Synthesis of 6,7-Dichloro-5,8-phthalazinedione and Its Derivatives

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Received July 24, 2002

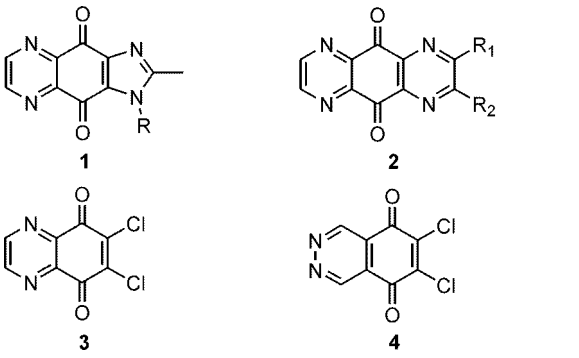
An efficient procedure for the synthesis of 6,7-dichloro-5,8-phthalazinedione (**4**) was developed in 49% overall yield *via* chloroxidation of 5,8-diaminophthalazine (**8**). And a series of its derivatives, 7-pyridinium-5,8-phthalazinedione-6-oxide (**9**), 6-chloro-7-phenylamino-5,8-phthalazinedione (**10**), 6,6-dimethoxy-6*H*-2,3,6b,11-tetraazabenzo[*a*]fluoren-5-one (**11a**), and 6,6-diethoxy-6*H*-2,3,6b,11-tetraazabenzo[*a*]fluoren-5-one (**11b**) have been synthesized.

Key Words : Phthalazine, Efficient synthetic route, Chloroxidation, 6,7-Dichloro-5,8-phthalazinedione

Introduction

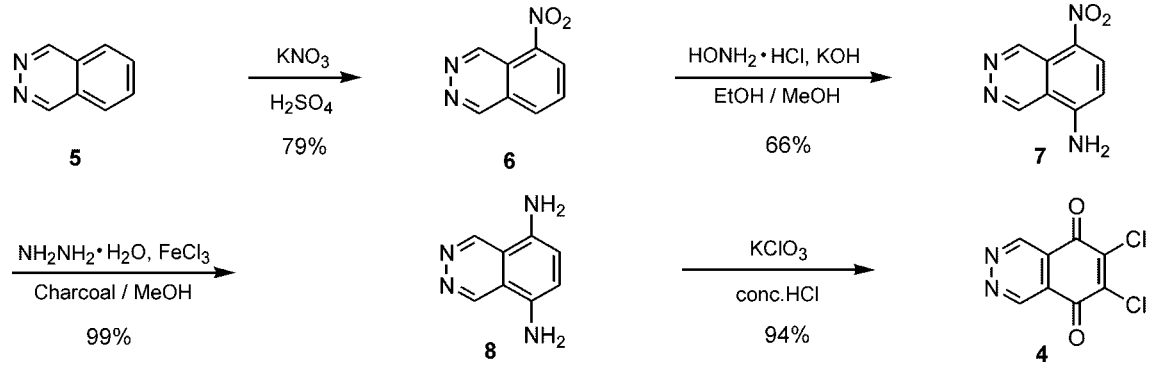
The quinone compounds show various biological activities[1] and some of the heterocyclic quinones are especially known to have an anticancer activity.[2] In a previous paper,[3] we described the synthesis and cytotoxicity of 2-methyl-4,9-dihydro-1-substituted-1*H*-imidazo[4,5-*g*]quinoxaline-4,9-diones (**1**) and 2,3-disubstituted-5,10-pyrazino[2,3-*g*]quinoxalinediones (**2**), respectively, which showed excellent biological activity against human gastric adenocarcinoma cells (MKN 45). The compounds **1** and **2** were obtained from 6,7-dichloro-5,8-quinoxalinedione (**3**) by an improved synthetic method.[3]

During the course of our program directed towards the development of novel DNA intercalators based on nitrogen-containing heterocyclic quinones, we envisaged that 6,7-dichloro-5,8-phthalazinedione could be an useful intermediate for the preparation of phthalazinedione derivatives which would be a novel DNA intercalator. Although the method has been described for the preparation of compound **4** in the literature,[4] its overall yield was very low (total yield: 10%). We describe here an efficient procedure for the syntheses of 6,7-dichloro-5,8-phthalazinedione (**4**) and its derivatives **9**, **10**, **11a** and **11b** from **4**.



