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, 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. 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. 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°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. In this paper, we describe this improved method for the preparation of the isatin derivatives 3 from indoles 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 $80^\circ$C under ambient pressure, rapid decomposition of DMSO by the generated hydrogen bromide predominantly proceeded. \cite{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 $80^\circ$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 $60^\circ$C for 6 h under ambient pressure and then at above $80^\circ$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.

In a similar manner, 5-cyanoindole $1d$ gave the corresponding 1-alkyled 5-cyanoisatins $3e$, $3f$, $3g$, and $3h$. 

Scheme 1

Scheme 2
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.

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. 1H and 13C NMR spectra were recorded on a Varian Gemini-200 from a solution CDCl₃ of the product. 1H 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. Commercial 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 (MgSO₄) 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) ν = 1596, 1571, 1516, 1440, 1410, 1348, 1315, 1279, 797, 773, 719 cm⁻¹; ¹H NMR (CDCl₃) δ : 3.86 (s, 3H, CH₃), 6.42 (d, J = 3.6 Hz, 1H, 1-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); ¹³C NMR (CDCl₃) 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 C₈H₈N₂: 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) ν = 1594, 1569, 1508, 1428, 1403, 1358, 1347, 1319, 1305, 1268, 1206, 797 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.45 (t, J = 7.2 Hz, 3H, CH₃), 4.32 (q, J = 7.2 Hz, 2H, CH₂), 6.42 (d, J = 3.6 Hz, 1H, 1-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); ¹³C NMR (CDCl₃) 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 C₉H₁₀N₂: 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) ν = 1592, 1568, 1511, 1494, 1454, 1435, 1421, 1349, 1314, 1211, 800, 749, 733 cm⁻¹; ¹H NMR (CDCl₃) δ : 5.50 (s, 2H, CH₂), 6.47 (d, J = 3.6 Hz, 1H, 1-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, C₆H₅), 7.92 (dd, J = 1.6, 7.8 Hz, 1H, 4-H), 8.34 (dd, J = 1.6, 4.8 Hz, 1H, 6-H); ¹³C NMR (CDCl₃) 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 C₁₄H₁₂N₂: 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) ν = 2221 (CN), 1611, 1513, 1488, 1342, 1292, 1249 cm⁻¹; ¹H NMR (CDCl₃) δ : 3.82 (s, 3H, CH₃), 6.55 (d, J = 3.0 Hz, 1H, 1-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); ¹³C NMR (CDCl₃) 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) ν = 2220 (CN), 1609, 1452, 1401, 1340, 1294, 1223 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.47 (t, J = 7.4 Hz, 3H, CH₃), 4.20 (q, J = 7.4 Hz, 2H, CH₂), 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); ¹³C NMR (CDCl₃) δ : 15.3, 41.2, 102.2, 102.5, 110.0, 120.9, 124.2, 126.5, 128.2, 139.3, 137.1; MS m/z (%) = 170 (M⁺, 90), 155...
Benzyl-5-cyanoindole (2g). Yield 85%, colorless plates; mp 108 - 109 °C (CH2Cl2); IR (KBr) n = 2223 (CN), 1606, 1483, 1452, 1341, 768, 740, 725 cm⁻¹; ¹H NMR (CDCl3) δ : 5.32 (s, 2H, CH2), 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, C6H5), 7.95 (s, 1H, 4-H); ¹³C NMR (CDCl3) 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 (MgSO₄). 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 (CH2Cl2); IR(KBr) n = 1750 (C=O), 1607, 1594, 1458 cm⁻¹; UV(CH2Cl2): λmax (log ε) = 275 nm (3.396), 406 (2.672); ¹H NMR (CDCl3) δ : 3.36 (s, 3H, CH3), 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); ¹³C 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 C₈H₆N₂O₂ 162.0428, Found 162.0429; Anal. Calcd for C₈H₆N₂O₂: 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 (CH2Cl2); IR(KBr) n = 1742 (C=O), 1607, 1593, 1358 cm⁻¹; UV(CH2Cl2): λmax (log ε) = 275 nm (2.991), 409 (2.230); ¹H NMR (CDCl3) δ : 1.36 (t, J=7.2 Hz, 3H,), 3.93 (q, 2H, J=7.2 Hz, CH2), 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); ¹³C 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 C₉H₈N₂O₂ 176.0585, Found 176.0561. Anal. Calcd for C₉H₈N₂O₂: 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 (CH2Cl2), IR(KBr) n = 1742 (C=O), 1603, 1592, 1443 cm⁻¹; UV(CH2Cl2): λmax (log ε) = 277 nm (3.762), 423 (2.626); ¹H NMR (CDCl3) δ : 5.03 (s, 2H, CH2), 7.08 (dd, J = 7.2, 7.5 Hz, 1H, 5-H), 7.26 - 7.52 (m, 5H, C₆H₅), 7.82 (d, J = 7.5 Hz, 1H, 4-H), 8.46 (d, J = 7.2 Hz, 1H, 6-H); ¹³C 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 C₁₄H₁₀N₂O₂ 238.0741, Found 238.0736. Anal. Calcd for C₁₄H₁₀N₂O₂: 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 (CH2Cl2), IR(KBr) n = 2232 (CN), 1743(C=O), 1621, 1590, 1489 cm\(^{-1}\); UV(CH2Cl2): \(\lambda_{\text{max}}\) (log \(\varepsilon\) ) = 250 nm (4.637), 4 (2.672); \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 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 \(\delta\): 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\(_8\)N\(_2\)O\(_2\) 186.0428, Found 186.0428.

5-Cyano-1-ethylisatin (3f). Yield = 57%, orange plates; mp 182 - 184 °C (CH2Cl2), IR(KBr) \(n = 2227\) (CN), 1745 (C=O), 1616, 1587, 1489 cm\(^{-1}\); UV(CH2Cl2): \(\lambda_{\text{max}}\) (log \(\varepsilon\) ) = 253 nm (4.417), 428 (2.681); \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 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 \(\delta\): 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\(_8\)N\(_2\)O\(_2\) 200.0584, Found 200.0557.

5-Cyano-1-benzylisatin (3g). Yield = 20%, orange needles; mp 193 - 195 °C (CH2Cl2), IR(KBr) \(n = 2227\) (CN), 1745 (C=O), 1621, 1589, 1489 cm\(^{-1}\); UV(CH2Cl2): \(\lambda_{\text{max}}\) (log \(\varepsilon\) ) = 256 nm (4.242), 406 (2.591); \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 4.98 (s, 2H, CH\(_2\)), 6.92 (d, \(J = 8.4\) Hz, 1H, 7-H), 7.32 - 7.38 (m, 5H, C\(_6\)H\(_5\)), 7.77 (dd, \(J = 1.8, 8.4\) Hz, 1H, 6-H), 7.87 (dd, \(J = 1.8\) Hz, 1H, 4-H); \(^13\)C NMR \(\delta\): 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\(_{16}\)H\(_{10}\)N\(_2\)O\(_2\) 262.0741, Found 262.0766.

Isatin (3h). 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 (CH2Cl2), IR(KBr) n = 1566, 1497, 1482, 1318, 1296, 947, 791, 766, 552 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 3.36 (s, 3H, CH\(_3\)), 7.11 (dd, \(J = 5.2, 7.8\) Hz, 1H, 5-H), 7.32 (dd, \(J = 5.2, 7.8\) Hz, 1H, 6-H); \(^13\)C NMR \(\delta\): 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).

References