Tetrahedron Letters, Vol. 33, No. 29, pp. 4099-4102, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

ENANTIOSELECTIVE ROUTES TO CHIRAL BENZYLIC THIOLS, SULFINIC ESTERS AND SULFONIC ACIDS ILLUSTRATED BY THE 1-PHENYLETHYL SERIES

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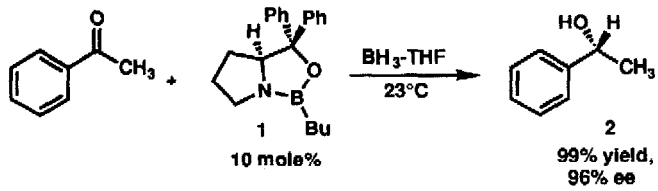
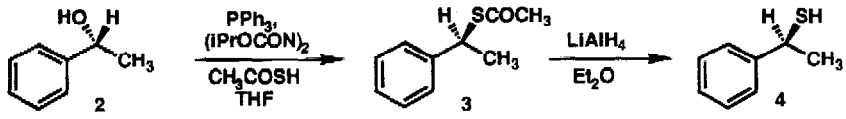
Summary: *Chiral benzylic thiols, sulfinic esters and sulfonic acids can be produced readily and in excellent enantiomeric purity from the corresponding achiral ketones.*

Chiral benzylic amine, alcohol and carboxylic acid derivatives occupy an important position in synthetic methodology. In contrast, enantiopure chiral benzylic thiol or sulfonic acid derivatives have rarely been used as reagents or reactants in synthesis, largely due to the fact that their preparation has traditionally entailed cumbersome resolution procedures. We describe herein a simple and effective enantiocontrolled route to these chiral sulfur compounds which takes advantage of recent advances in the enantioselective reduction of achiral ketones R_LCOR_S to chiral secondary alcohols $R_LCH(OH)R_S$ by means of a catalytic amount of oxazaborolidine **1** (or enantiomer, 5-10%) with borane or catecholborane as the stoichiometric reductant (CBS reduction). This process has been shown to be a powerful method for the preparation of a variety of optically active alcohols and has led to a rapid growth in the number of starting materials and reagents available for synthesis.[1] The present work also demonstrates the applicability of nucleophilic displacement reactions to the formation of benzylic sulfur compounds with efficient inversion of configuration.[2-4]

The *R* alcohol **2** was prepared in 99% yield and 96% ee with a catalytic amount of oxazaborolidine **1** and a stoichiometric quantity of borane in THF.[1,5] Submission of this material to Mitsunobu conditions[2a]

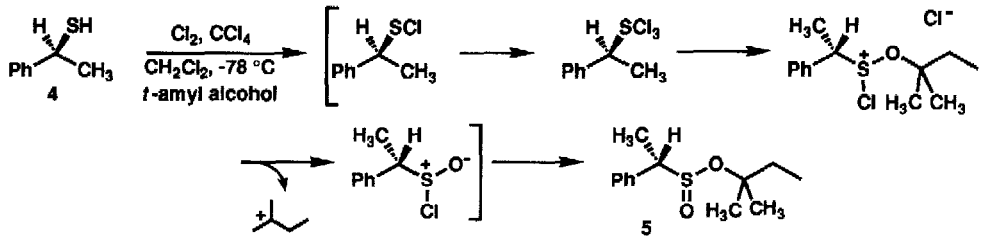


(diisopropylazodicarboxylate, triphenylphosphine, thiolacetic acid) yielded the *S* thioacetate **3** in 72% yield and 96% ee with clean inversion.[6] This is particularly noteworthy considering the propensity of such systems to undergo C-O heterolysis in the activation of the hydroxyl group. Reduction of the *S* thioacetate **3** to the *S*

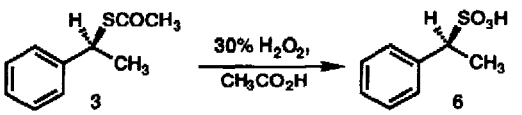


benzylic mercaptan **4** occurred smoothly ($LiAlH_4$, Et_2O, 0 °C to 23 °C, 1 h, 85%, 96% ee).[7,8] Treatment of the *S* mercaptan **4** with chlorine gas in the presence of *t*-amyl alcohol resulted in isolation of the *S* sulfinate

ester **5**. Presumably, the sulfenyl chloride is generated *in situ*, converted to the trichloride, attacked by *t*-amyl alcohol and decomposed, as shown, to form the sulfinyl chloride and eventually the ester **5**.[9] It is interesting that attempts to convert (*S*)-1-phenylethane thiol to the corresponding sulfenyl chloride, using chlorine or sulfuryl chloride, under the mildest conditions which successfully transform benzyl thiol to benzylsulfenyl chloride, afforded only racemic 1-phenylethyl chloride.



