A FACILE SYNTHESIS OF 1-ALKYL-7-AZAISATINS

Jiro Tatsugi,* Tong Zhiwei, Tomohiro Amano, and Yasuji Izawa

Department of Applied Chemistry, Aichi Institute of Technology, Yachigusa, Yakusa-cho, Toyota 470-0392, Japan

Abstract - 1-Alkyl-7-azaizatins are synthesized from the reaction of 1-alkyl-7-azaindoles with bromine in dichloromethane and subsequent oxidation with N-bromosuccinimide - dimethyl sulfoxide reagent. 1-Alkyl-7-azaindoles are readily available in high yields from the reaction of sodium salt of 7-azaindole with the appropriate alkyl halides in dimethylacetamide.

In the course of our studies on the photochemical behavior of cyclic vicinal polycarbonyl compounds, 1 we needed to prepare 1-alkyl-7-azaizatins as structurally related compounds for study on the photochemical reactions of heterocyclic vicinal polycarbonyl compounds. 7-Azaizatin was first obtained by treatment of 7-azaizoxindole (1) with nitrous acid to give its 3-oxime, followed by hydrolysis of the oxime. 2 Another route for the preparation of 7-azaizatin from 1 in five steps was reported in 1989. 3 Recently, we reported one-pot synthesis of vicinal polycarbonyl compounds via N-bromo carbonyl derivatives from -methylene carbonyl compounds by NBS-DMSO oxidation. 4 This oxidation method with NBS-DMSO reagent prompted us to explore an improved synthesis of 1-alkyl-7-azaizatins from 1-alkyl-7-azaindoles. We have examined to apply this NBS-DMSO oxidation to the conversion of 3-bromo-1-methyl-7-azaindole (3a) into 1-methyl-7-azaizatin (4a) as shown in Scheme 1. Initially, we prepared 1-
methyl-7-azaindole (2a) from the reaction of sodium salt of 1 with methyl iodide in dimethylacetamide (DMAc). The preparation of 3a was carried out by the reaction of 2a with bromine in dichloromethane. Finally, it was found that the oxidation of 3a with NBS in DMSO to 4a 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 wish to describe this improved method for preparation of the 1-alkyl-7-azaisatins (4) from 1.

1-Alkyl-7-azaindoles (2a, b, and c) were prepared in excellent yields by the reaction of sodium salt of 1 with appropriate alkyl halides in DMAc at room temperature. Bromination of 2 with Br₂ in CH₂Cl₂ produced 1-alkyl-3-bromo-7-azaindoles (3a, b, and c) in high yields. The resulting bromo derivatives (3) were subsequently oxidized to 4 with NBS-DMSO reagent. When oxidation of 3a with NBS in anhydrous DMSO was carried out at room temperature for 12 h, a small amount of 4a was detected by GC-MS analysis. Unfortunately, when this oxidation reaction was performed at above 80 °C under ambient pressure, rapid decomposition of DMSO by the generated hydrogen bromide predominantly proceeded. 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 4a was obtained in 90% yield by treatment of 3a 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, 3-bromo-1-ethyl- and 3-bromo-1-benzyl-7-azaindoles (3b and 3c) were converted to the corresponding 1-alkylated 7-azaisatins (4b and 4c) in 87 and 88% yields, respectively.

A plausible mechanism for the formation of 4 is illustrated in Scheme 2. The initial bromination of 3 would yield 2,3-dibromo derivative (A), which would react further with DMSO to yield intermediate (B). Intermediate (B) would lead to 4 via intermediate (C). To confirm the reaction pathway to 4, the
reaction of 2,3-dibromo-1-methyl-7-azaisatin prepared by the bromination of 2a with two equivalents of bromine used in dichloromethane with DMSO was carried out under above similar oxidation conditions afforded 4a in excellent yield. The results indicate that the formation of 4 is considered to proceed via A. In addition, we describe the scope and limitations of the present oxidation of certain brominated 7-azaindoles. Although bromination of 1-acetyl- and 1-benzoyl-7-azaindoles took place readily, the oxidation of the corresponding brominated 1-acyl-7-azaindoles did not proceed, and a deacylation reaction took place under the present oxidation conditions.

