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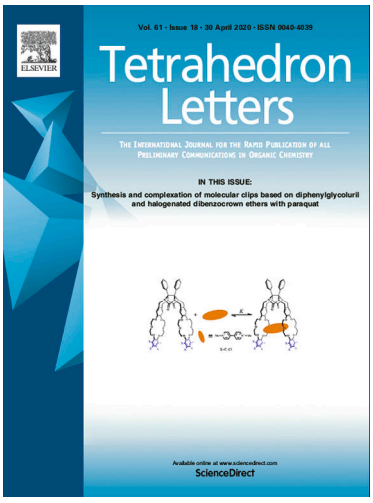

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$CuCl_2$-promoted decomposition of sulfonyl hydrazides for the synthesis of thiosulfonates

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ABSTRACT

Sulfonyl hydrazides recently received much attention as reagents for the introduction of sulfur-containing functional groups into organic compounds, because both sulfonyl and sulfenyl sources could be generated by the oxidation and decomposition of the sulfonyl hydrazides, respectively. However, the transformations of sulfonyl hydrazides into thiosulfonates, which could be produced by the reaction between sulfonyl and sulfenyl sources, have been less investigated. In this manuscript, we describe $CuCl_2$-promoted selective synthesis of thiosulfonates from sulfonyl hydrazides. A variety of thiosulfonates were produced in moderate to good yields. The mechanism involving radical intermediates such as sulfonyl radical and thiyl radical was proposed on the basis of the previously reported references and mechanistic investigations. In addition, quantum chemical simulations revealed that Cu-promoted decomposition of sulfonyl hydrazides is thermodynamically viable in the developed conditions.

Sulfonyl hydrazides have emerged as versatile reagents in organic synthesis due to their interesting property and reactivity.[1] The sulfonyl hydrazides are readily accessible from the reaction of the corresponding sulfonyl chlorides with aqueous hydrazine solution.[2] They generally exist as stable solids, and are relatively less sensitive to air compared to other sulfur-containing reagents. The condensation of the sulfonyl hydrazides with aldehydes or ketones easily produce *N*-sulfonylhydrazones, which could be employed in important transformations such as Shapiro reaction[3] and other cross-coupling reactions.[4] The thermal decomposition of sulfonyl hydrazides generates sulfinic acid and diimide, and the generated diimide was utilized in the reduction of alkenes.[5] Recently, the sulfonyl hydrazides received much attention as reagents to introduce sulfur-containing functional groups such as sulfonyl and sulfenyl group into organic compounds.[6]

Thiosulfonates are not only important moieties of biological active compounds but also useful building blocks in organic synthesis.[7] Interestingly, the thiosulfonates were often observed as intermediates, side products, or byproducts in the organic reactions using sulfonyl hydrazides.[8] Because both sulfonyl and sulfenyl sources could be generated by the oxidation and decomposition of sulfonyl hydrazides respectively, the production of thiosulfonates from sulfonyl hydrazides might be regarded as facile transformations. However, only few protocols were reported for the selective thiosulfonates synthesis from sulfonyl hydrazides.[9]

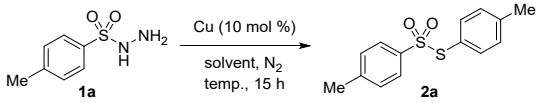
Although the first example of the thiosulfonates synthesis from sulfonyl hydrazides was reported in 1972,[10] the protocols for the selective thiosulfonates synthesis from sulfonyl hydrazides were developed over the past decade. Tian group revealed that the use of molecular iodine accelerated the decomposition of the *p*-toluenesulfonyl hydrazide to produce thiosulfonate in moderate yield (44%).[8a] After Tian's work, the decomposition of sulfonyl hydrazides into thiosulfonates catalyzed by I_2 or *N*-iodosuccinimide (NIS) were disclosed in the presence of stoichiometric oxidants.[8f,11] In addition to iodine-catalysis, visible light induced decomposition of sulfonyl hydrazides using Pd/ZrO_2 nanocomposite photocatalyst was developed for the synthesis of thiosulfonates.[12] Herein, we describe Cu-promoted synthesis of thiosulfonates from sulfonyl hydrazides without the use of stoichiometric amounts of oxidants.

