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Cu-catalyzed aerobic oxidative synthesis of sulfonamides from sulfonyl hydrazides and amines

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ABSTRACT

An environmentally friendly route for sulfonamides has been developed. The oxidative coupling of sulfonyl hydrazides and amines was catalyzed by $CuBr_2$ to produce various sulfonamides with the water and nitrogen gas as byproducts. Preliminary experiments revealed that the sulfonyl radical is likely to be involved in the reaction mechanism.

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The synthesis of sulfonamide functional group is important in medicinal and synthetic chemistry, because the sulfonamide moiety is not only a key structural motif of many natural products, pharmaceuticals, and bioactive compounds [1] but also a versatile amine protecting group [2]. In order to introduce the sulfonamide moiety in organic compounds, a construction of S—N bond has been regarded as a crucial process. Traditionally, the S—N bond formation could be achieved by nucleophilic substitutions of sulfonyl chlorides with amines in the presence of a base [3,4].

An alternative S—N bond formation for the synthesis of sulfonamides has been reported by Jiang and co-workers in 2013 [5]. They revealed that an oxidative coupling of sodium sulfinates and amines facilitated S—N bond formation to generate sulfonamides in the presence of $CuBr_2$ and DMSO as a catalyst and an oxidant, respectively. In their proposed mechanism, the used sodium sulfinates underwent one electron oxidation by Cu(II) and a sulfonyl radical intermediate was generated. Finally, the generated sulfonyl radical combined with copper amine complex to cause the S—N bond formation for the desired sulfonamide products. After Jiang's pioneering work, various oxidative coupling methods of sodium sulfinates using stoichiometric amounts of iodine [6] or catalytic amounts of iodine with an external oxidant [7] have been reported [8].

In 2016, elegant S—N bond formations for sulfonamides, which employed sulfonyl hydrazides [9] as precursors for sulfonyl radicals, have been independently developed by Yotphan [10], Yu [11], and Peddinti [12] (Scheme 1A). The conditions of these protocols are quite similar and commonly required iodine catalyst such as I_2 or NH_4I and *tert*-butyl hydroperoxide (TBHP) oxidant to generate sulfonyl radicals from sulfonyl hydrazides. Although these reactions exhibited interesting utilizations of sulfonyl hydrazides for sulfonamides through the generation of sulfonyl radicals, the substrate scope of sulfonyl hydrazides was limited to aromatic sulfonyl hydrazides and the use of superstoichiometric amounts of TBHP was less attractive.

Aerobic oxidative transformations using oxygen as an oxidant have emerged as environmentally friendly protocols because these reactions utilize the readily accessible and inexpensive molecular oxygen, and produce only water as a byproduct [13]. However, no aerobic methods for sulfonamides synthesis from sulfonyl hydrazides have been reported. Recently, our group revealed that the use of copper efficiently catalyzed the aerobic oxidation of several hydrazines such as di-*tert*-butyl hydrazodicarboxylates and alkyl 2-phenylhydrazinecarboxylates [14]. On the basis of these results and our continued interest in aerobic oxidations [15], we tried to apply copper and oxygen system to the oxidative coupling of sulfonyl hydrazides and amines. Herein, we describe a Cu-catalyzed aerobic oxidative synthesis of sulfonamides from sulfonyl hydrazides and amines (Scheme 1B) [16]. The developed sulfonamide synthesis fulfills the requirement for green and sustainable chemistry because only Cu catalyst is required without any additive or base, and water and nitrogen gas are produced as byproducts.

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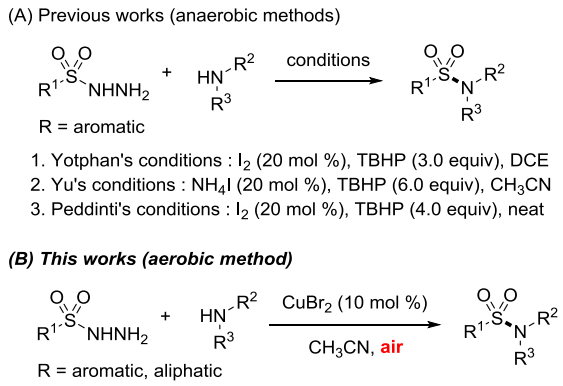
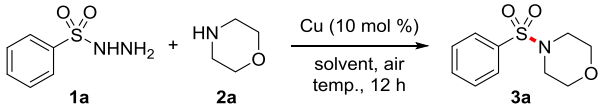


Scheme 1. (A) Previously reported sulfonamides synthesis (B) Aerobic oxidative sulfonamides synthesis.

