Thesis

By Alam Toufique

Organic C-X (X = N & O) Bond Synthesis Using Organo-Iodine Reagents

By

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DECLARATION

I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree / diploma at this or any other Institution / University.

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List of Publications arising from the thesis

Journal Published

[#]1. **Alam, M. T.**; Maiti, S.; Mal, P. An Intramolecular C(sp2)–H Amidation Using *N*-Iodosuccinimide, *Eur. J. Org. Chem.* **2018**, 4178-4186.

[#]2. **Alam, M. T.**; Maiti, S.; Mal, P. The mechanochemical synthesis of quinazolin-4(3*H*)-ones by controlling the reactivity of IBX, *Beilstein J. Org. Chem.* **2018**, *14*, 2396-2403.

[#]3. Maiti, S.; **Alam, M. T.**; Mal, P. Soft–Hard Acid–Base-Controlled C-H Trifluoroethoxylation and Trideuteriomethoxylation of Anilides, *Asian J. Org. Chem.* **2018**, 7, 715-719.

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1. RSC Publishing workshop at NISER, Bhubaneswar on 23rd September 2016.
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Md Toufique Alam

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Dedicated
To

My Mother, Brother & Wife

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Md Toufique Alam

Contents

SUMMARY

Several *N*-containing heterocycles and also trifluoroethoxy and trideuteriomethoxy group containing aryl ethers are found in various biological active and pharmaceutical valued molecules. Several researchers have participated in substantial progress towards transition metal catalyzed/mediated dehydrogenative C-X (X = N & O) bond coupling reactions. Metal free approaches (i.e. using organo-iodine reagents) are preferably mild and environment friendly as trace amount of metal impurities with the isolated product of metal mediated reaction may alter the biological and physical properties of products. These iodine-based reagents are preferred because of their ease of availability, less toxicity, high reactivity, impressive functional group tolerance, and environmentally benign nature. Iodine derivatives such as *N*-iodosuccinimide(NIS), phenyliodine(III)diacetate (PIDA), phenyliodine(III)-bis(trifluoroacetate) (PIFA), iodosobenzene (PhIO), IBX, and DMP are commonly used in organic synthesis. We have applied these type of iodine-based reagents for synthesis of *N*-containing heterocycles and also trifluoroethoxy and trideuteriomethoxy group containing ether molecules Herein, we depict our first project as an intramolecular C(sp2)-H amidation for preparation of *N*-Substituted Benzimidazole using N-iodosuccinimide in 2,2,2-trifluoroethanol for construction of C-N bond. Different functional groups were well tolerated, which gives a library of N-substituted benzimidazoles.

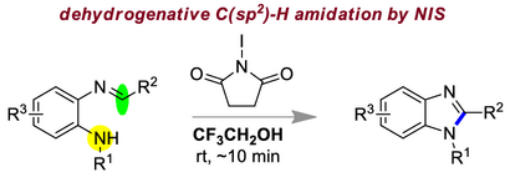

Figure I. Dehydrogenative C(sp2)–H amidation using NIS.

Second work is substituted quinazolin-4(3H)-one synthesis developed in ball mill by controlling the reactivity of IBX with amine. Any combination of reaction by using contact-explosive (combination of amine and hypervalent iodine) in extreme condition is realistically challenging. Following, a methodology is developed for the successful preparation of quinazolin-4(3*H*)-one derivatives using of 2-aminobenzamides, aryl or alkyl aldehydes and *o*-iodoxybenzoic acid (IBX) of under solvent-free ball-milling condition.

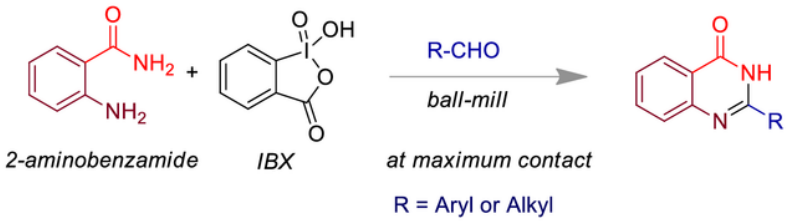

Figure II. Quinazolin-4(3*H*)-ones synthesis from 2-aminobenzamide and aldehydes in presence of IBX.

Apart from these dehydrogenative C-H trifluoroethoxylation and trideuteriomethoxylation has been reported using phenyliodinetrifluoroacetate controlled by HSAB principle. The hard electrophiles carbenium ion preferably reacted with the hard oxygen based nucleophilic alcohols and the -OCH_2CF_3 and -OCD_3 was incorporated in aryl ether synthesis.

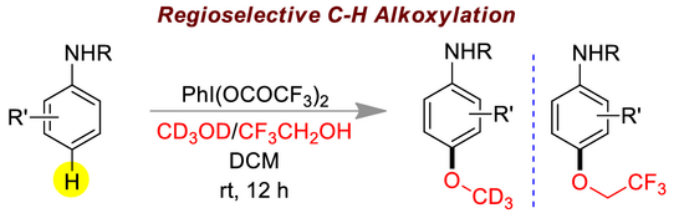

Figure III. I (III) mediated C-H Etherification of anilides.

List of Schemes

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List of Abbreviations Used

Å	Angstrom
Ac	Acetyl
AcOH	Acetic Acid
AcOOH	Peracetic acid
Anhyd	Anhydrous
aq	Aqueous
Bn	benzyl
Bp	Boiling Point
BPO	Benzoyl Peroxide
br	Broad
Bz	Benzoyl
ºC	Degree Celcius
Calcd	Calculated
cm	Centimeter
Conc	Concentrated
Cy	Cyclohexyl
d	Doublet, Days
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Doublet of a Doublet
dil	Dilute
DTBP	Di-tert-butyl peroxide
DMF	*N,N*-Dimethyl Formamide
DMP	Dess-Martin Periodinane
DMSO	Dimethyl Sulfoxide
DTBP	Di-tert-butyl peroxide
equiv	Equivalent
ESI-TOF	Electrospray ionization time-of-flight

Et	Ethyl
EtOAC	Ethyl Acetate
g	Grams
h	Hours
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HRMS	High-Resolution Mass Spectrometry
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IBA	Iodosobenzoic acid
IDB	Iodosylbenzene
IR	Infrared
lit	Liter
m	Multiplet
*m*CPBA	*meta*-chloroperbenzoic acid
*m*CPBA	*meta*-chlorobenzoic acid
NIS	N-iodosuccinimide
M	Molar
MeCN	Acetonitrile
mp	Melting point
Me	Methyl
Min	Minutes
mL	Milliliter
mmol	Millimole
mol	Mole
MS	Mass Spectra, Molecular Sieves
Ms	Methane sulfonyl
M/Z	Mass to charge ratio
nm	Nanometer
NMP	N-Methyl-2-pyrrolidine
NMR	Nuclear Magnetic Resonance
Piv	Pivaloyl
PIDA	Phenyliodine(III) diacetate

PIFA	Phenyliodine bis(trifluoroacetate)
Py	Pyridine
rt	Room Temperature
s	Singlet, Seconds
t	*tert*
TBHP	Tert-Butylhydroperoxide
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFE	2,2,2-Trifluoroethanol
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
TFA	Trifluoroacetic acid
XRD	X-Ray Diffraction

CHAPTER 1

Introduction: Iodine-Based Reagents and Organic C-X (X = N & O) Bond Synthesis

1.1 ABSTRACT

The discussion in this chapter is primarily focused on an overview of organo-iodine based reagents and their utilization in organic transformation. It is divided in three parts: (1) Types of iodine reagents utilized in organic synthesis, (2) C-N bond construction reaction and (3) C-O bond formation reaction. As well as, a space of discussion for the evolution of these reagents and their recent developments in context of C-X (X = C, S, P & halogen) bond formation reactions has also been explored. At the end of this chapter, justification has been placed toward the aim of present thesis.

1.2 INTRODUCTION

Iodine is a trace element in human body that is found in food. The symbol of iodine is 'I' and atomic number is 53. In the periodic table the position of iodine is indexed in period 5 and group 17- the heaviest member of halogen group. It was discovered in elemental form by the French chemist Bernard Courtois[1] in 1811.[2] This lustrous and black non-metallic solid sublimes readily to form purple vapour. In 1813, Joseph Louis Gay-Lussac named iodine from its colouring feature after the Greek word 'iodos' means violet.[3] Its electronic configuration is $[Kr]d^{10}s^2p^5$, which characterizes it as a p-block element. Melting point of iodine is 113.7 °C and boiling point is 184.4 °C.

Reportedly iodine was extracted from seaweed at early days while at present time iodate minerals remains the main source of iodine. It is the least abundant element among halogens, present in trace amount (0.46 ppm relative to bromine 2.5 ppm, chlorine 126 ppm and fluorine 544 ppm). Japan and Chile are the World's main manufacturer of iodine.[4] It is basically available in supplement form and an average human being requires a daily intake of about 0.1 mg of iodide. Almost 20 mg of iodine is present in human body is mainly in thyroid gland. Iodine is necessary for the synthesis of thyroid hormone. A deficiency of iodine causes a disease known as 'goitre' i.e. enlargement of the thyroid gland. We get sufficient iodine as iodized salt to avoid iodine deficiency in most cost-effective way. Among 37 known isotopes of iodine ($_{53}I$) (from ^{108}I to ^{144}I), ^{129}I is the longest-lived radioactive isotopes of iodine. It has half-life about 15.7 million years. ^{131}I may be used to destroy thyroid cancer tissues.[5]

1.3 IODINE-BASED REAGENTS

Commonly used iodine reagents in organic synthesis are given below (Figure 1.1) from oxidation state -1 to λ^3 & λ^5 –iodanes. These reagents are applied for synthesis of various C-O, C-N, C-S and carbon halogen bonds in many reactions like oxidative carbon halogen bond synthesis of organic substance, oxidative cationic ring formation, functionalization of organic unsaturated compounds and oxidative rearrangements of organic substrate etc.

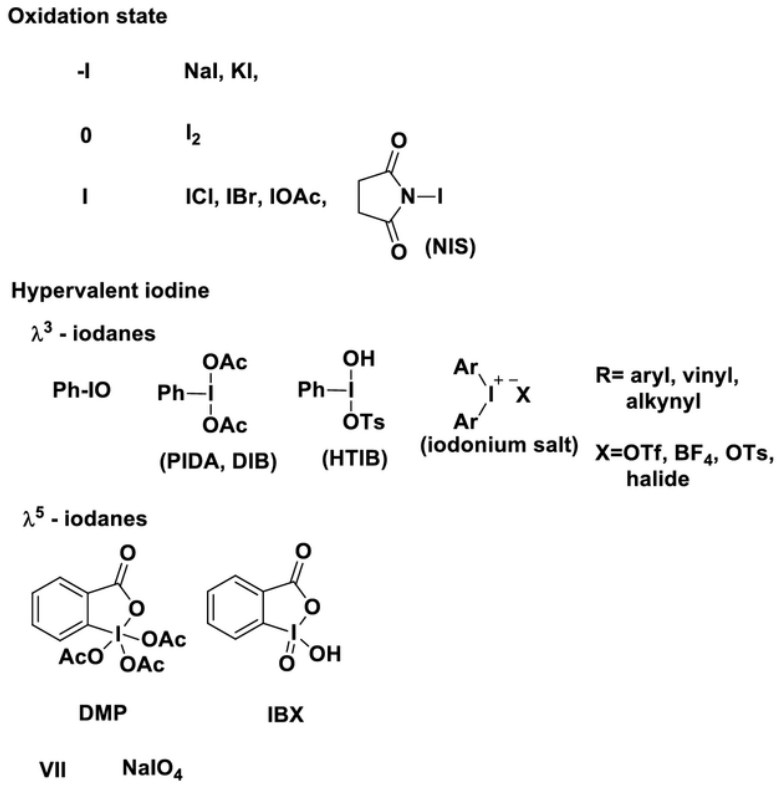
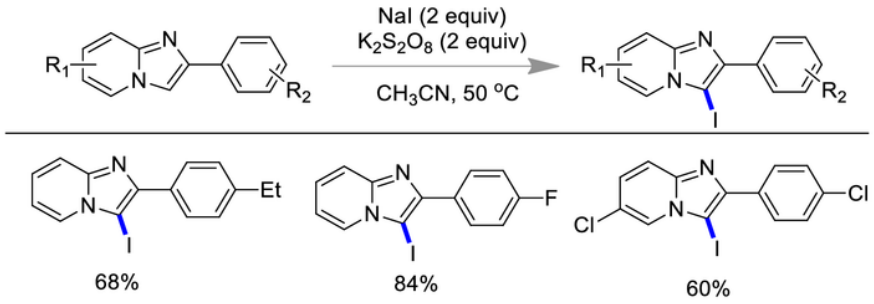


Figure 1.1. Common iodine reagents.

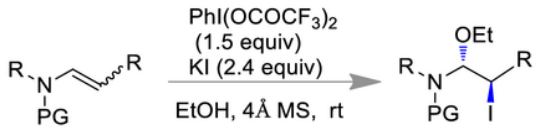
1.3.1 -I oxidation state iodine reagent

The iodine centre of these type of reagents is nucleophilic in nature. The iodide anion basically acts as iodinating agent for preparation of alkyl or aryl iodide. Various investigators applied sodium salts such as sodium iodide (NaI) for iodination of different type of aromatic systems. Such type of iodination of imidazo-fused heterocycles was reported using sodium iodide as the iodine source and a promoter, $K_2S_2O_8$ (or) oxone (Scheme 1.1).[6]



Scheme 1.1. NaI mediated iodination of Imidazo[1,2-a]pyridines.

Iodide anion of KI also acts as nucleophilic agent and is used as iodine source in organic synthesis. The mixture of iodine (III) reagent PIFA and KI mediated regioselective etothoxyiodination of enamides has been developed using ethanol as a solvent at room temperature (Scheme 1.2).[7]

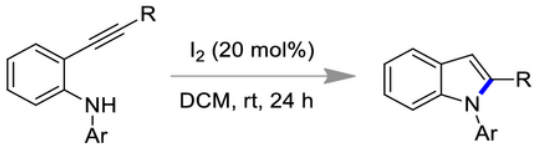


Scheme 1.2. Ethoxyiodination of enamides.

1.3.2 Molecular iodine as a reagent

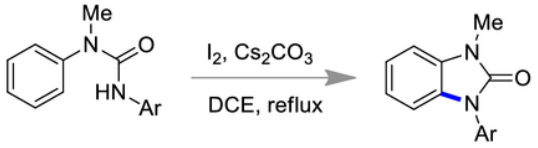
Commercially available, eco-friendly and inexpensive molecular iodine is considered as the alternatives for traditional metal-based reagents towards the C-H bond activation in organic synthesis.[8] Recently, molecular iodine has been widely used in numerous organic transformations by the virtue of its low toxicity, greater atom economy and to overcome the problem of making the final product free from any trace amount of metal for metal-mediated reactions.[9] Molecular iodine majorly finds its potential applications for oxidative transformations like iodocyclization, amination of

C-H bond and aromatization. Based on literature reported plausible mechanism, the exact role of iodine in these type of synthesis has been understood. In 2017, metal free iodine catalyzed iodocyclization of *N*-substituted-2-alkynylanilines followed by protodeiodination for the preparation of N-substituted indole has been reported in dichloromethane solvent at room temperature condition (Scheme 1.3).[10]



Scheme 1.3. Iodine catalyzed cyclisation of N-aryl-2-alkynylanilines.

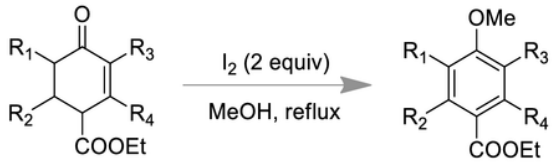
Junbiao Chang's group reported molecular iodine mediated aromatic C-H amination of 1, 3-diarylurea derivatives afforded benzimidazol-2-ones.[11] This synthetic procedure is simply operative and applicable for a large number of urea derivatives (Scheme 1.4)



Scheme 1.4. I_2-Mediated aromatic C−H amination.

An oxidative aromatization promoted by iodine has been reported using methanol as solvent in heating condition.[12] A spectrum of variously substituted anisole

derivatives afforded from cyclohexenones in presence of iodine in refluxing methanol (Scheme 1.5).

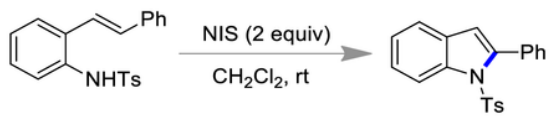


Scheme 1.5. I_2 mediated aromatization reaction.

1.3.3 Monovalent iodine (I) reagent

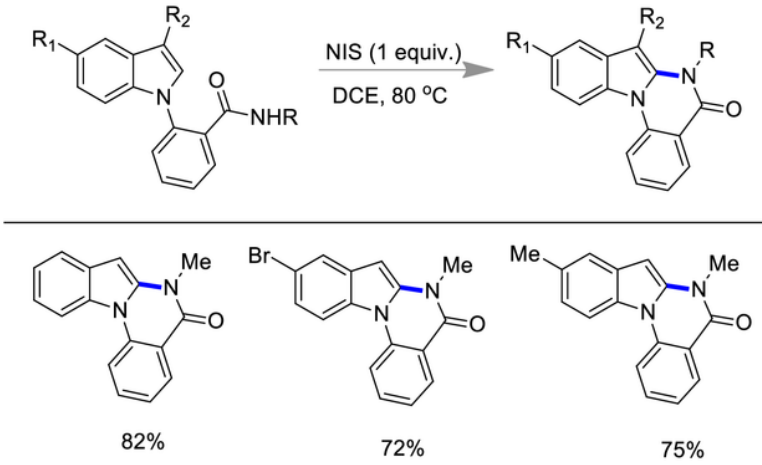
Iodine centre of (+I) iodine reagents behave as electrophilic iodine sources in organic bond formation reaction. These type of reagents are environmentally benign, economic, metal free and non- toxic reagent. Among these, N-iodosuccinimide (NIS) is the frequently used monovalent iodine reagent in organic synthesis. It is soluble in MeCN, THF and dioxane but insoluble in ether and CCl_4. Recently, NIS has been applied as a leading reagent for the replacement of metal catalyst in organic synthesis. It has been utilized as efficient electrophilic reagent for carbon-nitrogen bond formation reaction to form various N- heterocycles through C(sp2-H) amidation.

A metal free rapid preparation of indole from N-protected 2-vinylanilines has been depicted using NIS in DCM solvent at room temperature.[13] The reaction proceeds through formation of C-N bond followed by aromatization afforded N-substituted indole derivatives (Scheme 1.6).



Scheme 1.6. Metal-less indole synthesis using NIS.

In 2017, G. Sekar and coworkers developed a methodology for base and additive free intramolecular carbon nitrogen bond formation reaction through cross-coupling of N-H and aromatic C-H bonds by the use of *N*-iodosuccinimide (NIS) (Scheme 1.7).[14] Substrate having electron withdrawing group like 5-nitro substituent and 7-azaindole did not afford the corresponding product under the standard condition.



Scheme 1.7. NIS mediated indolo[1,2-*a*]quinazolinones preparation.

1.3.4 Hypervalent iodine reagent

The word 'Hypervalent' is implied for that main group element which does not follow octet rule precisely and containing more than 8 electrons in its outermost shell. Thus, compounds with higher oxidation state iodine are called under general name of hypervalent iodine compounds or iodanes.[15] There are three types of hypervalent iodine reagents which are identified as - (1) trivalent iodine or λ^3-iodanes compound, (2) pentavalent iodine or λ^5-iodanes compound and (3) heptavalent iodine or λ^7-iodanes compound (according to IUPAC) which have ten, twelve and fourteen electrons in valence shell of iodine centre respectively.[16] There are a very few example of λ^7-iodanes

compounds like inorganic IF_7, HIO_4 & $NaIO_4$ compounds which have hardly used in organic transformation.

1.3.4.1 Trivalent iodine compound

In 1969, J. J. Musher introduced the concept of hypervalent iodine. German chemist, Conrad Willgerodt synthesized (dicholoroiodo)benzene ($PhICl_2$) which is reportedly the first hypervalent iodine compound.[17] Trivalent iodine centers are found both the inorganic as well as organic compounds.

Inorganic trivalent iodine agents

Iodine (III) halides are known I (III) inorganic compounds which are very unstable compound. As for example IF_3 & ICl_3 decomposes at -28 °C and 47 – 62 °C respectively. Therefore, these are hardly used in organic transformation as a reagent.[18] Various inorganic I(III) oxide derivatives are presented in literature like $I(OR_3)$, $(IO)_2SO_4$, $(IO)_2SeO_4$ and OIOTf.

Organoiodine(III) compound:

Recently, organo-hypervalent iodine (III) regents have been extensively used for the development of new methodology in organic synthesis. Iodine (III) reagents show similar kind of reaction (like various reductive elimination, several oxidative addition and ligand coupling) in accordance with that of inorganic transition metals containing reagents, although conversely, these are preferred due to selective oxidant property & environmentally benign nature.[19] There are variety of reactions reported e.g. reductive elimination, oxidative transformation & ligand coupling by applying I(III)

derivatives such as iodobenzene diacetate, iodobenzene trifluoroacetate and other iodine(III) & iodine (V) hypervalent derivatives afford construction of C-C, C-O, C-N and C-S bond.[20] Most Common and commercially available I(III) reagents, phenyliodine(III) diacetate, phenyliodine(III)-bistrifluoroacetate are abbreviated as PIDA (or DIB) & PIFA respectively.[15] The important derivatives of hypervalent I(III) compounds are given below (Figure 1.2).

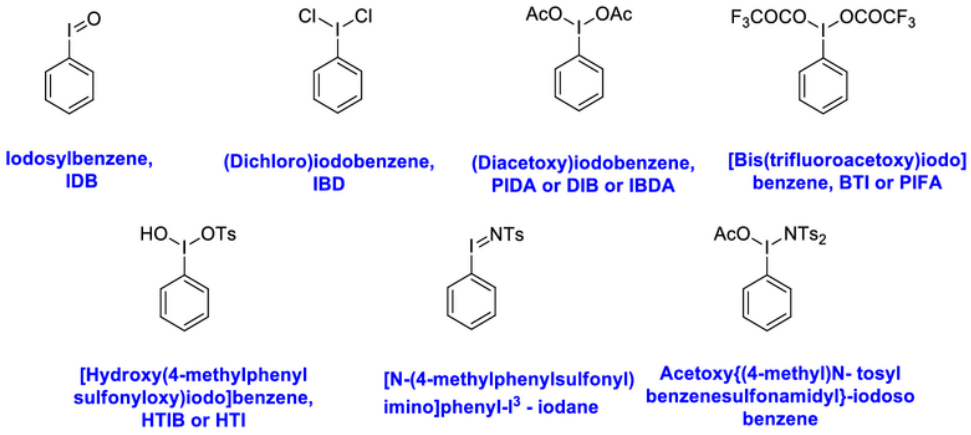


Figure 1.2. Common organoiodine (III) reagents.

Typical procedure for synthesis of common I(III) compounds

In principle, two strategies are followed for preparation of hypervalent iodine (III) compounds. They are i) oxidative addition of suitable ligand to low valent iodine & ii) ligand exchange in trivalent iodine derivatives (Table 1.1). Organic iodine (III) dichloride is routinely synthesized by direct chlorination of aryl iodide in chloroform or dichloromethane with chlorine gas at low temperature. It can be also prepared by ligand exchange in other I (III) derivatives. The direct chlorination method has been utilized

to the kilogram-scale preparation of (dichloroiodo)arenes at -3 to 4 °C temperature condition.[21] Generally, (dichloroiodo)arenes are crystalline yellow solids which are light sensitive. These iodine (III) chlorides are also thermally unstable for prolonged storage even at low temperature. Practically most important I (III) acetate, PIDA can be synthesized by oxidation of phenyl iodide with oxidant such as sodium perborate ($NaBO_3.10H_2O$) or peracetic acid (AcOOH) or *meta*-chloroperbenzoic acid (*m*CPBA) or potassium peroxodisulfate ($K_2S_2O_8$) in acetic acid.[22] The second important I(III)acetate, PIFA can be prepared by both oxidative addition as well as ligand exchange approach.[23]

Table 1.1. Typical procedure of preparation of iodine (III) reagents.

Substrate	Reagents & condition	Product	Type of srtategy
PhI	Cl_2, $CHCl_3$, rt	$PhICl_2$	Oxidative addition
PhI	Oxone, CF_3COOH, rt	$PhI(OCOCF_3)_2$	Oxidative addition
PhI	$NaBO_3$, $4H_2O$ or *m*CPBA or AcOOH, AcOH, rt or 45 °C	$PhI(OCOCH_3)_2$	Oxidative addition
$PhI(OCOCH_3)_2$	CF_3COOH, rt	$PhI(OCOCF_3)_2$	Ligand exchange
$PhI(OCOCH_3)_2$	NaOH, H_2O, rt, 2h	PhIO	–
$PhI(OCOCH_3)_2$	$TsOH.H_2O$, MeCN, rt	PhI(OH)(OTs)	Ligand exchange
$PhI(OCOCH_3)_2$	Ts_2NH, CH_2Cl_2, rt	$PhI(OAc)(NTs_2)$	Ligand exchange
$PhI(OCOCH_3)_2$	RCOOH, Toluene/$CHCl_3$ (1:1), 45 °C	$PhI(OCOR)_2$	Ligand exchange

Synthesis of this oxidising agent from iodoarenes and oxone combination in trifluoroacetic acid solvent has been developed at room temperature. In ligand exchange approach, PIFA is readily isolated when PIDA is treated with TFA under room temperature condition. When PIDA is hydrolyzed with aqueous NaOH, iodosylarenes is isolated.[24]

"Koser's reagent" i.e. [Hydroxy(tosyloxy)iodo]benzene (HTIB) is prepared by treating (diacetoxyiodo)benzene with $TsOH.H_2O$ in acetonitrile at room temperature.[25] Acetoxy(bistosyl)imido iodobenzene [$PhI(NTs_2)(OAc)$] is prepared from PIDA with bis(tosyl)imide combination in dichloromethane solvent.[26]

Phenyliodine diacetate (PIDA) with appropriate carboxylic acid readily gave [bis(aceloxy)iodo]arenes [$PhI(OCOR)_2$] through ligand exchange strategy.[27]

Structure and reactivity of I (III) Compounds

According to IUPAC recommendations, iodine (III) compounds are known as λ^3-iodanes.The most general type of λ^3-iodanes are RIL_2 (L = heteroatom ligands and R = C-ligands) which contains ten electrons at central iodine atom. It shows an overall distorted trigonal bipyramidal geometry with approximately T-shaped structure bearing R (less electronegative C-ligand) and two lone pairs remain in an equatorial site, while most electronegative heteroatom ligands, L are projected toward axial position.[15] The linear L-I-L bond in RIL_2 which is less stronger as compared to normal covalent bond between two atoms, is a highly polarized 3c-4e bond[28] composed from the central iodine nonhybridized 5p orbital and one orbital from each apical L, ligand.

There are two fundamental modes of the reaction of iodine (III) reagents involving i) Ligand exchange where no change of oxidation state of iodine centre and

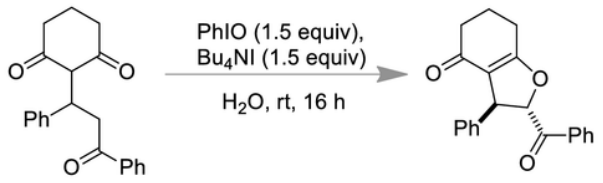
ii) reductive elimination where reduction of hypervalent I (III) to iodide.[29] Single-electron transfer reaction,[30] ligand coupling and radical type reaction are also seen for λ^3-iodanes under suitable conditions.

Synthetic transformations of trivalent iodine compounds

Being an electron deficient species the iodine centre of hypervalent iodine compounds are highly electrophilic thus these type of reagents have tendency to accept electron from nucleophilic centre. Therefore it always reduced to form low valent iodine compound i.e. iodoarene. The following section focuses only the utilization of common hypervalent iodine (III) compound in organic transformations.

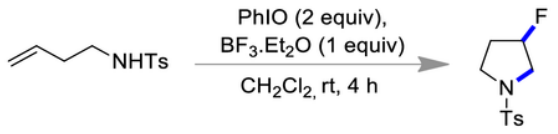
Iodosylbenzene

Iodosylbenzene is commonly abbreviated as IDB. It is a fruitful oxidant and only soluble in methanol and DMSO among common organic solvents. Recently, myriad oxidation reactions using iodosylbenzene have been developed by various groups. Isolation of dihydrofuran from Michael adduct was possible using iodosylbenzene and tetrabutylammonium iodide (Scheme 1.8).[31]



Scheme 1.8. PhIO and tetrabutylammonium iodide induced dihydrofurans preparation.

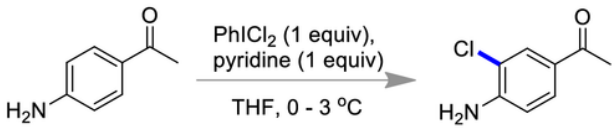
The treatment of N-(but-3-en-1-yl)-4-methylbenzenesulfonamide with iodosylbenzene in the presence of additive, $BF_3 \cdot Et_2O$ provide 3-fluoro-1-tosylpyrrolidine (Scheme 1.9).[32] The transformation follows cyclic carbocation intermediate pathway. Herein, fluorine atom comes from the additive, $BF_3 \cdot Et_2O$.



Scheme 1.9. Oxidative fluorinative cyclization of N-(but-3-en-1-yl)-4-methylbenzenesulfonamide.

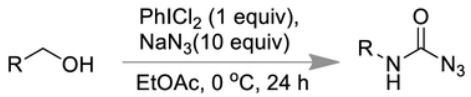
(Dichloroiodo)benzene

(Dichloroiodo)benzene is shortened as IBD. (Dichloroiodo)benzene is extensively utilized as chlorinating reagents. A regioselective chlorination of aryl ring was achieved with an aromatic electron-rich ketone using (dichloroiodo)benzene affording 4-amino-3-chloroacetophenone instead of *ortho*-chlorination of ketone (Scheme 1.10).[33]



Scheme 1.10. I (III) mediated regioselective chlorination.

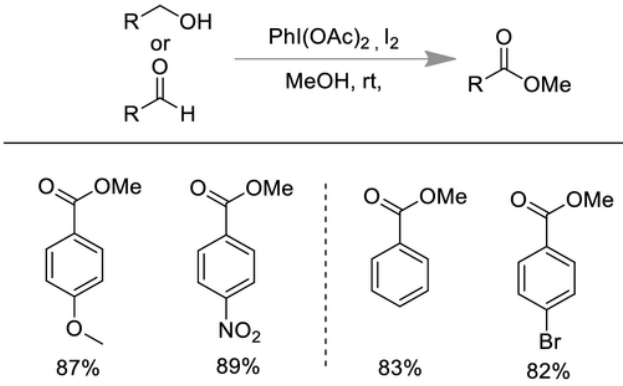
Through Curtious type rearrangement, carbamoyl azides were isolated from primary alcohol using $PhICl_2$-NaN_3 in ethyl acetate solvent (Scheme 1.11).[34]



Scheme 1.11. Oxidative rearrangement to synthesis carbamoyl azides.

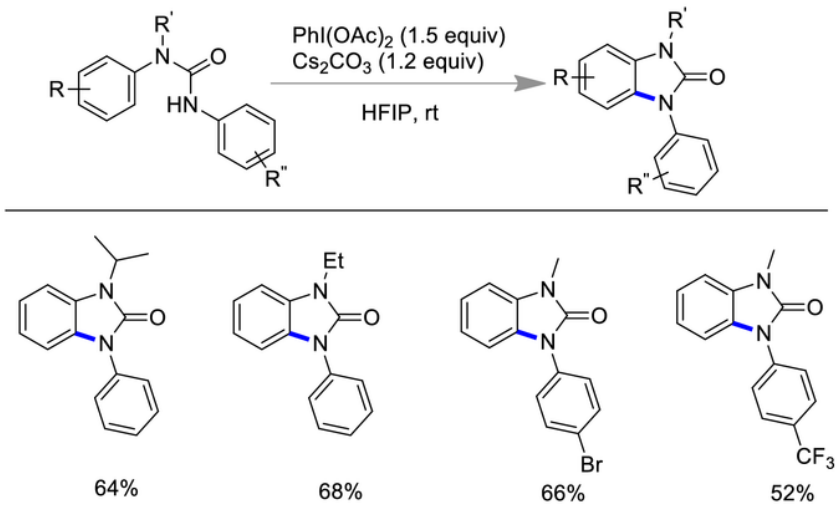
(Diacetoxyiodo)benzene

(Diacetoxyiodo)benzene is commonly known as PIDA or DIB. It is the most potent, practically convenient and well-investigated oxidant among iodine (III) reagents. One of the application of PIDA is the synthesis of similar type of reagents by ligand exchange of acetate group. It is closely related with PIFA in reactivity though PIFA is stronger oxidant than that of PIDA. DIB can be used as oxidant to oxidize various alcohol. PIDA with combination of molecular iodine can be utilized for oxidation of alcohol (primary and secondary) to ketones and carboxylic acid respectively. $PhI(OAc)_2$ and I_2 combination furnished methyl ester from aldehyde or alcohol in methanol with high efficiency (Scheme1.12).[35]



Scheme 1.12. Efficient oxidation of alcohols & aldehyde by PIDA-I_2.

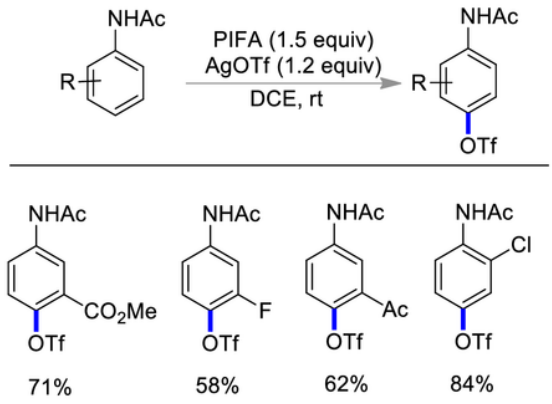
Various chemists utilized (diacetoxyiodo)benzene to construct carbon-heteroatom bond through nitrenium ion intermediate. In 2015, Fu and his co-workers developed oxidative C-H amination for the synthesis of benzimidazol-2-one from *N*, *N′*-diarylureas using an oxidant PIDA and an additive Cs_2CO_3 in HFIP solvent (Scheme 1.13).[36]



Scheme 1.13. DIB enabled benzimidazolinones synthesis.

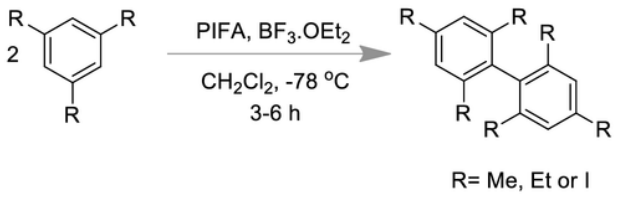
Iodosobenzene bis(trifluroacetate)

(Bis(trifluoroacetoxy)iodo)benzene, PIFA is more costlier than PIDA, although it has been extensively used as an oxidant in organic transformation. This reagent assists to formation of an aryl radical cation when treated with aryl ether. PIFA and Lewis acid combination can oxidise aromatic ring. Such as para-triflation of anilides was achieved using PIFA and AgOTf mixture in DCE solvent (Scheme 1.14).[37]



Scheme 1.14. PIFA mediated oxidative C-O bond synthesis.

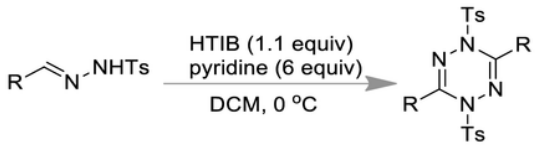
Kita's group developed a homo-coupling reaction for synthesis of C-C bond by taking substituted arenes, using PIFA as an oxidant and $BF_3.OEt_2$ as a Lewis acid at – 78 °C (Scheme 1.15).[38]



Scheme 1.15. BTI mediated homo-coupling of alkyl arenes.

[Hydroxy(tosyloxy)iodo]benzene (HTIB)

HTIB is valuable sulphur containing hypervalent I(III) reagent which is used as oxidant for sulfonyloxylation of unsaturated C-C bond & phenyliodonation in organic synthesis. HTIB is commercially available iodine (III) reagents. Wei and co-workers discovered a methodology for preparation of 3,6-disubstituted-1,2,4,5-tetrazines by taking hydrazones in presence of HTIB in DCM at 0 °C (Scheme 1.16).[39]

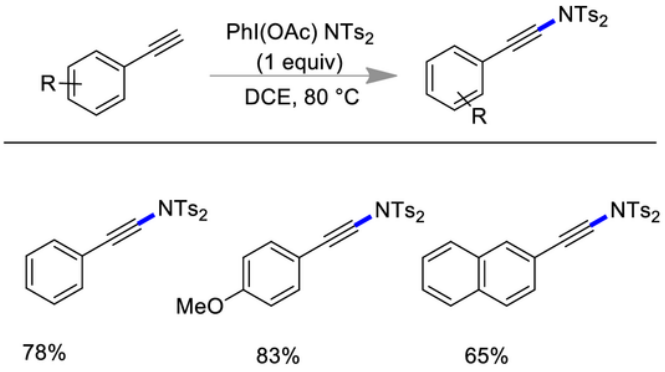


Scheme 1.16. HTIB enabled 3,6-Disubstituted-1,2,4,5-tetrazines synthesis.

N-ligands containing I(III) reagent

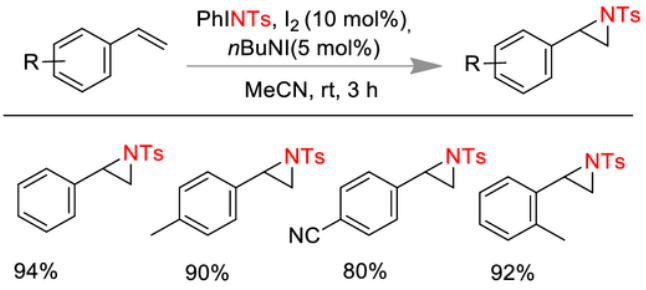
Hypervalent iodine (III) compounds having I-O bonds are more familiar than that of I-N bonds. Thermal stability of acylic hypervalent iodine (III) derivatives with nitrogen ligands is less compared to their counterpart with oxygen ligands. These nitrogen ligands containing reagents are extensively applied for nitrogen transfer reactions in synthesis. Several group reported, alkyl, alkenyl, acetylenic and allylic amination using aryliodine(III) derivatives having nitrogen ligands. The Muniz's group

reported intermolecular oxidative alkenyl amination using $PhI(OAc)NTs_2$ (Scheme 1.17).[40]



Scheme 1.17. Terminal alkynes C−H amination using I(III) reagent.

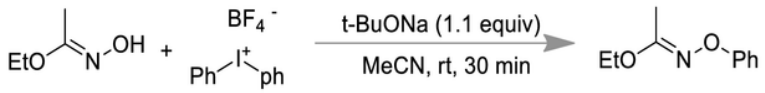
In 1974, Abramovitch & co-workers presented iodonium ylides with nitrogen analogous known as iodonium imides.[41] The procedure for synthesis of iminoiodanes was developed one year later by Yamada and Okawara.[42] Aziridination of alkenes was possible by using this iminoiodanes which acts as precursor of nitrene. As an example, in presence of N-tosyliminophenyliodane with molecular iodine and tetrabutylammonium iodide (TBAI), metal free, radical induced aziridination of styrene compounds has been developed by Minakata and coworkers (Scheme 1.18).[43]



Scheme 1.18. Aziridination of syrenes utilising N-Tosyliminoiodane.

Diaryliodonium salts

Iodonium salts are habitually assigned as 8-I-2 ionic species having two carbon substituents connected with an appropriate counter ion $R_2I^+X^-$. It is not formally hypervalent iodine compound due to 8-electron at iodine centre in its valence shell.[15] X- ray structural data confirms, it has pseudo trigonal bipyramidal geometry at iodine centre that is identical with that of iodine (III) compounds. Also the structures described the existence of sturdy secondary interaction between centre iodine and anionic counterpart. Therefore, from structural point of view iodonium salts are generally categorized 10 electrons hypervalent derivatives. Diarylaiodonium salts provides direct arylation of inactivated C-H bonds. Olofsson and co-workers reported O-arylaion of ethyl acetohydroxamate (Scheme 1.19).[44]

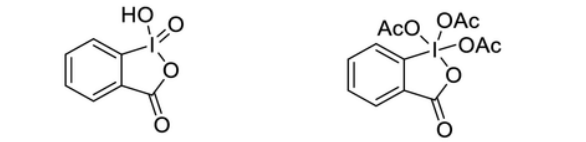


Scheme 1.19. Metal free O-Arylation of ethyl acetohydroxamate.

1.3.4.2 Pentavalent iodine compounds

Due to their easy accessibility iodine (V) reagents are considered as an excellent alternative of metal mediated inorganic reagents. λ^5-iodanes or pentavalent iodine are influential hypervalent iodine compound. Iodine (V) reagents have been utilized for selective oxidation in organic transformation.[45] In 1893, Hartmann and Meyer started the use of 2-iodoxybenzoic acid, commonly known as IBX.[46] But gram scale use of it in any large scale reaction was confined owing to explosion at elevated temperature[47]

and hardly soluble in common organic solvent excluding DMSO.[48] However in DMSO solvent, IBX cannot be handled as it lacks ease of isolation and purification. Therefore people interested to develop modified IBX. In 1983, Dess and Martin first developed modified IBX i.e. triacetoxybenziodoxolone which is generally known as Dess-Martin Periodinane (Figure 1.3) [49] abbreviated as DMP. Several other modified derivatives of IBX such as solid supported IBX[50], pseudo-IBX[15] are described by various investigators.

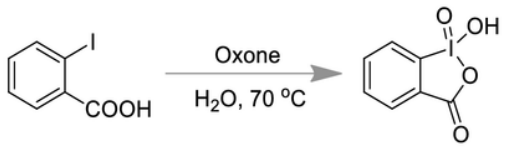


o-iodoxybenzoic acid (IBX) **Dess-Martin Periodinane (DMP)**

Figure 1.3. Commercially available iodine (V) reagents.

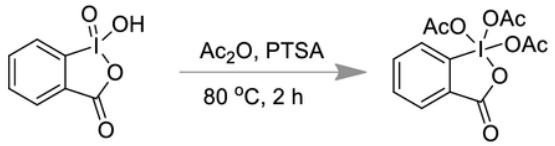
Typical procedure for synthesis of common iodine (V) reagents

A safe and appropriate method for preparation of IBX was developed by Santagostino and coworkers in 1999 by taking *o*-iodobenzoic acid and oxone ($2KHSO_5.KHSO_4.K_2SO_4$) in de-ionised water at 70 °C.[51] This method is also suitable for gram-scale synthesis of IBX (Scheme 1.20).



Scheme 1.20. Synthesis of IBX using oxone.

Although DMP is commercially available, but it can easily prepare by treatment of IBX in presence of acetic anhydride and PTSA at 80 ºC for 2 h (Scheme1.21).[49]



Scheme 1.21. Preparation of DMP using PTSA.

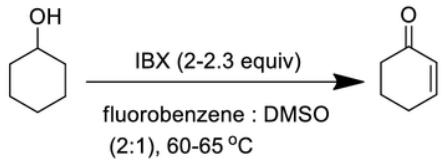
Structure and reactivity of iodine (V) reagents

According to IUPAC nomenclature, iodine (V) compounds are called λ^5-iodane.The Geometry of these compounds (RIL_4) is square bipyramidal bearing C-ligand, R & non-bonding electrons pair remain in an apical position and four electronegative hetero-atomic ligand reside in a basal position.[18] The C-ligand, R is joined by usual covalent bond with iodine and remaining ligands are joined to iodine atom through two orthogonal three centre four electron bonds.[15] Organoiodine(V) compounds mostly IBX and DMP are applied as an efficient oxidizing reagents.[45] However, there are some drawback with these reagents such as limited solubility of IBX in many solvents, and its violent nature at elevated temperature, while DMP is moisture sensitive.

Synthetic transformation of pentavalent iodine compound

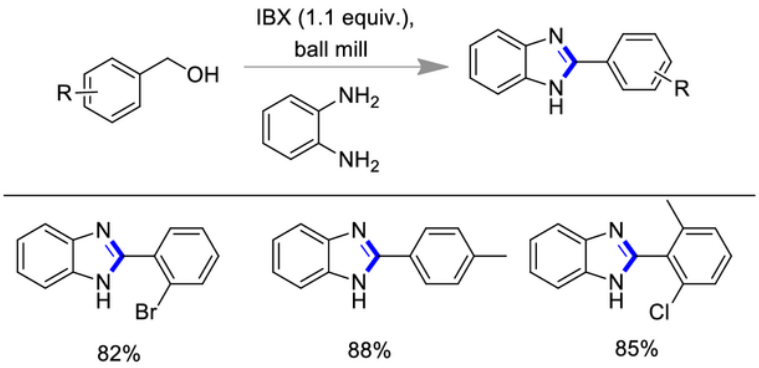
Selective oxidation of alcohol to ketone has been carried out using IBX and its derivatives. Nicolaou and co-worker discovered various methodology using IBX such as selective benzylic oxidation, formation of α,β-unsaturated carbonyl compound, oxidative cyclisation of anilides and preparation of amino sugars. α,β-unsaturated

compounds are able to prepare in one step from corresponding alcohol by using IBX (Scheme 1.22).[52]



Scheme 1.22. Preparation of α, β-unsaturated ketones by applying IBX.

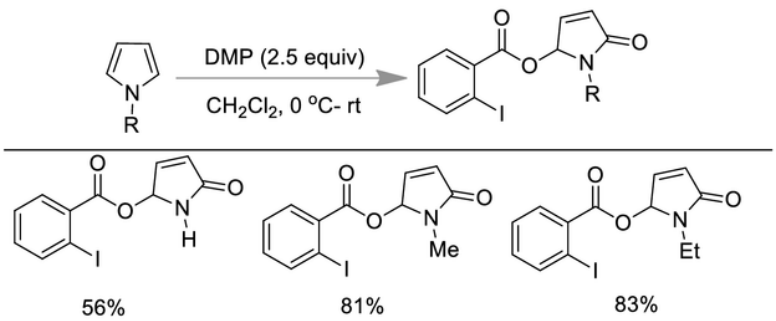
To avoid solubility problem of IBX, P. Mal and co-workers applied IBX in solvent free mechanochemical procedure.[53] Using IBX in Ball mill, several oxidation procedure like oxidation of amine to imine, sulphide to sulfoxide, synthesis of benzimidazol, dithiane deprotection and conversion of olefin to haloketone have been developed in 2015. Likewise, preparation of 2-substituted benzimidazole from benzyl alcohol and o-phenylenediamine by treatment of IBX was reported (Scheme1.23).



Scheme 1.23. Synthesis of 2-substituted benzimidazole using IBX in ball-mill.

DMP is crystalline[54] and soluble in common organic solvents such as chloroform and dichloromethane. DMP must be stored moisture free condition.

Selective oxidative power and mild reaction condition makes DMP as an important oxidizing reagents. Addition of water accelerate the oxidizing power of DMP in reaction system. Preparation of γ-lactam from pyrrole by using DMP has been discovered in good yields (Scheme 1.24).[55]

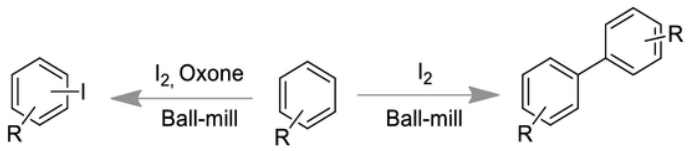


Scheme 1.24. Transformation to γ-lactams from pyrroles using DMP.

1.3.5 Iodine reagent in ball-mill

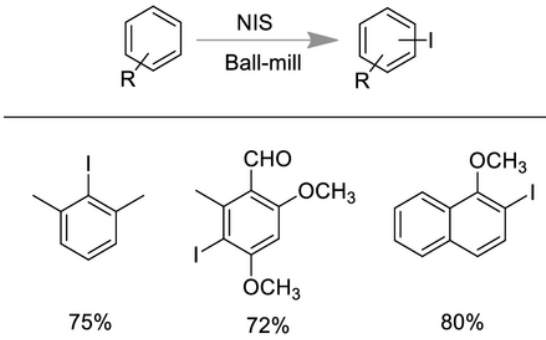
At an early stage of chemistry, mechanochemical reaction were carried out by taking a mortar and pestle. But, this technique is restricted due to irregular and relatively modest grinding strength, also speed and for moisture and air sensitive reactants.[56] To avoid this type of limitation, well-equipped programmed electrical shaker or mixture mill or planetary mill was accomplished for mechanochemical reactions in a sealed vessel (ceramic or metal jar) which is more authenticate than that of hand pestle. Therefore, such a control manner grinding is needed a milling ball that is generally made with tungsten carbide, agate, stainless steel and zirconia etc. So, it is called as ball mill. Various investigators reported iodine reagents mediated organic transformation in ball mill for synthesis of C-C or carbon-heteroatom bonds.[57] For construction of C-C

bond, our group developed elemental iodine mediated solvent free biaryl preparation from electron rich arenes and also I_2/oxone mediated electrophilic iodination of electron rich arenes (Scheme 1.25).[58]



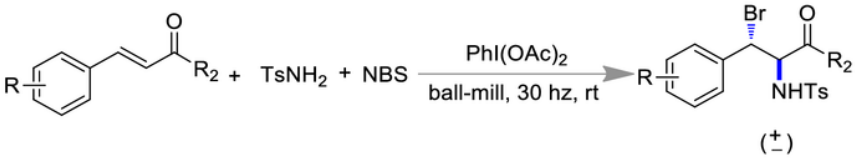
Scheme 1.25. I_2/oxone mediated aryl iodination & biaryl preparation in ball mill.

Our group also developed regioselective aryl iodination using iodine (I) reagent N-iodosuccinimide under ball-milling condition.[59] Instead of benzylic iodinations, aryl iodination was occurred for corresponding electron rich alkyl arenes with good to excellent yield (Scheme1.26).



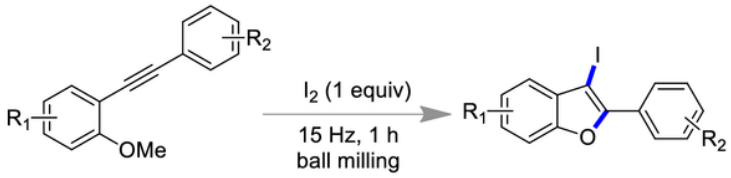
Scheme 1.26. Regioselective iodination of electron rich arenes.

PIDA promoted aminobromination of electron deficient olefin has been reported using the combination of $TsNH_2$ and NBS in ball-mill at room temperature (Scheme1.27).[60] Using this methodology, various system such as α, β-unsaturated ketones, cinnamates and cinnamides could be aminobrominated in solvent free system.



Scheme 1.27. I (III) mediated aminobromination reaction in ball-mill.

To develop better synthetic methodology to overcome the restriction in traditional methods like solubility of reacting substrate solvent-less ball milling technique has paid a reputation in organic synthesis. In 2018, Carsten Bolm's group presented solvent free iodocyclization of *o*-alkynylanisoles in ball mill. Molecular iodine facilitate this electrophilic iodocyclization, yielded 3-iodobenzofurans derivatives through 5-*endo*-*dig* cyclization (Scheme 1.28).[61]



Scheme 1.28. Molecular iodine induced electrophilic cyclization in ball-mill.

1.4 IODINE REAGENTS IN ORGANIC SYNTHESIS

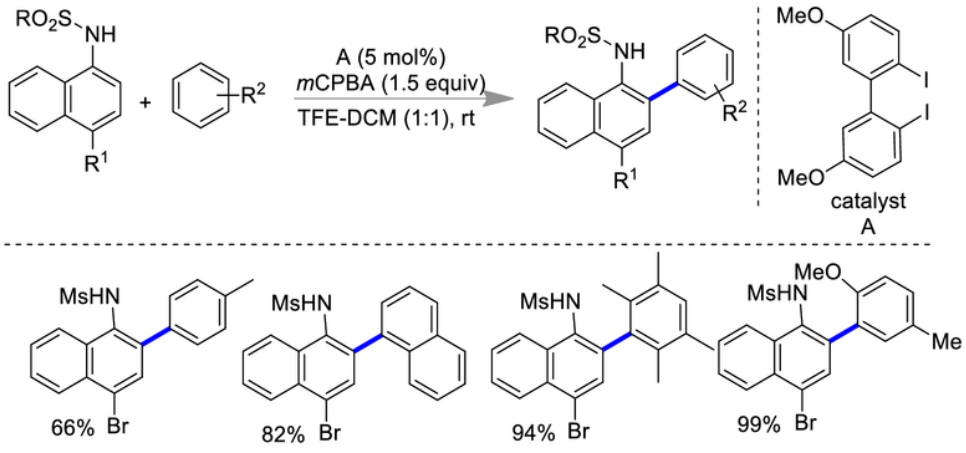
Methodology using iodine-based reagents instead of metal base reagents in organic synthesis have gained significant attention to the researchers. In this section, we will discussed various organic transformations mediated by iodine-based reagents towards development of C-C, C-O, C-N, C-S, C-P and carbon- halogen bonds which

are believed to have utilization in several pharmaceuticals, industrial and agrochemical process.

1.4.1 Carbon-carbon bond synthesis

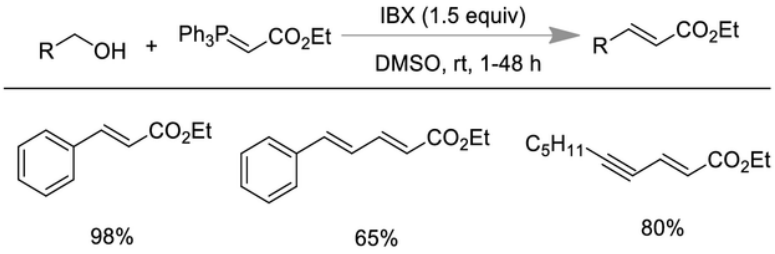
Intermolecular C-C bond construction

Kita and coworkers developed C-C bond forming selective arylation of anildes using 2, 2′-iodobiphenyls and an oxidant *m*CPBA.[62] Treatment of aromatic amine and sulfonanilides leads to the C-C bond construction reaction with in-situ generated iodine-based reagent through the nitrenium/carbenium ion intermediate. This cross-biaryl coupling methodology gave C-selective product with good to excellent yield under ambient reaction condition (Scheme 1.29).



