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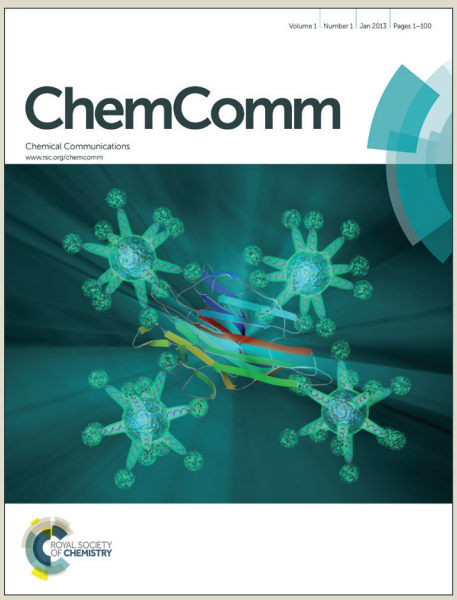

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ARTICLE TYPE

Copper-mediated S-N formation via oxygen-activated radical process: A new synthesis method for sulfonamide

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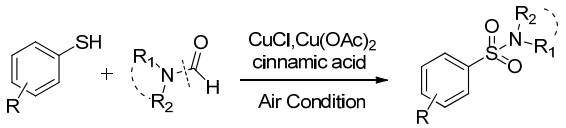
Copper-mediated direct S-N formation using readily available starting materials via oxygen-activated radical process has been developed. This method provides a novel and direct approach for synthesis of sulfonamides under air condition.

Sulfonamides that possess a wide range of biological activities have been widely used in the pharmaceutical industry.[1] The traditional methods for the synthesis of sulfonamides principally involve (1) reaction of amines with sulfonyl chlorides or sulfonic esters;[2a] (2) coupling of N-unsubstituted/N-monosubstituted sulfonamides with amines or organo halides;[2b] and (3) oxidation of sulfenamides.[2c] Although these methods are available and can be used to easily build S-N bond, they are limited by their not readily available reactants, multistep reactions, strong oxidants and toxic derivatives. Transition metal-catalyzed reaction is a new strategy for the synthesis of sulfonamides.[3] In 2010, Taniguchi et al.[4] developed a method of copper-catalyzed synthesis of sulfonamides from thiols and amines under oxygen atmosphere. Recently, Jiang et al.[5] reported on copper-catalyzed sulfonamide formation using sodium sulfinates and amines under oxygen balloon. Using oxygen as oxidant is favorable for green chemistry. However, limited substrate scope and restricted reaction condition hinder the wide application of oxygen as oxidant. Thus, developing an efficient and versatile strategy for the synthesis of sulfonamide is necessary.

Dimethyl formamide (DMF) is a polar solvent that has been used as a precursor of -NMe_2, -$CONMe_2$, and -Me group.[6] Among these reaction units, the decarbonylation of DMF as a source of -NMe_2 has elicited the attention of chemists.[7] In 2009, Chang et al.[8] developed a silver-mediated amination of benzoxazoles with DMF. Meanwhile, Wan et al.[9] introduced DMF as the source of aminyl radical in the synthesis of amides.

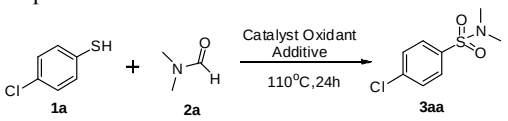


Scheme 1 Strategy for the synthesis of Sulfonamide.

Based on increasing interest on thiols,[10] we report a copper-mediated direct sulfonamide formation from thiols and formamides under air condition (Scheme 1). To the best of our knowledge, this study is the first to use formamides as the N sources in the synthesis of sulfonamides.

4-Chlorothiophenol **1a** and DMF **2a** were used as the model substrates to optimize the reaction condition. The results are summarized in Table 1.

