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## Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information: <u>http://www.tandfonline.com/loi/lncn20</u>

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

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To cite this article: Shigetada Kozai, Tomoyo Fuzikawa, Keisuke Harumoto & Tokumi Maruyama (2003) Introduction of a Benzyl Group onto the 2'-OH of 6-Chloropurine 3'-O-Benzoylriboside, Nucleosides, Nucleotides and Nucleic Acids, 22:5-8, 779-781, DOI: <u>10.1081/NCN-120022633</u>

To link to this article: <u>http://dx.doi.org/10.1081/NCN-120022633</u>

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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.<sup>[1]</sup> One exceptional case is a sterically hindered sugar,<sup>[2]</sup> in which resistance to  $S_N^2$  displacement was reported. Also, Wentwarth and Janda reported the displacement of arabinoside to 2'-O-benzylated riboside using the Mitsunobu reaction with benzyl alcohol.<sup>[3]</sup> This method could be an alternative approach to obtain the 2'-O-alkylated

779

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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.<sup>[4]</sup> 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)]<sup>[5]</sup> 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**<sup>[6]</sup> 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.<sup>[7]</sup> It appeared that the 5'-O-protection did not benefit the condensation. Compound **2b** was treated with NH<sub>3</sub> in MeOH to afford 2'-O-benzyladenosine (3),<sup>[8]</sup> 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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### 2'-O-Benzoylation of Purine Nucleoside

- 6. A caramel. MS m/z: 479, 481 (M<sup>+</sup>-Tr). <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.95– 7.11 (5H, m, CH<sub>2</sub>C<sub>6</sub><u>H</u><sub>5</sub>), 4.63 (1H, d, J = 12.4, one of C<u>H</u><sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 4.45 (1H, d, J = 12.4, one of C<u>H</u><sub>2</sub>C<sub>6</sub>H<sub>5</sub>).
- 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<sup>+</sup>-CH<sub>2</sub>O). UV  $\lambda_{max}$  (MeOH) nm: 265. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.84–6.94 (5H, m, CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 4.55–4.57 (2H, m, H4', one of CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 4.29 (1H, d, J = 12.1 Hz, one of CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>).
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781

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