Scheme 1.29. Metal free cross biaryl coupling.

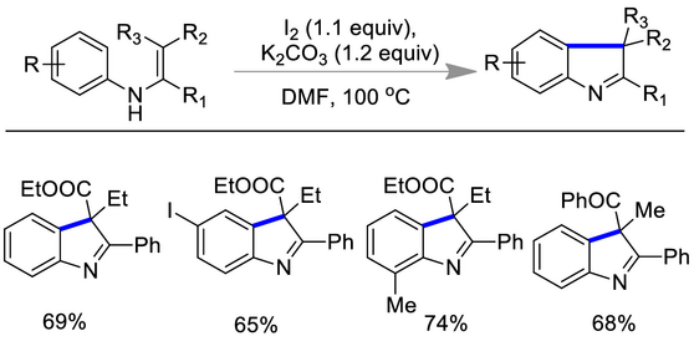
α ,β-unsaturated esters can be achieved through intermolecular C-C bond formation using IBX in DMSO solvent from unsaturated alcohol and stabilized Wittig ylide. This one pot oxidation strategy furnished corresponding esters with high efficiency (Scheme 1.30).[63]



Scheme 1.30. Preparation of α,β-unsaturated esters using Wittig ylide.

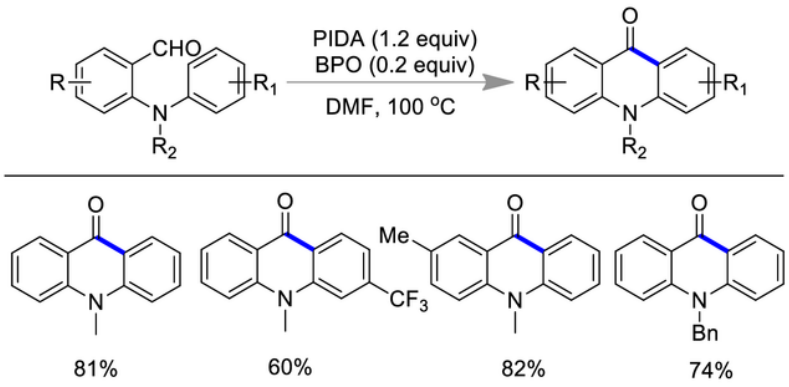
Intramolecular C-C bond synthesis

3H-indoles was efficiently synthesized from enamines through intramolecular cyclisation, mediated by iodine in DMF solvent. A wide spectrum of enamines having different functional groups are treated in optimum condition and respective 3H-indoles were isolated in good yields (Scheme 1.31).[64]



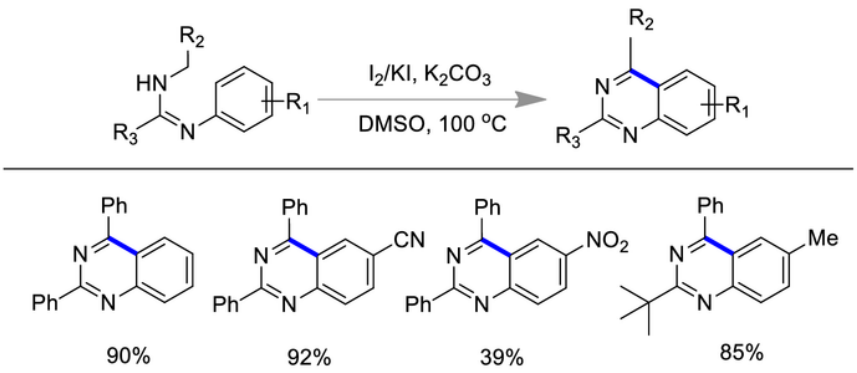
Scheme 1.31. Iodine mediated intramolecular cyclisation of enamines.

In 2014, Kang Zhao's group developed a metal-less methodology for making of acridones skeletons by direct carbon-carbon bond formation.[65] A spectrum of 2-(N-arylamino)aldehydes was allowed for intramolecular CDC reaction using PIDA as an oxidant and BPO as an additives in DMF solvent at 100 ºC (Scheme1.32).



Scheme 1.32. Preparation of acridones derivatives using PIDA.

Junbiao Chang and co-workers reported I_2 and KI induced oxidative intramolecular carbon-carbon bond formation reaction from N, N′-disubstituted amidines in DMSO solvent.[66] The corresponding substrates were treated in standard reaction condition and respective product were isolated good to medium efficiency (Scheme 1.33).



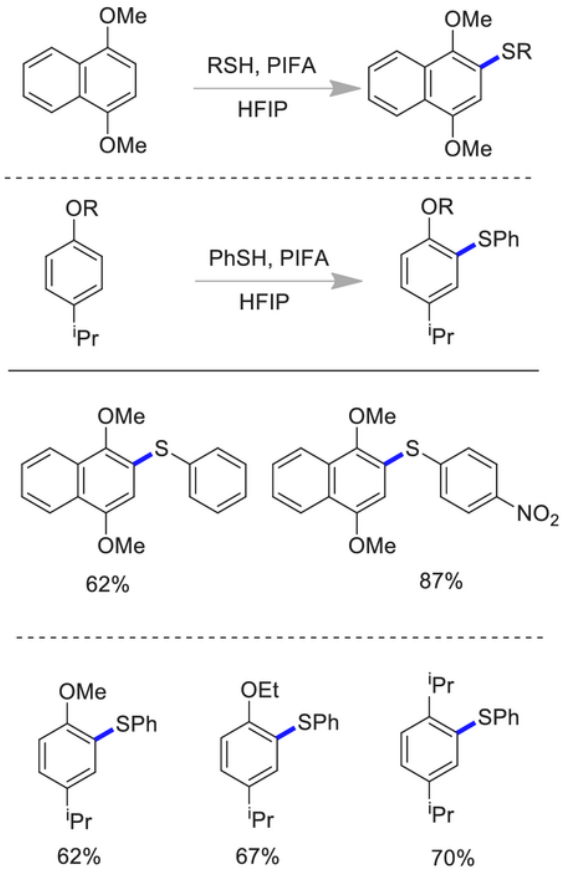
Scheme 1.33. Chang's approach for synthesis of quinazoline.

1.4.2 Carbon-Sulphur bond synthesis

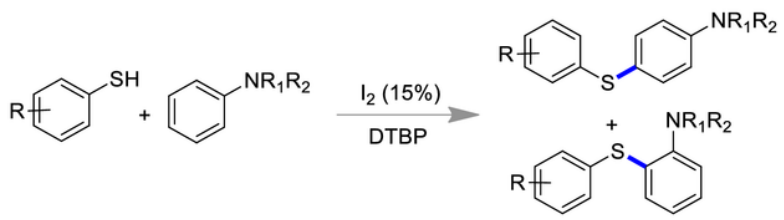
Intermolecular C-S bond synthesis

In 1995, Kita and co-workers accomplished nucleophilic sulfenylation of aryl ethers and alkoxynaphthalenes using iodine-based reagents.[67] Thiophenol was applied as sulphur source. Several diarylsulfied was isolated in good efficiency (Scheme 1.34).

Direct arylthiation of anilines derivatives using thiophenol was accomplished in presence of catalytic amount of iodine and an oxidant DTBP under solvent free conditions (Scheme1.35).[68]

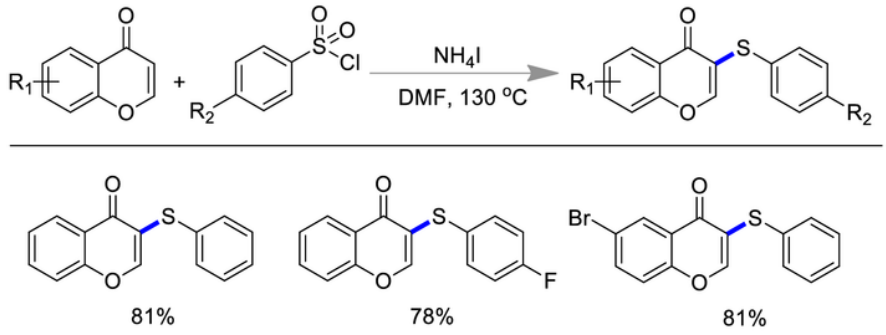


Scheme 1.34. Kita's strategy for sulfinylation.



Scheme 1.35. Iodine-catalyzed direct arylthiation.

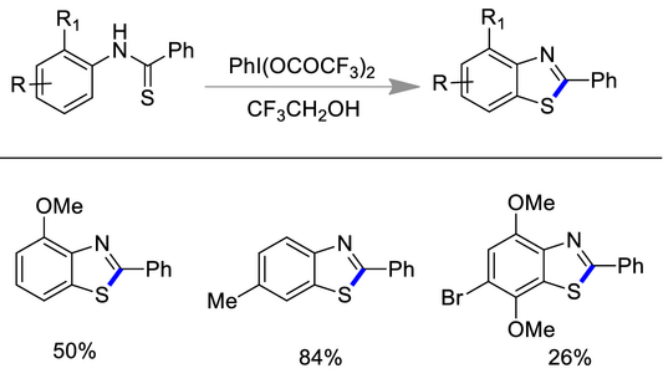
A regioselective intermolecular C-S bond construction using flavones has been developed in presence of sulfonyl chloride by the treatment of NH_4I. Valuable thioether compounds having different functional group were isolated with good to excellent yield by this methodology (Scheme 1.36).[69]



Scheme 1.36. Regioselective sulfenylation using ammonium iodide.

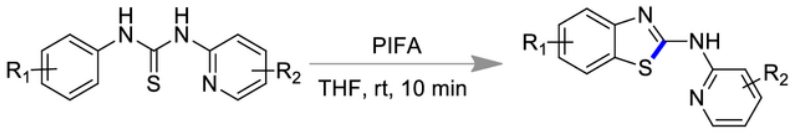
Intramolecular C-S bond synthesis

Intramolecular cyclisation via C-S bond construction of thiobenzamides to the formation of benzothiazoles has been presented under metal free condition through radical cation intermediate (Scheme 1.37).[70]



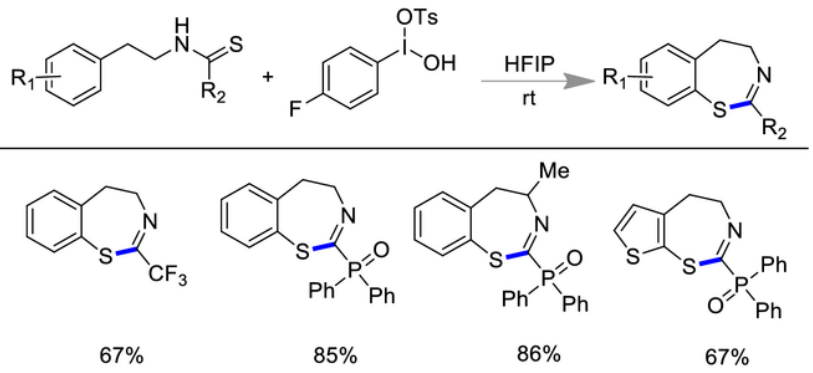
Scheme 1.37. BTI mediated cyclization of thiobenzamides.

Heteroarylthioureas derivatives can be transformed into *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine compounds via an oxidative intramolecular C-S bond construction method using PIFA as oxidant (Scheme1.38).[71]



Scheme 1.38. PIFA mediated synthesis of *N*-(Pyridin-2-yl)benzo[*d*]thiazol-2-amines.

Under metal free, intramolecular dehydrogenative carbon-sulfur bond synthesis of thioamides leads to 1,3-benzothiazepine derivatives has been established by Ming Li and co-workers using organo-iodine regent. This methodology is operationally simple and has broad substrate scope (Scheme 1.39).[72]

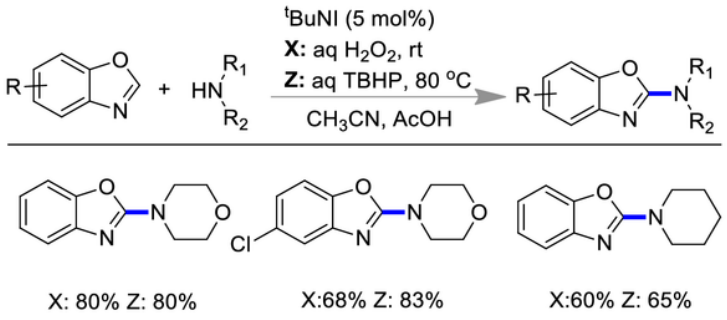


Scheme 1.39. Ming Li's approach for construction of 1,3-benzothiazepines.

1.4.3 Carbon-nitrogen bond formation

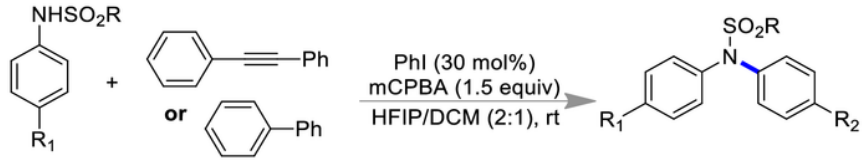
Intramolecular C-N bond synthesis

In aqueous solution of H_2O_2 or TBHP, an intermolecular amination of benxoxazoles was developed in presence of catalytic amount of teterabutylammonium iodide. Respective 2-aminobenzoxazoles was efficiently prepared (Scheme 1.40).[73]



Scheme 1.40. TBAI -catalyzed intermolecular amination of benxoxazoles.

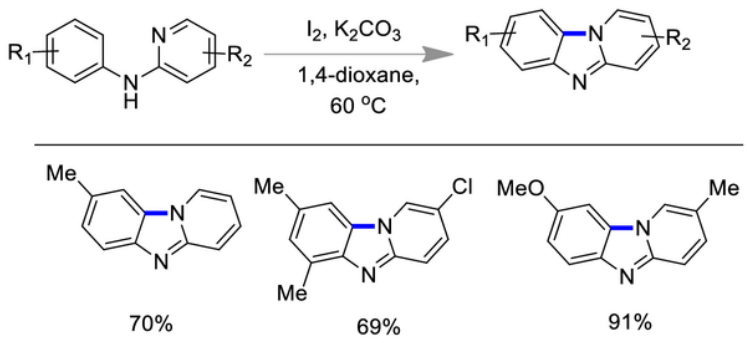
Our group have presented selective N-arylation of sulfonanilides. N-arylsulfonaanilides could be attained using appropriate soft nuclephile. Nitrenium ions are known to be soft electrophile which resulted in formation intermolecular C-N bond formation (Scheme 1.41).[74]



Scheme 1.41. Mal's approach for N-selective arylation of sulfonanilides.

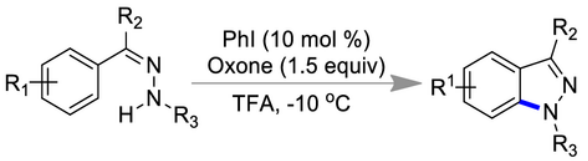
Intramolecular C-N bond synthesis

Junbiao Chang's group have reported molecular iodine promoted C-N bond synthesis reaction.[75] Pyrido[1,2-a]benzimidazoles derivatives could be isolated from N-arylpyridin-2-amines by the use of iodine & base combination at 60 °C (Scheme 1.42).



Scheme 1.42. Chang's strategy for synthesis of pyrido[1,2-a]benzimidazoles.

In 2014, Tanimori and co-workers presented N-substituted indazole synthesis from arylhydrazones.[76] They established an iodobenzene catalysed C-H amination protocol of using oxone as an oxidant at -10 ^{0}C (Scheme 1.43).

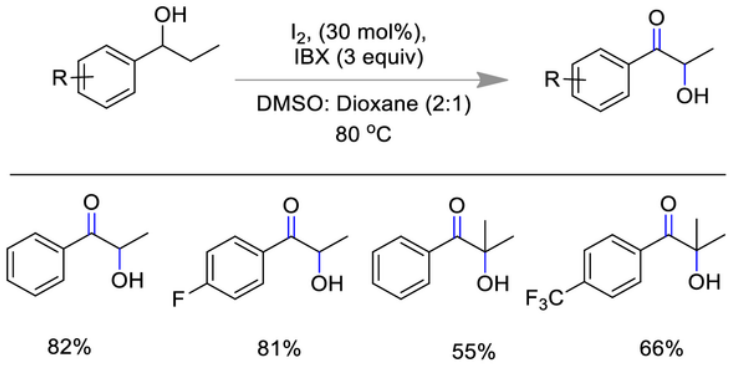


Scheme 1.43. Iodobenzene catalysed C-H amination reaction.

1.4.4 Carbon-oxygen bond synthesis

Intermolecular C-O bond construction

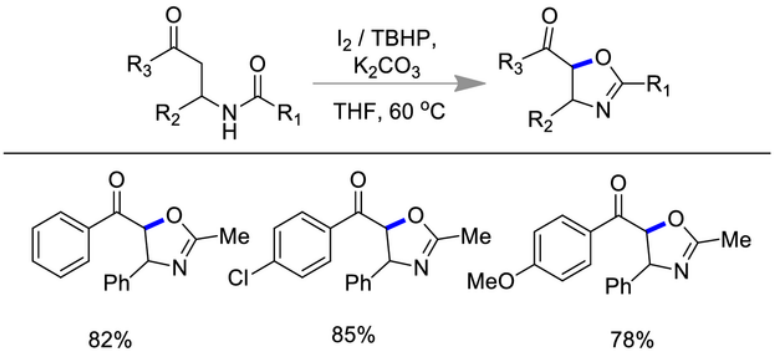
α-hydroxy ketones were synthesized from benzylic secondary alcohol using IBX and I_2 combination in DMSO & dioxane solvent. A variety of α-hydroxy ketones was efficiently prepared by this methodology (Scheme1.44).[77]



Scheme 1.44. Sekar's approach for preparation of a-hydroxy ketone.

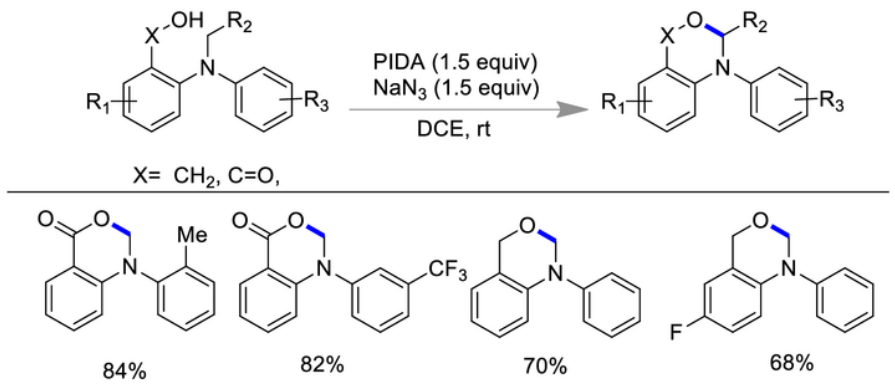
Intramolecular C-O bond construction

Several C-O bond synthesis reaction has been achieved in presence of iodine-based reagents.[78] A metal free intramolecular C-O bond construction catalyzed by molecular iodine, was discovered in THF in presence of TBHP.[78a] As a result, oxazolines were obtained from β-acylamino ketones with good to high efficiency (Scheme 1.45).



Scheme 1.45. I_2 catalysed oxazolines synthesis.

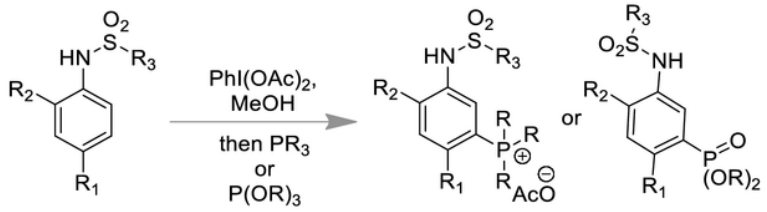
Kang Zhao and coworkers reported an intramolecular metal free C(sp3)-O bond synthesis by the use of PIDA-NaN_3.[78b] This dehydrogenative strategy gave us a large spectrum of aminal skeleton under mild reaction condition (Scheme1.46).



Scheme 1.46. Zhao's approach for oxygenation of N, N-diaryl tertiary amines.

1.4.5 Carbon- phosphorus bond synthesis

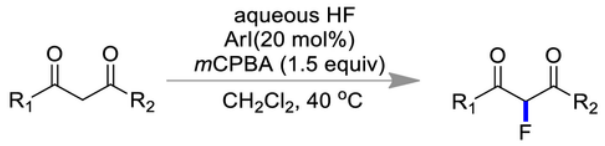
Regioselective *meta* C-H functionalization of sulfanilide furnished C-P bond when treated with PIDA in methanol followed by addition of phosphorous moiety.[79] This one pot C-H activation methodology did not require any metal catalyst. The reaction proceeded active dienimine intermediate which is formed by the reaction of sulfanilide and PIDA in methanol. Then subsequent attacks happened from nucleophile phosphines or phosphites provided aryl phosphonium salts or phosphonates (Scheme 1.47).



Scheme 1.47. Canesi's approach for DIB mediated C-P bond formation.

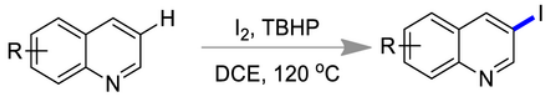
1.4.6 Carbon- halogen bond synthesis

Various carbon halogen bond construction reaction was developed by several investigators using iodine reagents.[80] In 2013, an iodoarene-catalyzed fluorination of 1,3-dicarbonyl compounds was discovered by Kitamura's group. (Difluoroiodo)arene, a trivalent iodine compound was first formed from the mixture of *m*-CPBA, an aqueous HF and iodoarenes.[80a] Then this iodine reagent react with enols afforded desired fluorinating compounds (Scheme1.48).



Scheme 1.48. Iodoarene catalysed fluorination of 1,3-dicarbonyl compounds.

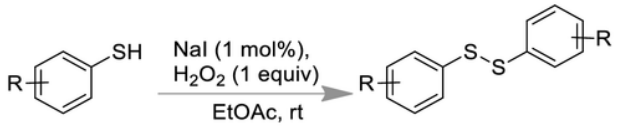
Iodine substituted quinolones are important building block in natural product and medicinal agent. Therefore, preparation of iodinated quinolones are always reputed task for organic chemists. A metal free regioselective iodination of quinolines at the C3 position was reported using molecular iodine and TBHP combination (Scheme1.49).[80b]



Scheme 1.49. C3 iodination of quinolines using molecular iodine.

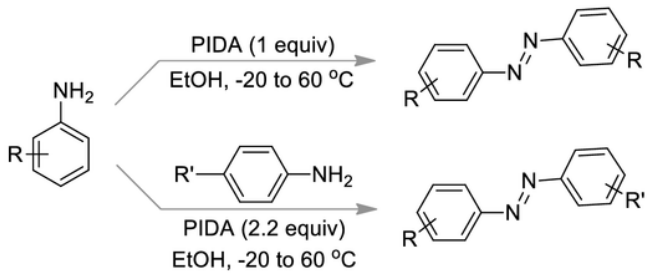
1.4.7 Heteroatom-heteroatom bond synthesis[81]

Kirihara and co-workers developed NaI/H_2O_2 mediated oxidative homocoupling of thiols to provide disulfides.[81a] From mechanistic sight of view iodine was produced from oxidation of NaI by oxidant H_2O_2. This iodine supposed to react with a thiol to furnish iodosulfonium intermediate followed by react with another molecule of thiol to give disulfide product (Scheme1.50).



Scheme 1.50. NaI/H_2O_2 mediated disulfides synthesis from thiols.

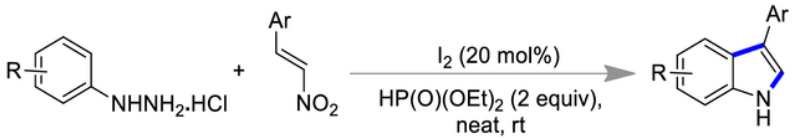
In 2014, dehydrogenative N-N bond coupling reaction of anilines was revealed by Hazra and co-workers. Using 1.0 equivalent of PIDA symmetrical azobenzenes via homocoupling and increasing it to 2.2 equiv. unsymmetrical azobenzenes through cross coupling are isolated in ethanol at low temperature (Scheme1.51).[81b]



Scheme 1.51. Hazra's approach for preparation of azoderivatives.

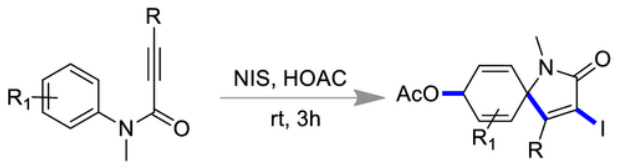
1.4.8 Tandem C-C & C-X (X= N, O & I) bond Synthesis

Direct synthesis of indole derivatives under room temperature condition from mixture of arylhydrazines & nitroalkenes was possible by taking molecular iodine and diethyl phosphite combination. A large spectrum of indole compounds were isolating by this strategy in good yield.[82] The reaction supposed to go via hydrazone intermediate followed by [3, 3]-sigmatropic rearrangements (Scheme 1.52).



Scheme 1.52. Iodine catalysed synthesis of indole derivatives from arylhydrazines.

Metal free an efficient electrophilic intramolecular ipso-iodocyclization of para-unsubstituted arylalkynes has been reported to achieve spiro[4,5]trienyl acetates. When, para-unsubstituted arylalkynes were treating with NIS (N-iodosuccimide) and acetic acid, ipso-iodocyclization was possible (Scheme1.53).[83]



Scheme 1.53. NIS mediated *ipso*-iodocyclizations of para-unactivated arylalkynes.

1.5 CONCLUSION & OBJECTIVE

Therefore, we have herein mainly summarized historical background of iodine based reagents and its application towards organic synthetic methodology. The objective of this thesis was to improve iodine-based reagents mediated metal free

synthetic methodologies for construction of C-N (Figure 1.4) and C-O (Figure 1.5) bonds.

❖ *Dehydrogenative intra and intermolecular C-N bond synthesis.*

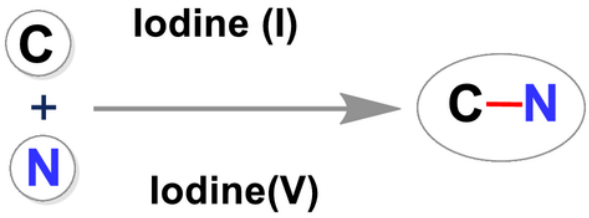


Figure 1.4. Approach for *dehydrogenative C-N bond synthesis.*

❖ *Dehydrogenative intermolecular C-O bond synthesis.*

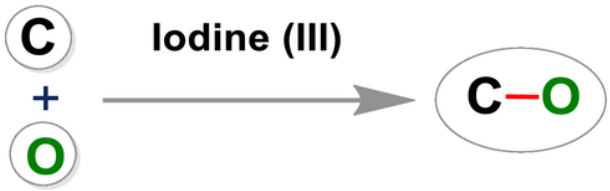


Figure 1.5. Approach for *dehydrogenative C-O bond synthesis.*

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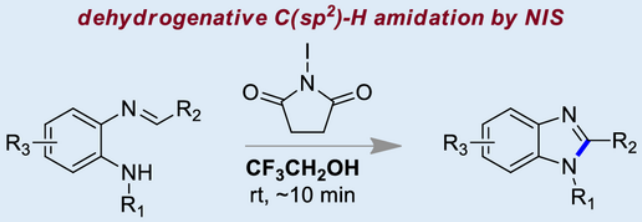
CHAPTER 2

Metal Free Intramolecular C(sp2)-H Amidation for Synthesis of 1,2-Disubstituted Benzimidazole

2.1 ABSTRACT



This section mainly focuses on the development of simplest approach towards the utilization of monovalent electrophilic iodine reagent, *N*-iodosuccinimide (NIS) for an intramolecular dehydrogenative C(sp2)H-NH bond formation reaction. The stronger oxidising properties of hypervalent iodine(III) reagents restricted their use for oxidative C-H amination reactions. However, the C-N synthesis reaction of non-prefunctionalized C-H and N-H bonds works fine without any trouble under base-free and metal-free mild condition. The reaction is simply operative under room temperature condition and 1,2-disubstituted benzimidazoles are prepared with high efficiency of yield.

2.2 INTRODUCTION

The mimetic synthetic approach based on small molecular system chemistry[1] is well known for knowing the nature of complex chemical reactions and thereby applying them accordingly in a simplified manner. In this context, the soft forces or cooperative multiple weak interactions[2] such as hydrophobic effect[3], halogen bonding[4], charge-transfer[5], cation-π and anion-π[6] etc. are also significantly explored within the scope of chemical reaction systems.[7] To understand the role of such weak supramolecular interactions controlling a chemical reaction it is therefore necessary to analyze the reaction system as a whole at molecular level.[8]

Improvement of environmentally benign methods[9] for making carbon-nitrogen bond is of huge importance[10] because of the abundance of nitrogen containing compounds among numerous synthetic intermediates, natural products, pharmaceutical agents and biologically active molecules etc. In contrast to metal enabled carbon-nitrogen bond construction reactions[11], direct amination of C-H bond without any use of metal-based reagent is of great significant to convey various amines by sustainable methods.[12] Therefore, waste free and cost effective methods for the synthesis of C-N bonds utilizing metal-less and organo-iodine reagents are in demand[13] towards exploring several cross-dehydrogenative coupling (CDC) or oxidative cross C-N bond formation reactions.[14] However, C-H amination reactions by using monovalent iodine(I) reagent like *N*-iodosuccinimide (NIS) are very limited.[15]

Chapter 2: Metal Free Intramolecular C(sp2)-H Amidation for Synthesis of 1,2-Disubstituted Benzimidazole

Benzimidazoles being a heterocyclic moieties are well recognized due to their substantial utility in pharmaceutical and material chemistry.[16] These molecules are known to exhibit anti-cancer,[17] anti-infective,[18] anti-inflamatory,[19] anti-hepatitis B,[20] anti-HIV,[21] anti-depressant,[22] and anti-tumor[23] activities. The drug esomeprazole (Nexium), having a benzimidazole moiety was found to be one of the best-demanding drugs in 2009.[24] 1,2-Disubstituted benzimidazoles are also important heterocyclic scaffolds holding a broad range of biological activities (Figure 2.1).[19-20,25] Therefore, the methodology for preparation of 1,2 disubstituted benzimidazoles has been paid a large of attention by investigators. Although there are variety of methods available for construction of N-H benzimidazoles skeletal, but metal-less direct access to *N*-substituted benzimidazoles were limited.

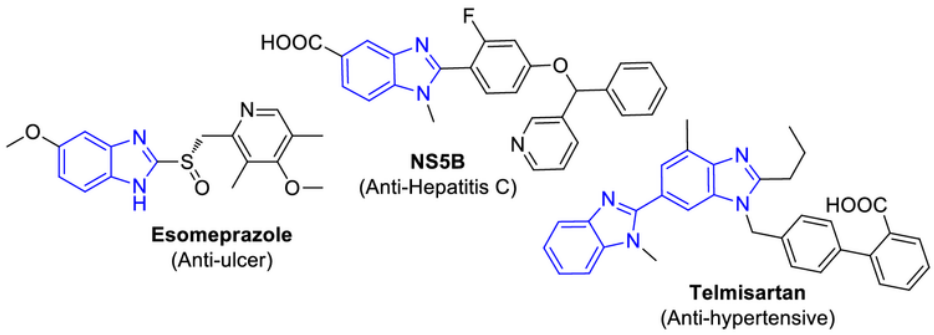
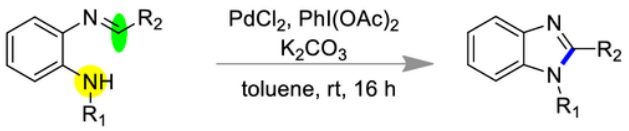


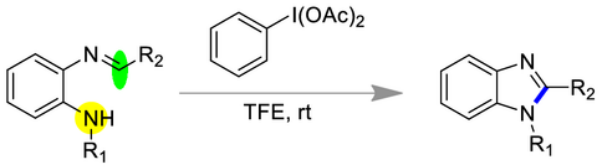
Figure 2.1. Drugs having benzimidazoles moiety.

In 2011, Zeng's group developed Pd-catalyzed dehydrogenative intramolecular amidation using an oxidant, PIDA in solvent toluene for 16 h constant stirring at room temperature (Scheme 2.1).[26]



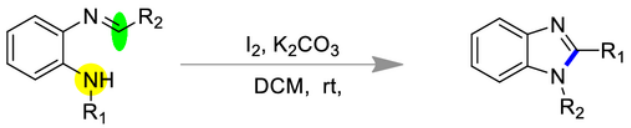
Scheme 2.1. Zeng's intramolecular amidation catalyzed by Pd (II).

Gratifyingly, similar type of reaction was carried out without using Pd catalyst and base, treated with PIDA at room temperature condition. The reaction took less than 30 min while instead of toluene fluorinated solvent, TFE was used (Scheme 2.2).[27]



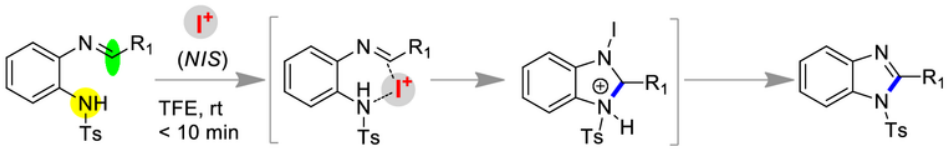
Scheme 2.2. Mal's approach for PIDA mediated amidation.

Very recently, Yu and Chang with co-workers presented molecular iodine and base induced intramolecular C-H amidation reaction (Scheme 2.3).[28] In this reaction, they did not isolate any imine derivative.



Scheme 2.3. Yu and Chang's of C-H amidation approach using iodine.

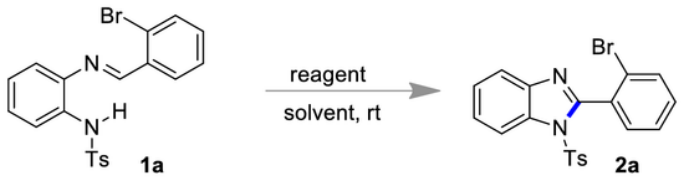
However, a simpler methodology for similar transformation for the synthesis of *N*-substituted benzimidazole from *o*-sulfonamidophenyldiamines has been reported. We have developed an intramolecular C(sp2)-H amidation reaction (Scheme 2.4)[29] using monovalent iodine instead of strong oxidant such as phenylene iodine diacetate (PIDA).



Scheme 2.4. NIS enabled intramolecular C(sp2)–H amidation.

2.3 RESULTS AND DISCUSSIONS

Table 2.1. Screening of reaction conditions.



Entry	Reagent (equiv)	Solvent	Time (min)	Yield[d] (%)
1	*N*-iodosuccinimide (1.1)	TFE	15 min	81
2	*N*-iodosuccinimide (1.5)	TFE	15 min	91
3	*N*-iodosuccinimide (1.8)	TFE	10 min	98
4	*N*-iodosuccinimide (1.8)	MeCN	10 min	81
5	*N*-iodosuccinimide (1.8)	Dichloromethane	30 min	85
6	*N*-iodosuccinimide (1.8)	DCM	20 min	86
7	*N*-iodosuccinimide (1.8)	THF	30 min	40
8	*N*-iodosuccinimide (1.8)	DMF	10 min	56
9	*N*-iodosuccinimide (1.8)	EtOAc	25 min	61
10	*N*-iodosuccinimide (1.8)	Ethanol	15 min	85
11	*N*-iodosuccinimide (1.8)	Acetone	20 min	61
12	*N*-iodosuccinimide (1.8)	1,4-Dioxane	30 min	80
13	*N*-iodosuccinimide (1.8)	$MeNO_2$	25 min	50
14	Iodine (1.8)	TFE	40 min	50

15	*N*-chlorosuccinimide(1.8)	TFE	25 min	55
16	*N*-bromosuccinimide (1.8)	TFE	35 min	75
17	TBAI (1.8) [a]	TFE	1 h	--[c]
18	TEAI (1.8)[b]	TFE	1h	--[c]

[a]Tetrabutyl ammonium iodide. [b]Tetraethyl ammonium iodide. [c]No Reaction. [d]Isolated yield after column purification.

Initially, N-tosyl imine (**1a**) [26] was taken as the model substrate for screening the reaction conditions. The N-tosyl benzimidazole product (**2a**) was formed in 98% yield when 1.8 equiv of *N*-iodosuccinimide (NIS) was utilized as a reagent in 2,2,2-trifluoroethanol (TFE) in open atmosphere under room temperature condition (Table 2.1, entry 3). Screening of other non-fluorinated solvents indicated TFE is the most productive solvent for this reaction (Table 2.1, entries 4-13). Using molecular iodine in TFE, without utilizing any base within 40 min, transformation led to the product with 50% of yield (Table 2.1, entry 14). Treatment with NCS or NBS as reagent in TFE substrate **1a** gave desired product with 55% and 75% yield respectively (Table 2.1, entries 15 and 16). An effort to use of alkyliodide salts as reagent did not provide desired product (Table 1, entries 17 & 18). Therefore, the reaction was standardized under this reaction condition with 1.8 equiv. of *N*-iodosuccinimide in TFE solvent (Table 2.1, entry 3).

Then, for further synthetic utility we focus on exploring substrate scope using the optimum condition for this carbon-nitrogen coupling strategy for preparation of 1,2-disubstituted benzimidazoles (Figure 2.2). *N*-Tosyl 2-substituted benzimidazoles

having differently substituted aryl ring at 2-position have been well studied. Benzimidazole derivatives containing electron deficient halogen groups (**2a-f**), -NO_2 (**2j-k**), -CN (**2i**) groups on aryl moiety were synthesized with high efficiency. Correspondingly, electron releasing alkyl (**2g-h**) or alkoxy (**2f**) groups bearing benzimidazole compounds were isolated in excellent yields. Construction of benzimidazole skeletal with fused aryl rings e.g. anthracenyl (**2l**), pyrenyl (**2m**) and heteroaromatic (**2n**) at 2-position were prepared with high efficiency. Benzimidazole derivative having cyclohexyl substitutent (**2o**) was successfully synthesized with 96% yield. X-ray crystallographic analysis data indicated the structure of compound **2h.**

Benzimidazoles bearing several functional groups such as hydroxy, carbonyl, olefin, alkyne, etc. on aryl ring at 2-position were also isolated with good to high efficiency (Figure 2.3). All the sensitive functional groups were well tolerated in the optimum condition.

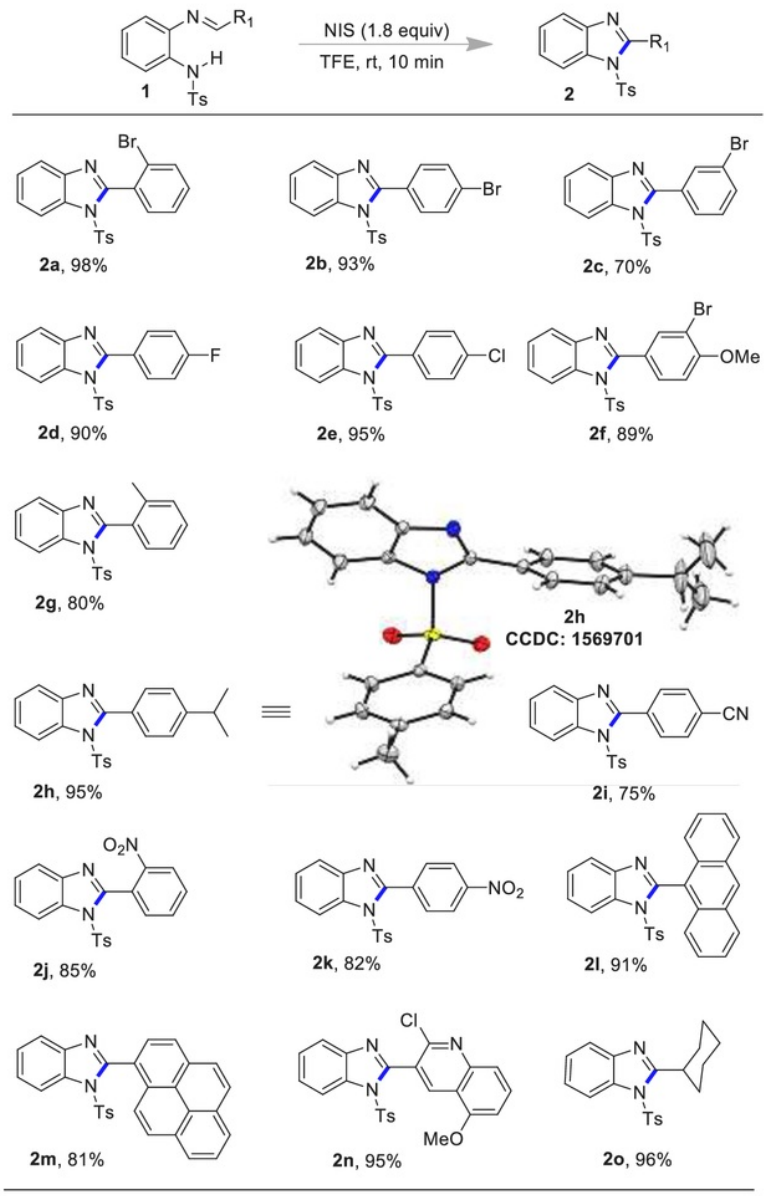


Figure 2.2. Exploring C-H amidation.

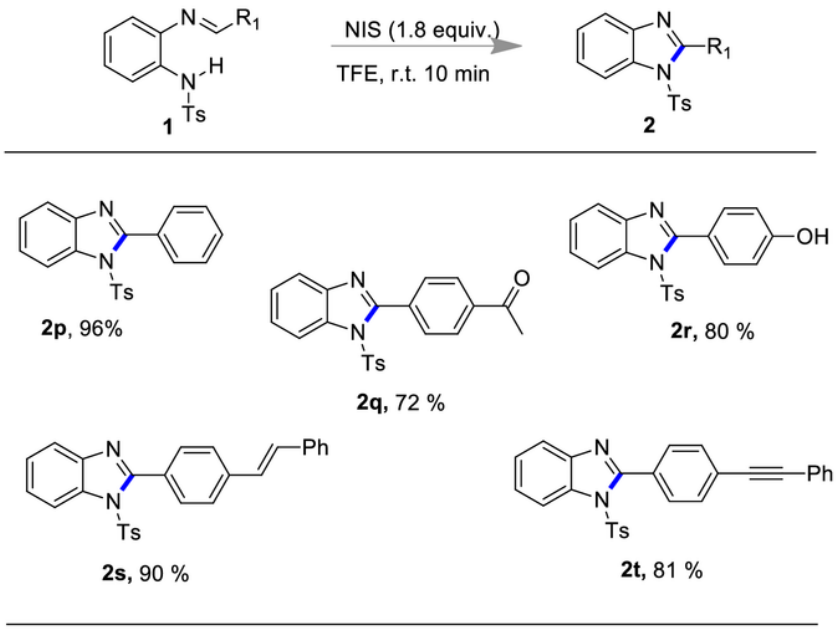


Figure 2.3. Functional group tolerance of C-H amidation.

Multi-substituted benzene core benzimidazoles (Figure 2.4) were also prepared with high efficiency. Substituents such as -Cl, -Me, -NO_2 and -COOH gave good yield of product. Electron rich methyl substituents (**2ab-ac**) furnished corresponding benzimidazoles in better yields than that of electron deficient groups (**2aa**, **2ad-af**).

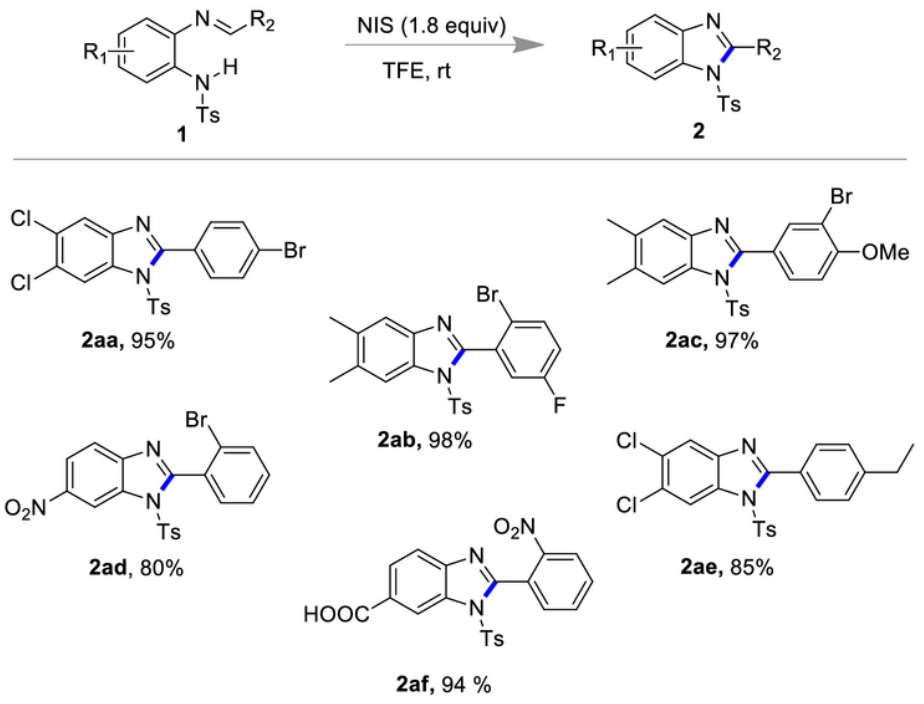


Figure 2.4. Synthesis of core-modified benzimidazoles.

Benzimidazoles containing different *N*-protecting groups were also applied towards this C-H amidation reaction. Also with *p*-methylbenzenesulfonyl (Ts) groups, other protecting groups such as methane sulfonyl, benzoyl groups and benzene sulfonyl were treated to isolate 1,2-disubstituted benzimidazole derivatives (Figure 2.5). Specially, products with sulfonyl protecting groups (**2ba-bc**) were isolated in comparatively higher yields than carbonyl protecting groups (**2bd, 2be**).

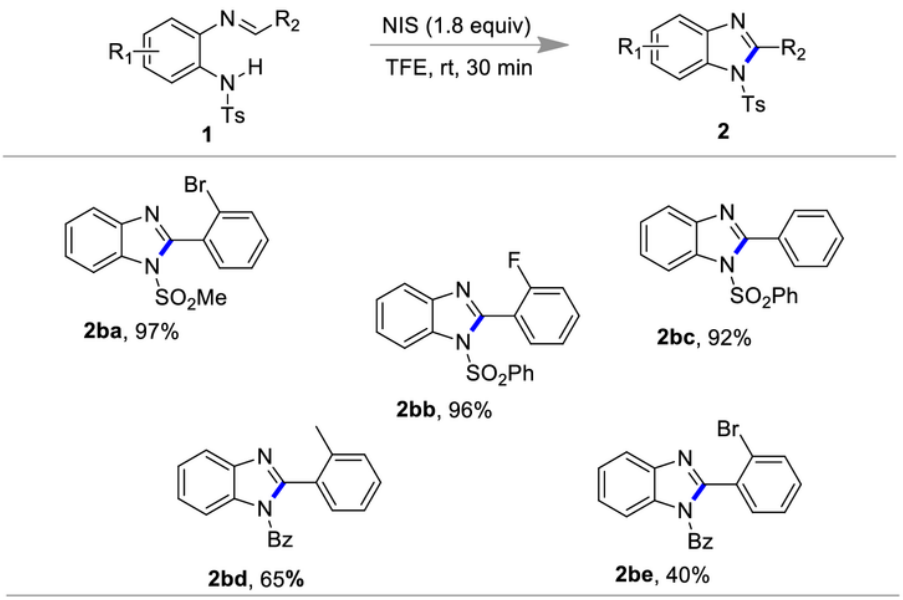


Figure 2.5. Benzimidazoles having different protecting groups.

Preparation of *N*-substituted benzimidazole was attained in one-pot approach. Amine and aldehyde (equimolar amount) are refluxed in ethanol and followed by adding 1.8 equiv. *N*-iodosuccinimide under room temperature condition, the benzimidazole **2a** could be formed in good yield (Figure 2.6).

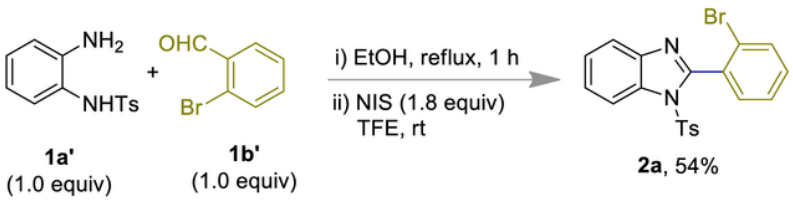


Figure 2.6. One-pot synthesis of 1,2-disubstituted benzimidazols.

De-protection of the *para*-toulenesulfonyl (-Ts) group from **2a** was carried out by the use of NaOH (5 M) in refluxing ethanol solvent [30] (Figure 2.7) and the de-protected benzimidazole compound 2-(2-bromophenyl)-1H-benzo[d]imidazole (**2a'**) was obtained in 73% yield.

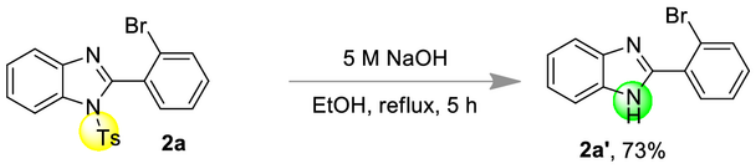


Figure 2.7. De-protection of tosyl(-Ts) group.

Some control experiments have been done and was shown in Figure 2.8. In presence TEMPO (Figure 2.8-i) or in the dark condition (Figure 2.8-ii), the substrate **1a** was treated under optimum condition, produced the product **2a** with similar yield as in standard condition. The kinetic isotopic effect[31] (Figure 2.8-iii) was calculated to be as k_H/k_D = 1.45. This indicates that the C (sp^2)-H bond is taking part in the transformation.

Based on our previous work,[32] & the control experiments on whatever we have done, a possible mechanism for reaction is outlined in Figure 2.9. Iodide moiety of N-iodosuccinimide being an electropositive species, is supposed to co-ordinate with the imine bond which is electron rich and *N*-center of –NH simultaneously to furnish an intermediate **3** followed by formation of cyclic iodonium ion intermediate **4**. Subsequently, the carbon-nitrogen bond construction with the formation of another intermediate **5** was anticipated. Anion formed from succinimide would assist to take

proton to form compound **6**. Finally, the aromatization by HI elimination furnished product **2**.

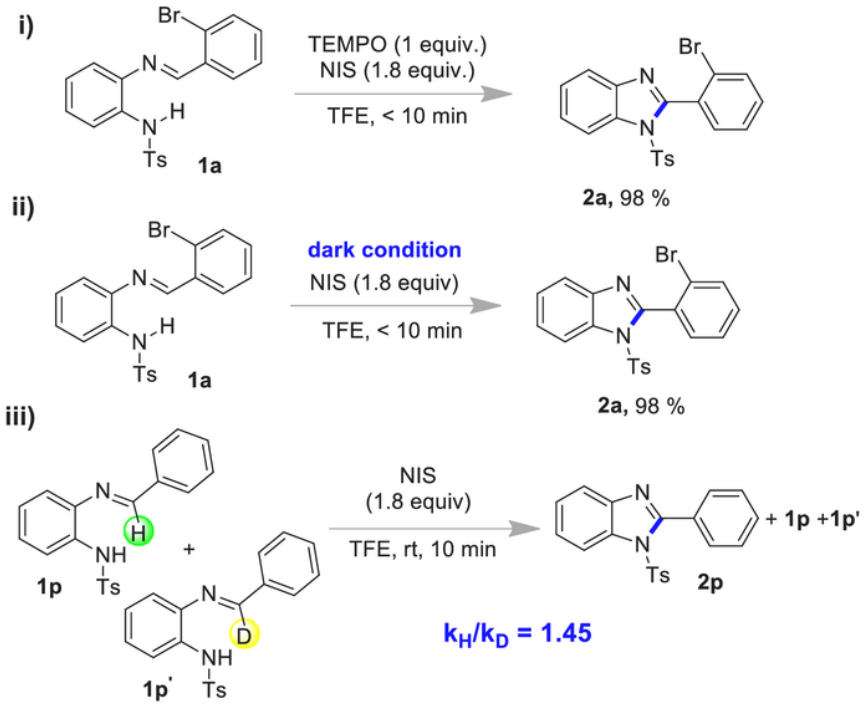


Figure 2.8. Control experiments. i) Reaction with TEMPO as a radical scavenger. ii) Reaction in the dark condition. iii)) KIE experiment.

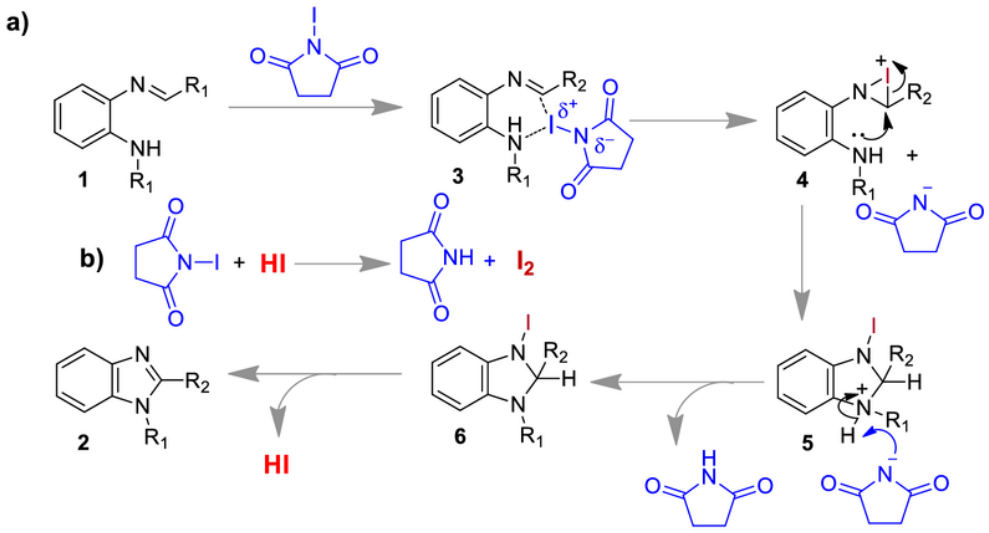


Figure 2.9. Possible mechanistic pathway.

