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Application of Silicon-Phosphorus Based Reagents in Synthesis of Aminophosphonates. Part 2: Reactions of *N*-(Triphenylmethyl)-aldimines with the Silylated Phosphorus Acid Esters*

by B. Boduszek and M. Soroka

Institute of Organic Chemistry, Biochemistry and Biotechnology, Wrocław University of Technology, 50-370 Wrocław, Poland

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Reactions of silylated phosphorus acid esters with *N*-triphenylmethylaldimines (*N*-tritylaldimines) were investigated. *N*-Tritylmethaneimine reacts at room temperature with a mixture of $P(OMe)_3$ and Me_3SiBr forming the corresponding aminophosphonate derivatives in high yield. Other *N*-tritylimines are resistant toward the silylated reagents at room temperature, but undergo a similar phosphonylation reaction at elevated temperatures to form the expected aminophosphonic acids.

Key words: trimethyl phosphite, bromotrimethylsilane, silylation, *N*-tritylaldimines, *N*-(triphenylmethyl)aminomethylphosphonic acid, aminophosphonic acids

Employment of silicon-phosphorus based reagents for synthetic work on organophosphorus compounds is of growing interest [1,2]. Recently, we found a new way for an easy and efficient preparation of various aminophosphonic acids, in reaction of silylated esters of phosphorus acid with aldimines [1]. The silylated phosphorus esters were prepared *in situ* from dialkyl or trialkyl phosphites and bromotrimethylsilane. The aldimines were likewise obtained *in situ* from aromatic or heteroaromatic aldehydes. The phosphonylation proceeded in mild conditions at ambient temperature for aldimines [1,3], having a general structure shown in Scheme 1 (**1**: R′ = Bu, $PhCH_2$, Ph_2CH).

The tritylamine (Ph_3C-NH_2) is frequently considered as "a substitute of ammonia" in organic reactions [4], because the Ph_3C moiety can be easily removed from a molecule in acidic conditions, leaving a product with a unsubstituted amino group. Therefore, *N*-tritylimines are also considered as valuable starting materials for synthesis of aminophosphonates [4], because the *N*-trityl aminophosphonate derivatives may be easily transformed into the simple aminophosphonates. However, we found that reactions of the *N*-tritylimines with silylated phosphorus agents take sometimes a different course in comparison with previous results [1].

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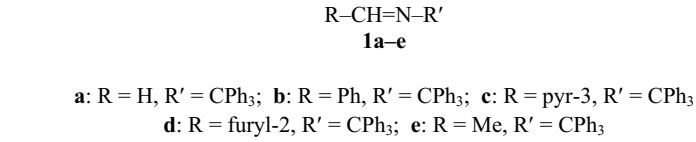
*Part 1 – see [1].

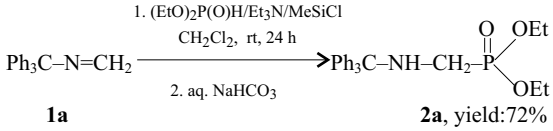


Scheme 1. Structures of imines.

In this work, we present the results of studies on the reactions of *N*-(trityl)aldimines with silylated phosphorous esters.

RESULTS AND DISCUSSION

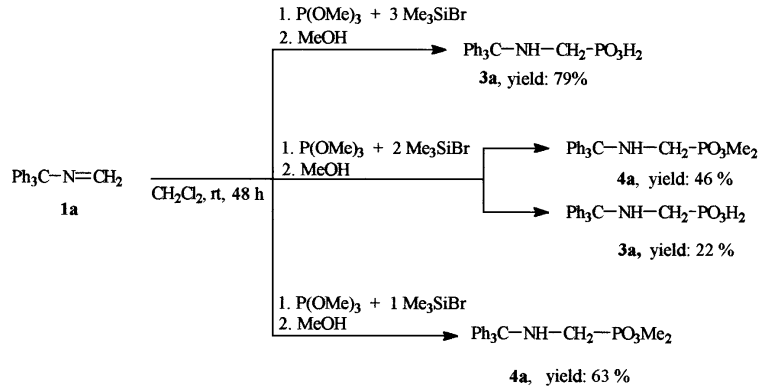
We examined first the *N*-(trityl)-methaneimine (**1a**, Scheme 1), in reaction with some silylated phosphorus acid esters [2], finding that phosphonylation of that methaneimine at room temperature proceeded smoothly to the expected product; *i.e.* diethyl *N*-(trityl)-aminomethylphosphonate (**2a**, Scheme 2), when monosilylated phos-



Scheme 2. Phosphonylation of **1a** by a mixture: $(EtO)_2P(O)H/Et_3N/Me_3SiCl$.

phorus ester [$(EtO)_2POSiMe_3$] was used. Similarly reacted the tris(trimethylsilyl)phosphite [$P(OSiMe_3)_3$], giving with methaneimine the *N*-(trityl)-aminomethylphosphonic acid (**3a**, Scheme 3).

