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Synthesis of diaryl disulfides via the reductive coupling of arylsulfonyl chlorides

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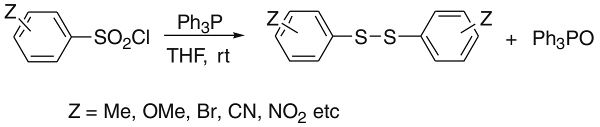
ABSTRACT

A facile synthesis of diaryl disulfides from arylsulfonyl chlorides in the presence of triphenylphosphine has been developed.

Diaryl disulfides are valuable intermediates[1] in the synthesis of natural products and medicinal compounds.[2] They are also important starting materials in the preparation of sulfenyl[3] and sulfinyl[4] reagents. Diaryl disulfides are generally synthesized from aryl thiols,[5] aryl sulfonyl esters,[6] aryl sulfonic acids,[6] and their corresponding salts.[7] In the last decade, the preparation of diaryl disulfides using sulfonyl chlorides has been of interest because of their ready availability.[8] Each of the reagents such as silphos $[PCl_{3-n}(SiO_2)_n]$/molecular iodine,[9] samarium in DMF,[10] SmI_2/HMPA,[11] piperidinium tetrathiotungstate,[12] HI/glacial acetic acid,[13] $Mo(CO)_6$ in tetramethylurea,[14] WCl_6/NaI or WCl_6/Zn,[15] BI_3 or BBr_3/KI,[16] iodotrimethylsilane,[17] tri-*n*-propylamine/trichlorosilane,[18] aluminum iodide (AlI_3),[19] and diphosphorus tetraiodide (P_2I_4)[7] has been used to reduce sulfonyl halides to the corresponding disulfides. Previously, we[20] demonstrated that the reduction of alkyl or aryl sulfonic acid derivatives and sulfoxides to the corresponding disulfides could be achieved by using a boron triiodide-*N*,*N*-diethylaniline system. Fujimori et al.[21] reported that the aryl sulfonic acids, their salts, and alkyl sulfonates can be reduced to the corresponding aryl thiols quantitatively using triphenylphosphine in the presence of iodine. We now wish to report that triphenylphosphine itself is an efficient reagent for the conversion of arylsulfonyl chlorides to the corresponding diaryl disulfides under mild reaction conditions (Scheme 1).

para-Toluenesulfonyl chloride[22] was chosen as the model system for the initial investigation. Preliminary experiments were carried out using varying ratios of triphenylphosphine and *para*-toluenesulfonyl chloride. Initially a 1:1 ratio of *para*-toluenesulfonyl chloride and triphenylphosphine was used and the reactions were carried out in THF at room temperature; approximately 50% of the sulfonyl chloride was consumed within 30 min to give disulfide in 42% yield. Lengthening the reaction time to 24 h did not affect the yield of the reaction. When the ratio of triphenylphosphine *to para*-toluenesulfonyl chloride increased to 2:1, under the same reaction conditions, the disulfide product was isolated in 92% yield within 30 min. The need for 1 equiv of triphenylphoshine for each oxygen in the sulfonyl chloride reagents is not surprising based on earlier studies involving the reduction of arylsulfonyl iodides (proposed intermediates generated in situ from aryl sulfonic acids and I_2) using triphenylphospine.[6] Dichloromethane and benzene were also evaluated as reaction solvents and the yields were 80% and 72%, respectively. However, tetrahydrofuran was the most effective solvent. The reaction was found to be sensitive to water and a trace amount of aryl thiol was detected in its presence, which resulted in decreased isolated yield of the desired disulfide. When the reactions were carried out in the presence of 0.5 equiv of water, a 1:1 mixture of thiol and disulfide formed in 80% yield. Using aqueous THF: (v:v = 1:1) inhibited the reaction completely.

Various arylsulfonyl chlorides were then evaluated.[23] As the data in Table 1 reveal, reaction yields were not affected by the electronic nature of the substituents present on the aryl rings. However, reactions of arylsulfonyl chlorides bearing a nitro group



Scheme 1. Reductive coupling of arylsulfonyl chloride using triphenylphosphine.

