# A Facile Synthesis of 3-Hydroxymethyl- and 3-Formylindoles from *o*-Nitrotoluene

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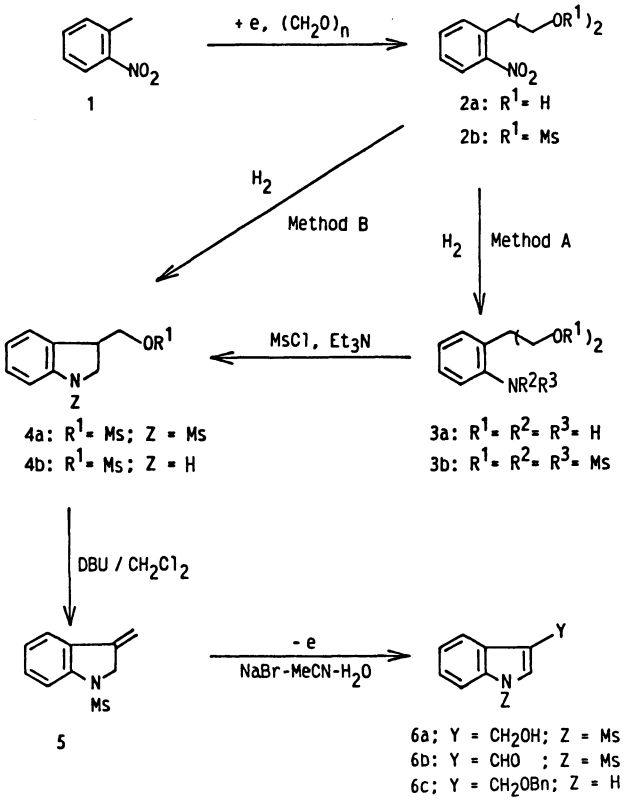
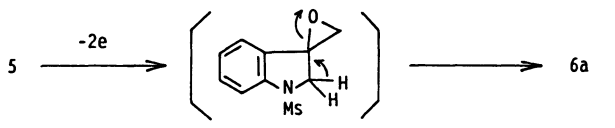
**Synopsis.** A synthesis of 3-hydroxymethyl- and 3-formylindoles has been performed by manipulation of the side chain of 3-hydroxymethylindoline derived from *o*-nitrotoluene. Electro-reductive cyclization of 2-(2-nitrophenyl)-1,3-bis(methylsulfonyloxy)propane to 3-(benzyloxymethyl)indole, is also discussed.

The conversion of readily available *o*-nitrotoluene (**1**) into useful 3-substituted indoles **6** is of current interest.[1] We have recently reported an efficient electrogenerated base (EG Base) induced double hydroxymethylation of the methyl group of *o*-nitrotoluene (**1**) with formaldehyde.[2] The adduct **2a** ($R^1$=H) possesses all of the framework elements required for the formation of 3-hydroxymethyl- or 3-formylindole (**6a**, **6b**), which are intermediates for the synthesis of useful indole derivatives.[3] Herewith, we describe a convenient synthesis of **6a** (Y=$CH_2OH$, Z=Ms) and **6b** (Y=CHO, Z=Ms) by manipulation of the C(3)-side chain of indolines **4**, derived from **2a**, together with electroreductive transformation of **2b** ($R^1$=Ms) to **6c** (Y=$CH_2OCH_2Ph$, Z=H).




Scheme 1.




Scheme 2.

Our approach to indoles **6** is outlined in Scheme 1. The key intermediate **4a** ($R^1$=Z=Ms) was prepared by two different pathways (Methods A and B).[4,5] Thus, hydrogenation of **2a** over Pd/C catalyst gave amine **3a** ($R^1$=$R^2$=$R^3$=H; 96%) which, upon treatment with methanesulfonyl chloride (MsCl) and $Et_3N$ in $CH_2Cl_2$, was converted to indoline **4a** (85%) along with **3b** ($R^1$=$R^2$=$R^3$=Ms, 3%) (Method A).[4] Cyclization of the by-product **3b** to **4a** was successfully performed in 91% yield by the electroreduction in DMF containing ascorbic acid and anthracene.[6] Alternatively (Method B), hydrogenation of methanesulfonate **2b** over $PtO_2$ in benzene containing $K_2CO_3$ afforded indoline **4b** ($R^1$=Ms, Z=H) exclusively (80%).[5] Treatment of **4b** with MsCl/$Et_3N$ in $CH_2Cl_2$ afforded **4a** (88%).

