A Facile New Synthesis of DL-Azetidine-2-Carboxylic Acid (1a)

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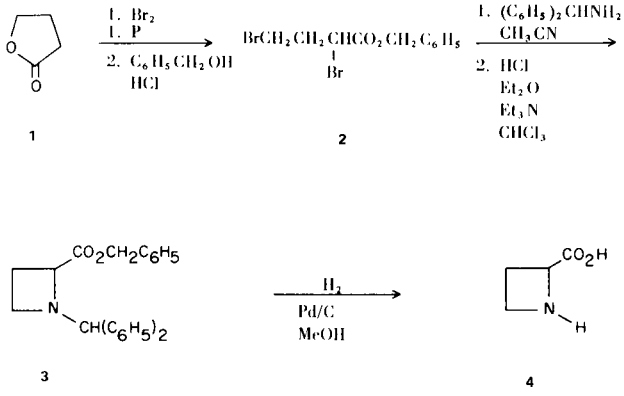
Sir:

Recently we reported (2) the development of a useful method of synthesis of azetidines with functional groups in the 2-position. We have now extended this method to provide, in a facile and economical manner, the DL-form of the naturally occurring imino acid, L-azetidine-2-carboxylic acid.

This acid, which is reported to be a powerful proline antagonist in plant tissue cultures (3), was first isolated and synthesized by Fowden in 1956 (4). Fowden's method of synthesis is tedious, however, and since the yield is relatively low the method is not readily applicable to the production of large quantities of the acid.

We have found that the sequence of reactions shown in Scheme I affords DL-azetidine-2-carboxylic acid (4) in 53.5% overall yield.

SCHEME I



Benzyl α,γ-dibromobutyrate (**2**) was prepared by a modification of the method used by Wladislow for methyl α,γ-dibromobutyrate (5). Bromination of γ-butyrolactone (**1**) in the presence of red phosphorus followed by treatment with a slight excess of benzyl alcohol saturated with dry hydrogen chloride gas gave **2** (70% yield), isolated by vacuum fractional distillation through a 50 cm. Vigreaux column as a colorless oil, b.p. 126-128° (0.2 mm.). Compound **2** gave infrared absorption (carbon tetrachloride) at 1740 cm^{-1} (ester ν C=O). The nmr spectrum (carbon tetrachloride) contained a singlet (5H) at 442 Hz (aromatic), a singlet (2H) at 311 Hz ($CH_2C_6H_5$), a triplet (1H) at 270 Hz (J = 7.4 Hz, CHBrCO), a triplet (1H) at 207 Hz (J = 6.6 Hz, $BrCH_2CH_2$), and a quartet at 147 Hz (J = 6.8 Hz, $BrCH_2CH_2$).

Anal. Calcd. for $C_{11}H_{12}Br_2O_2$: C, 39.32; H, 3.61; Br, 47.56. Found: C, 39.31; H, 3.81; Br, 47.56.

The dibromo ester (**2**) (13.46 g., 0.04 mole) was refluxed with 22.0 g. (0.12 mole) of benzhydrylamine in 200 ml. of acetonitrile for twenty hours. The solvent was evaporated under reduced pressure and ethyl ether was added to the residue. Filtration to remove benzhydrylamine hydrobromide followed by exposure of the filtrate to a stream of hydrogen chloride gas for five minutes gave a syrupy precipitate from which the ether was decanted. The precipitate was dissolved in chloroform and treated with three molar equivalents of triethylamine. The chloroform was evaporated under reduced pressure and the residue was extracted with ether. Filtration of the ethereal extract and evaporation of the solvent from the filtrate yielded an orange oil which was chromatographed on florisil (425 g.). Elution with ethyl acetate-hexane (15:85) provided 11.8 g. (82.7% yield) of **3** as a viscous yellow oil which was crystallized from an ethyl ether-pentane mixture as colorless crystals, m.p. 61-63°. Compound **3** gave infrared absorption (carbon tetrachloride) at 1745 cm^{-1} (ester ν C=O). The nmr spectrum contained a multiplet (15H) in the range 414 to 456 Hz (aromatic), two overlapping singlets (2H) at 287 and 285 Hz ($CO_2CH_2C_6H_5$) a singlet (1H) at 270 Hz ($CH(C_6H_5)_2$) a triplet (1H) at 234 Hz (J = 7.8 Hz, CHCO), a multiplet (2H) in the range 160 to 216 Hz (CH_2N), and a multiplet (2H) in the range 114 to 146 Hz (CH_2CHCO).

Anal. Calcd. for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.52; H, 6.51; N, 3.85.

