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Phosphorylation of (1-aryl-1-hydroxymethyl)phosphonates

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The reaction of dimethyl (1-aryl-1-hydroxymethyl)phosphonates with 1-chloro-3-phospholene 1-oxides, diphenylphosphinic chloride or diphenyl chloridophosphonate affords the corresponding (1-phosphoryloxymethyl)phosphonates. The products with two different >P(O)– moieties exhibit characteristic δ_P shifts and $^3J_{P,P}$ couplings in the ^{31}P NMR spectra.

R = Ph, OPh

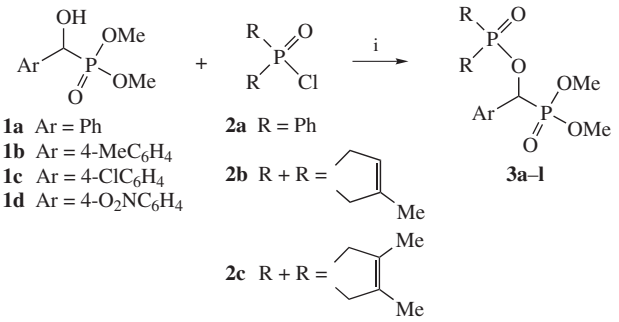
R + R = $CH_2CH=C(Me)CH_2$, $CH_2C(Me)=C(Me)CH_2$

α-Hydroxy phosphonates have attracted attention due to their biological effects, *e.g.*, some of them are known as enzyme inhibitors, antibacterial and antibiotic agents, fungicides, herbicides, antioxidants and anticancer agents.[1] Our recent research revealed that dibenzyl (α-hydroxymethyl)phosphonates may be promising anticancer agents against the Mes-Sa human uterine sarcoma cell line.[2] The versatile bioactivity of α-hydroxy phosphonates stimulated the synthesis of related derivatives. α-Acyloxy phosphonates (recognized as potential enzyme inhibitors,[3,4] herbicides,[5–12] fungicides,[13] insecticides[14] and anticancer agents[15]) were synthesized through the O-acylation of the corresponding α-hydroxy phosphonates, mostly with carboxylic chlorides usually applied together with triethylamine[4,5,9–13] or pyridine.[4,6–9,16] The acylation of α-hydroxy phosphonates with acetic anhydride may be catalyzed by $Cu(OTf)_2$[17] or $TiCl_3(OTf)$,[18] or carried out under microwave irradiation.[19] The reaction of the α-hydroxy function with free carboxylic acids was performed in the presence of *N*,*N'*-dicyclohexylcarbodiimide,[3,15,20] or under Mitsunobu conditions.[21] Iso(thio)cyanates were applied to afford the corresponding α-(thio)carbamoyloxyphosphonates.[22–24] In addition to carboxylic acid derivatives, sulfonyl chlorides[25–28] were also used.

Surprisingly, the analogous phosphorylation of α-hydroxy phosphonates has remained a neglected area. Although, a few >P(O)OCHP(O)< type compounds have been described, they were obtained by different ways, namely, by thermo-induced[29] or base-catalyzed[30–32] rearrangement of α-hydroxy bisphosphonates or by the reaction of α-mesyloxy phosphonates with sodium diethyl phosphite.[33] The reaction of α-hydroxy phosphonates with tris(diethylamino)phosphine followed by treatment with sulfur or selenium resulted in >P(X)OCHP(O)< (X = S or Se) systems.[34]

Here, we report the reaction of dimethyl (1-aryl-1-hydroxymethyl)phosphonates with different *P*-chlorides to afford >P(O)OCHP(O)< derivatives as new compounds of potential bioactivity. Phosphinic, as well as phosphoryl chlorides were chosen as 'acylating' agents to compare their reactivity. The series of phosphinic chlorides included 1-chloro-3-phospholene 1-oxides, as these reagents have been applied successfully in the phosphinoylation of primary amines in our laboratory.[35]

(1-Aryl-1-hydroxymethyl)phosphonates **1a–d** (prepared from the corresponding benzaldehydes and dimethyl phosphite in the presence of triethylamine[36]) were reacted with phosphinic chlorides to result in 1-phosphinoyloxyphosphonates (Scheme 1).[†] Diphenylphosphinic chloride **2a**, 1-chloro-3-methyl-3-phospholene 1-oxide **2b**, and 1-chloro-3,4-dimethyl-3-phospholene 1-oxide **2c** were used as the P-reagents (compounds **2b**,**c** were prepared by treatment of the corresponding cyclic phosphinic



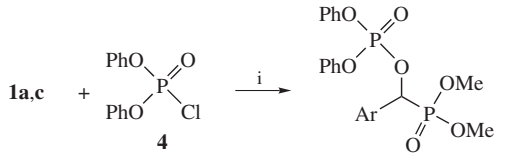
Reactants	Reaction time/h	Product	Yield (%)
1a + **2a**	48	**3a**	57
1a + **2b**	24	**3b**	59
1a + **2c**	24	**3c**	59
1b + **2a**	48	**3d**	49
1b + **2b**	24	**3e**	46
1b + **2c**	24	**3f**	50
1c + **2a**	48	**3g**	61
1c + **2b**	24	**3h**	54
1c + **2c**	24	**3i**	51
1d + **2a**	48	**3j**	70
1d + **2b**	24	**3k**	72
1d + **2c**	24	**3l**	80

Scheme 1 *Conditions*: i, Et_3N, PhMe, 26 °C, 24–48 h.

