Notes

Cyclic Sulfamate from N-Substituted-2-amino-3-phenyl-2-propanol and Its Nucleophilic Reactions

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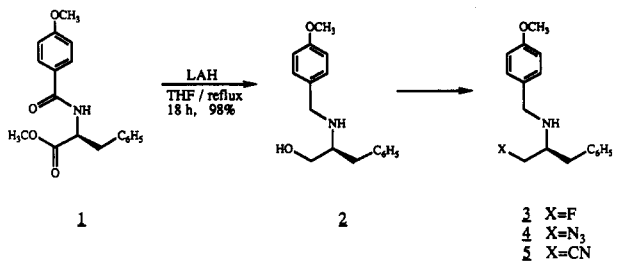
We recently required (fluoromethyl)phenylalanine **3**, which we planned to make from amino alcohol **2** derived from phenylalanine (Scheme I). Attempts to convert the alcohol into a leaving group with and without protected NH gave products associated with neighboring group participation that could not be converted into **3**.[1] We then sought to modify the Sharpless application of cyclic sulfates of glycols to the corresponding sulfamates of amino alcohols.[2] We report here the successful synthesis of these cyclic sulfamates and their susceptibility to nucleophilic ring opening and subsequent hydrolysis to yield three α-substituted chiral phenyl amines (Scheme II).

Cyclic structures, such as **6** or **7**, have not been subject to great synthetic scrutiny. Noda[3] reported the synthesis of L-serine *O*-sulfate but did not examine its reactivity. Several groups have reported the synthesis of 1,2,3-oxathiazolidine *S*-oxides.[4-8] Wudl and Lee[4] found that these *S*-oxides underwent nucleophilic addition at sulfur followed by ring opening to β-hydroxy sulfinamides.

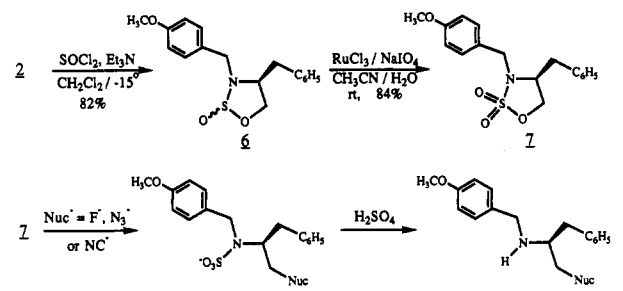
We found the preparation of **6** and **7** to be straightforward using the procedures of Wudl and Lee[4] followed by Sharpless oxidation.[2] *S*-Oxide **6** is formed in 84% yield as a 3:2 ratio of isomers at sulfur. Oxidation with ruthenium catalyst and periodate afforded **7** in 84% yield. Treatment of **7** with Bu_4NF in tetrahydrofuran (THF) followed by hydrolysis with 20% H_2SO_4 for 2 h gave **3** in 61% yield. Likewise treatment of **7** with sodium azide in DMF or sodium cyanide in DMF and hydrolysis provided **4** and **5** in 79% and 86%, respectively. We have made four noteworthy observations concerning the preparation of **7**. As Deyrup and Sharpless noted, we have been unable to convert **2** into **7** directly with sulfuryl chloride, although a 1,2,3-thiadiazolidine *S*,*S*-dioxide has been prepared by this route.[1b] We were unable to convert the primary amine, 2-amino-3-phenyl-1-propanol, to the non-benzylated analogue of **6** with thionyl chloride.[9] Oxidation of **6** to **7** also occurs with MCPBA or TPAP/NMO[10] but in substantially lower yields than with ruthenium/periodate. Finally, hydrolysis of the intermediate sulfamic acid does not occur completely under less rigorous conditions.

