One-Pot Synthesis of Indoles from 1-Benzyl-2,3-dihydroindoles

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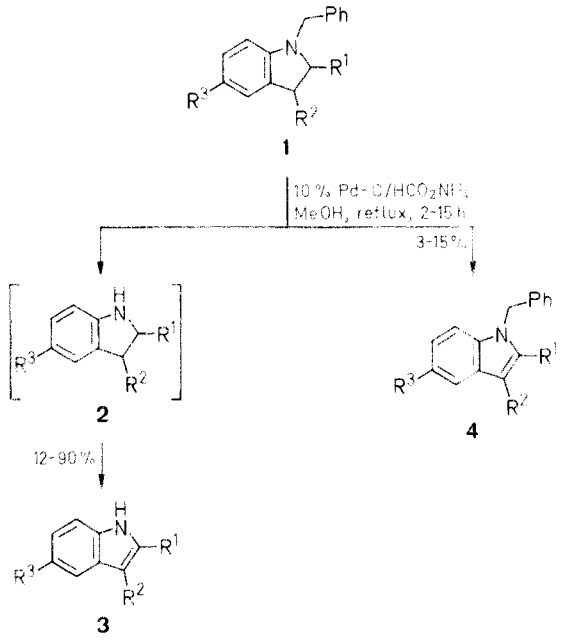
A facile one-pot dehydrodebenzylation of 1-benzyl-2,3-dihydroindoles to indoles uses 10% palladium on carbon as catalyst and ammonium formate as hydrogen donor in methanol.

Most of the biologically active 5-substituted indole derivatives have been efficiently prepared via a four-step route involving reduction of indole to 2,3-dihydroindole, protection of the secondary amino group, introduction of a substituent into the 5-position, and oxidative regeneration of the indole nucleus. In this context, we have focused our attention on the readily available 1-benzyl-2,3-dihydroindoles (**1**, *N*-benzylindolines) as key precursors of substituted indoles, an *N*-protecting group would also serve to facilitate smooth electrophilic substitution at C-5, as exemplified by the synthesis of the indoles having amino,[1] formyl,[2] methoxy,[3,4] and silyl groups.[5]

Known methods for the conversion of 1-benzyl-2,3-dihydroindoles into indoles consist of two steps: reductive debenzylation[6] followed by oxidative regeneration of the indole.[7,8]

We now report a facile one-pot synthesis of indoles from 1-benzyl-2,3-dihydroindoles by catalytic transfer hydrogenation using 10% palladium on carbon as catalyst and ammonium formate as hydrogen donor in methanol,[9] as already recommended for the debenzylation of the *N*-benzylamines[10,11] and -ethers.[12] When 1-benzyl-2,3-dihydroindole (**1a**) was subjected

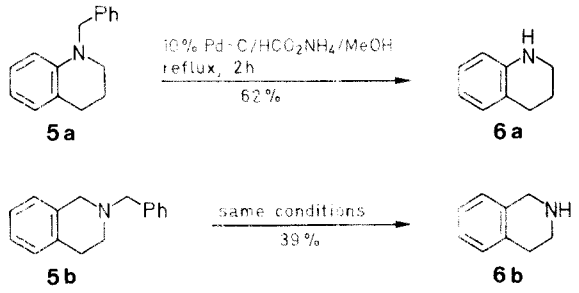
to this debenzylation procedure under the reported conditions,[10] the isolated products were indole **(3a)** and its 1-benzylindole **(4a)** in 74 and 3% yields, respectively. Monitoring the reaction by TLC and isolation of products at the intermediary stage showed that, at the beginning of the reaction, the product was the debenzylated 2,3-dihydroindole **(2a)** which was then dehydrogenated to give the desired indole **(3a)** simply by prolonged heating of the solution. In the absence of ammonium formate, indole **(3a)** and 1-benzylindole **(4a)** were obtained in 45 and 35% yields, respectively, suggesting the effectiveness of ammonium formate and, partially, the solvent methanol as hydrogen donor. However, 1-benzylindole **(4a)** was not debenzylated and recovered completely under the reaction conditions even in the presence of ammonium formate. Although several attempts to suppress the formation of the undesired by-product 1-benzylindole **(4a)** were unsuccessful, optimum conditions have been established by slight modification of the reported conditions[10] as described in the general procedure (see also Table 1).



1–4	R^1	R^2	R^3
a	H	H	H
b	CH_3	H	H
c	H	CH_3	H
d[a]	CH_3	CH_3	H
e[b]	CH_3	CH_3	H
f	$-(CH_2)_4-$		H
g	H	H	OMe
h	H	$(CH_2)_2NHBz$	H
i	H	$(CH_2)_2NHBz$	OMe

[a] **1d:** *cis*. [b] **1e:** *trans*.

