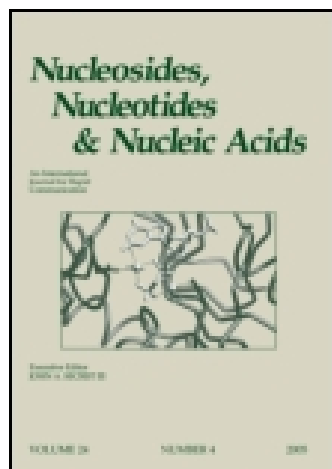


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Satyam Nampalli^a, Inna Livshin^a & Shiv Kumar^a

^a Amersham Pharmacia Biotech, 26111 Miles Road, Cleveland, OHIO, 44128, USA

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

Satyam Nampalli, Inna Livshin and Shiv Kumar*

Amersham Pharmacia Biotech, 26111 Miles Road, Cleveland, OHIO, USA 44128.

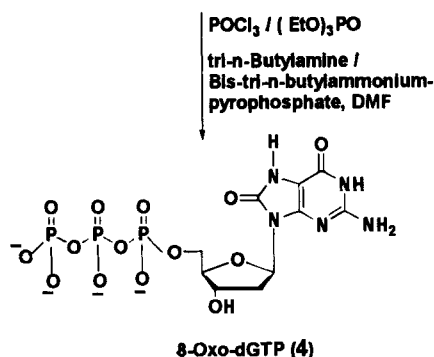
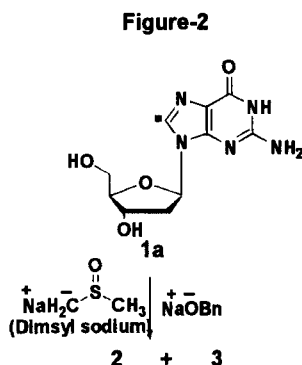
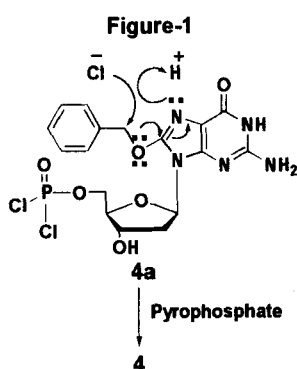
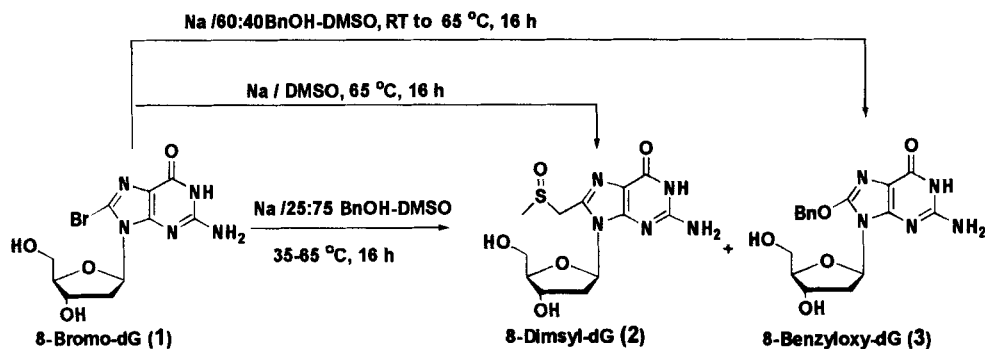
ABSTRACT: A serendipitous synthesis of 8-dimsyl-dG (**2**) has been achieved along with the known 8-benzyloxy-dG (**3**) in a nucleophilic substitution reaction of 8-bromo-dG (**1**) with *in situ* generated dimsyl and benzyloxy sodium. Compound **3** was directly converted into the mutagenic oxidative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

As part of the research program directed towards the development of a random mutagenesis¹ kit, we needed to synthesize oxidative² DNA damage product, 8-Oxo-dGTP (**4**) (**Scheme-1**) in commercially viable quantities. 8-Bromo-2'-deoxyguanosine (**1**) has been widely used to synthesize 8-substituted-2'-deoxyguanosine derivatives for different purposes⁴. 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 dGTP⁵ to yield 8-oxo-dGTP (**4**).

In an attempt to prepare **3** from **1** following the literature procedure⁶, 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 radical⁸ mechanism (**Figure-1**) has been

Scheme-1



invoked to have been operated to help explain the formation of compounds 2 and 3 via iminyl radical (1a) being attacked by dimsyl sodium⁹ 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 POCl₃ 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. ¹H-NMR (DMSO-d₆): δ (ppm) 10.65 (1H, bs, D₂O exch. NH), 6.37 (2H, bs, D₂O exch. NH₂), 6.13 (1H, dd, J= 6.0 Hz, 9.0Hz, 1'-H), 5.24 (1H, d, J = 6.0 Hz, D₂O exch. 3'-OH), 4.86 (1H, t, J = 6.0 Hz, D₂O exch. 5'-OH), 4.35 (1H, m, 3'-H), 3.80 (1H, m, 4'-H), 3.56 (2H, m, 5'-H₂), 3.30 (1H, m, CH₂-SO-CH₃), 2.97 (1H, m, 2'-H_a), 2.82 (1H, m, CH₂-SO-CH₃), 2.58 (3H, s, -SO-CH₃), 2.08 (1H, m, 2'-H_b). UV: (Tris, pH 7.4) λ_{max} 271 nm. C₁₂H₁₇N₅O₅S: Calculated S, 9.33; Found S, 9.78.
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