Study of Copper-Based *C-S, C-Se* and *C-N* Bonds Formation

A Thesis Submitted
in Partial Fulfillment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

by

Ramana Tamminana
Roll No. 09612212

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati- 781039
October 2012

Dedicated

To

My Family Members

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India under the supervision of Prof. Tharmalingam Punniyamurthy.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Guwahati   Ramana Tamminana

October 2012

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Mr. Ramana Tamminana has been working under my supervision since July 2009. I am forwarding his thesis entitled "*Study of Copper-Based C-S, C-Se and C-N Bonds Formation*" being submitted for the Ph.D. degree of this institute. I certify that he has fulfilled all the requirements according to the rules of this institute and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Guwahati — Prof. Tharmalingam Punniyamurthy

October 2012 — Supervisor

ACKNOWLEDGEMENT

I would like to express my deep and sincere gratitude to my thesis supervisor Prof. Tharmalingam Punniyamurthy for his expert guidance, teaching, enthusiasm and suggestions throughout my research period. His suggestions, criticisms and constant encouragement helped me immensely to achieve this target. His true scientific spirit has helped me a lot during my research work. I shall remain indebted to him forever.

I would like to thank my doctoral committee members Dr. S. S. Bag, Dr. Biplab Mondal and Prof. Arun Goyal for their evaluation and valuable suggestions during the entire period of the Ph. D. program.

I owe my sincere thanks to my lab mates Dr. Suribabu Jammi, Dr. Prasenji Saha, Dr. S. Sakthivel, Rajesh Paul, Md Ashif Ali, Rapolu Kiran Kumar, M. Kannan, Murali Mohan Guru, Santhosh Kumar Alla, M. Sengoden, G. Murugavel, S. Pradeep, G. Bharathiraja, S. Dinabandhu, D. Sathyaraj, D. Mahesh, M. Vijay, Sudeshna Manna, Soumen Mukherjee, Abhishek Ray, Bulbul Maji and Manas Das for their timely help, support and for creating pleasant atmosphere in lab.

I extend my sincere thank to my best friends G. Sudharsanadevi, S. Jagadeeswara Rao, P. Atchyutha Rao, M. Siddhardha, M. Narayana Reddy, I. Subba Rao, P. Seethamnaidu, Sunil, Vasu for their encouragement, unfailing support. I also wish thank to my seniours Dr. Siva Murru, Dr. Chandramouli Reddy, Dr. Ramesh Yella, Dr. Somasekhar, Dr. Saitanya, Dr. Subash Sahu for lending their hands of support whenever needed. I also take this opportunity to thank all of my Ph.D batch mates (July 2009) and other friends @iitg Nani Babu, Chiatanya, Kishore, Laxman, Narasimha, Kiran, Santhi Raju, Himanshu Sekhar Jena, Babulal Das, Pankaj Kumar, Aswini Kalita, Apurba Kalita, Bhaskar Nath, Bigyan R. Jali for their timely help and joyful moments shared with me at iit.

I thank all the faculty members, research scholars, supporting staff of the department of chemistry and CIF for their kind cooperation in all respects.

I acknowledge CSIR for fellowship for the entire period of the Ph.D. program.

Finally, my deepest gratitude goes to my family for their unflagging love and support throughout my life. I feel deeply indebted to them for whatever I have achieved so far.

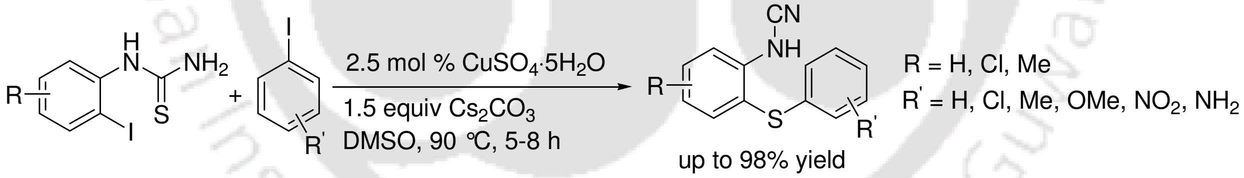
Ramana Tamminana

Abstract

The thesis contains five chapters. First two chapters focus on the copper-catalyzed synthesis of 2-(arylthio)arylcyanamides and 2-(arylselanyl)arylcyanamides *via* domino *C-S* and *C-Se* cross-coupling reactions. The chapter three describes copper-mediated three-component strategy for the synthesis of 5-aminotetrazoles. The chapter four deals with copper-catalyzed synthesis of 2-azidobenzimidazoles and the chapter five having two parts focuses on copper-catalyzed synthesis of 2-aminobenzimidazoles and 2-(1*H*-1,2,3-triazo-1-yl)benzimidazoles, respectively.

Chapter I. Copper(II)-Catalyzed Synthesis of 2-(Arylthio)arylcyanamides from *N*-(2-Iodoaryl)thiourea and Aryl Iodides

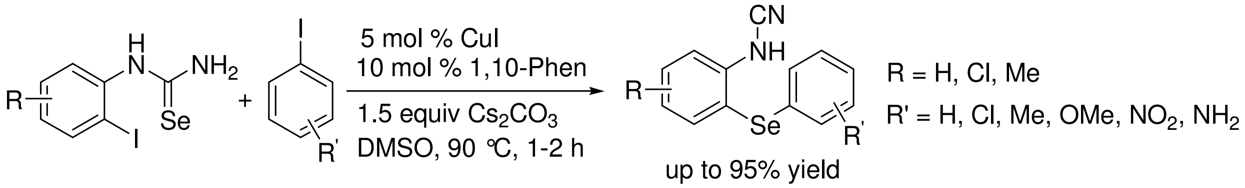
Transition-metal catalyzed cross-coupling reactions provide effective method for the formation of carbon-carbon and carbon-heteroatom bonds. Among these, the construction of *C-S* bond has received considerable attention due to their presence in many molecules that are of biological, pharmaceutical and material interest. This chapter describes copper-catalyzed synthesis of 2-(arylthio)arylcyanamides by domino intra- and intermolecular *C-S* cross-coupling reactions of aryl thioureas with aryl iodides (Scheme 1).



Scheme 1

Chapter 2. Copper(I)-Catalyzed Synthesis of 2-(Arylselanyl)arylcyanamides from *N*-(2-Iodoaryl)selenourea with Aryl Iodides

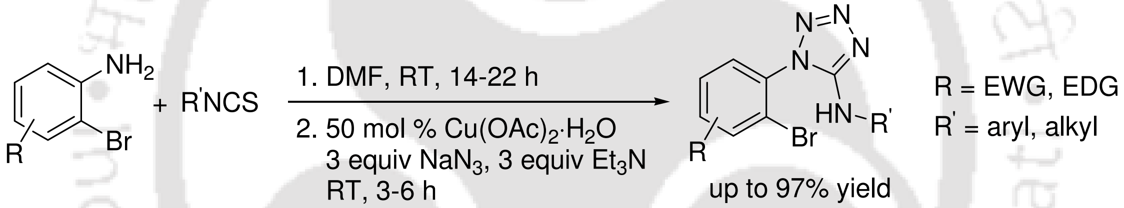
Study of organoselenium compounds is an active topic due to their interesting biological and medicinal properties. This chapter describes synthesis of 2-(arylselanyl)arylcyanamides from 2-(iodoaryl)selenourea with aryl iodides *via* domino intra- and intermolecular *C-Se* cross-coupling reaction in the presence of copper(I) complex under moderate temperature (Scheme 2). A variety of substrates undergo reactions to give the cross-coupled products in good yield.



Scheme 2

Chapter 3. Copper(II)-Promoted Three-Component Synthesis of Substituted 5-Aminotetrazoles

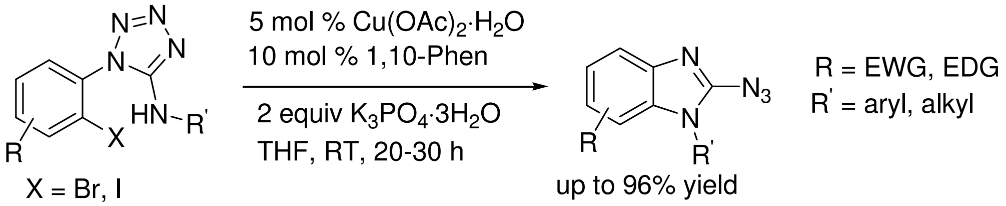
Tetrazoles are an important class of heterocyclic compounds. Due to their unique structure and reactivity, they have attracted noticeable interest in medicinal applications. This chapter describes the synthesis of substituted 5-aminotetrazoles *via* copper-promoted three component reaction from isothiocyanates, bromoanilines and sodium azide via tandem addition, substitution and electrocyclization (Scheme 3).



Scheme 3

Chapter 4. Copper(II)-Catalyzed Conversion of 1-(2-Bromoaryl)-*N*-Aryl-1*H*-Tetrazol-5-Amines to 2-Azidobenzimidazoles

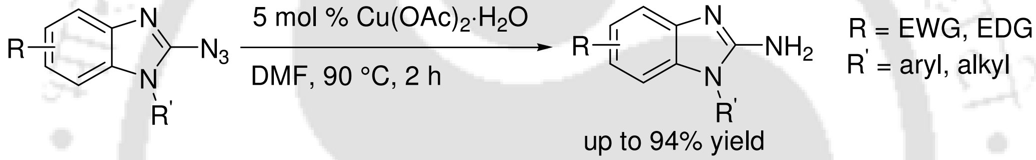
"Benzimidazole" is an important structural unit present in many molecules that are of biological and medicinal interest. Development of effective method for the construction of benzimidazole structural framework has thus been important in organic synthesis. This chapter describes the synthesis of 2-azidobenzimidazoles from 5-aminotetrazoles *via* copper-catalyzed intramolecular *C-N* cross-coupling reaction followed by tautomerization (Scheme 4).



Scheme 4

Chapter 5A. Copper-Catalyzed Reduction of 2-Azidobenzimidazoles to 2-Aminobenzimidazoles

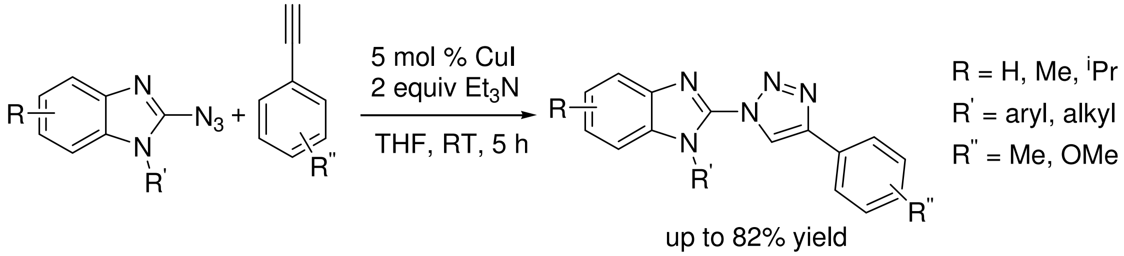
2-Aminobenzimidazols are privileged organic compounds due to their recognition in biological and therapeutic activities. This chapter focuses on copper-catalyzed reduction of 2-azidobenzimidazoles to 2-aminobenzimidazoles at moderate temperature (Scheme 5). The reactions are simple, general and proceed reactions to provide the target products in high yield.



Scheme 5

Chapter 5B. Copper(I)-Catalyzed Click Reaction of 2-Azidobenzimidazoles with Alkynes

Click chemistry provides an effective route for the construction of five membered heterocycles with molecular diversity from readily available substrates precursors. This chapter demonstrates the copper(I)-catalyzed synthesis of substituted 2-(1*H*-1,2,3-triazo-1-yl)benzimidazoles from 2-azidobenzimidazoles and alkynes by click chemistry. A series of substituted 2-(1*H*-1,2,3-triazo-1-yl)benzimidazoles have been synthesized *via* click reaction of 2-azidobenzimidazoles with substituted alkynes (Scheme 6).



Scheme 6

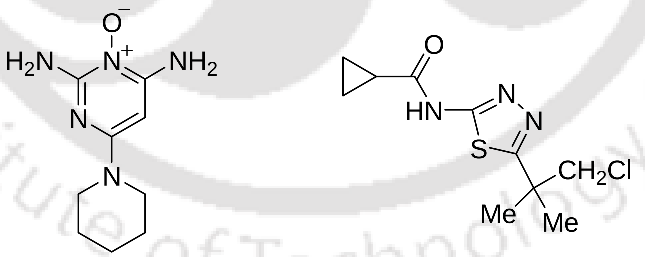
Contents

5B Copper(I)-Catalyzed Click Reaction of 2-Azidobenzimidazoles with Alkynes 133

Copper(II)-Catalyzed Synthesis of 2-(Arylthio)arylcyanamides from *N*-(2-Iodoaryl)thiourea and Aryl Iodides

Transition-metal catalyzed cross-coupling reactions provide effective method for the formation of carbon-carbon and carbon-heteroatom bonds.[1] Among these, the construction of *C*-*S* bonds has received considerable attention due to their presence in many molecules that are of biological, pharmaceutical and material interest.[2] Organosulfur compounds also play an important role in synthetic chemistry as versatile reagents for synthesis and catalysis. Traditional methods for the formation of aryl chalcogen bond often require harsh reaction conditions such as the use of toxic solvents and elevated temperatures.[3] Some of these limitations have been overcome by the recent developments in the cross-coupling reactions.

Cyanamides have attracted much attention in biological, pharmaceutical and material sciences due to their unique structure[4] and reactivities.[5] For example, cyanamides are important intermediates for the synthesis of many biologically active compounds, such as minoxidil[6] and herbicides.[7] Cyanamides are also extensively used in agriculture, as precursors for the synthesis of pharmaceutically important heterocycles[8] and *N*-alkyl or *N*-aryl imides.[9,10] Furthermore, the CN group can be easily removed from cyanamides, and hence, they can be used as a protecting group for the synthesis of primary and secondary amines.



Minoxidil

Treatment of High Blood Pressure

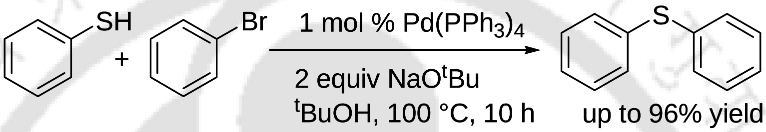
Herbicide (Cyprazole)

Figure 1. Examples of some biologically active compounds

1.1 Palladium Catalysts

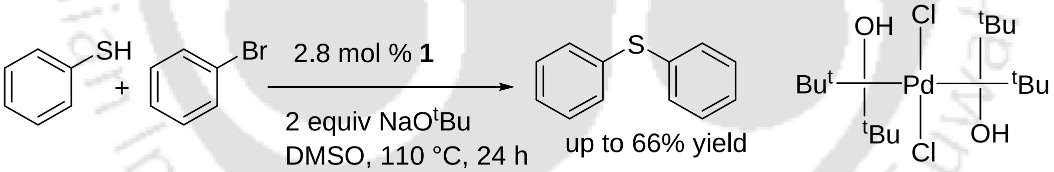
Palladium based catalytic systems have been extensively explored for the carbon-heteroatom bond formation *via* cross-coupling reactions for over the past three decades and considerable progress has been made.

In 1980, Migita and co-workers first reported the synthesis of diphenylthioether from thiols and aryl halides using $Pd(PPh_3)_4$ in the presence of NaO^tBu in *tert*-butanol. Aryl iodides and bromides are compatible with this procedure affording the cross-coupled products in high yield (Scheme 1).[11a]



Scheme 1

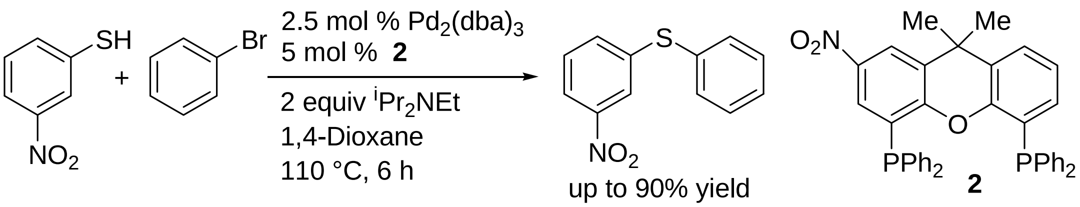
Subsequently, the use of palladium(II) complex **1** has been demonstrated for the coupling of thiols with aryl bromides in the presence of NaO^tBu. Both electron donating and electron withdrawing substituents on the phenyl rings work well under these conditions (Scheme 2).[11b]



1

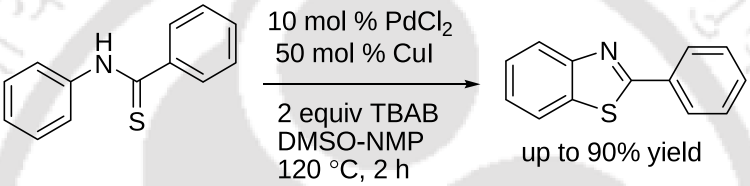
Scheme 2

Then, Itoh and co-workers have reported the cross-coupling of thiols with aryl bromides using *in situ* generated palladium(II) complex from $Pd_2(dba)_3$ and xantphos **2** in the presence of $^iPr_2NEt$ in 1,4-dioxane (Scheme 3).[11c] In contrast to the above methods that employ inorganic bases, the present protocol is compatible with organic base.



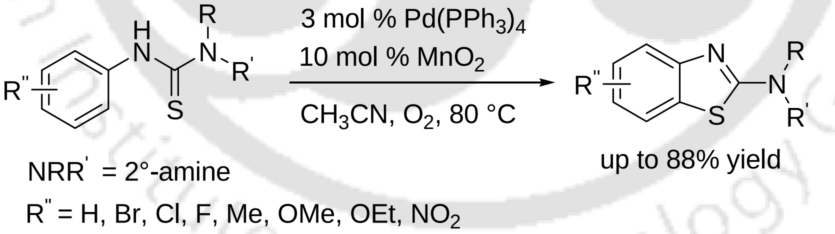
Scheme 3

While, Doi and co-workers have shown the intramolecular cyclization of *N*-arylbenzothioamide *via C-H* functionalization/*C-S* bond formation employing $PdCl_2$ and CuI in the presence of tetrabutylammonium bromide (TBAB). The presence of TBAB increases the yield of the target products (Scheme 4).[11d]



Scheme 4

Furthermore, Batey and co-workers have described the synthesis of 2-aminobenzothiazoles from *N*-arylthiourea *via C–S* bond formation/*C–H* bond functionalization using $Pd(PPh_3)_4$ and MnO_2 under oxygen atmosphere (Scheme 5).[11e]

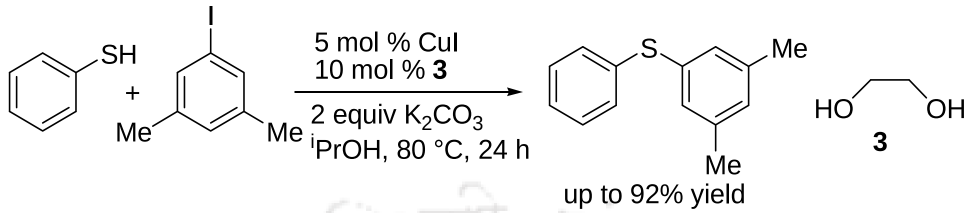


Scheme 5

1.2 Copper Catalysts

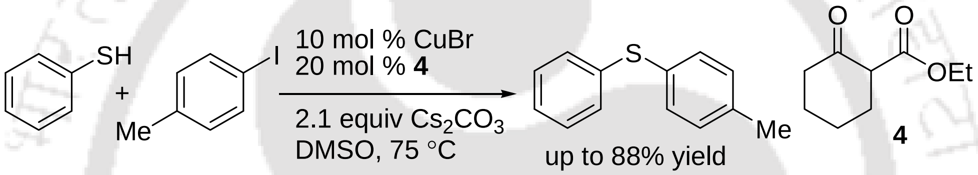
Copper based catalytic systems have more advantages compared to palladium catalysis because copper based catalysts are generally less expensive, less toxic, less sensitive to air and free from the requirement of bulky phosphine ligands.

Copper(I) complex generated *in situ* from CuI and 1,2-ethylene glycol **3** has been used for the coupling of thiols with aryl iodides in 2-propanol. The procedure is effective and the target products are obtained in good to excellent yields (Scheme 6).[12a]



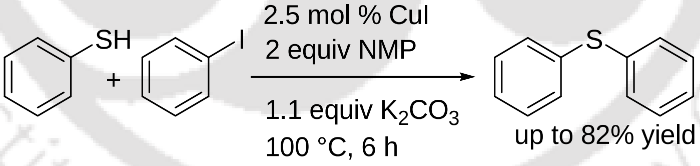
Scheme 6

A similar results are obtained using copper(I) complex derived from CuBr and β-keto ester **4** for the coupling of thiols with aryl iodides in DMSO (Scheme 7).[12b]



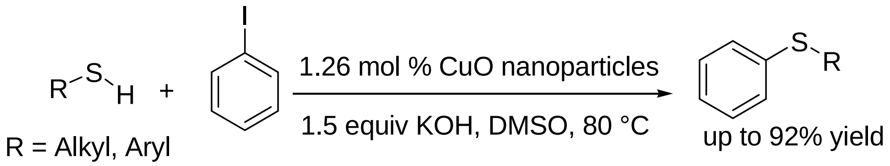
Scheme 7

While Koten and co-workers have shown the cross-coupling of thiophenols with aryl iodides using CuI in the presence of K_2CO_3 in NMP (Scheme 8).[12c]



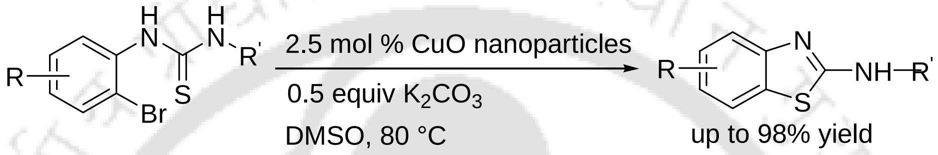
Scheme 8

Our group showed the use of CuO nanoparticles for the coupling of both aryl and alkyl thiols with aryl iodides in DMSO (Scheme 9).[12d] The procedure involves ligand-free conditions and the catalyst can be recovered and recycled without loss of activity.



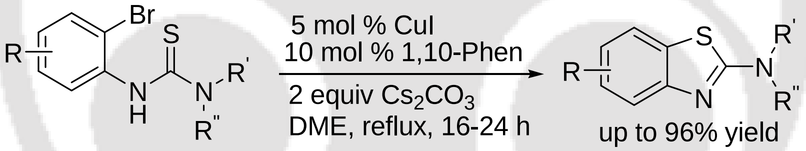
Scheme 9

The above catalytic system is also effective for the cyclization of *N*,*N*-diaryl thiourea to afford 2-aminobenzothiazole in quantitative yield (Scheme 10).[12e]



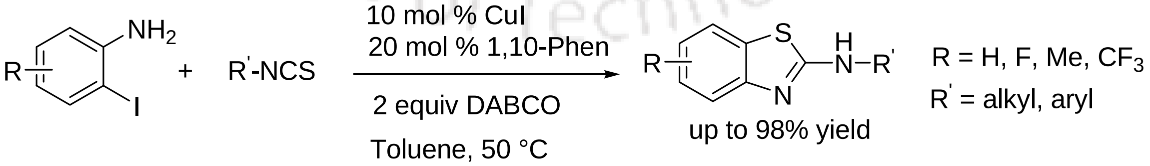
Scheme 10

The cyclization of *o*-halothiourea has also been carried out by Batey and co-workers using CuI/1,10-phenanthroline in the presence of Cs_2CO_3 in DME (Scheme 11).[12f]



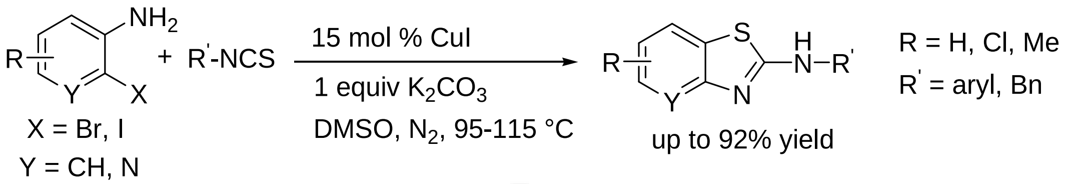
Scheme 11

While, Ding and co-workers have showed the synthesis of 2-aminobenzothioazoles from 2-iodoanilines and isothiocyanates employing CuI/1,10-phenanthroline in the presence of DABCO at moderate temperature (Scheme 12).[12g]



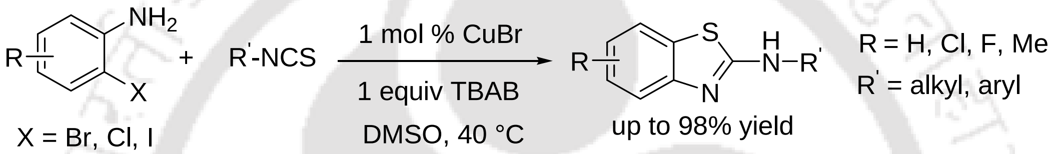
Scheme 12

The above reaction has been found to be effective by Bao and co-workers under ligand-free conditions (Scheme 13). The reactions of a variety of 2-haloanilines are demonstrated with isothiocyanates in good yields.[12h]



Scheme 13

Li and co-workers have accomplished the above protocol at lesser temperature in the presence of TBAB under base free conditions (Scheme 14).[12i]

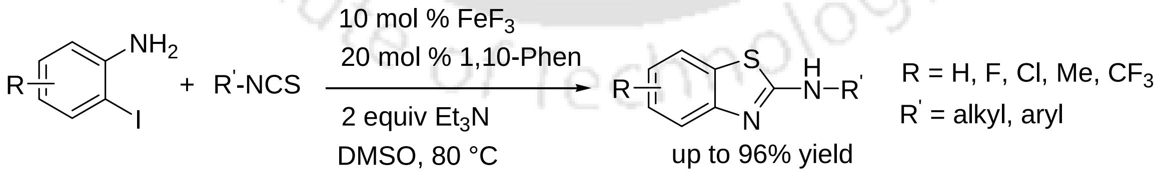


Scheme 14

1.3 Iron Catalysts

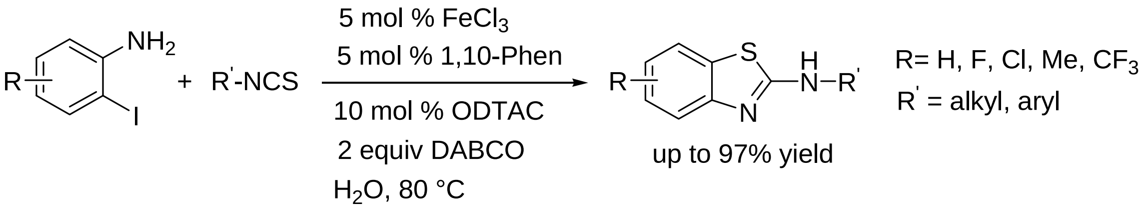
Few studies are focused on the use of iron-catalyzed cross-coupling reactions. The use of iron catalysts is attractive because it is cheap, environmentally benign and non toxic.

Li and co-workers have reported the synthesis of 2-aminobenzothiazoles from 2-haloanilines and isothiocyanates in the presence of FeF_3/1,10-phenanthroline in moderate to good yield (Scheme 15).[13a]



Scheme 15

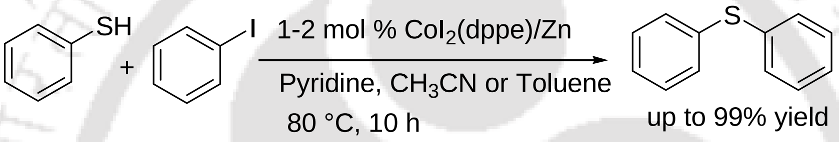
The above reaction has also been found to be effective utilizing $FeCl_3$ in water in the presence of octadecyltrimethylammonium chloride (ODTAC) (Scheme 16). The reaction media can be recovered and reused without loss of activity.[13b]



Scheme 16

1.4 Cobalt Catalysts

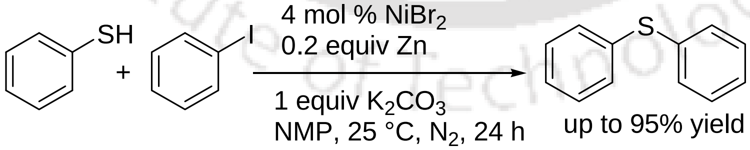
Cheng and co-authors have shown the synthesis of diaryl sulfide from aryl thiols and aryl iodides using CoI_2(dppe)/Zn in CH_3CN or toluene under reflux conditions (Scheme 17).[14] Aryl bromides have also been used for *S*-arylation of thiols under above reaction conditions.



Scheme 17

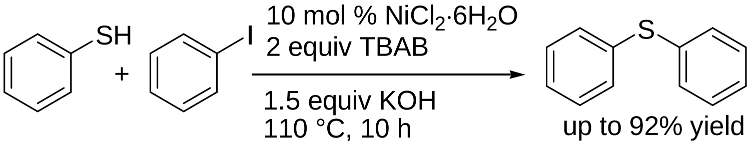
1.5 Nickel Catalysts

Few studies have also focused on nickel catalyzed *C-S* cross-coupling reactions. The combination of $NiBr_2$-dppf [dppf =1,1'-bis(diphenylphosphino ferrocene)] and Zn has been used for coupling of thiols with aryl iodides in the presence of K_2CO_3 at ambient temperature (Scheme 18).[15a]



Scheme 18

Our group has shown the synthesis of diaryl ether using $NiCl_2.6H_2O$ in the presence of TBAB from thiols with aryl iodides (Scheme 19).[15b] The products were separated from the solid material by extraction with diethyl ether and the insoluble catalyst can be recycled without loss of activity.

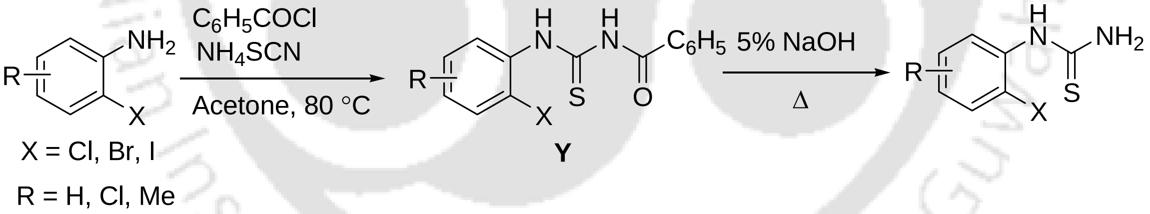


Scheme 19

1.6 Present Study

The first report of the synthesis of 2-(arylthio)arylcyanamides has been accomplished from *N*-(2-haloaryl)thiourea and aryl iodides employing copper-based systems. The reactions take place via intra- followed by intermolecular domino *C-S* cross-coupling reactions.

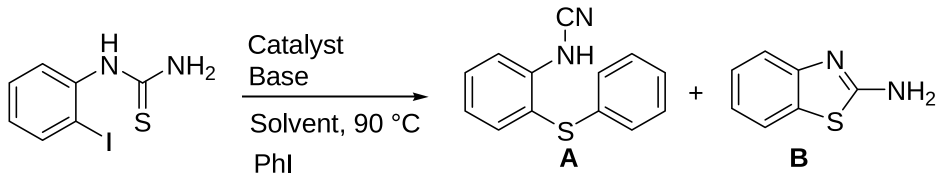
The reaction of 2-haloaniline, benzoylchloride and ammoniumisothiocyanate gave **Y** in acetone, which could be treated with NaOH to afford required substrate precursor *N*-(2-haloaryl)thiourea in good yield (Scheme 20).[16]



Scheme 20

The optimization of the reaction conditions was carried out with *N*-(2-iodophenyl)thiourea and iodobenzene as model substrates using different bases, solvents and copper sources at varied temperatures (Table 1). The best result was obtained when the reaction was pursued at 90 °C using 2.5 mol % of the copper salts such as $CuSO_4·5H_2O$, CuI, CuBr, Cu_2O, $CuBr_2$, $CuCl_2·2H_2O$ and $Cu(OAc)_2·H_2O$ in the presence of Cs_2CO_3 in DMSO affording the desired 2-(phenylthio)phenylcyanamide **A** in 100% conversion.The reactions with solvent, DMF, and base, K_2CO_3, required longer reaction time to afford **A** in quantitative yield. In contrast, the solvents such as, toluene, 1,4-dioxane, CH3CN and 2-propanol, and base, K3PO4, were less effective

Table 1. Optimization of the Reaction Conditions[a]



Entry	Catalyst	Solvent	Base	Time (h)	Product(s) (%)[b]	
					A	**B**
1	$CuSO_4 \cdot 5H_2O$	DMSO	Cs_2CO_3	3	100	n.d.
2	$CuSO_4 \cdot 5H_2O$	DMSO	K_2CO_3	6	100	n.d.
3	$CuSO_4 \cdot 5H_2O$	DMSO	$K_3PO_4 \cdot 3H_2O$	6	45	55
4	$CuSO_4 \cdot 5H_2O$	DMF	Cs_2CO_3	5	100	n.d.
5	$CuSO_4 \cdot 5H_2O$	Toluene	Cs_2CO_3	6	n.d.	100
6	$CuSO_4 \cdot 5H_2O$	1,4-Dioxane	Cs_2CO_3	6	n.d.	100
7	$CuSO_4 \cdot 5H_2O$	CH_3CN	Cs_2CO_3	6	40	60
8	$CuSO_4 \cdot 5H_2O$	2-Propanol	Cs_2CO_3	6	n.d.	100
9[c]	$CuSO_4 \cdot 5H_2O$	DMSO	Cs_2CO_3	5	65	35
10[d]	$CuSO_4 \cdot 5H_2O$	DMSO	Cs_2CO_3	5	59	41
11	CuI	DMSO	Cs_2CO_3	3	100	n.d.
12	CuBr	DMSO	Cs_2CO_3	3	100	n.d.
13	Cu_2O	DMSO	Cs_2CO_3	3	100	n.d.
14	$CuBr_2$	DMSO	Cs_2CO_3	3	100	n.d.
15	$CuCl_2 \cdot 2H_2O$	DMSO	Cs_2CO_3	3	100	n.d.
16	$Cu(OAc)_2 \cdot H_2O$	DMSO	Cs_2CO_3	3	100	n.d.

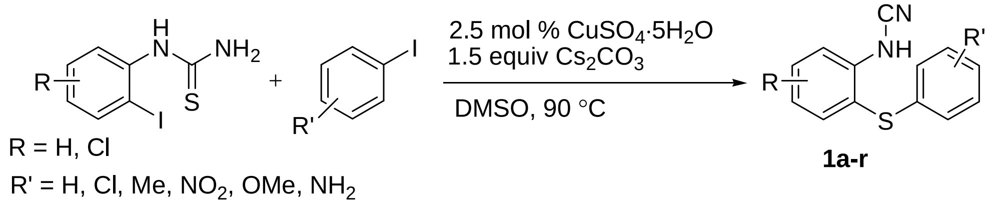
[a] *N*-(2-Iodophenyl)thiourea (0.5 mmol), iodobenzene (0.5 mmol), catalyst (2.5 mol %), base (0.75 mmol) and solvent (1 mL) were stirred at 90 °C.

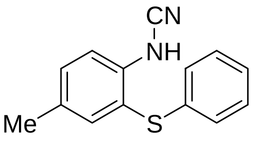
[b] Determined by ^1H NMR.

[c] Cs_2CO_3 (0.5 mmol) used.

[d] Reaction temperature 80 °C. n.d. = not detected.

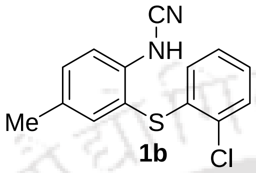
Table 2. Copper(II)-Catalyzed Domino Reaction of Substituted Thioureas with Aryl Iodides [a-b]





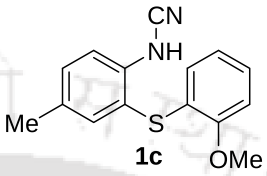
1a

5 h, 97%



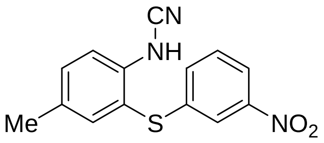
1b

5 h, 96%



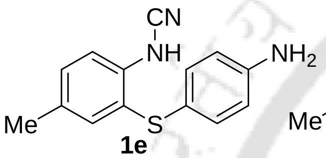
1c

7 h, 83%



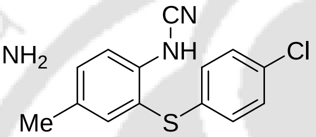
1d

8 h, 90%



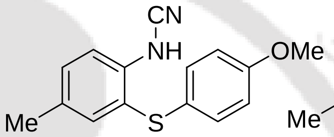
1e

5 h, 95%



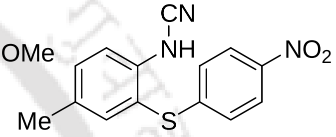
1f

5 h, 98%



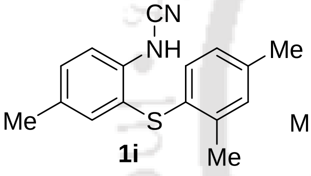
1g

8 h, 88%



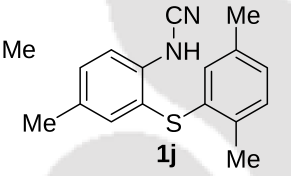
1h

5 h, 95%



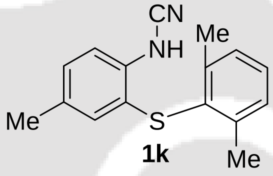
1i

5 h, 89%



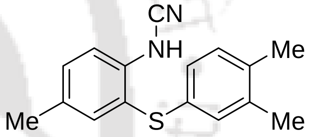
1j

5 h, 89%



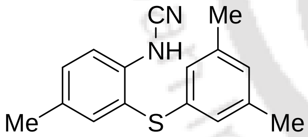
1k

5 h, 87%



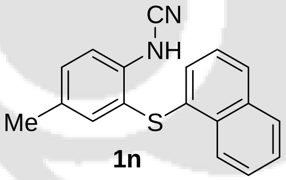
1l

5 h, 94%



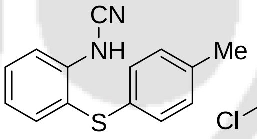
1m

7 h, 98%



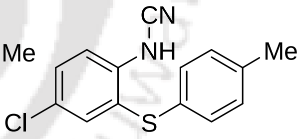
1n

7 h, 90%



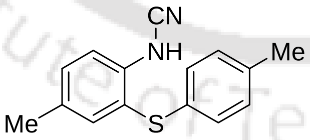
1o

3 h, 95%



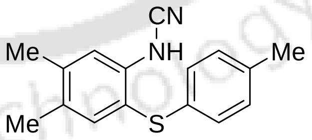
1p

3 h, 95%



1q

3 h, 91%



1r

3 h, 90%

[a] *N*-(2-Iodophenyl)thiourea (0.5 mmol), aryl iodide (0.5 mmol), $CuSO_4·5H_2O$ (2.5 mol %) and Cs_2CO_3 (0.75 mmol) were stirred at 90 °C in DMSO (1 mL).

[b] Isolated yield.

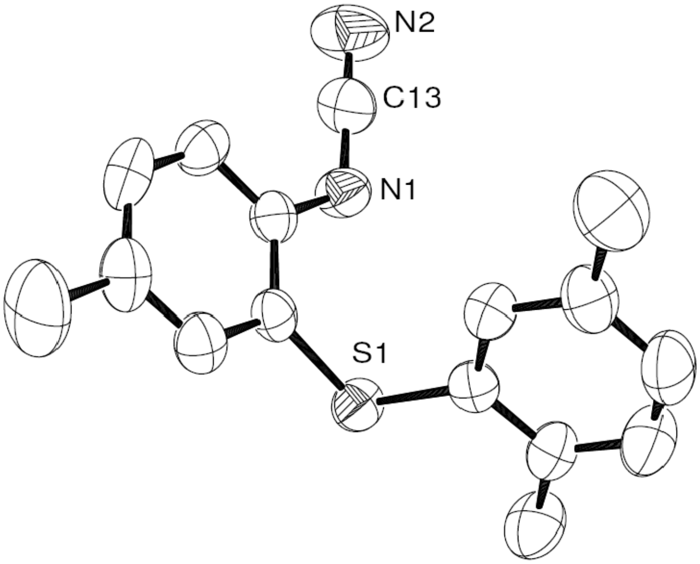


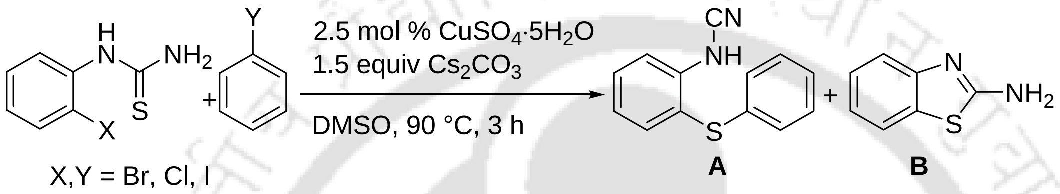
Figure 2. ORTEP diagram of 2-(2,5-dimethylphenylthio)-4-methylphenylcyanamide **1j** with 50% ellipsoid. H-atoms are omitted for clarity.

providing either aminobenzothiazole[17] **B** or a mixture of **A** and **B** as the product(s). Similarly, lowering of the reaction temperature (80 °C) or base (1 equiv) led to the formation of a mixture of **A** and **B**. The control experiment confirmed that in the absence of the copper salts no reaction was occured.

Encouraged by these results, we further pursued the scope of the process with respect to the other substrates. Aryl iodides having 2-Cl, 2-OMe, 3-NO_2, 4-NH_2, 4-Cl, 4-OMe, 4-NO_2, 2,4-dimethyl, 2,5-dimethyl, 2,6-dimethyl, 3,4-dimethyl and 3,5-dimethyl substituents and 1-naphthyl iodide proceeded reactions with *N*-(2-iodo-4-methylphenyl)thiourea to give the corresponding products **1a-n** in 83-98% yield (Table 2). Similarly, *N*-(2-iodophenyl)thiourea having 4-Cl, 4-Me and 4,5-dimethyl substituents underwent reactions with 1-iodo-4-methylbenzene gave target molecules **1o-r** in 90-95% yield (Table 2). These studies clearly reveal that the substrates having electron donating and -withdrawing groups are compatible with this process to afford the substituted 2-(arylthio)arylcyanamides in high yield. Recrystallization of 2-(2,5-dimethylphenylthio)-4-methylphenylcyanamide in MeOH provided single crystals whose X-ray structure is shown in figure 2.

Next, the reactions of the aryl halides were screened (Table 3). Iodobenzene proceeded reactions with *N*-(2-iodophenyl)thiourea to give 2-(phenylthio)phenylcyanamide **A** in 100% conversion. In contrast, bromobenzene and chlorobenzene exhibited moderate reactivity and yielding either a mixture of **A** and **B** or **B** as the sole product(s). In contrast, *N*-(2-bromo) and *N*-(2-chloro)phenylthioureas proceeded reactions with iodobenzene to afford **A** in <20% yield along with 2-halophenylcyanamide.

Table 3. Reactions of Aryl Halides[a]



Entry	X	Y	Product(s) (%)[b]	
			A	**B**
1	I	I	100	n.d.
2[c]	Br	I	20	n.d.
3[d]	Cl	I	<5	n.d.
4	I	Br	10	90
5	I	Cl	n.d.	100

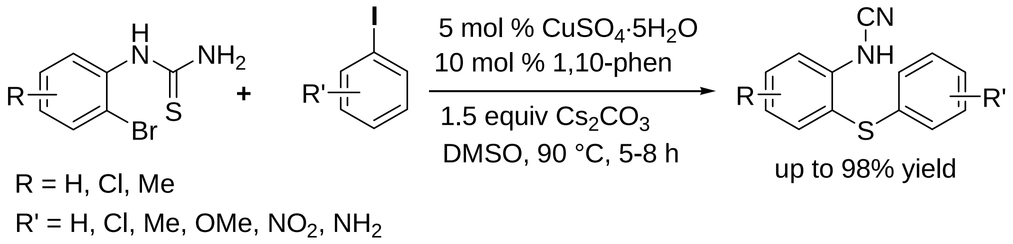
[a] Thiourea (0.5 mmol), aryl halide (0.5 mmol), $CuSO_4·5H_2O$ (2.5 mol %) and Cs_2CO_3 (0.75 mmol) were stirred at 90 °C for 3 h in DMSO (1 mL).

[b] Determined by 400 MHz ^{1}H NMR.

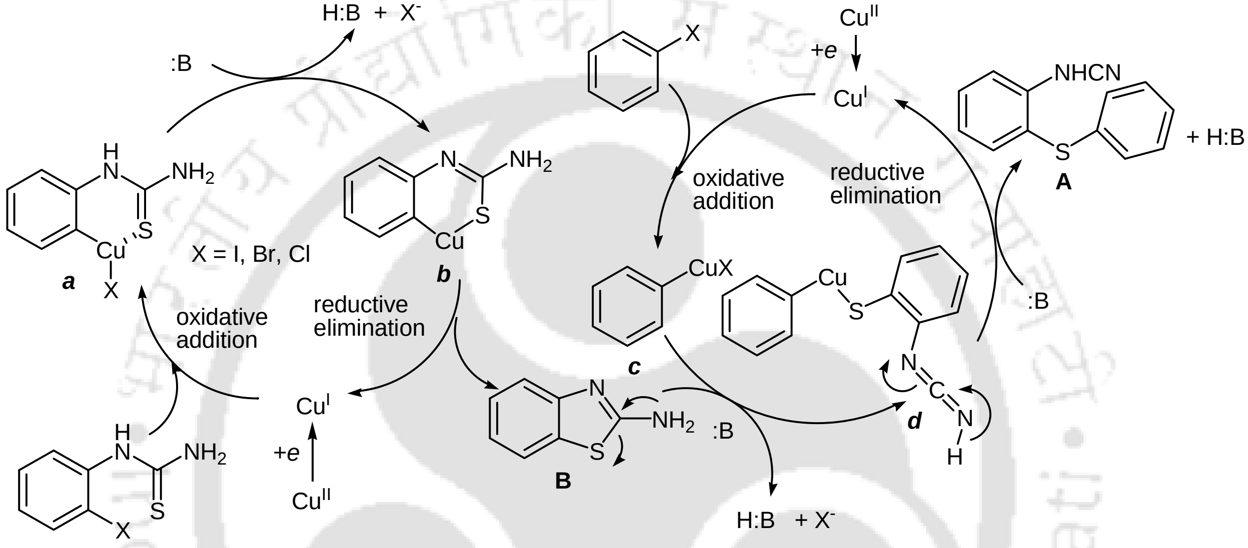
[c] *N*-(2-Bromophenyl)cyanamide obtained in 70% yield as a byproduct.

[d] *N*-(2-Chlorophenyl)cyanamide obtained in 82% yield as a byproduct.

However, the reaction of *N*-(2-bromo)phenylthiourea could be carried out with iodobenzene in the presenc of 1,10-phenanthroline to afford the target 2-(arylthio)arylcyanmides in excellent yield (Scheme 21). A sereis of substrates were examined and the reactions proceeded efficiently to afford the target products in 83-98% yield.



Scheme 21



Scheme 22. Proposed catalytic cycle

The proposed catalytic cycle is shown in Scheme 22. Reduction of the copper(II) salt with thiourea[18] can give copper(I) species which can undergo oxidative addition with *N*-(2-iodoaryl)thiourea to yield copper(III) intermediate ***a***. The latter can react with base to undergo intramolecular cyclization *via* ***b*** to give thiazole **B**. Oxidative addition of aryl iodide with copper(I) species can lead to the formation of ***c*** which can undergo intermolecular *C-S* cross-coupling reaction with thiazole **B** to give the intermediate ***d*** that can complete the catalytic cycle by reductive eliminaton of 2-(arylthio)arylcyanamide **A**. For example, when *N*-(2-iodoaryl)thiourea was reacted with $CuSO_4·5H_2O$ in the absence of iodobenzene, thiazole **B** was obtained in 0.5 h with 100% conversion. Moreover, thiazole **B** readily underwent reaction with iodobenzene in the presence of 2.5 mol % of $CuSO_4·5H_2O$ and 2.5 mol % of *N*-(2-iodoaryl)thiourea to afford the cyanamide **A** quantitatively. These studies clearly suggest that *N*-(2-iodoaryl)thiourea first may undergo intramolecular *C-S* cross-coupling reaction to give thiazole **B** which could be transformed to cyanamide **A** by intermolecular *C-S* cross-coupling reaction.

In summary, the synthesis of 2-(arylthio)arylcyanamides has been accomplihsed from *N*-(2-iodoaryl)thioureas and aryl iodides usisng copper-catalyzed intra- followed by intermolecular *C-S* cross-coupling reactions under ligand-free conditions. In case of *N*-(2-bromoaryl)thioureas, the reactions are effective using $CuSO_4 \cdot 5HO$ and 1,10-phenanthroline. However, the reactions are simple and general to afford the target products in hign yield under air.

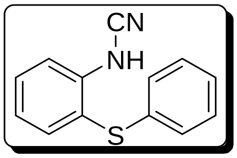
Experimental Section

General Information. Iodobenzene, bromobenzene, chlorobenzene, $CuSO_4 \cdot 5H_2O$ (98%), CuI (98%), CuBr (98%), Cu_2O (97%), $CuBr_2$ (99%), $CuCl_2 \cdot 2H_2O$ (99%) and $Cu(OAc)_2 \cdot H_2O$ (98%), Cs_2CO_3 and $K_3PO_4 \cdot 3H_2O$ were purchased from Aldrich and used without further purification. Substituted aryl iodides ware prepared according to procedure.[19] The solvents were purchased and dried according to standard procedure. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Varian 400 spectrometer. Infrared (IR) spectra recorded on a Perkin Elmer Spectrum one FT-IR spectrometer. Melting points were determined with a Büchi B-545 apparatus and are uncorrected. Elemental analyses were recorded with Perkin Elmer CHNS analyzer.

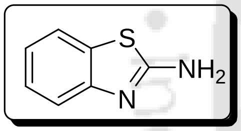
General Procedure for the Synthesis of 2-(Phenylthio)phenylcyanamides. *N*-(2-Iodoaryl)thiourea (0.5 mmol), aryl iodide (0.6 mmol), Cs_2CO_3 (244 mg, 0.75 mmol) and $CuSO_4 \cdot 5H_2O$ (2.5 mol %) were stirred at 70 ^{o}C for 0.5 h followed by 90 ^{o}C for the appropriate time in DMSO (1 mL). Progress of the reaction was monitored by TLC using ethyl acetate and hexane (1:9). The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (10 mL). The solution was washed successively with 1 N HCl (1 x 3 mL) and water (3 x 3 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to afford the titled 2-(arylthio)phenylcyanamide.

General Procedure for the Synthesis of *N*-(2-Haloaryl)thioureas. To a stirred solution of NH_4SCN (0.55 mmol) in acetone (2 ml) was added benzoyl chloride (0.55 mmol) and 2-

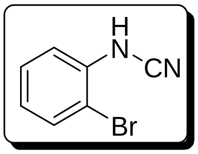
haloaniline (0.5 mmol) at room temperature and the mixture is heated under reflux for 30 min, then poured onto excess cracked ice with vigorous stirring. The resulting solid pH is adjusted to 8.5 with $NaHCO_3$ to remove the benzoic acid, then the resulting precipitate was recrystallized from ethanol to afford the *N*-(2-haloaryl)thiourea with pure form.



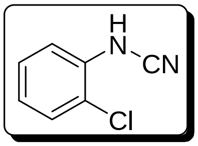
2-(Phenylthio)phenylcyanamide (Table 1, entry 1): White solid; yield 97%; mp 92-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 1.6 Hz, 7.6 Hz, 1H), 7.49 (td, *J* = 1.6 Hz, 7.6 Hz, 1H), 7.32 (dd, *J* = 1.2 Hz, 8.4 Hz, 1H), 7.26-7.21 (m, 2H), 7.18-7.08 (m, 2H), 7.01-6.99 (m, 1H), 6.95 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 137.7, 135.1, 131.9, 129.6, 127.1, 126.7, 124.3, 117.5, 115.4, 110.3; FT-IR (KBr) 3148, 2964, 2917, 2237, 1590, 1578, 1490, 1438, 1409, 1288, 1261, 1078, 1023 cm^{-1}. Anal. Calcd. for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38; S, 14.17. Found: C, 69.10; H, 4.44; N, 12.35; S 14.11.



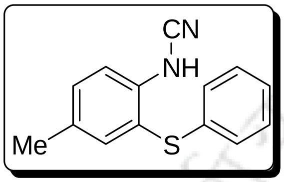
2-Benzothiazolamine[21] (Table 1, entry 6): White solid; mp 129-130 °C (lit.[22] mp 129 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (td, *J* = 8.0, 0.4 Hz, 1H), 7.51 (td, *J* = 8.0, 0.8 Hz, 1H), 7.31-7.27 (m, 1H), 7.11 (dt, *J* = 7.6, 1.2 Hz, 1H), 5.62 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 151.9, 131.0, 125.5, 121.4, 120.6, 118.2; FT-IR (KBr) 3396, 3063, 1626, 1530, 1444, 1309, 1105 cm^{-1}. Anal. Calcd. for $C_7H_6N_2S$: C, 55.97; H, 4.03; N, 18.65; S, 21.35. Found: C, 56.08; H, 4.01; N, 18.60; S 21.31.



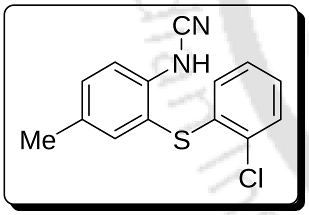
***N*-(2-Bromophenyl)cyanamide** (Table 3, entry 2): White solid; mp 95-96 °C (lit.[23] mp 94 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.35 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.28 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.96 (dt, *J* = 8.0, 1.6 Hz, 1H), 6.35 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 133.0, 129.2, 124.8, 116.2, 110.3, 109.9; FT-IR (KBr) 3146, 2907, 2838, 2236, 1601, 1583, 1491, 1423, 1287, 1146, 1027 cm^{-1}. Anal. Calcd. for $C_7H_5BrN_2$: C, 42.67; H, 2.56; N, 14.22. Found: C, 42.80; H, 2.53; N, 14.16.



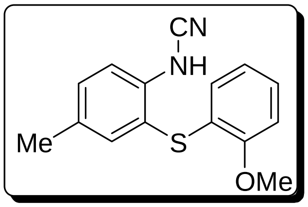
***N*-(2-Chlorophenyl)cyanamide**[24](Table 3, entry 3): White solid; mp 105-106 °C (lit.[25] mp 105-106 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 3H), 7.05-7.01 (m, 1H), 6.29 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 129.9, 128.5, 124.5, 120.4, 116.2, 110.1; FT-IR (KBr) 3162, 2914, 2877, 2842, 2243, 1598, 1500, 1426, 1295, 1112, 1048 cm^{-1}. Anal. Calcd. for $C_7H_5ClN_2$: C, 55.10; H, 3.30; N, 18.36. Found: C, 55.23; H, 3.28; N, 18.29.



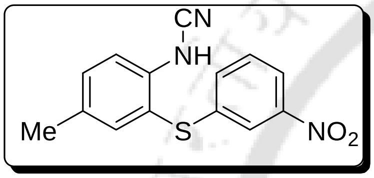
4-Methyl-2-(phenylthio)phenylcyanamide 1a: White solid; yield 97%; mp 127-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.30-7.19 (m, 5H), 7.04-7.01 (m, 2H), 6.81 (br s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.4, 135.3, 134.1, 132.7, 129.6, 127.0, 126.7, 115.3, 110.0, 20.7; FT-IR (KBr) 3210, 2922, 2224, 1605, 1580, 1497, 1439, 1405, 1388, 1286, 1154, 1025 cm^{-1}. Anal. Calcd. for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66; S, 13.34. Found: C, 70.09; H, 5.02; N, 11.62; S, 13.27.



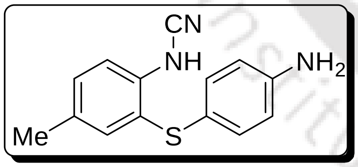
2-(2-Chlorophenylthio)-4-methylphenylcyanamide 1b: White solid; yield 96%; mp 147-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 4H), 7.12-7.05 (m, 2H), 6.76 (br s, 1H), 6.54-6.51 (m, 1H) 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 137.9, 134.8, 134.5, 133.2, 131.6, 130.0, 127.8, 127.3, 126.9, 115.5, 110.4, 20.7; FT-IR (KBr) 3132, 2923, 2233, 1683, 1604, 1495, 1449, 1290, 1154, 1115, 1028 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}N_2SCl$: C, 61.20; H, 4.04; N, 10.20; S, 11.67. Found: C, 61.28; H, 4.02; N, 10.16; S, 11.63.



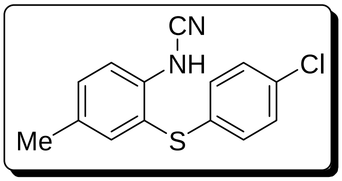
2-(2-Methoxyphenylthio)-4-methylphenylcyanamide 1c: White solid; yield 83%; mp 83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.25-7.18 (m, 4H), 6.89-6.84 (m, 3H), 3.98 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 138.0, 137.8, 133.9, 132.3, 130.1, 128.7, 123.2, 121.9, 117.8, 115.1, 111.1, 56.12, 20.6; FT-IR (KBr) 3060, 2935, 2242, 1670, 1579, 1499, 1473, 1388, 1270, 1243, 1023 cm^{-1}. Anal. Calcd. for $C_{15}H_{14}N_2SO$: C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.75; H, 5.19; N, 10.30; S, 11.81.



