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Dialkylation of Diethyl Ethoxycarbonylmethylphosphonate under Microwave and Solventless Conditions

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ABSTRACT: *To further broaden the methods for the heterogeneous phase alkylation of CH acidic compounds, the dialkylation of diethyl ethoxycarbonylmethylphosphonate was studied in the presence of Cs_2CO_3 under microwave and solvent-free conditions. It was found that after repeating the alkylations by the addition of newer portions of the alkylating agent and the base on a few occasions, the dialkylation was quite efficient. Even dialkyl derivatives with different alkyl groups could be synthesized. The presence of a phase-transfer catalyst was harmful, as prevented the formation of the dialkyl products.* © 2014 Wiley Periodicals, Inc. Heteroatom Chem. 25:107–113, 2014; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21142

INTRODUCTION

The dialkylation of simple CH acidic compounds by the classical method of generating the anion with sodium ethylate in ethanol and reacting it with an alkyl halide followed by the repetition of this procedure with the same or another alkyl halide is well known [1,2]. A more developed version is the dialkylation under the conditions of phase-transfer catalysis (PTC). The few examples described in the literature comprise liquid–liquid (L–L) and solid–liquid (S–L) accomplishments. In the L–L two-phase alkylations, aqueous sodium hydroxide was the base and dichloromethane [3] or chloroform [4], the solvent. The S–L alkylations applied K_2CO_3 base in toluene [5], acetonitrile [6], or dimethylformamide [7] as the reaction medium. In the above cases, quaternary ammonium salts (Bu_4NX and triethylbenzylammonium chloride, i.e., TEBAC) or 18-crown-6 served as the catalyst. The "homo" dialkylated products were isolated in yields of 68%–96%.

Regarding the dialkylation of P-functionalized CH acidic compounds, mostly, ethoxycarbonylmethylphosphonate was the starting material. It was dialkylated in two steps, applying potassium in xylene [8], or in benzene [9]. Using different alkyl halides, the yields were variable (54%–75%). It was also an option to use sodium hydride as the base in tetrahydrofuran [10, 11] or in 1,2-dimethoxyethane [12]. In most cases, the mixtures of the mono- and dialkylated products were formed. Only one example is known for phase-transfer catalyzed dialkylation, which is the dialkylation of ethyl cyanomethylphosphonate with methyl and ethyl iodide, as well as allyl and benzyl halides in the presence of TEBAC and aqueous NaOH to afford the dialkylphosphonate derivatives in yields of 46%–88% [13].

The combination of PTC [14] with microwave (MW) [15–17] may offer additional advantages [18].

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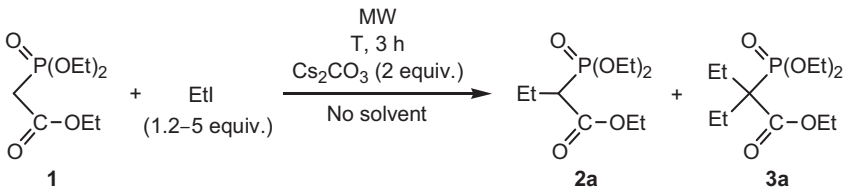


SCHEME 1 The ethylation of ethoxycarbonylmethylphosphonate.

This was the case also within a few alkylations of CH acidic compounds [19, 20]. Recently, we have studied the effect of MW and PTC on the alkylation of a variety of CH acidic compounds in detail [21]. We found that diethyl malonate, ethyl acetoacetate, and ethyl cianoacetate could be alkylated efficiently under MW and solvent-free conditions in the presence of K_2CO_3 and in the absence of a phase-transfer catalyst [22, 23]. It means that MW irradiation substituted the catalyst. A similar situation was experienced for the ethylation of tetraethyl methylenebisphosphonate using Cs_2CO_3 [24], for the alkylation of ethoxycarbonylmethylphosphonate [25], and for the alkylation of diethyl cyanomethylphosphonate [26]. Tetraphenylmethylene(bisphosphine oxide), which is a hindered model, underwent alkylations in the presence of 5% of TEBAC in acetonitrile solution using Cs_2CO_3 [26].

