High-yield regioselective synthesis of 9-glycosyl guanine nucleosides and analogues via coupling with 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine[1]

RUIMING ZOU AND MORRIS J. ROBINS
Department of Chemistry, University of Alberta, Edmonton, Alta., Canada T6G 2G2

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Treatment of 2-*N*,9-diacetylguanine with diphenylcarbamoyl chloride followed by heating with aqueous ethanol gave 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine (2-acetamido-6-diphenylcarbamoyloxypurine). Bis-trimethylsilylation of this product followed by coupling with glycosyl acetates (trimethylsilyl triflate catalysis) or α-haloethers in *anhydrous toluene* gave 9-substituted guanine compounds in high yields with no 7-isomers detected.

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La réaction de la diacétyl-2-*N*,-9 guanine avec le chlorure de diphénylcarbamoyle, suivie d'un chauffage avec de l'éthanol aqueux, conduit à la *N*-acétyl-2 *O*-diphénylcarbamoyl-6 guanine (acétamido-2 diphénylcarbamoyloxy-6 purine). La bis-triméthylsilylation de ce produit, suivie d'un couplage avec soit les acétates de glycosyle (catalyse par le triflate de triméthylsilyle) ou les α-haloéthers dans le *toluène anhydre*, conduit aux composés de la guanine substitués en position 9; les rendements sont élevés et on ne détecte pas la présence d'isomères 7.

[Traduit par la revue]

Of the five heterocyclic bases commonly found in DNA and RNA, guanine (**1**) causes markedly enhanced experimental problems. Guanosine and its analogues are amphoteric ($pK_a1 \sim 1.7$, $pK_a2 \sim 9.2$) polyfunctional compounds that are sparingly soluble in water and polar aprotic solvents, and effectively insoluble in all other common solvents. They often self-associate in solution to form viscous gels and hydrate tenaciously in the crystalline state. Direct coupling with guanine-type bases produces N7/N9 isomeric mixtures (*1*) that are frequently difficult to separate for the above reasons. Changes in experimental variables affect the isomer ratios, but do not eliminate contamination of the desired thermodynamic N9 product by significant quantities of the kinetic N7 isomer (2).

Discovery (3) of the potent activity against herpes simplex type 1 and 2 viruses and low mammalian toxicity of 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir) triggered a massive worldwide effort to synthesize and test guanine nucleosides and "acyclic nucleoside" analogues. Very recent syntheses of acyclovir analogues have employed 2-amino-6-alkoxypurines (4, 5) to enhance selectivity for N9 coupling.

Reese and Ubasawa (6) and Hata and co-workers (7) had observed O6 functionalization of guanine during phosphate activation for oligonucleotide synthesis, and Hata and co-workers have exploited O6 diphenylcarbamoylation of guanosine derivatives as a protection strategy (8). We now report regioselective coupling of bis-trimethylsilylated 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine (**2**) with acetylated pentofuranoses and α-haloethers as a convenient new route to guanine N9 products.

A suspension of 30.22 g (0.2 mol) of guanine (**1**) in 250 mL of dry DMAc and 50 mL of Ac_2O was stirred at 160°C for 7 h. The brown solution was cooled and crystalline 2-*N*,9-diacetylguanine[2,3] (9) was filtered and washed with EtOH. A second crop raised the yield to 42.53 g (90%). A stirred suspension of 5.88 g (25 mmol) of 2-*N*,9-diacetylguanine in 8.7 mL of $EtN(i\text{-}Pr)_2$ and 120 mL of dry C_5H_5N was treated with 6.37 g (27.5 mmol) of Ph_2NCOCl for 1 h at ambient temperature. H_2O (10 mL) was added and stirring continued for 10 min. Evaporation *in vacuo* and coevaporation (3 × 20 mL of $PhCH_3$) was followed by heating (steam bath) the residue with 300 mL of 50% $EtOH/H_2O$ for 1.5 h. Cooling, filtration, washing (EtOH), and drying gave 8.93 g (92%) of **2**.[3,4]

