Abstract: An efficient synthesis of 2’- and 3’-substituted diethyl 1-methylthio-2-oxo-2-phenylethylphosphonates 3a–k from 2’- and 3’-substituted benzyl chlorides 2a–k using diethyl methylthio-1-lithiomethylphosphonate is described.

Key words: diethyl 1-methylthio-2-oxo-2-phenylethylphosphonates, diethyl methylthiomethylphosphonate, Michaelis–Arbuzov reaction, acylation reaction

β-Ketophosphonates are valuable intermediates in organic synthesis. The preparation of α,β-unsaturated carbonyl compounds by the Horner–Wadsworth–Emmons reaction has been the main application of the phosphonates, which are also used as ligands in the synthesis of complexes. One of the methods commonly used for the preparation of phosphonates is the Michaelis–Arbuzov reaction. The Michaelis–Arbuzov reaction of trialkyl phosphites and α-halogenoketones leads to β-ketophosphonates, but this method is restricted to highly reactive α-halogenoketones, taking into account competition with the Perkow reaction which gives enol phosphates. Many other synthetic approaches for preparing β-ketophosphonates, although successful, are limited by the availability of starting materials. Other methods include Claisen condensation between α-lithiokylphosphonates and esters, acylation of 1-(trimethylsilyl)vinyl phosphonates, hydrolysis of vinylogous phosphoramides, acylation of α-cuprophosphonates, enantioselective synthesis of γ-hydroxy-β-ketophosphonates via allenic intermediates, Pd(0)-catalysed rearrangement of the 2,3-epoxyalkyl phosphonates, reaction of phosphate with epoxysulfones, oxidation of β-hydroxyalkyl phosphonates, and reaction of silyl enol ethers with phosphate using a hypervalent iodine compound. Recently, β-ketophosphonates have also been obtained by: a) acylation of in situ generated trimethylsilyl diethylphosphonoacetate using MgCl₂/Et₃N, b) acylation of triethyl phosphonoacetate and diethyl phosphonoacetic acid via the Mg(OEt)₂ or MgCl₂/Et₃N system, and c) reaction of α-haloenophosphonates with esters in the presence of a soluble Co(0) complex or magnesium.

As described above, several methods for the synthesis of β-ketophosphonates have been reported, however, few studies aimed at the preparation of α-hetero-substituted β-ketophosphonates are known. This is due to the experimental limitations of the existing methods or the availability of starting reagents. In an elaborate approach, Coutrot explored the reaction of 1-substituted (Me, Ph, SPh, Cl) diethyl 2-chloro-2-oxoethylphosphonate with organometallic reagents (Grignard or organocuprates reagents), in order to obtain the corresponding 2-oxoalkephosphonates. However, the drawback of this method is the preparation of the starting reagents, which involves some steps.

The present paper reports a simple method for the synthesis of 2’- and 3’-substituted diethyl 1-methylthio-2-oxo-2-phenylethylphosphonates 3a–k. As shown in Scheme 1, diethyl methylthiomethylphosphonate (1) reacts with 1 equivalent of butyllithium. To the thus obtained carbocation, a solution of 1 equivalent of LDA in THF was added, followed by benzyl chloride 2a–k at −78 °C in THF, to give the corresponding phosphonates 3a–k in moderate yields. The results are shown in Table 1.

Preparation of 2-oxoalkylphosphonates via the carbanion route is a process of limited scope. The low yields often achieved in the initial phosphorylation step are certainly due to regeneration of the starting phosphate through
acid-base equilibrium. This drawback can be overcome by proper choice of the metalating agent. The use of butyllithium and LDA (1:1 equiv) and 1 equivalent of diethyl methylthiomethylphosphonate (1) makes the procedure efficient, due to the conversion of 3 into the corresponding lithium enolate and shifting the equilibrium towards the reaction product, leading to the preparation of a wide range of 2′- and 3′-substituted diethyl 1-methylthio-2-oxo-2-phenylethylphosphonates 3a–k free of by products.

Several other attempts to obtain phosphonates 3 failed or gave only modest results, e.g. the sulfonylation reaction of the β-ketophosphonates gave only 20–30% yields of phosphonates 3.

In conclusion, the present procedure is a new and practical method for the synthesis of 2′- and 3′-substituted diethyl 1-methylthio-2-oxo-2-phenylethylphosphonates 3a–k. The compounds 3 are promising synthons in the Horner–Wadsworth–Emmons reaction for the preparation of α,β-unsaturated ketones, which can be used in Michael additions and Diels–Alder reactions.

