 1H), 7.18 – 7.13 (m, 1H), 6.97 (d, 2H), 6.75 (t, 1H), 3.85 (s, 3H); **^{13}C**

NMR (126 MHz, CDCl3) δ (ppm): 159.7, 145.8, 145.7, 127.4, 126.5, 125.5, 124.6, 117.4, 114.2, 112.4, 107.3, 55.4.

4.6.4 2-(3-Nitrophenyl)imidazo[1,2-a]pyridine (3da): Yellow solid; yield 227 mg (95%); m.p. 202-203 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.77 – 8.74 (m, 1H), 8.32 (d, 1H), 8.17 (dd, 2H), 7.98 (s, 1H), 7.65 (d, 1H), 7.60 (t, 1H), 7.23 (d, 1H), 6.84 (t, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 148.8, 146.0, 143.5, 135.8, 131.9, 129.8, 125.9, 125.5, 122.6, 120.9, 117.9, 113.1, 109.1.

4.6.5 2-(4-Chlorophenyl)imidazo[1,2-a]pyridine (3ea): Yellow solid; yield 211 mg (92%); m.p. 206-207 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.11 (d, 1H), 7.89 (d, 2H), 7.84 (s, 1H), 7.62 (d, 1H), 7.40 (d, 2H), 7.18 (dd, 1H), 6.79 (t, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 145.8, 144.8, 133.8, 132.4, 129.0, 127.4, 125.7, 125.0, 117.7, 112.7, 108.3.

4.6.6 2-(4-Bromophenyl)imidazo[1,2-a]pyridine (3fa): Off white solid; yield 246 mg (90%); m.p. 200-201 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.10 (dt, 1H), 7.85 – 7.78 (m, 3H), 7.61 (d, 1H), 7.57 – 7.49 (m, 2H), 7.20 – 7.12 (m, 1H), 6.78 (td, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 145.8, 144.8, 132.9, 131.9, 127.6, 125.7, 125.0, 122.0, 117.7, 112.7, 108.3.

4.6.7 2-(4-Fluorophenyl)imidazo[1,2-a]pyridine (3ga): Pale yellow solid; yield 199 mg (94%); m.p. 164-165 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.11 (d, 1H), 7.95 – 7.90 (m, 2H), 7.80 (s, 1H), 7.62 (d, 1H), 7.17 (t, 1H), 7.14 – 7.09 (m, 2H), 6.78 (t, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.8, 161.8, 145.8, 145.1, 130.1, 130.1, 127.8, 127.8, 125.7, 124.9, 117.6, 115.8, 115.7, 112.6, 107.9.

4.6.8 2-(Imidazo[1,2-a]pyridin-2-yl)phenol (3ha): Colourless solid; yield 187 mg (89%); m.p. 200-201 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 12.72 (s, 1H), 8.16 (d, 1H), 7.87 (s, 1H), 7.60 (d, 2H), 7.23 (t, 2H), 7.04 (dd, 1H), 6.93 – 6.82 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 157.4, 145.5, 143.6, 129.8, 125.8, 125.5, 125.2, 119.1, 117.8, 116.9, 116.3, 113.2, 106.8.

4.6.9 4-(Imidazo[1,2-a]pyridin-2-yl)phenol (3ia): Brown solid; yield 185 mg (88%); m.p. 230-231 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 9.62 (s, 1H), 8.47 (d, 1H), 8.20 (s, 1H), 7.78 (d, 2H), 7.53 (d, 1H), 7.22 – 7.17 (m, 1H), 6.85 (d, 2H), 6.83 (s, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 157.3, 144.6, 127.0, 126.7, 126.6, 124.9, 124.6, 115.5, 115.5, 112.0, 107.6, 107.5.

4.6.10 2-(Pyridin-2-yl)imidazo[1,2-a]pyridine (3ja): Brown solid; yield 166 mg (85%); m.p. 240-241 °C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 8.61 – 8.55 (m, 2H), 8.48 (s, 1H), 8.11 (dd, 1H), 7.87 (d, 1H), 7.60 (d, 1H), 7.34 – 7.27 (m, 2H), 6.92 (d, 1H); **^{13}C NMR** (126

MHz, DMSO) δ (ppm): 152.8, 149.5, 147.6, 144.9, 144.6, 137.0, 127.3, 125.4, 122.8, 119.8, 116.9, 112.6, 111.4, 108.0.

4.6.11 2-(Thiophen-2-yl)imidazo[1,2-a]pyridine (3ka): Yellowish white solid; yield 184 mg (92%); m.p. 135-136 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.07 (d, 1H), 7.76 (s, 1H), 7.60 (d, 1H), 7.49 – 7.45 (m, 1H), 7.32 – 7.28 (m, 1H), 7.18 – 7.13 (m, 1H), 7.11 – 7.07 (m, 1H), 6.76 (t, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 145.63, 141.06, 137.67, 127.88, 125.56, 125.20, 124.96, 123.86, 117.53, 112.71, 107.58.

4.6.12 2-(Naphthalen-1-yl)imidazo[1,2-a]pyridine (3la): Yellowish liquid; yield 227 mg (93%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.63 – 8.56 (m, 1H), 8.17 (d, 1H), 7.92 – 7.87 (m, 2H), 7.83 (d, 2H), 7.71 (d, 1H), 7.58 – 7.49 (m, 3H), 7.23 – 7.18 (m, 1H), 6.82 (s, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 145.48, 145.34, 134.08, 131.87, 131.63, 128.59, 128.47, 127.83, 126.55, 126.06, 125.89, 125.66, 125.52, 124.71, 117.85, 112.55, 111.32.

4.6.13 8-Methyl-2-phenylimidazo[1,2-a]pyridine (3ab): Pale yellow solid; yield 189 mg (91%); m.p. 119-120 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.00 (t, 1H), 7.98 (d, 2H), 7.83 (s, 1H), 7.45 (dd, 2H), 7.37 – 7.31 (m, 1H), 6.96 (d, 1H), 6.68 (t, 1H), 2.68 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 146.3, 145.3, 134.2, 128.7, 127.8, 126.2, 123.5, 123.3, 112.4, 108.6, 17.2.

4.6.14 2-(4-Methoxyphenyl)-8-methylimidazo[1,2-a]pyridine (3cb): Pale yellow solid; yield 209 mg (88%); m.p. 132-133 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.95 (d, 1H), 7.89 (d, 2H), 7.73 (s, 1H), 6.97 (d, 2H), 6.92 (d, 1H), 6.64 (t, 1H), 3.84 (s, 3H), 2.65 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 159.5, 146.2, 145.2, 127.5, 127.4, 126.9, 123.4, 123.2, 114.1, 112.2, 107.8. 55.4, 17.2.

4.6.15 8-Methyl-2-(3-nitrophenyl)imidazo[1,2-a]pyridine (3db): Yellow solid; yield 233 mg (92%); m.p. 168-169 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.79 – 8.73 (m, 1H), 8.31 (dd, 1H), 8.16 – 8.11 (m, 1H), 8.00 (d, 1H), 7.92 (s, 1H), 7.57 (t, 1H), 6.98 (dd, 1H), 6.71 (t, 1H), 2.65 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 148.7, 146.5, 142.8, 136.1, 132.0, 129.6, 128.0, 124.0, 123.7, 122.3, 120.9, 113.0, 109.5, 17.1.

4.6.16 2-(4-Chlorophenyl)-8-methylimidazo[1,2-a]pyridine (3eb): White solid; yield 226 mg (93%); m.p. 119-120 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.98 (d, 1H), 7.90 (d, 2H), 7.81 (s, 1H), 7.39 (d, 2H), 6.96 (d, 1H), 6.69 (t, 1H), 2.65 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 146.4, 144.2, 133.5, 132.8, 128.9, 127.7, 127.5, 123.6, 123.5, 112.6, 108.7, 17.2.

4.6.17 2-(4-Bromophenyl)-8-methylimidazo[1,2-a]pyridine (3fb): Yellow solid; yield 261 mg (91%); m.p. 131-132°C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.97 (d, 1H), 7.87 – 7.82 (m, 2H), 7.79 (s, 1H), 7.55 (d, 2H), 6.96 (d, 1H), 6.71 – 6.64 (m, 1H), 2.65 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 146.4, 144.2, 133.2, 131.8, 123.6, 123.5, 121.7, 112.6, 108.8, 17.2

4.6.18. 2-(4-Fluorophenyl)-8-methylimidazo[1,2-a]pyridine (3gb): White solid; yield 199 mg (88%); m.p. 128-129 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.96 (s, 1H), 7.93 (dd, 2H), 7.77 (s, 1H), 7.16 – 7.07 (m, 2H), 6.98 – 6.92 (m, 1H), 6.67 (t, 1H), 2.65 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.7, 161.8, 146.3, 144.5, 130.5, 130.4, 127.9, 127.9, 127.7, 123.5, 115.78, 115.6, 112.5, 108.3, 77.4, 77.1, 76.9, 17.1.

4.6.19 2-(8-Methylimidazo[1,2-a]pyridin-2-yl)phenol (3hb): White solid; yield 195 mg (87%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 12.94 (s, 1H), 8.00 (s, 1H), 7.83 (dd, 1H), 7.58 (d, 1H), 7.26 – 7.19 (m, 1H), 7.06 – 6.98 (m, 2H), 6.88 (t, 1H), 6.76 (d, 1H), 2.59 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 157.4, 144.7, 144.0, 129.6, 126.8, 125.7, 124.1, 123.2, 119.0, 117.7, 116.4, 113.3, 107.2, 16.9.

4.6.20 4-(8-Methylimidazo[1,2-a]pyridin-2-yl)phenol (3ib): Brown solid; yield 199 mg (89%); **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 10.50 (s, 1H), 9.56 (s, 1H), 8.32 (dd, 2H), 8.26 (s, 1H), 8.18 (s, 1H), 7.80 – 7.75 (m, 3H), 6.99 – 6.95 (m, 1H), 6.84 (d, 1H), 6.77 – 6.75 (m, 1H), 2.51 (s, 3H); **^{13}C NMR** (126 MHz, DMSO) δ (ppm): 157.6, 156.7, 145.6, 145.5, 144.7, 143.0, 136.2, 127.7, 127.4, 126.2, 125.5, 124.8, 123.4, 115.9, 112.3, 109.0, 108.4, 17.1.

4.6.21 6-Chloro-2-phenylimidazo[1,2-a]pyridine (3ac): White solid; yield 213 mg (93%); m.p. 207-208 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.17 (d, 1H), 7.94 (d, 2H), 7.84 (s, 1H), 7.58 (d, 1H), 7.44 (t, 2H), 7.36 (d, 1H), 7.14 (dd, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 147.0, 144.2, 133.4, 128.9, 128.4, 126.2, 126.1, 123.5, 120.7, 118.0, 108.6.

4.6.22 6-Chloro-2-(p-tolyl)imidazo[1,2-a]pyridine (3bc): Pale yellow solid; yield 228 mg (94%); m.p. 125-126 °C; **^{1}H NMR** (500 MHz, CDCl3) δ (ppm): 8.13 (d, 1H), 7.81 (d, 2H), 7.77 (s, 1H), 7.56 (d, 1H), 7.24 (d, 2H), 7.12 (d, 1H), 2.39 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 147.0, 144.1, 138.3, 130.5, 129.6, 126.0, 126.0, 123.4, 120.5, 117.8, 108.2, 21.4.

