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CuI promoted sulfenylation of organozinc reagents with arylsulfonyl chlorides†

Ying Fu,* Yuhu Su, Qin-shan Xu, Zhengyin Du, Yulai Hu, Ke-Hu Wang and Danfeng Huang

A CuI promoted sulfenylation of organozinc reagents with arylsulfonyl chlorides/PPh_3 has been explored. This reaction proceeded smoothly through an alkyl/aryl radical (generated from organometallics) under mild conditions and produced the desired sulfide products in excellent yields.

Thioether is a very important structural motif in numerous natural products and bioactive molecules, and is widely used as a versatile building block in organic molecules. As a consequence, novel synthetic protocols have been continuously developed[1] and much of recent attention has focused on exploitation environmental friendly, thiol-free materials such as Bunte Salts,[2] potassium ethyl xanthogenate,[3] NaS_2O_3,[4] KSCN,[5] CS_2,[6] sulfonyl hydrazides,[7] DMSO[8] and *N*-(aryl/alkylthio)succinimides[9] *etc.* as the sulfur source.

Recently, arylsulfonyl chloride, considering its abundance and inexpensiveness, has emerged as a promising thiol-free sulfur source in thioether synthesis. In 2011, You *et al.* first demonstrated that arylsulfonyl chlorides can be employed as sulfur source for sulfenylation of electron-rich arenes or heteroarenes.[10] This promising sulfenylation protocol was quickly recognized and was further enlarged in sulfenylation of (hetero) arenes in PEG-400,[11] quinones[12] and iodoarenes.[13] However, these methodologies are limited to diaryl sulfide synthesis and require high temperature.

Organozinc reagents are mild organometallics and were used extensively in organic synthesis.[14] However, these privileged organometallics have rarely been employed in C–S bond formation reactions unless a reactive sulfur electrophile such as sulfenyl chlorides[15] or SO_2 (ref. 16) *etc.* were introduced as the substrates. Previously, we developed a CuI catalyzed synthesis of arylsulfones from organozinc reagents and arylsulfonyl chlorides.[17] During this study, we accidentally found that when PPh_3 was employed as the ligand, thioether can be formed unexpectedly. Owing to our interests on the synthesis and application of organozinc reagents in organic synthesis,[18] we here report an CuI promoted sulfenylation of organozinc reagents employing commercially available arylsulfonyl chlorides as the sulfur source under mild reaction (Scheme 1).

College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, P. R. China. E-mail: fuying@iccas.ac.cn; Fax: +86-931-7971989; Tel: +86-931-7971533

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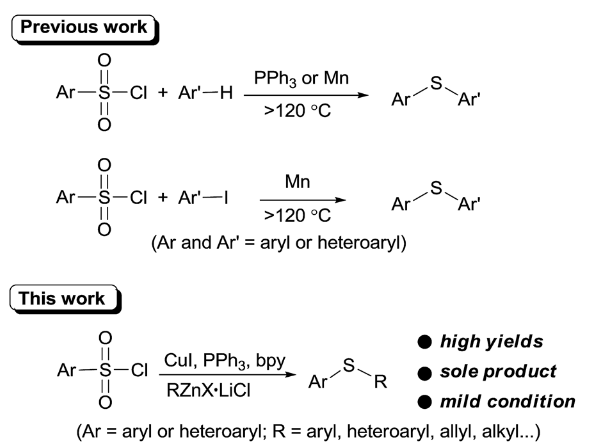
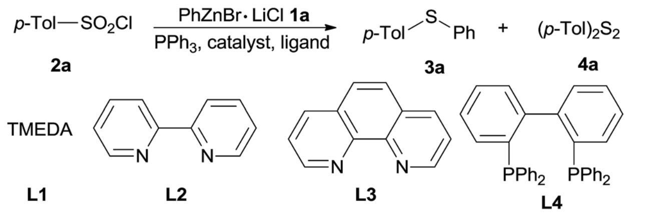
At the outset of this investigation, optimization of the reaction parameters was performed using phenylzinc bromide **1a** and *p*-tolylsulfonyl chloride **2a** as the model substrates (Table 1). When the reaction was conducted by adding *p*-tolylsulfonyl chloride **2a** into phenylzinc bromide **1a** in the presence of CuI (1.0 equiv.) and PPh_3 (2.2 equiv.) in THF at room temperature, phenyl *p*-tolyl sulfone was formed in 68% isolated yield without formation of any sulfides product. Alternatively, when phenylzinc bromide **1a** was added into a mixture of *p*-tolylsulfonyl chloride **2a** and PPh_3 (2.2 equiv.) in the presence of CuI (1.0 equiv.) in THF at room temperature, *p*-tolyl disulfide **4a** was obtained in nearly quantitative yield (95%, entry 1). The appearance of disulfide **4a** can be ascribed to immediate reduction of *p*-tolylsulfonyl chloride **2a** by PPh_3.[19] However, this experimental result also illustrates the fact that organozinc reagents are inert organometallic species towards organodisulfides. To further improve the reactivity of organozinc reagents, two equivalents of TMEDA (tetramethylethylenediamine, **L1**) was added and heating to reflux overnight, the yield of **3a** was improved to 35% (entry 2). Replacement of CuI with



