An Improved Synthesis of Hydroxyindoles

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Abstract: An improved synthetic procedure for the synthesis of 6- and 7-hydroxyindoles is described. In this method, the addition of two chlorine atoms in 1-benzyloxy-4,5-dichloro-2-nitrobenzene (**3**) and 1-benzyloxy-2,6-dichloro-3-nitrobenzene (**9**) facilitated the subsequent cyanomethylation step to give substituted cyanomethyl-dichloronitrobenzenes **4** and **10**, leading to an overall increase in the yield of the hydroxyindoles **6** and **12**.

Key words: indole synthesis, hydroxyindoles, cyanomethylation

Hydroxyindoles serve as useful starting materials and intermediates in various fields. Both 4- and 5-hydroxyindoles are readily available from commercial sources, whereas 6- and 7-hydroxyindoles are supplied only in minute amounts from combinatorial libraries.

Recently, 4-hydroxyindole was used as a starting material in the synthesis of a new generation of dopaminergic agents,[1] and products of electrochemical oxidation of 4-hydroxyindole were reported to produce substantial changes in blood parameters of albino mice.[2] 5-Hydroxyindole has been used as an intermediate in the synthesis of novel non-steroidal inhibitors of human prostatic α-reductase[3] and was reported to exhibit neuroprotective properties without estrogenic side effects.[4] Some 4-, 6- and 7-hydroxyindoles have been used in the manufacture of hair dyes.[5]

Mixtures of all four isomeric 4-, 5-, 6- and 7-hydroxyindoles have been isolated in poor yields by direct oxidation of indole with H_2O_2–SbF_5 or Fe^{+3}–H_2O_2.[6] 6-Hydroxyindole has been obtained in an overall 62% yield via a Baeyer–Villiger oxidation of 6-chloroacetyl-1-pivaloylindole.[7] 7-Hydroxyindole was prepared via a multi-step approach in an overall 35% yield involving DDQ oxidation of a 4,5,6,7-tetrahydroindole.[8] Makosza et al. obtained it in 39% overall yield via the 2-benzyloxy-4-chloro-6-cyanomethyl-nitrobenzene intermediate, that was prepared in turn from 2-benzyloxy-4-chloronitrobenzene in 68%.[9]

In the course of our investigations we have developed an improved synthesis for the 6- and 7-hydroxyindoles leading to better yields of the products.

Makosza's procedure for 7-hydroxyindole is based on a nucleophilic substitution of hydrogen on a nitrobenzene ring by the carbanion obtained from 4-chlorophenoxyacetonitrile. To facilitate the reaction, the nitrobenzene ring was activated by the addition of an electron-withdrawing chloro substituent, to give the desired product in 68% yield. In our investigations, the addition of a second chloro substituent further enhanced the reactivity of the substituted nitrobenzene ring, whereby the yield of the cyanoalkyl product increased to 82–85%. In addition, in the course of the subsequent reductive cyclization, Makosza, using 10% Pd/C in a mixture of EtOH–AcOH, reported a 39% yield of 7-hydroxyindole. All our attempts to repeat this procedure failed. However, when the reaction was carried out in 95% EtOH in the presence of PtO_2 but in the absence of acid, the 7-benzyloxy-4,5-dichloroindole was obtained in 35% yield. Reductive removal of the benzyl and chloro groups was accomplished with ammonium formate–MeOH–10% Pd/C, to give 7-hydroxyindole in 85% yield.

Our inability to carry out the reductive cyclization in the presence of acetic acid is in agreement with Walker's observation that in an attempted synthesis of indoles via an analogous path to that described herein, the reduction stopped at the amidinium stage when carried out in acetic acid, due to a resonance stabilization or the inability of the catalyst to adsorb the protonated amidinium intermediate.[10] Under neutral conditions in EtOAc, the reaction proceeded satisfactorily, presumably via an intramolecular cyclization followed by loss of ammonia. An alternative mechanism involves hydrolysis of the imine (obtained by reduction of the nitrile) to the corresponding aldehyde, which cyclizes to an indoline intermediate that then isomerizes to the indole.[11] Our procedure calls for the use of 95% EtOH as solvent in the absence of acid.

