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Letter

Switchable Copper-Catalyzed Approach to Benzodithiole, Benzothiaselenole, and Dibenzodithiocine Skeletons

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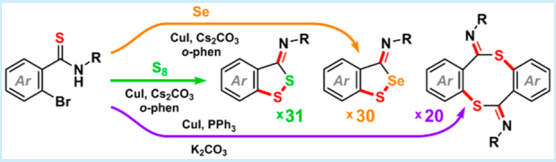
ABSTRACT: A copper-catalyzed reaction between 2-bromo-benzothioamides and S_8 or Se involving sulfur rearrangement is reported, enabling access to benzodithioles **2** and benzothiaselenoles **6** in the presence of Cs_2CO_3. In the absence of S_8 or Se, the reaction affords dibenzodithiocines **7** via two consecutive C(sp^2)−S Ullmann couplings.



Organosulfur compounds display prominent potential for diverse functionalization and exhibit attractive pharmacological properties.[1] In this regard, copper-catalyzed cross-coupling reactions between aryl halides and carbon- or heteroatom-based nucleophiles represent an established synthetic strategy for forging carbon−carbon and carbon−heteroatom bonds.[2] In recent years, elemental sulfur (S_8) has been demonstrated to be an effective sulfur source for C(sp^2)−S bond formation under copper-catalyzed conditions. For example, Liu and coworkers disclosed a copper-catalyzed three-component reaction involving *o*-iodobenzamides, S_8, and CH_2Cl_2 to afford 2,3-dihydrobenzothiazinones in good yields (Figure 1).[3] Similarly, the Shi group reported a copper-mediated C−S bond-forming protocol to access benzoisothiazolones from benzamides via C−H activation.[4] Recently, a solvent-free method for the synthesis of 2-acylthieno[2,3-*b*]quinolines was described through dual copper/nitroxyl radical catalysis.[5]

In this regard, benzodithiols (BDTs) and derivatives thereof, which contain a fused bicyclic molecule bearing a benzene ring connected to a five-membered 1,2- or 1,3-dithiol-containing ring, have been reported to possess promising bioactivity including anti-HBV,[6] antitumor,[7] antimicrobial,[8] anti-*Mycobacterium avium*,[9] and antibovine viral diarrhea virus activities.[10] Therefore, numerous methods have been explored for accessing more potent and structurally diverse BDTs.[11−15] Here 3*H*-benzo[*c*][1,2]dithiol-3-ones is an important member of 1,2-BDTs and has, for example, been utilized in the preparation of fluorescent probes.[16]

In our recent study, 2-bromo-*N*-phenylbenzothioamide (**1a**) was subjected to a terminal alkyne in the presence of a copper catalyst to afford the corresponding 4*H*-thiochromen-4-imine.[17] We reasoned that replacing the alkyne with S_8 as a sulfur source would furnish benzo[*d*]isothiazole-3(2*H*)-thione through C_{aryl}−Br thiolation. However, the reaction underwent an unexpected sulfur rearrangement, leading to 3*H*-benzo[*c*]-[1,2]dithiol-3-imine. As a continuation of our studies on

