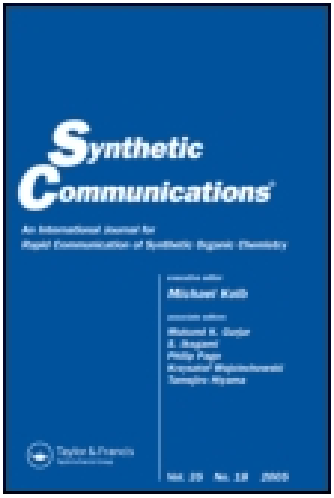

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An Efficient Synthetic Method for 2-Methoxy-L,2-dihydro-3H-indol-3-ones

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AN EFFICIENT SYNTHETIC METHOD FOR 2-METHOXY-1,2-DIHYDRO-3*H*-INDOL-3-ONES

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Abstract: An efficient method for synthesis of 2-methoxy-1,2-dihydro-3*H*-indol-3-ones using two successive oxidations of indoles is described.

1,2-Dihydro-3*H*-indol-3-ones are useful synthetic intermediates for the synthesis of alkaloids and biologically active compounds.[1] 2-Alkoxy-1,2-dihydro-3*H*-indol-3-ones are particularly attractive intermediates for the synthesis of the alkaloids hyellazole,[2] 4-demethoxycarbazomycin B,[3] flustramine C,[4] and mitomycin K.[5] Although several methods for synthesis of 1,2-dihydro-3*H*-indol-3-ones have been reported,[6] 2-alkoxy-1,2-dihydro-3*H*-indol-3-ones are still difficult to obtain.[5,7]

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Thus, we previously reported the synthesis of 2-methoxy-1,2-dihydro-3*H*-indol-3-ones using oxidation of 1-acylindoles with oxodiperoxymolybdenum hexamethylphophoramide ($MoO_5 \cdot$ HMPA: MoH) giving 3-hydroxy-2-methoxyindoline followed by Sarett oxidation (CrO_3-pyridine).[8] This Sarett oxidation, however, has some disadvantages: insufficient yield of the product, complicated post-treatment and toxicity of the chromium compound. We tried some oxidations of 3-hydroxy-2-methoxyindolines to improve this step, and now report an efficient method for synthesis of 2-methoxy-1,2-dihydro-3*H*-indol-3-ones.

1-Acetyl- and 1-methoxycarbonyl-indoles (**1**) were readily obtained in 81-99% yield by Illi's method.[9] Oxidation of **1** with MoH in methanol at room temperature gave 3-hydroxy-2-methoxyindolines (**2**) in good yield (56-78%) (Table 1). We first tried Albright-Goldman oxidation of **2b** using the dimethyl sulfoxide (DMSO)/acetic anhydride system,[10] but the reaction proceeded unsuccessfully to give the desired 2-methoxyindol-3-one (**3b**) in only 33% yield together with the formation of *O*-acetate (**4**; 15%) and the Pummerer rearrangement product (**5**; 12%), which were well-known as the by-products in the oxidation using this reagent system.[11] Next, Onodera's oxidation of **2b** using phosphorous (V) oxide/triethylamine instead of acetyl anhydride, the known method for repressing the the formation of the Pummerer rearrangement product,[12] resulted in improved yield (67%). Swern oxidation of **2a** using DMSO, oxalyl chloride and triethylamine was carried out to afford successfully **3a** in 98% yield.