Scheme 1 Approaches toward transformation of sulfonyl chlorides into thioethers.

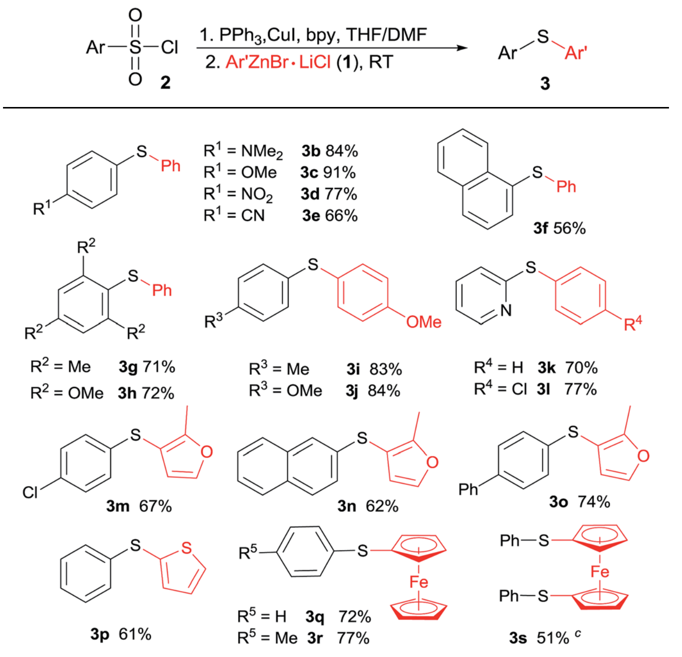
Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	Cat./ligand	Temp.	3a[b] [%]	4a[b] [%]
1	THF	CuI/—	RT	0	95
2	THF	CuI/**L1**	Reflux	35	61
3	THF	CuBr/**L1**	Reflux	29	61
4	THF	CuCl/**L1**	Reflux	32	62
5	THF	CuCN/**L1**	Reflux	28	64
6	THF	$Cu(OAc)_2$/**L1**	Reflux	31	67
7	THF	CuI/**L2**	Reflux	63	31
8	THF	CuI/**L3**	Reflux	56	32
9	THF	CuI/**L4**	Reflux	42	51
10	THF/DMF	CuI/**L2**	RT	88[c]	0

[a] Reaction conditions: **1a** (2 mmol) in THF (4 mL) was added into a THF (4 mL) solution containing catalyst (1.0 mmol), ligand (2.0 mmol), **2a** (1.0 mmol) and PPh_3 (2.2 mmol) under argon atmosphere and was then stirred overnight. [b] Isolated yields. [c] 1.0 mL of DMF was added.

