Heteroatom Chemistry
Volume 23, Number 3, 2012

Microwave-Assisted Alkylation of Diethyl Ethoxycarbonylmethylphosphonate under Solventless Conditions

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Received 25 November 2011

ABSTRACT: *The reaction of diethyl ethoxycarbonylmethylphosphonate with a series of alkyl halides, under microwave (MW) and solventless conditions at 120°C, in the presence of Cs_2CO_3 and in the absence of a phase transfer catalyst afforded the corresponding monoalkylated products in yields of >70%. The thermal variant carried out in boiling acetonitrile was slow and led to incomplete conversions. In the MW method, the phase transfer catalyst is substituted by MW irradiation and there is no need for a solvent.* © 2012 Wiley Periodicals, Inc. Heteroatom Chem 23:241–246, 2012; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21009

INTRODUCTION

Substituted CH acidic compounds, such as malonates and cyanomethylacetic esters, that are intermediates in the preparation of barbiturates may be synthesized efficiently by phase transfer catalysis (PTC) [1,2]. A combination of PTC with microwave (MW) irradiation, which is another powerful technique [3–5], may offer additional advantages in general [6]. This was also demonstrated within the alkylation of CH acidic compounds [7,8]. In these cases, typically the solvent-free, solid–liquid phase reactions were irradiated in the presence of a phase transfer catalyst. Tetraalkyl methylenebisphosphonates and methylenebis(phosphine oxides) form a special class of CH acidic compounds. Among these substrates, the tetraethyl methylenebisphosphonate and, especially, bis(diphenylphosphinyl)methane are not too reactive in C-alkylations. Consequently, the C-alkylation of these species requires harsher conditions than for malonic esters, acetoacetic esters, and analogues. Accordingly, $[(EtO)_2P(O)]_2CH_2$ and $[Ph_2P(O)]_2CH_2$ were alkylated via salt formation with potassium [9,10], or sodium hydride [11–14]. In these cases, the alkylated species were obtained in variable (in most cases in poor) yields. The CH acidic compounds with mixed functionalities, for example, ethyl cyanomethylphosphonate are more reactive and were converted to the alkylated derivatives via salt formation with sodium hydride [15], or by liquid–liquid PTC [16].

The benzylation of diethyl ethoxycarbonylmethylphosphonate was carried out using potassium [17], sodium hydride (in tetrahydrofuran

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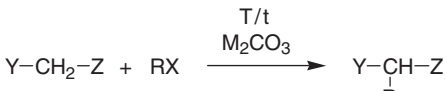
Contract grant sponsor: Hungarian Scientific and Research Fund.
Contract grant number: OTKA K83118.

TABLE 1 Alkylation of CH Acidic Compounds in Solid–Liquid Phase, in the Presence of Alkali Carbonate



Y	*Z*	*RX*	M_2CO_3	*Solvent*	*Mode of heating*	*T/p (°C/bar)*	*t*	*Yield of Y–CHR–Z*	*Ref*	*Entry*
CO_2Et	CO_2Et	EtI	K_2CO_3	–	MW	160/12	45 min	93	[29,30]	1
CO_2Et	CO_2Et	^{n}PrBr	K_2CO_3	–	MW	185/12	45 min	92	[29,30]	2
CO_2Et	CO_2Et	^{n}BuBr	K_2CO_3	–	MW	185/12	45 min	81	[29,30]	3
CO_2Et	CO_2Et	EtI	K_2CO_3[a]	Acetone	Δ	56	20 h	78	[29,30]	4
CO_2Et	C(O)Me	EtI	K_2CO_3	–	MW	140/11	30 min	85	[29,30]	5
CO_2Et	C(O)Me	^{n}PrBr	K_2CO_3	–	MW	140/11	30 min	87	[29,30]	6
CO_2Et	CN	EtI	K_2CO_3	–	MW	120/9	45 min	75	[29,30]	7
CO_2Et	CN	^{n}PrBr	K_2CO_3	–	MW	120/9	45 min	78	[29,30]	8
$P(O)(OEt)_2$	$P(O)(OEt)_2$	EtI	Cs_2CO_3	–	MW	140/11	1.5 h	80	[31]	9
$P(O)(OEt)_2$	$P(O)(OEt)_2$	^{n}PrBr	Cs_2CO_3	–	MW	120/6	4 h	57[b,c]	[31]	10
$Ph_2P(O)$	PhP(O)	^{n}PrBr	Cs_2CO_3[a]	MeCN	MW	180/13.5	4 h	40[d]	[32]	11
		^{n}PrBr	Cs_2CO_3	MeCN	MW	180/13.5	4 h	46[e]	[32]	12
		BnBr	Cs_2CO_3	MeCN	MW	120/9	3 h	45[f]	[32]	13
		BnBr	Cs_2CO_3	MeCN	Δ	82	24 h	44[g]	[32]	14
$P(O)(OEt)_2$	CN	^{n}PrBr	K_2CO_3	–	MW	100/2.5	2 h	64	[32]	15
		^{n}BuBr	K_2CO_3	–	MW	120/3	2 h	59	[32]	16
		^{n}PrBr	Cs_2CO_3	MeCN	Δ	82	24 h	75	[32]	17
		^{n}BuBr	Cs_2CO_3	MeCN	Δ	82	24 h	82	[32]	18

