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A Free Radical Approach to Functionalization of Phosphonates Utilizing Novel 2- and 3-Phosphonyl Radicals[1].

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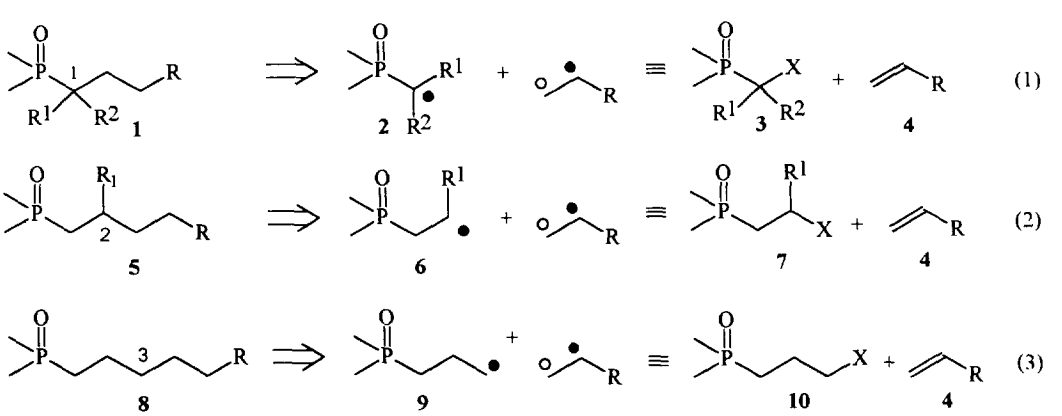
Abstract: A general method for the phosphonyl C_2,C_3-C bond formation under the free radical, reductive conditions is described. The new approach is based on the synthesis of novel 2- and 3- phosphonyl radicals **6**, **9** derived from the corresponding 2- and 3-halo (X=Cl, Br, I) substituted phosphonates **7**, **10** and their reaction with alkenes **4**. Functionalized phosphonates **5**, **8** possessing the 2+2 and 3+2 elongated carbon chain were obtained in 24÷73% yields. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

In a period of over two decades, radical reactions have emerged as a very powerful, synthetic transformations. The last years have brought rapid development in the use of radicals for the formation of the C-C and C-heteroatom bonds in regio- and stereocontrolled reactions[2]. A lot of fascinating results have been gained in this field and later applied in synthesis of target molecules[3].

In the course of our investigations on the chemistry of 1-heterosubstituted phosphonates[4], we have also switched to this challenging area. We have first, developed a direct synthesis of 1-phosphonyl radicals **2** (Scheme 1, Eq. 1) derived from 1-thio[5], 1-seleno[5] and 1-halo[6] substituted derivatives **3** and demonstrated their applications[7] including total synthesis of Methylenomycin B - a cyclopentanoid antibiotic[1].

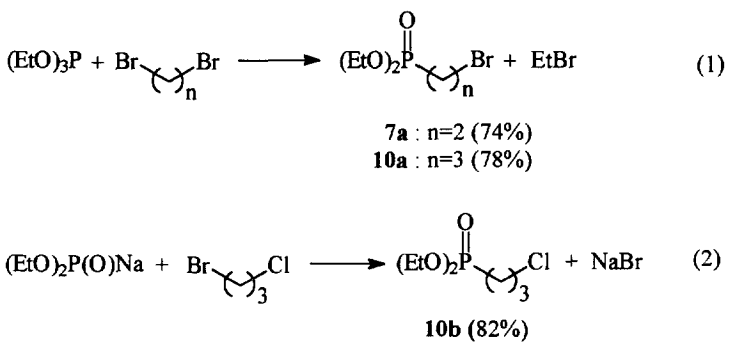


SCHEME 1

Although numerous methods exist for the preparation of phosphonates, most of them are restricted to the formation of the phosphonate C_1-P and C_1-C bonds[8]. A great synthetic value of stabilized phosphonates[4,9] requires more general methods of their synthesis which should be adequate to increasing demands of chemists. Having this in mind, we undertook a task to elaborate a novel, free radical approach to the synthesis of the phosphonates **1**, **5** and **8** utilizing the phosphonate C_1, C_2...Cn-C coupling reactions of the corresponding radical C_1, C_2...Cn species **2**, **6**, **9** with molecules containing terminal multiply bonds (Scheme 1, Eq. 1-3). Recently, we have published the first part of these investigations concerning the free radical C_1-C coupling reaction of the C_1 radicals **2** with alkenes or alkynes[6]. In this paper, we would like to disclose further results on the C_2-C and C_3-C coupling reactions. Free elongation of the phosphonate chain connected with the additional possibility of its functionalization, is particularly important in the synthesis of some products of biological interests, for instance such as sex pheromones[10].