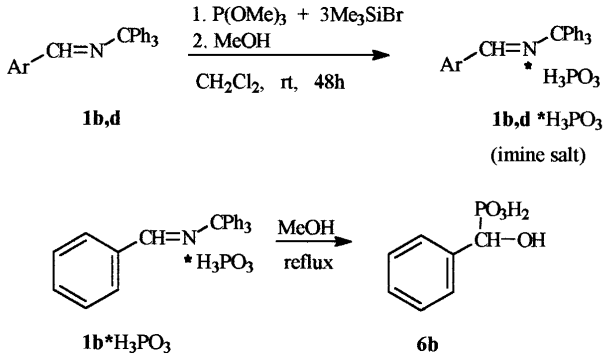
Treatment of **1a** with one equivalent of $P(OMe)_3$ and two equivalents of Me_3SiBr led to a mixture of two products; *i.e.* the dimethyl *N*-(trityl)-aminomethylphosphonate (**4a**) and the *N*-(trityl)-aminomethylphosphonic acid (**3b**), respectively (Scheme 3).



Scheme 3. Phosphonylation of **1a** by a mixture: $P(OMe)_3$/1-3eq., Me_3SiBr.

An expected monomethyl ester of *N*-(trityl)-aminomethylphosphonic acid was not found [1]. An equimolar mixture of $P(OMe)_3$ and Me_3SiBr, used in the reaction with **1a**, led to dimethyl *N*-(trityl)aminomethylphosphonate (**4a**, Scheme 3).

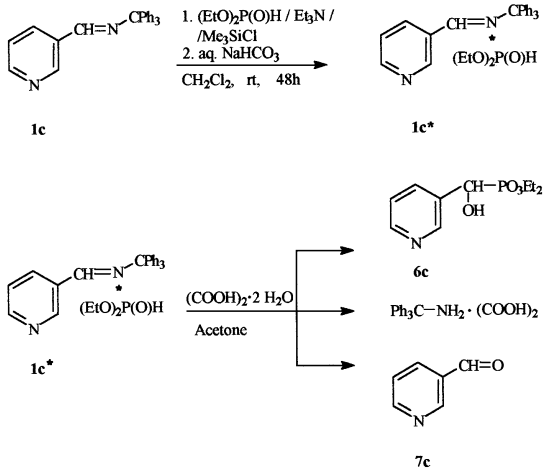
The results showed, that the course of reaction of *N*-(trityl)-methaneimine with silylated phosphorus esters is similar to that already proved for various, typical imines, not being the *N*-trityl derivatives [1,3]. Treatment of other *N*-tritylimines (**1b,d**) with a mixture of $P(OMe)_3$ and Me_3SiBr *did not* lead to the corresponding *N*-trityl aminophosphonates, although it was expected. The phosphonylation reaction did not take place in this case and, instead, phosphorus acid salts of proper imines were formed (**1b**·H_3PO_3 and **1d**·H_3PO_3, Scheme 4). However, when the salt (**1b**·H_3PO_3) was refluxed in methanol, a conversion (48%) to α-hydroxybenzylphosphonic acid **6b** was observed (Scheme 4).



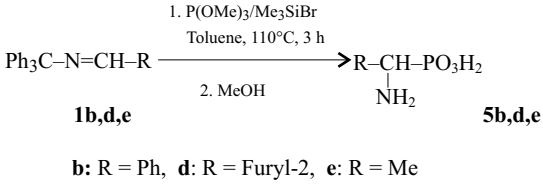
Scheme 4. Reactions of imines **1b,d** with a mixture: $P(OMe)_3$/3eq. Me_3SiBr. Conversion of the imine salt to hydroxyphosphonic acid, **6b**.

