Acylation of *in situ* generated trimethylsilyl diethylphosphonoacetate using magnesium chloride–triethylamine: a practical synthesis of β-keto phosphonates

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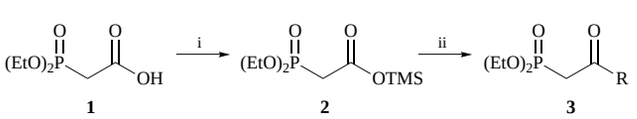
***In situ* generated trimethylsilyl diethylphosphonoacetate from diethyl phosphonoacetic acid can be acylated with carboxylic acid chlorides in the presence of magnesium chloride to prepare a variety of β-keto phosphonates. This synthetic method is suitable for the preparation of β-keto phosphonates in the laboratory and also for large-scale production.**

β-Keto phosphonates are valuable intermediates for organic synthesis, especially for the preparation of α,β-unsaturated carbonyl compounds by the Horner–Wadsworth–Emmons condensation.[1] Although a number of syntheses have been developed with the goal of providing a route to this class of compounds, they have limitations in terms of the conditions employed, competition from other reactions, and the preparation of starting materials. Commonly, β-keto phosphonates are prepared by the Arbuzov reaction and acylation of alkylphosphonate anions. The Arbuzov reaction of trialkyl phosphite and α-halogeno ketones leads to β-keto phosphonates. The latter method is restricted to highly reactive α-halogeno ketones or α-halogeno ketones containing a carbonyl protecting group, because of the nucleophilicity of phosphites and competition from the Perkow reaction to give enol phosphates.[2] The most commonly used method for preparing β-keto phosphonates is the Claisen condensation between organocopper reagents of alkylphosphonates α-anions and acylating species.[3–6] Recently, β-keto phosphonates were also obtained by either base-induced isomerization of enol phosphates or reaction of ketone enolates with dialkyl phosphorochloridite followed by aerial oxidation.[7] These synthetic methods using butyllithium are not convenient in terms of economical cost and safety. Other miscellaneous methods include acylation of 1-(trimethylsilyl)vinyl phosphonates,[8] hydrolysis of vinylogous phosphoramides,[9] reaction of 2-(diethoxyphosphinoyl) carboxylic acid chlorides with organometallic reagents,[10] the use of (diethoxyphosphoryl)acetonitrile oxide,[11] *via* allenic intermediates,[12] Pd^0-catalysed rearrangement of the 2,3-epoxyalkyl phosphonates,[13] reaction of phosphite with epoxy sulfones,[14] chloro epoxide,[15] or α-nitro epoxides,[16] oxidation of β-hydroxyalkyl phosphonates,[17] reaction of silyl enol ethers with phosphite using hypervalent iodine compound,[18] alkylation of β-keto phosphonates,[19] acylation of triethyl phosphonoacetate[20] and reaction of nitroalkenes with phosphite.[21]

Herein we report a practical synthesis of β-keto phosphonates **3** from diethylphosphonoacetic acid **1** (Scheme 1). It was performed by the acylation of trimethylsilyl diethylphosphonoacetate **2** with carboxylic acid chlorides in the presence of magnesium chloride–triethylamine[22] followed by decarboxylation. The diethylphosphonoacetic acid **1** was treated with triethylamine and trimethylsilyl chloride in dry toluene at 0 °C and to the resulting trimethylsilyl diethylphosphonoacetate was added magnesium chloride followed by the carboxylic acid chloride. The reaction mixture was stirred for 6 h at room temperature, and hydrolysed with aqueous NH_4Cl to afford the β-keto phosphonate **3** in good yield.



1 **2** **3**

Scheme 1 *Reagents and conditions:* i, TMSCl, Et_3N, toluene; ii, $MgCl_2$, RCOCl, room temp.

