Reaction of the Trichloromethyl Group with Di- and Trialkyl Phosphites

J. A. KEPLER, F. I. CARROLL, R. A. GARNER, AND M. E. WALL

The Natural Products Laboratory, Research Triangle Institute, Durham, North Carolina

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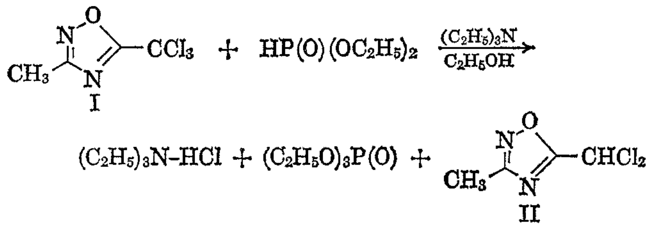
3-Methyl-5-trichloromethyl-1,2,4-oxadiazole and some substituted 2′,2′,2′-trichloroacetophenones were found to give the corresponding dichloro derivatives when treated with diethyl phosphite in the presence of a tertiary amine.

In the course of the synthesis of some potential insecticides, it was of interest to us to prepare some phosphonate esters in which the phosphorus atom was attached directly to the 1,2,4-oxadiazole ring system. Since it has been reported by Kober[1] and Kreutzberger[2] that the trichloromethyl group attached to an *s*-triazine nucleus was susceptible to nucleophilic displacement, a possible route to the desired phosphonate esters could involve the nucleophilic displacement of a trichloromethyl group from the 1,2,4-oxadiazole ring system.

It was established that 3-methyl-5-trichloromethyl-1,2,4-oxadiazole (I) readily underwent nucleophilic displacement of the trichloromethyl group in liquid ammonia to give the corresponding amine. However, when I was treated with sodium diethyl phosphite under a variety of conditions, extensive decomposition occurred. Because of the extensive decomposition, milder conditions were employed in which I was allowed to react with an ethanolic solution of diethyl phosphite in the presence of 1 equiv. of a tertiary amine. None of the desired product was observed under these conditions. However, a 91% yield of 3-methyl-5-dichloromethyl-1,2,4-oxadiazole (II), a 94% yield of triethyl phosphate, and a quantitative yield of triethylamine hydrochloride were detected. When the reaction was repeated using ether as a solvent, the yield of II was reduced to 69% and that of triethylamine hydrochloride to 51%. Two new products, tetraethyl hypophosphate and tetraethyl pyrophosphate, were also found to be present. But no triethyl phosphate could be detected.



$$\mathrm{I} + \mathrm{HP(O)(OC_2H_5)_2} \xrightarrow[(C_2H_5)_2O]{(C_2H_5)_3N} \mathrm{II} + \mathrm{(C_2H_5)_3N\text{-}HCl} + \mathrm{(C_2H_5O)_2POP(O)(OC_2H_5)_2} + \mathrm{[(C_2H_5O)_2P(O)]_2O}$$

The observations made can readily be explained on the basis of a mechanism which involves nucleophilic attack on halogen by phosphorus. This type of reaction is well known and has recently been reviewed by Miller.[3] The mechanism outlined in Scheme I is similar to that proposed by Atherton and Todd[4] and later confirmed by Steinberg[5] for the oxidation of dialkyl phosphates with carbon tetrachloride in the presence of an amine.

