# A NEW SYNTHESIS OF 1-HYDROXYINDOLES AND SPECTRA OF 1-HYDROXYINDOLE

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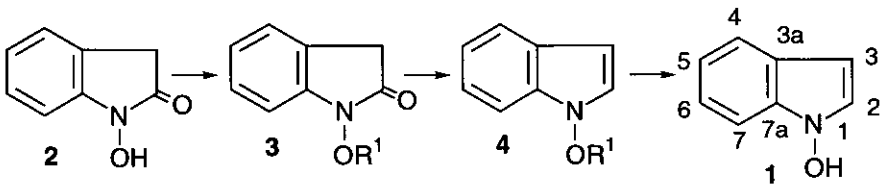
**Abstract** - Partial reduction of 1-[2-(trimethylsilyl)ethoxy]-2-oxindole (**3**) with AlH(*iso*-Bu)$_2$ (DIBAL) and subsequent removal of the protecting group with ($n$-Bu)$_4$NF affords 1-hydroxyindole (**1**) in sufficiently pure form to produce reliable spectral data (nmr, ms, and uv) for the first time; this methodology is applicable to the synthesis of other 1-hydroxyindoles.

1-Hydroxyindole (**1**), the symbolic compound in 1-hydroxyindoles, was synthesized by Acheson *et al.*[1] by the reduction of 2-nitrophenylacetaldehyde with zinc and ammonium chloride in poor yield and later by Pachter *et al.* [2] using the same reaction procedure. Somei *et al.* [3] obtained a solution of **1** in aqueous methanol by the oxidation of 2,3-dihydroindole with 30% aqueous hydrogen peroxide in the presence of sodium tungstate, but no attempt was made to isolate the product. To date, **1** has not been obtained in a form suitable for recording of spectra.

We now report a new facile synthesis of **1** and its spectral data, and demonstrate the versatility of the synthetic method to be applicable to other 1-hydroxyindoles.

In our current studies, we have successfully used the 2-(trimethylsilyl)ethyl group for the protection of hydroxamic acids[4] and this methodology was applied to the synthesis of 1-hydroxyindole. Thus, 1-hydroxy-2-oxindole (**2**), which is readily accessible by literature methods,[5] was converted to 1-[2-(trimethylsilyl)ethoxy]-2-oxindole (**3**) with 2-(trimethylsilyl)ethanol under Mitsunobu conditions[6] in 95% yield. DIBAL reduction of **3** in tetrahydrofuran (THF) gave an 88% yield of **4**, which was purified by column

chromatography ($SiO_2$, benzene) before the next step. Removal of the 2-(trimethylsilyl)ethyl group from **4** was achieved in high yield by reaction with ($n$-Bu)$_4$NF (eq. mol) in THF for 2 h at ambient temperature, while use of $BF_3$·$Et_2O$ or CsF instead of ($n$-Bu)$_4$NF induced decomposition or recovery of **4**.



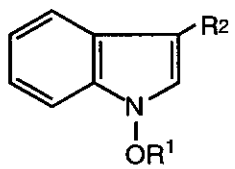

R1=$CH_2CH_2SiMe_3$

The product thus obtained gave satisfactory mass, uv, and nmr spectra for the first time and the proton nmr signals of **1** were assigned unambiguously (Table 1). The assignments were aided by use of COSY, HSQC, and HMBC spectra of **1** and were confirmed by comparison with those of 1-methoxyindole and 1-acetoxyindole.

**Table 1.** Proton and carbon chemical shifts (δ) in 1-hydroxyindole (**1**) in $CDCl_3$

| Position | Proton | Proton[a] | Carbon |
|---|---|---|---|
| OH | 5.56 | (7.75) | --- |
| 2 | 7.21 | unassigned | 125.06 |
| 3 | 6.31 | (6.02) | 96.51 |
| 3a | --- | --- | 124.23 |
| 4 | 7.56 | unassigned | 120.75 |
| 5 | 7.06 | (6.7) | 119.21 |
| 6 | 7.20 | (7.5) | 121.67 |
| 7 | 7.43 | unassigned | 108.38 |
| 7a | --- | --- | 133.73 |

[a]Solvent: $CCl_4$. From ref. 1b.