NMR spectra were recorded on a Varian Inova 1 spectrometer operating at 300 MHz for proton, and 75.4 MHz for carbon. 1H and 13C chemical shifts (δ) are reported in ppm relative to TMS as internal standard. Coupling constants (J) are given in Hz. IR spectra were measured on a Michelson-Bomen FTIR instrument. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN-standard analyser. Low-resolution mass spectra were recorded on a Shimadzu QP5050A GC-MS spectrometer (DB5 column, EI). Column chromatography was performed on Merck silica gel 60 (230–400 mesh). Diethyl methylthiomethylphosphonate (1) and substituted benzoyl chlorides 2 were prepared according to the procedures described in literature.

All reactions were conducted with magnetic stirring in oven-dried glassware under dry N2. Solvents were purified and dried according to standard procedures. Other reagents were commercially available.

### Phosphonates 3a–k; General Procedure

BuLi (19.3 mL of 1.5 M solution in hexane, 29 mmol) was added to THF (20 mL) and cooled to –78 °C. A solution of diethyl methylthiomethylphosphonate (1; 5.55 g, 28 mmol) in THF (10 mL) was then slowly added at this temperature via a syringe. After 30 min, a solution of LDA [previously prepared from BuLi (18.6 mL of 1.5 M in hexane, 28 mmol), i-Pr2NH (4.2 mL, 30 mmol) and THF (20 mL) at –78 °C] was transferred via a cannula into the first solution. To the resulting pale-yellow mixture a solution of substituted benzoyl chloride 2a–k (30 mmol) in THF (10 mL) was added at –78 °C. This solution was allowed to reach r.t. Stirring was continued for 1 h, then cooled at 0 °C and the reaction product was quenched with aq 1 M HCl (60 mL) and extracted with CH2Cl2 (3 × 50 mL). The combined CH2Cl2 solution was washed with aq 1 M NaOH to extract the sodium enolate of 3a–k from the starting material (3 × 15 mL). The combined alkaline solution was additionally washed with CH2Cl2 (45 mL) to obtain the free 3a–k and finally extracted with CH2Cl2 (3 × 50 mL). The combined CH2Cl2 solution was washed with H2O (15 mL) and dried (MgSO4). Filtration and evaporation yielded the crude compounds 3a–k. The compounds 3f and 3h were purified by recrystallisation (hexane–Et2O). In the other cases, the crude oil was purified by flash chromatography on silica gel with hexane–aceton gradient as eluent.

### Diethyl 2-(2-Methoxyphenyl)-1-(methylthio)-2-oxoethylphosphonate (3a)

Yield: 67%; colorless oil.

1H NMR (CDCl3/TMS): δ = 7.76 (dd, 1 H, JHH = 4.9 Hz, JHP = 0.9 Hz, JHH = 7.5 Hz), 7.50 (ddd, 1 H, JHH = 7.5 Hz, JHP = 8.5 Hz, HH = 5.00 (dt, 1 H, JHH = 0.9 Hz, JHH = 8.5 Hz), 6.97 (dd, 1 H, JHH = 0.9 Hz, JHH = 8.5 Hz), 5.00 (d, 1 H, JHP = 18.0 Hz), 4.14–4.34 (m, 4 H), 3.93 (s, 3 H), 2.24 (d, 3 H, JHP = 0.9 Hz), 1.33 (dt, 3 H, JCP = 6.6 Hz, JHH = 7.2 Hz), 1.31 (dt, 3 H, JCP = 0.6 Hz, JHH = 7.2 Hz), 1.23 (dt, 3 H, JCP = 0.6 Hz, JHH = 6.6 Hz).

13C NMR (CDCl3/TMS): δ = 192.4, 157.9, 134.1, 131.4, 121.6, 126.2 (d, JCP = 6.4 Hz), 120.8, 111.4, 63.2 (d, JCP = 0.6 Hz), 62.8 (d, JCP = 6.6 Hz), 55.6, 49.0 (d, JCP = 142.7 Hz), 162.2 (d, JCP = 5.4 Hz), 14.4 (d, JCP = 2.0 Hz).


### Diethyl 2-(2-Methylphenyl)-1-(methylthio)-2-oxoethylphosphonate (3b)

Yield: 58%; colorless oil.