SCHEME I

$$\mathrm{HP(O)(OC_2H_5)_2} + \mathrm{(C_2H_5)_3N} \longrightarrow \mathrm{C_2H_5N{:}H^+[P(O)(OC_2H_5)_2]^-} \quad (1)$$

$$\mathrm{RCCl_3} + \mathrm{[P(O)(OC_2H_5)_2]^-} \longrightarrow \mathrm{RCCl_2^-} + \mathrm{ClP(O)(OC_2H_5)_2} \quad (2)$$

$$\mathrm{RCCl_2^-} + \mathrm{(C_2H_5)_3N{:}H^+} \longrightarrow \mathrm{RCHCl_2} + \mathrm{(C_2H_5)_3N} \quad (3)$$

$$\mathrm{ClP(O)(OC_2H_5)_2} + \mathrm{C_2H_5OH} \xrightarrow{(C_2H_5)_3N} \mathrm{(C_2H_5O)_3P(O)} + \mathrm{(C_2H_5)_3N\text{-}HCl} \quad (4a)$$

$$\mathrm{ClP(O)(OC_2H_5)_2} + \mathrm{HP(O)(OC_2H_5)_2} \xrightarrow{(C_2H_5)_3N} \mathrm{(C_2H_5)_3N\text{-}HCl} + \mathrm{(C_2H_5O)_2POP(O)(OC_2H_5)_2} + \mathrm{[(C_2H_5O)_2P(O)]_2O} \quad (4b)$$

Step 4a occurs when ethanol is used as solvent and 4b occurs when ether is used as the solvent.

That diethyl phosphorochloridate is an intermediate is substantiated by the nature of the phosphorus-containing compounds isolated from the reaction. The base-catalyzed reaction of diethyl chlorophosphate with alcohols (eq. 4a) is well known. This would account for the isolation of triethyl phosphate when ethanol is used as a solvent. When ether is used as a solvent the diethyl phosphorochloridate will react with unreacted diethyl phosphite to form a mixture of tetraethyl hypophosphate and tetraethyl pyrophosphate[5] (eq. 4b). Reaction 4b also explains the lower yield of reduction product when ether is substituted for ethanol as the reaction solvent since a portion of the diethyl phosphite is consumed by this reaction. The mechanistic scheme would infer that when ether is used as the reaction medium that a greater yield of reduction product II would be observed upon increasing the amount of diethyl phosphite. Experimental confirmation for this inference was obtained when it was observed that a twofold excess of diethyl phosphite increased the yield of II from 69 to 94%.

The over-all ionic mechanism is preferred to a radical mechanism since the reaction does not occur in the absence of a basic catalyst even in the presence of radical initiators such as benzoyl peroxide or ultraviolet light.

Other compounds that underwent the reaction are listed in Table I. 9-Bromocaffeine failed to undergo the reaction even under forcing conditions. 2,4-Dichloro-5-nitro-6-methylpyrimidine underwent extensive decomposition under the reaction conditions.

3-Methyl-4-trichloromethyl-1,2,4-oxadiazole (I) will also undergo a similar reaction with triethyl phosphite. If I is allowed to react with triethyl phosphite employing ethanol as a solvent good yields of II and triethyl phosphate are obtained. However, in benzene

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[1] E. Kober, *J. Org. Chem.*, **25**, 1728 (1960).

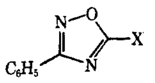
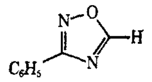
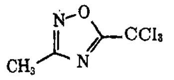
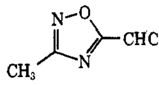
[2] A. Kreutzberger, *J. Am. Chem. Soc.*, **79**, 2629 (1957).

[3] B. Miller in "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, Inc., New York, N. Y., 1965, p. 133.

[4] F. R. Atherton and A. R. Todd, *J. Chem. Soc.*, 674 (1947).

[5] G. M. Steinberg, *J. Org. Chem.*, **15**, 637 (1950).