Next task is the introduction of the C=C double bond at the C(2)-position of indoline **4a**. At first, we investigated the direct dehydrogenation of **4a** using catalysts, e.g., $PtO_2$ and Pd/C. All attempts, however, resulted in the formation of a complex mixture and failed in obtaining an appreciable amount of the desired products **6**.[7] Finally, we found a new route involving two-step operation (**4a**→**5**→**6a**); heating **4a** with diazabicyclo[5.4.0]undec-7-ene (DBU) in $CH_2Cl_2$ afforded 3-methyleneindoline (**5**) (94%), which was, in turn, electrolyzed in an aqueous $CH_3CN$ solution containing NaBr to give indole **6a** (Y=$CH_2OH$) in 85% yield. The electrochemical transformation (**5**→**6a**) can be explained by assuming that the intermediary epoxide **7** (Scheme 2), formed by an electrolytic epoxidation of **5**,[8] is isomerized to **6a** in the electrolysis media. In fact, treatment of **5** with *m*-chloroperbenzoic acid and $CH_2Cl_2$ also afforded alcohol **6a** (49%). Aldehyde **6b** was obtained in 89% yield by oxidation of **6a** under $O_2$ (1 atm) in the presence of $RuCl_2(PPh_3)_3$ catalyst.[9]

As an alternative route to 3-substituted indoles, transformation of **2b** ($R^1$=Ms) to indole **6c** was performed by electroreduction of **2b** ($R^1$=Ms) in a benzyl chloride/$Et_4NBr$/DMF (Pt electrodes) system, affording **6c** (60%) after passage of 3.2 F $mol^{-1}$ (1 F=96480C) of electricity. The presence of benzyl chloride in the electrolysis media is indispensable since absence of benzyl chloride resulted in the formation of a complex mixture. Although the mechanism is still unclear, it is likely that anion species, generated from electroreduction of the nitro group,[10] attack the methylsulfonyloxy group on the side chain.

## Experimental

**Apparatus and Procedures.** IR spectra were recorded on a JASCO IRA-1 grating spectrometer. $^1$H NMR spectra were measured at 60 MHz with a Hitachi R-24 spectrometer and $^{13}$C NMR spectra were recorded with a JEOL FX-100 (25.05 MHz) spectrometer. Melting and boiling points are uncorrected. Column chromatography was carried out using Wako C-200 (silica gel) with hexane–EtOAc as an eluent. Elemental analysis were performed in our laboratory.

**2-(2-Nitrophenyl)-1,3-bis(methylsulfonyloxy)propane (2b).** To a mixture of **2a** (2.27 g, 11.5 mmol)[2] and $Et_3N$ (10 ml) in $CH_2Cl_2$ (20 ml) was added MsCl (5 ml) at 0 °C. After stirring for 2 h at room temperature, usual workup of the mixture followed by chromatography (3:1 hexane–EtOAc) afforded **2b** (3.92 g, 97%) as colorless crystals: mp 90—91 °C (from benzene–$CH_2Cl_2$); IR (Nujol) 1355, 1175 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.89 (3H, s, $CH_3SO_3$), 3.9—4.2 (1H, m, CH), 4.56 (4H, d, $J$=5 Hz, $CH_2O$), 7.4—7.9 (4H, m, Ar). Anal. ($C_{11}H_{15}NO_8S_2$) C, H.

**2-(2-Aminophenyl)-1,3-propanediol (3a).** A mixture of **2a** (1.02 g, 5.2 mmol) and 5% Pd/C (100 mg) in EtOAc (20 ml) was stirred at room temperature under $H_2$ (1 atm) for 15 h. After the catalysts were removed by filtration, evaporation of the solvent afforded **3a** (840 mg, 96%) as colorless crystals: mp 72—75 °C (from benzene–$CH_2Cl_2$); IR (Nujol) 3360, 3330, 3300, 3200 cm$^{-1}$; $^1$H NMR ($CDCl_3$–acetone-$d_6$) $\delta$=3.0—3.4 (1H, m, CH), 3.6—4.1 (8H, m, $NH_2$, $CH_2OH$), 6.4—7.1 (4H, m, Ar). Anal. ($C_9H_{13}NO_2$) C, H.