Hydroiodic acid (HI) is one of the by-product of the reaction, which can protonate the *N*-center of -NHTs group leading to decrease of the nucleophilic character of nitrogen N-centre.

The excess use of NIS is attributed for the neutralization of by-product HI with the help of succinimide. Succinimide was isolated using 3:2 (hexane: ethyl acetate) mixture as eluent by column chromatography during detection of polar compound 2-(2-nitrophenyl)-1-tosyl-1H-benzo[d]imidazole-6-carboxylic acid (**2af**, Figure 2.4). Iodine was released when the reaction mixture was evaporated to dryness which indicates HI possibly react with excess NIS (Figure 2.9). The ^{1}H NMR spectra of separate reaction mixtures of deuterated aldimine (**1p′**) and aldimine (**1p**), suggest that the proton of succinimide comes from NH proton but not from aldimine C (sp^2)-H proton (Figure 2.48 & 2.49).

2.4 ROLE OF FLUORINATED SOLVENT[33] (TFE)

In order to reduce the charge transfer reactivity between amine nitrogen and iodine reagents, the nitrogen centers were protected with π-acceptors like -S=O (sulfonyl) or –C=O (benzoyl) group by the n→π* control.[34] Thus, utilizing the weak interactions like halogen bonding (N…I^+…π), n→π*, solvent effect etc. this C(sp^2)-H amidation reaction could be done easily. Kita's group have investigated that hypervalent iodine reagents in fluorinated solvent such as hexafluoroisopropanol (HFIP), the radical cationic intermediate finds stabilization by solvent due to its high polarity and low-nucleophilic nature of the solvent.[33e] Also Donohoe, Compton and coworkers presented how HFIP acts with the hypervalent iodine reagents.[35] Trifluoroethanol is also one of the commonly used important fluorinated solvents to stabilize cationic or cation-radical species produced in presence of iodine-based reagents.[33b,33c,33f] Following, the use of a highly polar and non-nucleophilic solvent 2,2,2-trifluoroethanol (TFE) was essential towards the success of the reaction because solvent TFE is known to stabilize the cationic iodonium ion. Therefore, we concluded that TFE promoted the reaction by helping to stabilize intermediate **4** and **5** (Figure 2.9).

2.5 KINETIC ISOTOPIC EFFECT (KIE) EXPERIMENT

The kinetic isotopic study[31] is given in Figure 2.8. It has been carried out by following the general procedure for synthesis of *N*-substituted benzimidazoles. The reaction was performed using of aldimine (**1p**) and deuterated aldimine (**1p′**) equimolar amount in presence of 1.8 equiv *N*-iodosuccinimide in TFE. The reaction mixture was dried by evaporation and crude mixture was passed through a short-pad silica gel column applying hexane: ethyl acetate (9:1) mixture as eluent. The ^{1}H NMR spectra of the mixture for whole sample was taken in CD_3Cl for the calculation of k_H/k_D.

2.6 CONCLUSIONS

In conclusion, the reaction system and the mechanistic insight suggest an efficient route to synthesis of functional molecules with help of multiple weak interactions. The selection of appropriate reaction condition helps to carry out difficult reactions. Through the C(sp^2)-H amination reaction using *N*-iodosuccinimide, 1,2-disubstituted benzimidazole were synthesized easily. Thus, we have achieved an additive base free synthesis of benzimidazoles. A plethora of substrate scopes define the synthetic utility of the methodology.

2.7 EXPERIMENTAL PORTION

General information. All reaction are performed in normal condition not in inert condition. Chemical yields are indicated as isolated yield which were purified by Column chromatographic using silica gel (mesh 100-200) and hexane-ethyl acetate mixtures as eluent, unless otherwise specified. NMR spectra were recorded either on a Bruker 400 MHz or on a Bruker 700 MHz instrument at room temperature. The chemical shift values are given in parts per million (ppm) with respect to residual chloroform (7.26 ppm for ^{1}H and 77.16 for ^{13}C) (in case of DMSO-d_6: 2.5 ppm for ^{1}H and 39.5 for ^{13}C). The peak patterns are indicated as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, m = multiplet). The coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were obtained on an ESI-TOF (time of flight) mass spectrometer. FT-IR spectra were recorded in wave number (cm^{-1}). Melting points of the compounds were measured using a digital melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was done on Merck Silica Gel F254 plates (0.25 mm). Solvents (both for reaction and chromatography), o-phenylenediamine and its derivatives, all corresponding aldehydes were bought from commercial source and used without further purification. All starting materials were prepared by following literature report.[26]

General Procedure for Preparation of N-Substituted Benzimidazoles. NIS (0.251 mmol, 1.8 equiv) was added to a stirred solution of *N*-substituted imine **1** (0.139 mmol, 1 equiv) in 0.5 ml TFE (2,2,2-trifluoroethanol) at room temperature. The progress of the reaction was monitored by thin layer chromatography (TLC) using appropriate mixture of ethyl acetate and hexane as eluent. Upon completion of the reaction, solvent

was completely evaporated to dryness. Then the crude reaction mixture was purified by silica gel column chromatography using n-hexane and ethyl acetate as eluent.

Procedure for Preparation of 2-(2-Bromophenyl)-1-tosyl-benzo[d]imidazole (2a). NIS (57 mg, 0.251 mmol) was added to a stirred solution of *N*-(2-((2-bromobenzylidene)amino)phenyl)-4-methylbenzenesulfonamide **1a** (60 mg, 0.139 mmol) in TFE (0.5 mL) at room temperature. Upon completion (ca. 10 min) of the reaction, TFE was completely evaporated to dryness. The crude mixture was purified by silica gel column chromatography using n-hexane and ethyl acetate (92:8) as eluent to 2-(2-bromophenyl)-1-tosyl-benzo[d]imidazole **2a** (58.5 mg, 0.137 mmol, yield: 98%).

Compound characterization data

2-(2-Bromophenyl)-1-tosyl-benzo[d]imidazole (2a).[27] 58.5 mg; Yield: 98%; R_f = 0.5 (hexane:ethyl acetate 4:1); white solid; lit.[27] mp 154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J*=8 Hz, 1H), 7.8 (d, *J* = 8 Hz, 1H), 7.66 (d, *J* = 8 Hz, 1H), 7.54 (d, *J* = 8 Hz, 2H), 7.48–7.39 (m, 5H), 7.19 (d, *J* = 8 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 146.1, 142.2, 135.1, 132.8, 132.6, 132.4, 132.0, 131.7, 129.9, 127.5, 126.5, 125.8, 125.1, 124.7, 120.8, 114.2, 21.7.

2-(4-Bromophenyl)-1-tosyl-benzo[d]imidazole (2b). 55 mg; Yield: 93%; R_f = 0.5 (hexane: ethyl acetate 4:1); white solid; mp 135-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8 Hz, 1H), 7.10 (d, *J* = 8 Hz, 1H), 7.61 (d, *J* = 8 Hz, 2H), 7.50 (d, *J* = 8 Hz, 2H), 7.41 (m, 2H), 7.33 (d, *J* = 8, 2H), 7.11 (d, 2H), 2.32 (s, 3H); ^{13}C NMR (175

MHz, $CDCl_3$): δ 153.1, 146.0, 142.7, 134.9, 133.9, 132.5, 131.1, 129.9, 129.1, 127.0, 125.8, 125.6, 125.5, 120.5, 115.3, 121.7; IR (KBr): $\tilde{\nu}$ = 2921, 1562,1480, 1450, 1377, 1250, 1189, 1177, 1072, 1057 cm^{-1}; HR-MS (ESI-TOF): m/z = 427.0114, calcd for $C_{20}H_{15}BrN_2O_2S$ ($M+H^+$): 427.0110.

2-(3-Bromophenyl)-1-tosyl-benzo[d]imidazole (2c). 62 mg; Yield: 70%; R_f = 0.5 (hexane:ethyl acetate 4:1); white semi-solid; ^1H NMR (700 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.60 (s, 2H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.4 Hz, 3H), 7.13 (d, *J* = 8.1 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 152.2, 146.1, 142.5, 135.0, 133.9, 133.5, 133.4, 132.0, 130.0, 129.7, 129.3, 127.1, 125.8, 125.5, 121.7, 120.3, 115.2, 21.8; IR (KBr): $\tilde{\nu}$ = 2924, 2108, 1640, 1536, 1448, 1381, 1253, 1177, 1084, 1012 cm^{-1}; HR-MS (ESI-TOF): m/z = 427.0106, calcd for $C_{20}H_{15}BrN_2O_2S$ ($M+H^+$): 427.0110.

2-(4-Fluorophenyl)-1-tosyl-benzo[d]imidazole (2d).[27] 32 mg; Yield: 90%; R_f = 0.5 (hexane:ethyl acetate 4:1); white solid; lit.[27] mp 118–120 °C; ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8 Hz, 1H), 7.71 (d, *J* = 8 Hz, 1H), 7.62 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 2H), 7.46–7.37 (m, 2H), 7.31 (d, *J* = 8 Hz, 2H), 7.18–7.10 (m, 4H), 2.33 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 164.3 (d, $^1J_{C,F}$ = 249.9 Hz), 153.2, 146.0, 142.6, 135.0, 134.0, 131.7 (d, $^3J_{C,F}$ = 8.6 Hz), 129.9, 127.0, 126.1 (d, $^4J_{C,F}$ = 3.4 Hz), 125.7, 125.6, 120.5, 115.3, 115.1 (d, $^2J_{C,F}$ = 21.8 Hz), 21.7.

2-(4-Chlorophenyl)-1-tosyl-benzo[d]imidazole(2e).[28] 76 mg; Yield: 95%; R_f = 0.5 (hexane:ethyl acetate 4:1); white solid; lit.[28] mp 138–139 °C; ^1H NMR (700 MHz,

$CDCl_3$): δ 8.19 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.48 – 7.42 (m, 3H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 153.1, 146.1, 142.7, 137.1, 135.0, 134.0, 132.3, 130.0, 128.6, 128.2, 127.0, 125.8, 125.6 120.6, 115.3, 21.8.

2-(3-Bromo-4-methoxyphenyl)-1-tosyl-benzo[d]imidazole (2f).[27] 53 mg; Yield: 89%; R_f = 0.4 (hexane:ethyl acetate 4:1); white solid; lit.[27] mp 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8 Hz, 1H), 7.70 (d, *J* =7.2 Hz, 1H), 7.66–7.64 (m, 2H), 7.44–7.37 (m, 2H), 7.34 (d, *J* = 8 Hz, 2H), 7.12 (d, *J* = 8 Hz, 2H), 6.99 (d, *J* = 8 Hz, 1H), 4.00 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 157.8, 152.6, 146.0, 142.6, 135.4, 135.0, 134.0, 131.9, 129.9, 127.0, 125.6, 125.5, 123.5,120.4, 115.3, 110.9, 110.8, 56.5, 21.8.

2-(Ortho-Tolyl)-1-tosyl-benzo[d]imidazole (2g).[27] 25 mg; Yield: 80%; R_f = 0.5 (hexane:ethyl acetate 4:1); white solid; lit.[27] mp 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8 Hz, 1H), 7.79 (d, *J* = 8 Hz, 1H), 7.50–7.44 (m, 5H), 7.31–7.28 (m, 2H), 7.22–7.18 (m, 3H), 2.40 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 152.5, 146.0, 142.3, 139.1, 135.4, 133.3, 130.8, 130.5, 130.3, 129.9, 129.8, 127.5, 125.5, 125.0, 124.9, 120.5, 114.5, 21.8, 20.0.

2-(4-Isopropylphenyl)-1-tosyl-benzo[d]imidazole (2h).[27] 48 mg; Yield: 95%; R_f =0.5 (hexane:ethyl acetate 4:1); white solid; lit.[27] mp 135–137 °C; ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8 Hz, 1H), 7.71(d, *J* = 8 Hz, 1H), 7.53 (d, *J* = 8 Hz, 2H), 7.42–7.29 (m, 6H), 7.07 (d, *J* = 8 Hz, 2H), 3.01 (sept, *J* = 8 Hz, 1H), 2.32 (s, 3H), 1.32 (d, *J*

= 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 151.8, 145.7, 142.8, 135.1, 134.1, 131.0, 129.8, 127.5,127.2, 125.9, 125.4, 125.3, 120.4, 115.3, 34.3, 24.0, 21.7.

4-(1-Tosyl-benzo[d]imidazol-2-yl)benzonitrile(2i).[27] 45 mg**;** Yield: 75%; R_f = 0.4 (hexane:ethyl acetate 4:1); white solid; lit.[27] mp 146–148 °C; ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8 Hz, 1H), 7.77–7.73 (m, 5H), 7.50–7.44 (m, 2H), 7.34 (d, *J* = 8 Hz, 2H), 7.13 (d, *J* = 8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 152.0, 146.4, 142.7, 134.8, 134.7, 133.9, 131.7, 131.5, 130.1, 126.9, 126.3, 125.9, 120.8, 118.3,115.2, 114.3, 21.8.

2-(2-Nitrophenyl)-1-tosyl-benzo[d]imidazole (2j). 68 mg; Yield: 85%, R_f = 0.3 (hexane:ethyl acetate 4:1); Yellow solid, mp 80-81 °C; ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 7.1 Hz, 3H), 7.54 – 7.45 (m, 4H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 148.9, 148.5, 146.4, 142.4, 134.9, 133.2, 133.1, 132.9, 131.6, 130.1, 127.4, 126.3, 126.0, 125.2, 124.8, 120.8, 114.0, 21.8; IR (KBr): $\tilde{\nu}$ = 2924, 1638, 1531, 1448, 1347, 1253, 1176, 1087,1013 cm^{-1}; HR-MS (ESI-TOF): m/z=394.0855, calcd for $C_{20}H_{15}N_3O_4S(M+H^+)$: 394.0856.

2-(4-Nitrophenyl)-1-tosyl-benzo[d]imidazole(2k).[28] 65 mg; Yield: 82%; R_f =0.4 (hexane:ethyl acetate 4:1): Yellow solid, lit.[28] mp 168–170 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7 Hz, 2H), 8.20 (d, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 7 Hz, 1H),7.50−7.43 (m, 2H), 7.35 (d, *J* = 6.3 Hz, 2H), 7.15 (d, *J* = 6.3 Hz, 2H),

2.35 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 151.7, 149.0, 146.4, 142.7, 136.5, 134.8, 133.9, 132.1, 130.1, 126.9, 126.4, 125.9, 122.9, 120.9, 115.3, 21.8.

2-(Anthracen-9-yl)-1-tosyl-benzo[d]imidazole (2l).[27] 54 mg; Yield: 91%; R_f =0.45 (hexane:ethyl acetate 4:1); yellow solid; lit.[27] mp 195–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.36 (d, *J* = 8 Hz, 1H), 8.05 (d, *J*= 8.4 Hz, 2H), 7.89 (d, *J* = 8 Hz, 1H), 7.56 –7.50 (m, 2H), 7.44-7.40(m, 2H), 7.23–7.17 (m, 4H), 6.97 (d, *J*=8 Hz, 2H), 6.77 (d, *J*=8 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 150.3, 145.6, 142.6, 134.4, 133.6, 131.9, 130.9, 130.4, 130.1, 129.5, 128.5, 127.5, 127.2, 126.6, 125.8, 125.7, 125.3, 125.0, 123.6, 120.8, 114.5, 21.7.

2-(Pyren-1-yl)-1-tosyl-benzo[d]imidazole (2m).[27] 42 mg; Yield: 81%; R_f=0.45 (hexane:ethyl acetate 4:1); white solid; lit.[27] mp 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, *J* = 8 Hz, 1H), 8.26 (d, *J* = 8 Hz, 2H), 8.20–8.13 (m, 4H), 8.04 (t, *J* = 8 Hz, 1H), 7.90 (d, *J* = 8 Hz, 1H), 7.82 (d, *J* = 9.2 Hz, 1H), 7.57–7.49 (m, 3H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 2H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 145.7, 142.6, 134.8, 133.8, 132.8, 131.2, 131.0, 130.6, 129.4, 129.3, 129.0, 128.4, 127.4, 127.2, 126.4, 126.0, 125.8, 125.7, 125.2, 124.4, 124.3, 124.3, 124.1, 123.6, 120.7, 114.9, 21.3.

2-Chloro-6-methoxy-3-(1-tosyl-benzo[d]imidazol-2-yl)-quinolone (2n).[27] 57 mg; Yield: 95%; R_f = 0.4 (hexane:ethyl acetate 3:1); white solid; lit.[27] mp 171–173 °C; ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.17 (s, 2H), 8.02 (d, *J* = 9.1 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.51–7.45 (m, 5H), 7.19 (d, *J* = 7.7 Hz, 2H), 7.12 (s, 1H), 3.96 (s, 3H), 2.37 (s, 3H) ; ^{13}C NMR (175 MHz, $CDCl_3$): δ 158.8, 148.2, 146.7, 146.4, 144.2, 142.3, 140.5,

134.9, 133.0, 130.2, 130.1 127.4, 126.9, 126.2, 125.3, 124.8, 124.3, 121.0, 114.3, 105.6, 55.9, 21.8.

2-Cyclohexyl-1-tosyl-benzo[d]imidazole (2o). [27] 65 mg; Yield: 96%; R_f=0.5 (hexane: ethyl acetate 4:1); white solid; lit.[27] mp 107-109 ºC; ^{1}H NMR (400 MHz, CDCl3): δ8.05–8.03 (m, 1H), 7.75 (d, *J* = 8 Hz, 2H), 7.68–7.66 (m, 1H), 7.35–7.30 (m, 2H), 7.27 (d, *J* = 8 Hz, 2H), 3.52–3.45 (m, 1H), 2.38 (s, 3H), 1.93–1.84 (m, 4H), 1.75–1.66 (m, 3H), 1.43–1.30 (m, 3H); ^{13}C NMR (100 MHz,$CDCl_3$): δ159.8, 145.9, 142.1, 136.1, 133.0, 130.3, 126.7, 124.8, 124.7, 119.9, 114.1, 38.3, 32.7, 26.4, 25.9, 21.8.

2-Phenyl-1-tosyl-1H-benzo[d]imidazole (2p).[28] 57 mg; Yield: 96 %; R_f = 0.4 (hexane:ethyl acetate 4:1): white solid, lit.[28] mp 103 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8 Hz, 1H), 7.73 (d, *J* = 8 Hz, 1H), 7.62 (d, *J* = 8 Hz, 2H), 7.55 (t, *J* = 8 Hz, 1H), 7.50 – 7.36 (m, 4H), 7.33 (d, J = 8.0 Hz, 2H), 7.08 (d, *J* = 8 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 145.8, 142.7, 135.0, 133.9, 130.9, 130.6, 130.1, 129.8, 127.7, 127.0, 125.5, 125.4, 120.5, 115.2, 21.7.

1-(4-(1-Tosyl-1H-benzo[d]imidazol-2-yl)phenyl)ethanone (2q). 40 mg; Yield: 72 %; R_f = 4.5 (hexane:ethyl acetate 4:1); white solid; mp 164-165 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 7.81 – 7.68 (m, 3H), 7.48-7.39 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 2.69 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 153.0, 146.1, 142.8, 138.4, 134.9, 134.7, 133.9, 131.3, 130.0, 127.7, 127.0, 126.0, 125.7, 120.8, 115.3, 26.9, 21.8. ; IR (KBr): $\tilde{\nu}$

= 2063, 1645, 1380, 1256, 1174, 1080 cm^{-1}; HR-MS (ESI-TOF): m/z = 391.1112, calculated for $C_{22}H_{18}N_2O_3S$ ($M+H^+$): 391.1111.

4-(1-Tosyl-1H-benzo[d]imidazol-2-yl)phenol (2r).[28] 48 mg; Yield: 80 %; R_f = 0.4 (hexane:ethyl acetate 7:3); light brown solid; lit.[28] mp 163–164 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.22 (d, *J* = 8 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H), 7.08 (d, *J* = 8 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 154.9, 145.9, 145.8, 141.8, 134.9, 133.8, 132.7, 129.8, 127.2, 125.6, 120.5, 119.8, 115.5, 115.2, 21.7. HR-MS (ESI-TOF): m/z = 365.0984, calculated for $C_{20}H_{16}N_2O_3S$ ($M+H^+$): 365.0954.

(E)-2-(4-styrylphenyl)-1-tosyl-1H-benzo[d]imidazole (2s): 54 mg; Yield: 90%; R_f = 0.5 (hexane:ethyl acetate 9:1); white solid; mp 170 – 172 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.47 – 7.41 (m, 2H), 7.41 – 7.27 (m, 5H), 7.26 (d, *J* = 8 Hz, 1H), 7.19 (d, *J* = 16.4 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 145.8, 142.9, 139.7, 137.1, 135.1, 134.1, 131.4, 130.6, 129.83, 129.0, 128.9, 128.2, 127.9, 127.1, 126.9, 125.8, 125.6, 125.5, 120.5, 115.4, 21.7. IR (KBr): $\tilde{\nu}$ = 2081, 1629, 1378, 1187, 1172, 1117 1072 cm^{-1}; HR-MS (ESI-TOF): m/z = 451.1471, calculated for $C_{28}H_{22}N_2O_2S$ ($M+H^+$): 451.1475.

2-(4-(Phenylethynyl)phenyl)-1-tosyl-1H-benzo[d]imidazole (2t).[36] 48 mg; Yield: 81 %; R_f = 0.5 (hexane:ethyl acetate 9:1); white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.64 (m, 4H), 7.59 (dd, J_1 = 7.6, J_2 = 4 Hz, 2H), 7.51 – 7.41 (m, 2H), 7.41 – 7.32 (m, 5H), 7.11 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100

MHz, $CDCl_3$) δ 153.6 145.9, 142.8, 135.0, 134.1, 131.8, 131.0, 130.9, 129.9, 129.7, 128.8, 128.6, 127.0, 125.7, 125.5, 123.0, 120.5, 115.4, 91.7, 88.9, 21.7. HR-MS (ESI-TOF): m/z = 449.1333, calculated for $C_{28}H_{20}N_2O_2S$ ($M+H^+$): 449.1318

2-(4-Bromophenyl)-5,6-dichloro-1-tosyl-benzo[d]imidazole (2aa).[27] 57 mg; Yield: 95%; R_f = 0.7 (hexane:ethyl acetate4:1); white solid; lit.[27] mp 206–208 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.79 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR (175, MHz, $CDCl_3$): δ 154.8, 146.7, 142.0, 134.5, 133.1, 132.5, 131.3, 130.2, 130.00, 129.9, 128.2, 127.1, 126.1, 121.7, 116.8, 21.6.

2-(2-Bromo-5-fluorophenyl)-5,6-dimethyl-1-tosyl-benzo[d]imidazole (2ab).[27] 59 mg; Yield: 98%; R_f = 0.5 (hexane:ethyl acetate 4:1); white solid; lit.[27] mp 121–123 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.63–7.58 (m, 1H), 7.56 (s, 1H), 7.54 (d, *J* = 4.0 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.16–7.10 (m, 1H), 7.07 (dd, J_1 = 8.4, J_2 = 3.0 Hz, 1H), 2.46 (s, 3H), 2.38 (s, 6H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 160.5 (d, $^1J_{C,F}$=247.1 Hz), 148.6, 146.3, 140.4, 135.7, 135.2, 134.6, 134.0 (d, $^3J_{C,F}$ = 8.0 Hz), 133.6 (d, $^3J_{C,F}$ =8.4 Hz), 131.2, 130.1, 127.5, 120.9, 119.9 (d, $^2J_{C,F}$ = 23.6 Hz), 119.5 (d, $^4J_{C,F}$=3.0 Hz), 119.1 (d, $^2J_{C,F}$ = 21.7 Hz),114.4, 21.9, 21.0, 20.3.

2-(3-Bromo-4-methoxyphenyl)-5,6-dimethyl-1-tosyl-benzo[d]imidazole (2ac). 59 mg; Yield: 97 %; R_f = 0.4 (hexane: ethyl acetate 4:1), white solid; mp 140-141 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.68 – 7.56 (m, 2H), 7.46 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 1H), 4.00 (s, 3H), 2.45 (s,

3H), 2.36 (s, 3H), 2.34 (s, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.6, 151.8, 145.8, 135.4, 135.2, 135.1, 134.7, 132.4, 131.9, 130.4, 129.8, 127.0, 123.6, 120.4, 115.5, 110.9, 110.8, 56.5, 21.8, 20.9, 20.3; IR (KBr): $\tilde{\nu}$ = 2920, 1847, 1629, 1487, 1377, 1269, 1175, 1081, 1019 cm^{-1}; HR-MS (ESI-TOF): m/z = 485.0534, calcd for $C_{23}H_{21}BrN_2O_3S$ ($M+H^+$): 485.0529.

2-(2-Bromophenyl)-6-nitro-1-tosyl-benzo[d]imidazole (2ad). 42 mg; Yield: 90%; R_f = 0.4 (hexane:ethyl acetate 4:1); white solid; mp 150-152 °C; ^{1}H NMR (700 MHz, $CDCl_3$): δ 9.10(s, 1H), 8.36 (dd, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.49–7.42 (m, 3H), 7.30–7.19 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 155.1, 147.1, 146.2, 145.7, 134.3,132.8, 132.5, 132.4, 132.3, 131.0, 130.4, 128.0, 126.8, 124.5, 121.2, 120.7, 111.2, 22.0; IR (KBr): $\tilde{\nu}$ = 2097, 1641, 1595, 1523, 1461, 1385, 1271, 1176, 1086, 1012; HR-MS (ESI-TOF): m/z = 471.9937, calcd for $C_{20}H_{14}BrN_3O_4S$ ($M+H^+$): 471.9961.

2-(4-Ethylphenyl)-5, 6-dichloro-1-tosyl-benzo[d]imidazole (2ae). 51 mg; Yield: 85%; R_f = 0.6 (hexane:ethyl acetate 4:1) white solid; mp 170-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.78 (s, 1H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.37–7.21 (m, 4H), 7.11 (d, *J* = 8.1 Hz, 2H), 2.76 (q, *J* = 7.6 Hz, 2H), 2.34 (s, 3H), 1.31 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 147.8, 146.3, 142.1, 134.6, 133.2, 131.0, 130.0, 129.6, 129.5, 127.5, 127.2, 126.6, 121.5, 116.8, 29.0, 21.8, 15.5; IR (KBr): $\tilde{\nu}$ =2965, 2362, 1624, 1595, 1433, 1383, 1281, 1190, 1177, 1075, 1018 cm^{-1}; HR-MS (ESI-TOF): m/z = 445.0539, calcd for $C_{22}H_{18}Cl_2N_2O_2S$ ($M+H^+$): 445.0539.

2-(2-nitrophenyl)-1-tosyl-1H-benzo[d]imidazole-6-carboxylic acid (2af).[27] 56 mg; Yield: 94%; R_f = 0.3 (hexane:ethyl acetate 1:1); white solid; lit.[27] mp 158–160 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.58 (s, 1H), 8.41 (m, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.96 (m, 2H), 7.89 (d, J = 8.0, 1H), 7.71 (m, 1H), 7.48 (d, J = 7.6 Hz, 2H), 7.39 (d, J = 7.6 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 166.9, 151.2, 147.7, 147.0, 145.0, 134.3, 133.3, 132.9, 132.6, 131.9, 130.6, 128.3, 126.9, 126.3, 124.8, 124.8, 120.5, 114.8, 21.2.

2-(2-Bromophenyl)-1-methylsulfonyl-benzo[d]imidazole (2ba). 78 mg; Yield: 97%; R_f=0.3 (hexane:ethyl acetate 4:1); yellow solid; mp 155-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, J_1 = 6.0, J_2= 2.9 Hz, 1H), 7.89–7.84 (m, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.53–7.46 (m, 3H), 7.45–7.37 (m, 2H), 3.28 (s, 3H);^{13}C NMR (175 MHz, $CDCl_3$): δ 150.7, 132.5, 132.4, 132.3, 132.3, 131.8, 127.1, 126.1, 125.4, 123.5, 121.2, 113.5, 42.27;IR (KBr): $\tilde{\nu}$ = 1604, 1641, 1462, 1450, 1185, 1049 cm^{-1}; HR-MS (ESI-TOF): m/z = 350.9791, calcd for $C_{14}H_{11}BrN_2O_2S$ ($M+H^+$): 350.9797.

2-(2-Fluorophenyl)-1-(phenylsulfonyl)-benzo[d]imidazole (2bb). 76 mg; Yield: 96%; R_f= 0.5 (hexane:ethyl acetate 4:1); white semi-solid, ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.14 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.2 Hz, 2H), 7.57–7.51 (m, 2H), 7.47–7.42 (m, 2H), 7.38 (dt, J_1= 21.1, J_2 = 7.6 Hz, 3H), 7.30–7.24 (m, 1H), 7.17 (dd, J_1 = 16.9, J_2 = 8.0 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 161.1 (d, $^1J_{C,F}$ = 250 Hz), 147.9, 143.0, 137.9, 134.6, 133.3, 132.8(d, $^3J_{C,F}$= 8.75 Hz), 132.2, 129.4, 127.1, 125.9, 125.3, 123.7 (d, $^4J_{C,F}$ = 3.5Hz), 120.8, 118.8 (d,$^3J_{C,F}$ = 14 Hz), 115.7(d, $^2J_{C,F}$ = 21 Hz), 114.4; IR (KBr): $\tilde{\nu}$ = 2096, 1624, 1583, 1482, 1448, 1382, 1311, 1253,

1187, 1125, 1187, 1079, 1018 cm^{-1}; HR-MS (ESI-TOF): m/z= 353.0767, calcd for $C_{19}H_{13}FN_2O_2S$ ($M+H^+$): 353.0755.

2-Phenyl-1-(phenylsulfonyl)-benzo[d]imidazole (2bc).[28] 72 mg; Yield: 92%; R_f= 0.5 (hexane:ethyl acetate 4:1); white solid; lit.[28] mp 64-65 ºC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 7.7 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.0 Hz, 2H), 7.53 (m, 1H), 7.50 – 7.45 (m, 2H), 7.50 – 7.39 (m, 5H), 7.28 (t, *J* = 7.9 Hz, 2H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 154.0, 142.6, 137.9, 134.5, 133.9, 130.9, 130.6, 129.9, 129.2, 127.7, 126.9, 125.6, 125.4, 120.5, 115.2.

2-(Ortho-Tolyl)-1-benzoyl-benzo[d]imidazole (2bd). 25 mg; Yield: 65%; R_f=0.5 (hexane:ethyl acetate 4:1); yellow semi-solid; ^1H NMR (700 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.31 (dt, J_1 = 23.0, J_2 = 7.8 Hz, 4H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.07-7.10 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 168.8, 153.6, 142.9, 137.1, 134.1, 133.6, 133.3, 130.8, 130.5, 130.5, 130.1, 129.8, 128.5, 125.6, 124.8, 124.6, 120.3, 113.7, 20.2; IR (KBr): $\tilde{\nu}$ = 2107, 1641, 1311, 1259, 1223, 1146, 1101, 1073 cm^{-1}; HR-MS (ESI-TOF):m/z=313.1308, calcd for $C_{21}H_{16}BrN_2O$ ($M+H^+$): 313.1335.

2-(2-Bromophenyl)-1-benzoyl-benzo[d]imidazole (2be). 16 mg; Yield: 40%; R_f = 0.6 (hexane:ethyl acetate 4:1); semi-solid;^1H NMR (700 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.45 – 7.38 (m, 3H), 7.35 (d, *J* = 8.1 Hz, 4H), 7.19 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (175

MHz, $CDCl_3$): δ 168.2, 152.2, 142.3, 133.9, 133.8, 132.9, 132.8, 132.6, 131.4, 130.7, 128.5, 127.5, 125.4, 124.9, 123.0, 120.6, 114.1; IR (KBr): $\tilde{\nu}$ =2093.07, 1642, 1448, 1310,1225, 1147 cm^{-1};HR-MS (ESI-TOF): m/z=377.0271, calcd for $C_{20}H_{13}BrN_2O$ ($M+H^+$): 377.0284.

2-(2-Bromophenyl)-1H-benzo[d]imidazole (2a').[37] 37 mg; Yield: 73%; R_f = 0.4 (hexane:ethyl acetate 4:1); white solid; ^1H NMR (700 MHz, DMSO-D_6): δ 7.82 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.29 – 7.23 (m, 2H); ^{13}C NMR (175 MHz, DMSO-D_6): δ 150.3, 133.4, 132.3, 132.1, 131.5, 127.8, 122.4, 121.6.

1p′: Mp 102-104 ^0C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8 Hz, 2H), 7.72 (s, 1H), 7.63 (d, *J* = 8 Hz, 1H), 7.58 (d, *J* = 8 Hz, 2H), 7.53-7.48 (m, 3H), 7.22 (dd, J_1 = 16, J_2 = 8 Hz, 1H), 7.12-7.08 (m,1H), 7.03 (d, *J* = 8. Hz, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (t, *J* = 25.0 Hz), 143.7, 140.9, 136.1, 135.5, 132.3, 132.2, 129.5, 129.1, 128.9, 127.8, 127.2, 125.5, 121.3, 117.0, 21.6; IR (KBr): $\tilde{\nu}$ =3285, 2165, 1916, 1613, 1485, 1337, 1165, 1215 cm^{-1}; HR-MS (ESI-TOF): m/z = 352.1215, calculated for $C_{20}H_{17}DN_2O_2S$ ($M+H^+$): 352.1225.

2.8 Notes and References

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^{1}H and ^{13}C NMR Spectra of selected the compounds

NMR Spectra

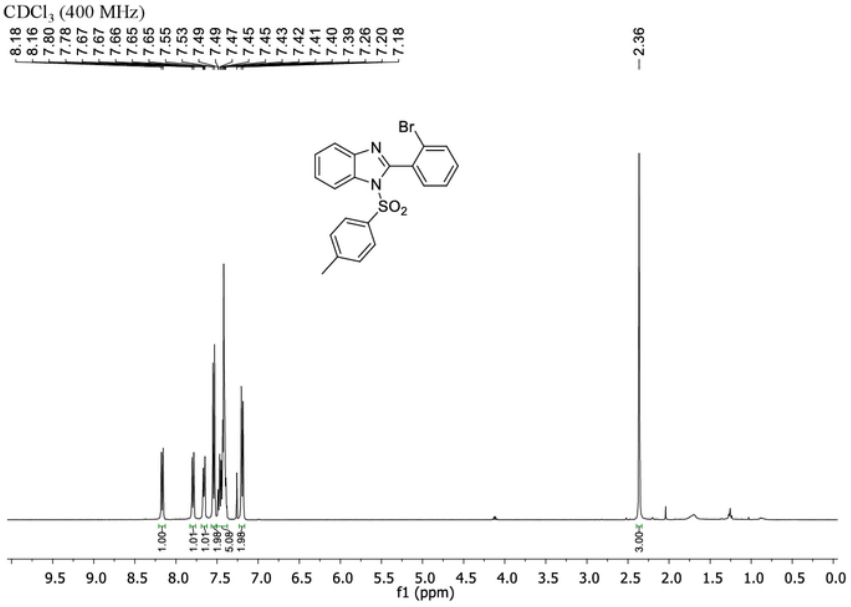


Figure 2.10. ^{1}H-NMR of 2-(2-Bromophenyl)-1-tosyl-benzo[d]imidazole **(2a)**.

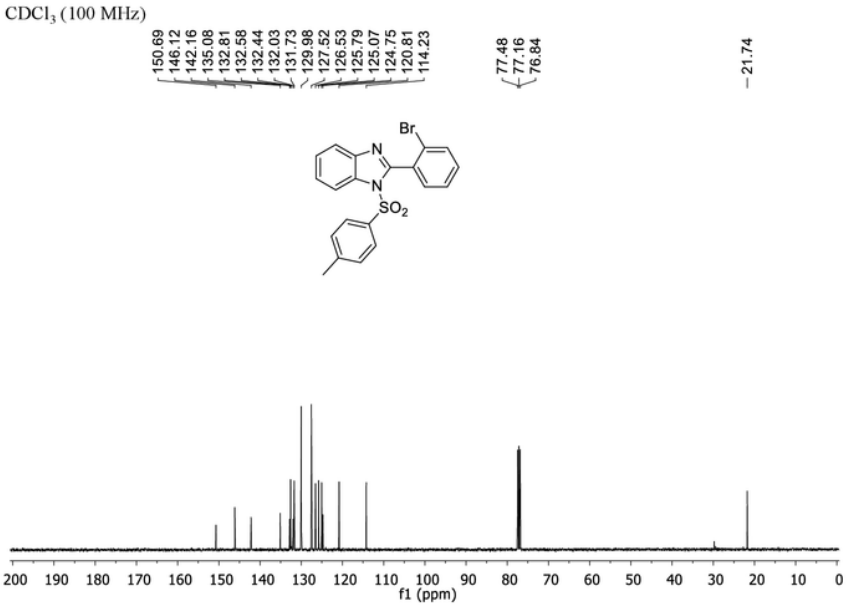


Figure 2.11. ^{13}C-NMR of 2-(2-Bromophenyl)-1-tosyl-benzo[d]imidazole **(2a)**.

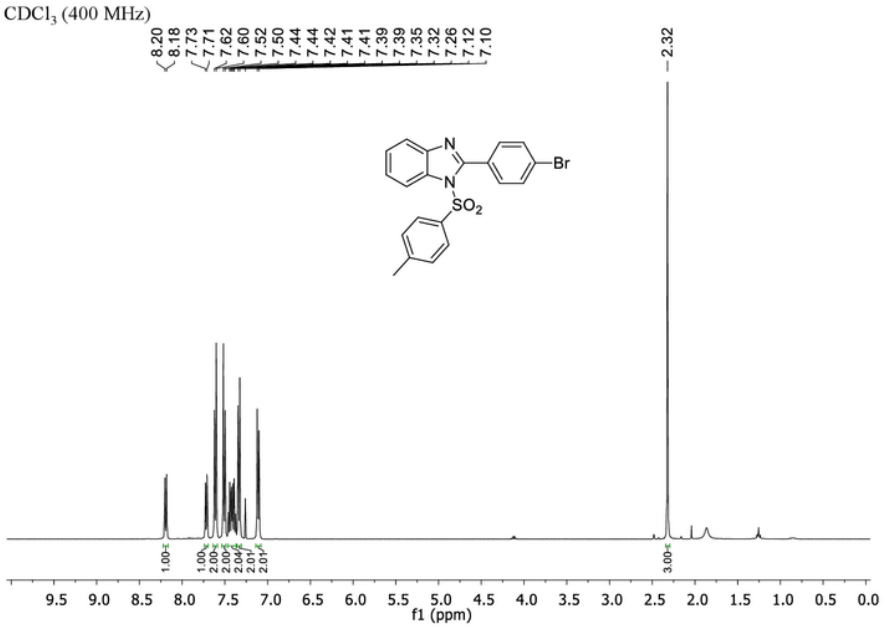


Figure 2.12. ^{1}H-NMR of 2-(4-Bromophenyl)-1-tosyl-benzo[d]imidazole **(2b)**.

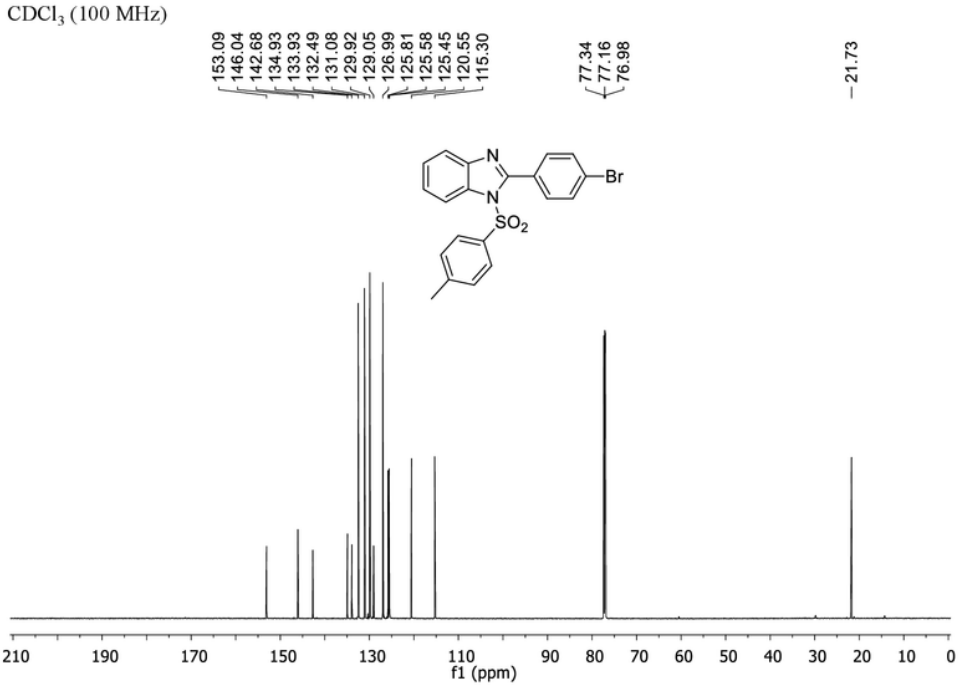


Figure 2.13. ^{13}C-NMR of 2-(4-Bromophenyl)-1-tosyl-benzo[d]imidazole **(2b)**.

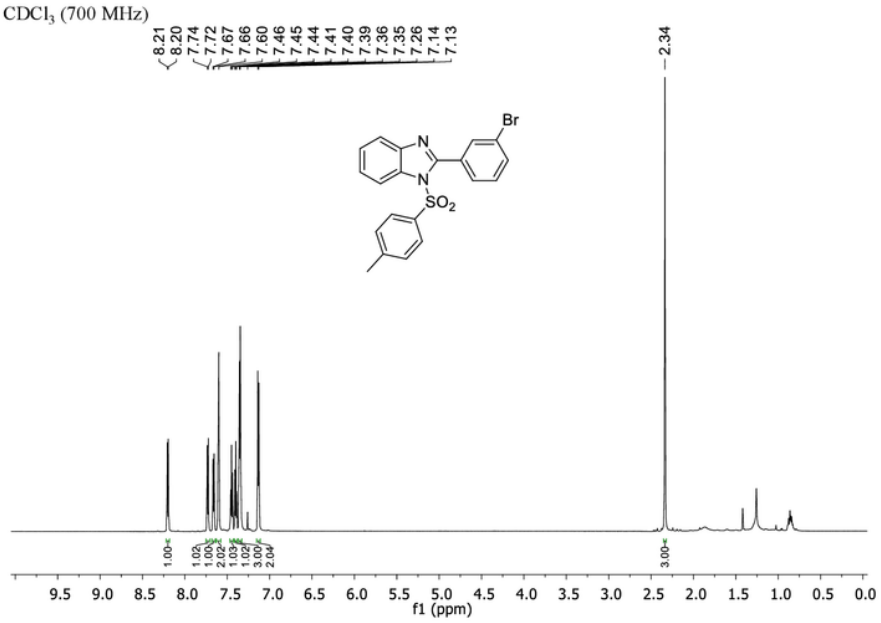


Figure 2.14. ^{1}H-NMR of 2-(3-Bromophenyl)-1-tosyl-benzo[d]imidazole **(2c)**.

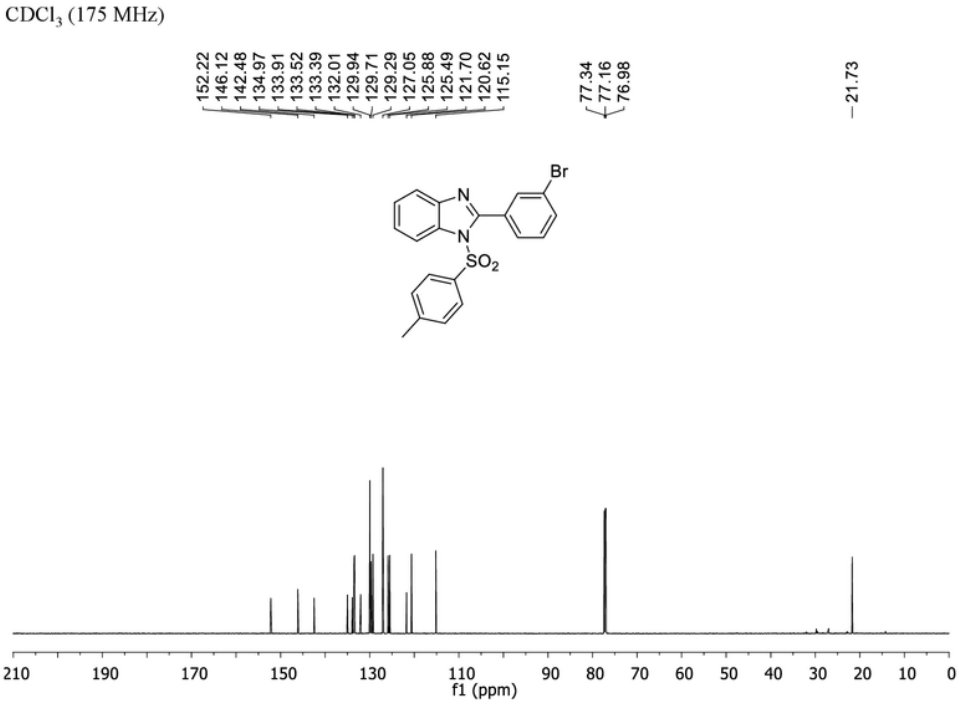


Figure 2.15. ^{13}C-NMR of 2-(3-Bromophenyl)-1-tosyl-benzo[d]imidazole **(2c)**.

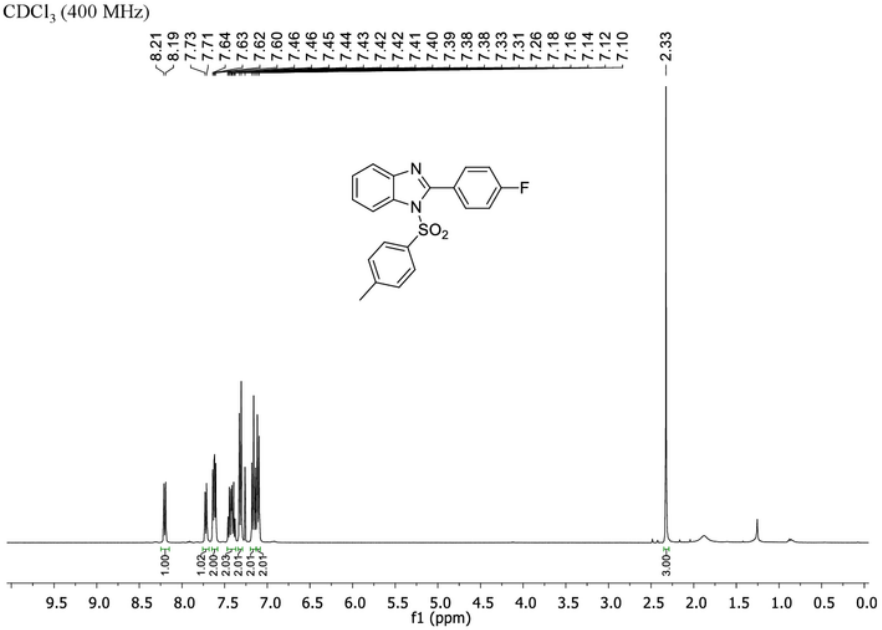


Figure 2.16. ^{1}H-NMR of 2-(4-Fluorophenyl)-1-tosyl-benzo[d]imidazole **(2d)**.

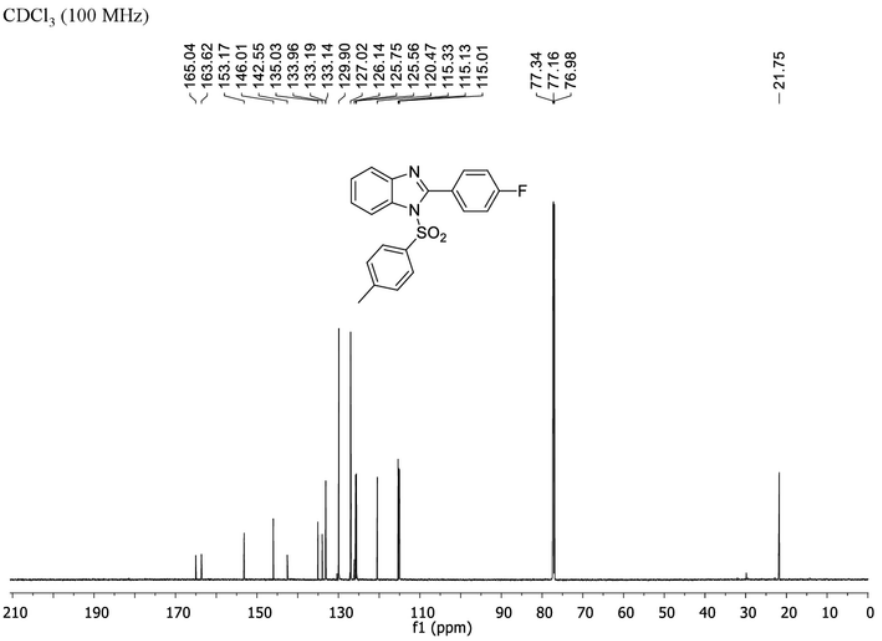


Figure 2.17. ^{13}C-NMR of 2-(4-Fluorophenyl)-1-tosyl-benzo[d]imidazole **(2d)**.

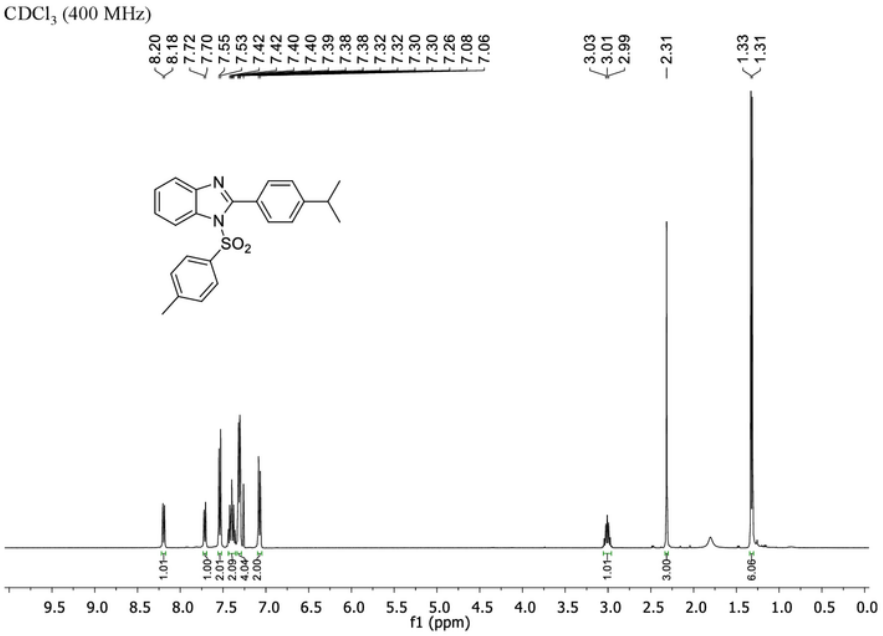


Figure 2.18. ^{1}H-NMR of 2-(4-Isopropylphenyl)-1-tosyl-benzo[d]imidazole (**2h**).

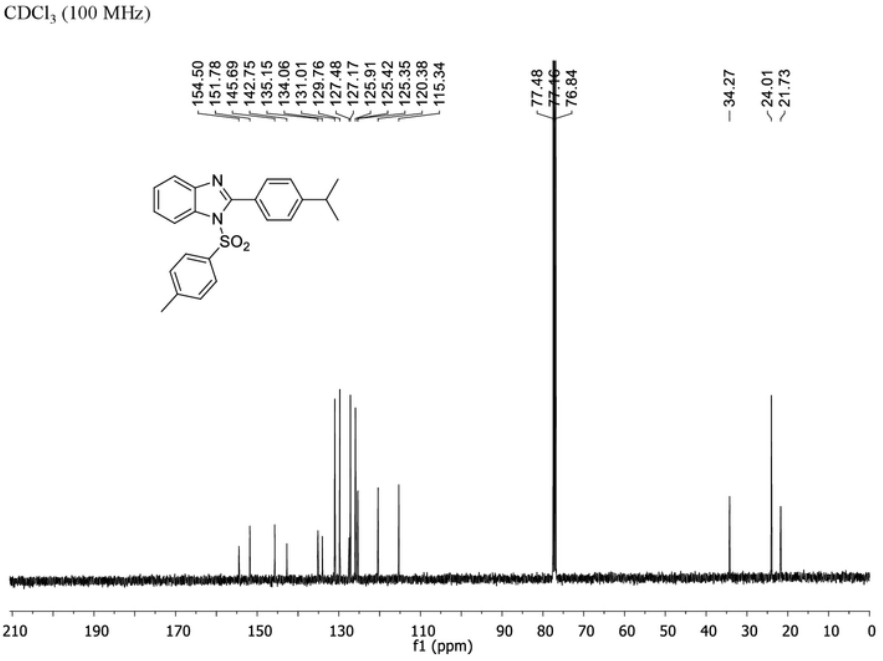


Figure 2.19. ^{13}C-NMR of 2-(4-Isopropylphenyl)-1-tosyl-benzo[d]imidazole (**2h**).

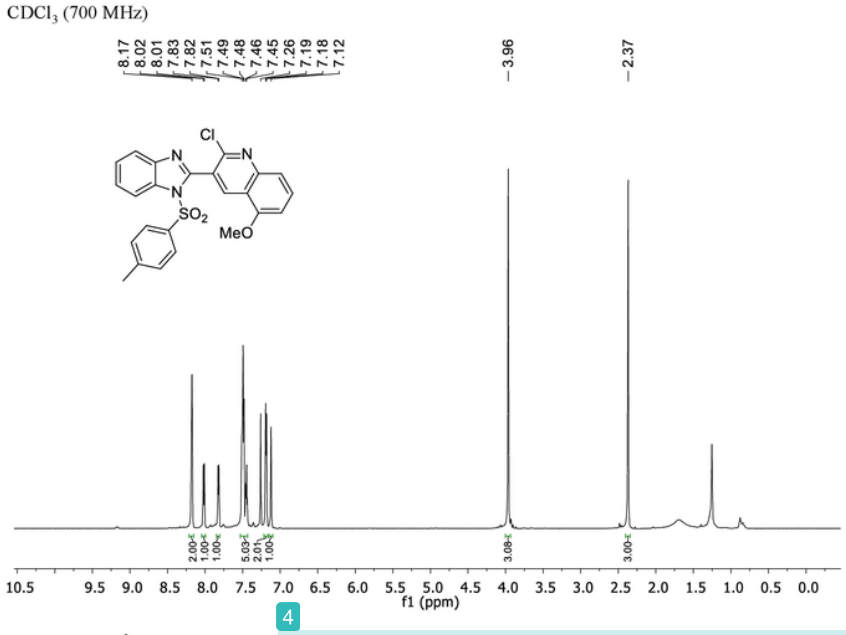


Figure 2.20. ^{1}H-NMR of 2-Chloro-6-methoxy-3-(1-tosyl-benzo[d]imidazol-2-yl)-quinolone (**2n**).

