Selective Oxidation of Methyl Substituted 1,3-Dimethyllumazine Derivatives with Nitric acid

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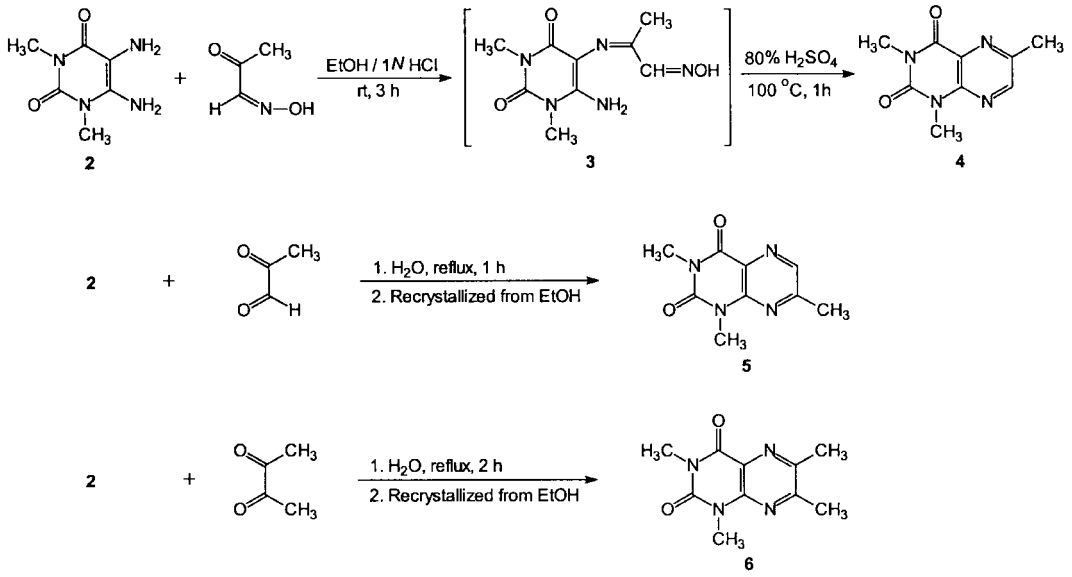
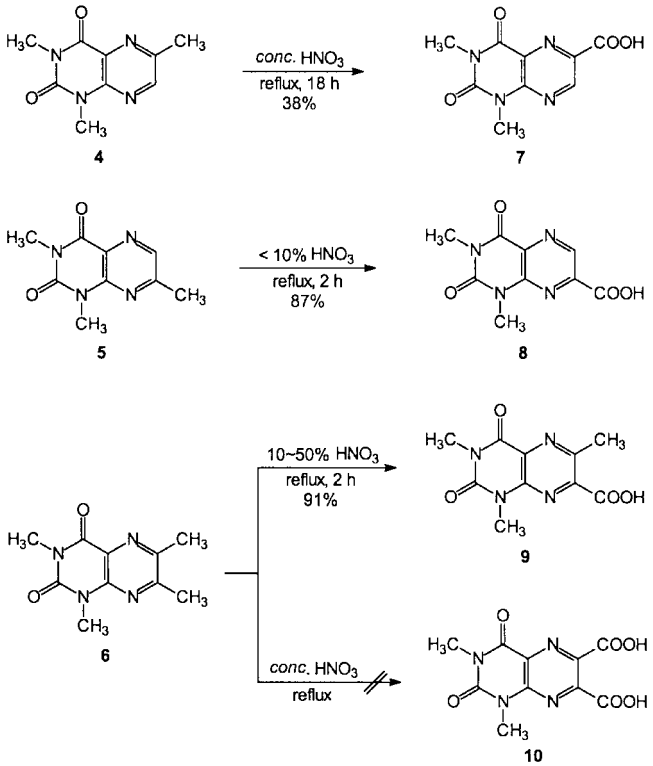
Usually the alkyl side chains of the pteridine system are oxidized to the corresponding pteridine carboxylic acid with potassium permanganate.[1] However the oxidation of 1,3-dimethyllumazine (1,3-dimethyl-2,4-dioxopteridine) derivatives with potassium permanganate yielded the corresponding carboxylic acids in low yield[2] because 1,3-dimethyllumazines are insoluble in water and the pyrimidine moeity in the pteridine ring is cleaved under alkaline medium converting them to pyrazine derivatives.[3] Recently we found that the oxidation of 6-acetyl-1,3,7-trimethyllumazine (**1**)[4] strongly depended upon the concentration of the nitric acid employed. **1** was converted to 1,3,7-trimethyllumazine-6-carboxylic acid by heating under reflux with 10% nitric acid. On the other hand, concentrated nitric acid of more than 50% was able to completely oxidize both 6-acetyl and 7-methyl groups providing 1,3-dimethyllumazine-6,7-dicarboxylic acid.[5] We, therefore, expected that the oxidation of 6- and 7-alkyl side chain of 1,3-dimethyllumazine can be controlled by using a different concentration of nitric acid.