In this paper, we wished to extend our study to the dialkylation of a P═O-functionalized CH acidic compound, that is, diethyl ethoxycarbonylmethylphosphonate, investigating the role of the MW and PTC techniques.

RESULTS AND DISCUSSION

First, we wished to study how the outcome of the ethylations of ethoxycarbonylmethylphosphonate (**1**) may be influenced by the molar ratios and the temperature (Scheme 1, Table 1). Working at 120°C in the presence of 1.2 equiv. of ethyl iodide and 1 equiv. of Cs_2CO_3, the conversion was 89% after a reaction time of 2 h. The monoethylated product (**2a**) predominated over the diethyl species (**3a**) formed in 83% and 6%, respectively (Table 1, entry 1). Remaining at 120°C, but using 3 equiv. of ethyl iodide and 2 equiv. of Cs_2CO_3, the ratio of products **2a** and **3a** was 58:42 after 3 h (Table 1, entry 2). The increase of the temperature to 140°C had practically no effect on the product ratio (Table 1, entry 3). Returning to 120°C, but measuring in 5 equiv. of ethyl iodide resulted in a slight increase in the proportion of the diethylated product (**3a**) that was found 48% (Table 1, entry 4). One can see that varying the different parameters, a maximum amount of only approximately 48% of the diethyl species (**3a**) can be attained.

TABLE 1 The Alkylation of Ethoxycarbonylmethylphosphonate (**1**) under Different Conditions

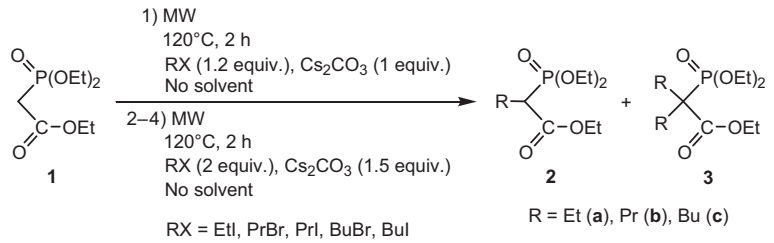
			Product Ratio (%)[a]		
Entry	*EtI (equivalent)*	*T (°C)*	***2a***	***3a***	***Other***
1	1.2	120[b]	83	6	[c]
2	3	120	58	42	
3	3	140	60	40	
4	5	120	52	48	

[a]On the basis GC.
[b]Cs_2CO_3: 1 equivalent; reaction time: 2 h.
[c]Starting material (**1**): 11%.

Hence, in the next experiments, a multistep approach was followed as shown in Scheme 2 and Table 2. The first step was performed as shown by the experiment specified by Table 1, entry 1. The reaction mixture was then diluted with ethyl acetate, and the solid components were removed by filtration. The filtrate was concentrated and reacted further with a second portion (2 equiv.) of ethyl iodide in the presence of 1.5 equiv. of Cs_2CO_3 at 120°C for 2 h. After the second ethylation, the ratio of the monoethyl and diethyl product (**3a**) was 41%–59% (Table 2, entry 1, step 2). Repeating the procedure twice, the proportion of the diethyl compound (**3a**) was, in order, 91% and 98% (Table 2, entry 1, steps 3 and 4). Column chromatography afforded the final product (**3a**) in a yield of 64%.

Then, the procedure elaborated was applied for the preparation of the dipropyl product **3b** (Table 2, entries 2 and 3). Applying propyl bromide and propyl iodide, the proportion of the dipropyl species (**3b**) was 61% and 70%, respectively, after the fourth alkylation (Table 2, entry 2, step 4 and Table 2, entry 3, step 4). Chromatography furnished product **3b** in 29/41% yields.

The dibutylation was also performed (Table 2, entries 4 and 5). The final outcome was more modest with butyl bromide than with butyl iodide; in the fourth step, product **3c** was obtained in 36% and 76%, respectively (Table 2, entry 4, step 4 and Table 2, entry 5, step 4). The preparative yield of



SCHEME 2 The alkylation/dialkylation of ethoxycarbonylmethylphosphonate.

dibutyl compound **3c** was 48% in respect of the last experiment.

