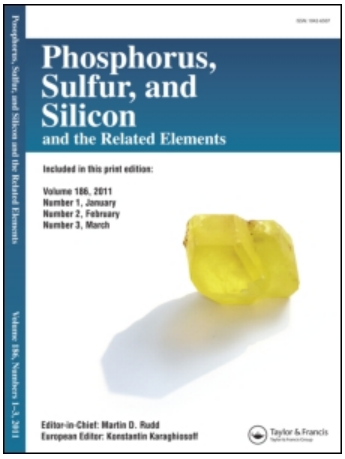

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SYNTHESIS OF DIALKYL 1,2-EPOXYPHOSPHONATES UNDER PHASE-TRANSFER CATALYST CONDITIONS

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SYNTHESIS OF DIALKYL 1,2-EPOXYPHOSPHONATES UNDER PHASE-TRANSFER CATALYST CONDITIONS

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The reaction of dialkyl phosphonates with chloroacetone and base under phase-transfer catalyst conditions has been investigated. Dialkyl 1,2-epoxyalkylphosphonates are obtained in good yield from the reaction. A two-step mechanism involving deprotonation of the dialkyl phosphonate, followed by nucleophilic attack by the phosphonate anion at the carbonyl group of the ketone is proposed. The oxirane formation during the second stage of the reaction involves displacement of chloride ion. The reaction is highly selective.

Key words: Dialkyl phosphonates; phase-transfer catalysts; epoxyphosphonates.

INTRODUCTION

Dialkyl epoxyalkylphosphonates are of interest because of their use as intermediates in the synthesis of bioactive substances,[1–4] and as modifiers of natural and synthetic polymers.[5–7] Different methods are known for the synthesis of dialkyl 1,2-epoxyalkylphosphonates.[8,9] Present methods for the synthesis of epoxyphosphonates have been reviewed.[8] These methods, which are shown in Scheme 1, include (a) the reaction of a dialkyl phosphonate halohydrin with base[10,11]; (b) the reaction of sodium dialkylphosphonate with and α-halo ketone[11]; (c) the Darzen's reaction of dialkyl chloromethylphosphonates with carbonyl compounds; (d) the direct epoxidation of unsaturated phosphonates with a peroxide and an added catalyst, or with a peracid[12]; and (e) the reaction between a dialkyl phosphonates, an α-halo ketone, and sodium alkoxide.[13] In general the yields for methods (a–d) are optimally in the 60–70% range, and for method (e) the optimal yields are in the 53–87% range. Although the yields of these reactions are generally acceptable, these procedures have limitations that may make them unapplicable in certain circumstances. The reaction of sodium dialkyl phosphonate has been reported to also give the isomeric enol or vinyl phosphate,[10,11] and the α-halo carbon cannot be tertiary.[11] The Darzen's reaction is limited to ketones and aryl aldehydes, and this reaction has, as yet, been carried out only with the methyl and ethyl esters of

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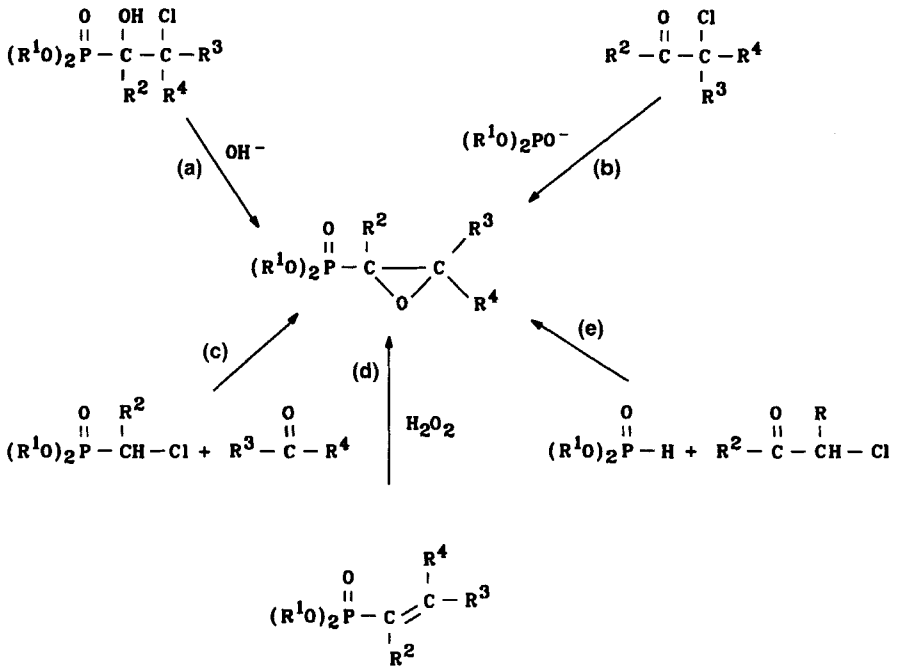


