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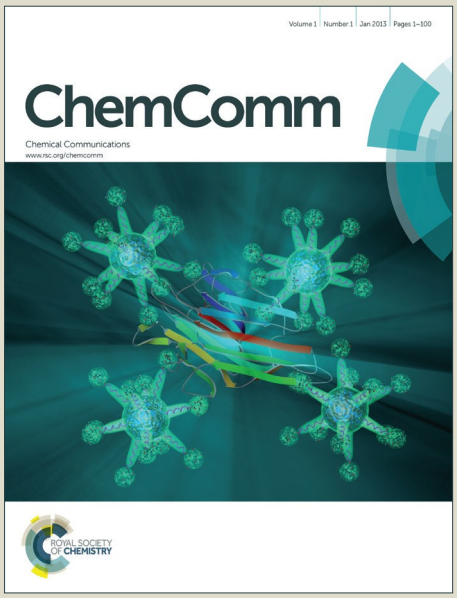

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ARTICLE TYPE

Copper-catalyzed *N*-thioetherification of sulfoximines using disulfides

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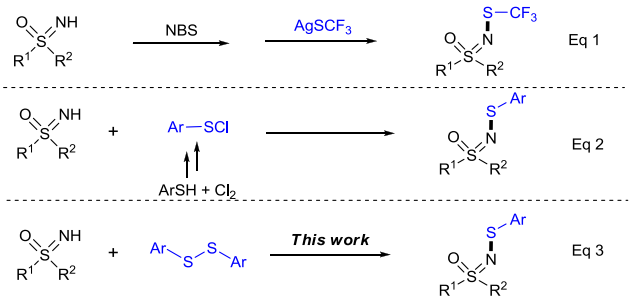
A novel copper-catalyzed *N*-thioetherification of sulfoximines under mild reaction conditions was developed. In this procedure, the N-S bond formation was achieved using readily available disulfides as sulfur source.

Organosulfur compounds play key and irreplaceable roles in biochemical processes,[1] serving as versatile intermediates in organic synthesis[2] and function as crucial structures in material science.[3] This fact prompted widespread investigations on the synthesis of sulfur-containing molecules over the years.[4] However, in comparison with the well-developed C-S bond formation, the construction of heteroatom-S bonds, especially the N-S bond has not yet been actively explored. There were only a few examples dealing with the formation of N-S bond, which is an important linkage that widely exists in many bioactive and synthetic useful molecules. For example, Taniguchi reported the copper-catalyzed reaction of secondary amines with diaryl disulfides or aryl thiols towards sulfenamides.[5] The synthesis of compounds with N-S bond in cyclic motif, such as the bioactive benzoisothiazolones, could be realized by condensation of 2-(chlorocarbamoyl)phenyl hypochlorothioites with amines,[6] metal-catalyzed reaction of 2-halo-arylamides/benzamides with proper S sources[7] or catalytic dehydrogenative N−H/S−H coupling reaction of 2-mercaptobenzamides.[8]

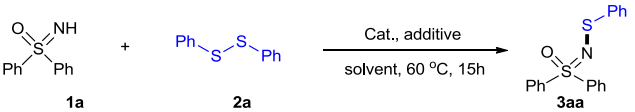
As a special kind of imine, sulfoximines show significant bioactivities in medicinal chemistry and have attracted considerable attention in crop protection.[9] Additionally, they can be chemically modified by *N*-substitution to afford complex structures with fine-tuning chemical and physical properties.[10] Among those works, the construction of N-S bond was developed by Bolm through two-step *N*-trifluoromethylthiolation of sulfoximines using NBS followed by silver trifluoromethanethiolate (Eq 1, Scheme 1).[10a] *N*-Sulfenylsulfoximines are important intermediates in organic synthesis. In the case of direct *N*-thioetherification of sulfoximines, traditional methods required the employment of arylsulfonyl chloride as the sulfur source (Eq 2, Scheme 1).[11] This procedure suffered from limited substrate scope and the employment of odorous, highly toxic and corrosive agents such as thiols and chlorine gas. Therefore, the development of an efficient and environmentally benign protocol, by which a diverse library of *N*-sulfenylsulfoximines could be produced using readily available starting materials under mild conditions, would be highly desirable. Disulfides are frequently used as efficient sulfur source in the thiolation/thioetherification processes to form C-S or heteroatom-S bonds, in terms of their chemical stability, synthetic availability and less odorous.[5a,12,13] Thus, in this paper, we wish to describe the methodology of the copper-catalyzed *N*-thioetherification of sulfoximines using disulfides as sulfur source (Eq 3, Scheme 1).



