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### Microwave-Enhanced Synthesis of Phosphonoacetamides

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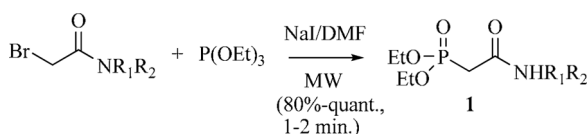
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## MICROWAVE-ENHANCED SYNTHESIS OF PHOSPHONOACETAMIDES

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### GRAPHICAL ABSTRACT



**Abstract** An efficient microwave protocol is described for the Michaelis–Arbuzov synthesis of secondary and tertiary N-aryl (and alkyl) (diethylphosphono)acetamides **1**, by reaction of chloro- and bromoacetamides with triethyl phosphite in the presence of catalytic amounts of sodium iodide. Remarkable acceleration of the reaction (minutes vs. several hours) over conventional heating was achieved, together with improved product yields and purity, when bromoacetamides were employed as the substrates. Chloroacetamides were comparatively less reactive, leading to satisfactory yields only when a high excess of the reagent was employed.

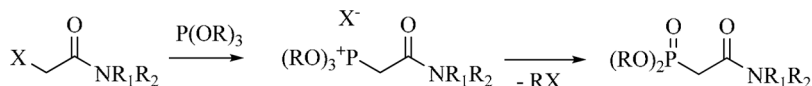
**Keywords** Michaelis–Arbuzov reaction; microwaves; phosphonoacetamides; phosphorus compounds; sodium iodide

## INTRODUCTION

Phosphonoacetamides are interesting because of their capability to complex different metals. They have found application in the diagnosis and treatment of several diseases,<sup>[1]</sup> as extracting agents for alkaline, alkaline earth, and transition metals,<sup>[2]</sup> and as reaction catalysts.<sup>[3]</sup> Some selectively substituted phosphonoacetamides behave as potent inhibitors of carbamylphosphatase, an enzyme involved in pyrimidine biosynthesis.<sup>[4]</sup> Such compounds show strong antiproliferative and anti-tumor activities.<sup>[5]</sup> In organic synthesis, phosphonoacetamides represent the starting materials of choice for the preparation of  $\alpha,\beta$ -unsaturated amides, which are versatile synthons.<sup>[6]</sup> In the course of our research on the LiOH-promoted Horner–Wadsworth–Emmons reaction,<sup>[7]</sup> we recently needed to prepare a series of secondary and tertiary phosphonoacetamides. The preparation of phosphonoacetamides is

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Scheme 1.

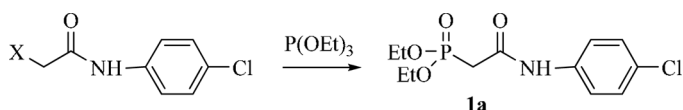
generally carried out by nucleophilic displacement of chlorine in chloroacetamides either by the Michaelis–Arbuzov reaction<sup>[8]</sup> (thermal path) or by the Michaelis–Becker reaction<sup>[9]</sup> (anionic path). *N*-Alkyl phosphonoacetamides can also be synthesized by aminolysis of phosphonate esters<sup>[10]</sup> or phosphonoacetic acid.<sup>[11]</sup> Two alternative methodologies have also been reported, namely reaction between an  $\alpha$ -phosphonyl carbanion and an isocyanate or a carbamate and condensation of an amide enolate with diethylchlorophosphate.<sup>[12]</sup> However, both methods are actually restricted to the synthesis of  $\alpha$ -substituted phosphonoacetamides. The Michaelis–Arbuzov reaction,<sup>[13]</sup> which is one of the most versatile pathways for the formation of carbon–phosphorus bonds,<sup>[14]</sup> is the most generally employed strategy. Two disadvantages of this method are that it generally requires an excess of the reagent<sup>[15]</sup> and prolonged reaction times (from several hours to days).<sup>[16,17]</sup> This may result in partial or total decomposition of sensitive substrates.

