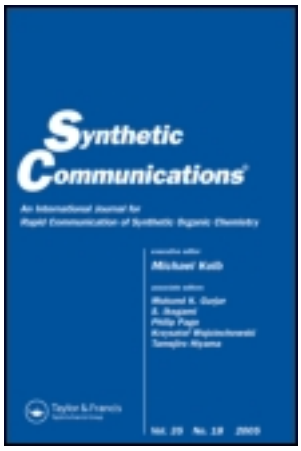

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 17 Aug 2006.

To cite this article: Imre Petneházy, Zsuzsa M. Jászay, Andrea Szabó & Kinga Everaert (2003): Convenient One Pot Synthesis of Phosphonites and H-Phosphinates, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:10, 1665-1674

To link to this article: http://dx.doi.org/10.1081/SCC-120018928

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SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 10, pp. 1665–1674, 2003

Convenient One Pot Synthesis of Phosphonites and H-Phosphinates

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ABSTRACT

A convenient and simple one-pot method is described for the synthesis of phosphonites [$RP(OEt)_2$, **1**] and H-phosphinates [HP(O)R(OEt), **2**] from triethyl phosphite and appropriate Grignard reagents.

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DOI: 10.1081/SCC-120018928 0039-7911 (Print); 1532-2432 (Online)

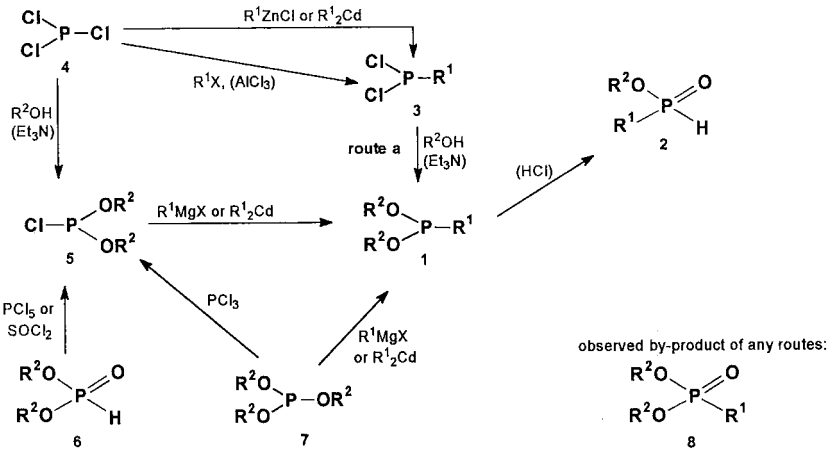
Key Words: Phosphonites; H-phosphinates; Grignard reaction.

Phosphonites (**1**) and H-phosphinates (**2**) are fundamental starting compounds in P–C forming reactions such as in Michaelis–Arbuzov reaction resulting in alkyl- and aryl phosphinates, in Kabachnik–Field reaction resulting in α-aminophosphinates and in Abramov reaction resulting in α-hydroxyphosphinates. The latter two have special attention due to their ability to function as transition state analogue of carboxylic acid moiety in natural α-amino- and α-hydroxycarboxylic acids.[1–3]

Despite the importance of **1** and **2** as precursors, there is no convenient and simple method for their synthesis so far. The methods found in the literature are summarised in Sch. 1.

The oldest method for the synthesis of 1 is the alcoholysis of dichloro phosphinates[4] (**3**) (route a), the latter on the other hand can be prepared in Kinnear–Perren reaction[5] by treating alkyl chlorides with phosphorus trichloride (**4**) in the presence of aluminium–chloride and decomposing the complex with a mixture of aluminium powder and sodium chloride in reflux. The disadvantage of this procedure is that **3** is obtained only in very low yield, especially in case of the preparation of the alkyl derivatives.