With benzenesulfonyl hydrazide **1a** and morpholine **2a** as model substrates, the reactivity of various copper sources was screened in acetonitrile solvent under air (Table 1) [17]. Gratifyingly, the used copper sources catalyzed oxidative coupling of **1a** and **2a**, and $CuBr_2$ exhibited a superior result to other copper sources (entries 1–6). The use of other solvents such as DMF, DMSO, and toluene gave the desired sulfonamide **3a** in moderate yields (entries 7–9). The Cu-catalyzed aerobic oxidative coupling was effective even using reduced amounts of **2a** (3.0 equiv) (entry 10). The use of reduced amounts of $CuBr_2$ showed a moderate yield and no significant increase of the yield was observed even in the high loading of $CuBr_2$ (entry 11). Although the present reaction took place at 25 °C, we found that increasing the temperature to 50 °C generally showed better results for the broader range of sulfonyl hydrazides (entry 12). However, the present reaction showed a decreased yield at 70 °C in spite of full conversion of **1a** (entry 13). When the present reaction was carried out under O_2 balloon, instead of under air, **3a** was produced in 50% yield (entry 14).

Table 1
Optimization of Cu-catalyzed aerobic oxidative coupling of benzenesulfonyl hydrazide and morpholine.[a]

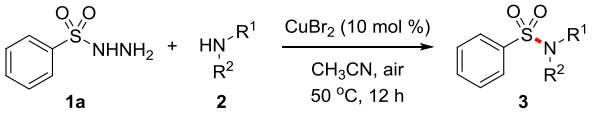


1a 2a 3a

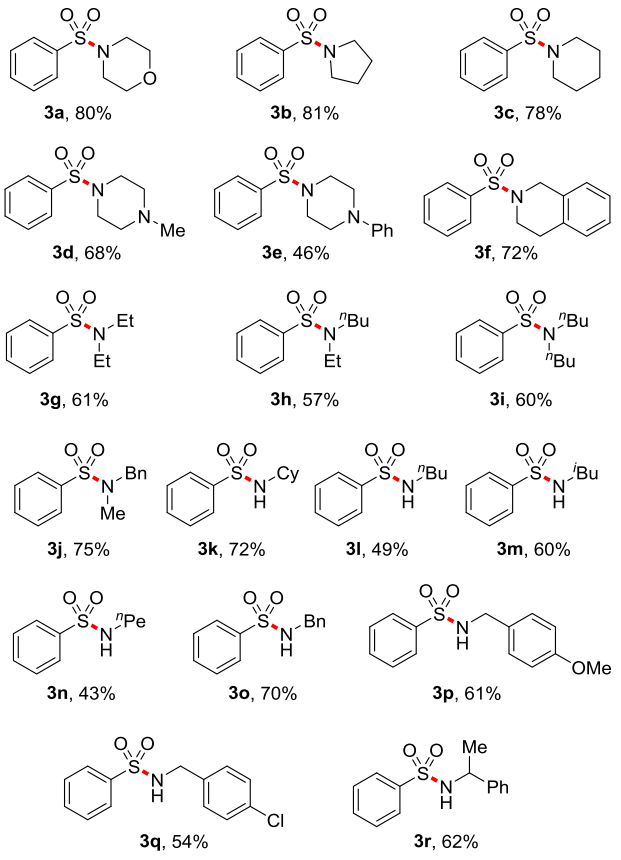
Entry	Cu source	Solvent	Temp. (°C)	Yield (%)[b]
1	CuCl	CH_3CN	50	68
2	CuBr	CH_3CN	50	64
3	CuI	CH_3CN	50	50
4	$Cu(CH_3CN)_4PF_6$	CH_3CN	50	29
5	$CuBr_2$	CH_3CN	50	78
6	$Cu(OAc)_2$	CH_3CN	50	20
7	$CuBr_2$	DMF	50	52
8	$CuBr_2$	DMSO	50	40
9	$CuBr_2$	toluene	50	63
10[c]	$CuBr_2$	CH_3CN	50	80
11[c]	$CuBr_2$	CH_3CN	50	57[d], 81[e]
12[c]	$CuBr_2$	CH_3CN	25	79
13[c]	$CuBr_2$	CH_3CN	70	61
14[c,f]	$CuBr_2$	CH_3CN	50	50

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.0 mmol, 4.0 equiv), and Cu source (10 mol %) in solvent (4.0 mL) under air for 12 h.
[b] Yield determined by ^1H NMR spectroscopy (internal standard: 1,1,2,2-tetrachloroethane).
[c] 3.0 equiv of **2a** was used.
[d] The use of 5 mol % of $CuBr_2$.
[e] The use of 20 mol % of $CuBr_2$.
[f] Under O_2 balloon.

Table 2
Substrate scope of amines for Cu-catalyzed aerobic oxidative coupling.[a]



1a 2 3



[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.5 mmol), and $CuBr_2$ (10 mol %) in CH_3CN (4.0 mL) under air at 50 °C for 12 h, isolated yield. [b] n.r.: no reaction.

