1-Alkylazetidine-2-carboxylic Acids

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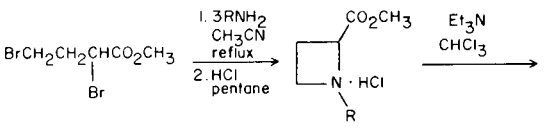
Sir:

In connection with our continuing (2) studies of azetidines with functional groups attached to the carbons of the four-ring, we now wish to report our development of a useful method of synthesis which is expected to lead to azetidines with a wide variety of functional groups in the 2-position (3).

Methyl α,γ-dibromobutyrate **1**, which can be obtained in high yield by the bromination of γ-butyrolacetone (4), seemed, on the basis of early work by Drake and McElvain (5), to be an appropriate starting material for the synthesis of 1-alkyl-2-carbomethoxyazetidines. Drake and McElvain observed that at 90° the rate of displacement by piperidine of the bromine atom from ethyl γ-bromobutyrate is greater than that for ethyl α-bromobutyrate. If a rate difference is assumed in the displacement of the two types (α and γ) of bromine atoms from **1** by primary amines, then one might expect to observe, at least to some extent, the formation of the azetidine ring in this reaction. Thus 5.20 g. (0.02 mole) of **1** was refluxed with 4.69 g. (0.06 mole) of *t*-butylamine in 100 ml. of acetonitrile for 24 hours. The solvent was removed under reduced pressure and pentane was added to the residue. Filtration to remove *t*-butylamine hydrobromide followed by exposure of the filtrate to a stream of hydrogen chloride gas for 5 minutes yielded 2.0 g. (48.2%) of **2a** as a white crystalline solid, m.p. 117-118°, which gave infrared absorption (chloroform) at 2440, 2280 ($^+$N-H) and 1748 cm^{-1} (ester ν C=O). The nmr spectrum (deuteriochloroform, 60 Mc/sec) showed a multiplet (1H) centered at δ 10.00 (N$^+$H), a triplet (1H) at 5.08 (J = 9 cps, C*H*CO), a multiplet (2H) at 4.14 (C*H*$_2$N$^+$), a singlet (3H) at 3.92 (CO$_2$C*H*$_3$), a multiplet (2H) at 2.79 (C*H*$_2$CHCO), and a singlet (9H) at 1.41 ppm (C(CH$_3$)$_3$).



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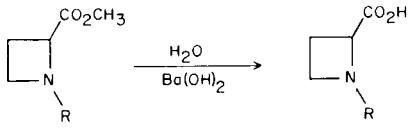
2a, R = t-C$_4$H$_9$
2b, R = C$_6$H$_{11}$
2c, R = CH$_2$C$_6$H$_5$



3a,b,c

4a,b,c

Anal. Calcd. for C$_9$H$_{18}$ClNO$_2$: C, 52.04; H, 8.73; Cl, 17.07; N, 6.74. Found: C, 51.99; H, 8.74; Cl, 17.18; N, 6.78.

Compounds **2b** and **2c**, being extremely hygroscopic, were obtained as viscous oils. Compound **2b** (65% yield) gave infrared absorption (chloroform) at 2560, 2470 ($^+$N-H) and 1750 cm^{-1} (ester ν C=O). The nmr spectrum (deuteriochloroform) showed a multiplet (1H) centered at δ 11.15 (N$^+$*H*), a triplet (1H) at 5.54 (J = 9 cps, C*H*CO), a multiplet (2H) at 4.23 (C*H*$_2$N$^+$), a singlet (3H) at 3.85 (CO$_2$C*H*$_3$), a multiplet (1H) at 3.50 (cyclohexyl C$_1$*H*), a multiplet (2H) at 2.78 (C*H*$_2$CHCO), and a multiplet (10 H) at 1.58 ppm (cyclohexyl less C$_1$ H). Compound **2c** (79.2% yield) gave infrared absorption (chloroform) at 2530, 2250 ($^+$N-H) and 1742 cm^{-1} (ester ν C=O). The nmr spectrum (deuteriochloroform) showed a multiplet (1H) centered at 11.91 (N$^+$*H*), a multiplet (5H) at 7.48 (C$_6$*H*$_5$), two doublets (apparent quartet, 1H) at 5.71 (C*H*CO), two broad overlapping singlets (1H each) at 4.78 and 4.69 (C*H*$_2$C$_6$H$_5$), a multiplet (2H) at 4.19 (C*H*$_2$N$^+$), a singlet (3H) at 3.66 (CO$_2$C*H*$_3$), and a multiplet (2H) at 2.73 ppm (C*H*$_2$CHCO).

