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

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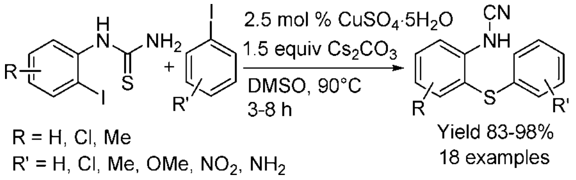
ABSTRACT



One-pot synthesis of 2-(arylthio)arylcyanamides is accomplished using cheap and air-stable $CuSO_4·5H_2O$ as a catalyst by domino intra- and intermolecular C−S cross-coupling reactions of 2-(iodoaryl)thioureas with aryl iodides under ligand-free conditions.

The recent development in cross-coupling reactions using transition-metal catalysis affords powerful tools for the formation of carbon−heteroatom bonds.[1] Among these, carbon−sulfur 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] Similarly, compounds containing a cyanamide functional group have received considerable attention in synthetic chemistry due to their unique structure and reactivity.[3,4] For example, cyanamides are important intermediates for the synthesis of biologically active compounds such as monoxidil[5] and herbicides.[6] Cyanamides are also used as tumor inhibitors[7] and precursors for the synthesis of pharmaceutically important heterocyclic compounds.[8] Herein, we report the one-pot synthesis of these two aforementioned moieties containing 2-(arylthio)arylcyanamides by copper-catalyzed domino intra- and intermolecular C−S cross-coupling reactions of aryl thioureas with aryl iodides under air. The catalyst is commercially available, cheap, and air stable and functions under ligand-free conditions. Furthermore, both the substrates containing the electron-donating and -withdrawing

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(1) For some recent reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364. (b) Hartwig, J. F. *Synlett* **2006**, 1283–1294. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (d) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710. (e) Evano, G.; Blanchard, N.; Toymi, M. *Chem. Rev.* **2008**, *108*, 3054–3131. (f) Kondo, T.; mitsudo, T.-A. *Chem. Rev.* **2000**, *100*, 3205–3220. (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*, 374–385. (h) Correa, A.; García Mancheño, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108–1117. (i) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954–6971. (j) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523–1533.

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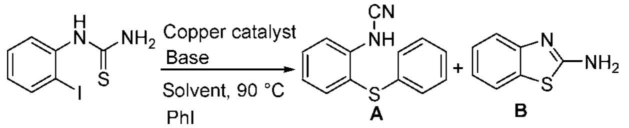
10.1021/ol9024088

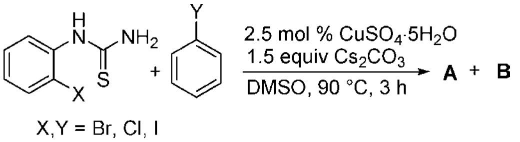
Table 1. Synthesis of 2-(Arylthio)arylcyanamides: Optimization of the Reaction Conditions[a]



entry	catalyst	base	solvent	time (h)	product(s) (%)[b] A	B
1	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	DMSO	3	100	n.d.
2	$CuSO_4{\cdot}5H_2O$	K_2CO_3	DMSO	6	100	n.d.
3	$CuSO_4{\cdot}5H_2O$	K_3PO_4	DMSO	6	45	55
4	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	DMF	5	100	n.d
6	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	Toluene	6	n.d.	100
7	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	1,4-dioxane	6	n.d.	100
8	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	CH_3CN	6	40	60
9	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	2-propanol	6	n.d.	100
10	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	DMSO	5	65[c]	35
11	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	DMSO	5	59[d]	41
12	CuI	Cs_2CO_3	DMSO	3	100	n.d.
13	CuBr	Cs_2CO_3	DMSO	3	100	n.d.
14	Cu_2O	Cs_2CO_3	DMSO	3	100	n.d.
15	$CuBr_2$	Cs_2CO_3	DMSO	3	100	n.d.
16	$CuCl_2{\cdot}2H_2O$	Cs_2CO_3	DMSO	3	100	n.d.
17	$Cu(OAc)_2{\cdot}H_2O$	Cs_2CO_3	DMSO	3	100	n.d.

[a] *N*-(2-Iodophenyl)thiourea (0.5 mmol), iodobenzene (0.5 mmol), copper catalyst (2.5 mol %), and base (0.75 mmol) were stirred at 90 °C for an appropriate time in solvent (1 mL). [b] Determined by ^1H NMR. [c] Cs_2CO_3 (0.5 mmol) used. [d] Reaction temperature 80 °C. n.d. = not detected.

Table 2. 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), $CuSO_4{\cdot}5H_2O$ (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 ^1H 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.

substituents are compatible with this protocol to provide the rearranged cross-coupled 2-thioarylcyanamides in high yield.

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 $CuSO_4{\cdot}5H_2O$, CuI, CuBr, Cu_2O, $CuBr_2$, $CuCl_2{\cdot}2H_2O$, and $Cu(OAc)_2{\cdot}H_2O$ 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, solvents such as toluene, 1,4-dioxane, CH_3CN, and 2-propanol, and base, K_3PO_4, were less effective providing either aminobenzothiazole[9] **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 occurred.

