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5-Formylindole (**2**) was synthesized in good overall yield starting from 3-methyl-4-nitrobenzaldehyde (**4**) by utilization of the Batcho-Leimgruber indole synthesis.

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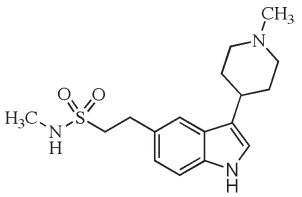
Functionalised indoles are of interest in pharmaceutical industry as the indole ring is a structural element of many biologically active compounds. In the course of making plans for the elaboration of a new manufacturing synthesis of the antimigraine drug naratriptan (**1**, Figure 1) [1], we came to the conclusion that 5-formylindole (**2**) could serve as the starting compound.



1 (naratriptan)

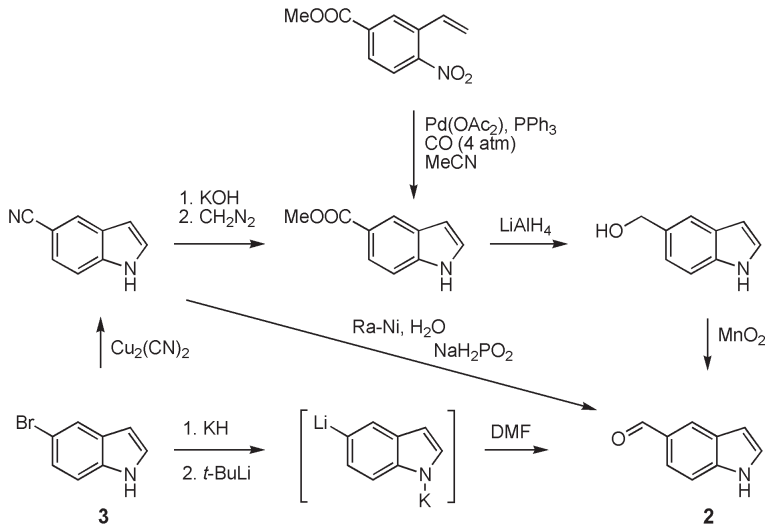
Figure 1

The traditional approach for the synthesis of 5-formylindole is based on the transformation of 5-bromoindole (**3**) [2,3] to the corresponding nitrile followed by hydrolysis and esterification (Scheme 1). Lithium aluminium hydride reduction of the carboxylate and subsequent oxidation of the 5-hydroxymethyl derivative with manganese dioxide leads to the desired 5-formylindole (**2**) [4]. Direct transformation of 5-cyanoindole to 5-formylindole (**2**) has been described in the patent literature by treatment with Raney nickel (0.5 to 1 equiv weight) and sodium hypophosphite (3 equiv) in a mixture of acetic acid, water and pyridine (1:1:2) [5]. More recently, methyl indole-5-carboxylate has been prepared by palladium-phosphine catalysed reductive cyclisation of the corresponding 2-nitrostyrene, in the presence of carbon monoxide [6]. Another method starting from 5-bromoindole (**3**) relies on lithium-halogen exchange followed by treatment with DMF. However, reproducible yields could be achieved only by lithiation of the potassium salt of 5-bromoindole (prepared by deprotonation with potassium hydride in diethyl ether at –78°) with *tert*-butyllithium [3].

All of the methods available in the literature for the synthesis of 5-formylindole are circuitous, inefficient in yield, difficult to handle on large scale and hence do not meet our requirements.

We report here a new and efficient synthesis of 5-formylindole by utilizing the Batcho-Leimgruber indole synthesis starting from a benzenoid precursor containing the formyl group in protected (acetal) form. A similar

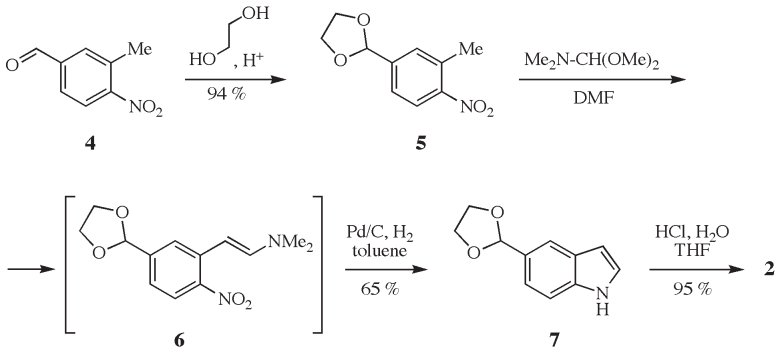
Scheme 1



procedure has been described in the patent literature for the synthesis of 6-formylindole [7].