RESULTS AND DISCUSSION

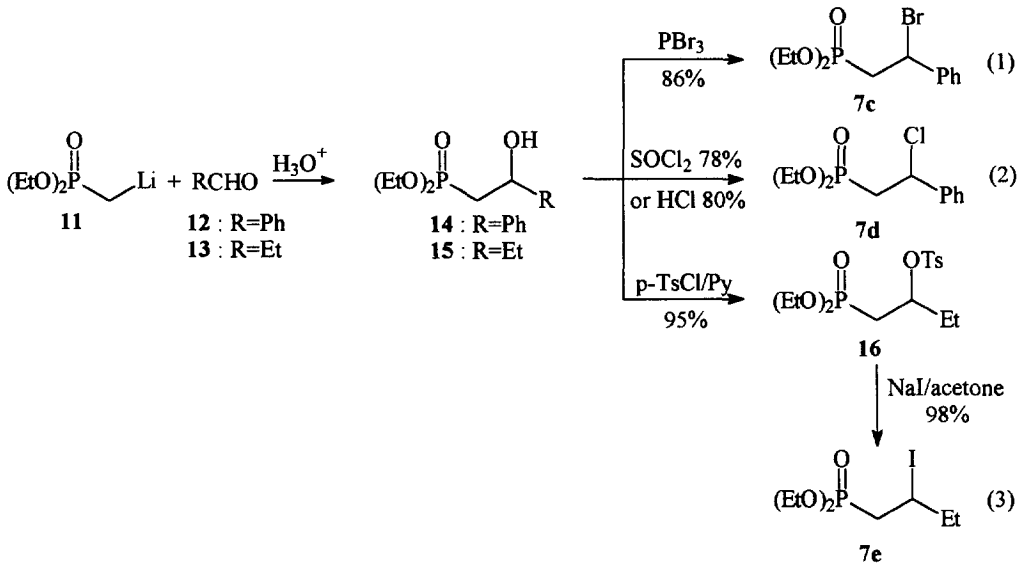
In the discussed reactions 2-bromo, 2-chloro, 2-iodo substituted phosphonates **7a-e** and 3-bromo **10a**, 3-chloro **10b** substituted ones were used as the radical precursors of 2-phosphonyl radicals **6** and 3-phosphonyl radicals **9**, respectively (Scheme 1, 2 and 3). Thus, unsubstituted 2-bromoethyl- **7a** and 3-bromo-n-propyl- **10a** phosphonates were synthesized in the Arbuzov reaction of the relevant 1,2-dibromoethane and 1,3-dibromopropane with triethyl phosphite (Scheme 2, Eq. 1). Diethyl 2-chloroethyl phosphonate **7b** was a commercial product, whereas 3-chloro-n-propyl one **10b** was obtained in the Michaelis-Becker reaction of 1-bromo-3-chloropropane with sodium diethyl phosphite (Scheme 2, Eq. 2).



SCHEME 2

Finally, 2-halo (X=Cl, Br, I) substituted phosphonates **7c-7e** were synthesized in the two (X=Cl, Br) or three (X=I) step reactions (Scheme 3, Eq. 1÷3). The first step involved condensation of diethyl lithiomethylphosphonate **11** with benzaldehyde **12** or n-propanal **13** to give the relevant 2-hydroxy substituted

phosphonates **14** and **15**[11]. The phosphonates **7c** and **7d** were obtained from the phosphonate **14** through conversion of the OH group to a halogen with phosphorus tribromide and concentrated hydrogen chloride (or $SOCl_2$), respectively (Scheme 3, Eq. 1, 2). The 2-iodo substituted phosphonate **7e** was synthesized *via* the OTs/I exchange from the corresponding tosylate **16** (Scheme 3, Eq. 3).

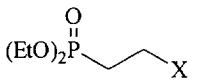
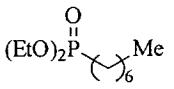
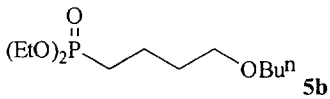
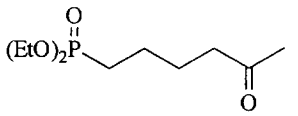
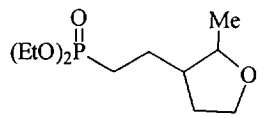
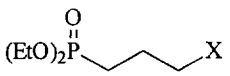
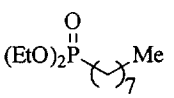
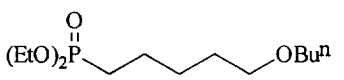
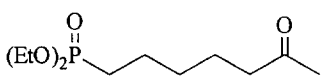
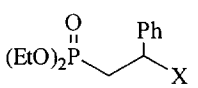
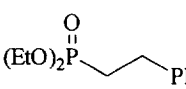
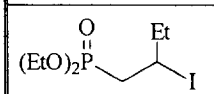
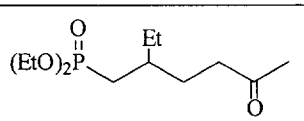


SCHEME 3.

As the olefin reagents **4**, both electron rich (n-butoxyethene, n-pentene-1, 4,5-dihydro-2-methylfuran, 3,4-dihydro-2-H-pyran, 3,4-dihydro-4-methoxy-2H-pyran) and electron deficient alkenes (3-buten-2-one) were chosen. The free radical reactions (Scheme 4, Table 1) of the phosphonate precursors **7** and **10** with excess of alkenes **4** (5-30 equivalents) were performed under the Giese's reductive conditions[2a] using n-Bu_3SnH or the n-$Bu_3SnCl/NaBH_4$ reagent system as its "in situ" generated equivalent, in combination with different radical initiators (UV light, azabisisobutyronitrile - AIBN or Et_3B/O_2). For the photochemical (UV light) or thermal (AIBN) initiations, the Aldrich micro photochemical reaction assembly and a syringe pump were employed, respectively. The Et_3B/O_2[12] initiation required the iodo precursor **7e**, and allowed to perform the reaction at lower temperatures (**7e** is unstable at elevated temperatures) and in an unrestricted scale.

