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Synthesis of *N*-Protected/Free Indole-7-Carboxaldehyde

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Abstract: A direct method for the preparation of *N*-protected/free indole-7-carboxaldehyde is reported from the corresponding *N*-protected 7-bromomethylindoles using three different conditions.

Keywords: bromomethylindole, 7-cyanomethylindole, 7-hydroxyindole, indole-7-carboxaldehyde

INTRODUCTION

Synthesis of 3- and 2-substituted indoles are easily achieved through direct electrophilic substitution[1] and lithiation[2] procedures, respectively. However, the syntheses of indoles having substituents at the benzene portion (4-, 5-, 6-, and 7-positions) are very limited.[3] In particular, the synthesis of 7-substituted indoles are difficult.

Moyer and coworkers reported the first synthesis of indole-7-carboxaldehyde[4] using halogen–metal exchange reaction of 7-bromoindole followed by its subsequent reaction with dry dimethylformamide (DMF). Bartoli et al. reported a synthesis of 7-substituted indoles[5] via the reaction of 2-substituted nitrobenzene with vinylmagnesium bromide. Dobson et al. reported a facile synthesis of 7-formylindole[6] following the procedure developed by Bartoli and coworkers. Dobbs et al. reported a simple synthesis of 7-bromoindole

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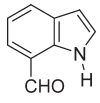
derivatives[7] involving the Bartoli protocol. Recently, Pirrung and coworkers reported a novel synthesis of a variety of 7-substituted indoles[8] involving an improved Bartoli protocol. Kolis and coworkers reported[9] a simple synthesis of 7-cyanomethylindoles and 7-acetamidomethylindoles starting from the *N*-protected indole-7-carboxaldehydes. Hartung and coworkers reported[10] a facile synthesis of 7-substituted indoles, involving a directed lithiation of *N*-protected-2-trimethylsilylindole. Ishiyama and Yamada reported a simple synthesis of 7-hydroxyindole,[11] a crucial intermediate of natural product AJ-9766, a potent and selective adrenaline β-3 agonist. Over the years, *N*-protected bromomethylindoles at the 2/3-position have been extensively used for the synthesis of various indole alkaloids.[12]



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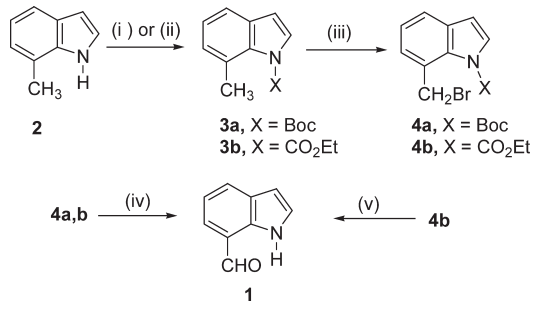
RESULTS AND DISCUSSION

The required 7-methylindole **2** was prepared using a published procedure.[13] Attempted phenylsulfonylation of **2** using various conditions (NaH/THF or LDA/THF) did not afford the *N*-phenylsulfonyl-7-methylindole; instead, only the starting material was recovered. However, *t*-butoxycarbonylation of **2** was smoothly achieved in 85% yield using Boc_2O and 4-dimethylaminopyridine (DMAP) in acetonitrile. Similarly, a carbethoxylation of **2** was also achieved in 69% yield using the phase transfer catalyst (PTC) condition via a slow addition of ethyl chloroformate. The *N*-protected 7-methylindoles **3a** and **3b** were smoothly converted into the respective bromomethylindoles **4a** and **4b** using N-bromosuccinimide (NBS) in the presence of a catalytic amount of benzoylperoxide in CCl_4 at reflux. The bromo compound **4a** or **4b** was smoothly converted into the indole-7-carboxaldehyde **1** using $NaHCO_3$ and dry DMSO under microwave irradiation conditions in 47% and 54% yields, respectively. The hydrolysis of the *N*-carbethoxybromomethylindole **4b** using 10% NaOH in ethanol followed by MnO_2 oxidation afforded indole-7-carboxaldehyde **1** in 40% overall yield (Scheme 1).

