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Simple and effective synthesis of functionalized (hydroxymethylene)bis(phosphonic) acids

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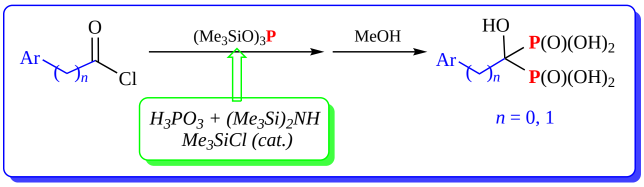
‘Technical’ tris(trimethylsilyl) phosphite, $(Me_3SiO)_3P$, as a mixture with $(Me_3SiO)_2P(O)H$ and $(Me_3SiO)_3P(O)$ (71 : 20 : 9) was obtained upon the action of $(Me_3Si)_2NH$ on phosphorous acid H_3PO_3 in the presence of catalytic amount of Me_3SiCl. The action of this material on acid chlorides RC(O)Cl affords (hydroxymethylene)bis(phosphonic) acids $RC(OH)[P(O)(OH)_2]_2$ in preparative yields.



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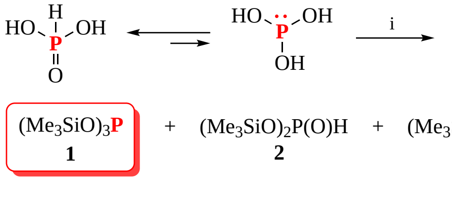
The interest in the study of substituted (hydroxymethylene)bis(phosphonic) acid derivatives is caused by their therapeutic[1] and chelating properties and high affinity for calcium phosphates (*e.g.*, hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$).[2] Such compounds may have applications both in medicine for the treatment of many bone diseases, one of which is osteoporosis,[3] and in ecology for selective sorption of metals.[4] So, expansion of the class of bis(phosphonates) and finding a simple, cheap and effective method for their synthesis are urgent tasks.

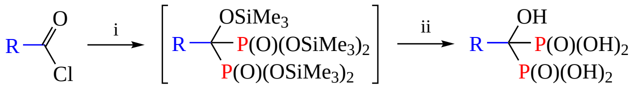
One of the earliest syntheses of substituted (hydroxymethylene)bis(phosphonic) acid is based on the reaction between phosphorus(III) trichloride, phosphorous acid and benzoic acid,[5,6] however the harsh reaction conditions are required and the mechanism is not fully understood. The reactions employing synthetically equivalent tris(trimethylsilyl) phosphite **1** proceed under mild conditions and provide good yields of the products.[7–9] Although reagent **1** is commercially available, it is expensive and highly sensitive to moisture and oxygen. Methods for the synthesis of phosphite **1** proposed by Hota and Iyer contain a number of inaccuracies.[10,11] Other works[12,13] describe the silylation of phosphorous acid to afford another product, namely, bis(trimethylsilyl) phosphite **2**. The formation of phosphite **1** *in situ* has also been reported,[14] however this approach may cause side reactions when using polyfunctional compounds.

The aim of this work was to obtain phosphite $(Me_3SiO)_3P$ **1** from available compounds and to use it for the synthesis of functionalized (hydroxymethylene)bis(phosphonic) acids. The target $(Me_3SiO)_3P$ **1** was synthesized by the reaction of phosphorous acid, H_3PO_3, with hexamethyldisilazane in the presence of catalytic amounts of Me_3SiCl (Scheme 1). Due to close boiling points, it is impossible to employ distillation to separate $(Me_3SiO)_3P$ **1** (bp[15] 129–130 °C/28 Torr, bp[11] 90–92 °C/20 Torr) from by-products, $(Me_3SiO)_2P(O)H$ **2** (bp[11] 77–79 °C/10 Torr) and $(Me_3SiO)_3P(O)$ **3** (bp[16] 108–111 °C/4 Torr). Apparently, the use of GPC or HPLC methods to separate **1**, **2** and **3** is unpractical. The composition of the herein obtained mixture, *i.e.* ‘technical grade’ $(Me_3SiO)_3P$ (bp 104 °C/29 Torr), is easily determined by ^{31}P NMR spectroscopy. The spectrum contains signals at δ_P 113.59 for **1**, –13.59 for **2** and –25.6 for **3** in a integral ratio 71 : 20 : 9. The formation of phosphate **3** is caused by the sensitivity of phosphite **1** to random atmospheric oxygen. The putative mechanism of the formation of tris(trimethylsilyl) phosphite **1** is presented in Online Supplementary Materials.

