An improved preparation of isatins from indoles

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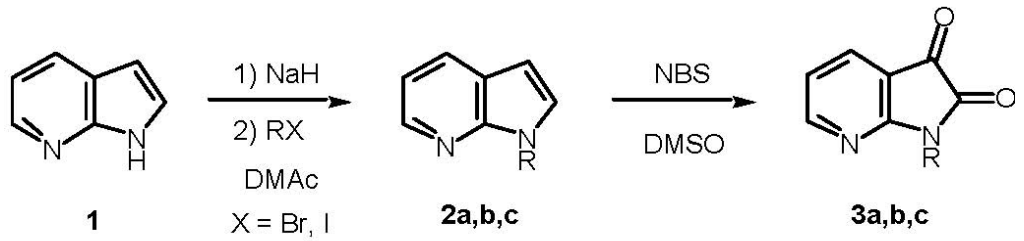
Abstract

A convenient method has been developed for the conversion of indoles into isatin derivatives in good to excellent yields. The general process utilizes our efficient one-pot method for bromination and oxidation with an N-bromosuccinimide - dimethyl sulfoxide reagent. 1-Alkyl-7-azaindoles are readily available in excellent yields from the reaction of the sodium salt of 7-azaindole with appropriate alkyl halides in dimethylacetamide. Similar reactions with 1-alkyl-5-cyanoindoles and indole gave 1-alkyl-5-cyanoisatins and isatin, respectively.

Key words: Indoles, isatin derivatives, *N*-bromosuccinimide-dimethyl sulfoxide oxidation

Introduction

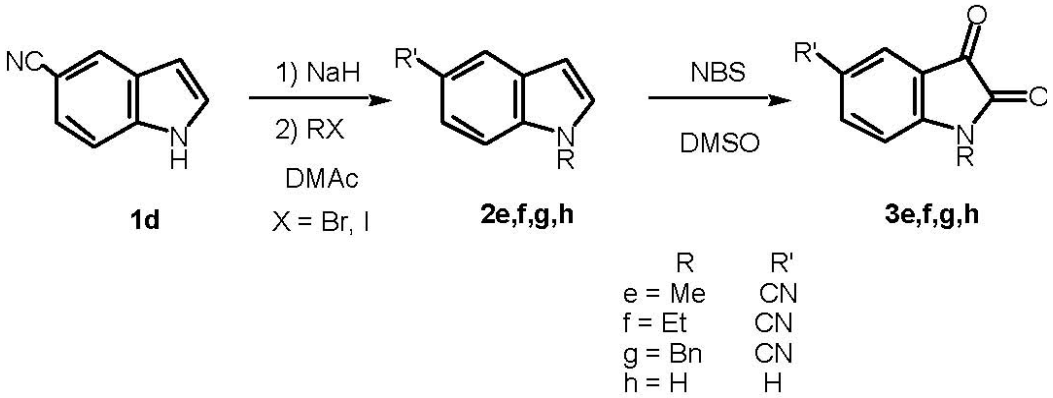
In connection with research developed in our studies on the photochemical behavior of cyclic vicinal polycarbonyl compounds, [1-3] we needed to prepare isatins as structurally related compounds to investigate the photochemical reactions of heterocyclic vicinal polycarbonyls. Recently, much attention has been paid to isatins in organic synthesis. [2-8] We reported one-pot synthesis of several vicinal polycarbonyl compounds *via* α-bromo carbonyl derivatives from α-methylene carbonyl compounds by N-bromosuccinimide (NBS) -DMSO oxidation.[9] This oxidation method with NBS-DMSO reagent prompted us to explore an improved synthesis of isatins from indoles. We have examined the applicability of this NBS-DMSO oxidation to the conversion of 1-methyl-7-azaindole **2a** into 1-methyl-7-azaisatin **3a** as shown in Scheme 1. Initially, we prepared 1- methyl-7-azaindole **2a** from the reaction of the sodium salt of 7-azaindole **1** with methyl iodide in dimethylacetamide. It was found that the oxidation of 2a with NBS in DMSO to 3a was carried out at 60^{o}C for 6 h under ambient pressure and then at above 80^{o}C for 20 h under reduced pressure to remove the generated hydrogen bromide. In this paper, we describe this improved method for the preparation of the isatin derivatives **3** from indoles **1**.



