A General Synthesis of 5′-Azido-5′-deoxy-2′,3′-*O*-isopropylidene Nucleosides

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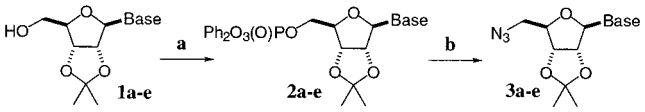
Introduction

Functional group transformation at the 5′-position of nucleosides has historically been an area of keen interest, due predominantly to the biological importance of these molecules.[1] Recently, an efficient preparation of 5′-carboxylic nucleosides was reported.[2] A comparably general and facile conversion of the 5′-hydroxyl group into its 5′-azido derivative would further expand the range of subsequent synthetic modification. The 5′-azide functionality can be readily reduced to generate 5′-amino-nucleoside nucleophiles,[3] which have been reported in a variety of subsequent transformations.[4] Herein, we report an efficient method for the preparation of 5′-azido analogues of five 2′,3′-*O*-isopropylidene-protected purine and pyrimidine nucleosides. The procedure is general, proceeds without cyclonucleoside side reactivity, and, for the nucleosides evaluated thus far, does not require chemical protection of the base functionality.

The primary difficulty in developing general and efficient methods for the synthesis of 5′-azido purine nucleosides lies mostly in the formation of undesired cyclonucleosides.[5] This side reactivity is primarily due to the intramolecular substitution of the 5′-activating group by the nucleophilic nitrogen on the base. Numerous reports have provided solutions to this problem; however, these methods involve electron-density reduction on the base by using electron-withdrawing groups, which lengthens the synthetic sequence.[6] We have previously reported a facile preparation of 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneadenosine in high yield.[7] In this report, our method utilizes a phosphate triester at the 5′-position, instead of using the conventional sulfonate or halide as the activating group.[8] The 5′-phosphate ester has a lower propensity to be substituted by weak intramolecular nucleophiles and therefore is selective for substitution by strong external nucleophiles such as azides. This activation is also strong enough that, in the case of pyrimidine nucleosides, the intermolecular substitution is favored over the competing cycloaddition reaction between the newly formed 5′-azide and the C_5-C_6 double bond on the pyrimidine base.[9] In this report, we establish the ability to use this method for the modification of four other nucleosides (guanosine, inosine, uridine, and cytidine) and give a full experimental description and characterization of three new compounds: 5′-diphenylphosphoryl-2′,3′-*O*-isopropylideneinosine (**2c**), 5′-diphenylphosphoryl-2′,3′-*O*-isopropylidenecytidine (**2e**), and 5′-azido-5′-deoxy-2′,3′-*O*-isopropylidenecytidine (**3e**).

Table 1. Conversion of 5′-OH (1a−e) to 5′-N_3 (3a−e) for Adenosine, Guanosine, Inosine, Uridine, and Cytidine Nucleosides (1 mmol Scale in the Starting Nucleoside)



nucleoside	molecules	yield[a]
adenosine	**1**−**3a**	75%[b]
guanosine	**1**−**3b**	52%[c]
inosine	**1**−**3c**	61%[d]
uridine	**1**−**3d**	76%[e]
cytidine	**1**−**3e**	69%[d]

[a] Isolated yields. [b] (a) DPPA (2 equiv), DBU (3 equiv), *p*-dioxane (3 mL), 110 °C; (b) NaN_3 (5 equiv), 15-crown-5 (0.1 equiv). [c] (a) DPPA (1 equiv), DBU (1 equiv), *p*-dioxane (2 mL), 98 °C; (b) NaN_3 (10 equiv), 15-crown-5 (0.1 equiv). [d] (a) DPPA (2 equiv), DBU (2 equiv), *p*-dioxane (2 mL), 95 °C; (b) NaN_3 (5 equiv), 15-crown-5 (0.1 equiv). [e] (a) DPPA (1.5 equiv), DBU (1 equiv), *p*-dioxane (2 mL), 80 °C; (b) NaN_3 (5 equiv), 15-crown-5 (0.1 equiv).

