Pergamon

Tetrahedron, Vol. 53, No. 21, pp. 7291-7304, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00405-5

A New, Effective Approach for the C-C Bond Formation Utilizing 1-, 2- and 3-Phosphonyl Substituted Radicals Derived From Iodoalkylphosphonates and *n*-$Bu_3SnH/Et_3B/O_2$ System[1]

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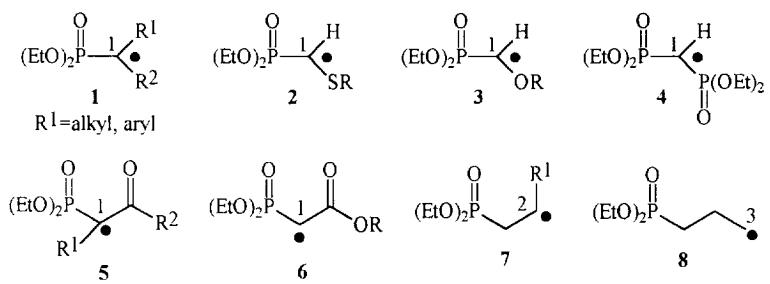
Abstract: A new, practical synthesis of highly substituted phosphonates utilizing 1-, 2- and 3-phosphonyl substituted radicals derived from iodoalkylphosphonates and a catalytic or stoichiometric amounts of the *n*-$Bu_3SnH/Et_3B/O_2$ reagent system is described. © 1997 Elsevier Science Ltd.

INTRODUCTION

Phosphonates constitute an important class of heteroorganic compounds in view of their application as popular olefination reagents[2] and a fact that some of them and their derivatives-phosphonic acids and salts were recognized as biologically active and technologically important compounds.[3] A multigram synthesis of simple phosphonates can be easily accomplished utilizing, for instance, the Arbuzov or Michaelis-Becker reactions.[4] However, a synthesis of structurally more complicated compounds sometimes creates a problem. Therefore, formation of the new carbon-carbon bond at the required position in the phosphonate chain is an essential and practical aspect of chemistry of phosphonates and their derivatives. Having this in mind, we have recently synthesized 1-,2- and 3-phosphonyl substituted radicals **1-8**[1,3c,5] (Scheme 1) and elaborated a new, free-radical approach for the C-C bond formation in phosphonates under reductive conditions.



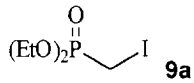
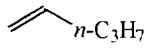
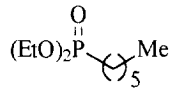
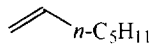
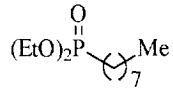
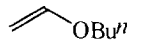
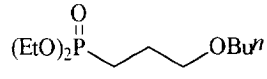
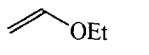
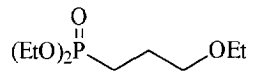
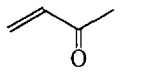
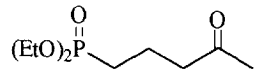
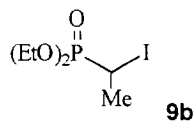
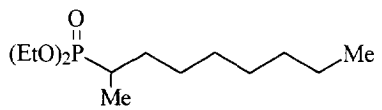
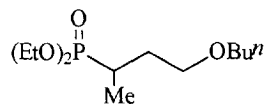
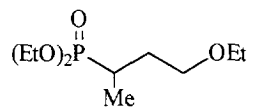
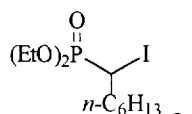
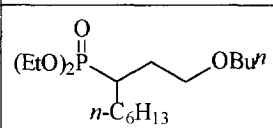
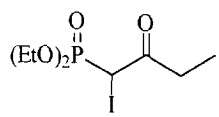
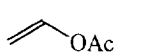
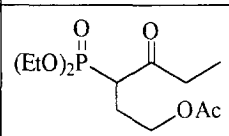
Scheme 1

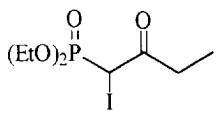
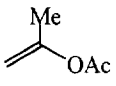
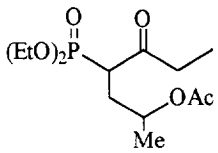
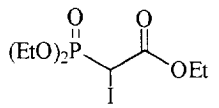
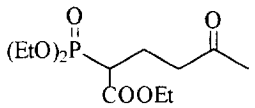
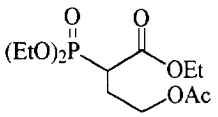
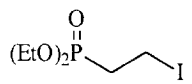
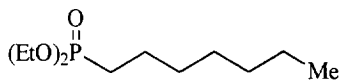
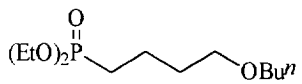
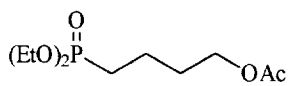
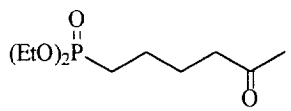
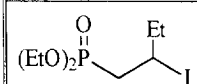
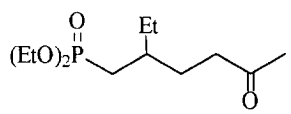
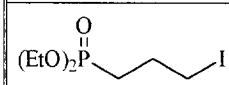
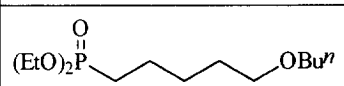
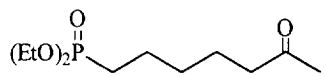
This new methodology can be generalized for the formation of the C_1, C_2...C_n-C phosphonate bonds from the corresponding C_1, C_2...C_n phosphonyl substituted radicals and alkenes or alkynes because, as we have recently found,[3c,5] n-phosphonyl radicals ($n \geq 3$) behave as simple, alkyl radicals, chemistry of which is already known.[6] Application of a typical *n*-Bu_3SnH/AIBN reagent system in these reactions for generation of the radical species possesses, however, a few drawbacks: a) a relatively small reaction scale limited by the use of a syringe pump technique for a slow addition of tin reagents, b) high reaction temperatures (boiling benzene or toluene for the effective decomposition of AIBN), c) at least stoichiometric amounts of tin salts (difficult to remove quantitatively during the workup procedure and ecologically dangerous), d) moderate reaction yields. During our studies on utilization of α-phoshoryl sulfides and selenides[3c] in synthesis of functionalized phosphonates, other reagents and radical initiators were also utilized (R_3SnX (cat.)/$NaBH_4$/UV light/25°C or *n*-Bu_3SnH/Et_3B/O_2/25°C) in order to overcome some of these drawback (a, b, c), however, the reaction yields still remained moderate and rather unsatisfactory from the synthetic point of view. Therefore, in this paper, we would like to disclose the new experimental procedure which is not limited to the magnitude of the reaction scale, is relatively high yielding and allows one to perform the reaction in a broad range of low temperatures (*vide infra*, Figure 1), thus making the whole synthesis of substituted phosphonates more practical and effective.