Table 2 Reaction of arylsulfonyl chlorides with arylzinc reagents[a,b]



[a] Reaction conditions: **1** (2 mmol) in THF (4 mL) was added into a THF–DMF (5 mL, 4 : 1, v/v) solution containing CuI (1.0 mmol), bpy (2.0 mmol), **2a** (1.0 mmol) and PPh_3 (2.2 mmol) under argon atmosphere and was then stirred at room temperature overnight. [b] Isolated yields. [c] Biszincation of ferrocene (1.0 mmol) was performed using *n*-butyllithium (2.2 mmol) and $ZnCl_2$ (2.0 mmol).

other cuprous salts such as CuBr, CuCl, CuCN and $Cu(OAc)_2$ are all effective, albeit without obvious yield improvement (entries 3–6). Ligands **L1–L4** screening showed that bipyridine (**L2**) was the best one, enhancing the yield of **3a** to 63% (entries 7–9). Organozinc reagents exhibit enhanced reactivity in a polar aprotic solvent, *e.g.* DMF.[20] Gratifyingly, the use of THF–DMF (8 : 1, v/v) as a solvent dramatically improved the yield of **3a** to 88% yield and disulfides **4a** was cleanly consumed at room temperature after 12 hours (entry 10).

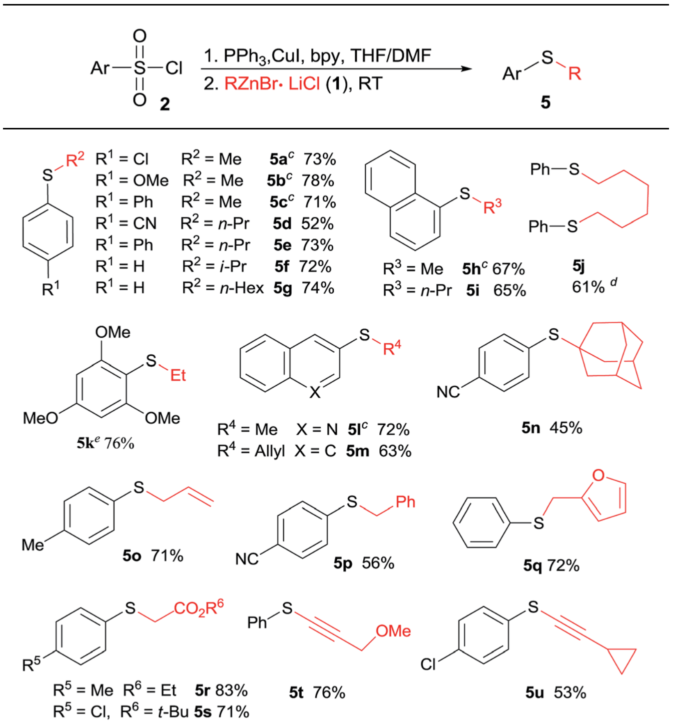
Although classic reactive organometallics such as Grignards,[21] organolithium reagents[22] and some mild organometallic species such as aryltrimethoxysilanes[23] and triarylbismuthanes[24] are able to convert disulfides into sulfides, there are some apparent problems relating to these protocols. Grignards and organolithium reagents will simultaneously cleave both C–S and S–S bonds of disulfides,[25] thus are limited in practical sulfides synthesis. On the other hand, triarylbismuthanes[26] and aryltrimethoxysilanes[27] themselves were prepared from corresponding Grignards, therefore, precludes existence of some important functional groups on these reagents. In this respect, our organozinc protocol[28] is advantageous both on their structural diversity and wide spectrum of functional groups tolerance.

The scope and generality of this CuI promoted sulfenylation of various aryl and heteroarylzinc bromides with aromatic sulfonyl chlorides/PPh_3 couple was investigated under the optimized conditions (Table 2). To PhZnBr·LiCl **1a**, arylsulfonyl chlorides containing either electron-donating or electron-withdrawing groups were smoothly converted into diaryl sulfides (**3a–h**) in good to excellent yields. A variety of important functional groups, including nitro (**3d**) and cyano (**3e**) were well tolerated under this optimized reaction conditions. The steric hindrance effect of this reaction was not obvious; 2,6-disubstituted arylsulfonyl chlorides could participate this transformation, giving the sulfide products (**3g**, **3h**) in good yields. Heteroaromatic sulfides containing furan (**3m–3o**), thiophene (**3p**) and ferrocene (**3q–3s**) moieties can be easily prepared from corresponding organozinc bromides in good isolated yields.