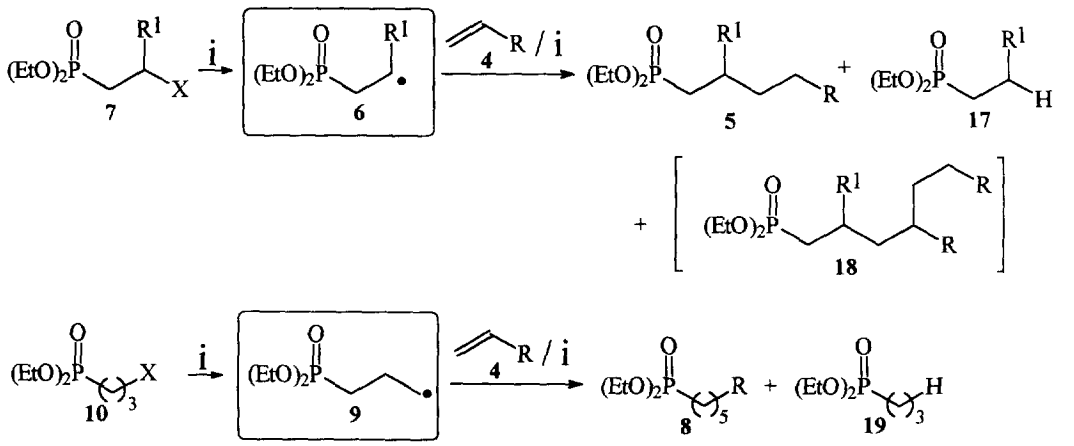
In a typical free radical reaction of **7** or **10** with **4**, the addition products (P)-**5**, **8** and reduced substrates (R)-**17**, **19** were obtained with the ratio P/R>1. When a large excess of alkene (30 equivs.) was used, traces of the corresponding diadduct **18** were detected in some cases (R=OBu, R^1=H, < 8% yield) by the GC-MSCI technique. Generally, the stoichiometry of the reagents was crucial for the reaction result. The experimental procedure used depended on whether electron rich or deficient alkene was employed. It was established for the reactions of n-butoxyethene with 2- or 3-bromoalkylphosphonates **7a** or **10a**, that the use of 1.3-1.5 equivalents of n-Bu_3SnH was sufficient to consume the whole phosphorus containing substrate. 1.7 equivalents

TABLE 1. Reactions of 2- and 3-phosphonyl radicals **6** and **9** with alkenes **4**.

Substrate	Product	Procedure *a*	Yield [%] *b*	P/R
 X = Br **7a** X = Cl **7b**	 **5a**	**C1**	55 *d*	1.09
		C2	58 *d*	1.17
	 **5b**	**A1**	43 *c*	1.34 *c*
			47 *d*	1.46 *d*
		A2	65 *c*	2.98 *c*
			65 *d*	2.92 *d*
		B	48 *c*	2.05 *c*
			52 *d*	1.88 *d*
	 **5c**	**A3**	63 *d*	2.48 *d*
	 **5d**	**A2**	24 *d*	0.25- -0.36
 X = Br **10a** X = Cl **10b**	 **8a**	**C2**	45 *d*	0.80
	 **8b**	**A2**	50 *d*	1.92 *d*
		B	46 *c*	1.41 *c*
			53 *d*	2.14 *d*
	 **8c**	**A3**	73 *d*	3.44
 X = Br **7c** X = Cl **7d**	 **17** (R^1=Ph)	**A2**	63 *c*	-
			88 *d*	-
		B	89 *d*	-
 **7e**	 **5e**	**D1**	68	2.58
		D2	68	2.54

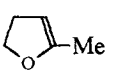
a - see Experimental Section; *b* - isolated yield; *c* - X=Cl; *d* - X=Br.

of n-Bu_3SnH were required to complete the reactions involving 2- or 3-chloroalkylphosphonates **7b** or **10b**. Bigger amounts of the hydride (up to 2.2 equivs.) did not worsen the reaction yields or the P/R ratios, both for chloro and bromo radical precursors. The optimum amount of n-butoxyethene for these precursors was established as 10 equivalents (procedure **A1**- see Experimental). The three fold increase of this amount for 2-haloethylphosphonates (**7a**, **7b**; procedure **A2**) caused the increase of the reaction yield (X=Cl: 43→65%; X=Br: 47→65%; see also Table 2).



i = n-Bu_3SnH or n-$Bu_3SnCl/NaBH_4$
+ initiator (AIBN, UV light or Et_3B/O_2)

X = Cl, Br, I
R^1 = H, Et, Ph

4a R = OBu^n
4b R = C(O)Me
4c R = n-C_3H_7
4d 

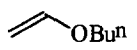
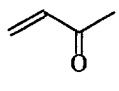
SCHEME 4

Slightly lesser effect was observed for 3-halo-n-propylphosphonates **10a**, **10b**. A further increase of the amount of n-butoxyethene (60 equivs.) did not improve the reaction yield and at the same time did not increase the amount of the diadduct **18** or other polymeric products. Application of the procedure **A2** to 5- and 6-membered vinyl ethers, such as 4,5-dihydro-2-methylfuran **4d**, 3,4-dihydro-2H-pyran and 3,4-dihydro-4-methoxy-2H-pyran resulted in reduction of the radical precursor **7a** and formation of the relevant products in low yields (**5d**, 24% yield). The experimental procedures **A1** and **A2** had to be modified for the electron deficient alkenes such as 3-buten-2-one. The new procedure **A3** involved only 5 equivs. of alkene and two fold lesser volume of the solvent giving up 73% yield of the reaction product **8c**. It was, namely, observed that in the standard procedure **A1** (with 10 equivs of alkene), the phosphonate radical precursor was not entirely consumed (Table 2). Thus, for the reactions involving 2- and 3-

bromoalkylphosphonates **7a**, **10a** and 3-buten-2-one **4b**, 50% of the unreacted, starting phosphonate was left, whereas for 2-chloroetylphosphonate **7b** - even 85%. The reason was a competitive consumption of the nucleophilic tri-n-butylstannyl radical by the electron deficient 3-buten-2-one. This effect was not observed for the four-fold lesser concentration of 3-buten-2-one and the solvent in the procedure **A3**. The stannylation reaction was practically not observed for the radical iodo precursors which usually are 10-100 times more reactive than the bromo ones[2a]. The new procedure **D1**, which was adopted for the iodo precursor **7e** possessed additional advantages: 1) could be performed at low or room temperatures what prevented thermal decomposition of **7e**, 2) could be performed on an unrestricted scale because did not require a syringe pump technique (compare the **D1** and **D2** procedures), 3) gave relatively high yields of products, 4) could be regarded as selective for iodides because the corresponding chlorides and bromides **7**, **10** did not react well with alkenes under these reaction conditions. The iodide approach opens a way for the synthesis of branched phosphonates which often are difficult to synthesize using usual methods of the phosphonate synthesis.

