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Unexpected Reactivity of N^2-Benzylidene Guanosine Derivatives

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Abstract

Guanosine derivatives masked at the sugar are protected at N^2 by a benzylideneamine group for the first time. The free 5'-hydroxyl function reveals to be incompatible with the N^2-protective group that is then rapidly hydrolyzed to regenerate the free exocyclic amine.

Keywords: Guanosine; benzylidene; protective group; hydrolysis.

For the chemical synthesis of modified nucleosides and nucleotides for biological evaluation considerable efforts have been undertaken. Most of the time such chemistry requires multiple protection and deprotection steps. The diversity of the target structures, as well as that of the chemical reactions involved, continuously requires the development of new protective groups and derivatization procedures.

In the course of our work on the synthesis of enzymatically non-hydrolyzable analogues of guanosine di- and triphosphate (GDP, GTP), we needed to protect the exocyclic primary amine in guanosine in such a way that the deprotection step could be achieved by hydrogenolysis. The use of the benzyl carbamate (Cbz) protective group however proved to be incompatible with some further transformations of our compounds due to the presence of a somehow acidic proton on the N^2-position of guanosine. In order to alleviate that difficulty, we wished to mask the primary amine as a *N*-benzylideneamine[1]. To our knowledge, there is no example in the literature of a guanosine or guanosine derivative masked at N^2 by an imine, except for the tricyclic nucleoside **2** which has been prepared by reacting guanosine **1** with malonaldehyde, generated *in situ* from tetraethoxypropane, in a yield which did not exceed 25 % (Sch. 1)[2,3].

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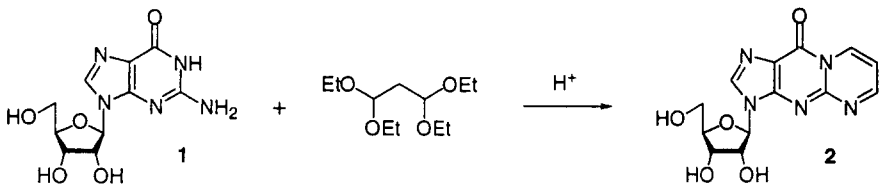
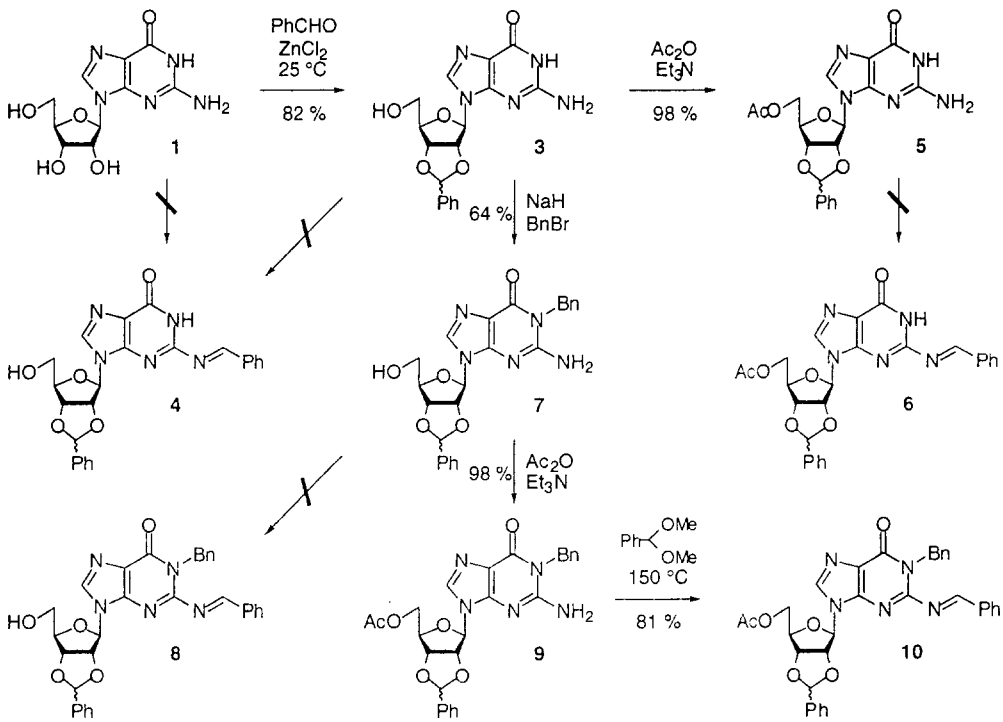