This oxidation was successfully applied to preparation of several 2-methoxyindol-3-ones (**3a-f**) as shown in Table 2. We also attempted other type oxidations using

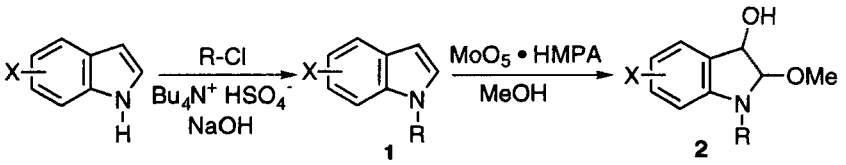


Table 1

	X	R	Yield (%) 1	Yield (%) 2
a	H	Ac	99	71
b	6-Br	Ac	90	64
c	5-Br	Ac	98	56
d	4-Br	CO_2Me	94	78
e	6-Cl	Ac	90	72
f	5-MeO	Ac	81	61

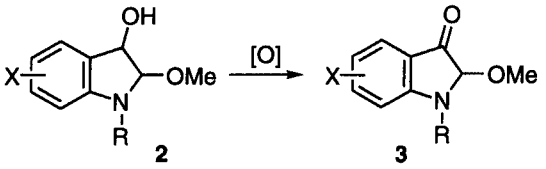
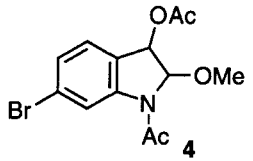


Table 2

[O]	X	R	3	Yield (%)
CrO_3/Py	H	Ac	**a**	81[8]
DMSO/Ac_2O	H	Ac	**a**	57
	6-Br	Ac	**b**	33
DMSO/P_2O_5/Et_3N	6-Br	Ac	**b**	67
DMSO/$(COCl)_2$/Et_3N	H	Ac	**a**	98
	6-Br	Ac	**b**	92
	5-Br	Ac	**c**	88
	4-Br	CO_2Me	**d**	77
	6-Cl	Ac	**e**	88
	5-MeO	Ac	**f**	66
TPAP/NMO	H	Ac	**a**	91
TMPO/KBr/NaOCl	H	Ac	**a**	97
	6-Br	Ac	**b**	86



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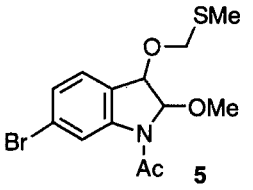

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the 2,2,6,6-tetramethylpiperidinooxy (TMPO)/KBr/NaOCl system[13] and tetra-*n*-propylammonium perruthenate (TPAP)/*N*-methyl-morpholine *N*-oxide (NMO).[14] Thus, treatment of **2a** with a catalytic amount of TPAP in the presence of NMO (co-oxidant) at 8-9 pH adjusting with sodium carbonate gave **3a** in 91% yield. Oxidation of **2a** and **2b** with TMPO (catalyst) and NaOCl/KBr (co-oxidant) also afforded good results, respectively; **3a** and **3b** were obtained in 97% and 86% yield.

In work-up procedure for these activated DMSO oxidations, a bad odor of dimethyl sulfide was generated. Swern oxidation is an efficient procedure for preparation of various **3**, however, a large-scale Swern oxidation was difficult due to the requirement of low reaction temperature. TMPO/KBr/NaOCl system can be applied in large scale oxidation of **2**. The oxidation using TPAP/NMO proceeded smoothly, however, TPAP is not suitable for a large-scale reaction because of its expense. Consequently, the TMPO/KBr/NaOCl system in the oxidation of **2** to **3** is preferable to the other oxidations described above.

EXPERIMENTAL

General: All m.p.s are uncorrected, and were measured on a Yanagimoto micromelting point apparatus. IR spectra were recorded with a Hitachi 270-30 or a Shimadzu FTIR-8100 spectrophotometer in $CHCl_3$. ^{1}H-NMR spectra were determined with a JEOL JNM-GX 270 spectrometer with tetramethylsilane as an internal standard in $CDCl_3$. *J*-Values are given in Hz. Mass spectra were obtained with a JEOL JMS-DX302 instrument with a direct inlet system operating at 70 eV. Elemental analyses were obtained using a Perkin-Elmer Model 240B elemental analyzer. Column chromatography was carried out on silica gel (Kanto

Chemical Co. Inc., 100-200 mesh and Merck, 400 mesh). Starting indoles were obtained from Aldrich.