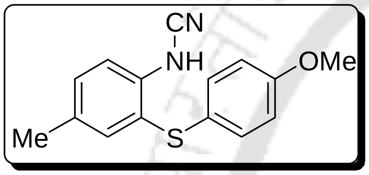
2-(3-Nitrophenylthio)-4-methylphenylcyanamide 1d: White solid; yield 90%; mp 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.98 (m, 1H), 7.85 (t, J = 1.6 Hz, 1H), 7.43-7.34 (m, 3H), 7.28 (d, J = 8.0 Hz, 1H), 7.24-7.21 (m, 1H), 6.73 (br s, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 138.6, 138.2, 137.7, 134.8, 133.8, 132.0, 130.3, 121.3, 115.9, 115.0, 110.1, 20.7; FT-IR (KBr) 3118, 2963, 2923, 2859, 2237, 1605, 1529, 1499, 1345, 1261, 1022 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}N_3SO_2$: C, 58.93; H, 3.89; N, 14.73; S, 11.24. Found: C, 59.02; H, 3.86; N, 14.68; S, 11.20.



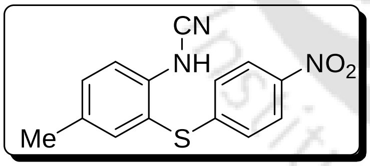
2-(4-Aminophenylthio)-4-methylphenylcyanamide 1e: White solid; yield 95%; mp 112-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.17 (d, J = 1.6 Hz, 2H), 7.03-7.01 (m, 2H), 6.84 (br s, 1H), 6.60 (d, J = 7.6 Hz, 2H), 3.74 (br s, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 136.2, 133.8, 131.5, 131.3, 121.8, 120.6, 116.2, 115.2, 110.9, 20.7; FT-IR (KBr) 3380, 2961, 2925, 2057, 2222, 2091, 1621, 1597, 1496, 1385, 1388, 1262, 1177 cm^{-1}. Anal. Calcd. for $C_{14}H_{13}N_3S$: C, 65.85; H, 5.13; N, 16.46; S, 12.56. Found: C, 65.96; H, 5.10; N, 16.41; S, 12.53.



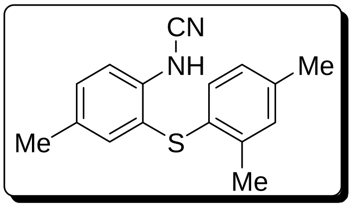
2-(4-Chlorophenylthio)-4-methylphenylcyanamide 1f: White solid; yield 98%; mp 104-105 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38 (s, 1H), 7.29 (d, *J* = 0.8 Hz, 1H), 7.27-7.21 (m, 3H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.78 (br s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.9, 137.4, 134.4, 133.9, 133.0, 132.7, 129.8, 128.4, 116.8, 115.5, 110.4, 20.7; FT-IR (KBr) 3183, 3028, 2921, 2960, 2853, 2232, 1892, 1605, 1580, 1563, 1495, 1473, 1387, 1288, 1262, 1155, 1090, 1051, 1008 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}N_2SCl$: C, 61.20; H, 4.04; N, 10.20; S, 11.67. Found: C, 61.31; H, 4.01; N, 10.14; S, 11.60.



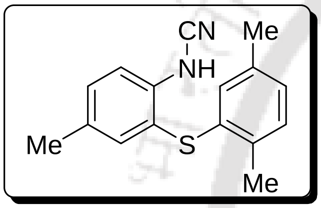
2-(4-Methoxyphenylthio)-4-methyiphenylcyanamide 1g: Gummy liquid; yield 88%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33 (s, 1H), 7.23-7.18 (m, 2H), 7.10-7.07 (m, 2H), 6.83-6.80 (m, 3H), 3.78 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.2, 136.9, 136.6, 134.0, 131.9, 130.5, 125.3, 119.5, 115.3, 115.2, 110.7, 55.6, 20.7; FT-IR (KBr) 2925, 2851, 2227, 1594, 1492, 1283, 1247, 1173, 1097, 1031 cm^{-1}. Anal. Calcd. for $C_{15}H_{14}N_2SO$: C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.76; H, 5.19; N, 10.31; S, 11.80.



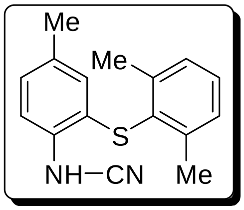
2-(4-Nitrophenylthio)-4-methylphenylcyanamide 1h: Gummy liquid; yield 95%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.40 (dd, *J* = 2.0 Hz, 6.8 Hz, 2H), 7.65 (dd, *J* = 2.0 Hz, 6.8 Hz, 2H), 7.12 (s, 1H), 6.92-6.90 (m, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 141.9, 137.9, 132.9, 131.0, 129.3, 126.9, 125.2, 124.5, 122.7, 121.2, 110.0, 20.8; FT-IR (KBr) 2923, 2857, 2208, 1628, 1514, 1341, 1248, 1108, 1034 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}N_3SO_2$: C, 58.93; H, 3.89; N, 14.73; S, 11.24. Found: C, 59.04; H, 3.87 ; N, 14.65; S, 11.19.



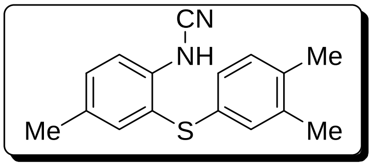
2-(2,4-Dimethylphenylthio)-4-methylphenylcyanamide 1i: Gummy liquid; yield 89%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28-7.21 (m, 3H), 7.01 (s, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.72 (br s, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 2.36 (s, 3H), 2.30 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.1, 137.0, 136.7, 136.2, 134.2, 132.0, 131.7, 130.5, 127.9, 127.1, 117.8, 115.3, 110.7, 21.0, 20.7, 20.2; FT-IR (KBr) 2923, 2857, 2235, 2098, 1615, 1498, 1380, 1259, 1237, 1049 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_2S$: C, 71.61; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.70; H, 5.98; N, 10.40; S, 11.92.



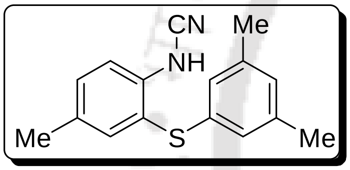
2-(2,5-Dimethylphenylthio)-4-methylphenylcyanamide 1j: White solid; yield 89%; mp 155-156 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.29-7.22 (m, 3H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 6.8 Hz, 1H), 6.66 (br s, 1H), 6.39 (s, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.6, 137.2, 137.0, 134.2, 133.8, 133.0, 132.3, 130.7, 127.5, 126.9, 126.8, 115.3, 110.7, 21.3, 20.7, 19.8; FT-IR (KBr) 3144, 2984, 2917, 2859, 2230, 1604, 1584, 1498, 1449, 1413, 1391, 1289, 1270, 1213, 1153, 1057 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_2S$: C, 71.61; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.75; H, 5.99; N, 10.39; S, 11.87.



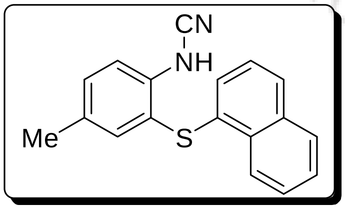
2-(2,6-Dimethylphenylthio)-4-methylphenylcyanamide 1k: White solid; yield 87%; mp 128 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.26-7.21 (m, 2H), 7.17-7.12 (m, 1H), 6.99 (dd, *J* = 0.8 Hz, 8.4 Hz, 2H), 6.57 (s, 1H), 6.40 (br s, 1H), 2.38 (s, 3H), 2.32 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 143.2, 134.2, 133.4, 130.5, 130.0, 129.6, 129.0, 128.6, 122.7, 115.5, 111.1, 22.1, 20.9; FT-IR (KBr) 3114, 2981, 2877, 2226, 1580, 1488, 1392, 1245, 1209, 1049, 1030 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_2S$: C, 71.61; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.69; H, 6.00 ; N, 10.40; S, 11.91.



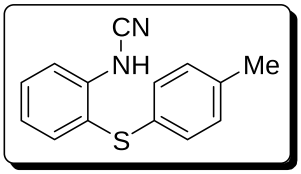
2-(3,4-Dimethylphenylthio)-4-methylphenylcyanamide 1l : White solid; yield 94%; mp 95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.26-7.20 (m, 2H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.88 (s, 1H), 6.83 (br s, 1H), 6.79-6.76 (m, 1H), 2.31 (s, 3H), 2.26 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.5, 137.0, 135.7, 134.0, 132.2, 131.6, 130.9, 129.0, 125.3, 118.2, 115.2, 20.7, 20.0, 19.5; FT-IR (KBr) 3175, 2917, 2226, 1892, 1596, 1486, 1385, 1286, 1155, 1021 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_2S$: C, 71.61; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.78; H, 5.99; N, 10.39; S, 11.84.



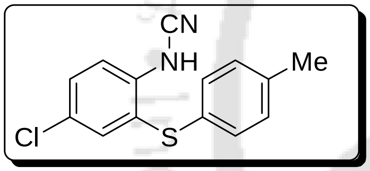
2-(3,5-Dimethylphenylthio)-4-methylphenylcyanamide 1m: Light yellow solid; yield 98 %; mp 136-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.28-7.20 (m, 2H), 6.81-6.80 (m, 2H), 6.65-6.64 (m, 2H), 2.32 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 137.8, 137.3, 134.7, 134.0, 132.4, 128.7, 124.9, 117.6, 115.3, 110.6, 21.4, 20.7; FT-IR (KBr) 3205, 2919, 2856, 2226, 1732, 1599, 1578, 1489, 1384, 1288, 1154, 1037 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_2S$: C, 71.61; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.72; H, 5.98; N, 10.38; S, 11.92.



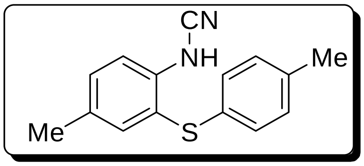
4-Methyl-2-(naphthalene-1-ylthio)phenylcyanamide 1n: White solid; yield 90%; mp 104-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.8 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.60-7.51 (m, 2H), 7.38 (s, 1H), 7.30-7.25 (m, 3H), 6.82 (dd, *J* = 0.8 Hz, 7.2 Hz, 1H), 6.75 (br s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 137.3, 134.3, 134.1, 132.5, 132.3, 131.1, 128.9, 127.2, 126.9, 126.8, 126.1, 124.4, 123.8, 116.8, 115.5, 20.7; FT-IR (KBr) 2925, 2851, 2214, 1625, 1511, 1382, 1251, 1031 cm^{-1}. Anal. Calcd. for $C_{18}H_{14}N_2S$: C, 74.45; H, 4.86; N, 9.65; S, 11.04. Found: C, 74.58; H, 4.88; N, 9.59; S, 10.95.



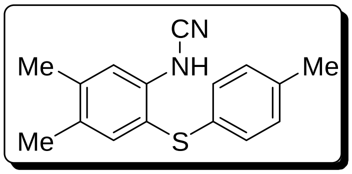
2-(*p*-Tolylthio)phenylcyanamide 1o: White solid: yield 95%; mp 87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.12-7.07 (m, 3H), 6.97 (d, *J* = 7.2 Hz, 2H), 6.93 (br s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 137.3, 137.1, 131.6, 131.3, 130.4, 127.9, 127.8, 124.3, 115.4, 110.3, 21.1; FT-IR (KBr) 3153, 2964, 2238, 1616, 1588, 1577, 1488, 1407, 1287, 1164, 1019 cm^{-1}. Anal. Calcd. for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66; S, 13.34. Found: C, 70.09; H, 5.00; N, 11.60; S, 13.31.



2-(*p*-Tolylthio)-4-chlorophenylcyanamide 1p: White solid; yield 95%; mp 130-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.4 Hz, 1H), 7.40-7.37 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.10-7.06 (m, 2H), 7.02-6.99 (m, 2H), 6.84 (br s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 137.8, 135.9, 131.1, 130.9, 130.6, 130.1, 128.9, 121.1, 116.5, 110.0, 21.1; FT-IR (KBr) 3153, 2919, 2237, 1572, 1486, 1455, 1408, 1384, 1284, 1260, 1100, 1017 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}N_2SCl$: C, 61.20; H, 4.04; N, 10.20; S, 11.67. Found: C, 61.32; H, 4.01; N, 10.15; S, 11.60.



2-(*p*-Tolylthio)-4-methylphenylcyanamide 1q: White solid; yield 91%; mp 94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.27-7.20 (m, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.97-6.95 (m, 2H), 6.83 (br s, 1H), 2.31 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 137.1, 136.9, 134.0, 132.2, 131.5, 130.3, 127.7, 118.0, 115.3, 110.7, 21.1, 20.7; FT-IR (KBr) 3154, 2922, 2862, 2232, 1607, 1581, 1948, 1453, 1410, 1389, 1388, 1268, 1155, 1018 cm^{-1}. Anal. Calcd. for $C_{15}H_{14}N_2S$: C, 70.83; H, 5.55; N, 11.01; S, 12.61. Found: C, 70.98; H, 5.51; N, 10.97; S, 12.54.



2-(*p*-Tolylthio)-4,5-dimethylphenylcyanamide 1r: White solid; yield 90%; mp 95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.09 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.92-6.90 (m, 2H), 6.74 (br s, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 138.5, 137.7, 136.9, 133.2, 132.4, 130.6, 127.6, 116.8, 114.9, 111.1, 21.4, 20.4, 19.4; FT-IR (KBr) 3157, 2917, 2230, 1608, 1567, 1498, 1411, 1272, 1197, 1081, 1022 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_2S$: C, 71.61; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.77; H, 5.98; N, 10.40; S, 11.85.

1.7 References

(1) For some recent reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (b) Hartwig, J. F. *Synlett* **2006**, 1283. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (d) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (e) Evano, G.; Blanchard, N.; Toymi, M. *Chem. Rev.* **2008**, *108*, 3054. (f) Kondo, T.; mitsudo, T.-A. *Chem. Rev.* **2000**, *100*, 3205. (g) Choi, T. A.; Czerwonka, R.; Forke, R.; Jaeger, A.; Knoell, J.; Krahl, M. P.; Krause, T.; Reddy, K. R.; Franzblau, S.G.; Knoelker, H.-J. *Med. Chem. Res.* **2008**, *17*, 374. (h) Correa, A.; García Mancheño, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (i) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954. (j) Würtz S.; Glorius F. *Acc. Chem. Res.* **2008**, *41*, 1523.

(2) For some studies on *C-S* coupling reactions, see: (a) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D.; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606. (b) Li, G. Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 1513. (c) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (d) Sperotto, E.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *J. Org. Chem.* **2008**, *73*, 5625. (e) Rout, L.; Saha, P.; Jammi, S.; Punniyamurthy, T. *Eur. J. Org. Chem.* **2008**, *4*, 640. (f) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 2880. (g) Buchwald, S. L.; Bolm, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5586.

(3) (a) Suzuki, H.; Abe, H.; Osuka, A. *Chem. Lett.* **1981**, 151. (b) Andersson, C. M.; Hallberg, A.; Hugberg, T. *Adv. Drug. Res.* **1996**, *28*, 65. (c) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (d) Yamamoto, T.; Sekine, Y. *Can. J. Chem.* **1984**, *62*, 1544. (e) Van Bierbeek, A.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 6283.

(4) For some studies on cyanamide synthesis, see: (a) Kaupp, G.; Schmeyers, J.; Boy, J.; *Chem. Eur. J.* **1998**, *4*, 2467. (b) Sato, R.; Itoh, K.; Nishina, H.; Goto, T.; Saito, M. *Chem. Lett*. **1984**, 1913. (c) Bakunov, S. A.; Rukavishnikov, A. V.; Tkachev, A. V. *Synthesis* **2000**, 1148. (d) Chen, C.-Y.; Wong, F. F.; Huang, J. J.; Lin, S.-K.; Yeh, M.-Y. *Tetrahedron Lett*. **2008**, *49*, 6505. (e) Chaudhuri, K. H.; Mahajan, U. S.; Bhalerao, D. S.; Akamanchi, K. G. *Synlett* **2007**, 2815.

(5) For structure and reactivity of cyanamides, see: (a) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations*, Vol. 3, Academic, New York, 1972, 286. (b) Miyasaka, H.; Clerac, R.; Campos-Fernandez, C. S.; Dunbar, K. R. *Inorg. Chem*. **2001**, *40*, 1663. (c) Hollebone, B. R.; Nyholm, R. S. *J. Chem. Soc*. A **1971**, 332. (d) Pombeiro, A. J. L. *Inorg. Chim. Acta* **1992**, *198*, 179. (e) Kamijo, S.; Jin, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2002**, *41*, 1780. (f) Brand, H.; Mayer, P.; Schulz, A.; Soller, T.; Villinger, A. *Chem. Asian. J.* **2008**, *3*, 1050. (g) Renodon-Corniere, A.; Dijols, S.; Perollier, C.; Lefevre-Groboillot, D.; Boucher, J.-L.; Attias, R.; Sari, M.-A.; Stuehr, D.; Mansuy, D. *J. Med. Chem*. **2002**, *45*, 944. (h) Hughes, T. V.; Hammond, S. D.; Cava, M. P. *J. Org. Chem.* **1998**, *63*, 401.

(6) McCall, J. M.; TenBrink, R. E.; Ursprung, J. J. *J. Org. Chem*. **1975**, *40*, 3304.

(7) (a) Hu, L. Y.; Guyo, J.; Magar, S. S.; Fischer, J. B.; Burke-Howie, K. J.; Durant, G. J. *J. Med. Chem*. **1997**, *40*, 4281. (b) Robinson, J. R.; Brown, W. H. *Can. J. Chem*. **1951**, *29*, 1069.

(8) (a) Sandler, S. R.; Karo, W. Organic Functional Group Preparations, Vol 2; Academic: New York, 1972, 174. (b) Nickon, A.; Fieser, L. F. *J. Am. Chem. Soc.* **1952**, *74*, 5566. (c) Jia, Q.; Cai, T.; Haung, M.; Li, H.; Xian, M.; Poulos, T. L.; Wang, P. G. *J. Med. Chem.* **2003**, *46*, 2271. (d) Cai, T.; Xian, M.; Wang, P. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1507. (e) Kumar, L. V.; Kaushik, M. P.; Mazumdar, A. *Eur. J. Org. Chem.* **2008**, 1910. (f) Saneyoshi, M.; Tokuzen, R.; Maeda, M.; Fukuoka, F. *Chem. Pharm. Bull.* **1968**, *16*, 505.

(9) Stephens, R. W.; Domeier, L. A.; Todd, M. G.; Nelson, V. A. *Tetrahedron Lett.* **1992**, *33*, 733.

(10) (a) Gilman, G.; Goodman, L. S.; Rall, T. W.; Murad, F. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 7th ed., Pergamon Press: New York, 1990, 89. (b) Saneyoshi, M.; Tokuzen, R.; Maeda, M.; Fukuoka, F. *Chem. Pharm. Bull.* **1968,** *16*, 505. (c) Nickon, A.; Fieser, L. F. *J. Am. Chem. Soc.* **1952**, *74*, 5566. (d) Jia, Q.; Cai, T.; Huang, M.; Li, H.; Xian, M.; Poulos, T. L.; Wang, P. G. *J. Med. Chem.* **2003**, *46*, 2271. (e) Kumar, L.; Kaushik, M. P.; Mazumdar, A. *Eur. J. Org. Chem.* **2008**, 1910.

(11) (a) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385. (b) Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3657. (c) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677. (d) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147. (e) Joyce, L. L.; Batey, R. A. *Org. Lett.* **2009**, *11*, 2792.

(12) (a) Fernandez Rodrıguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (b) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (c) Sperotto, E.; Klink, G. P. M. V.; Vries, J. G. D.; Koten, G. V. **2008**, *73*, 5625. (d) Rout, L.; Sen, T. K.; Punniyamurthy, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5583. (e) Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719. (f) Joyce, L. L.; Evindar, G.; Batey, R. A. *Chem. Commun.* **2004**, 446. (g) Ding, Q.; He, X.; Wu, J. *J. Comb. Chem.* **2009**, *11,* 587. (h) Shen, G.; Lv, X.; Bao, W. *Eur. J. Org. Chem.* **2009**, 5897. (i) Guo, Y.-J.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *Tetrahedron Lett.* **2010**, *51*, 649.

(13) (a) Qiu, J.-W.; Zhang, X.-G.; Tang, R-Y; Zhong, P.; Lia, J.-H. *Adv. Synth. Catal.* **2009**, *351*, 2319. (b) Ding, Q.; Cao, B.; Liu, X.; Zong, Z.; Peng, Y.-Y. *Green Chem.* **2010**, *12*, 1607.

(14) Ying, C. W.; Thiruvellore, T.; Cheng, C.-H. *Org. Lett.* **2006**, *8,* 5613.

(15) (a) Cristau, H. J.; Chabaud, B.; Chene, A.; Christol, H. *Synthesis* **1981**, 892. (b) Jammi, S.; Barua, P.; Rout, L.; Saha, P.; Punniyamurthy, T. *Tetrahedron Lett.* **2008**, *49*, 1484.

(16) Rasmussen, C. R.; Villani Jr., F. J.; Weaner, L. E.; Reynolds, B. E.; Hecker, A. R.; Hood, A. R.; Nortey, S. O.; Hanslin, A.; Costanzo, M. J.; Powell, E. T.; Molinari, A. J. *Synthesis* **1988**, 456.

(17) (a) Ding, Q.; He, X.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 587. (b) Wang, J.; Peng, F.; Jiang, J.; Lu, Z.; Wang, L.; Bai, J.; Pan, Y. *Tetrahedron Lett.* **2008**, *49*, 467.

(18) For the reduction of copper(II) salts to copper(I) species using thiourea, see: Bowmaker, G. A.; Hanna, J. V.; Pakawatchai, C.; Skelton, B. W.; Thanyasirikul, Y.; White, A. H. *Inorg. Chem.* **2009**, *48*, 350.

(19) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. In *Vogel's Textbook of Practical Organic Chemistry*, Fifth Edition, Pearson Education Pte. Ltd., Indian Branch, Delhi, 2004, 928.

(20) Fajkusova, D.; Pazdera, P. *Synthesis* **2008**, 1297.

(21) Bhargava, P. N.; Baliga, B. T. *J. Indian Chem. Soc.* **1958**, *35*, 807.

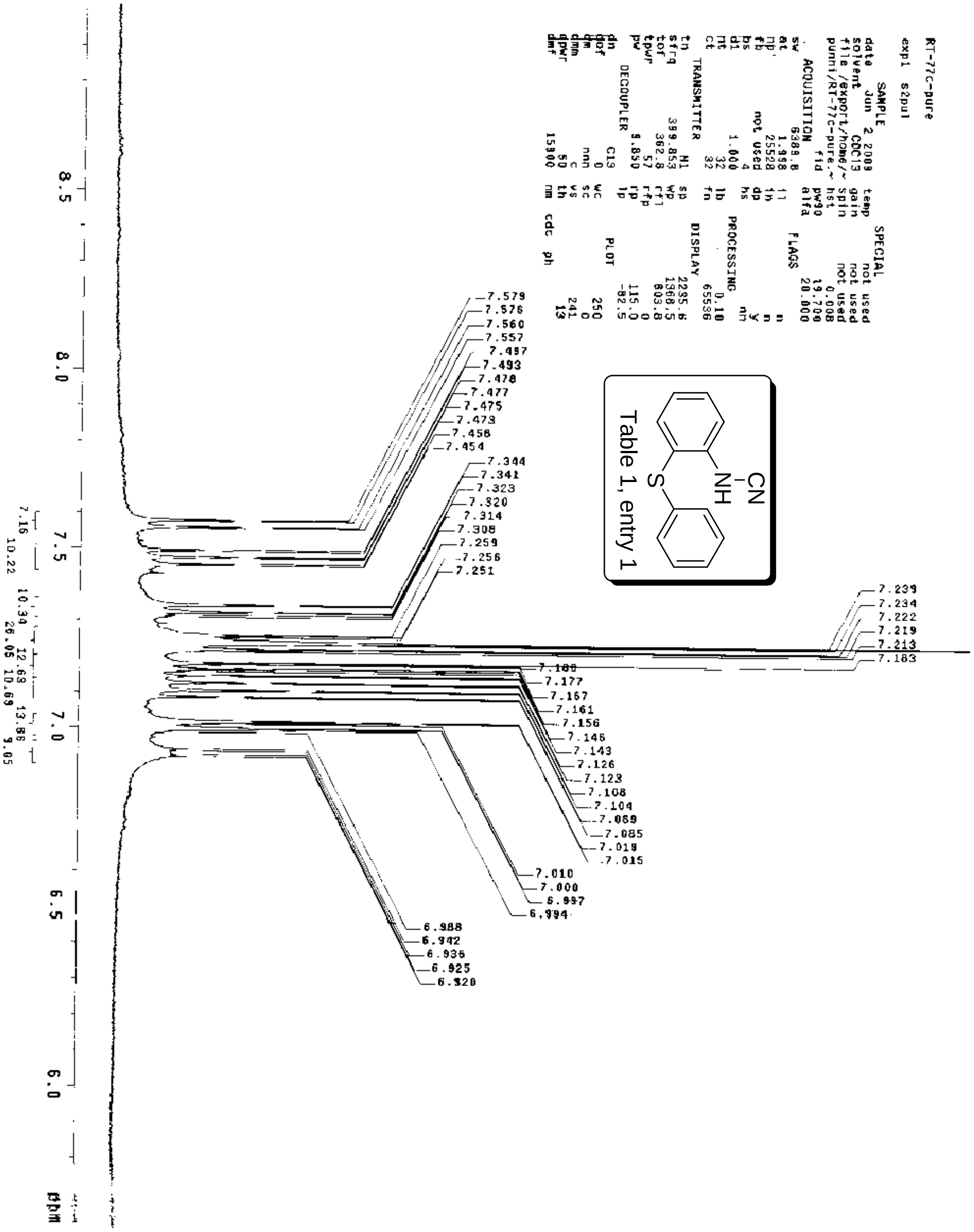
(22) Pierron, P. *Bull. Soc. Chim. Fr.* **1907**, *35*, 1197.

(23) Ghosh, H.; Yella, R.; Ali, A. R.; Sahoo, S. K.; Patel, B. K. *Tetrahedron Lett.* **2009**, *50*, 2407.

(24) Bunnett, J. F.; Hrutfiord, B. F. *J. Am. Chem. Soc.* **1961**, *83*, 1691.

Crystal Data for 2-(2,5-dimethylphenylthio)-4-ethylphenylcyanamide at 296(2) K

Identification code	**1j**	
Empirical formula	$C_{16}H_{16}N_2S$	
Formula weight	268.38	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	*P*na2(1)	
Unit cell dimensions	*a* = 22.1067(10)Å	α(°)= 90
	b = 8.7972(4) Å	β(°)= 90
	c = 7.6712(3) Å	γ(°)= 90
Volume	V = 1491.87(11) $Å^3$	
Z	4	
Density (calculated)	1.195 mg/m^3	
Absorption coefficient	0.315 mm^{-1}	
F(000)	568.0	
Crystal size	0.40×0.35×0.20 mm^3	
Index ranges	-29<=h<=29, -11<=k<=11, -10<=l<=9	
Reflections collected	2067	
Independent reflections	2023 [R (int) = 0.0640]	
Completeness to theta = 28.72°	98.1 %	
Max. and min. transmission	0.902 and 0.950	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3857 / 1 /179	
Goodness-of-fit on F^2	1.005	
Final R indices [I>2sigma (I)]	*R1* = 0.0396, *wR2* = 0.0654	
R indices (all data)	*R1* = 0.0798, *wR2* = 0.0705	


RT-77C-pure
exp1 s2pul
SAMPLE
SPECIAL
ACQUISITION
FLAGS
PROCESSING
TRANSMITTER
DISPLAY
DECOUPLER
PLOT
CN
NH
S
Table 1, entry 1
7.579
7.576
7.560
7.557
7.497
7.493
7.478
7.477
7.475
7.473
7.456
7.454
7.344
7.341
7.323
7.320
7.314
7.308
7.259
7.256
7.251
7.239
7.234
7.222
7.219
7.213
7.183
7.180
7.177
7.167
7.161
7.156
7.146
7.143
7.126
7.123
7.108
7.104
7.089
7.085
7.019
7.015
7.010
7.000
6.997
6.994
6.988
6.942
6.936
6.925
6.920
7.16
10.22
10.34
12.69
26.06
10.69
13.88
9.05
8.5
8.0
7.5
7.0
6.5
6.0
ppm

```
RT-79-13c

exp1  s2pul

      SAMPLE               SPECIAL
date   Jun 12 2009   temp        not used
solvent      CDCl3   gain        not used
file           exp   spin        not used
   ACQUISITION       hst            0.008
sw         25125.6   pw90          18.600
at           1.199   alfa          20.000
rp           60270          FLAGS
fb           13600   il                 n
ts              16   in                 n
d1           1.000   dp                 y
rt            2000   hs                nn
ct             592        PROCESSING
   TRANSMITTER       lb              2.00
tn             C13   fn             65536
sfrq       100.554          DISPLAY
tof         1536.3   sp            6410.8
tpwr            61   wp           11059.9
pw           9.300   rfl           9279.0
    DECOUPLER        rfp           7764.9
dn              H1   rp               2.9
dof              0   lp            -480.5
dm             yyy           PLOT
dmm              w   wc               250
dpwr            42   sc                 0
dmf           8900   vs                39
                     th                 3
                     nn  ro  ph
```

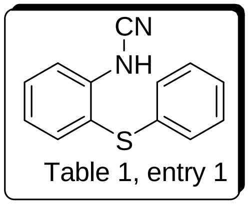
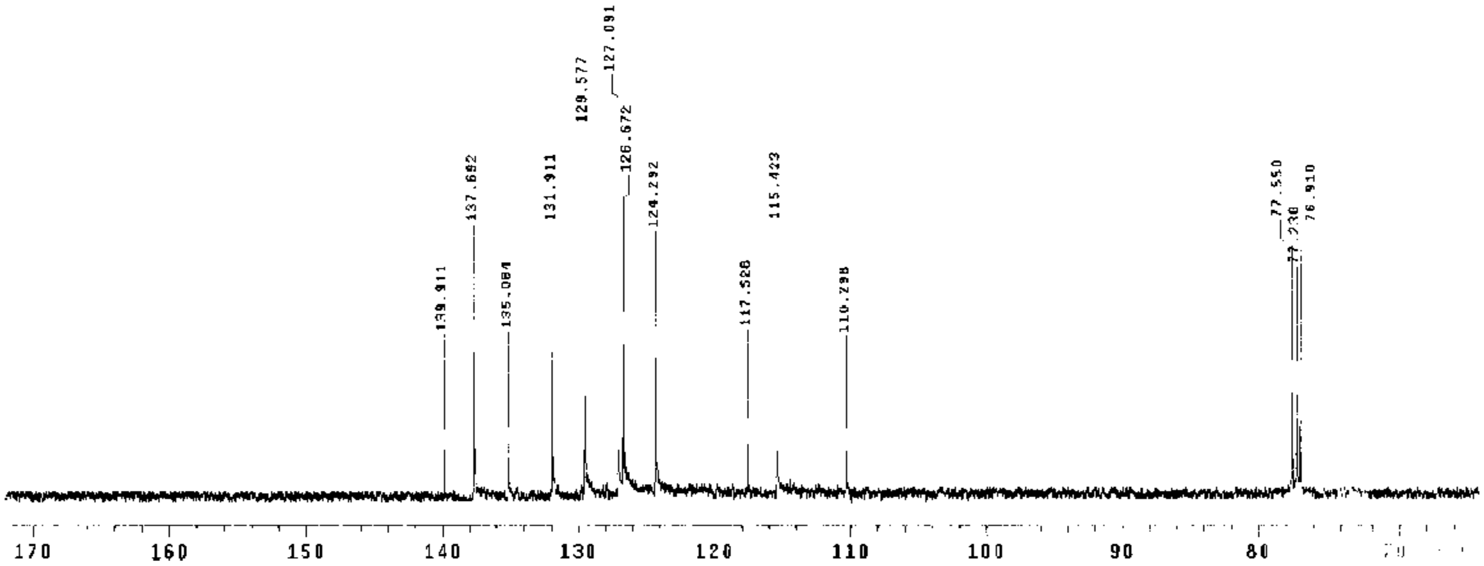
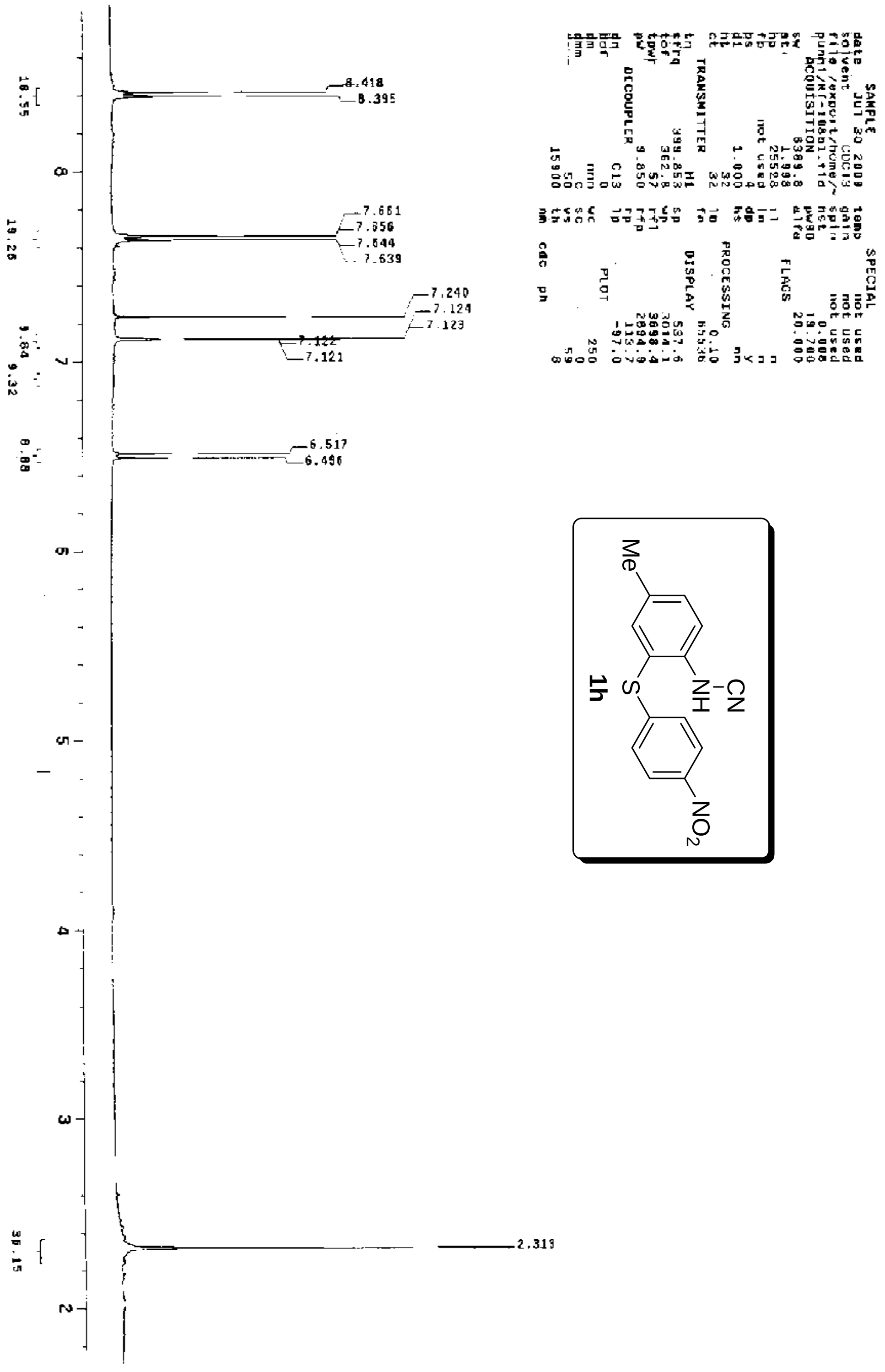
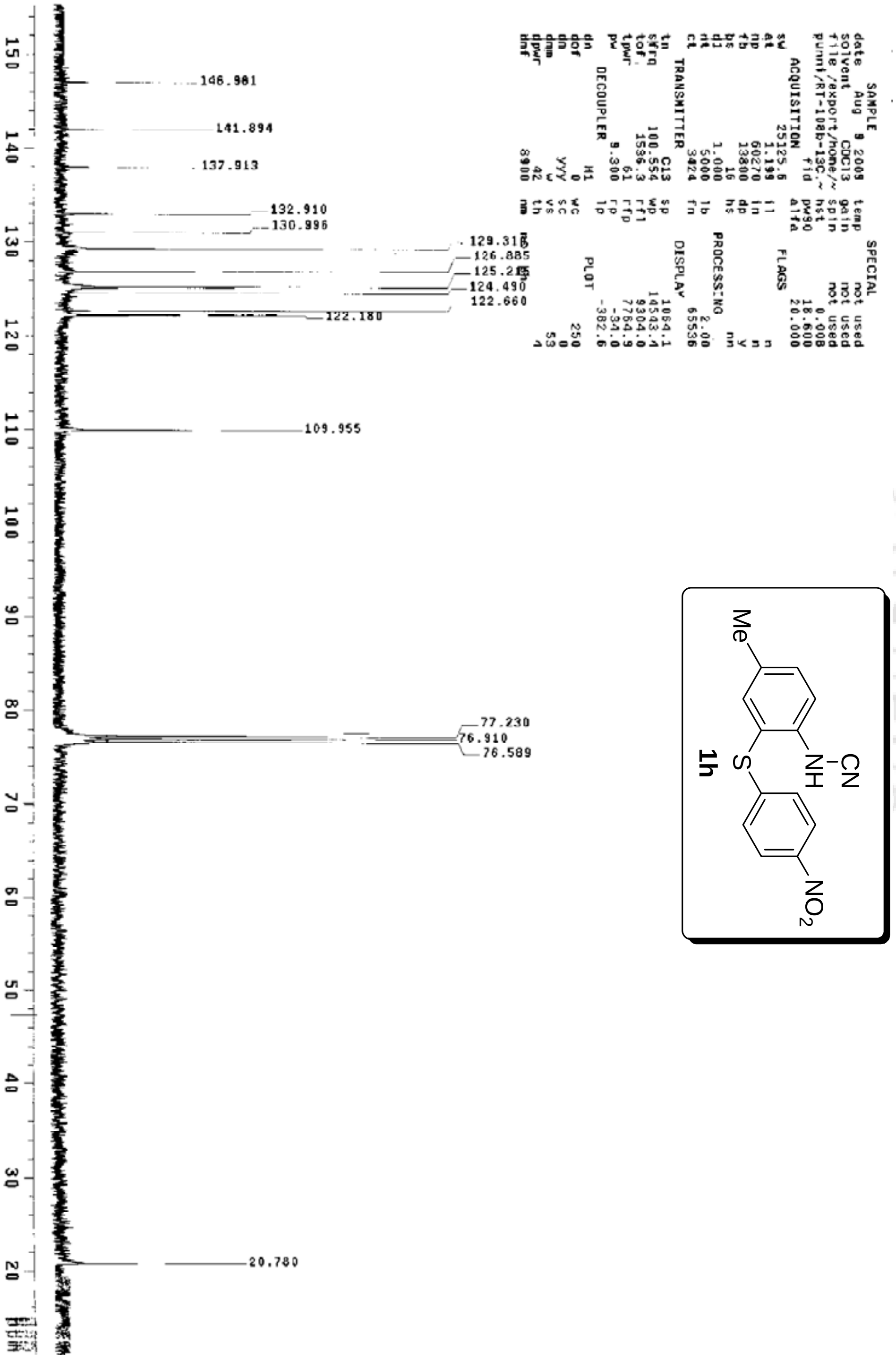


Table 1, entry 1




8.418
8.395
7.661
7.656
7.644
7.639
7.240
7.124
7.123
7.122
7.121
6.517
6.496
2.319
8
7
6
5
4
3
2
18.55
19.26
9.84
9.32
8.88
38.15
CN
NH
S
Me
NO2
1h


146.981
141.894
137.913
132.910
130.996
129.316
126.885
125.215
124.490
122.660
122.180
109.955
77.230
76.910
76.589
20.780
150
140
130
120
110
100
90
80
70
60
50
40
30
20
Me
CN
NH
S
NO2
1h

Chapter II

Copper(I)-Catalyzed Synthesis of 2-(Arylselanyl)arylcyanamides from *N*-(2-Iodoaryl)selenourea with Aryl Iodides

Selenium containing compounds like organoselenides are stable, easily handled, nucleophilic and radicophilic species. Thus, they have an important role in organic chemistry.[1] They have been used as intermediates for the synthesis of important biologically and pharmaceutically active compounds such as selenoxides, selenimines and selenide dihalides (Figure 1).[2] Hence, various traditional methods have been reported on the construction of *C-Se* bond formation.[3] However, those reports often require photochemical, strong reducing reagents, highly toxic gas and harsh reaction conditions such as the use of polar solvents, high temperature, toxic solvents like HMPA. Some of these drawbacks have been recently overcome by the development of more sustainable *C-Se* cross-coupling reactions using copper, palladium and nickel based catalysts under comparatively milder reaction conditions.

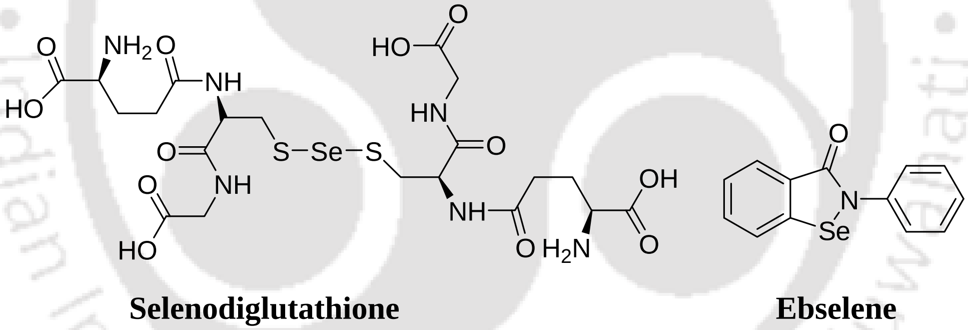
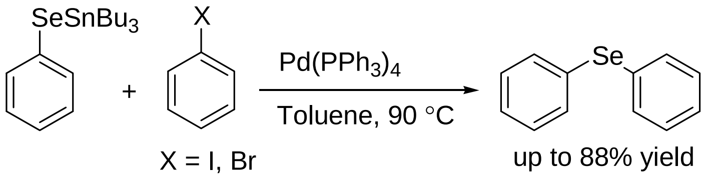


Figure 1. Examples of some biologically active selenium compounds

2.1 Palladium Catalyst

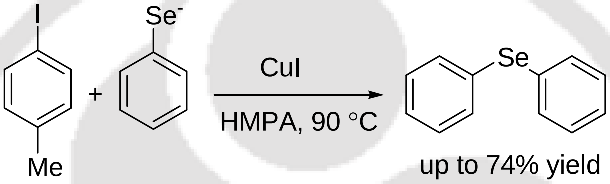
Noboru and co-workers have shown the use of $Pd(PPh_3)_4$ for the synthesis of diaryl selenides from tributylstannyl selenide ($PhSeSnBu_3$) and aryl halides at moderate temperature (Scheme 1).[4]



Scheme 1

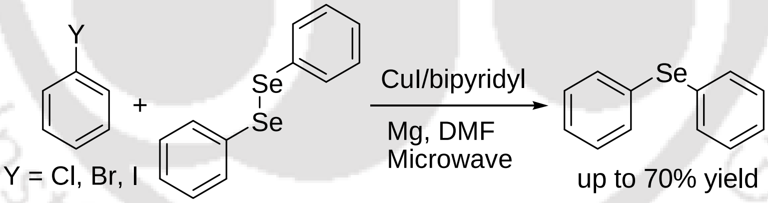
2.2 Copper Catalysts

Most of the *C-Se* cross-coupling reactions have been carried employing copper based catalysts. Suzuki and co-workers have accomplished the synthesis of dirayl selenides from areneselenolate and aryl iodides in the presence of CuI in hexamethylphosphoric triamide (HMPA) (Scheme 2).[5a]



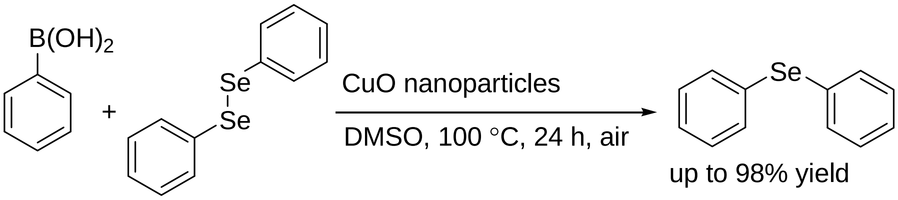
Scheme 2

Engman and co-workers have shown the synthesis of diaryl selenides from diphenyl diselenide and aryl halides using CuI and bipyridyl under microwave irradiation (Scheme 3).[5b]



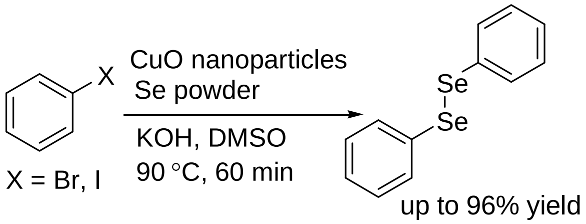
Scheme 3

Later, CuO nanoparticles have been employed for the synthesis of diaryl selenides from diaryl diselenides and aryl boronic acid in DMSO (Scheme 4).[5c]



Scheme 4

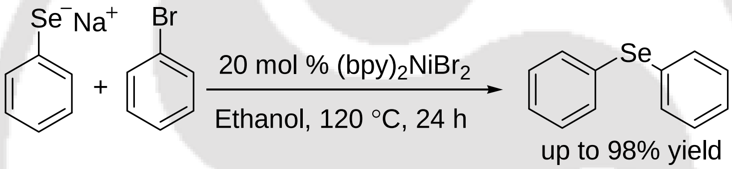
Subsequently, the synthesis of diphenyl diselenide has been shown using CuO nanoparticles, selenium powder and aryl halides (Scheme 5).[5d]



Scheme 5

2.3 Nickel Catalyst

The synthesis of diaryl selenide has been accomplished from aryl bromide and sodium seleniate in the presence of $(bpy)_2NiBr_2$ in ethanol (Scheme 6).[6]



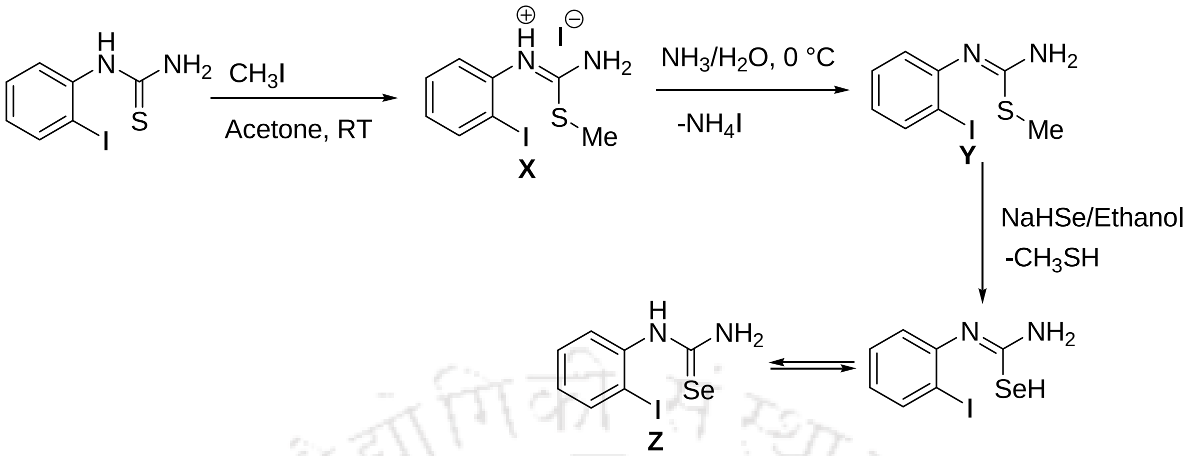
Scheme 6

2.4 Present Study

The success in the copper(II)-catalyzed synthesis of 2-(arylthio)arylcyanamides led to us to explore the construction of 2-(arylselanyl)arylcyanamides from *N*-(2-iodoaryl)selenoureas with aryl iodides. The reactions are found to be effective employing copper(I) complex derived from CuI and 1,10-phenanthroline and the target products are obtained in excellent yield.

The reaction of *N*-(2-iodoaryl)thiourea with iodomethane gave **X**, which could be treated with aqueous ammonia to yield the intermediate **Y**. The latter proceeded reaction with NaHSe to afford the desired substrate precursor *N*-(2-iodoaryl)selenoureas **Z** in high yield (Scheme 7).[7]

First, the reaction conditions were optimized with *N*-(2-iodo-4-methylphenyl)selenourea and iodobenzene as model substrates (Table 1). Among the set of ligands **L1-7** examined, 1,10-phenanthroline **L7** afforded the best results giving selectively the product **A** in 99% yield. In contrast, ethylene diamine **L1**, ethylene glycol **L2**, L-proline **L3**, 2,2'-bipyridine **L4**,

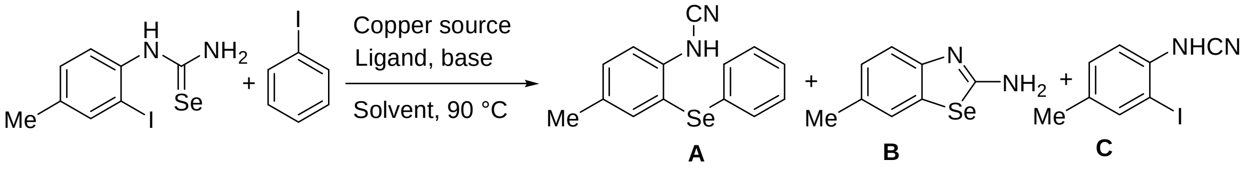


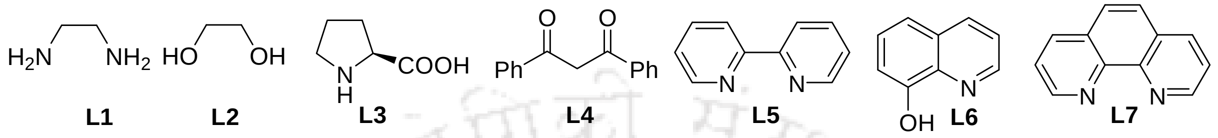
Scheme 7

8-hydroxyquinoline **L5** and dibenzoylmethane **L6** were found to be less selective giving **B** or **C** or both as by-products along with the target molecule **A**. The catalytic activity of different copper sources was evaluated, and CuI was found to be superior to CuBr, Cu_2O and $CuSO_4{\cdot}5H_2O$. DMSO was found to be the solvent of choice, whereas DMF, toluene and 1,4-dioxane gave inferior results. Of the screened bases, K_2CO_3, $K_3PO_4{\cdot}3H_2O$ and Cs_2CO_3, the former gave the best results. Reaction temperature was another important factor to affect the results and 90 ^{o}C was found to be the optimum temperature. A control experiment confirmed that a mixture of **A**, **B** and **C** were detected without the aid of the ligand **L7** (entry 2). Blank reaction without copper salt gave **C** as the sole product and the formation of **A** was not observed. This result suggests that, in the absence of copper(I) complex, the base promoted deselenization takes place to afford the cyanamide **C**.

Next, to reveal the scope of the procedure, the reaction of a series of substituted aryl iodides was explored with *N*-(2-iodophenyl)selenourea (Table 2). Aryl iodides having 2-Cl, 2-OMe, 3-NO_2, 4-NH_2, 4-Cl, 4-OMe and 4-NO_2 substituents were readily proceeded the *C-Se* domino cross-coupling to give the target molecules **2a-h** in 1-2 h with 75-95% yields. Similarly, aryl iodides with 2,4-dimethyl, 2,5-dimethyl and 2,6-dimethyl groups, and 1-naphthyl iodide underwent reactions to give the corresponding 2-(arylselanyl)arylcyanamides in high yield. Recrystallization of **A** in MeOH gave single crystals whose X-ray analysis is presented in figure 2.

Table 1. Optimization of the Reaction Conditions[a]





Entry	Copper source	Ligand	Solvent	Time (h)	Product(s) (%)[b]		
					A	**B**	**C**
1	$CuSO_4 \cdot 5H_2O$	-	DMSO	1	n.d.	n.d.	95
2	CuI	-	DMSO	3	30	45	20
3	CuI	**L7**	DMSO	1	95	n.d.	n.d.
4[c]	CuI	**L7**	DMSO	3	43	37	15
5[d]	CuI	**L7**	DMSO	3	53	26	16
6	CuI	**L7**	DMF	3	49	35	15
7	CuI	**L7**	Toluene	1	n.d.	n.d.	94
8	CuI	**L7**	1,4-Dioxane	1	n.d.	n.d.	94
9	CuI	**L1**	DMSO	3	45	35	15
10	CuI	**L2**	DMSO	1	n.d.	n.d.	32
11	CuI	**L3**	DMSO	3	25	45	25
12	CuI	**L4**	DMSO	3	37	35	23
13	CuI	**L5**	DMSO	3	25	60	10
14	CuI	**L6**	DMSO	3	35	45	18
15	CuBr	**L7**	DMSO	3	55	25	15
16	Cu_2O	**L7**	DMSO	1	95	n.d.	n.d.
17[e]	CuI	**L7**	DMSO	4	62	n.d.	33
18[f]	CuI	**L7**	DMSO	4	49	n.d.	46

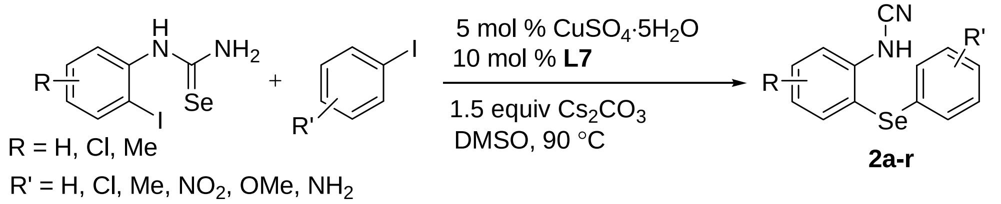
[a] Substrate (0.5 mmol), copper source (5 mol %), **L1-7** (5 mol %), Cs_2CO_3 (0.75 mmol) and iodobenzene (0.5 mmol) were stirred 90 °C in solvent (1 mL).

[b] Determined by 400 MHz ^{1}H NMR.

[c] K_2CO_3 used. [d] K_3PO_4 used.

[e] Temp = 80 °C. [f] Cs_2CO_3 (1 equiv.) used. n.d. = not detected.

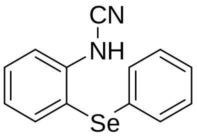
Table 2. Copper(I)-Catalyzed Domino Reaction of Substituted Selenoureas with Aryl Iodides.[a-b]



R = H, Cl, Me

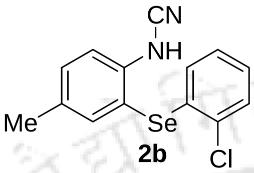
R' = H, Cl, Me, NO_2, OMe, NH_2

2a-r



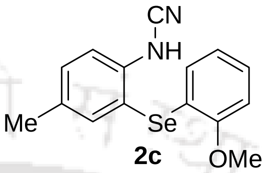
2a

1 h, 95%



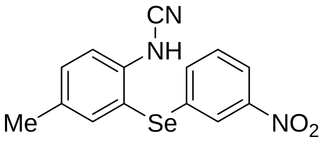
2b

1.5 h, 85%



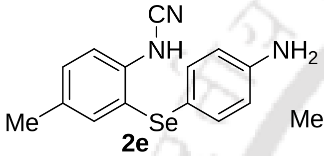
2c

2 h, 89%



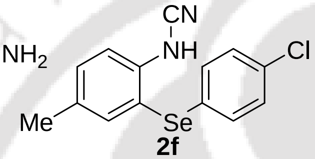
2d

1.5 h, 85%



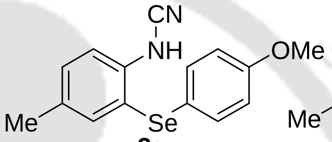
2e

2 h, 87%



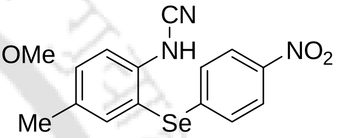
2f

1.5 h, 89%



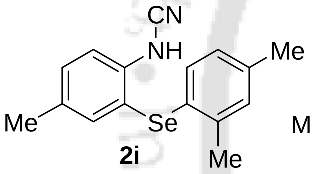
2g

2 h, 91%



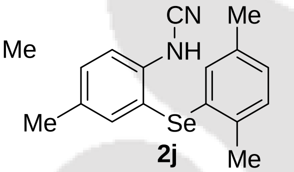
2h

1.5 h, 75%



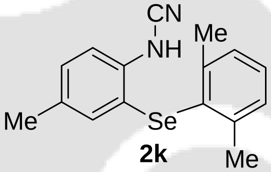
2i

1 h, 92%



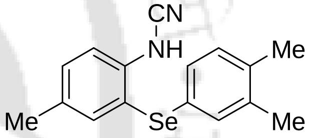
2j

1 h, 94%



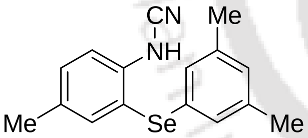
2k

1.5 h, 88%



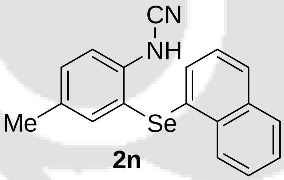
2l

1 h, 90%



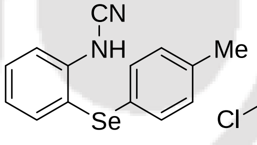
2m

1 h, 92%



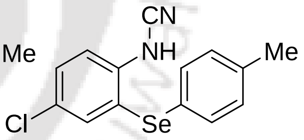
2n

1.5 h, 93%



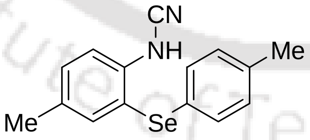
2o

1 h, 95%



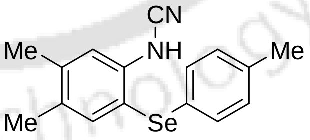
2p

1 h, 91%



2q

1 h, 95%



2r

1 h, 90%

---

[a] *N*-(2-Iodophenyl)selenourea (0.5 mmol), aryl iodide (0.5 mmol), CuI (5 mol %), 1,10-phenanthroline **L7** (5 mol %) and Cs_2CO_3 (0.75 mmol) were stirred at 90 °C in DMSO (1 mL) under air.

