BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 51 (5), 1577—1578 (1978)

Studies on Aziridine-2-carboxylic Acid. I. Synthesis of the Optically Active L-Aziridine-2-carboxylic Acid and Its Derivatives

Kiichiro NAKAJIMA, Fumiko TAKAI, Takumi TANAKA, and Kenji OKAWA
Department of Chemistry, Faculty of Science, Kwansei Gakuin University, Nishinomiya 662

(Received December 9, 1977)

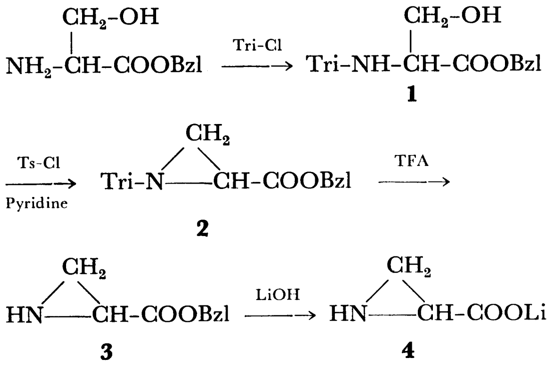
Synopsis. Lithium L-aziridine-2-carboxylate was synthesized from *N*-trityl-L-aziridine-carboxylic acid benzyl ester by the treatment with trifluoroacetic acid followed by the saponification with lithium hydroxide. Several *N*-acylaziridine-2-carboxylic acid esters were synthesized in good yield.

Due to acid labile properties of the aziridine ring, no optically active aziridine-2-carboxylic acid has been synthesized. Only racemic aziridine-2-carboxylic acid has been isolated as a lithium salt in poor yield from methyl 2,3-dibromopropionate by the treatment of liquefied ammonia.[1]

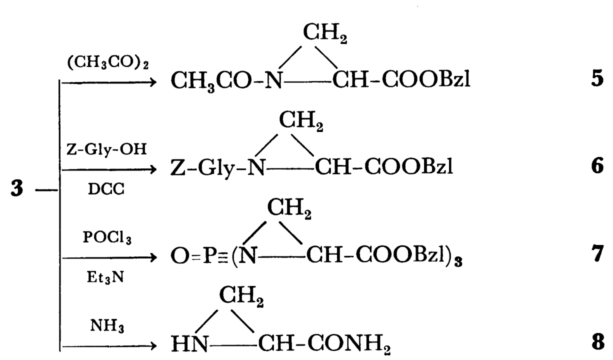
The peptide derivatives of aziridine-2-carboxylic-acid(Azy),[2] however, were prepared *via* *N*-trityl-*O*-tosyl(or *O*-mesyl)*β*-hydroxy amino acid peptides.[3]

We have undertaken to synthesize L-isomer of Azy since it is of great use in the synthesis of Azy containing peptides.

Lithium L-aziridine-2-carboxylate has been prepared from the corresponding *N*-trityl-*O*-tosyl-L-serine benzyl ester as shown in following Scheme 1. The key step of the detritylation procedure was accomplished by the action of trifluoroacetic acid solution at low temperature, several *N*-acyl-L-Azy–OBzl derivatives being synthesized in good yield as shown in Scheme 2.



Scheme 1.



Scheme 2.

Experimental

All the melting points are uncorrected. The IR and NMR spectra were recorded on Hitachi EPI-G3 and Hitachi R-20B spectrometers, respectively. The purity of the synthetic compounds was confirmed by thin layer chromatography on silica gel G.

Tri-L-Ser-OBzl (1): To a solution of L-Ser–OBzl benzenesulfonate (56 g, 0.15 mol) and Et_3N (42 ml, 0.3 mol) in $CHCl_3$ (100 ml) was added a solution of Tri-Cl (41.8 g, 0.15 mol) in $CHCl_3$ (80 ml) with stirring at 0 °C. After the reaction mixture had been stirred for 24 h at 0 °C, the solution was washed with 10% citric acid and water, and dried over Na_2SO_4. After removal of the solvent, **1** was obtained in theoretical yield as an oily product; $[\alpha]_D^{25}$ +64.8° (*c* 1.0, MeOH). Found: C, 79.43; H, 6.32; N, 3.42%. Calcd for $C_{29}H_{27}O_3N$: C, 79.61; H, 6.22; N, 3.20%.