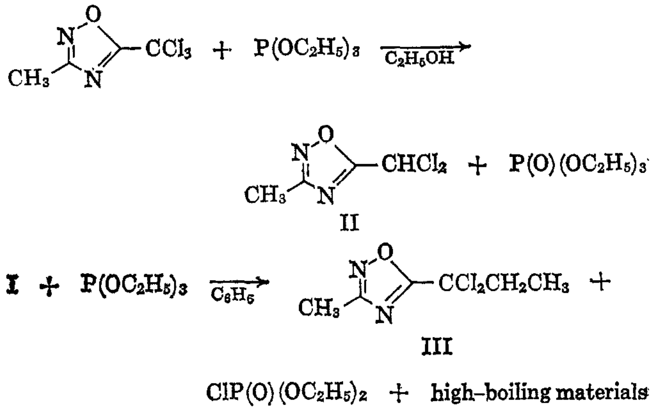
TABLE I

Reactant	Product	Yield, %
$p\text{-ClC}_6\text{H}_4\overset{\text{O}}{\overset{\Vert}{\text{C}}}\text{CCl}_3$	$p\text{-ClC}_6\text{H}_4\overset{\text{O}}{\overset{\Vert}{\text{C}}}\text{CHCl}_2$	48
$p\text{-FC}_6\text{H}_4\overset{\text{O}}{\overset{\Vert}{\text{C}}}\text{CCl}_3$	$p\text{-FC}_6\text{H}_4\overset{\text{O}}{\overset{\Vert}{\text{C}}}\text{CHCl}_2$	32
$\text{C}_6\text{H}_5\overset{\text{O}}{\overset{\Vert}{\text{C}}}\text{CCl}_3$	$\text{C}_6\text{H}_5\overset{\text{O}}{\overset{\Vert}{\text{C}}}\text{CHCl}_2$	46
$\text{C}_2\text{H}_5\text{O}\overset{\text{O}}{\overset{\Vert}{\text{C}}}\text{CCl}_3$	$\text{C}_2\text{H}_5\text{O}\overset{\text{O}}{\overset{\Vert}{\text{C}}}\text{CHCl}_2$	72
$\text{N}{\equiv}\text{CCCl}_3$	$\text{N}{\equiv}\text{CCHCl}_2$	37
 X = I, Br		[a]
		91

[a] The yield of 3-phenyl-1,2,4-oxadiazole was not determined. It was suggested by one of the referees that the reduction of these compounds may proceed *via* ring opening and closing.

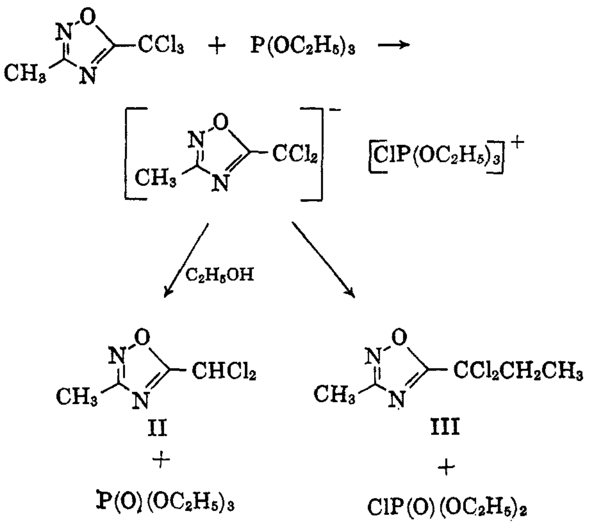
the only identifiable products have been 3-methyl-5-(α,α-dichloropropyl)-1,2,4-oxadiazole (III), diethyl phosphorochloridate, and triethyl phosphate. A high-boiling residue is also formed, which has not been positively identified. However, the infrared and n.m.r. spectra of the material indicate that it is a mixture of the normal Arbuzov products of I and III. (See Scheme II.)

SCHEME II



This reaction is very similar to that reported by Mark[6] for the alkylation of hexachlorocyclopentadiene with triethyl phosphite to give 1,2,3,4,5-pentachloroethylcyclopentadiene and probably occurs by a similar mechanism as shown in Scheme III.[3] This scheme suggests initial attack on halogen to give the anion and $[\text{ClP(OC}_2\text{H}_5)_3]^+$. The ion pair will decompose in ethanol to form II and triethyl phosphate.[7] In an aprotic solvent the anion attacks a carbon of the cation to give III and diethyl chlorophosphate.