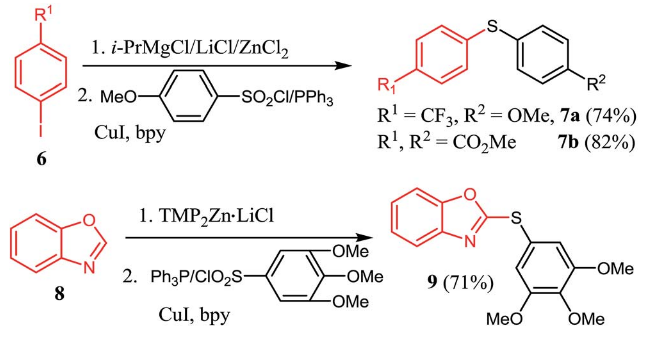
The application of aliphatic organozinc reagents with various aromatic sulfonyl chlorides was then investigated (Table 3). Gratifyingly, a range of aliphatic organozinc reagents, both commercial available dialkylzinc reagents (**5a–c**, **5h**, **5k** and **5l**) and aliphatic organozinc halides, prepared by $ZnCl_2$ mediated transmetalation of Grignards or organolithium reagents, were compatible with the developed conditions. Notably, adamantyl thioether **5n** was also successfully prepared using adamantylzinc bromide in 45% yield. Allylic and benzylic thioethers (**5m**, **5o–5q**) were easily prepared using allyl or benzylzinc bromides in good yields. Also of note are thioethers **5r** and **5s** were readily prepared in high yields *via* Reformasky type reaction. Zinc acetylides (*in situ* formed *via* zincation of terminal alkynes by Et_2Zn) were successfully employed to form alkynylsulfides in good yields (**5t** and **5u**).

The halogen/magnesium exchange reaction[29] and the direct deprotonative metalation[30] of arenes or heteroarenes with strong bases are now recognized as powerful method for highly functionalized organometallic reagents preparation. In this respect, iodobenzene bearing an electron-withdrawing CF_3

Table 3 Reaction of arylsulfonyl chlorides with aliphatic organozinc reagents[a,b]



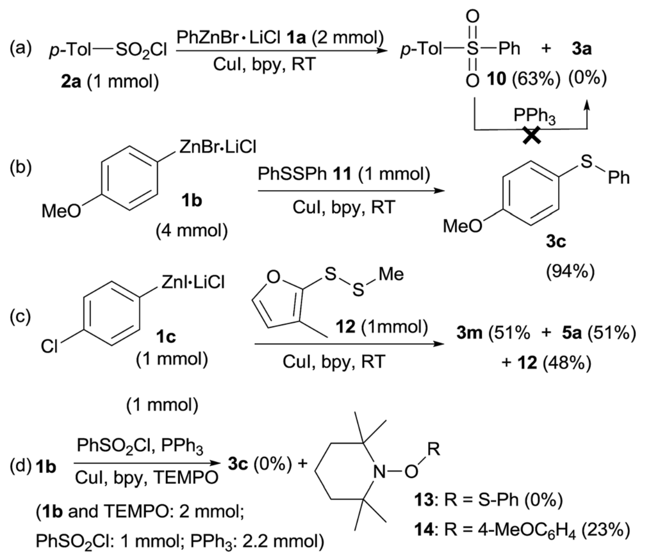
[a] **1** (2 mmol) in THF (4 mL) was added into a THF–DMF (5 mL, 4 : 1, v/v) solution containing CuI (1.0 mmol), bpy (2.0 mmol), **2a** (1.0 mmol) and PPh_3 (2.2 mmol) under argon atmosphere and was then stirred at room temperature overnight. [b] Isolated yields. [c] Me_2Zn (4 mmol) was used. [d] 1,6-Dibromozinc hexane (0.5 mmol) was used. [e] Et_2Zn (4 mmol) was used.



