  Bull. Chem. Soc. Jpn., 60, 2963—2965 (1987)

Synthesis of Opically Active 3-Morpholinecarboxylic Acid and Tetrahydro-2*H*-1,4-thiazine-3-carboxylic Acid

Yuji KOGAMI† and Kenji OKAWA*
Department of Chemistry, Faculty of Science, Kwansei Gakuin University, Nishinomiya 662
(Received March 31, 1987)

A convenient synthesis of optically active 3-morpholinecarboxylic acid and its thio analogue, tetrahydro-2*H*-1,4-thiazine-3-carboxylic acid, has been developed. These intermediates were obtained by reaction of benzyl (*S*)-*N*-benzyloxycarbonyl-2-aziridinecarboxylate and its enantiomer with 2-chloroethanol or 2-chloroethanethiol, respectively.

Many *N*-substituted morpholine analogues have been synthesized and widely used for medical purposes, however, only a few papers have been published on the synthesis of 3-morpholinecarboxylic acid (**3**) and its derivatives. In 1981, racemic *N*-acetyl-3-morpholinecarboxylic acid derivatives were first synthesized by Callens from *N*-acetylmorpholine,[1] but the yield was poor. The thio analogue, tetrahydro-2*H*-1,4-thiazine-3-carboxylic acid (**6**) had been already synthesized in 1964 by Wong as an optically active product from L-cysteine in good yield.[2] However, synthesis of the D-form of **6** remained a problem because optically pure D-cysteine is difficult to obtain.

We report here convenient syntheses of opically active **3** and **6** from benzyl (*S*)-*N*-benzyloxycarbonyl-2-aziridinecarboxylate (L-Z-Azy-OBzl) and its enantiomer (D-Z-Azy-OBzl).

Since several trials to synthesize *O*-(2-chloroethyl)-serine (**2**) from the serine derivative by several methods were unsuccessful, therefore we used Z-Azy-OBzl as the starting material. The synthetic routes via the ring-opening reaction of the aziridine derivatives[3,4] are shown in Scheme 1.

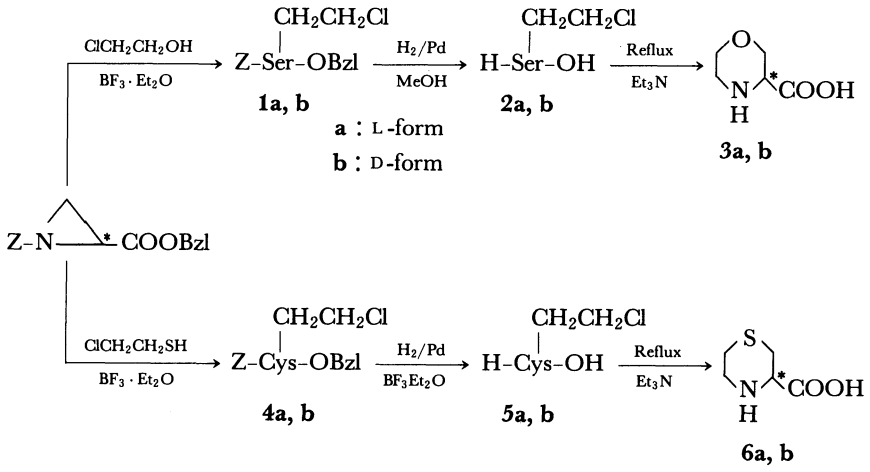
The reaction was carried out between Z-Azy-OBzl (3.0 mmol) and 2-chloroethanol (2 ml) in chloroform containing a catalytic amount of boron trifluoride etherate at room temperature. The expected ring-opening reaction easily occurred, and the intermediate, *N*-benzyloxycarbonyl-*O*-(2-chloroethyl)serine benzyl ester (**1**), of **3** was obtained. The benzyloxycarbonyl and benzyl ester groups were removed by catalytic hydrogenation, followed by cyclization (1.0 mmol in 15 mL of methanol at 64 °C for 7 h) in the presence of triethylamine (0.28 mL) to give **3**. The total yields of **3a** and **3b** from Z-Azy-OBzl were 65.9% and 63.9%, respectively.[5]

The synthesis of **6** is as follows. Z-Azy-OBzl (6.0 mmol) was treated with dichloromethane solution of 2-chloroethanethiol (4.2 g), prepared from thiirane with hydrogen chloride[6] to give **4**. Deprotection was carried out by use of catalytic hydrogenation (H_2/Pd) in the presence of boron trifluoride etherate to give **5** in good yield. This was treated in the same manner as above to give **6**. The total yields of **6a** and **6b** from Z-Azy-OBzl were 27.4 and 9.8%, respectively.

The physical properties of the synthetic products are summarized in Table 1.

Experimental

The melting points are uncorrected. Optical rotations were determined at the D line on a Perkin-Elmer 141 polarimeter. The NMR spectra were obtained with a Hitachi R-20B high-resolution NMR spectrometer, the chemical shifts being obtained using TMS as the internal reference.