Table 1 Preparation of β-keto phosphonates **3** from diethyl phosphonoacetic acid **1**

Entry	R	Product	Yield (%)[a]
1	Ph	**3a**	92
2	C_6H_4Me-*p*	**3b**	87
3	C_6H_4Cl-*p*	**3c**	84
4	C_6H_4Br-*m*	**3d**	84
5	C_6H_4OMe-*p*	**3e**	82
6	C_6F_5	**3f**	80
7	*trans*-CH=CHPh	**3g**	97
8	Et	**3h**	78
9	C_5H_{11}	**3i**	82
10	cyclo-C_6H_{11}	**3j**	80
11	CH(OAc)Me	**3k**	72
12[b]	$CBrMe_2$	**3l**	38
13	CO_2Et	**3m**	81

[a] Isolated yields are based on diethylphosphonoacetic acid. [b] Starting carboxylic acid was 2-bromoisobutyryl bromide.

As shown in the Table 1, the method has been applied to a number of different aromatic and aliphatic carboxylic acid chlorides. In general, the aromatic carboxylic acid chlorides reacted to give higher product yields than the aliphatic carboxylic acid chlorides. The aromatic carboxylic acid chlorides containing electron rich and electron deficient substituents reacted with equal efficiency (entries 1–6). In the aliphatic carboxylic acid chloride series, primary and secondary acid chlorides gave good yields (entries 8–11). However, acylation of a bulky aliphatic carboxylic acid bromide gave low yield (entry 12). Replacing magnesium chloride with magnesium bromide gives similar results but is less practical. A possible explanation of the reaction pathway involves formation of trimethysilyl diethyphosphonoacetate **2**, acylation of **2** with carboxylic acid chlorides in the presense of magnesium chloride as chelating agent and decarboxylation. Compared with the general synthetic route for the preparation of β-keto phosphonates by the acylation of alkylphosphonate,[3–6] which use strong bases such as BuLi, the present procedure is inexpensive, safe and conveni-

ent. Also, the present procedure provides good product yields under mild reaction conditions. The present synthetic route is recommended as a practical preparation of β-keto phosphonates.

In summary, we have developed a new method for the preparation of β-keto phosphonates by generating trimethylsilyl diethylphosphonoacetate *in situ* and treating this species with a carboxylic acid chloride in the presence of magnesium chloride–triethylamine.

Experimental

All reactions were carried out under nitrogen atmosphere. ^{1}H and ^{13}C NMR Spectra were measured at 200 and 50 MHz, respectively, in $CDCl_3$ with $SiMe_4$ as internal standard; *J* values given in Hz. Mass spectra were recorded on HP 5985A or JEOL HX100/HX110 instruments. Diethyl phosphonoacetic acid,[23] magnesium chloride, and all carboxylic acid chlorides were obtained from commercial suppliers and were used without further purification. Toluene and triethylamine were distilled from calcium hydride and stored over 4 Å molecular sieves. Column chromatography was performed on Merck silica gel 60 (230–400 mesh).

General experimental procedure

To stirred solution of diethylphosphonoacetic acid (0.392 g, 2.0 mmol) in toluene (5 cm^3) was added triethylamine (1.12 cm^3, 8.0 mmol) and trimethylsilyl chloride (0.38 cm^3, 3.0 mmol) at 0 °C. After being stirred for 1 h at room temperature, the mixture was treated with magnesiun chloride (0.190 g, 2.0 mmol) and stirred for 1 h. The appropriate carboxylic acid chloride (2.4 mmol) was then added dropwise to the mixture after which it was stirred for 6 h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl to the mixture, which was then extracted with diethyl ether. The extract was dried ($MgSO_4$) and concentrated and the residual oil was purified by silica gel column chromatography using ethyl acetate as eluent.

Diethyl 2-phenyl-2-oxoethylphosphonate 3a. Bp 153–156 °C/0.2 mmHg (lit.,[2c] 145 °C/0.02 mmHg); ν_{max}/cm^{-1} 2980, 1675 (C=O), 1260 (P=O), 1060, 1025 (P–O) and 970; δ_H($CDCl_3$, 200 MHz) 1.28 (t, 6 H, *J* 7.0), 3.65 (d, 2 H, *J* 22.7), 4.07–4.22 (dq, 4 H), 7.44–7.65 (m, 3 H) and 7.99–8.04 (m, 2 H); δ_C($CDCl_3$, 50.3 MHz) 16.21 (d, *J* 6.05), 38.51 (d, *J* 129.1), 62.63 (d, *J* 6.38), 128.58, 129.03, 133.61, 136.60 and 191.93 (d, *J* 5.52); *m/z* 256 (M^+, 0.7%), 151 (5.4) and 105 (100) (Found: M^+, 256.0868. $C_{12}H_{17}O_4P$ requires M^+, 256.0864).

