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Lewis Acid-Catalyzed, Copper(II)-Mediated Synthesis of Heteroaryl Thioethers under Base-Free Conditions

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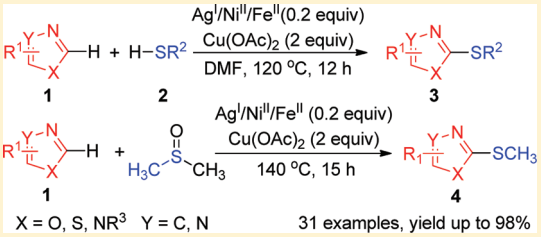
Supporting Information

ABSTRACT: A Lewis acid (Ag^{I}, Ni^{II}, or Fe^{II}) catalyzed, Cu^{II}-mediated thiolation reaction between heteroarenes and thiols was achieved with good yield under base-free conditions. DMSO could serve as an effective methylthiolation reagent for the synthesis of heterocyclic methyl thioethers.



Heteroaromatic compounds and their derivatives are known to exhibit interesting biological activities,[1] especially for heteroaryl sulfide structural motifs, which are found in many pharmaceutically active compounds and advanced materials.[2] Over the last decades, the activation of C−H bonds has emerged as an active field in organometallic catalysis, which allows superior step- and atom-economic transformations. Direct activation of heteroarene C−H bonds and coupling with a functional group represents the most straightforward way to functionalize heteroaryls. Recently, numerous methods have been reported for direct construction of heteroarene C−C, C−N, C−O, and C−halogen bonds by transition-metal-catalyzed C−H activations.[3] However, the synthesis of heteroaryl thioethers by direct thiolation of heteroarene C−H bonds with thiols still remains a challenge. In 2009, Daugulis reported a base-mediated direct thiolation of heterocycles by using disulfide as the thiolation reagent, but the products were limited to phenyl thioethers.[4a] Since the reaction proceeded under basic conditions with high temperature, when dialkyl disulfides were used as substrates, the thiolation product would further sulfenylate and dealkylate to give the thionone as the final product.[4a] Fukuzawa and co-workers first reported the synthesis of heterocyclic thioethers by Cu^{I}-catalyzed C−H/S−H cross-coupling, and the substrates were also limited to phenyl thiols.[4b] Very recently, Huang and Liu described a Cu^{I} and base mediated direct thiolation of thiazoles and imidazoles in the presence of stoichiometric 2,2′-bipyridine as ligand.[4c] However, the method was not effective for azole and its derivatives. In our study, we found that a proper Lewis acid could activate heteroarenes and coupling with thiols in the presence of a suitable mediator/oxidant. Several Lewis acids were effective to catalyze this reaction. Among them, Ag^{I} ($AgNO_3$, AgO_2CCF_3, and AgF), Ni^{II} ($NiCl_2$ and NiF_2), AuCl, $AuCl_3$, CuF_2, $Zn(OTf)_2$, and FeF_2 showed high reactivities and gave the thiolation products in good yields. Moreover, the reaction proceeded under neutral conditions that tolerate a broad range of substrates and functional groups. Remarkably, in our system, DMSO could serve as a simple, cheap, and easy-to-handle methylthiolation reagent and directly reacted with heteroarenes to give the corresponding heteroaryl methyl thioethers with good yields, which is a significant practical advantage.

We initially investigated the reaction of benzothiazole (**1a**) and *n*-butyl thiol (**2a**) in DMF at 120 °C under an argon atmosphere. To our delight, 48% of the desired product was obtained by using Ag_2CO_3 (0.2 equiv) as the catalyst and $Cu(OAc)_2$ (2 equiv) as the mediator/oxidant (Table 1, entry 1). After a brief screening of different Ag salts, $AgNO_3$, AgO_2CCF_3, and AgF showed high reactivities (entries 2−5). The reaction did not proceed in the absence of either Ag catalyst or $Cu(OAc)_2$ (entries 6 and 7). The use of a catalytic amount of $Cu(OAc)_2$ (0.2 equiv) and O_2 as co-oxidant sharply decreased the yield (entry 8). This result clearly revealed that a stoichiometric amount of $Cu(OAc)_2$ is necessary and $Cu(OAc)_2$ may assume the role of not only the oxidant but also the metal mediator. Variation of oxidants such as BQ (1,4-benzoquinone), $K_2S_2O_8$, $PhI(OAc)_2$, and TEMPO was ineffective (entries 9−12). Lowering the reaction temperature led to a poor yield (entry 13). Other Lewis acids were also employed in the reactions to compare their catalytic activities. $NiCl_2$, NiF_2, AuCl, $AuCl_3$, FeF_2, CuF_2, and $Zn(OTf)_2$ exhibited good catalytic activities (entries 14−20), whereas $FeCl_3$, CuI, $Sc(OTf)_3$, $BF_3{\cdot}Et_2O$, and $AlCl_3$ only gave moderate to low yields (entries 21−25).

