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Cu-Catalyzed Three-Component Coupling of Aryne, Alkyne, and Benzenesulfonothioate: Modular Synthesis of *o*-Alkynyl Arylsulfides

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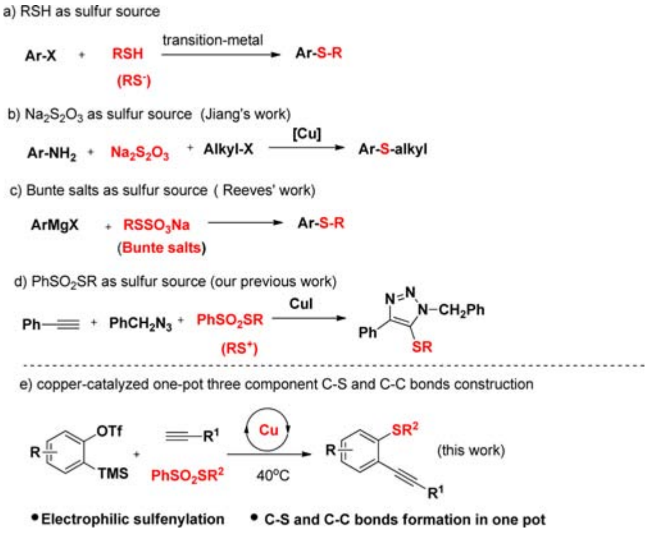
Supporting Information

ABSTRACT: A copper-catalyzed three-component coupling reaction of in situ formed arynes, terminal alkynes, and benzenesulfonothioates is described. This reaction provides an efficient modular synthesis of *o*-alkynyl arylsulfides from easily available starting materials. This process involves one C−S bond and one C−C bond formation in one pot.

Aryl sulfides are an important type of structural unit, widely presented in bioactive pharmaceuticals and also materials.[1] Aryl sulfides are important synthetic intermediates and chiral ligands in organic synthesis.[2] They could be easily transformed into different oxidative states, such as sulfoxide and sulfone, which are also important functional groups in medicinal and organic chemistry.[1] Thus, the construction of C−S bonds is of strategic importance in current synthetic chemistry. Traditionally, the C_{sp2}−S bond formation mainly relies on the transition-metal-catalyzed coupling reactions of aryl halide and nucleophilic thiols (RS^-), which are air-sensitive and extremely odorous (Scheme 1a).[3] Recently, the Jiang group used $Na_2S_2O_3$ as the sulfur source and developed a series of sulfur atom transfer reactions to construct aryl−sulfur bonds (Scheme 1b).[4a−c] The Reeves group developed an elegant C−S construction method by the reaction of Grignard reagents and Bunte salts (Scheme 1c).[5] Very recently, we noticed that benzenesulfonothioates are excellent electrophilic sulfenylating reagents (RS^+) and successfully introduced alkyl and aromatic thio groups onto the triazole ring (Scheme 1d).[6] The benzenesulfonothioates are bench-stable, generally have little or no odor, and can be easily prepared. We believe this type of electrophilic sulfenylation reaction will find more applications in other important C−S construction reactions.

Scheme 1. Methods for C_{sp2}−S Bond Construction



Aryne chemistry was developed as a powerful platform for 1,2-difunctionalization of aromatic rings in recent years.[7] The in situ formed arynes are highly reactive electron-deficient intermediates. Nucleophilic addition to benzyne and subsequent electrophilic trap cascade reactions are the fundamental reaction mode in current benzyne chemistry.[8] For example, in 2015, the Greaney group reported a three-component reaction of arynes, nucleophilic thiol, and electrophilic *O*-benzoyl *N*-hydroxylpiperidine, giving 1,2-diheterofunctionalized arenes in high yields.[8f] *o*-Alkynyl arylsulfides are important synthetic intermediates that could be easily transformed into benzothiophene heterocycles under electrophilic conditions.[9] *o*-Alkynyl arylsulfides were prepared by stepwise palladium-catalyzed C−S bond and Sonogashira coupling reactions. In this context, we envisioned that terminal alkynes nucleophilically attack in situ formed benzynes, and electrophilically trapping the reaction intermediate with benzenesulfonothioates (RS^+) would rapidly construct *o*-alkynyl arylsulfides in one step from easily available starting materials.

