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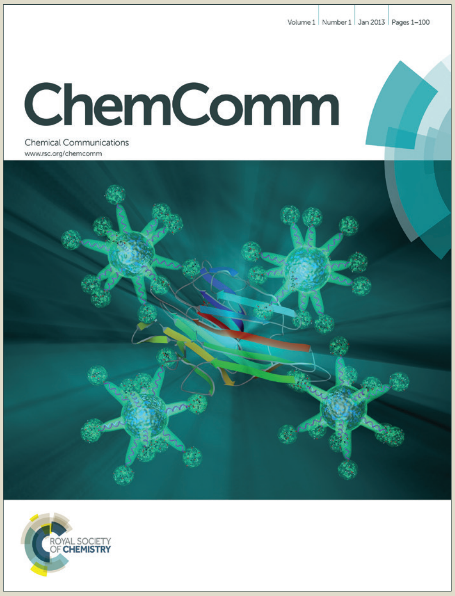

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Copper-Catalyzed Electrophilic Amination of Sodium Sulfinates at Room Temperature †

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By using *O*-benzoyl hydroxylamines as amine source, the first convenient copper-catalyzed electrophilic amination of sodium sulfinates has been realized. Even with 2 mol% catalyst loading, the protocol provided an efficient and straightforward synthesis of a broad range of functional sulfonamides under ambient reaction conditions without additional base and ligand. Based on the control experiments, a plausible mechanism was proposed.

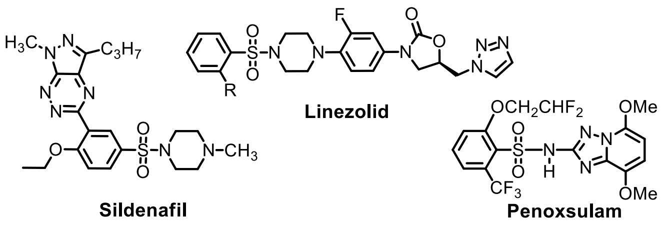
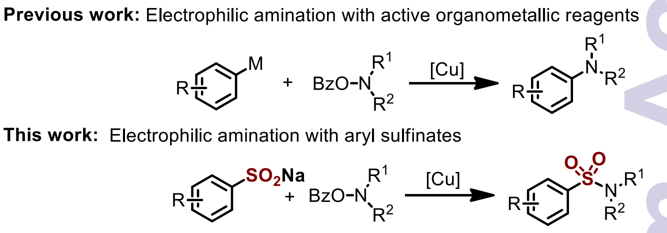


Fig. 1 Represented bioactive compounds with sulfonamide motif.

As a useful common structural fragment in a broad number of pharmaceutical compounds, sulfonamides usually exhibit promising bioactivities and are widely applied as HIV protease inhibitors, antibacterial, anticancer, anti-inflammatory reagents as well as herbicides (Figure 1).[1] Therefore, tremendous efforts have been devoted to develop the methodology to construct sulfonamides during past decades. Conventional protocols were intensively focused on nucleophilic substitutions of amines with isolated sulfonyl derivatives, especially, with difficult-to-handle sulfonyl chlorides.[2] Along with the development of modern organic synthesis, an impressive emphasis was addressed on transition-metal catalyzed sulfonamides-producing transformations of sulfonamides with arylhalides or arylboronic acids.[3] In particular, sulfonamides were also readily accessed by the coupling reactions of organometallic reagents with SO_2 surrogates,[4] in which the unit of SO_2 was readily introduced in a similar fashion as the carbonylation reactions.[5] Very recently, copper salts and I_2 have been demonstrated as good accelerators towards the synthesis of sulfonamides from sodium sulfinates with various amines.[6] Although various important achievements have been realized in this field, there are still several drawbacks in the reported methodologies including harsh reaction conditions, long reaction time, excess base requirements, high loading of expensive catalysts (additives), and difficulty in experiment handling.[7] It's worth noting that the nitrogen sources are restricted in nucleophilic amines in all the known protocols.



