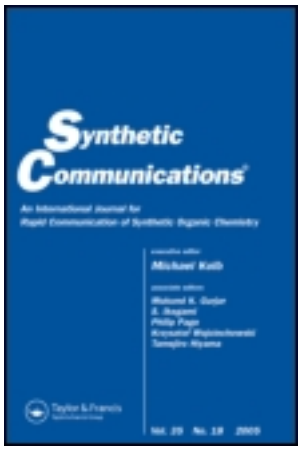

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An Efficient and Practical Synthesis of *N*,*N*-Diethyl-7-indolyloxyacetamide via 7-Hydroxyindole

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ABSTRACT

An efficient and practical synthesis of *N*,*N*-diethyl-7-indolyloxyacetamide (**1**) from 3-hydroxy-2-nitrotoluene (**4**) via 7-hydroxyindole (**2**) is described. Treatment of 3-benzyloxy-2-nitrotoluene (**5**) obtained from **4** with DMF dimethyl acetal and pyrrolidine afforded the (*E*)-2-nitro-β-pyrrolidinostyrene **6**, which can be readily converted into the 2-nitrophenylacetaldehyde semicarbazone **7** without isolation of **6**. Hydrogenation of **7** over Pd/C, followed by reaction of the resulting **2** with 2-chloro-*N*,*N*-diethylacetamide produced **1** in good yield.

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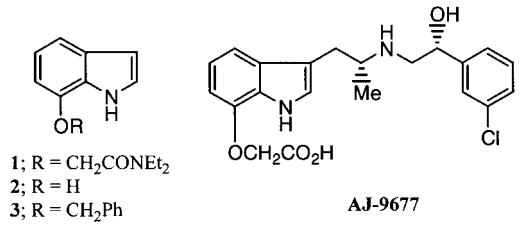
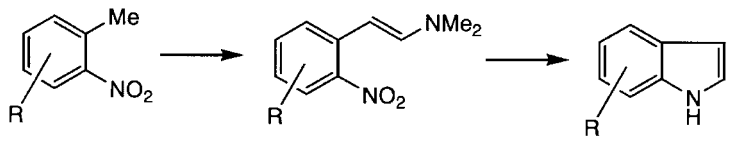


Figure 1.

N,*N*-Diethyl-7-indolyloxyacetamide (**1**), a key intermediate of AJ-9677 which is a potent and selective adrenalin β_3 receptor agonist developed in our laboratories,[1,2] was easily derived from 7-hydroxyindole (**2**), which in turn can be obtained from protected 7-hydroxyindole such as 7-benzyloxyindole (**3**, Fig. 1). In order to produce **1** on a large scale, an efficient and practical synthetic method of **3** was essential. To our knowledge, there are only few reports on the synthesis of protected 7-hydroxyindoles except 7-methoxyindole. 7-Benzyloxyindole (**3**), which is a protected 7-hydroxyindole, is usually prepared from 2-nitrophenol by Gassman's method[3] or from 3-hydroxy-2-nitrotoluene by Witkop's method.[4] In addition, Bartoli and Palmieri reported a novel and short synthetic route to 7-substituted indoles containing 7-trimethylsilyloxyindole. In this route, reaction of 2-substituted nitrobenzenes with 3 molar equivalents of vinylmagnesium bromide at $-40^{\circ}C$ directly gives the corresponding 7-substituted indoles in poor to moderate yield (in the case of 7-trimethylsilyloxyindole, the yield was 41%).[5] 7-Benzyloxyindole (**3**) and 7-benzhydryloxyindole were also prepared by Bartoli's method in 13% and 57% yield, respectively.[6] Recently, Murakami et al. reported a new method for the synthesis of indoles with electron-withdrawing oxygenated substituents at the 7-position e.g., 7-(*p*-toluenesulfonyloxy)indole, which can be converted into 7-hydroxyindole (**2**), via Fischer indolization of 2-(*p*-toluenesulfonyloxy)phenylhydrazones.[7] However, Gassman's, Witkop's, and Murakami's methods