4.6.23 6-Chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridine (3ec): Pale yellow solid; yield 242 mg (92%); m.p. 206-207 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.16 (d, 1H), 7.86 (d, 2H), 7.80 (s, 1H), 7.56 (d, 1H), 7.40 (d, 2H), 7.15 (dd, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 145.9, 144.2, 134.2, 131.9, 129.1, 127.4, 126.4, 123.5, 120.9, 118.0, 108.6.

4.6.24 2-(4-Bromophenyl)-6-chloroimidazo[1,2-a]pyridine (3fc): Yellow solid; yield 277 mg (90%); m.p. 199-200 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.15 (dd, 1H), 7.81 – 7.78 (m, 3H), 7.56 (d, 3H), 7.15 (dd, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 145.9, 144.2, 132.4, 132.0, 127.7, 126.5, 123.5, 122.4, 120.9, 118.0, 108.6.

4.6.25 2-(6-Chloroimidazo[1,2-a]pyridin-2-yl)phenol (3hc): White solid; yield 218 mg (89%); m.p. 197-199 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.24 (d, 1H), 7.87 (s, 1H), 7.61 – 7.56 (m, 2H), 7.25 (ddd, 2H), 7.06 (d, 1H), 6.92 (t, 1H), 6.68 (t, 1H), 1.27 (s, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 157.4, 146.5, 142.0, 130.1, 127.1, 126.6, 125.9, 123.3, 120.8, 119.2, 117.9, 117.2, 115.8, 107.2.

4.6.26 8-(Phenoxymethyl)-2-phenylimidazo[1,2-a]pyridine (3ad): Pale yellow solid; yield 337 mg (89%); m.p. 130-131 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.89 – 7.85 (m, 2H), 7.80 (s, 1H), 7.72 (dd, 1H), 7.55 – 7.49 (m, 4H), 7.38 (dd, 2H), 7.33 (d, 1H), 6.59 (dd, 1H), 6.45 (d, 1H), 5.39 (s, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 148.0, 144.0, 140.5, 136.3, 132.86, 131.8, 128.7, 128.2, 127.8, 127.3, 121.8, 118.8, 112.5, 109.3, 103.4, 70.98.

4.7 Spectral Data of Synthesized Product

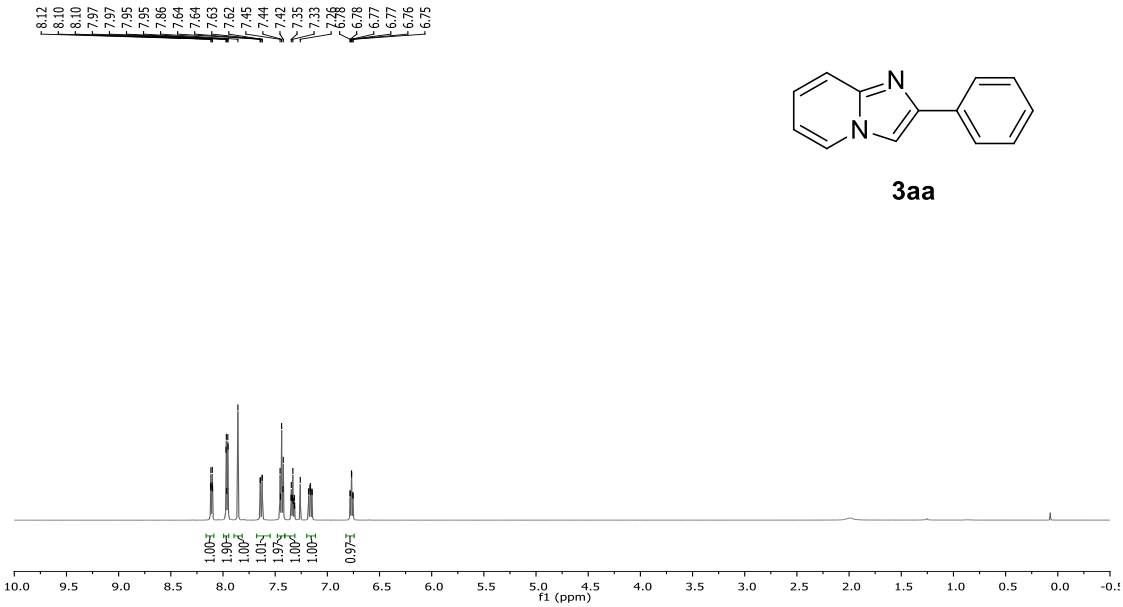


Figure 4.2: ^{1}H NMR of model compound **3aa**.

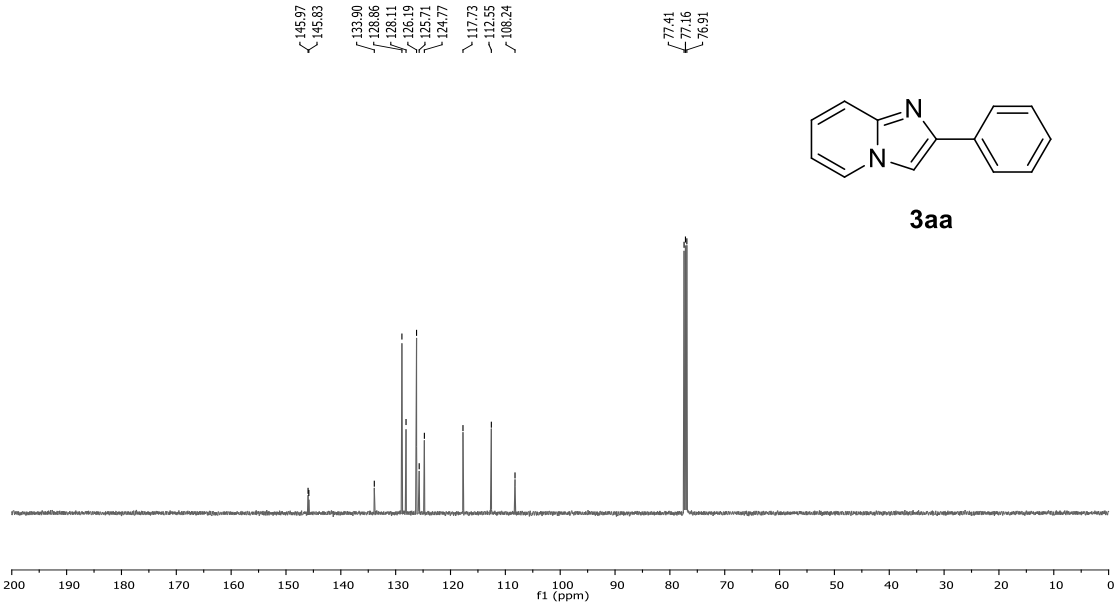


Figure 4.3: ^{13}C NMR of model compound **3aa**.

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CHAPTER 5

Solar Energy Mediated Green Synthesis of Tetrahydrobenzo[b]pyran using L-Ascorbic Acid as an Organocatalyst in Aqueous Medium

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Solar Energy Mediated Green Synthesis of Tetrahydrobenzo[b]pyran using L-Ascorbic Acid as an Organocatalyst in Aqueous Medium

5.1 Introduction

In the recent years, organic synthesis is mainly focused on the development of the greener and ecofriendly protocols involving the use of green solvents in place of toxic, volatile and hazardous organic solvents and green biodegradable catalysts in place of hazardous heavy metal catalysts and also alternate energy sources like microwave irradiation, ultrasound irradiation, UV light in place of conventional heating which saves time and energy. In this context, in recent times multicomponent reactions (MCRs) have gained much attention because in these reactions two or more molecules reacts together in one pot. MCRs helps in saving time and effort for isolation and purification of synthetic intermediates, high atom economy and also minimizing energy consumption, which is one of the most important principles of green chemistry and rapidly gaining attention of scientists worldwide. MCRs are highly efficient method for the synthesis of highly functionalized heterocycles by the reactions of small organic molecules. Among the heterocycles, 4*H*-pyrans has received considerable attention because these are the important units of natural products and also shows a variety of biological and pharmacological activities such as emetic, anti-coagulant, anticancer, diuretic, antimalarial, antitumor, antibacterial, antialzheimer, antileukemic, antihyperglycemic and antidyslipidemic

activities (Smith et al. 1995, Tanabe et al. 1988, Gao et al. 2008, Bolognese et al. 2004, Fokialakis et al. 2002, Beagley et al. 2003, Morgan et al. 2002, Bonsignore et al. 1993, Cannon et al. 1975, Biot et al. 1997). **Figure 5.1** shows some medicinally important compounds containing 2-amino-3-cyano-4*H*-pyrans functional group like **A & C** are antimicrobial, **B** is anti-bacterial, **D & E** are anti-tumor and **F** is an anticancer agent.

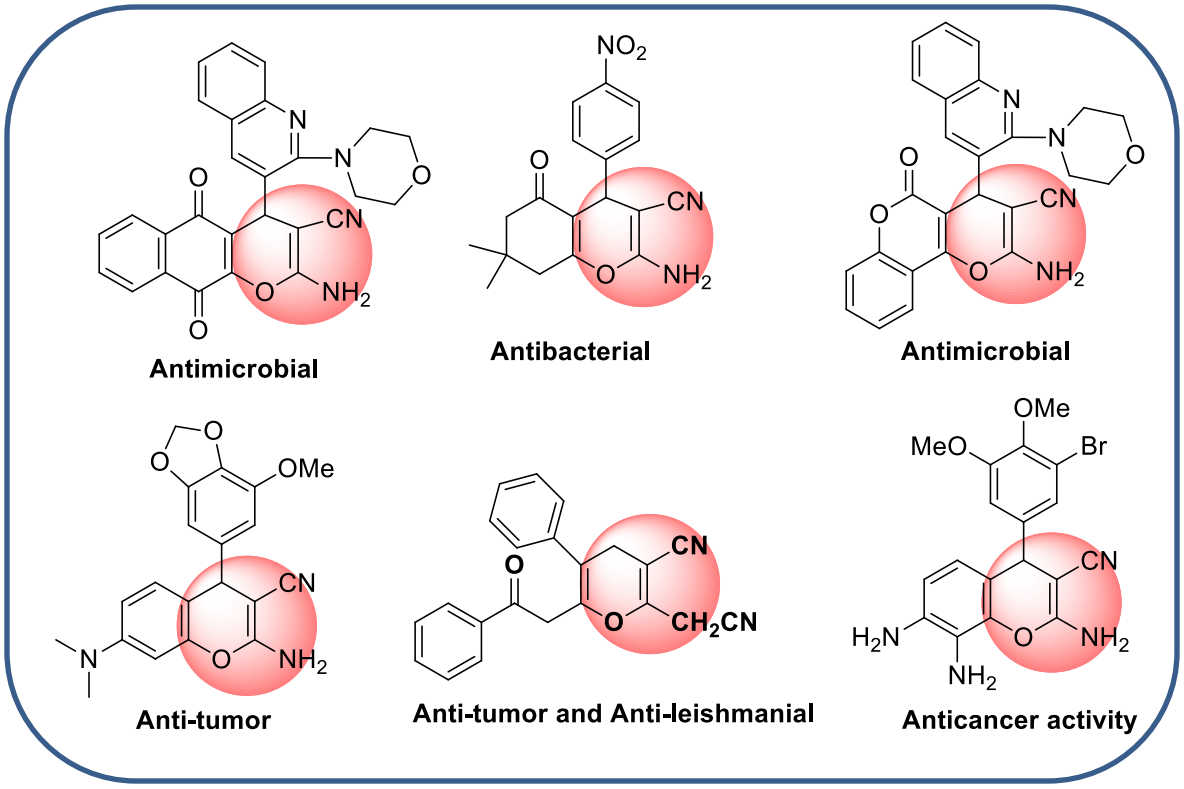


Figure 5.1: Examples of 2-amino-3-cyano-4*H*-pyrans derivatives with pharmacological activities.

