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Copper-Catalyzed Oxysulfenylation of Enolates with Sodium Sulfinates: A Strategy To Construct Sulfenylated Cyclic Ethers

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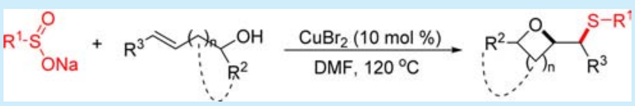
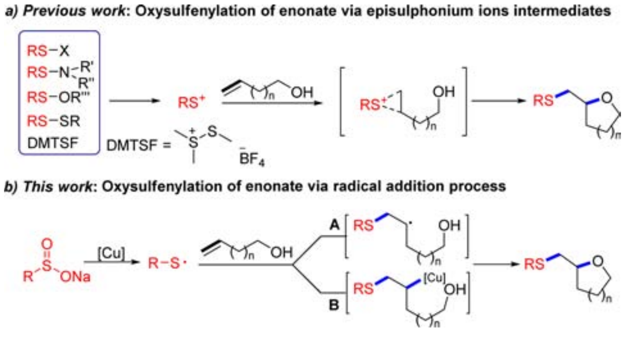
Ⓢ *Supporting Information*

ABSTRACT: A new copper-catalyzed oxysulfenylation reaction of enolates with sodium sulfinates has been disclosed. A series of sulfenylated heterocycles including four- and seven-membered cyclic ether were obtained in mild to good yields. This reaction is proposed to go through a radical process, and the sulfur radical ($RS^\bullet$) may be a reactive species.



The formation of the C−S bond has emerged as a significant field of research in organic chemistry[1] because organosulfur compounds are widely present in natural products and are applied in total synthesis, medical chemistry, and functional materials science.[2] Among them, sulfenylated cyclic ethers are useful chemical entities and important skeletons for various useful molecules that exhibit biological activities such as antiviral, antifungal, etc.[3] Therefore, C−S bond synthesis has received intensive attention and encouraged the development of new synthetic strategies. Traditionally, sulfenylated cyclic ethers were synthesized via the episulphonium ion intermediates, which were formed through the thiofunctionalization of alkenes with electrophilic sulfur(II) sources, and the cyclic products arose from the internal nucleophilic displacement (Scheme 1a).[4] Sulfenyl halides,[4a,b] sulfenamides,[4c−e] and sulfenate esters[4f,g] were reported as thiolating reagents to take part in this oxysulfenylation reaction, and dimethyl(methylthio)sulfonium fluoroborate (DMTSF)[4h] was used to introduce the MeS group. In addition, Mellor and Trost et al.[5] achieved this chemical process by employing the disulfides as thiolating reagents in the presence of Mn^{3+} or Pb^{4+} salts, respectively. Nevertheless, most of these methods suffer from several limitations: (i) the thiolating reagents are not amenable to preparation and handling; (ii) the reaction conditions usually require strong acid and low temperature. In view of green chemistry, new strategies starting from easily available reagents and going through a new chemical process for the synthesis of sulfenylated cyclic ethers under mild conditions with broad functional group tolerance remain highly desirable.

Scheme 1. Synthetic Methods for Sulfenylated Heterocycles



Sodium sulfinates as ideal sulfuration reagents have been widely used to construct the C−S bond since they are readily accessible and stable. Generally, sodium sulfinates are used as sulfone sources in radical-coupling reactions. For example, sulfones have been introduced into heteroaromatics, oxime acetates, alkenes, or/and alkynes via the radical process.[6] However, attempts to construct the sulfur ether bond using sodium sulfinates as the sulfur sources under reduction conditions are relatively rare.[7] Recently, Yi and co-workers reported the I_2-promoted iodothiolation of alkynes with sodium sulfinates using PPh_3 as a reducing reagent, and sulfur radical ($RS^\bullet$) was proposed to be a reactive species in the reaction.[8] As for the radical addition reaction, it has also emerged as a powerful method to achieve the 1,2-difunctionalization of alkenes,[9] and it can be applied to the construction of several heterocyclic systems as well.[10] In this regard, we conceived that the oxysulfenylation of alkenes via the sulfur radical ($RS^\bullet$) addition process might be an ideal strategy for the synthesis of sulfenylated heterocycles, which would serve as versatile building blocks in organic synthesis. As part of our continuing interest in the development of efficient and practical methods for the construction of C−S bonds,[6f,g,11] herein we present our recent progress on a new strategy for the construction of sulfenylated cyclic ethers via copper-catalyzed oxysulflation of enolates with sodium sulfinates.

