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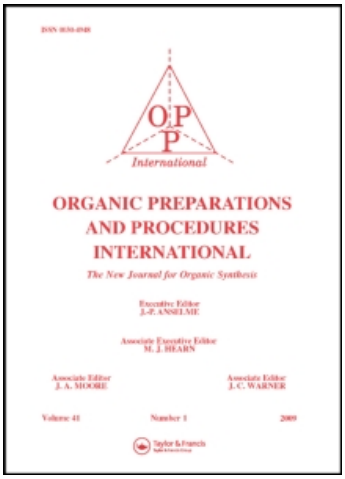

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AN IMPROVED SYNTHESIS OF ETHYL 5-CHLORO-4-FLUORO-1*H*-INDOLE-2-CARBOXYLATE

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9. Attempts to oxidize **2** using sodium hydrogen carbonate buffered trifluoroperacetic acid, prepared from trifluoroacetic anhydride and 30% aq. hydrogen peroxide, failed to give **3**.

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11. The saponification of **3** routinely gives a 95+% yield of **4**. Our overall yield to convert **2** to **4** is 71%, essentially identical to the yield reported by Grieco and Hunt.[8]

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AN IMPROVED SYNTHESIS OF ETHYL 5-CHLORO-4-FLUORO-1*H*-INDOLE-2-CARBOXYLATE

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Indolyl arylsulfones (IASs) are potent non-nucleoside inhibitors of HIV-1 reverse transcriptase (RT).[1] Compound **1** bearing the 5-chloro-4-fluoro substitution pattern at the indole ring, was exceptionally potent against RT WT and RTs carrying drug-resistant mutations. We selected **1** as a lead compound for the development of new second-generation analogues (*Fig 1*).[2]

In 2002, we described a procedure for the synthesis of ethyl 5-chloro-4-fluoro-1*H*-indole-2-carboxylate (**2**) and ethyl 5-chloro-6-fluoro-1*H*-indole-2-carboxylate (**3**)[3] through compound **5** obtained by *N*-chlorosuccinimide chlorination of the ethyl pyruvate 3-fluorophenylhydrazone (**4**) prepared from 3-fluoroaniline *via* the Japp-Klingemann[4] procedure. Fischer[5] cyclization of **5** in the presence of polyphosphoric acid (PPA) as a catalyst, gave the indole esters **2** and **3** which could be separated by repeated chromatography columns (*Scheme 1*). However, since compound **2** was obtained as minor isomer by this procedure,[2] we investigated a more convenient synthesis. We could not find literature describing the synthesis of 4,5-dihalodisubstituted indole-2-carboxylate as the sole isomer, we designed a new synthesis of **2** starting from commercially available 3-fluoro-2-methylaniline (**6**).

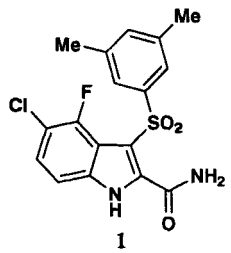

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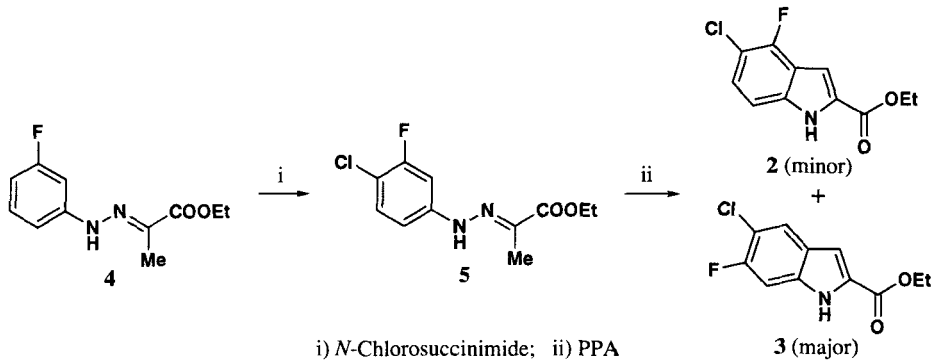
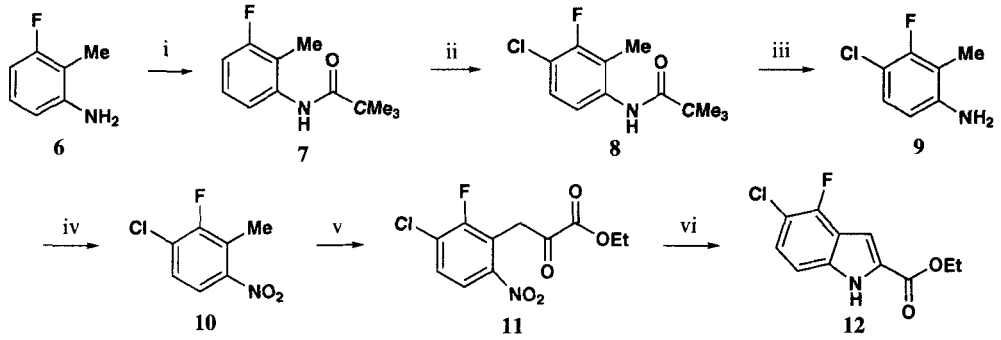
Fig. 1