Scheme 1. Sulfoximines based construction of N-S bond

With this idea in mind, we chose diphenylsulfoximine (**1a**) and diphenyl disulfide (**2a**) as the model substrates to find the optimal reaction conditions. To our delight, in the presence of Na_2CO_3 in DMSO, CuCl and $CuCl_2$ were both valid catalysts, giving the *N*-phenylthio product **3aa** in 60% and 62% yields, respectively (entries 1 & 2, Table 1). Cu_2O and CuO were unable to catalyze this transformation, while CuI gave a higher yield (entries 3-5, Table 1). Inspired by this result, other bases were screened and NaOAc was proved with best efficiency with 88% yield of **3aa** (entries 6-12, Table 1). Blank experiments revealed that, the reaction could occur without any base albeit in lower yield, but no product was obtained in the absence of any copper catalyst (entries 10 & 11, Table 1). Decrease the catalyst loading to 15 mol%, the yield dropped to 76%, and the yield didn't increase obviously if 30 mol% CuI was used (entry 9, Table 1). Other common solvents, such as trifluoromethylbenzene, DCE, chlorobenzene and DMF were not as effective as DMSO (entries 15-18, Table 1). The *N*-thioetherification could occur in the atmosphere of O_2, but in lower yield. No increase of yield was observed at higher temperature (entry 9, Table 1).

Table 1. Screening the optimal conditions[a]



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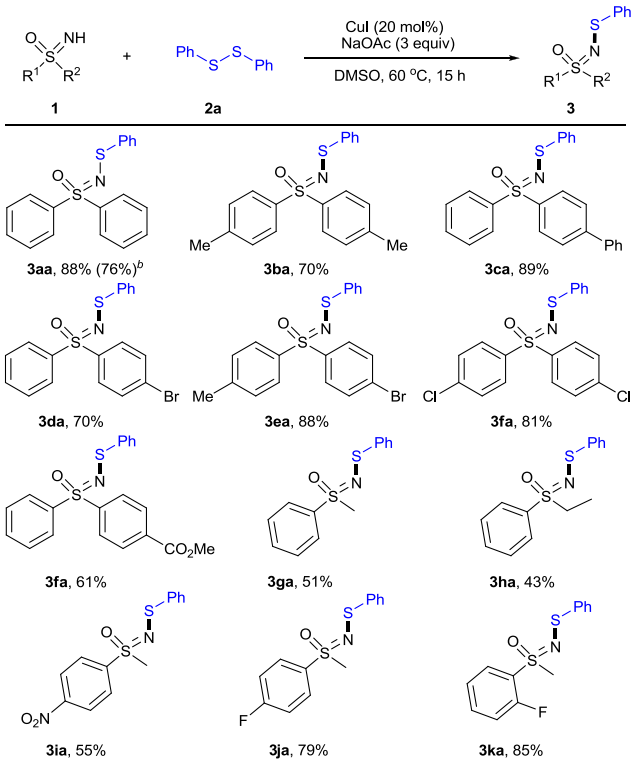
Entry	Catalyst	Additive	Solvent	Yield (%)
1	CuCl	Na_2CO_3	DMSO	60
2	$CuCl_2$	Na_2CO_3	DMSO	62
3	Cu_2O	Na_2CO_3	DMSO	trace
4	CuO	Na_2CO_3	DMSO	trace
5	CuI	Na_2CO_3	DMSO	69
6	CuI	K_2CO_3	DMSO	36
7	CuI	Cs_2CO_3	DMSO	trace
8	CuI	^{t}BuOK	DMSO	trace
9	CuI	NaOAc	DMSO	88 (72)[b] (58)[c] (76%)[d] (89)[e]
10	CuI	LiOAc	DMSO	75
11	CuI	KOAc	DMSO	83
12	CuI	CsOAc	DMSO	87
13	CuI	--	DMSO	56
14	--	NaOAc	DMSO	0
15	CuI	NaOAc	$PhCF_3$	trace
16	CuI	NaOAc	DCE	trace
17	CuI	NaOAc	PhCl	0
18	CuI	NaOAc	DMF	20

