BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 3287—3288 (1970)

Ring Expansion of Azetidines to Pyrrolidines*1

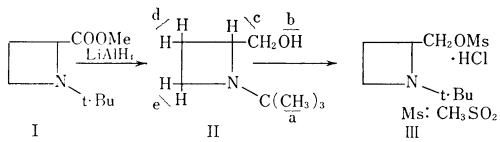
Takayoshi MASUDA, Akiko CHINONE and Masaki OHTA

Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo

(Received April 16, 1970)

Many examples are reported in which nucleophilic participation by amino group both in acyclic and cyclic haloamines lead to ring expansion, contraction or cleavage *via* cyclic quaternary salts.[1,2]

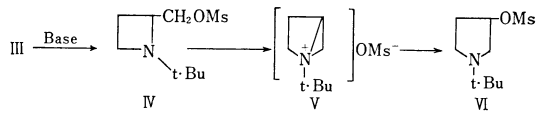
We were interested in the behavior of ring-nitrogen atom of azetidine as a neighboring group, since azetidine is highly strained and one of the strongest bases in cyclic amines. Methyl 1-*t*-butylazetidine-2-carboxylate (I), synthesized recently by Rodebaugh and Cromwell,[3] seems to be the best starting material for the studies.



I II III

Reduction of I by lithium aluminum hydride afforded 1-*t*-butyl-2-hydroxymethylazetidine (II) in good yield. II was treated with methanesulfonyl chloride in anhydrous pyridine to give 1-*t*-butyl-2-methanesulfonyloxymethylazetidine hydrochloride (III) almost quantitatively. III was carefully neutralized with triethylamine or aqueous potassium carbonate in methylene chloride, the temperature being kept below 10°C. From the organic layer a crude base was obtained which gave a picrate. The NMR spectrum of the picrate shows that the crude base is 1-*t*-butyl-2-methanesulfonyloxymethylazetidine (IV). However, IV is unstable and readily undergoes rearrangement to 1-*t*-butyl-3-methanesulfonyloxypyrrolidine (VI) by standing for a few hours at room temperature, probably *via* bicyclic quaternary salt (V).

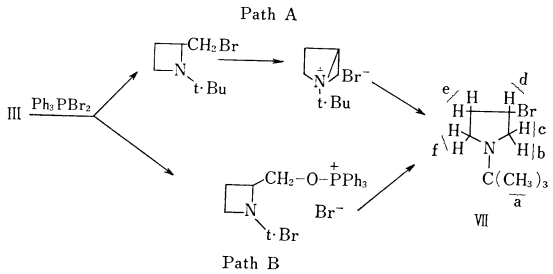
Owing to an insufficient amount of VI for purification, its structure was deduced on the basis of the elementary analysis and NMR spectrum of



IV V VI

the picrate prepared from the crude rearrangement product. The driving force for the rearrangement of IV to VI is probably due to the release of ring strain and the easiness of internal quaternization to V due to the strong basicity of azetidine.

Treatment of III with triphenylphosphine dibromide in the presence of equimolar amount of triethylamine gave 1-*t*-butyl-3-bromopyrrolidine (VII). The structure of VII is supported by the result of elementary analysis and NMR spectrum. Formation of VII might proceed either *via* bicyclic quaternary salt (pathway A) or *via* quaternary phosphonium salt (pathway B).



VII

Experimental*2

1-t-Butyl-2-hydroxymethylazetidine (II). To a suspension of lithium aluminum hydride (2.28 g, 0.06 mol) in anhydrous ether (75 m*l*) was added dropwise a solution of methyl 1-*t*-butylazetidine-2-carboxylate (8.6 g, 0.05 mol) in anhydrous ether (50 m*l*) with stirring and cooling with ice-water. Stirring was continued for further 4 hr and the reaction mixture was left standing overnight. Sodium hydroxide (1 g), ether (55 m*l*) and water (3—5 m*l*) were then added successively with cooling with ice-water. After filtration with sintered glass filter, the ethereal solution was dried over potassium hydroxide and the solvent was distilled off to give a colorless oil which was distilled in a vacuum: bp 50—53.5°C/2.5 mmHg, yield 6.3 g (88%).

Found: C, 67.29; H, 11.95; N, 9.70%. Calcd for $C_8H_{17}ON$: C, 67.13; H, 11.89; N, 9.79%.

*1 Presented at the 23rd Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1970.