**1-Methylsulfonyl-2-(methylsulfonyloxymethyl)indoline (4a).** Method A: To a mixture of **3a** (179 mg, 1.1 mmol) and $Et_3N$ (0.6 ml, 4.3 mmol) in dry $CH_2Cl_2$ (4 ml) was added MsCl (0.18 ml, 2.3 mmol) at −10 °C. After being stirred at room temperature for 2 h, MsCl (0.08 ml, 1.0 mmol) was added at 10 °C and stirring was continued for an additional 1 h at room temperature. Usual workup of the mixture followed by chromatography (4:1 hexane–EtOAc) afforded **4a** (278 mg, 85%) as colorless crystals along with **3b** (16 mg, 3%). Compound **4a**: mp 99—101 °C (from benzene–$CH_2Cl_2$); IR ($CHCl_3$) 1370, 1355, 1175, 1160 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.89 (3H, s, $CH_3SO_2N$), 2.95 (3H, s, $CH_3SO_3$), 3.6—4.1 (3H, m, $CHCH_2N$), 4.32 (2H, dd, $J$=6, 1 Hz, $CH_2O$), 7.0—7.4 (4H, m, Ar). Anal. ($C_{11}H_{15}NO_5S_2$) C, H. Compound **3b**: mp 184—186 °C (from benzene–$CH_2Cl_2$); IR (Nujol) 3330—3380, 1190, 1185, 1170, 1160 cm$^{-1}$; $^1$H NMR ($CDCl_3$–acetone-$d_6$) $\delta$=2.95 (6H, s, $CH_3SO_3$), 3.51 (6H, s, $CH_3SO_2N$), 3.8—4.1 (1H, m, CH), 4.53 (4H, d, $J$=6 Hz, $CH_2O$), 7.4—7.7 (4H, m, Ar). Anal. ($C_{13}H_{21}NO_{10}S_4$) C, H.

Method B: To a solution of **2b** (1.13 g, 3.2 mmol) in benzene (80 ml) were added $K_2CO_3$ (800 mg) and $PtO_2 \cdot 3H_2O$ (120 mg). After stirring at room temperature under $H_2$ (1 atm) for 4 h, the catalysts were removed by filtration. Evaporation of the solvents followed by chromatography (2:1 hexane–EtOAc) afforded **4b** (580 mg, 80%): IR (neat) 3360, 1360, 1180 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.90 (3H, s, $SO_2CH_3$), 3.3—3.8 (2H, m, $CH_2N$), 3.55 (1H, br. s, H, NH), 3.3—3.8 (1H, m, CH), 4.1—4.4 (2H, m, $CH_2O$), 6.5—7.3 (4H, m, Ar). The structure of **4b** was confirmed by the following transformation into **4a**. To a mixture of **4b** (39 mg, 0.17 mmol) and $Et_3N$ (0.2 ml) in $CH_2Cl_2$ (3 ml) was added MsCl (0.06 ml, 1.43 mmol) at −10 °C. After stirring for 3 h at room temperature, usual workup of the mixture followed by chromatography (3:1 hexane–EtOAc) afforded **4a** (46 mg, 88%), whose IR spectra and $^1$H NMR were fully identical with those of **4a** described above.

**1-Methylsulfonyl-3-methyleneindoline (5).** A mixture of **4a** (125 mg, 0.41 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.25 ml, 1.67 mmol) in $CH_2Cl_2$ (4 ml) was heated at reflux for 15 h. Usual workup of the mixture followed by chromatography (3:1 hexane–EtOAc) afforded **5** (81 mg, 94%) as colorless crystals: mp 114—116 °C (from benzene); IR ($CHCl_3$) 1640, 1355, 1160 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.83 (3H, s, $CH_3SO_2N$), 4.55 (1H, dd, $J$=3 Hz, HC=C), 6.8—7.5 (4H, m, Ar). Anal. ($C_{10}H_{11}NO_2S$) C, H.