SCHEME III



Experimental Section[8]

Reactions of Trichloromethyl Compounds with Diethyl Phosphite and Triethylamine in Ethanol.—Diethyl phosphite (0.05 mole) and the trichloromethyl compound (0.05 mole) were dissolved in 75 ml. of anhydrous ethanol and triethylamine (0.05 mole) was added dropwise to the stirred solution at ambient temperature. After 20 hr. the solvent was removed *in vacuo* and then the residual oil then was treated with 100 ml. of ether. The precipitated triethylamine hydrochloride was removed by filtration. The filtrate was concentrated *in vacuo* and the oily residue was fractionally distilled to give the dichloromethyl compounds. The dichloromethyl compounds were identified by comparison of their infrared and n.m.r. spectra with authentic samples. Table I lists the compounds which were dehalogenated by this procedure and the yield of reduction product.

Reaction of I with Diethyl Phosphite and Triethylamine in Ethanol.—A solution of 4.14 g. (0.03 mole) of diethyl phosphite and 6.04 g. (0.03 mole) of 3-methyl-5-trichloromethyl-1,2,4-oxadiazole[9] (I) in 20 ml. of absolute ethanol was cooled to 7° in the ice bath. Triethylamine (3.3 g., 0.033 mole) was added dropwise to the solution at such a rate that the temperature did not exceed 20°. The ice bath was removed and the solution was allowed to stir at room temperature for 18 hr. The solution was filtered, diluted with 100 ml. of ether, and filtered again to give a combined weight of 4.10 g. (100%) of triethylamine hydrochloride. The solution was concentrated *in vacuo*. The residual oil was fractionally distilled on a 24-in. spinning-band column to give 3.69 g. (74.1%) of II, b.p. 43° (1.5 mm), and 3.61 g. (70%) of triethyl phosphate, b.p. 56° (1.5 mm.), $n^{10}\text{D}$ 1.4056 (lit.[10] $n^{10}\text{D}$ 1.4062). The infrared and n.m.r. spectra of these compounds were identical with the spectra of the authentic samples. In a similar experiment the reaction products were analyzed by vapor phase chromatography (v.p.c.).[11] The yield of II obtained by this method was 91% and that of triethylphosphate was 94%. In another experiment run at 0° with the triethylamine added in one portion it was ascertained by v.p.c. analysis[11] that the reaction had gone to 58% completion after 2 min. and to 90% completion after 12 min. In an experiment identical with that above, except that 0.50 g. of benzoyl peroxide was added to the reaction mixture, it was determined by v.p.c.

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[6] V. Mark, *Tetrahedron Letters*, 295 (1961).

[7] T. Mukaiyama, O. Mitsunobu, and T. Obata, *J. Org. Chem.*, **30**, 101 (1965).

[8] The boiling points are uncorrected. The n.m.r. spectra were obtained using a Varian A-60 spectrometer with samples dissolved in deuteriochloroform with tetramethylsilane as an internal standard. Microanalysis was by Micro-Tech Laboratories, Inc., Skokie, Ill.

[9] We wish to express our appreciation to the Union Carbide Chemicals Corp., South Charleston, W. Va., for providing us with generous samples of 3-methyl-5-trichloromethyl-1,2,4-oxadiazole and 3-methyl-5-dichloromethyl-1,2,4-oxadiazole.

[10] D. P. Evans, W. C. Davies, and W. S. Jones, *J. Chem. Soc.*, 1310 (1930).

[11] Diethyl oxylate was used as an internal standard. The analysis was carried out on a 5% Apiezon L on 60–80 Chromosorb W column operated at 110° with a helium flow of 75 cc./min.

analysis[11] that the reaction had gone to 56% completion after 2 min. and 97% completion after 13 min.

