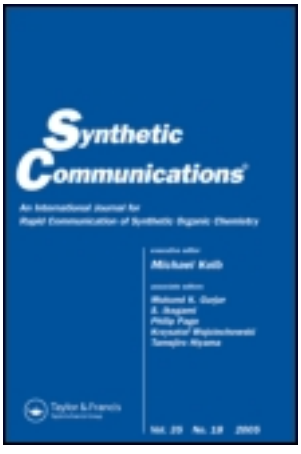

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Simple Synthesis of 7-Formyl-indole

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Simple Synthesis of 7-Formyl-indole

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Abstract: A simple route to 7-formyl-indole (**5**) is described in which appropriately functionalized o-nitrotoluenes (**1**) are converted to 7-hydroxymethyl-indole (**4**) using the Batcho–Leimgruber process. Condensation of 3-methyl-2-nitrobenzyl alcohol (**1a**) with *N*,*N*-dimethylformamide dimethyl acetal yields the enamine **2a**, which upon catalytic hydrogenation affords **4** in 22% yield. When the hydroxyl function in **1** is protected with pivaloyl or tetrahydropyranyl group, the yields of **4** are increased to 39% and 48%, respectively. Finally, **4** is oxidized with pyridinium chlorochromate (PCC) to afford **5** in 86% yield.

Keywords: Batcho–Leimgruber reaction, benzyltriethylammonium borohydride, 7-formyl-indole, 7-hydroxymethyl-indole, pyridinium chlorochromate

INTRODUCTION

In the context of our ongoing research on 7-substituted-indole-based β_3-agonists, it became necessary for us to prepare substantial amounts of 7-formyl-indole. Literature methods[1] to prepare 7-formyl-indole have limitations, and therefore a simple alternative method that utilizes cheap or easily synthesizable starting materials was desirable to overcome difficulties such as the use of highly toxic, air- and moisture-sensitive organometallic reagents and extremes in reaction temperature, and that is amenable to large-scale production.

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Dedicated to Professors H. Junjappa and H. Ila in recognition of their contribution to organosulfur chemistry.

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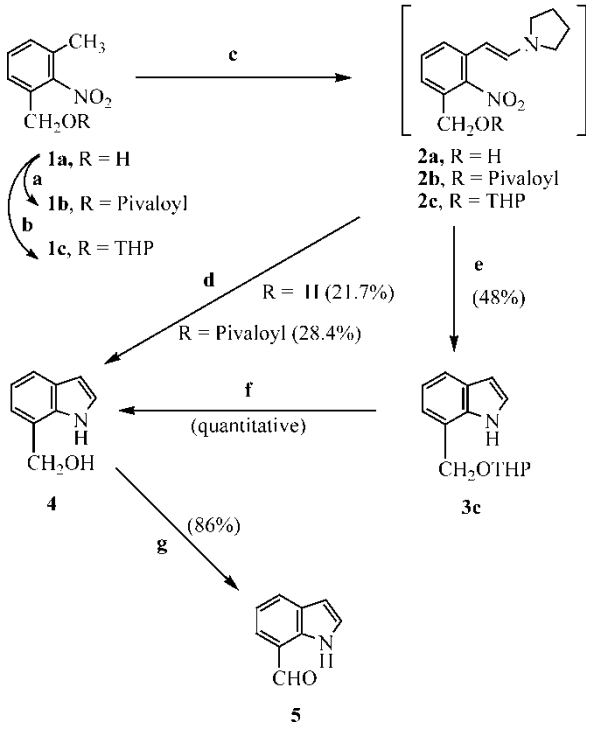
As depicted in Scheme 1, 3-methyl-2-nitrobenzyl alcohol (**1a**)[2] was condensed with *N*,*N*-dimethylformamide dimethyl acetal to yield the corresponding enamine **2a**, which was subjected to catalytic hydrogenation over Raney nickel (type W-2) in the presence of hydrazine hydrate to afford 7-hydroxymethyl-indole (**4**)[1b] in only 22% yield. To improve the yield of **4**, we protected the hydroxyl with a pivaloyl group and subjected (**1b**) to the Batcho–Leimgruber process[3] to obtain 7-hydroxymethyl-indole (**4**) in 39% yield. The pivaloyl group cleaved during the reaction. However, using 2-nitro-3-tetrahydropyranyloxymethyltoluene (**1c**), in which the hydroxyl group was protected as a THP-ether, the Batcho–Leimgruber reaction gave the corresponding 7-tetrahydropyranyloxymethyl-indole (**3c**) in 48% yield. Subsequent cleavage of the THP group gave, almost quantitatively, 7-hydroxymethyl-indole (**4**). Finally, oxidation of 7-hydroxymethyl-indole (**4**) with pyridinium chlorochromate (PCC) afforded 7-formyl-indole (**5**) in 86% yield.



