Preliminary accounts of new works in chemistry from Russia and elsewhere.


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

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The interest in the study of substituted (hydroxymethylene)bis(phosphonic) acid derivatives is caused by their therapeutic and chelating properties and high affinity for calcium phosphates (e.g., hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$). Such compounds may have applications both in medicine for the treatment of many bone diseases, one of which is osteoporosis, and in ecology for selective sorption of metals. 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 phosphorous(III) trichloride, phosphorous acid and benzoic acid, however the harsh reaction conditions are required and the mechanism is not fully understood. The reactions employing synthetically equivalent tris(trimethylsilyl)phosphate proceed under mild conditions and provide good yields of the products. Although reagent 1 is commercially available, it is expensive and highly sensitive to moisture and oxygen. Methods for the synthesis of phosphate in situ have also been reported, however this approach may cause side reactions when using polyfunctional compounds.

The aim of this work was to obtain phosphate (Me$_3$SiO)$_3$P 1 from available compounds and to use it for the synthesis of functionalized (hydroxymethylene)bis(phosphonic) acids. The target (Me$_3$SiO)$_3$P 1 was synthesized by the reaction of phosphorous acid, H$_3$PO$_4$, with hexamethyldisilazane in the presence of catalytic amounts of Me$_3$SiCl (Scheme 1). Due to close boiling points, it is impossible to employ distillation to separate (Me$_3$SiO)$_3$P 1 (bp 130−130 °C/28 Torr, bp 90−92 °C/20 Torr) from by-products, (Me$_3$SiO)$_2$P(O)H 2 (bp 77−79 °C/10 Torr) and (Me$_3$SiO)$_2$P(O) 3 (bp 108−111 °C/4 Torr). Apparently, the use of GPC or HPLC methods to separate 1, 2 and 3 is impractical. The composition of the herein obtained mixture, i.e.Technical grade’ (Me$_3$SiO)$_3$P (bp 104 °C/29 Torr), is easily determined by $^{31}$P NMR spectroscopy. The spectrum contains signals at $\delta_p$ 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 phosphate 1 to random atmospheric oxygen. The putative mechanism of the formation of tris(trimethylsilyl)phosphate 1 is presented in Online Supplementary Materials.

Despite numerous attempts to access compound 1 in individual state (Schlenk technique, using excess of (Me$_3$Si)$_2$NH up to 5 equiv., post-reaction addition of Na followed by the treatment with Me$_3$SiCl), we obtained only the 1−3 mixtures in ratios weakly differed from those under standard conditions. Although (Me$_3$SiO)$_3$ 1 is known, the related procedures have been described only in patent literature with application of additional highly dangerous co-reagents (NaH, 1−Na$_2$3). Other works describe the silylation of phosphorous acid to afford another product, namely, bis(trimethylsilyl)phosphate 2. The formation of phosphate 1 in situ has also been reported, however this approach may cause side reactions when using polyfunctional compounds.

The use of GPC or HPLC methods to separate 1, 2 and 3 is impractical. The composition of the herein obtained mixture, i.e. ‘technical grade’ (Me$_3$SiO)$_3$P (bp 104 °C/29 Torr), is easily determined by $^{31}$P NMR spectroscopy. The spectrum contains signals at $\delta_p$ 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 phosphate 1 to random atmospheric oxygen. The putative mechanism of the formation of tris(trimethylsilyl)phosphate 1 is presented in Online Supplementary Materials.

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Scheme 2 Reagents and conditions: i, (Me₃SiO)₃P ('technical' with 2 and 3, or 95% commercial), reflux, 1 h; ii, MeOH.

We established that 'technical' (Me₃SiO)₃P 1 (contaminated with 2 and 3) in a reaction with several aromatic carboxylic acid chlorides 4a–c truly gave the target substituted (hydroxy)methylene)bis(phosphonic) acids 5a–e (Scheme 2, cf. refs. 24, 25). Compounds 5b,c,e 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 Me₃SiBr. The mechanism of the reaction (nucleophilic substitution and the Arbusov reaction are key steps) is presented in the Online Supplementary Materials. The success of this procedure employing the ‘technical’ (Me₃SiO)₃P 1 may be explained by higher reactivity of 1 compared to 2 and 3.

According to the NMR data, compounds 5a–e are characterized by signals in the ³¹P NMR spectra at δₚ 14.92–19.42 region, what is typical of CP(O)(OH)₂ group; both C and O resonate as triplets (δₚ 73.2–75.7; ¹JC=IP 145.0 Hz).

When we tested commercial (Me₃SiO)₃P (>95% purity) in the Online Supplementary Materials. The success 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

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