Initiation of the reaction by the UV light (procedures **C**) brought additional benefits, namely, allowed to perform the reaction of bromides with low boiling alkenes at room temperature (**5a**, 58%), (**8a**, 45%).

TABLE 2. Correlation between the amount of the alkene **4** and the reaction yields involving 1-, 2- and 3-phosphonyl radicals.

Alkene						
Equivalents of alkene	5	10	30	60	5	10
$(EtO)_2P(O)CH_2Cl$		55*				
$(EtO)_2P(O)CH_2Br$		32*			43	39*
$(EtO)_2P(O)CH_2I$		20*				
$(EtO)_2P(O)CH_2CH_2Br$	17	41	65	65	63	20*
$(EtO)_2P(O)CH_2CH_2CH_2Br$		23	50	48	73	23*

* ref. 6

Analysis of data from Table 1 and Table 2 leads to the conclusion that based on the selectivity requirements[2a], the matching of radical precursors to the electron rich n-butoxyethene decreases in the following order: 1->2->3-phosphonyl radical precursors. This bias was well observed for 1-chloro[6], 2-bromo and 3-bromo substituted precursors. Thus, the reaction yields of the corresponding addition products decreased in the order: 55, 41 and 23%, respectively (see Table 2). On the other hand, the matching to the electron deficient 3-buten-2-one stands in the opposite order: 1-< 2-<3-phosphonyl precursors. It was confirmed by the increasing yields of the relevant adduct products: 43, 63, 73%, respectively (Table 2). All these results indicate

that in contrast to the typically electrophilic 1-phosphonyl radicals, both 2- and 3-phosphonyl ones are nucleophilic in nature, although not in equal degree, due to the increasing distance between the radical carbon centre and the phosphoryl group. 3-Phosphonyl radicals can even be regarded as usual alkyl radicals. However, a small stabilizing effect of the phosphoryl group on the radical centre was observed for 2-phosphonyl radicals on comparison of the relative difference in yields of the reaction products for these radicals and 3- phosphonyl ones (41 and 23% for the unmatched n-butoxyethene **4a**; 63 and 73% for the matched 3-buten-2-one **4b**, respectively).

In conclusion, in this paper, novel 2- and 3-phosphonyl radicals **6**, **9** were synthesized under the reductive conditions and applied in the C_2,C_3-C phosphonyl bond formation reactions with alkenes **4**. This work in connection with our previous investigations on 1-phosphonyl radicals[6] **2**, allows the one, two or three carbon homologation of alkenes and synthesis of the corresponding phosphonates, importance of which is established in organic synthesis[4,9]. Through modification of the standard procedure **A1**, it was possible to perform these reactions effectively both with electron rich (procedure **A2**) and deficient (procedure **A3**) alkenes. Thus, our investigations brought us the following generalizations: 1) the influence of the phosphoryl group on the developing radical decreases in function of distance and reactions with the electron deficient alkenes are favoured in these cases; 2) the increase of concentration (less solvent) and amount of alkene favours the increase of the reaction yields with the electron rich alkenes; 3) iodides are radical precursors of choice for the reactions performed at low or room temperatures with the n-Bu_3SnH (or n-$Bu_3SnCl/NaBH_4$)/ Et_3B/O_2 reagent system which reduces the problem of the limited scale, usually accompanying the use of the syringe pump technique. Bromides and chlorides should be used for the reactions initiated thermally with AIBN, however, better yields were obtained with the former.

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.

Diethyl 2-Hydroxy-2-phenylethylphosphonate **14**

was obtained in the condensation reaction of diethyl lithiomethylphosphonate **11** (prepared from diethyl methyl phosphonate and stoichiometric amount of n-BuLi, THF, -78°C, Ar) with benzaldehyde **12** (-78°C÷25°C). Typical work-up and distillation using the Kugelrohr apparatus gave pure **14** in 94% yield. n_D^{22}=1.4361; ^{1}H-NMR ($CDCl_3$), δ = 1.29, 1.33 (2×t, 6H, $^3J_{H\text{-}H}$=7.1Hz, $POCH_2C\underline{H}_3$); 2.16÷2.30 (m, 2H, P-$C\underline{H}_2$); 3.15 (s, 1H, O$\underline{H}$); 4.01÷4.22 (m, 4H, $POC\underline{H}_2CH_3$); 5.12 (ddd, 1H, $^3J_{H\text{-}H_A}$=8.3Hz, $^3J_{H\text{-}H_B}$=6.7Hz, $^3J_{H\text{-}P}$=12.8Hz, $PCH_2C\underline{H}$); 7.22÷7.48 (m, 5H, $C_6\underline{H}_5$); ^{31}P-NMR ($CDCl_3$), δ = 29.7ppm; Anal. Calcd/Found: C-55.81/55.75; H-7.42 /7.39