Other authors used Grignard-reagents such as alkyl-[6] or arylzinc halogenide[7] and dialkyl cadmium,[8] respectively in formation of P–C bond starting also from phosphorus trichloride resulting in alkyl- and



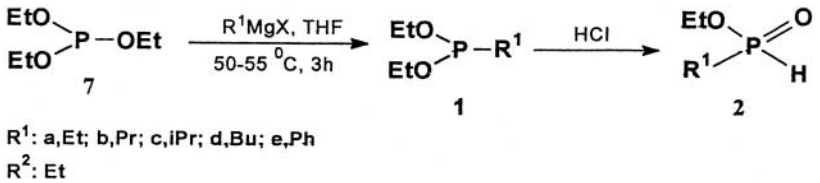
Scheme 1.

aryldichloro phosphine (**3**) in very low yield. Although the chlorine alkoxy exchange (route a) with different alcohols occurs in presence of tertiary amines in suitable yield,[9] overall yield of the two steps is low and because of the presence of some by-products difficult to purify.

Dialkyl phosphorous chloride (**5**) can also be reacted with reagents of Grignard-type to give phosphonites (**1**) in medium yield (route b).[10] However obtaining 5 in pure form is difficult, namely the alcoholysis of phosphorus trichloride with two moles of alcohols results in a mixture of mono-, di- and triesters. The other two routes leading to 5, i.e., the chlorination of dialkyl phosphates[11] (**6**) and trialkyl phosphates[12] (**7**) are also inconvenient and give low yield. The most promising method for the preparation of phosphonites (**1**) and H-phosphinates (**2**) has been reported by Sander.[13] According to this procedure (route c) triethyl phosphite (**7**) is reacted with alkyl- or arylmagnesium bromide in diethyl ether at room temperature, then the solvent is gradually changed to benzene by removing the ether by distillation, because the completion of the Grignard reaction needs higher temperature then that of the boiling point of the ether. For production of **2** Sander suggested hydrolysis of **1** by aqueous hydrochloric acid. To synthesize **1** in good yield and in high quality the above mentioned methods were studied by us. Starting from phosphorus trichloride (**4**) large amount of dialkyl phosphite (**6**), trialkyl phosphite (**7**) and alkylphosphonates (**8**) were formed as by-products beside phosphonite (**1**) by routes a and b, according to Sch. 1.

Starting from trialkyl phosphite (**7**) according to Sander's procedure (route c) we unexpectedly realized that the desired product (**1**) was present only in a little amount compared to **2** and **8** by-products and the unreacted **7** starting material, by the ^{31}P-NMR spectra. We assumed that the differences in results might be due to the fact that at the time of Sander's experiment the results could not be interpreted by ^{31}P-NMR.

The reaction of the appropriate Grignard reagent and triethyl phosphite (**7**, $R^2 = Et$) was optimized by us first aiming **1** and **2** (Sch. 2). The ethyl esters of the phosphinous acids to be formed are more



Scheme 2.

favorable in their application as starting materials in subsequent synthesis than their homologues.

We supposed that the reason of the side reactions was the heterogeneity of the reaction mixture in case of benzene as solvent. Therefore we examined several solvents and mixture of solvents taking into consideration their boiling points. Finally, tetrahydrofuran proved to be the best, which resulted in homogenous reaction mixture, therefore the change of solvent was not necessary. According to our experiments the optimum reaction temperature was 50–55° and the application of tetrahydrofuran was also advantageous in this point of view. We experienced that the reaction does not occur on lower temperature namely in diethyl ether at reflux, moreover oxidised by-products were also formed on elevated temperature. The molar ratio of the Grignard reagent and triethyl phosphite proved to be also substantial, we found that using a ratio of 1.5:1 provided clean **1** and **2**, adding the previously prepared Grignard compound into the solution of triethyl phosphite in tetrahydrofuran at 50°.

