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Efficient copper-catalyzed C–S cross-coupling of heterocyclic thiols with aryl iodides

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ABSTRACT

A copper-catalyzed cross-coupling of heterocyclic thiols with aryl iodides is reported. The reaction was carried out in the presence of CuI (5 mol %), 1,10-phenanthroline (10 mol %) and K_2CO_3 (1.3 equiv) in DMF at 120 °C. A variety of heterocyclic sulfides were prepared in high selectivities and yields.

1. Introduction

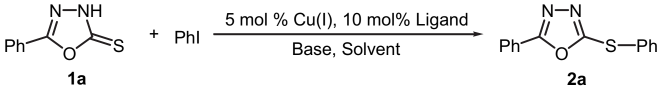
The formation of C(aryl)–S bonds represents a key step in the synthesis of many molecules that are of biological, pharmaceutical, and material interest.[1] In the past decade, many catalytic systems of transition-metal (palladium,[2] nickel,[3] copper,[4] cobalt,[5] iron,[6] and indium[7]) with appropriate ligands have been developed to catalyze the cross-coupling reactions of aryl halides with thiols and enable the synthesis of aryl sulfides in high yields.

Heterocyclic sulfides are an important class of organic compounds, which exhibit numerous pharmaceutical activities. In contrast to aryl sulfides, methods for the synthesis of heterocyclic sulfides including azole moiety are very limited. Alemagna et al.[8] reported that 2-phenylthio-5-phenyl-1,3,4-thiadiazole could be prepared by nucleophilic substituted reaction of benzenethiol with 2-aryl-5-chloro-1,3,4-thiadiazole. In 1997, Alam and Koldobskii[9] found that 2-alkyl(aryl)thio-5-aryl-1,3,4-oxadiazoles were successfully achieved by treatment of 5-alkyl(aryl)thiotetrazoles with of benzoic anhydride. Recently, Wunderlich and Knochel[10] discovered that 2-phenyl-5-(phenylthio)-1,3,4-oxadiazole was obtained in 75% yield by quenching di(5-phenyl-1,3,4-oxadiazol-2-yl)zinc with $PhSSO_2Ph$ in the presence of catalytic amount of CuCN·2LiCl. Accordingly, development of alterative inexpensive, non-air sensitive catalytic systems for heterocyclic sulfides is highly desirable. Herein, we present our preliminary results of a copper-catalyzed coupling reaction between heterocyclic thiols and aryl iodides.

2. Results and discussion

A preliminary survey of reaction conditions was conducted with 5-phenyl-1,3,4-oxadiazl-2-thione (**1a**) and iodobenzene as a model reaction. In the first instance, the impact of catalyst was tested. As shown in Table 1, in the absence of copper(I) sources, no C(aryl)–S

Table 1
Screening of the reaction conditions[a]



Entry	Catalyst	Solvent	Base	Ligand	Yield (%)[b]
1	—	DMF	K_2CO_3 (1.3 equiv)	1,10-phenanthroline	n.r.
2	CuI	DMF	K_2CO_3 (1.3 equiv)	—	59
3	CuCl	DMF	K_2CO_3 (1.3 equiv)	1,10-phenanthroline	81
4	Cu_2O	DMF	K_2CO_3 (1.3 equiv)	1,10-phenanthroline	93
5	CuI	DMF	K_2CO_3 (1.3 equiv)	1,10-phenanthroline	98
6	CuI	DMF	K_2CO_3 (1.3 equiv)	ethane-1,2-diol	50
7	CuI	DMF	K_2CO_3 (1.3 equiv)	L-proline	70
8	CuI	DMF	K_2CO_3 (1.3 equiv)	4-OH-L-proline	76
9	CuI	DMF	Cs_2CO_3 (1.3 equiv)	1,10-phenanthroline	83
10	CuI	DMF	K_3PO_4 (1.3 equiv)	1,10-phenanthroline	86
11	CuI	DMF	K_2CO_3 (1.1 equiv)	1,10-phenanthroline	94
12	CuI	DMF	K_2CO_3 (1.5 equiv)	1,10-phenanthroline	94
13	CuI	DMSO	K_2CO_3 (1.3 equiv)	1,10-phenanthroline	59
14	CuI	Xylene	K_2CO_3 (1.3 equiv)	1,10-phenanthroline	31

[a] Reaction conditions: **1a**/PhI=1:1.2 (molar ratio); reaction temperature: 120 °C; reaction time: 10 h.
[b] Isolated yield.

