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Copper-Catalyzed Synthesis of Thiosulfonates by Oxidative Coupling of Thiols with Sodium Sulfinates

Nobukazu Taniguchi*[a]

Keywords: Synthetic methods / Oxidative coupling / Sulfur / Thiols / Sulfinates / Copper

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The copper-catalyzed sulfonylation of thiols was performed by using sodium sulfinates under an oxygen atmosphere. The procedure afforded thiosulfonates in good yields by using a CuI–Phen·H_2O (Phen = 1,10-phenanthroline) catalyst and tolerated numerous combinations of arene- and alkanethiols with sodium sulfinates. Furthermore, it was found that the coupling of diaryl disulfides with sodium arylsulfinates proceeded in air and both sulfide groups on the disulfide were available.

Introduction

The development of organosulfur synthetic methodology is an important field in organic chemistry, and various reactions have been reported to date.[1] In particular, the transition-metal-catalyzed formation of carbon–sulfur bonds has been well investigated.[2] The obtained compounds have found widespread utilization as useful intermediates and reagents.[3] In contrast, research on the useful construction of sulfur–heteroatom bonds has been very restricted to date. Similarly, the transition-metal-catalyzed synthesis of thiosulfonates with sulfur–sulfone bonds has been scarcely investigated, and these compounds have been prepared by traditional methods. However, they are convenient derivatives that can be used in sulfenylation reactions that have been employed for the formation of unsymmetrical disulfides, including the immobilization of enzymes.[4,5a] Regrettably, an efficient synthetic procedure has not been exploited yet.

As shown in Figure 1, thiosulfonates have been generally prepared by oxidation of disulfides[5] or through sulfenylation of sulfinic acid salts by using sulfenyl halides.[6] The reaction of disulfides with sodium sulfinates has also been performed in the presence of Lewis acids.[7,8] These reactions often require the use of excess amounts of oxidants. Unfortunately, the coupling of thiols with sulfonyl chlorides has not yet been reported owing to the rapid formation of disulfides from thiols with thiosulfonates.

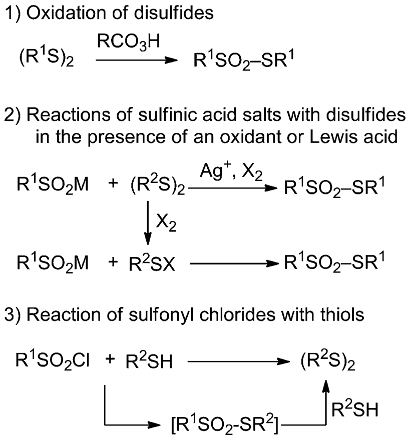

Figure 1. A general preparation of thiosulfonates.

In general, reaction performed with the use of thiols cannot be controlled completely. Exploitation of a simple method with the use of thiols is accordingly desired. To achieve this, suppression or treatment of the disulfides produced from thiosulfinates with thiols becomes the important process.

As an approach to solve this problem, it is considered that the employment of transition-metal catalysts is appropriate, because transition metals have the ability to cleave disulfide bonds.[9] For instance, it is well known that the copper-catalyzed sulfenylation of various compounds can be performed under oxidative conditions.[10,11] This shows that the copper-catalyzed procedure is never affected by the generation of disulfides, and therefore, disulfides can be utilized (Figure 2).

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[a] Department of Chemistry, Fukushima Medical University,
Fukushima 960-1295, Japan
E-mail: taniguti@fmu.ac.jp
http://www.fmu.ac.jp/

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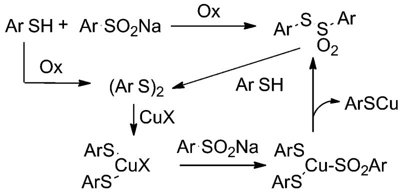


Figure 2. Strategy for the synthesis of thiosulfonate from thiols with sodium sulfinates.

Therefore, the copper-catalyzed oxidative coupling of thiols with sodium sulfinates was investigated. It was found that the procedure could produce the desired thiosulfonates in excellent yields. In this paper, the methodology will be described.