N,*O*-Bis(trimethylsilyl)acetamide (0.5 mL) was added to a suspension of 388 mg (1 mmol) of **2** in 10 mL of dry 1,2-dichloroethane. Stirring at 80°C for 15 min gave a clear solution that was evaporated *in vacuo*. The residue was dissolved in 5 mL of dry $PhCH_3$ and 0.25 mL of $CF_3SO_3SiMe_3$, and 382 mg (1.2 mmol) of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in 5 mL of dry $PhCH_3$ was added. The solution was stirred at 80°C for 1 h and cooled, 50 mL of EtOAc was added, and the solution was worked up in the usual manner. The crude product was chromatographed (25 g silica, 2 × 15 cm; Et_2O/Me_2CO 8:2) to give 589 mg (91%) of **3**: ms (FAB) m/z 647 ($M + 1$); ^1H and ^{13}C nmr spectra were compatible with structure **3**.

Trace quantities (<3%) of a more rapidly migrating bis-ribosylated product (2-N,9 by nmr) were separated from **3** by the column chromatography. Deprotection of **3** with NH_3/H_2O/MeOH gave 75% (68% from **2**) of guanosine (**4**) hemihydrate[3] after recrystallization from water.

Analogous coupling reactions with $\mathbf{2}(SiMe_3)_2$ and tetra-*O*-acetyl-D-furanosyl derivatives of arabinose and xylose gave good yields of the corresponding 9-α- and 9-β-guanine nucleosides, respectively. Coupling of $\mathbf{2}(SiMe_3)_2$ and (2-acetoxyethoxy)methyl bromide (10) in toluene proceeded readily at ambient temperature without catalyst. The resulting acyclovir derivative was obtained in 63% yield after column chromatography and crystallization. X-ray crystallographic analysis of this intermediate confirmed the 6-diphenylcarbamoyloxy structure.[5] Deprotection gave acyclovir hemihydrate[3] (10) in 91% yield after recrystallization (H_2O).

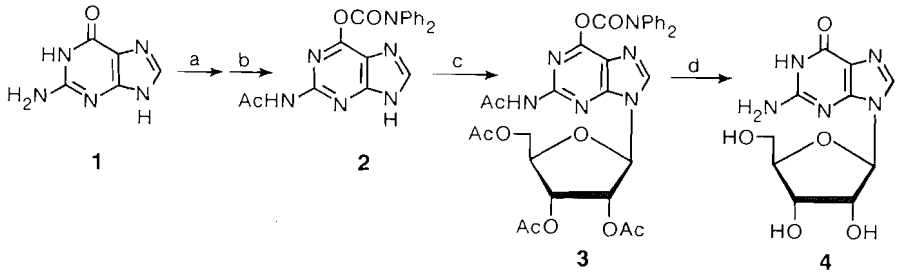
[1](*a*) This paper constitutes "Nucleic acid related compounds. 52." For the previous paper in this series, see ref. 12. (*b*) A preliminary account was presented at the Annual Chemical Congress of the Royal Society of Chemistry, University of Warwick, U.K. April 11, 1986.

[2]Mass spectrum, m/z 235.0706 (M^+ 235.0706); ^1H nmr (Me_2SO-d_6) δ: 2.20 (2NAc), 2.80 (N9Ac), 8.42 (H8).

[3]These compounds had elemental analyses (C, H, N) within ±0.3% of theory.

[4]Mass spectrum, m/z 388.1283 (M^+ 388.1284); ^1H nmr (Me_2SO-d_6) δ: 2.18 (2NAc), 7.26–7.56 (NPh_2), 8.46 (H8).

[5]We thank Dr. R. Ball of the Structure Determination Laboratory of this Department for the X-ray analysis. Details will be published separately.



(a) Ac_2O/DMAc/Δ. (b) (i) Ph_2NCOCl/EtN(i-Pr)$_2$/Pyridine. (ii) EtOH/H_2O/Δ.
(c) (i) BSA/$ClCH_2CH_2Cl$/Δ/Evaporate. (ii) Tetraacetylribose/$CF_3SO_3SiMe_3$/$PhCH_3$/Δ.
(d) NH_3/H_2O/MeOH/60° C.

