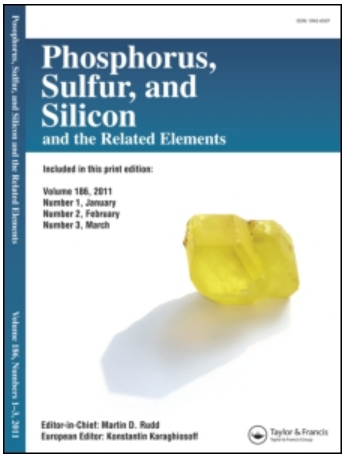

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PREPARATION OF DIETHYL 1-BROMOALKYLPHOSPHONATES

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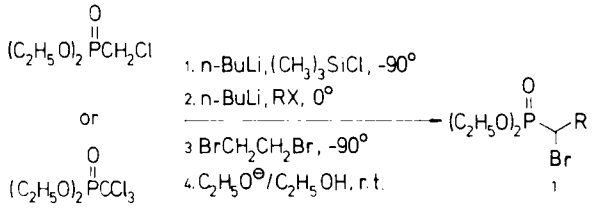
Diethyl 1-bromoalkylphosphonates **1** have been obtained in good to moderate yields by the reaction of diethyl 1-hydroxyalkylphosphonates **2** with the triphenylphosphine–carbon tetrabromide system or dibromotriphenylphosphorane.

Key words: Diethyl 1-bromoalkylphosphonates; diethyl 1-hydroxyalkylphosphonates; triphenylphosphine; carbon tetrabromide; dibromotriphenylphosphorane.

INTRODUCTION

Though diethyl 1-bromoalkylphosphonates **1** have found interesting application as synthetic tool[1,2] during the past few years, their synthesis has acquired little attention as yet. The most promising synthetic gateway, Arbusov reaction between triethyl phosphite and methylene bromide provides the desired bromophosphonate only in a poor yield (13–15%).[1,3] Much better results are obtained from the ethanolysis of 1-bromomethylphosphonic dichloride,[4] and bromolysis of the diethylphosphonylmethyl magnesium chloride[5] as well as by direct bromination of diethyl benzylphosphonate by means of *N*-bromosuccinimide.[6] In the literature is reported only one example of direct OH→Br exchange i.e. diethyl 1-hydroxypropylphosphonate by dibromotriphenylphosphorane, but no yield is given.[7] Recently Savignac *et al.*[8] proposed a new and efficient synthesis of this class of compounds based on diethyl chloromethylphosphonate or diethyl trichloromethylphosphonate as substrates (Scheme 1).

The scope of this one-pot, but multistep reaction is, however, limited by the



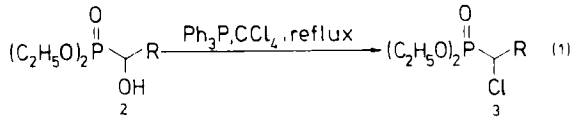
R=CH_3 , C_2H_5 , n-C_3H_7 , Allyl ; X=Br, I

SCHEME 1

structure of the alkylating agent (primary halides) as well as the cost of the used reagents.

RESULTS AND DISCUSSION

Diethyl 1-hydroxyalkylphosphonates **2**, which are easily accessible from diethyl phosphite and the appropriate aldehyde,[9,10] can be used as convenient starting materials for further transformations.[10,11] Previous work from this laboratory[12] has shown that treatment of the phosphonate **2** with triphenylphosphine and carbon tetrachloride leads to the formation of diethyl 1-chloroalkylphosphonates **3** in high yields (equation 1).



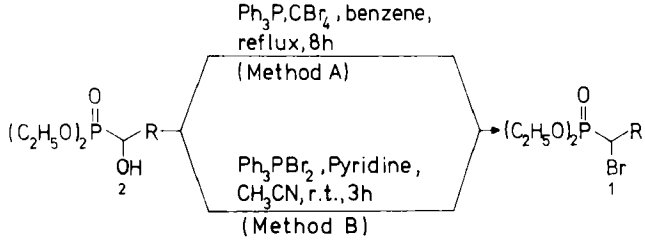
(1)

R=H, Alkyl, Ph.

