# A New Method for the Preparation of Alkyl Aryl Sulfides from Alcohols via Alkoxydiphenylphosphines by Oxidation–Reduction Condensation

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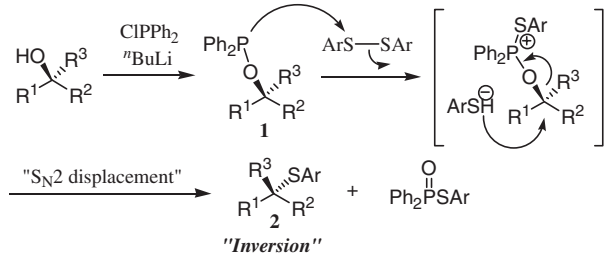
A new method for the preparation of alkyl aryl sulfides from alcohols via alkoxydiphenylphosphines by oxidation–reduction condensation was established. Various primary, secondary, and tertiary alcohols were successfully converted into the corresponding sulfides in moderate to high yields.

To prepare alkyl aryl sulfides is one of the important synthetic problem in organic[1] and medicinal chemistry,[2] and therefore many trials have been made to develop its synthetic methods. Of the methods, conversion of alcohols into alkyl aryl sulfides by oxidation–reduction condensation using phosphorus reagent systems[3] such as $Ph_3P$–DEAD–RSH[3a] or $n$-$Bu_3P$–RSSR[3b,c] is considered useful. Though the phosphorus reagents showed powerfulness and broad substrate generality, thioetherification of tertiary alcohols still remained a difficult problem even when *tert*-butyl alcohol was used.[3b–e]

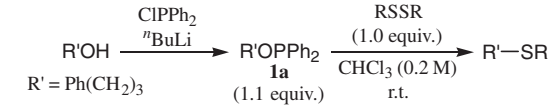
Recently, a new type of oxidation–reduction condensation using alkoxydiphenylphosphines, 2,6-dimethyl-1,4-benzoquinone (DMBQ), and carboxylic acids was reported from our laboratory and various alkyl carboxylates were prepared from alcohols including chiral tertiary ones in good to high yields with inversion of configurations in high levels (up to >99.9% inversion).[4] This method was further applied to the synthesis of symmetrical/unsymmetrical dialkyl ethers by using tetrafluoro-1,4-benzoquinone as an oxidant.[5] As a constitution to our investigation on this novel oxidation–reduction condensation, we would like to describe here a new synthetic method of alkyl aryl sulfides from primary, secondary, and tertiary alcohols via alkoxydiphenylphosphines. As shown in Scheme 1, it was assumed that the alkoxydiphenylphosphines **1** derived from lithiated alcohols and chlorodiphenylphosphine ($ClPPh_2$)[6] were readily transformed into the inverted sulfides **2** on treatment with diaryl disulfides or with arylthiols and DMBQ via the phosphonium salt intermediates.

In the first place, condensation reaction of alkoxydiphenylphosphine **1a** prepared from 3-phenyl-1-propanol with several




**Scheme 1.** Preparation of alkyl aryl sulfides from alcohols via **1**.

**Table 1.** Thioetherification of 3-phenyl-1-propanol via **1a** using various disulfides




| Entry | RSSR R | Time /h | Yield /% | Entry | RSSR R | Time /h | Yield /% |
|---|---|---|---|---|---|---|---|
| 1 | Ph | 20 | 55 | 5 | 4-$NO_2$-Ph | 20 | 78 |
| 2 | 4-Me-Ph | 20 | 68 | 6 | Py | 3 | 77 |
| 3 | 4-Cl-Ph | 20 | 74 | 7 | Bt | 0.5 | 89 |
| 4 | 2-$NO_2$-Ph | 20 | 72 | 8 | Box | 0.5 | 90 |

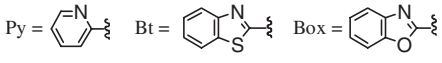
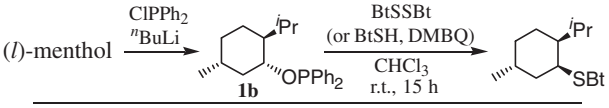