Results and Discussion

Formation of 5′-Phosphate Nucleosides 2a−e. Synthesis of the 5′-azide nucleosides begins with activation of the 5′-hydroxyl of each isopropylidene-protected nucleoside, as shown in Table 1. Of the five 2′,3′-*O*-isopropylidene nucleosides (**1a**−**e**) examined, adenosine **1a**, inosine **1c**, and cytidine **1e** were able to form the 5′-phosphate ester intermediates in nearly quantitative yields by reacting with excess diphenyl phosphoryl (DPPA, 2 equiv) and DBU (2−3 equiv) at room temperature. Facile separation of the phosphate intermediate

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was achieved for phosphate adenosine **2a**[10] and inosine **2c**, while in the case of cytidine **2e**, separation was more difficult because of the close polarity exhibited by **1e** and **2e**, resulting in a ca. 80% recovery of the product after column purification.

In the formation of phosphate uridine **2d**,[11] a side product was observed when excess DBU was used. Lowering the reaction temperature to 4 °C did not reduce the extent of side-product formation, but varying the concentration of reaction and the equivalence of both DPPA and DBU was effective. An optimal yield of the desired phosphate ester **2d** was achieved by applying 1.5 equiv of DPPA and 1 equiv of DBU at a 0.5 M concentration of the starting material **1d**. Good separation of **2d** from the side product and residual starting material was readily obtained to provide a 72% isolated yield.

In the case of guanosine **1b**, the 5′-phosphate formation was most difficult. The use of excess reagents produced multiple side products, and attempts to isolate some desired product by column chromatography produced only complex mixtures. When 1 equiv of DPPA and 1 equiv of DBU were used under concentrated conditions, side-product formation was minimal, although the conversion of the starting material was also compromised. The ^{1}H NMR spectrum of the crude mixture did reveal the presence of the 5′-phosphate intermediate **2b** in addition to starting material. Isolation of **2b** was problematic, and for this reason the reaction mixture was used directly in the azide displacement, described below, without purification.

Formation of 5′-Azido Nucleosides 3a−e. The azide displacement reactions proceeded smoothly in the presence of excess sodium azide (NaN_3), a catalytic amount of tetrabutylammonium iodide (TBAI), and 15-crown-5. A catalytic amount of TBAI was added to the reaction mixture along with excess NaN_3 and 15-crown-5 to facilitate reactivity in a heterogeneous mixture. It was reasoned that the TBAI and NaN_3 could form the organic azide in situ, thus providing an improved solubility conducive to the desired bimolecular substitution reaction. In addition, the presence of a cation sequester such as 15-crown-5 would further increase the effective concentration of the nucleophile. Adenosine phosphate ester **2a**, as reported previously, gave the desired product in high yield, although an elevated temperature (110 °C) was required for complete conversion.[7] Uridine phosphate ester **2d** and cytidine phosphate ester **2e** were converted to their corresponding azides **3d**[12] and **3e** in high yields at 80 °C. This high conversion rate was warranted by the effective purification of the products by column chromatography. To achieve an optimal conversion of inosine phosphate ester **2c** to its azide analogue **3c**,[13] careful control of temperature was required. No conversion to product was achieved until the reaction temperature was raised to 90 °C. However, at temperatures of 100 °C and above, a significant formation of side product was observed. It was found that the reaction could be carried out at 95 °C for a prolonged period of time to provide **3c** in 63% isolated yield.

Since the 5′-phosphate ester of guanosine **2b** was not isolated in its pure form, the conversion to its azide **3b** was conducted directly on the crude reaction mixture. It was discovered, however, that the presence of TBAI had an adverse effect on the one-pot conversion, resulting in a complex mixture from which little desired product could be isolated efficiently. Therefore, we sought to assess the general necessity of TBAI in the conversion from the phosphate ester to the azide. The conversion of cytidine phosphate ester **2e** to the corresponding azide **3e** was evaluated with (1) NaN_3 alone and (2) NaN_3 along with a catalytic amount of 15-crown-5. After 8 h at 80 °C with NaN_3 alone, 59% of the starting material (**2e**) was converted to product (**3e**), while the reaction with 15-crown-5 showed a 69% conversion (as indicated by ^{1}H NMR). This indicated that the presence of TBAI may not be required for efficient conversion to the azide.