Diethyl 2-Bromo-2-phenylethylphosphonate **7c**

was obtained from the phosphonate **14** using the two fold excess of PBr_3 (25°C, 8hrs). The reaction mixture was washed with aqueous solution of $NaHCO_3$ (1×), water (2×), dried over anhydrous $MgSO_4$, evaporated and distilled using the Kugelrohr apparatus to give pure **7c** in 86% yield. n_D^{22}=1.5035; ^{1}H-NMR ($CDCl_3$), δ = 1.10, 1.18 (2×t, 6H, $^3J_{H\text{-}H}$=7.0Hz, $POCH_2C\underline{H}_3$); 2.84 (ddd, 2H, $^3J_{H\text{-}H_A}$=8.4Hz, $^3J_{H\text{-}H_B}$=6.8Hz, $^2J_{H\text{-}P}$=18.2Hz, P-$C\underline{H}_2$); 3.69÷4.18 (m, 4H, $POC\underline{H}_2CH_3$); 5.25÷5.34 (m, 1H, $PCH_2C\underline{H}$); 7.14÷7.49 (m, 5H, $C_6\underline{H}_5$); ^{31}P-NMR ($CDCl_3$), δ = 24.57ppm; Anal. Calcd/Found: C- 52.09/51.84; H-6.56 /6.51

Diethyl 2-Chloro-2-phenylethylphosphonate **7d**

was obtained from the phosphonate **14** in two alternative ways using : 1) 10 fold excess of concentrated hydrogen chloride in CH_2Cl_2 (25°C, 8hrs, 80% yield after the work-up as for **7c**) 2) four fold excess of $SOCl_2$ in CH_2Cl_2 (25°C, 8hrs, 78% yield after the work-up as for **7c**). n_D^{20}=1.4989; ^{1}H-NMR ($CDCl_3$), δ = 1.15, 1.22 (2×t, 6H, $^3J_{H\text{-}H}$=7.0Hz, $POCH_2C\underline{H}_3$); 2.84 (ddd, 2H, $^3J_{H\text{-}H_A}$=8.0Hz, $^3J_{H\text{-}H_B}$=6.9Hz, $^2J_{H\text{-}P}$=18.3Hz, P-$C\underline{H}_2$); 3.75÷4.08 (m, 4H, $POC\underline{H}_2CH_3$); 5.25 (ddd, 1H, $^3J_{H\text{-}H_A}$=8.0Hz, $^3J_{H\text{-}H_B}$=6.9Hz, $^3J_{H\text{-}P}$=14.9Hz, $PCH_2C\underline{H}$); 7.24÷7.51 (m, 5H, $C_6\underline{H}_5$); ^{31}P-NMR ($CDCl_3$), δ = 24.85ppm; Anal. Calcd/Found: C-52.09/51.84; H-6.56/6.51

Diethyl 2-O-(p-toluenesulfonyl)-n-butylphosphonate **16**

To a stirred solution of the phosphonate **15**[11] (4.48g, 20mmol) in dry pyridine (6.5ml), p-toluenesulfonyl chloride (4.2g, 20mmol) was added over 3hrs at the temperature not exceeding 15°C. The reaction mixture was stirred for additional 1hr and neutralized with aqueous solution of 10% HCl. The crude product was extracted with ethyl ether (3×30ml), washed with aqueous solution of $NaHCO_3$, water and dried over anhydrous $MgSO_4$. A careful evaporation of the solvent gave the crude phosphonate **16** of 95% purity. Analytically pure product was obtained by column chromatography over silica gel using a gradient of n-hexane/acetone as eluent to give pure **16** (6.9g, 95% yield). n_D^{22}=1.5176; ^{1}H-NMR ($CDCl_3$), δ = 0.74 (t, 3H, $^3J_{H\text{-}H}$=7.2Hz, $CHCH_2C\underline{H}_3$); 1.26 (t, 6H, $^3J_{H\text{-}H}$=7.0Hz, $POCH_2C\underline{H}_3$); 1.61 (quintet, 2H, $^3J_{H\text{-}H}$=7.2Hz, $CHC\underline{H}_2CH_3$); 2.06÷2.27 (m, 2H, P$C\underline{H}_2$); 2.39 (s, 3H, C_6H_4-p.-$C\underline{H}_3$); 4.00÷4.13 (m, 4H, $POC\underline{H}_2CH_3$);

4.57÷4.74 (m, 1H, C<u>H</u>); 7.29, 7.75 (AB system, 4H, J_{AB}=8.4Hz, $C_6\underline{H}_4$-p-CH_3); ^{31}P-NMR ($CDCl_3$), δ = 25.3ppm; Anal. Calcd/Found: C- 49.44/49.33; H-6.92 /6.88

Diethyl 2-Iodo-n-butylphosphonate **7e**

To a stirred solution of the phosphonate **16** (1.82g, 5mmol) in dry acetone (50ml), anhydrous NaI (3.0g, 20mmol) was added in one portion. The resulting mixture was stirred overnight for 12-16hrs then filtred and evaporated. The crude product was dissolved in dry benzene (3×30ml) and carefully evaporated to give analytically pure **7e** (1.57g) in almost quantitative yield. n_D^{20}=1.4884; ^{1}H-NMR ($CDCl_3$), δ = 1.02 (t, 3H, $^3J_{H-H}$=7.1Hz, $CHCH_2C\underline{H}_3$); 1.32 (t, 6H, $^3J_{H-H}$=7.0Hz, $POCH_2C\underline{H}_3$); 1.62÷2.05 (m, 2H, $CHC\underline{H}_2CH_3$); 2.15÷2.24 (m, 2H, $PC\underline{H}_2$); 4.01÷4.13 (m, 4H, $POC\underline{H}_2CH_3$); 4.14÷4.41 (m, 1H, C<u>H</u>I); ^{31}P-NMR ($CDCl_3$), δ=25.3ppm; Anal. Calcd/Found: C- 30.02/29.86; H-5.67/5.63

The Arbuzov reaction of 1,2-dibromoethane and 1,3-dibromopropane with triethyl phosphite

To 1,2 dibromoethane (0.46mol, 86.4g, 39.6ml) or 1,3-dibromopropane (0.46 mol, 92.9g, 46.9ml), triethyl phosphite (0.115mmol, 19.09g, 19.7ml) was added at room temperature. In the latler case reaction mixture was gently refluxed for 4 hrs and distilled under reduced pressure using a Vigreux column (twice) to give 23.3g (78%) of **10a**. In the former, the reaction mixture was refluxed at 206°C using a packing distilling column to remove EtBr and then distilled under reduced pressure (88-90°C /0.2 Torr) to give 20.8g (74%) of **7a**. Physical and spectroscopic data of **7a** were identical with the commercial product (Aldrich Chemical Co.).

