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A Selective and Mild Synthetic Route to Dialkyl Phosphates

Johanna M. Kuiper,^a Ron Hulst,^b Jan B. F. N. Engberts^{*a}

^a Physical Organic Chemistry Unit, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

^b Kiadis B.V., Niels Bohrweg 11-13, 2333 CA Leiden, The Netherlands

Fax +31(50)3634296; E-mail: J.B.F.N.Engberts@chem.rug.nl

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Abstract: A very mild synthetic route to dialkyl phosphates is described. Reaction of the appropriate alcohol with PCl_3 followed by treatment with pyridine and CCl_4 afforded the corresponding trichloromethyl ester. Subsequent reaction with the triethylamine salt of acetic acid followed by hydrolysis of the formed mixed anhydride under very mild conditions afforded the dialkyl phosphates in high yield.

Key words: dialkyl phosphates, lipids, alcohols, dialkyl phosphonates, azobenzene

Important aspects of the chemistry of biological cell membranes can be successfully mimicked by using bilayer vesicles formed from synthetically available amphiphiles. For this purpose, sodium dialkyl phosphates are, among others, often used.¹⁻³ A variety of methods have been developed for the preparation of dialkyl phosphates.⁴⁻⁷ Most of these are multi-step syntheses, which are either difficult to perform or involve oxidation steps combined with the necessity of elevated temperatures, often excluding the use of alcohols containing functional groups. A frequently applied method is the stepwise preparation of the dialkyl phosphate via the mono-alkyl phosphate from pyrophosphoric acid using tetramethylammonium hydroxide (TMAH) as base.^{8,9} The application of this procedure for the preparation of long-chain lipid phosphates, however, appeared troublesome due to the long reaction times needed and difficult isolation of the product from the reaction mixtures.¹⁰ Another standard procedure employs the reaction of exactly two equivalents of alcohol with POCl_3 , followed by aggressive (basic) hydrolysis of the intermediate phosphorylchloride.^{3,11} Although this procedure allows straightforward preparation of short-chain phosphates, the use of longer chain alcohols leads to less selective bis-esterification and significant saponification during the hydrolysis of the phosphorylchloride intermediate. Moreover, isolation of the products from the crude reaction mixtures appeared troublesome and includes preparative TLC¹¹ or exceedingly long crystallization times to isolate e.g. dioleoyl phosphate.¹² In search for improved phosphorylation methods, several routes were proposed using 'exotic' reagent settings.^{5,13,14} A major drawback, however, is the need for preparation of the reagents, whereas the removal of the protecting groups can also

lead to severe problems.¹⁰ Also routes including oxidative steps^{4,15} appeared unsuccessful for the preparation of long-chain dialkyl phosphates and/or the synthesis of dialkyl phosphates with functionalized groups.

Driven by the need for a better synthetic protocol, we report the synthesis of long- and/or functionalized-chain dialkyl phosphates via a new and very mild route.

The first step of the procedure (Scheme 1) consists of an Arbuzov reaction¹⁶ at room temperature using 3 equivalents of the appropriate alcohol, 2 equivalents of pyridine and PCl_3 ,¹⁷ yielding dialkyl phosphonates **2** in 53-75% isolated yield. The reaction proceeds smoothly and can be monitored by TLC and ^1H or ^{31}P NMR (^{31}P NMR δ = ca. 7.5 ppm). If necessary, additional aliquots of pyridine and PCl_3 were added in order to ensure complete consumption of the alcohol, since traces of alcohol can cause purification problems. The dialkyl phosphonates are stable and can be purified by crystallization or column chromatography. Subsequently, phosphonates **2** are treated with CCl_4 and Et_3N , under the Atherton-Openshaw-Todd conditions,¹⁸ yielding quantitatively the trichloromethyl esters **3** (^{31}P NMR δ = ca. -13 ppm), which were not isolated. A catalytic amount of diisopropylethylamine may be added to accelerate the reaction rate. After evaporation of the reagents, the trichloromethyl esters **3** were converted into the mixed anhydrides **4** (^{31}P NMR δ = ca. -1 ppm) by treatment with acetic acid and Et_3N .^{19,20} Mild acidic hydrolysis of the anhydrides **4** afforded dialkyl phosphates **5** (^{31}P NMR δ = ca. 1 ppm) in 56-73% isolated yield.²¹

In summary, starting from a suitable alcohol a simple and mild synthetic protocol has been developed to obtain long and/or functionalized chained dialkyl phosphates. Moreover, no oxidative or basic hydrolytic steps are involved.