Results and Discussion

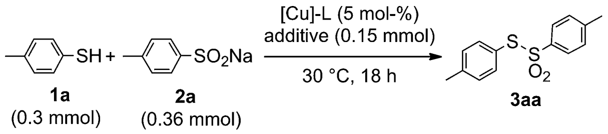
The evaluation of copper catalysts and ligands was commenced by using 4-toluenethiol (**1a**) and sodium 4-tolylsulfinate (**2a**) as starting materials (Table 1). Upon performing the reaction in the absence of the CuI catalyst at 30 °C in air, corresponding thiosulfonate **3aa** was not obtained at all and the disulfide was produced in 81% yield (Table 1, entry 1). Similarly, the CuI catalyst itself could not promote the reaction (Table 1, entry 2). By examining the amine ligands, reactions performed by using *N*,*N*,*N''*,*N''*-tetramethyl-1,2-ethylenediamine (TMEDA), bpy (bipyridyl), and Phen·H_2O (1,10-phenanthroline·H_2O) provided the product in about 10% yield (Table 1, entries 3–5). However, upon adding water and NH_4BF_4 to improve the cationic nature of the copper catalyst, the yield of **3aa** increased to 43 and 59% yield, respectively (Table 1, entries 6 and 7). Fortunately, the reaction that was performed under an oxygen atmosphere proceeded satisfactorily and gave **3aa** in 96% yield (Table 1, entry 8). Regrettably, other additives (NH_4PF_6 and Cs_2CO_3), solvents, and copper catalysts did not adequately promote the reaction (Table 1, entries 9–15). Thus, it became apparent that the copper-catalyzed coupling of thiols with sodium sulfinates gave excellent results under an oxygen atmosphere.

On the basis of the established results, various combinations of thiols with sodium sulfinates were surveyed. A mixture of thiol **1** (0.3 mmol), sodium sulfinate **2** (0.36 mmol), NH_4BF_4 (0.15 mmol), and CuI–Phen·H_2O (1:1, 5 mmol) in DMA (0.3 mL) and water (0.1 mL) was stirred at 30 °C under an oxygen atmosphere. As shown in Table 2, this procedure afforded the expected thiosulfonates in 41–96% yields (Table 2, entries 1–17), and it also tolerated numerous combinations of arenethiols with sodium sulfinates. However, the reaction performed with the use of 2-pyridinethiol (2-PySH) did not proceed well (Table 2, entry 18). In the sulfonylation reaction, not only arenethiols but also alkanethiols could be used. However, it was necessary to use 10 mol-% of the CuI–Phen·H_2O catalyst and to prolong the reaction time owing to the stability of alkanethiolate–copper complexes (Table 2, entries 19 and 20).

To determine the reaction mechanism, some experiments were next screened. Upon performing the reaction in the absence of oxygen, the expected thiosulfonate was produced in 2% yield (Scheme 1). This result supports the fact that the coupling of thiols with sodium sulfinates requires the presence of oxygen.

The reactivity of the phenylthiolate(I)–copper complex,[12] which was considered to be the intermediate, was also researched (Scheme 2). This reaction gave the corresponding product in 49% yield. It is clear that oxidation of thiolate–copper complexes promotes the synthesis of thiosulfonates.

Table 1. Investigation of suitable conditions.



1a (0.3 mmol) **2a** (0.36 mmol) **3aa**

Entry	[Cu]	Solvent [mL][a]	Additive	Conditions	Yield **3aa** [%][b]
1	none	DMA (0.3)	none	air	0
2	CuI	DMA (0.3)	none	air	0
3	CuI–TMEDA	DMA (0.3)	none	air	9
4	CuI–bpy	DMA (0.3)	none	air	12
5	CuI–Phen·H_2O	DMA (0.3)	none	air	10
6	CuI–Phen·H_2O	DMA/H_2O (0.3:0.1)	none	air	43
7	CuI–Phen·H_2O	DMA/H_2O (0.3:0.1)	NH_4BF_4	air	59
8	CuI–Phen·H_2O	DMA/H_2O (0.3:0.1)	NH_4BF_4	O_2	96
9	CuI–Phen·H_2O	DMF/H_2O (0.3:0.1)	NH_4PF_6	O_2	71
10	CuI–Phen·H_2O	DMSO/H_2O (0.3:0.1)	NH_4BF_4	O_2	65
11	CuCl–Phen·H_2O	DMA/H_2O (0.3:0.1)	NH_4BF_4	O_2	43
12	CuBr–Phen·H_2O	DMA/H_2O (0.3:0.1)	NH_4BF_4	O_2	43
13	$CuCl_2$–Phen·H_2O	DMA/H_2O (0.3:0.1)	NH_4BF_4	O_2	49
14	$CuBr_2$–Phen·H_2O	DMA/H_2O (0.3:0.1)	NH_4BF_4	O_2	54
15	$Cu(OAc)_2$–Phen·H_2O	DMA/H_2O (0.3:0.1)	NH_4BF_4	O_2	69

[a] DMA = dimethylacetamide.[a] Yield of isolated product after silica gel chromatography.

