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PAPER

Efficient and 'green' microwave-assisted synthesis of haloalkylphosphonates *via* the Michaelis–Arbuzov reaction†

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This paper deals with a novel, efficient and environmentally friendly synthesis of dialkyl haloalkylphosphonates *via* a microwave-assisted Michaelis–Arbuzov reaction. The approach is solventless, requires only one equivalent of each of the starting compounds, and provides high yields of pure products from which the impurities are easy to remove. The process has been optimised for batch and flow reactors and is especially profitable for the production of key intermediates in synthesis of Ethephon or acyclic nucleoside phosphonates such as adefovir, tenofovir, and cidofovir.

Introduction

Phosphonates represent a class of stable organophosphorus compounds containing a single carbon-phosphorus (C–P) bond, which makes them resistant to chemical and enzymatic hydrolysis, thermal decomposition,[1] and photolysis.[2] A phosphonate motif is present in biomolecules which can act as inhibitors of certain biosynthetic pathways and can be degraded only by some prokaryotic microorganisms.[3] The high chemical stability of phosphonates, together with their resistance to biodegradation, makes this class of compounds of particular interest for the drug design. This approach is particularly attractive considering that phosphonic acids derivatives can be conveniently synthesised by the Michaelis–Arbuzov (M–A) reaction, discovered at the end of the 19th century.[4]

Synthetic phosphonates are now widely used as herbicides,[5] stimulants of the latex production of *Hevea brasiliensis*,[5b] pesticides,[6] detergents,[7] chelating agents for di- and trivalent metals ions,[8] agents that inhibit crystal growth and scale formation,[9] reagents for Wittig–Horner reactions,[10] hybrid organic-inorganic supports and catalysts,[11] antiviral agents,[12] agents with antitumor activity[13] or as chemical weapons of mass destruction (the V-series of nerve agents).[14] The latest achievements in the structure-based design of phosphonate inhibitors have been summarised and reviewed.[15]

One of the most important compounds of this class is 2-chloroethylphosphonic acid (Ethephon), the most widely used plant growth regulator.[16,17] Ethephon was first synthesised in 1946,[18] and its enormous commercial importance is demonstrated by the fact that 290 tons of Ethephon were used in 2005 in California alone.[19]

Ethephon is usually prepared by an acid hydrolysis of *bis*(2-chloroethyl) 2-chloroethylphosphonate[20] prepared by an isomerisation of *tris*(2-chloroethyl) phosphite *via* the M–A reaction.[21] It has been demonstrated that the isomerisation produces low yields (~55%) and the subsequent hydrolysis does not go to completion,[22] yielding Ethephon contaminated with 2-chloroethyl 2-chloroethylphosphonate.[22] In an attempt to replace *bis*(2-chloroethyl) 2-chloroethylphosphonate, diisopropyl 2-chloroethylphosphonate was prepared from triisopropyl phosphite and 1,2-dichloroethane by the M–A procedure.[22,23] However, the observed yield was only 54%. The reaction was slightly improved by the use of 1-bromo-2-chloroethane,[22,23] but this reaction is not ideal for the commercial application since the yield of the M–A reaction varies with the bromochloroalkane used.[24]

Dialkyl tosyloxymethylphosphonate is a cornerstone in the chemistry of methylphosphonates.[12b] Its analogue, dialkyl iodomethylphosphonate, is not used so often since its preparation is more problematic compared to the tosyl congener.[25] It was prepared in 47% yield by the classical M–A reaction of triisopropyl phosphite with methylene diiodide,[25] however our numerous attempts to reproduce this experiment afforded much lower yields (3–17%).

In the last decade, several attempts to accelerate the M–A reaction by microwave irradiation were published, mostly using monoiodo- or monobromoalkyl derivatives as starting material.[26] To the best of our knowledge, there have been no examples of analogous reactions starting with dichloro- or diiodoalkanes. Only one paper deals with the application of microwaves to the M–A reaction of dibromoalkyl derivatives

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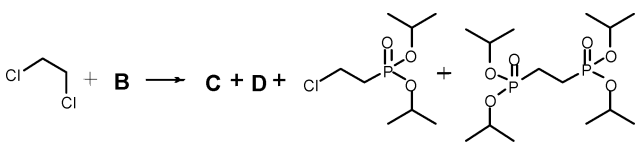
Table 1 The optimisation of the reaction of 1,2-dichloroethane (**A**) with triisopropyl phosphite (**B**)