Table 1 Optimization of the reaction conditions [a]



1a **2a** **3aa**

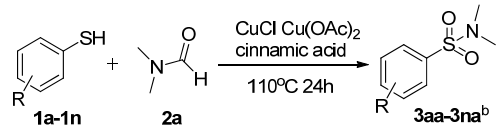
Entry	Copper Salts(equiv.)	Oxidant (equiv.)	Additive(equiv.)	Yield [b] (%)
1	CuCl (1)	$Cu(OAc)_2$ (1)	benzoic acid (1)	81
2	CuI (1)	$Cu(OAc)_2$ (1)	benzoic acid (1)	15
3	CuBr (1)	$Cu(OAc)_2$ (1)	benzoic acid (1)	28
4	$CuCl_2$ (1)	$Cu(OAc)_2$ (1)	benzoic acid (1)	37
5	/	$Cu(OAc)_2$ (1)	benzoic acid (1)	0
6	CuCl (2)	$Cu(OAc)_2$ (1)	benzoic acid (1)	78
7	CuCl (0.1)	$Cu(OAc)_2$ (1)	benzoic acid (1)	trace
8	CuCl (1)	$Cu(OAc)_2$ (1)	cinnamic acid (1)	83
9	CuCl (1)	$Cu(OAc)_2$ (1)	L-proline (1)	57
10	CuCl (1)	$Cu(OAc)_2$ (1)	L-phenylalanie (1)	44
11	CuCl (1)	$Cu(OAc)_2$ (1)	CH_3COOH (2)	48
12	CuCl (1)	$Cu(OAc)_2$ (1)	H_2SO_4 (2)	37
13	CuCl(1)	$Cu(OAc)_2$ (1)	/	38

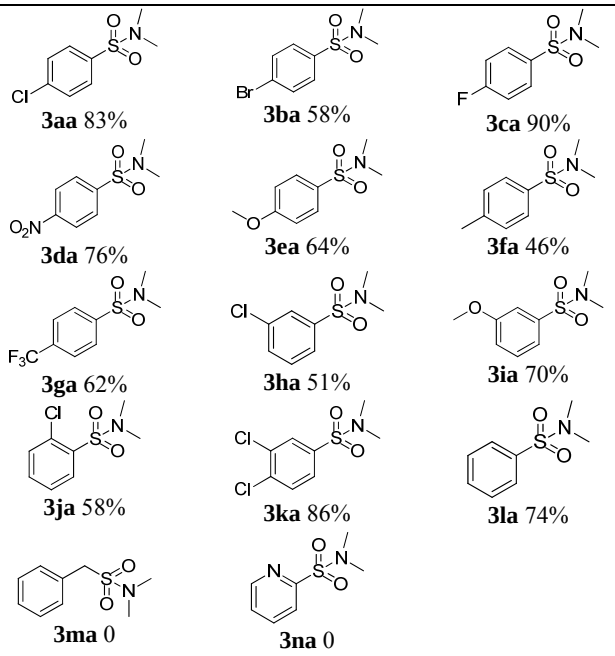
[a] Reaction Condition: **1a** (0.5 mmol),**2a** (1.5 ml), Copper Salts, Oxidant, Additive under air condition at 110°C for 24h. [b] Isolated yield.

The reaction was performed at 110°C in the presence of CuCl (1equiv), $Cu(OAc)_2$ (1equiv) and benzoic acid (1equiv) (as additive) under air condition for 24h. The desired product **3aa** was isolated and reached a yield of 81% (Table 1, Entry 1). Then, different copper salts were introduced, among which CuCl showed the best activity (Table 1, entries 1 to 4). However, no desired product was obtained when no copper salt was added, implying that the Cu(I) was necessary for the transformation (Table 1, entry 5). The amount of copper salt was also investigated, when 2 equiv of CuCl was used, the yield slightly decreased to 78% (Table 1, entry 6). By contrast, only a trace amount of the product was obtained when 0.1 equiv of CuCl was

used (Table 1, entry 7). This result indicated that the stoichiometric amount of copper salt was essential for the fluent conversion. A series of additives was also examined (Table 1, entries 8 to 13). Only 38% yield of the product was obtained in the absence of acid (Table 1, entry 13), suggesting the importance of acid in the reaction. Cinnamic acid and benzoic acid proved to be better than other acids.[11] Moreover, $Cu(OAc)_2$ produced the best result among different oxidants.[12] The reaction time, temperature and solvent were also tested (See ESI Table S1). Thus, the optimal reaction condition involved CuCl (1equiv)/$Cu(OAc)_2$ (1equiv)/cinnamic acid (1equiv) under air condition.

