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H-Phosphonylphosphonate triethylester: the first member of a novel family of stable bisphosphorylated compounds; its short synthesis and reactivity with aldehydes

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Abstract—A short preparation of the first member (**1**) of the novel *H*-phosphonylphosphonate family is described. Its reaction with aldehydes provides a straightforward access to the hitherto almost unprecedented class of α-hydroxyphosphinylphosphonates **3** of potential value in particular in medicinal chemistry.

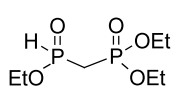
Like simpler *H*-phosphonates, *H*-phosphonylphosphonates (exemplified by the triethylester **1**) are expected to be reasonably stable to air and water and to react readily with various unsaturated systems, like carbonyl compounds including α,β-unsaturated ketones and esters.[1] More specifically, their reaction with aldehydes would offer a direct route to the yet largely unprecedented series of hydroxyphosphinylphosphonates of type **3**.[2] Apart from synthetic chemistry, these compounds are also interesting from the medicinal chemistry viewpoint as novel isosters of the widespread and biologically relevant pyrophosphates.

Despite these potentials, it seems that no members of the *H*-phosphonylphosphonate family have been described so far in the literature;[3] this probably reflects the difficulty to prepare and to handle their obvious precursors like the phosphonylphosphonite **2**.[4–6] In fact, it has been proved that the original preparation of tetra-alkyl derivatives of type **2**[5] is difficult to repeat, leading others to propose instead a detailed but inconvenient procedure based on the non-obvious access to bis(dichloroalumino)methane.[6,7]

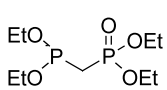
We present here an easy, two-step preparation of **1**, as well as a study of its reactivity with various aldehydes. As shown in Scheme 1, this preparation involves a key-bisphosphorylated borane complex **5** resulting from the nucleophilic attack of lithiomethyl(diethyl)phosphonate on the preformed borane adduct **4** of commercial chlorodiethylphosphite.

In preliminary experiments, the BH_3 adduct **4** appeared partly labile during SiO_2 flash column chromatography. Later on, this adduct was better prepared and used in situ. The higher acidity of the methylenic protons flanked by the two phosphorus in **5** compared to the acidity of the methyl group in the starting diethylmethylphosphonate required at least 2.5 equiv. of the lithio reagent to be used, in order to obtain good yields of **5**. This latter adduct proved to be perfectly stable to air, water and SiO_2 column chromatography and could be stored over a long period of time at room temperature without any decomposition.[8]

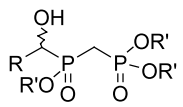
Although a few related displacements by simpler lithiated nucleophiles on borane complexes of dialkylchlorophosphine have already been described,[9] the reaction starting from dialkylchlorophosphite appears not to have been studied. To our knowledge, the resulting borane complex **5** is totally unprecedented and represents a valuable new class of bisphosphorylated compounds.



1



2



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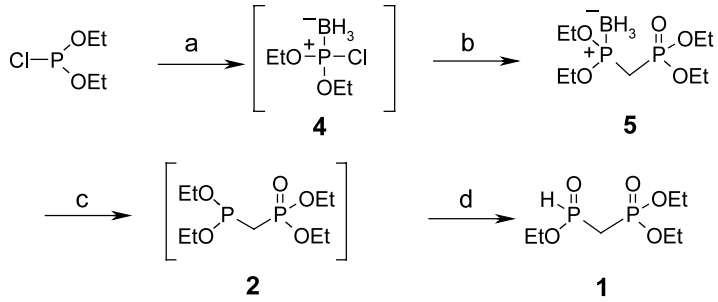
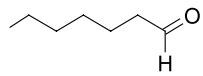
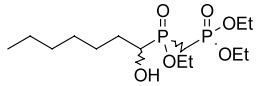
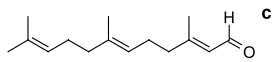
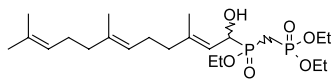
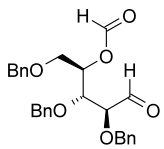
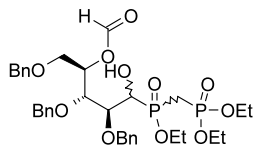
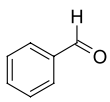
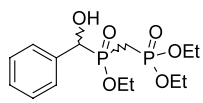
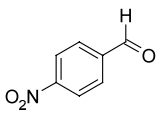
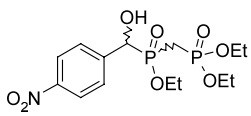
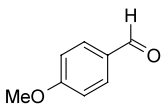
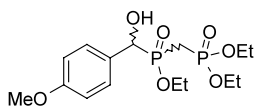
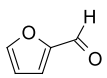
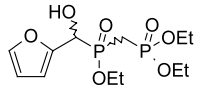