Results and Discussion

The synthesis of 6,7-dichloro-5,8-phthalazinedione (**4**) is depicted in Scheme 1. Nitrophthalazine (**6**) was obtained by treatment of phthalazine (**5**) with KNO_3 in H_2SO_4.[4] Introduction of the amino group was realized by exposure to $HONH_2$ in a mixture of EtOH and MeOH in the presence of KOH at



Scheme 1

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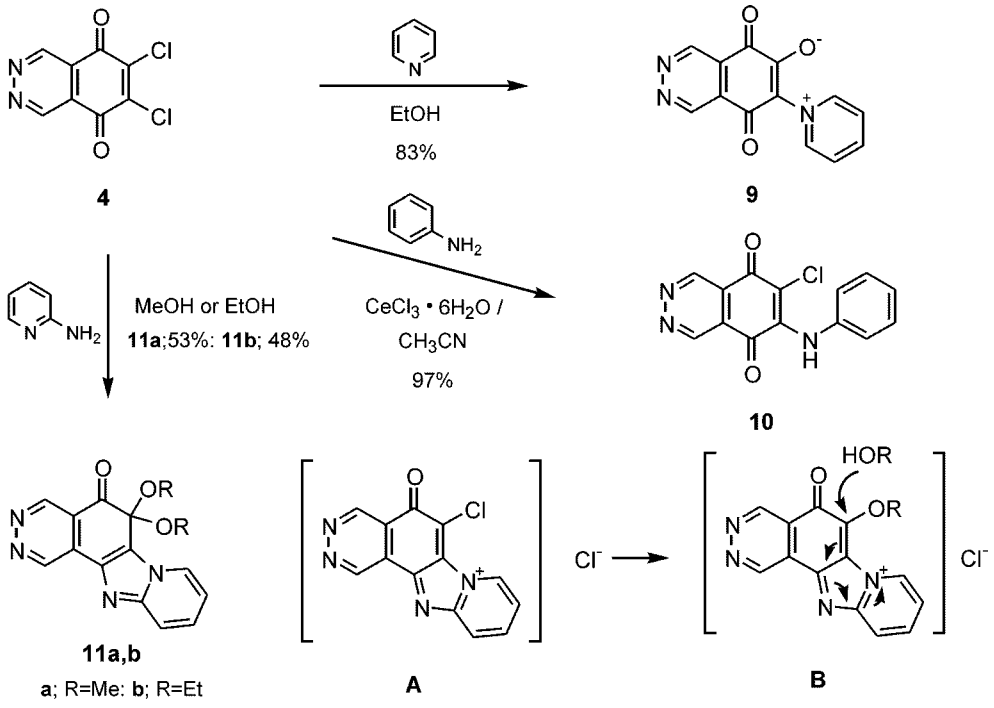

Scheme 2

50-55 °C to give 4-nitro-7-aminophthalazine (**7**) in 66% yield.[5] In the presence of $FeCl_3$ catalyst, reduction of **7** with hydrazine hydrate gave diaminophthalazine **8** in quantitative yield. Subsequently chloroxidation with $NaClO_3$ in concentrated hydrochloric acid led to 6,7-dichloro-5,8-phthalazinedione (**4**) in 94% yield.[5,6] Under these conditions, the key intermediate **4** could be prepared in improved yield compared to the previous process (total yield: 49%).

Having the key intermediate **4** in hand, we carried out the reactions of **4** with the appropriate nucleophiles in alcoholic solvents or CH_3CN (Scheme 2). The 6,7-dichloro-5,8-phthalazinedione **4** was treated with pyridine in EtOH at 60 °C to furnish zwitterionic compound **9** in 83% yield.[6] Treatment of **4** with aniline in CH_3CN in the presence of $CeCl_3 \cdot 6H_2O$ gave compound **10**.[6] Interestingly, when **4** was treated with 2-aminopyridine in alcoholic solvents (MeOH, EtOH) at 60 °C, we obtained the tetracyclic compounds **11a** and **11b**.[6,7] The structure of tetracyclic compound **11b** was unambiguously determined by X-ray crystallographic analysis (Figure 1).