Scheme 1 Reaction design for the synthesis of sulfonamides by using *O*-benzoyl hydroxylamines

In contrast, as a kind of electrophilic nitrogen sources, nowadays, hydroxylamine derivatives have received considerable attention and successfully been applied in the transition-metal catalyzed amination reactions.[8] In the presence of proper cooper salts, hydroxylamines have been efficiently applied in the amnination of a plethora of organometallic reagents, such as aryl Grignard reagents, aryl zinc reagents, organoboranes and so on (Scheme 1).[9] However, to the best of our knowledge, there is no precedent utilizing any hydroxylamines as an electrophilic amine source in the copper-catalyzed sulfonamidation reactions. In consideration of aryl sulfinates are useful and easy-to-handle intermediates in organic synthesis,[10] we would like to explore the possibility of direct amination of sulfinates by using hydroxylamines as

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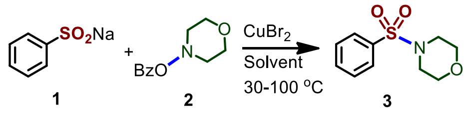
electrophilic nitrogen sources to synthesize sulfonamides (Scheme 1). Delightedly, herein, even under very mild reaction condition and a low catalyst loading, a variety of sodium sulfinates are readily coupled with *O*-benzoyl hydroxylamines with broad substrate scopes.

Table 1 Optimization of the reaction conditions [a]

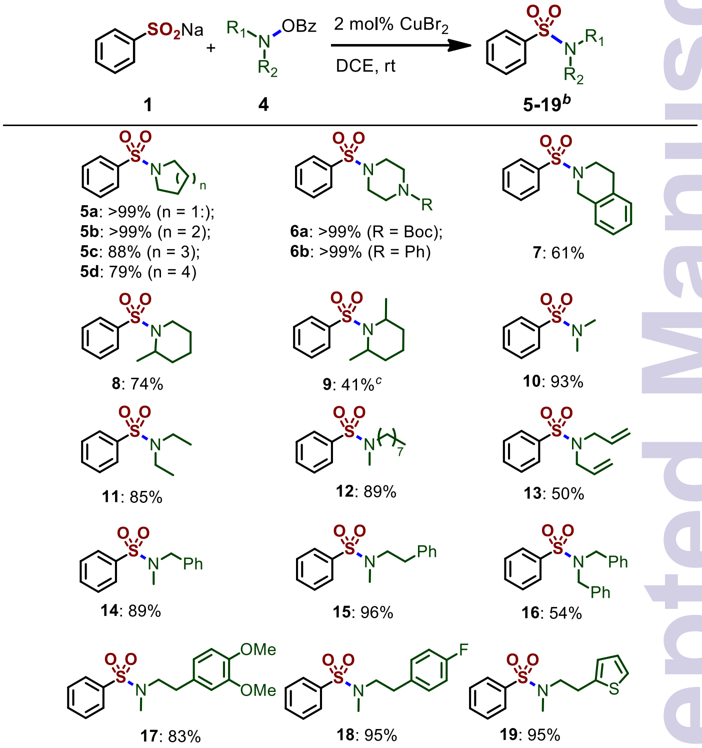


Entry	Solvent	Temp. (°C)	CuBr$_2$. (mol%)	Yield (%)[b]
1	Dioxane	100	10	80
2	Toluene	100	10	68
3	DMSO	100	10	65
4	THF	100	10	60
5	Bu$_2$O	100	10	77
6	EtOH	100	10	92
7	MeOH	100	10	23
8	H$_2$O	100	10	N.R.
9	DCE	100	10	>99
10	DCE	100	5	93
11	DCE	80	5	94
12	DCE	60	5	>99
13	DCE	40	5	>99
14	DCE	30	5	>99
15	DCE	30	2	98
16	DCE	30	/	NR

[a] Reaction was carried out with 0.5 mmol scale: 2 equiv. **1** and 1equiv. **2** were dissolved in 4 mL solvent and stirred in 12 h under atmosphere of N$_2$, then the catalyst was added and stirred for additional 12 h. [b] Isolate yield based on **2.**

Initially, the amination of sodium benzenesulfinate (**1**) by electrophilic *O*-benzoyl hydroxylmorpholine (**2**) was selected as a model reaction for the condition optimization. To our delight, by using 10 mol% CuBr$_2$ as a catalyst under N$_2$ atmosphere after 24 h at 100 °C, up to 80 % yield was observed when dioxane was applied as a solvent (Table 1, entry 1). No further enhancement was found when other solvents (including toluene, THF, DMSO and Bu$_2$O) were used instead (Table 1, entries 2-5). Interestingly, ethanol dramatically improved the transformation efficiency and produced the product **3**[6c] in a 92% isolated yield (Table 1, entry 6), probably due to better solubility of substrates in ethanol. In contrast, an inferior yield was found when methanol was used instead (Table 1, entry 7). After intensively optimization of the other solvent mixtures and metal salts (see ESI†), the best outcome was found when dichloroethane (DCE) and CuBr$_2$ were utilized, and sulfonamide **3** was formed almost in a quantitative yield (Table 1, entry 9). Delightedly, an identical yield was still obtained when the catalyst loading was reduced to 5 mol%. Meanwhile, the reaction temperature was decreased steadily, no significant impact on their yields was found (Table 1, entries 10-14), especially, a quantitative yield was still observed when the reaction was carried at 30 °C. Remarkably, at such mild reaction condition, the catalyst loading could be further reduced to 2 mol % with a slight yield decrease for sulfonamide **3** (98%, Table 1, entry 15). Additionally, no reaction took place with a blank test under the identical reaction conditions (entry 16, table 1). Therefore, the optimal reaction condition for the cooper-catalyzed electrophilic amination of sodium benzenesulfinate was established.

