*Journal of Fluorine Chemistry, 36* (1987) 163–170



Received: October 3, 1986; accepted: February 26, 1987

# SYNTHESIS OF 5,5,5-TRIFLUORO-DL-ISOLEUCINE AND 5,5,5-TRIFLUORO-DL-ALLOISOLEUCINE

NORBERT MULLER

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907 (U.S.A.)

## SUMMARY

Three methods of synthesis are described for 2-amino-3-methyl-5,5,5-trifluoropentanoic acid, a mixture of diastereomers which on separation affords the title compounds. The least cumbersome involves bromination and subsequent amination of 3-methyl-5,5,5-trifluoropentanoic acid, with overall yields near 45% in several trials. The starting material is readily obtainable from the products of an anodic trifluoromethylation of methallyl cyanide.

## INTRODUCTION

The synthesis of fluorinated analogues of biologically active compounds is often rewarding, either because it provides novel bioactive materials [1,2] or because of the attractiveness of using $^{19}F$ NMR to study the physicochemical behavior of the products, e.g. their binding by cosolute species [3,4]. Analogues of the protein-derived amino acids began to be studied in the 1950's [5]. They are particularly interesting in light of the possibility of incorporating them biosynthetically into various proteins [6]. In this context, trifluoromethylated compounds offer the advantages of low toxicity and relatively large $^{19}F$ NMR signal strength.

A search was recently undertaken in this laboratory for a convenient synthesis of 5,5,5-trifluoro-DL-isoleucine (1). Three procedures were found, each starting with material obtained by an electrochemical trifluoromethylation of an olefinic compound. Each gave 2-amino-3-methyl-5,5,5-trifluoropentanoic acid (2), which was a mixture of about equal amounts of

0022-1139/87/$3.50 

(1) and 5,5,5-trifluoro-DL-alloisoleucine (3). The diastereomers were easily separated by taking advantage of solubility differences.

## RESULTS AND DISCUSSION

### Synthesis of (2) from 4,4,4-trifluoro-2-butanone (4). Scheme I

Ketone (4), prepared by electrochemical trifluoromethylation of isopropenyl acetate [7], was condensed with ethyl cyanoacetate in the presence of acetic acid and ammonium acetate [8] to give the unsaturated ester (5), which was catalytically hydrogenated to produce ethyl

$$CF_3CH_2C(O)CH_3\ (4) + NCCH_2COOEt \xrightarrow{HOAc,NH_4OAc} CF_3CH_2C(CH_3)=C(CN)COOEt\ (5)$$

$$(5) \xrightarrow{H_2/Pd/C} RCH(CN)COOEt\ (6)$$

$$(6) \xrightarrow{N_2H_4\cdot H_2O} RCH(CN)CON_2H_3\ (7)$$

$$(7) \xrightarrow{NaNO_2} RCH(CN)CON_3\ (8)$$

$$(8) \xrightarrow{EtOH} RCH(CN)NHCOOEt\ (9)$$

$$(9) \xrightarrow{aq.\ HCl} RCH(COOH)NH_3Cl\ (10)$$

$$(10) \xrightarrow{C_5H_5N,EtOH} (2)$$

R = $CF_3CH_2CH(CH_3)$-

Scheme I

2-cyano-3-methyl-5,5,5-trifluoropentanoate (6). Although (6) could not be efficiently separated from unreacted excess ethyl cyanoacetate, the impure material was successfully converted to the desired amino acid, essentially by the Darapsky procedure [9,10]. This involved first, treatment with hydrazine hydrate to obtain hydrazide (7), which on reaction with sodium nitrite gave azide (8). This was not isolated but refluxed with ethanol to give the urethane (9), which on acid hydrolysis formed the hydrochloride of (2). This was dissolved in ethanol and treated with pyridine to precipitate the free amino acid. The overall yield in several trials was about 20%, based on (4).

