[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, THE FLORIDA STATE UNIVERSITY]

Chemical Effects of the Trifluoromethyl Group: III. Synthesis of 2-Amino-4,4,4-trifluorobutyric Acid[1,2]

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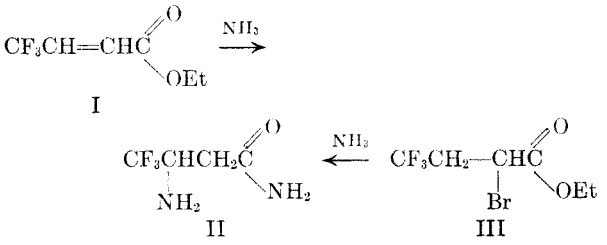
Ammonolysis of ethyl 2-bromo-4,4,4-trifluorobutyrate yielded 3-amino-4,4,4-trifluorobutyric acid due to the elimination of hydrogen bromide by the basic ammonia followed by the addition of ammonia to the double bond. To prevent the elimination reaction and to effect the direct substitution of the bromide the weakly basic and highly nucleophilic azide ion was used. The azido derivative was converted to the desired 2-amino-4,4,4-trifluorobutyric acid.

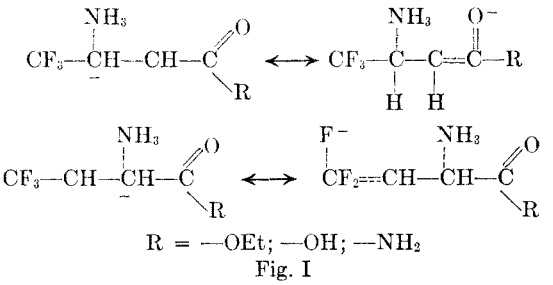
The synthesis of 2-amino-4,4,4-trifluorobutyric acid has been previously attempted without success. One of the methods[3] tried was the addition of ammonia to 4,4,4-trifluorocrotonic acid and its ethyl ester and amide derivatives. This led to the formation of the 3-amino derivatives (I → II). Another method[2] utilized was the ammonolysis of the ethyl 2-bromo-4,4,4-trifluorobutyrate (III) which resulted in the formation of 3-amino-4,4,4-trifluorobutyramide (III → II).



The formation of the 3-amino isomer from III likely follows from dehydrohalogenation of III to I and then normal addition to the double bond by ammonia. The acidity of the 3-hydrogens of III is undoubtedly enhanced by the inductive effect of the trifluoromethyl group, thus facilitating elimination by the basic reagent.

Apparently the trifluoromethyl group is a poor competitor with the carboxamide, carboxyl, and carbethoxy groups as a stabilizer of a negative charge on an adjacent carbon in the transition state (Fig. I). The orientation of addition thus is unchanged from that of the unfluorinated analogs.[4]

A less basic and more nucleophilic reagent than ammonia might be expected to preserve the positional isomerism, by decreasing the propensity for elimination and by abetting the substitution reaction. The azide ion meets these specifications, it being a weaker base than ammonia by a factor of 4.6×10^4; K_bNH_3[5] $= 1.8 \times 10^{-5}$, K_aHN_3[5] $= 2.6 \times 10^{-5}$, $K_bN^-{}_3 = 3.9 \times 10^{-10}$ (calc'd from $K_aK_b = 1.01 \times 10^{-14}$). This reagent has another distinct feature which makes it all the more attractive in that it stands high in relative nucleophilicity, as has been shown by Swain[6] and Ingold.[7]

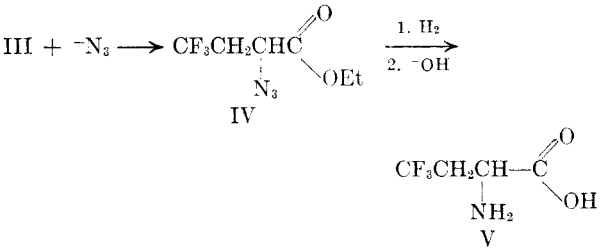


R = —OEt; —OH; —NH_2

Fig. I

In addition, azido compounds can be conveniently reduced to amines by a variety of reagents.[8-10]

The synthesis of 2-amino-4,4,4-trifluorobutyric acid (V) was achieved according to the following reaction scheme:



The reaction of III with sodium azide according to the method of Forster and Fierz[11] gave the azido

(1) This investigation was supported by a research grant, number C-1461 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) Paper II of this series: Walborsky, Baum, and Loncrini, *J. Am. Chem. Soc.*, **77**, 3637 (1955).

(3) Walborsky and Schwarz, *J. Am. Chem. Soc.*, **75**, 3241 (1953).

(4) Morsch, *Monatsh.*, **60**, 50 (1932).

(5) Walton, *Principles and Methods of Chemical Analysis*, Prentice Hall, Inc., New York, 1952, p. 416.