Δ = traditional heating.
[a]In the presence of 10% of TEBAC.
[b]Proportion in the mixture on the basis of GC.
[c]The mixed esters with one or two PrO groups were also present in 33% and 10%, respectively.
[d]At a conversion of 64%.
[e]At a conversion of 74%.
[f] At a conversion of 57%.
[g]At a conversion of 60%.

[18,19], *N*,*N*-dimethylformamide (DMF) [20,21]), or potassium carbonate [22,23] as the deprotonating agent generating the anion in a separate step, or in the presence of the benzyl halide. In most cases, the benzylation required prolonged reaction times and the yields were variable.

The alkylation of diethyl ethoxycarbonylmethylphosphonate was also described using sodium hydride in DMF [24] or ethylene glycol dimethyl ether [25], or using potassium *tert*-butylate in dimethyl sulfoxide [26–28]. At the same time, the butylation was also accomplished using K_2CO_3/NaI [23].

Recently, we have systematically studied the effect of MW and PTC on the alkylation of a variety of CH acidic compounds. It was found by us that diethyl malonate, ethyl acetoacetate, and ethyl cyanoacetate could be efficiently alkylated under MW and solventless conditions in the presence of K_2CO_3 and in the absence of a phase transfer catalyst (triethylbenzylammonium chloride, TEBAC). It means that MW irradiation substituted the phase transfer catalyst (Table 1, entries 1–8) [29,30]. The same was experienced for the ethylation of tetraethyl methylenebisphosphonate using Cs_2CO_3 (Table 1, entry 9) [31]. Applying *n*-propyl bromide as the alkylating agent, the ester with one or two PrO groups also appeared in the mixture (Table 1, entry 10) [31]. Tetraphenylmethylene(bisphosphine oxide) was a very hindered model. The alkylations were best carried out in the presence of 5% of TEBAC and in an acetonitrile solution using Cs_2CO_3 as the base. The conversions were far from complete, and the yields of the alkylated products were only 40–46% (Table 1, entries 11–13) [32]. In this instance, the preparation under traditional thermal conditions led to similar results (Table 1, entry 14) [32]. Finally, the MW-assisted solventless alkylation of diethyl cyanomethylphosphonate provided the alkylated products in a 59–64% yield (Table 1, entries 15 and 16). The application of TEBAC was harmful, as it promoted the formation of phosphonates with mixed ester functionalities [32]. The alkylation carried out in the presence of Cs_2CO_3 in boiling acetonitrile furnished the C-alkyl derivatives in a 75–82% yield after a 24-h reaction time (Table 1, entries 17, 18).

It can be seen that the MW-assisted solventless and catalyst-free accomplishment, in most of the

TABLE 2 Solid–Liquid Phase Alkylation of Diethyl Ethoxycarbonylmethylphosphonate **1** under MW Conditions (See the Experimental Section)

