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An efficient method for the preparation of silyl esters of diphosphoric, phosphoric, and phosphorous acid

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ABSTRACT

Tetrakis(trialkylsilyl) diphosphate (alkyl = Me, Et, *i*Pr, *t*Bu) can be obtained in quantitative yield by reacting commercial disodium dihydrogen diphosphate with the respective trialkyl chlorosilane in a triphasic system with formamide. The alkylsilane residues of the diphosphate silyl esters can be either partially or completely hydrolyzed without concurrent cleavage of the P–O–P bond of the diphosphate moiety. The method can be expanded to efficiently produce other persilylated or partially silylated phosphates and phosphites.

1. Introduction

The diphosphate moiety comprehends a critical structural element in a series of important biological metabolites and cofactors (i.e. diphosphorylated terpenols, sugars, nucleotides, and nicotineamide-based dinucleotides) which play central roles in both primary and secondary metabolisms of all living organisms. Silylated derivatives of diphosphoric acid are potential precursors for the chemical synthesis of these biologically relevant molecules. Tetraalkyl diphosphates (alkyl = Et, *n*Pr, *i*Pr, *n*Bu) were shown to be toxic to some organisms [1]. E.g., tetraethyl diphosphate was used as a pesticide [2], as it expresses powerful anticholinesterase activity with actions similar to eserine and neostigmine [3]. Tetrabenzyl diphosphate has been used for the phosphorylation of inositol derivatives (e.g. D-*myo*-inositol-1,4,5-trisphosphate a cellular second messenger) [4–6] and in the synthesis of (−)-5-enolpyruvylshikimate-3-phosphate (a principle metabolite in the shikimic acid pathway) [7]. Trimethylsilyl (TMS) esters of a series of oxyanions of main group elements have been synthesized and spectroscopically studied in the past [8]. However, the effective silylation of diphosphoric acid or its salts on preparative scale to give pure product has not been reported until now. Formation has been observed in different reaction systems. Thus, tetrakis(trimethylsilyl) diphosphate (**2a**) is formed as a byproduct in the preparation of polyphosphoric acid trimethylsilyl ester (PPSE). PPSE is obtained from phosphorus pentoxide upon reaction with excess hexamethyldisiloxane. In an early account, Mileshkevich and Karlin reported the isolation of **2a** in up to 18% from crude PPSE [9]. The authors, though, did not provide a definitive proof of structure and purity of the isolated product at that time. Later, Yamamoto and Watanabe disclosed the composition of crude PPSE by means of ^{31}P NMR spectroscopy [10]. According to the latter authors, the share of **2a** in the crude product mixture is somewhat influenced by the reaction conditions, but in no case it has been found to be higher than 7%. Similarly, the silyl ester **2a** also forms in ca. 6% yield upon treatment of phosphorus pentoxide with hexamethyldisilazane [11].

The direct reaction of (nucleophilic) inorganic diphosphate and (electrocphilic) activated trialkylsilyl compounds, e.g. TMS-chloride, does not work without solvent mediation. All solvents commonly applied for such reactions either do not further the reaction, e.g. they are unable to dissolve the diphosphate, or they react with the activated TMS or with the product with its sensitive (activated) P–O–P or Si–O–P bonds. Furthermore, active strong acid or nucleophiles deteriorate the product, sometimes even catalytically. Isolation of the products thus was a major challenge not yet tackled. The stability of sterically hindered higher silyl esters is expected to be better, but they also promise less applicability at a much higher price.

To the best of our knowledge, the only example of a purposeful preparation of a diphosphate silyl ester is given by Mawhinney [12]. Accordingly, both diphosphoric acid and its ammonium salt were converted into tetrakis(*tert*-butyldimethylsilyl) diphosphate (**2d**) with *N*-methyl-*N*-(*tert*-butyldimethylsilyl) trifluoroacetamide in *N*,*N*-dimethylformamide (DMF). The silyl es-

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ter **2d**, however, was prepared for analytical purposes in no more than a few micro-grams and has not been isolated from the crude reaction mixture. Unfortunately, silyl protected diphosphates are also unavailable by an inverse approach starting from (electrophilic) diphosphoryl chloride and nucleophiles (like R_3SiO^-) because these cleave the P–O–P bond rather than the P–Cl bond [13,14].