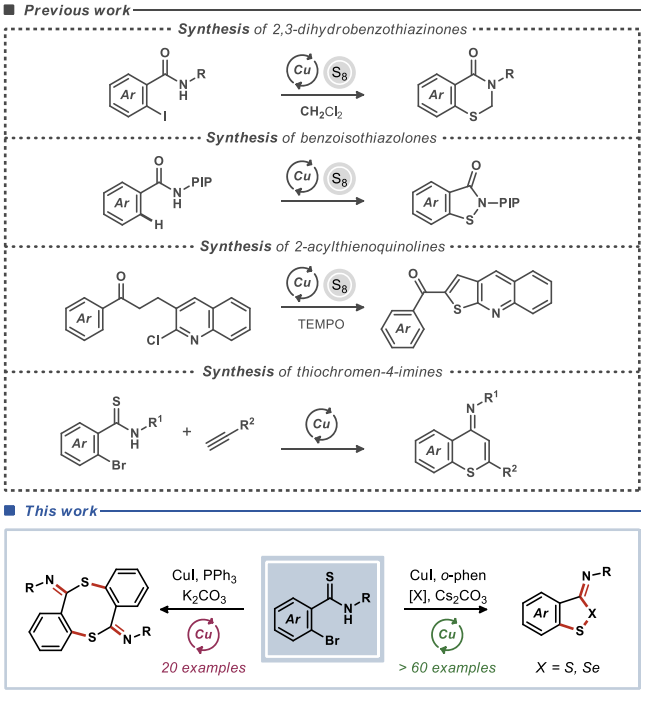


Figure 1. Copper-catalyzed approaches to carbon−sulfur bond formation. PIP = (pyridin-2-yl)isopropyl.

construction of heterocycles catalyzed by copper(I) or silver(I),[18] herein we disclose an efficient and modular

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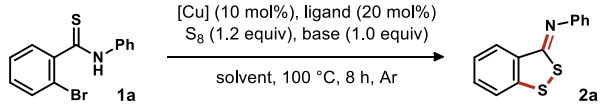
copper-catalyzed protocol for synthesis of benzodithiole derivatives **2** through the reaction of 2-bromo-benzothioamides **1** with S_8 under alkaline conditions. Furthermore, this copper-mediated reaction provided benzothiaselenole derivatives **6** when S_8 was replaced with Se powder.

As shown in Table 1, the model reaction of 2-bromo-*N*-phenylbenzothioamide (**1a**) and S_8 was performed in refluxing

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	base	ligand	solvent	yield (%)[b]
1	CuI			py	46
2	CuBr			py	37
3	CuCl			py	26
4	CuOAc			py	39
5	$CuBr_2$			py	
6	$Cu(OAc)_2$			py	
7	CuI		PPh_3	py	62
8	CuI		L-proline	py	58
9	CuI		*o*-phen	py	68
10	CuI	Cs_2CO_3	*o*-phen	py	76
11	CuI	K_2CO_3	*o*-phen	py	72
12	CuI	Na_2CO_3	*o*-phen	py	73
13	CuI	$NaHCO_3$[c]	*o*-phen	py	69
14	**CuI**	**Cs_2CO_3**	***o*-phen**	**DMF**	**85**
15	CuI[d]	Cs_2CO_3	*o*-phen	DMF	37
16	CuI[e]	Cs_2CO_3	*o*-phen	DMF	86
17	CuI	Cs_2CO_3	*o*-phen	dioxane	76
18	CuI	Cs_2CO_3	*o*-phen	DMSO	79
19	CuI	Cs_2CO_3	*o*-phen	DMA	82
20	CuI	Cs_2CO_3	*o*-phen	toluene	69

[a]Reaction conditions: **1a** (146 mg, 0.5 mmol), S_8 (154 mg, 0.6 mmol), catalyst (0.05 mmol), ligand (0.1 mmol), base (0.5 mmol), solvent (5.0 mL), 100 °C. [b]Isolated yield. [c]Reaction carried out with 1.0 mmol $NaHCO_3$ (100 mg, 1.2 mmol). [d]Reaction run with 5 mol % CuI (0.025 mmol). [e]Reaction run with 20 mol % CuI (0.1 mmol).