The optimized reaction conditions were then tested in the aerobic oxidative couplings of **1a** and a number of different amines (Table 2). The employment of cyclic amines such as pyrrolidine and piperidine efficiently produced the corresponding sulfonamides in good yields (**3b** and **3c**). Piperazines having a methyl or phenyl group at nitrogen showed moderate yields (**3d** and **3e**). While the oxidative coupling of **1a** and 1,2,3,4-tetrahydroquinoline was sluggish, a successful transformation was observed in the oxidative coupling of **1a** and 1,2,3,4-tetrahydroisoquinoline (**3f**). A variety of secondary acyclic amines including diethylamine, *N*-ethylbutylamine, dibutylamine, and *N*-methylbenzylamine underwent the developed oxidative coupling in moderate to good yields (**3g**–**3j**). The reactivity of primary amines was also investigated in the present oxidative coupling, and it was revealed that the desired secondary sulfonamides were efficiently synthesized in moderate yields (**3k**–**3n**). No signification influence of the para-substitutions was observed in the used benzylamines (**3o**–**3q**). The present aerobic oxidative coupling of **1a** and α-methylbenzylamine **2r** produced the corresponding sulfonamide **3r** in 62% yield. Unfortunately, aniline, 2-pyrrolidinone, pyrrole, imidazole, and pyrazole did not produce any sulfonamides presumably due to the poor basicity. The present aerobic oxidative sulfonamide synthesis was effective on a larger scale [17]. The use of 7 mmol of **1a** in the present reaction conditions with **2a** provide **3a** in 72% yield (1.15 g). Although the optimized conditions were not

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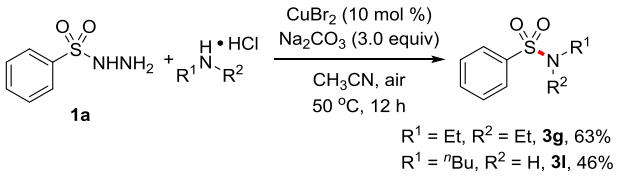
effective in the oxidative couplings of **1a** and amine hydrochloride salts, comparable results to the reactions of simple amine substrate were observed in the presence of a stoichiometric amount of base such as Na_2CO_3 (Scheme 2).

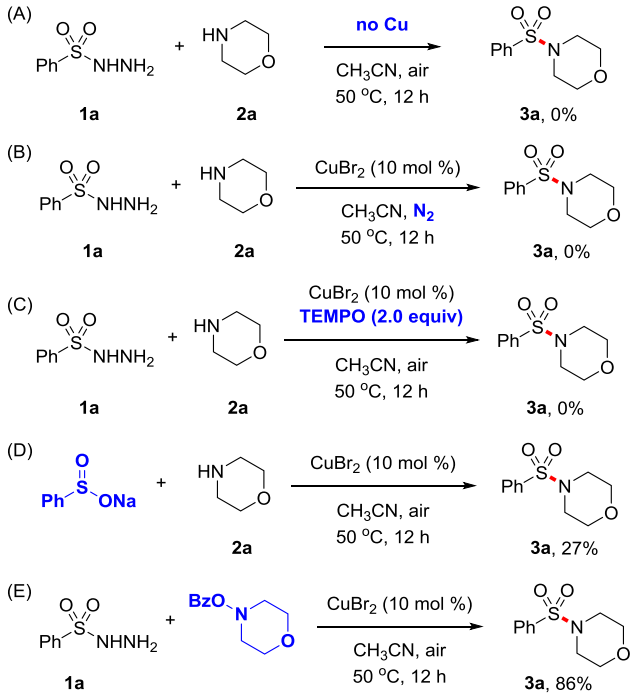
Next, the substrate scope of sulfonyl hydrazides was investigated, and the results were illustrated in Table 3. A variety of para-substituted sulfonyl hydrazides produced the corresponding sulfonamides in good yields regardless of their electronic environments (**4a**-**4f**). Not only ortho-substituted benzene sulfonyl hydrazides but also 1-naphthalene sulfonyl hydrazide efficiently underwent the present oxidative coupling to produce corresponding sulfonamides (**4g**-**4i**). It is noteworthy that aliphatic sulfonyl hydrazides could be employed in the developed Cu-catalyzed aerobic oxidative coupling, while the previously reported iodine systems were not effective in aliphatic substrates (**4j** and **4k**) [10–12]. Notably, the medicinally relevant sulfonamide **4l**, an intermediate for probenecid, was able to be synthesized by the developed coupling reaction in 42% yield [18].