					Composition (%)[a]				
RX	M_2CO_3	*TEBAC (10%)*	*T (°C)*	*t(h)*	**1**	**2**	*Other*	*Yield of **2***	*Entry*
EtI	K_2CO_3	–	120	2	13	82 (**2a**)	5		1
EtI	K_2CO_3	–	120	3	11	85 (**2a**)	4		2
EtI	K_2CO_3	–	130	2	5	85 (**2a**)	10	72 (**2a**)	3
EtI	K_2CO_3	+	120	2	30	57 (**2a**)	13		4
EtI	Cs_2CO_3	–	120	2	5	86 (**2a**)	9	70 (**2a**)	5
EtI	Cs_2CO_3	+	120	2	12	75 (**2a**)	13		6
^{n}PrBr	K_2CO_3	–	130	2	28	57 (**2b**)	15		7
^{n}PrBr	K_2CO_3	–	130	3	25	59 (**2b**)	16		8
^{n}PrBr	K_2CO_3	+	120	2	31	34 (**2b**)	35		9
^{n}PrBr	Cs_2CO_3	–	120	2	10	79 (**2b**)	11	71 (**2b**)	10
^{n}PrBr	Cs_2CO_3	+	120	2	34	22 (**2b**)	44		11
^{n}BuBr	Cs_2CO_3	–	120	2	7	83 (**2c**)	10	70 (**2c**)	12
BnBr	K_2CO_3	–	120	2	18	63 (**2d**)	19[b]	53 (**2d**)	13
BnBr	K_2CO_3	–	130	3	16	63 (**2d**)	21[c]		14
BnBr	K_2CO_3	+	130	3	17	32 (**2d**)	51[d]		15
BnBr	Cs_2CO_3	–	120	3	27	59 (**2d**)	14[e]		16

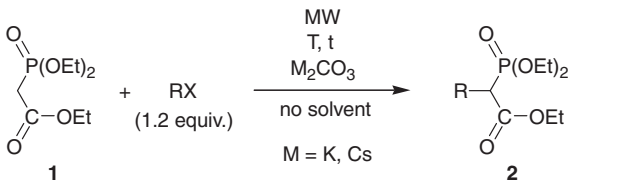
[a]On the basis of GC.
[b]Including 7% of the dibenzylated product.
[c]Including 8% of the dibenzylated product.
[d]Including 6% of the dibenzylated product.
[e]Including 11% of the dibenzylated product.

cases, is a good alternative to other variations, for example, to the solid–liquid phase, typically the phase transfer catalyzed method applying alkali carbonate in acetonitrile at the boiling point.

As the MW-assisted method elaborated by us seemed to be of general value, we wished to try it out in the alkylation of diethyl ethoxycarbonylmethylphosphonate and we wished to find the optimum conditions.

RESULTS AND DISCUSSION

We wished to try out the MW-assisted solventless and catalyst-free alkylation of diethyl ethoxycarbonylmethylphosphonate in the presence of K_2CO_3 and Cs_2CO_3 applying ethyl iodide, *n*-propyl bromide, *n*-butyl bromide, and benzyl bromide as simple alkylating agents (Scheme 1). The mixtures were analyzed by gas chromatography (GC).

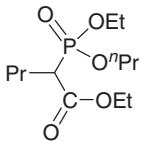


SCHEME 1

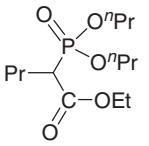
Using ethyl iodide and K_2CO_3 at 120°C, the proportion of the ethyl-substituted product (**2a**) was 82% and 85%, respectively, after a 2-h reaction time (Table 2, entries 1 and 2). Almost similar results were obtained at 130°C for 3 h (Table 2, entry 3). It is noteworthy that the use of 10% TEBAC as the phase transfer catalyst led to a decreased conversion of 70% and an increase in the proportion of the by-products (Table 2, entry 4). Performing the ethylation in the presence of Cs_2CO_3 at 120°C for 2 h, the outcome was similar to that with K_2CO_3 at 120°C for 3 h or at 130°C for 2 h (Table 2, entries 5 vs. 2 and 3). The presence of TEBAC was again harmful (Table 2, entry 6).

Changing for *n*-propyl bromide, a similar trend was experienced as with ethyl iodide. At the same time, K_2CO_3 was not as effective as Cs_2CO_3. Using K_2CO_3, the maximum proportion of the propylated compound **2b** was 57–59%, and this was even lower (34%) in the presence of TEBAC (Table 2, entries 7–9). The application of Cs_2CO_3 led to better results; the proportion of the desired product (**2b**) was 79% at 120°C after a 2-h reaction time (Table 2, entry 10). It is a noteworthy observation that in this case the phase transfer catalyst had a dramatic impact on the conversion and proportion of product **2b**. Instead of 96%, the conversion was only 66% and the proportion of the propylated substrate was only 22% instead of 75%. At the same time, the by-products represented as much as 44% instead of 21% (Table 2, entry 11 vs. 10). Among

the by-products, the propylated ethoxycarbonylmethylphosphonate with ethyl *n*-propyl and di-*n*-propyl ester functions (**3b** [δ_P ($CDCl_3$) 23.05, $(M + H)^+_{found}$ = 281.1519, $C_{12}H_{26}O_5P$ requires 281.1518] and **4b** [δ_P ($CDCl_3$) 23.00, $(M + H)^+_{found}$ = 295.1676, $C_{13}H_{28}O_5P$ requires 295.1674], respectively) could be identified.



