Preparation of Alkyl Aryl Sulfides from Alcohols and 2-Sulfanylbenzothiazole by a New Type of Oxidation–Reduction Condensation Using Aryl Diphenylphosphinite and Benzoquinone Derivatives

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A method for the preparation of alkyl aryl sulfides from alcohols and 2-sulfanylbenzothiazole by a new type of oxidation–reduction condensation using phenyl diphenylphosphinite and 2,6-dimethoxy-1,4-benzoquinone is described. In this reaction, the chiral alcohols are converted into the corresponding chiral sulfides with almost complete inversion of configurations under mild and neutral conditions.

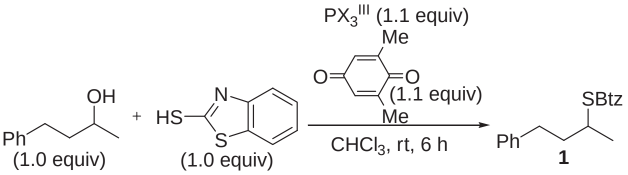
Preparation of alkyl aryl sulfides is an important procedure in organic chemistry[1] and, therefore many trials have been made so as to develop synthetic methods. For example, the conversion of alcohols into alkyl aryl sulfides[2] by oxidation–reduction condensation using trivalent phosphorus compounds such as PPh_3–DEAD–RSH (Mitsunobu conditions)[3] or n-Bu_3P–RSSR (Hata conditions)[4] is recognized useful and versatile. In these reaction systems, chiral secondary sulfides were formed from chiral secondary alcohols with complete inversion of configurations by an S_N2 pathway. However, it is generally known that sterically hindered tertiary alcohols are not converted to the corresponding sulfides.

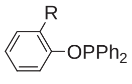
Recently, it was also shown from our laboratory that oxidation–reduction condensation[5] of alkyl diphenylphosphinites ($ROPPh_2$) with various nucleophiles (Nu–H) gave condensation products (R–Nu) in the presence of benzoquinone derivatives as oxidant.[6] It is noteworthy that tertiary alcohols could be converted into the corresponding *tert*-alkyl products by preparing a key intermediate of the alkyl diphenylphosphinites from the corresponding alcohols and chlorodiphenylphosphine in advance. When 2-sulfanylbenzothiazole (BtzSH) was employed as sulfur nucleophile, chiral *tert*-alkyl diphenylphosphinites were converted into inverted sulfides in the presence of 2,6-di-*tert*-butyl-1,4-benzoquinone (DBBQ).[2b–2d] To improve the synthetic utility of this reaction system ($ROPPh_2$–BQ–RSH), it is important to develop a new method for direct synthesis of sulfides from alcohols without forming an intermediate, $ROPPh_2$.

In this communication, we would like to describe a new type of oxidation–reduction condensation by the combined use of a phosphorus compound and a benzoquinone derivative that was successfully applied to the stereospecific syntheses of sulfides from alcohols and 2-sulfanylbenzothiazole.

First, effects of phosphorus(III) compounds were examined in order to choose a suitable reductant by taking condensation reaction of 4-phenyl-2-butanol and 2-sulfanylbenzothiazole in the presence of 2,6-dimethyl-1,4-benzoquinone (DMBQ) as a model (Table 1). The desired sulfide **1** was not obtained when a phosphine such as PPh_3 and PBu_3 or triphenylphosphite was used (Entries 1–3). On the other hand, chlorodiphenylphosphine afforded **1** in 8% yield (Entry 4). In the case of aryl diphenylphosphinites,[7] the yield of **1** markedly increased (Entries 5–7). As a result of examining the influence of substituents on the aryl group, it was shown that phenyl diphenylphosphinite gave a better result.

Table 1. Screening of phosphorus(III) compound



Entry	PX_3	Yield/%[a]	Entry	PX_3		Yield/%[a]
1	PPh_3	N.D.	5		R = H	64
2	PBu_3	N.D.	6		R = Cl	54
3	$P(OPh)_3$	N.D.				
4	Ph_2PCl	8	7		R = OMe	58

[a]Isolated yield.

