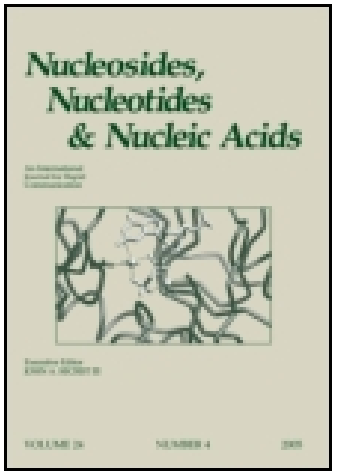

Nucleosides and Nucleotides
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn19

A Serendipitous Synthesis of 8-Dimsyl-2′-deoxyguanosine

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Published online: 04 Oct 2006.

To cite this article: Satyam Nampalli , Inna Livshin & Shiv Kumar (1999) A Serendipitous Synthesis of 8-Dimsyl-2′-deoxyguanosine, Nucleosides and Nucleotides, 18:4-5, 697-699, DOI: 10.1080/15257779908041545

To link to this article: http://dx.doi.org/10.1080/15257779908041545

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 697-699 (1999)

A SERENDIPITOUS SYNTHESIS OF 8-DIMSYL-2'-DEOXYGUANOSINE

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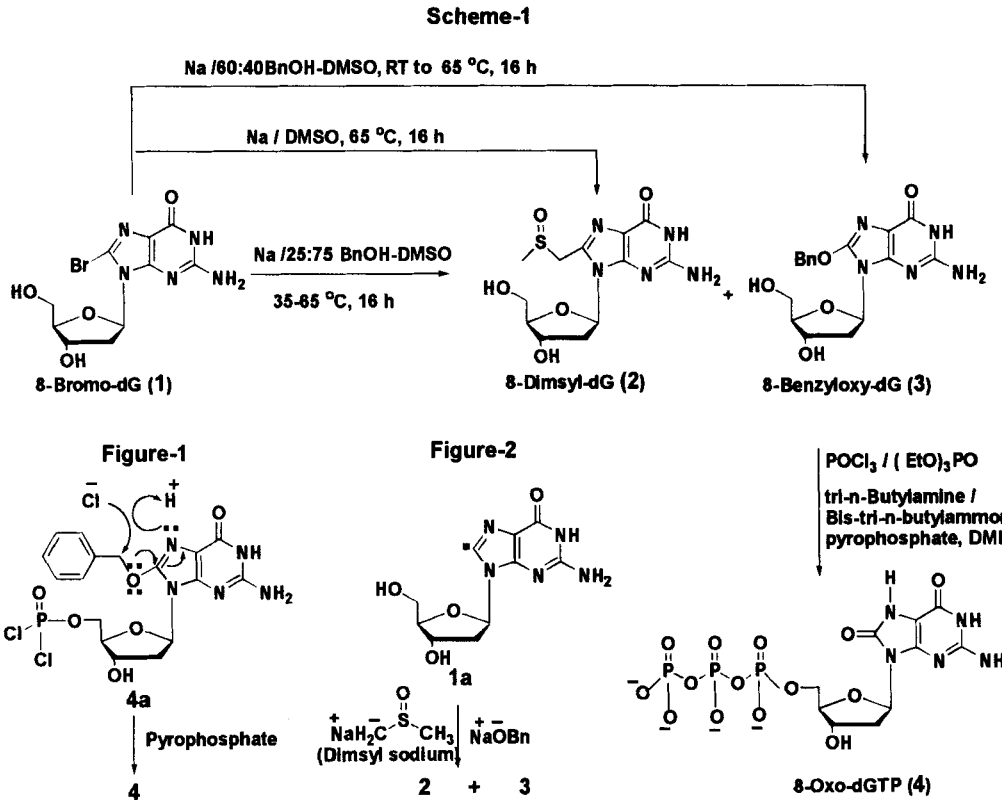
ABSTRACT: A serendipitous synthesis of 8-dimsyl-dG (**2**) has been achieved along with the known 8-benzyloxy-dG (**3**) in a nucleophilic substitution reaction of 8-bromo-dG (**1**) with *in situ* generated dimsyl and benzyloxy sodium. Compound **3** was directly converted into the mutagenic oxidative DNA damage product, 8-oxo-dGTP (**4**).