[†] *General procedure for the phosphorylation and phosphinoylation of dimethyl (1-aryl-1-hydroxymethyl)phosphonates* **1** *with phosphorus acid chlorides* **2**, **4**. A mixture of α-hydroxy phosphonate (1.0 mmol; **1a**, 0.22 g; **1b**, 0.23 g; **1c**, 0.25 g; **1d**, 0.26 g), toluene (5 ml), triethylamine (1.2 mmol, 0.17 ml) and P-acid chloride (1.1 mmol; **2a**, 0.21 ml; **2b**, 0.17 g; **2c**, 0.18 g; **4**, 0.23 ml) was stirred at 26 °C for 24–72 h under N_2 atmosphere. The precipitated triethylamine hydrochloride was filtered off, and the volatiles were removed *in vacuo*. The crude product was purified by column chromatography [silica gel, acetone–dichloromethane (2 : 1)] to afford the corresponding phosphorylated products **3** or **5**.

acids with thionyl chloride[37]). The phosphorylation reactions were carried out with 1.1 equiv. of phosphinic chloride in the presence of 1.2 equiv. of triethylamine in toluene. In case of 1-chloro-3-phospholene 1-oxides **2b** and **2c**, the mixture was stirred at 25 °C for 24 h, while with diphenylphosphinic chloride **2a** the reaction was complete within 48 h. Compounds **2**–**4** were purified by column chromatography and isolated in yields of 46–80%. In case of (1-aryl-1-hydroxymethyl)phosphonates with chloro or nitro substituent in the aromatic ring (**1c** and **1d**) somewhat higher yields (51–80%) were attained, as compared with those starting from the tolyl-substituted hydroxy phosphonate **1b** (46–50%).

The reaction of (1-aryl-1-hydroxymethyl)phosphonates **1a** and **1c** with diphenyl chloridophosphate **4** (Scheme 2)† gave the desired phosphoryloxy phosphonates **5a** and **5b** in modest yields of ~16% after purification by column chromatography, which can be caused by the lower reactivity of the phosphorylating agent, and the sensitivity of the products towards moisture. Heating the reaction mixture did not improve the yields, resulting in the decomposition of the product.



Scheme 2 *Conditions*: i, Et_3N, PhMe, 26 °C, 72 h.

New compounds **3** and **5** obtained by the phosphinoylation and phosphorylation of (1-aryl-1-hydroxymethyl)phosphonates **1** were identified by ^{31}P, ^{13}C and ^{1}H NMR, as well as by HRMS data. In the $^{31}P\{^{1}H\}$ NMR spectra of compounds **3a**,**c**,**d**,**f**,**g**,**i**,**j**,**l**, signals of the phosphorus atoms appeared as doublets due to the $^{3}J_{P,P}$ coupling [Figure S1(*a*), see Online Supplementary Materials]. Derivatives **3b**,**e**,**h**,**k** containing the 3-methyl-3-phospholene 1-oxide moiety exhibited two sets of doublets resulting from the presence of two diastereomers due to the two chirality centers [Figure S1(*b*)]. The same phenomenon was observed in their ^{13}C NMR spectra. The phospholene carbon atoms resonate as doublets due to their coupling with the P atom and the duplication of signals is referred to the presence of the diastereomers (Figure S2).

In summary, a new series of >P(O)OCHP(O)< derivatives has been synthesized by the phosphorylation of (1-aryl-1-hydroxymethyl)phosphonates with *P*-chlorides. The new compounds are of potential biological activity.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.011.

