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A Facile Approach to Phosphonic Acid Diesters

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ABSTRACT: *The symmetric H-phosphonates of carbohydrate and other compounds were conveniently prepared by direct transesterification of the corresponding monohydroxylic compounds with diphenyl phosphite. The approach has the merits of mild reaction conditions and high yields.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:208–210, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10130

INTRODUCTION

Recently, there is an increasing interest in phosphodiesters with respect to their particular biological and chemical properties. The phosphodiester structures, such as nucleic acids [1] and phospholipids [2], are fully studied. On the contrary, there is little information about the significance and the properties of phosphodiesters that link saccharides exclusively [3,4]. For the study of the biological significance of carbohydrate phosphonates, we primarily synthesized symmetric H-phosphonates of saccharides, which are versatile intermediates in the synthesis of phosphonate derivatives of carbohydrate. It can be further conjugated with amino acid using Todd reaction [5] and can also be oxidized by iodine, sulfur, or selenium to obtain phosphonate, phosphorothioate, and phosphoroselenoate of carbohydrate respectively [6].

There were three methods reported in the literature for the synthesis of symmetric H-phosphonates. The first is the phosphoramidate method, which has been greatly developed in the synthesis of oligonucleotides [7]. Using this method, phosphoramidate diesters are synthesized and hydrolyzed under the activation of 1*H*-tetrazole. The second is the H-phosphonate method [8], which was first described by Todd in 1952 [9] and later developed by Stawinski [10]. It has become a powerful method for the introduction of phosphodiesters in natural products. It is necessary to prepare H-monophosphonates and then couple with another alcohol. The third is the condensation of phosphonic acid and hydroxy compounds by dicyclohexycarbodiimide [11]. Although this method has the advantage to start from commercially available compounds, its yield is moderate and the by-product dicyclohexylurea is hard to remove. Therefore, it is necessary to set up a facile way.

RESULTS AND DISCUSSION

Diphenyl phosphite (**2**; DPP) is a commercially available, inexpensive phosphorylation reagent. It can

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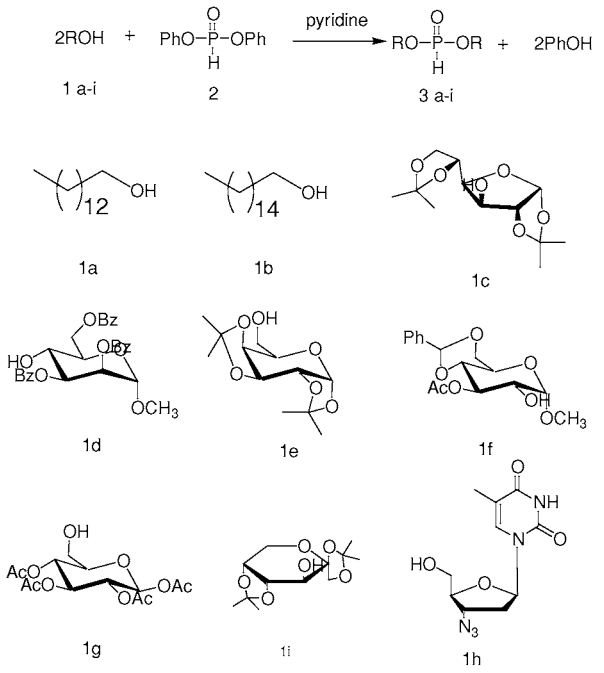
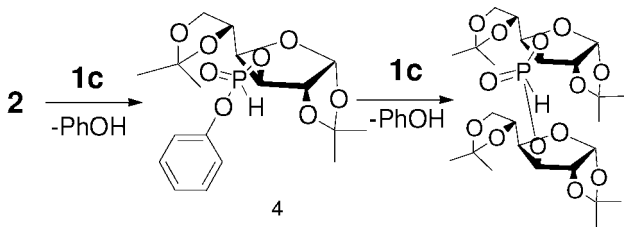


SCHEME 1 Symmetric H-phosphonate prepared via transesterification with DPP (**2**).

undergo fast transesterification with alcohols in pyridine to afford mixtures of the corresponding dialkyl and alkyl phenyl H-phosphonate [12]. Inspired by this observation, a new approach to symmetrical disaccharide H-phosphonate diesters was investigated (Scheme 1). Tetradecanol **1a** was selected to explore the possibility. DPP was treated with 2 equiv. of tetradecanol in anhydrous pyridine at room temperature. The reaction was monitored by ^{31}P NMR spectroscopy. After 1.5 h, all the DPP (signal $\delta_p = 1.7$ ppm) was quantitatively converted into a new peak ($\delta_p = 8.5$ ppm), which was assigned to the H-phosphonate **3a** by an authentic sample [13]. Hexadecanol **1b** was also tested and the result was excellent.

The reaction of 1,2:5,6-diisopropylidene-D-glucose (**1c**) with DPP (Scheme 2) was monitored by the ^{31}P NMR spectrum (Fig. 1). Three new peaks



SCHEME 2 Reaction of 1,2:5,6-diisopropylidene-D-glucose (**1c**) with DPP (**2**).

