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LETTERS TO THE EDITOR

Reactions of Aromatic Aldehydes and Their Acetals with Phosphorous Acid Esters

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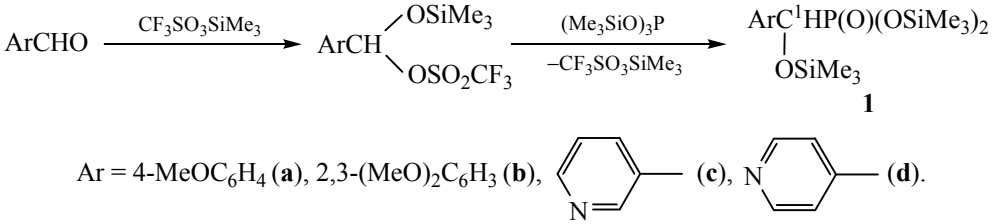
Functionalized hydroxymethylphosphonates, methylenediphosphonates, and their derivatives are of great interest as promising ligands and biologically active substances. They are widely used in organic synthesis [1, 2]. In order to synthesize new types of aryl-substituted methylenediphosphonates and hydroxymethylphosphonates we performed reactions of trimethylsilyl esters of phosphorous acid, taken in excess, with aromatic aldehydes and their acetals [3]. Thus, the addition of tris(trimethylsilyl) phosphite to the carbonyl group of aromatic aldehyde promoted by trimethylsilyl triflate led to the formation of phosphonates **1a–1d** in high yields. Obviously, this is due to the formation of intermediate adducts, electrophilic sulfoacetals (see [4, 5]) (Scheme 1).

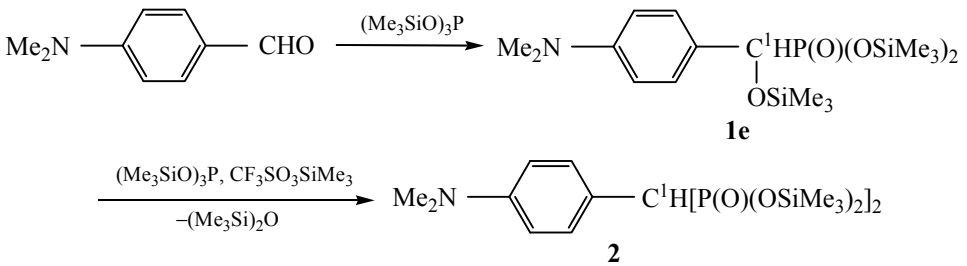
Note that the phosphonate **1e** was isolated in a high yield only when reaction was performed in the absence of a catalyst, since the presence of trimethylsilyl triflate afforded diphosphonate **2** instead of the expected product (Scheme 2).

Undoubtedly, easy replacement of trimethylsiloxy group at the C^1 atom in phosphonate 1e is due to the activating effect of *para*-positioned dimethylamino

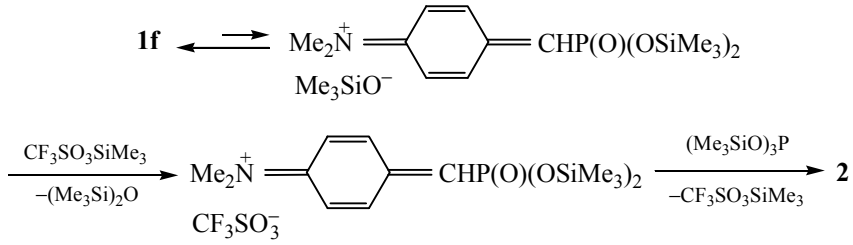
Scheme 1.



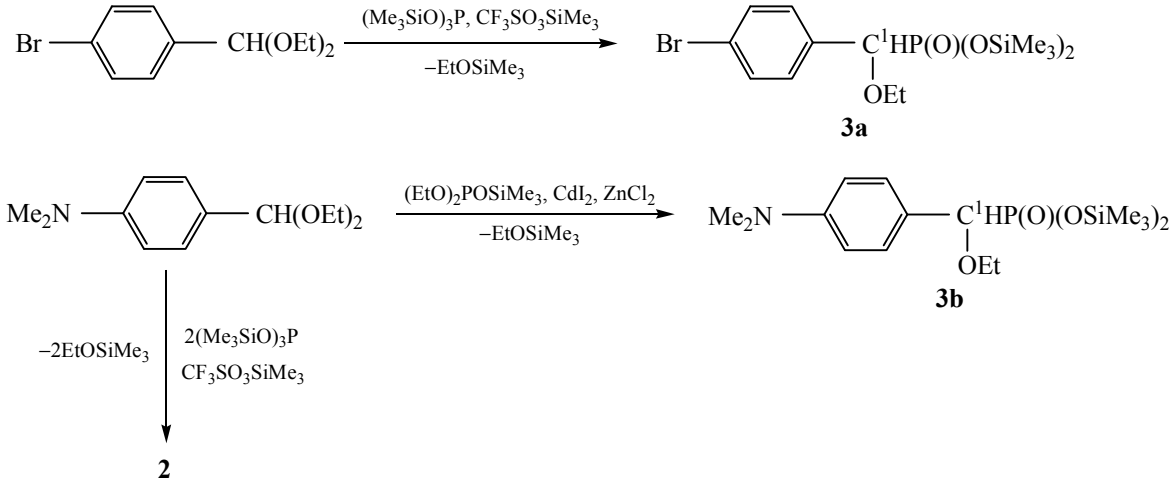
Scheme 2.