For the application of this method, 1,3,6-trimethyllumazine (**4**),[6] 1,3,7-trimethyllumazine (**5**),[6] and 1,3,6,7-tetramethyllumazine (**6**) were prepared. After being stirred at room temperature for 3 h with pyruvic aldehyde 1-oxime,[7] 4,5-diamino-1,3-dimethyluracil hydrochloride (**2**) provided 6-amino-5-(2-oximino-1-methylethyleneamino)-1,3-dimethyluracil (**3**)[6] which was converted to 1,3,6-trimethyllumazine (**4**) by the treatment of 80% sulfuric acid (Scheme 1). The reaction of compound **2** with pyruvic aldehyde provided a mixture of 1,3,7-trimethyllumazine (**5**) as a major product and small amounts of 1,3,6-trimethyllumazine (**4**). Isomer free compound **5** was obtained from recrystallization of the mixture in ethanol. Analogous to the synthesis of compound **5**, 1,3,6,7-tetramethyllumazine (**6**) was prepared from the reaction of **2** with 2,3-butanedione.

After being heated under reflux for 18h in concentrated nitric acid with more than 50% concentration, the 6-methyl group of 1,3,6-trimethyllumazine (**4**) was oxidized to provide 1,3-dimethyllumazine-6-carboxylic acid (**7**) in 38% yield. On the other hand, nitric acid of lower than 10% concentration was able to completely oxidize 7-methyl group of 1,3,7-trimethyllumazine (**5**) giving 1,3-dimethyllumazine-7-carboxylic acid (**8**) in 87% yield. The oxidation of 1,3,6,7-tetramethyl-lumazine (**6**) with various concentration of nitric acid provided only the 1,3,6-trimethyllumazine-7-carboxylic



Scheme 1



Scheme 2

acid (**9**) in high yield, but the formation of 1,3-dimethyllumazine-6,7-dicarboxylic acid (**10**) was not observed (Scheme 2).

The oxidation mechanism of 6- or/and 7-methyl substituted derivatives was expected through the formation of nitromethyl group, so called Nef reaction.[8] We expected the oxidation was carried out by the protonation at N-5 or N-8 to activate the 6- or 7-methyl group. From the experimental results, N-8 could be protonated prior to N-5 position. Besides, 7-methyl group could be tautomerized with 4-oxo group. Therefore, 1,3,7-trimethyllumazine (**5**) was easily oxidized by nitric acid in low concentration. While, the oxidation of 1,3,6-trimethyllumazine (**4**) was perfomed in drastic condition, *i.e.*, concentrated nitric acid. In case of 1,3,6,7-tetramethyllumazine (**6**), 7-methyl group was selectively oxidized. Once 7-methyl group of **6** was converted to carboxylic acid, electron density of pyrazine ring in **9** would be reduced. Therefore, the conversion of 6-methyl group of **9** into carboxylic acid could not be proceeded.

In UV spectra, the absorption bands of 1,3-dimethyllumazine-7-carboxylic acid (**8**) were observed at 242 and 334 nm, while those of 1,3-dimethyllumazine-6-carboxylic acid (**7**) at 264 and 334 nm, and a shoulder at 247 nm.[9,10] The UV spectra of 1,3,6-trimethyllumazine-7-carboxylic acid (**9**) showed two absorption bands at 240 and 332 nm which was quite similar to that of 1,3-dimethyllumazine-7-carboxylic acid (**8**).

Experimental Section

Materials and instruments. All chemicals used were purchased from commercial sources with an analytical grade. The solvents were purified by distillation and the other reagents were used without further purification. ^{1}H NMR spectra were measured at 300 MHz using a Varian Unity Plus 300 spectrometer. The chemical shift values are reported as δ downfield from TMS as an internal standard. Melting points were determined on a Büchi 530 and a Mettler FP62 melting point apparatus and were uncorrected. UV spectra were performed on a Perkin Elmer Lambda 7, and the samples were prepared as a concentration of 10^{-2} molL^{-1}. Elemental analyses were performed by Fisions EA 1108.

