Synthetic Studies for Novel Structure of α-Nitrogenously Functionalized α-Fluorocarboxylic Acids. II.[1] Synthesis and Some Reactions of α-Fluoro-α-nitrocarboxylic Ester and Carboxamide Derivatives

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The first synthesis of α-fluoro-α-nitrocarboxamides 11b, c has been achieved by ammonolysis of the corresponding ethyl esters 6b, c. However, α-fluoro-α-nitrocarboxylic acids 8a—c derived from the corresponding esters 6a—c were found to decarboxylate readily to form 1-fluoro-1-nitroalkanes 9a—c. Reduction of the α-fluoro-α-nitrocarboxamide derivatives 11b, c produced the defluorination products 12b, c instead of the desired novel α-fluoro-α-aminocarboxamide 2.

Keywords α-fluoro-α-amino acid; fluoroglycine; fluorination; perchloryl fluoride; α-fluoro-α-nitrocarboxamide; α-nitrocarboxamide; reductive defluorination

α-Fluoro-α-amino acids **1** and the amides **2** have aroused much interest from both biological[2] and structural[3] chemistry viewpoints. However, the interest has been theoretical, since no report of success in the construction of such α-halogenated amino acid structures exists in the literature. We have recently reported[1] the first synthesis of some *N*-protected α-fluoroglycine derivatives, **3** and **4**, and the attempted conversion of them into α-fluoroglycine **1** (R = H) itself. However, we could not find conditions mild enough for complete removal of the *N*-protecting groups in **3** or **4** without damaging the C–F bond. We therefore attempted the synthesis of novel α-fluoro-α-nitrocarboxylic acid and α-fluoro-α-nitrocarboxamide precursors and the conversion of these new candidates into the α-fluoro-α-amino acid derivatives. The chemical behavior of the geminally functionalized molecules toward hydrogenolysis was also a point of interest.

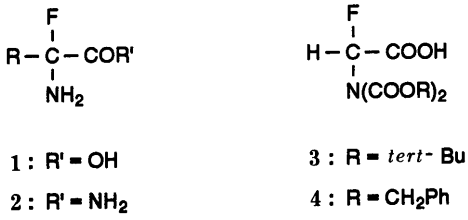

Fig. 1

Results and Discussion

In our previous work,[1] we selected bis(alkoxycarbonyl)-amino groups as an amino group precursor, as shown by the structures **3** and **4**. However, the carbamate structure generated at the final deprotecting stage easily formed an oxazolone with a free carboxylic acid, ultimately producing unwanted products instead of the free amine. We have therefore focused on the nitro group as an amino functionality precursor, since a nitro group can usually be reduced easily into an amino group under neutral conditions. Furthermore, fluorination of the position α to the nitro group seemed to proceed smoothly.[4]

The direct introduction of a nitro group into fluorocarboxylic esters proved to be difficult.[5] Therefore, some α-fluoro-α-nitrocarboxylic acid esters **6a—c** were prepared by direct fluorination of ethyl nitroacetate **5a** with perchloryl fluoride[6] or by fluorination of alkylated products **5b, c** which were prepared from **5a**.[7] Reduction of **6a—c** with H_2/Pd–C, H_2/Raney Ni T-1,[8] or H_2/Pd–$BaSO_4$,[9] however,