The phosphinates (**1**) were isolated by distillation in vacuum simply from the reaction mixture. For the preparation of **2** the hydrolysis was performed by adding diluted hydrochloric acid directly into the concentrated reaction mixture of **1**. The products were characterized by their ^{31}P-NMR spectra, according to which in case of **1** three, in case of **2**, two types of the above mentioned contaminations could be observed only in very low quantity (Tables 1 and 2).

We observed however, that using the trimethyl equivalent of **7** phosphinate **9** occurred as main product instead of required **1** ($R^2 = Me$). We assume that **1** formed in the Grignard reaction is not stable,

Table 1. Isolated yield and boiling point of **1a–e** and impurities by ^{31}P-NMR data.

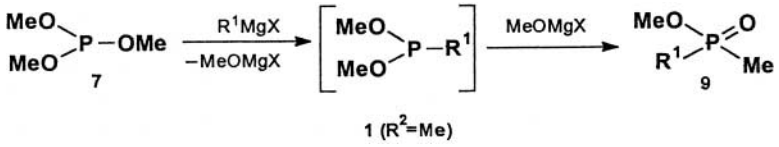
		Product			Impurities		
		Yield	Bp.	$RP(OEt)_2$ **1**	$P(OEt)_3$ **7**	$HP(O)R(OEt)$ **2**	$RP(O)(OEt)_2$ **8**
	R	(%)	(°C/Hgmm)	Ratio in % (^{31}P-NMR in ppm)			
a	Et	50	54–56/35	93 (185.6)	2.5 (140.8)	2.0 (40.6)	2.5 (33.4)
b	Pr	76	53–55/39	96 (184.9)	2.5	0 (38.4)	1.5 (34.9)
d	Bu	82	71–73/32	92.5 (185.1)	4.0	2.0 (38.9)	1.5 (35.0)
e	Ph	79	78–81/1	97 (158.0)	0.6	0 (26.5)	2.5 (21.4)
d[a]	Bu			19.7 (185.1)	20.0	15.3 (38.9)	46.0 (35.0)

[a]Distribution of products in reproduction of Sander's procedure.

Table 2. Isolated yield and boiling point of **2a–e** and impurities by ^{31}P-NMR data.

		Product			Impurities	
	R	Yield (%)	B.p. (°C/Hgmm)	HP(O)R(OEt) **2**	$RP(O)(OEt)_2$ **8** % (ppm)	$HP(O)(OEt)_2$ **6**
a	Et	56	78–80/10	97.5 (40.6)	2.3 (33.4)	0.2 (7.15)
b	Pr	73	88/10	98.0 (38.4[b])	1.9 (34.9)	0.1
c	*i*Pr	84	88–90/10	95.5 (43.9)	4.0 (34.7)	0.5
d	Bu	85	106/20	97.5 (38.9)	2.0 (35.0)	0.5
e	Ph	82	108–110/0.9	95.0 (26.5)	4.8 (21.4)	0.2
d[a]	Bu			42.6 (38.9)	10.4 (35.0)	47

[a]Distribution of products in reproduction of Sander's procedure.
[b]There is a difference in ^{31}P-NMR date given in literature[14,15] (see Experimental).



Scheme 3.

the methyl ester undergoes an Arbuzov fission in the reaction conditions (Sch. 3).

In conclusion a simple one pot, high yielding modified procedure was elaborated starting from triethyl phosphite (**7** $R = Et$) leading to phosphonite **1** and H-phosphinate **2**, though in case of 1a the yield is lower. We observed that in case of trimethyl phosphite a further reaction occurs resulting in phosphinate **9** in medium yield.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC 250 instrument, ^{31}P-NMR spectra on a Bruker DRX-500 instrument using tetramethylsilane (^{1}H, ^{13}C) as internal standard and 85% H_3PO_4 (^{31}P) as external standard, all in $CDCl_3$ solution. MS spectra were measured on a Finnigan Automass GC/MS spectrometer.