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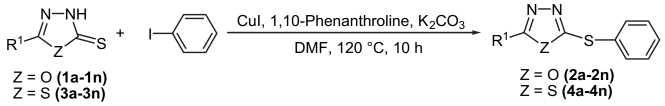
Table 2
Coupling of iodobenzene with 1,3,4-oxadiazol-2-thiones or 1,3,4-thiadiazol-2-thiones[a]



Entry	R^1	Z	Products	Yield (%)[b]	Entry	R^1	Z	Products	Yield (%)[b]
1	C_6H_5	O	**2a**	98	15	C_6H_5	S	**4a**	95
2	2-$CH_3C_6H_4$	O	**2b**	91	16	2-$CH_3C_6H_4$	S	**4b**	95
3	3-$CH_3C_6H_4$	O	**2c**	90	17	3-$CH_3C_6H_4$	S	**4c**	98
4	4-$CH_3C_6H_4$	O	**2d**	90	18	4-$CH_3C_6H_4$	S	**4d**	97
5	4-$MeOC_6H_4$	O	**2e**	95	19	4-$CH_3OC_6H_4$	S	**4e**	95
6	3-FC_6H_4	O	**2f**	88	20	3-FC_6H_4	S	**4f**	90
7	4-FC_6H_4	O	**2g**	86	21	4-FC_6H_4	S	**4g**	94
8	3-ClC_6H_4	O	**2h**	75	22	3-ClC_6H_4	S	**4h**	97
9	4-ClC_6H_4	O	**2i**	77	23	4-ClC_6H_4	S	**4i**	95
10	4-BrC_6H_4	O	**2j**	73	24	4-BrC_6H_4	S	**4j**	80
11	1-$C_{10}H_7$	O	**2k**	76	25	1-$C_{10}H_7$	S	**4k**	91
12	4-Py	O	**2l**	61	26	4-Py	S	**4l**	83
13	CH_3	O	**2m**	97	27	CH_3	S	**4m**	98
14	$CH_3(CH_2)_4$	O	**2n**	97	28	$CH_3(CH_2)_4$	S	**4n**	98

[a] Reaction condition: CuI/1,10-phenanthroline/K_2CO_3/PhI/**1** or **3**=0.05:0.1:1.3:1.2:1 (molar ratio).

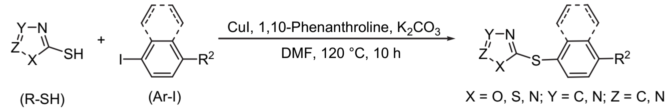
[b] Isolated yield.

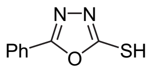
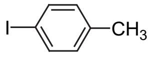
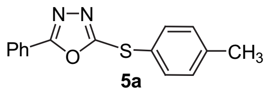
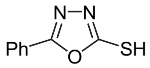
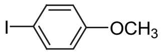
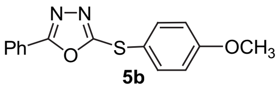
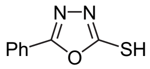
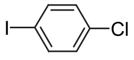
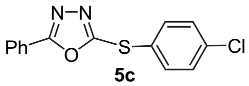
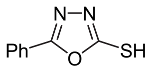
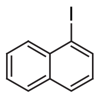
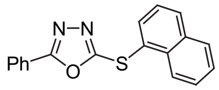
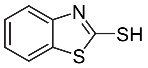
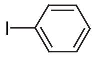
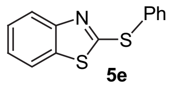
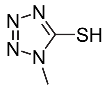
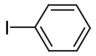
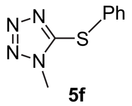
bond coupling product 2-phenyl-5-(phenylthio)-1,3,4-oxadiazole (**2a**) was obtained (entry 1). The heterocyclic sulfide **2a** was obtained in low yield in the absence of ligand (entry 2). Though CuCl, CuI, and Cu_2O were efficient catalysts (entries 3–5), we chose to focus on the use of CuI due to its stability to air. Among the ligands tested, amino acids and diol showed a poor ability to promote this reaction and low yields were observed (entries 6–8). The system of CuI and 1,10-phenanthroline was the most effective and gave heterocyclic sulfide **2a** in 98% yield when heating a mixture of iodobenzene, 5-phenyl-1,3,4-oxadiazole-2-thione, K_2CO_3, CuI, and 1,10-phenanthroline in DMF at 120 °C for 10 h (entry 5). After screening the kind and amount of bases, we found that K_2CO_3 gave excellent yield, whereas Cs_2CO_3 and K_3PO_4 were effective to some extent (entries 5, 9–12). In addition, we investigated the coupling reaction in different solvents, DMF was found to be the best (entries 5, 13 and 14). Thus, the optimized reaction conditions turned out to be using CuI (5 mol %), K_2CO_3 (1.3 equiv), and 1,10-phenanthroline (10 mol %) in reagent-grade DMF at 120 °C for 10 h.