It can be seen that the four-step procedure is suitable to "enrich" the content of the dialkyl ethoxycarbonylmethylphosphonate (**3a–c**) to an extent of 70%–98%.

The three products (**3a–c**) were characterized by ^{31}P, ^{13}C, and ^{1}H nuclear magnetic resonance (NMR), as well as high-resolution mass spectrometry (HR-MS).

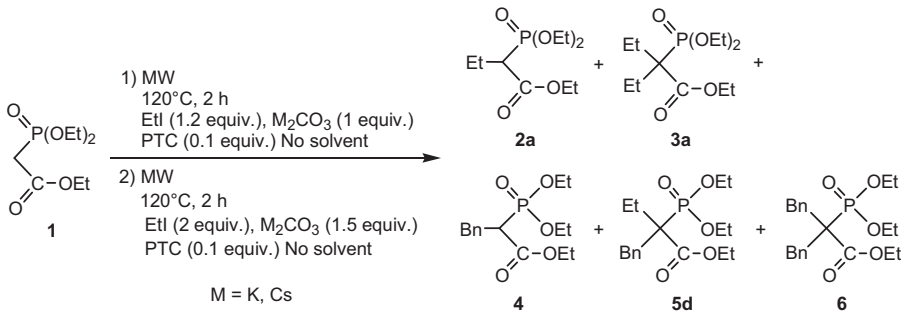
Comparative thermal experiments were also carried out for the four-step alkylation with propyl iodide. It can be seen that after the fourth step, the proportion of the dialkylated product (**3b**) was somewhat lower and, at the same time, that of the by-products was somewhat higher as compared with the MW variation (Table 2, entries 6 vs. 3 in respect of step 4).

In the next part of our work, we investigated the effect of a phase-transfer catalyst, such as TEBAC or tetrabutylammonium bromide (TBAB) (Scheme 3, Table 3). Using 10% of TEBAC, the relative proportion of the monoethyl product (**2a**) decreased from 83% to 75%, while that of the starting material (**1**) and diethyl product (**3a**) remained almost unchanged (11/8% and 6/7%, respectively). A total of 10% of unidentified by-products also appeared in the mixture (Table 2, entry 1, step 1 vs. Table 3, entry 1, step 1). After the second ethylation, the ratio of **2a** and **3a** was 62:21 (Table 3, entry 1,

TABLE 2 MW-Assisted Dialkylation of Ethoxycarbonylmethylphosphonate **1** by a Four-Step Alkylation Fashion

					Composition (%)[a]				
Entry	*Step*	*RX*	*Equivalent*	*Cs_2CO_3 (equivalent)*	***1***	***2***	***3***	*Other*	*Yield of **3** (%)*
1	1	EtI	1.2	1	11	83 (**2a**)	6 (**3a**)		64 (**3a**)
	2	EtI	2	1.5	–	41 (**2a**)	59 (**3a**)		
	3	EtI	2	1.5	–	9 (**2a**)	91 (**3a**)		
	4	EtI	2	1.5	–	2 (**2a**)	98 (**3a**)		
2	1	PrBr	1.2	1	10	81 (**2b**)	4 (**3b**)	5	29 (**3b**)
	2	PrBr	2	1.5	–	62 (**2b**)	33 (**3b**)	5	
	3	PrBr	2	1.5	–	41 (**2b**)	51 (**3b**)	8	
	4	PrBr	2	1.5	–	29 (**2b**)	61 (**3b**)	10	
3	1	PrI	1.2	1	12	77 (**2b**)	3 (**3b**)	8	41 (**3b**)
	2	PrI	2	1.5	–	64 (**2b**)	27 (**3b**)	9	
	3	PrI	2	1.5	–	32 (**2b**)	55 (**3b**)	13	
	4	PrI	2	1.5	–	16 (**2b**)	70 (**3b**)	14	
4	1	BuBr	1.2	1	14	79 (**2c**)	3 (**3c**)	4	
	2	BuBr	2	1.5	–	73 (**2c**)	19 (**3c**)	8	
	3	BuBr	2	1.5	–	66 (**2c**)	26 (**3c**)	8	
	4	BuBr	2	1.5	–	55 (**2c**)	36 (**3c**)	9	
5	1	BuI	1.2	1	14	77 (**2c**)	5 (**3c**)	4	48 (**3c**)
	2	BuI	2	1.5	–	67 (**2c**)	27 (**3c**)	6	
	3	BuI	2	1.5	–	29 (**2c**)	62 (**3c**)	9	
	4	BuI	2	1.5	–	13 (**2c**)	76 (**3c**)	11	
6[b]	1	PrI	1.2	1	12	72 (**2b**)	3 (**3b**)	13	
	2	PrI	2	1.5	–	62 (**2b**)	20 (**3b**)	18	
	3	PrI	2	1.5	–	28 (**2b**)	49 (**3b**)	23	
	4	PrI	2	1.5	–	17 (**2b**)	59 (**3b**)	24	