Scheme 3.



Scheme 4.



group which promotes the formation of highly reactive methylenequinone intermediate (Scheme 3).

Available diethylacetals [3] reacted with trimethylsilyl phosphites similarly only when heated to 100–150°C to form ethoxymethylphosphonates **3** and diphosphonate **2** in high yields. The synthesis of phosphonate **3b** required the use of CdI and ZnCl as catalysts, since the use of trimethylsilyl triflate was accompanied by the exchange of ethoxyl moieties at the phosphorus atom for trimethylsilyl resulting in a mixture of products (Scheme 4).

The resulting compounds are convenient synthons for the preparation of the corresponding functionalized phosphonic and diphosphonic acids which are promising polydentate ligands and biologically active substances.

Bis(trimethylsilyl) 4-methoxyphenyl(trimethylsiloxy)methylphosphonate (1a). To a solution of 30 g of tris(trimethylsilyl)phosphite and 5.5 g of anisaldehyde in 40 mL of methylene chloride was added 0.5 mL of trimethylsilyl trifluoromethanesulfonate. After completion of the exothermic reaction the mixture was refluxed for 1 h, then the solvent was removed in a vacuum, the residue was distilled. Yield 15.1 g (86%), bp 144°C (2 mmHg). ^{1}H NMR spectrum, δ, ppm: –0.17 s (9H, Me_3SiOC), –0.06 s (18H, Me_3Si), 3.56 s (3H, MeO), 4.62 d (1H, C^1H, $^2J_{PH}$ = = 12.0 Hz), 6.62 d (1H, CH_{Ph}, $^3J_{PH}$ = 8.0 Hz), 7.08 d (1H, CH_{Ph}, $^3J_{PH}$ = 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: –0.26 (Me_3Si), 0.49 (Me_3Si), 54.89 (MeO), 71.76 d (C^1, $^1J_{PC}$ = 180.0 Hz), 113.14 (C_{Ph}), 128.32 d (C_{Ph}, $^3J_{PC}$ = 7.0 Hz), 129.92 (C_{Ph}), 159.20 (C_{Ph}). ^{31}P NMR spectrum: δ_P –3.96 ppm.

Phosphonates **1b–1e** were prepared similarly.

Bis(trimethylsilyl) 2,3-dimethoxyphenyl(trimethylsiloxy)methylphosphonate (1b). Yield 84%, bp 143°C (0.5 mmHg), mp 29°C. ^{1}H NMR spectrum, δ, ppm: –0.21 s (9H, Me_3SiOC), –0.02 s (18H, Me_3Si), 3.56 s (3H, MeO), 3.63 s (3H, MeO), 5.17 d (1H, C^1H, $^2J_{PH}$ = 14.4 Hz), 6.55–6.90 m (3H, C_6H_3). ^{13}C NMR spectrum, δ_C, ppm: –0.31 (Me_3Si), 0.52 (Me_3Si), 55.44 (MeO), 60.25 (MeO), 65.16 d (C^1, $^1J_{PC}$ = 182.8 Hz), 111.93 (C_{Ph}), 120.41 d (C_{Ph}, $^3J_{PC}$ = 3.2 Hz), 123.34 (C_{Ph}), 130.96 (C_{Ph}), 145.94 d (C_{Ph}, $^3J_{PC}$ = 8.0 Hz), 151.89 (C_{Ph}). ^{31}P NMR spectrum: δ_P 3.71 ppm. Found, %: C 46.26; H 7.94. $C_{18}H_{37}O_6PSi_3$. Calculated, %: C 46.52; H 8.02.

