Organoiodines in the Synthesis and Functionalization of Some Novel Bioactive Heterocycles

THESIS

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of

DOCTOR OF PHILOSOPHY

by

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Under the Supervision of

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CERTIFICATE

This is to certify that the thesis entitled **"Organoiodines in the Synthesis and Functionalization of Some Novel Bioactive Heterocycles"** and submitted by **Ms. Meenakshi Pilania** ID No **2011PHXF022P** for the award of Ph. D. Degree of the Institute embodies the original work done by her under my supervision.

Signature of the Supervisor:

Name in capital block letters: **PROF. DALIP KUMAR**

Designation: Professor

Date:

Dedicated to

My Family and Teachers

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Ms. Meenakshi Pilania

ABSTRACT

Over the past decade, there has been unparalleled growth in the use of organoiodine reagents in the construction of various heterocycles due to their inherent low toxicity, high stability and commercial availability. The highly selective oxidizing properties associated with organoiodine reagents, make them superior to toxic heavy metal-based oxidants to carry out many useful organic transformations. The present thesis deals with the utilization of organoiodine reagents for the functionalizations and construction of diverse five- and six-membered azaheterocycles.

The **first chapter** briefly highlights structures and properties of organoiodine reagents. Up-to-date review of recent advances in the chemistry of organoiodine reagents, particularly in the construction of various natural and synthetic bioactive heterocycles has been provided in this chapter.

Chapter two deals with the organoiodine-promoted synthesis of 1,3,4-oxadiazoles. The chapter is divided into two parts. P**art A** provides an efficient protocol for the preparation of α-keto-1,3,4-oxadiazoles has been developed in good to excellent yield via the IBX-TEAB mediated oxidative cyclization of *in-situ* generated hydrazide-hydrazones prepared from the reaction of aryl glyoxal and hydrazides. Identified one-pot protocol is fairly general to prepare α-keto-1,3,4-oxadiazoles in high yields and short reaction times. **Part B** of this chapter describes a facile one-pot and solvent-free synthesis of 2-arylamino-1,3,4-oxadiazoles. The methodology involves simple grinding of aryl hydrazides with arylthiosemicarbazides in presence of iodobenzene diacetate. The reaction proceeds through *in situ* formation of acyl thiosemicarbazides at room temperature. Highlights of the protocol are mild reaction conditions, use of easily accessible starting materials, solvent-free greener synthetic approach, simple work ups and excellent yields.

In **third chapter,** copper-catalyzed direct C-H arylation of azaheterocycles including oxadiazoles, thiadiazoles, benzoxazoles and benzothiazoles has been achieved by employing easily accessible diaryliodonium salts in high yields. The developed methodology offers advantages including shorter reaction times, milder reaction conditions, a wider substrate scope and high product yields. The reaction condition were utilized to prepare various useful molecules such as ESIPT fluorescence and chelating agents including 2-(4'-metho-xyphenyl)benzoxazole, 2-(2'-methoxyphenyl)-benzoxazole and 2-(2'-methoxy-phenyl)benzo-thiazole, analogues of anticancer agents 2,5-diaryl-1,3,4-oxadiazoles and methyl ester of Tafamidis.

The **fourth chapter** illustrates the functionalization of azaheterocycles *via* formation of C-N bond and it has been divided into part A and part B. **Part A** includes the preparation of *N*-benzyl-aminoheterocycles from the coupling of *N*-tosylhydrazones with various heterocyclic amines in the presence of CuI (10 mol%) under microwave irradiation. Further, organoiodine-promoted oxidation of synthesized *N*-benzylaminoheteroarenes has been utilized to prepare an important imine derivative. Moreover this protocol was extended to prepare 1,2-disubstituted benzimidazoles derivative from the reaction of *o*-phenylenediamine with *N*-tosylhydrazones under similar reaction conditions in good yields. **Part B** of chapter includes diaryliodonium salts-promoted arylation of fused triazoles in the presence of a copper catalyst to prepare various triazolium salts. Synthetic usefulness of prepared triazolium salts has been demonstrated by preparing α-hydroxyketones in a benzoin condensation. Photophysical properties of triazolium salts have been systematically investigated in variety of solvents. Clear, intense and largely Stokes-shifted fluorescence emission observed in 427-452 nm in aqueous medium, makes these group of compounds a potential probe to explore the biological medium.

Finally, summary and conclusions of the thesis are reported in **chapter five**. Future scope of organoiodine reagents in continuation of the research results achieved in the thesis has also described in this chapter.

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LIST OF ABBREVIATIONS / SYMBOLS

Abbreviation/Symbol	Description
α	Alpha
β	Beta
Δ	Delta
°C	Degree centigrade
Å	Angstrom
Ac	Acetyl
Ac_2O	Acetic anhydride
ACN	Acetonitrile
Ar	Aryl
Bn	Benzyl
BTI	[Bis(trifluoroacetoxy)iodo]benzene
Me_3SiBr	Bromotrimethylsilane
Bu	Butyl
t-BuOK	Potassium *tert*-butoxide
t-BuOLi	Lithium *tert*-butoxide
Calcd.	Calculated
^{13}C	Carbon-13
Cat.	Catalyst
CAN	Ceric ammonium nitrate
$CDCl_3$	Deuterated chloroform
Conc	Concentration
Cu	Copper

$Cu(acac)_2$	Copper(II) acetylacetonate
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dd	Doublet of doublet
DCE	Dichloroethane
DCM	Dichloromethane
DG	Directing group
DIB	(Diacetoxy)iodobenzene
DMA	*N,N*-Dimethylacetamide
DMP	Dess-Martin periodinane
DMF	*N,N*-Dimethylformamide
DMSO-d_6	Deuterated dimethylsulfoxide
EI	Electron ionization
ESI	Electrospray ionization
EtOAc	Ethyl acetate
EtOH	Ethanol
Equiv	Equivalent
FAAH	Fatty acid amide hydrolase
g	Gram
h	Hours
NHCs	*N*-Heterocyclic carbenes
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HRMS	High resolution mass spectra
HNE	Human neutrophil elastase

HTIB	(Hydroxy(tosyloxy)iodo)benzene
IBX	2-Iodoxybenzoic acid
IC_{50}	Half maximal inhibitory concentration
IR	Infrared
Hz	Hertz
J	Coupling constant
Lit.	Literature
m-CPBA	*m*-Choroperbenzoic acid
Me	Methyl
MS	Mass spectrometry
mp	Melting point
m	Multiplet
MeOH	Methanol
mg	Milligram
MHz	Mega Hertz
min	Minutes
mL	Milliliter
mmol	Millimole
MW	Microwave
NH_3	Ammonia
N_2	Nitrogen gas
NMP	*N*-Methyl pyrrolidine
NMR	Nuclear magnetic resonance
O_2	Oxygen gas
PIFA	Bis(trifluoroacetoxy)iodobenzen

PEG	Polyethylene glycol
PIDA	Phenyl iodonium diacetate
Ph	Phenyl
$K_2Cr_2O_7$	Potassium dichromate
%	Percentage
p-TsOH	*p*-Toluenesulfonic acid
R	Hydrocarbon
rt	Room temperature
SeO_2	Selenium dioxide
s	Singlet
$NaHCO_3$	Sodium bicarbonate
Na_2SO_4	Sodium sulphate
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
t	Triplet
t-Bu	Tertiary butyl
TBAI	Tetrabutylammonium iodide
TBHP	*tert*-Butyl hydroperoxide
TEAB	Tetraethylammonium bromide
Et_3N	Triethylamine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
BF_4	Tetrafluoroborate
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran

TLC	Thin layer chromatography
TMS	Tetramethylsilane
δ	Parts per million
UV	Ultraviolet
w	Watt
μM	Micromolar

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CHAPTER 1

Introduction

1.1 Introduction

Organoiodine reagents are commercially available environmentally benign compounds with potential oxidizing properties.[1] In recent years, discovery of organoiodine catalytic systems, recyclable reagents and new enantioselective reactions using chiral hypervalent iodine compounds are the remarkable achievements in the field of organoiodine chemistry.[2] The term hypervalent was established in 1969 for molecules with elements of groups 15-18 bearing more than eight electrons in their valence shell. The most common forms of iodine compounds with an oxidation state of -1. Because it is the largest in size, most polarisable, and most electropositive of the group 17 elements, it also forms stable polycoordinate, multivalent compounds. According to IUPAC nomenclature, compounds with nonstandard bonding number are shown by the λ notation such as H_3I and H_5I are represented as λ^3 and λ^5-iodane, respectively. In organoiodine species the electronic structures are indicated by the [N-X-L] designation, in which N is the number of electrons formally associated with central atom X, L is the number of ligands (Figure 1.1).[3]

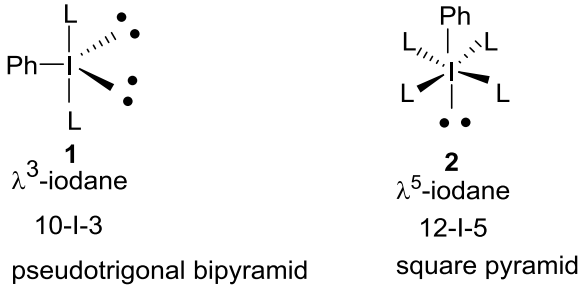
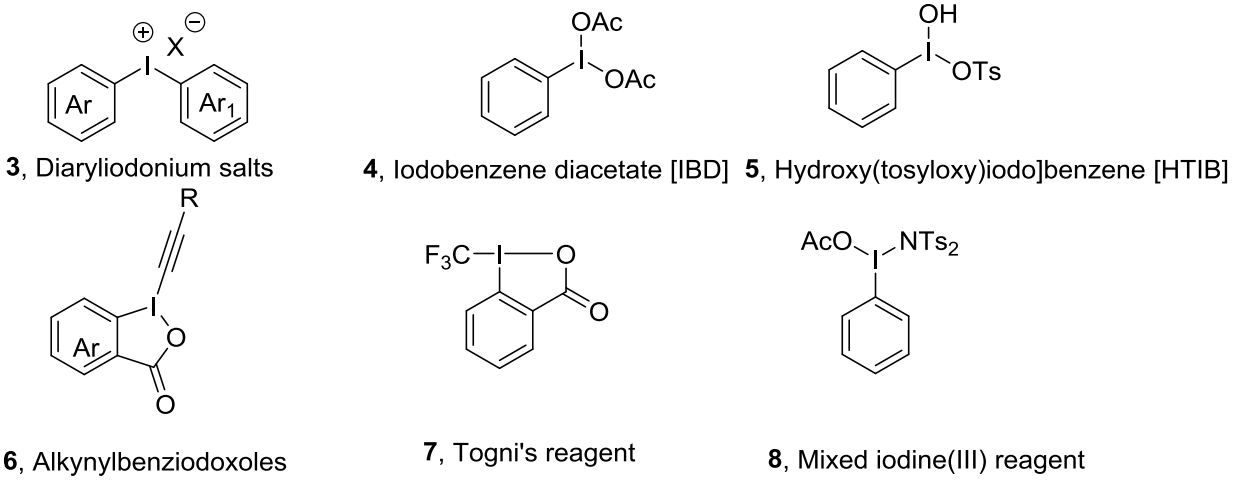


Figure 1.1 Lambda (λ) notation in organoiodines

Organoiodine compounds with electrophilic character are generally used as mild oxidizing agents. These compounds are known to undergo ligand exchange at iodine(III) atom, in analogy with transition metals. The high leaving group ability of the iodobenzene group is a valuable property for the widespread use of organoiodine reagents in synthetic chemistry.[3] Organoiodine(III) reagents are now popular for their applications in carbon–carbon, carbon–heteroatom and heteroatom–heteroatom bonds formation reactions.[4] The activation of carbon-hydrogen bond, rearrangements and fragmentations can also be induced by these reagents[5]. Organoiodine(III) compounds such as diaryliodonium salts (**3**) iodobenzene diacetate (**4**, IBD), [bis(trifluoroacetoxy)]iodobenzene (PIFA) and iodosylbenzene, are employed in oxidations of

alcohols and alkenes, as well as in α-functionalization of carbonyl compounds. Some of the leading examples of iodine(III) reagents are shown in Figure 1.2.

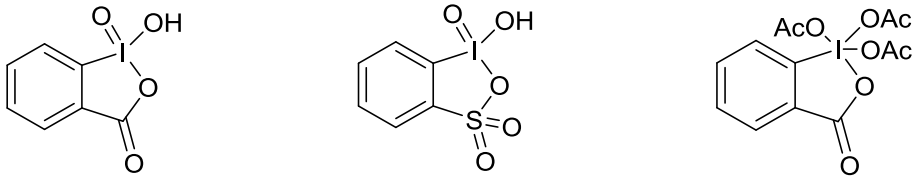


3, Diaryliodonium salts **4**, Iodobenzene diacetate [IBD] **5**, Hydroxy(tosyloxy)iodo]benzene [HTIB]

6, Alkynylbenziodoxoles **7**, Togni's reagent **8**, Mixed iodine(III) reagent

Figure 1.2 Structures of some organoiodine(III) reagents

In iodine(V) compounds, both 2-iodoxybenzoic acid (**9**, IBX)[6], 2-iodoxybenzenesulfonic acid (**10**) and Dess-Martin periodinane (**11**, DMP)[7] are extensively employed in organic synthesis as mild and highly selective reagents for the oxidation of alcohols to carbonyl compounds as well as for a variety of other synthetically useful oxidative transformations. A variety of heterocycles have been synthesized by the treatment of unsaturated aryl amides, carbamates, thiocarbamates, and ureas using IBX. Some of the important iodine(V) reagents are illustrated in Figure 1.3.



9, 2-Iodoxybenzoic acid **10**, 2-Iodoxybenzenesulfonic acid **11**, Dess-Martin periodinane

Figure 1.3 Structures of some organoiodine(V) reagents

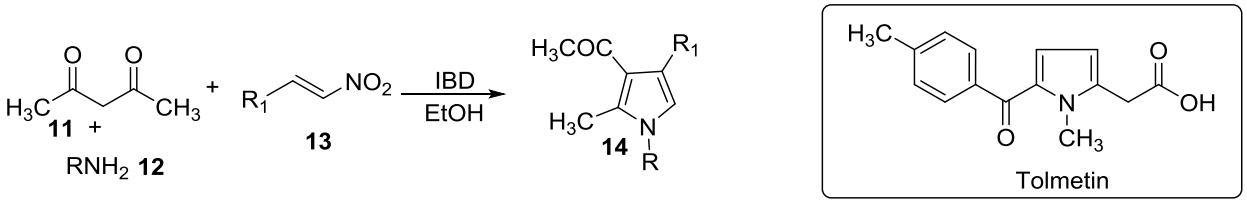
In most cases, the reactivities of organoiodine reagents are typically explained by the two-electron-transfer processes involving the initial ligand exchange of substrates at the iodine center and successive reductive elimination step to release the iodoarene as a co-product. On the other hand, the organoiodine(III) reagents are also known to act as selective and efficient single-electron-transfer (SET) oxidizing agents for electron-rich aromatic compounds if treated under specific reaction conditions.

Organoiodine reagents have shown broad synthetic utility in various oxidative transformation and rearrangement reactions for the construction of highly functionalized molecules. These reagents serve as a useful synthetic tool due to their low toxicity, high stability, ready availability, easy handling, and unique reactivities similar to that of a series of heavy metals, such as lead(IV), mercury(II), cadmium(IV) and thallium(III)-based agents. Recently, organoiodine reagents have been explored in the total synthesis of various biologically active natural products including quinones, flavanoids, alkaloids, and bisindoles.[8] Biologically active heterocycles, especially the nitrogen containing natural products have attracted attention of many research groups working in medicinal chemistry due to their diverse biological activities including antimalarial, antiviral, antibacterial, antifungal, antidepressant and antitumor.

1.2 Organoiodine reagents in the constructions and functionalizations of heterocycles

1.2.1 Pyrrole

Recently, a well-known trivalent iodine reagent, IBD with low toxicity and high stability was used in the synthesis of substituted pyrroles. The multi-component reaction (MCR) of acetylacetone **11**, primary amines **12** and nitrostyrenes **13** was smoothly performed in presence of IBD to deliver substituted pyrroles **14** in good yields. This facile and simple IBD-mediated MCR is applicable for the synthesis of biologically significant Tolmetin and related pyrroles (Scheme 1.1).[9]

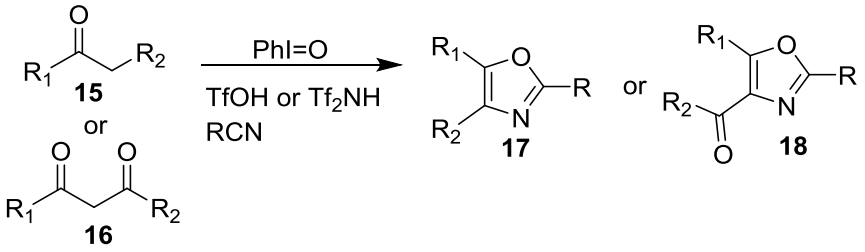


Scheme 1.1 One-pot **s**ynthesis of 2,3,4-trisubstituted pyrroles using IBD

1.2.2 Oxazole

The *in situ* prepared I(III) reagent from iodosobenzene and triflic acid was utilized to prepare substituted oxazoles **17** and **18** from enolizable ketones **15** and **16**. The generated iodine(III) reagent was reacted with various enolizable ketones in presence of different nitriles to furnish highly substituted oxazoles **17** and **18** in good yields. The developed methodology is likely to be

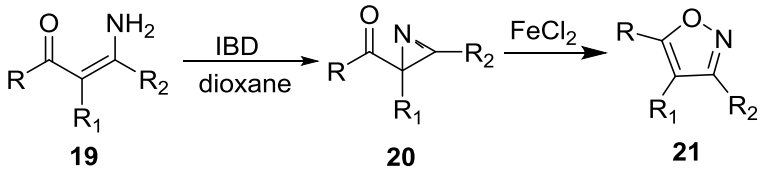
useful for the synthesis of various pharmaceutically important substituted oxazoles (Scheme 1.2).[10]



Scheme 1.2 Synthesis of substituted oxazoles from enolizable ketones

1.2.3 Isoxazoles

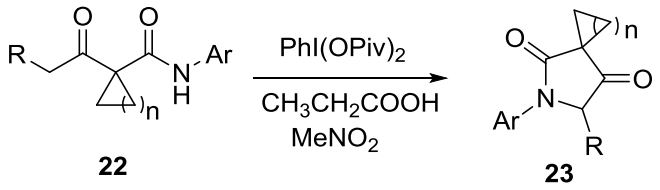
Isoxazole is a key heterocyclic motif that is widely present in natural products and pharmaceuticals. Recently, Zhao *et al* have successfully reported IBD-mediated synthesis of substituted isoxazoles **21** from enaminones **19**. This one-pot synthesis involves first iodine(III) oxidation of easily accessible enaminones **19** to generate three-membered intermediate azirines **20** and followed by ferric chloride catalyzed ring expansion. This iodine(III) catalyzed one-pot protocol is applicable for the preparation of diverse isoxazoles (Scheme 1.3).[11]



Scheme 1.3 Synthesis of tri-substituted isoxazoles **21**

1.2.4 Pyrrolidine-2,4-diones

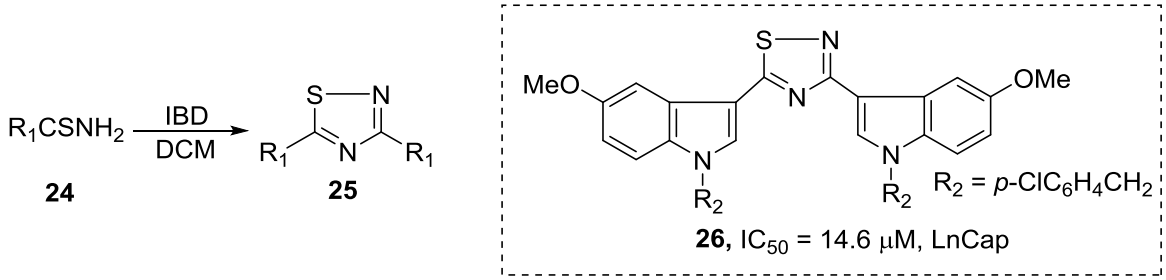
Tetramic acids with a pyrrolidine-2,4-dione ring system **23** represent an interesting class of azaheterocycles, which are found to be core structural units of many natural products exhibiting promising biological activities. A non-toxic and mild I(III) oxidant, $PhI(OPiv)_2$ was smoothly utilized for the intramolecular sp^3 C-H amination of 1-acetyl *N*-aryl carboxamides **22** to deliver a series of tetramic acid derivatives **23** (Scheme 1.4).[12]



Scheme 1.4 Organoiodine(III)-promoted synthesis of tetramic acid derivatives **23**

1.2.5 Thiadiazoles

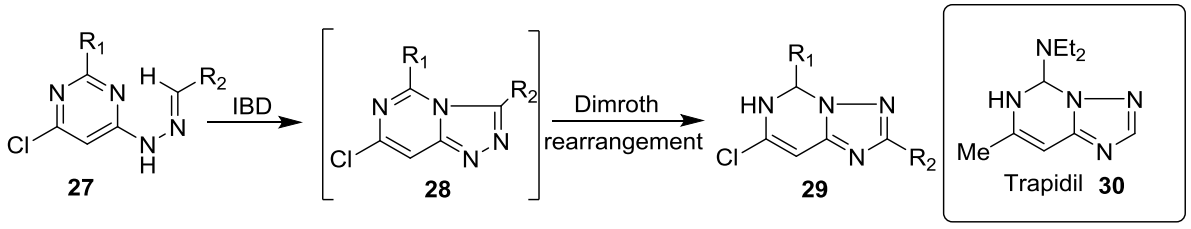
In an effort to prepare analogues of bis(indolyl)alkaloids, Kumar et al. prepared different bis(indolyl)-1,2,4-thiadiazoles **25** by the I(III)-mediated cyclodimerisation of easily accessible indole-3-thioamides **24**. Out of the synthesized compounds, 5-methoxy substituted bis(indolyl)-12,4-thiadiazole **26** was found to be the most potent with an IC_{50} value of 14.6 μM against pancreatic cancer cell line (Scheme 1.5).[13]



Scheme 1.5 Iodine(III)-mediated cyclodimerisation of thioamides to thiadiazoles

1.2.6 Triazolopyrimidines

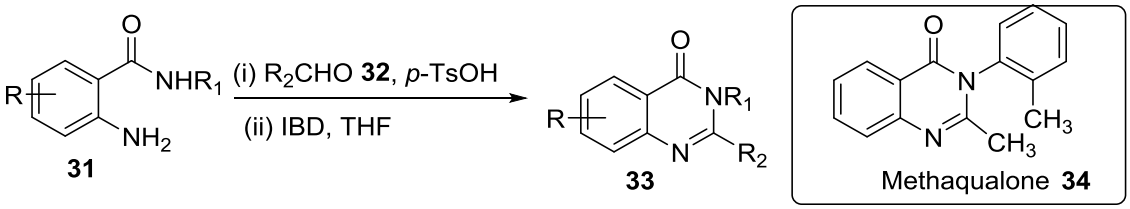
Triazolo[1,5-*c*]pyrimidine is a well recognized pharmacophore for being selective antagonists for human A_{2A} and A_3 adenosine receptor sub-types. For example, Trapidil **30** is a triazolo[1,5-*c*]pyrimidine which is the first registered drug exhibiting antiproliferative activity in glioma cells and vascular smooth muscle cells. The IBD-promoted oxidative cyclization of 6-chloro-4-pyrimidinylhydrazones **27** led to triazolo[4,3-*c*]pyrimidines **28** which underwent Dimroth rearrangement to produce the desired triazolo[4,3-*c*]pyrimidines **29** in good yields. This efficient methodology can be extended to achieve triazolopyrimidine containing heterocycles (Scheme 1.6).[14]



Scheme 1.6 Organoiodine(III)-promoted synthesis of triazolo[1,5-*c*]pyrimidines **29**

1.2.7 Quinazolines

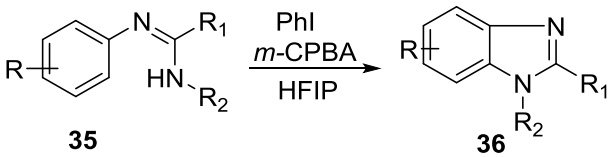
An efficient one-pot procedure for the quinazoline derivatives **33** is outlined in Scheme 1.7. The cyclocondensation of aminobenzamides **31** with aldehydes **32** in the presence of *p*-TsOH.H_2O produced quinazolinones which upon oxidative dehydrogenation with IBD delivered *N*-alkoxy quinazolinones in good yields. Additionally, the present method enables to prepare quinazolines containing drug molecules, for example, a sedative agent methaqualone **34**.[15]



Scheme 1.7 Synthesis of quinazoline derivatives **33**

1.2.8 Benzimidazoles

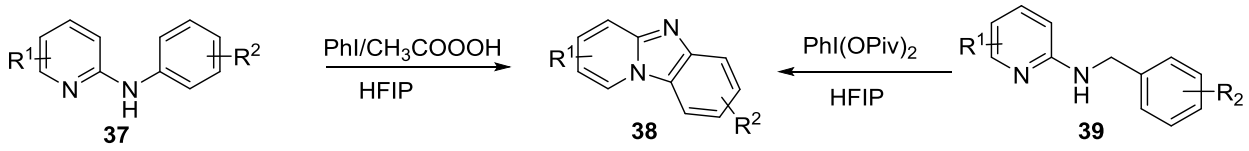
The oxidative C-N bond formation by organoiodine(III) species continued to be an efficient organic tool in the synthesis of various benzofused heterocycles. A catalytic amount of iodine(III) species was sufficient to drive the reaction to yield various *N*-substituted benzimidazoles **36** (Scheme 1.8). Active I(III) was produced by the oxidation of a catalytic amount of iodobenzene using co-oxidant *m*-CPBA. The reactive I(III) species reacted with amidines **35** to generate nitrenium ion which upon addition of arenes delivered various benzimidazoles **36** in good to excellent yields. It is one of the milder and metal-free procedure to achieve biologically important benzimidazoles [16].



Scheme 1.8 Catalytic iodine(III)-promoted synthesis of *N*-substituted benzimidazoles **36**

1.2.9 Pyrido[1,2-*a*]imidazoles

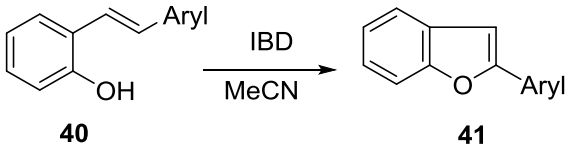
Another application of catalytic organoiodine(III) was developed in the synthesis of pyrido[1,2-*a*]imidazoles **38** (Scheme 1.9). The iodine(III) generated from catalytic iodobenzene and peracetic acid, catalyzed the C-H cycloamination of *N*-aryl-2-aminopyridines **37** to produce diversified *N*-heterocycles **38**.[17] On other hand, the same products were prepared from *N*-benzyl-2-aminopyidines **39**. The conversion of *N*-benzyl-2-aminopyidines **39** into pyrido[1,2-*a*]benzimidazoles **38** involve tandem demethylation and C-N bond formation to afford the desired products in good yields.[18]



Scheme 1.9 Synthesis of pyrido[1,2-*a*]benzimidazoles

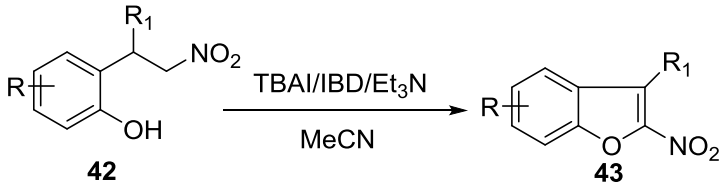
1.2.10 Benzofurans

Benzofuran is a core structural unit found in many naturally occurring compounds endowed with varied biological properties. Several approaches were reported for the construction of benzofurans **41** and naphthofurans. Recently, Singh and Writh utilized IBD-promoted metal-free cyclization of *o*-hydroxystilbenes **40** to prepare 2-arylbenzofurans (Scheme 1.10). Formation of benzofurans was postulated to occur *via* the initial IBD-induced activation of double bond followed by an intramolecular cyclization. This simple and economical strategy can be applied to synthesize pharmaceutically important benzofurans and naphthofurans.[19]



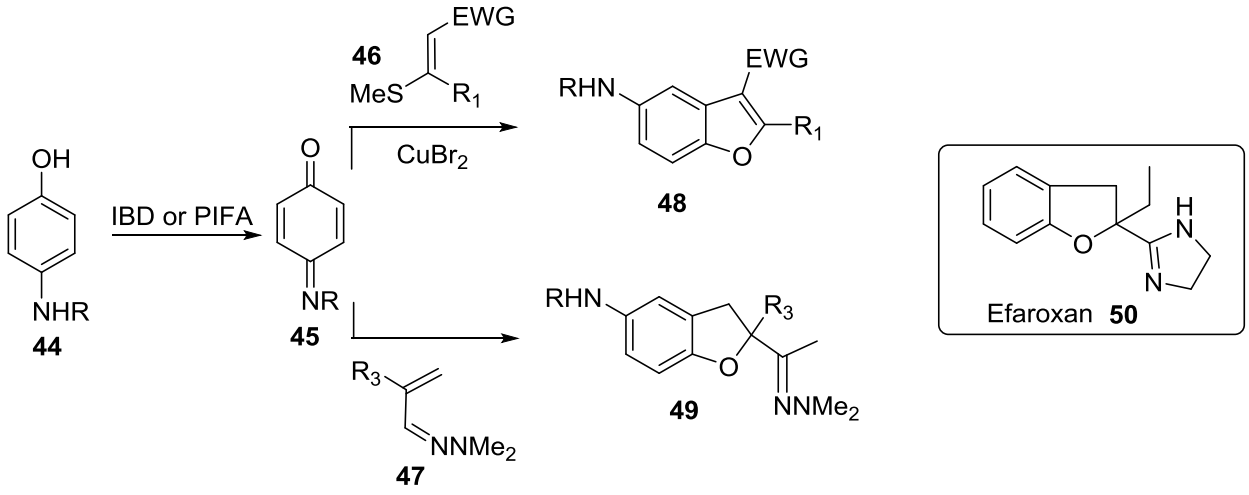
Scheme 1.10 I(III)-mediated cyclization of *o*-hydroxystilbenes to 2-arylbenzofurans **41**

By using similar approach, Lu *et al.* developed a practical and high yielding method to prepare a series of 2-nitrobenzofurans **43** from 2-(2-nitroethyl)phenols **42** (Scheme 1.11). IBD-mediated tandem oxidative cyclization of different 2-(2-nitroethyl)phenols **42** could be useful to prepare various 2-nitrobenzofurans.[20]



Scheme 1.11 Organoiodine(III)-promoted cyclization of 2-(2-nitroethyl)phenols to 2-nitrobenzofurans **43**

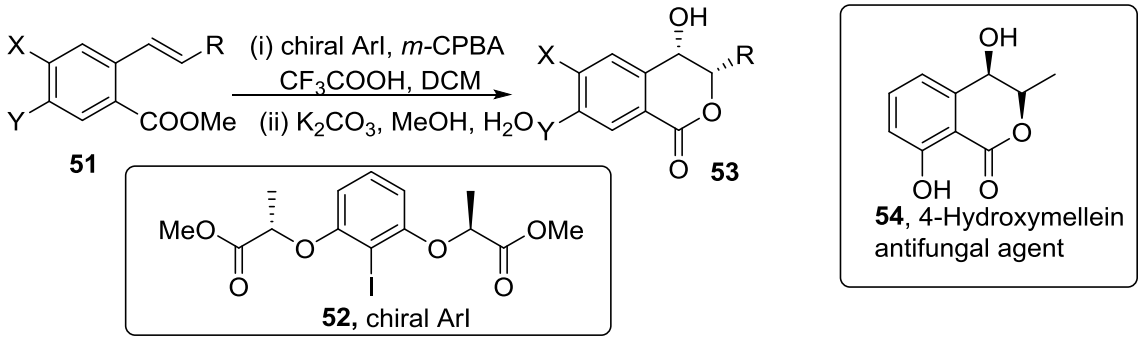
A series of 5-aminobenzofurnas **48** and 2,3-dihydrobenzofurans **49** were successfully prepared from the reactive precursor, quinone monoamine **45**, readily obtained through the IBD or PIFA-mediated oxidation of *p*-aminophenols **44** (Scheme 1.12). Reaction of quinone monoamine with ketene acetals **46** afforded the corresponding benzofurans **48.**[21] Using this strategy, Roland et al. independently reported the synthesis of 2,3-dihydrobenzofurans **49** *via* [3+2] cycloaddition of quinone monoamine with various azadienes **47**. The utility of developed protocol was demonstrated for the construction of 2,3-dihydrobenzofurans containing adrenergic antagonist Efaroxan **50**.[22]



Scheme 1.12 Synthesis of various benzofurans and dihydrobenzofurans

1.2.11 Isochromanones

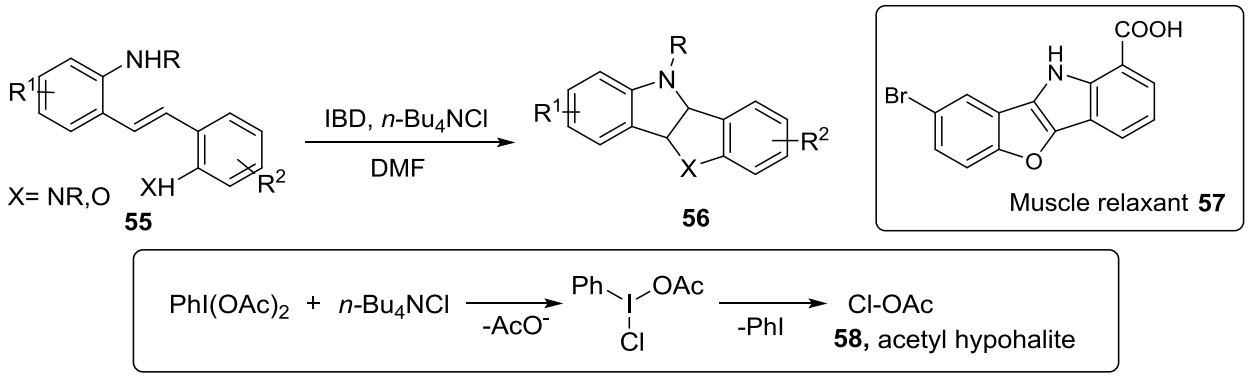
Very recently, Fujita et al. described an interesting synthesis of 3-alkyl- 4-hydroxyiso-chroman-1-ones **53** by employing chiral iodine(III) species **52** generated *in situ* by the oxidation of a catalytic amount of chiral iodoarenes with *m*-CPBA (Scheme 1.13). The enantioselective oxylactonization of achiral precursors, alkenylbenzoates **51** were carried out by the catalytic amount of chiral iodine(III) reagent and prepared various 3-alkyl- 4-hydroxyisochroman-1-ones **53** with high enantiomeric purity (90% *ee*). The advantage of the present methodology is catalytic cycle of chiral iodine(III) reagent continued to deliver the final product with enhanced enantioselectivity. The developed method facilitates to access biologically important 4-hydroxy-isochroman-1-one motifs **54.**[23]



Scheme 1.13 Iodine(III)-mediated enantioselective oxylactonization of alkenylbenzoates **51**

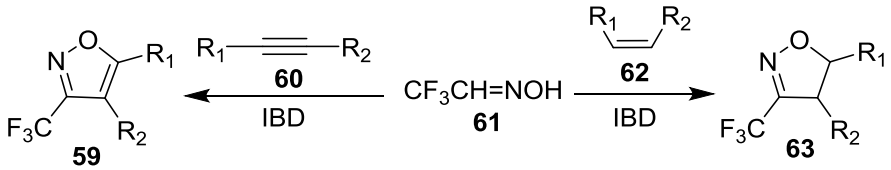
1.2.12 Indolines

Enhanced electrophilicity of IBD was successfully applied in the intramolecular oxidative diamination of olefins **55**, which resulted in bisindoline derivatives **56** (Scheme 1.14). Addition of *n*-BuNCl to IBD released highly reactive species acetylhypohalite **58** which underwent an electrophilic addition to the double bond to produce three-membered halonium intermediate which upon sequential ring opening and nucleophilic substitution led to desired bisindolines **56** in good yields. This oxidative diamination of olefins proceeded well with IBD and a halide additive to produce various bisindolines. Moreover, the developed method is useful for the preparation of therapeutic muscle relaxant agent **57.**[24]



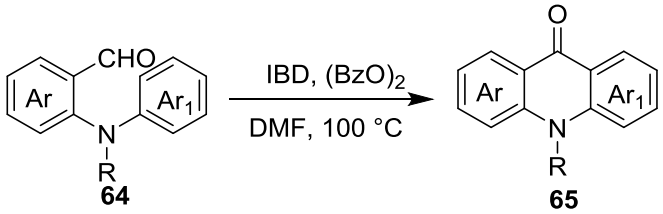
Scheme 1.14 Oxidative diamination of olefins to bisindolines

Trifluoromethyl group is one of the important moieties to improve liphophilicity and stability of the drug molecules. Benoit et al. synthesized various series of 3-trifluoromethyl-2-isoxazolines **63** and 3-trifluoromethyl-2-isoxazoles **59** by utilizing IBD-induced oxidation of trifluoromethyl aldoximes **61** followed by 1,3-dipolar cycloaddition of resulting nitrile oxides with different dipolarophiles (alkynes **60** and alkenes **62**). This one-pot and metal-free IBD-mediated 1,3-dipolar cycloaddition protocol enables to prepare valuable fluorinated bioactive oxazoles and isoxazolines (Scheme 1.15). [25]



Scheme 1.15 Synthesis of trifluoromethylated bioactive oxazoles and isoxazolines

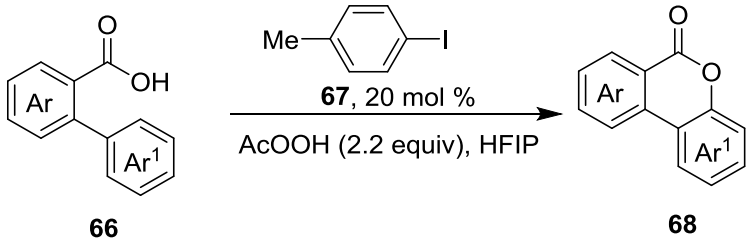
Zhao and Du's group disclosed a metal-free cross-dehydrogenative coupling (CDC) of various 2-(*N*-arylamino)aldehydes **64** for direct aryl-aldehyde C(sp^2)–C(sp^2) bond formation to provide a convenient approach for the synthesis of biologically important acridone derivatives **65** (Scheme 1.16). IBD was used in combination with a substoichiometric amount of benzoyl peroxide as a radical initiator for this oxidative intramolecular annulation reaction[26] which presumably proceeds *via* the intermediacy of acyl radicals .



Scheme 1.16 Cross-dehydrogenative coupling between aldehydes and arenes

1.2.13 Benzolactones

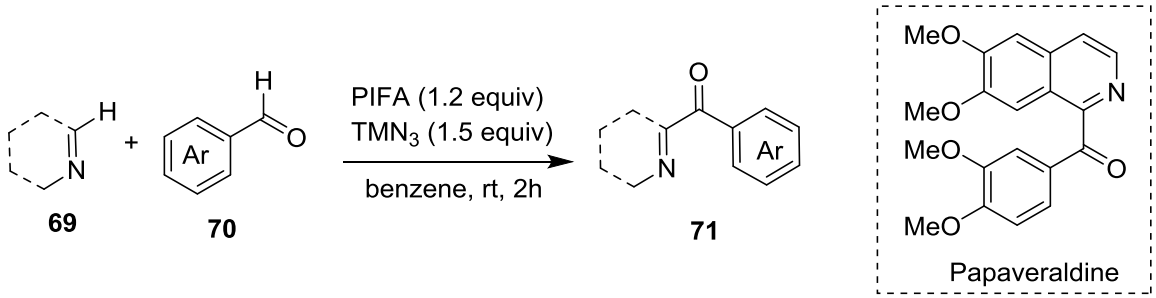
Martin and coworkers[27] reported a mild organocatalytic C(sp^2)–H bond functionalization/C–O bond forming process to prepare benzolactones **68** in good yields. In this reaction catalytic amount of 4-iodotoluene (**67**, 20 mol%) was treated with excess of peracetic acid (2.2 equiv) to generate *in situ* iodine(III) species which catalyse the C-O bond formation of **66** (Scheme 1.17).



Scheme 1.17 Construction of C-O bond to prepare benzolactones **68**

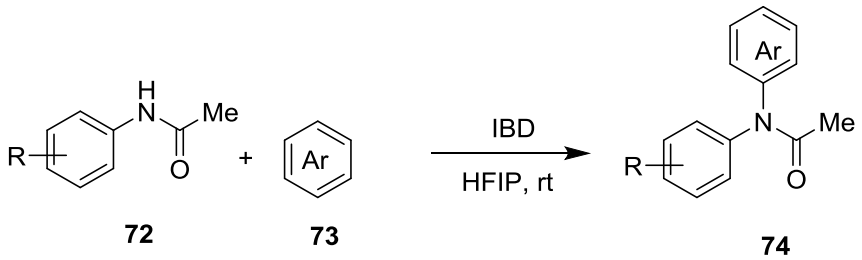
1.2.14 Aroyl heterocycles

Antonchick et al.[28] disclosed an efficient PIFA-mediated cross-dehydrogenative coupling (CDC) between heterocycles **69** and aldehydes **70** in the presence of trimethylsilyl azide ($TMSN_3$) as an additive (Scheme 1.18). Several *N*-containing heterocycles such as quinoline, isoquinoline, quinoxazaline, β-carboline and caffeine successfully cross-coupled to furnish the corresponding acylated heterocycles **71** in good yields. Interestingly, this protocol was proved to afford one-step access to many isoquinoline alkaloids such as papaveraldine which exhibit important biological and medicinal properties.



Scheme 1.18 PIFA-mediated direct functionalization of heterocycles and aldehydes

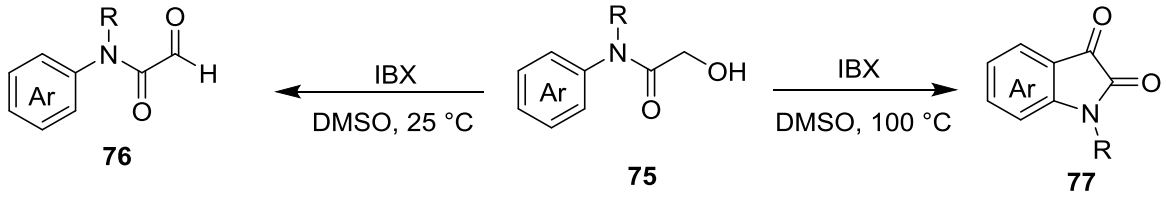
Subsequently, Antonchick co-workers developed an interesting direct oxidative C–N bond formation between acetanilide **72** and unfunctionalized arenes **73** using IBD as an oxidant (Scheme 1.19).



Scheme 1.19 IBD-mediated direct C-N bond formation

1.2.15 Isatin

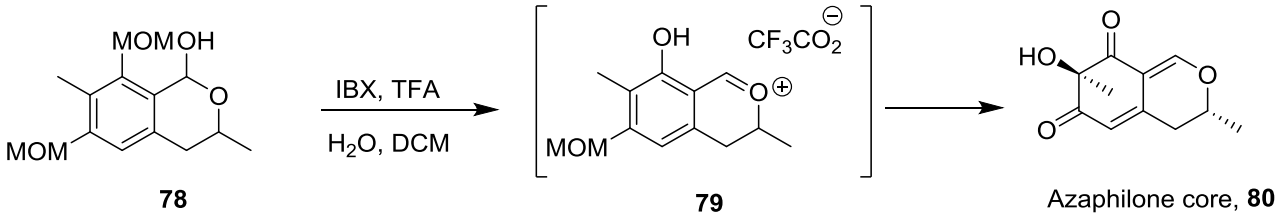
An interesting temperature-controlled oxidation of α-hydroxy amides in the presence of IBX was developed by Li and co-workers.[29] This metal-free procedure furnished substituted isatins **77** at higher temperature (100 °C) whereas at reduced temperature (25 °C) α-formyl amides **76** were obtained in good to excellent yields (Scheme 1.20).



Scheme 1.20 IBX-promoted synthesis of isatin

1.2.16 Azaphilone

Franck and co-workers synthesized azaphilone core in a highly diastereoselective manner. It was accomplished by the treatment of MOM-bisprotected phenolic hemiketal **78** in TFA, which *in situ* generated the mono-deprotected oxonium ion **79**, and IBX (2 equiv) in the presence of water. Under these conditions, hydroxylated dearomatized product **80** was furnished in 48% yield in a 90:10 diastereomeric ratio (Scheme 1.21).



Scheme 1.21 Synthesis of azaphilone core

1.3 Diaryliodonium salts

The synthetic applications of diaryliodonium salts **81** (Ar_2IX) have been developed enormously in the last decade.[30] Diaryliodonium salts are air and moisture stable solid compounds which are easily available and applicable in a wide variety of transformations under both metal-free and metal-catalyzed conditions.[31] Advantages of these electrophilic arylation reagents include their low toxicity, good selectivity, and high reactivity, making difficult transformations possible at ambient temperature without need for excess reagents. Their properties resemble those of aryl-substituted heavy metal reagents, which make them green alternatives to stoichiometric reactions with, for example, lead, thallium, and tin derivatives.

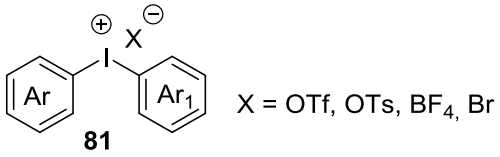


Figure 1.4 Diaryliodonium salts **81**

Metal-free reactions with Ar_2IX provide a solution to the problems with low threshold values for transition metals in the pharmaceutical industry. In addition to the arylating properties, diaryliodonium salts are used as photoinitiators in cationic polymerizations.[32] They have been

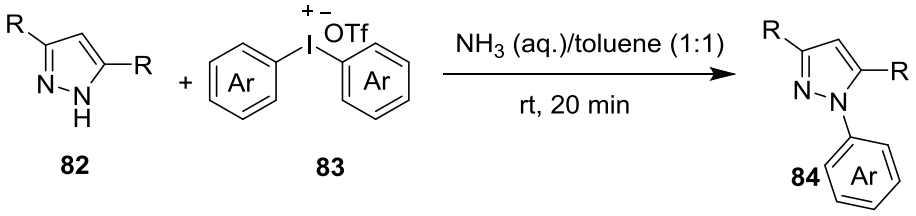
employed as Lewis acid, as oxidants (*via* formation of phenyl radicals) and in the area of macromolecular chemistry.[33]

X-Ray studies of diaryliodonium salts show the T-shaped structure typical for iodine(III) compounds, with the "counterion" X sharing a three-center four-electron (3c–4e) bond with the iodine and the apical aryl group. Hence, the iodine has more than eight electrons in its valence shell, and fulfills the criteria for being hypervalent. The degree of dissociation to Ar_2I^+ and X– in solution depends on both the solvent and the counterion. The term diaryliodonium salt and drawings with 109 bond angle are thus somewhat misleading, but the IUPAC name diaryl-λ3-iodanes has not become standardized yet. The structure and general reactivity of iodine(III) compounds has been described by Ochiai and co-workers.[34] The reactivity of iodine(III) compounds is based on the electrophilic nature of the iodine, which is derived from the electron distribution in the 3c–4e bond. In reactions with Ar_2IX, one aryl group is transferred to the nucleophile, and the other is reductively eliminated as ArI. The "hyperleaving group ability" of ArI as a neutral ligand is highly advantageous compared to anionic ligands which are expelled in nucleophilic aromatic substitutions or cross-coupling reactions.[35]

1.3.1 Arylation of various nucelophiles

1.3.1.1 *N*-Arylpyrazoles

Novak and Gonda developed a new synthetic protocol for the *N*-arylation of pyrazoles **82** using diaryliodonium salts **83** under metal-free conditions. This transformation proceeded in the presence of aqueous ammonia solution as a mild base (Scheme 1.22). In this reaction both sterically and electronically different diaryliodonium salts were investigated and revealed that transfer of ortho substituted and electron-deficient iodonium salts to the pyrazole ring is highly preferable.

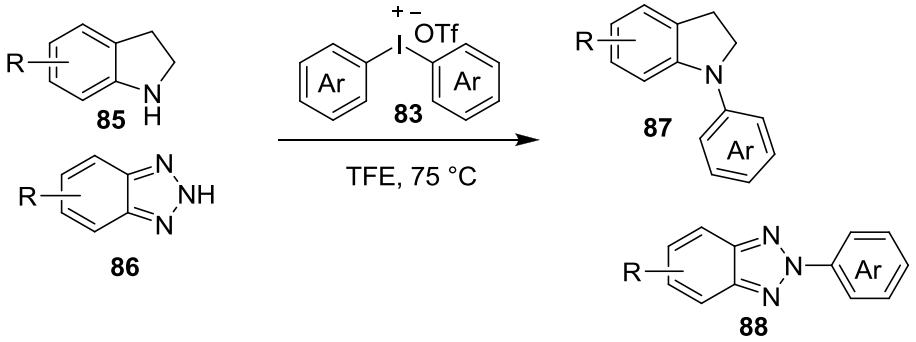


82 83 84

Scheme 1.22 Synthesis of *N*-arylpyrazoles **84**

1.3.1.2 *N*-Arylindolines

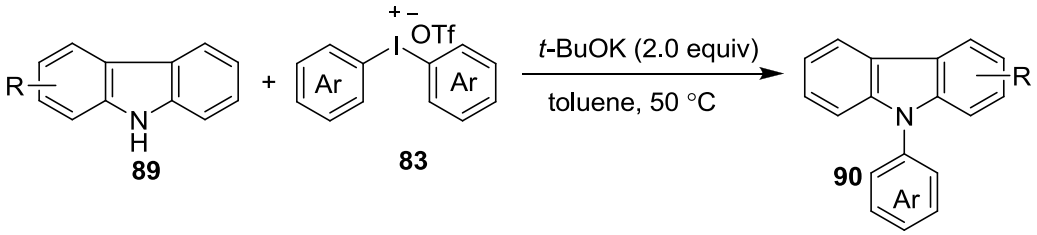
Boris and Stefan[36] developed a metal-free *N*-arylation of indoline **85** frameworks using diaryliodonium salts in the presence trifluoroethanol. This reaction conditions were successfully extended to arylate 1*H*-benzotriazole **86** to deliver the corresponding arylated products **88** in good yields (Scheme 1.23).



Scheme 1.23 *N*-Arylation of indolines and benzotriazoles

1.3.1.3 *N*-Arylcarbazoles

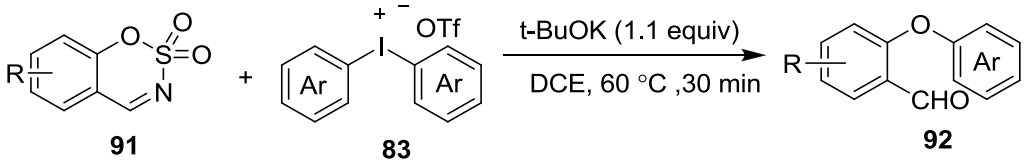
Recently, a transition-metal free protocol for the *N*-arylation of carbazoles **89** using diaryliodonium salts **83** was developed. Both electron-rich and poor substituted carbazoles and iodonium salts were smoothly coupled to afford the *N*-arylcarbazoles **90** in good to excellent yields as shown in Scheme 1.24.[37]



Scheme 1.24 Synthesis of *N*-arylcarbazoles **90**

1.3.1.4 2-Aryloxybenzaldehydes

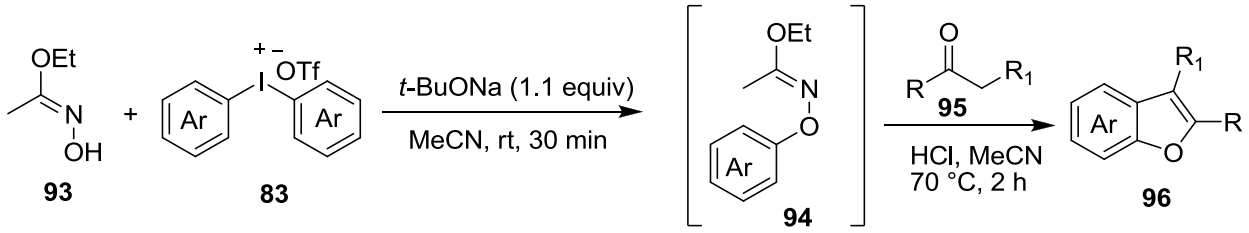
Wang et al. developed a novel O-arylation method through a domino reaction of benzo[*e*][1,2,3]oxathiazine 2,2-dioxides **91** by using diaryliodonium salts **83** under metal-free conditions (Scheme 1.25). A variety of substituted diaryl ethers possessing aldehydic group were acquired in this procedure. Moreover, the 2-aryloxybenzaldehydes are used as versatile intermediates for the synthesis of valuable molecules.[38]



Scheme 1.25 Synthesis of 2-aryloxybenzaldehydes

1.3.1.5 Benzofurans

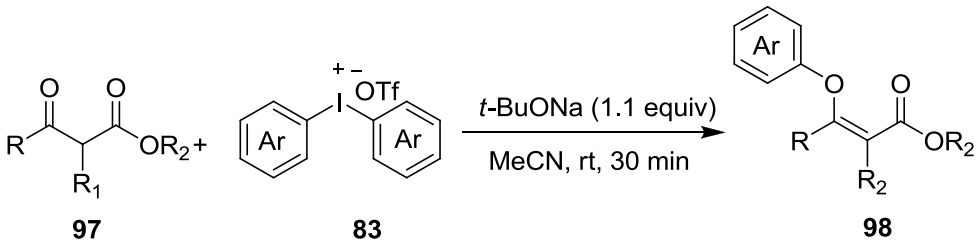
Olofsson group reported the base-catalyzed O-arylation of ethyl acetohydroxamates aryloxyamines **93** in good to excellent yields. The yielded aryloxyamines **94** were converted into benzofurans **96** by the subsequent addition of α-enolizable ketones **95** under acidic conditions (Scheme 1.26).[39]



Scheme 1.26 Synthesis of benzofurans **96**

1.3.1.6 β-keto esters

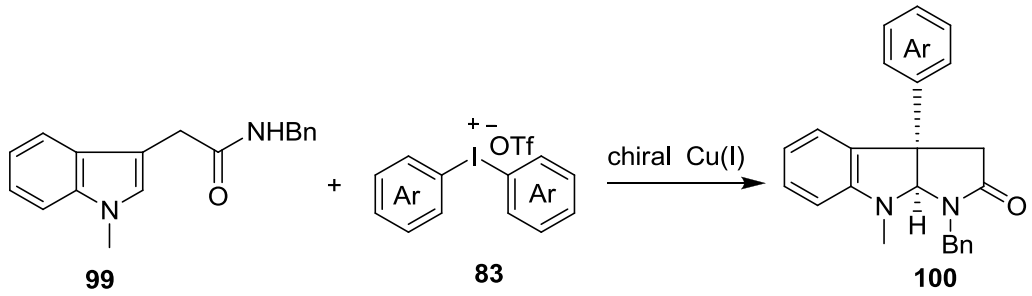
A chemoselective O-arylation of β-keto esters **97** was possible using copper-catalyzed reaction conditions with Li_2CO_3 at 70 °C for a long time (Scheme 1.27). Products **98** were obtained with excellent Z-stereoselectivity independent of the substitution pattern. Reaction conditions were successfully extended to cyclic β-diketones **97**. The observed C/O-selectivity is opposite to that found in reactions under metal-free conditions.[40]



Scheme 1.27 Chemoselective O-arylation of β-keto esters **97**

1.3.1.7 Pyrroloindolines

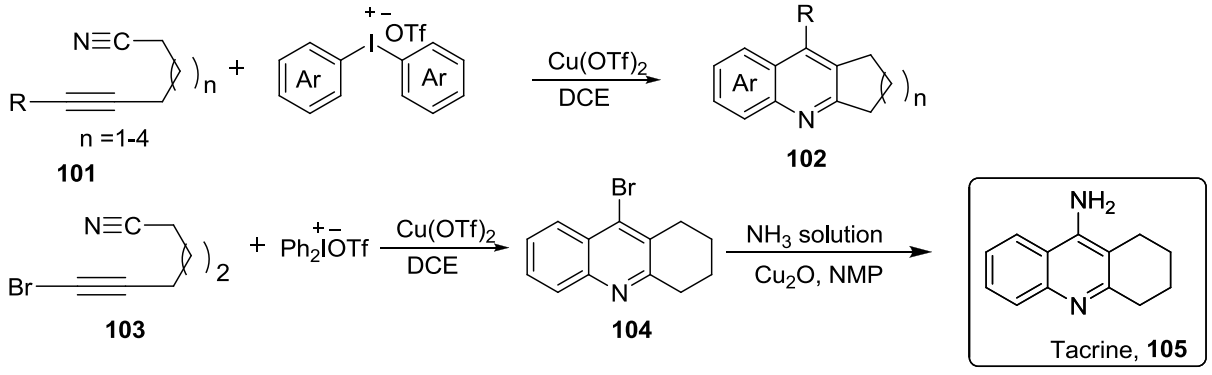
Pyrroloindolines are associated with a diverse family of structurally complex polyindoline alkaloids endowed with diverse biological activities. Macmillan and Zhu reported an enantioselective tandem arylation-cyclization of indole acetamides **99** and diphenyliodonium triflate **83** in presence of Cu(I) to obtain pyrroloindolines **100**. This rapid and enantioselective protocol provides a new strategy for the enantioselective synthesis of various pyrroloindolines (Scheme 1.28).[41]



Scheme 1.28 Enantioselective synthesis of bioactive pyrroloindolines **100**

1.3.1.8 Quinolines

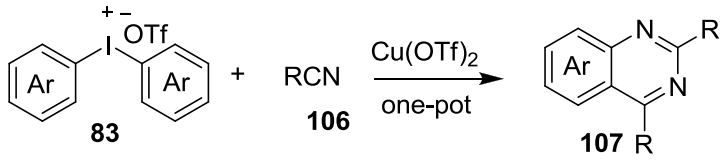
Diaryliodonium salts are proved to be versatile arylating agents due to their advantageous features including easy availability, stability and easy to handle. Recently, Wang et al utilized an intramolecular [2+2+2] annulation of ω-cyano-1-alkynes **101** and **103** with diaryliodonium salts in the construction of polycyclic quinolines **102** and **104**. This concise method was applied to prepare Alzheimer drug 'Tacrine' **105** (Scheme 1.29).[42]



Scheme 1.29 Synthesis of polycyclic quinolines

1.3.1.9 Quinazolines

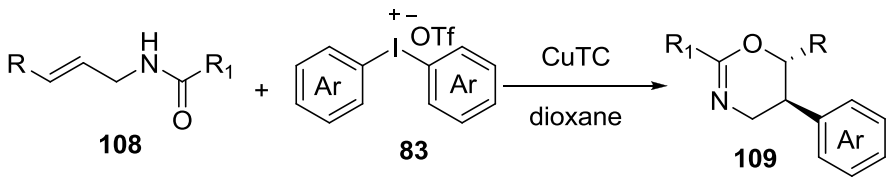
Another successful application of diaryliodonium salts was demonstrated in the construction of quinazolines **107** (Scheme 1.30). The developed one-pot strategy involved the reaction of aromatic nitriles **106** (two moles) with diaryliodonium salts **83** (one mole) in presence of copper triflate as a catalyst. The proposed mechanistic pathway is believed to involve [2+2+2] cascade annulation. This novel synthesis of quinazolines **107** further extended the scope and reactivity of diaryliodonium salts to prepare azaheterocycles.[43]



Scheme 1.30 Aromatic nitriles and diaryliodonium salts cascade annulations to quinazolines **107**

1.3.1.10 Oxazines

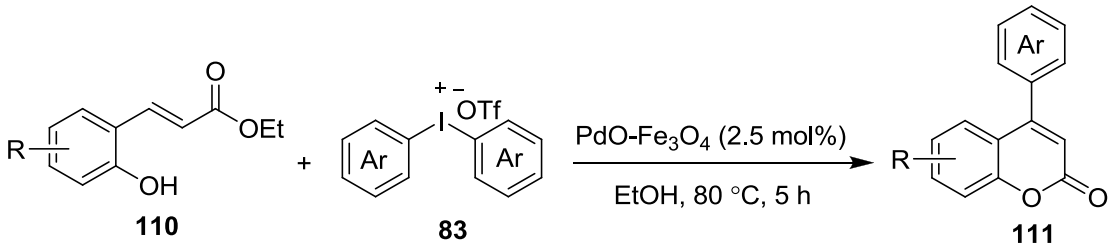
Gaunt et al showed utility of diaryliodonium salts in the oxyarylation of allylic amides **108** to achieve various oxazines **109** (Scheme 1.31). Treatment of **108** with easily accessible diaryliodonium salts **83** in the presence of a catalytic amount of copperthiophenecarboxylate furnished highly functionalized oxazines **109**. Formation of an oxazine ring through sequential C-O and C-C bonds formation delivered oxazine derivatives **109** with high stereoselectivity.[44]



Scheme 1.31 Oxyarylation of allylic amides to aryl-substituted oxazines **109**

1.3.1.11 4-Arylcoumarins

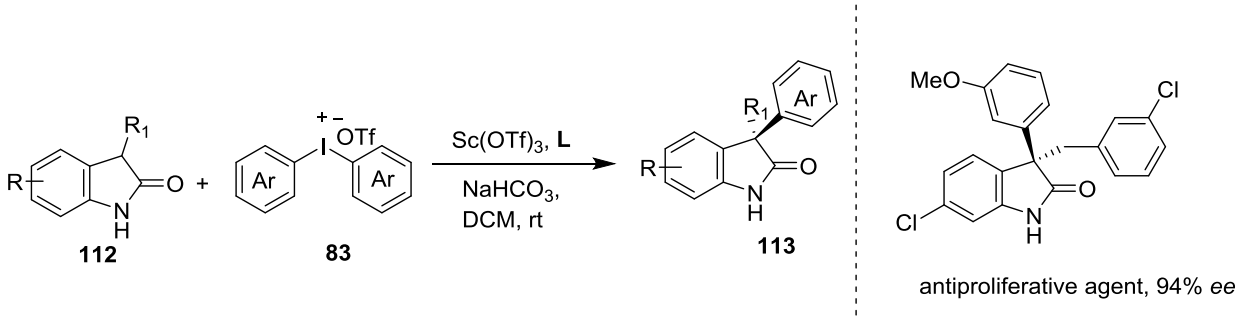
By using heterogeneous palladium(II) oxide magnetite catalyst Ramon *et al.*[45] described the Heck-arylation/cyclization reaction of *o*-hydroxyphenylacrylates **110** and diaryliodonium salts to produce 4-arylcoumarins **111** in excellent yields (Scheme 1.32). The advantages of the catalyst are cheap, selective, versatile and easily recovered from the reaction mixture.



