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Synthesis of Pyridyl-β-ketophosphonates

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Abstract. In this paper we report a three-stage synthesis of alkyl ethyl 2-oxo-2-(pyridin-2-, -3- and -4-yl)ethylphosphonates (2a-e, 3a-e, 4a-e) starting from commercially-available triethyl phosphite. Triethyl phosphite was first transesterified with alcohols in the presence of sodium catalyst to give the alkyl diethyl phosphites (1b-e) in low to moderate yields. The Claisen condensation between 2-lithioalkylphosphonates and ethyl pyridine-2-,-3- and -4-carboxylate, followed by an Arbusov reaction with methyl iodide, gave the final products in moderate yields. The structures of the products were confirmed by 1H-NMR, 13C-NMR, and 31P-NMR. Estimation of the pharmacotherapeutic potential has been accomplished for synthesized compounds on the basis of Prediction of Activity Spectra for Substances (PASS).

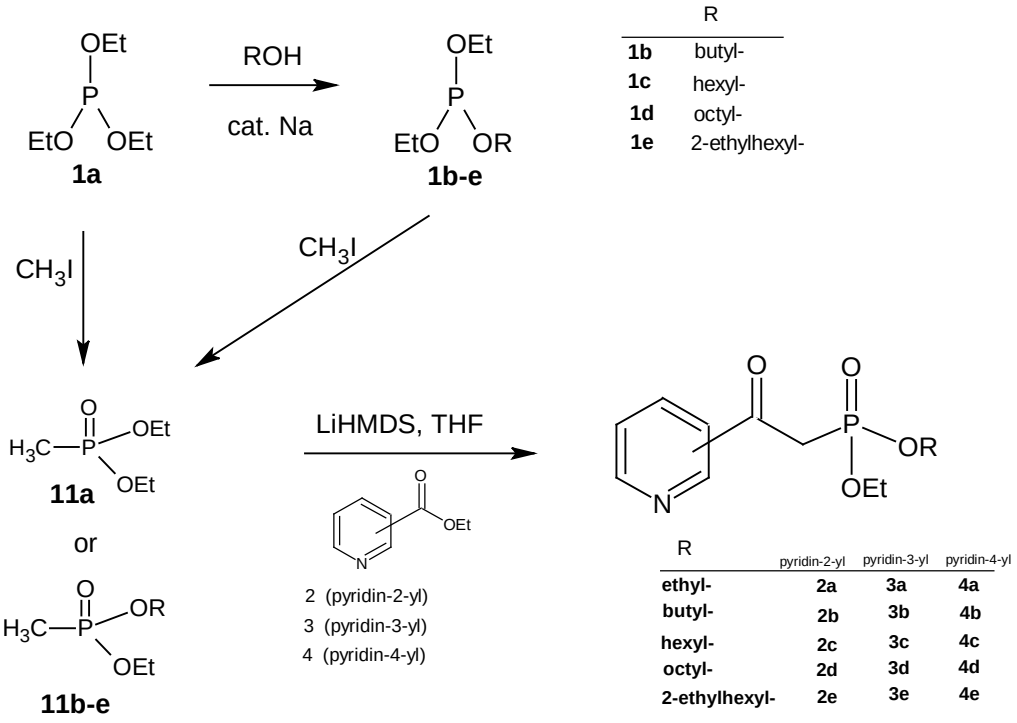
Keywords: Claisen condensation, synthesis, 2-oxo-2-pyridylethylphosphonates, bioactive compounds

1 Introduction

β-ketophosphonate aliphatic, thioaliphatic and aromatic derivatives are frequently used as bioactive agents. For example, aromatic β-ketophosphonates have been shown to be potent β-lactamase inhibitors [1], dual inhibitor of human neutrophil Cat G and human mast cell chymase [2], but in the acid form the compounds have been proposed as a novel class of serine protease inhibitors [3]. The synthesis of β-ketophosphonates is the reaction of trialkyl phosphites and β-halogenoketones, but this method requires highly reactive β-halogenoketones [4]. Other methods include acylation of 1-(trimethylsilyl)vinyl phosphonates [5] or cuprophosphonates [6], hydrolysis of vinylogous phosphoramides [7], and the reaction of phosphite with epoxysulfones [8] or with silyl enol ethers using a hypervalent iodine compound [9]. Cyclic β-ketophosphonates can also be prepared in good yields by the reaction of a dialkyl phosphite anion and α-nitro epoxides [10]. The present paper, reports a simple method for the synthesis of 2-oxo-2-(pyridin-2-, -3- and -4-yl)ethylphosphonates (2a-e, 3a-e and 4a-e) starting from triethyl phosphite.