Scheme 1

Results and Discussion

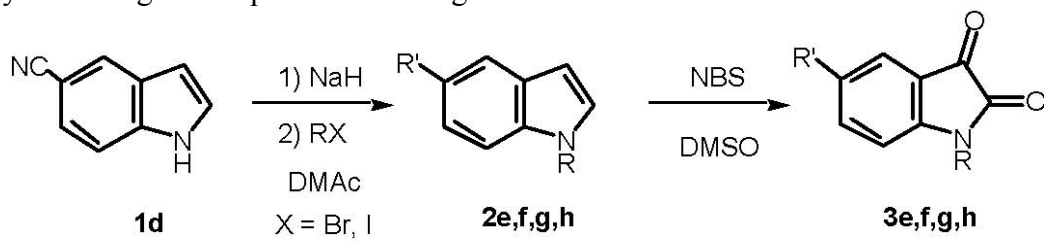
Alkyl-7-azaindoles **2a**, **2b**, and **2c** were prepared in excellent yields by the reaction of the sodium salt of **1** with appropriate alkyl halides in dimethylacetamide at room temperature. The resulting 1-alkylated derivatives **2** were subsequently oxidized to **3** with the NBS-DMSO reagent. When oxidation of **2a** with NBS in anhydrous DMSO was carried out at room temperature for 12 h, a small amount of **3a** was detected by GC-MS analysis. Unfortunately, when this oxidation reaction was performed at above 80 □ under ambient pressure, rapid decomposition of DMSO by the generated hydrogen bromide predominantly proceeded.[10,11] Therefore, it was necessary in the present oxidation reaction to prevent the acid-catalyzed decomposition of DMSO. In order to remove the generated hydrogen bromide, the oxidation with NBS in DMSO at above 80°C was carried out under reduced pressure. Thus, the desired **3a** was obtained in 95% yield by treatment of **2a** with NBS in DMSO at 60°C for 6 h under ambient pressure and then at above 80°C for 20 h under reduced pressure to remove the generated hydrogen bromide. Similarly, 1-ethyl- and 1-benzyl-7-azaindoles **2b** and **2c** were converted to the corresponding 1-alkylated 7-azaisatins **3b** and **3c** in 95 and 92% yields, respectively.



Scheme 2

In a similar manner, 5-cyanoindole **1d** gave the corresponding 1-alkyled 5-cyanoisatins **3e, 3f,**

and **3g** in fair yields *via* 1-alkyl-5-cyanoindoles **2e, 2f,** and **2g,** and indole **1h** gave isatin **3h** in 90% yield (Scheme 2). A plausible reaction pathway for the formation of **3** is illustrated in Scheme 3. The initial bromination of **2** would yield 2,3-dibromo derivative **A**. The dibromoindole is brominated a third time at C-3, generating a 2,3,3-tribromo-3H-indolium salt **B** which is hydrolysed during work up with water to give the isatin **3**.



	R	R'
e	Me	CN
f	Et	CN
g	Bn	CN
h	H	H

Scheme 3

To confirm the reaction pathway to **3**, the reaction of 2,3-dibromo-1-methyl-7-azaindole which was prepared by the bromination of **2a** with two equivalents of bromine in dichloromethane with DMSO was carried out under the above similar oxidation conditions to afford **3a** in excellent yield. The results indicate that the formation of **3** is considered to proceed *via* **A**.

In summary, a convenient synthesis of isatin derivatives from commercially available indoles *via* 1-alkylindoles is described.

