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Cu-Mediated C−H Thioetherification of Arenes at Room Temperature

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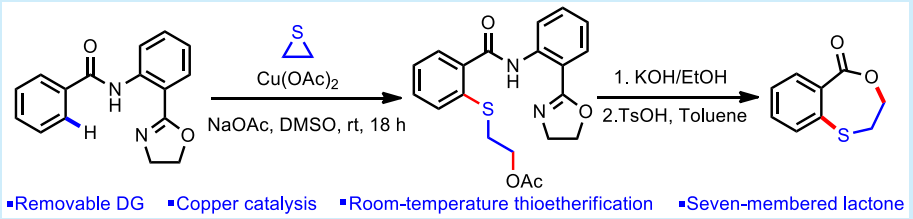
Supporting Information



ABSTRACT: Cu-mediated C−H thioetherification of arenes with ethylene sulfide has been developed using a readily removable directing group. The reaction proceeded at room temperature, and a variety of sensitive functional groups including chloro, bromo, and vinyl were well tolerated. The thiolated products could be converted to the seven-membered benzoxathiepinones derivatives by a sequence of hydrolysis−lactonization reactions.

Aryl thioethers are an important structural motif ubiquity in numerous biologically active compounds and pharmaceuticals (Figure 1).[1−5] For instance, craniformin is a natural product isolated from *Calvatia craniformis*.[2] Axitinib as a tyrosine kinase inhibitor is used as a treatment for renal cell carcinoma.[3] Moreover, aryl thioethers are also important intermediates for the synthesis of aryl sulfones and sulfoxides.[6] Therefore, the development of efficient and facile protocols for the construction of sulfur-containing compounds is highly desirable.

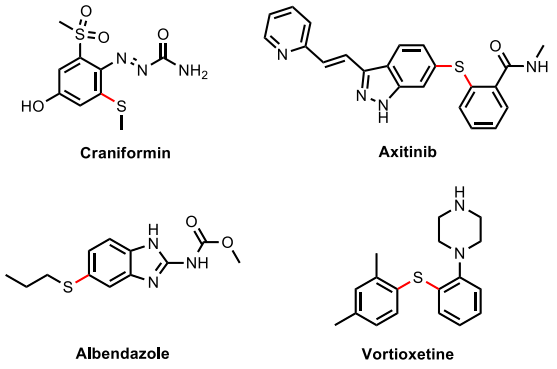
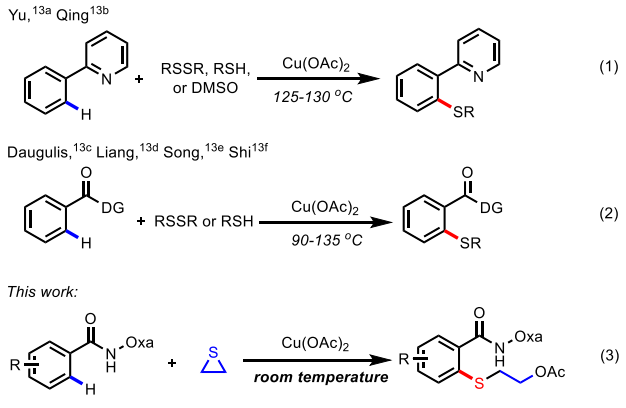


Figure 1. Bioactive aryl thioethers and pharmaceuticals.

