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Synthesis and Reactions of 2,2,2-Trihaloethyl α-Hydroxyiminobenzylphosphonates. The Influence of the Ester Group on the Chemistry of Phosphonates

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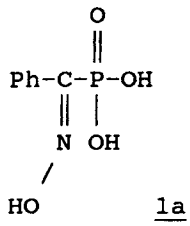
ABSTRACT

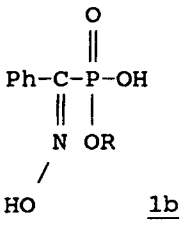
*Arbuzov reactions of diethyl 2,2,2-trihaloethyl phosphites (**3**) with benzoyl chloride afforded ethyl 2,2,2-trihaloethyl benzoylphosphonates (**4**). The reactions of **4** with $NH_2OH.HCl$ led to the formation of methyl benzoate and ethyl methyl H-phosphonate as a result of alcoholysis of **4**, followed by alkoxy group exchange. Methanol solutions of benzoylphosphonates **4** were found by ^{31}P NMR spectroscopy to contain considerable proportions of hemiacetals, **7**, which undergo base-catalyzed C—P bond cleavage. The formation of hemiacetals from benzoylphosphonates **4** is suppressed in 2-propanol, and in this solvent the corresponding oximes **2** could be obtained in good yields. Reactions of methyl benzoylphosphonochloridate (**10**) with 2,2,2-trihaloethanols, in CH_2Cl_2, gave methyl 2,2,2-trihaloethyl benzoylphosphonates (**11**) which could be converted directly to oximes **12** by $NH_2OH.HCl$ in a one-pot procedure. In contrast to the previously studied dimethyl (E)-α-hydroxyiminobenzylphosphonate, which underwent thermal Beckmann rearrangement to afford N-benzoylphosphoramidates, both (E) and (Z)-trihaloethyl esters **2** and **12** underwent fragmentation to benzonitrile and to the corresponding dialkyl hydrogen phosphate, reflecting the increased electrophilicity of the phosphorus in these compounds. Demethylation of methyl esters **12** was effected smoothly by iodide or bromide ions to yield benzoylphosphonate salts **15**, which in turn were converted to oxime salts **14** by treatment with hydroxylamine. In contrast, attempted deethylation of ethyl esters **2** in refluxing acetonitrile led to benzonitrile and pyrophosphate type product as indicated by ^{31}P spectroscopic examination of the reaction mixture. Oxime salts **14** behaved similarly when heated. Acidification of lithium 2,2,2-trifluoroethyl α-hydroxyiminobenzylphosphonate (**14a**) gave the corresponding hydrogen trifluoroethyl phosphonate (**19a**). The fragmentation of **19a** in 0.6 N ethanolic hydrogen chloride to ethyl trifluoroethyl hydrogen phosphate and benzonitrile at room temperature had a $T_{1/2}$ value of approx 18 hours, which is greater by a factor of 2 than that of the corresponding methyl ester. When the fragmentation of **19** was carried out in solvent mixtures of either water with methanol or 2-propanol, or methanol with t-butanol, the composition of the solvents was reflected in the products, indicating a dissociative type mechanism, involving metaphosphate as reactive intermediates.*

INTRODUCTION

We previously reported that α-hydroxyiminophosphonic acids (e.g., **1a**) and monoesters (**1b**) can serve as precursors to



1a



1b

*To whom correspondence should be addressed.
This paper is dedicated to Professor Herbert C. Brown on the occasion of his 80th birthday.

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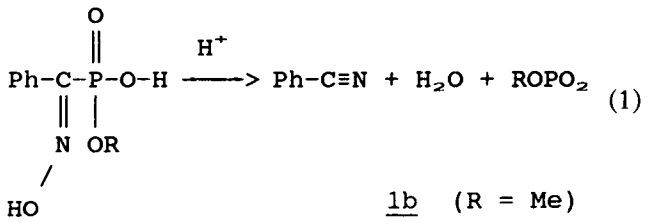
monomeric metaphosphoric acid [1], its anion [1] or ester [2], respectively, and may act as phosphorylating agents [1–3]. Thus, α-hydroxyiminobenzylphosphonic acid (**1a**) is unstable as the free acid or as a salt and undergoes facile decomposition in solution of a wide range of pH [1].

The corresponding monoesters (e. g., **1b**, R = Me) are unstable as free acids, which undergo spontaneous fragmentation as shown in equation 1 [2]. Their salts are stable but are unsuitable for use



(1)

1b (R = Me)

as reagents in organic solvents because of their lack of solubility. Their conversion in situ to the active **1b** would require acid treatment, which could be harmful to some substrates to be phosphorylated. Consequently, we seek various types of ester derivatives that can serve as protecting groups for the phosphonic function. These can serve either as stable precursors from which the reactive, free hydroxyiminophosphonic acids can be liberated or alternatively, the protecting group may be carried over to the product (in the case of the monoester fragmentation). In either case, the free acids could be liberated by selective and mild methods. We recently reported the synthesis and photochemical debenzylationfragmentation of α-hydroxyiminophosphonate benzyl esters which constitute one solution to this problem [4].