**3-Hydroxymethyl-1-(methylsulfonyl)indole (6a).** A solution of **5** (35 mg, 0.17 mmol) in MeCN (10 ml)–$H_2O$ (2 ml) contaning NaBr (27 mg, 0.26 mmol) was electrolyzed under a constant current density of 3.3 mA cm$^{-2}$ at room temperature in a beaker type cell fitted with two platinum electrodes (3 cm$^2$).[12] After passage of 3 F mol$^{-1}$ of electricity (2.8 h), workup of the electrolytes followed by chromatography (4:1 hexane–EtOAc) afforded **6a** (33 mg, 85%) as colorless crystals: mp 117—120 °C (from benzene–$CH_2Cl_2$); IR ($CHCl_3$) 3400, 1370, 1170, 1110 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.45 (1H, br. s, OH), 3.02 (3H, s, $CH_3SO_2N$), 4.79 (2H, br. s, $CH_2O$), 7.2—7.9 (5H, m, Ar, HC=C). Anal. ($C_{10}H_{11}NO_3S$) C, H.

**3-Formyl-1-(methylsulfonyl)indole (6b).** A mixture of **6a** (240 mg, 1.1 mmol) and $RuCl_2(PPh_3)_3$ (310 mg, 0.3 mmol)[10] in $CH_2ClCH_2Cl$ (10 ml) was stirred under $O_2$ (1 atm) at 50—60 °C for 4 h. After evaporation of the solvent, the residue was passed through short Florisil column (hexane–EtOAc). The eluents were concentrated and chromatographed (4:1 hexane–EtOAc), affording colorless crystals **6b** (192 mg, 80%): mp 170—171 °C (from benzene–$CH_2Cl_2$); IR (Nujol) 1690, 1380, 1185 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=3.25 (3H, s, $CH_3SO_2N$), 7.4—8.4 (4H, m, Ar), 8.04 (1H, s, HC=C), 10.07 (1H, s, CHO). Anal. ($C_{10}H_9NSO_3$) C, H.

**Electroreductive Cyclization of 2-[2-[Bis(methylsulfonyl)-amino]phenyl]-1,3-bis(methylsulfonyloxy)propane (3b).** Electrolysis was carried out in an H-shaped divided cell fitted with Pt-cathode (3 cm$^2$) and Pt-anode (3 cm$^2$).[12] Into both anode and cathode compartments was charged a DMF solution of $Et_4NOTs$ (6 ml/133 mg each). To the catholyte were added **3b** (48 mg, 0.1 mmol), ascorbic acid (35 mg, 0.2 mmol), and anthracene (18 mg, 0.1 mmol). The mixture was electrolyzed under a constant current density of 3.3 mA cm$^{-2}$ at room temperature for 2.4 h (4.5 F mol$^{-1}$). The catholyte was worked up in the usual manner, yielding colorless crystals **4a** (28 mg, 90%), whose IR and $^1$H NMR spectra were fully identical with those of **4a** described above.

**3-(Benzyloxymethyl)indole (6c).** Electrolysis was carried out in the same cell as described above. Into both the anode and cathode compartments was placed a DMF solution of $Et_4NBr$ (6 ml, 315 mg each). To the catholyte were added **2b** (107 mg, 0.3 mmol) and benzyl chloride (0.17 ml, 1.48 mmol). The mixture was electrolyzed under a constant current (1.7 mA cm$^{-2}$) at room temperature for 5.2 h (3.2 F mol$^{-1}$). Usual workup of the catholyte followed by chromatography on Florisil (10:1 hexane–EtOAc) afforded 3-(benzyloxymethyl)indole (**6c**)[13] (43 mg, 60%): IR (neat) 3340, 1455, 1105 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.86 (1H, br. s, NH), 4.67 (2H, s, C=$CCH_2O$), 5.07 (2H, s, $OCH_2Ph$), 6.9—7.7 (5H, m, Ar, NCH=C), 7.29 (4H, s, Ph); $^{13}$C NMR ($CDCl_3$) $\delta$=56.8 (t), 80.2 (t), 108.6 (d), 111.5 (s), 119.2 (d), 120.0 (d), 122.6 (d), 122.8 (d), 122.8 (s), 128.6 (d), 129.1 (d), 129.5 (d), 132.9 (s), 134.6 (s).

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