With the optimized conditions defined, we started to investigate the scope of the coupling reaction. The results are summarized in Table 2. As could be seen, in general, the process was highly tolerant for a variety of common functional groups and the heterocyclic sulfides **2a**–**n** were formed in 61–98% yields. For 1,3,4-oxadiazol-2-thiones, electron-withdrawing groups in the *para* and *meta* position led to moderate yields (entries 6–10). When 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione was used as substrate, product **2l** was obtained in 61% yield (entry 12). For 1,3,4-thiadiazol-2-thiones, electron-rich and electron-poor thiones were tolerated and the yields of coupling products **4a**–**n** (entries 15–28) are higher than 1,3,4-oxadizol-2-thiones counterparts did.

To continue exploring the scope of the reaction, various aryl iodides were also reacted with 5-phenyl-1,3,4-oxadiazol-2-thione (Table 3). Aryl iodides bearing electron-donating substituents gave lower yields (Table 1, entry 5; Table 3, entries 1–2). Under the same conditions, benzo[*d*]thiazole-2-thiol, 1-methyl-1*H*-tetrazole-5-thiol and 4,6-dimethylpyrimidine-2-thiol reacted similarly and the products **5e**–**f** were obtained in excellent yields (entries 5 and 6). The reaction of 4,5-diphenyl-4*H*-1,2,4-triazole-3-thione with iodobenzene exhibited a moderate yield (entry 7).

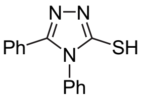
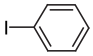
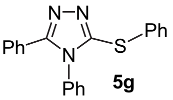
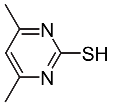
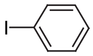
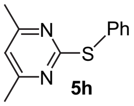
Table 3
CuI-catalyzed carbon-sulfur bond formation of heterocyclic thiols with aryl iodides[a]



Entry	R–SH	Ar–I	Product	Yield (%)[b]
1			 **5a**	95
2			 **5b**	86
3			 **5c**	91
4			 **5d**	85
5			 **5e**	98
6			 **5f**	98

(*continued on next page*)

Table 3 (*continued*)

Entry	R–SH	Ar–I	Product	Yield (%)[b]
7			 **5g**	77
8			 **5h**	85

[a] Reaction condition: CuI/1,10-phenanthroline/K_2CO_3/Ar–I/R–SH=0.05:0.1:1.3:1.2:1 (molar ratio).

[b] Isolated yield.

Because compounds **1a**–**n** and **3a**–**n** existed preferably in thiones rather than in thiols forms, and both sulfur and nitrogen atoms could proceed arylation reaction. By analyzing the mass spectrum of compound **2d**, base peak at *m*/*z* 159 corresponding to $[M-SC_6H_5]^+$ confirming that S-arylation product was formed under this reaction. In addition, the structure of the coupling product **4a** was proven to be an S-arylation product by single-crystal X-ray diffraction analysis (Fig. 1).[11] Other products were assigned by analogy.

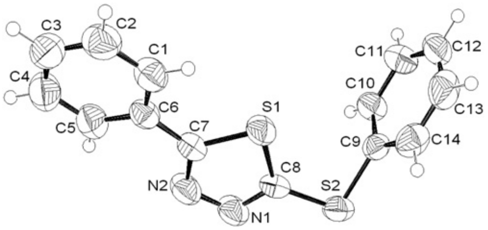


Fig. 1. X-ray crystallography structure of compound **4a**.

3. Conclusions

In summary, we have developed an efficient copper(I)-catalyzed cross-coupling reaction of heterocyclic thiols with aryl iodides. Noteworthy, the coupling products heterocyclic sulfides could be obtained in high selectivities and yields. Thus, our protocol is a convenient, and efficient alternative.

