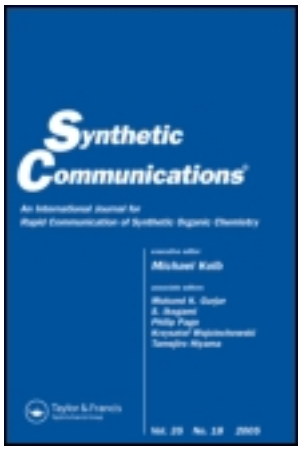

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AN IMPROVED SYNTHESIS OF 9-DEAZAGUANINE

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ABSTRACT

A new, improved synthesis of 9-deazaguanine is described. The method involves use of the benzyloxymethyl group to protect the N^3-position of 2-[(dimethylaminomethylene)-amino]-6-methyl-5-nitro-4(3*H*)-pyrimidinone, followed by treatment with DMF-dimethylacetal, reductive cyclization, treatment with ethanolic ammonia and removal of the protecting group by catalytic hydrogenation.

Key Words: 9-Deazaguanine; 9-Deazapurine nucleosides

The carbon–carbon linked 9-deazapurine nucleosides are resistant to cleavage by purine nucleoside phosphorylase[1] and several exhibit anti-cancer,[2,3] antileishmanial,[4] and antitripanosomal[5] activity. As part of an ongoing program to synthesize 9-deazapurine nucleosides as potential

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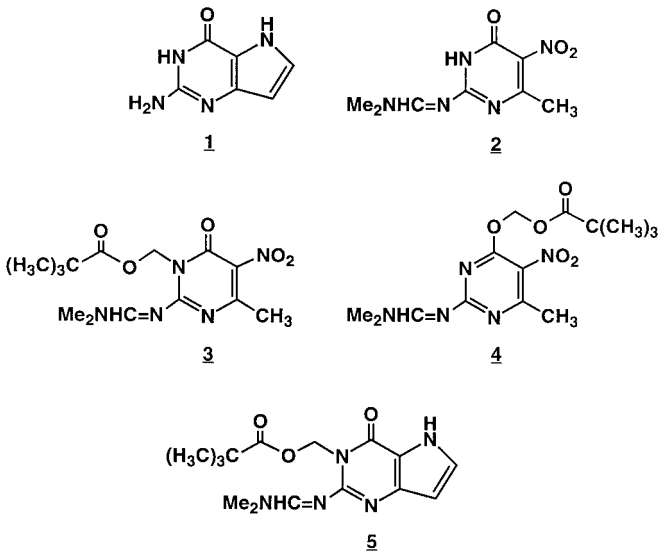
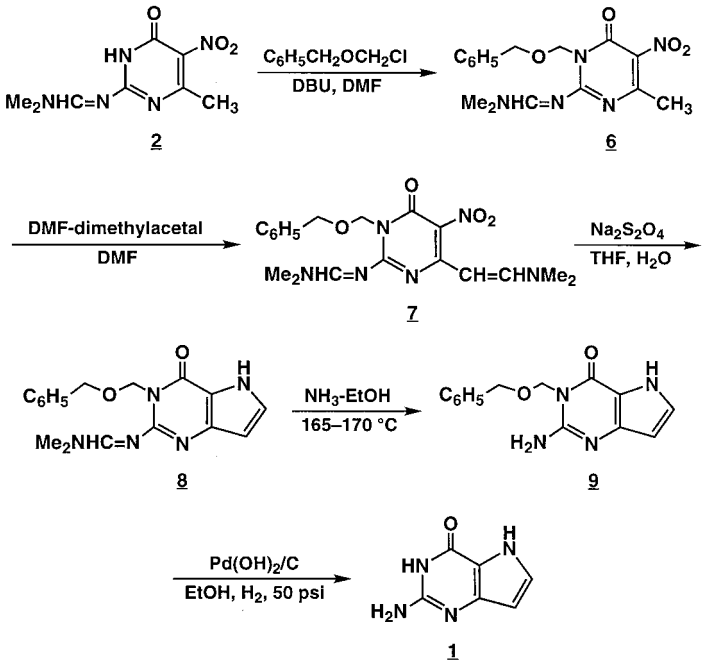
anticancer and antiviral agents, we required 9-deazaguanine (**1**) as a starting material. The methods reported earlier by Imai[6] and Klein et al.[7] for the synthesis of 9-deazaguanine were either long and low-yielding[6] or nonreproducible.[7,8] The most recent method described by Taylor and coworkers[8,9] was a facile synthesis from 2-amino-6-methyl-5-nitro-4(3*H*)-pyrimidinone, which was first converted into the 2-dimethylaminomethylene derivative **2**. Protection of N^3-position of **2** with a pivaloyloxymethyl group produced the N^3-protected derivative **3** (60% yield) and 15% of the O^4-protected by-product **4**. Further treatment of **3** with DMF-dimethylacetal, followed by reductive cyclization gave the protected 9-deazaguanine **5**. Basic removal of the protecting groups produced 9-deazaguanine (**1**). However, selection of pivaloyloxymethyl as a protecting group was not the optimum choice. First, it produced an O^4-protected by-product which needed to be removed, thereby reducing the yield of the product. Second, the pivaloyloxymethyl protecting group is difficult to remove under mild alkaline conditions, and the 9-deazaguanine ring is not stable in strong basic solutions. Thus, treatment of **5** with a mixture of 1 N NaOH and THF at room temperature for 4 days gave only 48% of 9-deazaguanine.[9]



