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A NOVEL SYNTHESIS OF OPTICALLY ACTIVE AZETIDINE-2-CARBOXYLIC ACID

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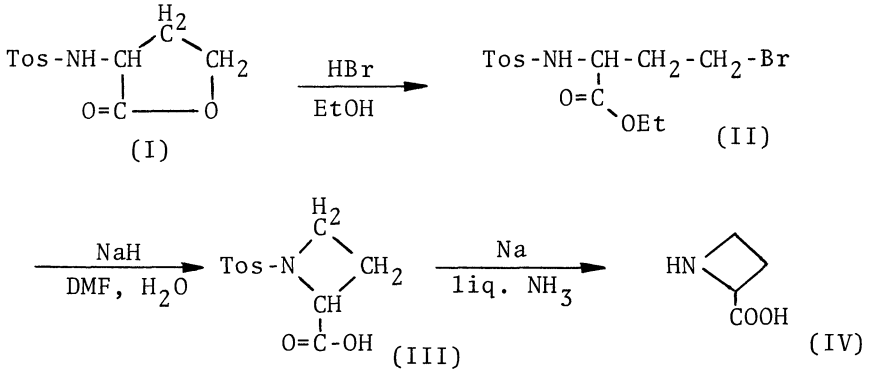
Treatment of tosyl-L-homoserine lactone (I) with hydrogen bromide, followed by recyclization by the use of sodium hydride below 20°C, gave tosyl-L-azetidine-2-carboxylic acid (III). After the detosylation, the optically active azetidine-2-carboxylic acid (IV) was obtained in a good yield.

L-Azetidine-2-carboxylic acid (IV), which was first isolated from *Convallaria majalis* by Fowden[1] in 1955, is believed to be a powerful proline antagonist.[2,3] In the course of his studies, he found that a partial racemization took place during the diazotization of L-α,γ-diaminobutyric acid to form D-γ-amino-α-chlorobutyric acid.[1] Recently, Rodebaugh *et al.* obtained IV by the optical resolution[4,5] of the DL form synthesized *via* ethyl α,γ-dibromobutyrate. However, no direct synthesis of IV has been established as yet.

In a series of our studies on the conversion of L-amino acid to the other optically active one, IV was synthesized from tosyl-L-homoserine lactone (I)[6] which was easily prepared from tosyl-L-methionine.[7] Since this new route does not involve any substitution reaction on the asymmetric carbon, the full optical activity may be retained throughout the reaction.



A suspension of I (100 g) in absolute ethanol (750 ml) was treated with hydrogen bromide under bubbling at 60-70°C. After standing overnight at room temperature, the reaction mixture was concentrated, and the resulting residue was crystallized from ether and n-hexane (1:1) to afford II (131 g, 90%), mp 45-47°C, $[\alpha]_D^{25}$ -10.1° (C=1, EtOH). Found: C, 42.86; H, 4.98; N, 3.84; S, 8.80; Br, 21.93%. Calcd for $C_{13}H_{18}NO_4SBr$: C, 42.78; H, 5.04; N, 3.72; S, 8.33; Br, 21.33%.

To a solution of II (10 g) in DMF (300 ml) and water (1.5 ml) was added sodium hydride (3 g, 66%, oil dispersion) under cooling, and the reaction mixture was stirred at 10-20°C for 20-30 min. After filtration of the insoluble materials, the filtrate was neutralized with *N* hydrochloric acid and was evaporated *in vacuo* below 50°C. To the residue was added 10% hydrochloric acid and the resulting precipitate was collected by filtration. Recrystallization from ethyl acetate and petroleum ether gave III (4.5 g, 95%), mp 145.5-147°C, $[\alpha]_D^{25}$ -144° (C=0.6, $CHCl_3$), IR (nujol) $\nu_{C=O}$: 1720, 1705 cm^{-1}, NMR ($CDCl_3$, δ): 8.4 (s, 1H), 7.75 (d, 2H), 7.35 (d, 2H), 4.53 (t, 1H), 2.45 (s, 3H), 3.72 (t, 2H), 2.0-2.6 (m, 2H). Found: C, 51.99; H, 5.25; N, 5.57; S, 12.38%. Calcd for $C_{11}H_{13}NO_4S$: C, 51.76; H, 5.13; N, 5.49; S, 12.38%.

The detosylation of III (5.5 g) was carried out with metallic sodium (1.4 g) in liquid ammonia (200 ml) in the usual manner. After treatment with Amberlite IR-120 (H^+ form), the eluate with 5% pyridine was evaporated and the residue was recrystallized from 95% methanol to afford IV (1.63 g, 73.0%), mp 210°C, $[\alpha]_D^{25}$ -120° (C=1, H_2O), IR (nujol) $\nu_{C=O}$: 1640, 1600 cm^{-1}, NMR (D_2O, δ): 4.8 (t, 1H), 3.18-4.21 (m, 2H), 2.31-3.0 (m, 2H). Found: C, 47.62; H, 6.92; N, 13.84%. Calcd for $C_4H_7NO_2$: C, 47.52; H, 6.98; N, 13.86%. These data agreed with those reported previously.[1,2,5]

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