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Copper-catalyzed synthesis of 2-aminophenyl benzothiazoles: A novel approach

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A novel, convenient and efficient protocol for the construction of various 2-aminophenyl benzothiazoles by domino intra and inter molecular *C-N* cross-coupling reactions of arylisothioureas with aryl iodides using cheap, air stable and readily available copper catalyst is described.The arylisothioureas were obtained from thiourea *via* copper promoted desulfurization followed by nucleophilic substitution . In addition, the reactivity of arylhalides and the reaction mechanism have also been studied. The protocol features operational simplicity and broad substrate scope.

Introduction

Benzothiazole and its derivatives belong to an enormously important family of synthetic compounds of heterocyclic systems. In recent years, many diverse natural products and biologically active compounds[1] (Figure 1) like benzimidazoles,[2] benzothiazoles,[3] 2-aminobenzimidazoles[4] and benzoxazoles[5] have been constructed because of their immense interest in synthetic chemistry. Especially, benzothiazoles have been widely utilized over the years as drugs for several diseases such as alzheimer's,[6a] inflammatory,[6b] diabetes,[6c] tuberculosis[6d] and viral infections.[6e] In addition, benzothiazole derivatives show the medicinal chemistry applications which includes antitumor,[6f] anticancer,[6g] orexin receptor antagonist,[6h] calcium antagonistic activity,[6i] AKT (protein kinase B) inhibitor-IV[6e] and inhibitors for several enzymes.[6j] Therefore, the development of various synthetic strategies to access these class of compounds are highly desirable. In this connection, researchers have developed many methodologies for the construction of benzothiazole derivatives *via* traditional methods.[7] Despite the wide generality and efficiency of the above reported methods, they use harsh reaction conditions like high temperature, toxic reagents like liquid bromine, involving strong acids. Some of these disadvantages were recently defeated by cross-coupling reactions using transition metals Cu,[8] Pd,[9] Ru,[10] Fe[11] under comparatively milder reaction conditions. In addition, very recently this core is developed based on iodine-catalyzed dehydrogenative coupling of isothiocyanatobenzenes with amines[12] and these compounds are also prepared under metal free conditions.[13] Still the progress is desired for development of a simple, commercially available and environmentally acceptable methodology for the preparation of benzothiazole compounds. In this connection, the authors would like to prepare benzothiazoles from 2-iodophenyl isothiourea through domino intra and intermolecular *C-N* cross-coupling reaction by using readily available, cheap and air stable copper source as catalyst under mild reaction conditions. Generally, these compounds have been constructed through *C-S* cross-coupling reactions, but we construct these compounds through domino *C-N* cross-coupling reaction. To the best of our knowledge no report is available for the synthesis of benzothiazoles through domino *C-N* cross-coupling reaction using copper source.

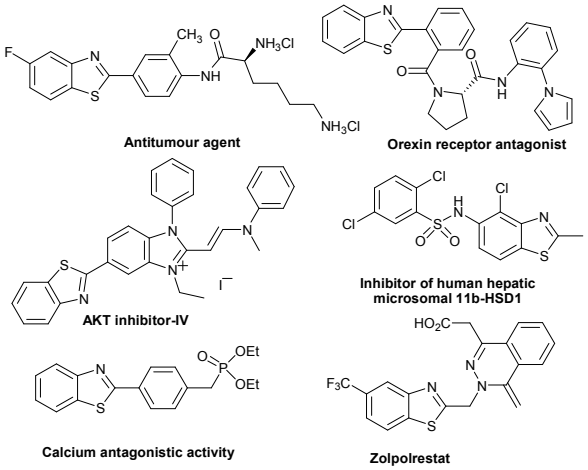

Figure 1: Examples of biologically active compounds of benzothiazoles.

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† Footnotes relating to the title and/or authors should appear here.
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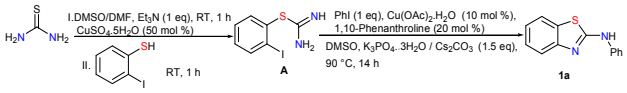
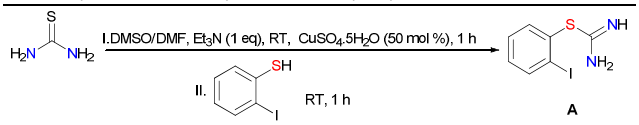
Results and discussion



Scheme 1. Synthetic route for *N*-phenylbenzo[*d*]thiazol-2-amine

Thiourea on desulfurization using copper source followed by substitution reaction with 2-iodothiophenol gave 2-iodophenyl isothiourea **A**. The reaction proceeds *via* desulfurization followed by nucleophilic substitution. Further this 2-iodophenyl isothiourea reacts with iodobenzene using a copper source as catalyst under moderate reaction conditions to afford the target product 2-aminophenyl benzothiazole *via* intra and intermolecular *C-N* cross coupling reactions respectively (**Scheme 1**).