First, we investigated the reactivity of 4-methylbenzenesulfonyl hydrazide **1a** using our previously reported conditions in the Cu-catalyzed synthesis of sulfonamides from sulfonyl hydrazides and amines (Table 1).[13] Gratifyingly, the desired thiosulfonate **2a** was produced albeit in a low yield (entry 1). The decomposition of **1a** at higher temperature caused the increased product yield (entry 2). Interestingly, the reasonable yield was obtained when the reaction was carried out under N_2 instead of O_2 (entry 3). This result indicated that no stoichiometric oxidant such as molecular oxygen was required in the present method.[8f,11] Among the copper sources screened, the use of $CuCl_2$ showed the best result to produce **2a** in 81% yield (entry 4). It was noteworthy that Cu(II) generally showed better reactivity than Cu(I) (entries 3–9). The used of polar solvents such as DMSO, DMF, and 1,4-dioxane gave inferior results to toluene (entries 10–12). We tried to reduce the reaction temperature, however, the thiosulfonate synthesis was sluggish at 70 °C (entry 13). In order to investigate

the

were carried out. When the developed protocol was conducted without $CuCl_2$, thermal decomposition of sulfonyl hydrazide took place to produce **2a** in 24% yield.[8e,8g,8i] It was revealed that the reaction rate with copper is much faster than that without copper (Figure 1). These results indicated that the use of $CuCl_2$ efficiently facilitates the decomposition of **1a** for the selective synthesis of thiosulfonate **2a**. The developed thiosulfonate synthesis was effective even in the dark, therefore, it was assumed that the photochemical reaction was not involved in the present decomposition.[12]

Table 1. Optimization for Cu-promoted decomposition of sulfonyl hydrazides into thiosulfonates.[a]



Entry	Cu source	Solvent	Temp. (°C)	Yield (%)[b]
1[c]	$CuBr_2$	CH_3CN	50	21
2[c]	$CuBr_2$	toluene	90	54
3	$CuBr_2$	toluene	90	76
4	**$CuCl_2$**	**toluene**	**90**	**82**
5	$Cu(OAc)_2$	toluene	90	41
6	$Cu(OTf)_2$	toluene	90	67
7	CuCl	toluene	90	54
8	CuBr	toluene	90	28
9	CuI	toluene	90	25
10	$CuCl_2$	DMSO	90	10
11	$CuCl_2$	DMF	90	0
12	$CuCl_2$	1,4-dioxane	90	59
13	$CuCl_2$	toluene	70	35

[a] Reaction conditions: **1a** (0.5 mmol) and Cu source (10 mol %) in solvent (1.0 mL) under N_2 for 15 h. [b] Yield determined by ^1H NMR spectroscopy (internal standard: 1,1,2,2-tetrachloroethane). [c] Under O_2 balloon.

The substrate scope of our method was then explored with a number of different sulfonyl hydrazides (Table 2). Generally, benzenesulfonyl hydrazides were converted into the corresponding thiosulfonates in moderate to good yields regardless of the substituents (**2a**–**2f**, **2h**, **2i**, and **2k**–**2m**). The thiosulfonate synthesis from **1g** was not effective in the optimized conditions because of the poor solubility of **1g** in toluene, however, the replacement of toluene with 1,4-dioxane generated the desired thiosulfonate **2g** in a moderate yield. The conversion of benzenesulfonyl hydrazide bearing cyano group at meta position was sluggish, presumably due to the coordination of Cu on the nitrogen of cyano group (**2j**). Both 1-naphthalenesulfonyl hydrazide **1n** and multi-substituted benzenesulfonyl hydrazides such as **1o**, **1p**, and **1q** underwent the present decomposition to produce the corresponding thiosulfonates in good yields. It is noteworthy that aliphatic sulfonyl hydrazides such as **1r** and **1s** could be employed in the developed thiosulfonate synthesis.[11,12] The present thiosulfonate synthesis was effective on a larger scale. The use of 10 mmol of **1a** in the present reaction conditions provided **2a** in 94% yield (1.31 g) (Scheme 1).