We first investigated the substrate scope with respect to heteroarenes by using *n*-butyl thiol as coupling partner and AgO_2CCF_3 as the catalyst under optimal conditions. As shown in Table 2, uniformly good yields and high selectivities were achieved with a variety of heteroarenes (**3a**−**u**). Benzothiazoles, thiazoles, benzoxazoles, azoles, benzimidazole, imidazole, oxadiazole, as well as their analogues, all provided good yields

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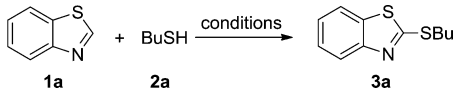
Table 1. Optimizing Reaction Conditions[a]



1a 2a 3a

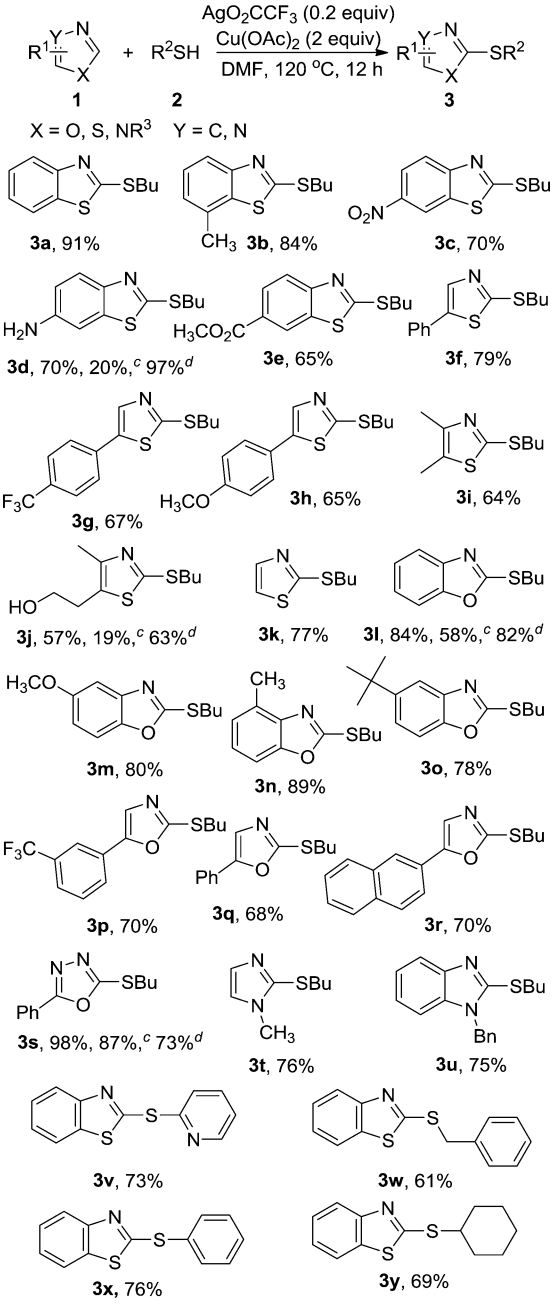
entry	cat.	oxidant	yield[b] (%)
1	Ag_2CO_3	$Cu(OAc)_2$	48
2	AgOAc	$Cu(OAc)_2$	60
3	$AgNO_3$	$Cu(OAc)_2$	95
4	**AgO_2CCF_3**	**$Cu(OAc)_2$**	**>99 (91)**
5	AgF	$Cu(OAc)_2$	97
6[c]		$Cu(OAc)_2$	trace
7[d]	AgO_2CCF_3		N.D.
8[e]	AgO_2CCF_3	$Cu(OAc)_2 + O_2$	15
9	AgO_2CCF_3	BQ	N.D.
10	AgO_2CCF_3	$K_2S_2O_8$	trace
11	AgO_2CCF_3	$PhI(OAc)_2$	N.D.
12	AgO_2CCF_3	TEMPO	N.D.
13[f]	AgO_2CCF_3	$Cu(OAc)_2$	32
14	**$NiCl_2$**	**$Cu(OAc)_2$**	**98**
15	NiF_2	$Cu(OAc)_2$	80
16	AuCl	$Cu(OAc)_2$	79
17	$AuCl_3$	$Cu(OAc)_2$	88
18	**FeF_2**	**$Cu(OAc)_2$**	**79**
19	CuF_2	$Cu(OAc)_2$	78
20	$Zn(OTf)_2$	$Cu(OAc)_2$	92
21	$FeCl_3$	$Cu(OAc)_2$	65
22	CuI	$Cu(OAc)_2$	69
23	$Sc(OTf)_3$	$Cu(OAc)_2$	50
24	$AlCl_3$	$Cu(OAc)_2$	10
25	$BF_3{\cdot}Et_2O$	$Cu(OAc)_2$	14

