An Alternative Synthesis of 5-Aminopyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one

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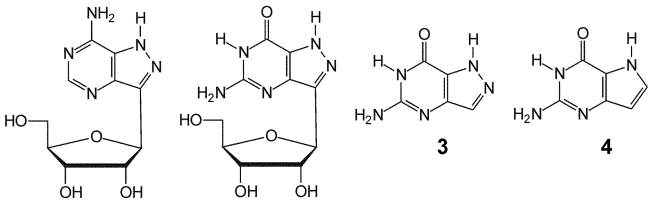
The naturally occurring adenosine analog *C*-nucleoside formycin[1] (**1**) isolated from the rice mold, *Norcardia interforma*, is constituted with β-D-ribofuranose and 7-amino-1*H*-pyrazolo-[4,3-*d*]pyrimidine and has showed antitumor, antibacterial, antifungal, and antiviral activities.[2,3] A variety of biological effects of formycin (**1**) has led interests derivatives of **1**.[4-7] *C*-Nucleoside guanosine analogue 5-amino-3-(β-D-ribofuranosyl)-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one (**2**) has been prepared from **1**. However, the synthetic route using an initial ring opening of **1** followed by a series of chemical transformation and subsequent ring closure afforded **2** in poor overall yield.[4]



1 **2** **3** **4**

Derivatives of guanosine widely studied as potential antitumor agents and as probes in biological reactions[8] have prompted our research to focus on the synthesis of 5-aminopyrazolo[4,3-*d*]-pyrimidin-7(6*H*)-one (**3**). The synthesis of **3** was first reported by Rose.[9] However, this method provides a very low yield of **3** with byproducts forcing us to investigate an alternate synthetic route.

Results and Discussion

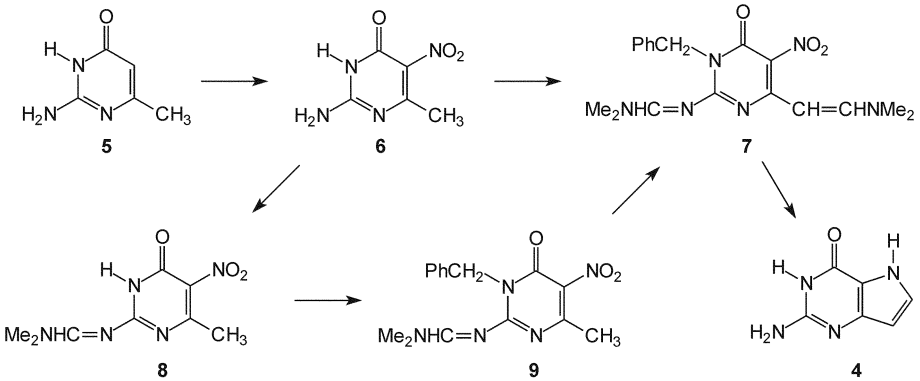
Recently, the synthesis of 9-deazaguanine (**4**), pyrrolo[3,2-*d*]-pyrimidine ring system was developed[10] by using the commercially available 2-amino-6-methylpyrimidin-4(3*H*)-one (**5**) as a starting material, and this procedure (Scheme 1) was expected to be very efficient in synthesizing our target molecule **3**.

The treatment of **6** with 2.2 equivalent of *N*,*N*-dimethylformamide dimethyl acetal at room temperature provided the corresponding 2-(dimethylamino)methyleneimino derivative **8**, which was converted to 3-benzyl-2-[(dimethylamino)methyleneimino]-5-nitro-6-methylpyrimidin-4-one (**9**) by treating with benzyl chloride in the presence of DBU.[10]

5-Amino-3-benzyl-2-[(dimethylamino)methyleneimino]-6-methylpyrimidin-4-one (**10**) was produced with a high yield on catalytic reduction. After diazotiation of the 5-amino group of **10**, the diazonium intermediate was converted to 6-benzyl-5-[(dimethylamino)methyleneimino]-pyrazolo[4,3-*d*]pyrimidin-7-one (**11**) *in situ* by intramolecular cyclization due to the coupling reaction between the 6-methyl group and 5-diazo function in acidic medium (Scheme 2).