pyridine using 10 mol % CuI as a catalyst, affording **2a** in 46% yield (Table 1, entry 1). To improve the yield, several reaction parameters were varied, including the copper source, base, ligand, and solvent. Using alternative copper precursors, such as CuBr, CuCl, and CuOAc, demonstrated that CuI was superior (cf. Table 1, entry 1 and entries 2−4). Furthermore, the use of copper(II) precursors, such as $CuBr_2$ and $Cu(OAc)_2$, led to no desired product formation (Table 1, entries 5 and 6). The addition of frequently used ligands, such as Ph_3P, *o*-phen, and L-proline, revealed that a substantial increase in yield was possible when using *o*-phen, providing **2a** in 68% yield (Table 1, entry 9). A survey of inorganic bases showed that Cs_2CO_3 furnished product **2a** in 76% yield (Table 1, entry 10). Other carbonate bases, such as K_2CO_3, Na_2CO_3, and $NaHCO_3$, also promoted the reaction (Table 1, entries 11−13) but provided lower yields of **2a** compared with Cs_2CO_3. Finally, the reaction also proceeded in common organic solvents, such as DMF, dioxane, DMSO, DMA, and toluene (Table 1, entries 14−20). Here DMF was found to be the best solvent for this reaction, leading to **2a** in 85% yield (Table 1, entry 14).[19−21]

With the optimized reaction conditions in hand, we examined the generality of the protocol (Scheme 1). Initially, substrates with various substituents on the imine nitrogen atom were investigated.

In addition to aliphatic groups, the reaction tolerated various aromatic substituents bearing either electron-donating (methyl, methoxy, iso-propyl) or electron-withdrawing substituents, such as nitro and chloro, as well as heteroaryl motifs. All of these substrates underwent the cascade coupling/cyclization smoothly to afford products **2a−q** in good to excellent yields (62−90%, Scheme 1). The structure of product **2** was supported through single-crystal X-ray diffraction analysis of **2l**, as shown in Scheme 1.

With respect to the substituents on the benzene ring, we were delighted to find that various groups, such as methyl, methoxy, chloro, and fluoro, at either the five- or seven-position could be employed, furnishing the corresponding benzodithiole products **2r−ad** in 75−91% yields (Scheme 1). Additionally, a pyridine derivative was also an effective coupling/cyclization partner, affording product **2ae** in 91% yield.

To evaluate possible further applications of the developed protocol, several benzodithioles were transformed into their corresponding BDT derivatives (**3a−e**) in high yields via acidic hydrolysis (Scheme 1). The developed protocol undoubtedly provides an efficient and practical method for the preparation of these valuable and medicinally relevant compounds. Furthermore, the synthetic conversion of **3a** into the important compounds **4**[22] (Beaucage's reagent) and **5**[23] was attained in good yield by reacting with *m*-CPBA and hydrogen peroxide, respectively.

Next, we reasoned that the corresponding selenium analogue of **2** would be accessible by replacing the sulfur source with an appropriate selenium source. Intriguingly, conducting the reaction under the optimized reaction conditions using Se powder instead of S_8 provided (*Z*)-*N*-aryl-3*H*-benzo[*d*][1,2]-thiaselenol-3-imines **6** rather than (*Z*)-*N*-aryl-3*H*-benzo[*c*]-[1,2]thiaselenol-3-imines. The structure of product **6u** was supported by X-ray diffraction analysis. (See Scheme 2.) Gratifyingly, a variety of substituted aromatic motifs, such as alkylphenyl (e.g., methyl, isopropyl, and *tert*-butyl), alkoxyphenyl (e.g., methoxy and ethoxy), and mono- and dihalogenated phenyl (e.g., F and Cl) reacted smoothly to give the desired products under the optimized reaction conditions. A total of 30 benzothiaselenoles were obtained in moderate to high yields (56−78%, Scheme 2).

A proposed mechanism for the synthesis of **2** and **6** is detailed in Scheme 3. According to the structure of the products **2** and **6**, benzothietane-2-imine **B** is envisioned as a key intermediate. Initially, benzothioamide **1** is believed to be converted to anion **A** in the presence of a base. Then, benzothietane-2-imine **B** is produced via an intramolecular copper-catalyzed Ullmann coupling reaction to form thietane adduct **B**.[24] Subsequent cleavage of the C−S bond occurs to give the ring-opened thiophenolate **D**. In the following step, intermediate **D** reacts with S_8 or Se to form an S−S or S−Se bond, which is similar to reacting Na_2S with S_8 to form Na_2S_2. Finally, intermediate **E** undergoes an addition/elimination process to give the target structure **2** or **6**. An alternative mechanism involves the initial formation of a copper thiolate adduct (**G**), which undergoes oxidative addition into the C−Br bond to form the five-membered cupracycle **H**. The subsequent migration and insertion of sulfur or selenium

