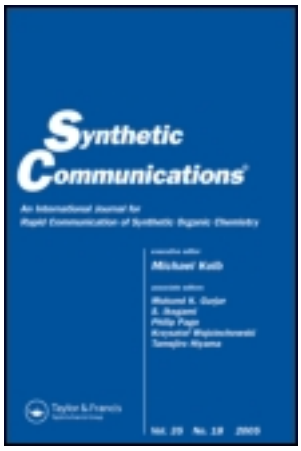

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

AN IMPROVED SYNTHESIS OF 5′-AMINO-5′-DEOXYGUANOSINE

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Version of record first published: 12 Dec 2006.

To cite this article: David K. Dean (2002): AN IMPROVED SYNTHESIS OF 5′-AMINO-5′-DEOXYGUANOSINE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:10, 1517-1521

To link to this article: http://dx.doi.org/10.1081/SCC-120004140

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SYNTHETIC COMMUNICATIONS, 32(10), 1517–1521 (2002)

AN IMPROVED SYNTHESIS OF 5′-AMINO-5′-DEOXYGUANOSINE

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ABSTRACT

A short and efficient three step synthesis of 5′-amino-5′-deoxyguanosine **1** from guanosine **2** is reported.

During the course of our research we required gram quantities of 5′-amino-5′-deoxyguanosine **1** for biological studies. Whilst 5′-amino-5′-deoxyadenosine and thymidine are well described and commercially available, this is not the case for 5′-amino-5′-deoxyguanosine **1**. A review of the literature revealed a handful of syntheses of 5′-amino-5′-deoxyguanosine **1**[1] and its *N*-substituted analogues,[1,2] however there are issues associated with each approach.

Schattka and Jastorff[1] reported the synthesis of 5′-amino-5′-deoxyguanosine **1** in 1972 starting from commercially available 2′,3′-*O*-isopropylidene protected guanosine. The route involved activation of the 5′-hydroxyl group as a tosylate (TsCl, pyridine, 4°C, 3 days), followed by removal of the 2′,3′-diol protecting group (formic acid) and subsequent displacement of the 5′-tosyl group with ammonia (bomb, 7 days) to give the target 5′-amino-5′-deoxyguanosine **1**.[1] The first step in this synthesis was severely hampered by a competing intramolecular cyclisation of N-3 in the guanine unit onto the

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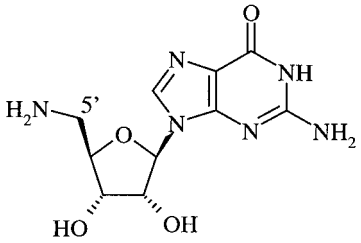
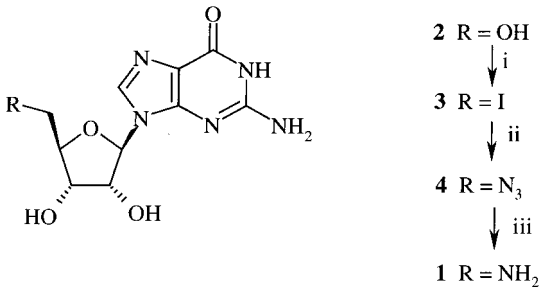


5'-Amino-5'-deoxyguanosine **1**

activated C-5′ position, leading to the formation of an unwanted cyclonucleoside.[1,3,4] We were unable to suppress the formation of the cyclonucleoside and purification of the resultant mixture proved difficult on a reasonable scale which severely compromised the efficiency of this synthetic route. Other syntheses of 5′-amino-5′-deoxyguanosine analogues involve *N*-acylation of the guanine base prior to incorporation of the amino (or substituted amino) group at C-5′.[2] However removal of the guanosine protecting group is generally not trivial and acyl migration onto the newly formed 5′-amino group leads to complications. These issues prompted us to investigate an alternative synthesis of 5′-amino-5′-deoxyguanosine **1**.

We chose commercially available guanosine **2** as the starting material for our synthesis of 5′-amino-5′-deoxyguanosine **1** (see scheme). Our synthetic strategy was based on the work of McGee and Martin,[5] who reported the clean conversion of guanosine **2** into 5′-deoxy-5′-iodoguanosine **3**



Reagents: (i) Triphenylphosphine, imidazole, iodine, 1-methyl-2-pyrrolidinone, 72%; (ii) sodium azide, DMF, 69%; (iii) triphenylphosphine pyridine, aqueous ammonium hydroxide, 78%.

Scheme. Synthesis of 5′-amino-5′-deoxyguanosine **1**.

using triphenylphosphine, imidazole and iodine in 1-methyl-2-pyrrolidinone without the need to protect the 2′,3′-*cis* diol. In our hands, this reaction proceeds cleanly in high yield giving iodide **3** as a stable compound in 72% isolated yield and none of the corresponding cyclonucleoside byproduct was detected. This regioselective iodination reaction (**2** → **3**) represents a major advance in the synthesis of 5′-functionalised guanosine derivatives.

Treatment of iodide **3** with sodium azide in DMF at 80°C gave the corresponding 5′-azide **4** in 69% yield. Attempts to convert guanosine **2** directly to azide **4** using triphenylphosphine, carbon tetrabromide and sodium or lithium azide[6] were unsuccessful. Azide **4** was subsequently reduced under mild conditions using triphenylphosphine and pyridine followed by aqueous ammonium hydroxide[7] to give 5′-amino-5′-deoxyguanosine **1** as a colourless solid in 78% yield. Following this straightforward three step synthetic scheme (**2** → **3** → **4** → **1**), we were able to prepare gram quantities of 5′-amino-5′-deoxyguanosine **1** in a few days without recourse to any difficult chromatographic separations.

