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Copper promoted *C*-*S* and *C*-*N* cross-coupling Reactions:The synthesis of 2-(*N*-Aryolamino)benzothiazoles and 2-(*N*-Aryolamino)benzimidazoles

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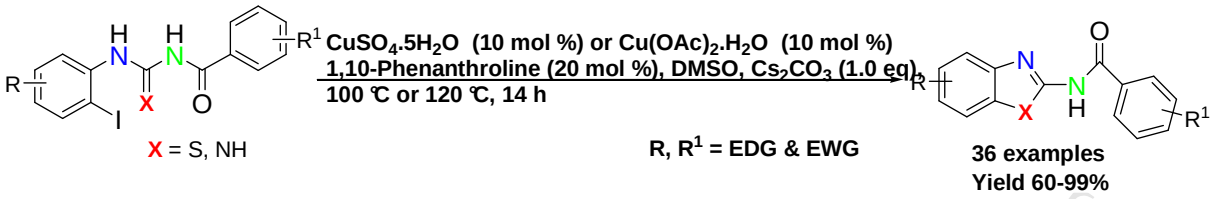

EDG-Electron Donating Group
EWG-Electron Withdrawing Group

GRAPHICAL ABSTRACT

Graphical abstract synopsis: Multistep reaction has been developed for the synthesis of substituted 2-(*N*-Aryolamino)benzothiazoles and 2-(*N*-Aryolamino)benzimidazoles under moderate reaction conditions.

Copper Promoted *C-S* and *C-N* Cross-Coupling Reactions:The Synthesis of 2-(*N*-Aryolamino)benzothiazoles and 2-(*N*-Aryolamino)benzimidazoles

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ABSTRACT

The synthesis of 2-(*N*-aryolamino)benzothiazoles and 2-(*N*-aryolamino)benzimidazoles has been accomplished in the presence of copper catalyst. These reactions involve *C-S* and *C-N* cross-coupling reaction. All electron donating and withdrawing substituent's readily underwent the reaction to give target products in good to excellent yield. In addition, the reaction also gave target product in high yield with bulk scale.

KEYWORDS

- 2-(*N*-Aryolamino)benzothiazoles
- 2-(*N*-Aryolamino)benzimidazoles
- Copper catalyst
- *C-S* and *C-N* Cross-coupling reaction
- Mild reaction conditions

1. Introduction

In recent decades, the formation of powerful carbon-heteroatom bonds has been developed through cross-coupling reactions using transition-metal.[1] Among these, carbon-nitrogen and carbon-sulphur bond formation has received much attention due to the presence of this moiety in many molecules that are of biological, pharmaceutical, and material interest.[2] Especially, benzimidazoles and benzothiazoles are very important benzofused compounds because of their applications in therapeutic,[3] and biological sciences (Figure 1).[4]

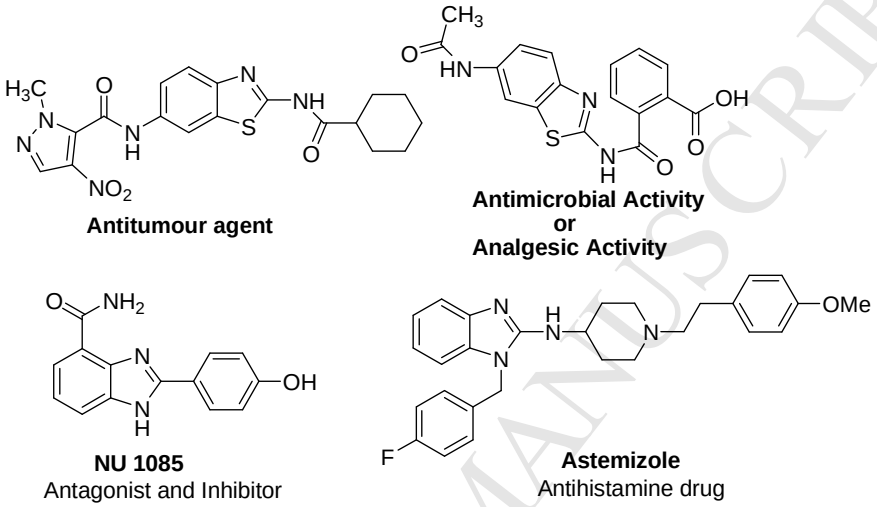


Fig 1: Examples of biological active compounds

Thus the synthesis of benzothiazole and benzimidazoles have been developed by traditional methods,[5] and using various transition metals like Cu,[6] Pd,[7] Ru,[8] Fe,[9] Co,[10] Zn,[11] and some of them have developed under metal free conditions.[12] However, very less reports are available for the synthesis of 2-(*N*-Aroylamino)benzothiazoles and benzimidazoles using transition metal. For example, Pan and co-workers[13] have accomplished method for the synthesis of 2-(*N*-aroylamino) benzothiazoles using copper. However, they have used different from our ligand. Later on, Yadav *et al*,[14] have reported using brominating reagent under strong acidic conditions. In addition, other researchers[4g-j] have also accomplished for the construction of 2-(*N*-aroylamino) benzothiazoles. Whereas, no report is available for the synthesis of 2-(*N*-aroylamino)benzimidazoles. Therefore, in view of the above observation which is slightly complex, herein, we demonstrate simple and general method for the synthesis of 2-(*N*-Benzoylamino) benzothiazoles through *C-S* cross-coupling reaction and similarly, we also would like to report for the construction of 2-(*N*-Benzoylamino) benzimidazoles through *C-N* cross-coupling reaction using cheap, readily available, non-toxic and air stable copper source as catalyst under mild reaction conditions.

2. Materials and methods

***2.1 General information*:** Aniline, CS_2, $CuSO_4 \cdot 5H_2O$ (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%), K_2CO_3, KOH, $K_3PO_4 \cdot 3H_2O$ and Cs_2CO_3 were purchased from Aldrich and used without further purification. The solvents were purchased and dried according to standard procedure prior to use. ^{1}H NMR (400 MHz) spectra were recorded with a Varian 400 spectrometer. Infrared (IR) spectra recorded on a Perkin Elmer Spectrum one FT-IR spectrometer. Elemental analyses were recorded with Perkin Elmer CHNS analyzer.

