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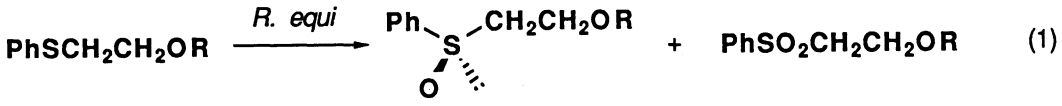
# Microbial Asymmetric Oxidation of 2-Alkoxyethylsulfides and a Facile Synthesis of Chiral Vinyl Sulfoxide

Hiromichi OHTA, Shinsuke MATSUMOTO, Yasushi OKAMOTO, and Takeshi SUGAI
Department of Chemistry, Faculty of Science and Technology, Keio University,
Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223

2-Alkoxyethyl phenyl sulfides were oxidized by incubation with *Rhodococcus equi* IFO 3730 to afford chiral sulfoxides of high enantio excess. Phenyl vinyl sulfoxide and 2-hydroxyethyl phenyl sulfoxide were obtained from microbial oxidation products without any loss of their optical purities.

Chiral sulfoxides are well known as useful building blocks in asymmetric synthesis.[1] We have already demonstrated that some optically active sulfoxides are obtained by oxidation of the corresponding sulfides by the aid of a microorganism, *Rhodococcus equi* IFO 3730.[2] In this paper, we would like to report a microbial oxidation of 2-alkoxyethyl sulfides to optically active sulfoxides and their derivation to the vinyl sulfoxide.

First, the oxidation of 2-hydroxyethyl phenyl sulfide (**1a**) was tried to obtain only disappointing results. Both the reactivity and enantioselectivity were unexpectedly low resulting in the formation of the corresponding sulfoxide of 32% e.e. in only a 7% yield with 2-day incubation. As is supposed from the results obtained before, the more lipophylic the substrates are, the more susceptible they would be to microbial oxidation.[2] Thus we tried next the oxidation of 2-alkoxyethyl phenyl sulfides. The seed culture (10 ml) of *R. equi* IFO 3730 grown on hexadecane and 0.1 to 0.2 ml of sulfide was added to 90 ml of the same medium[3] and cultured at 30 °C for 2 to 7 days specified in Table 1. The broth was extracted with ethyl acetate and the products were isolated and purified by preparative TLC on silica gel (eluent, ethyl acetate; $R_f$ 0.4-0.5). As shown in Table 1, the selectivity for the formation of sulfoxides was higher when the carbon number

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R : a, H; b, $CH_3$; c, $C_4H_9$; d, $CH_2$=$CHCH_2$;
e, $PhCH_2$; f, $CH_3OCH_2$; g, $C_4H_9OCH_2$

Table 1. Oxidation of 2-Alkoxyethyl Phenyl Sulfides with *R. equi*

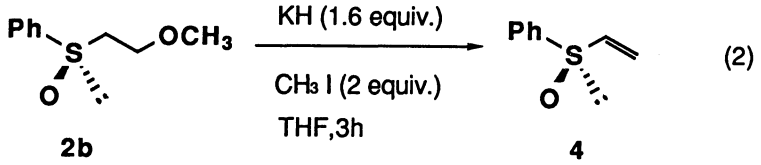
| | R | Concn. % | Cult. d | Yield/%[a] S | SO | $SO_2$ | %e.e.[b] | $[\alpha]_D$/°[c] |
|---|---|---|---|---|---|---|---|---|
| **a** | H | 0.1 | 2 | 81 | 7 | 0 | 32 | |
| **b** | $CH_3$ | 0.1 | 5 | 0 | 80 | 13 | >99 | +207 |
| **c** | $C_4H_9$ | 0.2 | 3 | 29 | 42 | 17 | 99 | +143 |
| **d** | Allyl | 0.2 | 5 | 27 | 73 | 0 | 98 | +189 |
| **e** | $PhCH_2$ | 0.2 | 7 | 55 | 11 | 24 | nd | |
| **f** | $MeOCH_2$ | 0.2 | 3 | 5 | 72 | 10 | >99.5 | +189 |
| | | 0.1 | 5 | 0 | 78 | 14 | >99.5 | |
| **g** | $BuOCH_2$ | 0.1 | 2 | 22 | 32 | 39 | >99.5 | |

a) Isolated yield. b) Determined by HPLC analysis. c) Measured in acetone (c ~1) at room temperature.

of alkoxy groups were smaller. While butyl ether (**1c**), benzyl ether (**1e**) and butoxymethyl ether (**1g**) resulted fairly large amount of sulfones, methyl ether (**1b**) and methoxymethyl ether (**1f**) afforded optically active sulfoxides in good yields. The enantio excess of the resulting sulfoxides were uniformly high as determined by HPLC analysis.[4] Oxidation of **1b** in a preparative scale (2 g in 2 l of the medium) gave the same results, the chiral sulfoxide **2b** being isolated by distillation (yield: 72%, bp 150 °C/3 mmHg, bath temp).