General Procedure for Diethyl Alkyl (or Aryl) Phosphonites (1)

Alkyl or aryl bromide (0.15 mol) was added dropwise to a mixture of magnesium (3.6 g) and dry tetrahydrofuran (40 mL) under N_2 atmosphere at 50°. After addition, the reaction mixture was stirred at 50° for additional 1–2 h to complete the reaction. Then the mixture is added dropwise to a solution of triethyl phosphite (0.1 mol, 16.6 g) and THF (25 mL) between 40 and 50° in N_2 atmosphere, then stirred 3 h at 50°. After removal the solvent under reduced pressure, the product (**1**) was purified by distilled out from the semisolid residue in vacuum (Table 1).

Diethyl ethylphosphonite (1a): Yield: 50%; b.p.: 54–56°C/35 Hgmm (lit.: 53°C/30 Hgmm[13]); ^{1}H-NMR δ (ppm) = 1.05 (dt, $J_{HH} = 6.5$ Hz, $J_{PH} = 14.3$ Hz, 3H, $C\underline{H}_3CH_2P$), 1.26 (t, $J_{HH} = 7.1$ Hz, 6H, $C\underline{H}_3CH_2O$), 1.86 (dt, $J_{HH} = 6.4$ Hz, $J_{PH} = 12.8$ Hz, 2H, $CH_3C\underline{H}_2P$), 3.72–3.97 (m, $J_{PH} = 12.1$ Hz, 4H $CH_3C\underline{H}_2O$); ^{31}P-NMR: δ (ppm) = 185.6 (lit.: 186[16] and 184[17]).

Diethyl propylphosphonite (1b): Yield: 76%; b.p.: 53–55°C/39 Hgmm (lit.: 52–53°C/12 Hgmm[18]); ^{1}H-NMR δ (ppm) = 0.99 (t, $J_{HH} = 6.6$ Hz, 3H, $C\underline{H}_3CH_2$), 1.24 (t, $J_{HH} = 7.0$ Hz, 6H, $C\underline{H}_3CH_2O$), 1.42–1.51 (m, 2H, $CH_3C\underline{H}_2$), 1.85 (dt, $J_{HH} = 6.6$ Hz, $J_{PH} = 12.0$ Hz, 2H, $C\underline{H}_2P$), 3.70–3.91 (m, $J_{PH} = 11.7$ Hz, 4H, $CH_3C\underline{H}_2O$); ^{13}C-NMR: δ (ppm) = 15.08 (d, $J_{PC} = 10.7$ Hz, $\underline{C}H_3CH_2CH_2$), 15.29 (d, $J_{PC} = 16.9$ Hz, $CH_3\underline{C}H_2CH_2$), 16.69 (d, $J_{PC} = 5.5$ Hz, $\underline{C}H_3CH_2O$), 36.04 (d, $J_{PC} = 16.6$ Hz, $CH_3CH_2\underline{C}H_2$), 62.15 (d, $J_{PC} = 13.1$ Hz, $CH_3\underline{C}H_2O$); ^{31}P-NMR: δ (ppm) = 184.9.

Diethyl butylphosphonite (1d) Yield: 82%; b.p.: 71–73°C/32 Hgmm (lit.: 68.5–70°C/12 Hgmm,[18] 39–40°C/0.5 Hgmm[19]); ^{1}H-NMR δ (ppm) = 0.92 (t, $J_{HH} = 6.7$ Hz, 3H, $C\underline{H}_3CH_2$), 1.26 (t, $J_{HH} = 7.1$ Hz, 6H, $C\underline{H}_3CH_2O$), 1.28–1.37 (m, 2H, $CH_3C\underline{H}_2$), 1.38–1.45 (m, 2H, $CH_3CH_2C\underline{H}_2$), 1.45–1.60 (m, 2H,$C\underline{H}_2P$), 3.72–4.13 (m, $J_{PH} = 15.0$ Hz, 4H, $CH_3C\underline{H}_2O$); ^{31}P-NMR: δ (ppm) = 185.1.

