The Syntheses of Pteridin-2-one Derivatives from Diaminomaleonitrile (DAMN)

Koichi Tsuzuki and Masaru Tada*

Department of Chemistry, School of Science and Engineering, Waseda University, Shinjuku-ku
Tokyo 160, Japan

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1,3-Dimethyl-4-iminopteridin-2-one, 1,3-dimethylpteridine-2,4-dione, 1-methylpteridine-2,4-dione, 4-alkoxy-1-methylpteridin-2-one, and 4-alkylamino-1-methylpteridin-2-one were synthesized from diaminomaleonitrile (DAMN) through pyrazine-2,3-dicarbonitrile. The synthetic procedures consist of the condensation of DAMN with glyoxal, the nucleophilic substitution of pyrazine-2,3-dicarbonitrile with methylamine, the reaction of 3-methylaminopyrazine-2-carbonitrile with electrophiles such as methyl isocyanate and methyl chloroformate in the presence of sodium hydride, and the transformation of 3-(methoxycarbonylmethyl)aminopyrazine-2-carbonitrile into the pteridine derivatives.

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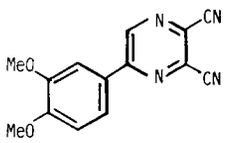
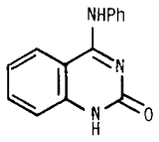
3-Aminopyrazine-2-carbonitrile is an important synthetic intermediate of bio-active pterines [1]. Among them are biopterin, folic acid, methotrexate, and other insect pigments [2].

We reported the facile substitution reaction of 5-(3,4-dimethoxyphenyl)pyrazine-2,3-dicarbonitrile (**A**) with an amine and an alcohol [3]. The substitution with methylamine takes place also on pyrazine-2,3-dicarbonitrile (**1**), which is easily prepared by the condensation of diaminomaleonitrile (DAMN) and glyoxal [4], and gives 3-methylaminopyrazine-2-carbonitrile (**2**). Most of the bio-active pteridines have the functional groups such as carbonyl and amino group at the 2 and 4 positions, and therefore we tried to lead **2** into pteridin-2-one derivatives having the functional group on the 4-position.