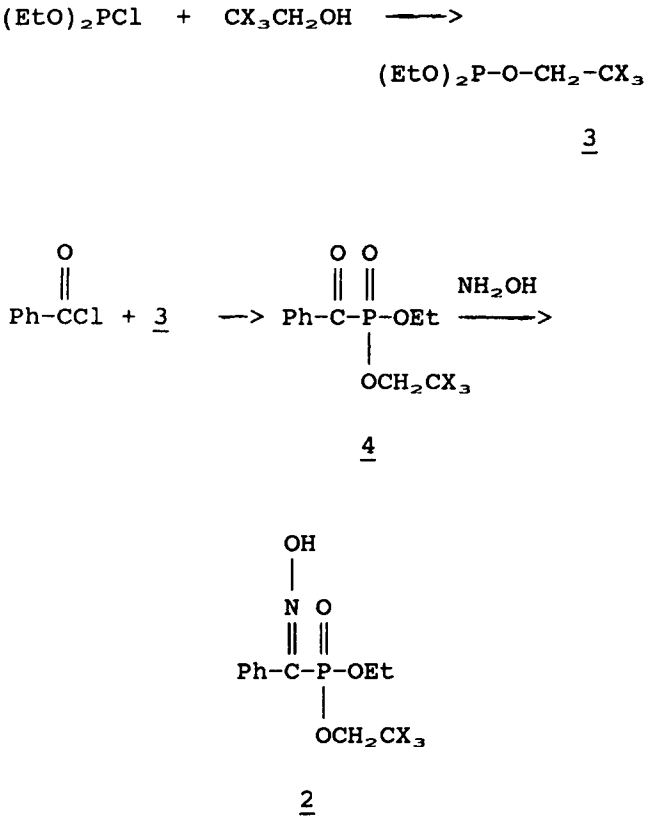
The 2,2,2-trichloroethyl group is a well known protecting group for carboxylate [5] and phosphate [6]. Similarly, the 2,2,2-trifluoroethyl group has also been shown, to be removable under mild conditions [7]. Consequently, we decided to synthesize a series of trihaloethyl α-hydroxyiminobenzylphosphonates in order to examine their chemical properties.

RESULTS AND DISCUSSION

Synthesis and Properties of Alkyl 2,2,2-Trihaloethyl α-Hydroxyiminobenzylphosphonates 2 and 12

The first synthetic approach to alkyl 2,2,2-trihaloethyl α-hydroxyiminobenzylphosphonates **2** is illustrated in Scheme 1. This synthesis consists of three steps: 1) The preparation of diethyl 2,2,2-trihaloethyl phosphites (**3**); 2) Arbuzov reaction of **3** with benzoyl chloride to give ethyl 2,2,2-trihaloethyl benzoylphosphonates (**4**), and 3) Conversion of the ketones **4** to the corresponding oximes **2**.

Diethyl 2,2,2–trihaloethyl phosphites (**3a** and **3b**) were prepared in high yields by reacting diethyl phosphorochloridite [8] with the corresponding 2,2,2-trihaloethanol in the presence of N,N-diethylaniline in ether. Arbuzov reactions of **3a** and **3b** with benzoyl chloride afforded benzoylphosphonate mixed esters **4a** and **4b** in about 40–50% yield. It is worthy to point out that the Arbuzov reactions of **3a**



SCHEME 1

and **3b** were notably slower than those of triethyl phobshite (their completion required ≈24 hours versus ≈1 hour at ambient temperature for the latter). This low reaction rate probably results from the reduced nucleophilicity of the phosphorus in **3**, caused by the electron withdrawing effect of the trihaloethyl group. Ethyl trihaloethyl benzoylphosphonates **4a** and **4b** were identified by the usual analytical and spectroscopic methods. In the ^{31}P spectrum benzoylphosphonates **4** resonate in the range of δ = –1.2 to –1.4, which is at significantly higher field than the chemical shift observed for diethyl benzoylphosphonate (δ = 0.73).

The conversion of ketophosphonates **4** to the corresponding oximes (**2**) was first attempted using treatment by hydroxylamine hydrochloride and pyridine in methanol [9]. This experiment, using **4a**, led to the formation of methyl benzoate and ethyl methyl H-phosphonate in ≈90% yield, resulting

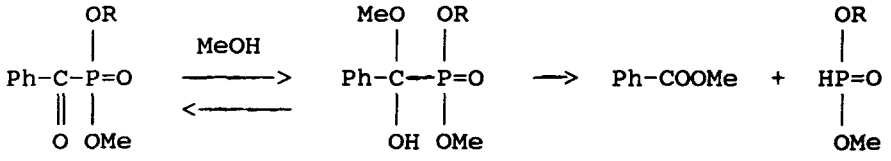
TABLE 1 Composition of Solutions of Benzoylphosphonates 6a and 6b (0.37 M) in Methanol at Room Temperature in the Presence or Absence of Pyridine as Function of Time.

A) methyl 2,2,2-trifluoroethyl benzoylphosphonate (6a)					
		Composition[a]			
Pyridine Molarity	*Time Min.*	*Acylphosphonate*	*Hemiketal*	*H-phosphonates*	
		6a	**7a**	**8a**	**8b**
0	4	39%	61%	0	0
0	15	27%	73%	0	0
0	60	24%	60%	16%	0%
0.037	4	10%	22%	68%	0
0.037	15	0	1%	86%	13%
0.037	60	0	0	50%	50%
B) Dimethyl Benzoylphosphonate (6b)					
		Composition[a]			
Pyridine Molarity	*Time Min.*	*Acylphosphonate*	*Hemiketal*	*H-phosphonates*	
		6b	**7a**		**8b**
0	4	51%	49%		0
0	60	49%	48%		3%
0	270	44%	40%		16%
0.037	4	56%	44%		0
0.037	60	44%	40%		16%
0.037	270	25%	23%		52%

[a]The percentage figures for the components in the solutions presented are raw data obtained from the integrated ^{31}P nmr spectra and thus, possibly, they are not a precise representation of the actual molar ratios of the components.

apparently from methanolysis of the C—P bond of **4a**, followed by exchange of the alkoxy groups [10].

