

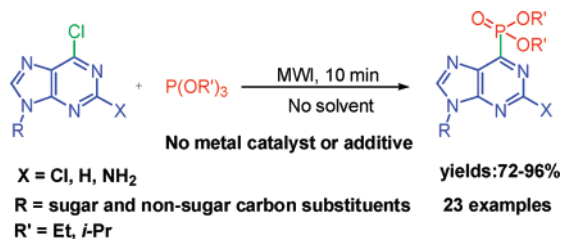
Synthesis of Novel C6-Phosphonated Purine Nucleosides under Microwave Irradiation by S_NAr–Arbuzov Reaction

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Novel C6-phosphonated purine nucleosides were obtained in good to excellent isolated yields by the simple and catalyst-free S_NAr–Arbuzov reaction of trialkyl phosphite with 6-chloropurine nucleosides, including a series of nonsugar carbon nucleosides. Shorter reaction times were needed, and substantially higher yields were obtained under microwave irradiation conditions compared with conventional heating conditions.

Natural purine nucleobases play important roles in many biological processes. Purine derivatives with various substituents at C6 have received considerable attention due to their broad spectrum of biological activities.¹ From a biological standpoint, modification at C6 could adjust the number of H-bond in the purine moiety.² Advances in the synthesis of purines modified at C6 include the use of S_NAr (nucleophilic aromatic substitution),³ Stille coupling,⁴ Suzuki–Miyaura,⁵ and Sonogashira

reactions.⁶ Many carbon-, nitrogen-, oxygen-, and sulfur-linked substituents have been introduced at C6 by these reactions with 6-halopurine nucleosides.

Organophosphorus compounds are remarkable for their diverse and potent biological activities.⁷ Their efficacy is often enhanced by their association with various heterocycles. Phosphonated azaheterocycles are an important class of compounds with high biological potential as conformationally restricted bioisosteres of amino acids.⁸ Very recently, the heterocycles bearing the phosphorus functionalities have been synthesized, which would serve in further functionalizations to produce molecular diversity and produce biologically active compounds.⁹ However, there is no report on the purine containing phosphorus substituents up to date.

Phosphonation reactions can be carried out in a number of ways,¹⁰ the Arbuzov reaction probably being the most classical one,^{10a,b} together with S_NAr^{10c} or the Pd-coupling reaction on unsaturated halides,^{10d–f} and especially on electron-deficient aromatic systems.^{10g,h} As far as Arbuzov-catalyzed¹⁰ⁱ or catalyst-free reaction is concerned, alkyl halides (mostly primary) and acyl halides are commonly used as substrates,¹¹ and aromatic halides as well as heteraromatic halides can also undergo this reaction at certain conditions.¹²

Microwave irradiation is used as an alternative thermal energy source to conventional heating in organic synthesis. The use of microwave irradiation has been applied to a wide range of reaction types, including S_NAr, cycloaddition, and organometallic reactions. Many of these reactions have been demonstrated to result in higher yield and/or selectivity under microwave irradiation compared with using a heating bath.¹³

Herein, during the ongoing course of our study on the development of new methods for the synthesis of nucleoside analogues under microwave irradiation,¹⁴ we applied microwave-

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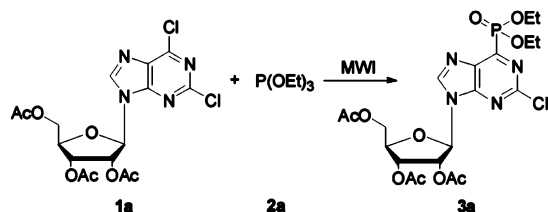
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SCHEME 1. Reaction of 2,6-Dichloro-9-(β -D-triacetoxy-ribofuranosyl)purine Nucleoside with Triethyl Phosphate


assisted S_NAr –Arbuzov reaction to the synthesis of a novel series of C6-phosphonated purine nucleosides, which opens a new route for modification at C6 of purine nucleosides.