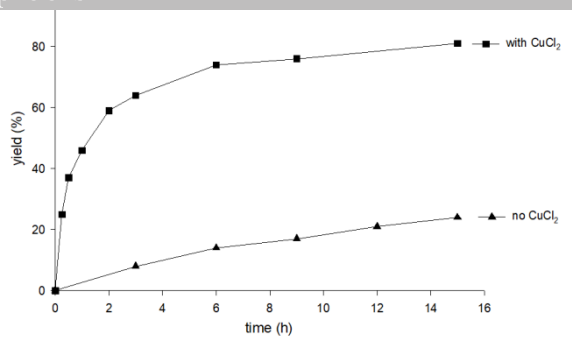
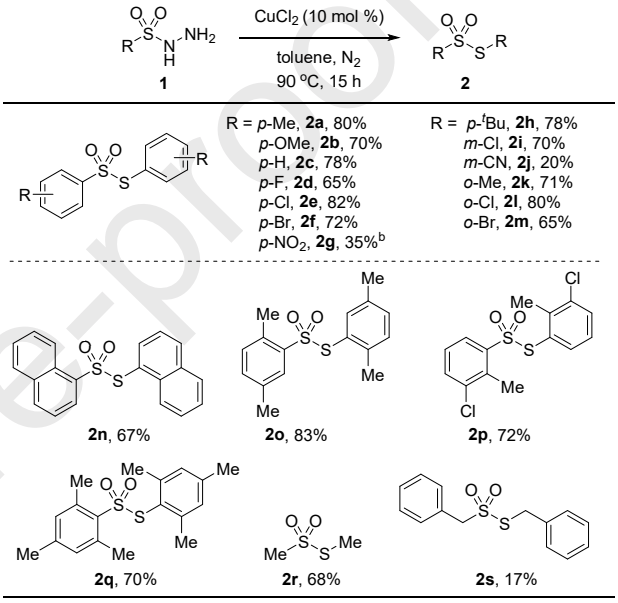


Figure 1. The comparison of reaction rates between the developed reaction with $CuCl_2$ and that with no Cu.

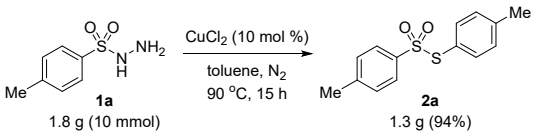
Table 2. Substrate scope of sulfonyl hydrazides.[a]



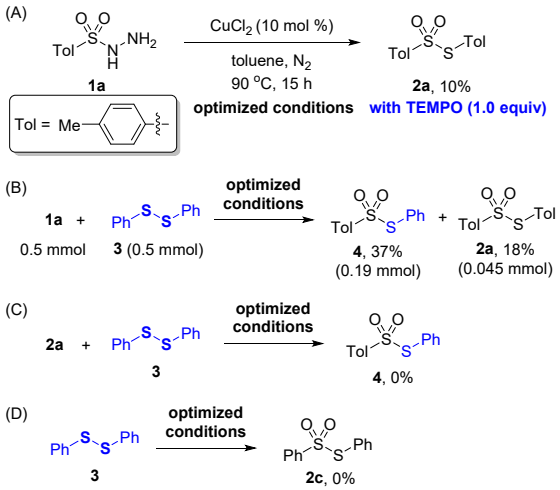
[a] Reaction conditions: **1** (0.5 mmol) and $CuCl_2$ (10 mol %) in toluene (1.0 mL) under N_2 at 90 °C for 15 h, isolated yield. [b] The use of 1,4-dioxane instead of toluene.

Several control experiments were carried out to understand the mechanism of the present thiosulfonate synthesis (Scheme 2). It was observed that the addition of radical scavenger such as TEMPO (1.0 equiv) to the model reaction caused the significant drop of the product yield (Scheme 2 A). This result supports that the developed thiosulfonate synthesis would proceed through the radical intermediate. Interestingly, the considerable amounts of the crossover thiosulfonate was produced, when the model reaction was carried out in the presence of disulfide **3**, which was observed as a side product in the developed reaction with **1c** (below 10%) (Scheme 2 B). However, the employment of **2a** and **3** in the model reaction did not gave any the crossover product, and both thiosulfonate and disulfide were recovered (Scheme 2 C). These observations revealed that the radical intermediate such as the sulfonyl radical might be generated from the sulfonyl hydrazide, and the reaction of the generated sulfonyl radical with disulfide could produce the thiosulfonate.[14] Therefore, the poor yield of **1s** in Scheme 1 could be ascribed to the facile decomposition of the generated benzyl sulfonyl radical intermediate, because the desulfonation of the benzyl sulfonyl radical results the relatively stable toluene radical.[15] When the disulfide **3** was employed in the developed reaction conditions, no thiosulfonate was generated and the used disulfide **3** was

reco as a disulfide to thiosulfonate pathway was able to be ruled out.[8i]