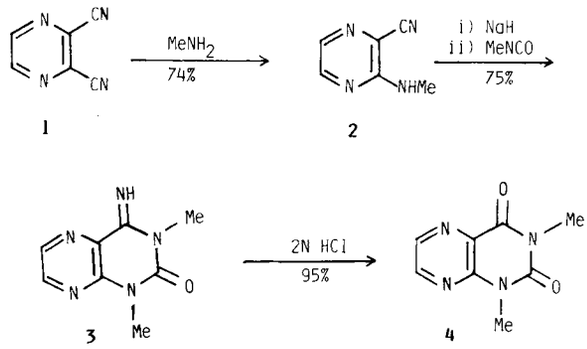


A



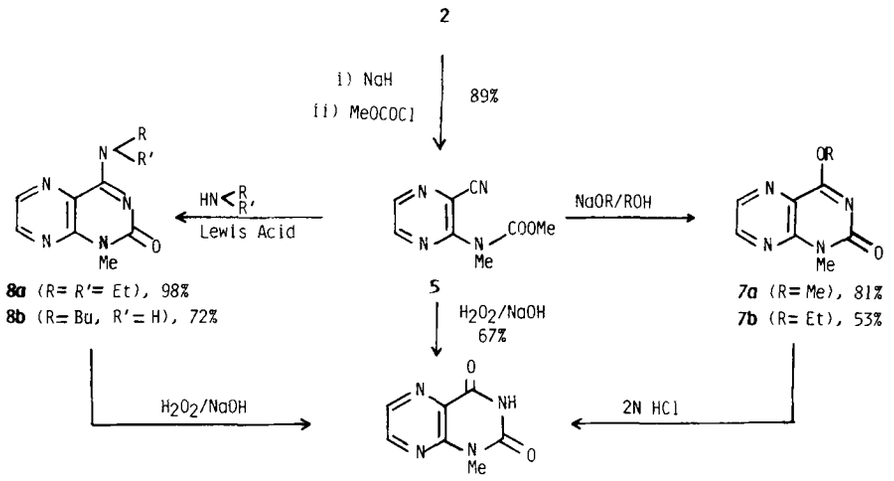
B

The reaction of 2-aminobenzonitrile with phenyl isocyanate has been reported to give *N*-(2-cyanophenyl)-*N'*-phenylurea which is in turn transformed into 4-anilinoquinazolin-2-one (**B**) [5]. 3-Methylaminopyrazine-2-carbonitrile (**2**), however, does not react with methyl isocyanate in the variety of solvents under reflux; benzene, toluene, chloroform, ethanenitrile, triethylamine, or pyridine. The amino group in **2** is much less nucleophilic than that of 2-aminobenzonitrile due to the pi-deficient nature of a pyrazine ring. The treatment of **2** with sodium hydride followed by methyl isocyanate, however, afforded 1,3-dimethyl-4-iminopteridin-2-one (**3**) in 74% yield. The structure of **3** was settled by its conversion into 1,3-dimethylpteridine-2,4-dione (**4**) [6] by acid treatment. The compound **2** showed again poor reactivity to acid chlorides



such as benzoyl chloride and methyl chloroformate. 3-(Methoxycarbonylmethyl)aminopyrazine-2-carbonitrile (**5**), however, was obtained in good yield by the first treatment of **2** with sodium hydride or potassium *t*-butoxide followed by the treatment with methyl chloroformate. The treatment of **5** with alkaline hydrogen peroxide gave 1-methylpteridine-2,4-dione (**6**) in 67% yield. The structure of **6** was settled by methylation to give 1,3-dimethylpteridine-2,4-dione (**4**) [6]. The treatment of **5** with a sodium alkoxide gave a 4-alkoxy-1-methylpteridin-2-one (**7a**, 81%; **7b**, 53%). The structures of compounds **7** were deduced from spectroscopic data and confirmed by the acid-catalyzed conversion of **7** into 1-methylpteridine-2,4-dione (**6**). Similarly the treatment of **5** with an amine in the presence of Lewis acid (aluminium(III) chloride or titanium(IV) chloride) gave 4-amino-1-methylpteridin-2-one (**8a**, 98%; **8b**, 72%). The structures of compounds **8** were deduced from spectroscopic data and confirmed by the conversion of **8a** into 1-methylpteridine-2,4-dione (**6**) by the treatment with alkaline hydrogen peroxide.

It is a versatile and general method to transform 2-aminobenzonitrile into a quinazoline system. On the other hand, the transformation of 3-aminopyrazine-2-carbonitrile into a pteridine system is limited due to the pi-deficient nature of a pyrazine ring, and a pteridine-2,4-



dione derivative is generally synthesized from a diaminouracil derivative [6].

3-Aminopyrazine-2-carbonitrile (**2**) is easily obtained from DAMN and therefore the present findings provide a general method of the synthesis of pteridin-2-one derivative having a functional group such as imino, amino, alkoxy, and carbonyl at the 4-position.

EXPERIMENTAL

Preparation of 3-Methylaminopyrazine-2-carbonitrile (**2**).

Pyrazine-2,3-dicarbonitrile (**1**) was prepared from DAMN and 40% solution of glyoxal by the reported method [4], mp 127-127.5°. Compound **1** (5.40 g, 42 mmoles) in 80 ml of THF was treated during 3 hours with a mixture of 12 ml of 40% aqueous solution of methylamine (0.14 mole) and 80 ml of THF solution of triethylamine (15 ml, 0.16 mole), and the mixture was stirred for an additional 2 hours at room temperature.

After the removal of the precipitate by a celite filter, the filtrate was condensed under reduced pressure to *ca.* ¼ volume and the *p*H of the condensate was adjusted to 2 by 2*N* hydrochloric acid. The chloroform extract (200 ml x 3) was washed with sodium hydrogen carbonate solution and dried over sodium sulfate. Evaporation of chloroform gave the brown solid of crude **2** (4.10 g, 74%). Purification of **2** by passing a short column of silica gel with chloroform and recrystallization from methanol gave pale yellow crystals of **2**. Compound **2** sublimed at 89°/0.06 mm Hg and had mp 142-143°; ir (chloroform): 3430, 2235, 1587 cm^{-1}; H-nmr (deuteriochloroform): (J in Hz) 8.24 (d, J = 2.5, 1H), 7.88 (d, J = 2.5, 1H), 5.52 (broad s, 1H), 3.06 (d, J = 5.6, 3H); ms: Calcd. for $C_6H_6N_4$: m/z = 134.0592. Found: m/z = 134.0592.