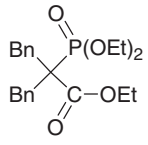
3b



4b

The butylation with *n*-butyl bromide was carried out under the best conditions found in the case of the *n*-propyl analogue. Hence, applying 120°C for 2 h in the presence of Cs_2CO_3 and in the absence of a catalyst, the proportion of the *n*-butyl product (**2c**) was 83% (Table 2, entry 12).

The benzylation of CH acidic compound **1** was also studied. It was found that in the presence of K_2CO_3 as the base, the proportion of the benzylated product **2d** was 63% working at 120°C for 2 h or 130°C for 3 h, showing that no complete conversion could be achieved under such conditions (Table 2, entries 13 and 14). The effect of the phase transfer catalyst was the same as in the previous cases: The relative proportion of the by-products increased to 51% (Table 2, entry 15). Replacing K_2CO_3 with Cs_2CO_3, the outcome of the benzylation remained practically unchanged (Table 2, entry 16). It was observed that the by-products included the dibenzylated product, diethyl 1,1-dibenzyl(ethoxycarbonyl)methylphosphonate (**5d**). In the aforementioned cases, its proportion amounted to 7–11%.



5d

From the best experiments, the alkylated derivatives were prepared by column chromatography. Hence, product **2a** was obtained in 72–70% yields from the experiments covered by Table 2 (entries 3 and 5). Similarly compounds **2b**, **2c**, and **2d** were obtained in 71%, 70%, and 53% yields, respectively, based on experiments outlined by entries 10, 12, and 14 of Table 2.

The alkylated ethoxycarbonylmethylphosphonates **2a–d** were described in the literature [33–38], but they were characterized only partially. All the products synthesized have now been subjected to spectral characterization by ^{31}P, ^{13}C, and ^1H NMR, as well as mass spectrometry (MS) methods.

For comparative purposes, the alkylations were also carried out under traditional thermal conditions in acetonitrile at the boiling point for 24 h. On the one hand, the ethoxycarbonylmethylphosphonate (**1**) was alkylated in the presence of K_2CO_3 and TEBAC at the boiling point of acetonitrile. On the other hand, Cs_2CO_3 was used without a catalyst. This was possible due to the better liphophility of Cs_2CO_3. All these reactions were reluctant and stopped at incomplete conversions. In the presence of K_2CO_3 and TEBAC, the maximum proportion of alkylated products **2a–c** was 11–28% with 72–80% unreacted starting material **1** present. Using Cs_2CO_3 without a catalyst, the reaction mixture contained 45–74% of product **2** (Table 3). In the presence of TEBAC, side reactions could be observed. The beneficial effect of the application of MW irradiation in the alkylation reactions under discussion is obvious.

TABLE 3 Solid–Liquid Phase Alkylation of Diethyl Ethoxycarbonylmethylphosphonate **1** under Thermal Conditions in Boiling Acetonitrile for 24 h

			Composition (%)[a]			
RX	*M_2CO_3*	*TEBAC (10%)*	**1**	**2**	*Other*	*Entry*
EtI	K_2CO_3	+	79	11 (**2a**)	10	1
^{n}PrBr	K_2CO_3	+	80	14 (**2b**)	6	2
^{n}BuBr	K_2CO_3	+	72	28 (**2c**)	–	3
EtI	Cs_2CO_3	–	24	74 (**2a**)	2[b]	4
^{n}PrBr	Cs_2CO_3	–	55	45 (**2b**)	–[c]	5
^{n}BuBr	Cs_2CO_3	–	31	69 (**2c**)	–[d]	6

[a]On the basis of GC.
[b–d]No change on prolonged heating.

In summary, the MW-assisted and solventless method was extended to the alkylation of another CH acidic compound, diethyl ethoxycarbonylmethylphosphonate **1**, where K_2CO_3 or Cs_2CO_3 is the solid phase and the substrate, along with the alkyl halide, forms the liquid phase. Regarding yields and reaction times, the MW-assisted and solventless procedure is more efficient as compared to the thermal variant, when the CH acidic substrate is alkylated using alkali carbonates in boiling acetonitrile in the presence or absence of a phase transfer catalyst leading to incomplete conversions. Additional advantages are that the phase transfer catalyst is substituted by MW irradiation, and there is no need for a solvent.