RESULTS AND DISCUSSION

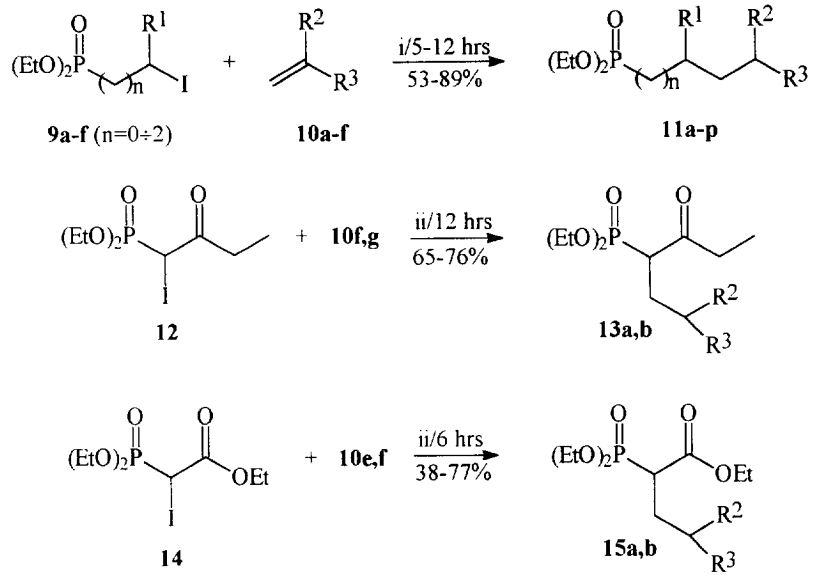
The new procedure utilizes 1-, 2- and 3-iodo-substituted phosphonates **9a-f**, **12** and **14** (Scheme 2) as precursors of the 1-, 2- and 3-phosphonyl substituted radicals **1**, **5-8**, terminally unsubstituted alkenes **10** and commercially available, *n*-hexane solution of triethyl borane in the presence of the air oxygen as the radical initiator[7] under reductive conditions (*n*-Bu_3SnCl-cat./$NaBH_4$ or *n*-Bu_3SnH). In the case of precursors **12** and **14**, the catalytic *n*-Bu_3SnCl/$NaBH_4$ reagents system had to be replaced by the stoichiometric amount of *n*-Bu_3SnH, most probably due to the competitive reaction of tri-*n*-butyltin radicals with the 2-oxoalkylphosphonyl, carbonyl group.[8] New reactions were generally carried out at low temperatures within 5-12 hrs. The main reaction products (P)-**11a-p**, **13a,b** and **15a,b** were accompanied by varying amounts of the reduced substrates (R)-(I → H) in the P/R ratios given in Table 1. An inspection of the table shows that the discussed reactions lead to higher reaction yields than those in which we used other phosphonyl radical precursors (X=Cl, Br, SR, SeR) and reaction conditions[1,3c,5]. It is also worthy to note that diethyl 1-iodomethylphosphonate, earlier used by us as the radical precursor, gave with *n*-butoxyethene only 13-20% yield of the corresponding product at elevated temperatures (boiling cyclopentane or benzene with AIBN/*n*-Bu_3SnH).[5a] Under the low temperature reaction conditions of the present method, good yields were obtained for electrophilic and nucleophilic 1-, 2- and 3-phosphonyl substituted radicals synthesized from the corresponding iodoalkylphosphonates and reacting with both electron-rich and -deficient alkenes. These ambiphilic properties were manifested in comparable yields of the products (see, for instance **11c**-76%, **11e**-88% and **11o**-70%, **11p**-82%).

Table 1. Reactions of 1-, 2,- 3-phosphonyl substituted radicals with alkenes.

