SELECTIVE OXIDATION OF 6-ACETYL-1,3,7-TRIMETHYLLUMAZINE BY NITRIC ACID

Yeonhee Kim, Jaeseung Kim, Shinho Jang, and Yonghan Kang*

Department of Chemistry, Hanyang University, Ansan, Kyunggi-do 425-791, Korea

Abstract–6-Acetyl and 7-methyl groups of 6-acetyl-1,3,7-trimethyllumazine were oxidized to carboxylic acid by nitric acid. The oxidation of 6-acetyl-1,3,7-trimethyllumazine afforded 1,3,7-trimethyllumazine-6-carboxylic acid or 1,3-dimethyllumazine-6,7-dicarboxylic acid depending on the concentration of nitric acid.

Pteridine derivatives have been naturally produced from biosynthesis of guanosine triphosphate (GTP) in biological systems.[1] The various pteridine derivatives were discovered from all living things including amphibia,[2] fish,[3] microorganisms,[4] insects,[5] mammals and human bodies.[6,7]

The pteridine derivatives play crucial roles in human body. For example, folic acid[8] acts as a growth cofactor and an insufficiency of biopterin[9] causes phenylketouria disease. In addition, tumor progress is able to be monitored by the amount of neopterin[10] in human urine. Thus, the fundamental mechanism of biosynthetic processes for the pteridine derivatives and their chemical syntheses have been studied.[11,12]

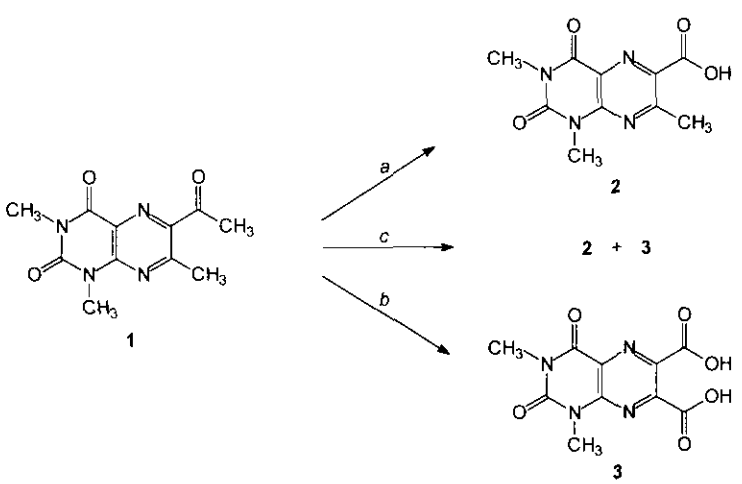
In particular, it has been known that the conversion of the side chain of pteridines to other functional groups is very useful and important for the syntheses of the naturally occurring pteridine derivatives. For instance, the 6-methyl group in 6-methylpterin is transferred to the formyl group *via* the dibromomethyl group, and then the reaction with 4-aminobenzoyl-1-glutamic acid produces folic acid.[13] On the other hand, pteridine-6- or 7-carboxylic acid is obtained by the oxidation of 6- or 7-alkylpteridine derivatives using potassium permanganate. The alkyl side chains of the pteridine system, such as pterin (2-amino-4-oxo-3*H*-pteridine), 2,4-diaminopteridine, and lumazine (2,4-dioxopteridine), are easily oxidized to the corresponding pteridinecarboxylic acids by the treatment of potassium permanganate.[14] However, the oxidation of 6- or 7-substituted 1,3-dimethyllumazine derivatives with potassium permanganate provided the corresponding carboxylic acids in low yield.[15] This can be explained by the fact that 1,3-dimethyllumazine derivatives are insoluble in water and the pyrimidine in the pteridine ring is cleaved under the alkaline solution converting them to pyrazine derivatives.[16]

In this study, nitric acid has been selected as an oxidizing agent because it can selectively oxidize the side chain in the alkylbenzene derivatives. When the alkylbenzene was oxidized with concentrated nitric acid, the benzoic acid derivative was obtained as a major product. When diluted nitric acid was used, benzaldehyde derivatives or α-hydroxyalkylbenzene derivatives were obtained.[17]

The reaction of 4-amino-1,3-dimethyl-5-nitrosouracil with 2,4-pentanedione under reflux for 18 h afforded 6-acetyl-1,3,7-trimethyllumazine (**1**)[18] in 69% yield. The oxidation of the 6-acetyl and 7-methyl groups of **1** with potassium permanganate was tried, but the reaction did not proceed due to the insolubility of the compound (**1**) in water. When aqueous dioxane or aqueous dioxane / KOH (pH 10) was used as the solvent system, many inseparable products were obtained.

After being heated under reflux for 18 h with 10% nitric acid, compound (**1**) only provided 1,3,7-trimethyllumazine-6-carboxylic acid (**2**) in 79% yield (Scheme 1). On the other hand, concentrated nitric acid of more than 50% was able to completely oxidize both the 6-acetyl and 7-methyl groups giving a 59% yield of 1,3-dimethyllumazine-6,7-dicarboxylic acid (**3**). Therefore, it turned out that the oxidation of 6-acetyl-1,3,7-trimethyllumazine (**1**) strongly depended upon the concentration of the nitric acid employed.