Reactions performed under microwave irradiation in general proceed faster, more cleanly, and with better yields than those performed under conventional heating.<sup>[18]</sup> It is widely accepted that reactions involving ionic intermediates are accelerated by microwaves.<sup>[18,19]</sup> The mechanism advanced for the Arbuzov reaction<sup>[20]</sup> (Scheme 1) involves the formation of a phosphonium salt followed by nucleophilic displacement and should therefore be improved by microwaves.

Microwave optimization is of special practical interest for reactions involving prolonged heating at high temperatures. Kiddle et al. reported the microwave-assisted synthesis of phosphonium salts and phosphonates in pressure tubes.<sup>[16,21]</sup> The possibility of employing a microwave oven adapted for reflux heating<sup>[22]</sup> allows the reactions to be conducted at controlled (reflux) temperature under atmospheric pressure, preventing the risk of explosions associated with the use of closed vessels.<sup>[23]</sup> Such characteristics, together with the previously mentioned drawbacks of the conventional Michaelis–Arbuzov method and the lack of an expeditious procedure for the synthesis of *N*-arylphosphonoacetamides, prompted us to explore the use of microwave irradiation to enhance the Michaelis–Arbuzov reaction. We also investigated the use of sodium and potassium iodides to enhance product yields.

## RESULTS AND DISCUSSION

We examined first the reaction between equimolar amounts of *N*-(4-chlorophenyl)chloroacetamide and triethyl phosphite. The results obtained under different reaction conditions are summarized in Table 1. Under conventional heating, the reaction (neat) was completed in 10 h, with 59% yield. Under microwave irradiation at maximum power (700 W), the reaction was remarkably accelerated, while the product yield was not improved. The possibility of conducting the reaction in solvent-free conditions on a solid support (Alumina) was also tested (entry 3) but

**Table 1.** Optimization of the reaction conditions

Entry	X	Molar ratio Substr.:P(OEt) <sub>3</sub>	Reaction time (min)	Solvent	Catalyst	Power (Watt)	Yield (%) <sup>a</sup>
1 <sup>b</sup>	Cl	1:1	600	–	–	–	59
2	Cl	1:1	1.5	–	–	700	60
3 <sup>c</sup>	Cl	1:1	20	–	–	350	traces
4	Cl	1:1	15	THF	–	700	traces
5	Cl	1:1	15	Acetonitrile	–	700	traces
6	Cl	1:1	15	DME	–	700	traces
7	Cl	1:1	1.75	DMF	–	700	62
8	Cl	1:1	1.75	DMF	KI	700	64
9	Cl	1:1	1.75	DMF	NaI	700	68
10	Cl	1:2	1.75	DMF	NaI	700	72
11	Cl	1:4	1.75	DMF	NaI	700	92
12 <sup>b</sup>	Br	1:1	600	–	–	–	68
13	Br	1:1	2	–	–	350	70
14	Br	1:1	5	THF	NaI	210	46
15	Br	1:1	10	Acetonitrile	NaI	210–350	45
16	Br	1:1	5	DME	NaI	210–350	55
17	Br	1:1	2	DMF	NaI	210	91
18	Br	1:1.5	1.7	DMF	NaI	210	98
19	Br	1:1.5	1	DMF	NaI	350	97
20 <sup>d</sup>	Br	1:1.5	9	DMF	NaI	210	97
21	Br	1:1	2	DMF	–	210	73
22	Br	1:1.5	2	DMF	–	210	75
23	Cl	1:4	1.75	DMF	–	700	66

<sup>a</sup>Yields correspond to pure compound **1a**.

<sup>b</sup>Conventional heating at 110 °C.

<sup>c</sup>Reactants were supported on neutral Alumina.