Compound **2a** was treated with 1.5 molar equivalents of triethylamine in chloroform. The chloroform was removed under reduced pressure and the residue extracted with pentane. Filtration to remove triethylamine hydrochloride and evaporation of the solvent from the filtrate, followed by vacuum distillation of the residue gave **3a** (6) (74.5%) as a colorless oil, b.p. 55-56° (2 mm.), which gave infrared absorption (carbon tetrachloride) at 1753/92 (ester ν$_1$ C=O/% abs) and 1725 cm^{-1}/86 (ester ν$_2$ C=O/% abs). The nmr spectrum (deuteriochloro-

form) showed a triplet (1H) at δ 4.05 (J = 8 cps, C*H*CO), a singlet (3H) at 3.81 (CO_2CH_3), a multiplet (2H) centered at 3.28 (CH_2N), a multiplet (2H) at 2.25 (CH_2CHCO), and a singlet (9H) at 1.00 ppm ($C(CH_3)_3$).

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 62.89; H, 9.88; N, 8.46.

Compound **3b** (6) was obtained similarly (58.5%) as a colorless oil, b.p. 95-97° (2 mm.), which gave infrared absorption (carbon tetrachloride) at 1754/92 (ester ν_1 C=O/% abs) and 1727 cm^{-1}/86 (ester ν_2 C=O/% abs). The nmr spectrum (deuteriochloroform) showed a singlet (3H) at δ 3.78 (CO_2CH_3), a triplet (1H) at 3.74 (J = 8 cps, C*H*CO), a multiplet (2H) centered at 3.20 (CH_2N), a multiplet (3H) at 2.27 (CH_2CHCO and cyclohexyl C_1H), and a multiplet (10 H) at 1.32 ppm (cyclohexyl less C_1H).

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.72; H, 9.77; N, 7.34.

Compound **3c** (6) (43% yield), b.p. 112-113° (1.5 mm.), gave infrared absorption at 1743 cm^{-1} (ester ν C=O). The nmr spectrum (carbon tetrachloride) showed a singlet (5H) at δ 7.16 (C_6H_5), two doublets (1H each) at 3.89 and 3.38 (J = 12.6 cps, $CH_2C_6H_5$), a triplet (1H) at 3.60 (J = 8.4 cps, C*H*CO), a singlet at 3.58 (CO_2CH_3), and a complex multiplet (4H) centered at 3.47 ppm (C_3 and C_4 ring protons).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.83. Found: C, 70.44; H, 7.61; N, 7.01.

Basic hydrolysis of the esters **3a**, **3b** and **3c** gave the corresponding acids **4a**, **4b** and **4c**. Thus 1.71 g. (0.01 mole) of **3a** was added to a solution of 2.0 g. (0.006 mole) of barium hydroxide octahydrate in 30 ml. of water and refluxed for 30 minutes; 40 ml. of water was added and the hot mixture was neutralized by passing in carbon dioxide until precipitation of barium carbonate was complete. The barium carbonate was removed by filtration, the water was evaporated from the filtrate under reduced pressure, and the residue was dissolved in hot chloroform. Concentration of the solution gave 1.08 g. (69%) of **4a** as a white solid, m.p. 173-175°, which gave infrared absorption (chloroform) at 1632 cm^{-1} (ionic carboxylate ν C=O). The nmr spectrum (deuterium oxide) showed a singlet (1H) at δ 4.76 (COO*H*-exchanged with deuterium oxide), a triplet (1H) at 4.65 (J = 9 cps, C*H*CO), a multiplet (2H) centered at 3.93 (CH_2N), a multiplet (2H) at 2.50 (CH_2CHCO), and a singlet (9H) at 1.22 ppm ($C(CH_3)_3$).