Tri-L-Azy-OBzl (2): To a solution of **1** (65.6 g, 0.15 mol) in dry pyridine (200 ml) was added a solution of Ts-Cl (85.8 g, 0.45 mol) in dry pyridine (50 ml) at −10 °C for 1 h. After the reaction mixture had been stirred for 24 h at 0 °C, the solvent was removed *in vacuo* and the residual oil was partitioned between ethyl acetate and water. The organic layer was washed with 10% citric acid and water, and dried over Na_2SO_4. The ethyl acetate was removed *in vacuo* to give an oily product (84.3 g, 95% yield as a *O*-tosylate). The oil was dissolved in dry THF (100 ml), and Et_3N (39.2 ml, 0.28 mol) was added. After the THF solution had been refluxed at 75 °C for 24 h, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate. The organic layer was washed with 10% citric acid, 1M sodium hydrogencarbonate and water, and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the product was crystallized from ethyl acetate–ether–hexane; yield, 31.4 g (57.8%); mp 114—116 °C; $[\alpha]_D^{20}$ −95.5° (*c* 1.0, THF). IR: 1722, 1590, 1095 cm^{-1}; NMR (CCl_4): δ 2.10, 1.32 (2H 2q, J_{trans}=3.1 Hz, J_{cis}=6.3 Hz, J_{gem}=1.8 Hz, *β*-proton); 1.87 (1H q, J_{trans}=3.1 Hz, J_{cis}=6.3 Hz, *α*-proton). Found: C, 82.90; H, 5.84; N, 3.25%. Calcd for $C_{29}H_{25}O_2N$: C, 83.03; H, 6.01; N, 3.34%.

L-Azy-OBzl (3): To a solution of **2** (5.04 g, 12 mmol) in $CHCl_3$ (10 ml) and absolute MeOH (10 ml, used as a scavenger of trityl group), was added TFA (20 ml) with stirring at −5 °C, and the solution was stirred for 2 h. The solvent was removed *in vacuo* and the residual oil was partitioned between ether and water. Sodium hydrogencarbonate was added to the aqueous layer producing alkaline solution, and the isolated oil was extracted with ether. After being dried over Na_2SO_4, the solvent was removed *in vacuo* to give an oily product; yield, 1.92 g (90.2%); $[\alpha]_D^{23}$ −56.8° (*c* 1.0, THF). IR: 3320, 1730, 1090 cm^{-1}; NMR ($CDCl_3$): δ 2.03, 1.88 (2H 2q, J_{trans}=3.0 Hz, J_{cis}=6.0 Hz, J_{gem}=1.5 Hz, *β*-proton); 2.58 (1H q, J_{trans}=3.0 Hz, J_{cis}=6.0 Hz, *α*-proton); 1.43 (1H bs, $\underline{H}$-N⟨); 5.19 (2H s, C_6H_5–

C$\underline{H}_2$-O-); 7.36 (5H s, $C_6\underline{H}_5$-CH_2-O-). Found: C, 67.52; H, 6.31; N, 7.76%. Calcd for $C_{10}H_{11}O_2N$: C, 67.78; H, 6.26; N, 7.91%.

L-*Azy-OLi (4)*: To a solution of **3** (540 mg, 3.05 mmol) in absolute MeOH (3 ml) was added a solution of LiOH (115.2 mg, 2.74 mmol) in water (1 ml) with stirring at −10 °C. After the reaction mixture had been stirred for 6 h at −5 °C, the solvent was removed *in vacuo*. EtOH was added to a residual oily product and the crystals obtained were collected by filtration. The crystals (**6**) were obtained in theoretical yield; mp 260 °C dec; $[\alpha]^{23}_{D}$ −39.5° (*c* 1.0, H_2O). IR: 3440, 3275, 1590, 1095 cm^{-1}; NMR (D_2O): δ 1.80, 1.75 (2H 2q, J_{trans}=3.6 Hz, J_{cis}=5.8 Hz, J_{gem}=1.5 Hz, β-proton); 2.36 (1H q, J_{trans}=3.6 Hz, J_{cis}=5.8 Hz, α-proton). Found: C, 38.68; H, 4.18; N, 15.21%. Calcd for $C_3H_4O_2NLi$: C. 38.73; H, 4.34; N, 15.05%.

Ac-L-*Azy-OBzl (5)*: To a solution of **3** (2.2 g, 12.4 mmol) and Et_3N (3.5 ml, 24.8 mmol) in $CHCl_3$ (20 ml) was added acetic anhydride (1.1 ml, 12.4 mmol) with stirring at −5 °C, followed by stirring at 0 °C for 4 h. The reaction mixture was washed with 10% citric acid and water, and dried over Na_2SO_4. The solvent was removed *in vacuo* to give an oily product; yield, 2.28 g (84.4%); $[\alpha]^{23}_{D}$ −39.6° (*c* 1.0, MeOH). IR: 1740, 1708, 1081 cm^{-1}; NMR ($CDCl_3$): δ 2.59, 2.48 (2H 2q, J_{trans}=2.9 Hz, J_{cis}=5.9 Hz, J_{gem}=1.5 Hz, β-proton); 3.18 (1H q, J_{trans}=2.9 Hz, J_{cis}=5.9 Hz, α-proton); 2.21 (3H s, C$\underline{H}_3$-CO-); 5.20 (2H s, C_6H_5-C$\underline{H}_2$-O-); 7.37 (5H s, $C_6\underline{H}_5$-CH_2-O-). Found: C, 65.58; H, 5.86; N, 6.20%. Calcd for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39%.