In recent years, transition-metal-catalyzed C−H activation has provided a direct and powerful tool for the synthesis of thioethers compounds.[7] Various transition-metal catalysts such as Pd,[8] Rh,[9] Ru,[10] Ni,[11] and Co[12] have been developed for C−H thioetherification. Since Yu and co-workers reported the first example of Cu-mediated thioetherification of 2-phenylpyridine with PhSH and MeSSMe in 2006 (eq 1, Scheme 1), copper-catalyzed or -mediated direct C−H thioetherification has attracted considerable attention owing to the abundance, inexpensiveness, and versatile reactivity of copper catalysts.[7d,f,g,13] Subsequently, Qing and co-workers disclosed an

Scheme 1. Cu-Mediated Directed *Ortho* C−H Thioetherification of Arenes



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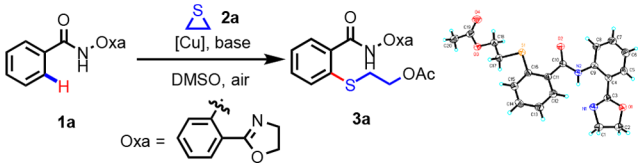
interesting example of Cu-mediated C−H bonds methylthiolation of 2-phenylpyridine using DMSO as the methylthiolation reagent.[13b] Both the Yu and Qing groups have demonstrated Cu-mediated thioetherification of 2-phenylpyridine at temperatures above 125 °C. In 2012, Daugulis made a great breakthrough in Cu-promoted C−H bond sulfenylation by adopting a removable 8-aminoquinoline directing group in which the reaction temperature could be lowered to 90−110 °C (eq 2, Scheme 1).[13c] Subsequently, similar work was reported by Liu's group.[13d] Recently, Song reported a copper-promoted thiolation of benzamides using the 2-aminoalkylbenzimidazole (MBIP) directing group at 135 °C.[13e] Assisted by the 2-(pyridin-2-yl)isopropylamine (PIP) directing group, Shi's group developed a Cu-mediated C−H thiolation of various arenes with disulfides and S_8 at 100−130 °C.[13f,j] Copper-catalyzed regioselective C−H thiolation of indolines (C7 position) and indoles (C2 position) was reported by Ackermann.[13i]

Despite significant advances in this research field, a high reaction temperature is commonly required in copper-catalyzed C−H thioetherification. Previously, our group developed the first copper-mediated diastereoselective C−H thiolation of ferrocenes with the bidentate chiral oxazoline directing group.[13g] In this work, we detail a facile Cu(II)-promoted room-temperature *ortho* C−H thioetherification of arenes using ethylene sulfide as the thiolation reagent (eq 3, Scheme 1). Under the mild reaction conditions, substrates bearing chloro, bromo, and vinyl could be well tolerated. The products are useful synthons and could be converted to the seven-membered benzoxathiepinone derivatives by a sequence of hydrolysis−lactonization reactions.

Based on the successful application of the amide−oxazoline directing group in copper-mediated C−H functionalization,[14] we initially treated substrate **1a** with 1 equiv of $Cu(OAc)_2$, 2 equiv of ethylene sulfide **2a**, and 2 equiv of KOAc at 80 °C. Only the dithiolated benzamide **3a′** was obtained in 24% yield (Table 1, entry 1). The substrate **1a** was completely converted, which implied that the substrate was partially decomposed. Next, we screened the reaction temperature (Table 1, entries 1−4) and were delighted to find that the thiolated product could be obtained at room temperature with a total yield of 39% (entry 4). The structure of product **3a** was confirmed by X-ray crystallography. The influence of base was examined, and NaOAc showed the best results (entries 4−9). Other copper catalysts, including CuI, $CuCl_2$, $CuBr_2$, and $Cu(OTf)_2$, were also investigated, and $Cu(OAc)_2$ gave the highest yields (entries 10−14). Lowering the concentration and increasing the reaction time could improve the yield to 65% with a 47/18 mono- to dithiolation ratio (entry 15). Moreover, we found that the lower yield was achieved under N_2 (entry 16). Substrates bearing other bidentate directing groups, such as 8-aminoquinoline, gave the thiolated products with lower yields (see the Supporting Information).