In order to gain more understanding of the causes of this facile methanolysis, we examined solutions of methyl 2,2,2-trifluoroethyl benzoylphosphonate (**6a**) and dimethyl benzoylphosphonate (**6b**) by ^{31}P NMR spectroscopy. We found that 0.37 molar solutions of both phosphonates in methanol at room temperature exhibited strong signals in the neighborhood of $\delta = 18$ in addition to those of the benzoylphosphonates close to 0. The signals at $\delta = 18$ are assigned to the corresponding hemiacetals (**7a** and **7b**, Scheme 2) [11]. Representative data from further monitoring of the spectra of the solutions by ^{31}P nmr spectroscopy as a function of time are listed in Table 1. As it can be seen from this Table, slow appearance of new signals belonging to dialkyl H-phosphonates (**8a** and **8b**) was also observed [10]. These signals were assigned by virtue of their large P-H coupling and the multiplicities, which were consistent with the P–O–alkyl groups present in each case. From Table 1 it can also be seen that benzoylphosphonates **6a** and **6b** differed considerably in their behavior in the presence of 10% pyridine in methanol. While, in the case of **6b**, the presence of pyridine caused an approximately 5–6 fold increase in the rate of dialkyl phosphite product formation (16 vs. 3% in 1 hour), in



6a, δ = -0.92 ppm 7a, δ = 18.1 ppm

6b, δ = 0.71 ppm 7b, δ = 18.8 ppm

8a, δ = 8.3 ppm
d sextet, J_{HP} = 738 Hz

8b, δ = 9.9 ppm
d septet, J_{HP} = 710 Hz

a, R = CH_2CF_3 b, R = Me

SCHEME 2

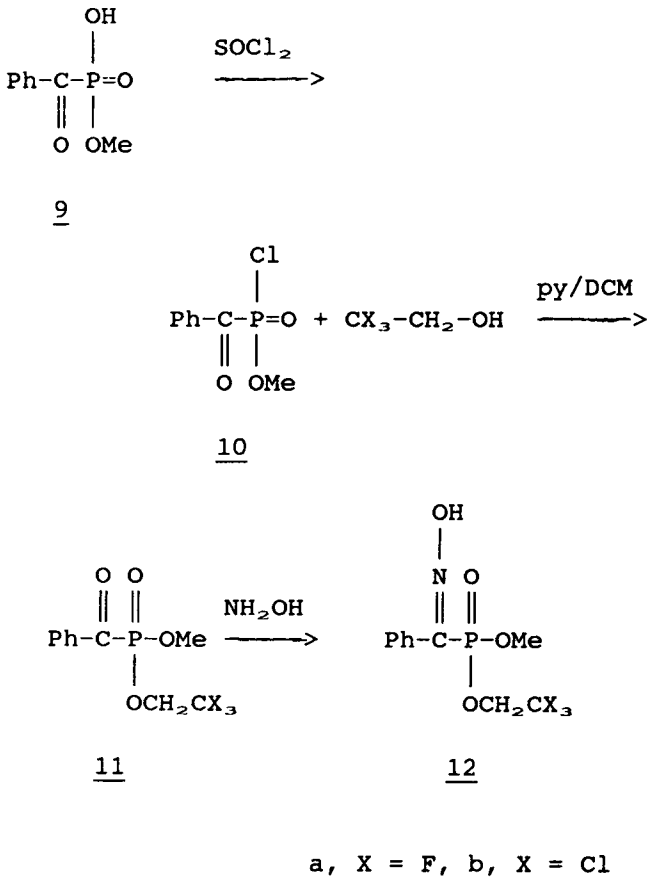
the case of the trifluoroethyl ester, **6a**, 99% of the acylphosphonate was decomposed after 15 minutes in the presence of pyridine, vs. only 16% after 1 hour in the absence of pyridine.

From these data we conclude that, in alcohol solution, the acylphosphonates are in equilibrium with the corresponding hemiacetals, which decompose under the influence of base catalysis. The high rate of **6a**'s decomposition is a reflection of the good leaving group characteristics of the anion of **8a**, relative to **8b**, which is again attributed to the electron withdrawing properties of the trifluoroethyl group. From these results it follows that conversion of **6a** to oxime could be improved if the formation of hemiacetals **7** were suppressed. Consequently, we examined the behavior of solutions of benzoylphosphonates in the more hindered 2-propanol at room temperature. After 30 minutes in this solvent, 4% and 2% of hemiacetals were observed for solutions of **6a** and **6b**, respectively. The addition of *equimolar* amount of pyridine to the solution of **6a**, produced a relatively slow formation of dialkyl phosphites (14% in 10 min), and no C—P bond cleavage at all in **6b**.

As expected, the reaction of **4a** with hydroxylamine proceeded reasonably well in 2-propanol, and **2a** could be obtained in an isolated (chromatography) yield of about 50%, accompanied by about 10% of 2-propyl benzoate. Similarly, treatment of **4b** with hydroxylamine gave oxime, **2b**, in 4% yield in methanol but in 35% yield in 2-propanol.

Subsequently, a more efficient and general method for the synthesis of oximes of type **2** was developed (Scheme 3). This method is based upon alkyl benzoylphosphonochloridates (e.g., **10**), which can be prepared from alkyl hydrogen benzoylphosphonates (e.g., **9**) [4]. Compounds **10** could be reacted with the selected alcohol in dichloromethane in the presence of pyridine to give the mixed benzoylphosphonate esters **4**, which, upon treatment with hydroxylamine hydrochloride, gave the desired oximes **2** in overall yields of ≈50%. The two steps can be carried out conveniently as a one-pot procedure. Furthermore, this method is applicable for the synthesis of mixed methyl esters **11** and **12**, which could not be made by the procedure in Scheme 2 because of difficulties in the accessibility of dimethyl phosphorochloridite, $(MeO)_2PCl$.

