Synthesis of N-Alkylated 4-Fluoro-5-phenylpyrrole-2-carboxylate via Isolable Pyrroline Ionic Intermediates

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Organic fluorine chemistry produces many useful products. This paper elucidates the reaction of ethyl-4,4-difluoro-2-iodo-5-oxo-5-phenylpentanoate (2) with primary amines in a one-pot scheme. The reaction produced a series of β-fluoropyrrole derivatives at ambient temperatures. In this reaction, the less bulky the primary amine the higher was the resultant yield. When (2) and aqueous methylamine (40%) were allowed to react below 0 °C, 5-(ethoxycarbonyl)-3-methyl-3,3-difluoro-2-hydroxy-2-phenylpyrrolidine, an intermediate molecule for 2-ethyl-4-flouro-1-methyl-5-phenylpyrrole-2-carboxylate (5), was isolated first. Then, (5) reacted with hydroperchloric acid and acetic anhydride to form 5-(ethoxycarbonyl)-1-methyl-3,3-difluoro-2-phenylpyrroline perchlorate (6), which was converted to 2-ethyl-4-flouro-1-methyl-5-phenylpyrrole-2-carboxylate gradually in the presence of a base. Our experiments demonstrate that the formation of 2-ethyl-4-flouro-1-methyl-5-phenylpyrrole-2-carboxylate occurs via both one-pot schemes and stepwise pathways, depending on the reaction conditions. The isolation and characterization of the isolated intermediate (6) suggest an anionic pathway for this reaction.

Key Words: β-Fluoropyrrole, Pyrrole derivatives, Anionic pathway

Introduction

Organic fluorine chemistry has attracted wide interest in pharmaceutical and medical research involving drug delivery and physiological activities. Recent advances in medicine are partially based on the development of proper compounds of biological activities. Especially, selective fluorination of organic compounds is very important because their biological activities can be greatly modified by the presence of fluorine atoms at specific sites in the molecules. Pyrrole derivatives have been examined thoroughly for antimicrobial activity because of the recent resurgence of tuberculosis, which is due to several factors, three of which are the most difficult to overcome. They are multiple drug-resistant, or MDR, strains of Mycobacterium tuberculosis versus the conventional therapeutic regimens, the particular virulence of M. avium, very often responsible for the death of HIV-infected patients, and the particularly resistant mycobacterium cell wall structure, which is very waxy and hydrophobic, with a high lipid content. The cell wall presents a lipidic bilayer and a peptidoglican layer (as that of the bacteria) and a thick mycolate rich outer covering that functions as an exceptionally efficient barrier. Thus, in this case, the search for new active compounds possessing a different mode of action could be very useful. Previous studies on the effect of pyrrole derivatives modified their boundary substituents systematically. However, pyrroles with fluorine atoms directly attached have not been studied for this purpose yet. Selectively fluorinated pyrrole compounds also have been known to exhibit valuable biological properties, such as fungicidal, bactericidal, and analgesic activities.

Only a few synthetic methods for the preparation of β-fluoropyrroles have been reported. They include the ring expansion of 2-azido-3,3-difluorocyclobutene, the thermal [2+3] cycloaddition of 2-carbonethoxy-1-t-butyl-aziridine with chlorotrifluoroethylene, the photoreaction of pyrrole-β-diazoniumtetrafluoroborate, and the reaction of 3-bromo-1-(trisopropylsilyl)pyrrole with N-fluorobenzene sulfonamide. However, all of these methods have drawbacks inherent in their multiple reaction schemes, and relatively harsh reaction conditions would further limit economic use of them. Moreover, these methods often require the blocking of the amino group in the pyrroles before the introduction of substituents to the pyrrole ring.

In the present report, we develop better economic preparative methods via a reduced reaction scheme. We herein report the synthesis of 2-carboxylate derivatives of N-substituted-β-fluoropyrroles from ethyl-4,4-difluoro-2-iodo-5-phenylpentanoate, which works by a very efficient pathway under mild conditions. A possible reaction mechanism for the synthesis is suggested, which is supported by the separation and identification of the intermediates.