With the optimized reaction conditions in hand, we turned our attention to investigate the substrate scope. As shown in Scheme 2, a variety of benzamide derivatives with electron-rich methyl, methoxy, and *tert*-butyl substituents could be thiolated smoothly, providing the thiolated products in moderate to good yields (**3a**−**3f**). When the *meta*-positions of the benzamides were substituted with a methoxyl group, two regioisomeric products were formed, with the less sterically hindered 6-position-thiolated product as the major one (**3c**). Notably, the halogen (F, Cl, Br) and vinyl groups in the

Table 1. Optimization of the Reaction Conditions[a,b]



entry	[Cu] (equiv)	base	temp (°C)	yield (%) [mono/di]
1	$Cu(OAc)_2$ (1.0)	KOAc	80	24[0:24]
2	$Cu(OAc)_2$ (1.0)	KOAc	60	23[0:23]
3	$Cu(OAc)_2$ (1.0)	KOAc	40	51[34:17]
4	$Cu(OAc)_2$ (1.0)	KOAc	rt	39[34:5]
5	$Cu(OAc)_2$ (1.0)	LiOAc	rt	41[35:6]
6	$Cu(OAc)_2$ (1.0)	NaOAc	rt	56[43:13]
7	$Cu(OAc)_2$ (1.0)	CsOAc	rt	25[13:12]
8	$Cu(OAc)_2$ (1.0)	NH_4OAc	rt	0
9	$Cu(OAc)_2$ (1.0)	Na_2CO_3	rt	22[19:3]
10	CuOAc (1.0)	NaOAc	rt	14[9:5]
11	CuI (1.0)	NaOAc	rt	0
12	$CuCl_2$ (1.0)	NaOAc	rt	12[12:0]
13	$CuBr_2$ (1.0)	NaOAc	rt	26[22:4]
14	$Cu(OTf)_2$ (1.0)	NaOAc	rt	10[10:0]
15[c]	$Cu(OAc)_2$ (1.0)	NaOAc	rt	65[47:18]
16[d]	$Cu(OAc)_2$ (1.0)	NaOAc	rt	25[22:3]

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), [Cu], base (0.2 mmol), DMSO (1.0 mL), temperature, air, 12 h. [b]Yield was determined by ^1H NMR analysis of crude reaction mixture using CH_2Br_2 as the internal standard. [c]18 h, DMSO (2.0 mL). [d]The reaction was carried out under N_2 atmosphere.

substrates could be tolerated well, providing a useful handle for further structural elaborations (**3g**−**3m**). Intestinally, the *meta*-fluoro substrate **1h** was regioselectively thiolated to give product **3h** with trace formation of the other regioisomer, perhaps due to the small size and electronic properties of the fluorine atom.[15] Thiolation of arenes containing electron-withdrawing acetyl and trifluoromethyl groups also gave moderate to good yields (**3n**−**3p**). For 2-naphthalene-derived substrates, thiolation occurred at both the 1- and 3-positions, affording the mono- and diproducts $\mathbf{3q_{1\text{-}mono}}$, $\mathbf{3q_{3\text{-}mono}}$, and $\mathbf{3q_{1,3\text{-}di}}$ in isolated yields of 34%, 13%, and 7%, respectively. The protocol could be extended to heterocycle-containing compounds (**1r**), giving the corresponding products in 48% yields.

Removal of the amide-oxazoline directing group was demonstrated by treating product **3a** with 2 N KOH/EtOH at 80 °C, releasing the deacetylated carboxylic acid **4a** and the directing group **6a** in good yields (Scheme 3).

Seven-membered ring compounds containing two heteroatoms have drawn more and more attention due to their important pharmacological properties.[16] To our delight, the monothiolated product **3** could be converted to the seven-membered benzoxathiepinones derivatives **5** by a sequence of hydrolysis−lactonization reactions (Scheme 4).