Substrate	Alkene	Product	Procedure *a*	Yield [%] *b*	P/R *c*
 **9a**	 **10a**	 **11a**	**A1**	71	85/25
	 **10b**	 **11b**	**A1**	77	94/6
	 **10c**	 **11c**	**A2** **B**	76 75	81/19 80/20
	 **10d**	 **11d**	**A1**	53	58/42
	 **10e**	 **11e**	**A3**	88	91/9
 **9b**	**10b**	 **11f**	**A1**	73	79/21
	10c	 **11g**	**A2** **B**	80 82	86/14 89/11
	10d	 **11h**	**A1**	81	84/16
 **9c**	**10c**	 **11i**	**A1**	60	64/36
 **12**	 **10f**	 **13a**	**C**	65	73/27

 **12**	 **10g**	 **13b**	**C**	76	80/20
 **13**	**10e**	 **15a**	**C**	77	82/18
	10f	 **15b**	**C**	38 (76)*c*	79/21
 **9d**	**10a**	 **11j**	**A1**	75	80/20
	10c	 **11k**	**A2** **B**	78 78	84/16 85/15
	10f	 **11l**	**A3**	81	87/13
	10e	 **11m**	**A3** **B**	89 89	95/5 95/5
 **9e**	**10e**	 **11n**	**A1**	68 *d*	72/28
 **9f**	**10c**	 **11o**	**A3**	70	76/24
	10e	 **11p**	**A2**	82	99/1

a - see Experimental Section; *b* - isolated yield; *c* - a product/reduced substrate ratio based on the ^{31}P-NMR spectroscopy; *d* - ref. 5c



i: *n*-Bu_3SnCl (cat.)/$NaBH_4$/Et_3B/O_2; -78°C
ii: *n*-$Bu_3SnH/Et_3B/O_2$; -78°C

Scheme 2

The possibility to carry out the reactions at low temperatures enabled us to utilize low boiling alkenes (pent-1-ene and ethoxyethene) to give products **11a**, **11d** and **11h** in 71, 53 and 81% yields, respectively. The dependence of the reaction temperature versus yield and P/R ratio was also investigated to show the high and practical values of these factors at -78°C (see Figure 1).

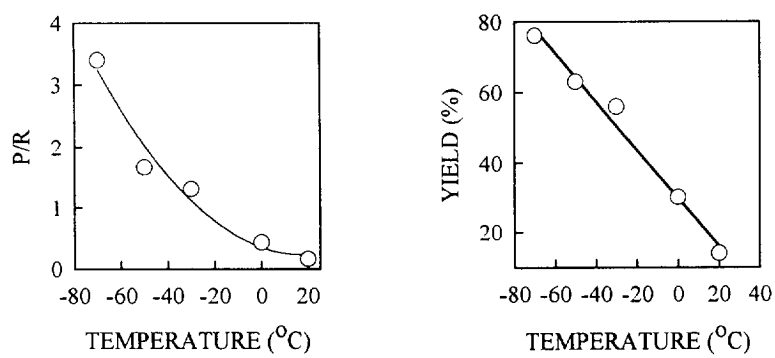
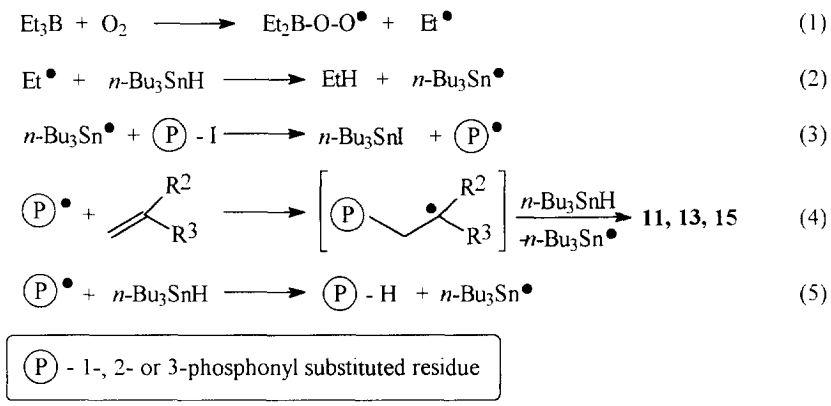


Figure 1

These findings were crucial for the utility of the presented, experimental procedure and corresponded well to the reaction mechanism (Scheme 3).

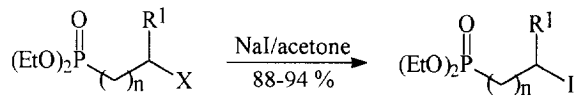


Scheme 3

According to this mechanism, triethyl borane undergoes autooxidation in the presence of the air oxygen with formation of ethyl radicals[9] (Eq 1, Scheme 3). This reaction must be, in comparison to higher temperatures, so slow at -78°C, that it guarantees a necessary low concentration of radicals, usually in other methods gained by a slow addition of reagents (syringe pump technique) and low concentration (compare procedures A2 and A3 with B). Thus, this reaction procedure does not require the argon protection and the special equipment that limits the reaction scale. The free access of the atmospheric oxygen to the reaction mixture (greater at lower temperatures) involves, however, the necessity of use of stoichiometric amount of triethyl borane otherwise the latter would be quickly consumed and the reaction would not be maintained. On the other hand, when a catalytic amount (20%) of Et_3B was employed in the absence of air (argon atmposphere), the conversion for 1-phosphonyl substituted radicals was 80% and for 3-phosphonyl substituted ones only 50%. This means that these reactions require only traces of oxygen, a complete removal of which is usually very difficult even under argon protection. In the next step of the reaction, ethyl radicals react with *n*-Bu_3SnH that is known to possess a high radical scavenging power ($k \approx 10^{-6}\ M^{-1}\ s^{-1}$)[10] to give tri-*n*-butyltin radicals (Eq 2, Scheme 3). Then, it was established that at least a catalytic amount of tin chloride was necessary to maintain the chain process. Thus, regarding a combination of two reagents: *n*-Bu_3SnH (cat.), $NaBH_4$ (1 eq.) and the initiator Et_3B (1 eq.)/O_2 in the reactions involving either *n*-$Bu_3SnCl/Et_3B/O_2$ in the absence of $NaBH_4$ or $NaBH_4/Et_3B/O_2$ in the absence of *n*-Bu_3SnCl, iodoalkyl phosphonates were regenerated. The next two steps (Eq 3 and 4, Scheme 3) are typical for the chain reaction involving tin radicals[6] and afford 1-, 2- or 3-phosphonyl substituted radicals (Eq 3) followed by the adduct radicals being reduced to the products **11**, **13** and **15** (Eq 4). The final step which is the undesired reduction reaction of the substrate radical (Eq 5, Scheme 3) deserves a comment. This reaction competes with the desired process leading to the products **11**, **13** and **15** (Eq 4) and this competition is reflected in the P/R ratios. The high values of the latter at low temperatures (see Figure 1) shows a beneficial