The triphenylphosphine–carbon tetrabromide system and dibromotriphenylphosphorane were found to be versatile reagents for conversion of alcohols into alkyl bromides,[13–16] generally in good yields.

Their reactions with alcohols lead to rapid formation of the corresponding alkoxyphosphonium salts that decompose by a slow substitution to form alkyl bromides.[14]

This paper describes a transformation of diethyl 1-hydroxyalkylphosphonates **2** into diethyl 1-bromoalkylphosphonates **1**, by means of triphenylphosphine–carbon tetrabromide system (method A) or dibromotriphenylphosphorane in the presence of pyridine (method B) (Scheme 2). The reaction proceeds smoothly in boiling benzene (method A) affording, after vacuum distillation, pure compounds **1** in good to moderate yields. The best results are obtained when the mixture of diethyl 1-hydroxyalkylphosphonate **2**, carbon tetrabromide, and triphenylphosphine is used in a molar ratio of 1:1.15:1.25.



1,2	a	b	c	d	e
R	H	CH_3	C_2H_5	n-C_3H_7	Ph

SCHEME 2

TABLE I

Diethyl 1-Bromoalkylphosphonates **1a–e** Prepared

Product	Yield[a] (%) Method: A	B	b.p. (°C)/Torr and n_D^{20}	lit. b.p. and n_D^{20}	Molecular Formula[b]
1a	65	67	62–64/0.1 1.4589	99/1[17] 1.4585[17]	$C_5H_{12}BrO_3P$ (231.1)
1b	57	49	58–60/0.1 1.4569	86–89/2[8]	$C_6H_{14}BrO_3P$ (245.1)
1c	43	46	66–68/0.2 1.4587	93–96/2[8]	$C_7H_{16}BrO_3P$ (259.1)
1d	39	22	78–80/0.1 1.4583	101–103/2[8]	$C_8H_{18}BrO_3P$ (273.1)
1e	42	42	124–125/0.2 1.5304	164–165/1[6] 1.5310[6]	$C_{11}H_{16}BrO_3P$ (307.1)

[a] Yield of isolated pure product, based on **2**.
[b] Satisfactory microanalyses obtained: C ± 0.15, H ± 0.10, P ± 0.05.

TABLE II

Spectroscopic data of the diethyl 1-bromoalkylphosphonates **1a–e**

Compound	IR (film)[a] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[b] δ (ppm), J (Hz)	^{31}P-NMR (neat, H_3PO_{4ext})[c] δ (ppm)
1a	1260, 1096, 1024, 968	1.37 (t, 6H, J = 7.1, $2CH_3$); 3.29 (d, 2H, J = 9.7, CH_2); 4.22 (qu, 4H, J = 7.1, $2CH_2$)	18.9
1b	1254, 1096, 1024, 964	1.36 (t, 6H, J = 7.0, $2CH_3$); 1.85 (dd, 3H, J = 16.7, 7.3, CH_3); 3.91 (dq, 1H, J = 9.0, 7.3, CH); 4.04–4.41 (m, 4H, $2CH_2$)	20.8
1c	1258, 1098, 1014, 964	1.14 (t, 3H, J = 7.0, CH_3); 1.27 (t, 6H, J = 7.1, $2CH_3$); 1.70–2.35 (m, 2H, CH_2); 3.59–3.88 (m, 1H, CH); 4.03–4.41 (m, 4H, $2CH_2$)	19.9
1d	1260, 1096, 1060, 968	0.94 (bt, 3H, J = 7.0, CH_3); 1.36 (t, 6H, J = 7.0, $2CH_3$); 1.56–2.10 (m, 4H, $2CH_2$); 3.67–3.96 (m, 1H, CH); 4.03–4.39 (m, 4H, $2CH_2$)	20.0
1e	1260, 1096, 1032, 972	1.15, 1.33 (2t, 6H, J = 7.1, $2CH_3$); 3.69–4.39 (m, 4H, $2CH_2$); 4.85 (d, 1H, J = 13.0, CH); 7.27–7.65 (m, $5H_{arom}$)	17.5