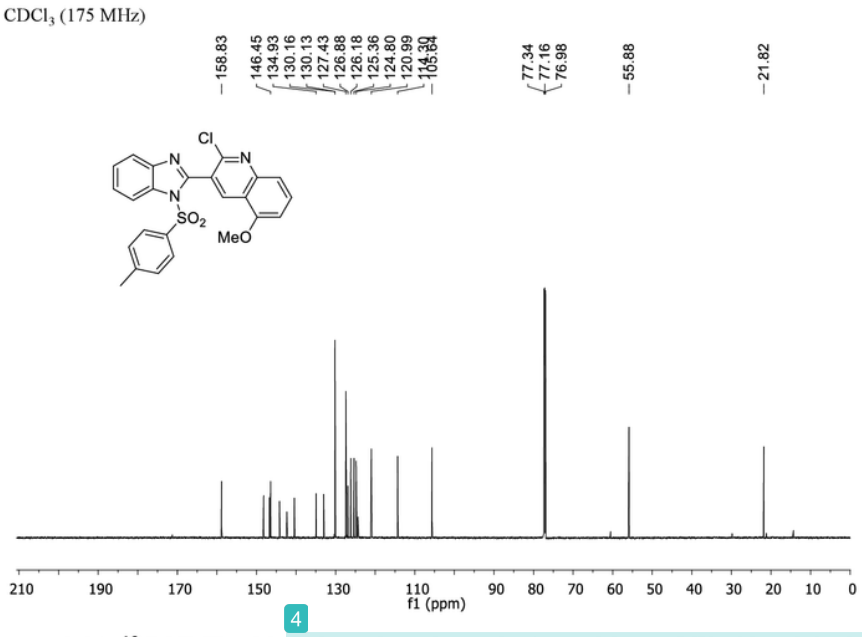


Figure 2.21. ^{13}C-NMR of 2-Chloro-6-methoxy-3-(1-tosyl-benzo[d]imidazol-2-yl)-quinolone (**2n**).

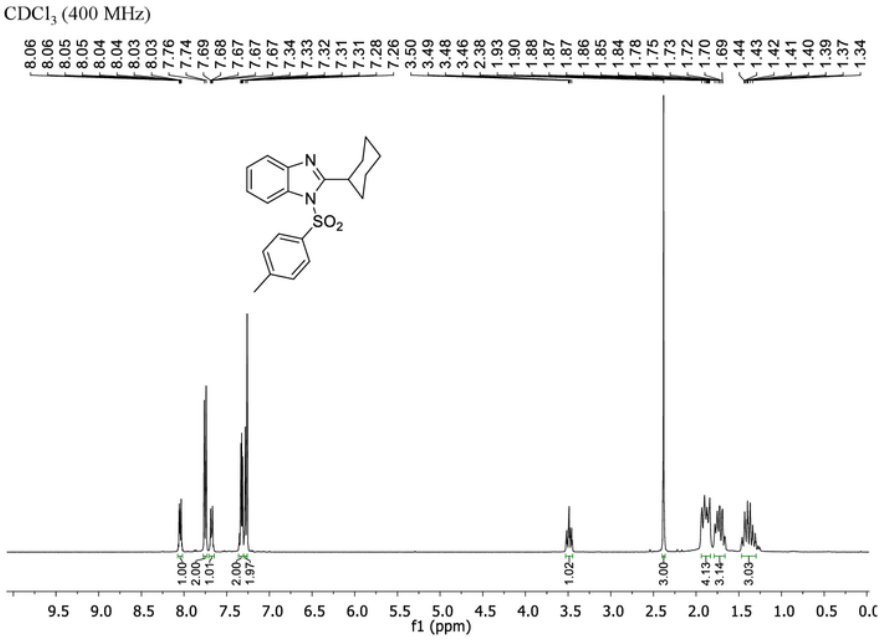


Figure 2.22. ^{1}H-NMR of 2-Cyclohexyl-1-tosyl-benzo[d]imidazole (**2o**).

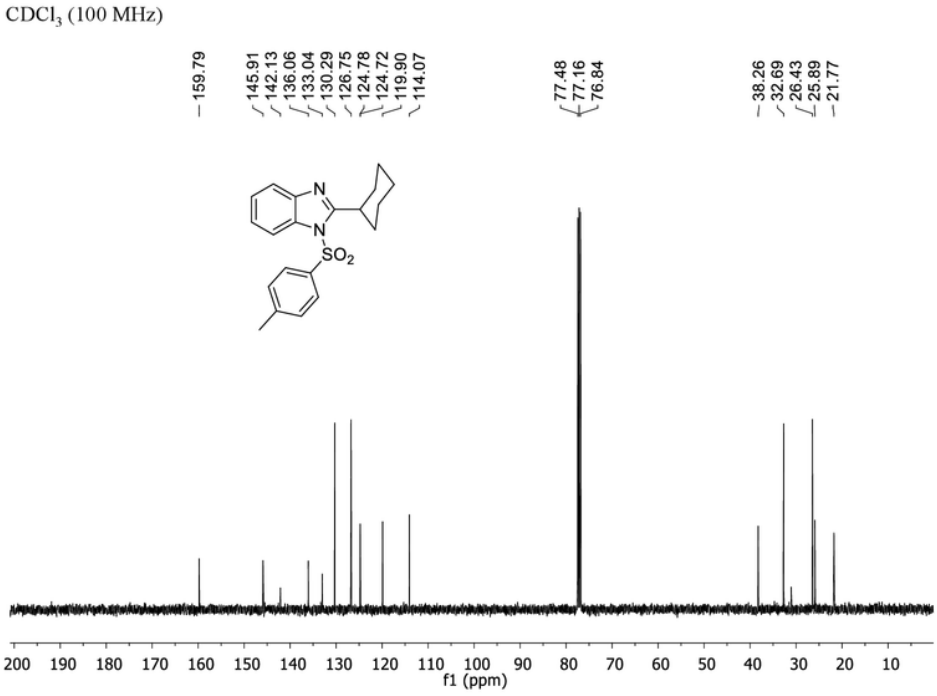


Figure 2.23. ^{13}C-NMR of 2-Cyclohexyl-1-tosyl-benzo[d]imidazole (**2o**).

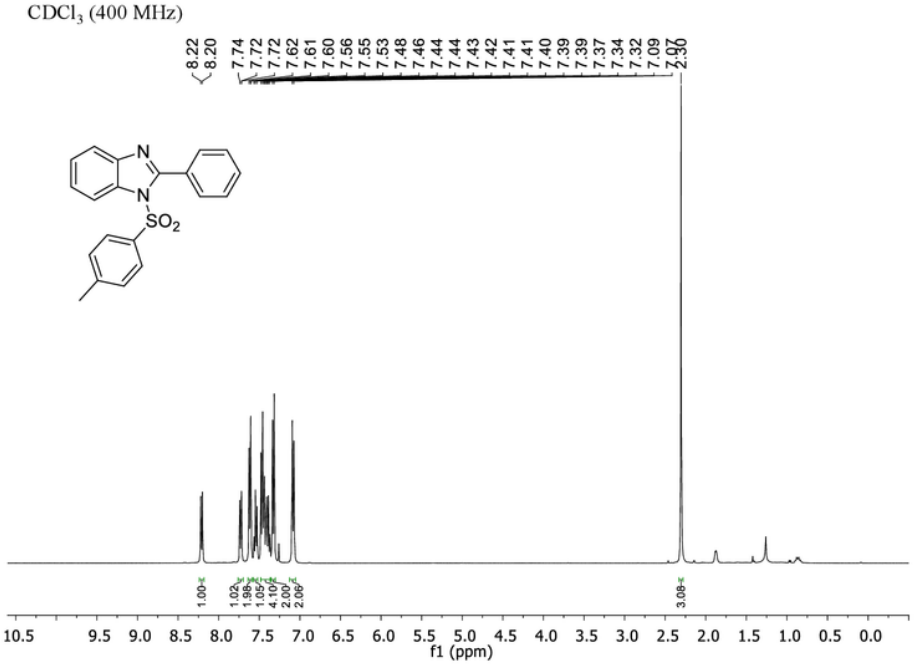


Figure 2.24. ^{1}H-NMR of 2-phenyl-1-tosyl-1H-benzo[d]imidazole **(2p).**

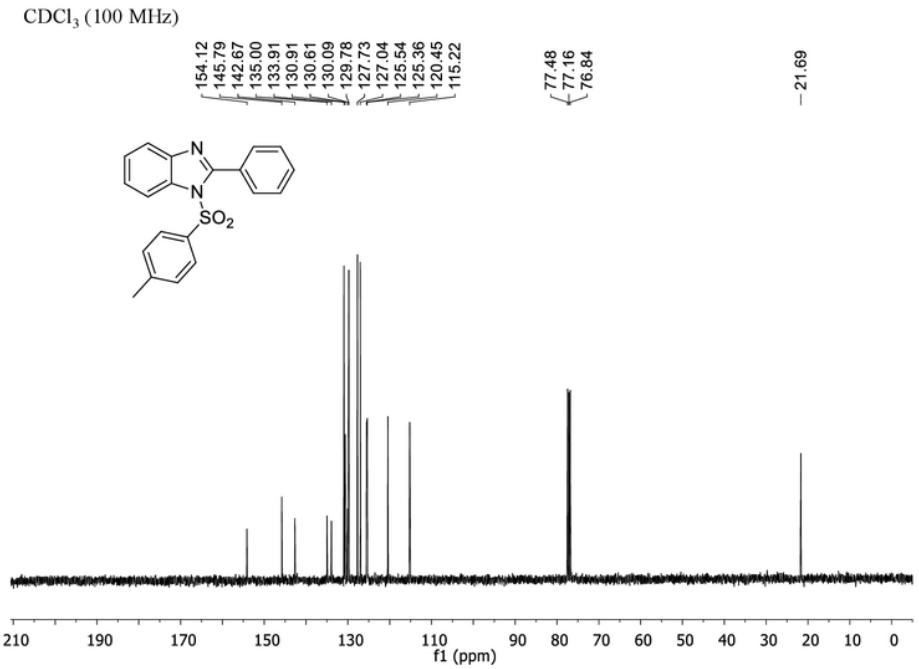


Figure 2.25. ^{13}C-NMR of 2-phenyl-1-tosyl-1H-benzo[d]imidazole **(2p)**.

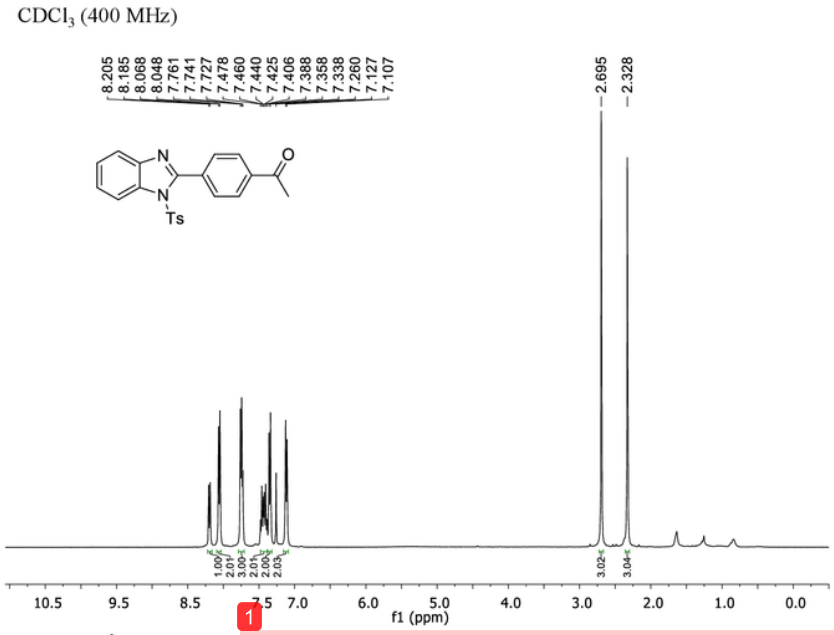


Figure 2.26. ^{1}H-NMR of 1-(4-(1-Tosyl-1H-benzo[d]imidazol-2-yl)phenyl)ethanone **(2q)**.

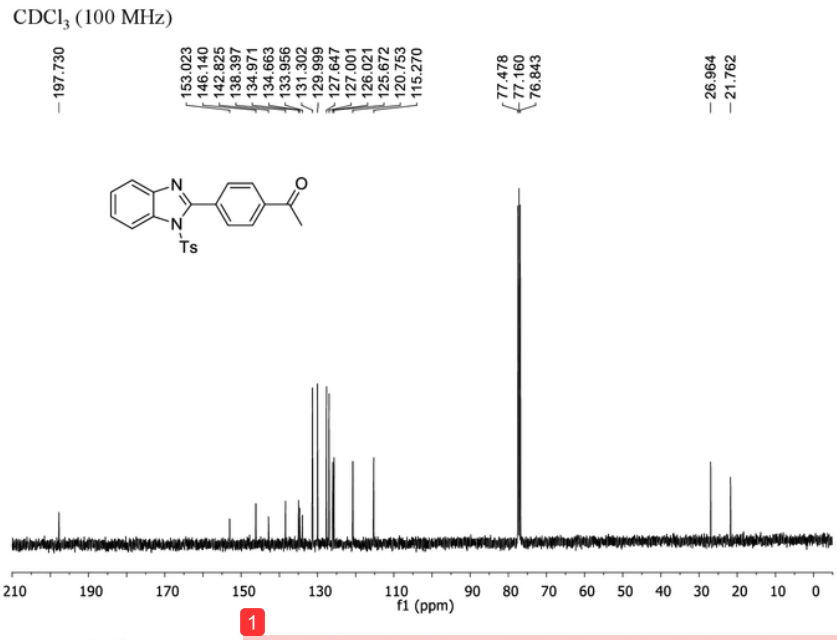


Figure 2.27. ^{13}C-NMR of 1-(4-(1-Tosyl-1H-benzo[d]imidazol-2-yl)phenyl)ethanone **(2q)**.

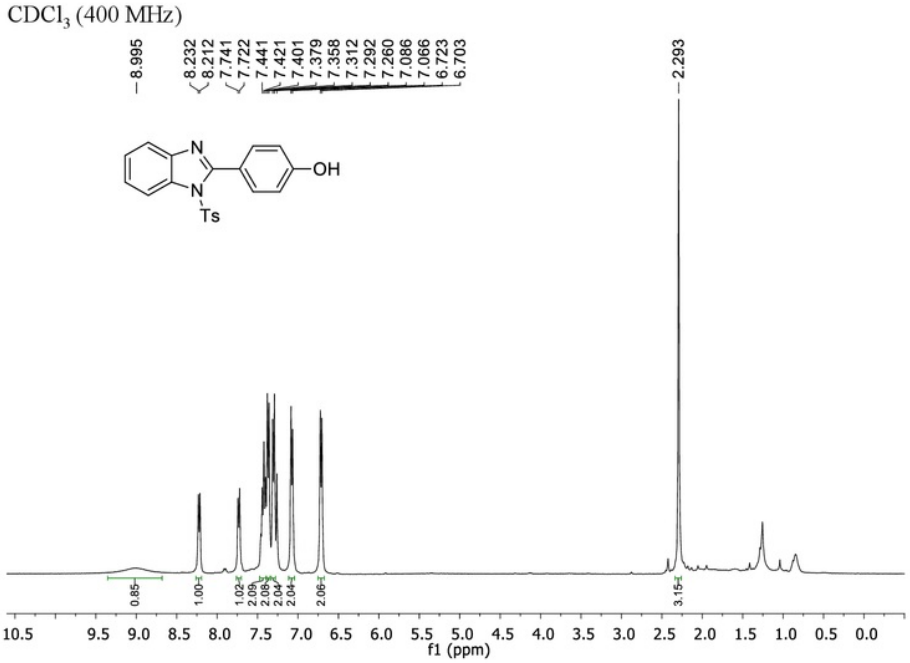


Figure 2.28. ^{1}H-NMR of 4-(1-Tosyl-1H-benzo[d]imidazol-2-yl)phenol **(2r)**.

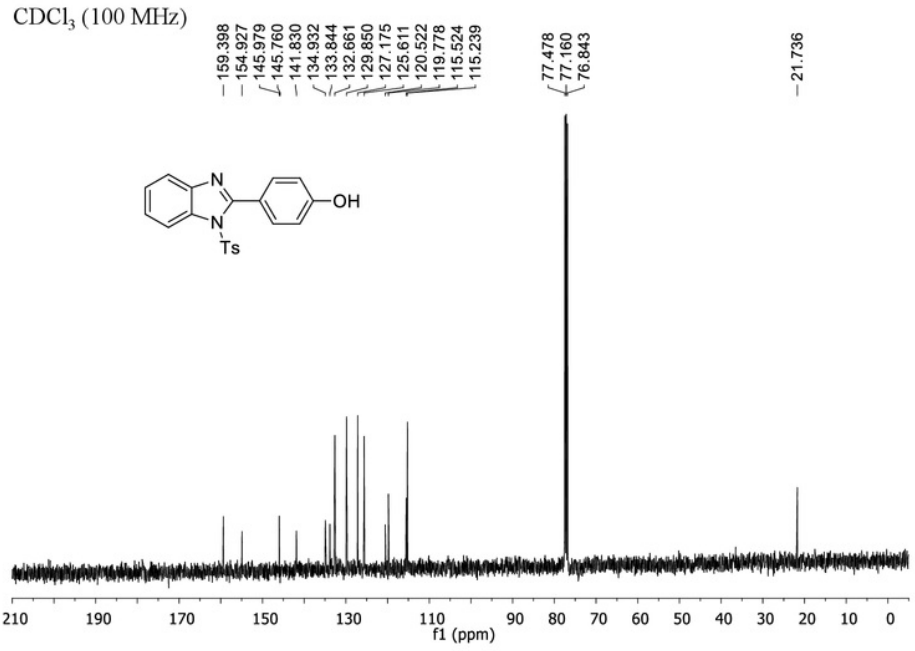


Figure 2.29. ^{13}C-NMR of 4-(1-Tosyl-1H-benzo[d]imidazol-2-yl)phenol **(2r)**.

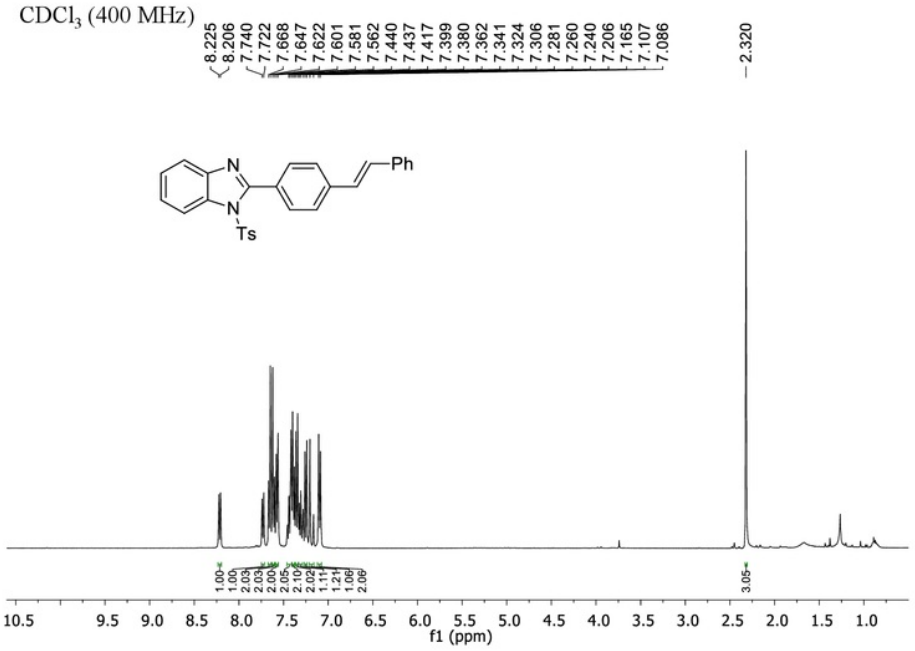


Figure 2.30. ^{1}H-NMR of (E)-2-(4-styrylphenyl)-1-tosyl-1H-benzo[d]imidazole **(2s)**.

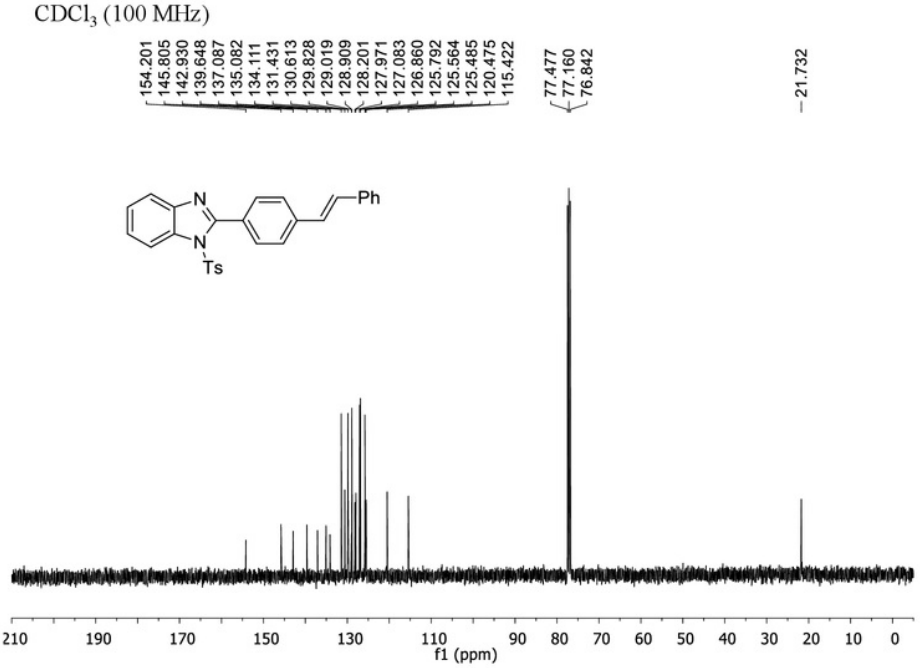


Figure 2.31. ^{13}C-NMR of (E)-2-(4-styrylphenyl)-1-tosyl-1H-benzo[d]imidazole **(2s)**.

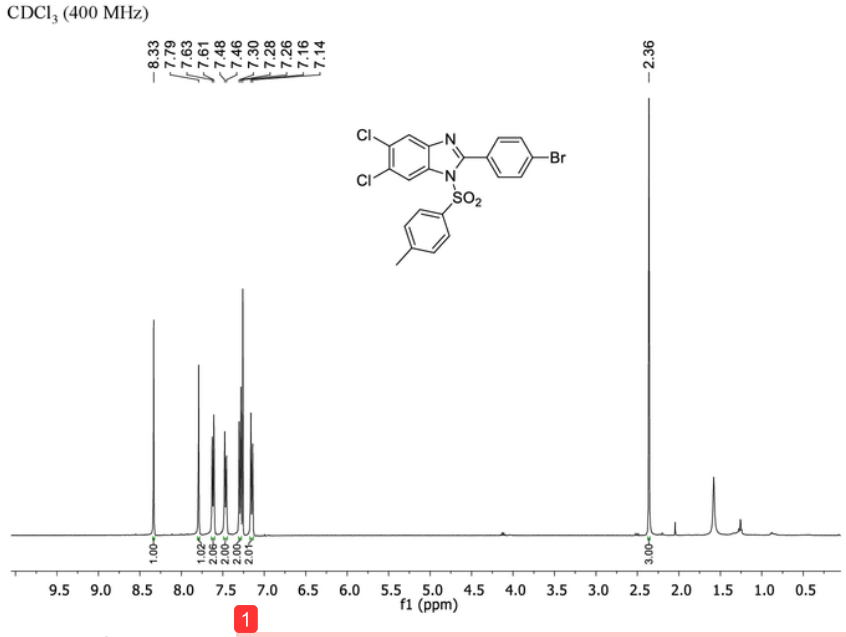


Figure 2.32. ^{1}H-NMR of 2-(4-Bromophenyl)-5,6-dichloro-1-tosyl-benzo[d]imidazole (**2aa**).

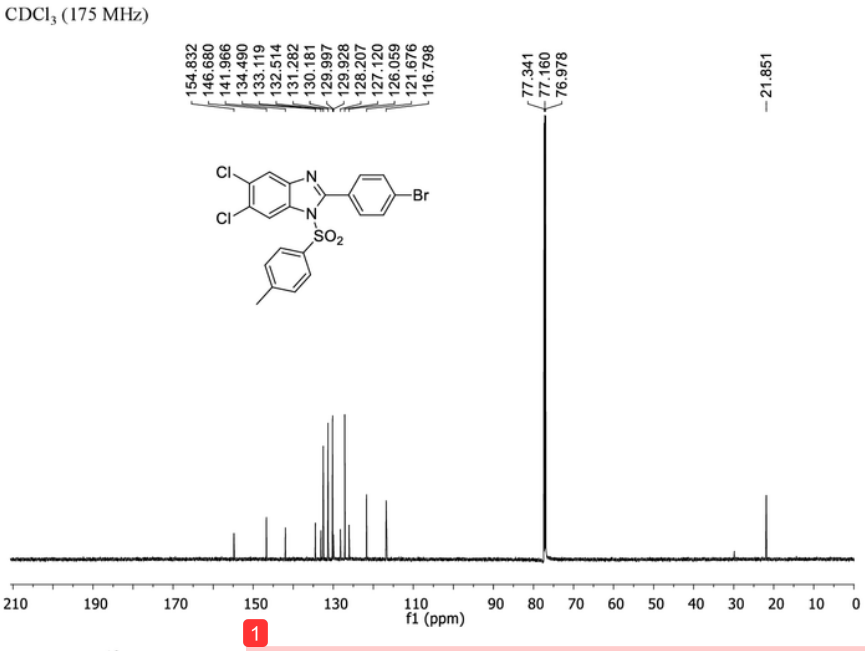


Figure 2.33. ^{13}C-NMR of 2-(4-Bromophenyl)-5,6-dichloro-1-tosyl-benzo[d]imidazole (**2aa**).

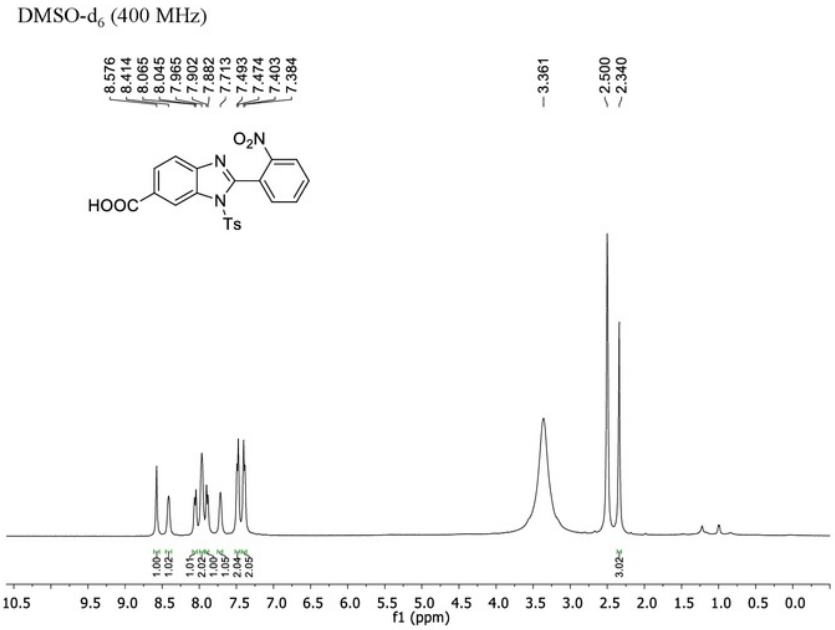


Figure 2.34. ^{1}H-NMR of 2-(2-nitrophenyl)-1-tosyl-1H-benzo[d]imidazole-6-carboxylic acid **(2af)**.

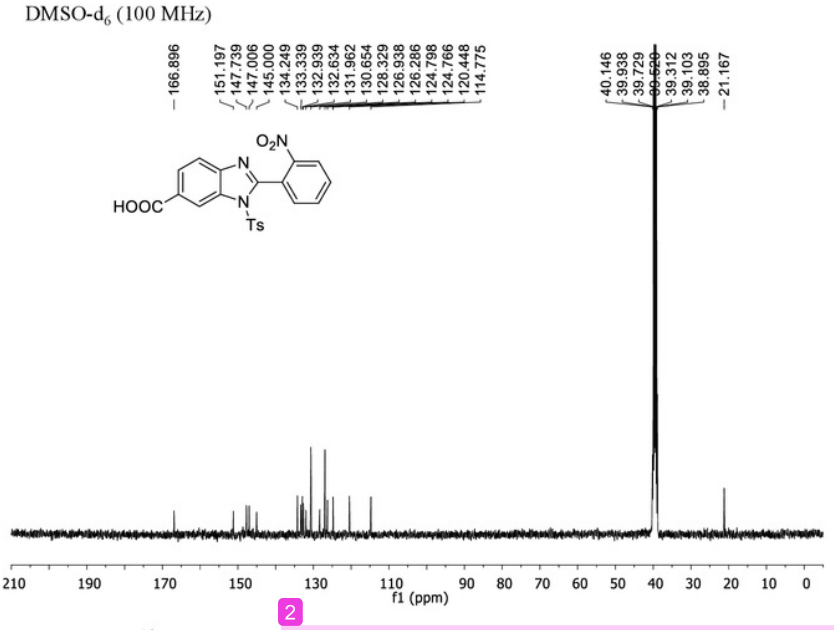


Figure 2.35. ^{13}C-NMR of 2-(2-nitrophenyl)-1-tosyl-1H-benzo[d]imidazole-6-carboxylic acid **(2af)**.

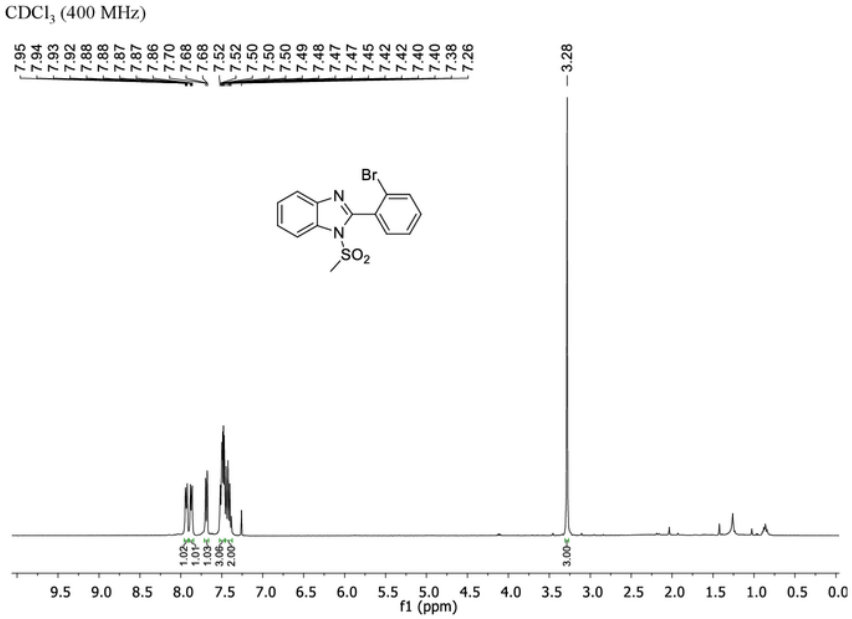


Figure 2.36. ^{1}H-NMR of 2-(2-bromophenyl)-1-methylsulfonyl-benzo[d]imidazole (**2ba**).

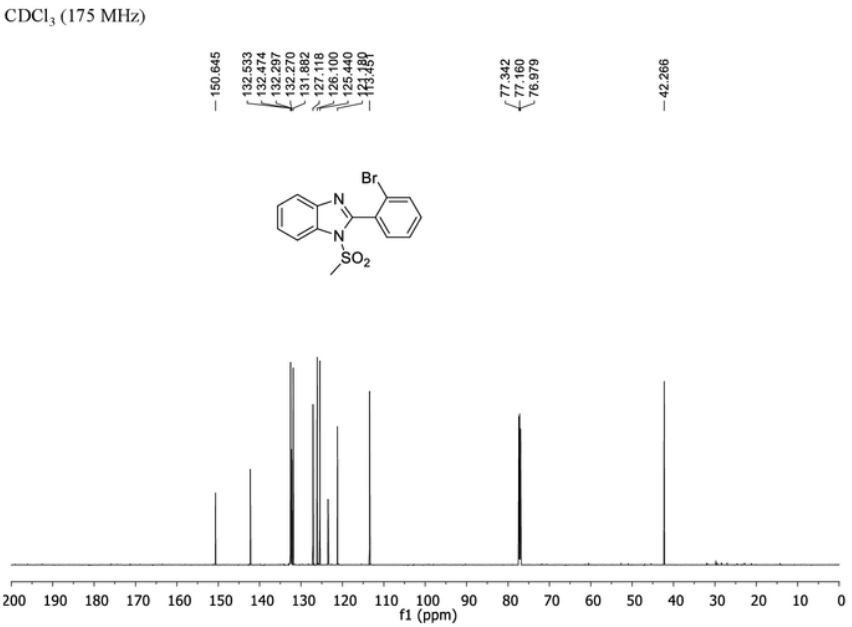


Figure 2.37. ^{13}C-NMR of 2-(2-bromophenyl)-1-methylsulfonyl-benzo[d]imidazole (**2ba**).

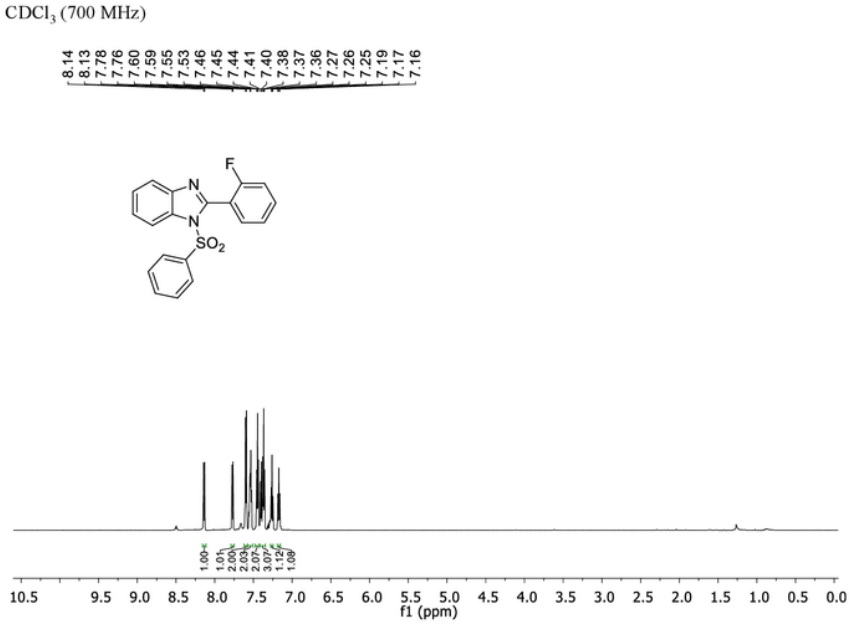


Figure 2.38. ^{1}H-NMR of 2- (2- Fluorophenyl)-1-(phenylsulfonyl)-benzo[d]imidazole (**2bb**).

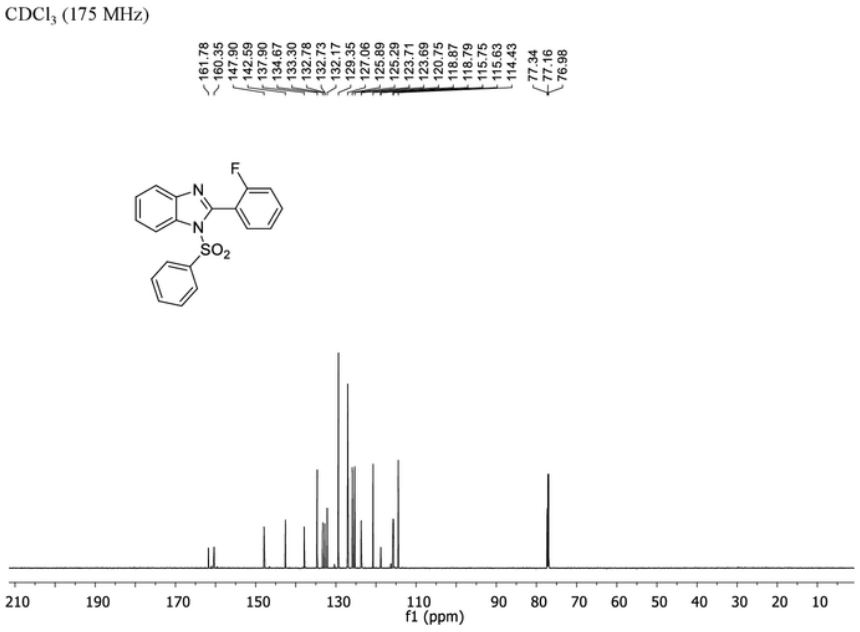


Figure 2.39. ^{13}C-NMR of 2- (2- Fluorophenyl)-1-(phenylsulfonyl)-benzo[d]imidazole (**2bb**).

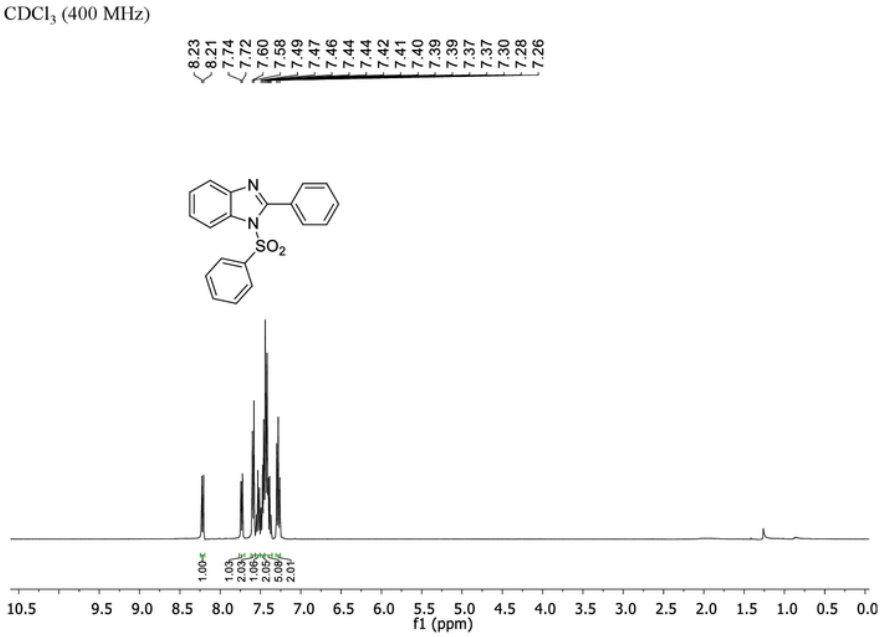


Figure 2.40. ^{1}H-NMR of 2-Phenyl-1-(phenylsulfonyl)-benzo[d]imidazole (**2bc**).

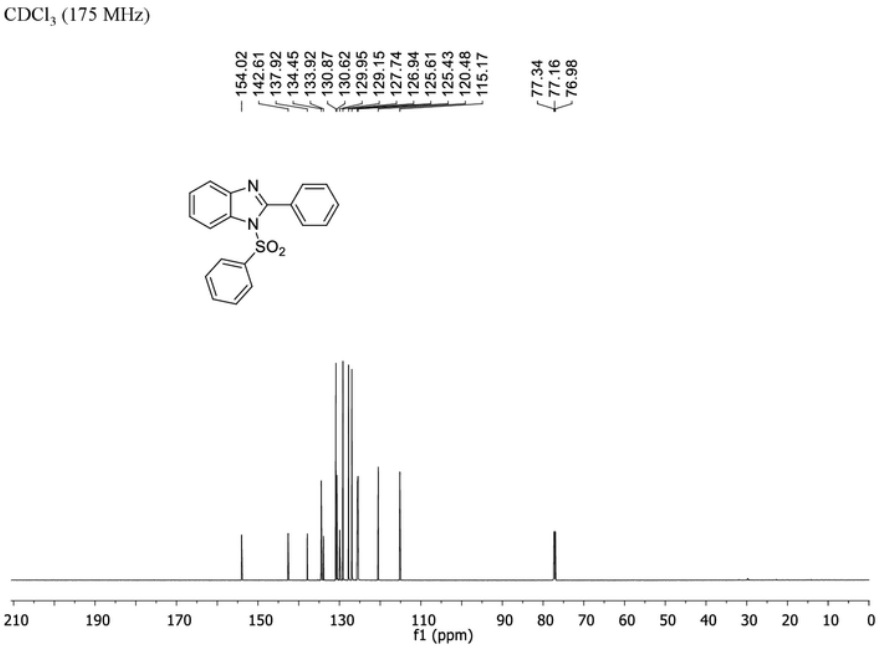


Figure 2.41. ^{13}C-NMR of 2-Phenyl-1-(phenylsulfonyl)-benzo[d]imidazole (**2bc**).

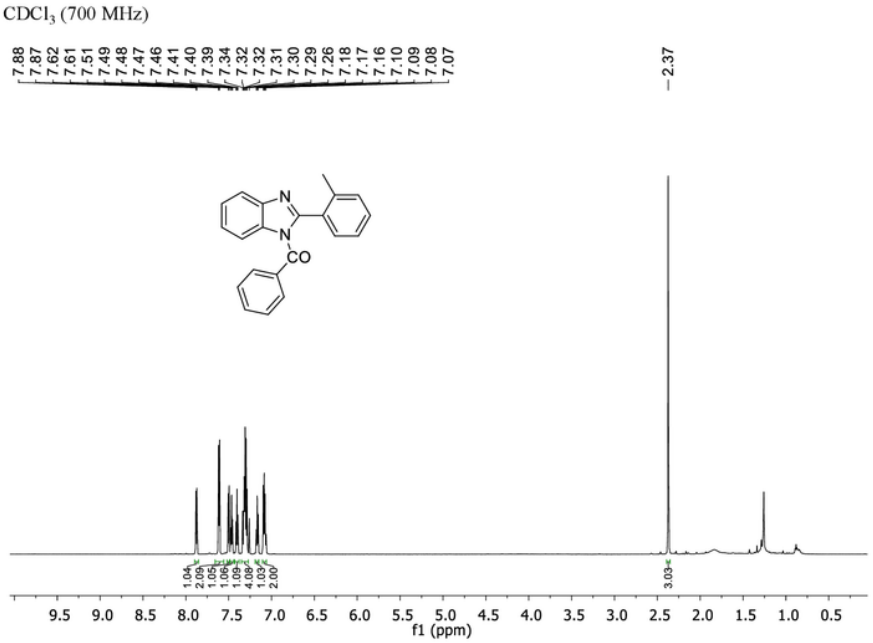


Figure 2.42. ^{1}H-NMR of 2-(Ortho-Tolyl)-1-benzoyl-benzo[d]imidazole (**2bd**).

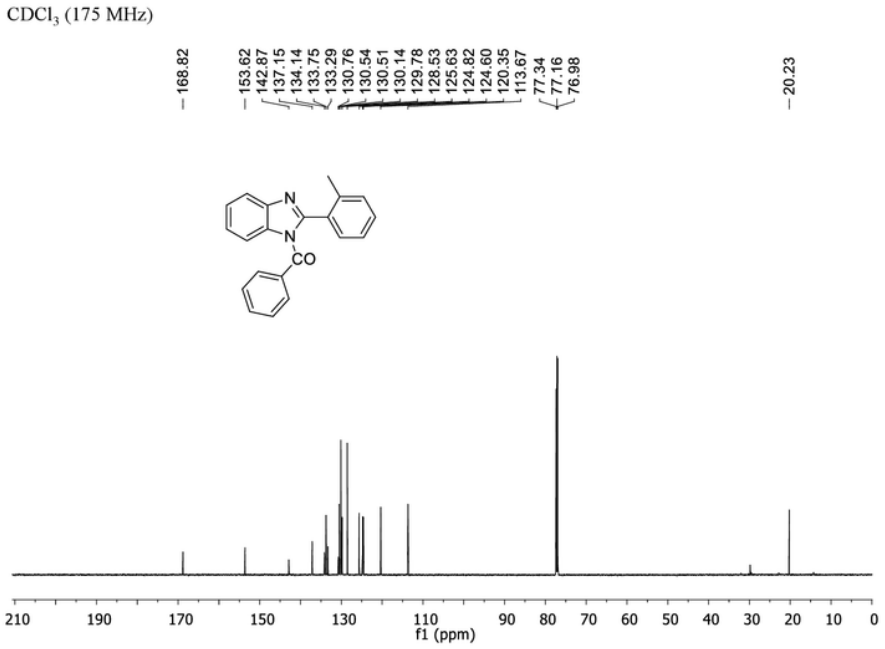


Figure 2.43. ^{13}C-NMR of 2-(Ortho-Tolyl)-1-benzoyl-benzo[d]imidazole (**2bd**).

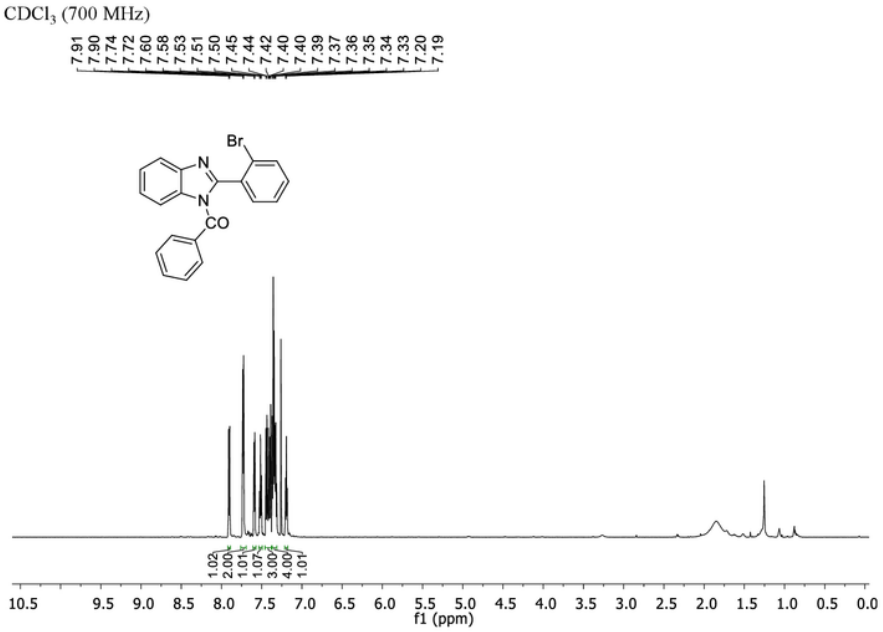


Figure 2.44. ^{1}H-NMR of 2-(2-Bromophenyl)-1-benzoyl-benzo[d]imidazole (**2be**).

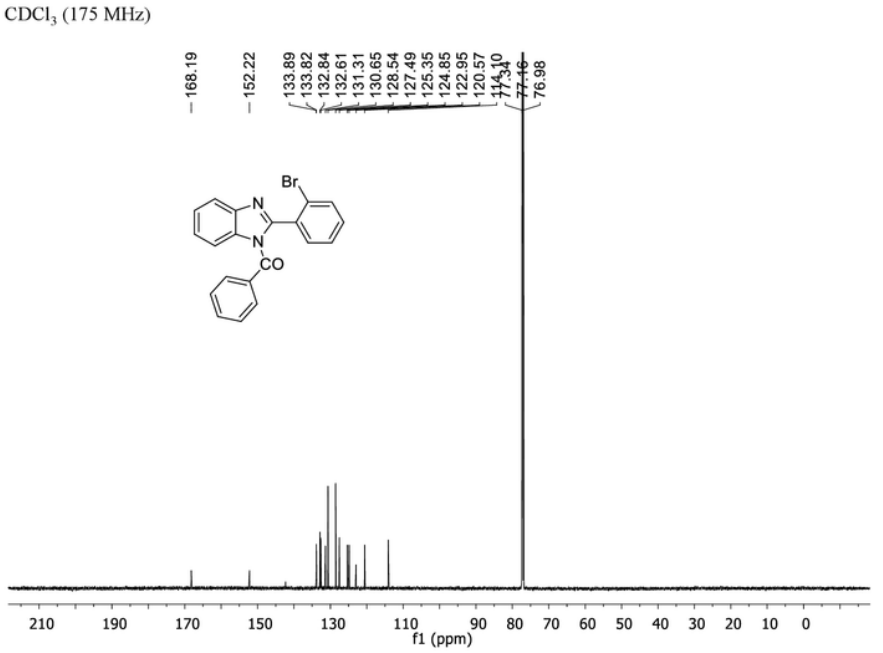


Figure 2.45. ^{13}C-NMR of 2-(2-Bromophenyl)-1-benzoyl-benzo[d]imidazole (**2be**).

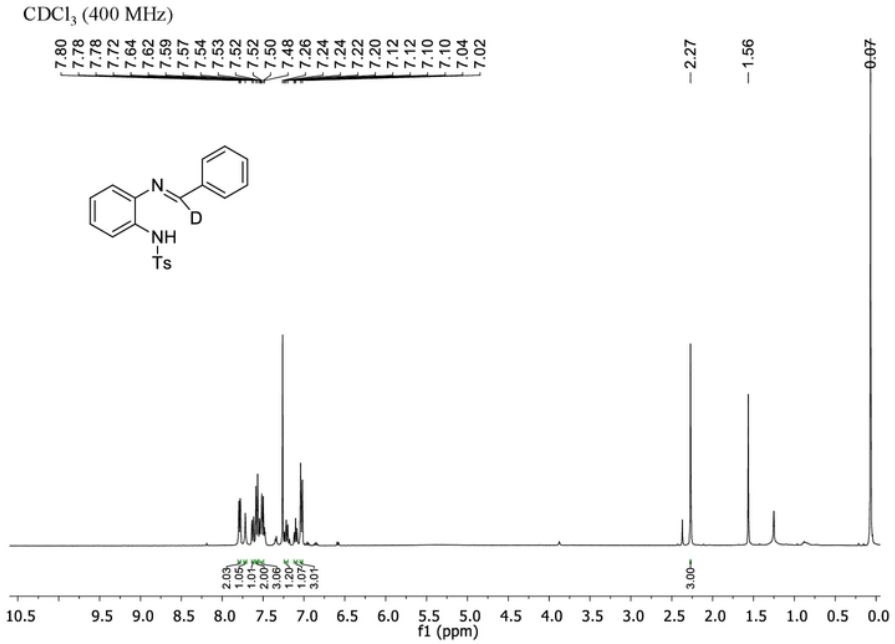


Figure 2.46 ^{1}H-NMR of **1p′**.

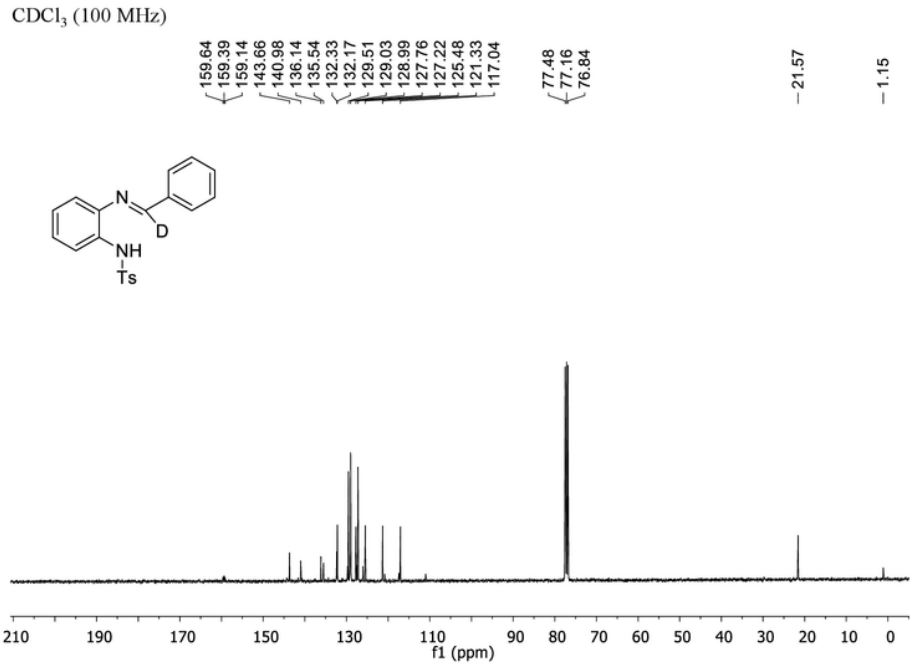


Figure 2.47. ^{13}C-NMR of **1p′**.

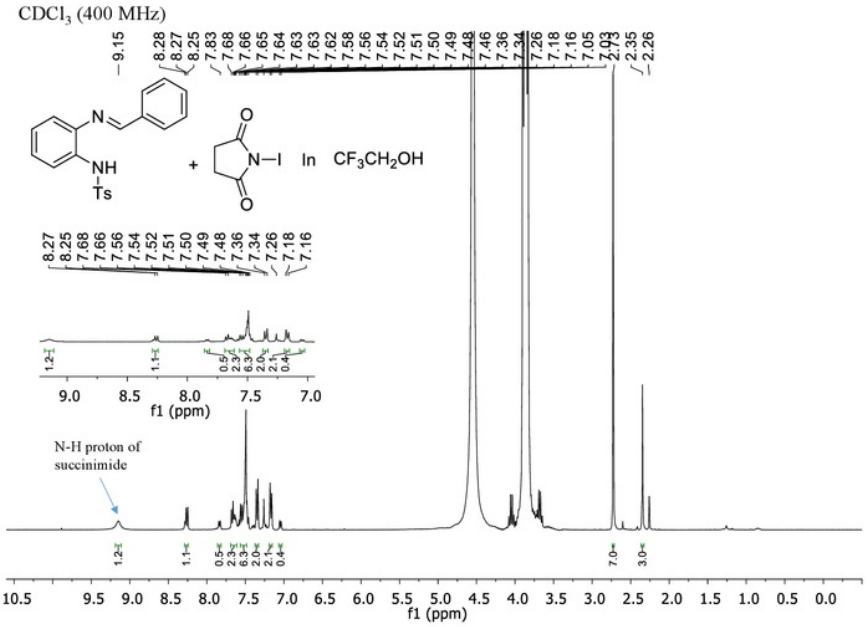


Figure 2.48. ^{1}H-NMR of the mixture of (E)-N-(2-(benzylideneamino)phenyl)-4-methylbenzene sulphonamide (**1p**) with NIS in TFE.