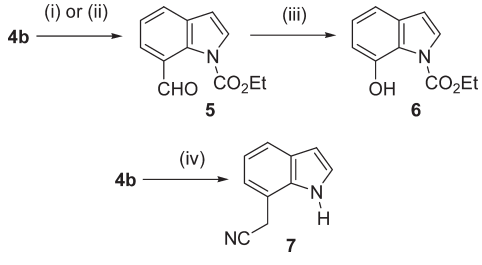
The bromomethylindole **4b** can be smoothly converted into *N*-carbethoxyindole-7-carboxaldehyde **5** in 61% yield using a modified Hass condition.[14] Alternatively, on refluxing bromo compound **4b** with tetrabutylammonium dichromate[15] in dry chloroform led to the isolation of *N*-carbethoxyindole-7-carboxaldehyde **5** in 73% yield. The attempted Baeyer–Villiger reaction of *N*-carbethoxyindole-7-carboxaldehyde **5** using *m*-CPBA in dicholoromethane (DCM) was complicated. However, a smooth Baeyer–Villiger reaction of *N*-carbethoxyindole-7-carboxaldehyde **5** was performed using a 30% solution of H_2O_2 containing a catalytic amount of sulfuric acid in methanol at reflux.



Scheme 1. Reagents and conditions: (i) Boc_2O/DMAP, CH_3CN 85%; (ii) (a) benzene/50% NaOH, n-Bu_4NHSO_4 (cat.), (b) $ClCO_2$ Et (slow addition), 69%; (iii) NBS/$(PhCOO)_2$ (cat.), CCl_4, reflux; (iv) $NaHCO_3$/DMSO, MW (3 × 10 s), 47%, 54%; (v) (a) 10% NaOH/EtOH, (b) MnO_2/DCM, rt, 40%.

Removal of methanol followed by column chromatographic purification afforded 7-hydroxy-*N*-carbethoxyindole **6** in 57% yield. Finally, the bromo compound **4b** was converted into the 7-cyanomethylindole **7** in 60% yield (Scheme 2).

In conclusion, we have reported an efficient preparation of *N*-protected/free indole-7-carboxaldehydes. In comparison to the existing procedures,[4,7] the methods described herein are simple, straightforward, and cost-effective. We hope the *N*-protected 7-bromomethylindoles, *N*-protected indole-7-carboxaldehydes, and *N*-protected 7-hydroxyindole will be useful as intermediates for the synthesis of cyclin dependent kinase (CDK) inhibitors,[9,16] and 7-hydroxylated indole alkaloids.[11,17]



Scheme 2. Reagents and conditions: (i) n-$(Bu_4N)_2Cr_2O_7/CHCl_3$, N_2, reflux, 73%; (ii) 2-nitropropane/NaH, DMF, N_2, 0°C to rt, 61%; (iii) 30% H_2O_2/MeOH, H_2SO_4 (cat.), reflux, 57%; (iv) (a) NaCN/DMSO-THF, (b) 40% aq. KOH, EtOH, 60%.

EXPERIMENTAL

All melting points were uncorrected. Reagents were purchased from commercial sources and used as received without purification. Solvents were dried by

standard procedures. Column chromatography was carried on silica gel (grade 60, mesh size 230–400, Merck). IR spectra were recorded on a Shimadzu 8300 instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol 400-MHz spectrometer with solvent signals as internal standard. Chemical shift values were quoted in parts per million (ppm), and coupling constants were quoted in hertz. Chemical shift multiplicities were reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Mass spectra were obtained on a Jeol DX-303 (electron impact, 70 ev) spectrometer. Elemental analyses were carried out on a Perkin-Elmer 240B analyzer.

Preparation of 7-Methylindole 2

To a solution of anhydrous $FeCl_3$ (12.5 g, 77.06 mmol) in dry methanol (300 mL), (E)-1-(3-methyl-2-nitrostyryl)pyrrolidine[13] (43.78 g, 0.19 mol) was added. To a solution of anhydrous F_eCl_3 (12.5 g, 77.06 mmol) in dry methanol (300 ml), activated charcoal (32.0 g) was added and refluxed in a water bath. After 10 min, 80% hydrazine hydrate (34 mL) was carefully added drop wise via addition funnel (1 h). After the addition of hydrazine hydrate was completed, the reaction mixture was refluxed for 3 h. It was then cooled to room temperature, and the insoluble residue was filtered off through a Celite® bed. The insoluble residue was washed with methylene chloride (4 × 30 mL). The combined organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo to afford a dark liquid. The crude product was purified via Soxhlet extraction (pure hexane) to give compound **4** (16.6 g, 67%) as a colorless solid, mp 82°C (lit.[13] 83–84°C).

