Synthetic approaches to difluoroindolecarboxylic acid ethyl esters

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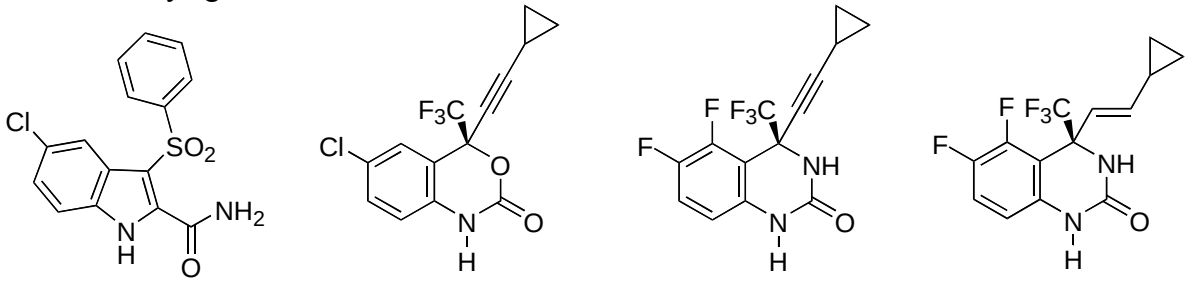
Abstract
Synthetic approaches to ethyl 4,5-difluoroindole-2-carboxylate and ethyl 5,6-difluoroindole-2-carboxylate by Fischer indole synthesis and by the reaction of lithiated *N*-BOC-3,4-difluoro-2-methylaniline with diethyl oxalate or ethyl bromopyruvate were investigated. A simple and direct preparation of ethyl 4,5-difluoroindole-3-carboxylate from lithiated *N*-BOC-3,4-difluoroaniline and ethyl bromopyruvate was found.

Keywords: Indolecarboxylate, heterocyclic, synthesis

Introduction

A search on anti-HIV-1 agents led us to investigate the structure-activity relationships (SARs) of various indolyl aryl sulfones (IASs) related to Merck NNRT agent L-737,126 **1**[1] (Figure 1).

In order to improve the antiviral activity of **1** against wt-HIV-1 and some clinically relevant strains of resistant mutants, we planned the synthesis of IAS derivatives having a 4,5-difluorosubstituted indole nucleus. Such a substitution performed on bicyclic heterocycles related to efavirenz **2** led to DCP 963 **3** and DCP 082 **4**, two derivatives endowed with potent antiviral activity against various resistant mutants.[2,3]



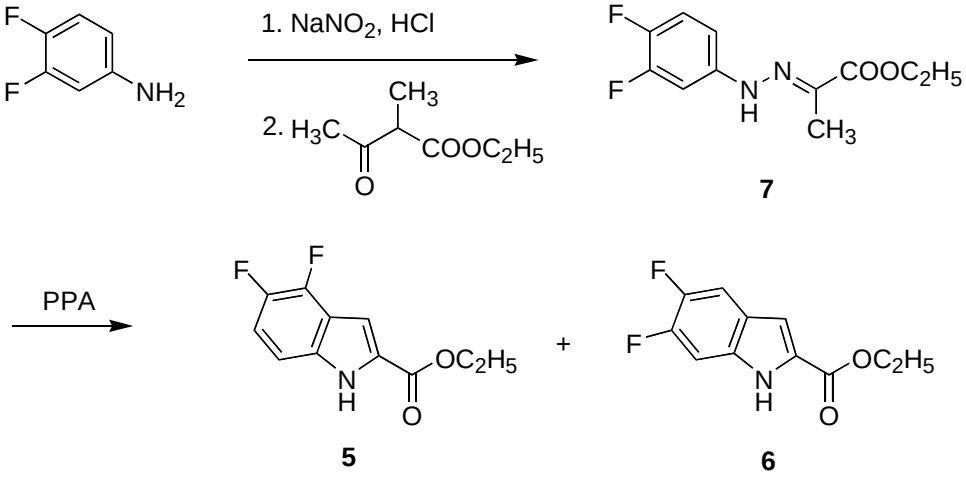
L-737,126 (**1**) Efavirenz (**2**) DCP 963 (**3**) DCP 082 (**4**)

Figure 1

Results and Discussion

The approach to 4,5-difluorosubstituted IASs required the ethyl ester of 4,5-difluoroindole-2-carboxylic acid **5** as starting material. To our knowledge, the preparation of **5**, and the related 5,6-difluoroanalog **6**, have been reported in patents only.[4,5]

As a first approach, we attempted to prepare **5** by the standard Fischer indole synthesis.[6] Reaction of 3,4-difluoroaniline according to Japp-Klingemann method[7] furnished the 3,4-difluorophenyl hydrazone of ethyl pyruvate **7**, which was converted to a mixture of **5** and **6** by heating with polyphosphoric acid (PPA)[8] (Scheme 1). The isomeric mixture was separated by repeated passages on chromatography column to afford pure **5** (15%) and **6** (22%).