[a]On the basis GC.
[b]Comparative thermal experiments.



SCHEME 3 The ethylation of ethoxycarbonylmethylphosphonate in the presence of a phase transfer catalyst.

step 2), while in the absence of TEBAC, this ratio was 41:59 (Table 2, entry 1, step 2). Moreover, the proportion of the by-products amounted to 17% when TEBAC was used (Table 3, entry 1, step 2). It can be concluded that the presence of the phase-transfer catalyst disfavored the formation of the monoethyl compound **2a** in the first step and that of the diethyl species **3a**, to a higher extent, in the second step. The by-products were identified as the benzyl, benzyl–ethyl, and the dibenzyl compounds formulated as **4**, **5d**, and **6**, respectively. Their formation suggested that TEBAC also took part in the reaction as an alkylating agent. Quaternary onium salts may act, or may be used as alkylating agents [27]. Structure of the C-benzyl by-products (**4**, **5d**, and **6**) was supported by ^{31}P NMR and HR-MS.

Carrying out the two-step ethylation in the presence of K_2CO_3 as the base, proportion of the diethyl product (**3a**) was even lower (10%) and proportion of the by-products was 20% (Table 3, entry 2, step 2). It is confirmed that the presence of TEBAC as a phase-transfer catalyst is harmful in the MW-assisted diethylation of ethoxycarbonylmethylphosphonate **1**.

However the use of 10% of TBAB did not prevent so much the formation of the diethyl compound (**3a**), as, in this case, after the second ethylation, the proportion of **3a** was 43% (Table 3, entry 3, step 2).

Finally, we aimed at the synthesis dialkylated ethoxycarbonylmethylphosphonates with two different alkyl groups. Our previous protocol was followed as shown in Scheme 2 and Table 2, with the difference that in the first step, propyl iodide, butyl iodide, or benzyl bromide was used, while, in all cases, ethyl iodide was applied in the second, third, and fourth alkylation steps (Scheme 4, Table 4). In all instances, by-products up to 26% appeared in the mixtures. Proportion of the ethyl–propyl product (**5b**) was 74% after the fourth alkylation step, which was isolated in a yield of 39% by column chromatography (Table 4, entry 1, step 4). The ethyl–butyl and ethyl–benzyl compounds (**5c** and **5d**) were obtained in similar proportions and yields (Table 4, entry 2 step 4 and entry 3 step 3).

5b, **5c**, and **5d** are new compounds that were characterized by ^{31}P, ^{13}C, and ^{1}H NMR, as well as HR-MS.

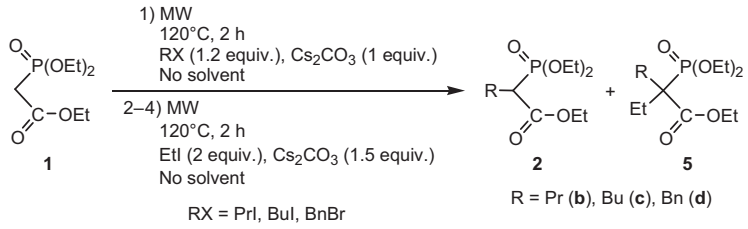
It can be said that mixed dialkylated products (**5b–d**) could also be prepared by the three- or four-step MW-assisted, solvent-free alkylation.