Scheme 2 Reaction of organozinc reagents delivered *via* Mg/I exchange reaction and deprotonation method.

substituent found difficulty in direct magnesium insertion.[31] Nevertheless, treatment of 4-iodotrifluorobenzene **6** by turbo Grignards (*i*-PrMgCl·LiCl)[32] and then transmetalated with $ZnCl_2$ afforded the corresponding organozinc reagents, which reacted with 4-methoxybenzenesulfonyl chloride/PPh_3, giving sulfide **7a** in 74% yield (Scheme 2). Similarly, dimethyl 4,4′-thiodibenzoate **7b** was prepared in 82% yield. Furthermore, zincation of benzo[*d*]oxazole **8** with TMPZnCl·LiCl[33] and then reaction with 3,4,5-trimethoxybenzenesulfonyl chloride/PPh_3 couple yielded the sulfide **9** in 71% yield.

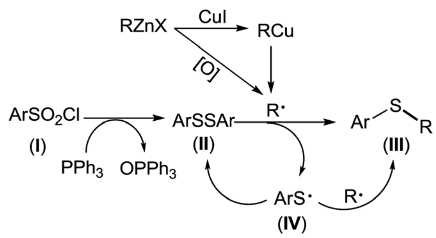
To illustrate a possible mechanism for this transformation, some control experiments were conducted (Scheme 3). When *p*-tolylsulfonyl chloride **2a** was treated with PhZnBr·LiCl **1a** at the same reaction without PPh_3, sulfone **10** was obtained in 63% isolated yield and sulfide **3a** was not detected at all (Scheme 3a), indicating that PPh_3 was the only reductant. However, PPh_3 could not reduce sulfone **10** at room temperature in THF/DMF (5 : 1, v/v). When diphenyl disulfide **11** (1 mmol) instead of phenylsulfonyl chloride/PPh_3 was used in reaction with 4-methoxyphenylzinc bromide **1b**, sulfide **3c** was obtained in 94% isolated yield, indicating that diaryl disulfide *in situ* formed by reduction of sulfonyl chlorides and PPh_3 were the reactive intermediates (Scheme 3b). Interestingly, treatment of 4-chlorophenylzinc iodide **1c** (1 equiv.) with mixed disulfide **12** (1



Scheme 3 Some control experiments.

equiv.) gave sulfides **3m** and **5a** in exactly 1 : 1 ratio along with quantitative remaining of **12** according to crude ^1H NMR analysis, addressing a radical mechanism of this reaction as in a nucleophilic displacement reaction, **3m** and **5a** will be formed in different ratio owing to the unsymmetric structure nature of the mixed disulfide **12**. The significant difference between organozinc reagents and Grignard reagents was also highlighted here as Grignards normally nucleophilically cleave S–S bond of disulfides and leaving another part of disulfide as thiol by-product. Furthermore, when a radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO, 2 equivalent) was added into the sulfenylation reaction of 4-methoxyphenylzinc bromide **1b** (2 equiv.) with phenylsulfonyl chloride (1 equiv.), sulfide **3c** was not produced (Scheme 3d). Meanwhile, adduct (**13**) of the thiyl radical[34] with TEMPO was also not obtained. TEMPO was totally decomposed by organozinc reagents, leaving disulfide **4a** untouched, whereas adduct (**14**) of **1b** with TEMPO was obtained in 23% yield (GC-MS analysis).

Based on aforementioned experimental facts, a plausible mechanism was proposed (Scheme 4). Arylsulfonyl chloride (**I**) was reduced by PPh_3 to give diaryl disulfide (**II**).[19]



Scheme 4 Proposed mechanism.

Transmetalation of RZnX with CuI gave the organocopper reagents RCu[35] which underwent a homolytic dissociation to generate a R˙ radical.[36] It should be noted here that R˙ radical can also be generated from organozinc reagents in presence of trace amount of oxygen.[37] Disulfide (**II**) captured R˙ radical to form thioether (**III**). Meanwhile, a thiyl radical (**IV**) was produced which either underwent homocoupling to regenerate the disulfide (**II**) or was captured by another R˙ radical to give thioether (**III**).

Conclusion

In summary, we have developed an efficient and practical method for the preparation of aromatic sulfides based on CuI promoted reaction of organozinc reagents with aromatic sulfonyl chlorides. This reaction initiated *via* a alkyl/aryl radical generated from organozinc reagents rather than thiyl radical generated from diaryl disulfides. A plausible reaction mechanism has been given on the basis of the control experiments.

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