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Copper-catalyzed direct thiolation of benzoxazole with diaryl disulfides and aryl thiols

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ABSTRACT

The cross-coupling reaction of benzoxazole with aryl thiols using the CuI/2,2′-bipyridine complex as a catalyst in DMF at 80 °C under oxygen produced the corresponding aryl thioethers in moderate to good yields. The coupling reaction with diaryl disulfide also occurred under similar oxidative conditions.

Metal-catalyzed cross-coupling reactions have become a principal method of forming carbon–carbon and carbon–heteroatom bonds. Among this class of reactions, a process that forms aromatic thioethers from aryl halides and thiols has been of current interest and intensively studied.[1] This reaction provides unsymmetrical aryl thioethers, which are not only valuable synthetic intermediates, but are also frequently found in biologically and pharmaceutically active molecules. Palladium,[2] nickel,[3] copper,[4] iron,[5] and cobalt[6] complexes smoothly catalyzed the cross-coupling reactions of aryl halides with thiols to provide aryl thioethers with a variety of functional groups. Aryl triflates[7] and boric acids[8] are sometimes used as good counterparts instead of aryl halides. An alternative method for the access of aryl thioethers is the coupling reaction of aryl halides with diaryl disulfides.[9] Contrary to the intensive studies on the coupling reaction with an aryl thiol, only a few examples have been reported.

The direct arylation of the C–H bonds of heterocycles, that is, the functionalization of aromatic heterocycles, is of current interest because it represents a possible alternative approach to conventional cross-coupling reactions with organometallic reagents and would not require reactive functional groups such as halogens or metal moieties.[10] The analogous reaction forming the carbon–sulfur bond without aryl halides should be desirable from the viewpoint of atom economy and the waste treatment of hydrogen halides. We have designed the direct thiolation of a heteroaromatic compound with an aryl thiol and found that the copper/2,2′-bipydine complex catalyzed the reaction of benzoxazole with benzene thiol under oxygen to give the 2-benzoxazole thioether in moderated to good yields; some 2-azole thioethers are biologically active compounds.[11] To the best of our knowledge, this is the first direct thiolation of heteroaromatic compounds. We now report the preliminary results of the direct thiolation with benzoxazole.

Due to the oxidative reaction conditions, aryl thiols could be oxidized to the corresponding diaryl disulfides that should be an actual counter part. We started with the coupling reaction of benzoxazole (**1a**) with diphenyl disulfide (**2a**) to assess the catalyst activity and determine the optimum reaction conditions. The coupling reactions were conducted with DMF as the solvent, Cs_2CO_3 as the base and a copper salt/2,2′-bipyridine as the catalyst (10 mol %) under oxygen (1 atm).[12] The products and yields are analyzed by GC/MS. These results are shown in Table 1. The use of any Cu(I) and Cu(II) salts to give the desired 2-(phenylthio)benzoxazole (**3aa**) in moderate to good yields under oxygen without the formation of appreciable amounts of side products; CuI gave the highest product yield (entry 2). The reaction was completed in 2 h at 80 °C and part of the product was decomposed in an extended reaction time (24 h) and/or at higher temperature (140 °C). The addition of 2,2′-bipyridine as the ligand was required for a satisfactory yield (entry 3).[13] The other bases, such as Na_2CO_3 and K_2CO_3, were not effective as trace reaction products were produced. DMF was the best choice of solvent; the yields of the products were 14% (MeCN), 7% (NMP), and 5% (DMSO). The reaction under oxygen was critical for the reaction while the reaction under nitrogen (in the absence of oxygen) produced a low yield (14%) of the product (entry 5).[14]