Scheme 1.32 Synthesis of 4-arylcoumarins

1.3.1.12 α-Arylation of oxindoles

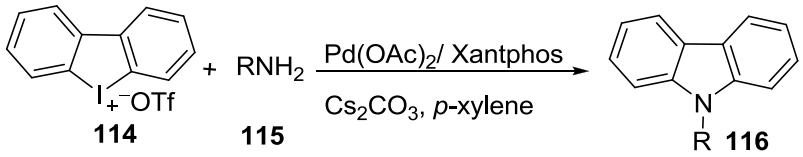
A new chiral Lewis acid-catalyzed asymmetric α-arylation for *N*-unprotected 3-substituted oxindoles **112** by employing diaryliodonium salts was developed. The scandium(III) triflate complex[46] bearing tetrahydroisoquinoline ligand produces desired oxindole derivatives in high enantioselectivity and reactivity as shown in Scheme 1.33. The developed protocol was further utilized to prepare an antiproliferative agent in 70% yield with high enantioselectivity (94% *ee*).



Scheme 1.33 Asymmetric α-arylation of oxindoles

1.3.1.13 Carbazoles

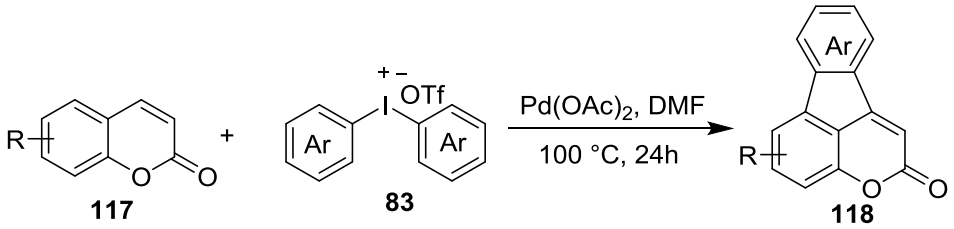
Another exciting application of cyclic diaryliodonium salts **114** was developed by Riedmüller and Nachtsheim as depicted in Scheme 1.34 Various *N*-arylcarbazoles **116** were synthesized from the cyclic iodonium salts **114** and amines **115** through tandem C-N bond formation and Buchwald-amination.[47]



Scheme 1.34 Synthesis of carbazoles **116**

1.3.1.14 Dibenzocoumarins

A novel, Pd-catalyzed C-C bonds forming strategy was employed between diaryliodonium salts **83** and coumarins **117** to prepare π-expanded 4,5-dibenzo-coumarins **118**. Construction of dibenzocoumarins **118** was smoothly proceeded without any ligand, oxidant and directing groups. The proposed diarylation proceeded *via* Pd(II/IV) catalytic cycles with the consecutive activation of C-I and vicinal C-H bonds in diaryliodonium salts (Scheme 1.35).[48]



Scheme 1.35 Synthesis of 4,5-dibenzocoumarins **118**

1.4 References

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CHAPTER 2

Organoiodine-Promoted Synthesis of 1,3,4-Oxadiazoles

Part A: A facile and expeditious one-pot synthesis of *α*-keto-1,3,4-oxadiazoles

Part B: IBD-promoted facile synthesis of 2-arylamino-1,3,4-oxadiazoles and fused arylamino-[1,2,4]triazoles

2.1 1,3,4-Oxadiazoles

Oxadiazoles are very good bioisosteres of amides and esters, which can contribute significant pharmacokinetic property due to presence of azole (-N=C-O) group in oxadiazole nucleus which increases the lipophilicity that influence the ability of drug to reach the target by transmembrane diffusion.[1] Compounds containing oxadiazole nucleus have a wide range of biological activity including antimicrobial, analgesic, anti-inflammatory, anti-diabetic, antiviral, antihypertensive, anticonvulsant and anticancer properties.[2] The ability of 1,3,4-oxadiazole compounds to undergo various chemical reactions has made them important for molecule planning because of their privileged structure, which has enormous biological potential.[3] In drug discovery and development, a number of compounds containing an 1,3,4-oxadiazole moiety are in late stage clinical trials as shown in Figure 2.1. For examples, Zibotentan as an anticancer agent, Raltegravir an antiretroviral drug for the treatment of HIV infection,[4] Furamizole as antibacterial,[5] antihypertensive agents Tiodazosin and Nesapidil[5] are based on 1,3, 4-oxadiazole moiety.

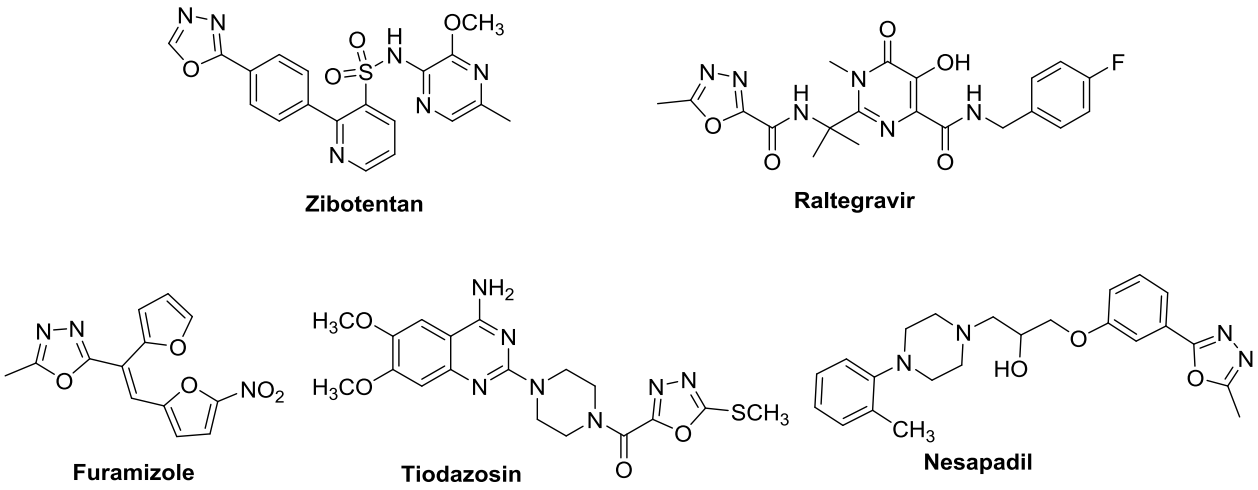


Figure 2.1 Structures of some representative 1,3,4-oxadiazole containing drug candidates

In this chapter, development of novel synthetic protocols for the construction of two different 1,3,4-oxadiazoles have been discussed. Part A describes IBX-promoted expeditious synthesis of *α*-keto-1,3,4-oxadiazoles and fused keto triazoles. Part B deals with synthesis of a diverse series of 2-arylamino-1,3,4-oxadiazoles and fused arylamino-[1,2,4]triazoles.

2.2 Part A

A facile and expeditious one-pot synthesis of *α*-keto-1,3,4-oxadiazoles

2.2.1 Introduction

The broad spectrum of biological activities of *α*-keto-1,3,4 oxadiazoles have generated a significant interest to synthesize and explore these compounds as useful targets. Recently, *α*-keto-1,3,4-oxadiazoles have been identified as cathepsin K inhibitors, a cysteine protease expressed in osteoclasts and responsible for bone resorption.[6] *α*-Keto-1,3,4-oxadiazoles also displayed good potency against human neutrophil elastase (HNE)[7] and fatty acid amide hydrolase (FAAH).[8] Rydzewski et al. described a series of oxadiazoles as remarkably potent inhibitors of the 20S proteasome.[9] Other analogues of *α*-keto-1,3,4-oxadiazoles such as 2-aryl-4-benzoylthiazoles and 4-aryl-2-benzoylimidazoles have been reported to show excellent inhibition activity against various cancer cells.[10] Papaveralidine, an isoquinoline alkaloid with *α*-keto functionality exhibits antispasmodic activity (Figure 2.2.1).[11]

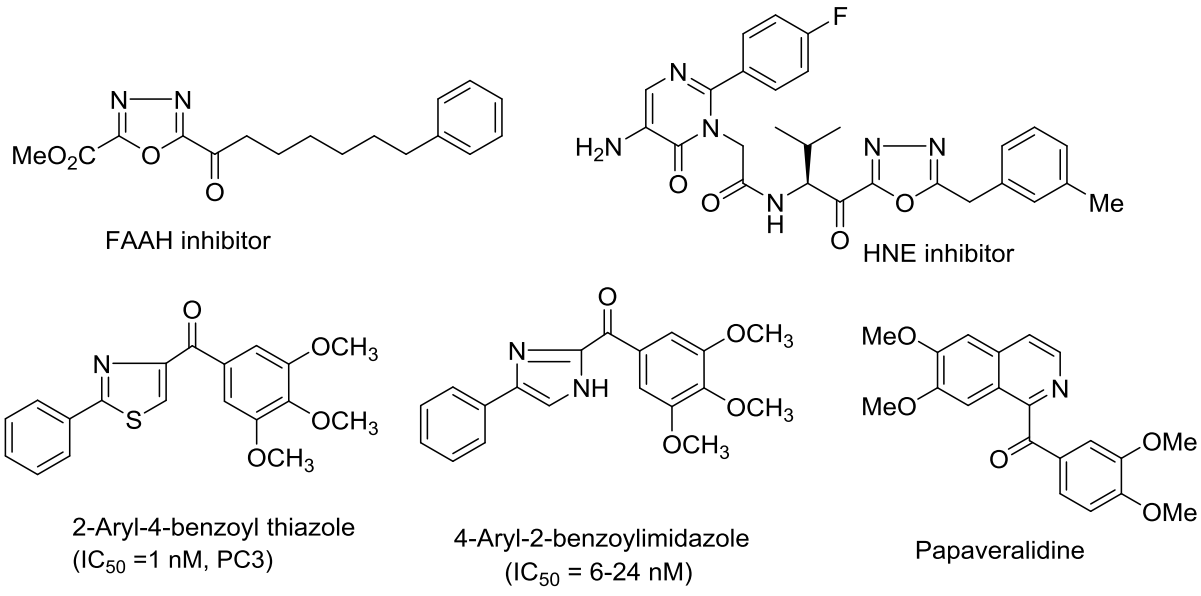
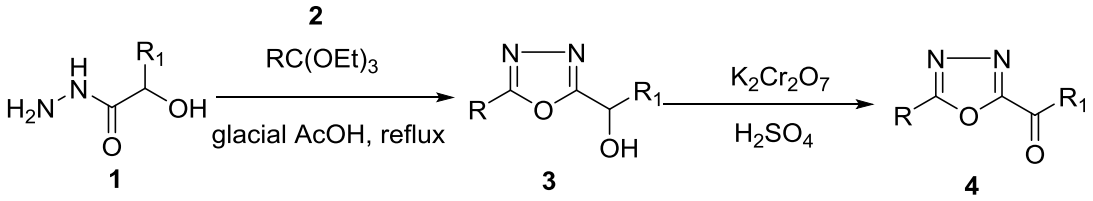


Figure 2.2.1 Representative bioactive *α*-keto-1,3,4-oxadiazoles and their analogues

Due to notable significance of these keto-oxadiazoles in medicinal chemistry, the methodology for the construction of these heterocycles have been less explored. To the best of our knowledge there are only four reports as summarized below present in literature.

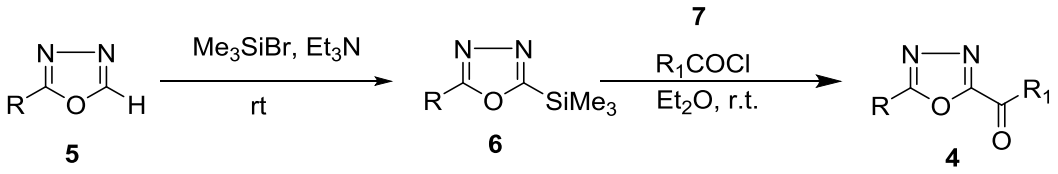
An earlier strategy for the synthesis of *α*-keto-1,3,4-oxadiazoles **4** deals with the oxidation of 2-(1-hydroxy-1-phenylmethyl)-1,3,4-oxadiazoles **1** utilizing a mixture of $K_2Cr_2O_7/H_2SO_4$.[12]

The intermediate **3** was synthesized from the reaction of benzylic acid hydrazide **1** with triethyl orthoester **2** in acetic acid under refluxing condition (Scheme 2.2.1).[13]



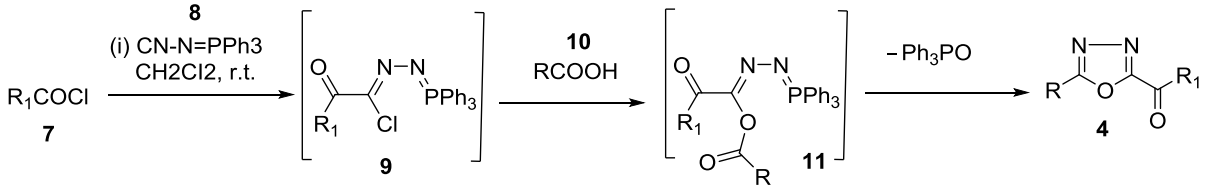
Scheme 2.2.1 Synthesis of *α*-keto-1,3,4-oxadiazoles using $K_2Cr_2O_7$ as an oxidizing agent

Another method involves acylation of 2-aryl-5-trimethylsilyl-1,3,4-oxadiazoles **6** with an appropriate amount of acid chloride **7** in 2-96 h to produce *α*-keto-1,3,4-oxadiazoles **4** in 54-81% yields.[14] The precursor **6** was synthesized from the reaction of 2-aryl-1,3,4-oxadiazole **5** with bromotrimethylsilane in the presence of triethylamine (Scheme 2.2.2).[15]



Scheme 2.2.2 Synthesis of *α*-keto-1,3,4-oxadiazoles **4**

Recently, Cui et al. have reported synthesis of *α*-keto-1,3,4-oxadiazoles **4** in moderate yields (36-69%) by employing acyl chlorides **7** and (*N*-isocyanimine) triphenylphosphorane **8** *via* *α*-keto imidoyl chloride intermediate **9** trapped by carboxylic acids **10** which converted into adduct **11.** Next, intramolecular aza-Wittig condensation sequence yielded the final product **4** by the removal of triphenylphosphine oxide as a side product (Scheme 2.2.3).[16]



Scheme 2.2.3 Synthesis of *α*-keto-1,3,4-oxadiazoles from acyl chlorides **7** with (*N*-isocyanimine) triphenylphosphorane **8**

In recent past, organoiodine reagents especially 2-iodoxybenzoic acid (IBX) has found an increasing number of applications in organic synthesis.[17] IBX, an example of iodine(V) reagent, belongs to the class of aryl-λ^5 iodanes and highly selective reagent for the oxidation

of alcohols to carbonyl compounds.[18] Besides the oxidation of alcohols to carbonyl compounds a large variety of unique oxidative transformations leading to useful compounds have been developed which establish IBX as an universally applicable oxidizing agent (Figure 2.2.2).[6]

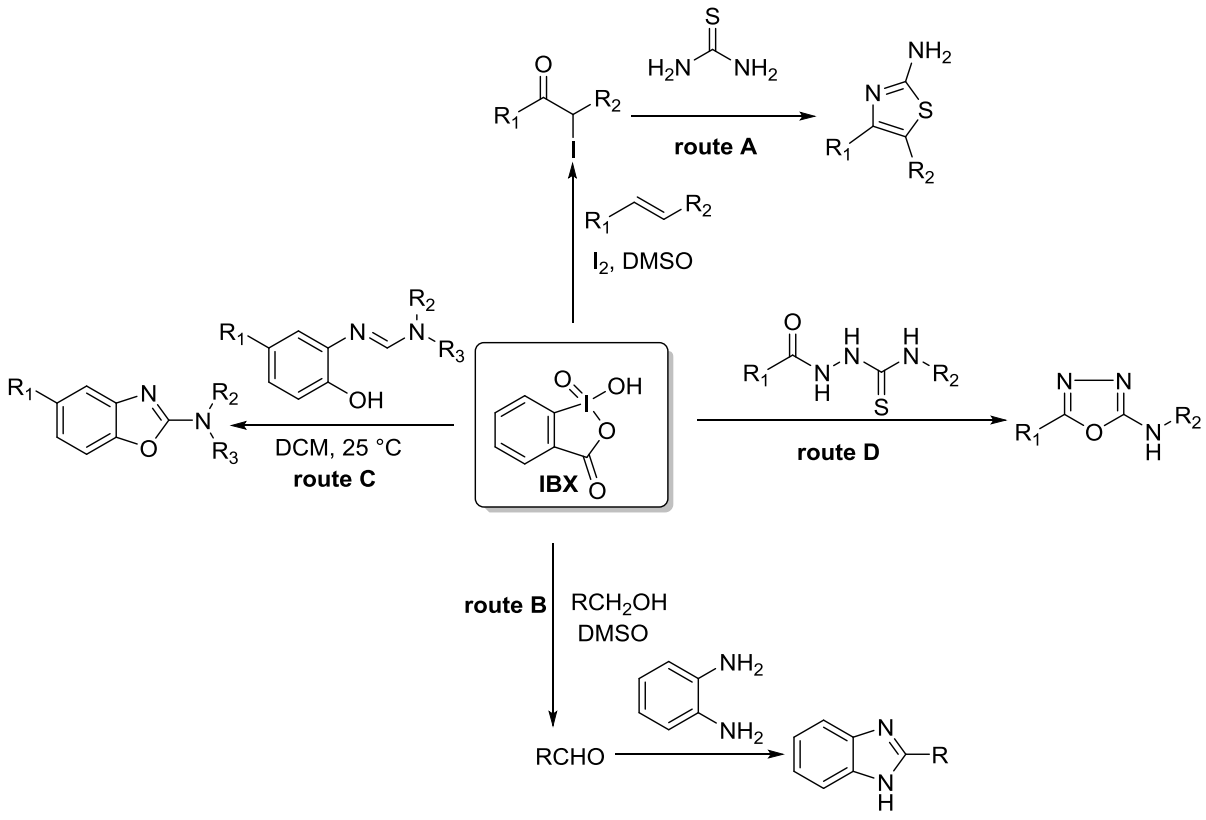


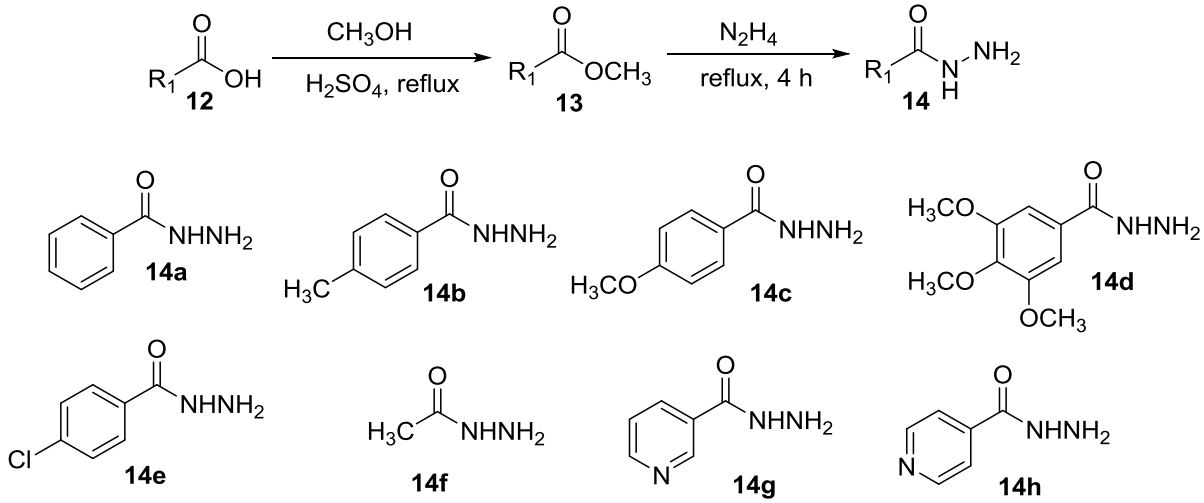
Figure 2.2.2 Synthetic applications of IBX

In 2012, Donohoe et al. explored the utility of IBX in the construction of various heterocycles including thiazoles, thiazolines, imidazoles and imidazo-pyridines (route A).[7] Moorthy et al. prepared various benzimidazoles using the oxidative property of IBX from primary alcohols and arylmethyl bromides (route B).[8] Recently, Bhanage and co-workers developed a metal-free protocol for the synthesis of 2-amino-benzoxazoles *via* oxidative C–H bond amination of benzoxazoles with amines in the presence of IBX (route C).[9] By employing IBX, Prabhu et al. developed a mild protocol to synthesize 2-amino-1,3,4-oxadiazoles (route D).[10] As a part of our ongoing research to develop efficient methods for the construction of bioactive azaheterocycles using relatively benign organoiodine reagents, we became interested to explore oxidative cyclization of hydrazide-hydrazones using IBX in the synthesis of biologically important α-keto-1,3,4-oxadiazoles.

2.2.2 Results and discussion

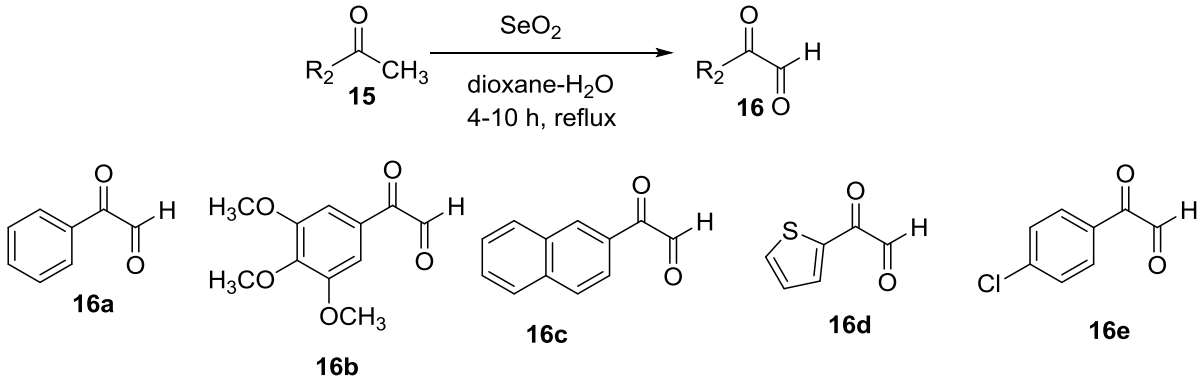
2.2.2.1 Synthesis

Synthesis of *α*-keto-1,3,4-oxadiazoles **18a** was carried out as described in Scheme 2.2.4. The key intermediate hydrazide-hydrazone **17a** was synthesized by the reaction of phenylglyoxal **16a** with phenylhydrazide **14a** in acetonitrile at room temperature. Starting material aryl hydrazide **14** and arylglyoxal were synthesized according to literature reported protocols.[14-17] Arylhydrazides **14** were synthesized from corresponding acids **12** through consecutive reaction of esterification **13** and hydrazinolysis using hydrazine-hydrate.



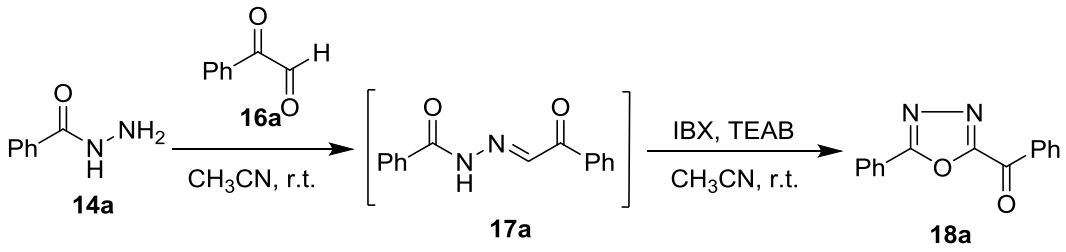
Scheme 2.2.4 Synthesis of arylhydrazide **14** from corresponding acid **12**

Arylglyoxals **16** were synthesized by the oxidation of ketones **15** with selenium dioxide (Scheme 2.2.5).[19]



Scheme 2.2.5 Synthesis of arylglyoxals **16** from ketones **15**

Table 2.2.1 Optimization of reaction conditions for the synthesis of *α*-keto-1,3,4-oxadiazoles



Entry[a]	Reagent	Additive	Time (h)	Yields (%)[b]
1.	IBD	-	24	no reaction
2.	IBX	-	24	no reaction
3.	DMP	-	24	no reaction
4.	IBX	TEAB (0.2 equiv)	12	40
5.	IBX	TEAB (1.2 equiv)	3	90
6.	DMP	TEAB (1.2 equiv)	6	65

[a] Reaction conditions: benzhydrazide **14a** (1.0 equiv), phenylglyoxal **16a** (1.0 equiv), IBX (1.0 equiv), TEAB (1.2 equiv), [b] Isolated yield

On treatment of **17a** with IBX in acetonitrile at room temperature, it was found that both the starting materials remained unchanged even after stirring the reaction mixture for 24 h. As reported IBX can be activated by using tetraethylammonium bromide (TEAB),[20] we explored oxidative cyclization of hydrazide-hydrazone **17a** using IBX along with a catalytic amount of TEAB. However, the expected *α*-keto-1,3,4-oxadiazole **18a** was formed in 40% yield (Table 2.2.1, entry 4). Subsequently, after several trials employing higher temperatures and substoichiometric ratios of reagents, we optimized the conditions with 1 equiv. of IBX and 1.2 equiv. of TEAB for the oxidative cyclization of hydrazide-hydrazone **17a** to achieve *α*-keto-1,3,4-oxadiazole **18a** in 90% yield (Table 2.2.1, entry 5). Different organoiodine reagents (Iodobenzene diacetate, IBD; IBX and Dess-Martin Periodinane, DMP) were also screened, wherein IBX/TEAB was found to be best in terms of isolated product yield and reaction time as shown in Table 2.2.1. Till now we approached this reaction in two steps, the first step was preparation of intermediate hydrazide-hydrazone **17a** and in second step isolated **17a** was treated with IBX/TEAB to produce *α*-keto-1,3,4-oxadiazole **18a**. Encouraged by this successful reaction, our next effort was to execute this protocol in one-pot. The reaction of phenylglyoxal **16a** and phenylhydrazide **14a** in acetonitrile at room

temperature *in-situ* generated hydrazide-hydrazone **17a** and then treated with IBX/TEAB combination to produce **18a** in 90% yield. To explore the generality of the developed protocol under optimized conditions it was extended to a variety of aryl/heteroaryl glyoxaldehydes and alkyl/aryl/ heteroaryl hydrazides and prepared a series of diverse α-keto-1,3,4-oxadiazoles **18a-m** (Table 2.2.2).[21]

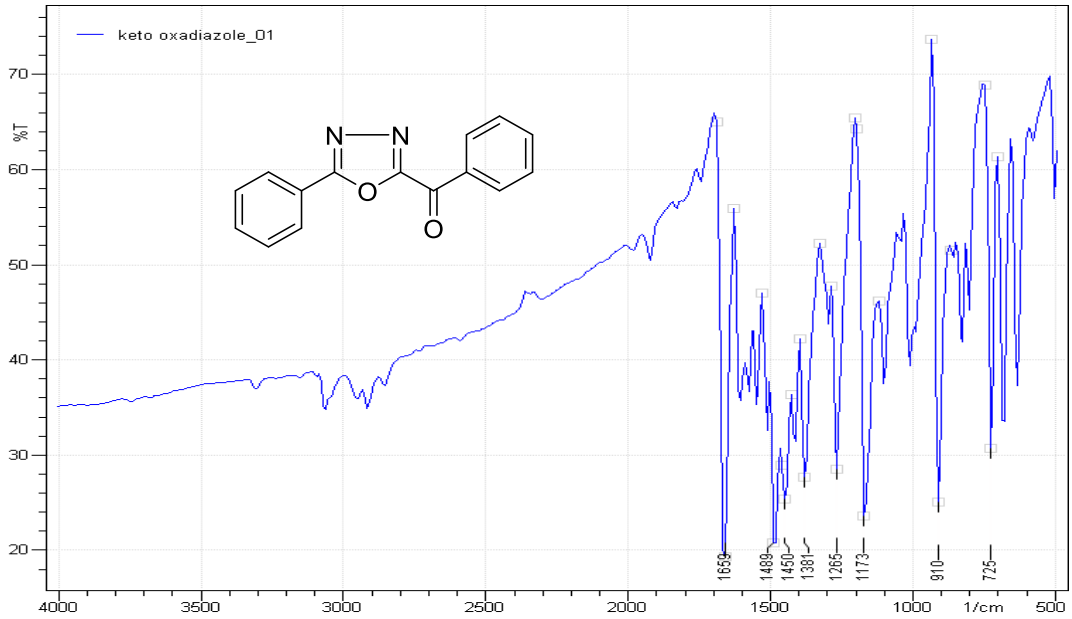


Figure 2.2.3 IR spectrum of **18a**

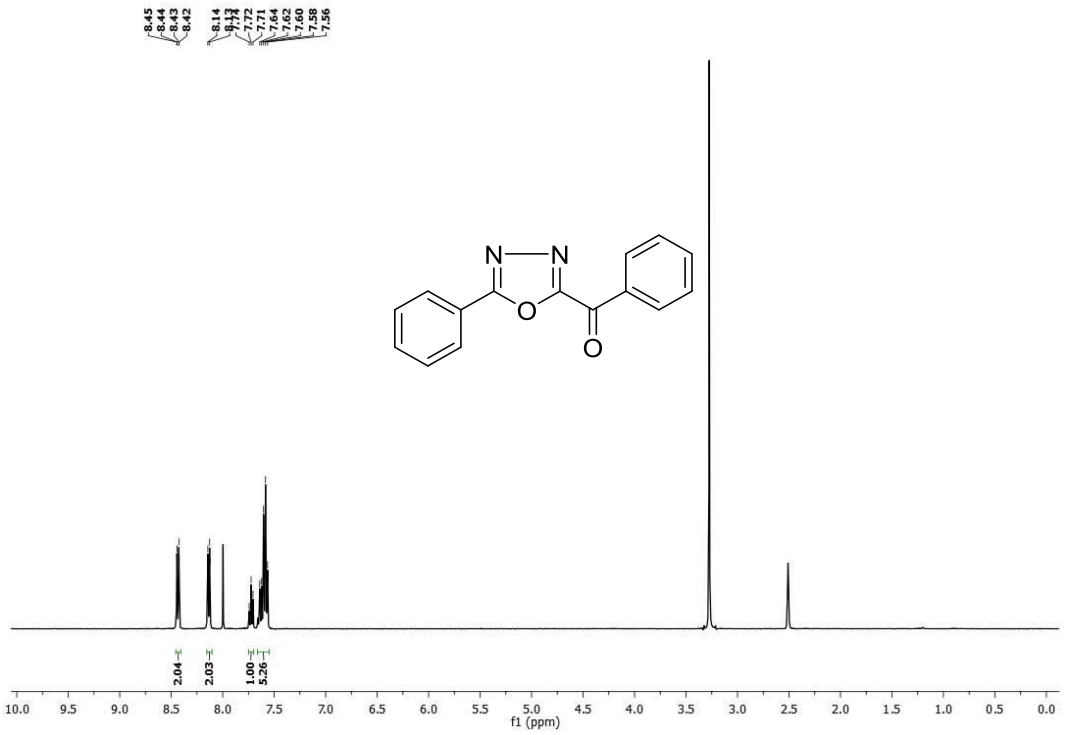


Figure 2.2.4 ^{1}H NMR spectrum of **18a**

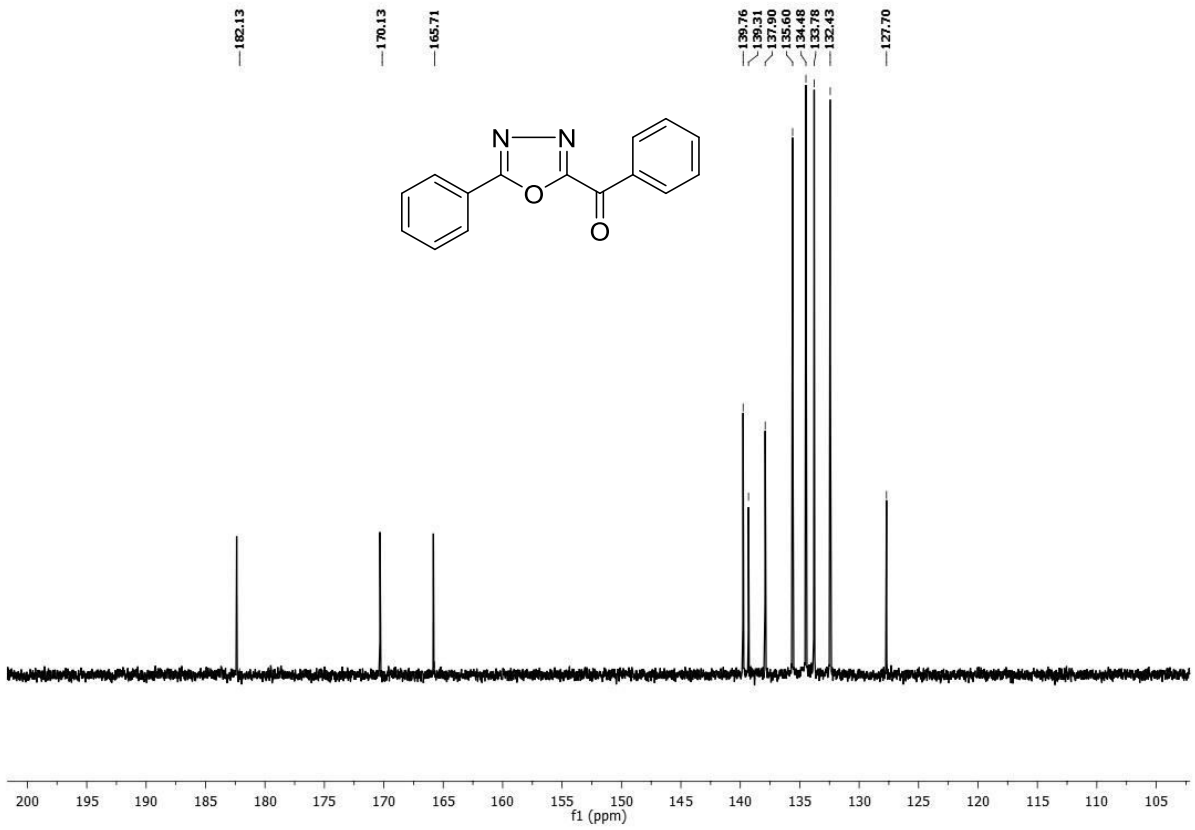


Figure 2.2.5 ^{13}C NMR spectrum of **18a**

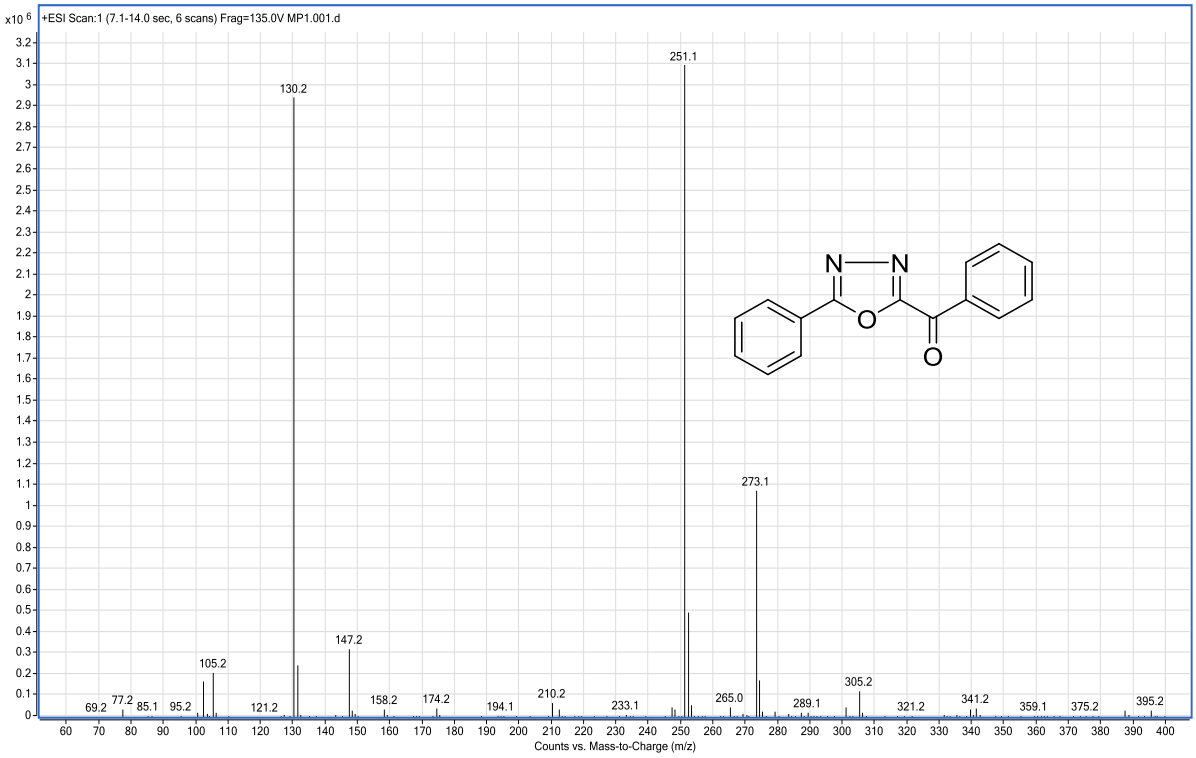
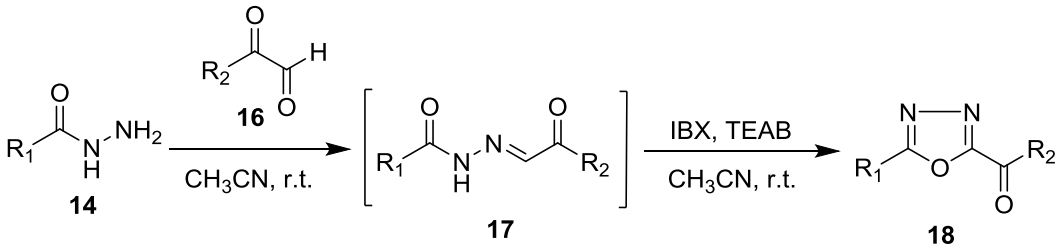


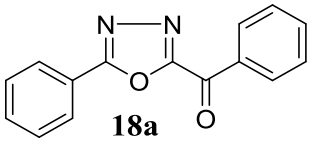
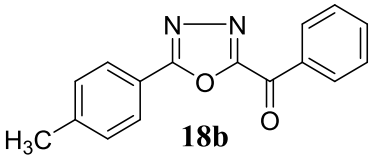
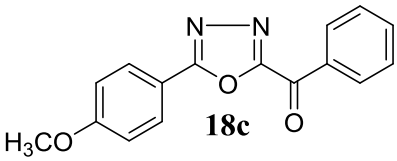
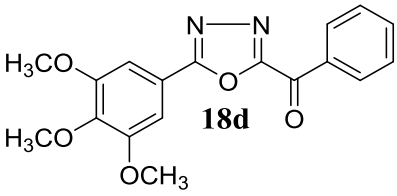
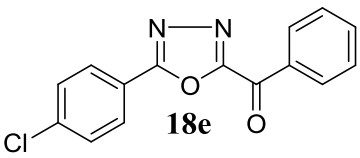
Figure 2.2.6 Mass spectrum of **18a**

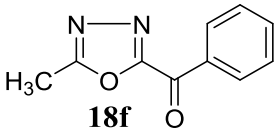
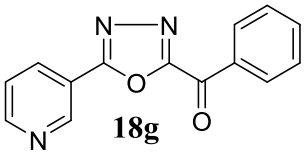
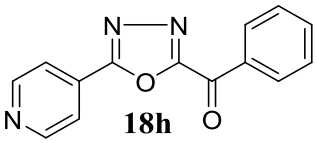
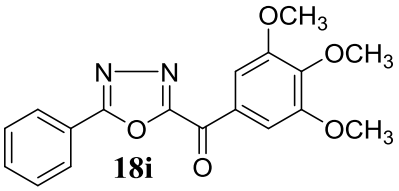
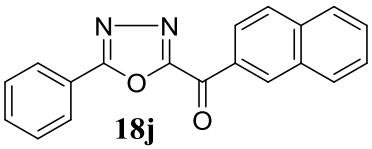
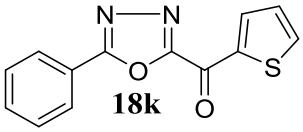
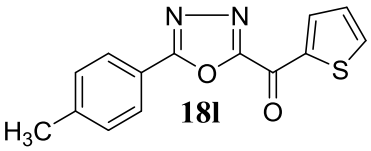
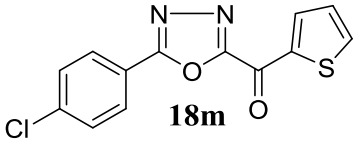
Synthesized compounds were well characterized by their IR, NMR and Mass spectral data (Figure 2.2.3-2.2.6). IR spectrum of **18a** showed a band at 1659 cm^{-1} (C=O str.). In ^{13}C NMR spectrum, quaternary C=O carbon of **18a** displayed a characteristic signal at δ 182.13. Mass spectrum of **18a** displayed a molecular ion peak at *m/z* 251.1 in agreement with the calculated value.



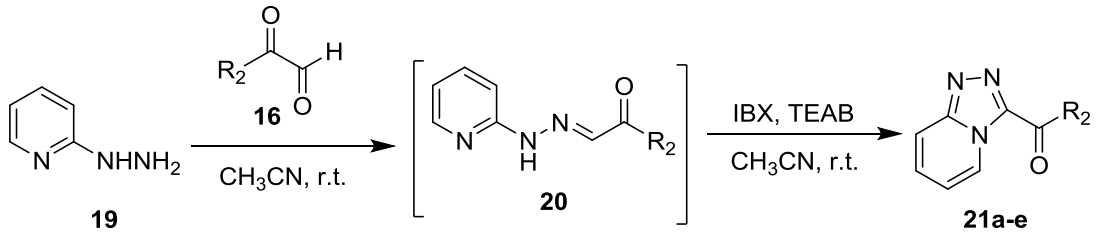
Scheme 2.2.4 Synthesized α-keto-1,3,4-oxadiazoles using arylhydrazide and arylglyoxal

Table 2.2.2 Synthesized α-keto-1,3,4-oxadiazoles

S.No.	Compounds	Yields (%)	Mp (°C)
1	 **18a**	90	143-144
2	 **18b**	91	142-143
3	 **18c**	91	169-170
4	 **18d**	94	132
5	 **18e**	86	183-184

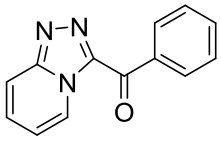
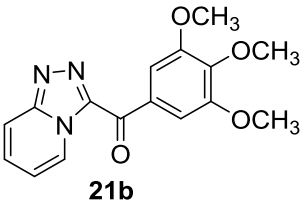
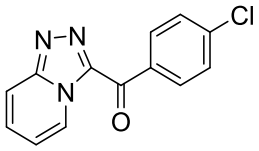
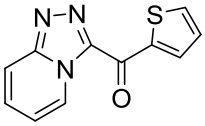
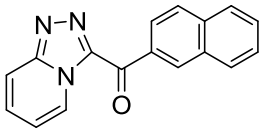
6	 **18f**	82	110
7	 **18g**	87	105
8	 **18h**	88	167-168
9	 **18i**	86	144
10	 **18j**	85	165
11	 **18k**	93	167
12	 **18l**	95	185
13	 **18m**	90	210-211

In continuation, we extended our protocol to prepare *α*-keto-1,2,4-triazolo[4,3-*a*]pyridines **21a-e** based on the same strategy utilizing readily available starting material arylglyoxal **16** and 2-hydrazinopyridine **19** (Scheme 2.2.5). The optimized reaction conditions were well tolerated towards a variety of aryl/heteroaryl glyoxaldehydes with 2-hydrazinopyridine **19** and prepared a series of diverse *α*-keto-1,2,4-triazolo[4,3-*a*]pyridines **21a-e** (Table 2.2.3).



Scheme 2.2.5 Synthesis of *α*-keto-1,2,4-triazolo[4,3-*a*]pyridines

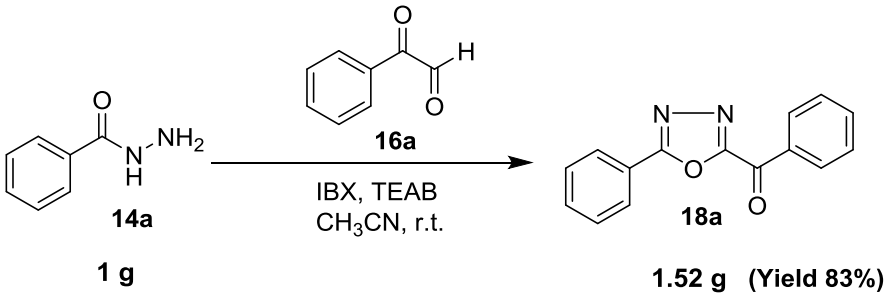
Table 2.2.3 Synthesized *α*-keto-1,2,4-triazolo[4,3-*a*]pyridines[a]

S.No.	Compounds	Yields (%)[b]	Mp (°c)
1	 **21a**	90	167
2	 **21b**	92	152-153
3	 **21c**	85	165-166
4	 **21d**	85	192
5	 **21e**	85	182

[a] Reaction conditions: arylglyoxal **16** (1.0 equiv), 2-hydrazinopyridine **19** (1.0 equiv), IBX (1.0 equiv), TEAB (1.2 equiv), [b] Isolated yield

2.2.2.2 Gram-scale experiment for the synthesis of phenyl(5-phenyl-1,3,4-oxadiazol-2-yl)methanone

For practical purposes, we also performed the synthesis in gram scale by reacting phenylhydrazide (1 g) **14a** with phenylglyoxal **16a** in CH_3CN and then treated the *in situ* generated hydrazide-hydrazone **17a** with IBX to afford **18a** in 83% yield. After the reaction, released *o*-iodosylbenzoic acid was recovered in 80% yield and reused in the preparation of IBX (Scheme 2.2.6).



Scheme 2.2.6 Gram-scale synthesis of **18a**

2.2.2.3 Proposed reaction mechanism

The plausible mechanism of this IBX-promoted oxidative cyclization is depicted in Figure 2.2.7. Initially TEAB likely to facilitates the polarization of I=O bond of IBX to generate reactive adduct **I**. Subsequent nucleophilic displacement of bromine in **I** by imine nitrogen of hydrazide-hydrazone **17** believed to form another adduct **II** which upon oxidative cyclization and loss of water generates *α*-keto-1,3,4-oxadiazoles **18**.

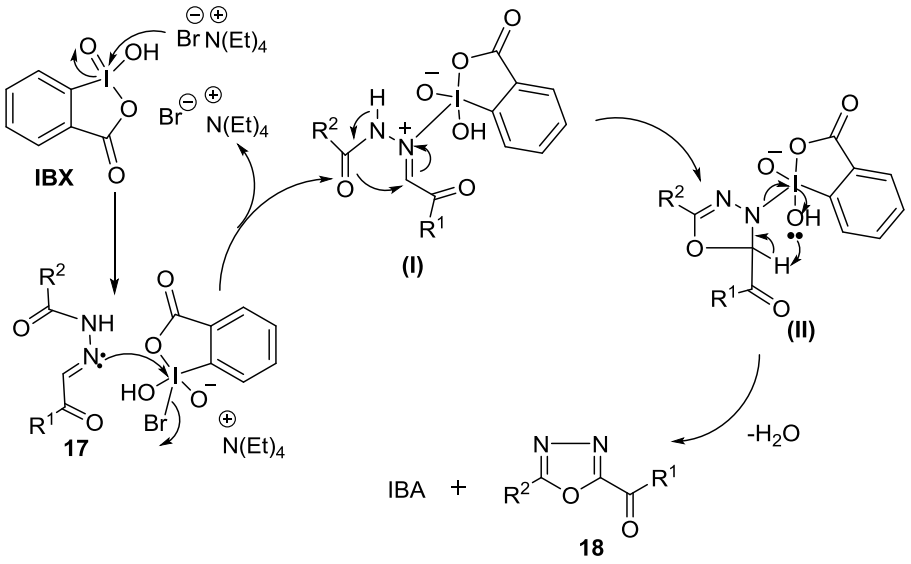


Figure 2.2.7 Plausible pathway for the formation of **18**

2.2.3 Conclusions

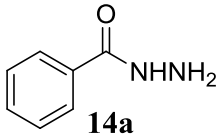
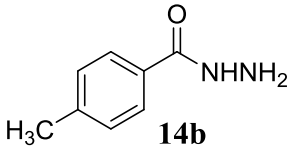
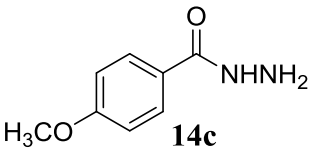
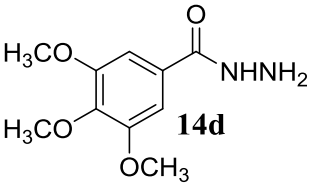
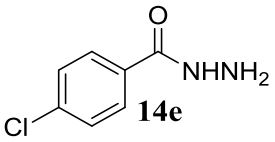
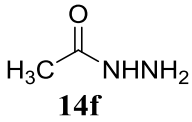
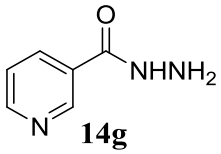
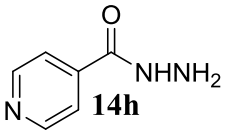
In conclusion, we have developed a facile one-pot procedure for the synthesis of *α*-keto-1,3,4-oxadiazoles and *α*-keto-1,2,4-triazolo[4,3-*a*]pyridines starting from readily available arylglyoxals and hydrazides *via* IBX-TEAB mediated oxidative cyclization of the *in-situ* generated intermediate hydrazide-hydrazones. Our approach provides a greener, efficient and scalable alternate route without any special precaution to biologically potent *α*-keto-1,3,4-oxadiazoles and *α*-keto-1,2,4-triazolo[4,3-*a*]pyridines in excellent yields. The biological evaluation of the synthesized *α*-keto azoles is underway in our laboratory.

2.2.4 Experimental section

2.2.4.1 General materials and methods

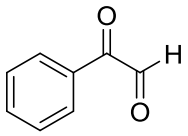
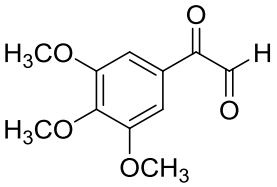
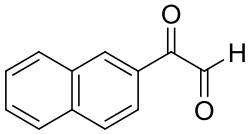
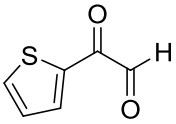
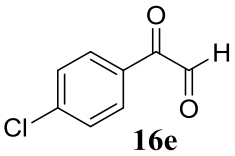
All the laboratory reagents were obtained commercially. The reaction was monitored by thin layer chromatography, which was performed on Merck pre-coated plates (silica gel 60 F_{254}, 0.2 mm). Melting points were determined by E-Z melting point apparatus and reported uncorrected. IR spectra were recorded on Shimadzu FT-IR spectrophotometer. NMR spectra were recorded in (DMSO-d_6) Bruker Advance II (400 MHz & 500 MHz) spectrometer using TMS as an internal standard. The spectral data are presented as: Chemical shift; multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets), coupling constant (*J*) in Hertz (Hz). Mass spectra were recorded by using 'Hewlett-Packard' HP GS/MS 5890/5972.

General experimental procedure for the synthesis of arylhydrazides 14:[20] To a solution of arylcarboxylic acid **12** (1 mmol) in anhydrous ethanol (15 mL) was added catalytic amount of concentrated sulfuric acid (0.2 mL) and allowed to reflux for 3 h. After completion of reaction, ethanol was evaporated under reduced pressure and residue was extracted with ethyl acetate (2 × 20 mL). Combined organic layer was washed with saturated sodium bicarbonate solution (25 mL). Organic layer was dried over anhydrous sodium sulphate and evaporated to give corresponding ester **13**. Prepared ester **13** (1 mmol) and hydrazine hydrate (3 mmol) dissolved in ethanol and refluxed for 6 h. After completion of reaction as indicated by TLC, reaction mixture was cooled at room temperature, the solid so obtained was filtered, washed with cold water (10 mL) and dried. Crude solid was recrystalized from ethanol to obtain pure hydrazides **14** in 60-85% yields.

S.No.	Arylhydrazides	Yields (%)	Mp (°C)
1	 **14a**	85	121-122 (Lit.[20] 121)
2	 **14b**	85	116-117 (Lit.[21] 116-117)
3	 **14c**	85	136-137 (Lit.[20] 136)
4	 **14d**	75	153-154 (Lit.[22] 152-154)
5	 **14e**	80	131-132 (Lit.[20] 131)
6	 **14f**	60	60-61 (Lit.[23] 60-61)
7	 **14g**	80	154-155 (Lit.[23]154-155)
8	 **14h**	80	160

General experimental procedure for the synthesis of arylglyoxals 16:[24] Ketones **15** (1 equiv) was added to a stirred solution of selenium dioxide (SeO_2) (1.1 equiv) in 1,4-dioxane : water mixture (16:1). The reaction mixture was stirred and heated under reflux for 8-10 h as monitored by TLC. Once the reaction was completed, the mixture was filtered through a filter paper and then filtered through a pad of celite to remove selenium residues. The liquid was then concentrated *in vacuo* to give crude form of glyoxal **16**. To convert this glyoxal in

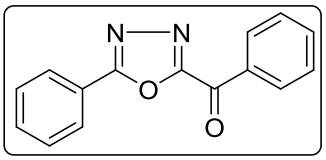
monohydrate form, dissolve it in water (5 mL per mmol) and continue stirring at 100 ^{o}C for 2 h. Filtered the aqueous solution and allowed to precipitate at room temperature. Filtered the precipitated solid, washed with water and dried under reduced pressure to afford pure arylglyoxals **16a-e** in good yields.

