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Regioisomers in Vorbrüggen's guanine nucleoside synthesis; N9 selectivity with a glucosamine derivative and 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine[1]☆

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Abstract—Vorbrüggen coupling of trimethylsilylated 2-*N*-acetylguanine with pentofuranose derivatives gives N7/N9 glycosyl mixtures. The N9 isomers can be obtained selectively with 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine, and even with a less reactive glucosamine derivative.

The methodology developed by Vorbrüggen and co-workers for coupling trimethylsilylated-heterocycle derivatives and acylated sugars revolutionized the synthesis of nucleosides.[2,3] The pyrimidine-type derivatives undergo coupling with acylated pentofuranoses in the presence of Lewis acid catalysts such as trimethylsilyl trifluoromethylsulfonate (TMSOTf) or tin(IV) chloride to give excellent yields of the acylated nucleosides. Adenine-type bases were usually converted to 6-*N*-acyladenine derivatives prior to trimethylsilylation. Coupling yields were good,[4] but lower than in the pyrimidine series.[2,3] The method of Saneyoshi and Satoh with $SnCl_4$ and adenine in acetonitrile usually provides clean adenine N9 nucleosides in yields of $\geq 75\%$.[5]

In 1981, Vorbrüggen, Krolikiewicz, and Bennua (V–K–B) reported a convenient synthesis of guanosine (Guo).[4] The silylated derivative of 2-*N*-acetylguanine (**1**) (Fig. 1) was coupled with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2a**) with TMSOTf catalysis. The product mixture was deprotected, and the material was recrystallized from water to give Guo (**3**) in 66% yield. This appeared to solve the long-standing problem of poor N7/N9 regioselectivity upon coupling of guanine derivatives with acyl-furanoses and acyclic analogues or their α-haloether counterparts.[6] However, when we applied the V–K–B procedure to **1** and 1,2,3,5-tetra-*O*-acetyl-D-arabinofuranose, an N7/N9 isomer mixture was obtained.[7,8] We carefully repeated the procedure with **1** and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**2b**), and then with **1** and **2a**, the identical ribofuranose derivative employed by V–K–B.[4] In both cases, we obtained N7/N9 isomers (NMR) in the crude coupling mixtures.[7,8] Deprotection and recrystallization of the mixtures from water as described[4] resulted in separation of the naturally occurring N9 isomer, **3**, containing $\leq 3\%$ of **4**.[9] An additional recrystallization gave **3** virtually free of **4**. However, simple fractional crystallization from water (which provided Guo in $\geq 66\%$, as reported[4]) did not separate the N7 and N9 isomers of the arabino- or xylofuranosyl guanine nucleosides. In those cases, separation of the protected regioisomers by chromatography before deblocking was required.

Vorbrüggen has continued to claim that we have misrepresented his work,† which is not accurate. We have stated,[7,8] and repeat here, that the V–K–B procedure for synthesis of Guo, per se, was found to proceed exactly as described and provided the crystalline N9 isomer **3** in $\geq 66\%$ yield with only trace contamination of **4**. However, as we also have stated,[7,8] the fortuitous fractional crystallization from water that provided essentially pure Guo from the N7/N9 mixture does not readily separate the arabino- or xylofuranosyl derivatives, and in those cases chromatographic resolution of the N7 and N9 isomers was required. This stimulated our attempts to discover a guanine derivative that

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☆ See Ref. 1.

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† See Ref. 2, page 21.

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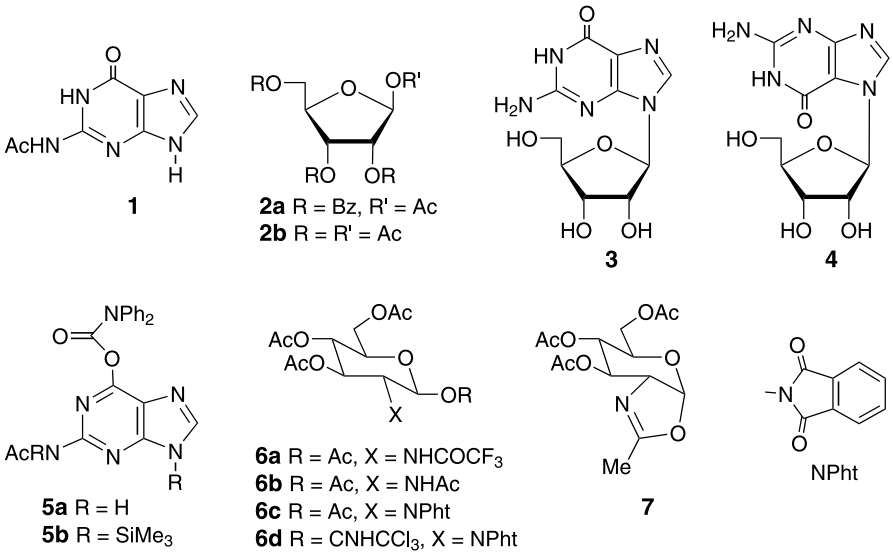


Figure 1.