General procedure for the oxidation of 1-acetyl- and 1-methoxycarbonyl-indoles (1) with MoH in methanol: A solution of $MoO_5 \cdot HMPA$ (4.9 mmol) and 1-acetylindole (**1**) (2.4 mmol) in methanol (150 ml) was stirred at room temperature for 1-2 weeks. After concentration of the mixture *in vacuo*, ethyl acetate solution of the residue was washed with sat. Na_2SO_3, dried over $MgSO_4$ and concentrated *in vacuo* to give a residue, which was purified by column chromatography on silica gel using AcOEt-hexane as an eluate to give 1-acetyl-3-hydroxy-2-methoxyindoline (**2**).

1-Acetyl-6-bromo-3-hydroxy-2-methoxyindoline (**2b**) (430 mg, 64 %) was obtained from **1b** (560 mg, 2.35 mmol); m.p. 117 ℃: IR ν 3013, 1674, 1476, 1420, 1397, 1086 cm^{-1}: ^{1}H-NMR δ: 2.10 (3 H, s), 3.06 (1 H, brs), 3.37 (3 H, s), .4.90 (1 H, d, *J* =7.6 Hz), 5.16 (1 H, s), 7.27 (1 H, dd, *J* =7.9, 1.7 Hz), 7.32 (1 H, d, *J* =7.9 Hz), 8.32 (1 H, brs): MS *m/z* (%) : 287 (M+2, 32), 285 (M^+, 33), 244 (62), 242 (61), 227 (25), 225 (24), 212 (100), 210 (94), 185 (16), 183 (17), 133 (19), 43 (44): *Anal* Calcd. for. $C_{11}H_{12}NO_3Br$: C, 46.16; H, 4.23; N, 4.89. Found: C, 46.25; H, 4.23; N, 4.89.

1-Methoxycarbonyl-4-bromo-3-hydroxy-2-methoxyindoline (**2d**) (1.12 g, 78 %) was obtained from **1d** (1.22 g, 4.8 mmol), m.p.82-106 ℃: IR ν 3437, 1717, 1456, 1443, 1385, 1318, 1318, 1200, 1090 cm^{-1}: ^{1}H-NMR δ: 2.27 (1 H, brs), 3.50 (3 H, s), 3.80 (3 H, s), .4.93 (1 H, d, *J* =4.6 Hz), 5.16 (1 H, s), 7.20 (2 H,

brq), 7.72 (1 H, brs): *Anal* Calcd. for. $C_{11}H_{12}NO_4Br$: C, 43.73; H, 4.00; N, 4.64. Found: C, 43.69; H, 3.93; N, 4.60.

1-Acetyl-6-chloro-3-hydroxy-2-methoxyindoline (**2e**) (632 mg, 72 %) was obtained from **1e** (708 mg, 3.65 mmol), m.p.102-108 ℃: IR ν 1684, 1478, 1397 cm^{-1}: ^{1}H-NMR δ: 2.23 (3 H, s), 3.38 (3 H, s), 3.58 (1 H, s), 4.93 (1 H, brd, *J* =7.3 Hz), 5.22 (1 H, s), 7.11 (1 H, dd, *J* =7.9, 2.0 Hz), 7.36 (1 H, d, *J* =7.9 Hz), 8.21 (1 H, brs): *Anal* Calcd. for. $C_{11}H_{12}NO_3Cl$: C, 54.66; H, 5.00; N, 5.79. Found: C, 54.58; H, 5.06; N, 5.73.

1-Acetyl-3-hydroxy-2-methoxyindoline (**2a**),[8] *1-acetyl-5-bromo-3-hydroxy-2-methoxyindoline* (**2c**)[8] and *1-acetyl-3-hydroxy-2,5-dimethoxyindoline* (**2f**)[6f] were reported previously.

Preparation of 1-acetyl-2-methoxy-1,2-dihydroindol-3-ones (3) using oxidation of 2-methoxy-3-hydroxyindolines (2).