Hence, when the crude mixture of phosphate guanosine **2b** was treated with excess NaN_3 and a catalytic amount of 15-crown-5, conversion to the 5′-azide **3b** was observed at 85 °C.[14] This one-pot procedure for the conversion of **2b** was found to be amenable for the other four bases using 1,4-dioxane as the solvent, without the need for TBAI. The application of appropriate equivalents of DPPA and DBU and control of both reaction concentration and temperature allowed the 5′-phosphate intermediate to be formed efficiently with minimal side-product formation (Table 1).

In summary, we have shown a mild and efficient route for the conversion of 5′-hydroxyl nucleosides into their 5′-azido analogues. The procedure does not require a protection strategy and is applicable for the following five common nucleosides: adenosine, guanosine, inosine, uridine, and cytidine. The two-step, one-pot procedure provided the desired products in good yield for all five bases, providing the synthesis of three previously unreported nucleoside derivatives.

Experimental Section

Unless otherwise specified, reactions were performed under a nitrogen atmosphere with exclusion of moisture. Dry dioxane was purchased from Aldrich, and all other commercially available reagents were used as received. All mixtures were magnetically stirred and monitored by thin-layer chromatography (TLC) using Si250F precoated plates from J. T. Baker (0.25 mm). Flash column chromatography was performed on 32−63 D 60 Å silica gel from ICN SiliTech (ICN Biomedicals GmbH). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance DPX-500 or DPX-400 spectrometer. Chemical shifts are reported using chloroform (^{1}H, δ 7.24 ppm; ^{13}C, δ 77.0 ppm) or methanol (^{1}H, δ 3.30 ppm; ^{13}C, δ 49.9 ppm). Infrared spectra were taken on a Midac M-1200 FTIR spectrometer. All optical rotation data were acquired on a Perkin-Elmer 341 Polarimeter (Na lamp, 546 nm, 20 °C). *The melting points were taken on an Electrothermal melting point apparatus*. High-resolution mass analysis was conducted at The University of Illinois Mass Spectrometry Center.

General Procedure for the Synthesis of 5′-Azido-2′,3′-isopropylidene Nucleosides. In a typical experiment, the starting 2′,3′-*O*-isopropylidene nucleoside (1 mmol) was suspended in dry 1,4-dioxane (0.5 M) at room temperature under a nitrogen atmosphere with magnetic agitation. DPPA (1−2 equiv) and DBU (1−3 equiv) were then added dropwise. The reaction

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(14) The reaction was monitored by HPLC (C_{18}, 70% acetonitrile in water): $t_{\mathbf{3b}}$ = 2.8 min and $t_{\mathbf{2b}}$ = 3.6 min. Although the 5′-azide **3b** has been reported before in literature, this paper provides the first full NMR and mass data of this compound. See: Stout, M. G.; Robins, M. J.; Olsen, R. K.; Robins, R. K. *J. Med. Chem.* **1969**, *12*, 658−62.

was usually completed overnight. The reaction mixture was then heated under nitrogen in an oil bath after the addition of sodium azide (5−10 equiv) and 15-crown-5 (0.1 equiv). The reaction mixture was usually allowed to stir overnight for completion. The solvent was then evaporated, and the crude mixture was purified by column chromatography using a gradient eluent system (from 1:1 hexanes/ethyl acetate to 1:5 ethanol/ethyl acetate).

5′-Azido-5′-deoxy-2′,3′-*O*-isopropylideneadenosine (3a). For this synthesis, 3 equiv of DPPA and 2 equiv of DBU were used, and the temperature was maintained at 110 °C overnight for the conversion to the azide (white solid): mp 137−139 °C (lit.[15] 140−141 °C); $[\alpha]^{20}_D$ +18.8° (*c* 0.166, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.56 (s, 3H), 3.52 (dd, *J* = 5.7, 13.0 Hz, 1H), 3.57 (dd, *J* = 4.7, 13.1 Hz, 1H), 4.34 (dd, *J* = 5.0, 8.6 Hz, 1H), 4.95 (dd, *J* = 3.5, 6.4 Hz, 1H), 5.30 (dd, *J* = 2.4, 6.6 Hz, 1H), 6.07 (d, *J* = 2.8 Hz, 1H), 7.06 (br s, 2H), 8.04 (s, 1H), 8.30 (s, 1H); ^{13}C NMR (125 MHz, d_4-MeOH) δ 24.0, 27.4, 52.4, 83.4, 81.7, 87.2, 84.2, 85.3, 90.7, 115.5, 119.6, 140.6, 148.36, 148.43, 153.1; IR (thin film/NaCl) 3324, 3170, 2988, 2937, 2103, 1646, 1598, 1210, 1096, 1079, 869 cm^{-1}.