A 2.20 g. sample (0.00616 mole) of 1-benzhydryl-2-carbobenzyloxyazetidine (**3**) was dissolved in 35 ml. of

methanol and hydrogenolyzed at a pressure of 45 psi over 0.5 g. of 5% palladium-on-carbon catalyst. After twelve hours the suspension was filtered and the catalyst was washed with water. The methanol was evaporated from the filtrate under reduced pressure and the residual aqueous portion was extracted with ether to remove the toluene and diphenylmethane. The water was then evaporated under reduced pressure from the aqueous layer, methanol was added to the residual solid, and the suspension was filtered affording 0.38 g. of white solid. The methanol was evaporated from the filtrate, ether was added to the residue and the suspension was filtered providing an additional 0.15 g. of solid. The combined solids were recrystallized from 95% methanol, 0.50 g. of **4** being obtained as white crystals which slowly darkened without melting upon heating above 200° (4). Compound **4** gave infrared absorption (Nujol mull) at 1580 cm^{-1} (ionic carboxylate ν C=O). The nmr spectrum (deuterium oxide) (6) contained a singlet (2H) at 281 Hz (COO*H* and N*H* exchanged with deuterium oxide), a triplet (1H) at 279 Hz (J = 9.7 Hz, C*H*CO), a multiplet (2H) in the range 211 to 254 Hz (CH_2N), and a multiplet (2H) in the range 121 to 179 Hz (CH_2CHCO).

Anal. Calcd. for $C_4H_7NO_2$: C, 47.52; H, 6.98; N, 13.86. Found: C, 47.36; H, 7.06; N, 13.82.

In an effort to minimize the time involved in carrying out the procedure and to optimize the overall yield of **4** it was found that the crude azetidinyl ester (**3**), obtained in quantitative yield before purification by column chromatography, could be directly hydrogenolyzed over Pearlman catalyst (20% palladium hydroxide-on-carbon) (7) providing the acid **4** in 76.5% yield. The overall yield from γ-butyrolactone (1) is 53.5%.

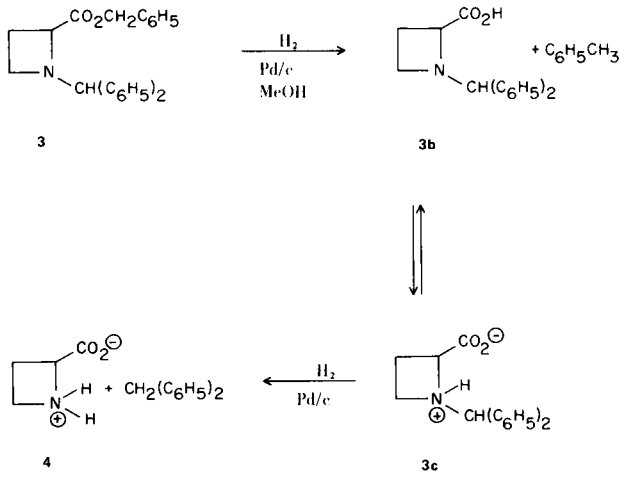
Originally we had considered the possibility that 1-benzylazetidine-2-carboxylic acid (2) might provide azetidine-2-carboxylic acid (**4**) by hydrogenolysis. No reaction was observed with this azetidinyl acid when palladium-on-carbon catalysts were employed under a variety of conditions and the Pearlman catalyst effected the reaction to an extent of only 40%. It was concluded that a benzhydryl-nitrogen bond might cleave more readily than a benzyl-nitrogen bond. Thus 1-benzhydryl-2-carbomethoxyazetidine (**5**) (8) was prepared by treating methyl α,γ-dibromobutyrate with benzhydrylamine under conditions analogous to those described previously (2).

However, attempts to hydrolyze ester (**5**) in aqueous base to the corresponding acid were unsuccessful. Hydrogenolysis of compound **5** itself gave, after twenty-four hours, a 61% recovery of starting material plus a solid decomposition product. Hydrogenolysis of the hydrochloride salt of ester (**5**) gave a 90% yield of diphenylmethane together with a complex mixture of products most likely resulting from ring cleavage concomitant with the intended hydrogenolysis reaction.

In order to test the feasibility of obtaining an acid by hydrogenolyzing a benzyl ester in the azetidine system, 1-(*t*-butyl)-2-carbobenzyloxyazetidine (**6**) (8) was obtained by the reaction of *t*-butylamine with benzyl α,γ-dibromobutyrate under the conditions described above. Catalytic hydrogenolysis of ester (**6**) occurred within one hour providing 1-*t*-butylazetidine-2-carboxylic acid (2) in 94% yield.

These results indicate that the formation of azetidine-2-carboxylic acid (**4**) probably occurs *via* the pathway shown in Scheme II in which the benzhydryl-nitrogen bond cleavage of **3** is preceded by cleavage of the benzyl-oxygen bond and subsequent formation of zwitterion **3c**.

SCHEME II



Efforts are currently underway to resolve DL-azetidine-2-carboxylic acid (**4**) into its optical antipodes.

Acknowledgment.

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