Synthesis of (2) from 2-methyl-4,4,4-trifluoro-1-butanol (11). Scheme II

Electrochemical trifluoromethylation of methyl methacrylate gave a mixture from which, after catalytic hydrogenation of olefinic products and reduction of the ester moiety, alcohol (11) was obtained [11]. The

$$CF_3CH_2CH(CH_3)CH_2OH\ (11) \xrightarrow{C_5H_5NHClCrO_3} RCHO\ (12)$$

$$(12) \xrightarrow{KCN,NH_4Cl,NH_4OH} RCH(CN)NH_2\ (13)$$

$$(13) \xrightarrow{\text{aq. HCl}} (10)$$

$R = CF_3CH_2CH(CH_3)-$

Scheme II

material was oxidized [12] with pyridinium chlorochromate to the aldehyde, (12), which was converted to (10) via the amino nitrile (13), by the Strecker method [13], and then treated as above to obtain (2) in yields of about 25%, based on (11).

Synthesis of (2) from 3-methyl-5,5,5-trifluoropentanoic acid (14). Scheme III

After electrolysis of trifluoroacetic acid in the presence of methallyl cyanide, further treatment of the product mixture afforded (14) in yields of 35 - 40%, based on methallyl cyanide. The acid was brominated in the usual way [14]. Several procedures were tried for the amination of bromoacid (15), and the best results were obtained on simply warming a

$$CF_3CH_2CH(CH_3)CH_2COOH\ (14) \xrightarrow{Br_2,PCl_3} CF_3CH_2CH(CH_3)CHBrCOOH\ (15)$$

$$(15) \xrightarrow{\text{aq. } NH_4OH} (2)$$

Scheme III

solution in excess aqueous ammonia [15]. This synthesis requires the least time and effort, but the other two methods may prove valuable in case an isotopically labelled sample of (2) is desired.

Separation of the diastereomers of (2)

On concentrating aqueous solutions of (2), one obtains as the first solid essentially pure crystals of one diastereomer (2A). Pure crystals of the more water soluble isomer (2B) can be obtained from the material remaining in solution (see below). It is known that DL-isoleucine is considerably less water soluble than DL-alloisoleucine [16], and it seems very unlikely that replacement of a methyl group by trifluoromethyl could reverse the relative solubilities [11]. It was tentatively concluded that (2A) is in fact (1) and (2B) is (3); further work to confirm this assignment is planned. It is probable that (2A) and (2B) can be resolved as described for the parent amino acids [16, 17], but this has not been attempted thus far.

EXPERIMENTAL

Nuclear magnetic resonance spectra were recorded at 34° with a Perkin Elmer R-32 spectrometer at 90 MHz ($^{1}H$) or 84.669 MHz ($^{19}F$). Fluorine shifts were measured with 1,1,2-trichlorotrifluoro-1-propene as external reference, negative values assigned to upfield shifts, and no bulk susceptibility corrections made. The shifts may be converted approximately to the $\phi^*$ scale by adding -62.8 ppm, but such a conversion is never entirely satisfactory because the values are extremely sensitive to even small changes in temperature, solvent composition, or concentration [18]. No attempt was made here to control these variables very precisely.

Melting and boiling points are uncorrected.

3-Methyl-5,5,5-trifluoropentanoic acid (14)

Methallyl cyanide (30.7 mL, 0.312 mol), trifluoroacetic acid (41.5 mL, 0.54 mol) and sodium acetate (1.2 g) were dissolved in 200 mL of aqueous 90% methanol and electrolyzed between platinum electrodes [7] at 1 amp until 0.56 F had passed through the cell. The mixture was poured into 700 mL of water, the dense oil collected, and the aqueous layer extracted with two 40 mL portions of dichloromethane. The combined organic layers from three identical runs were distilled to remove the solvent and then steam distilled. The nonaqueous layer was a mixture of 3-methyl-5,5,5-trifluoropentanonitrile, several isomeric 3-methyl-5,5,5-trifluoropentenonitriles, methallyl cyanide, and unidentified by-products. It was diluted