Table 1: Optimization for the synthesis of 2-iodophenyl isothiourea[a]

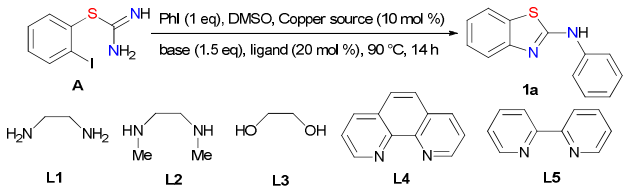


Entry	Solvent	Copper source	Conversion(%)[b] A
1	EtOH	CuI	100
2	EtOAc	CuI	100
3	*n*-Hexane	CuI	n.d
4	*n*-Heptane	CuI	n.d
5	H_2O	CuI	60
6	DMF	CuI	100
7	DMSO	CuI	100 (95)*
8	DMSO	CuCl	100
9	DMSO	CuBr	100
10	DMSO	Cu_2O	100
11	DMSO	$CuSO_4.5H_2O$	100 (95)*
12	DMSO	$Cu(OAc)_2.H_2O$	100 (95)*
13[c]	DMSO	$CuSO_4.5H_2O$	100
14[d]	DMSO	$CuSO_4.5H_2O$	63 (57)*
15	DMSO	$AlCl_3$	n.d.
16	DMSO	$FeCl_3$	55
17	DMSO	$ZnCl_2$	15
18	DMSO	-	n.d

[a] Reaction conditions: Thiourea (1 mmol), solvent (2 mL), Et_3N (1 eq), Copper source (1 eq), 1 h, room temperature. [b]Conversion was confirmed based on diagnostic peaks integration in ^{1}H NMR of crude reaction mixture. [c] Copper source (50 mol %) was used. [d] Copper source (25 mol %) was used. n.d. = not detected. * Isolated yield (given in brackets) is mentioned for that reactions.

Initially the standardization was started for the synthesis of starting precursor 2-iodophenyl isothiourea **A** using thiourea as model substrate with various solvents and copper sources at room temperature (**Table 1**). We were glad to observe that the substrate proceeded reactions with 1 equiv. Et_3N and 50 mol % copper source (Both Cu (I) and Cu (II) salts) in the presence of solvents EtOH, EtOAC, DMSO and DMF at room temperature to afford the corresponding 2-iodophenyl isothiourea **A** in complete conversion. The reaction using non polar solvents like *n*-hexane and *n*-heptane didn't give2-iodophenyl isothiourea (**Table 1**, entries 3 and 4). Control experiments confirmed that the reaction didn't proceed in the absence of copper source (**Table 1**, entry 15).

Table 2: Optimization for the synthesis of 2-aminophenyl benzothiazole[a]



Entry	Copper source	Base	Ligand	Conversion(%)[b] 1a
1	CuI	$K_3PO_4{\cdot}3H_2O$	**L1**	65
2	CuI	$K_3PO_4{\cdot}3H_2O$	**L2**	70
3	CuI	$K_3PO_4{\cdot}3H_2O$	**L3**	60
4	CuI	$K_3PO_4{\cdot}3H_2O$	**L4**	100
5	CuI	$K_3PO_4{\cdot}3H_2O$	**L5**	85
6	CuI	KOH	**L4**	65
7	CuI	K_2CO_3	**L4**	95
8	CuI	Cs_2CO_3	**L4**	100
9	CuBr	Cs_2CO_3	**L4**	100
10	CuCl	Cs_2CO_3	**L4**	100
11	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	**L4**	100
12	$Cu(OAc)_2{\cdot}H_2O$	Cs_2CO_3	**L4**	100
13	$Cu(OAc)_2{\cdot}H_2O$	$K_3PO_4{\cdot}3H_2O$	**L4**	100
14[c]	$Cu(OAc)_2{\cdot}H_2O$	$K_3PO_4{\cdot}3H_2O$	**L4**	52
15[d]	$Cu(OAc)_2{\cdot}H_2O$	$K_3PO_4{\cdot}3H_2O$	**L4**	47
16	$Cu(OAc)_2{\cdot}H_2O$	$K_3PO_4{\cdot}3H_2O$	-	12
17	-	$K_3PO_4{\cdot}3H_2O$	-	n.d.