Scheme 1. Synthetic routes of **3a, b** and **6a, b.**

†Present address: Research Center, Toyo jozo Co., Ltd., Ohito, Shizuoka 410-23.

Table 1. Physical Properties of 3-Morpholinecarboxylic Acid (**3a, b**) and Tetrahydro-2*H*-1,4-thiazine-3-carboxylic Acid (**6a, b**)

Characteristic	3a	3b	6a	6b
Melting point θ_m/°C	218(decomp)	216—218(decomp)	251(decomp)	250—251(decomp)
Optical rotation[a] $[\alpha]_D^{25}$/°	−14.4	+13.8	−51.7	+52.0
Solubility (g mL^{-1})[b]	1.26	—	—	—

a) **3a, b**: c 2.0, 1 M $HCl_{aq.}$, **6a, b**: c 2.0, H_2O. b) Solubility in water at 25 °C; Pro 1.63 g mL^{-1}.

The homogeneity of the products was checked by thin-layer chromatogrphy on silica-gel plates.

L-Z-Ser(OCH_2CH_2Cl)-OBzl (1a). L-Z-Azy-OBzl (0.93 g, 3.0 mmol) was dissolved in $CHCl_3$ (10 mL) and $HOCH_2CH_2Cl$ (2 mL), then $BF_3 \cdot OEt_2$ (2 drops) was added at room temperature. The reaction mixture were stirred for 4 h, then washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to silica-gel column chromatography with elution with ethyl acetate-hexane (1 : 3 v/v). The eluent was concentrated in vacuo and 1.04 g (88.0%) of **1a** was obtained as colorless needles. mp 52.0—52.5 °C, $[\alpha]_D^{25}$ +13.4° (*c* 1.0, MeOH). ^1H NMR ($CDCl_3$): δ=3.52 (4H, m), 3.80 (2H, m, $-CH_2-Cl$), 4.41 (1H, α-proton), 5.08, 5.18 (4H, 2s), 7.26 (10H, s). Found: C, 61.15; H, 5.63; N, 3.60%. Calcd for $C_{20}H_{22}O_5NCl$: C, 61.30; H, 5.66; N, 3.58%.

D-Z-Ser(OCH_2CH_2Cl)-OBzl (1b). D-Z-Azy-OBzl (0.93 g, 3.0 mmol) was dissolved in $CHCl_3$ (10 mL) and $HOCH_2CH_2Cl$ (2 mL), then $BF_3 \cdot OEt_2$ (2 drops) was added at room temperature. The reaction mixture was worked up as described above to give **1b**.

L-H-Ser(OCH_2CH_2Cl)-OH (2a). The solution of **1a** (0.78 g, 2.0 mmol) in methanol (10 mL) was hydrogenated over Pd black. After 30 min, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was crystallized from methanol, 258 mg (77.0%), mp 136.0—137.0 °C, $[\alpha]_D^{25}$ +11.0° (*c* 2.0, 1 M HCl (1 M=1 mol dm^{-3})). Found: C, 35.78; H, 6.04; N, 8.49%. Calcd for $C_5H_{10}O_3NCl$: C, 35.79; H, 6.02; N, 8.36%.

D-H-Ser(OCH_2CH_2Cl)-OH (2b). The solution of **1b** (0.78 g, 2.0 mmol) in methanol was worked up as described above to give **2a**.

L-3-Morpholinecarboxylic Acid (3a). To the solution of **2a** (168 mg, 1.00 mmol) in methanol (15 mL) was added Et_3N (0.28 mL, 2.0 mmol) at room temperature. The reaction mixture was refluxed for 7 h at 64 °C, and concentrated in vacuo. Chloroform was added to the residue and an insoluble material was filtered and recrystallized from water and methanol to give **3a**, 128 mg (97.3%), mp 218 °C (decomp), $[\alpha]_D^{25}$ −14.4° (*c* 2.0, 1 M HCl). NMR (D_2O) δ=3.00 (2H, m, $C-CH_2-N$), 3.50, 3.55 (4H, m, $-CH_2-O-CH_2-$), 3.88 (1H, dd, α-proton). Found: C, 45.42; H, 6.94; N, 10.66%. Calcd for $C_5H_9O_3N$: C, 45.79; H, 6.92; N, 10.70%.

D-3-Morpholinecarboxylic Acid (3b). The reaction mixture in methanol was worked up as described above to give **3b**, mp 216.0—218.0 °C (decomp), $[\alpha]_D^{25}$ +13.8° (*c* 1.0, 1 M HCl). Found: C, 45.78; H, 6.91; N, 10.46%. Calcd for $C_5H_9O_3N$: C, 45.79; H, 6.92; N, 10.70%.

