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Cu-Catalyzed Electrophilic Disulfur Transfer: Synthesis of Unsymmetrical Disulfides

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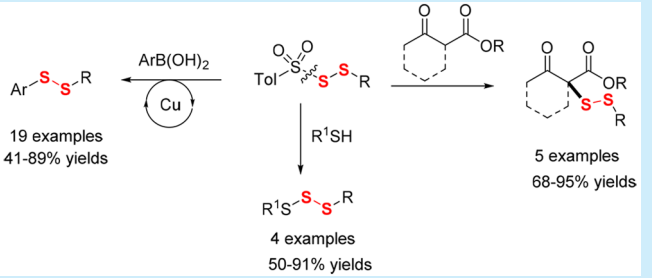
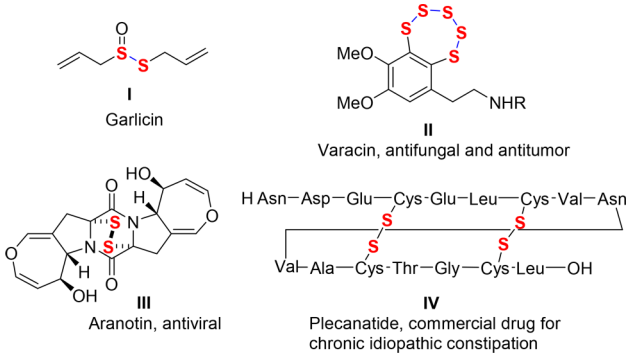
Supporting Information

ABSTRACT: An efficient electrophilic persulfuration reaction leading to unsymmetrical disulfides and polysulfides has been developed. Various nucleophiles, including aryl boronic acids, β-keto esters, and thiols, can be used as substrates. The notable features of this method include very simple and practical conditions, general scope, and inexpensive copper catalysts.



Molecules containing sulfur−sulfur bonds (S−S), including disulfides and polysulfides, have attracted significant attention because of their unique structural, chemical, and biological properties[1] and their wide use in food chemistry[2] and in the pharmaceutical industry.[3] This structural unit is present in garlic and other allium compounds, such as garlicin (**I**), which are used in food flavoring and also as traditional medicines (Scheme 1). Recently, abundant disulfide- and polysulfide-containing natural products isolated from marine organisms have been shown to exhibit important biological activities, and many of them have been used as lead and candidate drugs.[4] The disulfide or polysulfide moieties play important roles in their bioactivities. For instance, varacin (**II**), a dopamine alkaloid, exhibits potent antifungal and antitumor activity,[5,5a] and aranotin (**III**) has significant antiviral properties.[5b] In peptide therapeutics, disulfide bond formation between two cysteine residues is an excellent method with which to stabilize the secondary structure of a protein and enhance its pharmacological properties.[1b] Many well-known commercial peptide drugs such as insulin, lantus, vasopressin, and plecanatide contain one or more disulfide bonds. In addition, by taking advantage of the unstable nature of the disulfide bond, it has been used in drug discovery and delivery as a readily cleavable linkage.[3a] Consequently, the development of efficient synthetic methods to produce disulfides and polysulfides is important.[6,7]

Scheme 1. Representative Natural Products and Pharmaceuticals Containing Disulfides and Polysulfides



Symmetrical disulfides can be easily formed by oxidative coupling of thiols, but synthesis of asymmetric disulfides in this way is complicated by the byproducts inevitably formed by homocoupling.[6a,d] Retrosynthetic analysis suggests two possible pathways to asymmetric disulfides: S−S bond formation and C−S bond formation (Scheme 2A). The currently used synthetic methods depend on S−S bond formation in the reaction between a thiol substrate and electrophilic sulfenylation reagent such as $RSSO_2Me$ and require multiple steps to prepare malodorous thiols and the sulfenylation reagent in advance.[6a] A more straightforward approach is a persulfur group transfer reaction through C−S bond formation, which could introduce "SSR" moieties directly into an organic molecule in one step. However, this is challenging because preserving the fragile S−S bond intact is difficult in such reactions. Only two examples of a persulfur group transfer have been reported and both used a nucleophilic disulfur reagent. In 2016, Xian's group reported a nucleophilic reaction of 9-fluorenymethyl disulfides[7] and Jiang et al. developed an elegant

