A New and Easy Synthesis of Diethyl 2-Formylalkylphosphonates

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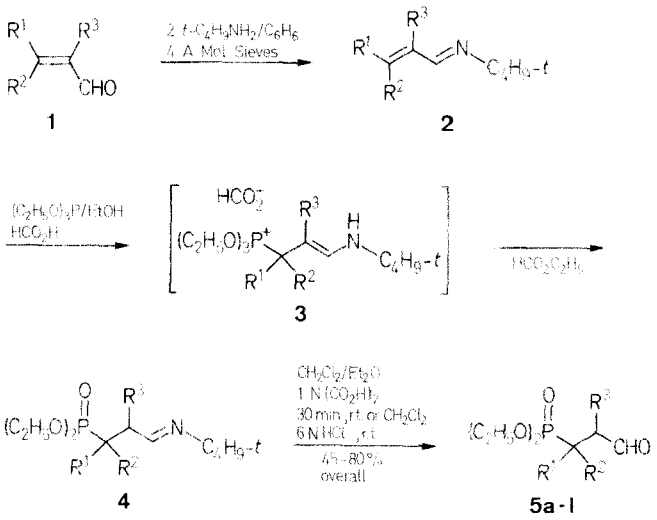
Aldimines obtained from 2-alkenals are condensed with triethyl phosphite in ethanol in the presence of formic acid to give diethyl iminoalkylphosphonates; these are readily converted into diethyl formylalkylphosphonates in acidic medium.

Phosphonates bearing a formyl group are compounds of particularly interest as versatile precursors in synthetic approaches to amino- and aminocarboxy-substituted alkylphosphonic acids by amination or cyanoamination.[1] Although this type of phosphonates has been extensively studied in the 1-formylated series[2] little attention has been paid to the higher homologues, i.e., the 2-formylalkylphosphonates **5**. A precedent for the formation of such compounds is provided by the direct phosphonylation of 2-alkenals using a trialkyl phosphite as nucleophile.[3] Unfortunately, the usual procedure involves long reaction times and high temperatures and is only suitable for unhindered substrates such as crotonaldehyde or cinnamaldehyde. Further, the reported reaction, being carried out in protic solvents (ethanol, phenol), produces protected formylalkylphosphonates whose hydrolysis under strongly acidic conditions gives low yields of the desired products and renders purification difficult. According to the same Michael/Michaelis-Arbuzov strategy, we report the results of an investigation of the use of 2-alkenal imines **2** activated as imminium salts for the synthesis of 2-formylalkylphosphonates **5**.

Triethyl phosphite does not react with aldimines **2** in ethanol except for imine **2a** (R^1=CH_3, R^2=R^3=H: obtained from crotonaldehyde) which is slowly transformed into iminoalkylphosphonate **4a** (60 h at 50 °C or two weeks at room temperature). By contrast, the addition of an equimolecular amount of formic acid to the mixture $(EtO)_3P$/EtOH/**2** induces an exothermic reaction resulting in the instantaneous formation of **4**. The reaction is easily monitored by ^{31}P-NMR spectroscopy using the disappearance of the signal of $(EtO)_3P$. Complete consumption of the phosphite requires ~ 10 min for monosubstituted aldimines (**2a, b, c**) and 1–2 h for disubstituted aldimines (**2d–l**). The intermediates **4** are quite stable; they were characterized by IR spectrometry for all examples listed in Table 1 [$\nu_{CH=N}$ ~ 1580 cm^{-1} (**4a, b, k, l**) or 1680 (**4d–j**)]. Compounds were also identified by comparison of their ^{1}H-NMR data with those of pure iminoalkylphosphonates obtained independently from *tert*-butylamine and the final products **5a–d** [^{1}H-NMR ($CDCl_3$): δ (CH=N) 7.5 (t; **4a, b**) or 7.3 (t; **4c**) or 7.4 (dd; **4d**)].