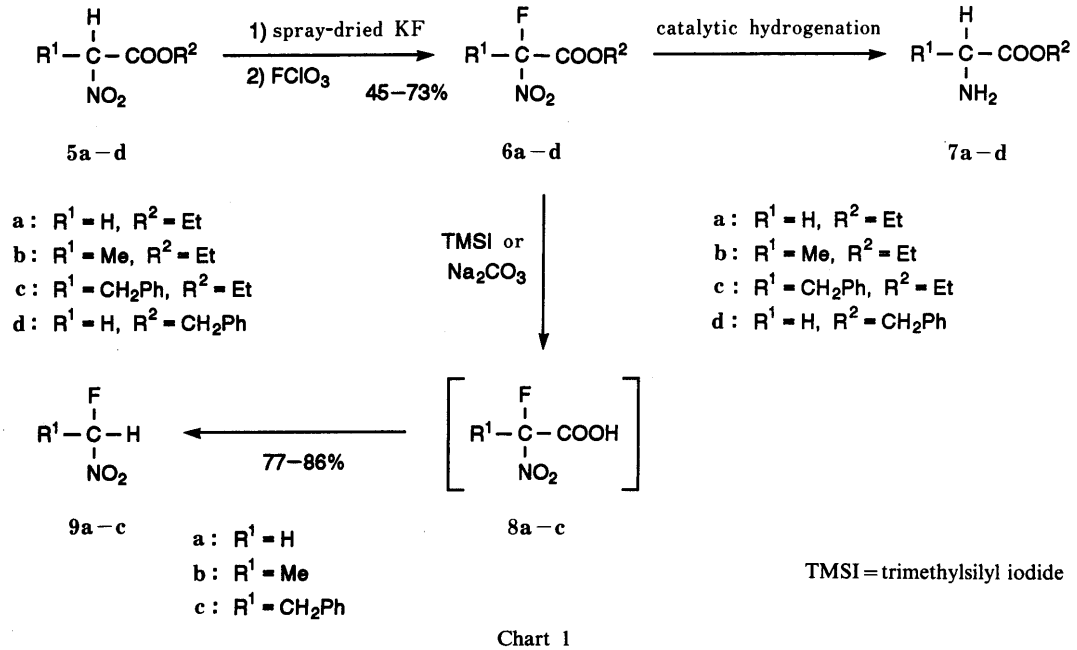

Chart 1

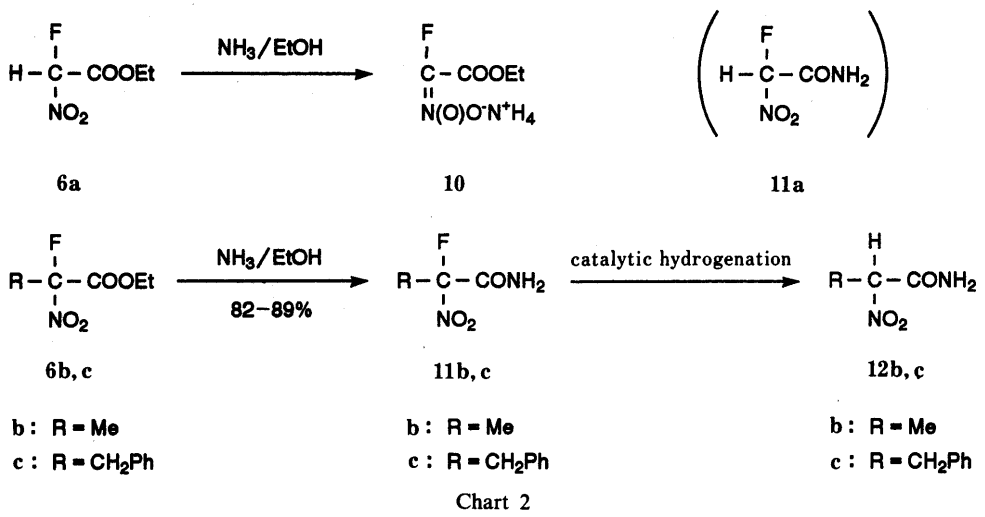

Chart 2

did not afford the desired products, usually giving the corresponding amino acid ethyl esters **7a—c** in good yield.

We thought that the free carboxylate form, which is deactivated as compared with the ester, would allow us to avoid the problematic step of hydrogenative defluorination. However, attempted conversion of the ethyl esters **6a—c** into the corresponding carboxylic acids **8a—c** by saponificative[10] and nonsaponificative[11] methods resulted in the formation of the decarboxylated[12] products **9a—c** instead of the desired **8a—c**.

We next focused on the benzyl ester **6d**, an analogous compound to the ethyl esters **6a—c**. Hydrogenative debenzylation and concomitant reduction of the nitro group should certainly form the zwitterion of the target structure **1**.[1] Thus, benzyl α-fluoro-α-nitroacetate **6d** prepared from benzyl nitroacetate **5d**[13] was subjected to hydrogenation using Pd–C or Raney Ni T-1[8] as a catalyst. However, only glycine benzyl ester **7d** was obtained, which suggested that both cleavage of the fluorine atom and reduction of the nitro group had proceeded prior to debenzylation (Chart 1).