(6) Swain and Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953).

(7) Brewster, Hughes, Ingold, and Rao, *Nature*, **166**, 178 (1950).

(8) Adams and Blomstrom, *J. Am. Chem. Soc.*, **75**, 3405 (1953).

(9) Boyer, *J. Am. Chem. Soc.*, **73**, 5865 (1951).

(10) Lieber, Sherman, Henry, and Cohen, *J. Am. Chem. Soc.*, **73**, 2327 (1951).

(11) Forster and Fierz, *J. Chem. Soc.*, **93**, 669 (1908).

derivative (IV) in 63% yield. Catalytic reduction of IV to the amino ester, which was isolated as the hydrochloride, was almost quantitative. Saponification afforded a 63% yield of V. In distinction to the behavior of the 3-amino acid isomer to ninhydrin, this amino acid gave a positive test.

EXPERIMENTAL[12]

Ethyl 2-bromo-4,4,4-trifluorobutyrate (III). This material was prepared from 4,4,4-trifluorobutyric acid, bromine, and phosphorus trichloride, followed by treatment with alcohol according to the procedure in the literature,[2] to yield 43% of product, b.p. 153–156°, n_D^{23} 1.3960.

Ethyl 2-azido-4,4,4-trifluorobutyrate (IV). A two-phase mixture of 21.0 g. (0.0845 mole) of ethyl 2-bromo-4,4,4-trifluorobutyrate dissolved in 10 cc. of alcohol, and 7.65 g. (0.118 mole) of sodium azide dissolved in 25 cc. of water was stirred and refluxed for 24 hours. The mixture was steam-distilled, and the distillate was extracted with ether. The ether was washed twice with water, dried over calcium chloride, the solvent stripped off, and the residue distilled. After a small forerun (5.1 g.), the main fraction, b.p. 74–75° (20 mm.), n_D^{23} 1.3935, weighing 11.2 g. (63% yield) was collected.

Anal. Calc'd for $C_6H_8F_3N_3O_2$: C, 34.13; H, 3.82. Found: C, 34.61; H, 4.07.

Ethyl 2-amino-4,4,4-trifluorobutyrate. A solution of 8.5 g. (0.04 mole) of ethyl 2-azido-4,4,4-trifluorobutyrate in 10 cc. of alcohol was hydrogenated with 0.5 g. of 5% palladium-on-charcoal at an initial pressure of 55 lbs. for 8 hours. The catalyst was removed by filtration, and the filtrate was acidified with 40 cc. of 1.3 *N* (0.052 mole) methanolic hydrogen chloride. The alcohol was removed *in vacuo*, and the residue was washed with ether to remove unreduced material. The crystalline insolubles weighed 8.5 g. (96%). A sample of the hydrochloride was recrystallized several times from ethanol-ether, m.p. 152–153°.

Anal. Calc'd for $C_6H_{11}ClF_3N$: C, 32.52; H, 5.00; N, 6.32. Found: C, 32.79; H, 5.31; N, 6.53.

2-Amino-4,4,4-trifluorobutyric acid (V). A mixture of 8.5 g. (0.038 mole) of the crude hydrochloride of ethyl 2-amino-4,4,4-trifluorobutyrate and 33.4 cc. of 3.0 *N* sodium hydroxide (0.100 equiv.) was heated on the steam-bath for 3 minutes until solution was effected. The solution was acidified with concentrated hydrochloric acid, evaporated to dryness *in vacuo*, and the residue was redissolved in absolute alcohol and dried *in vacuo* again. The residue was triturated with 20 cc. of absolute alcohol, concentrated to 10 cc., cooled, and a small amount of solids was removed by centrifugation; pyridine was added to precipitate the amino acid which was collected after cooling and yielded 3.8 g. (63%) of V. Recrystallization from ethanol and water yielded pure amino acid, m.p. 260–265° (dec.).

Anal. Calc'd for $C_4H_6F_3NO_2$: C, 30.58; H, 3.85; N, 8.95. Found: C, 30.80; H, 4.05; N, 8.81.

3-Amino-4,4,4-trifluorobutyric acid.[13] A solution of 2.1 g. of 4,4,4-trifluorocrotonic acid and 3 cc. of liquid ammonia was heated in a sealed tube at 100° for 16 hours. The viscous residue was dissolved in ethanol, concentrated to a small volume, and the amino acid was precipitated by the addition of ether to yield 0.9 g. (39%) of product, m.p. 180–181°. Recrystallization from ethanol raised the m.p. to 189–190° (dec.).

Anal. Calc'd for $C_4H_6F_3NO_2$: C, 30.58; H, 3.85; N, 8.95. Found: C, 30.76; H, 4.05; N, 8.84.

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(12) Melting points and boiling points are uncorrected. Analyses were performed by E. Thommen, Basel, Switzerland.

(13) This experiment was performed by Dr. M. Schwarz.