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

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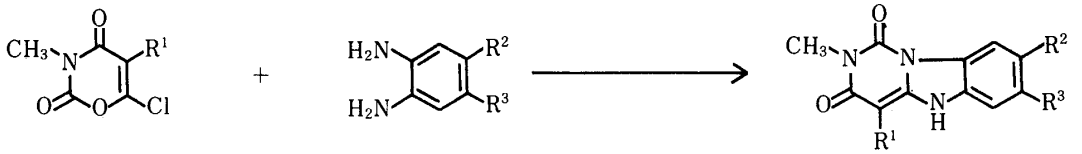
The reaction of 6-chloro-1,3-oxazine-2,4-diones (**1**) with *o*-phenylenediamines (**2**) in the presence of acetic acid afforded pyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-dione derivatives (**3**) *via* a 1,3-oxazine-to-pyrimidine ring transformation.

Keywords——ring transformation; 6-chloro-2*H*-1,3-oxazine-2,4(3*H*)-dione; *o*-phenylenediamine; pyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-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-2*H*-1,3-oxazine-2,4(3*H*)-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(2*H*,5*H*)-diones (**3**) *via* a 1,3-oxazine-to–pyrimidine ring transformation.



1a: $R^1=H$
1b: $R^1=CH_3$

2a: $R^2=R^3=H$
2b: $R^2=R^3=CH_3$
2c: $R^2=H$, $R^3=Cl$

3a: $R^1=R^2=R^3=H$
3b: $R^1=H$, $R^2=R^3=CH_3$
3c: $R^1=R^2=H$, $R^3=Cl$
3d: $R^1=CH_3$, $R^2=R^3=H$
3e: $R^1=R^2=R^3=CH_3$
3f: $R^1=CH_3$, $R^2=H$, $R^3=Cl$

Chart 1

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(2*H*,5*H*)-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 $C_{11}H_9N_3O_2$. The proton nuclear magnetic resonance (^{1}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 (NCH_3) 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[5] 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.*[6]

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 ^{1}H-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 ^{1}H-NMR results suggest the presence of the chloro group at the 7-position.

Similarly, the reaction of 6-chloro-3,5-dimethyl-2*H*-1,3-oxazine-2,4(3*H*)-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(2*H*,5*H*)-dione derivatives (**3**).

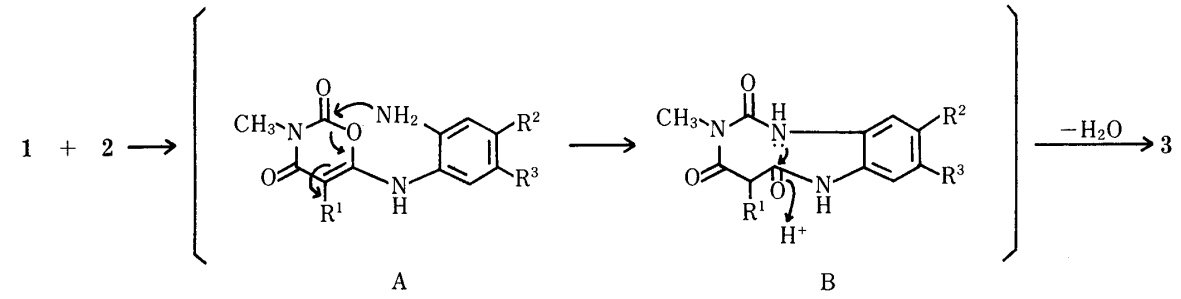


Chart 2

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,[2,4] a plausible mechanism for the formation of **3** is suggested (Chart 2). The initial step is the formation of a 6-anilinooxazine intermediate (A).[2,3] Subsequent attack of another amino group of A on the 2-position of the 1,3-oxazine ring, followed by fission of the O^1–C^2 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. ^{1}H-NMR spectra were recorded on a JEOL JNM-FX-100 Fourier transform spectrometer with tetramethylsilane as an internal standard in DMSO-d_6. 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(2*H*,5*H*)-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 $C_{11}H_9N_3O_2$: 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

(sh), 303 (sh), 309 (sh), 314. ^{1}H-NMR δ: 12.04 (1H, br, NH, exchanged in D_2O), 8.07 (1H, distorted d, J=7 Hz, C_9–H), 7.40—7.04 (3H, m, C_6–, C_7–, and C_8–H), 5.19 (1H, s, C_4–H), 3.23 (3H, s, NCH_3).

2,7,8-Trimethylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-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.* Calcd for $C_{13}H_{13}N_3O_2$: 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 λ_{max} nm: 216, 232 (sh), 246, 253, 292 (sh), 308, 314 (sh), 319. ^{1}H-NMR δ: 11.86 (1H, br, NH, exchanged in D_2O), 7.86 (1H, s, C_9–H), 7.05 (1H, s, C_6–H), 5.15 (1H, s, C_4–H), 3.22 (3H, s, NCH_3), 2.27 (6H, s, C_7– and C_8–CH_3).

7-Chloro-2-methylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-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. *Anal.* Calcd for $C_{11}H_8ClN_3O_2$: C, 52.92; H, 3.23; N, 16.83. Found: C, 52.67; H, 3.27; N, 16.58. MS *m/z*: 251 (M^++2), 249 (M^+). UV λ_{max} nm: 210, 223, 240, 254, 290 (sh), 310 (sh), 317 (sh), 322. ^{1}H-NMR δ: 12.14 (1H, br, NH, exchanged in D_2O), 8.00 (1H, d, J=9 Hz, C_9–H), 7.32 (1H, d, J=2 Hz, C_6–H), 7.19 (1H, dd, J=2 and 9 Hz, C_8–H), 5.23 (1H, s, C_4–H), 3.23 (3H, s, NCH_3).

2,4-Dimethylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-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.* Calcd for $C_{12}H_{11}N_3O_2$: 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 λ_{max} (H_2O) nm: 212, 235 (sh), 251, 292 (sh), 312 (sh), 322. ^{1}H-NMR δ: 11.75 (1H, br, NH, exchanged in D_2O), 8.05 (1H, distorted d, J=7 Hz, C_9–H), 7.38—6.96 (3H, m, C_6–, C_7–, and C_8–H), 3.25 (3H, s, NCH_3), 1.91 (3H, s, C_4–CH_3).

2,4,7,8-Tetramethylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-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.* Calcd for $C_{14}H_{15}N_3O_2$: 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 λ_{max} nm: 212, 234 (sh), 256, 294 (sh), 315 (sh), 321 (sh), 327. ^{1}H-NMR δ: 11.23 (1H, br, NH, exchanged in D_2O), 7.88 (1H, s, C_9–H), 7.04 (1H, s, C_6–H), 3.26 (3H, s, NCH_3), 2.29 (6H, s, C_7– and C_8–CH_3), 1.92 (3H, s, C_4–CH_3).

7-Chloro-2,4-dimethylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-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.* Calcd for $C_{12}H_{10}ClN_3O_2$: 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 λ_{max} nm: 210, 220 (sh), 234 (sh), 242 (sh), 259, 294 (sh), 317 (sh), 328. ^{1}H-NMR δ: 11.93 (1H, br, NH, exchanged in D_2O), 7.96 (1H, d, J=9 Hz, C_9–H), 7.16 (1H, d, J=2 Hz, C_6–H), 7.13 (1H, dd, J=2 and 9 Hz, C_8–H), 3.23 (3H, s, NCH_3), 1.89 (3H, s, C_4–CH_3).

References and Notes

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