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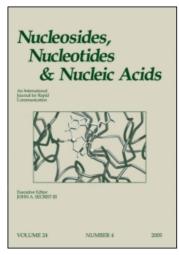
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Introduction of a Benzyl Group onto the 2'-OH of 6-Chloropurine 3'-O-Benzoylriboside

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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. One exceptional case is a sterically hindered sugar, 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. This method could be an alternative approach to obtain the 2'-O-alkylated

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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 highperformance 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'-Obenzyolriboside 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 NH₃ 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). ¹H-NMR (600 MHz, CDCl₃) δ : 6.95–7.11 (5H, m, CH₂C₆H₅), 4.63 (1H, d, J=12.4, one of CH₂C₆H₅), 4.45 (1H, d, J=12.4, one of CH₂C₆H₅).
- 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⁺-CH₂O). UV λ_{max} (MeOH) nm: 265. ¹H-NMR (600 MHz, CDCl₃) δ : 6.84–6.94 (5H, m, CH₂C₆H₅), 4.55–4.57 (2H, m, H4', one of CH₂C₆H₅), 4.29 (1H, d, J=12.1 Hz, one of CH₂C₆H₅).
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