2.2. General Procedure for the synthesis of 2-(N-aroylamino)benzothiazole:

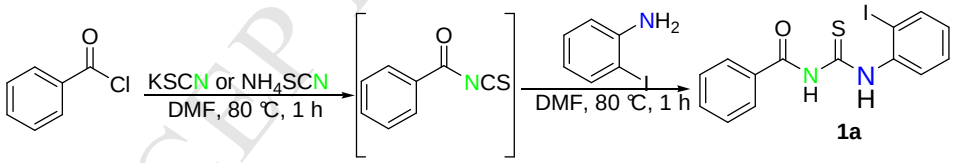
To a stirred mixture of DMSO (2 ml), *N*-(2-iodophenyl)-*N'*-benzoyl thiourea (1 mmol) was added slowly and the reaction mixture stirred for several minutes at room temperature. To that previous reaction mixture K_2CO_3 (138 mg, 1 mmol), $CuSO_4.5H_2O$ (10 mol %, 16 mg) and 1,10-phenonthroline (20 mol %, 36 mg) were added and stirred at 100 ^oC for 14 h. Progress of the reaction was monitored by TLC using ethyl acetate and hexane (2:8). After finish the reaction, the reaction mixture was cooled to room temperature. Then, the solution was washed with ethyl acetate (7 ml) and water (3 mL) for 5 times. The organic layer was evoparated and crude reaction mixture was purified by by silica gel (60-120 mesh) column chromatography using ethylacetate in hexane as eluent to obtain final product 2-(*N*-aroylamino)benzothiozole which was characterized by NMR (^{1}H and ^{13}C), IR and elemental analysis.

2.3 General Procedure for the synthesis of 2-(N-aroylamino)benzimidazole:

To a stirred mixture of DMSO (2 ml), *N*-(2-iodophenyl)-*N'*-benzoyl guanidine (1 mmol) was added slowly and the reaction mixture stirred for several minutes at room temperature. To that previous reaction mixture Cs_2CO_3 (325 mg, 1 mmol), $Cu(OAc)_2.H_2O$ (10 mol %, 18.1 mg) and 1,10-phenonthroline (20 mol %, 36 mg) were added and stirred at 120 ^oC for 14 h. Progress of the reaction was monitored by TLC using ethyl acetate and hexane (2:8). After finish the reaction, the reaction mixture was cooled to room temperature. Then, the solution was washed with ethyl acetate (7 ml) and water (3 mL) for 5 times. The organic layer was evoparated and crude reaction mixture was purified by by silica gel (60-120 mesh) column chromatography using ethylacetate in hexane as eluent to obtain final product 2-(*N*-aroylamino)benzimidazole which was characterized by NMR (^{1}H and ^{13}C), IR and elemental analysis.

3. Results and discussions

Synthesis of 2-(*N*-benzoyl)benzothiazoles: The starting materials were prepared using our recent reported procedure (Scheme 1).[15] This reaction proceeds *via* nucleiophilic substitution/addition. Soon after the end of the preparation of starting material, the optimization of reaction conditions was carried out using *N*-(2-iodophenyl)-*N'*-benzoyl thiourea as model substrate with various solvents, different copper sources, and bases at 100 °C (Table 1). Initially, we tried the reaction with CuI as catalyst in the absence of ligand and fortunately the reaction gave target product **2a** in 10% yield (Table 1, entry 1). Taking advantage of this result, later, we have checked various ligands, among them ligand **L4** gave desired product **2a** in complete conversion (Table 1, entry 5). In contrast, other ligands **L1-L3** gave final product in less to moderate yield (Table 1, entries 2-4). The reaction with bases like, K_2CO_3 and Cs_2CO_3 to provide target product **2a** in quantitative yield are used. In contrast, bases such as KOH, $K_3PO_4 \cdot 3H_2O$ were less effective in providing desired product (Table 1, entries 6& 7). In set of solvents, DMSO and DMF gave desired product **2a** in complete conversation. Whereas, other solvents like THF, Toluene, CH_3CN were shown less activity to give target product. Both copper (I) and copper (II) species (CuI, CuBr, CuCl, $CuSO_4.5H_2O$ and $Cu(OAc)_2.H_2O$) have been exhibited similar catalytic activity (Table 1, entries 13-16). Lowering the catalyst amount (5 mol %) and base (0.5 eq) led to S-arylation to afford the cyclised expected product **2a** in less conversion (Table 1, entries 17-18). The control experiment confirmed that no target product could be obtained in the absence of catalyst and ligand (Table 1, entry 19).

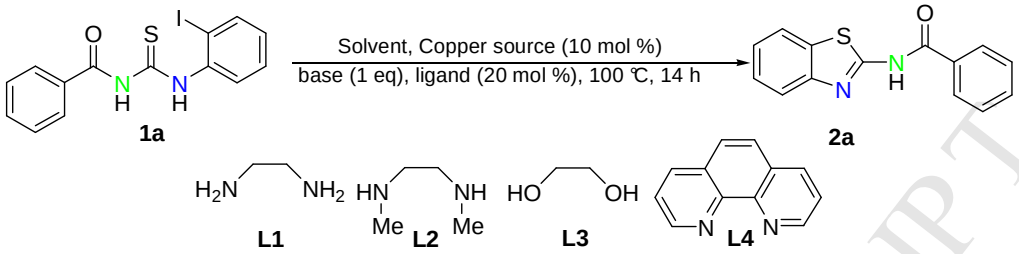


Scheme 1: The synthetic route for the synthesis of *N*-benzoyl-*N'*-(2-iodophenyl) thiourea

Encouraged by these results, we further pursued the scope of the process with respect to other substrates. The substrates **1b, 1c, 1d and 1e** having electron donating substituents like 4-Me, 4-OMe, 2-Me and 2,4-DiMe were carried out under optimized reaction condition to afford respective target products **2b, 2c, 2d and 2e** in high yield. The substrates **1f, 1g** hold weak electron withdrawing substituents readily underwent the reaction to obtain cyclised products **2f, 2g** in good yield, whereas, the substrates **1h, 1i** bearing strong electron withdrawing groups proceeded the reaction to provide respective desired products **2h, 2i** in moderate yield. On the other hand the cyclisation of the substrates **1j, 1k, 1l, 1m & 1n** having 4-Me, 4-OMe,

2,4-DiMe, 4-Cl & 4-F proceeded to give desired products **2j, 2k, 2l, 2m & 2n** in 66-94% yield.