2 Results

As shown in Scheme 1, the alkyl ethyl 2-oxo-2-(pyridin-2-, -3- and -4-yl)ethylphosphonates (2a-e, 3a-e, 4a-e) can be prepared using a three-stage procedure starting from commercially-available triethyl phosphite. In the first stage, alkyl diethyl phosphites (1b-e) are prepared by reaction of alcohols (butan-1-ol, hexan-1-ol, octan-1-ol and 2-ethylhexan-1-ol) with triethyl phosphite in the presence of Na as catalyst [11]. Then, the Arbusov rearrangement of alkyl diethyl phosphites was used to prepare alkyl ethyl methylphosphonates [12]. According to this procedure ethyl pyridine-2-, -3- or-4-carboxylate is transformed into the corresponding β-ketophosphonate by treatment with 1.2 equivalents of the lithium anion of diethyl methylphosphonate (11a) or alkyl ethyl methylphosphonate (11b-e) in THF at −78 ℃, in good yields. The results are shown in Table 1, Table 2 and Table 3.



Scheme 1. Synthesis of alkyl ethyl 2-oxo-2-(pyridin-2-, -3- and -4-yl)ethylphosphonates.

Table 1. Yields and characteristic spectral data of synthesized alkyl diethyl phosphites (1b-e).

Compound	R	Yield [%]	Form	Bp(℃/mmHg)	^{31}P-NMR[ppm]
1b	butyl-	78	oil	61/10	139.6
1c	hexyl-	61	oil	78/10	139.4
1d	octyl-	63	oil	90/8	139.1
1e	2-ethylhexyl-	32	oil	90/10	138.8

Table 2. Yields and characteristic spectral data of synthesized alkyl ethyl methylphosphonate (11a-e).

Compound	R	Yield[%]	Form	Bp(℃/mmHg)	^{31}P-NMR [ppm]
11a	ethyl-	71	oil	51/1.0	31.1
11b	butyl-	68	oil	55/1.0	31.1
11c	hexyl-	64	oil	59/1.0	31.3
11d	octyl-	53	oil	60/0.4	31.4
11e	2-ethylhexyl-	55	oil	73/0.4	29.6

Table 3. Yields and characteristic spectral data of synthesized alkyl ethyl 2-oxo-2-(pyridin-2-, -3- and -4-yl)ethylphosphonates (2a-e, 3a-e, 4a-e).

Compound	R	Yield[%]	Form	^{13}C-NMR[ppm]C=O	^{31}P-NMR[ppm]P=O
2a	ethyl-	73	oil	192.66	22.8
2b	butyl-	47	oil	192.69	23.1
2c	hexyl-	51	oil	192.72	23.2
2d	octyl-	38	Viscous oil	192.71	23.4
2e	2-ethylhexyl-	23	oil	192.56	22.9

3a	ethyl-	79	oil	190.41	22.6
3b	butyl-	73	oil	190.68	22.9
3c	hexyl-	65	oil	190.75	23.1
3d	octyl-	43	Viscous oil	190.84	23.4
3e	2-ethylhexyl-	22	Viscous oil	191.06	24.7
4a	ethyl-	69	oil	191.48	22.8
4b	butyl-	64	oil	191.54	22.9
4c	hexyl-	52	oil	191.61	23.0
4d	octyl-	31	Viscous oil	191.58	23.3
4e	2-ethylhexyl-	27	Viscous oil	191.38	24.5