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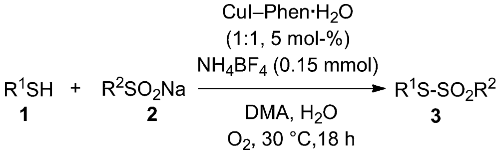
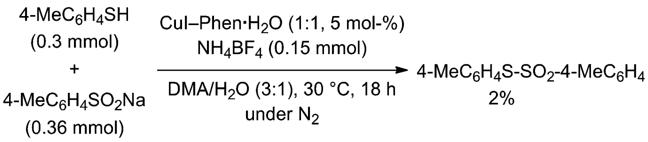
Table 2. Copper-catalyzed sulfonylation of thiols.[a]

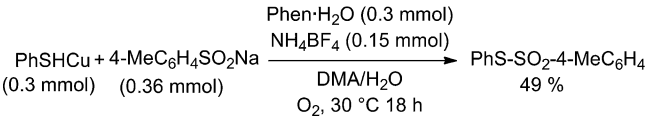


Entry	R1	R2	**3** [%][b]
1	C_6H_5SH	$4\text{-}MeC_6H_4SO_2Na$	85
2	$4\text{-}MeC_6H_4SH$	$C_6H_5SO_2Na$	85
3	$4\text{-}MeC_6H_4SH$	$4\text{-}MeC_6H_4SO_2Na$	96
4	$4\text{-}MeC_6H_4SH$	$4\text{-}MeOC_6H_4SO_2Na$	81
5	$4\text{-}MeC_6H_4SH$	$4\text{-}AcHNC_6H_4SO_2Na$	62
6	$4\text{-}MeC_6H_4SH$	$4\text{-}ClC_6H_4SO_2Na$	76[c]
7	$4\text{-}MeC_6H_4SH$	$4\text{-}FC_6H_4SO_2Na$	72[d]
8	$4\text{-}MeC_6H_4SH$	$MeSO_2Na$	87
9	$4\text{-}MeOC_6H_4SH$	$4\text{-}MeC_6H_4SO_2Na$	90
10	$4\text{-}ClC_6H_4SH$	$4\text{-}MeC_6H_4SO_2Na$	80
11	$4\text{-}BrC_6H_4SH$	$4\text{-}MeC_6H_4SO_2Na$	73
12	$4\text{-}HOC_6H_4SH$	$4\text{-}MeC_6H_4SO_2Na$	41[c]
13	$4\text{-}H_2NC_6H_4SH$	$4\text{-}MeC_6H_4SO_2Na$	42[c]
14	$2\text{-}MeC_6H_4SH$	$4\text{-}MeC_6H_4SO_2Na$	82
15	$2\text{-}MeOC_6H_4SH$	$4\text{-}MeC_6H_4SO_2Na$	70
16	$2\text{-}BrC_6H_4SH$	$4\text{-}MeC_6H_4SO_2Na$	69
17	2-naphthylSH	$4\text{-}MeC_6H_4SO_2Na$	73
18	2-PySH	$4\text{-}MeC_6H_4SO_2Na$	trace
19	*n*BuSH	$4\text{-}MeC_6H_4SO_2Na$	68[c,e]
20	*i*PrSH	$4\text{-}MeC_6H_4SO_2Na$	40[c,e]

[a] Reaction conditions: A mixture of thiol **1** (0.3 mmol), sodium sulfinate **2** (0.36 mmol), NH_4BF_4 (0.15 mmol), and CuI–Phen·H_2O (1:1, 5 mol-%) in DMA (0.3 mL) and water (0.1 mL) at 30 °C under an oxygen atmosphere. [b] Yield of isolated product after silica gel chromatography. [c] 36 h. [d] 24 h. [e] The reaction was performed by using CuI–Phen·H_2O (1:1, 10 mol-%).