Scheme I



1 2 3 X=F 4 X=N_3 5 X=CN

Scheme II



We have demonstrated that 1,2,3-oxathiazolidine *S*,*S*-dioxide (**7**) serves as a useful intermediate in the conversion of β-hydroxy amines into (fluoromethyl)-, (cyanomethyl)-, and (azidomethyl)phenylalanine. This reaction should find application with other nucleophiles and amino alcohols. The use of weak nucleophiles with **7** complements the ring opening of aziridines reported with organometallics or acid catalysis.[11]

Experimental Section

General. Tetrahydrofuran was distilled immediately prior to use from sodium/benzophenone. Unless otherwise noted, all reactions were carried out under an argon atmosphere. Temperatures refer to bath temperatures. Proton and carbon spectra were measured in $CDCl_3$. Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

(2*S*)-Methyl 2-[*N*-(*p*-Methoxybenzoyl)amino]-3-phenyl-1-propanoate (1). To a solution of L-phenylalanine methyl ester hydrochloride (9.51 g, 44.1 mmol) and triethylamine (9.3 g, 92.6 mmol) in THF (100 mL) at 0 °C was added *p*-anisoyl chloride (8.37 g, 49.1 mmol). The solution was stirred at room temperature for 5 h, followed by the addition of a 1:1 brine/water mixture. The mixture was extracted once with ether and twice with CH_2Cl_2. The organic extracts were combined, dried (Na_2SO_4), and con-

(1) For recent reports of similar problems with alternative solutions, see: (a) Kim, T. H.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3699. (b) Rosenberg, S. H.; Dellaria, J. F.; Kempf, D. J.; Hutchins, C. W.; Woods, K. W.; Maki, R. G.; de Lara, E.; Spina, K. P.; Stein, H. H.; Cohen, J.; Baker, W. R.; Plattner, J. J.; Kleinert, H. D.; Perun, T. J. *J. Med. Chem.* **1990**, *33*, 1582.

(2) (a) Gao, V.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538. (b) Brandes, S. J.; Katzenellenbogen, J. A. *Mol. Pharm.* **1987**, *32*, 391. (c) Berridge, M. S.; Franceschini, M. P.; Rosenfeld, E.; Tewson, T. J. *J. Org. Chem.* **1990**, *55*, 1211.

(3) Noda, Y. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1554.

(4) Wudl, F.; Lee, T. B. K. *J. Am. Chem. Soc.* **1973**, *95*, 6349.

(5) Deyrup, J. A.; Moyer, C. L. *J. Org. Chem.* **1969**, *34*, 175.

(6) Takei, H.; Shimizu, H.; Higo, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1925.

(7) Cox, S.; El Dusouqui, O. M. H.; McCormack, W.; Tillett, J. G. *J. Org. Chem.* **1975**, *40*, 949.

(8) Huestis, L. D.; Walsh, M. L.; Hahn, N. *J. Org. Chem.* **1965**, *30*, 2763.

(9) We were able to convert *N*-ethyl-2-amino-3-phenyl-1-propanol into the N-ethylated analogues of **4**, **6**, and **7** in comparable yields.

(10) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

(11) Jones, D. S.; Srinivasan, A.; Kasina, S.; Fritzberg, A. R.; Wilkening, D. W. *J. Org. Chem.* **1989**, *54*, 1940.

(12) **Note Added in Proof.** Two related articles have appeared: Alker, D.; Doyle, K. J.; Harwood, L. M.; McGregor, A. *Tetrahedron Assym.* **1990**, *1*, 877. Baldwin, J. E.; Spivey, A. C.; Schofield, C. J. *Tetrahedron Assym.* **1990**, *1*, 881. We are grateful to Prof. K. B. Sharpless for alerting us to this work.