Diethyl 2-(*p*-tolyl)-2-oxoethylphosphonate 3b. Bp 158–161 °C/0.2 mmHg (lit.,[2e] 149–153 °C/0.7 mmHg); ν_{max}/cm^{-1} 2930, 1670 (C=O), 1260 (P=O), 1029 and 970; δ_H($CDCl_3$, 200 MHz) 1.28 (t, 6 H, *J* 7.1), 2.42 (s, 3 H), 3.61 (d, 2 H, *J* 22.7), 4.06–4.21 (m, 4 H), 7.24–7.30 (m, 2 H) and 7.80–7.94 (m, 2 H); δ_C($CDCl_3$, 50 MHz) 16.38, 21.86, 38.62 (d, *J* 129.0), 62.73 and 129.41; *m/z* 270 (M^+, 2.1%) and 119 (100) (Found: M^+, 270.1033. $C_{13}H_{19}O_4P$ requires M^+, 270.1021).

Diethyl 2-(*p*-chlorophenyl)-2-oxoethylphosphonate 3c. Bp 165–169 °C/0.1 mmHg (lit.,[2c] 160 °C/0.2 mmHg); ν_{max}/cm^{-1} 2990, 1675 (C=O), 1255 (P=O), 1129 and 970; δ_H($CDCl_3$, 200 MHz) 1.29 (t, 6 H, *J* 6.0), 3.61 (d, 2 H, *J* 22.8), 4.06–4.22 (m, 4 H), 7.40–7.48 (m, 2 H) and 7.90–7.99 (m, 2 H); δ_C($CDCl_3$, 50 MHz) 16.30 (d, *J* 5.75), 38.71 (d, *J* 128.6), 62.80 (d, *J* 6.15), 128.98, 130.58 and 190.73; *m/z* 292 (M + 2, 1.2%), 290 (M^+, 0.7), 180 (7.1), 154 (19.5) and 139 (100) (Found: M + 2, 292.0437. $C_{12}H_{16}O_4ClP$ requires *M* + 2, 192.0445).

Diethyl 2-(*m*-bromophenyl)-2-oxoethylphosphonate 3d. Bp 169–171 °C/0.1 mmHg; ν_{max}/cm^{-1} 2990, 1679 (C=O), 1255 (P=O), 1025 and 970; δ_H($CDCl_3$, 200 MHz) 1.30 (t, 6 H, *J* 7.0), 3.65 (d, 2 H, *J* 22.8), 4.01–4.26 (m, 4 H) and 7.30–8.18 (m, 4 H); δ_C($CDCl_3$, 50 MHz) 16.00 (d, *J* 6.15), 38.37 (d, *J* 128.9), 62.63 (d, *J* 6.35), 127.47, 130.00, 131.72, 136.22 and 190.38 (d, *J* 6.55); *m/z* 336 (M + 2, 1.5), 334 (M^+, 1.6%), 224 (6.5) and 183 (100).

Diethyl 2-(*p*-methoxyphenyl)-2-oxoethylphosphonate 3e. Bp 158–161 °C/0.5 mmHg (lit.,[2e] 152–155 °C/0.7 mmHg); ν_{max}/cm^{-1} 2920, 1670 (C=O), 1265 (P=O), 1020 and 975; δ_H($CDCl_3$, 200 MHz) 1.29 (t, 6 H, *J* 7.1), 3.59 (d, 2 H, *J* 22.7), 4.06–4.23 (m, 4 H), 6.91–6.98 (m, 2 H) and 7.97–8.04 (m, 2 H); δ_C($CDCl_3$, 50 MHz) 16.16, 38.05 (d, *J* 128.9), 55.36, 62.43 (d, *J* 6.1), 113.58, 129.38, 131.34, 131.86, 163.81 and 190.12 (d, *J* 6.41); *m/z* 286 (M^+, 2.5%) and 135 (100).