A detailed description of our proposed mechanistic cycle for the copper-catalyzed three-component coupling reaction is outlined in Scheme 2. Copper(I) acetylide $\mathbf{M^1}$ was formed from terminal alkyne **1** in the presence of base and copper catalyst. $\mathbf{M^1}$ reacted with electrophilic sulfenylating reagent **3** to

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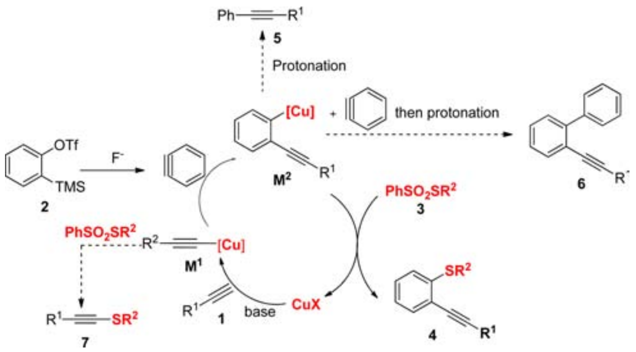
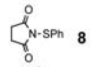
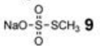
Scheme 2. Proposed Mechanism of the Copper-Catalyzed Three-Component Reaction to *o*-Alkynyl Arylsulfides



form the internal thioalkyne **7**. However, when the highly reactive benzyne was formed in situ, $\mathbf{M^1}$ reacted with benzyne, forming the aryl copper intermediate $\mathbf{M^2}$, which was trapped by the electrophilic reagent **3** to give the final product **4** and regenerate the copper catalyst. Achieving this catalytic cycle is challenging because the aryl copper intermediate is easily protonated to form the internal alkyne **5** and attack another molecule of the benzyne intermediate to form byproduct **6**. To inhibit the sulfenylation reaction of copper(I) acetylide $\mathbf{M^1}$, we needed to increase the benzyne formation rate; however, this would also increase the amount of two benzyne addition byproducts **6**. Thus, controlling the benzyne formation rate and choosing a reactivity-matched electrophile are very crucial for this reaction.

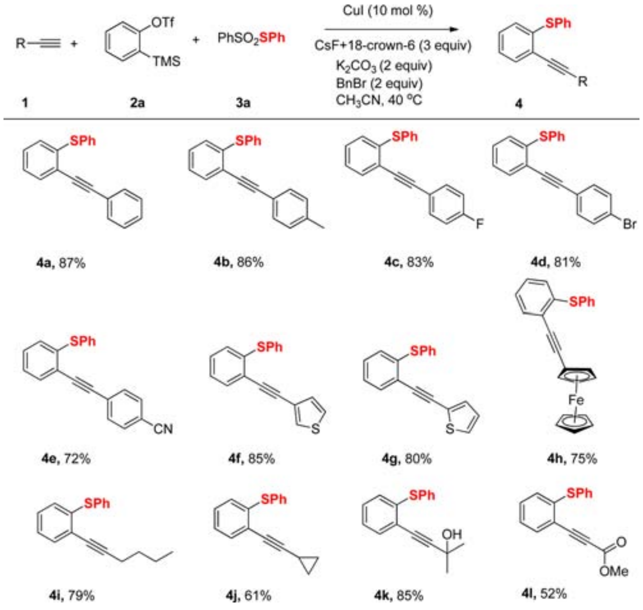
Initially, alkyne **1a**, benzyne precursor **2a**, and electrophilic sulfenylating reagents **3a** (PhS^+) were chosen as the model substrates to optimize the reaction conditions (Table 1; for details, see Supporting Information). When TBAF was selected as the fluoride source, K_2CO_3 as the base, and 10 mol % of CuI as the catalyst, the target three-component coupling product **4a** could be isolated in 25% yield (entry 1). Two major byproducts, **5** and **6**, were observed in the reaction system. Varying different bases did not give better results (entries 2 and 3). When we increased the reaction temperature from room temperature to 40 °C, the isolated yield increased to 50% (entry 4). Other fluorides, such as CsF, led to lower yields under this condition (entries 5 and 6). When we tuned the ratios of the three reactants and increased the amounts of electrophile **3**, the yield increased to 64% (entry 7). Under these conditions, sulfonyldibenzene **10** became the major byproduct, which was formed between the addition reaction of released $PhSO_2^-$ with benzyne.[10] To inhibit this undesired side reaction, 2 equiv of BnBr was added into the reaction system as a scavenger to trap the $PhSO_2^-$, and formation of $PhSO_2Bn$ was isolated and also confirmed by GC-MS. When CsF and 18-crown-6 were used as the fluoride source, the target product **4a** was isolated in 87% yield, which is the optimal reaction conditions (entry 9). Other electrophilic sulfenylating reagents (**8** and **9**) were also tested. The expected **4a** was not observed, but only product **5** and **6** were (entries 10 and 11).