To gain insight into the reaction mechanism of the C−H thiolation, several control experiments have been carried out. First, significant intra- and intermolecular kinetic isotope effects (KIE) indicate that the cleavage of C−H bond could be involved in the rate-determining step (Scheme 5). In addition, the addition of 2 equiv of radical scavenger 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) has a negligible effect on the yield, which indicates that a radical pathway is unlikely

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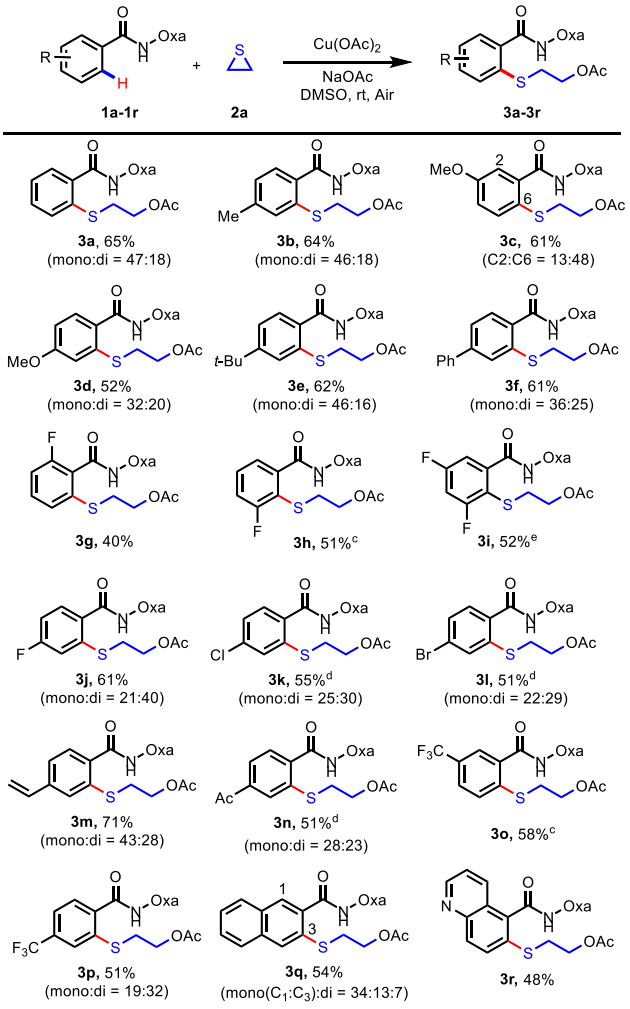
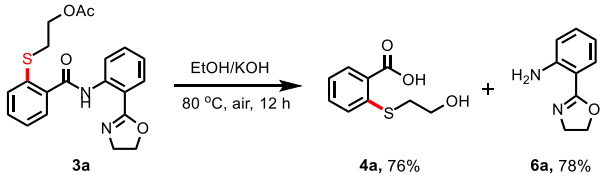
Scheme 2. Scope of Thioetherification Reaction[a,b]



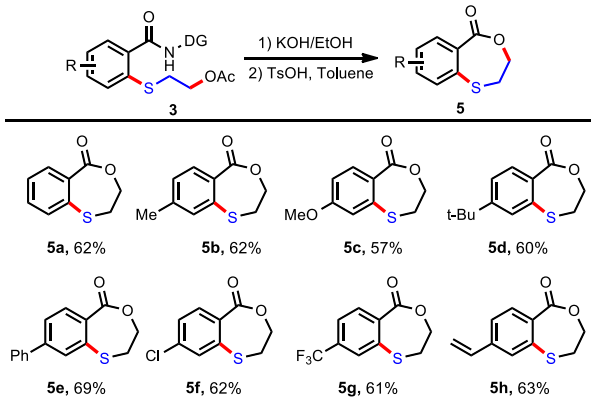
[a]Reaction conditions: **1a−1r** (0.1 mmol), **2** (0.2 mmol), $Cu(OAc)_2$ (1 equiv), NaOAc (2 equiv), DMSO (2.0 mL), air, rt, 18 h. [b]Isolated yield. [c]8 h. [d]12 h. [e]5 h.

