# Studies on 2-Aziridinecarboxylic Acid. VI.[1] Synthesis of β-Alkoxy-α-Amino Acids *via* Ring-opening Reaction of Aziridine

Kiichiro NAKAJIMA, Masahiro NEYA, Shinichi YAMADA, and Kenji OKAWA*

*Department of Chemistry, Faculty of Science, Kwansei Gakuin University, Nishinomiya 662*

(Received February 12, 1982)

**Synopsis.** The reaction of aziridine derivatives having a urethane-type protecting group with several alcohols in the presence of boron trifluoride etherate afford the corresponding optically pure *O*-alkylserine and *O*-alkylthreonine derivatives *via* a ring-opening reaction of aziridine in good yield.

In 1976, we reported that *N*-aminoacyl 2-aziridinecarboxylic acid derivatives, *e.g.*, Z-Gly-(2*S*)-Azy-Gly-OBzl, were coverted into the corresponding *O*-alkylserine peptide by the reaction of several alcohols in the presence of boron trifluoride etherate.[2] The yields, however, were usually very poor.

In this communication, we describe the results of aziridine derivatives having a urethane-type protecting group, benzyl (2*S*)-1-benzyloxycarbonyl-2-aziridinecarboxylate[(2*S*)-Z-Azy-OBzl(**1**)] and methyl (2*S*,3*S*)-1-benzyloxycarbonyl-3-methyl-2-aziridinecarboxylate [(2*S*,3*S*)-Z-3-MeAzy-OMe(**2**)], with several alcohols. **1** and **2** were synthesized according to our previous report.[3,4]

(2*S*)-Z-Azy-OBzl(**1**) and (2*S*,3*S*)-Z-3-MeAzy-OMe (**2**) were very stable in alcoholic solution at a room temperature, even under heating and no ring-opening reaction of the aziridine residue with alcohols was observed. However, if a catalytic amount of boron trifluoride etherate was added to the alcoholic solution of the aziridine derivatives, the reaction occurred easily to give the corresponding *O*-alkylserine(**3**—**9**) and -threonine(**10**—**16**) derivatives in good yield as shown in Scheme 1 and Table 1.

The synthesized *O*-alkylserine and threonine derivatives were easily transformed into the corresponding L-*O*-alkyl serine(**17**, **18**, **19**) and L-*O*-alkylthreonine (**20**, **21**, **22**, **23**) by catalytic hydrogenolysis or the combination of catalytic hydrogenolysis and hydrolysis as shown in Scheme 1, giving the titled compounds.

This study showed that the ring-opening reaction of aziridine derivatives having the urethane-type protecting groups is an effective method for synthesizing optically active β-alkoxy-α-amino acids.

## Experimental

The melting points given 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-20 B high resolution spectrometer using TMS as the internal reference.

*(2S)-Z-Azy-OBzl (1).* To a solution of (2*S*)-H-Azy-OBzl[3] (1.2 g, 6.7 mmol) and $Et_3N$ (0.76 ml, 5.4 mmol) in $CHCl_3$ was added benzyloxycarbonyl chloride (0.86 ml, 5.4 mmol) at 0 °C with stirring. After being stirred overnight, it was washed with 10% citric acid, 1 M (1 M=1 mol $dm^{-3}$) $NaHCO_3$, and water, then dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography and 1.61 g (96% from Z–Cl[1]) of **1** was obtained, $[\alpha]_D^{23}$ −18.1° (*c* 1.0, MeOH). NMR ($CDCl_3$) δ: 2.37 (1H q, *J*=1.5, 5 Hz), 3.08 (1H q, *J*=3.0, 5.0 Hz), 5.05, 5.07 (4H 2s), 2.54 (1H q, *J*=1.5, 3.0 Hz), 7.26 (10H s).

Found: C, 69.15; H, 5.53; N, 4.42%. Calcd for $C_{18}H_{17}O_4N$: C, 69.44; H, 5.50; N, 4.50%.

*(2S,3S)-Z-3-MeAzy-OMe (2).* To a solution of (2*S*,3*S*)-H-3-MeAzy-OMe[4] (11.3 g, 78 mmol) and $Et_3N$ (10.9 ml, 78 mmol) in $CHCl_3$ (200 ml) was added 2-benzyloxycarbonyloximino-2-phenylacetonitrile (Z–ON) (19.7 g, 70 mmol) at room temperature with stirring. After the reaction mixture was worked up as described above, 14.8 g (85% from Z–ON) of **2** was isolated as syrup, $[\alpha]_D^{23}$ −66.2° (*c* 1.1, MeOH). NMR ($CDCl_3$) δ: 1.25 (3H d, *J*=6.0 Hz), 2.75 (1H m), 3.20 (1H d, *J*=6.5 Hz), 3.35 (3H s), 5.10 (2H s), 7.28 (5H s).