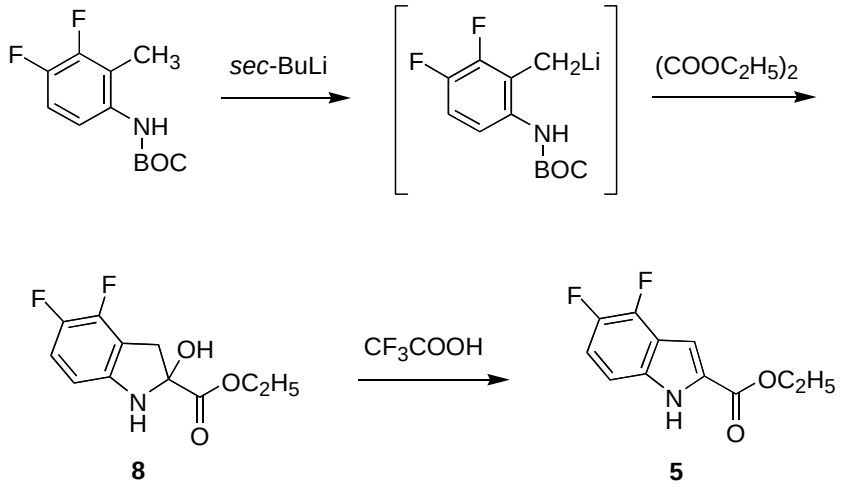


Scheme 1

The low overall yield obtained with the Fischer method and the difficulties encountered in the separation/purification of isomers **5** and **6**, prompted us to synthesize the required 4,5-difluoroderivative **5** by the procedure reported by Clark,[9] and later by Allen,[10] concerning the synthesis of indole-2-carboxylic acid esters by lateral lithiation of *N*-BOC-protected toluidines.

We therefore treated *N*-BOC-2-methyl-3,4-difuoroaniline, prepared by the reaction between lithiated *N*-BOC-3,4-difluoroaniline and iodomethane,[11] with 2 equivalents of *sec*-BuLi at -40°C as reported by Clark,[9] and then with diethyl oxalate (Scheme 2). After quenching, the proposed intermediate hydroxy ester **8** was treated with trifluoroacetic acid to afford **5** in 8 % yield.

This procedure gave overall yield considerably lower than those reported by Allen[10] for monofluoroindoles. We can argue that the presence of the fluorine atom *ortho* to the methyl group of toluidine would reduce dramatically the reactivity of the lithiated *N*-BOC-3,4-difluoro-2-methylaniline. This result was supported by the fact that *N*-BOC-2-methyl-6-fluoroaniline underwent easily lateral lithiation (*sec*-BuLi, THF, -40 °C),[10] whereas the isomeric *N*-BOC-2-methyl-5-fluoroaniline failed to undergo lithiation.[12]



8 **5**

Scheme 2

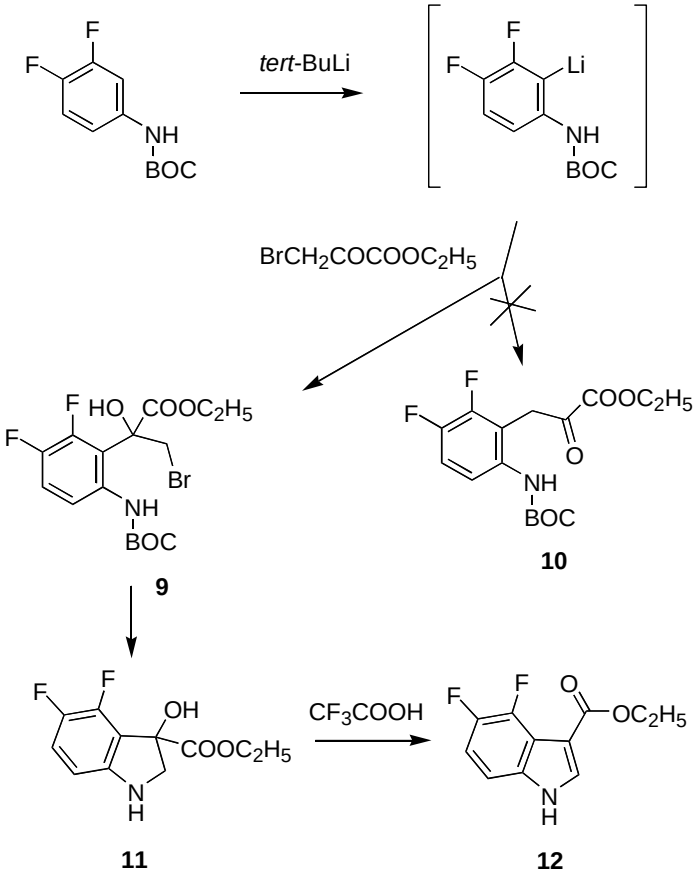
In order to improve the yield of required indole ester, we attempted to prepare **5** by reacting lithiated *N*-BOC-3,4-difluoroaniline with ethyl bromopyruvate. Contrary to our expectations, ethyl 4,5-difluoroindole-3-carboxylate **12** was the sole product obtained from this reaction (Scheme 3). This result was probably due to the formation of the intermediate **9** as a consequence of the reaction of the lithiated C-2 with the ketone group of pyruvate instead of with the bromomethyl group (intermediate **10**).[13]