[a]Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (0.04 mmol), oxidant (0.4 mmol), 2 mL of DMF, 120 °C, except as noted. [b]GC yield with isolated yield in parentheses. [c]Without AgO_2CCF_3. [d]Without $Cu(OAc)_2$. [e]0.2 equiv of $Cu(OAc)_2$ was used. [f]Run at 100 °C.

regardless of the electronic property of the substituent. It is worth mentioning that with these neutral conditions, sensitive functional groups such as $-NO_2$, $-NH_2$, $-CF_3$, $-CO_2CH_3$, and −OH were all compatible (**3c−e,g,j**). We then chose $NiCl_2$ and FeF_2 as the model catalysts to compare their catalytic relativities with AgO_2CCF_3 for other heteroarene substrates (**3d,j,l,s**). FeF_2 showed competitive reactivity, whereas $NiCl_2$ gave only moderate results. In some cases, compared with AgO_2CCF_3 catalyst, FeF_2 exhibited better catalytic activities (**3d** and **3j**). The scope with respect to thiols was also investigated. To our delight, the thiols with aryl, benzyl, heteroaryl, and cyclohexyl groups were also suitable and exhibited good reactivities (**3v−y**).

Heterocyclic methyl thioether structural motifs play important roles in biological and pharmaceutical areas.[5] Very few examples have been reported for transition-metal-catalyzed C−H functionalization to synthesize heterocyclic methyl thioethers. Furthermore, there is no report about cross-coupling of heteroarene C−H bonds and methanethiol to prepare heteroaryl methyl thioethers. The boiling point of CH_3SH is around 7 °C, which may cause a technical problem for its handling and measurement at room temperature. Hence, the development of a simple and facile method for heteroarene methylthiolation remains a highly desired goal for chemists. In 2006, Yu reported a Cu^{II}-catalyzed methyl thioetherification of 2-phenylpyridine C−H bond with MeSSMe.[6a] Qing and co-workers disclosed a CuF_2-mediated methylthiolation of 2-phenylpyridine by using DMSO as the methylthiolation reagent.[6b] Very recently, Yamaguchi reported a Rh-catalyzed synthesis of benzothiazole and benzoxazole methyl thioether using α-(methylthio)isobutyrophenone as methylthiolation reagent. The reaction required a large excess (5 equiv) of heterocycles, and the yields were moderate.[6c] To our knowledge, no general and facile method has been reported for the synthesis of thiazole/azole/imidazole methyl thioethers by direct C−H methylthiolation. We envisioned that DMSO could serve as an effective methylthiolation reagent in our system. Indeed, by using AgF as catalyst and $Cu(OAc)_2$ as

Table 2. Thiolation with a Variety of Heteroarenes and Thiols[a,b]



[a]Conditions: **1** (0.2 mmol), **2** (0.4 mmol), AgO_2CCF_3 (0.04 mmol), $Cu(OAc)_2$ (0.4 mmol), 2 mL DMF, 120 °C, except as noted. [b]Isolated yields. [c]$NiCl_2$ (0.04 mmol) was used. [d]FeF_2 (0.04 mmol) was used.

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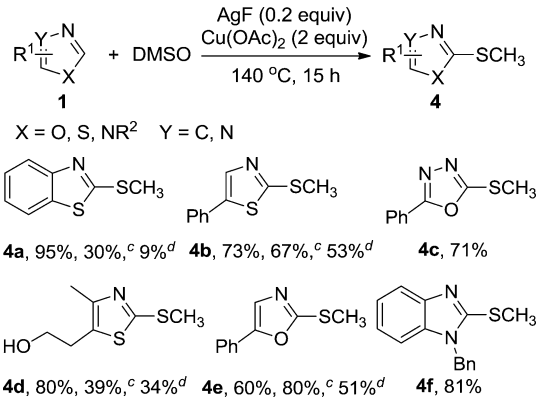
mediator/oxidant, the reactions went smoothly and gave the desired products with good yields (Table 3, **4a–f**). Thiazoles,