In summary, a multistep MW-assisted, solvent- and catalyst-free method was elaborated for the synthesis of dialkyl ethoxycarbonylmethylphosphonates with identical or mixed alkyl groups. The products with two different alkyl groups are of special importance. The method developed completes well

TABLE 3 Two-Step Ethylation of Ethoxycarbonylmethylphosphonate **1** under MW Conditions in the Presence of a Phase-Transfer Catalyst

					Composition (%)[a]			
Entry	*Step*	*PTC*	*M_2CO_3*	*Equivalent*	***1***	***2a***	***3a***	*Other*[b]
1	1	TEBAC	Cs_2CO_3	1	8	75	7	10
	2	TEBAC	Cs_2CO_3	1.5	–	62	21	17
2	1	TEBAC	K_2CO_3	1	21	68	1	9
	2	TEBAC	K_2CO_3	1.5	–	70	10	20
3	1	TBAB	Cs_2CO_3	1	–	75	25	–
	2	TBAB	Cs_2CO_3	1.5	–	57	43	–

[a]On the basis of GC.
[b]C-benzyl- product (**4**, **5d**, and **6**).



SCHEME 4

the earlier procedures and offers the advantage of using an up-to-date approach comprising MW irradiation without a solvent and phase-transfer catalyst.

EXPERIMENTAL

General

The ^{31}P, ^{13}C, and ^{1}H NMR spectra were obtained on a Bruker DRX-500 spectrometer (Bruker Corp. Billerica, MA, USA) operating at 202.4, 125.7, and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or tetramethylsilane. The couplings are given in Hz. Mass spectrometry was performed on a Q-TOF Premier mass spectrometer (Waters Corp., Milford, MA, USA) in positive electrospray mode. The MW-assisted reactions were carried out in a CEM Discover MW reactor (CEM, Microwave Technology Ltd., Buckingham, UK) equipped with a pressure controller using *ca.* 50 W irradiation.

*One-Step Diethylation of Diethyl Ethoxycarbonylmethylphosphonate (**1**) under MW Conditions (Table 1, entry 4)*

Ethoxycarbonylmethylphosphonate **1**, (0.20 g; 0.89 mmol), ethyl iodide (0.36 mL; 4.5 mmol), and cesium carbonate (0.65 g; 1.8 mmol) were measured in a tube that was placed in the MW reactor and was irradiated under pressure control at 50 W at 120°C for 3 h. Then the mixture was taken up in 10 mL of ethyl acetate, the resulting suspension was filtered, and the filtrate was concentrated in vacuum. The residue so obtained contained 52% of the monoethyl compound (**2a**) and 48% of the diethyl species (**3a**) according to gas chromatography (GC).

General Procedure for the Multiple-Step Dialkylation of Diethyl Ethoxycarbonylmethylphosphonate under MW Conditions

First step: 0.20 g (0.89 mmol) of ethoxycarbonylmethylphosphonate **1**, 1.1 mmol of alkyl halide (ethyl iodide: 0.09 mL, *n*-propyl bromide: 0.10 mL, *n*-propyl iodide: 0.10 mL, *n*-butyl bromide: 0.12 mL, *n*-butyl iodide: 0.12 mL, benzyl chloride: 0.13 mL, and benzyl bromide: 0.13 mL), and 0.32 g (0.89 mmol) of Cs_2CO_3 were measured in a tube that was placed in the MW reactor and was irradiated under pressure control at 50 W at 120°C for 2 h. Then the mixture was taken up in 10 mL of ethyl acetate, the resulting suspension was filtered, and the filtrate was

TABLE 4 MW-Assisted Dialkylation of Ethoxycarbonylmethylphosphonate **1** in a Four-Step Fashion

