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Synthesis of biologically active N^2-amine adducts of 2′-deoxyguanosine

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Abstract

Several biologically important N^2-adducts of 2′-deoxyguanosine (dG) that previously were difficultly accessible, have been synthesized directly by means of the Buchwald–Hartwig reaction. The reaction employed in each case involves the coupling of 2′-deoxy-2-bromoinosine with the appropriate amine. Deprotection in all cases gave good yields of the desired 2-alkylated or -arylated deoxynucleoside.

Keywords: 2′-deoxyguanosine; N^2-adducts; Buchwald–Hartwig reaction.

The N^2 position of deoxyguanosine residues in DNA appears to be one of the biologically most important sites for modification by mutagenic substances. In recent years a variety of methods for the synthesis of such N^2-substituted derivatives of the dG have been reported.[1–4] Most of these processes are either compound specific or limited in scope. In general, flexibility in terms of product range is poor and overall yields are in most cases only modest. One apparent exception is the method of Steinbrecher et al.[2] who reported that the triflate esters of hydroxypurines will react with aliphatic and aryl amines to give the corresponding exocyclic *N*-alkyl or *N*-aryl deoxynucleosides in good yield. However, our experience with this approach has been that the triflates are difficult to prepare and the yields are capricious.[5] Recently, in searching for a method that would be reliable and efficient, we examined[6] the coupling of *o*-nitroaryl triflates or bromides with protected forms of 2′-deoxyguanosine and 2′-deoxyadenosine using the conditions of the Buchwald–Hartwig reaction. This gave high yields of the 2-nitroaryl derivatives of dG and dA arylated at the exocyclic amine group (Scheme 1; illustrated for dG only). However, it cannot be used with alkyl or aralkyl halides.

Now we present an alternative approach which allows the synthesis of essentially any N^2-(carbon-coupled) derivative of 2′-deoxyguanosine reproducibly and in excellent yield. The new method is

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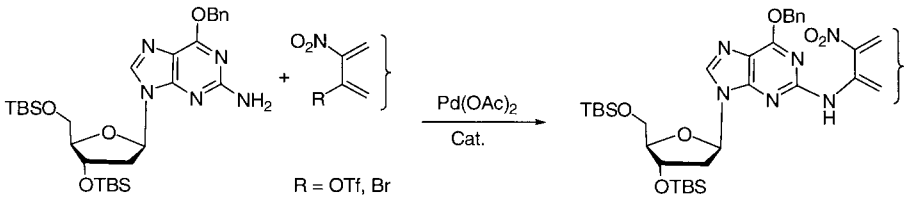
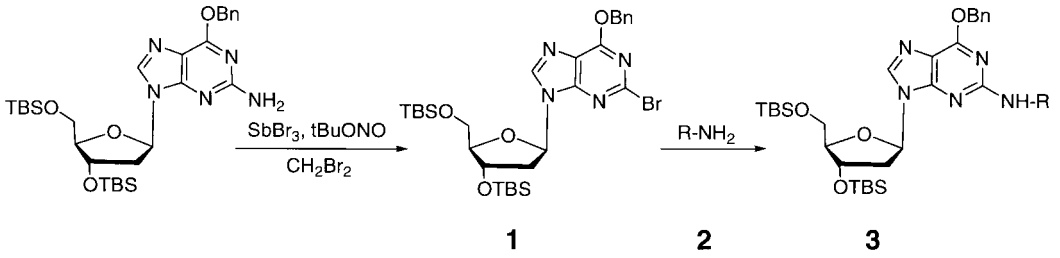


Scheme 1.