4. Experimental

4.1. General

Melting points were determined using an XT-4 melting point apparatus and were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-400 MHz or Bruker AM-400 spectrometer with TMS as an internal standard. IR spectra were obtained on Nicolet NEXUS 670 FT-IR instrument. Elemental analyses were performed on Elementar vario EL. HRMS data were performed on Bruker Apex II mass instrument (ESI). Mass spectra were performed on Thermo DSQ mass instrument (EI at 70 eV). Copper(I) iodide, 1,10-phenanthroline and *N*,*N*-dimethylformamide were commercially available and used without further purification.

4,5-Diphenyl-1,2,4-triazol-3-thione was prepared according to literature method.[12]

4.2. General procedure for copper-catalyzed cross-coupling of heterocyclic thiols with aryl iodides

To a solution of CuI (0.025 mmol, 4.8 mg), 1,10-phenanthroline (0.05 mmol, 9 mg), and K_2CO_3 (0.65 mmol, 90 mg) in DMF (1.5 mL) was added aryl iodides (0.6 mmol) followed by heterocyclic thiols (0.5 mmol) in DMF (1.5 mL). The reaction mixture was then stirred at 120 °C for 10 h. The mixture was allowed to cool to room temperature. Ethyl acetate (10 mL) and H_2O (10 mL) were added, and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (10 mL×3). The combined organic phases were washed with saturated brine, dried over anhydrous Na_2SO_4. The organic solvent was removed in vacuo, and the residue was purified by chromatography on silica gel to afford the desired products.[13]

*4.2.1. 2-Phenyl-5-(phenylthio)-1,3,4-oxadiazole (**2a**).* 126 mg (yield: 98%). White solid. Mp 59.5–60 °C (lit.[2] 62.4–63.1 °C). ^1H NMR (300 MHz, $CDCl_3$): δ=7.98–7.94 (m, 2H, ArH), 7.69–7.66 (m, 2H, ArH), 7.51–7.42 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.24, 162.79, 133.51, 131.74, 129.72, 128.92, 126.96, 126.65, 123.38. IR (KBr): 3064, 1550, 1468, 1440, 1166, 1068, 751, 691 cm^{-1}. EI–MS (*m*/*z*): 254 (M^+, 48), 145 (100), 109 (16), 77 (79).

Acknowledgements

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.02.064. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046; (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805; (c) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359; (d) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337; (e) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651.
2. (a) Dickens, M. J.; Gilday, J. P.; Mowlem, T. J.; Widdowson, D. A. *Tetrahedron* **1991**, *47*, 8621; (b) Ishiyama, T.; Mori, M.; Suzuki, A.; Miyaura, N. *J. Organomet. Chem.* **1996**, *525*, 225; (c) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D.; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606; (d) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205; (e) Schopfer, U.; Schlapbach, A. *Tetrahedron* **2001**, *57*, 3069; (f) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513; (g) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677; (h) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397; (i) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587; (j) Mispelaere-Canivet, C.; Spindler, J. F.; Perrio, S.; Beslin, P. *Tetrahedron* **2005**, *61*, 5253; (k) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *Chem.—Eur. J.* **2006**, *12*, 7782; (l) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180; (m) Barbiéri, R. S.; Bellato, C. R.; Dias, A. K. C.; Massabni, A. C. *Catal. Lett.* **2006**, *109*, 171.
3. (a) Zhang, Y.; Ngeow, K. N.; Ying, J. Y. *Org. Lett.* **2007**, *9*, 3495; (b) Saxena, A.; Kumar, A.; Mozumdar, S. *Appl. Catal., A* **2007**, *317*, 210; (c) Jammi, S.; Barua, P.; Rout, L.; Saha, P.; Punniyamurthy, T. *Tetrahedron Lett.* **2008**, *49*, 1484.
4. (a) Palomo, C.; Oiarbide, M.; Lopez, R.; Gomez-Bengoa, E. *Tetrahedron Lett.* **2000**, *41*, 1283; (b) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019; (c) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517; (d) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803; (e) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309; (f) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400; (g) Deng, W.; Zou, Y.; Wang, Y. F.; Liu, L.; Guo, Q. X.