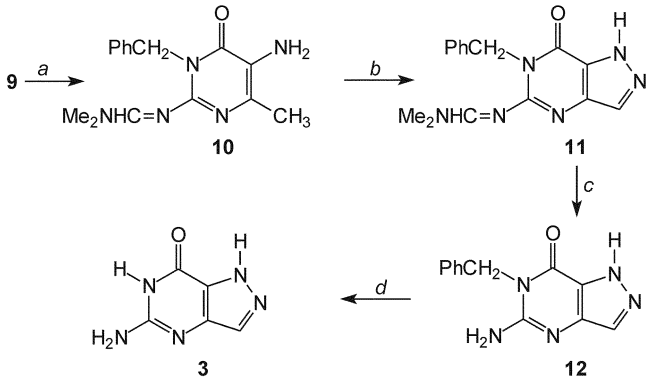
^{1}H-NMR spectrum of **11** showed a singlet peak of an aromatic proton due to a C3 position at 8.31 ppm, which was not detected in previous compounds **6**-**10**.

Debenzylation of 5-amino-6-benzylpyrazolo[4,3-*d*]pyrimidin-7-one (**12**) on catalytic reduction with palladium on



5 **6** **7** **8** **9** **4**

Scheme 1



Scheme 2. (a) Pd/C, H_2 (60 psi), MeOH, rt; (b) $NaNO_2$, AcOH, ~10 °C, 3 h; (c) NH_3/MeOH, rt, 3 h; (d) HCO_2NH_4, MeOH, Pd/C, reflux.

carbon and ammonium formate under reflux provided the target compound, 5-aminopyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one (**3**) in excellent yield.

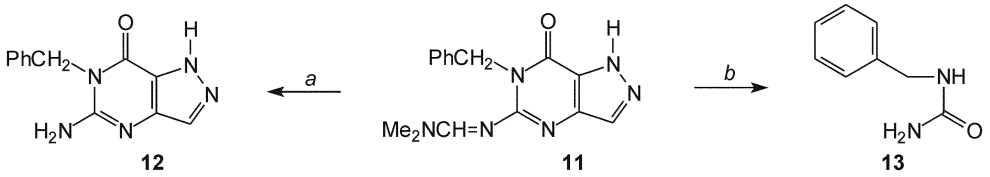
Various kinds of DMF dialkyl acetal have been used for the protection of the amino group by formation of the corresponding imines since imines are easily hydrolyzed to the starting amine in acidic or basic medium.[11-13] After **11** was treated under various reaction conditions to remove the 2-(dimethylamino)methylene group, 5-amino-6-benzyl-pyrazolo[4,3-*d*]pyrimidin-7-one (**12**) was obtained when **11** was coupled with saturated methanolic ammonia solution in excellent yield (Scheme 3).

An unexpected pyrimidine ring opening reaction was observed during the treatment of **11** with 1 *N* methanolic potassium hydroxide solution. It was assumed that the ring opening was incurred by the attack of hydroxide anion on the 7-oxo group as shown in Scheme 4 after the 2-(dimethylamino)methylene group of **11** was detached in a relatively strong basic medium.