S.No.	Arylglyoxals	Yields (%)	Mp (°C)
1	 **16a**	72	96–97 (Lit.[24] 95–97)
2	 **16b**	70	100-102 (Lit.[25] 101-102)
3	 **16c**	70	108-111 (Lit.[26] 108-111)
4	 **16d**	75	89-90 (Lit.[26] 89-92)
5	 **16e**	75	40-41 (Lit.[26] 40-41)

General experimental procedure for the synthesis of *α*-keto-1,3,4-oxadiazoles (18a-m): A mixture of arylhydrazide **14** (1 mmol) and arylglyoxal **16** (1 mmol) was stirred in acetonitrile at r.t. for 3 h. After consumption of the starting materials, IBX (1 mmol) was added in the reaction mixture followed by addition of TEAB (1.2 mmol) and the stirring was continued at r.t. for another 3 h. After completion of the reaction, solvent was removed *in vacuo* and the crude thus obtained was diluted with water and extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with saturated $NaHCO_3$ (20 mL), brine (20

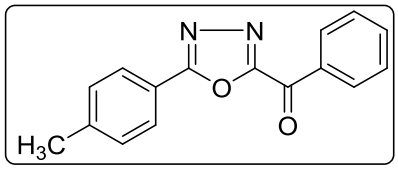
mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was recrystallized from ethanol to afford analytically pure α-keto-1,3,4-oxadiazoles **18a-m** in excellent yields.

Phenyl(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (18a)



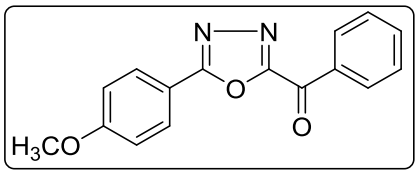
Yield 90%; white solid; mp 143-144 °C (lit.[16] mp 143-145 °C); IR (KBr) 1666, 1535, 1411, 1380, 1280, 1180 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.45 (dd, J = 8.3, 1.1 Hz, 2H), 8.15 (dd, J = 8.2, 1.3 Hz, 2H), 7.74 (t, J = 7.4 Hz, 1H), 7.64-7.56 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.1, 170.1, 165.7, 139.8, 139.3, 137.9, 135.6, 134.5, 133.8, 132.4, 127.7; ESI-MS: *m/z* $[M+H]^+$calcd for $C_{15}H_{10}N_2O_2$: 251.0; found 251.1.

Phenyl(5-p-tolyl-1,3,4-oxadiazol-2-yl)methanone (18b)



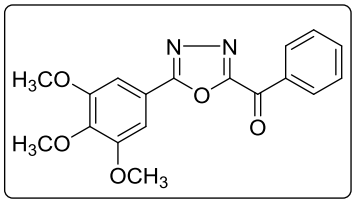
Yield 91%; white solid; mp 142-143 °C (lit.[16] mp 139-141°C); IR (KBr) 1659, 1489, 1450, 1381, 1265, 1173 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.47 (dd, J = 8.4, 1.2 Hz, 2H), 8.06-8.04 (m, 2H), 7.79-7.75 (m, 1H), 7.65-7.61 (m, 2H), 7.45 (d, J = 8 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.8, 165.5, 160.3, 143.1, 134.4, 133.6, 130.3, 129.7, 128.4, 127.1, 119.5, 21.2; ESI-MS: *m/z* $[M+H]^+$ calcd. for $C_{16}H_{12}N_2O_2$: 265.1; found 265.2.

(5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenyl)methanone (18c)



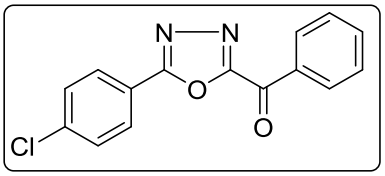
Yield 91%; white crystalline solid; mp 169.6-170 °C; IR (KBr) 1612, 1574, 1551, 1489, 1380, 1285 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.41 (d, J = 7.7 Hz, 2H), 8.10 (d, J = 8.5 Hz, 2H), 7.81 (t, J = 7.2 Hz, 1H), 7.68 (t, J = 7.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 3.89 (s, 3H); ESI-MS: *m/z* $[M+H]^+$ calcd. for $C_{16}H_{12}N_2O_3$: 281.1; found 281.2.

(5-(3,4,5-Trimethoxyphenyl)-1,3,4-oxadiazol-2-yl)(phenyl)methanone (18d)



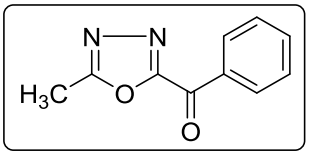
Yield 94%; light yellow solid; mp 131.8 °C; IR (KBr) 1674, 1589, 1489, 1420, 1381, 1237, 1173 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.48 (dd, J = 8.5, 1.2 Hz, 2H), 7.79-7.75 (m, 1H), 7.65-7.61 (m, 2H), 7.40 (s, 2H), 3.96 (s, 6H) 3.86 (s, 3H); ESI-MS: *m/z* $[M+H]^+$calcd for $C_{18}H_{16}N_2O_5$: 341.1; found 341.2.

(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)(phenyl)methanone (18e)



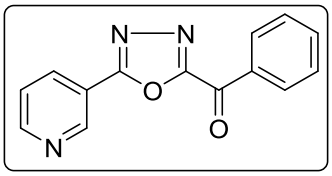
Yield 86%; white solid; mp 183-184 °C; IR (KBr); 1666, 1597, 1520, 1481, 1373, 1173, 1095 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.48-8.46 (m, 2H), 8.18-8.16 (m, 2H), 7.79-7.75 (m, 1H), 7.67-7.61 (m, 4H); ^{13}C NMR (100 MHz, DMSO) δ 177.1, 164.3, 160.6, 138.2, 134.5, 134.0, 130.4, 129.5, 128.8, 128.6, 121.1; ESI-MS: *m/z* $[M+H]^+$calcd for $C_{15}H_9ClN_2O_2$: 285.0: found 285.1.

(5-Methyl-1,3,4-oxadiazol-2-yl)(phenyl)methanone (18f)



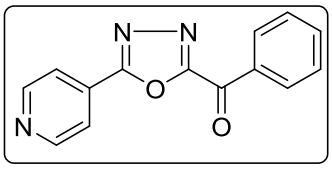
Yield 82%; light brown solid; mp 110 °C; IR (KBr) 1666, 1558, 1520, 1396, 1366, 1257, 1173, 1003 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.41 (d, J = 8.5 Hz, 2H) 7.78 (t, J = 7.4 Hz, 1H) 7.58 (t, J = 7.8 Hz, 2H) 2.68 (s, 3H); ESI-MS: *m/z* $[M+H]^+$ calcd for $C_{10}H_8N_2O_2$: 189.1; found 189.2.

Phenyl(5-(pyridine-3-yl)-1,3,4-oxadiazol-2-yl)methanone (18g)



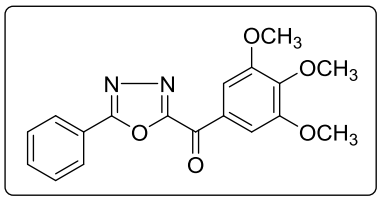
Yield 87%; light yellow solid; mp 105°C; IR (KBr) 1658, 1596, 1535, 1450, 1411, 1280, 1242 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.35 (d, J = 1.5 Hz, 1H), 8.87-8.85 (m, 1H), 8.53–8.51 (m, 1H), 8.52-8.47 (m, 2H), 7.80-7.76 (m, 1H), 7.67-7.62 (m, 3H); ESI-MS: *m/z* $[M+H]^+$calcd for $C_{14}H_9N_3O_2$: 252.1; found 252.2.

Phenyl(5-(pyridine-4-yl)-1,3,4-oxadiazol-2-yl)methanone (18h)



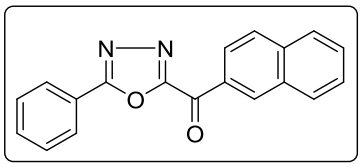
Yield 88%; white solid; mp 167-168°C; IR (KBr) 1659, 1597, 1520, 1443, 1412, 1373, 1173 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.92 (d, J = 5.9 Hz, 2H), 8.43 (d, J = 8.4 Hz, 2H), 8.08-8.07 (m, 2H), 7.84 (t, J = 7.4 Hz, 1H), 7.70 (t, J = 7.8 Hz, 2H); *m/z* $[M+H]^+$calcd for $C_{14}H_9N_3O_2$: 252.1; found 252.1.

(3,4,5-Trimethoxyphenyl)(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (18i)



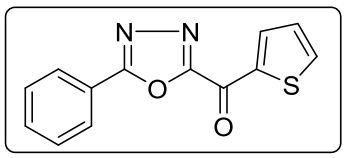
Yield 86%; white solid; mp 144 °C; IR (KBr) 1658, 1573, 1498, 1450, 1411, 1380, 1319 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.16 (d, J = 7.9 Hz, 2H), 7.80 (s, 2H), 7.75–7.67 (m, 3H), 3.90 (s, 6H), 3.84 (s, 2H); *m/z* $[M+H]^+$calcd for $C_{18}H_{16}N_2O_5$: 341.1; found 341.2.

Naphthalen-2-yl)(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (18j)



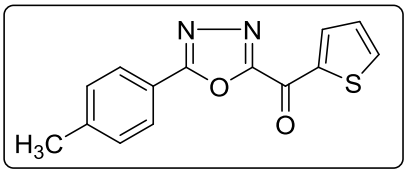
Yield 85%; yellow solid; mp 165 °C; IR (KBr) 1651, 1620, 1512, 1450, 1373, 1273 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.25 (d, J = 8.1 Hz, 1H), 8.19 (t, J = 8.1 Hz, 3H), 8.10 (d, J = 8.1 Hz, 1H), 7.79-7.69 (m, 2H), 7.70 (t, J = 6.7 Hz, 3H); *m/z* $[M+H]^+$calcd for $C_{19}H_{12}N_2O_2$: 301.1; found 301.2.

(5-Phenyl-1,3,4-oxadiazol-2-yl)(thiophen-2-yl)methanone (18k)



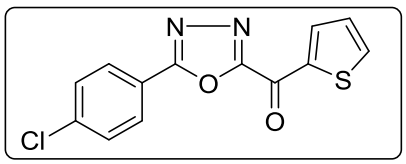
Yield 93%; light yellow solid; mp 167 °C; IR (KBr) 1635, 1519, 1481, 1450, 1411, 1280, 1180 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, J = 3.4 Hz, 1H), 8.32 (d, J = 4.6 Hz, 1H), 8.15 (d, J = 7.4 Hz, 2H), 7.75-7.72 (m, 1H), 7.69 (t, J = 7.4 Hz, 2H), 7.44 (t, J = 4.2 Hz, 1H); *m/z* $[M+H]^+$calcd for $C_{13}H_8N_2O_2S$: 257.0; found 257.1.

(Thiophen-2-yl)(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)methanone (18l)



Yield 95%; light yellow solid; mp 185 °C; IR (KBr) 1636, 1520, 1484, 1412, 1180, 825 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, J = 3.2 Hz, 1H), 8.32 (d, J = 4.5 Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.43 (t, J = 4.3 Hz, 1H), 2.44 (s, 3H); *m/z* $[M+H]^+$calcd for $C_{14}H_{10}N_2O_2S$: 271.1; found 271.1.

(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)(thiophen-2-yl)methanone (18m)

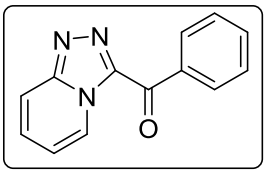


Yield 90%; white solid; mp 210-211 °C; IR (KBr) 1643, 1597, 1520, 1481, 1420, 1273, 1188 cm^{-1};^1H NMR (500 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.33 (d, J = 2.5 Hz, 1H), 8.16 (d, J = 7.6 Hz, 2H), 7.76 (d, J = 7.7 Hz, 2H), 7.43 (s, 1H); *m/z* $[M+H]^+$calcd for $C_{13}H_7ClN_2O_2S$: 291.0; found 291.1.

General experimental procedure for the synthesis of *α*-keto-1,2,4-triazolo[4,3-*a*]pyridines (21a-e): A mixture of arylglyoxal **16** (1 mmol) and 2-hydrazinopyridine **19** (1 mmol) was stirred in acetonitrile at room temperature for 5 min. Subsequently, IBX (1 mmol) was added in the reaction mixture and then TEAB (1.2 mmol) in portions. The resulting mixture was stirred at room temperature for 15 min. After completion of the reaction, solvent was removed *in vacuo*, the contents were diluted with water and extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with saturated $NaHCO_3$ (20 mL), brine (20

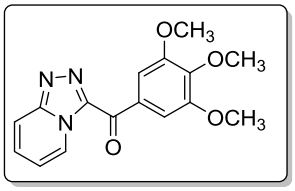
mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue thus obtained was recrystallized with ethanol to afford α-keto-1,2,4-triazolo[4,3-a]pyridines **21a-e** in excellent yields.

1,2,4-Triazolo[4,3-*a*]pyridine-3-yl)(phenyl)methanone (21a)



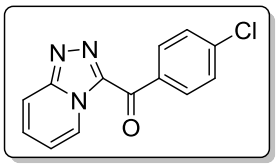
Yield 90%; light yellow solid; mp 167 °C; IR (KBr) 1658, 1573, 1496, 1450, 1411, 1380 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.52 (dd, J = 7.0, 1.0 Hz, 1H), 8.52 (dd, J = 5.2, 3.3 Hz, 2H), 8.06 (dd, J = 8.1, 1.0 Hz, 1H), 7.72–7.67 (m, 2H), 7.61–7.57 (m, 2H), 7.34 (t, J = 7.4 Hz, 1H); *m/z* $[M+H]^+$ calcd for $C_{13}H_9N_3O$: 224.1; found 224.2.

1,2,4-Triazolo[4,3-*a*]pyridine-3-yl)(3,4,5-trimethoxyphenyl)methanone (21b)



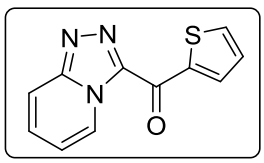
Yield 92%; light yellow solid; mp 152-153 °C; IR (KBr) 1628, 1582, 1504, 1450, 1335, 1242, 1211 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.47 (d, J = 7.0 Hz, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.94 (s, 2H), 7.71 – 7.67 (m, 1H), 7.34 (t, J = 6.7 Hz, 1H), 3.95 (s, 6H), 3.89 (s, 3H).

1,2,4-Triazolo[4,3-*a*]pyridine-3-yl)(4-chlorophenyl)methanone (21c)



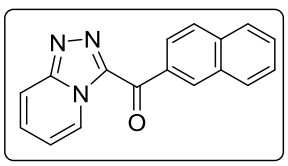
Yield 85%; off white solid; mp 165-166 °C; IR (KBr) 1636, 1597, 1574, 1489, 1443, 1319, 1088 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.44 (d, J = 7.0 Hz, 1H), 8.51–8.47 (m, 2H), 8.09 (d, J = 9.1 Hz, 1H), 7.73 (dd, J = 6.7, 0.9 Hz, 1H), 7.63 (dd, J = 8.0, 3.0 Hz, 2H), 7.36 (t, J = 6.8 Hz, 1H).

1,2,4-Triazolo[4,3-*a*]pyridine-3-yl)(thiophen-2-yl)methanone (21d)



Yield 85%; light yellow solid; mp 192 °C; IR (KBr) 1605, 1489, 1450, 1319, 1273, 1234, 1095 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.35 (d, J = 7.0 Hz, 1H), 8.66 (d, J = 2.7 Hz, 1), 8.19 (d, J = 6.1 Hz, 1H), 8.12 (d, J = 9.2 Hz, 1H), 7.75-7.70 (m, 1H), 7.40-7.33 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.2, 150.7, 142.6, 140.8, 137.1, 136.4, 131.1, 128.8, 126.7, 117.0, 115.7.

1,2,4-Triazolo[4,3-*a*]pyridine-3-yl)(naphthalen-3-yl)methanone (21e)



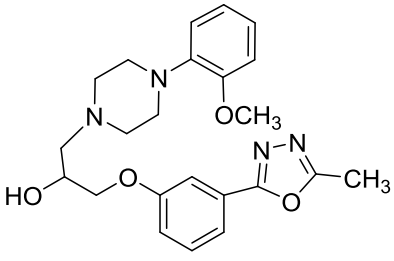
Yield 85%; light yellow solid; mp 182 °C; IR (KBr) 1659, 1489, 1450, 1173, 910 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J = 1.4 Hz, 1H), 8.02-8.00 (m, 3H), 7.97-7.92(m, 2H), 7.86 (d, J = 7.5 Hz, 2H), 7.69 (td, J = 7.4, 0.9 Hz, 2H).

2.3 Part B

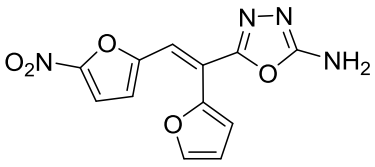
IBD-promoted facile synthesis of 2-arylamino-1,3,4-oxadiazoles and fused arylamino-[1,2,4]triazoles

2.3.1 Introduction

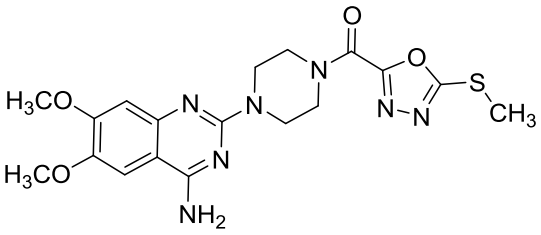
1,3,4-Oxadiazoles are a class of important heterocycles which have been well documented for their significant biological properties.[27] More particularly, 2-amino-1,3,4-oxadiazoles are highlighted in the literature due to their pharmacological properties such as antimicrobial,[28] antibacterial, anticancer,[29] hypertensive,[30] diuretic, ,antiinflammatory,[31] muscle relaxants[32] and anti-consultant agents.[32-33] Besides medicinal applications, substituted 1,3,4-oxadiazoles are also used as key components for the preparation of agro products, herbicides, insecticides and polymer materials.[34] Some of the derivatives of 1,3,4-oxadiazole derivatives exhibited prominent applications in material science because of good electron transporting and hole-blocking properties in organic light emitting diodes.[35] Recently, Hammouti et al. studied the 2,5-bis(4-methoxyphenyl)-1,3,4-oxadiazoles as corrosion inhibitors.[36] Oxadiazoles are demonstrated as popular bioisosteric replacement of amides, esters and ureas.[37] Several marketed drugs[38] such as MK-0633 *p*-toluenesulfonate (as 5-lipoxygenase inhibitor),[38a] Nesapidil (as antiarrhythemic drug),[38b] Tiodazosin (as an antihypertensive drug),[38c] Furamizole (as antibacterial drug),[38d] Raltegravir (as an antiretroviral drug)[38e] and anticancer molecules indolyl-1,3,4-oxadiazoles[38f] (Figure 2.3.1) show-case the significance of 2-amino-1,3,4-oxadiazole's in drug discovery research.



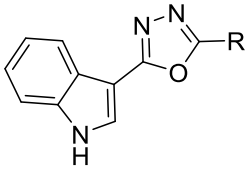
Nesapidil



Furamizole



Tiodazosin



Cytotoxic agents

Figure 2.3.1 1,3,4-Oxadiazole containing drug candidates

Use of organoiodine reagents for organic transformation has been experienced tremendous growth, especially, for the construction of bio-active heterocycles. The broad variety of multivalent iodine reagent were utilized in the organic synthesis as a mild, safe and cost-effective alternatives to the lead(IV), thallium(III), mercury(II) and chromium(VI).[39] Iodine(III) reagents have wide spread synthetic applicability for the preparation of medicinal and natural products.[40] In addition the use of relatively benign reagents for the organic transformations, an additional strategy to conduct reaction in safer, efficient and greener way is by adopting environmentally benign reaction media.[41] In this regard solvent-free reaction conditions have become the more attractive tool for the synthetic chemist to carry out several organic transformations free from toxic and volatile solvents.[42] Besides solvent-free protocols, "One-pot" reactions have emerged as a powerful synthetic strategy to achieve diversely substituted organic compounds.[43] Owing to many advantages in terms of molecular diversity, operational simplicity, easy isolation and purification of products, One-pot, solvent-free protocols comply with most of the stringent requirements of green chemistry.[44]

The broad spectrum of biological applications of 2-amino-1,3,4-oxadiazole scaffolds have created an interest to the synthetic chemist to develop mild and efficient methodologies to synthesize these moieties. Several synthetic protocols have been documented for the construction of 2-amino-1,3,4-oxadiazoles. The most commonly used strategies are cyclodehydration of semicarbazides using dehydrating agents such as $POCl_3$, conc. H_2SO_4, tosyl chloride and $SOCl_2$.[45] The dehydration was also reported in Burgess-type of reagents[46] or phosphonium salts.[47] Another strategy is cyclodesulfurization of thiosemicarbazides by use of thiophilic reagents, salts of mercury and lead,[48] I_2/NaOH,[49] tosyl chloride/pyridine in refluxing conditions,[45f] carbodiimides (DCC, EDCI and PS-carbodiimides),[50] alkylating agents methyl iodide and bromo ethylacetate.[51] Levins et al. have alternatively reported synthesis 2-amino/arylamino-1,3,4-oxadiazoles in moderate yields by amination of oxadiazol-2-ones using phosphonium reagents.[52] The new strategy approached by Xie et al. utilizes the cyclodeselenization of selenosemicarbazide reaction using triethyl amine at high temperatures.[53] The most recently, Akamanchi research group has reported IBX/TEA mediated synthesis of various azoles by desulfurization process in low temperature reaction conditions.[54] Patel et al. have reported desulfurization of dithiocarbamate salts using molecular iodine.[55] Although several protocols are enumerated in the literature for the synthesis of 2-amino-1,3,4-oxadiazoles, most of them utilized either strong acidic or basic conditions. Some of the protocols require expensive reagents (EDC or BOP), reactions conducted at elevated temperatures, longer reaction times and usage of halogenated solvents

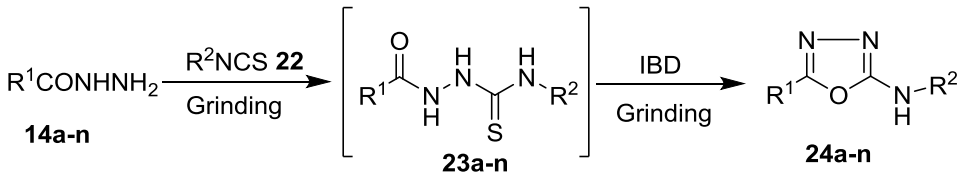
are the major constrains to stand them in greener and environmentally benign protocols. Hence, still there is more generalized and eco-friendly protocol is necessary for the synthesis of oxadiazoles to address challenging problems like usage of non-toxic reagents, benign reaction media and simple workup procedures to isolate the pure products.

Our research group strong compliance to adopt eco-friendly and solvent-free synthetic protocols for the construction of bio-active heterocycles has led to the total synthesis of naturally occurring isocryptolepines, anticancer agents 5-(3′-indolyl)oxazoles, 4-(3′-indolyl)-oxazoles and indolyl-1,3,4-oxadiazoles.[38f, 40d, 56] In continuation of our efforts to develop novel synthetic protocols for privileged heterocycles, herein, we report a solvent-free and one-pot synthesis of 2-arylamino-1,3,4-oxadiazoles by neat grinding of arylhydrazide and arylisothiocyanate in the presence of IBD.

2.3.2 Results and discussion

2.3.2.1 Synthesis

Synthesis of 2-arylamino-1,3,4-oxadiazoles **24** was carried out as outlined in the Scheme 2.3.1. Initial attempts to synthesize the 2-amino-1,3,4-oxadiazoles involve the step-wise isolation of intermediate thiosemicarbazide **23**. In a model reaction, phenylhydrazide **14a** and phenylisothiocyanate **22a** were grinded thoroughly for 4 minutes to get homogenous paste. The intermediate **23a** was isolated and subjected to cyclodesulfurization using iodobenzene diacetate to give the desired 2-arylamino-1,3,4-oxadiazole **24a** in 80% yield.



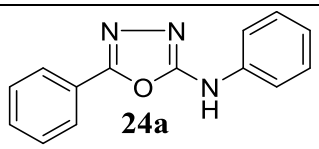
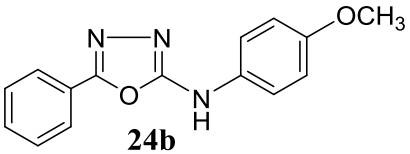
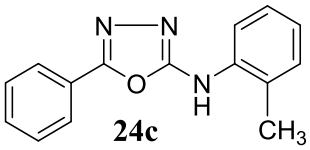
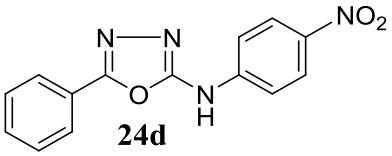
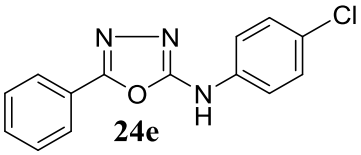
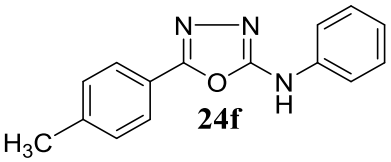
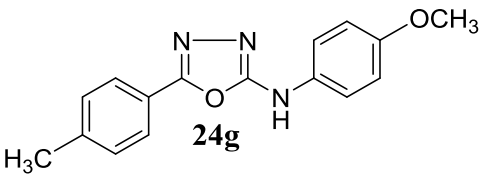
Scheme 2.3.1 One-pot synthesis of 2-arylamino-1,3,4-oxadiazoles **24**

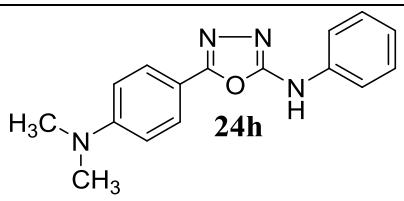
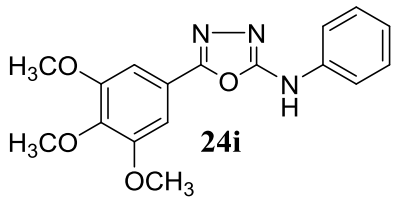
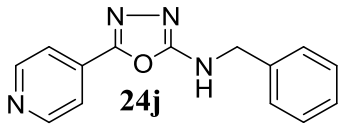
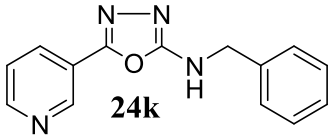
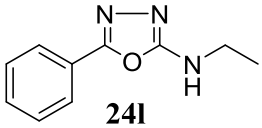
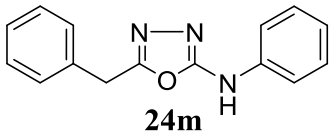
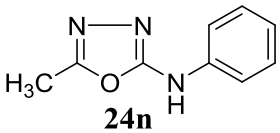
Recently, our research group has reported iodobenzene diacetate mediated cyclo dimerization of thioamides to give symmetrical 1,2,4-thiadiazoles.[40c] This protocol involves the desulfurization of indole-3-carbothioamide during course of the reaction. In a similar manner, due to high polarizability of sulfur and electrophilic nature of iodine in iodobenzene diacetate, the intermediate thiosemicarbazide is activated by IBD to generate final 2-arylamino-1,3,4-oxadiazoles.

The protocol was further optimized in one-pot strategy. In this case reactants aryl hydrazide **14** and isothiocyanate **22** were initially grinded and based on TLC once formation of

intermediate thiosemicarbazide **23** was observed, iodobenzene diacetate was added in portion wise and continued grinding till formation of desired 2-arylamino-1,3,4-oxadiazole **24** (usually it takes 4 min.). After completion of the reaction the water was added to the reaction mixture and pure product was isolated without further purification with excellent yields (Table 2.3.1).

Table 2.3.1 Synthesis of 2-arylamino-1,3,4-oxadiazoles (**24a-n**)

S.No.	Compounds	Yields (%)	Mp (°C)
1	 **24a**	80	215 (Lit.[53] 215)
2	 **24b**	75	216.2-217.1(Lit.[53] 217.1-217.8)
3	 **24c**	72	165.2-166 (Lit.[53] 164-165.6)
4	 **24d**	70	244.2-245
5	 **24e**	65	135-137.2 (Lit.[53]137.1-138.6)
6	 **24f**	72	225 (Lit.[27] 226-227)
7	 **24g**	76	212-213.3 (Lit.[27] 213.2-213.9)

8	 **24h**	74	199.5-200.7 (Lit.[45f] 200-201.4)
9	 **24i**	74	182.3-183
10	 **24j**	78	175 (Lit.[45f] 173-174.2)
11	 **24k**	88	199-200.5
12	 **24l**	75	129-130 (Lit.[57] 128-130)
13	 **24m**	72	178-179 (Lit.[45f] 178.1-180.6)
14	 **24n**	60	158.6-159.2 (Lit.[53] 160-160.9)

The optimized one-pot strategy was further generalized by reacting various aryl/heteroaryl/alkyl hydrazides with aryl/alkyl isothiocyanates. Various hydrazides and isothiocynates were smoothly converted into 2-arylamino-1,3,4-oxadiazoles in good yields without any further purification.[33] However, in case of alkyl isothiocyanates reaction failed to produce expected 2-alkylamino-1,3,4-oxadiazoles. Synthesized 2-arylamino-1,3,4-oxadiazoles were well characterized using IR, NMR and mass spectral data. Melting points of some 2-arylamino-1,3,4-oxadiazoles were found to be in agreement with literature melting points. (Table 2.3.1).[34]

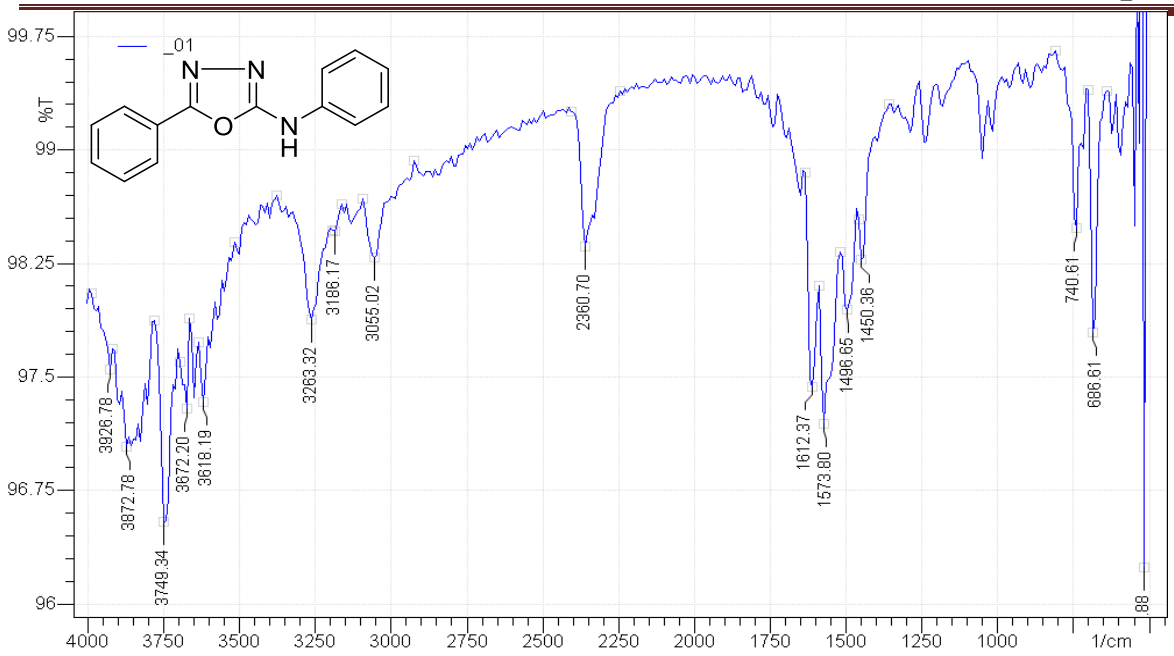


Figure 2.3.2 IR spectrum of **24a**

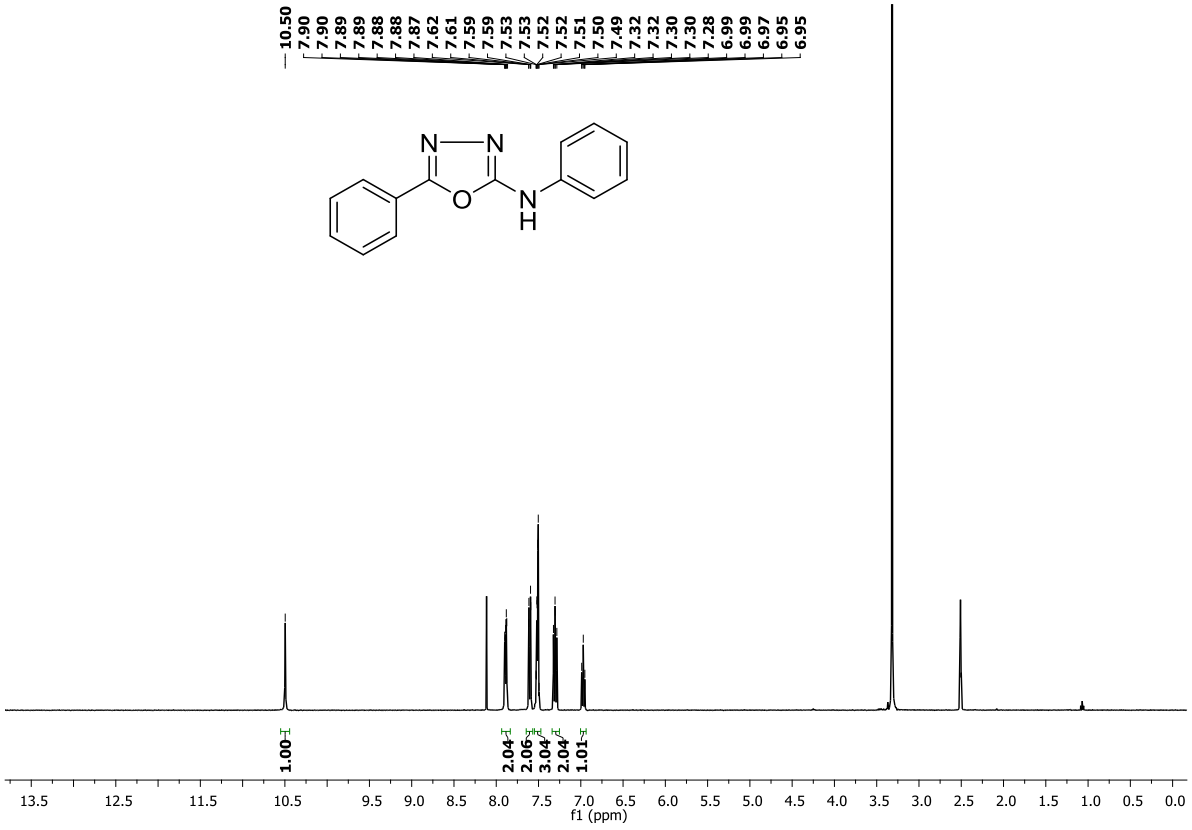
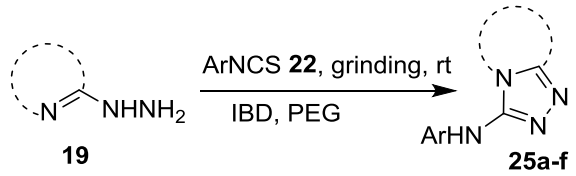


Figure 2.3.3 ^{1}H NMR spectrum of **24a**

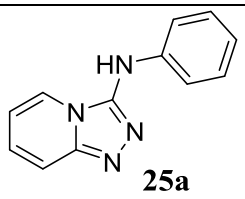
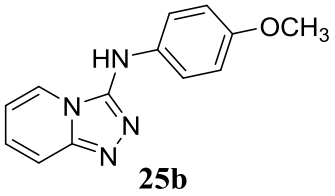
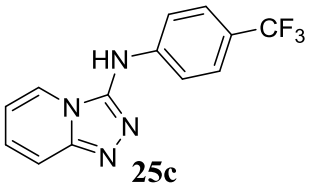
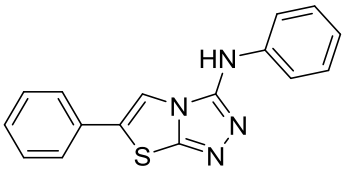
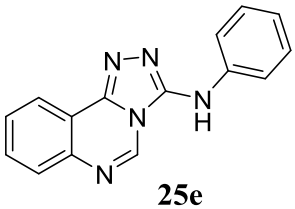
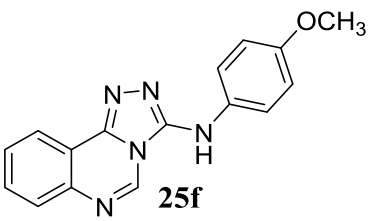
Reaction conditions were extended to prepare arylamino-[1,2,4]triazoles **25a-f** from the reaction of arylisothiocyanate **22** with heteroarylhydrazines **19** (Table 2.3.2). All the prepared

arylamino-[1,2,4]triazoles **25a-f** were well characterized using NMR, mass spectral data and by comparing their melting points with the reported in literature.

Table 2.3.2 Synthesis of fused arylamino-[1,2,4]triazoles



19 25a-f

S.No.	Compounds	Yields (%)	Mp (°C)
1	 **25a**	69	230 (Lit.[32c] 232-233)
2	 **25b**	70	238-239 (Lit.[32c] 240)
3	 **25c**	68	268 (Lit.[32c] 270)
4	 **25d**	68	185
5	 **25e**	68	168-169
6	 **25f**	70	172-173

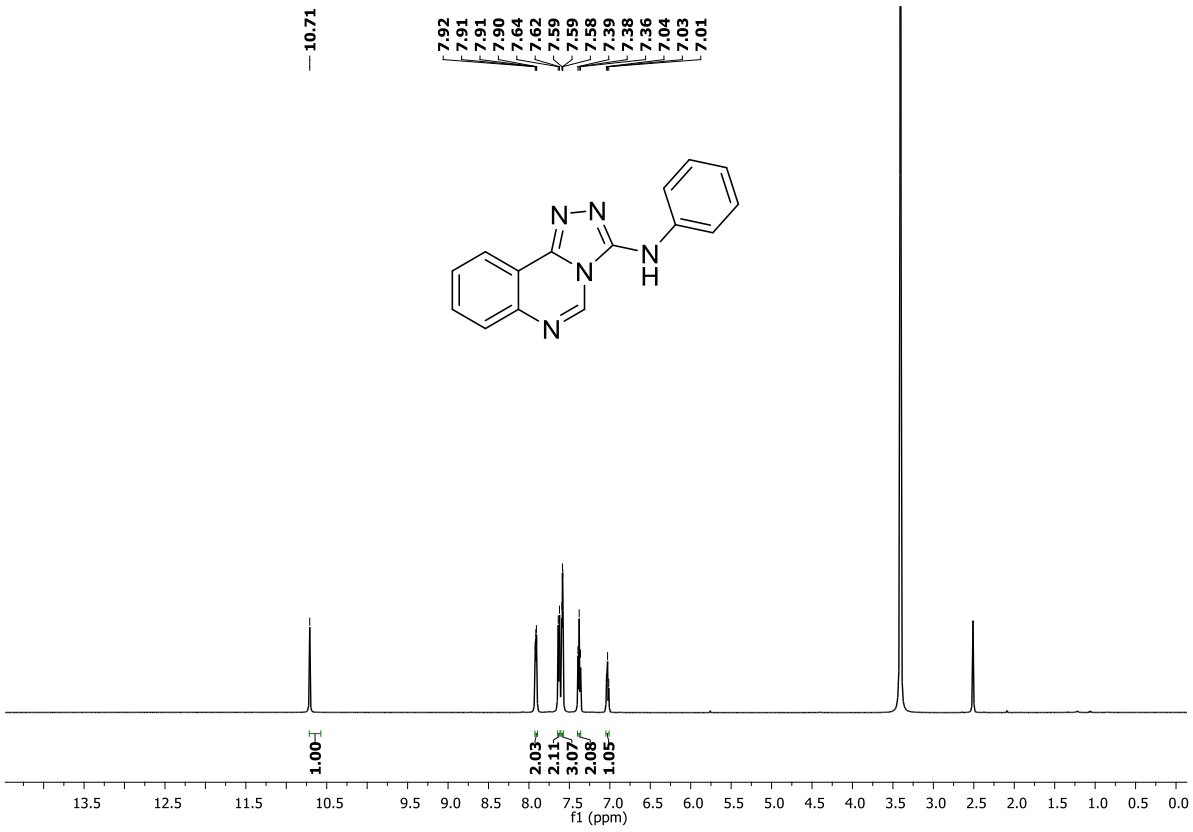


Figure 2.3.4 ^{1}H NMR spectrum of **25e**

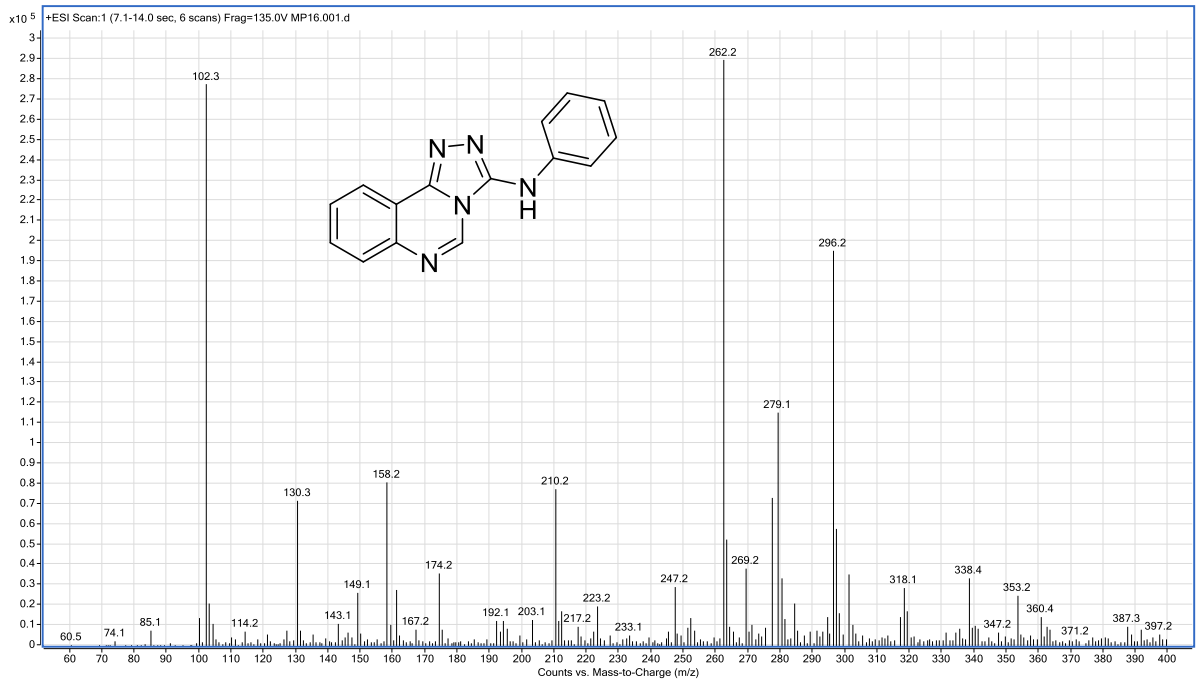
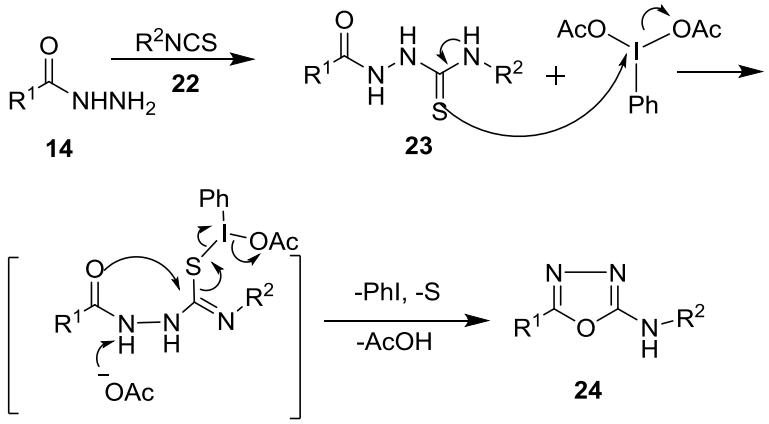


Figure 2.3.5 Mass spectrum of **25e**

2.3.3.2 Possible reaction mechanism

The possible mechanism for the formation of 2-arylamino-1,3,4-oxadiazole **24** is described in Scheme 2.3.2. The mechanism was proposed in analogy to the literature reports supporting the desulfurization involving organoiodine reagents.[54, 58] Initial nucleophilic attack of sulfur displaces one of the ligand of IBD to generate an intermediate **A**. Subsequent internal nucleophilic attack of oxygen and cyclization afforded the desired 2-arylamino-1,3,4-oxadiazoles **24** (Scheme 2.3.2).



Scheme 2.3.2 Possible mechanism for the formation of 2-arylamino-1,3,4-oxadiazoles **24**

2.3.3 Conclusions

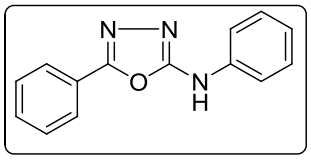
In conclusion, we have developed a solvent-free and one-pot protocol for the synthesis of 2-arylamino-1,3,4-oxadiazoles from easily accessible arylhydrazides and arylisothiocynates. The methodology involves iodobenzene diacetate promoted desulfurization of *in situ* generated thiosemicarbazide under solvent-free condition at room temperature. In comparison to the reported methods, our protocol provides an easy access to biologically important heterocyclic scaffold aminooxadiazoles and aminotriazoles, as it avoids toxic, corrosive reagents and halogenated solvents.

2.3.4 Experimental section

General procedure for the synthesis of 2-arylamino-1,3,4-oxadiazoles 24 and aryamino-[1,2,4]triazoles (25): Finely powdered aryl/heteroaryl/alkyl hydrazide (**14**, 1 mmol) and aryl isothiocynate (**22**, 1 mmol) were grinded in a mortar and pestle at room temperature for 3 min. After formation of intermediate thiosemicarbazide (**23**) as observed by TLC, iodobenzene diacetate (1 mmol) was added portion wise and continued the grinding for 5

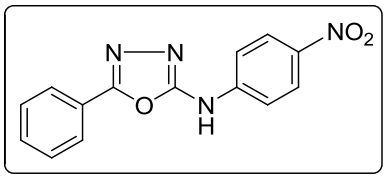
min. to afford desired 2-arylamino-1,3,4-oxadiazoles **24**. Water (5 mL) was added to the reaction mixture and the product was filtered and washed with hexane (10 mL).

***N*,5-Diphenyl-1,3,4-oxadiazol-2-amine (24a)**



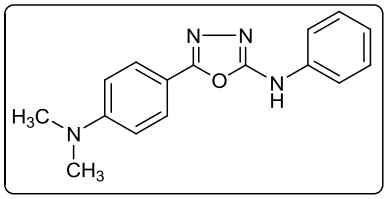
White solid; mp 215 °C; IR (KBr) 3263, 3055, 1612, 1573, 1496, 1450, 740 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H, NH), 7.94-7.82 (m, 2H), 7.60 (dd, J = 8.6, 1.0 Hz, 2H), 7.53-7.48 (m, 3H), 7.33-7.27 (m, 2H), 7.00-6.93 (m, 1H).

***N*-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (24d)**



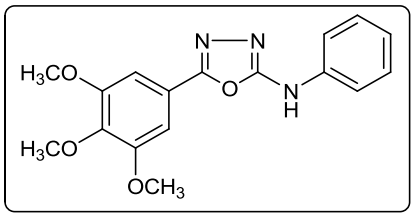
Yellow solid; mp 244.2-245 °C; IR (KBr) 3618, 3255, 1620, 1573, 1504, 1342, 1249, 686 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.35 (s, 1H, NH), 8.19 (d, J =9.2 Hz, 2H), 7.90 (dd, J = 6.6, 2.9 Hz), 7.80 (d, J = 9.2 Hz, 2H), 7.54-7.50 (m, 4H); ESI-MS *m/z* calcd. for $C_{14}H_{10}N_4O_3$ 282.0, found 282.0.

5-(4-(Dimethylamino)phenyl)-*N*-phenyl-1,3,4-oxadiazol-2-amine (24h)



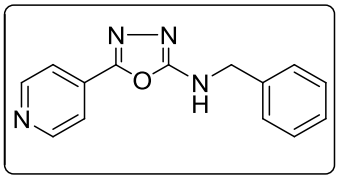
Light brown solid; mp 199.5-200.7 °C; IR (KBr) 3726, 3618, 1666, 1581, 1496, 1488, 1126, 516 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6): δ 10.51 (s, 1H, NH), 7.61 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 7.6 Hz, 2H), 7.13 (s, 2H), 6.97 (d, J = 11.6 Hz, 1H), 3.87 (s, 6H), 3.76 (s, 3H);

***N*-Phenyl-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-amine (24i)**



Yield 74%; light brown, mp 182.3-183 °C; IR (KBr) 3726, 3618, 1666, 1581, 1496, 1488, 1126, 516 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6): δ 10.51 (s, 1H), 7.61 (d, J = 7.8 Hz, 2H), 7.32 (d, J =7.6 Hz, 2H), 7.13 (s, 2H), 6.97 (d, J =11.6 Hz, 1H), 3.87 (s, 6H), 3.76 (s, 3H); ESI-MS *m/z* calcd. for $C_{17}H_{17}N_3O_4$ 327.1, found 327.0.

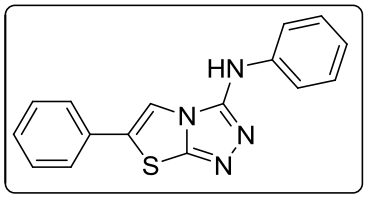
***N*-Benzyl-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (24j)**



Pale yellow solid; mp 173-174.2 °C; IR (KBr) 3733, 3618, 3232, 1612, 1427, 694, 516 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.98 (d, J = 1.5 Hz, 1H), 8.63 (dd, J = 4.8, 1.6

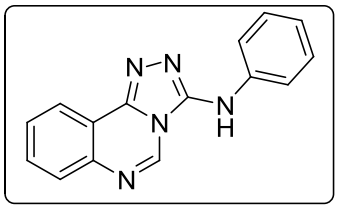
Hz, 1H), 8.36 (t, *J* = 6.2 Hz, 1H), 8.14-8.10 (m, 1H), 7.48 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.37 (d, *J* = 7.1 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 2H), 7.23 (t, *J* = 6.6 Hz, 1H), 4.47 (d, *J* = 6.2 Hz, 2H, CH_2); ESI-MS *m/z* calcd. for $C_{14}H_{12}N_4O$ 252.1, found 252.0.

_N_,6-Diphenylthiazolo[2,3-c][1,2,4]triazol-3-amine (25d)



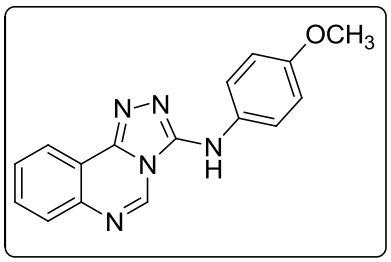
Yield 68%; light brown, mp 185 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.48 (d, *J* = 8 Hz, 3H), 7.45 (d, *J* = 7.8 Hz, 1H) 7.35 (t, *J* = 7.8 Hz, 1H), 7.21 (S, 1H), 7.14-7.10 (m, 4H) 7.04-6.99 (m, 1H); ESI-MS *m/z* calcd. for $C_{16}H_{12}N_4S$ 292.07, found 292.1.

***N*-Phenyl-[1,2,4]triazolo[4,3-c]quinazolin-3-amine (25e)**



Yield 68%; off white, mp 168-169 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.71 (s, 1H), 7.91 (dd, *J* = 6.4, 3 Hz, 2H) 7.63 (d, *J* = 7.8 Hz, 2H), 7.59 (m, 3H), 7.38 (t, *J* = 7.9 Hz, 2H) 7.03 (t, 7.3 Hz, 1H); ESI-MS *m/z* calcd. for $C_{15}H_{11}N_5$ 261.10, found 262.2

***N*-(4-Methoxyphenyl)-[1,2,4]triazolo[4,3-c]quinazolin-3-amine (25f)**



Yield 70%; light brown, mp 172-173 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.48(s,1H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.68-7.57(m, 3H), 7.54(d, *J* = 8.9 Hz, 2H), 6.97(d, *J* = 8.9 Hz, 2H), 3.74(s, 1H); ESI-MS *m/z* calcd. for $C_{16}H_{13}N_5O$ 291.30, found 292.2

2.3.5 References

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CHAPTER 3

Diaryliodonium Salts-Promoted C-H Arylation of Heterocycles: Synthesis of Bioactive Arylheterocycles

3.1 Introduction

Diaryliodonium salts are versatile electrophilic arylating agents in organic synthesis because of low toxicity, easy handling, high reactivity and excellent selectivity against various nucleopliles.[1] These are stable crystalline solids which serve as powerful arylating agents in various transition metal-catalyzed and metal-free coupling reactions.[2] A general structure of diaryliodonium salts shown in Figure 3.1, in which two aryl ring attached to central iodine atom with a counter ion. The X-ray structure of these diaryliodonium salts comfirmed a T-shaped geometry, in which bond angle in between two aryl rings are close to 90^0. The reactivity and solubility of these diaryliodonium salts can be tuned by changing the counter ion. Generally, non-nucleophilic anion mainly triflate (OTf) and tetrafluoroborate (BF_4) are preferred over nucleophilic anion such as Cl, Br and I in organic synthesis.[3] Reactivity of unsymmetrical diaryliodonium salts are different in metal-catalyzed and metal-free conditions, usually in the presence of metal catalyst most electron-rich arene is preferentially transferred whereas in metal-free conditions the most-electron deficient arene ring is transferred.[2b]

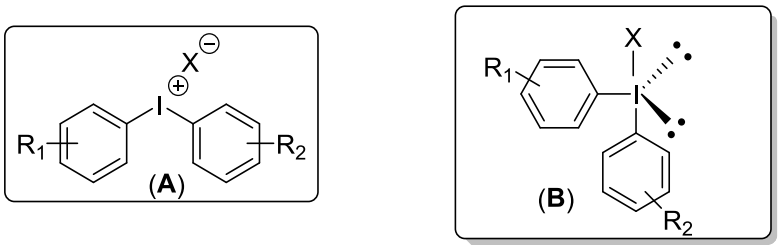


Figure 3.1 Diaryliodonium salts (A) General structure, (B) T-shaped geometry

Recently, C-H functionalization of bioactive heterocycles have received increasing attention due to many advantages such as use of catalytic amounts of reagents and avoidance of activating agents, thereby generating fewer by-products.[4] The heteroarylazole nucleus such as oxadiazole, thiadiazole, benzoxazole and benzothiazole are key structural unit in various biologically active compounds[5] and which shows diverse applications in medicinal chemistry as well as material sciences (electron transport in organic light emitting diodes (OLED)).[6] In recent past various azaheterocycles like 2,5-diphenyl-1,3,4-oxadiazole (**1a**)[7] and 5-phenyl-2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (**1b**)[6] identified as a anticancer agents against various human cancer cells. Furthermore, a well known marketed drug Tafamidis (**1c**) which is 3,5-dichloro derivative of

benzoxazole, frequently used for the treatment of neurodegenerative diseases.[8] Subsequently, Nesapidil (**1d**) has also been identified as antihypertensive agent.[9] Additionally, butyl PBD (**1e**) which contain 1,3,4-oxadiazole nucleus used in liquid scintillator neutrino detector (LSND)[10] (Figure 3.2). Azaheterocycles especially, 2,5-disubstituted-1,3,4-oxadiazoles have been used as a bioisosteres of ester, amide and acid functionalities in pharmaceutical chemistry.[11]

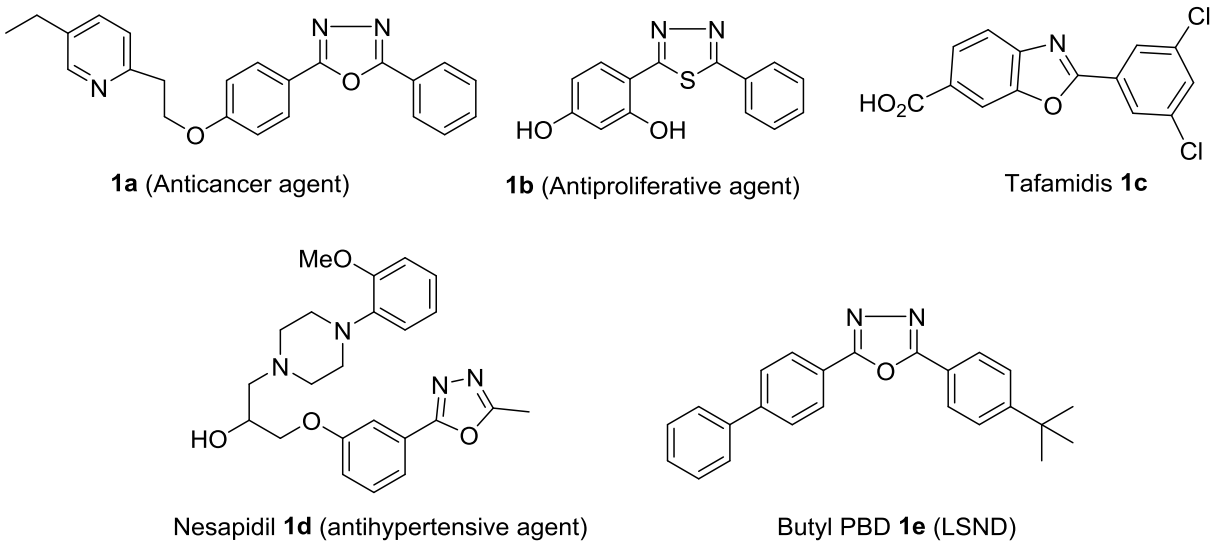
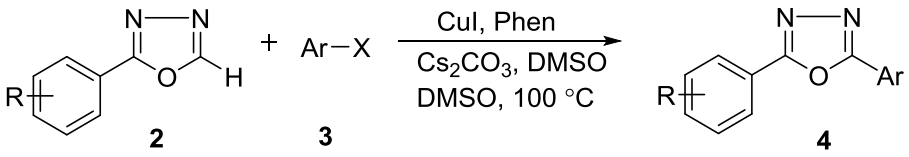


Figure 3.2 Structures of some important bioactive azaheterocycles

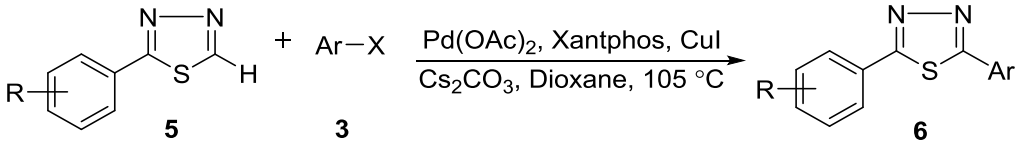
Due to the importance of these arylated azaheterocycles in the medicinal and material chemistry, it received considerable attention of chemist to develop novel and convenient protocol to arylate diverse heterocycles through C-H activation. In last decades several leading research groups explored the arylation of azaheterocycles using a variety of arylating agents such as aryl halides/pseudohalides, arylamides, sodium arylsulfinates and boronic acid.