In summary, a convenient synthesis of 1-alkyl-7-azaisatins from commercially available 7-azaindole in a three-step sequence (alkylation, bromination, and oxidation with NBS-DMSO reagent) is described.

EXPERIMENTAL

General: 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$^{-1}$. $^1$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 $\delta$ 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, SiO$_2$ (nacalai tesque, 230 - 400 mesh) was used. Commercial dimethyl sulfoxide was purified by drying over calcium hydride and distillation. 7-Azaindole (Aldrich), methyl iodide, ethyl iodide, benzyl bromide, and NBS were commercially available and were used without purification.

1-Methyl-7-azaindole (2a): Sodium hydride (0.1 g, 4 mmol) free of mineral oil was added to 7-azaindole (1) (0.35 g, 3 mmol) in dimethylacetamide (DMAc) (10 mL) under an inert atmosphere. After 30 min, methyl iodide (0.5 g, 3.5 mmol) was added slowly as a solution in DMAc (2 mL), and the solution was stirred at rt for 12 h to give a pale yellow solution. The reaction is quenched by careful addition of water (20 mL) and 1-methyl-7-azaindole was extracted with dichloromethane. The dichloromethane layer was washed with distilled water. After drying the dichloromethane layer and removal of the solvent, the residue was chromatographed on SiO$_2$ with dichloromethane as an eluent to give 1a (0.375 g, 95%): pale yellow oil; IR (neat) 1596, 1571, 1516, 1440, 1410, 1348, 1315, 1279, 797, 773, 719 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$: 3.86 (s, 3H), 6.42 (d, 1H, $J$= 3.6 Hz), 7.02 (dd, 1H, $J$=4.8, 7.8 Hz), 7.13 (d, $J$=3.6 Hz), 7.88 (dd, 1H, $J$=1.6, 7.8 Hz), 8.33 (dd, 1H, $J$=1.6, 4.8 Hz); $^{13}$C NMR (CDCl$_3$) $\delta$: 31.07, 99.17, 115.33,
120.42, 128.61, 128.87, 142.52, 147.54; 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) 1594, 1569, 1508, 1428, 1403, 1358, 1347, 1319, 1305, 1268, 1206, 797 cm⁻¹; ¹H NMR (CDCl₃) □: 1.45 (t, 3H, J=7.2 Hz), 4.32 (q, 2H, J=7.2 Hz), 7.02 (dd, 1H, J=4.8, 7.8 Hz), 7.19 (d, J=3.6 Hz), 7.87 (dd, 1H, J=1.6, 7.8 Hz), 8.32 (dd, 1H, J=1.6, 4.8 Hz); ¹³C NMR (CDCl₃) □: 15.51, 39.13, 99.22, 115.34, 120.55, 127.13, 128.55, 142.38, 146.97; 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.

1-Benzyl-7-azaindole (2c): Yield 96%, pale yellow oil; IR (neat) 1592, 1568, 1511, 1494, 1454, 1435, 1421, 1349, 1314, 1211, 800, 749, 733 cm⁻¹; ¹H NMR (CDCl₃) □: 5.50 (s, 2H), 6.47 (d, 1H, J= 3.6 Hz), 7.02 (dd, 1H, J=4.8, 7.8 Hz), 7.13 (d, J=3.6 Hz), 7.88 (dd, 1H, J=1.6, 7.8 Hz), 8.33 (dd, 1H, J=1.6, 4.8 Hz); ¹³C NMR (CDCl₃) □: 47.86, 100.17, 115.82, 120.62, 127.46, 127.61, 127.97, 128.70, 129.04, 137.69, 142.71, 147.37; 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.