All reactions proceed with total conversion, except for the first step. No work-up, isolation or purification procedures were required for the intermediate compounds **3** and **4**. 4-Butyl aniline was distilled before use.

^1H , ^{31}P and ^{13}C NMR spectra were recorded at 25 °C on a Varian VXR-300 spectrometer operating at 300 MHz for ^1H , at 75.43 MHz for ^{13}C , and on a Varian Gemini-200 spectrometer operating at 200 MHz for the ^1H , at 80.96 MHz for the ^{31}P and at 50.29 MHz for ^{13}C channels. For compounds **2a**, **2d**, and **2e** no exact mass could be determined, but the parent peak was in accordance with the structure. The residual ^1H signals of the deuterated solvents were used as internal chemical shift standard. Melting points (uncorrected) were recorded using a Kofler hot stage apparatus equipped with a microscope. Oleic acid, 9-bromononan-1-ol, 4-butylaniline, 6-bromohex-

Scheme 1 Reagents: (i) PCl_3 , pyridine (ii) CCl_4 , Et_3N (iii) $\text{CH}_3\text{CO}_2\text{H}$, Et_3N , $i\text{-Pr}_2\text{NEt}$ (iv) $\text{H}^+/\text{H}_2\text{O}$.

an-1-ol, diethyl phosphite and 4-phenyl-azophenol were obtained from Aldrich.

9-[(4-Phenylazo)-phenoxy]-nonan-1-ol (1a)

To 4-phenylazophenol (4.00 g, 20.16 mmol) in acetone (150 mL) was added 9-bromononan-1-ol (4.52 g, 20.16 mmol), K_2CO_3 (5.56 g, 40.32 mmol) and a catalytic amount of KI (0.3 g, 1.8 mmol). The mixture was refluxed for 5 d. The acetone was removed by evaporation under reduced pressure. CH_2Cl_2 (300 mL) was added and the organic layer was washed with H_2O (3×150 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting yellow solid material was purified by crystallization from EtOAc (ca. 120 mL) affording yellow crystals in 75% yield (5.14 g).

Mp 107–108 °C.

^1H NMR (200 MHz, CDCl_3): $\delta = 1.35\text{--}1.61$ (m, 12 H), 1.75–1.86 (m, 2 H), 3.65 (t, $J = 6.5$ Hz, 2 H), 4.04 (t, $J = 6.5$ Hz, 2 H), 6.97–7.04 (m, 2 H), 7.39–7.55 (m, 3 H), 7.85–7.96 (m, 4 H).

^{13}C NMR (50 MHz, CDCl_3): $\delta = 25.7$, 26.0, 29.1, 29.3, 29.3, 29.5, 32.7, 63.0, 68.3, 114.7, 122.5, 124.7, 129.0, 130.3, 146.8, 152.7, 161.6.

HRMS: m/z calcd for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2$, 340.21506; found, 340.21440.

4-Butyl-4'-hydroxy-azobenzene²²

4-Butylaniline (12 g, 0.08 mol) was dissolved in a mixture of H_2O -acetone (200 mL, 1:1) and concd. HCl (20 mL). To the cooled soln, NaNO_2 (5.6 g, 0.08 mol) in cold H_2O (100 mL) was added. The soln was allowed to stand for 20 min in an ice bath. The resulting diazonium soln was added to a cold soln of phenol (7.6 g, 0.08 mol),

NaOH (3.2 g, 0.08 mol) and Na_2CO_3 (14 g, 0.13 mol) in cold H_2O (200 mL). The precipitate was filtered off and crystallized from acetone.