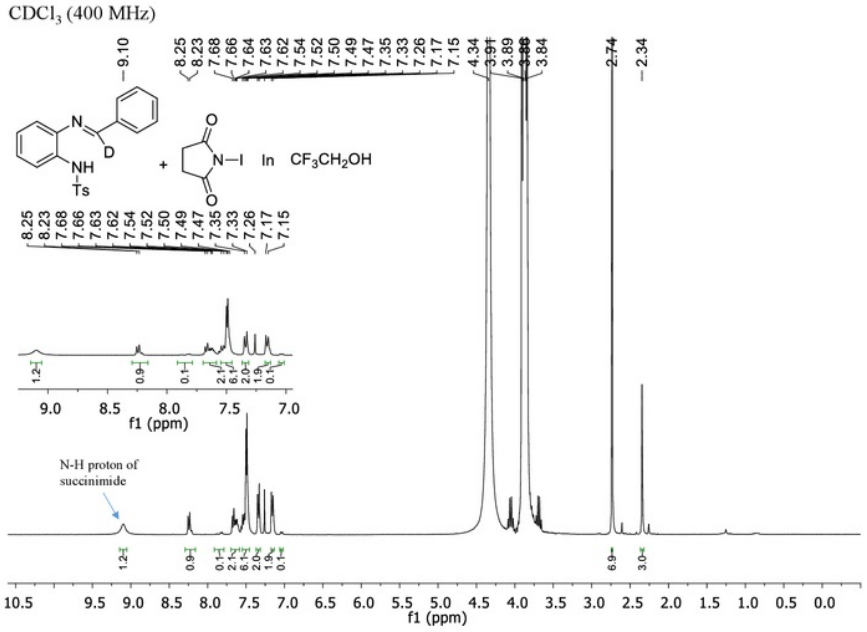


Figure 2.49 ^{1}H-NMR of the mixture of **1p′** with NIS in TFE.

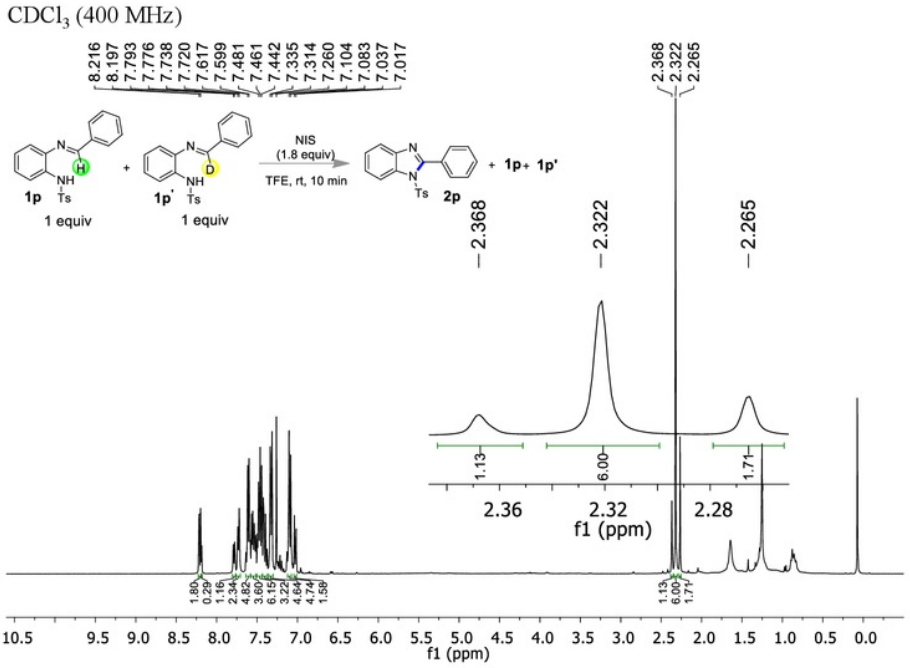
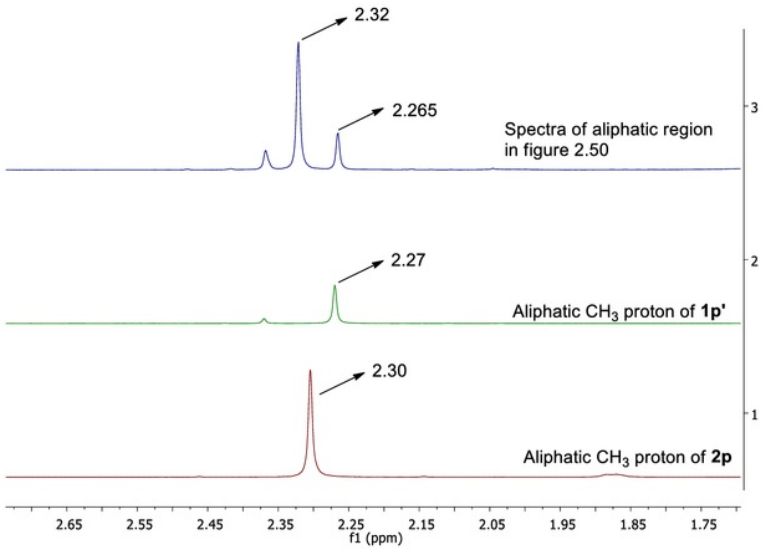


Figure 2.50. ^{1}H-NMR of the mixture of **1p**, **1p′** and **2p**.

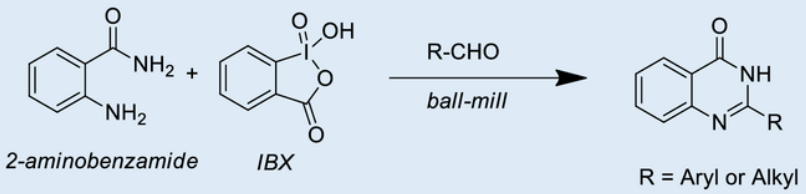


Comparison of ^{1}H-NMR spectra of aliphatic proton of compound **1p′**, **2p** and spectra of figure 2.50.

CHAPTER 3

Mechanochemical Synthesis of Substituted Quinazolin-4(3*H*)-one by Using IBX

3.1 ABSTRACT



Conducting any transformation using unsubstituted aryl amines and hypervalent iodine (V) reagents by simply adding is unworkable due to lofty exothermic reaction or explosive decompostion. Diverting the explosion *via* intramolecular control led to a successful chemical reaction when anilines containing -$CONH_2$ group at ortho-position. In constrained media i.e., extreme condition of the reactants under solvent-free ball-milling condition, anthranilamide, aromatic or aliphatic aldehydes and I (V) reagent e.g. *2*-iodoxybenzoic acid (IBX) delivered substituted quinazolin-4(3*H*)-one derivatives in good to high yields.

3.2 INTRODUCTION

Reaction environment can control the reactivity of a chemical system such as encapsulation within the cavity of a container molecule like cyclotrisiloxane[1] or cyclobutadiene,[2] which a kind of reactive species that do not undergo oligomerization.

Similarly, white phosphorus was also found to be air-stable upon encapsulation within a tetrahedral metallo-supramolecular cage molecule.[3] Hemiaminals are unstable which is stabilized by fitting into a molecular receptor. It was developed by Rebek and co-workers.[4] Combination of iodine and ammonia is popular *contact explosive* because of formation of nitrogen triiodide (NI_3).[5] Likewise, hypervalent iodine compounds being an oxidizer[6] react with amines[7] explosively without using any solvent. Aryliodonium imides or iminoiodane are synthesized by the reaction of iodine(III) derivatives and electron deficient amines. At higher temperature, this type of compound explode[8] and hence kept at low temperature[9] and inert atmosphere. Hypervalent iodine compounds are used as reagents for carbon-nitrogen bond synthesis reactions.[8,10] Mechanochemical conditions like ball milling is found to be one of the superior techniques in solvent-less synthesis.[11] Under solvent free ball-milling condition[11] maximum concentration puts in the system under high stress and therefore high exothermic reaction or explosion possibly occur between hypervalent iodine derivatives reagents and electron rich amines.Therefore, synthetic applications using hypervalent iodine compounds and primary amines under solvent-less condition are confined.[12] Our group developed a method of controlling the reactivity of primary amine and hypervalent iodine(III) into a successful chemical transformation in presence of the acid-salt $NaHSO_4$.[13] Herein, taming of aryl amine-iodine(V) explosion through an intramolecular control was demonstrated towards the synthesis substituted quinazolin-4(3*H*)-one.[14] This synthesis protocol is reported to be simple and is expected to have wide application in synthetic chemistry. Also, it may be possible hereafter to work with explosives for development of newer methodologies in organic synthesis or in supramolecular chemistry.

3.3 RESULTS AND DISCUSSIONS

Last few decades have gained significant interest to develop newer methodologies using hypervalent iodines in organic synthesis.[15] Easy commercial availability, high stability at room temperature (most of them), selective oxidizing ability and environmental sustainability of hypervalent iodine reagents build it highly widespread in establishing new synthetic methodology.[16] We report here a method for preparation of quinazolin-4(3*H*)-ones[17] (Figure 3.1) from o-aminobenzamide and aryl or alkyl aldehydes with treatment of *o*-iodoxybenzoic acid (IBX).[18] An explosion was noticed (Figure 3.1-a) during mixing of benzaldehydes, aniline in presence of IBX in ball-mill.[19] Identical observations were also found with Dess-Martin periodinane reagent (DMP). However, benzamide was not reacted with IBX and no such explosion was perceived under identical condition (Figure 3.1-b).Additionally, no explosive decomposition occurred when the reaction was carried out with 2-aminobenzamide and IBX without any aldehyde (Figure 3.1-c). On the other hand the reaction was fruitful with 2-aminobenzamide under similar condition (Figure 3.1-d).

Our group have reported a CDC (cross dehydrogenative coupling) reaction using primary amines in presence phenyleneiodine diacetate (PIDA) under solvent-less ball milling condition, i.e., at maximum contacts of the reactants.[13] The treatment of amine with PIDA as stronger oxidant, the amine's basicity was modulated using an additive $NaHSO_4$ acid-salt (Figure 3.2-a).

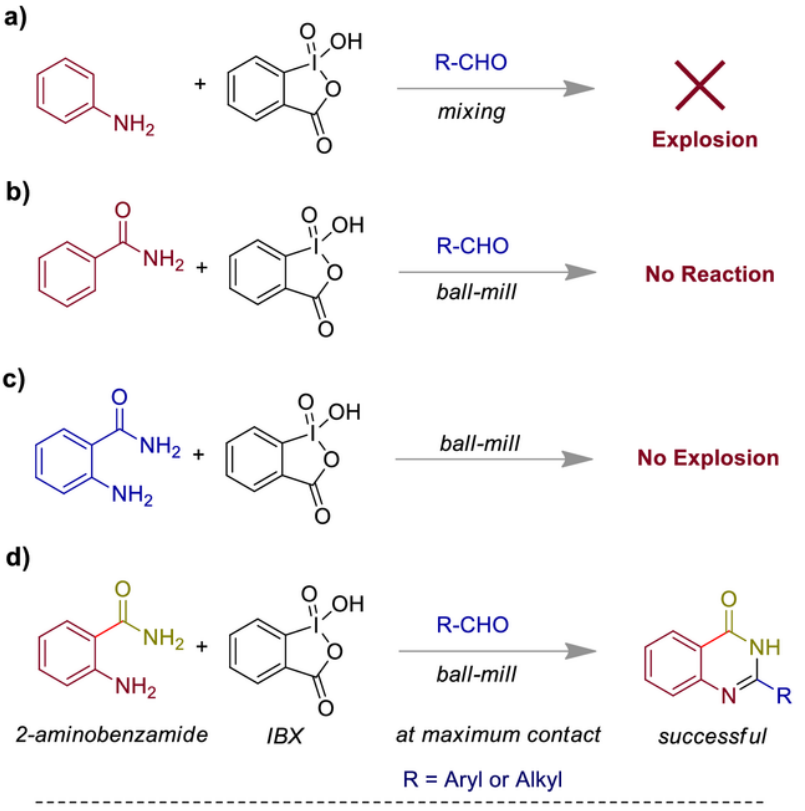


Figure 3.1. Reaction of iodine (V) and amine group of different system. a) Explosion observed when aryl amine treated with the aldehydes in presence of IBX. b) Benzamide was observed to be unreactive with IBX. c) No explosion was observed of reaction of 2-aminobenzamide and IBX d) 2-aminobenzamide treated with aldehydes in presence of IBX provided quinazolin-4(3*H*)-one with IBX under ball milling condition.

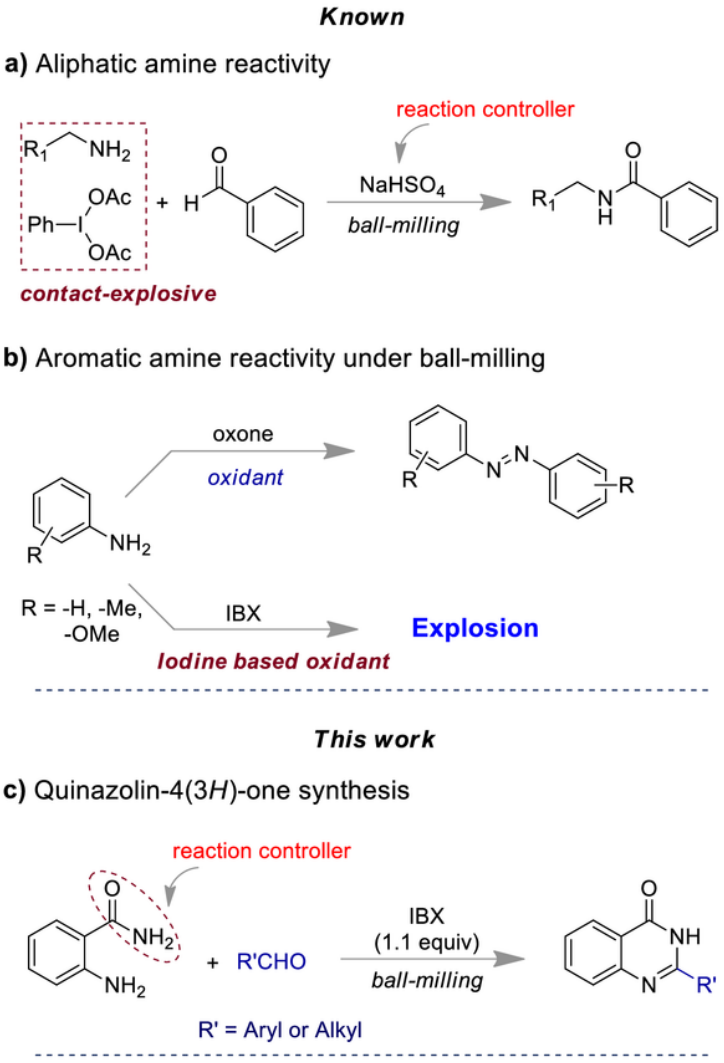
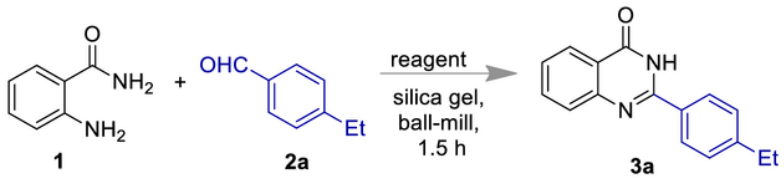


Figure 3.2. Comparing the recent work with the reported literature reports.

A correlation in the reactivities of the aryl amines with treatment of oxone (non-iodine based oxidant)[20] and IBX (iodine based oxidant) are given in figure 3.2-b. Anilines treated with oxone and led to the generation of the azo-derivatives while IBX reacts differently which caused an explosion. Reactions of 2-aminobenzamide and aryl aldehydes led to quinazolin-4(3*H*)-one in presence of IBX at maximum concentration of the reactants *i.e.*, in ball-mill (Figure 3.2-c).

For searching optimum condition of the reaction, anthranilimide (**1**) and 2-ethylbenzaldehyde (**2a**) were used as representative substrates (Table 3.1). At first, 70% of the 2-(4-ethylphenyl)quinazolin-4(3*H*)-one (**3a**) product was observed, when **1**, **2a** with 1.1 equiv of IBX were shredded together in a 10 mL of ball-milling jar for 1.5 h (entry 1). IBX was successively added after 30 mins of mixing **1** and **2a** however, the yield was increased to 91% (entry 2). It was found that yield appreciably decreased when other equimolar proportions of IBX was used (entries 3-4). Also various oxidants like Dess Martin periodinate and oxone (entries 7 to 8) were applied but none of them provided better results compare to IBX. IBX under *in situ* conditions obtained from 2-iodobenzoic acid-oxone combination gave lower yields of product (entry 5). Gratifyingly, when silica-gel[21] was utilized as an additives during the griping of liquid aldehydes, the yield of the products were observed to be consistent in repetition of the reactions. Interestingly no explosion could be found, when IBX was mixed during the starting of the reaction (entry 1, Table 3.1), at 30 min (Entry 2) or 1 h (entry 6) after mixing of **1** and **2**. Therefore, we got an explosion free methodology.

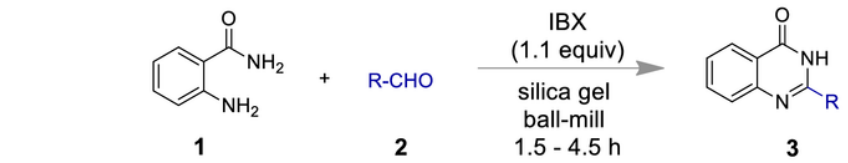
Table 3.1. Screening of reaction conditions.[a]



Entry	Reagent (equiv) [b]	Yield (%)[c]
1[d]	*o*-iodoxybenzoic acid (1.1)	70
2	*o*-iodoxybenzoic acid (1.1)	91
3	*o*-iodoxybenzoic acid (1)	78
4	*o*-iodoxybenzoic acid (1.2)	85
5[e]	IBA (1.1) - oxone (1.5)	59
6[f]	*o*-iodoxybenzoic acid (1.1)	90
7[g]	DMP (1.1)	44
8	Oxone (1.1)	42

[a]Reaction condition: **1a** (1 equiv) and **2a** (1 equiv) and 60 mg silica gel for approximately 60 µL of **2a**, [b]Reagent was mixed after 30 min. [c]Isolated yields. [d]**1**, **2a**

and IBX were added together. [e]2-Iodobenzoic acid (IBA). [f] IBX was mixed after 1 h. [g]Dess Martin periodinate.



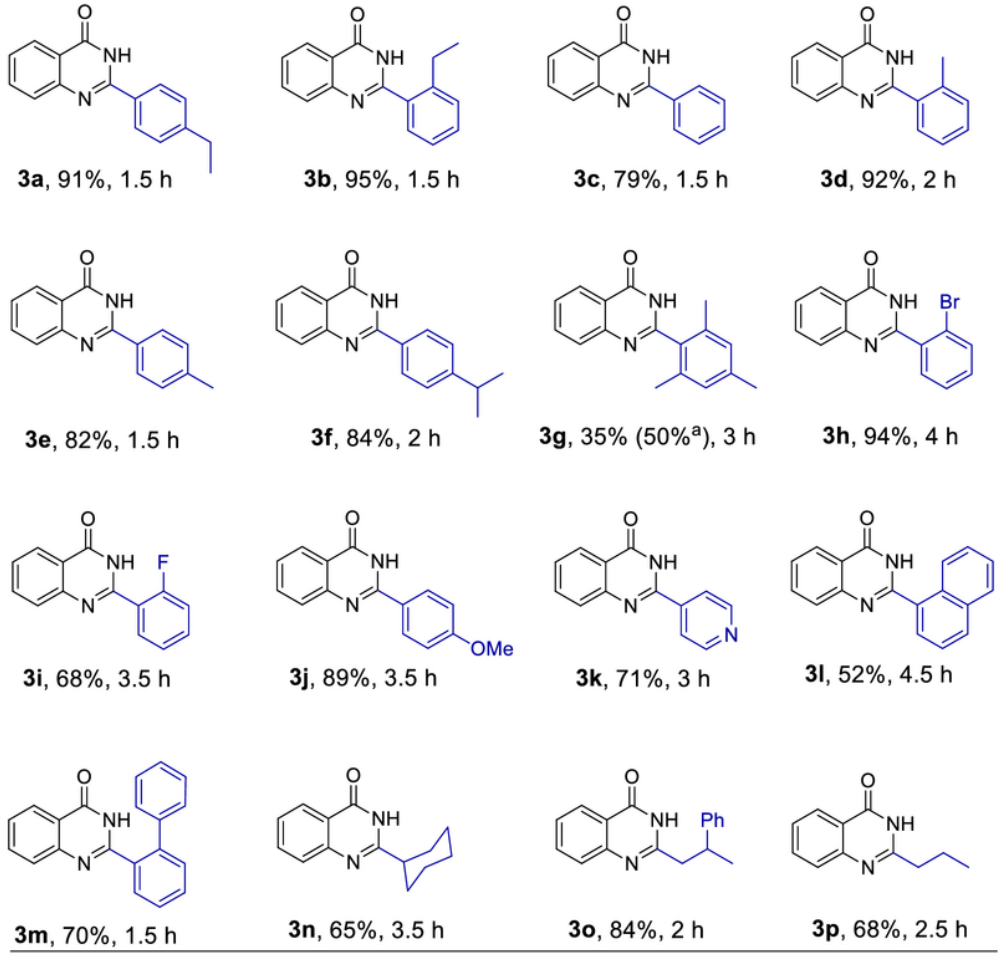


Figure 3.3. Preparation of quinazolin-4(3*H*)-one compounds from reaction of **1** and

liquid aldehydes. [a] Yields based on recovered aldehydes, for compound **3k** IBX is put after 1 h.

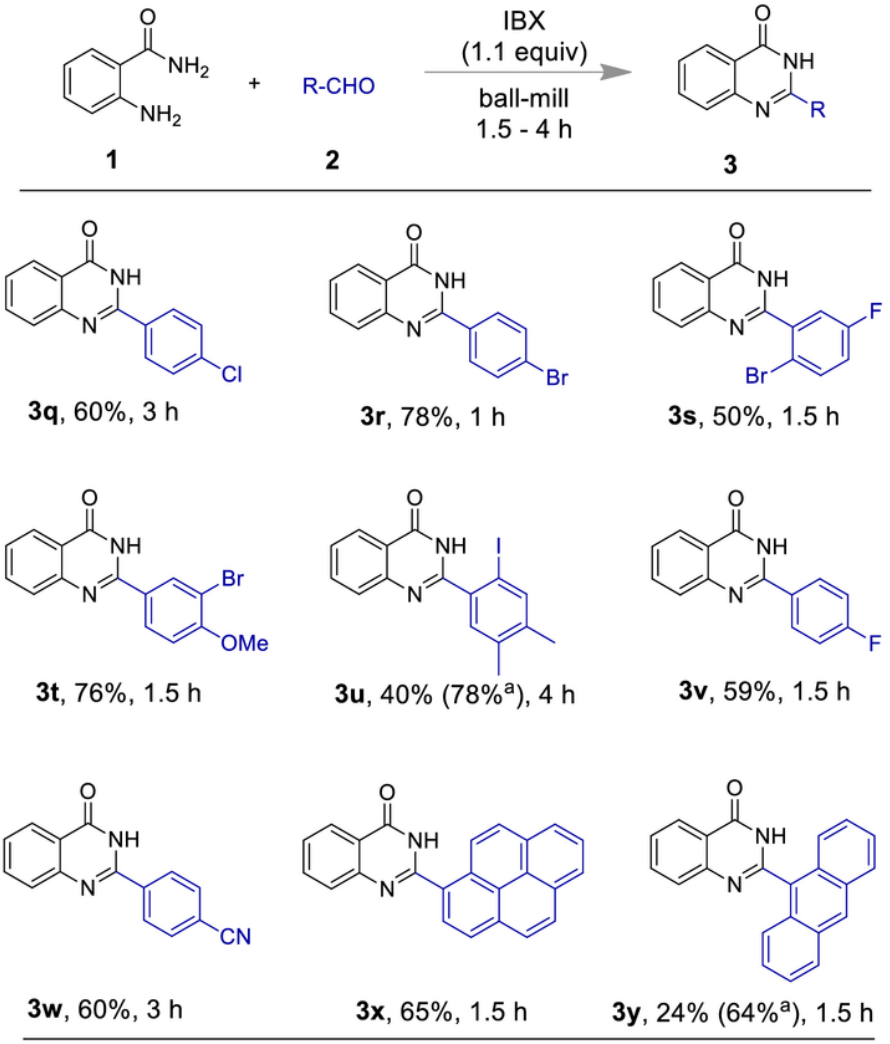


Figure 3.4. Preparation of quinazolin-4(3*H*)-one compounds from reaction of **1** and solid aldehydes. [a] Yields based on recovered aldehydes, for compound **3y,** IBX was added after 1 h.

Using optimum condition, the substrate scope of this methodology was further explored for the preparation of quinazolin-4(3*H*)-one derivatives (Figure 3.3-3.4) and the respective products were formed in good to excellent yields. Mono-alkyl substituted benzaldehydes gave better yield of corresponding quinazolin-4(3*H*)-one derivatives (**3a-b** and **3d,e-f**) than that of benzaldehyde (**3c**). Nevertheless, sterically crowded aryl aldehydes furnished the corresponding quinazolin-4(3*H*)-ones (**3g, 3u**) in comparatively inferior yields. The reactions were observed to be smooth and productive with aldehydes bearing halogen atom (**3h, 3i, 3q-s, 3v**) and cyano group at para position (**3w**). Aldehydes having methoxy substitution rendered quinazolin-4(3*H*)-ones in lofty yields (**3j, 3t**). Similarly, the reaction also took place with aldehydes including fused aromatic ring system such as napthyl (**3l**), pyranyl **(3x),** anthryl (**3y**), etc. Various aliphatic aldehydes such as cyclohexyl (**3n**), 3-phenylbutraldehyde (**3o**) and butraldehyde (**3p**) afforded desired heterocycles with high yield. X-ray crystallographic analysis data indicated the structure of compound **3a.** (Figure 3.5).

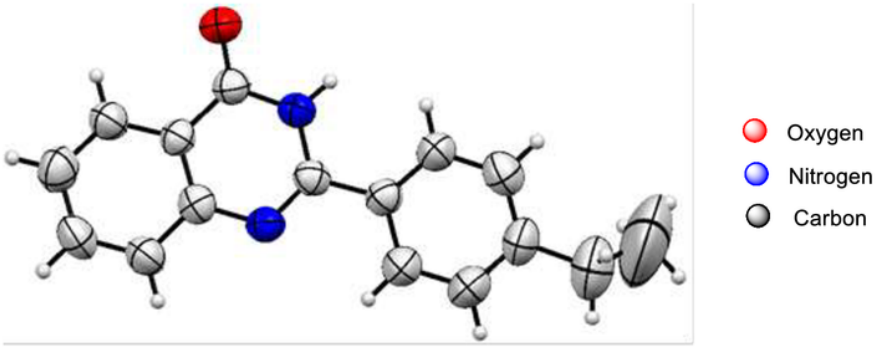


Figure 3.5. Crystal structure of **3a** (CCDC No. 1823611).

The mechanistic pathway of the quinazolin-4(3*H*)-ones synthesis is described in Figure 3.6 based on the observations shown in Table 3.1 and the literature reports.[22] The yield

of the reaction was increased significantly when IBX was mixed after 30 min of initial grinding of the reactants **1** and **2**. It has expected that the adduct **4** is generated from the mixture of 2-aminobenzamaide and the aryl aldehyde followed by reaction with the *o*-iodoxybenzoic acid to provide **5**. Finally, from **5** the quinazolin-4(3*H*)-one **3** was produced with the formation of the iodosobenzoic acid **6**.

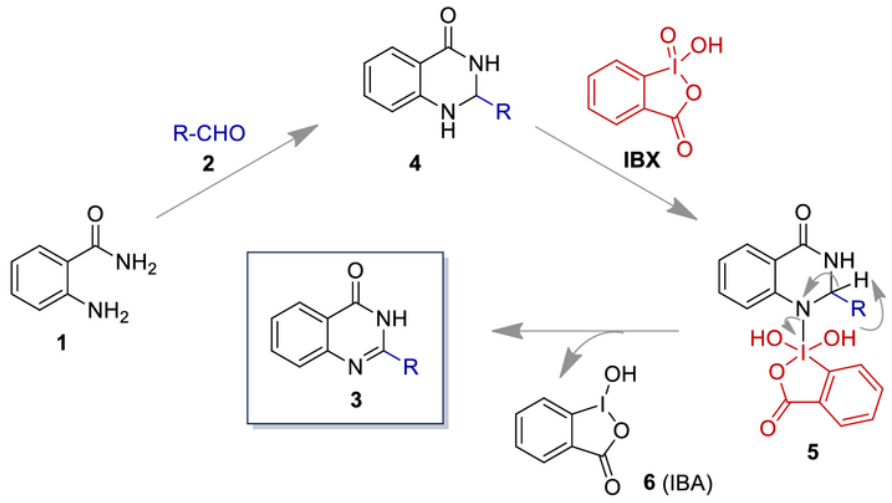


Figure 3.6. Possible mechanism for the quinazolin-4(3*H*)-ones preparation using IBX.

Aryl amines created explosion where there was no reaction of benzamide with IBX. Although, quinazolin-4(3*H*)-ones was isolated from 2-aminobenzamide under identical condition (Figure 1). 2-Aminobenzamide bearing one amine part (highly reactive) and another unreactive part supposed to be an aniline derivative with ordinary reactivity. Therefore, we controlled the reactivity of *o*-iodoxybenzoic acid under mechanomilling condition which afforded successful chemical reaction in presence of 2-aminobenzamide.

In addition, a large scale preparation was done to establish the synthetic utility of this transformation. By treating 2-aminobenzamide (**1**, 0.550 g) with 4-ethyl benzaldehyde (**2a**, 0.541 mL) under optimized reaction condition, product 2-(4-ethylphenyl)quinazolin-4(3*H*)-one (**3a**) was formed in 68 % yield (Figure 3.7).

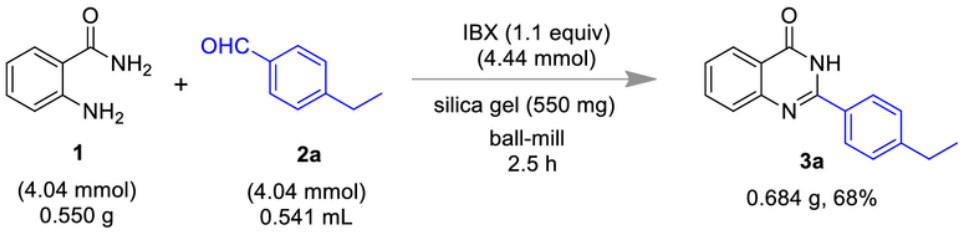


Figure 3.7. Large scale synthesis of **3a**.

3.4 CONCLUSIONS

In conclusion, we foresee an explosion of contact-explosives, aryl amines-IBX is curbed and the safety benefits of using them are substantial, e.g. complex challenging reactions can be achieved easily by selecting suitable reaction environment. The presented methodology also describes the introduction of quinazolin-4(3H)-ones preparation chemistry and may find broad use in the context of mechanochemical reaction towards synthesis of natural product and pharmaceutical chemistry.

3.5 EXPERIMENTAL SECTION

General Methods. Ball Milling experiments were carried out in an open atmosphere and at room temperature conditions in Retsch MM 200 high speed vibration mixture milling instrument (21 Hz). All yields are mentioned as isolated yields after column chromatographic purifications of the compounds using silica gel (mesh 230-400) and hexane-ethyl acetate mixtures as eluent, unless otherwise specified. NMR spectra were recorded on either a 400 MHz or a 700 MHz instrument at 25 ºC. The chemical shift values are reported in ppm (parts per million) with respect to residual chloroform (7.26 ppm for ^{1}H and 77.16 for ^{13}C) or DMSO (2.5 ppm for ^{1}H and 39.5 for ^{13}C). Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, m = multiplet), coupling constant (Hz) and integration. High-resolution mass spectra (HR-MS) were recorded on an ESI-TOF (time of flight) mass spectrometer. IR (infrared) spectral data are reported in wave number (cm^{-1}). Melting points (mp) of the compounds were determined using a digital melting point apparatus and are uncorrected.

Caution. When aniline and IBX were mixed under solvent free condition or at maximum contact, immediate explosion was observed. However, no such explosion could be observed under similar condition when 2-aminobenzamide and aryl aldehydes were reacted in presence of IBX. However, recommended that the general safety protocols at the laboratory should be cautiously exercised and all the reactions should be carried out in fume hoods behind a blast shield.

2-Iodoxybenzoic acid (IBX) was prepared by following reported literature procedure.[23]

General Procedure for Preparation of quinazolin-4(*3H*)-ones. 2-Aminobenzamide (**1**, 0.44 mmol, 1.0 equiv), aldehyde (**2**, 0.44 mmol, 1.0 equiv), 60 mg silica gel (only for liquid aldehyde) and a stainless-steel milling ball were added to 10 mL of stainless-steel jar. Milling was carried out for 30 min and then IBX (0.484 mmol, 1.1 equiv) was added to the mixture. Again milling was performed for 1 h. The progress of the reaction were monitored by TLC after taking a small portion of the reaction mixture and dissolving in DCM (with appropriate solvent as eluent). After completion, dichloromethane was used for extracting the compound from the solid reaction mixture. The solvent was evaporated to dryness and the crude reaction mixture was purified by silica gel column chromatography using appropriate hexane-ethyl acetate mixture.

Large scale preparation of 3a: One third of the 25 ml stainless steel milling jar was filled with 2-aminobenzamide (550 mg, 4.04 mmol), 2- ethylbenzaldehyde (541.5 µl, 4.04 mmol), 550 mg silica gel and one ball (15 mm dia). After 1 h milling, IBX (1.24 g, 4.44 mmol) was added and also milled for 1.5 h. Then, after extraction of the reaction mixture with DCM, followed by silica gel column chromatography with (1: 5.7) ethyl acetate - hexane mixture as eluent provided product **3a** (684 mg, 68%).

Spectral Data of the Compounds

2-(4-Ethylphenyl)quinazolin-4(*3H*)-one (3a).[24] R_f = 0.5 (hexane/ethyl acetate 4:1); white solid; Yield: 91% (100 mg); lit.[24] mp 201–204 °C; ^{1}H NMR (700 MHz, $CDCl_3$)

δ 11.38 (s, 1H), 8.33 (dd, J_1 = 7.7, J_2 = 0.7 Hz, 1H), 8.16 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 1H), 7.82 – 7.78 (m, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 2.76 (q, J = 7.7 Hz, 2H), 1.31 (t, J = 7.7 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 163.7, 152.1, 149.2, 148.9, 135.2, 129.8, 128.8, 127.8, 127.6, 126.9, 126.6, 120.8, 29.0, 15.4; HR-MS (ESI-TOF): m/z calculated for $C_{16}H_{14}NO_2$ $[M+H]^+$: 251.1179, found: 251.1200.

2-(2-Ethylphenyl)quinazolin-4(3*H*)-one (3b). R_f = 0.5 (hexane/ethyl acetate 7:3); white solid; Yield: 95% (105 mg); mp 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 8.20 (d, J = 8 Hz, 1H), 7.79 (m, 2H), 7.55 (d, J = 7.6 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.39 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 2.89 (q, J = 7.2 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 153.8, 149.3, 143.2, 134.5, 133.4, 130.8, 129.8, 128.9, 127.9, 127.1, 126.5, 126.3, 120.8, 26.9, 15.7; IR (KBr): $\bar{\upsilon}$ = 1962, 2862, 2096, 1651, 1302, 1267, 1148 cm^{-1}; HR-MS (ESI-TOF): m/z calculated for $C_{16}H_{14}NO_2$ $[M+H]^+$: 251.1179, found: 251.1191.

2-Phenylquinazolin-4(3H)-one (3c).[25] R_f = 0.5 (hexane/ethyl acetate 4:1); white solid; Yield: 79% (76mg); lit.[27] mp 239–241 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.69 (s, 1H), 8.34 (d, J = 8 Hz, 1H), 8.27 (m, 2H), 7.86-7.79 (m, 2H), 7.60 (m, 3H), 7.51 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 151.9, 149.7, 135.1, 132.9, 131.8, 129.2, 128.2, 127.5, 126.9, 126.5, 121.0

2-(*o*-Tolyl)quinazolin-4(3*H*)-one (3d).[25] R_f = 0.4 (hexane: ethyl acetate 4:1); white solid; Yield: 92% (96 mg) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.79 (s, 1H), 8.24 (d, J = 8

Hz, 1H), 7.80 (d, J = 4 Hz, 2H), 7.57 (d, J = 7.2 Hz, 1H), 7.50 (dt, J_1 = 8, J_2 = 4 Hz, 1H), 7.43 (t, J = 7.2 Hz, 1H), 7.35 (d, J = 7.2 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.14, 153.6, 149.2, 137.0, 134.9, 133.7, 131.6, 130.7, 128.9, 127.9, 127.1, 126.5, 126.4, 120.9, 20.2.

2-(*p*-Tolyl)quinazolin-4(3*H*)-one (3e).[25] R_f = 0.5 (hexane/ethyl acetate 4:1); white solid; Yield: 82% (86 mg); ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.46 (s, 1H), 8.14 (d, J = 7.7 Hz, 1H), 8.10 (d, J = 8.4 Hz, 2H), 7.83 (t, J = 7.7 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.36 (d, J = 7.7 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 162.3, 152.3, 148.8, 141.5, 134.6, 129.9, 129.2, 127.7, 127.4, 126.4, 125.9, 21.0; HR-MS (ESI-TOF): m/z calculated for $C_{15}H_{12}NO_2$ $[M+H]^+$: 237.1022, found: 237.1026.

2-(4-Isopropylphenyl)quinazolin-4(3*H*)-one (3f).[25] R_f = 0.5 (hexane/ethyl acetate 4:1); white solid; Yield: 84% (97 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.73 (s, 1H), 8.34 (d, J = 7.6 Hz, 1H), 8.21 (d, J = 8 Hz, 2H), 7.89 – 7.74 (m, 2H), 7.57 – 7.47 (m, 1H), 7.44 (d, J = 8.4 Hz, 2H), 3.15 – 2.91 (m, 1H), 1.32 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 153.2, 151.9, 149.8, 134.9, 130.4, 128.1, 127.6, 127.3, 126.7, 126.5, 120.9, 34.3, 23.9.

2-Mesitylquinazolin-4(3H)-one (3g).[26] R_f = 0.5 (hexane/ethyl acetate 4:1); white solid; Yield: 35% (40 mg), 50% (based on recovered aldehyde); lit.[26] mp 192–194 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.83 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 6.97 (s, 2H), 2.29 (s, 3H),

2.12 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.8, 154.3, 148.9, 138.4, 135.4, 134.5, 132.0, 128.0, 127.4, 126.7, 125.9, 121.1, 20.8, 19.1.

2-(2-Bromophenyl)quinazolin-4(3*H*)-one (3h).[27] R_f = 0.4 (hexane/ethyl acetate 4:1); white solid; Yield: 94% (126 mg); lit.[27] mp 159-160 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.26 (d, *J* = 8 Hz, 1H), 7.82 (d, *J* = 4 Hz, 2H), 7.71 (t, *J* = 7.2 Hz, 2H), 7.57 – 7.49 (m, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 152.2, 149.1, 135.3, 135.0, 133.9, 132.1, 131.4, 128.1, 128.1, 127.5, 126.6, 121.2, 121.1.

2-(2-Fluorophenyl)quinazolin-4(3*H*)-one (3i).[25] R_f = 0.4 (hexane/ethyl acetate 4:1); white solid; Yield: 68% (72 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.30 (m, 2H), 7.81 (m, 2H), 7.52 (m, 1H), 7.52 (d, *J* = 8 Hz, 1H), 7.35 (t, *J* = 8 Hz, 1H),7.23 (t, *J* = 8 Hz,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 160.9 (d, $^1J_{C,F}$ = 249.9 Hz), 149.1, 148.6 (d, $^4J_{C,F}$ = 1.6 Hz), 134.9, 133.6 (d, $^3J_{C,F}$ = 9.2 Hz), 131.5 (d, $^4J_{C,F}$ = 2.0 Hz), 128.13, 127.3, 126.7, 125.3 (d, $^4J_{C,F}$ = 3.3 Hz), 121.3, 120.4 (d, $^3J_{C,F}$ = 9.3 Hz), 116.8 (d, $^2J_{C,F}$ = 23 Hz).

2-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (3j).[25] R_f = 0.5 (hexane/ethyl acetate 4:1); white solid; Yield: 89% (99 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.41 (s, 1H), 8.19 (d, *J* = 7.6 Hz, 2H), 8.13 (d, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 162.1, 151.9, 148.9, 134.5, 129.5, 127.3, 126.1, 125.9, 124.8, 120.7, 114.0, 55.5.

2-(Pyridin-4-yl)quinazolin-4(3*H*)-one (3k).[28] R_f = 0.3 (hexane/ethyl acetate 1:1); white solid; Yield: 71 % (70 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (s, 1H), 8.79 (d, *J* = 5.2 Hz, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 8.12 (d, *J* = 6 Hz, 2H), 7.88 (t, *J* = 8 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 150.7, 150.4, 148.4, 139.9, 134.9, 127.8, 127.5, 125.9, 121.7. 121.5.

2-(Naphthalen-1-yl)quinazolin-4(3*H*)-one (3l).[29] R_f = 0.4 (hexane/ethyl acetate 7:3); white solid; Yield: 52% (62 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.66 (s, 1H), 8.23 (d, *J* = 8 Hz, 1H), 8.47 (d, *J* = 8.8, 1H), 8.13 (d, *J* = 8 Hz, 1H), 8.07 – 8.03 (m, 1H), 7.90 – 7.84 (m, 1H), 7.80 (d, *J* = 6.8 Hz, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.62 – 7.56 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.9, 153.7, 148.7, 134.5, 133.1, 131.7, 130.3, 130.3, 128.3, 127.7, 127.5, 127.0, 126.8, 126.3, 125.8, 125.2, 125.0, 121.2; HR-MS (ESI-TOF): m/z calculated for $C_{18}H_{12}NO_2$ $[M+H]^+$: 273.1022, found: 273.1039.

2-([1,1'-biphenyl]-2-yl)quinazolin-4(3*H*)-one (3m).[30] R_f = 0.4 (hexane/ethyl acetate 4:1); white solid; Yield: 70% (92 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), 7.87 (d, *J* =7.6, 1H), 7.78 (m, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 3H), 7.32-7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 153.7, 149.2, 140.7, 139.3, 134.8, 132.8, 131.1, 131.0, 130.5, 129.1, 128.9, 128.2, 128.1, 127.9, 127.1, 126.5, 120.8.

2-Cyclohexylquinazolin-4(3*H*)-one (3n).[31] R_f = 0.5 (hexane/ethyl acetate 3:2); white solid; Yield: 65% (65 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 7.79- 7.70 (m, 2H), 7.46 (t, *J* = 7.6 Hz, 1H), 2.70 (t, *J* = 12 Hz, 1H), 2.06 (d, *J* = 11.6 Hz, 2H), 1.92 (d, *J* = 12.8 Hz, 2H), 1.87 – 1.65 (m, 3H), 1.54 – 1.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 160.4, 149.7, 134.9, 127.5, 126.4, 126.3, 120.9, 44.9, 30.6, 26.1, 25.8.

2-(3-Phenylbutyl)quinazolin-4(3*H*)-one (3o). R_f = 0.5 (hexane/ethyl acetate 7:3); white solid; Yield: 84% (102 mg); mp 165-166 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.05 (s, 1H), 8.33 (d, *J* = 7.6 Hz, 1H), 7.79 (m, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 6.8 Hz, 2H), 7.28 (d, *J* = 6.4 Hz, 2H), 7.20 (d, *J* = 6.8 Hz, 1H), 3.55 (m, 1H), 3.19 – 2.94 (m, 2H), 1.42 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 155.7, 149.6, 145.5, 134.9, 128.7, 127.5, 127.1, 126.7, 126.6, 126.4, 120.6, 44.7, 38.8, 21.1; IR (KBr): $\bar{\upsilon}$ = 2973, 2923, 2103, 1653, 1467, 1335, 1251 cm^{-1}; HR-MS (ESI-TOF): m/z calculated for $C_{17}H_{16}NO_2$ $[M+H]^+$: 265.1335, found: 265.1361.

2-Butylquinazolin-4(3*H*)-one (3p).[32] R_f = 0.3 (hexane/ethyl acetate 7:3); white solid; Yield: 68% (57 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 6.8 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.1 Hz, 1H), 2.57 (t, *J* = 6.4 Hz, 2H), 1.74 (m, 2H), 0.93 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.9, 157.3, 148.9, 134.3, 126.8, 125.9, 125.7, 120.8, 36.4, 20.2, 13.5.

2-(4-Chlorophenyl)quinazolin-4(3*H*)-one (3q).[27] R_f = 0.5 (hexane/ethyl acetate 4:1); white solid; Yield: 60% (67 mg); lit.[27] mp 298–299 ºC; ^{1}H NMR (400 MHz, DMSO-

d_6) δ 12.62 (s, 1H), 8.20 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.53 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 151.4, 148.6, 136.3, 134.7, 131.6, 129.6, 128.7, 127.5, 126.8, 125.9, 120.9; HR-MS (ESI-TOF): m/z calculated for $C_{14}H_9NO_2Cl$ [M+ H] $^+$: 257.0476, found: 257.0479.

2-(4-Bromophenyl)quinazolin-4(3*H*)-one (3r).[27] R_f = 0.6 (hexane/ethyl acetate 4:1); white solid; Yield: 78% (104 mg); lit.[27] mp 298–300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 8.13 (d, J = 8.4 Hz, 3H), 7.84 (t, J = 6.4, 1H), 7.76 (d, J = 6.4 Hz, 3H), 7.53 (t, J = 6.4, 1H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 162.2, 151.5, 148.6, 134.7, 131.9, 131.7, 129.8, 127.5, 126.8, 125.9, 125.2, 121.0

2-(2-Bromo-5-fluorophenyl)quinazolin-4(3*H*)-one (3s). R_f = 0.5 (hexane/ethyl acetate 7:3); white solid; Yield: 50% (69 mg); mp 229-230 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.28 (d, J = 8 Hz, 1H), 7.82 (m, 2H), 7.68 (dd, J_1 = 8.8, J_2 = 4 Hz, 1H), 7.61 – 7.49 (m, 2H), 7.16 (dd, J_1 = 8.4, J_2 = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 162.0 (d, $^1J_{C,F}$ = 250.3), 150.9, 148.9, 136.5 (d, $^3J_{C,F}$ = 7.9 Hz), 135.5 (d, $^3J_{C,F}$ = 7.9 Hz), 135.2, 128.2, 127.8, 126.7, 121.3, 119.6 (d, $^2J_{C,F}$ = 22.3 Hz), 118.9 (d, $^2J_{C,F}$ =24.6 Hz), 115.3 (d, $^4J_{C,F}$ = 3.5 Hz); IR (KBr): $\tilde{\upsilon}$ = 3427, 2096, 1651, 1338, 1251, 1203 cm^{-1}; HR-MS (ESI-TOF): m/z calculated for $C_{14}H_8NO_2{}^{79}BrF$ [M + H]$^+$: 318.9877, found: 318.9904, $C_{14}H_8NO_2{}^{81}Br$ [M + H] $^+$: 320.9857, found: 320.9885.

2-(3-Bromo-4-methoxyphenyl)quinazolin-4(3*H*)-one (3t). R_f = 0.5 (hexane/ethyl acetate 7:3); white solid; Yield: 76% (110 mg); mp charred at 250 ºC; ^{1}H NMR (400

MHz, DMSO-d_6) δ 12.50 (s, 1H), 8.47 (s, 1H), 8.25 (d, J = 8 Hz, 1H), 8.13 (d, J = 8 Hz, 1H), 7.83 (t, J = 8.4 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 158.0, 150.8, 148.7, 134.7, 132.4, 128.8, 127.5, 126.5, 126.2, 125.9, 120.7, 112.7, 110.73, 56.7; IR (KBr): $\bar{\upsilon}$ = 3193, 2089, 1643, 1224, 1141, 1055 cm^{-1}; HR-MS (ESI-TOF): m/z calculated for $C_{15}H_{11}NO_2{}^{79}Br$ [M + H] $^+$: 331.0077, found: 331.0081, $C_{15}H_{11}NO_2{}^{81}Br$ [M + H] $^+$: 333.0057, found: 333.0059.

2-(2-Iodo-4,5-dimethylphenyl)quinazolin-4(3*H*)-one (3u). R_f = 0.4 (hexane/ethyl acetate 4:1); white solid; Yield: 40% (66 mg), 78% (based on recovered aldehyde) ; mp 215-216 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.49 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.85 (t, J = 7.2 Hz, 1H), 7.76 (s, 1H), 7.69 (d, J = 8 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.35 (s, 1H), 2.26 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.6, 155.2, 148.6, 140.5, 139.3, 137.1, 136.6, 134.6, 130.8, 127.5, 126.9, 125.9, 121.2, 92.5, 18.8, 18.7; IR (KBr): $\bar{\upsilon}$ = 2873, 2090, 1644, 1463, 1288, 1138, 1020 cm^{-1}; HR-MS (ESI-TOF): m/z calculated for $C_{16}H_{13}NO_2I$ $[M+H]^+$: 377.0145, found: 377.0174.

2-(4-Fluorophenyl)quinazolin-4(3*H*)-one(3v).[25] R_f = 0.5 (hexane/ethyl acetate 7:3); white solid; Yield: 59% (62 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (s, 1H), 8.25 (t, J = 8.0, Hz, 2H), 8.15 (d, J = 7.6 Hz, 1H), 7.84 (t, J = 7.6 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0 (d, $^1J_{C,F}$ = 247.0 Hz), 161.9, 150.7, 148.3, 134.7, 130.4 (d, $^3J_{C,F}$ = 9.1 Hz), 129.3 (d, $^4J_{C,F}$ = 2.5 Hz), 127.5, 126.7, 125.9, 120.7, 115.7 (d, $^2J_{C,F}$ =22.0 Hz).

4-(4-Oxo-3,4-dihydroquinazolin-2-yl)benzonitrile (3w).[29] R_f = 0.4 (hexane/ethyl acetate 4:1); white solid; Yield: 60% (65 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 8.34 (d, *J* = 8.4 Hz, 2H), 8.18 (d, *J* = 8 Hz, 1H), 8.04 (d, *J* = 8 Hz, 2H), 7.87 (t, *J* = 7.2 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 151.1, 148.2,137.0, 134.8, 132.6, 128.7, 127.7, 127.2,125.9, 121.3, 118.4, 113.6.

2-(Pyren-1-yl)quinazolin-4(3*H*)-one (3x). R_f = 0.4 (hexane/ethyl acetate 7:3); yellow solid; Yield: 65% (99 mg); mp charred at 250 °C ; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.48 (d, *J* = 9.2 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 8.42 – 8.36 (m, 2H), 8.34 – 8.32 (m, 2H), 8.30 – 8.25 (m, 3H), 8.15 (t, *J* = 7.6 Hz, 1H), 7.90 (t, *J* = 8.4, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 154.1, 148.9, 134.6, 131.9, 130.8, 130.2, 128.9, 128.8, 128.6, 128.5, 127.6, 127.3 (2C), 126.9, 126.8, 126.1, 125.9, 125.8, 124.5 (2C), 123.8, 123.6, 121.3; IR (KBr): $\bar{\upsilon}$ = 3308, 2862, 2089, 1636, 1278, 1148 cm^{-1}; HR-MS (ESI-TOF): m/z calculated for $C_{24}H_{14}NO_2$ $[M+H]^+$: 347.1179, found: 347.1199.

.**2-(Anthracen-9-yl)quinazolin-4(3*H*)-one (3y).**[17b] R_f = 0.4 (hexane/ethyl acetate 7:3); white solid; Yield: 27% (34 mg), 64% (based on recovered aldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.63 (s, 1H), 8.41 (d, *J* = 7.6 Hz, 1H), 8.12 – 8.04 (m, 2H), 7.92 – 7.84 (m, 4H), 7.63 (m, Hz, 1H), 7.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 152.2, 149.1, 135.2, 131.2, 130.1, 129.7, 128.9, 128.3, 127.7, 127.6, 127.2, 126.8, 125.8, 124.6, 121.4.

3.6 Notes and References

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^{1}H & ^{13}C NMR spectra of selected compounds

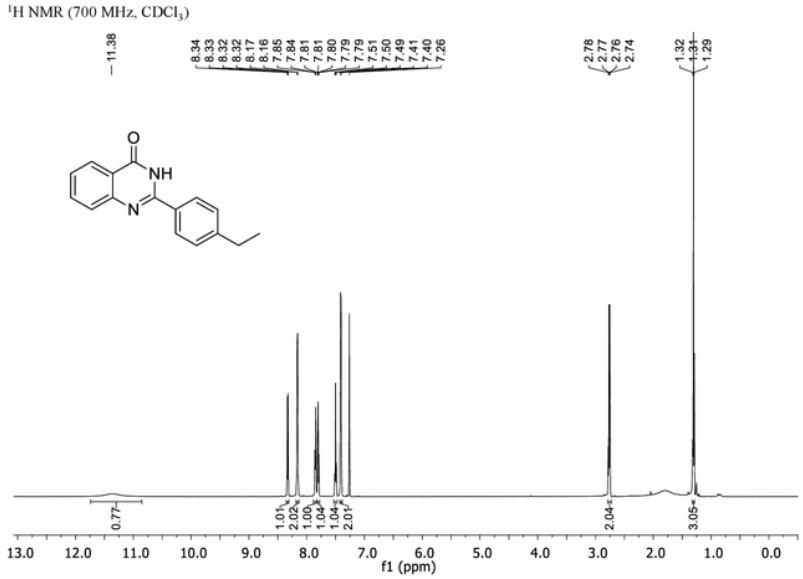


Figure 3.8. ^{1}H NMR spectra of 2-(4-Ethylphenyl)quinazolin-4(3*H*)-one **(3a)**.