Bis(trimethylsilyl) pyrid-3-yl(trimethylsiloxy)-methylphosphonate (1c). Yield 89%, bp 152°C (1 mmHg). ^{1}H NMR spectrum, δ, ppm: –0.11 s (9H, Me_3Si), –0.10 s (9H, Me_3Si), 0.02 s (9H, Me_3Si), 4.72 d (1H, C^{1}H, $^2J_{PH}$ = 15.2 Hz), 7.09–7.13 m (1H, CH_{Py}), 7.65 d (1H, CH_{Py}, $^3J_{HH}$ = 8.0 Hz), 8.32–8.34 m (1H, CH_{Py}), 8.43 s (1H, CH_{Py}). ^{13}C NMR spectrum, δ_C, ppm: –0.26 (Me_3Si), 0.62 (Me_3Si), 0.74 (Me_3Si), 69.90 d (C^1, $^1J_{PC}$ = 179.3 Hz), 123.05 (C_{Py}), 134.32 (C_{Py}), 135.37 d (C_{Py}, $^3J_{PC}$ = 4.6 Hz), 147.85 d (C_{Py}, $^3J_{PC}$ = 6.5 Hz), 148.39 (C_{Py}). ^{31}P NMR spectrum: δ_P 2.43 ppm. Found, %: C 44.26; H 7.89. $C_{15}H_{32}NO_4PSi_3$. Calculated, %: C 44.41; H 7.95.

Bis(trimethylsilyl) pyrid-4-yl(trimethylsiloxy)methylphosphonate (1d). Yield 86%, bp 149°C (1 mmHg). ^{1}H NMR spectrum, δ, ppm: –0.09 s (Me_3Si), –0.07 s (Me_3Si), 0.06 s (Me_3Si), 4.68 d (C^{1}H, $^2J_{PH}$ = 17.2 Hz), 7.18 d (CH_{Py}, $^3J_{HH}$ = 5.6 Hz), 8.35 d (CH_{Py}, $^3J_{HH}$ = 5.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: –0.70 s (Me_3Si), 0.15 s (Me_3Si), 0.38 s (Me_3Si), 70.59 d (C^1, $^1J_{PC}$ = 174.7 Hz, C_{Py}), 121.45 s (C_{Py}), 147.21 br.s (C_{Py}), 148.54 d ($^3J_{PC}$ = 2.0 Hz, C_{Py}). ^{31}P NMR spectrum: δ_P 1.85 ppm. Found, %: C 44.28; H 7.86. $C_{15}H_{32}NO_4PSi_3$. Calculated, %: C 44.41; H 7.95.

Bis(trimethylsilyl) 4-dimethylaminophenyl(trimethylsiloxy)methylphosphonate (1e). Yield 89%, bp 164°C (1 mmHg), mp 55°C. ^{1}H NMR spectrum, δ, ppm: –0.29 s (9H, Me_3Si), –0.19 s (9H, Me_3Si), –0.16 s (9H, Me_3Si), 2.59 s (6H, Me_2N), 4.64 d (1H, C^{1}H, $^2J_{PH}$ = 16.0 Hz), 6.43 d (2H, CH_{Ph}, $^3J_{HH}$ = 7.2 Hz), 6.93 d (2H, CH_{Ph}, $^3J_{HH}$ = 7.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: –0.68 (Me_3Si), 0.12 (Me_3Si), 40.47 (Me_2N), 71.40 d (C^1, $^1J_{PC}$ = 181.4 Hz), 112.22 (C_{Ph}), 127.79 d (C_{Ph}, $^3J_{PC}$ = 6.0 Hz), 130.52 (C_{Ph}), 148.76 (C_{Ph}). ^{31}P NMR spectrum: δ_P 4.44 ppm.

Tetra(trimethylsilyl) 4-dimethylaminophenylmethylenediphosphonate (2). A solution of 0.9 g of trimethylsilyl trifluoromethylsulfonate in 5 mL of methylene chloride was added to a solution of 3.4 g of 4-dimethylaminobenzaldehyde diethyl acetal and 18.0 g of tris(trimethylsilyl) phosphite in 15 mL of methylene chloride. After completion of the exothermic reaction, the mixture was kept overnight at 20°C. The solvent was removed in a vacuum, the crystals were washed with cold hexane. Yield 8.6 g (96%), mp 144°C. ^{1}H NMR spectrum, δ, ppm: 0.07 s (36H, Me_3Si), 3.22 s (6H, Me_2N), 3.48 t (1H, C^{1}H, $^2J_{PH}$ = 25.2 Hz), 7.53 d (2H, $C_{Ph}H$, $^3J_{HH}$ = 8.4 Hz), 7.65 d (2H, $C_{Ph}H$, $^3J_{HH}$ = 8.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 0.32 (Me_3Si), 46.82 (Me_2N), 48.33 t (C^1, $^1J_{PC}$ = 135.9 Hz), 120.28 (C_{Ph}), 132.12 t (C_{Ph}, $^2J_{PC}$ = 5.9 Hz), 135.42 t (C_{Ph}, $^3J_{PC}$ = 8.5 Hz), 141.60 (C_{Ph}). ^{31}P NMR spectrum: δ_P –1.47 ppm. Found, %: C 43.06; H 8.06. $C_{21}H_{47}NO_6P_2Si_4$. Calculated, %: C 43.20; H 8.11.