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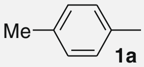
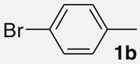
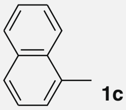
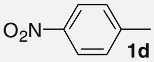
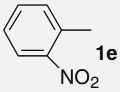
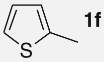
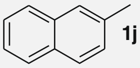
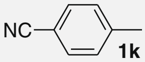
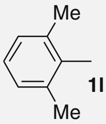
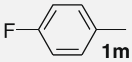
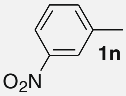
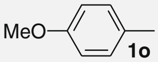
Table 1
Reduction of arylsulfonyl chlorides to disulfides using triphenylphosphine[a]

$$\text{Ar-SO}_2\text{Cl} \xrightarrow[\text{anhydrous THF/ rt}]{\text{2.0 equiv. PPh}_3} \underset{\mathbf{1}}{\text{Ar-S-S-Ar}}$$

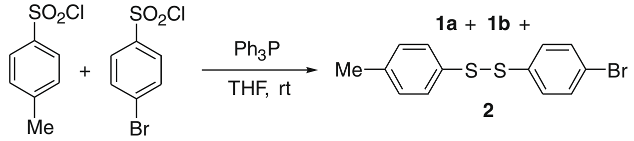
Entry	Ar	Yield[b] (%)
1	 **1a**	92
2	 **1b**	92
3	 **1c**	91
4[c]	 **1d**	75
5[c]	 **1e**	85
6	 **1f**	95
7	 **1j**	80
8	 **1k**	90
9	 **1l**	80
10	 **1m**	91
11[c]	 **1n**	85
12	 **1o**	92

[a] Reactions were carried out on a 1.0 mmol scale in dry THF (5 mL) at room temperature unless noted otherwise.

[b] All products gave satisfactory ^{1}H NMR and ^{13}C NMR spectra.

[c] Reactions were carried out at 0 °C.

(entries 4, 5, and 11) generated complex mixtures at room temperature due to a known side reaction between the nitro group and triphenylphosphine,[24] but this side reaction could be eliminated if the reactions were carried out at 0 °C. In addition, in some cases, small amounts of aryl thiols were detected due to the presence of trace amounts of sulfonic acids in the starting sulfonyl chlorides. The formation of aryl thiols could be totally eliminated by purifying the arylsulfonyl chlorides (recrystallization) prior to use.



Scheme 2. Cross-coupling reaction of the sulfonyl chlorides.

At present, the reaction mechanism is not well defined. The isolation of Ph_3PO indicates that the reaction proceeds through an ArSCl intermediate since Ph_3P is capable of extracting oxygen from a variety of substrates[6,25] including aryl sulfonyl iodides to form the corresponding deoxygenated derivatives.[6] In addition, the spontaneous decomposition of MeSCl to MeSSMe is also known in the literature.[26] The detection of the cross-coupling product 4-bromophenyl 4-methylphenyl disulfide (**2**) by GC–MS from a reaction using an equimolar mixture of *para*-toluenesulfonyl chloride and *para*-bromosulfonyl chloride suggests the possibility of radical intermediates in the process although an ionic process cannot be ruled out at this time.[19,27] (Scheme 2).

In conclusion, a practical method for the synthesis of diaryl disulfides using commercially available and inexpensive triphenylphosphine and arylsulfonyl chlorides in anhydrous tetrahydrofuran under mild reaction conditions has been developed.

Acknowledgments

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22. To remove a trace amount of sulfonic acid, *para*-toluenesulfonyl chloride was recrystalized from hexanes prior to use.
23. *Typical reaction procedure*: To a solution of *para*-toluenesulfonyl chloride (190 mg, 1.0 mmol) in tetrahydrofuran (5 mL) was added triphenylphosphine (524 mg, 2.0 mmol). The mixture was stirred at room temperature and

monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and the residue was dissolved in a minimum amount of ethyl acetate (4 mL). To this solution, hexane was added dropwise (about 30 mL) and the byproduct triphenylphosphine oxide was precipitated and was removed by filtration. Concentration of the filtrate under reduced pressure and silica gel column chromatography using hexane as eluant yielded the desired product (114 mg, 92% yield).

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27. The light yellow color of the reaction mixtures suggests that chlorine may be a byproduct. However, attempts to detect chlorine using wet KI-Starch paper were unsuccessful.