General procedure for DMSO/Ac_2O oxidation: The solution of dimethyl sulfoxide (74 mmol) and acetic anhydride (37 mmol) was stirred for one hour under argon atmosphere. Then, 3-hydroxy-2-methoxyindoline (**2**) (1.75 mmol) was added to the mixture followed by stirring at room temperature for 12 hours. The reaction mixture was concentrated *in vacuo*. An ethyl acetate extract of the residue was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using AcOEt-hexane to give 2-methoxy-1,2-dihydroindol-3-one (**3**) as shown in Table 2.

3-Acetoxy-1-acetyl-6-bromo-2-methoxyindoline (**4**); a viscous oil, ^{1}H-NMR δ:

2.10 (3 H, s), 2.33 (3 H, s), 3.44 (3 H, s), 5.26 (1 H, brs), 5.94 (1 H, brs), 7.25 (1 H, dd, J=7.9, 1.7 Hz), 7.30 (1 H, d, J=7.9 Hz), 8.8.43 (1 H, brs).

1-Acetyl-6-bromo-2-methoxy-3-methylthiomethoxyindoline (**5**); a viscous oil, ^{1}H-NMR δ: 2.22 (3 H, s), 2.34 (3 H, s), 3.45 (3 H, s), 4.73 (2 H, s), 5.12 (1 H, brs), 5.34 (1 H, s), 7.21 (1 H, d, J =7.9 Hz), 7.28 (1 H, dd, J =7.9, 1.7 Hz), 8.8.43 (1 H, brs).

DMSO/P_2O_5/Et_3N oxidation: Dimethyl sulfoxide (175 ml, 1.23 mmol) and P_2O_5 (500 mg, 3.50 mmol) were added to a solution of 1-acetyl-6-bromo-3-hydroxy-2-methoxyindoline (**2b**) (100 mg, 0.35 mmol) in dichloromethane (1.0 ml) at 0 ℃ under argon atmosphere, and the mixture was stirred at room temperature for 30 min. Triethylamine (171 ml, 1.23 mmol) was added dropwise to the mixture over 10 min. at 0 ℃ followed by stirring for one hour at the same temperature. The mixture was allowed to warm to room temperature over 70 min. After adding 10% HCl and sat.NaCl, the mixture was extracted with dichloromethane. The extract was dried over $MgSO_4$ and concentrated *in vacuo* to give a residue, which was purified by column chromatography on silica gel using AcOEt-hexane (1 : 3)to give 1-acetyl-6-bromo-2-methoxy-1,2-dihydroindolin-3-one (**3b**) (66.7 mg, 67 %).

General procedure for the Swern oxidation: Oxalyl chloride (11 mmol) was added to a solution of dimethyl sulfoxide (1.7 ml) in dichloromethane (25 ml) at -78 ℃ and the mixture was stirred at -60 ℃ for 2 hours. A solution of **2** (7.6 mmol) in dry dichloromethane (25 ml) was then added to the mixture. After 30 min., triethylamine (34 mmol) was added. After 5 min, dichloromethane (25 ml) and sat.NaCl aq. (15 ml) were added to quench the reaction. The mixture was

allowed to warm up to room temperature and extracted with dichloromethane. The extract was dried over $MgSO_4$ and concentrated *in vacuo* to give a residue, which was purified by column chromatography on silica gel using AcOEt-hexane to give **3** as shown in Table 2.

TPAP/NMO oxidation: A solution of **2a** (207 mg, 1 mmol), TPAP (104 mg, 0.3 mmol) and NMO (350 mg, 3 mmol) in dichloromethane (30 ml) was stirred at room temperature for 15 min. The reaction mixture was washed with dil. HCl, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel column using AcOEt-hexane (1 : 3) to give **3a** (187 mg, 91%).