Table 2 Copper-Mediated S-N formation by DMF and various thiols [a]

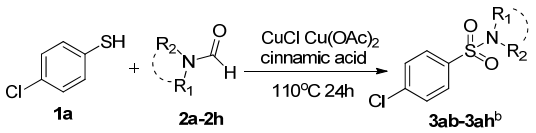


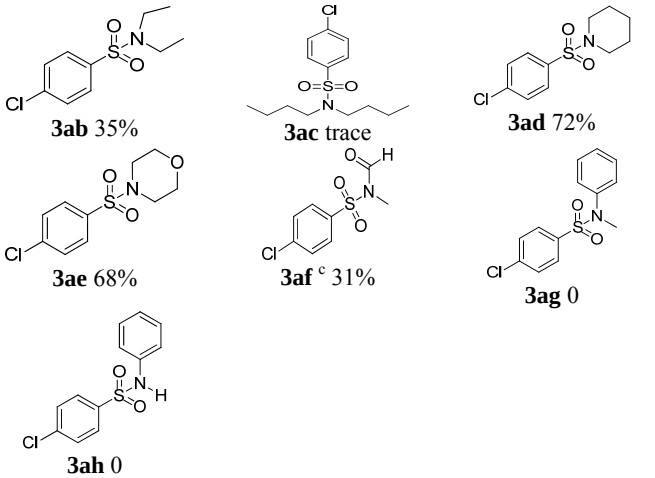


[a] Conditions: **1** (0.5 mmol), DMF (1.5 ml), CuCl (1equiv), $Cu(OAc)_2$ (1equiv), cinnamic acid (1equiv) under air condition at 110°C for 24h. [b] Isolated yield.

With the optimal reaction condition in hand, we then investigated the substrate scope of thiols. As shown in Table 2, the reaction proceeded smoothly with substrates containing electron-withdrawing groups and electron-donating groups in moderate to good yield (**3aa-3la**). In general, thiophenols bearing electron-donating groups produced lower yields. For example, when 4-methylthiophenol reacted with DMF under the optimal condition, the isolated yield was 46% (**3fa**), whereas strong electron-withdrawing groups such as 4-CF_3 (**3ga**) and 4-NO_2 (**3da**) could produce products with yields of 62% and 76%, respectively. Halide groups **(3aa-3ca, 3ka**) were all well tolerated and the corresponding products could be applied in further reactions. When 3,4-dichlorothiophenol was used, the desired product (**3ka**) was isolated in good yield. The steric effects had minimal influence on the transformation as confirmed by the higher yield facilitated by 2-Cl substrate (**3ja**) than 3-Cl substitute (**3ha**) (58% to 51%). However, neither the aliphatic thiol (**3ma**) nor the heterocycle thiol (**3na**) was suitable for the smooth conversion. These results indicated that the aromatic groups were essential for the reaction.

Table 3 Substrate scope of formamides with 4-Chlorothiophenol[a]



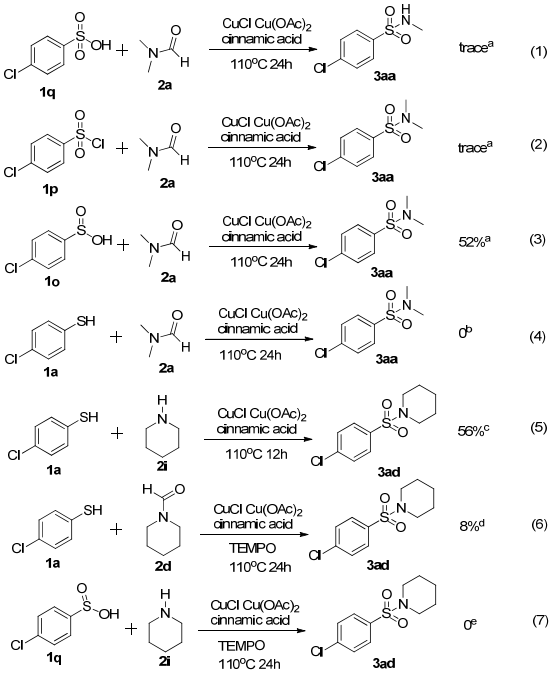


[a] Conditions:**1a** (0.5 mmol), **2** (1.5 ml), $Cu(OAc)_2$ (1equiv), cinnamic acid (1equiv), CuCl (1equiv) under air condition at 110°C for 24h. [b] Isolated yield. [c] **2f** (1mmol), DMA (1.5 ml), 6h.

