JOC*Note*

Selective Oxidation of Polyfunctional 2-Amino-1,3-propanediol Derivatives

Zixing Shan* and Guojian Lu

Department of Chemistry, Wuhan University, Wuhan 430072, China

kenshan@public.wh.hb.cn

Received January 2, 2004

Abstract: Oxidation of polyfunctional *threo*-(1*S*,2*S*)-2-amino-1,3-propanediol derivatives with a 717 anion-exchange resin-supported bromine has been investigated. The result showed that oxidized products were in close relationship with the substituents at nitrogen in the starting materials. Its primary and secondary amine derivatives were oxidized in the presence of Na_2HPO_4 to give essentially a substituted chiral oxazoline or C(3)−O acylated product in high yield, while oxidation of its *N*,*N*-dimethyl derivative mainly gave a chiral *N*-methyl oxidation−formylation product. This selective oxidation was first observed in 2-amino-1,3-propanediol chemistry.

2-Amino-1,3-propanediol derivatives can be widely modified at a molecular level and have rich reaction chemistry owing to their polyfunctional group structures. *threo*-(1*S*,2*S*)-2-Amino-1-(4′-nitrophenyl)-1,3-propanediol [*threo*-(1*S*,2*S*)-**ANP**], as a "chiral waste" in the production of chloromycetin, is one of the least expensive artificial chiral materials available. Investigation on the modification of *threo*-(1*S*,2*S*)-**ANP** and its derivatives is of practical significance for developing new kinds of inexpensive chiral materials. It was previously reported that *threo*-(1*S*,2*S*)-**ANP** could condense with carbonyl compounds under different conditions to give Schiff bases, 1,2-, 1,3-, or 2,3-cyclocondensation products,[1] respectively. Recently, we reported boration reaction[2] and a highly chemoselective 1,2-cyclocondensation[3] for *threo*-(1*S*,2*S*)-**ANP** and successfully applied the condensate of *threo*-(1*S*,2*S*)-**ANP** with 1,2-cyclohexanone, i.e., *trans*-(2*S*,3*S*)-3-(hydroxymethyl)-2-(4′-nitrophenyl)-1,4-oxoazospiro[4.5]-decane [*trans*-(2*S*,3*S*)-**HNOAD**], to the preparations of a nonsteroidal antiinflammatory chiral drug (*S*)-ibuprofen[4] and versatile chiral auxiliaries enantiopure 1,1′-bi-2-naphthols.[5] In the present note, we report our new discovery for selective oxidation of *threo*-(1*S*,2*S*)-**ANP** and its derivatives.

There have been some investigations for oxidation of *threo*-(1*S*,2*S*)-**ANP** and its derivatives. It was reported that *threo*-(1*S*,2*S*)-2-acetamino-1-(4′-nitrophenyl)-1,3-propanediol [*threo*-(1*S*,2S)-**AANP**] was oxidized by $KMnO_4$ (H_2SO_4)[6] and $KBrO_3$ (H_2SO_4)[7] to produce 2-acetamido-3-acetooxy-1-(4′-nitrophenyl)acetone and 2-acetamido-3-hydroxyl-1-(4′-nitrophenyl)acetone, respectively, in high yield. However, it was oxidized by NaOCl in HOAc to give *threo*-(1*S*,2*S*)-2-(*N*-chloro-*N*-acetamido)-1-(4′-nitrophenyl)-1,3-propanediol.[8] It was also reported that *threo*-(1*S*,2*S*)-**ANP** was oxidized by $Na_2H_3IO_6$ (H_2SO_4) to furnish 4-nitrobenzaldehyde in 96% yield.[9] To our knowledge, oxidation of *threo*-(1*S*,2*S*)-**ANP** and its derivatives with a polymer-supported oxidizing agent has not been reported.