EXPERIMENTAL

General

The ^{31}P, ^{13}C, and ^{1}H NMR spectra were obtained on a Bruker DRX-500 spectrometer operating at 202.4, 125.7, and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or tetramethylsilane (TMS). The couplings are given in Hz. MS was performed on a ZAB-2SEQ instrument.

The MW-assisted reactions were carried out in a CEM Discover microwave reactor (CEM Microwave Technology Ltd., Buckingham, UK) equipped with a pressure controller using ca. 30-W irradiation.

General Procedure for the MW-Assisted and Solventless Alkylation of Diethyl Ethoxycarbonylmethylphosphonate under MW Conditions

0.20 g (0.89 mmol) of triethyl phosphonoacetate, 1.07 mmol of alkyl halide (ethyl iodide: 0.09 mL, *n*-propyl bromide: 0.10 mL, *n*-butyl bromide: 0.12 mL, benzyl bromide: 0.13 mL), 0.89 mmol of alkali carbonate (K_2CO_3: 0.12 g, Cs_2CO_3: 0.32 g), and if necessary 0.02 g (0.09 mmol) of TEBAC were measured in a tube that was placed in the MW reactor and was irradiated under pressure control at 30 W at the appropriate temperature (T) for the appropriate time (t). Then the mixture was taken up in 20 mL of acetonitrile, and the resulting suspension filtered and the filtrate concentrated in vacuum. The residue so obtained was analyzed by GC and in certain cases (indicated in Table 2 and below) purified by column chromatography (3% methanol in dichloromethane, silica gel) to afford products **2a–d**.

The following products were thus prepared.

*Diethyl 1-(Ethoxycarbonyl)propylphosphonate (**2a**) (Table 2, Entry 3).* Yield: 72%; ^{31}P NMR ($CDCl_3$) δ: 22.9, δ_P: [33] 22.1; ^{13}C NMR [34] ($CDCl_3$) δ: 13.1 (d, J = 15.9, CH_2), 14.4 (s, CH_3), 16.4 (d, J = 2.4, CH_3), 16.5 (d, J = 2.0, CH_3), 20.8 (d, J = 5.0, CH_3), 47.6 (d, J = 131.5, CH), 61.4 (s, CH_2O), 62.7 (d, J = 6.9, CH_2O), 62.8 (d, J = 6.5, CH_2O), 169.3 (d, J = 4.7, C = O); ^{1}H NMR [34] ($CDCl_3$) δ: 0.99 (t, 3H, J = 7.3, CH_3), 1.38–1.27 (m, 9H, CH_3), 2.07–1.86 (m, 2H, CH_2), 2.92–2.79 (m, 1H, CH), 4.26–4.10 (m, 6H, CH_2); HRMS, $(M + H)^+$ = 253.1207, $C_{10}H_{22}O_5P$ requires 253.1205, $(M + Na)^+$ = 275.1028, $C_{10}H_{21}O_5PNa$ requires 275.1019.

*Diethyl 1-(Ethoxycarbonyl)butylphosphonate (**2b**) (Table 2, Entry 10).* Yield: 71%; ^{31}P NMR ($CDCl_3$) δ: 23.10, δ_P: [35] 20.3; ^{13}C NMR ($CDCl_3$) δ: 13.6 (s, CH_3), 14.1 (s, CH_3), 16.3 (d, J = 2.4, CH_3), 16.4 (d, J = 2.1, CH_3), 21.6 (d, J = 15.4, CH_2), 29.0 (d, J = 5.1, CH_2), 45.7 (d, J = 131.4, CH), 61.3 (s, OCH_2), 62.6 (d, J = 6.6, $POCH_2$), 62.7 (d, J = 6.1, $POCH_2$), 169.3 (d, J = 4.8, C=O); ^{1}H NMR ($CDCl_3$) δ: 0.93 (t, 3H, J = 7.3, CH_3), 1.48–1.27 (m, 2H + 3H + 6H, CH_2, CH_3), 1.88–1.74 (m, 1H, CH_2), 2.07–1.90 (m, 1H, CH_2), 3.01–2.89 (m, 1H, CH), 4.25–4.10 (m, 6H, OCH_2); HRMS, $(M + H)^+$ = 267.1360, $C_{11}H_{24}O_5P$ requires 267.1361, $(M + Na)^+$ = 289.1181, $C_{11}H_{23}O_5PNa$ requires 289.1175.