Table 3. Methylthiolation of Heteroarenes with DMSO[a,b]

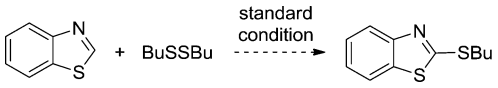


[a]Conditions: **1** (0.2 mmol), AgF (0.04 mmol), $Cu(OAc)_2$ (0.4 mmol), 1 mL of DMSO, 140 °C, except as noted. [b]Isolated yields. [c]$NiCl_2$ (0.04 mmol) was used. [d]FeF_2 (0.04 mmol) was used.

azoles, imidazole, and oxadiazole with sensitive functional groups (**4d**), as well as different electronic property substituents, were all tolerable. Other Lewis acid catalysts such as $NiCl_2$ and FeF_2 were also employed in the reactions (**4a,b,d,e**). The product yields were significantly lower than when AgF was used. Only in the case of **4e** did $NiCl_2$ give better results. In the reaction, Cu^{II} might serve for trapping the methylmercaptan formed in situ from the thermal decomposition of DMSO.[7]

To obtain some mechanistic insights, the following experiments were performed. In $CuBr_2$-catalyzed azole C–H/S–H cross-coupling, Fukuzawa proved that thiols were first oxidized to form disulfides, which then served as the thiolation reagents.[4b] However, under our standard conditions, dibutyl disulfide led to no formation of thiolation product, indicating that the disulfides were not involved in the reaction (Scheme 1).

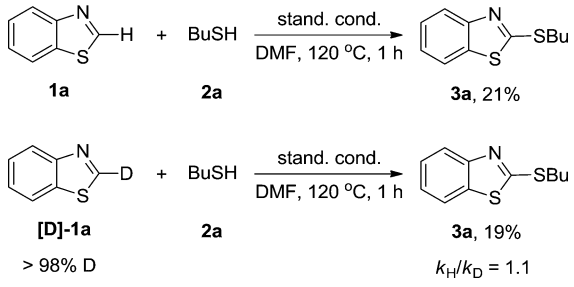
Scheme 1. Disulfide as Thiolation Reagent



The intermolecular kinetic isotope effect (KIE) was also investigated by using 2-deuteriobenzothiazole. At an early stage in the reaction, a KIE of 1.1 was observed, suggesting that C–H bond cleavage at the C2 position(s) of the heteroarene substrates is not involved in the rate-determining step (Scheme 2).[8]

It is known that Lewis acid bonding to azole could increase the azole C2 C–H bond acidity,[9] which could facilitate a carboxylated-assisted concerted metalation–deprotonation under base free conditions.[10] On the basis of the above considerations and experimental results, the reaction could consist of (1) thiols reacting with $Cu(OAc)_2$ to form a RSCuOAc species **A**,[11] (2) a Lewis acid promoted carboxylated-assisted concerted metalation–deprotonation to give the $C_{ar}CuSR$ intermediate **B**,[9,12] (3) , disproportion of Cu^{II} into Cu^{I} and Cu^{III} in view of the necessity of a stoichiometric amount of $Cu(OAc)_2$,[8,13] and (4) productive reductive

Scheme 2. Kinetic Isotope Effect (KIE) Study



elimination. The KIE experiments suggested that the rate-determining step could be the reductive elimination or disproportion step (Figure 1). However, at the present stage,

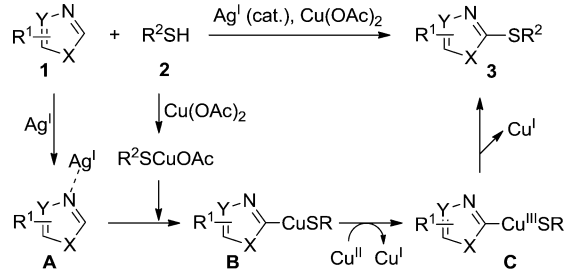


Figure 1. Plausible mechanism.

the pathway of nucleophilic addition to heteroarene C=N by thiols in the presence of a suitable mediator/oxidant (Cu, Ag, et al.) and subsequent oxidative rearomatization to give heteroaromatic thioether cannot be ruled out.[4c,14–16]

In conclusion, we have developed a new Lewis acid–Cu^{II} catalyst system for the synthesis of heteroaryl thioethers by direct C–H thiolation of heteroarenes. The base-free conditions tolerate a broad range of substrates and functional groups. Moreover, in our system, DMSO could serve as a methylthiolation reagent, which is a significant practical advantage.