Scheme 1

chloromethylphosphonic acid. The epoxidation of unsaturated phosphonates can also result in side reactions,[12] and the stoichiometric reaction between a dialkyl phosphonate, an α-halo ketone and sodium alkoxide has only been carried out with the methyl, ethyl and benzyl phosphonates. With respect to the synthesis of dialkyl 1,2-epoxyalkylphosphonates, methods that involve the formation of a P—C bond and an epoxy ring in a single step are likely to be most useful. As an example of such a procedure, the reaction of sodium salts of dialkyl phosphonates with α-halogenated carbonyl compounds such as chloroacetone[13] affords dialkyl 1,2-epoxyphosphonates in high yield.

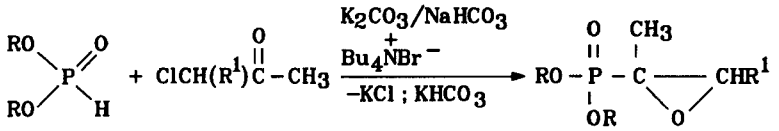
The activation of P—H bonds under phase-transfer catalyst conditions has been investigated for the Atherton-Todd reaction.[14–19] This modification offers substantial advantages in simplicity and effectiveness as compared to conventional methods. The phase-transfer conditions simplify and accelerate numerous reactions traditionally performed in non-aqueous media. The two-phase version of the classical Atherton-Todd reaction has been successfully applied for the phosphorylation of amines,[14] *O*-alkylhydroxylamine[15] and alcohols.[16] This technique can also be used for the preparation of pure phosphoroamidates in high yield, and for the preparation of pure di-t-butylphosphorochloridate.[17] The phase-transfer catalyzed modification of the Atherton-Todd reaction can be used for the preparation of diethyl *N*-arylphosphoramidates from formanilides and chloroacetanilides.[18]

In this paper we now report the synthesis of dialkyl 1,2-epoxyphosphonates from dialkyl phosphonates and α-halogenated carbonyl compounds under phase-transfer

catalyst conditions, and show how this modification improves the product yield, and also allows the reaction to be carried out under aerobic conditions.

RESULTS AND DISCUSSION

We find that 1,2-epoxyalkylphosphonates can be obtained in good yield from $(RO)_2P(O)H$ and $ClCH(R^1)C(O)CH_3$ under phase transfer catalyst conditions according to Scheme 2. The two system liquid/solid reaction has been carried out under two sets of conditions with different bases. The first procedure (A) uses 50 mol% excess of potassium carbonate, and the second procedure (B) uses a mixture of potassium carbonate and sodium hydrogen carbonate. Tetrabutylammonium bromide (TBAB) is used as a catalyst in each procedure. Each reaction is carried out in the absence of any solvent. The starting reagents form the liquid phase. The experimental results are collected in Table I. The differences in the substituents



1 *2*

1	2	R	R^1
a	a	CH_3	H
b	b	C_2H_5	H
c	c	C_4H_9	H
d	d	iso Pr	H
b	e	C_2H_5	CH_3

Scheme 2

TABLE I

Yield data and boiling points for dialkyl 1,2-epoxyphosphonates **2** from dialkyl phosphonate **1** based on the procedures A or B with different substituents on the dialkyl phosphonate

1	2	R	b.p., °C/mm	R^1	Yield %	Procedure
a	a	CH_3	74-76/0.6	H	74.4	A
b	b	C_2H_5	76-77/0.5	H	76.6	A
c	c	n-C_4H_9	98-100/0.15	H	69.1	A
d	d	iso-Pr	76-77/0.3	H	68.7	B
b	e	C_2H_5	60-66/0.1	CH_3	52.6	B

TABLE II

Yield data for dialkyl 1,2-epoxyphosphonates based on the type of dialkyl phosphonate in the presence of the solvent

Procedure	Yield, %	Solvent	
A	76.7	CH_2Cl_2	
B	83.2	None	
C	81.1	CH_2Cl_2	
D	85.2	CH_3CN	