**5**, $R^1$=$CH_2CH_2SiMe_3$
**6**, $R^1$=H

| 5, 6 | R2 |
|---|---|
| a | CHO |
| b | CN |
| c | $CONH_2$ |

The key features of the assignments are : (a) The NOESY spectrum of 1-methoxyindole showed that NOEs were observed between methyl protons and 2-H and 7-H, respectively, and between 3-H and 4-H, which indicates the most downfield resonance to be that of 4-H (δ 7.56) and the next one 7-H (δ 7.43). (b) Aromatic proton chemical shifts and coupling patterns in **1** and 1-methoxyindole are similar to each other. The HSQC spectrum of **1** showed the correlation between protons and carbons. (c) The HMBC spectra of **1**, 1-methoxyindole and 1-acetoxyindole showed long range couplings

between C7a and 4-H and 6-H, respectively, but not between C7a and 7-H; also between C3a and 5-H and 7-H, respectively, but not between C2a and 4-H. The mass spectrum of **1** showed a molecular ion peak (*m/z* 133, 40.2%) and a base peak (*m/z* 117, 100%) corresponding to the loss of oxygen characteristic of mass spectra of 1-hydroxyindoles.[1b] Uv absorptions: λ(EtOH)/nm 274, 287. Ir: $\nu_{max}$(neat)/cm$^{-1}$ 3200 (OH).

For the synthesis of other 1-hydroxyindoles, electrophilic substitution reactions on **4** occurred in a way similar to those of 1-acetoxyindole[1a] to give **5**. Removal of the 2-(trimethylsilyl)ethyl group from **5** was performed in high yield with $BF_3$·$Et_2O$ (eq. mol) at ambient temperature in MeCN. After the usual work up, the extraction solvent ($Et_2O$) was evaporated to dryness *in vacuo* to give pure **6**. Compound **6b**, previously reported as an oil, which decomposed rapidly at *ca.* 60 °C,[1a] was obtained as a solid (mp 127-128 °C, see EXPERIMENTAL). The present methodology has the advantage of facile removal of the protecting group under mild reaction conditions, which is very suitable for the synthesis of 1-hydroxyindoles.

## EXPERIMENTAL

All the melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected. $^1$H Nmr spectra were measured at 270 or 500 MHz on a JEOL JNM-EX270 or a JEOL JNM-A500 spectrometer with tetramethylsilane ($Me_4Si$) as an internal reference and $CDCl_3$ as the solvent, unless otherwise noted. $^1$H Nmr spectral data are reported in parts per million ($\delta$) relative to $Me_4Si$. Infrared (ir) spectra were recorded on a JASCO IR 810 spectrophotometer. Electron-impact mass spectra and fast atom bombardment mass spectra were obtained with a JEOL JMX-DX 300 spectrometer. Elemental analyses were performed in the Microanalytical Laboratory of this University.

### Synthesis of 1-[2-(Trimethylsilyl)ethoxy]-2-oxindole (3)

Diethyl diazocarbonate (0.62 ml, 4.00 mmol) was added with stirring to a mixture of **2** (497 mg, 3.33 mmol), 2-(trimethylsilyl)ethanol (0.5 ml, 4.00 mmol), $PPh_3$ (1.06 g, 4.00 mmol), and anhydrous $CHCl_3$ (20 ml) under ice cooling. After the solution was

stirred for 1 h, it was concentrated under reduced pressure, and the residue was chromatographed on a column of silica gel with benzene-AcOEt (5:1) as the eluent to give **3** (793 mg, 95%), mp 38-39 °C (pentane). $^1$H Nmr $\delta$ 0.07 (9H, s, $CH_3$x3), 0.93-1.50 (2H, m, $CH_2$), 3.47 (2H, s, $CH_2$), 4.00-4.50 (2H, m, $OCH_2$), 6.67-7.47 (4H, m, ArH); $\nu_{max}$ (KBr)/cm$^{-1}$ 1720, 1625, 1250. FAB ms m/z : 250 ($M^+$+1). Anal. Calcd for $C_{13}H_{19}NO_2Si$: C, 62.61; H, 7.68; N, 5.62. Found: C, 62.45; H, 7.65; N, 5.58.

**Synthesis of 1-[2-(Trimethylsilyl)ethoxy]indole (4)**

1.5 M Solution (in toluene) of DIBAL (7.24 ml, 10.88 mmol) was slowly added with syringe to a mixture of **3** (1.81 g, 7.25 mmol) and THF (8 ml) with cooling (dry ice-acetone, -78 °C) under Ar atmosphere. After the solution was stirred for 1 h, the reaction mixture was quenched with 10% HCl (30 ml) and the aqueous layer was extracted with $Et_2O$ (70 ml x 2). The organic layer was washed with brine (30 ml), dried over $Na_2SO_4$, filtered, and concentrated. The crude product was chromatographed on a column of silica gel with benzene as the eluent to give **4** (1.49 g, 88.2%). $^1$H Nmr $\delta$ 0.07 (9H, s, $CH_3$x3), 0.87-1.43 (2H, m, $CH_2$), 3.97-4.53 (2H, m, OCH2), 6.27 (1H, d, J=4.0, H-3), 6.80-7.73 (5H, m, ArH); $\nu_{max}$ (neat)/cm$^{-1}$ 2950, 1540, 1460. High ms m/z ($M^+$): 233.1236. Found: 233.1220.

