A one pot synthesis of 4-hydroxymethylindole

A ONE POT SYNTHESIS OF 4-HYDROXYMETHYLINDOLE[1]

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Abstract — A practical one pot synthetic method of 4-hydroxymethylindole is developed. The method consists of three operations, in which a novel ring transformation reaction of isocoumarins into isochromans is included. Product analysis and distribution of each operation are also described in detail.

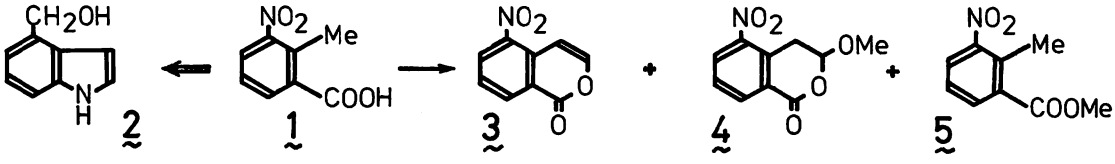
In our continuing work on searching for a facile synthetic route to 4-substituted indoles, we have developed a simple and practical one pot synthetic method of 4-hydroxymethylindole (2), an important building block for ergot alkaloids[2] and 4-substituted indoles,[3] from 2-methyl-3-nitrobenzoic acid (1).

The one pot synthetic procedure involves the following sequential three operations: 1) treatment of 1 with N,N-dimethylformamide dimethyl acetal (DMFDMA), 2) reduction of the resultant residue with lithium aluminum hydride ($LiAlH_4$), and 3) acidic reduction of the reaction mixture with aq. titanium (III) chloride ($TiCl_3$). Herein we report these results in detail.

I. Illustration of the First Operation

Refluxing of a solution of 1 with 3 mol equiv. of DMFDMA in abs. N,N-dimethylformamide (DMF) for 12.5 hr is the first operation. We have already reported[4] that the reaction results in the formation of 5-nitroisocoumarin (3), 3,4-dihydro-3-methoxy-5-nitroisocoumarin (4), and methyl 2-methyl-3-nitrobenzoate (5) in yields of 30.2%, 20.8%, and 1.6%, respectively (Chart 1).

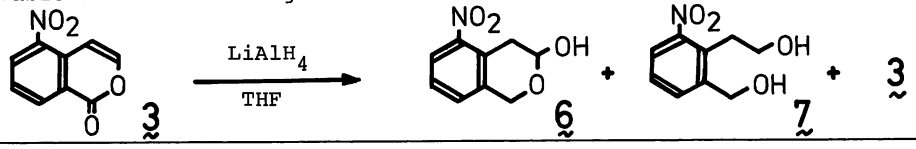
Chart 1



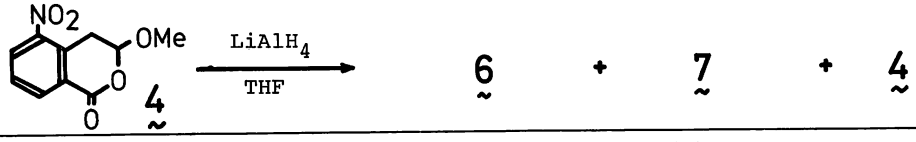
II. Illustration of the Second Operation

Treatment of either compound, 3 or 4, with $LiAlH_4$ in abs. tetrahydrofuran (THF) at room temperature afforded 3-hydroxy-5-nitroisochroman (6) and 2-(2-hydroxyethyl)-3-hydroxymethylnitrobenzene (7) together with the starting material. The effects of the reaction time and the amount of $LiAlH_4$ on the yields of the products are summarized in Table I. The best yield of 6 was attained when 1.2 mol equiv. of

Table I. A Novel Ring Transformation of Isocoumarin into Isochroman



Reaction Time (hr)	$LiAlH_4$ (mol equiv.)	Yield (%) of 6	7	3
5	3.8	21.1	38.3	0
1	1.3	46.9	16.3	0
1	1.2	62.8	24.0	6.2

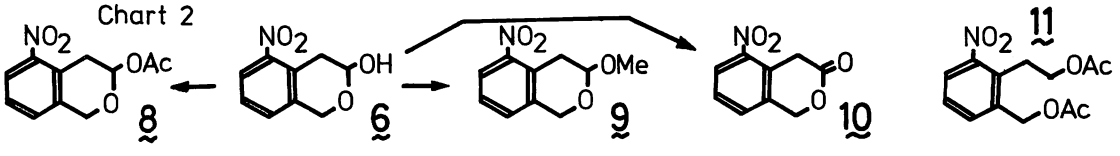


Reaction Time (hr)	$LiAlH_4$ (mol equiv.)	Yield (%) of 6	7	4
1	1.3	57.7	24.8	7.6
1	1.2	62.0	15.0	15.2

the reagent was employed to either 3 or 4.

