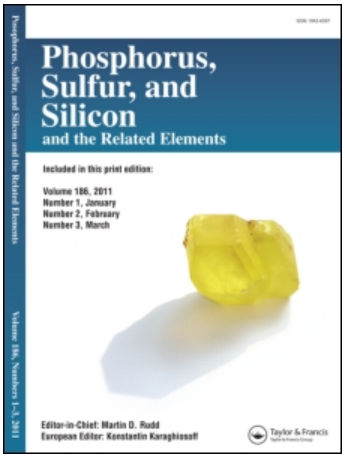


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# A MECHANISTIC STUDY OF THE REACTION OF PHOSPHONITE ESTERS WITH ETHYL AND METHYL *N*-CHLOROACETIMIDE[1]

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# A MECHANISTIC STUDY OF THE REACTION OF PHOSPHONITE ESTERS WITH ETHYL AND METHYL *N*-CHLOROACETIMIDE[1]

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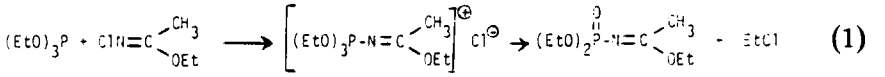
The reaction of a dialkyl methylphosphonite with an alkyl *N*-chloroacetimide leads to the formation of the expected Arbusov reaction product (**3**) plus a dialkyl methylphosphonate and acetonitrile. For dissimilarly substituted reagents, a mixture of symmetrical (**4**) and unsymmetrical (**5**) dialkyl methylphosphonates are produced. We have shown that the latter (**4** and **5**) result from a phosphonium intermediate (**6**), formed from an initial attack by phosphorus on the chlorine atom of the acetimide, followed by ligand exchange with alkoxide, and not from a simple air oxidation of the dialkyl methylphosphonite starting material. However, it is uncertain whether the Arbusov product is also formed via the same initial phosphonium intermediate (**6**), or whether competing paths of attack by tervalent phosphorus on the halogen *vs.* the nitrogen atom of the *N*-chloroacetimide are operative in this system.



## INTRODUCTION

As part of our continuing interest in the chemistry of organophosphorus compounds in general, and phosphonite esters[2] in particular, we examined the reaction of diethyl methylphosphonite (**1a**) with ethyl *N*-chloracetamide (**2a**). Phosphite esters and **2a** have been reported[3] to undergo the Michaelis-Arbusov reaction e.g. (1), to give fair yields of phosphoramidates as the sole isolated product:



(1)

Thus, we assumed that this reaction could be readily applied to phosphonite esters as a convenient route to the corresponding, apparently unknown, phosphonamidate analogs (**3**).

## RESULTS

We found that **1a** readily reacted with **2a** to give the expected Arbusov product (**3a**) in a 42% yield. Unexpectedly, however, a large amount (44%) of diethyl methylphos-

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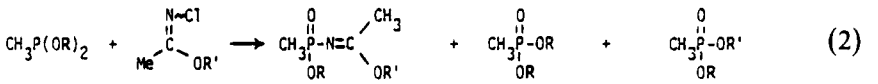
phonate (**4a**) was also obtained (2):



(2)

**1a**, R=Et **2a**, R'=Et **3a**, R=Et,R'=Et **4a**, R=Et **5** R=Et,R'=Me
**b**, R=Me **b**, R'=Me **b**, R=Me,R'=Et **b**, R=Me
**c**, R=Et,R'=Me

The diester **4a** represents oxidized starting material, and its presence in small amount would not be unexpected, since **1a** is easily air oxidized. However, the sizeable quantity obtained and the fact that the reaction was run under dry nitrogen led us to consider an alternate mechanism to account for the formation of this side product. Therefore, to further explore the reaction and to better define the probable mechanism involved, the reactions of the pairs of dissimilarly substituted reagents **1b** + **2a** and **1a** + **2b**, respectively, were also carried out, the results of which are summarized in Table I. As shown in the table, the latter reactions also produced varying (in one case, predominant) amounts of the unsymmetrical phosphonate ester **5**, which does not correspond to a direct oxidation product of the starting material. Thus, these results establish that a more complicated process must be taking place, in addition to or instead of that which is given in equation (1).