Ethanol is the only convenient solvent for the reaction, providing the best conditions of solubility and polarity(ε = 24), and thus confirming the ionic pathway of the reaction. Although the reaction is much slower and incomplete in aprotic and low-polarity solvents (dichloromethane, benzene), it does occur providing evidence of dealkylation by formate ion. To prevent competitive attack at the trivalent P-atom, the protonating agent must be selective. Only two organic acids are suitable: formic and acetic acids, formic acid giving the best results. Formic acid must be introduced in stoichiometric amounts, absolutely after triethyl phosphite; the reverse order of addition results in a slower and incomplete reaction. Undoubtedly, the nucleophilic attack of triethyl phosphite is promoted by initial protonation at nitrogen thus activating the double bond. The sp^2 carbon in the 4-position becomes the soft center towards the soft nucleophile; this results most likely in the formation of the 1,4-adduct **3**; the so generated quasi-phosphonium salt appears to be the more reasonable intermediate but has never been detected. In solution, the rearrangement to phosphonate **4** is in accordance with a Michaelis-Arbuzov mechanism. A general account of these observations is illustrated in the Scheme.



After removal of ethanol, acidic hydrolysis of the imine **4** liberates the aldehyde **5**. This step is critical and requires special

Table 1. Diethyl 2-Formylalkylphosphonates **5** Prepared

Product 5	R^1	R^2	R^3	Yield (%)	b.p. (°C)/Torr	Molecular Formula[a] or Lit. b.p. (°C)/Torr
a	CH_3	H	H	60	94–96/1	86.87/0.5[1]
b	*n*-C_3H_7	H	H	55	118–121/1	$C_{10}H_{21}O_4P$ (236.1)
c	C_6H_5	H	H	50	140–145/1	$C_{13}H_{19}O_4P$ (270.1)
d	CH_3	H	CH_3	80	125–135/1	$C_9H_{19}O_4P$ (222.1)
e	C_2H_5	H	CH_3	60	106–109/1.5	$C_{10}H_{21}O_4P$ (236.1)
f	*n*-C_3H_7	H	C_2H_5	57	99–103/0.4	$C_{12}H_{25}O_4P$ (264.1)
g	*n*-C_4H_9	H	*n*-C_3H_7	66	114–116/0.7	$C_{14}H_{29}O_4P$ (292.1)
h	C_6H_5	H	CH_3	60	134–136/0.5	$C_{14}H_{21}O_4P$ (284.1)
i	C_6H_5	H	*n*-C_5H_{11}	50	155–165/0.6	$C_{18}H_{29}O_4P$ (340.15)
j	C_6H_5	H	*n*-C_6H_{13}	45	165–175/1	$C_9H_{31}O_4P$ (354.2)
k	CH_3	CH_3	H	45	76/1	$C_9H_{19}O_4P$ (222.1)
l	$(CH_2)_2CH=C(CH_3)_2$	CH_3	H	55	130/0.7	$C_{14}H_{27}O_4P$ (290.1)

[a] Satisfactory microanalyses obtained: C ±0.22, H +0.40.