				Composition of the reaction mixture GC-MS (%)					
Entry	Time (min)	Temp. (°C)	Ratio A : B	**B**	**C**	**D**	**1**	**E**	Comments[a]
1	20	130	4 : 1	98.7	0.0	1.3	0.0	0.0	*a*
2	20	150	4 : 1	98.6	0.0	1.4	0.0	0.0	*a*
3	20	130	4 : 1	96.0	0.0	4.0	0.0	0.0	*a,b*
4	20	150	4 : 1	98.2	0.0	1.8	0.0	0.0	*a,b*
5	20	180	4 : 1	93.0	0.0	3.1	3.9	0.0	*a*
6	20	200	4 : 1	85.2	0.0	3.5	11.4	0.0	*a*
7	20	180	4 : 1	97.3	0.0	2.7	0.0	0.0	*a,b*
8	20	200	4 : 1	95.5	0.0	4.5	0.0	0.0	*a,b*
9	80	210	4 : 1	8.6	15.5	28.7	46.7	0.5	*a*
10	80	200	4 : 1	15.5	10.1	20.4	54.0	0.0	*a*
11	80	180	4 : 1	78.1	0.0	21.9	0.0	0.0	*a,b*
12	80	200	4 : 1	81.2	0.0	18.8	0.0	0.0	*a,b*
13	80	200	4 : 1	0.0	13.4	3.2	83.4	0.0	*c*
14	80	200	4 : 1	0.0	13.9	5.0	81.1	0.0	*d*
15	80	190	4 : 1	19.5	5.3	1.3	73.9	0.0	*c*
16	80	190	4 : 1	0.0	12.0	3.3	84.8	0.0	*e*
17	80	190	4 : 1	98.9	0.0	1.1	0.0	0.0	*c,f*
18	160	180	4 : 1	44.2	1.9	1.4	52.6	0.0	*c*
19	160	190	4 : 1	0.0	10.3	2.2	87.5	0.0	*c*
20	160	190	10 : 1	0.0	8.5	2.3	89.2	0.0	*c*
21	160	190	4 : 1	87.9	0.0	3.3	8.8	0.0	*c,g*
22	160	190	4 : 1	85.3	0.3	3.5	10.9	0.0	*c,h*
23	160	190	4 : 1	0.0	73.9	23.7	2.4	0.0	*c,i*
24	160	190	4 : 1	82.9	0.6	3.7	12.8	0.0	*c,j*
25	160	190	4 : 1	15.3	13.0	5.9	65.8	0.0	*c,k*
26	160	190	4 : 1	0.0	22.0	8.6	69.5	0.0	*c,l*
27	160	190	3 : 1	1.4	11.2	10.8	76.1	0.5	*a*
28	160	190	2 : 1	0.1	13.5	12.8	72.3	1.3	*a*
29	160	190	1 : 1	4.4	15.8	14.3	63.1	2.4	*a*
30	190	190	1.2 : 1	0.0	15.7	2.9	79.1	2.3	*c*

For the general conditions, see the ESI† (the optimisation of the reaction of 1,2-dichloroethane with triisopropyl phosphite).[a] Comments: *a* (under air), *b* (+20 eq. of toluene), *c* (5× argon-purged – see the experimental part), *d* (5× argon-purged, then opened for air and then closed), *e* (Entry 15 after the reaction was opened for air and then closed and treated for another 80 min.), *f* (+1 eq. of toluene), *g* (+10 eq. of xylene), *h* (+10 eq. of THF), *i* (+10 eq. of pyridine), *j* (+10 eq. of diglyme), *k* (+10 eq. of CH_3CN), *l* (+10 eq. of DMF). For an explanation of **B**, **C**, **D**, **1** and **F**, see Scheme 1.

under reflux,[27] and obviously, such reaction conditions cannot be used generally.

We have developed a universal approach for the preparation of various haloalkylphosphonates. To avoid the problem of volatility of dichloroalkanes used in the M–A reaction, a closed-vessel mode was the logical option for such a procedure. The general problems with the reactivity of the reagents and by-product formation were effectively solved by means of accurate temperature control.



Scheme 1 The synthesis of diisopropyl 2-chloroethylphosphonate (**1**) by the reaction of 1,2-dichloroethane (**A**) with triisopropyl phosphite (**B**), where diisopropyl phosphonate (**C**), triisopropyl phosphate (**D**) and tetraisopropyl ethane-1,2-diyldiphosphonate (**E**) are formed as by-products.