[b] Isolated yield.

Finally, the reactions of the substituted *N*-(2-iodo-4-methylphenyl)selenoureas with aryl iodide were studied. For example, *N*-(2-iodo-4-methylphenyl)selenourea having 4-Cl, 4-Me and 4,5-dimethyl substituents proceeded the domino *C-Se* cross-coupling with 1-iodo-4-methylbenzene to afford the respective target molecules **2o-r** in 1 h with 90-95% yields. These results clearly suggest that the present protocol can be used for the one-pot synthesis of 2-(arylselanyl)arylcyanamides.

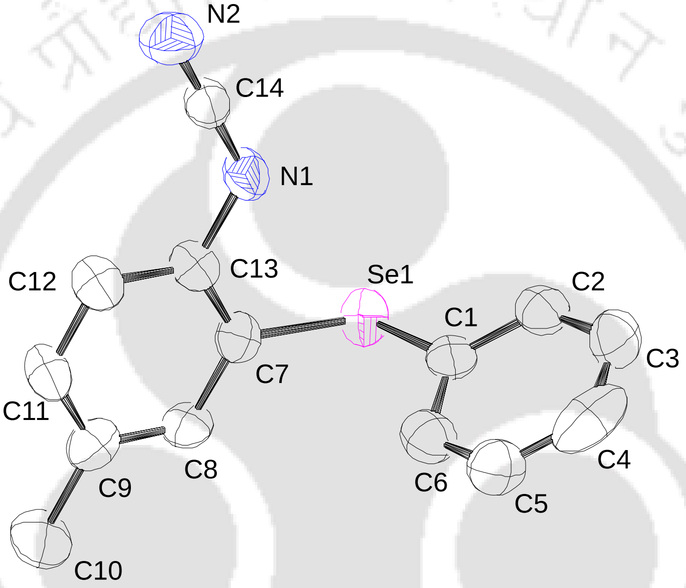
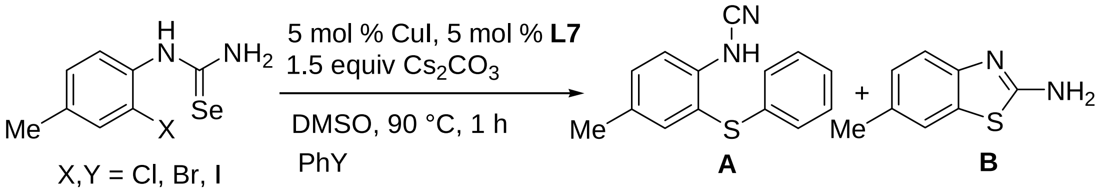


Figure 2. ORTEP diagram of 2-(phenylselanyl)-4-methylphenylcyanamide with 50% ellipsoid. H-Atoms omitted for clarity.

The reactivities of other aryl halides were further compared (Table 3). The reactions with bromobenzene and chlorobenzene gave **B** as the only product. Likewise, *N*-(2-bromo-4-methylphenyl)selenourea with iodobenzene gave a 1:10 mixture of **A** and 2-bromo-4-methylphenylcyanamide in >99% yield, whereas *N*-(2-chloro-4-methylphenyl)selenourea did not undergo any reaction with iodobenzene and afforded 2-chloro-4-methylphenylcyanamide as sole product in >99% yield.

Table 3. Reactions of Aryl Halides[a]



Entry	X	Y	Product(s) (%)[b]	
			A	**B**
1	I	I	100	n.d.
2[c]	Br	I	10	n.d.
3[d]	Cl	I	2	n.d.
4	I	Br	20	75
5	I	Cl	n.d.	94

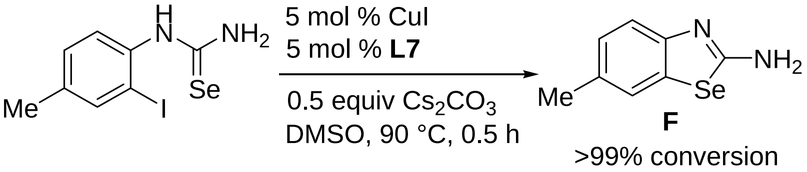
[a] Selenourea (0.5 mmol), aryl halide (0.5 mmol), CuI (5 mol %), **L7** (5 mol %) and Cs_2CO_3 (0.75 mmol) were stirred at 90 °C for 1 h in DMSO (1 mL).

[b] Determined by ^{1}H NMR.

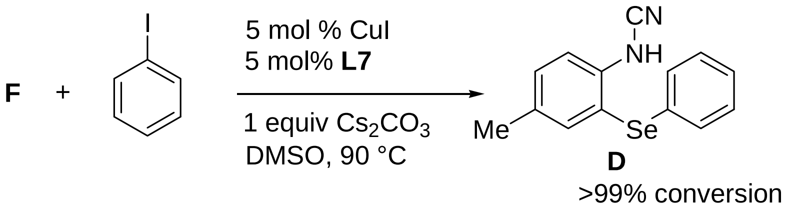
[c] *N*-(2-Bromophenyl)cyanamide obtained in 90% yield as a byproduct.

[d] *N*-(2-Chlorophenyl)cyanamide obtained in 95% yield as a byproduct.

Regarding the mechanism, control experiments were pursued. The cyclization of (2-iodo-4-methylphenyl)selenourea was studied with 0.5 equiv of Cs_2CO_3 in the absence of aryl iodide (Scheme 8). The cyclization occurred to give 2-aminobenzoselanazole **F** in 0.5 h with 100% selectivity. Next, the reaction of **F** was studied with iodobenzene in the presence of 1 equiv of Cs_2CO_3 and 2-(arylselanyl)arylcyanamide was obtained as a sole product (Scheme 9).

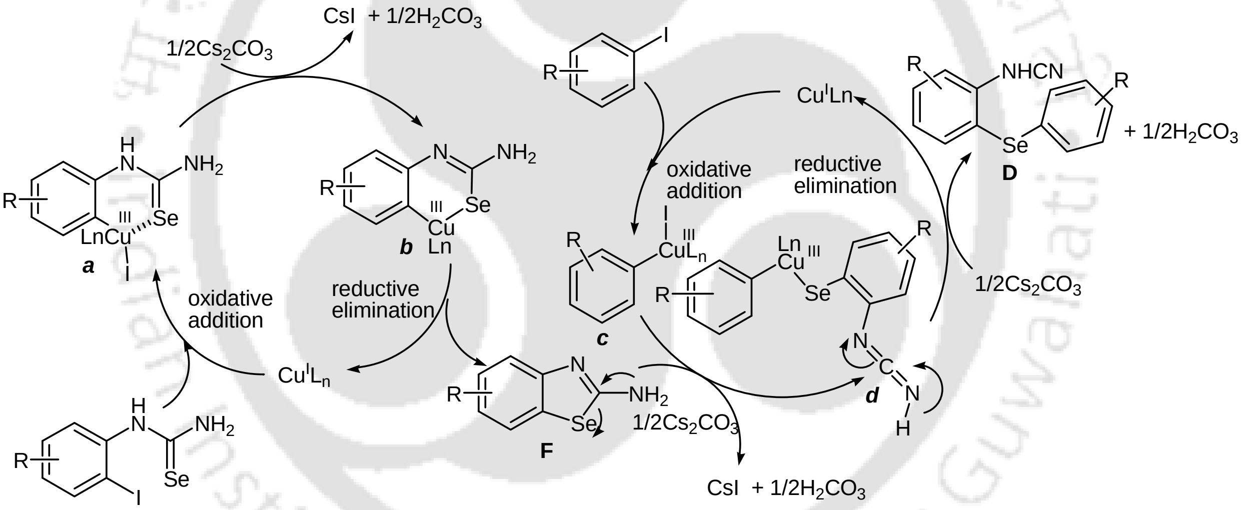


Scheme 8



Scheme 9

Based on the above experimental observations a plausible pathway for the synthesis of substituted 2-(arylselanyl)arylcyanamides has been proposed (Scheme 10). Benzoselanazole **F** underwent reaction in the presence of CuI-1,10-phenanthroline to give **D** in quantitative yield. The intramolecular cyclization was found to be faster compared to the intermolecular reaction. These results suggest that the reactions involve intra- followed by intermolecular *C-Se* domino cross-coupling reactions. Thus, the selenourea may undergo chelation followed by oxidative addition with copper(I)-1,10-phenanthroline complex to give the metallocycle ***b*** that could lead to the formation of **F** by the reductive elimination. The cross-coupling of **F** with ***c*** may afford the intermediate ***d*** that could complete the catalytic cycle by the reductive elimination of the target molecule **D**.



Scheme 10. Plausible reaction pathway

In conclusion, a novel copper-catalyzed domino *C-Se* cross coupling of (2-iodoaryl)selenoureas with aryl iodides has been developed to afford the substituted (2-

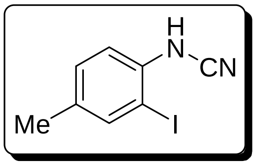
selanylaryl)arylcyanamides. The procedure involves intra- and intermolecular *C-Se* cross coupling reactions at moderate temperature.

Experimental Section

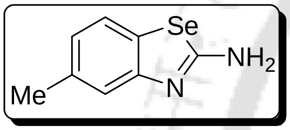
General Information. Iodobenzene, bromobenzene, chlorobenzene, $CuSO_4 \cdot 5H_2O$ (98%), CuI (98%), CuBr (98%), Cu_2O (97%), K_2CO_3, Cs_2CO_3 and $K_3PO_4 \cdot 3H_2O$ were purchased from Aldrich and selenium powder (99%) was obtained from SRL and used without further purification. Substituted aryl iodides[10] according to literature. The solvents were purchased and dried according to standard procedure prior to use. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Varian 400 spectrometer. Infrared (IR) spectra recorded on a Perkin Elmer Spectrum one FT-IR spectrometer. Melting points were determined with a Büchi B-545 apparatus and are uncorrected. Elemental analyses were recorded with Perkin Elmer CHNS analyzer.

General Procedure for the Synthesis of 2-(Arylselanyl)arylcyanamide. To a stirred solution of 1,10-phenanthroline (5 mol %) and CuI (5 mol %) in DMSO (1 mL) was added *N*-(2-iodoaryl)selenourea (0.5 mmol), aryl iodide (0.5 mmol) and Cs_2CO_3 (244 mg, 0.75 mmol) at ambient temperature and the mixture was allowed to stir at 90 ^{o}C for the appropriate time (Table 1-3). Progress of the reaction was monitored by TLC using ethyl acetate and hexane as solvent. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (10 mL). The solution was washed successively with 1 N HCl (1 x 3 mL) and water (3 x 3 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane to afford 2-(arylselanyl)arylcyanamide in analytically pure form.

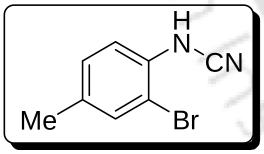
General Procedure for the Synthesis of *N*-(2-Iodoaryl)selenourea. To a stirred solution of *N*-(2-haloaryl)thiourea (0.5 mmol) in acetone was added iodomethane (0.5 mmol) and NaHSe ($NaBH_4$ was added dropwise over 30 min to suspension of selinium powder in dry ethanol under nitrogen atmosphere). The mixture is allowed to stnd at room temperature overnight. Progress of the reaction was monitored by TLC using ethyl acetate and hexane as a solvent and evaporation of solvent gave residue that was purified on silica gel column chromatography using ethyl acetate and hexane to give *N*-(2-iodoaryl)selenourea.



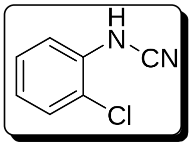
2-Iodo-4-methylphenylcyanamide (Table 1, entry 1): White solid; mp 141-142 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.20-7.12 (m, 2H), 6.12 (br s, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 135.5, 135.4, 130.8, 115.5, 110.8, 84.2, 20.3; FT-IR (KBr) 3146, 2907, 2838, 2236, 1601, 1583, 1491, 1423, 1287, 1146, 1027 cm^{-1}. Anal. Calcd. for $C_8H_7IN_2$: C, 37.23; H, 2.73; N, 10.86. Found: C, 37.34; H, 2.71; N, 10.81.



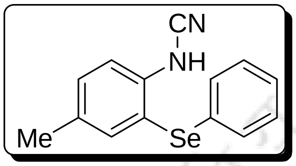
5-Methylbenzo[*d*][1,3]selenazol-2-amine (Table 3, entry 5): White solid; mp 151-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.8, 2H), 7.10 (d, *J* = 4.0, 1H), 5.52 (br s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 151.3, 134.6, 132.4, 127.5, 124.6, 120.0, 21.3; FT-IR (KBr) 3396, 3063, 1626, 1530, 1444, 1309, 1105 cm^{-1}. Anal. Calcd. for $C_8H_8N_2Se$: C, 45.51; H, 3.82; N, 13.27; Found: C, 45.61; H, 3.79; N, 13.22.



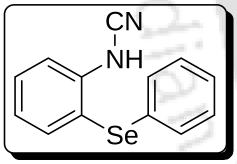
***N*-(2-Bromophenyl)cyanamide** (Table 3, entry 2)**:** White solid; mp 94-95 °C (lit.[9] mp 94 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.49 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.37-7.33 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.30-7.27 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.99-6.94 (dt, *J* = 8.0, 1.6 Hz, 1H), 6.35 (br s, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 133.0, 129.2, 124.8, 116.2, 110.3, 109.9, 20.3; FT-IR (KBr) 3146, 2907, 2838, 2236, 1601, 1583, 1491, 1423, 1287, 1146, 1027 cm^{-1}. Anal. Calcd. for C_8H7BrN_2: C, 45.53; H, 3.34; N, 13.27. Found: C, 42.63; H, 3.31; N, 13.22.



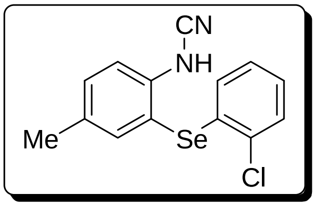
***N*-(2-Chlorophenyl)cyanamide** (Table 3, entry 3)**:**[10] White solid; mp 105-106 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 3H), 7.05-7.01 (m, 1H), 6.29 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 129.9, 128.5, 124.5, 120.4, 116.2, 110.1; FT-IR (KBr) 3162, 2914, 2877, 2842, 2243, 1598, 1500, 1426, 1295, 1112, 1048 cm^{-1}. Anal. Calcd. for $C_7H_5ClN_2$: C, 55.10; H, 3.30; N, 18.36. Found: C, 55.23; H, 3.28; N, 18.29.



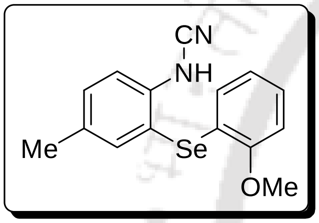
4-Methyl-2-(phenylselanyl)phenylcyanamide (Table 1, entry 3): White solid; yield 95%; mp 138-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.29-7.25 (m, 5H), 7.17 (d, *J* = 6.8 Hz, 2H), 6.84 (br s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 137.23, 134.2, 132.6, 130.5, 129.9, 129.7, 127.3, 115.0, 114.7, 110.8, 20.65; FT-IR (KBr) 3205, 2922, 2220, 1496, 1405, 1283, 1020 cm^{-1}. Anal. Calcd. for $C_{14}H_{12}N_2Se$: C, 58.54; H, 4.21; N, 9.75; Found: C, 58.64; H, 4.19; N, 9.71.



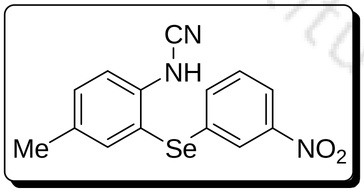
2-(Phenylselanyl)phenylcyanamide 2a: White solid; yield 95%; mp 120-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 1.6 Hz, 7.6 Hz**,** 1H), 7.47 (td, *J* = 1.6 Hz, 7.6 Hz, 1H), 7.28 (dd, *J* = 1.2 Hz, 8.4 Hz, 1H), 7.25-7.19 (m, 2H), 7.18-7.08 (m, 2H), 7.01-6.99 (m, 1H), 6.92 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 137.7, 134.1, 132.9, 129.6, 127.1, 125.3, 121.3, 117.5, 115.4, 111.3; FT-IR (KBr) 3148, 2964, 2917, 2237, 1590, 1578, 1490, 1438, 1409, 1288, 1261, 1078, 1023 cm^{-1}. Anal. Calcd. for $C_{13}H_{10}N_2Se$: C, 57.15; H, 3.69; N, 10.25. Found: C, 57.27; H, 3.67; N, 10.18.



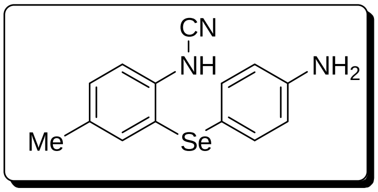
2-(2-Chlorophenylselanyl)-4-methylphenylcyanamide 2b: White solid; yield 85%; mp 104-105 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 (s, 1H), 7.37-7.28 (m, 3H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.79 (br s, 1H), 6.58 (d, *J* = 8 Hz, 1H) 2.34 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 139.8, 139.6, 137.8, 134.6, 133.3, 130.9, 129.9, 128.9, 128.0, 127.9, 115.4, 115.2, 110.6, 20.6; FT-IR (KBr) 3137, 2921, 2220, 1573, 1495, 1386, 1285, 1020 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}N_2SeCl$: C, 52.28; H, 3.45; N, 8.71; Found: C, 52.38; H, 3.43; N, 8.67.



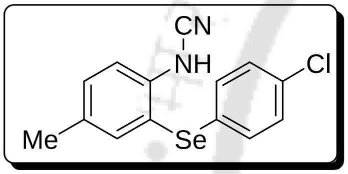
2-(2-Methoxyphenylselanyl)-4-methylphenylcyanamide 2c: White solid; yield 89%; mp 130-131 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 (s, 1H), 7.28-7.20 (m, 3H), 7.09 (br s, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.81 (t, *J* = 8 Hz, 2H), 3.93 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.8, 139.6, 137.9, 134.0, 132.5, 130.3, 128.6, 122.2, 119.4, 114.7, 113.8, 111.0, 110.8, 56.1, 20.5; FT-IR (KBr) 3233, 2218, 1574, 1472, 1382, 1271, 1020 cm^{-1}. Anal. Calcd. for $C_{15}H_{14}N_2SeO$: C, 56.79; H, 4.45; N, 8.83; Found: C, 56.89; H, 4.44; N, 8.80.



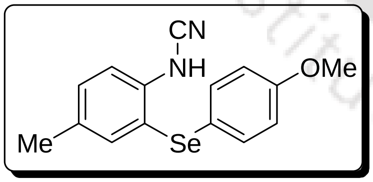
2-(3-Nitrophenylselanyl)-4-methylphenylcyanamide 2d: White solid; yield 85%; mp 118-119 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.07-8.04 (m, 2H), 7.55 (s, 1H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.36 (d, *J* = 9.6 Hz, 1H), 7.30 (t, *J* = 11.2 Hz, 1H), 6.70 (br s, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.0, 139.4, 137.4, 134.9, 133.6, 133.1, 130.5, 124.0, 122.0, 115.5, 113.1, 110.4, 20.6; FT-IR (KBr) 3191, 2224, 1495, 1403, 1386, 1341, 1286, 1061 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}N_3SeO_2$: C, 50.61; H, 3.34; N, 12.65. Found: C, 50.70; H, 3.32; N, 12.63.



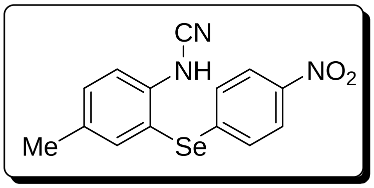
2-(4-Aminophenylselanyl)-4-methylphenylcyanamide 2e: Gummy; yield 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.19-7.17 (m, 4H), 6.56 (d, J = 7.2 Hz, 2H), 3.72 (br s, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 137.9, 136.5, 133.8, 133.4, 131.6, 117.3, 116.7, 116.4, 114.9, 111.1, 20.6; FT-IR (KBr) 3454, 2923, 2238, 1626, 1493, 1385, 1285 cm^{-1}. Anal. Calcd. for $C_{14}H_{13}N_3Se$: C, 55.64; H, 4.34; N, 13.90. Found: C, 55.75; H, 4.33; N, 13.86.



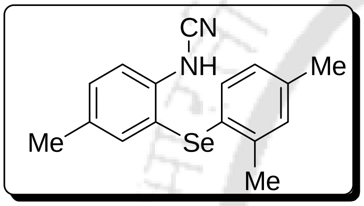
2-(4-Chlorophenylselanyl)-4-methylphenylcyanamide 2f : Gummy; yield 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.30-7.26 (m, 2H), 7.22-7.19 (m, 2H), 7.11-7.08 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 137.2, 134.3, 132.8, 131.0, 130.8, 129.9, 128.7, 115.2, 114.5, 110.7, 20.6; FT-IR (KBr) 2922, 2237, 1644, 1473, 1385, 1089 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}N_2SeCl$: C, 52.28; H, 3.45; N, 8.71. Found: C, 52.38; H, 3.43; N, 8.67.



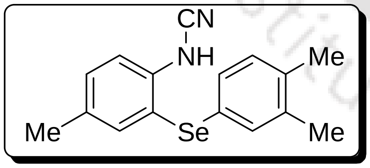
2-(4-Methoxyphenylselanyl)-4-methylphenylcyanamide 2g: White solid; yield 91%; mp 107-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.23-7.18 (m, 4H), 6.81-6.80 (m, 2H), 3.77 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 138.4, 136.7, 134.0, 132.7, 132.0, 120.0, 116.4, 115.6, 115.0, 110.9, 55.5, 20.6; FT-IR (KBr) 3271, 2960, 2924, 2213, 1727, 1588, 1489, 1386, 1288, 1247, 1174, 1024 cm^{-1}. Anal. Calcd. for $C_{15}H_{14}N_2SeO$: C, 56.79; H, 4.45; N, 8.83. Found: C, 56.90; H, 4.42; N, 8.78.



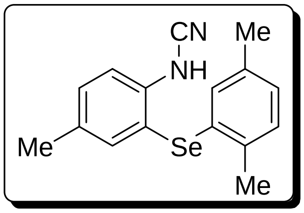
2-(4-Nitrophenylselanyl)-4-methylphenylcyanamide 2h : Block solid; yield 75%; mp 124-125 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98 (d, *J* = 2.4 Hz, 2H), 7.90 (dd, *J* = 2.4 Hz, 8.4 Hz, 2H), 6.92 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.53 (t, *J* = 7.6 Hz, 1H), 6.27 (br s, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.2, 136.7, 133.5, 128.9, 128.4, 124.5, 124.2, 115.8, 113.4, 111.7, 110.7, 20.2; FT-IR (KBr) 3322, 2919, 2227, 1606, 1572, 1470, 1275, 1229, 1117 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}N_3SeO_2$: C, 50.61; H, 3.34; N, 12.65. Found: C, 50.70; H, 3.32; N, 12.59.



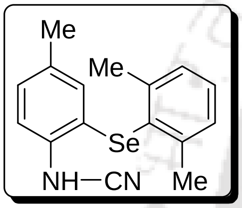
2-(2,4-Dimethylphenylselanyl)-4-methylphenylcyanamide 2i: Gummy liquid; yield 92%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46 (s, 1H), 7.28-7.23 (m, 2H), 7.02 (s, 1H), 6.83 (d, *J* = 8 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 2.36 (s, 3H), 2.31 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 138.6, 137.0, 136.9, 133.8, 131.9, 131.3, 128.7, 127.8, 126.9, 114.7, 114.2, 110.5, 21.4, 20.6, 20.3; FT-IR (KBr) 3304, 2922, 2241, 1627, 1603, 1495, 1408, 1386, 1287, 1233, 1030 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_2Se$: C, 60.95; H, 5.12; N, 8.89. Found: C, 61.05; H, 5.10; N, 8.84.



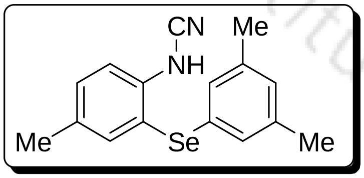
2-(3,4-Dimethylphenylselanyl)-4-methylphenylcyanamide 2j: White solid; yield 90%; mp 107-108 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 (s, 1H), 7.24-7.20 (m, 2H), 7.01 (d, *J* = 9.6 Hz, 1H), 6.99 (s, 1H), 6.92 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 6.83 (br s, 1H), 2.31 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 138.8, 138.5, 137.0, 136.3, 134.0, 132.2, 131.5, 131.1, 127.9, 126.6, 115.6, 115.0, 110.9, 20.6, 20.0, 19.5; FT-IR (KBr) 3181, 2919, 2224, 1636, 1491, 1447, 1404, 1285, 1154, 1040 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_2Se$: C, 60.95; H, 5.12; N, 8.89. Found: C, 61.08; H, 5.10; N, 8.84.



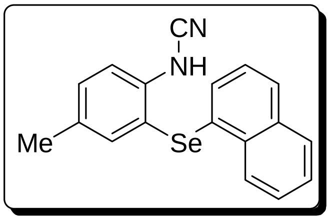
2-(2,5-Dimethylphenylselanyl)-4-methylphenylcyanamide 2k: White solid; yield 94%; mp 125-126 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47 (s, 1H), 7.31-7.25 (m, 2H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 8 Hz, 1H), 6.74 (br s, 1H), 6.54 (s, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 139.2, 137.4, 137.1, 134.2, 132.5, 130.7, 130.6, 129.1, 128.1, 115.0, 114.2, 110.9, 21.2, 21.1, 20.6; FT-IR (KBr) 3149, 2918, 2225, 1600, 1494, 1410, 1385, 1273, 1042 cm^{-1}. Anal. Calcd. for C$_{16}$H$_{16}$N$_2$Se: C, 60.95; H, 5.12; N, 8.89. Found: C, 61.04; H, 5.11; N, 8.86.



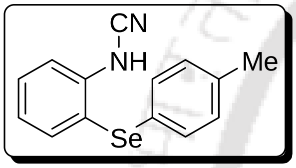
2-(2,6-Dimethylphenylselanyl)-4-methylphenylcyanamide 2l: White solid; yield 88%; mp 134-135 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.22-7.17 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = , 8.8 Hz, 1H), 6.97 (s, 1H), 6.35 (br s, 1H), 2.43 (s, 6H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 142.8, 135.2, 134.4, 134.3, 130.5, 130.1, 129.5, 128.7, 118.4, 115.5, 111.2, 24.5, 20.7; FT-IR (KBr) 3094, 2921, 2867, 2222, 1574, 1486, 1456, 1374, 1241, 1208, 1027 cm^{-1}. Anal. Calcd. for C$_{16}$H$_{16}$N$_2$Se: C, 60.95; H, 5.12; N, 8.89. Found: C, 61.06; H, 5.10; N, 8.85.



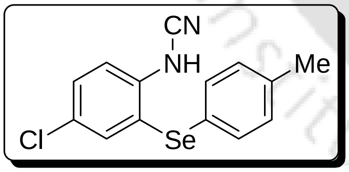
2-(3,5-Dimethylphenylselanyl)-4-methylphenylcyanamide 2m: White solid; yield 92 %; mp 142 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 (s, 1H), 7.28-7.22 (m, 2H), 6.84-6.80 (m, 3H), 2.33 (s, 3H), 2.23 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 139.6, 139.0, 137.1, 134.0, 132.4, 129.8, 129.3, 127.5, 114.9, 110.9, 109.9, 21.4, 20.6; FT-IR (KBr) 3197, 2920, 2854, 2222, 1598, 1573, 1492, 1402, 1383, 1286, 1261, 1040 cm^{-1}. Anal. Calcd. for C$_{16}$H$_{16}$N$_2$Se: C, 60.95; H, 5.12; N, 8.89. Found: C, 61.04; H, 5.09; N, 8.84.



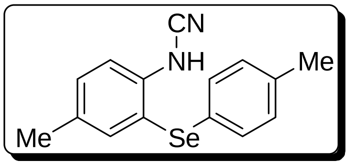
4-Methyl-2-(naphthalene-1-ylselanyl)phenylcyanamide 2n: White solid; yield 93%; mp 112-113 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.62-7.53 (m, 3H), 7.31-7.25 (m, 3H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.78 (br s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 139.1, 137.4, 134.2, 132.5, 129.4, 129.0, 127.9, 127.6, 127.0, 126.7, 126.4, 125.5, 115.4, 115.2, 114.2, 110.8, 20.6; FT-IR (KBr) 3199, 2921, 2216, 1560, 1493, 1385, 1283, 1260, 1022 cm^{-1}. Anal. Calcd. for $C_{18}H_{14}N_2Se$: C, 64.10; H, 4.18; N, 8.31. Found: C, 64.21; H, 4.16; N, 8.27.



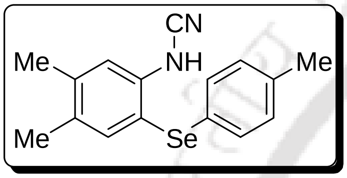
2-(*p*-Tolylselanyl)-phenylcyanamide 2o: White solid: yield 95%; mp 83-84 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.12-7.07 (m, 3H), 6.97 (d, *J* = 7.2 Hz, 2H), 6.93 (br s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 139.6, 137.3, 137.1, 131.6, 131.3, 130.4, 127.9, 127.8, 124.3, 115.4, 110.3, 21.1; FT-IR (KBr) 3153, 2964, 2238, 1616, 1588, 1577, 1488, 1407, 1287, 1164, 1019 cm^{-1}. Anal. Calcd. for $C_{14}H_{12}N_2Se$: C, 58.54; H, 4.21; N 9.75. Found: C, 58.63; H, 4.19; N 9.72.



2-(*p*-Tolylselanyl)-4-chlorophenylcyanamide 2p: White solid; yield 91%; mp 130-131 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50 (d, *J* = 2.4 Hz, 1H), 7.40-7.37 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.10-7.06 (m, 2H), 7.02-6.99 (m, 2H), 6.84 (br s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.9, 137.8, 135.9, 131.1, 130.9, 130.6, 130.1, 128.9, 121.1, 116.5, 110.0, 21.1; FT-IR (KBr) 3153, 2919, 2237, 1572, 1486, 1455, 1408, 1384, 1284, 1260, 1100, 1017 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}N_2SeCl$: C, 52.28; H, 3.45; N, 8.71. Found: C, 52.38; H, 3.44; N, 8.67.



2-(*p*-Tolylselanyl)-4-methylphenylcyanamide 2q: White solid; yield 95%; mp 107-108 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 (s, 1H), 7.26-7.20 (m, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 7.6 Hz, 2H), 6.84 (br s, 1H), 2.31 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 138.5, 137.1, 136.7, 133.7, 131.9, 130.3, 129.9, 126.2, 115.1, 114.6, 110.6, 20.8, 20.2; FT-IR (KBr) 3143, 2923, 2854, 2228, 1604, 1488, 1386, 1153, 1015 cm^{-1}. Anal. Calcd. for $C_{15}H_{14}N_2Se$: C, 59.81; H, 4.68; N, 9.30. Found: C, 59.89; H, 4.67; N, 9.27.



2-(*p*-Tolylselanyl)-4,5-dimethylphenylcyanamide 2r: White solid; yield 90%; mp 91-92 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30 (s, 1H), 7.09 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.92-6.90 (m, 2H), 6.74 (br s, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 141.5, 138.5, 137.7, 136.9, 133.2, 132.4, 130.6, 127.6, 116.8, 114.9, 111.1, 21.4, 20.4, 19.4; FT-IR (KBr) 3157, 2917, 2230, 1608, 1567, 1498, 1411, 1272, 1197, 1081, 1022 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_2Se$: C, 60.95; H, 5.12; N, 8.89. Found: C, 61.05; H, 5.10; N, 8.86.

2.5 References

(1) (a) Klayman, D. L.; Gunther, W. H. H. *Organic Selenium Compounds: Their Chemistry and Biology;* Wiley & Sons: NewYork, 1973. (b) El-Bay-oumy, K. *Nutr. Cancer* **2001**, *40*, 4. (c) Krief, A.; Abel, E. W.; Stone, F. G. A.; Wilkinson, G.; McKillop, A. *In Comprehensive Organometallic Chemistry II;* Pergamon Press: Oxford, 1995, Vol. 11. (d) Wirth, T.; Crabtree, R. H.; Mingos, D. M. P. *Comprehensive Organometallic Chemistry III;* Elsevier: Oxford, 2006; Vol. 9. (e) Ip, C.; Lisk, D. J.; Ganther, H.; Thompson, H. *J. Anticancer Res.* **1997**, *17*, 3195. (f) Kesharwani, T.; Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 2307. (g) Taniguchi, N.; Onami, T. *J. Org. Chem.* **2004**, *69*, 915. (h) Braga, A. L.; Ludtke, D. S.; Vargas, F.; Braga, R. C. *Synlett* **2006**, 1453. (i) Braga, A. L.; Vargas, F.; Sehnem, J. A.; Braga, R. C. *J. Org. Chem.* **2005**, *70*, 9021. (j) Freudendahl, D. M.; Shahzad, S. A.; Wirth, T. *Eur. J. Org. Chem.* **2009**, 1649.

(2) (a) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D.; Volante, R. P. *J. Org. Chem*. **1998**, *63*, 9606. (b) Li, G. Y. *Angew. Chem. Int. Ed*. **2001**, *40*, 1513. (c) Comprehensive Organic Chemistry; Krief, A., Ed.; Pergamon: Oxford, 1991. Organo selenium Chemistry; Krief, A., Ed.; Springer-Verlag: Berlin, 1988. (d) Organo selenium Chemistry; Liotta, D., Ed.; Wiley Interscience: NewYork, 1987. (e) Back, T. G.; Moussa, Z. *J. Am. Chem. Soc*. **2003**, *125*, 13455. (f) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev*. **2004**, *104*, 6255. (g) Anderson, C.-M.; Hallberg, A.; Hogberg, T. *Adv. Drug. Res*. **1996**, *28,* 65.

(3) (a) Osuka, A.; Ohmasa, N.; Suzuki, H. *Synth. Commun.* **1982**, 857. (b) Anderson, C. M.; Hallberg, A.; Linden, M.; Brattsand, R.; Moldeus, P.; Cotgreave, I. *Free Radic. Biol. Med.* **1994**, *16*, 17. (c) Andersson, C. M.; Hallberg, A.; Hugberg, T. *Adv. Drug Res*. **1996**, *28*, 65. (d) Baird, C. P.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1973. (e) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 641. (g) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 335. (f) Vasil'ev, A. A.; Engman, L.; Storm, J. P.; Andersson, C.-M. *Organometallics* **1999**, *18*, 1318. (g) Ayrey, G.; Barnard, D.; Woodbridge, D. T. *J. Chem. Soc*. **1962**, 2089. (h) Pierini, A. B.; Rossi, R. A. *J. Organomet. Chem.* **1978**, 144.

(4) Nishiyama, Y.; Tokunaga, K.; Sonoda, N. *Org. Lett.* **1999**, *1*, 1725.

(5) (a) Suzuki, H.; Abe, H.; Osuka, A. *Chem. Lett.* **1981**, 151. (b) Kumar, S.; Engman, L. *J. Org. Chem.* **2006**, *71*, 5400. (c) Alves, D.; Santos, C. G.; Paixao, M. W.; Soares, L. C.; De Souza, D.; Rodrigues, O. E. D.; Braga, A. L. *Tetrahedron Lett.* **2009**, *50*, 6635. (d) Singh, D.; Deobald, A. M.; Camargo, L. R. S.; Tabarelli, G.; Rodrigues O. E. D.; Braga, A. L. *Org. Lett*. **2010**, *12*, 3288.

(6) Cristau, H. J.; Chabaud, B.; Labaudiniere, R.; Christol, H. *Organomettallics* **1985**, *4*, 657.

(7) (*a*) Cohen, V. I. *Synthesis* **1980**, 60. (b) Al-Rubaie, A. Z.; Yousif, L. Z.; Al-Hamad, A. J. H.; *J. Organomet. Chem.* **2002**, *656*, 274.

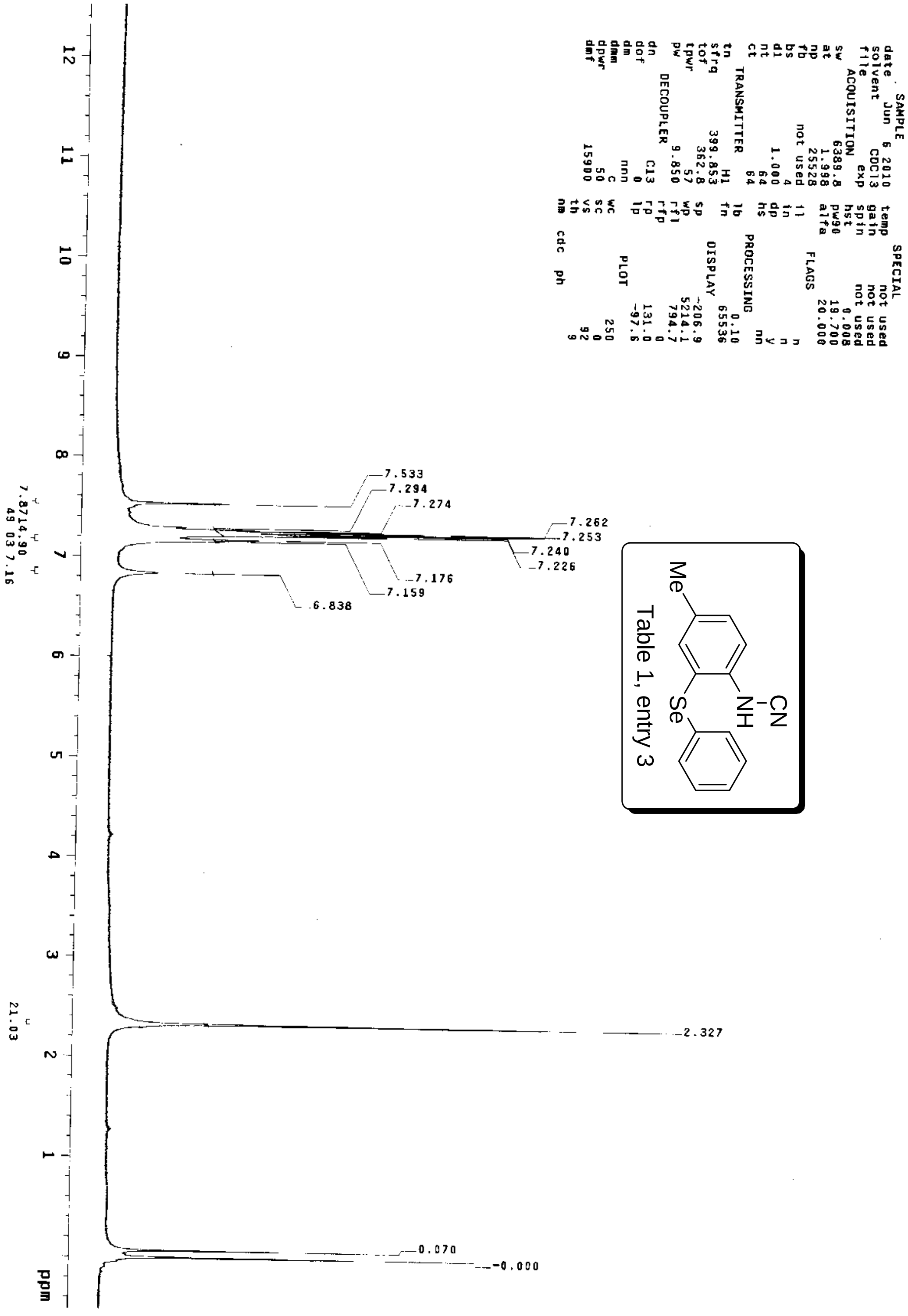
(8) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. In *Vogel's Textbook of Practical Organic Chemistry*, Fifth Edition, Pearson Education Pte. Ltd., Indian Branch, Delhi, 2004, 928.

(9) Pierron, P. *Bull. Soc. Chim. Fr.* **1907**, *35*, 1197.

(10) Ramana, T.; Saha, P.; Das, M.; Punniyamurthy, T. *Org. Lett.* **2010**, *12*, 84.

Crystal Data for 2-(phenylselanyl)-4-methylphenylcyanamide at 298(2) K

Identification code	Table 1, entry 3	
Empirical formula	$C_{14}H_{12}N_2Se$	
Formula weight	287.22	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	*Pca21*	
Unit cell dimensions	a = 8.0688(3) Å	α(°)= 90
	b = 19.6845(9) Å	β(°)= 90
	c = 15.9556(7) Å	γ(°)= 90
Volume	V = 2534.23(19) $Å^3$	
Z	8	
Density (calculated)	1.506 mg/m^3	
Absorption coefficient	2.941 mm^{-1}	
F(000)	1152.0	
Crystal size	0.30×0.20×0.20 mm^3	
Index ranges	-9<=h<=8, -21<=k<=20, -17<=l<=18	
Reflections collected	1895	
Independent reflections	1845 [R (int) = 0.0640]	
Completeness to theta = 23.25°	98.0 %	
Max. and min. transmission	0.555 and 0.499	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3551 / 1 / 313	
Goodness-of-fit on F^2	0.905	
Final R indices [I>2sigma (I)]	$R1$ = 0.0636, $wR2$ = 0.1617	
R indices (all data)	$R1$ = 0.0771, $wR2$ = 0.1721	



```
RT-phenyl
exp1  s2pul
       SAMPLE              SPECIAL
date    Jun  6 2010   temp      not used
solvent      CDCl3    gain      not used
file           exp    spin      not used
     ACQUISITION      hst          0.008
sw          6389.8    pw90        19.700
at           1.998    alfa        20.000
np           25528          FLAGS
fb        not used    il             n
bs               4    in             n
d1           1.000    dp             y
nt              64    hs            nn
ct              64         PROCESSING
     TRANSMITTER      lb          0.10
tn              H1    fn         65536
sfrq       399.853         DISPLAY
tof          362.8    sp        -206.9
tpwr            57    wp        5214.1
pw           9.850    rfl        794.7
     DECOUPLER        rfp            0
dn             C13    rp         131.0
dof              0    lp         -97.6
dm             nnn         PLOT
dmm              c    wc           250
dpwr            50    sc             0
dmf          15900    vs            92
                      th             9
                      nm  cdc  ph
```

```
RT-phenyl-13C

exp1  s2pul

       SAMPLE                 SPECIAL
date   Jun  6 2010   temp       not used
solvent       CDCl3   gain       not used
file            exp   spin       not used
   ACQUISITION        hst           0.008
sw          25125.6   pw90         18.600
at            1.199   alfa         20.000
np            60270           FLAGS
fb            13800   il                n
bs               16   in                n
d1            1.000   dp                y
nt             5000   hs               nn
ct             3808          PROCESSING
   TRANSMITTER        lb             2.00
tn              C13   fn            65536
sfrq        100.554           DISPLAY
tof          1536.3   sp          -1503.1
tpwr             61   wp          25125.6
pw            9.300   rfl          1503.1
    DECOUPLER         rfp               0
dn               H1   rp            -57.9
dof               0   lp           -360.3
dm              yyy             PLOT
dmm               w   wc              250
dpwr             42   sc                0
dmf            8900   vs               20
                      th                2
                      nm   no   ph
```

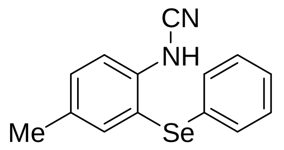
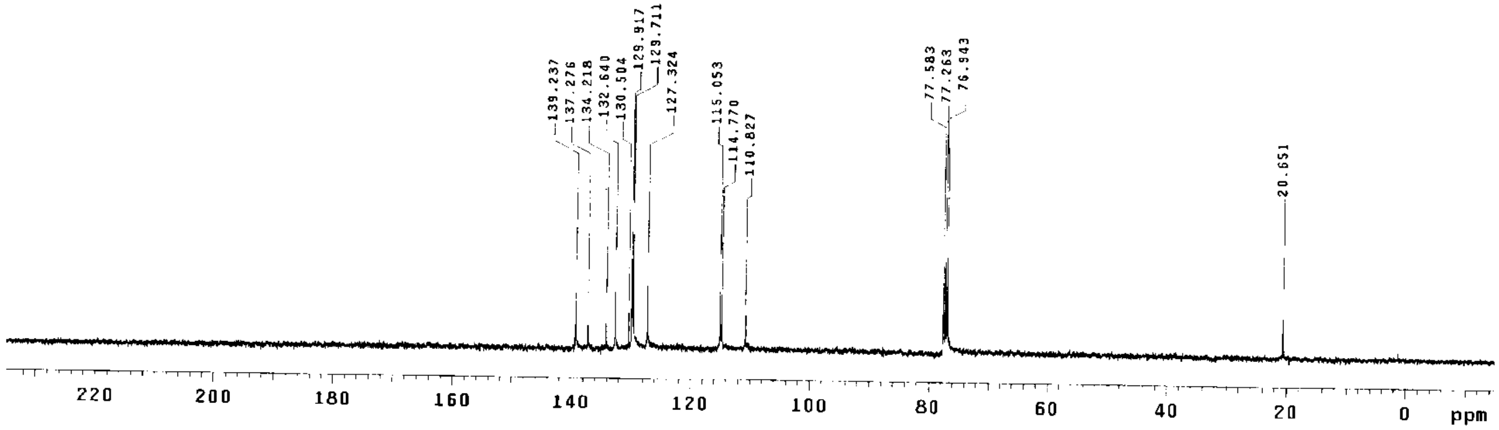
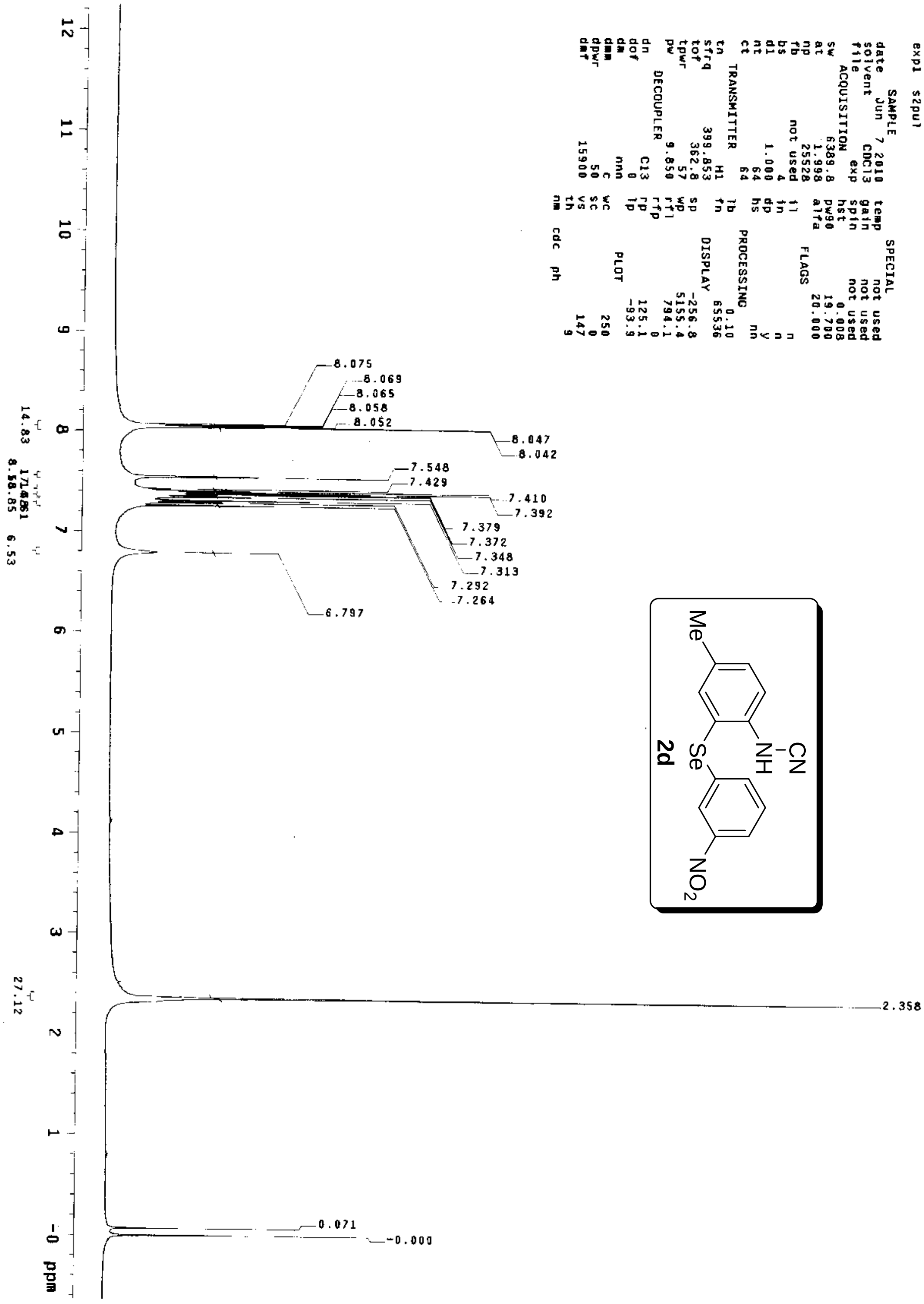


Table 1, entry 3

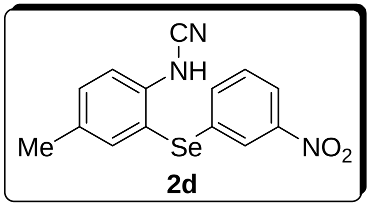



12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm
8.075
8.069
8.065
8.058
8.052
8.047
8.042
7.548
7.429
7.410
7.392
7.379
7.372
7.348
7.313
7.292
7.264
6.797
2.358
0.071
-0.000
14.83
6.53
27.12

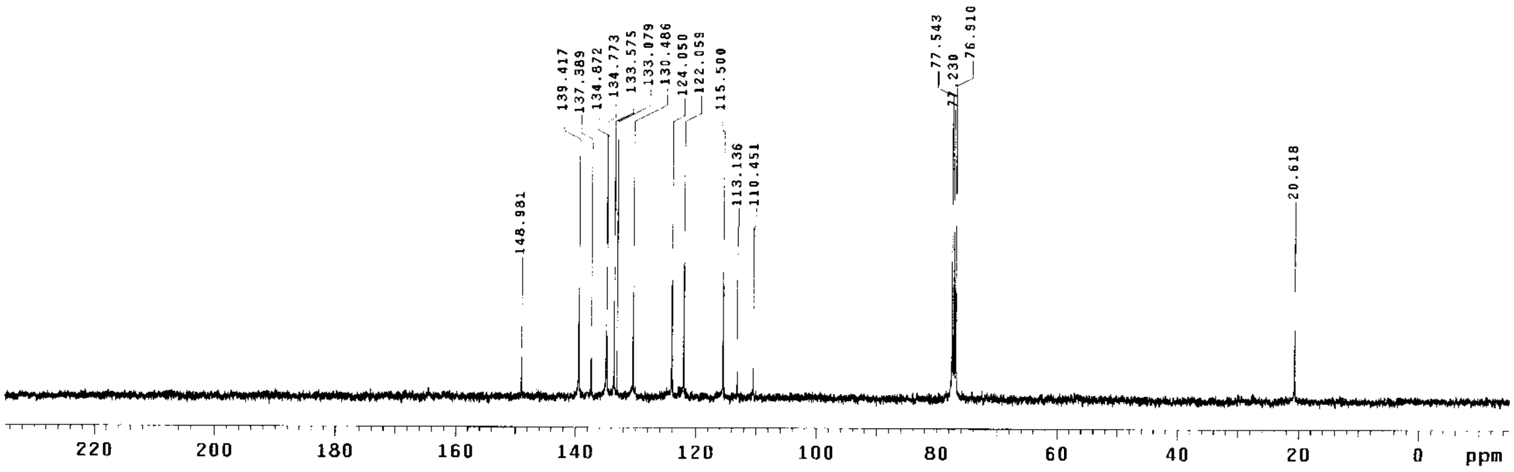
Me
CN
NH
Se
NO$_2$

2d

```
RT-229-c

exp1  s2pul

      SAMPLE               SPECIAL
date    Jun  8 2010   temp        not used
solvent       CDCl3   gain        not used
file            exp   spin        not used
    ACQUISITION       hst            0.008
sw          25125.6   pw90          18.600
at            1.199   alfa          20.000
np            60270           FLAGS
fb            13800   il                 n
bs               16   in                 n
d1            1.000   dp                 y
nt             5000   hs                nn
ct             5000          PROCESSING
    TRANSMITTER       lb              2.00
tn              C13   fn             65536
sfrq        100.554           DISPLAY
tof          1536.3   sp           -1507.2
tpwr             61   wp           25125.6
pw            9.300   rfl           9272.1
     DECOUPLER        rfp           7764.9
dn               H1   rp             -56.5
dof               0   lp            -323.6
dm              yyy             PLOT
dmm               w   wc               250
dpwr             42   sc                 0
dmf            8900   vs                28
                      th                 3
                      nm   no   ph
```



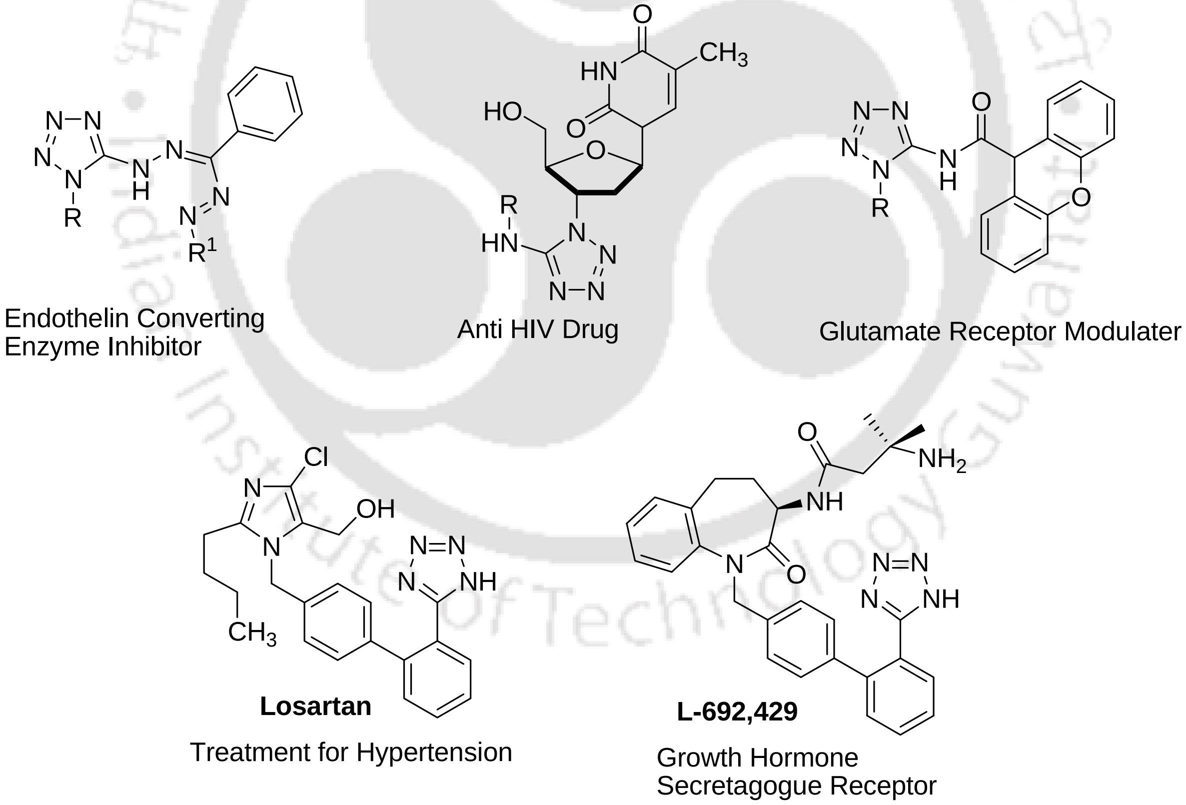
2d



Chapter III

Copper(II)-Promoted Three-Component Synthesis of Substituted 5-Aminotetrazoles

Tetrazoles are an important class of heterocyclic compounds. Due to their unique structure and reactivity, they have attracted noticeable interest in medicinal applications[1] and are also applied as ligands in coordination chemistry.[2] They also have been used as important synthetic intermediates for the preparation of imidoylazides.[3] In recent years, substituted tetrazoles have found common usage as an isosteric replacement for the carboxylic acid moiety in biologically active molecules.[4] Carboxylic acid counterparts and tetrazoles do exhibit a planar structure. However, anionic tetrazoles are ten times more lipophilic in nature than the corresponding carboxylates, which is an important factor in design of a drug molecule to pass through cell membrane.[5] 5-Aminotetrazoles are found in compounds bearing antiasthmatic,[6] antiviral,[7] anti-



Endothelin Converting Enzyme Inhibitor

Anti HIV Drug

Glutamate Receptor Modulater

Losartan

Treatment for Hypertension

L-692,429

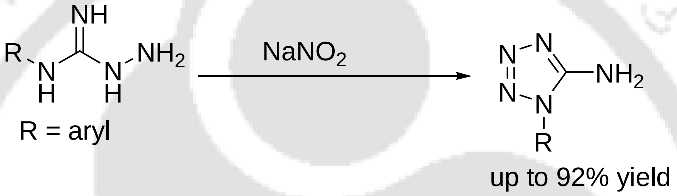
Growth Hormone Secretagogue Receptor

Figure 1. Some examples of biologically active tetrazole compounds

inflammatory,[8] antineoplastic[9] and cognition disorder activities.[10] Tetrazoles also possess pharmacological and receptor modulator activities (Figure 1).[11] Thus owing to their synthetic and medicinal importance, significant efforts have been made on the development of effective methods for the construction of the 5-aminotetrazole structural frameworks.