References

1 Á. Tajti and G. Keglevich, in *Organophosphorus Chemistry: Novel Developments*, ed. G. Keglevich, Walter de Gruyter, Berlin, Boston, 2018, pp. 53–65.
2 Z. Rádai, P. Szeles, N. Z. Kiss, L. Hegedűs, T. Windt, V. Nagy and G. Keglevich, *Heteroatom Chem*., 2018, **29**, e21436.
3 D. Green, S. Elgendy, G. Patel, E. Skordalakes, C. A. Goodwin, M. F. Scully, V. V. Kakkar and J. J. Deadman, *Phosphorus Sulfur Silicon Relat. Elem*., 2000, **156**, 151.
4 H.-W. He, J.-L. Yuan, H. Peng, T. Chen, P. Shen, S.-Q. Wan, Y. Li, H.-L. Tan, Y.-H. He, J.-B. He and Y. Li, *J. Agric. Food Chem*., 2011, **59**, 4801.
5 T. Chen, P. Shen, Y. Li and H.-W. He, *J. Fluorine Chem*., 2006, **127**, 291.
6 Q. Long, X. Deng, Y. Gao, H. Xie, H. Peng and H. He, *Phosphorus Sulfur Silicon Relat. Elem*., 2013, **188**, 819.
7 L. Meng, R. Joshi, M. Li and H. He, *J. Nepal Chem. Soc*., 2009, **23**, 11.
8 H. Peng, Q. Long, X. Deng and H. He, *Phosphorus Sulfur Silicon Relat. Elem*., 2013, **188**, 1874.
9 W. Wang, H.-W. He, N. Zuo, X. Zhang, J.-S. Lin, W. Chen and H. Peng, *J. Fluorine Chem*., 2012, **142**, 24.
10 W. Wang, H.-W. He, N. Zuo, H.-F. He, H. Peng and X.-S. Tan, *J. Agric. Food Chem*., 2012, **60**, 7581.
11 T. Wang, W. Wang, H. Peng and H.-W. He, *Chem. Res. Chin. Univ*., 2013, **29**, 690.
12 W. Wang, Y. Zhou, H. Peng, H.-W. He and X.-T. Lu, *J. Fluorine Chem*., 2017, **193**, 8.
13 X.-B. Chen and D.-Q. Shi, *Phosphorus Sulfur Silicon Relat. Elem*., 2008, **183**, 1134.
14 W. Wang, L.-P. Wang, B.-K. Ning, M.-Z. Mao, C. Xue and H.-Y. Wang, *Phosphorus Sulfur Silicon Relat. Elem*., 2016, **191**, 1362.
15 J. Yang, J. Ma, W. Che, M. Li, G. Li and B. Song, *Chin. J. Org. Chem*., 2014, **34**, 2566.
16 T. Wang and H.-W. He, *Synth. Commun*., 2004, **34**, 1415.
17 H. Firouzabadi, N. Iranpoor, S. Sobhani and Z. Amoozgar, *Synthesis*, 2004, **2**, 295.
18 H. Firouzabadi, N. Iranpoor and S. Farahi, *J. Mol. Catal. A: Chem*., 2008, **289**, 61.
19 H. Firouzabadi, N. Iranpoor, S. Sobhani and Z. Amoozgar, *Synthesis*, 2004, **11**, 1771.
20 C. Jin and H. He, *Phosphorus Sulfur Silicon Relat. Elem*., 2011, **186**, 1397.
21 N. Iranpoor, H. Firouzabadi and D. Khalili, *Phosphorus Sulfur Silicon Relat. Elem*., 2011, **186**, 2166.
22 L. Xu, G. You, H. Peng and H. He, *Phosphorus Sulfur Silicon Relat. Elem*., 2014, **189**, 812.
23 B. Kaboudin, S. Emadi, M. R. Faghihi, M. Fallahi and V. Sheikh-Hasani, *J. Enzyme Inhib. Med. Chem*., 2013, **28**, 576.
24 J.-P. Li, J.-G. Zhu, R.-J. Liu, F.-L. Cui, P. Liu and G.-S. Liu, *S. Afr. J. Chem*., 2008, **61**, 5.
25 X. Creary, C. C. Geiger and K. Hilton, *J. Am. Chem. Soc*., 1983, **105**, 2851.
26 Z.-G. Li, H.-K. Sun, Q.-M. Wang and R.-Q. Huang, *Heteroatom Chem*., 2003, **14**, 384.
27 L. Hu, S. Lu, F. Yang, J. Feng, Z. Liu, H. Xu and H. He, *Phosphorus Sulfur Silicon Relat. Elem*., 2002, **177**, 2785.
28 D.-L. Kong, G.-Z. Li and R.-D. Liu, *Asian J. Chem*., 2014, **26**, 2138.
29 R. S. Davidson, R. A. Sheldon and S. Trippett, *J. Chem. Soc. C*, 1967, 1547.
30 R. Ruel, J.-P. Bouvier and R. N. Young, *J. Org. Chem*., 1995, **60**, 5209.
31 A. Grün, I. G. Molnár, B. Bertók, I. Greiner and G. Keglevich, *Heteroatom Chem*., 2009, **20**, 350.
32 G. Keglevich, A. Grün, I. G. Molnár and I. Greiner, *Heteroatom Chem*., 2011, **22**, 640.
33 E. Årstad and L. Skattebøl, *Tetrahedron Lett*., 2002, **43**, 8711.
34 J. Zhou, R. Chen and X. Yang, *Heteroatom Chem*., 1998, **9**, 369.
35 N. Z. Kiss, A. Simon, L. Drahos, K. Huben, S. Jankowski and G. Keglevich, *Synthesis*, 2013, **45**, 199.
36 G. Keglevich, Z. Rádai and N. Z. Kiss, *Green Process Synth*., 2017, **6**, 197.
37 G. Keglevich, I. Petneházy, P. Miklós, A. Almásy, G. Tóth, L. Töke and L. D. Qiun, *J. Org. Chem*., 1987, **52**, 3983.

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