EFFICIENT REGIOSELECTIVE SYNTHESIS OF GUANOSINE ANALOGS

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Abstract: Reaction conditions are presented that allow regioselective introduction (N9 versus N7) of guanine into sugar analogs under Vorbrüggen conditions. Using these conditions, a set of N2-protected guanosine analogs has been prepared with N2-isobutyryl-06-[2-(p-nitrophenyl)ethyl]guanine (1) as nucleophile. This approach helps solve an important synthetic problem in the preparation of guanosine analogs.

Although methods, reagents, and conditions for the preparation of nucleoside analogs containing pyrimidine and purine bases are in widespread use, nucleoside analogs containing guanosine as the aglycone remain problematic synthetic goals. Standard procedures1,2 for attaching a guanine unit to a sugar generally proceed with unacceptable regioselectivity (N7 versus N9 of the purine ring). Methods specifically designed for the regioselective synthesis of guanosine analogs3,4 (N7 under kinetic control, N9 under thermodynamic control) usually proceed only in moderate yield or are limited to specially functionalised sugar units5.

Because of intense interest, both in this laboratory and elsewhere, in preparing nucleoside analogs containing an oxycyclic unit (e.g., ribose and hexose derivatives6) as anti-viral reagents7, as starting materials for creating anti-sense oligonucleotide analogs8, or simply to better understand molecular recognition in nucleic acids, we have searched for new methods for preparing N9 derivatives of guanine. We report here that N2-isobutyryl-06-[2-(p-nitrophenyl)ethyl]guanine (1), recently introduced for the synthesis of carbocyclic guanosine analogs9,10, offers a solution to the problem of regioselectivity in oxycyclic analogs as well. We have applied this reagent to the synthesis of compounds 4a, 4b and 4c. These are ribose analogs homologated at the C-3' and C-5' positions, and can serve as building blocks for oligonucleotide analogs in which the phosphate diester linking groups have been replaced by dimethylene sulfide, sulfoxide, or sulfone groups11,12. In all three cases, the desired N9-substituted guanine derivatives were obtained as anomic mixtures in yields of 60% to 70%.

Surprisingly, the yields depended strongly on the amount of Lewis acid used as catalyst. Best results were obtained with only 5 to 10 mol% of trimethylsilyl triflate (TMS triflate) as catalyst. Stoichiometric amounts of Lewis acid produced yields under 40%. Another critical factor was the procedure used to silylate 1. Very strong conditions were needed for the complete conversion of 1 to the corresponding silylated base: either refluxing (bath temp. 150°C) in an excess of 1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of trimethylchlorosilane (TMSCl) and (NH4)2SO413 as catalysts, or heating to 100°C with an excess of N-methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA) and TMSCl for 18 h. Removal of the p-nitrophenylethyl-group (NPE) with
1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) required reaction in carefully dried pyridine. Otherwise the O-acetyl and S-benzoyl protective groups in the final compounds 4a, 4b and 4c were partially lost.

In a typical procedure (synthesis of 4c), N°-isobutyryl-O°-6-[2-(p-nitrophenyl)ethyl]guanine (1, 278 mg, 0.75 mmol) suspended in MSTFA (3 ml) and TMSCl (0.25 ml) was heated under Ar at 100°C for 18 h. The clear solution was cooled to r.t. and the reagents completely removed under high vacuum. The residue was dried (3 h, high vacuum). A solution of the bis-homo-sugar analog (2c, 175 mg, 0.5 mmol) in acetonitrile (8 ml, freshly distilled from CaH₂) was then added to the silylated base. After stirring at r.t. for 30 min, the solution was cooled to -20°C and TMS triflate (5 μl, 0.025 mmol, 5 mol%) was added slowly. The resulting slightly green solution was stirred for 18 h at 60°C. After hydrolysis with aqueous half-sat. NaHCO₃-solution (20 ml) at r.t., the reaction mixture was extracted three times with CH₂Cl₂. The organic layers were washed with brine, dried (MgSO₄), filtered, and the solvent evaporated. The residue was carefully dried (high vacuum) to give 3c in quantitative yield. The O°-protected intermediate 3c (0.5 mmol) in pyridine (absolute, 10 ml) was treated with DBU (0.33 ml, 2.25 mmol) at 0°C. The reaction mixture was stirred at r.t. for 8 h, neutralized with glacial acetic acid (0.13 ml, 2.25 mmol), and the pyridine evaporated (twice with toluene as cosolvent). Chromatography on Kieselgel (50 g, CH₂Cl₂:MeOH 96:4) yielded 4c (175 mg, 69%) as a slightly yellow foam.

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References and Notes

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