EXPERIMENTAL SECTION

General Methods. The solvents were dried and distilled prior to use by the literature methods. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a 400 and 100 MHz FT-NMR spectrometer, and all chemical shift values refer to δ_{TMS} = 0.00 ppm or $CDCl_3$ ($\delta(^1H)$, 7.26 ppm; $\delta(^{13}C)$, 77.16 ppm). The HRMS analysis was obtained on a GC-TOF mass spectrometer. All chemical reagents were purchased from commercial sources and used as received unless otherwise indicated. Literature procedures were used to synthesize 5-chlorobenzothiazole,[17] 6-methylbenzothiazole,[18] 5-*tert*-butylbenzoxazole,[17] 5-phenyloxazole,[19] 5-(4-methoxyphenyl)oxazole,[19] 5-(naphthalene-2-yl)-oxazole,[19] 3-(trifluoromethyl)phenyloxazole,[19] 5-(4-chlorophenyl)-oxazole,[19] 5-phenylthiazole,[20] 5-(4-methoxyphenyl)thiazole,[20] 5-*p*-tolylthiazole,[20] 5-(3-(trifluoromethyl)phenyl)thiazole,[20] and 1-benzylbenzimidazole,[21] respectively.

Typical Procedure for the Synthesis of 3 and 4. For the synthesis of **3a**,[21] under an argon atmosphere, a 15-mL Schlenk tube was charged with $Cu(OAc)_2$ (73 mg, 0.4 mmol), AgO_2CCF_3 (10 mg, 0.04 mmol), benzothiazole **1a** (27 mg, 0.2 mmol), BuSH (42 μL, 0.4 mmol), and DMF (2 mL). The resultant mixture was stirred at 120 °C for 12 h. After the reaction was completed by TLC monitoring, the mixture was cooled to ambient temperature, poured into 20 mL of brine, and extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and filtered, and all of the volatiles were removed under reduced pressure. The resulting

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residue was purified by flash silica gel column chromatography (eluent: petroleum ether (30−60 °C)/EtOAc, v/v = 50/1) to afford the desired products **3a** as a yellow oil (41 mg, 91%). For the synthesis of **4**, the synthetic reactions were carried out at 140 °C for 15 h under an argon atmosphere and used DMSO as the methylthiolation reagent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8 Hz, 1 H), 7.82 (d, J = 8 Hz, 1 H), 7.5−7.45 (t, J = 8 Hz, 1 H), 7.4−7.35 (t, J = 8 Hz, 1 H), 3.45−3.4 (t, J = 8 Hz, 2 H), 1.9−1.8 (m, 2 H), 1.65−1.55 (m, 2 H), 1.04 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 153.4, 135.1, 126.0. 124.1, 121.5, 120.9, 33.4, 31.3, 21.9, 13.6.

2-(Butylthio)-7-methylbenzothiazole (3b): 40 mg, 84% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.3 (m, 1 H), 7.2−7.1 (m, 2 H), 7.25 (d, J = 8 Hz, 1 H), 3.39 (t, J = 8 Hz, 2 H), 2.64 (s, 3 H), 1.88 (t, J = 8 Hz, 2 H), 1.65−1.55 (m, 2 H), 1.02 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 160.6, 138.1, 137.6, 129.8. 128.4, 126.4, 34.3, 31.4, 21.9, 21.2, 13.6; HRMS calcd for $C_{12}H_{15}NS_2$ 237.0646, found 237.0644.

2-Butylsulfanyl-6-nitrobenzothiazole (3c):[22] 40 mg, 70% yield; white solid; mp 61−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1 H), 8.36 (d, J = 9 Hz, 1 H), 7.96 (d, J = 9.0 Hz, 1 H), 3.48 (t, J = 7 Hz, 2 H), 1.9−1.8 (m, 2 H), 1.55−1.65 (m, 2 H), 1.06 (t, J = 7 Hz, 3 H).

2-Butylsulfanyl-benzothiazol-6-ylamine (3d):[23] 34 mg, 70% yield; yellow solid; mp 39−41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 9 Hz, 1 H), 7.09 (s, 1 H), 6.83 (d, J = 8 Hz, 1 H), 3.35 (t, J = 7 Hz, 2 H), 1.91−1.79 (m, 2 H), 1.6−1.5 (m, 2 H), 1.02 (t, J = 7 Hz, 3 H).