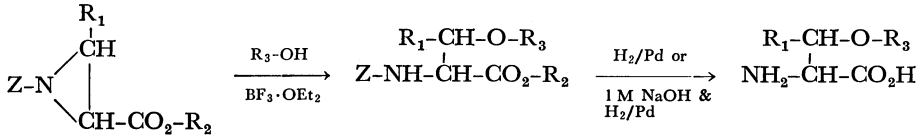
Found: C, 62.34; H, 6.15; N, 5.48%. Calcd for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07; N, 5.62%.

L-*Z-Ser(OMe)-OBzl (3).* *General Method* via *Ring-opening Reaction of Azy*: **1** (0.3 g, 0.96 mmol) was dissolved in $CHCl_3$ (3 ml) and MeOH (5 ml), then $BF_3 \cdot OEt_2$ (3 drops) was added at room temperature. The reaction mixture was left standing for 12 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 by $CHCl_3$. The effluent was concentrated *in vacuo* and 0.21 g (64%) of **3** was obtained. NMR ($CDCl_3$) δ: 3.26 (3H s), 3.69 (2H m, β-proton), 4.52 (1H, α-proton), 5.74 (1H bd).

Found: C, 66.39; H, 6.21; N, 4.16%. Calcd for $C_{19}H_{21}O_5N$: C, 66.46; H, 6.16; N, 4.08%.

L-*Z-Thr(OBu$^t$)-OMe (13).* Via *Ring-opening Reaction of 3-MeAzy*: **2** (0.2 g, 0.8 mmol) was dissolved in $CHCl_3$ (2 ml) and *t*-BuOH (5 ml), then $BF_3 \cdot OEt_2$ (3 drops) was added at room temperature. The reaction mixture was left standing overnight at room temperature and was worked up as described above. 243 mg (94%) of **13** was obtained. NMR ($CDCl_3$) δ: 1.10 (9H s), 1.19 (3H d), 4.15 (1H m, β-proton), 4.25 (1H q, α-proton), 5.50 (1H b).

Found: C, 63.25; H, 7.94; N, 4.21%. Calcd for $C_{17}H_{25}O_5N$: C, 63.14; H, 7.79; N, 4.33%.




**1**: $R_1$=H, $R_2$=Bzl
**2**: $R_1$=Me, $R_2$=Me

**3—9**: $R_1$=H, $R_2$=Bzl
**10—16**: $R_1$=Me, $R_2$=Me

**17—19**: $R_1$=H
**20—23**: $R_1$=Me

Scheme 1.

Table 1. Properties and yields of *O*-alkyl-L-serine, L-threonine, and their derivatives

| No. | Product[c] $R_1$ | $R_2$ | $R_3$ | Yield/% | $[\alpha]_D^{24}$/°(MeOH) | Mp $\theta_m$/°C |
|---|---|---|---|---|---|---|
| **3** | H | Bzl | Me | 64 | −19.1 (*c* 1.4) | syrup |
| **4** | H | Bzl | $Pr^i$ | 95 | −19.5 (*c* 1.1) | syrup |
| **5** | H | Brl | $Bu^s$ | 73 | −17.4 (*c* 0.9) | syrup |
| **6** | H | Bzl | $Bu^t$ | 58 | −20.0 (*c* 1.1) | syrup |
| **7** | H | Bzl | Hex[c] | 57 | −20.1 (*c* 1.1) | 57—58 |
| **8** | H | Bzl | Bzl | 100 | −9.8 (*c* 1.1) | 86—87 |
| **9** | H | Bzl | Ph | 27 | −8.6 (*c* 1.1) | syrup |
| **10** | Me | Me | Me | 98 | −6.4 (*c* 1.1) | syrup |
| **11** | Me | Me | $Pr^i$ | 98 | −10.7 (*c* 1.4) | syrup |
| **12** | Me | Me | $Bu^s$ | 92 | −14.1 (*c* 1.2) | syrup |
| **13** | Me | Me | $Bu^t$ | 94 | −3.1 (*c* 1.1) | syrup |
| **14** | Me | Me | Hex[c] | 92 | −9.1 (*c* 1.1) | syrup |
| **15** | Me | Me | Bzl | 98 | −6.9 (*c* 1.1) | 72.5—73.0 |
| **16** | Me | Me | Ph | 57 | +24.2 (*c* 1.1) | syrup |
| **17** | H | H | $Pr^i$ | 87 | −11.8 (*c* 1.0)[a] | 221 (d.) |
| **18** | H | H | $Bu^t$ | 100 | −14.8 (*c* 1.0)[a] | 209 (d.) |
| **19** | H | H | Hex[c] | 82 | −10.0 (*c* 1.0)[a] | 193 (d.) |
| **20** | Me | H | $Pr^i$ | 86 | −29.8 (*c* 1.1)[b] | 212 (d.) |
| **21** | Me | H | $Bu^s$ | 75 | −28.8 (*c* 1.0)[b] | 198 (d.) |
| **22** | Me | H | $Bu^t$ | 82 | −37.8 (*c* 1.0)[a] | 207 (d.) |
| **23** | Me | H | Hex[c] | 83 | −35.5 (*c* 0.8)[a] | 201 (d·) |