Preparation of 1-*Tert*-butyloxycarbonyl-7-methylindole 3a

To a solution of 7-methylindole **2** (1.0 g, 7.63 mmol) in acetonitrile (25 mL) under nitrogen atmosphere, di-*tert*-butyl dicarbonate (2 mL, 8.71 mmol) and DMAP (0.18 g, 1.47 mmol) were added and stirred at room temperature for 30 min. The solvent was removed in vacuo, and the resultant crude product was diluted with ethyl acetate and washed with an aqueous solution of 1 N HCl (2 × 50 mL) and brine (100 mL) and dried (Na_2SO_4). After the removal of solvent, the crude product was purified by column chromatography (silica gel) using pure hexane as an eluant to afford product **3a** (1.50 g, 85%) as a thick colorless liquid. IR (KBr): 1749 (CO_2 ^{t}Bu) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.68$ (s, 9H), 2.70 (s, 3H), 6.58 (d, $J = 3.2$ Hz, 1H), 7.14–7.20 (m, 2H), 7.44 (d, $J = 7.2$ Hz, 1H), 7.57 (d, $J = 3.2$ Hz, 1H). Anal. calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.76; H, 7.36; N, 6.10.

Preparation of 1-Carbethoxy-7-methylindole 3b

7-Methylindole **2** (5 g, 38.1 mmol) was dissolved in benzene (70 mL). To this, 50% NaOH solution (30 mL) and a catalytic amount of tetrabutylammonium hydrogen sulfate were added and stirred vigorously for 15 min. Ethyl chloroformate (7.3 mL, 76.3 mmol) was slowly added (15 min). Then the two-phase system was stirred at room temperature for 10 min and diluted with water (30 mL). The organic layer was separated, and the aqueous layer was extracted with benzene (2 × 10 mL). The combined organic layer was dried (Na_2SO_4). Benzene was then removed completely, and the crude product was purified by flash column chromatography (silica gel) using pure hexane as an eluant to afford product **3b** (5.34 g, 69%). IR (KBr): 1740 cm^{-1} (CO_2Et). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.43$ (t, $J = 7.1$ Hz, 3H), 2.65 (s, 3H), 4.44 (q, $J = 7.2$ Hz, 2H), 6.56 (d, $J = 3.6$ Hz, 1H), 7.09–7.17 (m, 2H), 7.39 (d, $J = 7.4$ Hz, 1H), 7.59 (d, $J = 3.7$ Hz, 1H). MS (EI, 70 eV): m/z (%): 203.4 (M^+, 59.7), 144.2 (61.8), 131.2, 130.3 (52.3). Anal. calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.83; H, 6.49; N, 6.78.

Preparation of 1-*Tert*-butyloxycarbonyl-7-bromomethylindole 4a

A mixture of 1-*tert*-butyloxycarbonyl-7-methylindole **3a** (1.2 g, 5.19 mmol) and finely powdered NBS (0.92 g, 5.19 mmol) in dry CCl_4 (20 mL) containing a catalytic amount of dibenzoyl peroxide was refluxed for 1 h and cooled. The floated succinimide was filtered off and washed with CCl_4 (5 mL). The solvent was then completely removed in vacuo to afford bromo compound **4a** (1.40 g, 87%) as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.66$ (s, 9H), 5.24 (s, 2H), 6.55 (d, $J = 3.2$ Hz, 1H), 7.17 (t, $J = 7.2$ Hz, 1H), 7.25 (d, $J = 7.2$ Hz, 1H), 7.55 (d, $J = 3.9$ Hz, 1H), 8.06 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 28.01$, 35.89, 83.86, 107.10, 122.01, 122.96, 127.12, 128.28, 128.38, 128.78, 134.21, 149.28.