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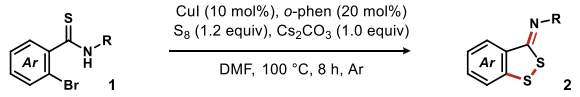
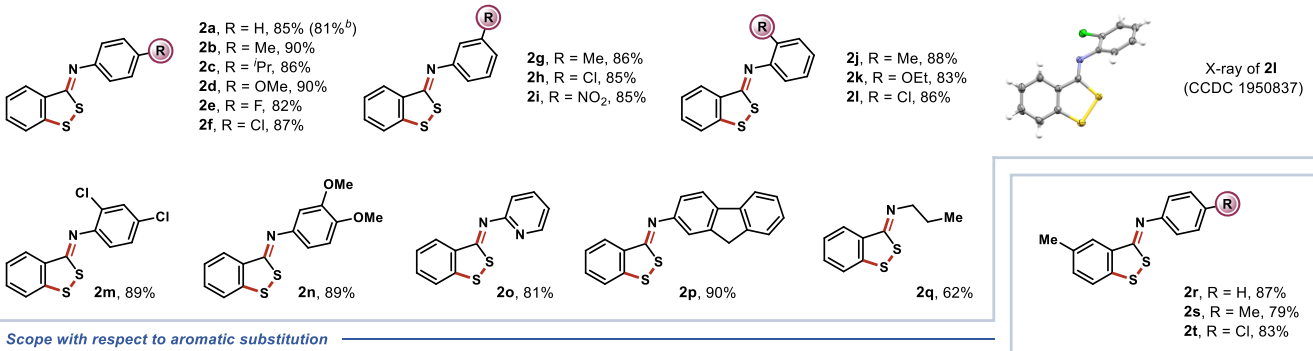
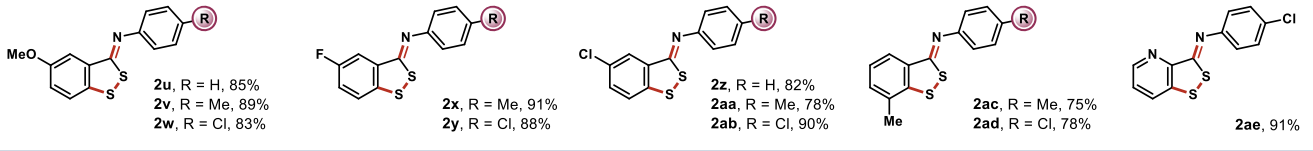
Scheme 1. Substrate Scope for Synthesis of Benzodithiole 2[a]