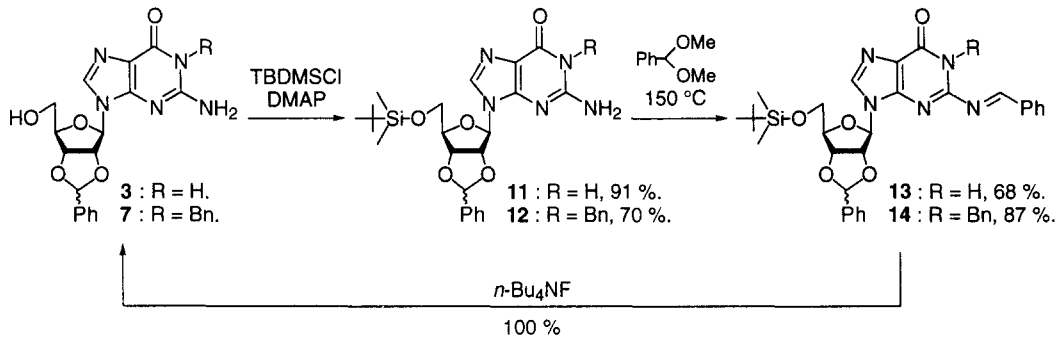
- Scheme 1 -

Herein we have explored the reaction sequences described in Scheme 2 in order to introduce an *N*-benzylideneamine protective group at N^2 on different guanosine derivatives. All our attempts to transform compounds **1** and **3**[4,5] directly into 2',3'-*O*-benzylidene-N^2-benzylidene guanosine **4** , or 5'-*O*-acetyl-2',3'-*O*-benzylidene guanosine **5** into **6**, invariably failed. Besides, compound **3**, in the presence of NaH reacted with benzyl bromide to give N^1-benzyl-2',3'-*O*-benzylidene guanosine **7**[6] . The latter compound could not be directly protected at its exocyclic amine function to give **8**, whatever the reaction conditions used. Nevertheless, acetylation of compound **7** into **9** did allow the subsequent introduction of the amine protective group by heating the compound in benzaldehyde dimethyl acetal at 150 °C for 24 hours, giving guanosine derivative **10**[7] in 81 % yield.



- Scheme 2 -

When compound **10** was treated with potassium carbonate (0.1 eq.) in $MeOH/H_2O$, a reaction occurred to produce quantitatively compound **7** within 15 minutes. The use of an excess of potassium carbonate (1.5 eq.) did not change the course of the reaction. The simultaneous removal of the 5'-*O*-acetyl and N^2-benzylidene protective groups is somehow unexpected as imines are supposed to be fairly stable in basic conditions[1]. In order to avoid the use of basic reaction conditions for the deprotection of the 5'-hydroxyl group, 5'-*O*-*t*-butyldimethylsilyl derivatives were prepared (Sch. 3).



- Scheme 3 -

Compounds **3** and **7** were silylated following a standard procedure to yield **11** and **12**, and the exocyclic primary amines could be masked as benzylideneamines in the conditions described above to give compound **13**[8] and **14**[9]. Compound **13** was unstable and could not be fully purified. Treatment with tetrabutylammonium fluoride quantitatively produced compound **4** that decomposed into **3** over silica gel (treated or not with Et_3N) and on standing in chloroform at room temperature. Compound **14** revealed more stable than **13** and could be satisfactorily purified. Desilylation however quantitatively produced compound **7** and the intermediate nucleoside **8** could not be isolated.

Though the instability of the imine function in compounds **4** and **8** is actually not understood, it is assumed that the free 5'-hydroxyl group is directly responsible for its hydrolysis in these guanosine derivatives, which is fully consistent with the failure to introduce the imine protective group in compounds **1**, **3** and **7**.