The best protocol to synthesize 4*H*-pyrans is the Knoevenagel condensation-Michael cyclization reaction by using aldehyde, carbonitrile and 1,3-dicarbonyl compound by one-

pot multicomponent reaction. A number of conventional reported methods for the synthesis of 4*H*-pyrans performed under various reaction uses different catalysts like piperidine (Ye et al. 2010), DABCO (Tahmassebi et al. 2011), NH_4OAc (Zonouz et al. 2016), K_2CO_3 (Heydari et al. 2017), ethylenediammonium diacetate (EDDA) (Hari et al. 2010), potassium phthalimide (Dekamin et al. 2014), CsF (Wagh et al. 2015), glutamic acid (Hatamjafari et al. 2016), alum (Mohammadi et al. 2017), sulfonic Acid (Ziarani et al. 2011), nano ZnO (Bhattacharyya et al. 2012), nano TiO_2 (Anandgaonker et al. 2014), Fe_3O_4 NPs/MWCNTs (Fallah et al. 2014), MNPs@Cu (Wanzheng et al. 2019), γ-cyclodextrin (Xiong et al. 2019), PEG/Water (Lu et al. 2018).

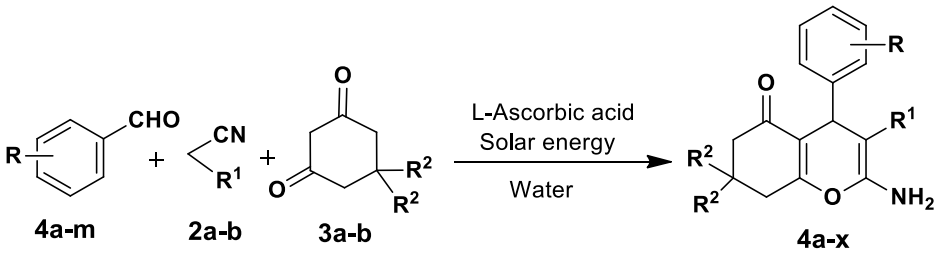
Each of these methods has their own limitations. Therefore, we went ahead and found an alternative green method for synthesis of 4*H*-pyran using biodegradable/biocatalyst natural catalyst. Ascorbic acid has immense possibilities of being used as an organocatalyst in organic transformations. L-Ascorbic acid is biodegradable, natural, inexpensive, non-toxic and easy to handle organocatalyst. Therefore, use of ascorbic acid as a catalyst in MCRs under solar energy is the best selection from green chemistry point of view (Arvind et al. 2016, Das et al. 2018).

To perform an organic reaction, if solvent is necessary, water is the best option in comparison to toxic organic solvents from green and sustainable chemistry point of view. Despite of the economic and environmental friendly nature of water, it also has its own

unique qualities like high surface tension, high polarity, non-toxic, easy handling etc. Since most of the organic compounds are not soluble in water therefore after completion of reaction product can be easily separated by filtration (Gawande et al. 2013, Lindstrom et al. 2008).

Further, to develop a green synthetic approach, naturally available sun light that is solar thermal energy can be utilized as an alternative renewable energy source to induce the chemical transformation. Solar thermochemical method provides more selectivity and mild reaction condition than the conventional energy sources which are also helpful to reduce the side reaction caused by conventional thermal heating process. Sunlight is an exclusive natural source that is cheap, non-polluting, plentiful and endlessly renewable source of clean energy (Yoon et al. 2010, Kumavat et al. 2013).

Considering these aspects we herein report solar energy induced an efficient, ecofriendly, simple and practical way for the synthesis of tetrahydrobenzo[b]pyran derivatives using a biodegradable L-ascorbic acid in aqueous medium (**Scheme 5.1**).

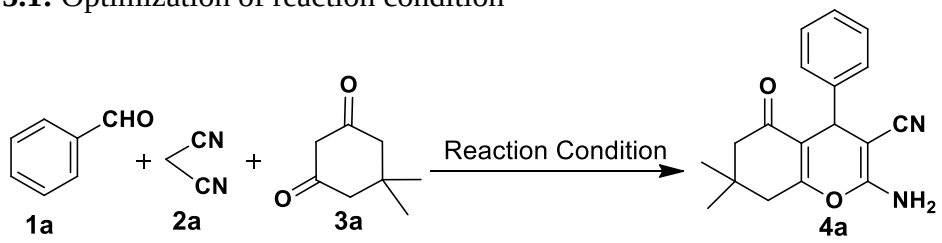


Scheme 5.1: Solar energy mediated synthesis of 4*H*-pyran.

5.2 Results and Discussion

The reaction of benzaldehyde, malononitrile and dimedone was chosen as a model reaction in order to set the optimized reaction condition for the synthesis of 4*H*-pyran. First of all, the model reaction was performed without catalyst in water under sun light (35-40 °C) and in 60 minutes, the maximum 32% yield of product **4a** was obtained. Further, the reaction time increased up to 6 h but only a small increment in product yield was observed (35%). In order to increase the yield of the product, model reaction was performed by using 1 mol% of L-ascorbic acid as a catalyst in water under similar reaction condition and it gave 65% yield in 60 minutes. Further the catalyst amount had been increased from 2-5 mol% and the best result was observed in case of 3 mol% of L-ascorbic acid. It gave the 95% yield of product **4a** in 10 minutes and the results are concise in **Table 5.1** (**entries 1-6**). Further, numerous polar and non-polar solvents were screened over the model reaction performed by using 3 mol% of L-ascorbic acid. In polar solvents like ethanol, methanol, acetonitrile, 1,4-dioxane, dichloromethane and chloroform moderate to good yield (40-80%) was obtained (**Table 5.1, entries 7-12**) while in case of DMF and DMSO poor yield of product was achieved (**Table 5.1, entries 13 and 14**) and in case of nonpolar solvents like hexane, benzene and toluene no reaction was obtained (**Table 5.1, entries 15-17**). Therefore, the optimized reaction condition for model reaction was with 3 mol% of L-ascorbic acid in water under sun light (**Table 5.1, entry 4**). Structure of the model compound (**4a**) was confirmed by ^{1}H & ^{13}C NMR spectral data (**Figure 5.1 & 5.2**).

Table 5.1: Optimization of reaction condition[a]



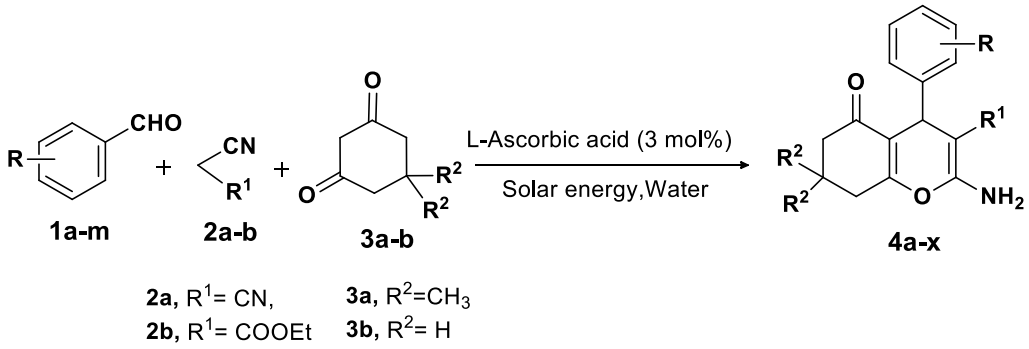
Entry	Solvent	Catalyst (mol%)	Time (min)	Yield[b] (%)
1	Water	Nil	60	32
2	Water	1	60	65
3	Water	2	45	78
4	**Water**	**3**	**10**	**95**
5	Water	4	10	95
6	Water	5	10	95
7	Ethanol	3	40	80
8	Methanol	3	45	73
9	Acetonitrile	3	45	50
10	1,4-Dioxane	3	60	40
11	Dichloromethane	3	60	45
12	Chloroform	3	60	42
13	DMF	3	60	10
14	DMSO	3	60	12
15	Hexane	3	60	NR
16	Benzene	3	60	NR
17	Toluene	3	60	NR

[a] **Reaction condition**: Benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), dimedone (1.0 mmol) and L-ascorbic acid in 5 mL solvent are placed under sunlight. [b] Isolated yield.

After optimizing the reaction conditions, the substrate scope was explored by using different substituted aromatic aldehydes with malononitrile and dimedone. It was observed that aldehyde derivatives with electron withdrawing groups like NO_2, Cl, Br *viz. o*-nitro benzaldehyde (**1e**), *m*-nitro benzaldehyde (**1f**), *p*-nitro benzaldehyde (**1g**), *o*-chloro benzaldehyde (**1h**), *p*-chloro benzaldehyde (**1i**), *p*-bromo benzaldehyde (**1j**), (**Table 5.2, entry 5-10**) and electron donating groups like CH_3, OCH_3 *viz*. *o*-tolualdehyde (**1b**), *p*-tolualdehyde (**1c**) and *p*-methoxy benzaldehyde (**1d**) (**Table 5.2, entries 2-4**) undergo the reaction smoothly to give corresponding 4*H*-pyrans *viz.* 2-amino-7,7-dimethyl-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4e**), 2-amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4f**), 2-amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3carbonitrile (**4g**), 2-amino-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4h**), 2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4i**) and 2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitril (**4j**), 2-amino-7,7-dimethyl-5-oxo-4-(o-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4b**), 2-amino-7,7-dimethyl-5-oxo-4-(p-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3 carbonitrile (**4c**), 2-amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4d**) with 91-97% yield in short reaction time. To our surprise, the optimized condition was also found suitable for the heterocyclic aldehyde, furfuraldehyde and gave 2-amino-4-(furan-2-yl)-7,7-dimethyl-5-

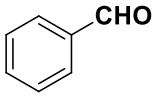
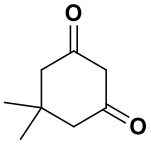
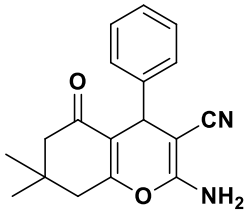
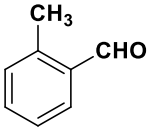
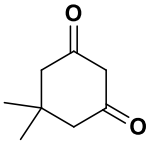
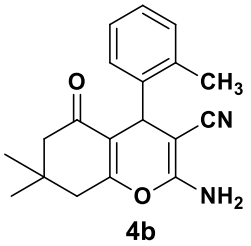
oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4k**) with 94% yield (**Table 5.2, entry 11**). Likewise, 2-naphthylaldehyde was successfully gave the desired product 2-amino-7,7-dimethyl-4-(naphthalen-2-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4l**) in 93% yield (**Table 5.2, entry 12**). In order to explore further substrate scope, the reactions were performed by varying different active methylene compounds like ethylcyano acetate and dimedone/1,3-cyclohexadione to give corresponding 4*H*-pyran derivatives *viz.* 2-amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4m**), 2-amino-5-oxo-4-(o-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4n**), 2-amino-4-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4o**), 2-Amino-4-(2-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4p**), 2-amino-4-(4-bromophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4q**), 2-amino-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4r**), 2-Amino-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3carbonitrile (**4s**), ethyl 2-amino-5-oxo-4-phenyl- 5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**4t**), ethyl 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**4u**), ethyl 2-amino-4-(4-bromophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**4v**), ethyl 2-amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3 carboxylate (**4w**) and ethyl 2-amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**4x**) in good to excellent yield under this optimized reaction condition (**Table 5.2, entries 13-24**).