2-Butylsulfanylbenzothiazole-6-carboxylic acid methyl ester (3e): 37 mg, 65% yield; white solid, mp 69−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1 H), 8.15 (d, J = 8.5 Hz, 1 H), 7.92 (d, J = 8 Hz, 1 H), 4.00 (s, 3 H), 3.44 (t, J = 7 Hz, 2 H), 1.9−1.85 (m, 2 H), 1.6−1.55 (m, 2 H), 1.04 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 166.6, 156.3, 135.4, 127.4, 125.8, 122.9, 120.9, 52.2, 33.3, 31.1, 21.9, 13.5; HRMS calcd for $C_{13}H_{15}NO_2S_2$ 281.0544, found 281.0531.

2-Butylsulfanyl-5-phenylthiazole (3f):[24] 39 mg, 79% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 7.6−7.55 (m, 2 H), 7.5−7.35 (m, 3 H), 7.38 (t, J = 7 Hz, 1 H), 3.30 (t, J = 7 Hz, 2 H), 1.85−1.8 (m, 2 H), 1.6−1.55 (m, 2 H), 1.1−0.95 (m, 3 H).

2-Butylsulfanyl-5-(4-trifluoromethylphenyl)thiazole (3g): 42 mg, 67% yield; yellow solid; mp 38−40 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1 H), 7.7−7.6 (m, 4 H), 3.32 (t, J = 7 Hz, 2 H), 1.85−1.8 (m, 2 H), 1.6−1.5 (m, 2 H), 1.03 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, C−F coupling not assigned) δ 161.6, 151.2, 131.3, 129.4, 128.6, 126.7, 124.4, 124.5, 124.3, 120.5, 120.4, 32.3, 31.5, 21.9, 13.5; HRMS calcd for $C_{14}H_{14}F_3NS_2$ 317.0520, found 317.0538.

2-Butylsulfanyl-5-(4-methoxyphenyl)thiazole (3h): 36 mg, 65% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.6 Hz, 2 H), 7.24 (s, 1 H), 7.00 (d, J = 8 Hz, 2 H), 3.90 (s, 3 H), 3.27 (t, J = 7 Hz, 2 H), 1.9−1.8 (m, 2 H), 1.6−1.5 (m, 2 H), 1.1−0.95 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 159.2, 138.9, 125.3, 121.6, 120.7, 114.3, 55.3. 32.3, 31.6, 21.8, 13.6; HRMS calcd for $C_{14}H_{17}NOS_2$ 279.0752, found 279.0759.

2-Butylsulfanyl-4,5-dimethylthiazole (3i):[25] 26 mg, 64% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (t, J = 7 Hz, 2 H), 2.36 (s, 3 H), 2.34 (s, 3 H), 1.76 (t, J = 8 Hz, 2 H), 1.6−1.45 (m, 2 H), 0.99 (t, J = 7 Hz, 3 H).

2-(2-Butylsulfanyl-4-methylthiazol-5-yl)ethanol (3j):[26] 27 mg, 57% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 2 H), 3.20 (t, J = 7 Hz, 2 H), 3.01 (t, J = 6 Hz, 2 H), 2.39 (s, 3 H), 1.85−1.75 (m, 2 H), 1.55−1.5 (m, 2 H), 1.01 (t, J = 7 Hz, 3 H).

2-Butylsulfanylthiazole (3k):[24] 27 mg, 77% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1 H), 7.27 (s, 1 H), 3.28 (t, J = 7 Hz, 2 H), 1.85−1.8 (m J = 7 Hz, 2 H), 1.54 (dd, J = 15, 7 Hz, 2 H), 1.01 (t, J = 7 Hz, 3 H).

2-Butylsulfanylbenzoxazole (3l):[27] 35 mg, 84% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.5 Hz, 1 H), 7.50 (d, J = 8 Hz, 1 H), 7.35−7.25 (m, 3 H), 3.39 (t, J = 8 Hz, 2 H), 1.95−1.85 (m, 2 H), 1.6−1.55 (m, 2 H), 1.04 (t, J = 7 Hz, 3 H).

2-Butylsulfanyl-5-methoxybenzoxazole (3m): 38 mg, 80% yield; white solid; mp 34−36 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1 H), 8.15 (d, J = 9 Hz, 1 H), 7.93 (d, J = 9 Hz, 1 H), 4.02 (s, 3 H), 3.44 (t, J = 8 Hz, 2 H), 1.9−1.85 (m, 2 H), 1.6−1.55 (m, 2 H), 1.05 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 156.7, 142.2, 140.5, 127.5, 122.9, 120.9, 52.3, 33.3, 31.1, 21.9, 13.5; HRMS calcd for $C_{12}H_{15}NO_2S$ 237.0823, found 237.0824.