Chiral (*S*)-α-phenylethane sulfonic acid (**6**) could be obtained directly from the *S* thioacetate **3** in a single step. The transformation was accomplished by treatment of a solution of **3** in acetic acid with 30% hydrogen peroxide at 60 °C.[10,11] The sodium salt of **6** was isolated after removal of acetic acid and neutralization with aqueous sodium hydroxide. The free acid was obtained (91% yield) by cation exchange chromatography. Since the neat free acid is very hygroscopic and also subject to gradual decomposition, it is advisable to store material as the sodium salt. The methyl ester of **6**, prepared using diazomethane in ether, was shown to be of 95% ee by HPLC analysis.



In conclusion, we have demonstrated an approach to optically active benzylic thiols and sulfonic acids which provides ready access to **4**, **5** and **6** and which may be broadly applicable. The intermediate chiral secondary alcohol is available in high enantiomeric purity in a single step which uses a recoverable chiral reagent in catalytic amount. The CBS reduction provides access to a wide range of alcohols including allylic and benzylic types in high enantiomeric purity, and it is anticipated that the conditions described herein will prove suitable for the conversion of many of these compounds to their corresponding mercaptans and sulfonic acids. The following experimental details indicate the ease of this preparative approach.

(*S*)-1-Phenylethyl Thioacetate 3. To a magnetically stirred solution of triphenylphosphine (0.859 g, 3.27 mmol) in THF (6 mL) at 0 °C in a 25 mL round bottom flask was added diisopropylazodicarboxylate (645 μL, 0.661g, 3.27 mmol) dropwise. After stirring for 30 min at 0 °C, the cloudy white mixture was treated dropwise with a solution of (*R*)-1-phenylethanol **2** (0.200 g, 1.64 mmol) and thiolacetic acid (235 μL, 3.27 mmol) in THF (4 mL). After 1 h at 0 °C the resulting greenish-black solution was warmed to 23 °C and stirred for an additional 1 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (4 x 25 mL), concentrated to a quarter of its original volume and diluted with an equal volume of hexane to produce a white slurry which was filtered through Celite. The filtrate was concentrated *in vacuo*, filtered through a pad of silica gel which was then washed with hexane, dried over $MgSO_4$ and again concentrated to afford an orange oil

which was purified by flash chromatography (33% EtOAc in hexane) to provide 0.212 g (72%) of **3** as a colorless oil. The enantiomeric excess was determined to be 96% by HPLC analysis using 1.5 % isopropanol in hexane with a Diacel OJ column; t_R (*S*) = 10.5 min, (*R*) = 21.9 min. R_f = 0.36 (50% CH_2Cl_2 in hexane, anisaldehyde); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 (d, *J* = 7.2 Hz, 3 H, CH(C<u>H</u>$_3$)SCOMe), 2.30 (s, 3 H, CH(CH$_3$)SCO<u>Me</u>), 4.75 (q, *J* = 7.2 Hz, 1 H, C<u>H</u>(CH$_3$)SCOMe) and 7.34 (m, 5 H, Ph-<u>H</u>); FTIR (thin film, cm^{-1}) 2933, 1692, 1134; MS (m/e): calc'd for $C_{10}H_{12}OS$, 180.0609; found 180.0607; $[\alpha]_D^{23}$ -287.0 ° (c = 0.84, $CHCl_3$).

(*S*)-1-Phenylethane Thiol 4. To a 1M solution of $LiAlH_4$ in Et_2O (5.61 mL, 5.61 mmol) in a 50 mL round bottom flask at 0 °C was added dropwise a solution of the thioacetate **3** (0.918 g, 5.10 mmol) in Et_2O (15 mL) *via* cannula. The resulting mixture was stirred vigorously for 20 min at 0 °C then warmed to 23 °C and stirred an additional 30 min. The mixture was recooled to 0 °C and treated with 3 N aqueous HCl under an argon atmosphere until all the solid had dissolved. The resulting biphasic mixture was diluted with Et_2O (15 mL) and water (20 mL), and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to afford 0.644 g of **4** (91%) as a colorless oil. This material was used without purification in subsequent reactions. R_f = 0.63 (50% CH_2Cl_2 in hexane, anisaldehyde); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (d, *J* = 7.0 Hz, 3 H, CH(C<u>H</u>$_3$)SH), 1.99 (d, *J* = 5.1 Hz, 1 H, CH(CH$_3$)S<u>H</u>), 4.23 (dq, *J* = 5.1, 7.0 Hz, 1 H, C<u>H</u>(CH$_3$)SH) and 7.31 (m, 5 H, Ph-<u>H</u>); FTIR (thin film, cm^{-1}) 2970, 1492, 1452; $[\alpha]_D^{23}$ -84.9° (c = 1.19, abs. EtOH). Conversion of a small portion of this material to the Mosher ester was accomplished by treatment with (*S*)-(-)-MTPA chloride (from (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Aldrich)) and 4-*N*,*N*-dimethylaminopyridine in CH_2Cl_2. The enantiomeric excess was determined to be 96% by integration of the methyl doublet in the ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (d, *J* = 7.20 Hz, 3 H, CH(C<u>H</u>$_3$)-minor), 1.62 (d, *J* = 7.15 Hz, 3 H, CH(C<u>H</u>$_3$)-major).