The chemical structure and inhibitory molecules of 2-oxo-2-(pyridin-2-, -3- and -4-yl) ethylphosphonates (2a-e, 3a-e and 4a-e) were retrieved from Pub Chem database. The molecules were retrieved in standard 3D SDF format and activities of the compounds were predicted using PASS (Prediction of Activity Spectra for substances) [13]. If predicted activity is higher than 0.7 (Pa > 0.7), the substance is very likely to exhibit the activity in experiment, but the chance of the substance being the analogue of a known pharmaceutical agent is also high. According to data from PASS program the most frequently predicted types of biological activity are: inhibitor of glutamate-5-semialdehyde dehydrogenase, phosphatase, glyceryl-ether monooxygenase, carboxypeptidase Taq and cutinase. The results of the bioactivity analysis are presented in Table 4.

Table 4. "Probability to be Active" (PA) values for the predicted biological activity of 2a-e, 3a-e and 4a-e.

Bioactivity (PA>0.7)	**Compounds**				
	2a	**2b**	**2c**	**2d**	**2e**
Glutamate-5-semialdehyde dehydrogenase inhibitor	0.867	0.817	0.807	0.807	0.761
Dehydro-L-gulonate decarboxylase inhibitor	0.733	-	-	-	-
Phosphatase inhibitor	0.710	-	-	-	-
Glyceryl-ether monooxygenase inhibitor	-	0.779	-	-	-
Carboxypeptidase Taq inhibitor	-	0.708	0.737	0.737	-
Cutinase inhibitor	-	-	-	-	0.81

Bioactivity (PA>0.7)	**3a**	**3b**	**3c**	**3d**	**3e**
Glutamate-5-semialdehyde dehydrogenase inhibitor	0.866	0.818	0.807	0.807	0.764
Steroid 9-α-monooxygenase inhibitor	0.719	-	-	-	-
Phosphatase inhibitor	0.708	-	-	-	-
Dehydro-L-gulonate decarboxylase inhibitor	0.707	-	-	-	-
Glyceryl-ether monooxygenase inhibitor	-	0.770	0.779	0.779	-
Ecdysone 20-monooxygenase inhibitor	-	0.712	-	-	-
Cutinase inhibitor	-	-	-	-	0.718

Bioactivity (PA>0.7)	**4a**	**4b**	**4c**	**4d**	**4e**
Glutamate-5-semialdehyde dehydrogenase inhibitor	0.877	0.83	0.82	0.82	0.777
Phosphatase inhibitor	0.721	-	-	-	-
Nicotinic acetylcholine receptor	0.701	-	-	-	-
Glyceryl-ether monooxygenase inhibitor	-	0.76	0.771	0.771	-
Carboxypeptidase Taq inhibitor	-	-	-	-	-
Cutinase inhibitor	-	-	-	-	0.791

3 Conclusion

In conclusion, alkyl ethyl 2-oxo-2-pyridylphosphonates containing ethyl, butyl, hexyl and octyl chain and the pyridine ring (substitution at 2, 3 and 4 position) (2a-d, 3a-d, 4a-d) were prepared in good yields using the three-step procedure (Scheme 1). The reaction was noted to be sensitive to steric hindrance, as yields were lower with the branched alkyl ethyl methylphosphonates (2-ethylhexyl; 2e, 3e, 4e). The presented procedure is generally applicable for the synthesis of the target molecules.

4 Experimental

4.1 Methods

The nuclear magnetic resonance (NMR) spectra were measured with a Bruker Avance II 400 MHz UltraShield Plus spectrometer, operating at 400.6 and 101.2 MHz for ^{1}H and ^{13}C or ^{31}P, respectively. The number of scans varied from 1000 to 5,000 per spectrum with digital resolution of ± 0.01 ppm. All the chemical shifts are expressed in ppm. The chemical shifts were measured in $CDCl_3$ relative to an internal standard of TMS (^{1}H, ^{13}C). ^{31}P NMR spectra were measured without the external standard. Silica gel 60 (E. Merck 70–230 mesh) was used for column chromatography.