					Composition (%)[a]				
Entry	*Step*	*RX*	*Equivalent*	*Cs_2CO_3 (Equivalent)*	***1***	***2***	***5***	*Other*	*Yield of **5** (%)*
1	1	PrI	1.2	1	12	77 (**2b**)	–	11	39 (**5b**)
	2	EtI	2	1.5	–	37 (**2b**)	43 (**5b**)	20	
	3	EtI	2	1.5	–	16 (**2b**)	59 (**5b**)	25	
	4	EtI	2	1.5	–	1 (**2b**)	74 (**5b**)	25	
2	1	BuBr	1.2	1	14	79 (**2c**)	–	7	36 (**5c**)
	2	EtI	2	1.5	–	51 (**2c**)	26 (**5c**)	23	
	3	EtI	2	1.5	–	25 (**2c**)	50 (**5c**)	25	
	4	EtI	2	1.5	–	6 (**2c**)	71 (**5c**)	23	
3	1[b]	BnBr	1.2	1	–	75 (**2d**)	–	25	40 (**5d**)
	2	EtI	2	1.5	–	21 (**2d**)	53 (**5d**)	26	
	3	EtI	2	1.5	–	–	74 (**5d**)	26	

[a]On the basis of GC.
[b]Purified by column chromatography.

concentrated in vacuum. The residue so obtained was analyzed by GC.

Next steps: According to the quantity of the product of previous step, 2 equiv. alkyl halide (ethyl iodide, *n*-propyl bromide, *n*-propyl iodide, *n*-butyl bromide, *n*-butyl iodide, and 1.5 equiv. Cs_2CO_3 were measured in a tube that was irradiated as in the previous case. Then the mixture was taken up in 10 mL of ethyl acetate, the resulting suspension was filtered, and the filtrate was concentrated in vacuum. The residue so obtained was analyzed by GC. The residue of the last step was purified by column chromatography (hexane–ethyl acetate 6:4, silica gel) to give the products as colorless oils (see Table 2).

*Diethyl 1-ethyl-1-(ethoxycarbonyl)propylphosphonate (***3a***).* Yield: 64%, ^{31}P NMR ($CDCl_3$) δ: 27.3; ^{13}C NMR ($CDCl_3$) δ: 9.3 (d, J = 7.5, CCH_2CH_3), 14.2 (s, OCH_2CH_3), 16.5 (d, J = 5.9, $POCH_2CH_3$), 24.8 (d, J = 3.6, CCH_2CH_3), 53.1 (d, J = 133.9, PCC), 61.1 (s, OCH_2), 62.4 (d, J = 7.2, $POCH_2$), 171.4 (d, J = 3.1, C=O); ^{1}H NMR ($CDCl_3$) δ: 0.98 (t, 6H, J = 7.4, CH_3), 1.34–1.26 (m, 6H + 3H, CH_3), 2.04–1.89 (m, 4H, CH_2), 4.25–4.10 (m, 6H, CH_2); HR-MS, $(M + H)^+_{found}$ = 281.1520, $C_{12}H_{25}O_5P$ requires 281.1518, $(M + Na)^+_{found}$ = 303.1341, $C_{12}H_{24}O_5PNa$ requires 303.1337.

*Diethyl 1-propyl-1-(ethoxycarbonyl)butylphosphonate (***3b***).* Yield: 41%, ^{31}P NMR ($CDCl_3$) δ: 27.1; ^{13}C NMR ($CDCl_3$) δ: 14.1 (s, OCH_2CH_3), 14.7 (s, $CH_2CH_2CH_3$), 16.5 (d, J = 5.9, $POCH_2CH_3$), 18.1 (d, J = 7.3, CH_2), 34.5 (d, J = 3.7, CH_2), 52.6 (d, J = 133.4, PCC), 61.1 (s, OCH_2), 62.4 (d, J = 7.2, $POCH_2$), 171.5 (d, J = 3.1, C=O); ^{1}H NMR ($CDCl_3$) δ: 0.92 (t, 6H, J = 7.3, CH_3), 1.34–1.26 (m, 9H + 2H, CH_2, CH_3), 1.51–1.37 (m, 2H, CH_2), 1.94–1.76 (m, 4H, CH_2), 4.24–4.10 (m, 6H, OCH_2); HR-MS, $(M + H)^+_{found}$ = 309.1830, $C_{14}H_{30}O_5P$ requires 309.1831, $(M + Na)^+_{found}$ = 331.1651, $C_{14}H_{29}O_5PNa$ requires 331.1650.

