A Simple One-Pot and Transition Metal-free Synthesis of Diaryl- and Dialkyl Sulfides via Grignard Reaction/Deoxygenation

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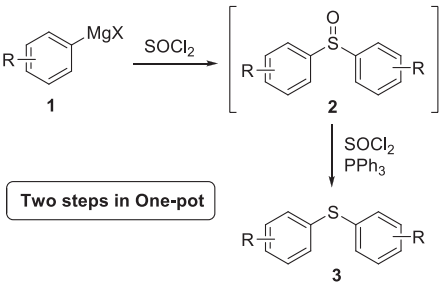
Sulfur-containing organic compounds are a highly attractive motif. In particular, diaryl sulfides and their derivatives have been recognized as significant molecules because of their potent biological activities[1] and material interests.[2] Increasing interest in and applications of diaryl sulfides have prompted investigations of novel methodologies for the preparation of these compounds.

For the last few decades, many types of methods have been developed to construct the thioether linkage for the conversion of aryl halides to diaryl sulfides.[3] Among them, a variety of transition-metals such as palladium (Pd),[4] copper (Cu),[5] nickel (Ni),[6] cobalt (Co),[7] and iron (Fe)[8] have been widely employed as catalysts for the coupling reaction between aryl halides and thiols as the most general method. Less general synthetic methods have used thiourea,[9] thiocyanate,[10] xanthate,[11] or thioacetate[12] as a sulfur source with aryl halides and transition-metal catalysts for the synthesis of diaryl sulfides. However, the formation of aryl-sulfur bond including diaryl sulfides by the coupling of aryllithium or Grignard reagents with phenyldisulfide, thiosulfonates, sulfur, or sulfenyl chlorides without the use of transition metals has only been reported in a few articles[13] and still requires the preparation of disulfides or the use of aryl or alkyl thiols in certain cases. For these reasons, a need remains for alternative efficient and reliable methods that utilize readily available reagents under mild reaction conditions for the synthesis of aryl sulfides from aryl halides.

In our recent endeavors, sulfoxides were readily reduced to sulfides with thionyl chloride and triphenylphosphine.[14] In our continuing effort to develop a method for the synthesis of diaryl sulfides from aryl halides using our method of sulfoxide deoxygenation, we envisioned that diaryl sulfides would be prepared using arylmagnesium halide and thionyl chloride[15] by the Grignard reaction followed by our deoxygenation reaction (two steps in one pot). The treatment of arylmagnesium halide **1** with thionyl chloride would provide the corresponding diaryl sulfoxide **2** (Scheme 1). The deoxygenation of **2** by additional thionyl chloride and triphenylphosphine would afford the desired diaryl sulfides **3**.

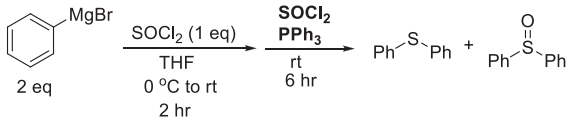
Regarding the Grignard reaction and deoxygenation in one pot, initial experiments were performed with phenylmagnesium bromide (2 equiv) and thionyl chloride (1 equiv) at various reaction temperatures for the Grignard reaction. Although no great difference was shown for the synthesis of diphenyl sulfoxide when the reactions were performed below 0 °C, we found that the best result was afforded by a slow increase from 0 °C to room temperature. Then, the deoxygenation reaction provided different results for the use of various amounts of additional thionyl chloride and triphenylphosphine, as shown in Table 1, when the reactions were performed for 6 h. The best yield of diphenyl sulfide was obtained when 2 equiv of each reagent was used.

Next, the generality of this method for the direct synthesis of diaryl sulfides from aryl Grignard reagents and thionyl chloride was investigated, as shown in Table 2. First, a variety of arylmagnesium halides (2 equiv) were added to thionyl chloride (1 equiv) in THF (tetrahydrofuran) at 0 °C, and the reaction temperature was slowly increased to room temperature for 2 h. Then, triphenylphosphine (2 equiv) and additional thionyl chloride (2 equiv) were subsequently added to the reaction mixture at room temperature. All arylmagnesium bromides investigated gave the corresponding diaryl sulfides in moderate to excellent yields. The reaction proceeded smoothly and tolerated various functional groups such as 4-chloro- (entry 2), 4-fluoro- (entry 3), 4-methylthio- (entry 4), 4-methoxy- (entry 5), 3,5-di(trifluoromethyl)- (entry 8), and 4-phenyl- (entry 9) to afford the



Scheme 1. Synthetic route of diaryl sulfides

Table 1. Optimization of the amounts of $SOCl_2$ and PPh_3



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	Amount (equiv)		Yield (%)[a]	
Entry	$SOCl_2$	PPh_3	Sulfide	Sulfoxide
1	0.5	0.5	10	84
2	1.0	1.0	51	33
3	1.5	1.5	84	6
4	2.0	2.0	88	—

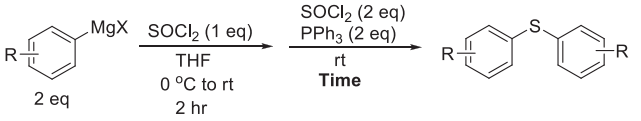
[a] Isolated yield.

corresponding sulfides in good yields. With (2-methoxyphenyl)magnesium bromide (entry 6) and (2,4,6-trimethylphenyl)magnesium bromide (entry 7), which have *ortho*-substituent groups, to investigate the steric issue, the one-pot reactions produced the corresponding sulfides in yields of 82 and 93%, respectively, under the same reaction conditions. These results indicate that our Grignard reaction followed by deoxygenation for sulfide synthesis is not affected by steric hindrance. In addition, 2-naphthylmagnesium bromide was readily converted into dinaphthyl sulfide in 92% yield (entry 10). On the other hand, alkyl Grignard reagents such as benzylmagnesium chloride (entry 11) and cyclohexylmagnesium chloride (entry 12) were treated with thionyl chloride (1 equiv), and the subsequent deoxygenation of the resulting dialkyl sulfoxides afforded better yields, 52 and 65%, respectively, when treated with triphenylphosphine (1 equiv) and additional thionyl chloride (0.2 equiv) than with additional thionyl chloride (1 equiv), as mentioned in our previous report.[14] Clearly, the Grignard reaction with thionyl chloride followed by deoxygenation with triphenylphosphine and additional thionyl chloride produced the desired diaryl and dialkyl sulfides from all types of Grignard reagents in good yields.