**Table 2.** Thioetherification of (*l*)-menthol via **1b**



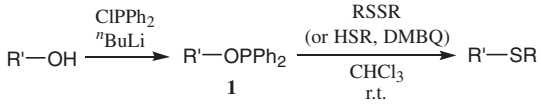

| Entry | Reagents /equiv. | **1b** /equiv. | Conc. /M | Yield /% |
|---|---|---|---|---|
| 1 | BtSSBt (1.0) | 1.1 | 0.2 | 48 |
| 2 | BtSH (1.0), DMBQ (1.1) | 1.1 | 0.2 | 44 |
| 3 | BtSH (1.0), DMBQ (1.5) | 1.5 | 0.2 | 66 |
| 4 | BtSH (1.0), DMBQ (1.5) | 1.5 | 1.5 | 77 |
| 5 | BtSH (1.0), DMBQ (2.0) | 2.0 | 1.5 | 96 |

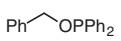
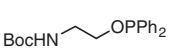
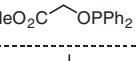
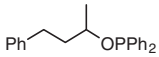
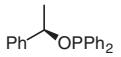
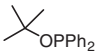
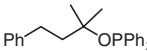
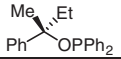
diaryl disulfides was tried (Table 1). Substituted diphenyl disulfide derivatives reacted in chloroform smoothly with **1a** at room temperature to give the corresponding sulfides in good yields within 24 h (Entries 1–5), as expected. It is interesting to note that 2,2′-dibenzothiazolyl disulfide and its bezoxazolyl derivative were much more reactive than diphenyl disulfide and that the desired sulfides were provided in high yields within 30 min or less whereas the reaction proceeded relatively slower with 2,2′-dipyridyl disulfide (Entries 6–8).

Next, thioetherification of more hindered alkoxydiphenylphosphine **1b**[6] derived from (−)-(*l*)-menthol was tried (see Table 2). When 1.1 equiv. of **1b** and 1.0 equiv. of 2,2′-dibenzothiazolyl disulfide were used, the desired sulfide was obtained only in 48% yield with complete inversion at the reaction center (Entry 1). The combined use of 2-mercaptobenzothiazole (BtSH) and DMBQ[4] gave the corresponding sulfide in nearly the same yield (Entry 2). When 2 equiv. of **1b** and DMBQ were used under highly concentrated condition, on the other hand, the yield was improved up to 96% (Entries 3–5).

Thioetherification of various primary, secondary, and tertiary alcohols were further examined by employing the disulfide and DMBQ systems (methods A and B represent the respective systems.; Table 3). Condensation reactions of less hindered pri-

**Table 3.** Thioetherification of various alcohols via **1**




| Entry | R′OPPh$_2$ | | RSSR/HSR R | Method[a] A or B | Time / h | Yield / % |
|---|---|---|---|---|---|---|
| 1 |  | **1c** | 4-ClPh | A | 0.5 | 98 |
| 2 | | | Bt | A | 0.5 | 91 |
| 3[b] |  | **1d** | 4-ClPh | A | 20 | 84 |
| 4[b] | | | Bt | A | 0.5 | 90 |
| 5[b] |  | **1e** | 4-ClPh | A | 20 | 83 |
| 6[b] | | | Bt | A | 0.5 | 89 |
| 7 |  | **1f** | 4-ClPh | A | 48 | 61 |
| 8 | | | Bt | A | 0.5 | 82 |
| 9 |  | **1g** | Ph | A | 40 | 70[c] |
| 10 | | | Bt | A | 0.5 | 58[c] (17[d]) |
| 11 | **1b** | | Box | B | 15 | 96[e] |
| 12 |  | **1h** | Py | B | 24 | 41 |
| 13 | | | Bt | B | 15 | 64 |
| 14 | | | Box | B | 20 | 61 |
| 15 |  | **1i** | Bt | B | 18 | 36 |
| 16 | | | Box | B | 18 | 40 |
| 17 |  | **1j** | Bt | B | 18 | 35 |
| 18 | | | Box | B | 18 | 42 |
| 19 |  | **1k** | Bt | B | 6 | 48 |
| 20 | | | Box | B | 6 | 48 |
| 21 |  | **1l** | Bt | B | 6 | 74[f] |
| 22 | | | Box | B | 6 | 77[g] |