Yield: 15.20 g (74%).

Mp 81 °C (lit.²² 79–82 °C).

^1H NMR (200 MHz, CDCl_3): $\delta = 0.95$ (t, $J = 7.2$ Hz, 3 H), 1.29–1.47 (m, 2 H), 1.56–1.71 (m, 2 H), 2.66 (t, $J = 7.6$ Hz, 2 H), 6.62–6.69 (m, 2 H), 7.24–7.28 (m, 2 H), 7.62–7.70 (m, 2 H).

^{13}C NMR (50 MHz, CDCl_3): $\delta = 14.3$, 23.4, 34.9, 36.4, 120.2, 122.7, 126.5, 129.9, 143.7, 145.1, 152.9, 174.0.

5-[[4-(4-butylphenyl)azo]-phenoxy]-pentan-1-ol (1d)

An identical protocol as described for **1a** was followed. Starting from 4-*n*-butyl-4'-hydroxy-azobenzene and 5-bromopentan-1-ol,²³ the product was isolated in a 57% yield (1.43 g). The resulting yellow solid material was purified by crystallization from hexane.

Mp 74–75 °C.

^1H NMR (200 MHz, CDCl_3): $\delta = 0.94$ (t, $J = 7.2$ Hz, 3 H), 1.30–1.47 (m, 2 H), 1.52–1.72 (m, 6 H), 1.79–1.93 (m, 2 H), 2.68 (t, $J = 7.7$ Hz, 2 H), 3.70 (m, 2 H), 4.05 (t, $J = 6.5$ Hz, 2 H), 6.97–7.01 (m, 2 H), 7.28–7.32 (m, 2 H), 7.78–7.82 (m, 2 H), 7.87–7.91 (m, 2 H).

^{13}C NMR (50 MHz, CDCl_3): $\delta = 13.9$, 22.3, 28.9, 32.4, 33.4, 35.5, 62.7, 68.1, 114.6, 122.5, 124.5, 129.0, 145.8, 146.9, 151.0, 161.3.

HRMS: m/z calcd for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_2$, 340.21506; found, 340.21408.

6-[[4-(4-butylphenyl)azo]-phenoxy]-hexan-1-ol (1e)

An identical protocol as described for **1a** was followed. Starting from 4-*n*-butyl-4'-hydroxy-azobenzene and 6-bromohexan-1-ol the product was isolated in a 55% yield (3.07 g). The resulting yellow solid material was purified by crystallization from hexane.

Mp 75–76 °C.

^1H NMR (200 MHz, CDCl_3): $\delta = 0.89$ (t, $J = 7.3$ Hz, 3 H), 1.27–1.64 (m, 10 H), 1.74–1.83 (m, 2 H), 2.63 (t, $J = 7.7$ Hz, 2 H), 3.59–3.65 (m, 2 H), 3.99 (t, $J = 6.4$ Hz, 2 H), 6.94 (d, $J = 8.8$ Hz, 2 H), 7.25 (d, $J = 8.1$ Hz, 2 H), 7.75 (d, $J = 8.4$ Hz, 2 H), 7.84 (m, 2 H).

^{13}C NMR (50 MHz, CDCl_3): $\delta = 13.9$, 22.3, 25.5, 25.8, 29.1, 32.6, 33.4, 35.5, 62.8, 68.1, 114.6, 122.5, 124.5, 129.0, 145.7, 146.9, 151.0, 161.3.

HRMS: m/z calcd for $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_2$, 354.23071; found, 354.23061.

Di-[9-[(4-phenylazo)-phenoxy]-nonyl] Phosphonate (2a)

To **1a** (1.5 g, 4.41 mmol) in anhyd CH_2Cl_2 (15 mL) under a nitrogen atmosphere, pyridine (2.94 mmol, 238 μL , 232 mg) and PCl_3 (1.47 mmol, 128 μL , 202 mg) were slowly added. The reaction was monitored using TLC (Silica, Et₂O) or ^{31}P NMR and additional portions of pyridine and PCl_3 (ratio 2:1) were added until all alcohol had reacted. After completion, the mixture was washed with brine (2×25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting material was stirred overnight in hexane (ca. 30 mL) yielding small crystals. The crystalline material was further purified by crystallization from EtOH ($2 \times$). Pure yellow crystals were obtained in 53% yield (0.57 g).