The claim of Nifant'ev et al. to have synthesized **2a** in 44% yield from bis(trimethylsilyl) phosphite (**4a**) via a Todd-Atherton-like reaction could not be verified (v.i.) [15]. In reality, the authors obtained tris(trimethylsilyl) phosphate (**4b**, δ ^{31}P NMR = −24.8 ppm) and have erroneously assigned the structure of this compound to **2a**.

Herein we wish to report the first efficient synthesis of a series of diphosphate trialkylsilyl esters (**2a**–**2d**) and improved access to silylphosphate and silylphosphite.

2. Experimental

2.1. Materials and methods

Formamide (cat. No. 47670), chlortrimethylsilane (cat. No. 92361), chlorotriethylsilane, chlortriisoproylsilane, chlordimethyl-*tert*-butylsilane, and pyridine (cat. No. 82704) were purchased from Fluka. P.a. grade $H_2Na_2O_7P_2$ was purchased either from Fluka (cat. No. 71501) or Aldrich (cat. No. 34,073-1) [the amount of phosphate impurity correlates directly with the later amount of impurity of silylated phosphate]. Petrol ether (b.p. 40–60 °C, Roth) was used as received. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury 400 spectrometer, operating at 400, 100, and 162 MHz, respectively. ^{29}Si NMR spectra were recorded on a Varian Inova 500 spectrometer, at an operational frequency of 99 MHz. Unless otherwise stated, the spectra were recorded in $CDCl_3$. ^{1}H, ^{13}C and ^{29}Si NMR spectra were referenced to tetramethylsilane (TMS, δ = 0 ppm, s = singlet, d = doublet, t = triplet, bt = broad triplet, q = quartet, hep = heptet). ^{31}P NMR spectra were externally referenced to an 85% H_3PO_4 capillary (δ = 0 ppm). High-resolution mass spectra were recorded with a Bruker BioApex 70e FT-ICR (Bruker Daltonics, USA) and low-resolution mass spectra (MS-ESI) were recorded with an API 150Ex (Applied Biosystems) mass spectrometer, equipped with a turbo ion spray source.

2.2. Synthesis of tetrakis(trialkylsilyl) diphosphate esters **2a**–**2d**

2.2.1. Tetrakis(trimethylsilyl) diphosphate **2a**

A 250 mL dry flask was loaded with finely powdered dihydrogen disodium diphosphate (22.2 g, 0.1 mol), formamide (50 mL), and under vivid stirring by trimethylsilyl chloride (45.5 g, 0.44 mol). Refluxing TMSCl must be cooled for larger scale synthesis (caution: exothermic reaction with hydrogenchloride gas evolving!). After 1 h of stirring, petrol ether (200 mL) was added and stirring was continued for *ca.* 5 min. The clear top layer was transferred into a dry 250 mL Schlenk-tube and the solvent as well as excess TMSCl were evaporated off under reduced pressure (*ca.* 12 mbar) at 40 °C to give 46 g (100%) of the title compound as an colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.24 (s, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 0.60 (s, *C*H$_3$). ^{31}P NMR ($CDCl_3$, 162 MHz, δ, ppm): −30.76 (s). ^{29}Si NMR ($CDCl_3$, 99 MHz, δ, ppm): 24.6 (t, $^{2,4}J_{SiP} \approx 2.8$ Hz); HRMS: calculated for $C_{12}H_{37}O_7P_2Si_4$ $[M+H]^+$: 467.10861, found: 467.10860.

2.2.2. General procedure for the preparation of tetrakis(trialkylsilyl) diphosphate esters **2b**–**2d**

A 50 mL dry Schlenk tube flushed with dry nitrogen is loaded with finely powdered dihydrogen disodium diphosphate (1.11 g, 5 mmol), formamide (5 mL), and the corresponding trialkylsilyl chloride (20 mmol) is added. The ternary system is vigorously stirred at 55 °C during the time (time intervals for **2b**–**2d**: 4, 10 and 5 h, respectively). Petrol ether (20 mL) is added and stirring is continued for ca. 5 min. The clear top layer is transferred into a second dry 50 mL Schlenk-tube and the solvent is evaporated under reduced pressure (ca. 12 mbar or lower, depending on the silylether formed) at 40 °C.

