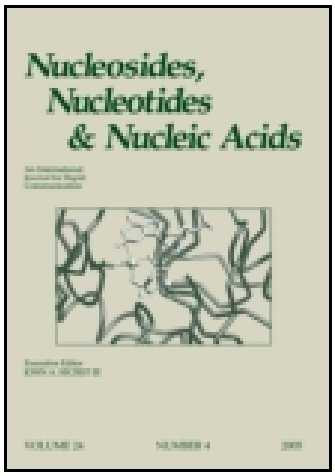

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Introduction of a Benzyl Group onto the 2′-OH of 6-Chloropurine 3′-*O*-Benzoylriboside

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ABSTRACT

A new method to introduce a benzyl group onto the 2′-OH of purine ribonucleoside is described. Thus, 6-chloropurine 3′-*O*-benzoylriboside and its 5′-*O*-trityl congener were condensed with benzyl alcohol using the Mitsunobu reaction to give the 2′-*O*-benzyl derivative. The yields were varied from 4.6 to 62.9% depending on the solvent. The product was converted to adenosine, indicating that the stereochemistry at C-2′ is retained.

The Mitsunobu reaction is a universal method to condense the acid and alcohol accompanied with inversion of the configuration of the alcoholic hydroxyl group.[1] One exceptional case is a sterically hindered sugar,[2] in which resistance to S_N2 displacement was reported. Also, Wentwarth and Janda reported the displacement of arabinoside to 2′-*O*-benzylated riboside using the Mitsunobu reaction with benzyl alcohol.[3] This method could be an alternative approach to obtain the 2′-*O*-alkylated

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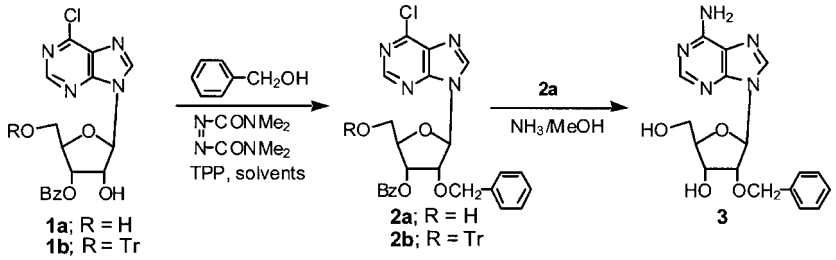

Chart.

ribonucleoside. However, it takes several steps to prepare arabinoside. This background prompted us to develop a method to introduce an alkyl group onto the purine ribonucleoside.

6-Chloropurine 3′-*O*-benzylriboside (**1a**) and its 5′-*O*-trityl congener (**1b**) were prepared by the method as described in an earlier report.[4] Then, compound **1b** was subjected to the reaction with benzyl alcohol (4 eq.) in the presence of *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide [TMAD, 1,1′-azobis-(*N*,*N*-dimethylformamide)][5] and triphenylphosphine (TPP) in a solvent. The reaction was monitored by high-performance liquid chromatography (HPLC). In a non-proton polar solvent such as *N*,*N*-dimethyl-formamide (DMF), the peak of the 2′-*O*-benzyl congener (**2b**) appeared in low yield (4.6%). Also, a trial in tetrahydrofuran (THF) gave **2b** in 14% yield. In spite of this result, a similar reaction performed in 1,4-dioxane gave **2b**[6] in 45% yield. The best result was obtained when the reaction was carried out in benzene, in which conversion was estimated to be 62.5% yield. After work-up of the solution, **2b** was obtained in 57% yield. An attempt to change TMAD to diisopropyl azodicarboxylate (DIAD) decreased the yield of **2b** to 17.7% in the 1,4-dioxane solvent system. To evaluate the role of the 5′-*O*-protecting group, 3′-*O*-benzyolriboside **1a** was subjected to a similar reaction to afford **2a**.[7] It appeared that the 5′-*O*-protection did not benefit the condensation. Compound **2b** was treated with NH_3 in MeOH to afford 2′-*O*-benzyladenosine (**3**),[8] which showed nuclear Overhauser effect (NOE) between H2′ and H3′ in the two-dimensional NOE (NOESY) spectrum. Thus, the configuration of **3** was identified as a 2'(*R*)-riboside structure.

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6. A caramel. MS m/z: 479, 481 (M^+-Tr). ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 6.95–7.11 (5H, m, $CH_2C_6\underline{H}_5$), 4.63 (1H, d, $J = 12.4$, one of $C\underline{H}_2C_6H_5$), 4.45 (1H, d, $J = 12.4$, one of $C\underline{H}_2C_6H_5$).
7. White crystals. mp 167.5–169.5°C. *Anal* Calcd for $C_{24}H_{21}ClN_4O_5$: C, 59.94; H, 4.40; N, 11.65. Found: C, 59.97; H, 4.49; N, 11.60. MS m/z: 450, 452 (M^+-CH_2O). UV λ_{max} (MeOH) nm: 265. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 6.84–6.94 (5H, m, $CH_2C_6\underline{H}_5$), 4.55–4.57 (2H, m, H4′ , one of $C\underline{H}_2C_6H_5$), 4.29 (1H, d, $J = 12.1$ Hz, one of $C\underline{H}_2C_6H_5$).
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