Formation of hydroxyphosphonic acid **6b** can be rationalized because the imine salt undergoes a decomposition to benzaldehyde, trityl amine and H_3PO_3, and a subsequent reaction of the formed benzaldehyde with the H_3PO_3, gives the **6b**. Similarly, reaction of pyridyl *N*-tritylimine (**1c**) with silylated diethyl trimethylsilyl phosphite led also to an imine salt of diethyl phosphite [**1c***· $(EtO)_2P(O)H$] (Scheme 5). Treatment of the salt with an equimolar amount of oxalic acid led to a mixture of products, in which diethyl α-hydroxy-3-pyridylmethylphosphonate (**6c**), 3-pyridinecarboxaldehyde (**7c**), tritylamine oxalate and diethyl phosphite were found (Scheme 5). Yield of the hydroxyphosphonate **6c** such formed was moderate (~ 40%).

When the reaction of the imine **1b** with a mixture of $P(OMe)_3$ and 3 equivalents of Me_3SiBr was carried out in refluxing toluene (110°C), α-amino-benzylphosphonic acid (**5b**) was formed as the main product. Similarly, reactions of *N*-(trityl)imines (**1d** and **1e**) with $P(OMe)_3$ and 3eq. Me_3SiBr at 110°C led to the corresponding aminophosphonic acids; **5d** and **5e**, respectively (Scheme 6).

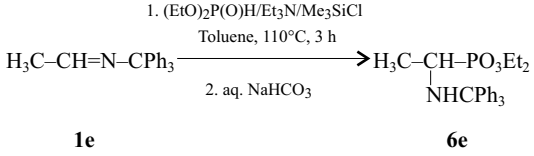


Scheme 5. Reaction of **1c** with a mixture: $(EtO)_2P(O)H/Et_3N/Me_3SiCl$. Conversion of the **1c*** to hydroxyphosphonate **6c**.



Scheme 6. Phosphonylation of imines **1b,d,e** by a mixture: $P(OMe)_3$/3eq. Me_3SiBr at 110°C.

Phosphonylation of the imine **1e** by a mixture of $(EtO)_2P(O)H/Et_3N/Me_3SiCl$ at 110°C gives diethyl 1-[*N*-(triphenylmethyl)amino]ethylphosphonate (**6e**), as a predominant product (Scheme 7). There was an important change in the course of this reaction, in comparison with the previous one. When Me_3SiCl was used instead of Me_3SiBr, the trityl group remained in the product.



Scheme 7. Phosphonylation of imine **1e** by a mixture: $(EtO)_2P(O)H/Et_3N/Me_3SiCl$ at 110°C.

CONCLUSIONS

Reaction of *N*-tritylmethaneimine with silylated phosphorus acid esters led to the corresponding *N*-trityl-aminophosphonates in high yields. The other *N*-tritylaldimines, derived from aromatic or heteroaromatic aldehydes, were resistant toward silylated phosphorus esters. The products isolated in this case were imine salts. However, during work-up of these imine salts with oxalic acid the related hydroxyphosphonates were formed. *N*-Tritylaldimines reacted at elevated temperature with silylated phosphorus acid esters to form respective aminophosphonic acids.

EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz in $CDCl_3$ or DMSO-d_6 solutions, using 300.13 MHz for ^{1}H NMR and 121.51 MHz for ^{31}P NMR spectra, respectively. Melting points were determined on a Digital Melting Point Apparatus Electrothermal 9200. Elemental analyses were performed in the Laboratory of Instrumental Analysis, by Ms Cz. Andrzejewska. All commercially available reagents were used as received from the supplier (the Aldrich Company).

1. Preparation of *N*-(trityl)aldimines. *N*-Tritylaldimines **1a–e** were prepared according to the published procedure [4]. Imines **1c** and **1d** are new compounds and their physico-chemical data are given below. **1c**: Yield: 75%, m.p. 160–162°C. ^{1}H NMR ($CDCl_3$): 8.76 (s, 1H, *py-2)*, 8.55 (d, 1H, *py-6*, J = 4.74 Hz), 8.19 (d, 1H, *py-4*, J = 7.89 Hz), 7.78 (s, 1H, CH=N), 7.30–7.16 (m, 16 H, *py-5, Ph*). **1d**: Yield: ~90%, m.p. 135–137°C. ^{1}H NMR ($CDCl_3$): 7.62 (s, 1H, CH=N), 7.50 (d, 1H, *fur*-5, J = 1.5 Hz), 7.27–7.16 (m, 15H, *Ph's*), 6.76 (d, 1H, *fur-3*, J = 3.4 Hz), 6.43 (m, 1H, *fur-4*).