Compound 6 gave acceptable combustion and mass spectral data and in its nuclear magnetic resonance (NMR) spectrum, characteristic protons on C-3 and C-4 of 3-substituted isochromans appeared as ABX pattern. In the infrared (IR) spectrum, strong absorption bands were observed at 3383, 1535, and 1362 cm^{-1}, which indicated the presence of both hydroxyl and nitro groups. The structure of 6 was further confirmed by the following experiments (Chart 2). Thus, acetylation of 6 with acetic anhydride and pyridine afforded 3-acetoxy-5-nitroisochroman (8) in 92.3% yield. Furthermore, refluxing of 6 in methanolic hydrochloric acid produced 3-

Chart 2



methoxy-5-nitroisochroman (9) in 79.4% yield. The final confirmation was provided by the oxidation of 6 with pyridinium chlorochromate giving 5-nitroisochroman-3-one (10) in 65.1% yield together with 19.2% recovery of the starting material. The compound (10) exhibited strong IR absorption band at 1745 cm^{-1} indicating the presence of a six-membered lactone ring.

It should be noted that this is the first example of the conversion of isocoumarins into isochromans. The reaction mechanism[5] and the synthesis of various isochromans according to this novel ring transformation method are currently under investigation.

The structure of 7 was established by the comparison of its spectral data with those of 11, which was readily obtained in 92.5% yield by the acetylation of 7 with acetic anhydride and pyridine.

III. Illustration of the Third Operation

In order to convert 3-hydroxy-5-nitroisochroman (6) into 4-hydroxymethylindole (2), the following requirements are needed: 1) reduction of the nitro group, 2) acid catalyzed ring opening, and 3) subsequent ring closure to an indole ring as shown in Chart 3. To satisfy these demands, we have already demonstrated that an aq. $TiCl_3$ is a reagent of choice.[6] Actually, reduction of 3-hydroxy-5-nitroisochroman (6) with aq. $TiCl_3$ was found to produce 2, 9, and 4-methoxymethylindole (12). The yield of 2 changed remarkably depending on the solvent system and the

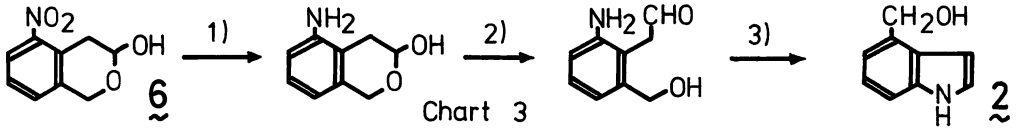
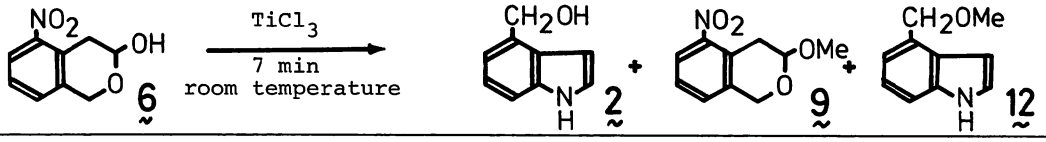


Chart 3

Table II. Preparation of 4-Hydroxymethylindole from 3-Hydroxy-5-nitroisochroman



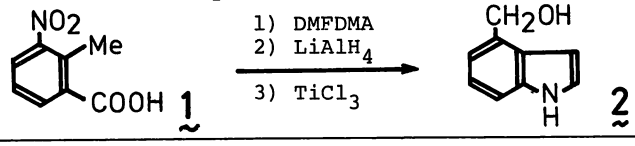
Entry	$TiCl_3$ (mol equiv.)	Solvent System	Yield (%) of 2	9	12
1	8.0	AcOH-H_2O (2:1, v/v)	1.7	0	0
2	6.5	THF-H_2O (5:2, v/v)	8.0	0	0
3	6.5	MeOH	24.0	11.1	9.5
4	6.0	MeOH	27.0	25.1	6.7
5	6.5	MeOH-H_2O (19:1, v/v) NH_4OAc (26 mol equiv.)	93.5	0	0.8

amount of aq. $TiCl_3$ as shown in Table II. Since the results (entries 1-4) showed that the compound (2) was sensitive to acid, the reduction was carried out in the presence of 26 mol equiv. of ammonium acetate in methanol-water (19:1, v/v) and found, as expected, to afford 2 in yield as high as 93.5% (entry 5). The structure of 12 was determined on the basis of its spectral data.