In summary, we have developed a short and efficient three step synthesis of 5′-amino-5′-deoxyguanosine **1** from guanosine which overcomes the limitations of previous syntheses.

EXPERIMENTAL

5′-Azido-5′-deoxyguanosine 4

A mixture of 5′-deoxy-5′-iodoguanosine **3**[5] (7.4 g, 19 mmol) and sodium azide (2.5 g, 38 mmol) in dry DMF (50 ml) was stirred at 80°C under argon for 20 h [CAUTION! Use of inorganic azide: reaction carried out behind a safety shield]. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was stirred in water (100 ml) for 30 min. The resultant solid was collected by filtration then washed successively with water (2 × 50 ml), cold ethanol (30 ml) and diethyl ether (20 ml) before drying in vacuo to give 5′-azido-5′-deoxyguanosine **4** (4.0 g, 69%) as a colourless solid: $[\alpha]_D + 52.8^\circ$ (c0.5, DMSO); λ_{max} (MeOH): 255 nm (ε12900), 270 nm (sh) (ε9100); ν_{max} 2104 cm^{-1} (azide); ^{1}H NMR (DMSO-d_6, 400 MHz): δ3.52 (1 H, dd, J = 13.2, 3.6 Hz, *H*-5′), 3.67 (1 H, dd, J = 13.2, 7.2 Hz, *H*-5′), 3.99 (1 H, m, *H*-4′), 4.06 (1 H, m, *H*-3′), 4.58 (1 H, m, *H*-2′), 5.2–5.7 (2 H, br, exchanged with D_2O, 2 × *OH*), 5.72 (1 H, d, J = 5.6 Hz, *H*-1′), 6.50 (2 H, br, exchanged with D_2O, NH_2), 7.90 (1 H, s, *H*-8) and 10.3–10.9 (1 H, br, exchanged with D_2O, *NH*) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 51.8, 70.9, 72.8, 82.7, 86.8, 116.8, 135.8, 151.3,

153.8 and 156.9 ppm; MS: (FAB, positive ion + Na) *m/e* 309 $[M+H]^+$, 331 $[M+Na]^+$.

5′-Amino-5′-deoxyguanosine 1

A stirred solution of 5′-azido-5′-deoxyguanosine **4** (3.1 g, 10 mmol) in dry pyridine (50 ml) at 0°C was treated with triphenylphosphine (5.2 g, 20 mmol). After stirring at room temperature for 3 h, the resulting thick suspension was re-cooled to 0°C, treated with ammonium hydroxide solution (0.880 ammonia, 15 ml) and water (50 ml), then stirred at room temperature for 18 h. The solvent was removed under reduced pressure, and the residue was suspended in ethyl acetate (300 ml) and stirred at room temperature for 15 min. The resultant solid was collected by filtration, washed with ethyl acetate (50 ml), cold ethyl acetate/methanol (1 : 1, 50 ml) and water (50 ml), then dried at 50°C under vacuum to give 5′-amino-5′-deoxyguanosine **1**[1] (2.2 g, 78%) as a colourless solid: m.p. 219–220°C (from water) [m.p. 221°C[1]]; $[\alpha]_D - 41.6°$ (c 0.5, DMSO); λ_{max} (MeOH): 254 nm (ε 12600), 268 nm (sh) (ε 9100); (0.01 N HCl); 254 nm (ε 12000), 270 nm (sh) ε 8500); (0.01 N KOH): 264 nm (ε 10600); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.72 (1 H, dd, $J = 13.6$, 5.4 Hz, *H*-5′), 2.79 (1 H, dd, $J = 13.6$, 4.8 Hz, *H*-5′), 3.78 (1 H, m, *H*-4′), 4.08 (1 H, m, *H*-3′), 4.44 (1 H, m, *H*-2′), 4.5–5.6 (5 H, br, exchanged with D_2O), 5.66 (1 H, d, $J = 6.0$ Hz, *H*-1′), 6.47 (2 H, br, exchanged with D_2O, NH_2) and 7.93 (1 H, s, *H*-8) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 43.5, 70.6, 73.2, 85.6, 86.2, 116.7, 135.7, 151.3, 153.6 and 156.7 ppm; MS: (FAB positive ion) *m/e* 283 $[M+H]^+$. Found: C, 39.8, H, 5.3, N, 27.5%. $C_{10}H_{14}N_6O_4 \cdot H_2O$ requires C, 40.0, H, 5.33, N, 28.0%.

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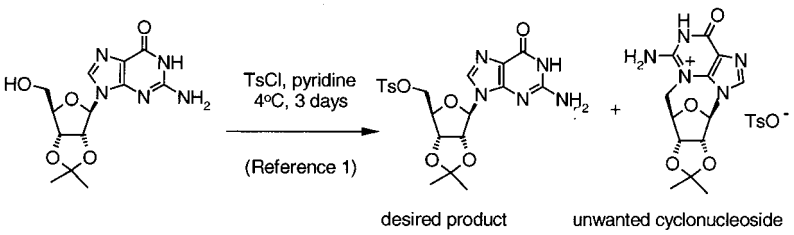

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Received in the UK February 12, 2001

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