A series of formamides was also examined to enlarge the synthetic utility of the protocol (Table 3). For N,N-disubstituted formamides, lower yields of products (**3aa** vs **3ab** and **3ac**) were obtained as the carbon chain on the N atom increased. These results could be attributed to the larger steric hindrance on the N atom of formamides. Meanwhile, the formamides derived from cyclic amines produced higher yields (**3ad** and **3ae**) compared with those derived from linear amine. However, no desired product was obtained for the N-monosubstituted formamide, In addition, **3af** was isolated when N-methyl formamide reacted with **1a** through a dehydrogenation process. Besides, N-methylformanilide (**3ag**) and formanilide (**3ah**) did not exhibit good results. This finding could be attributed to the strong conjugation between the amide group and phenyl ring that inhibited the decarbonylation of formamides.[9]

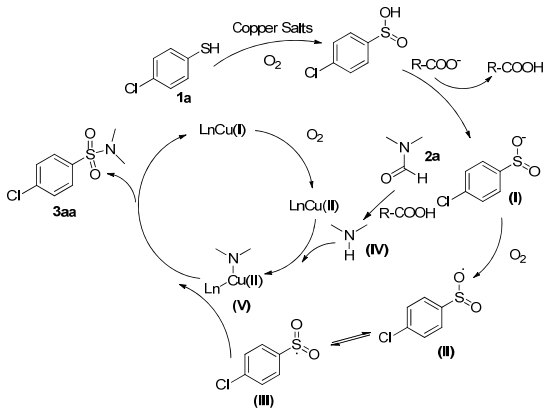
To gain further insights into the mechanism, a series of control experiments was carried out. The results are shown in Table 4. Only a trace amount of **3aa** was detected when 4-chlorobenzenesulfonic acid and 4-chlorobenzenesulfonyl chloride reacted with DMF under the optimal condition (Table 4, Eq. 1-2). However, the desired product produced a yield of 52% when 4-chlorobenzenesulfinic acid was used as the reactant (Table 4, Eq. 3). No desired product was detected when we changed the reaction atmosphere from air to nitrogen (Table 4, Eq. 4). These results suggested that benzenesulfinic acid may act as the intermediate from the oxidation of thiol under air condition. Then, 56% yield of **3ad** was obtained when formamide was changed to amine (Table 4, Eq. 5). This result indicated that amine may be another intermediate from the decarbonylation of formamide.

Table 4 Investigation into the mechanism of reaction



[a] Condition: **1** (0.5 mmol), **2a** (1.5 ml), $Cu(OAc)_2$ (1equiv), cinnamic acid (1equiv), CuCl (1equiv) under air condition in 110°C for 24h. [b] Condition: under N_2 atmosphere. [c] Condition: **1a** (0.5 mmol), **2i** (1 mmol), DMA (1.5 ml), $Cu(OAc)_2.H_2O$ (1equiv), cinnamic acid (1equiv), CuCl (1equiv) under air condition in 110°C for 12h. [d] Condition: **1a** (0.5 mmol), **2d** (1.5 ml), $Cu(OAc)_2$ (1equiv), cinnamic acid (1equiv), CuCl (1equiv),TEMPO (1.5equiv.) under air condition in 110°C for 24h.
[e] Condition: **1q** (0.5 mmol), **2i** (1 mmol), DMA (1.5 ml), $Cu(OAc)_2$ (1equiv), cinnamic acid (1equiv), CuCl (1equiv), TEMPO (1.5equiv.) under air condition in 110°C for 24h. Isolated yield.

Furthermore, only a trace amount of the product was detected in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidine-N-oxyl (Table 4, Eqs. 6 and 7). This result implied that a radical step was involved in the reaction.



Scheme 2 Proposed reaction mechanism

A plausible mechanism deduced according to the results above and recent publications[5, 13] is presented in Scheme 2. First, thiol (**1a**) was oxidized to sulfinic acid with copper salts under air condition and then translated into sulfinyl anion (**I**). The sulfinyl anion (**I**) was activated by oxygen via single electron transfer, providing an oxygen-centered radical (**II**) that could resonate with sulfonyl radical (**III**). Meanwhile, Cu^I was oxidized to form Cu^{II} species by oxygen. Formamide (**2a**) was decarbonylated by the acid to form amine (**IV**), which could then coordinate with Cu^{II} species to form intermediate (**V**). Finally, the copper complex (**V**) coupled with sulfonyl radical (**III**) to generate the desired product **3aa** with Cu^I released.