4.2 Synthesis

Procedure for synthesis of alkyl diethyl phosphites (**1b-e**)

An alcohol (0.25 mol) was weighed into the dropping funnel and triethyl phosphite (0.4 mol) with sodium metal was added to a round-bottom flask equiped. The mixture was stirred and heated to 100 ℃, then the alcohol was added dropwise over 30 min. After evolution of ethanol ceased, the residue was fractionated under reduced pressure.

Procedure for synthesis of alkyl ethyl methylphosphonate (**11a-e**)

Methyl iodide (0.25 mol) was added to a round-bottomed flask fitted with an efficient water-cooled condenser and a dropping funnel. Next, dialkyl alkyl phosphite (0.25 mol) was added dropwise. After the addition was complete, the mixture was refluxed for 2 h. The residue was then distilled in vacuo to give alkyl ethyl methylphosphonate in low to good yields.

Procedure for synthesis of alkyl ethyl 2-oxo-2-(pyridin-2-,-3- and -4-yl)ethylphosphonate (**2a-e, 3a-e, 4a-e**)

To a solution of alkyl ethyl methylphosphonate (**11a-e**, 33 mmol) in THF (10 mL) lithium *bis*(trimethylsilyl)amide (3.3 mL, 0.1M in THF) was slowly added via a syringe. To the resulting pale-yellow mixture a solution of ethyl pyridine-2-, -3- or -4-carboxylate (**2, 3** and **4**) (40 mmol) in THF (10 mL) was added at –78 °C. This solution was allowed to reach r.t. Stirring was continued for 4 h and then allowed to reach 23°C over 1 h. The reaction was quenched with a solution of ammonium chloride and extracted twice with CH_2Cl_2 and ethyl acetate. After drying over $MgSO_4$ and concentration under vacuum, the crude oil was first distilled at low pressure to remove excess alkyl ethyl methylphosphonate, and the residue was then purified by column chromatography (eluent: chlorophorm: ethyl acetate:acetone 10:5:3).

Diethyl 2-oxo-2-(pyridin-2-yl)ethylphosphonate (2a): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 8.43 (1H, ddd, J=5.33, J=4.47, J=1.79), 8.01 (1H, ddd, J=8.11, J=5.33, J=1.12), 7.84 (1H, ddd, J=8.10, J=7.00, J=1.79), 7.57 (1H, ddd, J=7.60, J=4.47, J=1.13), 3.89 (2H, s), 4.11 (2H, q, J=7.10), 4.12 (2H, q, J=7.11), 1.21 (3H, t, J=6.80), 1.23 (3H, t, J=6.84); ^{13}C NMR (101.2 MHz, $CDCl_3$): δ = 192.66, 153.06, 148.83, 137.14, 123.38, 123.16, 41.69, 16.28, 62.19; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 22.8.

Diethyl 2-oxo-2-(pyridin-3-yl)ethylphosphonate (3a): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 9.03 (1H, ddd, J=5.41, J=1.30, J=1.44), 8.54 (1H, ddd, J=4.63, J=1.30, J=1.48), 8.01 (1H, ddd, J=8.07, J=1.81, J=1.44), 7.45 (1H, ddd, J=8.07, J=5.19, J=4.3), 4.12 (2H, q, J=7.10), 4.11 (2H, q, J=7.11), 3.72 (2H, s), 1.23 (3H, t, J=6.80), 1.24 (3H, t, J=7.11). ^{13}C NMR (101.2 MHz, $CDCl_3$): δ = 190.41, 150.67, 149.71, 136.13, 130.25, 123.33, 62.18, 62.17, 41.67, 16.28, 16.27; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 22.6.

Diethyl 2-oxo-2-(pyridin-4-yl)ethylphosphonate (4a): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 8.54 (1H, ddd, J=4.41, J=0.44, J=0.1), 8.53 (1H, ddd, J=4.51, J=0.52, J=0.1), 7.90 (1H, ddd, J=4.51, J=0.52, J=0.1), 7.86 (1H, ddd, J=4.51, J=0.64, J=0.2), 4.09 (2H, q, J=7.108), 4.06 (2H, q, J=7.108), 3.82 (2H, s), 1.23 -1.25 (6H, m). ^{13}C NMR (101.2 MHz, $CDCl_3$): δ = 191.48, 150.12, 149.28, 135.11, 122.79, 122.72, 62.19, 62.24, 41.66, 16.23, 16.29; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 22.8.