*Diethyl 1-(Ethoxycarbonyl)pentylphosphonate (**2c**) (Table 2, Entry 12).* Yield: 70%; ^{31}P NMR ($CDCl_3$) δ: 23.8; ^{13}C NMR [36] ($CDCl_3$) δ: 13.8 (s, CH_3), 14.2 (s, CH_3), 16.4 (d, J = 2.4, CH_3), 16.4 (d, J = 2.1, CH_3), 22.2 (s, CH_2), 26.8 (d, J = 5.0, CH_2), 30.6 (d, J = 14.9, CH_2), 45.9 (d, J = 131.2, CH), 61.3 (s, OCH_2), 62.6 (d, J = 6.4, $POCH_2$), 62.7 (d, J = 6.1, $POCH_2$), 169.2 (d, J = 4.7, C=O); ^{1}H NMR [36] ($CDCl_3$) δ: 0.90 (t, 3H, J = 6.6, CH_3), 1.42–1.27 (m, 3H + 6H + 4H, CH_2, CH_3), 2.06–1.77 (m, 2H, CH_2), 3.00–2.86 (m, 1H, CH), 4.25–4.10 (m, 6H, OCH_2); HRMS, $(M + H)^+$ = 281.1519, $C_{12}H_{26}O_5P$ requires 281.1518, $(M + Na)^+$ = 303.1343, $C_{12}H_{25}O_5PNa$ requires 303.1332.

*Diethyl 2-Phenyl-1-(ethoxycarbonyl)ethylphosphonate (**2d**) (Table 2, Entry 13).* Yield: 53%; ^{31}P NMR ($CDCl_3$) δ: 22.0; ^{13}C NMR [37] ($CDCl_3$) δ: 14.1 (s, CH_3), 16.4 (d, J = 2.3, CH_3), 16.5 (d, J = 2.1, CH_3), 32.9 (d, J = 4.4, CH_2), 47.8 (d, J = 129.2, CH), 61.4 (s, CH_2), 62.9 (d, J = 3.7, CH_2), 63.0 (d, J = 6.5, CH_2), 126.8 (s, Ar), 128.6 (d, J = 7.3, Ar), 129.4 (d, J = 242.1, Ar), 138.5 (d, J = 16.0, Ar), 168.5 (d, J = 4.7, C=O); ^{1}H NMR [38] ($CDCl_3$) δ: 1.14 (t, 3H, J = 7.1, CH_3), 1.35 (t, 6H, J = 7.1, CH_3), 3.33–2.92 (m, 2H + 1H, CH_2, CH), 4.23–4.06

(m, 6H, CH_2), 7.29–7.18 (m, 5H, ArH); HRMS, $(M + H)^+ = 315.1365$, $C_{15}H_{24}O_5P$ requires 315.1361, $(M + Na)^+ = 337.1187$, $C_{15}H_{23}O_5PNa$ requires 337.1175.

*General Procedure for the Alkylation of Diethyl Ethoxycarbonylmethylphosphonate (**1**) under Traditional Thermal Conditions*

A mixture of 0.40 g (1.78 mmol) of diethyl ethoxycarbonylmethylphosphonate (**1**), 2.14 mmol of the alkylating agent (0.17 mL of EtI, 0.19 mL of *n*-propyl bromide, 0.23 mL of *n*-butyl bromide, and 0.25 mL of benzyl bromide), 0.25 g (1.78 mmol) of K_2CO_3 and 0.040 g (0.18 mmol) of TEBAC (variation A), or 0.63 g (1.78 mmol) of Cs_2CO_3 (instead of K_2CO_3 and TEBAC) (variation B) in 10 mL of acetonitrile was stirred at the boiling point for 24 h. Then, the mixture was filtrated, the solid was washed with 3 mL of acetonitrile, and the combined organic phase was concentrated. The oil so obtained was taken up in 6 mL of dichloromethane and filtered through a small silica gel layer. The residue was analyzed by GC. For details, see Table 3.

ACKNOWLEDGMENTS

This work is connected to the scientific program of the "Development of quality-oriented and harmonized R + D + I strategy and functional model at BME" project. This project is supported by the New Széchenyi Plan (Project ID: TÁMOP-4.2.1/B-09/1/KMR-2010-0002).

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