[a] Reaction conditions: 2-Iodophenylisothiourea (1 mmol), DMSO (2 mL), iodo benzene (1 mmol), catalyst (10 mol %), ligand (20 mol %), base (1.5 mmol), 14 h, 90 °C. [b] Conversion based on diagnostic peaks integration in ^{1}H NMR of crude reaction mixture. [c] $Cu(OAc)_2{\cdot}H_2O$ (5 mol %) used. [d] $K_3PO_4{\cdot}3H_2O$ (1.0 equiv) used. n.d. = not detected.

Later, we conducted the optimization for the synthesis of 2-aminophenyl benzothiazole using 2-iodophenyl isothiourea and iodobenzene as model substrates with various bases, ligands and copper sources. Initially, we checked the reaction with various ligands, among them ligand **L4** could give target product in quantitative yield (**Table 2,** entry 4). Other ligands such as **L1, L2, L3** and **L5** were shown less reactive in comparison to **L4**. In case of bases, both $K_3PO_4{\cdot}3H_2O$ and Cs_2CO_3 gave final product in complete conversion (**Table 2,** entry 4 and entry 8**)**. Very fortunately, weak base K_2CO_3 gave target product in high yield (**Table 2,** entry 7**)**. In contrast, strong base KOH could obtain target product in moderate yield (**Table 2,** entry 6). It might be reasoned that KOH may give hydrolyzed product, which we observed in TLC. Both copper (I) and (II) sources (CuI, CuBr, CuCl, $Cu(OAc)_2.H_2O$ and $CuSO_4.5H_2O$) exhibited similar catalytic activity (**Table 2**, entries 9-12).Further, Lowering the amount of copper source (5 mol %) or the base (1.0 equiv) could give target product in less conversion (**Table 2**, entries 13-14). In order to know the role of the ligand the reaction was also performed without ligand (**Table 2**, entry 15) and it resulted in very lower yield of target product even after prolonged reaction times. Control

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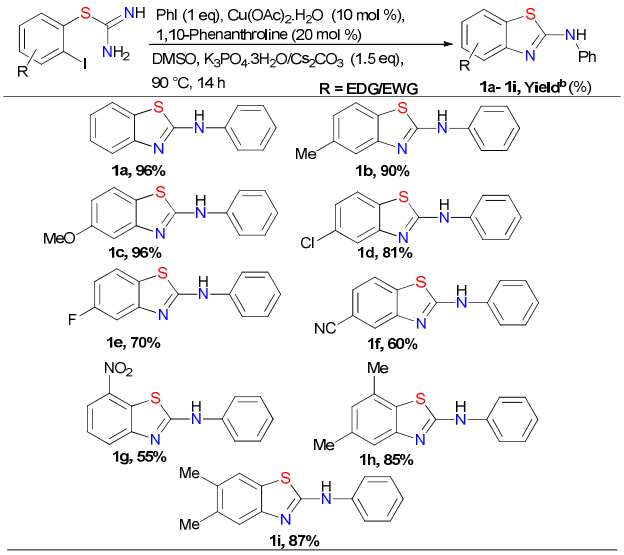
experiments without ligand and the copper source confirmed that the formation of final product was not observed (**Table 2**, entry 16).

Table 3: Substrate scope for the synthesis of 2-phenylaminobenzothiazole[a]