Reaction of I and Diethyl Phosphate with Triethylamine in Ether.—A solution of 13.8 g. (0.10 mole) of diethyl phosphite and 20.10 g. (0.10 mole) of I in 150 ml. of ether was cooled in an ice bath. A solution of 10.12 g. (0.10 mole) of triethylamine in 50 ml. of ether was added to the solution over a 4-hr. period. The solution was allowed to warm and was stirred for 18 hr. at room temperature. Filtration afforded 8.0 g. (53%) of triethylamine hydrochloride. Vacuum distillation afforded 11.20 g. (67%) of a material, b.p. 53–58° (4.5 mm.), that exhibited one peak in the v.p.c. which had the same retention time as authentic 3-methyl-5-dichloromethyl-1,2,4-oxadiazole.[9] The infrared spectrum of the material was identical with that of an authentic sample of II.

The pot residue gave two peaks in the v.p.c., which had retention times identical with those of an authentic mixture of tetraethyl pyrophosphate and tetraethyl hypophosphate.[5] The infrared spectra of the two materials were identical. Attempted distillation of the pot residue resulted in considerable decomposition. However, a small amount of impure tetraethyl hypophosphate, b.p. 109–117° (1.0 mm.), n^{25}_{D} 1.4305 (lit.[12] b.p. 116–117°, n^{20}_{D} 1.4284), and a small amount of tetraethyl pyrophosphate, b.p. 132–140° (1.0 mm.), n^{25}_{D} 1.4196 [lit.[13] b.p. 135–138° (1.0 mm.), n^{25}_{D} 1.4180] were isolated. In a similar experiment analysis by v.p.c.[11] indicated that a 69% yield of II was obtained. Also isolated was a 51% yield of triethylamine hydrochloride.

Reaction of I with Triethylamine and an Excess of Diethyl Phosphite in Ether.—The reaction was carried out as above except that 2 equiv. of diethyl phosphite was used instead of 1. A 44.3% yield, based on triethylamine, of triethylamine hydrochloride was isolated. A v.p.c. analysis[11] indicated that a 94% yield of II was formed.

Reaction of I with Triethyl Phosphite in Benzene.—To a solution of 40.30 g. (0.20 mole) of I in 100 ml. of benzene was added 67.20 g. (0.40 mole) of triethyl phosphite over a 1-hr. period. After standing overnight at ambient temperature the benzene was removed at the water pump without heating. Vacuum distillation afforded 8.8 g. (13%) of triethyl phosphite, b.p. 35–40° (15 mm.). Another fraction was collected, b.p. 80–86° (0.1 mm.) (26.51 g.), which was shown to contain III, triethyl phosphate, and one other compound by v.p.c. analysis. Attempted redistillation of this fraction on a 24-in. stainless steel spinning-band column afforded no separation. The distillates were combined and separated by preparative v.p.c. using a 10 ft. × $^3/_8$ in. column packed with 20% SE30 on 60–80 Chromosorb W. The operating temperature was 130° with a flow rate of 200 cc. of helium/min. Considerable decomposition occurred and only small amounts of two peaks could be collected. The first fraction was shown to be triethyl phosphate by comparison of its n.m.r. spectra and its retention time on v.p.c. with an authentic sample. That the second fraction was 3-methyl-5-(α,α-dichloropropyl)-1,2,4-oxadiazole is supported by the following data. The n.m.r. spectra showed resonances at δ 1.25, triplet (J = 7 c.p.s.) (CH_2CH_3, three protons); δ 2.75, quartet (J = 7 c.p.s.) (CH_2CH_3); and at δ 2.48, singlet (ring methyl). The resonances at δ 2.75 and 2.48 had a combined integration of 4.65 protons. *Anal.* Calcd. for $C_6H_8Cl_2N_2O$: C, 37.80; H, 4.13; Cl, 36.35; N, 14.36. Found: C, 38.09; H, 4.51; Cl, 36.12; N, 14.08.