It was reported that a 717 anion-exchange resin-supported bromine oxidized ketones to give brominated products, and oxidized primary alcohols, simple ethers, α,ω-diols, and cyclic ethers to give esters and inner esters, respectively.[10] We recently examined oxidation of *threo*-(1*S*,2*S*)-**ANP** and its derivatives, such as *trans*-(2*S*,3*S*)-**HNOAD**, *threo*-(1*S*,2S)-**AANP**, and *threo*-(1*S*,2*S*)-2-(dimethylamino)-1-(4′-nitrophenyl)-1,3-propanediol [*threo*-(1*S*,2*S*)-**DMANP**] (Figure 1) with this solid-supported bromine, and observed that oxidized products were in close relationship with the substituents at nitrogen in the starting materials. When *threo*-(1*S*,2*S*)-**ANP** was oxidized by the solid-supported bromine in an aqueous Na_2HPO_4 solution at 60 °C, a part of the C(1)−C(2) bond underwent cleavage and 4-nitrobenzoic acid formed. 4-Nitrobenzoic acid thus was generated cyclocondensed with unchanged *threo*-(1*S*,2*S*)-**ANP** in the reaction system to furnish (4*S*,5*S*)-2,5-bis(4′-nitrophenyl)-4-hydroxymethyloxazoline [(4*S*,5*S*)-**BNHOA**] in up to 81% yield. However, the yield of (4*S*,5*S*)-**BNHOA** was only 44% if oxidation was carried out in a mixed system of CCl_4 and H_2O. Oxidation of *trans*-(2*S*,3*S*)-**HNOAD** under similar conditions gave complicated products, and (4*S*,5*S*)-**BNHOA** (more than 30% yield) and t*hreo*-(1*S*,2*S*)-1-(4′-nitrophenyl)-2-(4″-nitrobenzoylamino)-1,3-propanediol [*threo*-(1*S*,2*S*)-**NNP**, 13% yield] were separated from the solid stained on the resin. This fact implied that *trans*-(2*S*,3*S*)-**HNOAD** underwent initially both oxidation−1,2-cleavage and hydrolysis, and then 1,2-cyclocondensation and acylation occurred between 4-nitrobenzoic acid and *threo*-(1*S*,2*S*)-**ANP** generated in situ. Oxidation of *threo*-(1*S*,2*S*)-**AANP** was also similar to that of *threo*-(1*S*,2*S*)-**ANP**. Namely, 4-nitrobenzoic acid formed from the 1,2-cleavage was esterified in situ by unchanged *threo*-

(1) (a) Werner, W.; Tresselt, D.; Ihn, W. *J. Prakt. Chem.* **1987**, *329*, 1031. (b) Potapov, V. M.; Dem'yanovich, V. M.; Zaitsev, V. P.; Sharipova, S. Kh. *Zh. Org. Khim.* **1990**, *26* (12), 2574. (c) Darabantu, M.; Ple, G.; Mager, S.; Puscas, C.; Cotora, E. *Tetrahedron* **1997**, *53* (5), 1909. (d) Darabantu, M.; Ple, G.; Mager, S.; Cotora, E.; Gaina, L.; Costas, L.; Mates, A. *Tetrahedron* **1997**, *53* (5), 1873. (e) Darabantu M.; Mager S.; Puscas C.; Bogdan, M.; Cotora, E.; Kovacs, D. *Rev. Roum. Chem.* **1995**, *40*, 453.

(2) Shan, Z. X.; Chen, J. G.; Yang, X.; Zhao, D. J. *Huaxue Shiji* **1998**, *20* (3), 163 (in Chinese).

(3) (a) Shan, Z. X.; Wan, B. Y.; Wang, G. P. *Zhongguo Faming Zhuanli* CN 001 14346.8 2000. (b) Shan, Z. X.; Wan, B. Y.; Wang, G. P. *Helv. Chim. Acta* **2002**, *85* (4), 1062.

(4) Shan, Z. X.; Wan, B. Y. *Zhongguo Faming Zhuanli* CN 011 06592.3, 2001.

(5) Liu, D. J.; Shan, Z. X.; Liu, F.; Xiao, C. G.; Lu, G. J.; Qin, J. G. *Helv. Chim. Acta* **2003**, *86* (1), 157.

(6) Detrusilvin, T.; Valentin, M.; Ioan, B. T.; Elena, H. Romanian patent, RO 77178, 1979.

(7) Zhang, G. Z.; Li, Y. Z.; Ding, S. M. *Zhongguo Yiyao Gongye Zazhi* **1994**, *25* (1), 34.

(8) Zhestrov, V. P.; Voronin, V. G.; Portnov, Yu. N. *Khim.-Farm Zh.* **1983**, *17* (9), 1090.

(9) Ohle, H.; Hansel, W. East German patent 14237, 1957.

(10) (a) Cacchi, S.; Caglioti, L.; Cernn, E. *Synthesis* **1979**, 64. (b) Borginni, A.; Cainelli, G.; Contento, M. *Synthesis* **1980**, 143. (c) Yang, G. C.; Chen, Z. X.; Zhang, S. L.; Chen, J. W. *Lizi Jiaohuan Yu Xifu* **1998**, *14* (6), 475 (in Chinese).