In summary, for the first time a benzylideneamine group is introduced at the N^2-position of guanosine derivatives. The transformation requires prior masking of the ribose hydroxyl groups and reveals to be moderately stable unless the purine base is alkylated at N^1. Regeneration of the 5'-hydroxyl function unexpectedly and quantitatively induces the hydrolysis of the imine at N^2.

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7. Selected spectral data for compound **10** (mixture of 2 diastereomers). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 9.01 and 8.99 (2s, 1H); 8.02 and 7.98 (2s, 1H); 7.65-7.19 (m, 15H); 6.27 and 6.20 (2d, *J* = 2.2 Hz, 1H); 6.21 and 6.06 (2s, 1H); 5.65 (s, 2H); 5.47-5.38 (m, 1H); 5.13-5.03 (m, 1H); 4.69-4.52 (m, 1H); 4.48-4.27 (m, 2H); 2.03 (s, 3H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 170.34; 167.34; 157.20; 156.47; 146.30; 138.45; 138.32; 137.20; 135.57; 134.36; 133.90; 130.56; 129.95; 129.13; 128.43; 127.46; 126.60; 126.46; 123.08; 108.06; 104.62; 89.71; 85.28; 83.93; 82.28; 81.34; 63.93; 45.99; 20.59. MS (CI/NH_3): 592 $[M+H]^+$.
8. Selected spectral data for compound **13** (mixture of 2 diastereomers). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.35 and 9.34 (2s, 1H); 8.10 and 8.06 (2s, 1H); 7.66-7.39 (m, 10H); 6.37 (d, *J* = 3.0 Hz, 0.5H); 6.32 (d, *J* = 2.6 Hz, 0.5H); 6.25 and 6.11 (2s, 1H); 5.34 (dd, *J* = 2.6, 6.4 Hz, 0.5H); 5.26 (dd, *J* = 3.0, 6.4 Hz, 0.5H); 5.19 (d, *J* = 3.4, 6.0 Hz, 0.5H); 5.09 (dd, *J* = 2.3, 6.4 Hz, 0.5H); 4.61 (td, *J* = 3.6, 2.3 Hz, 0.5H); 4.48 (td, *J* = 3.7, 3.7 Hz, 0.5H); 3.96-3.89 (m, 2H); 0.91 and 0.88 (2s, 9H); 0.10, 0.08, 0.07 and 0.06 (4s, 6H).
9. Selected spectral data for compound **14** (mixture of 2 diastereomers). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.06 and 9.05 (2s, 1H); 8.14 and 8.12 (2s, 1H); 7.64-7.17 (m, 15H); 6.33 (d, *J* = 3.0 Hz, 0.5H); 6.27 (d, *J* = 2.6 Hz, 0.5H); 6.22 and 6.08 (2s, 1H); 5.70 and 5.69 (2s, 2H); 5.34 (dd, *J* = 2.6, 6.4 Hz, 0.5H); 5.25 (dd, *J* = 3.0, 6.0 Hz, 0.5H); 5.15 (dd, *J* = 3.8, 6.4 Hz, 0.5H); 5.06 (dd, *J* = 2.3, 6.4 Hz, 0.5H); 4.57 (m, 0.5H); 4.45 (m, 0.5H); 3.77-3.58 (m, 2H); 0.89 and 0.86 (2s, 9H); 0.07 (d, *J* = 4.9 Hz, 3H); 0.04 (d, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 9167.63 and 167.60; 157.52 and 157.49; 156.37; 156.22; 137.67 and 137.60; 133.99 and 133.95; 133.65; 130.76; 130.30; 129.27; 128.71; 128.68; 128.57; 128.50; 126.89; 126.67; 122.75; 107.79 and 104.54; 90.08 and 89.57; 86.28 and 85.66; 85.82 and 84.90; 82.87 and 81.00; 63.62 and 63.44; 46.10 and 46.07; 26.05 and 26.02; 18.51; -5.25 and -5.32. MS (CI/NH_3): 680 $[M+H]^+$.