Scheme 1. Reagents and conditions: (a) pivaloyl chloride, pyridine, reflux, 3 h, 99%; (b) 3,4-dihydro-2H-pyran, pyridinium p-toluenesulfonate (catalytic amount), CH_2Cl_2, rt, 3 h, 79%; (c) $Me_2NCH(OMe)_2$, pyrrolidine/DMF, 130–140 °C, 3–6 h; (d) Raney nickel, THF/MeOH, hydrazine–hydrate, 40–50 °C, 1–1.5 h; (e) Raney nickel, THF/MeOH, hydrazine–hydrate, rt, 45 min; (f) p-toluenesulfonic acid monohydrate (catalytic amount), MeOH, 60 °C, 30 min; and (g) pyridinium chlorochromate, CH_2Cl_2, rt, 1.5 h.

In summary, we have developed a simple synthetic method for 7-formyl-indole by utilizing easily synthesizable or commercially available cheap starting materials and reagents.

EXPERIMENTAL

General

Melting points were recorded on Labindia MR-VIS apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 300 (300-MHz) instrument. Chemical shifts are given in parts per million (ppm) relative to tetramethylsilane (TMS). Mass spectra (MS) were obtained on Finnegan Navigator ESI instrument, and the data are reported as m/z (mass spectral service was obtained from Ashco Labs, Mumbai). Microanalysis was done on a Perkin-Elmer CHN Analyzer 2400. Column chromatography was done on silica gel, 100–200 mesh (Sisco Labs., India). Thin-layer chromatography (TLC) was done on aluminum plates precoated with Merck silica gel 60 F_{254}. If not otherwise indicated, commercially available chemicals were used as received. All solvents were laboratory grade, and anhydrous solvents were prepared according to literature procedures and handled under nitrogen.

3-Methyl-2-nitrobenzyl Alchol (1a)

Chlorotrimethylsilane (2.12 mL, 14.3 mmol) in dichloromethane (5 mL) was added to a stirred solution of benzyltriethylammonium borohydride[2d] (2.98 g, 14.3 mmol) in dry dichloromethane (10 mL) at 0 °C. The mixture was stirred for 20 min. Then, a solution of 1.3 g (7.1 mmol) of 3-methyl-2-nitrobenzoic acid[4] in dichloromethane (5 mL) was added to the mixture, and it was stirred at rt for 24 h. The reaction was quenched by adding saturated $NaHCO_3$ solution (20 mL) with cooling. The organic layer was separated and washed with a brine solution (2 × 20 mL), dried ($CaCl_2$), and concentrated to afford 0.7 g (58%) of 3-methyl-2-nitrobenzyl alcohol (**1a**) as a light yellow solid, mp 44–46 °C (lit.[2a] mp: 45–47 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.19 (bs, 1H, D_2O exchangeable) 2.37 (s, 3H, $-C\underline{H_3}$), 4.66 (s, 2H, $C\underline{H_2}$-OH), 7.22–7.43 (m, $3H_{arom}$).

2-Nitro-3-pivaloyloxymethyltoluene (1b)

Pivaloyl chloride (2.16 g, 17.96 mmol) was added to a stirred mixture of **1a** (1.0 g, 5.98 mmol) and pyridine (3 mL). The mixture was stirred under reflux for 3 h. Volatiles were removed under vacuum, and the residue was purified on silica gel by using 5% ethyl acetate in light petroleum as eluent

to afford 1.48 g (99%) of **1b** as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 9H), 2.36 (s, 3H), 5.12 (s, 2H), 7.26–7.39 (m, $3H_{arom}$).

2-Nitro-3-tetrahydropyranyloxymethyltoluene (1c)

3,4-Dihydro-*2H*-pyran (0.55 g, 6.58 mmol) was added to a stirred solution of benzyl alcohol **1a** (1.0 g, 5.98 mmol) in dry methylene chloride (15 mL) at 0 °C, followed by pyridinium-*p*-toluene sulfonate (0.18 g). The mixture stirred at room temperature for 3 h. The mixture was concentrated, and the residue was purified on silica gel by using 5% ethyl acetate in light petroleum containing 0.5% triethylamine. The fractions containing the pure product were concentrated to afford 1.2 g (79%) of **1c** as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.5–1.82 (m, 6H), 2.34 (s, 3H), 3.49–3.56 (m, 1H), 3.79–3.86 (m, 1H), 4.52 (d, 1H, $J = 12.6$ Hz), 4.63 (t, 1H, $J = 3.3$ Hz), 4.81 (d, 1H, $J = 12.9$ Hz), 7.20–7.35 (m, $3H_{arom}$).