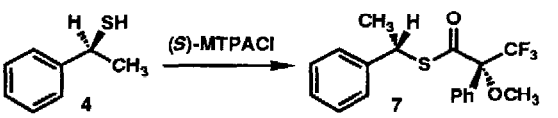
(S)-1-Phenylethanesulfonic Acid 6. A solution of **3** (0.161g, 0.896 mmol) in acetic acid (1.5 mL) in a 10 mL round bottom flask equipped with a reflux condenser was stirred at 60 °C and treated dropwise with 30% H_2O_2 (0.560 mL, 4.48 mmol). The resulting clear solution was stirred for 2 h at 60 °C then cooled to 23 °C and the acetic acid was removed azeotropically with heptane. The residue was diluted with water (5 mL), neutralized with 1 N aqueous NaOH, washed with Et_2O, and concentrated *in vacuo* to provide the sodium salt of **6** as a colorless solid. This material could be stored indefinitely. The free acid was obtained by filtration through a column packed with Amberlite IR-120 resin (H^+ form) using water as an eluant. Concentration of the aqueous fractions afforded 0.152g (91%) of the acid as a pasty oil. ^{1}H NMR (500 MHz, D_2O) δ 1.71 (d, *J* = 7.2 Hz, 3 H, CH(C<u>H</u>$_3$)), 4.22 (q, *J* = 7.1 Hz, 1 H, C<u>H</u>(CH$_3$)), 7.4-7.5 (m, 5 H, Ph-<u>H</u>). Treatment of a portion of the acid with diazomethane in Et_2O, concentration and preparative TLC (50% ether in hexane) afforded the methyl ester of **6**. Enantiomeric excess was determined to be 95% by HPLC analysis using 60% isopropanol in hexanes with a Diacel OJ column; t_R (*S*) = 16.1 min, (*R*) = 22.0 min. R_f = 0.45 (50% hexane in ether, anisaldehyde); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83 (d, *J* = 7.1 Hz, 3 H, CH(C<u>H</u>$_3$)), 3.66 (s, 3 H, SO_3C<u>H</u>$_3$), 4.39 (q, *J* = 7.1 Hz, 1 H, C<u>H</u>(CH$_3$)), 7.40 (m, 5 H, Ph-<u>H</u>); FTIR (thin film, cm^{-1}) 2934, 1352, 1168; $[\alpha]_D^{23}$ - 24.1° (c = 1.13, $CHCl_3$); MS (m/e): calc'd for $C_9H_{12}SO_3$, 200.0507; found 200.0521.

Sulfinate Ester 5. To a solution of the mercaptan **4** (0.0686 g, 0.496 mmol) in methylene chloride (7 mL) and *t*-amyl alcohol (1 mL) in a 25 mL round bottom flask at -78 °C was added quickly a freshly titrated solution of chlorine in carbon tetrachloride (1.15 mL, 1.49 mmol). After stirring 30 min at -78 °C,