Synlett **2004**, 1254; (h) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005; (i) Zeni, G. *Tetrahedron Lett.* **2005**, *46*, 2647; (j) Chen, Y. J.; Chen, H. H. *Org. Lett.* **2006**, *8*, 5609; (k) Zhu, D.; Xu, L.; Wu, F.; Wan, B. *Tetrahedron Lett.* **2006**, *47*, 5781; (l) Verma, A. K.; Singh, J.; Chaudhary, R. *Tetrahedron Lett.* **2007**, *48*, 7199; (m) Rout, L.; Sen, T. K.; Punniyamurty, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5583; (n) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863; (o) Sperotto, E.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *J. Org. Chem.* **2008**, *73*, 5625; (p) Xu, H. J.; Zhao, X. Y.; Deng, J.; Fu, Y.; Feng, Y. S. *Tetrahedron Lett.* **2009**, *50*, 434; (q) Murru, S.; Ghosh, H.; Sahoo, S. K.; Patel, B. K. *Org. Lett.* **2009**, *11*, 4254; (r) Feng, Y.; Zhao, X.; Wang, J.; Zheng, F.; Xu, H. *Chin. J. Chem.* **2009**, *27*, 2423; (s) Jogdand, N. R.; Shingate, B. B.; Shingare, M. S. *Tetrahedron Lett.* **2009**, *50*, 6092; (t) Feng, Y.; Wang, H.; Sun, F.; Li, Y.; Fu, X. ,; Jin, K. *Tetrahedron* **2009**, *65*, 9737; (u) Prasad, D. J. C.; Naidu, A. B.; Sekar, G. *Tetrahedron Lett.* **2009**, *50*, 1411; (v) Larsson, P.-F.; Correa, A.; Carril, M.; Norrby, P.-O.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5691; (w) Chen, C.-K.; Chen, Y.-W.; Lin, C.-H.; Lin, H.-P.; Lee, C.-F. *Chem. Commun.* **2010**, 282; (x) Ramana, T.; Saha, P.; Das, M.; Punniyamurthy, T. *Org. Lett.* **2010**, *12*, 84; (y) Kabir, M. S.; Lorenz, M.; Van Linn, M. L.; Namjoshi, O. A.; Ara, S.; Cook, J. M. *J. Org. Chem.* **2010**, *75*, 3626; (z) Feng, Y.-S.; Li, Y.-Y.; Tang, L.; Wu, W.; Xu, H.-J. *Tetrahedron Lett.* **2010**, *51*, 2489.

5. Wong, Y. C.; Jayanth, T. T.; Cheng, C. H. *Org. Lett.* **2006**, *8*, 5613.
6. (a) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880; (b) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108.
7. (a) Reddy, V. P.; Swapna, K.; Kumar, A. V.; Rao, K. R. *J. Org. Chem.* **2009**, *74*, 3189; (b) Reddy, V. P.; Kumar, A. V.; Swapna, K.; Rao, K. R. *Org. Lett.* **2009**, *11*, 1697.
8. Alemagna, A.; Bacchetti, T.; Beltrame, P. *Tetrahedron* **1968**, *24*, 3209.
9. Alam, L. M.; Koldobskii, G. I. *Russ. J. Org. Chem.* **1997**, *33*, 1149.
10. Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7685.
11. The CCDC number is 796990. The data were collected on a Kappa CCD diffractometer equipped with a graphite mono- chromated Mo Kα (λ=0.71073 Å) radiation by using Envaf Nonius 591 Kappa CCD single crystal diffraction ($1.49<\theta<27.71°$) at 296 K. Orthorhombic crystals; $C_{14}H_{10}N_2S_2$; unit cell parameters: a=5.8604 (11), b=8.1663(15), c=27.369(5) Å, α=90.00°, β=90.00°, γ=90.00°, Z=4, V=1309.8 (4) Å^3, space group $P2_12_12_1$, D_x=1.371 Mg m^{-3}, μ (Mo Kα)=0.388 mm^{-1}, F(000)=560. The structure was refined to the final R=0.0437 and wR=0.1059 for 8008 independent reflections (Rint=0.0286) and 3021 observed reflections ($I>2\sigma(I)$).
12. Nigam, S. C.; Saharia, G. S.; Sharma, H. R. *J. Indian Chem. Soc.* **1983**, *60*, 583.
13. All new compounds give satisfied analytical and spectral data, which is available via the Internet at http://www.sciencedirect.com/.