Bis(trimethylsilyl) 4-bromophenyl(ethoxy)methylphosphonate (3a). A solution of 1.0 g of trimethylsilyl trifluoromethylsulfonate in 5 mL of methylene chloride was added to a solution of 3.9 g of 4-bromobenzaldehyde diethyl acetal and 19.0 g of tris(trimethylsilyl)phosphite in 15 mL of methylene chloride. The mixture was heated on a boiling water bath for 2 h to distill off methylene chloride, then the residue was distilled. Yield 5.0 g (74%), bp 104°C (2 mmHg). ^{1}H NMR spectrum, δ, ppm: 0.07 s (18H, Me_3Si), 1.05 t (3H, Me, $^3J_{HH}$ = 7.2 Hz), 3.30–3.40 m (2H, CH_2O), 4.43 d (1H, C^{1}H, $^2J_{PH}$ = 7.2 Hz), 7.15 d (2H, CH_{Ph}, $^2J_{HH}$ = 8.0 Hz), 7.30 d (2H, CH_{Ph}, $^2J_{HH}$ = 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 0.67 (Me_3Si), 15.03 (Me), 66.38 d (CH_2O, $^3J_{PC}$ = 13.8 Hz), 78.11 d (C^1, $^1J_{PC}$ = 175.6 Hz), 121.89 d (C_{Ph}, $^2J_{PC}$ = 4.6 Hz), 129.49 d (C_{Ph}, $^2J_{PC}$ = 5.6 Hz), 131.16 (C_{Ph}), 134.70 (C_{Ph}). ^{31}P NMR spectrum: δ_P 0.65 ppm. Found, %: C 40.86; H 6.33. $C_{15}H_{28}BrO_4PSi_2$. Calculated, %: C 41.00; H 6.42.

Bis(trimethylsilyl) {[4-(dimethylamino)phenyl](ethoxy)methyl}phosphonate (3b). A mixture of 3.4 g of 4-dimethylaminobenzaldehyde diethyl acetal and 6.12 g of diethyl(trimethylsilyl) phosphite, 0.1 g of cadmium iodide, and 0.1 g of zinc chloride was heated at 140°C until complete distillation off of ethoxytrimethylsilane (bp 74°C). The residue was distilled. Yield 4.2 g (86%), bp 195°C (2 mmHg). ^{1}H NMR spectrum, δ, ppm: 0.97 t (3H, Me, $^3J_{HH}$ = 7.2 Hz), 0.98 t (3H, Me, $^3J_{HH}$ = 7.2 Hz), 1.05 t (3H, Me, $^3J_{HH}$ = 6.8 Hz), 2.72 s (6H, Me_2N), 3.20–3.35 m (2H, CH_2O), 3.60–3.90 m (4H, CH_2O), 4.29 d (1H, C^{1}H, $^2J_{PH}$ = 15.2 Hz), 6.47 d (2H, CH_{Ph}, $^3J_{HH}$ = 8.8 Hz), 7.08 d (2H, CH_{Ph}, $^2J_{HH}$ = 8.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.93 (Me), 16.17 d (Me, $^3J_{PC}$ = 5.5 Hz), 40.15 (Me_2N), 62.37 d (CH_2O, $^2J_{PC}$ = 6.5 Hz), 62.58 d (CH_2O, $^2J_{PC}$ = 6.41 Hz), 65.39 d (CH_2O, $^3J_{PC}$ = 14.7 Hz), 77.99 t (C^1, $^1J_{PC}$ = 171.0 Hz), 111.84 (C_{Ph}), 121.87 (C_{Ph}), 128.86 d (C_{Ph}, $^3J_{PC}$ = 5.5 Hz), 150.33 (C_{Ph}). ^{31}P NMR spectrum: δ_P 19.97 ppm. Found, %: C 56.94; H 8.26. $C_{15}H_{26}NO_4P$. Calculated, %: C 57.13; H 8.31.

NMR spectra ($CDCl_3$) were obtained on a Bruker Avance 400 spectrometer, internal reference TMS (^{1}H, ^{13}C) or external reference 85% solution of H_3PO_4 in D_2O (^{31}P).

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