**Synthesis of 1-Hydroxyindole (1)**

1.0 M Solution (in THF) of (*n*-Bu)$_4$NF (0.73 ml) was added to a mixture of **4** (170 mg, 0.728 mmol) and THF (3 ml) and the solution was stirred for 2 h at room temperature. After evaporation of most of the solvent at ambient temperature, the residual solution was diluted with $Et_2O$ (60 ml) and the solution was washed with $H_2O$ (30 ml), brine (20 ml), dried over $Na_2SO_4$, and filtered. The colorless solution was concentrated (rotary vacuum evaporator) under reduced pressure (about 50 mmHg) at ambient temperature to a greenish oil. An attempt to evaporate the solvent to dryness with a vacuum pump brought about decomposition of **1**. The product, which contained small amounts of $Et_2O$ and THF, showed a single spot on a thin layer chromatoplate [*Rf* 0.63, benzene-AcOEt (5:1)] and its purity was sufficient to give satisfactory spectra (see the text).

**Synthesis of 1-[2-(Trimethylsilyl)ethoxy]indole-3-carboxaldehyde (5a), 1-[2-(Trimethylsilyl)ethoxy]indole-3-carbonitrile (5b), and 1-[2-(Trimethylsilyl)ethoxy]indole-3-carboxamide (5c)**

Electrophilic substitution reactions on **4** were performed in a way similar to those of 1-acetoxyindole by the literature method[1a] to give **5**.

**1-[2-(Trimethylsilyl)ethoxy]indole-3-carboxaldehyde (5a)**

$POCl_3$ (0.8 ml, 8.61 mmol) was added to dry *N,N*-dimethylformamide (DMF) (5 ml) with ice cooling. After the solution was stirred for 15 min, **4** (671 mg, 2.87 mmol) in dry DMF (1 ml) was added in 20 min and the solution was stirred for 20 min with ice cooling and an additional 3 h at room temperature. The reaction mixture was quenched with 10% NaOH (30 ml) with cooling and the aqueous layer was extracted with $Et_2O$ (70 ml x 2). The organic layer was washed with brine (40 ml), dried over $Na_2SO_4$, filtered, and concentrated. The crude product was chromatographed on a column of silica gel with benzene-AcOEt (1:1) as the eluent to give **5a** (653 mg, 86.9%), mp 62-63 °C (ether-hexane). $^1$H Nmr $\delta$ 0.07 (9H, s, $CH_3$x3), 0.83-1.47 (2H, m, $CH_2$), 4.03-4.60 (2H, m, $OCH_2$), 6.97-7.53 (3H, m, ArH), 7.73 (1H, s, ArH), 8.00-8.43 (1H, m, ArH), 9.80 (1H, s, CHO); $\nu_{max}$ (KBr)/cm$^{-1}$ 1660; m/z: 261 ($M^+$). Anal. Calcd for $C_{14}H_{19}NO_2Si$: C, 64.33; H, 7.33; N, 5.36. Found: C, 64.19; H, 7.15; N, 5.16.

**1-[2-(Trimethylsilyl)ethoxy]indole-3-carbonitrile (5b)**

Chlorosulfonyl isocyanate (0.38 ml, 4.40 mmol) in dry MeCN (1 ml) was added to a mixture of **4** (514 mg, 2.20 mmol) and dry MeCN (5 ml) in 3 min with ice cooling. After the solution was stirred for 3.5 h at room temperature, the reaction mixture was quenched with $H_2O$ (50 ml) and the aqueous layer was extracted with $Et_2O$ (70 ml x 2). The organic layer was washed with brine (40 ml), dried over $Na_2SO_4$, filtered, and concentrated. The crude product was chromatographed on a column of silica gel with benzene as the eluent to give **5b** (368 mg, 64.7%). $^1$H Nmr $\delta$ 0.07 (9H, s, $CH_3$x3), 0.90-1.47 (2H, m, $CH_2$), 4.03-4.60 (2H, m, $OCH_2$), 6.97-7.50 (3H, m, H-5, -6, -7), 7.53-7.93 (2H, m, H-2, -4); $\nu_{max}$ (neat)/cm$^{-1}$ 2210. High ms m/z ($M^+$): 258.1189. Found: 258.1215.