10.1021/jo049973y CCC: $27.50
Published on Web 04/20/2004

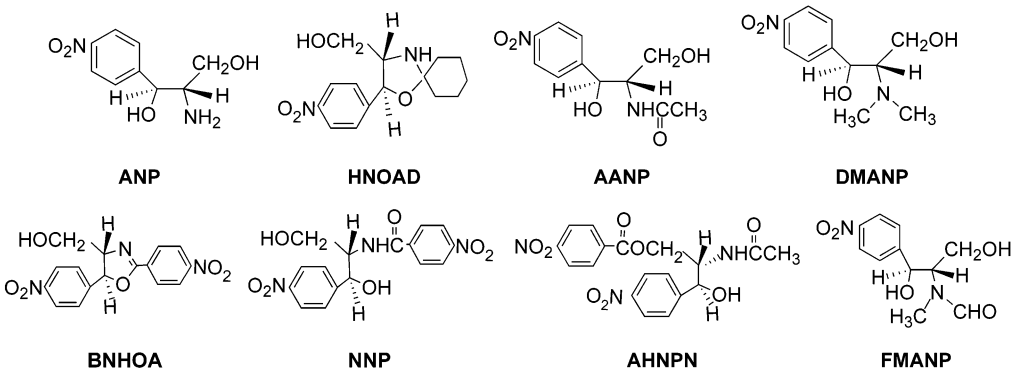

FIGURE 1. Oxidation products (bottom) of *threo*-(1*S*,2*S*)-**ANP** and its derivatives (top) by 717 anionic-exchange resin-supported bromine.

(1*S*,2*S*)-**AANP** in the reaction system to give (2*S*,3*S*)-2-acetamino-3-hydroxy-3-(4′-nitrophenyl)propyl 4-nitrobenzoate [*threo*-(2*S*,3*S*)-**AHNPN**] in 78% yield. However, in contrast to *threo*-(1*S*,2*S*)-**ANP** and its secondary amine derivatives, tertiary amine derivative *threo*-(1*S*,2*S*)-**DMANP** essentially underwent a selective monomethyl oxidation−formylation of the 2-(*N*,*N*-dimethylamino) group and formed *threo*-(1*S*,2*S*)-2-(*N*-formyl-*N*-methylamino)-1-(4′-nitrophenyl)-1,3-propanediol [*threo*-(1*S*,2*S*)-**FMANP**] in 51% yield. This controllable, highly chemoselective oxidation−1,2-cleavage and *N*-methyl oxidation−formylation was first observed in 2-amino-1,3-propanediol chemistry. It suggested that a 717 anion-exchange resin-supported bromine was a mild, selective oxidizing agent under the experimental conditions for polyfunctional 2-amino-1,3-propanediol derivatives.

In conclusion, novel selective oxidation of polyfunctional 2-amino-1,3-propanediol derivatives with a 717 anion-exchange resin-supported bromine has been observed. Oxidized products were mainly influenced by the substituents at nitrogen in the starting materials. *threo*-(1*S*,2*S*)-2-Amino-1-(4′-nitrophenyl)-1,3-propanediol and its secondary amine derivatives were oxidized by the solid-supporting oxidizing agent in an aqueous Na_2HPO_4 solution at 60 °C for 24 h to give mainly a chiral oxazoline and C(3)−O acylated product, respectively, while oxidation of its 2-dimethylamino derivative, under similar conditions, gave an *N*-methyl oxidation−formylation product.

Experimental Section

In a 100-mL round-bottom flask 2.12 g of *threo*-(1*S*,2*S*)-ANP (10 mmol), 15 g of 717 anion-exchange resin-supported bromine (1.4 mmol equivalent/g), 10.7 g of Na_2HPO_4 (75.3 mmol), and 30 mL of H_2O were charged and reacted with stirring for 12 h at 60 °C, and then an equal amount of Na_2HPO_4 was added and the reaction was continued with stirring for an additional 12 h at the same temperature. The reaction mixture was cooled to ambient temperature and the pH of the system was readjusted to 8−9 with Na_2HPO_4, the solution was filtered, and the solid was washed with MeOH and extracted with hot THF (40 mL) until the white solid on the resin dissolved completely. The THF solution was cooled to give 0.6 g of white needle crystals of *trans*-(4*S*,5*S*)-**BNHOA**; the mother liquor was concentrated, and an additional crop of 0.8 g was obtained: overall yield, 81%; mp 249−251 °C; $[\alpha]^{20}_D$ +216 (*c*, 2.028, THF); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.35 (d, J = 8.7 Hz, 2 H), 8.26 (d, J = 8.7, 2 H), 8.20 (d, J = 8.7 Hz, 2 H), 7.65 (d, J = 7.5 Hz, 2 H), 5.81 (d, 1 H), 5.20 (t, 1 H, disappeared after adding D_2O), 4.20 (m, 1 H), 3.80 (m, 1 H), 3.65 (m, 1 H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 161.4, 150.0, 149.0, 147.9, 133.3, 130.2, 127.2, 124.7, 124.6, 82.7, 77.9, 63.3; IR (KBr, cm^{-1}) ν 3287 m, 1650 s, 1600 s, 1516 s, 1493 m, 1347 s, 1316 s, 1093 s, 850 s; MS (FAB, m/z) 344 (M^+ + 1, 10, $C_{16}H_{13}N_3O_6$ requires 343), 289 (12). Anal. Calcd for $C_{16}H_{13}N_3O_6$: C 55.97, H 3.82, N 12.24. Found: C 55.64, H 3.66, N 12.15.