3-Bromo-1-methyl-7-azaindole (3a): Bromine (0.48 g, 3.0 mmol) was added to 1-methyl-7-azaindole (2a) (0.35 g, 2.7 mmol) in dichloromethane (10 mL). The mixture was stirred at 0 °C for 1 h and then rt. for 12 h. The mixture was poured onto crushed ice (30 g) and 3-bromo-1-methyl-7-azaindole was extracted with dichloromethane (3 × 20 mL). The combined organic layer was washed with distilled water. After drying the organics layer and removal of the solvent, the residue was chromatographed on SiO₂ with dichloromethane as an eluent to give a pale yellow oil 3a (0.54 g, 94%); IR (neat) 1598, 1566, 1519, 1440, 1405, 1322, 1305, 1297, 947, 791, 766 cm⁻¹; ¹H NMR (CDCl₃) □: 3.86 (s, 3H), 7.35 (dd, 1H, J=5.1, 8.0 Hz), 7.92 (s, 1H), 8.10 (dd, 1H, J=1.4, 8.0 Hz), 8.46 (dd, 1H, J=1.4, 5.1 Hz); ¹³C NMR (CDCl₃) □: 32.59, 87.51, 116.63, 120.49, 130.75, 131.04, 140.76, 143.42; MS m/z (%) 212 (M⁺ + 2, 98), 210 (M⁺, 100), 131 (76), 102 (36), 65 (27). Anal. Calcd for C₈H₇N₂Br: C, 45.53; H, 3.34; N, 13.27. Found: C, 45.33; H, 3.45; N, 13.17.

3-Bromo-1-ethyl-7-azaindole (3b): Yield 91%, pale yellow oil; IR (neat) 1597, 1566, 1514, 1422, 1322, 1305, 1139, 933, 791, 766 cm⁻¹; ¹H NMR (CDCl₃) □: 1.41 (t, 3H, J=7.2 Hz), 4.28 (q, 2H, J=7.2 Hz), 7.07 (dd, 1H, J=4.8, 8.0 Hz), 7.20 (s, 1H), 7.80 (dd, 1H, J=1.6, 8.0 Hz), 8.33 (dd, 1H, J=1.6, 4.8 Hz); ¹³C NMR (CDCl₃) □: 15.45, 45.39, 87.52, 115.98, 119.73, 126.06, 127.15, 143.50, 145.90, MS m/z (%) 226 (M⁺ + 2, 90), 224 (M⁺, 93), 196 (100), 145 (20), 116 (62), 89 (59), 65 (51). Anal. Calcd for C₉H₁₀N₂Br:
1-Benzyl-3-bromo-7-azaindole (3c): Yield 95%, mp 56 - 58 °C (dichloromethane); IR (KBr) 1594, 1565, 1438, 1421, 1317, 1302, 972, 767, 739, 704 cm⁻¹; ¹H NMR (CDCl₃) 5.48 (s, 2H), 7.15 (dd, 1H, J=4.0, 8.0 Hz), 7.19 (s, 1H), 7.2 − 7.3 (m, 5H), 7.87 (dd, 1H, J=1.6, 8.0 Hz), 8.38 (dd, 1H, J=1.6, 4.0 Hz); ¹³C NMR (CDCl₃) δ: 48.17, 88.82, 116.45, 120.20, 126.93, 127.70, 127.91, 128.06, 128.79, 136.80, 143.53, 146.08; MS m/z (%): 288 (M⁺ + 2, 23), 286 (M⁺, 25), 207 (18), 115 (6), 91 (100), 66 (18).


