ORGANIC LETTERS

2007
Vol. 9, No. 26
5469−5472

Ring Enlargement of Cyclic Acetals and Ketals: A Way to Seven-Membered Nucleoside Phostones

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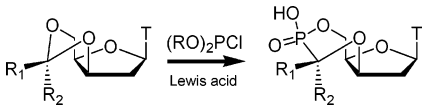
Received October 1, 2007

ABSTRACT



Novel seven-membered nucleoside phostones were prepared by the reaction of chlorodiethyl phosphite with 3′,5′-acetals or ketals derived from *xylo*-dT. A mechanism for the ring enlargement was proposed, and support for it was provided by ab initio calculations.

Cyclic nucleoside phosphates (cNMP) are biologically significant compounds that play a key regulatory role in cell signaling and metabolism.[1] Since these compounds have been observed to modulate protein kinase activity, the search for active analogues—agonists or antagonists—is highly desirable. Interest in these compounds is evident from the number of commercially available modified 3′,5′-cyclic nucleotides used for various biochemical and biological studies.[2] Typical modifications of cyclic nucleotides comprise either a change of configuration of the sugar hydroxyls[3,4] or a replacement of both the bridging and nonbridging oxygen atoms of the six-membered cyclic phosphodiester moiety with another heteroatom. Thus, compounds with the modified phosphodiester moiety, e.g., 5′C-SP(=O)O-3′C,[5,6] 5′C-OP(=O)S-3′C,[7] 5′C-N(R)P(=O)O-3′C,[8] 5′C-N(R)P(=S)O-3′C,[9] 5′C-OP(=O)N(R)-3′C,[10,11] 5′C-OP(=S)N(R)-3′C,[12] 5′C−NH−P(=S)-NH-3′C,[12] 5′C-CH_2P(=O)O-3′C,[13] 5′C-CF_2P(=O)O-3′C,[14] and 5′C-OP(=O)CH_2-3′C,[15,16] have been prepared and biologically evaluated. In contrast to nucleoside cyclothiophosphates and cyclophosphoamides, the three latter compounds, i.e., six-membered cyclic nucleoside phosphonates (nucleoside phostones) with the bridging P−C linkage, exhibited extraordinary chemical and nuclease stabilities.[13−16]

A direct synthesis of simple, seven-membered phostones via ring enlargement of six-membered acetals in their reaction with 2-chloro[1,3,2]dioxaphospholane under Lewis acid catalysis has already been described in the literature.[17]

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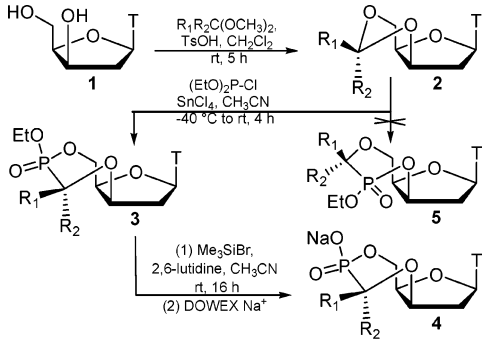
10.1021/ol7023899 CCC: $37.00
Published on Web 11/30/2007

Moreover, a seven-membered carbohydrate 4,6-phostone was obtained as an unexpected product from methyl 4,6-*O*-benzylidene-D-galactopyranoside and triethyl phosphite under TMSOTf catalysis.[18] Our systematic study on the synthesis and biological properties of the nucleoside phosphonic acids and related compounds provided a number of structurally diverse isopolar nucleotide analogues.[19] Among them, a seven-membered nucleoside phostone was prepared by intramolecular esterification of adenosine-5′-*O*-methylphosphonic acid.[20]

In continuation of our research on the reactivity of alkyl phosphites,[21,22] we report here a synthetic route to a new class of analogues of nucleoside-3′,5′-cyclophosphates **4** with a substituted seven-membered phostone ring. These compounds were prepared by the reaction of cyclic 3′,5′-acetals and ketals **2** with chlorodiethyl phosphite (Scheme 1). This reaction resulted in enlargement of the six-membered

Scheme 1. Preparation of Nucleoside Phostones **4**



R_1	R_2	Isolated yield
CH_3	CH_3	**2a** (88%); **3a** (85%); **4a** (72%)
C_6H_5	H	**2b** (91%); **3b** (84%); **4b** (78%)
C_6H_{11}	H	**2c** (86%); **3c** (76%); **4c** (67%)

acetal or ketal ring to that of a seven-membered phostone.

The starting compounds **2a**−**c** were prepared by the reaction of *xylo*-dT **1** with 2,2′-dimethoxypropane, benzaldehyde dimethyl acetal, and cyclohexylcarbaldehyde dimethyl acetal, respectively, in the presence of *p*-toluenesulfonic acid (Scheme 1). In the case of acetals **2b** and **2c**, the *S* epimer was the only isolated product. Its configuration was determined by 2D-ROESY NMR experiments from the observed NOE contacts of the O-C*H*R-O proton to H-3′ and H-5′a in compounds **2b** and **2c**. The vicinal couplings in furanose ring indicate that it adopts a ^3E (C3′-*endo*) conformation, while the annealed 1,3-dioxane ring is in a chair form (Figure 1, form A).