General procedure for TMPO/NaOCl/KBr oxidation: A solution of NaOCl (0.35 M, 123 ml, 50 mmol) was added to a solution of **2** (40 mmol), TMPO (0.04 mmol) and 0.5 M KBr aq. (3 mmol) in dichloromethane (320 ml) under control of pH at 8-9 adding sodium carbonate at room temperature. The reaction mixture was stirred at the same temperature for 1 hour and extracted with dichloromethane. The extract was washed with $NaHCO_3$ aq., dried over $MgSO_4$, and concentrated *in vacuo* to give a residue, which was chromatographed on silica gel column using AcOEt-hexane to give **3** (86-97%).

The ^{1}H-NMR spectra data (270 MHz) of **3** are summarized in Table 3.

1-Acetyl-6-bromo-2-methoxy-1,2-dihydro-3H-indol-3-one (**3b**); m.p.118 ℃: IR ν 1734, 1694, 1599, 1426, 1383 cm^{-1}: MS *m/z* (%) 285 (M+2, 37), 283 (M^+, 38), 242 (99), 240 (100), 210 (36), 208 (29), 157 (5), 155 (5), 75 (10), 43 (22): HRMS found 282.9846, calculated 282.9845 for. $C_{11}H_{12}NO_3Br$.

1-Acetyl-5-bromo-2-methoxy-1,2-dihydro-3H-indol-3-one (**3c**); m.p. 101 ℃: IR ν

Table 3 Chemical shifts (coupling constants: Hz) of 2-methoxy-1,2-dihydro-3*H*-indol-3-ones (**3**) in ^{1}H-NMR spectra data (270 MHz)

	2-H[a]	4-H[b]	5-H[b]	6-H[b]	7-H[b]	2-OMe[a]	1-Ac or OMe[a]
3a[c, 8]	5.17	7.75 (7.6)	7.21 (7.6, 6.5)	7.68 (8.2, 6.5)	8.50 (8.2)	3.40	2.40
3b	5.16	7.58 (8.2)	7.36 (8.2, 1.7)	-	8.76 (1.7)	3.40	2.40
3c	5.16	7.83 (2.0)	-	7.76 (8.9, 2.0)	8.42 (8.9)	3.41	2.39
3d	5.14	-	7.31 (7.9, 1.0)	7.46 (8.3, 7.9)	8.08 (8.3)	3.59	3.94
3e	5.18	7.66 (8.3)	7.26 (8.3, 1.7)	-	8.57 (1.7)	3.40	2.40
3f[c, 6f]	5.17	7.15 (2.6)	-	7.28 (8.9, 2.6)	8.45 (8.9)	3.38	2.37 3.83

a: singlet, b: doublet or double-doublet,

c: Since the reference 8 and 6f reported the ^{1}H-NMR spectrum data (60 MHz) of **3a** and **3f**, NMR spectrum data (270 MHz) is shown here.

1736, 1685, 1462, 1379 cm^{-1}: *Anal* Calcd. for. $C_{11}H_{12}NO_3Br$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.42; H, 3.51; N, 4.90.

1-Methoxycarbonyl-4-bromo-2-methoxy-1,2-dihydro-3H-indol-3-one (**3d**); m.p. 113 ℃: IR ν 1730, 1593, 1449, 1370, 1277, 1248 cm^{-1}: *Anal* Calcd. for. $C_{11}H_{10}NO_4Br$: C, 44.0; H, 3.36; N, 4.67. Found: C, 44.0; H, 3.35; N, 4.67.

1-Acetyl-6-chloro-2-methoxy-1,2-dihydro-3H-indol-3-one (**3e**); m.p.122 ℃: IR ν 1734, 1694, 1601, 1431, 1385 cm^{-1}: *Anal* Calcd. for. $C_{11}H_{10}NO_3Cl$: C, 55.13; H, 4.21; N, 5.84. Found: C, 54.71; H, 4.23; N, 5.76.

1-Acetyl-2-methoxy-1,2-dihydro-3H-indol-3-one (**3a**)[8] and *1-acetyl-2,5-dimethoxy-1,2-dihydro-3H-indol-3-one* (**3f**)[6f] were reported previously.

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