At first sight, the C6 chloride atom of 6-chloropurines appears as an inactive and/or unexciting chemical entity for S_NAr –Arbuzov reaction compared with commonly used substrates, such as primary alkyl halides or acyl halides. However, from our experience with the facile synthesis of C6-substituted aminopurine analogues under microwave irradiation,^{14b} we knew that the S_NAr reaction of 6-chloropurines could be enhanced by microwave irradiation, so we still envisioned that an S_NAr –Arbuzov reaction of 6-halide purines with trialkyl phosphite could be carried out. With this idea in mind, we initiated the study to generate the C6-phosphonated purine under microwave irradiation. However, the reaction of 6-chloropurine and triethyl phosphonite (**2a**) gave a complex mixture under several temperatures from rt to 150 °C.

Although the side products in the above reaction were not carefully analyzed, a possible postulation was that the unprotected N–H at N9 position prevented the usual reaction. To avoid this side reaction, we decided to use N9-substituted purine nucleosides as substrates. We were pleased to find that the reaction of 2,6-dichloro-9-(β -D-triacetoxyribofuranosyl)purine nucleoside (**1a**) with triethyl phosphite at 100 °C provided the desired C6-phosphonated purine nucleoside (**3a**) in 92% yield within 25 min (Scheme 1).

Spectroscopic data were in agreement with the assigned structure of the compound. High-resolution mass spectrometry shows a clear molecular ion peak at $m/e = 549.1142$, which shows that only one chlorine atom was substituted. ^{31}P NMR indicated a single peak at $\delta = 4.5$ ppm. The C6 atom at $\delta_C = 152.6$ ppm appears as a doublet with a coupling constant, $^1J_{P-C} = 193.6$ Hz. C4 and C5 also appear as a doublet with a smaller coupling constant, $^2J_{P-C} = 21.0$ Hz and $^3J_{P-C} = 11.6$ Hz, respectively. This demonstrated that phosphorus group was attached to C-6 as expected.

Intriguing solvent effects were observed and the results are shown in Table 1. No reaction was observed in CH_2Cl_2 (entry 1), a nonpolar solvent with low boiling point, while a higher yield was obtained in CH_3CN , a polar solvent (entry 2). Although use of ionic liquid improved the yield to 61% (entry

TABLE 1. Effect of Solvent and the Optimization of Reaction Conditions^a

entry	solvent	time (min)	T (°C)	yield ^b (%)
1	CH_2Cl_2	25	41–42	no reaction
2	CH_3CN	25	81–82	13
3	[bmim]BF ₄	25	120	61
4	solvent-free	10	120	96
5	solvent-free	8	150	93
6	solvent-free ^c	20 h	120	8

^a The reaction was conducted with 0.15 mmol of **1a**, 5.8 mmol (1 mL) of **2a**, and 5 mL of solvent under microwave irradiation. ^b Isolated yields based on **1a**. ^c The reaction was carried out in the convectional heating bath.

3), the yield was not higher than in neat conditions (entry 4), so the solvent-free condition was selected for the reaction. At room temperature or 50 °C, the substrate was not fully soluble in $P(OEt)_3$, and the yield was low. Increasing the temperature to 120 °C, the reaction completed within 10 min in the yield of 96% (entry 4). Increasing the temperature to 150 °C, the reaction completed within 8 min in 93% yield (entry 5). That is to say, when the reaction temperature was lower than 120 °C, lower yield was obtained. When the temperature was higher than 120 °C, significant change in yield was not observed. Therefore, 120 °C and 10 min were the optimized reaction conditions. It is noteworthy that this method does not require the use of a catalyst, whereas in most cases, the synthesis of (hetero)-arylphosphonates cannot be performed without a suitable metal complex.¹⁵

