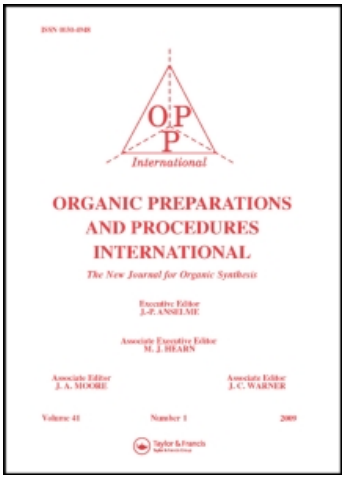


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A SIMPLIFIED SYNTHESIS OF ETHYL 5-CHLORO-4-FLUORO-1*H*-INDOLE-2-CARBOXYLATE AND ETHYL 5-CHLORO-6-FLUORO-1*H*-H-INDOLE-2-CARBOXYLATE

Romano Silvestri[a]; Gabriella De Martino[a]; Gianluca Sbardella[b]
[a] Dipartimento di Studi Farmaceutici, Università di Roma "La Sapienza", Roma, Italy [b] Dipartimento di Scienze Farmaceutiche, Università di Salerno, Fisciano (Salerno), Italy

To cite this Article Silvestri, Romano , De Martino, Gabriella and Sbardella, Gianluca(2002) 'A SIMPLIFIED SYNTHESIS OF ETHYL 5-CHLORO-4-FLUORO-1*H*-INDOLE-2-CARBOXYLATE AND ETHYL 5-CHLORO-6-FLUORO-1*H*-H-INDOLE-2-CARBOXYLATE', Organic Preparations and Procedures International, 34: 5, 517 — 520
To link to this Article: DOI: 10.1080/00304940209355772
URL: http://dx.doi.org/10.1080/00304940209355772

11. J. T. Liu and W. Y. Huang, *J. Fluorine Chem.*, **95,** 131 (1999).

M. Matsui, K. Shibata, H. Muramatsu, H. Sawada and M. Nakayama, *Synlett,* 113 (**1991**); *Chem. Ber.,* **125**, 467 (1992).

13. For references see: W. Dmowski, *Introduction of Fluorine in Organic Compounds using Sulphur Tetrafluoride,* in B. Baasner, H. Hagemann, J.C. Tatlow (Ed.), *Houben-Weyl Methods in Organic Chemistry,* Vol. E10a, Georg Thieme Verlag, Stuttgart, New York, 1999, pp 321-405.

14. S. M. Lavagna, *J. Heterocyclic Chem.*, **32**, 573 (1995).

****

A SIMPLIFIED SYNTHESIS OF ETHYL 5-CHLORO-4-FLUORO-1*H*-INDOLE-2-CARBOXYLATE AND ETHYL 5-CHLORO-6-FLUORO-1*H*-INDOLE-2-CARBOXYLATE

Submitted by (12/03/01) Romano Silvestri*†, Gabriella De Martino† and Gianluca Sbardella††

† *Dipartimento di Studi Farmaceutici, Università di Roma "La Sapienza", Box 36 - Roma 62, P.le Aldo Moro 5, I-00185 Roma, ITALY*

†† *Dipartimento di Scienze Farmaceutiche, Università di Salerno, Via Ponte Don Melillo, I-84084 Fisciano (Salerno), ITALY*

Tel. +39 06 49913800; E-mail: romano.silvestri@uniroma1.it

During a search for novel anti-HIV-1 agents, we planned the synthesis of the indolyl aryl sulfones **7** and **8**, whose preparation required ethyl 5-chloro-6-fluoro-1*H*-indole-2-carboxylate (**5**) and ethyl 5-chloro-4-fluoro-1*H*-indole-2-carboxylate (**6**) as starting materials, respectively *(Fig. 1)*.[1]