The second carbonyl candidate chosen as an alternative to the ester group was the corresponding carboxamide structure, which would be expected to suppress the removal of fluorine under conditions of hydrogenolysis. However, the synthesis of α-fluoro-α-nitrocarboxamides has not yet been reported. Reaction of **6a** with ethanolic ammonia did not give the corresponding amide **11a**, yielding instead simply the salt **10**, presumably due to the presence of a proton α to the nitro group. We then investigated alkylated analogues having no acidic protons. Treatment of **6b, c** with ethanolic ammonia produced successfully the desired amides **11b, c** (82—89%).

The key compounds **11b, c** now being in hand, we started to investigate their possible conversion into the novel α-amino-α-fluorocarboxamide structure **2**. α-Fluoro-α-nitrocarboxamides **11b, c** were submitted to reduction under various conditions.[8,9,14–16] To our extreme disappointment again no amine compounds were obtained and the only detectable products were the defluorinated amides **12b, c**. Therefore, direct defluorination occurred before nitro group reduction even for the amide structure (Chart 2).

In the course of our study, we showed that α-fluoro-α-nitrocarboxamides can be obtained as stable molecules, although we were unable to achieve the construction of an α-amino-α-fluorocarboxamide structure. We are now investigating the use of an azido group as an amino group precursor, since an azido group can generally be reduced much more easily than the corresponding nitro group.[17] However, the synthesis of α-azido-α-fluorocarboxylic acid derivatives seems at this time to be very challenging.

Experimental

Infrared (IR) spectra were recorded on a JASCO A-102 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured in $CDCl_3$, unless otherwise noted, with Me_4Si as an internal standard and recorded on JEOL PMX-60 (60 MHz), Varian XL-200 (200 MHz), and JEOL GX-270 (270 MHz) spectrometers. ^{19}F-NMR spectra were measured in $CDCl_3$ with $CFCl_3$ as an internal standard and taken with a JEOL GX-270 (254 MHz) spectrometer. Upfield shifts are quoted as negative. Electron impact mass spectra (EI-MS) were taken with a JEOL JMS-D300 spectrometer. Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Elemental analyses were performed with a Hitachi 026 elemental analyzer. Column chromatography and preparative thin layer chromatography were performed using Kieselgel 60 (Merck, Art. 9385 and Art. 7748, respectively). α-Fluoro-α-nitrocarboxylic esters **6a—c** were prepared according to our method.[18]

Benzyl Fluoronitroacetate (6d) Spray-dried KF[19] (1.16 g, 20 mmol) was added to a solution of benzyl nitroacetate **5d** (1.95 g, 10 mmol) in dry MeOH (30 ml), and the mixture was stirred at room temperature for 0.5 h. The solvent was evaporated off, and the residual salt was dissolved in dry tetrahydrofuran (THF) (50 ml). Into this solution was introduced diluted perchloryl fluoride generated from $KClO_4$ (4 g) and FSO_3H (40 g) at 0 °C for 1 h. Evaporation of the solvent gave a solid, which was dissolved in AcOEt (50 ml) and washed with water (10 ml). The organic layer was dried on $MgSO_4$ and concentrated to give an oil. Purification by silica gel chromatography gave **6d** as a colorless oil in 54% yield (1.15 g). IR ν_{max}(neat) cm^{-1}: 1770 (CO), 1590 (NO_2). ^{1}H-NMR δ: 5.3 (2H, s, CH_2), 6.0 (1H, d, J=48 Hz, CH), 7.3 (5H, s, Ph). MS m/z: 213 (M^+), 267 (M^+-NO_2), 266 (M^+-HNO_2). High MS: Calcd for $C_9H_8FNO_4$ (mol. weight 213.0435), Found: 213.0397 (M^+). Calcd for $C_9H_8FO_2$ (mol. weight 167.0508), Found: 167.0478 (M^+-NO_2). Calcd for $C_9H_7FO_2$ (mol. weight 166.0428), Found: 166.0416 (M^+-HNO_2).