In addition, we could find that diphenyl sulfide was produced in good yield when phenyllithium, instead of phenylmagnesium bromide, was treated under the same reaction conditions, as shown in Scheme 2.

In conclusion, we obtained the desired symmetrical sulfides in good yields when aryl or alkylmagnesium halides were treated with thionyl chloride and subsequently with additional thionyl chloride and triphenylphosphine in one pot at ambient temperature. Notably, aryl Grignard reagents with *ortho*-substituent groups were also converted to the corresponding diaryl sulfides in excellent yields under mild reaction conditions, showing that the steric hindrance does not hinder the reaction. Due to the ease of operation, mild reaction conditions, absence of transition metal, and high generality of the substrates, this protocol demonstrates promise in broad applications in organic synthesis.

Table 2. One-pot sulfide synthesis using various Grignard reagents with $SOCl_2$ and PPh_3



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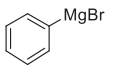
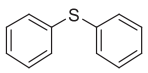
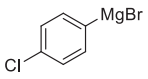
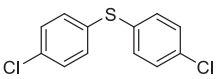
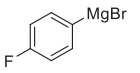
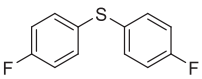
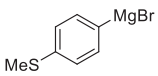
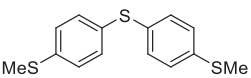
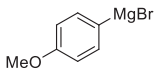
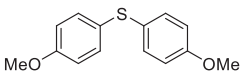
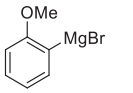
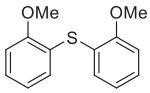
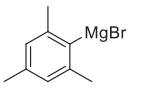
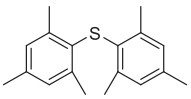
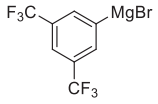
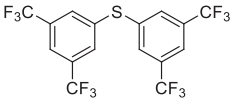
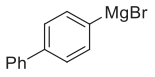
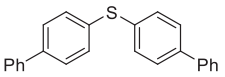
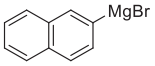
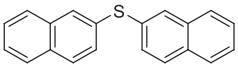
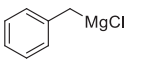
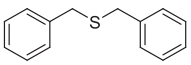
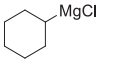
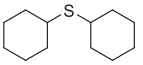
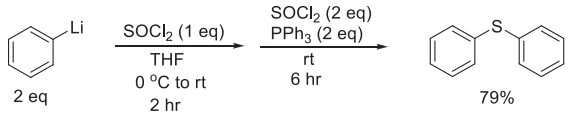
Entry	Substrate	Product	Time (h)	Yield (%)[a]
1			6	88
2			5.5	78
3			5	78
4			4	97
5			7	80
6			4	82
7			8	96
8			7.5	56
9			4	81
10			8	92
11			2	52[b]
12			3	65[b]

[a] Isolated yield when $SOCl_2$ (2 equiv) and PPh_3 (2 equiv) were used in second step.
[b] Isolated yield when $SOCl_2$ (0.2 equiv) and PPh_3 (1 equiv) were used in second step.

Experimental

Typical Procedure for Diaryl Sulfide. To a solution of $SOCl_2$ (1.5 mmol) in dry THF (10 mL) was added dropwise aryl magnesium halide (3.0 mmol in THF or Et_2O) at 0 °C. The resulting solution was stirred for 2 h at a slow rising from 0 °C to room temperature. To the reaction mixture were added dropwise a solution of PPh_3 (3.0 mmol) in



Scheme 2. Synthesis of diphenyl sulfide using phenyl lithium

dry THF (2 mL) via cannula and subsequently additional $SOCl_2$ (3.0 mmol) at room temperature. The resulting solution was stirred until the sulfoxide intermediate was consumed completely by TLC (thin layer chromatography) monitoring at room temperature and quenched with H_2O. The reaction mixture was extracted with Et_2O and H_2O. The organic layer was separated, dried over Na_2SO_4, and concentrated. The residue was subjected to column chromatography with only hexanes or hexanes-EtOAc (30:1 – 20:1) as eluent to afford the corresponding sulfide.

1,1′-Bis[3,5-bis(trifluoromethyl)phenyl]sulfide (entry 8 in Table 2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 2H), 7.79 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 133.3 (q, J = 34 Hz), 130.9 (q, J = 3 Hz), 122.7 (q, J = 272 Hz), 122.1 (sep, J = 3 Hz); ESI MS m/z 458 [M^+].

Dicyclohexyl sulfide (entry 12 in Table 2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76–2.69 (m, 2H), 1.97–1.91 (m, 4H), 1.79–1.74 (m, 4H), 1.63–1.60 (m, 2H), 1.37–1.21 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.8, 34.2, 26.1, 25.8; ESI MS m/z 198 [M^+].

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Supporting Information. Additional supporting information (^{1}H and ^{13}C NMR of all compounds in Table 2) is available in the online version of this article.

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