Diethyl phenylphosphonite (1e): Yield: 79%; b.p.: 78–81°C/1 Hgmm (lit.: 74–78°C/1 Hgmm,[20] 79–80°C/1 Hgmm[21]); ^{1}H-NMR δ (ppm) = 1.28 (t, $J_{HH} = 7.0$ Hz, 6H, $C\underline{H}_3CH_2O$), 3.80–3.96 (m, $J_{HH} = 7.0$ Hz, 4H, $CH_3C\underline{H}_2O$), 7.38–7.41 (m, 3H, Ar$\underline{H}$), 7.58–7.61 (m, 2H, Ar$\underline{H}$);) (lit.[22] in good accordance with our date); ^{13}C-NMR δ (ppm) = 16.94 (d, $J_{PC} = 5.0$ Hz, $\underline{C}H_3CH_2O$), 62.27 (d, $J_{PC} = 10.2$ Hz, $CH_3\underline{C}H_2O$), 127.97 (d, $J_{PC} = 5.0$ Hz, *m*-CH), 129.37 (*p*-CH), 129.60 (d, $J_{PC} = 10.1$ Hz, *o*-CH), 141.16 (d, $J_{PC} = 19.6$ Hz, C) (lit.[22] in good accordance with our data); ^{31}P-NMR: δ (ppm) = 158.0 (lit.: 155.9[23]).

General Procedure for Ethyl Alkyl (or Aryl)-H-phosphinates (2)

The reaction mixture of **1** prepared according to the previous general procedure was concentrated by distillation to the half in vacuum. Diluted hydrochloric acid (1:1) was added to this stirred residue at room temperature until pH = 2. The solvent (tetrahydrofuran and water) was evaporated and chloroform (60 mL) was added to the colourless, semi-solid residue. The mixture was extracted with 3×30 mL of water. The organic phase was dried over Na_2SO_4. After evaporating the solvent, the product was distilled in vacuum to give pure (**2**) (Table 2).

Ethyl ethyl-H-phosphinate (2a): Yield: 56%; b.p.: 78–80°C/10 Hgmm (lit.: 80–81°C/16 Hgmm[24]); ^{1}H-NMR δ (ppm) = 1.08 (dt, $J_{HH} = 7.8$ Hz, $J_{PH} = 21.2$ Hz, 3H, C$\underline{H}_3$CH$_2$P), 1.30 (t, $J = 7.0$ Hz, 3H, C$\underline{H}_3$CH$_2$O), 1.71 (qd, $J_{HH} = 7.8$ Hz, 2H, CH$_3$C$\underline{H}_2$P), 4.05 (dq, $J_{HH} = 7.0$ Hz, 2H, CH$_3$C$\underline{H}_2$O), 6.97 (d, $J_{PH} = 526.0$ Hz, 1H, P$\underline{H}$) (lit.[25] in good accordance with our data); ^{13}C-NMR: (ppm) = 4.16 (d, $J_{PC} = 3.9$ Hz, $\underline{C}$H$_3$CH$_2$), 15.76 (d, $J_{PC} = 6$ Hz, $\underline{C}$H$_3$CH$_2$O), 21.27 (d, $J_{PC} = 94.5$ Hz, CH$_3\underline{C}$H$_2$), 61.73 (d, $J_{PC} = 6.8$ Hz, CH$_3\underline{C}$H$_2$O); ^{31}P-NMR: δ (ppm) = 40.6 (lit.: 38[26] and 40[27]); MS (*m*/*z*): 93 ([EtPO$_2$H]$^+$, 1%), 78 ((EtPOH$_2$]$^+$, 32%), 65 ([PO$_2$H$_2$]$^+$, 100), 47 ([PO]$^+$, 67%).