In 2009, Miura and co-workers arylated the 2-aryl-1,3,4-oxadiazoles **2** with aryl halide **3** using CuI, phenanthrene and Cs_2CO_3 in DMSO at 100 °C to produce 2,5-diaryl-1,3,4-oxadiazoles **4** in good yields (Scheme 3.1).[12]



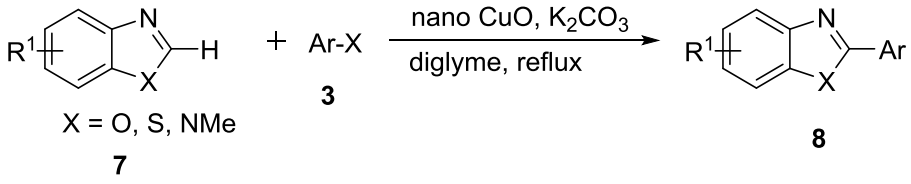
Scheme 3.1 Synthesis of 2,5-diaryl-1,3,4-oxadiazoles **4**

Eycken et al. reported Pd/Cu-catalyzed direct C-H arylation of 2-aryl-1,3,4-thiadiazoles **5** with a wide range of aryl halides **3** at 105 °C to prepare 2,5-diaryl-1,3,4-thiadiazoles **6** as shown in Scheme 3.2. This developed protocol well tolerates a variety of heteroaryl halides bearing thiophene, pyridine, indole moieties as well as sterically hindered aryl halides.[13]



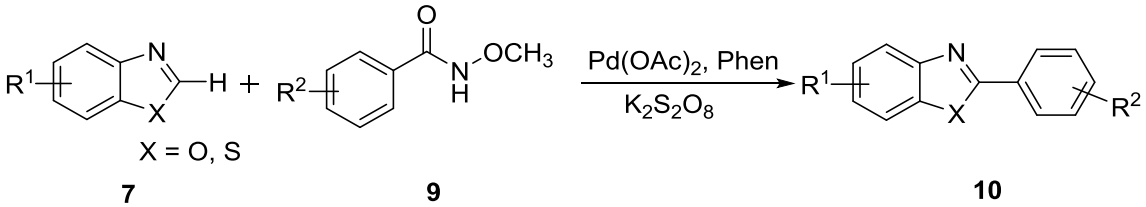
Scheme 3.2 Arylation of 2-phenyl-1,3-4-thiadiazoles **5**

Wang group established ligand free CuO nanospindles catalyzed direct arylation of C-H bond of benzoxazole (**7**) using aryl halides **3** in diglyme at reflux condition. This protocol was further extended to arylate benzothiazole and 1-methylbenzimidazole under similar reaction conditions with increasing reaction time from 3 h to 8 h and 16 h, respectively. Next, the CuO nanospindles which act as an heterogenous catalyst was recycled and reused without any significant decrease in catalytic activity (Scheme 3.3).[14]



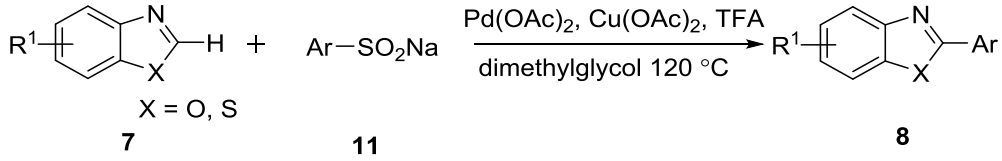
Scheme 3.3 Arylation of benzofused heterocycles **7**

In 2012, Wang et al. reported the chemo- and regioselective palladium-catalyzed deamidative arylation of benzoxazoles/benzthiazoles **7** with arylamides **9** through tandem decarbonylation–C–H functionalizations (Scheme 3.4). The reaction proceed smoothly in the presence of $Pd(OAc)_2$, phenanthrene and $K_2S_2O_8$ in toluene–DMSO through a tandem decarbonylation C–H activation process to give the corresponding arylated products **10**.[15]



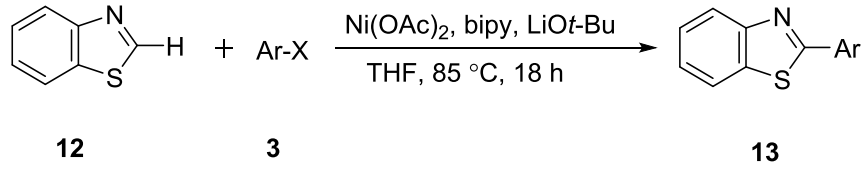
Scheme 3.4 Deamidative arylations of azoles with arylamides

Wang group used the sodium arylsulfinates **11** as aryl sources for the arylation of azoles **7** at C2-position. The developed palladium-catalyzed direct desulfitative arylation of azoles such as benzoxazoles, oxazoles, benzothiazole, thiazoles and 1,3,4-oxadiazoles was smoothly arylated using arylsulfinates as depicted in Scheme 3.5.[16]



Scheme 3.5 Arylation of azoles **7** using arylsulfinates

In 2009, Itami developed a nickel based catalytic systems for the arylation of benzothiazole **12** with aryl halides/pseudohalides **3**. Combination of $Ni(OAc)_2$ and bipyridine was general catalyst for the effective arylation of benzothiazole with diverse aryl halides (chlorides/triflates) as depicted in Scheme 3.6.[17]

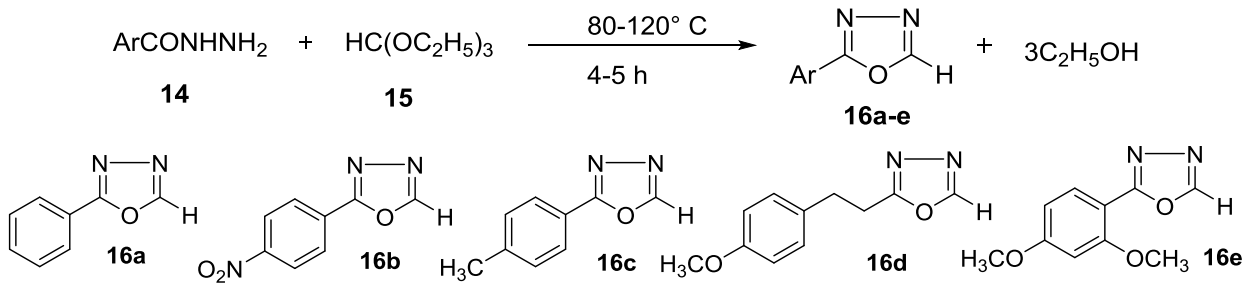


Scheme 3.6 Synthesis of 2-arylbenzothiazoles **13**

3.2 Results and discussion

3.2.1 Synthesis

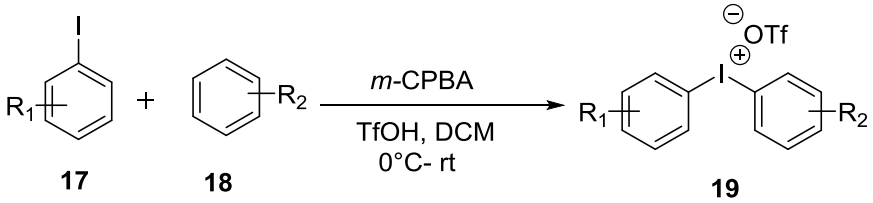
Starting material 2-aryl-1,3,4-oxadiazoles **16a-e** were synthesized using literature procedure. The arylcarboxylic acid hydrazide **14** mixed with triethylorthoformate **15** and heated under reflux temperature for 3-4 h as described in experimental section (Scheme 3.7).[18]

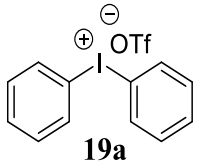
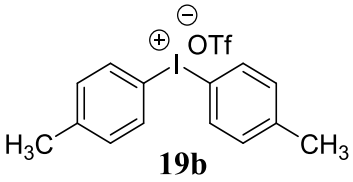
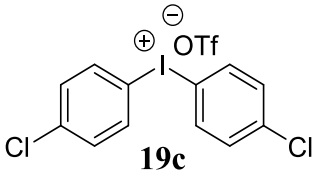
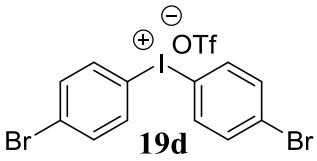
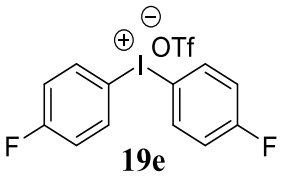


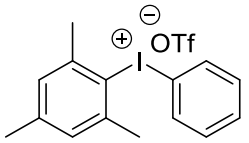
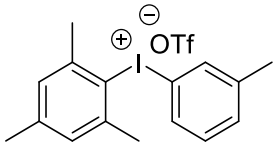
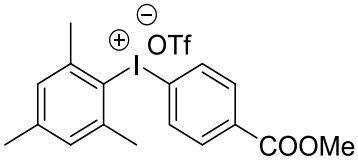
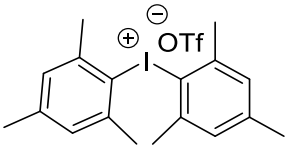
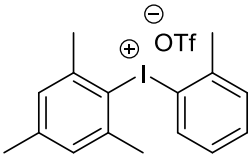
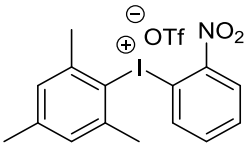
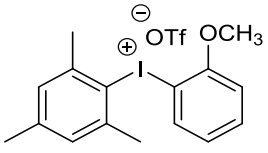
Scheme 3.7 Synthesis of 2-aryl-1,3,4-oxadiazoles **16**

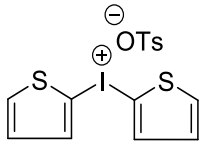
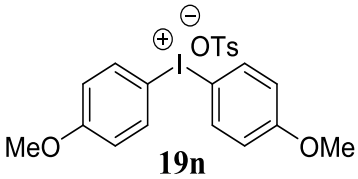
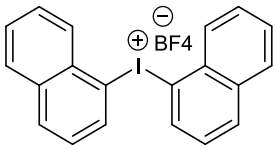
Diaryliodonium salts **19a-n**[19] were prepared by following literature methods involving the reaction of aryl halides **17** with corresponding arenes **18** in the presence of oxidizing agent *m*-CPBA and TfOH . Synthesized diaryliodonium salts **19a-n** were confirmed by comparing their literature melting points as shown in Table 3.1.

Table 3.1. Synthesized diaryliodonium salts



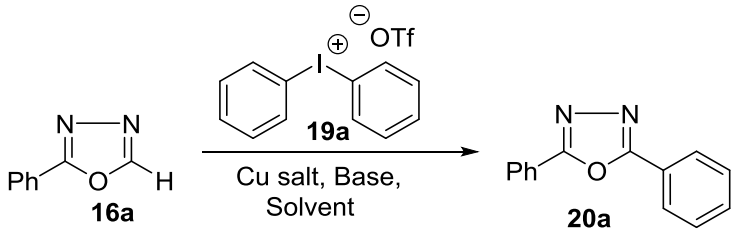
S.No	Structure	Yields (%)	Mp (°C)
1	 **19a**	88	177-178 (Lit.[19b] 178-180)
2	 **19b**	52	183-184 (Lit.[19b] 182-184)
3	 **19c**	90	180-181 (Lit.[19b] 181-183)
4	 **19d**	88	189-190 (Lit.[19b] 190-191)
5	 **19e**	90	166-167 (Lit.[19b] 167-168)

6	 **19f**	78	145-146 (Lit.[19c] 147-148)
7	 **19g**	81	169-170 (Lit.[19c] 171-172)
8	 **19h**	79	172-173 (Lit.[19c] 174-175)
9	 **19i**	88	187-188 (Lit.[19a]187-188) (decomposed)
10	 **19j**	84	165-166 (Lit.[19a] 164-166)
11	 **19k**	65	155-156 (decomposed)
12	 **19l**	65	123-124

13	 **19m**	66	133-134 (Lit.[20] 134) (decomposed)
14	 **19n**	60	136-137 (Lit.[20] 138-139)
15	 **19o**	37	153-154 (Lit. [21] 155) (decomposed)

Arylation of 2-phenyl-1,3,4-oxadiazole was achieved as depicted in Table 3.2. Initially, the C-H arylation of easily accessible 2-phenyl-1,3,4-oxadiazole (**16a**) with diphenyliodonium triflate (**19a**) was explored to generate 2,5-diphenyl-1,3,4-oxadiazole (**20a**) (Table 3.2). The C_5-H in **16a** being next to a heteroatom, initially we tried to generate an anion using bases (Na_2CO_3, Cs_2CO_3 and *t*-BuOK) in polyethylene glycol-400 (PEG-400) and DMSO. The arylation of **16a** using a catalytic amount of CuBr (20 mol%) and a stronger base (*t*-BuOK) was examined in PEG-400 at 100 °C; CuBr triggered the arylation of **16a** after 18 h. to deliver **20a** in 68% yield (Table 3.2, entry 6). To optimize the reaction conditions further, various bases, copper salts and solvents were screened. Interesting results were obtained, however, when alternate form of energy, microwave (MW) irradiation was deployed; the same reaction conducted in a focused MW system for 30 min afforded **20a** in 80% yield (Table 3.2, entry 7) substantiating earlier MW-enhanced accelerated C-C bond formation.[22] Among other bases, Cs_2CO_3 and K_3PO_4, failed to deliver **20a** (Table 3.2, entries 8 and 9). Similar fate was met by replacing CuBr with CuI; no improvement in the yield was observed (Table 3.2, entry 10). The arylation was then examined at room temperature in DMSO using a stronger base (*t*-BuOLi) when efforts were amply rewarded with much higher yield of **20a** (89%) in 15 min by simply changing the solvent from PEG-400

Table 3.2. Optimization of arylation of 1,3,4-oxadiazoles using diaryliodonium salts[a]



Entry	Catalyst	Base	Solvent	Counterion (X)	Yield (%)
1.	-	Na_2CO_3	PEG-400	OTf	NR[b]
2.	-	Cs_2CO_3	PEG-400	OTf	NR[b]
3.	-	Na_2CO_3	DMSO	OTf	NR[b]
4.	-	Cs_2CO_3	DMSO	OTf	NR[b]
5.	-	*t*-BuOK	DMSO	OTf	NR[b]
6.	CuBr	*t*-BuOK	PEG-400	OTf	68[b]
7.	CuBr	*t*-BuOK	PEG-400	OTf	80[c]
8.	CuBr	Cs_2CO_3	PEG-400	OTf	Trace[c]
9.	CuBr	K_3PO_4	PEG-400	OTf	NR[c]
10.	CuI	*t*-BuOK	PEG-400	OTf	Trace[d]
11.	CuBr	*t*-BuOK	DMSO	OTf	80[d]
12.	CuBr	*t*-BuOLi	DMSO	OTf	89[d]
13.	CuBr	Cs_2CO_3	DMSO	OTf	NR[d]
14.	CuBr	*t*-BuOLi	DMSO	BF_4	65[d]

[a] A mixture of **16a** (1 equiv.), **19a** (1 equiv.), Cu catalyst (20 mol%), base (3 equiv.) was stirred in DMSO for 15 min. at rt. [b] Conventional heating at 100 °C for 18-24 h. [c] reaction under microwave irradiation at 100 °C for 30 min. [d] stirring at rt for 10-15 min, NR = no reaction

to DMSO and base from *t*-BuOK to *t*-BuOLi (Table 3.2, entry 12), presumably due to better solubility of the substrate, catalyst and base in DMSO. For the arylation of **16a-e**, use of CuBr (20 mol%) and *t*-BuOLi (3.0 equiv) at room temperature in DMSO was the ideal optimized condition. During the arylation of oxadiazoles, we found that the use of corresponding iodonium triflate was more effective when compared to iodonium salts with Br, OTs and BF_4 counter ions. In some cases iodonium salts with OTs or Br counterions were preferred due to their easy access.

Having optimized the reaction conditions as mentioned in Scheme 3.8, we explored this protocol for the arylation of various oxadiazoles **16** by utilizing different symmetrical and unsymmetrical diaryliodonium salts and prepared a variety of 2,5-diaryl-1,3,4-oxadiazoles **20a-q** (Table 3.2). Substituted oxadiazoles **16** having nitro (**16b**), tolyl (**16c**) and dimethoxyphenyl (**16e**) moieties were arylated smoothly to furnish **20h-l** (75-88%) and **20p** (60%) in good to excellent yields. Alkyl substituted oxadiazole (**20d**) could also be coupled to furnish **20n** in 74% yield. Interestingly, when **16a** was coupled with **19g, 20o** was obtained in 70% yield along with **20q** in 8% yield. All the 2,5-diaryl-1,3,4-oxadiazoles **20a-q** were well characterized by their IR, NMR (^{1}H & ^{13}C) and mass spectral data (Figures 3.3 and 3.4).

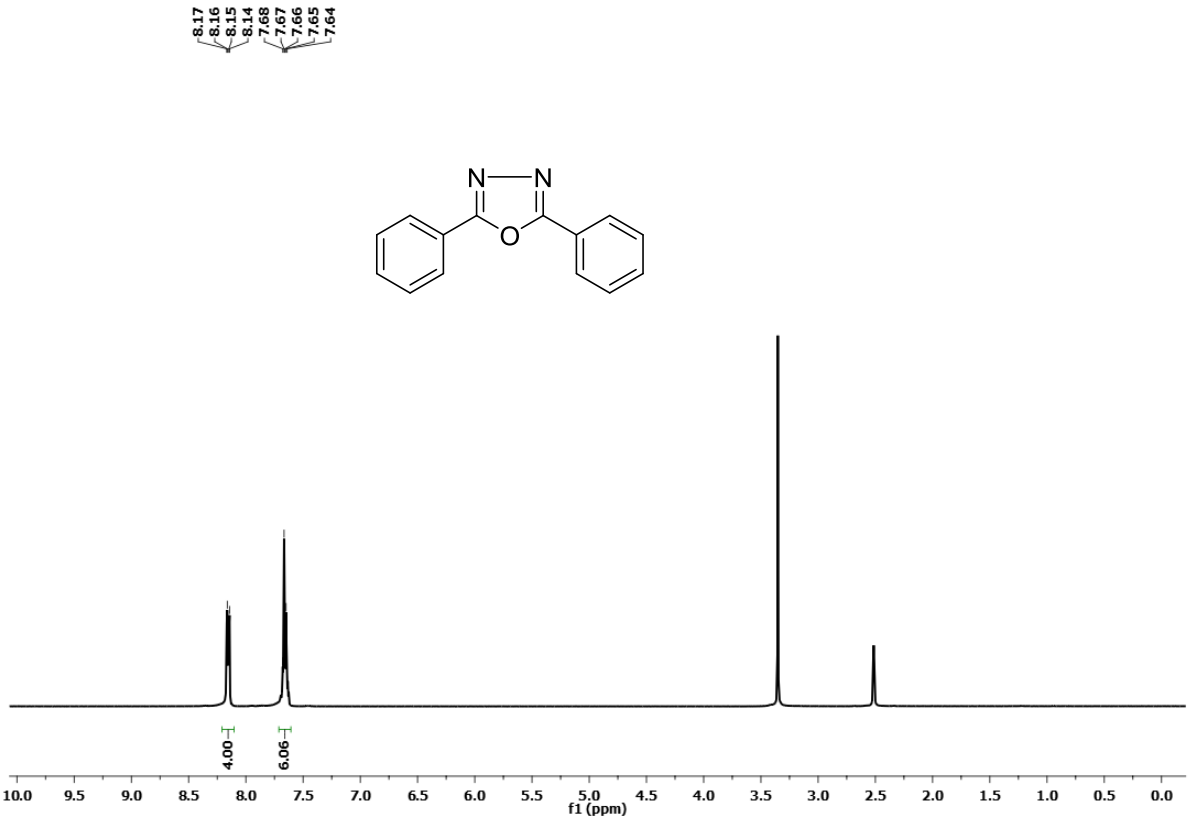


Figure 3.3 ^{1}H NMR spectrum of **20a**

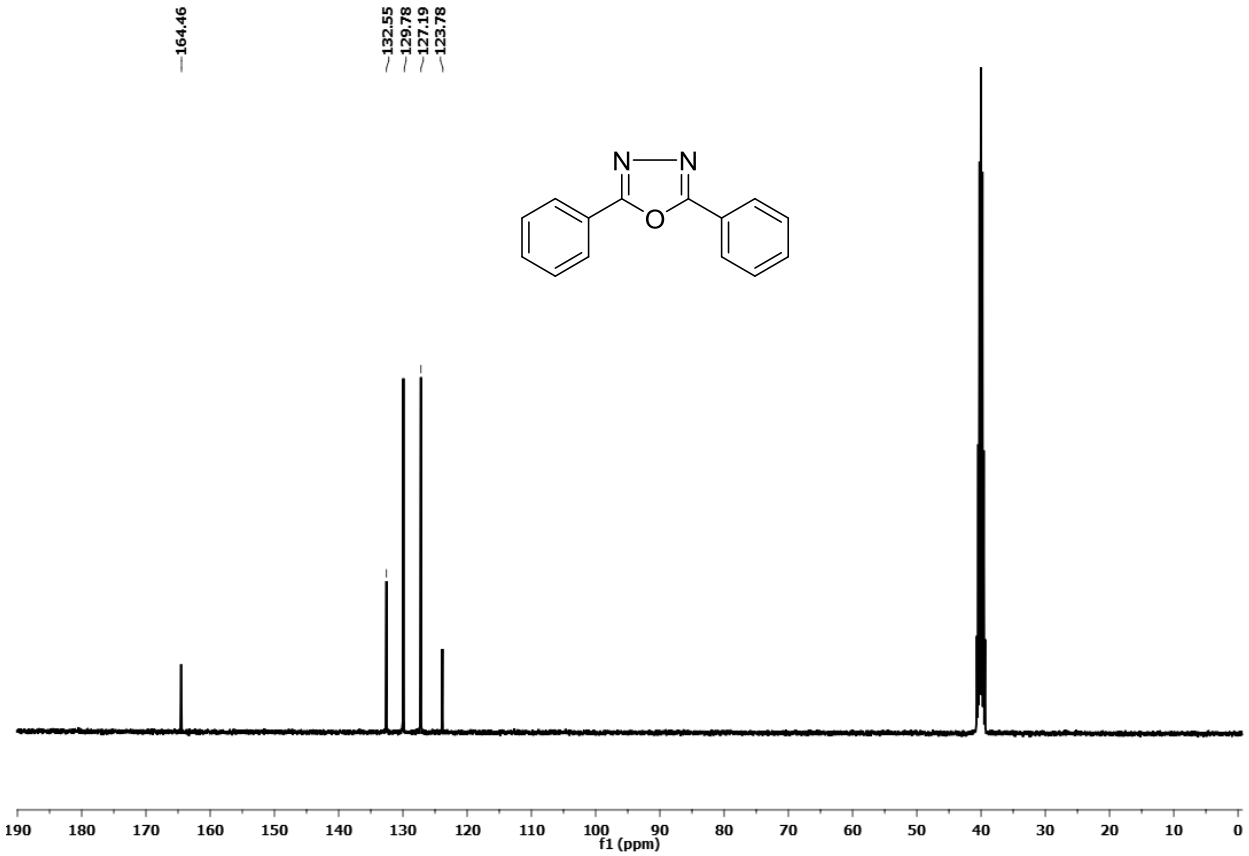
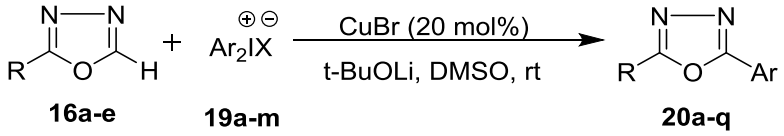
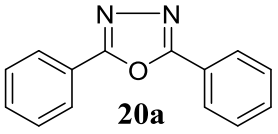
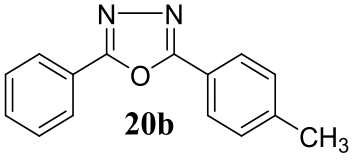


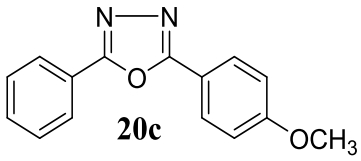
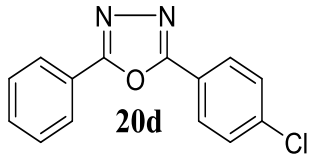
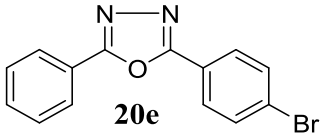
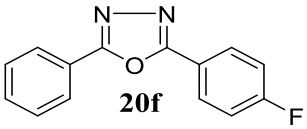
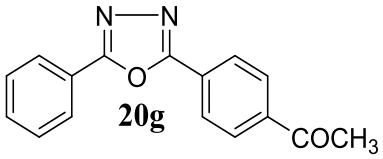
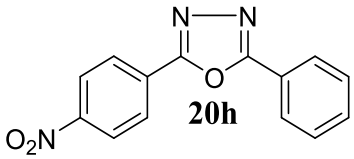
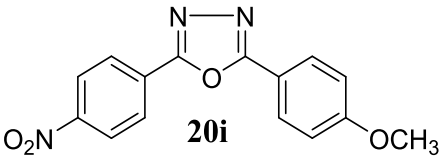
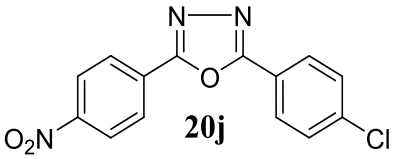
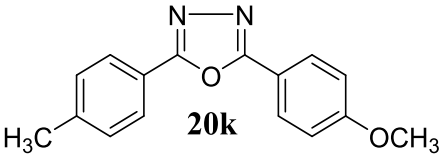
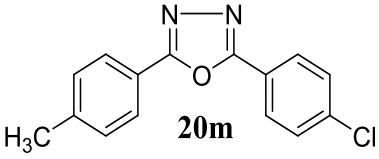
Figure 3.4 ^{13}C NMR spectrum of **20a**

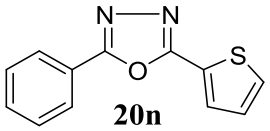
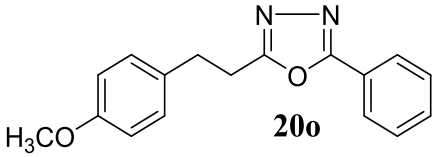
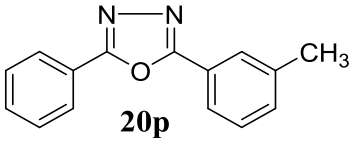
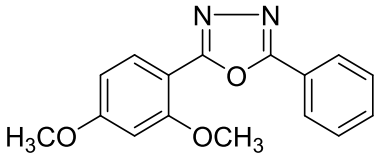
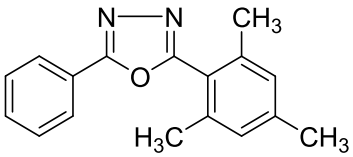


Scheme 3.8 Arylation of 2-aryl-1,3,4-oxadaizoles using diaryliodonium salts

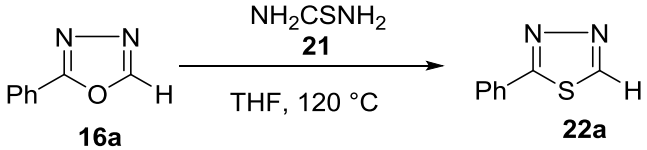
Table 3.3 Synthesized 2-aryl-1,3,4-oxadaizoles using diaryliodonium salts

S.No.	Compounds	Yields (%)	Mp (°C)
1	 **20a**	89	138-139
2	 **20b**	79	125-126

3	 **20c**	75	147-148
4	 **20d**	89	161-162
5	 **20e**	88	171-172
6	 **20f**	88	154-155
7	 **20g**	70	167-168
8	 **20h**	77	209-210
9	 **20i**	75	250-251
10	 **20j**	81	238-239
11	 **20k**	78	138-139
12	 **20m**	88	209-210

13	 **20n**	85	114-115
14	 **20o**	74	liquid
15	 **20p**	70	110-111
16	 **20q**	60	85-86
17	 **20r**	8	93-94

Next, we carried out the arylation of structurally similar 2-phenyl-1,3,4-thiadiazole (**22**) to prepare diversely substituted 2,5-diaryl-1,3,4-thiadiazoles **23a-f** which are of paramount importance in medicinal chemistry due to their interesting biological activities (**1b**, Figure 3.2).[4e,f] Starting material 2-phenyl-1,3,4-thiadiazole (**22**) was prepared by the reaction of 2-phenyl-1,3,4-oxadiazole **16a** and thiourea (**21**) in THF at 120 °C by following literature reported method as mentioned in Scheme 3.9.[23]

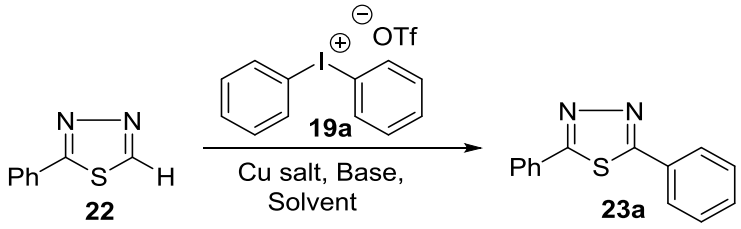


Scheme 3.9 Synthesis of 2-phenyl-1,3,4-thiadiazole **22**

There is only solitary precedence for the direct C-H arylation of 1,3,4-thiadiazoles by using aryl halides/aryl triflates involving $Pd(OAc)_2$, Xantphos, Cs_2CO_3 and CuI catalytic system at 105 °C

for 12 h.[13] Screening study was initiated for the reaction between **22** and **19a** by employing a catalytic amount of copper salts (CuI and CuBr) and bases (*t*-BuOK, Cs_2CO_3, K_3PO_4) in DMSO and PEG-400 at room temperature, but the arylation did not proceed as expected. In some cases traces of **23a** was obtained. Gratifyingly, the arylation of thiadiazole **22** proceeded elegantly with a catalytic amount of CuBr (30 mol%) and *t*-BuOLi (3.5 equiv) in DMF at room temperature within 15 min and afforded **23a** in 83% yield (Scheme 3.10). With these optimized reaction conditions, we conducted the C-H arylation of thiadiazole **22** by employing various diaryliodonium salts **19a-f** (Table 3.4) and could successfully generate a variety of 2,5-diaryl-1,3,4-thiadiazoles **23a-f** in 72-84% yields. Structure of newly synthesized 2,5-diaryl-1,3,4-thiadiazoles **23a-f** were elucidated through their IR, NMR (^1H & ^{13}C) and mass spectral analysis (Figures 3.5 and 3.6).

Table 3.4. Optimization of arylation of 1,3,4-thiadiazoles using diaryliodonium salts[a]



S.No.	Catalyst	Base	Solvent	Yield (%)
1[b]	CuBr	*t*-BuOK	PEG-400	trace
2[b]	CuBr	Cs_2CO_3	PEG-400	trace
3[b]	CuBr	K_3PO_4	PEG-400	NR
4[b]	CuI	*t*-BuOK	DMSO	30
5[b]	CuBr	*t*-BuOK	DMSO	35
6[b]	CuBr	*t*-BuOLi	DMF	83

[a] A mixture of **22** (1 equiv.), **19a** (1 equiv.), Cu catalyst (30 mol%), base (3.5 equiv) was stirred in DMF for 15 min. at rt. [b] stirring at rt for 10-15 min, NR = no reaction

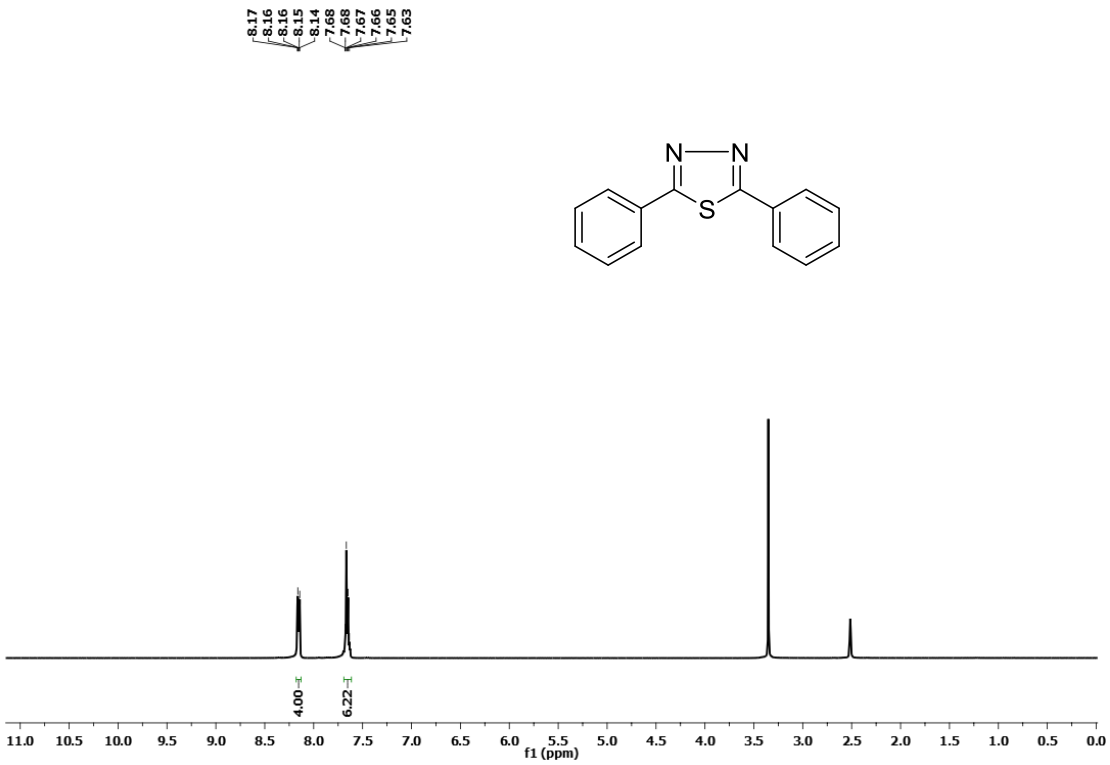


Figure 3.5 ^{1}H NMR spectrum of **23a**

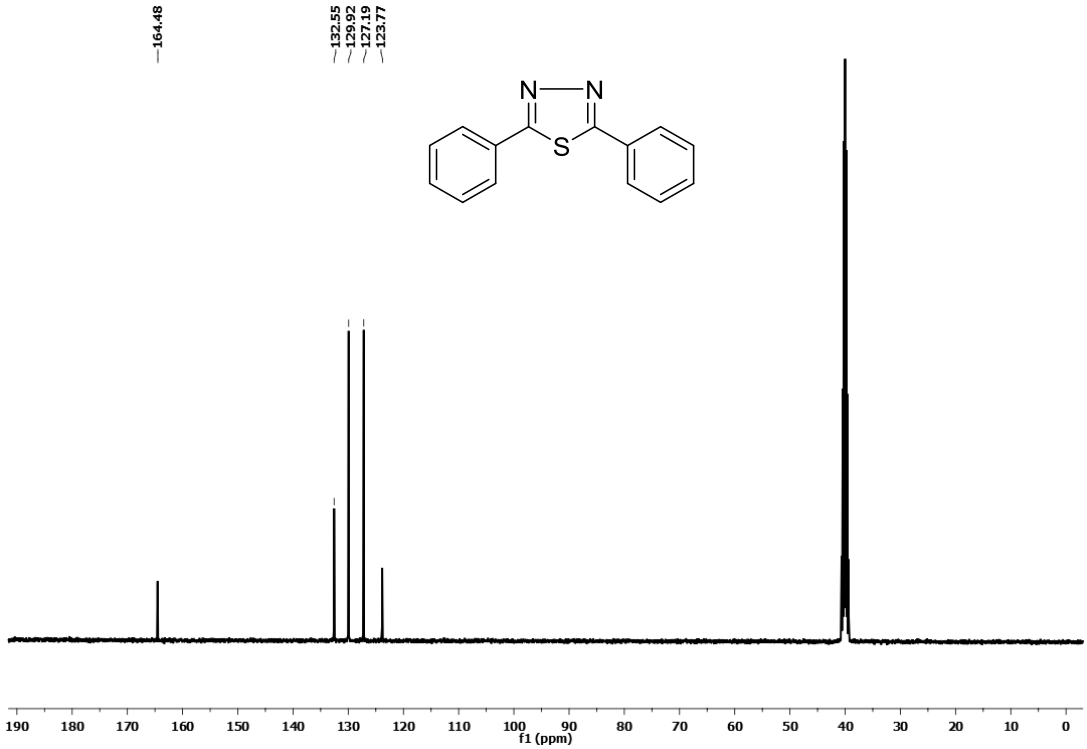
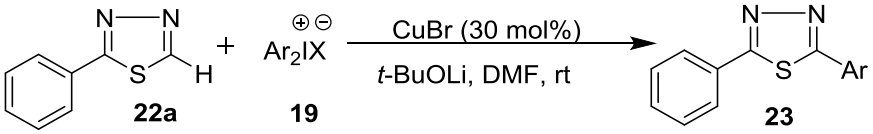
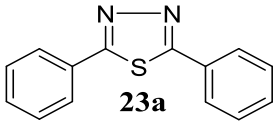
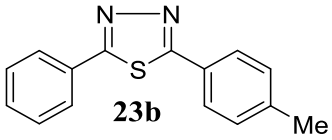
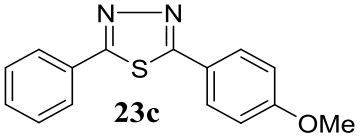
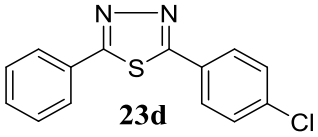
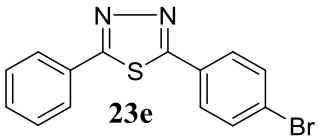
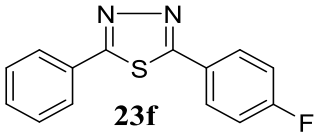


Figure 3.6 ^{13}C NMR spectrum of **23a**



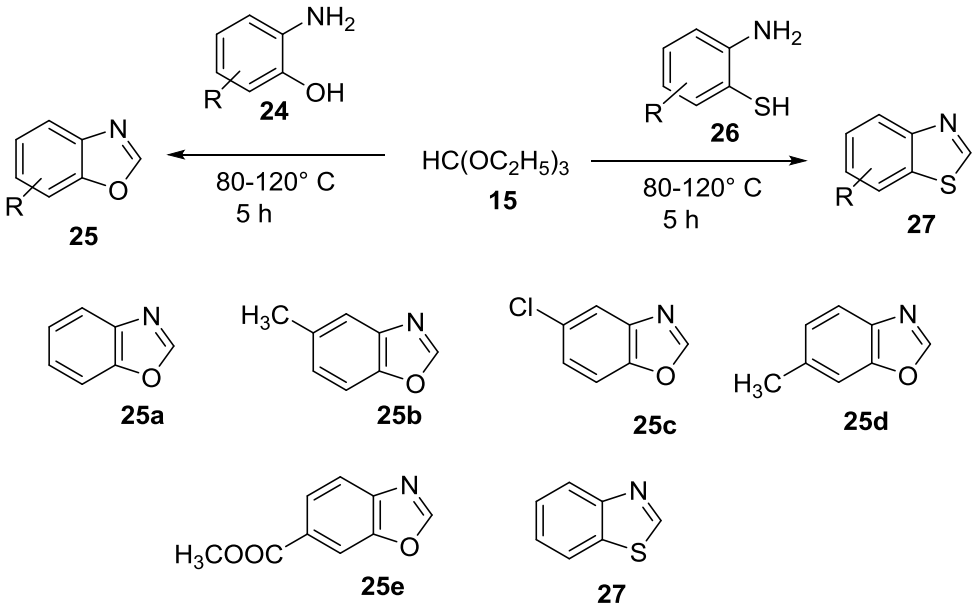
Scheme 3.10 Arylation of 2-aryl-1,3,4-thiadaizoles using diaryliodonium salts

Table 3.5 Synthesized 2-aryl-1,3,4-thiadiazoles using diaryliodonium salts

S.No.	Compounds	Yields (%)	Mp (°C)
1	 **23a**	83	132
2	 **23b**	72	122
3	 **23c**	78	136
4	 **23d**	84	180
5	 **23e**	82	152
6	 **23f**	83	173

Next the arylation of benzofused heterocycles[24] e.g., benzoxazole and benzothiazole was explored to synthesize diverse 2-arylbenzoxazoles and 2-arylbenzothiazoles endowed with interesting biological properties (**2**, Figure 3.2).[4c-d, 19] Daugulis and Miura have independently studied the copper-mediated direct C-H arylation of various heterocycles using different conditions.[25] Later, Huang et al. reported arylation of benzoxazoles using $Pd(OAc)_2$ /Cu(II)/PPh_3 co-catalytic system.[26]

Starting material benzoxazoles **25** and benzothiazole **27** were prepared from the reaction of 2-amionphenol **24** or 2-aminothiophenol **26** in triethylorthoformate **15** under refluxing conditions (Scheme 3.11).[27]



Scheme 3.11 Synthesis of benzofused heterocycles **25** and **27**

In our efforts various benzoxazoles were coupled with diaryliodonium salts under the optimized reaction conditions identified for 2-aryl-1,3,4-oxadiazoles **16** (Scheme 3.12). It was found that benzoxazoles **25** could react with a relatively broad range of iodonium salts **19** to afford 2-arylbenzoxazoles **28a-n** in 79-89% yields (Table 3.6). Substituted benzoxazoles **25b** (Me) and **25c** (Cl) furnished **28j-l** in excellent yields (80-85%); *ortho*-substituted diaryliodonium salts **19k** (NO_2) and **19l** (OMe) were well tolerated under these conditions to obtain **28h-i** in good yields (72-80%). Prepared 2-arylbenzoxazoles **28a-n** were analyzed through their NMR (^1H & ^{13}C) spectral data (Figures 3.7 and 3.8).

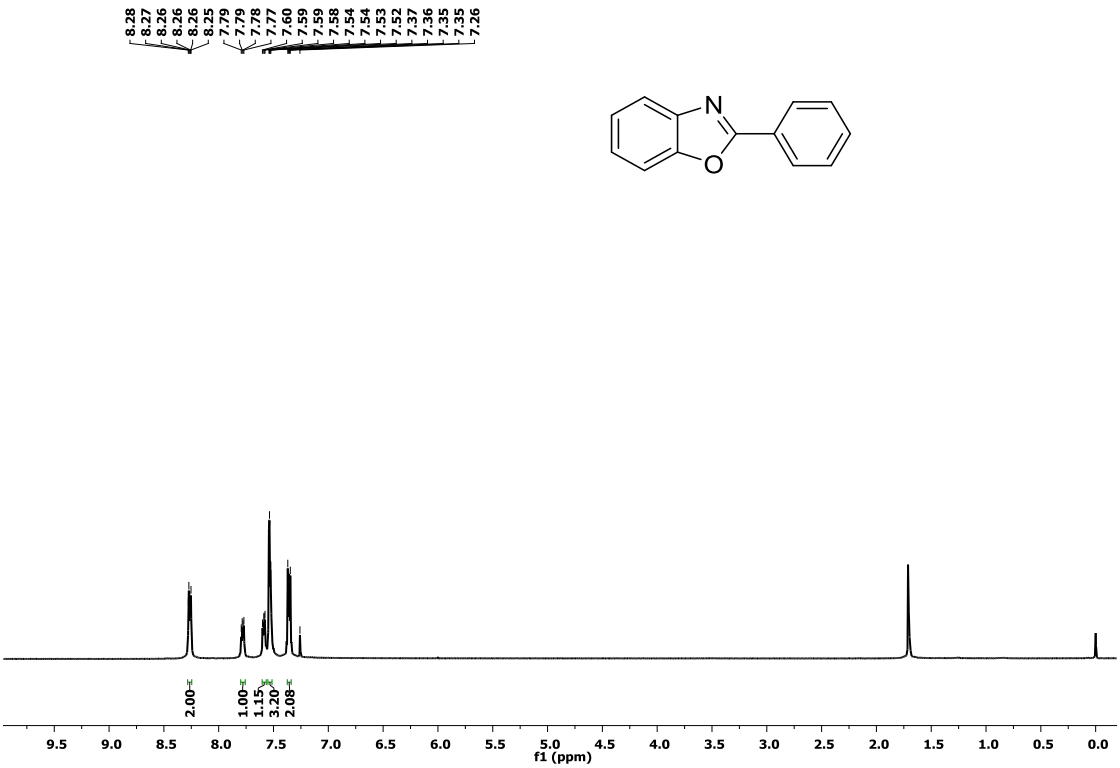


Figure 3.7 ^{1}H NMR spectrum of **28a**

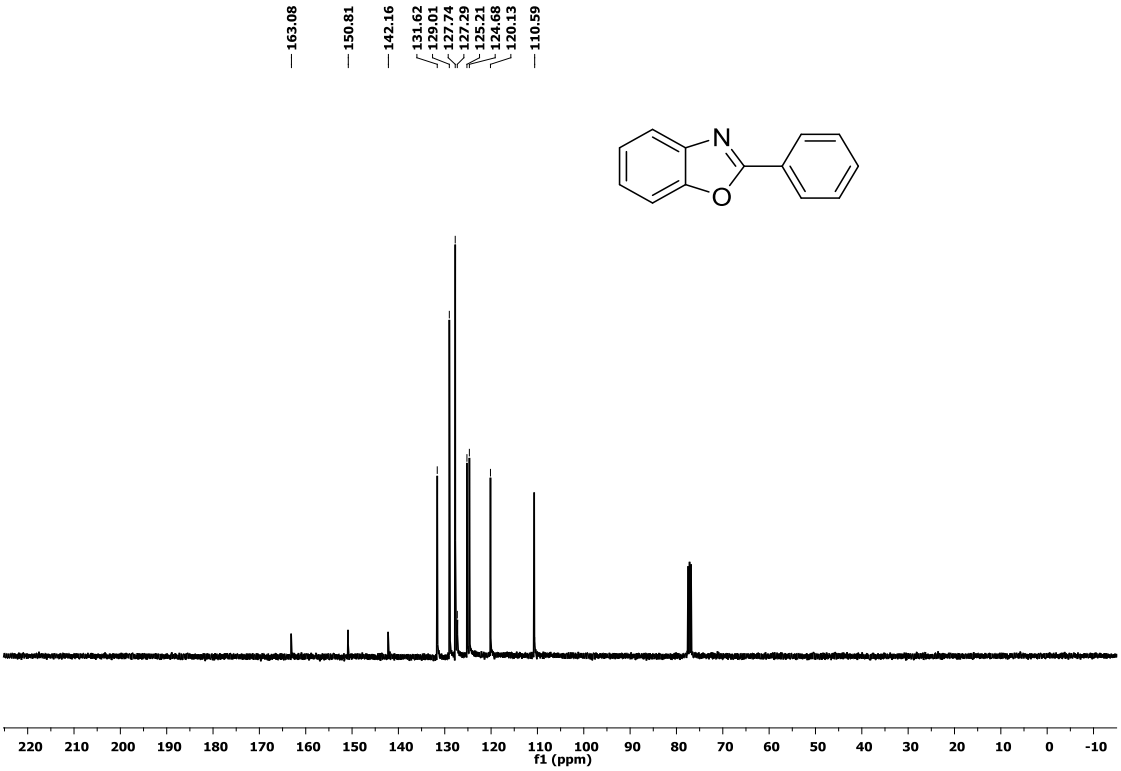
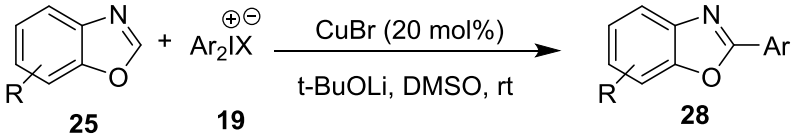
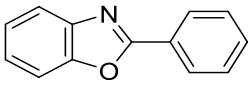
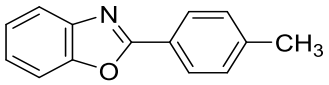
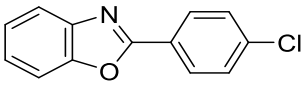
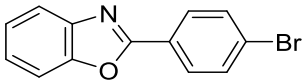
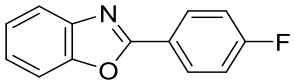
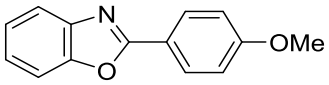
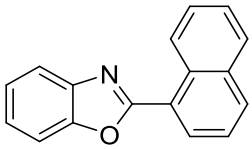


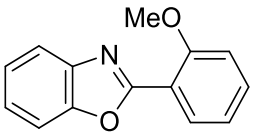
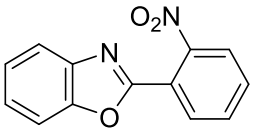
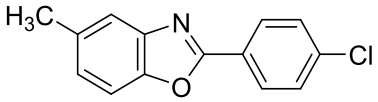
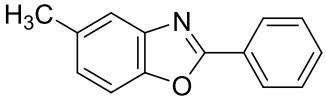
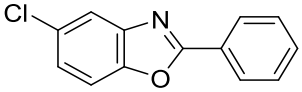
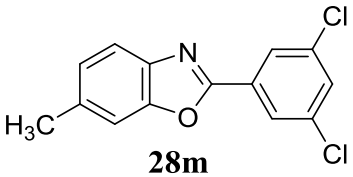
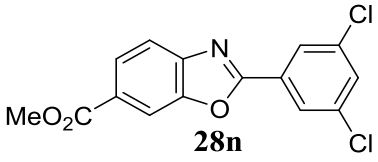
Figure 3.8 ^{13}C NMR spectrum of **28a**



Scheme 3.12 Arylation of benzoxazoles using diaryliodonium salts

Table 3.6 Synthesized 2-arylbenzoxazoles using diaryliodonium salts

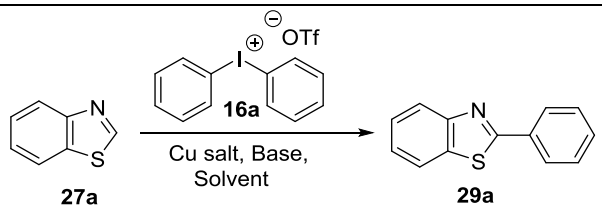
S.No.	Compounds	Yields (%)	Mp (°C)
1	 **28a**	89	102-103
2	 **28b**	79	113-114
3	 **28c**	83	148-149
4	 **28d**	89	158-159
5	 **28e**	88	97-98
6	 **28f**	72	98-99
7	 **28g**	67	98-99

8	 **28h**	72	54-55
9	 **28i**	80	98-99
10	 **28j**	85	151-153
11	 **28k**	85	102-104
12	 **28l**	80	105-106
13	 **28m**	69	146-147
14	 **28n**	67	151-153

Finally, the scope of arylation reaction was extended to benzothiazoles **27** to prepare 2-arylbenzothiazoles **29**; such C-H arylations has been achieved using various catalysts such as Pd,[28] Pd/Cu/additive[29] combination and aryl halides. However, our earlier optimized C-H arylation conditions failed to deliver 2-phenylbenzothiazole (**29a**). Therefore, we explored the reaction between **27** and **16a** in the presence of CuBr by varying bases, solvents and reaction

temperature from rt to 130 °C. Bases such as *t*-BuOLi and AgOAc could not produce **29a** even under conventional heating. So, next we attempted the arylation of **27** with **16a** in DMF under MW irradiation; however, it was unsuccessful. Various copper salts such as CuI, $Cu(OAc)_2$, Cu/Pd and Cu/Ag catalytic combinations also failed to give **29a**. No desired product was detected by varying bases and ligand combinations (K_3PO_4/PPh_3 and K_3PO_4/1,10-phenanthroline) in the presence of CuI. After successive failures under conventional heating and at ambient temperature, the arylation reaction of **27** was performed under MW in the presence of CuI and *t*-BuOLi in DMSO or DMF. Interestingly, under these conditions formation of 2-aminothiophenol **26** was observed instead of the desired **29a.** This indicated that the polar-aprotic solvents such as DMSO and DMF enhanced the ring opening of benzothiazole to produce aminothiophenol.[30] To diminish the ring-opening of benzothiazole, we attempted the arylation of **27** using **16a** in dioxane and obtained the desired 2-phenylbenzothiazole **29a** in 85% yield (Scheme 3.13). Finally, we found that CuI (30 mol%) and *t*-BuOLi (3.5 equiv) in dioxane under MW-irradiation (30 min, 130 °C) was the best conditions to prepare **29a**. (Table 3.7)

Table 3.7 Optimization of arylation of benzothiozoles using diaryliodonium salts



S.No.	Catalyst/Ligand	Base	Solvent	Yield (%)
1[a]	CuI/PPh_3	K_3PO_4	DMSO	NR
2[a]	CuBr	*t*-BuOK	DMSO	NR
3[b]	CuI/PPh_3	K_3PO4	DMSO	NR
4[b]	CuI/Phen	K_3PO4	DMF	NR
5[b]	CuI	Cs_2CO_3	DMF	NR
6[b]	CuI	*t*-BuOLi	DMF	Trace
7[b]	CuBr	*t*-BuOK	DMSO	NR
8[b]	CuBr	AgOAc	DMSO	NR
9[b]	CuBr	*t*-BuOLi	DMSO	Trace
10[b]	$Cu(OAc)_2$	*t*-BuOK	DMSO	NR

11[b]	$Cu(OAc)_2$	AgOAc	DMF	NR
12[b]	$CuCl_2$	*t*-BuOK	DMSO	NR
13[b]	$Cu(OAc)_2$	NaOAc	DMF	NR
14[b]	$Cu(OTf)_2$	AgOAc	DMF	NR
15[b]	$Pd(OAc)_2$	K_2CO_3	DMF	Trace
16[b]	$Pd(OAc)_2$/ $Cu(OAc)_2$	K_2CO_3	DMF	NR
17[c]	$Pd(OAc)_2$	*t*-BuOLi	DMF	Trace
18[c]	$Pd(OAc)_2$	AgOAc	DMF	60
19[c]	$CuBr_2$	AgOAc	DMF	NR
20[c]	CuI	Cs_2CO_3	DMSO	Trace
21[c]	CuI	AgOAc	DMSO	NR
22[c]	CuI	*t*-BuOLi	DMF	40
23[c]	CuI	*t*-BuOLi	DMSO	40
24[c]	CuI	*t*-BuOLi	PEG-400	NR
25[c]	CuI	*t*-BuOLi	NMP	NR
26[c]	CuI	*t*-BuOLi	1,4-dioxane	85

[a] A mixture of **27a** (1 equiv.), **16a** (1 equiv.), Cu catalyst (30 mol%), ligand (10 mol%), and base (3.5 equiv) was stirred in DMSO for 24 h at rt. [b] Conventional heating at 130 °C for 18-24 h. [c] reaction under microwave irradiation at 130 °C for 25-30 min., NR = no reaction

With an optimized set of reaction conditions, we studied the arylation of benzothiazole **27** by employing various diaryliodonium salts **16a-h** (Table 3.8) and prepared diversely substituted 2-arylbenzothiazoles **29a-h**. Prepared 2-arylbenzothiazoles **29a-h** were analyzed through their NMR (^1H & ^{13}C) spectral data (Figures 3.9 and 3.10).