Results and discussion

1. The reaction of 1,2-dichloroethane with triisopropyl phosphite

At first, the reaction of 1,2-dichloroethane with triisopropyl phosphite leading to an Ethephon intermediate **1** (Scheme 1), was chosen as a test case. The overall optimisation of this reaction is shown in Table 1. First of all, we have focused on the effect of the reaction temperature (ReT) at constant reaction time (20 min, entries 1, 2, 5 and 6).

No product was detected in the reactions carried out at 130 °C and 150 °C (entries 1 and 2). Some product was formed during reactions at 180 °C (3.9% of **1**, entry 5) and 200 °C (11.4% of **1**, 200 °C, entry 6). We have found that the increase of both reaction time (80 min) and reaction temperature leads to a higher consumption of the starting material **B** (at 200 °C 15.5% of **B** is remaining, entry 10 and at 210 °C 9.1% of **B** is remaining, entry 9), but simultaneously, the product formation decreased (54.0% of **1**, entry 10 and only 46.7% of **1**, entry 9). In addition, formation of by-products was observed and especially the elimination reaction (by-product **C**) is accelerated by higher temperatures. The elimination was not observed at 180 °C. It should be noted that compound **C** can be formed by a hydrolysis of starting compound **B** if the reagents are not completely dry. The oxidation reaction (by-product **D**) is also accelerated by higher temperatures (entries 9 and 10), but it can be easily suppressed by removal of oxygen from the reaction

mixture (only 3.2% of **D**, entry 13, as compared to 20.4% of **D**, entry 10). Even a short contact of the well argon-purged reaction mixture with air leads to the increase of **D** formation (only 3.2% of **D**, entry 13, as compared to 5.0% of **D**, entry 14).

To suppress elimination, the reaction temperature was decreased. Then however, the reaction requires a longer reaction time (19.5% of **B** is remaining, 190 °C, 80 min, entry 15). When the experiment (entry 15) was treated for another 80 min, total conversion was observed (entry 16). The amount of the by-products was significantly reduced and the yield of product increased when the experiment was run for 160 min (87.5% of **1**, 190 °C, entry 19, as compared to 83.4% of **1**, 200 °C, entry 13). Further reaction temperature decrease resulted in an extremely slow reaction (44.2% of **B** is remaining, 180 °C, 160 min, entry 18). Thus, all subsequent experiments were conducted at 190 °C.

Subsequently, the effect of the **A** : **B** ratio on the reaction yield was scrutinised. An increase of the **A** : **B** ratio leads to only slightly higher yields (89.2%, **A** : **B** = 10 : 1, entry 20 and 87.5%, **A** : **B** = 4 : 1, entry 19). Interestingly, lowering the **A** : **B** ratio also leads to only slightly lower yields as well (76.1% of **1**, **A** : **B** = 3 : 1, entry 27; 72.3% of **1**, **A** : **B** = 2 : 1, entry 28 and 63.1% of **1**, **A** : **B** = 1 : 1, entry 29). The reaction yield was further improved by purging the reaction mixture with dry inert gas (**A** : **B** ratio 1.2 : 1, entry 30, 79.1% of **1**; the slight excess (1.2 equiv.) of volatile **A** is used to compensate its loss during argon-purging).

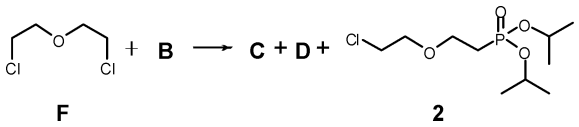
Finally, the solvent effect was studied. The M–A reaction is usually performed without a solvent or the corresponding dihaloalkane can serve as a solvent. However, for some special applications (solid starting material, scale-up) the use of solvent could be beneficial.

The presence of toluene showed the total suppression of the MW-assisted M–A reaction (0% of **1**, entries 7, 8, 11 and 12). The negative effect of toluene is so strong that even 1 equiv. of toluene fully suppresses the reaction (73.9% of **1**, entry 15, compared to 0% of **1**, entry 17). A number of other solvents were scrutinised to study their effect on the reaction progress (xylene, entry 21; THF, entry 22; pyridine, entry 23; diglyme, entry 24; CH_3CN, entry 25; DMF, entry 26). The MW-assisted M–A reaction works well in either CH_3CN (65.8% of **1**, entry 25) or DMF (69.5% of **1**, entry 26). The reaction is faster in DMF but less of by-products **C** and **D** are formed in CH_3CN. Thus, CH_3CN was selected as the solvent for the further scale-up of the M–A reactions using a continuous MW-reactor. Entries 19 and 30 were repeated on a preparative scale and diisopropyl 2-chloroethylphosphonate (**1**) was isolated in 83% resp. 74% yield (see ESI†, procedure **1.1** and **1.2**).