7-Hydroxyindole (**6**) (Scheme 1) was prepared in five steps starting from 3,4-dichlorophenol (**1**). Nitration of **1** led to a mixture of mono- and di-nitrophenols that was separated. Isomer **2** was further benzylated to provide **3**. Cyanomethylation of **3** followed by catalytic hydrogenation gave the substituted indole **5**. In an attempted hydrogenolytic cyclization of **4** in the presence of **5** or 10% Pd/C catalyst, containing varying weight percentages of water, only removal of the benzylic group was observed, without concomitant cyclization. These results led us to use platinum oxide as an alternative catalyst. Hydrogenation in non-acidic media, as described above, using the PtO_2 was found to provide the best reaction conditions. Finally, the concomitant removal of the both chlorides together with the benzyl group gave the desired 7-hydroxyindole (**6**) in an overall 8% yield.

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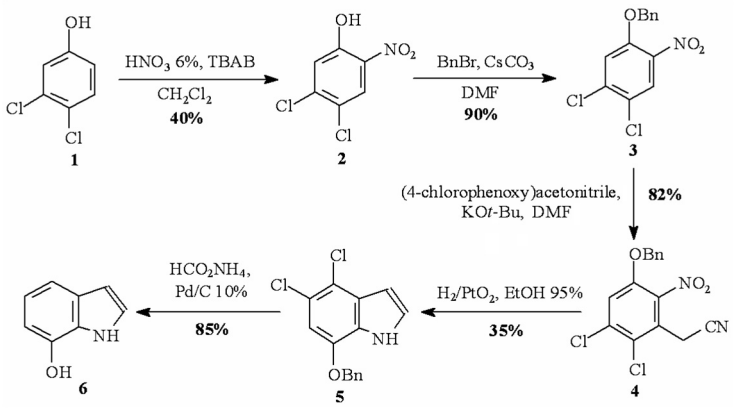


Scheme 1

The presence of the chloride atoms increased the electrophilicity of the nitro-aryl group towards the cyanomethylation, while preventing the unfavored *para*-substitution of the ring. Thus, in the course of cyanomethylation of **9** (Scheme 2) the presence of two chlorides helped to direct the substitution only to the desired, available *ortho*-position, to give **10**.

m-Nitrophenol (**7**) underwent dichlorination at the *ortho* positions to the phenolic OH to give 2,6-dichloro-3-nitrophenol (**8**),[12] which was benzylated to provide the protected analog **9**. Cyanomethylation of **9**, followed by catalytic hydrogenation, as in the case of 7-hydroxyindole, followed by removal of the protective groups gave the 6-hydroxyindole (**12**).

^{1}H and ^{13}C NMR spectra were obtained on Bruker AC-200 and AM-300 spectrometers at 200 MHz and 300 MHz, respectively. Chemical shifts are expressed in ppm downfield from TMS, which was used as internal standard. The values are given in δ scale. Mass spectra were obtained on a Varian Mat 731 spectrometer (CI = chemical ionization). HRMS were obtained on a VG AutoSpec E spectrometer. Progress of the reactions was monitored by TLC on silica gel (Merck, Art. 5554) or alumina (Riedel-de Haen, Art. 37349). Flash chromatography was carried out on silica gel (Merck, Art. 9385). Commercially available 3,4-dichlorophenol (**1**) and *m*-nitrophenol (**7**) were used without further purification.

4,5-Dichloro-2-nitrophenol (2)

A solution of 3,4-dichlorophenol (**1**) (1.63 g, 10 mmol) and tetra-*n*-butylammonium bromide (TBAB) (32 mg, 10% mol) in CH_2Cl_2 (30 mL) was added to a 6% aq solution of HNO_3 (20 mmol). The reaction mixture was stirred at r.t. for 24 h. The organic phase was separated, dried over $MgSO_4$ and evaporated. The crude residue was purified by silica gel flash chromatography (hexane–EtOAc, 15:1) to give the **2** as a yellow solid (0.83 g, 40% yield); mp 60–65 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.45 (br s, 1 H, OH), 8.23 (s, 1 H, H-C3), 7.35 (s, 1 H, H-C6).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 153.5 (C1), 142.3 (C5), 125.8 (C3), 124.4 (C2), 124.1 (C4), 121.5 (C6).

MS (DCI, CH_4): *m*/*z* (%) = 206.95 (100) [M].