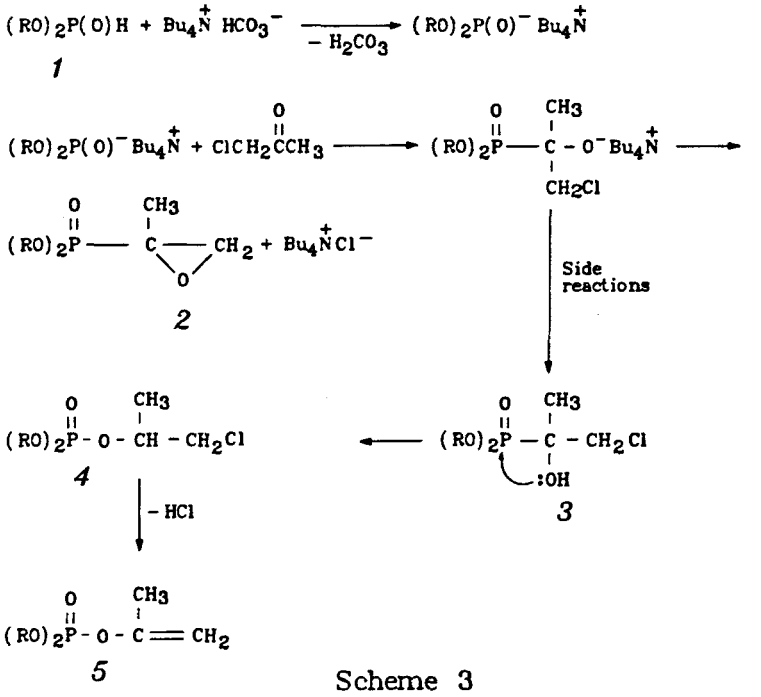
TABLE III

^1H, ^{13}C and ^{31}P NMR data for the dialkyl-1,2-epoxyphosphonates **2**

1	2				
	R	**R¹**	**^{1}H NMR, δ [ppm]**	**^{13}C NMR, δ [ppm]**	**^{31}P{H}, δ[ppm]**
a	CH_3	H	1.51 (d, ^{3}J(PH) = 11.3 Hz, 3H) 2.75 (tt, ^{2}J(HH) + ^{3}J(PH) = 5.1 Hz, 1H) 3.11 (t, ^{2}J(HH) + ^{3}J(PH) = 5.2 Hz, 1H) 3.81 (d, ^{3}JPH) = 10.5 Hz, 6H)	17.15 (^{2}J(PC) = 15.3 Hz) 50.7 (^{1}J(PC) = 203 Hz) 58.88 52.97	21.08
b	C_2H_5	H	1.35 (t, ^{3}J(HH) = 7. 0 Hz, 6H) 1.52 (d, ^{3}J(PH) = 11.3 Hz, 3H) 2.72 (t, ^{2}J(HH) + ^{3}J(PH) = 5.1 Hz, 1H) 3.12 (t, ^{2}J(HH) + ^{3}J(PH) = 5.2 Hz, 1H) 4.15-4.25 (m, 4H)	16.30 17.28 (^{2}J(PC) = 15.3 Hz) 51.8 (^{1}J(PC) = 198.7 Hz) 62.5 (^{2}J(PC) = 6.8 Hz) 62.9 (^{2}J(PC) = 5.9 Hz)	21.36
c	n-C_4H_9	H	0.94 (t, ^{3}J(HH) = 7.3 Hz, 6H) 1.37-1.47 (m, ^{3}J(HH) =7.2 Hz, 4H) 1.52 (d, ^{3}J(PH) = 11.2 Hz, 3H) 1.62-1.73 (m, ^{3}J(HH) = 7. 1 Hz, 4H) 2.72 (t, ^{2}J(HH) + ^{3}J(PH) = 5.1 Hz, 1H) 3.12 (t, ^{2}J(HH) + ^{3}J(PH) = 5.2 Hz, 1H) 4.1 - 4.16 (m, 4H)	12.95 17.4 (^{2}J(PC) = 14.8 Hz) 18.26 32.0 (^{3}J(PC) = 5.9 Hz) 53.2 (^{1}J(PC) = 194.6 Hz) 63.1 (^{2}J(PC) = 6.8 Hz) 65.06 (^{2}J(PC) = 5.8 Hz)	21.57

TABLE III (*Continued*)

1	2				
	R	R^1	^{1}H NMR, δ [ppm]	^{13}C NMR, δ [ppm]	^{31}P{H}, δ[ppm]
d	$(CH_3)_2CH$	H	1.33-1.52 (m, 12H) 1.50 (d, ^{3}J(PH) = 11.1 Hz, 3H) 2.71 (t, ^{2}J(HH) + ^{3}J(PH) = 5. 1 Hz, 1H) 3.12 (t, ^{2}J(HH) + ^{3}J(PH) = 5.2 Hz, 1H) 4.66 - 4.83 (m, 1H)	17.5 (^{2}J(PC) = 14.1 Hz) 23.8 51.61 71.46 (^{2}J(PC) = 6. O Hz)	19.61
b	C_2H_5	CH_3	1.25 (m, 9H) 1.36 (q, ^{3}J(HH) = 12.0 Hz, 3H) 3.33 (q, ^{3}J(HH) + ^{3}J(PH) = 5.6 Hz, 1H) 4.03 - 4.12 (m, 4H).	12.55 16.30 55.0 (^{1}J(PC) = 198.4 Hz) 62.54 (^{2}J(PC) = 6. 8 Hz) 62.87 (^{2}J(PC) = 5. 9 Hz)	22.20



Scheme 3

on the dialkyl phosphonate **1** does not significantly influence the yield of 1,2-epoxyphosphonate **2** formed, which ranges from 76.6% to 52.6%. The same products and yields are obtained when the reaction is carried out in the presence of a solvent. The two solvents that have been used are dichloromethane (procedure C) and acetonitrile (procedure D). The yields of the 1,2-epoxyphosphonates are similar in the presence of either solvent (Table II). The structure of the final products has been verified by a combination of ^{1}H, ^{31}P and ^{13}C NMR spectroscopy (Table III).