Scheme 3. Removal of the Directing Group



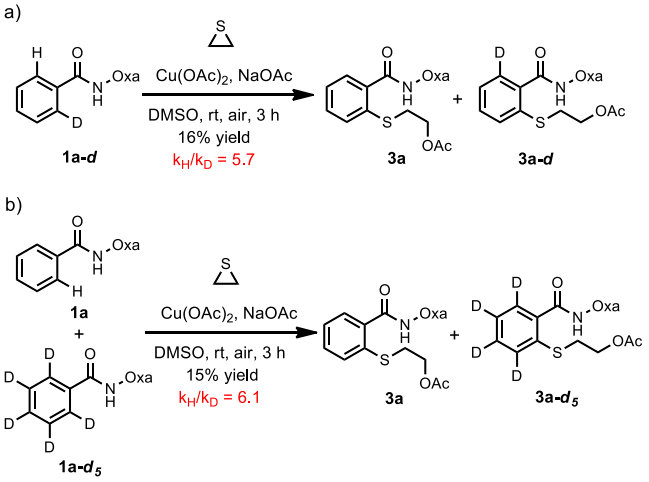
to be involved in the reaction (Scheme 6). We used 2-acetoxyethanethiol as the thiolated reagent under the standard reaction conditions, and only <5% of the desired product **3e** could be formed (see the Supporting Information). By combining these results, we proposed a copper(II)-mediated C−H thiolation pathway (Scheme 7). Compound **1a** coordinated with $Cu(OAc)_2$ with the bidentate amide−oxazoline directing group. Subsequently, C−H activation of benzamide took place, giving the intermediate **A**. The Cu(II) in **A** was disproportioned to give Cu(III) complex **B**.[17] Ethylene sulfide coordinated with Cu(III) complex **B** to form intermediate **C**. OAc^- attacked the coordinated ethylene sulfide via a six-membered-ring transition state, leading to the formation of the intermediated **D**, which then underwent reductive elimination to release the desired product **3a** and Cu(I) species.

Scheme 4. Transformation of Thiolated Product[a]

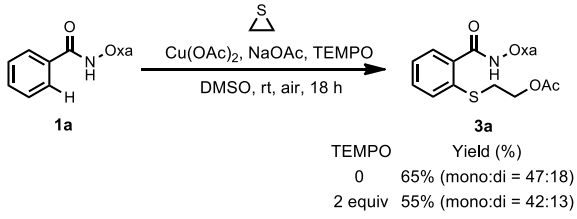


[a]Key: (1) **3** (0.25 mmol), KOH (10 mmol), EtOH (4.0 mL), air, 80 °C, 12 h; (2) TsOH (20 mol %), PhMe (1.0 mL), air, 120 °C, 2 h.

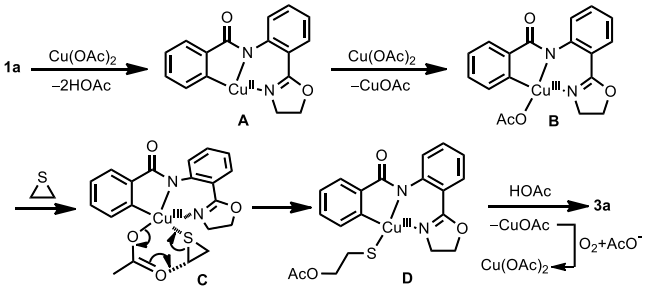
Scheme 5. (a) Intramolecular KIE; (b) Intermolecular KIE



Scheme 6. Effect of TEMPO



Scheme 7. Plausible Pathway



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In summary, we have developed a copper(II)-mediated *ortho* C−H thioetherification of arenes at room temperature. The reaction is compatible with a wide variety of functional groups. The resulting thiolated products can be easily converted to seven-membered benzoxathiepinone derivatives by a sequence of hydrolysis−lactonization reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02120.

Experimental procedures, characterizations of new compounds, NMR spectra data (PDF)

Accession Codes

CCDC 1918024 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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