The reaction between 2,6-dichloro-9-(β -D-triacetoxyribofuranosyl)purine nucleoside and triethyl phosphate under convectional heating conditions and MWI heating conditions was investigated to demonstrate the specific microwave effect. It was found that under conventional heating conditions the reaction gave a low yield (ca. 8.5%) within 20 h at 120 °C (Table 1, entry 6). Microwave-assisted reaction exhibited several advantages over the conventional heating by not only significantly reducing the reaction time but also by improving the reaction yield dramatically and, in the process, eliminating the side reactions, implying the involvement of a specific nonthermal microwave effect.^{14b,16}

Our first attempt to generate the C6-phosphonated purine nucleoside using an S_NAr –Arbuzov procedure was successful. To evaluate the generality of the reaction, a number of 2,6-dichloropurines with various substituents, including a nonsugar carbon substituent, at N9 were subjected to the optimized reaction conditions (Table 2), affording the desired phosphonates in good to excellent isolated yields (74–96%). The kind of substituents at N9 had little impact on the yields of the products, other than the triacysugar- and allyl-substituted substrates giving much higher yields.

To study the influence of substituent groups at C2, a series of 6-chloropurines and 2-amino-6-chloropurines were employed as the substrates under optimized reaction conditions (Table 3). In most cases, replacement of the chloride by H or NH_2 led to lower yields of the corresponding phosphonates after

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noteworthy that this method does not require the use of a catalyst. The resulting phosphonated purine nucleosides are important candidates for biologically active compounds. Our report opens an effective new route for modification at C6 of purine nucleosides. The pharmacological evaluation of these compounds is undergoing in our laboratories.

Experimental Section

Preparation of Diethyl 2-Chloro-9-(β -D-triacetoxiribofuranosyl)purinyl Phosphonate (3a). Purine nucleoside **1a** (0.15 mmol) was put in a 5 mL glass vial equipped with a small magnetic stirring bar. To this was added 1 mL of triethyl phosphite. Then the mixture was put into the cavity of the microwave synthesis apparatus and irradiated at 400 W at 120 °C for 10 min. After completion of the reaction, the vial was cooled to room temperature. After evaporation of the unreacted P(OEt)₃, the crude product was purified by column chromatography over silica gel using neat ethyl acetate as the eluent, to give purine phosphonate **3a**. Light yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ ppm 8.39 (s, 1H), 6.18 (d, J = 5.2 Hz, 1H), 5.75 (t, J = 5.6 Hz, 1H), 5.51 (t, J = 5.2 Hz, 1H), 4.38 (t, J = 4 Hz, 1H), 4.35–4.28 (m, 6H), 2.06 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.32 (t, J = 7.2 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 169.8, 169.1, 168.9, 153.9, 153.7 (d, $^1J_{C-P}$ = 193.6 Hz), 153.3–153.1 (d, $^3J_{C-P}$ = 11.6 Hz), 145.4, 134.4–134.2 (d, $^2J_{C-P}$ = 21.0 Hz), 85.8, 80.2,

72.6, 70.0, 63.9 (d, $^2J_{C-P}$ = 6.0 Hz), 62.4, 20.2, 20.0, 19.8, 15.9 (d, $^3J_{C-P}$ = 6.0 Hz); ³¹P NMR (CDCl₃, 100 MHz) δ 4.5; HRMS calcd for C₂₀H₂₇ClN₄O₁₀P [M + H⁺] 549.1153, found 549.1142.

The reaction conditions described in the experimental section were representative and all ratios and concentrations of reactants remained constant for the other substrates.

Preparation of Diethyl 2-Chloro-9-(β -D-triacetoxiribofuranosyl)purinyl Phosphonate (3a) with Conventional Heating. Purine nucleoside **1a** (0.15 mmol) was put in a 5 mL glass vial equipped with a small magnetic stirring bar. To this was added 1 mL of triethyl phosphite. The mixture was stirred in oil heating bath at 120 °C for 20 h. Then the vial was cooled to room temperature. After evaporation of the unreacted P(OEt)₃, the resulted residue was purified by column chromatography over silica gel using neat ethyl acetate as the eluent, to give purine phosphonate **3a**.

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Supporting Information Available: NMR data of all synthesized compounds and full characterization of novel compounds as well as X-ray crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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