We selected the benzyloxymethyl group to protect the N^3-position of **2** instead of the pivaloyloxymethyl group, since the benzyloxymethyl group not only produced solely the N^3-protected product, but it also could be



Scheme 1.

removed readily by mild reduction under neutral conditions. Treatment of **2** with benzyl chloromethyl ether in DMF in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) at room temperature afforded compound **6** in 90% yield. Condensation of **6** with DMF-dimethylacetal in DMF gave compound **7** (91%). Subsequent reductive cyclization of **7** produced the protected 9-deazaguanine derivative **8** (95%). Treatment of **8** with ethanolic ammonia at an elevated temperature gave compound **9** (95%), which was converted to 9-deazaguanine (**1**) by catalytic hydrogenation in 90% yield (Sch. 1).

In summary, we report an improved method for the synthesis of 9-deazaguanine (**1**) from the intermediate **2** with an overall yield of 66.5%.

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a

Varian EM-390 (90 MHz) or Gemini-300 (300 MHz) NMR spectrometer with Me_4Si as the internal reference. Column chromatography was conducted with Merck silica gel 60, 230–400 mesh. TLC was performed on EM precoated silica gel sheets containing a fluorescent indicator. Elemental analyses were carried out by the Baron Consulting Co., Orange, CT, USA.

3-Benzyloxymethyl-2-[(dimethylamino)methyleneimino]-6-methyl-5-nitro-4(3*H*)-oxopyrimidine (6): To a suspension of compound **2** (11.25 g, 50 mmol) in anhydrous DMF (250 mL) was added DBU (8.0 mL, 52 mmol) with stirring. After the reaction mixture became a clear solution (~5 min), benzyl chloromethyl ether (9.4 g, 60 mmol) was added dropwise to this solution at 0–5°C (ice-water bath). The reaction mixture was stirred at room temperature until TLC showed the reaction was complete (~2 h). The reaction mixture was evaporated in vacuo to dryness, and the residue was dissolved in methylene chloride (400 mL), washed with water (2 × 100 mL), dried ($MgSO_4$), filtered and washed with methylene chloride. The filtrate and washings were combined and evaporated in vacuo to dryness and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 4 : 1, v/v) to yield **6** (16.6 g, 90%) as yellow crystals: m.p. 93–95°C; R_f 0.77 (CH_2Cl_2/EtOAc, 4 : 1, v/v); ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H, CH_3), 3.12 and 3.28 (two s, 6H, NMe_2), 4.75 (s, 2H, CH_2), 5.75 (s, 2H, CH_2), 7.30 (m, 5H, ArH), 8.70 (s, 1H, CH). Anal. calcd. for $C_{16}H_{19}N_5O_4$: C, 55.62; H, 5.55; N, 20.28. Found: C, 55.67; H, 5.86; N, 19.90.

