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Facile Synthesis of O^6-Alkyl-, O^6-Aryl-, and Diaminopurine Nucleosides from 2′-Deoxyguanosine

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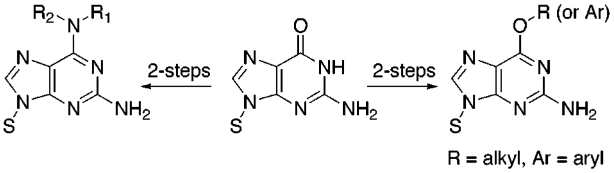
ABSTRACT



The 3′,5′-bis-O-TBDMS derivative of 2′-deoxyguanosine can be converted to its O^6-alkyl and O^6-aryl ethers as well as to N^6-substituted diaminopurine nucleosides in two simple steps. Also described is a novel, nonaqueous, one-step O^6-desulfonylation method that leads to deprotection of the carbonyl moiety of 2′-deoxyguanosine.

O^6-Alkylated derivatives of 2′-deoxyguanosine (dG) are extremely important for a variety of reasons. From a biological standpoint, alkylation at O^6 has been proposed to reduce the number of H-bonding sites in the guanine moiety which could lead to a mutagenic event.[1] In support of this hypothesis O^6-methyl and ethyl dG have been shown to produce G → A transitions.[2,3] Thus, *O*-alkyl guanines are of interest for mutagenesis and carcinogenesis studies. From a synthetic standpoint, several O^6-protected deoxyguanosine derivatives are precursors to electrophilic inosine nucleosides bearing leaving groups at the C-2 position.[4] On the basis of the severalfold importance of O^6-modified dG derivatives, we began to evaluate methods for their facile synthesis. In addition, we wanted to identify a strategy wherein a common intermediate could be converted not only to the O^6-alkyl derivatives but also to O^6-aryl as well as the biologically important 2,6-diaminopurine nucleosides.

Introduction of a sulfonate at the O^6 position of N^2-3′,5′-triacyl dG is well documented.[5,6] Such a derivative, when exposed to Me_3N, undergoes displacement of the sulfonate, producing a quaternary ammonium salt that has been converted to O^6-alkyl ethers.[5] However, we were interested only in protection of the carbohydrate hydroxyls and wanted to avoid acylation of the N^2. More recently, O^6-allyl 3′,5′-bis-*O*-TBDMS dG has been synthesized from an O^6-sulfonate precursor devoid of an amine protection, but the reaction requires the use of allyl alcohol as solvent.[7] This feature poses obvious problems when high-boiling, solid and/or expensive alcohols are utilized. Also, in our view, another major drawback of these procedures is the use of the unpleasant, highly volatile Me_3N (bp 3 °C).[5,7] Recognizing this, Reese

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[†] University of Oklahoma.

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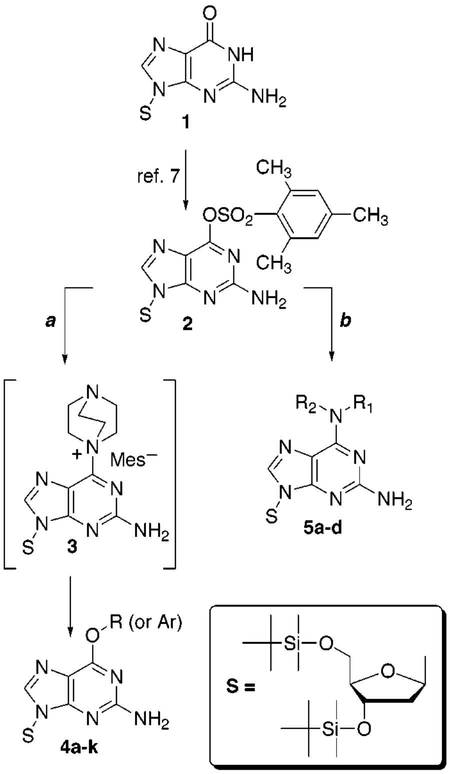
and Skone have used 1-methylpyrrolidine in place of Me_3N.[8] However, 1-methylpyrrolidine is relatively volatile (bp 80−81 °C), and only one example involving its use is reported.[8] Jones and co-workers have developed a protocol that does not utilize Me_3N.[9] This method, though very useful, utilizes sodium alkoxides which would be incompatible with silyl protecting groups. The Mitsunobu reaction offers entry to O^6-alkyl dG derivatives devoid of N^2 protection,[10] and the conditions are compatible with silyl protecting groups.[4,11] However, in many cases separation of products from residual reactants and byproducts is cumbersome. There are fewer routes to O^6-aryl dG derivatives. The methods of Jones[9] and Reese[12] for the preparation of some of these compounds provide the N^2-acylated products. We therefore became interested in developing a procedure that (a) was operationally simple, (b) provided 3′,5′-*O*-disilyl nucleoside products devoid of N^2 protection, (c) obviated the use of Me_3N, (d) did not require the reactant to be the reaction medium, and, importantly, (e) could be utilized to prepare a variety of compounds from a single precursor.