Diethyl 2-(pentafluorophenyl)-2-oxoethylphosphonate 3f. Bp 149–152 °C/0.5 mmHg ν_{max}/cm^{-1} 2995, 2930, 1750 (C=O), 1648, 1495, 1321 (P=O), 1035 and 990; δ_H($CDCl_3$, 200 MHz) 1.30 (t, 6 H, *J* 7.1), 3.60 (d, 2 H, *J* 22.4) and 4.00–4.30 (m, 4 H); δ_C($CDCl_3$, 50 MHz) 16.13 (d, *J* 6.15), 44.49 (d, *J* 127.0), 62.98 (d, *J* 5.20), 135.1, 140.08, 140.51, 142.02, 145.81, 147.08 and 185.21; *m/z* 346 (M^+, 7.7%), 291 (17.5), 270 (24.7), 210 (20.2), 195 (100), 188 (33.7), 168 (48.2), 149 (41.4) and 123 (63.6).

Diethyl (4-phenyl-2-oxobut-3-enyl)phosphonate 3g. Bp 176–180 °C/0.1 mmHg (lit.,[4f] 190–195 °C/1 mmHg); ν_{max}/cm^{-1} 3005, 2990, 1650 (C=O), 1255 (P=O) and 970; δ_H($CDCl_3$, 200 MHz) 1.34 (t, 6 H, *J* 7.1), 3.33 (d, 2 H, *J* 22.7), 4.09–4.25 (m, 4 H), 6.90 (d, 1 H, *J* 16.1) and 7.30–7.70 (m, 6 H); δ_C($CDCl_3$, 50 MHz) 16.27, 41.08 (d, *J* 127.1), 62.57, 125.74, 128.59, 128.98, 130.88 and 144.75.

Diethyl 2-oxobutylphosphonate 3h. Bp 91–95 °C/0.2 mmHg (lit.,[4e] 90–93 °C/0.5 mmHg); ν_{max}/cm^{-1} 2990, 1710 (C=O), 1255 (P=O), 1036 and 970; δ_H($CDCl_3$, 200 MHz) 1.07 (t, 3 H, *J* 7.23), 1.34 (t, 6 H, *J* 7.0), 2.65 (q, 2 H, *J* 7.3), 3.08 (d, 2 H, *J* 22.8) and 4.07–4.23 (m, 4 H); δ_C($CDCl_3$, 50 MHz) 7.54, 16.27, 37.35, 42.12 (d, 126.7) and 62.50; *m/z* 208 (M^+, 10.3%), 180 (11.5), 179 (100) and 151 (52.5) (Found: M^+, 208.0855. $C_{12}H_{17}O_4P$ requires M^+, 208.0864).

Diethyl 2-oxoheptylphosphonate 3i. Bp 106–109 °C/0.2 mmHg (lit.,[4f] 105–109 °C/0.5 mmHg); ν_{max}/cm^{-1} 2990, 1710 (C=O), 1254 (P=O), 1035 and 970; δ_H($CDCl_3$, 200 MHz) 4.08–4.19 (dq, 4 H), 3.09 (d, 2 H, *J* 22.8), 2.63 (t, 2 H, *J* 7.2), 1.62–1.23 (m, 12 H) and 0.89 (t, 3 H, *J* 6.5); δ_C($CDCl_3$, 50 MHz) 202.16 (d, *J* 5.8), 62.51, 43.98, 42.24 (d, *J* 122.1), 31.05, 23.04, 22.33, 16.28 and 13.80; *m/z* 250 (M^+, 1.4%), 221, 179 (100) and 151 (Found: M^+, 250.1341. $C_{11}H_{23}O_4P$ requires M^+, 250.1334).