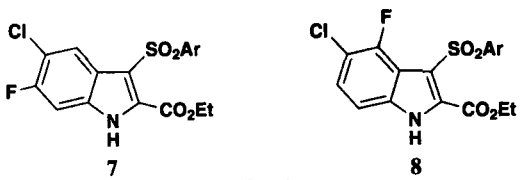
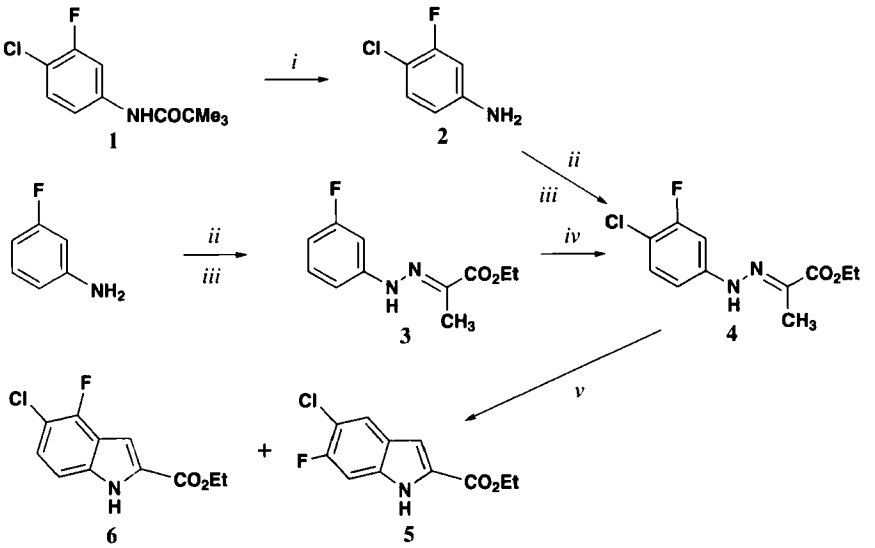


Fig. 1

Compounds **5** and **6** were obtained according to literature procedures[2,3] from commercially available 3-fluoroaniline in five steps *via* 4-chloro-3-fluoroaniline (**2**) as a key intermediate. This compound was obtained by hydrolysis of *N*-pivaloyl 4-chloro-3-fluoroaniline (**1**) prepared as reported[4] by chlorination of *N*-pivaloyl 3-fluoroaniline[5] with *N*-chlorosuccinimide. Coupling of the diazonium salt of 4-

chloro-3-fluoroaniline (**2**) with ethyl 2-methylacetoacetate according to the Japp-Klingemann reaction[6] afforded the 4-chloro-3-fluorophenylhydrazone of the ethyl pyruvate (**4**). Subsequent intramolecular cyclization of **4** following Fischer indole cyclization, in the presence of polyphosphoric acid (PPA)[6] as a catalyst, gave the required indole esters **5** and **6** *(Scheme 1)*.



i) 6N HCl *ii)* $NaNO_2$, H^+ *iii)* Etyl 2-methylacetoacetate *iv)* *N*-Chlorosuccinimide *v)* PPA

Scheme 1

In order to simplify the above procedure, to lower its overall cost and to increase the yield of indoles **5** and **6**, we synthesized the hydrazone by a different procedure. We thus prepared compound **4**, the immediate precursor of indoles **5** and **6**, by treatment of the ethyl pyruvate 3-fluorophenylhydrazone (**3**), obtained from 3-fluoroaniline *via* the Japp-Klingemann procedure, with *N*-chlorosuccinimide. The latter three-step procedure allowed us to prepare indole esters **5** and **6** from 3-fluoroaniline in a very simple and more efficient way with overall yields increments of 50%, and with a cost lower than that of the five-step procedure described in Scheme 1.

EXPERIMENTAL SECTION

Mps were determined on a Büchi 510 apparatus and are uncorrected. Infrared spectra (IR) were run on a Perkin-Elmer 1310 spectrophotometer. Proton nuclear magnetic resonance (1H-NMR) spectra were recorded on a Bruker A-300 (200 MHz) FT spectrometer in the indicated solvent. Chemical shifts are expressed in δ units (ppm) from tetramethylsilane. Column chromatographies were packed with silica gel Merck 60 (70-230 mesh). Fluka aluminum oxide/TLC-cards (aluminum oxide precoated aluminum cards with fluorescent indicator at 254 nm), Fluka silica gel/TLC-cards and Macherey-Nagel Alugram® Sil G/UV254 (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. Elemental analyses were performed by the laboratory of Dr. M. Zancato, Dipartimento di Scienze Farmaceutiche, University of Padova (Italy). Analytical results were within ± 0.3% of the theoretical values.