1) J. F. Kerwin, G. E. Ullyot, R. C. Fuson and C. L. Zirkle, *J. Amer. Chem. Soc.*, **69**, 2961 (1947); E. M. Schultz and J. M. Sprague, *ibid.*, **70**, 48 (1948).

2) R. C. Fuson and C. L. Zirkle, *ibid.*, **70**, 2760 (1948); R. H. Reitsema, *ibid.*, **71**, 2041 (1949); E. G. Brain, F. P. Doyl and M. D. Mehta, *J. Chem. Soc.*, **1961**, 633; V. R. Gaertner, *Tetrahedron Lett.*, **1968**, 5919; J. A. Deyrup and C. L. Moyer, *ibid.*, **1968**, 6179.

3) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocycl. Chem.*, **5**, 309 (1968).

*2 All melting points were determined on a micro hot stage and are not corrected.

The NMR spectrum of II shows signals at τ 9.1 (H_a, singlet), 7.8—8.2 (H_d, multiplet), 6.8—7.1 (H_e, multiplet), 6.3—6.7 (H_c, multiplet) and 5.9 (H_b, singlet).

Picrate: mp 194—195°C (decomp.).

Found: C, 45.42; H, 5.26; N, 15.29%. Calcd for $C_{14}H_{20}O_8N_4$: C, 45.16; H, 5.41; N, 15.05%.

1-*t*-Butyl-2-methanesulfonyloxymethylazetidine Hydrochloride (III). To a stirred solution of II (7.15 g, 0.05 mol) in anhydrous pyridine (60 m*l*) was added dropwise methanesulfonyl chloride (6.5 g), the temperature being kept at 0—5°C by cooling. The mixture was stirred for 4—5 hr, kept in a refrigerator overnight and then anhydrous ether (200 m*l*) was added to precipitate the hydrochloride which was collected by filtration and washed with petroleum ether to remove pyridine. Recrystallized from ethyl methyl ketone: mp 108.5—109.5°C, yield 12.7 g.

Found: C, 41.98; H, 8.06; N, 5.44%. Calcd for $C_9H_{20}O_3NSCl$: C, 41.93; H, 7.82; N, 5.43%. IR (KBr): 2390—2670 cm^{-1} (ammonium salt).

Picrate: mp 148.5—149.5°C (decomp.). (CH_3CN–EtOH).

Found: C, 40.43; H, 4.82; N, 12.36; S, 7.05%. Calcd for $C_{15}H_{22}O_{10}N_4S$: C, 40.00; H, 4.92; N, 12.44; S, 7.12%. The NMR spectrum of the picrate exhibits at τ 8.67 (9H, singlet, *t*-butyl), 7.45—7.87 (2H, multiplet, methylene at 3-position of azetidine ring), 6.97 (3H, singlet, methyl of methanesulfonyl group), 5.83—6.15 (2H, multiplet, methylene at 4-position), 5.31—5.62 (3H, multiplet, methine at 2-position and methylene of methanesulfonyloxymethyl group) and 1.33 (2H, singlet, phenyl).

Reaction of III with Triphenylphosphine Dibromide. To a solution of triphenylphosphine dibromide in acetonitrile (50 m*l*) (prepared from 13.1 g of triphenylphosphine and 8.8 g of bromide) was added dropwise triethylamine (5.6 g, 0.055 mol) at 0—5°C and after 20 min 7.15 g (0.05 mol) of III was added below 10°C. The solution was stirred for 1 hr, heated up to 60—70°C and kept at this temperature for 20 min when the solution turned dark brown. After cooling, acetonitrile was distilled off under reduced pressure and the residue was extracted with petroleum ether. The extract was dried over magnesium sulphate and distilled to remove the solvent. The residual oil was distilled under reduced pressure and 6.5 g (63%) of III, bp 83.5—84°C/13 mmHg was obtained.

Found: C, 46.97; H, 7.78; N, 7.06%. Calcd for $C_8H_{16}NBr$: C, 46.62; H, 7.82; N, 6.80%.

Picrate: mp 193.5—195.5°C (decomp).

Found: C, 38.50; H, 4.27; N, 13.00%. Calcd for $C_{14}H_{19}O_7N_4Br$: C, 38.63; H, 4.40; N, 12.87%.

The NMR spectrum of VII shows signals at τ 8.91 (H_a, singlet), 7.40—8.05 (H_e, multiplet), 7.14—7.35 (H_f, multiplet), 7.09 (H_b, doublet of doublet), 6.67 (H_c, doublet of doublet) and 5.54—5.77 (H_d, multiplet).