We then examined the scope with respect to the diaryl disulfides under the optimized conditions; CuI as the copper salt, DMF as the solvent, at 80 °C for 2 h under oxygen. Typical results are shown in Table 2. The diaryl disulfides **2b–c** with an electron-donating substituent, such as *p*-methoxy and *p*-methyl, afforded the corresponding thioethers **3ab–3ac** in moderate to good yields (entries 2 and 3), and for the *o*-methyl substrate, the thioether **3ad** was obtained in a low yield probably due to steric hindrance (entry 4). The cross-coupling reaction with di(*p*-chlorophenyl) disulfide (**2e**) occurred only at thio group to give the thioether **3ae** in a moderate yield accompanied by the partial decomposition of the disulfide (ca 5%) (entry 5). The coupling product at the chloro position was hardly observed. The electron-deficient diaryl

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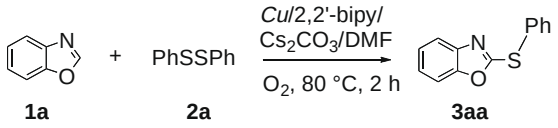
Table 1
The Cu-catalyzed direct thiolation of benzoxazole **1a** with diphenyl disulfide **2a**[a]



1a **2a** **3aa**

Entry	Cu salts	Yield of **3aa**[b] (%)
1	—	0
2	CuI	81
3[c]	CuI	22
4[d]	CuI	0
5[e]	CuI	14
6	CuBr	74
7	CuCl	51
8	CuCN	80
9	$CuBr_2$	78

[a] **1a** (0.6 mmol), **2a** (0.25 mmol), Cu salt (0.05 mmol), 2,2′-bipyridine (0.05 mmol), Cs_2CO_3 (1.0 mmol), DMF (3 mL); 80 °C, 2 h, 1 atm O_2.
[b] Determined by GC.
[c] Without 2,2′-bipyridine.
[d] No base added.
[e] Under N_2.

disulfides, such as **2f** (Ar = *p*-$NO_2C_6H_4$) and **2g** (Ar = 2-pyridyl), hardly produced the corresponding thioethers (entries 6 and 7).

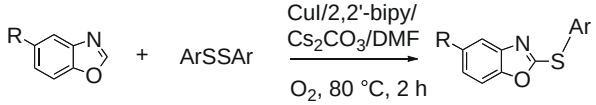
The reaction with the 5-substituted benzoxazole was examined, and the results are also shown in Table 2 (entries 8 and 9). The reaction of diphenyl disulfide **2a** with the 5-methyl substituted derivative **1b** gave the corresponding thioether **3ba** in a moderate yield. For the reaction with the 5-chloro substituted derivatives **1c**, 2-phenylthio **3ca** and 2,5-dithioether were observed by GC/MS analysis; **3ca** could be isolated by preparative TLC in a 33% yield. In this case, the reaction at the 5-chloro position should be involved. The reaction with other azoles, such as oxazole, thiazole, 1-methyl-1*H*-imidazole, benzothiazole, and 1-methyl-1*H*-benzoimidazole, were examined, and only the benzothiazole gave the corresponding 2-phenylthiobenzothiazole in 17% yield.

As more varieties of substituted aryl thiols are commercially available than diaryl disulfides, aryl thiols would be preferable as thiolating agents, although the actual species would be a diaryl disulfide. The direct thiolation was examined using an aryl thiol instead of diaryl disulfides. The reaction of **1a** with aryl thiols was carried out using a catalytic amount (10 mol %) of $CuBr_2$ and 2,2′-bipyridine, and Cs_2CO_3 as a base in DMF in the presence of MS4A at 80 °C for 2 h under oxygen. These results are summarized in Table 3. The reaction of **1a** with benzene thiol (**4a**) smoothly proceeded to give **3aa** in good yield (72%) (entry 1), while in the absence of MS4A, the product yield decreased to 42% (entry 2). MS4A probably worked as a dehydrating agent; in this reaction, water should be generated as a by-product. The thiols **4b–c** with an electron-donating substituent, such as *p*-methoxy and *p*-methyl, afforded the corresponding thioether **3ab–ac** in moderate to good yields (entries 3 and 4). For the *o*-methylphenyl thiol **4d**, the thioether 3**ad** was obtained in a moderate yield (55%) although the di(*o*-methylphenyl) disulfide **2d** gave **3ad** in a lower yield (34%) (entry 5). For the *p*-chlorophenyl thiol **4e**, the coupling product was the only thioether **3ae** without producing any C–C coupling product as well as the disulfide **2e** (entry 6). 2-Naphthalene thiol **4h** could react with **1a**, but the yield of the product **3ah** was low (entry 7).