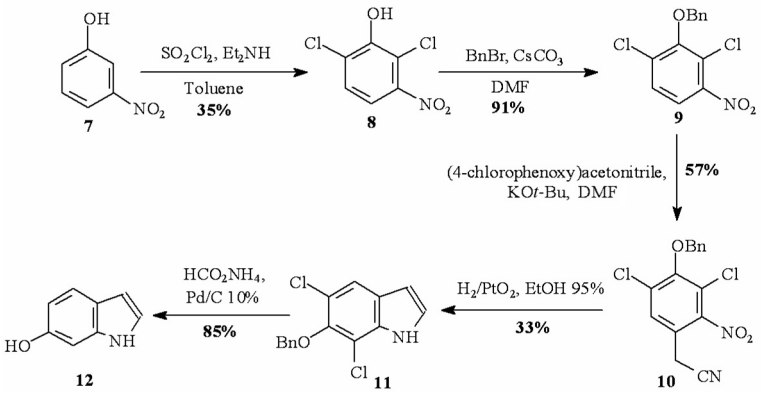
HRMS (DCI, CH_4): *m*/*z* [MH^+] calcd for $C_6H_3Cl_2NO_3$: 206.948999; found: 206.947236.

Anal. Calcd for $C_6H_3Cl_2NO_3$ (207.8): C, 34.65; H, 1.45; N, 6.73. Found: C, 34.63; H, 1.49; N, 6.53.

2,6-Dichloro-3-nitrophenol (8)[12]

To a solution of *m*-nitrophenol (**7**) (2 g, 14.3 mmol) in toluene (100 mL) was added sulfuryl chloride (2.18 mL, 28.6 mmol) and distilled diethylamine (0.11 mL, 1.12 mmol). The reaction mixture was stirred at 70 °C overnight. The mixture was concentrated under reduced pressure and the crude residue was purified by flash chromatography (hexane–EtOAc, 10:1) to provide **8** as a white solid (1.04 g, 35% yield); mp 105–110 °C [lit.[12] 107–108 °C].

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.52–7.39 (ABq, *J* = 8.8 Hz, 2 H, H-C5, H-C4), 6.31 (br s, 1 H, OH).



Scheme 2

^{13}C NMR (200 MHz, $CDCl_3$): δ = 149.5 (C1), 146.9 (C3), 127.8 (C5), 125.7 (C6), 117.2 (C4), 115.1 (C2).

MS (EI): *m/z* (%) = 207 (70) [M].

HRMS (DCI, CH_4): *m/z* [MH^+] calcd for $C_6H_3Cl_2NO_3$: 206.948999; found: 206.941014.

Anal. Calcd for $C_6H_3Cl_2NO_3$ (207.8): C, 34.65; H, 1.45; N, 6.73. Found: C, 34.64; H, 1.47; N, 6.6.

General Procedure A

To a solution of a phenol (0.13 mol) in DMF (200 mL), $CsCO_3$ (0.13 mol) was added portion-wise. To this vigorously stirred suspension was rapidly added benzyl bromide (0.13 mol) and the obtained mixture was stirred at r.t. for 16 h, giving a mustard colored suspension. To the mixture was added toluene (100 mL) and 1 N aq NaOH (100 mL), and the layers were separated. The organic phase was washed with 1 N aq HCl (100 mL). Both the acidic and alkaline aqueous layers were further extracted with toluene (1 × 20 mL and 3 × 20 mL, respectively) and the combined organic phase was washed with water (40 mL), brine (40 mL), dried with $MgSO_4$, and concentrated to provide the *O*-benzylated phenol.

1-Benzyloxy-4,5-dichloro-2-nitrobenzene (3)

Compound **3**, prepared from **2** by general procedure A, was isolated as a yellow solid (90% yield); mp 103–107 °C and used without further purification.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.03 (s, 1 H, H-C3), 7.47–7.35 (m, 5 H, Ph), 7.22 (s, 1 H, H-C6), 5.22 (s, 2 H, *C*H_2Ph).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 150.9 (C1), 141.2 (C5), 138.5 (C2), 134.5 (Ph), 128.6 (Ph), 128.6 (Ph), 127.1 (C3), 124.4 (C4), 117.1 (C6), 71.5 (*C*H_2Ph).

MS (DCI/CH_4): *m/z* (%) = 91 (100) [$C_7H_7^+$], 181 (20) [M – C_3HClNO_2].

HRMS (DCI, CH_4): *m/z* [M^+] calcd for $C_{13}H_9Cl_2NO_3$: 296.995949; found: 296.988127.

1-Benzyloxy-2,6-dichloro-3-nitrobenzene (9)

Compound **9**, prepared from **8** by general procedure A, was isolated as a white solid (91% yield); mp 65–68 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.67–7.60 (d, *J* = 9.5 Hz, 1 H, H-C4), 7.58–7.35 (m, 6 H, H-C5, Ph), 5.10 (s, 2 H, CH_2Ph).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 152.8 (C1), 135.4 (C3), 134.5 (Ph), 128.9 (Ph), 128.7 (C5), 128.6 (Ph), 128.6 (Ph), 124.1 (C6), 121.0 (C4), 116.6 (C2), 75.5 (*C*H_2Ph).