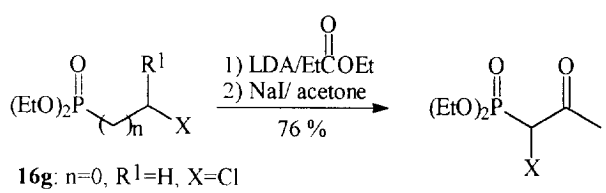
increase of the rate of the reduction reaction leading to the products (Eq 4) over the rate of the reduction reaction of the substrate radicals (Eq 5) in comparison to other methods used by us so far.[1,3e,5]. It was observed in particular for the reaction of diethyl methylselenyl-*n*-hexylphosphonate with methyl-vinyl ketone. Although the reaction was carried out with the *n*-$Bu_3SnH/Et_3B/O_2$ reagent system at -78°C (procedure C with 5eqs of alkene), the yields of the corresponding product (δ_P = 35.2ppm in $CDCl_3$) remained low ~34% (P/R=40/60). Although, selenides possess a bit lower reactivity towards tin radicals than iodides, it was characteristic that the yield did not increase much, as was observed for iodides, when the reaction temperature was lowered to -78°C (see Figure 1).

Most of iodo-substituted phosphonates were obtained by the Cl, Br or OTs/I exchange under conditions of the Finkelstein reaction using sodium iodide in acetone[11] (Scheme 4).



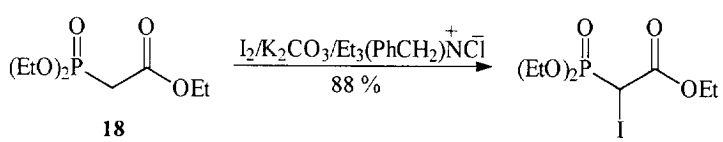
9a-9f

16a: n=0, R^1=H, X=OTs
16b: n=0, R^1=Me, X=Cl
16c: n=0, R^1=*n*-C_5H_{11}, X=Cl
16d: n=1, R^1=H, X=Br
16e: n=1, R^1=Et, X=OTs
16f: n=2, R^1=H, X=Cl



16g: n=0, R^1=H, X=Cl

93% → **17**: X=Cl, **12**: X=I



18 **14**

Scheme 4

The crude products were sufficiently pure to be used in the radical reactions without a special purification. Such a simplified procedure allowed one to use some iodo-substituted phosphonates which were thermally unstable, for instance **9e** and **12**. Synthesis of diethyl iodomethylphosphonate **9a** was carried out in two different ways starting from the common substrate, i.e. diethyl hydroxymethylphosphonate: 1) OH→Cl→I and 2) OH→OTs→I. However, a better overall yield and a simplicity of the workup procedure was achieved in

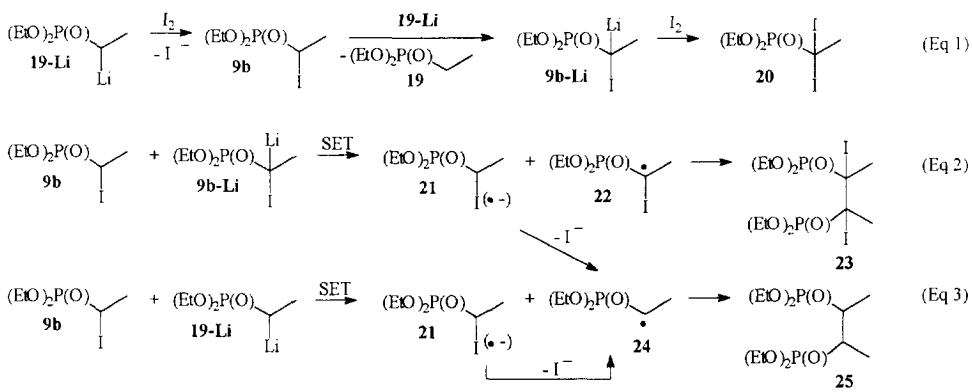
the latter process. Therefore, it was also applied to the synthesis of **9e**. The phosphonate **9a** was also obtained in the Arbuzov reaction of the commercially available diiodomethane and triethylphosphite according to the literature procedure.[5a] This reaction was, however, in our hands capricious and proceeded in a wide range of yields. The Finkelstein reaction applied for simple 1-, 2- and 3-haloalkylphosphophosphonates could be spread over 1 chloro-2-oxoalkylphosphonates, for example **17**, which was synthesized by the acylation reaction of the corresponding **16g-Li** with ethyl propionate (Scheme 4). Thus, diethyl 1-iodo-2-oxo-*n*-butylphosphonate **12** was obtained in 93% yield from **17**. Diethyl 1-iodo-1-carboethoxymethylphosphonate **14** was obtained from the corresponding phosphonate **18** under the phase transfer catalysis reaction conditions (I, K_2CO_3, $Et_3(PhCH_2)N^+Cl^-$) according to the modified procedure by Töke et al.[12] The modification was necessary because, we have found that **14** decomposed upon treatment with water (see Experimental).

Finally, we would like to disclose, briefly, our results on the reaction of diethyl 1-lithioethylphosphonate **19-Li** with iodine aimed at the direct synthesis of 1-alkyl-substituted 1-iodoalkylphosphonates as the radical precursors (Table 2).

Table 2. Reaction of diethyl 1-lithioethylphosphonate with x moles of iodine.