1,3,6-Trimethyllumazine (4). Pyruvic aldehyde 1-oxime[7] (24.4 g, 0.28 mol) was added portionswise to a stirred suspension of 4,5-diamino-1,3-dimethyluracil hydrochloride (**2**, 39.2 g, 0.23 mol) in ethanol (800 mL) at 0 °C. The reaction mixture was stirred for 1 h, and then the resulting precipitate was filtered and washed with cold ethanol to give 6-amino-5-(2-oximino-1-methyl-ethyleneamino)-1,3-dimethyluracil (**3**) as a yellow powder. Without further purification, **3** was heated in 80% H_2SO_4 (800 mL) at 80-90 °C for 1 h. The resulting dark brown solution was poured into ice (800 g). The aqueous phase was extracted two times with methylene chloride (500 mL). The organic phase was washed with 5% $NaHCO_3$ and water, dried over sodium sulfate, and evaporated under reduced pressure. The crude product was recrystallized from ethanol to give **4** (26.7 g, 56%) as a pale yellow needle, mp 204 °C (Lit.[6] 202-203 °C). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.71 (s, 3H, C6-CH_3), 3.55 (s, 3H, N3-CH_3), 3.69 (s, 3H, N1-CH_3), 8.52 (s, 1H, C7-H).

1,3,7-Trimethyllumazine (5). Pyruvic aldehyde (40%, 100 mL) was added to a stirred suspension of 5,6-diamino-1,3-dimethyluracil hydrochloride (**2**, 55 g, 0.27 mol) in water (600 mL). The reaction mixture was heated at 95-100 °C for 1 h and cooled to ambient temperature. The resulting dark brown solution was extracted with methylene chloride. The organic layer was dried over sodium sulfate and evaporated to dryness under reduced pressure. The crude product was recrystallized twice from ethanol to provide **5** (36.9 g, 67%) as a pale yellow needle, mp 163 °C (Lit.[6] 163 °C). ^{1}H NMR($CDCl_3$) δ (ppm): 2.69 (s, 3H, C7-CH_3), 3.54 (s, 3H, N3-CH_3), 3.71 (s, 3H, N1-CH_3), 8.45 (s, 1H, C6-H).

1,3,6,7-Tetramethyllumazine (6). 2,3-Butanedione (10.5 mL, 0.12 mol) was added to a stirred suspension of 5,6-diamino-1,3-dimethyluracil hydrochloride (**2**, 6.2 g, 30 mmol) in water (100 mL). The reaction mixture was heated at 95-100 °C for 2 h and cooled to ambient temperature. The resulting precipitate was filtered and recrystallized from ethanol to provide **6** (4.63 g, 70%) as a pale yellow needle, mp 160-161 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.66 (s, 3H, C6-CH_3), 2.67 (s, 3H, C7-CH_3), 3.54 (s, 3H, N3-CH_3), 3.70 (s, 3H, N1-CH_3). UV (methanol) λ_{max} (nm/logε): 234 (4.14), 333 (4.02). Anal. Calcd for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found C, 54.60; H, 5.40; N, 25.08.

1,3-Dimethyllumazine-6-carboxylic acid (7). A mixture of **4** (2 g, 9.9 mmol) and 50% nitric acid (100 mL) was heated under reflux for 18 h and cooled to rt. The precipitate was filtered and washed with water and acetone. The crude

product was recrystallized from methanol to give **7** (0.85 g, 38%) as a pale yellow solid, mp 249-250 °C (Lit.[2] 248-250 °C). ^{1}H NMR (DMSO-d_6) δ (ppm): 3.29 (s, 3H, N3-CH_3), 3.56 (s, 3H, N1-CH_3), 9.20 (s, 1H, C7-H).

1,3-Dimethyllumazine-7-carboxylic acid (8). A mixture of **5** (2 g, 9.9 mmol) and 10% nitric acid (100 mL) was heated under reflux for 2 h and cooled to rt. The precipitate was filtered and washed with water and acetone. The crude product was recrystallized from methanol to give **8** (2.03 g, 87%) as a pale yellow solid, mp 226-227 °C (Lit.[6] 226-227 °C). ^{1}H NMR (DMSO-d_6) δ (ppm): 3.33 (s, 3H, N3-CH_3), 3.55 (s, 3H, N1-CH_3), 9.03 (s, 1H, C6-H).

1,3,6-Trimethyllumazine-7-carboxylic acid (9). In a similar manner as compound **8**, the reaction of **6** with 10% nitric acid provided **9** (91%) as a pale yellow solid, mp 228 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.73 (s, 3H, C6-CH3), 3.27 (s, 3H, N3-CH_3), 3.57 (s, 3H, N1-CH_3). UV (methanol) λ_{max} (nm/logε): 240 (4.17), 332 (3.96). Anal. Calcd for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.03; N, 22.39. Found C, 47.91; H, 4.22; N, 22.02.

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