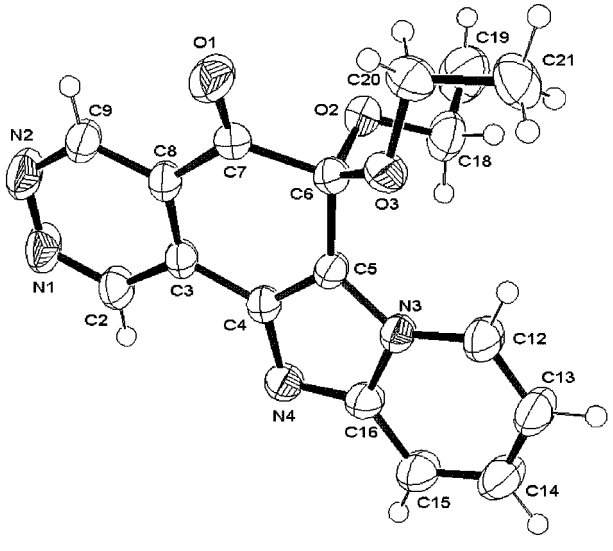

Figure 1. The ORTEP drawing of the molecular structure of **11b**.

The mechanism might be postulated as follows: the chlorine atom in the initial cyclized product **A** is replaced by an alkoxy group to give the intermediate **B**. And then attack of one more alkoxy group is followed to provide the products **11a** and **11b**.

In conclusion, we developed an efficient procedure for the synthesis of 6,7-dichloro-5,8-phthalazinedione (**4**), and prepared four of its derivatives **9**, **10**, **11a** and **11b** by the treatment of **4** with pyridine, aniline and 2-aminopyridine in alcoholic solvents or CH_3CN, respectively. The illustrated method for the preparation of **4** and its reaction with nucleophiles may serve as a important tool for the synthesis of phthalazine derivatives.

Experimental Section

Melting points were determined on Thomas-Hoover capillary apparatus and were uncorrected. IR spectra were measured with a Perkin-Elmer 1710 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300. Mass spectra were obtained on Jeol SX-102. Elemental analyses were performed with FISONS instruments EA 1108 elemental analyzer. The X-Ray diffraction was measured on an Enraf Nonius CAD4 diffractometer.

5-Nitrophthalazine (6). Potassium nitrate (73.2 g, 0.72 mol) was added in small portions to a solution of phthalazine (20.0 g, 0.15 mol) in conc. H_2SO_4 (150 mL) at 0 °C. After the addition was completed, the mixture was heated at 55-60 °C for 2 days, and then diluted with water at 0 °C. The mixture was neutralized with sodium hydroxide solution. The precipitate was filtered, and washed with water. The filtrate was extracted with EtOAc, and the extract was washed with brine, dried over $MgSO_4$ and concentrated to dryness. The residue was washed with cold MeOH and combined with the precipitate obtained above. The small amount of water in the product was removed by evaporation with toluene to afford **6** (21.3 g, 79%) as a pale yellow solid: mp 186-189 °C (from EtOH) (lit.[4], 188-189 °C).

5-Nitro-8-amino-phthalazine (7). A solution of $HONH_2$·HCl (62.0 g, 0.89 mol) in MeOH (1 L) was added to a solution of **6** (26.0 g, 0.15 mol) in EtOH (1.5 L) slowly with stirring over a period of 3 h at 50-55 °C. The reaction mixture was quenched by addition of ice water. The precipitate was filtered, and washed with water. The solvents of filtrate were evaporated off and the residue was taken up in EtOAc and water, which was extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and concentrated to dryness. The residue was combined with the precipitate obtained above, and which was washed with cold MeOH to give **7** (18.7 g, 66%) as a pale yellow solid: mp >300 °C (from EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.29 (s, 1H), 9.76 (s, 1H), 8.50 (d, J = 9.2 Hz, 1H), 8.23 (s, 2H), 6.97 (d, J = 9.2 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.0, 146.8, 146.4, 134.7, 129.4, 122.0, 113.5, 112.4. IR (KBr): 3346, 3136, 1682, 1610, 1574, 1504, 1342 cm^{-1}. HR-FABMS Calcd for $C_8H_6N_4O_2$ (M^++H): 191.0569. Found: 191.0573. Anal. Calcd for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.46. Found: C, 50.74; H, 3.25; N, 28.61.