$MH^+(m/z)^a$	$(EtO)_2P(O)Et$ **19**	$(EtO)_2P(O)CH(I)Me$ **9b**	$(EtO)_2P(O)CI_2Me$ **20**	$[(EtO)_2P(O)CHMe]_2$ **25**	$[(EtO)_2P(O)C(I)Me]_2$ **23**
$\delta^{31}P$ (ppm)[b]	MH^+=167, $\delta^{31}P$=34.1	MH^+=293, $\delta^{31}P$=23.3	MH^+=419, $\delta^{31}P$=14.4	MH^+=331, $\delta^{31}P$=28.8	MH^+=583, $\delta^{31}P$=26.6
x=0.5	35	15	0	21	29
x=1	53-62	3-4	25-43	0	0-10
x=2	44	0	34	2	2

a) MSCI (isobutane), b) in [$CHCl_3$ (1.5ml)/$CDCl_3$ (3 drops)].



Scheme 5

The reaction, however, did not stop at the stage of monoiodoproduct **9b**. With 1 or 2 equivalents of the iodine used, the main product constituted diethyl 1,1-diiodoethylphosphonate **20** which could be easily separated from the accompanying starting material **19** by chromatography on silica gel.[13] The diiodo product **20** was formed

in the iodination reaction of the initially formed diethyl 1-lithio-1-iodoethylphosphonate **9b-Li** (Eq 1, Scheme 5) as a result of a difference in acidity of the phosphonate hydrogen atoms in a substrate **19-Li** and in the 1-heterosubstituted product **9b**[14]. Although the diiodoproduct **20** was not formed with 0.5 equivalent of iodine, the yield of the monoiodoproduct **9b** remained low (15%). In this case, the mechanism of the proton exchange (*vide supra*) is accompanied by the single electron transfer (SET) induced radical type process, well evidenced by Töke et al[12] with the ESR technique for 1-iodophosphonoacetic esters and leading to the formation of two bisphosphonyl dimers **23** and **25** (Eq 2 and 3, Scheme 5). The source of electrons in the two SET processes are 1-lithio-1-iodoethylphosphonate **9b-Li** (Eq 2) and 1-lithioethylphosphonate **19-Li** (Eq 3) which are transferred onto 1-iodoethylphosphonate **9b** to form the 1-iodoethylphosphonyl radical anion **21** and two 1-phosphonyl substituted radicals: 1 iodoethylphosphonyl radical **22** (Eq 2) and ethylphosphonyl one **24** (Eq 3). Thus, the direct iodination of substituted 1-lithioalkylphosphonates with iodine is not a practical method for the synthesis of 1-iodoalkylphosphonates.[15]

In conclusion, in this paper, an effective modification of our free radical approach to the synthesis of functionalized phosphonates is described. The new protocol is based on application of 1-, 2- and 3-phosphonyl substituted radicals derived from the relevant iodo-substituted phosphonates. Its advantages involve: 1) easy substrates that can be applied even in a crude form; 2) a simplicity of the reaction procedure that does not require the argon protection and a syringe pump technique limiting the reaction scale; 3) relatively high reaction yields in comparison to other free radical syntheses of substituted phosphonates (the 76% yield for **11c** in the present method and the 13-20% yield using the *n*-Bu_3SnH/AIBN reagents system); 4) a catalytic usage of tin salts with exception of the procedure for the radicals **5** and **6**; 5) a low reaction temperature (-78°C) allowing an use of thermally sensitive substrates and low boiling alkenes; 6) expected greater reaction control and stereocontrol at low reaction temperatures. Thus, this work constitutes a summary of our investigations on the free-radical synthesis of functionalized phosphonates utilizing the intermolecular reaction of 1-, 2- and 3-phosphonyl substituted radicals with alkenes.

EXPERIMENTAL SECTION

The ^{1}H-NMR (200 MHz) and ^{31}P-NMR (81MHz) spectra were recorded using a Bruker AC 200 spectrometer. The mass spectra were obtained using a Finnigan Mat 95 spectrometer. The models A and A-D of a syringe pump (Razel Scientific Instruments Inc.) were employed for a slow addition of tin reagents. Flash column chromatography was performed using a Merck silica gel (60, 230-400 mesh) and a gradient of solvents (toluene/acetone, n-hexane/acetone or n-hexane/ethyl acetate).

All reagents were of commercial quality or were purified before use. Organic solvents were purified by standard procedures. Toluene was deaerated with stirring under vacuum and kept under argon. All alkenes were commercial reagents (Aldrich Chemical Co.) and were finally purified by a medium pressure distillation before use.

The free radical reaction of ***9, 12 and 14*** *with alkenes* ***10****; General procedures for synthesis of phosphonates* ***11, 13 and 15****.*

Procedures A1, A2 and A3 : To a stirred cold (-78°C, acetone/dry ice) solution containing iodosubstituted phosphonates **9** (1mmol), the corresponding alkene **10** (10 mmol - procedure **A1**, 30 mmol - procedure **A2**, 5 mmol - procedure **A3**), *n*-Bu_3SnCl (54.2µl, 0.2 mmol) and $NaBH_4$ (75.7mg, 2mmol) in dry toluene (30 ml - procedure **A1** and **A3**; 15 ml - procedure **A2**), a solution of Et_3B (1.1 mmol, 1.1 ml, 1M solution in *n*-hexane) in dry toluene (30 ml) was added in two portions, within the 4hrs intervals. The resulting mixture was stirred for 8 - 12hrs at -78°C under room atmosphere. The progress of reactions was monitored by TLC or ^{31}P-NMR spectrometry. When the reaction was completed, the solution was warmed to room temperature and the solvents were evaporated. The crude product was purified by column chromatography over silica gel using a gradient of AcOEt/*n*-hexane as eluent to give pure phosphonates **11** in yields which are given in Table 1.