[a] Recorded on a Specord M80 (C. Zeiss) spectrometer. Only the most characteristic bands are given.
[b] Recorded at 80 MHz with a Tesla BS 587 FT spectrometer. Abbreviations: t—triplet, d—doublet, q—quartet, qu—quintet, m—multiplet, b—broad.
[c] Recorded at 36.43 MHz with Bruker HFX-90 spectrometer. Positive chemical shifts are downfield from H_3PO_4 (85%).

In the method B, which is a modification of the procedure proposed by Baban *et al.*,[7] the reaction occurs at room temperature in acetonitrile, when a 5% molar excess of dibromotriphenylphosphorane prepared "in situ" is used in the presence of pyridine. In most cases the corresponding bromophosphonates **1** are formed in yields comparable to those obtained by method A. The results are summarized in Table I. The structure of diethyl 1-bromoalkylphosphonates **1** was confirmed by ^{31}P-NMR and ^{1}H-NMR spectroscopy (Table II). The above mentioned methods are restricted to the primary and secondary (alkyl or aryl substituted) diethyl 1-hydroxyalkylphosphonates **2**. Both methods A and B give the best results for primary diethyl bromomethylphosphonate **1a**. In the case of secondary substrates (**2b–e**), yields are considerably lower. This does not resemble chlorination[12] of the same compounds by means of triphenylphosphine–carbon tetrachloride system, where the conversion is practically independent on the structure of hydroxyphosphonate **2**.

In conclusion, the main advantage of the methodology presented here is the possibility of direct transformation of the readily available diethyl 1-hydroxyalkylphosphonates **2** into primary and secondary (alkyl or aryl substituted) diethyl 1-bromoalkylphosphonates **1**. Despite the moderate yields obtained it could be a useful alternative for the alkylative approach proposed by Savignac *et al.*[8]

EXPERIMENTAL

Diethyl 1-hydroxyalkylphosphonates **2** are prepared, according to the previously described procedure,[10] from diethyl phosphite and the appropriate aldehyde in the presence of triethylamine.

Diethyl 1-bromoalkylphosphonates **1a–e**; *General procedure. Method A.* Carbon tetrabromide (7.63 g, 0.023 mol) is added in one portion to a stirred solution of diethyl 1-hydroxyalkylphosphonate **2** (0.02 mol) and triphenylphosphine (6.56 g, 0.025 mol) in dry benzene (25 ml) at room temperature (ice-water bath). Stirring is continued for 15 min at room temperature, and the mixture is then refluxed for 8 h. The solvent is removed in vacuo, and the brown, semisolid residue is extracted with hexane (3 × 50 ml). The combined extracts are filtered, and the solvent is evaporated under reduced pressure. The oily residue is distilled in vacuo to give analytically pure **1**.

Method B. Bromine (3.36 g, 0.021 mol) is added dropwise to a stirred suspension of triphenylphosphine (5.51 g, 0.021 mol) in dry acetonitrile (35 ml). The temperature is kept below 30°C (ice-water bath). Stirring is then continued for 30 min at room temperature. The mixture is cooled to −20°C and a solution of diethyl 1-hydroxyalkylphosphonate **2** (0.02 mol) and pyridine (1.58 g, 0.02 mol) in acetonitrile (5 ml) is added in one portion. After the addition is completed, the suspension is allowed to warm to room temperature and the stirring is continued for additional 3 h. After about 1 hr a clear solution is obtained. Acetonitrile is evaporated under reduced pressure and the semisolid residue is extracted with hexane (4 × 50 ml). The combined extracts are filtered and the solvent removed in vacuo. The oily residue is distilled under reduced pressure to afford analytically pure **1**.

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