1H NMR (CDCl3/TMS): δ = 7.50 (dd, 1 H, JHH = 4.9 Hz, JHP = 0.9 Hz, JHH = 7.2 Hz), 7.30 (ddd, 1 H, JHH = 7.5 Hz, JHP = 8.5 Hz, HH = 5.00 (dt, 1 H, JHH = 0.9 Hz, JHH = 8.5 Hz), 6.97 (dd, 1 H, JHH = 0.9 Hz, JHH = 8.5 Hz), 5.00 (d, 1 H, JHP = 18.0 Hz), 4.14–4.34 (m, 4 H), 3.93 (s, 3 H), 2.24 (d, 3 H, JHP = 0.9 Hz), 1.33 (dt, 3 H, JCP = 6.6 Hz, JHH = 7.2 Hz), 1.31 (dt, 3 H, JCP = 0.6 Hz, JHH = 7.2 Hz), 1.23 (dt, 3 H, JCP = 0.6 Hz, JHH = 6.6 Hz).

13C NMR (CDCl3/TMS): δ = 192.4, 157.9, 134.1, 131.4, 121.6, 126.2 (d, JCP = 6.4 Hz), 120.8, 111.4, 63.2 (d, JCP = 0.6 Hz), 62.8 (d, JCP = 6.6 Hz), 55.6, 49.0 (d, JCP = 142.7 Hz), 162.2 (d, JCP = 5.4 Hz), 14.4 (d, JCP = 2.0 Hz).


### Table 1: Synthesis of Phosphonates 3a–k

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
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<tr>
<td>3a</td>
<td>2′-MeO</td>
<td>67</td>
</tr>
<tr>
<td>3b</td>
<td>2′-Me</td>
<td>58</td>
</tr>
<tr>
<td>3c</td>
<td>2′-F</td>
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<tr>
<td>3d</td>
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<tr>
<td>3e</td>
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<td>3′-MeO</td>
<td>70</td>
</tr>
<tr>
<td>3g</td>
<td>3′-Me</td>
<td>55</td>
</tr>
<tr>
<td>3h</td>
<td>3′-F</td>
<td>74</td>
</tr>
<tr>
<td>3i</td>
<td>3′-Cl</td>
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</tr>
<tr>
<td>3k</td>
<td>3′-NO2</td>
<td>60</td>
</tr>
</tbody>
</table>

*The yield of the isolated product is based on diethyl methylthiomethylphosphonate (1).
Diethyl 2-(5-Fluorophenyl)-1-(methylthio)-2-oxyethylphosphonate (3e)

Yield: 67%; yellowish oily.

IR (film): 3064 (w), 2985 (m), 2925 (m), 1665 (vs), 1594 (vs), 1244 (vs), 1052 (vs) cm⁻¹.

¹H NMR (CDCl₃/TMS): δ = 7.59 (dt, 1 H, JHH = 6.9 Hz), 6.35 (d, JCF = 6.9 Hz), 6.33 (d, JCF = 6.6 Hz), 49.3 (d, JCP = 8.1 Hz, JHH = 147.6 Hz), 16.3 (d, JCF = 5.8 Hz), 16.2 (d, JCP = 6.1 Hz), 14.6 (d, JCP = 1.9 Hz).

MS (EI): m/z (%) = 320 (10), 274 (18), 166 (40), 123 (100).


Diethyl 2-(2-Chlorophenyl)-1-(methylthio)-2-oxyethylphosphonate (3d)

Yield: 67%; yellowish oily.

IR (film): 3064 (w), 2985 (m), 2925 (m), 1665 (vs), 1594 (vs), 1244 (vs), 1052 (vs) cm⁻¹.

¹H NMR (CDCl₃/TMS): δ = 7.59 (dt, 1 H, JHH = 6.9 Hz), 6.35 (d, JCF = 6.9 Hz), 6.33 (d, JCF = 6.6 Hz), 49.3 (d, JCP = 8.1 Hz, JHH = 147.6 Hz), 16.3 (d, JCF = 5.8 Hz), 16.2 (d, JCP = 6.1 Hz), 14.6 (d, JCP = 1.9 Hz).

MS (EI): m/z (%) = 320 (10), 274 (18), 166 (40), 123 (100).


Diethyl 2-(2-Bromophenyl)-1-(methylthio)-2-oxyethylphosphonate (3e)

Yield: 68%; colorless oil.

IR (film): 3060 (w), 2985 (m), 2924 (m), 1697 (m), 1605 (vs), 1572 (vs), 1309 (vs), 1255 (s), 1024 (vs) cm⁻¹.