*Diethyl 1-butyl-1-(ethoxycarbonyl)pentylphosphonate (***3c***) [8].* Yield: 48%, ^{31}P NMR ($CDCl_3$) δ: 26.4; ^{13}C NMR ($CDCl_3$) δ: 14.0 (s, CH_3), 14.3 (s, OCH_2CH_3), 16.6 (d, J = 5.9, $POCH_2CH_3$), 23.4 (s, CH_2), 26.9 (d, J = 7.0, CH_2), 32.1 (d, J = 3.6, CH_2), 52.6 (d, J = 133.2, PCC), 61.2 (s, OCH_2), 62.5 (d, J = 7.2, $POCH_2$), 171.7 (d, J = 3.1, C=O); ^{1}H NMR ($CDCl_3$) δ: 0.91 (t, 6H, J = 6.7, CH_3), 1.46–1.23 (m, 9H + 8H, CH_2, CH_3), 1.92–1.82 (m, 4H, CH_2), 4.24–4.09 (m, 6H, OCH_2); HR-MS, $(M + H)^+_{found}$ = 337.2142, $C_{16}H_{34}O_5P$ requires 337.2144, $(M + Na)^+_{found}$ = 359.1964, $C_{16}H_{33}O_5PNa$ requires 359.1963.

The mixed alkyl products (**5b–d**) were also prepared by the general procedure.

*Diethyl 1-ethyl-1-(ethoxycarbonyl)butylphosphonate (***5b***).* Yield: 39%, ^{31}P NMR ($CDCl_3$) δ: 26.4; ^{13}C NMR ($CDCl_3$) δ: 9.3 (d, J = 7.4, OCH_2CH_3), 14.1 (s, CH_2CH_3), 14.6 (s, $CH_2CH_2CH_3$), 16.4 (d, J = 5.9, $POCH_2CH_3$), 17.9 (d, J = 7.4, $CH_2CH_2CH_3$), 25.2 (d, J = 3.7, CCH_2), 34.0 (d, J = 3.6, CCH_2), 52.8 (d, J = 133.6, PCC), 61.0 (s, OCH_2), 62.3 (d, J = 7.2, $POCH_2$), 171.4 (d, J = 3.0, C=O); ^{1}H NMR ($CDCl_3$) δ: 0.92 (t, 3H, J = 7.5, CH_3), 0.98 (t, 3H, J = 7.4, CH_3), 1.34–1.26 (m, 9H + 1H, CH_2, CH_3), 1.51–1.43 (m, 1H, CH_2), 1.98–1.80 (m, 2H + 2H, CH_2), 4.24–4.10 (m, 6H, OCH_2); HR-MS, $(M + H)^+_{found}$ = 295.1673, $C_{13}H_{28}O_5P$ requires 295.1674, $(M + Na)^+_{found}$ = 317.1492, $C_{13}H_{27}O_5PNa$ requires 317.1494.

*Diethyl 1-ethyl-1-(ethoxycarbonyl)pentylphosphonate (***5c***).* Yield: 36%, ^{31}P NMR ($CDCl_3$) δ: 26.4; ^{13}C NMR ($CDCl_3$) δ: 9.4 (d, J = 7.2, CCH_2CH_3), 13.9 (s, $CH_2CH_2CH_3$), 14.1 (s, OCH_2CH_3), 16.5 (d, J = 5.9, $POCH_2CH_3$), 23.3 (s, CH_2), 25.2 (d, J = 3.7, CH_2), 26.7 (d, J = 7.3, CCH_2CH_3), 31.5 (d, J = 3.6, CH_2), 52.7 (d, J = 133.5, PCC), 61.1 (s, OCH_2), 62.4 (d, J = 7.2, $POCH_2$), 171.5 (d, J = 3.1, C=O); ^{1}H NMR ($CDCl_3$) δ: 0.91 (t, 3H, J = 6.8, CH_3), 0.99 (t, 3H, J = 7.4, CH_3), 1.45–1.26 (m, 9H + 4H, CH_2, CH_3), 2.17–1.82 (m, 4H, CH_2), 4.24–4.10 (m, 6H, OCH_2); HR-MS, $(M + H)^+_{found}$ = 309.1832, $C_{14}H_{30}O_5P$ requires 309.1831, $(M + Na)^+_{found}$ = 331.1654, $C_{14}H_{29}O_5PNa$ requires 331.1650.