The reactions of the aryl halides were next screened using $CuSO_4{\cdot}5H_2O$ as a catalyst. Iodobenzene proceeded cross-coupling with *N*-(2-iodophenyl)thiourea to give 2-(phenylthio)phenylcyanamide **A** in 100% conversion. In contrast, bromobenzene and chlorobenzene exhibited moderate reactivity yielding either a mixture of **A** and **B** or **B** as the product(s) (Table 2). In contrast, *N*-(2-bromo-) and *N*-(2-chlorophenyl)thioureas proceeded reactions with iodobenzene to afford **A** in <20% yield along with 2-halophenylcyanamide.

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-di-Me, 2,5-di-Me, 2,6-di-Me, 3,4-di-Me, and 3,5-di-Me substituents and 1-naphthyl iodide proceeded reactions with *N*-(2-iodo-4-methylphenyl)thiourea to give the corresponding 2-(arylthio)arylcyanamide in 83−98% yield (Table

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(3) For some studies on cyanamide synthesis, see: (a) Kaupp, G.; Schmeyers, J.; Boy, J. *Chem.—Eur. J.* **1998**, *4*, 2467–2474. (b) Sato, R.; Itoh, K.; Itoh, K.; Nishina, H.; Goto, T.; Saito, M. *Chem. Lett.* **1984**, 1913–1916. (c) Bakunov, S. A.; Rukavishnikov, A. V.; Tkachev, A. V. *Synthesis* **2000**, 1148–1159. (d) Chen, C.-Y.; Wong, F. F.; Huang, J. J.; Lin, S.-K.; Yeh, M.-Y. *Tetrahedron Lett.* **2008**, *49*, 6505–6507. (e) Chaudhuri, K. H.; Mahajan, U. S.; Bhalerao, D. S.; Akamanchi, K. G. *Synlett* **2007**, 2815–2818.

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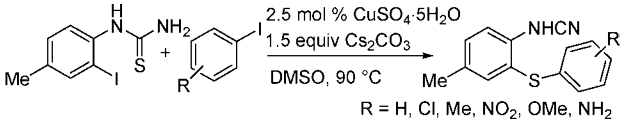
Table 3. Reactions of *N*-(2-Iodo-4-methylphenyl)thiourea with Different Substituted Aryl Iodides[a]



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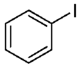
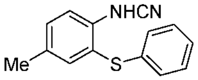
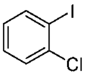
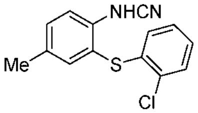
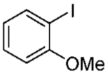
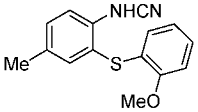
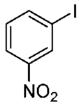
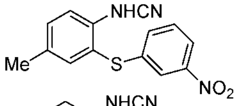
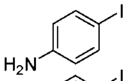
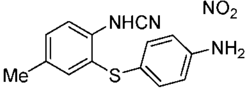
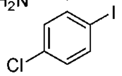
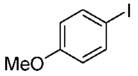
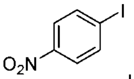
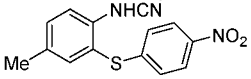
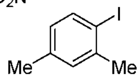
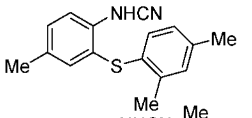
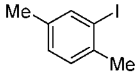
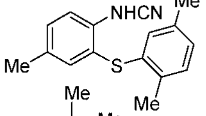
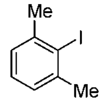
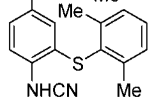
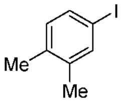
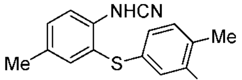
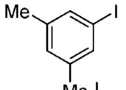
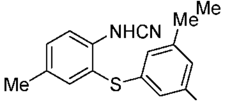
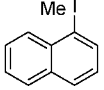
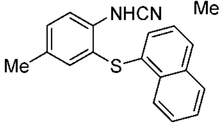
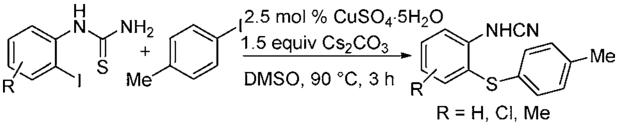
1		5		97
2		5		96
3		7		83
4		8		90
5		5		95
6		5		98
7		8		88
8		5		95
9		5		89
10		5		89
11		5		87
12		5		94
13		7		98
14		7		90

[a] *N*-(2-Iodo-4-methylphenyl)thiourea (0.5 mmol), aryl iodide (0.5 mmol), $CuSO_4 \cdot 5H_2O$ (2.5 mol %), and Cs_2CO_3 (0.75 mmol) were stirred at 90 °C in DMSO (1 mL).