¹H NMR (CDCl₃/TMS): δ = 7.81 (m, 1 H), 7.79 (m, 1 H), 7.40 (m, 1 H), 7.36 (m, 1 H), 4.53 (d, 1 H, JHH = 18.0 Hz), 4.15–4.35 (m, 4 H, JHH = 6.6 Hz), 2.42 (s, 3 H), 2.27 (d, 3 H, JHH = 0.9 Hz), 1.32 (dt, 6 H, JHH = 0.9 Hz, JHF = 6.9 Hz).

C NMR (CDCl₃/TMS): δ = 191.6, 138.5, 135.4 (d, JCP = 5.7 Hz), 134.4, 129.3, 128.5, 126.1, 63.6 (d, JCP = 6.8 Hz), 63.4 (d, JCP = 6.6 Hz), 45.3 (d, JCP = 147.4 Hz), 21.3, 16.4 (d, JCP = 6.0 Hz), 14.9 (d, JCP = 2.3 Hz).

MS (EI): m/z (%) = 316 (6), 270 (10), 162 (8), 119 (100), 91 (26), 65 (11).

Diethyl 2-(3-Fluorophenyl)-(1-methylthio)-2-oxoethylphosphonate (3b)
Yield: 74%; yellow solid; mp 63 °C.
IR (KBr): 3087 (w), 2984 (m), 2927 (m), 1655 (vs), 1584s, 1440 (s), 1291 (vs), 1248 (vs), 1061 (vs), 1021 (vs) cm⁻¹.

^1^H NMR (CDCl₃/TMS): δ = 7.81 (ddd, 1 H, ^J^HH = 0.9 Hz, ^J^HP = 1.5 Hz, ^J^HF = 7.9 Hz), 7.70 (ddd, 1 H, ^J^HH = 1.5 Hz, ^J^HP = 2.4 Hz, ^J^HF = 9.4 Hz), 7.46 (dt, 1 H, ^J^HP = 5.5 Hz, ^J^HF = 9.4 Hz), 7.30 (ddt, 1 H, ^J^HH = 0.9 Hz, ^J^HP = 2.4 Hz, ^J^HF = 7.9 Hz), 4.45 (d, 1 H, ^J^HF = 18.3 Hz), 4.15-4.36 (m, 4 H), 2.27 (d, 1 H, ^J^HF = 0.9 Hz), 1.33 (dt, 3 H, ^J^HP = 0.6 Hz, ^J^HH = 7.2 Hz), 1.32 (dt, 3 H, ^J^HF = 0.6 Hz, ^J^HH = 7.2 Hz).

^1^C NMR (CDCl₃/TMS): δ = 180.3 (d, ^J^CP = 5.5 Hz), 184.8 (d, ^J^CP = 5.5 Hz), 137.4 (d, ^J^CP = 5.8 Hz), 130.3 (d, ^J^CP = 7.7 Hz), 124.7 (d, ^J^CP = 2.9 Hz), 120.7 (d, ^J^CP = 22.1 Hz), 115.7 (d, ^J^CP = 23.0 Hz), 63.8 (d, ^J^CP = 6.7 Hz), 63.6 (d, ^J^CP = 6.7 Hz), 45.8 (d, ^J^CP = 147.1 Hz), 16.4 (d, ^J^CP = 4.8 Hz), 15.0 (d, ^J^CP = 2.9 Hz).

MS (EI): m/z (%) = 230 (7), 274 (19), 166 (17), 123 (100), 95 (27).

Diethyl 2-(3-Chlorophenyl)-(1-methylthio)-2-oxoethylphosphonate (3i)
Yield: 60%; light-orange oil.
IR (film): 3066 (w), 2984 (m), 2928 (m), 1679 (s), 1572 (m), 1286 (s), 1252 (vs), 1055 (vs), 1025 (vs) cm⁻¹.

^1^H NMR (CDCl₃/TMS): δ = 7.99 (t, 1 H, ^J^HH = 1.8 Hz), 7.90 (ddd, 1 H, ^J^HH = 1.2 Hz, ^J^HP = 1.8 Hz, ^J^HF = 7.8 Hz), 7.57 (ddd, 1 H, ^J^HH = 1.2 Hz, 1.2 Hz, 1.2 Hz, 1.2 Hz, ^J^HF = 7.8 Hz), 7.43 (t, 1 H, ^J^HF = 7.8 Hz), 4.46 (d, 1 H, ^J^HF = 18.3 Hz), 4.17–4.34 (m, 4 H), 2.27 (d, 3 H, ^J^HF = 0.9 Hz), 1.33 (dt, 3 H, ^J^HF = 0.6 Hz, ^J^HH = 7.2 Hz), 1.32 (dt, 3 H, ^J^HF = 0.6 Hz, ^J^HH = 7.2 Hz).