Experimental Section

General. 19F NMR were recorded on a JEOL FX90Q (83.81 MHz) or Bruker AC-300 (282.44 MHz); spectra were recorded on the AC-300 spectrometer. All samples were taken in CDCl3 solvent and all chemical shifts are reported in parts per million downfield (positive) of the standard: TMS of 1H and 13C; CFCI3 for 19F NMR. FT-IR spectra were recorded as CCl4 solutions and reported in wavenumber (cm−1) GC-MS spectra were obtained at 70 eV in the
5-(Ethoxycarbonyl)-1-methyl-3,3-difluoro-2-hydroxy-2-phenylpyrroline (5). A 50 mL round bottom flask was charged with 0.78 mL of methylamine and 1 mL water (40% H2O solution). The solution was cooled at 0 °C; then 0.95 g (2.5 mmol) of 2 was added via syringe. After 1 hour, the reaction mixture was extracted with 5 mL dichloromethane, washed in deionized water, and separated by column chromatography (Rf: 0.73) (ethyl acetate/n-hexane, 1:3). The white solid of diastereomeric mixture 5 (0.65 g, 92%) was obtained. mp 85-86 °C; 19F-NMR (CDCl3) δ = 93.91 (d, J = 226.8 Hz, JHF = 17.8 Hz), 98.54 (d, J = 228.9 Hz, JHF = 21.6 Hz), 109.10 (dd, J = 226.3 Hz, JHF = 5.1 Hz), 115.49 (dd, J = 226.4 Hz, JHF = 10.2 Hz); 1H-NMR (CDCl3) δ = 7.61 (m, 2H), 7.36 (m, 3H), 4.83 (m, 4H), 4.24 (m, 2H), 4.13 and 3.76 (m, 1H), 2.77 (m, 1H), 2.50 (m, 1H), 2.35 and 2.30 (m, 1H), 1.30 (m, J = 7.2 Hz); 13C-NMR (CDCl3): δ = 179.14 (s), 172.10 (s), 135.96 (s), 127.90 (s), 125.15 (d, J = 63.5 Hz, JHF = 3.5 Hz), 121.74 (d, J = 61.2 Hz, JHF = 25.7 Hz, 92.11 (t, J = 25.0 Hz), 68.27 (s), 61.15 (s), 60.88 (s), 36.34 (t, J = 26.9 Hz), 35.06 (t, J = 25.3 Hz), 32.41 (s), 29.89 (s) 14.10 (s), 13.99 (s); FT-IR (CCl4) 2959, 2996, 1653 cm⁻¹; GC-MS (relative intensity) 285 (M⁺), 268 (-OH, 30.01), 266 (-C=H, 37.05). HRMS observed, 285.1125, C14H12F2NO2F, calculated, 285.1177.

5-(Ethoxycarbonyl)-1-methyl-3,3-difluoro-2-phenylpyrroline perchlorate (6). A 50 mL round flask was charged with 0.5 g (1.8 mmol) of 5 and 1.3 mL of acetic anhydride, and 1.6 mL (2.7 mmol) of hydroperchloric acid was added under nitrogen gas. After the flask was stirred for 20 minutes, anhydrous diethyl ether (5 mL) was added. The colorless compound was crystallized out and filtered before re-crystallization from dry dichloromethane and anhydrous ethyl ether. A white solid 6 (0.59 g, 91%) was obtained. mp 140-142 °C; 19F-NMR (DMSO-d₆ and CDCl3) δ = 95.38 (dd, J = 288.9 Hz, 21.7 Hz, 9.0 Hz, 1F), −93.88 (dd, J = 267.3 Hz, 19.9 Hz, 9.0 Hz, 1F); 1H-NMR (DMSO-d₆ and CDCl3) δ = 7.80 (m, 5H), 4.40 (t, J = 7.0 Hz), 4.02 (s, 1H), 3.15 (m, 3H), 1.38 (t, J = 7.2 Hz); 13C-NMR (DMSO-d₆ and CDCl3) δ = 174.07 (t, J = 29.9 Hz), 164.48 (s), 136.15 (s), 130.13 (s), 129.27 (s), 128.27 (s), 125.50 (d, J = 250.3 Hz), 122.15 (d, J = 250.3 Hz), 120.86 (s), 69.85 (s), 63.40 (s), 41.05 (s), 34.25 (t, J = 24.0 Hz), 13.10 (s); FT-IR (CCl4) 2998, 2338, 2310, 1717, 1616, 1406 cm⁻¹. HRMS observed, 322.0854, C14H12F2NO2F, calculated, 322.0946.