Mp 89–95 °C.

^1H NMR (300 MHz, CDCl_3): $\delta = 1.30\text{--}1.42$ (m, 10 H), 1.60–1.67 (m, 2 H), 1.71–1.81 (m, 2 H), 3.96–4.05 (m, 4 H), 6.76 (d, $J = 6.92$ Hz, 1 H), 6.94 (d, $J = 8.8$ Hz, 2 H), 7.35–7.47 (m, 3 H), 7.81–7.91 (m, 4 H).

^{13}C NMR (50 MHz, CDCl_3): $\delta = 25.5$, 26.0, 29.0, 29.1, 29.2, 29.4, 30.4, 65.7, 68.2, 114.6, 122.5, 125.7, 129.0, 130.3, 146.8, 152.7, 161.6.

^{31}P NMR (81 MHz, CDCl_3): δ = 7.51 ppm.

MS (EI^+): m/z = 742.

Dioleoyl Phosphonate (**2b**)²⁴

An identical protocol as described for **2a** was followed starting from oleyl alcohol.²⁵ The product was purified by means of column chromatography (Silica, hexane-Et₂O, 1:1). Product **2b** was obtained as a viscous oil in 75% yield (5.43 g).

^1H NMR (200 MHz, CDCl_3): δ = 0.88 (t, J = 6.5 Hz, 6 H), 1.20–1.45 (m, 44 H), 1.61–1.80 (m, 4 H), 1.95–2.10 (m, 8 H), 4.00–4.11 (m, 4 H), 5.20–5.41 (m, 4 H), 6.80 (d, J = 692 Hz, 1 H).

^{13}C NMR (50 MHz, CDCl_3): δ = 14.1, 22.6, 25.5, 27.1, 27.2, 29.0, 29.1, 29.3, 29.4, 29.5, 29.7, 29.7, 30.3, 30.4, 31.9, 65.7, 129.7, 129.9.

^{31}P NMR (81 MHz, CDCl_3): δ = 7.47 ppm.

Di-(5-[[4-(4-butylphenyl)azo]-phenoxy]-pentyl) Phosphonate (**2d**)

An identical protocol as described for **2a** was followed. The resulting yellow crystals were isolated in 64% yield (0.68 g).

Mp 85–86 °C.

^1H NMR (200 MHz, CDCl_3): δ = 0.94 (t, J = 7.2 Hz, 6 H), 1.28–1.47 (m, 4 H), 1.56–1.71 (m, 8 H), 1.73–1.89 (m, 8 H), 2.68 (t, J = 7.7 Hz, 4 H), 4.00–4.18 (m, 8 H), 6.84 (d, J = 694 Hz, 1 H), 6.94–7.01 (m, 4 H), 7.26–7.31 (m, 4 H), 7.78–7.82 (m, 4 H), 7.86–7.93 (m, 4 H).

^{13}C NMR (50 MHz, CD_3OD): δ = 14.3, 23.4, 29.8, 31.2, 34.8, 36.5, 67.1, 69.1, 115.7, 123.4, 125.5, 130.0, 147.0, 148.0, 152.1, 162.8.

^{31}P NMR (81 MHz, CDCl_3): δ = 7.51(s).

MS (EI^+): m/z = 742.

Di-(6-[[4-(4-butylphenyl)azo]-phenoxy]-hexyl) Phosphonate (**2e**)

An identical protocol as described for **2a** was followed. The resulting yellow crystals were isolated in 70% yield (0.26 g).

Mp 106–109 °C.