5′-Azido-5′-deoxy-2′,3′-*O*-isopropylideneguanosine (3b). For this synthesis, 1 equiv of DPPA and 1 equiv of DBU were used, and the temperature was maintained at 80 °C overnight for the conversion to the azide (white solid): mp 224 °C dec (lit.[14] 244 °C dec); $[\alpha]^{20}_D$ +40° (*c* 0.03, $CHCl_3$); ^{1}H NMR (500 MHz, d_4-MeOH) δ 1.37 (s, 3H), 1.57 (s, 3H), *3.45 (dd, J = 4.7, 13.0 Hz, 1H), 3.54 (dd, J = 4.7, 6.9 Hz, 1H)*, 4.30 (m, 1H), 5.06 (dd, *J* = 3.6, 6.3 Hz, 1H), 5.39 (dd, *J* = 2.4, 6.2 Hz, 1H), 6.05 (d, *J* = 2.1 Hz, 1H), 7.86 (s, 1H); ^{13}C NMR (125 MHz, d_4-MeOH) δ 25.6, 27.5, 53.5, 83.4, 85.4, 87.2, 91.5, 115.5, 118.3, 138.8, 152.5, 155.4, 159.4; IR (thin film/NaCl) 3317, 3107, 2995, 2909, 2398, 2088, 1622, 1578, 1533, 1489, 1374, 1092, 1077, 1059 cm^{-1}; HRMSFAB (*m*/*z*) calcd for $C_{13}H_{16}N_8O_4$ (MH^+) 349.1373, found 349.1372.

5′-Diphenylphosphoryl-2′,3′-*O*-isopropylideneinosine (2c). For this synthesis, 2 equiv of DPPA and 2 equiv of DBU were used to give a white solid: mp 152−154 °C; $[\alpha]^{20}_D$ −13.2° (*c* 0.078, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.61 (s, 3H), 4.46 (m, 3H), 4.96 (dd, *J* = 3.1, 6.3 Hz, 1H), 4.97 (dd, *J* = 3.6, 6.3 Hz, 1H), 6.07 (d, *J* = 2.5 Hz, 1H), 7.12−7.31 (m, 10H), 7.86 (s, 1H), 8.08 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.3, 27.1, 67.8, 80.9, 84.4, 84.7, 90.9, 114.9, 119.9, 125.6, 129.6, 139.0, 145.1, 148.2, 150.2, 158.8; IR (thin film/NaCl) 3059, 2990, 2939, 2874, 1700, 1588, 1213, 1189, 1162, 957, 757, 689 cm^{-1}; HRMSFAB (*m*/*z*) calcd for $C_{25}H_{25}N_4O_8P$ (MNa^+) 563.1308, found 563.1308.

5′-Azido-5′-deoxy-2′,3′-*O*-isopropylideneinosine (3c). The temperature for conversion was maintained below 95 °C overnight to give a white solid: mp 205 °C dec (lit.[13] 222 °C dec); $[\alpha]^{20}_D$ +17.8° (*c* 0.067, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.61 (s, 3H), 3.59 (ddd, *J* = 4.8, 6.0, 13.1 Hz, 2H), 4.36 (dd, *J* = 4.4, 8.5 Hz, 1H), 4.97 (dd, *J* = 3.6, 6.3 Hz, 1H), 5.29 (dd, *J* = 2.5, 6.2 Hz, 1H), 6.09 (d, *J* = 2.4 Hz, 1H), 7.95 (s, 1H), 8.23 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 27.2, 52.3, 81.6, 84.4, 85.2, 90.6, 115.1, 125.6, 139.3, 145.4, 148.3, 159.1; IR (thin film/NaCl) 3054, 2990, 2937, 2868, 2103, 1700, 1587, 1212, 1092, 1079 cm^{-1}; HRMSFAB (*m*/*z*) calcd for $C_{13}H_{16}N_7O_4$ (MH^+) 334.1264, found 334.1263.

