Pyrimidines. L1.1) Synthesis of Pyrimido[1,6-a]benzimidazole-1,3(2H,5H)-dione Derivatives by the Reaction of 6-Chloro-2H-1,3-oxazine-2,4(3H)-diones with o-Phenylenediamines

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The reaction of 6-chloro-1,3-oxazine-2,4-diones (1) with o-phenylenediamines (2) in the presence of acetic acid afforded pyrimido[1,6-a]benzimidazole-1,3(2H,5H)-dione derivatives (3) via a 1,3-oxazine-to-pyrimidine ring transformation.

Keywords—ring transformation; 6-chloro-2H-1,3-oxazine-2,4(3H)-dione; o-phenylenediamine; pyrimido[1,6-a]benzimidazole-1,3(2H,5H)-dione; paramagnetic anisotropy

In the course of our investigations on the reaction of 6-chloro-1,3-oxazine-2,4-dione derivatives with amines, it has been found that treatment of 6-chloro-3-methyl-2H-1,3-oxazine-2,4(3H)-dione (1a) with aromatic amines such as anilines 2,3 affords the corresponding 6-anilinooxazine derivatives, whereas the reaction with ammonia and aliphatic amines causes a ring transformation to the corresponding barbituric acids 2,4.

As a continuation of the above studies, we investigated the reaction of 6-chloro-1,3-oxazine-2,4-dione derivatives (1) with o-phenylenediamines (2) and found a novel synthesis of pyrimido[1,6-a]benzimidazole-1,3(2H,5H)-diones (3) via a 1,3-oxazine-to-pyrimidine ring transformation.

Refluxing of 1a with 2 molar equivalents of 2a in tetrahydrofuran (THF) in the presence of acetic acid afforded 2-methylpyrimido[1,6-a]benzimidazole-1,3(2H,5H)-dione (3a) in 29% yield. The characterization of 3a was based on the following evidence. The analytical and mass spectral (MS) data established the molecular formula as C_{11}H_{11}N_{3}O_{2}. The proton nuclear magnetic resonance (H-NMR) spectrum of 3a revealed a deuterium oxide-exchangeable broad signal (NH) at δ 12.04, a 1H distorted doublet signal (C_9-H) at δ 8.07, a 3H multiplet signal (C_6-, C_7-, and C_8-H) at δ 7.40—7.04, a 1H singlet signal (C_4-H) at δ 5.19,
and a 3H singlet signal (NCH₃) at δ 3.23. The appearance of one of the aromatic proton signals at lower field (δ 8.07) can be explained as being due to the paramagnetic anisotropy of the carbonyl group at the 1-position.

To the best of our knowledge, synthesis of pyrimido[1,6-a]benzimidazole-1,3-diones has previously been reported only by Davies et al. Analogous treatment of 1a with other o-phenylenediamines (2b and 2c) gave the corresponding pyrimido[1,6-a]benzimidazoles (3b and 3c), respectively. The position of the chloro group of 3c was determined on the basis of the splitting and coupling constants in the ¹H-NMR signals due to the aromatic protons as follows. In the aromatic proton region, typical ABX-type signals were observed. A 1H ortho-and-meta-coupled double doublet signal (J=2 and 9 Hz) and a 1H meta-coupled doublet signal (J=2 Hz) appeared at δ 7.19 and 7.32, respectively. On the other hand, a 1H ortho-coupled doublet signal (J=9 Hz) was observed at lower field (δ 8.00) on account of the deshielding effect of the carbonyl group at the 1-position as described above for 3a. The ¹H-NMR results suggest the presence of the chloro group at the 7-position.

Similarly, the reaction of 6-chloro-3,5-dimethyl-2H-1,3-oxide-2,4(3H)-dione (1b) with o-phenylenediamines (2a–c) afforded the corresponding 4-methylpyrimido[1,6-a]benzimidazoles (3d–f). Thus, the present procedure is useful for the preparation of the pyrimido[1,6-a]benzimidazole-1,3(2H,5H)-dione derivatives (3).