Table 2 Reaction scope with *O*-benzoyl hydroxylamines [a]

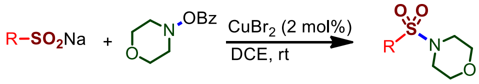


[a] Reaction was carried out with 0.5 mmol scale: 2 equiv. **1** and 1 equiv. **4** were dissolved in 4 mL DCE and stirred in 12 h, then the CuBr$_2$ was added and stirred for additional 12 h; [b] Isolate yield based on **4**; [c] with 5 mol% catalyst loading at 80 °C.

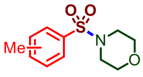
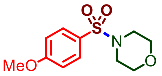
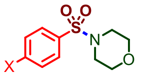
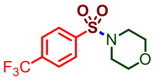
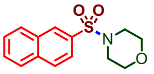
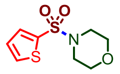
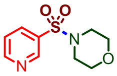
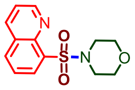
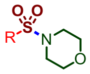
With the optimized conditions in hand, the scope of the protocol with respect to a number of selected *O*-benzoyl hydroxylamines (**4**) was then investigated (Table 2). The ring size of cyclic amines exhibited noticeable effects: pyrrolidine and piperidine derivatives resulted in quantitative yields (>99%, **5a-b**[6c]), meanwhile, more flexible azepane and azocane analogues produced decreased yields probably due to the steric hindrance caused by the ring-flexibility (88% and 79% respectively, **5c-d**[11,12]). The amination of sodium benzenesulfinate with six-member ring *N*-Boc-piperazine or *N*-phenyl-piperazine derivative with suitable ring-sizes all provided up to quantitative yields (**6a**[13] and **6b**[14], >99%). However, 1,2,3,4-tetrahydroisoquinoline analogue only resulted in a moderate yield (**7**[15], 61%) even with a suitable ring-sizes. Still, when steric demanding 2-methylpiperidine derivative was involved, a 74% yield of product **8**[16] was obtained. However, 2,6-lupetidine substitute only gave a 41% yield for product **9**[17] even with the increased catalyst loading (5 mol%) and elevated reaction temperature (80 °C). Besides the cyclic *O*-benzoyl hydroxylamines, acyclic amines are also compatible substrates and readily introduced into the corresponding sulfonamides **10-13**[6c,18,19] in good to excellent yields. Particularly, N,N-diallyl-substituted product **13** was a delivered into an acceptable yield when the corresponding electrophilic amino reagent was used (**13**, 50%). Moreover, other electrophilic amines with (heterocyclic-)aryl groups were also examined in this protocol, affording the corresponding products in moderate to excellent yields (54-96%，**14-19**[20-24]).

Subsequently, a series of sodium sulfinates were involved to investigate the generality of the protocol and the results were summarized in Table 3. Both electron-rich and electron-deficient substituents on the aromatic ring of sodium salts were well tolerated (Table 3, **20-23**[6c]). To our delight, the reactions with electron-deficient sulfinates still processed very efficiently, even with strong electron-withdrawing groups (**22c** and **23**, 93% and 88%, respectively). Different position of substituents on the aromatic ring of sodium benzenesulfinates hardly exhibited remarkable effects on the transform efficiency. For example, in comparison to the substrates with *meta*- and *para*- substituents, the *ortho*- one resulted in a similar yield (**20a-c)**. Additionally, bulky sodium naphthalene-2-sulfinate was also well tolerated; an excellent yield was observed (**24**[6c], 93%). Heterocyclic aryl sulfinates also constituted suitable substrates: sodium furan-2-sulfinate, sodium pyridine-3-sulfinate and sodium quinoline-8-sulfinate all led in good yields, although, in some case the elevated temperature was required to achieve satisfactory outcomes (**26**[25] and **27**[6c], 83% and 72%, respectively). Intriguingly, when challenging aliphatic salt (sodium methanesulfinate) was applied, the corresponding product **28a**[6a] was still produced in a 32% yield. However, none of the desired product was detected when more ionic sodium trifluoromethanesulfinate was used (Table 3, **28b**). To our delight, the reaction was readily scaled up to gram level: a 90% yield was obtained when 5 mmol-scaled reaction was carried with *O*-benzoyl hydroxylmorpholine (**2**) and sodium benzenesulfinate (**1**) under standard conditions, which might suggest a potential industrial application.