Most examples show the superiority of this one-pot procedure over the conventional methods in terms of simple performance and good yields, except for *trans*-1-benzyl-2,3-dimethyl-2,3-dihydroindole **(1e)** which is only debenzylated to 2,3-dihydroindole **(2e)** as the major product in 72% yield, the second step (dehydrogenation) proceeding at a slow rate due to steric hindrance by the *trans*-substituted at C-2 and C-3 and affording product **3e** in only 12% yield after 2 hours. The debenzylation of 1-benzyl-1,2,3,4-tetrahydroquinoline **(5a)** and 2-benzyl-1,2,3,4-tetrahydroisoquinoline **(5b)** under the same reaction conditions proceeded without dehydrogenation to give 1,2,3,4-tetrahydroquinoline **(6a)** and 1,2,3,4-tetrahydroisoquinoline **(6b)**, respectively.



The present smooth one-pot conversion of 1-benzyl-2,3-dihydroindoles into indoles was successfully applied to the synthesis of serotonin precursor **3i** in 54% overall yield from N^b-benzoyl-N^a-benzyl-2,3-dihydrotryptamine **(1h)** via bromination at the 5-position (Br_2/AcOH),[5] substitution of the bromine-atom by a methoxy group (MeONa + CuI in MeOH/DMF).[4]

Table 1. Reaction of *N*-Benzyl Compounds **1** and **5** with 10% Palladium on Carbon and Ammonium Formate in Methanol

Substrate	Reaction Time (h)	Product	Yield (%)[a]	mp (°C) (solvent)[b] or bp (°C)/Torr	Lit. mp (°C) or bp (°C)/Torr or Molecular Formula
1a	2	**3a**	78 (74)	52–53 (PE)	52–54[13]
		4a	3 (3)	43–44 (PE)	43–44[14]
1b	2	**3b**	85	56–58 (PE)	58–60[13]
		4b	4	49–50 (PE)	49[15]
1c	2	**3c**	76 (73)	95–98 (PE)	95–96[13]
		4c	8 (12)	72–73 (PE)	72–73[16]
1d	2	**3d**	77	103–105 (PE)	105–107[13]
		4d	15	53.5–55 (PE)	58–59[15]
1e	2	**3d**	12		
		2e[c]	72	105–108/3	$C_{10}H_{13}N$ (147.2)
1f	2	**3f**	75 (62)	120–121 (PE)	118–120[13]
		4f	11 (25)	155–160/0.1	158–168/0.3[17]
1g	5	**3g**	84	55–57 (PE)	56–58[13]
		4g	6	71–73 (Et_2O)	74–75[18]
1h	4.5	**3h**	68	135–137 (benzene)	139.5–141[8]
		4h[d]	9	103–104 (Et_2O)	$C_{24}H_{22}N_2O$ (354.4)
1i	15	**3i**	90	114–115 (Et_2O)	113–114[19]
5a	2	**6a**	62	125–128/13	249/760[13]
5b	2	**6b**	39	106–108/13	232–233/760[13]

[a] Yield of isolated pure product. Figures in parenthesis indicate yield under the conditions of Lit. [10].

[b] PE = Petroleum ether.

[c] Exact Mass: $C_{10}H_{13}N$ requires: 147.1047; found: 147.1040.
^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 1.27 (d, 3H, J = 7 Hz); 1.31 (d, 3H, J = 7 Hz); 2.81 (m, 1H); 3.35 (br s, 1H); 3.45 (dq, 1H, J = 9, 7 Hz); 6.63 (d, 1H, J = 8 Hz); 6.74 (t, 1H, J = 8 Hz); 6.96–7.18 (m, 2H).

[d] Exact Mass: $C_{24}H_{22}N_2O$ requires: 354.1730; found: 354.1724.
^{1}H-NMR (60 MHz, $CDCl_3$/TMS): δ = 3.05 (t, 2H, J = 7 Hz); 3.75 (q, 2H, J = 7 Hz); 5.18 (s, 2H); 6.17 (br s, 1H); 6.83–7.63 (15H, m).