Oximes **2** and **12** were obtained as mixtures of (**E**) and (**Z**)-isomers, which could be best identified by means of ^{31}P NMR spectroscopy. Based on our earlier reports [12], we assign the (**E**) structure to the isomer that appears at lower field in the ^{31}P nmr spectrum. It is worthy of note that, contrary to what was observed in the syntheses of simple dimethyl α-hydroxyiminobenzylphosphonates [12], in the product mixtures of trihaloethyl derivatives **2** and **12**, the (**Z**)-isomers usually predominated (E:Z ≈ 10:90). These ratios were obtained in the

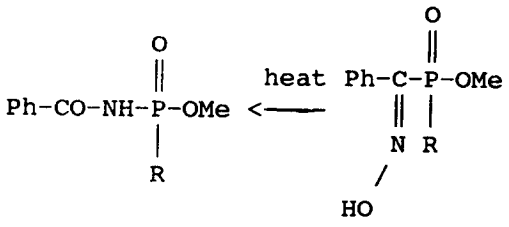


SCHEME 3

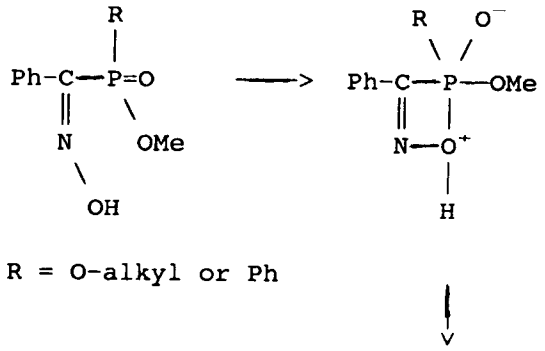
synthesis and are likely to result from kinetic control. This conclusion is supported by the results of acid treatment of **2b**. The latter was obtained in one experiment as pure (**Z**)-isomer. To determine the equilibrium composition, a solution of (**Z**)-**2b** (δ ^{31}P = 4.20) in 2 N methanolic hydrochloric acid was monitored by ^{31}P NMR spectroscopy. Equilibrium was reached after 72 hours, and consisted of 90% (E)-2b and 10% of the starting (**Z**)-isomer. This equilibrium composition is identical with that found for dimethyl α-hydroxyiminobenzylphosphonate [12]. In that case, however, this composition was reached far more rapidly.

In our previous studies concerning the chemical properties of α-hydroxyiminophosphonates [12] and -phosphinates [13] we noted their stereoselective behavior when heated. (**E**)-oximes underwent Beckmann rearrangement, while (**Z**)-oximes fragmented to benzonitrile and the corresponding acidic phosphate or phosphonate ester (Scheme 4) [13].

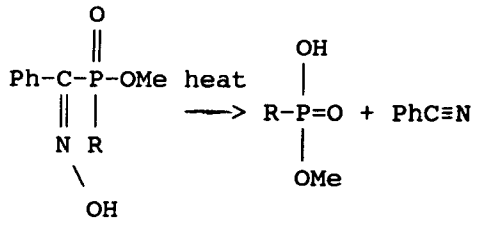
It was considered that the introduction of the strongly electron withdrawing trihaloethoxy groups into the molecule may change the electron density on the phosphorus, which may in turn be reflected in the chemical properties of the resulting α-hydroxyiminophosphonates. Consequently, the thermal



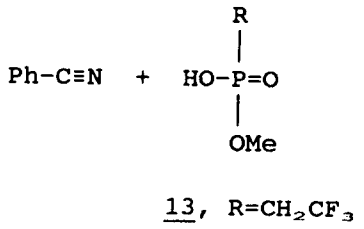
R = OMe or Ph



R = O-alkyl or Ph



SCHEME 4

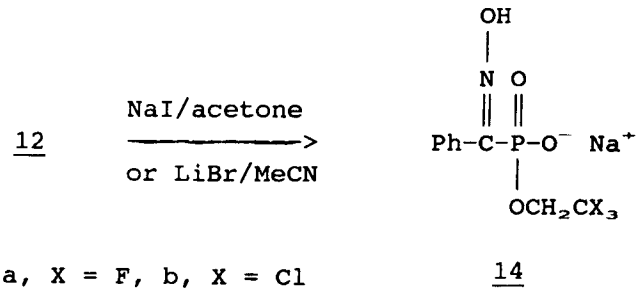


SCHEME 5

behavior of **12a**, as a representative, was examined. Refluxing a solution of **12a** (E:Z ≈ 1:1) in toluene for 5 hours, yielded methyl 2,2,2-trifluoroethyl hydrogen phosphate (**13**) as the sole phosphorus containing product. Examination of the reaction mixture after 3 hours reaction (75% conversion) showed that the reaction mixture was composed of 20% (**E**)-**12a**, 5% of (**Z**)-**12a**, and 75% of **13**. The absence of phosphoramidate in the mixture indicates that (**E**)-**12a** does not undergo Beckmann rearrangement. (**E**)-**12a** apparently equilibrates slowly to (**Z**)-**12a**, which in turn undergoes a relatively rapid fragmentation. These results seem to be in accordance with the known relationship between the electron density of a group and its migratory aptitude [14]. The electron withdrawing trifluoroethoxy group reduces the electron density of the phosphorus and with it the migratory aptitude of the phosphoryl group. The increased electrophilicity of the phosphorus also promotes the fragmentation of the (**Z**)-isomer, which was assumed to take place by an intramolecular nucleophilic attack of the oxime hydroxyl group on the phosphorus, and the formation of a four-membered cyclic intermediate (Scheme 5) [12].

Preparation of 2,2,2-Trihaloethyl α-Hydroxyiminobenzylphosphonate Monoesters

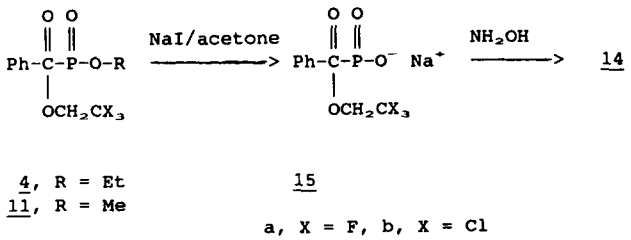
Oximes of type **12** could be smoothly demethylated to the corresponding monosodium salts **14** by treatment with sodium iodide in dry acetone (Scheme 6) or by using lithium bromide in acetonitrile at room temperature [12] (for ethyl esters **2**, see following section). In all reactions, selective removal of methyl rather than the 2,2,2-trihaloethyl groups was seen. Similar to what was reported earlier, the distribution of the geometrical isomers was maintained during the dealkylation reactions [12]. Thus, by this sequence of reactions sodium 2,2,2-trihaloethyl α-hydroxyiminobenzylphosphonates, containing predominantly the (**Z**)-isomers, could be prepared.



a, X = F, b, X = Cl

SCHEME 6

Alternatively, oxime salts (**14**) could also be prepared by first monodealkylating the mixed benzoylphosphonate esters (**4** or **11**) to the respective salts (**15**) and treating a suspension of these in methanol with hydroxylamine free base (Scheme 7). This reaction is characterized by excellent yields. The isomeric composition, however, was very different (≈ 90% of isomer **E**) from that obtained by the previously described method.