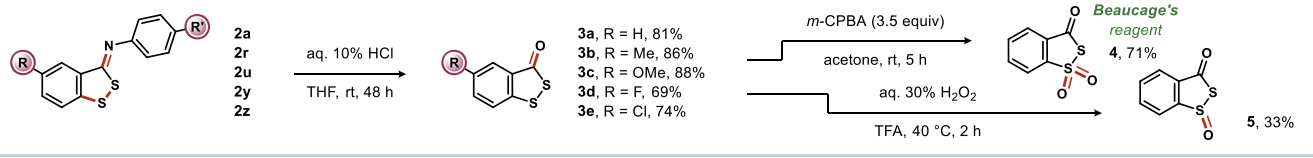
Scope with respect to N-substituents



Scope with respect to aromatic substitution

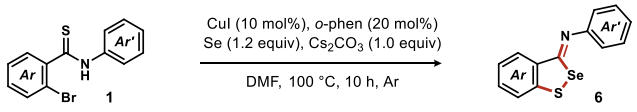


Further derivatization

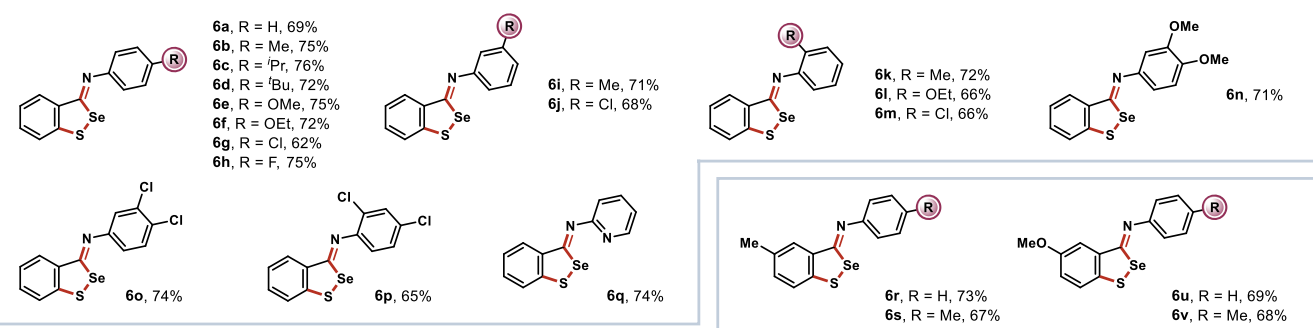


[a]Reaction conditions: **1** (0.5 mmol), S_8 (154 mg, 0.6 mmol), CuI (10 mg, 0.05 mmol), *o*-phen (18 mg, 0.1 mmol), Cs_2CO_3 (163 mg, 0.5 mmol), DMF (5.0 mL), 100 °C. Yields are of isolated products after purification by column chromatography. [b]Reaction run on a 2.0 mmol scale.

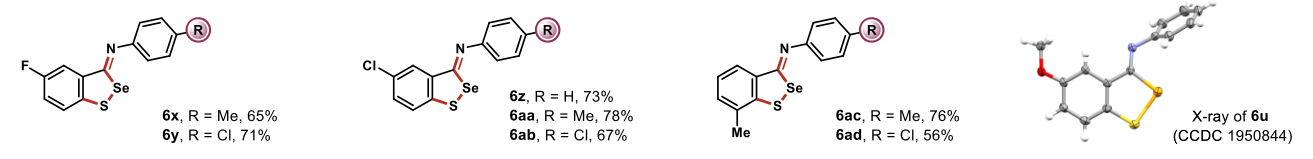
Scheme 2. Substrate Scope for Synthesis of Benzothiaselenole 6[a]



Scope with respect to N-substituents



Scope with respect to aromatic substitution



[a]Reaction conditions: **1** (0.5 mmol), Se (48 mg, 0.6 mmol), CuI (10 mg, 0.05 mmol), *o*-phen (18 mg, 0.1 mmol), Cs_2CO_3 (163 mg, 0.5 mmol), DMF (5.0 mL), 100 °C. Yields are of isolated products after purification by column chromatography.

