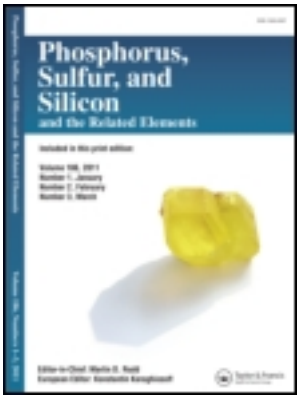

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Tetrakis(trimethylsilyl) Ethenylidenebisphosphonate: A Mild and Useful Reagent for the Synthesis of Substituted 2-Aminoethylidene-1,1-bisphosphonic Acids

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Published online: 25 Apr 2011.

To cite this article: Michael V. Shevchuk , Vadim D. Romanenko & Valery P. Kukhar (2011) Tetrakis(trimethylsilyl) Ethenylidenebisphosphonate: A Mild and Useful Reagent for the Synthesis of Substituted 2-Aminoethylidene-1,1-bisphosphonic Acids, Phosphorus, Sulfur, and Silicon and the Related Elements, 186:4, 799-801, DOI: 10.1080/10426507.2010.500640

To link to this article: http://dx.doi.org/10.1080/10426507.2010.500640

Phosphorus, Sulfur, and Silicon, 186:799–801, 2011

ISSN: 1042-6507 print / 1563-5325 online
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TETRAKIS(TRIMETHYLSILYL) ETHENYLIDENEBISPHOSPHONATE: A MILD AND USEFUL REAGENT FOR THE SYNTHESIS OF SUBSTITUTED 2-AMINOETHYLIDENE-1,1-BISPHOSPHONIC ACIDS

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Abstract *Tetrakis(trimethylsilyl) ethenylidenebisphosphonate is proposed as a substrate in the preparations of N-substituted 2-aminoethylidene-1,1-bisphosphonic acids. The method provides an extremely mild protocol for the synthesis of these compounds and is compatible with a wide range of functional groups.*

Keywords Aminobisphosphonic acids; Michael addition; tetrakis(trimethylsilyl) ethenylidenebisphosphonate

Aminomethylenebisphosphonic acids are approved drugs for the treatment of bone diseases and have been widely used as antiresorptive agents for over two decades.[1] Their antiparasitic activity as well as their ability to stimulate $\gamma\delta$ T cells of the immune system that kill tumor cells are also rigorously studied.[2,3] So far, the widely used method of methylenebisphosphonic acids synthesis is based on the Michael addition of a nucleophilic reagent to tetraalkyl ethenylidenebisphosphonate **1** followed by hydrolysis of tetraalkyl bisphosphonate in boiling hydrochloric acid[2] or bromotrimethylsilane-mediated methanolysis.[4] Unfortunately, these reaction conditions are incompatible with acid- and bromotrimethylsilane-labile functionalities (ester, amide, phosphonate to aq. HCl, phosphonate to bromotrimethylsilane). Moreover, under these conditions a retro-Michael reaction can take place in some cases.

To overcome these difficulties, the use of ethenylidenebisphosphonic acid tetrakis(trimethylsilyl) ester (**2**) instead of conventional tetraethyl ester is proposed. According to a slightly modified original procedure,[5,6] bisphosphonate **1** when treated with bromotrimethylsilane is fully converted to a silylated product with only trace amounts of by-products. Purification via distillation affords pure tetrasilyl ester **2** in 90% yield that can be stored for months (Scheme 1).

Received 9 April 2010; accepted 1 June 2010.
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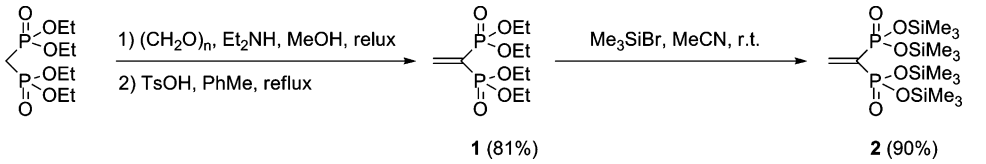
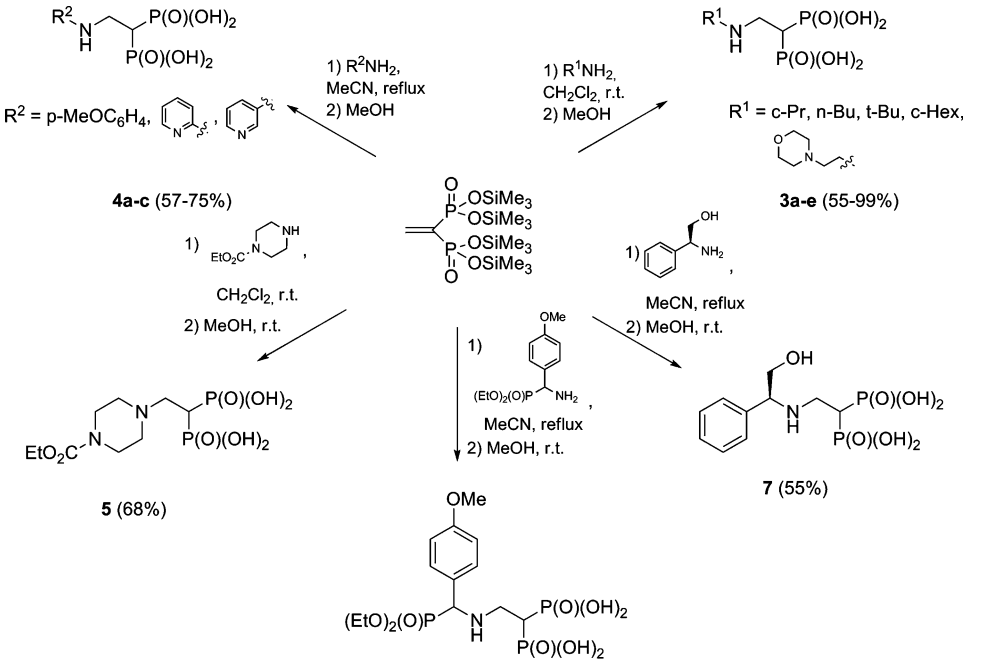