7-Hydroxymethyl-indole, General Procedures

A mixture of appropriately substituted *o*-nitrotoluene **1** (5 mmol), *N*,*N*-dimethylformamide dimethyl acetal (10 mmol), and pyrrolidine (10 mmol) in DMF (3 mL) was stirred at rt for 10 min. The reaction flask was then heated at 130 °C for 4 h. (Note: In the case of hydroxymethyl derivative **1a**, an additional 2 equivalents of dimethylformamide dimethyl acetal and pyrrolidine were added after 3 h of reaction time and the mixture continued stirring at 130 °C for additional 3 h to drive the reaction to completion.) TLC indicated completion of the reaction. The mixture was concentrated in vacuo to afford the crude enamine **2** as highly viscous dark red oil, which was used as such in the next step. Raney nickel (type W-2, 0.42 g) and hydrazine hydrate (6.74 mmol) were added to the solution of crude enamine **2** (~4.2 mmol) in dry methanol (15 mL) and THF (10 mL) at rt under nitrogen atmosphere. The mixture stirred for 3 h. Hydrazine hydrate (1.6 equiv) was added to the mixture, which continued stirring at rt for additional 3 h, when TLC indicated completion of the reaction. The mixture was filtered through a Celite pad and washed with hot methanol (25 mL). The filtrate was concentrated to afford the crude 7-hydroxymethyl-indole (**4**). (Note: In the case of O-THP derivative **1c**, the corresponding 7-tetrahydropyranyloxymethyl-indole (**3c**) was obtained.) It was purified on silica gel to furnish pure 7-hydroxymethyl-indole (**4**), mp 53–54 °C (lit.[1b] mp: 56–56.5 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83–2.08 (bs, 1H, D_2O exchangeable), 4.98 (s, 2H), 6.54 (dd, 1H, $J = 2.1$, 1.8 Hz), 6.95–7.06 (m, 2H), 7.24 (dd, 1H, $J = 6.6$, 2.7 Hz), 7.58 (d, 1H, $J = 8.1$ Hz), 8.88 (bs, 1H); IR (neat): 3423, 1438, 1338, 730 cm^{-1}. Anal. calcd for C_9H_9NO: C, 73.44; H, 6.16; N, 9.51. Found C, 73.32; H, 6.67; N, 9.72.

7-Tetrahydropyranyloxymethyl-indole (3c)

It was obtained as a light yellow solid, mp 60–61 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55–1.82 (m, 6H), 3.53–3.57 (m, 1H), 3.86–3.92 (m, 1H), 4.73 (bs, 1H), 4.98 (d, 1H, $J = 11.7$ Hz), 5.31 (d, 1H, $J = 11.7$ Hz), 6.31 (d, 1H, $J = 3.3$ Hz). 6.96–7.06 (m, $2H_{arom}$), 7.21–7.23 (t, 1H, $J = 3.6$ Hz), 7.53 (d, $1H_{arom}$, $J = 7.8$ Hz), 9.60 (s, 1H, indole –NH). Anal. calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.40; N, 6.05. Found: C, 72.33; H, 7.69; N, 6.20.

Deprotection of THP Derivative 3c

p-Toluenesulfonic acid monohydrate (~10 mg) was added to a stirred solution of 7-tetrahydropyranyloxymethyl-indole (**3c**) (200 mg, 0.86 mmol) in anhydrous methanol (10 mL) at room temperature under nitrogen atmosphere. The mixture stirred at 60 °C for 0.5 h. The mixture was concentrated, diluted with ethyl acetate (50 mL), and washed with brine solution (2 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give 130 mg (quantitative) of **4**, and the product was identical (^{1}H NMR, mp, and TLC R_f value) to that obtained from other approaches.

7-Formyl-indole (5)

A solution of **4** (70 mg, 0.47 mmol) in dichloromethane (3 mL) was added to a stirred solution of pyridinium chlorochromate (PCC) (153 mg, 0.71 mmol) in dry dichloromethane (2 mL) at room temperature under inert atmosphere. The mixture was stirred at rt for 1.5 h. The mixture was filtered through a Celite pad and washed with dichloromethane (20 mL). The filtrate, on concentration, afforded 59 mg (86%) of 7-formyl indole (**5**) as a light yellow solid, mp 86–87 °C (lit.[1b] mp: 86.5–87 °C). TLC R_f: 0.5 (1 : 4 ethyl acetate/petroleum ether). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.58 (t, 1H, $J = 2.4$ Hz), 7.22 (t, 1H, $J = 7.2$, 7.8 Hz), 7.39 (t, 1H, $J = 2.7$ Hz), 7.72 (d, 1H, $J = 7.2$ Hz), 7.93 (d, 1H, $J = 7.5$ Hz), 10.12 (s, $1H_{aldehyde}$), 11.51 (bs, 1H, NH_{indole}). Anal. calcd. for C_9H_7NO: C, 74.46; H, 4.86; N, 9.65. Found: C, 74.39; H, 5.24; N, 9.87.

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