Our initial investigation of this transformation commenced with pent-4-en-1-ol (**2a**) and sodium 4-methylbenzenesulfinate (**1a**) as model substrates under conditions that used **1a** (0.25 mmol), **2a** (0.25 mmol), and $CuBr_2$ (10 mol %) in DMSO (2 mL) at 120 °C (Table 1). Interestingly, the sulfenylation product 2-((*p*-tolylthio)methyl)tetrahydrofuran (**3aa**) instead of the sulfonylation product was detected in 45% GC yield after 24 h (entry 1). This result prompted us to screen different external reducing reagents. However, the addition of PPh_3,

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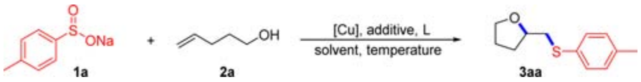
Table 1. Optimization of Reaction Conditions[a]

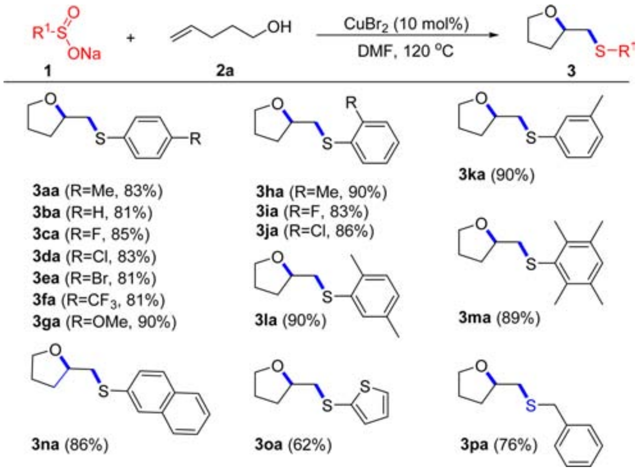


entry	catalyst	ligand	additive	solvent	yield[b] (%)
1	$CuBr_2$			DMSO	45
2	$CuBr_2$		PPh_3	DMSO	43
3	$CuBr_2$		Na_2S	DMSO	nd
4	$CuBr_2$		Zn	DMSO	30
5	**$CuBr_2$**			**DMF**	**88 (83)**
6	$CuBr_2$			toluene	nd
7	$CuBr_2$			DCE	nd
8	$CuCl_2$			DMF	58
9	CuBr			DMF	32
10	CuI			DMF	47
11	CuCl			DMF	20
12	$CuBr_2$		K_2CO_3	DMF	32
13	$CuBr_2$		EtN_3	DMF	48
14	$CuBr_2$		CH_3SO_3H	DMF	80
15	$CuBr_2$		$TsOH{\cdot}H_2O$	DMF	58
16[c]	$CuBr_2$	1,10-phen		DMF	65
17[c]	$CuBr_2$	2,2-Bipy		DMF	76
18				DMF	nd

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), Cu salts (10 mol %), and additive (1.0 equiv) in the indicated solvent (2 mL) at 120 °C under air for 24 h. [b] Determined by GC analysis. Dodecane is used as internal standard. Data in parentheses is isolated yield. nd = not detected. [c] 10 mol % of ligand was added.