pyridine (125 μL, 1.54 mmol) was added, the solution was allowed to warm to 23 °C and it was stirred for an additional 12 h. Concentration *in vacuo* followed by dilution with hexane resulted in the precipitation of a colorless solid which was removed by filtration through Celite. Concentration of the filtrate yielded a pale oil which was purified by preparative TLC (25 % ether in hexane) to provide 0.108 g (91%) of **5** (1 : 1 mixture of diastereomers at S) as a colorless oil. R_f = 0.25 (25% ether in hexane, anisaldehyde); ^{1}H NMR (500 MHz, $CDCl_3$), δ 0.76 (t, *J* = 7.5Hz, 3 H, $CH_2C\underline{H}_3$), 0.82 (t, *J* = 7.5 Hz, 3 H, $CH_2C\underline{H}_3$), 1.05 (s, 3 H, $C(CH_3)(C\underline{H}_3)CH_2CH_3$), 1.11 (s, 3 H, $C(C\underline{H}_3)(CH_3)CH_2CH_3$), 1.20 (s, 3 H, $C(CH_3)(C\underline{H}_3)CH_2CH_3$), 1.25 (s, 3 H, $C(C\underline{H}_3)(CH_3)CH_2CH_3$), 1.40-1.64 (m, 4 H, $C\underline{H}_2CH_3$), 1.64 (d, *J* = 7.3 Hz, 3 H, $CH(C\underline{H}_3)$), 1.65 (d, *J* = 7.0 Hz, 3 H, $CH(C\underline{H}_3)$), 3.76 (q, *J* = 7.3 Hz, 1 H, $C\underline{H}(CH_3)$), 3.88 (q, *J* = 7.1 Hz, 3 H, $C\underline{H}(CH_3)$), 7.25 (m, 10 H, Ph-H); FTIR (thin film, cm^{-1}) 2975, 1453, 1370, 1121; MS (m/e): calc'd for $C_{13}H_{20}SO_2$, 240.1262; found 240.1263.[12]

Reference and Notes

1. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926. (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861-2863. (d) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611-614. (e) Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209-1216.
2. Such displacements have long been used for the preparation of chiral aliphatic sulfur compounds. For example see (a) Volante, R. P. *Tetrahedron Lett.* **1981**, 3119-3122. (b) Hojo, K.; Yoshino, H.; Mukaiyama, T. *Chem. Lett.* **1977**, 437-440. (c) Beretta, E.; Cinquini, M.; Colonna, S.; Fornasier, R. *Synthesis* **1974**, 425-426. (d) Arcus, C. L.; Hallgarten, P. A. *J. Chem. Soc.* **1956**, 2987-2991. (e) Gauthier, J. Y.; Bourdon, F.; Young, R. N. *Tetrahedron Lett.* **1986**, 15-18.
3. For the preparation of chiral benzylic organosulfur compounds by the use of resolution procedures see (a) Isola, M.; Ciuffarin, E.; Sagramora, L. *Synthesis* **1976**, 326-329. (b) Yoshioka, R.; Ohtsuki, O.; Senuma, M.; Tosa, T. *Chem. Pharm. Bull.* **1989**, *37*, 883-886. (c) Evans, E. B.; Mabbott, E. E.; Turner, E. E. *J. Chem. Soc.* **1927**, 1159-1168.
4. For recent research on chiral benzylic organosulfur compounds see (a) Freer, A.; Gilmore, C. J. *Tetrahedron Lett.* **1980**, 205-208. (b) Oae, S.; Uchida, Y. *Acc. Chem. Res.*. **1991**, 202-208. (c) Chiellini, E.; Marchetti, M.; Ceccarelli, G. *Int. J. Sulfur Chem., A.* **1971**, *1*, 73-78.
5. A chiral Diacel OD column was used with 2.5% isopropanol in hexane for elution at a flow rate of 1 mL per minute; $t_R(S)$ = 13.9 min, $t_R(R)$ = 18.6 min.
6. Absolute configuration was determined by correlating the optical rotation of the mercaptan **4** with the reported rotation.[3a]
7. Enantiomeric excess was determined by conversion of **4** to its Mosher ester **7** and NMR analysis of the resulting diastereomers.



8. Compare the procedure of Smith, H. E.; Fontana, L. P. *J. Org. Chem.* **1991**, *56*, 432-435 which appeared after the completion of this work.
9. For another preparation of benzylsulfinic acids see Ueno, Y.; Kojima, A.; Okawara, M. *Chem. Lett.* **1984**, 2125-2128.
10. See Showell, J. S.; Russell, J. R.; Swern, D. *J. Org. Chem.* **1962**, *27*, 2853-2858. Treatment of the thioacetate with commercially available peracetic acid also afforded the desired product, but the former conditions were found to be more convenient and to afford a product of higher purity.
11. (a) For a general review of the oxidation of mercaptans see: Capozzi, G.; Modena, G. *The Chemistry of the Thiol Group pt. 2* Patai, S., Ed.; Wiley: New York, 1974, 785-839. (b) For a review on the oxidation to sulfonic acids, see Gilbert, E. E. *Sulfonation and Related Reactions;* Interscience: New York, 1965, 215-239. (c) Agami, C.; Prince, B.; Puchot, C. *Synthetic Communications* **1990**, *20*, 3289-3294.
12. This research was assisted financially by a grant from the National Science Foundation.

(Received in USA 2 April 1992)