with methanol and hydrogenated at low pressure over 5% Pd/C. On workup this afforded 66 g of nearly pure 3-methyl-5,5,5-trifluoropentanonitrile, b.p. 166-171°. This was stirred with 210 mL of concentrated aqueous hydrochloric acid for several days, bringing most of the organic material into solution, and then diluted with 210 mL of water and refluxed overnight. The organic layer was isolated, dried, and distilled at 6 torr, giving 58.3 g of (14) (nc), b.p. 76-81°. A sample redistilled at atmospheric pressure had b.p. 200-200.5°. Analysis: Found: C, 42.59; H, 5.58%. $C_6H_9F_3O_2$ requires C, 42.36; H, 5.33%. NMR ($CDCl_3/Me_4Si$): $^{19}F$: -1.26 ppm (t, J = 10.7 Hz). $^1H$: δ 11.25 (1H, s), 1.7-2.7 (5H, c.m.), 1.12 (3H, m).

Isomers (2A) and (2B) of 2-amino-3-methyl-5,5,5-trifluoropentanoic acid (2)

58.3 g (0.343 mol) of (14), 19.1 mL of bromine and 0.6 mL of phosphorus trichloride were refluxed with a trap to absorb gaseous hydrogen bromide until the color of bromine had disappeared. On distilling at 6 torr, about 6 g of (14) were recovered. 60 g of material boiling at 100-106° consisted mainly of nearly equal amounts of the two diastereomers of 2-bromo-3-methyl-5,5,5-trifluoropentanoic acid (15). A 10% solution in chloroform gave two triplet $^{19}F$ NMR signals at -1.35 and -1.87 ppm, each with J = 10.7 Hz. This mixture could be used for the preparation of (2) without further purification.

64.4 g (0.259 mol) of this nearly pure (15) and 225 mL of concentrated aqueous ammonia were cautiously mixed and stored in a closed flask at 44-48° for 4 days. The stopper was removed and the mixture gently heated with a water bath to drive off excess ammonia and reduce the volume to about 90 mL. The cooled mixture deposited 19.8 g of crude solid amino acid (2). The filtrate was evaporated under vacuum at 40-50° and the residue washed with 100 mL of ether, leaving about 35 g of fairly clean 'second solid' consisting mostly of (2) and ammonium bromide. Recrystallization of the first solid from aqueous 20% ethanol gave 10.25 g of pure (2A) (nc), m.p. 284-286° (sealed tube). Analysis: Found: C, 39.28; H, 5.60%. $C_6H_{10}F_3NO_2$ requires C, 38.92; H, 5.44%. NMR (50 mg/mL, 20% $DCl/D_2O$, dioxane): $^{19}F$: -1.18 ppm (t, J = 10.7 Hz). $^1H$: δ 4.22 (1H, br. s.), 2.1 - 2.9 (3H, m), 1.10 (3H, d, J = 6.3 Hz).

After reducing the volume of the mother liquor, a second crop of nearly pure (2A), 5.5 g, was obtained. The filtrate was added to a water solution of the second solid. After decolorizing, the volume was reduced to 90 mL and 15 mL of ethanol were added. On cooling, a further 6.0 g of

amino acid precipitated. The filtrate was acidified with hydrochloric acid and evaporated to dryness. Extraction of the solid residue with several portions of ethanol dissolved the amino acid hydrochloride and allowed most of the ammonium bromide to be removed by filtration. Treatment of the solution with 9 mL of pyridine afforded a further 7.3 g of solid (2) which, by NMR analysis, contained roughly 15% (2A), 85% (2B). The total yield of (2) was 29 g (60%).