Procedure B. As in procedure **A.** A syringe pump was used for a slow addition of a solution of *n*-Bu_3SnCl (54.2µl, 0.2 mmol) and Et_3B (1.1 mmol, 1.1 ml, 1M solution in *n*-hexane) in toluene (14 ml) to the reaction mixture within 6-8hrs at -78°C. The crude product was purified as in procedure **A**.

Procedure C. As in procedure **A**. The *n*-$Bu_3SnCl/NaBH_4$ reagents system was replaced by *n*-Bu_3SnH. A syringe pump was used for addition of a solution of *n*-Bu_3SnH (1.4 mmol, 376.5µl) and Et_3B (1.1 mmol, 1.1 ml, 1M solution in *n*-hexane) in toluene (14 ml) to the reaction mixture within 6-8hrs at -78°C. After the addition was completed, the reaction mixture was stirred within 2hrs. The crude product was purified as in procedure **A**. This procedure was employed for synthesis of phosphonates **13** and **15**.

Spectral data for *n*-alkylphosphonates **11a**, **11b** and **11j** were identical with those reported in literature and obtained from the original samples[5c]. Spectral data of the compounds **11c-e** (Ref. 5a), **11f-i** (Ref. 3c), **11k** (Ref. 5c), **11m-p** (Ref. 5c), **13a-b** (Ref. 1) were identical with those reported by us earlier.

Diethyl 4-acetoxy-n-butylphosphonate **11l**; oil, ^{1}H-NMR ($CDCl_3$), δ = 1.31 (t, 6H, $^3J_{H-H}$=7.1Hz, $POCH_2\underline{CH_3}$); 1.55÷1.92 (m, 6H, $P(\underline{CH_2})_3$), 2.01 (s, 3H, $OC(O)\underline{CH_3}$); 4.02÷4.15 (m, 6H, $POCH_2CH_3$ and $\underline{CH_2}OAc$); ^{31}P-NMR ($CDCl_3$), δ = 33.1ppm; Anal. for $C_{10}H_{21}O_5P$: Calcd/Found- C-46.87/46.72; H-9.83/9.81.

Diethyl 1-carboethoxy-4-oxo-n-pentylphosphonate **15a**; oil; ^{1}H-NMR ($CDCl_3$), δ = 1.25 (t, 3H, $^3J_{H-H}$=7.1Hz, $C(O)OCH_2\underline{CH_3}$); 1.28 (t, 6H, $^3J_{H-H}$=7.1Hz, $POCH_2\underline{CH_3}$); 1.57÷1.66 (m, 2H, $PCHC\underline{H_2}$); 2.19 (s, 3H, $C(O)\underline{CH_3}$); 2.37÷2.58 (m, 2H, $\underline{CH_2}C(O)CH_3$); 2.85÷3.14 (m, 1H, $PC\underline{H}$);); 4.01÷4.25 (m, 4H, $POC\underline{H_2}CH_3$); 4.12 (q, 2H, $^3J_{H-H}$=7.1Hz, $C(O)OC\underline{H_2}$); ^{31}P-NMR ($CDCl_3$), δ = 24.3ppm; MS-EI (15eV, m/z, %)-294 ($M^{+\cdot}$, 42), 237(100), 208(19), 139 (50); MS-HR-CI: Anal. for $C_{12}H_{23}O_6P$: Calcd/Found-294.1232/294.1231.

Diethyl 1-carboethoxy-4-acyl-n-butylphosphonate **15b**; oil; ^{1}H-NMR ($CDCl_3$), δ=1.27 (t, 3H, $^3J_{H-H}$=7.1Hz, $C(O)OCH_2C\underline{H}_3$); 1.31 (t, 6H, $^3J_{H-H}$=7.1Hz, $POCH_2C\underline{H}_3$); 2.00 (s, 3H, $O(O)C\underline{H}_3$); 2.05÷2.38 (m, 4H, $PCHC\underline{H}_2C\underline{H}_2$); 2.96 (ddd, 1H, $^3J_{H-H_A}$=10.4Hz, $^3J_{H-H_B}$=4.2Hz, $^2J_{H-P}$=23.3Hz, $PC\underline{H}$), 4.01÷4.31 (m, 6H, $POC\underline{H}_2CH_3$; $C(O)OC\underline{H}_2$); ^{31}P-NMR ($CDCl_3$), δ = 22.6ppm; MS-EI (70eV, m/z, %)-310 (M^+, 1), 251(15), 230(56), 223(75), 197(31), 195(24), 165(26), 152(27), 43(100); MS-HR-CI: Anal. for $C_{12}H_{23}O_7P$: Calcd/Found-310.1181/310.1180.

Diethyl methylphosphonate, diethyl ethylphosphonate, diethyl n-heptylphosphonate, diethyl n-propyl-phosphonate, diethyl 2-oxo-n-butylphosphonate, diethyl carboethoxy-methylphosphonate were obtained as by-products as the result of reduction of the corresponding precursors **9a-d**, **9f**, **12**, **14** in yields given in Table 1 (as R). All of these phosphonates have a good agreement of physical and spectroscopic data with those obtained from the original samples.

Synthesis of radical precursors. General procedures for synthesis of iodo-substituted phosphonates **9, 12** *and* **14** *from chloro-, bromo- or tosyl-substituted phosphonates.*

To a stirred solution of the phosphonate **16** or **17** (5mmol) in dry acetone (50ml), anhydrous NaI (3.0g, 20mmol) was added in one portion. The resulting mixture was stirred overnight for 12-16hrs (for phosphonates **16a** and **17**) or refuxed 5-8hrs (for phosphonates **16b-d**, **16f**). The end of the reaction was monitored by ^{31}PNMR technique. Then the reaction mixture was filtered and the solvent was evaporated. The crude products were dissolved in dry benzene (3×30ml) and carefully evaporated to give analytically pure iodo-phosphonates **9** and **12** in almost quantitative yields. Before use in radical reactions all of the precursors were dissolved in $CHCl_3$, the resulting solution was filtered off through the $Na_2S_2O_3$ pad and evaporated.