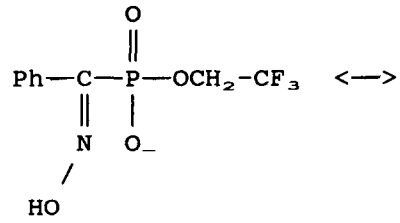


SCHEME 7

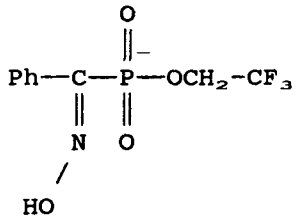
Fragmentation of Trihaloethyl α-Hydroxyiminobenzylphosphonates

In analogy to our previous work, [1–4] we were interested in examining trihaloethyl hydrogen α-hydroxyiminobenzylphosphonates as potential sources of metaphosphate. These compounds are available through acidification of the corresponding alkyl α-hydroxyiminobenzylphosphonate salts of (e.g., **14**). The nucleophilic, halide-induced monodealkylation of dimethyl α-hydroxyiminobenzylphosphonate proceeds smoothly at room temperature [12]. In contrast, removal of an ethyl group from such compounds in a solution of lithium bromide in acetonitrile requires refluxing for several hours. When ethyl 2,2,2-trifluoroethyl α-hydroxyiminobenzylphosphonate (**2a**) was refluxed with lithium bromide in acetonitrile, decomposition occurred. ^{31}P NMR analysis showed the presence of one signal at $\delta = -11.3$ indicating a pyrophosphate-like structure [16]. In order to study this result further, we examined the thermal behavior of monoanion **14** obtained through the route shown in Scheme 7. When a suspension of **14** in acetonitrile was refluxed for 14 hours, only one signal at $\delta = 11$ could be seen in the ^{31}P spectrum, indicating a pyrophosphate type product, presumably of structure **17**. HPLC revealed also the presence of benzonitrile (97%) in the reaction mixture as the only aromatic derivative. The formation of pyrophosphate type compounds in fragmentation of hydroxyiminophosphonates in aprotic solvents was noted previously [4]. Such behavior is consistent with a dissociative type mechanism (Scheme 8) involving the formation of metaphosphate **16** in the first step, and its subsequent dimerization in the absence of reactive compounds, as seen in the fragmentation of other types of metaphosphate precursors in such conditions [17–19].

The tendency of the trifluoroethyl ester anion (**14a**) to undergo thermal fragmentation is apparently linked to the electron withdrawing properties of the trifluoroethyl group. The electron withdrawing group might increase the contribution of resonance form **18** with hexavalent, negatively charged phosphorus (Scheme 9), and thus provide the electrons for the C—P bond breaking and the departure of the hydroxide anion. This result deserves further study especially since monoanions of simple monoalkyl α-hydroxyiminobenzylphosphonates are known to be stable thermally.

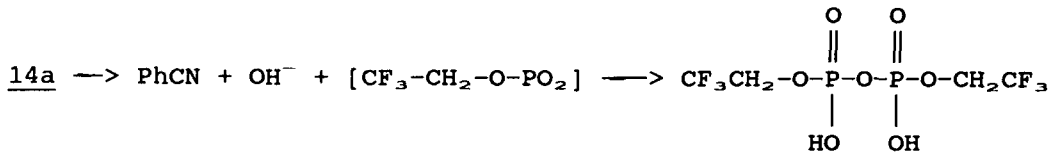


(14a)



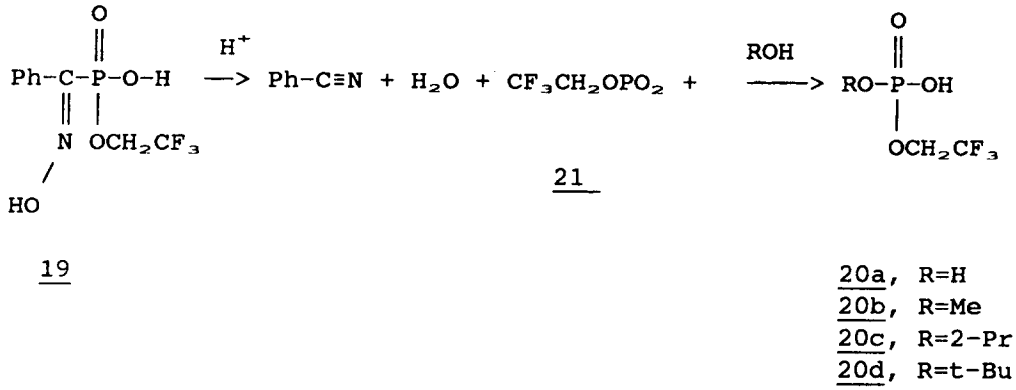
18

In order to study the influence of the 2,2,2-trifluoroethoxy group on the acidic fragmentation of α-hydroxyiminobenzylphosphonates, oxime **19** was prepared by acidification of **14a** in various alcoholic solutions of 0.6 N HCl, and its fragmentation was monitored by ^{31}P NMR spectroscopy. The decrease of the signal of **19** at $\delta = 6.4$ was accompanied by the evolvement of a signal [δ - 2.34 (quint)] corresponding to ethyl hydrogen 2,2,2-trifluoroethyl phosphate. The value of $T_{1/2}$ of the reaction was estimated to be approximately 18 hours. Comparison of this value to that reported earlier [2] for the fragmentation of methyl hydrogen α-hydroxyiminobenzylphosphonate ($T_{1/2} \approx 9$ hours) revealed that the 2,2,2-trifluoroethoxy group retarded the fragmentation by a factor



16 17

SCHEME 8



SCHEME 9

of approximately 2. The fragmentation of methyl hydrogen α-hydroxyiminobenzylphosphonate, **1b** (R = Me), was shown to proceed by a dissociative mechanism involving the formation of methyl metaphosphate [2, 3]. For the trifluoroethyl derivatives, we considered the probability that an associative type mechanism would increase as a result of the increased electrophilicity of the phosphorus. One of the commonly accepted diagnostic tests for a dissociative mechanism involving monomeric metaphosphate as a reactive intermediate is the absence of a steric effect in the phosphorylation of a hindered alcohol, as compared to a primary alcohol [19–22].