2-Butylsulfanyl-5-methyl-benzoxazole (3n): 39 mg, 89% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1 H), 7.44 (d, J = 8 Hz, 1 H), 7.25 (d, J = 8 Hz, 1 H), 3.29 (t, J = 7 Hz, 2 H), 2.43 (s, 3 H), 1.83 (t, J = 7 Hz, 2 H), 1.6−1.55 (m, 2 H), 1.03 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 151.5, 141.3, 129.2, 124.8, 123.4, 107.1, 31.9, 31.5, 21.7, 16.3, 13.5; HRMS calcd for $C_{12}H_{15}NOS$ 221.0874, found 221.0891.

5-*tert*-Butyl-2-butylsulfanylbenzoxazole (3o): 41 mg, 78% yield; yellow solid; mp 53−55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1 H), 7.45−7.3 (m, 2 H), 3.38 (t, J = 7 Hz, 2 H), 1.90−1.8 (m, 2 H), 1.6−1.55 (m, 2 H), 1.43 (s, 9 H), 1.04 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 142.0, 121.2, 115.0, 108.9, 38.9, 34.9, 32.0, 31.7 (3 C), 21.8, 13.5; HRMS calcd for $C_{15}H_{21}NOS$ 263.1344, found 263.1361.

2-Butylsulfanyl-5-(3-trifluoromethylphenyl)oxazole (3p): 42 mg, 70% yield; white solid; mp 46−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1 H), 7.8−7.75 (m, 1 H), 7.6−7.55 (m, 1 H), 7.44 (s, 1 H), 3.29 (t, J = 7 Hz, 2 H), 1.95−1.80 (m, 2 H), 1.55 (m, 2 H), 1.02 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, C−F coupling not assigned) δ 151.2, 131.3, 129.4, 128.5, 126.7, 124.6, 124.5, 124.2, 120.4, 120.4, 32.3, 31.4, 21.8, 13.5; HRMS calcd for $C_{14}H_{14}NOSF_3$ 301.0748, found 301.0735.

2-Butylsulfanyl-5-phenyloxazole (3q):[28] 32 mg, 68% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.6 (m, 2 H), 7.5−7.45 (m, 2 H), 7.4−7.35 (m, 1 H), 7.36 (s, 1 H), 3.28 (t, J = 7.3 Hz, 2 H), 1.9−1.8 (m, 2 H), 1.6−1.5 (m, 2 H), 1.03 (t, J = 8 Hz, 3 H).

2-Butylsulfanyl-5-naphthalen-2-yl-oxazole (3r): 40 mg, 70% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1 H), 7.95−7.85 (m, 3 H), 7.72 (d, J = 8 Hz, 1 H), 7.6−7.5 (m, 2 H), 7.48 (s, 1 H), 3.33 (t, J = 7 Hz, 2 H), 1.9−1.8 (m, 2 H), 1.6−1.55 (m, 2 H), 1.05−1.0 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4, 132.9, 128.7, 128.2, 127.8, 126.7, 126.4, 125.1, 123.6, 122.4, 121.7, 32.4, 31.5, 21.8, 13.6; HRMS calcd for $C_{17}H_{17}NOS$ 283.1031, found 283.1026.

2-Butylsulfanyl-5-phenyl[1,3,4]oxadiazole (3s):[29] 46 mg, 98% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 2 H), 7.6−7.55 (m, 3 H), 3.38 (t, J = 7 Hz, 2 H), 1.95−1.85 (m, 2 H), 1.6−1.5 (m, 2 H), 1.02 (t, J = 8 Hz, 3 H).

2-Butylsulfanyl-1-methylimidazole (3t):[30] 26 mg, 76% yield; yellow solid; mp 89−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1 H), 6.98 (s, 1 H), 3.69 (s, 3 H), 3.13 (t, J = 7 Hz, 2 H), 1.75−1.7 (m, 2 H), 1.55−1.45 (m, 2 H), 0.98 (t, J = 7 Hz, 3 H).