a) Solvent: $H_2O$, b) solvent: 1 M HCl, c) Me: methyl, Bzl: benzyl, $Pr^i$: isopropyl, $Bu^s$: *s*-butyl, $Bu^t$: *t*-butyl, Ph: phenyl, Hex[c]: cyclohexyl.

Via t-*Butylation with Isobutylene of* L-*Z-Thr-OMe*: To a solution of L-Z-Thr-OMe (2.67 g, 10 mmol) and isobutylene (15 ml) in $CH_2Cl_2$ (15 ml) was added conc. $H_2SO_4$ (1 ml). The reaction mixture was left standing at room temperature for 3 d, and then washed with 1 M $NaHCO_3$ and water, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography. 2.42 g (75%) of **13** was obtained, $[\alpha]_D^{24}$ +4.7° (*c* 2.0, DMF).

L-*Z-Ser(OBzl)-OH.* Via *Ring-opening Reaction of Azy*: **1** (0.2 g, 0.64 mmol) was dissolved in $CHCl_3$ (2 ml) and benzyl alcohol (5 ml), then $BF_3 \cdot OEt_2$ (3 drops) was added at room temperarure. The reaction mixture was left standing overnight and then worked up as described above. The obtained **8** (100% yield) was dissolved in MeOH (3 ml) and 2 M NaOH (5 ml) was added with stirring at room temperature for 2 h, then the solution was concentrated *in vacuo*. The residue was dissolved in water and adjusted to pH 2 with 3 M HCl, and the product was extracted with ethyl acetate. The solution was washed with water, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was crystallized from $CCl_4$, 211 mg (100%), mp 99.5—100 °C, $[\alpha]_D^{24}$ +9.4° (*c* 1.3, MeOH). [mp 99—100 °C, $[\alpha]_D^{24}$ +9.5° (*c* 1.1, MeOH), prepared from Z–Cl and L-H-Ser(OBzl)-OH].

Found: 65.38; H, 5.85; N, 4.32%. Calcd for $C_{18}H_{19}O_5N$: C, 65.64; H, 5.81; N, 4.25%.

*O-Isopropyl-*L-*serine (18)*: $H_2$ gas was bubbled through a solution of **4** (218 mg, 0.59 mmol) in MeOH (10 ml) containing Pd black (100 mg) for 2 h. The catalyst removed by filtration and the filtrate was concentrated *in vacuo*. The residue was crystallized from water–acetone, and 75.5 mg (87%) of **18** was obtained.

O-*Isopropyl-*L-*threonine (20)*. **11** (224 mg, 0.72 mmol) was hydrolyzed with 1 M NaOH (2.5 ml) in MeOH (3 ml) at room temperature for 1 h. After L-Z-Thr($OPr^i$) had been isolated by the usual procedure, the benzyloxycarbonyl group was removed by the catalytic hydrogenation described above. The product was crystallized from water-acetone, and 100 mg (85.7%) of **20** was obtained.

## References

1) Part V. K. Okawa, K. Nakajima, T. Tanaka, and M. Neya, *Bull. Chem. Soc. Jpn.*, **55**, 174 (1982). Abbreviations of the IUPAC-IUB commission, *J. Biol. Chem.*, **247**, 977 (1972), are used. Z: benzyloxycarbonyl, OBzl: benzyl ester, OMe: methyl ester, Z–Cl: benzyloxycarbonyl chloride, Z–ON: 2-benzyloxycarbonyloximino-2-phenylacetonitrile. "Azyline" is used as the name of 2-aziridinecarboxylic acid, "Azy" being its abbreviation. 3-MeAzy: (2*S*,3*S*)-3-methyl-2-aziridinecarboxylic acid.

2) K. Okawa, K. Nakajima, T. Tanaka, and T. Maeda, "Peptide Chemistry 1976," ed by T. Nakajima, Protein Research Foundation, Osaka (1977) p. 13.

3) K. Nakajima, F. Takai, T. Tanaka, and K. Okawa, *Bull. Chem. Soc. Jpn.*, **51**, 1577 (1978).

4) K. Okawa and K. Nakajima, *Biopolymers*, **20**, 1811 (1891).