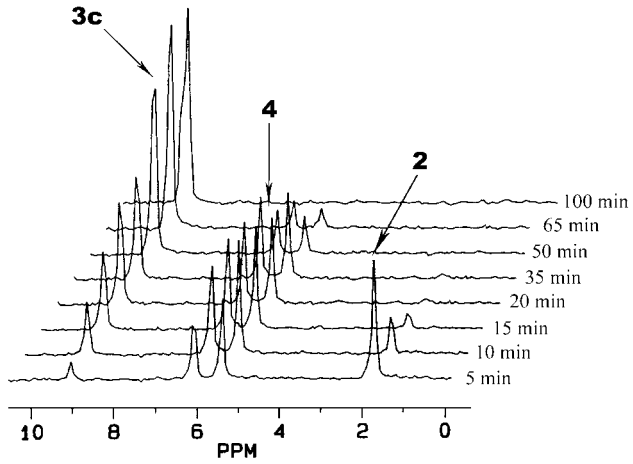


FIGURE 1 The ^{31}P NMR spectra of the reaction of DPP (**2**) with **1c** in pyridine.

appeared immediately. Those at $\delta = 5.3$ and 6.0 ppm are the signals of H-phosphonate **4**, which is a pair of diastereoisomers. The peak at $\delta = 9.0$ ppm is **3c**. The H-phosphonate **4** was gradually converted to **3c** in almost quantitative yield after 1.5 h. Other monohydroxylic carbohydrate derivatives were investigated and the results are listed in Table 1. In the same way, symmetric H-phosphonate of zidovudine **3h** was synthesized in almost quantitative yield. Compound **3h** is an important intermediate in the synthesis of phosphoramidate prodrugs of zidovudine and has been previously synthesized in moderate yield using the third method [14].

In conclusion, an effective method was set up to prepare symmetric H-phosphonate diesters of carbohydrates. After the pyridine was removed under reduced pressure, the products were obtained in purity of >95% and could be used directly

TABLE 1 The Spectral Data of Symmetric H-Phosphonates[a]

	^{31}P NMR[b]			*ESI-MS*	
	δ	$^1J_{P\text{-}H}$ (Hz)	$^3J_{P\text{-}H}$ (Hz)	$(M+H)^+$	$(M+Na)^+$
3a	8.4	677	8.4	475	497
3b	8.7	686	8.5	531	553
3c	9.0	717	10.4	567	589
3d	10.3	717	10.4	599	621
3e	9.9	717	10.6	567	589
3f	10.2	716	10.5	695	717
3g	10.1	714	10.4	743	765
3h	9.7	718	10.3	567	589
3i	10.6	717	10.4	581	603

[a]All reactions were performed in 1 mmol scale.
[b]The values were determined in pyridine using a Bruker AMP 200 at 81 Hz (85% H_3PO_4 as internal standard).

without further purification [15]. The mild conditions are compatible with the presence of sensitive protecting groups and they make the method useful for synthetic purposes. Efforts to employ this approach in the synthesis of the conjugates carbohydrate with amino acid, some oligosaccharides having phosphonate units and phosphoramidate prodrugs of zidovudine are currently under way in our laboratory.

EXPERIMENTAL

General Experimental Procedure: 1 mmol **1a–j** was co-distilled twice with 2 ml anhydrous pyridine, and then dissolved in 3 ml pyridine. DPP (**2**) (0.5 mmol) in 2 ml pyridine was added in one portion. The mixture was stirred for 2 h. After ^{31}P NMR showed that all the DPP had converted, pyridine was evaporated under vacuum at 40°C. Compounds **3a–j** were obtained in >95% purity judged by ^{31}P NMR.

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[15] For example, compound **3c** has been oxidized to phosphonate directly by I_2 in pridine/H_2O (49:1) in 90% overall yield. Spectroscopic data of the phosphonate (triethylammonium salt): ^{31}P NMR: (81 MHz, $CDCl_3$): −2.81; ^{1}H NMR (500 MHz, $CDCl_3$): 11.32 (br, 1H, Et_3NH^+), 5.87 (d, $J = 3.3$ Hz, 2H, H-1), 4.97 (d, $J = 3.6$ Hz, 2H), 4.66 (dd, $J = 2.7$ Hz, 9 Hz, 2H), 4.42 (dd, $J = 6$ Hz, $J = 12.6$ Hz, 2H), 4.20 (m, 1H, H-5), 4.01 (dd, $J = 6$ Hz, $J = 8.1$ Hz, H-6a, 2H), 4.09 (dd, $J = 6.6$ Hz, 8.1 Hz, H-6b, 2H), 3.09 (m, 6H ($CH_3CH_2)_3NH^+$), 1.12–1.46 (m, 33H); ^{13}C NMR (125 MHz, $CDCl_3$): 111.45, 108.63, 104.83 (C-1), 83.65 (C-2), 80.71 (C-4), 77.74 (C-3), 72.53 (C-5), 66.45 (C-6), 45.80 (2C, ($CH_3CH_2)_3NH^+$), 26.49, 25.15, 8.44 (3C, ($CH_3CH_2)_3NH^+$); ESI–MS (-): 581.