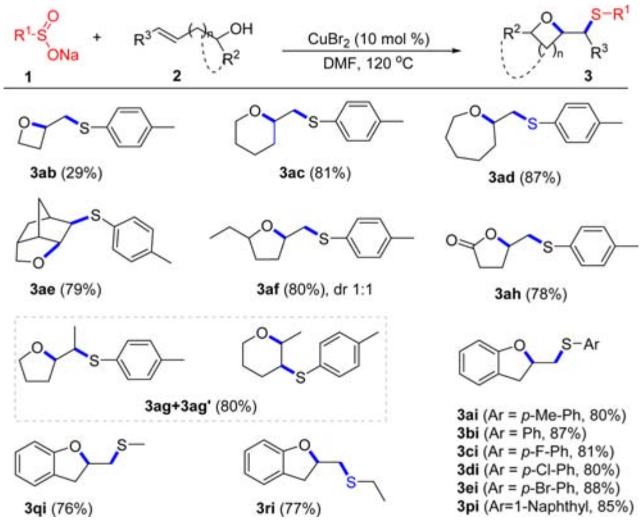
Na_2S, or Zn did not improve the yield of **3aa** (entries 2–4). The examination of solvent effects revealed that the solvent played an important role in this reaction (entries 5–7). Notably, when the reaction was carried out in DMF, which has been reported as a reducing solvent,[12] the yield of **3aa** increased to 88% (entry 5). Among the copper salts examined, both Cu(I) and Cu(II) catalysts could facilitate this transformation, and $CuBr_2$ was shown to be optimal (entries 8–11). Neither base nor acid additives could further improve the yield (entries 12–15). In addition, ligands such as 2,2′-bipyridine and 1,10-phenanthroline were tested; however, no obvious influence on the reaction could be observed (entries 16 and 17). Finally, control experiments demonstrated that copper catalyst was necessary for this transformation (entry 18).

Scheme 2. Substrate Scope of Sodium Sulfinate[a]



[a] Reaction conditions: all reactions were performed with **1** (0.25 mmol), **2a** (0.25 mmol), and $CuBr_2$ (10 mol %) in DMF (2.0 mL) at 120 °C under air for 24 h. Isolated yields were given.

Scheme 3. Substrate Scope of Enols[a]



[a] Reaction conditions: unless otherwise noted, all reactions were performed with **1** (0.25 mmol), **2** (0.25 mmol), and $CuBr_2$ (10 mol %) in DMF (2.0 mL) at 120 °C under air for 24 h. Isolated yields are given.

With the optimal reaction conditions in hand, we then examined the scope of this transformation. As shown in Scheme 2, various sodium sulfinates were found to be suitable substrates for this transformation. First, a series of *para*-substituted sodium benzenesulfinates including some with electron-donating groups (Me, OMe) and some with electron-withdrawing groups (F, Cl, Br, CF_3) were well tolerated and converted to the corresponding tetrahydrofuran products **3aa–ga** in good yields. Notably, halo substituents, such as –Cl and –Br, were well tolerated, providing the possibility for further functionalization (**3da** and **3ea**). Next, no significant effect was found for the substituents at the *para-*, *ortho-*, and *meta-*positions of the phenyl ring (**3ha**, **3ka**, and **3aa**). Polysubstituted sodium benzenesulfinates were also found to be good reaction partners. Products **3la** and **3ma** were isolated in 90% and 89% yields, respectively. When sodium 2-naphthalenesulfinate and 2-thiophenesulfinate were employed as the substrates, the desired products **3na** and **3oa** were obtained in 86% and 62% yields. To our delight, in addition to aromatic sodium sulfinates, alkyl sodium sulfinates were also suitable substrates which delivered **3pa** in 76% yield.

To further demonstrate the synthetic potential of this method, various enols were employed in this copper-catalyzed cyclization reaction (Scheme 3). Pleasingly, besides tetrahydrofuran and tetrahydropyran products, four-membered ring product **3ab**, which is known to be a strained ring system, could be constructed by this method, albeit in medium yield. The formation of the seven-membered ring ether **3ad** is particularly noteworthy in view of the synthesis of oxepane terpenes.[4e] 5-Norbornen-2-methanol was also a suitable reaction partner for this reaction, and the corresponding product **3ae** was obtained in 79% yield. To our delight, 4-pentenoic acid could react smoothly with **1a** to give **3ah** in 78% yield. Nonterminal enolate was then tested, and the mixed products of **3ag** and