Butyl ethyl 2-oxo-2-(pyridin-2-yl)ethylphosphonate (2b): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) =8.42 (1H, ddd, J=5.31, J=4.47, J=1.72), 8.02 (1H, ddd, J=8.12, J=5.31, J=1.13), 7.83 (1H, ddd, J=8.15, J=7.51, J=1.79), 7.57 (1H, ddd, J=7.43, J=4.47, J=1.13), 4.13 (2H, t, J=6.10), 4.12 (2H, q, J=7.08), 3.90 (2H, s), 1.66 (2H, tt, J=7.10, J=7.37), 1.22-1.23 (5H, m), 0.83 (3H, t, J=7.10); ^{13}C NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 192.69, 153.08, 148.84, 137.15, 123.38, 123.18, 62.20, 69.06, 41.67, 32.57, 18.84, 16.29, 13.85; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 23.1.

Butyl ethyl 2-oxo-2-(pyridin-3-yl)ethylphosphonate (3b): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 9.02 (1H, ddd, J=4.20, J=1.31, J=1.32), 8.05 (1H, ddd, J=8.07, J=1.18, J=1.43), 7.43 (1H, ddd, J=8.07, J=5.20, J=3.13), 8.53 (1H, ddd, J=4.63, J=1.01, J=1.18), 4.13 (2H, t, J=7.04), 4.12 (2H, q, J=6.18), 3.84 (2H, s), 1.66 (2H, tt, J=7.22, J=6.37), 1.21-1.23 (5H, m), 0.83 (3H, t, J=6.11); ^{13}C NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 190.68, 150.26, 149.7598, 136.21, 130.25, 123.33, 62.15, 69.02, 41.59, 32.57, 18.25, 16.28143, 13.34; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 22.9.

Butyl ethyl 2-oxo-2-(pyridin-4-yl)ethylphosphonate (4b): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 7.90 (1H, ddd, J=4.51, J=0.63, J=0.07), 7.86 (1H, ddd, J=3.50, J=0.51, J=0.01), 8.54 (1H, ddd, J=3.51, J=0.61, J=0.02), 8.74 (1H, ddd, J=3.55, J=0.53, J=0.09). 3.86 (2H,s), 4.12 (2H, t, J=6.50), 4.13 (2H, q, J=6.18), 1.76 (2H, tt, J=6.80, J=7.37), 1.21-1.23 (5H, m), 0.83 (3H, t, J=6.11); ^{13}C NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 191.54, 150.31, 150.27, 134.89, 122.64, 122.71, 69.12, 62.17, 32.57, 41.59, 18.25, 16.23, 13.38; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 22.9.

Ethyl hexyl 2-oxo-2-(pyridin-2-yl)ethylphosphonate (2c): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 8.60 (1H, ddd, J=5.32, J=3.66, J=1.19), 8.02 (1H, ddd, J=8.11, J=4.42, J=1.03), 7.86 (1H, ddd, J=8.15, J=7.61, J=1.81), 7.55 (1H, ddd, J=6.601, J=3.66, J=1.23), 4.13 (2H, t, J=6.58), 4.19 (2H, q, J=5.10), 3.91 (2H, s), 1.82 (2H, tt, J=6.40, J=6.38), 1.36 (2H, tt, J=7.41, J=6.80), 1.27-1.23 (7H, m), 0.865 (3H, t); ^{13}C NMR (101.2 MHz, $CDCl_3$): δ (ppm) =192.72, 153.06, 148.84, 137.13, 123.38, 123.16, 69.05, 62.19, 41.68, 31.02, 31.51, 25.91, 22.63, 16.28, 14.01; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 23.2.