Table 1. Reaction Condition Optimization[a]

entry	F^-	base	electrophile	*t* °C	yield (%)
1	TBAF	K_2CO_3	**3a**	rt	25
2	TBAF	^{t}BuOLi	**3a**	rt	15
3	TBAF	^{t}BuONa	**3a**	rt	10
4	TBAF	K_2CO_3	**3a**	40	50
5	CsF	K_2CO_3	**3a**	40	32
6	CsF+18-C-6	K_2CO_3	**3a**	40	39
7[b]	TBAF	K_2CO_3	**3a**	40	64
8[bc]	TBAF	K_2CO_3	**3a**	40	70
9[bc]	**CsF+18-C-6**	$\mathbf{K_2CO_3}$	**3a**	**40**	**87**
10[b]	CsF+18-C-6	K_2CO_3	 N-SPh **8**	40	0
11[b]	CsF+18-C-6	K_2CO_3	 NaO-S-SCH3 **9**	40	0

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), [Cu] (10 mol %), F^- (0.6 mmol), base (0.6 mmol), 4 Å MS (100 mg), and solvent (2 mL) were stirred under N_2 atmosphere for 5 h. Isolated yields of **4a** were reported. [b] **1a** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.4 mmol), CuI (10 mol %), F^- (0.6 mmol), base (0.4 mmol). [c] BnBr (0.4 mmol) was added. 18-C-6 = 18-crown-6.

Scheme 3. Scope of the Terminal Alkynes[a]



[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.4 mmol), CuI (10 mol %), F^- (0.6 mmol), 18-crown-6 (0.6 mmol), K_2CO_3 (0.4 mmol), BnBr (0.4 mmol), 4 Å MS (100 mg), and solvent (2 mL) were stirred under N_2 atmosphere for 5 h.

The scope of the three-component reaction with a variety of terminal acetylenes was explored (Scheme 3). A variety of electronically varied aryl acetylenes were compatible with the system, providing expected α-alkynylated aryl sulfides **4a**−**4e** in excellent yields. Heterocycles, including thiophenes and ferrocene-substituted alkynes, were also efficient coupling partners, giving corresponding aryl sulfides **4f**−**4h** in 75−85% yields. Moreover, alkyl acetylenes were also suitable substrates for this reaction, and commonly encountered functional groups such as cyclopropyl (**4j**) and sterically hindered alcohol (**4k**) were well-tolerated. Additionally, electron-deficient methyl