i) *N*-Chlorosuccinimide; ii) PPA

Scheme 1

Aniline **6** was protected as *N*-pivalamide (**7**) and then chlorinated with NCS to give *N*-(4-chloro-3-fluoro-2-methylphenyl)pivalamide (**8**). Acidic hydrolysis of *N*-pivalamide **8** afforded 4-chloro-3-fluoro-2-methylaniline (**9**) which was oxidized to the corresponding nitro derivative **10** with 3-chloroperoxybenzoic acid (MCPBA). Reaction of **10** with diethyl oxalate in the presence of sodium ethoxide gave ethyl 3-(3-chloro-2-fluoro-6-nitrophenyl)-2-oxopropanoate (**11**). Finally, reduction of **11** with iron powder by heating at 60 °C in acetic acid and subsequent intramolecular cyclization of the intermediate amino derivative provided the ester **2** (*Scheme 2*).



i) Pivaloyl chloride; ii) NCS; iii) 6N HCl; iv) MCPBA; v) diethyl oxalate, EtONa; vi) Fe, H+

Scheme 2

The latter six-steps procedure provided **2** in 37% overall yield starting from the commercially available aniline **6** (the overall yield with the older proedure[2] was only 5%). In addition, it is faster because it avoides tedious repeated chromatographies needed for the separation of the isomers. The procedure described in *Scheme 2* is a major improvement in the synthesis of **2** in 37% overall yield from **6**.

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EXPERIMENTAL SECTION

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 a Bruker Avance 400 (400 MHz) FT spectrometers in the indicated solvent. Chemical shifts are expressed in δ units (ppm) from tetramethylsilane. Chromatography columns were packed with Merck alumina (70-230 mesh) and Merck silica gel (70-230 mesh). Aluminum oxide TLC cards from Fluka (aluminum oxide precoated aluminum cards with fluorescent indicator at 254 nm) and silica gel TLC cards from Fluka

(silica gel precoated aluminum cards with fluorescent indicator at 254 nm) were used for thin layer chromatography (TLC). Developed plates were visualized by a Spectroline ENF 260C/F UV apparatus. Organic solutions were dried over anhydrous sodium sulfate. Concentration and evaporation of the solvent after reaction were carried out on a Büchi Rotavapor R-210 equipped with a Büchi V-850 vacuum controller and Büchi V-700 and V-710 vacuum pumps. Elemental analysis results were within (0.3% of the theoretical values).

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***N*-(3-Fluoro-2-methylphenyl)pivalamide (7)**.- Pivaloyl chloride (1.59 g, 1.62 mL, 0.0132 mol) was added dropwise at 0 °C to a solution of 3-fluoro-2-methylaniline (**6**) (1.50 g, 0.012 mol), triethylamine (1.33 g, 1.84 mL, 0.0132 mol) in anhydrous tetrahydrofuran (20 mL). The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated at reduced pressure to give a residue which was treated with water (30 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The crude solid residue was crystallized from cyclohexane to give **7** as a white solid (1.93 g, 77%), mp 99-101 °C (from cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9H), 2.16 (d, J = 1.80 Hz, 3H), 6.86 (t, J = 8.77 Hz, 1H), 7.16 (q, J = 7.61 Hz, 1H), 7.26 (broad s, 1H, disappeared on treatment with D_2O), 7.64 ppm (d, J = 8.15 Hz, 1H). IR: 1648, 3294 cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}FNO$: C, 68.88; H, 7.71; N, 6.69; F, 9.08

Found: C, 68.65, H, 7.69; N, 6.41; F, 8.87

***N*-(4-Chloro-3-fluoro-2-methylphenyl)pivalamide (8)**.- A solution of **7** (1.77 g, 0.0084 mol) in DMF (10 mL) was added dropwise and under an argon stream to a solution of *N*-chlorosuccinimide (NCS) (1.12 g, 0.0084 mol) in the same solvent (10 mL). The reaction mixture was heated at 80 °C in the argon atmosphere for 30 min. After cooling, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated at reduced pressure. The crude solid residue was crystallized from cyclohexane to give **8** as a white solid (1.83 g, 89%), mp 114-116 °C (from cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 9H), 2.18 (d, J = 2.13 Hz, 3H), 7.19-7.24 (m, 2H, t, J = 8.46 Hz, 1H after treatment with D_2O), 7.59 ppm (dd, J = 8.77 and 1,55 Hz, 1H). IR: 1649, 3319 cm^{-1}.