Table 3 Reaction of **2** with various sodium sulfinates [a]

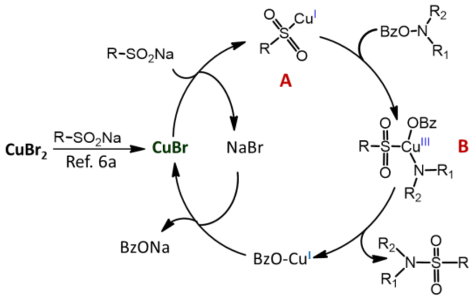


2 **20-28**[b]

 **20a**: 98% (*o*-); **20b**: >99% (*m*-); **20c**: >99% (*p*-)	 **21**: 97%	 **22a**: 99% (X = Cl); **22b**: 99% (X = Br); **22c**: 93% (X = F)
 **23**: 88%	 **24**: 93%	 **25**: 98%
 **26**: 46% (83%)[c]	 **27**: 52%(72%)[c]	 **28a**: 32% (R = CH$_3$); **28b**: NR (R = CF$_3$)

[a] Reaction was carried out with 0.5 mmol scale: 2 equiv. Sodium sulfinate and 1 equiv. **2** were dissolved in 4 mL DCE and stirred in 12 h, then the CuBr$_2$ was added and stirred for additional 12 h; [b] Isolate yield based on **2**; [c] with 5 mol% catalyst loading at 80 °C.

In order to investigate the plausible reaction mechanis several control experiments were performed. No sulfonamid product was detected in the presence of the radical scavenge TEMPO, and decreased yields were obtained when TEMPO added to the reaction mixture in different reaction interv (detail see ESI†). In addition, sodium sulfinates analogues such as benzenesulphinic acid[26] or benzenesulfonyl hydrazide which can initiate sulfonyl radical, however, did not afford the desired product under the identical reaction conditions (ESI† In combination with the previous reports,[6a] the plausible catalytic mechanism via the oxidative addition/reductive elimination route[28] was proposed in the Scheme 3. CuBr readily generated from CuBr$_2$ by coordination of copper to th sodium sulfonate via a free sulfonyl radical route,[29,30] whic was further react with sodium sulfinate to produce C intermediate **A** along with release of NaBr. After oxidativ addition with *O*-benzoyl hydroxylamine, sulfonamide prod is readily formed after elimination of a Cu^{III} intermediate **B**. The resulted BzO-Cu^{I} subsequently reacted with NaBr regenerate CuBr and complete the catalytical cycle. The low yields with all bulky *O*-benzoyl hydroxylamines (Table 2) no reaction with electronic deficient sodium trifluorometha sulfinate may further support this plausible reaction route.[31]



Scheme 3 Proposed mechanism.

In conclusion, we have developed a novel method for th synthesis of sulfonamides using *O*-benzoyl hydroxylamines as a novel type of amine source and sodium sulfinates under th catalytic of copper dibromide at ambient temperature. Th reaction proceeds smoothly at very mild condition with hig efficiency and shows broad functional group tolerance. Compared with previous studies, this work shows extreme mild reaction conditions, high efficiency of transformatio broad substrate scope and low-cost. More detailed studies about the mechanism and synthetic applications of th reaction are under exploring in our laboratory, and the result will be reported in due course.

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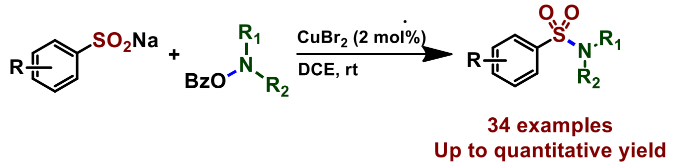
Formation of sulfonamides with electrophilic amines



Copper-catalyzed electrophilic amination of sodium sulfinates for the synthesis of sulfonamides using *O*-benzoyl hydroxylamines at ambient temperature.