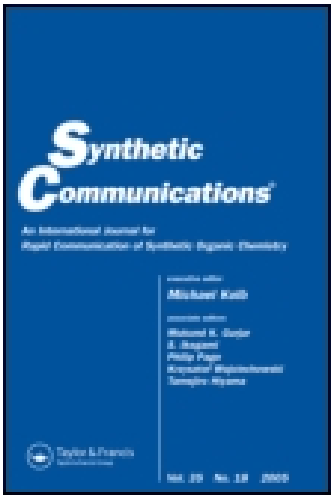

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An Efficient Protocol for the Synthesis of 2-Chloroethylphosphonic Acid

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AN EFFICIENT PROTOCOL FOR THE SYNTHESIS OF 2-CHLOROETHYLPHOSPHONIC ACID

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ABSTRACT : An efficient synthetic route to prepare 2-chloroethylphosphonic acid (ethephon) with high purity was developed.

2-Chloroethylphosphonic acid (ethephon) **1** is very much used in agriculture as a plant regulator[1]. It is an especially good stimulant used to increase the latex production of *Hevea brasiliensis.* Ethephon was first synthesized by Kabachnick and Rossiiskaya[2] in 1946. It is most of the time prepared by acid hydrolysis of *bis*(2-chloroethyl)-2-chloroethylphosphonate by hydrochlorhydric acid[2-8] previously prepared by isomerization of *tris*(2-chloroethyl)phosphite (Michaelis-Arbuzov rearrangement)[2, 9-14] (Scheme I).

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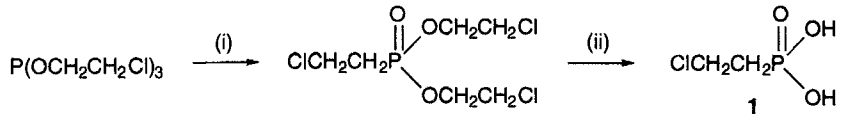


(i) Isomerization is obtained by heating to reflux ; (ii) hydrolysis is carried out with HCl 37% or HCl gaz.

Scheme I.

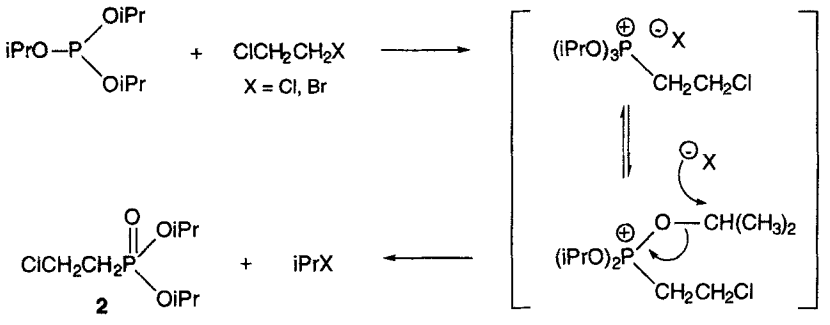
Because the field of our research required the use of pure ethephon[15], we searched to optimize the preparation of this product. At first, we tried to prepare ethephon according to the usually used method described above, after several tests, its was noticed that the *Bis*(2-chloroethyl)-2-chloroethylphosphonate is generally obtained in low yield (55%), and its hydrolysis by HCl is never complete. The ethephon so prepared is always polluted by presence of 2-chloroethyl-2-chloroethylphosphonate (Scheme II).

(i) limited hydrolysis by HCl 37% or HCl gaz.

Scheme II.

The low reactivity of P-O-CH_2CH_2Cl ester bond towards acid hydrolysis may be explained by the strong bonding energy of P-O-C bond. To solve this problem, it was considered to change the *bis*(2-chloroethyl)-2-chloroethylphosphonate intermediate by a new one having more labile alkyl ester groups : the diisopropyl-2-chloroethyl-phosphonate **2**. **2** was prepared according to Michaelis-Arbuzov reaction between triisopropylphosphite and a 1,2-dihalogenoethane compound [1-bromo-2-chloroethane **3** or 1,2-dichloroethane **4**].

The first product formed by the S_N2 reaction[16] is a phosphonium salt which immediately decomposes to the diisopropyl-2-chloroethylphosphonate intermediate (Scheme III).



Scheme III.

Whatever the nature of the 1,2-dihalogenoethane **3** or **4** reagent, the end product was obtained (diisopropyl-2-chloroethyl phosphonate), but the yields were very different (Table 1). The reaction was more efficient in the presence of the 1-bromo-2-chloroethane, which requires mild experimental conditions.

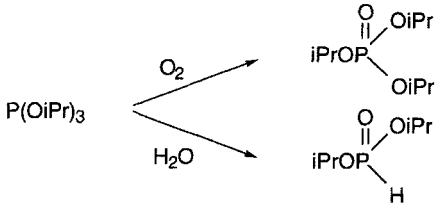
Table 1 : Experimental conditions and yields

X in XCH_2CH_2Cl	$[XCH_2CH_2Cl]/[P(OiPr)_3]$	Times of reflux	Yield[a)]
Br	1,5	24 hours	78%
Cl	2	48 days	54%

a) : Determined from pure distillated product.