Diethyl 2-cyclohexyl-2-oxoethylphosphonate 3j. Bp 89–101 °C/0.2 mmHg (lit.,[4f] 132–135 °C/2 mmHg) ν_{max}/cm^{-1} 2990, 1715 (C=O), 1255 (P=O), 1030 and 970; δ_H($CDCl_3$, 200 MHz) 4.04–4.27 (dq, 4 H), 3.12 (d, 2 H, *J* 22.4), 2.52–2.70 (m, 1 H) and 1.60–1.98 (m, 8 H); δ_C($CDCl_3$, 50 MHz) 205.07 (d, *J* 5.8), 62.29, 51.19, 40.05 (d, *J* 128.1), 28.01, 25.54 and 16.14; *m/z* 262 (M^+, 0.5), 179 and 151.

Diethyl 3-acetoxy-2-oxoheptylphosphonate 3k. Bp 95–97 °C/0.2 mmHg; ν_{max}/cm^{-1} 2990, 1720 (C=O), 1250 (P=O), 1025 and 970; δ_H($CDCl_3$, 200 MHz) 5.16 (q, 1 H, *J* 7.1), 4.00–4.23 (m, 4 H), 3.14 (dq, 2 H, *J* 14.2, 27.4), 2.08 (s, 3 H), 1.37 (d, 3 H, *J* 6.8) and 1.15–1.31 (m, 6 H); δ_C($CDCl_3$, 50 MHz) 199.38 (d, *J* 6.15), 75.05, 62.63, 38.12 (d, *J* 130.1), 20.57, 16.19 and 16.07; *m/z* 267 (M^+ + 1), 266, 238, 194, 179, 153, 152, 137, 125 and 109 (Found: M^+ + 1, 267.0991. $C_{10}H_{19}O_6P$ requires M^+ + 1, 267.0998).

Diethyl 3-bromo-3-methyl-2-oxobutylphosphonate 3l. Bp 78–80 °C/0.2 mmHg; ν_{max}/cm^{-1} 2990, 1710 (C=O), 1255 (P=O), 1035 and 970; δ_H($CDCl_3$, 200 MHz) 4.12–4.30 (m, 4 H), 3.65 (d, 2 H, *J* 20.4), 1.87 (d, 6 H, *J* 11.0) and 1.12–1.45 (m, 6 H); δ_C($CDCl_3$, 50 MHz) 174.88, 63.03, 35.43 (d, *J* 136.9), 30.72, 29.65 and 16.31; *m/z* 302 (M^+ + 2, 1.1%), 300 (M^+, 1.0), 221 and 179.

Diethyl (2-ethoxycarbonyl)-2-oxoethylphosphonate 3m. Bp 91–93 °C/0.1 mmHg; δ_H($CDCl_3$, 200 MHz) 4.05–4.54 (m, 4 H), 2.97 (d, 2 H, *J* 21.7) and 1.20–1.45 (m, 9 H); δ_C($CDCl_3$, 50 MHz) 165.65 (d, *J* 6.0), 62.59, 61.39, 34.23 (d, *J* 133.5), 16.21

and 13.93; *m/z* 252 (M^+, 1.6%), 203 and 151 (Found: M^+, 252.0768. $C_9H_{17}O_6P$ requires M^+, 252.0763).

Large-scale preparation of diethyl 2-phenyl-2-oxoethylphosphonate 3a: typical procedure

To stirred solution of diethylphosphonoacetic acid (9.81 g, 0.05 mol) and triethylamine (27.9 cm^3, 0.2 mol) in toluene (100 cm^3) was added dropwise trimethylsilyl chloride (9.5 cm^3, 0.075 mol) at 0 °C. After being stirred for 1 h at room temperature the reaction mixture was treated with magnesium chloride (4.76 g, 0.05 mol) and stirred for 1 h. Benzoyl chloride (8.43 g, 0.06 mol) was then added dropwise to the mixture after which it was stirred for 12 h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl to the mixture after which it was extracted with diethyl ether (3 × 100 cm^3). The extract was dried ($MgSO_4$) and evaporated, and the residual oil was distilled to give title compound **3a** (11.78 g, 92%), bp 153–156 °C/0.2 mmHg (lit.,[2c] 145 °C/0.02 mmHg).

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