Table 2. Spectral Data of Compounds **5**

Product 5	^{1}H-NMR ($CDCl_3$)[a] δ, J(Hz)	^{13}C-NMR ($CDCl_3$)[a] δ, J(Hz)	^{31}P-NMR ($CDCl_3$)[b] δ
a	1.1 (dd, 3H, $^3J_{PH}$ = 18.2); 1.25 (t, 6H); 2.3 (m, 1H); 2.8 (dd, 2H); 4.0 (quin, 4H); 9.70 (m, 1H)	13.6 ($\underline{C}H_3CH$); 16.2 ($\underline{C}H_3CH_2O$); 24.5 (d, J_{CP} = 146.1); 44.2 ($\underline{C}H_2CHO$); 61.8 (CH_2O); 199.3 (d, CHO)	+30.0
b	0.82 (t, 3H); 1.22 (t, 6H); 1.2–1.4 (m, 2H); 1.65 (m, 2H); 2.35 (m, 1H); 2.7 (ddd, 2H); 4.0 (quin, 4H); 9.65 (d, 1H)	13.4 ($\underline{C}H_3CH_2CH_2$); 16.1 ($\underline{C}H_3CH_2O$); 20.5 ($CH_3\underline{C}HCH_2$); 29.7 (d, J_{CP} = 142.6); 30.8 ($CH_3CH_2\underline{C}H_2$); 42.6 ($\underline{C}H_2CHO$); 61.6 (CH_2O); 199.7 (d, CHO)	+29.6
c[d]	1.0 (dd, 3H); 1.2 (t, 3H); 3.0 (m, 1H); 3.6 (m, 2H); 3.9 (d quin, 4H); 7.1–7.4 (m, 5H); 9.0 (t, 1H)	15.7, 15.8 ($\underline{C}H_3CH_2O$); 37.2 (d, J_{CP} = 140.9); 43.3 ($\underline{C}H_2CHO$); 61.6, 62.3 ($\underline{C}H_2O$); 128.2 (C_{phenyl}); 134.7 (C_{phenyl}); 198.3 (d, CHO)	+24.4
d[c]	1.0 (dd, 3H, $^3J_{PH}$ = 18.0); 1.1 (d, 3H, $\underline{C}H_3CHCHO$); 1.2 (d, 3H, $\underline{C}H_3CHCHO$); 1.2 (t, 6H, $2\underline{C}H_3CH_2O$); 2.3 (m, 1H); 2.7 (m, 1H); 4.0 (quin, 4H); 9.55 (d, 1H); 9.65 (s, 1H)	8.8 ($\underline{C}H_3CHP$); 10.9 ($\underline{C}H_3CHCHO$); 15.6 ($\underline{C}H_3CH_2O$); 27.1 (d, J_{CP} = 141.4), 30.2 (d, J_{CP} = 144.3); 44.6 ($\underline{C}HCHO$); 46.2 ($\underline{C}HCHO$); 61.1 (CH_2O); 202.9 (d, CHO)	+29.7[e], +28.7
e[c]	0.8 (t, 3H, $\underline{C}H_3CH_2$); 0.9 (t, 3H, $\underline{C}H_3CH_2$); 1.1 (d, 3H, $\underline{C}H_3CH$); 1.16 (t, 6H, $2\underline{C}H_3CH_2O$); 1.2 (d, 3H, $\underline{C}H_3CH$); 1.3–1.7 (m, 2H); 2.25 (m, 1H); 2.7 (ddq, 1H); 3.95 (q, 4H); 9.51 (d, 1H); 9.56 (s, 1H)	9.0, 9.8 ($\underline{C}H_3CH_2CH$); 12.1, 12.7 ($\underline{C}H_3CH$); 15.9 ($\underline{C}H_3CHO$); 18.0, 18.7 ($\underline{C}H_2CH$); 36.8 (d, J_{CP} = 141.5); 38.8 (d, J_{CP} = 139.3); 42.4 ($\underline{C}HCHO$); 61.2 (CH_2O); 202.5 (d, CHO)	+29.4[e], +28.0
f[c]	0.7–0.9 (m, 6H, $2\underline{C}H_3CH_2CH_2$); 1.22 (m, 6H, $2\underline{C}H_3CH_2O$); 1.0–1.7 (m, 6H, 3-CH_2); 2.1 (m, 1H); 2.5 (m, 1H); 4.0 (quin, 4H); 9.60 (d, 1H); 9.65 (d, 1H)	12.3, 13.6 ($\underline{C}H_3CH_2$); 16.1 ($\underline{C}H_3CH_2O$); 18.6, 21, 27.9 (CH_2); 35.8 (d, J_{CP} = 140.9); 36.8 (d, J_{CP} = 140.0); 51.6 ($\underline{C}HCHO$); 61.5 (CH_2O); 203.1 (d, CHO)	+29.3[e], +28.7