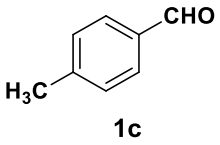
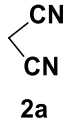
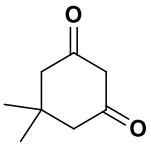
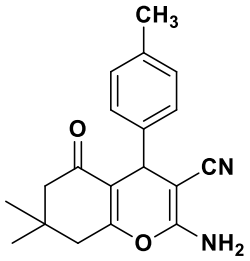
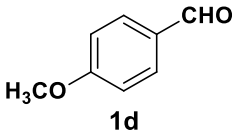
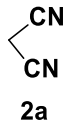
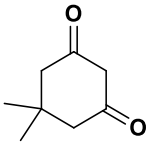
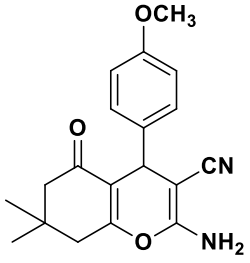
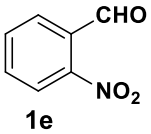
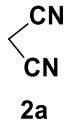
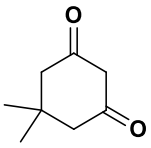
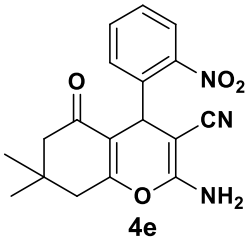
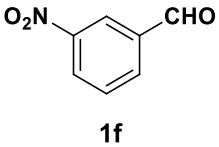
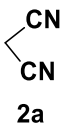
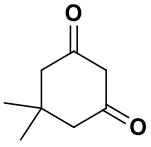
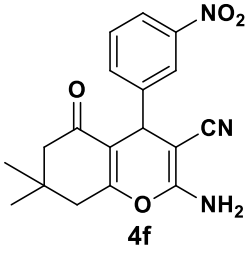
Table 5.2: Synthesis of 4*H*-pyran[a]

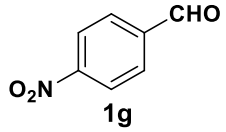
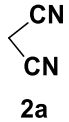
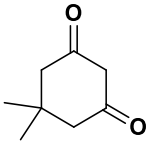
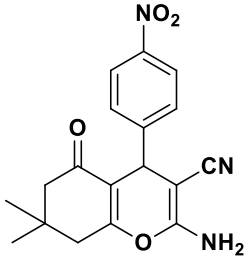
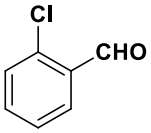
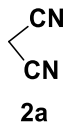
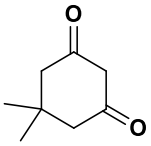
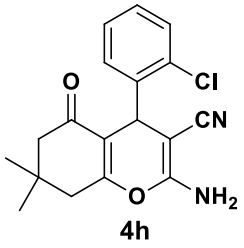
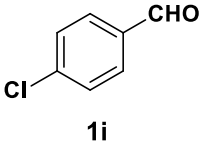
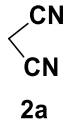
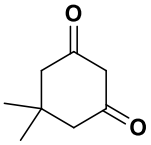
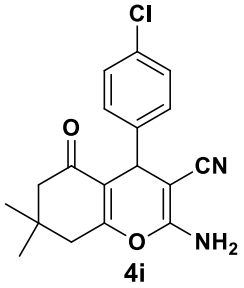
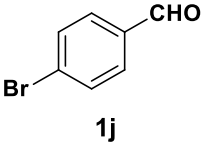
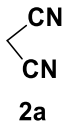
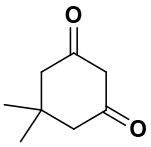
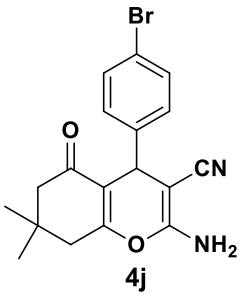


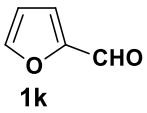
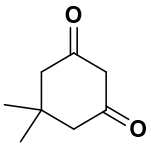
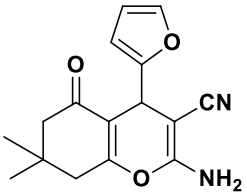
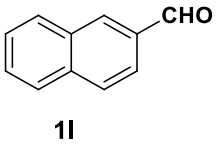
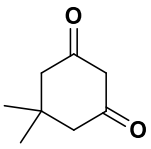
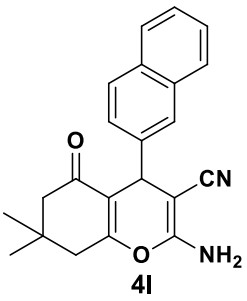
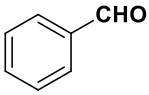
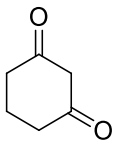
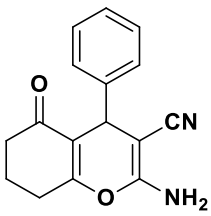
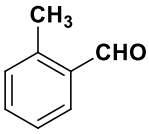
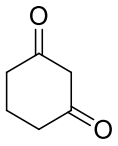
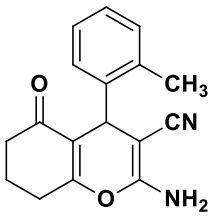
1a-m 2a-b 3a-b 4a-x

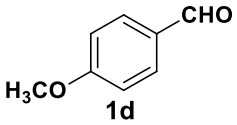
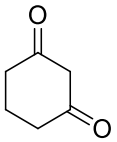
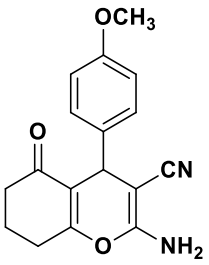
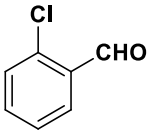
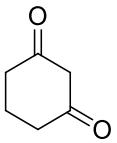
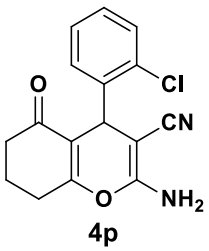
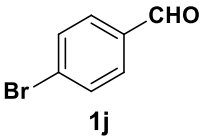
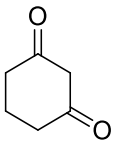
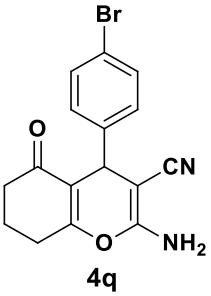
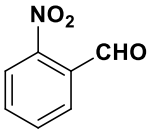
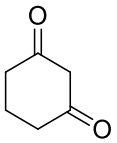
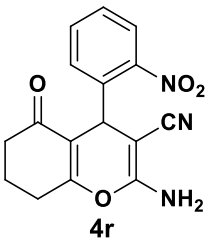
2a, R^1= CN, **3a,** R^2=CH_3
2b, R^1= COOEt **3b,** R^2= H

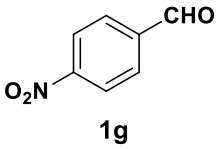
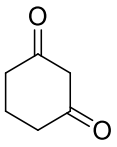
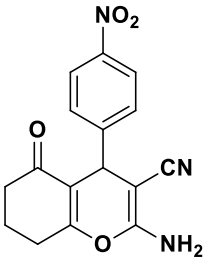
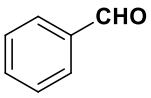
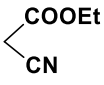
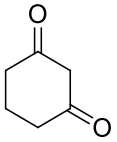
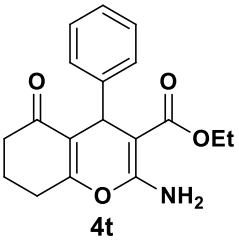
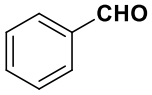
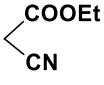
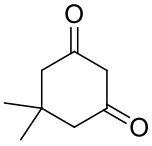
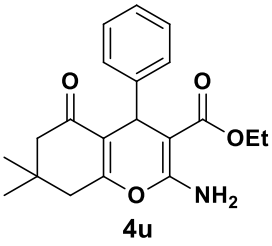
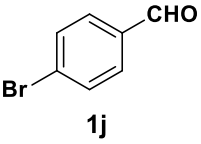
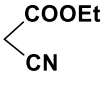
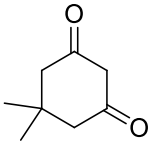
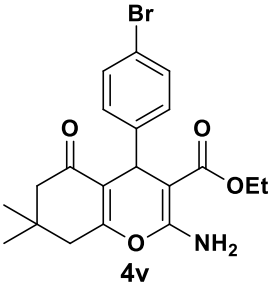
S. No.	Aldehyde	Carbonitrile	1,3-dicarbonyl compound	Product	Time (min)	Yield[b] (%)
1	 1a	 2a	 3a	 4a	10	95
2	 1b	 2a	 3a	 4b	12	93

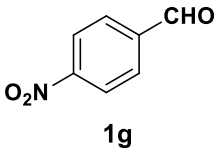
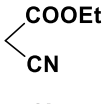
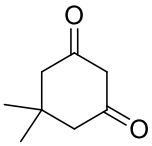
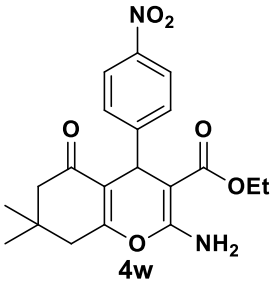
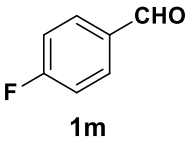
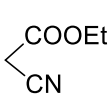
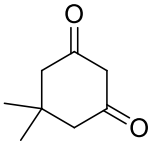
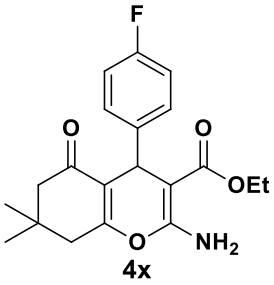
3	 1c	 2a	 3a	 4c	13	92
4	 1d	 2a	 3a	 4d	15	91
5	 1e	 2a	 3a	 4e	10	96
6	 1f	 2a	 3a	 4f	10	96