Scheme 1

Reactions of various amines with tetrakis(trimethylsilyl) ethenylidenebisphosphonate were investigated. Aliphatic amines react smoothly in dichloromethane at room temperature over several hours to produce the corresponding substituted 2-aminoethylidene-1,1-bisphosphonic acids **3a-e** upon treatment with methanol in moderate to excellent yields.[7] Aromatic amines, heteroaromatic amines, and substituted benzylamines react somewhat slower, and heating in more polar acetonitrile over a prolonged time is usually required to obtain products **4a-c** in satisfactory yields. In general, the reactivity of tetrakis(trimethylsilyl) ester of ethenylidenebisphosphonic acid is lower compared to the corresponding tetraethyl ester. This method opens access to bisphosphonic acids bearing amidate or phosphonate groups (compounds **5** and **6**, respectively). The reaction can be carried out in the presence of a free hydroxyl group, and preparation of **7** is an example (Scheme 2).



Scheme 2

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6. Modified experimental procedure for **2**: to a stirred solution of **1** (4.5 g, 15 mmol) in dry acetonitrile (5 mL) freshly distilled bromotrimethylsilane (8.9 mL, 67.5 mmol) was added dropwise at ambient temperature. A slightly exothermic reaction was observed, and the reaction mixture was stirred overnight. The next day the yellowish solution was concentrated in a vacuum to approximately three-quarters of starting volume and transferred to a distillation flask. The remaining volatiles (which kept the solution fluid to facilitate transportation) were completely removed and the silyl ester **2** was distilled as clear viscous uncolored liquid (6.4 g, 13.5 mmol, 90%), b.p. 116–117°C/0.05 mm. ^{1}H-NMR (400 MHz, C_6D_6) $\delta = 0.29$ (s, 36H, CH_3), 6.68 (dd, $J_{HP} = 35$ Hz, $J_{HP} = 39$ Hz, 2H, CH_2); ^{13}C-NMR (100 MHz, C_6D_6) $\delta = 1.2$ (s, *C*H$_3$), 140.0 (t, $J_{CP} = 173$ Hz, P*C*P), 142.8 (s, *C*H$_2$); ^{31}P-NMR (162 MHz, C_6D_6) $\delta = -3.1$ (dd, $J_{PH} = 35$Hz, $J_{PH} = 39$ Hz), ^{29}Si-NMR (C_6D_6) $\delta = 21.7$ (m). Spectral data were in good agreement with those found in the literature[5].
7. Experimental procedure for 2-(cyclopropylamino)ethane-1,1-diylbisphosphonic acid **3a**: to a stirred solution of **2** (436 mg, 0.92 mmol) in dry dichloromethane (2 mL) cyclopropylamine (60 mg, 1.05 mmol) was added. The mixture was stirred for 2 h and the solvent was evaporated. Methanol (3–5 mL) was added and the mixture was stirred for another 0.5 h. Precipitate was collected on the filter and washed twice with methanol (3 mL) and then several times with ether (20 mL). Compound **3a** (209 mg, 0.86 mmol) was obtained as a colorless crystalline solid in 93% yield. ^{1}H-NMR (400 MHz, D_2O) $\delta = 0.81$–0.89 (m, 4H, C$H_{2\text{cyclopropane}}$), 2.52 (tt, $J_{HP} = 22$ Hz, $J_{HH} = 7$ Hz, 1H, PC*H*P); 2.74 (m, 1H, C$H_{\text{cyclopropane}}$); 3.50 (td, $J_{HP} = 14$ Hz, $J_{HH} = 7$ Hz); ^{13}C-NMR (100 MHz, D_2O) $\delta = 3.3$ (s, C$H_{2\text{cyclopropane}}$), 30.2, 36.4 (d, $J_{CP} = 122$ Hz), 45.6; ^{31}P-NMR (162 MHz, D_2O) $\delta = 16.3$.