## DISCUSSION

Tervalent phosphorus compounds are known to react with certain halogenated species by attack at a positive halogen atom,[4] and such a mechanism could well produce a high yield of **4**. Thus, as shown in Scheme 1, the initial product would be a phosphonium salt (**6**), plus (if one assumes a concerted process) an alkoxide ion and acetonitrile. For the subsequent pathway that we favor, based upon considerations given below, **6** can undergo a ligand exchange with alkoxide with displacement of chloride and formation of a new phosphonium specie (**7**). The latter, a typical Michaelis-Arbusov intermediate, would directly yield the indicated products. A similar mechanism has been shown to be operative for the reaction of alkyl

TABLE I

Summary of Products[a]

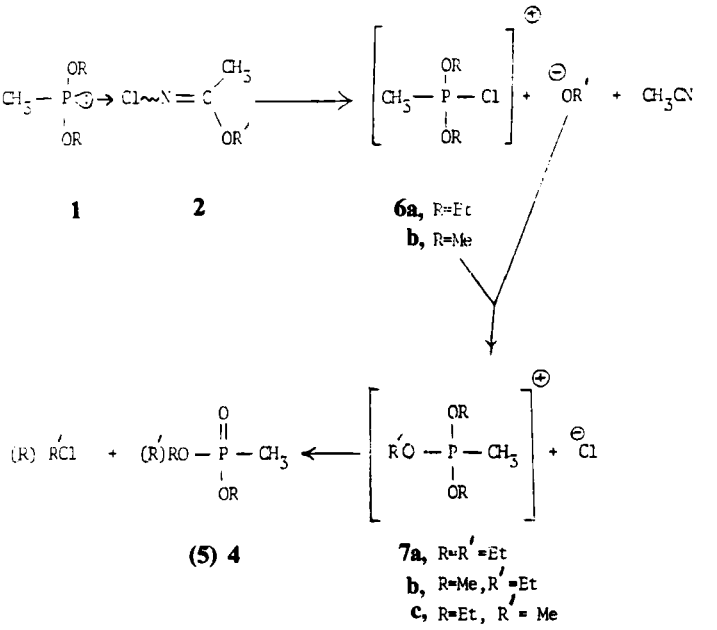
| Reactants | Arbusov Product 3, mol% | Diester Products | |
|---|---|---|---|
| | | Symmetrical 4, mol% | Unsymmetrical 5, mol% |
| **1a** + **2a** | **3a**, 42 | **4a**, 44 | N.A.[b] |
| **1b** + **2a** | **3b**, 39 | **4b**, 9 | 43 |
| **1a** + **2b** | **3c**, 49 | **4a**, 41 | 7 |

[a] From $^{31}P$ NMR integration of total reaction mixture.
[b] Not applicable.

hypochlorites with phosphines or phosphites.[5] Preliminary support for the proposed mechanism in this system came from GLC analysis of the reaction mixture, which indicated the presence of acetonitrile.

The mechanism given in Scheme 1 readily accounts for the formation of the unsymmetrical ester **5** product. Indeed, for the reaction of **1b** and **2a**, the phosphonium intermediate **7b** should produce a relative preponderance of the unsymmetrical (**5**) compared to symmetrical (**4b**) ester, as was observed, due to the more favored elimination of methyl chloride, compared to ethyl chloride, in this system.[6]

An alternate mechanism that would account for the observed products was also considered (Scheme 2). Thus, for the reaction of **1b** and **2a** by this mechanism, the

