A Convenient Preparation of Ethyl 5,6-Dimethoxyindole-3-acetate

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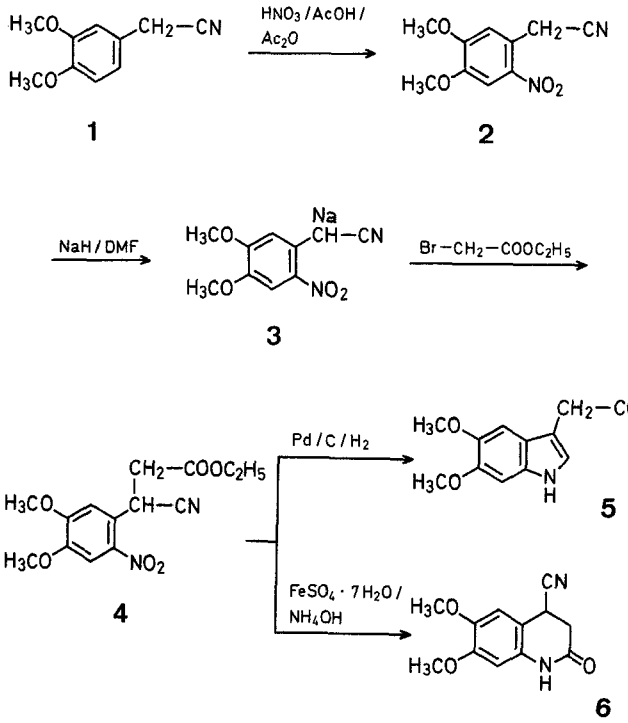
As a part of a study on the synthesis and pharmacological evaluation of derivatives of natural products, ethyl 5,6-dimethoxyindole-3-acetate (**5**) was needed as a synthetic intermediate. One logical preparation of this ester is the direct esterification of the corresponding acid which is known but its conventional preparation involves a sequence of seven steps[2]. An alternative, attractive preparation of this compound starting from commercially available (3,4-dimethoxyphenyl)-acetonitrile (**1**) in three-steps was apparently not successful[3]. It is specifically claimed that **4** was prepared in 17% yield by nitration of ethyl 3-cyano-3-(3,4-dimethoxyphenyl)-propanoate which in turn was prepared in 10% yield by alkylation of **1** with ethyl bromoacetate. Subsequently hydrogenation of **4** gave a solid with m.p. 145–172 °C, attributed to a mixture of products. Similarly, certain dicyano derivatives subjected to hydrogenation/hydrogenolysis conditions gave unpromising results.



This work has now been reinvestigated and modified as necessary. Compound **1** was first nitrated according to Ref.[4] with some modifications to give **2** in 75% yield. Treatment of **2** with sodium hydride in dimethylformamide gave the deep purple colored derivative **3** which was alkylated with ethyl bromoacetate to give ethyl 3-cyano-3-(4,5-dimethoxy-2-nitrophenyl)-propanoate (**4**) in 90% yield. Crystallization of **4** from benzene/ethyl ether/petroleum ether gave pale yellow crystals of m.p. 90–91 °C as compared to the reported 120 °C. The identity of **4** was established by I.R. and ^{1}H-N.M.R. spectroscopy and microanalysis.

Hydrogenation/hydrogenolysis of **4** under the reported conditions (10% Pd/C, ethyl acetate, ~80 °C) gave **5** as a dark red syrup in 30% yield together with the previously unknown 4-cyano-6,7-dimethoxy-2-oxo-1,2,3,4-tetrahydroquinoline (**6**) in 17% yield. However, use of 5% Pd/C[5] repeatedly gave **5** as a colorless syrup in 71% yield; traces of **6** were detected by T.L.C. The structure of **5** was confirmed by I.R., ^{1}H-N.M.R., and mass spectrometry and by microanalysis. The product also developed a bright blue color with van Urk's reagent, characteristic of simple indole derivatives[6].

Finally, an authentic sample of compound **6** was prepared independently in high yield by reduction of the nitro group of **4** with iron(II) hydroxide generated *in situ*[7]. Its structural assignment is based on spectroscopic data and microanalysis.

The basic synthetic strategy confirmed by these results should be generally applicable for the preparation of other indole derivatives.