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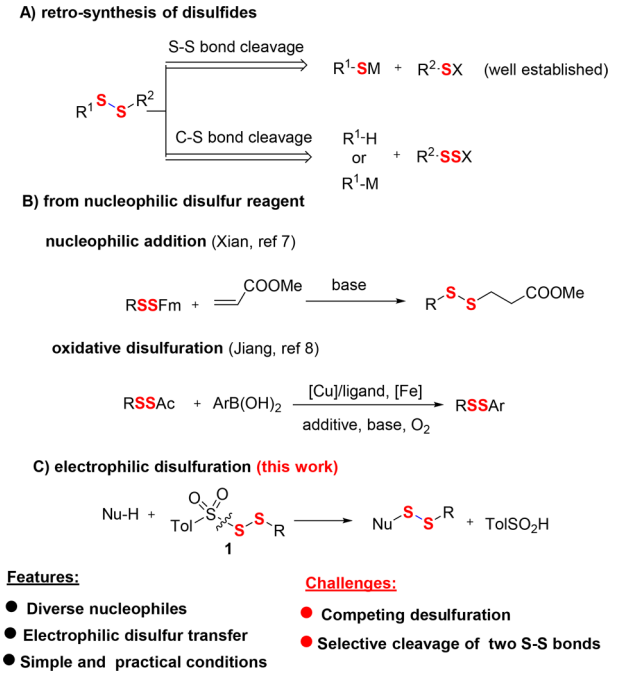
Scheme 2. Synthetic Strategies for Unsymmetrical Disulfides

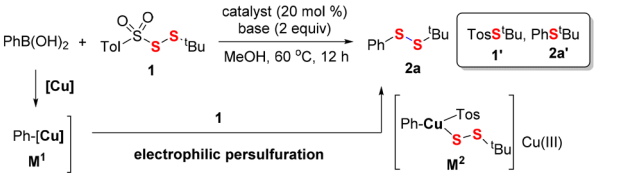


copper-catalyzed disulfuration reaction that can be used in oxidative coupling reactions[8] (Scheme 2B). However, this oxidative coupling reaction requires extra oxidants and complex reaction conditions and we reasoned that direct electrophilic disulfuration of various nucleophiles (Scheme 2C) is a simpler and more practical approach. In this paper, we report our preliminary results.

Benzenesulfonothioate is an effective electrophilic sulfenylating reagent as a result of the leaving properties of benzenesulphinate, with the pK_a of corresponding acid being 2.76.[9] Previously, we have used this reagent to trap arylcopper(I) intermediates and form C−S bonds.[9a] The Shen group has also developed $PhSO_2SCF_2H$ as an efficient electrophilic difluoromethylthiolation reagent.[10] We sought to apply this strategy in electrophilic disulfuration reactions using *SS-tert*-butyl *p*-toluenesulfono(dithioperoxoate) (**1**), which could be prepared easily from potassium *p*-toluenesulfonothioate with *tert*-butyl thiochloride.[11] There are two weak S−S bonds in this reagent (**1**), and how to cleave one S−S bond over another is a challenge. We reasoned that the good leaving tendency of the arylsulfone moiety may help cleave the thioester bond rather than the persulfur bond, realizing the desired persulfur transfer reaction. Recently, we have successfully applied this reagent in an efficient copper(I)-catalyzed three-component click/persulfuration cascade reaction for the synthesis of triazole disulfides.[12]

The viability of electrophilic persulfuration with different nucleophiles was explored. The reactivity of aryl boronic acid, a commercially available, easily prepared, and widely used arylation reagent, was evaluated. We reasoned that a copper reagent maybe a suitable catalyst to promote this reaction through boron to copper transmetalation,[9d,10b] generating aryl copper intermediate **M**^{1}, followed by an electrophilic persulfuration reaction, which could form the target product. This step might go through an oxidative addition and reductive elimination sequence (Table 1). Various copper catalysts were