7	 1g	 2a	 3a	 4g	10	97
8	 1h	 2a	 3a	 4h	12	96
9	 1i	 2a	 3a	 4i	13	96
10	 1j	 2a	 3a	 4j	12	95

11	 1k	 2a	 3a	 4k	10	94
12	 1l	 2a	 3a	 4l	12	93
13	 1a	 2a	 3b	 4m	10	94
14	 1b	 2a	 3b	 4n	12	93

15	 1d	 2a	 3b	 4o	13	92
16	 1h	 2a	 3b	 4p	12	95
17	 1j	 2a	 3b	 4q	13	95
18	 1e	 2a	 3b	 4r	10	96

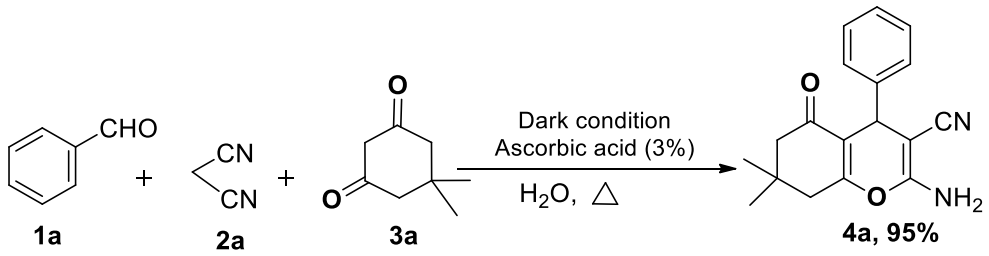
19	 1g	 2a	 3b	 4s	10	96
20	 1a	 2b	 3b	 4t	17	93
21	 1a	 2b	 3a	 4u	15	94
22	 1j	 2b	 3a	 4v	15	95

23	 1g	 2b	 3a	 4w	16	96
24	 1m	 2b	 3a	 4x	15	95

[a]**Reaction conditions**: Benzaldehyde (1.0 mmol), malononitrile/ ethylcyanoacetatae (1.0 mmol), dimedone / 1,3 cyclohexanedione (1.0 mmol) and L-ascorbic acid in 5.0 mL water are placed under sunlight. [b] Isolated yield.

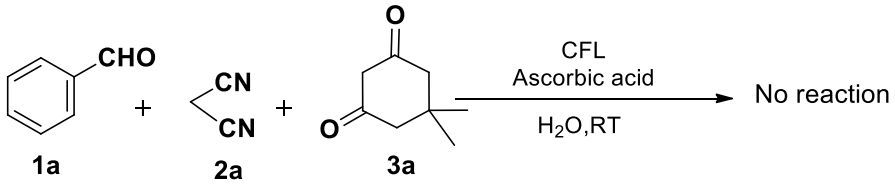
5.3 Mechanistic Study

Deep diving in to the path of reaction, few controlled experiment have been performed in order to confirm whether the reaction proceed via solar thermal or solar photochemical process. The reaction was carried out under dark reaction condition and reaction temperature has been maintained similar as obtained under solar condition (35-40 °C) with 3 mol% of L-ascorbic acid in aqueous medium and it afforded the same product (**4a**) (**Scheme 5.2**).



Scheme 5.2: Control experiment under dark reaction condition.

Further a series of experiments using visible light of different intensities (8 W, 15 W, 20 W) have been performed on the model reaction and no product was obtained. Hence, it rules out the possibility of photochemical reaction (**Scheme 5.3, Table 5.3**).



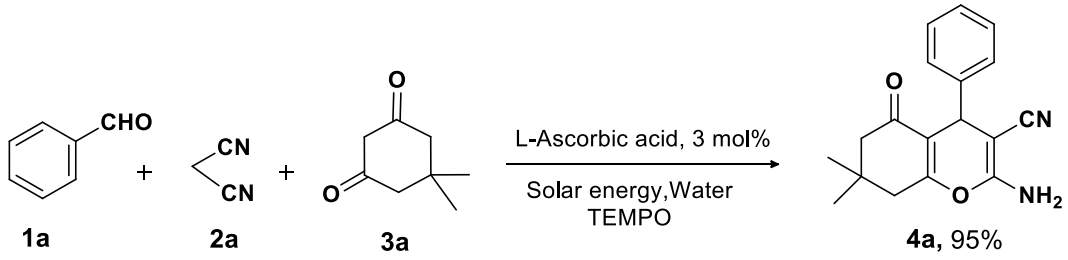
Scheme 5.3: Control experiment under visible light.

Table 5.3: Reaction under solar, thermal and photochemical condition[a]

Entry	Reaction condition	Time (min)	Yield[b]%
1	Solar energy	10	95
2	Dark condition, 35-40 °C	10	95
3	CFL (8W), RT	30	NR
4	CFL (15W), RT	30	NR
5	CFL (20W), RT	30	NR

[a]**Reaction conditions**: Benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), dimedone (1.0 mmol), L-ascorbic acid (3 mol%) in water (5.0 mL). [b] Isolated yield.

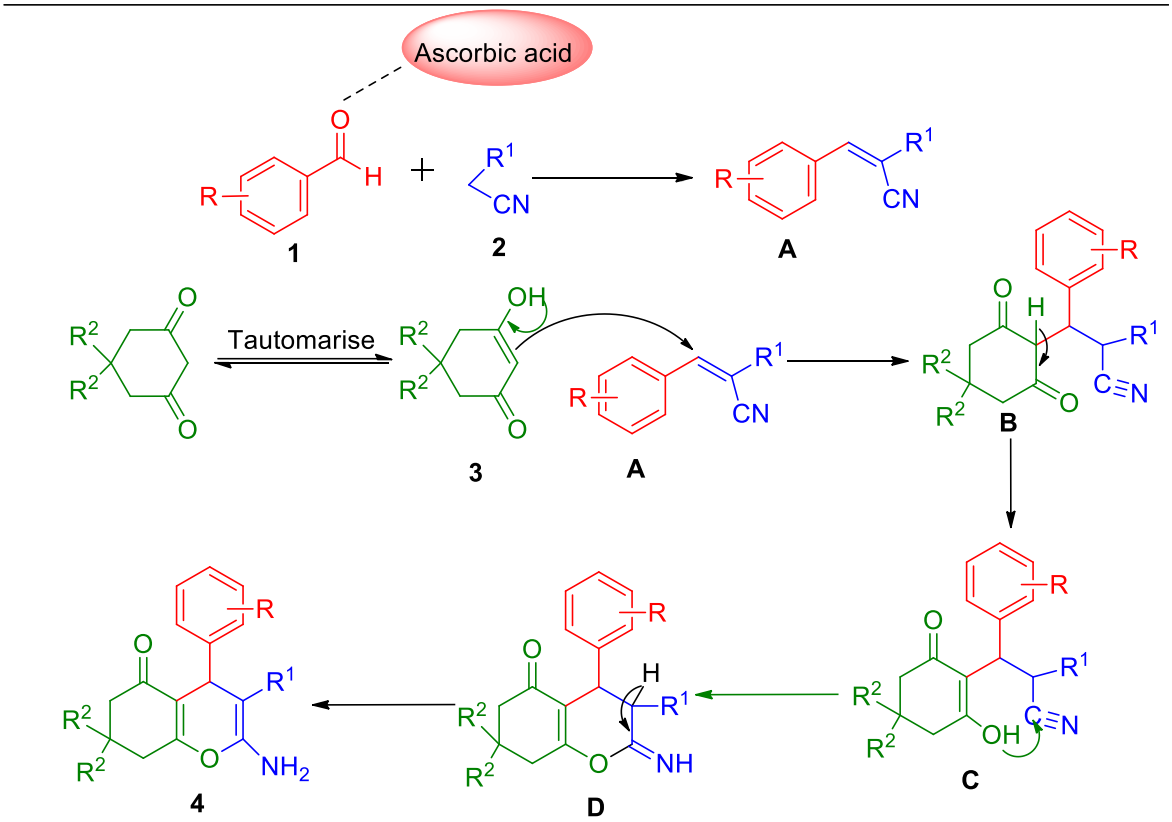
Likewise, when model reaction was performed with radical scavengers like TEMPO and BHT the same product (**4a**) was obtained in good yield and these results show that it is not a radical reaction. This also support that the formation of tetrahydrobenzo[b]pyran catalyzed by ascorbic acid in water is mediated by solar thermal energy and discard the possibility of solar photochemical process (**Scheme 5.4**).



Scheme 5.4: Control experiment with TEMPO.

5.4 Plausible Reaction Mechanism

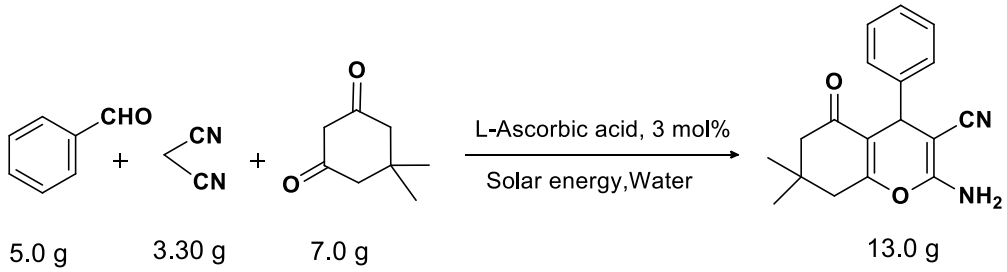
In the proposed mechanism (**Scheme 5.5**), aldehyde (**1**) first condenses with active methylene compound (**2**) and producs α-cyanocinnamonitrile (**A**) via the Knoevenagel condensation. Further, α-cyanocinnamonitrile (**A**) reacts with 1,3-diketone (**3**) give intermediate **B** via Michael addition and finally enolization occurs, followed by amine-enamine tautomarization to produce the expected product 4*H*-pyran (**4**).



Scheme 5.5: Plausible reaction mechanism for the ascorbic acid assisted synthesis of tetrahydrobenzo[b]pyran.

5.5 Gram Scale Synthesis of Tetrahydrobenzo[b]pyran

The reaction was tried on gram scale where 5.30 g of benzaldehyde (**1a**), 3.30 g of malononitrile (**2a**) and 7.0 g of dimedone (**3a**) was successfully converted into desired product (**4a**) in 13.0 g (90%) which evidently validates the practical applicability of the established methodology (**Scheme 5.6**).



Scheme 5.6: Gram scale synthesis of tetrahydrobenzo[b]pyran.

5.6 Experimental Section

5.6.1 General procedure for the synthesis of compounds (4a-4x)

In a stoppered, flat-bottom flask charged with aromatic aldehyde derivatives (1.0 mmol), malononitrile/ethylcyanoacetate (1.0 mmol) dimedone/1,3-cyclohexanedione (1.0 mmol), L-ascorbic acid (3 mol%) and water (5 mL). The reaction mixture was kept in the sunlight for 10 min. The progress of reaction was checked by thin-layer chromatography (TLC). After completion of the reaction, solid product was filtered, dried and recrystallized from hot ethanol to give pure product (**4a-4x**).