Melting points were taken on a Buchi melting point apparatus and are uncorrected. I.R. spectra were determined with a Perkin-Elmer 177 or Beckman Model 33 spectrophotometer. ^{1}H-N.M.R. spectra were recorded on a Varian EM-360A spectrometer using TMS as internal standard. Mass spectra were obtained on a CEC 21-110 instrument. T.L.C. was performed on glass plates of silica gel GF-254 from E. Merck AG. Silica gel from Macherey Nagel & Co. and alumina from E. Merck AG were used as adsorbents for column chromatography.

(4,5-Dimethoxy-2-nitrophenyl)-acetonitrile (2):

A solution of (3,4-dimethoxyphenyl)-acetonitrile (**1**; 8 g, 45 mmol, Aldrich-Europe Division) in a 1:1 mixture of glacial acetic acid (50 ml) and acetic anhydride (50 ml) is cooled at 0 °C with an ice bath. Concentrated nitric acid (65%, 7.5 ml) is added dropwise with a pipet with magnetic stirring. After a few min, the solution turns orange-brown, the temperature rises rapidly to 60 °C and drops to 0 °C again within the ensuing 15 min and a precipitate appears. [In larger scale runs, **1** (28 g) in 1:1 acetic acid/acetic anhydride (300 ml) cooled at 0 °C is nitrated with 65% nitric acid (28 ml) over a period of 80 min. In this case the nitric acid is added in small portions at the beginning and then dropwise allowing the temperature of the solution to rise to 30 °C over a period of 45 min and drop to 8 °C in the ensuing 35 min. The yield of the product is 74%. With a still slower rate of the addition of nitric acid, the temperature rises to only 18 °C over a longer period of time and the yield is 73%. It appears that a short nitration time of **1** affords a better yield of **2**.] The mixture is added into ice/water (400 ml), the solid product is filtered, washed with cold water (3 × 200 ml) and air dried to give **2**

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as a yellow solid which is recrystallized from methanol; yield: 7.8 g (78%). The mother liquor from the recrystallization is concentrated and filtered through a short little column of alumina (benzene/methanol) to give a small quantity of additional product; total yield: 7.56 g (75%); m.p. 110–112 °C (Lit.[4] m.p. 111–113 °C).

Ethyl 3-Cyano-3-(4,5-dimethoxy-2-nitrophenyl)-propanoate (4):
A solution of (4,5-dimethoxy-2-nitrophenyl)-acetonitrile (**2**; 42 g, 189 mmol) in dry dimethylformamide (430 ml) is slowly added in ~30 min with stirring to a suspension of sodium hydride (6.05–6.60 g, 252–275 mmol, from 11.0 g of 55–60% NaH in oil dispersion washed with petroleum ether) in dimethylformamide (200 ml) under nitrogen. The deep purple-colored reaction mixture is stirred at room temperature for 3 h and then cooled below 0 °C with an ice/salt bath. Ethyl bromoacetate (46 g, 275 mmol) is added rapidly and the mixture is stirred for 2 h at ice/water temperature and for 1 h at room temperature. It is then diluted with cold water (1500 ml) and extracted with benzene/ethyl acetate (800 ml, 1:1). The organic layer is washed well with water, dried with sodium sulfate, concentrated, and filtered through a column of alumina (benzene). Most of the benzene is evaporated and the concentrated oily solution is diluted with diethyl ether (200 ml) and then with petroleum ether (40–60 °C; 50 ml). Crystallization is induced by scratching the inside of the Erlenmeyer flask containing the solution with a glass rod to give **4** as pale yellow crystals; yield: 50.7 g; m.p. 90–91 °C. The mother liquor from recrystallization is concentrated and chromatographed on alumina (ethyl ether) to give an additional 2.1 g of the product; total yield: 52.8 g (91%).

$C_{14}H_{16}N_2O_6$	calc.	C 54.54	H 5.19
(459.5)	found	54.71	5.02

I.R. (KBr): ν = 2255 (CN); 1735 cm^{-1} (CO).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.30 (t, 3H, CH_3); 3.0 (d, 2H, J = 7 Hz, CH_2—CO—); 3.95 (s, 3H, H_3CO); 4.0 (s, 3H, H_3CO); 4.20 (q, 2H, OCH_2); 5.18 (t, 1H, J = 7 Hz, —CH—CN); 7.15 (s, 1 H_{arom}); 7.65 ppm (s, 1 H_{arom}).