To discuss the reaction mechanism, we conducted the following experiment. When we carried out the reaction of **1a** with phenylthiocopper (PhSCu) in the presence of 2,2′-bipyridine (1 equiv to PhSCu) and Cs_2CO_3 (2 equiv) in DMF at 80 °C for 2 h under oxygen (1 atm), the corresponding thioether **3aa** was obtained in 38% yield. On the other hand, for the reaction under nitrogen (excluding oxygen), no thioether was obtained. These results suggest that the formation and oxidation of PhSCu should be involved in the reaction. Based on this fact, we assumed the following catalytic cycle illustrated in Scheme 1.[15] The initial step of the reaction involves the deprotonation of benzoxazole (Ar-H) at the C-2 position by Cs_2CO_3 followed by cupration via transmetallation. In the next step, the Ar*Cu* species reacted with diphenyl disulfide to afford the thioether and PhS*Cu*(I). PhS*Cu*(I) is oxidized to the Cu(II) species which reacts with Ar-H to produce the Ar*Cu*SPh intermediate. The reductive elimination of the thioether from the Cu(II) complex afforded the *Cu*(0) which is oxidized to *Cu*X with oxygen and a halogen ion.[16]

In conclusion, we have succeeded for the first time in the copper-catalyzed direct thiolation of benzoxazole using diaryl disulfides or aryl thiols, and 2-benzoxazole thioethers were obtained in moderate to good yields. The sulfide with an electron-donating substituent afforded products in good yields, while the sulfides with an electron-deficient group hardly gave the desired product.

Table 2
Scope of the thiolation of benzoxazoles with diaryl disulfides[a]

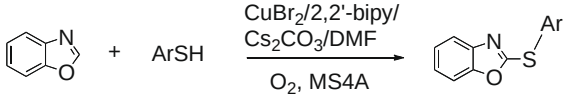


1a-c **2a-g** **3aa-ag** **3ba-3ca**

Entry	R	Ar	Yield[b] (%)
1	R = H, **1a**	Ph, **2a**	**3aa**, 81
2	R = H, **1a**	*p*-$MeOC_6H_4$, **2b**	**3ab**, 71
3	R = H, **1a**	*p*-MeC_6H_4, **2c**	**3ac**, 64
4	R = H, **1a**	*o*-MeC_6H_4, **2d**	**3ad**, 34
5	R = H, **1a**	*p*-ClC_6H_4, **2e**	**3ae**, 54[c]
6	R = H, **1a**	*p*-$NO_2C_6H_4$, **2f**	**3af**, 0[c]
7	R = H, **1a**	2-pyridyl, **2g**	**3ag**, 0
8	R = Me, **1b**	Ph, **2a**	**3ba**, 49
9	R = Cl, **1c**	Ph, **2a**	**3ca**, 33

[a] **1a** (0.6 mmol), **2a** (0.25 mmol), CuI (0.05 mmol), 2,2′-bipyridine (0.05 mmol), Cs_2CO_3 (1.0 mmol), DMF (3 mL); 80 °C, 2 h, 1 atm O_2.
[b] Isolated yield.
[c] Mono sulfide was formed as a by-product.

