Tetrahedron Letters,Vol.26,No.20,pp 2445-2448,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

FLUORINE-CONTAINING AMINO ACIDS AND THEIR DERIVATIVES. 6.[1] AN EFFICIENT SYNTHESIS OF β-FLUORINATED ALANINES VIA FLUOROHALOMETHYLATION OF AMINOMALONATES

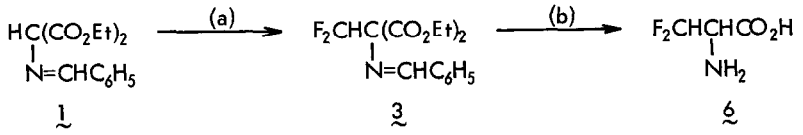
Tadahiko Tsushima* and Kenji Kawada
Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

Abstract: Aminomalonates, e.g., 1 and 2, smoothly reacted with difluoro- and chlorofluorocarbene to produce the adducts (3, 4, and 5) in good yields. These products were successfully converted to various versatile β-fluorinated alanine derivatives, i.e., β,β-difluoroalanine (6), N-acyl-β-fluorodehydroalaninate (7), and fluoropyruvic acid (8).

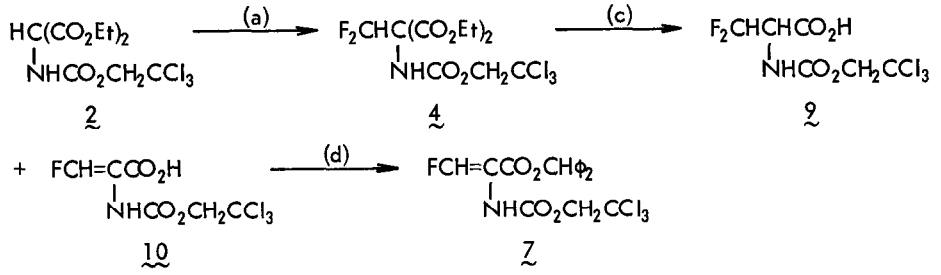
Some β-fluorinated amino acids have been receiving increasing attention as suicide substrates with various interesting biological activities.[2] As a part of our studies in this field, we recently reported on the stereoselective synthesis of both erythro and threo diastereomers of β-fluorophenylalanine via direct fluorination of phenylpyruvates.[3] Usually, the synthesis of these compounds requires the use of toxic or dangerous fluorinating reagents.[4] To circumvent the use of such reagents, an attractive method is the fluorohalomethylation reaction[5] for the synthesis of fluoroamino acids. Several studies of this kind have already been reported,[6] but successful results have only been obtained with tertiary substituted compounds, such as alkyl-substituted malonates or amino acids, and not with the secondary cases, such as unsubstituted malonates or glycinates, as complex products are formed instead. To overcome this problem, we conceived of using nitrogen-substituted malonates, e.g., aminomalonates, as substrates in this halomethylation to prepare fluorohalomethylated glycines which could not be obtained directly from the reaction with unsubstituted glycine. Here we report a convenient synthesis of various β-fluorinated alanine derivatives, i.e., β,β-difluoroalanine (6), N-acyl-β-fluorodehydroalaninate (7), and fluoropyruvic acid (8), via fluorohalomethylation of aminomalonates (1 and 2).

After careful examination of the reaction conditions, we found that the carbanion generated from the Schiff base of diethyl aminomalonate (1) upon treatment with 3 equiv of the sodium salt of the non-nucleophilic base, bis(trimethylsilyl)amine, in tetrahydrofuran could react smoothly with difluorocarbene at -30°C to give the difluoromethylated product (3) in a good yield of more than 50% (Scheme 1). This product (3) was subsequently hydrolyzed and decarboxylated under acidic conditions to β,β-difluoroalanine (6)[7] in 36% overall yield from 1. β,β-Difluoroalanine (6) has been prepared previously either by photofluorination of alanine or by fluorodesulfurization of cysteine but only in extremely low yield, e.g., a maximum of 3%.[8] Also, both methods require dangerous reagents, fluoroxytrifluoro-

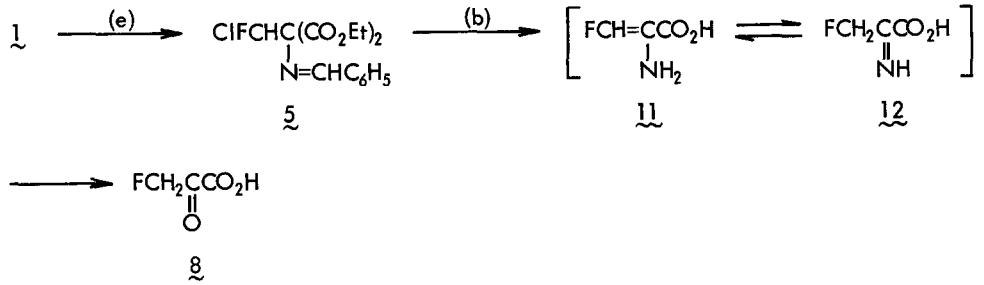
Scheme 1



Scheme 2



Scheme 3



(a) $CHClF_2$, $NaN(SiMe_3)_2/THF$. (b) 3N-HCl 80℃. (c) Me_3SiI reflux.
(d) (i) Φ_2CN_2/CH_2Cl_2 (ii) Et_3N/CH_2Cl_2. (e) $CHCl_2F$, $NaN(SiMe_3)_2/THF$.

methane or elementary fluorine. Therefore, our method is the first practical and convenient route to 6.