3-Methyl-4-nitrobenzaldehyde (**4**) is easily available by chromic acid oxidation of 2,4-dimethyl-1-nitrobenzene [8] (Scheme 2). Our strategy for the synthesis of 5-formylindole (**2**) was to use compound **4**, after protection of the aldehyde function, in Batcho-Leimgruber indole synthesis. Therefore, ethylene acetal **5** was prepared from aldehyde **4** by conventional method [9]. Treatment of acetal **5** with dimethylformamide dimethyl acetal in DMF at 140° and subsequent catalytic reduction of the nitro group of crude enamine **6** in toluene afforded the ethylene acetal **7** of 5-formylindole in 65% yield. Acetal **7** was easily cleaved with hydrochloric acid in aqueous THF to give the desired 5-formylindole (**2**). The synthetic sequence starting from 3-methyl-4-nitrobenzaldehyde gives 49% overall yield and represents, to our knowledge, the best route to 5-formylindole (**2**).

Scheme 2



EXPERIMENTAL

The melting points were determined on a Büchi 535 apparatus. The IR spectra were recorded on an Aspect 2000 computer controlled Bruker IFS-113v vacuum optic FT spectrometer using KBr pellets or films of liquids. The ^{1}H NMR spectra were recorded on a Bruker WM 250 FT, or a Varian Gemini-200, or a Varian Unity Inova 400 spectrometer, in deuteriochloroform or dimethylsulfoxide-d_6. Chemical shifts were reported as δ values (ppm) downfield from internal tetramethylsilane.

2-(3-Methyl-4-nitrophenyl)-1,3-dioxolane (**5**).

A mixture of 3-methyl-4-nitrobenzaldehyde (**4**, 16.5 g, 0.1 mol), ethylene glycol (16.7 mL, 0.3 mol) and *p*-toluenesulfonic acid (0.16 g, 1 mmol) was stirred at 130° for 2 h. After cooling to room temperature dichloromethane (160 mL) was added and the solution was extracted with saturated aqueous sodium bicarbonate solution (2x50 mL). The organic phase was washed with water (2x30 mL), dried ($MgSO_4$) and evaporated to afford **5** (17.2, 82%) as a light yellow oil, which can be used in the next reaction step without further purification. After distillation (bp 113-114°, 0.05 mmHg) the product solidified, mp 34-35°; IR (potassium bromide) 1355, 1520 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.54 (s, 3H), 3.96-4.14 (m, 4H), 5.83 (s, 1H), 7.50 (d, *J*=8.2 Hz, 1H), 7.54 (s, 1H), 7.99 (d, *J*=8.2 Hz, 1H).

Anal. Calcd. for $C_{10}H_{11}NO_4$ (209.20): C, 57.41; H, 5.30; N, 6.70. Found: C, 57.25; H, 5.28; N, 6.58.

5-(1,3-Dioxolan-2-yl)-1*H*-indole (**7**).

A solution of acetal **5** (20.9 g, 0.1 mol), *N*,*N*-dimethylformamide dimethyl acetal (94%, 42.5 mL, 0.3 mol) and pyrrolidine (5.4 mL, 7.8 g, 0.11 mol) in DMF (100 ml) was heated at 140° for 7 h under nitrogen atmosphere. After evaporation *in vacuo* (bath temperature < 50°) the residue (**6**, 25.2 g) was dissolved in toluene (220 mL). The solution was hydrogenated in the presence of palladium on charcoal (10%, 3.5 g) under 7x10^5 Pa hydrogen at room temperature. After removal of the catalyst, the solvent was evaporated to dryness and the residue was triturated with toluene (50 mL) to give **7** (12.3 g, 65%) as light yellow crystals, mp 127-128° (toluene), IR (potassium bromide) 1400, 3330 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.83-4.11 (m, 4H), 5.76 (s, 1H), 6.45 (d, *J*=2.7 Hz, 1H), 7.16 (d, *J*=8.5 Hz, 1H), 7.35 (d, *J*=2.7 Hz, 1H), 7.38 (d, *J*=8.5 Hz, 1H), 7.61 (s, 1H), 11.15 (bs, 1H).

Anal. Calcd for $C_{11}H_{11}NO_2$ (189.22): C, 69.83; H, 5.86; N, 7.40. Found: C, 69.51; H, 5.91; N, 7.34.

1*H*-Indole-5-carboxaldehyde (**2**).

To a solution of acetal **7** (9.5 g, 50 mmol) in tetrahydrofuran (100 mL) was added aqueous hydrogen chloride solution (10%, 20 ml) at 0° and the mixture was stirred for 20 min. The reaction mixture was neutralised with saturated aqueous sodium bicarbonate solution. The organic solvent was evaporated and the aqueous residue was extracted with ethyl acetate (3x150 mL). The organic phase was washed with water (2x30 mL), dried ($MgSO_4$) and evaporated to give **2** (6.6 g, 91%), mp 99-101° (diethyl ether-hexane) as light yellow crystals, lit. [10] mp 99-101°.

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