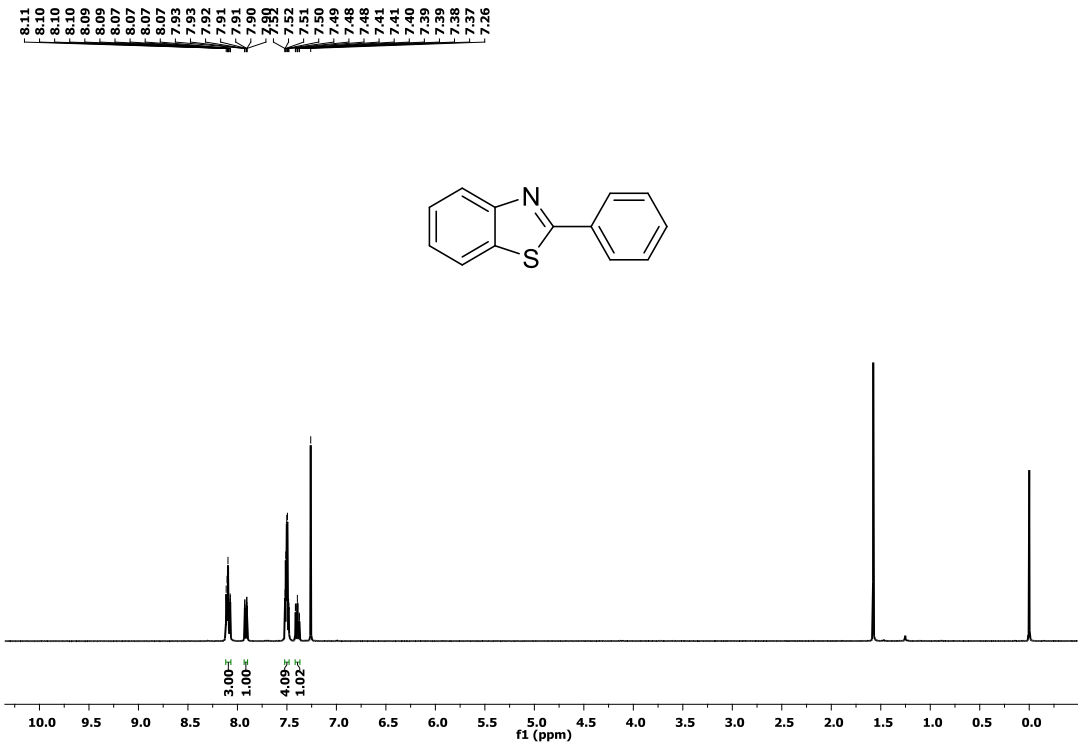


Figure 3.9 ^{1}H NMR spectrum of **29a**

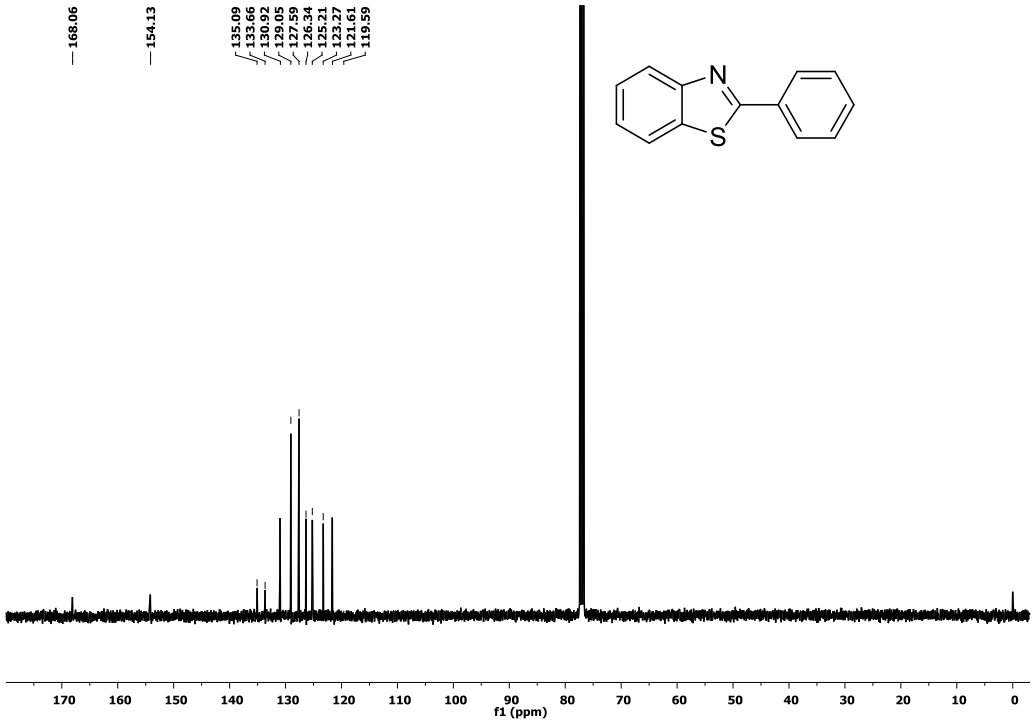
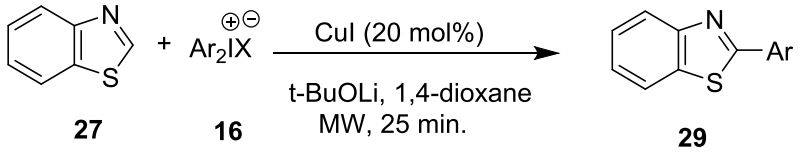


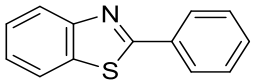
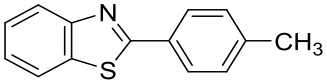
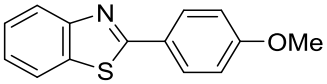
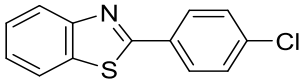
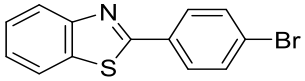
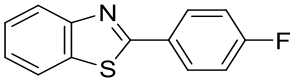
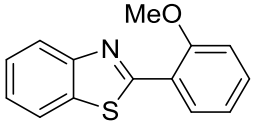
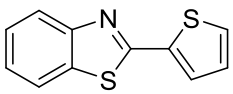
Figure 3.10 ^{13}C NMR spectrum of **29a**



27 16 29

Scheme 3.13 Arylation of benzothiazoles using diaryliodonium salts

Table 3.8 Synthesized 2-aryl-benzothiazoles using diaryliodonium salts

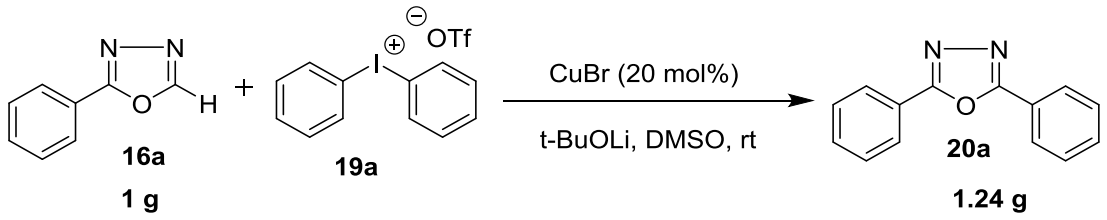
S.No.	Compounds	Yields (%)	Mp (°C)
1	 **29a**	85	113-114
2	 **29b**	75	85-86
3	 **29c**	78	120-121
4	 **29d**	80	118-119
5	 **29e**	83	132-133
6	 **29f**	85	99-100
7	 **29g**	73	121-122
8	 **29h**	78	110-111

Notably, the halo-substituted diaryliodonium salts **16c-e** afforded **20d-f**, **23d-f, 28c-e** and **29d-f** in good to excellent yields (81-89%). The tolerance of the bromo and chloro groups is particularly useful for further synthetic manipulations by traditional cross coupling methods. In unsymmetrical iodonium salts (**16g-i**) and (**16m-o**) the bulky mesityl moiety acts as a non-transferrable group, so only **20g, 20o, 28h, 28i** and **28m** were formed selectively in excellent yields. Iodonium salts **16c, 16g** and **16n** with electron-donating groups (Me and OMe) delivered **20b-c, 23c, 28f, 28h, 29b-c** and **29g** in relatively good yields. The bulky naphthyl and heteroaromatic thienyl motifs were successfully transferred using iodonium salts **16o** and **16m** led to **20m**, **28g** and **29h** in excellent yields.

To illustrate the synthetic utility of this copper-catalyzed arylation of diverse azoles, we prepared various useful molecules. From the reactions of benzoxazole and iodonium salts, we successfully prepared efficient ESIPT (excited state intramolecular proton transfer) fluorescence and chelating agents including 2-(4'-metho-xyphenyl)benzoxazole (**28f**), 2-(2'-methoxyphenyl)-benzoxazole (**28h**) and 2-(2'-methoxy-phenyl)benzothiazole (**29g**).[31] 2,5-Diaryl-1,3,4-oxadiazoles **20c** and **20p** analogues of anticancer agents (**1a-b**), were easily prepared from the reactions of an appropriate oxadiazole **16** with diphenyliodonium salts. Successfully installation of 3,5-dichlorophenyl moiety onto benzoxazole using **19o** allowed us to prepare the methyl ester (**28n**) of Tafamidis in 67% yield.[8]

Arylation of various azaheterocycles involving different equivalents of base (3.0 and 3.5 equiv) and reaction conditions (rt and MW) revealed that the acidity of the C_2-H bond plays a pivotal role. From aforementioned results, it was observed that the reactivity of various azoles (oxadiazoles = benzoxazoles (pK_a = 24.8) > thiadiazoles > benzothiazoles (pK_a = 27.3) parallels the acidity of C_2-H.[13b,32]

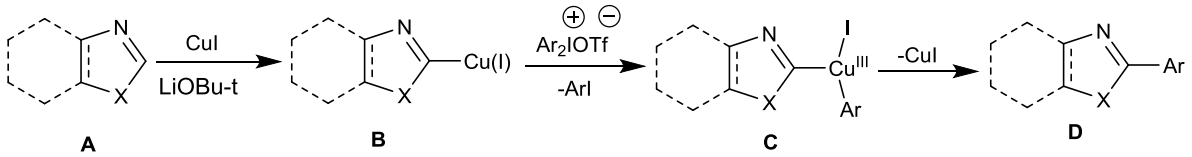
3.2.2 Gram-scale experiment for the synthesis of 2,5-diphenyl-1,3,4-oxadiazole: To check the feasibility of the developed protocol at gram-scale, we conducted the reaction of 2-phenyl-1,3,4-oxadiazole (**19a**, 1 g) with diphenyliodonium triflate **19a**. The anticipated 2,5-diphenyl-1,3,4-oxadiazole **20a** was obtained in 83% (1.24 g) yield as illustrated in Scheme 3.14.



Scheme 3.14 Gram-scale experiment for the synthesis of **20a**

3.2.3 Proposed reaction mechanism

Based on our results and literature reports,[22-23] mechanistically it is postulated that an initial cupration of 1,3-azoles **A** with the aid of *t*-BuOLi affords an azolyl-copper species **B**. Subsequent oxidative addition of **B** to the diaryliodonium salt facilitates the formation of an electrophilic Cu(III)-aryl species **C** with the generation of an appropriate iodoarene. Finally, the reductive elimination of **C** is assumed to afford the arylated azoles **D** with the concomitant release of Cu(I) catalyst (Scheme 3.15).



Scheme 3.15 Proposed mechanism for the arylation of azaheterocycles

3.3 Conclusions

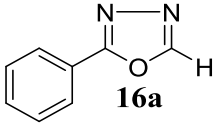
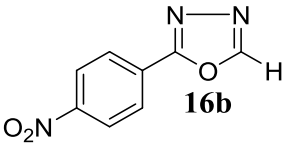
In summary, we have developed a facile, high yielding, scalable and ligand-free copper-catalyzed direct C-H arylation protocol that enables the synthesis of diverse class of bioactive azaheterocycles, namely aryloxadiazoles, arylthiadiazoles, arylbenzoxazoles and arylbenzothiazoles by employing readily accessible diaryliodonium salts. The present method offers advantages including shorter reaction times, milder reaction conditions, a wider substrate scope with high yields of the products. The arylmesityl iodonium salts can be effectively utilized to prepare appropriate arylated azaheterocycles in high yields. The generalized protocols enable easy access to an array of potentially useful molecules, halo-substituted azaheterocycles and prospective precursors to acquire complex bioactive heteroaryls.

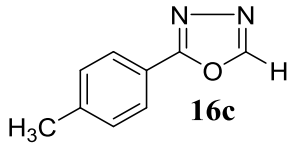
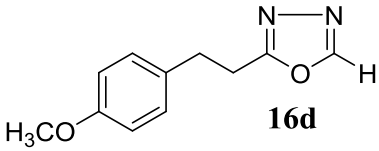
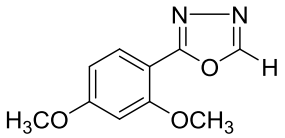
3.4 Experimental section

3.4.1 General materials and methods

All the laboratory reagents were obtained commercially. The progress of the reaction was monitored by thin layer chromatography, which was performed on Merck precoated plates (silica gel 60, F_{254}, 0.25 mm) and it was visualized by fluorescence quenching under hand-UV lamp (254 nm). The column chromatography was performed using 100-200 mesh silica gel. The solvents were evaporated using Buchi rotary evaporator. Microwave reactions were carried out in CEM DISCOVER instrument. Melting points were determined using E-Z melting point apparatus and were uncorrected. ^{1}H and ^{13}C spectra were recorded using Bruker-Avance II (400, 100 MHz) spectrometer. The coupling constants (*J*) were given in Hz, chemical shift (δ) in ppm. TMS was used as an internal standard. The proton multiplicities were described as: s= singlet, d= doublet, t = triplet, q = quartet, dd = doublet of doublet and m= multiplet. Mass spectra were obtained using Hewlett Packard HP 5973 quadrupole Mass Selective Detector with interface for 6890 series GC.

General experimental procedure for 2-aryl-1,3,4-oxadiazole (16a-e):[18] A mixture of 2 g of the carboxylic acid hydrazide **14** was dissolved in 15 mL of triethylorthoformate **15** and heated the reaction mixture at 120 °C. After heating at 120 °C for 30 min, reaction temperature was reduced to 80 °C and continued the reaction at this temperature for 4 h. Excess orthoester was removed by evaporation under reduced pressure. The residue so obtained was passed through a column chromatography using EtOAc/hexane (20%) as an eluent to afford **16a-e** in good yields.

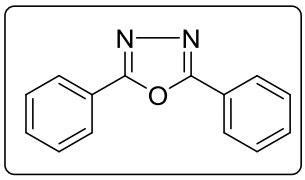
S.No.	2-Aryl-1,3,4-oxadiazole	Yield (%)	Mp (°C)
1	 **16a**	75	34-35 (Lit.[18] 34-35)
2	 **16b**	79	157-158 (Lit. [18] 156-157)

3	 **16c**	85	93-94 (Lit.[33] 92)
4	 **16d**	72	45-46 (Lit.[34] 45-46)
5	 **16e**	72	77-78

General experimental procedure for diaryliodonium triflate (19a-l):[19a] To a stirred solution of iodobenzene (0.5 g, 2.5 mmol) in dichloromethane (8 mL) was added *m*-chloroperbenzoic acid (0.455 g, 2.6 mmol) and followed by benzene (0.22 mL, 2.5 mmol) at room temperature. Reaction contents were cooled to 0 °C and then trifluoromethanesulfonic acid (0.23 mL, 2.6 mmol) was added dropwise while maintaining the same temperature. The mixture was allowed to stir at room temperature for additional 30 min. The solvent was evaporated under vaccum and diethyl ether (3 mL) was added to the residue under cooling (0 °C) conditions. The solid so obtained was washed twice with diethyl ether and dried to afford diphenyliodonium triflate (**19a**) as a white solid in 88% yield (0.924 g). Similarly other diaryliodonium salts **19b-l** were prepared.

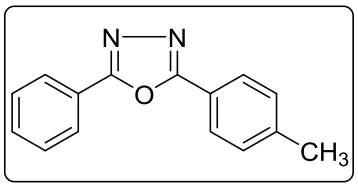
General experimental procedure for 2,5-diaryl-1,3,4-oxadiazoles (20a-q): To a stirred solution of oxadiazole **16a** (0.684 mmol) and CuBr (0.136 mmol) in DMSO (2 mL), *t*-BuOLi (2.05 mmol) was charged and continued stirring at room temperature for 5 min. Then the required amount of diphenyliodonium triflate **19a** (0.684 mmol) was added portionwise and stirred at room temperature for 15 min. Completion of the reaction was confirmed by the TLC (4:1 hexane:ethylacetate). Then the resulting reaction mixture was added to ice-cold water and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with ammonia solution, brine and dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The obtained crude product was purified by column chromatography using EtOAc/hexane (10%) as an eluent to afford **20a-q** in good yields.

2,5-Diphenyl-1,3,4-oxadiazole (20a)



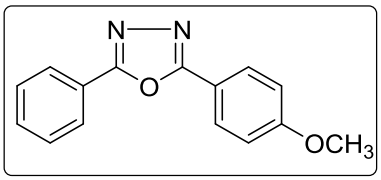
Yield 89%; White solid; mp 138-139 °C (lit.[12] 139-140 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15-8.13 (m, 4H), 7.69-7.63 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 132.5, 129.8, 127.2, 123.8; GC-MS *m/z* calcd for $C_{14}H_{10}N_2O$: 222.1 $[M]^+$, found: 222.0.

2-(4'-Methylphenyl)-5-phenyl-1,3,4-oxadiazole (20b)



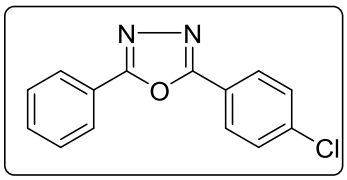
Yield 79%; White solid; mp 125-126 °C; (lit.[35] 121-122 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.13 (m, 2H), 8.03 (d, J = 8.0 Hz, 2H), 7.54-7.52 (m, 3H), 7.34 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 164.2, 142.4, 131.6, 129.6, 128.8, 126.9, 123.8, 121.2, 21.5; GC-MS *m/z* calcd. for $C_{15}H_{12}N_2O$: 236.1 $[M]^+$, found: 236.0.

2-(4'-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (20c)



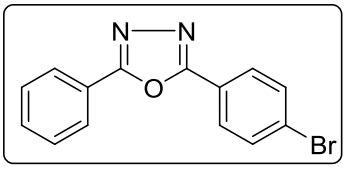
Yield 75%; White solid; mp 147-148 °C (lit.[35] 149-150 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.11 (m, 2H), 8.09 (d, J = 8.8 Hz 2H), 7.54-7.52 (m, 3H), 7.05 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 164.1, 162.4, 131.5, 129.1, 128.7, 126.8, 124.0, 116.5, 114.5, 55.2; GC-MS *m/z* calcd for $C_{15}H_{12}N_2O_2$: 252.1 $[M]^+$, found: 252.0.

2-(4'-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (20d)



Yield 89%; Off white solid; mp 161-162 °C; (lit.[35] 161-162 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.08 (m, 4H), 7.58-7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 160.2, 134.4, 128.3, 125.8, 125.5, 124.6, 123.4, 120.1, 118.8; GC-MS *m/z* calcd for $C_{14}H_9ClN_2O$: 256.0 $[M]^+$, found: 256.0.

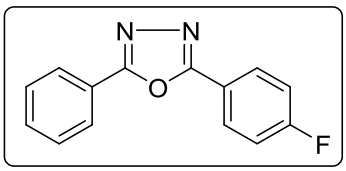
2-(4'-Bromophenyl)-5-phenyl-1,3,4-oxadiazole (20e)



Yield 88%; White solid; mp 171-172 °C (lit.[35] 169-170 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J = 7.6, 1.5 Hz, 2H), 8.03 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.58-7.54 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 163.9, 132.5, 131.8, 129.1,

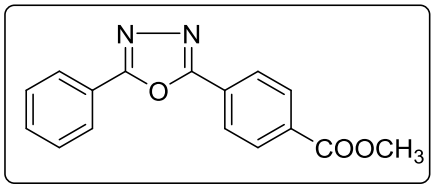
128.3, 126.9, 126.5, 123.7, 122.8; GC-MS m/z calcd for $C_{14}H_9BrN_2O$: 300.0 $[M]^+$, found: 300.0.

2-(4'-Fluorophenyl)-5-phenyl-1,3,4-oxadiazole (20f)



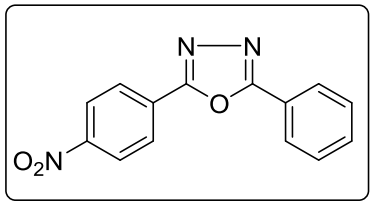
Yield 88%; Light pink solid; mp 154-155 °C (lit.[35] 151-152 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-8.11 (m, 4H), 7.56-7.54 (m, 3H), 7.27-7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 166.1, 164.6, 163.8, 163.6, 131.8, 129.2, 129.1, 126.9, 123.8, 120.3, 116.6, 116.4; GC-MS *m/z* calcd for $C_{14}H_9FN_2O$: 240.1 $[M]^+$, found: 240.0.

Methyl-4'-(5-phenyl-1,3,4-oxadiazol-2-yl)benzoate (20g)



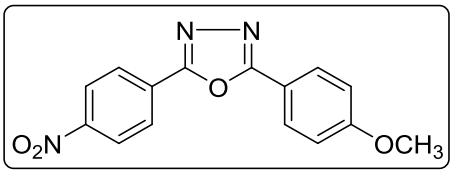
Yield 70%; White solid; mp 167-168 °C (lit.[35] 161-162 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29-8.21 (m, 4H), 8.21-8.16 (m, 2H), 7.63-7.54 (m, 3H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.1, 163.9, 132.8, 132.0, 130.2, 129.2, 127.7, 127.1, 126.8, 123.6, 52.3; GC-MS *m/z* calcd for $C_{16}H_{12}N_2O_3$: 280.1 $[M]^+$, found: 280.0.

2-(4'-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (20h)



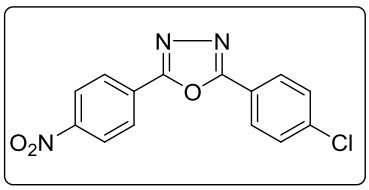
Yield 77%; Yellow solid; mp 209-210 °C (lit.[35] 220-222 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46-8.40 (m, 2H), 8.39-8.33 (m, 2H), 8.18 (dd, J = 8.1, 1.5 Hz, 2H), 7.65-7.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 163.0, 149.5, 132.3, 129.4, 129.3, 127.8, 127.2, 124.4, 123.2.

2-(4'-Methoxyphenyl)-5-(4''-nitrophenyl)-1,3,4-oxadiazole (20i)



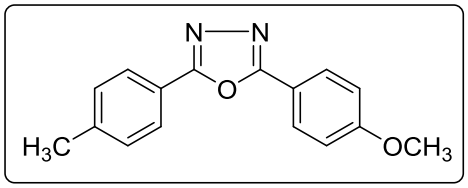
Yield; 75%; Yellow solid; mp 250-251 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42-8.38 (m, 2H), 8.33-8.29 (m, 2H), 8.12-8.08 (m, 2H), 7.08-7.04 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 162.8, 162.4, 149.4, 129.6, 128.9, 127.7, 124.3, 115.7, 114.7, 55.6; GC-MS *m/z* calcd for $C_{15}H_{11}N_3O_4$: 297.1 $[M]^+$, found: 297.0.

2-(4'-Chlorophenyl)-5-(4''-nitrophenyl)-1,3,4-oxadiazole (20j)



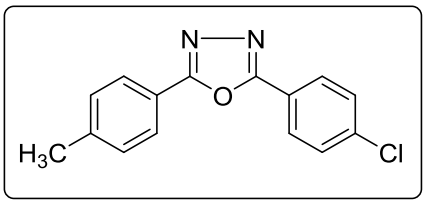
Yield 81%; Yellow solid; mp 238-239 °C (lit.[36] 236-238 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45-8.27 (m, 4H), 8.16-8.01 (m, 2H), 7.62-7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 162.9, 149.6, 138.8, 129.7, 129.3, 128.4, 127.8, 124.5, 121.8; GC-MS *m/z* calcd for $C_{14}H_8ClN_3O_3$: 301.0 $[M]^+$, found: 301.0.

2-(4'-Methoxyphenyl)-5-(4''-methylphenyl)-1,3,4-oxadiazole (20k)



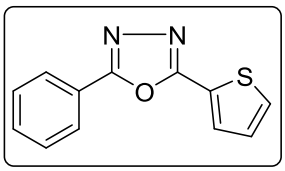
Yield 78%; Off white solid; mp 138-139 °C (lit.[35] 137-139 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 8.9 Hz, 2H), 8.00 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.2, 162.4, 142.2, 130.4, 128.9, 127.0, 121.2, 116.2, 115.3, 55.9, 21.6; GC-MS *m/z* calcd. for $C_{16}H_{14}N_2O_2$: 266.1, found: 266.0.

2-(4'-Chlorophenyl)-5-(4''-methylphenyl)-1,3,4-oxadiazole (20l)



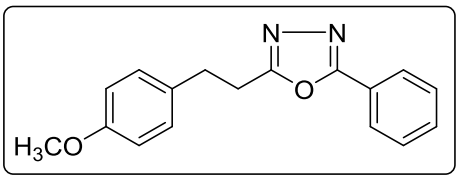
Yield 88%; White solid; mp 209-210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11-7.99 (m, 4H), 7.64-7.39 (m, 4H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 163.3, 142.6, 137.2, 130.3, 129.9, 128.6, 127.0, 122.6, 120.7, 21.7; GC-MS *m/z* calcd for $C_{15}H_{11}ClN_2O$: 270.1 $[M]^+$, found: 270.0.

2-Phenyl-5-(thiophen-2'-yl)-1,3,4-oxadiazole (20m)



Yield 85%; Yellow solid; mp 114-115 °C (lit.[35] 114-115 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.09 (m, 2H), 7.85-7.79 (m, 1H), 7.61-7.50 (m, 4H), 7.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 160.8, 131.8, 130.1, 129.8, 129.1, 127.0, 125.3, 123.7; GC-MS *m/z* calcd for $C_{12}H_8N_2OS$: 228.0 $[M]^+$, found: 228.0.

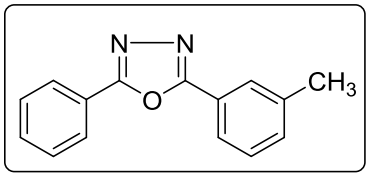
2-(4'-Methoxyphenethyl)-5-phenyl-1,3,4-oxadiazole (20n)



Yield 74%; Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 7.7, 1.4 Hz, 1H), 7.51-7.46 (m, 2H), 7.16-7.11 (m, 3H), 6.85-6.81 (m, 3H), 3.76 (s, 3H), 3.22 (t, J =

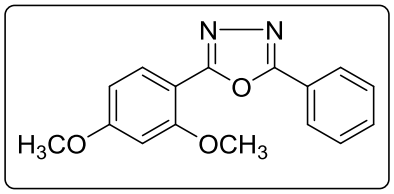
7.7 Hz, 1H), 3.12 (t, *J* = 7.5 Hz, 1H), 2.90 (t, *J* = 7.7 Hz, 1H), 2.64 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 158.23, 132.4, 129.5, 129.3, 129.2, 127.0, 114.3, 114.1, 55.5, 35.5, 29.5; GC-MS *m/z* calcd for $C_{17}H_{16}N_2O_2$: 280.1 $[M]^+$, found: 280.0.

2-(3'-Methylphenyl)-5-phenyl-1,3,4-oxadiazole (20o)



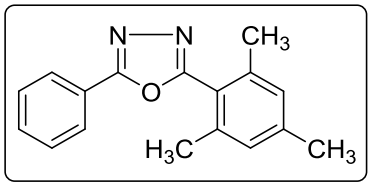
Yield 70%; Light pink solid; mp 110-111 °C (lit.[37] 112-113 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20-8.15 (m, 2H), 8.01-7.94 (m, 2H), 7.59-7.54 (m, 3H), 7.47-7.37 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 164.5, 139.0, 132.6, 131.7, 129.0, 129.0, 127.5, 126.9, 124.1, 124.0, 123.8, 21.4; GC-MS *m/z* calcd for $C_{15}H_{12}N_2O$: 236.1 $[M]^+$ found: 236.0.

2-(2',4'-Dimethoxyphenyl)-5-phenyl-1,3,4-oxadiazole (20p)



Yield 60%; White solid; mp 85-86°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.0 Hz, 2H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.51-7.49 (m, 3H), 6.61 (d, *J* = 8.6 Hz, 1H), 6.57 (s, 1H), 3.96 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 163.4, 159.4, 131.9, 131.4, 129.1, 126.9, 124.4, 106.1, 105.6, 99.2, 56.2, 55.7; GC-MS *m/z* calcd for $C_{16}H_{14}N_2O_3$: 282.1 $[M]^+$, found: 282.0.

2-(Mesityl)-5-phenyl-1,3,4-oxadiazole (20q)

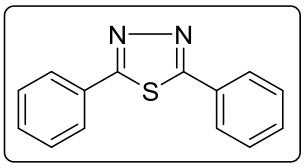


Yield 8%; White solid; mp 93-94 °C (lit.[38] 91-92 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.08 (m, 2H), 7.58-7.48 (m, 3H), 7.00 (s, 2H), 2.36 (s, 3H), 2.33 (s, 6H); GC-MS *m/z* calcd for $C_{17}H_{16}N_2O$: 264.1 $[M]^+$, found: 264.0.

General experimental procedure for 2-pheny-1,3,4-thiadiazoles (22):[23] In a sealed tube a mixture of 2-phenyl-1,3,4-oxadiazole **16a** (1 mmol), thiourea **21** (2.63 mmol) was added in 5 mL of THF. The mixture was then heated at 120 °C for 15 h. Once the starting material was consumed then reaction mixture extracted with DCM and washed with brine solution. The organic layer finally dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure to isolate crude 2-phenyl-1,3,4-thiadiazole, which was further purified by column chromatography to obtained final product **22a** in 65% yield, mp 50-52°C (Lit.[39] 50-51 °C).

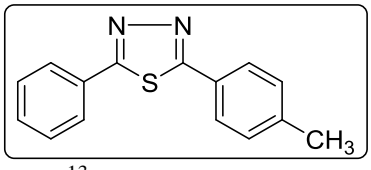
General experimental procedure for2, 5-diaryl-1,3,4-thiadiazoles (23): To a stirred solution of thiadiazole **22a** (0.617 mmol) and CuBr (0.136 mmol) in DMF (2 mL), *t*-BuOLi (2.16 mmol,) was charged and stirred at room temperature for 5 min. Then appropriate amount of diaryliodonium triflate **19a** (0.617 mmol) was added in portions. The reaction mixture was stirred at room temperature for 15 min. Completion of the reaction was confirmed by TLC (4:1 hexane:ethylacetate). Then the resulting reaction mixture was added to ice-cold water and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with ammonia, brine solution and dried over Na_2SO_4. The solvent was removed and the obtained crude product was purified by column chromatography eluting with 10% EtOAc/hexane to afford **23a-f** in 72-84% yields.

2,5-Diphenyl-1,3,4-thiadiazole (**23a**)



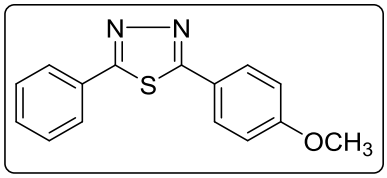
Yield 83%; White solid; mp 132-133 °C (lit.[13] 131-133 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18-8.13 (m, 4H), 7.70-7.62 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 132.6, 129.9, 127.2, 123.8.

2-(4'-Methylphenyl)-5-phenyl-1,3,4-thiadiazole (**23b**)



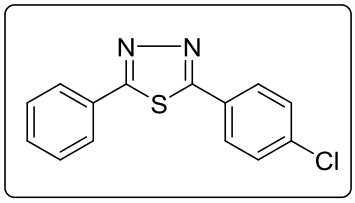
Yield 72%; White solid; mp 122-124 °C (lit.[13] 123-124 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.13 (m, 2H), 8.03 (d, J = 8.1 Hz, 2H), 7.55-7.52 (m, 3H), 7.34 (d, J = 8.1 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 164.3, 142.3, 131.6, 129.7, 129.0, 126.8, 124.1, 121.2, 21.6.

2-(4'-Methoxylphenyl)-5-phenyl-1,3,4-thiadiazole (**23c**)



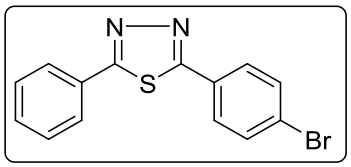
Yield 78%; White solid; mp 136-137 °C (lit.[13] 136-137 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.13 (m, 2H), 8.11-8.06 (dd, J = 8.96, 2.1 Hz, 2H), 7.56-7.55 (m, 3H), 7.07 (dd, J = 8.96, 2.1 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 164.2, 162.3, 131.5, 129.0, 128.7, 126.8, 124.1, 116.4, 114.5, 55.2.

2-(4'-Chlorophenyl)-5-phenyl-1,3,4-thiadiazole (**23d**)



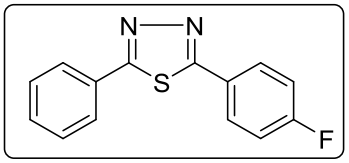
Yield 84%; White solid; mp 180-181 °C (lit.[13] 179-181°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-8.00 (m, 2H), 7.99-7.95 (m, 2H), 7.54-7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 166.9, 137.2, 131.3, 130.0, 129.5, 129.2, 129.1, 128.7, 128.0.

2-(4'-Bromophenyl)-5-phenyl-1,3,4-thiadiazole (**23e**)[3]



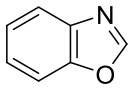
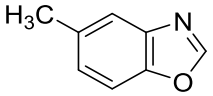
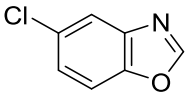
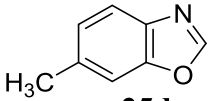
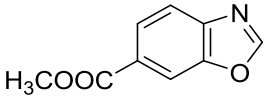
Yield 82%; White solid; mp 152-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 7.5, 1.9 Hz, 2H), 8.12-8.06 (m, 2H), 7.59-7.53 (m, 4H), 7.52 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 160.0, 134.4, 128.3, 125.9, 125.5, 124.6, 123.4, 120.1, 118.7.

2-(4-Fluorophenyl)-5-phenyl-1,3,4-thiadiazole (**23f**)



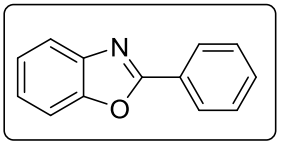
Yield 83%; White solid; mp 173-175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.00 (m, 4H), 7.54-7.52 (m, 3H), 7.27-7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 163.2, 131.2, 130.1, 130.0, 129.9, 129.2, 127.9, 116.5, 116.3. GC-MS *m/z* calcd for $C_{14}H_9FN_2S$: 256.0 $[M]^+$, found: 256.0.

General experimental procedure for benzoxazoles (25a-e)[27]: In a 100 mL round bottomed flask were placed 2-aminophenol **24** (0.17 mole), triethylorthoformate **15** (0.25 mole) and concentrated sulfuric acid (0.007 mole). The reaction mixture was stirred at 120 °C for 1h, then reduced the temperature (80 °C) and continue heating under mild reflux for 4 h, the excess triethylorthoformate was removed by evaporation under reduced pressure. The residue so obtained was passed through a column chromatography using EtOAc/hexane (20%) as an eluent to afford **25a-e** in good yields.

S.No.	Benzoxazoles	Yield (%)	Mp (°C)
1	 **25a**	70	Colourless liquid (Lit.[40] colourless liquid)
2	 **25b**	73	49-50 (Lit.[40] 49–51)
3	 **25c**	81	42-43 (Lit.[40] 41-44)
4	 **25d**	77	Colourless liquid (Lit.[40] colourless liquid)
5	 **25e**	75	liquid

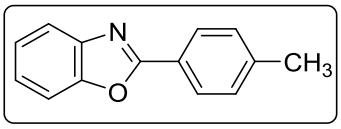
General experimental procedure for 2-arylbenzoxazoles (28a-n): To the oven dried 10 mL round bottomed flask, benzoxazole **25** (0.840 mmol), CuBr (0.136 mmol) and DMSO (2 mL) were added. Then *t*-BuOLi (2.52 mmol) was charged and stirred the reaction contents at room temperature for 5 min. Diphenyliodonium triflate **19a** (0.840 mmol) was added in portions and the reaction mixture was allowed to stir for 15 min. After completion of the reaction, the contents were taken into ice-cold water and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with ammonia and brine solutions, and dried over Na_2SO_4. The solvent was evaporated and the crude product so obtained was purified through column chromatography using 10% EtOAc/hexane as an eluent to give pure **28a-n** in 65-89% yields.

2-Phenylbenzoxazole (**28a**)



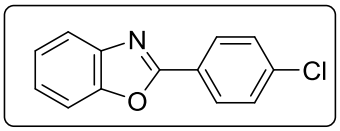
Yield 89%; White solid; mp 102-103 °C (lit.[41] 103-104 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.25 (m, 2H), 7.79-7.77 (m, 1H), 7.60-7.58 (m, 1H), 7.55-7.52 (m, 3H), 7.37-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 150.8, 142.2, 131.6, 129.0, 127.7, 127.3, 125.2, 124.7, 120.1, 110.6; GC-MS *m/z* calcd for $C_{13}H_9NO$: 195.1 $[M]^+$ found: 195.0.

2-(4'-Methylphenyl)benzoxazole (**28b**)



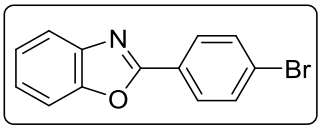
Yield 79%; White solid; mp 113-114 °C (lit.[41] 114-115 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.2 Hz, 2H), 7.79-7.73 (m, 1H), 7.59-7.53 (m, 1H), 7.35-7.32 (m, 4H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 150.7, 142.2, 142.1, 129.6, 127.6, 124.9, 124.5, 124.4, 120.0, 110.7, 21.7; GC-MS *m/z* calcd for $C_{14}H_{11}NO$: 209.1 $[M]^+$, found: 209.0.

2-(4'-Chlorophenyl)benzoxazole (**28c**)



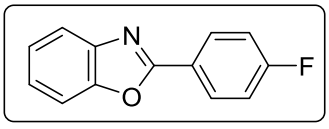
Yield 83%; White solid; mp 148-149 °C (lit.[42] 148-150 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.4 Hz, 2H), 7.79-7.76 (m,1H), 7.60-7.56 (m, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.37-7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 150.8, 142.1, 137.7, 129.2, 128.9, 125.7, 125.4, 124.8, 119.9, 110.6; GC-MS *m/z* calcd for $C_{13}H_8ClNO$: 229.0 $[M]^+$, found: 229.0.

2-(4'-Bromophenyl)benzoxazole (**28d**)



Yield 89%; Off white solid; mp 158-159 °C (lit.[42] 157-158 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.0 Hz, 2H), 7.79-7.76 (m, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.60-7.57 (m, 1H), 7.38-7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 150.7, 142.0, 132.2, 129.0, 126.2, 126.1, 125.4, 124.8, 120.1, 110.6; GC-MS *m/z* calcd for $C_{13}H_8BrNO$: 273.0 $[M]^+$ found: 273.0.

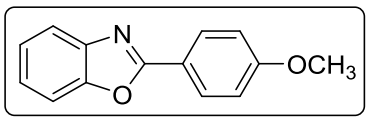
2-(4'-Fluorophenyl)benzoxazole (**28e**)



Yield 88%; Off white solid; mp 97-98 °C (lit.[43] 99-102 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.25 (m, 2H), 7.78-7.76 (m, 1H), 7.59-7.56 (m, 1H), 7.37-7.35 (m, 2H), 7.26-7.20 (m, 2H); ^{13}C NMR (100

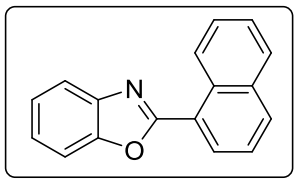
MHz, $CDCl_3$) δ 166.0, 163.6, 150.7, 142.0, 129.9, 129.8, 125.1, 124.7, 123.5, 123.5, 120.0, 116.3, 116.1, 110.3; GC-MS *m/z* calcd for $C_{13}H_8FNO$: 213.1 $[M]^+$, found: 213.0.

2-(4'-Methoxyphenyl)benzoxazole (28f)



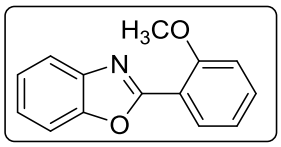
Yield 72%; White solid; mp 98-99 °C (lit.[43] 102-104 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.05-8.02 (m, 3H), 7.91-7.84 (m, 1H), 7.50-7.43 (m, 1H), 7.38-7.34 (m, 1H), 7.03 (dd, *J* = 8.8, 2.0Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 162.0, 134.5, 129.0, 126.7, 124.4, 122.8, 121.7, 114.3, 55.7, 7.7; GC-MS *m/z* calcd for $C_{14}H_{11}NO_2$: 225.0 $[M]^+$, found: 225.0.

2-(Naphthalen-1'-yl)benzoxazole (28g)[44]



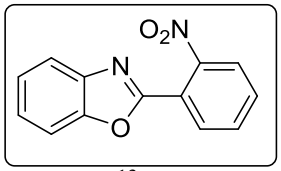
Yield 67%; Pale yellow solid; mp 98-99 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (dd, *J* = 8.6, 1.1 Hz, 1H), 8.47 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.94-7.89 (m, 1H), 7.74-7.71 (m, 1H), 7.69-7.59 (m, 3H), 7.46-7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 150.2, 142.3, 134.0, 132.3, 130.7, 129.4, 128.7, 127.9, 126.5, 127.0, 125.3, 125.0, 123.6, 120.3, 110.5; GC-MS *m/z* calcd for $C_{17}H_{11}NO$: 245.1 $[M]^+$, found: 245.0.

2-(2'-Methoxyphenyl)benzoxazole (28h)



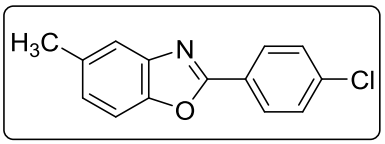
Yield 72%; White solid; mp 54-55 °C (lit.[42] 53-55 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 9.3 Hz, 1H), 7.87-7.80 (m, 1H), 7.63-7.57 (m, 1H), 7.53 (t, *J* = 7.1 Hz, 1H), 7.39-7.32 (m, 2H), 7.14-7.10 (m, 2H), 4.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 150.3, 142.2, 132.7, 131.3, 125.0, 124.3, 120.7, 120.1, 111.9, 110.4, 56.2; GC-MS *m/z* calcd for $C_{14}H_{11}NO_2$: 225.1 $[M]^+$, found: 225.0.

2-(2'-Nitrophenyl)benzoxazole (28i)



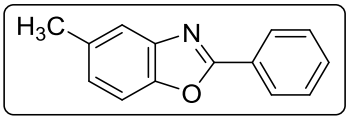
Yield 80%; Yellow solid; mp 98-99 °C (lit.[45] 99-102 °C) ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.87 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.83-7.78 (m, 1H), 7.75-7.63 (m, 2H), 7.59-7.52 (m, 1H), 7.43-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 154.1, 137.1, 135.0, 132.2, 129.3, 128.7, 126.57, 125.4, 123.3, 121.7; GC- MS *m/z* calcd for $C_{13}H_8N_2O_3$: 240.1 $[M]^+$, found: 240.0.

2-(4'-Chlorophenyl)-5-methylbenzoxazole (28j)



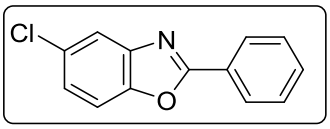
Yield 85%; White solid; mp 151-153 °C (lit.[46] 148-150 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.5 Hz, 2H), 7.56-7.42 (m, 4H), 7.17 (d, J = 8.2 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 162.7, 149.6, 142.9, 138.2, 135.1, 129.8, 129.4, 127.2, 126.6, 120.9, 110.6, 22.2; GC-MS *m/z* calcd for $C_{14}H_{10}ClNO$: 243.0 $[M]^+$, found: 243.0.

5-(Methyl-2-phenyl)benzoxaozle (28k)[4a]



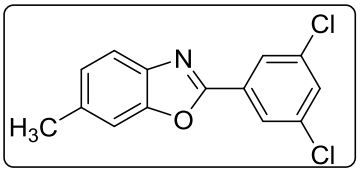
Yield 85%; White solid; mp 102-104 °C (lit.[46] 103-105 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.23 (m, 2H), 7.55-7.44 (m, 5H), 7.17-7.15 (m, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 149.0, 142.3, 134.3, 131.4, 128.9, 127.6, 127.3, 126.2, 120.0, 109.9, 21.4; GC-MS *m/z* calcd. for $C_{14}H_{11}NO$: 209.1, found: 209.0.

5-(Chloro-2-phenyl)benzoxaozle (28l)



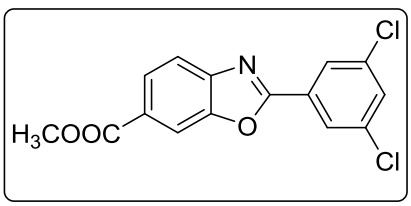
Yield 80%; White solid; mp 105-106 °C (lit.[47] 107-108 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, J = 7.6, 1.5 Hz, 2H), 7.75 (d, J = 2.0 Hz, 1H), 7.58-7.49 (m, 4H), 7.33 (dd, J = 8.6, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 154.1, 137.1, 135.0, 132.2, 129.3, 128.7, 126.6, 125.4, 123.4, 121.7; GC-MS *m/z* calcd for $C_{13}H_8ClNO$: 229.0 $[M]^+$, found: 229.0.

2-(3',5'-Dichlorophenyl)-6-methylbenzoxazole (28m)[48]



Yield 69%; White solid; mp 146-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 1.9 Hz, 2H), 7.66 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 1.9 Hz, 1H), 7.28 (s, 1H), 7.22 (dd, J = 8.1, 0.9 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 151.0, 139.5, 136.6, 135.7, 130.9, 130.0, 126.3, 125.6, 119.7, 110.9, 21.9; GC-MS *m/z* calcd for $C_{14}H_9Cl_2NO$: 277.0 $[M]^+$, found: 277.0.

Methyl-2-(3',5'-dichlorophenyl)benzoxazole-6-carboxylate (28n)[48]



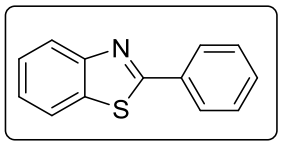
Yield 67%; White solid; mp 151-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 1.4 Hz, 1H), 8.20-8.14 (m, 2H), 7.89 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.46 (dd, J = 8.5, 2.1

Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 162.6, 150.2, 145.3, 138.3, 134.6, 132.6, 131.6, 127.6, 126.6, 120.2, 112.5, 52.6; GC-MS *m/z* calcd for $C_{15}H_9Cl_2NO_3$: 321.0 $[M]^+$, found: 321.

General experimental procedure for benzothiazoles (27):[27] A 100 mL round bottomed flask was charged with 2-aminothiophenol **26** (0.17 mole), triethylorthoformate **15** (0.25 mole) and concentrated sulfuric acid (0.007 mole). The reaction mixture was stirred at 120 °C for 1 h, then at 80 °C for 6 h. Excess of triethylorthoformate was removed by evaporation under reduced pressure and residue so obtained was passed through a column chromatography using EtOAc/hexane (30%) as an eluent to afford **27** in 70% yield (yellow liquid).

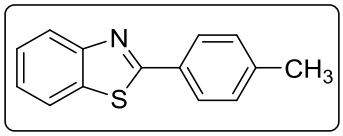
General experimental procedure for 2-arylbenzothiazoles (29a-h): Benzothiazole **27** (0.740 mmol), CuI (0.222 mmol) diphenyliodonium triflate **19a** (0.740 mmol), *t*-BuOLi (2.59 mmol) and 1,4-dioxane (2 mL) were charged in a sealed vial and irradiated in microwave (CEM Discover) with P = 200 w/ 100 psi at 130 °C for 30 min. Completion of the reaction was confirmed by the TLC (4:1 hexane:ethylacetate). The solvent was evaporated and extracted with EtOAc (3 × 5 mL). The organic layer was washed with ammonia and brine solutions, and dried over anhydrous Na_2SO_4 and removed the solvent *in vacuo*. The obtained crude product was purified by column chromatography using 10% EtOAc/hexane as an eluent to afford **29a-h** in 73-85% yields.

2-Phenylbenzothiazole (**29a**)



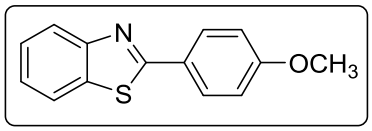
Yield 85%; Yellow solid; mp 113-114 °C (lit.[43] 112-114 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–8.07 (m, 3H), 7.93-7.90 (m, 1H), 7.52-7.48 (m, 4H), 7.41-7.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 154.1, 135.1, 133.7, 130.9, 129.1, 127.6, 126.3, 125.2, 123.3, 121.6, 119.6.

2-(4'-Methylphenyl)benzothiazole (**29b**)



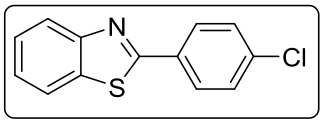
Yield 75%; light yellow solid; mp 85-86 °C (lit.[43] 85-87 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 1H), 8.01 (dd, *J* = 8.2, 1.7 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.52-7.48 (m, 1H), 7.40-7.36 (m, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 154.1, 141.4, 135.0, 131.0, 129.7, 127.5, 126.3, 125.0, 123.1, 121.6, 21.3.

2-(4'-Methoxylphenyl)benzothiazole (29c)



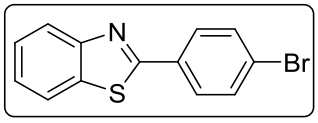
Yield 78%; Yellow solid; mp 120-121 °C (lit.[43] 122-124 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 8.9, 2.0 Hz, 3H), 7.90 (d, J = 7.5 Hz, 1H), 7.52-7.47 (m, 1H), 7.47-7.35 (m, 1H), 7.03 (dd, J = 8.9, 2.0 Hz 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 161.8, 154.1, 134.7, 129.1, 126.4, 126.2, 124.8, 122.8, 121.3, 114.5, 55.2.

2-(4'-Chlorophenyl)benzothiazole (29d)



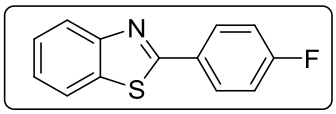
Yield 80%; Yellow solid; mp 118-119 °C (lit.[43] 116-117 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.00 (m, 3H), 7.90 (d, J = 8.0 Hz, 1H), 7.53-7.44 (m, 3H), 7.40 (t, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 154.2, 137.0, 135.0, 132.2, 129.3, 128.7, 126.5, 125.4, 123.3, 121.7.

2-(4'-Bromophenyl)benzothiazole (29e)



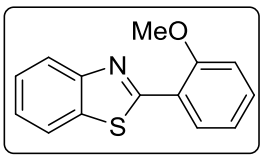
Yield 83%; Off white solid; mp 132-133 °C (lit.[49] 132 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.6 Hz, 1H), 7.98 (dd, J =8.6, 1.9 Hz, 2H), 7.92-7.90 (m, 1H), 7.65 (dd, J =8.6, 1.9 Hz, 2H), 7.54-7.50 (m, 1H), 7.44-7.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 154.0, 135.0, 132.5, 132.2, 128.9, 126.5, 125.4, 123.2, 121.7.

2-(4'-Fluorophenyl)benzothiazole (29f)



Yield 85%; Yellow solid; mp 99-100 °C (lit.[43] 102-103 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.04 (m, 3H), 7.90 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 8.2 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 165.7, 163.3, 154.0, 135.1, 129.5, 126.4, 125.27, 123.2, 121.5, 116.1.

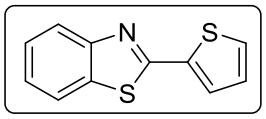
2-(2'-Methoxyphenyl)benzothiazole (29g)



Yield 73%; Yellow solid; mp 121-122 °C (lit.[50] 120.2-121.8 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, J = 7.9, 1.7 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.51-7.42 (m, 2H), 7.39-7.34 (m, 1H), 7.16-

7.10 (m, 1H), 7.05 (d, J = 8.3 Hz, 1H), 4.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 157.2, 151.9, 135.9, 131.8, 129.5, 125.9, 124.6, 122.7, 122.1, 121.2, 111.6, 55.7. GC-MS *m/z* calcd for $C_{14}H_{11}NOS$: 241.1 $[M]^+$, found: 241.0.

2-(Thiophen-2'-yl)benzothiazole (**29h**)[5d]



Yield 78%; Brown solid; mp 110-111 °C (lit.[50] 113.2−114.7 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.65-7.64 (m, 1H), 7.50-7.45 (m, 2H), 7.38 (t, J = 7.9 Hz, 1H), 7.13 (t, J = 8.1 Hz 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 153.6, 137.4, 134.6, 129.4, 128.7, 128.1, 126.5, 125.3, 123.0, 121.5.

3.4.2 References

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CHAPTER 4

Formation of C-N Bond: Functionalization of Azaheterocycles

Part A: Synthesis and organoiodine-promoted oxidation of *N*-benzylaminoheteroarenes

Part B: Utilization of diaryliodonium salts to access triazolium salts

4.1 *N*-Substituted azaheterocycles

N-Substituted azaheterocycles are important building blocks in organic synthesis for constructing natural products, as well as in pharmaceutical, agrochemical, and material sciences.[1] These azaheterocycles show significant biological properties including antimicrobial, antibacterial, anticancer, hypertensive and anticonvulsant.[2]. Although many methods are available for transition-metal-catalyzed C–N bond formation including, palladium-catalyzed Buchwald–Hartwig reactions and copper-catalyzed Ullman-type transformations.[3] Various arylating agents have been used for *N*-arylation such as aryl halide, boronic acid, arylamides, sodium arylsulfinates, and diaryliodonium salts.[4-5] Similarly for *N*-benzylation, benzylhalides[6], benzyl alcohols[7] and tosylhydrazones[8] have been used as a coupling partner. However some drawbacks associated to traditional conventional methods such as high reaction temperatures, stoichiometric amounts of copper salts, longer reaction times, activation of the aryl halide, removal of activating group and limited substrate scope. In particular, the recent introduction of diaryliodonium salts and *N*-tosylhydrazones as a coupling partner in the construction of *N*-substituted azaheterocycles displayed an significant improvement over traditional methodologies.

Owing to the importance of these heterocycles and development of milder, more-efficient method, in this chapter, synthesis of *N*-substituted azaheterocycles have been discussed. Part A includes the *N*-benzylation of various aminoheteroarenes using *N*-tosylhydrazones. *N*-Benzylaminoheteroarenes were oxidized using organoiodine reagent to accomplish useful imine derivative. Part B deals with the arylation of fused triazoles by employing diaryliodonium salts. Arylated triazolium salts were found to be the appropriate precursor of *N*-heterocyclic carbenes.

4.2 Part A

Synthesis and organoiodine-promoted oxidation of *N*-benzylaminoheteroarenes

4.2.1 Introduction

Selective construction of C-N bond in various azaheterocycles is an important task due to their pharmacological properties such as antimicrobial, antibacterial, anticancer, hypertensive, diuretic, antiinflammatory, muscle relaxants and anticonvulsant.[2] In recent past, various *N*-benzylaminoheterocycles such as Flupirtine,[9] Ferroquine,[10] aminothiazole derivative,[11] IMC-094332,[12] Tripelennamine[13] have been emerged as drug candidates (Figure 4.2.1). Besides medicinal uses, some of the *N*-benzylamino-heterocycles have been proved to exhibit prominent applications in materials science.[14]

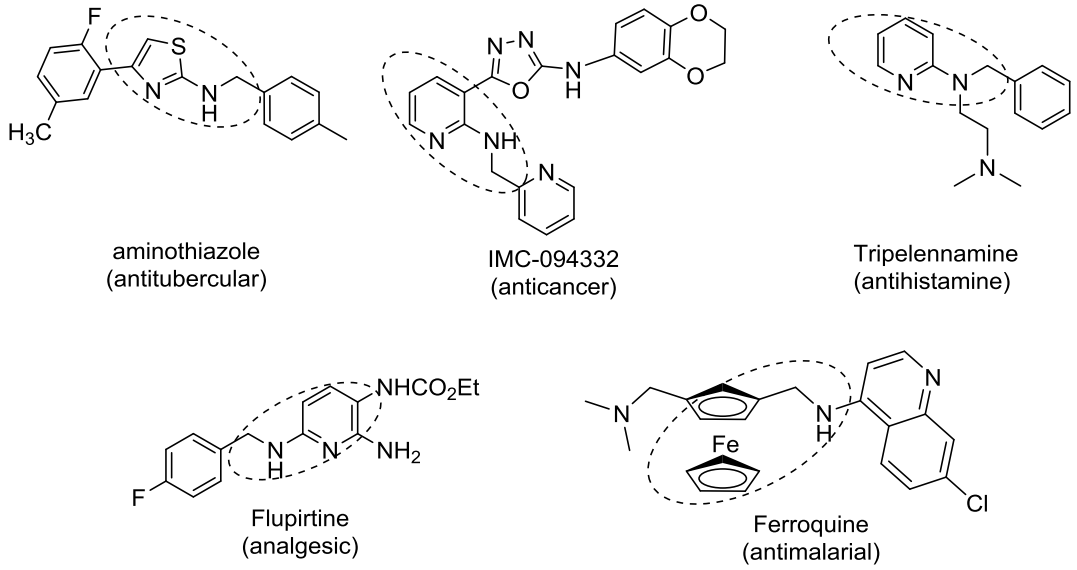


Figure 4.2.1 Representative azaheterocycles with benzylamine moiety

Owing to importance of *N*-benzylaminoheterocycles, in recent past many traditional methods to synthesize *N*-benzylaminoheterocycles have been developed by leading research groups. The exisiting methods for the preparation of *N*-benzylaminoheterocycles are described below: The most common approach for the *N*-benzylation of aminoheterocycles is reductive amination of carbonyl compounds in the presence of metal hydrides such as $NaBH_3CN$,[15] $NaBH_4$/ $Ti(O\text{-}i\text{-}Pr)_4$,[16] pyridine-borane complex (pyr-BH_3)[17] and Bu_3SnH/SiO_2,[18] $LiAlH_4$[19] and $NaBH_4$.[20]

Alternatively, *N*-benzylations of amines **1** were achieved by using lachrymatory benzylhalides[6] or benzyl alcohols[7] which often results in a mixture of secondary and tertiary amines. Though the existing protocols for the synthesis of *N*-benzyl-aminoheterocycles are promising, but some of the reported methods involve relatively high temperatures (80-100 °C), extended reaction times (2-10 h), limited substrates scope, use of unstable imines and excess reducing agents (2-4 equiv).

