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Synthesis of Novel C6-Phosphonated Purine Nucleosides under Microwave Irradiation by SNAr−Arbuzov Reaction

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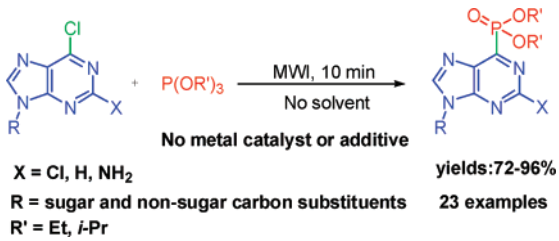
Received December 18, 2007



Novel C6-phosphonated purine nucleosides were obtained in good to excellent isolated yields by the simple and catalyst-free SNAr−Arbuzov reaction of trialkyl phosphite with 6-choloropurine 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.

Organphosphorus 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 SNAr[10c] or the Pd-coupling reaction on unsaturated halides,[10d−f] and especially on electron-deficient aromatic systems.[10g,h] As far as Arbuzov-catalyzed[10i] 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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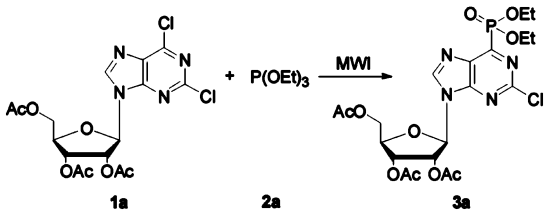
10.1021/jo702680p CCC: $40.75
Published on Web 02/29/2008

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



1a 2a 3a

assisted SNAr−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 SNAr−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-choloropurines could be enhanced by microwave irradiation, so we still envisioned that an SNAr−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-dicholoro-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 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]

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**, 5.8mmol (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.

The reaction between 2,6-dicholoro-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 SNAr−Arbuzov procedure was successful. To evaluate the generality of the reaction, a number of 2,6-dicholoropurines 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 triacylsugar- 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-choloropurines 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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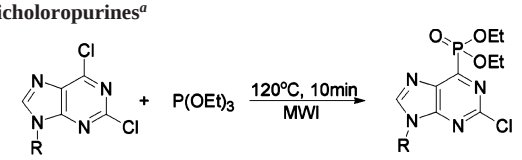
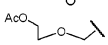
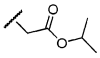
TABLE 2. Reaction of Triethyl Phosphite with Various 2,6-Dicholoropurines[a]



1a-1k 2a 3a-3k

entry	product	R	yield/% [b]
1	**3a**		96
2	**3b**		93
3	**3c**		82
4	**3d**		86
5	**3e**		80
6	**3f**		79
7	**3g**		80
8	**3h**		91
9	**3i**		78
10	**3j**		82
11	**3k**		74

[a] The reaction was conducted with 0.15 mmol of **1** and 5.8 mmol (1 mL) of **2a** under microwave irradiation. [b] Isolated yields based on **1**.

purification, indicating that the electron-donating effects on C2 could lead to decrease of the yields. Hydroxyl unprotected sugar nucleosides were not suitable for this reaction under the optimized conditions due to their poor solubility in $P(OEt)_3$. Interestingly, when 6-chloro-9-(β-D-2′,3′-isopropylribofuranosyl)purine nucleoside was employed, the reaction could proceed smoothly in good yield (entry 6). The exo-NH_2 of guanosine was also tolerated (entry 8).

These 6-chloropurine nucleosides can be easily obtained by chlorination of protected inosine or guansine with $POCl_3$ under previously developed conditions in good yields.[17] The nonsugar carbon purine nucleosides can be synthesized by alkylation of 6-chloropurine with nonsugar carbon chains. Thus, the method is a promising route for the synthesis of C6-phosphonated purine nucleosides.

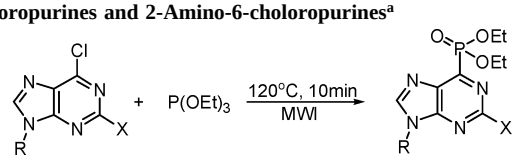
Final confirmation for the structures of phosphonated products was derived from an X-ray single crystal analysis. Furthermore, the oxygen atom of P═O can interact with other molecules through the H-bond, which can be applied to develop biologically active compounds.

We also extended triethyl phosphite to triisopropyl phosphate (**2b**) to afford phosphonated products **3t**−**v** with comparable yields (Scheme 2).

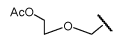
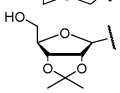
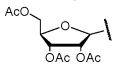
The use of microwave irradiation to generate phosphonated purines was also tested on other hetercyclic scaffolds. For example, 4-phosphonated pyrazolopyrimidine could also be synthesized in good yield from the corresponding 4-chloropyrazolopyrimidine[18] using the same reaction conditions (Scheme 3). This further demonstrates the generality of this microwave-assisted SNAr−Arbuzov reaction to generate phosphonated hetercyclic scaffolds.

In conclusion, the first synthesis of purine nucleosides containing a phosphonate group at C6 is developed, starting from easily accessible 6-chloropurine nucleosides, via Abuzov-type reaction. Microwaves can lead to dramatic reduction of reaction times and substantial increase of the yields. It is

TABLE 3. Reaction of Triethyl Phosphite with Various 6-Chloropurines and 2-Amino-6-choloropurines[a]

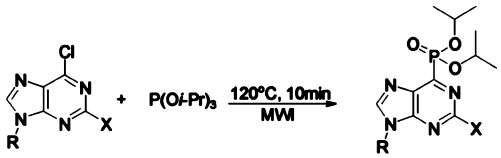


1l-1r: X = H
1s: X = NH_2
2a
3l-3r: X = H
3s: NH_2

entry	product	R	yield %[b]
1	**3l**		75
2	**3m**		76
3	**3n**		79
4	**3o**		78
5	**3p**		76
6	**3q**		81
7	**3r**		76
8	**3s**		74

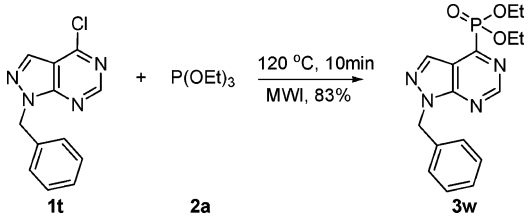
[a] The reaction was conducted with 0.15 mmol of **1** and 5.8 mmol (1 mL) of **2a** under microwave irradiation. [b] Isolated yields based on **1**.

SCHEME 2. Reaction of Triisopropyl Phosphite with 6-Chloropurines



1a
1c
1l
2b
3t: R = β-D-triacetoxyribofuranosyl, X = Cl, yield = 94%
3u: R = benzyl, X = Cl, yield = 83%
3v: R = benzyl, X = H, yield = 72%

SCHEME 3. The Reaction of Triethyl Phosphite with 4-Chloropyrazolopyrimidine



1t 2a 3w

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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-triacetoxyribofuranosyl)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. ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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); ^{31}P NMR ($CDCl_3$, 100 MHz) δ 4.5; HRMS calcd for $C_{20}H_{27}ClN_4O_{10}P$ [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-triacetoxyribofuranosyl)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**.

Acknowledgment. We are grateful to the National Natural Science Foundation of China (20772024) for financial support.

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.

JO702680P