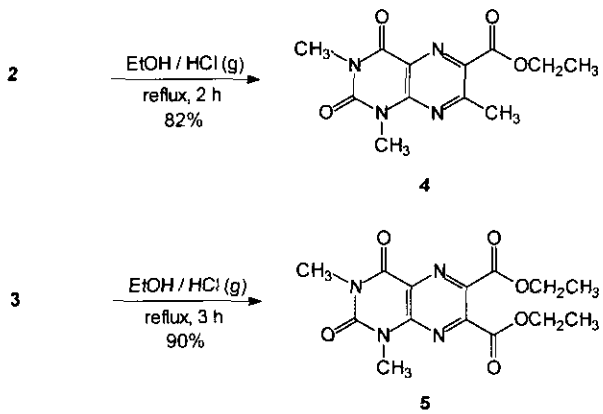
The compound (**1**) has two similar methyl groups. The 7-methyl group is expected to have analogous chemical reactivities to the methyl group of the 6-acetyl group due to a similarity to a keto-enol tautomeric relationship with the ring-N-8 atom. It is implied that the degree of oxidation towards two methyl groups of **1** can be controlled by using a different concentration of nitric acid and the application of this method can provide a useful intermediate for synthesis of the pteridine derivatives.



a : 10% HNO_3, reflux, 18 h b : 50% HNO_3, reflux, 18 h c : 20 ~ 40% HNO_3, reflux, 18 h

Scheme 1

It was reported that the absorption bands of 1,3-dimethyllumazine-7-carboxylic acid[19] in the UV spectrum were observed at 242 and 334 nm, while those of 1,3-dimethyllumazine-6-carboxylic acid[20] at 264 and 334 nm, and a shoulder at 247 nm. The pattern of the UV spectrum of 1,3,7-trimethyllumazine-6-carboxylic acid (**2**) having the absorption bands at 262 and 332 nm, and a shoulder at 240 nm was quite similar to that of 1,3-dimethyllumazine-6-carboxylic acid. Therefore, it is assumed that the 6-acetyl group of **1** was oxidized prior to the 7-methyl group. By the ^{1}H-NMR data, three methyl groups(δ = 2.79, 2.93, and 3.74 ppm) in compound (**2**) and two methyl groups (δ = 3.38 and 3.59 ppm) in compound (**3**) were identified, respectively. The presence of carboxylic groups in compounds (**2**) and (**3**) was confirmed by esterification (Scheme 2).



Scheme 2

EXPERIMENTAL

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 melting point apparatus and were uncorrected. UV spectra were performed on a Perkin Elmer Lambda 7 and Shimadzu UV-160A, and the samples were prepared as a concentration of 10^{-2} molL^{-1}. Elemental analyses were performed by Fisons EA 1108.

6-Acetyl-1,3,7-trimethyllumazine (1) A suspension of 4-amino-1,3-dimethyl-5-nitrosouracil (14.5 g, 78.7 mmol) in 2,4-pentanedione (180 mL) was heated under reflux for 18 h and cooled to rt. The

insoluble solid was removed by filtration and the residue was concentrated under reduced pressure. After addition of ethanol (100 mL) to the remains, the mixture was stirred at rt for 10 min. The precipitation was filtered and washed with ethanol and ether. Recrystallization of the crude product from ethanol afforded **1** (13.5 g, 69%) as a yellow needle, mp 162 °C (lit.,[17] mp 164~165 °C).

1,3,7-Trimethyllumazine-6-carboxylic acid (2) A mixture of **1** (1.0 g, 4 mmol) and 10% nitric acid (60 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 ethanol to give **2** (800 mg, 79%) as a pale yellow solid, mp 198~200 °C. Anal. Calcd for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.03; N, 22.39. Found: C, 47.87; H, 4.29; N, 22.11. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.80 (3H, s), 3.32 (3H, s), 3.54 (3H, s). UV (methanol) λ (nm): 240 (ε 14,800), 262 (sh, ε 9,800), 332 (ε 9,100).

1,3-Dimethyllumazine-6,7-dicarboxylic acid (3) In a similar manner as compound (**2**), the reaction of **1** with 50% nitric acid provided **3** (59%) after recrystallization from methanol as a yellow needle, mp 236~238 °C. Anal. Calcd for $C_{10}H_8N_4O_6$: C, 42.87; H, 2.88; N, 20.00. Found: C, 42.59; H, 3.02; N, 19.81. ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.38 (3H, s), 3.59 (3H, s). UV (methanol) λ (nm): 248 (ε 13,500), 335 (ε 7,400).

Ethyl 1,3,7-trimethyllumazine-6-carboxylate (4) Compound (**2**) (10.0 g, 40 mmol) was added to a solution of ethanol (500 mL) which was saturated with hydrogen chloride. The reaction mixture was heated under reflux for 2 h, and then cooled to rt. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (200 mL). The solution was washed with 5% $NaHCO_3$ and water. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The solid residue was recrystallized from ethanol to give **4** (8.56 g, 73%) as a pale yellow solid, mp 130~132 °C. Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13. Found: C, 51.69; H, 5.20; N, 19.88. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.45 (3H, t, J = 6.9 Hz), 2.89 (3H, s), 3.52 (3H, s), 3.75 (3H, s), 4.47 (2H, q, J = 6.9 Hz). UV (methanol) λ (nm): 245 (ε 12,000), 268 (sh, ε 8,300), 330 (ε 8,100).

Diethyl 1,3-dimethyllumazine-6,7-dicarboxylate (5) In a similar manner as compound (**4**), the reaction of **3** with saturated ethanolic hydrogen chloride gave **5** (90%) after recrystallization from ethanol as a yellow solid, mp 98~100 °C. Anal. Calcd for $C_{14}H_{16}N_4O_6$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.72; H, 5.01; N, 16.63. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.48 (6H, t, J = 7.2 Hz), 3.60 (3H, s), 3.87 (3H, s), 4.61 (4H, q, J = 7.2 Hz). UV (methanol) λ (nm): 253 (ε 14,800), 338 (ε 9,500).

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