Table 4. Reactions of Different Substituted Thioureas with 1-Iodo-4-methylbenzene[a]



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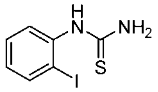
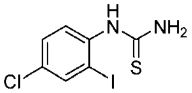
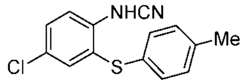
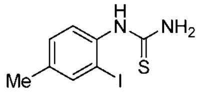
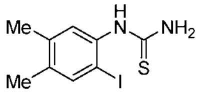
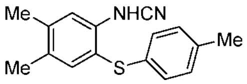
1			95
2			95
3			91
4			90

[a] *N*-(2-Iodoaryl)thiourea (0.5 mmol), 1-iodo-4-methylbenzene (0.5 mmol), $CuSO_4 \cdot 5H_2O$ (2.5 mol %), and Cs_2CO_3 (0.75 mmol) were stirred at 90 °C for 3 h in DMSO (1 mL).

3). Similarly, *N*-(2-iodophenyl)thiourea having 4-Cl, 4-Me, and 4,5-di-Me substituents underwent reactions with 1-iodo-4-methylbenzene in 90−95% yield (Table 4). 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-dimethylphenyl-thio)-4-methylphenylcyanamide in MeOH provided single crystals whose X-ray structure is given in Figure 1 (Table 3, entry 10).[10]

These reactions involve a homogeneous process, and the proposed catalytic cycle is shown in Scheme 1. Reduction of the copper(II) salt with thiourea[11] can give copper(I) species which can undergo oxidative addition with *N*-(2-iodoaryl)thiourea to yield copper(III) intermediate ***a***. The

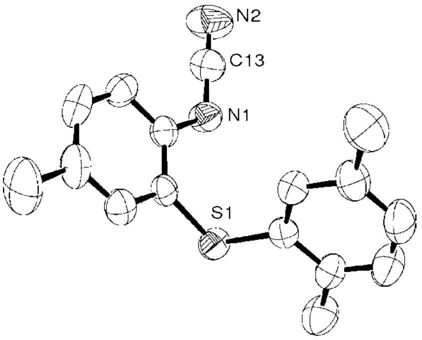
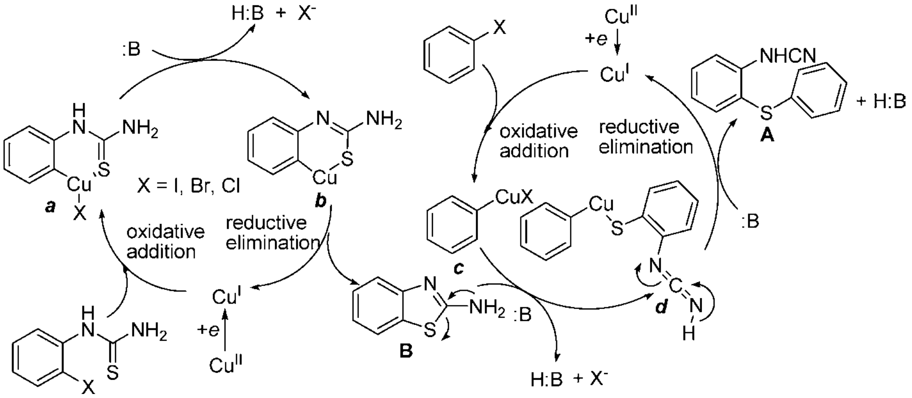


Figure 1. ORTEP diagram of 2-(2,5-dimethylphenylthio)-4-methylphenylcyanamide (Table 3, entry 10) with 50% ellipsoid. H-atoms are omitted for clarity.[10]

Scheme 1. Proposed Catalytic Cycle



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 $CuSO_4{\cdot}5H_2O$ 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 $CuSO_4{\cdot}5H_2O$ 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, we have developed a method for the synthesis of 2-(arylthio)arylcyanamides from substituted *N*-(2-haloaryl)thioureas with aryl iodides by domino intra- and intermolecular C−S cross-coupling reactions. The catalyst is cheap and air stable and functions under ligand-free conditions.

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Supporting Information Available: Materials and methods, experimental procedure, characterization data, and NMR spectra (^{1}H and ^{13}C) of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Recrystallization of 2-(2,5-dimethyl-phenylthio)-4-methyl-phenyl-cyanamide in MeOH afforded single crystals whose X-ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo Kα radiation in the scan range 1.20°−28.31°. $C_{16}H_{16}N_2S$, Mw = 268.38, orthorhombic; space group *P*na2(1), a = 22.1067(10), b = 8.7972(4), c = 7.6712(3) Å; $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, V = 1491.87(11) Å^3, Z = 4, D_{calcd} = 1.195 mg/m^3, T = 296(2) K, crystal dimension 0.40 × 0.35 × 0.20 mm^3; 19 186 reflections; ($I > 2\sigma(I)$); R_1 = 0.0396, wR_2 = 0.0654, GOF (on F^2) = 1.005.

(11) 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*, 350–368.