Recently, displacement of chloride from the C-6 position of purines by 1,4-diazabicyclo[2.2.2]octane (DABCO) has been demonstrated.[13,14] Although O^6-alkyl purines have been prepared from the ammonium salts with alkoxides, no applications of this method for the preparation of O^6-alkyl nucleosides have been reported.[14] For our studies the C-6 chloro derivative was not optimal due to the low-yielding (15%) chlorination of dG.[2] On the other hand, the easily prepared 3′,5′-bis-*O*-TBDMS O^6-mesitylenesulfonate of dG[7] (**2**) appeared to be a much better starting point. However, at the outset of our experimentation we could not be certain that DABCO would efficiently displace the mesitylenesulfonate (Mes) from the purine.

To test this critical step, we exposed **2** to DABCO in 1,2-dimethoxyethane (1,2-DME) at rt (Scheme 1). Much to our delight, immediate progress of the reaction was observed by TLC with the formation of a very polar, fluorescent spot. Within 45 min a precipitate, presumably salt **3**, began forming. Complete conversion of **2** to **3** required 13 h, but as described herein, it is not necessary to isolate **3** prior to the displacement step.

Preparation of the O^6-Alkyl and -Aryl Ethers of dG.[15] Synthesis of the O^6-alkyl or -aryl ethers (**2** → **4**) can be conveniently achieved as a two-step, one-pot reaction. To a solution of **2** in 1,2-DME (0.1 M) were added 4 Å molecular sieves (∼320 mg/mmol), the 1° alcohol[16] or phenol (5 molar equiv),[17] DABCO (2 molar equiv), and DBU (1.5 molar equiv). Reactions are normally complete within 24 h at rt. Upon completion, the reaction mixtures were diluted with EtOAc (reactions with alcohols) or Et_2O (reactions with phenols). Reaction mixtures with alcohols were extracted with H_2O, while those with phenols were initially extracted with 1 N NaOH to accomplish removal of excess (potentially recoverable) phenol, followed by H_2O extraction. When water-immiscible alcohols were used, excess alcohol was

Scheme 1



^{a} 1,2-DME, DABCO, DBU, R-OH (or Ar-OH), rt.
^{b} 1,2-DME, R-NH_2, 50 °C.

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[15] To a solution of **2** (0.074−0.15 mmol) in 1,2-DME were added DABCO, 4 Å molecular sieves, and the alcohol or phenol. After allowing the mixture to stir at room temperature for 30 min DBU was added. The mixture was allowed to stir at room temperature for 24 h and then diluted with either EtOAc (for reactions with alcohols) or Et_2O (for reactions with phenols). These mixtures were subjected either to aqueous extraction (reactions involving alcohols) or to sequential extractions with 1 N NaOH and H_2O (reactions involving phenols). The organic layer in each case was dried over Na_2SO_4 and evaporated. The crude products were chromatographed on silica gel using appropriate solvent systems.