[a]Method A: RSSR (1.0 equiv.), R′OPPh$_2$ (1.1 equiv.), $CHCl_3$ (0.2 M); B: RSH (1.0 equiv.), DMBQ (2.0 equiv.), R′OPPh$_2$ (2.0 equiv.), $CHCl_3$ (1.5 M). [b]The alkoxyphosphines were prepared using alcohol (1.0 equiv.), ClPPh$_2$ (1.0 equiv.) and $Et_3N$ (1.0 equiv.) in THF at r.t. [c]97% Ee. [d]Yield of N-alkylated product. [e]Complete inversion. [f]65% Ee. [g]63% Ee.

mary and secondary alcohols via alkoxyphosphines **1c–1f** with diaryl disulfides proceeded smoothly at room temperature even when methyl ester and *tert*-butyl carbamate (Boc) groups coexisted in the molecule and the desired sulfides were obtained in good to high yields (Entries 1–8). Next, the stereo course of the present reaction was studied by using **1g** and **1b** derived from chiral secondary alcohols (Entries 9–11). When **1g** derived from (*R*)-(+)-1-phenylethanol (>99% ee) which has a chiral center at benzylic position was allowed to react with diphenyl- or 2,2′-dibenzothiazolyl- disulfides, the corresponding (*S*)-sulfides were obtained with virtually complete inversion of stereochemistry (97% ee, respectively). In the case of **1b**, the desired 2-benzoxazolyl sulfide was obtained in 96% yield with complete inversion of configuration. *tert*-Alkyl aryl sulfides were also obtained according to the DMBQ method (Entries 12–22). Condensation reactions of **1h–1k** with heteroaromatic thiols afforded the corresponding sulfides in modelate to good yields (35–64%). The chiral *tert*-alkyl sulfides were formed in good yields (74–77%) with moderate stereo-inversion (63–65% ee), when **1l** prepared from (*S*)-2-phenyl-2-butanol (96% ee)[8] was used.

Thus, a novel condensation reaction for the preparation of alkyl aryl sulfides from alcohols *via* alkoxydiphenylphosphines is established. This method is applicable to the thioetherification of primary and chiral secondary alcohols as well as that of tertiary ones. Further studies on the scope and limitation of the present reaction are currently in progress.

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## References and Notes

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6 For the preparation of alkoxydiphenylphosphines, see Ref. 4; to a stirred solution of (*l*)-menthol (10 mmol) in fleshly distilled THF (20 mL) was dropped-$^n$BuLi/hexane (10 mmol) at 0 °C under argon atmosphere. After stirring for 30 min at 0 °C, ClPPh$_2$ (10 mmol) was added dropwise. The reaction mixture was further stirred at 0 °C for 1 h, then concentrated in vacuo (the white precipitate of LiCl was observed). The residue was diluted with hexane and filtered through a pad of basic alumina and Celite. After concentration in vacuo, **1b** was obtained as a colorless oil (3.19 g, 94%).

7 A typical experimental procedure is as follows; to a stirred solution of **1b** (1.2 mmol) in chloroform (0.4 mL) under argon atmosphere were added BtSH (0.6 mmol) followed by DMBQ (1.2 mmol) at room temperature. The color of the solution gradually changed from dark red to orange. After 15 h, the crude product was purified by preparative TLC on silica gel to afford the corresponding sulfide as a colorless oil (175 mg, 96%).

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