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centrated, and the residue was crystallized from hexane/ethyl acetate to give (2S)-methyl 2-[N-(p-methoxybenzoyl)amino]-3-phenyl-1-propanoate (10.3 g, 75% yield) as white crystals: ^{1}H NMR δ 7.73–7.68 (m, 2 H), 7.33–7.25 (m, 3 H), 7.15–7.12 (m, 2 H), 6.93–6.88 (m, 2 H), 6.54 (d, J = 7.7 Hz, 1 H), 5.11–5.05 (m, 1 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 3.28 (dd, J = 5.7, 13.8 Hz, 1 H), 3.21 (dd, J = 5.5, 13.8 Hz, 1 H); ^{13}C NMR δ 172.5, 166.6, 162.7, 136.1, 129.5, 129.0, 128.7, 127.3, 126.3, 113.9, 55.3, 53.3, 52.2, 37.8; MS, exact mass calcd for $C_{18}H_{20}NO_4$ (MH^+) 314.1393, found 314.1392.

(2S)-2-[N-(p-Methoxybenzyl)amino]-3-phenyl-1-propanol (2). To a 0 °C suspension of lithium aluminum hydride (3.08 g, 81.2 mmol) in THF (75 mL) was added dropwise (2S)-methyl 2-[N-(p-methoxybenzoyl)amino]-3-phenyl-1-propanoate (10.2 g, 32.6 mmol) in THF (60 mL). The reaction mixture was refluxed for 18 h and then cooled to 0 °C. The excess hydride was destroyed with 0.4 N KOH (3 mL), and the mixture was stirred at 0 °C for 5 min. Following the addition of water (ca. 10 mL), the mixture was heated at reflux for 20 min and filtered (hot) through Celite. The precipitate was rinsed four times with CH_2Cl_2, and the filtrates were combined, dried (Na_2SO_4), and concentrated. Recrystallization of the residue from hexane/ethyl acetate gave (2S)-2-[N-(p-methoxybenzyl)amino]-3-phenyl-1-propanol (8.66 g, 98% yield) as a pale-green solid: ^{1}H NMR δ 7.31–7.09 (m, 7 H), 6.82 (d, J = 8.6, 2 H), 3.77 (s, 3 H), 3.68 (s, 2 H), 3.61 (dd, J = 3.8, 10.8 Hz, 1 H), 3.32 (dd, J =5.3, 10.8 Hz, 1 H), 2.96–2.89 (m, 1 H), 2.83–2.69 (m, 2 H); ^{13}C NMR δ 158.6, 138.4, 132.0, 129.1, 128.5, 126.3, 113.8, 62.4, 59.2, 55.2, 50.4, 38.0; MS, exact mass calcd for $C_{17}H_{22}NO_2$ (MH^+) 272.1652, found 272.1650.

(4S)-4-Benzyl-3-(p-methoxybenzyl)-1,2,3-oxothiazolidine S-Oxide (6). To a mixture of (2S)-2-[N-(p-methoxybenzyl)-amino]-3-phenyl-1-propanol (6.38 g, 23.5 mmol) and triethylamine (4.76 g, 47 mmol) in CH_2Cl_2 (60 mL) at −15 °C was added dropwise thionyl chloride (3.1 g, 26 mmol) in CH_2Cl_2 (10 mL), followed by triethylamine (4.76 g, 47 mmol) in CH_2Cl_2 (10 mL). After 24 h at −15 °C, the reaction mixture was concentrated and the residue was chromatographed on silica gel (25% ethyl acetate/hexane) to give a diastereomeric mixture of (4S)-4-benzyl-3-(p-methoxybenzyl)-1,2,3-oxothiazolidine S-oxide (6.47 g, 82% yield) as a colorless oil: MS, exact mass calcd for $C_{17}H_{20}NO_3S$ (MH^+) 318.1165, found 318.1155.