Ethyl hexyl 2-oxo-2-(pyridin-3-yl)ethylphosphonate (3c): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 9.01 (1H, ddd, J=4.20, J=1.21, J=1.41), 8.53 (1H, ddd, J=4.63, J=1. 31, J=1.08), 8.03 (1H, ddd, J=7.01, J=0.89, J=1.44), 7.43 (1H, ddd, J=8.01, J=3.20, J=4.73), 4.12 (2H, t, J=6.10), 4.08 (2H, q, J=6.18), 3.84 (2H), 1.81 (2H, tt, J=6.20, J=6.49), 1.26-1.23 (4H, m), 0.87 (3H, t). ^{13}C NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 190.75, 150.67, 149.78, 136.11, 30.25, 123.06, 69.02, 62.47, 41.69, 31.71, 31.02, 25.14, 22.11, 16.03, 14.02; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 23.1.

Ethyl hexyl 2-oxo-2-(pyridin-4-yl)ethylphosphonate (4c): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 8.51 (1H, ddd, J=3.30, J=0.261, J=0.10), 8.49 (1H, ddd, J=3.28, J=0.21, J=0.09), 7.91 (1H, ddd, J=4.10, J=0.271, J=0.02), 7.89 (1H, ddd, J=2.50, J=0.21, J=0.01), 4.16 (2H, t, J=6.40), 4.14 (2H, q, J=6.18), 3.86 (2H, s), 1.82 (2H, tt, J=6.20, J=6.49), 1.36 (2H, tt, J=5.69, J=6.01), 1.28-1.24 (7H, m), 0.88 (3H, t); ^{13}C NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 191.61, 150.23, 150.31, 135.09, 122.14, 122.27, 69.02, 61.87, 31.47, 31.02, 25.24, 22.17, 16.23, 41.66, 13.90; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 23.0.

Ethyl octyl 2-oxo-2-(pyridin-2-yl)ethylphosphonate (2d): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 8.02 (1H, ddd, J=7.11, J=4.02, J=1.10), 8.53 (1H, ddd, J=4.42, J=3.46, J=0.89), 7.94 (1H, ddd, J=7.05, J=6.61, J=1.09), 7.56 (1H, ddd, J=6.01, J=4.46, J=1.01), 4.16 (2H, t, J=6.58), 4.13 (2H, q, J=5.88), 3.91 (2H, s), 1.82 (2H, tt, J=6.20, J=6.41), 1.37 (2H, tt, J=6.41, J=5.91), 1.28-1.23 (11H, m) 0.865 (3H, t.); ^{13}C NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 192.71, 153.08, 148.84, 137.15, 123.38, 123.17, 62.19, 69.04, 41.71, 32.41, 31.02, 29.37, 29.38, 25.63, 22.62, 16.29, 14.00; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 23.4.

Ethyl octyl 2-oxo-2-(pyridin-3-yl)ethylphosphonate (3d): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 9.06 (1H, ddd, J=4.21, J=1.31, J=1.04), 8.68 (1H, ddd, J=7.07, J=1.18, J=1.44), 7.44 (1H, ddd, J=7.07, J=4.21, J=3.64), 8.44 (1H, ddd, J=4.14, J=0.99, J=0.89), 3.86 (2H, s), 4.13 (2H, t, J=6.49), 4.15 (2H, q, J=5.98), 1.81 (2H, tt, J=7.500, J=7.46), 1.37 (2H, tt, J=6.49, J=7.12), 1.22-1.28 (11H, m), 0.85 (3H, t, J=5.89). ^{13}C NMR (101.2 MHz, $CDCl_3$): δ (ppm) =190.84, 149.94, 149.08, 135.12,

130.12, 123.16, 69.08, 62.15, 41.7, 32.31, 30.02, 29.35859, 28.76, 25.38, 22.69, 16.18, 13.91; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 23.4.