Ethyl propyl-H-phosphinate (2b): Yield: 73%; b.p.: 88°C/10 Hgmm; ^{1}H-NMR δ (ppm) = 1.05 (t, $J_{HH} = 7.0$ Hz, 3H, C$\underline{H}_3$CH$_2$CH$_2$), 1.36 (t, $J_{HH} = 7.0$ Hz, 3H, C$\underline{H}_3$CH$_2$O), 1.55–1.83 (m, 4H, CH$_3$C$\underline{H}_2$C$\underline{H}_2$), 3.99–4.14 (m, 2H, CH$_3$C$\underline{H}_2$O), 7.04 (d, $J_{PH} = 524.0$ Hz, 1H, P$\underline{H}$); ^{13}C-NMR: δ (ppm) = 14.40 (d, $J_{PC} = 2.6$ Hz, $\underline{C}$H$_3$CH$_2$CH$_2$), 14.86 (d, $J_{PC} = 16$ Hz, $\underline{C}$H$_3$CH$_2$O), 16.02 (d, $J_{PC} = 6$ Hz, CH$_3\underline{C}$H$_2$CH$_2$), 30.47 (d, $J_{PC} = 93.6$ Hz, CH$_3$CH$_2\underline{C}$H$_2$), 62.05 (d, $J_{PC} = 7$ Hz, CH$_3\underline{C}$H$_2$O); ^{31}P-NMR: δ (ppm) = 38.4 (lit.: 26.9 ppm,[14] 23.5 ppm[15]); MS (m/*z*): 136 ([M]$^+$, 1%), 121 ([CH$_2$CH$_2$PO$_2$EtH]$^+$, 2%), 108 ([CH$_2$PO$_2$EtH]$^+$, 3%), 93 ((EtPO$_2$H($^+$, 26%), 80 ([CH$_2$PO$_2$H]$^+$, 34%), 65 ([PO$_2$H$_2$]$^+$, 100%).

Ethyl isopropyl-H-phosphinate (2c): Yield: 84%; b.p.: 88–90°C/10 Hgmm; ^{1}H-NMR δ (ppm) = 1.14 (d, $J_{HH} = 7.23$ Hz, 3H), 1.22 (d, $J_{HH} = 7.23$ Hz, 3H) C$\underline{H}_3$C$\underline{H}_3$CH, 1.37 (t, $J_{HH} = 7.0$ Hz, 3H, C$\underline{H}_3$CH$_2$), 1.85–1.94 (m, 1H CH$_3$CH$_3$C$\underline{H}$), 4.00–4.22 (m, 2H, CH$_3$C$\underline{H}_2$), 6.88 (d, $J_{PH} = 518.3$ Hz, 1H, P$\underline{H}$); ^{31}P-NMR: δ (ppm) = 43.9.

Ethyl butyl-H-phosphinate (2d): Yield: 85%; b.p.: 106°C/20 Hgmm (lit.: 105°C/15 Hgmm[13]); ^{1}H-NMR δ (ppm) = 0.84 (t, $J_{HH} = 7.1$ Hz, 3H, C$\underline{H}_3$CH$_2$CH$_2$CH$_2$), 1.27 (t, $J = 7.1$ Hz, 3H, C$\underline{H}_3$CH$_2$O), 1.32–1.75 (m, 6H, CH$_3$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$), 3.97–4.11 (m, 2H, CH$_3$C$\underline{H}_2$O), 6.99 (d, $J_{PH} = 528.8$ Hz, 1H, P$\underline{H}$) (lit.[28] in good accordance with our data); ^{13}C-NMR: δ (ppm) = 13.40 (s, $\underline{C}$H$_3$CH$_2$CH$_2$CH$_2$), 16.11 (d, $J_{PC} = 6$ Hz,