2. The reaction of 2,2′-dichlorodiethyl ether with triisopropyl phosphite

The above optimised reaction conditions (*via* entry 30, Table 1) were used to study the reaction of 2,2′-dichlorodiethyl ether with triisopropyl phosphite (Scheme 2). The desired product **2** was obtained in a high preparative yield (81%, see the ESI†, procedure **2.1**).

We have scrutinised the scale-up procedure again (see the ESI†, procedure **2.2**) and it was found that the optimised reaction conditions can be applied generally. The desired product **2** (Scheme 2), was obtained in a slightly lower preparative yield



F 2

Scheme 2 The synthesis of diisopropyl 2-(2-chloroethoxy)ethylphosphonate (**2**) by the reaction of 2,2′-dichlorodiethyl ether (**F**) with triisopropyl phosphite (**B**), where diisopropyl phosphonate (**C**) and triisopropyl phosphate (**D**) are formed as by-products.

(73%) as compared to 81% yield in procedure **2.1**. A higher proportion of the elimination reaction during the scale-up can be explained by the higher actual MW power which is used to reach the same temperature of larger reaction mixture volumes.

Finally, the applicability of the continuous flow MW reactor was studied (Table 2, see the ESI†, procedure **2.3**). The reaction temperature of the experiments was elevated gradually from 120 to 210 °C in 10 °C increments every time after 45 min intervals. A significant acceleration of the product formation starts at 170 °C and the reaction proceeds well at temperatures ≥180 °C. This is in agreement with the results obtained from the discontinuous MW reactor (preparative yield of 70%). The slightly lower ReT (180 °C) in the flow reactor as compared to discontinuous reactor (190 °C) can be explained by the different technique of the ReT measurement (IR sensor in the batch reactor *versus* internal probe in the flow reactor).

3. The reaction of 1,2-dibromoethane with triisopropyl phosphite

Next, the MW-assisted M–A reaction of dibromoalkanes was studied. 1,2-Dibromoethane (**G**) was chosen to compare its reactivity to that of the previously studied 1,2-dichloroethane (**A**). Analogously, the reaction (Scheme 3) was carried out at various temperatures and reaction times (Table 3).

The reaction at lower temperature (130 °C) required longer reaction time and the starting compound **B** was completely consumed after 120 min (entry 4, Table 3). The reaction time is cut to 30 min at 150 °C with only a slightly higher content of by-products **C** and **D** (entry 5, Table 3). Eventually, the reaction is complete after 10 min at 170 °C with almost the same yield as in the previous runs (88.7% from GC-MS, entry 6). The isolated

Table 2 The optimisation of the reaction of 2,2′-dichlorodiethyl ether (**F**) with triisopropyl phosphite (**B**) in a continuous MW reactor

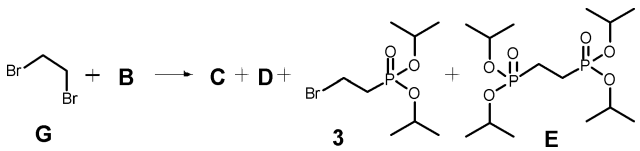
		Composition of the reaction mixture GC-MS (%)			
Sample	Temp. (°C)	**B**	**C**	**D**	**2**
1	120	91.0	3.7	1.5	3.8
2	140	88.0	3.1	1.6	7.3
3	150	83.4	4.5	1.9	10.2
4	160	78.9	5.4	2.4	13.4
5	170	64.6	7.3	2.3	25.8
6	180	38.6	9.2	2.3	50.0
7	190	19.2	11.6	2.6	66.5
8	200	11.2	12.8	2.2	73.9
9	210	0.0	15.5	2.4	82.0

For the general conditions, see the ESI† (procedure **2.3**). **F**:**B** loaded in a 1.2 : 1 ratio. For an explanation of **B**, **C**, **D** and **2**, see Scheme 2.