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\text{Chart 2}
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The present reaction in the absence of acetic acid proceeded in a complicated manner, and did not give the expected product (3). On the basis of this result and the reactivity of 1 with amines as reported previously, a plausible mechanism for the formation of 3 is suggested (Chart 2). The initial step is the formation of a 6-anilinoxazine intermediate (A), Subsequent attack of another amino group of A on the 2-position of the 1,3-oxide ring, followed by fission of the O¹−C² bond results in the formation of a nine-membered ring intermediate (B), which cyclizes to 3 via a transannular reaction, followed by dehydration in the presence of acetic acid.

**Experimental**

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. MS were taken on a JEOL JMS-D300 spectrometer. Ultraviolet (UV) spectra were recorded in ethanol on a Hitachi 525 spectrometer unless otherwise noted. ¹H-NMR spectra were recorded on a JEOL JNM-FX-100 Fourier transform spectrometer with tetramethylsilane as an internal standard in DMSO-d₆. Chemical shifts are quoted in parts per million (s=singlet, d=doublet, dd=double doublet, br=broad).

2-Methylpyrimido[1,6-a]benzimidazole-1,3(2H,5H)-dione (3a)—A mixture of 1a (570 mg, 3.5 mmol), 2a (830 mg, 7.7 mmol), acetic acid (210 mg, 3.5 mmol), and THF (10 ml) was refluxed for 1 h under a nitrogen atmosphere. After evaporation of the solvent in vacuo and addition of water to the residue, the precipitate was filtered off and recrystallized from ethanol to give 220 mg (29%) of 3a, mp >300 °C. Anal. Calcd for C₁₁H₆N₄O₂: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.16; H, 4.19; N, 19.62. MS m/z: 215 (M⁺). UV λ_max nm: 212, 233 (sh), 245 (sh), 250, 285
2.7,8-Trimethylpyrimidino[1,6-a]benzimidazole-1,3(2H,5H)-dione (3b) — A mixture of 1a (570 mg, 3.5 mmol), 2b (1050 mg, 7.7 mmol), a few drops of acetic acid, and THF (10 ml) was refluxed for 1.5 h under a nitrogen atmosphere. The same post-treatment as described above for 3a yielded a crude precipitate, which was recrystallized from N,N-dimethylformamide (DMF) to give 120 mg (14%) of 3b, mp 295 °C (dec.). Anal. Caled for C18H11N2O2: C, 64.18; H, 5.39; N, 17.28. Found: C, 63.90; H, 5.45; N, 17.31. MS m/z: 243 (M+). UV λmax nm: 216, 232 (sh), 246, 253, 292 (sh), 308, 314 (sh), 319. 1H-NMR δ: 11.86 (1H, br, NH, exchanged in D2O), 7.86 (1H, s, C6-H), 7.05 (1H, s, C6-H), 5.15 (1H, s, C6-H), 3.22 (3H, s, NCH3), 2.27 (6H, s, C7- and C8-CH3).

7-Chloro-2-methylpyrimidino[1,6-a]benzimidazole-1,3(2H,5H)-dione (3c) — A mixture of 1a (570 mg, 3.5 mmol), 2c (1100 mg, 7.7 mmol), acetic acid (210 mg, 3.5 mmol), and THF (10 ml) was refluxed for 6 h under a nitrogen atmosphere. The same post-treatment as described above for 3a yielded a crude precipitate, which was recrystallized from acetic acid to give 150 mg (17%) of 3c, mp > 300 °C (dec.). Anal. Caled for C20H15ClN2O2: C, 66.42; H, 4.97; N, 16.83. Found: C, 66.42; H, 4.87; N, 16.82. MS m/z: 251 (M+ + 2), 249 (M+). UV λmax nm: 210, 223, 240, 254, 290 (sh), 310 (sh), 317 (sh), 322. 1H-NMR δ: 12.14 (1H, br, NH, exchanged in D2O), 8.00 (1H, d, J = 9 Hz, C6-H), 7.32 (1H, d, J = 2 Hz, C6-H), 7.19 (1H, dd, J = 2 and 9 Hz, C6-H), 5.23 (1H, s, C6-H), 3.23 (3H, s, NCH3).