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol, 1 equiv.), catalyst (20 mol%), additive (3 equiv.) in solvent (2 mL) at 60 °C under air for 15 h, isolated yields. [b] At 80 °C. [c] Under O_2. [d] 15 mol% CuI. [e] 30 mol% CuI.

After the establishment of the optimized reaction conditions, the substrate scopes and limitations of this *N*-thioetherification procedure were investigated, as shown in Scheme 2 and 3. As expected, a series of *S*,*S*-diarylsulfoximines with either electron-donating or electron-withdrawing substituents all good reaction partners to give the corresponding *N*-thioetherificated sulfoximines in good yields (**3aa**-**3fa**, Scheme 2). In addition, alkyl aryl sulfoximines also reacted smoothly to deliver the desired products although in relatively lower yields (**3ga**-**3ka**, Scheme 2). Interestingly, *S*-aryl-*S*-methyl-sulfoximines with electron-withdrawing groups on *ortho*- or *para*-position of phenyl gave relatively higher yields (**3ia**-**3ka**). Moreover, the tolerance of halogen provided convenient handles for further functionalizations (**3da**-**3fa**, **3ja**, **3ka**). The practicability of this procedure was further evaluated using 1 mmol of **1a**, giving the product **3aa** in a comparable 76% yield.

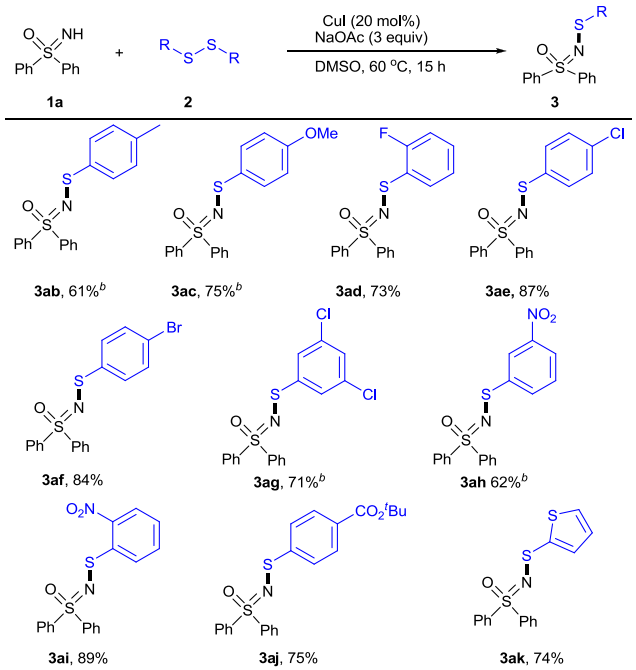
Next, the scope of disulfides was investigated as shown in Scheme 3. Diaryl disulfides with methyl, methoxy, nitro, chloro and carbonyl groups all reacted well with diphenyl sulfoximines leading to *N*-sulfenylsulfoximines with various aryls on S atom (**3ab**-**3aj**). Diaryl disulfides with electron-donating substituent on *para*-position of phenyl or with electron-withdrawing substituent on *meta*-position of phenyl were less reactive (**3ab**, **3ac**, **3ag** & **3ah**). It was worth to note that diheteroaryl disulfides such as di(thiophen-2-yl) disulfide (**2k**) also react smoothly under optimized conditions provided **3ak** in 74% yield. Unfortunately, when dialkyl disulfides were used, no corresponding products were detected even reacted for prolonged time.