To also conveniently prepare β-fluorodehydroalaninates, we examined the same reaction with the anion derived from the carbamate of diethyl aminomalonate (2) and obtained the difluoromethylated product (4)[7] in 41% yield (Scheme 2). This product (4) was extremely resistant to acid hydrolysis. Our attempts to hydrolyze the ester (4) under basic conditions also failed, resulting in defluorination.[9] Therefore, this product (4) was hydrolyzed and decarboxylated to a mixture of N-acyl-β,β-difluoroalanine (9) and N-acyl-β-fluorodehydroalanine (10) by treatment with iodotrimethylsilane. Esterification of the resulting products (9 and 10) followed by elimination of hydrogen fluoride with triethylamine led to the desired product, N-acyl-β-fluorodehydroalaninate (7),[7] in 58% overall yield from 4.

Compound 7 may be used as a versatile synthon in the synthesis of various β-fluorinated amino acids.

Chlorofluorocarbene was also found to react with the sodium salt of 1 under proper conditions at 10°C to give the chlorofluoromethylated derivative (5)[7] in almost the same yield as described above (Scheme 3). Compound 5 was easily converted to fluoropyruvic acid (8)[7] under acidic conditions through hydrolysis and decarboxylation in 31% overall yield from 1. The reaction probably occurs with the dehydroalanine intermediate (11) being formed first after a series of reactions including hydrolysis, decarboxylation, and dechlorination. This enamine intermediate (11), existing in the equiribrium with the imine form (12), is then converted to the final product, fluoropyruvic acid (8), upon hydrolysis. Fluoropyruvic acid (8) has previously been prepared from ethyl fluoroacetate[10] and used as a starting material for the synthesis of the well-known antibacterial agent, β-fluoro-D-alanine-α-d.[11] Our method, which avoids the use of very toxic ethyl fluoroacetate, provides an alternative route for 8.

In conclusion, we found fluorohalomethylation of aminomalonates (1 and 2) to be a useful and convenient method for preparing of various β-fluorinated alanine derivatives, i.e., β,β-difluoroalanine (6), N-acyl-β-fluorodehydroalaninate (7), and fluoropyruvic acid (8).

Acknowledgement. We thank Dr. Y. Terui and Miss S. Tominaga for their help with the NMR spectroscopic measurements and interpretation.

REFERENCES AND NOTES

(1) Part 5: Tsushima, T.; Kawada, K.; Shiratori, O.; Uchida, N. Heterocycles 1985, 23, 7539.

(2) (a) For recent reviews, see: Kollonitsch, J. In "Biochemical Aspects of Fluorine Chemistry"; Filler, R.; Kobayashi, Y., Eds.; Kodansha Ltd. and Elsevier Biomedical: Tokyo and New York, 1982; pp 93-122 and Walsh, C. Tetrahedron 1982, 38, 871. (b) For the biological activity of β,β-difluoroalanine, see: Wang E. A.; Walsh, C. Biochemistry 1981, 20, 7539.

(3) Tsushima, T.; Kawada, K.; Nishikawa, J.; Sato, T.; Tori, K.; Tsuji, T.; Misaki, S. J. Org. Chem. 1984, 49, 1163 and our papers cited therein.

(4) Hudlicky, M. "Chemistry of Organic Fluorine Compounds: A Laboratory Manual"; Ellis Horwood: Chichester, England, 1976.

(5) Shen, T. Y.; Lucas, S.; Sarett, L. H. Tetrahedron Lett. 1961, 43.

(6) (a) Bey, P.; Ducep, J. B.; Schirlin, D. Tetrahedron Lett. 1984, 25, 5657 and their papers cited therein. (b) Ref. 1.