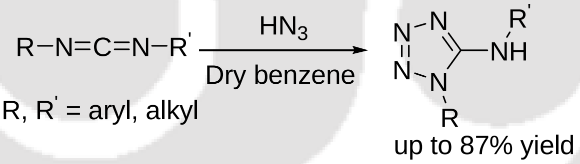
3.1 Electrocyclization

Most of the classical methods used for the synthesis of 5-aminotetrazoles involve electrocyclization. As an example diazotization of amino guanidine with $NaNO_2$ followed by electrocyclization in aqueous acid gives 5-aminotetrazoles in high yield (Scheme 1).[12a]



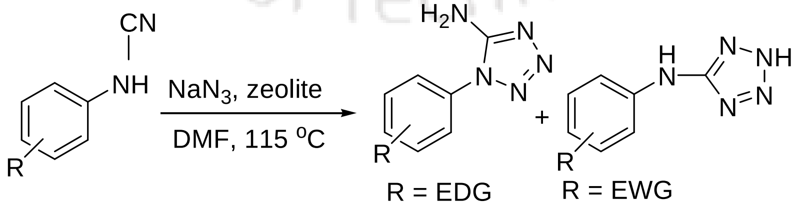
Scheme 1

Oe and co-workers accomplished the synthesis of 5-aminotetrazoles from carbodiimides and hydrazoic acid in benzene at 60 °C with good yield (Scheme 2).[12b]



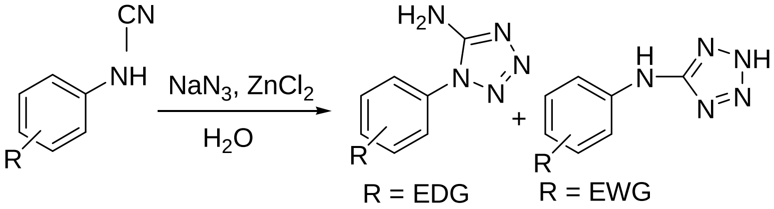
Scheme 2

Nasrollazadeh and co-workers reported the synthesis of substituted arylaminotetrazoles from arylcyanamides and NaN_3 using zeolite in DMF under heating (Scheme 3).[12c]



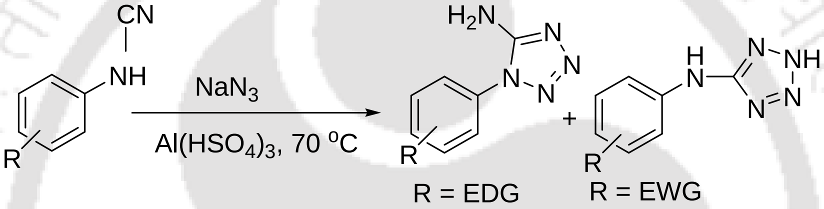
Scheme 3

Later, the above reaction has also been demonstrated using $ZnCl_2$ in water under reflux conditions (Scheme 4).[12d]



Scheme 4

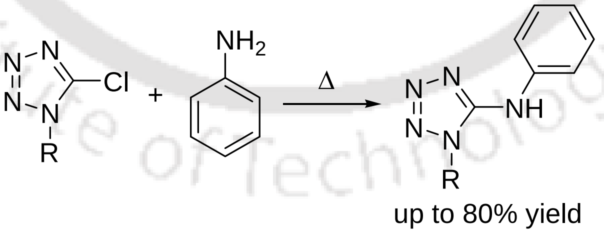
While Khamooshi and co-authors showed the above reaction employing $Al(HSO_4)_3$ at 70 °C under neat conditions (Scheme 5).[12e]



Scheme 5

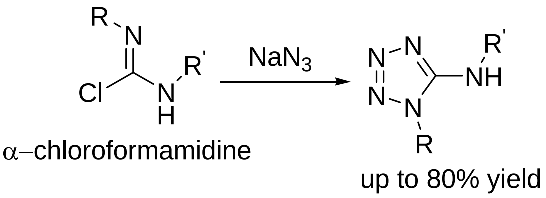
3.2 Nucleophilic Substitution

Teutsch and co-workers showed the synthesis of 5-aminotetrazoles from 5-chlorotetrazole and amines by nucleophilic substitution under heating conditions (Scheme 6).[13a]



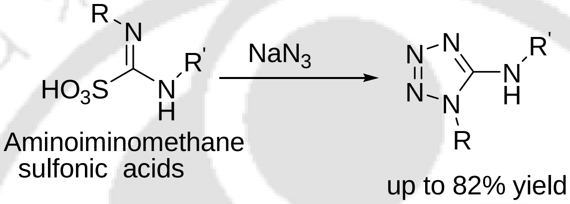
Scheme 6

While, Ried and co-workers demonstrated the synthesis of 5-aminotetrazoles via nucleophilic substitution followed by electrocyclization from sodium azide and α-chloroformamidine (Scheme 7).[13b]



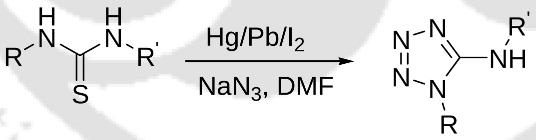
Scheme 7

Similarly, Miller and co-workers reported the synthesis of tetrazoles by nucleophilic substitution followed by electrocyclizaiton from sodium azide and aminoiminomethanesulfonic acids (Scheme 8).[13c]



Scheme 8

The synthesis of 5-aminotetraozle has also been shown by nucleophilic substitution followed by electrocyclization from thiourea and sodium azide in the presence of Hg, Pb or I_2 (Scheme 9).[13d-g] This method has been employed for the synthesis of mono-, di- and tri substituted tetrazoles.



Scheme 9

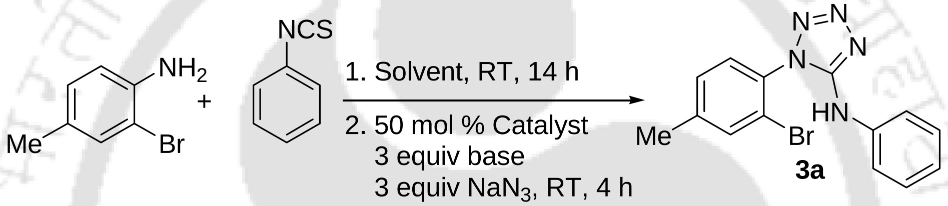
Most of these existing methods involve either toxic reagents or harsh reaction conditions such as high temperature and lack of regioselectivity.[14] Thus, the development an effective method for the regioselective synthesis of 5-aminotetrazoles will be valuable in organic synthesis.

3.3 Present Study

The recent development in organic synthesis using transition metal based systems provides effective method for the construction of valuable heterocyclic compounds. Copper based catalytic systems find extensive applications in the construction of heterocyclic compounds that led us to explore the synthesis of 5-aminotetrazoles from isothiocyanates, bromoanilines and sodium azide in the presence of copper salts *via* tandem addition, substitution and electrocyclization processes.

Firstly, the optimization of the reaction conditions was carried out with 4-methyl-2-bromoaniline, phenylisothiocyanate and sodium azide as model substrates using different copper sources, solvents and bases (Table 1). The best result was obtained when the reaction was pursued at room temperature using 50 mol % the copper salts such as $CuSO_4·5H_2O$, $Cu(OAc)_2·H_2O$, CuI and CuCl in the presence of Et_3N in DMF affording the desired tetrazole **3a** in 100% conversion. The reaction in solvents such as DMSO, THF and toluene were less effective and gave the target product in 60-70% conversion. The reactions with inorganic bases such as Cs_2CO_3 and K_2CO_3

Table 1. Optimization of the Reaction Conditions for the Synthesis of Tetrazole[a]

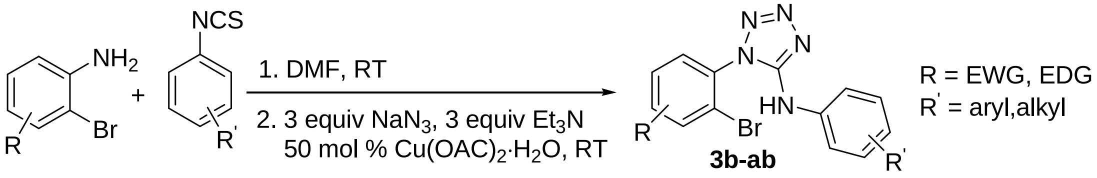


Entry	Catalyst	Solvent	Base	Product (**3a**) (%)[b]
1	$Cu(OAC)_2·H_2O$	DMF	Et_3N	100
2	$Cu(OAC)_2·H_2O$	DMSO	Et_3N	75
3	$Cu(OAC)_2·H_2O$	THF	Et_3N	60
4	$Cu(OAC)_2·H_2O$	Toluene	Et_3N	60
5	$Cu(OAC)_2·H_2O$	DMF	Cs_2CO_3	60
6	$Cu(OAC)_2·H_2O$	DMF	K_2CO_3	70
6	CuSO4·5H2O	DMF	Et_3N	100
7	CuI	DMF	Et_3N	100
8	CuCl	DMF	Et_3N	100

[a] Reaction conditions: Phenyl isothiocyanate (1 mmol), 2-bromo-4-methylbenzenamine (1 mmol), solvent (1.5 mL), room temperature, 14 h, then NaN_3 (3 mmol), base (3 mmol) and catalyst (50 mol %), room temperature, 4 h.

[b] Determined by 400 MHz ^1H NMR. n.d. = not detected.

Table 2. Substrate Scope of the Formation of Substituted 5-Aminotetrazoles[a-b]



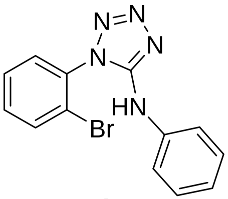
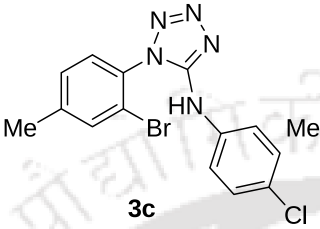
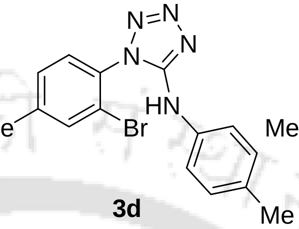
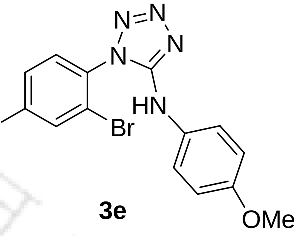
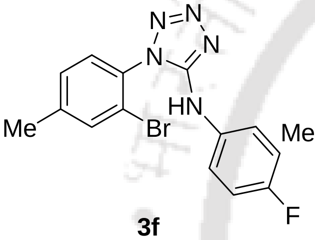
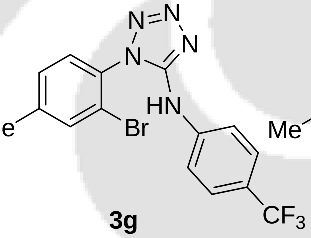
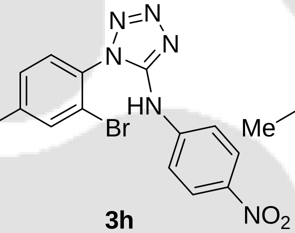
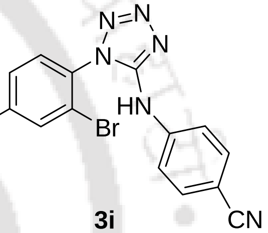
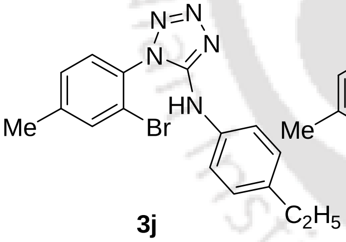
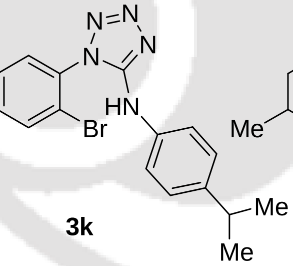
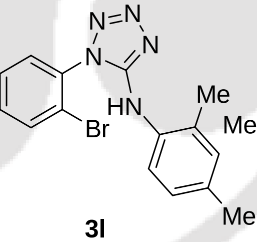
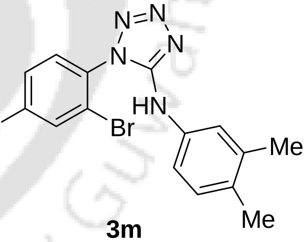
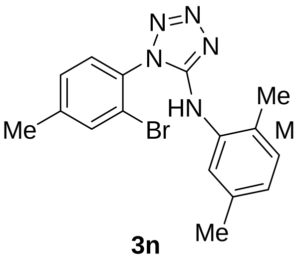
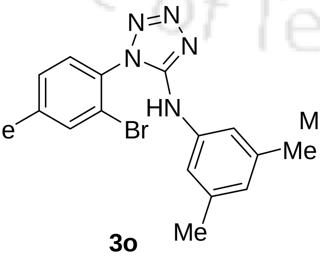
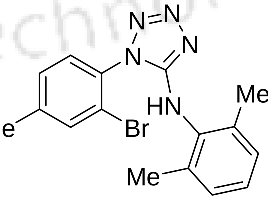
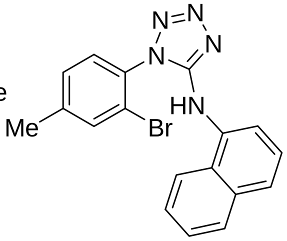
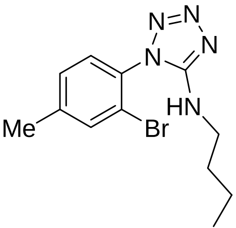
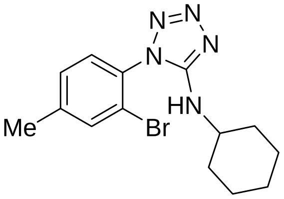
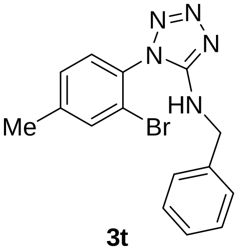
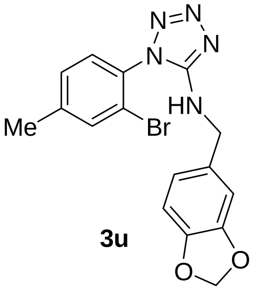
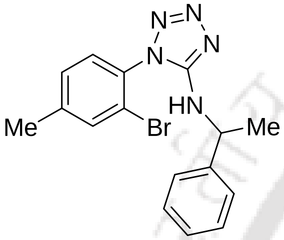
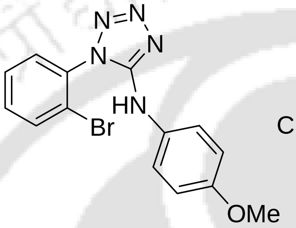
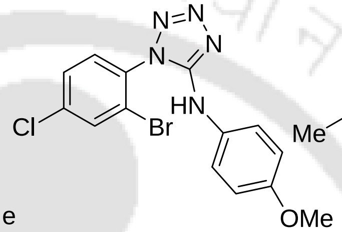
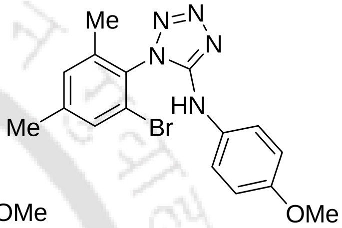
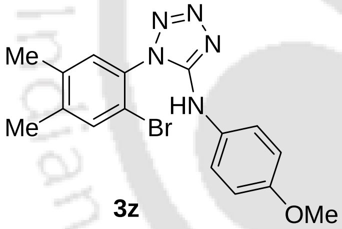
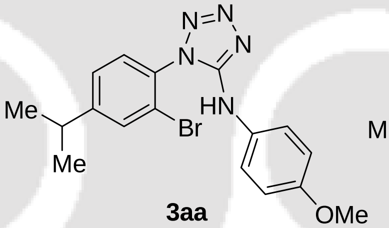
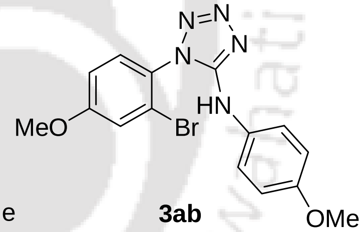
 **3b** 95%	 **3c** 90%	 **3d** 96%	 **3e** 97%
 **3f** 89%	 **3g** 85%	 **3h** 82%	 **3i** 84%
 **3j** 96%	 **3k** 92%	 **3l** 90%	 **3m** 91%
 **3n** 95%	 **3o** 87%	 **3p** 82%	 **3q** 77%

Table 2 conti……….

 **3r** 70%	 **3s** 67%	 **3t** 75%	 **3u** 72%
 **3v** 75%	 **3w** 89%	 **3x** 92%	 **3y** 92%
 **3z** 85%	 **3aa** 86%	 **3ab** 95%	

[a] Reaction conditions: Isothiocyanate (1 mmol), 2-bromo-4-methylbenzenamine (1 mmol), DMF (1.5 mL), room temperature, 11-22 h, then NaN_3 (3 mmol), Et_3N (3 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (50 mol %), room temperature, 3-6 h.

[b] Isolated yield.

gave inferior results. Both copper(I) and copper(II) were effective affording the target product in 100% conversion. Control experiments without the copper source showed no 5-aminotetrazole formation and thiourea was obtained as a sole product.

Next, the scope of the procedure was explored for the reaction of substituted isothiocyanates, 2-bromoanilines and sodium azide. A series of substrates proceeded reaction to give the corresponding tetrazoles **3a-ab** in moderate to high yield. Aryl isothiocyanates having electron donating substituents on the aryl ring (4-Me, 4-OMe, 4-^{i}Pr, 4-Et, 2,4-dimethyl, 3,4-dimethyl, 2,5-dimethyl, 2,6-dimethyl and 3,5-dimethyl groups) were more reactive than that bearing electron-withdrawing substituents (4-NO_2, 4-CN, 4-Cl, 4-F and 4-CF_3 groups), whereas, naphthyl isothiocyanate and aliphatic isothiocyanates gave the corresponding tetrazoles **3q-v** in 67-77% yield. In case of 2-bromoainiline component, the use of both 2-bromoaniline and substituted 2-bromoaniline with the 4-Me, 4-^{i}Pr, 4-Cl, 4-OMe, 2,4-dimethyl and 3,4-dimethylbromoaniline groups gave the tetrazoles **3w-ab** in good yield. Recrystallization of **3a** in MeOH gave crystals whose structure was confirmed by single-crystal X-ray analysis (Figure 2).

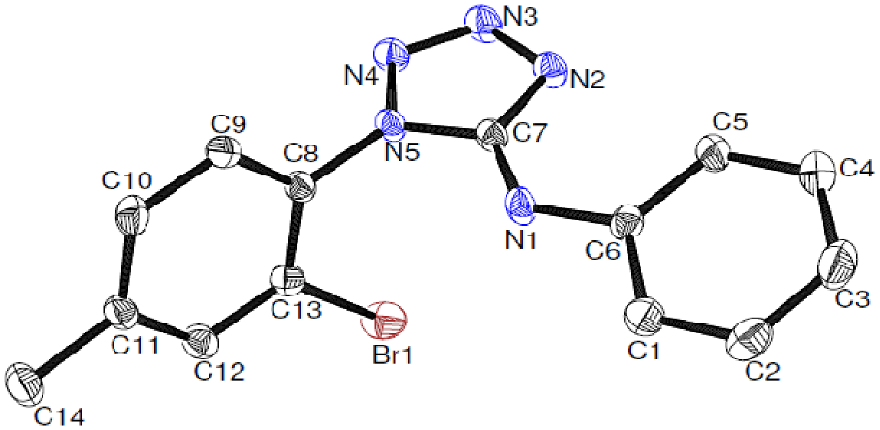
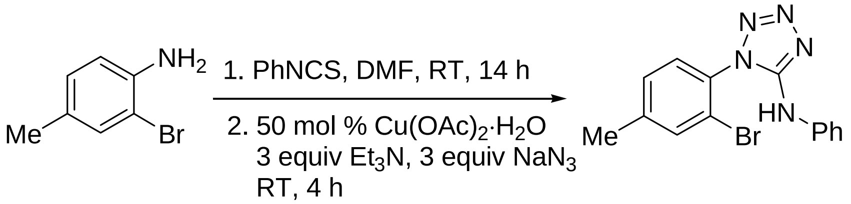


Figure 2. ORTEP diagram of 1-(2-bromo-4-methylphenyl)-*N*-phenyl-1*H*-tetrazol-5-amine **3a** with 50% ellipsoid. H-Atoms are omitted for clarity.

To reveal the reaction pathway, a 1:1 mixture of 4-methyl-2-bromoaniline and phenyl isothiocyanate was stirred in DMF at room temperature for 14 h to afford the corresponding



Scheme 10

thiourea.[15a] The latter when treated with a mixture of 3 equiv sodium azide, 3 equiv Et_3N and 50 mol % $Cu(OAc)_2 \cdot H_2O$, the reaction proceeded to give the tetrazole in 100% conversion (Scheme 10).

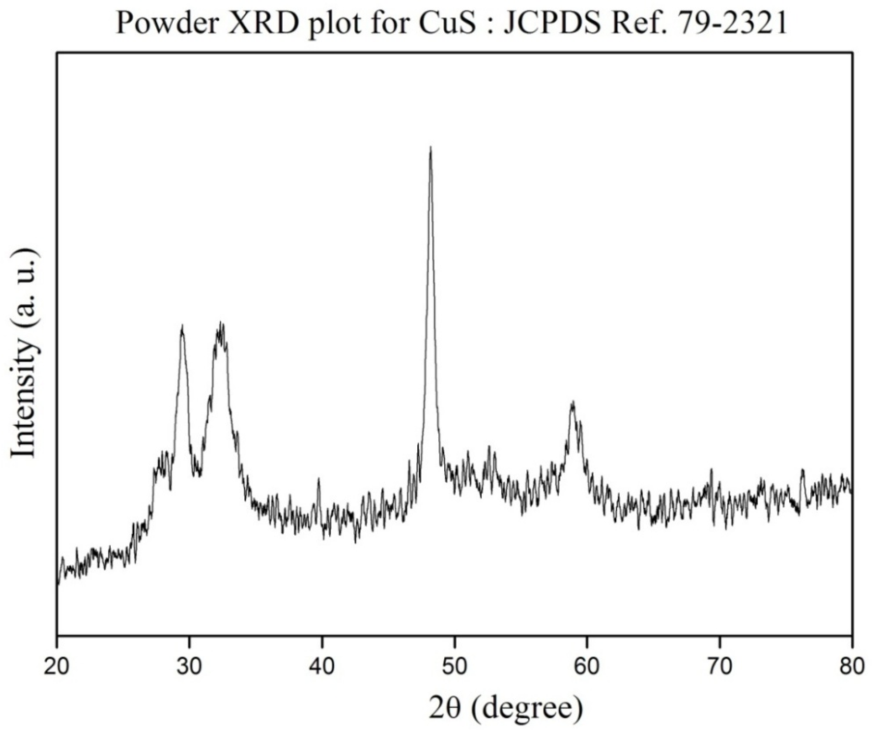
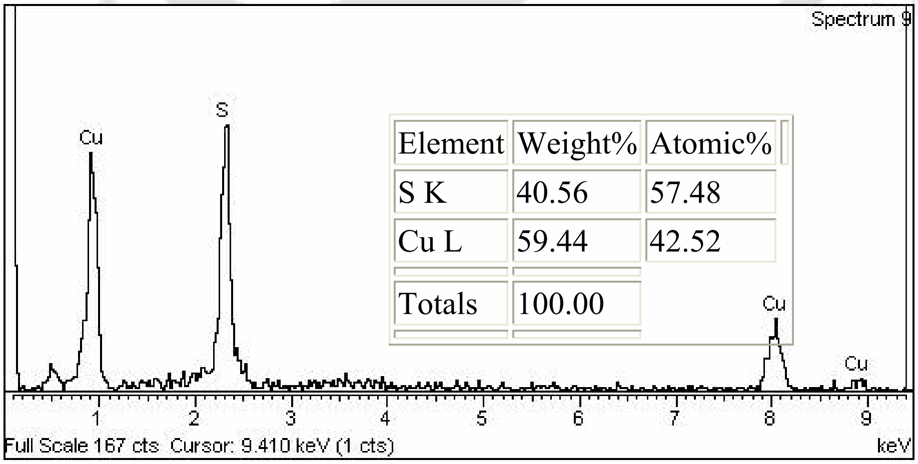


Figure 3. Powder XRD plot of isolated CuS



Element	Weight%	Atomic%
S K	40.56	57.48
Cu L	59.44	42.52
Totals	100.00	

Figure 4. EDX spectrum of isolated CuS

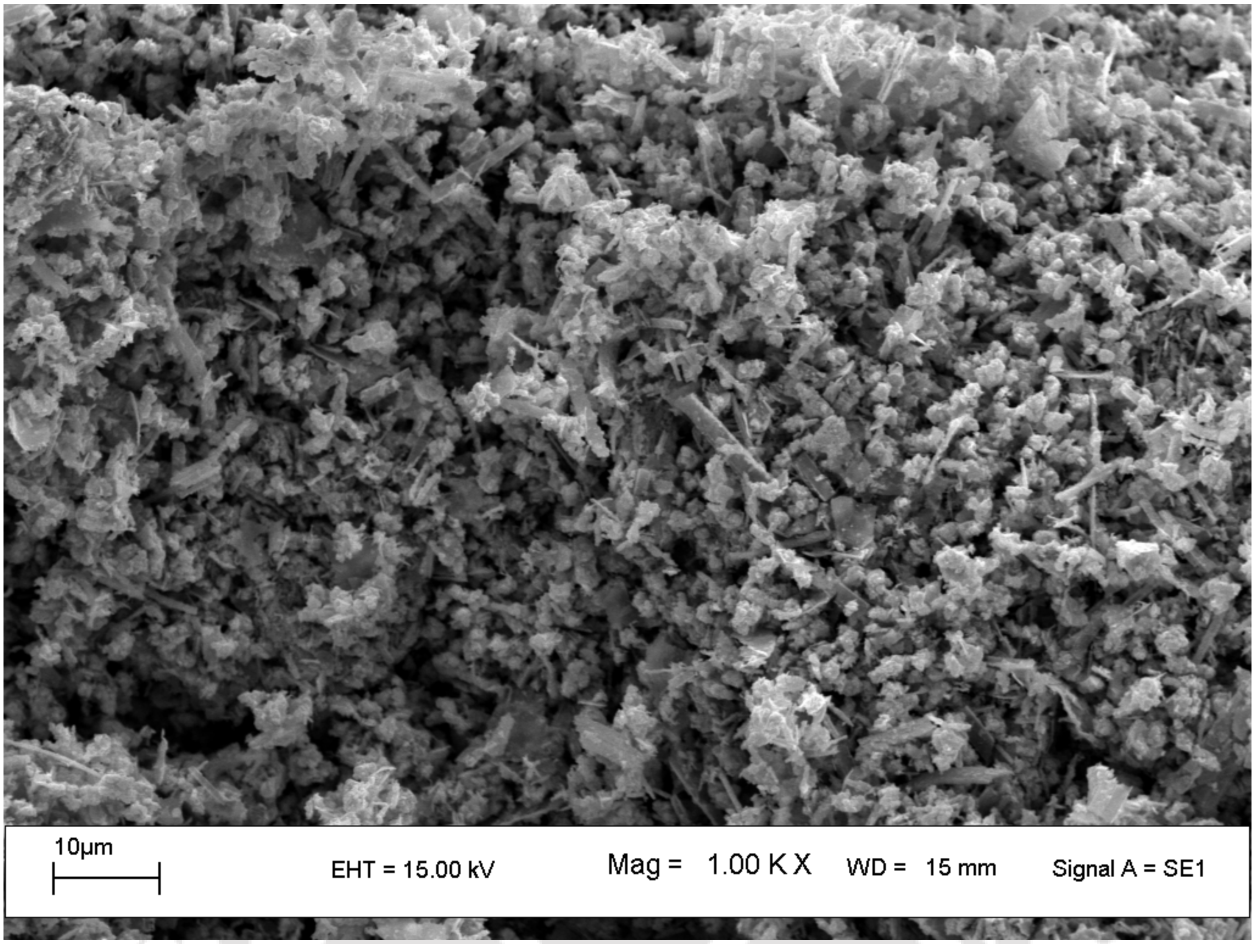
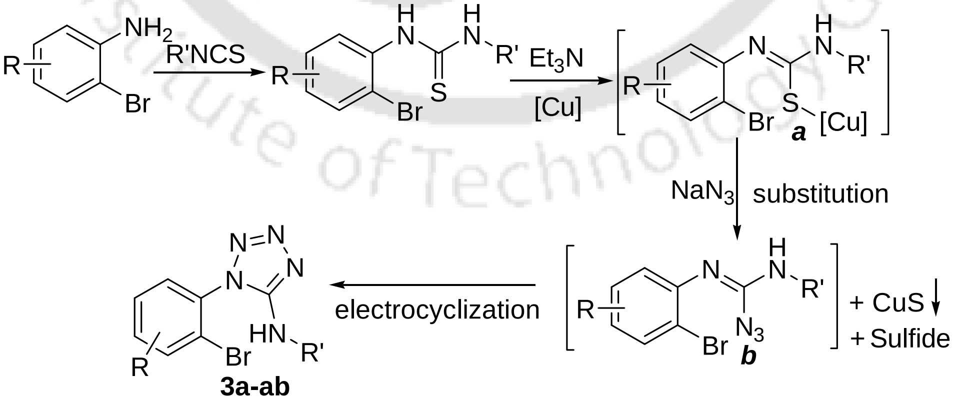


Figure 5. SEM image of isolated CuS and S



Scheme 11. Proposed catalytic cycle

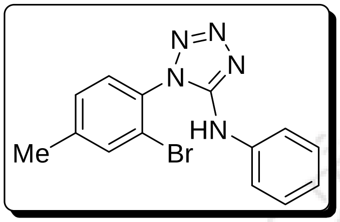
These results clearly show that the reaction of 2-bromoaniline and isothiocyanate gives a thiourea, which in the presence of copper source and Et_3N may give intermediate ***a*** (Scheme 11). Nucleophilic substitution of ***a*** with sodium azide gives ***b*** with CuS and a sulphide as byproduct, which were characterised by SEM and powder XRD analysis (Figures 3-5). Electrocyclization of ***b*** gave the tetrazole derivatives **3a-ab** in high yield.[15b]

In conclusion, copper-promoted three-component synthesis of substituted 5-aminotetrazoles has been developed from the readily accessible isothiocyanates, bromoanilines and sodium azide at room temperature. This procedure is simple and has wide substrate scope to afford the target products with excellent regioselectivity and yield.

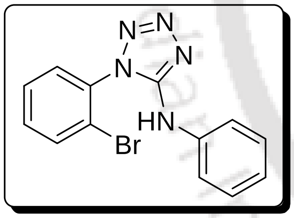
Experimental Section

General Information. NaN_3 and Et_3N were obtained from Merck. Substituted isothiocyantes[16] and bromo anilines[17] were prepared according to reported procedure. Product purification was carried out by silica gel column chromatography using Rankem silica gel (60-120 mesh). All reactions were monitored by analytical TLC on Merck silica gel G/GF 254 plates. NMR (^1H and ^{13}C) spectra were recorded on DRX-400 Varian spectrometer and the data are accounted as follows: chemical shifts (δ ppm) (multiplicity, coupling constant (J Hz), integration).The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet. Melting points were determined by Buchi B-540 melting point apparatus. FT-IR spectra of air-dried samples were recorded on PerkinElmer Spectrum One FT-IR spectrometer using KBr disks and are reported in frequency of absorption (cm^{-1}). Elemental analyses were recorded using PerkinElmer CHNS analyzer. Powder X-ray diffraction (XRD) pattern of dried crystalline catalyst was recorded on a X-ray diffractometer with Cu Kα irradiation ($\lambda = 1.54$ Å) at 40 kV and 40 mA with a scan rate of 0.1°/s for 2θ in the range of 20-80°. SEM image was recorded with Leo 1430vp instrument. For single crystal X-ray analysis the intensity data were collected using Bruker SMART APEX-II CCD diffractometer, equipped with 1.75 kW sealed-tube Mo Kα irradiation ($\lambda = 0.71073$ Å) at 296(2) K and the structures were solved by direct methods using *SHELLX-97* (Göttingen, Germany) and refined with full-matrix least squares on F^2 using SHELXL-97.

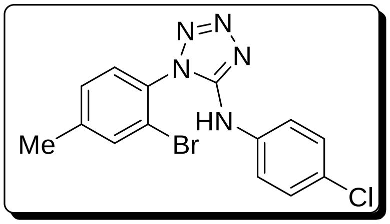
General Procedure for Regioselective Synthesis of Substituted Tetrazoles. Isothiocyanate (1 mmol) and substituted 2-bromoaniline (1 mmol) were stirred at room temperature in DMF (1.5 mL) for 11-22 h. Then, NaN_3 (3 mmol), $Cu(OAc)_2{\cdot}H_2O$ (50 mol %) and Et_3N (3 mmol) were added. The resulting mixture was stirred for 3-6 h at room temperature. The black colored CuS precipitate formed was removed from the reaction mixture by centrifugation, and the solution was extracted with EtOAc (3 x 10mL) and washed with brine (1 x 5 mL) and water (2 x 5 mL). Drying and evaporation of the solvent provided a residue which was purified by silica gel chromatography using ethyl acetate and hexane as eluent to provide the titled compound.



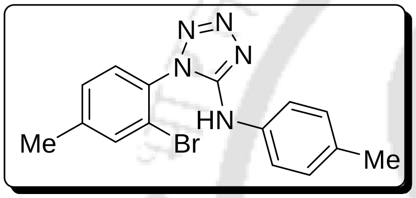
1-(2-Bromo-4-methylphenyl)-*N*-phenyl-1*H*-tetrazol-5-amine 3a: White solid; yield 95%; mp 146-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.52 (d, *J* = 8 Hz, 2H), 7.36-7.28 (m, 4H), 7.03 (t, *J* = 14.8 Hz, 1H), 6.55 (br s, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 152.7,142.4, 138.7, 133.2, 128.8, 128.7, 128.0, 121.6, 120.8, 117.7, 20.1; FT-IR (KBr) 3285, 3056, 1603, 1574, 1534, 1497, 1456, 1321, 1234, 1121, 1085 cm^{-1}. Anal. Calcd. for $C_{14}H_{12}N_5Br$: C, 50.93; H, 3.66; N, 21.21. Found: C, 51.06; H, 3.64; N, 21.14.



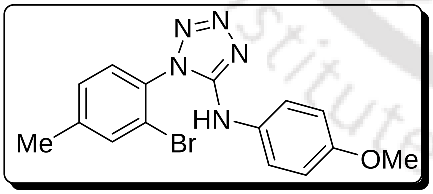
1-(2-Bromophenyl)-*N*-phenyl-1*H*-tetrazol-5-amine 3b: White solid; yield 95%; mp 159-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8 Hz**,** 1H), 7.46 (d, *J* = 8 Hz, 2H), 7.39-7.33 (m, 4H), 7.15 (t, *J* = 15.2 Hz, 2H), 6.9 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 152.0, 138.4, 132.8, 131.6, 129.2, 128.5, 128.1, 127.8, 121.5, 120.9, 117.6; FT-IR (KBr) 3076, 2924, 1614, 1574, 1529, 1497, 1485, 1318, 1242, 1082 cm^{-1}. Anal. Calcd. for $C_{13}H_{10}N_5Br$: C, 49.39; H, 3.19; N, 22.15. Found: C, 49.51; H, 3.18; N, 22.07.



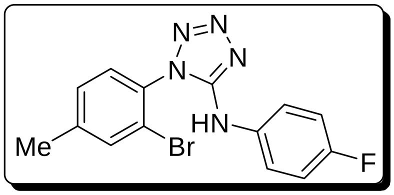
1-(2-Bromo-4-methylphenyl)-*N*-(4-chlorophenyl)-1*H*-tetrazol-5-amine 3c: White solid; yield 90%; mp 137-138 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.77 (s, 1H), 7.50 (t, *J* = 9.2 Hz, 2H), 7.26 (d, *J* = 7.6 Hz 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 4.66 (br s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-d$_6$) δ 151.1, 141.7, 136.9, 132.3, 128.3, 128.1, 127.7, 127.0, 124.7, 120.0, 118.1, 19.2; FT-IR (KBr) 3076, 2958, 2150, 1637, 1504, 1421, 1374, 1330, 1256, 1207, 1030 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}ClN_5Br$: C, 46.12; H, 3.04; N, 19.21. Found: C, 46.22; H, 3.03; N, 24.14.



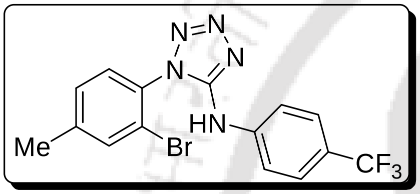
1-(2-Bromo-4-methylphenyl)-*N*-p-tolyl-1*H*-tetrazol-5-amine 3d: White solid; yield 96%; mp 144-145 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63 (s, 1H), 7.45-7.32 (m, 4H), 7.12 (d, *J* = 8 Hz, 2H), 5.98 (br s, 1H), 2.46 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-d$_6$) δ 152.3, 142.2, 135.9, 133.0, 130.8, 129.8, 128.7, 128.5, 123.2, 120.6, 117.8, 20.0, 19.6; FT-IR (KBr) 3256, 3095, 1613, 1574, 1514, 1315, 1234, 1120, 1094, 1017 cm^{-1}. Anal. Calcd. for $C_{15}H_{14}N_5Br$: C, 52.34; H, 4.10; N, 20.35. Found: C, 52.48; H, 4.08; N, 26.26.



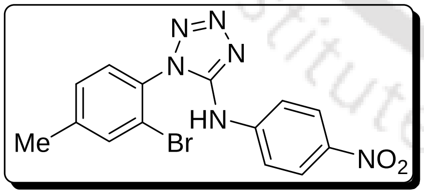
1-(2-Bromo-4-methylphenyl)-*N*-(4-methoxyphenyl)-1*H*-tetrazol-5-amine 3e: White solid; yield 97%; mp 131-132 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.28 (d, *J* = 8.4 Hz, 1H), 7.46-7.42 (m, 2H), 7.30 (s, 1H), 7.16-7.08 (m, 3H), 7.00 (br s, 1H), 3.87 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-d$_6$) δ 154.7, 153.1, 142.9, 133.7, 132.6, 129.7, 129.5, 129.3, 126.1, 121.3, 114.9, 55.02, 20.56; FT-IR (KBr) 3345, 2857, 1567, 1535, 1506, 1321, 1271, 1235, 1182, 1123, 1074, 1033 cm^{-1}. Anal. Calcd. for $C_{15}H_{14}N_5OBr$: C, 50.02; H, 3.92; N, 19.44. Found: C, 50.14; H, 3.91; N, 19.38.



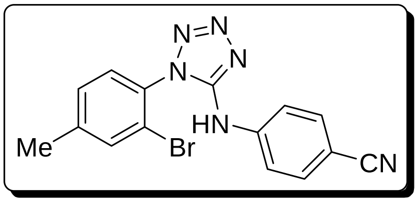
1-(2-Bromo-4-methylphenyl)-*N*-(4-fluorophenyl)-1*H*-tetrazol-5-amine 3f: White solid; yield 89%; mp 147-148 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (s, 1H), 7.49-7.34 (m, 4H), 7.00 (t, J = 8.4 Hz, 2H), 6.14 (br s, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-d$_6$) δ 158.2, 155.8, 152.1, 142.1, 134.7, 133.0, 128.6, 128.4 (d, $^3J_{CF}$ = 9.9 Hz), 120.6, 119.2 (d, $^4J_{CF}$ = 7.6 Hz), 114.2 (d, $^2J_{CF}$ = 22.8 Hz), 20.0; FT-IR (KBr) 3266, 3105, 1622, 1587, 1533, 1587, 1319, 12261087, 1018 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}FN_5Br$: C, 48.29; H, 3.18; N, 20.11. Found: C, 48.42; H, 3.17; N, 20.03.



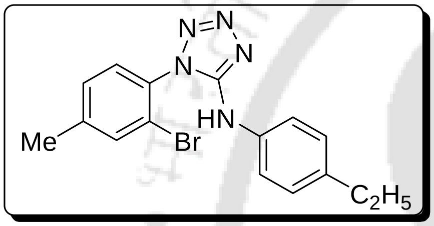
1-(2-Bromo-4-methylphenyl)-*N*-(4-(trifluoromethyl)-phenyl)-1*H*-tetrazol-5-amine 3g: White solid: yield 85%; mp 186-187 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.81 (d, J = 8.4 Hz, 2H), 7.65 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.43-7.36 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-d$_6$) δ 151.9, 142.8, 142.1, 133.5, 129.0, 128.7, 125.3, 125.1, 123.0, 122.7, 122.4, 121.0, 117.3, 20.3; FT-IR (KBr) 3284, 3127, 1613, 1576, 1534, 1499, 1402, 1338, 1252, 1198, 1164, 1115, 1016 cm^{-1}. Anal. Calcd. for $C_{15}H_{11}F_3N_5Br$: C, 45.25; H, 2.78; N, 17.59. Found: C, 45.40; H, 2.75; N, 17.51.



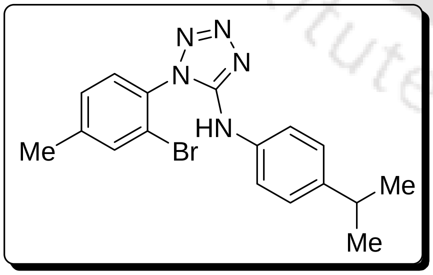
1-(2-Bromo-4-methylphenyl)-*N*-(4-nitrophenyl)-1*H*-tetrazol-5-amine 3h: White solid: yield 82%; mp 186-187 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.92 (br s, 1H), 8.09-8.05 (m, 2H), 7.78-7.75 (m, 2H), 7.26 (s, 1H), 7.07-7.04 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-d$_6$) δ 152.8, 146.3, 143.8, 141.8, 137.3, 129.6, 127.1, 125.6, 121.0, 120.7, 118.0, 21.5; FT-IR (KBr) 3314, 3109, 2115, 1619, 1509, 1330, 1250, 1112, 1088, 1025 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}BrN_6O_2$: C, 44.82; H, 2.96; N, 22.40. Found: C, 44.95; H, 2.94; N, 22.34.



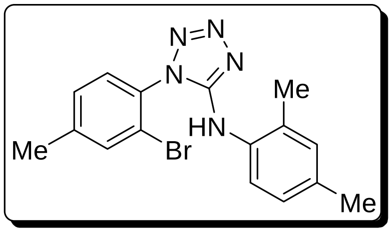
4-(1-(2-Bromo-4-methylphenyl)-1*H*-tetrazol-5-ylamino)-benzonitrile 3i: White solid: yield 84%; mp 186-187 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.66 (d, *J* = 7.6 Hz, 2H), 7.46 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 152.0, 143.5, 143.2, 133.8, 132.7, 129.4, 128.9, 121.2, 118.0, 117.4, 104.0, 20.7; FT-IR (KBr) 3269, 3188, 2227, 1602, 1532, 1324, 1248, 1175, 1085 cm^{-1}. Anal. Calcd. for $C_{15}H_{11}BrN_6$: C, 50.72; H, 3.12; N, 23.66. Found: C, 50.86; H, 3.10; N, 23.59.



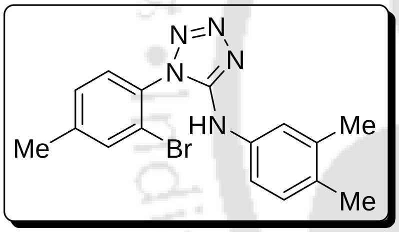
1-(2-Bromo-4-methylphenyl)-*N*-(4-ethylphenyl)-1*H*-tetrazol-5-amine 3j: White solid; yield 96%; mp 139-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.37-7.35 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.00 (br s, 1H), 2.62-2.56 (q, 2H), 2.46 (s, 3H), 1.20 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 151.5, 141.5, 136.3, 135.8, 132.4, 128.3, 128.1, 126.4, 122.8, 120.0, 117.1, 26.3, 19.3, 14.3; FT-IR (KBr) 3250, 3090, 2928, 1610, 1574, 1496, 1449, 1309, 1246, 1125, 1096 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_5Br$: C, 53.64; H, 4.50; N, 19.55. Found: C, 53.76; H, 4.49; N, 19.48.



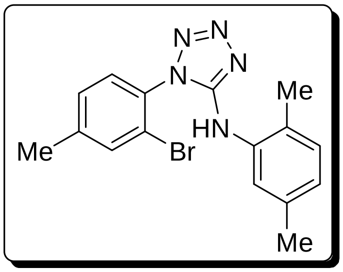
2-1-(2-Bromo-4-methylphenyl)-*N*-(4-isopropylphenyl)-1*H*-tetrazol-5-amine 3k: White solid; yield 92%; mp 144-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.37-7.32 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 5.99 (br s, 1H), 2.88-2.83 (m, 1H), 2.46 (s, 3H), 1.20 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 151.7, 141.6, 141.2, 135. 9, 132.5, 128.4, 128.2, 128.1, 125.0, 120.1, 117.2, 31.6, 22.6, 19.4; FT-IR (KBr) 3251, 3090, 2960, 1611, 1574, 1496, 1447, 1307, 1243, 1126, 1097 cm^{-1}. Anal. Calcd. for $C_{17}H_{18}N_5Br$: C, 54.85; H, 4.87; N, 18.81. Found: C,54.98; H, 4.86; N, 18.75.



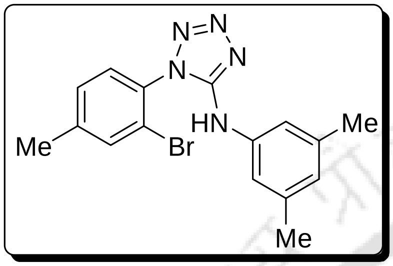
1-(2-Bromo-4-methylphenyl)-*N*-(2,4-dimethylphenyl)-1*H*-tetrazol-5-amine 3l: White solid; yield 90%; mp 138-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8 Hz, 1H), 7.22 (s, 1H), 7.16 (d, *J* = 8 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 2H), 6.71 (s, 1H), 2.43 (s, 3H), 2.39 (s, 1H), 2.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 154.9, 143.4, 135.3, 134.8, 134.1, 133.2, 133.1, 131.4, 130.0, 129.9, 127.1, 125.5, 121.4, 21.0, 20.9, 18.1; FT-IR (KBr) 3156, 2976, 1607, 1573, 1495, 1447, 1244, 1122, 1088, 1070 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_5Br$: C, 53.64; H, 4.50; N, 19.55. Found: C, 53.74; H, 4.49; N, 19.50.



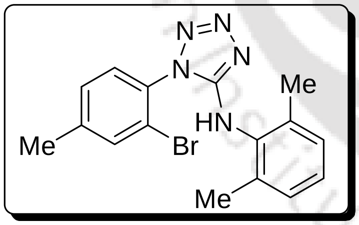
1-(2-Bromo-4-methylphenyl)-*N*-(3,4-dimethylphenyl)-1*H*-tetrazol-5-amine 3m: White solid; yield 91%; mp 120-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.30-7.22 (m, 4H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.59 (br s, 1H), 2.41 (s, 3H), 2.19 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 151.4, 141.5, 135.7, 134.8, 132.2, 128.3, 128.0, 127.8, 119.9, 118.0, 114.2, 19.0, 18.1, 17.1; FT-IR (KBr) 3275, 2923, 2856, 1574, 1533, 1498, 1455, 1375, 1315, 1254, 1218, 1168, 1115, 1092, 1020 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_5Br$: C, 53.64; H, 4.50; N, 19.55. Found: C, 53.77; H, 4.48; N, 19.47.



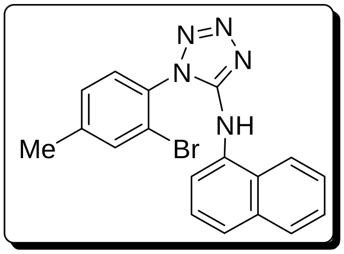
1-(2-Bromo-4-methylphenyl)-*N*-(2,5-dimethylphenyl)-1*H*-tetrazol-5-amine 3n: White solid; yield 95%; mp 120-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.65 (s, 1H), 7.38-7.33 (m, 2H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 1H), 5.90 (br s, 1H), 2.47 (s, 3H), 2.34 (s, 6H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 154.2, 142.8, 136.7, 135.4, 133.7, 130.3, 129.6, 129.4, 129.3, 126.1, 125.2, 121.0, 20.6, 20.5, 17.4; FT-IR (KBr) 2921, 1587, 1527, 1492, 1462, 1381, 1306, 1263, 1088 cm^{-1}. Anal. Calcd. for $C_{16}H_{15}N_5$: C, 53.64; H, 4.50; N, 19.55. Found: C, 53.76; H, 4.47; N, 19.48.



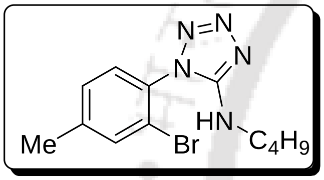
1-(2-Bromo-4-methylphenyl)-*N*-(3,5-dimethylphenyl)-1*H*-tetrazol-5-amine 3o: White solid; yield 87%; mp 132-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.15 (s, 2H), 6.70 (s, 1H), 5.93 (br s, 1H), 2.46 (s, 3H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 152.9, 142.9, 139.1, 138.0, 133.8, 129.5, 129.4, 129.3, 123.9, 121.4, 116.1, 21.2, 20.7; FT-IR (KBr) 3267, 3104, 1624, 1587, 1540, 1502, 1327, 1175, 1126, 1088 cm^{-1}. Anal. Calcd. for $C_{16}H_{15}N_5$: C, 53.64; H, 4.50; N, 19.55. Found: C, 53.75; H, 4.49; N, 19.47.



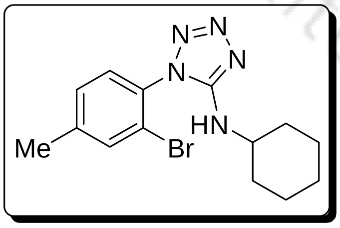
1-(2-Bromo-4-methylphenyl)-*N*-(3,5-dimethylphenyl)-1*H*-tetrazol-5-amine 3p: White solid; yield 82%; mp 147-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 5.96 (br s, 1H), 2.46 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 153.4, 152.3, 143.5, 139.8, 138.5, 134.4, 130.1, 129.9, 124.5, 122.1, 116.7, 21.8, 21.4; FT-IR (KBr) 3267, 3104, 2920, 1624, 1587, 1540, 1501, 1326, 1175, 1126, 1088 cm^{-1}. Anal. Calcd. for $C_{16}H_{15}N_5$: C, 53.64; H, 4.50; N, 19.55. Found: C, 53.76; H, 4.48 ; N, 19.49.



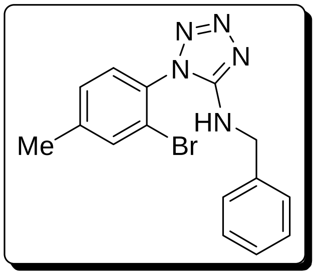
1-(2-Bromo-4-methylphenyl)-*N*-(naphthalen-1-yl)-1*H*-tetrazol-5-amine 3q: White solid; yield 77%; mp 123-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H), 7.71-7.63 (m, 3H), 7.51-7.47 (m, 2H), 7.35 (d, *J* = 8 Hz, 1H), 7.26 (d, *J* = 5.2 Hz, 2H), 6.60 (br s, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 154.6, 142.6, 134.2, 133.8, 133.6, 131.2, 129.4, 129.1, 128.8, 128.3, 127.8, 127.2, 125.8, 125.4, 122.4, 121.1, 120.8, 20.6; FT-IR (KBr) 3205, 3052, 1599, 1523, 1392, 1313, 1263, 1088, 1015 cm^{-1}. Anal. Calcd. for $C_{18}H_{14}N_5Br$: C, 56.86; H, 3.71; N, 18.42. Found: C, 56.96; H, 3.70; N, 18.36.



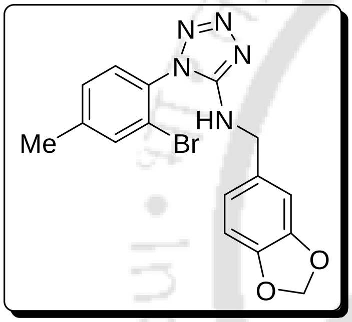
1-(2-Bromo-4-methylphenyl)-*N*-butyl-1*H*-tetrazol-5-amine 3r: White solid; yield 70%; mp 123-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 3.99 (br s, 1H), 3.48 (t, *J* = 6.8 Hz, 2H), 2.45 (s, 3H), 1.67-1.58 (m, 2H), 1.42-1.32 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 154.8, 141.9, 133.1, 128.6, 128.0, 120.5, 42.6, 30.3, 19.9, 18.7, 12.8; FT-IR (KBr) 3274, 2955, 2869, 1617, 1526, 1498, 1453, 1313, 1086, 1014 cm^{-1}. Anal. Calcd. for $C_{12}H_{16}N_5Br$: C, 46.46; H, 5.20; N, 22.58. Found: C, 46.59; H, 5.18; N, 22.50.



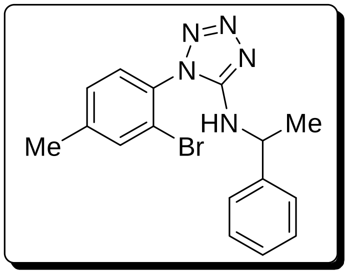
1-(2-Bromo-4-methylphenyl)-*N*-cyclohexyl-1*H*-tetrazol-5-amine 3s: White solid; yield 67%; mp 132-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.12 (d, *J* = 8.8 Hz , 2H), 4.57 (d, *J* = 8 Hz, 1H), 2.38 (s, 3H), 1.54-1.40 (m, 3H), 1.20-0.89 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 153.6, 141.2, 132.4, 128.4, 128.1, 128.0, 120.0, 51.9, 31.2, 23.9, 23.6, 19.4; FT-IR (KBr) 3242, 2920, 2852, 1587, 1510, 1452, 1132, 1093 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}N_5Br$: C, 50.01; H, 5.40; N, 20.83. Found: C, 50.12; H, 5.39 ; N, 20.75.



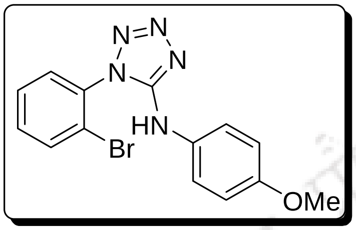
***N*-Benzyl-1-(2-bromo-4-methylphenyl)-1*H*-tetrazol-5-amine 3t**: White solid; yield 75%; mp 124-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.34-7.32 (m, 4H), 7.30-7-28 (m, 3H), 4.64 (d, *J* = 5.6 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 154.2, 141.3, 137.3, 132.2, 128.0, 127.9, 126.5, 125.6, 125.3, 119.7, 45.3, 19.0; FT-IR (KBr) 3183, 3002, 1614, 1524, 1497, 1145, 1093 cm^{-1}. Anal. Calcd. for $C_{15}H_{14}N_5Br$: C, 52.34; H, 4.10; N, 20.35. Found: C, 52.48; H, 4.09; N, 20.28.



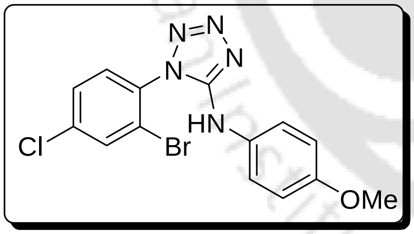
***N*-((Benzo[*d*][1,3]dioxol-5-yl)methyl)-1-(2-bromo-4-methyl-phenyl)-1*H*-tetrazol-5-amine 3u**: White solid; yield 72%; mp 159-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 6.82 (t, *J* = 6 Hz, 1H), 6.76 (s, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.61 (d, *J* = 8 Hz, 1H), 5.82 (s, 2H), 4. 33 (d, *J* = 5.6 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ154.2, 145.8, 144.8, 141.4, 132.3, 131.2, 128.1, 119.9, 119.1, 106.5, 106.3, 99.3, 45.3, 19.2; FT-IR (KBr) 3360, 2933, 1622, 1516, 1463, 1257, 1232, 1154, 1091, 1026 cm^{-1}. Anal. Calcd. for $C_{16}H_{14}N_5O_2Br$: C, 49.50; H, 3.63; N, 18.04. Found: C, 49.61; H, 3.61; N, 17.98.



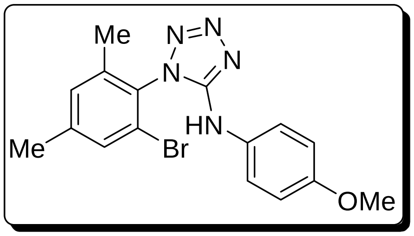
1-(2-bromo-4-methylphenyl)-*N*-(1-phenylethyl)-1*H*-tetrazol-5-amine 3v: White solid; yield 75%; mp 124-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, 1H), 7.42-7.3 (m, 3H), 7.30-7-26 (m, 4H), 5.11-5.08 (q, 1H), 2.47 (s, 3H), 1.60 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 154.6, 143.4, 142.3, 133.4, 129.3, 129.1, 128.2, 127.7, 126.4, 125.6, 121.1, 53.2, 22.1, 20.4; FT-IR (KBr) 3349, 3083, 2902, 1614, 1524, 1497,1201, 1145, 1093, 1101 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}BrN_5$: C, 53.64; H, 4.50; N, 19.55. Found: C, 53.78; H, 4.48; N, 19.49.