Diethyl iodomethylphosphonate **9a** was prepared from O-(p-toluenesulfonyl)-methyl-phosphonate in 88% yield. Spectral data of this compound was identical with that reported by us earlier[5a]. n_D^{20}=1.4978; ^{31}P-NMR ($CDCl_3$), δ = 20.8ppm; MS-EI (15eV, m/z, %)-278(M^+, 62), 250(100), 222(45), 151(42), 123(68), 95(75); Anal. for $C_5H_{12}O_3PI$: Calcd/Found-C-21.60/21.50; H-4.35/4.33.

Diethyl 1-iodoethylphosphonate **9b** was prepared from diethyl 1-chloroethylphosphonate[16]. Yield 94%. n_D^{20}=1.5120; ^{1}H-NMR ($CDCl_3$), δ = 1.34 (t, 3H, $^3J_{H-H}$=7.1Hz, $POCH_2C\underline{H}_3$); 1.67 (dd, 3H, $^3J_{H-H}$=7.2Hz, $^3J_{H-P}$=16.6Hz, $CHC\underline{H}_3$); 3.95 (dq, 1H, $^3J_{H-H}$=7.1Hz, $^2J_{H-P}$=9.7Hz, $PC\underline{H}I$); 4.19 (m, 4H, $POC\underline{H}_2CH_3$); ^{31}P-NMR ($CDCl_3$), δ = 21.6ppm; MS-EI (15eV, m/z, %)-no M^+, 165(16), 137(35), 109(100); Anal. for $C_6H_{14}O_3PI$: Calcd/Found-C-24.68/24.54; H-4.83/4.79.

Diethyl 1-iodo-n-heptylphosphonate **9c** was prepared from diethyl 1-chloro-*n*-heptyl-phosphonate[16]. Yield 90%. oil; ^{1}H-NMR ($CDCl_3$), δ = 0.84 (t, 3H, $^3J_{H-H}$=7.0Hz, $(CH_2)_5C\underline{H}_3$); 1.31 (t, 6H, $^3J_{H-H}$=7.1Hz, $POCH_2C\underline{H}_3$); 1.24÷2.18 (m, 10H, $(C\underline{H}_2)_5$); 3.78÷3.86 (m, 1H, PC<u>H</u>); 4.02÷4.16 (m, 4H, $POC\underline{H}_2CH_3$); ^{31}P-NMR ($CDCl_3$), δ = 20.8ppm; Anal. for $C_{11}H_{24}O_3PI$: Calcd/Found-C-56.15/55.94; H-10.28/ 10.11.

Diethyl 2-iodoethylphosphonate **9d** was prepared from diethyl 2-bromoethylphosphonate. Yield 93%. n_D^{20}=1.5184; ^{1}H-NMR ($CDCl_3$), δ = 1.27 (t, 6H, $^3J_{H-H}$=7.1Hz, $POCH_2C\underline{H}_3$); 2.35 (m, 2H, $CH_2C\underline{H}_2$); 3.27 (m, 2H, PC<u>H</u>); 4.02÷4.15 (m, 4H, $POC\underline{H}_2CH_3$); ^{31}P-NMR ($CDCl_3$), δ = 26.7ppm; MS-EI (15eV, m/z, %)-292 ($M^{+\cdot}$, 21), 165(76), 138(18) 137(84), 109(100); Anal. for $C_6H_{14}O_3PI$: Calcd/Found-C-24.68/24.75; H-4.83/4.88.

Diethyl 3-iodo-n-propylphosphonate **9f** was prepared from diethyl 3-chloro-*n*-propylphosphonate[5c]. Yield 88%. n_D^{20}=1.4880; ^{1}H-NMR ($CDCl_3$), δ = 1.31 (t, 3H, $^3J_{H-H}$=7.1Hz, $POCH_2C\underline{H}_3$); 1.74÷1.91 (m, 2H, $PCH_2C\underline{H}_2$); 2.02÷2.18 (m, 2H, PC<u>H</u>$_2$); 3.24 (t, 2H, $^3J_{H-H}$=7.1Hz, $C\underline{H}_2I$); 4.02÷4.13 (m, 4H, $POC\underline{H}_2CH_3$); ^{31}P-NMR ($CDCl_3$), δ = 30.1ppm; MS-EI (15eV, m/z, %)-306 (M^+,14), 179(88), 152(75), 151(20), 125(67), 123(100); Anal. for $C_7H_{16}O_3PI$: Calcd/Found-C-27.47/27.45; H-5.27/5.24.

Diethyl 1-iodo-2-oxo-n-butylphosphonate **12** was prepared from diethyl 1-chloro-2-oxo-*n*-butylphosphonate. Yield 93%. oil; ^{1}H-NMR ($CDCl_3$), δ = 1.10 (t, 3H, $^3J_{H-H}$=7.0 Hz, $C(O)CH_2C\underline{H}_3$); 1.34 (t, 6H, $^3J_{H-H}$=7.0Hz, $POCH_2C\underline{H}_3$); 2.54÷2.98 (m, 2H, $C(O)C\underline{H}_2CH_3$); 4.03÷4.25 (m, 6H, $POC\underline{H}_2CH_3$); 4.43 (d, 1H, $^2J_{H-P}$=16.4 Hz, PCH); ^{31}P-NMR ($CDCl_3$), δ = 14.6ppm; Anal. for $C_8H_{16}O_4PI$: Calcd/Found-C-28.76/28.74; H-4.83/4.85 .