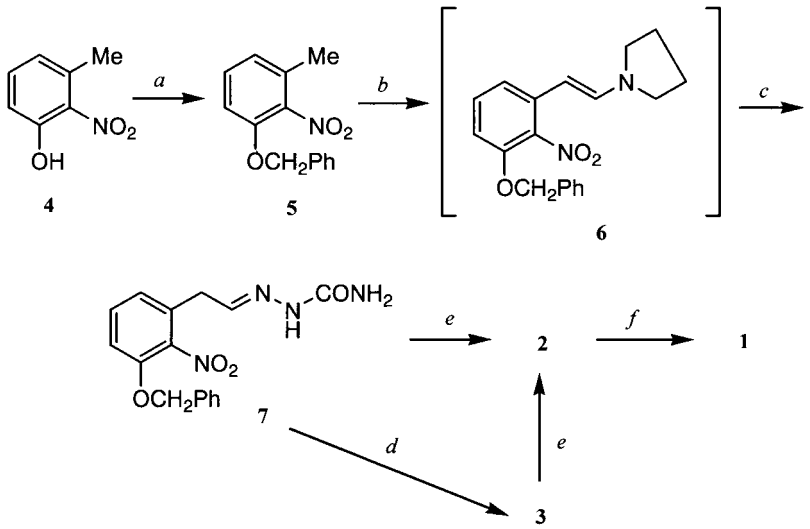


Scheme 1. Substituted indole synthesis by Leimgruber and Batcho's method.

have the disadvantage of being multi-step routes with a low overall yield. In addition, Bartoli's method requires low temperature and chromatographic purification.

Leimgruber and Batcho reported an efficient and novel indole synthesis based on the condensation of 2-nitrotoluene with *N*,*N*-dimethylformamide (DMF) dimethyl acetal, followed by reduction of the resulting (*E*)-2-nitro-β-dimethylaminostyrene (Sch. 1).[8] Many substituted indoles were synthesized by this method.[8,9] In the reaction of 2-nitrotoluene derivatives with DMF dimethyl acetal, addition of an amine such as pyrrolidine or triethylamine was found to be effective in facilitating the enamine formation.[10] On the other hand, attempts to apply this method to the preparation of indoles having bulky or electron-donating group resulted in only limited success. In general, the unsuccessful preparations were due to less reactive (*E*)-2-nitro-β-dimethylaminostyrenes. Kruse resolved this difficult problem by pivotal modification in which the very insoluble phenylacetaldehyde semicarbazone derivatives are prepared from the (*E*)-2-nitro-β-dimethylaminostyrenes by treatment with acidic aqueous semicarbazide. Indole derivatives such as 4-methoxyindole and 4-benzyloxyindole were obtained in good yield by reducing the corresponding phenylacetaldehyde semicarbazones (modified Leimgruber and Batcho's method).[11] However, the preparation of **3**, which can be converted into **2**, by the modified Leimgruber and Batcho's method has so far not been reported. In this study, we examined the preparation of **3**, a protected 7-hydroxyindole, using the modified Leimgruber and Batcho's method.

Treatment of the commercially available 3-hydroxy-2-nitrotoluene (**4**) with benzyl bromide in the presence of potassium carbonate gave 3-benzyloxy-2-nitrotoluene (**5**) in quantitative yield. Crude **5** thus obtained was used in the next reaction without further purification. Reaction of crude **5** with 2.0 molar equivalents of DMF dimethyl acetal and pyrrolidine in refluxing DMF for 5 h, followed by treatment of the resulting (*E*)-3-benzyloxy-2-nitro-β-pyrrolidinostyrene (**6**) with semicarbazide hydrochloride and aqueous HCl solution produced the very insoluble 3-benzyloxy-2-nitrophenylacetaldehyde semicarbazone (**7**) as a pale yellow powder in 74% yield from the starting **4**. When 1.1 molar equivalents of DMF dimethyl acetal was used, complete reaction of **5** needed 18 h. Reduction of the isolated **7** with Fe in the presence of ammonium chloride in aqueous ethyl alcohol afforded 7-benzyloxyindole (**3**) in good yield. Hydrogenation of **3** over palladium on carbon produced the desired 7-hydroxyindole (**2**). Although the reduction of the (*E*)-2-nitro-β-dimethylaminostyrenes having a benzyl-