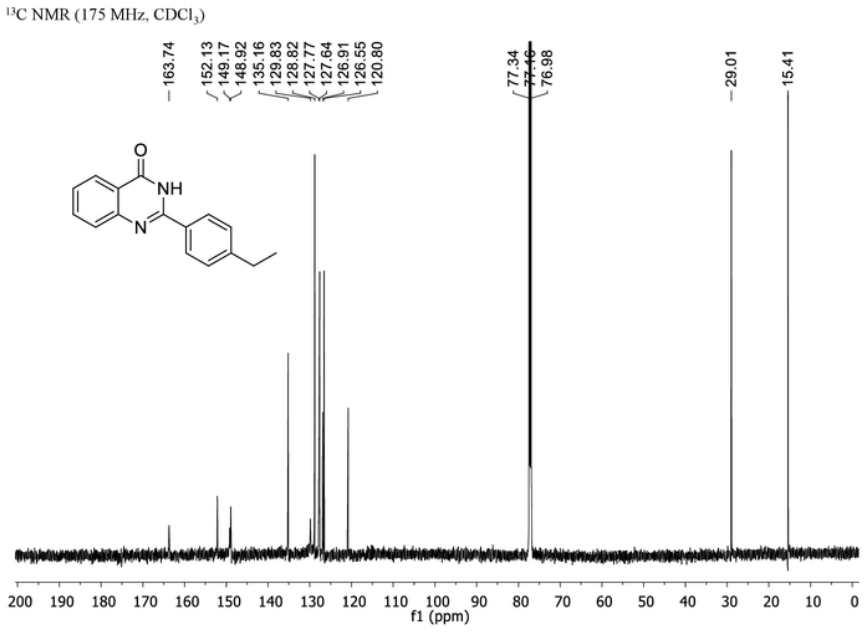


Figure 3.9. ^{13}C NMR spectra of 2-(4-Ethylphenyl)quinazolin-4(3*H*)-one **(3a)**.

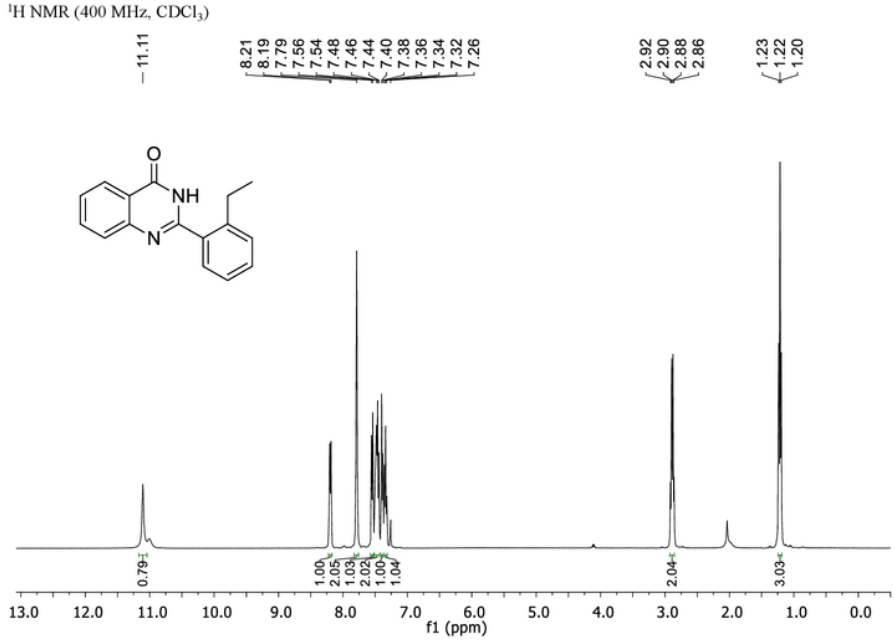


Figure 3.10. ^{1}H NMR spectra of 2-(2-Ethylphenyl)quinazolin-4(3*H*)-one **(3b)**.

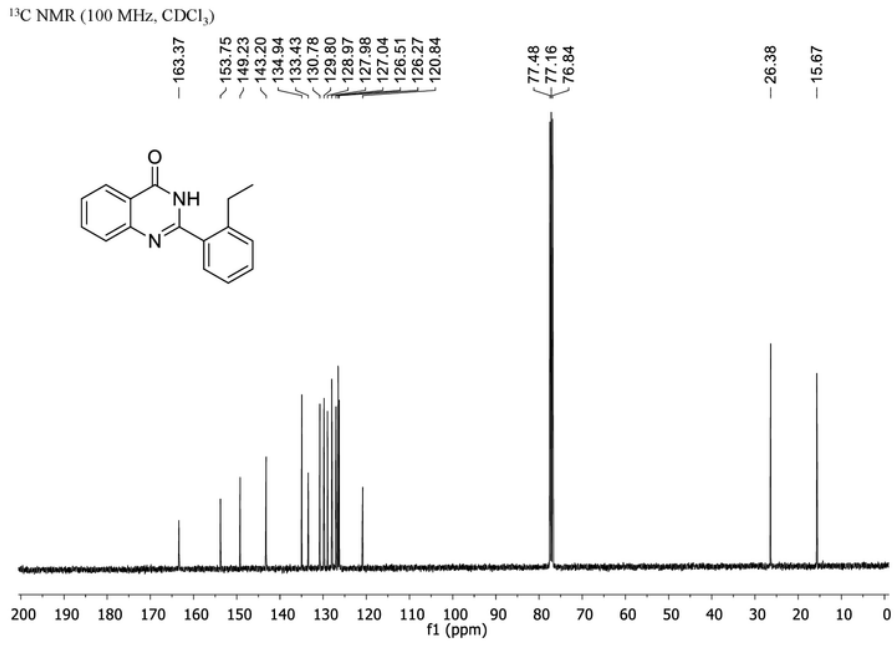


Figure 3.11. ^{13}C NMR spectra of 2-(2-Ethylphenyl)quinazolin-4(3*H*)-one **(3b)**

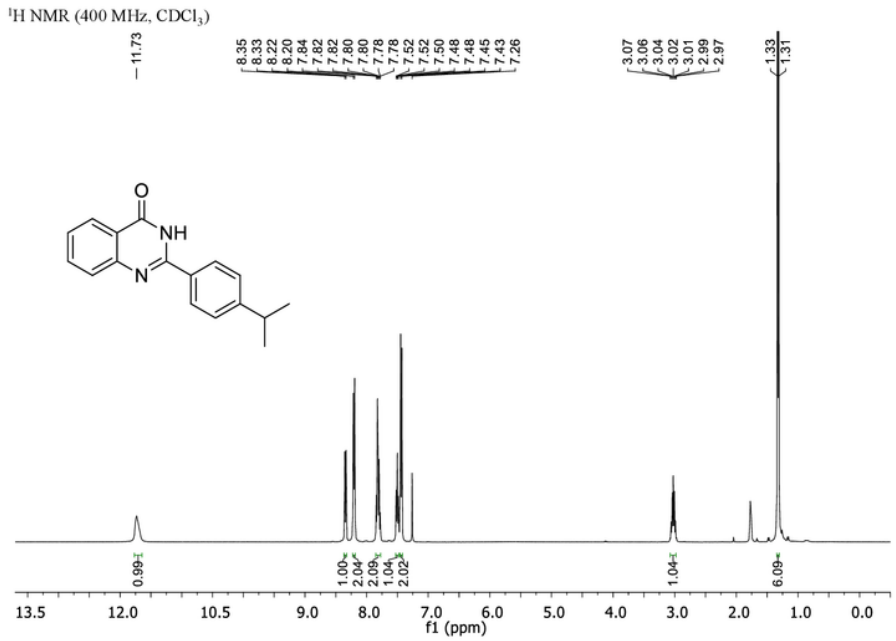


Figure 3.12. ^{1}H NMR spectra of 2-(4-Isopropylphenyl)quinazolin-4(3*H*)-one **(3f)**.

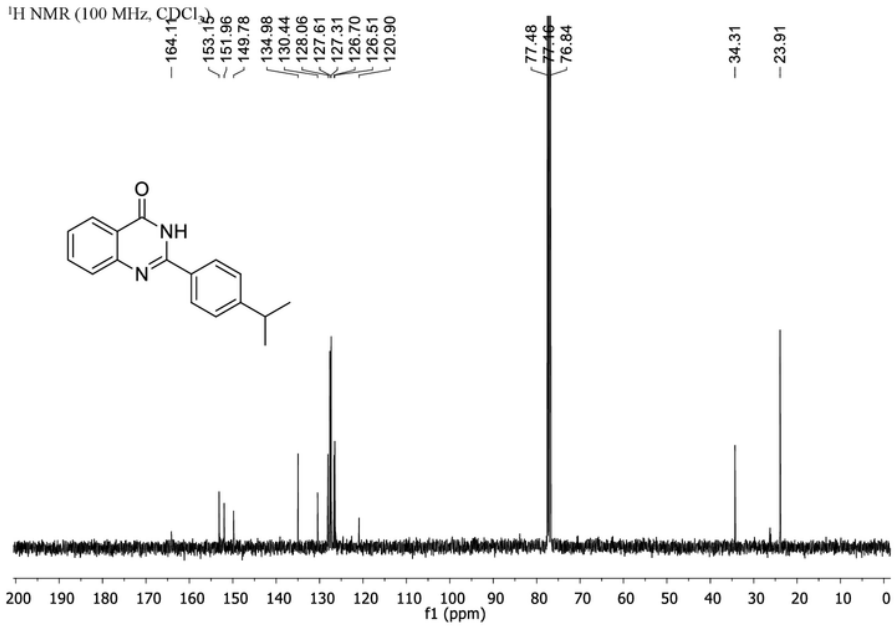


Figure 3.13. ^{13}C NMR spectra of 2-(4-Isopropylphenyl)quinazolin-4(3*H*)-one **(3f)**.

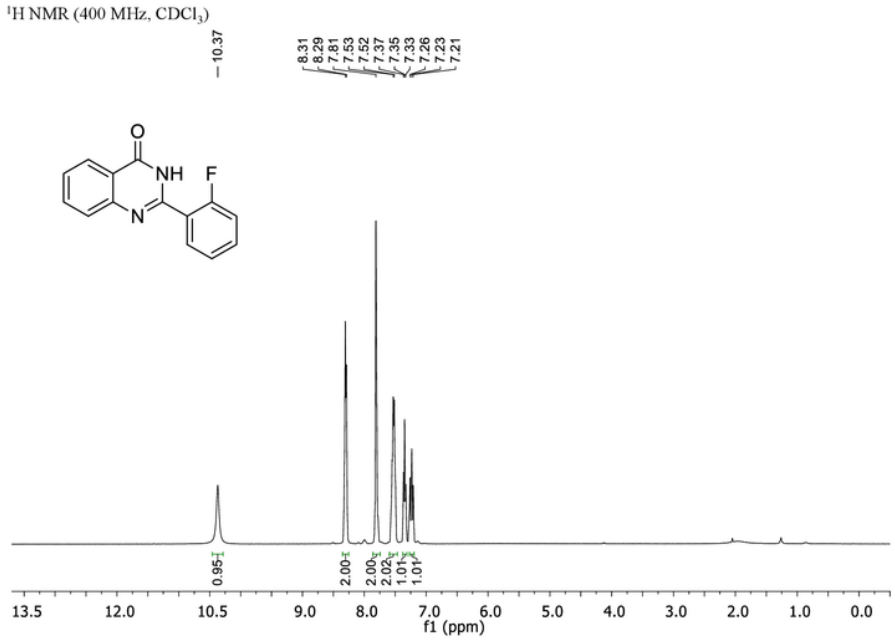


Figure 3.14. ^{1}H NMR spectra of 2-(2-Fluorophenyl)quinazolin-4(3*H*)-one **(3i)**.

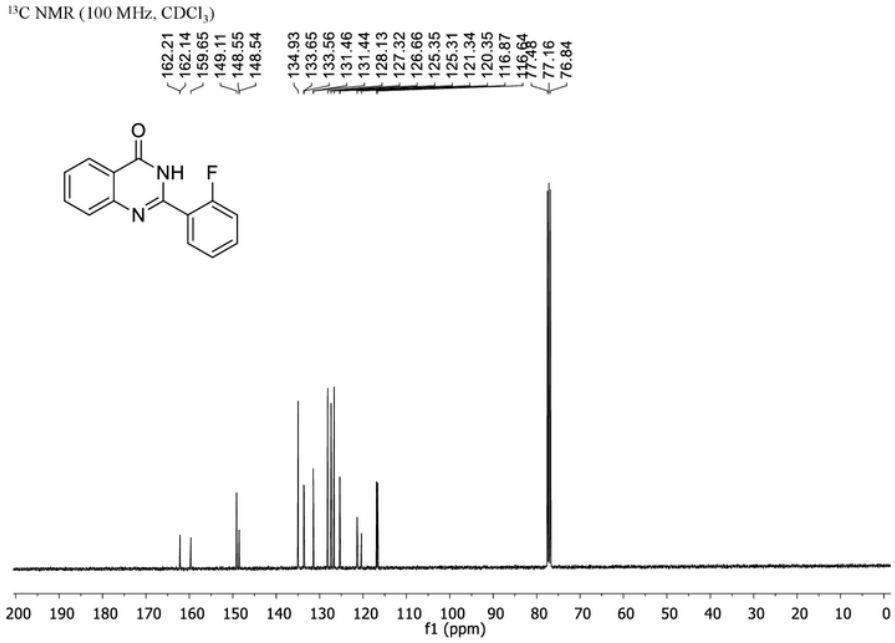


Figure 3.15. ^{13}C NMR spectra of 2-(2-Fluorophenyl)quinazolin-4(3*H*)-one **(3i)**.

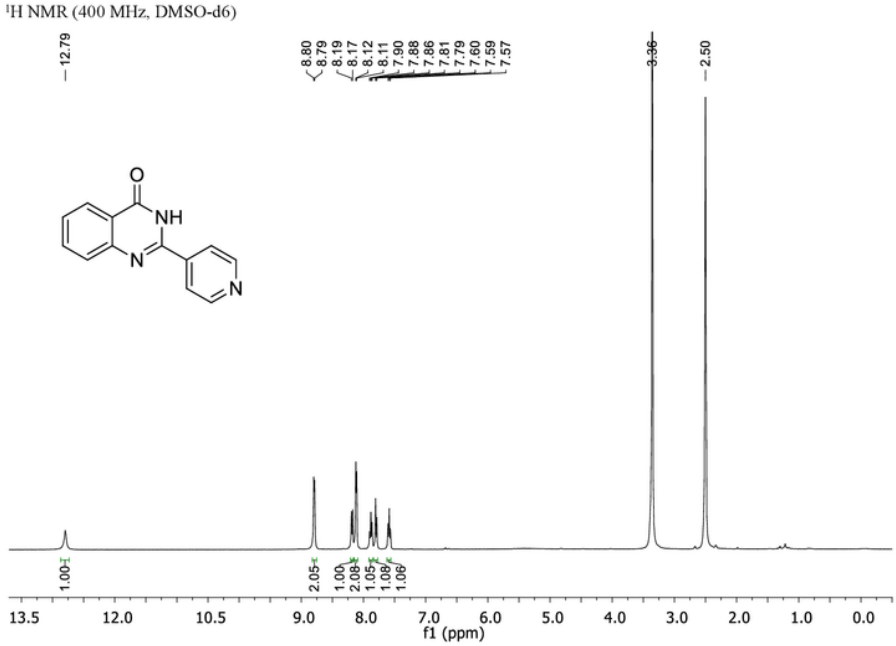


Figure 3.16. ^{1}H NMR spectra of 2-(Pyridin-4-yl)quinazolin-4(3*H*)-one **(3k)**.

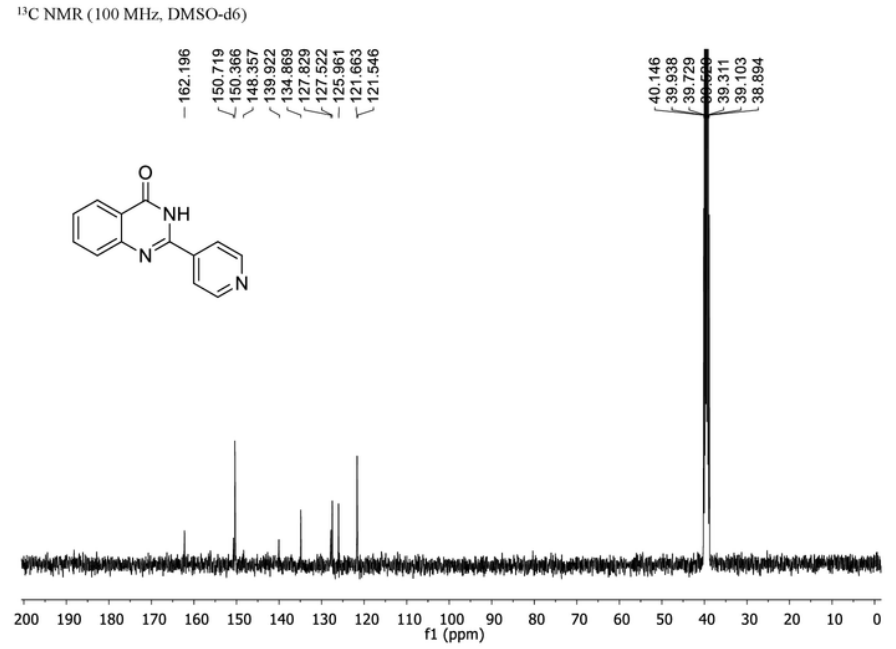


Figure 3.17. ^{13}C NMR spectra of 2-(Pyridin-4-yl)quinazolin-4(3*H*)-one **(3k)**.

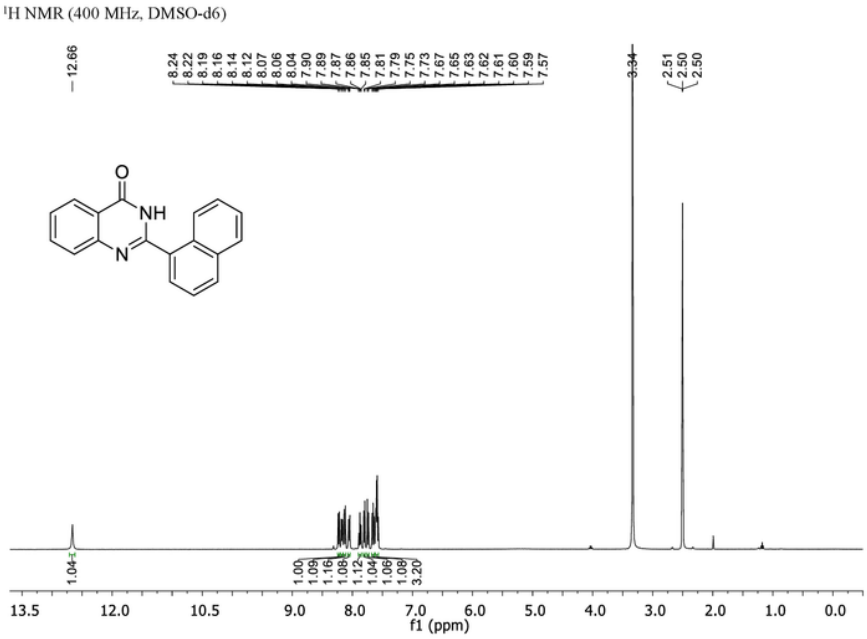


Figure 3.18. ^{1}H NMR spectra of 2-(Naphthalen-1-yl)quinazolin-4(3*H*)-one **(3l)**.

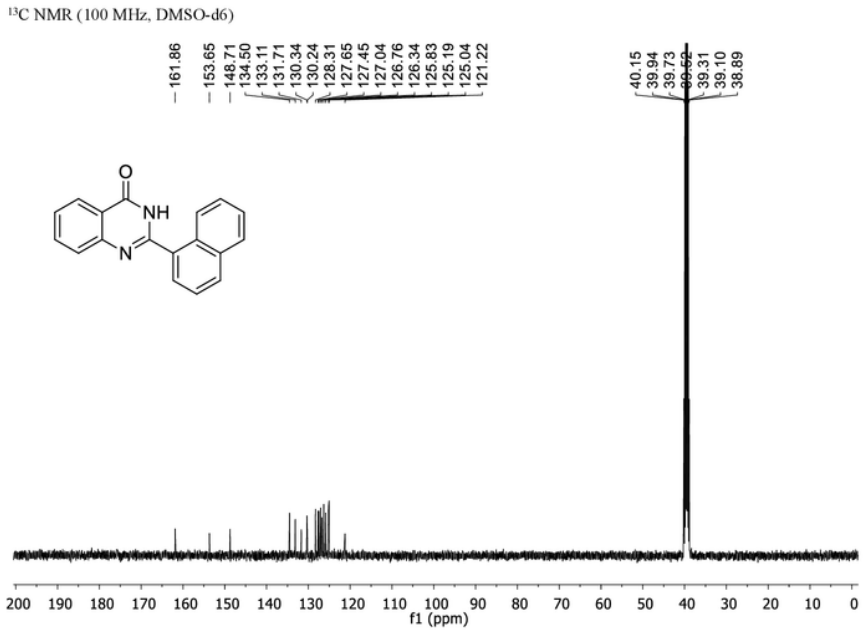


Figure 3.19. ^{13}C NMR spectra of 2-(Naphthalen-1-yl)quinazolin-4(3*H*)-one **(3l)**.

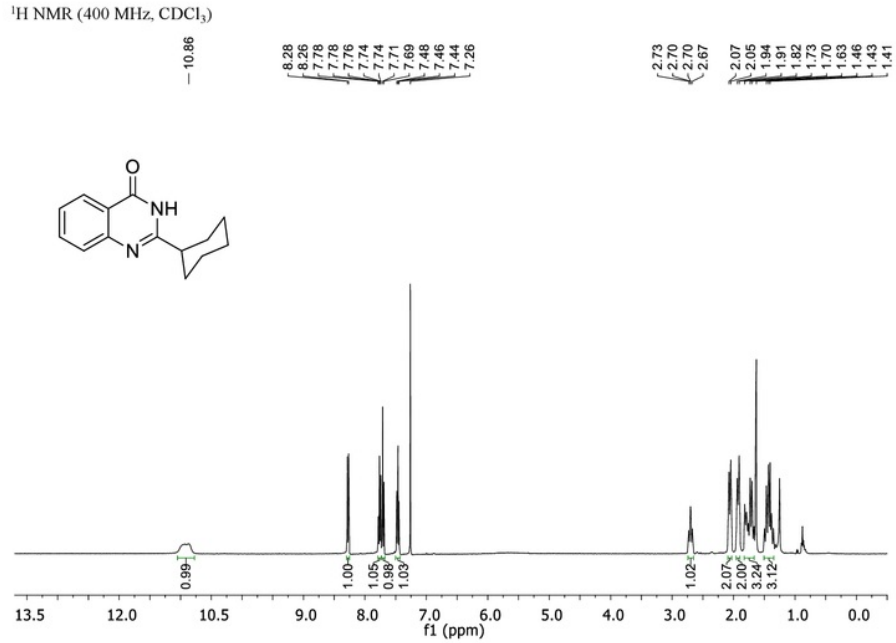


Figure 3.20. ^{1}H NMR spectra of 2-Cyclohexylquinazolin-4(3*H*)-one **(3n)**.

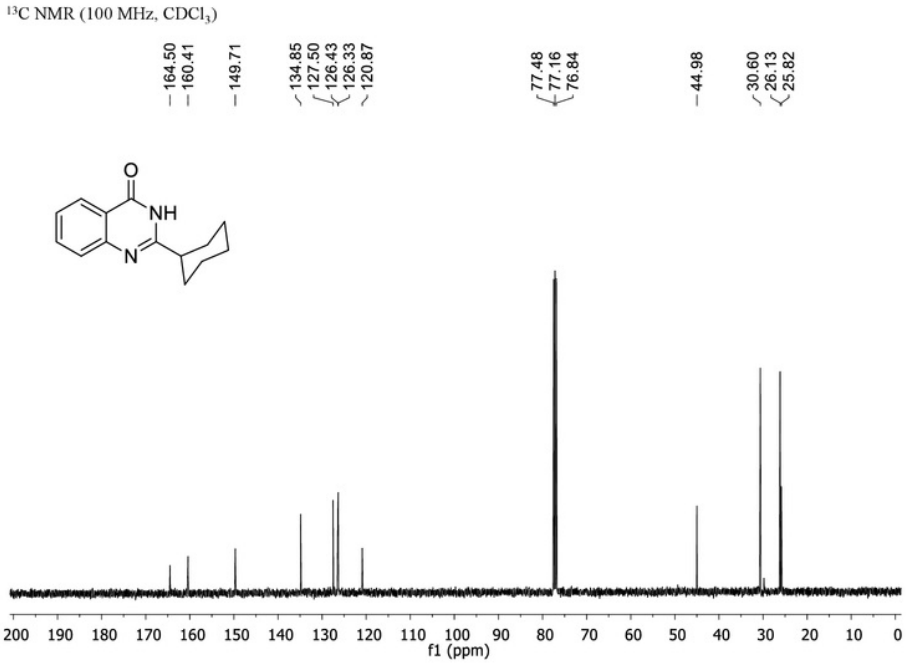


Figure 3.21. ^{13}C NMR spectra of 2-Cyclohexylquinazolin-4(3*H*)-one **(3n)**.

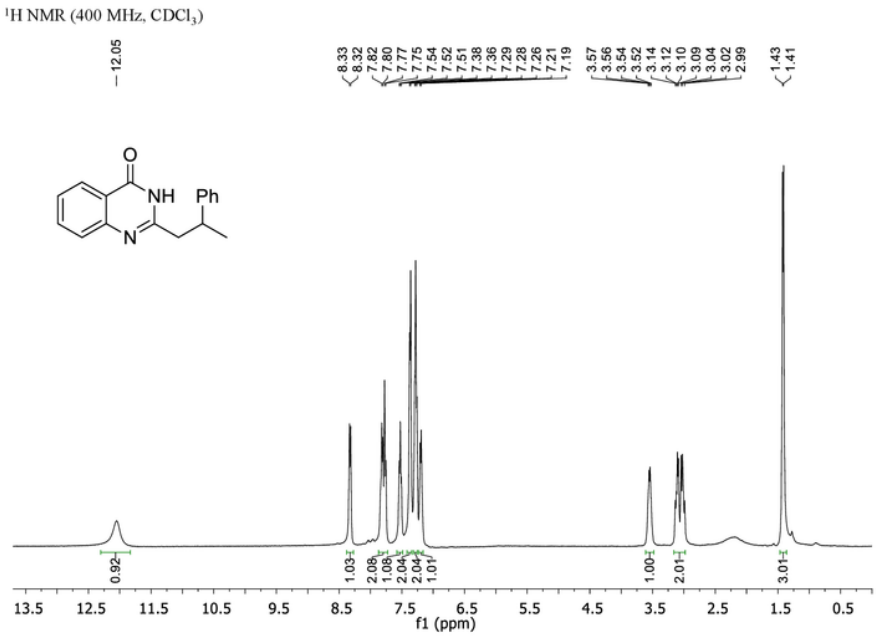


Figure 3.22. ^{1}H NMR spectra of 2-(3-Phenylbutyl)quinazolin-4(3*H*)-one **(3o)**.

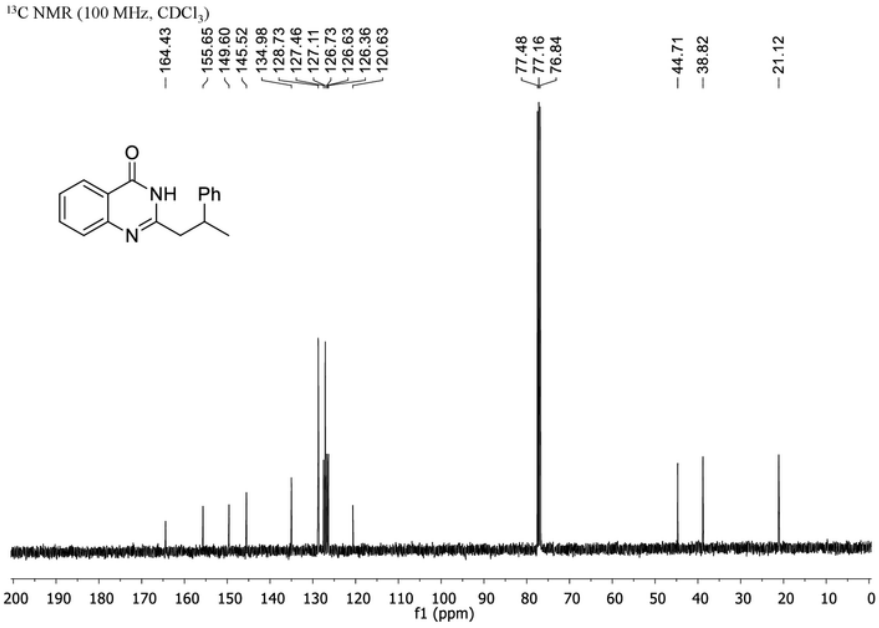


Figure 3.23. ^{13}C NMR spectra of 2-(3-Phenylbutyl)quinazolin-4(3*H*)-one **(3o)**.

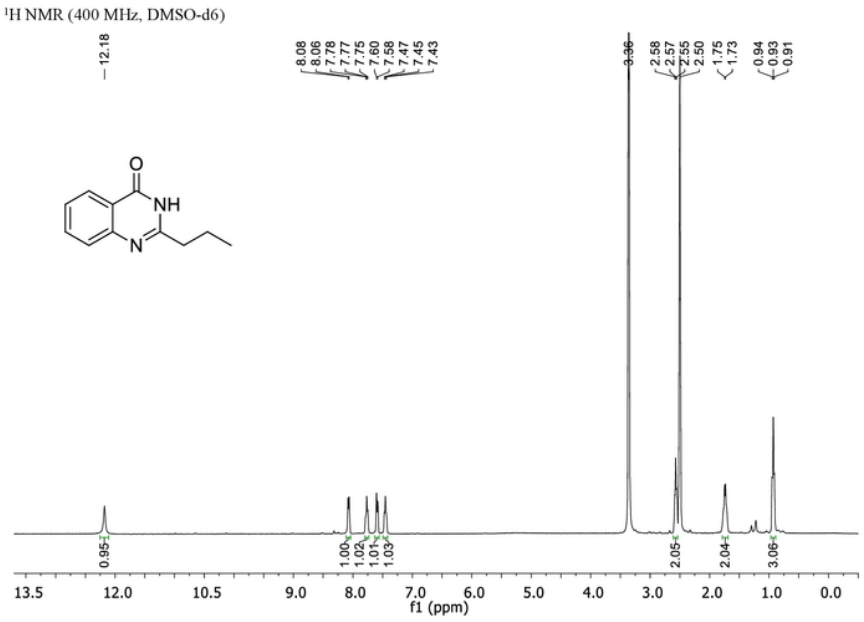


Figure 3.24. ^{1}H NMR spectra of 2-Butylquinazolin-4(3*H*)-one **(3p)**.

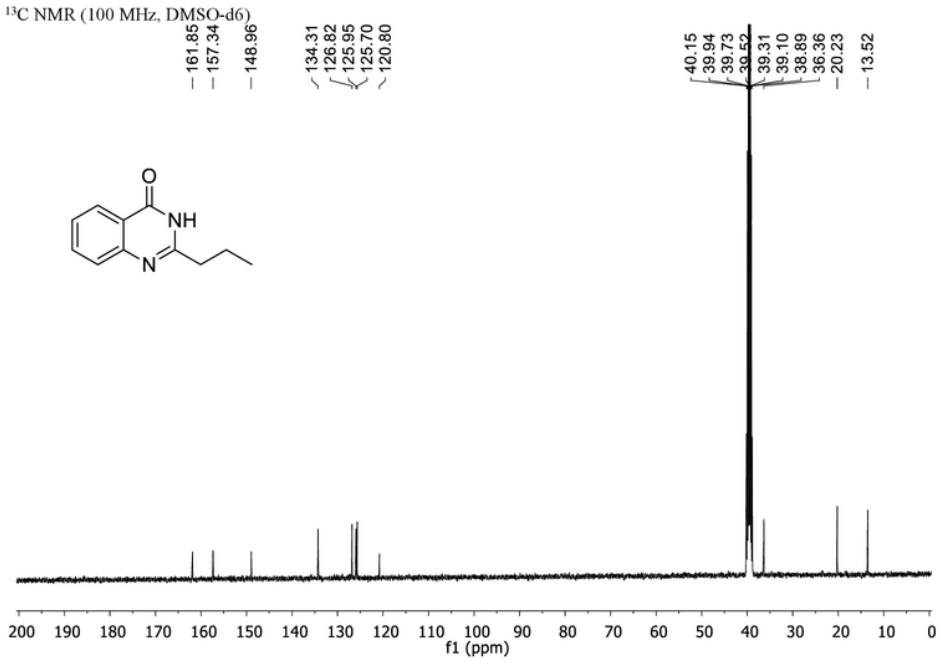


Figure 3.25. ^{13}C NMR spectra of 2-Butylquinazolin-4(3*H*)-one **(3p)**.

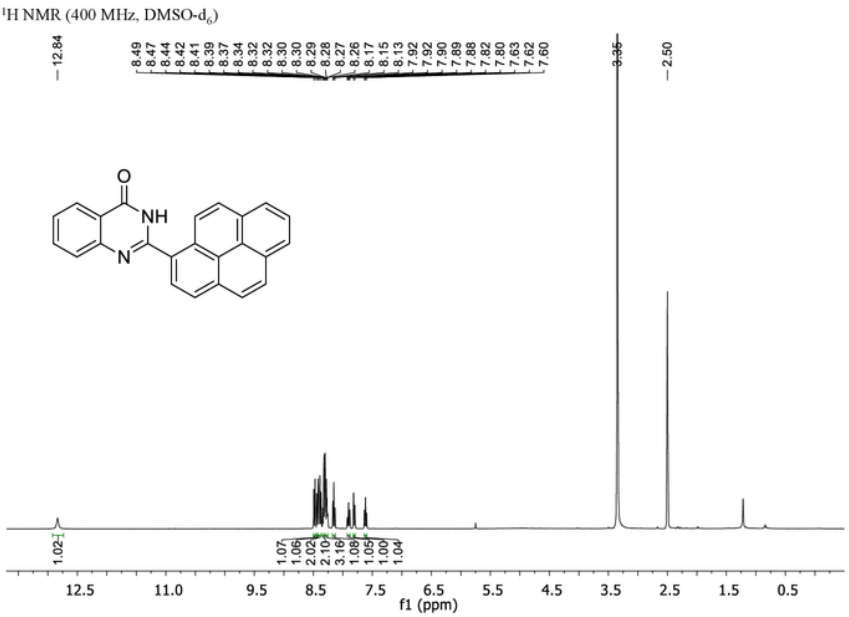


Figure 3.26. ^{1}H NMR spectra of 2-(Pyren-1-yl)quinazolin-4(3*H*)-one **(3x)**.

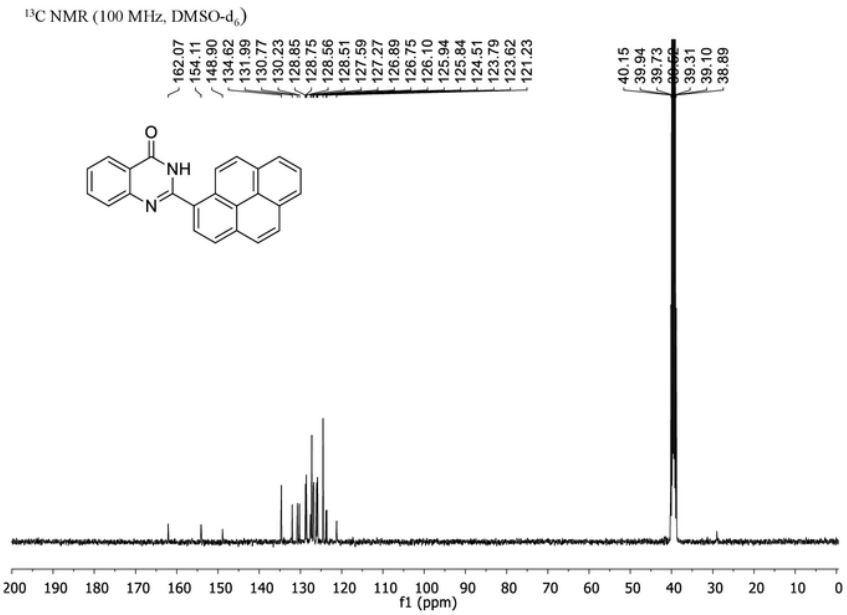


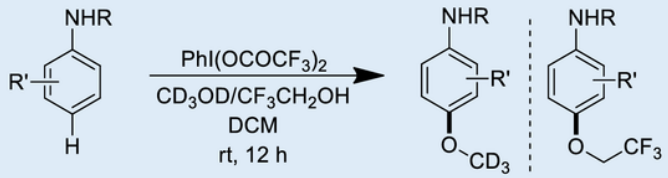
Figure 3.27. ^{13}C NMR spectra of 2-(Pyren-1-yl)quinazolin-4(3*H*)-one **(3x)**.

CHAPTER 4

PIFA Mediated C-H Trifluoroethoxylation and Trideuteriomethoxylation of Anilides Controlled by HSAB Principle

4.1 ABSTRACT

Regioselective C-H Alkoxylation



Phenyliodine bis(trifluoroacetate) (PIFA) assisted methodology on intermolecular C-H etherification of anilides has been shown for preparation of $-OCH_2CF_3$ and $-OCD_3$ containing aromatic ethers. By utilizing non-covalent interactions and hard-soft acid-base (HSAB), the reactivity of the system has been controlled with respect to the feature of added nucleophiles. The combination of anilides and PIFA furnished electrophilic nitrenium ions (soft), however, due to presence of hard nucleophiles like alcohols the reactivity was found exclusively on carbenium ions (hard).

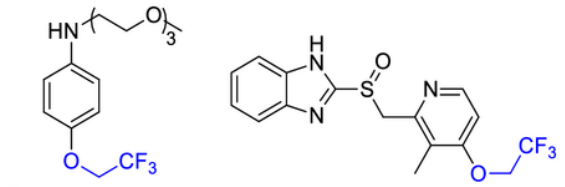
4.2 INTRODUCTION

The reactivity of a chemical systems can be altered by its reaction environment.[1] Therefore it is essential to understand the role of cooperative weak interactions (soft force)[2] in making new functional molecules. The weak interactions[3] like charge-

transfer,[4] hydrophobic effect,[5] cation-π,[2b, 6] anion-π,[7] halogen bonding,[8] etc. are being explored to control reactivity of certain chemical systems.[9] Recently, we have explored that the weak interactions can be used for C-H functionalization reactions on non-functionalized aromatic systems.[10] In this regard we have also shown the utility of iodine(III) reagents for the C-H functionalization reactions.[6c,11] Herein, we demonstrate the C-H etherification of anilides for the preparation of several -OCH_2CF_3 and -OCD_3 incorporated aryl ethers through the reactivity switch to carbenium ion[11] over nitrenium ion[12] *via* hard-soft acid-base (HSAB) control.[13]

Intrinsic physical and chemical properties of –OCH_2CF_3 group such as great metabolic stability, high electronegativity and improved lipophilicity drawn trifluoroethoxy containing molecules special attention and made them important synthetic targets.[14] Trifluoroethyl aryl ethers exist in various pharmaceutically crucial molecules like para-trifluoroethoxy-aniline derivative is utilized as ^{19}F-MRI probe for the purpose of hypochlorite ion detection,[15] and lansoprazole is familiar to be applied for of proton pump inhibition.[16] However, several deuterated organic molecules are also popular due to their particular bioactivities.[17] CD_3O- containing fewer biologically important molecules have been shown in Figure 4.1.[18] Thus development of expedient synthetic methods for preparation of trifluoromethoxylation and trideuteriomethoxylation are of great significance.

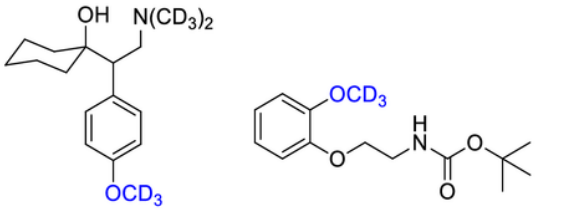
a) Trifluoroethoxy containing molecules



^{19}F MRI probe for ClO^- detection

Lansoprazole

b) Trideuteriomethoxy containing molecules

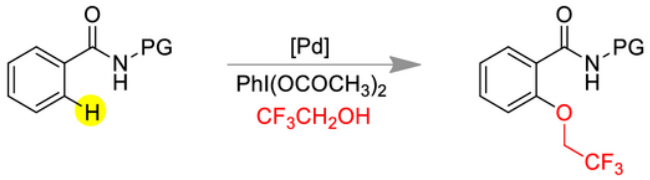


Venlafaxine (SD-254) 2-(2'-Boc-aminoethoxy)[D_3]anisole

Figure 4.1 Trifluoroethoxy and trideuteriomethoxy motif containing essential molecules.

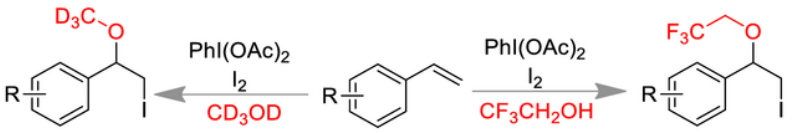
The general protocol for trifluoroethoxy aryl ether synthesis by the nucleophilic addition of phenol or phenoxide to trifluoroethyl electrophiles like trifluoroethyl iodide or trifluoroethyl mesylate.[19] However, several developments have been reported using metal catalyzed (e. g Pd-, Cu- or Fe-based catalysts) from haloarenes assisted by ligand and base at higher temperature condition.[20] Reported literatures for aromatic trideuteriomethoxylation are also mostly through metal catalyzed C-halogen bond functionalization.[21] Intermolecular dehydrogenative coupling reactions for C-C or C-heteroatom bond formation are more engrossing than conventional coupling reactions because of hardly demanded prefunctionalized substrates.[22] Very recently, Ji and Li

have described a directing group assisted Pd-catalyzed dehydrogenative trifluoroethoxylation on arene in presence of iodine(III) oxidant (Scheme 4.1).[23]



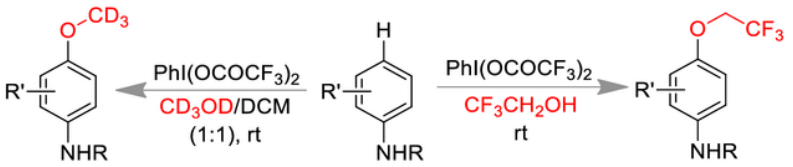
Scheme 4.1. Pd-catalyzed dehydrogenative etherification.

However, in order to diminish toxic metal contamination in drug molecules, metal-free pathways are more popular in pharmaceuticals synthesis. Our group reported PIDA and iodine mixture mediated aliphatic etherification in CF_3CH_2OH and CD_3OD is shown in scheme 4.2.[6c]



Scheme 4.2. Metal free aliphatic etherification.

There is no metal free synthetic method reported for trifluoroethoxylation and trideuteriomethoxylation by aromatic selective C(sp2)-H bond functionalization. Previously we have presented PIDA-iodine mediated aliphatic etherification using CF_3CH_2OH and CD_3OD. Herein we have reported a metal and additive free simple method for aromatic etherification towards incorporation of $–OCH_2CF_3$ and $–OCD_3$ by using inexpensive $PhI(OCOCF_3)_2$ (PIFA) as an oxidant (Scheme 4.3).[24]



Scheme 4.3. Our approach for selective C-alkoxylation reaction.

It is shown in Figure 4.2 that the soft electrophile[25] nitrenium ion can be switched to the hard electrophile carbenium ion by breaking the aromatic ring current. Interestingly, Kikugawa's group have shown that in absence of any added nucleophile, the by-product benzene iodide obtained from the reactions of anilides and PIFA can act as nucleophile for the dehydrogenative C-N bond construction.[26] However, in the present reaction system, the solvents trifluoroethanol (TFE) and methanol-d_4 (CD_3OD) led to their selective incorporation *via* para C-H functionalization of the anilides. The reactivity of the anilides system could be rationalized in preference for C-O bond formation in presence of hard nucleophile alcohols due to the formation of carbenium ion (hard electrophile) [11] over nitrenium ion (soft electrophile).[12b, 27] The nitrenium ion is considered as softer electrophile[25] over carbenium ion because during formation the carbenium ion loses the aromatic ring current (Figure 4.2). Thus *via* HSAB control, [28] the competitive reactivity of carbenium ion over nitrenium is presented here for the dehydrogenative C-O bond synthesis on the aromatic ring of anilides. Although there are several reports on the hypervalent iodine induced aromatic carbon-oxygen bond formations with alcohols,[29] however, through this work we show systematically that HSAB principle can be applied to module the reactivity of a chemical system in presence of added nucleophiles. To the best of our knowledge, there is hardly a method present on metal-less synthetic method for trifluoroethoxy and trideuteriomethoxy by

selective aryl C(sp2)-H bond functionalization. This metal-less, base-free, directing group-free and room temperature condition provides a robust alternate to conventional metal catalyzed C-O bond synthesis reactions. The trifluoroethoxy[14a] and trideuteriomethoxy[30] aryl ethers are essential structural candidate in innumerable drug molecules and we present a simple and easy method for preparation of them.

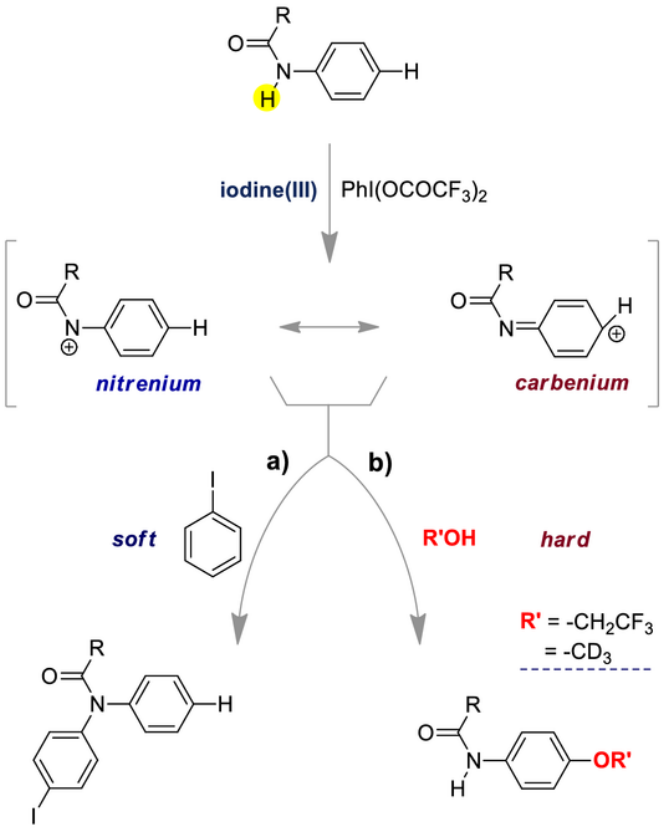
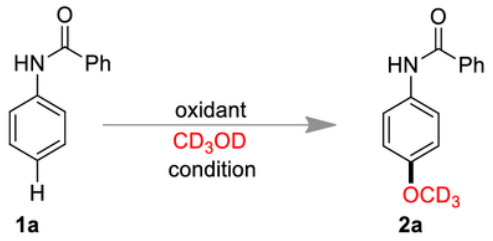


Figure 4.2 N-H arylation Vs C-H etherification by HSAB control.

4.3 RESULTS AND DISCUSSION

We started our investigation by treating benzanilide (**1a**) with 1.2 equivalent of phenyliodinetrifluoroacetate (PIFA) in CD_3OD (Table 4.1). After 12 h, 59% yield of the corresponding product **2a** was observed. Applying $BF_3.Et_2O$ as an additive, notable improvement of the reaction could not be reached, while the reaction went in vain completely in presence of strong base, K_2CO_3. Maximum yield of the respective product was attained with 1.5 equivalent of PIFA oxidant in the solvent CD_3OD–DCM (1:1) at room temperature condition. Instead of PIFA, phenyliodinediacetate (PIDA) or iodosylbenzene (PhIO) was used, it furnishes inferior results. Also the condition i.e., in-situ formed iodine(III) from PhI-*m*CPBA was attempted but no desired product was isolated.

Table 4.1. Optimization conditions of trideuteriomethoxylation.



1a **2a**

entry	oxidant	solvent	Yield[a] (%)
1	PIFA (1.2)	CD_3OD	59
2[b]	PIFA (1.2)	CD_3OD	61
3	PIFA (1.2)	CD_3OD-ACN (1:1)	68
4	PIFA (1.2)	CD_3OD-DCM (1:1)	73
5[c]	PIFA (1.2)	CD_3OD	NR
6	PIFA (1.5)	CD_3OD-DCM (1:1)	77

7	PIDA (1.5)	CD_3OD-DCM (1:1)	14
8	PhIO (1.5)	CD_3OD-DCM (1:1)	0
9	PhI(1)-*m*CPBA (1.5)	CD_3OD-DCM (1:1)	trace

All reactions were done at room temperature conditions. [a]The yield was determined after isolation by column chromatography and based on recovered starting materials. [b]2.0 equivalent of $BF_3.Et_2O$ was used as additive. [c]1.5 equiv of K_2CO_3, was used as an additive.

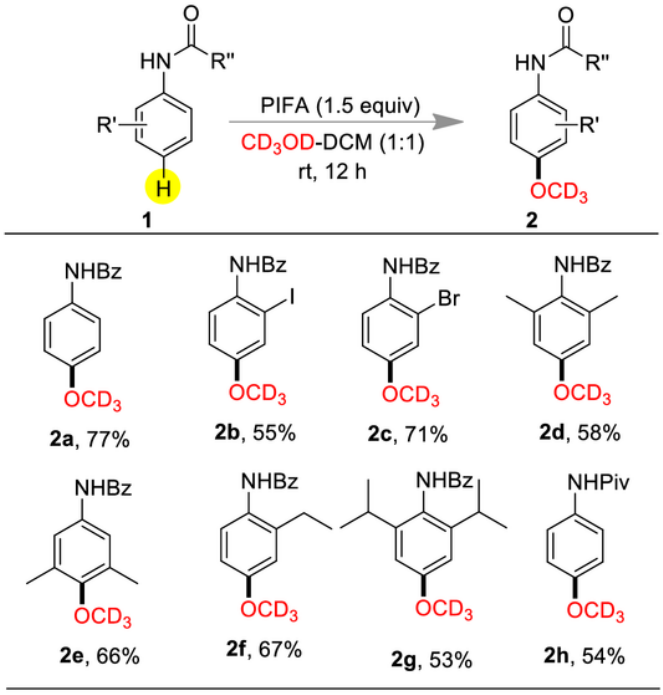


Figure 4.3. Scope of CD_3O- incorporation reaction.

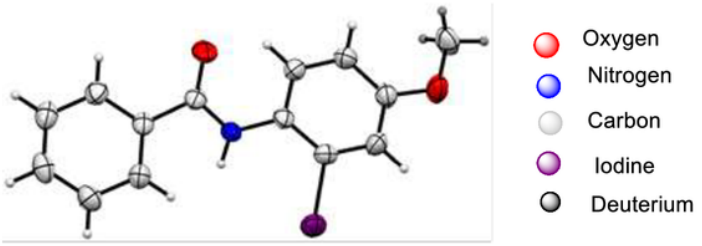
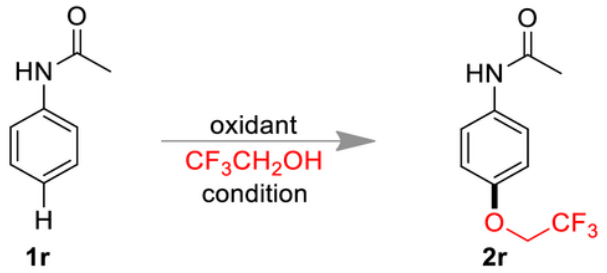


Figure 4.4. X-ray crystal structure of compound **2b** (CCDC No. 1811546).

To test the generality of this carbon-oxygen bond formation reaction, several carboanilide substrates were used under standard reaction condition (Figure 4.3). Electron deficient halogen groups such as Br-, I- containing anilides as well as alkyl substituted electron rich anilides tolerated tridueteromethoxylation to produce $-OCD_3$ incorporated products in moderated to good yields. Besides from pivoanilide, **2h** trideuteriomethoxylation was possible with good yield. X-ray crystallographic analysis data confirmed the structure of compound **2b** (Figure 4.4).

Besides, the optimum probable condition for the trifluoroethoxylation was the use 1.5 equiv of PIFA in TFE-DCM (1:1) at room temperature (entry 5, Table 4.2).

Table 4.2. Optimization conditions of trifluoroethoxylation.



1r **2r**

entry	oxidant	solvent	yield (%)[a]
1	PIFA (1.2)	TFE (3 equiv) in DCM	<5
2[b]	PIFA (1.2)	TFE (3 equiv) in DCM	10
3	PIFA (1.2)	CF_3CH_2OH	29
4	PIFA (1.5)	CF_3CH_2OH	42
5	PIFA (1.5)	TFE-DCM (1:1)	47
6	PhI-Oxone (1:2)	TFE	<10
7	PhI – *m*CPBA (1:4)	TFE	11

[a]The yield was determined after isolation by column chromatography and based on recovered starting materials. [b]2.0 equivalent of $BF_3.Et_2O$ was used as additive.

Next, the standardized protocol was verified towards trifluoroethoxylation reaction by using TFE as nucleophile (Figure 4.5). As expected, electronically diverse several benzanilides were allowed to react with iodine(III) condition to furnish para-trifluoroethoxy anilides. In addition, corresponding trifluoroethoxylation was possible from acetanilide substrate **1r** and pivoanilide substrate **1s** although in low yield.