^1H NMR (200 MHz, CDCl_3): δ = 0.94 (t, J = 7.2 Hz, 6 H), 1.29–1.86 (m, 24 H), 2.68 (t, J = 7.7, 4 H), 4.03–4.15 (m, 8 H), 6.83 (d, J = 693 Hz, 1 H), 6.94–7.00 (m, 4 H), 7.21–7.31 (m, 4 H), 7.77–7.81 (m, 4 H), 7.85–7.92 (m, 4 H).

^{13}C NMR (50 MHz, CDCl_3): δ = 13.9, 22.3, 25.3, 25.6, 29.0, 30.3 (d, J = 6.5 Hz), 33.5, 35.5, 65.6 (d, J = 6.1 Hz), 68.0, 114.6, 122.5, 124.5, 129.0, 145.8, 147.0, 151.0, 161.3.

^{31}P NMR (81 MHz, CDCl_3): δ = 7.50 (s).

MS (EI^+): m/z = 770.

Di-[9-[(4-phenylazo)-phenoxy]-nonyl] phosphate (**5a**)

To **2a** (0.42 mmol, 0.305 mg) in CCl_4 (15 mL) was added Et₃N (1.68 mmol, 234 μL , 170 mg) and *i*-Pr₂EtN (0.42 μmol , 7.3 μL , 5.4 mg). The mixture was stirred at r.t. for 1–3 d while monitoring the conversion by means of ^{31}P NMR. The volatile compounds were removed by evaporation under reduced pressure. To the resulting material **3**, HOAc (10 mmol, 0.60 mL, 0.62 g) and Et₃N (22 mmol, 3 mL, 2.2 g) were added. If necessary, CH_2Cl_2 was added to obtain a clear solution. The mixture was stirred for 1–2 d leading to complete conversion. The mixture was concentrated under reduced pressure. The obtained crude product **4** was, subsequently, hydrolyzed by stirring in acidic H₂O (pH 4–5, 100 mL) for 30 min. The resulting mixture was extracted with CH_2Cl_2 (150 mL). The organic layer was washed with brine (2 $\times$ 150 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The solid material was further

purified by crystallization from EtOH affording yellow crystals in 66% yield (0.206 g),

Mp 124–128 °C.

^1H NMR (200 MHz, CDCl_3): δ = 1.21–1.61 (m, 20 H), 1.66–1.84 (m, 8 H), 3.99–4.08 (m, 8 H), 6.99 (d, J = 8.8 Hz, 4 H), 7.42–7.53 (m, 6 H), 7.87–7.95 (m, 8 H).

^{13}C NMR (75 MHz, $\text{C}_6\text{D}_6\text{-CD}_3\text{OD}$, 5:1; 65 °C): δ = 25.8, 26.3, 29.4, 29.5, 29.6, 29.7, 30.7, 67.6, 68.5, 115.2, 123.0, 125.2, 129.2, 130.5, 147.7, 153.6, 162.3.

^{31}P NMR (81 MHz, CDCl_3): δ = 1.32 ppm.

Anal. Calcd for $\text{C}_{42}\text{H}_{55}\text{N}_4\text{O}_6\text{P}$ (742.9): C, 67.90; H, 7.46; N, 7.54. Found: C, 67.80; H, 7.56; N, 7.44.

Dioleoyl Phosphate (**5b**)⁵

An identical protocol as described for **5a** was followed starting from **2b** yielding **5b** that was purified according to literature procedures⁸ and obtained as an oil in a 70% yield (0.72 g).

^1H NMR (200 MHz, CDCl_3): δ = 0.88 (t, J = 6.2 Hz, 6 H), 1.20–1.40 (m, 44 H), 1.61–1.75 (m, 4 H), 1.91–2.11 (m, 8 H), 4.01 (q, J = 6.6 Hz, 4 H), 5.31–5.37 (m, 4 H).

^{13}C NMR (50 MHz, CDCl_3): δ = 14.1, 22.7, 25.4, 27.2, 29.1, 29.2, 29.3, 29.5, 29.6, 29.7, 30.1, 30.2, 31.9, 32.6, 67.6, 129.7, 129.9.