In the present work we carried out two competition experiments. In the first experiment, **19** was allowed to undergo fragmentation in a medium consisting of methanol and water in a 1:1 molar ratio. In the second experiment, the fragmentation was carried out in water:2–propanol also in a 1:1 ratio. In both experiments the formation of dihydrogen 2,2,2-trifluoroethyl phosphate [**20a**, δ^{31}P –0.8 (t), 55–57%) was accompanied by the corresponding 2,2,2-trifluoroethyl alkyl hydrogen phosphate, **20b** or **20c** [**20b**, δ^{31} P–1.5 (sext), 43%; **20c**, δ^{31}P –2.1 45%]. In addition, we allowed the fragmentation of **19** to proceed in 1 N HCl in a mixture of methanol and t-butanol (1:1). Monitoring this reaction by ^{31}P NMR spectroscopy revealed the evolvement of peaks at δ = 1.6 (m, **20b**) and –2.4 (t, **20d**) in the ratio of 2:1. A similar ratio was observed for the trapping of ethyl thiometaphosphate [19]. As the reaction proceeded, the latter peak slowly decayed and a new peak corresponding to **20a** appeared instead. These results indicate that the water and/or the alcohols are not involved in the rate determining step of the fragmentation, which therefore is a unimolecular process involving the formation of a metaphosphate **21**. This then reacts with the hydroxylic solvent to yield the phosphates **20** (Scheme 9).

Conclusion

The results presented indicate that the linking of a trihaloethoxy group to the phosphorus exerts profound quantitative and sometimes even qualitative effects on the reactivities of the organophosphorus compounds examined. These included acylphosphonates, H-phosphonates and α-hydroxyiminophosphonates.

EXPERIMENTAL

General Elemental analyses were performed by the Analytical Laboratories of the Hebrew University, Givat-Ram, Jerusalem. Infrared spectra were determined on an Analect FTIR spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian VXR-300S instrument. Chemical shifts are reported in ppm downfield from TMS or TSP as internal standards in ^{1}H spectra and from 85% H_3PO_4. as external standard in ^{31}P spectra. Positive chemical shifts are at low field with respect to the standard. Peak multiplicities are given in parentheses.

*Diethyl 2,2,2-Trihaloethyl Phosphites (**3**)* To a solution of diethyl phosphochloridite (15.6 g, 0.1 mol) in dry ether (150 mL), stirred under nitrogen at O°C, was added dropwise a solution of N,N-diethylaniline (17.5 mL, 0.11 mol) and 2,2,2-trihaloethanol (0.1 mol) in dry ether (100 mL) over a period of 90 minutes. After the addition was completed, the reaction mixture was refluxed for 1 hour. N,N-Diethylanilin-ium chloride was removed by filtration and the solvent was evaporated. The product was purified by vacuum distillation.

*Diethyl 2,2,2-Trifluoroethyl Phosphite (**3a**)* Yield 79%. Bp 48–51°C at 18 mm; NMR ($CDCl_3$) ^{1}H: 4.12 (2 H, m), 3.91 (4 H, m), 1.32 (6 H, t).

*Diethyl 2,2,2-Trichloroethyl Phosphite (**3b**)* Yield 58%. bp 62°C/ 0.15 mm; NMR ($CDCl_3$) ^{1}H: 4.37 (2 H, d, J = 6 Hz), 3.96 (4 H, m), 1.30 (6 H, t).

*Synthesis of Ethyl 2,2,2-TrihaloethylBenzoylphosphonates (**4**)* To benzoyl chloride (14 g, 0.1 mol) stirred at 5°C was added dropwise diethyl 2,2,2-tri-

haloethyl phosphite (**3**, 0.1 mol). After the addition was completed, the cooling bath was removed and the mixture was stirred for 24 hours at ambient temperature. The product was isolated by vacuum distillation.

*Ethyl 2,2,2-Trifluoroethyl Benzoylphosphonate (**4a**)* Yield 47%. Bp 112–114°C at 0.1 mm. IR (neat): 1656, 1260, 1031, cm^{-1}. NMR ($CDCl_3$) ^{31}P: –1.2 (quint). Anal. Calcd. for $C_{11}H_{12}F_3O_4P$: C, 44.6; H, 4.05; P, 10.47. Found: C, 44.36: H 3.98: P, 10.35.

*Ethyl 2,2,2-Trifluoroethyl Benzoylphosphonate (**4b**)* Yield 49%. Bp 150°C at 0.2 mm. IR (neat): 1653, 1595, 1260, 1023 cm^{-1}. NMR ($CDCl_3$) ^1H: 8.2 (2 H, m), 7.49 (3 H, m), 4.78 (2 H, q), 3.43 (2 H, m), 1.43 (3 H, t); ^{31}P: –1.37 (quint.).