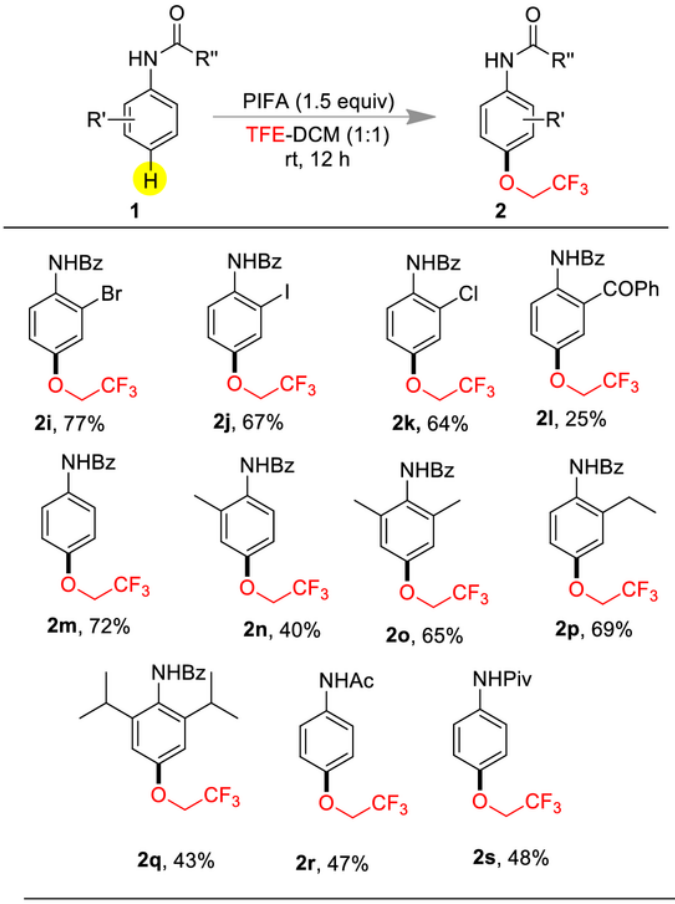


Figure 4.5. Scope of CF_3CH_2O- incorporation reaction.

Based on literature reports,[31] a plausible mechanism for the iodine(III) mediated alkoxylation reaction is depicted in Figure 4.6. The formation of intermediate **3** through nucleophilic attack was possible from *N*-center of benzanilide to iodine center of iodine (III) with the generation of one molecule of TFA. The elevated reactivity of the *N*-center are not usually controllable in presence of I (III) reagents and thus essential to be controlled either intra- or intermolecularly. Previously, our group reported that a CDC reaction was possible using contact-explosives primary amines and phenyliodine diacetate under solvent-less condition i.e., at maximum concentration of the reactants.[4] However, it is probably due to the $n \rightarrow \pi^*_{CO}$ non-covalent interaction the lone-pair of nitrogen can be protected to react with very oxidizing agent PIFA.[10] *N*-arylation reaction was observed through the by-product iodobenzene due to π-π stacking by the two phenyl rings. However, the alkyl ethers would experience steric effect for the *N*-alkoxylation and led to the C-alkoxylation at the para position *via* carbenium ion intermediate. On the other hand, possibly due to the interaction of anilide and the iodine(III) could lead to the generation of nitrenium ion **4**.[12a, 32] This nitrenium ion (**4**) should be the softer electrophile compare to the carbenium ion (**5**) because during the formation *via* resonance the aromatic ring current in the carbenium ion would get lost.

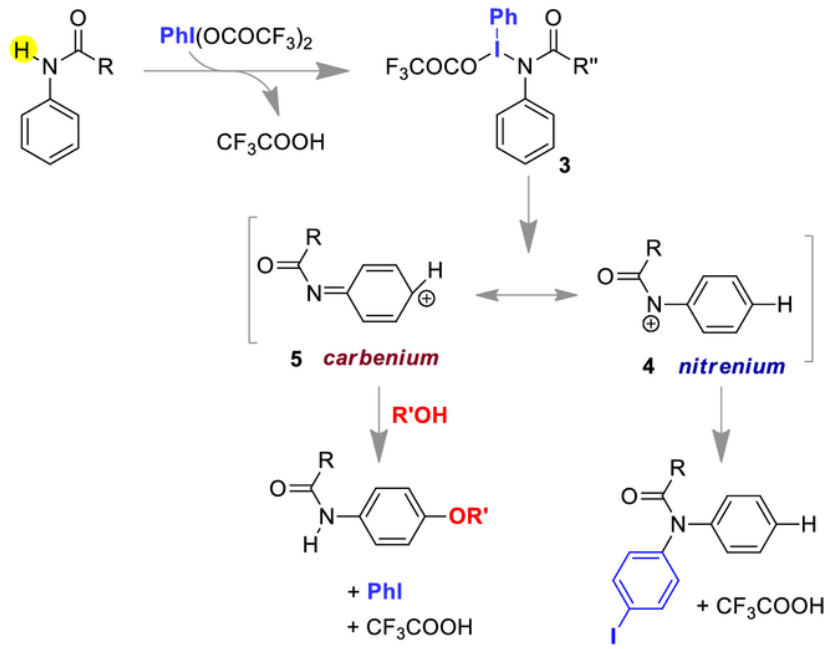
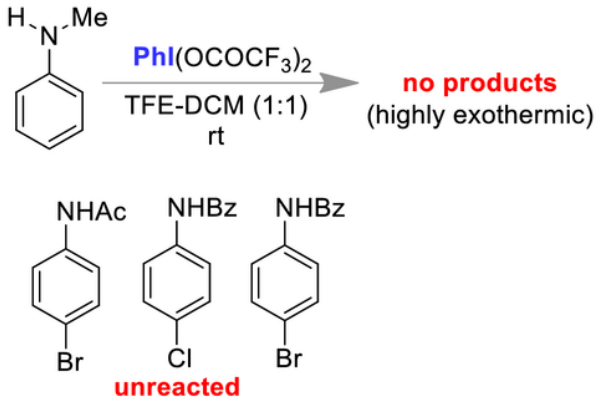


Figure 4.6. Proposed mechanism of the C-alkoxylation over N-arylation.

Therefore, trifluoroethanol or methanol-d_4 acted as nucleophile to facilitate the addition to electrophilic carbon center of **5** and followed by deprotonation with the help of trifluoroacetate ion to give the final alkoxylated product. Canesi et al. have also disclosed for the synthesis of nitrenium ion in sulfonanilides and their reactions with aromatic compounds.[33] Consequently, the HSAB principle and weak interactions play a crucial role to perceive nitrenium vs. carbenium ion reactivities

During the reaction of N-methyl aniline with phenyliodine trifluoroacetate under optimum reaction condition caused highly exothermic reaction and no product was observed. Under optimisation reaction condition para-halo substituted anilides (Scheme 4.4) was treated, no products was detected because of steric factor.



Scheme 4.4. Treatment N-methyl aniline with PIFA and unreacted para-substituted anilides.

4.4 CONCLUSIONS

In conclusion, we have developed an intermolecular oxidative carbon-oxygen bond formation reaction towards trifluoroethoxylation and trideuteriomethoxylation on anilines. Metal-free, additive-free and room temperature condition transformation offers an alternative to traditional metal catalyzed coupling reactions. We anticipate that this oxidative transformation protocol for $-OCH_2CF_3$ and $-OCD_3$ incorporated aromatic ethers might have a beneficial effect in pharmaceuicals synthesis.

4.5 EXPERIMENTAL SECTION

General information

All reactions have been done at room temperature condition. Isolated yields are reported after purified by column chromatography using silica gel (mesh 100-200) and hexane-ethyl acetate mixtures as eluent. NMR spectra were recorded on either 400 MHz

or 700 MHz instrument at room temperature. The chemical shift values are given in parts per million (ppm) with respect to residual chloroform (7.26 ppm for ^{1}H and 77.16 for ^{13}C) (in case of DMSO-d_6: 2.5 ppm for ^{1}H and 39.5 for ^{13}C). The peak patterns are indicated as: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, m = multiplet). The coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were obtained on an ESI-TOF (time of flight) mass spectrometer. FT-IR spectra was recorded in wave number (cm^{-1}). Melting points of the compounds were determined using a digital melting point apparatus and are uncorrected.

Chemicals: Solvents (both for reaction and chromatography), aniline derivatives, and PIFA were purchased from commercial source and used after purification wherever necessary. Carboanilides were synthesized from aniline derivatives by following literature report.[34]

General Procedure for Synthesis of N-(4 trideuteriomethoxymethoxyphenyl) anilides

(0.761 mmol, 1.5 equiv.) PIFA was added to the stirred solution of N- Substituted aniline **1a** (0.507 mmol, 1 equiv.) in DCM and CD_3OD (1:1) mixture at room temperature. The reaction mixture was stirred for 12 h. Upon formation of the reaction it was completely evaporated to dryness. Then the resulting crude mixture was purified by column chromatography on silica gel using n-hexane and ethyl acetate as eluent.

Procedure for Synthesis of N-(4- trideuteriomethoxyphenyl)benzamide (2a): (327 mg, 0.761 mmol) PIFA was added to the stirred solution of anilide **1a** (100 mg, 0.507

mmol) in DCM and CD_3OD (1:1) mixture at room temperature. The reaction mixture was stirred for 12 h. Upon formation of the product it was completely evaporated to dryness. Then the resulting crude mixture was purified by column chromatography on silica gel using n-hexane and ethyl acetate as eluent to N-(4-trideuteriomethoxyphenyl)benzamide (40 mg, 0.173 mmol, yield: 77%).

Yield: 77% (40 mg, 35%), R_f = 0.5 (hexane: ethyl acetate 4:1); white solid; mp 156-158 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.12 (s, 1H), 7.94 (d, *J* = 8 Hz, 2H), 7.67 (d, *J* = 8 Hz, 2H), 7.65-7.49 (m, 3H), 6.94-6.90 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ 165.1, 155.5, 135.0, 132.2, 131.3, 128.3, 127.5, 121.9, 113.7, 54.5-53.9 (m); IR (KBr): $\tilde{\nu}$ = 2259, 2131, 1651, 1515, 1259, 1115, 1046 cm^{-1}; HR-MS (ESI-TOF): m/z = 231.1195, calculated for $C_{14}H_{10}D_3NO_2$ ($M+H^+$): 231.1207.

N- (2-Iodo-4- trideuterimethoxyphenyl)benzamide (2b): Yield: 55% (30 mg, 34%); R_f =0.5 (hexane: ethyl acetate 4:1); white solid; mp 156-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 12 Hz, 1H), 8.07 (s, 1H), 7.95 (d, *J* = 8 Hz, 2H), 7.59-7.49 (m, 3H), 7.35 (s, 1H), 6.97-6.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 156.9, 134.7, 132.1, 131.8, 129.0, 127.2, 123.9, 123.2, 114.9, 91.5, 55.4-54.8 (m); IR (KBr): $\tilde{\nu}$ = 2071, 1643, 1524, 1281, 1102 cm^{-1}; HR-MS (ESI-TOF): m/z = 378.9994, calculated for $C_{14}H_9D_3INO_2$ ($M+H^+$): 378.9993.

N-(2-Bromo-4- trideuterimethoxyphenyl)benzamide (2c): Yield: 81% (82 mg, 74%); R_f = 0.4 (hexane: ethyl acetate 4:1); white solid; mp 160-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 12 Hz, 1H), 8.23 (s, 1H), 7.92 (d, *J* = 8 Hz, 2H), 7.59-7.49 (m, 3H), 7.14 (s, 1H), 6.93 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3,

156.6, 134.8, 132.1, 129.3, 129.0, 127.2, 123.2, 117.7, 114.9, 114.0, 55.5-54.8 (m); IR (KBr): $\tilde{\nu}$ = 2069, 1647, 1490, 1290, 1262, 1219, 1106, 1003 cm^{-1}; HR-MS (ESI-TOF): m/z = 309.0321 & 311.0301, calculated for $C_{14}H_9D_3BrNO_2$ ($M+H^+$): 309.0312 & 311.0293.

N-(2,6-Dimethyl-4-trideuterimethoxy-phenyl)benzamide (2d): Yield: 48% (47 mg, 41%); R_f = 0.35 (hexane: ethyl acetate 4:1); white solid; mp 178-180 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8 Hz, 2H), 7.56-7.52 (m, 2H), 7.47-7.43 (m, 2H), 6.63 (s, 2H), 2.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 158.4, 137.1, 134.6, 131.7, 128.7, 127.3, 127.0, 113.5, 54.7-54.1 (m), 18.2; IR (KBr): $\tilde{\nu}$ = 2359, 2071, 1638, 1489, 1331, 1278, 1226, 1165, 1114, 1053 cm^{-1}; HR-MS (ESI-TOF): m/z = 259.1511, calculated for $C_{16}H_{14}D_3NO_2$ ($M+H^+$): 259.1520.

N-(3,5-Dimethylphenyl-4-trideuterimethoxy)benzamide (2e): Yield: 66% (53 mg, 46%); R_f = 0.5 (hexane: ethyl acetate 4:1); deep yellow solid; mp 132-133 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 10.04 (s, 1H), 7.94 (d, *J* = 8 Hz, 2H), 7.59-7.49 (m, 3H), 7.44 (d, 2H), 2.22 (s, 6H); ^{13}C NMR (100 MHz, DMSO) δ 165.2, 152.7, 135.0, 134.5, 131.4, 130.1, 128.3, 127.6, 120.9, 58.9, 58.7-58.1 (m), 16.0; IR (KBr): $\tilde{\nu}$ = 2065, 1648, 1489, 1291, 1224, 1100, 1026 cm^{-1}; HR-MS (ESI-TOF): m/z = 259.1547, calculated for $C_{16}H_{14}D_3NO_2$ ($M+H^+$): 259.1520.

N-(2-Ethyl-4-trideuterimethoxyphenyl)benzamide (2f): Yield: 67% (70 mg, 61%); R_f = 0.4 (hexane: ethyl acetate 4:1); white solid; mp 165-166 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8 Hz, 2H), 7.68 (s, 1H), 7.60 (d, *J* = 8 Hz, 1H), 7.56-7.52 (m,

1H), 7.49-7.45 (m, 2H), 6.80-6.75 (m, 2H), 2.63 (q, $J_1 = J_2 = J_3 = 8$ Hz, 2H), 1.24 (t, $J_1 = J_2 = 8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 157.9, 138.8, 135.0, 131.8, 128.8, 128.0, 127.1, 126.5, 114.5, 111.4, 55.1-54.5, 24.73, 14.09; IR (KBr): $\tilde{\nu}$ = 2359, 2067, 1643, 1494, 1300, 1217, 1111 cm^{-1}; HR-MS (ESI-TOF): m/z = 259.1506, calculated for $C_{16}H_{14}D_3NO_2$ (M+H$^+$): 259.1520.

N-(2,6-Diisopropyl-4-trideuterimethoxyphenyl)benzamide (2g): Yield: 43% (38 mg, 34%); R_f = 0.5 (hexane: ethyl acetate 9:1); white solid; mp 233-234 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 8 Hz, 2H), 7.55 (t, q, $J_1 = J_2 = 8$ Hz, 1H), 7.48-7.45 (m, 2H), 7.39 (s, 1H), 6.75 (s, 2H), 3.17-3.07 (m, 2H), 1.20 (d, J = 8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 159.5, 148.1, 134.7, 131.8, 128.8, 127.3, 124.2, 109.1, 55.0-54.1 (m), 29.2, 23.7; IR (KBr): $\tilde{\nu}$ = 2069, 1647, 1515, 1485, 1341, 1276, 1114 cm^{-1}; HR-MS (ESI-TOF): m/z = 315.2150, calculated for $C_{20}H_{22}D_3NO_2$ (M+H$^+$): 315.2146.

N-(2-Methyl-4-trideuterimethoxyphenyl)pivalamide (2h): Yield: 54% (31 mg, 28%); R_f = 0.4 (hexane: ethyl acetate 4:1); white solid; mp 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 12 Hz, 1H), 7.08 (s, 1H), 6.74-6.72 (m, 2H), 2.21 (s, 3H), 1.33 (S, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 176.8, 157.2, 132.3, 128.8, 125.6, 116.0, 111.6, 54.9-54.4 (m), 39.5, 27.8, 18.1; IR (KBr): $\tilde{\nu}$ = 2961, 2216, 2066, 1643, 1294, 1235, 1109, 1032 cm^{-1} HR-MS (ESI-TOF): m/z = 247.1494, calculated for $C_{13}H_{16}D_3NO_2$(M+H$^+$): 247.1496.

General Procedure for Synthesis N-(2,2,2-trifluoroethoxymethoxyphenyl)anilides: PIFA (1.109 mmol, 1.5 equiv.) was added to the stirred solution of N- Substituted aniline 1 (0.739 mmol, 1 equiv.) in DCM and TFE (1:1) mixture at room temperature. The reaction mixture was stirred for 12h. Upon formation of the product it was completely evaporated to dryness. Then the resulting crude mixture was purified by column chromatography on silica gel using n-hexane and ethyl acetate as eluent.

Procedure for Synthesis of N-{2-bromo-4-(2,2,2-trifluoroethoxy)phenyl} benzamide (2i): (233 mg, 0.543 mmol) PIFA was added to the stirred solution of N-Substituted aniline 1a (100 mg, 0.362 mmol) in DCM and TFE (1:1) mixture at room temperature. The reaction mixture was stirred for 12 h. Upon formation of the product it was completely evaporated to dryness. Then the resulting crude mixture was purified by column chromatography on silica gel using n-hexane and ethyl acetate as eluent to N-{2-bromo-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (68 mg, 0.181 mmol, yield: 77%).

Yield: 77% (88 mg, 65%); R_f = 0.5 (hexane: ethyl acetate 4:1); white solid; mp 120-122 ºC; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ -73.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 8 Hz, 1H), 8.29 (s, 1H), 7.92 (d, J = 8 Hz, 2H), 7.59-7.52 (m, 3H), 7.23 (s, 1H), 6.99 (dd, $J_1 = J_2$ = 4 Hz, 1H), 4.35 (q, $J_1 = J_2 = J_3$ = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 154.1, 134.6, 132.3, 131.1, 129.1, 127.2, 123.2 (q, J_{C-F} = 277 Hz), 123.0, 119.46, 114.95, 114.62, 66.5 (q, J_{C-F} = 36 Hz); IR (KBr): $\tilde{\nu}$ = 2095, 1647, 1495, 1266, 1163, 1084 cm^{-1}; HR-MS (ESI-TOF): m/z = 373.9994 & 375.9974, calculated for $C_{15}H_{11}BrF_3NO_2$ ($M+H^+$): 373.9998 & 375.9978.

N-{2-Iodo-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (2j): Yield: 67% (52 mg, 50%); R_f =0.5 (hexane: ethyl acetate 4:1); light pink solid; mp 141-142 °C; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ -73.9; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 8 Hz, 1H), 8.13 (s, 1H), 7.96 (d, J = 8 Hz, 2H), 7.59-7.53 (m, 3H), 7.45 (s, 1H), 7.02 (dd, $J_1 = J_2$ = 4 Hz, 1H), 4.35 (q, $J_1 = J_2 = J_3$ = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 154.3, 134.5, 133.7, 132.3, 129.1, 127.3, 125.6, 123.2 (q, J_{C-F} = 276 Hz) 124.62, 122.9, 115.8, 90.8, 66.5 (q, J_{C-F} = 35 Hz); IR (KBr): $\tilde{\nu}$ = 2098, 1644, 1266, 1162 cm^{-1}; HR-MS (ESI-TOF): m/z = 421.9845, calculated for $C_{15}H_{11}F_3INO_2$ ($M+H^+$): 421.9859.

N-{2-Chloro-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (2k): Yield: 64% (67 mg, 47%); R_f =0.5 (hexane: ethyl acetate 4:1); white solid; mp 125-126 °C; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ -73.9; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8 Hz, 1H), 8.28 (s, 1H), 7.91 (d, J = 8 Hz, 2H), 7.59-7.52 (m, 3H), 7.07 (s, 1H), 6.94 (dd, $J_1 = J_2$ = 4 Hz, 1H), 4.35 (q, $J_1 = J_2 = J_3$ = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 153.9, 134.6, 132.3, 129.9, 129.1, 127.2, 124.3, 123.2 (q, J_{C-F} = 277 Hz), 122.9, 116.4, 114.3, 66.5 (q, J_{C-F} = 36 Hz); IR (KBr): $\tilde{\nu}$ = 2360, 1645, 1479, 1286, 1159, 1084 cm^{-1}; HR-MS (ESI-TOF): m/z = 330.0504, calculated for $C_{15}H_{11}ClF_3NO_2$ ($M+H^+$): 330.0503.

N-{2-Benzoyl-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (2l): Yield: 25% (19 mg, 15%); R_f = 0.4 (hexane: ethyl acetate 4:1); yellow solid; mp 156-157 °C; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ -73.8; ^1H NMR (400 MHz, $CDCl_3$) δ 11.57 (s, 1H), 8.85 (d, J = 12 Hz, 1H), 8.03 (d, J = 8 Hz, 2H), 7.74 (d, J = 8 Hz, 2H), 7.65-7.62 (m, 1H), 7.57-7.49 (m, 5H), 7.27-7.20 (m, 2H), 4.32 (q, $J_1 = J_2 = J_3$ = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 165.8, 151.9, 138.3, 136.0, 134.6, 133.0, 132.2, 130.0, 128.9, 128.7,

127.4, 124.8, 123.51, 122.7 (q, J_{C-F} = 277 Hz), 120.9, 120.3, 66.5 (q, J_{C-F} = 35 Hz); IR (KBr): $\tilde{\nu}$ = 2113, 1634, 1288, 1173, 1074 cm^{-1}; HR-MS (ESI-TOF): m/z = 400.1148, calculated for $C_{22}H_{16}F_3NO_3$ ($M+H^+$): 400.1155.

N-{4-(2,2,2-Trifluoroethoxy)phenyl}benzamide (2m): Yield: 72% (70 mg, 47%); R_f = 0.5 (hexane: ethyl acetate 4:1); white solid; mp 179-181 °C; ^{19}F NMR (376.3 MHz, DMSO-d_6) δ -72.5; ^1H NMR (400 MHz, DMSO-d_6) δ 10.2 (s, 1H), 7.94 (d, J = 8 Hz, 2H), 7.72 (d, J = 8 Hz, 2H), 7.58-7.52 (m, 3H), 7.06 (d, J = 8 Hz, 2H), 4.73 (q, $J_1 = J_2 = J_3$ = 8 Hz, 2H) ; ^{13}C NMR (100 MHz, DMSO) δ 165.3, 153.1, 134.9, 133.7, 131.5, 128.4, 127.6, 124.1 (q, J_{C-F} = 276 Hz), 121.9, 114.9, 64.9 (q, J_{C-F} = 33 Hz); IR (KBr): $\tilde{\nu}$ = 2091, 1648, 1281, 1157, 1075 cm^{-1}; HR-MS (ESI-TOF): m/z = 296.0872, calculated for $C_{15}H_{12}F_3NO_2$ ($M+H^+$): 296.0893.

N-{2-Methyl-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (2n): Yield: 40% (50 mg, 34 %); R_f = 0.4 (hexane: ethyl acetate 4:1); white solid; mp 154-156 °C; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ -74.0; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8 Hz, 2H), 7.74 (d, J = 8 Hz, ^1H), 7.60-7.48 (m, 4H), 6.86-6.80 (m, 2H), 4.34 (q, $J_1 = J_2 = J_3$ = 8 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 155.1, 134.8, 132.8, 132.0, 130.5, 128.9, 127.2, 125.67, 123.5 (q, J_{C-F} = 275 Hz), 117.5, 112.8, 66.3 (q, J_{C-F} = 36 Hz), 18.23; IR (KBr): $\tilde{\nu}$ = 2358, 2087, 1639, 1279, 1221, 1156, 1109 cm^{-1}; HR-MS (ESI-TOF): m/z = 310.1072, calculated for $C_{16}H_{14}F_3NO_2$($M+H^+$): 310.1049.

N-{2,6-Dimethyl-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (2o): Yield: 65% (75 mg, 52%); R_f = 0.5 (hexane: ethyl acetate 4:1); white solid; mp 178-179 °C; ^{19}F NMR

(376.3 MHz, DMSO-d_6) δ -72.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, ^{1}H), 7.99 (d, J = 8 Hz, 2H), 7.60-7.50 (m 3H), 6.85 (s, 2H), 4.73 (q, $J_1 = J_2 = J_3$ = 8 Hz, 2H), 2.16 (s, 6H); ^{13}C NMR (100 MHz, DMSO) δ 165.2, 155.2, 137.2, 134.4, 131.4, 129.6, 128.4, 128.2, 127.5, 124.1 (q, J_{C-F} = 276 Hz), 113.9, 64.7 (q, J_{C-F} = 34 Hz), 18.25; IR (KBr): $\tilde{\nu}$ =2097, 1640, 1522, 1490, 1271, 1154, 1083cm^{-1}; HR-MS (ESI-TOF): m/z = 324.1210, calculated for $C_{17}H_{16}F_3NO_2$(M+H$^+$): 324.1206.

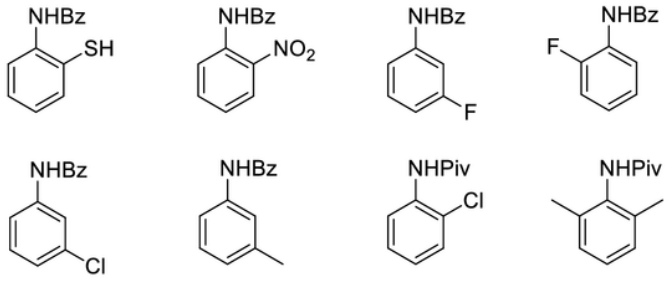
N-{2-Ethyl-6-methyl-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (2p): Yield: 69% (79 mg, 55%); R_f = 0.5 (hexane: ethyl acetate 4:1); white solid; mp 130-132 °C; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ -73.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8 Hz, 2H), 7.69 (d, J = 8 Hz, 2H), 7.57-7.54 (m, 1H), 7.50-7.46 (m, 2H), 6.86 (s, 1H), 6.81-6.78 (m 1H), 4.35 (q, $J_1 = J_2 = J_3$ = 8 Hz, 2H), 2.64 (q, $J_1 = J_2 = J_3$ = 8 Hz, 2H), 1.25 (t, $J_1 = J_2$ = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 155.5, 138.8, 134.8, 131.9, 129.8, 128.9, 128.4, 127.2, 126.3, 123.8 (q, J_{C-F} = 277 Hz), 115.80, 112.45, 66.2 (q, J_{C-F} = 36 Hz), 24.6, 13.9; IR (KBr): $\tilde{\nu}$ = 2360, 2103, 1640, 1531, 1271, 1211, 1163, 1109 cm^{-1}; HR-MS (ESI-TOF): m/z = 324.1211, calculated for $C_{17}H_{16}F_3NO_2$(M+H$^+$): 324.1206.

N-{2,6-Diisopropyl-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (2q): Yield: 43% ; R_f =0.5 (hexane: ethyl acetate 9:1); white solid; mp 215-217 °C; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ -73.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8 Hz, 2H), 7.60-7.56 (m, 1H), 7.51 (t, J_1 = 8 Hz, J_2 = 2H), 7.27 (s, 1H), 6.78 (s, 2H), 4.38 (q, $J_1 = J_2 = J_3$ = 8 Hz, 2H), 3.13 (sept, J = 8 Hz, 2H), 1.21 (d, J = 8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 157.5, 148.7, 134.6, 132.0, 129.0, 127.7, 127.3, 125.8, 123.6 (q, J_{C-F} = 276 Hz), 110.20, 66.1 (q, J_{C-F} = 35 Hz), 29.3, 23.6; IR (KBr): $\tilde{\nu}$ = 2966, 2872, 1646, 1525, 1339,

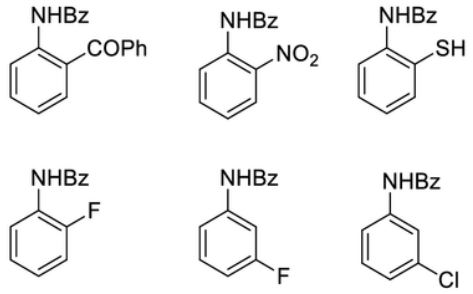
1209, 1177 cm^{-1}; HR-MS (ESI-TOF): m/z = 380.1838, calculated for $C_{21}H_{24}F_3NO_2$(M+H^+): 380.1832.

N-{4-(2,2,2-Trifluoroethoxy)phenyl}acetamide) (2r): Yield: 47% (54 mg, 28%); R_f = 0.5 (hexane: ethyl acetate 4:1); white solid; mp 135-136 °C; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ -74.0; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 12 Hz, 2H), 6.88 (d, J = 8 Hz, 2H), 4.31 (q, $J_1 = J_2 = J_3$ = 8 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 154.2, 123.4 (q, J_{C-F} = 274 Hz), 122.0, 115.6, 66.3 (q, J_{C-F} = 35 Hz), 24.4; IR (KBr): $\tilde{\nu}$ =2089, 1640, 1286, 1246, 1163 cm^{-1}; HR-MS (ESI-TOF): m/z = 234.0729, calculated for $C_{10}H_{10}F_3NO_2$(M+H^+): 234.0736.

N-{4-(2,2,2-Trifluoroethoxy)phenyl}pivalamide (2s): Yield: 48% (68 mg, 44%); R_f = 0.5 (hexane: ethyl acetate 4:1); white solid; mp 123-124 °C; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ -74.0; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8 Hz, 2H), 7.29 (s, 1H), 6.90 (d, J = 8 Hz, 2H), 4.32 (q, $J_1 = J_2 = J_3$ = 8 Hz, 2H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 154.1, 132.9, 123.4 (q, J_{C-F} = 276 Hz), 121.9, 115.6, 66.5 (q, J_{C-F} = 35 Hz), 39.6, 27.7; IR (KBr): $\tilde{\nu}$ =2977, 2359, 2096, 1651, 1515, 1409, 1368, 1286, 1236, 1160, 1082 cm^{-1}; HR-MS (ESI-TOF): m/z = 276.1220, calculated for $C_{13}H_{16}F_3NO_2$(M+H^+): 276.1206.



Scheme 4.5. Carboanilides failed to produce any trifluoroethoxylation product under optimized condition.



Scheme 4.6. Unsuccessful trideuteriomethoxylation reaction on the above substrates.

4.6 NOTES & REFERENCES

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^{1}H, ^{13}C and ^{19}F NMR Spectra of selected compound

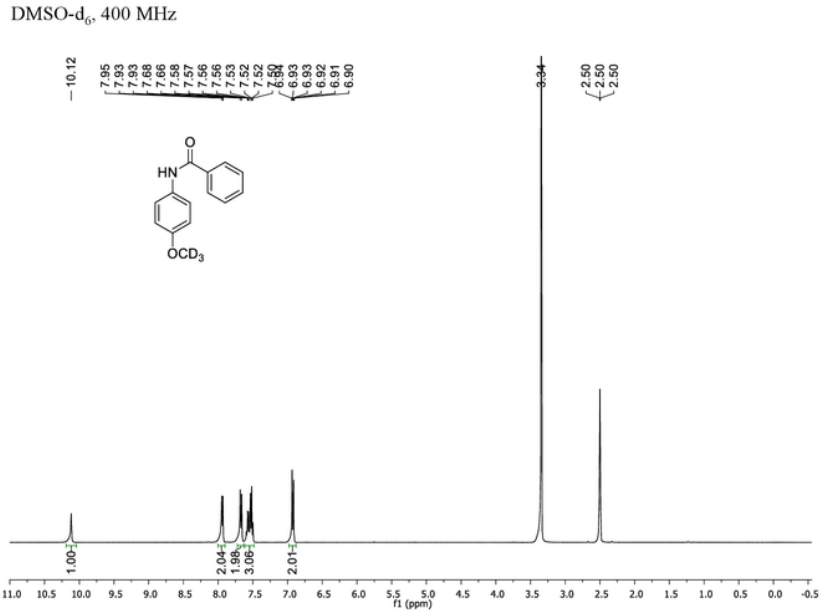


Figure 4.7. ^{1}H-NMR of N-(4- trideuteriomethoxyphenyl)benzamide (**2a**).

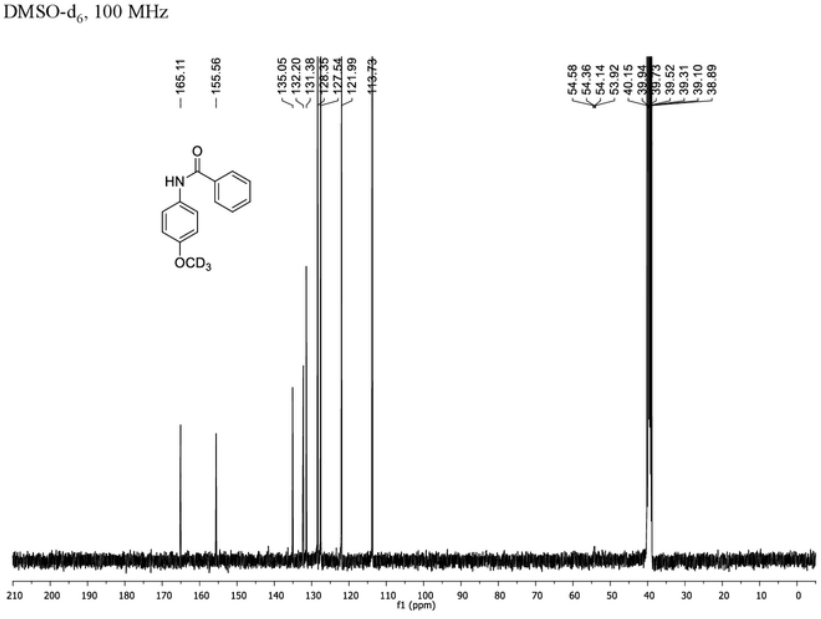


Figure 4.8. ^{13}C-NMR of N-(4- trideuteriomethoxyphenyl)benzamide (**2a**).

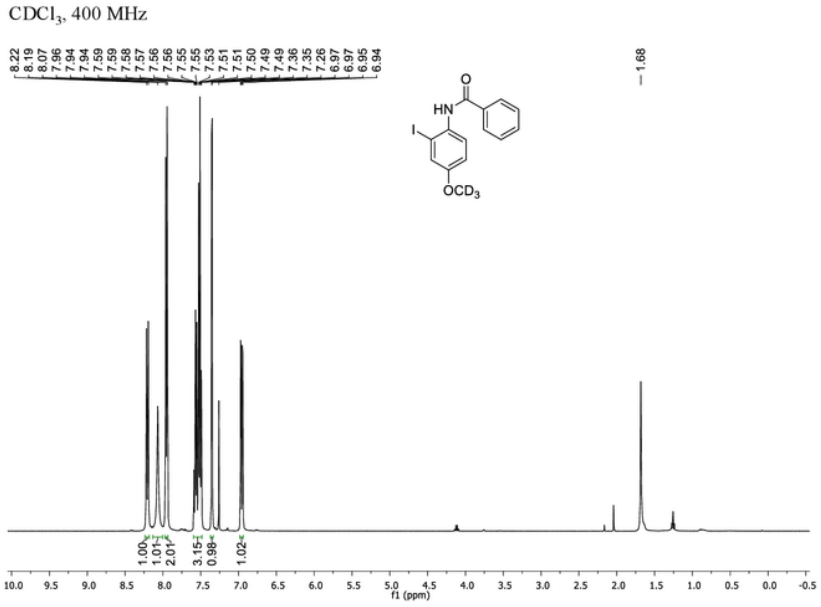


Figure 4.9. ^{1}H-NMR of N- (2-iodo-4- trideuterimethoxyphenyl)benzamide (**2b**).

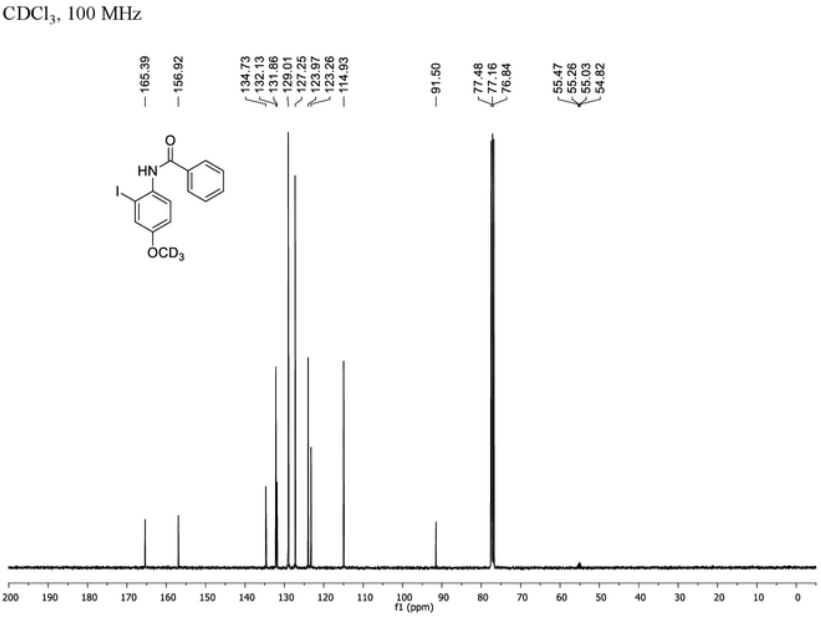


Figure 4.10. ^{13}C-NMR N- (2-iodo-4- trideuterimethoxyphenyl)benzamide (**2b**).

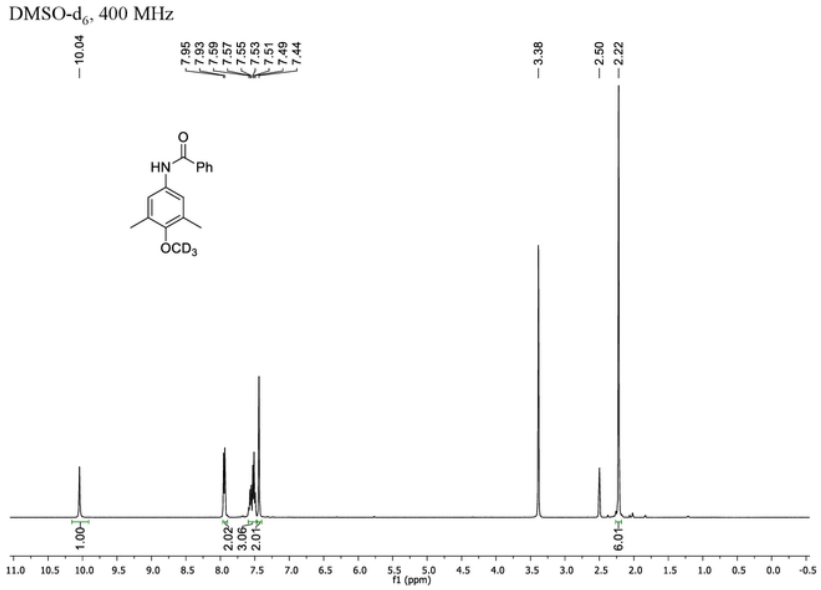


Figure 4.11. ^{1}H-NMR of N-(3,5-dimethylphenyl-4-trideuterimethoxy)benzamide (**2e**).

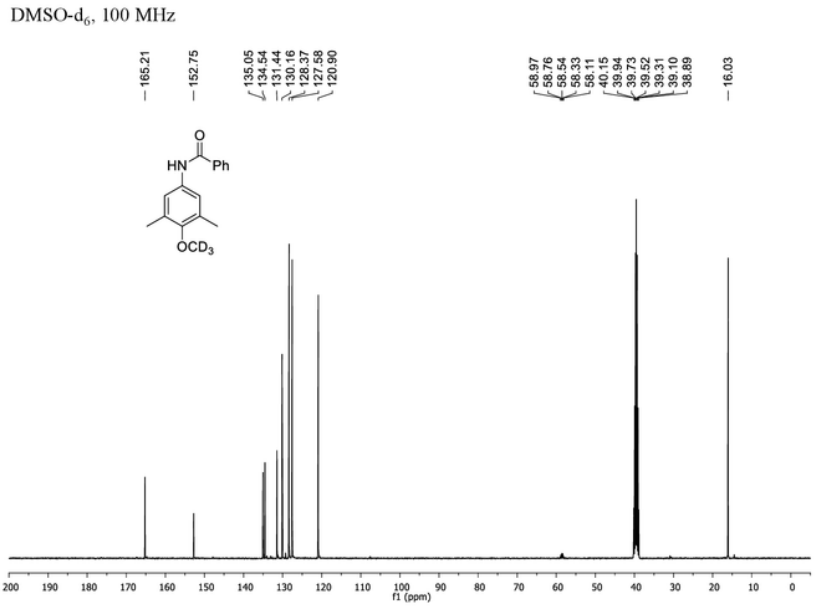


Figure 4.12.^{13}C-NMR of N-(3,5-dimethylphenyl-4-trideuterimethoxy)benzamide (**2e**).

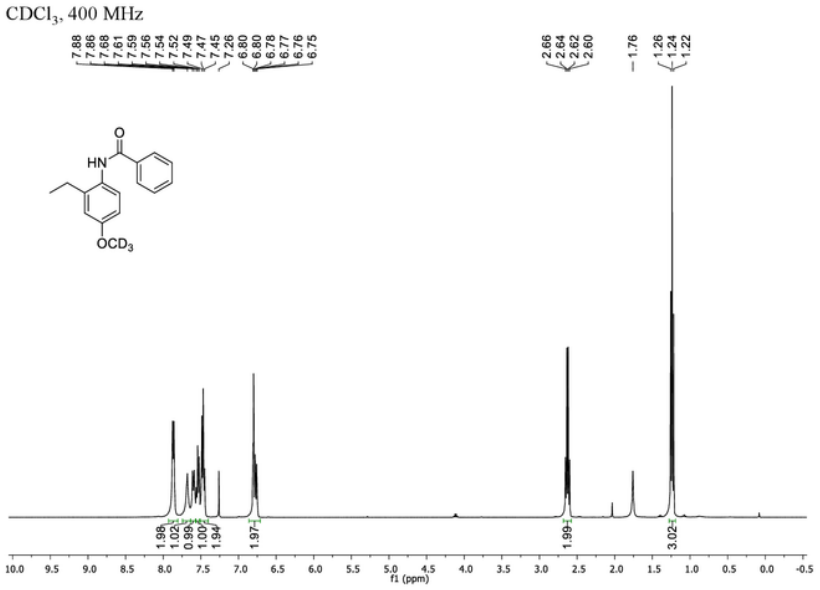


Figure 4.13. ^{1}H-NMR of N-(2-ethyl-4-trideuterimethoxyphenyl)benzamide (**2f**).

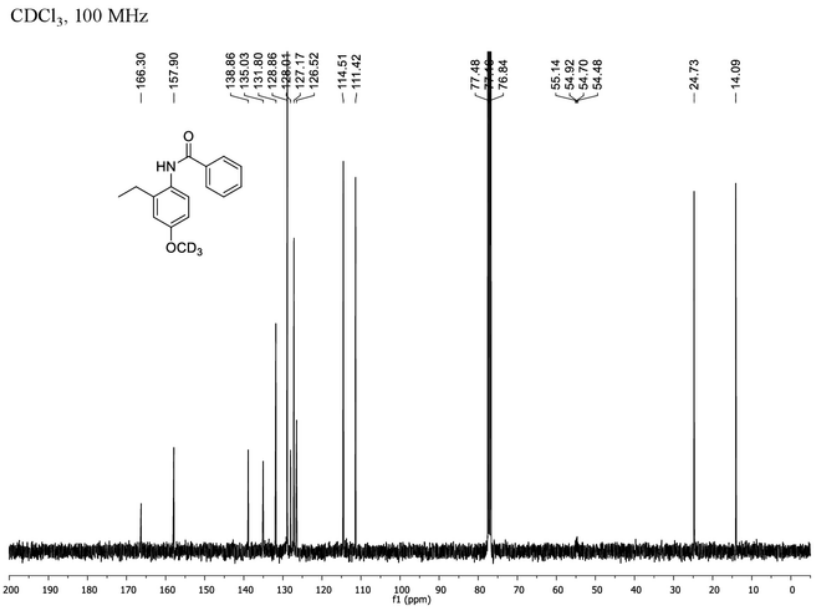


Figure 4.14. ^{13}C-NMR of N-(2-ethyl-4-trideuterimethoxyphenyl)benzamide (**2f**).

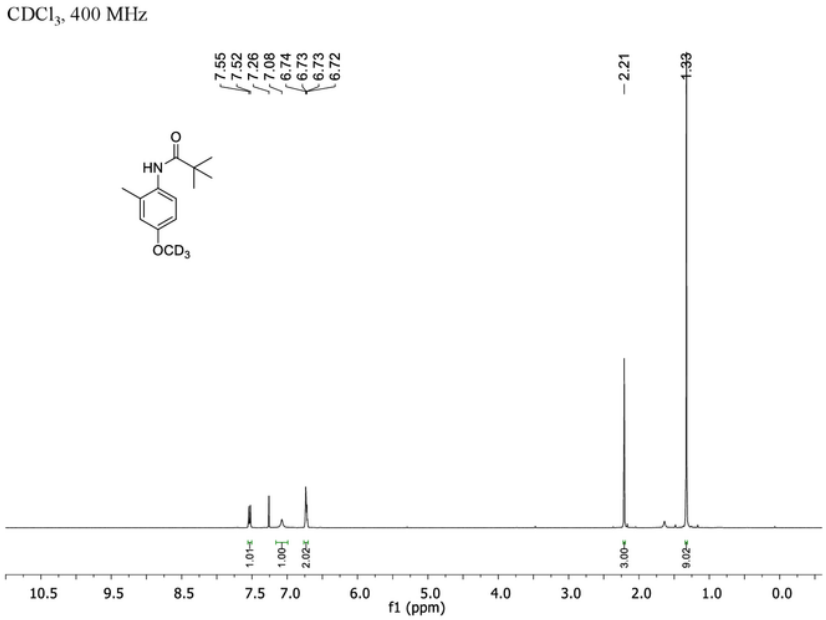


Figure 4.15. ^{1}H-NMR of N-(2-methyl-4- trideuterimethoxyphenyl)pivalamide (**2h**).

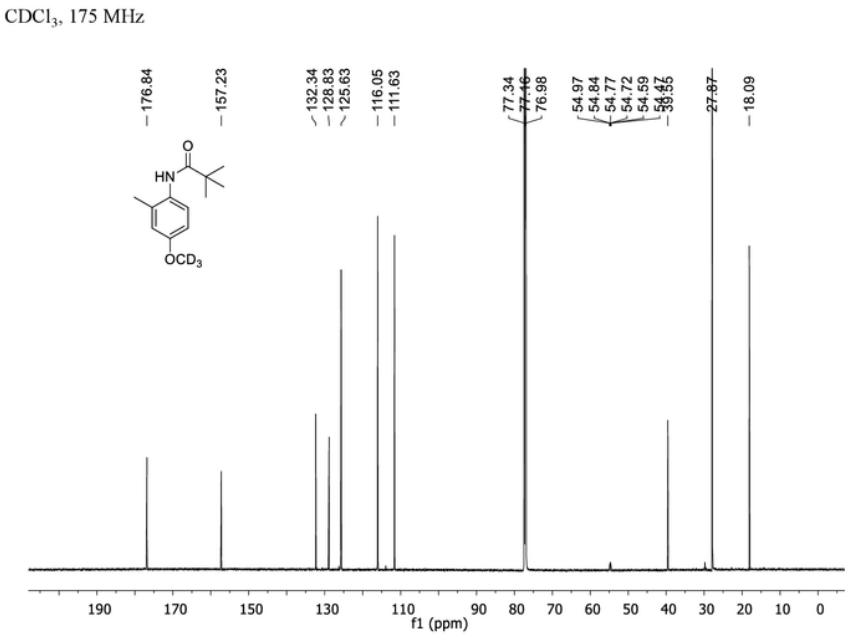


Figure 4.16. ^{13}C-NMR of N-(2-methyl-4- trideuterimethoxyphenyl)pivalamide (**2h**).

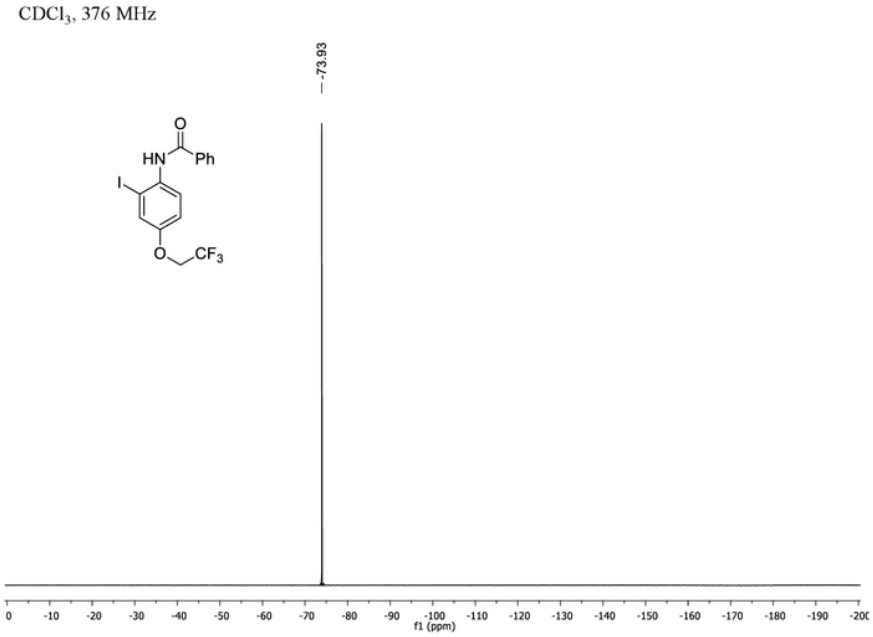


Figure 4.17. ^{19}F-NMR of N-{2-iodo-4-(2,2,2-trifluoroethoxy)phenyl}benzamide **(2j).**

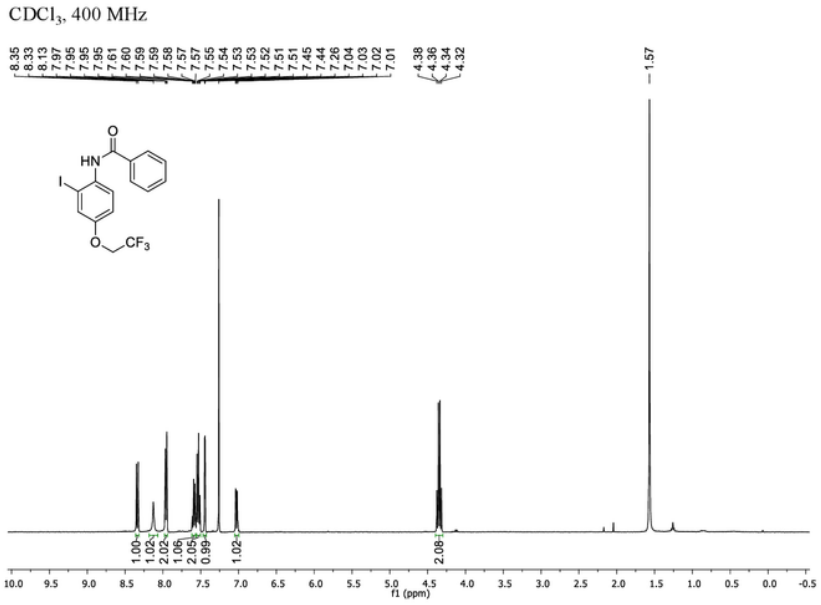


Figure 4.18. ^{1}H-NMR of N-{2-iodo-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (**2j**).

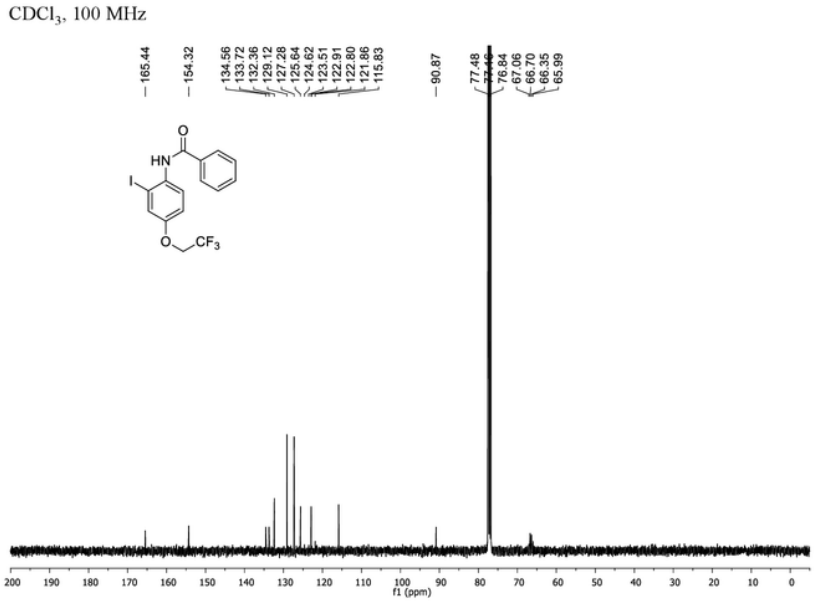


Figure 4.19. [13] C-NMR of N-{2-iodo-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (**2j**).

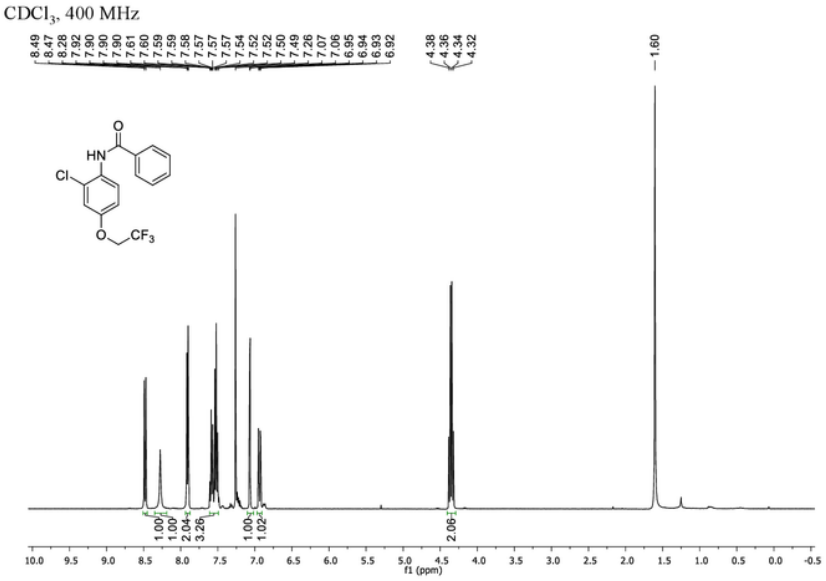


Figure 4.20. [1]H-NMR of N-{2-chloro-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (**2k**).