Under similar conditions, *trans*-(2*S*,3*S*)-**HNOAD**, *threo*-(1*S*,2*S*)-**AANP**, and *threo*-(1*S*,2*S*)-**DMANP** were oxidized to give *trans*-(4*S*,5*S*)-**BNHOA** and *threo*-(1*S*,2*S*)-**NNP**, *threo*-(2*S*,3*S*)-**AHNPN**, and t*hreo*-(1*S*,2*S*)-**FMANP**, respectively. The data are as follows:

***threo*-(1*S*,2*S*)-NNP:** yellowish brown, mp 202−204 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.35 (d, J = 8.7 Hz, 1 H), 8.23 (d, J = 9.0 Hz, 2H), 8.12 (d, J = 8.4 Hz, 2 H), 7.92 (d, J = 8.4 Hz, 2 H), 7.60 (d, J = 8.7 Hz, 2 H), 5.87 (d, J = 4.8 Hz, 1H; disappeared after adding D_2O), 5.07 (d, J = 3.0 Hz, 1 H), 4.88 (t, J = 5.4 Hz, 1 H; disappeared after adding D_2O), 4.27 (m, 1 H), 3.70 (m, 1 H), 3.42 (m, 1 H); IR(KBr, cm^{-1}) ν 3317 s, 1638 s, 1599 s, 1555 m, 1529 s, 1354 s, 856 m. Anal. Calcd for $C_{16}H_{15}N_3O_7$: C 54.70, H 4.30, N 11.96. Found: C 54.54, H 4.25, N 11.87.

***threo*-(2*S*,3*S*)-AHNPN:** needle crystal (in MeOH); mp 190−192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.30 (d, J = 8.7 Hz, 2 H), 8.18−8.10 (m, 4 H), 7.93 (d, J = 7.8 Hz, 1 H), 7.62 (d, J = 8.7 Hz, 2 H), 6.06 (d, J = 5.4 Hz, 1 H; disappeared after adding D_2O), 5.03 (d, J = 7.8 Hz, 1 H), 4.45 (m, 2 H), 4.25 (m, 1 H), 1.71 (s, 3 H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 170.1, 164.8, 151.4, 151.0, 147.3, 135.7, 131.4, 128.2, 124.5, 123.5, 70.9, 65.6, 53.2, 23.0; IR (KBr, cm^{-1}) ν 3405 s, 3296 m br, 1732 s, 1645 s, 1604 s, 1521 vs, 1348 s, 1278 vs. Anal. Cacld for $C_{18}H_{17}N_3O_8$: C 53.60, H 4.25, N 10.42. Found: C 53.38, H 4.01, N 10.35.

***threo*-(1*S*,2*S*)-FMANP:** mp 190−192 °C, $[\alpha]^{20}_D$ +0.593 (*c* 0.447, CH_3OH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.15 (d, J = 8.1 Hz, 2 H), 7.67 (s, 1 H), 7.58 (d, J = 8.7 Hz, 2 H), 5.81 (d, J = 4.2 Hz, 1 H; disappeared after adding D_2O), 4.88 (d, J = 5.2 Hz, 1 H), 4.73 (t, J = 5.1 Hz, 1 H; disappeared after adding D_2O), 3.65−3.54 (m. 2 H), 3.50−3.20 (m, 1 H), 2.73 (s, 3 H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 164.4, 151.8, 147.4, 128.3, 123.9, 123.7, 71.0, 70.9, 65.8, 58.9, 32.7, 27.3; IR (KBr, cm^{-1}) ν 3382 s, 1665 s, 1600 w, 1522 s, 1351 s, 1070 s, 1010 m, 835 s. Anal. Calcd for $C_{11}H_{14}N_2O_5$: C 51.96, H 5.55, N 11.02. Found: C 51.62, H 5.47, N 10.93.

Acknowledgment. We thank the National Natural Science Foundation of China (29972033 and 20372053) for financial support.

Supporting Information Available: IR, ^{1}H NMR, and ^{13}C NMR spectra of *trans*-(4*S*,5*S*)-**BNHOA**, *threo*-(1*S*,2*S*)-**NNP**, *threo*-(2*S*,3*S*)-**AHNPN**, and t*hreo*-(1*S*,2*S*)-**FMANP**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049973Y