IV. A One Pot Synthesis of 4-Hydroxymethylindole

When the above three operations are conducted successively without separation of the products formed in each operation, a one pot synthesis of 2 is attained. A crucial factor in varying the yield of 2 in this one pot synthesis is the relative amount of $LiAlH_4$ to the starting material (1) in the second operation as summarized in Table III. In the case that a 0.8 mol equiv. of $LiAlH_4$ was used, the best overall yield (30.0%, entry 3) of 4-hydroxymethylindole was obtained.

Table III. A One Pot Synthesis of 4-Hydroxymethylindole*



Entry	$LiAlH_4$ (mol equiv. to 1)	Yield (%) of 2
1	0.6	11.9
2	0.7	27.8
3	0.8	30.0
4	0.9	26.9
5	1.2	23.6

* 3 Mol equiv. of DMFDMA (in the first operation), 6.5 mol equiv. of $TiCl_3$ and 26 mol equiv. of NH_4OAc (in the third operation) were used.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu IR-420 spectrophotometer, and NMR spectra with a JEOL JNM-C-60H spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JNM-01SG spectrometer. N,N-Dimethylformamide dimethyl acetal (DMFDMA) was purchased from Aldrich Chemical Co., Inc. and used without further purification. Commercially available aq. titanium (III) chloride ($TiCl_3$, 16%, d=1.5, from Kanto Chemical Co., Inc.) was used. Preparative thin-layer chromatography (p-TLC) was performed on Merck Kiesel-gel GF_{254} (Type 60, SiO_2). Column chromatography was performed on silica gel (SiO_2, 100-200 mesh), purchased from Kanto Chemical Co., Inc.

A One Pot Synthetic Procedure of 4-Hydroxymethylindole (2) from 2-Methyl-3-nitrobenzoic acid (1)———— A solution of 1 (1.017 g) and DMFDMA (2.003 g, 3 mol eq.) in abs. N,N-dimethylformamide (DMF, 8.0 ml) was refluxed for 12.5 hr. The solvent was evaporated to dryness in vacuo. Abs. tetrahydrofuran (THF, 30.0 ml) was added and the whole was stirred with lithium aluminum hydride ($LiAlH_4$, 172.7 mg, 0.8 mol to 1) for 1 hr at room temperature. After addition of MeOH (5.0 ml), the solvent was evaporated to dryness in vacuo. A mixture of MeOH-H_2O (19:1, v/v, 50.0 ml) and ammonium acetate (NH_4OAc, 11.266g, 26 mol eq. to 1) was added to the residue. Aq. $TiCl_3$ (23.5 ml, 6.5 mol eq. to 1) was added to the resultant solution as a single portion and stirred for 7 min at room temperature. After the whole was made alkaline by adding sat. aq. $NaHCO_3$, MeOH was evaporated off under a reduced pressure. Conc. NH_4OH and aq. potassium sodium tartrate were added to the resultant solution and the whole was extracted with CH_2Cl_2-MeOH (99:1, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave an oil. Subsequent purification by column chromatography on SiO_2 with CH_2Cl_2 as an eluent gave 2 (248.0 mg, 30.0% overall yield from 1) as colorless prisms, mp 56.5-57.5° (lit.[2] mp 56-57°). All spectral data were identical with those of an authentic sample.