(4S)-4-Benzyl-3-(p-methoxybenzyl)-1,2,3-oxothiazolidine S,S-Dioxide (7). To a solution of (4S)-4-benzyl-3-(p-methoxybenzyl)-1,2,3-oxothiazolidine S-oxide (1.98 g, 6.2 mmol) in acetonitrile (9 mL) at 0 °C was added sequentially ruthenium(III) chloride hydrate (ca. 2 mg), sodium periodate (1.97 g, 9.2 mmol), and water (9 mL), and the reaction mixture was warmed to room temperature. After 3 h, the mixture was extracted twice with ether. The organic extracts were combined, washed with water and brine, dried (Na_2SO_4), and concentrated, and the residue was chromatographed on silica gel (22% ethyl acetate/hexane) to give (4S)-4-benzyl-3-(p-methoxybenzyl)-1,2,3-oxothiazolidine S,S-dioxide (1.74 g, 84% yield) as a white solid. This white solid could be recrystallized from ethyl ether/hexane to give white crystals, mp 64–65 °C: ^{1}H NMR δ 7.33–7.25 (m, 5 H), 7.06–7.03 (m, 2 H), 6.92–6.87 (m, 2 H), 4.32–4.19 (m, 4 H), 3.82 (s, 3 H), 3.76–3.71 (m, 1 H), 3.02 (dd, J = 5.6, 13.6 Hz, 1 H), 2.73 (dd, J = 9.4, 13.6 Hz, 1 H); ^{13}C NMR δ 160.0, 135.5, 130.5, 129.3, 129.1, 127.6, 126.5, 114.3, 70.3, 59.6, 55.2, 50.1, 38.2; MS, exact mass calcd for $C_{17}H_{19}NO_4S$ (M^+) 333.1036, found 333.1049. Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.39; H, 5.88; N, 4.19.

(2S)-1-Fluoro-2-[N-(p-methoxybenzyl)amino]-3-phenylpropane (3). To a solution of (4S)-4-benzyl-3-(p-methoxybenzyl)-1,2,3-oxothiazolidine S,S-dioxide (104 mg, 0.31 mmol) in THF was added tetrabutylammonium fluoride (0.62 mL, 1.0 M in THF), and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated, and to the residue were added ether (1.0 mL) and 20% H_2SO_4 (1.0 mL). After being stirred at room temperature for 2 h, the mixture was neutralized with $NaHCO_3$(s) and extracted once with ether and twice with CH_2Cl_2. The organic extracts were combined, dried (Na_2SO_4), and concentrated, and the residue was chromatographed on silica gel (25% ethyl acetate/hexane) to give (2S)-1-fluoro-2-[N-(p-methoxybenzyl)amino]-3-phenylpropane (51.9 mg, 61% yield) as a colorless oil: ^{1}H NMR δ 7.32–7.12 (m, 7 H), 6.82 (d, J = 8.5 Hz, 2 H), 4.74–4.37 (m, 1 H), 4.32–4.21 (m, 1 H), 3.82–3.72 (m, 2 H), 3.78 (s, 3 H), 3.13–2.98 (m, 1 H), 2.79 (d, J = 6.8 Hz, 2 H), 1.63 (bs, 1 H); ^{13}C NMR δ 158.9, 138.3, 132.3, 129.4, 129.3, 128.7, 126.6, 113.9, 84.4 (J_{CF} = 170.6), 57.7 (J_{CCF} = 19.1), 55.1, 50.7, 36.9 (J_{CCCF} = 5.5); MS, exact mass calcd for $C_{17}H_{20}FNO$ (M^+) 273.1530, found 273.1515.