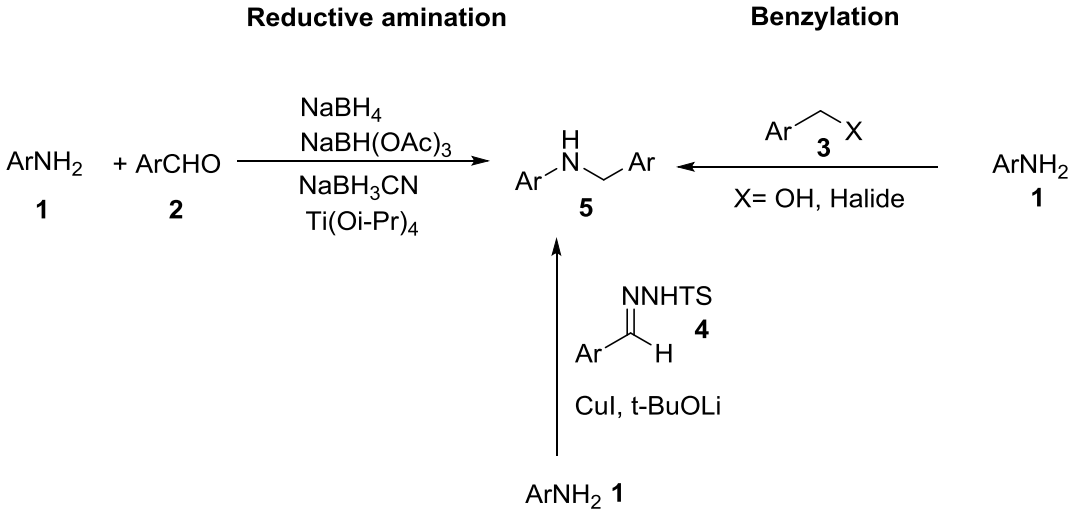
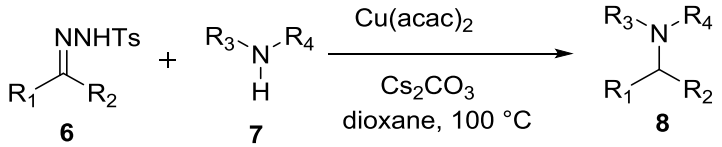


Figure 4.2.2 Literature reports for the synthesis of *N*-benzylaminoheterocycles

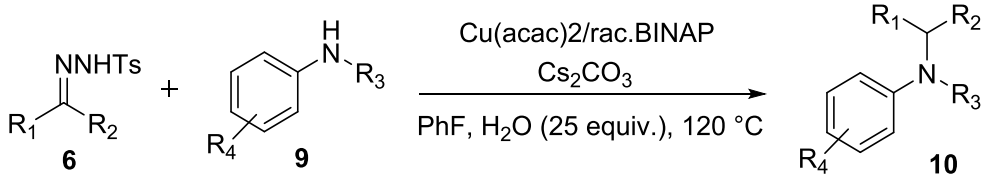
On the other hand, *N*-tosylhydrazones are versatile and stable synthetic intermediates that behave as precursors of carbenes and diazo compounds.[21] In view of convenient preparation and greater stability, *N*-tosylhydrazones have been frequently used in the transition metal-catalyzed and metal-free coupling reactions to form C–C, C–N, C-O and C–S bonds to produce bioactive azaheterocycles.[8, 22]

In 2011, Abdallah Hamze and his group reported the coupling of *N*-tosylhydrazones **6**, mainly with secondary aliphatic amines **7** and a few examples of primary amines using $Cu(acac)_2$ and Cs_2CO_3 in dioxane at 100 ^oC for 3 h. However, under these conditions benzylation of arylamine (anisidine) using *N*-tosylhydrazone of acetophenone failed to deliver the corresponding *N*-benzylated product and generated a styrene derivative (Scheme 4.2.1).[8]



Scheme 4.2.1 Synthesis of *N*-benzylaminoheterocycles using *N*-tosylhydrazones

Subsequently, the same group achieved branched arylamines **10** using $Cu(acac)_2$-catalyzed reductive coupling of *N*-tosylhydrazones **6** with arylamines **9** in the presence of rac-BINAP ligand (10%) and Cs_2CO_3 (2.5 equiv.) in fluorobenzene at 120 ^oC (Scheme 4.2.2)[23].



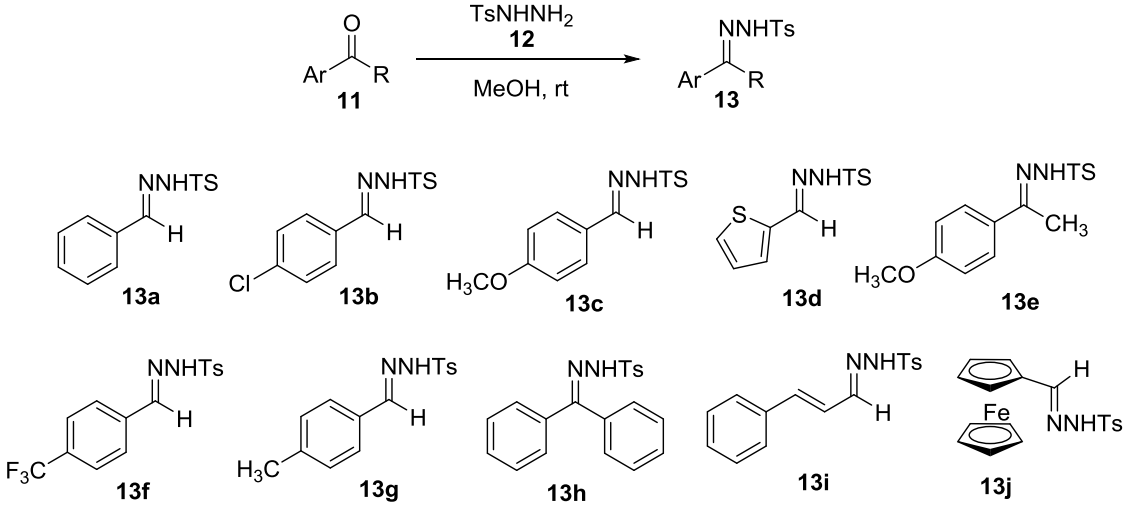
Scheme 4.2.2 Synthesis of *N*-benzylaminoheterocycles using *N*-tosylhydrazones

Surprisingly, in both reports we could not find any example of benzylation of heterocyclic primary amines using *N*-tosylhydrazones. In view of the importance of *N*-benzylaminoheterocycles and interesting chemistry of *N*-tosylhydrazones, we developed an efficient method for the synthesis of diversely substituted heteroarylamines utilizing Cu-catalyzed (10 mol%) reaction of readily available and stable *N*-tosylhydrazones **2** and appropriate amines.

4.2.2 Results and discussion

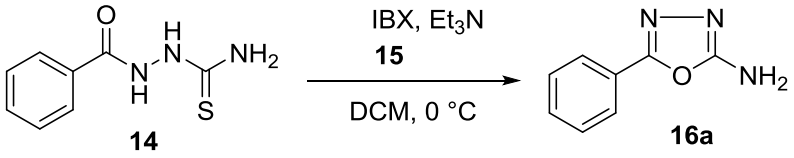
4.2.2.1 Synthesis

To begin our investigation, we chosen the reaction of **16a** with **13a** as a model reaction. Precursor *N*-tosylhydrazone **13** was prepared in high yield from the reaction of tosylhydrazine **12** with benzaldehyd/ketones **11** (Scheme 4.2.3).[21b]



Scheme 4.2.3 Synthesis of *N*-tosylhydrazones **13**

The required 5-phenyl-1,3,4-oxadiazol-2-amine **16a** was achieved by IBX **15** promoted oxidative cyclization of thiosemicarbazide **14** as reported in literature.[24]

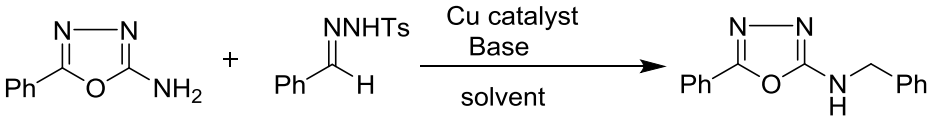


Scheme 4.2.4 Synthesis of 5-phenyl-1,3,4-oxadiazol-2-amine **16a**

Our initial attempts involving the reaction of **16a** and **13a** with or without copper catalyst (CuBr or CuI) in acetonitrile in the presence Cs_2CO_3 or *t*-BuOLi at 120 ^oC, were failed to generate the expected product **17a** (Table 4.2.1, entries 1-3). Aprotic solvents like toluene, dioxane, acetonitrile and DMF have been reported to play an important role to *in situ* generate carbene from *N*-tosyl-hydrazones.[22j] Therefore, reaction of **16a** with **13a** was performed in aprotic solvents. Interestingly, we found that toluene was the appropriate reaction solvent to prepare **17a** by the *N*-benzylation of **16a** in the presence of Cs_2CO_3 in 50% yield (Table 4.2.1, entry 4). Next, screening of different bases such as K_2CO_3, K_3PO_4, *t*-BuOLi and Cs_2CO_3 enabled us to identify *t*-BuOLi as the most suitable base to produce **16a** in 80% yield in the presence of CuI at 120 °C for 3 h (Table 4.2.1, entries 7-10). MW-assisted synthesis continues to attract considerable attention of organic and medicinal chemists with new and innovative applications are being reported routinely.[25] In many instances, the use of focused MW has been demonstrated to generate products with enhanced yields in short time when compared to conventional heating reaction. In the view of advantages associated with MW-assisted organic synthesis and to improve the reaction conditions, we explored the coupling of **16a** with **13a** in MW oven by varying reaction temperature (60-100 °C) at 100 Watt power. When the reaction mixture was exposed to MW for 15 min at lower temperatures (60-80 °C), compound **17a** was obtained in poor yields (Table 4.2.1, entries 11-12). Notably, by increasing the reaction temperature from 80 °C to 100 °C, **17a** was formed in 85% yield (Table 4.2.1, entry 13) in 15 min. However, in the presence of $Cu(acac)_2$ in place of CuI, this transformation was inefficient and delivered the desired product **17a** in 20% yield (Table 4.2.1, entry 14). Having the optimized reaction conditions in hand, we explored the scope of present methodology by using a variety of *N*-tosylhydrazones (**13a-j**) and heteroarylamines (**16a-j**). Reaction of **16a** with

N-tosylhydrazones (**13a-c**) afforded **17a-c** in excellent yields (80-85%) as mentioned in Table 4.2.2.

Table 4.2.1 Optimization reaction conditions for *N*-benzylation of 5-phenyl-1,3,4-oxadiazol-2-amine **16a** using *N*-tosylhydrazones **13a**[a]



16a **13a** **17a**

Entry	Catalyst	Base	Solvent	Method	Temp.(°C)	Yield[b] (%)
1.	-	Cs_2CO_3	MeCN	A	120	n.r.[c]
2.	CuBr	*t*-BuOLi	MeCN	A	120	n.r.
3.	CuI	*t*-BuOLi	MeCN	A	120	n.r.
4.	CuI	Cs_2CO_3	Toluene	A	120	50
5.	CuBr	Cs_2CO_3	Toluene	A	120	30
6.	CuCl	*t*-BuOLi	Toluene	A	120	10
7.	CuI	Cs_2CO_3	Dioxane	A	120	n.r.
8.	CuI	*t*-BuOLi	Toluene	A	120	80
9.	CuI	K_2CO_3	Toluene	A	120	10
10.	CuI	K_3PO_4	DMF	A	120	n.r.
11.	CuI	*t*-BuOLi	Toluene	B	60	trace
12.	CuI	*t*-BuOLi	Toluene	B	80	40
13.	CuI	*t*-BuOLi	Toluene	B	100	85
14.	$Cu(acac)_2$	*t*-BuOLi	Toluene	B	100	20

[a] Reaction conditions: 5-phenyl-1,3,4-oxadiazol-2-amine **16a** (1 equiv.), *N*-tosylhydrazone **13a** (1.2 equiv.), base (2.5 equiv.), Cu catalyst (10 mol%), Method A: Conventional heating at 120 °C for 3 h. Method B: MW irradiation for 15 min. [b] Isolated yield. [c] n.r.= no reaction

Next, it is worth mentioning that heteroaryl derivative of *N*-tosylhydrazone **13d** was also shown to be a feasible substrate to efficiently generate **17d** in 82% yield. No significant change in the outcome of reaction was observed with variation in aryl moiety of *N*-tosylhydrazones **13**. When *N*-tosylhydrazone of acetophenone **13e** was allowed to react under the optimized reaction conditions, **17e** was formed in 67% yield.

Synthesized compounds were well characterized by their NMR and mass spectral data (Figures 4.2.3 and 4.2.4)

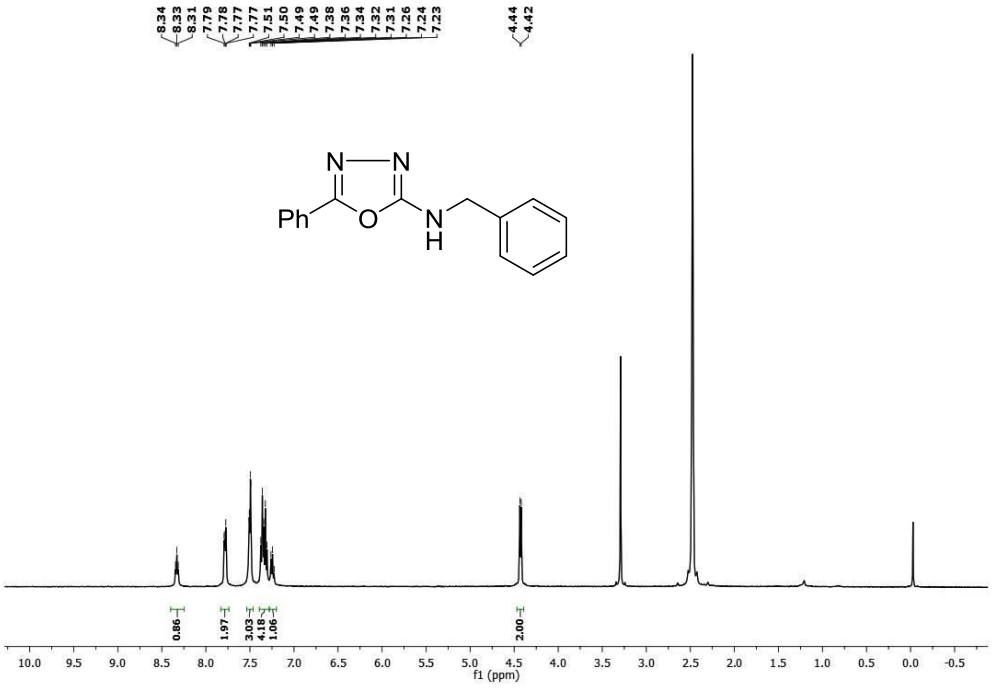


Figure 4.2.3 ^{1}H NMR spectrum of **17a**

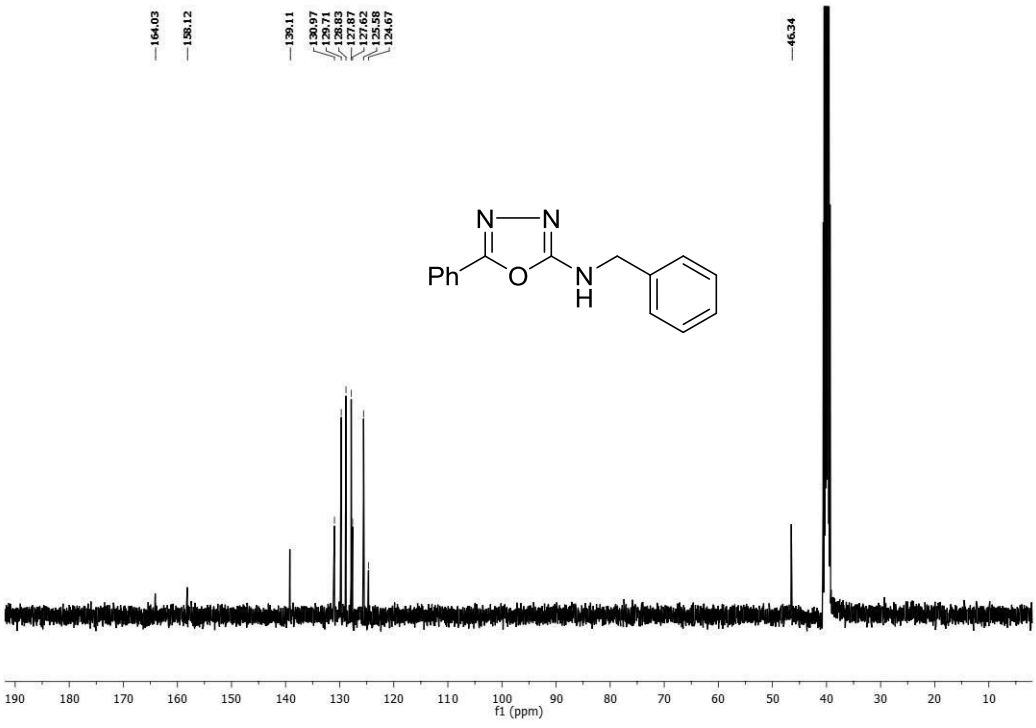
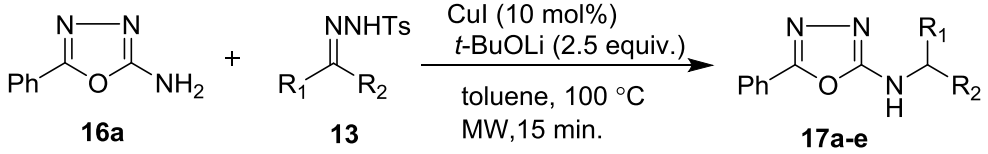
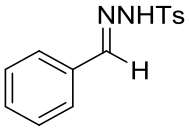
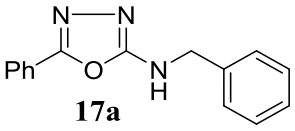
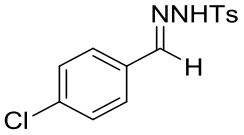
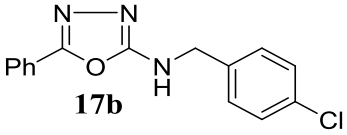
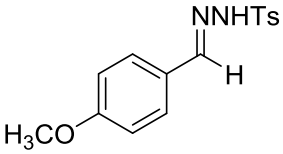
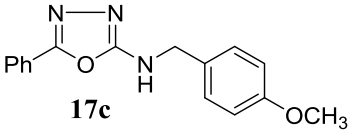
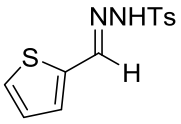
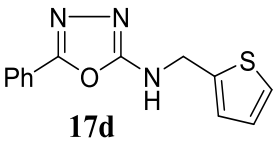
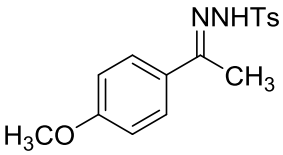
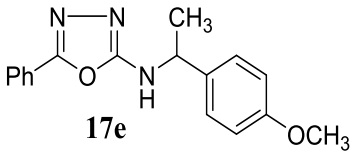


Figure 4.2.4 ^{13}C NMR spectrum of **17a**



Scheme 4.2.5 Benzylation of 5-phenyl-1,3,4-oxadiazol-2-amine **16a** using *N*-tosylhydrazones

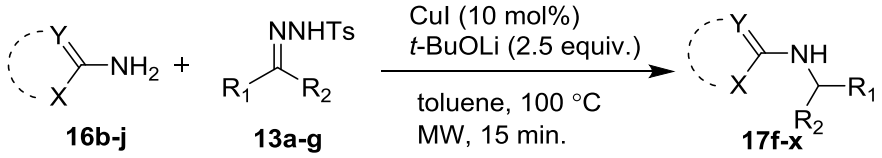
Table 4.2.2 Synthesized *N*-benzylaminoheterocycles (**17a-e**)[a]

S.No.	*N*-Tosylhydrazones	Compounds	Yields (%)[b]	Mp (°C)
1		 **17a**	85	209-210
2		 **17b**	80	190-191
3		 **17c**	80	183-184
4		 **17d**	82	183-185
5		 **17e**	67	178-179

[a] Reaction conditions: **16a** (1 equiv.), **13a-e** (1.2 equiv.), toluene (3 mL), MW (100 W), 100 °C, 15 min. [b] Isolated yields

Encouraged by the successful benzylation of 5-phenyl-1,3,4-oxadiazol-2-amine, next we moved to study the reaction of *N*-tosylhydrazones **13** with a variety of heteroaromatic systems, for example, 2-aminothiazole (**16b**), 4-phenylthiazol-2-amine (**16c**), 2-aminoimidazole (**16d**), 2-aminothiadiazole (**16e**), 2-aminopyridine (**16f**), 2-aminobenzo-thiazole (**16g**), 5-aminoisoquinoline (**16h**), 4-aminocoumarin (**16i**) and 4-methoxyaniline

(**16j**) under the optimized reaction conditions and prepared the corresponding benzylated amines **17f-x** up to 84% of yield as illustrated in Table 4.2.3. The reaction of 2-aminoimidazole (**16d**) with one equivalent of *N*-tosylhydrazone **13a** led to dibenzylated imidazole (**17l**) with unreacted 2-aminoimidazole (**16d**). However, with two equivalent of **13a**, complete conversion was observed to afford **16l** in 75% yield. *N*-Tosyl-hydrazones with electron-withdrawing (**13b**) and electron-releasing (**13c**) groups successfully delivered the desired products **17f-x** in 70-83% yields. Next, reaction of *N*-tosylhydrazone having strong electron-withdrawing substituent (CF_3) **13f** and **16b** successfully delivered *N*-benzylated product **17j** in 80% yield. Reaction of 2-aminobenzothiazole (**16g**) with *N*-tosylhydrazones derived from benzophenone (**13h**) and cinnamaldehyde (**13i**) also yielded **17t** and **17u** in 70% and 72% yields, respectively (Table 4.2.3). Fortunately, the reaction protocol was equally effective for the benzylation of anisidine (**16j**) to afford *N*-benzyl-4-methoxyaniline (**17x**) in 76% yield. A potent anti-tubercular 2-aminothiazole derivative[11] **17k** was successfully achieved in 83% yield from the reaction of 4-phenylthiazole-2-amine (**16c**) with *N*-tosylhydrazone (**13g**).



Scheme 4.2.6 Benzylation of various heterocyclic amines using *N*-tosylhydrazones

Used heteroarylamines (**16b-j**)

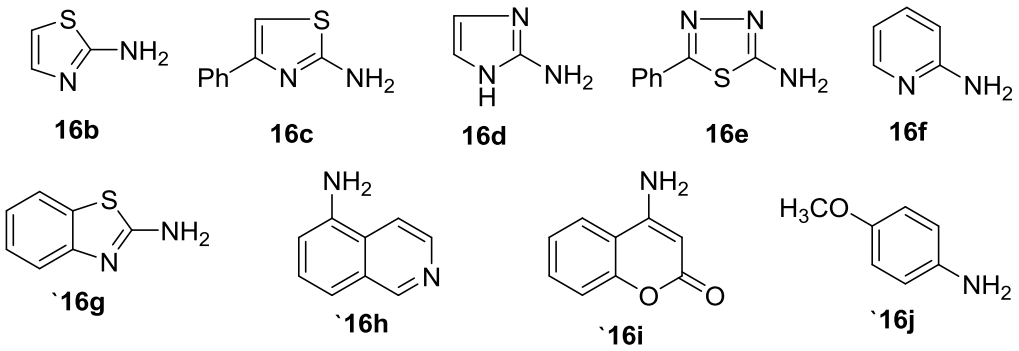
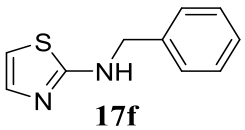
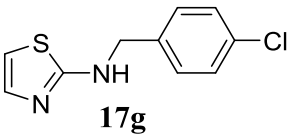
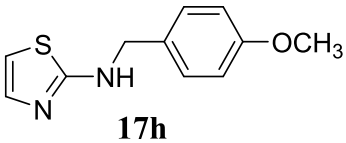
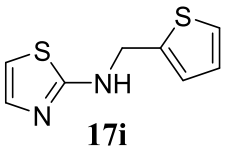
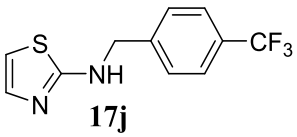
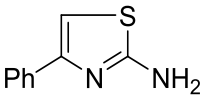
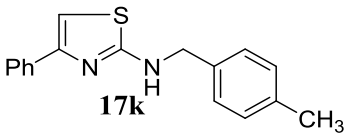
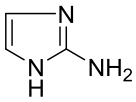
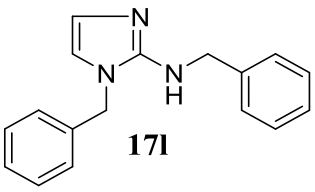
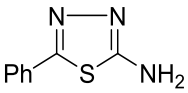
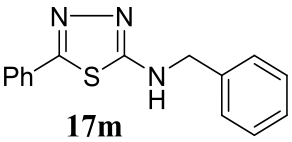
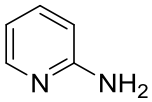
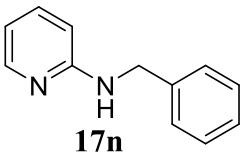
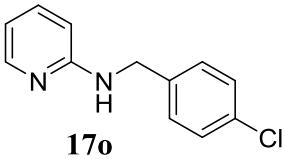
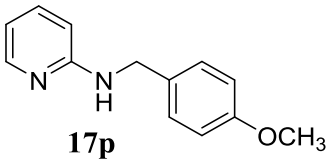
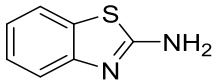
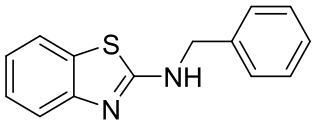
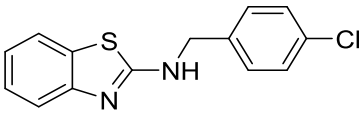
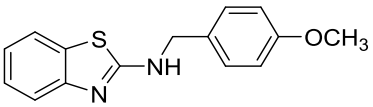
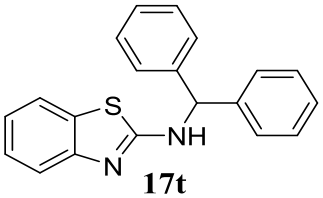
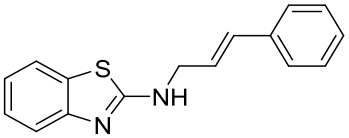
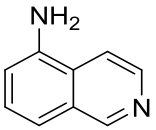
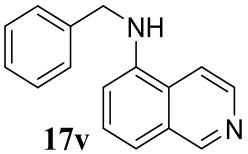
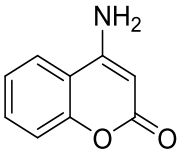
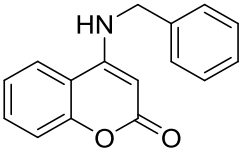
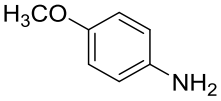
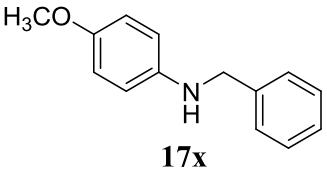


Table 4.2.3 Synthesized *N*-benzylaminoheterocycles (**17f-x**)[a]

S.No.	Heteroarylamines	*N*-Tosylhydrazones	Compounds	Yields (%)[b]
1	**16b**	**13a**	 **17f**	82
2	**16b**	**13b**	 **17g**	83
3	**16b**	**13c**	 **17h**	79
4	**16b**	**13d**	 **17i**	80
5	**16b**	**13f**	 **17j**	80
6		**13f**	 **17k**	83
7		**13a**	 **17l**	75
8		**13a**	 **17m**	70
9		**13a**	 **17n**	82
10	**16f**	**13b**	 **17o**	81

11	**16f**	**13c**	 **17p**	84
12		**13a**	 **17q**	82
13	**16g**	**13b**	 **17r**	78
14	**16g**	**13c**	 **17s**	80
15	**16g**	**13h**	 **17t**	70
16	**16g**	**13i**	 **17u**	72
17		**13a**	 **17v**	75
18		**13a**	 **17w**	80
19		**13a**	 **17x**	76

[a] Reaction conditions: **16b-j** (1 equiv.), **13a-i** (1.2 equiv.), toluene (3 mL), microwave irradiation (100 W), 100 °C, 15 min. [b] Isolated yields.

Ferrocene derivatives have gained significant attention in the field of materials science, bioorganic chemistry and catalysis.[2e,26-27] Especially, ferrocenyl moiety attached to azaheterocycles through *N*-alkylamino linkage displayed interesting medicinal properties, for example, ferroquine, an analogues of chloroquine with aminoquinoline and ferrocene moieties is an antimalarial drug.[28] Owing to the importance of ferrocenyl-based compounds, we extended the synthetic scope to ferrocenyl tosylhydrazone **13j** to prepare *N*-alkylamino-linked ferrocene-based compounds (**17y-z'**). Delightfully, under the identified conditions, reaction of ferrocenyl *N*-tosylhydrazone **13j** with 2-aminopyridine (**16f**), 2-amino-benzothiazole (**16g**) and 4-aminocoumarin (**16i**) afforded the corresponding products **17y-z'**in 75-85% yields as illustrated in Figure 4.2.5.

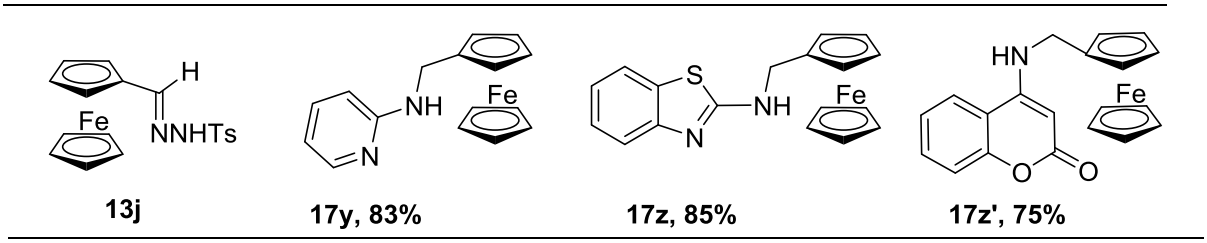


Figure 4.2.5 Couplings of ferrocenyl *N*-tosylhydrazone **13j** and heteroarylamines

Finally, reaction conditions were extended for the benzylation of *o*-phenylenediamine (**16k**) to access the corresponding dibenzylated amines. Reaction of **16k** with *N*-tosylhydrazone **13a** (2 equiv.) under the optimized conditions produced 1,2-disubstituted benzimidazoles **18a** instead of expected dibenzylated amine (Table 4.2.4).

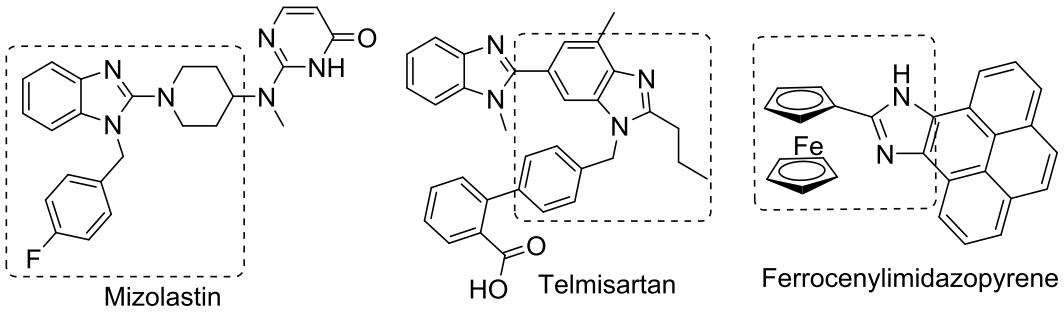
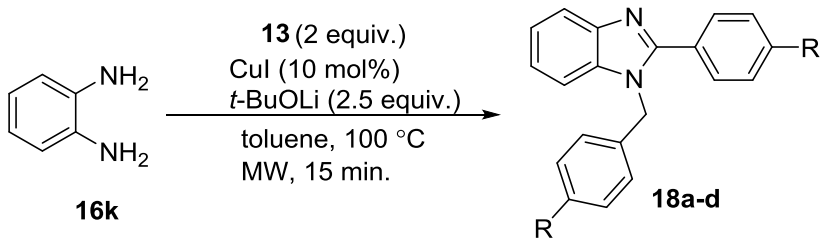


Figure 4.2.6 Drug-like molecules with benzimidazole scaffold.

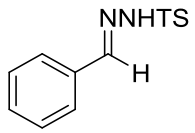
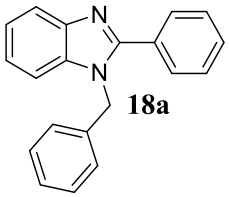
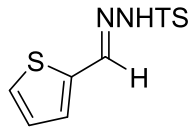
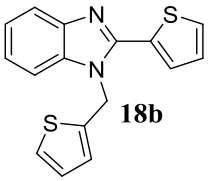
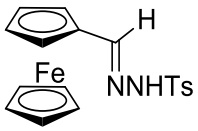
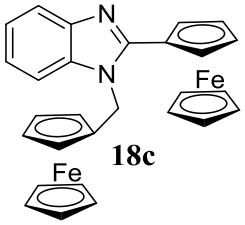
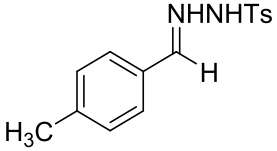
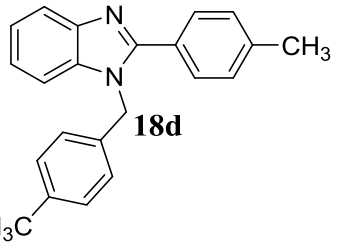
In literature, disubstituted benzimidazoles are reported to exhibit a wide range of biological properties including anticancer, antiviral, antibacterial and antifungal.[29] Benzimidazole motif is present in many therapeutic agents, for example, Mizolastin (H1 receptor antagonist) and

Telmisartan(antihypertensive agent).[30] Interestingly, ferrocenylimidazole possess an ion-pair receptor property which is useful to study many biochemical pathways (Figure 4.2.6).[31] Due to immense potential of 1,2-disubstituted benzimidazoles, we prepared thienyl and tolyl derivatives **18b** and **18d** by the coupling of *o*-phenylenediamine (**16k**) with tosylhydrazones **13d** and **13g**. It is noteworthy to mention that the valuable ferrocenyl benzimidazole (**18c**) was also successfully achieved in high yield (85%) by the coupling of **16k** with **13j** (Table 4.2.4).



Scheme 4.2.7 Preparation of benzimidazole derivatives **18a-d**

Table 4.2.4 Synthesized 1,2-disubstituted benzimidazole derivatives (**18a-d**)[a]

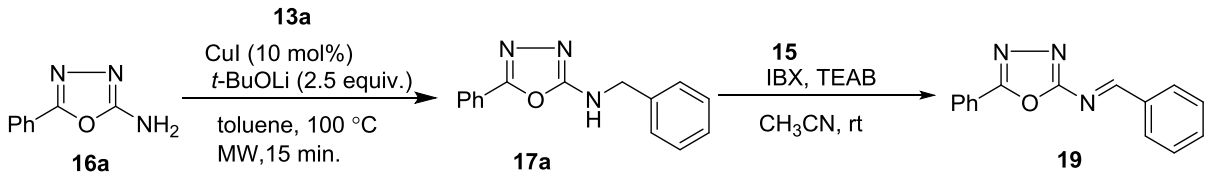
S.No.	*N*-Tosylhydrazones	Compounds	Yields (%)[b]	Mp (°C)
1		 **18a**	78	131-132
2		 **18b**	77	152-153
3		 **18c**	85	176-177
4		 **18d**	80	126-127

[a] Reaction conditions: **16k** (1 equiv.), **13** (2 equiv.), toluene (3 mL), microwave irradiation (100 W), 100 °C, 15 min. [b] Isolated yields.

4.2.2.2 Synthetic application: Organoiodine-promoted oxidation and cyclization

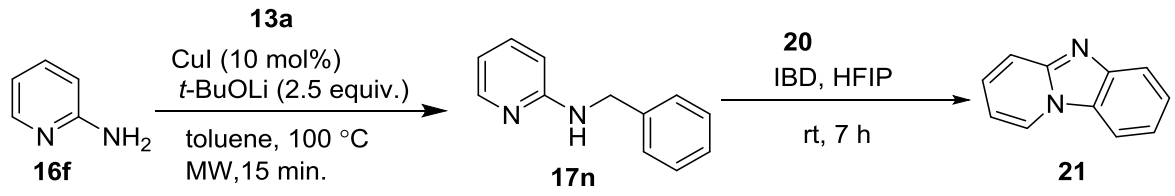
Synthesized *N*-benzylaminoheterocycles have been further used to prepare some useful bioactive heterocycles using organoiodine reagent as an oxidizing agent.

4.2.2.2.1 Organoiodine-promoted oxidation: Schiff bases are an important class of compounds reported to possess carbon nitrogen double bond which show significant biological activities such as antibacterial, antifungal, anti-inflammatory, antipyretic, antitumor, anticancer activities. Besides their biological properties in medicinal chemistry these schiff bases have also been reported to possess chelatogenic properties to form ligands in coordination chemistry. Within the past decade, IBX has been frequently used to oxidize benzylic position to convert amines to the corresponding imines under milder reaction conditions.[32] Due to prominent application of Schiff bases in synthetic and medicinal chemistry and to investigate the potential of IBX in this transformation, benzylic oxidation of **17a** has been done obtained from the reaction of **16a** and **13a**, utilized IBX **15** to prepare an important imine intermediate *N*-benzylidine-5-phenyl-1,3,4-oxadiazol-2-amine **19** in 80% yield (Scheme 4.2.8).



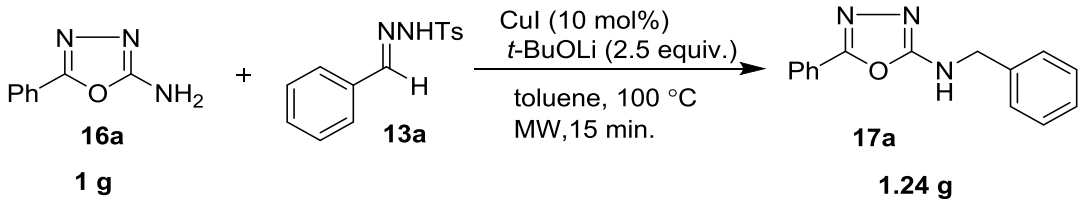
Scheme 4.2.8 Preparation of *N*-benzylidine-5-phenyl-1,3,4-oxadiazol-2-amine **19**

4.2.2.2.2 Organoiodine-promoted cyclization: *N*-benzyl-2-aminopyridine **17n** which synthesized from the reaction of **16f** with **13a** under optimized reaction condition, was treated with organoiodine(III) reagent (IBD) **20**. IBD promoted oxidative demethylation of **17n** involving C-N bond cleavage followed by intramolecular cyclization through C-N bond formation led to the synthesis of pyrido[1,2-*a*]benzimidazole **21** in 97% yield (Scheme 4.2.9).[33] These synthesized pyridobenzimidazole and related analogues are known to possess remarkable biological activities namely antibacterial, antitumor and antiviral.[34]



Scheme 4.2.9 Preparation of pyrido[1,2-*a*]benzimidazole

4.2.2.3 Gram-scale preparation of *N*-benzyl-5-phenyl-1,3,4-oxadiazol-2-amine: To demonstrate the feasibility of the developed protocol at gram-scale, under the optimized reaction conditions we prepared 1.24 g (80% yield) of **17a** from **16a** (6.21 mmol) and *N*-tosylhydrazone (**13a**, 7.45 mmol) (Scheme 4.2.10).



Scheme 4.2.10 Gram-scale synthesis of **17a**

4.2.3 Conclusions

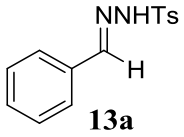
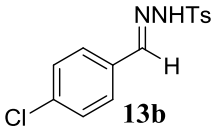
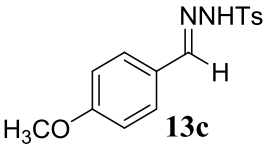
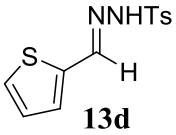
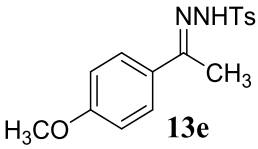
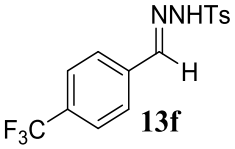
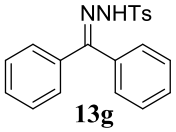
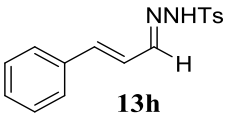
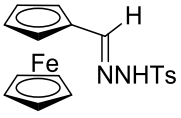
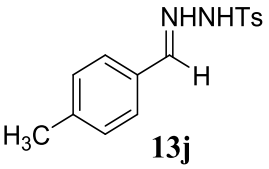
In summary, we have successfully developed ligand-free MW-assisted a new synthetic approach for the *N*-benzylation of diverse heteroarylamines. This operationally simple and efficient protocol involves the use of readily available *N*-tosylhydrazones which are easily prepared from the reaction of tosylhydrazines and the corresponding aldehyde or ketone. This developed protocol is widely applicable to a range of heterocyclic amines and *N*-tosylhydrazones to afford diverse *N*-benzylaminoheterocycles. The present methodology provides an easy access to bioactive pyrido[1,2-*a*]benzimidazoles, useful imine intermediates and *N*-substituted-2-aminothiazole. Overall, the protocol provides an alternate and convenient route to diverse *N*-benzylaminoheterocycles in high yields.

4.2.4 Experimental section

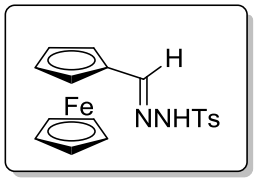
4.2.4.1 General materials and methods

All the laboratory reagents were obtained commercially. The progress of the reaction was monitored by thin layer chromatography, which was performed on Merck precoated plates (silica gel 60, F_{254}, 0.25mm) and it was visualized by fluorescence quenching under hand-UV lamp (254 nm). The column chromatography was performed using 100-200 mesh silica gel. The solvents were evaporated using Buchi rotary evaporator. Microwave reactions were carried out in CEM DISCOVER instrument. Melting points were determined using E-Z melting point apparatus and were uncorrected. Infrared spectra were recorded on Shimadzu IR Prestige-21 FT-IR spectrophotometer. ^{1}H and ^{13}C spectra were recorded using Bruker-Avance II (400, 100 MHz) spectrometer. The coupling constants (J) were given in Hz, chemical shift (δ) in ppm. TMS was used as an internal standard. The proton multiplicities were described as: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet and m = multiplet. Mass spectra were obtained using Hewlett Packard HP 5973 quadrupole Mass Selective Detector with interface for 6890 series GC.

General experimental procedure for the synthesis of *N*-tosylhydrazones (13a-j): To a rapidly stirred sulfonyl hydrazide **12** (2.0 g, 10.7 mmol) in methanol (10 mL) was added aldehyde or ketone **11** (9.22.0 mmol) dropwise which results a mildly exothermic reaction. After stirring the mixture for 10 min. hydrazide was completely dissolved and the tosylhydrazone began to precipitate. The mixture was cooled to 0 °C and the product removed by filtration, washed with methanol and dried. The crude product **13** so obtained was recrystallized through methanol in excellent yields.

S.No.	*N*-Tosylhydrazones	Yield (%)	Mp (°C)
1	 **13a**	96	127-128 (Lit.[35] 127-128)
2	 **13b**	91	147-148 (Lit. [35] 146-148)
3	 **13c**	84	110-112 (Lit.[35] 110-111)
4	 **13d**	75	131-132
5	 **13e**	70	184-185
6	 **13f**	80	167-168
7	 **13g**	80	186-187
8	 **13h**	83	162-163 (Lit.[35] 162-163)
9	 **13i**	80	155 °C
10	 **13j**	90	146-147 (Lit.[35] 147-149)

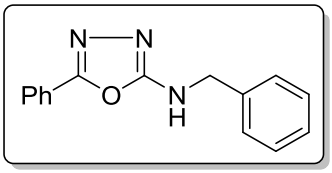
Ferrocenyl tosylhydrazone (13j)



Orange solid (1 g, 80%); mp 155 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–7.66 (m, 2H), 7.65–7.17 (m, 3H), 4.72–4.30 (m, 4H), 4.06 (s, 5H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 144.3, 135.5, 129.6, 128.0, 71.2, 70.6, 69.4, 68.1, 21.6.

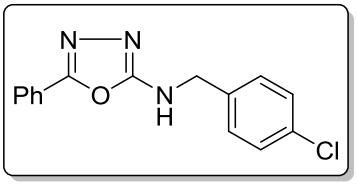
General experimental procedure for the synthesis of *N*-benzylaminoheterocycles 17a-z': In a 10 mL MW vial, heterocyclic amines **16** (1 mmol), *N*-tosylhydrazones **13** (1.2 mmol), CuI (0.1 mmol) and *t*-BuOLi (2.5 mmol) were mixed with toluene (4 mL). The reaction contents were irradiated in focused MW oven with P = 50 w/100 psi at 100 °C for 15 min. After the consumption of starting materials as indicated by TLC, the contents were allowed to reach at room temperature and the solvent was removed under reduced pressure. The residue so obtained was taken into water and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with ammonia solution (10 mL), brine (10 mL) solutions and dried over anhydrous Na_2SO_4. The solvent was evaporated and crude product was purified through column chromatography using ethylacetate-hexane (3:7, v/v) as an eluent to afford pure benzylated amines **17a-z'** in 67-85% yields. Analytical data for compounds **17a- z'** and **18a-d** are given below.

***N*-Benzyl-5-phenyl-1,3,4-oxadiazol-2-amine (17a)**



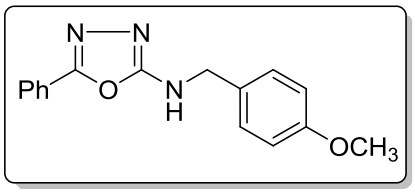
White solid (129 mg, 85%); mp 209-210 °C (lit.[36] mp 211-213 °C); IR (KBr, ν cm^{-1}): 3217, 3032, 2932, 1620, 1489, 1450, 1273, 1026, 733, 687; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (t, J = 6.2 Hz, 1H), 7.78 (dd, J = 8.0, 4.0 Hz, 2H), 7.51-7.49 (m, 3H), 7.38-7.34 (m, 4H), 7.24 (t, J = 8.1 Hz, 1H), 4.43 (d, J = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 158.1, 139.1, 130.9, 129.7, 128.8, 127.9, 127.6, 125.6, 124.7, 46.3.

***N*-(4-Chlorobenzyl)-5-phenyl-1,3,4-oxadiazol-2-amine (17b)**



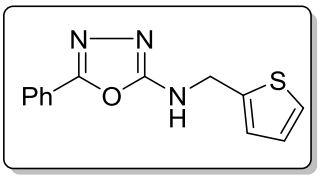
Off white solid (141 mg, 80%); mp 190-191 °C; IR (KBr, ν cm^{-1}): 3163, 3063, 2970, 2893, 2854, 1566, 1489, 1350, 1265, 1157, 1057, 833, 764, 625; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (t, J = 6.2 Hz, 1H), 7.82–7.80 (m, 2H), 7.54-7.53 (m, 3H), 7.52-7.42 (m, 4H), 4.45 (d, J = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 158.7, 138.2, 132.0, 131.0, 129.8, 129.7, 128.8, 125.6, 124.6, 45.8.

_N_-(4-Methoxybenzyl)-5-phenyl-1,3,4-oxadiazol-2-amine (17c)



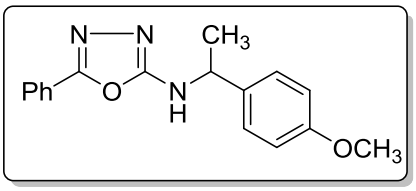
White solid (139 mg, 80%); mp 183-184 °C (lit.[37] mp 182-185 °C); IR (KBr, ν cm^{-1}): 3302, 3117, 3063, 1651, 1574, 1512, 1480, 1450, 1389, 764, 733, 687; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (t, J = 6.1 Hz, 1H), 7.89–7.75 (m, 2H), 7.54-7.52 (m, 3H), 7.32 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 4.38 (d, J = 6.1 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 158.9, 158.1, 131.1, 130.9, 129.7, 129.3, 125.6, 124.7, 114.2, 55.3, 45.8.

5-Phenyl-_N_-(thiophen-2-ylmethyl)-1,3,4-oxadiazol-2-amine (17d)



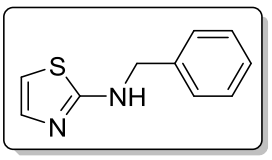
Light brown solid (130 mg, 82%); mp 183-185 °C; IR (KBr, ν cm^{-1}): 3163, 3070, 2955, 2924, 2893, 2839, 1566, 1512, 1458, 1350, 1242, 825; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (t, J = 6.1 Hz, 1H), 7.86–7.76 (m, 2H), 7.56–7.52 (m, 3H), 7.43 (dd, J = 5.1, 1.2 Hz, 1H), 7.11 (dd, J = 3.5, 1.0 Hz, 1H), 6.99 (dd, J = 5.1, 3.5 Hz, 1H), 4.63 (d, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 158.2, 139.47, 130.7, 128.0, 127.0, 126.7, 125.9, 125.7, 124.4, 42.3; HRMS (ESI) calcd for $C_{13}H_{11}N_3OS$ $[M]^+$ 257.0623, found: 257.0543.

_N_-(1-(4-Methoxyphenyl)ethyl)-5-phenyl-1,3,4-oxadiazol-2-amine (17e)



White solid (106 mg, 67%); mp 178-179 °C; IR (KBr, ν cm^{-1}): 3263, 3186, 3055, 2360, 1612, 1573, 1496, 1450, 740, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.85 (m, 2H), 7.46–7.44 (m, 3H), 7.37 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 5.20 (s, 1H), 4.95–4.90 (m, 1H), 3.82 (s, 3H), 1.67 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 156.4, 149.9, 142.1, 132.5, 129.4, 124.9, 122.2, 121.7, 109.6, 56.1, 52.2, 21.8; HRMS (ESI) calcd for $C_{17}H_{18}N_3O_2$ $[M + H]^+$ 296.1399, found: 296.1393.

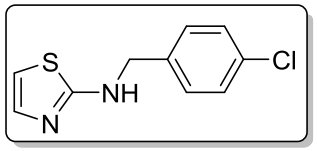
_N_-Benzylthiazol-2-amine (17f)



White crystalline solid (155 mg, 82%); mp 128-129 °C (lit.[38] mp 126-128 °C); IR (KBr, ν cm^{-1}): 3171, 3070, 2970, 2893, 1566, 1489, 1450, 1350, 1157, 764, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.30 (m,

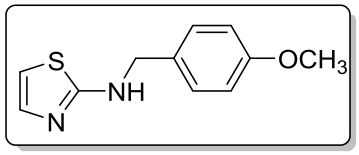
5H), 7.12 (d, *J* = 4.0 Hz, 1H), 6.52 (d, *J* = 4.0 Hz, 1H), 5.72 (s, 1H), 4.51 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.5, 139.8, 139.2, 128.7, 127.8, 127.3, 106.8, 48.1; HRMS (ESI) calcd for $C_{10}H_{11}N_2S$ $[M + H]^+$ 191.0643, found: 191.0632.

***N*-(4-Chlorobenzyl)thiazole-2-amine (17g)**



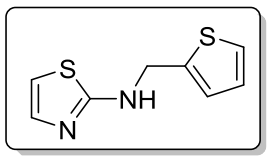
White solid (185 mg, 83%); mp 134-135 °C (lit.[39] mp 132-133 °C); IR (KBr, *v* cm^{-1}): 3171, 3070, 2962, 2893, 2854, 1556, 1489, 1450, 1350, 1165, 771, 717; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (t, *J* = 5.2 Hz, 1H), 7.40-7.34 (m, 4H), 7.01 (d, *J* = 4.0 Hz, 1H), 6.63 (d, *J* = 4.0 Hz, 1H), 4.43 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.5, 139.2, 138.1, 131.8, 129.7, 128.7, 106.7, 47.4; HRMS (ESI) calcd for $C_{10}H_{10}ClN_2S$ $[M + H]^+$ 225.0253, found: 225.0248.

***N*-(4-Methoxybenzyl)thiazole-2-amine (17h)**



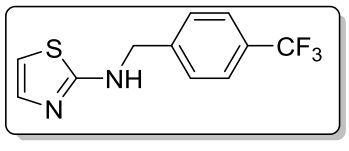
Off white solid (173 mg, 79%); mp 146-147 °C (lit.[39] mp 147-148 °C); IR (KBr, *v* cm^{-1}): 3209, 3086, 2970, 2893,1574, 1528, 1443, 1327, 1157, 1080, 741, 702; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 5.5 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.63 (d, *J* = 5.5 Hz, 1H), 4.35 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.6, 158.7, 139.4, 131.6, 129.2, 114.0, 106.9, 55.5, 47.7

***N*-(Thiophen-2-ylmethyl)thiazole-2-amine (17i)**



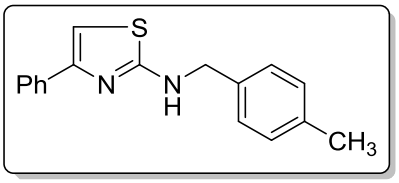
Brown solid (156 mg, 80%); mp 109-110 °C (lit.[40] mp 110 °C); IR (KBr, *v* cm^{-1}): 3178, 3070, 2970, 2847,1582, 1497, 1450, 1335, 1273, 833, 741, 702; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.39 (d, *J* = 3.9 Hz, 1H), 7.04 (d, *J* = 3.5 Hz, 2H), 6.96 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.70 (d, *J* = 4.0 Hz, 1H), 4.61 (d, *J* = 4.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.5, 142.9, 139.2, 127.1, 126.1, 125.5, 106.8, 43.1.

***N*-(4-(Trifluoromethyl)benzyl)thiazol-2-amine (17j)**



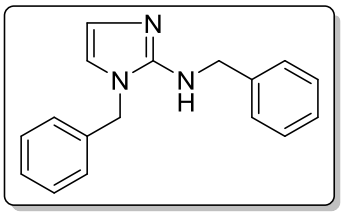
White solid (80 mg, 80%); mp 120-121 °C; ^{1}H NMR (400 MHz, CDCl3) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 3.6 Hz, 1H), 6.53 (d, *J* = 3.6 Hz, 1H), 6.10 (s, 1H), 4.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 141.9, 139.2, 130.2, 127.7, 125.7, 122.8, 107.2, 49.3.

N-(4-Methylbenzyl)-4-phenylthiazol-2-amine (17k)



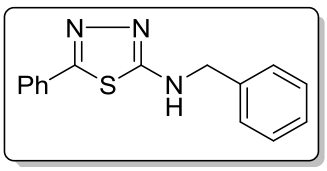
Yellow solid, (132 mg, 83%); mp 145-147 °C; IR (KBr, *v* cm^{-1}): 3202, 3086, 2962, 2916, 2878, 1574, 1327, 1342, 1281, 995, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.82 (m, 2H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.34–7.26 (m, 3H), 7.19 (d, *J* = 7.9 Hz, 2H), 6.72 (s, 1H), 5.78 (s, 1H), 4.48 (d, *J* = 5.0 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 151.5, 137.4, 135.0, 134.6, 129.4, 128.4, 127.6, 126.0, 101.0, 49.6, 21.2; HRMS (ESI) *m/z* calcd for $C_{17}H_{17}N_2S$ $[M + H]^+$ 281.1112, found: 281.1109.

***N*,1-Dibenzyl-1*H*-imidazo-2-amine (17l)**



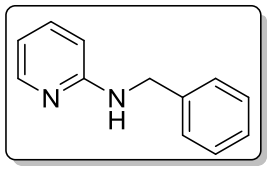
Pale yellow solid (237 mg, 75%); mp 95-96 °C; IR (KBr, *v* cm^{-1}): 3271, 1582, 1443, 1335, 1296, 1180, 1157, 1034, 818, 725; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46-7.28 (m, 9H), 7.21-7.14 (m, 3H), 5.70 (t, *J* = 5.5 Hz, 1H), 5.06 (s, 2H), 4.19 (d, *J* = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.6, 141.4, 138.9, 131.3, 128.7, 128.4, 127.9, 127.7, 127.6, 126.8, 91.5, 54.6, 48.0.

***N*-Benzyl-5-phenyl-1,3,4-thiadiazol-2-amine (17m)**



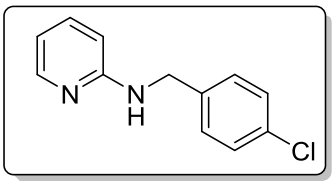
Yellow solid (105 mg, 70%); mp 178-179 °C (lit.[37] mp 179-181 °C); IR (KBr, *v* cm^{-1}): 3086, 2947, 2901, 1574, 1497, 1420, 1358, 1296, 1257, 1126, 1049, 980, 764, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.75 (m, 2H), 7.45–7.36 (m, 7H), 7.36–7.31 (m, 1H), 6.39 (s, 1H), 4.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 158.4, 136.9, 131.0, 129.8, 128.9, 128.9, 128.0, 127.8, 126.9, 50.8.

***N*-Benzylpyridin-2-amine (17n)**



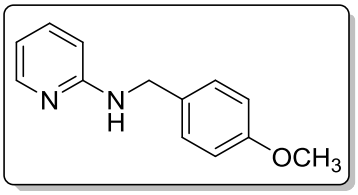
Yellow solid (160 mg, 82%); mp 103-104 °C (lit.[41] mp 105-107 °C); IR (KBr, *v* cm^{-1}): 3263, 3225, 2978, 2908,1597, 1528, 1443, 1373, 1227, 980, 910, 741, 694; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (t, *J* = 6.3 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.40–7.31 (m, 5H), 7.31–7.24 (m, 3H), 4.48 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.1, 147.9, 141.1, 137.0, 128.6, 127.6, 126.8, 112.0, 108.6, 44.2; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}N_2$ $[M + H]^+$ 185.1079, found: 185.1070.