Ethyl octyl 2-oxo-2-(pyridin-4-yl)ethylphosphonate (4d): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 7.87 (1H, ddd, J=2.23, J=0.51, J=0.21), 7.91 (1H, ddd, J=2.50, J=0.31, J=0.1), 8.72 (1H, ddd, J=3.53, J=0.41, J=0.1), 8.75 (1H, ddd, J=3.30, J=0.41, J=0.11), 3.70 (2H, s), 4.13 (2H, t, J=6.52), 4.04 (2H, q, J=6.18), 1.83 (2H, tt, J=5.27, J=5.41), 1.37 (2H, tt, J=7.469, J=6.11), 1.23 -1.28 (11H, m), 0.86 (3H, t, J=5.89). ^{13}C NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 191.58, 150.03, 149.73, 135.08, 122.04, 121.94, 68.02 61.74, 41.7, 31.02, 29.36, 28.89, 25.63, 21.97, 32.23, 16.21, 13.88; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 23.3.

Ethyl (2-ethylhexyl) 2-oxo-2-(pyridin-2-yl)ethylphosphonate (2e): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 8.53 (1H, ddd, J=4.38, J=4.66, J=1.10), 7.98 (1H, ddd, J=8.16, J=5.37, J=1.33), 7.99 (1H, ddd, J=8.17, J=7.60, J=1.89), 7.59 (1H, ddd, J=7.60, J=4.66, J=1.34), 3.92 (2H), 4.11 (2H, d, J=6.73), 4.12 (2H, q, J=7.11), 1.65 (1H, tquint, J=6.92, J=6.73), 1.24-1.29 (9H, m), 0.89 (2H, td, J=6.12, J=5.92), 0.87 (3H, t, J=6.51), 0.84 (3H, t, J=7.13); ^{13}C NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 191.56 153.05, 148.83, 137.14, 123.37, 123.16, 69.33, 62.19, 41.71, 40.24, 29.99, 29.06, 23.24, 22.87, 16.28, 14.04, 11.08; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 22.9.

Ethyl (2-ethylhexyl) 2-oxo-2-(pyridin-3-yl)ethylphosphonate (3e): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 9.01 (1H, ddd, J=4.23, J=1.31, J=1.42), 8.44 (1H, ddd, J=3.63, J=1.31, J=1.08), 8.06 (1H, ddd, J=7.02, J=0.98, J=1.472), 7.46 (1H, ddd, J=7.09, J=4.23, J=3.63), 3.71 (2H, s), 4.18 (2H, d, J=5.30), 4.06 (2H, q, J=6.10), 1.63 (1H, tquint, J=5.14, J=5.70), 1.23-1.26 (9H, m), 0.89 (2H, td, J=6.12, J=5.14), 0.83 (3H, t, J=6.11), 0.88 (3H, t, J=5.38); ^{13}C NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 191.06, 150.29, 149.98, 136.28, 130.95, 123.69, 69.35, 62.22, 41.70, 40.24, 30.07, 29.08, 23.27, 22.91, 16.31, 14.02, 11.09; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 24.7.

Ethyl (2-ethylhexyl) 2-oxo-2-(pyridin-4-yl)ethylphosphonate (4e): ^{1}H NMR (400.6 MHz, $CDCl_3$): δ (ppm) = 8.64 (1H, ddd, J=3.10, J=0.31, J=0.01), 8.75 (1H, ddd, J=3.30, J=0.26, J=0.01), 7.89 (1H, ddd, J=3.10, J=0.56, J=0.04), 7.91 (1H, ddd, J=2.50, J=0.17, J=0.02), 3.87 (2H, s), 4.12 (2H, d, J=5.30), 4.11 (2H, q, J=6.10), 1.64 (1H, tquint, J=5.14, J=5.30), 1.25-1.28 (9H, m), 0.89 (2H, td, J=6.12, J=5.14), 0.83 (3H, t, J=6.11), 0.872 (3H, t, J=5.19). ^{13}C NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 191.38, 150.42, 150.39, 135.09, 122.74, 122.76, 69.34, 62.21, 41.72, 40.24, 30.01, 29.06, 23.27, 22.91, 16.31, 14.04, 11.11; ^{31}P-NMR (101.2 MHz, $CDCl_3$): δ (ppm) = 24.5.

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