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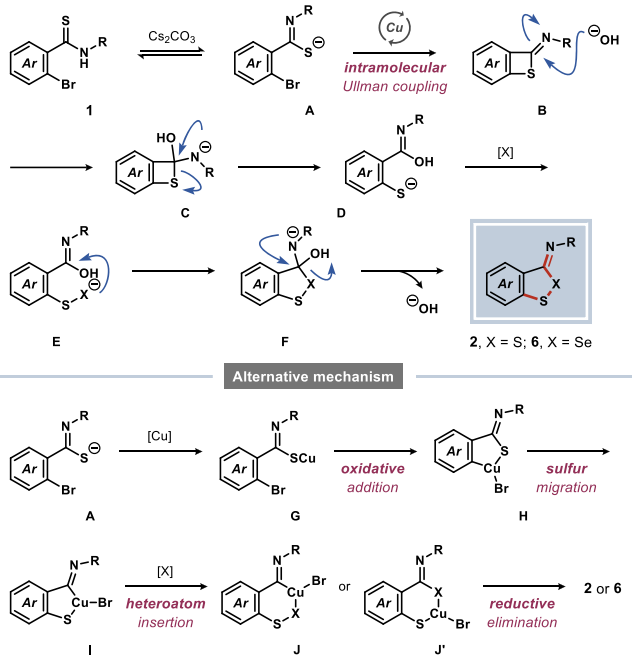
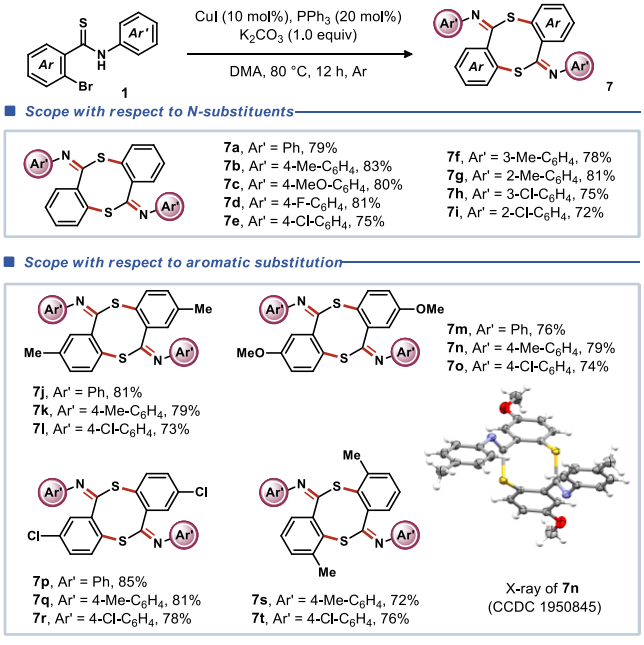
Scheme 3. Proposed Reaction Mechanism



into the Cu−S or Cu−C bond of intermediate **I** affords the six-membered metallacycle **J** or **J′**, respectively, which upon reductive elimination delivers product **2** or **6** and regenerates the copper(I) catalyst.

Finally, conducting the reaction under standard conditions but in the absence of S_8 or Se provided a new product, dibenzodithiocine **7a**, derived from two consecutive C(sp^2)−S coupling reactions (Scheme 4). The initial yield (42%) for this copper-catalyzed coupling product could be improved to 79% upon changing the ligand and base to PPh_3 and K_2CO_3, respectively. A total of 20 dibenzodithiocines (**7a**−**o**) were obtained in 72−85% yield, and the structure of **7n** was supported by X-ray diffraction analysis (Scheme 4).

Scheme 4. Synthesis of Dibenzodithiocine 7[a]



[a]Reaction conditions: **1** (0.5 mmol), CuI (10 mg, 0.05 mmol), PPh_3 (26 mg, 0.1 mmol), K_2CO_3 (69 mg, 0.5 mmol), DMA (5.0 mL), 80 °C. Yields are of isolated products after purification by column chromatography.

In conclusion, an efficient and switchable copper-catalyzed method for the synthesis of benzodithioles and benzothiaselenoles using S_8 or Se as the chalcogen source is disclosed. Conducting the reaction in the absence of S_8 or Se affords eight-membered dibenzodithiocine annulation products via two consecutive C(sp^2)−S coupling reactions. Considering the importance of sulfur and selenium compounds, this protocol may be of great value for synthetic chemists and pharmacologists in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00907.

Experimental details and NMR spectra of compounds **2**−**7** (PDF)

Accession Codes

CCDC 1950837 and 1950844−1950845 contain 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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(20) Attempts were made to access product **3a** through a C−H functionalization strategy. However, no reaction occurred for the substrate lacking the bromo group under the optimized reaction conditions.

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