Scheme 1. *Reagents and conditions* (all experiments under an Ar atmosphere): (a) BH_3·THF (1 equiv.), THF, 20°C, 2 h; (b) $LiCH_2P(O)(OEt)_2$ (2.5 equiv.) from *n*-BuLi and $CH_3P(O)(OEt)_2$, THF, −78°C→rt, 85% (for (a) and (b)); (c) Et_2NH, 53°C, 12 h; (d) AcOH, 40°C, 1 h, 60%.

Table 1. Reaction of **1** (1.2 equiv., unless specified) with various aldehydes

Entry	Substrate	Conditions	Products [a]	Yield [b]
1		Et_3N CH_2Cl_2, 40°C, 5h		60%
2	 [c]	K_2CO_3 CH_2Cl_2:DMF (9:1) 40°C, 2h (2 equiv. of **1**)		50%
3	 [d]	CsF THF, 40°C, 1h		60%
4		Et_3N CH_2Cl_2, 40°C, 5h		47%
5		Et_3N CH_2Cl_2, 40°C, 1h30		73%
6		K_2CO_3 CH_2Cl_2:DMF (9:1) 40°C, 2h (2 equiv. of **1**)		45%
7		Et_3N CH_2Cl_2, 40°C, 3h		50%

[a] In each case, an equimolar diastereoisomeric mixture was obtained.
[b] Unoptimized.
[c] Commercial mixture of isomers (FLUKA).
[d] Prepared from tri-*O*-benzyl-D-glucal according to Ref. 12.

Access to the *H*-phosphonylphosphonate **1** was best accomplished in a one-pot procedure, involving first a diethylamine deboronation as already recommended for other P–BH_3 adducts.[10] After evaporation of diethylamine under argon, tetraethylphosphonylphosphonite **2** appeared as the only significant bisphosphorylated species in ^{1}H NMR as evidenced by its characteristic dd ($J=19.5, 4.3$ Hz) at 2.21ppm.[5,6] Its conversion into **1** was completed using glacial acetic acid under a strict argon atmosphere,[4] in order to minimize the formation of tetraethylmethylenediphosphonate, the oxidation product of **2**, followed by SiO_2 flash chromatography using EtOAc/EtOH (9/1, v/v) as eluent. Although less stable than its precursor **5**,[11] *H*-phosphonate **1** could be stored without decomposition over a long period of time at −15°C under argon and could be routinely safely handled at room temperature in air.[8]

We then examined the reactivity of **1** on representative aromatic and aliphatic aldehydes, using basic conditions as already reported for the condensation of simpler *H*-phosphonates (Table 1).[1]

Triethylamine in CH_2Cl_2 gave satisfactory yields for the majority of aldehydes except for farnesal (entry 2) and *p*-anisaldehyde (entry 6). In these cases, using two equivalents of **1** and K_2CO_3 in the presence of DMF as a co-solvent was beneficial. In the case of the sugar-derived aldehyde (entry 3), triethylamine caused a total epimerization of the chiral center next to the aldehyde function. Using cesium fluoride in suspension in the medium instead completely prevented this racemization.