Table 1: Optimization for the synthesis of *N*-Benzoyl benzothiazole



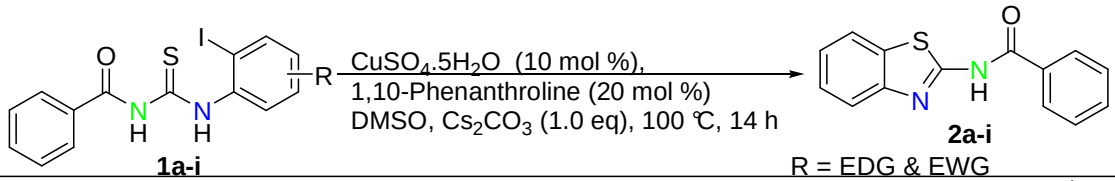
1a **2a**

L1 **L2** **L3** **L4**

Entry	Solvent	Copper source	Base	Ligand	Conversion[b] **2a**
1	DMSO	CuI	K_2CO_3	-	10
2	DMSO	CuI	K_2CO_3	**L1**	30
3	DMSO	CuI	K_2CO_3	**L2**	45
4	DMSO	CuI	K_2CO_3	**L3**	20
5	DMSO	CuI	K_2CO_3	**L4**	100
6	DMSO	CuI	KOH	**L4**	45
7	DMSO	CuI	$K_3PO_4 \cdot 3H_2O$	**L4**	65
8	DMSO	CuI	Cs_2CO_3	**L4**	100
9	DMF	CuI	K_2CO_3	**L4**	100
10	THF	CuI	K_2CO_3	**L4**	60
11	Toluene	CuI	K_2CO_3	**L4**	30
12	CH_3CN	CuI	K_2CO_3	**L4**	89
13	DMSO	CuBr	K_2CO_3	**L4**	100
14	DMSO	CuCl	K_2CO_3	**L4**	100
15	DMSO	$CuSO_4 \cdot 5H_2O$	K_2CO_3	**L4**	100
16	DMSO	$Cu(OAc)_2 \cdot H_2O$	K_2CO_3	**L4**	100
17[c]	DMSO	$CuSO_4 \cdot 5H_2O$	K_2CO_3	**L4**	54
18[d]	DMSO	$CuSO_4 \cdot 5H_2O$	K_2CO_3	**L4**	42
19	DMSO	-	K_2CO_3	-	n.d.

[a] Reaction conditions: *N*-(2-iodophenyl)-*N'*-benzoyl thiourea (1 mmol), solvent (2 mL), catalyst (10 mol %), ligand (20 mol %), base (1 mmol), 14 h, 100 °C. [b] Conversion based on diagnostic peaks integration in ^{1}H NMR of crude reaction mixture. [c] $CuSO_4 \cdot 5H_2O$ (5 mol %) used. [d] K_2CO_3 (0.5 equiv) used. n.d. = not detected.

Table 2: Substrate scope for the synthesis of 2-(*N*-Benzyol) benzothiazoles[a]

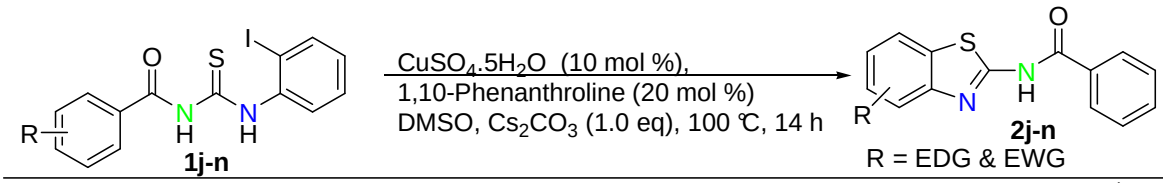


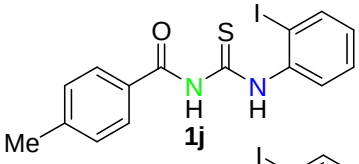
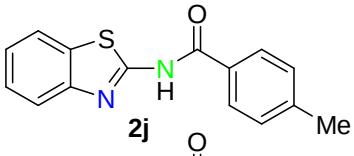
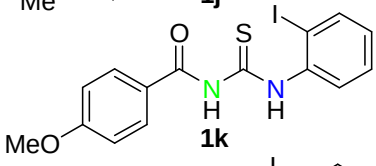
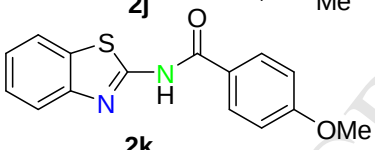
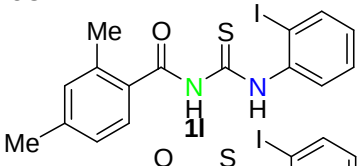
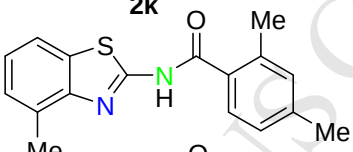
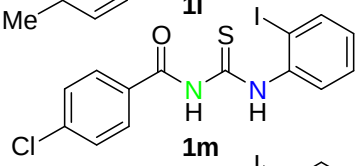
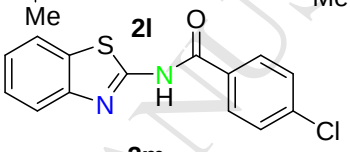
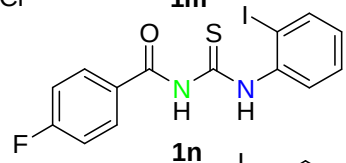
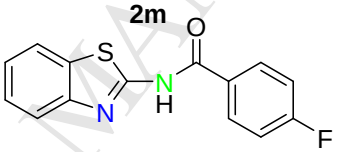
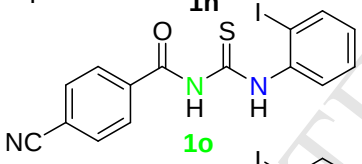
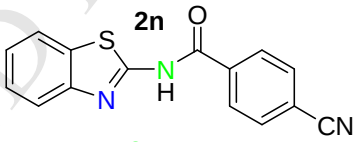
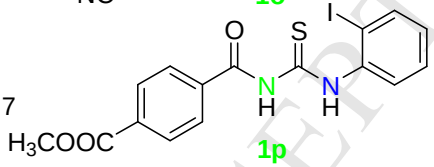
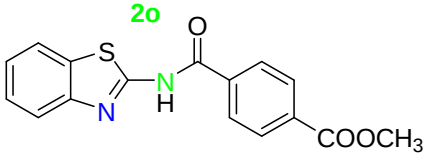
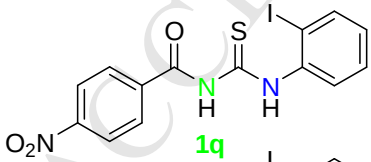
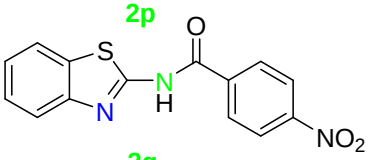
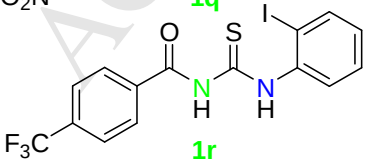
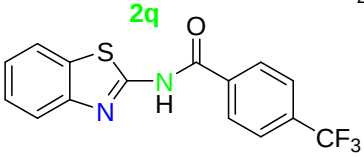
1a-i **2a-i** R = EDG & EWG