2. Reaction of *N*-(trityl)methaneimine (1a) with a mixture of $(EtO)_2P(O)H/Et_3N/Me_3SiCl$. Syntheses of the all aminophosphonates were carried out in the equipment, protected against moisture. The proper silylated phosphorylating reagent [$(EtO)_2POSiMe_3$] was prepared by adding diethyl phosphite (3.0 g, 21.7 mmol) to dry methylene chloride (50 mL), followed by triethylamine (2.2 g, 21.8 mmol) and then chlorotrimethylsilane (2.4 g, 22.1 mmol). A resulting mixture was stirred for 15 min and a solution of *N*-tritylmethaneimine (5.6 g, 20.7 mmol) in methylene chloride (50 mL) was added. A mixture was stirred at room temp. for 24 h, rinsed three times with 5% aq. sodium bicarbonate (50 mL), the organic layer was dried (anh. Na_2SO_4), filtered and evaporated to give a product (**2a)** as an oil, which solidified after short time. The product was recrystallized from hexane, containing a small amount of methylene chloride. **2a**: yield: 6.9 g (72%), m.p. 115–116°C lit. [4] 115–117°C, ^{1}H NMR ($CDCl_3$): 7.51–7.48 (m., 6H, arom.), 7.33–7.19 (m., 9H, arom.), 4.26–4.16 (qq, 4H, O**C**$\mathbf{H_2}$$CH_3$, J = 7.1 Hz), 2.52 (d, 2H, C$\mathbf{H_2}$-P, J = 13.8 Hz), 2.02 (bs, 1H, NH), 1.38 (t, 6H, CH_3, J = 7.1 Hz), ^{31}P NMR ($CDCl_3$): 28.47 (s).

3. Reaction of *N*-(trityl)methaneimine (1a) with a mixture of $P(OMe)_3$/3eq. Me_3SiBr. The silylated phosphorylating agent [$P(OSiMe_3)_3$] was prepared by adding dropwise Me_3SiBr (3.1 g, 20.2 mmol) to a solution of the $P(OMe)_3$ (0.75 g, 6.0 mmol) in dry methylene chloride (20 mL). To this silylated mixture, a solution of *N*-tritylmethaneimine (1.55 g, 5.7 mmol) in CH_2Cl_2 was added with stirring. The whole mixture obtained was stirred at room temp. for 48 h, then evaporated to dryness. A resulting oil (2.8 g) was dissolved in diethyl ether (25 mL), containing some methanol (1.5 mL) and the solution was refrigerated. It caused separation of the product (**3a**), as a white solid. The product separated was collected by filtration. **3a**: yield: 1.6 g (79%), m.p. 190–194°C. ^{1}H NMR (DMSO): 7.42–7.16 (m, 15H, arom.), 2.11 (d, 2H, $\mathbf{CH_2}$-P, J = 13.9 Hz), ^{31}P NMR (DMSO): 22.45 (s).

4. Reaction of *N*-(trityl)methaneimine (1a) with a mixture of $P(OMe)_3$/2eq. Me_3SiBr. Reaction was carried out as described above (procedure *no. 3*), in a 25 mmol scale, using two equivalents of Me_3SiBr to the $P(OMe)_3$. The products (**3a** and **4a**) were isolated by the following way: After 48 h, the reaction mixture was diluted with hexane (100 mL), then methanol (5 mL) was added and the final mixture was partially evaporated to a half-volume and refrigerated. A solid obtained (**4a**) was collected by filtration. Yield: 4.3 g (46%) m.p. 210–213°C lit. [4] 210–211°C. ^{1}H NMR ($CDCl_3$): 7.49–7.46 (m, 6H, arom.),

7.32–7.18 (m, 9H, arom.), 3.84 (d, 6H, 2x O**CH$_3$**, J = 10.65 Hz), 2.54 (d, **CH$_2$**-P, J = 13.92 Hz), 2.05 (bs, 1H, NH). ^{31}P NMR ($CDCl_3$): 30.95 (s). Spectroscopic data of the product obtained are in agreement for dimethyl *N*-(trityl)aminomethylphosphonate [4]. The remaining filtrate was evaporated to dryness, the residue was dissolved in methanol (20 mL), diethyl ether (20 mL) and hexane (5 mL) added and refrigerated. Separated white solid (**3a**) was collected by filtration. Yield: 1.9 g (22%).