Diethyl 1-iodo-1-carboethoxy-methylphosphonate **14** was prepared according to the modified literature procedure[12] in a part concerning the workup. The reaction mixture was evaporated and the crude product was dissolved in chloroform. This solution was filtred through the powdered $Na_2S_2O_3\times5H_2O$ pad until decolorization (in our hands it cannot be washed with water due to the practically total decomposition). After evaporation of the solvent, the product **14** of a very good purity was further used in radical reactions. This product also decomposes on attempted distillation or chromatography over silica gel. Yield 88%. ^{1}H-NMR ($CDCl_3$), δ = 1.26 (t, 3H, $^3J_{H-H}$=7.1 Hz, $C(O)CH_2C\underline{H}_3$); 1.29 (t, 6H, $^3J_{H-H}$=7.0Hz, $POCH_2C\underline{H}_3$); 4.21 (q, 2H, $^3J_{H-H}$=7.1 Hz, $C(O)CH_2$); 4.15÷4.32 (m, 4H, $POC\underline{H}_2CH_3$); 4.34 (d, 1H, $^2J_{H-P}$= 12.9 Hz, PC<u>H</u>); ^{31}P-NMR ($CDCl_3$) δ = 15.7ppm; MS-EI (15eV, m/z, %)-350 ($M^{+\cdot}$, 57), 305(16), 214(28), 197(27), 179(40), 155(100), 151(22), 137(12), 127(22), 123(28); Anal. for $C_8H_{16}O_5PI$: Calcd/Found-C-27.45/27.50; H-4.61/4.67.

Diethyl O-(p-toluenesulfonyl)-methylphosphonate **16e** was obtained from diethyl hydroxymethyl-phosphonate[17] according to the procedure published by us earlier[5c] in 78% yield. n_D^{22}=1.4936;

^{1}H-NMR ($CDCl_3$), δ = 1.25 (t, 6H, $^3J_{H-H}$=7.0Hz, $POCH_2C\underline{H}_3$); 2.39 (s, 3H, p-C_6H_4-$C\underline{H}_3$); 4.00÷4.15 (m, 4H, $POC\underline{H}_2CH_3$); 4.12 (d, 1H, C$\underline{H}$, $^2J_{H-P}$=9.9Hz); 7.31, 7.73 (AB system, 4H, J_{AB}=84.6Hz, $C_6\underline{H}_4$-p-CH_3); ^{31}P-NMR ($CDCl_3$), δ = 15.8 ppm; Anal. for $C_{12}H_{19}O_6PS$: Calcd/Found-C- 44.72 /44.71; H-5.94 /6.01.

Diethyl 1-chloro-2-oxo-n-butylphosphonate **17** was prepared according to the literature procedure[18] with a good agreement of physical and spectroscopic data. ^{1}H-NMR ($CDCl_3$), δ=1.05 (t, 3H, $^3J_{H-H}$=7.1Hz, $C(O)CH_2C\underline{H}_3$); 1.32 (m, 6H, $POCH_2C\underline{H}_3$); 2.55÷3.01 (m, 2H, $C(O)C\underline{H}_2CH_3$); 4.05÷4.25 (m, 4H, $POC\underline{H}_2CH_3$); 4.48 (d, 1H, $^2J_{H-P}$=17.4Hz, PC$\underline{H}$Cl); ^{31}P-NMR ($CDCl_3$), δ=13.2ppm (lit.[18] δ = 13.1ppm; lit.[18] δ = 10.0ppm); Anal. for $C_8H_{16}O_4PCl$: Calcd/Found-C-39.60/39.54; H-6.65/6.65.

Reaction of diethyl 1-lithioethylphosphonate **19-Li** *with iodine*

To a stirred solution of diethyl ethylphosphonate **19** (0.166 g, 1 mmol) in dry tetrahydrofuran (15 ml), *n*-butyllithium in *n*-hexane (1 mmol, 1.4 M; 0.17 ml) was added at -78°C under argon atmosphere. After stirring for 15 min., a solution of iodine (0.5, 1 or 2 mmol) in tetrahydrofuran was added at -78°C and the reaction mixture was slowly warmed to 10-15°C. At this temperature, a saturated solution of aqueous ammonium chloride was added, the solvents were evaporated and the residue dissolved in methylene chloride was washed with aqueous solution of sodium thiosulfate and water. The organic phase was dried in darkness over anhydrous $MgSO_4$, filtered and evaporated to give the crude product which was analyzed by GC-MSCI, ^{1}H and ^{31}P-NMR techniques (see Table 2). In the case of use of 1 mmol of iodine (1:1 stoichiometry), diethyl diiodoethylphosphonate **20** was easily separated from the crude reaction mixture using the preparative TLC and ethyl acetate as the eluent. On the other hand, bisphosphonates **23** and **25** were difficult to separate by this technique, especially from large amounts of **19** and therefore they were characterized only by the GC-MSCI technique and ^{31}P-NMR spectroscopy (see Table 2).

Diethyl 1,1 diiodoethylphosphonate **20** oil; ^{1}H-NMR ($CDCl_3$), δ=1.39 (t, 6H, $^3J_{H-H}$=7.0 Hz, $C\underline{H}_3CH_2O$); 3.00 (d, 3H, $^3J_{H-P}$ 14.6Hz, P-C-$C\underline{H}_3$); 4.34 (m, 4H, $CH_3C\underline{H}_2O$); ^{31}P-NMR ($CHCl_3$/$CDCl_3$), δ=14.4 ppm; MSCI (m/z, isobutane) MH^+=419. This compound is unstable on standing at room temperature.

Acknowledgements: The authors wish to acknowledge Professor Marian Mikołajczyk for his helpful discussion.

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(*Received in UK* 17 *March* 1997; *accepted* 7 *April* 1997)