MS (EI): *m/z* (%) = 181 (100) [$C_{10}H_8OCl$], 220 (67) [$C_7H_4NO_3Cl_2$], 299 (50) [M].

HRMS (DCI, CH_4): *m/z* [M – H] calcd for $C_{13}H_9Cl_2NO_3$: 295.988124; found: 295.988501.

Anal. Calcd for $C_{13}H_9Cl_2NO_3$ (298.12): C, 52.37; H, 3.04; N, 4.70. Found: C, 52.35; H, 3.08; N, 4.74.

General Procedure B

A solution of an *O*-benzyl protected nitrophenol (50 mmol) and (4-chlorophenoxy)acetonitrile (55 mmol) in DMF (40 mL) was added dropwise to a solution of *t*-BuOK (0.11 mol) in DMF (100 ml) at –20 °C to –10 °C. The purple mixture obtained was stirred at this temperature for 30 min and then poured into ice-cold 5% HCl giving a yellow colored suspension. In some cases the product solidified at this stage, and was isolated, otherwise the mixture was extracted several times with toluene. The combined organic phase was washed with water, brine, dried over $MgSO_4$ and evaporated to give a yellow-brown oil, which was further purified.

(3-Benzyloxy-5,6-dichloro-2-nitrophenyl)acetonitrile (4)

Compound **4**, prepared from **3** by general procedure B, precipitated as a white solid, when the 5% HCl was added to a reaction mixture. The precipitate was filtered and dried under vacuum over P_2O_5. Recrystallization from EtOH provided **4** as a white solid in 82% yield; mp 135–140 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.42–7.38 (m, 5 H, Ph), 7.22 (s, 1 H, H-C4), 5.20 (s, 2 H, CH_2Ph), 3.80 (s, 2 H, CH_2CN).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 149.0 (C3), 136.9 (C5), 134.0 (Ph), 129.0 (Ph), 128.9 (Ph), 128.6 (C2), 127.2 (Ph), 127.1 (Ph), 126.9 (C6), 123.7 (C1), 116.6 (C4), 113.9 (CN), 72.0 (CH_2Ph), 19.2 (*C*H_2CN).

MS (DCI, CH_4): *m/z* (%) = 91 (50) [$C_7H_7^+$], 336 (20) [M], 427 (100) [M + $C_7H_7^+$].

HRMS (DCI, CH_4): *m/z* [M] calcd for $C_{15}H_{10}Cl_2N_2O_3$: 336.006848; found: 336.015868.

Anal. Calcd for $C_{15}H_{10}Cl_2N_2O_3$ (336.8): C, 53.44; H, 2.99; N, 8.31. Found: C, 53.37; H, 2.98; N, 7.73.

(4-Benzyloxy-3,5-dichloro-2-nitrophenyl)acetonitrile (10)

Compound **10** was prepared from **9** by general procedure B. The crude residue was purified by flash chromatography (hexane–EtOAc, 20:1) and was isolated as a white solid in 57% yield; mp 75–80 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.63 (s, 1 H, H-C6), 7.58–7.50 (m, 2 H, Ph), 7.46–7.40 (m, 3 H, Ph), 5.10 (s, 2 H, CH_2Ph), 3.73 (s, 2 H, CH_2CN).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 152.3 (C4), 134.9 (C2), 132.8 (Ph), 131.0 (C5), 129.2 (Ph), 128.9 (Ph), 128.6 (Ph), 128.6 (C6), 123.2 (C1), 121.9 (C3), 114.7 (*C*N), 75.8 (*C*H_2Ph), 19.8 (*C*H_2CN).

MS (ES+): *m/z* (%) = 337 (30) [MH^+], 359 (30) [MNa^+].

HRMS (DCI, CH_4): *m/z* [MH^+] calcd for $C_{15}H_{10}Cl_2N_2O_3$: 337.014673; found: 337.007332.

Anal. Calcd for $C_{15}H_{10}Cl_2N_2O_3$ (336.8): C, 53.44; H, 2.99; N, 8.31. Found: C, 53.74; H, 3.16; N, 8.18.

General Procedure C

A suspension of a substituted (2-nitrophenyl)acetonitrile (10 mmol) and PtO_2 (0.25 g) in EtOH 95% (50 mL) was hydrogenated (30–35 psi) for 2 h at r.t. The catalyst was filtered through celite, and the filtrate was concentrated under vacuum to a yellow-brown oil, which was purified by flash chromatography (hexane–EtOAc, 15:1) to give the desired indole.