*Diethyl 1-benzyl-1-(ethoxycarbonyl)propylphosphonate (***5d***).* Yield: 40%, ^{31}P NMR ($CDCl_3$) δ: 25.5; ^{13}C NMR ($CDCl_3$) δ: 10.4 (d, J = 4.5, CCH_2CH_3), 14.3 (s, $COCH_2CH_3$), 16.6 (d, J = 5.9, $POCH_2CH_3$), 16.7 (d, J = 5.9, $POCH_2CH_3$), 25.8 (d, J = 3.4, CCH_2CH_3), 39.6 (d, J = 3.6, CCH_2Ar), 54.4 (d, J = 134.9, PCC), 61.4 (s, $COCH_2$), 62.5 (d, J = 7.1, $POCH_2$), 62.8 (d, J = 7.2, $POCH_2$), 127.0 (s, $C_{4'}$), 128.2 (s, $C_{2'}$)*, 130.7 (s, $C_{3'}$)*, 136.6 (d, J = 12.2, $C_{1'}$), 171.1 (d, J = 2.7, C=O), *tentative assignment; ^{1}H NMR ($CDCl_3$) δ: 1.07 (t, 3H, J = 7.5, CH_3), 1.34–1.25 (m, 9H, CH_3), 1.88–1.71 (m, 2H, CH_2), 3.08 (dd, 1H, J^1 = 13.6, J^2 = 10.9, CH_2Ar), 3.42 (dd, 1H, J^1 = 13.6, J^2 = 10.9, CH_2Ar), 4.24–4.09 (m, 6H, OCH_2), 7.27–7.16 (m, 5H, ArH); HR-MS, $(M + H)^+_{found}$ = 343.1670, $C_{17}H_{28}O_5P$ requires 343.1674, $(M + Na)^+_{found}$ = 365.1491, $C_{17}H_{27}O_5PNa$ requires 365.1494.

TABLE 5 Identification of the Minor Components (**4**, **5d**, and **6**) Formed in the Phase-Transfer Catalyzed Ethylation of Ethoxycarbonylmethylphosphonate **1**

Compound	δ_P *(CDCl$_3$)*	δ_P *[lit]*	*HR-MS, [M + H]$^+$ found*	*Requires*	
4	22.2	22.0 [25]	315.1365	315.1361	$C_{15}H_{24}O_5P$
5d	25.4		343.1671	343.1674	$C_{17}H_{28}O_5P$
6	24.2		405.1832	405.1831	$C_{22}H_{30}O_5P$

Two-Step Diethylation of Diethyl Ethoxycarbonylmethylphosphonate under MW-PTC Conditions (Table 3, entry 3)

First step: 0.20 g (0.89 mmol) of triethyl phosphonoacetate (**1**), 0.09 mL (1.07 mmol) ethyl iodide 0.29 g (0.89 mmol) of cesium carbonate, and 0.03 g (0.09 mmol) of TBAB were measured in a tube that was placed in the MW reactor and was irradiated as above at 120°C for 2 h. Then the mixture was taken up in 10 mL of ethyl acetate, the resulting suspension was filtered, and the filtrate was concentrated in vacuum. The residue contained 8% of the starting material **1**, 75% of the monoethylated product, and 7% of the diethylated product (**2a** and **3a**, respectively) according to GC (Table 3, entry 1, step 1).

Second step: The residue of first step, 2 equiv. of ethyl iodide, 1.5 equiv. of cesium carbonate, and 0.1 equiv. of TBAB were measured in a tube that was placed in the MW reactor and was irradiated under pressure control at 50 W at 120°C for 2 h. Then the mixture was taken up in 10 mL of ethyl acetate, the resulting suspension was filtered, and the filtrate was concentrated in vacuum. The residue contained 62% of the monoethyl compound (**2a** and 21% of the diethyl species (**3a**) along with 17% of other products (**4**, **5d**, and **6**) according to GC and gas chromatography–mass spectrometry (Table 3, entry 1, step 2). The ^{31}P NMR shifts and HR-MS data for minor components **4**, **5d**, and **6** are shown in Table 5.

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