Entry	Substrate (R)	Product	Yield (%)[b]
1	**1a**	**2a**	99
2	**1b**	**2b**	98
3	**1c**	**2c**	96
4	**1d**	**2d**	92
5	**1e**	**2e**	87
6	**1f**	**2f**	80
7	**1g**	**2g**	82
8	**1h**	**2h**	68
9	**1i**	**2i**	65

[a] Reaction conditions: Substituted *N*-(2-iodophenyl)-*N'*-benzoyl thiourea (1 mmol), DMSO (2 mL), $CuSO_4 \cdot 5H_2O$ (10 mol %), 1,10-phennanthroline (20 mol %), K_2CO_3 (1 mmol), 14 h, 100 °C. [b] Isolated yield. [c] $CuSO_4 \cdot 5H_2O$ (5 mol %) used. [d] K_2CO_3 (0.5 equiv) used. n.d. = not detected.

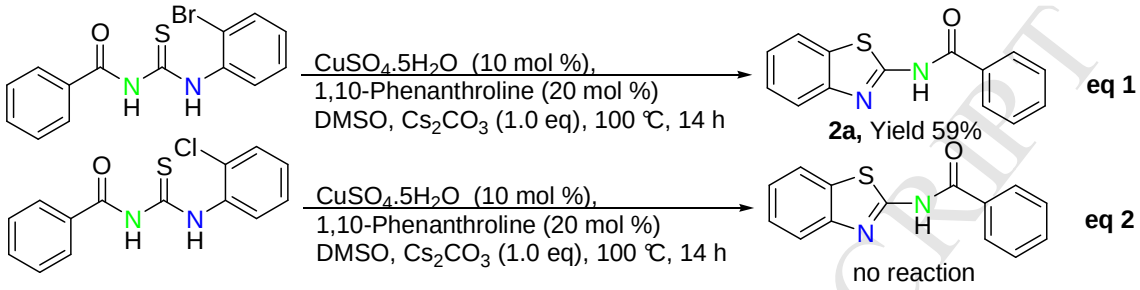
Table 3: Substrate scope for the synthesis of *N*-Benzyol benzothiazoles[a]



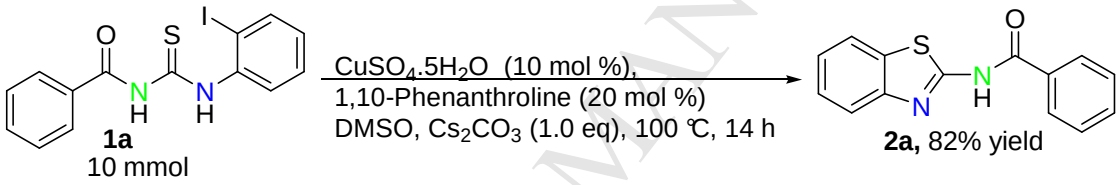
Entry	Substrate (R)	Product	Yield (%)[b]
1	 **1j**	 **2j**	94
2	 **1k**	 **2k**	96
3	 **1l**	 **2l**	89
4	 **1m**	 **2m**	74
5	 **1n**	 **2n**	66
6	 **1o**	 **2o**	65
7	 **1p**	 **2p**	60
8	 **1q**	 **2q**	60
9	 **1r**	 **2r**	62

[a] Reaction conditions: Substituted *N*-(2-iodophenyl)-*N'*-benzoyl thiourea (1 mmol), DMSO (2 mL), $CuSO_4 \cdot 5H_2O$ (10 mol %), 1,10-phennanthroline (20 mol %), K_2CO_3 (1 mmol), 14 h, 100 °C. [b] Isolated yield. [c] $CuSO_4 \cdot 5H_2O$ (5 mol %) used. [d] K_2CO_3 (0.5 equiv) used. n.d. = not detected.

Finally, we have also examined reactivity of *N*-(2-halophenyl)-*N'*-benzoyl thiourea under optimized reaction conditions. The reaction with *N*-(2-bromophenyl)-*N'*-benzoyl thiourea were used to provide a target product **2a** in 59% yield (eq 1). In contrast, no target product could be occurred in case of *N*-(2-chlorophenyl)-*N'*-benzoyl thiourea under optimized reaction conditions (eq 2).