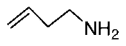
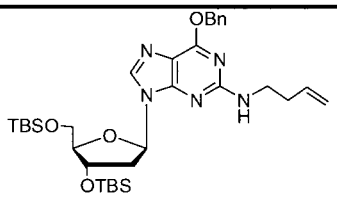
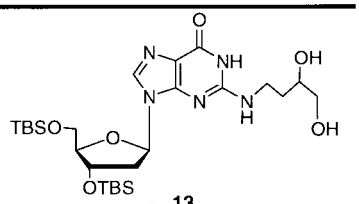
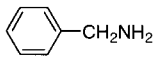
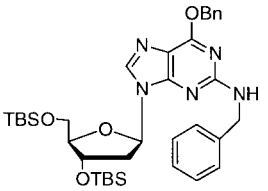
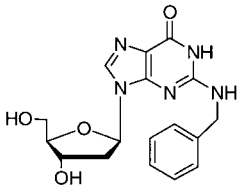
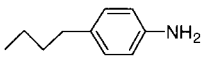
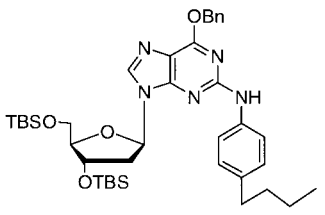
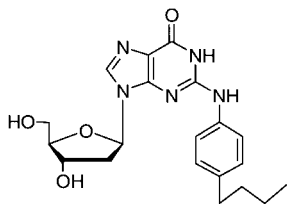
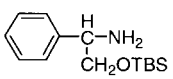
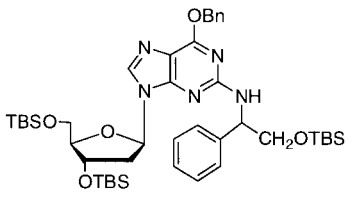
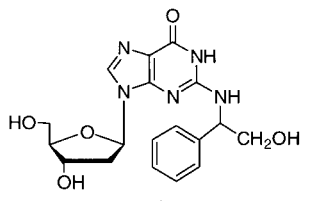
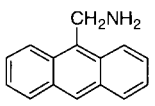
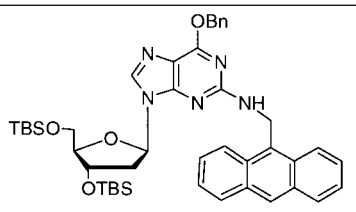
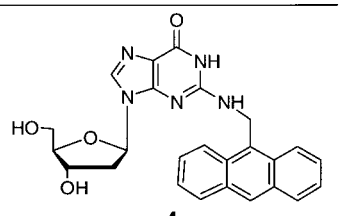
essentially the inverse of the above process in that a bromopurine is coupled to an amine. This is similar both to the procedure that Hopkins[7] and we ourselves[8] used previously for the synthesis of the cross-linked adducts of dG and to the work of Lakshman[9] who coupled 6-bromo-2′-deoxynebularine with a series of aromatic amino compounds. The synthetic strategy (Scheme 2) again involves a palladium-catalyzed amination reaction, this time between 2-bromo-O^6-benzyl-3′,5′-bis-*O*-*tert*-butyldimethylsilyl-2′-deoxyinosine (**1**) and a series of aryl or alkyl amines (**2a**–**2e**) in the presence of the complexing agent 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) and cesium carbonate, as the base[10]. The protected 2-bromo-2′-deoxyinosine (**1**) was prepared as previously described.[8,11] The results of the coupling reactions are given in Table 1. All reactions were carried out at 80°C in toluene with the exception of **2e** in which case THF was the solvent of choice because of solubility problems with toluene.



Scheme 2.

Each of the products **3** was then converted by conventional chemistry in high yield to the desired compound **4**, known from previously published work. In all cases, except for that of **3e** (where reduction of the central ring of the anthracene group is facile), the benzyl group was removed by catalytic hydrogenation over a 10% Pd/C catalyst. Compound **3e** was debenzylated by means of trimethylsilyl iodide in boiling THF.[12] The *tert*-butyldimethylsilyl (TBS) protecting groups were then easily removed by 1 M TBAF in THF, to give in each case the known reference compound **4** in good to excellent yield (Table 1). In all cases the ^{1}H NMR, ^{13}C NMR and FAB mass spectral data were identical to those previously reported. Compound **4a** is an intermediate that was used by our group to generate[13] an acrolein adduct site-specifically in oligomeric DNA whereas **4b**[14] was simply the pilot compound for the series. Both compound **4c** and its 5′-*O*-triphosphate, powerful inhibitors of specific DNA polymerases, were available[15] previously only by total synthesis from guanine and 2′-deoxyribose. The α-phenylglycidol adduct **4d** is a known[1] surrogate for the coupling of the aminotriol derivatives of the polycyclic aromatic hydrocarbons such as the precarcinogen benzo[*a*]pyrene. Finally **4e**, a hydrocarbon adduct of dG that has been

Table 1
Reaction of amines with 2-bromo-2′-deoxyinosine

Amine	N^2-adduct of dG (yield)	Reference Compound
 **2a**	 **3a** (90%)	 **4a**[13]
 **2b**	 **3b** (88%)	 **4b**[14]
 **2c**	 **3c** (93%)	 **4c**[15]
 **2d**	 **3d** (94%)	 **4d**[1]
 **2e**	 **3e** (40%)	 **4e**[4]

incorporated into oligomeric DNA for biological studies, has been available[4] by a four-step elegant synthesis from 2′-deoxyguanisine, but in only ~12% overall yield.

The advantages of the method now reported for the synthesis of these N^2-derivatives of dG are its simplicity, its versatility and the excellent yields that are achievable. Further studies on the application of the Buchwald–Hartwig reaction to the synthesis of other substituted nucleosides are in progress.