The high-boiling residue from the first distillation was molecularly distilled at 83° and 12 μ. Four fractions were collected whose refractive indices ranged from 1.4613 to 1.4633; however, v.p.c. and thin layer chromatography indicated that one major product and at least two minor products were present. The products were not positively identified. A similar experiment was performed at ice-bath temperature in which the presence of diethyl chlorophosphate was determined by v.p.c. analysis. It was observed that the amount of diethyl chlorophosphate would increase while the reaction was kept cold; however, after 18 hr. at room temperature, only a small amount of diethyl chlorophosphate could be detected. No diethyl chlorophosphate could be isolated from the reaction mixture by distillation or preparative v.p.c.

Reaction of 3-Methyl-5-trichloromethyl-1,2,4-oxadiazole with Triethyl Phosphite in Ethanol.—A 20.0-g. (0.10-mole) sample of II was dissolved in 100 ml. of ethanol. Triethyl phosphite (33.60 g., 0.20 mole) was added to the solution with stirring over a 1-hr. period. After 18 hr. at ambient temperature, the solvent was removed and the residue was analyzed qualitatively by v.p.c. Triethyl phosphite, triethyl phosphate, and II were shown to be present by comparison of their v.p.c. retention times with those of authentic samples. Diethyl chlorophosphate, I, and III were shown to be absent. Vacuum distillation on a 24-in stainless steel spinning-band column afforded 12.69 g. (36%) of triethyl phosphite, b.p. 45–50° (25 mm.), n^{25}_{D} 1.4114; 16.35 g. (44%) of triethyl phosphate, b.p. 105–108° (25 mm.), n^{25}_{D} 1.4081; 10.07 g. (62%) of II, b.p. 95–105° (25 mm.). The infrared spectra of the different fractions were identical with those of authentic samples as were their retention times on v.p.c.

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[12] A. F. Arbuzov and B. A. Arbuzov, *J. prakt. Chem.*, **130**, 103 (1931).

[13] A. D. F. Toy, *J. Am. Chem. Soc.*, **70**, 3883 (1948).

The Acylation of Phosphine–Methylene Derivatives. The Preparation and Properties of Mixed Phosphorane–Phosphonium Salts

P. A. CHOPARD

Cyanamid European Research Institute, Cologny, Geneva, Switzerland

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The reaction of triphenylphosphine and chloroacetyl chloride does not lead to chlorocarbonylmethylene triphenylphosphorane, $Ph_3P{=}CH{-}COA$ (**1d**, A = Cl), but to **2**, which is a mixed phosphorane–phosphonium salt (actually, a formal dimer of **1d**). This reaction is probably analogous to the acylation of the stable phosphoranes **1** (A = OAlk) by the esters of carboxylic acids. The reactions of **2** show its potential synthetic utility in the fields of acetylenic and olefinic ketones, esters, amides, and related compounds.

Phosphine–methylene derivatives (Wittig reagents) have been acylated with acid halides,[1] anhydrides,[2] and certain amide derivatives[1]; only the most reactive ones have been reported to react with esters[1] or thio esters.[1]

We find that esters formed from some strong carboxylic acids can be used to acylate the stable phosphoranes **1** as shown in eq. 1, Scheme I.

The scope of this reaction and its limitations have not been explored; however, it is potentially useful since the diketophosphoranes **4** are intermediates in the preparation of acetylenic esters and ketones.[2–4]

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[1] S. Trippett, *Quart. Rev.* (London), 406 (1963).

[2] P. A. Chopard, R. J. G. Searle, and F. H. Devitt, *J. Org. Chem.*, **30**, 1015 (1965).

[3] G. Märkl, *Chem. Ber.*, **94**, 3005 (1961).

[4] S. T. D. Gough and S. Trippett, *J. Chem. Soc.* 2332 (1962).