*Reaction of Ethyl 2,2,2-Trihaloethyl Benzoylphosphonates **4** with Hydroxylamine Hydrochloride* Phosphonate **4** (0.1 mol) was added to a solution of hydroxylamine hydrochloride (8.3 g, 0.12 mol) and dry pyridine (10.5 mL, 0.13 mol) in absolute methanol (100 mL). After the reaction mixture had been stirred overnight, methanol was evaporated to leave a syrup which was mixed with 1 M HCl (50 mL). The aqueous mixture was extracted with chloroform (4 × 70 mL), and the combined extracts were dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated to yield a viscous residue. The oily residue was analyzed by IR and ^{31}P NMR spectroscopy. The strong absorption at 1720 cm^{-1} in the infrared spectrum of the residue indicated the presence of methyl benzoate. The ^{31}P NMR spectrum of the residue indicated that it contained ethyl methyl hydrogen phosphonate (δ = 9.7 PPM, J_{H-P} = 704 Hz) (94%) and the desired oxime (**2**, 4%). In other experiments, methanol was replaced by 2–propanol as a solvent, and oximes **2** were obtained in yields of 35%–50%.

*Ethyl 2,2,2-Trifluoroethyl α-Hydroxyiminobenzylphosphonate (**2a**)* This compound was prepared (50%) as a mixture of (E) + (Z)-isomers (viscous oil). IR (neat): 3150, 1640, 1600, 1260, 1030 cm^{-1}. NMR ($CDCl_3$) ^{31}P: 7.34 (quint, 50%, **E–2a**), 2.95 (quint, 50%, **Z–2b**); ^1H: 7.45 (5 H, m), 4.55–4.35 (2 H, m), 3.82 (2 H, m), 1.21 (3 H, t).

*Ethyl 2,2,2-Trichloroethyl α-Hydroxyiminobenzylphosphonate (**2b**)* Yield 35%, mp 102°C, IR (KBr): 3150, 1640, 1596, 1260, 1030 cm^{-1} NMR ($CDCl_3$) ^1H: 7.38 (5 H, m), 4.69 (2 H, m), 4.23 (2 H, m), 1.26 (3H, t). δ ^{31}P 3.82 (quint, 95%, **Z–2a**), 8.08 (quint, 5%, **E–2b**).

*Reaction of Ethyl 2,2,2-trichloroethyl α-Hydroxyiminobenzylphosphonate (**2**) with lithium bromide* Ethyl 2,2,2–trichloroethyl α-hydroxyiminobenzylphosphonate (**2a**) (7.2 g, 0.02 mol) was dissolved in dry acetonitrile (40 mL), and the solution was added to a solution of lithium bromide (1.9 g, 0.022 mol) in dry acetonitrile (30 mL). The reaction mixture was refluxed for 30 hours. The ^{31}P NMR spectrum of the solution showed only one peak at δ = 11.3 (t), which indicates a pyrophosphate-like structure. Examination of the reaction mixture by HPLC indicated the presence of benzonitrile (1.9 g, 96%) as the only aromatic derivative.

*Methyl Hydrogen Benzoylphosphonate (**9**)* To a solution of methyl lithium benzoylphosphonate (10.3 g, 0.05 mol) in distilled water (15 mL) was added conc. HCl (20 mL). The solution was extracted with chloroform (3 × 60 mL). The combined chloroform layers were dried over anhydrous magnesium sulfate, filtered and the filtrate evaporated under reduced pressure. Yield 90%. IR (neat): 3600–3400, 1654, 1220, 1180, 1046 cm–1. NMR (CDCl3) 1H: 8.19 (2 H, m), 7.52 (3 H, m), 3.85 (3 H, d, J = 11 Hz); 31P: –0.55 (q).

*Methyl 2,2,2-Trichloroethyl Benzoylphosphonate (**11b**)* To a solution of methyl benzoylphosphonochloridate (**10**, 21.8 g, 0.1 mol) in dry dichloromethane (70 mL), stirred under nitrogen at 0°C, was added dropwise a solution of pyridine (8 mL, 0.1 mol) and 2,2,2–trichloroethanol (15 g, 0.1 mol) in dry di-chloromethane (70 mL) over a period of 30 minutes. After the reaction mixture had been stirred for 2 hours at ambient temperature, the solvent was removed at reduced pressure and the residue was taken up in anhydrous ether. Pyridinium chloride was removed by filtration, evaporation of the ether yielded 29 g (87%) of crude **11b** as an oil. IR (neat); 1656, 1260, 1031 cm^{-1}. NMR ($CDCl_3$) ^1H: 8.2 (2H, m), 7.49 (3H, m), 4.77 (2H, m), 4.0 (3H, d, J = 11 Hz); ^{31}P: –1.53 (sext).

*Methyl 2,2,2-Trifluoroethyl Benzovlphosphonate (**11a**)* The procedure used to prepare **11b** was followed. Crude yield 90%. NMR ($CDCl_3$) ^{31}P: –1.9 (sext). This product was used immediately without further purification for the synthesis of **15a**.

*Synthesis of 2,2,2-Trihaloethyl Benzoylphosphonate Monosalts (**15**)* A solution of **11** (0.1 mol) in dry acetonitrile (100 mL), was added to a solution of lithium bromide (9.5 g, 0.11 mol) in dry acetonitrile (30 mL). The reaction mixture was stirred at room temperature overnight. The precipitated salt was filtered off, washed with dry acetone and dried in air.

*Lithium 2,2,2-Trifluoroethyl Benzoylphosphonate (**15a**)* Yield 91%; IR (KBr): 1656, 1260, 1090 cm^{-1}. NMR (D_2O) ^{31}P: –4.55 (t); ^1H: 8.2 (2 H), 7.75 (1 H, t), 7.6 (2 H, t), 4.46 (2 H, quint).

*Lithium 2,2,2-Trichloroethyl Benzoylphosphonate (**15b**)* Yield 86%; IR (KBr): 1656, 1600, 1260, 1090

cm^{-1}. NMR (D_2O) ^{31}P: −4.78 (t); ^1H: 8.19 (2 H, m), 7.73 (1 H, t), 7.59 (2 H, t), 4.63 (2 H, d, J = 6 Hz).