<sup>d</sup>5 mmoles of the substrate and 7.5 mmoles of the reagent were employed.

proved to be ineffective. The reaction was then examined employing different solvents (Table 1, entries 4–7). Among them, dimethylformamide was the most efficient, probably because of its higher dielectric constant and boiling point. In tetrahydrofuran (THF), acetonitrile, and dimethoxyethane, very low conversion to the desired product was observed. In previous work, we demonstrated that potassium and sodium iodides significantly improve the yields of nucleophilic substitutions,<sup>[24]</sup> probably because of in situ generation of a more reactive iodoalkyl compound. To test this hypothesis, we next explored potassium and sodium iodides as catalysts. A slight improvement in the reaction yield was observed in both cases (entries 8 and 9), and the sodium salt was more efficient. Finally, the use of a large excess of the reagent was necessary to achieve a good yield of the product (entry 11).

Bearing in mind the relative reactivity of organic halides, which follows the sequence RI > RBr > RCl,<sup>[25]</sup> we next turned to the corresponding bromoacetamide

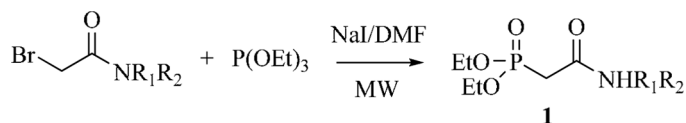
as the substrate (Table 1). As expected, much lower irradiation powers afforded comparatively better yields in all the examined conditions (entries 12–17). Complete conversion of the substrate was achieved with 50% molar excess of the reagent (entry 18). Remarkably, the reaction outcome was similar with irradiation powers from 210 to 350 W (entries 18 and 19) and also when a fivefold amount of the reagents was employed (entry 20).

To clarify the role of NaI in the outcome of the reactions, we performed some additional control experiments. In the absence of NaI, only partial conversion to the desired product was observed for both the bromo and chloroacetamides, even in the presence of an excess of the reagent (entries 21–23). This confirms the purported catalytic role of NaI.

Employing the optimized reaction conditions, we synthesized a series of *N*-aryl(diethylphosphono)acetamides **1b–g** with good yields in very short reaction times (Table 2, entries 1–6). *N*-Alkyl derivatives **1h–k** (Table 2) were also obtained with satisfactory yields (entries 7–10).

To further explore the scope of the method, we examined next the synthesis of *N*-aryl (and alkyl) tertiary phosphonoacetamides. *N,N*-Disubstituted bromoacetamides were comparatively less reactive and required a slightly higher irradiation power to achieve complete conversion. Yields for compounds **1l–o**,<sup>[26]</sup> **1p**,<sup>[26,27]</sup> and **1q**<sup>[27]</sup> were satisfactory and in all cases better than those reported in the literature synthesized with conventional heating.

Table 2. Microwave-enhanced synthesis of phosphonoacetamides **1**



Entry	Cpd. <b>1</b>	R <sub>1</sub>	R <sub>2</sub>	Reaction time (min)	Power (Watt)	Yield (%) <sup>a</sup>
1	b	C <sub>6</sub> H <sub>5</sub>	H	2	210	90
2	c	4-BrC <sub>6</sub> H <sub>4</sub>	H	1.5	210	93
3	d	4-FC <sub>6</sub> H <sub>4</sub>	H	1	210	94
4	e	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	1	210	94
5	f	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	H	1.5	210	Quant.
6	g	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	2	210	84
7	h	CH(CH <sub>3</sub> )C <sub>6</sub> H <sub>5</sub>	H	1.5	210	88
8	i	(CH <sub>2</sub> ) <sub>2</sub> [3,4-(OCH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ]	H	2	210	84
9	j	<i>ter</i> -C <sub>4</sub> H <sub>9</sub>	H	2	210	81
10	k <sup>b</sup>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	2	210	87
11	l	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	1.5	280	98
12	m	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	1.5	280	84
13	n	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	<i>iso</i> -C <sub>3</sub> H <sub>7</sub>	1.5	280	80
14	o	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	1.5	280	86
15	p	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	1.5	280	91
16	q	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	2	280	98

<sup>a</sup>Yields correspond to pure compounds.