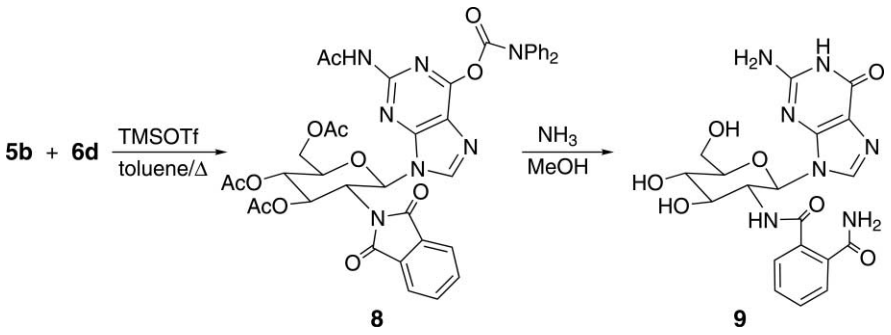
would undergo coupling exclusively (or with high selectivity) at N9. Our results with 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine (**5a**) have demonstrated that coupling at N9 (exclusive of NMR-detected N7 isomer contamination) is feasible with acylated pentofuranose or α-bromoether derivatives.[7,8,10] Others have confirmed the utility of couplings with **5a** for syntheses of guanine nucleosides and analogues.[11]

In 2000, Cheung et al. reported that attempted coupling of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(trifluoroacetamido)-β-D-glucopyranose (**6a**) and **5b** (Robins' reagent) with TMSOTf in toluene gave low yields of N7/N9 isomeric products.[11a] Even more surprising was the finding that an analogous coupling reaction in 1,2-dichloroethane gave the N7 isomer, and that this compound was not isomerized to N9 upon heating in toluene with TMSOTf. Our studies with furanosyl sugar derivatives had demonstrated that the N9 isomer was both the kinetic and thermodynamic product. It was the only isomer observed by NMR during couplings performed at lower temperature over an extended period, and an N7 isomer prepared by an alternative route was isomerized completely into the N9 product upon heating in toluene with TMSOTf.[8] Therefore, we have briefly re-examined this problem and now report our results. Coupling of **2a** and **5b** proceeded as described[7,8] to give the protected N9 isomer (96%). Analogous coupling of **5b** and 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose occurred at a slower rate and gave a moderate yield (68%) of the N9 product. Formation of the N7 isomers was not detected.[12]

Attempted coupling of **5b** with 2-*N*-trifluoroacetyl derivative **6a** gave a complex mixture as noted.[11a] Extensive decomposition of **5b** occurred with loss of the diphenylcarbamoyl (DPC) group, and the resulting **1** is known to undergo coupling at both N7 and N9.[6–8] The 2-*N*-trifluoroacetyl group in **6a** would be a less active anchimeric participant than a 2-*O*-acetyl, and pyranosides are more stable than furanosides. Activation of a pyranose via loss of an acetyloxy group to generate an anchimerically stabilized oxocarbenium species would be more difficult. Extended heating of **5b** in the presence of TMSOTf would result in more DPC hydrolysis by adventitious water. Coupling reaction mixtures remained complex with **5b** and **6b**, the pentaacetyl derivative of glucosamine, and NMR spectra indicated formation of the fused oxazoline **7** (protonated in the acid-containing mixture). Even the protonated form of oxazoline **7** is more stable than acyloxonium ions formed by neighboring group participation by 2-*O*-acyl sugars.

The 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido derivative,[13] **6c**, of glucosamine has no acidic proton on nitrogen, and anchimeric participation by the phthalimido group would form a charged species that would be more susceptible to nucleophilic attack. Nucleoside formation was observed with **6c**, but the reaction was sluggish and complex. Sugars activated with an anomeric trichloroacetimidate group have been used extensively for synthesis of complex glycosides,[14] but not in nucleoside synthesis. Selective hydrazinolysis of the 1-*O*-acetyl function of **6c**, and treatment of the resulting hemiacetal with trichloroacetonitrile and DBU gave 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl trichloroacetimidate[15] (**6d**). Compounds **5b**, **6d**, and TMSOTf were heated in dried toluene for 45 min to give 2-*N*-acetyl-9-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-6-*O*-diphenylcarbamoylguanine[16] (**8**) (Scheme 1) in moderate yield (54%).[17] Chromatography of the mixture and treatment of **8** with methanolic ammonia gave 9-[2-*N*-(2-carboxamidobenzoyl)amino-2-deoxy-β-D-glucopyranosyl]-guanine[12,16] (**9**).