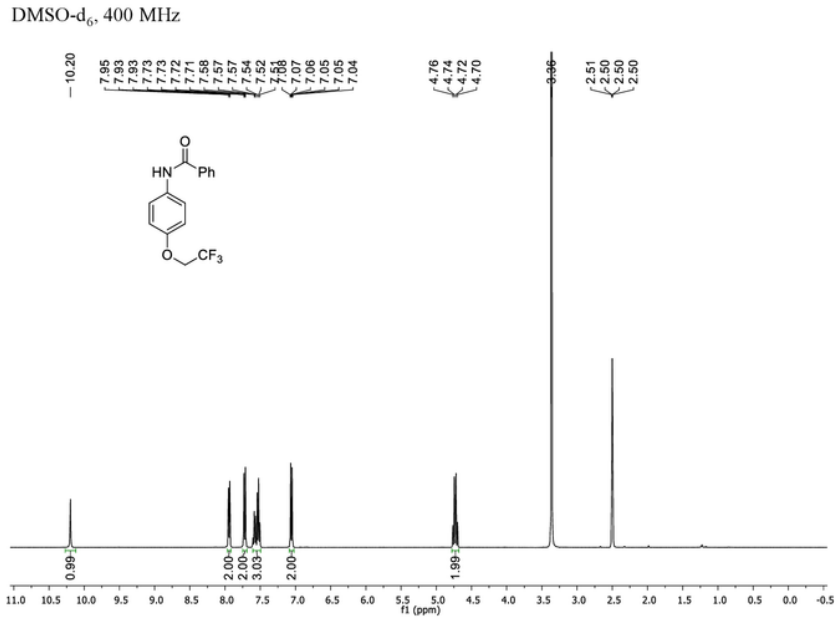


Figure 4.21. ^{1}H-NMR of N-{4-(2,2,2-trifluoroethoxy)phenyl}benzamide (**2m**).

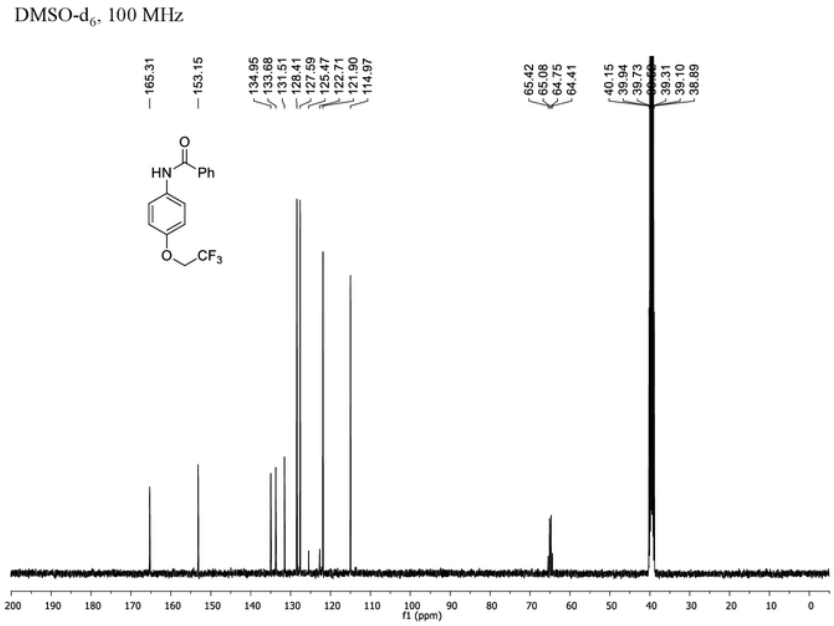


Figure 4.22. ^{13}C-NMR of N-{4-(2,2,2-trifluoroethoxy)phenyl}benzamide (**2m**).

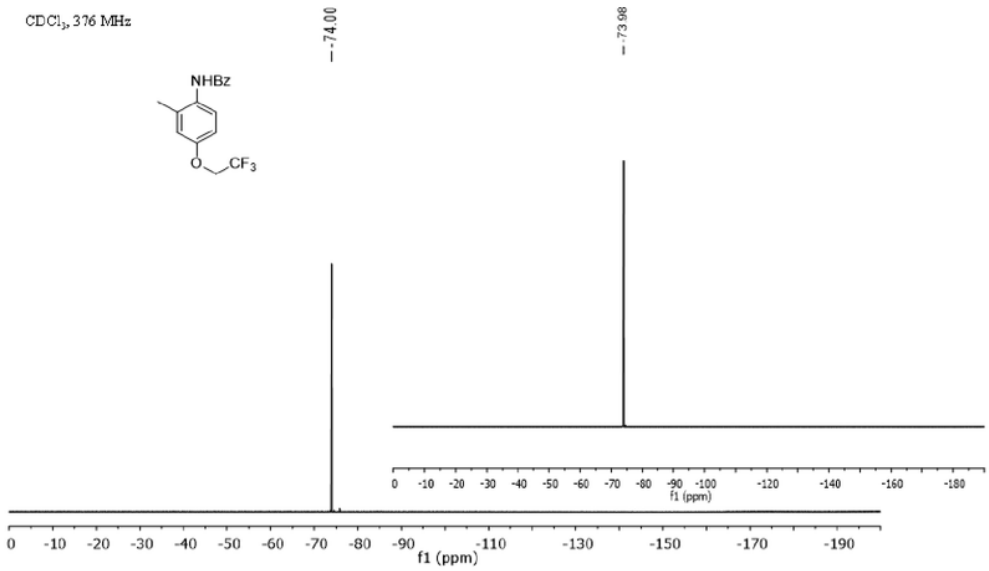


Figure 4.23. ^{19}F-NMR of N-{2-methyl-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (**2n**). Inset: the ^{19}F spectra recorded for the same sample after few months.

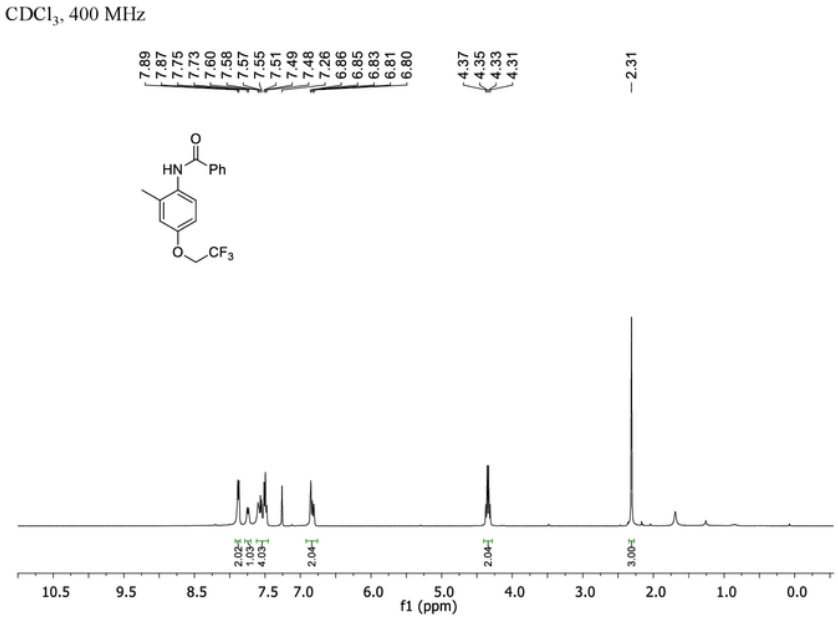


Figure 4.24. ^{1}H-NMR of of N-{2-methyl-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (**2n**).

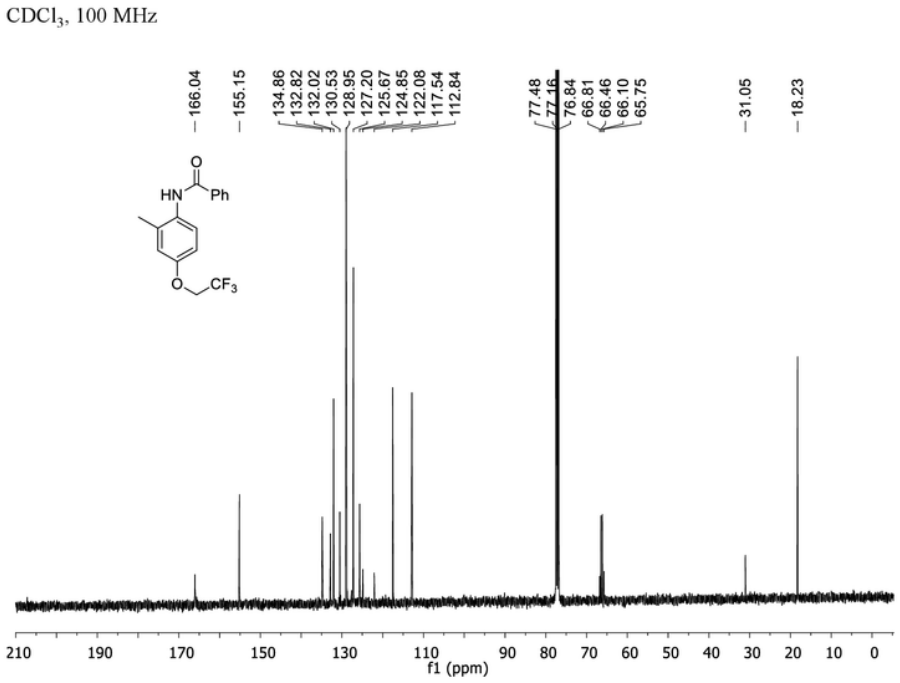


Figure 4.25. ^{13}C-NMR of N-{2-methyl-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (**2n**).

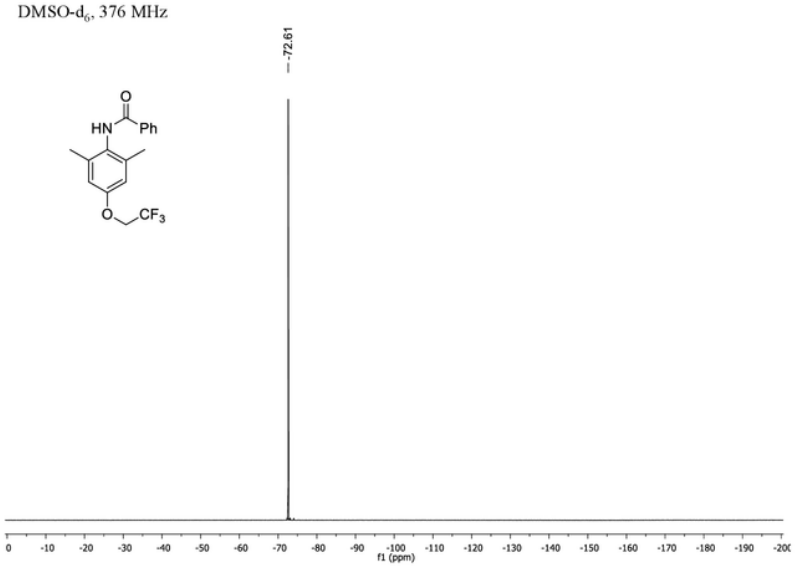


Figure 4.26. ^{19}F-NMR of N-{2,6-dimethyl-4-(2,2,2-trifluoroethoxy)phenyl}benzamide (**2o**).

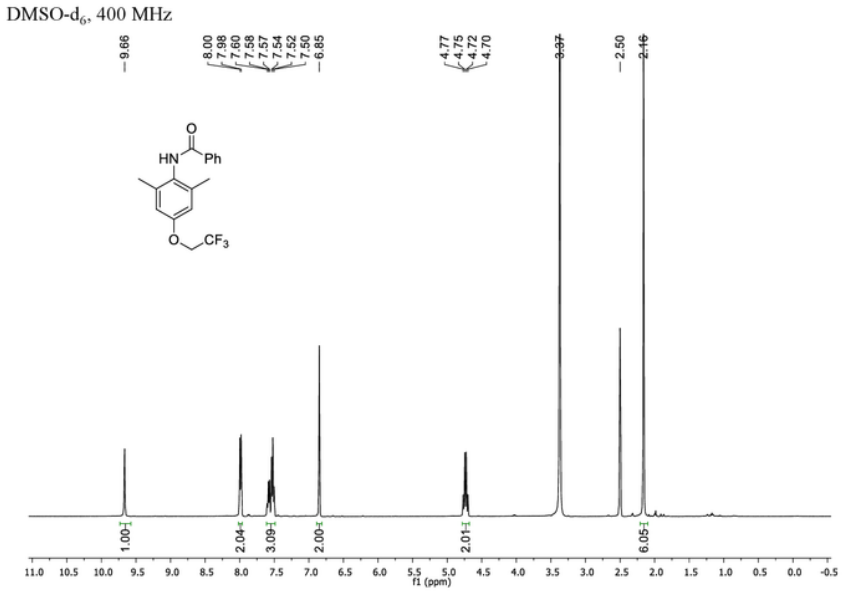


Figure 4.27. ^{1}H-NMR of N-{2,6-dimethyl-4-(2,2,2-trifluoroethoxy)phenyl} benzamide (**2o**).

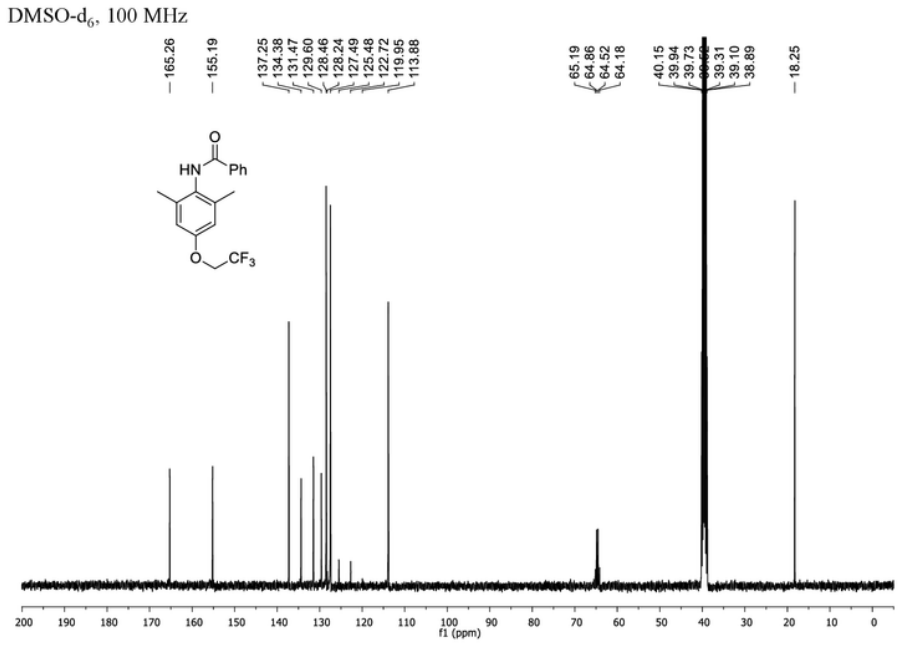


Figure 4.28. ^{13}C-NMR of N-{2,6-dimethyl-4-(2,2,2-trifluoroethoxy)phenyl} benzamide (**2o**).

Figure 4.29. ^{19}F-NMR of N-{2-ethyl-6-methyl-4-(2,2,2-trifluoroethoxy)phenyl} benzamide (**2p**).

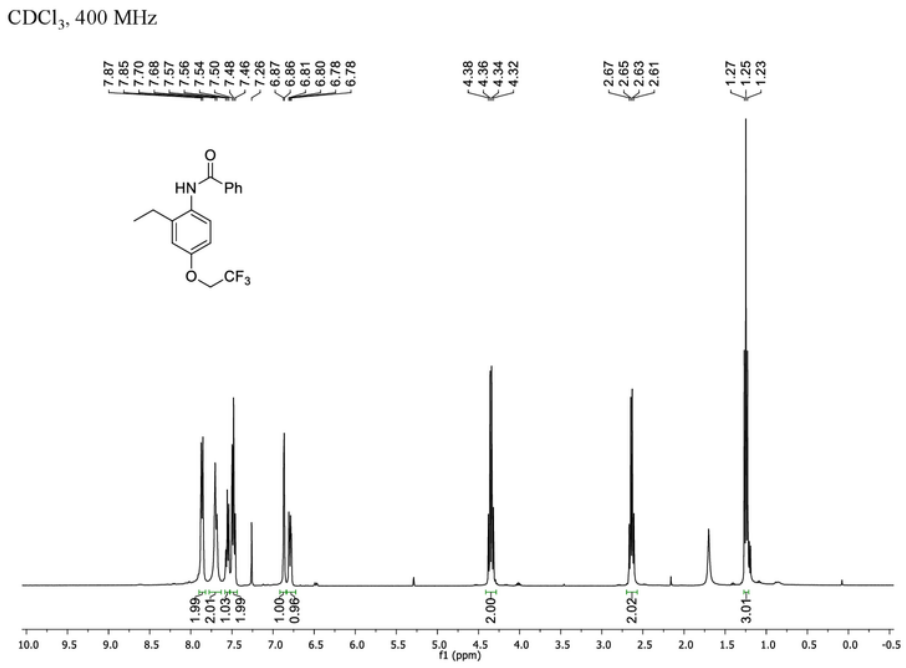


Figure 4.30. ^{1}H-NMR of N-{2-ethyl-6-methyl-4-(2,2,2-trifluoroethoxy)phenyl} benzamide (**2p**).

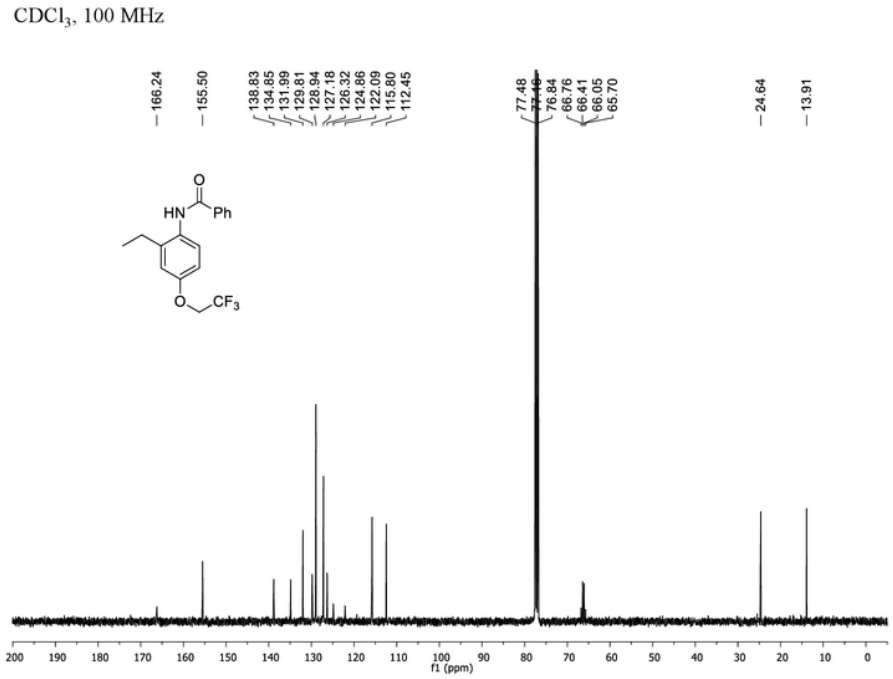


Figure 4.31. ^{13}C-NMR of N-{2-ethyl-6-methyl-4-(2,2,2-trifluoroethoxy)phenyl} benzamide (**2p**).

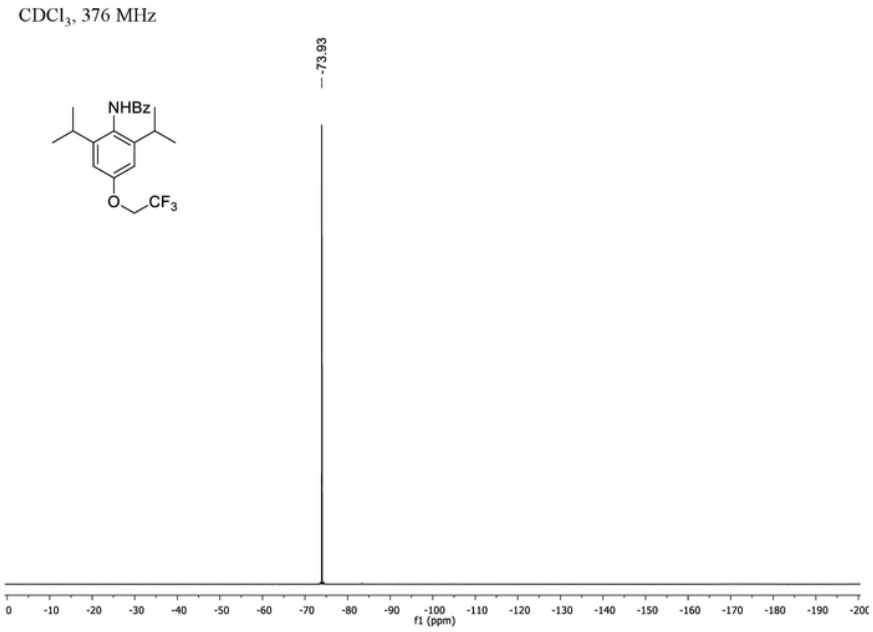


Figure 4.32. ^{19}F-NMR of N-{2,6-diisopropyl-4-(2,2,2 trifluoroethoxy)phenyl} benzamide (**2q**).

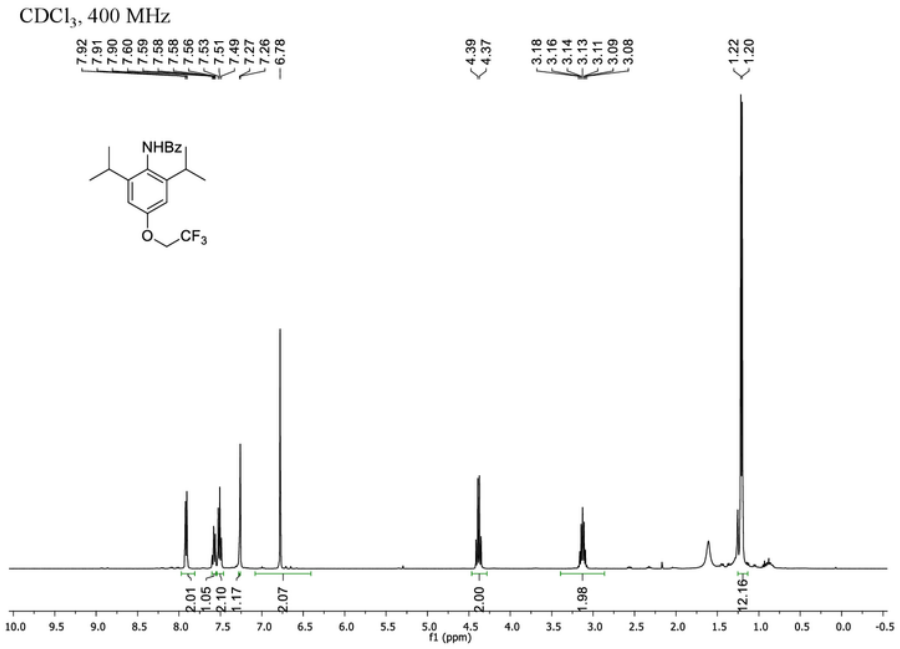


Figure 4.33. ^{1}H-NMR of N-{2,6-diisopropyl-4-(2,2,2-trifluoroethoxy)phenyl} benzamide (**2q**).

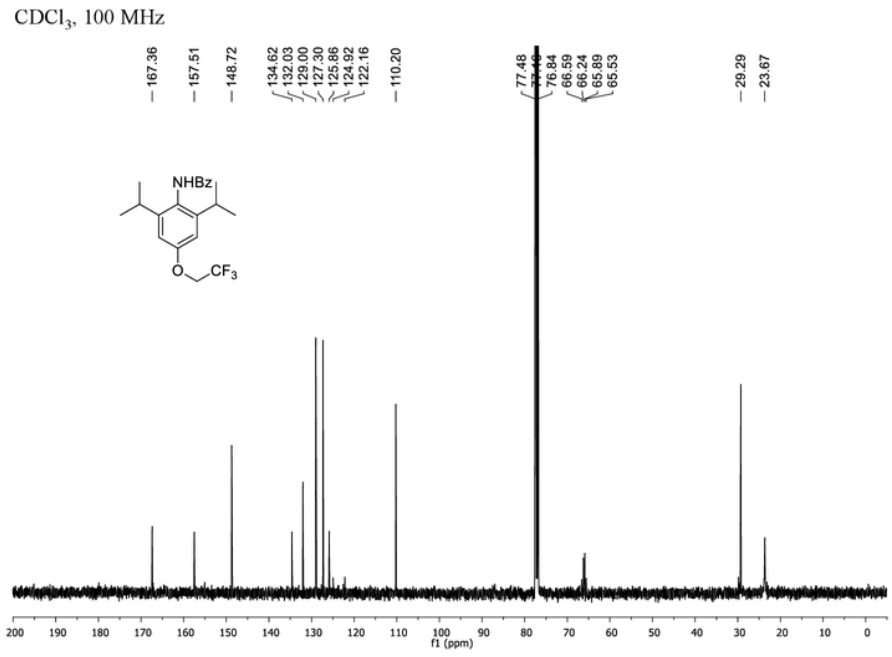


Figure 4.34. ^{13}C-NMR of N-{2,6-diisopropyl-4-(2,2,2-trifluoroethoxy)phenyl} benzamide (**2q**).

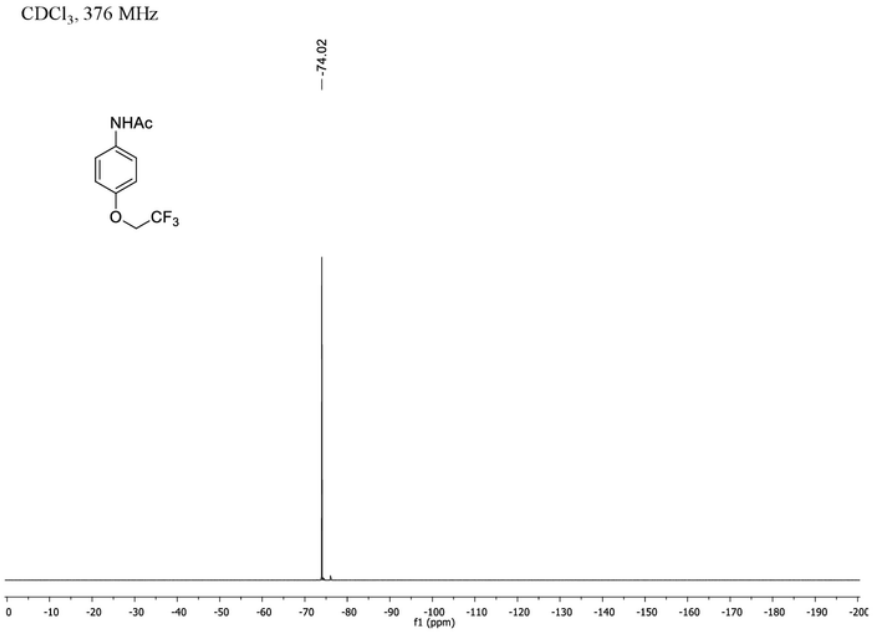


Figure 4.35. ^{19}F-NMR of N-{4-(2,2,2-trifluoroethoxy)phenyl}acetamide (**2r**).

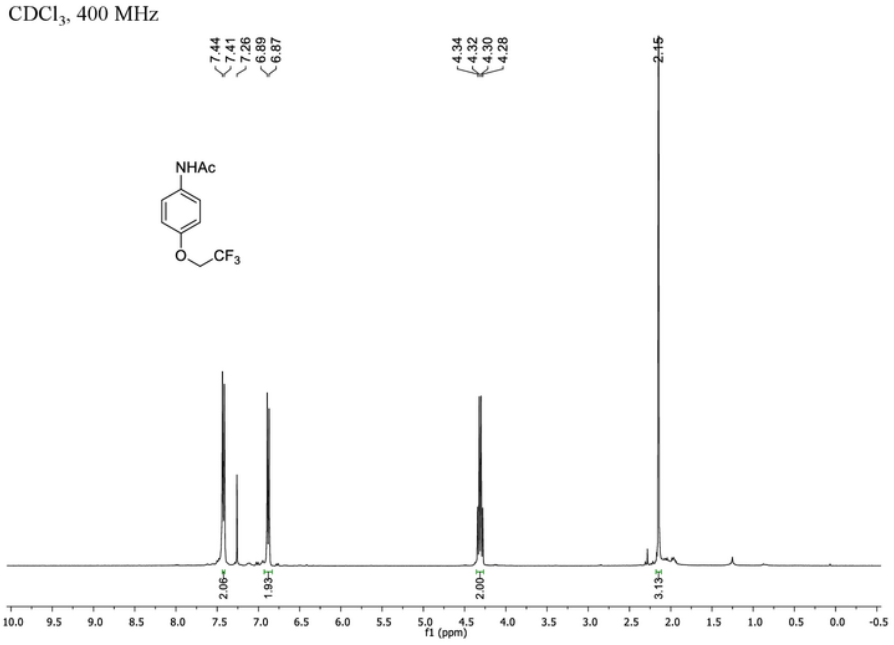


Figure 4.36. ^{1}H-NMR of N-{4-(2,2,2-trifluoroethoxy)phenyl}acetamide (**2r**).

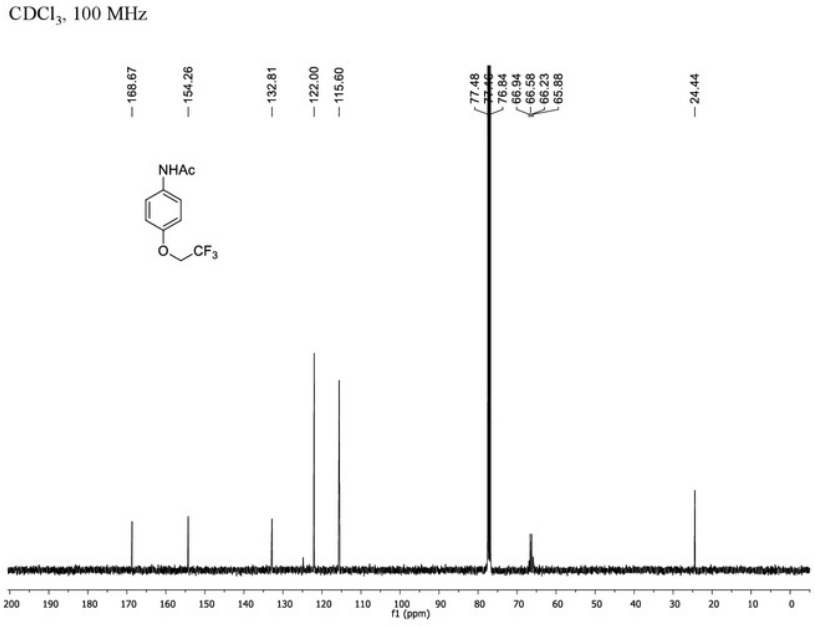


Figure 4.37. ^{13}C-NMR of N-{4-(2,2,2-trifluoroethoxy)phenyl}acetamide (**2r**).

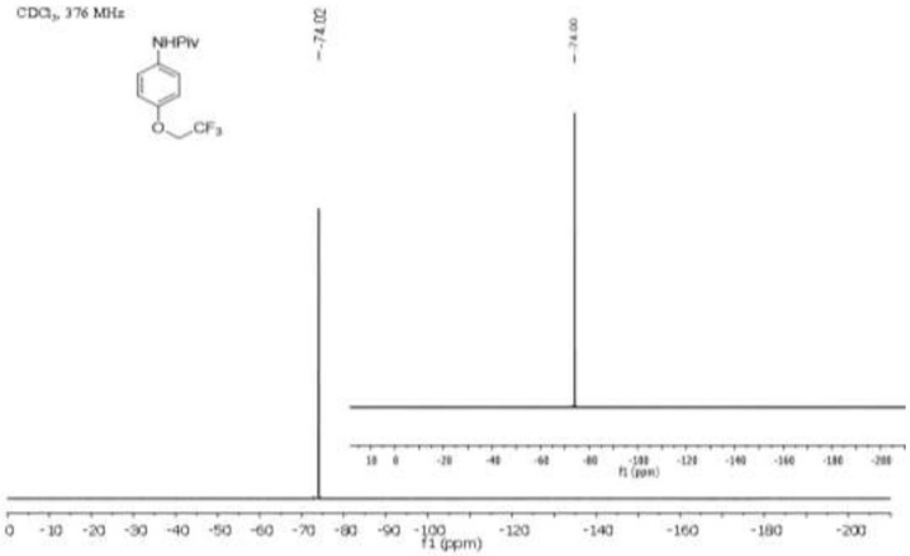


Figure 4.38. ^{19}F-NMR of N-{4-(2,2,2-trifluoroethoxy)phenyl}pivalamide (**2s**). Inset: the ^{19}F spectra recorded for the same sample after few months.

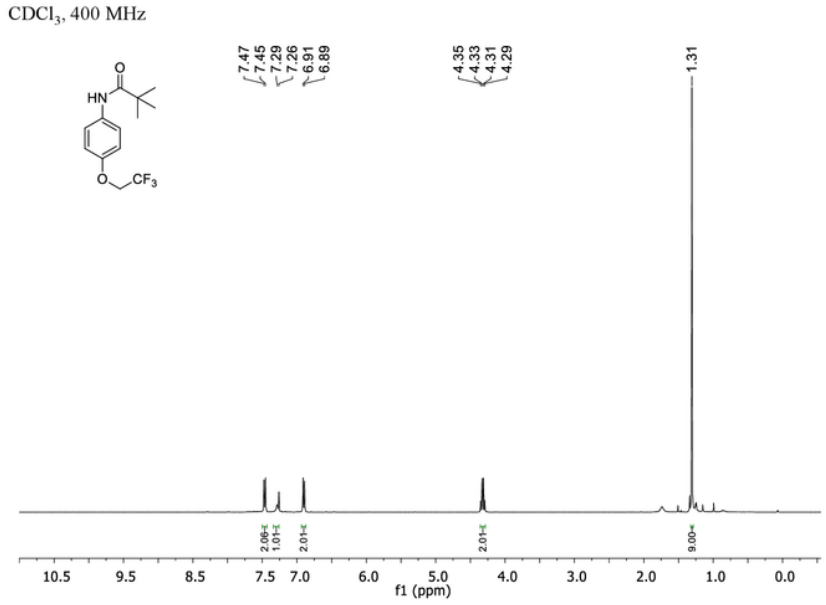


Figure 4.39. ^{1}H-NMR of N-{4-(2,2,2-trifluoroethoxy)phenyl}pivalamide (**2s**).

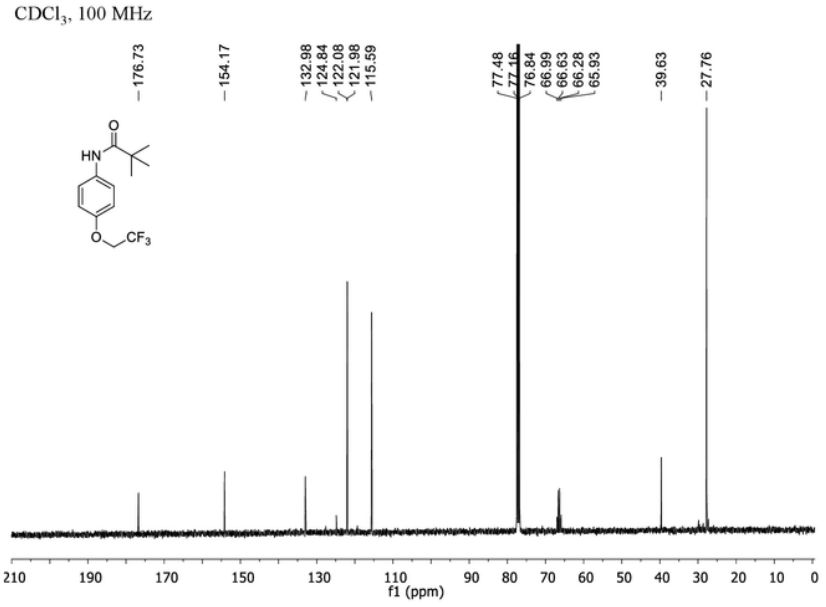
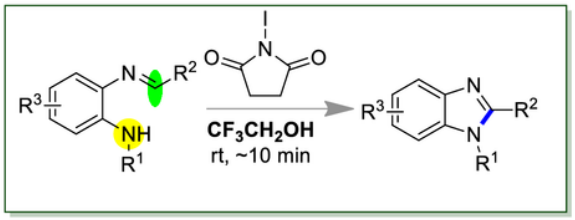


Figure 4.40. ^{13}C-NMR of N-{4-(2,2,2-trifluoroethoxy)phenyl}pivalamide (**2s**).

Conclusion

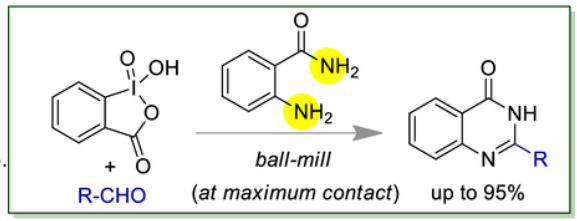
C(sp2) –H Amidation

Eur. J. Org. Chem. **2018**, 4178–4186



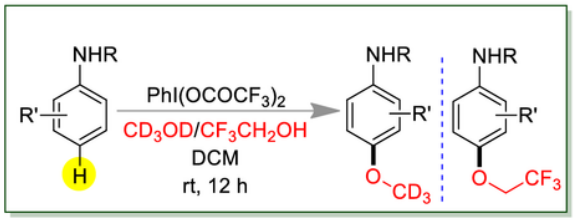
Quinazolin-4(3*H*)-one Synthesis

Beilstein J. Org. Chem. **2018**, *14*, 2396–2403.

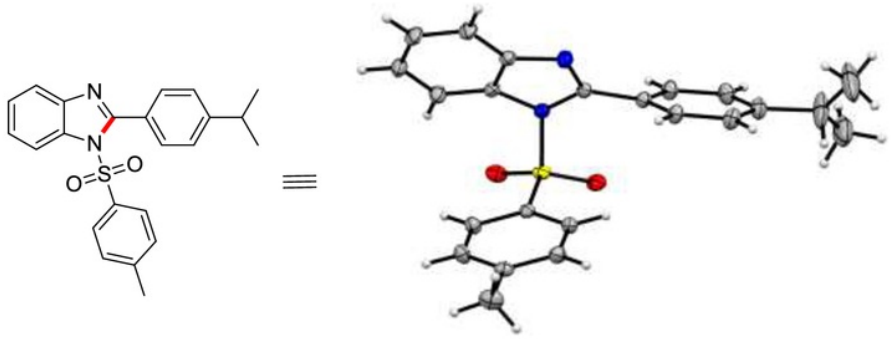


C-H Etherification of Anilides

Asian J. Org. Chem. **2018**, *7*, 715 – 719



➢ Crystallographic Data for **2h** (Chapter 2, figure 2.2); CCDC 1569701.

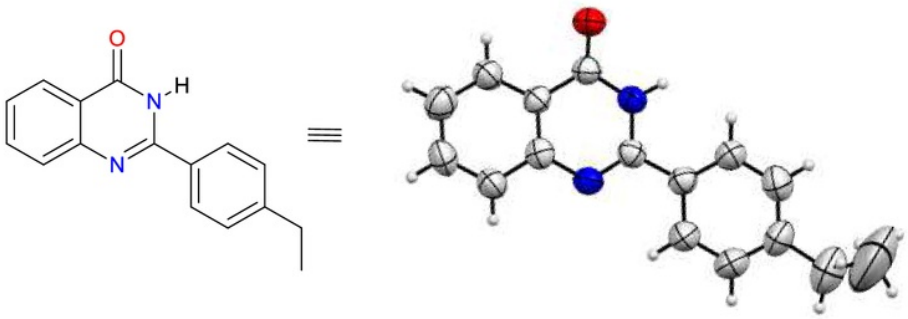


Empirical formula	$C_{23}H_{22}N_2O_2S$
Formula weight	390.48
Temperature	296.15 K
Crystal system	monoclinic
Space group	$P2_1/c$
a	9.7529(2) Å
B	11.4965(2) Å
c	18.1948(4) Å
A	90°
β	95.5910(10)°
γ	90°
Volume	2030.37(7) $Å^3$
Z	4
ρ_{calc}	1.277 g/cm^3
μ	0.180 mm^{-1}
F(000)	824.0
Crystal size	0.33 × 0.29 × 0.22 mm^3
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	4.196 to 51.998 °

Crystallography Data

Index ranges	$-12 \leq h \leq 12$, $-14 \leq k \leq 13$, $-22 \leq l \leq 22$
Reflections collected	29248
Independent reflections	3985 [R_{int} = 0.0404, R_{sigma} = 0.0231]
Data/restraints/parameters	3985/0/256
Goodness-of-fit on F^2	1.045
Final R indexes [I>=2σ (I)]	R_1 = 0.0503, wR_2 = 0.1421
Final R indexes [all data]	R_1 = 0.0661, wR_2 = 0.1573
Largest diff. peak/hole	0.51/-0.30 e $Å^{-3}$

- Crystallographic Data for **3a** (Chapter 3, figure 3.5); CCDC 1823611

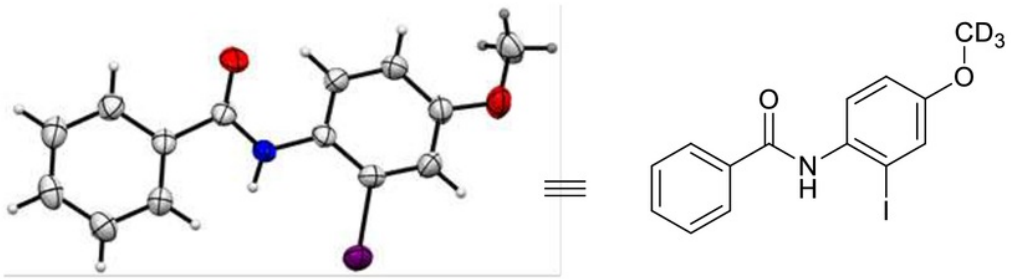


Empirical formula	$C_{32}H_{28}N_4O_2$
Formula weight	500.58
Temperature	296.15 K
Crystal system	triclinic
Space group	P-1

Crystallography Data

Unit cell dimensions	a = 5.0503(3) Å α = 92.215(6)°
	b = 15.3328(10) β = 91.359(4)°
	c = 17.0240(10) γ = 99.349(4)°
Volume	1299.17(14) $Å^3$
Z	2
Density (calculated)	1.280 g/cm^3
Absorption coefficient	0.081 mm^{-1}
F(000)	528.0
Crystal size	0.31 × 0.26 × 0.21 mm^3
Radiation	MoKα (λ = 0.71073)
Theta range for data collection	2.396 to 50.922°
Index ranges	$-6 \leq h \leq 6$, $-18 \leq k \leq 18$, $-20 \leq l \leq 20$
Reflections collected	14947
Independent reflections	4773 [R_{int} = 0.0653, R_{sigma} = 0.1250]
Data/restraints/parameters	4773/3/345
Goodness-of-fit on F^2	0.971
Final R indexes [I>=2σ (I)]	R_1 = 0.0857, wR_2 = 0.2434
Final R indexes [all data]	R_1 = 0.2356, wR_2 = 0.3599
Largest diff. peak/hole	0.61/-0.35 e $Å^{-3}$

- Crystallographic Data for **2b** (Chapter 4, figure 4.4); CCDC 1811546.



Empirical formula	$C_{14}H_{12}INO_2$
Formula weight	353.15
Temperature/K	296(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	13.5248(4)
b/Å	4.75210(10)
c/Å	20.5802(6)
α/°	90
β/°	103.3740(10)
γ/°	90
Volume/Å^3	1286.84(6)
Z	4
ρ_{calc}g/cm^3	1.823

Crystallography Data

6	
μ/mm^{-1}	2.481
F(000)	688.0
Crystal size/mm^3	0.21 × 0.18 × 0.15
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.288 to 61.066
Index ranges	-19 ≤ h ≤ 19, -6 ≤ k ≤ 6, -29 ≤ l ≤ 29
Reflections collected	21340
Independent reflections	3935 [R_{int} = 0.0298, R_{sigma} = 0.0206]
Data/restraints/parameters	3935/0/164
Goodness-of-fit on F^2	1.228
Final R indexes [I>=2σ (I)]	R_1 = 0.0186, wR_2 = 0.0532
Final R indexes [all data]	R_1 = 0.0218, wR_2 = 0.0659
Largest diff. peak/hole / e $Å^{-3}$	0.44/-1.00

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EurJOC European Journal of Organic Chemistry

Full Paper

Synthetic Methods

An Intramolecular C(sp^2)–H Amidation Using *N*-Iodosuccinimide

Md Toufique Alam,[a] Saikat Maiti,[a] and Prasenjit Mal*[a]

Abstract: An *N*-iodosuccinimide (NIS) mediated intramolecular dehydrogenative C(sp^2)–H amidation is reported for easy and convenient access to 1,2-disubstituted benzimidazoles. The nonprefunctionalized C(sp^2)–H and N(sp^3)–H bonds were directly coupled using NIS in trifluoroethanol, which proved to be mild alternative to strong oxidative iodine(III) reagents. The reaction worked at room temperature, under an air atmosphere, and in the absence of any base additive.

Introduction

Benzimidazoles are heterocyclic systems that are well known for their extensive use in pharmaceutical chemistry and materials science.[1] These molecules have also shown anticancer,[2] anti-infective,[3] anti-inflamatory,[4] anti-hepatitis B,[5] anti-HIV,[6] anti-depressant,[7] and antitumor[8] activities. The drug esomeprazole (Nexium), which contains a benzimidazole moiety, was reported to be one of the best-selling drugs in 2009 (Figure 1a).[9] *N*-Substituted benzimidazole systems are also found in various biologically active molecules.[4,5,10] Therefore, the synthesis of benzimidazoles has attracted a lot of attention from organic chemists.

The development of environmentally benign methods[11] for C–N-bond synthesis is hugely significant.[12] In contrast to metal mediated C–N coupling reactions,[13] metal-free direct C–H amination reactions represent an important approach for the synthesis of various amines by sustainable methods.[14] Cost-effective and waste-free methods for the construction of C–N bonds using metal-free iodine-based reagents are popular,[15] and various cross-dehydrogenative coupling (CDC) or oxidative C–N cross-coupling reactions have been reported.[16] However, the number of examples that have been reported for C–H amination reactions using *N*-iodosuccinimide (NIS) is limited.[17]

Small-molecule systems chemistry[18] is an increasingly popular approach to understanding the complexity of chemical reactions and working towards implementing them in a simplified manner. Cooperative multiple weak interactions[19] like hydrophobic effects,[20] halogen bonding,[21] charge-transfer interactions,[22] cation–π interactions, anion–π interactions,[23] hard–soft acid–base (HSAB) control,[24] etc. are being explored in chemical reaction systems.[25] Therefore, in order to control a chemical reaction through weak supramolecular interactions it is important to understand the reactivity of the system as a whole.[26]

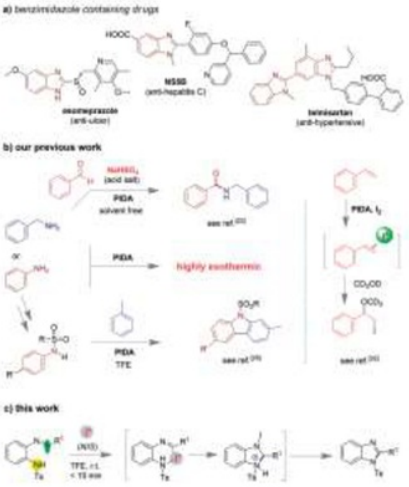

Figure 1. a) Benzimidazole-containing drug molecules. b) Control of the reactivity of amines in presence of phenyliodine diacetate (PIDA). For example, the usually explosive reaction of benzylamines and PIDA was controlled by the addition of $NaHSO_4$.[23] sulfonamides in fluorinated solvents led to carbazoles,[24] styrene was difunctionalized through cation–π interactions.[26] c) Dehydrogenative C(sp^2)–H amidation using NIS (this work).

Results and Discussion

In a continuation of our research interests towards controlling chemical reactions using weak interactions[27] in nonprefunctionalized aromatic systems,[28] in this paper we report an intra-

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The mechanochemical synthesis of quinazolin-4(3*H*)-ones by controlling the reactivity of IBX

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Abstract

Performing any synthesis using several arylamines and hypervalent iodine(V) reagents by direct mixing is unrealistic because of the high exothermic reaction or explosion. Herein we demonstrate, when anilines were substituted with an amide group at the *ortho*-position, successful chemical reactions could be performed due to intramolecular control. At maximum contact of the reacting substances, i.e., under solvent-free mechanochemical conditions, 2-aminobenzamides, aryl-, alkylaldehydes and the iodine(V) reagent *o*-iodoxybenzoic acid (IBX) led to substituted quinazolin-4(3*H*)-one derivatives in fair yields.

Introduction

An iodine and ammonia mixture is a well-known contact explosive due to formation of NI_3 [1]. Similarly, hypervalent iodines as oxidizing compounds [2] react violently with amines under solvent-free conditions [3]. Aryliodonium imides or iminoiodanes can be prepared by the treatment of electron-deficient amines with iodine(III). However, these compounds explode at higher temperatures [4] and hence are stored under inert atmosphere and low temperature [5]. Polyvalent iodine derivatives are versatile reagents for C–N bond constructions [4,6]. Mechanochemical conditions such as ball milling are considered to be one of the premium techniques in solvent-free synthesis [7]. Under these conditions, maximum concentration is expected to put those systems under high stress and therefore violent exothermic reactions or even explosions may take place between hypervalent iodine reagents and electron-rich amines. For this reason, synthetic methods based on hypervalent iodine reagents and primary amines under solvent-free conditions or constrained media are limited [8]. Recently, we have described a method for the successful reaction of primary amines and hypervalent iodine(III) reagents by controlling the reactivity using an acid salt, $NaHSO_4$, as additive [9].

Results and Discussion

The last few decades have witnessed a significant growth in organic synthesis using hypervalent iodines [10-12]. Their easy availability, high stability, controlled oxidizing ability, and en-

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ASIAN JOURNAL OF ORGANIC CHEMISTRY Communication

Synthetic Methods

Soft–Hard Acid–Base-Controlled C–H Trifluoroethoxylation and Trideuteriomethoxylation of Anilides

Saikat Maiti, Toufique Alam, and Prasenjit Mal*[a]

Abstract: Phenyliodinetrifluoroacetate (PIFA)-mediated dehydrogenative C–H etherification of anilides is reported for the synthesis of -OCH_2CF_3 and -OCD_3 incorporated aryl ethers. Nucleophilicity of the added nucleophiles and soft–hard acid–base (SHAB) principle were rationalized to understand those reactions. Anilides and PIFA led to the electrophiles either softer nitrenium ions or harder carbenium ions. The harder nucleophile alcohols exclusively reacted with the carbenium ions to produce aryl ethers.

Intrinsic physiochemical properties like greater metabolic stability, high electronegativity and improved lipophilicity due to the -OCH_2CF_3 group, the trifluoroethoxy containing molecules become significant in organic synthesis.[1] Trifluoroethyl aryl ethers are present in several pharmaceutically valued molecules such as *para*-trifluoroethoxyaniline derivative is used as ^{19}F-MRI probe for the detection of hypochlorite ion,[2] and lansoprazole is well-known to be used for the purpose of proton pump inhibition (Figure 1 a).[3] Similarly, several trideuteriomethoxy containing molecules are also well recognized due to their specific bioactivities.[4] Two -OCD_3 containing fewer biologically important molecules are shown in Figure 1 b.[5] Thus the development of expedient synthetic methods for trifluoromethoxylation and trideuteriomethoxylation are of great importance.

The reactivity of a chemical systems are known to be controlled by local environment.[6] The cooperative weak interactions[7] like charge-transfer,[8] hydrophobic effect,[9] cation-π,[10] anion-π,[11] halogen bonding,[12] are significantly explored in chemical synthesis.[13] We have reported recently that weak interactions can be used for C–H mono-nitration reaction on indolines,[14] soft–hard acid–base (SHAB) principle could be applied in C–N bond formation reactions on sulfonanilides using hypervalent iodine(III),[15] potential use of iodine(III) reagents for various C–H functionalization reactions, etc.[16] In continuation, we demonstrate here C–H etherification of aromatic anilides for the synthesis of -OCH_2CF_3 and -OCD_3 incorporated aryl ethers through the reactivity regulation of nitrenium ion[17] over carbenium ion[16] via SHAB control.[18] Hypervalent iodine(III) compounds are well reputed as non-toxic potential oxidizing agents. Application of iodine(III) reagents in C-heteroatom bond formation by oxidative functionalization of anilides have been documented in several reviews.[19]

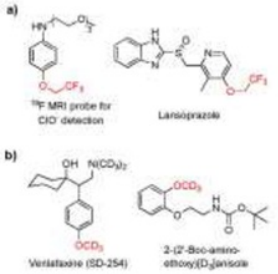

Figure 1. Trifluoroethoxy and trideuteriomethoxy containing important molecules.

As shown in Scheme 1, the softer electrophile[20] nitrenium ion is switchable to the harder electrophile carbenium ion by losing the aromatic ring current.[15] Kikugawa and co-workers have shown that by-product iodobenzene from the reactions of anilides and phenyliodinetrifluoroacetate (PIFA)[19c,21] reacted further for a dehydrogenative C–N bond formation reaction.[22] However, in this work the solvents 2,2,2-trifluoroethanol (TFE) and [D_4]MeOH (CD_3OD) led to selective incorporation at *para* position of anilides by C–O bond formation. These reactions were favored due to hard–hard preference by the alcohols with harder carbenium ions[16] over the softer nitrenium ions.[17b,23] Thus the role of SHAB principle[24] is clearly established for the dehydrogenative C–O bond formation of anilides. Although there are reports on the hypervalent iodine mediated aromatic C–O bond formations with alcohols,[25] nevertheless, this work can be considered as a proof-of-concept of SHAB principle to regulate chemical reactions by added nucleophiles. To the best of our knowledge, there is no metal free synthesis method for trifluoroethoxylation and trideuteriomethoxylation by selective aromatic C(sp2)–H bond functionalization. So, this metal-free, additive-free and directing group-free

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