<sup>b</sup>DME was employed as the solvent.

## CONCLUSIONS

In conclusion, we developed an efficient microwave-based protocol for the Michaelis–Arbuzov synthesis of phosphonoacetamides **1** by reaction of the corresponding bromoacetamides and triethyl phosphite in the presence of catalytic amounts of NaI. The method is safe and general, leading to good yields of secondary and tertiary *N*-alkyl or aryl derivatives. Its main advantages are the remarkably short reaction times and the improvement in product yields. No collateral products arising either from rearrangement of the products or decomposition of the reagent<sup>[14]</sup> were observed.

## EXPERIMENTAL

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker MSL 300-MHz spectrometer. Deuteriochloroform was used as the solvent, and the standard concentrations of the samples were 10 and 30 mg/mL for <sup>1</sup>H and <sup>13</sup>C spectra, respectively. Chemical shifts are reported in ppm ( $\delta$ ) relative to tetramethylsilane (TMS) as an internal standard. Splitting multiplicities are reported as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), multiplet (m), and broad signal, exchangeable (bs ex). Elemental analyses were performed in an Exeter CE 440 (CHNS) elemental analyzer.

### General Procedure for Preparation of Diethylphosphonoacetamides **1a–k** and **1q**

Sodium iodide (0.1 mmol) was added to a solution of the corresponding bromoacetamide (1 mmol) and triethylphosphite (1.5 mmol) in dry dimethylformamide (2 mL). The reaction mixture was intermittently irradiated<sup>[28]</sup> in a domestic microwave oven (Sanyo EM-D2013) adapted with a reflux condenser. After completion of the reaction was disclosed by thin-layer chromatography (TLC), the mixture was diluted with ethyl acetate (50 mL), treated with active charcoal, filtered, and extracted with water (3  $\times$  5 mL). The organic phase was dried over sodium sulfate, filtered, and evaporated in vacuo. The crude products were purified by flash chromatography employing chloroform–ethyl acetate mixtures.

### Physical Data and Spectral Characterization of New Compounds

***N*-(4-Chlorophenyl)diethylphosphonoacetamide (1a).** This compound had mp 80–81 °C (from ethyl acetate). <sup>1</sup>H NMR  $\delta$  9.17 (bs ex, 1H, NH), 7.44 (dd,  $J$  = 8.8 and 3.6 Hz, 2H, aromatics), 7.20 (dd,  $J$  = 8.8 and 3.6 Hz, 2H, aromatics), 4.08–4.23 (m, 4H, OCH<sub>2</sub>), 3.02 (d,  $J$  = 20.5 Hz, 2H, CH<sub>2</sub>P), 1.36 (t,  $J$  = 7.1 Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  162.32 (d,  $J$  = 4.5 Hz), 136.65, 128.51, 128.25, 120.42, 62.88 (d,  $J$  = 6.8 Hz), 36.10 (d,  $J$  = 131.1 Hz), 16.11 (d,  $J$  = 5.6 Hz). Anal. calcd. for C<sub>12</sub>H<sub>17</sub>ClNO<sub>4</sub>P: C, 47.15; H, 5.61; N, 4.58. Found: C, 47.05; H, 5.63; N, 4.57.

***N*-(Phenyl)diethylphosphonoacetamide (1b).** This compound was obtained as an oil. <sup>1</sup>H NMR  $\delta$  8.98 (bs ex, 1H, NH), 7.51 (dd,  $J$  = 8.7 and 1.1 Hz, 2H, aromatics), 7.23–7.30 (m, 2H, aromatics), 7.04–7.09 (m, 1H, aromatics),

4.13–4.23 (m, 4H, OCH<sub>2</sub>), 3.03 (d,  $J=20.8$  Hz, 2H, CH<sub>2</sub>P), 1.35 (dt,  $J=7.2$  and 0.5 Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  162.47 (d,  $J=5.6$  Hz), 137.85, 128.36, 123.80, 119.55, 62.68 (d,  $J=5.6$  Hz), 35.92 (d,  $J=131.12$  Hz), 15.97 (d,  $J=5.6$  Hz). Anal. calcd. for C<sub>12</sub>H<sub>18</sub>NO<sub>4</sub>P: C, 53.14; H, 6.69; N, 5.16. Found: C, 52.92; H, 6.71; N, 5.15.