Anal. Calcd. for $C_6H_6N_4$: C, 53.72; H, 4.51; N, 41.77. Found: C, 54.03; H, 4.47; N, 41.43.

Reaction of 3-Methylaminopyrazine-2-carbonitrile (**2**) with Methyl Isocyanate.

Compound **2** (135 mg, 1.0 mmole) in 5 ml of dry THF was added under nitrogen to 55% sodium hydride-mineral oil dispersion (15 mg, 0.3 mmole) and the mixture was stirred for 20 minutes. The mixture was then added with 0.2 ml of methyl isocyanate (3.4 mmoles) and stirred for 19 hours at room temperature. The mixture was once acidified with 10 ml of 2*N* hydrochloric acid to remove a by-product, trimethyl cyanurate (methyl isocyanate trimer), by washing with dichloromethane and brought back to *p*H = 7 by adding sodium hydrogencarbonate. Dichloromethane extraction (10 ml x 4) gave a yellow solid which gave pure 1,3-dimethyl-4-iminopteridin-2-one (**3**) in 75% yield after recrystallization from benzene-hexane (1:1). Compound **3** sublimed at 94°, 0.05 mm Hg and had mp 148°; ir (chloroform): 3288, 1687, 1624 cm^{-1}; H-nmr (deuteriochloroform): (J in Hz) 9.14 (broad, 1H), 8.39 (d, J = 2.5, 1H), 8.24 (d, J = 2.5, 1H), 3.53 (s, 3H), 3.48 (s, 3H); ms: Calcd. for $C_8H_9N_5O$: m/z = 191.0807. Found: m/z 191.0832.

Compound **3** was unstable and did not give the correct values in elemental analyses, and it was transformed into 1,3-dimethylpteridine-2,4-dione (**4**) [6] by the treatment with 2*N* hydrochloric acid in ethanenitrile (95%).

Reaction of 3-Methylaminopyrazine-2-carbonitrile (**2**) with Methyl Chloroformate.

Compound **2** (1.70 g, 13 mmoles) in 25 ml of dry THF was added under nitrogen to 55% sodium hydride-mineral oil dispersion (564 mg, 14 mmoles) and the mixture was stirred for 30 minutes. The mixture was then added with methyl chloroformate (1.6 ml, 20 mmoles) and stirred for 4 hours at room temperature. The mixture was extracted with dichloromethane (30 ml x 3) after the addition of 20 ml of 2*N* hydrochloric acid and 10 ml of water. The extract was washed with aqueous sodium hydrogencarbonate and brine, and then it was dried over sodium sulfate. Condensation of the extract yielded crude 3-(methoxycarbonylmethyl)aminopteridine-2-carbonitrile (**5**) in 89% yield. The purified **5** by recrystallization from methanol sublimed at 63°/0.06 mm Hg and had mp 71°; ir (chloroform): 2240, 1720 cm^{-1}; H-nmr (deuteriochloroform): (J in Hz) 8.71 (d, J = 2.5, 1H), 8.60 (d, J = 2.5, 1H), 3.89 (s, 3H), 3.49 (s, 3H); ms: Calcd. for $C_8H_8N_4O_2$: m/z = 192.0647. Found: m/z = 192.0647.

Anal. Calcd. for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.10. Found: C, 49.50; H, 4.04; N, 29.35.

Preparation of 1-Methylpteridine-2,4-dione (**6**).

