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EFFICIENT REGIOSELECTIVE SYNTHESIS OF GUANOSINE ANALOGS

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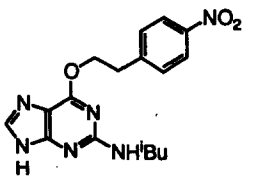
Abstract: Reaction conditions are presented that allow regioselective introduction (N^9 versus N^7) of guanine into sugar analogs under Vorbrüggen conditions. Using these conditions, a set of N^2-protected guanosine analogs has been prepared with N^2-isobutyryl-O^6-[2-(*p*-nitrophenyl)ethyl]guanine (1) 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 procedures[1,2] for attaching a guanine unit to a sugar generally proceed with unacceptable regioselectivity (N^7 versus N^9 of the purine ring). Methods specifically designed for the regioselective synthesis of guanosine analogs[3,4] (N^7 under kinetic control, N^9 under thermodynamic control) usually proceed only in moderate yield or are limited to specially functionalised sugar units[5].



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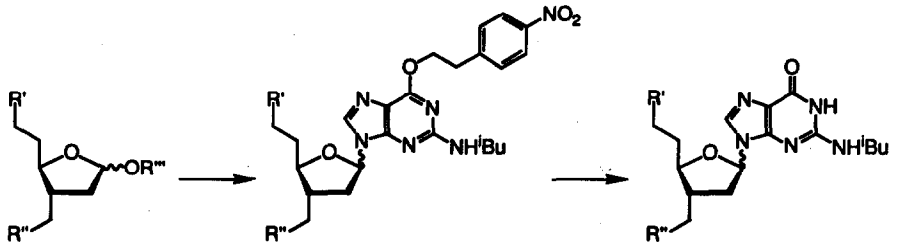
Because of intense interest, both in this laboratory and elsewhere, in preparing nucleoside analogs containing an oxycyclic unit (e.g., ribose and hexose derivatives[6]) as anti-viral reagents[7], as starting materials for creating anti-sense oligonucleotide analogs[8], or simply to better understand molecular recognition in nucleic acids, we have searched for new methods for preparing N^9 derivatives of guanine. We report here that N^2-isobutyryl-O^6-[2-(*p*-nitrophenyl)ethyl]guanine (**1**), recently introduced for the synthesis of carbocyclic guanosine analogs[9,10], 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 groups[11,12]. In all three cases, the desired N^9-substituted guanine derivatives were obtained as anomeric 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 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of trimethylchlorosilane (TMSCl) and $(NH_4)_2SO_4$[13] 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.



2a-c **3a-c** **4a-c**

a: R'= OBz, R"= SBz, R'''= Me
b: R'= OAc, R"= OBz, R'''= Ac
c: R'= OBz, R"= OAc, R'''= Ac

In a typical procedure (synthesis of **4c**), N^2-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)[14] in acetonitrile (8 ml, freshly distilled from CaH_2) 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. $NaHCO_3$-solution (20 ml) at r.t., the reaction mixture was extracted three times with CH_2Cl_2. The organic layers were washed with brine, dried ($MgSO_4$), filtered, and the solvent evaporated. The residue was carefully dried (high vacuum) to give **3c** in quantitative yield. The O^6-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 (50g, CH_2Cl_2:MeOH 96:4) yielded **4c** (175 mg, 69%) as a slightly yellow foam.

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