Experimental Section

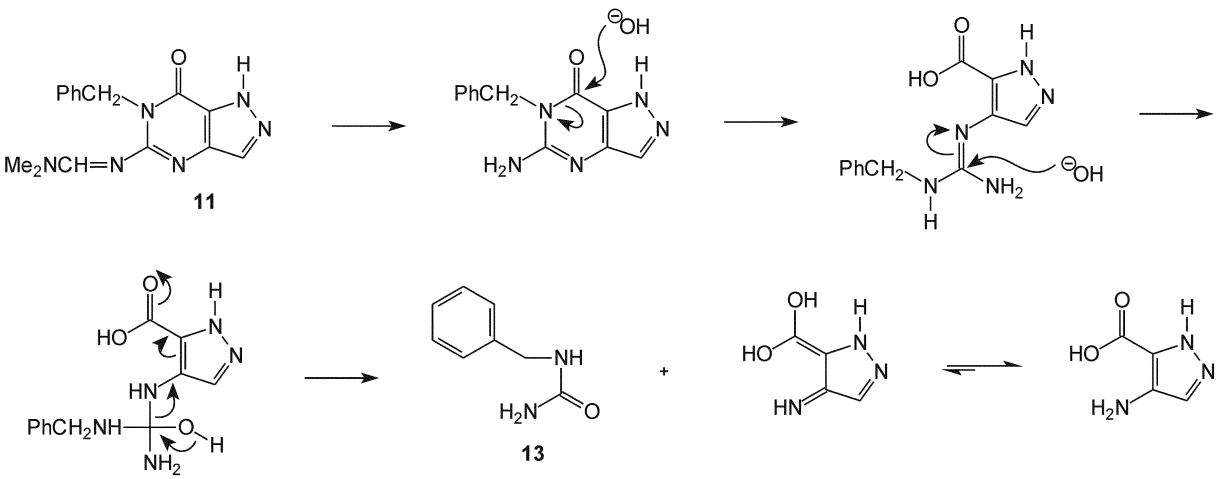
All chemicals were used as purchased from commercial sources (Aldrich, Merck, Duksan, and Jin Chemicals). The solvents were purified by distillation and the other reagents were used without further purification. ^{1}H- and ^{13}C-NMR spectra were measured using a Varian Mercury 300. The chemical shifts are reported in ppm (δ), and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and bs (broad singlet). Melting points were determined on a Buchi 530 melting point apparatus, and the results were uncorrected. TLC was carried out using Merck silica gel plates (F254) with distilled solvents. Elemental analyses were performed on a Fisons EA 1108.

5-Amino-3-benzyl-2-[(dimethylamino)methyleneimino]-6-methylpyrimidin-4-one (10). Compound **9** (5.2 g, 16.5 mmol) in methanol (250 mL) was hydrogenated using 10% palladium on carbon as catalyst under pressure of 60 psi. The mixture was filtered through Celite, and the filtrate was evaporated to dryness. The crude amine was recrystallized from methanol to give **10** (4.7 g, 90%) as a yellow powder: mp 175 °C; R_f = 0.36 (silica gel, dichloromethane : methanol = 10:1, v/v); ^{1}H NMR (DMSO-d_6) δ 2.09 (s, 2H, 6-CH_3), 2.93 (s, 3H, N-CH_3), 3.05 (s, 3H, N-CH_3), 4.11 (s, 2H, 5-



(a) NH_3/MeOH, rt, 3 h; (b) 1 *N* KOH/MeOH, reflux, 1 h.

Scheme 3



Scheme 4

NH_2), 5.33 (s, 2H, CH_2-Ph), 7.19-7.30 (m, 5H, Ph), 8.40 (s, 1H, -CH=N-); ^{13}C NMR (DMSO-d_6) δ 19.72, 34.93, 40.70, 45.41, 124.14, 127.04, 127.95, 128.34, 137.14, 138.63, 148.81, 156.23, 158.63; MS: m/z 285 (M). Anal. Calcd. For $C_{15}H_{19}N_5O$: C, 63.14; H, 6.71; N, 24.54. Found: C, 62.89; H, 6.89; N, 24.27.