Scheme 1. Reaction in the absence of oxygen.



Scheme 2. Reactivity of the copper–phenylthiolate complex.

From these investigations, a plausible reaction mechanism is considered as follows (Figure 3). In cycle A, thiolate–copper(I) complex **9** is formed from copper iodide and the thiol or sodium sulfinate. Oxidation of **9** gives Cu^{II} complex **10**; and $R^1S(R^2SO_2)Cu^{II}L_n$ **11** is produced by transmetalation. Finally, thiosulfonate is produced by reductive elimination and Cu^IX is regenerated.[11a] In cycle B, after the formation of the disulfide by the oxidation of the thiol, reaction of Cu^IX with the disulfide and sodium sulfinate affords complex **12**. Reductive elimination of **12** produces thiosulfinate and **9**. Consequently, the oxidation of **9** affords **10**, and **11** is reproduced.

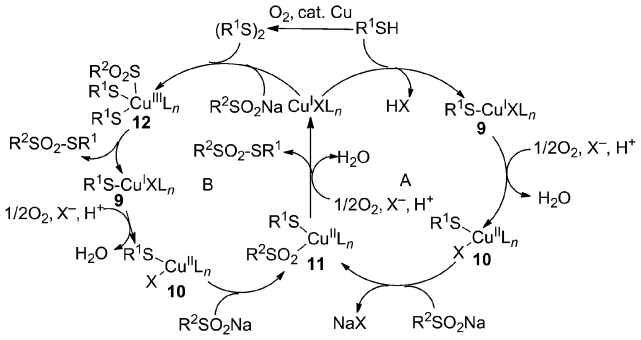
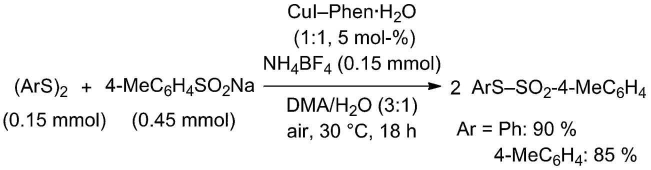


Figure 3. A plausible reaction mechanism.

From the described plausible mechanism, it was believed that the coupling of disulfides with sodium sulfinates could be performed. To date, an excess amount of the iodine oxidant was necessary for the reaction. To solve this problem, attention was focused on the coupling of disulfides with sodium sulfinates. Notably, the reaction could be performed at 30 °C in air, and the expected thiosulfonates were obtained in excellent yields. Furthermore, both sulfide groups of the disulfide were available to the reaction (Scheme 3). Further investigation into the exact details of the conditions and the mechanism are now in progress.



Scheme 3. Sulfonylation of disulfides.

Conclusions

In conclusion, the copper-catalyzed coupling of thiols with sodium sulfinates was achieved under an oxygen atmosphere. The procedure could be used to synthesize various thiosulfonates in good yields. The coupling of disulfides with sodium sulfinates also proceeded in air, and the two sulfide groups on the disulfides were available.

Experimental Section

General Method: CuI (2.9 mg, 0.015 mmol) and Phen·H_2O (3.0 mg, 0.015 mmol) were added to a mixture of benzenethiol (33.1 mg, 0.3 mmol), sodium 4-tolylsulfinate (64.1 mg, 0.36 mmol), and NH_4BF_4 (15.7 mg, 0.15 mmol) in DMA (0.3 mL) and H_2O (0.1 mL), and the mixture was stirred at 30 °C for 18 h under an oxygen atmosphere. After the residue was dissolved in Et_2O, the solution was washed with H_2O and saturated sodium chloride and dried with anhydrous magnesium sulfate. Chromatography on silica gel (30% diethyl ether/hexane) gave PhS-SO_2-4-MeC_6H_4 (67.5 mg, 85%).

Supporting Information (see footnote on the first page of this article): Experimental details, analytical data. and copies of the ^1H NMR and ^{13}C NMR spectra.

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Oxidative Coupling

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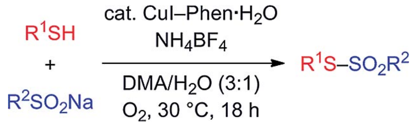

N. Taniguchi* 1–5

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