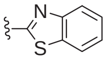
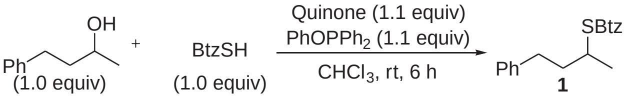
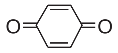
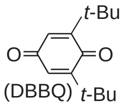
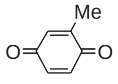
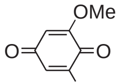
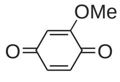
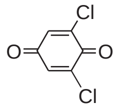
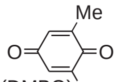
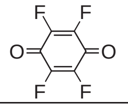
Btz = 

Table 2. Effects of quinone derivatives

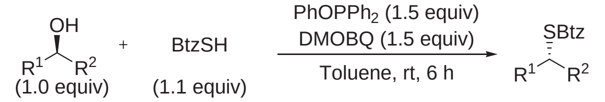


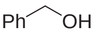
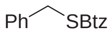
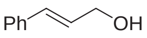
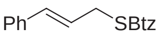
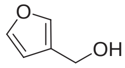
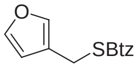
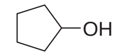
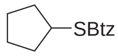
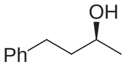
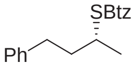
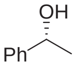
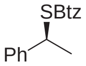
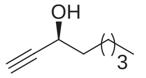
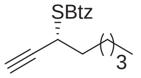
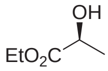
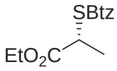
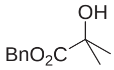
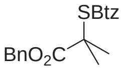
Entry	Quinone	Yield/%[a]	Entry	Quinone	Yield/%[a]
1		33	5	 (DBBQ)	61[b]
2		41	6	 (DMOBQ)	73 (81)[c]
3		23	7		3
4	 (DMBQ)	64 (62)[c]	8		3

[a]Isolated yield. [b]Determined by ^1H NMR analysis. [c]Toluene was used instead of $CHCl_3$.

Next, various 1,4-benzoquinone derivatives were examined to find a suitable oxidant (Table 2). A condensation reaction using simple 1,4-benzoquinone afforded the desired product **1**

Table 3. Thioetherification of various alcohols



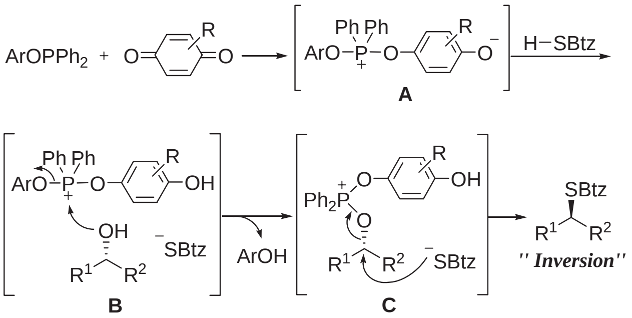
Entry	ROH	Product	Yield/%^{a} (%ee)^b
1			97
2			98
3			90
4			89
5			99 (>99)
6			77 (96)
7			87 (98)
8			85 (98)
9			65^c 86^d

^{a}Isolated yield. ^{b}Determined by HPLC using DAICEL CHIRALCEL OD-H. ^{c}The reaction was carried out by using BtzSH (2.0 equiv), DMOBQ (3.0 equiv), and PhOPPh$_2$ (3.0 equiv) for 24 h. ^{d}The reaction was carried out by using BtzSH (2.0 equiv), DMBQ (3.0 equiv), and PhOPPh$_2$ (3.0 equiv) for 17 h.

in lower yield compared to that of DMBQ (Entry 1). Introduction of one substituent at the 2-position of 1,4-benzoquinones did not give good results (Entries 2 and 3) while the yield of **1** improved when disubstituted 1,4-benzoquinones were used (Entries 4–6). The reaction with DMOBQ having electron-donating 2,6-dimethoxy groups afforded **1** in 73% yield. On the other hand, when electron-withdrawing groups are introduced to benzoquinones, **1** was obtained in quite low yield (Entries 7 and 8). In the case of DMOBQ, the yield increased up to 81% by changing the solvent to toluene (Entry 6).

After a suitable reductant and an oxidant were chosen, condensation of various alcohols were tried to investigate the scope of this reaction (Table 3).[8] The reactions of primary alcohols having olefin and a furan ring or cyclic secondary alcohols proceeded smoothly to afford the corresponding sulfides in high yields (Entries 1–4). Next, thioetherification of chiral secondary alcohols was examined and the inverted products were obtained in good to excellent yields with almost complete inversions of stereochemistries even when acetylene and ethyl ester groups coexisted in the same molecules (Entries 5–8). Further, the reaction of a sterically hindered tertiary alcohol gave the desired product in high yield when DMBQ was employed instead of DMOBQ (Entry 9).