1-Benzyl-2-butylsulfanylbenzoimidazole (3u): 45 mg, 75% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8 Hz, 1 H), 7.4−7.2 (m, 8 H), 5.38 (s, 2 H), 3.49 (t, J = 7 Hz, 2 H), 1.85−1.8 (m, 2 H), 1.6−1.5 (m, 2 H), 1.02 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 143.6, 136.2, 135.7, 128.8 (2 C), 127.9, 126.9 (2 C), 122.0, 121.9, 118.3, 109.1, 47.5, 32.5, 31.3, 21.9, 13.6; HRMS calcd for $C_{18}H_{20}N_2S$ 296.1347, found 296.1366.

2-(Pyridin-2-ylthio)benzothiazole (3v):[31] 36 mg, 73% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8 Hz, 2 H), 8.03 (d, J = 8 Hz, 2 H), 7.65−7.45 (m, 4 H).

2-Benzylsulfanylbenzothiazole (3w):[32] 32 mg, 61% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8 Hz, 1 H), 7.83 (d, J = 8 Hz, 1 H), 7.55−7.3 (m, 7 H), 4.69 (s, 2 H).

2-Phenylsulfanyl-benzothiazole (3x):[4c] 37 mg, 76% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8 Hz, 1 H), 7.82 (d, J = 7 Hz, 2 H), 7.73 (d, J = 8 Hz, 1 H), 7.65−7.45 (m, 4 H), 7.35 (d, J = 8 Hz, 1 H).

2-Cyclohexylsulfanylbenzothiazole (3y):[33] 35 mg, 69% yield; yellow solid; mp 46−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8 Hz, 1 H), 7.82 (d, J = 8 Hz, 1 H), 7.5−7.45 (t, J = 4 Hz, 1 H), 7.4−7.35 (m, 1 H), 2.27 (d, J = 10 Hz, 2 H), 1.9−1.85 (m, 2 H), 1.7−1.3 (m, 7 H).

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2-(Methylthio)benzothiazole (4a):[34] 30 mg, 73% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8 Hz, 1 H), 7.84 (d, J = 8 Hz, 1 H), 7.49 (t, J = 8 Hz, 1 H), 7.37 (d, J = 8 Hz, 1 H), 2.88 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 153.4, 135.2, 126.1, 124.1, 121.4, 120.9, 15.9.

2-Methylsulfanyl-5-phenylthiazole (4b):[35] 30 mg, 73% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.7−7.65 (m, 2 H), 7.5−7.45 (m, 2 H), 7.4−7.35 (m, 1 H), 7.37 (s, 1 H), 2.78 (s, 3 H).

2-Methylsulfanyl-5-phenyl[1,3,4]oxadiazole (4c):[29] 27 mg, 71% yield; yellow solid; mp 32−34 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.1−8.05 (m, 2 H), 7.6−7.5 (m, 3 H), 2.86 (s, 3 H).

2-(5-Methyl-2-methylsulfanylthiazol-4-yl)ethanol (4d):[36] 30 mg, 80% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (t, J = 6 Hz, 2 H), 3.01 (t, J = 6 Hz, 2 H), 2.70 (s, 3 H), 2.39 (s, 3 H).

2-Methylsulfanyl-5-phenyloxazole (4e):[37] 23 mg, 60% yield; yellow solid; mp 57−59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6−7.55 (m, 2 H), 7.5−7.4 (m, 3 H), 7.38 (s, 1 H), 2.81 (s, 3 H).

1-Benzyl-2-methylbenzoimidazole (4f):[38] 41 mg, 81% yield; yellow solid; mp 77−79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8 Hz, 1 H), 7.4−7.2 (m, 8 H), 5.37 (s, 2 H), 2.89 (s, 3 H).

Disulfide as Thiolation Reagent (Scheme 1). Under an argon atmosphere, a 15-mL Schlenk tube was charged with $Cu(OAc)_2$ (73 mg, 0.4 mmol), AgO_2CCF_3 (10 mg, 0.04 mmol), benzothiazole **1a** (27 mg, 0.2 mmol), BuSSBu (76 μL, 0.4 mmol), and DMF (2 mL). The resultant mixture was stirred at 120 °C for 12 h. After completion, the mixture was cooled to room temperature and subject to GC analysis by using *n*-dodecane as the internal standard.

Kinetic Isotope Effect Study (Scheme 2). Two sets of reaction were carried out in a parallel manner under the optimized conditions (Table 1, entry 4) using **1a** and its deuterated derivatives[**D**]-**1a**. The GC yields from the reactions were carefully checked by the signal integration of the desired product **3a** by using *n*-dodecane as the internal standard. The k_H/k_D (0.21/0.19 = 1.1) value was calculated according to the yields of **3a** at the point of 1 h.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org."

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Notes

The authors declare no competing financial interest.

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