3-Hydroxy-5-nitroisochroman (6) and 2-(2-Hydroxyethyl)-3-hydroxymethylnitrobenzene (7) ———— i) from 5-Nitroisocoumarin (3): $LiAlH_4$ (12.4 mg, 1.2 mol eq.) was added to a solution of 3 (52.9 mg) in abs. THF (3.0 ml) and the mixture was stirred for 1 hr at room temperature. After the reaction was stopped by adding MeOH (1.0 ml), the solvent was evaporated off under a reduced pressure. An aq. potassium sodium tartrate was added and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave an oil, which was subjected to p-TLC on SiO_2 with CH_2Cl_2-MeOH (99:1, v/v) as a developing solvent. Under a UV lamp, three dark bands were detected on the whole luminescent plate. Extraction of the upper band with CH_2Cl_2-MeOH (95:5, v/v) gave the starting material (3, 3.3 mg, y. 6.2%). Extraction of the middle band with the same solvent afforded 6 (33.9 mg, y. 62.8%). Extraction of the lower band with the same solvent gave 7 (13.1 mg, y. 24.0%). 6: mp 118.0-119.0° (colorless leaflets, recrystallized from CH_2Cl_2-hexane). IR ν_{max}^{KBr} cm^{-1}: 3383, 1535, 1362. NMR ($CDCl_3$) δ: 2.97 (1H, dd, J=18.0 and 4.5 Hz), 3.35 (1H, dd, J=18.0 and 4.0 Hz), 4.70 (1H, d, J=15.0 Hz), 5.05 (1H, d, J=15.0 Hz), 5.32 (1H, dd, J=4.5 and 4.0 Hz), 7.23 (1H, d, J=4.0 Hz), 7.25 (1H, d, J=6.0 Hz), 7.65 (1H, dd, J=6.0 and 4.0 Hz). MS m/e: 195 (M^+). Anal. Calcd for $C_9H_9NO_4$: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.34; H, 4.57; N, 7.12. 7: mp 68.0-69.0° (colorless prisms, recrystallized from benzene-acetone). IR ν_{max}^{KBr} cm^{-1}: 3355, 1526, 1351. NMR ($CDCl_3$) δ: 3.09 (2H, t, J=6.0 Hz), 3.58 (2H, br s, OH x 2), 3.82 (2H, t, J=6.0 Hz), 4.59 (2H, s), 7.21 (1H, t, J=7.5 Hz), 7.48 (1H, dd, J=7.5 and 2.0 Hz), 7.65 (1H, dd, J=7.5 and 2.0 Hz). MS m/e: 197 (M^+). Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.79; H, 5.65; N, 7.03.

ii) from 3,4-Dihydro-3-methoxy-5-nitroisocoumarin (4): $LiAlH_4$ (11.1 mg, 1.2 mol eq.), 4 (52.7 mg), and abs. THF (3.0 ml) were used. After work-up and subsequent p-TLC, as described above, 4 (8.0 mg, y. 15.2%), 6 (28.6 mg, y. 62.0%), and 7 (7.0 mg, y. 15.0%) were obtained.

3-Acetoxy-5-nitroisochroman (8) from 3-Hydroxy-5-nitroisochroman (6) ——— A solution of 6 (31.4 mg) in dry pyridine (2.0 ml) and Ac_2O (1.0 ml) was stirred for 14 hr at room temperature. The solvent was evaporated off under a reduced pressure and then H_2O was added. The whole was extracted with CH_2Cl_2, washed with aq. $NaHCO_3$, then with H_2O, dried over Na_2SO_4, and concentrated to leave an oil. Purification by p-TLC on SiO_2 with CH_2Cl_2-hexane (7:3, v/v) as a developing solvent gave 8 (35.8 mg, y. 92.3%). Recrystallization from MeOH gave colorless leaflets, mp 139.0-141.0°. IR $\nu_{max}^{KBr}cm^{-1}$: 1752, 1528, 1349. NMR ($CDCl_3$) δ: 2.05 (3H, s), 3.07 (1H, dd, J=19.0 and 3.2 Hz), 3.58 (1H, dd, J=19.0 and 4.5 Hz), 4.87 (2H, s), 6.32 (1H, dd, J=4.5 and 3.2 Hz), 7.26 (1H, d, J=3.5 Hz), 7.28 (1H, dd, J=6.5 Hz), 7.87 (1H, dd, J=6.5 and 3.5 Hz). MS m/e: 177 (M^+-CH_3COOH). Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.69; H, 4.67; N, 5.91. Found: C, 55.74; H, 4.49; N, 6.04.

3-Methoxy-5-nitroisochroman (9) from 3-Hydroxy-5-nitroisochroman (6) ——— A solution of 6 (50.5 mg) in MeOH (4.0 ml) and concd. HCl (1.0 ml) was refluxed for 2.5 hr. After evaporation of the solvent under a reduced pressure, the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave an oil, which was purified by p-TLC on SiO_2 with CH_2Cl_2-hexane (7:3, v/v) as a developing solvent to afford 9 (43.0 mg, y. 79.4%). Recrystallization from MeOH-H_2O gave colorless needles, mp 74.0-75.0°. IR $\nu_{max}^{KBr}cm^{-1}$: 1523, 1334. NMR ($CDCl_3$) δ: 2.98 (1H, dd, J=18.0 and 3.0 Hz), 3.38 (1H, dd, J=18.0 and 4.0 Hz), 3.43 (3H, s), 4.74 (2H, br s), 4.95 (1H, dd, J=4.0 and 3.0 Hz), 7.20 (1H, d, J=4.0 Hz), 7.22 (1H, d, J=6.0 Hz), 7.78 (1H, dd, J=6.0 and 4.0 Hz). MS m/e: 209 (M^+). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.22; H, 5.24; N, 6.56.