1-Methyl-7-azaisatin (4a): A mixture of 3-bromo-1-methyl-7-azaindole (3a) (0.50 g, 2.4 mmol), NBS (0.45 g, 2.5 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 the 3-bromo derivative, the reaction mixture was poured into water (50 mL), followed by extracting with dichloromethane (10 mL × 3). The extract was washed with distilled water and dried (MgSO₄). After removal of the solvent, the residue was chromatographed on SiO₂ with dichloromethane as an eluent. The first fraction was evaporated to afford a mixture (0.034 g) of 2,3-dibromo-1-methyl-7-azaindole and 3,3-dibromo-1-methyl-7-azaoxindole in 3.2% and 2.2% yields respectively. The ratio of this mixture was estimated by using ¹H-NMR, and their structures were established on the basis of spectral data. The 2,3-Dibromo-1-methyl-7-azaindole was confirmed by the comparison with the compound which was prepared by bromination of 2a with two equivalents of bromine used in dichloromethane. 2,3-Dibromo-1-methyl-7-azaindole: yield 80%, mp 90 - 92 °C (CH₂Cl₂); IR(KBr) 1566, 1497, 1482, 1403, 1318, 1296, 947, 791, 766, 552 cm⁻¹; ¹H NMR (CDCl₃) δ: 3.36 (s, 3H), 7.11 (dd, 1H, J=5.2, 7.8 Hz), 7.81 (dd, 1H, J=1.6, 7.8 Hz), 8.26 (dd, 1H, J=1.6, 5.2 Hz); ¹³C NMR δ: 26.31, 116.50, 119.70, 125.96, 128.11, 133.20, 150.14, 152.49; MS m/z (%): 292 (M⁺ + 2, 70), 290 (M⁺, 100), 288 (M⁺ - 2, 68), 211 (38), 209 (40), 130 (50).

3,3-Dibromo-1-methyl-7-azaoxindole: IR(KBr) 1739, 1607, 1594, 1458 cm⁻¹; ¹H NMR (CDCl₃) δ: 3.92 (s, 3H), 7.10 (dd, 1H, J=7.2, 7.5 Hz), 7.84 (d, 1H, J=7.5 Hz), 8.47 (d, 1H, J=7.2 Hz); ¹³C NMR δ: 30.89, 90.80, 116.97, 120.14, 126.87, 143.76, 146.63, 169.31; MS m/z (%): 308 (M⁺ + 2, 5), 306 (M⁺, 10), 304 (M⁺ - 2, 6), 292 (5), 290 (8), 288 (6), 227 (100), 225 (98), 118 (45). The second fraction collected was evaporated and the residue was recrystallized from dichloromethane to give 0.35 g (90%) of 1-methyl-7-azaisatin (4a). Yellow plates; mp 160 - 161 °C (CH₂Cl₂); IR(KBr) 1750, 1607, 1594, 1458 cm⁻¹; ¹H NMR (CDCl₃) δ: 3.36 (s, 3H), 7.10 (dd, 1H, J=7.2, 7.5 Hz), 7.84 (d, 1H, J=7.5 Hz), 8.47 (d, 1H, J=7.2 Hz); ¹³C NMR δ: 25.03, 111.95,
119.59, 132.76, 155.84, 158.31, 163.81, 181.86; 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 (4b): Yield 87%, yellow plates; mp 127 - 128 ^°(CH_2Cl_2); IR(KBr), 1742, 1607, 1593, 1358 cm⁻¹; ^1H NMR (CDCl₃) δ: 1.36 (t, 3H, J=7.2 Hz), 3.93 (q, 2H, J=7.2 Hz), 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: 12.80, 34.12, 111.96, 119.37, 132.83, 155.64, 157.91, 163.55, 182.10; 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 (4c): Yield 88%, yellow plates; mp 187 - 188 ^°(CH_2Cl_2), IR(KBr) 1742, 1603, 1592, 1443 cm⁻¹; ^1H NMR (CDCl₃) δ: 5.03 (s, 2H), 7.08 (dd, 1H, J=7.2, 7.5 Hz), 7.26 - 7.52 (m, 5H), 7.82 (d, 1H, J=7.5 Hz), 8.46 (d, 1H, J=7.2 Hz); ^13C NMR δ: 42.69, 112.14, 119.64, 128.08, 128.71, 128.84, 132.93, 135.41, 155.72, 158.05, 163.47, 181.83; 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.

REFERENCES