It is noteworthy that the one-pot preparation of ethyl 4,5-difluoroindole-3-carboxylate **12** (Scheme 3) is a very simple and more convenient procedure compared to other standard synthetic methods requiring 3-lithium-1-(phenylsulfonyl)indole as intermediate,[14] or based on Grignard reaction of indole ring with ethyl chloroformate.[15]

Experimental Section

General Procedures. Melting points (mp) were determined on a Büchi 510 apparatus and are uncorrected. Infrared spectra (IR) were run on Perkin-Elmer 1310 and SpectrumOne spectrophotometers. Band position and absorption ranges are given in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Bruker AM-200 (200 MHz) and Bruker Advance 400 MHz FT spectrometers in the indicated solvent. Chemical shifts are expressed in □ units (ppm) from tetramethylsilane. Column chromatographies were packed with alumina Merck (70-230 mesh) and silica gel Merck (70-230 mesh). Aluminum oxide TLC cards Fluka (aluminum oxide precoated aluminum cards with fluorescent indicator at 254 nm) and silica gel TLC cards Fluka (silica gel precoated aluminum cards with fluorescent indicator at 254 nm) were used for thin layer chromatography (TLC). Developed plates were visualized by Spectroline ENF 260C/F UV apparatus. Organic solutions were dried over anhydrous sodium sulfate. Concentration and evaporation of the solvent after reaction or extraction was carried out

on a rotary evaporator Büchi Rotavapor operating at reduced pressure. Elemental analyses were found within ±0.4% of the theoretical values.



Scheme 3

Ethyl pyruvate 3,4-difluorophenylhydrazone (7). To an ice-cooled mixture of 3,4-difluoroaniline (20.9 g, 0.16 mol), 37% HCl (39 mL) and water (39 mL) was dropped a solution of sodium nitrite (11.2 g, 0.16 mol) in water (14.7 mL). Stirred was maintained on ice-bath for 20 min, then sodium acetate trihydrate (18.2 g, 0.22 mol) was added and the resulting mixture was added to an ice-cooled well-stirred solution of ethyl 2-methylacetoacetate (90 %, 25.6 g, 0.162 mol), potassium acetate (31.7 g, 0.32 mol) in methanol (157 mL). The reaction was stirred at 0 °C for 3 h, and then extracted with diethyl ether. The organic layer was separated, washed with brine and dried. Evaporation of the solvent gave a red oily residue which was dissolved in ethanol (250 mL) and stirred at room-temperature for 3 days. The resulting suspension was cooled at 4 °C overnight and then filtered to afford 16.0 g of **7** as a red salmon solid. The mother solution was concentrated in vacuo and, again, cooled at 4 °C and filtered to furnish additional 4.9 g of product. Overall yield of **7** was 20.9 g (53 %), mp 112-114 °C, after crystallization from ethanol. ^{1}H NMR (DMSO-d_6): δ 1.26 (t, J = 7.1 Hz, 3H), 2.05 (s, 3H), 4.20 (q, J = 7.1 Hz), 6.95-7.45 (m, 3H), 9.97 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 760, 815, 1110, 1130, 1180, 1200, 1300, 3495, 4050 cm^{-1}. Anal. Calcd. For $C_{11}H_{12}F_2N_2O_2$ (242.22): C, 54.54; H, 4.99; N, 11.57; F, 15.69. Found: C, 54.37; H, 4.91; N, 11.50; F, 15.54.