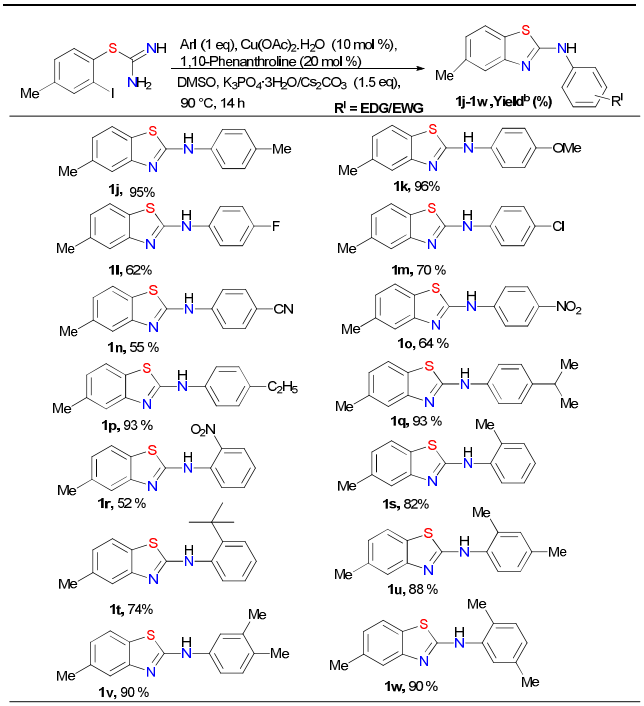


[a] Reaction conditions: Substituted 2-iodophenyl isothiourea (1 mmol), DMSO (2 mL), $Cu(OAc)_2.H_2O$ (10 mol %), PhI (1 mmol), 1,10-phenanthroline (20 mol %), Cs_2CO_3/ $K_3PO_4{\cdot}3H_2O$ (1.5 mmol), 14 h, 90 °C. b Isolated yield.

Using the above optimization reaction conditions, the domino intra and inter molecular *C-N* cross-coupling reaction of substituted 2-iodophenyl isothioureas were next studied (**Table 3**). The cyclization reaction proceeded effectively to obtain substituted 2-aminophenyl benzothiazoles **1a-1i** in 55-96% yields. 2-Iodophenyl isothioureas having electron donating groups exhibited greater reactivity compared to those bearing electron withdrawing groups. 2-iodophenylisothioureas bearing both mono and di substituted groups like 4-Me, 4-OMe, 2,4-DiMe and 3,4-DiMe readily underwent the reaction to give their respective domino cross-coupled products **1b, 1c, 1h and 1i** in 90%, 96%, 85% and 87% yields. The reaction of 2-iodophenyl isothioureas having weak electron withdrawing group's such as 4-Cl and 4-F with iodobenzene to afford the target products **1d** and **1e** in moderate yield. In contrast, 2-iodophenyl isothioureas containing strong electron withdrawing groups like 4-CN and 2-NO_2 could give the desired cyclised products **1f** and **1g** in fewer yields. Similarly, the reactions of aryl iodide with 2-iodo-4-methylphenyl isothiourea under standardised reaction conditions were next examined (**Table 4**). Aryl iodides holding substituent's like 4-Me, 4-OMe, 4-Cl, 4-F, 4-CN, 4-NO_2, 4-Et and 4-^{i}Pr readily carryout the reaction to afford their corresponding expected products **1j-1q** in 55-96% yields.

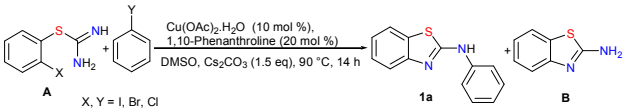
In addition, aryl iodides having ortho substituted groups like 2-NO_2, 2-Me and 2-^{t}Bu readily underwent the reaction to provide their corresponding target products **1r-1t** in 52-82% yields. Furthermore, the aryl iodides bearing disubstituted groups like 2,4-DiMe, 3,4-DiMe and 2,5-DiMe proceeded reaction to give respective domino cross-coupled products **1u-1w** in 88-90% yields. The above mentioned results clearly reveal that the present method is general and efficient; hence, it can be used for the construction of 2-aminophenyl benzothiazoles.

Table 4: Reactions between 2-iodophenyl isothiourea and various aryliodides[a]



[a] Reaction conditions: 4-Me-2-iodophenyl isothiourea (1 mmol), DMSO (2 mL), $Cu(OAc)_2.H_2O$ (10 mol %), PhI (1 mmol), 1,10-phenanthroline (20 mol %), Cs_2CO_3/ $K_3PO_4{\cdot}3H_2O$ (1.5 mmol), 14 h, 90 °C. [b] Isolated yield.

Table 5: Reactivity of halides[a]



Entry	X	Y	Conversion (%)[b]	
			1a	B
1	I	I	100	n.d
2	I	Br	<5	>95
3	I	Cl	n.d	>99
4[c]	Br	I	30	<15
5[d]	Cl	I	n.d	n.d

[a] Reaction conditions: 2-Halophenyl guanidine (1 mmol), ArX (1mmol), DMSO (2 mL), $Cu(OAc)_2.H_2O$ (10 mol %), 1,10-phenanthroline (20 mol %), Cs_2CO_3 (1.5 mmol), 18 h, 110 °C. [b] Conversion based on diagnostic peaks integration in ^{1}H NMR of crude reaction mixture. [c] Rest of percentage is starting material, which is recovered intact. [d]100% starting material is recovered intact. n.d. = not detected.