In all cases, besides some starting aldehyde (ca. 15%) and a few minor unidentified more polar compounds, the only major products detected corresponded to an equimolar diastereoisomeric mixture of the desired α-hydroxyphosphinylphosphonates.[13]

In summary, we have developed a straightforward preparation of a stable representative member of a novel family of bisphosphorylated compounds: the *H*-phosphonylphosphonates. Reaction of these compounds with aldehydes provides a direct entry into the almost unexplored class of hydroxyphosphinylphosphonate derivatives. From a biological standpoint, these latter compounds are very interesting, as they may mimic pyrophosphates. In particular, the farnesylated compound (Table 1, entry 2) represents the triethyl ester of a novel analog of farnesyldiphosphate.

We are currently applying our new methodology to the synthesis of highly functionalized, biologically active α-hydroxyphosphinylphosphonates.

Acknowledgements

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References

1. For a review article, see: Pudovik, A. N.; Konovalova, I. V. *Synthesis* **1979**, 81–96.
2. (a) The simple hydroxymethyl derivative (R = H in **3**) has been recently prepared in six steps: Flohr, A.; Aemissegger, A.; Hilvert, D. *J. Med. Chem.* **1999**, *42*, 2633–2640; (b) The related hydroxylated phosphinylphosphinites proved unstable: Novikova, Z. S.; Odinets, I. L.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1987**, *57*, 525–533.
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4. Phosphinites are known to be easily hydrolyzed under acidic conditions into the corresponding *H*-phosphonates; see for instance: Xu, Y.; Hengxu, W.; Jiazhi, X. *Liebigs Ann. Chem.* **1988**, 1139–1143.
5. Novikova, Z. S.; Prishchenko, A. A.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1977**, *47*, 775–781.
6. McClard, R. W.; Fujita, T. S.; Stremler, K. E.; Poulter, C. D. *J. Am. Chem. Soc.* **1987**, *109*, 5544–5545.
7. Explosions have been reported during the preparation of $Cl_2AlCH_2AlCl_2$; for a reported safe, but still not that easy preparation, see: Piotrowski, A. M.; Malpass, D. B.; Boleslawski, M. P.; Eisch, J. J. *J. Org. Chem.* **1988**, *53*, 2829–2835.
8. Selected analytical data:
1: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31 (1H, dt, $J=581.1$, 2.3 Hz, P-H), 4.15 (6H, m), 2.45 (2H, dt, $J=22.0$, 2.3 Hz), 1.31 (9H, m).^{13}C NMR (62.9 MHz, $CDCl_3$) δ 62.8 (d, $J=6.3$ Hz), 62.6 (d, $J=6.4$ Hz), 62.5 (d, $J=6.4$ Hz), 27.9 (dd, $J=133.0$, 84.0 Hz, PCH_2P), 16.0 (d, $J=10.5$ Hz), 15.9 (d, $J=11$ Hz). ^{31}P NMR (105.9 MHz, $CDCl_3$) δ 31.4 (d, $J=6.3$ Hz, H-P), 23.8 (d, $J=6.3$ Hz). SM (electronic impact) m/z 245 (M+1), 243 (M−H).
5: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.12 (8H, m), 2.42 (2H, dd, $J=20.7$, 10.5 Hz), 1.30 (12H, m), ca. 0.6 (3H, broad q, $J=$ca. 100 Hz, BH_3).^{13}C NMR (62.9 MHz, $CDCl_3$) δ 63.9 (d, $J=3.7$ Hz), 62.4 (d, $J=6.4$ Hz), 29.2 (dd, $J=$ 137.0, 43.7 Hz, PCH_2P), 16.5 (d, $J=6.1$ Hz), 6.4 (d, $J=6.1$ Hz). ^{31}P NMR (105.9 MHz, $CDCl_3$) δ 35.9 (s), 143.3 (q, $J=82.3$ Hz, P–BH_3). SM (electronic impact) m/z 285 (M−1, ^{11}B), 284 (M−1, ^{10}B).
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11. On prolonged reaction time under basic conditions or on simply standing in the air at room temperature, **1** tends to be converted to the more polar compound $(OH)(H)(O)PCH_2P(O)(OEt)_2$.
12. Harvey, T. C.; Simiand, C.; Weiler, L.; Withers, S. G. *J. Org. Chem.* **1997**, *62*, 6722–6725.
13. These hydroxyphosphinylphosphonates appeared in particular uncontaminated by any cyclized or rearranged products: see Ref. 2b.