4-Chloro-3-fluoroaniline (2).- A solution of *N*-pivaloyl 4-chloro-3-fluoroaniline (**1**) (5.0 g, 0.022 mol), 4N HCl (20 mL) and dioxane (40 mL) was stirred at room temperture for 1.5 h and then refluxed overnight. After cooling the reaction was diluted with water and made basic with solid sodium hydrogen carbonate (CO_2 evolution!). After extraction with diethyl ether, the organic solution was washed with brine and dried. Evaporation of the solvent gave 3.1 g (98%) of pure **2** as a brown oil which solidified on standing, mp 65-67°, *lit.*[8] 61°, after crystallization from *n*-hexane.

Ethyl Pyruvate 3-Fluorophenylhydrazone (3). The compound was prepared by the Japp-Klingemann procedure starting from 3-fluoroaniline. Yield 38%, mp 98-101°, *lit.*[9] 103°, after crystallization from ethanol. ^{1}H-NMR (DMSO-d_6): δ 1.22 (t, J = 7.0 Hz, 3H), 2.03 (s, 3H), 4.15 (q, J = 7.0 Hz, 2H), 6.30 (m, 1H), 6.95-7.10 (m, 2H), 7.24 (m, 1H), 10.03 ppm (broad s, 1H, disappeared on treatment with D_2O).

Ethyl Pyruvate 4-Chloro-3-fluorophenylhydrazone (4). *From compound 2.*- A solution of $NaNO_2$ (4.76 g, 0.069 mol) in water (6.3 mL) was dropped into an ice cooled mixture of **2** (10.0 g, 0.069 mol), 37 % HCl (17 mL) and water (17 mL). After stirring for 20 min. at 0°, sodium acetate trihydrate was added (12.87 g, 0.094 mol) and the mixture was added by portions to an ice cooled and well stirred solution of ethyl 2-methylacetoacetate (90%, 11.0 g, 0.069 mol), potassium acetate (13.54, 0.138 mol) and methyl alcohol (67 mL). The reaction was stirred at 0° for 3 h, then diluted with water and extracted with diethyl ether. The organic solution was washed with brine and dried to give, after evaporation of the solvent, an oily residue (7.9 g) which was treated with ethanol (100 mL) and stirred at room temperature overnight. The red salmon solid which formed was separated by suction to give 5.4 g (30%) of pure **4**, mp 161-163° after crystallization from ethanol. ^{1}H-NMR (DMSO-d_6): δ 1.28 (t, J = 7.1 Hz, 3H), 2.07 (s, 3H), 4.21 (q, J = 7.1 Hz, 2H), 7.05-7.23 (m, 2H), 7.54 (m, 1H), 10.08 ppm (s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 3285, 1674, 1661 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}ClFN_2O_2$: C, 51.08; H, 4.68; N, 10.83; Cl, 13.71; F, 7.34.

Found: C, 51.02; H, 4.66; N, 10.80; Cl, 13.59; F, 7.30.

From compound 3.- *N*-Chlorosuccinimide (0.65 g, 0.0049 mol) was added to a solution of **3** (1.0 g, 0.0044 mol) in anhydrous DMF (38 mL), then reaction was heated at 80° while stirring for 20 min. After cooling the reaction was diluted with water and extracted with ethyl acetate. Organic extracts were washed with brine and dried. Evaporation of the solvent gave a crude residue which was crystallized from ethanol to afford 0.79 g (70%) of **4**, whose mp. ^{1}H-NMR and IR data were identical to those of the analytical sample prepared starting from **2**.

Ethyl 5-Chloro-6-fluoroindole-2-carboxylate (5) and Ethyl 5-Chloro-4-fluoroindole-2-carboxylate (6). Ethyl pyruvate 4-chloro-3-fluorophenylhydrazone (**4**) (5.00 g, 0.0193 mol) was added by portions to PPA (50 g) pre-heated to 110°, then stirred for 30 min. After cooling at room temperature, ice water was added while stirring. The solid which formed was filtered, washed with water, dried.