**1-[2-(Trimethylsilyl)ethoxy]indole-3-carboxamide (5c)**

30% $H_2O_2$ (0.5 ml) was added to a mixture of **5b** (368 mg, 1.424 mmol), 1N NaOH (5 ml) and EtOH (10 ml) with cooling. After the solution was stirred for 2 h at room temperature and for an additional 3.5 h at 50 °C, the reaction mixture was quenched with $H_2O$ (10 ml) and acidified with 10% HCl (10 ml) with coolng and the aqueous layer was extracted with $Et_2O$ (40 ml x 2). The organic layer was washed with brine (30 ml), dried over $Na_2SO_4$, filtered, and concentrated. The crude product was chromatographed on a column of silica gel with benzene-AcOEt (1:1) as the eluent to give **5c** (196 mg, 50.0%), mp 145-147 °C (benzene-hexanes). $^1$H Nmr $\delta$ 0.07 (9H, s, $CH_3$x3), 0.90-1.43 (2H, m, $CH_2$), 4.07-4.57 (2H, m, $OCH_2$), 6.03 (2H, br s, $NH_2$), 7.00-7.57 (3H, m, H-5, -6, -7), 7.70-8.17 (2H, m, H-2, -4); $\nu_{max}$ (KBr)/cm$^{-1}$ 3400, 3200, 1640, 1610; m/z : 277 ($M^+$). Anal. Calcd for $C_{14}H_{20}N_2O_2Si$: C, 60.84; H, 7.29; N, 10.13. Found: C, 61.07; H, 7.08; N, 10.14.

**Synthesis of 1-Hydroyindole-3-carboxaldehyde (6a)**

$BF_3$·$Et_2O$ (0.065 ml, 0.52 mmol) was added to a mixture of **5a** (138 mg, 0.53 mmol) and dry MeCN (3 ml) at room temperature. After the solution was stirred for 1 h, the solvent was removed under reduced pressure. $H_2O$ (20 ml) was added to the residue and the aqueous layer was extracted with $Et_2O$ (50 ml). The organic layer was washed with brine (30 ml), dried over $Na_2SO_4$, filtered, and concentrated. The crude product was chromatographed on a column of silica gel with benzene-AcOEt (2:1) as the eluent to give **6a** (72 mg, mp 145-152 °C, 84.0%), mp 147-150 °C (AcOEt-hexane) (lit.,[1a] mp 146-150 °C).

**Synthesis of 1-Hydroxyindole-3-carbonitrile (6b)**

$BF_3$·$Et_2O$ (0.047 ml, 0.0.37 mmol) was added to a mixture of **5b** (132 mg, 0.51 mmol) and dry MeCN (4 ml) at room temperature. After the solution was stirred for 45 min, the solvent was removed under reduced pressure. $H_2O$ (20 ml) was added to the residue and the aqueous layer was extracted with $Et_2O$ (50 ml). The organic layer was washed with brine (30 ml), dried over $Na_2SO_4$, filtered, and concentrated to give **6b** (66 mg, mp 125-127 °C, 81.7%), mp 127-128 °C (benzene-hexane). $^1$H Nmr ($CD_3OD$) $\delta$ 6.97-7.70 (4H, m, H-4, -5, -6, -7), 7.90 (1H, s, H-2); $\nu_{max}$ (KBr)/cm$^{-1}$ 3175, 2225; m/z: 158

(M+). Anal. Calcd for $C_9H_6N_2O$: C, 68.35; H, 3.82; N, 17.71. Found: C, 68.43; H, 3.84; N, 17.73.

**Synthesis of 1-Hydroxyindole-3-carboxamide (6c)**

1.0 M Solution (in THF) of ($n$-Bu)$_4$NF (0.31 ml) was added to a mixture of **5c** (85 mg, 0.308 mmol) and dry THF (3 ml). After the solution was stirred for 40 min, the solvent was removed under reduced pressure and the residue was diluted with ethyl acetate (50 ml). The organic layer was washed with $H_2O$ (30 ml x 2), dried over $Na_2SO_4$, filtered, and concentrated to give **6c** (45 mg, mp 172-182 °C, 83.1%), mp 180-181 °C (decomp.) (benzene-hexane) [lit.,[1a] mp 181-182 °C (decomp.)].

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