Diethyl 3-Bromo-n-propylphosphonate **10a**

n_D^{20}=1.4523; ^{1}H-NMR ($CDCl_3$), δ = 1.28 (t, 6H, $^3J_{H-H}$=7.0Hz, $POCH_2C\underline{H}_3$); 1.77÷1.94 (m, 2H, $PCH_2C\underline{H}_2$); 2.01÷2.18 (m, 2H, $PC\underline{H}_2CH_2$); 3.44 (dt, 2H, $^3J_{H-H}$=6.5Hz, $^4J_{H-P}$=1.1Hz, $P(CH_2)_2C\underline{H}_2$); 3.98÷4.14 (m, 4H, $POC\underline{H}_2CH_3$); ^{31}P-NMR ($CDCl_3$), δ = 31.18ppm;; Anal. Calcd/Found: C-32.45/32.24; H-6.22/6.17; P-11.96/11.98

Diethyl 3-Chloro-n-prophylphosphonate **10b**

To a stirred solution of sodium ethanolate, prepared by dissolving of sodium (0.5 mol, 11.5g) in anhydrous EtOH (600ml), diethyl phosphite was added dropwise at room temperature within 30min. Then a solution of 1-bromo-3-chloropropane (0.5 mol, 78.7g) in EtOH (200ml) was added at this temperature. The reaction mixture was stirred for 3 hrs, refluxed for additional 1hr and evaporated. The crude product was partitioned between chloroform (500ml) and water (350ml). The chloroform layer was washed with water (2×100ml), dried over anhydrous $MgSO_4$, filtered and evaporated. The pure product **10b** (88g, 82%) was obtained by distillation under reduced pressure. n_D^{25}=1.4429 (Lit.[13] n_D^{20}=1.4695); ^{1}H-NMR ($CDCl_3$), δ = 1.28 (t, 6H, $^3J_{H-H}$=7.0Hz, $POCH_2C\underline{H}_3$); 1.75÷2.13 (m, 4H, $P(C\underline{H}_2)_2$); 3.56 (dt, 2H, $^3J_{H-H}$=6.3Hz, $^4J_{H-P}$=1.1Hz,

$P(CH_2)_2C\underline{H_2}$); 3.92÷4.18 (m, 4H, $POC\underline{H_2}CH_3$); ^{31}P-NMR ($CDCl_3$), $\delta = 31.18$ppm; Anal. Calcd/Found: C-39.17/39.14; H-7.51/7.29

The free radical addition of 7 or 10 to alkenes 4; General procedures for synthesis of phosphonates 5 or 8.

Procedures A1, A2 and A3 : To a stirred solution of 2- or 3-halosubstituted phosphonates **7** or **10** (1mmol) and the corresponding alkene **4** (10 mmol - procedure **A1**, 30 mmol -procedure **A2**, 5 mmol - procedure **A3**) in deaerated (water pump/argon) and refluxing toluene (30 ml - procedure **A1** and **A3**; 15 ml - procedure **A2**), a solution of n-Bu_3SnH (1.4 mmol, 376.5µl) and azabisisobutyronitrile (AIBN, 0.2 mmol, 32.8 mg) in toluene (14 ml - procedure **A1** and **A3**; 7 ml - procedure **A2**) was added through a syringe pump within 3 hrs under argon atmosphere. After the additional 1h reflux, the solution was cooled to room temperature and the solvent was evaporated to give the crude product that was purified by column chromatography over silica gel using a gradient of toluene/acetone or AcOEt/n-hexane as eluents to give pure phosphonates **5** (P) [**17** (R)] or **8** (P) [**19** (R)] in given P/R ratios (Table 1).

Procedure B : To a stirred solution of 2- or 3-halosubstituted phosphonates **7** or **10** (1mmol) n-butoxyethene **4a** (3.87ml; 30 mmol) and $NaBH_4$ (75.7mg, 2mmol) in a refluxing mixture of dry toluene, a solution of n-Bu_3SnCl (54.2µl, 0.2 mmol) and AIBN (2 mmol, 32.8 mg) in toluene (7 ml) was added through a syringe pump within 3 hrs under argon atmosphere. After the additional 1hr reflux, the solution was cooled to room temperature and the solvent was evaporated to give the crude products **5b** or **8b** which were purified as in procedure **A**.

Procedure C1 and C2 : A solution of 2- or 3-halosubstituted phosphonates **7a** or **10a** (0.25 mmol), pentene-1 **4c** (312µl, 2.5 mmol) and n-Bu_3SnH (0.35 mmol, 94.1µl) - **C1** or n-Bu_3SnCl (0.05 mmol, 13.6µl) and $NaBH_4$ (0.5mmol, 19mg) - **C2** in a toluene solution (5ml) was irradiated with a low-pressure, mercury lamp using the Aldrich micro photochemical reaction assembly at room temperature under argon atmosphere for 2 hrs to give crude products **5a** or **8a**. Analytical samples were obtained by a low pressure distillation of the crude products using the Kugelrohr apparatus.