[16] This reaction provides good yields with 1° alcohols. With a 2° alcohol (2-propanol) although the desired O^6-isopropyl ether was obtained, the yield was ∼15%. O^6-Isopropyl-3′,5′-bis-*O*-*tert*-butyldimethylsilyl-2′-deoxyguanosine: clear oil, R_f(silica/CH_2Cl_2) = 0.75. ^1H NMR (deacidified $CDCl_3$): 7.80 (s, $1H_8$), 6.23 (t, $1H_{1'}$, J = 6.4), 5.46 (sept, 1H, OC*H*, J = 6.2), 4.71 (s, 2H, NH_2), 4.51 (m, $1H_{3'}$), 3.87 (app q, $1H_{4'}$, J_{app} = 3.3), 3.74 (dd, $H_{5'}$, J = 4.3, 11.1), 3.65 (dd, $1H_{5'}$, J = 3.2, 11.1), 2.46 (app quint, $1H_{2'}$, J_{app} = 6.1), 2.24 (ddd, $1H_{2'}$, J = 3.6, 6.0, 13.1), 1.32 (d, 6H, CH_3, J = 6.2), 0.82, 0.81 (2s, 18H, t-Bu), 0.04−0.01 (3s, 12H, $SiCH_3$). HRMS calcd for $C_{25}H_{48}N_5O_4Si_2$ (M^+ + 1) 538.3245, found 538.3242.

[17] In the reaction involving EtOH, 10 molar equiv of the alcohol was used. The lower yield of **4b** compared to the other O^6-alkyl ethers may be due to competing elimination by deprotonation at the methyl group in **4b**.

readily removed by careful chromatography. Yields of both O^6-alkyl and -aryl ethers (**4a**−**4k**) were quite reasonable (see Figure 1).

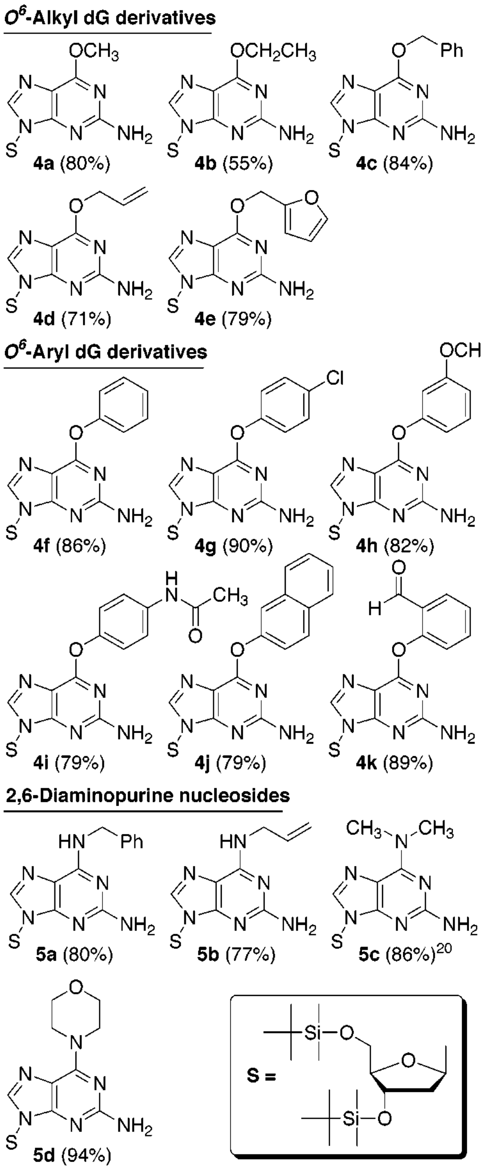

Figure 1. List of products prepared and yields.

Preparation of the N^6-Substituted Diaminopurine Nucleosides.[18] More commonly, N^6-substituted 2,6-diaminopurine nucleosides are also prepared by displacement of chloride from 2-amino-6-chloropurine nucleosides.[19] Again, based on the yield-limiting C-6 chlorination of dG, we reasoned that a direct S_NAr displacement of the sulfonate by amines would offer the simplest route to N^6-substituted diaminopurine nucleosides.

After initial experimentation we discovered that, unlike the reactions with alcohols and phenols which proceed at rt, reactions with amines required elevated temperatures. At 50 °C, these reactions proceeded smoothly to provide the N^6-substituted diaminopurine nucleosides (**5a**−**5d**) in good yields (see Figure 1).

Some features of and products from these reactions are noteworthy. For example, the O^6-benzyl and -allyl derivatives (**4c**, **4d**), which are intermediates in the synthesis of electrophilic nucleosides,[4,11] can be conveniently prepared without the need for the Mitsunobu reaction. The relatively exotic furfuryl derivative **4e** can be synthesized in good yield.

