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AN IMPROVED SYNTHESIS OF 8-BROMO-2'-DEOXYGUANOSINE

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ABSTRACT: A new synthesis of 8-bromo-2'-deoxyguanosine, a key intermediate in the synthesis of the mutagenic DNA adduct 8-oxo-2'-deoxyguanosine is described. The advantages of this method are significantly improved yields and ease of isolation.

The DNA adduct 8-oxo-2'-deoxyguanosine (**4**) has received considerable attention in recent years as a consequence of its importance in carcinogenesis[1,2]. Studies based on this adduct require its preparation for use as an HPLC standard, as an intermediate in the synthesis of oligonucleotides containing this adduct, etc.[3,4] The synthesis of **4** usually requires the preparation of 8-bromo-2'-deoxyguanosine (**2**).[5,6] In subsequent steps, **2** is readily converted to its benzyloxy derivative[3] and then hydrogenated to **4** (Figure 1).

The previously described preparations of **2** are based on the direct bromination of 2'-deoxyguanosine (**1**) with bromine in water. However, the success of these procedures is strongly dependent upon the reaction conditions. This is due to the acidic nature of the reaction conditions due to the generation of HBR which can cause the cleavage of the acid labile glycosidic bond[7]. In addition

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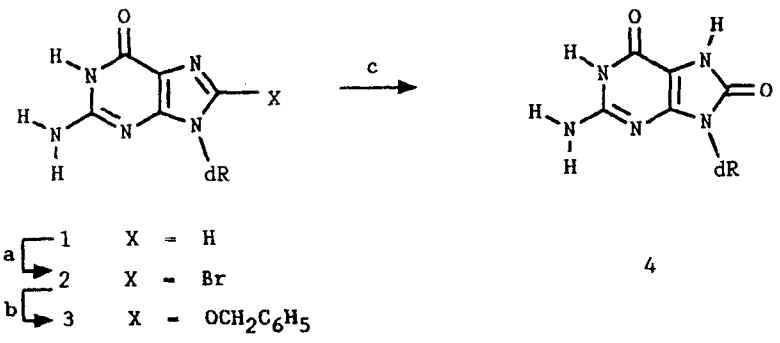

a) Br_2, H_2O, b) $C_6H_5CH_2ONa$, DMSO, 65°C, 18 h, c.) H_2, 10% Pd/C, Ethanol.

FIG 1

the product readily undergoes further reaction with bromine.[8,9] Finally, the product must be purified by HPLC since attempts to recrystallize **2** tend to lead to its decomposition.

Our requirement for gram quantities of **4** lead us to explore alternative methods for the synthesis of **2**. For this purpose we examined the N-bromoamides N-Bromoacetamide (NBA) and N-Bromosuccinimide (NBS). These reagents were selected based on their prior use as nucleoside brominating agents[8] and that the bromination can be carried out under neutral conditions.

The reaction conditions used in this study are shown in Table I. As shown, the reaction was carried out with either 2'-deoxyguanosine (**1**) or its 3',5'-diacetyl (**5**) or 3',5'-di-triisopropylsilyl (**6**) derivative. The reaction conditions which lead

Table I. Yields of 2 obtained from the Reaction of 1 with NBA and NBS.[a]

Entry	Starting Material	N-Bromoamide (Equivalents)	Solvent	Time (min)	Volume (mL)	Yield[b] 2
1	1	NBA (1.1)	H_2O	120.0	1.0	79
2	1	NBA (1.1)	H_2O	120.0	2.5	82
3	1	NBA (1.1)	H_2O	120.0	5.0	64
4	1	NBA (1.1)	DMF	c	2.5	NR
5	5	NBA (1.1)	$CHCl_3$	120.0	5.0	17
6	1	NBS (1.2)	H_2O	2.0	40.0	40
7	1	NBS (1.2)	H_2O	3.0	8.0	80
8	1	NBS (1.2)	H_2O	4.0	4.0	85
9	1	NBS (1.5)	H_2O	10.0	3.0	92
10	1	NBS (1.5)	H_2O	15.0	3.0	94
11	6	NBS (1.0)	DMF	d	2.0	38
12	7	NBA (1.5)	H_2O	d	5.0	<5

[a]All reaction mixtures contained 0.1 mmole 1. Abbreviations: N-Bromoacetamide (NBA), N-Bromosuccinimide (NBS), Triisopropylsilyl chloride (TIPS) [b]Yields are for the isolated product (2). [c]The reaction was allowed to proceed for 48 h. [d]Reaction time 48 h.

to the best yields of 2 used 1 as substrate, NBS as the brominating agent, and water as the reaction solvent (Table I, entry 10). The most significant aspect of the procedure presented here is that the product is isolated by simple filtration of the reaction mixture and is at least 99% pure by NMR and HPLC analysis.[11]

The bromination of 2'-deoxyadenosine (7) with NBA and NBS has also been explored. In this case no reaction was observed under conditions that brominated 1 (eg 1.1-1.5 equivalents NBA or NBS, 15 min). Allowing the reaction to run for 48 hours did not alter this much and less than 5% 8-bromo-2'-deoxyadenosine was produced.

It should be noted that while the procedure is simple, it does require some care with regard to the $1/H_2O$ ratio, the time for reaction to insure complete bromination, and the number of equivalents of brominating agent added. For example, if the $1/H_2O$ is small (compare entry 6 to 7) the yield decreases. The effect is due, in part, to the relative solubilities of **2** and **1**. At smaller ratios of $1/H_2O$ the solubility of **2** is such that less precipitates out of solution. Likewise, 1.1-1.5 equivalents of NBA or NBS should be used. Less than 1.1 equivalents produces an impure product while greater than 1.5-2.0 equivalents results in decreased yields. This is likely due to reaction of **2** with the excess brominating agent.

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10.) HPLC analysis: Elution solvent 1:9 methanol/water, flow 2 mL/min, UV detection at 263 nm, column: Waters Resolve C_{18}, 10 μm, 8mm x 100mm, Retention times: **1** 6.5 min, 8-bromoguanine 8.4 min, **2** 28.0 min. ^1H NMR analysis: Spectra of the product were obtained in D_2O. The presence of **1** in the sample could be determined by appearance of resonances at 7.904 and 6.410 ppm corresponding to the C-H^8 and H-1' protons, respectively, of **1**.

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