Cul promoted sulfenylation of organozinc reagents with arylsulfonyl chlorides†

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A Cul promoted sulfenylation of organozinc reagents with arylsulfonyl chlorides/PPh₃ 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 and much of recent attention has focused on exploitation environmentally friendly, thiol-free materials such as Bunte Salts, potassium ethyl xanthogenate, Na₂S₂O₃, KSCN, CS₂, sulfonyl hydrazides, DMSO and N-(aryl/alkylthio)succinimides 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. This promising sulfenylation protocol was quickly recognized and was further enlarged in sulfenylation of (hetero) arenes in PEG-400, quinones and iodoarenes. 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. However, these privileged organometallics have rarely been employed in C-S bond formation reactions unless a reactive sulfur electrophile such as sulfenyl chlorides or SO₂ was introduced as the sulfur source. Previously, we developed a Cul catalyzed synthesis of arylsulfones from organozinc reagents and arylsulfonyl chlorides. During this study, we accidentally found that when PPh₃ was employed as the ligand, thioether can be formed unexpectedly. Owing to our interests on the synthesis and application of organozoic reagents in organic synthesis, we here report an Cul promoted sulfenylation of organozinc reagents employing commercially available arylsulfonyl chlorides as the sulfur source under mild reaction (Scheme 1).

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 Cul (1.0 equiv.) and PPh₃ (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 PPh₃ (2.2 equiv.) in the presence of Cul (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 PPh₃. However, this experimental result also illustrates the fact that organozinc reagents are inert organometallic species towards organo-disulfides. To further improve the reactivity of organozinc reagents, two equivalents of TMEDA (tetramethylthelylenediamine, L1) was added and heating to reflux overnight, the yield of 3a was improved to 35% (entry 2). Replacement of Cul with

Scheme 1 Approaches toward transformation of sulfonil chlorides into thioethers.
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. Gratifyingly, the use of THF–DMF (8 : 1, v/v) as a solvent dramatically improved the yield of 3a to 88% and disulfides 4a was cleanly consumed at room temperature after 12 hours (entry 10).

Although classic reactive organometallics such as Grignards,¹¹ organolithium reagents²⁰ and some mild organometallic species such as arytrimethoxysilanes²¹ and triarylbumethanes²² 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,²³ thus are limited in practical sulfides synthesis. On the other hand, triarylbumethanes²⁴ and arytrimethoxysilanes²⁵ themselves were prepared from corresponding Grignards, therefore, precludes existence of some important functional groups on these reagents. In this respect, our organozinc protocol²⁶ 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 and PPh₃, 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.

Table 1. Optimization of the reaction conditions.⁶

| Entry | Solvent | Cat./ligand | Temp. | 3a [%] | 4a [%] |
|-------|---------|-------------|-------|--------|--------|
| 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     | Cu/L₂      | Reflux| 63     | 31     |
| 8     | THF     | Cu/L₃      | Reflux| 56     | 32     |
| 9     | THF     | Cu/L₄      | Reflux| 42     | 51     |
| 10    | THF/DMF | Cu/L₂      | RT    | 88     | 0      |

⁶ 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 PPh₃ (2.2 mmol) under argon atmosphere and was then stirred overnight. Isolated yields.

Table 2. Reaction of arylsulfonyl chlorides with arylzinc reagents.⁶⁻⁶

| Ar                      | PhS–O–Cl | 1. PPh₃CuI, bpy, THF/DMF | 2. ArZnBr·LiCl (1), RT |
|-------------------------|----------|--------------------------|------------------------|
| R¹                      | R²       | R³                       | R⁴                    |
| 3b 84%                  | 3c 91%   | 3d 77%                   | 3e 66%                |
| 3f 56%                  | 3g 71%   | 3h 72%                   | 3i 83%                |
| 3j 70%                  | 3k 70%   | 3l 77%                   | 3m 67%                |
| 3n 62%                  | 3o 74%   | 3p 51%                   | 3q 72%                |
| 3r 78%                  | 3s 77%   | 3t 55%                   | 3u 74%                |

⁶ 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 PPh₃ (2.2 mmol) under argon atmosphere and was then stirred at room temperature overnight. Isolated yields.

⁻ Biszincation of ferrocene (1.0 mmol) was performed using n-butyl lithium (2.2 mmol) and ZnCl₂ (2.0 mmol).
substituent found difficulty in direct magnesium insertion. Nevertheless, treatment of 4-iodotrifluorobenzene 6 by turbo Grignards (i-PrMgCl/ LiCl) and then transmetalated with ZnCl2 afforded the corresponding organozinc reagents, which reacted with 4-methoxybenzenesulfonyl chloride/PPh3, giving sulfide 7a in 74% yield (Scheme 2). Similarly, dimethyl 4,40-thiodibenzoate 7b was prepared in 82% yield. Furthermore, zincation of benzo[d]oxazole 8 with TMPZnCl/LiCl 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 (1 mmol) was treated with PhZnBr/LiCl 1a at the same reaction without PPh3, sulfone 10 was obtained in 63% isolated yield and sulfide 3a was not detected at all (Scheme 3a), indicating that PPh3 was the only reductant. However, PPh3 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/PPh3 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 PPh3 were the reactive intermediates (Scheme 3b). Interestingly, treatment of 4-chlorophenylzinc iodide 1c (1 equiv.) with mixed disulfide 12 (1 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 thyl radical14 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 PPh3 to give diaryl disulfide (II).
Transmetalation of RZnX with CuI gave the organocopper reagents RCu\textsuperscript{26} which underwent a homolytic dissociation to generate a R’ radical.\textsuperscript{27} It should be noted here that R’ radical can also be generated from organozinc reagents in presence of trace amount of oxygen.\textsuperscript{27} Disulfide (II) captured R’ radical to form thioether (III). Meanwhile, a thyl 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 thyl radical generated from diaryl disulfides. A plausible reaction mechanism has been given on the basis of the control experiments.

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