5.6.2 Gram-scale procedure

Benzaldehyde (**1a**) (5.30 g, 50.0 mmol), malononitrile (**2a**) (3.30 g 50.0 mmol), dimedone (**3a**) (7.0 g, 50 mmol), L-ascorbic acid (3 mol%) and water were taken in flat-bottom flask. The reaction mixture was kept in the sunlight for 10 min. The progress of the reaction was monitored by TLC. After completion of reaction, solid product was filtered, dried and recrystallized from hot ethanol to give pure product (**4a**).

5.6.3 Procedure for the controlled experiment with TEMPO

In a stoppered, flat-bottom flask charged with benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), dimedone (1.0 mmol), TEMPO (3 mol%), L-ascorbic acid (3 mol%) and water. The reaction mixture was kept in the sunlight and the progress of reaction was checked by thin-layer chromatography (TLC). After completion of the reaction, solid product was filtered, dried and recrystallized from hot ethanol to give pure product in 95% yield (**4a**).

5.7 Analytical Data

5.7.1 2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-*4H*-chromene-3-carbo nitrile (4a): White solid; yield 280 mg (95%); m.p. 228-229 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.26 (d, 2 H), 7.17 (d, 1H), 7.12 (d, 2H), 7.00 (s, 2H, D_2O exchangeable), 4.15 (s, 1H), 2.50 (d, 2H), 2.24 (d, 1H), 2.09 (d, 1H), 1.02 (s, 3H), 0.94 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.7, 162.5, 158.5, 144.7, 128.3, 127.1, 126.6, 119.7, 112.7, 58.3, 50.0, 39.3, 35.6, 31.8, 28.4, 26.8; Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.35; H, 6.14; N, 9.48.

5.7.2 2-Amino-7,7-dimethyl-5-oxo-4-(o-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbo nitrile (4b): White solid; yield 289 mg (93%); m.p. 211-212 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.09 (d, 2H), 7.04 (s, 1H), 6.95 (s, 2H), 6.93 (s, 1H, D_2O

exchangeable), 4.46 (s, 1H), 2.52 (d, 2H), 2.46 (s, 3H), 2.24 (d, 1H), 2.06 (d, 1H), 1.04 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.9, 162.6, 158.3, 143.6, 134.8, 130.0, 127.3, 126.5, 126.3, 119.8, 113.5, 58.3, 50.0, 31.9, 30.9, 28.5, 26.8, 19.1; Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N 9.08. Found: C, 73.89; H, 6.53; N, 9.04.

5.7.3 2-Amino-7,7-dimethyl-5-oxo-4-(p-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4c): Yellow solid; yield 283 mg (92%); m.p. 218-219 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.09 (d, 2H), 7.02 (d, 2H), 6.98 (s, 2H, D_2O exchangeable), 4.13 (s, 1H), 2.51 (d, 2H), 2.25 (s, 4H), 2.09 (d, 1H), 1.04 (s, 3H), 0.95 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.6, 162.3, 158.4, 141.8, 135.6, 128.9, 127.1, 119.7, 112.8, 58.4, 50.0, 35.2, 31.8, 28.4, 26.7, 20.6; Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.19; H, 6.17; N, 8.59.

5.7.4 2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4d): Yellow solid; yield 295 mg (91%); m.p. 200-202 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.05 (d, 2H), 6.94 (s, 2H), 6.84 (d, 2H, D_2O exchangeable), 4.12 (s, 1H), 3.70 (s, 3H), 2.49 (d, 2H), 2.24 (d, 1H), 2.08 (d, 1H), 1.02 (s, 3H), 0.94 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 196.2, 162.6, 158.8, 158.3, 137.3, 128.6, 120.2, 114.1, 113.4, 59.0, 55.4, 50.4, 35.2, 32.2, 28.8, 27.2; Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.19; H, 6.17; N, 8.59.

5.7.5 2-Amino-7,7-dimethyl-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4e): Yellow solid; yield 326 mg (96%); m.p. 229-230 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.81 (d, 1H), 7.66 (t, 1H), 7.42 (t, 1H), 7.35 (d, 1H), 7.20 (s, 2H,D_2O exchangeable), 4.93 (s, 1H), 2.45 (d, 2H), 2.20 (d, 1H), 2.01 (d, 1H), 1.01 (s, 3H), 0.88 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.8, 165.1, 158.5, 152.3, 146.2, 128.5, 123.6, 119.3, 112.7, 56.8, 40.0, 36.2, 35.5, 26.5, 19.7; Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.54; H, 5.01; N, 12.34.

5.7.6 2-Amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4f): Yellow solid; yield 326 mg (96%); m.p. 213-214 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.11 – 8.05 (m, 1H), 7.98 (s, 1H), 7.67 (d, 1H), 7.62 (d, 1H), 7.18 (s, 2H, D_2O exchangeable), 4.42 (s, 1H), 2.57 (d, 2H), 2.27 (d, 1H), 2.12 (d, 1H), 1.04 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.7, 163.1, 158.6, 147.7, 147.0, 134.2, 130.2, 121.7, 121.6, 119.3, 111.7, 57.2, 49.8, 35.4, 31.8, 28.3, 26.7; Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.56; H, 5.02; N, 12.31.

5.7.7 2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene -3-carbonitrile (4g): Yellow solid; yield 329 mg (97%); m.p. 183-184 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.17 (d, 2H), 7.44 (d, 2H), 7.18 (s, 2H, D_2O exchangeable), 4.36 (s, 1H), 2.54 (s, 2H), 2.26 (d, 1H), 2.11 (d, 1H), 1.04 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.7, 163.1, 158.6, 152.3, 146.2, 128.6, 123.6, 119.3, 111.7,

57.0, 49.8, 35.6, 31.8, 28.2, 26.9; Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.53; H, 5.03; N, 12.32

5.7.8 2-Amino-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene -3-carbonitrile (4h): White solid; yield 316 mg (96%); m.p. 212-214 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.33 (d, 1H), 7.24 (t, 1H), 7.15 (dd, 2H), 7.00 (s, 2H, D_2O exchangeable), 4.66 (s, 1H), 2.47 (s, 2H), 2.22 (d, 1H), 2.04 (d, 1H), 1.01 (s, 3H), 0.94 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.8, 163.3, 158.8, 141.6, 132.2, 130.0, 129.5, 128.3, 127.5, 119.4, 111.8, 56.9, 50.0, 40.0, 32.9, 31.8, 28.5, 26.9. Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52. Found: C, 65.61; H, 5.18; N, 8.48.

5.7.9 2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene -3-carbonitrile (4i): White solid; yield 316 mg (96%); m.p. 202-204 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.35 (d, 2H), 7.17 (d, 2H), 7.07 (s, 2H, D_2O exchangeable), 4.20 (s, 1H), 2.51 (d, 2H), 2.25 (d 1H), 2.11 (d, 1H), 1.04 (s, 3H), 0.95 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 196.1, 163.0, 158.9, 144.2, 131.5, 129.5, 128.7, 120.0, 112.8, 58.2, 50.4, 32.2, 28.7, 27.3; Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N 8.52. Found: C, 65.59; H, 5.17; N, 8.46.

5.7.10 2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene -3-carbonitril (4j): Yellow solid; yield 355 mg (95%); m.p. 202-203 °C; **^{1}H NMR** (500

MHz, DMSO-d_6) δ (ppm): 7.27 (d, 2H), 7.13 (d, 2H), 7.00 (s, 2H, D_2O exchangeable), 4.16 (s, 1H), 2.50 (s, 2H), 2.23 (s, 1H), 2.11 (s, 1H), 1.03 (s, 3H), 0.94 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 196.1, 162.9, 158.9, 145.2, 128.8, 127.6, 127.0, 120.2, 113.1, 58.7, 50.4, 36.0, 32.2, 28.8, 27.2; Anal. Calcd for $C_{18}H_{17}BrN_2O_2$: C, 57.92; H, 4.59; N, 7.5. Found: C, 57.74; H, 4.54; N, 7.45.

5.7.11 2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4k): Brown solid; yield 268 mg (94%); m.p. 223-225 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.47 (d, 1H), 7.06 (s, 2H, D_2O exchangeable), 6.32 (s, 1H), 6.05 (s, 1H), 4.32 (s, 1H), 2.50 – 2.49 (m, 2H), 2.28 (d, 1H), 2.16 (d, 1H), 1.04 (s, 3H), 0.98 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.4, 163.3, 159.3, 155.7, 141.8, 141.6, 119.5, 110.3, 55.4, 49.9, 31.8, 29.0, 28.2, 26.5; Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.4; H, 5.63; N, 9.81.

5.7.12 2-Amino-7,7-dimethyl-4-(naphthalen-2-yl)5-oxo-5,6,7,8-tetrahydro-4*H*-chromene -3-carbonitrile (4l): Cream solid; yield 320 mg (93%); m.p. 258-259 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.89 (d, 1H), 7.85 (d, 2H), 7.67 (s, 1H), 7.48 (t, 2H), 7.28 (d, 1H), 7.07 (s, 2H, D_2O exchangeable), 4.36 (s, 1H), 2.55 (s, 2H), 2.26 (d, 1H), 2.08 (d, 1H), 1.04 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.7, 162.6, 158.5, 142.0, 132.8, 132.0, 128.1, 127.6, 127.4, 126.2, 125.7, 125.6, 125.5, 119.7, 112.5, 58.1, 50.0, 39.1,

31.8, 28.4, 26.7; Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.54; H, 5.81; N, 8.10.

5.7.13 2-Amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4m): White solid; yield 251 mg (94%); m.p. 241-243 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.29 (dd, 2H), 7.21 – 7.17 (m, 1H), 7.17 – 7.14 (m, 2H), 7.00 (s, 2H, D_2O exchangeable), 4.19 (s, 1H), 2.62 (s, 2H), 2.27 (dt, 2H), 1.95 (s, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 196.1, 164.7, 158.6, 144.9, 128.52, 127.2, 126.7, 119.9, 113.9, 48.7, 36.4, 35.5, 26.6, 19.9; Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.96; H, 5.27; N, 10.48.

5.7.14 2-Amino-5-oxo-4-(o-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4n): White solid; yield 261 mg (93%); m.p. 198-200 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.13 – 7.08 (m, 2H), 7.05 (dd, 1H), 6.96 (d, 1H), 6.93 (s, 2H), 4.47 (s, 1H), 2.67 – 2.57 (m, 2H), 2.46 (s, 3H), 2.32 – 2.19 (m, 2H), 1.99 – 1.85 (m, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.9, 164.4, 158.2, 143.6, 134.7, 129.8, 127.3, 126.4, 126.1, 114.5, 58.1, 36.3, 31.0, 26.4, 19.8, 19.0; Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.69; H, 5.71; N, 9.94.