General Procedure for Catalytic Hydrogenation of α-Fluoro-α-nitrocarboxylic Acid Esters (6a—d) A solution of one of **6a—d** (2.5 mmol) in EtOH (50 ml) was hydrogenated over Pd–C, Raney Ni T-1,[8] or Pd–$BaSO_4$[9] using a Parr apparatus (4 kg/cm^2) for 20—24 h. Removal of the catalyst and evaporation of the solvent afforded the corresponding amino acid ethyl or benzyl ester **7a—d** as a colorless oil in 68—81% yield. The products were characterized through the spectral data.[20]

Hydrolysis of α-Fluoro-α-nitrocarboxylic Acid Esters (6a—d) The esters **6a—d** were hydrolyzed by a saponificative[10] or non-saponificative[11] method according to the literature. After usual work-up, 1-fluoro-1-nitroalkanes **9a—c** were obtained as colorless oils in 77—86% yields. The products were characterized through the spectral data.[18]

General Procedure for Preparation of α-Fluoro-α-nitrocarboxamides (11b, c) A solution of an ethyl ester **6b** or **c** (2 mmol) in EtOH (5 ml) was added to ammonia-saturated EtOH (15 ml) in an ice-bath and the whole was stirred at 0 °C for 2 h. Evaporation of the solvent under reduced pressure afforded colorless crystals, which were collected on a filter and dried.

2-Fluoro-2-nitropropionamide (11b) Colorless leaflets in 82% yield (224 mg). mp 50.0—50.5 °C (CCl_4/hexane). IR ν_{max} (KBr) cm^{-1}: 3400 (NH), 1690 (CO), 1570 (NO_2). ^{1}H-NMR δ: 2.13 (3H, d, J(H-F) = 21.0 Hz, Me), 6.57 (2H, br s, NH_2). ^{19}F-NMR δ: −123.78 (q, J(F-H) = 20.8 Hz). MS m/z: 136 (M^+), 90 ($M^+ - NO_2$), 46 ($M^+ - NO_2 - CONH_2$). *Anal.* Calcd for $C_3H_5FN_2O_3$: C, 26.48; H, 3.70; N, 20.59. Found: C, 26.27; H, 3.72; N, 20.47.

2-Fluoro-2-nitro-3-phenylpropionamide (11c) Colorless needles in 89% yield (377 mg). mp 116.5—118.5 °C ($CHCl_3$). IR ν_{max} (KBr) cm^{-1}: 3450 (NH), 1690 (CO), 1570 (NO_2). ^{1}H-NMR δ: 3.72 (1H, dd, J(H_a-F) = 21.5, J(H_a-H_b) = 14.9 Hz, CH_aH_b), 3.89 (1H, dd, J(H_b-F) = 26.5, J(H_b-H_a) = 14.9 Hz, CH_aH_b), 5.83 (1H, br s, NH_aH_b), 6.23 (1H, br s, NH_aH_b), 7.30—7.34 (5H, m, Ph). ^{19}F-NMR δ: −131.86 (dd, J(F-H_b) = 26.5, J(F-H_a) = 21.5 Hz). MS m/z: 212 (M^+), 166 ($M^+ - NO_2$), 122 ($M^+ - NO_2 - CONH_2$), 103 ($M^+ - NO_2 - CONH_2 - F$), 91 ($PhCH_2^+$). *Anal.* Calcd for $C_9H_9FN_2O_3$: C, 50.95; H, 4.28; N, 13.20. Found: C, 51.13; H, 4.36; N, 13.32.

General Procedure for Reduction of α-Fluoro-α-nitrocarboxamides (11b, c) A solution of **11b** or **c** (2 mmol) in EtOH (40 ml) was hydrogenated over Raney Ni T-1,[8] Raney Ni T-4,[14] Pd–$BaSO_4$,[9] or PtO_2[15] using a Parr apparatus (4 kg/cm^2) for 10—36 h. Removal of the catalyst and evaporation of the solvent under reduced pressure afforded the corresponding α-nitrocarboxamide derivative **12b** or **c** as a colorless solid in 68—77% yield. These products were characterized through spectral data.[20]

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