Despite numerous attempts to access compound **1** in individual state (Schlenk technique, using excess of $(Me_3Si)_2NH$ up to 5 equiv., post-reaction addition of Na followed by the treatment with Me_3SiCl), we obtained only the **1**–**3** mixtures in ratios weakly differed from those under standard conditions. Although $(Me_3SiO)_3P$ **1** is known, the related procedures have been described only in patent literature with application of additional highly dangerous co-reagents (NaH,[17] Na[18]). Moreover, our procedure results in a material containing compound **1** as a major component, and it is cheap especially in comparison with other known ways (*e.g.*, reaction of $(Me_3SiO)_2P(O)H$ with Me_3SiNEt_2).[11] As compound **1** is highly reactive, in some works it was generated *in situ* by the action of Me_3SiBr on $(EtO)_3P$[19] or $(MeO)_3P$.[20] Interestingly, in our hands other methods for the synthesis (including described action of Me_3SiCl/Et_3N and Py on phosphorous acid[11,21,22] or reaction between $(EtO)_2P(O)H$ and Me_3SiBr/Na[23]) resulted into $(Me_3SiO)_2P(O)H$ **2** containing $(Me_3SiO)_3P$ **1** only as an admixture.



Scheme 1 *Reagents and conditions*: i, $(Me_3Si)_2NH$ (3.0 equiv.), Me_3SiCl (4 mol%), reflux, 19 h.



4a–c **A** **5a–c**

a R = Ph (73%; 76% from commercial **1**)
b R = 3,4,5-$(MeO)_3C_6H_2$ (54%)
c R = 3-$MeOC_6H_4CH_2$ (30%)

Scheme 2 *Reagents and conditions*: i, $(Me_3SiO)_3P$ **1** (‘technical’ with **2** and **3**, or 95% commercial), reflux, 1 h; ii, MeOH.

We established that ‘technical’ $(Me_3SiO)_3P$ **1** (contaminated with **2** and **3**) in a reaction with several aromatic carboxylic acid chlorides **4a–c** truly gave the target substituted (hydroxymethylene)bis(phosphonic) acids **5a–c** (Scheme 2, *cf*. refs. 24, 25). Compounds **5b**,**c** are new. Interestingly, desilylation of intermediate silyl esters **A** can be achieved by simple action of MeOH,[26,27] which is more convenient in comparison with the case of dealkylation of $RP(O)(OAlk)_2$ by the treatment with Me_3SiBr. The mechanism of the reaction (nucleophilic substitution and the Arbuzov reaction are key steps) is presented in the Online Supplementary Materials. The success of this procedure employing the ‘technical’ $(Me_3SiO)_3P$ **1** may be explained by higher reactivity of **1** compared to **2** and **3**.

According to the NMR data, compounds **5a–c** are characterized by signals in the ^{31}P NMR spectra at δ_P 14.92–19.42 region, what is typical of $CP(O)(OH)_2$ group; both $P(O)(OH)_2$ are equivalent. In the ^{13}C NMR spectra, the signals for $C(OH)[P(O)(OH)_2]_2$ atoms resonate as triplets (δ_C 73.2–75.7; $^1J_{C-P}$ 145.0 Hz).

When we tested commercial $(Me_3SiO)_3P$ **1** (>95% purity) in the standard synthesis to obtain the representative compound $PhC(OH)[P(O)(OH)_2]_2$ **5a** (see Scheme 2), its yield was 76%, what is comparable with the case of application of ‘technical’ **1** (73%). Taking into account high price of commercial **1** and its high sensitivity to the oxidation, application of ‘technical’ **1** may be regarded a practical alternative.

In conclusion, valuable phosphorus reagent, $(Me_3SiO)_3P$ **1**, is obtained in a mixture with $(Me_3SiO)_2P(O)H$ **2** and $(Me_3SiO)_3P(O)$ **3** from available reagents $(H_3PO_3/(Me_3Si)_2NH)$; the synthesis may be easily scaled. We successfully used this ‘technical’ mixture in the synthesis of functionalized bis(phosphonic) acids, $RC(OH)[P(O)(OH)_2]_2$. The continuation of this research will be directed to the expansion of the scope of functionalized bis(phosphonic) acids and their application.

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Online Supplementary Materials

Supplementary data associated with this article (synthesis and characterization of the compounds, copies of their NMR spectra, mechanism of **1** formation) can be found in the online version at doi: 10.1016/j.mencom.2024.04.029.