(2S)-1-Azido-2-[N-(p-methoxybenzyl)amino]-3-phenylpropane (4). To a solution of (4S)-4-benzyl-3-(p-methoxybenzyl)-1,2,3-oxathiazolidine S,S-dioxide (96.5 mg, 0.29 mmol) in DMF (1.0 mL) was added sodium azide (99.9 mg, 1.5 mmol), and the mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated, and to the residue were added ether (2 mL) and 20% H_2SO_4 (1.5 mL). After being stirred at room temperature for 5 h, the mixture was neutralized with $NaHCO_3$(s) and extracted three times with $CHCl_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was chromatographed on silica gel (20% ethyl acetate/hexane) to give (2S)-1-azido-2-[N-(p-methoxybenzyl)amino]-3-phenylpropane (67.9 mg, 79% yield) as a colorless oil: ^{1}H NMR δ 7.32–7.14 (m, 7 H), 6.85–6.82 (m, 2 H), 3.79 (s, 3 H), 3.79 (d, J = 12.9 Hz, 1 H), 3.72 (d, J = 13.0 Hz, 1 H), 3.36 (dd, J = 4.5, 12.3 Hz, 1 H), 3.19 (dd, J = 5.3, 12.4 Hz, 1 H), 3.01–2.93 (m, 1 H), 2.82 (dd, J = 6.6, 13.5 Hz, 1 H), 2.74 (dd, J = 7.2, 13.6 Hz, 1 H), 1.50 (bs, 1 H); ^{13}C NMR δ 159.0, 138.4, 132.3, 129.4, 129.3, 128.7, 126.7, 114.0, 57.8, 55.2, 53.5, 50.7, 38.5; MS, exact mass calcd for $C_{17}H_{21}N_4O$ (MH^+) 297.1702, found 297.1723.

(3S)-3-[N-(p-Methoxybenzyl)amino]-4-phenylbutyronitrile (5). To a solution of (4S)-4-benzyl-3-(p-methoxybenzyl)-1,2,3-oxathiazolidine S,S-dioxide (103 mg, 0.31 mmol) in DMF (1.0 mL) was added sodium cyanide (73 mg, 1.5 mmol), and the mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated, and to the residue were added ether (2 mL) and 20% H_2SO_4 (1.5 mL). After being stirred at room temperature for 5 h, the mixture was neutralized with $NaHCO_3$(s) and extracted three times with $CHCl_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was chromatographed on silica gel (25% ethyl acetate/hexane) to give (3S)-3-[N-(p-methoxybenzyl)amino]-4-phenylbutyronitrile (74 mg, 86% yield) as a colorless oil: ^{1}H NMR δ 7.35–7.15 (m, 7 H), 6.86–6.83 (m, 2 H), 3.8 (d, coupling constant obscured by overlap with singlet, 1 H), 3.80 (s, 3 H), 3.72 (d, J = 13.2 Hz, 1 H), 3.16–3.08 (m, 1 H), 2.93 (dd, J = 6.7, 13.6 Hz, 1 H), 2.83 (dd, J = 7.2, 13.7 Hz, 1 H), 2.48 (dd, J = 5.6, 16.8 Hz, 1 H), 2.35 (dd, J = 4.7, 16.8 Hz, 1 H), 1.55 (bs, 1 H); ^{13}C NMR δ 159.0, 137.4, 131.7, 129.3, 129.26, 128.9, 127.0, 118.1, 114.0, 55.1, 54.6, 50.4, 40.2, 22.2; MS, exact mass calcd for $C_{18}H_{21}N_2O$ (MH^+) 281.1655, found 281.1642.

Registry No. 1, 59490-36-7; 2, 91373-74-9; 3, 132207-10-4; 4, 132207-11-5; 5, 132207-12-6; 6 (isomer 1), 132207-13-7; 6 (isomer 2), 132295-79-5; 7, 132233-11-5; $NaIO_4$, 7790-28-5; $Na(N_3)$, 26628-22-8; Na(CN), 143-33-9; L-phenylalanine methyl ester hydrochloride, 7524-50-7; p-anisoyl chloride, 100-07-2; thionyl chloride, 7719-09-7; ruthenium(III) chloride hydrate, 13815-94-6; tetrabutylammonium fluoride, 429-41-4.

Supplementary Material Available: ^{13}C NMR spectra for compounds 1–7 (7 pages). Ordering information is given on any current masthead page.

An Unusual Stereoelectronic Reversal of Reactivities in 2,2,4,4-Tetramethylcyclobutanedione Derivatives[1]

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In the course of our studies into the preparation and reactions of extremely sterically hindered molecules in the

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