Scheme 2. Substrate scope of sulfoximines in *N*-thioetherification[a]



[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.1 mmol, 1 equiv.), CuI (20 mol%), NaOAc (3 equiv.) in DMSO (2 mL) at 60 °C for 15 h, sealed tube, isolated yields. [b] Scale-up reaction using 1 mmol of **1a**.

Scheme 3. Substrate scope of disulfides in *N*-thioetherification[a]



Reaction conditions: **1a** (0.1 mmol), **2** (0.1 mmol), CuI (20 mol%), NaOAc (3 equiv.) in DMSO (2 mL) at 60 °C for 15 h, sealed tube. [b] 2 Equivalents of disulfide was used.

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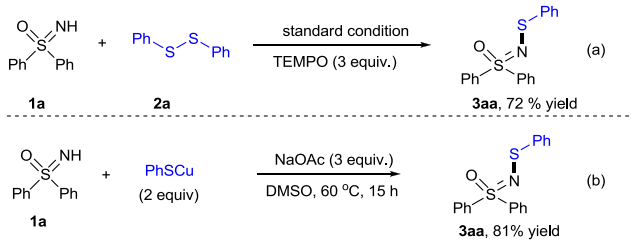
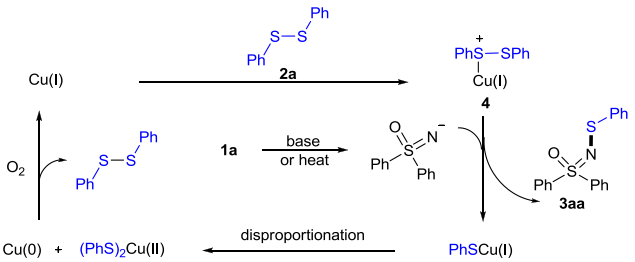
In order to gain some insights into the reaction mechanism, control experiments were conducted as shown in Scheme 2. Firstly, the transformation was not obviously affected after 3 equivalents of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) was added to the reaction as radical scavenger, thus the radical pathway could be ruled out (Eq (a), Scheme 4). Next, 2 equivalents of PhSCu(I) was subjected to the reaction, and the thioetherification product was isolated in 81% yield in the presence of NaOAc in DMSO (Eq (b), Scheme 4), which was comparable with the result obtained under standard conditions. This result indicated that PhSCu(I) maybe performed as crucial intermediate in this *N*-thioetherification process.



Scheme 4. Mechanistic studies.

Based on the above mentioned experimental results and former reported works,[14] the mechanism was outlined in Scheme 5. Initially, copper(I) catalyst coordinates to the diaryl disulfide (**2a**) to generate sulfonium ion intermediate **4**. Then **4** is subsequently attacked by the nucleophilic sulfoximine anion formed by deprotonation of **1a** in the assistance of base or on heat to provide product **3aa** and PhSCu(I). Succeeding disproportionation and oxygen-mediated reductive elimination regenerates the initial Cu(I) catalyst as well as a molecule of disulfide. This aerobic process was further supported by performing the reaction under a nitrogen atmosphere, where only trace amount of product was observed.



Scheme 5. Proposed mechanism.

In summary, we have demonstrated a copper-catalyzed *N*-thioetherification of sulfoximines under mild reaction conditions using the less toxic and readily available disulfides as sulfur source. A series of synthetic useful *N*-arylthiosulfoximines with various functional groups were obtained in moderate to good yields. This work represents a promising avenue to access *N*-sulfenylsulfoximines and is an important complement to sulfoximine chemistry.

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

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