***N*-(4-Bromophenyl)diethylphosphonoacetamide (1c).** This compound was obtained as an oil. <sup>1</sup>H NMR  $\delta$  9.21 (bs ex, 1H, NH), 7.39 (d,  $J=8.2$  Hz, 2H, aromatics), 7.08 (d,  $J=8.2$  Hz, 2H, aromatics), 4.08–4.22 (m, 4H, OCH<sub>2</sub>), 3.01 (d,  $J=20.8$  Hz, 2H, CH<sub>2</sub>P), 1.34 (t,  $J=7.1$  Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  162.41 (d,  $J=4.5$  Hz), 137.18, 131.29, 120.88, 116.33, 62.96 (d,  $J=5.6$  Hz), 36.18 (d,  $J=130.0$  Hz), 16.18 (d,  $J=5.6$  Hz). Anal. calcd. for C<sub>12</sub>H<sub>17</sub>BrNO<sub>4</sub>P: C, 41.16; H, 4.89; N, 4.00. Found: C, 41.24; H, 4.93; N, 3.97.

***N*-(4-Fluorophenyl)diethylphosphonoacetamide (1d).** This compound was obtained as an oil. <sup>1</sup>H NMR  $\delta$  9.21 (bs ex, 1H, NH), 7.53–7.58 (m, 2H, aromatics), 7.03 (dt,  $J=8.7$  and 1.0 Hz, 2H, aromatics), 4.22–4.30 (m, 4H, OCH<sub>2</sub>), 3.12 (dd,  $J=22.2$  and 1.1 Hz, 2H, CH<sub>2</sub>P), 1.44 (dt,  $J=7.0$  and 0.8 Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  162.27 (d,  $J=5.6$  Hz), 158.95 (d,  $J=243.0$  Hz), 134.12 (d,  $J=2.3$  Hz), 121.15 (d,  $J=7.9$  Hz), 114.98 (d,  $J=2.3$  Hz), 62.90 (d,  $J=5.6$  Hz), 36.03 (d,  $J=130.0$  Hz), 16.12 (d,  $J=6.8$  Hz). Anal. calcd. for C<sub>12</sub>H<sub>17</sub>FNO<sub>4</sub>P: C, 49.83; H, 5.92; N, 4.84. Found: C, 49.65; H, 5.94; N, 4.84.

***N*-(4-Methylphenyl)diethylphosphonoacetamide (1e).** This compound was obtained as an oil. <sup>1</sup>H NMR  $\delta$  8.87 (bs ex, 1H, NH), 7.48 (d,  $J=8.7$  Hz, 2H, aromatics), 7.28 (d,  $J=8.7$  Hz, 2H, aromatics), 4.12–4.21 (m, 4H, OCH<sub>2</sub>), 2.99 (d,  $J=20.5$  Hz, 2H, CH<sub>2</sub>P), 1.59 (s, 3H, ArCH<sub>3</sub>), 1.34 (t,  $J=7.0$  Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  162.33 (d,  $J=5.6$  Hz), 133.51, 129.07, 119.77, 62.91 (d,  $J=6.8$  Hz), 36.10 (d,  $J=131.1$  Hz), 20.67, 16.18 (d,  $J=6.8$  Hz). Anal. calcd. for C<sub>13</sub>H<sub>20</sub>NO<sub>4</sub>P: C, 54.73; H, 7.07; N, 4.91. Found: C, 54.56; H, 7.10; N, 4.90.