The experimental results obtained can be explained on the basis of the first stage of the reaction involving the deprotonation of the dialkyl phosphonate by $Bu_4N^+HCO_3^-$. The dialkyl phosphonate anion $(RO)_2P(O)^-$ can then react with chloroacetone according to Scheme 3.

On the basis of our results, it can be assumed that the reaction proceeds either on the phase boundary or in the organic phase. The established inhibition of the formation of the 1,2-epoxyphosphonates in the presence of the CO_2 allows us to assume that the interaction proceeds in the organic phase. It is likely, therefore, that the deprotonation of the dialkyl phosphonate occurs in the organic phase by reaction with a small amount of potassium hydrogen carbonate.

We find that when the reaction between dialkyl phosphonates and α-halogenated carbonyl compounds is carried out under phase-transfer catalyst conditions, the side reactions that usually accompany this reaction are strongly suppressed. One such reaction leads to the formation of 1-hydroxy-2-chloroalkylphosphonates **3**. From our ^1H NMR spectra data of samples taken from the organic phase, we have established that the amount of this product is approximately 3 to 5%. This low content of compound **3** results in the absence of the phosphonates **4** and the vinylphosphonates **5** in the reaction mixture.

These results show that 1,2-epoxyphosphonates **2** can be synthesized in good yields under phase transfer catalyst conditions.

EXPERIMENTAL

Dialkyl phosphonates, Fluka, were used without purification; chloroacetone, Merck (Techn. ~95%) and 3-chloro-2-butane was distilled prior to use; K_2CO_3, $NaHCO_3$ and $Bu_4N^+Br^-$ were used without additional purification.

Procedure A: Typical conditions are: dialkyl phosphonate **1** (0.1 mol) was added to a mixture of K_2CO_3 (0.1 mol), $NaHCO_3$ (0.05 mol) and $Bu_4N^+Br^-$ (1.10^{-3} mol) at 0°C. Chloroacetone (0.1 mol) was added dropwise for about 30 min., so that the temperature should not exceed 35°C. The mixture was stirred vigorously for 1 h at room temperature, and for an additional 1 h at 55–60°C. Methylene chloride (50 ml) was added, and the inorganic salts filtered. After removing the methylene chloride, the 1,2-epoxyphosphonate **2** was distilled under reduced pressure. The yields of the 1,2-epoxyphosphonates are given in Table I.

Procedure B: Typical conditions are: dialkyl phosphonate **1** (0.1 mol) was added to a mixture of K_2CO_3 (0.15 mol) and $Bu_4N^+Br^-$ (1.10^{-3} mol) at 0°C. Chloroacetone (0.1 mol) was added dropwise for about 30 min. so that the temperature of the reaction does not exceed 35°C. The mixture was stirred vigorously for 1 h at room temperature and for an additional 1 h at 55–60°C. Methylene chloride (50 ml) was added, and the inorganic salts filtered. After removing the methylene chloride, the 1,2-epoxyphosphonate **2** was distilled under reduced pressure. The yields of the 1,2-epoxyphosphonates are given in Table I. At the same conditions was carried out interaction between diethyl phosphonate and 3-chloro-2-butanone.

Procedure C: Typical conditions are: dialkyl phosphonate **1** (0.1 mol) was added to a mixture of K_2CO_3 (0.1 mol), $NaHCO_3$ (0.05 mol), $Bu_4N^+Br^-$ (1.10^{-3} mol) and methylene chloride (50 ml) at 0°C. Chloroacetone (0.1 mol) was added dropwise for about 30 min. so that the temperature should not exceed 35°C. The mixture was stirred vigorously for 1 h at room temperature, and for an additional 1 h at 55–60°C. The inorganic salts were filtered, and washed with methylene chloride (20 ml). After removing the methylene chloride, the 1,2-epoxyphosphonate **2** was distilled under reduced pressure. The yield of the 1,2-epoxyphosphonate is given in Table II.

Procedure D: In this case the reaction is carried out as in procedure C, but acetonitrile was now used as solvent. The yield of the corresponding 1,2-epoxyphosphonate is given in Table II.

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