Based on the above results, it was assumed that this condensation reaction proceeded as shown in Scheme 1: the reaction of aryl diphenylphosphinite (ArOPPh$_2$) and benzoquinone derivative initially gave a zwitterionic intermediate **A** and, the following deprotonation of BtzSH by phenoxide anion resulted in the formation of intermediate **B**. A subsequent nucleophilic attack of alcohol to the positively charged phosphorus atom formed an intermediate **C** along with elimination of aryloxy anion (ArO$^-$). Finally, nucleophilic attack of thiolate anion (BtzS$^-$) to its phosphonium part via S$_N$2 manner gave the inverted sulfide.



Scheme 1.

Thus, a new type of oxidation–reduction condensation by the combined use of PhOPPh$_2$ and DMOBQ was established. This reaction system was applicable to the thioetherification of various alcohols including tertiary alcohol. In the case of chiral alcohols, the inverted sulfides were obtained in good to excellent yields under neutral mild conditions. Further study on this type of condensation is now in progress.

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References and Notes

1 a) D. J. Procter, *J. Chem. Soc., Perkin Trans. 1* **2001**, 335. b) D. J. Procter, *J. Chem. Soc., Perkin Trans. 1* **2000**, 835. c) D. J. Procter, *J. Chem. Soc., Perkin Trans. 1* **1999**, 641. d) C. P. Baird, C. M. Rayner, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1973.

2 a) Y. Kawano, N. Kaneko, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 1612. b) K. Ikegai, W. Pluempanupat, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 780. c) K. Ikegai, W. Pluempanupat, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 638. d) T. Mukaiyama, K. Ikegai, *Chem. Lett.* **2004**, *33*, 1522.

3 For a recent review for Mitsunobu reaction, see: T. Y. S. But, P. H. Toy, *Chem. Asian J.* **2007**, *2*, 1340.

4 a) D. H. Valentine Jr., J. H. Hillhouse, *Synthesis* **2003**, 317. b) J. Skarżewski, A. Gupta, E. Wojaczyńska, R. Siedlecka, *Synlett* **2003**, 1615. c) H. Kotsuki, K. Matsumoto, H. Nishizawa, *Tetrahedron Lett.* **1991**, *32*, 4155. d) I. Nakagawa, K. Aki, T. Hata, *J. Chem. Soc., Perkin Trans. 1* **1983**, 1315.

5 For reviews on oxidation–reduction condensation, see: a) T. Mukaiyama, H. Yamabe, *Chem. Lett.* **2007**, *36*, 2. b) T. Mukaiyama, K. Ikegai, H. Aoki, W. Pluempanupat, K. Masutani, *Proc. Jpn. Acad., Ser. B* **2005**, *81*, 103. c) T. Mukaiyama, *Angew. Chem., Int. Ed.* **2004**, *43*, 5590.

6 For examples, see: a) K. Kuroda, Y. Hayashi, T. Mukaiyama, *Tetrahedron* **2007**, *63*, 6358. b) K. Masutani, T. Minowa, Y. Hagiwara, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1106. c) H. Aoki, K. Kuroda, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 1266. d) T. Mukaiyama, H. Aoki, *Chem. Lett.* **2005**, *34*, 142. e) T. Mukaiyama, T. Shintou, K. Fukumoto, *J. Am. Chem. Soc.* **2003**, *125*, 10538.

7 Aryl diphenylphosphinites are prepared according to a procedure for alkyl diphenylphosphinites, see ref. 2c.

8 Typical experimental procedure is as follows (Table 3, Entry 5): to a solution of PhOPPh$_2$ (125.2 mg, 0.45 mmol) and (*S*)-(+)-4-phenyl-2-butanol (45.1 mg, 0.30 mmol) in dry toluene (1.50 mL) were added BtzSH (55.2 mg, 0.33 mmol) followed by DMOBQ (75.7 mg, 0.45 mmol) at rt under argon atmosphere. The reaction mixture was stirred for 6 h and the crude product was purified by preparative TLC to the corresponding sulfide (89.2 mg, 99%).

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