Experimental Section

General Procedures. Melting points were determined on a Yanagimoto hot-stage apparatus and are uncorrected. IR spectra were recorded on a Nihon Bunko 7300 FT-IR spectrometer in KBr with absorptions in cm^{-1}. The UV-vis spectra were recorded using a Shimadzu UV-3100S spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 from a solution $CDCl_3$ of the product. ^{1}H chemical shifts are expressed as δ values (ppm) relative to TMS as an internal standard. MS spectra and HRMS were recorded on Hitachi 80-B spectrometer. Elemental analyses were performed at the Center of Instrumental Analysis, Meijo University, Nagoya, Japan. For column chromatography, silica gel (nacalai tesque, 230 – 400 mesh) was used. Commercal dimethyl sulfoxide was purified by drying over calcium hydride and distillation. 7-Azaindole (Aldrich), indole, methyl iodide, ethyl iodide, benzyl bromide, and NBS were commercially available and were used without purification.

General procedure I. Alkylation of 7-azaindole

Sodium hydride (0.1 g, 4 mmol) free of mineral oil was added to 7-azaindole **1** (0.35 g, 3 mmol) in dimethylacetamide (10 mL) under an inert atmosphere. After 30 min, the appropriate alkyl halide (3.5 mmol) was added slowly as a solution in dimethylacetamide (2 mL), and the solution was stirred at rt for 12 h to give a pale yellow solution. The reaction was quenched with water (20 mL) and extracted with dichloromethane. The combined extracts were washed three times with distilled water. After drying ($MgSO_4$)the dichloromethane layer and removal of the solvent, the residue was purified by chromatography on silica gel with dichloromethane as an eluent to give the respective 1-alkyl-7-azaindoles.

1-Methyl-7-azaindole (2a). According to procedure I, 7-azaindole was converted to **2a**; yield: 0.38 g (95%); pale yellow oil. IR (neat) n = 1596, 1571, 1516, 1440, 1410, 1348, 1315, 1279, 797, 773, 719 cm^{-1}; ^1H NMR ($CDCl_3$) δ : 3.86 (s, 3H, CH_3), 6.42 (d, *J* = 3.6 Hz, 1H, 3-H), 7.02 (dd, *J* = 4.8, 7.8 Hz, 1H, 5-H), 7.13 (d, J=3.6 Hz, 1H, 2-H), 7.88 (dd, *J* = 1.6, 7.8 Hz, 1H, 4-H), 8.33 (dd, *J* = 1.6, 4.8 Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$) δ : 31.1, 99.2, 115.3, 120.4, 128.6, 128.9, 142.5, 147.5; MS m/z (%) = 132 (M^+, 93), 131 (100), 103 (63), 65 (57). Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.25; H, 6.22; N, 20.97.

1-Ethyl-7-azaindole (2b). Yield 92%, pale yellow oil; IR (neat) n = 1594, 1569, 1508, 1428, 1403, 1358, 1347, 1319, 1305, 1268, 1206, 797 cm^{-1}; ^1H NMR ($CDCl_3$) δ : 1.45 (t, *J* = 7.2 Hz, 3H, CH_3), 4.32 (q, *J* = 7.2 Hz, 2H, CH_2), 6.42 (d, *J* = 3.6 Hz, 1H, 3-H), 7.02 (dd, *J* = 4.8, 7.8 Hz, 1H, 5-H), 7.19 (d, *J* = 3.6 Hz, 1H, 2-H), 7.87 (dd, *J* = 1.6, 7.8 Hz, 1H, 4-H), 8.32 (dd, *J* = 1.6, 4.8 Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$) δ : 15.5, 39.1, 99.2, 115.3, 120.6, 127.1, 128.6, 142.4, 1467.0; MS m/z (%) = 146 (M^+, 58), 131 (41), 118 (100), 91(10), 65(11). Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.47; H, 7.01; N, 18.89.