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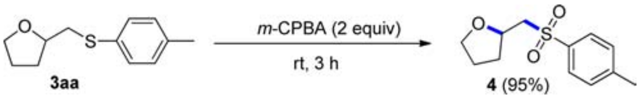
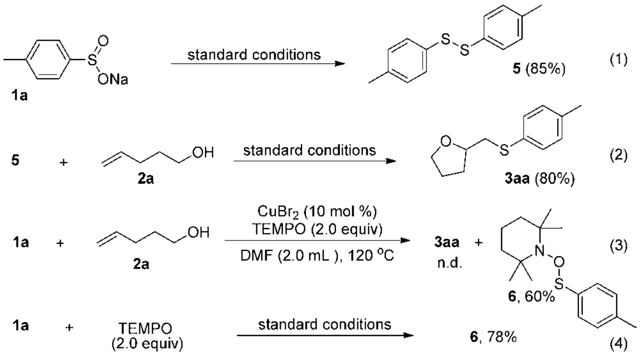
3ag′ were obtained. Moreover, 2-allylphenol could undergo this oxysulfuration reaction to give the corresponding 2,3-dihydrobenzofuran products in 76−88% yields. It is worth mentioning that MeS- and EtS-substituted products could also be obtained.

Furthermore, sulfone derivative **4** was generated in excellent yields via the oxidation with *m*-CPBA, which might be a robust method for the synthesis of sulfone cyclic ether, a versatile and essential building block in organic chemistry.[13]



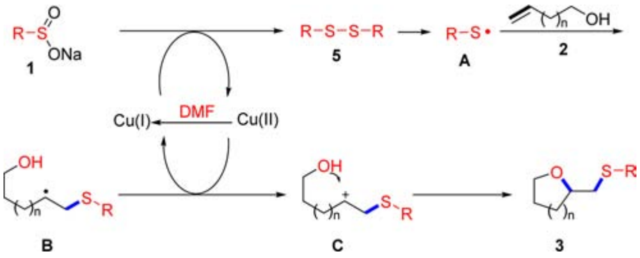
To gain insight into the mechanism of the chemical reaction, several control experiments were conducted. First, the reducing reagent for this reaction is a critical issue. Under the standard reaction conditions, disulfide **5** was obtained in good yield in the absence of the enolate substrate (eq 1). However, without



copper salts, disulfide **5** could not be detected even upon heating to 150 °C in DMF. Further experiments indicated that **5** could be transformed into **3aa** in 80% yield under the optimized conditions (eq 2). These observations indicated that disulfide **5** might be an intermediate for this reaction; sodium sulfinates were reduced by Cu(I), and the resulting Cu(II) was reduced to Cu(I) by DMF.[12] Next, when the radical scavenger TEMPO was employed in the reaction system, the oxysulfuration process was totally shut down and TEMPO-trapped compound **6** was isolated in 60% yield (eq 3) and further identified by ^{1}H and ^{13}C NMR. In addition, sodium sulfinate **1a** could react with TEMPO smoothly to provide **6** under the standard reaction conditions (eq 4), thus indicating that sulfur radical (RS$^\bullet$) should be involved as a reactive species in the reaction process.

On the basis of the experimental results and previous reports,[14] a plausible mechanism for this transformation is proposed in Scheme 4. The reaction was initially triggered by Cu-catalyzed dimerization of sodium sulfinates for the formation of disulfide intermediate **5**, which then converted to the sulfur radical (RS$^\bullet$) ether via direct radical cracking or the sulfenyl halide intermediate.[8,15,16] Subsequently, the sulfur radical (RS$^\bullet$) was added to the double bond of enolate to form the *α*-RS-alkyl radical **B**. Finally, a single-electron oxidation of the radical intermediate followed by internal nucleophilic trapping of the resulting carbocation **C** would lead to the desired oxysulfuration product.[10] Alternatively, a copper-mediated C−O bond formation though an *α*-RS-alkylcopper species is also possible.

Scheme 4. Proposed Mechanism



In conclusion, we have developed an efficient and practical copper-catalyzed oxysulfenylation reaction of enolates with sodium sulfinates for the synthesis of sulfenylated cyclic ethers. This novel transformation used easily available and stable sodium sulfinates as ideal thiolating reagents to construct various sulfenylated heterocycles, including four- and seven-membered cyclic ethers. The reaction conditions are mild, and no external reducing agents are needed; sodium sulfinates are proposed to be reduced by Cu(I), which can be regenerated by the reduction of DMF. Ongoing studies in our laboratory are dedicated to the detailed reaction mechanism and further synthetic applications of this transformation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00272.

General experimental procedure and characterization data of the products (PDF)

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Notes

The authors declare no competing financial interest.

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(16) The RS^+ mechanism mentioned in the introduction may be also possible, although the radical-trapping experiment with TEMPO can support the $RS^\bullet$ mechanism