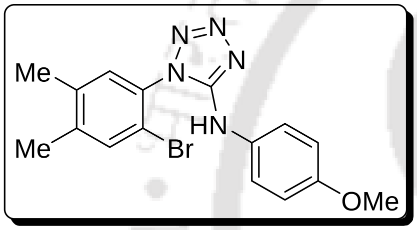
1-(2-Bromophenyl)-*N*-(4-methoxyphenyl)-1*H*-tetrazol-5-amine 3w: White solid: yield 89%; mp 150-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.6 Hz, 1H), 7.54-7.47 (m, 3H), 7.40 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.02 (br s, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 155.0, 153.0, 133.4, 132.1, 131.9, 129.7, 128.5, 121.7, 120.2, 114.6, 113.6, 55.0; FT-IR (KBr) 3057, 2961, 2835, 1616, 1513, 1498, 1431, 1331, 1301, 1292, 1253, 1183, 1035 cm^{-1}. Anal. Calcd. for $C_{14}H_{12}N_5OBr$: C, 48.57; H, 3.49; N, 20.23. Found: C, 48.68; H, 3.48; N, 20.15.



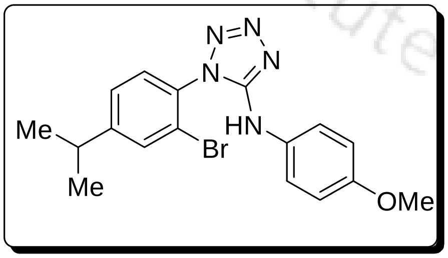
1-(2-Bromo-4-chlorophenyl)-*N*-(4-methoxyphenyl)-1*H*-tetrazol-5-amine 3x: White solid; yield 92%; mp 171-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.0 Hz, 1H), 7.47-7.44 (m, 1H), 7.40-7.37 (m, 2H), 7.10 (d, *J* = 9.2 Hz, 1H), 6.94 (br s, 1H), 6.81 (dd, *J* = 7.2, 2.4 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 153.9, 152.1, 135.8, 131.9, 131.2, 130.1, 129.9, 127.9, 121.8, 119.2, 112.7, 54.04; FT-IR (KBr) 3275, 3085, 2834, 1607, 1579, 1486, 1302, 1233, 1179, 1085, 1036 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}ClN_5OBr$: C, 44.18; H, 2.91; N, 18.40. Found: C, 44.30; H, 2.90; N, 18.34.



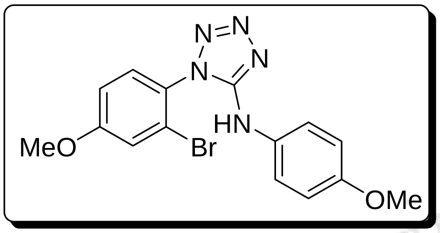
1-(2-Bromo-4,6-dimethylphenyl)-*N*-(4-methoxyphenyl)-1*H*-tetrazol-5-amine 3y: White solid; yield 92%; mp 167-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.42 (m, 3H), 7.19 (s, 1H), 6.87 (d, *J* = 7.2 Hz, 2H), 5.8 (br s, 1H), 3.89 (s, 3H), 2.42(s, 3H), 2.10(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 152.5, 152.4, 131.8, 130.7, 130.3, 127.6, 121.8, 119.9, 113.2, 54.6, 20.2, 17.3; FT-IR (KBr) 3289, 2957, 1607, 1575, 1516, 1301, 1261, 1235, 1182, 1113, 1094, 1033 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_5OBr$: C, 51.35; H, 4.31; N, 18.71. Found: C, 51.47; H, 4.29; N, 18.64.



1-(2-Bromo-4,5-dimethylphenyl)-*N*-(4-methoxyphenyl)-1*H*-tetrazol-5-amine 3z: White solid; yield 85%; mp 148-149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.57 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H), 2.37 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 153.3, 151.6, 140.3, 136.3, 132.3, 131.2, 129.1, 127.8, 118.6, 116.6, 112.3, 53.6, 17.6, 17.3; FT-IR (KBr) 3306, 2920, 2847, 1603, 1515, 1444, 1302, 1236, 1302, 1236, 1191, 1115, 1095, 1020 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_5OBr$: C, 51.35; H, 4.31; N, 18.71. Found: C, 51.49; H, 4.30; N, 18.65.



1-(2-Bromo-4-isopropylphenyl)-*N*-(4-methoxyphenyl)-1*H*-tetrazol-5-amine 3aa White solid; yield 86%; mp 137-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.41-7.37 (m, 4H), 6.85 (dd, *J* = 3.2, 9.2 Hz, 2H), 5.98 (br s, 1H), 3.76 (s, 3H), 3.02-2.96 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 155.7, 154.2, 153.9, 132.9, 132.1, 130.2, 127.4, 122.2, 121.2, 114.3, 55.7, 34.1, 24.0; FT-IR (KBr) 3307, 2956, 1608, 1578, 1513, 1466, 1301, 1266, 1232, 1180, 1112, 1092, 1039 cm^{-1}. Anal. Calcd. for $C_{17}H_{18}N_5OBr$: C, 52.59; H, 4.67; N, 18.04. Found: C, 52.70; H, 4.65; N, 17.97.



1-(2-Bromo-4-methoxyphenyl)-*N*-(4-methoxyphenyl)-1*H*-tetrazol-5-amine 3ab: White solid; yield 95%; mp 125-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.45-7.42 (m, 2H), 7.35 (d, *J* = 8.8 Hz, 1H), 6.98 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.77 (dd, *J* = 2.0, 9.2 Hz, 2H), 3.83 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 160.5, 154.0, 152.5, 131.6, 129.7, 123.6, 121.8, 119.3, 117.7, 113.2, 112.8, 54.9, 54.2; FT-IR (KBr) 3259, 3103, 2839, 1621, 1582, 1600, 1497, 1295, 1237, 1222, 1100, 1029 cm^{-1}. Anal. Calcd. for $C_{15}H_{14}N_5O_2Br$: C, 47.89; H, 3.75; N, 18.62. Found: C, 48.04; H, 3.73; N, 18.55.

3.4 References

(1) (a) Wittenberger, S. *Org. Prep. Proced. Int.* **1994**, *26*, 499. (b) Herr, R. J. *Biorg. Med. Chem.* **2002**, *10*, 3379.

(2) (a) Ek, F.; Wistrandand, L.-G.; Frejd, T. *Tetrahedron* **2003**, *59*, 6759. (b) Flippin, L. A. *Tetrahedron Lett.* **1991**, *32*, 6857. (c) Rhonnstad, P.; Wensbo, D. *Tetrahedron Lett.* **2002**, *43*, 3137.

(3) Modarresi-Alam, A. R.; Khamooshi, F.; Rostmizadeh, M.; Kieykha, H.; Nasrollahzadeh, M.; Bijanzadeh, H. R.; Kleinpeter, E. *J. Mol. Struct.* **2007**, *841*, 67.

(4) (a) Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379. (b) Butler, R. N.; *In Comprehensive Heterocyclic Chem.* II, Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Pergamon, E. New York, 1996, *4*, 621. (c) Burger, A. *Prog. Drug. Res.* **1991**, *37*, 287. (d) Voitekhovich, S. V.; Gaponikand, P. N.; Ivashkevich, O. A. *Russ. Chem. Rev.* **2002**, *71*, 721. (e) Thornber, C. W. *Chem. Soc. Rev.* **1979**, *8*, 563. (f) Singh, H.; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. *Prog. Med. Chem.* **1980**, *17*, 151. (g) Butler, R.

N. *Adv. Heterocycl. Chem.* **1977**, *21*, 323. (h) Lipinski, C. A. *Annu. Rep. Med. Chem.* **1986**, *27*, 283.

(5) Hansch, C.; Leo, L. *Exploring QSAR. Fundamentals and Applications in Chemistry and Biology;* American Chemical Society: Washington, DC, 1995; Chapter13.

(6) (a) Ford, R. E.; Knowles, P.; Lunt, E.; Marshall, S. M.; Penrose, A. J.; Ramsden, C. A.; Summers, A. J. H.; Walker, J. L.; Wright, D. E. *J. Med. Chem.* **1986**, *29*, 538. (b) Peet, N. P.; Baugh, L. E.; Sundler, S.; Lewis, J. E.; Matthews, E. H.; Olberding, E. L.; Shah, D. N. *J. Med. Chem.* **1986**, *29*, 2403.

(7) (a) Habich, D. *Synthesis* **1992**, 358. (b) Huskey, S.-E. W.; Doss, G. A.; Miller, R. R.; Schoen, W. R.; Chiu, S.-H. L. *Drug. Metab. Dispos.* **1994**, *22*, 651. (c) Huskey, S.-E. W.; Miller, R. R.; Chiu, S.-H. L. *Drug. Metab. Dispos.* **1993**, *21*, 792.

(8) Girijavallabhan, V. M.; Pinto, P. A.; Genguly, A. K.; Versace, R. W. Eur. Patent EP274867, **1988**; *Chem. Abstr.* **1989**, *110*, 23890.

(9) (a) Akimoto, H.; Ootsuand, K.; Itoh, F. Eur. Patent EP530537, **1993**; *Chem. Abstr.* **1993**, *119*, 226417. (b) Taveras, A. G.; Mallams, A. K.; Afonso, A. Int. patent WO9811093, **1998**; *Chem. Abstr.* **1998**, *128*, 230253.

(10) Mitch, C. H.; Quimby, S. J. Int. Patent WO 9851312, **1998**; *Chem. Abstr.* **1998**, *130*, 13997.

(11) (a) Yamazaki, K.; Hasegawa, H.; Umekawa, K.; Ueki, Y.; Ohashi, N.; Kanaoka, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1275. (b) DeVita, R. J.; Schoen, W. R.; Ok, D.; Barash, L.; Brown, J. E.; Fisher, M. H.; Hodges, P.; Wyvratt, W. J.; Cheng, K.; Chan, W. W.-S.; Butler, B. S.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1807. (c) Vieira, E.; Huwyler, S.; Jolidon, S.; Knoflach, F.; Mutel, J .; Wichmann, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4628.

(12) (a) Percival, D.; Herbst, R. M. *J. Org. Chem.* **1957**, *22*, 925. (b) Tsuge, O.; Satoshi, U.; Oe, K. *J. Org. Chem.* **1980**, *45*, 5130. (c) Nasrollahzadeh, M.; Habibi, D.; Shankarami. Z.; Bayay. Y. *Tetrahedron* **2009**, *65*, 10715. (d) Habibi, D.; Nasrollahzadeh, M.; Faraji, A. R.; Bayay. Y. *Tetrahedron* **2010**, *66*, 3866. (e) Khamooshi, F.; Modarresi-alam, A. R. *Chin. Chem. Lett.* **2010**, *21*, 892.

(13) (a) Klich, M.; Teutsch, G. *Tetrahedron* **1986**, *42*, 2677. (b) Barlin, G. B. *J. Chem. Soc. B* **1967**, 641. (c) Ried, W.; Erle, H.-E. *Liebigs Ann. Chem.* **1982**, 201. (d) Batey, R. A.;

Powell, D. A. *Org. Lett.* **2000**, *2*, 3237. (e) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron Lett.* **2004**, *45*, 7787. (f) Finnegan, W.G.; Henry, R. A.; Lieber, E. *J. Org. Chem.* **1953**, *18*, 779. (g) Ramesh, Y.; Nilufa, K.; SarojKumar, R.; Bhisma, K. P. *Org. Biomol. Chem.* **2011**, *9*, 3235.

(14) (a) Nasrollahzadeh, M.; Habibi, D.; Shahkarami, Z.; Bayat, Y. *Tetrahedron* **2009**, *65*, 10715. (b) Henry, R. A.; Finnegan, W. G.; Lieber, E. *J. Am. Chem. Soc.* **1954**, *76*, 88. (c) Henry, R. A.; Finnegan, W. G.; Lieber, E. *J. Am. Chem. Soc.* **1955**, *77*, 2264.

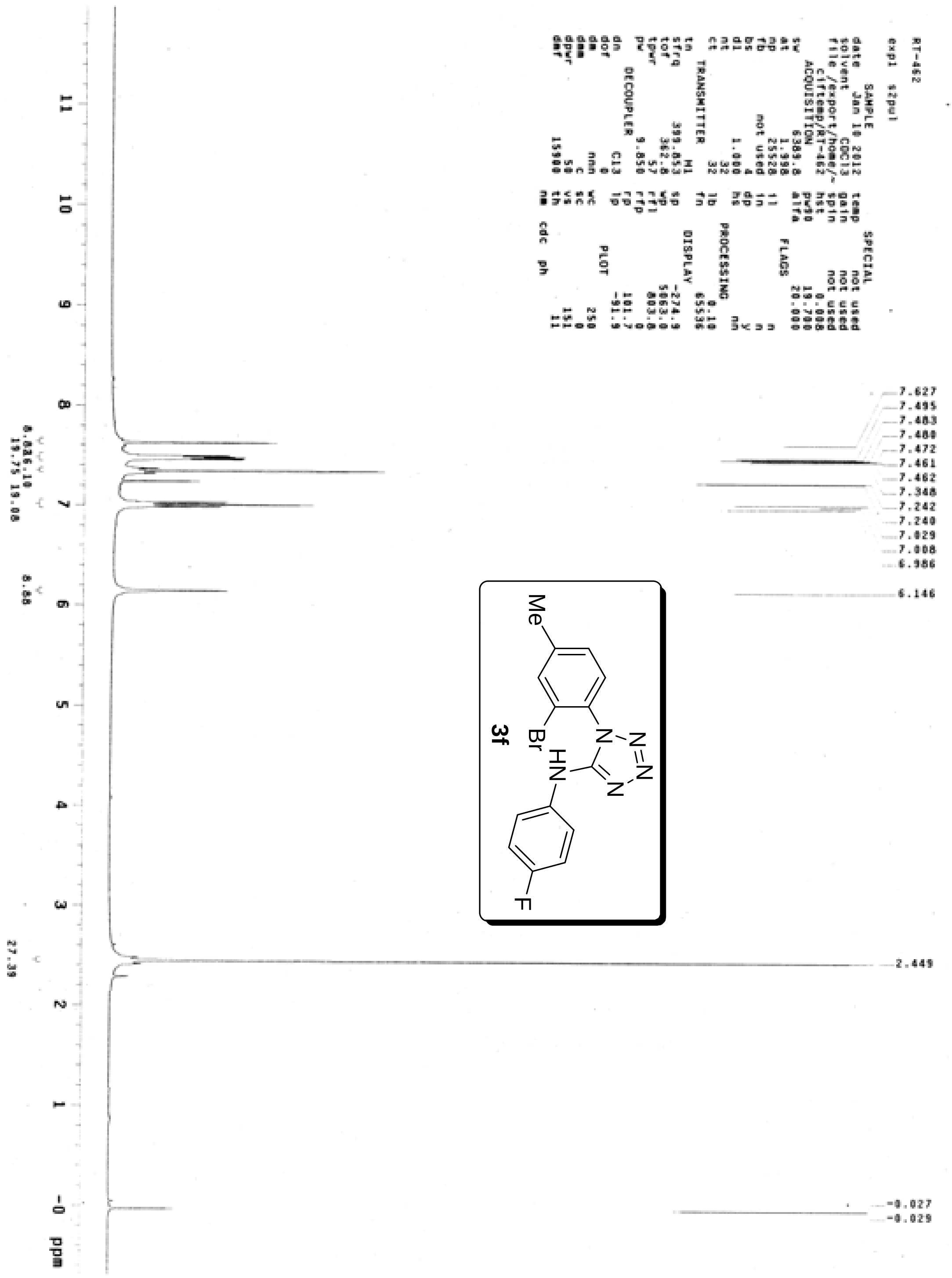
(15) (a) Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719. (b) Batey, R. A.; Powell, D. A. *Org. Lett.* **2000**, *2*, 3237.

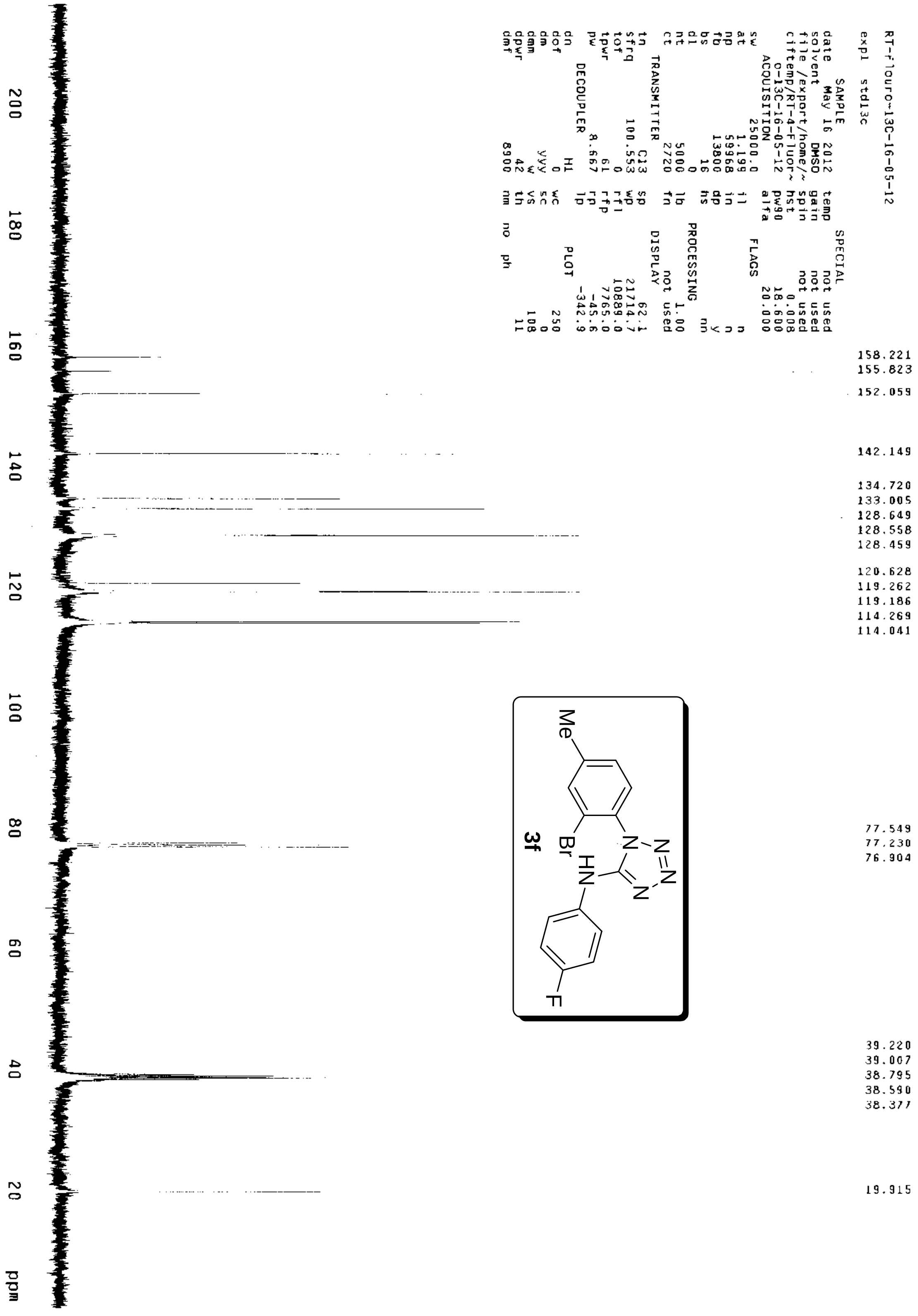
(16) Munch, H.; Hansen, J.-S.; Pittelkow, M.; Christensen, J.-B.; Boas, U. *Tetrahedron lett.* **2008**, *49*, 3117.

(17) Das, B.; Venkateswarlu, K.; Majhi, A.; Siddaiah, V.; Reddy, K. R. *J. Mol. Catal. A.* **2007**, *267*, 30.

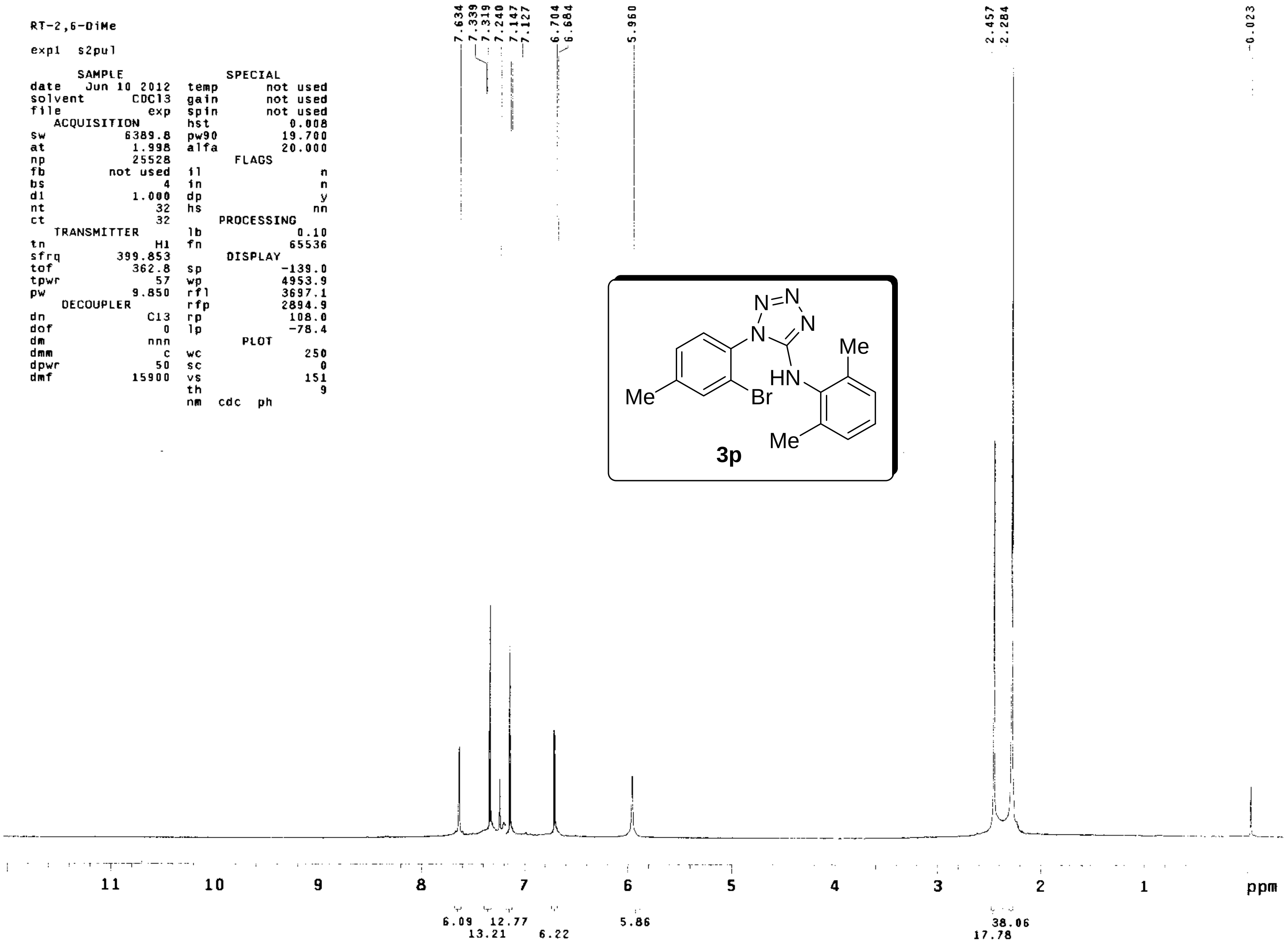
Crystal Data and Structure Refinement for 3a at 296(2) K

Empirical formula	$C_{14} H_{12} Br N_5$
Formula weight	330.20
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pbca loop_ _symmetry_equiv_pos_as_xyz 'x, y, z' '-x+1/2, -y, z+1/2' '-x, y+1/2, -z+1/2' 'x+1/2, -y+1/2, -z' '-x, -y, -z' 'x-1/2, y, -z-1/2' 'x, -y-1/2, z-1/2' '-x-1/2, y-1/2, z'
Unit cell dimensions	*a* = 8.3365(5) Å α(°)= 90.00 *b* = 10.4832(5) Å β(°)= 90.00 *c* = 32.5401(17) Å γ(°)= 90.00
Volume	2843.8(3) $Å^3$
Z	8
Density (calculated)	1.542 Mg/m^3
Absorption coefficient	2.888 mm^{-1}
F(000)	1328
Crystal size	0.26 x 0.22 x 0.16 mm
Theta range for data collection	1.25 to 28.36°
Index ranges	-11<=h<=11, -13<=k<=12, -42<=l<=43
Reflections collected	3545
Independent reflections	1589 [R (int) = 0.3143]
Completeness to theta = 28.36°	99.9 %
Absorption correction	Multi-scan
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3545 / 0 /182
Goodness-of-fit on F^2	0.928
Final R indices [I>2sigma (I)]	*R1* = 0.0422, *wR2* = 0.0943
R indices (all data)	*R1* = 0.1129, *wR2* = 0.1168

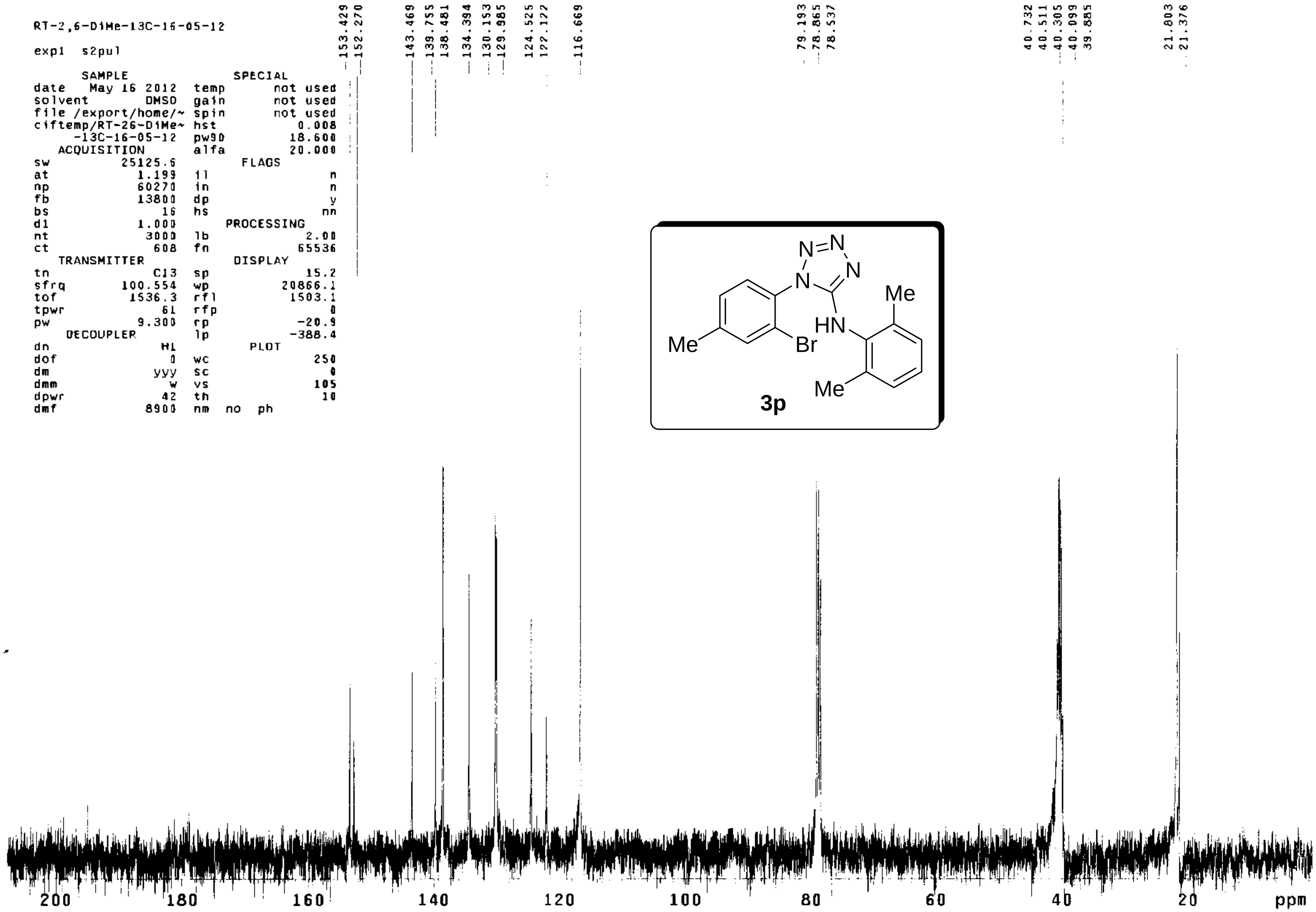

RT-462
exp1 s2pul
7.627
7.495
7.483
7.480
7.472
7.461
7.462
7.348
7.242
7.240
7.029
7.008
6.986
6.146
2.449
-0.027
-0.029
19.75
19.08
6.68
27.39
ppm
Me
Br
HN
N
F
3f


RT-flouro-13C-16-05-12
expl std13c
158.221
155.823
152.059
142.149
134.720
133.005
128.649
128.558
128.459
120.628
119.262
119.186
114.269
114.041
77.549
77.230
76.904
39.220
39.007
38.795
38.590
38.377
19.915
Me
Br
HN
N
N=N
F
200
180
160
140
120
100
80
60
40
20
ppm

3f



```
RT-2,6-DiMe

exp1  s2pul

       SAMPLE                 SPECIAL
date   Jun 10 2012    temp        not used
solvent       CDCl3   gain        not used
file            exp   spin        not used
   ACQUISITION        hst            0.008
sw           6389.8   pw90          19.700
at            1.998   alfa          20.000
np            25528          FLAGS
fb         not used   il                 n
bs                4   in                 n
d1            1.000   dp                 y
nt               32   hs                nn
ct               32        PROCESSING
   TRANSMITTER        lb              0.10
tn               H1   fn             65536
sfrq        399.853         DISPLAY
tof           362.8   sp            -139.0
tpwr             57   wp            4953.9
pw            9.850   rfl           3697.1
    DECOUPLER         rfp           2894.9
dn              C13   rp             108.0
dof               0   lp             -78.4
dm              nnn           PLOT
dmm               c   wc               250
dpwr             50   sc                 0
dmf           15900   vs               151
                      th                 9
                      nm   cdc   ph
```



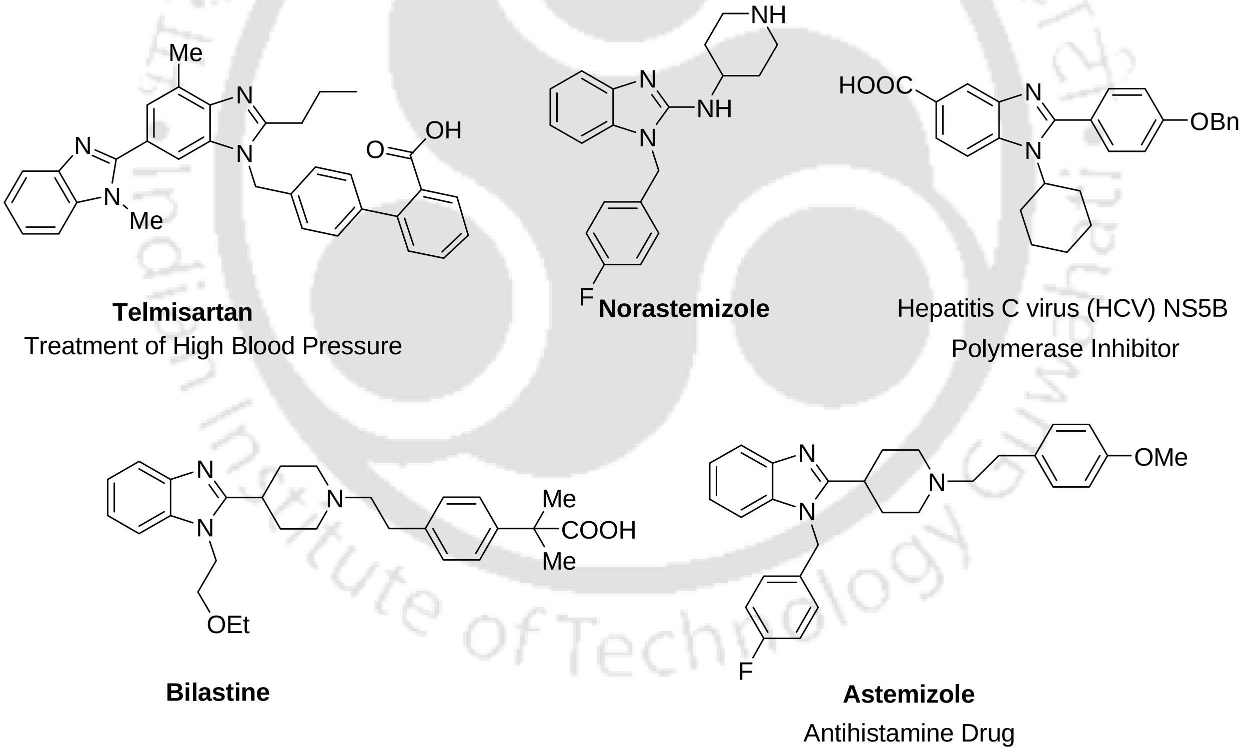
```
RT-2,6-DiMe-13C-16-05-12

exp1  s2pul

      SAMPLE               SPECIAL
date    May 16 2012  temp      not used
solvent        DMSO  gain      not used
file /export/home/~  spin      not used
ciftemp/RT-26-DiMe~  hst          0.008
    -13C-16-05-12    pw90        18.600
   ACQUISITION       alfa        20.000
sw          25125.6        FLAGS
at            1.199  il               n
np            60270  in               n
fb            13800  dp               y
bs               16  hs              nn
d1            1.000       PROCESSING
nt             3000  lb            2.00
ct              608  fn           65536
   TRANSMITTER             DISPLAY
tn              C13  sp            15.2
sfrq        100.554  wp         20866.1
tof          1536.3  rfl         1503.1
tpwr             61  rfp              0
pw            9.300  rp           -20.9
    DECOUPLER        lp          -388.4
dn               H1         PLOT
dof               0  wc             250
dm              yyy  sc               0
dmm               w  vs             105
dpwr             42  th              10
dmf            8900  nm  no  ph
```

3p

Chapter IV

Copper(II)-Catalyzed Conversion of 1-(2-Bromoaryl)-*N*-Aryl-1*H*-Tetrazol-5-Amines to 2-Azidobenzimidazoles

The recent advances in transition-metal-catalysis led to the development of effective methods for the construction of carbon-carbon and carbon-heteroatom bonds *via* cross-coupling reactions.[1] Among them, the construction of *C-N* bond has received considerable attention due to the presence of the moiety in many molecules that are important in biological, medicinal and material sciences.[2] Benzimidazole is an important structural motif present in several compounds that are of biological and medicinal importance (Figure 1).[3] For example, benzimidazole subunit can be found in commercially available drugs such as prilosec, nexium, protonix, atacand, famvir etc.[4]



Telmisartan
Treatment of High Blood Pressure

Norastemizole

Hepatitis C virus (HCV) NS5B
Polymerase Inhibitor

Bilastine

Astemizole
Antihistamine Drug

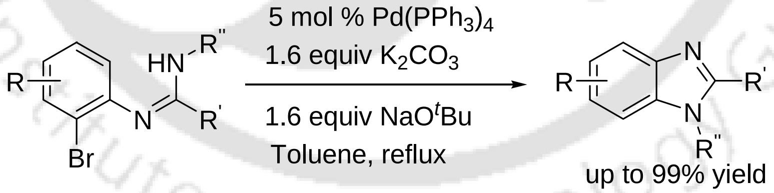
Figure 1. Some examples of pharmacologically important substituted benzimidazoles

Furthermore, they exhibit several other pharmacological activities including antidiabetic,[5a] antiinflammatory,[5b] antiviral,[5c] antiparasitic,[5d] antibacterial[5e] and antimicrobial properties.[5f] Other medicinal chemistry applications of these compounds include neuropeptide YY1 receptor antagonist,[6a] N-methyl-D-aspartate (NMDA) antagonist,[6b] factor Xa(FXa) inhibitor,[6c] poly(ADP-ribose)polymerase (PARP) inhibitor[6d] and nonpeptide thrombin inhibitor.[6e] Substituted benzimidazoles are also described as intermediates for the preparation of dyes and high-temperature resistance polymers.[7]

The classical methods used for the synthesis of 2-azidobenzimidazoles involve diazotization on 1-benzimidazolylidenehydrazine[8] which can be prepared from the reaction of 1,2-diamino benzene, carbon disulfide and ethyliodide.[9] Although, substituted benzimidazoles can be generated through condensation of 1,2-diaminoarene with either carboxylic acids or aldehydes followed by oxidation[10] and some other traditional methods,[11] most of these protocols suffer from major shortcomings such as limited substituents, strong alkaline conditions, troublesome management of the chemical process and elevated temperature. Some of these drawbacks have been recently overcome by the development of more sustainable cross-coupling reactions for the synthesis of benzimidazoles using transition-metal-catalysis.

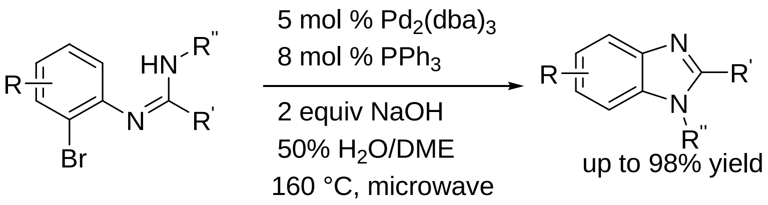
4.1 Palladium Catalysts

Few studies are focused on the use of palladium catalysis for the synthesis of benzimidazoles *via* intramolecular *C-N* cross-coupling reaction. For example, Brain and co-workers have reported the synthesis of substituted benzimidazoles using $Pd(PPh_3)_4$ *via* intramolecular *C–N* cross-coupling of 2-haloarylamidines in toluene under reflux condition (Scheme 1).[12a]



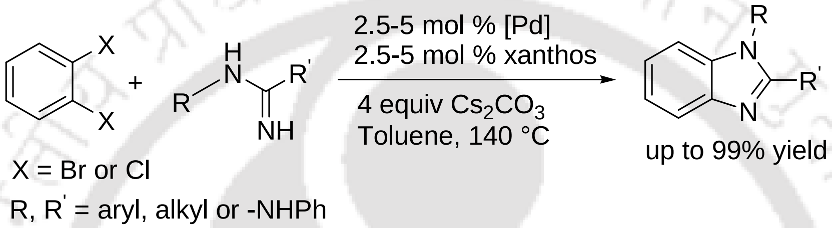
Scheme 1

They have also further showed the construction of substituted benzimidazoles using $Pd_2(dba)_2$ and PPh_3 under microwave conditions in aqueous DME (Scheme 2).[12b]



Scheme 2

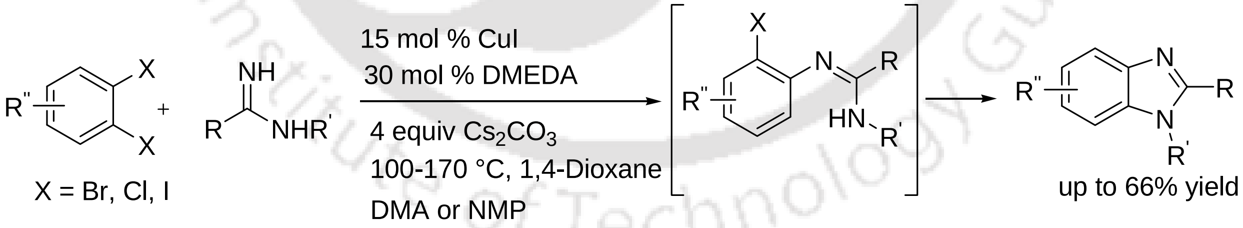
The synthesis of substituted benzimidazole has been described by You and co-workers through domino *C-N* cross-coupling reaction using palladium-catalyst in the presence of Cs_2CO_3 in toluene under reflux conditions (Scheme 3).[12c]



Scheme 3

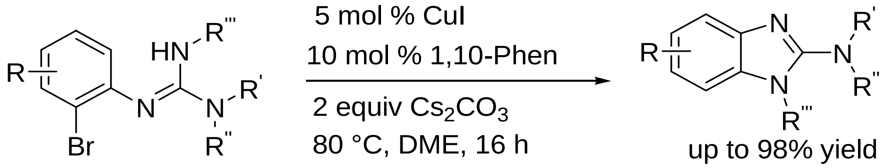
4.2 Copper Catalysts

Most of the cross-coupling reactions for the synthesis of benzimidazoles employ copper-based catalytic systems. Deng and co-workers have employed CuI and *N,N'*-dimethylethylenediamine for the synthesis of substituted benzimidazole from 1,2-dihaloarenes and amidines through domino inter- and intramolecular *C-N* cross-coupling reactions (Scheme 4).[13a]



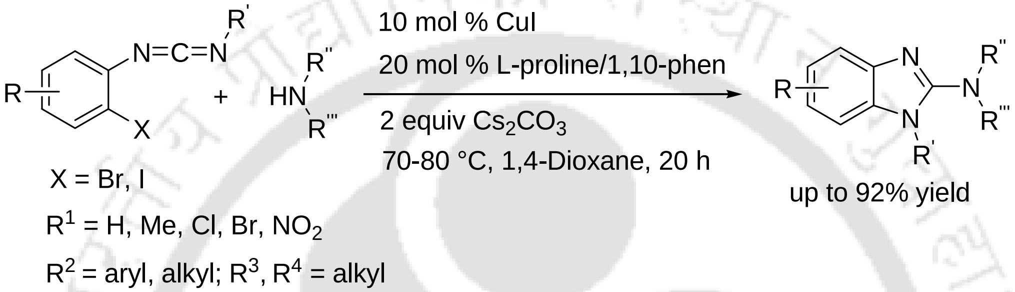
Scheme 4

Batey and co-workers have described the construction of substituted benzimidazole *via* an intramolecular aryl guanidinylation using CuI/1,10-phenanthroline in the presence of Cs_2CO_3 at moderate temperature (Scheme 5).[13b]



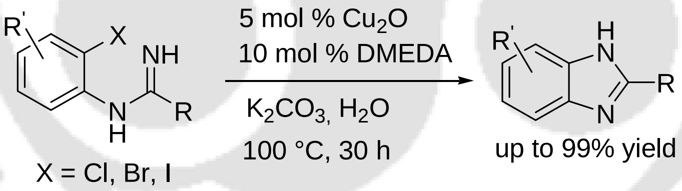
Scheme 5

Bao and co-authors have shown the synthesis of substituted benzimidazoles from amines and *o*-haloarylcarbodiimides using CuI and L-proline in the presence of Cs_2CO_3 at moderate temperature *via* cascade intermolecular addition/*C–N* cross-coupling reaction (Scheme 6).[13c]



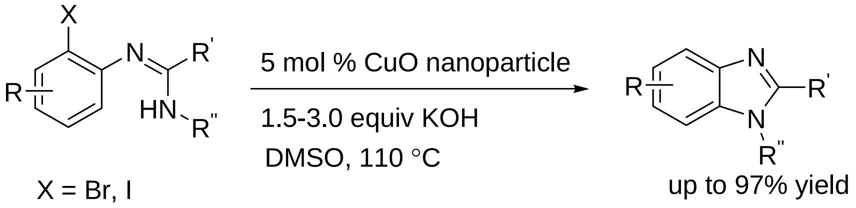
Scheme 6

Chen and co-authors have synthesized substituted benzimidazoles from 2-haloarylamidines by intramolecular cyclization using Cu_2O-DMEDA in water (Scheme 7).[13d]



Scheme 7

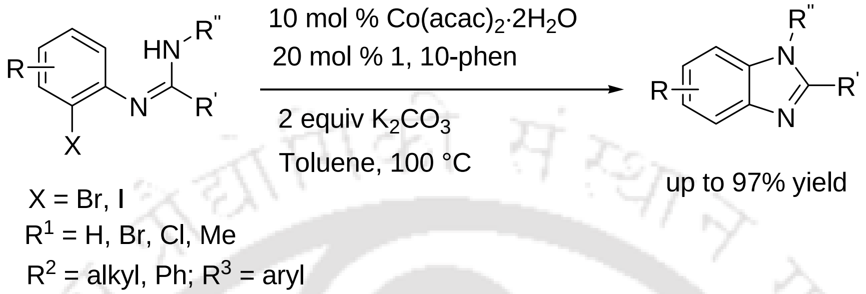
Our group has showed the use of CuO nanoparticles for the cyclization of 2-haloarylamidines to afford substituted benzimidazoles that is effective under ligand free conditions (Scheme 8).[13e]



Scheme 8

4.3 Cobalt-Catalyst

The cyclization of *o*-haloarylamidines has also been found to be effective using $Co(acac)_2{\cdot}2H_2O$ and 1,10-phenanthroline in the presence of K_2CO_3 in toluene under reflux conditions (Scheme 9).[14] This process is more attractive in terms of toxicity.



Scheme 9

4.4 Present Study

The tetrazoles reported in the last chapter readily proceed cyclization in the presence of copper based complexes to afford 2-azidobenzimidazoles at ambient temperature. The procedure is simple and has wide substrate scope to afford the target molecules in high yield.

Firstly, the optimization of the reaction conditions was performed with 1-(2-bromo-4-methylphenyl)-*N*-phenyl-1*H*-tetrazol-5-amine as a model substrate (Table 1). The best result was obtained when the reaction was carried out at room temperature using 5 mol % of copper sources such as CuI, CuBr, Cu_2O, $CuSO_4{\cdot}5H_2O$, $Cu(OAc)_2{\cdot}H_2O$ and 10 mol % 1,10-phenanthroline (**L5**) in the presence of $K_3PO_4{\cdot}3H_2O$ in THF or toluene affording the desired 2-azido-6-methyl-1-phenyl-1*H*-enzo[*d*]imidazole **4a** in 100% conversion. In contrast, the processes employing solvents such as DMSO, DMF and CH_3CN, and bases such as KOH, Cs_2CO_3, Et_3N and DABCO, and ligands such as ethylene diamine **L1,** ethylene glycol **L2**, L-proline **L3**, DMEDA **L4** gave inferior results. Similarly, either lowering the amount of the base (1.5 equiv) or the quantity of

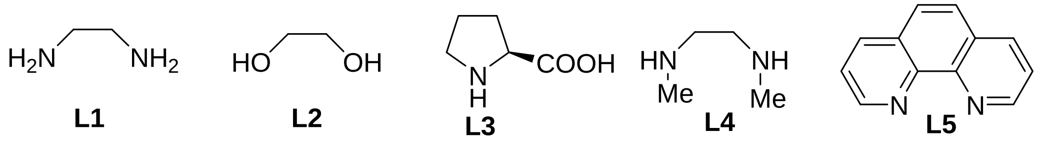
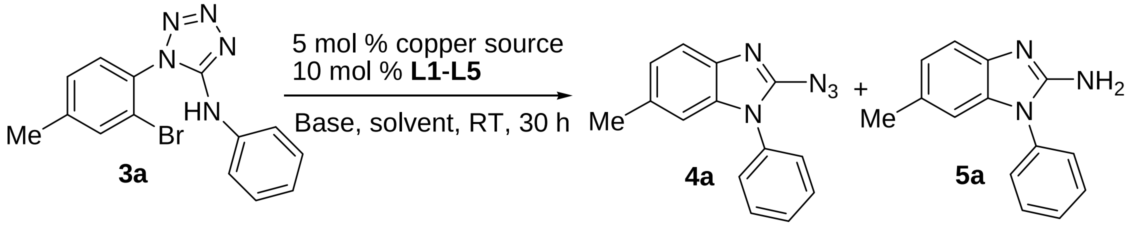


Table 1. Optimization of the Reaction Conditions[a]



Entry	Copper source	Solvent	Base	Ligand	Product(s) (%)[b]	
					4a	**5a**
1	CuI	DMF	$K_3PO_4{\cdot}3H_2O$	**L5**	90	10
2	CuI	DMSO	$K_3PO_4{\cdot}3H_2O$	**L5**	80	20
3	CuI	1,4-Dioxane	$K_3PO_4{\cdot}3H_2O$	**L5**	90	10
4	CuI	CH_3CN	$K_3PO_4{\cdot}3H_2O$	**L5**	75	25
5	CuI	THF	$K_3PO_4{\cdot}3H_2O$	**L5**	100	n.d.
6	CuI	Toluene	$K_3PO_4{\cdot}3H_2O$	**L5**	100	n.d.
7	CuI	THF	Et_3N	**L5**	n.d.	
8	CuI	THF	DABCO	**L5**	n.d.	
9	CuI	THF	KOH	**L5**	18	n.d.
10	CuI	THF	Cs_2CO_3	**L5**	45	n.d.
11	CuI	THF	$K_3PO_4{\cdot}3H_2O$	**L1**	15	n.d.
12	CuI	THF	$K_3PO_4{\cdot}3H_2O$	**L2**	20	n.d.
13	CuI	THF	$K_3PO_4{\cdot}3H_2O$	**L3**	25	n.d.
14	CuI	THF	$K_3PO_4{\cdot}3H_2O$	**L4**	30	n.d.
15	CuBr	THF	$K_3PO_4{\cdot}3H_2O$	**L5**	100	n.d.
16	Cu_2O	THF	$K_3PO_4{\cdot}3H_2O$	**L5**	100	n.d.
17	$CuSO_4{\cdot}5H_2O$	THF	$K_3PO_4{\cdot}3H_2O$	**L5**	100	n.d.
18	$Cu(OAc)_2{\cdot}H_2O$	THF	$K_3PO_4{\cdot}3H_2O$	**L5**	100	n.d.
19[c]	$Cu(OAc)_2{\cdot}H_2O$	THF	$K_3PO_4{\cdot}3H_2O$	**L5**	70	n.d.
20[d]	$Cu(OAc)_2{\cdot}H_2O$	THF	$K_3PO_4{\cdot}3H_2O$	**L5**	50	n.d.
21	-	THF	$K_3PO_4{\cdot}3H_2O$	-	n.d.	

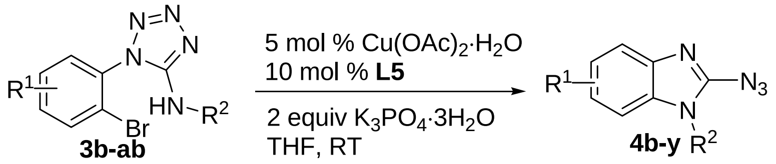
[a] Reaction conditions: Tetrazole **3a** (1 mmol), copper catalyst (5 mol %), ligand (10 mol %), base (2 mmol) and solvent (1 mL) were stirred at room temperature.

[b] Determined by 400 MHz ^1H NMR.

[c] Catalyst (2.5 mol %) was used.

[d] $K_3PO_4{\cdot}3H_2O$ (1.5 equiv) was used.

Table 2. Copper(II)-Catalyzed Cyclization of 1-(2-Bromoaryl)-*N*-Aryl-1*H*-Tetrazol-5-Amines [a-b]



R^1 = EWG, EDG
R^2 = aryl, alkyl

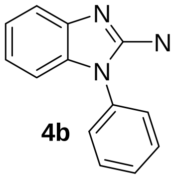
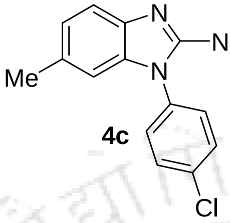
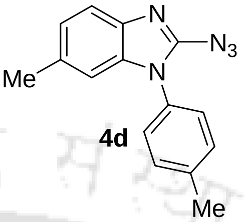
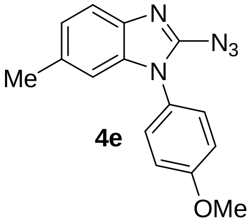
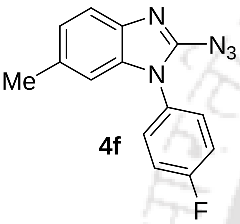
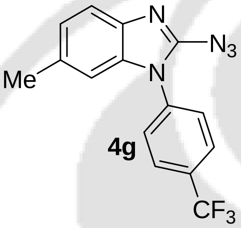
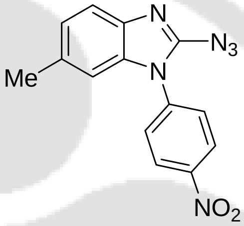
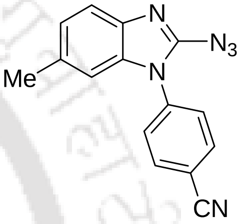
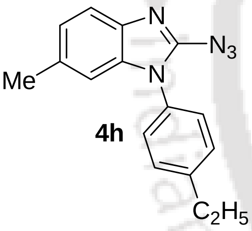
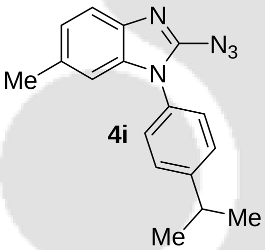
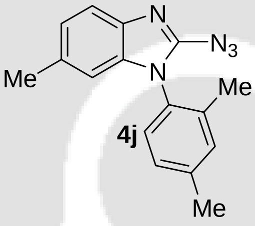
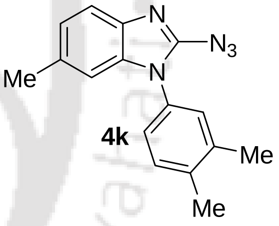
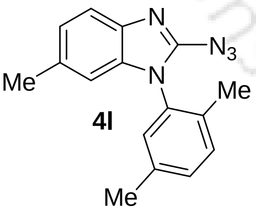
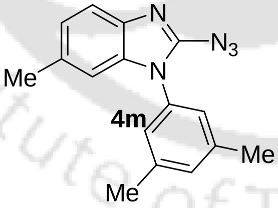
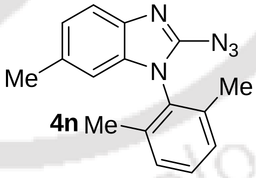
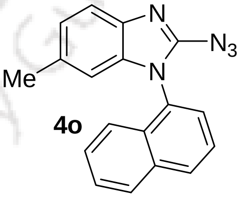
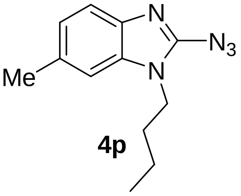
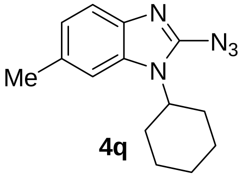
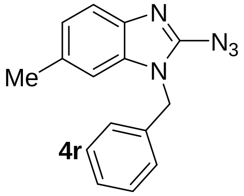
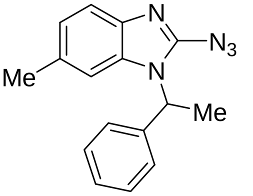
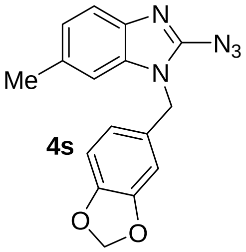
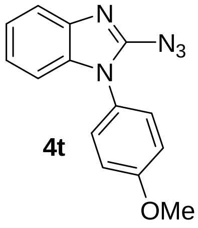
 **4b** 30 h, 87%	 **4c** 28 h, 83%	 **4d** 29 h, 92%	 **4e** 24 h, 95%
 **4f** 30 h, 72%	 **4g** 30 h, 55%	 n.d.	 n.d
 **4h** 30 h, 90%	 **4i** 30 h, 91%	 **4j** 30 h, 90%	 **4k** 30 h, 95%
 **4l** 30 h, 96%	 **4m** 30 h, 90%	 **4n** 30 h, 81%	 **4o** 30 h, 61%
 **4p** 30 h, 63%	 **4q** 30 h, 67%	 **4r** 30 h, 70%	 n.d.

Table 2 Conti…



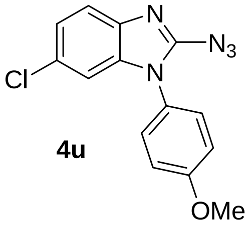
4s

30 h, 57%



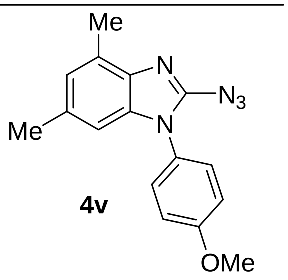
4t

23 h, 89%



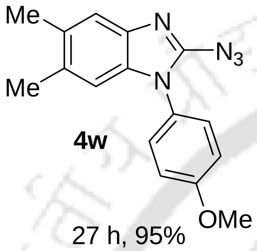
4u

25 h, 90%



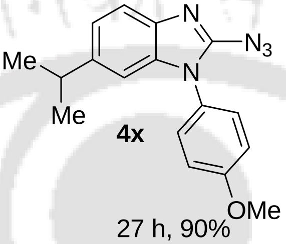
4v

27 h, 95%



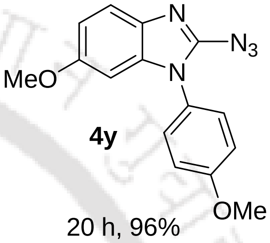
4w

27 h, 95%



4x

27 h, 90%



4y

20 h, 96%

[a] Reaction conditions: Tetrazole **3b-ab** (1 mmol), $Cu(OAc)_2 \cdot H_2O$ (5 mol %), **L5** (10 mol %), and $K_3PO_4 \cdot 3H_2O$ (2 mmol) were stirred in THF (1 mL) at room temperature.

[b] Isolated yield.