Benzyl-7-azaindole (2c). Yield 96%, pale yellow oil; IR (neat) n = 1592, 1568, 1511, 1494, 1454, 1435, 1421, 1349, 1314, 1211, 800, 749, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ : 5.50 (s, 2H, CH_2), 6.47 (d, *J* = 3.6 Hz, 1H, 3-H), 7.07 (dd, *J* = 4.8, 7.8 Hz, 1H, 5-H), 7.16 (d, *J* = 3.6 Hz, 1H, 2-H), 7.2 – 7.3 (m, 5H, C_6H_5), 7.92 (dd, *J* = 1.6, 7.8 Hz, 1H, 4-H), 8.34 (dd, *J* = 1.6, 4.8 Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$) δ : 47.9, 100.2, 115.8, 120.6, 127.5, 127.6, 128.0, 128.7, 129.0, 137.7, 142.7, 147.4; MS m/z (%) = 208 (M^+, 95), 207 (100), 131 (43), 103 (12), 91 (95), 66 (32). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.31; H, 5.89; N, 13.36.

1-Methyl-5-cyanoindole (2e). According to procedure I, 5-cyanoindole (**1d**) was converted to **2e**; yield: (91%); pale yellow oil. IR (neat) n = 2221 (CN), 1611, 1513, 1488, 1342, 1292, 1249cm^{-1}; ^1H NMR ($CDCl_3$) δ : 3.82 (s, 3H, CH_3), 6.55 (d, *J* = 3.0 Hz, 1H, 3-H), 7.16 (d, *J* = 3.0 Hz, 1H, 2-H), 7.34 (d, *J* = 8.4 Hz, 1H, 6-H),, 7.43 (d, *J* = 8.4 Hz, 1H, 7-H), 7.94(s, 1H, 4-H); ^{13}C NMR ($CDCl_3$) δ : 33.0, 102.2, 102.5, 110.0, 120.8, 124.4, 126.4, 128.2, 131.1, 138.2; MS m/z (%) = 156 (M^+, 100), 141 (28), 128 (30), 113 (55), 101 (32).

Ethyl-5-cyanoindole (2f). Yield 90%, pale yellow oil; IR (neat) n = 2220 (CN), 1609, 1452, 1401, 1340, 1294, 1223 cm^{-1}; ^1H NMR ($CDCl_3$) δ : 1.47 (t, *J* = 7.4 Hz, 3H, CH_3), 4.20 (q, *J* = 7.4 Hz, 2H, CH_2), 6.57 (d, *J* = 3.4 Hz, 1H, 3-H), 7.24 (d, *J* = 3.4 Hz, 1H, 2-H), 7.37 (d, *J* = 8.4 Hz, 1H, 6-H), 7.42 (d, *J* = 8.4 Hz, 1H, 7-H), 7.95 (s, 1H, 4-H); ^{13}C NMR ($CDCl_3$) δ : 15.3, 41.2, 102.2, 102.5, 110.0, 120.9, 124.2, 126.5, 128.2, 129.3, 137.1; MS m/z (%) = 170 (M^+, 90), 155

(100), 142 (25), 128 (20), 115 (35).

Benzyl-5-cyanoindole (2g). Yield 85%, colorless plates; mp 108 - 109 °C (CH_2Cl_2); IR (KBr) n = 2223 (CN), 1606, 1483, 1452, 1483, 1341, 768, 740, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ : 5.32 (s, 2H, CH_2), 6.61 (d, *J* = 3.2 Hz, 1H, 3-H), 7.05 – 7.10 (m, 2H, 6-H and 7-H), 7.24 (d, *J* = 3.2 Hz, 1H, 2-H), 7.28 – 7.38 (m, 5H, C_6H_5), 7.95 (s, 1H, 4-H); ^{13}C NMR ($CDCl_3$) δ : 50.3, 102.5, 102.7, 110.5, 120.7, 124.5, 126.5, 126.6, 128.0, 128.3, 128.9, 130.6, 137.7; MS m/z (%) = 232 (M^+, 85), 141 (25), 114 (27), 91 (100).

General procedure II. Synthesis of 1-alkylisatins by oxidation of 1-alkylindoles with NBS-DMSO

A mixture of 1-alkyl-7-azaindole (2.4 mmol), NBS (0.90 g, 5.0 mmol) and anhydrous DMSO (20 mL) was stirred at 60 °C for 6 h and then above 80 °C for 20 h under reduced pressure. The progress of the reaction was monitored by GC and GC-MS. After disappearance of **2**, the reaction mixture was poured into water (50 mL), followed by extracting with dichloromethane (10 mL × 3). The combined extracts were washed three times with distilled water and dried ($MgSO_4$). After removal of the solvent, the residue was purified chromatography on silica gel with dichloromethane as an eluent to give the pure product **3a-c** and **3e-g**.