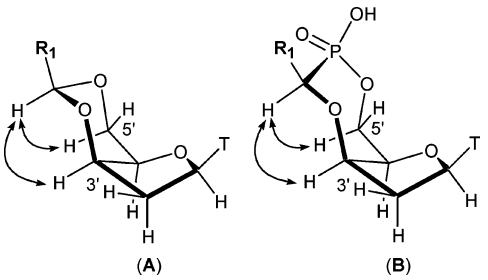


Figure 1. Preferred conformations and selected observed NOE contacts in compounds **2b** and **2c** (A) and **4b** and **4c** (B).

Because the initially employed experimental conditions for the reaction of acetals and ketals with triethyl phosphite in the presence of TMSOTf, which we took from the recently published work,[18] led to *N*-ethylthymine as a product of cleavage of the glycosidic bond, we modified the earlier established protocol.[17] Using chlorodiethyl phosphite and $SnCl_4$ catalysis, we transformed compounds **2a**−**c** into the appropriate phostones **3a**−**c** in good yields. Under these conditions, we did not observe the formation of regioisomer **5** (Scheme 1). In the case of acetals **2b** and **2c**, the reaction proceeded diastereoselectively (>95% de) with retention of configuration on the acetal carbon atom. The *R* configuration was again determined by 2D-ROESY NMR experiments from the observed NOE contacts of proton P-CHR-O to H-3′ and H-5′a in compounds **4b** and **4c**. The vicinal couplings in furanose rings are very similar to those found in **2b** and **2c** and indicate their ^3E (C3′-*endo*) conformation. Although the obtainable vicinal coupling constants do not form a sufficient set for detailed conformation analysis of the seven-membered ring, the above-discussed NOE contacts strongly support a chair form B shown in Figure 1.

In the case of 3′,5′-*O*-isopropylidene derivative **2a**, we examined the influence of several Lewis acids ($SnCl_4$, TMSOTf, $BF_3{\cdot}Et_2O$) and solvents (CH_3CN, CH_2Cl_2) on the course of the phosphonylation reaction in more detail. We found that the reaction catalyzed by 0.1 equiv of $SnCl_4$ or TMSOTf proceeded very rapidly to afford the desired product **3a**. On the other hand, the use of $BF_3{\cdot}Et_2O$ resulted only in the anomerization of the isopropylidene nucleoside **2a** to α-**2a** and in a partial hydrolysis of the thymine nucleobase. Furthermore, the presence of 1.0 equiv of $SnCl_4$ or TMSOTf resulted in the anomerization of **2a** and **3a** and, thus, in the isolation of **4a** and α-**4a** in an equimolar ratio. Regardless of the Lewis acid used, or its concentration, the phosphonylation reaction proceeded regioselectively and with retention of configuration at the acetal carbon atom. In contrast to CH_3CN, the use of CH_2Cl_2 as a solvent favored anomerization (see part 5 in the Supporting Information).

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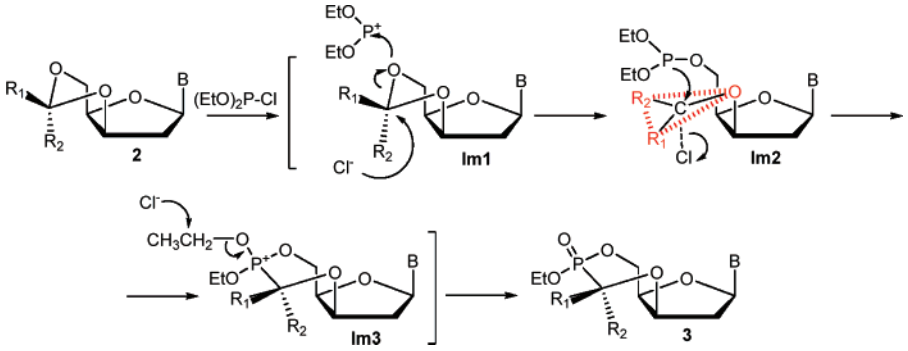
Scheme 2. Proposed Mechanism of Ring Enlargement (Im = Intermediate)



On the basis of our observation that the phosphonylation reaction also proceeded, though very slowly, under heating and in the absence of Lewis acid, we proposed the reaction mechanism depicted in Scheme 2. We reasoned that the $(EtO)_2P^+$ cation[23] (in fact, Lewis acid) formed via heterolysis of $(EtO)_2PCl$ coordinated to the 5′-oxygen atom, and as a consequence, a partial positive charge was induced on the acetal carbon atom. Ring opening of this "activated" acetal **Im1** followed by the intramolecular Arbuzov reaction of **Im2** could lead to the cyclic phosphonium intermediate **Im3**, which in turn could split off the ethyl ester group with the assistance of chloride anion to afford product **3**. Very probably, chloride anion participates both in the acetal ring opening (**Im1**) preventing racemization on the acetal carbon atom and in the stabilization of the phosphonium intermediate **Im3**. In order to check a possible influence of traces of HCl as a Lewis acid present in $(EtO)_2PCl$ on the course of the phosphonylation reaction, we added 0.1 equiv of HCl (anhydrous solution in DMF) to the reaction mixture. Cyclic phosphonates **3a**−**c** were not formed, and we observed only the cleavage of the nucleoside bond of **2a**−**c**.