Table 2. Physical and Spectral Data of *N*-Benzyl Compounds **1a–i** and **5a, b**

Compound	mp (°C) (solvent) or bp (°C)/Torr	Lit. mp (°C) or bp (°C)/Torr or Molecular Formula	High Resolution MS Found (Calc.)	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
1a	150–153/2	146–149/1[5]		2.67–3.50 (m, 4H); 4.16 (s, 2H); 6.37–7.50 (m, 9H)[b]
1b	173–175/2	181–182/19[20]		1.27 (d, 3H, J = 6); 2.26–4.00 (m, 3H); 4.20 (br s, 2H); 6.08–7.43 (m, 9H)[b]
1c	163–165/2	$C_{16}H_{17}N$ (223.3)	223.1338 (223.1359)	1.33 (d, 3H, J = 6); 2.67–3.66 (m, 3H); 4.05, 4.38 (ABq, 2H, J = 15); 6.41–7.41 (m, 9H)[b]
1d	170–175/4	$C_{17}H_{19}N$ (237.3)	237.1519 (237.1516)	1.14 (d, 3H, J = 6.5); 1.17 (d, 3H, J = 6.5); 3.25 (br quin, 1H, J = 6.5); 3.71 (quin, 1H, J = 6.5); 4.13, 4.40 (ABq, 2H, J = 16); 6.33 (d, 1H, J = 7.5); 6.66 (t, 1H, J = 7.5); 6.94–7.12 (m, 2H); 7.18–7.40 (m, 5H)[c]
1e	162–165/3	$C_{17}H_{19}N$ (237.3)	237.1496 (237.1516)	1.30 (d, 3H, J = 6); 1.32 (d, 3H, J = 7); 2.84 (m, 1H); 3.14 (dq, 1H, J = 9.5, 6); 4.17, 4.32 (ABq, 2H, J = 16); 6.32 (d, 1H, J = 7.5); 6.67 (t, 1H, J = 7.5); 6.94–7.08 (m, 2H); 7.18–7.40 (m, 5H)[c]
1f	192–195/2	147–149/0.35[17]		1.00–2.00 (m, 8H); 2.83–3.67 (m, 2H); 4.08, 4.47 (ABq, 2H, J = 16); 6.23–7.50 (m, 9H)[b]
1g	180–184 (dec)[a] (MeOH/Et_2O)	182–185 (dec)[a]		2.67–3.40 (m, 4H); 3.73 (s, 3H); 4.13 (s, 2H); 6.30–7.50 (m, 8H)[b]
1h	89–90 (Et_2O)	$C_{24}H_{24}N_2O$ (356.45)	356.1882 (356.1886)	1.80–2.20 (m, 2H); 2.93–3.73 (m, 5H); 4.23 (s, 2H); 6.23 (br s, 1H); 6.40–7.76 (m, 14H)[b]
1i	108–110 (Et_2O)	$C_{25}H_{26}N_2O$ (386.45)	386.1998 (386.1993)	1.90 (m, 1H); 2.11 (m, 1H); 3.04 (m, 1H); 3.20–3.60 (m, 4H); 3.74 (s, 3H); 4.20 (s, 2H); 6.23 (br s, 1H); 6.48 (d, 1H, J = 7.5); 6.67 (d, 1H, J = 7.5); 6.79 (br s, 1H); 7.20–7.56 (m, 8H); 7.68 (m, 2H)[c]
5a	180–185/5	178–180/4[21]		1.77–2.32 (m, 2H); 2.70–3.05 (m, 2H); 3.30–3.58 (m, 2H); 4.43 (s, 2H); 6.33–7.47 (m, 9H)[b]
5b	150–160/2	132–136/0.7[22]		3.07–3.50 (m, 4H); 3.60 (s, 2H); 3.65 (br s, 2H); 6.75–7.50 (m, 9H)[b]

[a] Melting point of hydrochloride salt.
[b] Measured with a JEOL PMX-60 (60 MHz) instrument.
[c] Measured with a Varian XL-200 (200 MHz) instrument.

and finally our one-pot procedure. This convenient synthesis is superior to other known methods[4] in terms of overall yield and ease of performance.

Melting points were determined with a Kofler-type hot-stage apparatus. Mass spectra were recorded with Hitachi M-80 spectrometers. IR spectra were measured with a Hitachi 270-30 spectrophotometer. ^{1}H-NMR spectra were recorded with JEOL PMX-60 (60 MHz) and Varian XL-200 (200 MHz) instruments.

Medium-pressure column chromatography was performed with a 530-4-RI (Yamazen) apparatus using Lobar grosse B (310-25, Lichroprep Si60, Merck).

All reactions are carried out under N_2.