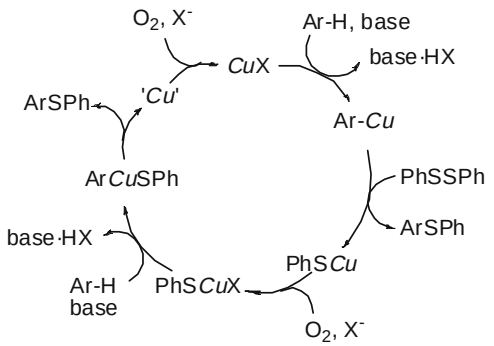
Table 3
Direct thiolation of benzoxazole with aryl thiols[a]



1a **4a-e, 4h** **3aa-ae, 3ah**

Entry	Ar	Yield[b] (%)
1	Ph, **4a**	**3aa**, 72
2[c]	Ph, **4a**	**3aa**, 42
3	*p*-$MeOC_6H_4$, **4b**	**3ab**, 51
4	*p*-MeC_6H_4, **4c**	**3ac**, 62
5	*o*-MeC_6H_4, **4d**	**3ad**, 55
6	*p*-ClC_6H_4, **4e**	**3ae**, 38
7	2-naphtyl, **4h**	**3ah**, 18

[a] **1a** (0.6 mmol), ArSH (0.5 mmol), $CuBr_2$ (0.05 mmol), 2,2′-bipyridine (0.05 mmol), Cs_2CO_3 (1.0 mmol), MS4A (100 mg), DMF (3 mL); 80 °C, 2 h, 1 atm O_2.
[b] Isolated yield.
[c] Without MS4A.



Scheme 1. Plausible catalytic cycle of the direct thiolation.

The scope and limitation of the substrate with respect to azoles have also been demonstrated.