In order to explain the accelerating effect of the used Lewis acids ($SnCl_4$ and TMSOTf) on the phosphonylation reaction, we examined the ^{31}P NMR spectra of an equimolar mixture of $(EtO)_2PCl$ and the appropriate Lewis acid in two solvents (CH_3CN, CH_2Cl_2), expecting the formation of $(EtO)_2P^+$ cation (shift from ∼160 to ∼300 ppm) as it was described for the $(EtO)_2PCl-AlCl_3$ system.[23] However, no signal at 300 ppm was detected in any case. In contrast to $SnCl_4$, $AlCl_3$ is a much stronger Lewis acid providing, in the reaction with $(EtO)_2PCl$, the $[(EtO)_2P]^+[AlCl_4]^-$ species—a source of the strong $(EtO)_2P^+$ electrophile. In summary, the results obtained suggest that a mechanism involving activation of the acetal ring with Lewis acid as the first reaction step should indeed be considered if Lewis acids are employed as catalysts (see part 8 in the Supporting Information).

Having obtained the phostones **3**, we attempted to open their seven-membered ring to obtain substituted 3′-*O*-methylphosphonates with defined chirality on the carbon atom of the P−C bond, a feature of importance for our further research. Thus, we studied the hydrolysis of phostones **3** to the free phosphonic acids and monomethyl esters using aqueous 1 M sodium hydroxide and methanolic 1 M sodium methoxide, respectively. Suprisingly, the expected products of the ring opening were not observed, and phostonic acids **4** were found as the only products even at elevated temperature. Under the same experimental conditions, the seven-membered carbohydrate phostone[18] was readily cleaved in 1 M aqueous sodium hydroxide to the corresponding phosphonic acid.

To support the proposed reaction mechanism, we attempted to obtain some relevant data from the ab initio calculations. The analysis of conformational energies, transition states, IRC, and electrostatic potential distributions of model systems representing compounds **2** and **4** supported the reaction mechanism depicted in Scheme 2.

The regioselectivity of the phosphonylation reaction could be explained on the basis of the electrostatic potential map of compound **2b** (Figure 2). The possible attack on the acetal carbon atom by chloride anion is allowed from the front side only, as to attack the acetal from the back side is shielded by the electronegative 4′- and 5′-oxygen atoms.

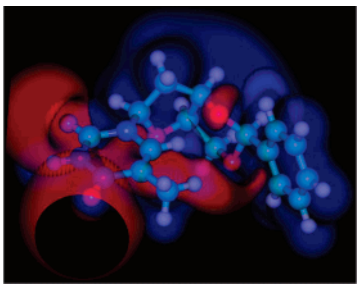


Figure 2. Electrostatic potential distribution in compound **2b**: positive, blue; negative, red (for *XYZ* coordinates, see the Supporting Information).

Ab initio calculations also revealed a tendency of chloride anion to attack acetal carbon from the front side whereas $(EtO)_2P^+$ was attracted to the 5′-hydroxyl (Figure 3).

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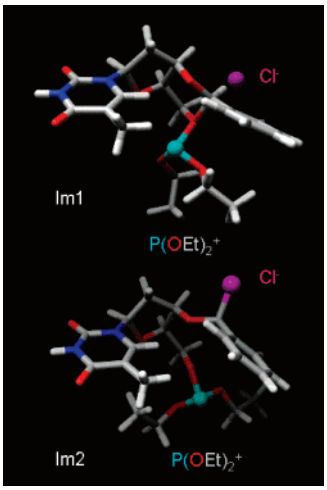

Figure 3. Structures of intermediates **Im1** and **Im2** obtained from ab initio calculations (Scheme 2, the reaction of acetal **2b** with $(EtO)_2PCl$).

In conclusion, we have synthesized novel seven-membered nucleoside phostones branched in α-position to the phosphorus atom, using a simple method based on the reaction of six-membered *xylo*-dT 3′,5′-acetals and ketals with chlorodiethyl phosphite in the presence of catalytic amount of $SnCl_4$. We found that this reaction proceeded in a regio- and diastereoselective manner. Proposed reaction mechanism was supported by a series of ab initio calculations. The elaborated methodology is currently being applied to the acetals and ketals of other nucleosides.

Acknowledgment. Support by Grant Nos. 203/05/0827 and 202/05/0628 (Czech Sci. Found.), Res. Centres LC06061 and LC06077, and Grant No. MSM 0021620835 (Czech M. of Educ.) under research project Z40550506 is gratefully acknowledged. We are indebted to the staff of the Department of Mass Spectrometry (IOCB) for measurements of HR-MS spectra and Dr. Z. Tocik for valuable discussions.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. Details of the phosphonylation reaction and coordinates obtained from ab initio calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

OL7023899