5-Nitroisochroman-3-one (10) from 3-Hydroxy-5-nitroisochroman (6) ——— Pyridinium chlorochromate (120.9 mg) was added to a solution of 6 (50.1 mg) in CH_2Cl_2 (3.0 ml) and AcOH (1.0 ml). After stirring for 11.5 hr at room temperature, EtOH (1.0 ml) was added. The whole was made alkaline by adding sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave an oil, which was subjected to p-TLC on SiO_2 with CH_2Cl_2-MeOH (99:1, v/v) as a developing solvent. Under a UV lamp, two dark bands were detected on the whole luminescent plate. Extraction of the upper band with CH_2Cl_2-MeOH (95:5, v/v) gave 10 (32.3 mg, y. 65.1%). Extraction of the lower band with the same solvent gave 6 (9.6 mg, y. 19.2%). 10: mp 142.0-143.0° (colorless prisms, recrystallized from MeOH). IR $\nu_{max}^{KBr}cm^{-1}$: 1745, 1520, 1354. NMR (10% CD_3OD in $CDCl_3$) δ: 4.15 (2H, s), 5.38 (2H, s), 7.48 (1H, d, J=6.5 Hz), 7.52 (1H, d, J=3.2 Hz), 8.02 (1H, dd, J=6.5 and 3.2 Hz). MS m/e: 193 (M^+). Anal. Calcd for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 56.00; H, 3.51; N, 7.50.

4-Hydroxymethylindole (2), 3-Methoxy-5-nitroisochroman (9), and 4-Methoxymethylindole (12) from 3-Hydroxy-5-nitroisochroman (6) ——— i) Aq. $TiCl_3$ (2.2 ml, 6.5 mol eq.) was added to a stirred solution of 6 (102.1 mg) in MeOH (5.0 ml) as a single portion and the mixture was stirred for 7 min at room temperature. The whole was made alkaline by adding sat. aq. $NaHCO_3$ and conc. NH_4OH, and then extracted with CH_2Cl_2. The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave an oil, which was subjected to p-TLC on SiO_2 with

CH_2Cl_2 as a developing solvent. Under a UV lamp, three dark bands were detected on the whole luminescent plate. Extraction of the upper band with CH_2Cl_2-MeOH (95:5, v/v) gave 9 (12.1 mg, y. 11.1%). Extraction of the middle band with the same solvent afforded 12 (8.0 mg, y. 9.5%). Extraction of the lower band with the same solvent gave 2 (18.5 mg, y. 24.0%). 12: colorless oil. IR ν_{max}^{film} cm^{-1}: 3398, 3278, 1345, 1118, 1080. NMR ($CDCl_3$) δ: 3.38 (3H, s), 4.72 (2H, s), 6.56 (1H, br t, J=3.0 Hz), 6.98-7.28 (4H, m), 8.09 (1H, br). MS m/e: 161 (M^+).

ii) Aq. $TiCl_3$ (2.2 ml, 6.5 mol eq.) was added to a stirred solution of 6 (102.0 mg) and NH_4OAc (1.042 g, 26 mol eq.) in MeOH-H_2O (19:1, v/v. 20.0 ml) as a single portion. The mixture was stirred for 7 min at room temperature. After work-up and subsequent p-TLC, as described in the item i), 2 (72.0 mg, y. 93.5%) and 12 (0.7 mg, y. 0.8%) were obtained. Even a trace amount of 9 was not formed.

2-(2-Acetoxyethyl)-3-acetoxymethylnitrobenzene (11) from 2-(2-Hydroxyethyl)-3-hydroxymethylnitrobenzene (7) ——— A solution of 7 (98.6 mg) in Ac_2O (1.0 ml) and pyridine (2.0 ml) was stirred for 19 hr at room temperature. The solvent was evaporated off under a reduced pressure and H_2O was added. The whole was extracted with CH_2Cl_2-MeOH (95:5, v/v), washed with sat. aq. $NaHCO_3$, then with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave an oil, which was purified by p-TLC on SiO_2 with CH_2Cl_2-MeOH (99:1, v/v) as a developing solvent to give 11 (129.2 mg, y. 92.5%). 11: colorless oil. IR ν_{max}^{film} cm^{-1}: 1740, 1531, 1356, 1220. NMR ($CDCl_3$) δ: 2.01 (3H, s), 2.11 (3H, s), 3.24 (2H, t, J=7.0 Hz), 4.27 (2H, t, J=7.0 Hz), 5.23 (2H, s), 7.29 (1H, t, J=8.0 Hz), 7.58 (1H, dd, J=8.0 and 2.0 Hz), 7.70 (1H, dd, J=8.0 and 2.0 Hz). MS m/e: 281 (M^+).

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