g[c]	0.7–0.9 (m, 6H, $2\underline{C}H_3CH_2CH_2$); 1.2 (m, 6H, $2\underline{C}H_3CH_2O$); 1.1–1.8 (m, 10H, 5-CH_2); 2.2 (m, 1H); 2.5 (m, 1H); 4.0 (m, 4H); 9.58 (d, 1H); 9.63 (d, 1H)	13.5, 13.6 ($\underline{C}H_3CH_2$); 16.1 ($\underline{C}H_3CH_2O$); 21.7, 25.6, 27.2, 28.1 (CH_2); 35.8 (d, J_{CP} = 140.7); 37.2 (d, J_{CP} = 139.7); 50.3 ($\underline{C}HCHO$); 61.4 (CH_2O); 203.2 (d, CHO)	+29.3[e], +28.7
h[c]	0.9 (d, 3H, $\underline{C}H_3CH$); 0.92 (t, 3H, $\underline{C}H_3CH_2$); 1.2 (d, 3H, $\underline{C}H_3CH$); 1.21 (t, 3H, $\underline{C}H_3CH_2O$); 3.1 (m, 1H); 3.3 (dd, 1H); 3.5–4.1 (m, 4H); 7.2–7.5 (m, 5H); 9.53 (d, 1H); 9.63 (d, 1H)	12.9 ($\underline{C}H_3CH$); 15.9, 16.0 (CH_3CH_2O); 45.7 (d, J_{CP} = 139.9); 46.4, 47.7 ($\underline{C}HCHO$); 61.8, 62.3 (CH_2O); 129.5 (C_{phenyl}); 132.2 (C_{phenyl}); 202.1 (d, CHO)	+23.6[e], +23.5
i[c,d]	0.8 (t, 3H); 1.0–2.0 (m, 14H); 2.9 (m, 1H); 3.25 (dd, 1H); 3.5–4.2 (m, 4H); 7.2–7.4 (m, 5H); 9.50 (d, 1H); 9.58 (d, 1H)	13.5 ($\underline{C}H_3CH_2CH_2$); 15.7, 15.8 ($\underline{C}H_3CH_2O$); 21.8, 25.7, 27.4, 31.1 (CH_2); 44.4 (d, J_{CP} = 148.9); 51.3, 52.3 ($\underline{C}HCHO$); 61.5, 62.5 (CH_2O); 128.3 (C_{phenyl}); 133.3 (C_{phenyl}); 201.8 (d, CHO)	+23.6[e], +23.4
j	0.8 (t, 3H); 1.0–2.0 (m, 16H); 2.9 (m, 1H); 3.3 (dd, 1H); 3.5–4.1 (m, 4H); 7.1–7.4 (m, 5H); 9.48 (d, 1H); 9.58 (d, 1H)	13.8 ($\underline{C}H_3CH_2CH_2$); 16.0 ($\underline{C}H_3CH_2O$); 22.3, 26.3, 27.7, 29.0, 31.3 (CH_2); 44.7 (d, J_{CP} = 139.1); 51.5, 52.5, ($\underline{C}HCHO$); 61.6, 62.0 (CH_2O); 128.5 (C_{phenyl}); 133.8 (C_{phenyl}); 202.2 (d, CHO)	+23.6[e], +23.3
k	1.2 (t, 6H); 1.2 (d, 6H, $^3J_{PH}$ = 16.6); 2.4 (dd, 2H, $^3J_{PH}$ = 15.4); 4.0 (quin, 4H); 9.7 (dt, 1H)	16.3 ($\underline{C}H_3CH_2O$); 22.3 [($\underline{C}H_3)_2C$]; 32.5 (d, J_{CP} = 145.1); 50.1 ($\underline{C}H_2CHO$); 62.1 (CH_2O); 200.0 (CHO)	+30.6
l	1.24 (d, 3H, $^3J_{PH}$ = 16.9); 1.25 (t, 6H); 1.5, (s, 3H); 1.6 (s, 3H); 1.6 (m, 2H); 2.0 (quin, 2H); 2.4 (dd, 2H, $^3J_{PH}$ = 17.5); 4.1 (quin, 4H); 4.9 (t, 1H); 9.8 (t, 1H)	16.2 ($\underline{C}H_3CH_2O$); 17.3, 19.9 [($\underline{C}H_3)_2C=$]; 22.0 ($\underline{C}H_2CP$); 25.3 ($\underline{C}H_2CH=$); 36.8 (d, J_{CP} = 147.6) 48.1 ($\underline{C}H_2CHO$); 61.9 (CH_2O); 123.2 ($CH=$); 131.9 [($CH_3)_2\underline{C}=$]; 201.0 (CHO)	+30.5