7-Benzyloxy-4,5-dichloro-1*H*-indole (5)

Compound **4** was hydrogenated as described in general procedure C. The isolated **5** was recrystallized from hexane as a white solid in 30% yield; mp 90–95 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.50 (br s, 1 H, NH), 7.46–7.38 (m, 5 H, Ph), 7.2–7.18 (m, 1 H, H-C2), 6.80 (s, 1 H, H-C6), 6.60–6.57 (m, 1 H, H-C3), 5.12 (s, 2 H, CH_2Ph).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 148.1 (C7), 136.2 (Ph), 128.8 (Ph), 128.5 (Ph), 127.9 (Ph), 125.0 (C5), 124.9 (C6), 123.7 (C9), 105.6 (C2), 102.5 (C3), 71.0 (*C*H_2Ph).

MS (ES+): *m/z* (%) = 158 (60) [C_6H3NCl_2], 294 (100) [MH^+].

HRMS (DCI, CH_4): *m/z* [M] calcd for $C_{15}H_{11}Cl_2NO$: 291.02177; found: 291.026236.

Anal. Calcd for $C_{15}H_{11}Cl_2NO{\cdot}1/4H_2O$ (296.5): C, 60.70; H, 3.88; N, 4.71. Found: C, 60.50; H, 3.86; N, 4.93.

6-Benzyloxy-5,7-dichloro-1*H*-indole (11)
Compound **11** was obtained from **10** by general procedure C as a white solid that was recrystallized from hexane as a white solid in 33% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.38 (br s, 1 H, NH), 7.67–7.62 (m, 3 H, H-C4, Ph), 7.45–7.42 (m, 3 H, Ph), 7.26–7.24 (m, 1 H, H-C2), 6.54–6.53 (m, 1 H, H-C3), 5.10 (s, 2 H, CH_2Ph).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 146.0 (C7), 136.8 (Ph), 135.0 (C8), 128.5 (Ph), 128.4 (Ph), 128.3 (Ph), 125.8 (C4), 125.2 (C9), 121.7 (C6), 119.8 (C2), 111.5 (C5), 103.2 (C3), 75.7 (*C*H_2Ph).

MS (ES+): *m*/*z* (%) = 200 (100) [$C_8H_4NOCl_2$], 291 (93) [M^+].

Anal. Calcd for $C_{15}H_{11}Cl_2NO{\cdot}1/4H_2O$ (296.5): C, 60.70; H, 3.88; N, 4.71. Found: C, 60.68; H, 4.09; N, 4.86.

General Procedure D
A stirred solution of a substituted benzyloxy dichloroindole (0.4 mmol) and ammonium formate (2 mmol) in a anhyd MeOH was degassed and then 10% Pd/C (50% wt) was added under nitrogen. The mixture was stirred at r.t. over night, the catalyst was filtered through celite and the filtrate was concentrated under vacuum. The crude residue was dissolved in acetone and filtered again through celite to remove salts. The filtrate was evaporated to give the hydroxyindole in 83–85% yield.

7-Hydroxyindole (6)[6]
Compound **6** was obtained from **5** using general procedure D, mp 95–98 °C [lit.[6] 96 °C].

^{1}H NMR [200 MHz, $(CD_3)_2CO$]: δ = 7.28–7.23 (d, *J* = 3.2 Hz, 1 H, H-C2), 7.11–7.05 (dd, *J* = 7.9, 1.1 Hz, 1 H, H-C4), 6.88–6.80 (t, *J* = 7.9 Hz, 1 H, H-C5), 6.65–6.61 (dd, *J* = 7.9, 1.1 Hz, 1 H, H-C6), 6.62–6.60 (d, *J* = 3.2 Hz, 1 H, H-C3).

^{13}C NMR [200 MHz, $(CD_3)_2CO$]: δ = 148.0 (C7), 124.6 (C2), 120.4 (C4), 116.0 (C8), 115.3 (C9), 112.6 (C5), 106.3 (C6), 102.5 (C3).

MS (ES+): *m*/*z* (%) = 134 (40) [MH^+].

6-Hydroxyindole (12)[7]
Compound **12** was obtained from **11** in 85% yield using general procedure D. The ^{1}H NMR data correspond to that described in the literature; mp 125–130 °C [lit.[7] 128–129 °C].

^{13}C NMR [200 MHz, $(CD_3)_2CO$]: δ = 149.8 (C6), 137.1 (C8), 124.7 (C2), 120.4 (C4), 120.2 (C9), 115.1 (C5), 102.2 (C3), 97.2 (C7).

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