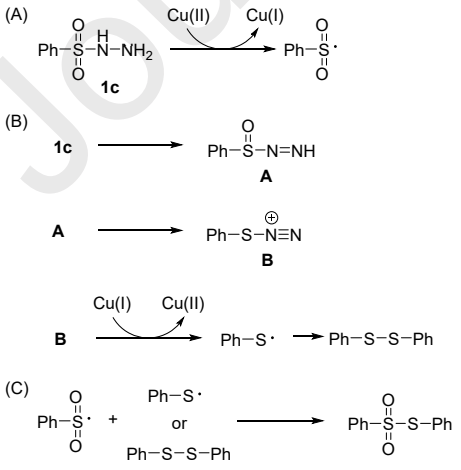


Scheme 1. Scale up process for Cu-promoted decomposition of sulfonyl hydrazide for thiosulfonate.



Scheme 2. Control experiments for mechanistic investigation.

On the basis of our observations and related references, a plausible proposed mechanism with **1c** was depicted in Scheme 3. At first, one sulfonyl hydrazide undergoes Cu(II)-promoted oxidative decomposition to produce a sulfonyl radical with Cu(I) (Scheme 3 A).[16] It is suggested the other sulfonyl hydrazide might undergo a couple of decompositions for the generation of sulfenyl compound **B** and the reduction of **B** with Cu(I) generates the crucial intermediate, thiyl radical, with releasing nitrogen gas (Scheme 3 B).[8a,8h,17] The production of disulfide as a side product would be attributed to dimerization of the generated thiyl radical. Finally, the reaction between sulfonyl radical and thiyl radical produces the desired thiosulfonate (Scheme 3 C). In some case, the thiosulfonate is able to be produced by the reaction of the sulfonyl radical with disulfide, according to the observation in Scheme 2 C. However, other mechanisms involving the generation of sulfinyl radical from **A** can not totally ruled out at this stage due to the complicate decompositions of sulfonyl hydrazides.[18]



Scheme 3. Proposed mechanism.

model substrate to investigate the Cu-promoted decomposition of sulfonyl hydrazides into **A**. It was predicted that the Cu-promoted decomposition of **1c** is thermodynamically viable with the accessible reaction barrier of 28.1 kcal/mol. However, this result does not necessarily exclude the other possible mechanisms such as Brønsted acid promoted or thermally activated decomposition of sulfonyl hydrazide.

In summary, we have achieved the selective transformation of sulfonyl hydrazides into thiosulfonates using catalytic amounts of $CuCl_2$. The use of stoichiometric oxidants such as O_2 or $K_2S_2O_8$ was not required in the developed protocol. Compared to the thermal decomposition of sulfonyl hydrazides, the reaction rate of the developed protocol was much faster. Both benzenesulfonyl hydrazides having either electron-withdrawing or electron-donating groups and aliphatic sulfonyl hydrazides efficiently underwent the present protocol to produce the corresponding thiosulfonates. From the mechanistic experiments and related references, it was proposed that the reaction of sulfonyl radical with thiyl radical or disulfide produced the desired thiosulfonates. The computational simulation suggested that the Cu-promoted decomposition of sulfonyl hydrazides is thermodynamically viable.

Acknowledgments

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Supplementary Material

Supplementary data (experimental procedures for sulfonamide synthesis, and ^{1}H and ^{13}C NMR spectra of the products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.

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19. See the supporting information for the details of quantum chemical simulations.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- Cu-promoted synthesis of thiosulfonates from sulfonyl hydrazides was achieved.
- The use of stoichiometric oxidants was not required in the developed protocol.
- The developed synthesis of thiosulfonates was effective on a larger scale.
- The generations of sulfonyl radical and thiyl radical were proposed