Preparation of 1-Carbethoxy-7-bromomethylindole 4b

A mixture of 1-carbethoxy-7-methylindole **3b** (1.0 g, 4.92 mmol) and finely powdered NBS (0.88 g, 4.92 mmol) in dry CCl_4 (20 mL) containing a catalytic amount of dibenzoyl peroxide was refluxed for 1 h and cooled. The floated succinimide was filtered off and washed with CCl_4 (5 mL). The solvent was then completely removed under vacuo to afford bromo compound **4b** (1.21 g, 87%) as an orange liquid. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.40$ (t, $J = 7.2$ Hz, 3H), 4.43 (q, $J = 7.2$ Hz, 2H), 5.12 (s, 2H), 6.53 (d, $J = 4.0$ Hz, 1H), 7.11–7.22 (m, 2H), 7.39 (d, $J = 7.6$ Hz, 1H), 7.55 (d, $J = 4.0$ Hz, 1H). MS (EI, 70 eV): m/z (%): 281.1 (M^+, 39.1), 283.1 ($M^+ + 2$, 36.5), 202.16 (100), 176.2 (93.9), 129.1 (69.5), 77.1 (39.0).

Preparation of Indole-7-carboxaldehyde 1 from 4a using Microwave Irradiation

To a solution of 1-*tert*-butyloxy-7-bromomethylindole **4a** (0.4 g, 1.33 mmol) in dry DMSO (2 mL), anhydrous $NaHCO_3$ (0.36 g, 2.6 mmol) was added. The reaction mixture was irradiated in a microwave oven for 30 s. Then it was poured over crushed ice, and the crude product was extracted with ethyl acetate (2 × 20 mL). The organic layer was washed with brine solution (20 mL) followed by water (2 × 25 mL). The combined organic layer was dried (Na_2SO_4). The solvent was completely removed, and the crude product was purified by flash column chromatography (silica gel; hexane–EtOAc, 97:3) to afford compound **1** (0.09 g, 47%) as a colorless solid, mp 86–87°C (lit.[4] 87–89°C).

Preparation of Indole-7-carboxaldehyde 1 from 3b

To a stirred suspension of bromo compound **4b** (0.5 g, 1.77 mmol) in ethanol (10 mL), 10% NaOH (5 mL) was added and stirred at room temperature for 30 min. Thin-layer chromatography (TLC) monitoring shows the disappearance of starting material. The crude product was extracted with EtOAc (2 × 15 mL), washed with water (2 × 30 mL), and dried (Na_2SO_4). Solvent was completely removed and the resulting crude indoly-7-methanol (0.38 g, 2.58 mmol) was dissolved in dry methylene chloride (20 mL). To this, active MnO_2 (1.76 g, 20.23 mmol) was added and stirred at room temperature for 2 h. The reaction mixture was then passed through the Celite® bed, and the filtrate was concentrated. The crude product was purified by column chromatography (silica gel; hexane–EtOAc, 97:3) to afford compound **1** (0.15 g, 40%), mp 86–87°C (lit.[4] 87–89°C).

Preparation of Indole-7-carboxaldehyde 1 under Microwave Conditions

To a solution of bromo compound **4b** (2 g, 7.01 mmol) in dry DMSO (5 mL), anhydrous $NaHCO_3$ (1.2 g, 14.2 mmol) was added. The reaction mixture was irradiated in a household microwave oven for 3 × 10 s. Then it was poured over crushed ice, and the crude product was extracted with ethyl acetate (2 × 30 mL). The combined organic layer was washed with brine solution (30 mL) followed by water (25 mL) and dried (Na_2SO_4). Removal of solvent followed by flash-column chromatographic purification (silica gel; hexane–EtOAc, 97:3) afforded **1** (0.56 g, 54%), mp 86–87°C (lit.[4] 87–89°C).

Preparation of 1-Carbethoxyindole-7-carboxaldehyde 5 using $(Bu_4N)_2Cr_2O_7$

To a solution of bromo compound **4b** (2 g, 7.1 mmol) in dry chloroform (20 mL), tetrabutylammonium dichromate (4.97 g, 7.1 mmol) was added and refluxed under a nitrogen atmosphere for 2 h. The reaction mixture was then filtered through Celite®. Removal of solvent followed by flash-column chromatographic purification (silica gel; hexane–EtOAc, 99:1) afforded product **5** (1.12 g, 72.7%) as a colorless solid, mp 54–56°C. IR (KBr): 1739 (CO_2Et), 1672 (CHO) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.43$ (t, $J = 7.3$ Hz, 3H), 4.47 (q, $J = 7.3$ Hz, 2H), 6.66 (d, $J = 3.9$ Hz, 1H), 7.32 (t, $J = 7.3$ Hz, 1H), 7.65 (d, $J = 3.9$ Hz, 1H), 7.72–7.74 (m, 2H), 10.55 (s, 1H, CHO). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.18$, 64.14, 108.51, 123.37, 125.05, 125.58, 125.99, 127.80, 132.03, 132.79, 151.34, 190.85. MS (EI, 70 eV): m/z (%) = 218 (M^+, 8), 186 (12), 106 (41), 85 (24), 58 (100). Anal. calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.17; H, 5.20; N; 6.58.