Table 3 The optimisation of the reaction of 1,2-dibromoethane (**G**) with triisopropyl phosphite (**B**)

			Composition of the reaction mixture GC-MS (%)				
Entry	Temp. (°C)	Time (min)	**B**	**C**	**D**	**3**	**E**
1	130	30	41.5	2.6	2.0	53.4	0.4
2	130	60	9.7	2.1	2.5	83.8	2.0
3	130	90	2.5	2.9	3.3	89.0	2.3
4	130	120	0.0	2.7	3.8	90.5	3.1
5	150	30	0.7	4.0	4.9	87.3	3.0
6	170	10	0.0	4.4	4.4	88.7	2.5

For the general conditions, see the ESI† (procedure **3**). **G**:**B** loaded in a 1.2 : 1 ratio. For an explanation of **B**, **C**, **D**, **3** and **E**, see Scheme 3.

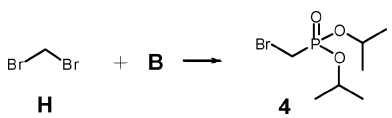


Scheme 3 The synthesis of diisopropyl 2-bromoethylphosphonate (**3**) by the reaction of 1,2-dibromoethane (**G**) with triisopropyl phosphite (**B**), where diisopropyl phosphonate (**C**), triisopropyl phosphate (**D**) and tetraisopropyl ethane-1,2-diyldiphosphonate (**E**) are formed as by-products.

yield of product **3** was high (84%, see the ESI†, procedure **3**) although it was contaminated (<3%) with the corresponding bisphosphonate (**E**).

4. The reaction of dibromomethane with triisopropyl phosphite

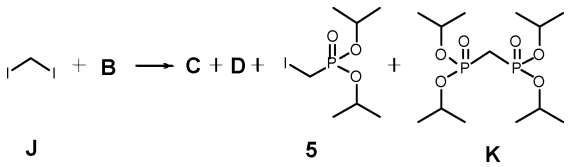
The mixture of dibromomethane (**H**) and triisopropyl phosphite (**B**) was treated at 150 °C for 30 min (Scheme 4), without further optimisation and the desired diisopropyl bromomethylphosphonate (**4**) was isolated in 78% yield (see the ESI†, procedure **4**).



Scheme 4 The synthesis of diisopropyl bromomethylphosphonate (**4**) by the reaction of dibromomethane (**H**) with triisopropyl phosphite (**B**).

5. The reaction of diiodomethane with triisopropyl phosphite

To compare the reactivity of dihalomethanes in the M–A reaction, the reaction of diiodomethane (**J**) with triisopropyl phosphite (**B**) (Scheme 5) was studied and optimised (Table 4, see the ESI†, procedure **5.1**).



Scheme 5 The synthesis of diisopropyl iodomethylphosphonate (**5**) by the reaction of diiodomethane (**J**) with triisopropyl phosphite (**B**), where diisopropyl phosphonate (**C**), triisopropyl phosphate (**D**) and tetraisopropyl ethane-1,2-diyldiphosphonate (**K**) are formed as by-products.

Analogously, the reactions of diiodomethane (**J**) with triisopropyl phosphite (**B**) were carried out at various temperatures (80 °C, 90 °C, 100 °C) and reaction times (Table 4). It was found that the reaction works well at 90 °C (73.5% of **5**, entry 2) and that the formation of the undesired bisphosphonate **K** can be controlled by the maximum power output of the MW reactor. While 5.3% of the by-product **K** was formed at max. power of 300 W (entry 2), only 1.9% of **K** was formed at max. power of 50 W (entry 3).

Fig. 1 demonstrates the thermal shock which leads to the overheating of the reaction mixture during the M–A reaction (30 °C jump, 30 W – model reaction, Scheme 5). The enormous increase in the temperature leads to production of higher amount of the corresponding bisphosphonate **K**, as well as higher amount of the elimination by-product **C**. Moreover, the reaction mixture is not ideally homogenous owing to the high difference in the densities of the starting compounds. It was found that a small amount of the desired product (**5**) added to the reaction mixture helped to homogenise the reaction mixture and the thermal shock was totally suppressed (Fig. 2).

Thus, the addition of **5** leads to the suppression of the by-products' formation (1.9% of **K**, 6.4% of **C**, entry 3 and 0% of **K**, 0.7% of **C**, entry 4; Table 4) and to much higher product formation (79.3% of **5**, entry 3 and 87.4% of **5**, entry 4; Table 4).