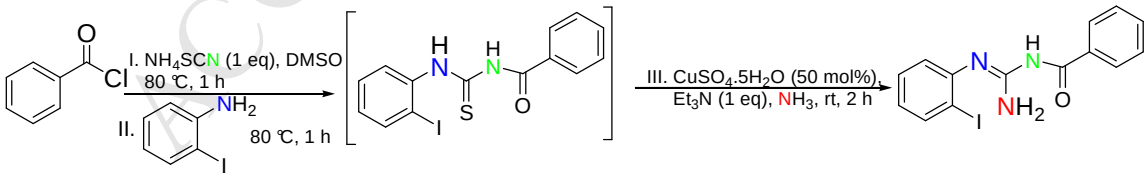


In order to explain the practical usage of this method, the reaction of *N*-(2-iodophenyl)-*N'*-benzoyl thiourea was examined **1a** with 10 mmol scale. Very fortunately the reaction could give their respective target products in good yield (Scheme 3).



Scheme 2: Large Scale Construction of 2-(*N*-Benzoyl) benzothiazole

Synthesis of 2-(*N*-benzoyl)benzimidazoles: Firstly, we prepared the starting precursor using our recent reported procedure (Scheme 2).[15] Using the above reaction conditions of the formation of 2-(*N*-benzyol)benzothiazole, the construction of 2-(*N*-benzyol)benzimidazole was studied. It was found that the target product have been obtained at 120 °C using all copper sources (10 mol %), 1,10-phenanthrolene (20 mol %), Cs_2CO_3 as base in the presence of DMSO solvent.

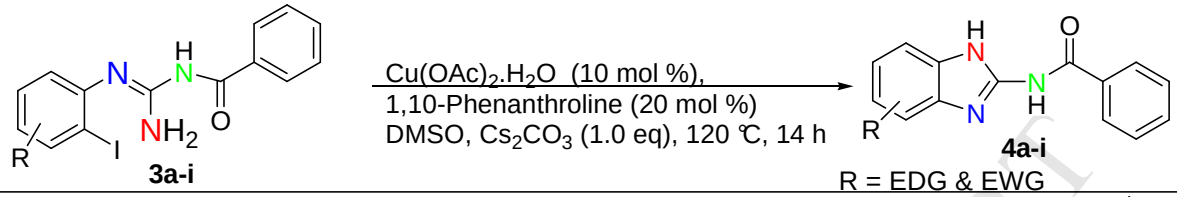


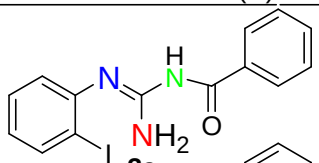
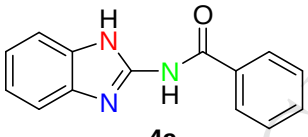
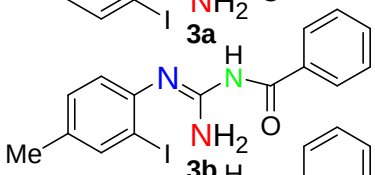
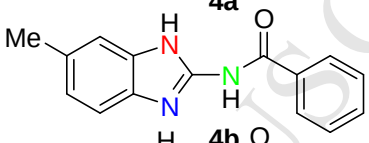
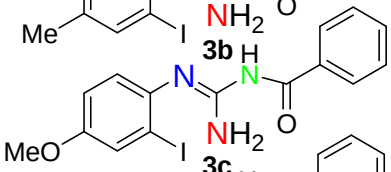
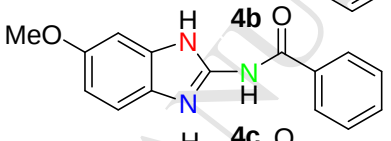
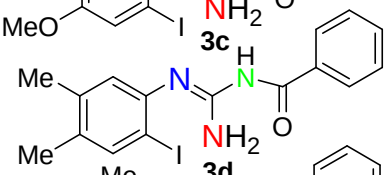
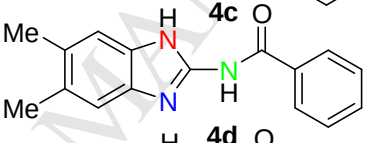
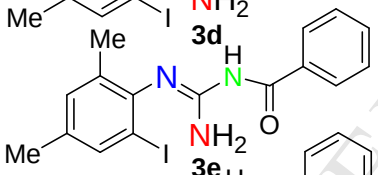
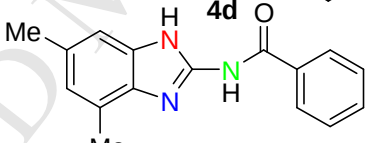
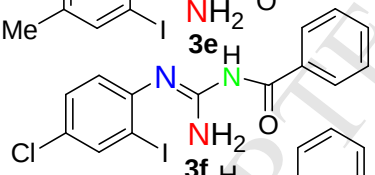
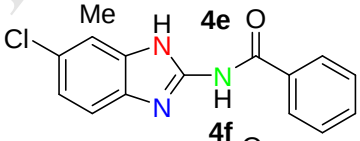
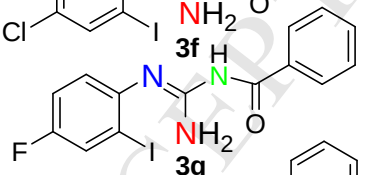
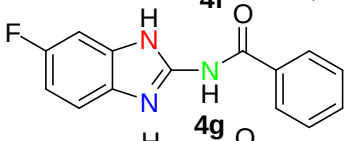
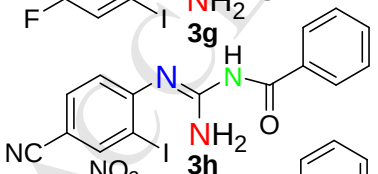
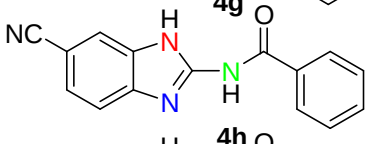
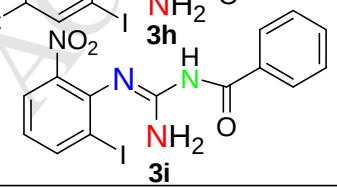
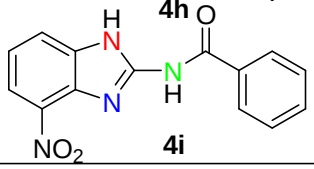
Scheme 3: Pathway for the synthesis of *N*-benzoyl-*N'*-(2-iodophenyl) guanidine