5. Reaction of *N*-(trityl)methaneimine (1a) with a mixture of P(OMe)$_3$/1eq. Me$_3$SiBr. Reaction was carried out as described (procedure *no. 4* for isolation of **4a**), in a 10 mmol scale, using one equivalent of Me_3SiBr to the $P(OMe)_3$. Yield of **4a**: 2.4 g (63%).

6. Reaction of *N*-(trityl)aldimines (1b,d) with a mixture of P(OMe)$_3$/3eq. Me$_3$SiBr. Reaction was carried out as described in the procedure *no. 3*, in a 5 mmol scale. After 48 h of stirring at room temp., the reaction mixture was evaporated and a remaining residue was treated with diethyl ether (25 mL), filtered and methanol (5 mL) was added and refrigerated. A solid separated was collected by filtration and dried. Products obtained (**1b***H_3PO_3**, 1d***H_3PO_3, Scheme 4) according to ^{1}H NMR and ^{31}P NMR data were salts of imines (**1b, 1d**) with H_3PO_3. Average yields of the salts were 50–60%. ^{1}H NMR (DMSO): the spectra were practically identical with the spectra of the starting imines. ^{31}P NMR (DMSO) spectra show only one phosphorus signal for both salts; having the same value (singlet, δ = 2.60 ppm). A sample of *N*-tritylphenylmethaneimine salt (**1b***H_3PO_3) (1.1 g, 2.5 mmol) was refluxed with methanol (5 mL) for 30 min., then the solution was diluted with CH_2Cl_2 (10 mL) and refrigerated. A solid separated was collected by filtration, washed with diethyl ether and dried. According to the NMR data, the product obtained was α-hydroxy-benzylphosphonic acid, (**6b**): yield: 0.23 g (48%); m.p. 220–221°C. lit. [11] m.p. 211°C. ^{1}H NMR (DMSO): 7.26 (m, 5H, Ph), 3.59 (d, 1H, CH-P, J = 21.3 Hz), ^{31}P NMR (DMSO): 19.23 (s).

7. Reaction of *N*-(trityl)-(3-pyridyl)methaneimine (1c) with a mixture of (EtO)$_2$P(O)H/Et$_3$N/Me$_3$SiCl. Reaction was carried out as described for preparation of the diethyl ester **2a**, (procedure *no. 2*), in a two mmol scale. After work-up, the imine salt **1c*** was obtained. Yield: 1.25 g (89%). ^{31}P NMR (DMSO): 8.54 (s). Salt (**1c***) (1.1 g) was dissolved in acetone (25 mL), treated with a solution of oxalic acid (0.5 g) in acetone (10 mL) and refrigerated. Separated crystals of tritylamine oxalate were filtered off (0.6 g), and the filtrate was evaporated. A residue obtained was treated with 5% aq. $NaHCO_3$ (20 mL) and extracted with methylene chloride (50 mL). The extract was dried (anh. Na_2SO_4), filtered and evaporated to give an oil, which solidified after short time (0.61 g). A product obtained (according to NMR data) was a mixture of diethyl 3-pyridylmethyl(α-hydroxy)phosphonate (**6c**) (45%), 3-pyridinecarboxaldehyde (15%), diethyl phosphite (15%), and unspecified trityl derivative (20%). The product was crystallized from a mixture of diethyl ether and hexane, to obtain the **6c** (white crystals). Yield: 0.24 g (38%), m.p. 78–79°C. lit. [9]. m.p. 74–77°C. ^{1}H NMR ($CDCl_3$): 8.62 (s, 1H, *pyr-2.*), 8.47 (d, 1H, *pyr-6.*, J = 4.8 Hz),7.87 (m, 1H, *pyr-4.*), 7.26 (m, 1H, *pyr-5.*), 5.2 (bs, 1H, OH), 5.05 (d, 1H, CH-P, J = 11.73 Hz), 4.08 (m, 4H, OCH_2), 1.23 (m, 6H, CH_3). ^{31}P NMR ($CDCl_3$): 21.68 (s).