3-Benzyloxymethyl-2-[(dimethylamino)methyleneimino]-6-[(2-dimethylamino)ethenyl]-5-nitro-4(3*H*)-oxopyrimidine (7): A mixture of **6** (6 g, 17.4 mmol) and DMF-dimethylacetal (11 mL) in 60 mL of anhydrous DMF was stirred at room temperature until TLC showed that the reaction was complete (~40 h). The reaction mixture was evaporated in vacuo to dryness and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 4 : 1, v/v) to yield **7** (6.3 g, 91%) as yellow crystals: m.p. 195–196°C; R_f 0.46 (CH_2Cl_2/EtOAc, 4:1, v/v); ^{1}H NMR (DMSO-d_6) δ 2.80–3.10 (m, 12H, $2NMe_2$), 4.70 (s, 2H, CH_2), 5.65 (d, 1H, =CH, J = 12.1 Hz), 5.67 (s, 2H, CH_2), 7.30 (m, 5H, ArH), 7.95 (d, 1H, =CH, J = 12.1 Hz), 8.58 (s, 1H, CH=N). Anal. calcd. for $C_{19}H_{24}N_6O_4$: C, 56.99; H, 6.04; N, 20.99. Found: C, 56.65; H, 6.13; N, 20.69.

3-Benzyloxymethyl-2-[(dimethylamino)methyleneimino]-4(3*H*)-oxo-5*H*-pyrrolo[3,2-d]pyrimidine (8): A suspension of **7** (4.9 g, 12.2 mmol), sodium hydrosulfite (12.0 g), THF (180 mL) and water (90 mL) was stirred at room temperature until the reaction mixture gradually became a clear orange solution and TLC showed that the reaction was complete (~12 h). The reaction mixture was evaporated in vacuo to dryness and the residue was stirred with water (30 mL) for 20 min. The solid was collected, washed with

water and purified by silica gel column chromatography (CH_2Cl_2/EtOH, 15 : 1, v/v) to yield **8** (3.8 g, 95%) as an off-white solid: m.p. 195–196°C; R_f 0.28 (CH_2Cl_2/EtOAc, 1 : 1, v/v); ^{1}H NMR ($CDCl_3$) δ 3.05 and 3.12 (two s, 6H, NMe_2), 4.80 (s, 2H, CH_2), 5.97 (s, 2H, CH_2), 6.30 (d, 1H, =CH, $J = 2.0$ Hz), 7.22 (d, 1H, =CH, $J = 2.0$ Hz), 7.30 (m, 5H, ArH), 8.50 (s, 1H, CH=N), 11.50 (br s, 1H, NH, D_2O exchangeable). Anal. calcd. for $C_{17}H_{19}N_5O_2$: C, 62.75; H, 5.88; N, 21.53. Found: C, 62.70; H, 5.80; N, 21.32.

1-Benzyloxymethyl-9-deazaguanine (9): A mixture of **8** (0.7 g, 2.2 mmol) and ethanolic ammonia (60 mL, saturated at 0°C) was heated in a steel bomb at 165–170°C with stirring for 4 h, then cooled in an ice bath. The cold reaction mixture was evaporated in vacuo to dryness and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 15 : 1, v/v) to yield **9** (0.55 g, 95%) as a white solid: m.p. 204–205°C; R_f 0.36 (CH_2Cl_2/EtOAc, 1 : 1, v/v); ^{1}H NMR (DMSO-d_6) δ 4.57 (s, 2H, CH_2), 5.54 (s, 2H, CH_2), 5.97 (d, 1H, =CH, $J = 2.1$ Hz), 6.20 (br s, 2H, NH_2, D_2O exchangeable), 7.21 (d, 1H, =CH, $J = 2.1$ Hz), 7.34 (m, 5H, ArH), 11.52 (br s, 1H, NH, D_2O exchangeable). Anal. calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.05; H, 4.98; N, 20.43.

9-Deazaguanine (1): To a solution of **9** (0.3 g, 1.1 mmol) in methanol (100 mL) was added palladium hydroxide on carbon (0.2 g), and the mixture was hydrogenated (H_2, 50 psi) for 5 h. The catalyst was removed by filtration, washed with methanol, and the filtrate and washings were combined and evaporated in vacuo to dryness. The residue was recrystallized from 50% ethanol to give 0.15 g of **1** (90%) as a white solid: m.p. gradually darkens over 310°C; (lit.[6] m.p. > 300°C; lit.[9] 310–315°C dec); ^{1}H NMR (DMSO-d_6) δ 5.95 (d, 1H, =CH, $J = 2.8$ Hz), 5.95 (br s, 2H, NH_2, D_2O exchangeable), 7.15 (d, 1H, =CH, $J = 2.8$ Hz), 10.70 (br s, 1H, NH, D_2O exchangeable), 11.51 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_6H_6N_4O \cdot 0.6H_2O$: C, 44.77; H, 4.51; N, 33.81. Found: C, 44.74; H, 4.13; N, 34.85.

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