In response to this encourage results, we used a range of substituted 2-(*N*-benzoyl)benzimidazoles to investigate the scope and limits of this reaction. As we shown in Table 4, both electron rich and electron withdrawing substituents can provide the

corresponding benzimidazoles in modearate to good yield. The substrates **3b, 3c, 3d** and **3e** having electron donating substituents like 4-Me, 4-OMe, 2-Me and 2,4-DiMe carried out

Table 4: Substrate scope for the synthesis of 2-(*N*-Benzyol) benzimidazoles[a]



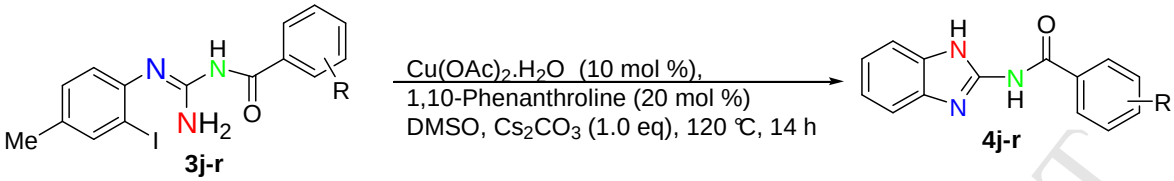
Entry	Substrate (R)	Product	Yield (%)[b]
1	 **3a**	 **4a**	93
2	 **3b**	 **4b**	95
3	 **3c**	 **4c**	96
4	 **3d**	 **4d**	88
5	 **3e**	 **4e**	87
6	 **3f**	 **4f**	76
7	 **3g**	 **4g**	72
8	 **3h**	 **4h**	64
9	 **3i**	 **4i**	60

[a] Reaction conditions: Substituted *N*-(2-iodophenyl)-*N'*-benzoyl guanidine (1 mmol), DMSO (2 mL), $Cu(OAc)_2 \cdot H_2O$ (10 mol %), 1,10-phenanthroline (20 mol %), Cs_2CO_3 (1 mmol), 14 h, 120 °C. [b] Isolated yield. n.d. = not detected.

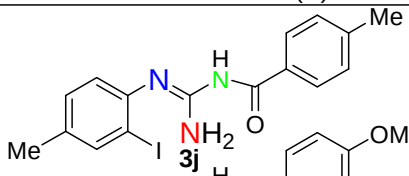
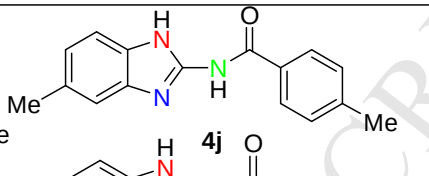
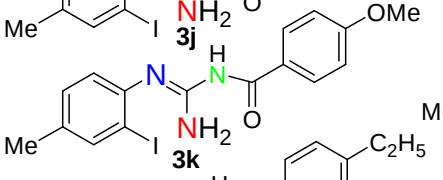
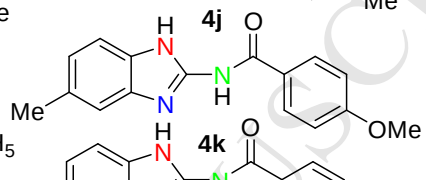
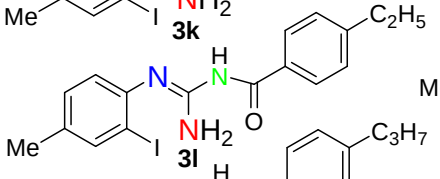
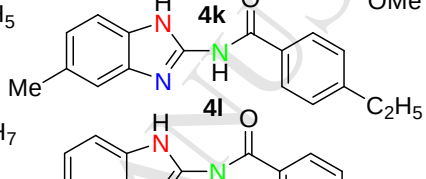
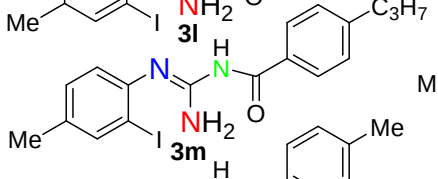
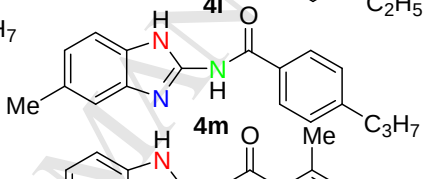
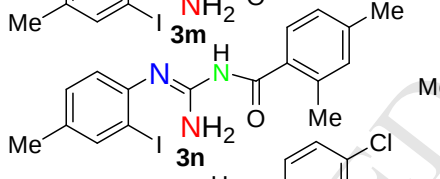
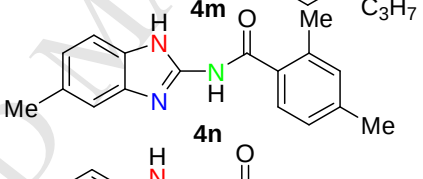
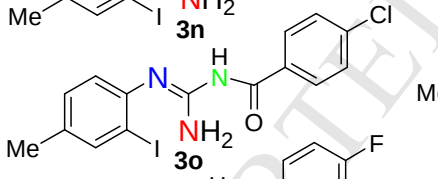
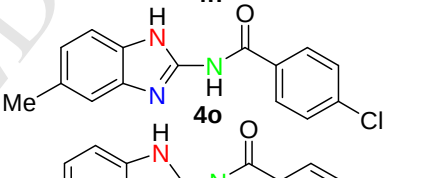
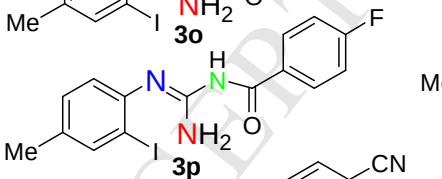
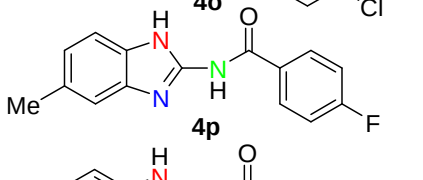
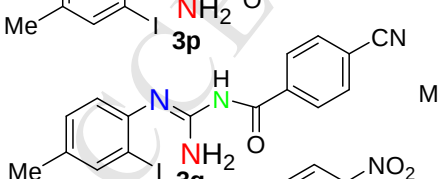
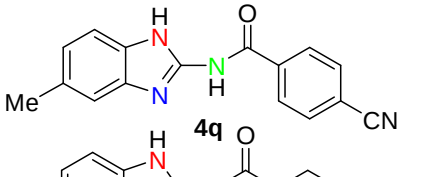
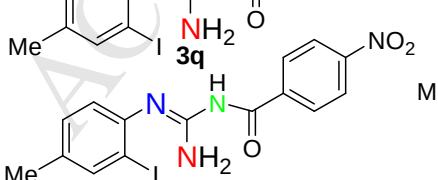
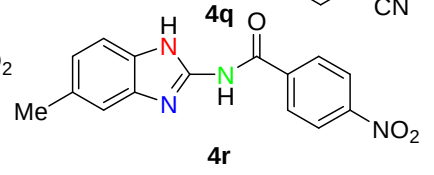
under optimized reaction condition to afford respective target products **4b, 4c, 4d and 4e** in high yield. The substrates **3f, 3g** bearing weak electron withdrawing substituents readily