***N*-(4-Chlorobenzyl)pyridine-2-amine (17o)**



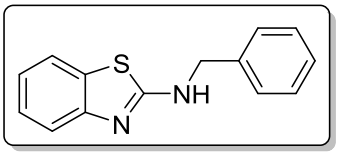
Colourless solid (187 mg, 81%); mp 99-100 °C, (lit.[41] mp 98-100 °C); IR (KBr, ν cm^{-1}): 3171, 3078, 2970, 2854, 1566, 1489, 1450, 1404, 1342, 841, 810, 717, 679; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (t, J = 6.1 Hz, 1H), 7.67 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.36–7.31 (m, 3H), 7.25 (d, J = 8.3 Hz, 1H), 3.95 (d, J = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.8, 147.9, 140.3, 137.1, 131.4, 129.4, 128.5, 112.2, 108.6, 43.7.

***N*-(4-Methoxybenzyl)pyridine-2-amine (17p)**



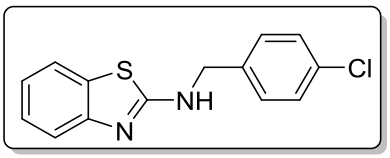
Yellow solid (177 mg, 78%); mp 90-92°C (lit.[41-42] mp 85-87 °C); IR (KBr, ν cm^{-1}): 3232, 3078, 1605, 1512, 1443, 1335, 1296, 1180, 1157, 1034, 818, 771; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, J = 3.0 Hz, 1H), 7.37–7.31 (m, 1H), 7.26 (d, J = 8.7 Hz, 2H), 6.96 (t, J = 5.8 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 6.53–6.41 (m, 2H), 4.39 (d, J = 5.9 Hz, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.1, 158.5, 148.0, 136.9, 132.9, 128.9, 114.0, 112.0, 108.6, 55.2, 43.9.

***N*-Benzylbenzo[d]thiazol-2-amine (17q)**



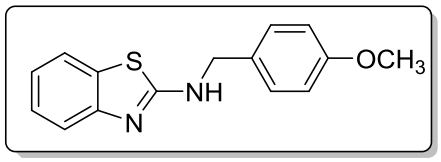
Off white solid (134 mg, 84%); mp 164-165 °C (lit.[2e, 7f] mp 164-165 °C); IR (KBr, ν cm^{-1}): 3186, 3140, 3086, 1620, 1574, 1358, 1319, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.7 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.46–7.36 (m, 4H), 7.34 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.14–7.08 (m, 1H), 6.16 (s, 1H), 4.66 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 152.2, 137.2, 128.9, 127.9, 127.7, 126.0, 121.7, 120.9, 119.0, 49.3.

***N*-(4-Chlorobenzyl)benzothiazol-2-amine (17r)**



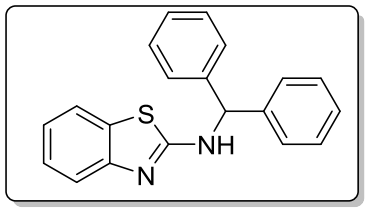
Off white solid (149 mg, 82%); mp 183-184 °C (lit.[7h] mp 184-186 °C); IR; IR (KBr, ν cm^{-1}): 2893, 2361, 2353, 1620, 1574, 1474, 1450, 1342, 1227, 756; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (t, J = 5.5 Hz, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.39-7.37 (m, 5H), 7.22 (t, J = 7.6 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 4.60 (d, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.6, 152.7, 138.5, 132.0, 130.9, 129.5, 128.1, 126.0, 121.4, 118.6, 46.9; HRMS (ESI) *m/z* calcd for $C_{14}H_{12}ClN_2S$ $[M + H]^+$ 275.0410, found: 275.0398.

***N*-(4-Methoxybenzyl)benzothiazol-2-amine (17s)**



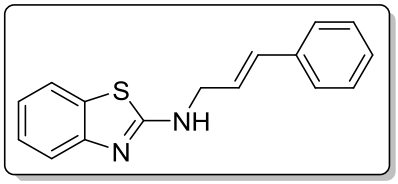
Pale yellow solid (144 mg, 80%); mp 172-173 °C (lit.[43] mp 173.5-174 °C); IR (KBr, *v* cm^{-1}): 3171, 2970, 2893, 2854, 1566, 1450, 1350, 764, 702; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (t, *J* = 5.6 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.27–7.19 (m, 1H), 7.07–6.98 (m, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 4.51 (d, *J* = 5.6 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.6, 158.9, 152.9, 131.2, 130.7, 129.3, 125.8, 121.3, 118.5, 114.1, 55.3, 47.1.

***N*-(2, 2-Diphenylethyl)benzothiazole-2-amine (17t)**



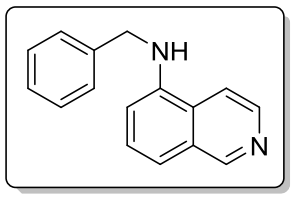
Light yellow solid (154 mg, 70%); mp 154-155 °C; IR (KBr, *v* cm^{-1}): 3202, 2993, 1597, 1535, 1450, 1311, 1288, 1257, 1211, 1149, 1080, 1026, 748, 656; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.42–7.37 (m, 5H), 7.36–7.30 (m, 5H), 7.27–7.21 (m, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.72 (s, 1H), 5.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 151.5, 140.7, 130.0, 128.9, 128.0, 127.5, 126.0, 121.8, 120.8, 119.2, 63.9; HRMS (ESI) calcd for $C_{20}H_{17}N_2S$ $[M + H]^+$ 317.1112, found: 317.1096.

***N*-Cinnamylbenzothiazol-2-amine (17u)**



Yellow solid (127 mg, 72%); mp 170-171 °C; IR (KBr, *v* cm^{-1}): 3302, 3117, 3063, 1651, 1612, 1574, 1489, 1450, 1389, 1342, 764, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.4 Hz, 2H), 7.43–7.26 (m, 6H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 15.8 Hz, 1H), 6.41–6.26 (m, 1H), 6.00 (s, 1H), 4.24 (d, *J* = 5.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 141.7, 136.4, 132.9, 128.6, 127.9, 126.5, 126.0, 124.4, 121.8, 121.0, 47.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}N_2S$ $[M]^+$ 266.0878, found: 266.0880.

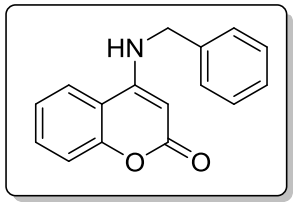
***N*-Benzylisoquinolin-5-amine (17v)**



Yellow oil (121 mg, 75%); IR (KBr, *v* cm^{-1}): 3217, 3032, 1620, 1489, 1450, 1273, 1026, 733, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.50 (d, *J* = 6.0 Hz, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.50–7.40 (m, 4H), 7.40–7.25 (m, 3H), 6.81 (d, *J* = 7.6 Hz, 1H), 4.76 (s, 1H), 4.53 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 142.4, 141.7, 138.4, 129.2, 128.7, 128.1,

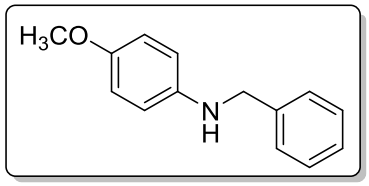
127.7, 127.4, 126.1, 116.4, 113.3, 108.2, 48.3; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}N_2$ $[M + H]^+$ 235.1235, found: 235.1229.

4-(Benzylamino)-2*H*-chromen-2-one (17w)



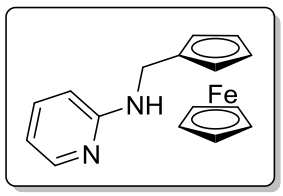
Yellow solid (124 mg, 80%); mp 175-176 °C; IR (KBr, *v* cm^{-1}): 3279, 1659, 1612, 1551, 1481, 1443, 1366, 1327, 1250, 1196, 941, 802; ^1H NMR (400 MHz, DMSO-d_6) δ 8.40 (t, *J* = 6.0 Hz, 1H), 8.13 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.64–7.58 (m, 1H), 7.39–7.34 (m, 5H), 7.31 (d, *J* = 1.0 Hz, 1H), 7.29–7.24 (m, 1H), 5.05 (s, 1H), 4.53 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.4, 153.3, 137.9, 132.3, 128.9, 127.0, 123.6, 122.7, 117.5, 114.6, 82.7, 45.9; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}NO_2$ $[M + H]^+$ 252.1025, found: 252.1019.

4-Methoxybenzyl(phenyl)amine (17x)[42, 44]



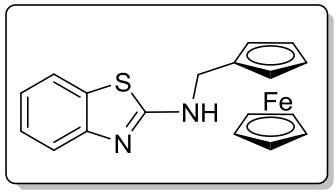
Pale yellow oil (142 mg, 76%); IR (KBr, *v* cm^{-1}): 3232, 3024, 2939, 2893, 1612, 1542, 1427, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.33 (m, 4H), 7.33–7.26 (m, 1H), 6.85–6.78 (m, 2H), 6.69–6.60 (m, 2H), 4.31 (s, 2H), 3.87 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 142.5, 139.6, 128.6, 127.6, 127.2, 115.0, 114.1, 56.0, 49.4.

***N*-(2-Pyridyl)aminomethylferrocene (17y)**[2e]



Light yellow solid (77 mg, 83%); mp 131-133 °C; IR (KBr, *v* cm^{-1}): 3202, 3086, 3009, 2901, 1574, 1497, 1420, 1358, 1257, 980, 764; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15-8.14 (m, 1H), 7.55–7.39 (m, 1H), 6.63-6.60 (m, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 4.71 (s, 1H), 4.27 (t, *J* = 2.0 Hz, 2H), 4.22 (s, 5H), 4.18-4.16 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 148.2, 137.4, 113.0, 106.9, 85.9, 68.6, 68.0, 67.9, 41.5.

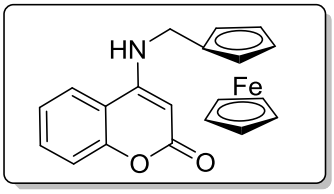
***N*-(Ferrocenylmethyl)benzothiazole-2-amine (17z)**



Light brown solid (59 mg, 85%); mp 180-182 °C; IR (KBr, *v* cm^{-1}): 3086, 2978, 2908, 1628, 1574, 1458, 1427, 1342, 1281, 995, 933, 879; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.58 (m, 2H), 7.37–7.31 (m, 1H), 7.15–7.10 (m, 1H), 5.36 (s, 1H), 4.34 (s, 2H), 4.31–4.29 (m, 2H), 4.24 (s, 5H), 4.22–4.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5,

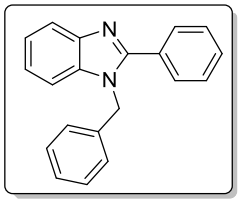
125.9, 121.6, 120.9, 119.0, 84.4, 68.7, 68.4, 68.2, 44.8; HRMS (ESI) *m/z* calcd for $C_{18}H_{16}FeN_2S$ $[M]^+$ 348.0384, found: 348.0376.

_N_-(Ferrocenylmethyl)chromenon-4-amine (17z')



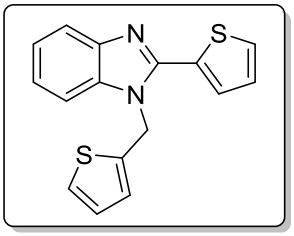
Light brown solid (87 mg, 75%); mp 160-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (t, J = 7.4 Hz, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.32–7.25 (m, 1H), 5.43 (s, 1H), 5.37 (s, 1H), 4.33 (s, 2H), 4.26 (s, 7H), 4.12 (d, J = 4.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 153.7, 151.9, 131.8, 123.3, 119.9, 118.1, 114.0, 84.2, 83.2, 68.7, 68.6, 68.5, 42.5.

1-Benzyl-2-phenyl-1H-benzo[d]imidazole (18a)



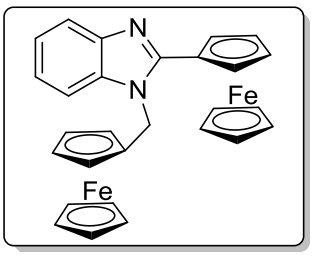
Off white solid (101 mg, 78%), mp 131-132 °C (lit.[39] mp 130-132 °C).

2-(Thiophen-2-yl)-1-(thiophen-2-ylmethyl)-1*H*-benzo[*d*]-imidazole (18b)



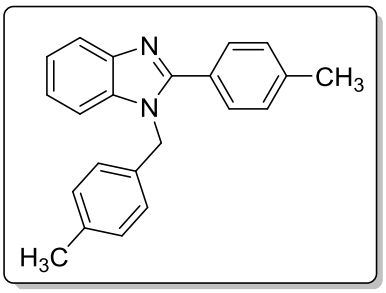
Dark yellow solid (105 mg, 77%); mp 152-153 °C (lit.[45] mp 150-152 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.83 (m, 1H), 7.55 (dd, J = 5.1, 1.1 Hz, 1H), 7.50 (dd, J = 3.7, 1.1 Hz, 1H), 7.42–7.39 (m, 1H), 7.35–7.30 (m, 2H), 7.27 (dd, J = 5.1, 1.1 Hz, 1H), 7.17 (dd, J = 5.1, 3.7 Hz, 1H), 6.98 (dd, J = 5.1, 3.5 Hz, 1H), 6.91–6.89 (m, 1H), 5.74 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 143.0, 138.8, 135.9, 131.8, 128.9, 128.0, 127.9, 127.3, 125.6, 125.4, 123.4, 123.0, 119.9, 109.9, 44.0.

2-(Ferrocenyl)-1-(ferrocenylmethyl)-1*H*-benzo[*d*]imidazole (18c)



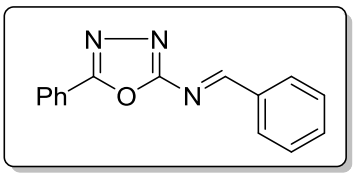
Dark yellow crystalline solid (196 mg, 85%); mp 176-177 °C (lit.[46] mp 179-181 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.71 (m, 1H), 7.49–7.38 (m, 1H), 7.32–7.22 (m, 2H), 5.45 (s, 2H), 5.07–4.98 (m, 2H), 4.55–4.44 (m, 2H), 4.29–4.26 (m, 2H), 4.23 (s, 10H), 4.17–4.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 143.1, 135.9, 122.2, 122.0, 119.0, 109.5, 84.0, 74.2, 70.0, 69.8, 69.4, 69.0, 68.6, 68.1, 44.0; HRMS (ESI) *m/z* calcd for $C_{28}H_{25}Fe_2N_2$ $[M + H]^+$ 501.0717, found: 501.0701.

1-(4-Methylbenzyl)-2-(4-methylphenyl)1-*H*-benzo[*d*]imidazole (18d)



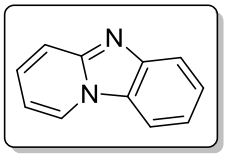
Off white solid, (115 mg, 80%); mp 126-127 °C (lit.[45] mp 128-129 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.32-7.30 (m, 1H), 7.29–7.21 (m, 4H), 7.16 (d, J = 7.9 Hz, 2H), 7.01 (d, J = 8.0 Hz, 2H), 5.44 (s, 2H), 2.41 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 142.9, 140.1, 137.5, 136.0, 133.3, 129.7, 129.4, 129.2, 126.9, 125.9, 122.9, 122.7, 119.8, 110.5, 48.2, 21.4, 21.1.

General experimental procedure for the synthesis of *N*-benzylidine-5-phenyl-1,3,4-oxadiazol-2-amine (19): To a stirred suspension of IBX **15** (1.2 mmol) in CH_3CN was added TEAB (1.2 mmol). A yellow suspension was observed to which *N*-benzyl-5-phenyl-1,3,4-oxadiazol-2-amine **(17a)** was added in one portion after 10 min stirring at room temperature. Stirring was continued at room temperature for another 30 min. After completion of reaction CH_3CN was removed under reduced pressure and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with saturated $NaHCO_3$ (20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and crude product was recrystallized from ethanol to afford pure **19** with 80% yield.



Yellow solid (79 mg, 80%); mp 233-234 °C (lit.[47] mp 235 °C); IR (KBr, ν cm^{-1}): 3113, 2978, 1591,1248, 1069, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.17–8.11 (m, 2H), 8.10–8.03 (m, 2H), 7.69–7.63 (m, 1H), 7.60–7.53 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 166.9, 164.0, 134.3, 134.2, 131.8, 130.5, 129.2, 129.1, 126.7, 124.0; HRMS (ESI) calcd for $C_{15}H_{12}N_3O$ $[M + H]^+$ 250.0980, found: 250.0973.

General experimental procedure for the synthesis of pyrido[1,2-*a*]benzimidazole (21): In a stirred solution of *N*-benzylpyridin-2-amine (**17n**) in HFIP (hexafluoroisopropanol, 1.5 mL), 2.2 equiv. of IBD **20** was added. Reaction mixture was stirred at room temperature for 7 h and monitered the progress of reaction through checking TLC. Once starting material was consumed, reaction mixtureextracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with saturated $NaHCO_3$ (20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and crude product so obtained was purified through columm chromatography in 97% yield.



Light brown solid (82 mg, 97%); mp 182-183 °C (lit.[33, 48] mp 181-182 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 6.9 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.58–7.51 (m, 1H), 7.46–7.35 (m, 2H), 6.86 (t, J = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 144.4, 129.3, 128.6, 125.7, 125.1, 121.0, 119.9, 118.0, 110.4, 110.3.

4.3 Part B

Utilization of diaryliodonium salts to access triazolium salts

4.3.1 Introduction

N-Heterocyclic carbenes (NHCs) **23** are widely used as umpolung reagents in unconventional bond forming strategies to prepare different bioactive heterocycles.[49] NHCs are powerful tactic that convert an electrophilic carbonyl group into a nucleophilic acyl anion which in turn reacts with electrophilic aldehyde **24** to generate α-hydroxyketones **26**.[50] Initially the reaction of NHCs with aldehyde generates the "Breslow intermediate **25**" as described by Ronald Breslow in 1958.[51] This Breslow intermediate behaves as a nucleophilic synthon and provides the feasibility to react with another electrophilic substrate to yield benzoin **26** as shown in Figure 4.3.1.

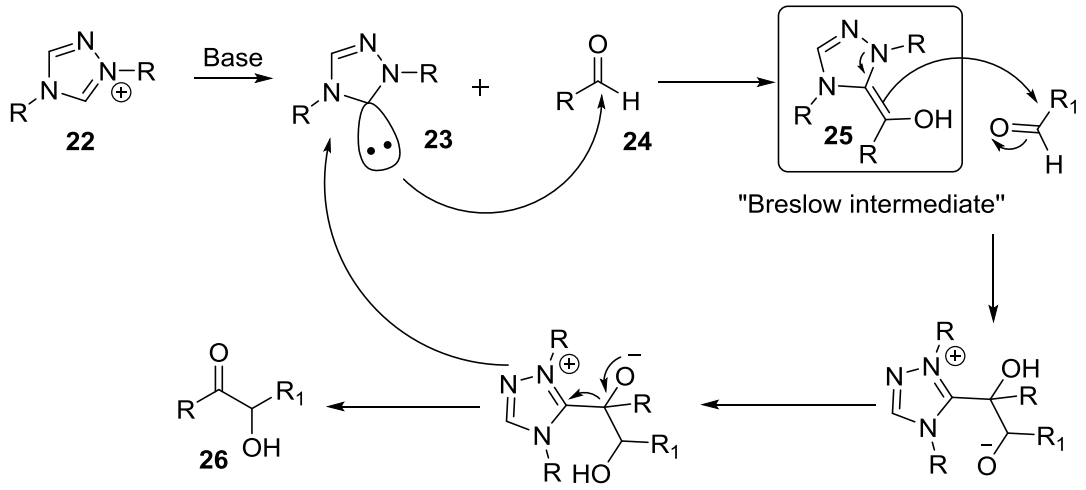


Figure 4.3.1 Mode of action in NHC organocatalysis through "Breslow intermediate"

Azolium salts which are the precursor of NHCs **22**, for example, imidazolium, triazolium and thiazolium salts have been demonstrated for their significant and versatile catalytic activities in a wide range of organic transformations.[52] Under basic reaction conditions these azoium salts are known to generate *N*-heterocyclic carbenes which facilitates benzoin and stetter condensations.[53] In the recent past, carbenes, namely imidazol-2-ylidenes **27**, and 1,2,4-triazol-5-ylidenes **28** have been reported as stable nucleophilic heterocyclic carbenes (Figure 4.3.2). In organocatalysis use of stable carbenes like triazolylidene are dominated over thiazolylidene or imidazolylidene carbenes.

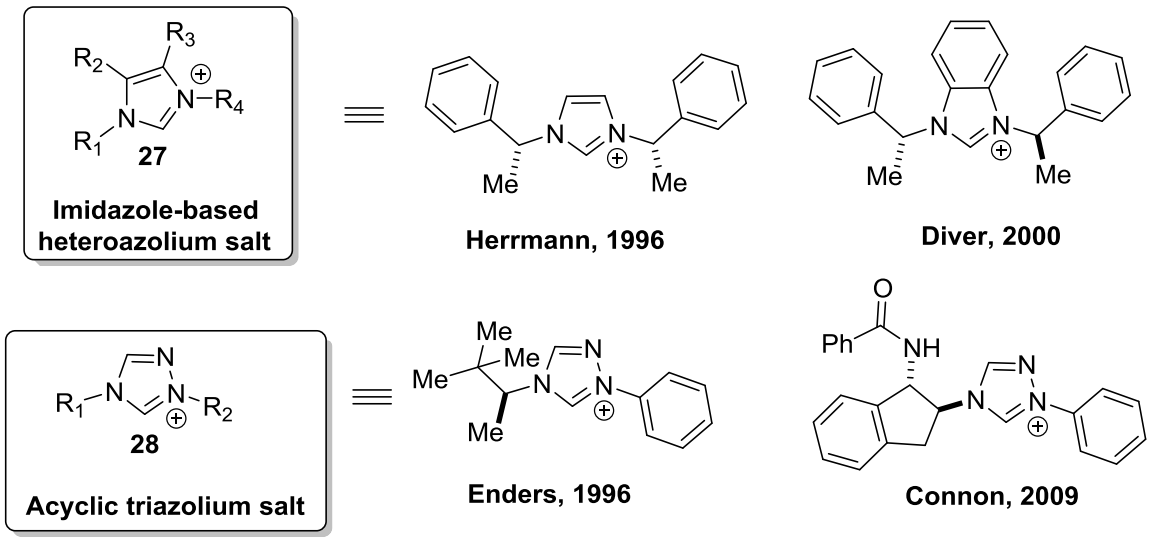


Figure 4.3.2 Example of some stable azolium salts as NHCs precursors

Subsequent efforts resulted in considerable improvement in the stability of annulated heterocyclic carbenes **29** such as bis(pyrido[*a*])-annulated imidazol-2-ylidene **29a**, quinoline[a]-annulated imidazol-2-ylidenes **29b**, pyrido-annulated imidazol-2-ylidenes **29c** pyrido[1,2-a][1,2,4]-triazol-3-ylidenes **29d** (Figure 4.3.3).[54]

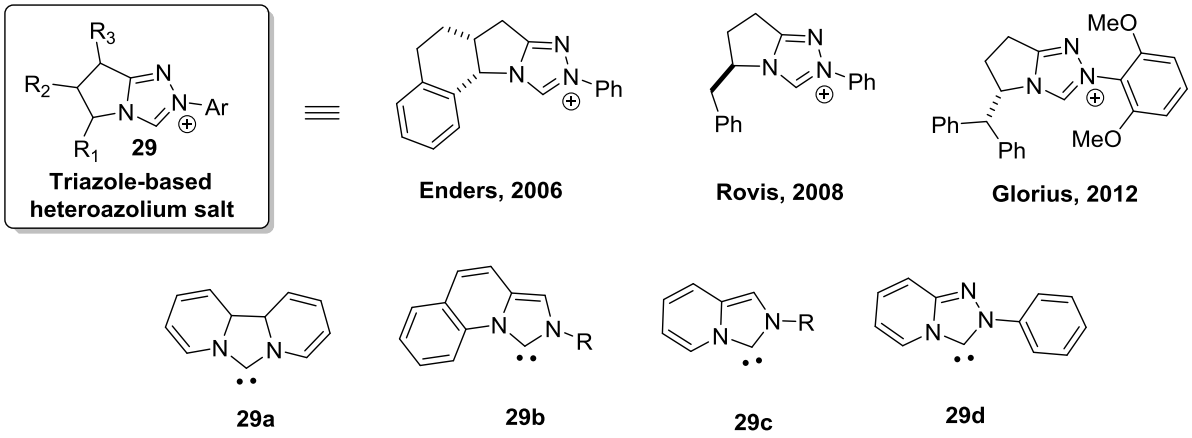


Figure 4.3.3 Pyrido-annulated triazolium salts and NHCs

This structural medication of heterocyclic carbenes may influences the σ-donor/π-acceptor ligand properties and could be useful in tuning the electronic properties.[54] Owing to the importance of annulated carbenes, various research groups[55] explored the properties of interesting pyrido-annulated NHCs. NHC catalyzed reaction of 3-(1-arylsulfonylalkyl)indoles **32** with aldehyde **24** in the presence of base yielded *α*-(3-indolyl) ketone derivatives **33**.[56]

Similarly, the combination of triazolium salts **30** with *α,* β-unsaturated compounds **34** led to the synthesis of 1,4-diketones **35** known as stetter reaction.[57] Moreover, transition metal-based *N*-heterocyclic carbenes have been frequently used in important coupling reactions including Suzuki-Miyaura, Sonogashira, Hiyama and nickel-catalyzed Michael reaction[58] as illustrated Figure 4.3.4.

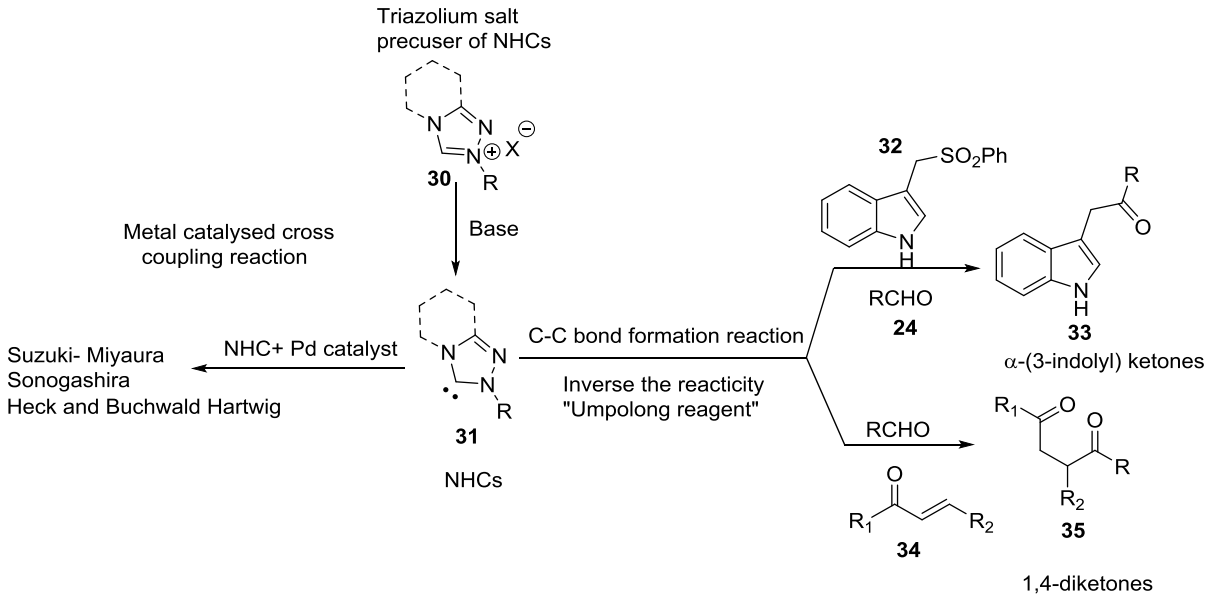


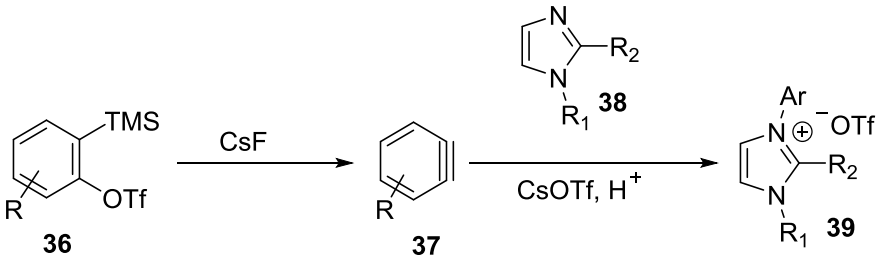
Figure 4.3.4 Examples of NHCs catalyzed useful transformations

Besides their usefulness as precursors, NHCs have been reported for their promising anti-malarial[59] and hole blocking properties.[60] Triazolylidene iridium scaffold showed enzymatic behavior for being a functional analogue of methyl transferases such as S-adenosyl-methionine (SAM).[61]

Due to the importance of these annulated-azolium salts as NHCs precursors in organic synthesis, it received considerable attention for quaternization of imidazole and triazoles moieties to develop a suitable protocol. Despite advances and usefulness of azolium salts, there are only few reports in literature with limited substrate scope and have not been explored for the quaternization of fused 1,2,4-triazole. The exisiting methods for the preparation of azolium salts are summarized below:

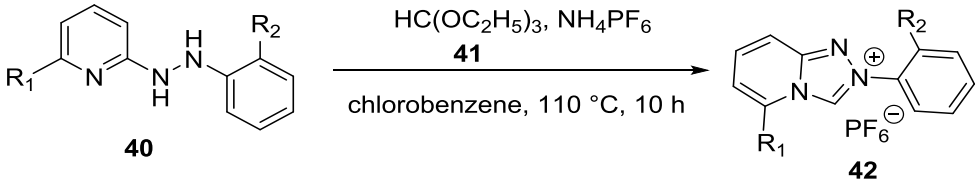
In 2002, Kunai et al. reported the direct quaternization of *N*-alkylimidazoles **38** involving the reaction of imidazoles with *in situ* generated arenes **37**. Developed protocol was successfully delivered *N*-alkyl-*N'*-arylimidazolium salts **39** in moderate to good yields. However, under these conditions *N*-arylimidazoles were failed to produce corresponding imidazolium salts.

The synthesized imidazolium salt was further utilized in palladium-catalyzed Suzuki-Miyaura coupling reaction (Scheme 4.3.1).[62]



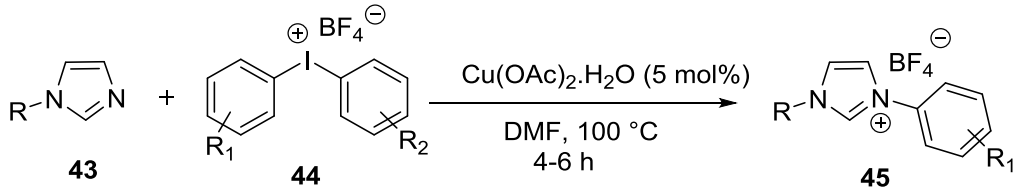
Scheme 4.3.1 Synthesis of *N*-alkyl-*N'*-arylimidazolium salts **39** arenes **37**

In 2008, You group reported the synthesis of pyrido-annulated triazolium salts **42** utilizing 1-(pyridin-2-yl)-2-phenylhydrazine **40**, ammonium hexafluorophosphate and triethyl orthoformate **41** under refluxing conditions for 10 h. The synthesized pyrido-annulated triazolium salts **42** was further treated with NaH to prepare stable carbene and further utilized in benzoin condensation reaction (Scheme 4.3.2).[54]



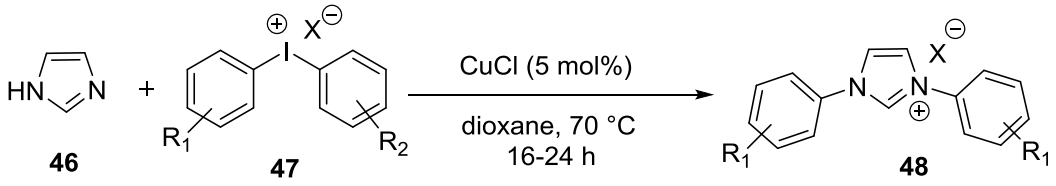
Scheme 4.3.2 Synthesis of pyrido-annulated triazolium salt

Another approach for the direct synthesis of imidazolium salts **45** have been achieved by Gao and You group in 2013. In this report a variety of diaryliodonium tetrafluoroborate **44** have been used to quaternized *N*-substituted imidazoles **43** to delivered imidazolium salts **45** in the presence of $Cu(OAc)_2.H_2O$ in DMF at 100 °C for 4-6 h. This protocol represents an efficient synthesis of various bis(imidazolium) salts as pre-catalysts of NHCs (Scheme 4.3.3.).[63]



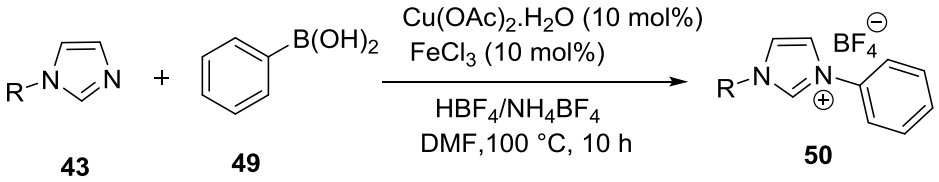
Scheme 4.3.3 Synthesis of imidazolium salts using diaryliodonium salts **9**

Later, same group has reported the synthesis of diarylimidazolium salts **48** based on the previous strategy but in their previous report *N*-substituted imidazole need to be prepare in advance. To reduce this step reaction has been carried out in between 1*H*-imidazole **46** and diaryl-iodonium salts **47** in prescence of CuCl using dioxane as a solvent at 70 °C for 16-24 h. This methodology provides an easy access to prepare diarylimidazolium salts **48** using symmetrical and unsymmetrical iodonium salts in one-pot (Scheme 4.3.4).[4]



Scheme 4.3.4 Synthesis of diarylimidazolium salts using *1H*-imidazole **46** and diaryliodonium salts **47**

Again in 2014, Gao and You group prepared unsymmetrical imidazolium salts **50** by the reaction of *N*-arylimidazoles **43** with arylboronic acids **49** as an aryl source in place of diaryliodonium salts **47**. The reaction proceeded through air oxidation in the presence of $Cu(OAc)_2.H_2O$ and $FeCl_3$ catalytic system using NH_4BF_4 as a counterion source (Scheme 4.3.5).[5]

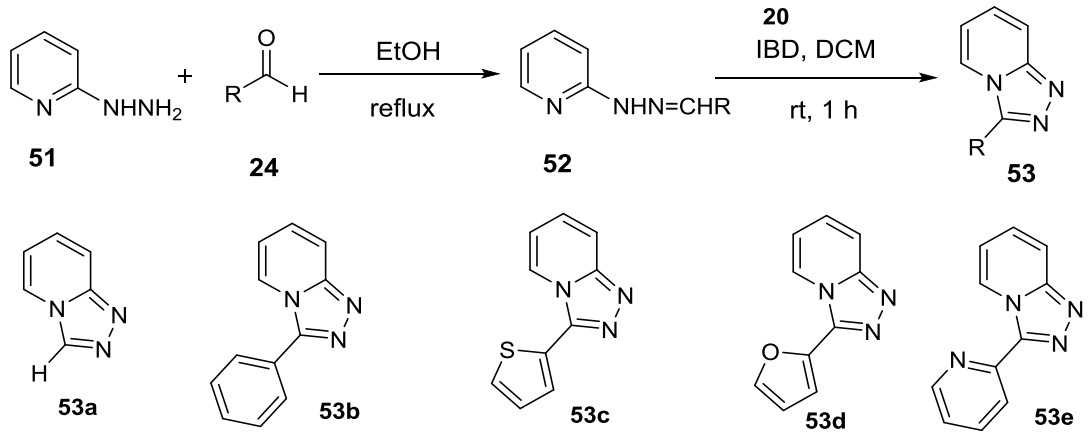


Scheme 4.3.5 Synthesis of unsymmetrical imidazolium salts using arylboronic acid **49**

4.3.2 Results and discussion

4.3.2.1 Synthesis

Initally, starting material [1,2,4]triazolo[4,3-*a*]pyridines **53** were prepared *via* IBD **20** mediated oxidative cyclization of *in situ* generated hydrazones **52** from the reaction of pyridylhydrazine **51** and corresponding aldehyde **24** (Scheme 4.3.6).[64]

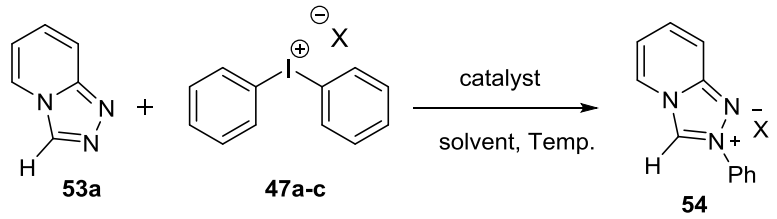


Scheme 4.3.6 Synthesis of [1,2,4]triazolo[4,3-*a*]pyridine **53**

On the other hand, diaryliodonium salts have emerged as an efficient arylating agent in organic syntheis due to less toxocity, easy handling, high electrophilicity and excellent selectivity. Recently, these diaryliodonium salts have been frequently used as a supplement for aryl halides in nucleophilic substitution reactions with various nucleophiles to form C-C and C-X bond in the presence of metal or metal-free conditions. Especially, several leading group have been published *N*-arylation of diverese heterocycles such as 2‑pyridones,[65] pyrazoles,[66] indolines[67], carbazoles[68] and indoles[69] using diaryliodonium salts. Besides their usefulness in arylations, diaryliodonium salts have been employed to construct different bioactive heterocycles.[70] Recently, we reported the synthesis of different class of bioactive compounds such as sulfones, arylazoles, biaryls and aryloxyquinolines by employing diaryliodonium salts.[71] In continuation of our ongoing efforts to discover applications of diaryliodonium salts, we have developed a facile copper-catalyzed protocol for the construction of useful [1,2,4]triazolopyridinium salt as NHCs precursors. These diaryliodonium salts can be easily synthesized based on literature reported methods.[72] *N*-Arylation of [1,2,4]triazolo[4,3-*a*]pyridine **53a** was achieved as depicted in Table 4.3.1. The reaction of **53a** with diaryliodonium salt **47a** occurred in the presence of $Cu(OAc)_2$ in DCE to afford triazolium salt **54a** with 85% yields. In successive efforts we found $Cu(OTf)_2$ showed the highest reactivity towards this reaction in DCE at 110 °C to furnish **54a** in 95% yield. In presence of $Pd(OAc)_2$ and $Ni(OAc)_2$ the reaction failed to deliver **54a** (Table 4.3.1, entries 3-4). Also, no product was formed (Table 4.3.1, entry 5) in absence of copper catalyst. Next, some other parameters like temperature and solvent were investigated. A sharp

decrease in product yield was observed by decreasing the temperature from 110 °C to 80 °C (Table 4.3.1, entry 6). DCE was found to solvent of choice to prepare azolium salts, whereas, the reaction was failed in acetontirile, DMF and DMSO (Table 4.3.1, entries 7-9).

Table 4.3.1 Optimization of quaternization of [1,2,4]triazolo[4,3-*a*]pyridine **53a** using diaryliodonium salts **47**[a]



Entry	Counterion (X)	Catalyst (5 mol%)	Solvent	Temperature (°C)	Yield(%)[b]
1.	OTf	$Cu(OAc)_2$	DCE	110	85
2.	OTf	$Cu(OTf)_2$	DCE	110	95
3.	OTf	$Pd(OAc)_2$	DCE	110	NR
4.	OTf	$Ni(OAc)_2$	DCE	110	NR
5.	OTf	-	DCE	110	NR
6.	OTf	$Cu(OTf)_2$	DCE	80	50
7.	OTf	$Cu(OTf)_2$	DMF	110	NR
8.	OTf	$Cu(OTf)_2$	DMSO	110	NR
9.	OTf	$Cu(OTf)_2$	CH_3CN	110	NR
10.	Br	$Cu(OTf)_2$	DCE	110	NR
11.	PF_6	$Cu(OTf)_2$	DCE	110	78

[a] Reaction conditions: [1,2,4]triazolo[4,3-*a*]pyridine **53a** (1equiv.), diaryliodonium salt **47** (1 equiv.) and Cu salt (5 mol%) were stirred in solvent (2 mL) for 3 h. [b] Isolated yield.
NR = No reaction

Diaryliodonium salts **47a-b** containing OTf and PF_6 counter ions smoothly transferred the aryl ring to the substrate with good yields as summarized in Table 4.3.1. However, diaryliodonium salts **47c** with bromide counter ion failed to arylate **53a** under the similar reaction conditions (Table 4.3.1, entry 10). Finally, quaternization of [1,2,4]triazolo pyridines **53a** were successfully achieved by using diaryliodonium salt **47a** (1.0 equiv.) in the presence of 5 mol% $Cu(OTf)_2$ in DCE at 110 °C for 3 h. With optimal reaction conditions, we investigated the scope of developed methodology by using different diaryliodonium salts **47a-f** and fused triazoles **53a** to prepare a series of diverse triazolium salts **54a-f** as illustrated

in Scheme 4.3.7. All the synthesized triazolium salts **54a-f** were well characterized using NMR (^{1}H & ^{13}C) and mass spectral data (Figures 4.3.5-4.3.7).

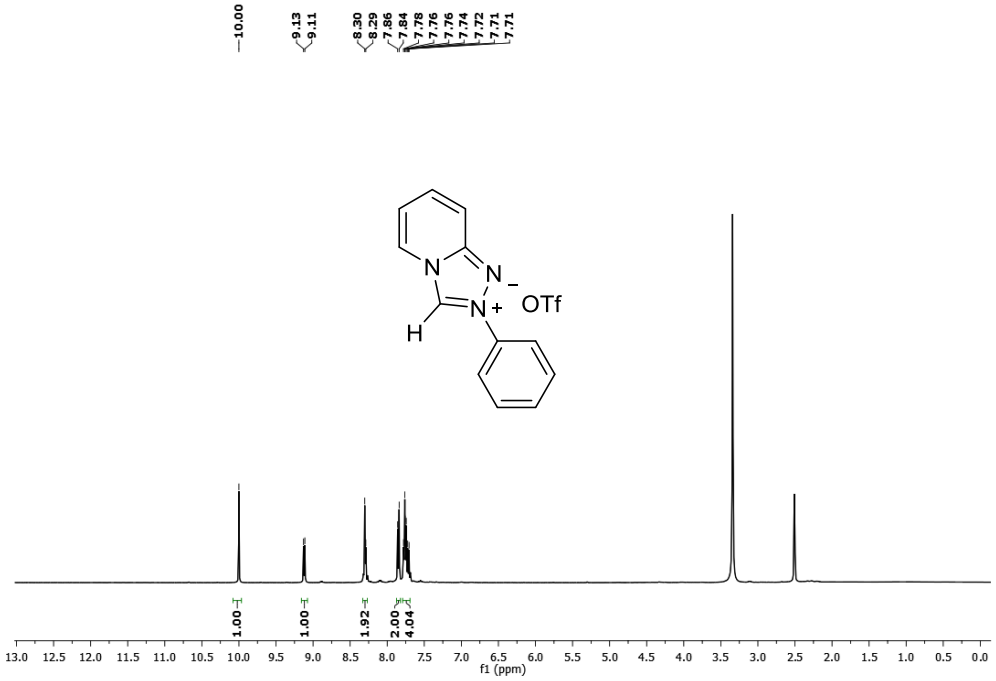


Figure 4.3.5 ^{1}H NMR spectrum of **54a**

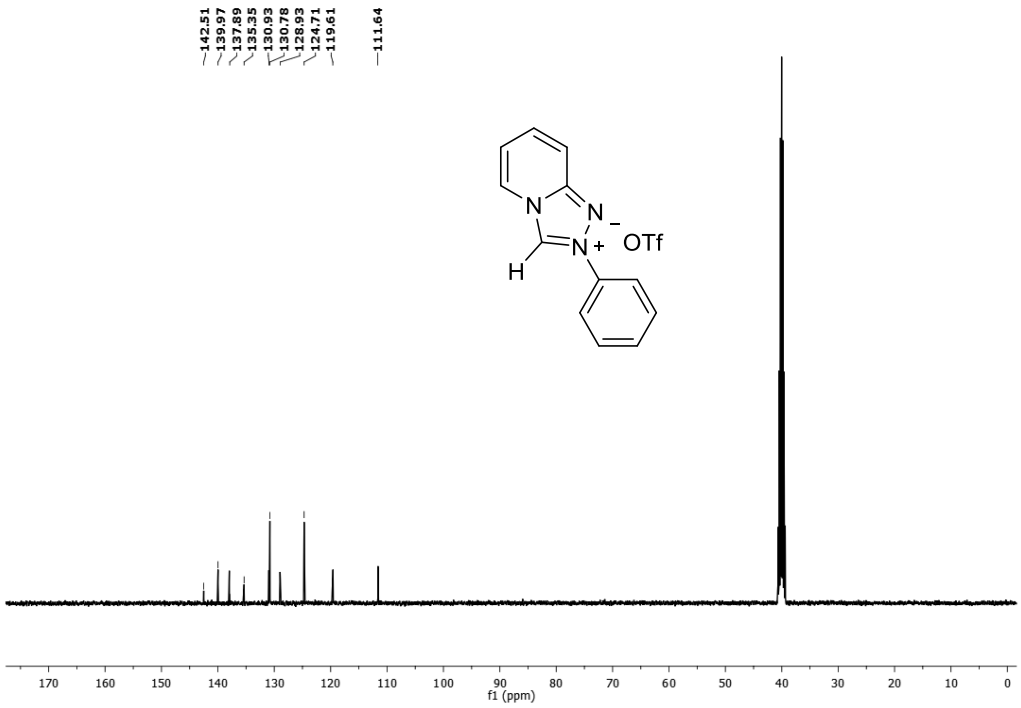


Figure 4.3.6 ^{13}C NMR spectrum of **54a**

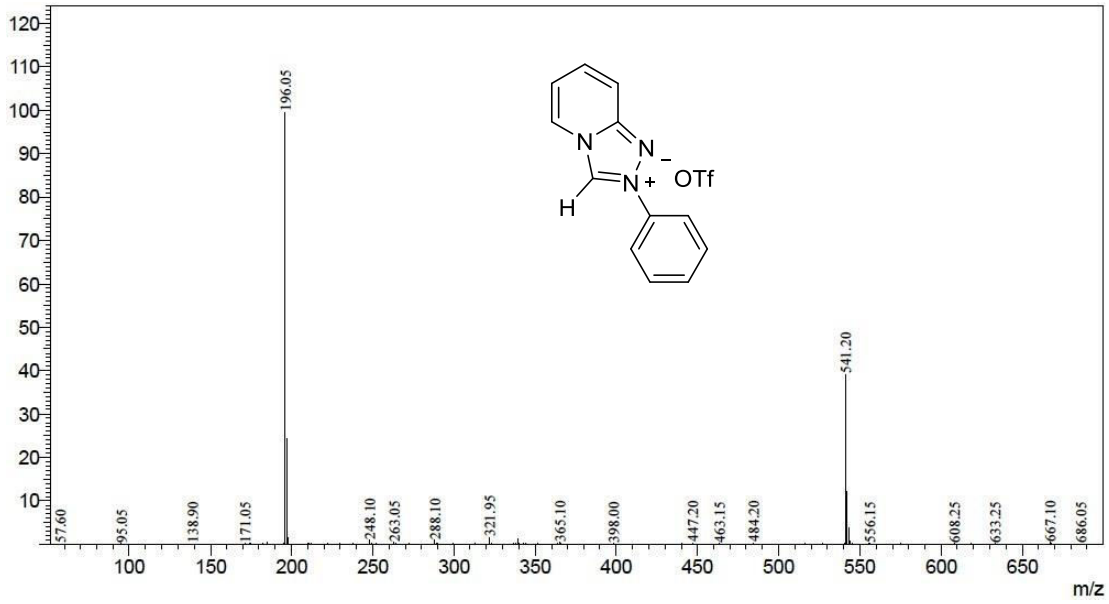
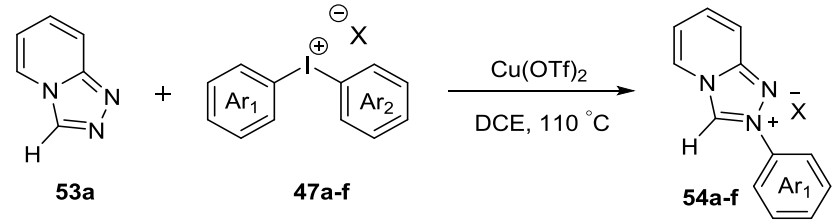
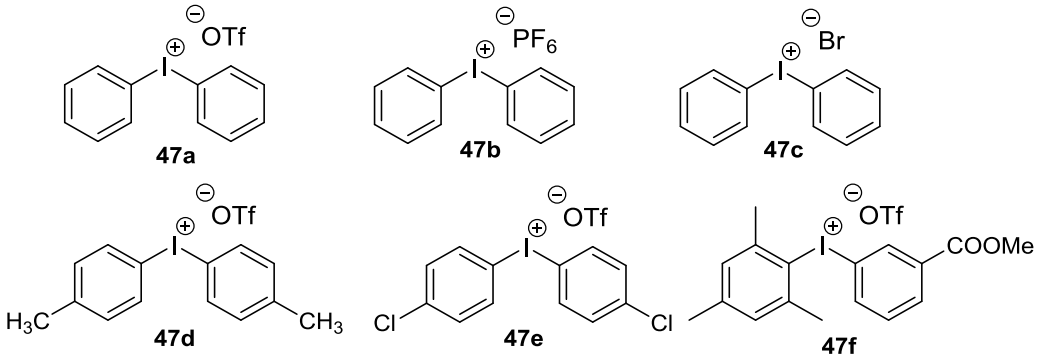


Figure 4.3.7 Mass spectrum of **54a**

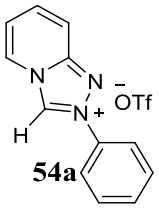
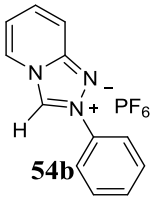
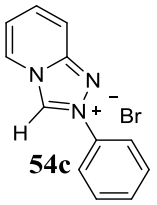
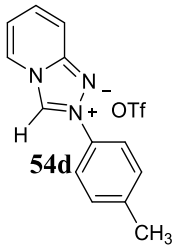
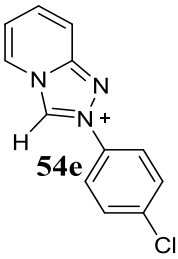
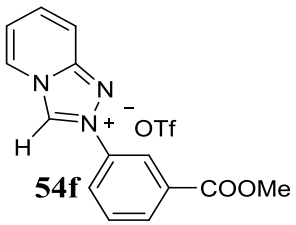


Used diaryliodonium salts



Scheme 4.3.7 Arylation of [1,2,4]triazolo[4,3-*a*]pyridine **53a** using diaryliodonium salts

Table 4.3.1 Synthesized triazolium salts using diaryliodonium salts (**54a-f**)[a]

S.No.	Structure	Yields (%)[b]	Mp (°C)
1	 **54a**	95	brown thick liquid
2	 **54b**	78	204-205 °C
3	 **54c**	0	
4	 **54d**	89	brown thick liquid
5	 **54e**	78	brown thick liquid
6	 **54f**	80	yellow liquid

[a] Reaction conditions: [1,2,4]triazolo[4,3-*a*]pyridine **53a** (1equiv.), diaryliodonium salt **47a-f** (1 equiv.) and $Cu(OTf)_2$ salt (5 mol%) were stirred in DCE (2 mL) for 3 h. [b] Isolated yield. NR = No reaction

Initially triazolium salt **54d** was obtained in 89% yield by using diaryliodonium salt **47d** with an electron-donating group (Me). Similarly, product **54e**, was prepared in 78% yield from diaryliodonium salt **47e** with an electron-deficient (Cl) group. This difference in product yield could be explained by the higher reactivity of diaryliodonium salt with electron-donating group over electron-deficient as described in previous reports.[4] Unsymmetrical diaryliodonium salt **47f** bearing ester group at *meta*-position, also afforded the desired **54f** in 80% yield. Next, we arylated 3-phenyl-[1,2,4]triazolo[4,3-*a*]pyridine **53b-e** using diverse diaryliodonium salts **47a-m** bearing different functionalities (Scheme 4.3.8). In the case of unsymmetrical diaryliodonium salts **47h-l** less sterically hindered aryl ring always transferred to the substrate **53b-e** while mesityl moiety acted as a dummy group. *o*-Nitro, ester, *meta*-methyl, dimethyl and di-fluorophenyl units were easily transferred to fused triazoles 3-phenyl-[1,2,4]triazolo[4,3-*a*]pyridine (**53b)** to prepare a variety of triazolium salts **54g-o** in 80-95% yields. Further, symmetrical [Mes-I-Mes] iodonium salt **47m** also afforded the corresponding mesityltriazolium salt (**54p**) in 84% yield. *N*-Heteroaryltriazoles bearing thienyl, furyl and pyridyl moieties were successfully arylated to afford the desired products **54q-s** in excellent yields (90-91%). In case of 3-(pyridin-2-yl)-[1,2,4]triazolo[4,3-*a*]pyridine (**53e**), diaryliodonium salt **47a** selectively quaternized the triazoles nitrogen instead of pyridine nitrogen to afford triazolium salt **54s** in 91% yield. It is worth mentioning that this protocol showed good compatibility towards diverse functional groups namely ester, methyl, methoxy, nitro and especially halogens (F, Cl, Br) which could be used in several organic synthetic transformations. Prepared triazolium salts **54g-s** were analyzed through their NMR (^{1}H & ^{13}C) and mass spectral data (Figures 4.3.8-4.3.10).