Ethyl-4-fluoro-1H-5-phenylpyrrole-2-carboxylate (4a). A 50 mL round flask was charged with 0.3 mL aqueous ammonia solution (29% H₂O solution) and 1 mL water. The solution was cooled at 0 °C and then 0.5 g (1.3 mmol) starting material (2) was added slowly via a syringe. After 1 hour of stirring, the reaction mixture was extracted with 10 mL dichloromethane, washed with water, dried with anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography (Rf: 0.68) (ethyl acetate/n-hexane, 1:3). A white solid 4a (0.22 g, 73%) was obtained. mp 110-111 °C; 19F-NMR (CDCl3) δ = –159.25 (s, 1F); 1H-NMR (CDCl3) δ = 7.59 (d, J = 7.5 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 6.59 (d, J = 2.8 Hz, 1H), 4.20 (q, J = 7.3 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H); 13C-NMR (CDCl3) δ = 132.13 (d, J = 4.9 Hz, 128.77 (s, J = 127.5 Hz), 125.25 (d, J = 4.5 Hz), 161.43 (d, J = 3.6 Hz), 120.93 (d, J = 19.1 Hz), 117.86 (d, J = 7.3 Hz), 103.34 (d, J = 15.6 Hz), 60.84 (s), 14.30 (s); FT-IR (CCl4) 2959, 1635 cm⁻¹; GC-MS (relative intensity) 237 (M⁺), 187 (-OEt, 100); HRMS observed, 233.0826 (M⁺), C13H14O4NF, calculated, 233.0852.

Ethyl-4-fluoro-1-methyl-5-phenylpyrrole-2-carboxylate (4b). (a) A 50 mL round flask was charged with 0.27 g (1 mmol) of 5 and acetic anhydride (1.3 mL) and the reaction mixture was stirred magnetically for 20 minutes at room temperature, followed by addition of 5 mL of dichloromethane and 0.7 mL (5 mmol) of triethylamine. After this solution was stirred for 3 hours, 5 mL of 0.01 N-HCl was added, followed by extraction with 5 mL dichloromethane, washing with saturated NaHCO₃ and brine, drying and evaporation. The yield of liquid was 97% (0.25 g). 99.9% GC purity. (b) 0.068 g (1 mmol) of 5 and 0.56 mL triethylamine were placed in 5 mL dichloromethane. After the solution was stirred for 3 hours at room temperature, it was worked up with a similar procedure (a) to give liquid 7 (0.25 g, 99%). 19F-NMR (CDCl3) δ = –165.53 (s); 1H-NMR (CDCl3) δ = 7.25-7.40 (m, 5H), 6.65 (s, 1H), 4.108 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); 13C-NMR (CDCl3) δ = 162.02 (s), 147.53 (d, J = 241.7 Hz), 125.32 (d, J = 22.0 Hz), 118.58 (d, J = 6.3 Hz), 103.41 (d, J = 14.9 Hz), 59.95 (s), 34.12 (s), 14.39 (s); FT-IR (CCl4) 3026, 1607, 1581 cm⁻¹; GC-MS (relative intensity) 247 (M⁺, 53.15), 248 (7.78), 219 (-C2H4, 35.49), 202 (-OEt, 35.31), 175 (53.45), 133 (100); HRMS observed, 247.0978, C13H14O4F, calculated, 247.1009.