(7) Some of the compounds characterized are as follows. 3: ^{1}H NMR ($CDCl_3$) δ 1.28 (6 H, t, J = 7.0 Hz, 2 CH_3), 4.32 (4 H, q, J = 7.0 Hz, 2 CH_2), 6.45 (1 H, t, J = 54.5 Hz, CHF_2), 7.20-7.97 (5 H, m, arom. H), 8.57 (1 H, s, CHAr); ^{19}F NMR ($CDCl_3$) δ (C_6F_6) 33.17 (2 F, d, J_{HF} = 54.5 Hz). 4: IR ($CHCl_3$) ν_{max} 3400 (NH), 2960 (CH_3), 1745 (ester and urethane C=O), 1490, 1370, 1320-1160 (ester), 1100, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (6 H, t,

J = 7.0 Hz, 2 $C\underline{H}_3$), 4.35 (4 H, q, J = 7.0 Hz, 2 $C\underline{H}_2CH_3$), 4.74 (2 H, s, $C\underline{H}_2CCl_3$), 6.34 (1 H, s, N$\underline{H}$), 6.50 (1 H, t, J_{HF} = 53.6 Hz, $C\underline{H}F_2$); ^{19}F NMR ($CDCl_3$) δ (C_6F_6) 31.83 (2 F, d, J_{HF} = 53.6 Hz); MS m/z 406, 404, 402, and 400 (M^+ + H), 368, 366, and 364 (M^+ - Cl), 332, 330, 328, and 326 (M^+ - CO_2Et), 158 ($C_5H_8O_2NF_2$). 5: ^{1}H NMR ($CDCl_3$) δ 1.46 (3 H, t, J = 7.0 Hz, $C\underline{H}_3$), 1.47 (3 H, t, J = 7.0 Hz, $C\underline{H}_3$), 4.32 (2 H, q, J = 7.0 Hz, $C\underline{H}_2$), 4.35 (2 H, q, J = 7.0 Hz, $C\underline{H}_2$), 6.87 (1 H, d, J_{HF} = 48.0 Hz, $C\underline{H}ClF$), 7.23-8.03 (5 H, m, arom. H), 8.65 (1 H, s, $C\underline{H}Ar$); ^{19}F NMR ($CDCl_3$) δ (C_6F_6) 18.23 (1 F, d, J_{HF} = 48.0 Hz). 6: mp 167-170°C (dec.); IR (KBr disc) ν_{max} 3600-2500 (NH_3^+), 1720-1560 (CO_2^- and NH_3^+), 1530, 1410, 1365, 1345, 1135, 1095, 1030, 720 cm^{-1}; ^{1}H NMR (D_2O) δ (ext. Me_4Si) 4.37 (1 H, ddd, J_{HF} = 23.5 Hz, J_{HF} = 8.5 Hz, J_{HH} = 2.5 Hz, $C\underline{H}N$), 6.72 (1 H, td, J_{HF} = 53.3 Hz, J_{HH} = 2.5 Hz, $C\underline{H}F_2$); ^{19}F NMF (D_2O) δ (ext. CF_3CO_2H) - 50.66 (1 F, ddd, J_{FF} = 282.2 Hz, J_{HF} = 53.3 Hz, J_{HF} = 23.5 Hz), - 44.88 (1 F, ddd, J_{FF} = 282.2 Hz, J_{HF} = 53.3 Hz, J_{HF} = 8.5 Hz); MS m/z 125 (M^+), 80 (M^+ - CO_2H), 74 (M^+ - CHF_2), 30 ($CH_2{=}NH_2$). Anal. Calcd for $C_3H_5O_2NF$: C, 28.81; H, 4.03; N, 11.20; F, 30.38. Found: C, 28.66; H, 3.98; N, 11.35; F, 30.38. 7: mp 94-95°C; IR ($CHCl_3$) ν_{max} 3405 (NH), 1730 (ester and urethane C=O), 1675 (C=C), 1600 and 1490 (arom.), 1450, 1375, 1300-1140 (ester), 1120, 1090, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.70 (2 H, s, $C\underline{H}_2CCl_3$), 6.35 (1 H, s, N$\underline{H}$), 6.95 (1 H, s, $C\underline{H}Ar_2$), 7.30 (10 H, s, arom. H), 7.59 (1 H, d, J_{HF} = 74.3 Hz, $C\underline{H}F$); ^{19}F NMR ($CDCl_3$) δ (C_6F_6) 46.32 (1 F, d, J_{HF} = 74.3 Hz). Anal. Calcd for $C_{19}H_{15}O_4NFCl_3$: C, 51.09; H, 3.38; N, 3.14; F, 4.25. Found: C, 51.32; H, 3.63; N, 3.51; F, 4.14. Semicarbazone of 8: mp 205-210°C (dec.) (lit.[10] 205°C).

(8) Kollonitsch, J.; Marburg, S.; Perkins, L. M. J. Org. Chem. 1976, 41, 3107.

(9) The hydrolysis reactivity of 4 resembled those of difluoromethylated alkyl-substituted malonates. See ref. 6 (a).

(10) (a) Blank, I.; Mager, J.; Bergmann, E. D. J. Chem. Soc. 1955, 2190. (b) Nair, P. V.; Busch, H. J. Org. Chem. 1958, 23, 137.

(11) Dolling, U.-H.; Douglas, A. W.; Grabowsky, E. J. J.; Schoenewaldt, E. F.; Sohar, P.; Sletzinger, M. J. Org. Chem. 1978, 43, 1634.

(Received in Japan 9 February 1985)