

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

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A convenient synthesis of optically active 3-morpholinecarboxylic acid and its thio analogue, tetrahydro-2H-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-2H-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 optically 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-

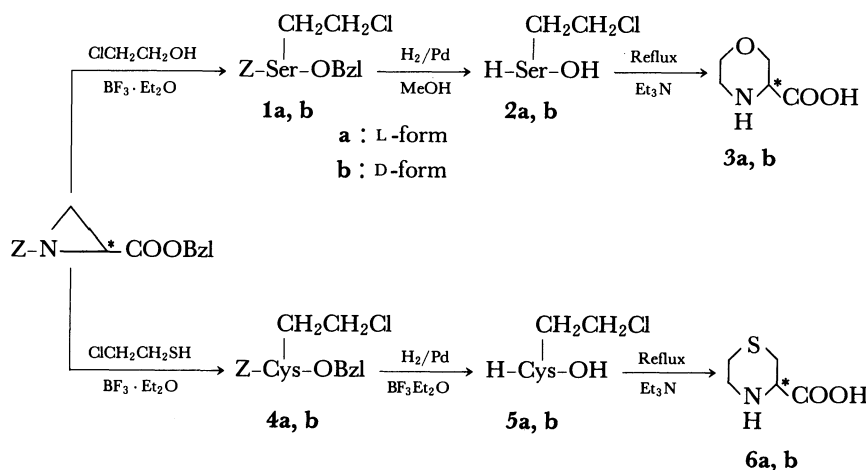
opening reaction easily occurred, and the intermediate, *N*-benzyloxycarbonyl-*O*-(2-chloroethyl)serine benzyl ester (**1**), of **3** was obtained. The benzyloxycarbonyl and benzyl ester groups were removed by catalytic hydrogenation, followed by cyclization (1.0 mmol in 15 mL of methanol at 64 °C for 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 chloride⁶⁾ to give **4**. Deprotection was carried out by use of catalytic hydrogenation (H₂/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**.

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

Characteristic	3a	3b	6a	6b
Melting point $\theta_m/^\circ\text{C}$	218(decomp)	216—218(decomp)	251(decomp)	250—251(decomp)
Optical rotation ^{a)} $[\alpha]_D^{25}/^\circ$	-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, H₂O. b) Solubility in water at 25°C; Pro 1.63 g mL⁻¹.

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

L-Z-Ser(OCH₂CH₂Cl)-OBzl (1a). L-Z-Azy-OBzl (0.93 g, 3.0 mmol) was dissolved in CHCl₃ (10 mL) and HOCH₂CH₂Cl (2 mL), then BF₃·OEt₂ (2 drops) was added at room temperature. The reaction mixture were stirred for 4 h, then washed with water, dried over Na₂SO₄, 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, $[\alpha]_D^{25} +13.4^\circ$ (c 1.0, MeOH). ¹H NMR (CDCl₃): $\delta=3.52$ (4H, m), 3.80 (2H, m, -CH₂-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 C₂₀H₂₂O₅NCl: C, 61.30; H, 5.66; N, 3.58%.

D-Z-Ser(OCH₂CH₂Cl)-OBzl (1b). D-Z-Azy-OBzl (0.93 g, 3.0 mmol) was dissolved in CHCl₃ (10 mL) and HOCH₂CH₂Cl (2 mL), then BF₃·OEt₂ (2 drops) was added at room temperature. The reaction mixture was worked up as described above to give **1b**.

L-H-Ser(OCH₂CH₂Cl)-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, $[\alpha]_D^{25} +11.0^\circ$ (c 2.0, 1 M HCl (1 M=1 mol dm⁻³)). Found: C, 35.78; H, 6.04; N, 8.49%. Calcd for C₅H₁₀O₃NCl: C, 35.79; H, 6.02; N, 8.36%.

D-H-Ser(OCH₂CH₂Cl)-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 Et₃N (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), $[\alpha]_D^{25} -14.4^\circ$ (c 2.0, 1 M HCl). NMR (D₂O) $\delta=3.00$ (2H, m, C-CH₂-N), 3.50, 3.55 (4H, m, -CH₂-O-CH₂-), 3.88 (1H, dd, α -proton). Found: C, 45.42; H, 6.94; N, 10.66%. Calcd for C₅H₉O₃N: 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), $[\alpha]_D^{25} +13.8^\circ$ (c 1.0, 1 M HCl). Found: C, 45.78; H, 6.91; N, 10.46%. Calcd for C₅H₉O₃N: C, 45.79; H, 6.92; N, 10.70%.

L-Z-Cys(SCH₂CH₂Cl)-OBzl (4a). L-Z-Azy-OBzl (1.86 g, 6.0 mmol) was dissolved in CH₂Cl₂ (20 mL) and HSCH₂CH₂Cl (4.2 g, 43.5 mmol), then BF₃·OEt₂ (5 drops) was added at room temperature. The reaction mixture was

stirred for 24 h, then washed with water, dried over Na₂SO₄, 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, $[\alpha]_D^{25} -14.3^\circ$ (c 1.0, MeOH). ¹H NMR (CDCl₃): $\delta=2.75$ (2H, t, -S-CH₂-), 3.01 (2H, d, β -protons), 3.50 (2H, t, -CH₂-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 C₂₀H₂₂O₄NSCl: C, 58.89; H, 5.44; N, 3.43%.

D-Z-Cys(SCH₂CH₂Cl)-OBzl (4b). D-Z-Azy-OBzl (0.93 g, 3.0 mmol) was dissolved in CH₂Cl₂ (10 mL) and pure HSCH₂CH₂Cl (2.1 g, 21.7 mmol), then BF₃·OEt₂ (3 drops) were added at room temperature. The reaction mixture was worked up as described above to give **4b**.

L-H-Cys(SCH₂CH₂Cl)-OH (5a). To the solution of **4a** (410 mg, 1.0 mmol) in abs MeOH were added BF₃·OEt₂ (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 Et₃N and concentrated in vacuo. The solid residue was washed with CHCl₃ and gave **5a**, 161 mg (88.0%), mp 156.5—157.0°C, $[\alpha]_D^{25} -2.0^\circ$ (c 1.0, 1 M HCl). Found: C, 32.54; H, 5.49; N, 7.54%. Calcd for C₅H₁₀O₂NSCl: C, 32.69; H, 5.47; N, 7.56%.

D-H-Cys(SCH₂CH₂Cl)-OH (5b). To the solution of **4b** (410 mg, 1.0 mmol) in abs MeOH (10 mL) were added BF₃·OEt₂ (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-2H-1,4-thiazine-3-carboxylic Acid (6a). To the solution of **5a** (91.8 mg, 0.5 mmol) in DMF (5 mL) was added Et₃N (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), $[\alpha]_D^{25} -51.7^\circ$ (c 1.0, H₂O) [lit,⁷⁾ $[\alpha]_D^{13} -52.94^\circ$ (c 2.0, H₂O)]. Found: C, 40.49; H, 6.38; N, 9.37%. Calcd for C₅H₉O₂NS: C, 40.79; H, 6.17; N, 9.52%.

D-Tetrahydro-2H-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), $[\alpha]_D^{25} +50.6^\circ$ (c 1.0, H₂O). Found: C, 40.46; H, 6.17; N, 9.41%. Calcd for C₅H₉O₂NS: C, 40.52; H, 6.12; N, 9.45%.

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