N-Benzyl Compounds:

The 1-benzyl-2,3-dihydroindoles **1a**,[5] **1b**,[20] **1c**,[5] **1d**,[5,17] **1e**,[5,17] **1f**,[17] **1g**,[4] and **1h**,[5] and 1-benzyl-1,2,3,4-tetrahydroquinoline **(5a)**,[21] and 2-benzyl-1,2,3,4-tetrahydroisoquinoline **(5b)**[22] are prepared according to reported procedures.

N^b-Benzoyl-N^a-benzyl-5-methoxy-2,3-dihydrotryptamine (1i):

Bromination of N^b-Benzoyl-N^a-benzyl-2,3-dihydrotryptamine **(1h)**: To a stirred solution of compound **1h** (240 mg, 0.67 mmol) in AcOH (5 mL), a solution of Br_2 (107 mg, 0.67 mmol) in AcOH (1 mL) is added over 15 min at 10 °C, and stirring is continued for 30 min at room temperature. Then, aqueous 10% NaOH (50 mL) is added and the mixture is extracted with EtOAc (2 × 100 mL). The extract is washed with H_2O (100 mL), dried (Na_2SO_4), and evaporated. The crude product thus obtained is submitted to medium-pressure column chromatography using EtOAc hexane (1:3) as eluent.

N^b-Benzoyl-N^a-benzyl-5-bromo-2,3-dihydrotryptamine; yield: 223 mg (76%); mp 94–95 °C (Et_2O).

Exact Mass: $C_{24}H_{23}BrN_2O$ requires: 434.0993; found: 434.1004.

IR ($CHCl_3$): ν = 3460 (NH); 1656 cm^{-1} (NCO).

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 1.87 (m, 1H); 2.06 (m, 1H); 3.18 (dd, 1H, J = 9, 6 Hz); 3.32 (m, 1H); 3.44–3.62 (m, 3H); 4.20, 4.29 (ABq, 2H, J = 14 Hz); 6.15 (br s, 1H); 6.36 (d, 1H, J = 8 Hz); 7.08–7.54 (m, 10H); 7.69 (m, 2H).

N^b-Benzoyl-N^a-benzyl-5,7-dibromo-2,3-dihydrotryptamine; yield: 52 mg (15%); mp 126–128 °C (Et_2O).

Exact Mass: $C_{24}H_{22}Br_2N_2O$ requires: 516.0059; found: 516.0047.

IR ($CHCl_3$): ν = 3460 (NH); 1658 cm^{-1} (NCO).

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 1.76 (m, 1H); 1.98 (m, 1H); 3.13–3.65 (m, 5H); 4.75, 4.82 (ABq, 2H, J = 15.5 Hz); 6.12 (br s, 1H); 7.12 (br s, 1H); 7.20–7.60 (m, 9H); 7.70 (m, 2H).

N^b-Benzoyl-N^a-benzyl-5-methoxy-2,3-dihydrotryptamine **(1i)**: To a stirred NaOMe solution [prepared from Na (143 mg, 6.2 mmol) and abs. MeOH (1.8 mL)], a solution of N^b-benzoyl-N^a-benzyl-5-bromo-2,3-dihydrotryptamine (270 mg, 0.62 mmol) in DMF (6 mL) and CuI (300 mg, 1.58 mmol) are added. The mixture is heated to reflux for 2 h (oil bath at 130–140 °C), then cooled. The precipitate is filtered off and washed with EtOAc (50 mL). Water (50 mL) is added to the filtrate, and the mixture is extracted with EtOAc (2 × 50 mL). The extract is washed with H_2O (2 × 50 mL), dried (Na_2SO_4), and evaporated. The residue is purified by medium-pressure column chromatography using EtOAc/hexane (3:2) as eluent to afford **1i**; yield: 190 mg (79%); m.p. 108–110 °C (from Et_2O).

IR ($CHCl_3$): ν = 3460 (NH); 1658 cm^{-1} (NCO).

Indoles 3 from 1-Benzyl-2,3-dihydroindoles 1; General Procedure:

To a stirred suspension of the 1-benzyl-2,3-dihydroindole **1** (1 mmol) and 10% Pd-C (200 mg) in MeOH (12 mL) is added $HCO_2NH_4 \cdot 5H_2O$ (1.532 g, 10 mmol) in a single portion. The mixture is then stirred at reflux temperature. After completion of the reaction (2–15 h) (TLC, EtOAC/hexane), the catalyst is filtered off using a celite pad, which is then washed with MeOH (200 mL). The solvent is evaporated and the residue extracted with CH_2Cl_2 (100 mL). The extract is washed with H_2O (50 mL), dried (Na_2SO_4), and evaporated and the crude product is submitted to medium-pressure column chromatography using EtOAc/hexane as eluent to afford the pure indole **3**.

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