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	base	temp (°C)	yield of **2a**[b] (%)
1	$CuSO_4$	$NaHCO_3$	25	37 (**2a**:**2a′** = 4:1)
2	$Cu(OAc)_2$	$NaHCO_3$	25	31 (**2a**:**2a′** = 3:1)
3	CuI	$NaHCO_3$	25	25 (**2a**:**2a′** = 3:1)
4	**$CuSO_4$**	**$NaHCO_3$**	**60**	**83**
5	$Cu(OAc)_2$	$NaHCO_3$	60	58
6	$Cu(OTf)_2$	$NaHCO_3$	60	32
7	$CuCl_2$	$NaHCO_3$	60	38
8	CuI	$NaHCO_3$	60	17
9	$CuSO_4$	CsF	60	61
10	$CuSO_4$	Cs_2CO_3	60	trace
11[c]	$CuSO_4$	$NaHCO_3$	60	57

[a]Reaction conditions: **1** (0.2 mmol), phenylboronic acid (0.4 mmol), catalyst (20 mol %), base (0.4 mmol), and MeOH (1 mL) were stirred at 60 °C under N_2 atmosphere for 12 h. [b]Isolated yield. [c]Catalyst (10 mol %).

screened, but it was found that at room temperature large amounts of undesired desulfuration products such as TsS^tBu and ArS^tBu and deboration products were formed (Table 1, entries 1−3). After detailed examination of different reaction conditions, we found that upon raising the reaction temperature to 60 °C and increasing the transmetalation rate the expected reaction proceeded well in the presence of a catalytic amount of $CuSO_4$. The desired disulfide (**2a**) was isolated in 83% yield, and formation of the desulfuration and deboration side products was largely inhibited (entry 4). Other copper catalysts such as $Cu(OAc)_2$, $Cu(OTf)_2$, $CuCl_2$, and CuI are all less effective than $CuSO_4$ (entries 5−8). Variation of other bases (entries 9 and 10) and trying to lower catalyst loadings (entry 11) all led to a lower reaction yield.

The scope of various commercial available aryl boronic acids was investigated, and a series of unsymmetrical disulfides were synthesized in good to excellent yields under the standard conditions (Scheme 3). Different electron-donating or electron-withdrawing functional groups at the *ortho*, *meta*, or *para* positions do not affect this reaction and give products **2b−k** in good yields. A series of functional groups such as bromo, cyano, ester, acetyl, and methylthio were well tolerated under these reaction conditions, thus allowing further functionalization if necessary. Various hydrocarbons such as naphthalene- and anthracene-derived boronic acids were also suitable for this transformation, giving the corresponding disulfides in 81% and 77% yields (**2l**,**m**).Various heterocycles such as pyridine (**2n**,**o**), quinoline (**2p**), and benzothiophene (**2q**) are all compatible with the reaction. Styrylboronic acid reacts efficiently to produce the target disulfide (**2r**) in 89% yield, and *p*-phenyldiboronic acid reacts smoothly, giving the persulfide (**2s**) in moderate yield.

We then began to extend this electrophilic persulfuration reaction to other nucleophiles. Various *β*-keto esters were explored and these Csp^3-S bond formation reactions were very successful (Scheme 4). Indanone- and tetralone-derived *β*-keto esters were subjected to this reaction in the presence of DMAP as a base; the target asymmetric disulfides **3a** and **3b** were