Anal. Calcd. for $C_{12}H_{15}ClFNO$: C, 59.14; H, 6.20; N, 5.75; Cl, 14.75; F, 7.80

Found: C, 58.91; H, 6.18; N, 5.60; Cl, 14.57; F, 7.55

4-Chloro-3-fluoro-2-methylaniline (9).- A solution of **8** (1.37 g, 0.0056 mol) in dioxane (20 mL) and 6N HCl (10 mL) was heated at 100 °C overnight. After cooling, a saturated aqueous solution of potassium carbonate was added to reach pH ~ 9 (CO_2 evolution!) and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporate at reduced pressure. The crude residue was purified by silica gel column chromatography (dichloromethane as eluent) to give **9** as a yellow oil (0.88 g, 99%), ^{1}H NMR ($CDCl_3$): δ 2.10 (d, J = 1.96 Hz, 3H), 3.70 (broad s, 2H, disappeared on treatment with D_2O), 6.41 (dd, J = 8.58 and 1.48 Hz, 1H), 7.01 ppm (t, J = 8.33 Hz, 1H). IR: 3394, 3476 cm^{-1}.

Anal. Calcd. for C_7H_7ClFN: C, 52.68; H, 4.42; N, 8.78; Cl, 22.22; F, 11.90

Found: C, 52.41; H, 4.34; N, 8.55; Cl, 22.12; F. 11.69

1-Chloro-2-fluoro-3-methyl-4-nitrobenzene (10).- A mixture of **9** (0.61 g, 0.0038 mol), 3-chloroperoxybenzoic acid (MCPBA) (70% wt, 4.68 g, 0.019 mol) in toluene (15 mL) was refluxed for 3 h. After cooling, dichloromethane was added; the mixture was filtered and the solid was washed with the same solvent. The organic layer was washed with a saturated solution of sodium hydrogen carbonate, with brine and dried over anhydrous sodium sulfate. After concentration to a small volume under reduced pressure, the crude oily residue was purified by silica gel column chromatography (dichloromethane as eluent) to give **10** as a colorless oil (0.60 g, 83%). ^{1}H NMR ($CDCl_3$): δ 2.54 (d, J = 2.54 Hz, 3H), 7.40 (t, J = 8.02 Hz, 1H), 7.75 ppm (dd, J = 8.88 and 1.46 Hz, 1H).

Anal. Calcd. for $C_7H_5ClFNO_2$: C, 44.35; H, 2.66; N, 7.39; Cl, 18.70; F, 10.02

Found: C, 44.12; H, 2.59; N, 7.11; Cl, 18.53; F, 9.81

Ethyl 3-(3-Chloro-2-fluoro-6-nitrophenyl)-2-oxopropanoate (11).- A solution of **10** (3.43 g, 0.018 mol) in anhydrous ethanol (5 mL) was added to a solution of sodium ethoxide (obtained for the dissolution of sodium (0.62 g, 0.027 ga) in the same solvent (35 mL). Diethyl oxalate (20 mL) was added, and the reaction mixture was stirred at room temperature overnight. The excess of diethyl oxalate was distilled off. A saturated solution of ammonium chloride was added and the mixture was extracted with ethyl acetate (20 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated at reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:*n*-hexane 3:7 as eluent) to give **11** as an yellow oil (3.47 g, 67%). ^{1}H NMR ($CDCl_3$): δ 1.43 (t, J = 7.16 Hz, 3H), 4.43 (q, J = 7.13 Hz, 2H), 4.64 (d, J = 1.38 Hz, 2H), 7.57 (dd, J = 8.13 and 7.30 Hz, 1H), 7.98 ppm (dd, J = 8.96 and 1.72 Hz, 1H). IR: δ 1730 cm^{-1}.

Anal. Calcd. for $C_{11}H_9ClFNO_5$: C, 54.04; H, 4.84; N, 7.39; Cl, 12.24; F, 6.56

Found: C, 53.92; H, 4.80; N, 7.28; Cl, 12.05; F, 6.41

Ethyl 5-Chloro-4-fluoro-1*H*-indole-2-carboxylate (12).- Iron powder (0.41 g, 0.0074 ga) was added to a solution of **11** (0.40 g, 0.0014 mol) in acetic acid (8 mL) at 60 °C, and the reaction mixture was heated at same temperature overnight. After cooling, the solvent was evaporated to

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dryness at reduced pressure. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated solution of sodium hydrogen carbonate and with brine, dried over anhydrous sodium sulfate, and evaporated at reduced pressure. The crude solid residue was purified by silica gel column chromatography (ethyl acetate:*n*-hexane 3:7 as eluent) to give **2** as a white solid (0.33 g, 100%), mp 191-193 °C (from ethanol), *lit.*[3] 186-190 °C. ^{1}HNMR and IR spectra were identical to those of the sample we previously described.[3]

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