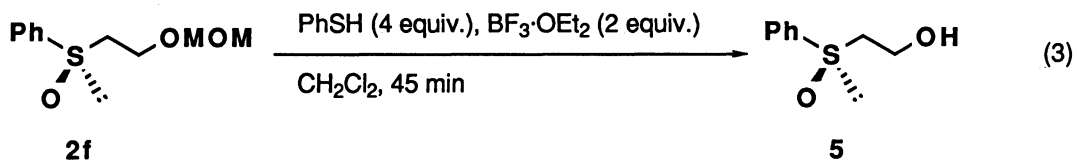
For the determination of the absolute configuration and further synthetic application,[5] elimination of methanol from **2b** to vinyl sulfoxide **4** was tried. Although a variety of bases were attempted for deprotonation, none of them gave satisfactory results. The low yield of vinyl sulfoxide **4** was considered to be due to Michael addition of once eliminated methoxide anion to resulting double bond, and anion catalyzed polymerization of vinyl sulfoxide. To minimize the formation of these undesirable side products, the reaction was carried out in the presence of an anion trapping reagent, methyl iodide being the reagent of choice. Thus,

reaction of 1.6 equiv. of KH with **2b** in the presence of methyl iodide (2 equiv.) in THF at room temperature for 3 h afforded (R)-(+)-phenyl vinyl sulfoxide (**4**)[6] in 85% yield: $[\alpha]_D^{26}$ +484° (c 0.48, acetone), lit.[7] +474° for (R)-**4**. The complete conservation of the enantio excess of original sulfoxide was confirmed by HPLC analysis. Because direct oxidation of phenyl vinyl sulfide with the aid of the bacterium gave only a poor result,[8] the formation of **4** via alkoxy sulfide **2b** is valuable for the alternative of this reaction.




**2b** **4** (2)

Further, the deprotection of MOM ether (**2f**) was developed because chiral 2-hydroxyethyl sulfoxides are known to be synthetically useful.[9] As chiral sulfoxides are known to be easily racemize under acidic conditions,[10] the usual method for deacetalization employing protonic acid cannot be applied in this case. Among some Lewis acid tested, combination of boron trifluoride etherate and thiophenol gave the best results.[11] Reaction in dichloromethane at 0 °C in the presence of the above catalyst cleanly eliminated the acetal group of **2f** to afford **5** without accompanying any racemization of sulfinyl moiety.[12]




**2f** **5** (3)

In conclusion, microbial oxidation of 2-alkoxyethyl phenyl sulfides were successfully performed by employing substrtes with appropriate alkoxy groups. Thus, optically pure vinyl and 2-hydroxyethyl sulfoxides, which are considered to be potentially useful in synthetic organic chemistry, have been obtained via further transformation of microbial oxidation products.

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Chem., 49, 671 (1985); Y. Okamoto, H. Ohta, and G. Tsuchihashi, Chem. Lett., 1986, 2049.

3) The medium consists of hexadecane (20 ml), $(NH_4)_2HPO_4$ (10 g), $K_2HPO_4$ (2 g), $MgSO_4 \cdot 7H_2O$ (0.3 g), $FeSO_4 \cdot 7H_2O$ (10 mg), $ZnSO_4 \cdot 7H_2O$ (8 mg), $MnSO_4 \cdot 4H_2O$ (8 mg), yeast extract (0.2 g), and $H_2O$ to make 1000 ml (pH 7.2).

4) Column, DAICEL CHIRALCEL OB 250 mm; eluent, MeOH/$H_2O$ = 4/6 (0.5 ml/min); retention time for racemic **2b**, 45, 62 min; **2f**, 42, 57 min; **2g**, 57, 85 min.

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6) IR $\nu_{max}$ (NaCl) $cm^{-1}$: 3075, 1443, 1082, 1050, 998, 957, 755, 700, 657, 621; $^1$H-NMR $\delta$ ($CCl_4$) 5.73 (d, 1, J=9.9), 6.08 (d, 1, J=16.5), 6.56 (dd, 1, J=9.9, 16.5), 7.17-7.73 (m, 5); MS (rel intensity) 152 ($M^+$, 2), 135 (26), 126 (21), 104 (100), 91 (18), 78 (50), 50 (31), 42 (49).

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8) Incubation of phenyl vinyl sulfide (concn. 0.1%) with *R. equi* for 2 days afforded **4** in only 14% yield, with consumption of the whole starting material. In addition, the enantio excess of the product was revealed to be only 47%.

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11) G. R. Kieczykowski and R. H. Schlessiger, J. Am. Chem. Soc., 100, 1938 (1978).

12) IR, $\nu_{max}$ (NaCl) $cm^{-1}$: 3350, 2880, 1650, 1582, 1475, 1442, 1390, 1143, 1035, 743, 688; $^1$H-NMR $\delta$ ($CDCl_3$) 2.72-3.33 (m, 2), 3.46 (s, 1), 3.78-4.33 (m, 2), 7.37-7.77 (m, 5); MS (rel intensity) 171 ($(M+1)^+$, 49), 170 ($M^+$, 31), 126 (100), 125 (21), 97 (11), 78 (74), 77 (21); $[\alpha]_D^{26}$ +209° (c 1.8, acetone). The e.e. was determined to be over 99% by HPLC analysis of the acetyl derivative: Column, DAICEL CHIRALCEL OB 250 mm; eluent, MeOH/$H_2O$=6/4 (0.5 ml/min); retention time, 25 min (the enantiomer, 33 min).

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