When the 7.3 g of (2B)-rich product mixture was dissolved in 25 mL of hot glacial acetic acid, diluted with 25 mL of aqueous 95% ethanol, and chilled, 3.1 g of (2B) (nc) crystallized, which was further purified by recrystallization from 95% ethanol; m.p. 280-282° (sealed tube). Analysis: Found: C, 39.10; H, 5.44%. $C_6H_{10}F_3NO_2$ requires C, 38.92; H, 5.44%. NMR (50 mg/mL, 20% DCl/$D_2O$, dioxane): $^{19}F$: - 0.98 (t, J = 10.8 Hz). $^1H$: $\delta$ 4.19 (1H, d, J = 3.4 Hz), 2.0 - 2.9 (3H, m), 1.11 (3H, d, J = 6.4 Hz).

Preparation of (2) from 4,4,4-trifluoro-2-butanone (4)

Samples of ketone (4) used as starting material in this procedure were of about 92% purity [7]. The ketone (38.0 g, 0.277 mol) was dissolved with 35.4 mL (0.332 mol) ethyl cyanoacetate, 12.7 mL (0.222 mol) acetic acid, and 1.2 g ammonium acetate in 60 mL of benzene. The mixture was refluxed with a water trap for 15 h while adding 10 successive 1.1 g batches of ammonium acetate at roughly equal intervals and then for an additional 2 h. It was cooled, diluted with 25 mL of benzene, and washed with 3 times 30 mL of water. The water solutions were extracted with benzene and the combined benzene layers distilled to remove the solvent. The residue was distilled at 4.5 torr; 52 g of material collected between 73 and 93° consisted mainly of cyanoester (5) and much unreacted ethyl cyanoacetate. This was dissolved in 75 mL ethanol and 10 mL acetic acid and hydrogenated at low pressure over 0.15 g of 5% Pd/C, 0.207 mol hydrogen being taken up. The mixture was poured into water, the oil isolated, and the aqueous layer extracted with dichloromethane. After removal of the solvent from the combined nonaqueous layers, distillation at 0.5 torr yielded 49 g of material at 47-57°. This was roughly 70% saturated cyanoester (6), still containing much ethyl cyanoacetate, but could be used for the next step without further purification. It was mixed with hydrazine hydrate (15.5 g, 0.31 mol) in 50 mL ethanol and allowed to stand overnight. The ethanol was pumped off, the residue dissolved in 95 mL of water, chilled, mixed

with 26 mL concentrated hydrochloric acid in 115 mL water, and covered with 175 mL of ether. Sodium nitrite (19.5 g, 0.282 mol) in 50 mL of water was added to the ice-cold mixture during 0.5 h. After a further 0.5 h of stirring at 0°, 200 mL water was added, the ethereal layer isolated, and the aqueous layer extracted with 4 times 75 mL ether. The combined ether solutions were dried briefly over anhydrous magnesium sulfate; 300 mL absolute ethanol was added and the ether distilled out. The solution was refluxed 2-3 h, until gas evolution had ceased, then cooled and the ethanol removed under vacuum. The residue was refluxed for 48 h with 240 mL of 20% hydrochloric acid, then evaporated to dryness, dissolved in 200 mL water, decolorized, and evaporated again. It was then boiled with 140 mL ethanol, cooled, and filtered to remove the insoluble ammonium chloride. 18 mL of pyridine was added to the solution which, after standing in the refrigerator for several days, afforded 10.2 g of nearly pure, solid (2).

Preparation of (2) from 2-methyl-4,4,4-trifluoro-1-butanol (11)

The starting material (14.2 g, 0.1 mol) was dissolved in 20 mL dichloromethane and added to a suspension of pyridinium chlorochromate (32.3 g, 0.15 mol) in 200 mL of the same solvent. The mixture was stirred for about 2 h after the initial exothermic reaction had subsided and then diluted with 200 mL anhydrous ether. The solid byproducts were filtered off and washed with several 50 mL portions of ether, and the combined ether solutions were concentrated and then distilled, giving 7 g of nearly pure 2-methyl-4,4,4-trifluorobutanal (12) (nc) collected between 104 and 114° (much at 108-109°). NMR ($CDCl_3/Me_4Si$): $^{19}F$: -2.49 ppm (t, J = 11.0 Hz). $^1H$: δ 9.61 (1H, s), 2.4 - 3.0 (2H, c.m.), 1.7 - 2.4 (1H, c.m.), 1.25 (3H, d, J = 6.5 Hz). On treatment with 2,4-dinitrophenylhydrazine it gave the 2,4-dinitrophenylhydrazone of (12), m.p. 132-133°. Analysis: Found: C, 41.28; H, 3.45%. $C_{11}H_{11}F_3N_4O_4$ requires C, 41.26; H, 3.46%.