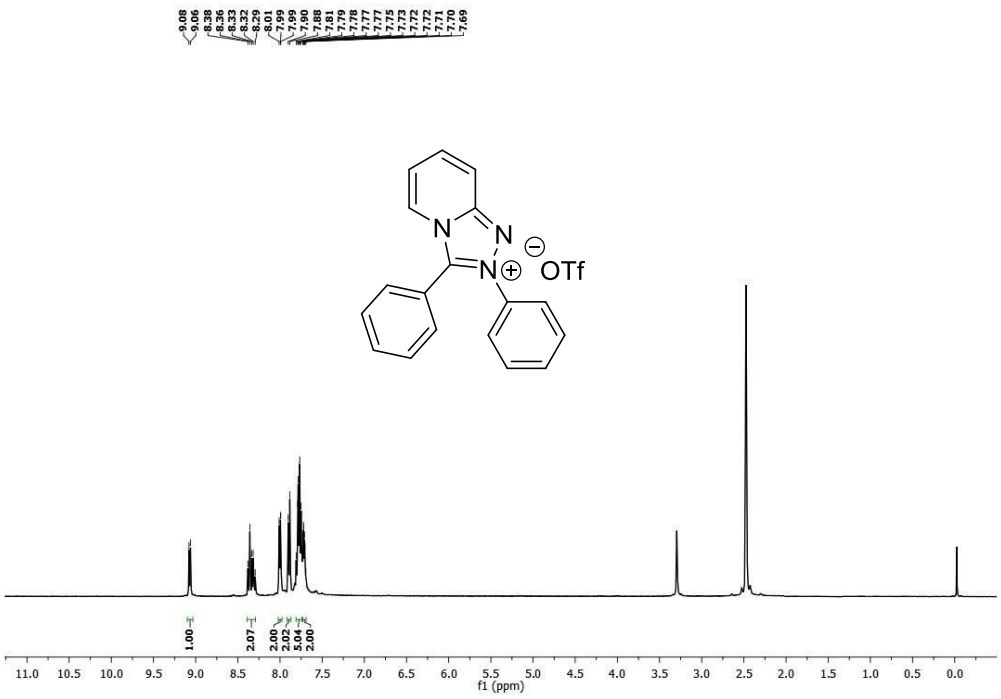


Figure 4.3.8 ^{1}H NMR spectrum of **54g**

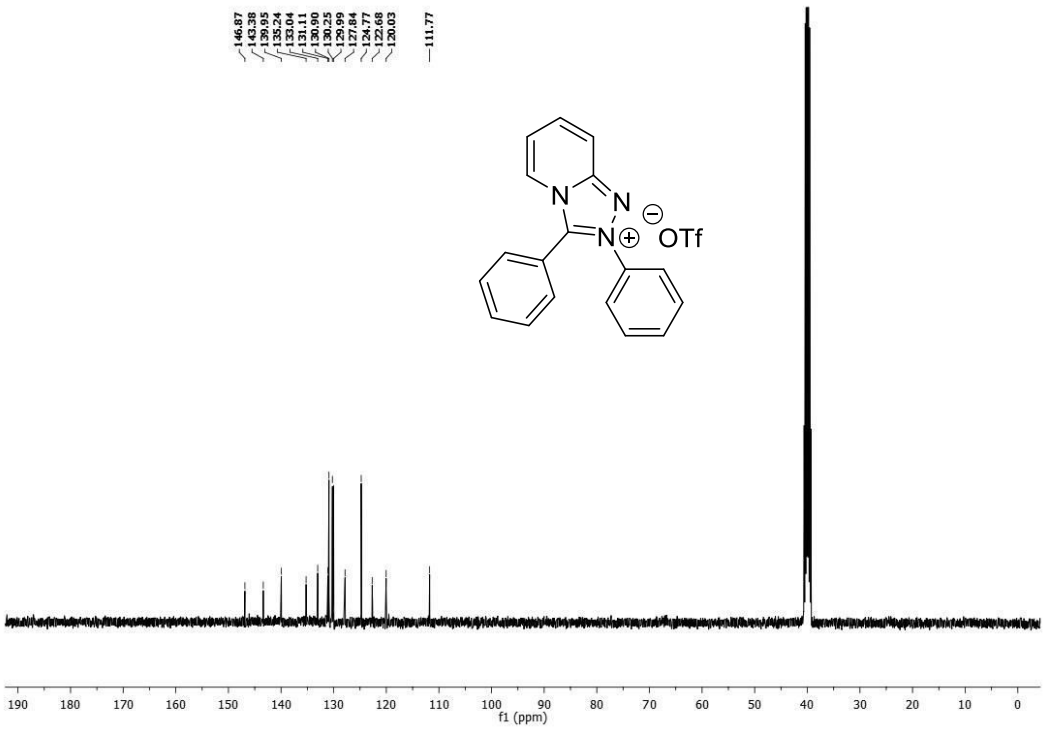


Figure 4.3.9 ^{13}C NMR spectrum of **54g**

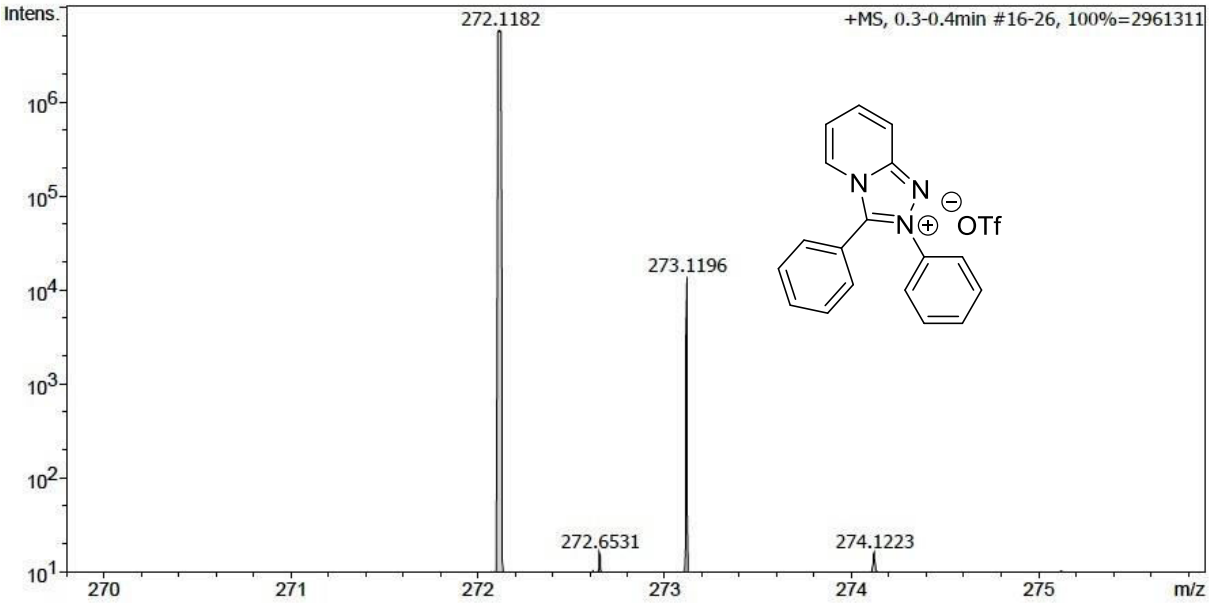
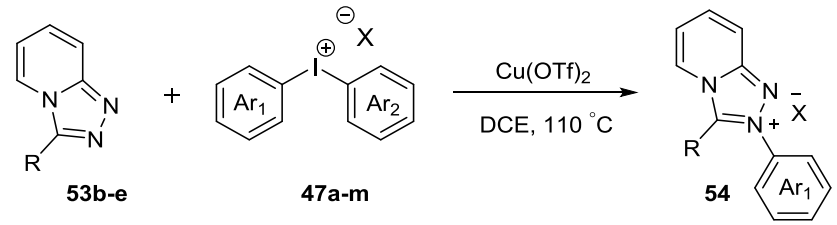


Figure 4.3.10 Mass spectrum of **54g**



Scheme 4.3.8 Arylation of [1,2,4]triazolo[4,3-a]pyridine **53b-e** using diaryliodonium salts

Used diaryliodonium salts:

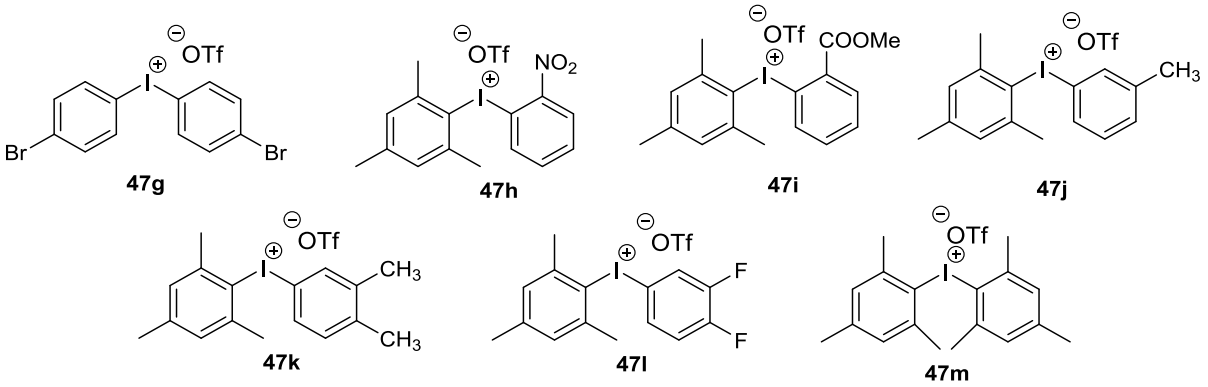
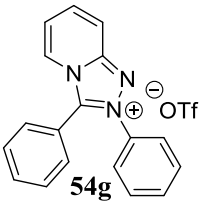
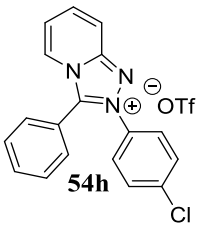
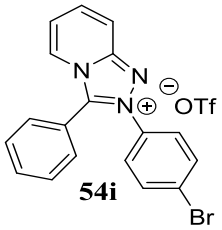
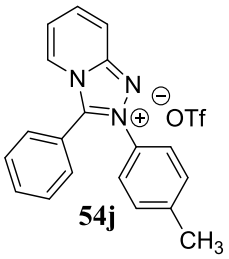
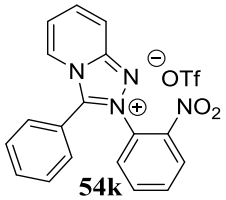
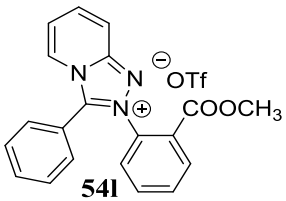
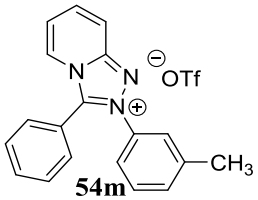
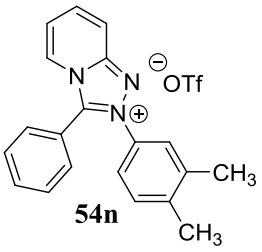
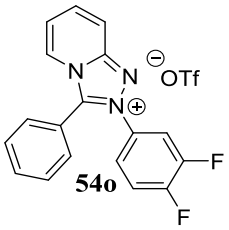
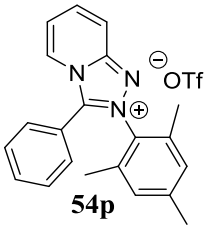
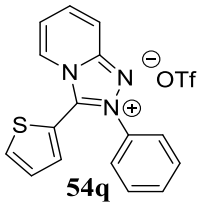
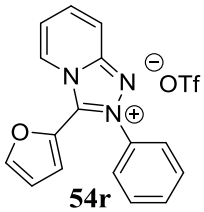
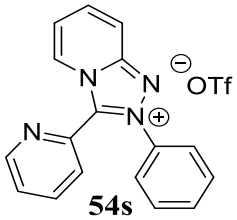


Table 4.3.3 Synthesized triazolium salts using diaryliodonium salts (**54g-s**)[a]

S.No.	Structure	Yields (%)[b]	Mp (°C)
1	 **54g**	95	138-139
2	 **54h**	85	brown liquid
3	 **54i**	85	brown liquid
4	 **54j**	90	203-204
5	 **54k**	89	209-210
6	 **54l**	90	140-141
7	 **54m**	90	130-131

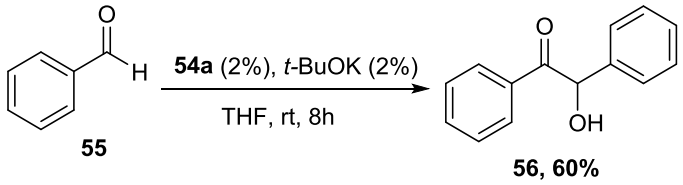
8	 **54n**	90	138-139
9	 **54o**	80	brown liquid
10	 **54p**	84	brown liquid
11	 **54q**	90	155-56
12	 **54r**	90	127-128
13	 **54s**	91	146-147

[a] Reaction conditions: [1,2,4]triazolo[4,3-*a*]pyridine **53b-e** (1equiv.), diaryliodonium salt **47a-m** (1 equiv.) and $Cu(OTf)_2$ salt (5 mol%) were stirred in DCE (2 mL) for 3 h. [b] Isolated yield. NR= No reaction

4.3.2.2 Synthetic application

To investigate the synthetic utility of this protocol, triazolium salt **54a** was further used as a precursor of *N*-heterocyclic carbene in a benzoin condensation reaction.

Initially, triazolium salt **54a** was treated with *t*-BuOK for the generation of *in situ* carbene, which converted benzaldehyde **55** into benzoin **56** as shown in Scheme 4.3.9.



Scheme 4.3.9 Triazolium salt **54a** catalysed Benzoin condensation

4.3.2.3 Proposed reaction mechanism

In view of literature findings[73] and results of present work, a plausible reaction mechanism for the formation of triazolium salts **54a-s** is depicted in Figure 4.3.11. Initially oxidative addition of diaryliodonium salt **47** to Cu(I) species generate highly reactive Cu(III)-aryl intermediate **I** with the release of iodobenzene. Further coordination of fused triazoles **53** to intermediate **I** facilitates the formation of intermediate **II**. Finally, reductive elimination of **II** delivered the product **54** with reforming the Cu(I) species for the cycle.

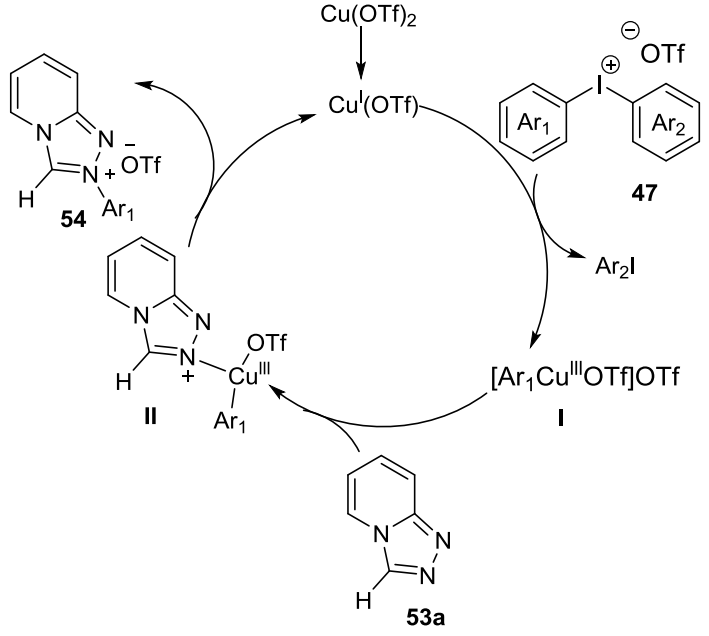


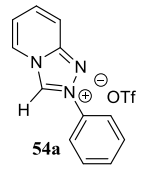
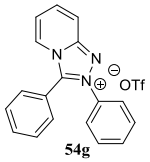
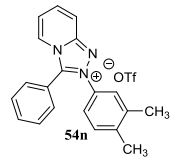
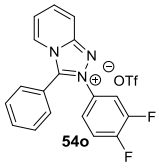
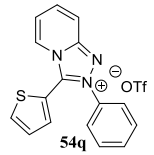
Figure 4.3.11 Plausible pathway for the formation of **54**

4.3.2.4 Photophysical properties

Photophysical properties of the synthesized triazolium salts have been systematically investigated and scantly discussed. In literature, the heteroleptic bis(tridentate) ruthenium(II) and other metal complexes comprised of a C, N, C-tridentate coordinating bis(triazolylidene)pyridine and 2,6-bis(1,2,3-triazol-4-yl)pyridine ligands are known to display interesting photochemical properties.[74] In view of the interesting photochemical properties of triazolium salts, some of the selected compounds such as **54a, 54g**, **54n**, **54o** and **54q** have been studied in representative homogeneous solvent systems like $CHCl_3$, acetonitrile, DMSO, methyl alcohol and water. The selected classes of compound represent varying electron density on the triazolium moiety due to different substitutions on the peripheral rings and the solvents were chosen to represent the variation in polarity, viscosity as well as hydrogen bond donation and acceptance ability. The results are summarized in Table 4.3.4 and compared with **54a** as a model system.

The principle absorption band of all the investigated compounds appear in the range of 290–330 nm in all the solvents ($\varepsilon = 0.6 - 1.0 \times 10^4$ M^{-1} cm^{-1}). Although the absorption spectral profile of a particular compound is insensitive to solvent properties, the electron donation and withdrawing nature of substituents in different derivatives has marked effect. The model compound **54a** shows well-shaped absorption peaking at ca. 290 nm; however, for the substituted derivatives (**54g**, **54n** and **54o**) the absorption is relatively broad with loss in spectral shape and red-shifted by about 10-15 nm in different cases. Interestingly, **54q** shows structured absorption with peaks at 260 and 290 nm (Figure 4.3.12). Excitation at the respective absorption band, all the compounds showed clean and unstructured fluorescence emission with 350-550 nm region (Figure 4.3.13). Substitution has very strong effect on emission spectral peak position.

Table 4.3.4 Summary of photophysical parameters of some selected triazolium salts (**54a, 54g**, **54n**, **54o** and **54q**) in different solvents[a]

	Solvents	λ_{abs}/nm	λ_{em}/nm	$\Delta\nu_{SS}$/cm^{-1}	ϕ_f	<τ>/ns	$\kappa_r/10^9 s^{-1}$	$\Sigma\kappa_{nr}/10^9 s^{-1}$
 54a	Acetonitrile	290	424	10898	0.19	1.9	0.10	0.42
	$CHCl_3$	294	413	9801	0.24	1.9	0.13	0.39
	DMSO	290	404	9730	1.2×10^{-3}	5.6	2.1×10^{-4}	0.18
	Methyl alcohol	292	427	10827	0.16	2.2	0.07	0.38
	Water	290	427	11064	0.12	1.6	0.07	0.54
 54g	Acetonitrile	300	426	9859	0.25	2.4	0.10	0.32
	$CHCl_3$	299	426	9971	0.19	1.7	0.11	0.47
	DMSO	304	430	9639	0.7×10^{-2}	1.4	5.0×10^{-3}	0.71
	Methyl alcohol	300	424	9748	0.22	1.1	0.20	0.69
	Water	297	426	10196	0.17	2.0	0.08	0.42
 54n	Acetonitrile	300	452	11209	0.34	3.8	0.09	0.17
	$CHCl_3$	300	452	11209	0.32	2.9	0.11	0.23
	DMSO	300	452	11209	1.9×10^{-2}	2.5	5.0×10^{-3}	0.40
	Methyl alcohol	300	452	11209	0.27	3.4	0.08	0.21
	Water	300	452	11209	0.14	1.3	0.11	0.67
 54o	Acetonitrile	295	421	10145	0.07	1.4	0.05	0.66
	$CHCl_3$	295	421	10145	0.19	1.5	0.13	0.54
	DMSO	295	396	8646	0.04	4.0	0.01	0.24
	Methyl alcohol	295	421	10145	0.17	1.6	0.11	0.51
	Water	295	421	10145	0.11	1.9	0.06	0.47
 54q	Acetonitrile	293	428	10765	0.08	1.0	0.08	0.95
	$CHCl_3$	295	428	10534	0.08	1.2	0.07	0.74
	DMSO	295	428	10534	0.4×10^{-2}	1.0	5.0×10^{-3}	1.01
	Methyl alcohol	294	428	10649	0.07	1.2	0.06	0.79
	Water	293	428	10765	0.06	2.0	0.03	0.46

[a] Absorption (λ_{abs}) and fluorescence emission (λ_{em}) maximum; Stokes shift ($\Delta\nu_{SS}$); Average fluorescence decay time ($<\tau> = \Sigma a_i\times\tau_i^2/\Sigma a_i\times\tau_i$, where a_i and τ_i represents pre-exponential factor and lifetime of i-th component, see table - S1for details); Fluorescence yield (ϕ_f); Radiative (κ_r) and total non-radiative ($\Sigma\kappa_{nr}$) decay rate constant.

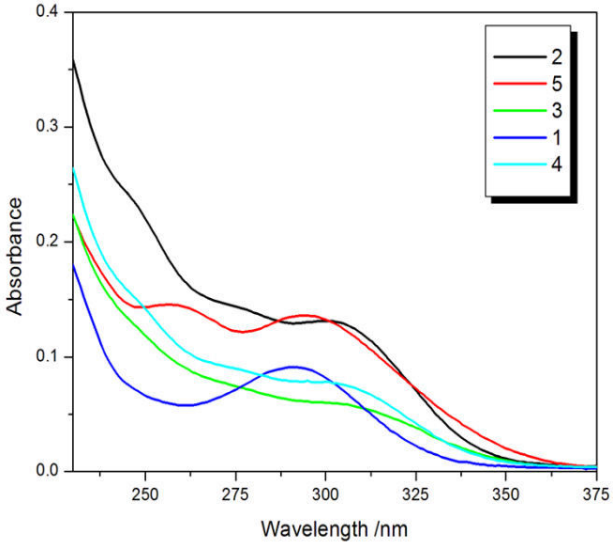


Figure 4.3.12 Steady state absorption spectra of the investigated systems in methanol. The number designation of the investigated compounds is as follows: **54a** (1), **54g** (2), **54n** (3), **54o** (4) and **54q** (5)

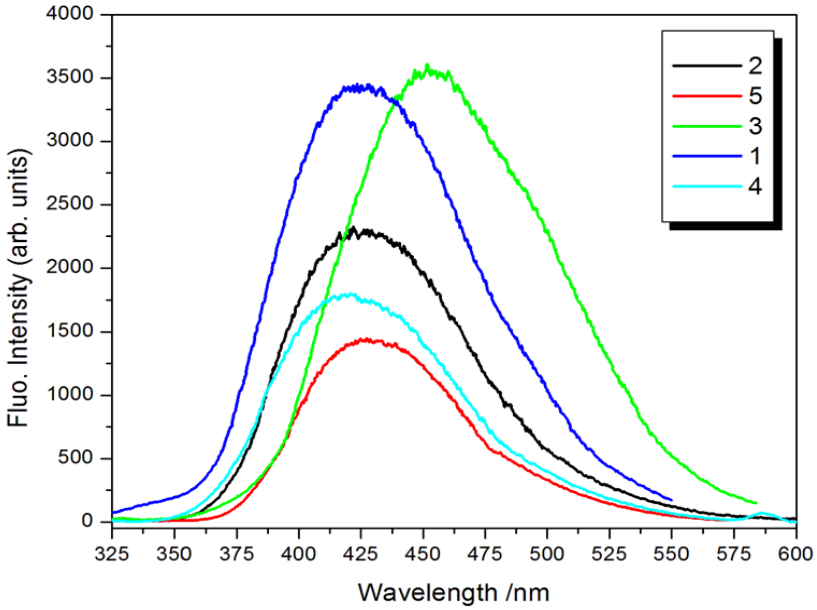


Figure 4.3.13 Steady state fluorescence emission spectra of the investigated systems in acetonitrile. The number designation of the investigated compounds is as follows: **54a** (1), **54g** (2), **54n** (3), **54o** (4) and **54q** (5)

For example, electron donating substation in **54n** caused the fluorescence emission to appear at ca. 454 nm in contrast to the other investigated systems showing fluorescence at 426 nm in methanol. Similar observation is also seen in other solvents as shown in Table 4.3.4**.** Interestingly all the compounds showed very large Stokes' shifted fluorescence emission.

Particularly, the highest Stokes shift for all the investigated systems in aqueous medium (ca. 11000 cm^{-1}), which eliminates the possibility of reabsorption, is promising for these class of compounds to be a precursor for biological as well as technological applications.[75]

Fluorescence quantum yields ((ϕ_f) of all the compounds were measured with respect to some standard following the procedure mentioned in the literature.[76] For all the systems, the quantum yield were found to be the lowest in DMSO, whereas, in aqueous medium the yield is moderate to high. The high value of molar absorptivity along with good fluorescence yield for these systems are indicative of $\pi \rightarrow \pi^*$ transition in molecular excitation process.[77] The extremely low fluorescence quantum yield in DMSO is rationalised on the basis of very inefficient radiative decay channel (see below).

Fluorescence decay behaviour of all these systems needs at least two exponential decay function to fit the experimental data adequately. A representative decay data along with the fitted parameter is shown in **Figure 4.3.14**.

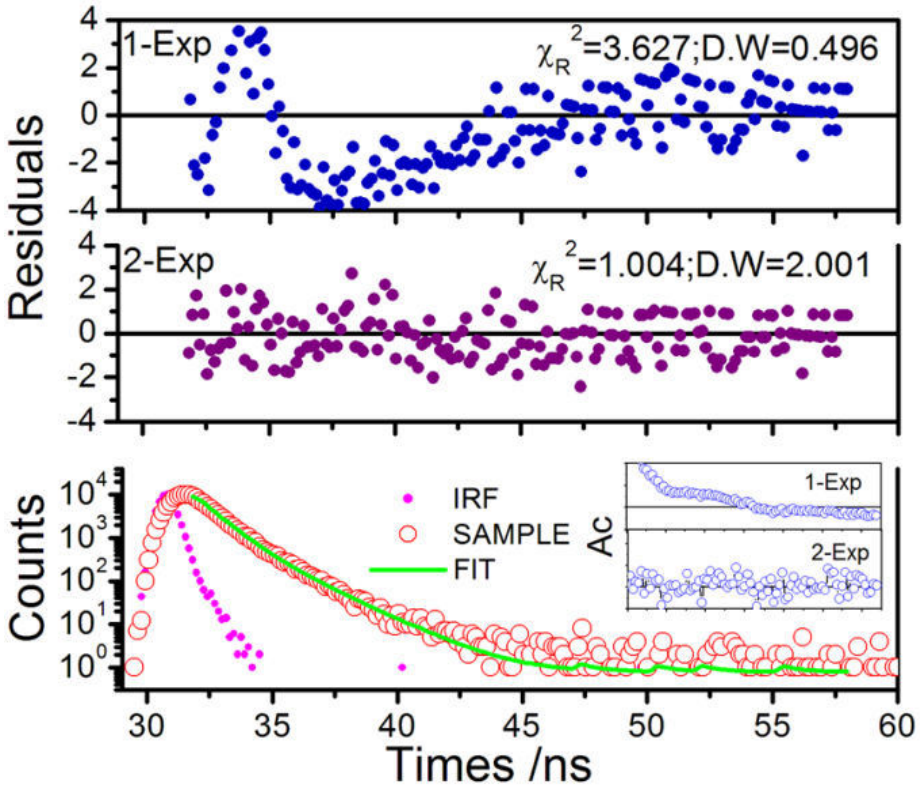


Figure 4.3.14 Time resolved fluorescence decay behavior of **54q** in chloroform along with the instrument response function (IRF). The fitted line is a deconvolution curve with 2-exp decay function. The comparative statistical parameters like reduced chi-square (χ_R^2), Durbin Watson (DW) parameter, distribution of weighted residuals (upper panels) and autocorrelation (Ac) function (inset) justifies the 2-exponential fitting model.

Interestingly, the contribution of the short decay component (τ_1 = 0.5 – 1.0 ns) is always very high and mostly contributes in the total fluorescence decay in comparison with the longer decay component (τ_2 > 2.0 ns). Nevertheless, the average fluorescence decay time (<τ>) and the kinetic parameters characterizing the excited state deactivation process, like radiative (κ_r) and total non-radiative ($\Sigma\kappa_{nr}$) decay rate constants were calculated with the following relations and listed in Table 4.3.4. The non-radiative rate is very high, particularly for the substituted derivatives in comparison with the model system and can be rationalized on the basis of free rotation of N–C single bond.

$$<\tau> = \frac{\sum a_i \times \tau_i^2}{\sum a_i \times \tau_i} \; ; \kappa_r = \frac{\phi_f}{<\tau>} \; ; \sum k_{nr} = \frac{1-\phi_f}{<\tau>} \qquad \text{-----[1]}$$

4.3.3 Conclusions

In conclusion, a rapid and efficient copper-catalyzed methodology has been developed to prepare a variety of triazolium salts from the reaction of fused triazoles and readily available diaryliodonium salts. In unsymmetrical diaryliodonium salts mesityl always act as a dummy group and less sterically hindered aryl ring transferred to the fused triazoles with concomitant release of iodomesitylene. In addition, the synthesized triazolium salts served as a precursor of NHCs and successfully utilized in benzoin condensation to prepare α-hydroxyketone. After the reaction, released iodoarenes were recovered and further reused in the preparation of diaryliodonium salts.This high-yielding, scalable, ligand and base-free protocol shows good compatibility towards various functional groups and complexity can be introduced to the molecule by further functionalization. Next, the photophysical properties and solvatochromism for selected group of compounds have been studied, which predicts the utility of this novel group of systems as biological stains and/or technological applications.

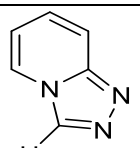
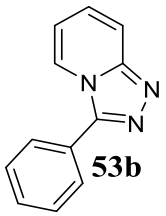
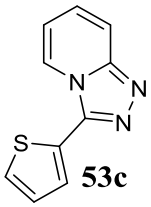
4.3.4 Experimental section

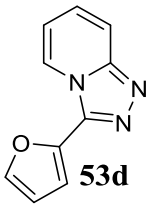
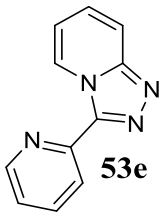
4.3.4.1 General materials and methods

Laboratory reagents were obtained commercially. Progress of the reaction was monitored by thin layer chromatography (TLC), which was performed on Merck pre-coated plates (silica gel 60, F_{254}, 0.25mm) and it was visualized by fluorescence quenching under hand-UV lamp

(254 nm). The column chromatography was performed using 60-120 mesh silica gel. All the reactions were performed in a CEM focused microwave oven at 100 Watt power. The solvents were evaporated using Buchi rotary evaporator. Melting points were determined using *E*-Z melting point apparatus and are uncorrected. NMR (^{1}H and ^{13}C) spectra were recorded using Bruker-Avance II (400 MHz). In ^{1}H NMR the coupling constants (*J*) were given in Hz, chemical shift (δ) in ppm. TMS was used as an internal standard. The proton multiplicities were described as: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet and m = multiplet. IR spectra are recorded on Shimadzu FT-IR spectrophotometer and are reported in wave numbers (cm^{-1}). Starting material fused triazoles (**53a-e**) and diaryliodonium salts[2] (**47a-m**) were prepared using literature reported methods.

General experimental procedure for [1,2,4]triazolo[4,3-*a*]pyridine (53a-e):[64b] Initally hydrazones **52** were prepared according to literature reported method in which pyridylhydrazine **51** (9.7 mmol) and corresponding aldehyde **24** (9.7 mmol) mixed in ethanol and refluxed for 1 h. Once starting materials were consumed then cooled the reaction mixture and filtered to obtain pure hydrazones (**52a-e**) in good yields. Further hydrazone **52** (5 mmol) was dissolved in DCM (10 mL) followed by the addition of IBD **20** (5 mmol) and the contents were stirred at room temperature for about 1 h. DCM was evapourated and crude product was recrystallized from ethanol to afford the pure product **53 a-e** in 70-80% yields.

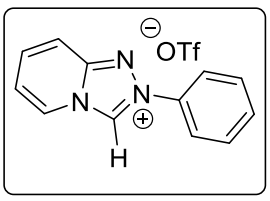
S.No.	[1,2,4]Triazolo[4,3-*a*]pyridines	Yield (%)	Mp (°C)
1	 **53a**	72	liquid
2	 **53b**	79	174-75 (Lit.[64b] 173-175)
3	 **53c**	80	168-169 (Lit.[60] 168-170)

4	 **53d**	75	131-132 (Lit.[78] 132-134)
5	 **53e**	70	130-131(Lit.[60] 129-131)

General experimental procedure for diaryliodonium triflate (47a-m): Diaryliodonium salts used for the arylation of fused triazoles were synthesized according to literature reported methods as detailed in section 3.4 of chapter 3.

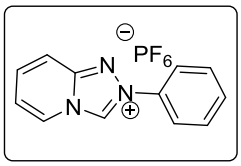
General experimental procedure for the synthesis of triazolium salts (54a-s): A dried round bottom flask was charged with triazolopyridine **53** (1.0 equiv), 5% of $Cu(OTf)_2$ and diaryliodonium salt **47** (1.0 equiv) in DCE (2 mL). The reaction mixture was stirred at 110 ^{o}C for 3 h in an oil bath. Progress of the reaction was monitored by checking TLC. After completion, reaction mixture was cool down to room temperature and DCE was removed under reduced pressure. The residue so obtained was passed through a column chromatography using dichloromethane/methanol (8:2, v/v) as an eluent to afford pure triazolium salt **54a-s** in 78-95% yields.

2-Phenyl-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethanesulfonate (54a)



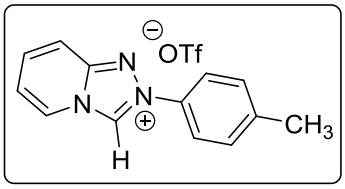
Brown thick liquid (137 mg, 95%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 9.12 (d, J = 6.8 Hz, 1H), 8.44–8.14 (m, 2H), 7.85 (d, J = 7.9 Hz, 2H), 7.81–7.60 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.5, 140.0, 137. 9, 135.5, 130.9, 130.8, 128.9, 124.7, 119.6, 111.6; ESI-MS $[M–OTf^{-}]^{+}$ calcd for $C_{12}H_{10}N_3$, 196.09; found, 196.05.

2-Phenyl-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium hexafluorophosphate (54b)



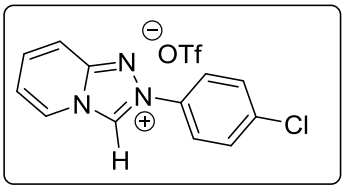
Off white solid (111 mg, 78%); mp 204-205 °C (lit.[54] mp 203-205 °C)

2-(*p*-Tolyl)-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethanesulfonate (54d)



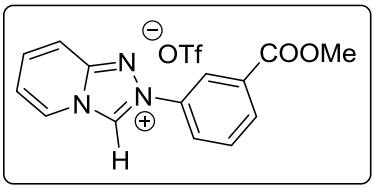
Brown thick liquid (134 mg, 89%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.11 (d, J = 6.8 Hz, 1H), 8.26 (d, J = 2.2 Hz, 2H), 7.72 (dd, J = 8.7, 2.2 Hz, 3H), 7.55 (d, J = 5.9 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)) δ 142.4, 140.9, 139.8, 137.8, 132.9, 131.1, 128.9, 124.6, 119.5, 111.5, 21.4.

2-(4-Chlorophenyl)-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethanesulfonate (54e)



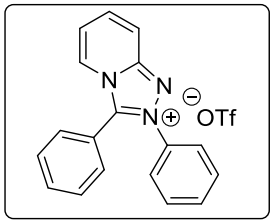
Brown thick liquid (124 mg, 78%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 9.13 (d, J = 6.8 Hz, 1H), 8.55–8.15 (m, 2H), 7.92–7.81 (m, 4H), 7.79-7.75 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.6, 140.1, 138.0, 135.5, 134.1, 130.8, 129.0, 126.7, 119.7, 111.6.

2-(3-(Methoxycarbonyl)phenyl)-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethanesulfonate (54f)



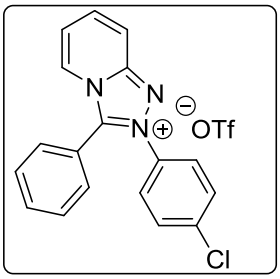
Yellow liquid (135 mg, 80%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 9.15 (d, J = 6.8 Hz, 1H), 8.41–8.30 (m, 4H), 8.29–8.22 (m, 1H), 8.16-8.13 (m, 1H), 7.98–7.88 (m, 1H), 7.85–7.74 (m, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.5, 142.8, 140.3, 138.1, 135.7, 132.0, 131.5, 131.3, 129.5, 129.0, 125.5, 119.7, 111.6, 53.6.

2,3-Diphenyl-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethanesulfonate (54g)



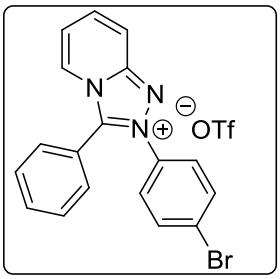
Brown solid (102 mg, 95%); mp 138-139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (d, J = 7.0 Hz, 1H), 8.38-8.29 (m, 2H), 8.01–7.99 (m, 2H), 7.89 (d, J = 7.4 Hz, 2H), 7.81-7.75 (m, 5H), 7.73–7.69 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.9, 143.4, 139.9, 135.2, 133.0, 131.1, 130.9, 130.2, 130.0, 127.8, 124.8, 122.7, 120.0, 111.7; HRMS (ESI) $[M–OTf^-]^+$ *m/z* calcd for $C_{18}H_{14}N_3$, 272.1188; found, 271.1182.

2-(4-Chlorophenyl)-3-phenyl-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethane Sulfonate (54h)



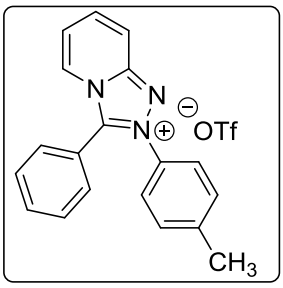
Brown liquid (99 mg, 85%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (d, J = 6.9 Hz, 1H), 8.46–8.31 (m, 2H), 8.03 (d, J = 6.9 Hz, 2H), 7.95 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.7 Hz, 2H), 7.79-7.75 (m, 4H); ^{13}C NMR (100 MHz, DMSO) δ 147.0, 143.6, 140.1, 135.6, 134.1, 133.0, 130.9, 130.2, 130.0, 127.9, 126.8, 122.5, 120.1, 111.7.

2-(4-Bromophenyl)-3-phenyl-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethane sulfonate (54i)



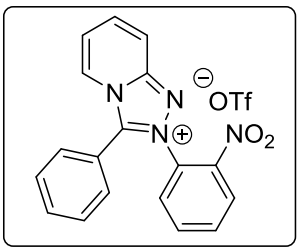
Brown liquid (108 mg, 85%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (d, J = 6.6 Hz, 1H), 8.62–8.26 (m, 2H), 8.01 (t, J = 6.7 Hz, 4H), 7.88 (d, J = 8.4 Hz, 2H), 7.84-7.74 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.5, 140.1, 134.5, 133.9, 133.1, 130.3, 130.0, 127.8, 126.8, 124.2, 122.5, 120.1, 111.7.

3-Phenyl-2-(p-tolyl)-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethanesulfonate (54j)



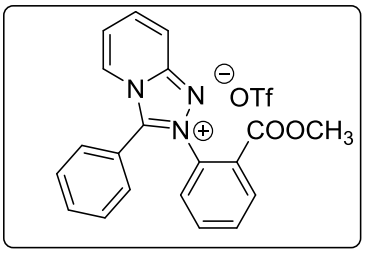
Off-white solid (100 mg, 90%); mp 203-204 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (d, J = 6.9 Hz, 1H), 8.36-8.30 (m, 2H), 8.02 (d, J = 6.9 Hz, 2H), 7.88–7.69 (m, 6H), 7.59 (d, J = 8.1 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.7, 143.3, 141.1, 139.8, 133.0, 132.8, 131.2, 130.2, 130.03, 127.76, 124.66, 122.74, 119.90, 111.68, 21.30.

2-(2-Nitrophenyl)-3-phenyl-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethane sulfonate (54k)



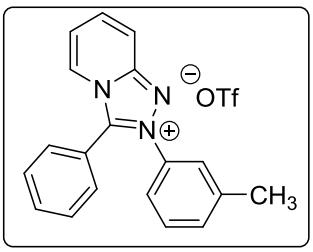
Off-white solid (106 mg, 89%); 209-210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (d, J = 6.9 Hz, 1H), 8.53 (d, J = 7.8 Hz, 1H), 8.49 – 8.42 (m, 1H), 8.37 (d, J = 7.8 Hz, 1H), 8.19 (t, J = 7.3 Hz, 1H), 8.11-8.08 (m, 2H), 8.05 (d, J = 7.0 Hz, 2H), 7.85-7.77 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.5, 144.7, 141.1, 136.4, 133.9, 133.3, 130.4, 130.3, 130.1, 128.6, 127.4, 127.3, 122.2, 120.4, 111.4.

2-(2-(Methoxycarbonyl)phenyl)-3-phenyl-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethanesulfonate (54l)



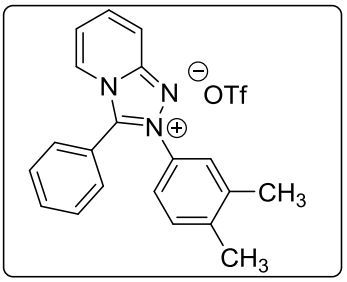
White solid (110 mg, 90%); mp 140-141 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (d, J = 6.9 Hz, 1H), 8.38 – 8.32 (m, 1H), 8.29 (d, J = 7.7 Hz, 1H), 8.17 (d, J = 9.2 Hz, 1H), 8.09 – 8.04 (m, 3H), 7.97-7.94 (m, 2H), 7.84-7.77 (m, 4H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.6, 146.7, 144.6, 140.3, 135.2, 133.4, 133.2, 132.6, 130.3, 129.9, 129.6, 128.1, 127.5, 122.3, 120.1, 111.4, 53.5.

3-Phenyl-2-(*m*-tolyl)-[1,2,4]triazolo[4,3-*a*]pyridin-2-iumtrifluoromethanesulfonate (54m)



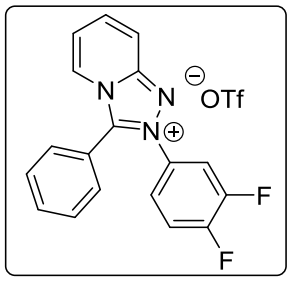
White solid (105 mg, 90%); mp 130-131 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (d, J = 6.9 Hz, 1H), 8.43 (d, J = 9.3 Hz, 1H), 8.36-8.32 (m, 1H), 8.04 (d, J = 6.6 Hz, 2H), 7.87 – 7.77 (m, 3H), 7.75-7.66 (m, 4H), 7.55 (d, J = 7.3 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.8, 143.3, 140.8, 139.9, 135.2, 133.0, 131.7, 130.6, 130.2, 130.0, 127.8, 124.9, 122.7, 121.8, 120.0, 111.8, 21.3; ESI-MS [M–OTf $^{-}$]$^{+}$ *m/z* calcd for $C_{19}H_{16}N_3$, 286.13; found, 286.05.

2-(3,4-Dimethylphenyl)-3-phenyl-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethane sulfonate (54n)



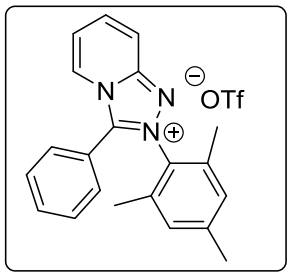
Light brown solid (103 mg, 90%); mp 138-139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (d, J = 6.9 Hz, 1H), 8.40 – 8.27 (m, 2H), 8.02 (d, J = 6.5 Hz, 2H), 7.84 – 7.76 (m, 3H), 7.76 – 7.70 (m, 1H), 7.68 (s, 1H), 7.64-7.62 (m, 1H), 7.54 (d, J = 8.2 Hz, 1H), 2.40 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.7, 143.2, 139.9, 139.7, 139.5, 132.9, 131.5, 130.2, 130.0, 127.7, 125.2, 122.7, 121.9, 119.9, 111.8, 19.9, 19.7.

2-(3,4-Difluorophenyl)-3-phenyl-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethane sulfonate (54o)



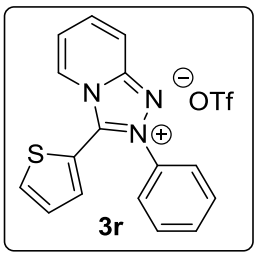
Brown liquid (93 mg, 80%); ^{1}H NMR (400 MHz, DMSO-d_6)) δ 9.13 (d, J = 6.9 Hz, 1H), 8.47 (d, J = 9.2 Hz, 1H), 8.44 – 8.36 (m, 1H), 8.17 – 8.10 (m, 1H), 8.04 (d, J = 7.0 Hz, 2H), 7.91 (d, J = 9.2 Hz, 1H), 7.87 – 7.76 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.9, 143.7, 140.3, 136.7, 133.1, 130.2, 130.0, 127.8, 122.7, 122.5, 120.3, 119.9, 119.6, 115.6, 115.4, 111.7; ESI-MS [M–OTf $^-$]$^+$ *m/z* calcd for $C_{18}H_{12}F_2N_3$, 308.10; found, 308.05.

2-Mesityl-3-phenyl-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethanesulfonate (54p)



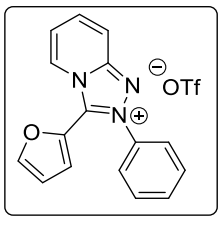
Brown liquid (99 mg, 84%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.39 – 8.24 (m, 1H), 8.08 (d, J = 6.4 Hz, 2H), 7.88 (d, J = 8.2 Hz, 1H), 7.85 – 7.73 (m, 4H), 7.25 (s, 2H), 2.41 (s, 3H), 2.08 (s, 6H);. ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.5, 144.0, 141.9, 140.4, 136.7, 132.8, 130.2, 130.0, 129.7, 128.5, 123.0, 119.7, 110.6, 21.4, 17.5.

2-Phenyl-3-(thiophen-2-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium trifluoromethane Sulfonate (54q)



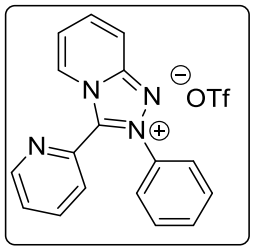
Brown solid (98 mg, 90%); mp 155-56 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (d, J = 6.9 Hz, 1H), 8.39-8.82 (m, 2H), 8.24-8.19 (m, 2H), 7.89 (d, J = 7.4 Hz, 2H), 7.83-7.74 (m, 4H), 7.53 – 7.51 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.5, 142.4, 139.9, 135.0, 133.3, 132.6, 131.2, 130.9, 129.6, 128.0, 124.9, 122.6, 120.2, 111.9; ESI-MS [M–OTf $^-$]$^+$ calcd for $C_{16}H_{12}N_3S$, 278.07; found, 278.00.

3-(Furan-2-yl)-2-phenyl-[1,2,4]triazolo[4,3-*a*]pyridin-2-iumtrifluoromethanesulfonate (54r)



Brown solid (94 mg, 90%); mp 127-128 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (d, J = 6.4 Hz, 1H), 8.39-8.31 (m, 3H), 7.89-7.75 (m, 7H), 7.03 (d, J = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 148.2, 143.2, 140.0, 138.9, 138.2, 135.1, 131.3, 130.9, 128.4, 124.9, 120.3, 116.6, 113.5, 111.9.

2-Phenyl-3-(pyridin-2-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-2-iumtrifluoromethanesulfonate (54s)



Dark brown solid (98 mg, 91%); mp 146-147 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (d, J = 7.0 Hz, 1H), 8.99 (d, J = 4.3 Hz, 1H), 8.48 (d, J = 7.9 Hz, 1H), 8.44 – 8.35 (m, 2H), 8.24 (t, J = 7.8 Hz, 1H), 7.94 (d, J = 7.4 Hz, 2H), 7.91 – 7.85 (m, 1H), 7.85 – 7.75 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.3, 144.8, 144.1, 143.3, 140.0, 139.3, 135.2, 131.4, 130.9, 130.2, 127.3, 125.1, 124.4, 120.3, 111.8.

General experimental procedure for benzoin condensation (synthesis of α-hydroxyketones):

A 10 mL dried round-bottomed flask was charged with the triazolium salt **54a** (6.5 mg, 0.0188 mmol) in 2 mL of dry THF at room temperature followed by the addition of *t*-BuOK (2.6 mg, 0.0188 mmol). The traction mixture was stirred for 15 min, then benzaldehyde **55** (100 mg, 0.943 mmol) was added. The stirring was continued at room temperature for another 8 h. Thereafter, reaction mixture was poured into water and extracted with ethylacetate. The organic layer was evaporated and crude product so obtained was passed through a column chromatography using hexane/ethylacetate (9:1, v/v) as an eluent to afford pure α-hydroxy ketone **56** in 60% yield.

4.3.5 References

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CHAPTER 5

Conclusions

5.1 General conclusions

The thesis is mainly focused on utilization of organoiodine reagents in the development of facile and efficient synthetic protocols for the construction of 1,3,4-oxadiazoles (α-keto-1,3,4-oxadiazoles and 2-arylamino-1,3,4-oxadiazoles), aryl heterocycles (oxadiazoles, thiadiazoles, benzoxazoles and benzothiazoles) and functionalization of azaheterocycles *via* formation of C-N bond.

The **first chapter** of thesis, briefly describe structures and properties of organoiodine reagents. Up-to-date applications of organoiodine reagents, especially in the preparation of diverse natural and synthetic bioactive heterocycles have also been discussed in this chapter.

The **second chapter** highlights utilization of organoiodine reagents for the synthesis of two different series of 1,3,4-oxadiazoles. **Part A** of this chapter reports a facile and one-pot procedure for the synthesis of α-keto-1,3,4-oxadiazoles and *α*-keto-1,2,4-triazolo[4,3-*a*]pyridines starting from readily available arylglyoxals and hydrazides *via* IBX-TEAB mediated oxidative cyclization of *in-situ* generated hydrazide-hydrazones. This developed methodology provides a greener, efficient and scalable alternate route to access analogues of bioactive α-keto-1,3,4-oxadiazoles and *α*-keto-1,2,4-triazolo[4,3-*a*]pyridines in excellent yields. **Part B** of this chapter includes one-pot and solvent-free protocol for the synthesis of 2-arylamino-1,3,4-oxadiazoles from easily accessible starting materials. The methodology involves desulfurization of *in situ* generated thiosemicarbazide by neat grinding with relatively benign iodobenzene diacetate at room temperature. The developed protocol provides an easy access to biologically important 2-arylamino-1,3,4-oxadiazoles by avoiding toxic and corrosive reagents and halogenated solvents.

The **third chapter** of thesis deals with the development of a facile, high yielding, scalable and ligand-free copper-catalyzed direct C-H arylation protocol enabling to achieve a diverse class of bioactive azaheterocycles, namely aryloxadiazoles, arylthiadiazoles, arylbenzoxazoles and arylbenzothiazoles by employing readily accessible diaryliodonium salts. This simple protocol offers many advantages including shorter reaction times, milder reaction conditions, wider substrate scope and high product yield. Using this methodology, arylmesityl iodonium salts were

effectively utilized to prepare arylated azaheterocycles in high yields. Further, the copper-catalyzed arylation of diverse azoles was utilized to prepare various useful ESIPT (Excited-state intramolecular proton-transfer) fluorescence and chelating agents including 2-(4'-methoxyphenyl)benzoxazole, 2-(2'-methoxyphenyl)-benzoxazole and 2-(2'-methoxy-phenyl)-benzothiazole, analogues of anticancer agents 2,5-diaryl-1,3,4-oxadiazoles and methyl ester of Tafamidis. Further, the developed protocol was extended for the gram scale synthesis of 2,5-diphenyl-1,3,4-oxadiazole.

Chapter four illustrates the formation of C-N bond leading to the functionalization of diverse azaheterocycles, is divided into two parts. **Part A** describes the ligand-free MW-assisted a new synthetic approach for the *N*-benzylation of diverse heteroarylamines. This operationally simple and efficient protocol involves the use of readily available *N*-tosylhydrazones which are easily prepared from the reaction of tosylhydrazines and the corresponding aldehyde or ketone. The protocol is widely applicable to access a range of *N*-benzylaminoheterocycles. **Part B** illustrates a rapid and efficient copper-catalyzed methodology to prepare a variety of triazolium salts from the reaction of fused triazoles and readily available diaryliodonium salts. In unsymmetrical diaryliodonium salts, mesityl always act as a dummy group and less sterically hindered aryl ring is transferred to the fused triazoles with concomitant release of iodomesitylene. In addition, prepared triazolium salts served as a precursor of *N*-heterocyclic carbenes (NHCs) and successfully utilized in benzoin condensation to prepare α-hydroxyketones. After the reaction, released iodoarenes were recovered and reused in the preparation of diaryliodonium salts. This high-yielding, scalable, ligand and base-free protocol shows good compatibility towards various functional groups. Next, the photophysical properties and solvatochromism for selected group of compounds have been studied, which predicts the utility of this novel group of systems as biological stains and/or technological applications.

5.2 Future scope of the research work

In last two decades organoiodine reagents received much attention of chemists is mainly due to their useful oxidizing properties, combined with their benign environmental character and commercial availability. Iodine(III) and iodine(V) derivatives are now routinely used in organic synthesis as reagents for various selective oxidative transformations of complex organic

molecules. Diaryliodonium salts are well renowned for their powerful electrophilic arylating behaviour. They have been used as aryl coupling partners for diverse range of alkenes, alkynes and heterocycles under metal and metal-free reaction conditions.

The scope of this thesis is to utilization of organoiodine reagents in the construction of various bioactive azaheterocycles. The developed protocols for the preparation of azaheterocycles can be extended to prepare various drug like molecules and also, design of metal-free or transition-metal-catalyzed reactions by utilizing organoiodine reagents to access novel bioactive heterocycles.

Appendices

List of publications *[A-1]*

1. **Meenakshi Pilania**, V. Arun, M. P. Tantak, Dalip Kumar, "Cu-catalyzed expeditious synthesis of *N*-benzylaminoheterocycles using *N*-tosylhydrazones and aminohetero-roarenes" ***ChemistrySelect, 2016****, 1, 6368.*

2. Dalip Kumar, **Meenakshi Pilania**, V. Arun, Savita Pooniya, "C-H arylation of azaheterocycles: A direct ligand-free and Cu-catalyzed approach using diaryliodonium salts" ***Organic and Biomolecular Chemistry, 2014****, 12, 6340.*

3. Dalip Kumar, **Meenakshi Pilania**, V.Arun, Bhupendra Mishra, "A facile and expeditious one-pot synthesis of α-keto-1,3,4-oxadiazoles" ***Synlett, 2014****, 1137.*

4. Dalip Kumar, V.Arun, **Meenakshi Pilania**, Manish K Mehra and Santosh B Khandagale, "Diaryliodonium salts: Emerging reagents for arylations and heterocycles synthesis" ***Chemistry Biology Interface 2016****, 6, 270 (review).*

5. Dalip Kumar, V.Arun, **Meenakshi Pilania**, N. Maruthi Kumar, "Organohypervalent iodine reagents in the synthesis of bioactive heterocycles" ***(Chapter 14), Elsevier, 2014*** *(book chapter)*

6. V.Arun, **Meenakshi Pilania**, Dalip Kumar, "An access to 2-arylindoles via decarboxylative C-C coupling in aqueous medium ligand and base-free access to diverse biaryls by the reductive coupling of diaryliodonium salts" ***Chemistry-An Asian Journal, 2016,*** *11, 3345.*

7. V.Arun, P.O.Venkataramana reddy, **Meenakshi Pilania**, Dalip Kumar, "Ligand and base-free access to diverse biaryls by the reductive coupling of diaryliodonium salts" ***European Journal Organic Chemistry, 2016****, 2096.*

8. Dalip Kumar, V.Arun, **Meenakshi Pilania**, K. P. Chandra Shekar, "A metal-free and microwave-assisted efficient synthesis of diaryl sulfones" ***Synlett, 2013****, 831.*

List of papers presented in conferences *[A-2]*

1. **Meenakshi Pilania** and Dalip Kumar, "An efficient synthesis of *N*-heterocyclic carbene precursor triazolium salts using diaryliodonium salts" at National Conference on **"Organic Chemistry in sustainable Development: Recent Advances and Future Challenges (OCSD 2016)**" Organized by Department of Chemistry, BITS Pilani, Pilani Campus, India, **August 29-30, 2016.**
2. **Meenakshi Pilania** and Dalip Kumar, "Copper-catalyzed cross-coupling of *N*-tosylhydrazones and aminoheteroarenes: A direct and efficient synthesis of useful *N*-Benzylatedamino-heterocycles" at International Conference on "**Current Challenges in Drug Discovery Research (CCDDR 2015)"** Organized by Department of Chemistry, Malaviya National Institute of Technology, Jaipur, India, **November 23-25, 2015.**
3. **Meenakshi Pilania** and Dalip Kumar "Copper-catalyzed cross-coupling of *N*-tosylhydrazones and aminoheteroarenes: A direct and efficient synthesis of useful *N*-benzylated aminoheterocycles" at "**International Conference on Nascent Developments in Chemical Sciences: Opportunities for Academia-Industry Collaboration (NDSC 2015)"** Organized by Department of Chemistry, BITS Pilani, Pilani Campus, India, **October 16-18, 2015.**
4. **Meenakshi Pilani**a and Dalip Kumar "Cu-catalyzed coupling of *N*-tosylhydrazones with various amino heterocycles: Synthesis of *N*-benzylaminoheterocycles" at 21st ISCB International Conference (ISCBC-2015) on "**Current Trends in Drug Discovery and Developments"** Organized by Department of Chemistry, Central Drug Research Institute, Lucknow, India, **February 25-28, 2015.**
5. **Meenakshi Pilania**, V. Arun, Savita Poonia and Dalip Kumar "Copper-catalyzed direct C-H arylation of azaheterocycles using diaryliodonium salts" at **"National Conference On "Emerging Areas in Chemical Education & Research and National Convention of Chemistry Teachers (NCCT) 2014"** Organized by Department of Chemistry, IIS University, Jaipur, **October 16-18, 2014.**
6. **Meenakshi Pilania,** V. Arun and Dalip Kumar, "Copper-catalyzed direct C-H arylation of azaheterocycles using diaryliodonium salts" at **"International Symposium on Recent Advances in Medicinal Chemistry"** Organized by National

Institute of Pharmaceutical Education & Research (NIPER) S.A.S.Nagar, Punjab, India, **September 8-10, 2014.**

7. **Meenakshi Pilania**, V.Arun, Bhupendra Mishra and Dalip Kumar "A rapid and facile synthesis of α-keto-1,3,4-oxadiazoles" at "**20th ISCB International Conference on "Chemistry and Medicinal Plants in Translational Medicine for Healthcare**" Organized by University of Delhi, India, **March 1-4, 2014.**
8. **Meenakshi Pilania**, V.Arun, Bhupendra Mishra and Dalip Kumar "Organo hypervalent iodine promoted synthesis of bioactive α-keto-1,3,4-oxadiazoles" at "**National Conference on Recent Developments in Chemical Sciences**" Organized by Guru Jambheswar University, Hisar , Haryana, India, **February 25-26, 2014.**

9. Dalip Kumar, **Meenakshi Pilania** and N. Maruthi Kumar "Iodobenzene diacetate-mediated synthesis of 2-arylamino-1,3,4-oxadiazoles" at "**19th International ISCB Conference on Recent advances and current trends in Chemical and Biological Sciences**" Organized by Mohanlal Sukhadia University, Udaipur, Rajasthan, India, **March 2-5, 2013.**

BRIEF BIOGRAPHY OF THE CANDIDATE [A-3]

Ms. Meenakshi Pilania born in Jaipur, Rajasthan, India. She pursued her Bachelor of Science from Maharani's college, Jaipur with first class distinction in 2007. Then she did her Master degree in organic chemistry from Department of Chemistry, Rajasthan University, Jaipur in 2010. In December 2010, she qualified CSIR-JRF (AIR-106). In August 2011, she joined Department of Chemistry, BITS Pilani as junior research fellow in Ph.D program under the supervision of Prof. Dalip Kumar. Subsequently, in 2013 she promoted to senior research fellow. During the Ph.D tenure, she has presented (oral/poster) her research work in various national and international conferences. She has published research articles in journal of international repute.

BRIEF BIOGRAPHY OF THE SUPERVISOR [A-4]

Dr. Dalip Kumar is a Professor of Chemistry at Department of Chemistry, Birla Institute of Technology and Science, Pilani. He received his Ph.D degree from Kurukshetra University, Kurukshetra, Haryana in 1997. For his doctoral degree, he worked with Prof. Shiv P. Singh in the research area of heterocyclic chemistry. After his doctorate, he worked as a post-doctoral fellow (1997-1999) with Prof. Rajender S. Varma at Sam Houston State University, TX, USA. He was also associated with Prof. Sean M. Kerwin as a post-doctoral fellow (1999-2000), College of Pharmacy, University of Texas at Austin, TX, USA. He joined BITS Pilani, Pilani campus, as a lecturer during 2000-2002. Later, in December 2002, he moved to University of Maryland, College Park, MD, USA as a Research Associate. In 2004, Prof. Kumar rejoined BITS Pilani, Pilani campus, as an Assistant Professor, at Department of Chemistry and since then he is continuing there. He was promoted to professor in year 2012. He has been involved in research for the last 20 years and in teaching for 13 years. As a result of his research accomplishment, he has around 120 international publications in peer reviewed journals. Prof. Kumar has guided six Ph.D students and currently he is supervising six Ph.D. students. He has one US patent, one Indian patent and handled several projects from DST, DRDO, UGC, CSIR and DBT. Currently, he has one DST-JSPS Indo-Japan project and a collaborative industrial project from Ranbaxy Research Laboratory Ltd.

Prof. Kumar is recipient of Honorary Diploma for Scientific Achievements and International Scientific Collaboration by Russian International Charitable Foundation “Scientific Partnership”, Moscow, Russia (March 2013). He received the Prof. R. D. Desai 80th Birthday Commemoration Medal and Prize from Indian Chemical Society for year 2015. He is an Associate Editor of Chemistry & Biology Interface Journal published by Indian Society of Chemists and Biologists, Lucknow. Prof. Kumar is life members of Indian Chemical Society, Indian Society of Chemists and Biologists, and Indian Council of Chemists. His current research pursuit is focused on synthesis of indole and porphyrin derived potential anticancer agents by employing transition-metals and organoiodine reagents.