Ethyl 4,5-difluoroindole-2-carboxylate (5) and ethyl 5,6-difluoroindole-2-carboxylate (6). From **7**. To PPA (160 g) pre-heated at 110 °C was added portionwise ethyl pyruvate 3,4-difluorophenylhydrazone **7** (16.0 g, 0.066 mol), then reaction was maintained under stirring for 30 min. After cooling at room temperature, crushed ice was added while stirring, and the solid which formed was separated by suction, washed with water and dried. The isomers were separated by repeated silica gel column chromatographies (*n*-hexane / ethyl acetate 2:1 as eluent). First eluates afforded ethyl 5,6-difluoroindole-2-carboxylate **6**, (3.3 g, 22 %), mp 172-173 °C, after crystallization from ethanol. ^{1}H NMR (DMSO-d_6): δ 1.33 (t, *J* = 7.1 Hz, 3H), 4.34 (q, *J* = 7.1 Hz, 2H), 7.14 (m, 1H), 7.36 (ddd, *J* = 0.7, 8.1 and 11.0 Hz, 1H), 7.66 (dd, *J* = 8.1 and 11.0 Hz, 1H), 12.07 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 770, 865, 1020, 1220, 1240, 1290, 1690, 3600 cm^{-1}. Anal. Calcd. For $C_{11}H_9F_2NO_2$ (225.19): C, 58.67; H, 4.03; N, 6.22; F, 16.87. Found: C, 58.55; H, 3.98; N, 6.16; F, 16.79.

Further elution with the same eluent afforded ethyl 4,5-difluoroindole-2-carboxylate **5**, (2.2 g, 15 %), mp 166-168 °C, after crystallization from ethanol. ^{1}H NMR (DMSO-d_6): δ 1.34 (t, *J* = 7.0 Hz, 3H), 4.35 (q, *J* = 7.0 Hz, 2H), 7.20 (m, 1H), 7.30-7.32 (m, 2H), 12.30 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 765, 1020, 1220, 1255, 1690, 3600 cm^{-1}. Anal. Calcd. For $C_{11}H_9F_2NO_2$ (225.19): C, 58.67; H, 4.03; N, 6.22; F, 16.87. Found: C, 58.48; H, 3.97; N, 6.07; F, 16.61.

Ethyl 4,5-difluoroindole-2-carboxylate (5) from *N*-*tert*-butoxycarbonyl-2-methyl-3,4-difluoroaniline. *sec*-Buthyl lithium (3.22 mL of a 1.4 M solution in pentane, 0.0045 mol) was added dropwise to a solution of *N*-tert-butoxycarbonyl-2-methyl-3,4-difluoroaniline[11] (0.50 g, 0.002 mol) in anhydrous THF (7.2 mL) at –40 °C. Temperature of solution was carefully maintained below -20 °C and, after cooling at –40 °C for 5 min, a solution of diethyl oxalate (0.35 g, 0.0025 mol) in anhydrous THF (2 mL) was added. Reaction was slowly heated at 0 °C, and then kept for 1 h under stirring. After quenching with ice water, diethyl ether was added while shaking. The organic layer was separated, washed with brine ad dried. Removal of the solvent gave a residue containing the hydroxy-ester **8**, which was dissolved in dichloromethane (10 mL) and treated with trifluoroacetic acid (2 mL) for 20 min at room temperature. After dilution with diethyl ether and water, the organic layer was washed with brine and dried. Evaporation of the solvent gave a residue which was purified on silica gel column chromatography (*n*-hexane / ethyl acetate 3:1 as eluent) to afford **5**, 37 mg, 8 %, chemico-physical and spectral data were identical to those of the product prepared starting from **7**.

Ethyl 4,5-difluoroindole-3-carboxylate (12). *tert*-Butyl lithium (21.2 mL of a 1.7 M solution in pentane, 0.033 mol) was slowly added by a syringe to a solution of *N*-(*tert*-butoxycarbonyl)-3,4-difluoroaniline[11] (3.4 g, 0.015 mol) in anhydrous THF (40 mL) at -78 °C under argon atmosphere. After stirring for 1 h at -78 °C, ethyl bromopyruvate (2.92 g, 0.015 mol) was added and the reaction was gradually heated to 0 °C in about 2 h while stirring. Ethyl acetate and water were added while stirring. The organic layer was separated, washed with brine and dried. Removal of the solvent gave an orange oily residue which was refluxed in xylene (10 mL) containing trifluoroacetic acid (2 mL) for 2 h. After dilution with diethyl ether and water, the

organic layer was washed with brine and dried. Evaporation of the solvent gave a residue which was purified on silica gel column chromatography (*n*-hexane / ethyl acetate 3:1 as eluent) to afford **12**, 0.88 g, 26 %, mp 115-118 °C, after crystallization from ethanol. ^{1}H NMR ($CDCl_3$): δ 1.40 (t, *J* = 7.1 Hz, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 7.10 (m, 2H), 7.95 (m, 1H), 8.80 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 800, 1021, 1081, 1208, 1261, 1694, 3268 cm^{-1}. Anal. Calcd. For $C_{11}H_9F_2NO_2$ (225.19): C, 58.67; H, 4.03; N, 6.22; F, 16.87. Found: C, 58.45; H, 3.97; N, 6.18; F, 16.55.

Acknowledgments

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