Vorbrüggen *et al.* (11) had reported coupling of tris-trimethylsilylated 2-*N*-acetylguanine and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in 1,2-dichloroethane at reflux with trimethylsilyl triflate as catalyst. The crude product was deprotected to give "pure guanosine" in 66% yield after recrystallization from water. Careful repetition of this sequence gave 66% of crystalline product that comigrated (tlc) with guanosine as described (11). However, the 400-MHz ^1H nmr spectrum of this material in Me_2SO-d_6 revealed a mixture of **4** and its N7 isomer. The nmr analysis of the crude coupling product showed a N9/N7 ratio of ~3:1.

Analysis (400-MHz ^1H and 100-MHz ^{13}C nmr) of our crude coupling product and the recrystallized deprotected nucleoside showed only **3** (plus trace amounts of the bis-ribosyl by-product) and **4**, respectively, with no detected N7 contaminant. Therefore, coupling of glycosyl acetate (and chloride) derivatives and α-haloethers with the readily accessible **2**$(SiMe_3)_2$ under *anhydrous* conditions in *toluene* as described herein represents a new and experimentally convenient route to 9-glycosyl guanine derivatives and analogues. These can be purified and manipulated readily and deprotected under mild conditions. It represents the method of choice among presently published alternatives for the preparation of guanine N9 nucleosides.[6] Further investigations on selective syntheses of N7 products and kinetic/thermodynamic isomer studies will be reported in detail.

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[6]Alkylation of **2**$(SiMe_3)_2$ did not proceed satisfactorily under comparable conditions with "unactivated" alkyl halides. The use of salts of 2-amino-6-alkoxypurines (4, 5) appears to be favorable for preparation of 9-alkylguanines.

1. (*a*) L. Goodman. *In* Basic principles in nucleic acid chemistry. Vol. I. *Edited by* P. O. P. Ts'o. Academic Press, New York. 1974. Chap. 2; (*b*) M. Imazawa and F. Eckstein. J. Org. Chem. **43**, 3044 (1978); (*c*) K. K. Ogilvie, U. O. Cheriyan, B. K. Radatus, K. O. Smith, K. S. Galloway, and W. L. Kennell. Can. J. Chem. **60**, 3005 (1982); (*d*) G. E. Wright and L. W. Dudycz. J. Med. Chem. **27**, 175 (1984).
2. L. W. Dudycz and G. E. Wright. Nucleosides Nucleotides, **3**, 33 (1984).
3. G. B. Elion, P. A. Furman, J. A. Fyfe, P. de Miranda, L. Beauchamp, and H. J. Schaeffer. Proc. Natl. Acad. Sci. U.S.A. **74**, 5716 (1977).
4. M. MacCoss, A. Chen, and R. L. Tolman. Tetrahedron Lett. **26**, 1815 (1985).
5. J. Kjellberg, M. Liljenberg, and N. G. Johansson. Tetrahedron Lett. **27**, 877 (1986).
6. C. B. Reese and A. Ubasawa. Tetrahedron Lett. **21**, 2265 (1980).
7. H. P. Daskalov, M. Sekine, and T. Hata. Tetrahedron Lett. **21**, 3899 (1980).
8. (*a*) T. Kamimura, M. Tsuchiya, K. Koura, M. Sekine, and T. Hata. Tetrahedron Lett. **24**, 2775 (1983); (*b*) T. Kamimura, M. Tsuchiya, K. Urakami, K. Koura, M. Sekine, K. Shinozaki, K. Miura, and T. Hata. J. Am. Chem. Soc. **106**, 4552 (1984).
9. Y. Ishido, A. Hosono, S. Isome, A. Maruyama, and T. Sato. Bull. Chem. Soc. Jpn. **37**, 1389 (1964).
10. M. J. Robins and P. W. Hatfield. Can. J. Chem. **60**, 547 (1982).
11. H. Vorbrüggen, K. Krolikiewicz, and B. Bennua. Chem. Ber. **114**, 1234 (1981).
12. E. De Clercq, J. Balzarini, D. Madej, F. Hansske, and M. J. Robins. J. Med. Chem. **30**, 481 (1987).