L-Z-Cys(SCH_2CH_2Cl)-OBzl (4a). L-Z-Azy-OBzl (1.86 g, 6.0 mmol) was dissolved in CH_2Cl_2 (20 mL) and $HSCH_2CH_2Cl$ (4.2 g, 43.5 mmol), then $BF_3 \cdot OEt_2$ (5 drops) was added at room temperature. The reaction mixture was stirred for 24 h, then washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography with elution by ethyl acetate-hexane (1 : 3 v/v). The effluent was concentrated in vacuo and 1.89 g (77.0%) of **4a** was obtained as colorless needles. mp 69.5—70.0 °C, $[\alpha]_D^{25}$ −14.3° (*c* 1.0, MeOH). ^1H NMR ($CDCl_3$): δ=2.75 (2H, t, $-S-CH_2-$), 3.01 (2H, d, β-protons), 3.50 (2H, t, $-CH_2-Cl$), 4.63 (1H, br, α-proton), 5.10, 5.17 (4H, 2s), 7.33 (10H, s). Found: C, 58.75; H, 5.38; N, 3.29%. Calcd for $C_{20}H_{22}O_4NSCl$: C, 58.89; H, 5.44; N, 3.43%.

D-Z-Cys(SCH_2CH_2Cl)-OBzl (4b). D-Z-Azy-OBzl (0.93 g, 3.0 mmol) was dissolved in CH_2Cl_2 (10 mL) and pure $HSCH_2CH_2Cl$ (2.1 g, 21.7 mmol), then $BF_3 \cdot OEt_2$ (3 drops) were added at room temperature. The reaction mixture was worked up as described above to give **4b**.

L-H-Cys(SCH_2CH_2Cl)-OH (5a). To the solution of **4a** (410 mg, 1.0 mmol) in abs MeOH were added $BF_3 \cdot OEt_2$ (0.37 mL, 3.0 mmol) and 11.8 M HCl/EtOH (0.16 mL, 2.0 mmol). The mixture solution was hydrogenated over Pd black for 1 h, and filtered. The filtrate was neutralized with Et_3N and concentrated in vacuo. The solid residue was washed with $CHCl_3$ and gave **5a**, 161 mg (88.0%), mp 156.5—157.0 °C, $[\alpha]_D^{25}$ −2.0° (*c* 1.0, 1 M HCl). Found: C, 32.54; H, 5.49; N, 7.54%. Calcd for $C_5H_{10}O_2NSCl$: C, 32.69; H, 5.47; N, 7.56%.

D-H-Cys(SCH_2CH_2Cl)-OH (5b). To the solution of **4b** (410 mg, 1.0 mmol) in abs MeOH (10 mL) were added $BF_3 \cdot OEt_2$ (0.37 mL, 3.0 mmol) and 11.8 M HCl/EtOH (0.16 mL, 2.0 mmol). The mixture solution was worked up as described above to give **5b**.

L-Tetrahydro-2*H*-1,4-thiazine-3-carboxylic Acid (6a). To the solution of **5a** (91.8 mg, 0.5 mmol) in DMF (5 mL) was added Et_3N (0.14 mL, 1.0 mmol) at room temperature. The reaction mixture was refluxed for 2 h at 94 °C and concentrated in vacuo. Chloroform was added to the residue and an insoluble material was filtered and recrystallized from water and methanol to give **6a**, 57.5 mg (78.0%), mp 250.0—251.0 °C, (decomp), $[\alpha]_D^{25}$ −51.7° (*c* 1.0, H_2O) [lit,[7] $[\alpha]_D^{13}$ −52.94° (*c* 2.0, H_2O)]. Found: C, 40.49; H, 6.38; N, 9.37%. Calcd for $C_5H_9O_2NS$: C, 40.79; H, 6.17; N, 9.52%.

D-Tetrahydro-2*H*-1,4-thiazine-3-carboxylic Acid (6b). The reaction mixture in DMF was worked up as described above to give **6b**, mp 248.0—249.0 °C (decomp), $[\alpha]_D^{25}$ +50.6° (*c* 1.0, H_2O). Found: C, 40.46; H, 6.17; N, 9.41%. Calcd for $C_5H_9O_2NS$: C, 40.52; H, 6.12; N, 9.45%.

The authors wish to thank the staff of the research laboratory of Toyo Jozo Co. for the elemental analyses, and Messrs. Tatsuya Inui, Yoshiya Matsuoka, and Shuichi Inaya for their kind assistance. This work was partially supported by a Grant-in-Aid for Scientific Research (No. 59340-034) from the Ministry of Education, Science and Culture.

References

1) V. Asner, C. Becu, M. J. O. Anteunis, and R. Callens, Tetrahedron Lett., **22**, 141 (1981).

2) J. F. Carson and F. F. Wong, *J. Org. Chem.*, **29**, 2203 (1964).

3) K. Nakajima, M. Neya, S. Yamada, and K. Okawa, *Bull. Chem. Soc. Jpn.*, **55**, 3049 (1982).

4) K. Nakajima, H. Oda, and K. Okawa, *Bull. Chem. Soc. Jpn.*, **56**, 520 (1983).

5) Y. Kogami and K. Okawa, "Peptide Chemistry 1985," Protein Research Foundation, Osaka (1986), p 153.

6) E. M. Meade, and F. N. Woodward, *J. Chem. Soc.*, **1948**, 1894.

7) M. Kuriyama, M. Takagi, and K. Murata, *Bull. Fac. Fish., Hokkaido Univ.*, **11**, 58 (1960).