5.7.15 2-Amino-4-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4o): White solid; yield 273 mg (92%); m.p. 194-196 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.08 – 7.05 (m, 2H), 6.95 (s, 2H), 6.83 (d, 2H, D_2O exchangeable),

4.14 (s, 1H), 3.71 (s, 3H), 2.59 (dd, 2H), 2.32 – 2.21 (m, 2H), 1.98 – 1.84 (m, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.8, 164.1, 158.4, 157.9, 136.9, 128.1, 119.8, 114.0, 113.6, 58.4, 55.0, 36.3, 34.6, 26.4, 19.8; Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.71; H, 5.40; N, 9.40.

5.7.16 2-Amino-4-(2-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbo nitrile (4p): White solid; yield 286 mg (95%); m.p. 210-212 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.37 – 7.35 (m, 1H), 7.28 – 7.24 (m, 1H), 7.19 (dd, 2H), 7.01 (s, 2H, D_2O exchangeable), 4.71 (s, 1H), 2.62 (dd, 2H), 2.32 – 2.19 (m, 2H), 2.32 – 2.21 (m, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.6, 165.0, 164.0, 158.5, 141.7, 132.0, 129.8, 129.3, 128.1, 127.5, 119.2, 112.8, 56.8, 36.3, 32.6, 26.4, 19.8; Anal. Calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31. Found: C, 63.71; H, 4.33; N, 9.27.

5.7.17 2-Amino-4-(4-bromophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbo nitrile (4q): White solid; yield 328 mg (95%); m.p. 239-240 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.46 (d, 2H), 7.12 (dd, 2H), 7.02 (s, 2H, D_2O exchangeable), 4.19 (s, 1H), 2.59 (dd, 2H), 2.33 – 2.20 (m, 2H), 2.00 – 1.81 (m, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 196.1, 164.8, 158.6, 144.3, 131.3, 129.6, 119.7, 113.4, 57.8, 36.4, 35.2, 26.6, 19.9; Anal. Calcd for $C_{16}H_{13}BrN_2O_2$: C, 55.67; H, 3.80; N, 8.12. Found: C, 55.49; H, 3.76; N, 8.08.

5.7.18 2-Amino-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbo nitrile (4r): Yellow solid; yield 299 mg (96%); m.p. 206-208 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.16 (d, 2H), 7.46 (d, 2H), 7.17 (s, 2H, D_2O exchangeable), 4.36 (s, 1H), 2.63 (t, 2H), 2.28 (d, 2H), 1.99 – 1.87 (m, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.8, 165.1, 158.5, 152.3, 146.2, 128.5, 123.6, 119.3, 112.7, 56.8, 36.2, 35.5, 26.5, 19.7; Anal. Calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.54; H, 4.18; N, 13.46.

5.7.19 2-Amino-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3carbonitrile (4s): Light yellow solid; yield 299 mg (96%); m.p. 237-238 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.16 (d, 2H), 7.46 (d, 2H), 7.17 (s, 2H, D_2O exchangeable), 4.36 (s, 1H), 2.63 (dd, 2H), 2.28 (dd, 2H), 1.99 – 1.88 (m, 2H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm): 195.8, 165.1, 158.5, 152.3, 146.2, 128.5, 123.6, 119.3, 112.7, 56.8, 36.2, 35.5, 26.5, 19.7; Anal. Calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.53; H, 4.19; N, 13.47.

5.7.20 Ethyl 2-amino-5-oxo-4-phenyl- 5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4t): White solid; yield 292 mg (93%); m.p. 183-184 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.21 – 7.18 (m, 2H), 7.13 (t, 2H), 7.04 (s, 1H), 6.11 (s, 2H, D_2O exchangeable), 4.66 (s, 1H), 3.95 (dd, 2H), 2.54 – 2.43 (m, 2H), 2.26 (dt, 2H), 1.97 – 1.83 (m, 2H), 1.07 (t, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 196.6, 169.2, 163.1, 158.4, 146.1, 128.3, 127.9,

126.1, 118.2, 80.9, 59.8, 37.0, 33.9, 27.1, 20.3, 14.3; Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.81; H, 6.07; N, 4.42.

5.7.21 Ethyl 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4u): White solid; yield 321 mg (94%); m.p. 155-157 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.32 – 7.29 (m, 2H), 7.25 (t, 2H), 7.15 (s, 1H), 6.22 (s, 2H, D_2O exchangeable), 4.75 (s, 1H), 4.08 (dd, 2H), 2.47 (s, 2H), 2.26 (s, 1H), 2.22 (s, 1H), 1.21 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 196.5, 169.2, 161.4, 158.4, 145.9, 128.3, 127.9, 126.1, 116.9, 80.9, 59.8, 50.8, 40.8, 33.9, 32.3, 29.2, 27.5, 14.3; Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.15; H, 6.77; N, 4.06.

5.7.22 Ethyl 2-amino-4-(4-bromophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4v): White solid; yield 399 mg (95%); m.p. 161-162 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.32 (d, 2H), 7.14 (d, 2H), 6.18 (s, 2H, D_2O exchangeable), 4.65 (s, 1H), 4.02 (dd, 2H), 2.45 – 2.38 (m, 2H), 2.22 (d, 1H), 2.17 (s, 1H), 1.15 (t, 3H), 1.09 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 196.5, 169.0, 161.6, 158.4, 145.0, 130.9, 130.2, 119.9, 116.4, 80.4, 59.9, 50.8, 40.7, 33.6, 32.3, 29.2, 27.5, 14.3; Anal. Calcd for $C_{20}H_{22}BrNO_4$: C, 57.15; H, 5.28; N, 3.33. Found: C, 56.94; H, 5.24; N, 3.30.

5.7.23 Ethyl 2-amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4w): Yellow solid; yield 371 mg (96%); m.p. 181-182 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.13–8.03 (m, 2H), 7.46–7.41 (m, 2H), 6.26 (s, 2H,

D_2O exchangeable), 4.79 (s, 1H), 4.02 (dd, 2H), 2.49 – 2.39 (m, 2H), 2.24 (d, 1H), 2.15 (d, 1H), 1.13 (t, 3H), 1.11 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 196.3, 168.7, 162.1, 158.5, 153.5, 146.4, 129.3, 123.3, 115.7, 79.5, 60.0, 50.7, 40.8, 34.4, 32.4, 29.2, 27.4, 14.3; Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.96; H, 5.70; N, 7.19.

5.7.24 Ethyl 2-amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4x): Yellow solid; yield 341 mg (95%); m.p. 160-161 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.23 – 7.19 (m, 2H), 6.88 (t, 2H), 6.17 (s, 2H, D_2O exchangeable), 4.68 (s, 1H), 4.03 (dd, 2H), 2.42 (s, 2H), 2.23 (d, 1H), 2.15 (d,1H), 1.14 (t, 3H), 1.09 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 196.5, 169.1, 162.3, 161.4, 160.4, 158.4, 141.7, 141.7, 129.8, 129.7, 116.8, 114.7, 114.5, 80.8, 59.8, 50.8, 40.8, 33.3, 32.3, 29.2, 27.5, 14.3. Anal. Calcd for $C_{20}H_{22}FNO_4$: C, 66.84; H, 6.17; N, 3.90. Found: C, 66.71; H, 6.13; N, 3.85.

5.8 Spectral Data of 4a

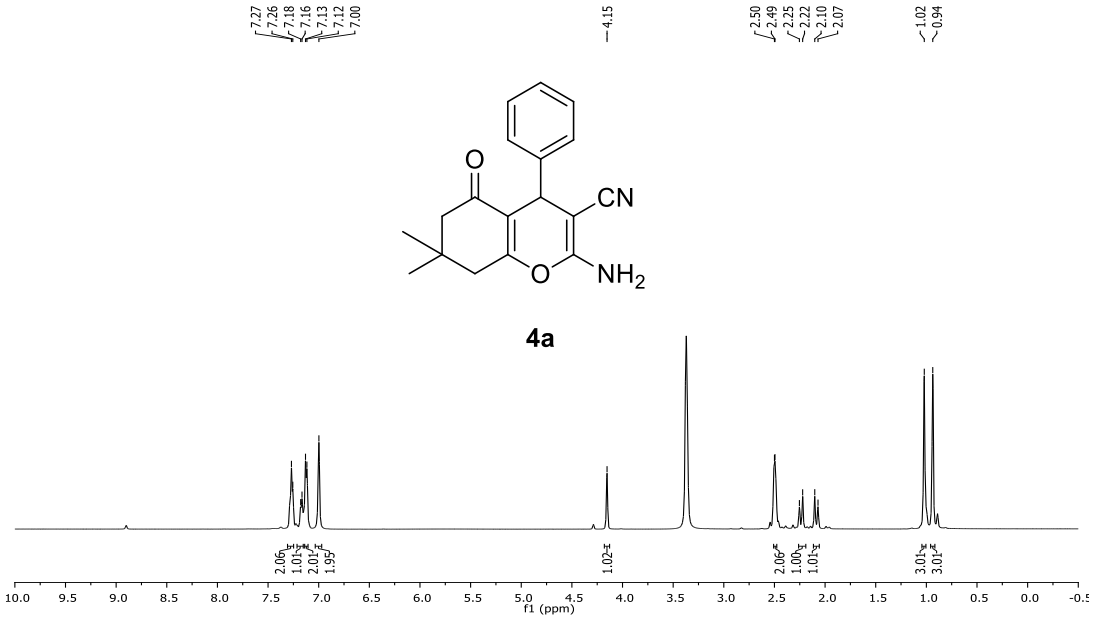


Figure 5.2: ^{1}H NMR spectra of model compound **4a.**

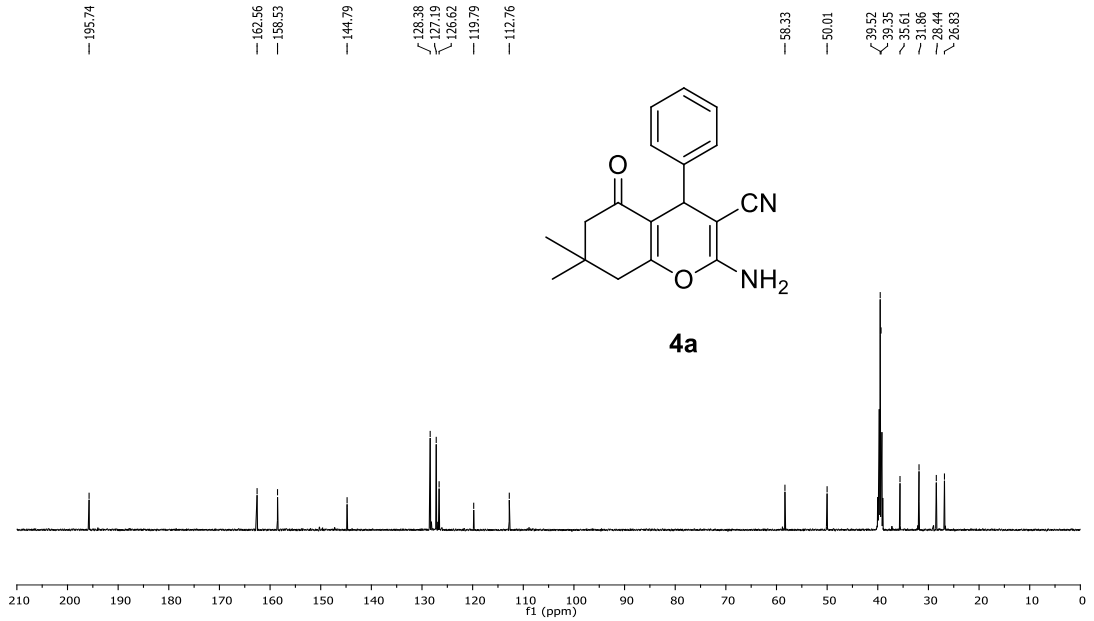


Figure 5.3: ^{13}C NMR spectra of model compound **4a.**

5.9 References

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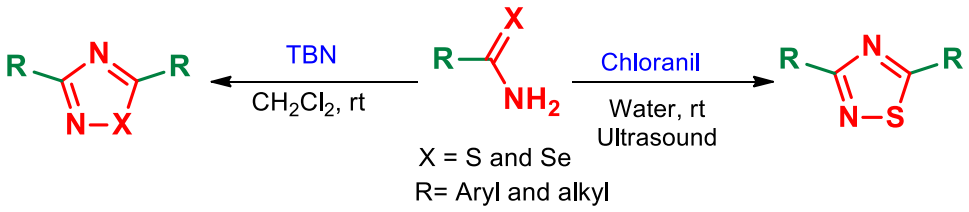
Summary and Conclusions