Scheme 2. (a) $PhCH_2Br$, K_2CO_3, methyl ethyl ketone; (b) DMF dimethyl acetal, pyrrolidine, DMF; (c) $NH_2OCNHNH_2$-HCl, HCl; (d) Fe, NH_4Cl, aq. EtOH; (e) Pd/C, H_2; (f) $ClCH_2CONEt_2$, KI, K_2CO_3, acetone.

oxy group with Raney nickel,[8] Raney nickel/hydrazine,[10] and titanium(III) chloride[12] has been reported, reduction of **7** with these reagents has not been examined. On the other hand, the reductive cyclization of **7** to the indole ring using hydrogen with palladium on carbon as a catalyst directly gave **2** in 81% yield. As **2** was relatively instable, the preparation of *N*,*N*-diethyl-7-indolyloxyacetamide (**1**) was performed from **7** without isolation of **2**; hydrogenation of **7** over palladium on carbon, followed by reaction of the resulting **2** with 2-chloro-*N*,*N*-diethylacetamide gave **1** in 87% yield. In a similar manner, **1** was obtained from the isolated **2** in 89% yield (Sch. 2).

In conclusion, *N*,*N*-diethyl-7-indolyloxyacetamide (**1**), an intermediate in the preparation of AJ-9677, was prepared from the pivotal intermediate phenylacetaldehyde semicarbazone **7**, which was in turn obtained from the commercially available 2-nitro-3-hydoxytoluene (**4**), via 7-hydroxyindole (**2**). This synthetic route could be dispensed from chromatographic purification and required neither low temperature nor expensive reagents. These advantages, therefore, make this synthetic route of **1** practical to be operated on an industrial scale.

EXPERIMENTAL SECTION

All melting points were determined on a Yanagimoto micromelting point apparatus without correction. IR spectra were recorded on a Shimadzu FTIR-8200PC spectrometer with KBr disks unless otherwise stated. Atmospheric pressure chemical ionization mass spectra were obtained on a Hitachi M-1000 spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini-200 (200 MHz) or a JEOL JNM-LA 300 (300 MHz) spectrometer using dilute solution in $CDCl_3$ unless otherwise stated. Chemical shifts are expressed as δ (ppm) values from tetramethylsilane as an internal standard. The solvents were evaporated under reduced pressure.

3-Benzyloxy-2-nitrophenylacetaldehyde Semicarbazone (7)

(1) A mixture of 3-hydroxy-2-nitrotoluene (**4**, 30.6 g, 0.20 mol), K_2CO_3 (27.6 g, 0.20 mol), benzyl bromide (34.2 g, 0.20 mol), and methyl ethyl ketone (300 mL) was heated to reflux for 4 h and cooled to room temperature. The reaction mixture was washed successively with water, aqueous NaOH, water, and brine and dried over anhydrous $MgSO_4$. The solvent was evaporated to give ca. 49 g of 3-benzyloxy-2-nitrotoluene (**5**) as a pale yellow oil, which was used in the next step without further purification. ^{1}H NMR: 2.38 (3H, s), 5.15 (2H, s, CH_2Ph), 6.81–6.91 (2H, m), 7.20–7.39 (6H, m). MS; m/z, 244 (MH^+).