Ethyl-4-fluoro-1-ethyl-5-phenylpyrrole-2-carboxylate (4c). Using the same method as in (4b), the reaction of ethyl 4,4-difluoro-2-iodo-5-oxo-5-phenylpentanoate (0.4 g, 1 mol) and ethylamine (0.26 g, 4 mmol, 70% aqueous solution) produced ethyl-4-fluoro-1-ethyl-5-phenylpyrrole-2-carboxylate (0.25 g, 96%).
Ethyl-4-fluoro-1-butanoyl-5-phenylpyrrole-2-carboxylate (4e). Following the method (4b), ethyl-4-fluoro-1-butanoyl-5-phenylpyrrole-2-carboxylate (0.23 g, 0.86 mmol, 88%) was formed from the reaction of ethyl 4,4-difluoro-2-iodo-5-oxo-5-phenylpentanoate (0.25 g, 1 mmol) and propylamine (0.24 g, 4 mmol).

1H NMR (CDCl₃): δ 7.47-7.44 (m, 2H), 7.41-7.37 (m, 3H), 6.73 (s, 1H), 4.28 (q, J = 7.3 Hz, 2H), 2.86 (q, J = 7.3 Hz, 2H), 1.55 (m, 2H) 1.34 (t, J = 7.3 Hz, 3H), 1.13 (m, 2H), 0.75 (t, J = 7.3 Hz, 3H). ¹³C NMR (CDCl₃): δ 161.04 (d, J = 2.9 Hz), 147.89 (d, J = 2.9 Hz), 130.32 (s), 128.86 (s), 128.70 (s), 128.56 (s), 125.52 (d, J = 22.1 Hz), 117.93 (d, J = 6.7 Hz), 104.29 (d, J = 15.4 Hz), 92.36 (s), 93.39 (s), 19.84 (s), 14.62 (s), 13.75 (s). IR (CDCl₃): 3030, 2990, 1710, 1568, 1444, 1253, 1215 cm⁻¹. GC-MS (m/e, relative intensity): 3020, 2900, 1421, 1296, 1213 cm⁻¹. GC-MS (m/e, relative intensity): 315.1473, C₁₉H₁₇NO₂F, calculated, 315.1635.

Ethyl-4-fluoro-1-cyclohexyl-5-phenylpyrrole-2-carboxylate (4e). The synthetic routes of the two N-methyl-β-fluoropyrrole derivatives with high yields, though substitution or abstractions on the fluorinated pyrrole rings. Thus, the ring formation reaction of Qui-Burton's and our results and discussion.

Unsubstituted pyrrole is electron rich compared with benzene, with a ratio of π electron distribution per nuclei of 1.161. The attack of electrophiles in pyrrole is, in general, more facile than in benzene and pyridine. The introduction of fluorine atoms, however, changes the pi electron density of pyrrole, aggravating its electron-rich nature. The synthesis of β-fluoropyrrole derivatives via difluoro-pyrroles cannot be further enhanced by a mechanism of electrophilic substitution or abstraction on the fluorinated pyrrole rings. Thus, the ring formation reaction of Qui-Burton's and our results and discussion.
Synthesis of N-Alkylated 4-Fluoro-5-phenylpyrrole-2-carboxylate