Preparation of 1-Carbethoxyindole-7-carboxaldehyde 5

To a suspension of hexane-washed sodium hydride (80 mg, 1.67 mmol) in dry DMF (5 mL) at 0°C, 2-nitropropane (0.2 mL, 2.23 mmol) was added. The mixture was stirred for 15 min at the same temperature under a nitrogen atmosphere and was treated dropwise with a solution of bromo compound **4b** (0.3 g, 1.06 mmol) dissolved in dry DMF (3 mL). After the bromo compound was consumed (monitored by TLC), the reaction mixture was quenched with ice water (10 mL), extracted with chloroform (2 × 10 mL), and dried (Na_2SO_4). Removal of solvent followed by column chromatographic purification (silica gel; hexane–EtOAc, 99:1) afforded aldehyde **5** (0.14 g, 61%) as a colorless solid, mp 54–56°C.

Preparation of *N*-Carbethoxy-7-hydroxyindole 6

To a solution of 1-carbethoxy-7-carboxaldehyde **5** (0.3 g, 1.38 mmol) in methanol (15 mL), 30% H_2O_2 (1 mL) and conc. H_2SO_4 (5 drops) were added and refluxed under a nitrogen atmosphere for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with DCM (25 mL). The organic layer was then washed with $NaHCO_3$ (2 × 10 mL) followed by brine solution (2 × 10 mL) and dried (Na_2SO_4). Removal of solvent followed by column chromatographic purification (silica gel; hexane–EtOAc, 98:2) afforded product **6** (0.16 g, 57%) as a colorless solid, mp 60°C. IR (KBr): 1697 (CO_2Et), 3146 (O-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.44

(t, $J = 7.3$ Hz, 3H), 4.47 (q, $J = 7.3$ Hz, 2H), 6.54 (d, $J = 3.4$ Hz, 1H), 6.84 (d, $J = 7.8$ Hz, 1H), 7.02 (d, $J = 7.8$ Hz, 1H), 7.14 (t, $J = 7.8$ Hz, 1H), 7.46 (d, $J = 3.9$ Hz, 1H), 10.63 (s, 1H, OH). Anal. calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.47; H, 5.34; N, 6.78.

Preparation of 7-Cyanomethylindole 7

To a stirred suspension of NaCN (0.36 g, 7.34 mmol) in DMSO (10 mL), dry THF (5 mL) was added, and the reaction mixture was stirred at 0°C for 10 min. To this, 1-carbethoxy-7-bromomethylindole **4b** (1.38 g, 4.89 mmol) was added. The reaction mixture was stirred at 0°C for 4 h. Then the reaction mixture was diluted with water (20 mL). The product was extracted with EtOAc (3 × 5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude 1-carbethoxy-7-cyanomethylindole was treated with 40% aqueous KOH (5 mL) in ethanol (15 mL). The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated under vacuo, and the residue so obtained was diluted with water (15 mL), extracted with EtOAc (2 × 10 mL), and dried (Na_2SO_4). Removal of the solvent followed by column chromatographic purification (silica gel; hexane–EtOAc, 97:3) afforded **8** (0.46 g, 60%) as a brown liquid. IR (KBr): 3359 (N-H), 2253 (CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 2H), 6.61 (t, $J = 3.1$ Hz, 1H), 7.10–7.14 (m, 2H), 7.24 (t, $J = 3.1$ Hz, 1H), 7.66 (d, $J = 2.4$ Hz, 1H), 8.61 [s (broad), 1H]. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 29.83, 103.45, 112.27, 117.85, 120.23, 121.32, 122.17, 125.20, 128.83, 133.95. MS (EI, 70 eV): m/z (%): 156.6 (M^+, 100), 130.4 (38.8), 85.4 (68.3). Anal. calcd. for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.93; H, 5.25; N, 17.89.

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