References

1 Y. Song, J. M. W. Chan, Z. Tovian, A. Secrest, E. Nagy, K. Krysiak, K. Bergan, M. A. Parniak and E. Oldfield, *Bioorg. Med. Chem*., 2008, **16**, 8959.
2 G. H. Nancollas, R. Tang, R. J. Phipps, Z. Henneman, S. Gulde, W. Wu, A. Mangood, R. G. G. Russell and F. H. Ebetino, *Bone*, 2006, **38**, 617.
3 J. Dussart, J. Deschamp, E. Migianu-Griffoni and M. Lecouvey, *Org. Process Res. Dev*., 2020, **24**, 637.
4 R. Thapa, A. Rahmani, P. Turhanen, A. Taskinen, T. Nissinen, R. Neitola, J. Vepsalainen, L. Vesa-Pekka and J. Riikonen, *Sep. Purif. Technol*., 2021, **272**, 118913.
5 M. Lecouvey and Y. Leroux, *Heteroat. Chem*., 2000, **11**, 556.
6 A. Grun, R. Kovacs, N. D. Illes, S. Garadnay, I. Greiner and G. Keglevich, *Lett. Org. Chem*., 2014, **11**, 368.
7 A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova, A. V. Maryashkin and E. R. Milaeva, *Russ. J. Gen. Chem.*, 2007, **77**, 1474 (*Zh. Obshch. Khim*., 2007, **77**, 1397).
8 E. Migianu, I. Mallard, N. Bouchemal and M. Lecouvey, *Tetrahedron Lett*., 2004, **45**, 4511.
9 G. Forlani, Ł. Berlicki, M. Duò, G. Dzięddzioła, S. Giberti, M. Bertazzini and P. Kafarski, *J. Agric. Food Chem*., 2013, **61**, 6792.
10 M. Sekine, K. Okimoto, K. Yamada and T. Hata, *J. Org. Chem*., 1981, **46**, 2097.
11 R. P. Iyer, J. H. Boal, L. R. Phillips, D. Thakkera and W. Egan, *J. Pharm. Sci*., 1994, **83**, 1269.
12 A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova and V. S. Petrosyan, *Heteroat. Chem.*, 2010, **21**, 430.
13 L. A. Wessjohann and M. A. Dessoy, *Polyhedron*, 2014, **70**, 133.
14 T. Yang, C. Lin, H. Fu, Y. Jiang and Y. Zhao, *Synth. Commun*., 2004, **34**, 1017.
15 M. G. Voronkov and Y. I. Skorik, *J. Gen. Chem. USSR*, 1965, **35**, 105 (*Zh. Obshch. Khim*., 1965, **35**, 106).
16 M. G. Voronkov, A. E. Pestunovich, A. I. Albanov and V. A. Kukhareva, *Russ. J. Gen. Chem*., 2009, **79**, 1080 (*Zh. Obshch. Khim*., 2009, **79**, 908).
17 J. Zhao, L. Xiao, A. Sun and Y. Xin, *Patent CN109232641A*, 2019.
18 N. S. Lee, Y. G. Kwon, U. H. Hwang, J. G. Lee and E. J. Jeon, *Patent KR2012067398A*, 2012.
19 M. Górny vel Górniak and P. Kafarski, *Phosphorus, Sulfur Silicon Relat. Elem*., 2016, **191**, 511.
20 B. Boduszek and T. K. Olszewski, *ARKIVOC*, 2017, (**ii**), 173.
21 T. R. Herrin, J. S. Fairgrieve, R. E. Bower, N. L. Shipkowitz and J. C. Y. Mao, *J. Med. Chem*., 1977, **20**, 660.
22 A.-S. Charvet, M. Camplo, P. Faury, J.-C. Graciet, N. Mourier, J.-C. Chermann and J.-L. Kraus, *J. Med. Chem*., 1994, **37**, 2216.
23 K. Issleib, M. Bubner and A. Balszuweit, *Z. Anorg. Allg. Chem*., 1987, **546**, 142.
24 M. Lecouvey, I. Mallard, T. Bailly, R. Burgada and Y. Leroux, *Tetrahedron Lett*., 2001, **42**, 8475.
25 E. Guenin, E. Degache, J. Liquier and M. Lecouvey, *Eur. J. Org. Chem*., 2004, 2983.
26 A. A. Prishchenko, R. S. Alekseyev, O. P. Novikova, M. V. Livantsov, L. I. Livantsova and S. V. Baranin, *Russ. Chem. Bull*., 2022, **71**, 1976.
27 A. A. Prishchenko, R. S. Alekseyev, O. P. Novikova, M. V. Livantsov, L. I. Livantsova and V. S. Petrosyan, *J. Organomet. Chem*., 2022, **957**, 122143.

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