***N*-(4-Nitrophenyl)diethylphosphonoacetamide (1f).** This compound had mp 130–131 °C (from ethyl acetate–methanol). <sup>1</sup>H NMR  $\delta$  9.85 (bs ex, 1H, NH), 8.06 (dd,  $J=7.0$  and 2.0 Hz, 2H, aromatics), 7.64 (dd,  $J=7.0$  and 2.0 Hz, 2H, aromatics), 4.17–4.26 (m, 4H, OCH<sub>2</sub>), 3.11 (d,  $J=21.3$  Hz, 2H, CH<sub>2</sub>P), 1.39 (t,  $J=7.0$  Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  163.08 (d,  $J=4.5$  Hz), 144.07, 142.58, 124.15, 118.46, 63.16 (d,  $J=6.8$  Hz), 36.29 (d,  $J=130.0$  Hz), 16.07 (d,  $J=6.8$  Hz). Anal. calcd. for C<sub>12</sub>H<sub>17</sub>N<sub>2</sub>O<sub>6</sub>P: C, 45.58; H, 5.42; N, 8.86. Found: C, 45.50; H, 5.45; N, 8.83.

***N*-(2-Methylphenyl)diethylphosphonoacetamide (1g).** This compound was obtained as an oil. <sup>1</sup>H NMR  $\delta$  8.68 (bs ex, 1H, NH), 7.85 (d,  $J=8.2$  Hz, 1H, aromatics), 7.12–7.22 (m, 2H, aromatics), 7.04–7.09 (m, 1H, aromatics), 4.13–4.23 (m, 4H, OCH<sub>2</sub>), 3.04 (d,  $J=20.5$  Hz, 2H, CH<sub>2</sub>P), 2.31 (s, 3H, ArCH<sub>3</sub>), 1.35 (t,  $J=7.0$  Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  162.24 (d,  $J=3.4$  Hz), 135.55, 130.36, 129.52, 126.38, 125.18, 122.92, 62.86 (d,  $J=6.8$  Hz), 35.61 (d,  $J=130.0$  Hz), 17.69, 16.18 (d,  $J=6.8$  Hz). Anal. calcd. for C<sub>13</sub>H<sub>20</sub>NO<sub>4</sub>P: C, 54.73; H, 7.07; N, 4.91. Found: C, 54.66; H, 7.10; N, 4.92.

**(±)-*N*-(1-Phenylethyl)diethylphosphonoacetamide (1h).** This compound was obtained as an oil. <sup>1</sup>H NMR  $\delta$  7.25–7.32 (m, 5H, aromatics), 7.12 (bs ex, 1H, NH), 5.09 (t,  $J=7.0$  Hz, 1H, CH), 4.10–4.15 (m, 2H, OCH<sub>2</sub>), 3.98–4.06 (m, 2H,

OCH<sub>2</sub>), 2.84 (dd,  $J = 20.7$  and  $6.2$  Hz, 1H, CHP), 3.83 (dd,  $J = 20.7$  and  $12.7$  Hz, 1H, CHP), 1.47 (d,  $J = 7.0$  Hz, 3H, CH<sub>3</sub>CH), 1.32 (t,  $J = 7.0$  Hz, 3H, CH<sub>3</sub>), 1.22 (t,  $J = 7.0$  Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  163.02 (d,  $J = 4.5$  Hz), 143.12, 128.36, 127.02, 125.98, 62.06 (d,  $J = 6.8$  Hz), 49.11, 34.95 (d,  $J = 131.1$  Hz), 21.87, 16.07 (d,  $J = 6.8$  Hz). Anal. calcd. for C<sub>14</sub>H<sub>22</sub>NO<sub>4</sub>P: C, 56.18; H, 7.41; N, 4.68. Found: C, 56.09; H, 7.44; N, 4.65.