The mixed isomers were separated by subsequent silica gel column chromatographies (*n*-hexane : ethyl acetate 1:2 as eluent). First fractions furnished ethyl 5-chloro-6-fluoroindole-2-carboxylate (**5**), (1.85 g, 40%), mp 160-164° after crystallization from ethanol. ^{1}H-NMR (DMSO-d_6): δ 1.34 (t, J = 7.1 Hz, 3H), 4.35 (q, J = 7.1 Hz, 2H), 7.14 (s, 1H), 7.36 (m, 1H), 7.89 (d, J = 7.35 Hz, 1H), 12.15 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 1675 and 3280 cm^{-1}.

Anal. Calcd for $C_{11}H_9ClFNO_2$: C, 54.67; H, 3.75; N, 5.80; Cl, 14.67; F, 7.86.

Found: C, 54.59, H, 3.72; N, 5.77; Cl, 14.60; F, 7.77.

Further elution with the same eluent gave ethyl 5-chloro-4-fluoroindole-2-carboxylate (**6**) (0.9 g, 19%), mp 186-190° after crystallization from ethanol. ^{1}H-NMR (DMSO-d_6): δ 1.33 (t, J = 7.1 Hz, 3H), 4.35 (q, J = 7.1 Hz, 2H), 7.16 (s, 1H), 7.26-7.38 (m, 2H), 12.41 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 1680 and 3290 cm^{-1}.

Anal. Calcd for $C_{11}H_9ClFNO_2$: C, 54.67; H, 3.75; N, 5.80; Cl, 14.67; F, 7.86.

Found: C, 54.47, H, 3.69; N, 5.68; Cl, 14.65; F, 7.80.

Acknowledgements.- Authors thank Prof. Marino Artico for helpful suggestions and critical review of the manuscript.

REFERENCES

1. (a) R. Silvestri, M. Artico, S. Massa, T. Marceddu, F. De Montis and P. La Colla, *Bioorg. Med. Chem. Lett.*, **10**, 253 (2000); (b) M. Artico, R. Silvestri, E. Pagnozzi, B. Bruno, E. Novellino, G. Greco, S. Massa, A Ettorre, A.G. Loi, F. Scintu and P. La Colla, *J. Med. Chem.*, **43**, 1886 (2000); (c) R. Silvestri, M. Artico, G. De Martino, E. Novellino, G. Greco, A. Lavecchia, S. Massa, A. G. Loi, S. Doratiotto and P. La Colla, *Bioorg. Med. Chem.*, **8**, 2305 (2000); (d) R. Silvestri, M. Artico, A. Pifferi, G. De Martino, C. Saturnino and M. Artico, *Heterocycles*, **53**, 2163 (2000).

2. B. Robinson, '*The Fischer Indole Synthesis*', J. Wiley and Sons, Chirchester, New York, NY, 1982.

3. D. L. Hughes, *Org. Prep. Proced. Int.*, **25**, 607 (1993).

4. J. W. Corbett, S. S. Ko, J. D. Rodgers, L. A. Gearhart, N. A. Magnus, L. T. Bacheler, S. Diamond, S. Jeffrey, R. M. Klabe, B. C. Cordova, S. Garber, K. Logue, G. L. Trainor, P. S. Anderson and S. K. Erickson-Viitanen, *J. Med. Chem.*, **43**, 2019, (2000).

5. P. Stanetty and B. Krumpak. *J. Org. Chem.*, **61**, 5130 (1996).

6. B. Heath-Brown and P. G. Philpott, *J. Chem. Soc.*, 7185 (**1965**).

7. H. M. Kissman, D. W. Farnsworth and B. Witkop, *J. Am. Chem. Soc.*, **74**, 3948 (1952).

8. T. De Crow, *Rec. Trav. Chim. Pays Bas*, **48**, 1061 (1929).

9. F. L. Allen, J. C. Brunton and H. Suschitzky, *J. Chem. Soc.*, 1283 (**1955**).