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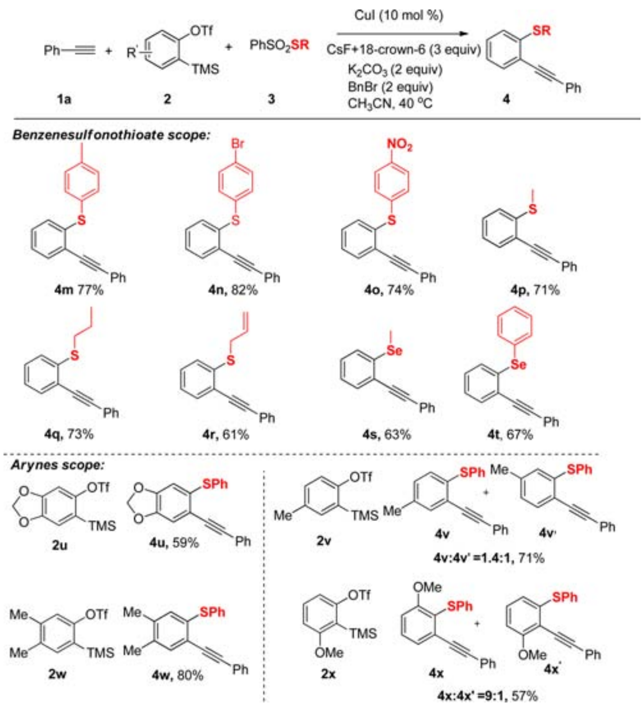
propiolate could also react efficiently in this three-component reaction (**4l**).

The scope of benzenesulfonothioates was examined (Scheme 4). Various aromatic thio and aliphatic thio groups could be easily introduced onto the adjacent position of an alkyne moiety in good yields (**4m**−**4r**). When the reaction was extended to the selenylation, the methylselenyl and phenylselenyl products **4s** and **4t** were obtained in 63 and 67% yields. The scope of various functionalized arynes was also examined. All arynes tested were compatible with the standard conditions, and the corresponding aryl sulfides could be isolated in reasonable yields. When the unsymmetrical **2v** was used, mixtures of **4v** and **4v′** were isolated in 71% yields (**4v**/**4v′** = 1.4:1). The reaction of methoxyl-substituted aryne **2x** was regioselective and led to arylsulfide **4x** as the major product (**4x**/**4x′** = 9:1).

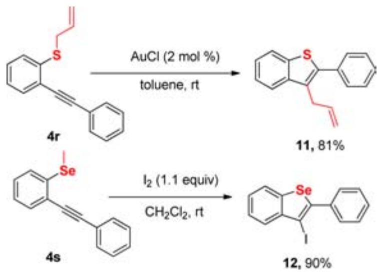
Scheme 4. Substrate Scope of Benzenesulfonothioates and Arynes[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.4 mmol), CuI (10 mol %), F$^-$ (0.6 mmol), 18-crown-6 (0.6 mmol), K$_2$CO$_3$ (0.4 mmol), BnBr (0.4 mmol), 4 Å MS (100 mg), and solvent (2 mL) were stirred under N$_2$ atmosphere for 5 h.

Further transformations of the generated *o*-alkynyl aryl sulfides were investigated. As shown in Scheme 5, allylic sulfide **4r** could isomerize into 3-allyl benzothiophene **11** in 81% yield in the presence of 2 mol % of AuCl.[11] Interestingly, iodine-mediated electrophilic cyclization of methyl selenide **4s** gave benzoselenophene **12** in 90% yield.[12]

Scheme 5. Further Transformations of *o*-Alkynyl Aryl Sulfides



In conclusion, a copper-catalyzed three-component coupling reaction of alkynes, arynes, and benzenesulfonothioates was described. This nucleophilic attack and electrophilic trap reaction involves efficient C−C and C_{sp2}−S bond formation in one pot. A wide variety of *o*-alkynyl aryl sulfides were modularly constructed from readily available starting materials, and various functional groups were tolerated under these mild conditions. We envision that the reaction mode outlined here will have potential applications in other significant synthetic transformations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02027.

> Experimental details and spectral data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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