As part of the research program directed towards the development of a random mutagenesis[1] kit, we needed to synthesize oxidative[2] DNA damage product, 8-Oxo-dGTP (**4**) (**Scheme-1**) in commercially viable quantities. 8-Bromo-2'-deoxyguanosine[3] (**1**) has been widely used to synthesize 8-substituted-2'-deoxyguanosine derivatives for different purposes[4]. We have decided to make use of suitably protected 8-benzyloxy-2'-deoxyguanosine (**3**), derivable from compound **1** for phosphorylation at the 5'-OH group in the face of problems encountered in achieving direct oxidation of dGTP[5] to yield 8-oxo-dGTP (**4**).

In an attempt to prepare **3** from **1** following the literature procedure[6], sodium metal dissolution in a 2.5:7.5 BnOH:DMSO mixture appeared to be taking a long time at room temperature. Heating the reaction mixture at 35 °C for an hour ensured complete dissolution of the sodium metal. Addition of 8-bromo-dG (**1**) to the warm sodium dissolved solution and further heating at 65 °C for 16 h resulted in an unexpected 8-dimsyl-2'-deoxyguanosine (**2**)[7] as the major (45%) and 8-benzyloxy-2'-deoxyguanosine (**3**) as the desired, minor (25%) compounds.

In contrast, addition of 8-bromo-dG (**1**) to the clearly dissolved solution of sodium metal in a 60:40 BnOH:DMSO mixture, at room temperature and heating at 65 °C, exclusively afforded the desired compound **3** in 80% yield. In the absence of BnOH, heating 8-bromo-dG (**1**) in sodium metal dissolved solution of DMSO at 65 °C for 16 h provided 8-dimsyl-dG (**2**) in 35% yield.SRN1 free radical[8] mechanism (**Figure-1**) has been



invoked to have been operated to help explain the formation of compounds **2** and **3** via iminyl radical (**1a**)being attacked by dimsyl sodium[9] and sodium benzyloxide.

Having obtained the desired 8-benzyloxy-dG (**3**) in an improved yield, it was phosphorylated to directly produce 8-oxo-dGTP (**4**) in 45% yield. Mechanistically (**Figure-2**), *in situ* generated HCl from the reaction of **3** with $POCl_3$ is believed to have catalyzed the cleavage of benzyl iminol ether in 5'-dichlorophosphate intermediate (**4a**), which upon treatment with pyrophosphate directly generated 8-oxo-dGTP (**4**).

In summary, a serendipitous formation of 8-dimsyl-dG (**2**) has been unraveled along with the desired 8-benzyloxy-dG (**3**), which was converted directly into 8-oxo-dGTP (**4**), needed for the development of a random mutagenesis kit. SRN1 mechanistic pathway for the formation of hitherto unknown 8-dimsyl-dG (**2**) as well as 8-benzyloxy-dG (**3**) and HCl catalyzed pathway for the cleavage of benzyl group in **3** during phosphorylation to 8-oxo-dGTP (**4**) have been invoked.

Currently, efforts are underway to convert 8-dimsyl-dG (**2**) to its triphosphate, 8-dimsyl-dGTP and study its DNA polymerase substrate activity including anti-HIV.

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7. 'H-NMR (DMSO-d_6): δ (ppm) 10.65 (1H, bs, D_2O exch. NH), 6.37 (2H, bs, D_2O exch. NH_2), 6.13 (1H, dd, J= 6.0 Hz, 9.0Hz, 1'-H), 5.24 (1H, d, J = 6.0 Hz, D_2O exch. 3'-OH), 4.86 (1H, t, J = 6.0 Hz, D_2O exch. 5'- OH), 4.35 (1H, m, 3'-H), 3.80 (1H, m, 4'-H), 3.56 (2H, m, 5'-H_2), 3.30 (1H, m, CH_a-SO-CH_3), 2.97 (1H, m, 2'-H_a), 2.82 (1H, m, CH_a-SO-CH_3), 2.58 (3H, s, -SO-CH_3), 2.08 (1H, m, 2'-H_b). UV: (Tris, pH 7.4) λmax 271 nm. $C_{12}H_{17}N_5O_5S$: Calculated S, 9.33; Found S, 9.78.
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