Noteworthy among the O^6-aryl derivatives, the *N*-acetyl moiety of *N*-acetylaminophenol, remains unaffected during the course of the reaction (**2** → **4i**). The amino group in **4i** can be deprotected and utilized for additional functionalization. Reaction of salicylaldehyde is also interesting. Despite the presence of the *o*-carbonyl group, salicylaldehyde reacts smoothly to provide **4k** in high yield. In this case also, the aldehyde functionality offers a site for subsequent functionalization.

At this stage we were interested in evaluating whether the Mes group in **2** could be used as a transient O^6-protection for dG, which could be displaced in a manner that would effect restoration of the dG carbonyl. Although **4c** and **4d** can be deprotected,[4a,b,7] additional steps are involved. We wanted to exploit the chemistry described herein for developing a nonaqueous, one-step procedure. It is known that the 2-cyanoethoxy group can be cleaved under basic conditions.[21] The question that remained was whether introduction and removal of an O^6-cyanoethyl group could be accomplished in one-step.

When **3** (produced in situ from **2**) was subjected to the reaction conditions with 2-cyanoethanol (Scheme 2), a single product (**1**) was obtained in 81% yield. This is the first example of a one-step desulfonylation at the C-6 position of purine nucleosides and shows that the Mes group, which can be readily removed under nonaqueous conditions, can be used for O^6-protection.

Mechanistically, we believe the reaction proceeds through the ammonium salt **3** and not by attack of the alcohol at the sulfur. This is because the desulfonylation is not observed in reactions with other alcohols. Thus, we propose that salt **3** reacts with 2-cyanoethanol as shown in Scheme 2 to produce the O^6-cyanoethyl derivative, which subsequently undergoes deprotection under the reaction conditions to furnish the 3′,5′-bis-*O*-TBDMS derivative of dG (**1**).

In conclusion, we have developed a very convenient and concise strategy for the synthesis of O^6-alkyl, O^6-aryl, and

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[18] Reactions with amines were performed in an identical fashion to those with alcohols or phenols,[15] except that DABCO and DBU were not added. Additionally, these reactions were conducted at 50 °C. For reactions involving nonvolatile amines, reaction workup consisted of dilution with EtOAc, followed by sequential extractions with 10% aqueous citric acid and saturated aqueous $NaHCO_3$. For water miscible or volatile amines, dilution of the reaction mixture with EtOAc was followed by aqueous extraction. In each instance drying of the organic layer over Na_2SO_4, evaporation, and chromatography provided the pure products.

[19] For examples, see: (a) Trivedi, B. K.; Bruns, R. F. *J. Med. Chem.* **1989**, *32*, 1667−1673. (b) Trivedi, B. K. *Nucleosides Nucleotides* **1988**, *7*, 393−402.

[20] For the reaction involving dimethylamine, a 2 M THF solution of the amine (5 molar equiv) was used. The overall molarity of the reaction mixture was adjusted to 0.1 M with 1,2-DME.

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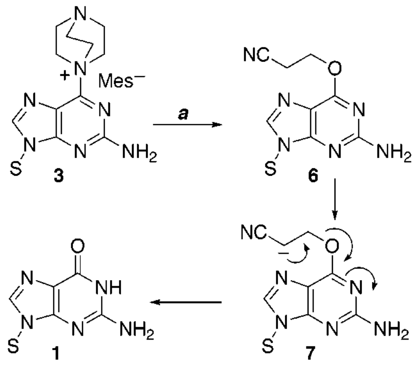
Scheme 2



^{a} 1,2-DME, DBU, $NCCH_2CH_2OH$, rt.

N^6-substituted diaminopurine nucleosides from 2′-deoxyguanosine. The reactions proceed smoothly with a variety of 1° alcohols, with phenols having different substituents and substitution patterns, as well as with 1° and 2° amines. Furthermore, since a single intermediate can be converted in a facile manner to a wide variety of compounds, this chemistry can be easily incorporated either into combinatorial technology or automated parallel synthesis. In addition, we have delineated a novel one-step desulfonylation that has important potential applications. For instance, the O^6-mesitylenesulfonate could serve as a dG protecting group during oligonucleotide assembly and can be removed using nonaqueous conditions. More interestingly, this method offers the possibility for facile isotopic labeling of the carbonyl groups in dG and other hypoxanthine nucleosides through the use of $H^{18}OCH_2CH_2CN$.

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Supporting Information Available: Compilation of the proton NMR and HRMS data for **4a**−**4k** and **5a**−**5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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