Procedure D1. A stirred solution of the 2-iodo substituted phosphonate **7e** (1mmol, 320.1 mg) and 3-buten-2-one **4b** (5 mmol, 415.6µl) in dry toluene (30 ml) was cooled to -78C (acetone/dry ice) in a reaction flask equipped with a short $CaCl_2$ tube (for a better air exchange), and a solution of Et_3B (1.1 mmol, 1.1 ml, 1M solution in n-hexane) was added. Then a solution of n-Bu_3SnH (1.4 mmol, 376.5µl) in toluene (14 ml) was added to the reaction mixture through a syringe pump within 6 hrs at -78C. After the additional 8 hrs the solution was warmed to room temperature and the solvent was evaporated. The crude product was purified by column chromatography over silica gel using a gradient of AcOEt/n-hexane as eluent to give a pure phosphonate **5e**.

Procedure D2 (without a syringe pump). A solution of n-Bu_3SnH (1.4 mmol, 376.5µl) in toluene (10 ml) was added to a cold (-78°C, acetone/dry ice) solution of the 2-iodo substituted phosphonate **7e** (1mmol, 320.1 mg),

3-buten-2-one **4b** (5 mmol, 415.6μl) and Et_3B (1.1 mmol, 1.1 ml, 1M solution in n-hexane) in dry toluene (30 ml) in two portions, within 3 hrs intervals. The resulting mixture was stirred for 8 - 12 hrs at -78°C. The work-up was identically performed as in procedure **D1**.

Spectral data of the compound **8a** was identical with that reported by us earlier[6].

Diethyl n-Heptylphosphonate **5a**

n_D^{20}=1.4263, (Lit.[14] n_D^{20}=1.4270); ^{1}H-NMR ($CDCl_3$), δ=0.87 (t, 3H, $^3J_{H-H}$=7.1Hz, $(CH_2)_6C\underline{H}_3$); 1.28 (t, 6H, $^3J_{H-H}$=7.0Hz, $POCH_2C\underline{H}_3$); 1.40÷1.88 (m, 12H, $(C\underline{H}_2)_6$); 4.02÷4.15 (m, 4H, $POC\underline{H}_2CH_3$); ^{31}P-NMR ($CDCl_3$), δ = 33.24ppm; Anal. Calcd/Found: C-55.91/56.08; H-10.66/10.74; P-13.11/13.19

Diethyl 4-n-butoxy-n-butylphosphonate **5b**

oil, ^{1}H-NMR ($CDCl_3$), δ=0.91 (t, 3H, $^3J_{H-H}$=7.0Hz, $O(CH_2)_3C\underline{H}_3$); 1.31 (t, 6H, $^3J_{H-H}$=7.1Hz, $POCH_2C\underline{H}_3$); 1.25÷1.89 (m, 10H, $PCH_2(C\underline{H}_2)_3$ and $OCH_2(C\underline{H}_2)_2CH_3$); 3.35÷3.46 (m, 4H, $C\underline{H}_2OC\underline{H}_2$); 4.07, 4.08 (dq, 4H, $^3J_{H-H}$=7.1Hz, $^3J_{H-P}$=8.6Hz $POC\underline{H}_2CH_3$); ^{31}P-NMR ($CDCl_3$), δ = 32.8ppm; MS-EI (70eV, m/z, %)-267 $[(M+1)^{+\cdot}$, 10], 209(100), 193(42), 165 (62), 152(22), 137(57), 57(53); MS-CI (isobutane) MH^+=267; MS-HR : Calcd/Found 266.1646/266.1650; Anal. Calcd/Found: C-54.11/53.85; H-10.71/10.33.

During purification of **5b** (Kugelrohr distillation + chromatography on silica gel; toluene/acetone in a gradient), diethyl 4, 6-di(n-butoxy)-n-hexylphosphonate **18** was detected by the MS-CI technique as a minor reaction product (< 8%). ^{31}P-NMR ($CDCl_3$), δ=32.7 ppm; MS-HRCI: Calcd./Found: 367.2613/367.2610.

Diethyl 5-oxo-n-hexylphosphonate **5c**

n_D^{20}=1.4434, (Lit.[14] n_D^{23}=1.4423); ^{1}H-NMR ($CDCl_3$), δ = 1.30 (t, 6H, $^3J_{H-H}$=7.1Hz, $POCH_2C\underline{H}_3$); 1.58÷1.85 (m, 6H, $P(C\underline{H}_2)_3$); 2.11 (s, 3H, $C(O)C\underline{H}_3$); 2.43 (t, 2H, $^3J_{H-H}$=7.1Hz, $C\underline{H}_2C(O)CH_3$); 3.93÷4.15 (m, 4H, $POC\underline{H}_2CH_3$); ^{31}P-NMR ($CDCl_3$), δ = 35.38ppm; ; MS-EI (15eV, m/z, %)-236 ($M^{+\cdot}$,7.5), 193(48), 179(100), 166 (58), 165(63), 152(47), 139(37), 138(25); Anal. Calcd/Found: C-50.84/50.84; H-8.96/8.95; P-13.11/13.09

Diethyl 2-(2-methyl-3-tetrahydrofuranyl)ethylphosphonate **5d**

oil; ^{1}H-NMR ($CDCl_3$), δ = 1.08, 1.09 (2×d, 3H, $^3J_{H-H}$=6.5Hz, $CHC\underline{H}_3$); 1.31, 1.32 (2×t, 6H, $^3J_{H-H}$=7.0Hz, $POCH_2C\underline{H}_3$); 1.50÷2.00 (m, 7H, $P(C\underline{H}_2)_2C\underline{H}C\underline{H}_2$); 3.50÷4.0 (m, 3H, $C\underline{H}_2OC\underline{H}$); 3.98÷4.18 (m, 4H, $POC\underline{H}_2CH_3$); ^{31}P-NMR ($CDCl_3$), δ =35.0, 31.54ppm as a mixture of diastereoisomers in a ratio 8/10. This compound was easily separated from diethyl ethylphosphonate **17** (R^1=H) and bulky amounts of tin salts with the Kugelrohr distillation. However, further acurate separation from the tin salts using the TLC technique (twice) caused its gradual decomposition until total loss of the material.