Ethyl 5,6-Dimethoxyindole-3-acetate (5):
A solution of **4** (12 g, 389 mmol) in reagent grade ethyl acetate (200 ml) containing 5% Pd/C[5] (6 g) is shaken under hydrogen at 2.9–3.1 atm and ~80 °C for 3 h. The mixture is allowed to cool before taking it out of the hydrogenator, filtered, the catalyst is washed with ethyl acetate, and the combined solvents are immediately evaporated in a rotary evaporator at ~40 °C. The residual oil is chromatographed on a column of silica gel using redistilled ether/petroleum ether (40–60 °C; 70:30). Evaporation of the solvent under reduced pressure in a rotary evaporator at 25–30 °C gives **5** as a colorless syrup, homogeneous by thin-layer chromatography [ether/petroleum ether, 70:30; visualization with van Urk's reagent or iodine] which resists crystallization; yield: 7.35 g (72%).

$C_{14}H_{17}NO_4$	calc.	C 63.88	H 6.46
(263.3)	found	63.55	6.57

I.R. (film): ν = 3400 (NH); 1730 cm^{-1} (CO).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.23 (t, 3H, CH_3); 3.68 (s, 2H, CH_2); 3.77 (s, 3H, H_3CO); 3.88 (s, 3H, H_3CO); 4.12 (q, 2H, OCH_2); 6.69 (s, 1 H_{arom}); 6.90 (s, 1H, indole H—C-2); 7.00 (s, 1 H_{arom}); 8.20 ppm (s, 1H, NH).

M.S.: m/e = 263.297 (M^+, calc. 263.295).

4-Cyano-6,7-dimethoxy-2-oxo-1,2,3,4-tetrahydroquinoline (6):
Into a flask containing iron(II) sulfate heptahydrate (3.4 g, 12.2 mmol) is added 10% aqueous ammonium hydroxide solution (25 ml) and then a warm, ethanolic solution (25 ml) of **4** (0.616 g, 2 mmol). The mixture is immediately heated under reflux in a water bath (85 °C) for 30 min with vigorous magnetic stirring. It is then filtered under suction through Celite, and the brown solid is washed with (water/ethanol, 1:1) dilute ammonium hydroxide (100 ml). The combined filtrate and washings are acidified with dilute hydrochloric acid, diluted further with ice/water (150 ml; solid formed), extracted with chloroform, dried with sodium sulfate, and solvent evaporated. The residue is dissolved in ethyl acetate (30 ml) with warming; the solution is transferred to a chromatographic column of alumina and eluted with benzene and benzene/ethyl acetate (8:2) to remove any unreacted starting material. The product is eluted with ethyl acetate/benzene (8:2). [Before the chromatography the product is contaminated with small quantities of two bright yellow solids which give yellow-blue fluorescent solutions.] The colorless fraction is concentrated in a rotary evaporator at 40 °C and diluted with petroleum ether to give **6** as a white solid. [On exposure to light for long periods of time or recrystallization from hot solutions it aquires a yellow tinge.]; yield: 441 mg (89%); m.p. 200–202 °C. [This product is freely soluble in chloroform, whereas during the hydrogenolysis under the reported[3] conditions another crystalline form (?) is also obtained which is only slightly soluble in chloroform and has m.p. 206–208 °C.]

$C_{12}H_{12}N_2O_3$	calc.	C 62.07	H 5.17
(232.1)	found	61.90	5.24

I.R. (KBr): ν = 3360; 3240; 3130 (NH); 2260 (CN); 1685 cm^{-1} (CO).

^{1}H-N.M.R. ($CDCl_3$): δ = 2.90 (d, 2H, J = 7 Hz, CH_2); 3.85 (s, 6H, $2H_3CO$); 4.15 (t, 1H, J = 7 Hz, >CH—CN); 6.40 (s, 1 H_{arom}); 6.85 (s, 1 H_{arom}); 9.15 ppm (s, 1H, NH).

M.S.: m/e = 232.086 (M^+, calc. 232.085).

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