Table 4 The optimisation of the reaction of diiodomethane (**J**) with triisopropyl phosphite (**B**)

				Composition of the reaction mixture GC-MS (%)					
Entry	Time (min)	Temp. (°C)	Ratio **J** : **B**	**B**	**C**	**D**	**5**	**K**	Comments[a]
1	15	80	4 : 1	93.8	0.6	1.5	4.1	0.0	*a*
2	120	90	4 : 1	4.9	8.9	7.4	73.5	5.3	*a*
3	120	90	4 : 1	5.7	6.4	6.7	79.3	1.9	*a*,*b*
4	120	90	4 : 1	9.6	0.7	2.3	87.4	0.0	*a*,*b*,*c*
5	150	90	4 : 1	2.3	1.2	4.1	92.4	0.0	*a*,*b*,*c*
6	60	100	4 : 1	0.0	2.2	2.1	95.5	0.2	*a*,*b*,*c*
7	180	90	2 : 1	0.5	1.6	3.2	94.6	0.1	*a*,*b*,*c*
8	180	90	1 : 1	6.7	2.7	3.4	87.1	0.1	*a*,*b*,*c*
9	200	90	1 : 1	0.2	3.1	3.6	92.8	0.3	*a*,*b*,*c*

For the general conditions, see the ESI† (procedure **5.1**). For an explanation of **B**, **C**, **D**, **5** and **K**, see Scheme 5.[a] Comments: *a* (5× argon-purged – see the ESI†), *b* (max. power = 50 W), *c* (+0.03 eq. of **5**).

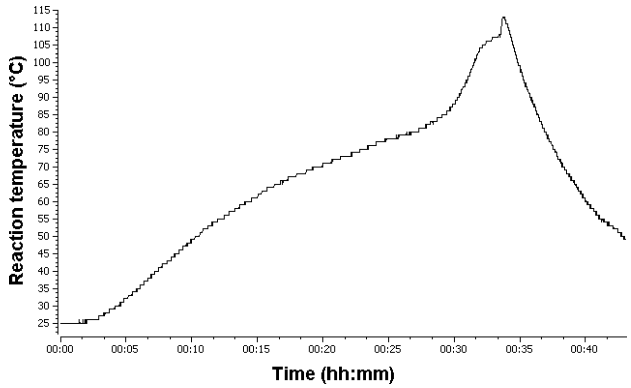


Fig. 1 The reaction temperature of the model reaction – the thermal shock during the formation of (**5**) *via* entry 2, Table 4 with constant power (30 W).

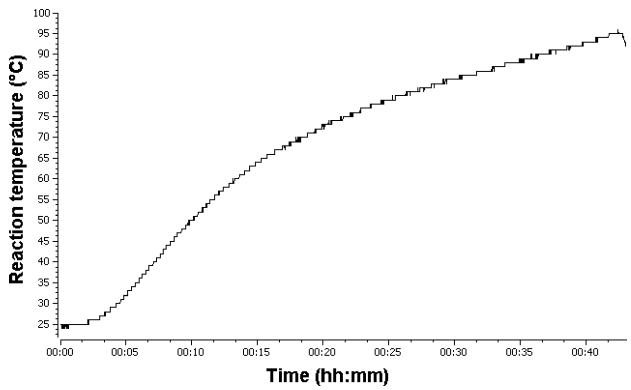


Fig. 2 The reaction temperature of the model reaction – no thermal shock during the formation of (**5**) after the addition of 0.03 eq. of (**5**) into the reaction mixture. Entry 4, Table 4 with constant power (30 W).

The elevation of the reaction temperature (100 °C, Entry 6) reduced the reaction time (60 min) and gave the best yield of product **5** (95.5%), but slightly more bisphosphonate **K** was formed.

In addition, the effect of the **J** : **B** ratio on the yields of the M–A reaction of diiodomethane was studied. It was shown that decreasing the **J** : **B** ratio does not dramatically affect the reaction yield (entries 7, 8 and 9; Table 4) but a longer reaction time is required to reach full conversion in the case of an equimolar ratio of the starting compounds (entry 9). Entry 9 was repeated on the preparative scale and the desired product was obtained in 86% yield (see the ESI†, procedure **5.1**).

Finally, the scale-up procedure of the MW-assisted M–A reaction for potential industrial application was scrutinised and optimised (Table 5, see the ESI†, procedure **5.2**).