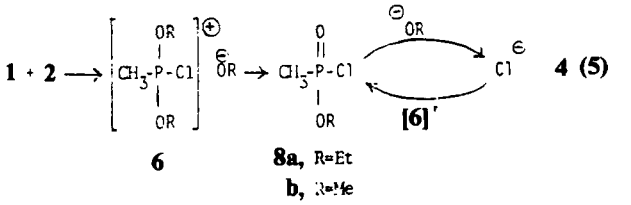


**1** **2** **6a**, R=Et; **b**, R=Me

(R) RCl + (R)RO—P(=O)—CH$_3$ (**5**) **4**

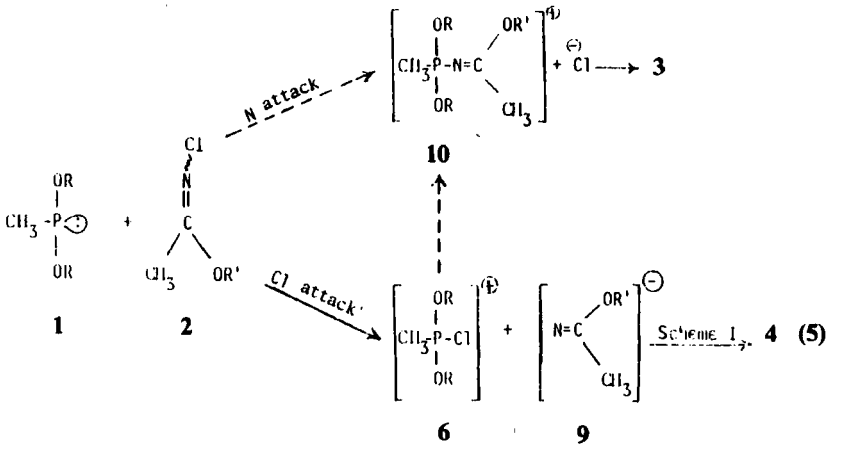
**7a**, R=R′=Et; **b**, R=Me, R′=Et; **c**, R=Et, R′=Me

SCHEME 1



**6** **8a**, R=Et; **b**, R=Me

SCHEME 2




SCHEME 3

initial phosphonium intermediate (**6b**) could directly undergo a Michaelis-Arbusov reaction with ethoxide ion to give the chloridate **8b** and methyl ethyl ether. As the **8b** concentration builds up, its own reaction with the ethoxide ion should occur to yield the unsymmetrical ester **5** plus chloride ion. The latter would then react with **6b** to produce more of **8** to complete the cycle. In this case, the small yield of **4b** (Table I) would be explained by air oxidation of **1b**.

The results of the reaction of **1a** and **2b**, however, are not consistent with this mechanism. Thus, if the chloridate **8a** were an intermediate in this reaction, then the unsymmetrical ester (**5**) should again be formed as the predominant diester, which is not the case. Moreover, no residual chloridate (**8**) was observed in the $^{31}P$ NMR spectrum of any of these product mixtures. From these results, we conclude that the mechanism shown in Scheme 1 is operative, and that for the **1a** and **2b** reaction, the phosphonium species **7c** must be formed. The predominance of **4a** compared to **4b** diester obtained in this reaction is due to the enhanced rate of dealkylation of the methoxy group, relative to an ethoxy group, from the **7c** intermediate.[6]

Although the mechanism leading to the formation of the diester products must involve an initial attack on chlorine, the mechanism leading to the formation of the Arbusov products (**3**) remains to be clarified. Thus, as shown in Scheme 3, it is uncertain whether the observed products are obtained as a result of two competing initial reactions, (N *vs.* Cl attack by phosphorus), or whether the entire process occurs via initial Cl attack to give the phosphonium intermediate **6**. In this case, depending upon its stability, the imide anion (**9**) may either (a) react with the phosphonium intermediate **6** by ligand exchange with chloride to produce the Arbusov product (**3**) via intermediate **10**, or (b) disproportionate into acetonitrile and alkoxide ion to give the diester products according to Scheme 1. These final mechanistic details presumably could be clarified by the use of chiral, optically active phosphonite reagent, to establish the stereochemistry of the reaction. We hope to pursue this question at a future date.

## EXPERIMENTAL

*General Procedures.* $^1$H NMR spectra were obtained on a Varian EM-360A spectrometer using neat liquid samples with tetramethylsilane as an external standard. $^{31}$P NMR spectra were recorded on a Varian FT-80A or Varian XL-200 spectrometer. A positive chemical shift value ($\delta$, ppm) is taken downfield from 85% phosphoric acid as an external reference. GLC separations were accomplished using a Varian Vista 6000 gas chromatograph equipped with a Varian 2m by 1/8 in. 10% OV-101 on Chromosorb W-HP (80/100 mesh) stainless steel column. Methyl and ethyl *N*-chloroacetimide (**2**) were prepared as described.[7] Subsequently, a commerical 5% household bleach solution (450 ml per 0.35 moles) was used with the same result. No attempt was made to control the pH in these reactions. However, a more recent reference, noted after this work had been completed, recommends that pH 7 be maintained for the best results.[8] Diethyl methylphosphonite (**1a**) was distilled prior to use.[9] *N,N,N,N*-Tetramethyl-*P*-methylphosphonous diamide was prepared from methylphosphonous dichloride[10] and converted into dimethyl methylphosphonite (**1b**) as described.[11] The reactions were all run under an atmosphere of dry nitrogen.