[a] Recorded with a Bruker AC-200 Spectrometer at 200 MHz (^{1}H) and 50 MHz (^{13}C).
[b] Recorded with a Bruker WP-80 spectrometer at 32.44 MHz.
[c] Diastereoisomers detected in equal amounts.
[d] Non-equivalence of the ethoxy substituants at P-atom.

care. The dialkyl-substituted formylphosphonates **5d–l** are obtained by hydrolysis with ~6 normal hydrochloric acid whereas the monoalkyl-substituted compounds **5a, b, c**, which tend to polycondense under strongly acidic conditions, are best hydrolyzed with ~1 normal oxalic acid. Considerable decomposition and polymerisation are also frequently observed during distillation, especially with the less substituted products **5**. Further the sensitivity of compounds **5** towards oxidation requires their storage in the cold under an inert atmosphere.

Our present method provides ready and convenient access to a broad range of substituted 2-formylalkylphosphonates in satisfactory yields. This synthesis, proceeding by protection/activation *via* an aldimine, considerably renews the interest in 2-alkenals as substrates for Michael-type additions.

Aldehydes **1a–d, h, k, l** are commercially available. Aldehydes **1e, f, g** were prepared according to Ref. 4. Aldehydes **1i, j** were obtained from Givaudan, France.

Aldimines **2** are obtained by treatment of aldehydes **1** with two equivalents of *tert*-butylamine in benzene in the presence of molecular sieves (4 Å), the disappearance of the C=O band in the IR spectrum being used for monitoring the reaction. Solvent and excess of amine are removed under reduced pressure; the aldimines **2** used without further purification.

Diethyl 2-Formylalkylphosphonates 5a–l; General Procedure:
In a 500 mL round-bottom flask kept under a nitrogen atmosphere, and equipped with a thermometer and a stirrer are placed the aldimine **2** (0.1 mol) and triethyl phosphite (16 g, 0.096 mol) in dry EtOH (100 mL). Formic acid (4.8 g, 0.104 mol) is then added dropwise; the mixture turns instantaneously reddish while the temperature rises to +50 °C. The mixture is allowed to cool to room temperature and

stirring is continued for 10 min **(5a, b, c)** or 2 h **(5d–l)**. After removal of EtOH under reduced pressure, the oily residue **(4)** is dissolved in a CH_2Cl_2/Et_2O (40/60; 150 mL) and this solution is stirred vigorously with normal aqueous oxalic acid (100 mL) during 30 min **(5a, b, c)** or the crude extract **(4)** is dissolved in CH_2Cl_2 (100 mL) and stirred vigorously with 6 normal aqueous HCl (10 mL) for a few minutes **(5d–l)**. The layers are separated and the aqueous layer is extracted with CH_2Cl_2 (2×50 mL). The combined organic fractions are washed with H_2O (2×10 mL), aqueous $NaHCO_3$ (2×10 mL), and H_2O (1×10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The product **5** is purified by distillation in vacuo (compound **5l** is purified on a silica gel column using EtOAc as solvent before distillation).

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