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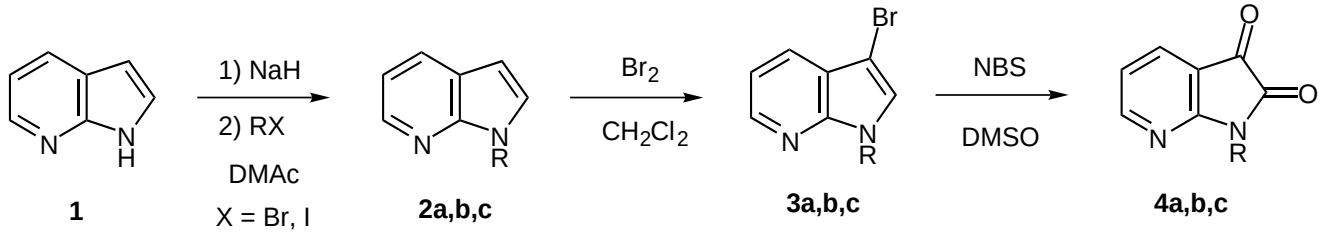
A FACILE SYNTHESIS OF 1-ALKYL-7-AZAISATINS

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-azaisatins 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-azaisatins as structurally related compounds for study on the photochemical reactions of heterocyclic vicinal polycarbonyl compounds. 7-Azaisatin was first obtained by treatment of 7-azaoxindole (**1**) with nitrous acid to give its 3-oxime, followed by hydrolysis of the oxime.[2] Another route for the preparation of 7-azaisatin from **1** in five steps was reported in 1989.[3] Recently, we reported one-pot synthesis of vicinal polycarbonyl compounds *via* α-bromo carbonyl derivatives from α-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-azaisatins 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-azaisatin (**4a**) as shown in Scheme **1**. Initially, we prepared 1-

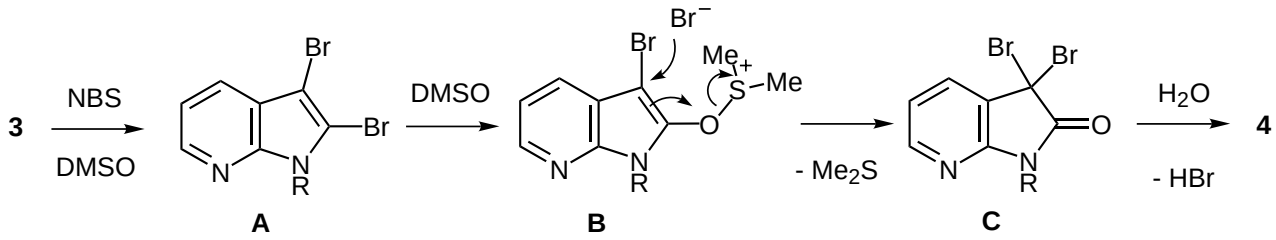


Scheme 1

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 Br_2 in CH_2Cl_2 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.[5] 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**



Scheme 2

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 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, SiO_2 (nacalai tesque, 230－400 mesh) was used. Commercal 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 ($CDCl_3$) δ : 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 ($CDCl_3$) δ : 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 $C_8H_8N_2$: 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) 1594, 1569, 1508, 1428, 1403, 1358, 1347, 1319, 1305, 1268, 1206, 797 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.45 (t, 3H, H=7.2 Hz), 4.32 (q, 2H, J=7.2 Hz), 6.42 (d, 1H, J= 3.6 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); ^{13}C NMR ($CDCl_3$) δ: 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 $C_9H_{10}N_2$: 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 ($CDCl_3$) δ: 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, 7.8Hz), 8.33 (dd, 1H, J=1.6, 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ: 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 $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.31; H, 5.89; N, 13.36.

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 ℃ 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 SiO_2 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 ($CDCl_3$) δ: 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); ^{13}C NMR ($CDCl_3$) δ: 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 $C_8H_7N_2Br$: 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 ($CDCl_3$) δ: 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); ^{13}C NMR ($CDCl_3$) δ: 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 $C_9H_9N_2Br$:

C, 48.03; H, 4.03; N, 12.45. Found: C, 47.78; H, 4.10; N, 12.29.

1-Benzyl-3-bromo-7-azaindole (3c): Yield 95%, mp 56 - 58 ℃ (dichloromethane); IR (KBr) 1594, 1565, 1513, 1438, 1421, 1317, 1302, 940, 792, 767, 739, 704 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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). Anal. Calcd for $C_{14}H_{11}N_2Br$: C, 58.56; H, 3.86; N, 9.76. Found: C, 58.24; H, 3.86; N, 9.59.

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 ℃ for 6 h and then above 80 ℃ 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 ($MgSO_4$). After removal of the solvent, the residue was chromatographed on SiO_2 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. 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 ℃ (CH_2Cl_2); IR(KBr) 1566, 1497, 1482, 1403, 1318, 1296, 947, 791, 766, 552 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR δ: 26.31, 116.50, 119.70, 125.96, 128.11, 133.20, 150.13, 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, 1464, 1104, 910, 642, 538, 500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 3H), 7.15 (dd, 1H, J=4.8, 7.4 Hz), 7.84 (dd, 1H, J=1.6, 7.4 Hz), 8.33 (dd, 1H, J=1.6, 4.8 Hz); ^{13}C 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℃ (CH_2Cl_2); IR(KBr) 1750, 1607, 1594, 1458 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C 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 ($CDCl_3$) 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); ^{13}C 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 ($CDCl_3$) 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); ^{13}C 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

1 J. Tatsugi, K. Ikuma, and Y. Izawa, *Tetrahedron Lett.*, 1995, **36**, 8611; J. Tatsugi, K. Ikuma, and Y. Izawa, *Heterocycles*, 1996, **43**, 7; J. Tatsugi, T. Hara, and Y. Izawa, *Chem. Lett*, 1997, 177.

2. H. Kägi, *Helv. Chim. Acta*, 1941, **24**,141E.

3. J. Parrick, A. Yahya , A. S. Ijaz, and J. Yizun, *J. Chem. Soc., Perkin Trans.* 1, **1989**, 2009.

4. J. Tatsugi and Y. Izawa, *Synth. Commun.*, 1998, **28**, 859.

5. V. J. Traynelis and W. C. Hergenvother, *J. Org. Chem.*,1964, **29**, 221; V. J. Traynelis and W. C. Hergenvother, *J. Am. Chem. Soc.*, 1964, **86**, 298.