1-Methyl-7-azaisatin (3a). Yield = 95%, yellow plates; mp 160 - 161 °C (CH_2Cl_2); IR(KBr) n = 1750 (C=O), 1607, 1594, 1458 cm^{-1}; UV(CH_2Cl_2): λ_{max} (log ε) = 275 nm (3.396), 406 (2.672); ^1H NMR ($CDCl_3$) δ : 3.36 (s, 3H, CH_3), 7.10 (dd, 1H, *J* = 7.2, 7.5 Hz, 5-H), 7.84 (d, 1H, *J* = 7.5 Hz, 4-H), 8.47 (d, 1H, *J* = 7.2 Hz, 6-H); ^{13}C NMR δ : 25.0, 112.0, 119.6, 132.8, 155.8, 158.3, 163.8, 181.9; MS m/z (%) = 162 (M^+, 58), 134 (34), 105 (40), 75 (100); HRMS Calcd for $C_8H_6N_2O_2$ 162.0428, Found 162.0429; Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.79; H, 3.86; N, 17.00.

1-Ethyl-7-azaisatin (3b). Yield = 95%, yellow plates; mp 127 - 128 °C (CH_2Cl_2); IR(KBr) n = 1742 (C=O), 1607, 1593, 1358 cm^{-1}; UV(CH_2Cl_2): λ_{max} (log ε) = 275 nm (2.991), 409 (2.230); ^1H NMR ($CDCl_3$) δ : 1.36 (t, J=7.2 Hz, 3H,), 3.93 (q, 2H, J=7.2 Hz, CH_2), 7.11 (dd, 1H, J=7.2, 7.5 Hz), 7.85 (d, 1H, J=7.5 Hz), 8.47 (d, 1H, J=7.2 Hz); ^{13}C NMR δ : 12.8, 34.1, 112.0, 119.4, 132.8, 155.6, 157.9, 163.6, 182.1; MS m/z (%) 176 (M^+, 74), 147 (10), 133 (46), 120 (100); HRMS Calcd for $C_9H_8N_2O_2$ 176.0585, Found 176.0561. Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.58; H, 4.50; N, 15.91.

1-Benzyl-7-azaisatin (3c). Yield = 92%, yellow plates; mp 187 - 188 °C (CH_2Cl_2), IR(KBr) n = 1742 (C=O), 1603, 1592, 1443 cm^{-1}; UV(CH_2Cl_2): λ_{max} (log ε) = 277 nm (3.762), 423 (2.626); ^1H NMR ($CDCl_3$) δ : 5.03 (s, 2H, CH_2), 7.08 (dd, *J* = 7.2, 7.5 Hz, 1H, 5-H), 7.26 - 7.52 (m, 5H, C_6H_5), 7.82 (d, *J* = 7.5 Hz, 1H, 4-H), 8.46 (d, *J* = 7.2 Hz, 1H, 6-H); ^{13}C NMR δ : 42.7, 112.1, 119.6, 128.1, 128.7, 128.8, 132.9, 135.4, 155.7, 158.1, 163.5, 181.8; MS m/z (%) 238 (M^+, 20), 210 (16), 181 (49), 147 (78), 119 (22), 92 (100); HRMS Calcd for $C_{14}H_{10}N_2O_2$ 238.0741, Found 238.0736. Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.30; H, 4.28; N, 11.72.