*2.2.2.1. Tetrakis(triethylsilyl) diphosphate **2b**.* 3.05 g (96%) of a viscous, colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.74 (q, $^3J_{HH}$ = 7.8 Hz, 24H, C*H*$_2$), 0.97 (t, $^3J_{HH}$ = 7.8 Hz, 36H, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 5.14 (*C*H$_3$), 6.31 (*C*H$_2$). ^{31}P NMR ($CDCl_3$, 162 MHz, δ, ppm): −30.59 (s). ^{29}Si NMR ($CDCl_3$, 99 MHz, δ, ppm): 25.77 (bt, $^{2,4}J_{SiP} \approx 3.6$ Hz). HRMS: calculated for $C_{24}H_{61}O_7P_2Si_4$ $[M+H]^+$: 635.29641, found: 635.29729.

*2.2.2.2. Tetrakis(triisopropylsilyl) diphosphate **2c**.* 3.8 g (95%) of a highly viscous, colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.11 (d, $^3J_{HH}$ = 7.4 Hz, 72H, C*H*$_3$), 1.23 (hep, $^3J_{HH}$ = 7.4 Hz, 12H, C*H*). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 12.65 (*C*H), 17.12 (*C*H$_3$). ^{31}P NMR ($CDCl_3$, 162 MHz, δ, ppm): −32.81. ^{29}Si NMR ($CDCl_3$, 99 MHz, δ, ppm): 20.91 (t, $^{2,4}J_{SiP} \approx 10.0$ Hz). HRMS: calculated for $C_{36}H_{85}O_7P_2Si_4$ $[M+H]^+$: 803.48421, found: 803.48613.

*2.2.2.3. Tetrakis(tert-butyldimethylsilyl) diphosphate **2d**.* 3.01 g (94%) as a white, amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.25 (s, 3H, C*H*$_3$), 0.26 (s, 3H, C*H*$_3$), 0.91 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): −4.01 (d, $^3J_{CP}$ = 3.8 Hz, *C*H$_3$), 17.98 (*C*(CH$_3$)$_3$), 25.27 (C(*C*H$_3$)$_3$). ^{31}P NMR ($CDCl_3$, 162 MHz, δ, ppm): −30.02. ^{29}Si NMR ($CDCl_3$, 99 MHz, δ, ppm): 25.98 (bt, $^{2,4}J_{SiP}$ - ≈ 3.6 Hz). HRMS: calculated for $C_{24}H_{61}O_7P_2Si_4$ $[M+H]^+$: 635.29641, found: 635.29802.

2.3. General procedure for the preparation of **4a** and **4b**

To a dry, nitrogen flushed 100 mL Schlenk-tube containing a solution of phosphorous acid (1.64 g, 20 mmol for the synthesis of **4a**) [or potassium dihydrogen phosphate (2.72 g, 20 mmol for the synthesis of **4b**)] in formamide (10 mL) trimethylsilyl chloride (5.4 g, 50 mmol) is added. The resulted binary (**4a**) or ternary system (**4b**) was vigorously stirred (caution: exothermic reaction, HCl gas formation). After 1 h stirring, petrol ether (40 mL) was added and stirring was continued for ca. 5 min. The top, clear layer of the new binary or ternary system was transferred to a dry 50 mL Schlenk-tube, and the solvent as well as excess TMSCl and TMS–O–TMS were evaporated off under reduced pressure (*ca.* 12 mbar) at 40 °C.

2.3.1. Bis(trimethylsilyl) phosphite **4a** [18]

Yield 4.41 g (97%), colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.22 (s, 9H, C*H*$_3$), 6.75 (d, $^1J_{HP}$ = 700 Hz, 1H, P*H*). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 0.72 (d, $^3J_{CP}$ = 1.6 Hz, *C*H$_3$). ^{31}P NMR ($CDCl_3$, 162 MHz, δ, ppm): −13.07 (d, $^1J_{PH}$ = 700 Hz, *C*H$_3$). MS(ESI): 227 $[M+H]^+$.

2.3.2. Tris(trimethylsilyl) phosphate **4b** [9,17,19]

Yield 6.20 g (98%), colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.19 (s, 9H, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 0.44 (d, $^3J_{CP}$ = 1.5 Hz, *C*H$_3$). ^{31}P NMR ($CDCl_3$, 162 MHz, δ, ppm): −25.11.