8. Reaction of *N*-(trityl)aldimines; 1b, 1d, 1e with a mixture of P(OMe)$_3$/3eq. MeSiBr at 110°C, in toluene solution. To a solution of imine **1b**, **1d** or **1e** (5.0 mmol) and trimethyl phosphite (0.63 g, 5.1 mmol) in dry toluene (100 mL) bromotrimethylsilane (3.1 g, 20.4 mmol) was added dropwise with stirring. A resulting mixture was refluxed for 3 h and evaporated. A remained semi-solid was treated with methylene chloride (5 mL), methanol (5 mL) and left for 24 h. An excess of diethyl ether (50 mL) was then added and refrigerated. A separated solid was collected by filtration, washed with ether and recrystallized from methanol to give the pure product (**5b**, **5d** or **5e**). An addition of a small amount of diethyl ether was needed to improve crystallization of the product. α-Aminobenzylphosphonic acid (**5b**): yield: 67%, m.p. 284–286°C. lit. [7] m.p. 283–285°C. lit. [10] m.p. 280–282°C. ^{1}H NMR (D_2O): 7.39 (bs, 5H, *Ph*), 4.39–4.33 (d, 1H, CH-P, J = 16.0 Hz), ^{31}P NMR (D_2O): 11.59 (s). Anal. for $C_7H_{10}NO_3P$ (187.13); calc.: N, 7.49; P, 16.55; found: N, 7.36; P, 16.50. α-Amino-2-furylmethylphosphonic acid (**5d**): yield: 52%; m.p. 215–220°C (dec.). lit. [5] m.p. 225–227°C. lit. [6] m.p. 212–215°C; ^{1}H NMR (DMSO): 7.76 (bs, 1H, *fur*-5), 6.43–6.32 (m, 2H, *fur*-3, 4), 3.74 (d, 1H, CH-P, J = 20.7 Hz); ^{31}P NMR (DMSO): 16.39 (s).
5e (1-Aminoethylphosphonic acid): yield: 71%, m.p. 271–275°C. lit. [7] m.p. 270–274°C. lit. [8] 273–275°C. ^{1}H NMR (D_2O): 3.36–3.25 (m, 1H, CH-P), 1.41–1.34 (dd, 3H, CH**CH$_3$**, $^2J_{H-P}$ = 14.8 Hz, J_{H-H} = 7.1 Hz). ^{31}P NMR (D_2O): 15.40 (s).

9. Reaction of *N*-(trityl)ethaneimine (1e) with a mixture of (EtO)$_2$P(O)H/Et$_3$N/Me$_3$SiCl at 110°C, in toluene solution. To a solution of imine **1e** (2.86 g, 10.0 mmol) in dry toluene (100 mL) diethyl phosphite (1.5 g, 10.8 mmol) was added, followed by triethylamine (1.12 g, 11.0 mmol). Then chloro-

trimethylsilane (1.36 g, 12.5 mmol) was added dropwise with stirring. A resulting mixture was refluxed for 3 h and cooled. It caused formation of a precipitate (triethylamine hydrochloride), which was removed by filtration. A remaining filtrate was evaporated and a residue remained was treated with aq. 5% sodium bicarbonate (50 mL) and extracted with methylene chloride (100 mL). The extract was dried (anh. Na_2SO_4), filtered and evaporated to give a product (4.0 g), as a yellowish solid. The product was recrystallized from a mixture of hexane (50 mL) and methylene chloride (5 mL) to give the pure diethyl 1-[*N*-(trityl)amino]-ethylphosphonate (**6e**), yield: 1.74 g (41%), m.p. 138–140°C. ^{1}H NMR ($CDCl_3$): 7.62–7.59 (m, 6H, arom.), 7.29–7.15 (m, 9H, arom.), 4.27–4.15 (m, 4H, O**CH$_2$**), 3.06–2.99 (m, 1H, **CH-P**), 2.28 (bs, 1H, **NH**), 1.39–1.34 (t, 6H, 2x **CH$_3$**), 0.48–0.40 (dd, 3H, CH**CH$_3$**, J_{H-H} = 6.87 Hz, $^2J_{H-P}$ = 18.24 Hz). ^{31}P NMR ($CDCl_3$): 30.24 (s).

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