$\underline{C}H_3CH_2O$), 22.59 (d, $J_{PC} = 2.5$ Hz, $CH_3\underline{C}H_2CH_2CH_2$), 23.39 (d, $J_{PC} = 16.2$ Hz, $CH_3CH_2\underline{C}H_2CH_2$), 28.29 (d, $J_{PC} = 93.7$ Hz, $CH_3CH_2CH_2\underline{C}H_2$), 62.08 (d, $J_{PC} = 6.9$ Hz, $CH_3\underline{C}H_2O$); ^{31}P-NMR: δ (ppm) = 38.9; MS (*m*/*z*): 121 ($[CH_2CH_2PO_2EtH]^+$, 4%), 108 (37%), 93 ($[EtPO_2H]^+$, 35%), 80 ($[CH_2PO_2H]^+$, 89%), 65 ($[PO_2H_2]^+$, 100%).

Ethyl phenyl-H-phosphinate (2e)Yield: 82%; b.p.: 108–110°C/0.9 Hgmm (lit.: 95°C/1 Hgmm[29]); ^{1}H-NMR δ (ppm) = 1.37 (t, $J = 7.2$ Hz, 3H, $C\underline{H}_3CH_2O$), 4.14 (m, 2H, $CH_3C\underline{H}_2O$), 7.58 (d, $J_{PH} = 562.79$ Hz, 1H, P$\underline{H}$), 7.48–7.57 (m, 3H, Ar$\underline{H}$), 7.61–7.83 (m, 3H, Ar$\underline{H}$) (lit.[30] in good accordance with our data); ^{13}C-NMR δ (ppm) = 16.07 (d, $J_{PC} = 6.3$ Hz, $\underline{C}H_3CH_2O$), 61.76 (d, $J_{PC} = 6.3$ Hz, $CH_3\underline{C}H_2O$), 128.47 (d, $J_{PC} = 13.83$ Hz, *m*-CH), 129.51 (d, $J_{PC} = 98.49$ Hz, C), 130.59 (d, $J_{PC} = 11.95$ Hz, *o*-CH), 132.81 (d, $J_{PC} = 3.14$ Hz, *p*-CH); ^{31}P-NMR: δ (ppm) = 26.5 (lit.: 23.5[29]); MS (m/*z*): 171 ($[M]^+$, 1%), 142 ($[PhPO_2H]^+$, 1%), 78 ($(EtPOH_2]^+$, 11%), 65 ($[PO_2H_2]^+$, 8%), 47 ($[PO]^+$, 100%).

Methyl methyl-propylphosphinite (9b): It was prepared in a similar way as (2) except trimethyl phosphite (0.1 mol, 12.4 g) was used instead of triethyl phosphite. Yield: 43%; b.p.: 98–99°C/14 Hgmm; ^{1}H-NMR δ (ppm) = 1.04 (t, $J_{HH} = 6.8$ Hz, 3H, $CH_2C\underline{H}_3$), 1.45 (d, $J_{PH} = 13$ Hz, 3H, $PC\underline{H}_3$), 1.5–1.8 (m, 4H, $C\underline{H}_2$), 3.7 (d, $J_{PH} = 10.7$ Hz, 3H, OCH_3); ^{13}C-NMR ($CDCl_3$): $\delta = 12.9$ (d, $J_{PC} = 90$ Hz, $P\underline{C}H_3$), 15.5 (d, $J_{PC} = 30$ Hz, $CH_2\underline{C}H_3$), 15.6 (d, $J_{PC} = 10$ Hz, $CH_2\underline{C}H_2CH_3$), 31.2 (d, $J_{PC} = 94$ Hz, $P\underline{C}H_2$), 50.6 (d, $J_{PC} = 7$ Hz, $O\underline{C}H_3$); ^{31}P-NMP: δ (ppm) = 58.2.

ACKNOWLEDGMENTS

Support from the Hungarian National Research Foundation (OTKA T026478) and the Ministry of Education (TÉT-Balaton F19/98) is acknowledged.

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Received in the UK April 10, 2002