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References

1. Harris, C. M.; Zhou, L.; Strand, E. A.; Harris, T. M. *J. Am. Chem. Soc*. **1991**, *113*, 4328–4329.
2. Steinbrecher, T.; Wameling, C.; Oesch, F.; Seidel, A. *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 404–406. Edwards, C.; Boche, G.; Steinbrecher, T.; Scheer, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1887–1893.
3. Bonala, R. R.; Yu, P.-L.; Johnson, F. *Tetrahedron Lett*. **1999**, *40*, 597–598.
4. Casale, R.; McLaughlin, W. *J. Am. Chem. Soc*. **1990**, *112*, 5264–5271. Kasai, H.; Goto, M.; Ikeda, K.; Zama, M.; Mizuno, Y.; Takemura, S.; Matsuura, S.; Sugimoto, T.; Goto, T. *Biochemistry* **1976**, *15*, 898–904.
5. See, however, a recent paper by Nechev et al. who have successfully used such a triflate in a post-synthetic coupling of aliphatic amines in DNA oligomers: Nechev, L. V.; Harris, C. M.; Harris, T. M. *Chem. Res. Toxicol*. **2000**, *13*, 421–429.
6. De Riccardis, F.; Bonala, R. R.; Johnson, F. *J. Am. Chem. Soc*. **1999**, *45*, 10453–10460.
7. Harwood, E. A.; Sigurdsson, S. T.; Edfeldt, N. B. F.; Reid, B. R.; Hopkins, P. B. *J. Am. Chem. Soc*. **1999**, *121*, 5081–5082.
8. De Riccardis, F.; Johnson, F. *Org. Lett*. **2000**, *2*, 293–295.
9. Lakshman, M. K.; Keeler, J. C.; Hilmer, J. H.; Martin, J. Q. *J. Am. Chem. Soc*. **1999**, *121*, 6090–6091.
10. Typical experimental procedure: An oven-dried reaction vial was charged with dry **1** (0.250 mmol), cesium carbonate (0.350 mmol), palladium acetate (0.025 mmol), BINAP (0.037 mmol), the amine **2** (0.350 mmol), and toluene (1 mL). The reaction mixture under nitrogen was stirred for 30 min at room temperature, heated at 80°C for 16 h, and then diluted with ethyl acetate. Centrifugation and concentration in a vacuum of the supernatant liquid afforded a residue, which was purified by flash chromatography (silica gel, hexane–ethyl acetate) to afford the desired compound **3**. ^{1}H NMR, ^{13}C NMR and FAB mass spectra were entirely consistent with the assigned structures. Selected data are as follows: compound **3c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (1H, s, H-8), 7.51 (4H, m, $C_6H_5CH_2$, -C_6H_4-NH), 7.38–7.29 (3H, m, $C_6H_5CH_2$), 7.13 (2H, d, J = 7.5 Hz, -C_6H_4-NH), 6.98 (1H, s, N-H), 6.40 (1H, t, J = 6.6 Hz, H-1′), 5.60 (2H, s, CH_2-Ph), 4.58 (1H, m, H-3′), 4.01 (1H, m, H-4′), 3.80 (2H, m, H-5′), 2.59 (2H, t, J = 7.5 Hz, $CH_2C_6H_4$), 2.53 (1H, m, H′-2′), 2.43 (1H, m, H-2′), 1.61 (2H, m, $CH_2CH_2C_6H_4$), 1.37 (2H, m, CH_2CH_3), 0.93 (21H, m, $(CH_3)_3C$, CH_3-CH_2), 0.12 (6H, s, CH_3Si), 0.09 (6H, s, CH_3Si). ^{13}C (62.9 MHz, $CDCl_3$) δ –4.7 (×2), –4.6 (×2), 14.0, 17.9, 18.2, 22.3, 25.8 (×3), 26.0 (×3), 33.8, 35.0, 41.4, 62.9, 68.1, 72.1, 83.9, 87.7, 116.1, 118.8, 119.0, 127.9 (×2), 128.1, 128.3, 128.7 (×2), 136.5, 136.7, 137.4, 137.9, 153.2, 156.0, 160.8. FABMS m/z 718 $[M+1]^+$.
11. Robins, M. J.; Uznanski, B. *Can. J. Chem*. **1981**, *59*, 2608–2611.
12. Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem*. **1979**, *44*, 1247–1251.
13. Khullar, S.; Varaprasad, C. V.; Johnson, F. *J. Med. Chem*. **1999**, *42*, 947–950.
14. Moon, Ki-Y.; Moschel, R. C. *Chem. Res. Toxicol*. **1998**, *11*, 696–702.
15. Wright, G. E.; Dudycz, L. W. *J. Med. Chem*. **1984**, *27*, 175–181.