5-Cyano-1-methylisatin (3e). Yield = 26%, orange needles; mp 222 - 223 °C (CH_2Cl_2), IR(KBr) n = 2232 (CN), 1743(C=O), 1621, 1590, 1489 cm^{-1}; UV(CH_2Cl_2): λ_{max} (log ε) = 250 nm (4.637), 4 (2.672); ^1H NMR ($CDCl_3$) δ : 3.33 (s, 3H, CH_3), 7.05 (d, *J* = 8.2 Hz, 1H, 7-H), 7.88 (s, 1H, 4-H), 7.92 (d, *J* = 8.2 Hz, 1H, 6-H); ^{13}C NMR δ : 26.6, 107.6, 110.8, 117.5, 128.1, 128.6, 141.9, 153.9, 157.4, 181.1; MS m/z (%) 186 (M^+, 81), 158 (40), 129 (100), 103 (60); HRMS Calcd for $C_{10}H_6N_2O_2$ 186.0428, Found 186.0428.

5-Cyano-1-ethylisatin (3f). Yield = 57%, orange plates; mp 182 - 184 °C (CH_2Cl_2), IR(KBr) n = 2227 (CN), 1745 (C=O), 1616, 1587, 1489 cm^{-1}; UV(CH_2Cl_2): λ_{max} (log ε) = 253 nm (4.417), 428 (2.681); ^1H NMR ($CDCl_3$) δ : 1.34 (t, *J* = 7.4 Hz, 3H, CH_3), 3.85 (q, *J* = 7.4 Hz, 2H, CH_2), 7.08 (d, *J* = 8.2 Hz, 1H, 7-H), 7.87 (s, 1H, 4-H), 7.90 (d, *J* = 8.2 Hz, 1H, 6-H); ^{13}C NMR δ : 12.4, 35.4, 107.3, 110.9, 117.4, 117.6, 128.8, 141.9, 153.3, 157.1, 181.5; MS m/z (%) 200 (M^+, 82), 171 (8), 158 (26), 144 (100), 120 (83), 115 (34); HRMS Calcd for $C_{11}H_8N_2O_2$ 200.0584, Found 200.0557.

5-Cyano-1-benzylisatin (3g). Yield = 20%, orange needles; mp 193 - 195 °C (CH_2Cl_2), IR(KBr) n = 2227 (CN), 1742 (C=O), 1619, 1589, 1483 cm^{-1}; UV(CH_2Cl_2): λ_{max} (log ε) = 256 nm (4.242), 406 (2.591); ^1H NMR ($CDCl_3$) δ : 4.98 (s, 2H, CH_2), 6.92 (d, *J* = 8.4 Hz, 1H, 7-H), 7.32 - 7.38 (m, 5H, C_6H_5), 7.77 (dd, *J* = 1.8, 8.4 Hz, 1H, 6-H), 7.87 (d, *J* = 1.8 Hz, 1H, 4-H); ^{13}C NMR δ : 44.4, 107.7, 111.9, 117.3, 117.6, 127.3, 128.6, 128.8, 129.3, 133.3, 141.7, 153.2, 157.5, 181.1; MS m/z (%) = 262 (M^+, 39), 205 (9), 171 (60), 114 (5), 91 (100); HRMS Calcd for $C_{16}H1_0N_2O_2$ 262.0741, Found 262.0766.

Isatin (3h) [12]. Yield=94%, orange crystal.

2,3-Dibromo-1-methyl-7-azaindole (**A**): Reaction of 1-methyl-7-azaindole (0.2 g, 1.5 mmol) with bromine (0.48 g, 3.0 mmol) in dichloromethane (10 mL) at rt. for 12 h gave **A** in 80% yield, mp 90 – 92 °C (CH_2Cl_2), IR(KBr) n = 1566, 1497, 1482, 1403, 1318, 1296, 947, 791, 766, 552 cm^{-1}; ^1H NMR ($CDCl_3$) δ : 3.36 (s, 3H, CH_3), 7.11 (dd, *J* = 5.2, 7.8 Hz, 1H, 5-H), 7.81 (dd, *J* = 1.6, 7.8 Hz, 1H, 4-H), 8.26 (dd, *J* = 1.6, 5.2 Hz, 1H, 6-H); ^{13}C NMR δ : 26.3, 116.5, 119.7, 126.0, 128.1, 133.2, 150.1, 152.5; MS m/z (%) = 292 (M^++ 2, 70), 290 (M^+, 100), 288 (M^+- 2, 68), 211 (38), 209 (40), 130(50).

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