^1^C NMR (CDCl₃/TMS): δ = 190.1, 136.8 (d, ^J^CP = 5.5 Hz), 134.9, 133.5, 129.9, 128.9, 126.9, 63.7 (d, ^J^CP = 6.9 Hz), 63.5 (d, ^J^CP = 6.6 Hz), 45.7 (d, ^J^CP = 147.4 Hz), 16.3 (d, ^J^CP = 6.1 Hz), 14.9 (d, ^J^CP = 2.3 Hz).

MS (EI): m/z (%) = 338 (3), 336 (7), 290 (17), 182 (20), 180 (10), 141 (38), 139 (100), 111 (23).

Diethyl 2-(3-Bromophenyl)-(1-methylthio)-2-oxoethylphosphonate (3j)
Yield: 62%; light-yellow oil.
IR (film): 3064 (w), 2981 (m), 2926 (m), 1681 (s), 1566 (m), 1285 (s), 1252 (vs), 1054 (vs), 1025 (vs) cm⁻¹.

^1^H NMR (CDCl₃/TMS): δ = 8.14 (t, 1 H, ^J^HH = 1.8 Hz), 7.95 (ddd, 1 H, ^J^HH = 0.9 Hz, ^J^HP = 1.8 Hz, ^J^HF = 7.8 Hz), 7.72 (ddd, 1 H, ^J^HH = 0.9 Hz, ^J^HP = 1.8 Hz, ^J^HF = 7.8 Hz), 7.36 (t, 1 H, ^J^HF = 7.8 Hz), 4.44 (d, 1 H, ^J^HF = 18.6 Hz), 4.17–4.33 (m, 4 H), 2.27 (d, 3 H, ^J^HF = 0.9 Hz), 1.33 (dt, 3 H, ^J^HF = 0.6 Hz, ^J^HH = 6.9 Hz), 1.32 (dt, 3 H, ^J^HF = 0.6 Hz, ^J^HH = 7.2 Hz).

^1^C NMR (CDCl₃/TMS): δ = 190.0, 137.0 (d, ^J^CP = 5.5 Hz), 136.4, 131.8, 130.1, 127.4, 122.8, 63.7 (d, ^J^CP = 7.2 Hz), 63.5 (d, ^J^CP = 6.9 Hz), 45.6 (d, ^J^CP = 147.1 Hz), 16.3 (d, ^J^CP = 5.7 Hz), 14.9 (d, ^J^CP = 2.2 Hz).

MS (EI): m/z (%) = 382 (8), 380 (8), 336 (17), 334 (18), 226 (28), 185 (90), 183 (100), 157 (20), 155 (20), 76 (17), 61 (20).
Anal. Caled for C₁₃H₁₁BrO₄PS: 381.32; C, 40.96; H, 4.76. Found: C, 40.80; H, 4.91.

Diethyl 1-(Methylthio)-2-(3-nitrophenyl)-2-oxoethylphosphonates (3k)
Yield: 60%; orange oil.
IR (film): 3089 (w), 2986 (m), 2929 (m), 1686 (s), 1615 (m), 1534 (vs), 1352 (vs), 1289 (m), 1253 (s), 1217 (s), 1053 (vs), 1025 (vs) cm⁻¹.

^1^H NMR (CDCl₃/TMS): δ = 8.87 (t, 1 H, ^J^HH = 1.8 Hz), 8.45 (ddd, 1 H, ^J^HH = 1.2 Hz, ^J^HP = 2.1 Hz, ^J^HF = 8.1 Hz), 8.39 (ddd, 1 H, ^J^HH = 1.2 Hz, ^J^HP = 1.8 Hz, ^J^HF = 8.1 Hz), 7.70 (t, 1 H, ^J^HF = 8.1 Hz), 4.48 (d, 1 H, ^J^HF = 19.2 Hz), 4.16–4.38 (m, 4 H), 2.28 (d, 3 H, ^J^HF = 0.9 Hz), 1.33 (t, 3 H, ^J^HF = 6.9 Hz), 1.32 (dt, 3 H, ^J^HF = 6.9 Hz, ^J^HH = 7.2 Hz).
(21) These reactions are in progress in our laboratory.