To a solution of potassium cyanide (9.0 g, 0.135 mol) and ammonium chloride (8.0 g, 0.150 mol) in 55 mL water and 21 mL concentrated ammonium hydroxide, 19.9 g (approx. 0.135 mol) of (12) was added dropwise during 0.5 h while keeping the temperature below 25°. 15 mL ether was added, and the mixture was stirred overnight. It was diluted with 70 mL water and subjected to continuous extraction with ether for 48 h to obtain amino nitrile (13) as a solution in 250 mL ether. Following evaporation of the solvent, the residue was refluxed with 100 mL of aqueous 20% hydrochloric

acid for 24 h, and then evaporated to dryness. The solid products were dissolved in 100 mL water, decolorized, and again evaporated to dryness. The residue was boiled with 80 mL absolute ethanol and filtered to remove ammonium chloride. After treatment with 14 mL pyridine and storage at 0° for several days, the filtrate yielded 13.1 g of nearly pure (2).

REFERENCES


1 R. Filler, in R. E. Banks (Editor), 'Organofluorine Compounds and their Industrial Applications,' Ellis Horwood, Chichester, England, 1979, Ch.6.

2 R. Filler and S. M. Naqvi, in R. Filler and Y. Kobayashi (Editors), 'Biomedical Aspects of Fluorine Chemistry,' Kodansha, Tokyo, Japan, 1982 pp 1-32.

3 J. T. Gerig, in L. J. Berliner and J. Reuben (Editors), 'Biological Magnetic Resonance,' Vol 1, Plenum, New York, 1978, Ch. 4.

4 J. T. Gerig in R. Filler and Y. Kobayashi (Editors), 'Biomedical Aspects of Fluorine Chemistry,' Kodansha, Tokyo, Japan, 1982 pp 163-89.

5 D. F. Loncrini and R. Filler, Adv. Fluorine Chem. 6 (1970) 43.

6 B. D. Sykes and J. H. Weiner, in J. S. Cohen (Editor), 'Magnetic Resonance in Biology,' Vol 1, Wiley, New York, 1980, Ch. 4.

7 N. Muller, J. Org. Chem. 48 (1983) 1370.

8 E. J. Cragoe, Jr., C. M. Robb, and J. M. Sprague, J. Org. Chem. 15 (1950) 381.

9 J. P. Greenstein and M. Winitz, 'Chemistry of the Amino Acids,' Vol 1, Wiley, New York, 1961, p. 704; also Vol 3, p. 2388.

10 P. A. S. Smith, in R. Adams, (Editor), 'Organic Reactions,' Vol 3, Wiley, New York, 1946, p. 385.

11 N. Muller, J. Pharm. Sci. 75 (1986) 987.

12 E. J. Corey and J. W. Suggs, Tetrahedron Lett. (1975) 2647.

13 R. Gaudry, Can. J. Res. 24B (1946) 301.

14 A. I. Vogel, 'A Text-book of Practical Organic Chemistry,' 3rd Ed., Longmans, Green and Co, London, 1956, p. 430.

15 C. S. Marvel, Org. Syn. Coll. Vol 3 (1955) 495.

16 W. A. H. Huffman and A. W. Ingersoll, J. Am. Chem. Soc. 73 (1951) 3366.

17 J. P. Greenstein, L. Levintow, C. G. Baker, and J. White, J. Biol. Chem. 188 (1951) 647.

18 N. Muller, J. Magn. Reson. 28 (1977) 203.