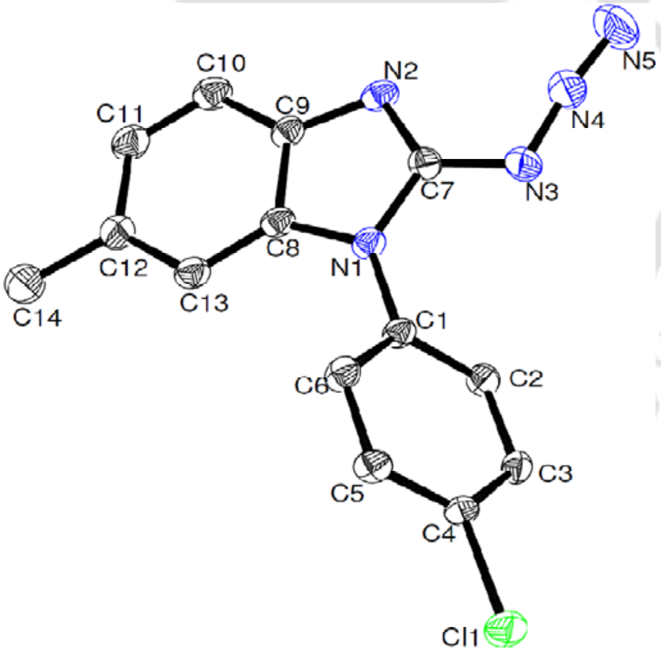
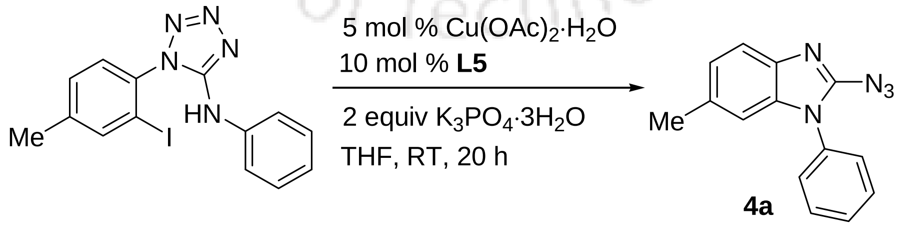


Figure 2. ORTEP diagram of 2-azido-1-(4-chlorophenyl)-6-methyl-1*H*-benzo[*d*]imidazole **4c** with 50% ellipsoid. H-Atoms are omitted for clarity

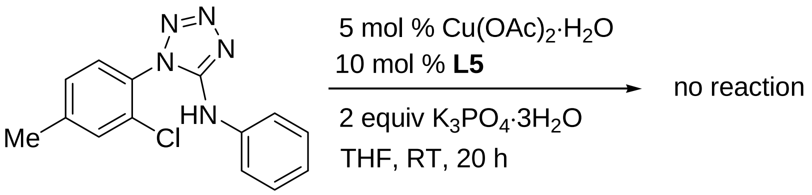
the catalyst (2.5 mol %) led to the formation **4a** in <70% conversion (Table 1, entries 19-20). The control experiments without the copper source confirmed that the formation of the target product was not observed and the starting material was recovered intact (Table 1, entry 21).

Next, the scope of the protocol was explored for the cyclization of substituted tetrazoles (Table 2). The substrates readily proceeded cyclization to give the corresponding 2-azidobenzimidazoles **4a-y** in good to excellent yield. The substrates having electron donating groups on the aromatic rings exhibited greater reactivity compared to that bearing electron withdrawing groups. For examples, the substrates having 4-Me, 4-OMe, 4-Et and 4-^{i}Pr substituents in aromatic ring gave the target products in 87-96% yield, while the substrates containing 4-Cl, 4-F and 4-CF_3 groups in the aromatic nucleus underwent reaction with 55-83% yield. However, the substrates with strong electron withdrawing substituents, 4-NO_2 and 4-CN, on phenyl ring showed no reaction and the starting material was recovered intact. Under these conditions, the substrates having *N*-alkyl group proceeded reactions to give the desired products in good yield. In case of *N*-α-methyl benzyl substituent no cyclization was observed which may due to the steric hindrance. However, the substrate bearing *N*-naphthyl substituent underwent reaction with 61% yield. Recrystallization of **4c** in MeOH gave crystals whose structure was confirmed by single X-ray analysis (Figure 2).

To reveal the relative reactivity of other halogenated tetrazoles, the cyclization of 1-(2-iodo-4-methylphenyl)-*N*-phenyl-1*H*-tetrazol-5-amine and 1-(2-chloro-4-methylphenyl)-*N*-phenyl-1*H*-tetrazol-5-amine were investigated. 1-(2-iodo-4-methylphenyl)-*N*-phenyl-1*H*-tetrazol-5-amine underwent reaction with greater reactivity compared to 1-(2-bromo-4-methylphenyl)-*N*-phenyl-1*H*-tetrazol-5-amine. In contrast, 1-(2-chloro-4-methylphenyl)-*N*-phenyl-1*H*-tetrazol-5-amine showed no cyclization and the starting material was recovered intact (Scheme 11).

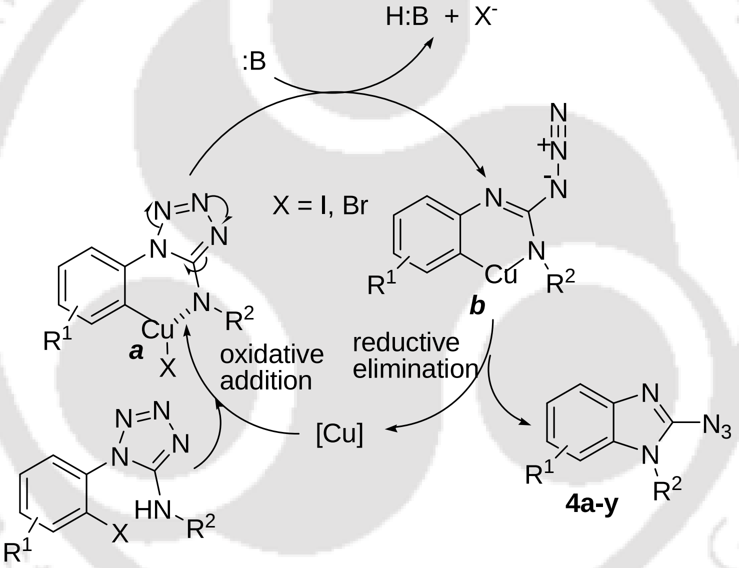


Scheme 10



Scheme 11

The proposed catalytic cycle is shown in Scheme 12. The observed results suggest that the tetrazole could undergo oxidative addition with copper(I) species (could be derived from copper(II) species)[15] to provide intermediate ***a***. *N*-Arylation followed by tautomerism of ***a*** can lead to the formation ***b*** that may complete the catalytic cycle by reductive elimination to give the target molecules **4a-y**.



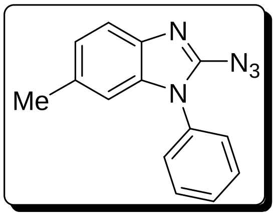
Scheme 12. Proposed catalytic cycle

In conclusion, copper-catalyzed cyclization of 1-(2-bromoaryl)-*N*-aryl-1*H*-tetrazol-5-amines to 2-azidobenzimidazoles has been accomplished at room temperature. The procedure is simple, general and efficient to provide the target products in moderate to high yield. The substrates having electron donating groups on the aromatic ring showed enhanced reactivity compared to that bearing electron withdrawing groups.

Experimental Section

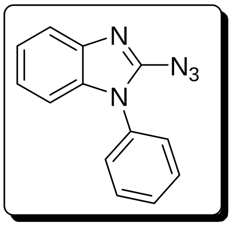
General Information: $CuSO_4\cdot5H_2O$ (98%), CuI (98%), CuBr (98%), Cu_2O (97%), $Cu(OAc)_2\cdot H_2O$ (98%), Cs_2CO_3 (99%), K_2CO_3 (99%) and $K_3PO_4\cdot3H_2O$ (98%) were purchased from Aldrich. Product purification was carried out by silica gel column chromatography using Rankem silica gel (60-120 mesh). All reactions were monitored by analytical TLC on Merck silica gel G/GF 254 plates. NMR (^{1}H and ^{13}C) spectra were recorded on DRX-400 Varian spectrometer and the data are accounted as follows: chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration).The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet. Melting points were determined by Buchi B-540 melting point apparatus. FT-IR spectra of air-dried samples were recorded on PerkinElmer Spectrum One FT-IR spectrometer using KBr disks and are reported in frequency of absorption (cm^{-1}). Elemental analyses were recorded using PerkinElmer CHNS analyzer. For single crystal X-ray analysis the intensity data were collected using Bruker SMART APEX-II CCD diffractometer, equipped with 1.75 kW sealed-tube Mo Kα irradiation (λ = 0.71073 Å) at 296(2) K and the structures were solved by direct methods using *SHELLX-97* (Göttingen, Germany) and refined with full-matrix least squares on F^2 using SHELXL-97.

General Procedure for the Synthesis of 2-Azidobenzimidazoles: Tetrazole (1 mmol), $K_3PO_4\cdot3H_2O$ (2 mmol), $Cu(OAc)_2\cdot H_2O$ (5 mol %) and 1,10-phenanthroline **L5** (10 mol %) were stirred at room temperature in THF for appropriate time. Progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was extracted with ethyl acetate (2 x 10 mL) and the organic layer was washed successively with brine (1 x 5 mL) and water (2 x 5 mL). Drying and evaporation of the solvent provided a residue which was purified by silica gel chromatography using ethyl acetate and hexane as eluent to provide the titled compounds in analytically pure form.

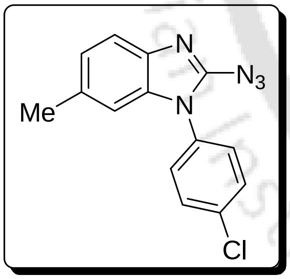


2-Azido-6-methyl-1-phenyl-1*H*-benzo[*d*]imidazole 4a: White solid; yield 80%; mp 81-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.52 (m, 3H), 7.49-7.47 (m, 1H), 7.39

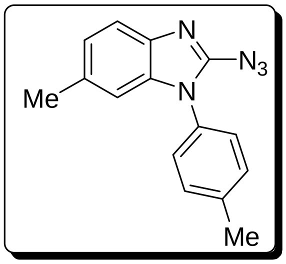
(d, *J* = 8 Hz, 2H), 7.09 (dd, *J* = 8.8, 0.8 Hz, 1H), 6.97 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 139.5, 135.5, 134.4, 132.8, 129.7, 128.7, 126.4, 124.5, 117.9, 110.0, 21.8; FT-IR (KBr) 3056, 2920, 2139, 1597, 1508, 1411, 1331, 1262, 1209, 1032 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}N_5$: C, 67.46; H, 4.45; N, 28.10. Found: C, 67.55; H, 4.43; N, 28.03.



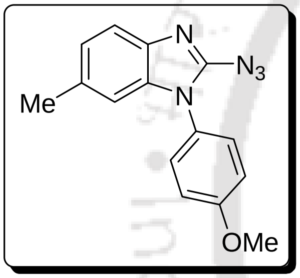
2-Azido-1-phenyl-1*H*-benzo[*d*]imidazole 4b: White solid; yield 72%; mp 85-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8 Hz**,** 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 6.8 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.29-7.24 (m, 1H), 7.18 (d, *J* = 4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ147.5, 141.5, 135.5, 134.4, 129.9, 128.9, 126.6, 123.3, 122.8, 118.5, 110.1; FT-IR (KBr) 3056, 2920, 2139, 1590, 1578, 1490, 1438, 1409, 1288, 1261, 1078, 1023 cm^{-1}. Anal. Calcd. for $C_{13}H_9N_5$: C, 66.37; H, 3.86; N, 29.77. Found: C, 66.47; H, 3.83; N, 29.70.



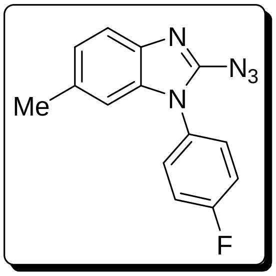
2-Azido-1-(4-chlorophenyl)-6-methyl-1*H*-benzo[*d*]imidazole 4c: White solid; yield 65%; mp 96-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.50 (m, 3H), 7.36-7.33 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.95 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 139.5, 135.3, 134.5, 132.9, 132.8, 129.9, 127.7, 124.7, 118.1, 109.8, 21.8; FT-IR (KBr) 2213, 2150, 1627, 1514, 1498, 1421, 1400, 1330, 1297, 1207, 1090 cm^{-1}. Anal. Calcd. for $C_{14}H_{10}ClN_5$: C, 59.27; H, 3.55; N, 24.68. Found: C, 59.39; H, 3.53; N, 24.60.



2-Azido-6-methyl-1-p-tolyl-1*H*-benzo[*d*]imidazole 4d: White solid; yield 75%; mp 87-88 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55 (d, *J* = 8 Hz, 1H), 7.34 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H), 7.08 (d, *J* = 8 Hz, 1H), 6.96 (s, 1H), 2.45 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.9,139.5, 138.9, 135.7, 132.7, 131.7, 130.3, 126.3, 124.4, 117.9, 110.0, 21.7, 21.3; FT-IR (KBr) 3034, 2921, 2859, 2139, 1626, 1510, 1327, 1274, 1205, 1107, 1005 cm^{-1}. Anal. Calcd. for $C_{15}H_{13}N_5$: C, 68.42; H, 4.98; N, 26.60. Found: C, 68.52; H, 4.95; N, 26.53.

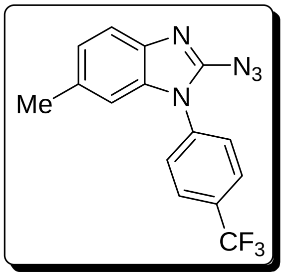


2-Azido-1-(4-methoxyphenyl)-6-methyl-1*H*-benzo[*d*]imidazole 4e: White solid; yield 77%; mp 77-78 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.09-7.02 (m, 3H), 6.92 (s, 1H), 3.87 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.9, 147.2, 139.6, 136.2, 132.8, 128.0, 127.1, 124.5, 118.0, 115.1, 110.1, 55.8, 21.9; FT-IR (KBr) 3009, 2842, 2149, 1624, 1519, 1427, 1327, 1305, 1254, 1031 cm^{-1}. Anal. Calcd. for $C_{15}H_{13}N_5O$: C, 64.51; H, 4.69; N, 25.07. Found: C, 64.61; H, 4.67; N, 25.01.

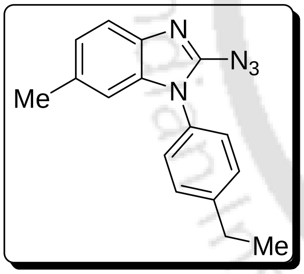


2-Azido-1-(4-fluorophenyl)-6-methyl-1*H*-benzo[*d*]imidazole 4f: White solid; yield 60%; mp 106-107 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, *J* = 8.4 Hz, 1H), 7.41-7.38 (m, 2H), 7.27-7.25 (m, 2H), 7.11 (d, *J* = 8 Hz, 1H), 6.94 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.4 (d, $^1J_{CF}$ = 9.2 Hz), 146.9, 139.5, 135.7, 133.0, 130.4, 128.5 (d, $^3J_{CF}$ =

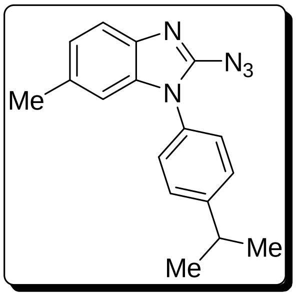
9.2 Hz), 124.7, 118.1, 116.9 (d, ${}^2J_{CF}$ = 22.9 Hz), 109.9, 21.8; FT-IR (KBr) 2962, 2143, 1509, 1429, 1329, 1261, 1093, 1021 cm^{-1}. Anal. Calcd. for $C_{14}H_{10}FN_5$: C, 62.92; H, 3.77; N, 26.20. Found: C, 63.04; H, 3.75; N, 26.13.



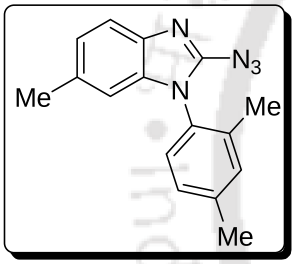
2-Azido-1-(4-(trifluoromethyl)phenyl)-6-methyl-1*H*-benzo[*d*]imidazole 4g: White solid: yield 45%; mp 135-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.56 (dd, *J* = 2.4, 8.4 Hz, 3H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.00 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 139.7, 137.7, 135.1, 133.4, 127.0 (q, ${}^1J_{CF}$ = 99.9 Hz), 125.1, 123.1, 118.3, 113.3, 109.9, 21.9; FT-IR (KBr) 3072, 2923, 2416, 2218, 2141, 1614, 1507, 1434, 1167, 1005 cm^{-1}. Anal. Calcd. for $C_{15}H_{10}F_3N_5$: C, 56.78; H, 3.18; N, 22.07. Found: C, 56.91; H, 3.17; N, 22.00.



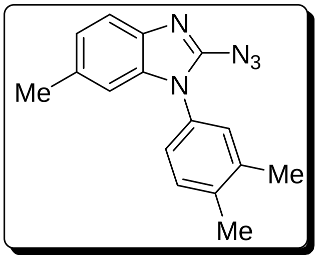
2-Azido-1-(4-ethylphenyl)-6-methyl-1*H*-benzo[*d*]imidazole 4h: White solid; yield 70%; mp 59-60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 1H), 7.40 (t, *J* = 8.8 Hz 2H), 7.34-7.31 (m, 2H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.99 (s, 1H), 2.79-2.73 (q, 2H), 2.42 (s, 3H), 1.32 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 139.5, 135.8, 132.7, 131.9, 129.2, 127.8, 126.4, 124.5, 117.9, 110.2, 34.1, 24.1, 15.5; FT-IR (KBr) 2963, 2140, 1623, 1516, 1434, 1329, 1261, 1210, 1095, 1024 cm^{-1}. Anal. Calcd. for $C_{16}H_{15}N_5$: C, 69.29; H, 5.45; N, 25.25. Found: C, 69.40; H, 5.42; N, 25.17.



2-Azido-1-(4-isopropylphenyl)-6-methyl-1*H*-benzo[*d*]imidazole 4i: Thick liquid; yield 75%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55 (d, *J* = 8.4 Hz, 1H), 7.40 (t, *J* = 8.4 Hz, 2H), 7.33-7.26 (m, 2H), 7.09 (d, *J* = 8 Hz, 1H), 6.96 (s, 1H), 3.03-3.00 (m, 1H), 2.41 (s, 3H), 1.32 (d, *J* = 6.46 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.0, 139.6, 135.8, 132.8, 132.0, 129.2, 127.8, 126.5, 124.5, 117.9, 110.2, 34.1, 24.1, 21.8; FT-IR (KBr) 2963, 2140, 1623, 1516, 1434, 1329, 1261, 1210, 1095, 1024 cm^{-1}. Anal. Calcd. for $C_{17}H_{17}N_5$: C, 70.08; H, 5.88; N, 24.04. Found: C, 70.17; H, 5.86; N, 23.97.

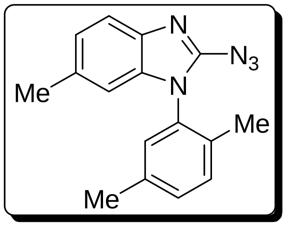


2-Azido-6-methyl-1-(2,4-dimethylphenyl)-1*H*-benzo[*d*]imidazole 4j: White solid; yield 70%; mp 112-113 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (d, *J* = 8 Hz, 1H), 7.22 (s, 1H), 7.16 (d, *J* = 8 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 2H), 6.71 (s, 1H), 2.43 (s, 3H), 2.39 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.4, 140.1, 139.7, 136.2, 132.8, 132.2, 130.4, 128.2, 128.0, 124.3, 117.9, 110.1, 21.8, 21.4, 17.6; FT-IR (KBr) 2964, 2919, 2138, 1591, 1567, 1495, 1315, 1120, 1088, 1029 cm^{-1}. Anal. Calcd. for $C_{16}H_{15}N_5$: C, 69.29; H, 5.45; N, 25.25. Found: C, 69.39; H, 5.43; N, 25.17.

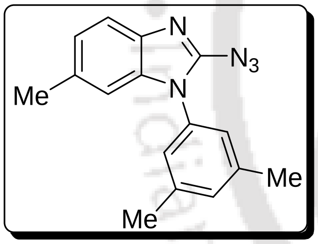


2-Azido-6-methyl-1-(3,4-dimethylphenyl)-1*H*-benzo[*d*]imidazole 4k: White solid; yield 77%; mp 108-109 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 8 Hz, 1H), 7.15-7.07 (m, 3H), 6.96 (s, 1H), 2.40 (s, 3H), 2.34 (s, 6H); ^{13}C NMR (100

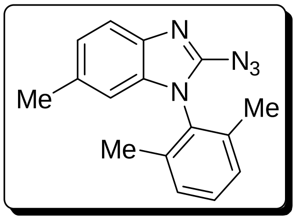
MHz, $CDCl_3$) δ146.9, 139.5, 138.3, 137.7, 135.8, 132.6, 131.9, 130.7, 127.4, 124.3, 123.8, 117.8, 110.1, 21.7, 20.0, 19.6; FT-IR (KBr) 3024, 2916, 2148, 1611, 1510, 1483, 1424, 1323, 1276, 1207, 1021 cm^{-1}. Anal. Calcd. for $C_{16}H_{15}N_5$: C, 69.29; H, 5.45; N, 25.25. Found: C, 69.37; H, 5.43; N, 25.18.



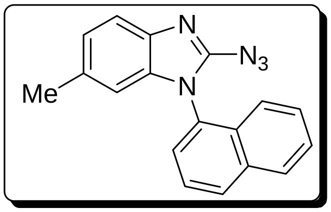
2-Azido-6-methyl-1-(2,5-dimethylphenyl)-1*H*-benzo[*d*]imidazole 4l: White solid; yield 65%; mp 104-105 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 1H), 7.28 (t, *J* = 8 Hz, 2H), 7.11-7.08 (m, 1H), 7.03 (s, 1H), 6.71 (s, 1H), 2.39 (s, 6H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ147.5, 141.1, 139.7, 136.2, 132.8, 132.2, 130.4, 129.1, 128.0, 124.3, 117.9, 110.1, 21.4, 17.6; FT-IR (KBr) 2961, 2923, 2854, 2144, 1508, 1426, 1399 cm^{-1}. Anal. Calcd. for $C_{16}H_{15}N_5$: C, 69.29; H, 5.45; N, 25.25. Found: C, 69.39; H, 5.43; N, 25.17.



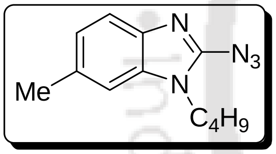
2-Azido-6-methyl-1-(3,5-dimethylphenyl)-1*H*-benzo[*d*]imidazole 4m: Thick liquid; yield 74%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8 Hz, 1H), 7.10 (t, *J* = 6.8 Hz, 2H), 7.00 (s, 2H), 6.96 (s, 1H), 2.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 139.6, 139.5, 135.7, 134.1, 132.6, 130.5, 124.3, 124.2, 117.8, 110.1, 21.7, 21.3; FT-IR (KBr) 2925, 2851, 2227, 1594, 1492, 1283, 1247, 1173, 1097, 1031 cm^{-1}. Anal. Calcd. for $C_{16}H_{15}N_5$: C, 69.29; H, 5.45; N, 25.25. Found: C, 69.40; H, 5.42; N, 25.17.



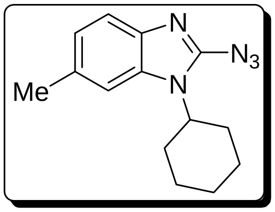
2-Azido-6-methyl-1-(2,6-dimethylphenyl)-1*H*-benzo[*d*]imidazole 4n: White solid; yield 59%; mp 109-110 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8 Hz, 1H), 7.13-7.19 (m, 2H), 7.00-6.96 (m, 3H), 2.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ146.9, 139.7, 135.8, 134.2, 132.7, 130.6, 124.4, 124.3, 117.9, 110.2, 21.8, 21.4; FT-IR (KBr) 2919, 2152, 1595, 1505, 1485, 1409, 1337, 1276, 1032 cm^{-1}. Anal. Calcd. for $C_{16}H_{15}N_5$: C, 69.29; H, 5.45; N, 25.25. Found: C, 69.37; H, 5.44 ; N, 25.18.



2-Azido-6-methyl-1-(naphthalen-1-yl)-1*H*-benzo[*d*]imidazole 4o: White solid; yield 50%; mp 112-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.0 Hz, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 8 Hz, 1H), 7.72-7.59 (m, 4H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.76 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 143.7, 134.8, 134.4, 133.3, 132.7, 132.1, 129.7, 128.9, 128.2, 127.9, 125.6, 125.4, 122.1, 119.2, 112.1, 20.6; FT-IR (KBr) 2919, 2152, 1625, 2098, 1615, 1498, 1380, 1259, 1237, 1049 cm^{-1}. Anal. Calcd. for $C_{18}H_{13}N_5$: C, 72.23; H, 4.38; N, 23.40. Found: C, 72.33; H, 4.36; N, 23.32.

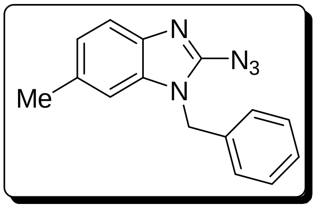


2-Azido-1-butyl-6-methyl-1*H*-benzo[*d*]imidazole 4p: Thick liquid; yield 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 7.00 (s, 1H), 3.91 (t, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 1.74-1.68 (m, 2H), 1.35-1.29 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 134.6, 131.8, 129.6, 123.6, 121.1, 109.2, 44.8, 31.2, 21.7, 21.0, 13.6; FT-IR (KBr) 2960, 2929, 2870, 2139, 1623, 1432, 1282, 1261, 1095, 1021 cm^{-1}. Anal. Calcd. for $C_{12}H_{15}N_5$: C, 62.86; H, 6.59; N, 30.54. Found: C, 62.97; H, 6.56; N, 30.46.

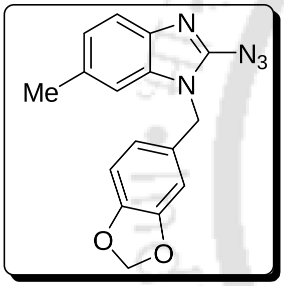


2-Azido-1-cyclohexyl-6-methyl-1*H*-benzo[*d*]imidazole 4q: Thick liquid; yield 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8 Hz, 1H), 7.17 (s, 1H), 7.01 (d, *J* = 8 Hz, 1H), 4.10 (t, *J* = 9.8 Hz, 1H), 2.45 (s, 3H), 2.16-1.75 (m, 7H), 1.46-1.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 139.9, 134.1, 131.6, 123.6, 118.0, 110.9, 55.6, 31.3, 26.2, 25.4, 22.0; FT-

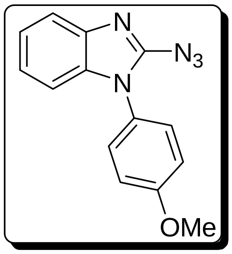
IR (KBr) 2932, 2856, 2142, 1505, 1484, 1424, 1283, 1257 cm^{-1}. Anal. Calcd. for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43. Found: C, 65.95; H, 6.69 ; N, 27.36.



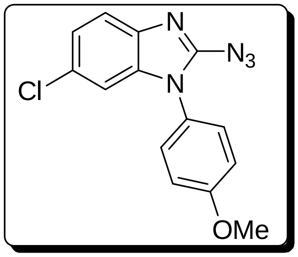
2-Azido-1-benzyl-6-methyl-1*H*-benzo[*d*]imidazole 4r: White solid; yield 60%; mp 132-133 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (d, *J* = 8.4 Hz, 1H), 7.31-7.26 (m, 3H), 7.17-7-15 (m, 2H), 7.02 (dd, *J* = 8 Hz, 0.4 Hz, 1H), 6.94 (s, 1H), 5.11 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.2, 139.7, 135.7, 134.9, 132.4, 129.0, 128.1, 126.9, 124.1, 118.0, 109.6, 46.5, 21.9; FT-IR (KBr) 2963, 2135, 1623, 1493, 1438, 1363, 1260, 1026 cm^{-1}. Anal. Calcd. for $C_{15}H_{13}N_5$: C, 68.42; H, 4.98; N, 26.60. Found: C, 68.52; H, 4.95; N, 26.53.



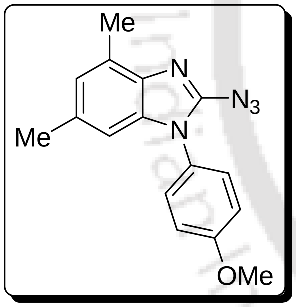
2-Azido-1-((benzo[*d*][1,3]dioxol-5-yl)methyl)-6-methyl-1*H*-benzo[*d*]imidazole 4s: White solid; yield 49%; mp 101-102 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.98 (s, 1H), 6.75-6.73 (m, 2H), 5.93 (s, 2H), 5.02 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ155.5, 148.1, 147.5, 134.7, 131.4, 129.9, 129.3, 124.1, 121.5, 121.2, 120.7, 117.9, 101.3, 48.4, 21.2; FT-IR (KBr) 3275, 2962, 2149, 1610, 1500, 1448, 1260, 1097, 1038 cm^{-1}. Anal. Calcd. for $C_{16}H_{13}N_5O_2$: C, 62.53; H, 4.26; N, 22.79. Found: C, 62.64; H, 4.24; N, 22.72.



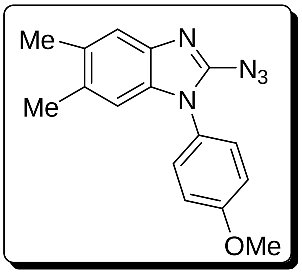
2-Azido-1-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole 4t: White solid: yield 74%; mp 96-97 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, *J* = 8.4 Hz, 1H), 7.33-7.26 (m, 2H), 7.21-7.13 (m, 3H), 7.05 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.9, 147.8, 141.5, 135.9, 127.9, 126.9, 123.1, 122.7, 118.4, 115.0, 110.1, 55.7; FT-IR (KBr) 3057, 2961, 2835, 2138, 1616, 1513, 1498, 1431, 1331, 1301, 1292, 1253, 1183, 1035 cm^{-1}. Anal. Calcd. for $C_{14}H_{11}N_5O$: C, 63.39; H, 4.18; N, 26.40. Found: C, 63.51; H, 4.16; N, 26.33.



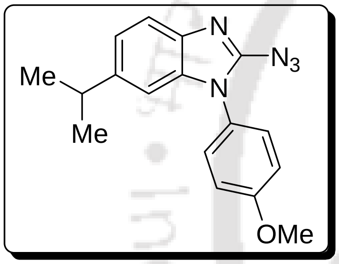
2-Azido-6-chloro-1-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole 4u: White solid; yield 70%; mp 104-105 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55 (d, *J* = 8.8 Hz, 1H), 7.29-7.20 (m, 3H), 7.11 (s, 1H), 7.04 (d, *J* = 7.2 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.2, 147.2, 136.5, 128.4, 127.9, 126.4, 123.7, 119.2, 115.1, 110.3, 55.8; FT-IR (KBr) 3066, 2965, 2147, 1610, 1514, 1410, 1326, 1304, 1253, 1207, 1108, 1031 cm^{-1}. Anal. Calcd. for $C_{14}H_{10}ClN_5O$: C, 56.10; H, 3.36; N, 23.37. Found: C, 56.23; H, 3.33; N, 23.30.



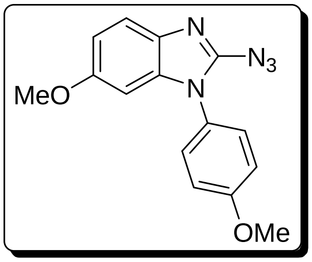
2-Azido-1-(4-methoxyphenyl)-4,6-dimethyl-1*H*-benzo[*d*]imidazole 4v: White solid; yield 75%; mp 111-112 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.27 (d, *J* = 9.2 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.89 (s, 1H), 6.74 (s, 1H), 3.86 (s, 3H), 2.59 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.7, 146.3, 138.7, 135.7, 132.5, 127.9, 127.3, 124.9, 114.9, 107.5, 55.7, 21.7, 16.6; FT-IR (KBr) 2953, 2137, 1629, 1496, 1257, 1107, 1032 cm^{-1}. Anal. Calcd. for $C_{16}H_{15}N_5O$: C, 65.52; H, 5.15; N, 23.88. Found: C, 65.62; H, 5.14; N, 23.81.



2-Azido-1-(4-methoxyphenyl)-5,6-dimethyl-1*H*-benzo[*d*]imidazole 4w: White solid; yield 75%; mp 107-108 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 (s, 1H), 7.28 (d, *J* = 9.2 Hz, 2H), 7.02 (d, *J* = 9.2 Hz, 2H), 6.90 (s, 1H), 3.86 (s, 1H), 2.34 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.7, 146.7, 139.9, 134.3, 131.8, 131.7, 127.8, 127.2, 118.6, 114.9, 110.3, 55.7, 20.5, 20.4; FT-IR (KBr) 2925, 2153, 1518, 1465, 1414, 1297, 1249, 1033 cm^{-1}. Anal. Calcd. for $C_{16}H_{15}N_5O$: C, 65.52; H, 5.15; N, 23.88. Found: C, 65.65; H, 5.13; N, 23.80.



2-Azido-6-isopropyl-1-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole 4x: White solid; yield 70%; mp 106-107 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 (d, *J* = 8.4 Hz, 1H), 7.34-7.31 (m, 2H), 7.18 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.08-7.06 (m, 2H), 6.98 (s, 1H), 3.89 (s, 3H), 2.98-2.95 (m, 1H), 1.25 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.8, 147.2, 144.1, 139.7, 135.9, 127.9, 126.9, 121.9, 118.0, 114.9, 107.3, 55.6, 34.5, 24.5; FT-IR (KBr) 2961, 2136, 1619, 1586, 1508, 1430, 1330, 1105, 1035 cm^{-1}. Anal. Calcd. for $C_{17}H_{17}N_5O$: C, 66.43; H, 5.58; N, 22.79. Found: C, 66.53; H, 5.57; N, 22.73.



2-Azido-6-methoxy-1-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole 4y: White solid; yield 78%; mp 122-123 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 (d, *J* = 8.8 Hz, 1H), 7.29-7.26 (m, 2H), 7.03 (dd, *J* = 2.0, 8.8 Hz, 2H), 6.86 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.59 (d, *J* = 2.4

Hz, 1H), 3.86 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 156.6, 146.5, 136.4, 135.7, 127.9, 126.9, 118.8, 115.0, 111.5, 94.3, 55.9, 55.7; FT-IR (KBr) 2950, 2839, 2144, 1630, 1516, 1484, 1422, 1408, 1329, 1276, 1243, 1204, 1147, 1025 cm^{-1}. Anal. Calcd. for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 61.15; H, 4.42; N, 23.64.

4.5 References

(1) For some studies on carbon-heteroatom cross-coupling reactions see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (b) Ullman, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382. (c) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691.(d) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (e) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (e) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (f) Evano, G.; Blanchard, N.; Toymi, M. *Chem. Rev.* **2008**, *108*, 3054. (g) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (h) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (i) Correa, A.; García Mancheño, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (j) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954. (k) Würtz S.; Glorius F. *Acc. Chem. Res.* **2008**, *41*, 1523.

(2) For some studies on C-N cross-coupling reactions, see: (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* ***1989**, 30,* 2581. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338. (c) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* ***2008**, 130,* 16184. (d) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* ***2011**, 133,* 5996. (e) Carril, M.; SanMartin, R.; Dominquez, E. *Chem. Soc. Rev.* **2008**, *37*, 639. (f) Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *J. Org. Chem.* **2011**, *76*, 5295. (g) Kumar, R. K.; Ali, M. A.; Punniyamurthy, T. *Org. Lett.* **2011**, *13*, 2102.

(3) (a) Alamgir, M.; Black, D. St. C.; Kumar, N. Synthesis, Reactivity and Biological Activity of Benzimidazoles. *Topics In Heterocyclic Chemistry*; Springer: Berlin, Heidelberg, 2007; Vol. 9, pp. 87-118 and references cited therin. (b) Ozden, S.; Atabey, D.; Yildiz, S.; Goker, H. *Eur. J. Med. Chem.* **2008**, *43*, 1390. (c) Zhang, G.; Ren, P.; Gray, N. S.; Sim, T.; Liu, Y.; Wang, X.; Che, J.; Tian, S.-S.; Sandberg, M. L.; Spalding, T. A.; Romeo, R.; Iskander, M.; Chow, D.; Seidel, H. M.; Karanewsky, D. S.; He, Y. *Bioorg. Med. Chem.*

Lett. **2008**, *18*, 5618. (d) Morphy, R.; Rankovic, Z. *J. Med. Chem.* **2005**, *48*, 6523. (e) Schnurch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283. (g) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(4) (a) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (c) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (d) Kondo, T.; Mitsudo, T.-A. *Chem. Rev.* **2000**, *100*, 3205. (e) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954.

(5) (a) Dang, Q.; Kasibhatla, S.; Xiao, W.; Liu, Y.; Dare, J.; Taplin, F.; Reddy, K.; Scarlato, G.; Gibson, T.; Poelje, P.; Potter, S.; Erion, M. *J. Med. Chem.* **2010**, *53*, 441. (b) Blythin, D. J.; Kaminski, J. J.; Domalski, M. S.; Spitler, J.; Solomon, D. M.; Conn, D. J.; Wong, S. C.; Verbiar, L. L.; Bober, L. A.; Chiu, P. J. S.; Watnick, A. S.; Siegel, M. I.; Hilbert, J. M.; McPhail, A. T. *J. Med. Chem.* **1986**, *29*, 1099. (c) Miller, J. F.; Turner, E. M.; Gudmundsson, K. S.; Jenkinson, S.; Spaltenstein, S.; Thomson, M.; Wheelan, P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2125. (d) Perez-Villanueva, J.; Santos, R.; Hernandez-Campos, A.; Giulianotti, M. A.; Castillo, R.; Medina-Franco, J. L. *Med. Chem. Commun.* **2011**, *2*, 44. (e) Ozden, S.; Atabey, D.; Yildiz, S.; Goker, H. *Eur. J. Med. Chem.* **2008**, *43*, 1390. (f) Weidner-Wells, M. A.; Ohemeng, K. A.; Nguyen, V. N.; Fraga-Spano, S.; Macielag, M. J.; Werblood, H. M.; Foleno, B. D.; Webb, G. C.; Barrett, J. F.; Hlasta, D. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1545.

(6) Examples in medicinal chemistry, see: (a) Zarrinmayeh, H.; Nunes, A. M.; Ornstein, P. L.; Zimmerman, D. M.; Arnold, M. B.; Schober, D. A.; Gackenheimer, S. L.; Bruns, R. F.; Hipskind, P. A.; Britton, T. C.; Cantrell, B. E.; Gehlert, D. *J. Med. Chem.* **1998**, *41*, 2709. (b) Baudy, R. B.; Fletcher III, H.; Yardley, J. P.; Zaleska, M. M.; Bramlett, D. R.; Tasse, R. P.; Kowal, D. M.; Katz, A. H.; Moyer, J. A.; Abou-Gharbia, M. *J. Med. Chem.* **2001**, *44*, 1516. (c) Zhao, Z. S.; Arnaiz, D. O.; Griedel, B.; Sakata, S.; Dallas, J. L.; Whitlow, M.; Trinh, L.; Post, J.; Liang, A.; Morrissey, M. M.; Shaw, K. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 963. (d) White, A. W.; Almassy, R.; Calvert, A. H.; Curtin, N. J.; Griffin, R. J.; Hostomsky, Z.; Maegley, K.; Newell, D. R.; Srinivasan, S.; Golding, B. T. *J. Med. Chem.* **2000**, *43*, 4084 (e) Hauel, N. H.; Nar, H.; Priepke, H.; Ries, U.; Stassen, J.; Wienen, W. *J. Med. Chem.* **2002**, *45*, 1757.

(7) (a) Schwartz, G.; Fehse, K.; Pfeiffer, M.; Walzer, K.; Leo, K. *Appl. Phys. Lett.* **2006**, *89*, 83509. (b) Plater, M. J.; Barnes, P.; McDonald, L. K.; Wallace, S.; Archer, N.; Gelbrich, T.; Horton, P. N.; Hursthouse, M. B. *Org. Biomol. Chem.* **2009**, *7*, 1633.

(8) (a) Reynolds, G. A.; Vanallan, J. A. *J. Org. Chem.* **1959**, *24*, 1478. (a) Denise Zornik, D.-C.; Robert M. M.; Tamer El Malah. D.-C.; Christina, M. T.; Stefan, H. *Chem. Eur. J.* **2011**, *17*, 1473. (b) Dehuri, S. N. *J. Ind. Chem. Soc.* **1983**, *60*, 475. (c) Takero, T.; Toshikazu, K.; Makoto, O. *Tetrahedron Lett.* **1975**, *18*, 1523.

(9) Abd-Elmotaleb, M. *Bull. Fac. Sci.* **2002**, *31*, 25.

(10) For some studies, see: (a) Preston, P. N. Benzimidazoles and Congeneric Tricyclic Compounds. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A.; Taylor, E. C., Eds.; John Wiley and Sons, 1981; Vol. 40, pp. 6-60. (b) Lim, H.-J.; Myung, D.; Lee, I. Y. C.; Jung, M. H. *J. Comb. Chem*. **2008**, *10*, 501.

(11) (a) Yang, D.; Fokas, D.; Li, J.; Yu, L.; Baldino, C. M. *Synthesis* **2005**, 47 and reference therein. (b) Wu, Z.; Rea, P.; Wickham, G. *Tetrahedron Lett*. **2000**, *41*, 9871.

(12) (a) Brain, C. T.; Brunton, S. A. *Tetrahedron Lett.* **2002**, *43*, 1893. (b) Brain, C. T.; Steer, J. T. *J. Org. Chem.* **2003**, *68*, 6814. (c) Zhao, D.; Hu, J.; Wu, N.; Huang, X.; Qin, X.; Lan, J.; You, J. *Org. Lett*. **2011**, *13*, 6516.

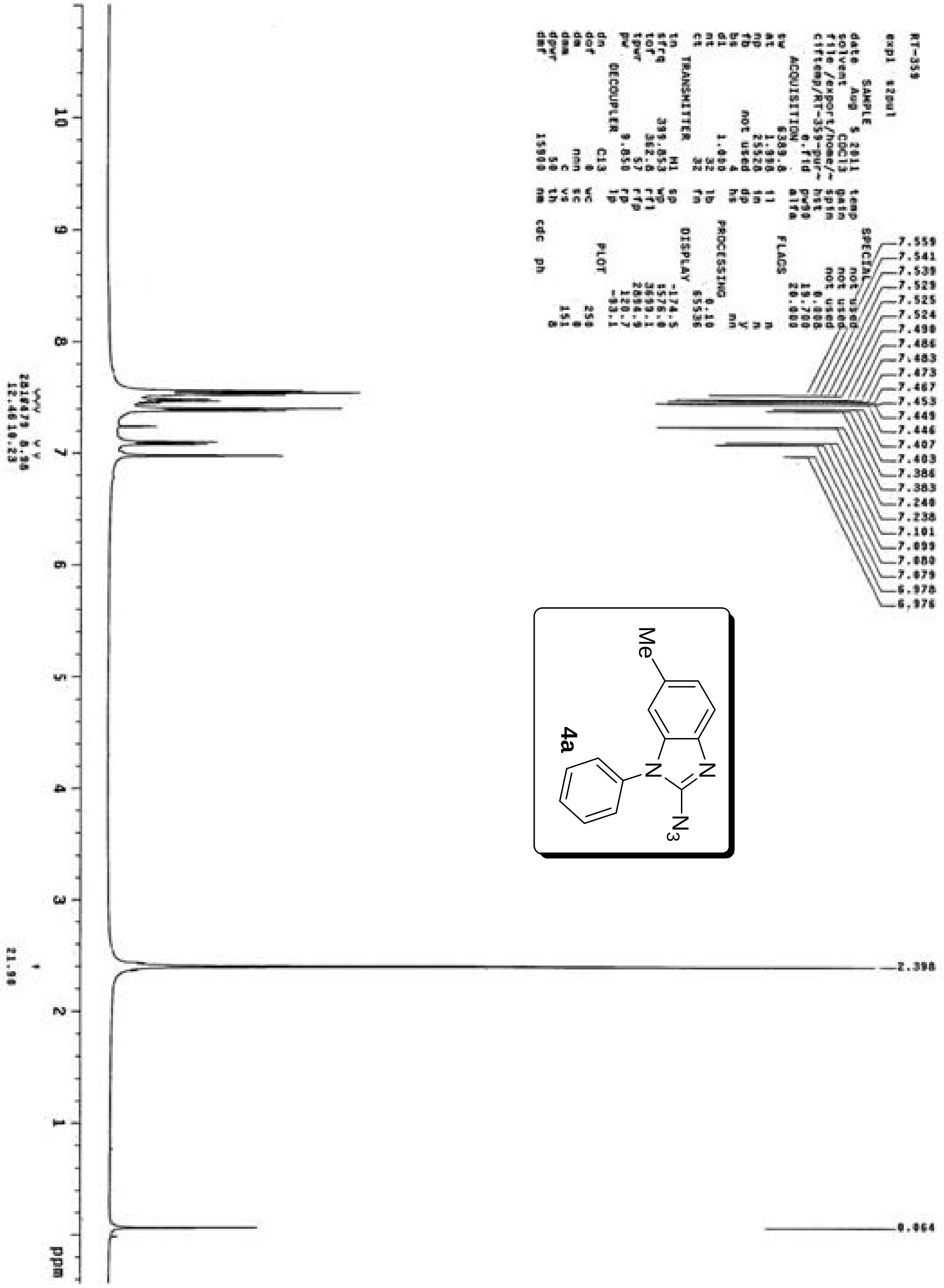
(13) (a) Deng, X.; McAllister, H.; Mani, N. S. *J. Org. Chem.* **2009**, *74*, 5742. (b) Evinder, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133. (c) Lv, X.; Bao, W. *J. Org. Chem.* **2009**, *74*, 5618. (d) Peng, J.; Ye, M.; Zong, C.; Hu, F.; Feng, L.; Wang, X.; Wang, Y.; Chen, C. *J. Org. Chem.* **2011**, *76*, 716. (e) Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719.

(14) Saha, P.; Ali, M. A.; Ghosh, P.; Punniyamurthy, T. *Org. Biomol. Chem*. **2010**, *8*, 5692.

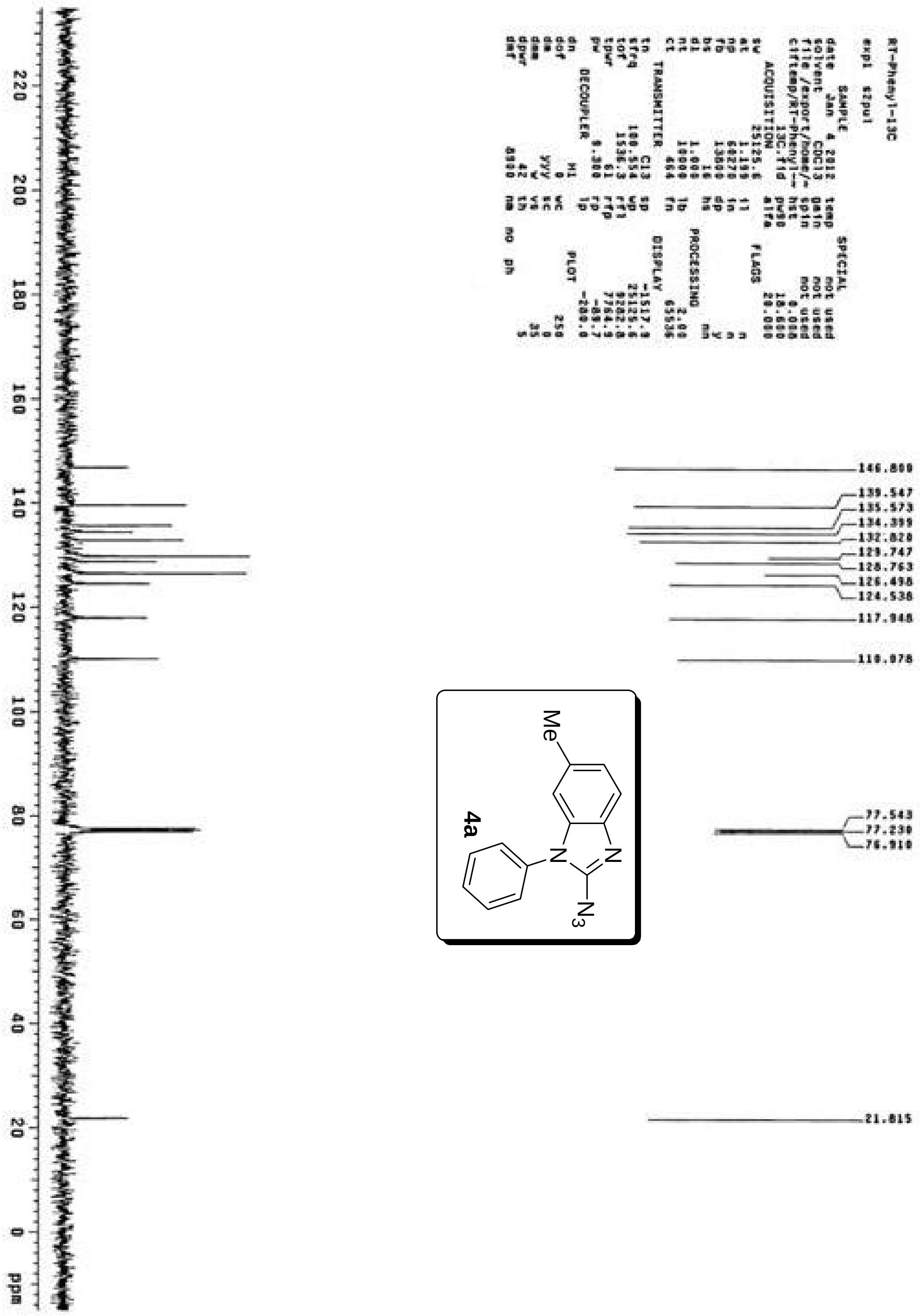
(15) For examples of reduction of copper(II) to copper(I) species, see: (a) Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496. (b) Lindley, J. *Tetrahedron.* **1984**, *40*, 1433. (c) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312. (d) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F.; Paine, A. J. *J. Am. Chem. Soc.* **1998**, *120*, 12459. (e) Bowmaker, G. A.; Hanna, J. V.; Pakawatchai, C.; Skelton, B. W.; Thanyasirikul, Y.; White, A. H. *Inorg. Chem.* **2009**, *48*, 350. (f) Ramana, T.; Saha, P.; Das, M.; Punniyamurthy, T. *Org. Lett.* **2010**, *12*, 84.

Crystal Data and Structure Refinement for 4c at 296(2) K

Identification code	**4c**	
Empirical formula	$C_{14}H_{10}ClN_5$	
Formula weight	283.80	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
	Loop xyz	
	'x, y, z' '-x, -y, -z'	
Unit cell dimensions	*a* = 7.5072(7) Å	α(°)= 86.685(4)
	b = 13.4813(12) Å	β(°)= 77.589(3)
	c = 14.4703(13) Å	γ(°)= 77.539(3)
Volume	1396.5(2) $Å^3$	
Z	4	
Density (calculated)	1.397 Mg/m^3	
Absorption coefficient	0.272 mm^{-1}	
F(000)	624.0	
Crystal size	0.32 x 0.26 x 0.14 mm	
Theta range for data collection	1.44 to 25.25°	
Index ranges	-8<=h<=8, -15<=k<=15, -17<=l<=13	
Reflections collected	3762	
Independent reflections	2422 [R (int) = 0.0339]	
Completeness to theta = 25.25°	74.4 %	
Absorption correction	Multi-scan	
Data / restraints / parameters	3762 / 0 /363	
Goodness-of-fit on F^2	1.086	
Final R indices [I>2sigma (I)]	*R1* = 0.0471, *wR2* = 0.0928	
R indices (all data)	*R1* = 0.0817, *wR2* = 0.1064	
CCDC	871225	

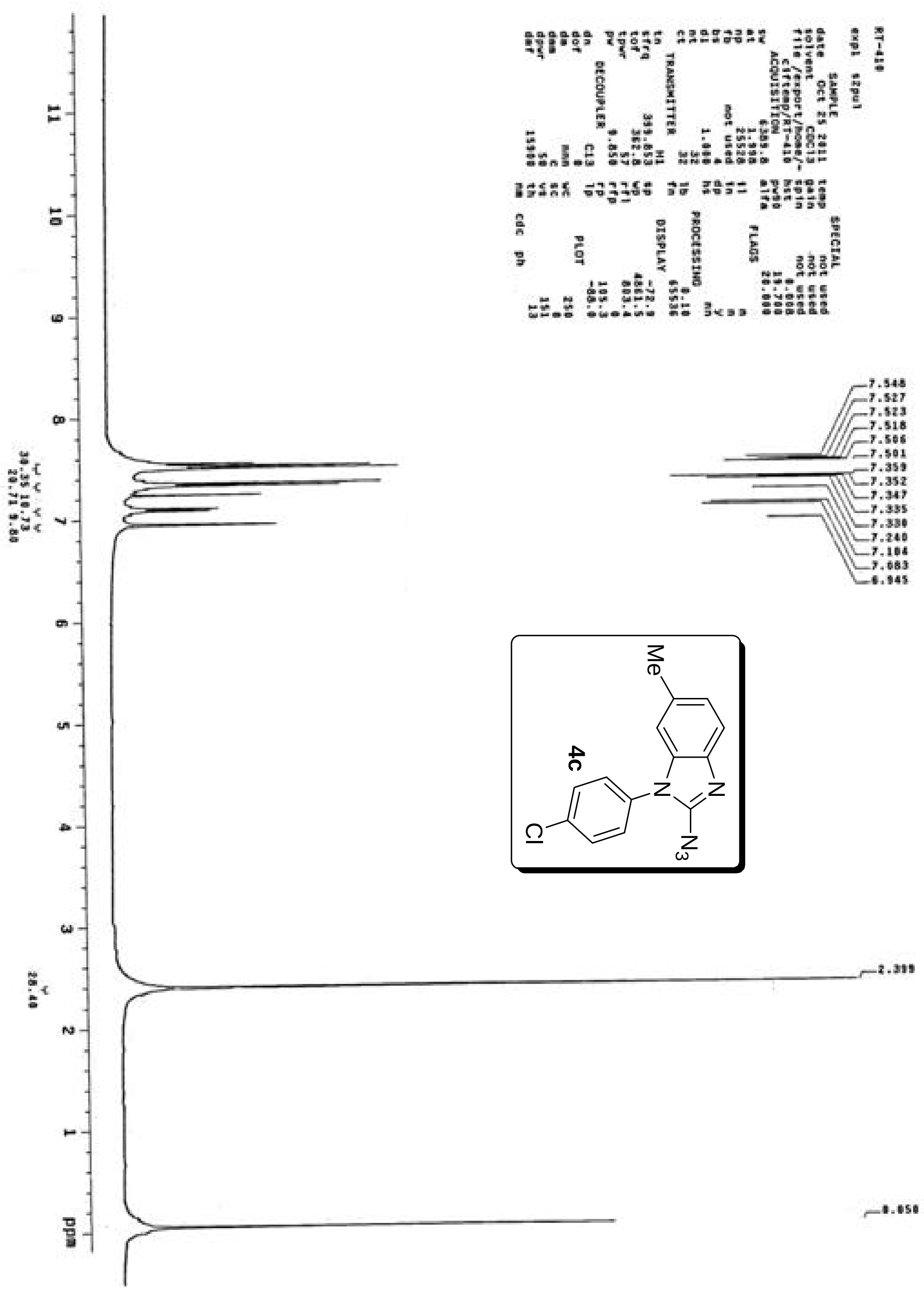

RT-359
7.559
7.541
7.539
7.529
7.525
7.524
7.498
7.486
7.483
7.473
7.467
7.453
7.449
7.446
7.407
7.403
7.386
7.383
7.240
7.238
7.101
7.099
7.080
7.079
6.978
6.976
2.398
0.064
Me
N
N
N3
10
9
8
7
6
5
4
3
2
1
ppm
12.46
10.23
21.98

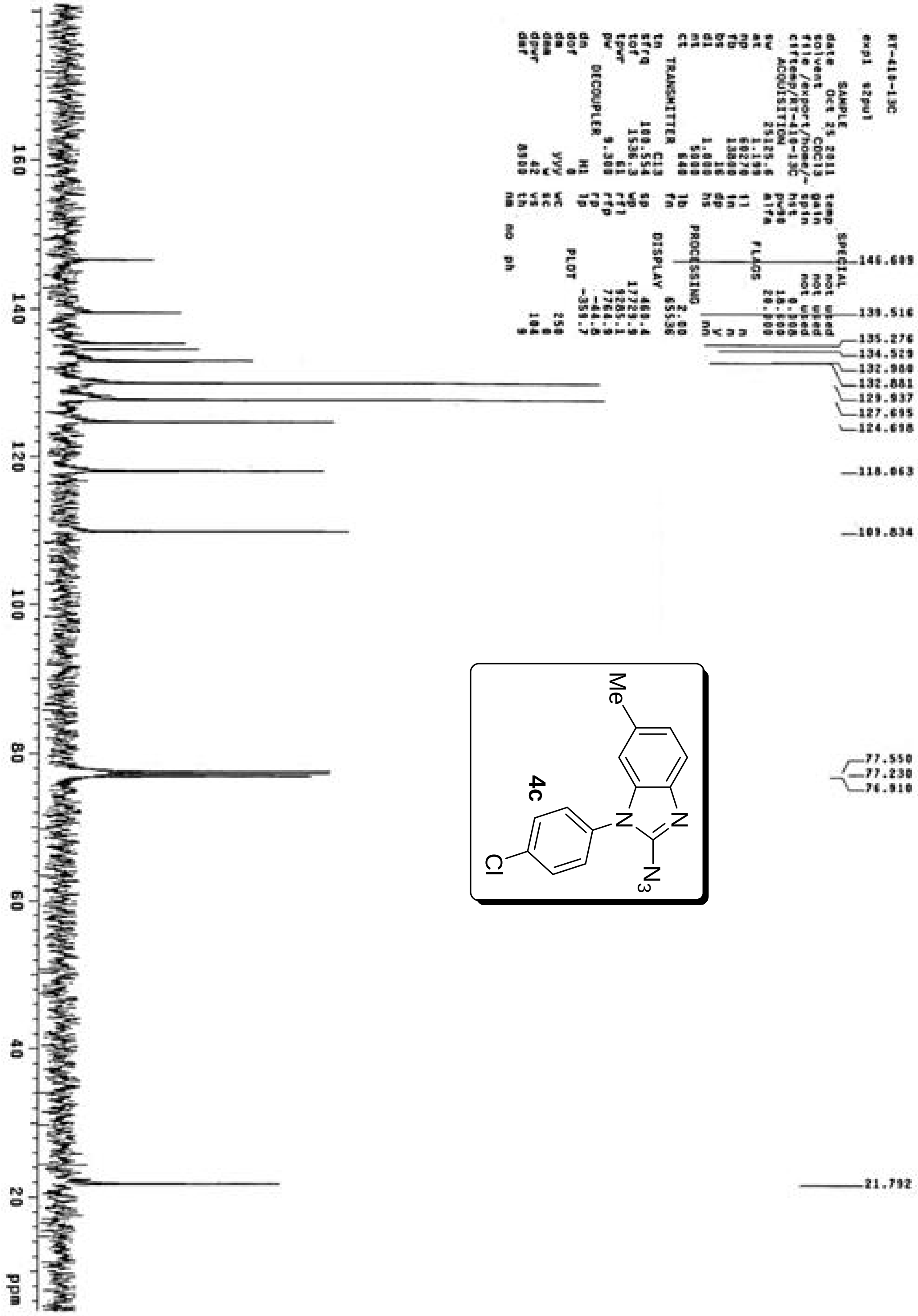
4a



4a

RT-Phenyl-13C
146.809
139.547
135.573
134.399
132.828
129.747
128.763
126.498
124.538
117.948
110.078
77.543
77.230
76.910
21.815
Me
N
N
N_3
220
200
180
160
140
120
100
80
60
40
20
0
ppm


4c
Me
N
N
N3
Cl
7.548
7.527
7.523
7.518
7.506
7.501
7.359
7.352
7.347
7.335
7.330
7.240
7.184
7.083
6.945
2.399
0.050
30.35 10.73
20.71 9.80
28.40
11
10
9
8
7
6
5
4
3
2
1
ppm



4c

RT-418-13C
146.609
139.516
135.276
134.529
132.980
132.881
129.937
127.695
124.698
118.063
109.834
77.550
77.230
76.910
21.792
160
140
120
100
80
60
40
20
ppm
Me
N
N
N_3
Cl

Copper-Catalyzed Reduction of 2-Azidobenzimidazoles to 2-Aminobenzimidazoles

Nitrogen containing heterocyclic compounds occur widely in drugs and possess pharmacological properties.[1] For example, 2-aminobenzimidazole derivatives exhibit antiaggregatory,[2a] anti-inflammatory,[2b] antitumoractivity,[2c] antimicrobial,[2d] antiallergic,[2e] antiviral[2f] and antibacterial activity (Figure 1).[2g-h] They have been also used as a benzodiazepine receptor,[3a] mare selective inhibitors of nitricoxide[3b] and neuronal calcium channel blockers.[3c] In addition, 2-aminobenzimidazoles serve as versatile synthetic intermediates for the construction of drugs.[4] They also show biological activities such as antihistaminic,[5a-c] diuretic,[5d] immunotropic[5e-f] and highly selective p38a MAP inhibition properties.[5g-h] Thus, the development of effective methods for the construction of the substituted 2-aminobenzimidazole structural framework has been important in organic synthesis.