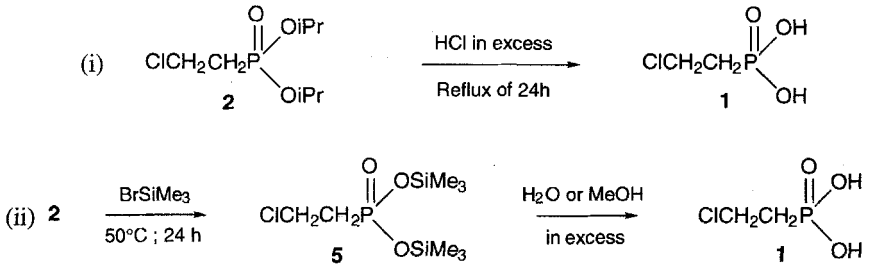
The Michaelis-Arbuzov reaction carried out with 1-bromo-2-chloroethane is more selective than with the dichloro derivative because the nucleophilicity of bromide atom is higher than that of chlorine atom. With 1,2-dichloroethane, the Arbuzov rearrangement is accompanied by other processes which lead to secondary products : triisopropylphosphate and diisopropylphosphite which respectively result from oxidation and hydrolysis of the starting phosphite (Scheme IV).

To generate 2-chloroethylphosphonic acid, two paths were prospected (Scheme V): (i) hydrolysis of diisopropyl-2-



Scheme IV.

chloroethylphosphonate with a 12 N hydrochloric acid solution ; (ii) the transformation of **2** in its di(trimethylsilyl)-2-chloroethyl-phosphonate derivative **5** by reaction with an bromotrimethyl silane[17-20], followed by reaction with a proton donor compound (water, methyl alcohol).



Scheme V.

In each case (i or ii), a pure ethephon was generated with high yield (> 99%). The different reaction products were characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopies (Table 2).

In ^{1}H NMR, **5** and ethephon show two doublets of triplets at 2,10 and 3,55 ppm which respectively correspond to CH_2-P and CH_2Cl proton from the 1-chloroethyl substituant. The presence of these doublets of triplets is explained by the coupling with the phosphorus atom. In the case of diisopropyl-2-chloroethylphosphonate, the ^{1}H NMR signals which respectively correspond to CH_2-P and CH_2Cl protons from 2-chloroethyl group are more complex.

Table 2 : Characterization by ^{1}H, ^{13}C and ^{31}P NMR spectroscopies.

		2[a]	5[a]	1[b]
RMN ^{1}H :	CH_3-	**1,32** : d ; $^{3}J_{H-H} = 6.3$	CH_3- **0.25** : s	CH_2P- **2.10** : d ; $^{2}J_{H-P} = 18.1$
	CH_2P-	**2.25** : m ; $^{2}J_{H-P} = 18.8$	CH_2P- **2.15** : t ; $^{2}J_{H-P} = 18.9$	$ClCH_2$- **3.55** : m ; $^{2}J_{H-P} = 14.2$
	$ClCH_2$-	**3.70** : m ; $^{3}J_{H-P} = 8.7$	$ClCH_2$- **3.65** : dt ; $^{2}J_{H-P} = 9.4$	
	-CH-	**4.71** d ; $^{3}J_{H-H} = 6.2$		
RMN ^{13}C :	CH_3-	**23.70** : s	CH_3- **0.98** : s	CH_2P- **30.02** : d ; $^{1}J_{P-C} = 133.2$
	CH_2P-	**33.38** : d ; $^{1}J_{P-C} = 137.7$	CH_2P- **33.1** : d ; $^{1}J_{PC} = 96.7$	$ClCH_2$- **37.45** : s
	$ClCH_2$-	**37.58** : s	CH_2Cl **38.25** : s	
	-CH-	**4.71** : d ; $^{2}J_{P-C} = 6.6$		
RMN ^{31}P :		**23.7**	**7.1**	**25.7**

a) ($CDCl_3$, δ : ppm and J : Hz) ; b) (D_2O, δ : ppm and J : Hz)

Experimental

General procedure for the synthesis of diisopropyl-2-chloroethylphosphonate : A mixture of triisopropylphosphite (1 eq) and 1-halogeno-2-chloroethane (1,5 eq or 2 eq) was refluxed for several hours (Table 1). The pure diisopropyl-2-chloroethylphosphonate was isolated by distillation at 62°C/0,1 mmHg with 78% yield.

2-chloroethylphosphonic acid generated from diisopropyl-2-chloroethylphosphonate : A mixture of diisopropyl-2-chloroethylphosphonate (1 eq) and hydrochloric acid 12N (8 eq) was refluxed for 24 hours. Then, the mixture was concentred under reduced pressure. The precipitated ethephon was filtered, then purified by washing with CH_2Cl_2. A pure ethephon (> 99%) was obtained with a 90% yield.

2-chloroethylphosphonic acid generated after transformation of diisopropyl-2-chloroethylphosphonate into the di(trimethylsilyl)-2-chloroethylphosphonate : Diisopropyl-2-chloroethylphosphonate (1 eq) in acetonitrile (50 ml) was heated at 50°C under nitrogen, and then the bromotrimethylsilane (1,5 eq) was added drop by drop. After 24 h, a pure di(trimethylsilyl)-2-chloroethylphosphonate (> 99%) was isolated by distillation at 70°C/0,2 mmHg with 70% yield. The di(trimethylsilyl)-2-chloroethylphosphonate intermediate (1 eq) was hydrolyzed by water or methyl alcohol (1,5 eq) at 20°C during 1 hour. Then, the mixture was concentred under reduced pressure. The precipitated ethephon was filtered and purified by washing with CH_2Cl_2. A pure ethephon (> 99%) was obtained with a 90% yield.

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