Compound **5** (600 mg, 3 mmoles) in 3 ml of THF was treated with 3 ml of 34% hydrogen peroxide, 5 ml of water, and 10 ml of 0.5*N* sodium hydroxide and the mixture was allowed to stand at room temperature for 2 hours. The *p*H of the mixture was adjusted to *ca.* 5 by concentrated sulfuric acid and then white crystals of **6** precipitated out (286 mg). The filtrate was condensed under reduced pressure and the residue was extracted with a mixed solvent of chloroform-methanol (1:1) to yield an additional crop of **6** (83 mg), total yield of 67%. The compound **6** sublimed at 145°/0.05 mm Hg and had mp 271°; ir (nujol mull): 3163, 3140, 1725, 1665 cm^{-1}; ^{1}H-nmr (DMSO-d_6): (DSS internal standard, J in Hz) 11.91 (broad, 1H), 8.67 (d, J = 2.5, 1H), 8.48 (d, J = 2.5, 1H), 3.48 (s, 3H); ms: Calcd. for $C_7H_6N_4O_2$: m/z = 178.0491. Found: m/z = 178.0495. Com-

pound **6** was methylated quantitatively by sodium hydride-methyl iodide to give known 1,3-dimethylpteridine-2,4-dione [6].

Preparation of 4-Methoxypteridin-2-one (**7a**).

Compound **5** (101 mg, 0.53 mmole) was dissolved in 5 ml of methanol containing methoxide (10 mg, 0.18 mmole) and the mixture was stirred under nitrogen for 24 hours at room temperature. After addition of 10 ml of water and 2 ml of brine, the mixture was extracted with dichloromethane (10 ml x 4). Evaporation of dichloromethane after drying over sodium sulfate gave the product **7a** in 81%. The purified sample of **7a** by recrystallization from benzene-hexane (3:1) sublimed at 124°/0.05 mm Hg and had mp 185°; ir (chloroform): 1677, 1614 cm^{-1}; ^{1}H-nmr (deuteriochloroform): (J in Hz) 8.70 (d, J = 2.5, 1H), 8.59 (d, J = 2.5, 1H), 4.28 (s, 3H), 3.75 (s, 3H); ms: Calcd. for $C_8H_8N_4O_2$: m/z = 192.0647. Found: m/z = 192.0656.

Anal. Calcd. for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.16. Found: C, 49.70; H, 4.10; N, 29.55.

Compound **7a** was converted to 1-methylpteridine-2,4-dione (**6**) by the treatment with 2*N* hydrochloric acid in ethanenitrile (57%).

Preparation of 4-Diethylamino-1-methylpteridin-2-one (**8a**).

Compound **5** (108 mg, 0.56 mmole) in 5 ml of dry dichloromethane was treated with 0.1 ml of titanium(IV) chloride (0.91 mmole) and the mixture was stirred for 30 minutes. The mixture was then added with 0.5 ml of diethylamine (4.8 mmoles) and stirred for 3 hours. After addition of 10 ml of saturated solution of sodium hydrogencarbonate, the *p*H of the mixture was adjusted to *ca.* 12 by 10*N* sodium hydroxide and extracted with dichloromethane (10 ml x 3). Evaporation of dichloromethane after washing with water and drying over sodium sulfate gave the product **8a** in 77% yield. Essentially the same procedure but using aluminium(III) chloride as a Lewis acid gave **8a** in 98% yield. The purified **8a** by recrystallization from benzene-hexane (1:2) sublimed at 90°/0.2 mm Hg and had mp 102-103°; ir (chloroform): 1639, 1589 cm^{-1}; ^{1}H-nmr (deuteriochloroform): (J in Hz) 8.30 (d, J = 2.5, 1H), 8.14 (d, J = 2.5, 1H), 3.92 (m, 4H), 3.65 (s, 3H), 1.30 (t, J = 6.8, 6H); ms: Calcd. for $C_{11}H_{15}N_5O$: m/z = 233.1277. Found: m/z = 233.1289.

Anal. Calcd. for $C_{11}H_{15}N_5O$: C, 56.63; H, 6.48; N, 30.03. Found: C, 56.44; H, 6.26; N, 30.09.

Compound **8a** (90 mg) was converted to 1-methylpteridine-2,4-dione (**6**) by the treatment with 1*N* sodium hydroxide (0.5 ml) and 30% hydrogen peroxide (0.05 ml) in 0.5 ml of THF. The reaction mixture was stirred for 2 hours at room temperature and the *p*H of the mixture was adjusted to *ca.* 9 by 2*N* sulfuric acid. The chloroform extract gave a colorless oil which crystallized on addition of diethyl ether and the spectroscopic data of this product are identical to those of compound **6**.

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