Z-Gly-L-*Azy-OBzl (6)*: To a solution of Z-Gly-OH (540 mg, 2.6 mmol) and **3** (460 mg, 2.6 mmol) in $CHCl_3$ (20 ml) was added a solution of DCC (540 mg, 2.6 mmol) in $CHCl_3$ (5 ml) with stirring at −5 °C. After the reaction mixture had been stirred for 6 h, the produced *N,N′*-dicyclohexylurea was filtered off. The filtrate was washed with 1M sodium hydrogencarbonate, 10% citric acid and water, and dried over Na_2SO_4. The solvent was removed *in vacuo* to give the desired product, which was crystallized from ethyl acetate–ether– hexane; yield, 870 mg (90.8%); mp 42—43 °C; $[\alpha]^{23}_{D}$ −44.5° (*c* 1.0, $CHCl_3$). NMR ($CDCl_3$): δ 2.51, 2.07 (2H m, β-proton); 3.22 (1H q, J=4.8, 3.5 Hz, α-proton); 4.00 (2H d, J=5.5 Hz, -NH-C$\underline{H}_2$-CO-); 5.09, 5.18 (4H 2s, 2C_6H_5-C$\underline{H}_2$-O-); 5.37 (1H bs, -N$\underline{H}$-CO-); 7.33 (10H s, 2$C_6\underline{H}_5$-CH_2-O-). Found: C, 65.29; H, 5.36; N, 7.48%. Calcd for $C_{20}H_{20}O_5N_2$: C, 65.21; H, 5.47; N, 7.61%.

O=P≡(L-*Azy-OBzl*)$_3$ *(7)*: To a solution of **3** (1.8 g, 10.1 mmol) and $POCl_3$ (0.23 ml, 2.5 mmol) in $CHCl_3$ (5 ml) at 0 °C was added a solution of Et_3N (1.06 ml, 7.63 mmol) in $CHCl_3$ (1ml) with stirring. After the reaction mixture had been stirred at 0 °C for 3 h, the solution was washed with 1M sodium hydrogencarbonate, 10% citric acid and water, and then dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residual oil was subjected to column chromatography on silica gel using ethyl acetate–$CHCl_3$–benzene (5:1:1 v/v) to give a pure product; yield, 1.09 g (76.0%); $[\alpha]^{23}_{D}$ −94.7° (*c* 1.0, MeOH). IR: 1745, 1082, 1175—1180, 1250—1290 cm^{-1}; NMR ($CDCl_3$): δ 2.59, 2.72, 3.34 (3H 3q, J=1.6, 3.0 Hz, J=1.6, 6.0 Hz, J=3.0, 6.0Hz, aziridine ring); 2.59, 2.52, 3.09 (3H 3q, J=1.6, 3.0 Hz, J=1.6, 6.0 Hz, J=3.0, 6.0 Hz, aziridine ring); 2.36, 2.36, 2.60 (3H 3q, J=1.6, 3.0 Hz, J=1.6, 6.0 Hz, J=3.0, 6.0 Hz, aziridine ring). Found: C, 62.65; H, 5.16; N, 7.04%. Calcd for $C_{30}H_{30}O_7N_3P$: C, 62.60; H, 5.26; N, 7.29%.

L-*Azy-NH*$_2$ *(8)*: Dry ammonia gas was bubbled into a solution of **3** (306.7 mg, 1.73 mmol) in absolute MeOH (10 ml) at 0 °C for 20 min. The reaction mixture was allowed to stand overnight at room temperature.. After the solvent had been removed *in vacuo*, ether was added to a residual oily product and the resulting crystals were collected; yield, 133.7 mg (89.7%); mp 141—142 °C; $[\alpha]^{23}_{D}$ −44.8° (*c* 1.07, DMF). NMR ($CDCl_3$): δ 1.78, 1.70 (2H 2q, J_{trans}=3.6 Hz, J_{cis}=5.7 Hz, J_{gem}=1.5 Hz, β-proton); 2.38 (1H q, J_{trans}=3.6 Hz, J_{cis}=5.7 Hz, α-proton); 1.78 (1H s, $\underline{H}$-N<); 7.50 (2H br, -CON$\underline{H}_2$). Found: C, 41.78; H, 7.16; N, 32.43%. Calcd for $C_3H_6ON_2$: C, 41.85; H, 7.02; N, 32.54%.

References

1) R. A. Clark, Ph. D. Thesis, University of Maryland, Maryland, U. S. A., 1966.

2) Abbreviations according to IUPAC-IUB commisison, *J. Biol. Chem.*, **247**, 977 (1972), are used. Z: benzyloxycarbonyl, Tri: trityl, DCC: dicyclohexylcarbodiimide, Bzl: benzyl. "Azyline" is used as the name of an aziridine-2-carboxylic acid, "Azy" being its abbreviation.

3) K. Okawa, K. Nakajima, T. Tanaka, and Y. Kawana, *Chem. Lett.*, **1975**, 591; K. Nakajima, O. Kanda, and K. Okawa, proceedings of the 14th Symposium on Peptide Chemistry, p. 17, Hiroshima, 1976.