5′-Azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine (3d). For this synthesis, 1.5 equiv of DPPA and 1 equiv of DBU were used, and the temperature for conversion was maintained at 80 °C overnight to give a colorless oil: $[\alpha]^{20}_D$ +32.0° (*c* 0.068, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.55 (s, 3H), 3.60 (d, *J* = 5.6 Hz, 2H), 4.23 (dd, *J* = 5.8, 9.2 Hz, 1H), 4.78 (dd, *J* = 4.4, 6.7 Hz, 1H), 4.96 (dd, *J* = 2.3, 6.7 Hz, 1H), 5.65 (d, *J* = 2.3 Hz, 1H), 5.74 (dd, *J* = 1.8, 7.9 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 8.59 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 27.5, 52.7, 81.8, 84.7, 86.0, 94.9, 103.3, 115.3, 142.6, 150.2, 163.1; IR (thin film/NaCl) 3178, 3061, 2988, 2938, 2103, 1691, 1457, 1380, 1270, 1213, 1158, 1092, 1069, 861, 812, 760 cm^{-1}; HRMSFAB (*m*/*z*) calcd for $C_{12}H_{16}N_5O_5$ (MH^+) 310.1151, found 310.1151.

5′-Diphenylphosphoryl-2′,3′-*O*-isopropylidenecytidine (2e). For this synthesis, 2 equiv of DPPA and 2 equiv of DBU were used to give a colorless oil: $[\alpha]^{20}_D$ +27.5° (*c* 0.152, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.52 (s, 3H), 4.38 (m, 1H), 4.54 (m, 1H), 4.84 (dd, *J* = 3.6, 6.4 Hz, 1H), 4.99 (dd, *J* = 1.8, 6.4 Hz, 1H), 5.71 (d, *J* = 1.8 Hz, 1H), 5.78 (d, *J* = 17.7 Hz, 1H), 7.18−7.40 (m, 10H), 7.60 (d, *J* = 17.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 27.3, 70.5, 82.6, 86.1, 87.7, 95.9, 97.6, 115.2, 121.1, 121.2, 126.9, 131.1, 145.9, 151.6, 151.7, 166.8; IR (thin film/NaCl) 3334, 3201, 3068, 2988, 2940, 1724, 1652, 1490, 1286, 1213, 1189, 1162, 957, 775, 688 cm^{-1}; HRMSFAB (*m*/*z*) calcd for $C_{24}H_{26}N_3O_8P$ (MH^+) 516.1536, found 516.1535.

5′-Azido-5′-deoxy-2′,3′-*O*-isopropylidenecytidine (3e). For this molecule, the temperature for conversion was maintained at 80 °C overnight to give a white solid: mp 97−100 °C; $[\alpha]^{20}_D$ +46.7° (*c* 0.472, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.53 (s, 3H), 3.62 (ddd, *J* = 4.5, 7.1, 12.5 Hz, 2H), 4.22 (m, 1H), 4.85 (t, *J* = 4.3 Hz, 1H), 5.10 (d, *J* = 4.3 Hz, 1H), 5.49 (br s, 1H), 5.70 (d, *J* = 7.4 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 25.7, 27.5, 53.1, 82.7, 85.3, 87.4, 95.2, 97.6, 101.2, 114.5, 144.7, 155.8, 166.5; IR (thin film/NaCl) 3335, 3179, 2988, 2937, 2102, 1650, 1490, 1376, 1287, 1275, 1210, 1090, 788, 756 cm^{-1}; HRMSFAB (*m*/*z*) calcd for $C_{12}H_{16}N_6O_4$ (MNa^+) 331.1131, found 331.1130.

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Supporting Information Available: Spectra (^{1}H and ^{13}C NMR) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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