The formation of 4a is reported as occurring by the reaction of 2 with excess ammonium hydroxide (29%) for 24 hr at room temperature. In our previous work, 4b was also synthesized from 2 in high yield under the same reaction conditions. However, when 2 and aqueous methyamine (40%) were allowed to react below 0 °C, 5-(ethoxycarboxyl)-1-methyl-3,3-difluoro-2-phenylpyrrolidine (5), an intermediate molecule for 2-ethyl-4-flouro-1-methyl-5-phenylpyrrole-2-carboxylate (4b), was isolated first. Then, 5 reacted with hydroperchloric acid and acetic anhydride to form 5-(ethoxycarboxyl)-1-methyl-3,3-difluoro-2-phenylpyrrolinium perchlorate (6), which was converted to 2-ethyl-4-flouro-1-methyl-5-phenylpyrrole-2-carboxylate (4b) in high yield. In this reaction, 6 was prepared by the reaction of 5 with acetic anhydride and hydroperchloric acid, which is illustrated as the intermediate (8) in Scheme 2. Treatment of 6 with triethylamine in methylene chloride gave 4 in 98% of yield. In a much simpler way, the final product 4 can also be obtained through the reaction of 5 with acetic anhydride and triethylamine in one step, though 6 may be stored. It is apparent that the current method utilizes a route of anionic pathway. That is, the intermediate molecule (6) has a structure in which C2-H is the most acidic and at which a base attack is expected to happen first. The environment around the C2-H is important to figure out the mechanism of the formation of 4 from 6 via a base attack.

Scheme 1

Scheme 2

R = H(4a), CH3(4b), C2H3(4c), cyclopropyl(4d), butyl(4e), cylopentanyl(4f), cyclohexyl(4g), benzyl(4h)
The carbonyl ester group, which is an electron withdrawing group, remained on the pyrrole ring, but made the protonic hydrogen vulnerable for a base attack. The reaction of (6) with Lewis bases resulted in the acidic protons leaving in sequence, whereas an electron-rich group, instead of the carbonyl ester, would be expected to leave first. Then, the deprotonation augments the anionic charge followed by removal of one β-fluorine atom. Therefore we expect that β-monofluoro-substituted 1H-pyroles compound would form in high yield as well, which contrasts with the results reported previously.25 Finally, the reaction of ethyl-4,4-difluoro-2-iodo-5-oxo-5-phenylpentanoate (2) with primary amines was controlled within a one-pot scheme, but with aqueous solvents, a series of β-monofluoropyrrole derivatives was prepared with high yields at ambient temperatures. The yield of products varied only with the bulkness of N-substituents. That is, cyclohexylamine gave a yield of 44%, whereas the benzylamine yield was 80%.

The two new compounds 5 and 6 were identified or characterized by 19F NMR, 1H-NMR, 13C-NMR, IR, and Mass Spectroscopic data. 19F NMR data of 6 revealed a typical coupling pattern due to two fluorine atoms. From the Mass and 1H-NMR data, the structure of 6 could be postulated as 5-(ethoxycarboxyl)-1-methyl-3,3-difluoro-2-phenylpyrrolinium perchlorate. The IR data confirms a carbonyl and C-H stretches as well as the C=N stretch appeared at 1717, 2998, 1617 cm−1, respectively. 1H-NMR data taken at room temperature revealed multiple but unresolved chemical shifts of phenyl hydrogen atoms. The complicated structure of 1H-NMR of 6 comes from the presence of fluorine atoms or/and its other possible solution structures as illustrated in Figure 2. However, complication from fluorine atoms is excluded because a similar difluorinated derivative 5 exhibits two distinct types of phenyl stretches. 4a through 4h were also characterized with spectroscopic methods.

Conclusion

N-sustituted-β-fluoropyrrole derivative, i.e., ethyl-4-fluoro-1-methyl-5-phenylpyrrole and its higher congener were successfully synthesized by one of the following three reaction conditions: the reaction of 5 with acetic anhydride and triethylamine, the reaction of 6 with triethylamine, and the spontaneous conversion reaction of 5. A possible mechanism is proposed based on the isolation and identification of the reaction intermediates (5, 6). The isolated intermediates support the presence of an acid proton, which would permit the facile attack of nucleophiles such as amines on the difluoropyrrole derivatives. Establishment of an anionic reaction pathway, including disubstituted β-fluoropyrroles, would allow high yields of selective β-fluoropyrrole derivatives. Thereby, the mono β-fluoropyrroles would be useful to design systems of biological importance, such as porphyrins and branched pyrrole amides.

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References