Conclusions

In summary, we developed a copper-mediated direct S-N bond formation from thiols and formamides. This protocol provides novel and direct synthesis of sulfonamides from readily available starting materials via oxygen-activated radical process. Further studies on the mechanism and related work are ongoing in our group.

Notes and references

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1 For selected papers, see: (a) C. T. Supuran, A. Casini, A.Scozzafava, Med. Res. Rev. 2003, **5**, 535; (b) H. Yoshino, N. Ueda, J. Niijima, H. Sugumi, Y. Kotake, N. Koyanagi, K. Yoshimatsu, M. Asada, T. Watanabe, T. Nagasu, K. Tsukahara,A. Iijima and K. Kitoh, J. Med. Chem., 1992, **35**, 2496; (c) M. Banerjee, A. Poddar, G. Mitra, A. Surolia, T. Owa and B. Bhattacharyya, J. Med. Chem., 2005, **48**, 547.

2 For selected papers, see: (a) T. Pandya, T. Murashima, L. Tedeschi, A. G. M. Barrett, J. Org. Chem. 2003, **68**, 8274; S. Caddick, J. D. Wilden, D. B. Judd, J. Am. Chem. Soc. 2004, **126**,1024; (b) J. Yin and S. L. Buchwald, Org. Lett., 2000, **2**, 1101; (c) F. Yuste, J. García Ruano, A. Parra and V. Mastranzo, Synthesis, 2008, **2**, 311.

3 (a) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, Chem.Rev., 2013, **113**,6234; (b) J. Kim and S. Chang, Angew. Chem. Int. Ed. 2014, **53**, 2203.

4 N. Taniguchi, Eur. J. Org. Chem., 2010, **14**, 2670.

5 X. Tang, L. Huang, C. Qi, X. Wu, W. Wu and H. Jiang, Chem. Commun., 2013, **49**, 6102.

6 S. Ding and N. Jiao, Angew. Chem., Int. Ed., 2012, **51**, 9226.

7 For recent selected papers, see: (a) Y. Li, Y. Xie, R. Zhang, K. Jin, X. Wang and C. Duan, J. Org. Chem., 2011, **76**, 5444; (b) W. X. Chen and L. X. Shao, J. Org. Chem., 2012, **77**, 9236; (c) H. Wang, L. N. Guo and X. H. Duan, Org. Biomol. Chem., 2013, **11**, 4573; (d) W. P. Mai, H. H. Wang, Z. C. Li, J. W. Yuan, Y. M. Xiao, L. R. Yang, P. Mao and L. B. Qu, Chem. Commun., 2012, **48**, 10117;(e) J. Wang, J. T. Hou, J. Wen, J. Zhang and X. Q. Yu, Chem. Commun., 2011, **47**, 3652.

8 S. H. Cho, J. Y. Kim, S. Y. Lee and S. Chang, Angew. Chem., Int. Ed., 2009, **48**, 9127.

9 Z. Liu, J. Zhang, S. Chen, E. Shi, Y. Xu and X. Wan, Angew. Chem., Int. Ed., 2012, **51**, 3231.

10 (a) R. Xu, J.P. Wan, H. Mao and Y. Pan, J. Am. Chem. Soc., 2010, **132**, 15531; (b) Z. Ni, S. Wang, H. Mao and Y. Pan, Tetrahedron Lett., 2012, **53**, 3907.

11 We thank for the reviewers for pointing out the aromatic acid could also acts as ligand to promote the reaction.

12 $Cu(OAc)_2$ is regarded as co-oxidant according to the results in ESI.

13 (a) Q. Lu, J. Zhang, F. Wei, Y. Qi, H. Wang, Z. Liu and A. Lei, Angew. Chem., Int. Ed., 2013, **52**, 7156; (b) Q. Lu, J. Zhang, G. Zhao, Y. Qi, H. Wang and A. Lei, J. Am. Chem. Soc., 2013, **135**, 11481; (c) R. Giri and J. F. Hartwig, J. Am. Chem. Soc., 2010, **132**, 15860.