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.24; H, 9.51; N, 8.77.

Compound **4b** was obtained likewise (71%) as a white solid, m.p. 176-178°, which gave infrared absorption (chloroform) at 1635 cm^{-1} (ionic carboxylate ν C=O). The nmr spectrum (deuterium oxide) showed a singlet (1H) at δ 4.76 (COO*H*-exchanged with deuterium oxide), a triplet (1H) at 4.67 (J = 9 cps, C*H*CO), a multiplet (2H) centered at 3.95 (CH_2N), a multiplet (1H) at 3.08 (cyclohexyl C_1H), a multiplet (2H) at 2.54 (CH_2CHCO), and a multiplet (10 H) at 1.49 ppm (cyclohexyl less C_1H).

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.45; H, 9.28; N, 7.56.

Compound **4c**, (81.8% yield), m.p. 159-161°, gave infrared absorption (Nujol mull) at 1612 cm^{-1} (ionic carboxylate ν C=O). The nmr spectrum (deuterium oxide) showed a singlet (5H) at δ7.33 (C_6H_5), a singlet (1H) at 4.63 (COO*H*-exchanged with deuterium oxide), a triplet (1H) at 4.61 (J = 9.2 cps, C*H*CO), a singlet (2H) at 4.25 ($CH_2C_6H_5$), a multiplet (2H) centered at 3.85 (CH_2N), and a multiplet (2H) at 2.48 ppm (CH_2CHCO).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.90; H, 6.93; N, 7.24.

A noteworthy characteristic of the azetidinyl esters **3a** and **3b** is that these compounds both exhibit two carbonyl bands in their infrared spectra. This may possibly be explained by the occurrence of some type of conformational isomerism (apparently not present in ester **3c**) perhaps similar to that suggested for carbonyl compounds in the related aziridine series, many of which also show two carbonyl absorptions in the infrared region (7). Studies of the effect of various temperatures, solvents and dilution on spectra will be undertaken in the future in order to further elucidate the nature of this phenomenon in the azetidine series. L-Azetidine-2-carboxylic acid is a naturally occurring imino acid which is reported to be a powerful proline antagonist for plant tissue cultures (8).

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(1) To whom inquiries should be addressed.

(2) For the first syntheses of azetidines with a carbonyl function attached to the 3-position of the four-ring, see (a) N. H. Cromwell and Earl Doomes, *Tetrahedron Letters*, No. 34, 4037 (1966); (b) J.-L. Imbach, E. Doomes, R. P. Rebman and N. H. Cromwell, *J. Org. Chem.*, 32, 78 (1967).

(3) After the work described here was essentially complete the excellent work of T. Chen, T. Sanjiki, H. Kato and M. Ohta, *Bull. Chem. Soc. Japan*, 40, 2398 (1967), appeared which

reports a related development of the synthesis of *N*-tosylazetidines with a variety of functional groups in the 2-position. These workers reported that they were unsuccessful in their attempts to react tosylamide with methyl α,γ-dibromobutyrate.

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(6) Compounds **3a**, **3b** and **3c** turn yellow upon standing at room temperature and should be stored at 0°.

(7) See for example (a) N. H. Cromwell, *Record Chem. Progr. (Kresge-Hooker Sci. Libr.)*, 19, 215 (1958); (b) N. H. Cromwell, R. E. Bambury and J. L. Adelfang, *J. Am. Chem. Soc.*, 82, 4241 (1960); (c) M. Protenik, N. P. Salzman and H. E. Carter, *ibid.*, 77, 1856 (1965).

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