^{31}P NMR (81 MHz, CDCl_3): δ = 1.23 ppm.

Anal. Calcd for $\text{C}_{36}\text{H}_{71}\text{O}_4\text{P}$ (598.93): C, 72.18; H, 11.96. Found: C, 72.10; H, 11.79.

Diethyl Phosphate (**5c**)²⁶

A similar method was used as described for **5a**, only in second step CHCl_3 was used instead of CH_2Cl_2 . However, due to the high H₂O solubility of diethyl phosphate, a different work-up procedure was used. After hydrolysis, the aqueous layer was extracted with CHCl_3 (10 $\times$ 50 mL aliquots). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting material was distilled at 80 °C (0.7 mm Hg) (lit. 203 °C, 1 bar)²⁷ yielding **5c** as a colorless oil in 60% yield (3.2 g).

^1H NMR (200 MHz, CDCl_3): δ = 1.30 (d, J = 7.2, 1.0 Hz, 6 H), 4.06 (m, 4 H), 12.54 (s, 1 H).

^{13}C NMR (50 MHz, CDCl_3): δ = 15.8 (d, J = 7.2 Hz), 63.4 (d, J = 5.7 Hz).

^{31}P NMR (81 MHz, CDCl_3): δ = -0.13 ppm.

Di-(5-[[4-(4-butylphenyl)azo]-phenoxy]-pentyl)-phosphate (**5d**)

An identical protocol as described for **5a** was followed. The resulting yellow crystals were isolated in a 56% yield (0.28 g).

Mp 126–131 °C.

^1H NMR (200 MHz, CDCl_3): δ = 0.84 (t, J = 7.2 Hz, 6 H), 1.2–1.3 (m, 4 H), 1.45–1.79 (m, 16 H), 2.58 (t, J = 7.6 Hz, 4 H), 3.90–4.00 (m, 8 H), 6.86–6.92 (m, 4 H), 7.17–7.22 (m, 4 H), 7.65–7.79 (m, 8 H).

^{13}C NMR (50 MHz, CDCl_3): δ = 13.6, 21.9, 22.1, 28.5, 29.8 (d, J = 6.9 Hz), 33.2, 35.3, 66.9 (d, J = 5.7 Hz), 67.8, 114.5, 122.3, 124.3, 128.9, 145.8, 146.7, 150.7, 161.2.

^{31}P NMR (81 MHz, CDCl_3): δ = -0.89 (s).

Anal. Calcd for $\text{C}_{42}\text{H}_{55}\text{N}_4\text{O}_6\text{P}$ (742.9): C, 67.90; H, 7.46; N, 7.54. Found: C, 67.75; H, 7.40; N, 7.45.

Di-(6-[[4-(4-butylphenyl)azo]-phenoxy]-hexanyl) Phosphate (**5e**)

An identical protocol as described for **5a** was followed. The resulting yellow crystals were isolated in a 73% yield (0.45 g).

Mp 114–120 °C.

¹H NMR (200 MHz, CDCl₃): δ = 0.94 (t, *J* = 7.2 Hz, 6 H), 1.32–1.82 (m, 24 H), 2.68 (t, *J* = 7.6 Hz, 4 H), 3.97–4.11 (m, 8 H), 6.95–6.99 (m, 4 H), 7.27–7.31 (m, 4 H), 7.77–7.81 (m, 4 H), 7.85–7.90 (m, 4 H).

¹³C NMR (50 MHz, CDCl₃): δ = 13.9, 22.3, 25.2, 25.6, 29.1, 30.1 (d, *J* = 6.9 Hz), 33.4, 35.5, 67.5 (d, *J* = 5.7 Hz), 68.0, 114.6, 122.5, 124.5, 129.0, 145.7, 146.9, 151.0, 161.3.

³¹P NMR (81 MHz, CDCl₃): δ = 1.09 (s).

Anal. Calcd for C₄₄H₅₉N₄O₆P (770.95): C, 68.55; H, 7.71; N, 7.27. Found: C, 68.67; H, 7.71; N, 7.28.

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