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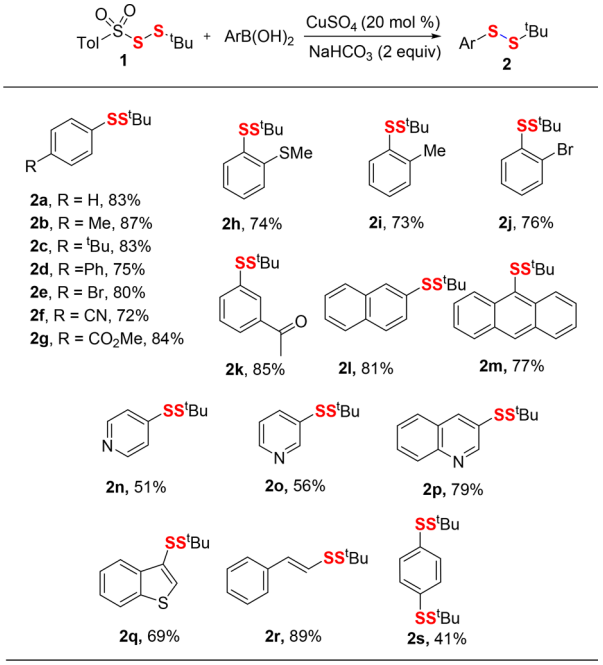
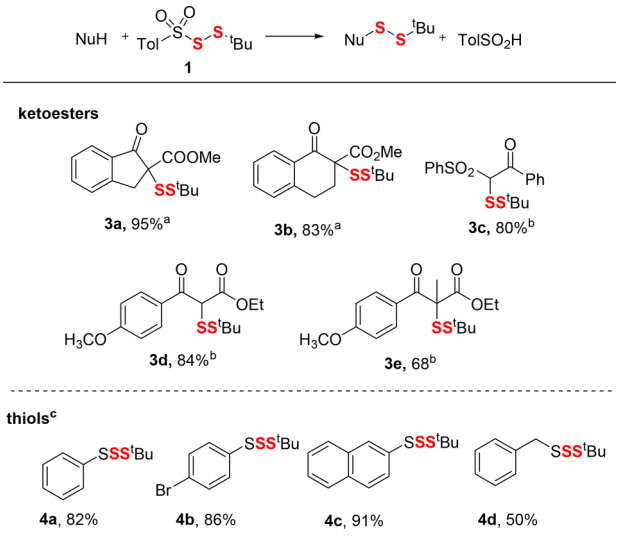
Scheme 3. Electrophilic Persulfuration of Aryl Boronic Acids[a]



[a]Reaction conditions: aryl or vinyl boronic acid (0.4 mmol), reagent **1** (0.2 mmol), $CuSO_4$ (20 mol %), and $NaHCO_3$ (0.4 mmol) in MeOH (1 mL) were stirred at 60 °C for 12 h. Isolated yields are reported.

Scheme 4. Substrate Scope of Thiols and Ketoesters



[a]β-Ketoester (0.2 mmol), **1** (0.4 mmol), DMAP (0.3 mmol) in DCM (1 mL) at 30 °C for 12 h. Isolated yields were reported. [b]β-Ketoester (0.2 mmol), **1** (0.4 mmol), DBU (0.3 mmol) in DCM (1 mL) at 30 °C for 12 h. [c]Thiol (0.2 mmol), **1** (0.3 mmol), DCM (1 mL), room temperature, 2 h.

isolated in 95% and 83% yields, resepectively. Other acyclic ketone esters are all viable substrates, and by using stronger DBU as the base, the corresponding disulfides were isolated in 68%−84% yields (**3c**−**e**).

Polysulfides are important molecules containing an S−S bond, but their synthesis still remains a challenge.[13] We anticipated that the electrophilic persulfuration of thiols would generate a trisulfide in a single step, and indeed, reactions of various thiols with **1** occur efficiently at room temperature without any catalyst or base, and the corresponding trisulfides **4a**−**c** can be isolated in excellent yields (Scheme 4). The reaction of an aliphatic thiol, benzyl mercaptan, gave the trisulfide (**4d**) in 50% yield. Such trisulfide products are difficult to synthesize by other methods.

In summary, we have developed an efficient electrophilic persulfuration reaction which constructs unsymmetrical disulfides and trisulfides by introducing two sulfur atoms in one step. Various nucleophiles, including aryl boronic acids and thiols, are all compatible substrates in this general electrophilic persulfur-transfer reaction. Notable features of this method include very simple and mild reaction conditions, inexpensive copper catalysts, and a very broad substrate scope. Further application of this methodology is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01418.

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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