(2) A solution of **5** (9.7 g, 40 mmol), pyrrolidine (6.6 mL, 80 mmol), and DMF dimethyl acetal (10.6 mL, 80 mmol) in DMF (30 mL) was heated to reflux for 5 h in argon atmosphere (the color of the reaction mixture gradually changed from yellow to red). After the TLC indicated that almost no starting material **5** remained, the reaction mixture was cooled to ca. 5°C. The solution containing (*E*)-3-benzyloxy-2-nitro-β-pyrrolidinostyrene (**6**) was diluted with diisopropyl ether (30 mL). A small amount of the authentic crystalline **7** was seeded, and a solution of semicarbazide hydrochloride (5.4 g, 48 mmol) in 2N aqueous HCl (60 mL) was added in a one portion under ice-cooling (the inner temperature raised from 7°C to 35°C, and the fine precipitates were deposited). A mixture of water (10 mL) and diisopropyl ether (10 mL) was added to the resulting unstirred reaction mixture, and the whole was stirred at room temperature for 10 min. The precipitates were collected by filtration, washed with water and diisopropyl ether, and dried to give 9.8 g (74%) of **7** as a pale yellow solid, m.p. 184–185°C. ^{1}H NMR

(DMSO-d_6): 3.46 (2H, d, $J = 6$ Hz, $ArCH_2$), 5.27 (2H, s, OCH_2), 6.15 (2H, s, NH_2), 7.01 (1H, d, $J = 8$ Hz), 7.16 (1H, t, $J = 6$ Hz), 7.27–7.43 (6H, m), 7.51 (1H, t, $J = 8$ Hz), 9.98 (1H, s, NH). Anal. calcd. for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.92; N, 17.06. Found: C, 58.82; H, 4.99; N, 16.76. MS; m/z, 329 (MH^+). IR cm^{-1}: 3460, 1699, 1529, 1367.

7-Benzyloxyindole (3)

To a mixture of ammonium chloride (1.1 g, 21 mmol), Fe (2.2 g, 39 mmol), water (20 mL), and EtOH (40 mL) was added portionwise **7** (3.3 g, 10 mmol) at room temperature. The mixture was heated to reflux for 1 h, after which it became homogeneous and then cooled to room temperature. The insoluble materials precipitated were filtrated through Celeit and washed with toluene. The filtrate was concentrated, diluted with water, and extracted with toluene. The extract was washed successively with 10% aqueous HCl, water, and brine. To the organic solution was added activated charcoal and anhydrous Na_2CO_3, and the whole was filtered off. The filtrate was concentrated to a volume of toluene of ca. 3 mL. After addition of hexane (ca. 6 mL), the filtrate was seeded with 7-benzyloxyindole (**3**) and left to stand at ambient temperature. The resulting precipitates were collected by filtration, washed with hexane, and dried to give 1.7 g (76%) of **3** as a pale brown crystal, m.p. 73°C (toluene/hexane) [lit.[4] 67–68°C]. ^1H NMR: 5.20 (2H, s, OCH_2), 6.54 (1H, t, $J = 3$ Hz, indole 3-H), 6.71 (1H, d, $J = 7$ Hz, indole 6-H), 7.02 (1H, t, $J = 7$ Hz, indole 5-H), 7.16 (1H, t, $J = 3$ Hz, indole 2-H), 7.27 (1H, d, $J = 7$ Hz, indole 4-H), 7.32–7.52 (5H, m), 8.40 (1H, s, NH). Anal. calcd. for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.75; H, 6.03; N, 6.21. MS; m/z, 224 (MH^+). IR cm^{-1}: 3373, 1577, 1255, 1072.

7-Hydroxyindole (2)

(1) Compound **3** (5.0 g, 22 mmol) was hydrogenated over 10% palladium on carbon (0.5 g) in EtOH (50 mL) at ambient temperature under atmospheric pressure to give 2.9 g (97%) of **2** as a pale purple crystal, m.p. 95–96°C [lit.[4] 100–100.5°C]. ^1H NMR: 5.15 (1H, s, OH), 6.53 (1H, t, $J = 3$ Hz, indole 3-H), 6.55 (1H, d, $J = 8$ Hz, indole 6-H), 6.94 (1H, t, $J = 8$ Hz, indole 5-H), 7.17 (1H, t, $J = 3$ Hz, indole 2-H), 7.25 (1H, d, $J = 8$ Hz, indole 4-H), 8.38 (1H, s, NH). IR cm^{-1}: 3423, 3408, 1580,

1489, 1315, 1244. 7-Hydroxyindole (**2**) was seemed to be instable in the solution.