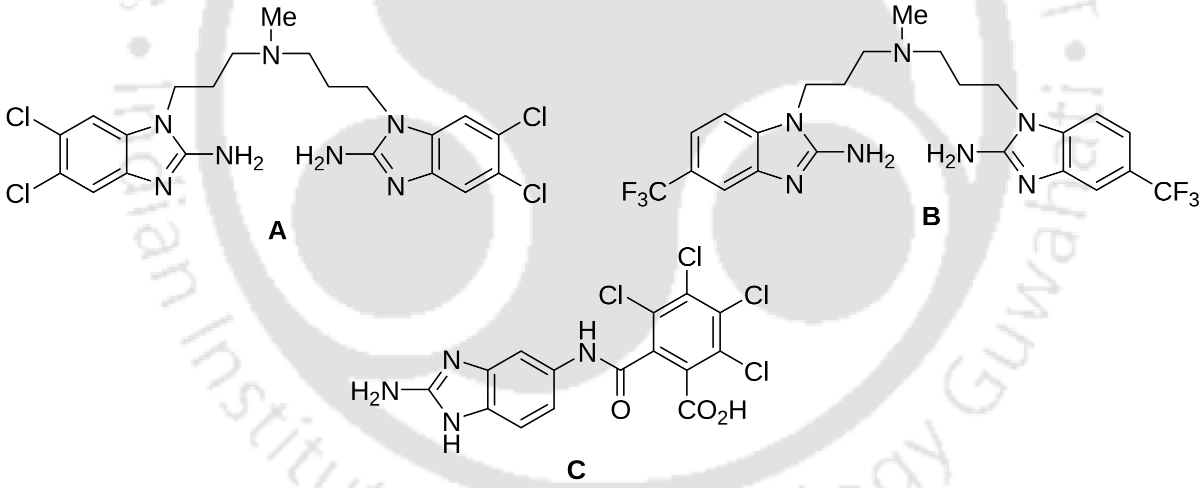
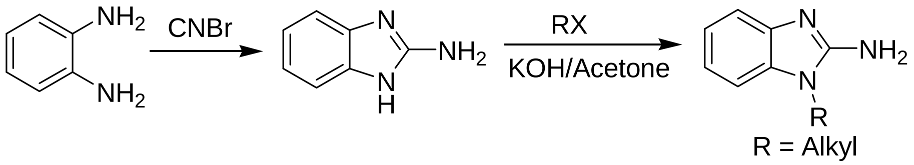


Figure 1. Examples of some antibacterial active compounds.

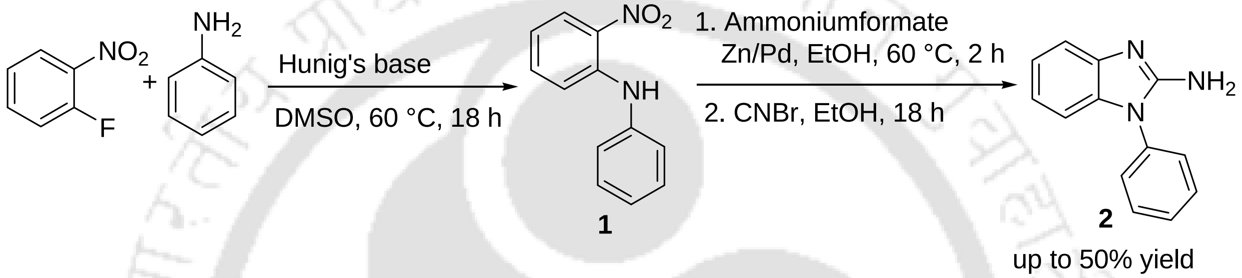
5.1 Classical Methods

Guida and co-workers have reported the synthesis of 2-aminobenzimidazole from substituted 1,2-diaminoarenes and cyanogen bromide (Scheme 1).[6a] The resulting product can be reacted with alkyl halide in the presence of KOH to give 1-alkyl-2-aminobenzimidazole.



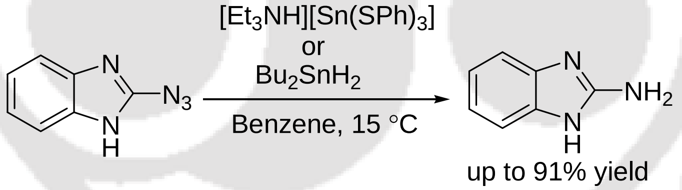
Scheme 1

The reaction of 2-fluoronitrobenzene with aniline in the presence of hunig's base gives **1** that could be converted into 1-aryl-2-aminobenzimidzole **2** by reduction using Zn or Pd followed by condensation with cyanogen bromide (Scheme 2).[6b]



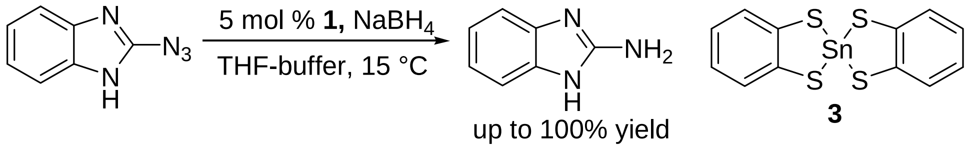
Scheme 2

Vilarrasa and co-authors have showed the preparation of 2-aminobenzimidazoles from 2-azidobenzimidazoles by reduction using tin hydride (Scheme 3).[6c]



Scheme 3

They also subsequently have demonstrated the reduction azide functional group into amine using tin complex **3** and $NaBH_4$ in THF-buffer with quantitative yield (Scheme 4).[6d]



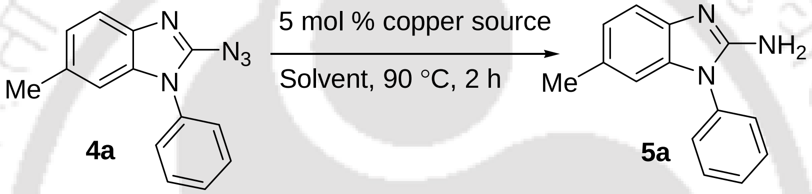
Scheme 4

Most of these existing protocols require stochiometric amount of the reagents and some of them are toxic. The development of effective methods is thus important for the construction of the target heterocyclic compounds.

5.2 Present Study

The direct conversion of 2-azidobenzimidazole to 2-amino-benzimidazoles has been described using copper-catalysis. The procedure is simple, efficient and affords a general method for the reduction of azides to amines under air.

Table 1. Optimization of the Reaction Conditions[a]



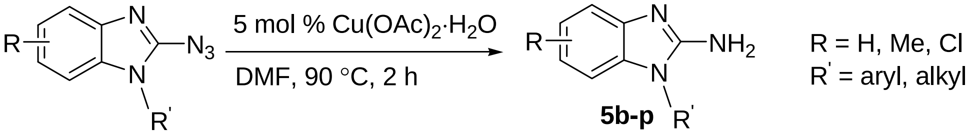
Entry	Copper source	Solvent	Product (**5a**) (%)[b]
1	$Cu(OAc)_2 \cdot H_2O$	DMF	100
2	$Cu(OAc)_2 \cdot H_2O$	DMSO	100
3	$Cu(OAc)_2 \cdot H_2O$	CH_3CN	100
4	$Cu(OAc)_2 \cdot H_2O$	Toluene	100
5	CuI	DMF	100
6	Cu_2O	DMF	100
7	CuBr	DMF	100
8	$CuSO_4 \cdot 5H_2O$	DMF	100

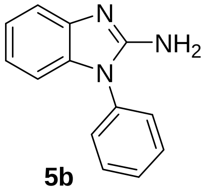
[a] Reaction conditions: 2-Azidobenzimidazole **4a** (1 mmol) and copper catalyst (5 mol %) were stirred at 90 °C in solvent (1 mL).

[b] Determined by 400 MHz ^{1}H NMR.

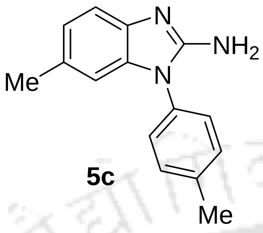
First, the optimization of the reaction conditions was carried out with 2-azido-6-methyl-1-phenyl-1*H*-benzo[*d*]imidazole **4a** as a model substrate using different solvents and copper

Table 2. Substrate Scope of the Formation of 2-Aminobenzimidazoles[a-b]

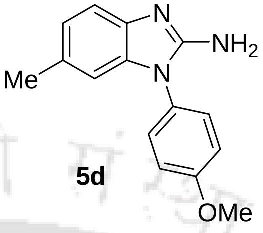



5b

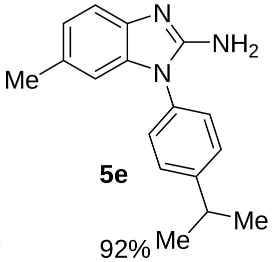
86%


5c

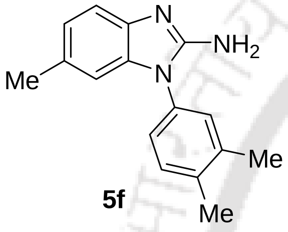
93%


5d

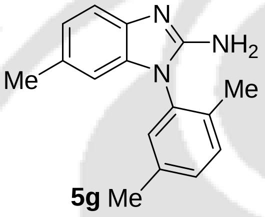
95%


5e

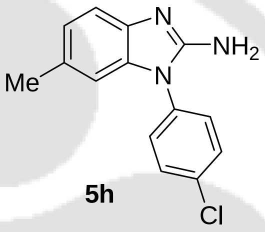
92%


5f

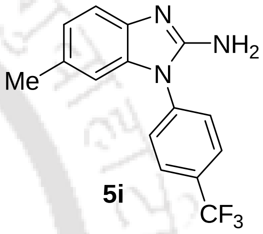
87%


5g

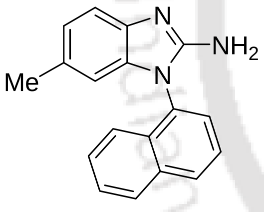
88%


5h

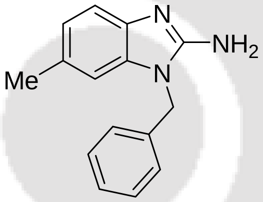
90%


5i

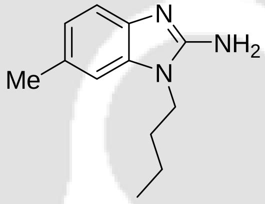
55%


5j

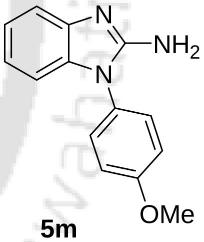
65%


5k

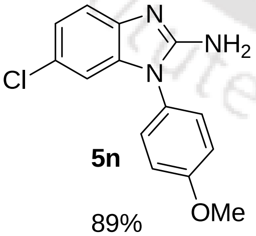
77%


5l

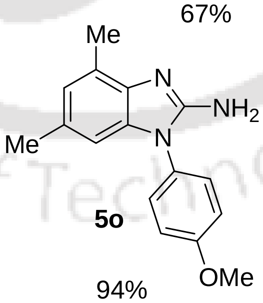
67%


5m

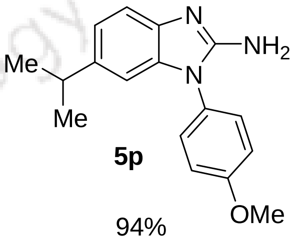
92%


5n

89%


5o

94%


5p

94%

---

[a] Reaction conditions: 2-Azidobenzimidazoles (1 mmol) and $Cu(OAc)_2·H_2O$ (5 mol %) were stirred at 90 °C in DMF (1 mL).

[b] Isolated yield.

sources at varied temperatures. The reaction proceeded to afford the target 2-amino-6-methyl-1-phenyl-1*H*-benzo[*d*]imidazole **5a** in 100% conversion when the substrate was stirred at 90 °C using 5 mol % of the copper salts such as $Cu(OAc)_2{\cdot}H_2O$, CuI, Cu_2O, CuBr and $CuSO_4{\cdot}5H_2O$ (Table 1, entries 1 and 5-8). The reaction was effective in solvents such as DMF, DMSO, CH_3CN and toluene affording the target product **5a** in 100% conversion (Table 1, entries 1-4). The control experiments confirmed that without the copper source the target molecule **5a** was not formed, and the starting material was recovered intact.

Next, the scope of the procedure was examined for the reduction a series other substituted 2-azidobenzimidazoles (Table 2). The reactions proceeded efficiently to afford the target products in moderate to high yield. The substrates having electron-donating groups (4-Me, 4-OMe, 4-^{i}Pr, 3,4-Dimethyl and 2,5-Dimethyl) on the 1-aryl ring underwent reduction to give the target molecules **5b-g** in 86-95% yield, while the substrates having electron withdrawing substituents (4-Cl, 4-CF_3) proceeded the reaction to provide **5h-i** in 55-90% yield. Furthermore, the substrates having 1-naphthyl and 1-alkyl substituents underwent reactions to give **5j-l** in 65-77% yield. In addition, the substrates having both electron donating and electron withdrawing substituents (Me, ^{i}Pr and Cl) on the fuzed aromatic nucleous proceeded reaction to give **5m-p** in 62-72% yield. Recrystallization of **5m** in MeOH gave crystals whose structure was confirmed by single crystal X-ray analysis (Figure 2).

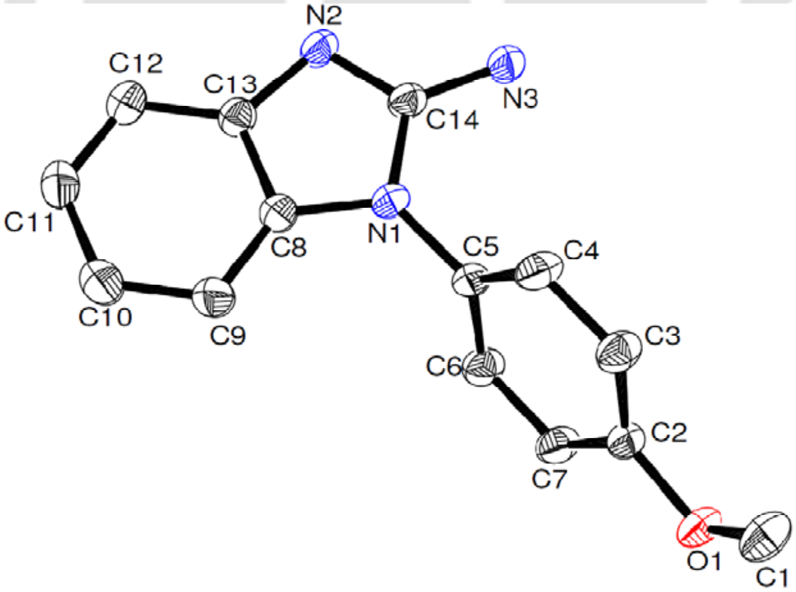
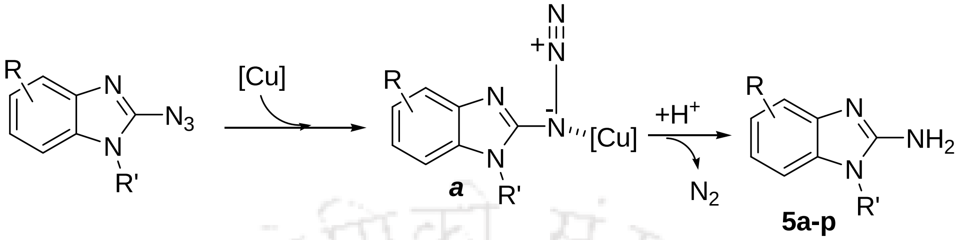


Figure 2. ORTEP diagram of 1-(4-methoxyphenyl)-1*H*-benzimidazol-2-amine **5m** with 50% ellipsoid. H-Atoms are omitted for clarity.

The observed experimental results suggest that 2-azidobenzimidazole may react with copper salts to give the intermediate ***a*** that could be transformed into the target 2-aminobenzimidazoles **5a-p** on protonation followed by the emission of N_2.[7]



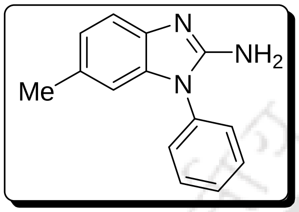
Scheme 5. Proposed catalytic cycle

In conclusion, copper-catalzyed reduction of 2-azidobenzimidazoles to 2-aminobenzimidazoles has been accomplished with moderate to excellent yield at moderate temperature. The procedure is simple, general and effective at moderate temperature under air.

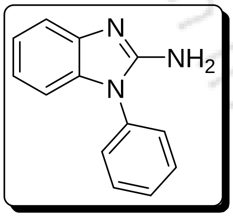
Experimental Section

General Information: $CuSO_4{\cdot}5H_2O$ (98%), CuI (98%), CuBr (98%), Cu_2O (97%) and $Cu(OAc)_2{\cdot}H_2O$ (98%) were obtained from Aldrich. Product purification was carried out by silica gel column chromatography using Rankem silica gel (60-120 mesh). The solvents were purchased and dried according to standard procedure prior to use. All reactions were monitored by analytical TLC on Merck silica gel G/GF 254 plates. NMR (^1H and ^{13}C) spectra were recorded on DRX-400 Varian spectrometer and the data are accounted as follows: chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet. Melting points were determined by Buchi B-540 melting point apparatus. FT-IR spectra of air-dried samples were recorded on PerkinElmer Spectrum One FT-IR spectrometer using KBr disks and are reported in frequency of absorption (cm^{-1}). Elemental analyses were recorded using PerkinElmer CHNS analyzer. For single crystal X-ray analysis the intensity data were collected using Bruker SMART APEX-II CCD diffractometer, equipped with 1.75 kW sealed-tube Mo Kα irradiation ($\lambda = 0.71073$ Å) at 296(2) K and the structures were solved by direct methods using *SHELLX-97* (Göttingen, Germany) and refined with full-matrix least squares on F^2 using SHELXL-97.

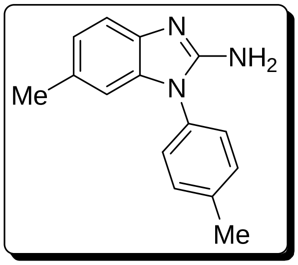
General Procedure for the Synthesis of 2-Aminobenzimidazoles. 2-Azidobenzimidazole and $Cu(OAc)_2 \cdot H_2O$ (5 mol %) were stirred at 90 °C in DMF for 2 h under air. Progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 x 10 mL), and the organic layer was washed with brine (1 x 5 mL) and water (1 x 5 mL). Drying and evaporation of the solvent gave a residue that was purified by silica gel chromatography using ethyl acetate and hexane as eluent to provide the titled compounds in analytically pure form.



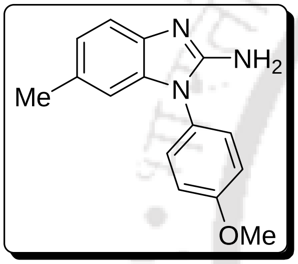
6-Methyl-1-phenyl-1*H*-benzo[*d*]imidazol-2-amine 5a: White solid; yield 89%; mp 104-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 2H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.75 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 137.5, 135.6, 134.4, 132.8, 129.7, 128.8, 126.5, 124.5, 117.9, 110.1, 24.8; FT-IR (KBr) 3153, 2919, 1572, 1486, 1455, 1408, 1384, 1284, 1260, 1100, 1017 cm^{-1}. Anal. Calcd. for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.40; H, 5.86; N, 18.74.



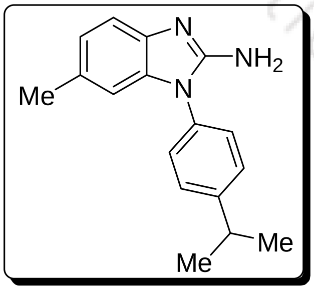
1-Phenyl-1*H*-benzo[*d*]imidazol-2-amine 5b:[6b] White solid; yield 86%; mp 96-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.26 (m, 5H), 7.11-6.97 (m, 4H), 6.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 142.7, 135.2, 133.5, 129.8, 128.0, 126.6, 123.4, 122.9, 119.5, 110.2; FT-IR (KBr) 3277, 2963, 2832, 1601, 1573, 1494, 1416, 1247, 1176, 1110, 1012 cm^{-1}. Anal. Calcd. for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.72; H, 5.28; N, 20.00.



6-Methyl-1-p-tolyl-1*H*-benzo[*d*]imidazol-2-amine 5c: White solid; yield 93%; mp 108-109 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36 (d, *J* = 7.2 Hz, 3H), 7.28 (d, *J* = 7.2 Hz, 2H), 6.99-6.95 (m, 2H), 2.44 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.7, 139.1, 132.2, 132.0, 131.7, 130.4, 127.7, 124.1, 123.4, 115.6, 109.0, 21.5, 21.2; FT-IR (KBr) 3307, 2918, 1639, 1542, 1515, 1470, 1441, 1259, 1210, 1043, 1018 cm^{-1}. Anal. Calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.99; H, 6.35; N, 17.66.

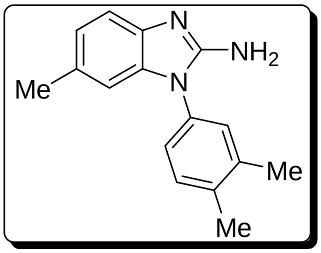


1-(4-Methoxyphenyl)-6-methyl-1*H*-benzo[*d*]imidazol-2-amine 5d: White solid; yield 95%; mp 124-125 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.25-7.22 (m, 4H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.88 (s, 1H), 6.61 (br s, 2H), 3.78 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.7, 147.6, 144.1, 139.3, 135.6, 127.9, 127.3, 122.4, 118.0, 114.5, 107.7, 55.9, 24.7; FT-IR (KBr) 3157, 2917, 1663, 1515, 1468, 1408, 1256, 1211, 1027 cm^{-1}. Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.25; H, 5.96; N, 16.52.

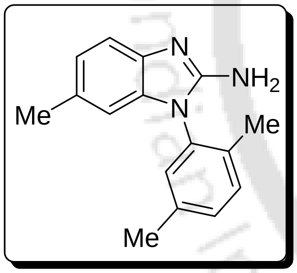


1-(4-Isopropylphenyl)-6-methyl-1*H*-benzo[*d*]imidazol-2-amine 5e: White solid; yield 92%; mp 112-113 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 3H), 6.93 (d, *J* = 5.6 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 5.01 (br s, 2H), 3.03-2.96 (m, 1H), 2.34 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.0, 139.5, 136.8, 134.8, 132.0, 129.2, 128.8, 126.4, 124.5, 118.9, 111.1, 34.2, 23.2, 20.7; FT-IR

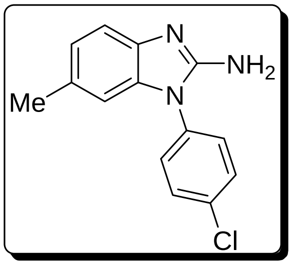
(KBr) 3248, 3190, 3078, 2960, 1642, 1584, 1475, 1447, 1377, 1263, 1166, 1077 cm^{-1}. Anal. Calcd. for $C_{17}H_{19}N_3$: C, 76.95; H, 7.22; N, 15.84. Found: C, 77.07; H, 7.19; N, 15.75.



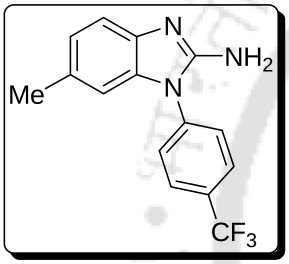
6-Methyl-1-(3,4-dimethylphenyl)-1*H*-benzo[*d*]imidazol-2-amine 5f: White solid; yield 87%; mp 87-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.18-7.13 (m, 2H), 6.94 (s, 1H), 6.77 (s, 1H), 6.11 (br s, 2H), 2.34 (s, 6H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 139.1, 137.9, 132.2, 132.0, 131.4, 130.1, 127.7, 124.1, 123.2, 115.0, 109.0, 21.5, 19.9, 19.6; FT-IR (KBr) 3253, 2920, 1644, 1436, 1407, 1384, 1261, 1206, 1172, 1012 cm^{-1}. Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.56; H, 6.80; N, 16.64.



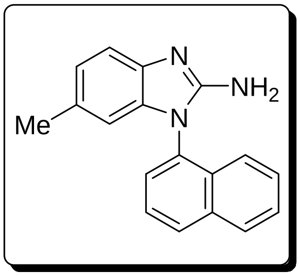
6-Methyl-1-(2,5-dimethylphenyl)-1*H*-benzo[*d*]imidazol-2-amine 5g: Thick liquid; yield 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 1H), 7.30 (t, *J* = 6.8 Hz, 2H), 7.11-7.08 (m, 1H), 7.03 (s, 1H), 6.72 (s, 1H), 5.43 (br s, 2H), 2.38 (s, 6H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 141.4, 139.6, 136.0, 132.9, 132.2, 130.5, 129.2, 128.0, 125.0, 118.5, 110.1, 24.1, 21.6, 17.7; FT-IR (KBr) 3267, 3098, 2912, 2842, 1651, 1579, 1523, 1496, 1423, 1345, 1277, 1178, 1025 cm^{-1}. Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.55; H, 6.81; N, 15.64.



1-(4-Chlorophenyl)-6-methyl-1*H*-benzo[*d*]imidazol-2-amine 5h: Thick liquid; yield 90%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54-7.50 (m, 3H), 7.38-7.33 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.95 (s, 1H), 6.61 (br s, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.7, 138.6, 135.2, 133.5, 133.0, 132.1, 128.9, 127.7, 124.9, 119.1, 111.8, 22.7; FT-IR (KBr) 3209, 3089, 2963, 2893, 1666, 1577, 1513, 1476, 1416, 1297, 1207, 1155, 1021 cm^{-1}. Anal. Calcd. for $C_{14}H_{12}ClN_3$: C, 65.25; H, 4.69; N, 16.30. Found: C, 65.37; H, 4.68; N, 16.23.

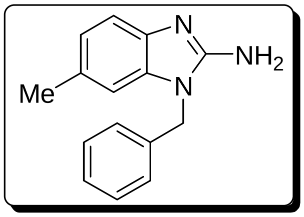


1-(4-(Trifluoromethyl)phenyl)-6-methyl-1*H*-benzo[*d*]imidazol-2-amine 5i: White solid; yield 55%; mp 129-130 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.25-7.22 (m, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.88 (s, 1H), 6.61 (br s, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.6, 139.8, 137.6, 135.0, 133.0, 128.0, 126.7, 124.1, 123.1, 119.3, 109.9, 22.0; FT-IR (KBr) 3278, 3177, 3058, 2958, 2863, 1633, 1545, 1499, 1422, 1377, 1292, 1195, 1114, 1023 cm^{-1}. Anal. Calcd. for $C_{15}H_{12}F_3N_3$: C, 61.85; H, 4.15; N, 14.43. Found: C, 61.99; H, 4.14; N, 14.36.

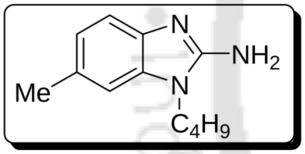


6-Methyl-1-(naphthalen-1-yl)-1*H*-benzo[*d*]imidazol-2-amine 5j: White solid; yield 65%; mp 110-111 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.34 (d, *J* = 5.2 Hz, 1H), 8.11 (d, *J* = 6.4 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.70-7.56 (m, 4H), 7.47 (d, *J* = 6.0 Hz, 1H), 7.20 (d, *J* = 6.4 Hz, 1H), 6.66 (s, 1H), 4.70 (br s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$)

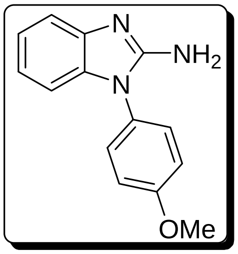
δ 153.7, 143.7, 134.8, 134.4, 133.4, 132.8, 132.1, 129.4, 128.9, 128.4, 127.1, 126.6, 124.9, 122.1, 119.3, 112.1, 21.1; FT-IR (KBr) 3288, 3158, 3088, 1646, 1574, 1510, 1453, 1392, 1252, 1194, 1071, 1015 cm^{-1}. Anal. Calcd. for $C_{18}H_{15}N_3$: C, 79.10; H, 5.53; N, 15.37. Found: C, 79.20; H, 5.51; N, 15.29.



1-Benzyl-6-methyl-1*H*-benzo[*d*]imidazol-2-amine 5k: White solid; yield 77%; mp 122-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.2 Hz, 3H), 7.28 (d, *J* = 6.4 Hz, 2H), 6.99-6.93 (m, 3H), 5.21 (s, 2H), 4.04 (br s, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 138.9, 135.7, 133.9, 132.3, 129.1, 127.1, 127.0, 124.2, 117.6, 110.6, 45.9, 22.0; FT-IR (KBr) 3205, 3053, 2912, 2863, 1606, 1574, 1501, 1466, 1416, 1271, 1123, 1076 cm^{-1}. Anal. Calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.00; H, 6.35; N, 17.65.

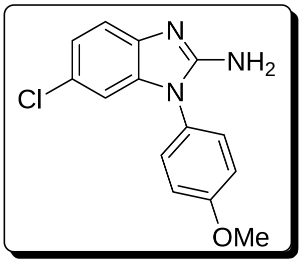


1-Butyl-6-methyl-1*H*-benzo[*d*]imidazol-2-amine 5l: Thick liquid; yield 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 7.00 (s, 1H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 1.74-1.68 (m, 2H), 1.34-1.31 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 134.7, 132.8, 129.7, 123.6, 120.9, 110.0, 43.8, 31.7, 21.5, 21.0, 14.1; FT-IR (KBr) 3227, 3167, 3067, 2963, 2854, 1621, 1587, 1513, 1474, 1426, 1281, 1187, 1121, 1025 cm^{-1}. Anal. Calcd. for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67. Found: C, 71.12; H, 8.40; N, 20.58.

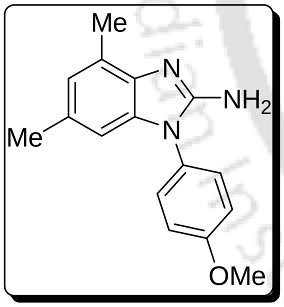


1-(4-Methoxyphenyl)-1*H*-benzo[*d*]imidazol-2-amine 5m: White solid; yield 92%; mp 101-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.91 (d, *J* =

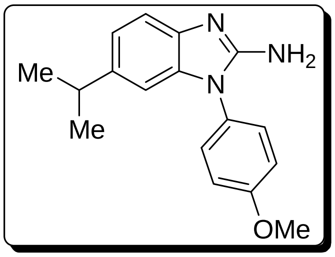
7.2 Hz, 1H), 4.70 (br s, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 147.8, 141.5, 135.9, 127.9, 126.9, 123.1, 122.7, 118.4, 115.0, 110.0, 55.7; FT-IR (KBr) 3154, 2922, 2862, 1607, 1581, 1948, 1453, 1410, 1389, 1388, 1268, 1155, 1018 cm^{-1}. Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.41; H, 5.47; N, 17.49.



6-Chloro-1-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazol-2-amine 5n: Thick liquid; yield 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 4.8 Hz, 1H), 7.29-7.20 (m, 3H), 7.10 (s, 1H), 7.03 (d, *J* = 6.0 Hz, 2H), 5.80 (br s, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 147.0, 136.4, 128.9, 127.1, 125.3, 123.7, 119.2, 116.1, 110.2, 56.8; FT-IR (KBr) 3268, 3157, 3072, 2982, 1633, 1582, 1501, 1476, 1416, 1277, 1151, 1100, 1038 cm^{-1}. Anal. Calcd. for $C_{14}H_{12}ClN_3O$: C, 61.43; H, 4.42; N, 15.35. Found: C, 61.57; H, 4.40; N, 15.28.



1-(4-Methoxyphenyl)-4,6-dimethyl-1*H*-benzo[*d*]imidazol-2-amine 5o: White solid; yield 94%; mp 96-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.81 (s, 1H), 6.56 (s, 1H), 3.87 (s, 3H), 2.50 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 146.2, 138.7, 134.9, 132.9, 127.9, 127.7, 124.5, 114.9, 108.2, 55.9, 21.7, 16.9; FT-IR (KBr) 3157, 2963, 1666, 1547, 1513, 1440, 1416, 1277, 1247, 1185, 1104, 1025 cm^{-1}. Anal. Calcd. for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.72. Found: C, 72.00; H, 6.40; N, 15.66.



6-Isopropyl-1-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazol-2-amine 5p: White solid; yield 94%; mp 112-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.26 (m, 3H), 7.10-7.05 (m, 4H), 3.89 (s, 3H), 2.92-2.89 (m, 1H), 1.21 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 146.3, 144.1, 139.7, 136.2, 128.8, 127.0, 121.8, 118.1, 114.3, 107.0, 56.0, 33.9, 24.6; FT-IR (KBr) 3266, 3148, 3058, 2898, 1628, 1575, 1508, 1444, 1397, 1310, 1248, 1150, 1079 cm^{-1}. Anal. Calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.94. Found: C, 72.68; H, 6.80; N, 14.88.

5.3 References

(1) (a) Xuan, X.; Zhiguang, X.; Yifang, L.; Weihua, L.; *J. Med. Chem.* **2001**, *11*, 317. (b) Henkel, T.; brunne, R. M.; reichel, F. *Angew. Chem. Int. Ed.* **1998**, *38*, 643. (c) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159. (d) Boaen, N. K.; Hillmyer, M. A. *Chem. Soc. Rev.* **2005**, *34*, 267. (e) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284.

(2) (a) Caroti, P.; Ceccotti, C.; Da Settimo, F.; Primofiore, G.; Franzone, J. S.; Reboani, M. C.; Cravanzola, C. *Farmaco* **1989**, *44*, 227. (b) DaSettimo, A.; Primofiore, G.; Da Settimo, F.; Marini, A. M. *Farmaco* **1992**, *47*, 1293. (c) Da Settimo, A.; Marini, A. M.; Primofiore, G.; Da Settimo, F. *Farmaco* **1995**, *50*, 321. (d) Kus, C.; Göker, H.; Ayhan, G.; Ertan, R.; Antanlar, N.; Akin, A. *Farmaco* **1996**, *51*, 413. (e) Orjales, A.; Bordell, M.; Rubio, V. *J. Heteocycl. Chem.* **1995**, *32*, 707. (f) Paget, C. J.; Kisner, K.; Stone, R. L.; De Long, D. G.; *J. Med. Chem.* **1969**, *12*, 1010. (g) Seth, P. P.; Jefferson, E. A.; Risen, L. M.; Osgood, S. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1669. (h) Steven, A. R.; Huigens III, R. W.; Christian, M. *J. Am. Chem. Soc.* **2009**, *131*, 9868.

(3) (a) Trapani, G.; Franco, M.; Latrofa, A.; Genchi, G.; Jacobazzi, V.; Ghiani, C. A.; Maciocco, M.; Liso, G.; *Eur. J. Med. Chem.* **1997**, *32*, 83. (b) Hamley, P.; Tinker, A. C.; *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1573. (c) Varming, T.; Christophersen, P.; Moller, A.; Peters, D.; Axellson, O.; Nielsen, E. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 245.

(4) (a) Fujisawa, S.; Atsumi,T.; Kaelowa, Y. *Toxicology* **2002**, *177*, 39. (b) Shetgiri, N. P.; Kokiktar, S. V. *Ind. J. Chem.* **1999**, *38B*, 312. (c) Ravina, E.; Sanches-Alfonso, R.; Fneyo, J. *Arzneimittelforschung* **1993**, *43*, 689. (d) Ho, Y.; Jörg, B.; Roman, W. F.; Steven, S. P.; Hnin, H. K.; Joseph, R.W.; Stanley, Z. K.; Mohammed, A. K.; Hidenori, T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6218.

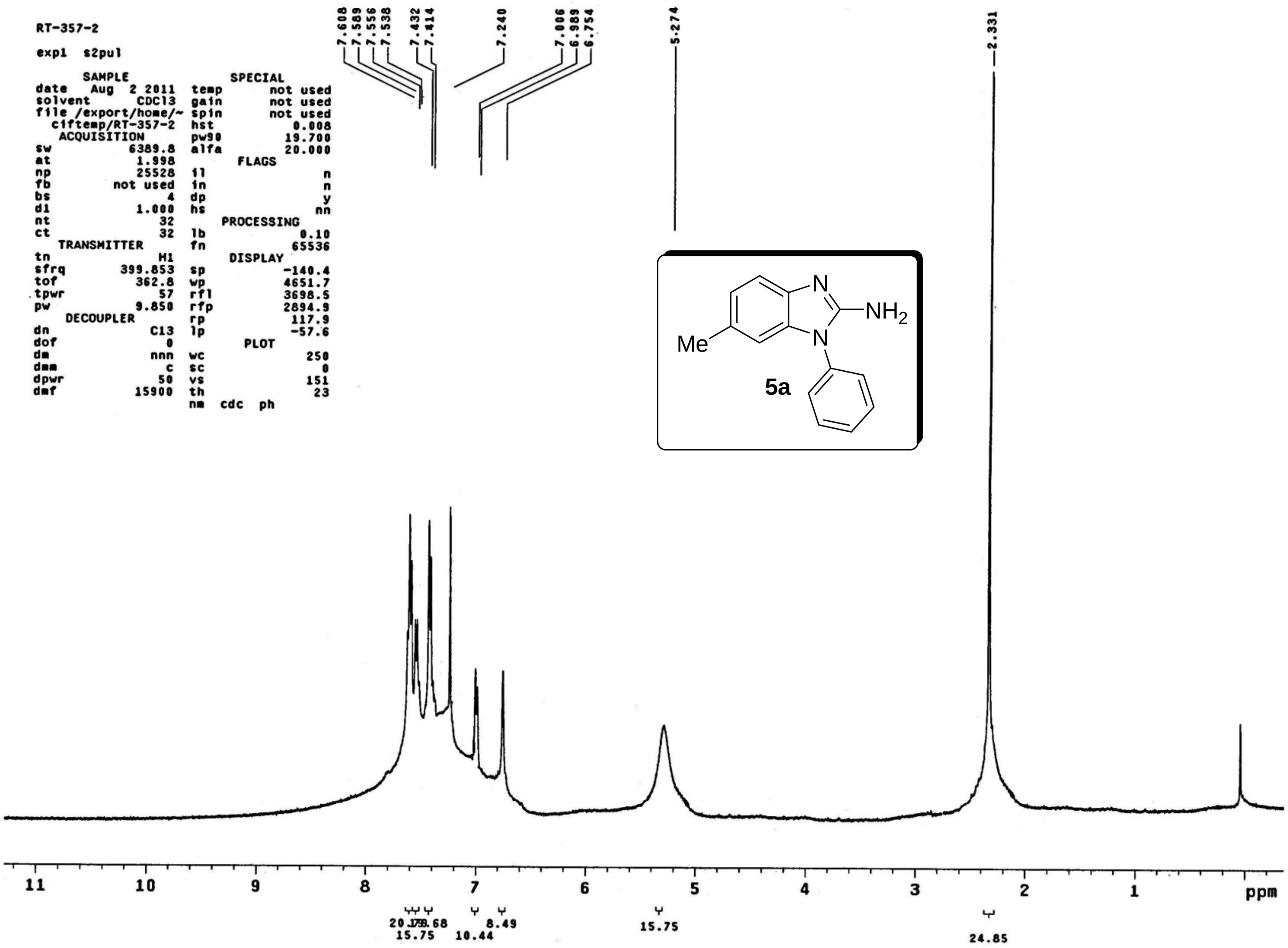
(5) (a) Nawrocka, W.; Zimecki, M.; Kuznicki, T. *Arch. Pharm.* **1999**, *332*, 85. (b) Wahe, H.; Asobo, P. F.; Cherkasov, R. A. *Arkivoc* **2003**, 170. (c) Cuberens, M.; Contijoch, M. R. *Chem. Pharm. Bull.* **1997**, *45*, 1287. (d) Mor, M.; Bordi, F.; Silva, C. *Bioorg. Med. Chem.* **2004**, *12*, 663. (e) DeDios, A.; Shih, Ch.; DeUralde, B. L. *J. Med. Chem.* **2005**, *48*, 2270. (f) Musk, D. J.; Hergenrother, P. J. *Curr. Med. Chem.* **2006**, *13*, 2163. (g) Ritter, T. K.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2001**, *40*, 3508. (h) He, Y.; Yang, J.; Wu, B.; Risen, L.; Swayze, E. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1217.

(6) (a) Guida, X.; Han, J.; Li, X. Eur. *J. Med. Chem.* **2006**, *41*, 1080. (b) Thomas, M. K.; Stephen, J. B.; Jennifer, B.; Xin, G.; Roger, J. S.; Lida, S.; Alan, S.; Yunlong, Z.; Jeffery, B. M.; Mohammed, K.; Stanley, K.; Margaret, M. O. N. *Bioorg. Med. Chem. Lett.* **2012**, *22,* 738. (c) Bartra, M.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1987**, *28*, 5941. (d) Bednyagina, N. P.; Postovskii, I. *Zhurnalobshcheikhimii* **1960**, *30*, 1431.

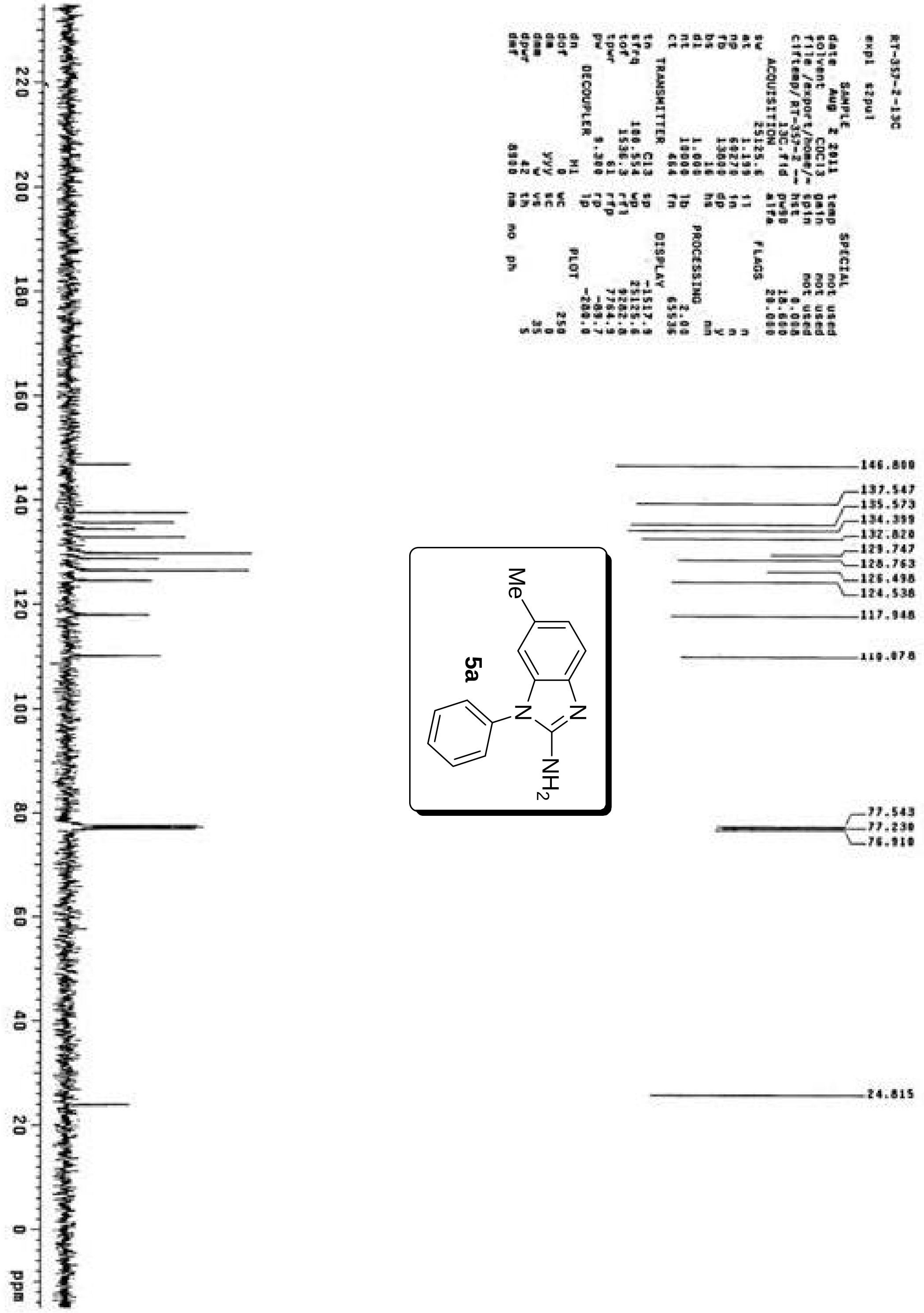
(7) (a) Wang, X.; Kuang, C.; Yang, Q. *Eur. J. Org. Chem.* **2012**, 424. (b) Chiba, S.; Zhang, L.; Ang, G. Y.; Hui, B. W.-Q. *Org. Lett.* **2010**, *12*, 2052. (c) Hu, J.; Cheng, Y.; Yang, Y.; Rao, Y. *Chem. Commun.* **2011**, *47*, 10133.

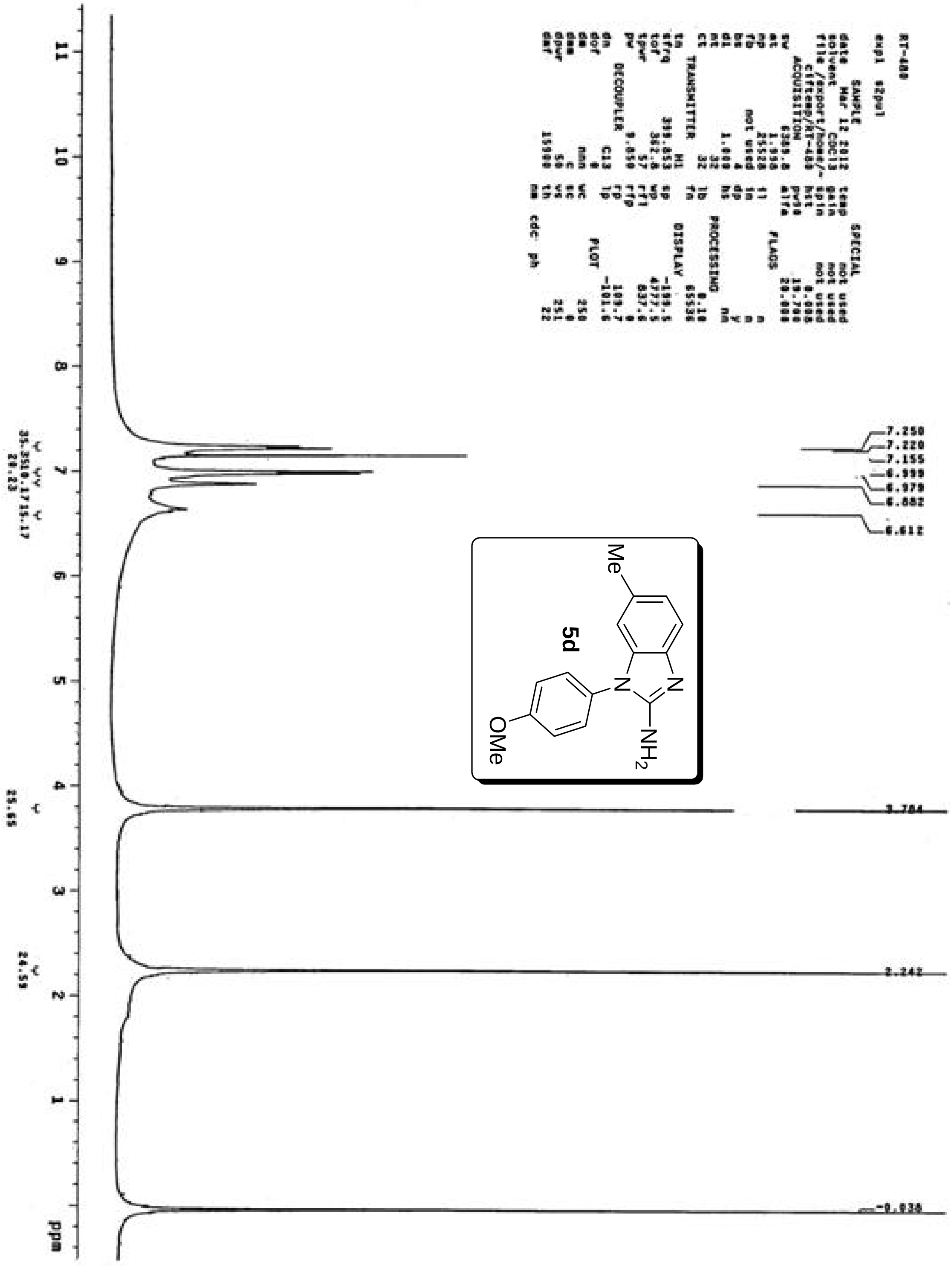
Crystal Data and Structure Refinement for 3m at 296(2) K

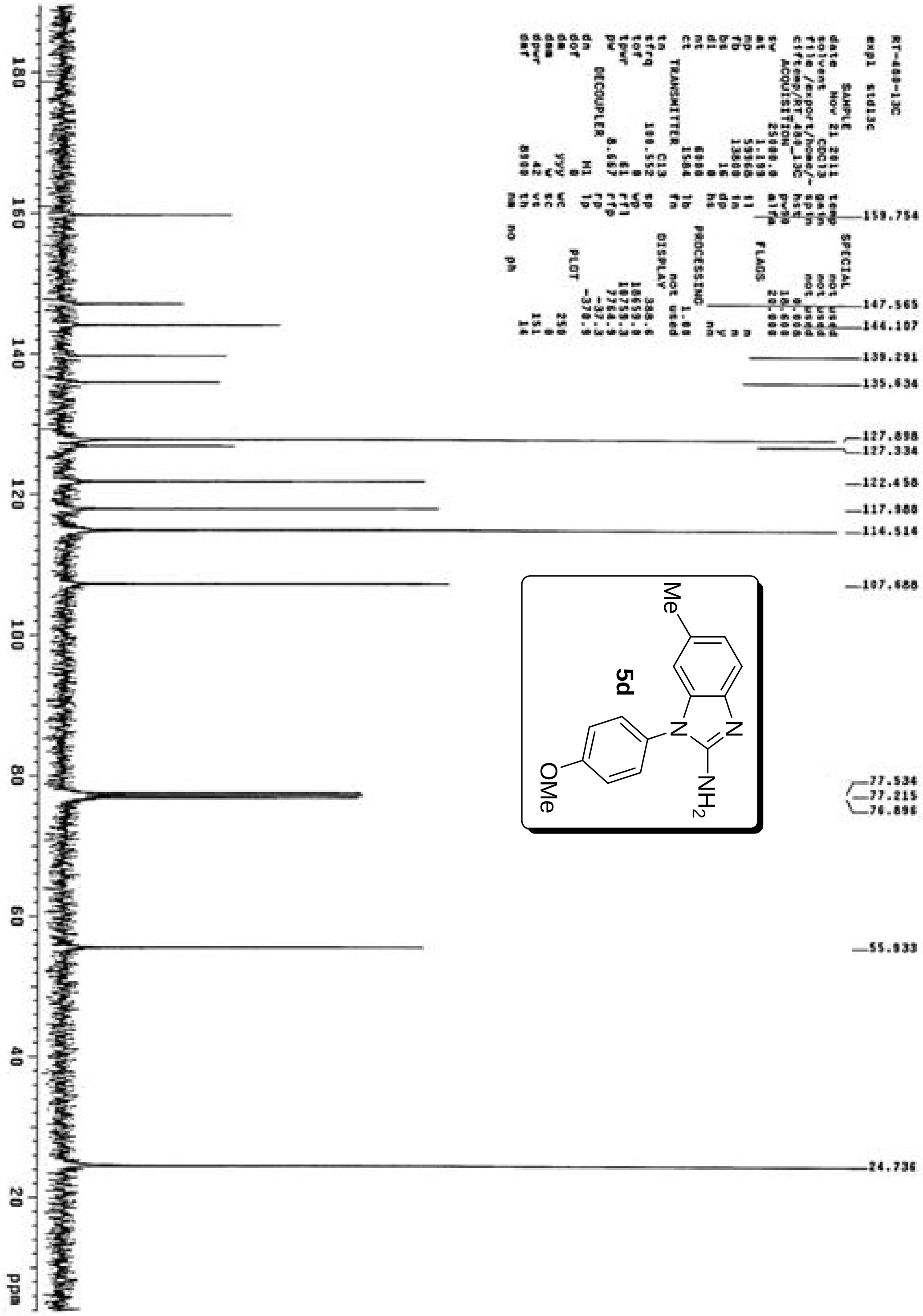
Identification code	**5m**	
Empirical formula	$C_{14}H_{13}N_3O$	
Formula weight	239.27	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
	Loop xyz	
	'x, y, z' '-x, -y, -z'	
Unit cell dimensions	*a* = 9.0574(7) Å	α(°)= 101.776(4)
	b = 11.6659(9) Å	β(°)= 97.499(5)
	c = 12.1521(8) Å	γ(°)= 94.819(5)
Volume	1238.12(16) $Å^3$	
Z	4	
Density (calculated)	1.284 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	504.0	
Crystal size	0.33 x 0.24 x 0.16 mm	
Theta range for data collection	1.73 to 25.25°	
Index ranges	-10<=h<=10, -14<=k<=11, -14<=l<=14	
Reflections collected	4408	
Independent reflections	2737 [R (int) = 0.0375]	
Completeness to theta = 25.25°	98.3 %	
Absorption correction	Multi-scan	
Data / restraints / parameters	4408 / 0 /327	
Goodness-of-fit on F^2	0.966	
Final R indices [I>2sigma (I)]	*R1* = 0.0505, *wR2* = 0.1368	
R indices (all data)	*R1* = 0.0865, *wR2* = 0.1619	
CCDC	871224	



```
RT-357-2

exp1  s2pul

       SAMPLE               SPECIAL
date    Aug  2 2011   temp        not used
solvent        CDCl3  gain        not used
file /export/home/~  spin        not used
  ciftemp/RT-357-2    hst            0.008
     ACQUISITION      pw90          19.700
sw            6389.8  alfa          20.000
at             1.998          FLAGS
np             25528  il                 n
fb          not used  in                 n
bs                 4  dp                 y
d1             1.000  hs                nn
nt                32        PROCESSING
ct                32  lb              0.10
     TRANSMITTER      fn             65536
tn                H1         DISPLAY
sfrq         399.853  sp            -140.4
tof            362.8  wp            4651.7
tpwr              57  rfl           3698.5
pw             9.850  rfp           2894.9
      DECOUPLER       rp             117.9
dn               C13  lp             -57.6
dof                0           PLOT
dm               nnn  wc               250
dmm                c  sc                 0
dpwr              50  vs               151
dmf            15900  th                23
                      nm   cdc   ph
```


RT-357-2-13C
146.800
137.547
135.573
134.399
132.820
129.747
128.763
126.498
124.538
117.948
110.078
77.543
77.230
76.910
24.815
Me
N
N
NH2
5a
220
200
180
160
140
120
100
80
60
40
20
0
ppm


RT-489
7.250
7.220
7.155
6.999
6.979
6.882
6.612
3.784
2.242
-0.036
35.25
10.17
15.17
20.23
25.65
24.59
11
10
9
8
7
6
5
4
3
2
1
ppm
Me
N
N
NH2
OMe
5d

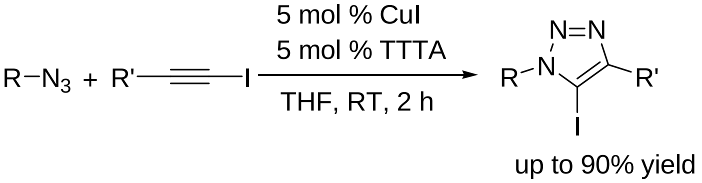

RT-488-13C
exp1 std13c
159.754
147.565
144.107
139.291
135.634
127.898
127.334
122.458
117.988
114.514
107.688
77.534
77.215
76.896
55.933
24.736
Me
N
N
NH2
OMe
5d
180
160
140
120
100
80
60
40
20
ppm

Copper(I)-Catalyzed Click Reaction of 2-Azidobenzimidazoles with Alkynes

Click chemistry[1]-"a modular synthetic approach towards the assembly of new molecular entities"-finds extensive applications, ranging from functionalizing biological molecules,[2] solubilizing carbon nanotubes,[3] to forming supramoleculer assemblies.[4] Among these, in particular, five-membered nitrogen containing heterocyclic compounds substituted with 1,2,3-triazoles have been found to have industrial applications and biologically importance.[5] These compounds have been synthesized by Huisgen 1,3-dipolar cycloaddition of azides with alkynes.[6] Out of these, the copper(I)-catalyzed [3+2]-cycloaddition also known as click chemistry of organic azides and terminal alkynes is emerged method for the synthesis of substituted 1,2,3-triazole compounds.[7] Thus, this method has been developed by several groups using Cu(I) salts along with triphenylphospine,[8] mono- or polydentate ligands,[9] as N-heterocyclic copper carbene complexes.[10] Recently, few groups have also demonstrated *via* Cu(I) species with various supports such as silica,[11] zeolites,[12] amine-functionalized polymers[13] and activated charcoal.[14] Cu(II) salts have been used in which the designed reaction conditions reduce the Cu(II) to Cu(I) by reducing agents such as sodium ascorbate,[15] elemental copper,[16] phosphorus(III) agents,[17] electro chemical reduction,[18] which further carried out the click chemistry.