*Reaction of Phosphonite Ester* (**1**) *with Alkyl N-Chloroacetimide* (**2**). *General Procedure.* A solution of 36 mmol of **1a** or **1b** in 7 ml dry ether was added dropwise with stirring over a period of 5 min to a cooled (−30°C) solution of 36 mmol of **2a** or **2b** in 7 ml of dry ether. After the addition was complete, a white solid separated and the mixture became viscous. As the mixture was allowed to warm, it became homogeneous, and a gaseous product evolved. After removal of the solvent under reduced pressure, the products were obtained by a simple vacuum distillation under a nitrogen bleed. No attempt was made to optimize either the yield or the purity.

*Ethyl N-(Ethoxymethylmethylene)methylphosphonamidate* (**3a**). The distilled product, bp 65–66°C/0.25 mm, was 94.6 mol-% pure by $^{31}$P NMR analysis ($\delta$ 28.9) and contained 5.4% **4a** ($\delta$ 30.6). $^1$H NMR: $\delta$ 1.22 (d, $J$ = 16.6 Hz, 3 H, P—$CH_3$), $\delta$ 2.11 (s, 3 H, $CH_3$—C=N). IR (neat): 1645, 1295, 1260, 1215, 1030, 940, 885 cm$^{-1}$. Anal. Calcd. for $C_7H_{16}NO_3P$: C, 43.30; H, 8.36; N, 7.25. Found: C, 43.03; H, 8.47; N, 7.05.

*Methyl N-(Ethoxymethylmethylene)methylphosphonamidate* (**3b**). The distilled product, bp 62–63°/0.3 mm, was 88.5 mol-% pure by $^{31}$P NMR analysis ($\delta$ 30.1) and contained 5.8% **5** ($\delta$ 28.7) and 5.0% **4b** ($\delta$ 31.7). $^1$H NMR: $\delta$ 1.26 (d, $J$ = 16.6 Hz, 3 H, $CH_3$—P), $\delta$ 2.15 (s, 3 H, $CH_3$—C=N), $\delta$ 3.46 (d, $J$ = 11.4 Hz, 3 H, $CH_3O$—P). IR (neat): 1650, 1300, 1225, 1045, 920, 890, 795 cm$^{-1}$. Anal. Calcd. for $C_6H_{14}NO_3P$: C, 40.22; H, 7.88; N, 7.82. Found: C, 39.95; H, 7.87; N, 7.79.

*Ethyl N-(Methoxymethylmethylene)methylphosphonamidate* (**3c**). The distilled product, bp 60–62°C/0.2 mm, was 98.6 mol-% pure by $^{31}$P NMR analysis ($\delta$ 28.8). $^1$H NMR: $\delta$ 1.27 (d, $J$ = 16.5 Hz, 3 H, $CH_3$—P), $\delta$ 2.16 (s, 3 H, $CH_3$—C=N), $\delta$ 3.54 (s, 3 H, $CH_3$—O—C=N). IR (neat): 1650, 1305, 1265, 1225, 1045, 895, 800, 745 cm$^{-1}$. Anal. Calcd. for $C_6H_{14}NO_3P$: C, 40.22; H, 7.88; N, 7.82. Found: C, 39.70; H, 7.71; N, 7.82.

*Ethyl Methyl Methylphosphonate* (**5**). This compound ($^{31}$P NMR, $\delta$ 31.7) was obtained in a mixture with **4b** ($\delta$ 33.1) and **3b** ($\delta$ 30.1) from the reaction of **1b** and **2a**. The distilled product, bp 69–71°C/7 mm (lit[6] 74–75°C/15 mm) was obtained *ca.* 85 mol-% pure from a simple distillation. The $^{31}$P, $^1$H and IR spectra were all consistent with the assigned structure. $^1$H NMR: $\delta$ 1.14 (t, $J$ = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$), $\delta$ 1.27 (d, $J$ = 18.0 Hz, 3 H, P—$CH_3$), $\delta$ 3.51 (d, $J$ = 11.2 Hz, 3 H, $OCH_3$), $\delta$ 3.9 (m, 2 H, $OC\underline{H}_2CH_3$).

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