*Methyl 2,2,2-Trichloroethyl α-Hydroxyiminobenzylphosphonate (**12**)* One-pot procedure: To a solution of methyl benzoylphosphonochloridate (10, 21.8 g, 0.1 mol) in dry dichloromethane (70 mL), stirred at 0°C, was added dropwise a solution of dry pyridine (8 mL, 0.1 mol) and 2,2,2-trichloroethanol (15 g, 0.1 mol) in dry dichloromethane (70 mL) over 30 minutes. After the reaction mixture had been stirred for 2 hours at room temperature, dry pyridine (10.4 mL, 0.13 mol) and hydroxylamine hydrochloride (9 g, 0.13 mol) were added. The reaction mixture was stirred for 3 hours, the solvent was removed at reduced pressure, and the residue wall mixed with 1 M HCl (50 mL). The aqueous mixture was extracted with chloroform (4 × 70 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered, evaporated and the product was purified by recrystallization from ethyl acetate; yield, based on **9**, 46%; mp 129°C; IR (KBr): 1640, 1260, 1030 cm^{-1}. NMR ($CDCl_3$) ^{31}P: 9.0 (sext, E–12), 4.2 (sext, Z–12); ^1H: 7.4 (2 H, m), 7.3 (3 H, m), 4.7–4.5 (2 H, m, (E) + (Z), 3.79 (3 H, d, J = 11 Hz). Anal. Calcd. for $C_{10}H_{11}Cl_3NO_4P$: C, 34.63; H, 3.17; N, 4.04; P, 8.94. Found: C, 35.00; H, 3.45; N, 3.90; P, 8.77.

*Synthesis of 2,2,2-trihaloethyl α-hydroxyiminobenzylphosphonate Salts (**14**)*

1. *Monodealkylation of 12 by lithium bromide* A solution of **12** (0.1 mol) in dry acetonitrile (100 mL), was added to a solution of lithium bromide (9.5 g, 0.11 mol) in dry acetonitrile (30 mL). The reaction mixture was stirred at room temperature overnight. Product **14** precipitated and was filtered off, washed with dry acetone and dried in air. Yield 80–85%.
2. *Reaction of 15 with hydroxylamine* Hydroxylamine free base was prepared by neutralizing hydroxylamine hydrochloride (8.34 g, 0.12 mol) in methanol (100 mL) with sodium methoxide (6.48 g, 0.12 mol). The precipitated sodium chloride was filtered off and lithium 2,2,2-trihaloethyl benzoylphosphonate (**15**, 0.1 mol) was added to the filtrate. The reaction mixture was stirred overnight, the solvent evaporated and the solid residue was washed with ether and dried. Yield 84–92%.

*Lithium 2,2,2-Trifluoroethyl α-Hydroxyiminobenzylphosphonate (**14a**)* IR (KBr): 1640, 1260, 1090 cm^{-1}. NMR (D_2O) ^{31}P: 4.92 (t, **E–14a**), 0.39 (t, **Z–14a**); ^1H: 7.4 (5 H, m), [4.30 (quint, E–14a) + 4.18 (quint, Z–14a) 2 H].

*Lithium 2,2,2-Trichloroethyl α-Hydroxyiminobenzylphosphonate (**14b**)* IR (KBr): 1640, 1600, 1260, 1087 cm^{-1}. NMR (D_2O) ^{31}P: 4.47 (t, **E–14b**), 0.15 (t, **Z–14b**); ^1H: 7.48 (5 H, m), [4.46 (d, J = 6.4 Hz) E–14) + 4.36 (d, j = 6.4 Hz) Z–14b) 2 H].

*Thermal Fragmentation of (**12a**)* A suspension of **12a** [(E):(Z) = 50:50] (100 mg, 0.33 mmol) in dry toluene (10 mL) was refluxed for 5 hours. The ^{31}P NMR spectrum of the cooled solution showed only one peak at −1.8 ppm, which was found to be identical with that of methyl 2,2,2–trifluoroethyl hydrogen phosphate. After removal of the solvent the residue was also analyzed by IR and HPLC. IR (neat) 2220, 1200, 1020 cm^{-1}. HPLC showed the presence of 31 mg benzonitrile (94%).

*Thermal Fragmentation of Lithium 2,2,2-Trifluoroethyl α-hydroxyiminobenzylphosphonate (**14a**)* A suspension of **14a** (100 mg, 10.35 mmol) in dry acetonitrile (10 mL) was heated to reflux. Examination of the reaction mixture by ^{31}P NMR spectroscopy after 14 hours showed the absence of starting material and only one peak at $\delta = -11.3$ (t). HPLC showed the presence of 33 mg benzonitrile (97%).

*Acid-Catalyzed Fragmentation of lithium 2,2,2-Trifluoroethyl α-Hydroxyiminobenzylphosphonate (**14a**)*

A) Solvent Competition Experiments 0.8 g (2.8 mmol) of **14a** was dissolved in 10 mL of 3 N HCl in methanol-water mixture (1:1 on a molar basis). Examination of the solution by ^{31}P NMR after 14 hours at room temperature showed the presence of two signals at $\delta = -0.8$ (t, **20a**) and $\delta = -1.5$ (sext, **20b**), in the ratio of 57:43. The same procedure was carried out using a 2–propanol-water mixture (1:1). Examination of the solution after 14 hours showed two signals at $\delta = -0.82$ (t, **20a**) and $\delta = -2.1$ (**20c**), in the ratio of 55:45.

The same procedure was carried out using a 1 N solution of HCl in a 1:1 mixture (on a molar basis) of methanol and 2–methyl–2–propanol at 35°C. Monitoring the reaction by ^{31}P NMR after 10 hours showed peaks: $\delta = -0.6$ (t, **20a**, 10%), −1.6 (m, **20b**, 61%) and −2.4 (t, **20d**, 29%). After 20 hours the NMR spectrum showed −0.5 (t, **20a**, 27%), −1.6 (m, **20b**, 57%), −2.5 (t, **20d**, 16%).

B) Kinetic Experiment 26 mg of **14a** was dissolved in 0.6 N ethanolic hydrogen chloride (1 mL). The solution was filtered to remove the precipitated lithium chloride, and the progress of the reaction was monitored at room temperature by ^{31}P NMR spectroscopy.

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