Diethyl 2-ethyl-5-oxo-n-hexylphosphonate **5e**

oil; ^{1}H-NMR ($CDCl_3$), δ = 0.87 (t, 3H, $^3J_{H-H}$=7.2Hz, $CHCH_2C\underline{H_3}$); 1.31 (t, 6H, $^3J_{H-H}$=7.0Hz, $POCH_2C\underline{H_3}$); 1.55÷1.74 (m, 6H, $PC\underline{H_2}$ and $C\underline{H_2}CHC\underline{H_2}$); 1.81÷1.90 (m, 1H, $PCH_2C\underline{H}$); 2.15 (s, 3H, $C(O)C\underline{H_3}$); 2.44 (dd, 2H, $^3J_{H-H_A}$=6.1Hz, $^3J_{H-H_B}$=8.2Hz $C\underline{H_2}C(O)CH_3$); 3.95÷4.18 (m, 4H, $POC\underline{H_2}CH_3$); ^{31}P-NMR ($CDCl_3$), δ = 35.25ppm; MS-EI (15eV, m/z, %) 264 ($M^{+\cdot}$,2)-221(12), 207(60), 193(27), 165(14), 152(100), 138(27), 125(33); Anal. Calcd/Found: C-54.53/54.50; H-9.53 /9.53; P-11.72/11.69

Diethyl 5-n-butoxy-n-pentylphosphonate **8b**

oil; ^{1}H-NMR ($CDCl_3$), δ=0.90 (t, 3H, $^3J_{H-H}$=7.2Hz, $O(CH_2)_3C\underline{H_3}$); 1.31 (t, 6H, $^3J_{H-H}$=7.0Hz, $POCH_2C\underline{H_3}$); 1.40÷1.68 (m, 10H, $PCH_2(C\underline{H_2})_3$ and $OCH_2(C\underline{H_2})_2CH_3$); 1.72÷1.81 (m, 2H, $PC\underline{H_2}$); 3.35÷3.46 (m, 4H, $C\underline{H_2}OC\underline{H_2}$); 4.02÷4.15 (m, 4H, $POC\underline{H_2}CH_3$); ^{31}P-NMR ($CDCl_3$), δ=33.0ppm; ; MS-EI (15eV, m/z, %)-280 ($M^{+\cdot}$, 1), 223(100), 207(26), 165 (32), 152(70); Anal. Calcd/Found: C-55.70/55.65; H-10.43 /10.33; P-11.05/10.96

Diethyl 6-oxo-n-heptylphosphonate **8c**

n_D^{20}=1.4368 (Lit.[15] n_D^{20}=1.4357); ^{1}H-NMR ($CDCl_3$), δ = 1.29 (t, 6H, $^3J_{H-H}$=7.1Hz, $POCH_2C\underline{H_3}$); 1.55÷1.81 (m, 8H, $P(C\underline{H_2})_4$); 2.11 (s, 3H, $C(O)C\underline{H_3}$); 2.42 (t, 2H, $^3J_{H-H}$=7.0Hz, $C\underline{H_2}C(O)CH_3$); 3.97÷4.14 (m, 4H, $POC\underline{H_2}CH_3$); ^{31}P-NMR ($CDCl_3$), δ = 32.8ppm; MS-EI (15eV, m/z, %)-250($M^{+\cdot}$,5.5), 207(32), 193(100), 179(29), 165(36), 152(27), 138(18); Anal. Calcd/Found: C-52.79/52.72; H-9.26/9.25; P-12.38/12.33

Diethyl ethylphosphonate **17** (R^1=H)

was obtained as a by-product in the reactions of radical precursors **7a** or **7b** with alkenes **4a-d** in 33÷77% yield; n_D^{20}=1.4158 (Lit.[16] n_D^{20}=1.4161)

Diethyl 2-phenyl-ethylphosphonate **17** (R^1=Ph)

was obtained in the reactions of **7c** or **7d** with **4a** in 63÷89 % yield or by alkylation of diethyl methylphosphonate (n-BuLi, THF, -78°C, Ar) with benzyl bromide (94% yield); n_D^{20}=1.4942 (Lit.[17] n_D^{27}=1.4910); ^{1}H-NMR ($CDCl_3$), δ = 1.32 (t, 6H, $^3J_{H-H}$=7.1Hz, $POCH_2C\underline{H_3}$); 1.52÷1.64 (m, 2H, $PCH_2C\underline{H_2}$); 1.96÷2.16 (m, 2H, $PC\underline{H_2}CH_2$); 4.06, 4.09 (2×q, 4H, $^3J_{H-H}$=7.0Hz $POC\underline{H_2}CH_3$); ^{31}P-NMR ($CDCl_3$), δ = 31.44ppm; MS-EI (15eV, m/z, %)-242($M^{+\cdot}$,96), 137(100); Anal. Calcd/Found: C-59.50/59.64; H-7.85/7.81

Diethyl n-butylphosphonate **17** (R^1=Et)

was obtained as a by-product in the reactions of **7e** with **4b** in 30% yield; n_D^{20}=1.4222 (Lit.[18] n_D^{20}=1.4213).

Diethyl n-propylphosphonate **19**

was obtained as a by-product in the reactions of **10a** or **10b** with alkenes **4a-c** in 25÷52% yield. n_D^{20}=1.4186, (Lit.[18] n_D^{20}=1.4172)

Spectral data for phosphonates **17** (R^1=H, Et) and **19** were identical with those reported in literature and obtained from the original samples.

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