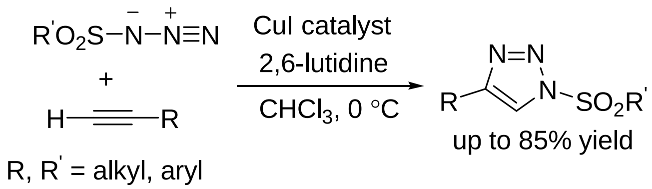
5.4 Copper Catalysts

Most of the click reactions are based on copper-catalyzed systems. Sharpless and co-authors have demonstrated the copper-catalyzed azide-alkyne cycloaddition reaction for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles. Substituted azides readily undergo reaction with 1-iodoalkyne in the presence of CuI, Et_3N in THF at room temperature to give triazoles in high yield (Scheme 1).[19a]



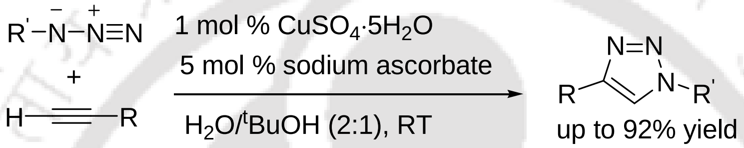
Scheme 1

4-Substituted 1-(*N*-sulfonyl)-1,2,3-triazoles have been prepared *via* copper(I)-catalyzed azide–alkyne cycloaddition of sulfonyl azides with alkynes in good yield (Scheme 2).[19b]



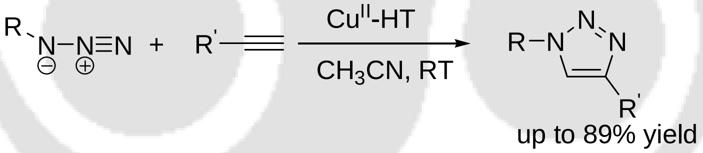
Scheme 2

Fokin and co-authors have showed the synthesis of 1,4-disubstuted 1,2,3-triazoles employing $CuSO_4{\cdot}5H_2O$ and sodium ascorbate in water (Scheme 3).[16b]



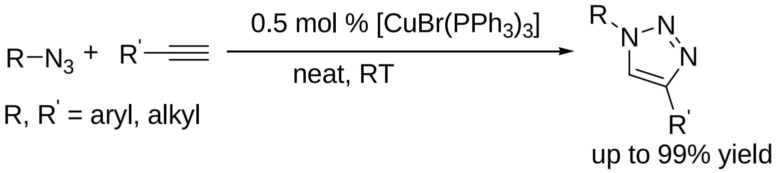
Scheme 3

Pitchumani and co-workers have showed the regiospecific synthesis of 1,4-disubstituted 1,2,3-triazoles from organic azides and terminal alkynes using Cu^{II}-HT at room temperature (Scheme 4).[19c]



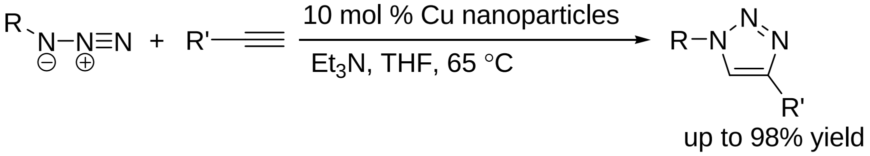
Scheme 4

Gonzalez and co-workers have utilized $[CuBr(PPh_3)_3]$ for the neat reaction of azides with alkenes to afford 1,4-disubstituted 1,2,3-triazoles with wide substrate scope (Scheme 5).[19d]



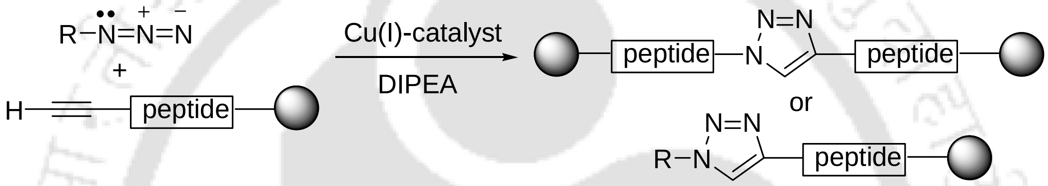
Scheme 5

Alonso and co-workers have demonstrated the use of Cu nanoparticles for the synthesis of 1,4-disubstitued 1,2,3-triazoles from azides and terminal alkynes (Scheme 6).[19e]



Scheme 6

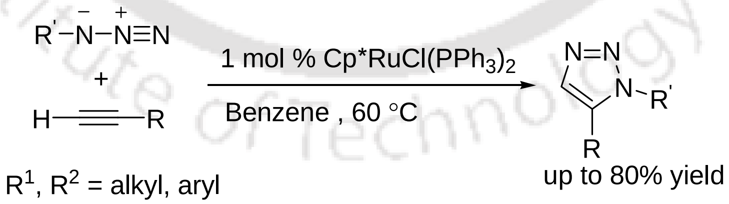
While, Meldal and co-workers have showed copper(I)-catalyzed [3+2] cycloaddition of terminal alkynes and azides on solid-phase. The reactions of alkyl- and aryl azides have been demonstrated (Scheme 7).[7a]



Scheme 7

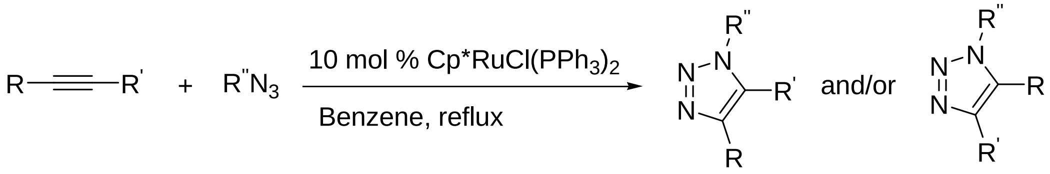
5.5 Ruthenium Catalysts

Few studies are focused on the ruthenium-catalyzed click reactions. Jia and co-workers have shown the regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles from organic azides and terminal and internal alkynes using ruthenium complex at moderate temperature (Scheme 8).[8a]



Scheme 8

Weinreb and co-workers have also employed the above described catalytic system for the construction of trisubstituted-1,2,3-triazoles from alkyl azides with unsymmetrical internal alkynes (Scheme 9).[19f]



Scheme 9

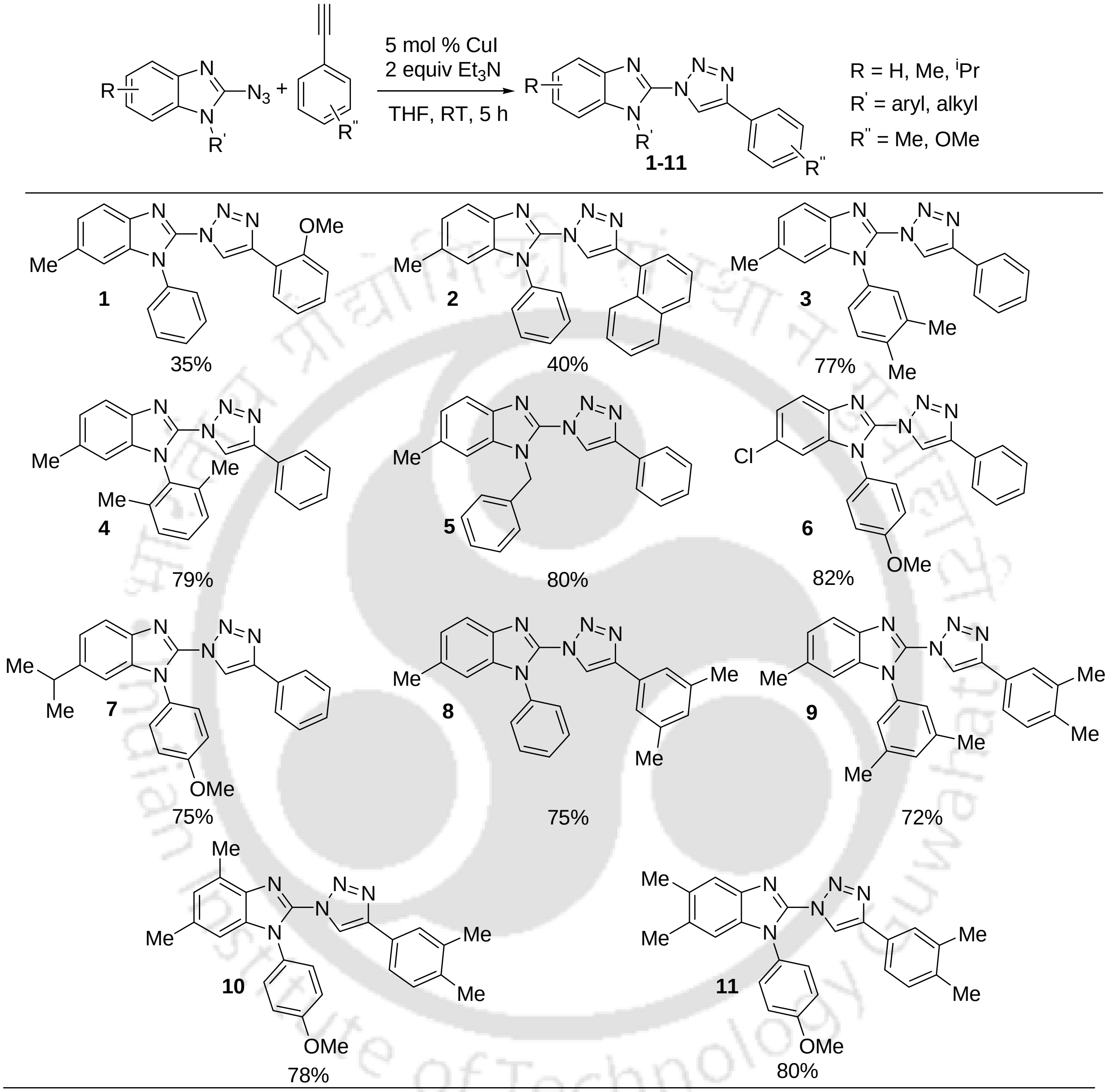
5.6 Present Study

2-Azidobenzimidazole is an important structural motif present in numerous compounds that are important in biological and medicinal sciences. Thus the development of effective method for the construction of analogue 2-(1*H*-1,2,3-triazo-1-yl)-benzimidazoles will be valuable in organic synthesis. In this context, the click reaction of 2-azidobenzimidazoles and aryl alkynes has been described using copper(I)-catalysis in the presence of Et_3N at moderate temperature.

First, the optimization of the reaction conditions was carried out with 2-azido-6-methyl-1-phenyl-1*H*-benzo[*d*]imidazole **4a** and 3,5-dimethylphenyl acetylene as model substrates employing the Sharpless procedure, 5 mol % CuI and 2 equiv Et_3N in THF solvent at room temperature.[21a] The reaction proceeded efficiently to afford the target 6-methyl-2-(4-(3,5-dimethylphenyl)-1*H*-1,2,3-triazo-1-yl)-1-phenyl-1*H*-benzo[*d*]imidazole **8** in 75% yield. The reactions of a series of substituted 2-azidobenzimidazole and aryl alkynes were next investigated (Table 1). The reactions with phenyl acetylene were found to be more effective affording the product in 75-82% compared to that bearing electron donating group in the aromatic ring and naphthyl acetylene that underwent reaction with 35-40% yield. Furthermore, phenyl acetylenes bearing the disubstituted groups could afford the target products **8-11** in 72-80% yield. Recrystallization **10** provided crystals whose structure was confirmed by X-ray analysis (Figure 1).

The observed results suggest that the reaction of 2-azidobenzimidazole with σ-acetylide ***a,*** which might be generated from Cu and substituted aryl acetylenes, can lead to the formation of ***b***. Intramolecular cyclization of ***b*** may lead to the generation of the intermediate ***c*** that on protonation can furnish the target molecules **1-11** to complete the catalytic cycle.[20]

Table 1. Substrate Scope of the Formation of 2-(1*H*-1,2,3-Triazo-1-yl)benzimidazoles$^{a\text{-}b}$



---

[a] Reaction conditions: 2-Azidobenzimidazole (1 mmol), aryl alkyne (1 mmol), CuI (5 mol %), and Et_3N (2 mmol) were stirred at room temperature in THF (6 mL).

[b] Isolated yield.

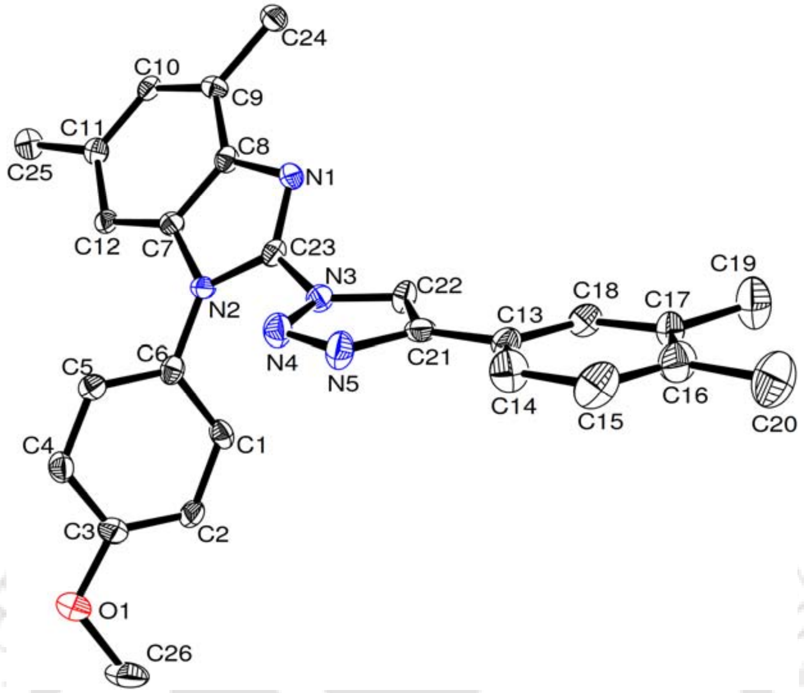
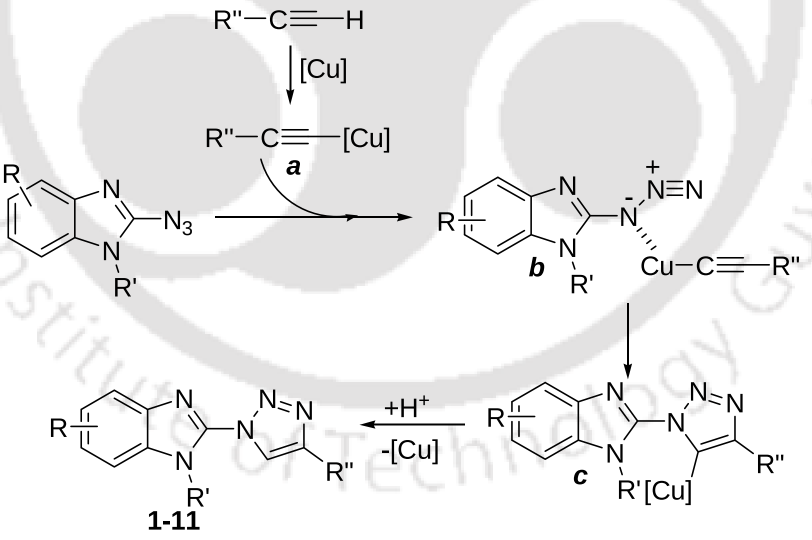


Figure 1. ORTEP diagram of 1-(4-methoxyphenyl)-4,6-dimethyl-2-(4-(3,4-dimethylphenyl)-1*H*-1,2,3-triazol-1-yl)-1*H*-benzo[*d*]imidazole **10** with 50% ellipsoid. H-Atoms are omitted for clarity.



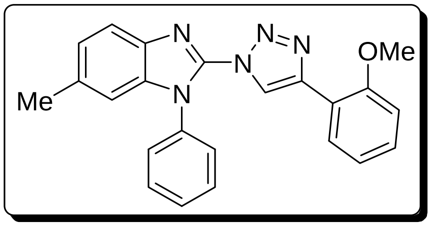
Scheme 10. Proposed catalytic cycle

In summary, copper(I)-catalyzed synthesis of 2-(1*H*-1,2,3-triazo-1-yl)benzimidazoles has been described from 2-azidobenzimidazoles and alkynes by click chemistry. The cyclization takes places with moderate to good yield.

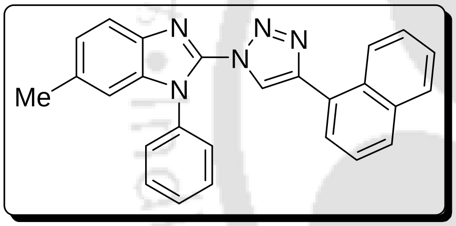
Experimental Section

General Information: CuI (98%) and Et_3N were purchased from Aldrich and Merck respectively. The solvents were purchased and dried according to standard procedure prior to use. Product purification was carried out by silica gel column chromatography using Rankem silica gel (60-120 mesh). All reactions were monitored by analytical TLC on Merck silica gel G/GF 254 plates. NMR (^{1}H and ^{13}C) spectra were recorded on DRX-400 Varian spectrometer and the data are accounted as follows: chemical shifts (δ ppm) (multiplicity, coupling constant (J Hz), integration).The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet. Melting points were determined by Buchi B-540 melting point apparatus. FT-IR spectra of air-dried samples were recorded on PerkinElmer Spectrum One FT-IR spectrometer using KBr disks and are reported in frequency of absorption (cm^{-1}). Elemental analyses were recorded using PerkinElmer CHNS analyzer. For single crystal X-ray analysis the intensity data were collected using Bruker SMART APEX-II CCD diffractometer, equipped with 1.75 kW sealed-tube Mo Kα irradiation (λ = 0.71073 Å) at 296(2) K and the structures were solved by direct methods using *SHELLX-97* (Göttingen, Germany) and refined with full-matrix least squares on F^2 using SHELXL-97.

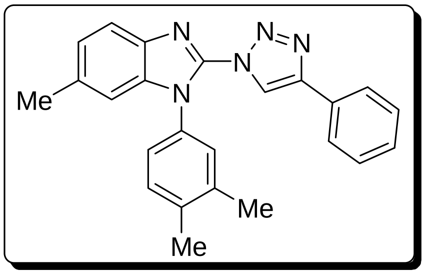
General Procedure for the Synthesis of 2-(1*H*-1,2,3-Triazo-1-yl)benzimidazoles : 2-Azidobenzimidazoles (1 mmol), aryl alkyne (1 mmol), CuI (5 mol %) and Et_3N (2 mmol) were stirred in THF at room temperature. Progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, the reaction mixture was quenched with NH_4OH solution and partitioned between ethyl acetate and water. The organic layer was washed with water (1 x 5 mL) and brine (1 x mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silicagel chromatography using ethyl acetate and hexane as eluent to give the titled compound in analytically pure form.



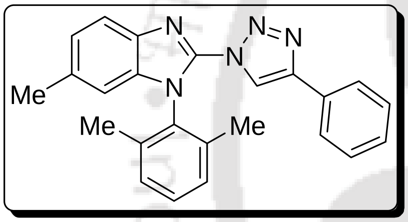
2-(4-(2-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-6-methyl-1-phenyl-1*H*-benzo[*d*]imidazole 1: White solid: yield 35%; mp 188-189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.36-7.33 (m, 4H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.06 (t, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 7.6 Hz, 2H), 6.89 (d, *J* = 6.8 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 3.34 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 148.5, 140.9, 137.9, 137.4, 136.9, 134.8, 130.9, 130.4, 128.1, 127.9, 127.4, 125.6, 124.0, 121.1, 115.6, 108.5, 56.8, 20.0; FT-IR (KBr) 3131, 3092, 2854, 1646, 1592, 1521, 1468, 1424, 1392, 1298, 1138, 1024 cm^{-1}. Anal. Calcd. for $C_{23}H_{19}N_5O$: C, 72.42; H, 5.02; N, 18.36. Found: C, 72.54; H, 4.99; N, 18.30.



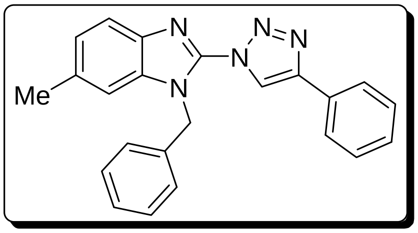
6-Methyl-2-(4-(naphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)-1-phenyl-1*H*-benzo[*d*]imidazole 2: White solid: yield 40%; mp 208-209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.89-7.70 (m, 4H), 7.53-7.41 (m, 5H), 7.13-7.06 (m, 3H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 6.4 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 143.8, 136.2, 134.8, 134.0, 133.3, 133.0, 131.6, 129.7, 128.9, 128.1, 127.9, 125.3, 124.9, 122.1, 119.2, 115.1, 114.1, 112.1, 110.0, 21.1; FT-IR (KBr) 3112, 3058, 2963, 2852, 1642, 1612, 1536, 1492, 1424, 1373, 1312, 1298, 1021 cm^{-1}. Anal. Calcd. for $C_{26}H_{19}N_5$: C, 77.79; H, 4.77; N, 17.44. Found: C, 77.89; H, 4.75; N, 17.36.



6-Methyl-1-(3,4-dimethylphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1*H*-benzo[*d*]imidazole 3: White solid: yield 77%; mp 191-192 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.49 (s, 1H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.44-7.33 (m, 4H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.14 (s, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 2.45 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.9, 143.6, 141.8, 138.2, 137.9, 135.2, 130.6, 130.0, 129.5, 128.4, 126.0, 123.9, 121.0, 120.0, 115.9, 114.6, 113.9, 111.6, 22.6, 21.5, 18.5; FT-IR (KBr) 3135, 2922, 1616, 1555, 1501, 1492, 1414, 1372, 1308, 1255, 1188, 1021 cm^{-1}. Anal. Calcd. for $C_{24}H_{21}N_5$: C, 75.97; H, 5.58; N, 18.46. Found: C, 76.08; H, 5.55; N, 16.38.

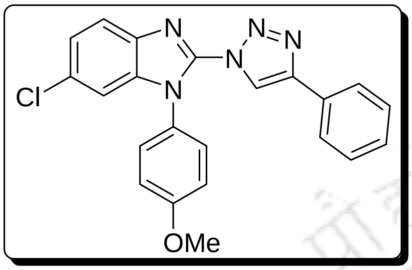


6-Methyl-1-(2,6-dimethylphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1*H*-benzo[*d*]imidazole 4: White solid: yield 79%; mp 198-199 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.49 (s, 1H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.45-7.36 (m, 4H), 7.12 (s, 1H), 7.02-6.96 (m, 4H), 2.47 (s, 3H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.7, 143.4, 140.7, 138.7, 137.8, 135.2, 130.9, 130.0, 129.5, 127.4, 124.4, 123.9, 120.9, 120.0, 116.0, 110.0, 20.1, 21.5; FT-IR (KBr) 3162, 2952, 1625, 1556, 1516, 1484, 1464, 1398, 1322, 1298, 1145, 1021 cm^{-1}. Anal. Calcd. for $C_{24}H_{21}N_5$: C, 75.97; H, 5.58; N, 18.46. Found: C, 76.06; H, 5.56; N, 18.39.

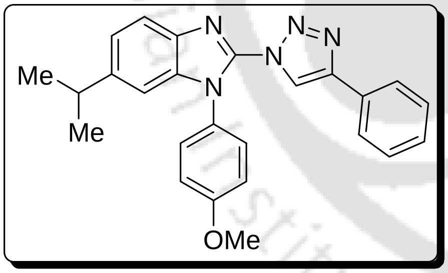


1-Benzyl-6-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1*H*-benzo[*d*]imidazole 5: White solid: yield 80%; mp 172-173 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.64 (s, 1H), 7.90 (d, *J* = 7.2 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.39 (d, *J* =

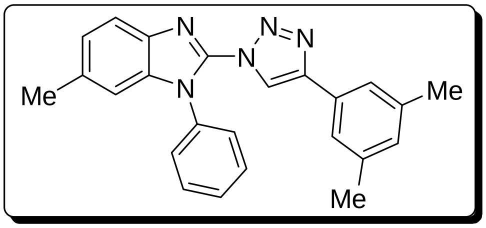
6.4 Hz, 2H), 7.26-7.15 (m, 6H), 5.86 (s, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.8, 142.4, 141.8, 139.7, 136.9, 135.2, 130.7, 130.0, 129.3, 127.4, 125.9, 123.9, 120.6, 115.6, 111.0, 48.5, 22.5; FT-IR (KBr) 2993, 2872, 1678, 1541, 1502, 1428, 1363, 1304, 1263, 1112, 1024 cm^{-1}. Anal. Calcd. for $C_{23}H_{19}N_5$: C, 75.59; H, 5.24; N, 19.16. Found: C, 75.70; H, 5.21; N, 19.08.



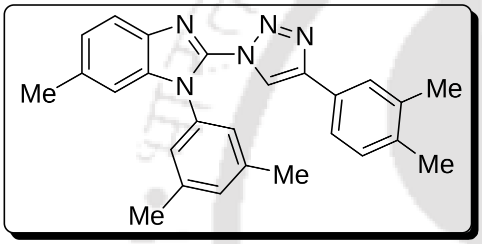
6-Chloro-1-(4-methoxyphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1*H*-benzo[*d*]imidazole 6: White solid: yield 82%; mp 171-172 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.51 (s, 1H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.45-7.21 (m, 6H), 7.02 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.6, 147.0, 140.9, 139.9, 137.9, 136.9, 134.8, 130.4, 128.8, 128.2, 127.8, 127.0, 126.7, 125.0, 121.0, 114.8, 108.8, 56.9; FT-IR (KBr) 3093, 2992, 2840, 1606, 1572, 1516, 1474, 1424, 1392, 1321, 1298, 1255, 1158, 1041 cm^{-1}. Anal. Calcd. for $C_{22}H_{16}ClN_5O$: C, 65.76; H, 4.01; N, 17.43. Found: C, 65.89; H, 4.00; N, 17.36.



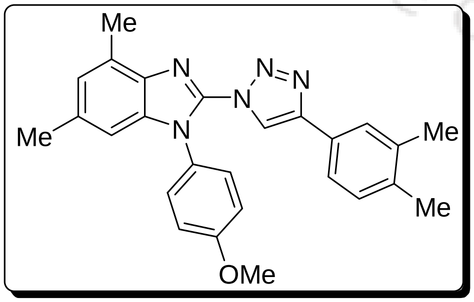
6-Isopropyl-1-(4-methoxyphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1*H*-benzo[*d*]imidazole 7: White solid: yield 75%; mp 200-201 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.47 (s, 1H), 7.85-7.82 (m, 2H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.43-7.28 (m, 6H), 7.02-7.00 (m, 3H), 3.85 (s, 3H), 3.04-2.97(m, 1H), 1.20 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.0, 147.9, 141.3, 138.4, 137.9, 136.9, 135.4, 130.9, 130.1, 129.7, 127.9, 127.0, 126.1, 124.1, 120.6, 115.5, 108.1, 55.7, 34.1, 22.1; FT-IR (KBr) 3121, 2962, 2860, 1627, 1586, 1521, 1492, 1414, 1372, 1282, 1255, 1175, 1096, 1021 cm^{-1}. Anal. Calcd. for $C_{25}H_{23}N_5O$: C, 73.33; H, 5.66; N, 17.10. Found: C, 73.47; H, 5.64; N, 17.03.



6-Methyl-2-(4-(3,5-dimethylphenyl)-1*H*-1,2,3-triazol-1-yl)-1-phenyl-1*H*-benzo[*d*]imidazole 8: White solid; yield 75 %; mp 201-202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.52-7.48 (m, 4H), 7.38-7.35 (m, 2H), 7.26-7.22 (m, 2H), 7.03-7.00 (m, 2H), 2.47 (s, 3H), 2.31 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 142.4, 141.7, 138.7, 136.8, 135.2, 130.6, 130.0, 129.5, 127.4, 125.7, 123.9, 120.5, 119.9, 115.6, 110.0, 22.1, 21.5; FT-IR (KBr) 3151, 2962, 1632, 1537, 1502, 1483, 1261, 1096, 1028 cm^{-1}. Anal. Calcd. for $C_{24}H_{21}N_5$: C, 75.97; H, 5.58; N, 18.46. Found: C, 76.06; H, 5.56; N, 18.39.

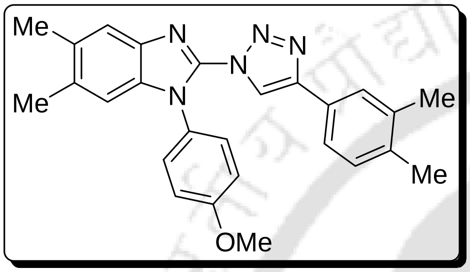


6-Methyl-1-(3,5-dimethylphenyl)-2-(4-(3,5-dimethyl-ph-enyl)-1*H*-1,2,3-triazol-1-yl)-1*H*-benzo[*d*]imidazole 9: White solid; yield 72%; mp 208-209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.67 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.22-7.18 (m, 2H), 7.11 (s, 1H), 7.02 (s, 1H), 2.47 (s, 3H), 2.34 (s, 6H), 2.30 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 142.6, 141.7, 138.2, 137.4, 135.2, 131.0, 129.5, 127.9, 125.4, 123.9, 120.9, 119.9, 115.6, 114.6, 113.4, 111.6, 104.0, 23.1, 22.1, 21.5, 17.9; FT-IR (KBr) 3024, 2963, 2858, 1618, 1541, 1492, 1408, 1333, 1263, 1124, 1024 cm^{-1}. Anal. Calcd. for $C_{26}H_{25}N_5$: C, 76.63; H, 6.18; N, 17.19. Found: C, 76.73; H, 6.16; N, 17.11.



1-(4-Methoxyphenyl)-4,6-dimethyl-2-(4-(3,4-dimethyl-phenyl)-1*H*-1,2,3-triazol-1-yl)-1*H*-benzo[*d*]imidazole 10: White solid: yield 78%; mp 180-181

°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 (s, 1H), 7.65 (s, 1H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 3.2 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.00 (s, 1H), 6.95 (d, *J* = 9.2 Hz, 2H), 6.81 (s, 1H), 3.82 (s, 3H), 2.66 (s, 3H), 2.40 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.2, 147.5, 141.3, 137.9, 137.4, 136.9, 135.0, 130.4, 130.1, 128.7, 127.7, 127.4, 126.1, 123.6, 120.6, 115.1, 108.1, 55.7, 20.1, 20.0, 19.9, 16.7; FT-IR (KBr) 3153, 2917, 1609, 1537, 1514, 1479, 1451, 1250, 1164, 1027 cm^{-1}. Anal. Calcd. for $C_{26}H_{25}N_5O$: C, 73.74; H, 5.95; N, 16.54. Found: C, 73.86; H, 5.94; N, 16.47.



1-(4-Methoxyphenyl)-5,6-dimethyl-2-(4-(3,4-dimethyl-phenyl)-1*H*-1,2,3-triazol-1-yl)-1*H*-benzo[*d*]imidazole 11: White solid: yield 80%; mp 188-189 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.41 (s, 1H), 7.66 (s, 1H), 7.60 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 3H), 3.85 (s, 3H), 2.41 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.2, 146.5, 141.3, 139.9, 137.4, 136.9, 135.0, 130.4, 129.1, 128.2, 127.8, 127.7, 126.7, 123.5, 120.9, 115.1, 108.5, 56.7, 23.1, 20.5, 19.9, 17.7; FT-IR (KBr) 3153, 2962, 1616, 1536, 1516, 1492, 1464, 1322, 1298, 1255, 1021 cm^{-1}. Anal. Calcd. for $C_{26}H_{25}N_5O$: C, 73.74; H, 5.95; N, 16.54. Found: C, 73.87; H, 5.93; N, 16.47.

5.7 References

(1) (a) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128. (b) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249. (c) Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2003**, *125*, 4686. (d) Deiters, A.; Cropp, T. A.; Mukherji, M.; Chin, J. W.; Anderson, J. C.; Schultz, P. G. *J. Am. Chem. Soc.* **2003**, *125*, 11782; reviews on the copper-catalyzed formation of triazoles. (e) Lutz, J. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1018.

(2) (a) Beatty, K.; Xie, F.; Wang, Q.; Tirrell, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 14150. (b) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2004**, *126*, 10598. (c) Oh, K.; Guan, Z. *Chem. Commun.* **2006**, 3069. (d) Seela, F.; Sirivolu, V. R.; Chittepu, P. *Bioconjugate Chem.* **2008**, *19*, 211.

(3) Li, H.; Cheng, F.; Duft, A. M.; Adronov, A. *J. Am. Chem. Soc.* **2005**, *127*, 14518.

(4) Parrish, B.; Breitenkamp, R. B.; Emrick, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 7404. (b) Malkoch, M.; Schleicher, K.; Drockenmuller, E.; Hawker, C. J.; Russell, T. P.; Wu, P.; Fokin, V. V. *Macromolecules* **2005**, *38*, 3663.

(5) Some examples of 1,2,3-triazoles, see: (a) Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Eds.; Pergamon: Oxford, 1984, 669. (b) Dehne, H. In *Methodender Organischen Chemie(Houben-Weyl)*; Schumann, E.; Ed.; Thieme: Stuttgart, 1994, 305. (c) Fan, W. Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry* II; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Eds.; Elsevier Science: Oxford, 1996, 1.

(6) Padwa,A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Ed.; Pergamon: Oxford, 1991, 1069. (b) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: NewYork, 1984; pp1. (c) Huisgen, R.; *Pure Appl. Chem.* **1989**, *61*, 613. (d) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(7) (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Labbe, G. *Bull. Soc. Chem. Belg.* **1984**, *93*, 579. (c) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952.

(8) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2004**, *43*, 3928.

(9) (a) Rodionov, V. O.; Presolski, S. I.; Gardinier, S.; Lim, Y.-H.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, *129*, 12696. (b) Rodionov, V. O.; Presolski, S. I.; Diaz, D.; Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, *129*, 12705. (c) Lewis, W. G.; Magallon, F. G.; Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc.* **2004**, *126*, 9152.

(10) Diez-Gonzalez, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 7558.

(11) Miao, T.; Wang, L. *Synthesis* **2008**, 363.

(12) (a) Chassaing, S.; Kumarraja, M.; Sido, A. S. S.; Pale, P.; Sommer, J. *Org. Lett.* **2007**, *9*, 883. (b) Chassaing, S.; Sido, A. S.; Alix, A.; Kumarraja, M.; Pale, P.; Sommer, J. *Chem. Eur. J.* **2008**, *14*, 6713.

(13) Girard, C.; Onen, E.; Aufort, M.; Beauviere, S.; Samson, E.; Herscovici, J. *Org. Lett.* **2006**, *8*, 1689.

(14) Lipshutz, B. H.; Taft, B. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 8235.

(15) (a) Kolarovic, A.; Schnurch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2011**, *76*, 2613. (b) (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.

(16) Brik, A.; Muldoon, J.; Lin, Y.-C.; Elder, J. H.; Goodsell, D. S.; Olson, A. J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *Chembiochem* **2003**, *4*, 1246.

(17) Wang, Q.; Chan, T. R.; Higraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192.

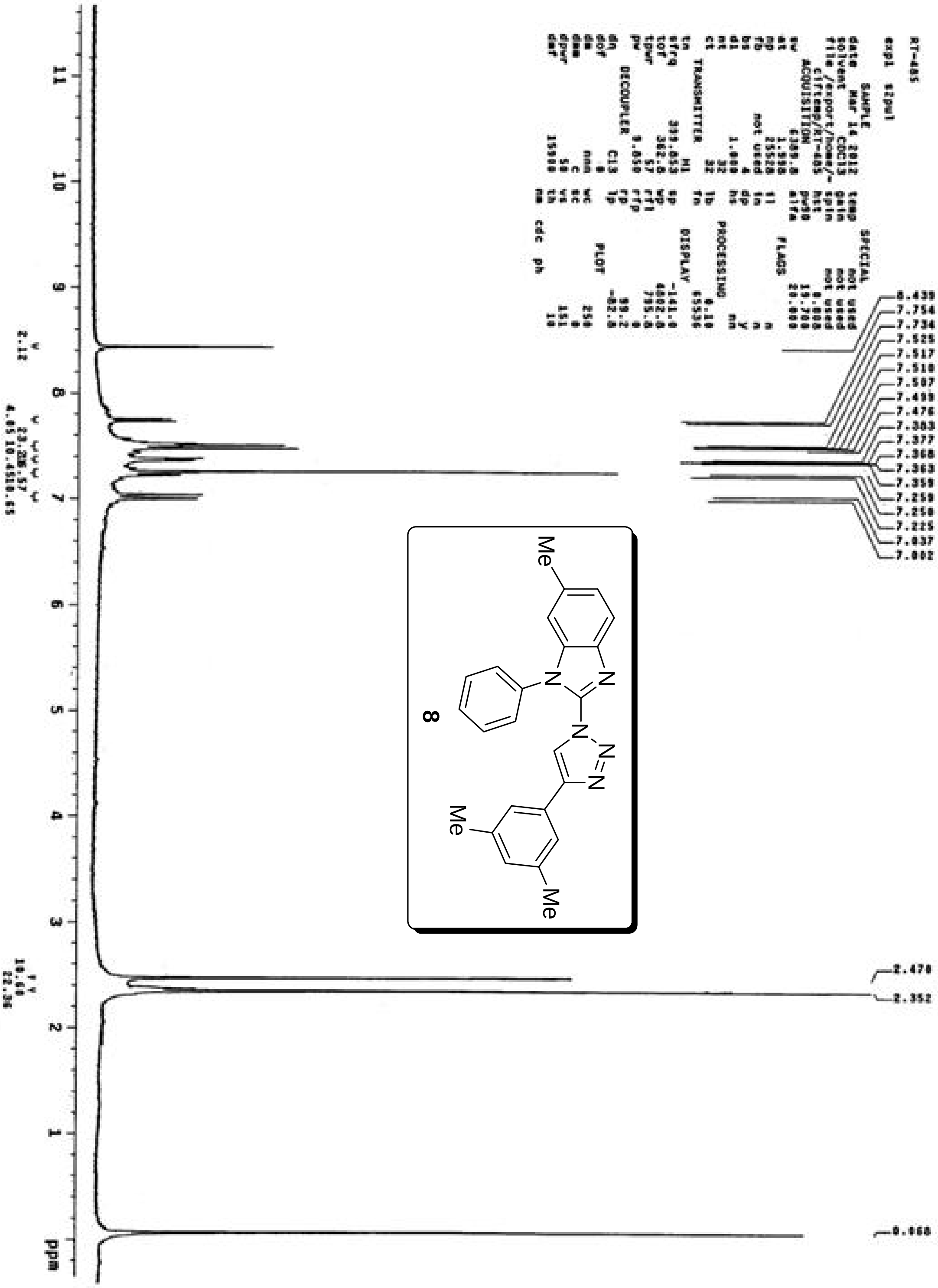
(18) Hong, V.; Udit, A. K.; Evans, R. A.; Finn, M. G. *Chembiochem* **2008**, *9*, 1481.

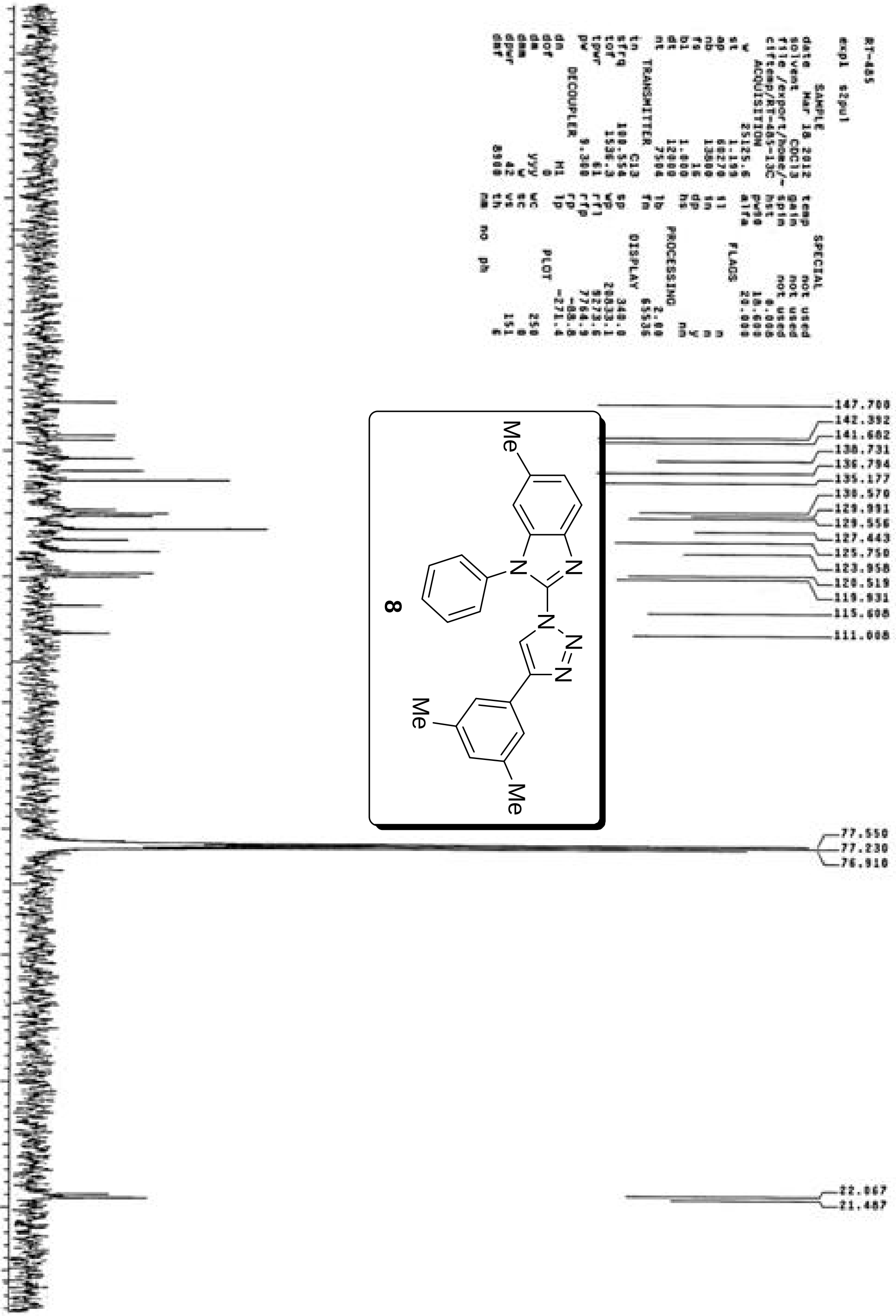
(19) (a) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2009**, *48*, 8018. (b) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 1730. (c) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998. (d) Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. *Org. Lett.* **2006**, *8*, 5337. (e) Lal, S.; Silvia, D.-G. *J. Org. Chem.* **2011**, *76*, 2367. (f) Majireck, M. M.; Weinreb, S. M. *J. Org. Chem*. **2006**, *71*, 8680.

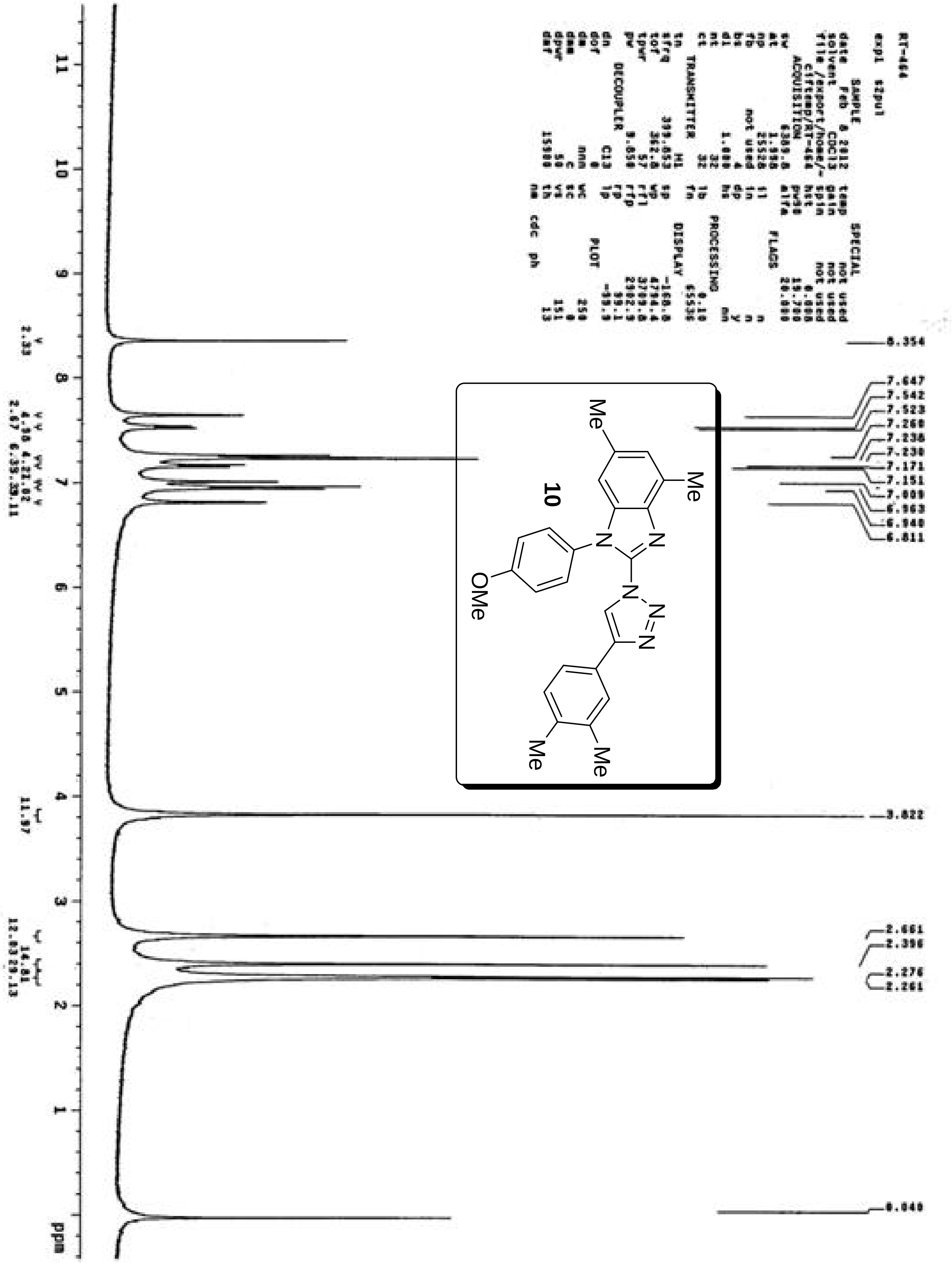
(20) For represenative examples on click reaction, see: (a) Qian, W.; Winternheimer, D.; Allen, J. *Org. Lett.* **2011**, *13*, 1682. (b) Arigela, R. K.; mandadap, A. K.; Sharma, S. K.; Kumar, B.; Kundu, B. *Org. Lett.* **2012**, *14*, 1804. (c) Yan, J.; Zhou, F.; Qin, D.; Cai, T.; Ding, K.; Cai, Q. *Org. Lett.* **2012**, *14*, 1262. (d) Zhang, Y.; Li, X.; Li, J.; Chen, J.; Meng, X.; Zhao, M.; Chen, B. *Org. Lett.* **2012**, *14*, 26.

Crystal Data and Structure Refinement for 10 at 296(2) K

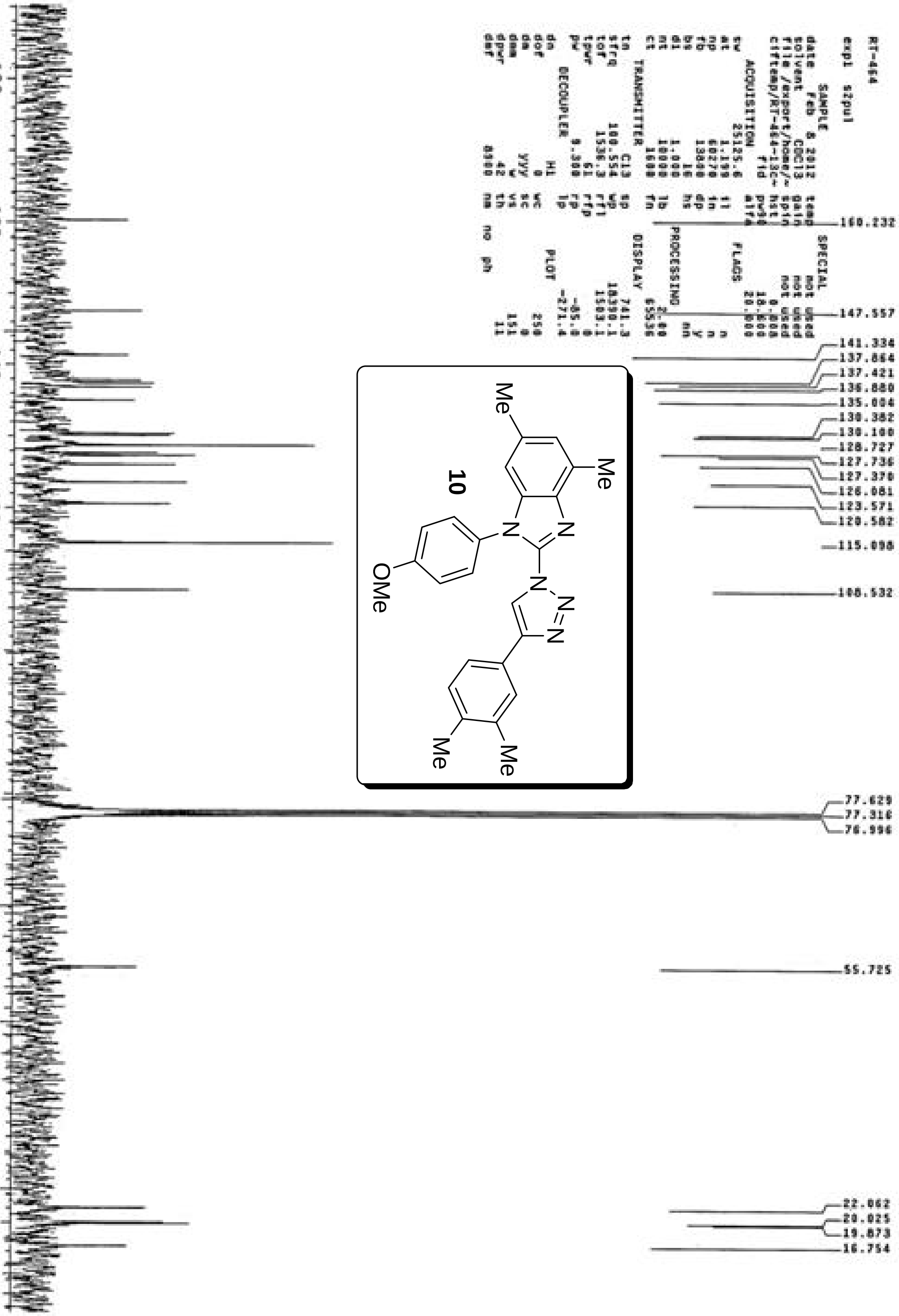
Identification code	**10**
Empirical formula	$C_{26}H_{25}N_5O$
Formula weight	423.51
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c Loop xyz ‘x, y, z’ ‘-x, y+1/2, -z+1/2’ ‘-x, -y, -z’ ‘x, -y-1/2, z-1/2’
Unit cell dimensions	*a* = 20.414(4) Å α(°)= 90.00 *b* = 8.9183(18) Å β(°)= 95.601(13) *c* = 12.332(3) Å γ(°)= 90.00
Volume	2234.5(8) $Å^3$
Z	4
Density (calculated)	1.259 Mg/m^3
Absorption coefficient	0.080 mm^{-1}
F(000)	896.0
Crystal size	0.33 x 0.25 x 0.16 mm
Theta range for data collection	1.00 to 25.25°
Index ranges	-22<=h<=24, -10<=k<=8, -14<=l<=13
Reflections collected	3845
Independent reflections	1890 [R (int) = 0.3143]
Completeness to theta = 25.25°	94.7 %
Absorption correction	Multi-scan
Data / restraints / parameters	3845 / 0 /294
Goodness-of-fit on F^2	1.397
Final R indices [I>2sigma (I)]	*R1* = 0.1986, *wR2* = 0.4543
R indices (all data)	*R1* = 0.2589, *wR2* = 0.4716
CCDC	871226


RT-485
8.439
7.754
7.734
7.525
7.517
7.510
7.507
7.499
7.476
7.383
7.377
7.368
7.363
7.359
7.259
7.250
7.225
7.037
7.002
2.470
2.352
0.068
11
10
9
8
7
6
5
4
3
2
1
ppm
Me
N
N
N
N
N
Me
Me
8


RT-485
exp1 s2pul
147.700
142.392
141.682
138.731
136.794
135.177
130.570
129.991
129.556
127.443
125.750
123.958
120.519
119.931
115.608
111.008
77.550
77.230
76.910
22.067
21.487
200
180
160
140
120
100
80
60
40
20
ppm
Me
N
N
N
N
N
Me
Me
8


RT-464
Me
Me
N
N
N
N
N
N
OMe
Me
Me
8.354
7.647
7.542
7.523
7.268
7.238
7.230
7.171
7.151
7.009
6.963
6.940
6.811
3.822
2.661
2.396
2.276
2.261
0.040
ppm
11
10
9
8
7
6
5
4
3
2
1

10


RT-464
exp1 s2pul
160.232
147.557
141.334
137.864
137.421
136.880
135.004
130.382
130.100
128.727
127.736
127.370
126.081
123.571
120.582
115.098
108.532
77.629
77.316
76.996
55.725
22.062
20.025
19.873
16.754
Me
Me
N
N
N
N
N
N
OMe
Me
Me
180
160
140
120
100
80
60
40
20
ppm

10

List of Publications

1. Preparation of 2-Azido-1-Substituted-1*H*-benzo[*d*]imidazoles Using a Copper-Promoted Three-Component Reaction and Their Further Conversion into 2-Amino and 2-Triazolyl Derivatives
   Ramana, **T**.; Punniyamurthy, T. *Chem. Eur. J.* **2012**, *18*, 13279.

2. Copper-Catalyzed Domino One-Pot Synthesis of 2-(Arylselanyl)arylcynamide
   Ramana. T.; Punniyamurthy, T. *Eur. J. Org. Chem.* **2011,** 4756.

3. Copper-Catalyzed Domino Intra and Intermolecular *C-S* Cross-Coupling Reactions: Synthesis of 2-(Arylthio)arylcyanamides
   Ramana, **T**.; Saha, P.; Das, M.; Punniyamurthy, T. *Org. Lett.* **2010**, *12*, 84.

4. Ligand-Free Copper-catalyzed Synthesis of Substituted Benzimidazoles, 2-Aminobenzimidazoles, 2-Aminobenzothiazoles and benzoxazoles
   Saha, P.; **Ramana, T**.; Purkit, N.; Ali, M. A.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719.

Conferences

1. Copper-Catalyzed Domino Intra and Intermolecular *C-S* Cross-Coupling Reactions: Synthesis of 2-(Arylthio)arylcyanamides
   Ramana, T.; Saha, P.; Das, M.; Punniyamurthy, T. Organic Synthesis and Human Well Being: Emerging Opportunities and Challenges **2010**, August 1-4, Indian Institute of Chemical Technology Hyderabad, India.

2. Copper-Catalyzed Domino Intra and Intermolecular *C-S* Cross-Coupling Reactions: Synthesis of 2-(Arylthio)arylcyanamides
   Ramana, T.; Saha, P.; Das, M.; Punniyamurthy, T. Frontier in Chemical Sciences **2010**, December 3-4, Indian Institute of Technology Guwahati, India.

3. Copper-Catalyzed Domino Intra and Intermolecular *C*-*S* Cross-Coupling Reactions: Synthesis of 2-(Arylthio)arylcyanamides

   Ramana, **T**.; Saha, P.; Das, M.; Punniyamurthy, T. 6th J-NOST Conference 2011, January 28-31, University of Hyderabad, India.