5,8-Diaminophthalazine (8). To a solution of **7** (14.2 g, 74.7 mmol) in MeOH (700 ml) was added $FeCl_3$ (70.0 mg, 0.43 mmol) and charcoal (4.50 g), and the mixture was refluxed for 5 h. The product was filtered through celite. Evaporation of the solvent gave **8** (11.9 g, 99%) as a pale yellow solid: mp 249-250 °C (from EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.54 (s, 2H), 6.93 (s, 2H), 5.44 (s, 4H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 147.5, 135.8, 118.3, 115.3. IR (KBr): 3312, 3170, 1556, 1472, 1372 cm^{-1}. FABMS *m/z* 161 (M^++H). Anal. Calcd for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 59.86; H, 5.04; N, 34.31.

6,7-Dichlorophthalazine-5,8-dione (4). To a solution of **8** (7.09 g, 44.3 mmol) in conc. HCl (90.0 mL) was added $NaClO_3$ (6.08 g, 49.6 mmol) in many portions at 0 °C. The reaction mixture was stirred for 1 h at rt, quenched by addition of water and the precipitate was filtered. The filtrate was neutralized with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extract was washed with water and brine, dried over $MgSO_4$ and concentrated to dryness. The residue was combined with the precipitate obtained above to give **4** (9.56 g, 94%) as a pale yellow solid: mp 223-225 °C (from EtOH) (lit.[4], 223-225 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.93 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.5, 147.1, 143.0, 125.5; IR (KBr): 1694, 1588, 1552 cm^{-1}. Anal. Calcd for $C_8H_2Cl_2N_2O_2$: C, 41.96; H, 0.88; N, 12.23. Found: C, 42.14; H, 1.00; N, 11.88.

7-Pyridinium-5,8-phthalazinedione-6-oxide (9). A suspension of **4** (200 mg, 0.88 mmol) in EtOH (40.0 mL) was heated until the starting material was dissolved. To this solution was added pyridine (0.30 mL, 3.96 mmol), and the reaction mixture was stirred for 3 h at 60 °C. After reaction was completed the mixture was cooled. The precipitate was collected by filtration to yield **9** (185 mg, 83%) as a deep purple solid: mp >300 °C (from EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.79 (d, J = 1.1 Hz, 1H), 9.57 (d, J = 1.1 Hz, 1H), 8.84 (d, J = 6.8 Hz, 2H), 8.64 (t, J = 6.8 Hz, 1H), 8.21 (t, J = 6.8 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 184.4, 170.3, 165.4, 148.6, 148.3, 146.2, 145.8, 128.3, 127.7, 126.8, 125.4; IR (KBr): 1704, 1590, 1552, 1470 cm^{-1}. HR-FABMS Calcd for $C_{13}H_7N_3O_3$ (M^++H): 254.0566. Found: 254.0566. Anal. Calcd for $C_{13}H_7N_3O_3$: C, 61.66; H, 2.79; N, 16.59. Found: C, 61.52; H, 2.70; N, 16.36.

6-Chloro-7-phenylamino-5,8-phthalazinedione (10). To a solution of **4** in CH_3CN was added cerium (III) chloride hexahydrate, and the reaction mixture was stirred for 10 min at rt. Aniline was added to the reaction mixture at same temperature. The reaction mixture was stirred for overnight at rt, the solvent was evaporated off. The residue was diluted with water and extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$ concentrated to dryness. The collected crude product was washed with hexane to give **10** as a purple solid: mp 226-227 °C (from EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.93 (d, J = 1.1 Hz, 1H), 9.78 (d, J = 1.1 Hz, 1H), 7.73 (bs, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.3, 175.6, 147.1, 145.3, 141.4, 136.4, 128.7, 126.9, 124.9, 124.5, 122.9, 115.0; IR (KBr): 3294, 1682, 1644, 1590, 1556, 1504, 1450 cm^{-1}. FABMS *m/z* 286 (M^++H), 288 (M^++2). HR-FABMS Calcd for $C_{14}H_8O_2ClN_3O_2$ (M^++H): 286.0383. Found: 286.0407. Anal. Calcd for $C_{14}H_8O_2ClN_3O_2$: C, 58.86; H, 2.82; N, 14.71. Found: C, 58.35; H, 2.82; N, 14.54.