Summary and Conclusions

The thesis entitled, "Green Approaches for the Synthesis of Some Biologically Relevant Heterocyclic Compounds," embodies the environmental friendly methods for synthesis of biologically important heterocyclic compounds containing nitrogen, oxygen and sulphur atoms. Characterization of the synthesized compounds have been performed by different analytical instrumental methods *viz.* ^{1}H & ^{13}C NMR, FT-IR spectroscopy, Mass spectrometry and elemental analysis The content of the thesis has been divided into five chapters.

Chapter 1 provides a general introduction and literature review of synthesis and application of some main class of nitrogen, oxygen and sulphur containing heterocyclic compounds.

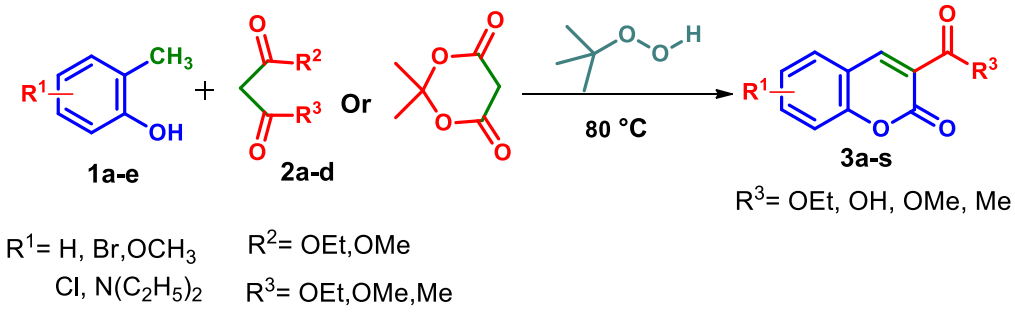
Chapter 2 deals with the detailed syntheses of 1,2,4-thiadiazole and 1,2,4-selenadiazole by two different methods. The synthesis were successfully achieved by *tert*-butyl nitrite induced radical dimerization of primary thioamides and selenoamides at room temperature and chloranil mediated ultrasound induced dimerization of primary thioamides under metal and catalyst free condition. The developed methods are simple, efficient and provide good to excellent yield in short span of time. (**Scheme A**).



Scheme A

The reactions were carried out without any catalyst which complies with the requirements for green and sustainable chemistry.

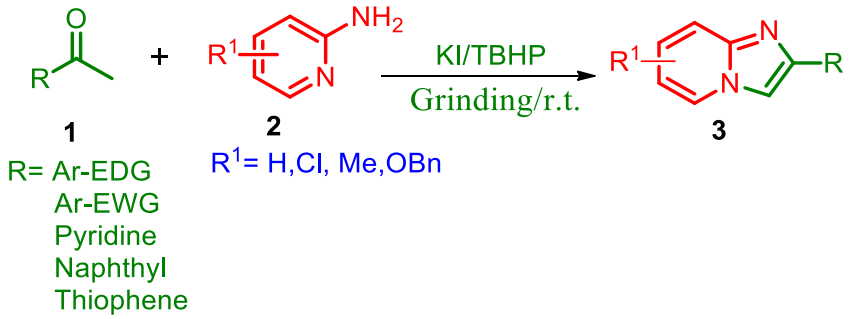
Chapter 3 describes the synthesis of 3-functionalized coumarins from *o*-cresols and active methylene compounds under metal and catalyst-free condition using *tert*-butyl hydrogen peroxide (**Scheme B**). Herein we have developed a facile, efficient and scalable protocol to successfully achieve the 3-functionalized coumarins. This methodology involves initial functionalization of *o*-cresol by TBHP.



Scheme B

Formation of C–O bond, followed by treatment of the *o*-cresol with active methylene in presence of TBHP under solvent-free codition to give desired products in good to excellent yield. The fascinating features of the protocol are as follows: functionalization of *o*-cresol, milder reaction conditions, catalyst free, broad substrate scope and good functional group tolrance.

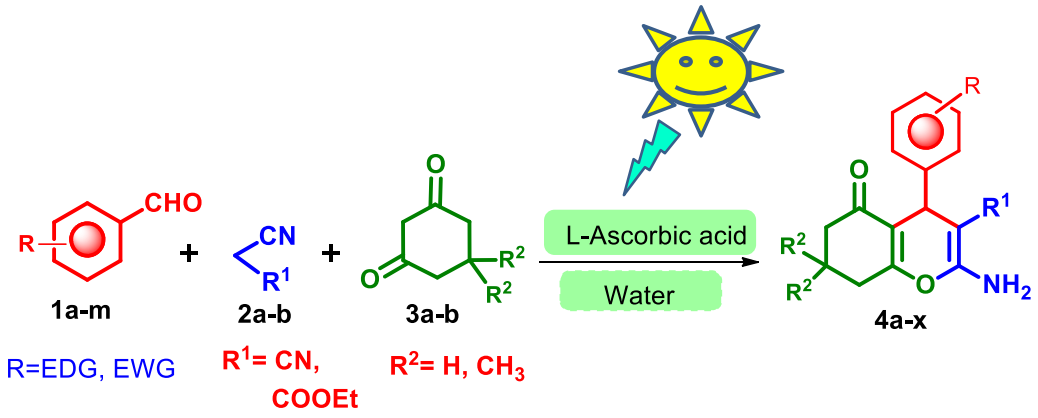
Chapter 4 is concerned with the development of novel, facile, efficient and scalable route for the synthesis of imidazo[1,2-a]pyridines. These imidazo[1,2-a]pyridines were successfully synthesized by easily available starting material aryl methyl ketone with 2-aminopyridine using KI/TBHP under grinding at room temperature (**Scheme C**).



Scheme C

We have developed first metal, acid, base and solvent-free synthesis of imidazo[1,2-a]pyridines under environment friendly condition.

Chapter 5 describes a solar energy mediated environmentally benign, simple and efficient method for one pot multicomponent synthesis of tetrahydrobenzo[b]pyran using L-ascorbic acid as an organocatalyst in aqueous medium and the isolated yields were up to 91-97% (**Scheme D**).



Scheme D

Herein, we have developed a rapid and facile method to achieve the tetrahydrobenzo[b]pyran starting from the Knoevenagel condensation of aromatic aldehyde with active methylene compound followed by Michel addition with 1,3-diketone. The methodology shows extensive functional group tolerance and good to excellent yield in short span of time. The noteworthy feature of the present methodology includes isolation of analytically pure products by simple crystallization method without using cumbersome column chromatographic method.

List of Research Publications

List of Research Publications

1. **Swati Chauhan**, Priyanka Chaudhary, Adesh Kumar Singh, Pratibha Verma, Vandana Srivastava, and Jeyakumar Kandasamy, "*tert*-Butyl nitrite induced radical dimerization of primary thioamides and selenoamides at room temperature," *Tetrahedron letters*, **59** (2018) 272-276.
2. **Swati Chauhan**, Pratibha Verma, Ankush Mishra, and Vandana Srivastava, "An Expeditious Ultrasound-Initiated Green Synthesis of 1, 2, 4-Thiadiazoles in Water," *Chemistry of Heterocyclic Compounds*, **56** (2020) 123-126.
3. **Swati Chauhan,** Pratibha Verma, Jeyakumar Kandasamy, and Vandana Srivastava, "A practical synthesis of 3-functionalized coumarins from *o*-cresols and active methylene compounds under metal and catalyst-free conditions using *tert*-butyl hydrogen peroxide" *ChemistrySelect*, **5** (2020) 9030-9033
4. **Swati Chauhan**, and Vandana Srivastava, "Development of a Scalable Route for the Synthesis of [1,2-a]pyridines under Metal and solvent Free Conditions," (Communicated).
5. **Swati Chauhan**, Ankush Mishra, Pratibha Verma, and Vandana Srivastava, "Solar Energy Mediated Green Synthesis of Tetrahydrobenzo[b]Pyran using L-Ascorbic Acid as an Organocatalyst in Aqueous Medium, "*Organic Preparations and Procedures International* (Accepted 2020).
6. Ankush Mishra, **Swati Chauhan**, Pratibha Verma, Sundaram Singh, and Vandana Srivastava, "TBHP-Initiated Transamidation of Secondary Amides via C− N Bond Activation: A Metal-Free Approach," *Asian Journal of Organic Chemistry*, **8** (2019) 853-857.
7. Pratibha Verma, Ankush Mishra, **Swati Chauhan**, Sundaram Singh, and Vandana Srivastava, "DABCO Catalyzed Synthesis of *β*-Hydroxy Ketones Derived from α-Methyl Ketones and Ninhydrin under Microwave Irradiations," *ChemistrySelect*, **4** (2019) 5394-5397.
8. Pratibha Verma, Shaili Pal, **Swati Chauhan**, Ankush Mishra, Indrajit Sinha, Sundaram Singh, and Vandana Srivastava, "Starch functionalized magnetite nanoparticles: A green, biocatalyst for one-pot multicomponent synthesis of imidazopyrimidine derivatives in aqueous medium under ultrasound irradiation," *Journal of Molecular Structure*, **1203** (2020) 127410.
9. Ankush Mishra, Chandrabhan Verma, **Swati Chauhan**, M. A. Quraishi, Eno E. Ebenso, and Vandana Srivastava, "Synthesis, characterization, and corrosion inhibition performance of 5-aminopyrazole carbonitriles towards mild steel acidic corrosion," *Journal of Bio-and Tribo-Corrosion*, **4** (2018) 53.
10. Chandrabhan Verma, Ankush Mishra, **Swati Chauhan**, Pratibha Verma, Vandana Srivastava, M. A. Quraishi, and Eno E. Ebenso, "Dissolution of cellulose in ionic liquids and their mixed cosolvents: A review," *Sustainable Chemistry and Pharmacy*, **13** (2019) 100162.