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12. *Typical experimental procedure*: Under oxygen (balloon), **2a** (55 mg, 0.25 mmol), CuI (9.5 mg, 0.05 mmol), 2,2′-bipyridine (7.8 mg, 0.05 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) were placed in a Schlenk tube containing a stirring bar, and a DMF solution (3.0 mL) of **1a** (71.5 mg, 0.6 mmol) was then added to the Schlenk tube, and the resulting mixture was heated at 80 °C for 2 h. Twenty milliliters of water were then added, and the mixture was then extracted with ethyl acetate (10 mL × 3). The combined organic phases were washed with brine, dried over $MgSO_4$, and filtered. GC/MS analysis of the solution showed the presence of 2-(phenylthio)benzoxazole (**3aa**) and yield was determined using biphenyl as the internal standard. Evaporation of the solvent left a residue, which was subjected to PTLC (silica gel, 8:1 hexane:ethyl acetate as eluent) to give the pure **3aa**.
Compound **3aa**: Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21–7.30 (m, 2H), 7.40–7.47 (m, 4H), 7.59–7.62 (m, 1H), 7.69–7.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 110.0 (CH), 119.0 (CH), 124.2 (CH), 124.3 (CH), 127.1 (C) 129.6 (CH), 129.8 (CH), 134.4 (CH), 141.9 (C), 151.8 (C), 163.3 (C). ESI HRMS calcd for $C_{13}H_9NOS$ [M + H] 228.0483, found 228.0481. EI MS *m/z* = 227.
Compound **3ab**: Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.84 (s, 3H), 6.98 (d, 2H, *J* = 8.6 Hz), 7.18–7.28 (m, 2H), 7.36–7.41 (m, 1H), 7.57–7.59 (m, 1H), 7.62 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 55.4 (CH_3), 109.9 (CH), 115.2 (CH), 117.0 (C), 118.9 (CH), 124.0 (CH), 124.2 (CH), 136.7 (CH), 142.0 (C), 151.8 (C), 161.1 (C), 164.4 (C). ESI HRMS calcd for $C_{14}H_{11}NO_2S$ [M + H] 258.0589, found 258.0585. EI MS *m/z* = 257.
Compound **3ac**: Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (s, 3H), 7.20–7.26 (m, 2H), 7.27 (d, 2H, *J* = 8.0 Hz), 7.39–7.42 (m, 1H), 7.59 (d, 2H, *J* = 8.0 Hz), 7.60 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3), 110.0 (CH), 119.0 (CH), 123.3 (C), 124.1 (CH), 124.3 (CH), 130.5 (CH), 134.7 (CH), 140.4 (C), 142.0 (C), 151.9 (C), 164.0 (C). ESI HRMS calcd for $C_{14}H_{11}NOS$ [M + H] 242.0640, found 242.0672. EI MS *m/z* = 241.
Compound **3ad**: Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.48 (s, 3H), 7.20–7.41(m, 6H), 7.56–7.60 (m, 1H), 7.70 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_3), 110.0 (CH), 118.9 (CH), 124.0 (CH), 124.2 (CH), 126.2 (C), 127.0 (CH), 130.6 (CH), 131.1 (CH), 136.1 (CH), 142.0 (C), 142.5 (C), 151.8 (C), 163.2 (C). ESI HRMS calcd for $C_{14}H_{11}NOS$ [M + H] 242.0640, found 242.0642. EI MS *m/z* = 241.
Compound **3ae**: Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18–7.30 (m, 2H), 7.35–7.46 (m, 1H), 7.42 (d, 2H, *J* = 8.8 Hz), 7.56-7.60 (m, 1H), 7.63 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 110.0 (CH), 119.1 (CH), 124.4 (CH), 124.4 (CH), 125.5 (C), 129.9 (CH), 135.7 (CH), 136.4 (CH), 141.8 (C), 151.8 (C), 162.7 (C). ESI HRMS calcd for $C_{13}H_8NOSCl$ [M + H] 262.0093, found 262.0099. EI MS *m/z* = 261, 263.
Compound **3ah**: White solid. Mp = 79–81 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21–7.26 (m, 2H), 7.38–7.41 (m, 1H), 7.52–7.61 (m, 3H), 7.69–7.72 (m, 1H), 7.84–7.93 (m, 3H), 8.23 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 110.0 (CH), 119.1 (CH), 124.2 (C), 124.3 (CH), 124.4 (CH), 126.9 (CH), 127.5 (CH), 127.8 (CH), 128.0 (CH), 129.4 (CH), 130.7 (CH), 133.5 (C), 133.6 (C), 134.3 (CH), 142.0 (C), 151.9 (C), 163.3 (C). ESI HRMS calcd for $C_{17}H_{11}NOS$ [M + H] 278.0640, found 278.0492. EI MS *m/z* = 277.
Compound **3ba**: Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.26–7.99 (m, 1H), 7.39–7.47 (m, 4H), 7.67–7.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3), 109.4 (CH), 119.1 (CH), 125.3 (CH), 127.3 (C), 129.6 (CH) , 129.7 (CH), 134.2 (CH), 134.2 (C), 142.1 (C), 150.1 (C), 163.0 (C). ESI HRMS calcd for $C_{14}H_{11}NOS$ [M + H] 242.0640, found 242.0612. EI MS *m/z* = 241.
Compound **3ca**: White Solid. Mp = 73–75 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19–7.20 (m, 1H), 7.22 (d, 1H, *J* = 8.2 Hz), 7.45–7.50 (m, 3H), 7.56–7.58 (m, 1H), 7.69–7.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 110.6 (CH), 119.0 (CH), 124.4 (CH), 126.5 (C), 129.7 (CH), 129.9 (C), 130.1 (CH), 134.6 (CH), 143.1 (C), 150.4 (C), 165.2 (C). ESI HRMS calcd for $C_{13}H_8NOSCl$ [M + H] 262.0093, found 262.0076. EI MS *m/z* = 261, 263.
13. 1,10-Phenanthroline and TMEDA were not effective as ligands.
14. The reaction in air gave the unsatisfactory yield of the product.
15. Taniguchi, N. *Synlett* **2006**, 1351–1354.
16. In the reaction using $CuBr_2$ as a catalyst, Cu(II) can be reduced Cu(I) species by thiol: thiol is oxidized to disulfide. Higashi, L. S.; Lundeen, M.; Hilti, E.; Seff, K. *Inorg. Chem.* **1977**, *16*, 310–313.