2,4-Dimethylpyrimidino[1,6-a]benzimidazole-1,3(2H,5H)-dione (3d) — A mixture of 1b (530 mg, 3 mmol), 2a (760 mg, 7 mmol), a few drops of acetic acid, and THF (10 ml) was refluxed for 8 h under a nitrogen atmosphere. The precipitate was filtered off and recrystallized from water to give 40 mg (6%) of 3d, mp 291–294 °C (dec.). Anal. Caled for C19H13N2O2: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.64; H, 4.72; N, 18.29. MS m/z: 229 (M+). UV λmax (H2O) nm: 212, 235 (sh), 251, 292 (sh), 312 (sh), 322. 1H-NMR δ: 11.75 (1H, br, NH, exchanged in D2O), 8.05 (1H, distorted d, J = 7 Hz, C6-H), 7.38–6.96 (3H, m, C7–, C8–, and C9–), 3.25 (3H, s, NCH3), 1.91 (3H, s, C2–CH3).

2,4,7,8-Tetramethylpyrimidino[1,6-a]benzimidazole-1,3(2H,5H)-dione (3e) — A mixture of 1b (530 mg, 3 mmol), 2b (950 mg, 7 mmol), a few drops of acetic acid, and THF (10 ml) was refluxed for 6 h under a nitrogen atmosphere. The precipitate was filtered off and recrystallized from DMF to give 70 mg (9%) of 3e, mp > 300 °C. Anal. Caled for C19H15N2O2: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.07; H, 5.91; N, 16.45. MS m/z: 257 (M+). UV λmax nm: 212, 234 (sh), 256, 294 (sh), 315 (sh), 321 (sh), 327. 1H-NMR δ: 11.23 (1H, br, NH, exchanged in D2O), 7.88 (1H, s, C6–H), 7.04 (1H, s, C6–H), 3.26 (3H, s, NCH3), 2.29 (6H, s, C7– and C8–CH3), 1.92 (3H, s, C2–CH3).

7-Chloro-2,4-dimethylpyrimidino[1,6-a]benzimidazole-1,3(2H,5H)-dione (3f) — A mixture of 1b (610 mg, 3.5 mmol), 2c (1100 mg, 7.7 mmol), acetic acid (420 mg, 7 mmol), and THF (10 ml) was refluxed for 12 h under a nitrogen atmosphere. The same post-treatment as described above for 3a yielded a crude precipitate, which was recrystallized from acetic acid to give 240 mg (26%) of 3f, mp > 300 °C. Anal. Caled for C20H17ClN2O2: C, 54.66; H, 3.82; N, 15.94. Found: C, 54.40; H, 3.76; N, 15.87. MS m/z: 265 (M+ + 2), 263 (M+). UV λmax nm: 210, 220 (sh), 234 (sh), 242 (sh), 259, 294 (sh), 317 (sh), 328. 1H-NMR δ: 11.93 (1H, br, NH, exchanged in D2O), 7.96 (1H, d, J = 9 Hz, C6–H), 7.16 (1H, d, J = 2 Hz, C6–H), 7.13 (1H, dd, J = 2 and 9 Hz, C6–H), 3.23 (3H, s, NCH3), 1.89 (3H, s, C2–CH3).

References and Notes

5) Such a downfield shift is also observed in the 1H-NMR spectra of pyrimidino[1,2-a]benzimidazol-4(10H)-one derivatives; Y. Shiokawa and S. Ohki, Chem. Pharm. Bull., 19, 401 (1971).