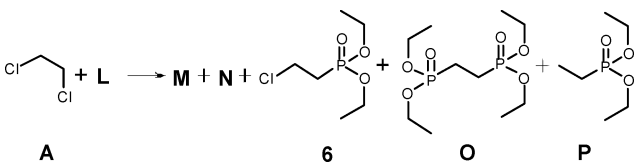
The optimum reaction temperature (120 °C) observed for the scale-up was about 20–30 °C higher than that of the small scales (90–100 °C). The difference can be caused by slightly different temperature reading techniques (see the ESI†). Another increase of the reaction temperature over 120 °C led again to higher by-product formation and thus to a less pure product and lower yield (87.9% of **5**, 120 °C, entry 5, as compared to 84.5% of **5**, 130 °C, Entry 6).

The higher by-product formation observed for scaled-up reactions can be explained by the higher actual MW power which is necessary to reach the same reaction temperature in larger volumes. Therefore, the effect of the maximum power output was also studied in detail. It was found that a decrease of the maximum power output led to a higher yield of the desired product (87.9% of **5**, 100 W, entry 5, as compared to 85.4% of **5**, 200 W, entry 3).

It was also found that addition of a small amount (0.03 eq.) of the desired product into the reaction mixture improves the yield (85.4% of **5**, with addition, entry 3, compared to 70.5% of **5**, without addition, entry 4). The desired product was isolated from entry 5 in a high yield (80%, see the ESI†, procedure **5.2**).

6. The reaction of 1,2-dichloroethane with triethyl phosphite

For comparison, the reaction of 1,2-dichloroethane (**A**) with triethyl phosphite (**L**) was carried out under two different reaction conditions (Scheme 6, Table 6).



Scheme 6 The synthesis of diethyl 2-chloroethylphosphonate (**6**) by the reaction of 1,2-dichloroethane (**A**) with triethyl phosphite (**L**), where diethyl phosphonate (**M**), triethyl phosphate (**N**), tetraethyl ethane-1,2-diyldiphosphonate (**O**) and diethyl ethylphosphonate (**P**) are formed as by-products.

While the reaction was slow at 170 °C (entry 1, Table 6), the reaction at 190 °C was completed in 120 min (entry 2) and the corresponding product **6** was formed in 77.3% yield. In this experiment, diethyl ethylphosphonate (**P**) was formed in 15.5%

Table 5 The optimisation of the scale-up reaction of diiodomethane (**J**) with triisopropyl phosphite (**B**)

				Composition of the reaction mixture GC-MS (%)					
Entry	Max. power (W)	Temp. (°C)	Ratio **J** : **B**	**B**	**C**	**D**	**5**	**K**	Comments[a]
1	200	100	1 : 1	51.2	1.5	3.2	43.9	0.2	*a*,*b*
2	200	110	1 : 1	12.5	2.3	4.6	80.1	0.5	*a*,*b*
3	200	120	1 : 1	0.0	4.1	6.0	85.4	4.5	*a*,*b*
4	200	120	1 : 1	0.0	10.4	11.4	70.5	7.7	*a*
5	100	120	1 : 1	0.0	3.8	6.2	87.9	2.1	*a*,*b*
6	100	130	1 : 1	0.0	4.8	5.2	84.5	5.5	*a*,*b*

For the general conditions, see the ESI† (procedure **5.2**). For an explanation of **B**, **C**, **D**, **5** and **K**, see Scheme 5.[a] Comments: *a* (5× argon-purged – see the ESI†), *b* (+0.03 eq. of **5**).

Table 6 The optimisation of the reaction of 1.2-dichloroethane (**A**) with triethyl phosphite (**L**)

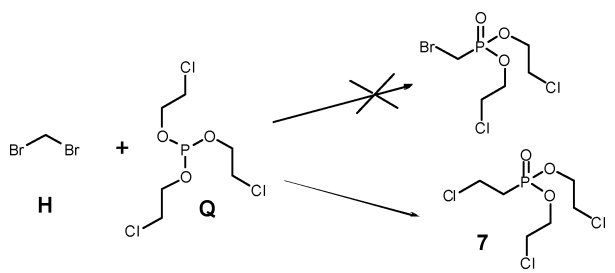
				Composition of the reaction mixture GC-MS (%)					
Entry	Time (min)	Temp. (°C)	Ratio **A** : **L**	**L**	**M**	**N**	**6**	**O**	**P**
1	60	170	4 : 1	85.1	0.0	0.3	14.1	0.5	0.3
2	120	190	4 : 1	0.0	1.0	2.9	77.3	3.3	15.5

For the general conditions, see the ESI† (procedure **6**). For an explanation of **A**, **L**, **M**, **N**, **6**, **O** and **P**, see Scheme 6.