In summary, coupling of **2a** with **5b** proceeded smoothly to give the N9 isomer (96%), and coupling of



Scheme 1.

glucose penta-acetate and **5b** proceeded at a slower rate to give the N9 product in reasonable yield (68%). Attempted coupling of **5b** with the 2-*N*-acetyl (**6b**) or trifluoroacetyl (**6a**) derivatives of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose gave complex mixtures with extensive decomposition of **5**. The 1-*O*-acetyl-*N*-phthaloyl derivative **6c** did not function well, but the more reactive 1-trichloroacetimidate **6d** was coupled with **5b** to give the N9 glycosyl isomer **8** in moderate yield (54%). Treatment of **8** with methanolic ammonia gave 9-[2-*N*-(2-carboxamidobenzoyl)amino-2-deoxy-β-D-glucopyranosyl]guanine (**9**). Thus, 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine (**5a**) is a very useful derivative of guanine for Lewis acid-catalyzed regiospecific N9 coupling with active glycosyl donors derived from 1,2,3,5-tetra-*O*-acylpentofuranoses or α-haloethers. However, **5b** does not couple readily with weak glycosyl donors, and it is susceptible to cleavage of the DPC group. The resulting 2-*N*-acetylguanine couples at both N7 and N9, as in the V–K–B method.

Acknowledgements

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16. **9-[2-*N*-(2-Carboxamidobenzoyl)amino-2-deoxy-β-D-glucopyranosyl]guanine (9)**. BSA (0.50 mL, 407 mg, 2.0 mmol) was added to a stirred suspension of **5a** (388 mg, 1 mmol) in dried DCE (10 mL), and stirring was continued under N_2 at 80°C for 30 min. The clear solution was evaporated, and the residue was dried under high vacuum for 15 min and dissolved in dried toluene (5 mL). TMSOTf (0.32 mL, 386 mg, 1.8 mmol) and a solution of **6d** (1.42 g, 1.5 mmol) in dried toluene (5 mL) were added. The solution was stirred at 80°C for 45 min, and volatiles were evaporated. The residue was dissolved in EtOAc, and the solution was washed ($NaHCO_3/H_2O$, 3×50 mL) and dried (Na_2SO_4). The residue was chromatographed ($CH_2Cl_2 \rightarrow MeOH/CH_2Cl_2$, 1:180→1:90) to give **8** (453 mg, 54%) as a white foam: HRMS (FAB) *m*/*z* 828.2258 (MNa^+ [$C_{40}H_{35}O_{12}N_7Na$] = 828.2241).

A solution of **8** (416 mg, 0.52 mmol) in NH_3/MeOH (20 mL, saturated at −10°C) in a sealed flask was kept at −12°C for 40 h and then stirred at ambient temperature for 24 h. The precipitated solid was washed with cold MeOH to give **9** (73 mg, 31%; no attempt was made to recover additional product from the mother liquor): mp >250°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.28–3.33 (m, 2H), 3.48–3.50 (m, 1H), 3.69–3.75 (m, 2H), 4.29–4.33 (m, 1H), 4.65–4.67 (m, 1H), 5.00 (s, 1H), 5.28 (s, 1H), 5.50 (d, $J=10.3$ Hz, 1H), 6.53 (s, 2H), 6.90 (d, $J=7.1$ Hz, 1H), 7.40–7.45 (m, 2H), 7.50 (s, 1H), 7.60 (d, $J=8.1$ Hz, 1H), 7.74 (s, 1H), 7.96 (s, 1H), 8.47(d, $J=9.4$ Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1, 169.7, 157.4, 154.5, 152.2, 137.6, 135.8, 134.6, 130.8, 129.8, 128.6, 127.9, 117.0, 80.8, 80.4, 75.4, 70.2, 61.4, 54.8; HRMS (FAB) m/z 482.1387 (MNa^+ $[C_{19}H_{21}N_7O_7Na]=482.1400$). Anal. calcd for $C_{19}H_{21}N_7O_7\cdot H_2O$: C, 47.80; H, 4.86; N, 20.54. Found: C, 47.85; H, 4.75; N, 20.22.

17. At 45 min, one major nucleoside product, **8**, was observed (TLC) plus more rapidly migrating (sugar) and slower (base) decomposition products (in addition to the starting materials **5a** and **6d**). Further heating resulted in minor enhancement of the amount of **8** and elevated formation of by-products.