(2) A mixture of **7** (4.9 g, 15 mmol), 10% palladium on carbon (0.4 g), and EtOH (50 mL) was stirred under an atmosphere of hydrogen with an initial pressure of 3.0 kg/cm^2 at ambient temperature for 2 h. After absorption of the theoretical amount of hydrogen, the catalyst was filtered off and washed with EtOH. The filtrate was concentrated below 40°C in order to prevent coloration, and the residue was dissolved in $CHCl_3$ (50 mL) and 10% aqueous citric acid (20 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. The solvent was evaporated to give 1.6 g (80%) of **2** as a pale purple crystal, m.p. 95–96°C. The ^{1}H NMR and IR spectra of the compound obtained were identical to those of the sample described above.

N,N-Diethyl-7-indolyloxyacetamide (1)

(1) A stirred mixture of **2** (13.3 g, 0.10 mol), potassium carbonate (16.6 g, 0.12 mol), potassium iodide (1.7 g, 10 mmol), 2-chloro-*N,N*-diethylacetamide (16.5 g, 0.11 mol), and acetone (100 mL) was heated to reflux for 3 h and cooled to room temperature. The insoluble materials were filtered off, and the filtrate was concentrated to dryness. The residue was dissolved in $CHCl_3$ (200 mL) and water (100 mL), and the organic layer was separated and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was triturated with diisopropyl ether to give 22.0 g (89%) of **1** as a colorless crystal m.p. 123–124°C (toluene). ^{1}H NMR: 1.16, 1.21 (each 3H, t, $J = 7$ Hz), 3.35, 3.43 (each 2H, q, $J = 7$ Hz), 4.80 (2H, s), 6.53 (1H, t, $J = 3$ Hz, indole 3-H), 6.69 (1H, d, $J = 7$ Hz, indole 6-H), 6.99 (1H, t, $J = 7$ Hz, indole 5-H), 7.21 (1H, t, $J = 3$ Hz, indole 2-H), 7.32 (1H, d, $J = 7$ Hz, indole 4-H), 9.44 (1H, s, NH). Anal. calcd. for $C_{14}H_{18}N_2O_2 \cdot 1/4H_2O$: C, 67.04; H, 7.43; N, 11.17. Found: C, 67.28; H, 7.26; N, 11.26. MS; m/z, 247 (MH^+). IR cm^{-1}: 3252, 1626, 1587, 1265, 1094.

(2) Compound **7** (4.9 g, 15 mmol) was reduced catalytically over 10% palladium on carbon (0.4 g) in EtOH (50 mL) at ambient temperature under medium pressure. After no further change of hydrogen was observed, the catalyst was filtered off. The filtrate was concentrated to dryness, and acetone (20 mL) was added to the oily residue containing the solid. The mixture was cooled to ca. 5°C, and the solid was filtered off and washed with acetone (10 mL). After addition of potassium carbonate (2.5 g, 18 mmol), potassium iodide (0.2 g, 1.2 mmol), and 2-chloro-*N,N*-diethylacetamide (2.7 g, 18 mmol) to the combined filtrate containing **2**,

the mixture was heated to reflux for 3 h and cooled to room temperature. The insoluble materials were filtered off, and the filtrate was concentrated to dryness. Water (100 mL) was added to the residue, and the resulting mixture was stirred. The solid was collected by filtration, washed with diisopropyl ether, and dried to 3.2 g (87%) of **1**. The ^{1}H NMR and IR spectra of the compound obtained were identical to those of the sample described above.

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