yield. This new type of by-product **P** is formed by the M–A reaction of triethyl phosphite with chloroethane formed during the process. The by-product **P** was not detected in the case of the M–A reaction with triisopropyl phosphite. This finding can be explained by the fact that 2-chloropropane (formed from triisopropyl phosphite) is a much worse substrate for the M–A reaction than chloroethane (formed from triethyl phosphite). Thus, the use of triisopropyl phosphite for the MW-assisted M–A reaction is clearly preferable to use of triethyl phosphite. Entry 1 was repeated on the preparative scale and diethyl 2-chloroethylphosphonate (**6**) was isolated in 62% yield (see the ESI†, procedure **6**).

7. The MW heating of the reaction mixture containing dibromomethane and tris(2-chloroethyl) phosphite

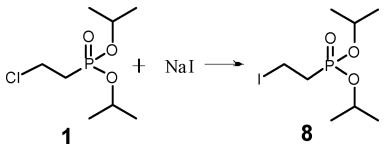
Previous results indicated that the reactions using more reactive bromoalkanes are initiated at lower temperature (130 °C) compared to those using the chloroalkanes (180 °C). For this reason, we have studied a reaction of dibromomethane (**H**) with tris(2-chloroethyl) phosphite (**Q**) under the MW conditions (Scheme 7). The optimised M–A reaction conditions for the preparation of diisopropyl 2-bromoethylphosphonate (**3**) and diisopropyl bromomethylphosphonate (**4**) were used and the formation of bis(2-chloroethyl) 2-chloroethylphosphonate (**7**) as the only product was observed. Bis(2-chloroethyl) 2-chloroethylphosphonate (**7**) was isolated in 83% yield (see the ESI†, procedure **7**). This result indicates that under MW conditions the intramolecular M–A reaction of phosphorus atom with chloroethyl substituent is even faster than the intermolecular M–A reaction with dibromomethane.



Scheme 7 The formation of bis(2-chloroethyl) 2-chloroethylphosphonate (**7**) by the MW heating of the reaction mixture containing dibromomethane (**H**) and tris(2-chloroethyl) phosphite (**Q**).

8. The preparation of diisopropyl 2-iodoethylphosphonate

To complete the series of 2-haloalkylphosphonates, an alternative pathway was used to prepare diisopropyl 2-iodoethylphosphonate (**8**, Scheme 8). The compound **8** was prepared in 88% yield by the Finkelstein reaction starting from diisopropyl 2-chloroethylphosphonate (**1**) (see the ESI†, procedure **8**). This alternative to the M–A reaction was chosen on account of the high price of 1,2-diiodoethane.



Scheme 8 The synthesis of diisopropyl 2-iodoethylphosphonate (**8**) by the reaction of diisopropyl 2-chloroethylphosphonate (**1**) with sodium iodide.

Finally, to prove the universal applicability of the MW-assisted Michaelis–Arbuzov reaction, another MW instrument was used. The above reaction was carried out in the MW-syntheses instrument Type II (see the ESI†) according to the procedures **1.1** and **5.1** and practically the same compositions of the reaction mixtures were observed. The slightly longer reaction times used to reach the same conversion can be explained by the efficiency of MW heating. The MW-syntheses instrument Type I issues focused MW heating, as compared to Type II with unfocused MW heating. For the same maximum power output, the real absorbed MW power is lower for Type II resulting in longer reaction times.

Conclusions

The selective formation of the desired dialkyl haloalkylphosphonates by the microwave-assisted M–A reactions of dihaloalkanes can be reached very effectively by the accurate control of the reaction temperature. The selective substitution of only one halogen atom performed well at 180–190 °C for dichloroalkanes, at 130–170 °C for dibromoalkanes, and at 90–100 °C for diiodoalkanes. The problem of the reaction mixture homogeneity was solved by the addition of a small amount (0.03 eq.) of the desired product into the reaction mixture. Surprisingly, the selectivity for the monosubstitution by M–A reaction is also preserved in the case of dihaloalkanes with five carbon atoms between the two halogen atoms, where the steric effects cannot play a significant role. We can speculate that this phenomenon is caused by much higher absorption of microwave irradiation by dihaloalkanes compared to dialkyl haloalkylphosphonates and/or by the different absorption by the corresponding transition states formed during the M–A reaction. Thus, under the MW-assisted conditions, the reactivity of the halogen atom would be higher in dihaloalkanes compared to dialkyl haloalkylphosphonates.

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