6-Benzyl-5-[(dimethylamino)methyleneimino]pyrazolo[4,3-*d*]-pyrimidin-7-one (11). To a solution of **10** (7 g, 24.5 mmol) in acetic acid (50 mL) was added sodium nitrite in water (50 mL, 20%, w/v) dropwise at a temperature maintained below 10 °C. After being stirred below 10 °C for 3 h, the reaction mixture was poured into ice-water and neutralized with saturated sodium bicarbonate solution. The precipitation was filtered and washed with water and ethanol. The solid residue was recrystallized from methanol, affording **11** (7.1 g, 98%) as a yellow powder: mp 198 °C; R_f = 0.36 (silica gel, dichloromethane : methanol = 15 : 1, v/v); ^{1}H NMR (DMSO-d_6) δ 3.11 (s, 3H, N-CH_3), 3.27 (s, 3H, N-CH_3), 5.37 (s, 2H, Ph-CH_2), 7.23-7.36 (m, 5H, Ph), 8.31 (s, 1H, 3-CH=), 8.80 (s, 1H, -CH=N-); ^{13}C NMR (DMSO-d_6) δ 35.76, 45.38, 125.63, 126.27, 126.92, 127.37, 128.08, 136.86, 144.21, 158.30, 159.68, 160.21; MS: m/z 297 (M). Anal. Calcd. For $C_{15}H_{16}N_6O$: C, 60.80; H, 5.44; N, 28.36. Found: C, 60.71; H, 5.53; N, 28.16.

5-Amino-6-benzylpyrazolo[4,3-*d*]pyrimidin-7-one (12). A solution of **11** (3 g, 10 mmol) in methanolic ammonia saturated at 0 °C was stirred in a pressure bottle at room temperature for 3 h and evaporated to dryness. The precipitate was filtered and recrystallized from water to afford **12** (1.54 g, 63%) as a yellow powder: mp > 300 °C; R_f = 0.49 (silica gel, dichloromethane : methanol = 9 : 1); ^{1}H NMR (DMSO-d_6) δ 5.25 (s, 2H, CH_2-Ph), 7.30-7.35 (m, 5H, Ph), 8.00-8.50 (bs, 3H, 3-CH= and -NH_2); ^{13}C NMR (DMSO-d_6) δ 44.25, 124.24, 125.54, 126.49, 127.24, 128.31, 134.57, 145.89, 156.60, 157.59; MS: m/z 241 (M). Anal. Calcd. For $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.43; H, 4.83; N, 28.72.

Benzylurea (13). A solution of **11** (0.5 g, 1.69 mmol) in 1 *N* methanolic potassium hydroxide solution (30 mL) was heated under reflux for 1 h and allowed to cool to room temperature. The reaction mixture was evaporated to dryness and then placed in hot water and neutralized with acetic acid. The precipitate was filtered and washed with water to give **13** (0.16 g, 64%) as a white powder: mp 173 °C; R_f = 0.63 (silica gel, dichloromethane : methanol = 9 : 1); ^{1}H NMR (DMSO-d_6) δ 4.20 (d, 2H, Ph-CH_2, J = 3.52 Hz), 5.50 (s, 2H, NH_2), 6.40 (s, 1H, -NH) 7.20-7.38 (m, 5H, Ph).

5-Aminopyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one (3). To a suspension of **12** (1.4 g, 5.8 mmol) and a small amount of 10 % palladium on carbon in methanol (50 mL) was added ammonium formate (1.83 g, 29 mmol) under nitrogen atmosphere. The reaction mixture was heated under reflux for 7 h and then filtered through Celite. The filtrate was evaporated to dryness. The residue was suspended in water (20 mL) to remove the excess ammonium formate. The precipitate was filtered and washed with water to give **3** (0.83 g, 95%) as a brown powder: mp > 300 °C; R_f = 0.53 (silica gel, dichloromethane : methanol = 5 : 1); ^{1}H NMR (DMSO-d_6) δ 7.21 (bs, 2H, NH_2), 8.01 (s, 1H, -CH=N-). Anal. Calcd. For $C_5H_5N_5O$: C, 39.74; H, 3.33; N, 46.34. Found: C, 39.51; H, 3.63; N, 45.95.

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