underwent the reaction to obtain domino products **4f, 4g** in good yield, whereas, the substrates **3h, 3i** bearing strong electron withdrawing groups proceeded the reaction to

Table 5: Substrate scope for the synthesis of *N*-Benzyol benzimidazoles[a]



R = EDG & EWG

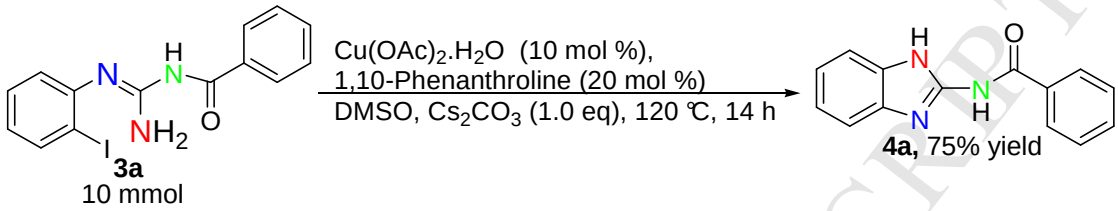
Entry	Substrate (R)	Product	Yield (%)[b]
1	 **3j**	 **4j**	91
2	 **3k**	 **4k**	93
3	 **3l**	 **4l**	93
4	 **3m**	 **4m**	93
5	 **3n**	 **4n**	89
6	 **3o**	 **4o**	71
7	 **3p**	 **4p**	70
8	 **3q**	 **4q**	65
9	 **3r**	 **4r**	62

[a] Reaction conditions: Substituted 4-Me-*N*-(2-iodophenyl)-*N'*-benzoyl guanidine (1 mmol), DMSO (2 mL), $Cu(OAc)_2 \cdot H_2O$ (10 mol %), 1,10-phennanthroline (20 mol %), Cs_2CO_3 (1 mmol), 14 h, 120 °C. n.d. = not detected.

provide respective desired products **4h, 4i** in moderate yield. On the other hand, the substrates **3j, 3k, 3l & 3m** having para substituted electron donating groups 4-Me, 4-OMe, 4-Et, 4-^{i}Pr proceeded to give desired products **4j, 4k, 4l & 4m** in 92-93% yield. Whereas

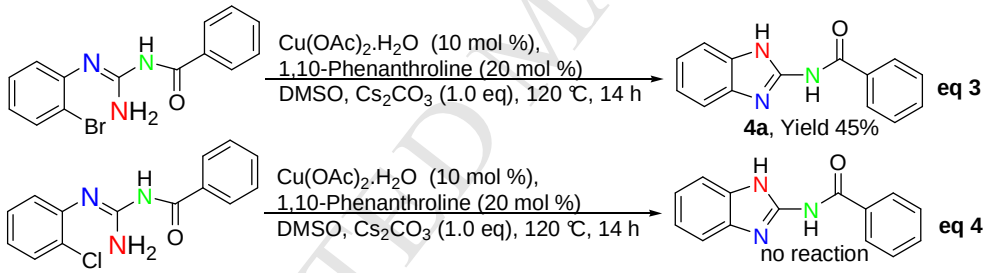
phenyl ring bearing electron withdrawing groups like 4-Cl, 4-F, 4-CN & 4-NO_2 to afford their corresponding target products **4o, 4p, 4q & 4r** in moderate yield. The phenyl ring holds disubstituted group 2, 4-diMe to obtain final product **4n** in 89% yield.

To reveal the practical utility of the protocol, *N*-(2-iodophenyl)-*N'*-benzoyl guanidine **3a** was tested with 10 mmol scale under optimized reaction conditions and the reaction gave expected product **4a** in 75% yield (Scheme 3).



Scheme 4: Bulk Scale Synthesis of 2-(*N*-Benzoyl) benzothiazole

Similarly, the reactivity of *N*-(2-halophenyl)-*N'*-benzoyl guanidine was also tested. In this connection, moderate yield was obtained in case of *N*-(2-bromophenyl)-*N'*-benzoyl guanidine (eq. 3), whereas, *N*-(2-chlorophenyl)-*N'*-benzoyl guanidine didn't give expected *C*-*N* cross-coupled product under optimized reaction conditions (eq. 4).