***N*-2-[(3,4-Dimethoxyphenyl)ethyl]diethylphosphonoacetamide (1i).** This compound was obtained as an oil. <sup>1</sup>H NMR  $\delta$  6.73–6.81 (m, 4H, aromatics and NH), 4.03–4.12 (m, 4H, OCH<sub>2</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 3.84 (s, 3H, OCH<sub>3</sub>), 3.48–3.53 (m, 2H, NCH<sub>2</sub>), 2.63–2.83 (m, 4H, ArCH<sub>2</sub> and CH<sub>2</sub>P), 1.06 (t,  $J = 7.1$  Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  163.63 (d,  $J = 3.4$  Hz), 148.23, 146.88, 130.87, 119.95, 111.36, 110.67, 61.91 (d,  $J = 5.6$  Hz), 59.54, 55.09, 40.65, 34.32 (d,  $J = 132.2$  Hz), 34.38, 15.57 (d,  $J = 6.7$  Hz). Anal. calcd. for C<sub>16</sub>H<sub>26</sub>NO<sub>6</sub>P: C, 53.48; H, 7.29; N, 3.90. Found: C, 53.38; H, 7.32; N, 3.89.

***N*-tert-Butyl diethylphosphonoacetamide (1j).** This compound was obtained as an oil. <sup>1</sup>H NMR  $\delta$  6.54 (bs ex, 1H, NH), 4.08–4.15 (m, 4H, OCH<sub>2</sub>), 2.76 (d,  $J = 20.5$  Hz, 2H, CH<sub>2</sub>P), 1.34 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 1.33 (t,  $J = 7.0$  Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  163.64 (d,  $J = 3.7$  Hz), 63.04 (d,  $J = 5.4$  Hz), 42.7548, 35.81 (d,  $J = 130.0$  Hz), 28.29, 16.01 (d,  $J = 6.3$  Hz). Anal. calcd. for C<sub>10</sub>H<sub>22</sub>NO<sub>4</sub>P: C, 47.80; H, 8.83; N, 5.57. Found: C, 47.76; H, 8.87; N, 5.55.

***N*-Benzyl diethylphosphonoacetamide (1k).** This compound was obtained as an oil. <sup>1</sup>H NMR  $\delta$  7.25–7.34 (m, 5H, aromatics), 7.09 (bs ex, 1H, NH), 4.46 (d,  $J = 5.9$  Hz, 2H, ArCH<sub>2</sub>), 4.05–4.15 (m, 4H, OCH<sub>2</sub>), 2.88 (d,  $J = 20.5$  Hz, 2H, CH<sub>2</sub>P), 1.31 (dd,  $J = 7.1$  and  $0.6$  Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  163.90 (d,  $J = 3.6$  Hz), 137.88, 128.26, 127.35, 127.04, 62.45 (d,  $J = 6.3$  Hz), 43.39, 34.82 (d,  $J = 131.7$  Hz), 15.98 (d,  $J = 6.4$  Hz). Anal. calcd. for C<sub>13</sub>H<sub>20</sub>NO<sub>4</sub>P: C, 54.73; H, 7.07; N, 4.91. Found: C, 54.70; H, 7.08; N, 4.88.

***N,N*-Diphenyl diethylphosphonoacetamide (1q).** This compound had mp 58–60 °C (from ethyl acetate). <sup>1</sup>H NMR  $\delta$  7.28–7.40 (m, 10H, aromatics), 4.11–4.19 (m, 4H, OCH<sub>2</sub>), 3.02 (dd,  $J = 21.7$  and  $1.4$  Hz, 2H, CH<sub>2</sub>P), 1.29–1.34 (m, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  165.18, 142.76, 142.31, 129.84, 128.96, 128.66, 128.13, 126.51, 62.05 (d,  $J = 5.6$  Hz), 34.28 (d,  $J = 136.8$  Hz), 16.31 (d,  $J = 6.8$  Hz). Anal. calcd. for C<sub>18</sub>H<sub>22</sub>NO<sub>4</sub>P: C, 62.24; H, 6.38; N, 4.03. Found: C, 61.97; H, 6.39; N, 4.01.

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