6,6-Dimethoxy-6*H*-2,3,6b,11-tetraazabenzo[*a*]fluoren-5-one (11a). A suspension of **4** (150 mg, 0.66 mmol) in MeOH (20 mL) was heated until the starting material was dissolved. To this solution was added 2-aminopyridine (154 mg, 1.64 mmol). After being stirred for 6 h at 60 °C, the reaction mixture was cooled. The solvent was removed by evaporation, and the residue was extracted with water and CH_2Cl_2. The organic extract was washed with brine, dried over $MgSO_4$, concentrated to dryness. The residue was purified by column chromatography (EtOAc) to give **11a** (103 mg, 53%) as a pale yellow solid; mp 200-205 °C (decomp) (from MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.03 (d, J = 1.2 Hz, 1H), 9.50 (d, J = 1.2 Hz, 1H), 8.52 (dt, J = 6.8, 1.1 Hz, 1H), 7.76 (dt, J = 9.1, 1.1 Hz, 1H), 7.41 (ddd, J = 9.1, 6.8, 1.1 Hz, 1H), 7.00 (td, J = 6.8, 1.1 Hz, 1H), 3.42 (s, 6H). ^{13}C NMR (75MHz, $CDCl_3$): δ 193.1, 148.6, 147.3, 146.8, 137.1, 129.6, 128.0, 126.8, 122.7, 121.6, 119.1, 115.0, 95.7, 52.6. IR (KBr): 1716, 1594, 1572 cm^{-1}.

FABMS *m/z* 297 (M^++H); Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.66; H, 4.02; N, 18.70.

6,6-Diethoxy-6*H*-2,3,6b,11-tetraazabenzo[*a*]fluoren-5-one (11b). According to the procedure described for the preparation of the **11a** from **4**, the title compound **11b** (137 mg, 48%) was obtained from the reaction of **4** (200 mg, 0.87 mmol) in ethanol as a pale yellow solid: mp 174-175 °C (from EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.04 (d, J = 1.2 Hz, 1H), 9.52 (d, J = 1.2 Hz, 1H), 8.58 (dt, J = 6.8, 1.1 Hz, 1H), 7.77 (dt, J = 9.2, 1.1 Hz, 1H), 7.42 (ddd, J = 9.2, 6.8, 1.1 Hz, 1H), 7.01 (td, J = 6.8, 1.1 Hz, 1H), 3.71 (qd, J = 7.0, 2.1 Hz, 2H), 3.58 (qd, J = 7.0, 2.1 Hz, 2H), 1.22 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.8, 148.5, 147.4, 146.9, 136.6, 129.7, 127.9, 126.6, 122.7, 122.6, 119.1, 114.8, 95.2, 60.8, 15.7. IR (KBr): 1718, 1588, 1568 cm^{-1}. HR-FABMS Calcd for $C_{17}H_{16}N_4O_3$ (M^++H): 325.1301. Found: 325.1302. Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.62; H, 4.82; N, 16.93.

Crystal struture determination of compound 11b. Single crystals of **11b** were obtained from EtOH. Crystal data: $C_{17}H_{16}N_4O_3$, M_W = 324.34, Wavelength = 0.71073 Å, triclinic, $P\bar{1}$ (No. 2), Z = 2, a = 8.389 (2) Å, b = 9.232 (2) Å, c = 11.699 (2) Å, α = 68.10 (2) deg, β = 72.69 (2) deg, γ = 67.61 (2) deg, V = 764.4 (3) Å ^{3}, d_{calc} = 1.409 g/cm^3, $R1$ = 0.0501, $wR2$ = 0.1369 for 2007 unique reflections ($I > 2\sigma(I)$) and 217 variables.

Acknowledgment. We thank the Il Dong Pharm. Co. for its donation of Chair Fund to KIST, and wish also to thank Dr. Kwan Mook Kim for the X-ray structure determination.

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