To reveal the mechanism in more details the catalyst was extracted after finish the reaction. The isolated catalyst was subjected to Powder XRD analyses (Figure 2). The spectrum shows the peaks corresponding to 2θ = 73.65, 61.53, 42.45, 36.12, 29.59. The peaks are very close to that given by JCPDS data of XRD for copper (I) species.[16] No other diffraction peaks have

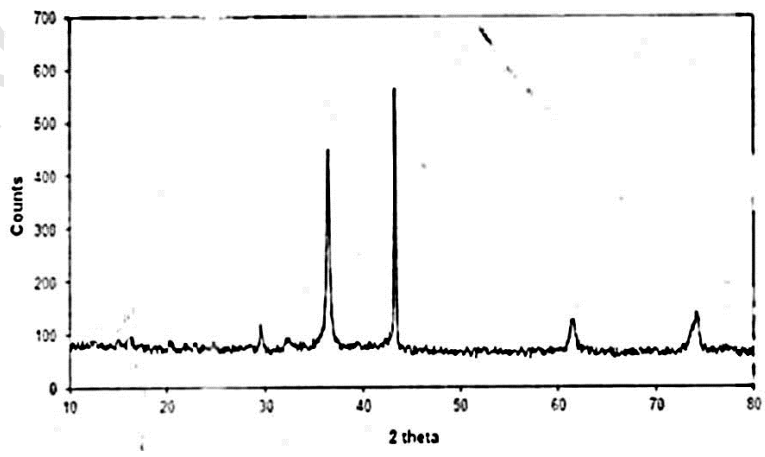
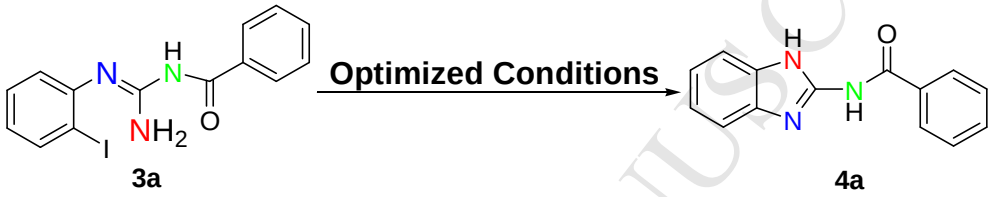


Fig 2: XRD of Cu (I) species

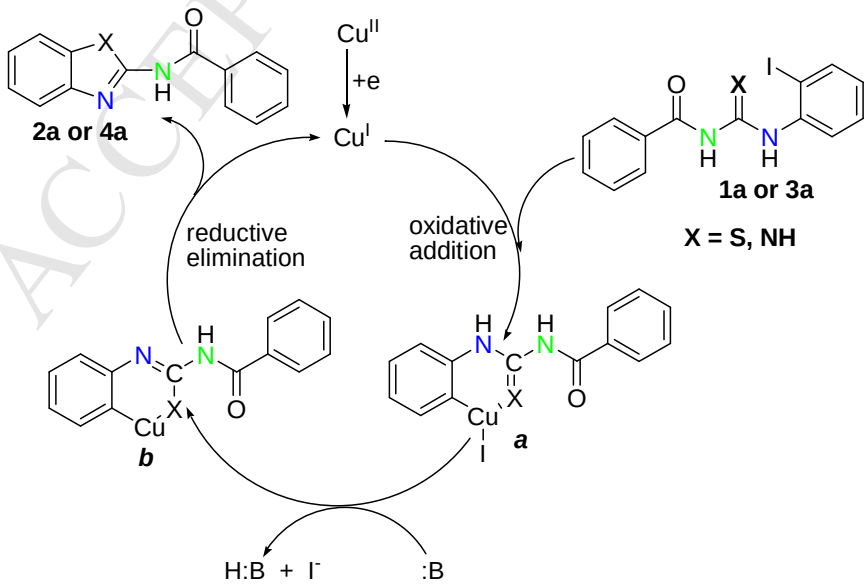
been appeared in the XRD pattern. Therefore, we believe that Cu(I) species have formed in the reaction medium. In addition, a radical inhibition test was carried out for checking the radical path mechanism. As result shown in the Table 6, the yield of the reaction was not changed when TEMPO (radical scavenger) was added to the reaction mixture. This result strongly believes that the reaction may not proceed *via* radical mechanism and it undergoes *via* oxidative-reductive mechanism.

Table 6. Effects of Radical Inhibitor on the Synthesis of Substituted *N*-Benzyol benzimidazoles [a]



Entry	Radical Scavenger	**4a** (%)
1	-	92
2[b]	TEMPO	93

[a] Reaction conditions: Substituted *N*-(2-iodophenyl)-*N'*-benzoyl guanidine (1 mmol), DMSO (2 mL), $Cu(OAc)_2 \cdot H_2O$ (10 mol %), 1,10-phenanthroline (20 mol %), Cs_2CO_3 (1 mmol), 14 h, 120 °C. [b] TEMPO (0.5 mmol) used.



Scheme 5: Proposed catalytic cycle for the synthesis of 2-(*N*-Benzoyl)benzothiazole and 2-(*N*-Benzoyl)benzimidazole.

Based on the experimental evidence the reaction pathway is proposed in the Scheme 5. The copper (I) species undergoes oxidative addition with thiourea or guanidine to yield copper (III) intermediate ***a***, which can complete the catalytic cycle by reductive elimination to afford the target product **2a or 4a** using base *via* intermediate ***b*.** The above results and proposed mechanism clearly suggest that the reported methodology involves intra molecular *C-S*[17] and *C-N*[18] cross-coupling reaction.

4. Conclusion

In summary we have developed simple and new route for the synthesis of 2-(*N*-Benzoyl)benzothiazole and 2-(*N*-Benzoyl)benzimidazole under mild reaction conditions. Cheap, readily available and air stable copper source as catalyst was used for this methodology. This method involves intra molecular *C-S* and *C-N* cross-coupling technique. All the substrates were found to give their corresponding target products in good to excellent yields.

Acknowledgments

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Highlights

- To the best of our knowledge no one has reported for the synthesis of substituted 2-(*N*-Aryolamino)benzimidazoles in the presence of copper catalyst.
- This methodology is general, clean and efficient.
- We could find cheap, readily available and air stable copper catalyst for desulphurization.
- The reactions are rapid, facile and accomplished at room temperature.
- Moreover, all substituents readily underwent the reaction to provide their corresponding target products in good to high yield.