Next the reaction of aryl halides were screened under optimized reaction conditions (**Table 5**). Iodobenzene proceeded the reaction with 2-iodophenyl isothiourea to afford target product **1a** in complete conversion (**Table 5**, entry 1). On the other hand, bromo benzene gave target

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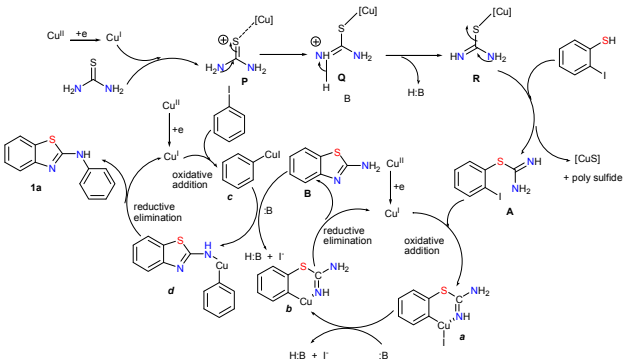
product **1a** in <5% yield and the product 2-aminobenzothiazole **B** in >95% yield (**Table 5**, entry 2). However, no target product could be obtained in case of chloro benzene and it gave 2-aminobenzothiazole **B** in complete conversion (**Table 5**, entry 3). The reaction of 2-bromphenyl isothiourea with iodobenzene to afford target product **1a** in less conversion (**Table 5**, entry 4), however, no reaction could be occurred in case of 2-chlorophenyl isothiourea (**Table 5**, entry 5). The above studies revealed that the target products are obtained in high yield with aryliodide whereas arylbromide and arylchloride gave trace amount of target product.

The proposed reaction mechanism is shown in below **Scheme 2**, which is proved by experimental evidence (**see supporting information**) and literature reports. Copper can co-ordinate with thiourea and followed by removal of protons to afford intermediate **R** *via* intermediates **P** and **Q**. The intermediate **R** may react with 2-iodothiophenol to provide 2-iodophenyl isothiourea **A** along with by-products CuS and poly sulphide [14] *via* desulphurization/substitution.[15] Oxidative addition of **A** with copper (I) species (it could be formed from copper (II) species)[16] can lead to the formation of ***a*** which can undergo intramolecular *C-N* cyclised product **B**[17] using base *via* intermediate ***b***. On the other hand iodobenzene can undergo oxidative addition with copper (I) species to obtain intermediate ***c***, which can carry out inter molecular *C-N* cross-coupling reaction[18] with 2-aminobenzothiazole **B** to afford intermediate ***d*** that can complete catalytic cycle *via* reductive elimination to obtain 2- aminophenyl benzothiazole **1a**. The above mechanistic investigations disclosed that the reported reaction proceeded *via* domino intra and intermolecular *C-N* cross-coupling reactions.



Scheme 2 : Proposed mechanism for the formation of 2-phenyl amino benzothiazole.

Conclusions

In summary, we have developed a general and simple methodology for the synthesis of substituted 2-aminophenyl benzothiazoles under mild reaction conditions. Furthermore, the synthesis of 2-iodophenyl isothiourea from thiourea has been accomplished. The reported methodology involves domino intra and intermolecular *C-N* cross-coupling reactions. We have also compared the aryl halides reactivity under optimized reaction conditions. Although the overall isolated yields look moderate, considering that the reactions are multiprocesses, the yields are in fact good to high.

Acknowledgments

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Conflicts of interest

There are no conflicts to declare.

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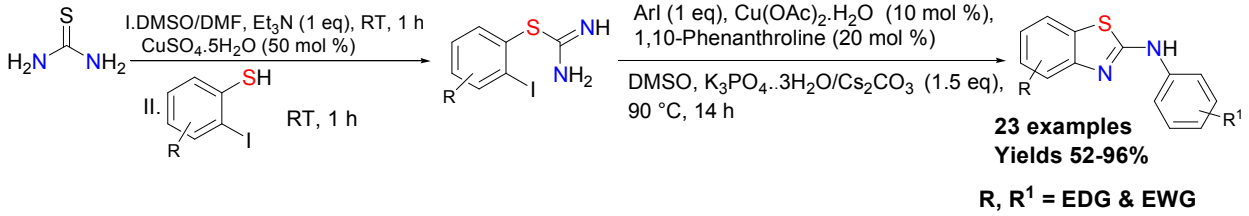

EDG-Electron Donating Group; EWG-Electron Withdrawing Group

Substituted 2-aminophenyl benzothiazoles have been constructed from thiourea *via* copper-catalyzed desulfurization/nucleophilic substitution followed by domino intra and inter molecular *C-N* cross-coupling reactions under moderate reaction conditions.

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