In order to understand the mechanism of the present protocol, several experiments were carried out. When the aerobic oxidative coupling of **1a** and **2a** was carried out without copper or under N_2 balloon, **3a** was not produced, and 78% or 14% of **1a** were recovered, respectively (Scheme 3A and B). These results indicate that the copper catalyst and oxygen are essential for the synthesis of sulfonamides, and the decomposition of sulfonyl hydrazides was facilitated by copper rather than oxygen [19]. It was observed that the addition of TEMPO (2.0 equiv) to the model reaction inhibited the production of sulfonamides in spite of the full conversion of **1a** (Scheme 3C). In addition, the use of sodium benzenesulfinate, instead of **1a**, in the model reaction produced **3a** in 27% yield (Scheme 3D). These observations imply that the developed oxidative coupling proceeds through the benzenesulfonyl radical [5,16c,20]. When 4-(benzoyloxy)morpholine was employed instead of morpholine, the corresponding sulfonamide **3a** was efficiently produced, suggesting the copper amine complex might be involved in the reaction pathway (Scheme 3E) [21].

On the basis of our observations and related Ref. [22], a plausible mechanism was proposed in Scheme 4. Initially, the sulfonyl radical **A** is generated by the Cu-catalyzed aerobic oxidation of sulfonyl hydrazides [10–12,22a]. The generated sulfonyl radical **A** reacts with Cu(II) to give Cu(III) complex **B**. Then, ligand substitution takes place to form Cu(III) intermediate **C**. The desired sulfonamide and Cu(I) species **D** are produced by reductive elimination of intermediate **C**. Finally, the regeneration of $Cu(II)Br_2$ by the aerobic oxidation of **D** in the presence of HBr finishes the catalytic cycle of the developed reaction.

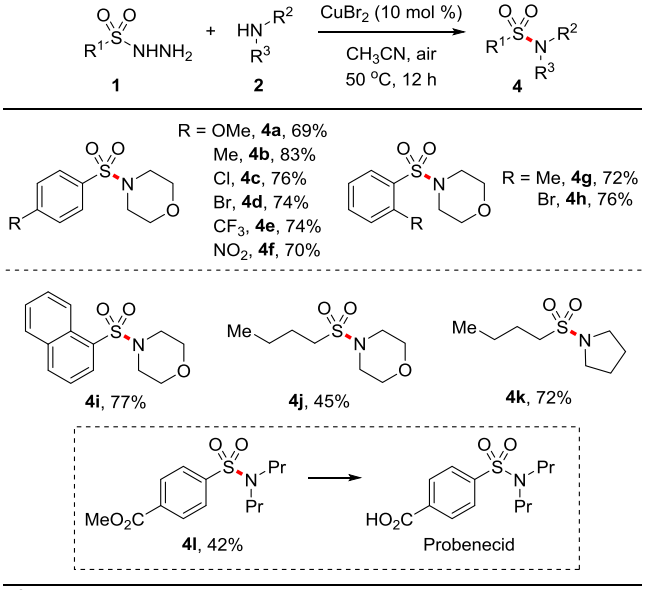


Scheme 2. Sulfonylation of amine hydrochloride salts.

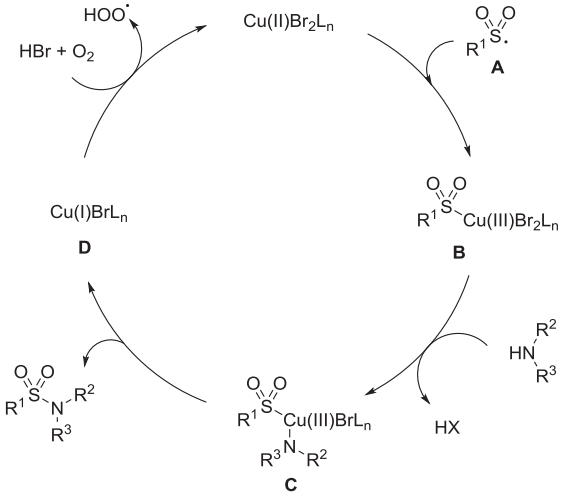


Scheme 3. Control experiments for mechanistic investigation.

Table 3
Substrate scope of sulfonyl hydrazides.[a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), and $CuBr_2$ (10 mol %) in CH_3CN (4.0 mL) under air at 50 °C for 12 h, isolated yield.



Scheme 4. Proposed mechanism.

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In conclusion, we have developed an environmentally friendly protocol for sulfonamides. Cu-catalyzed aerobic oxidative coupling of sulfonyl hydrazides and amines produced the desired sulfonamides with water and nitrogen gas as byproducts. The developed coupling showed broad substrate scope in amines including secondary amines, primary amines, and amine hydrochloride salts. It is noteworthy that aliphatic sulfonyl hydrazides, which were unreactive in the previously reported anaerobic systems, could be employed in the developed aerobic oxidative coupling. The developed coupling was effective on a larger scale. The plausible mechanism was proposed, and further studies are underway to provide mechanistic details.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data (experimental procedures for sulfonamide synthesis, and ^{1}H and ^{13}C NMR spectra of the products) to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.02.016.

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