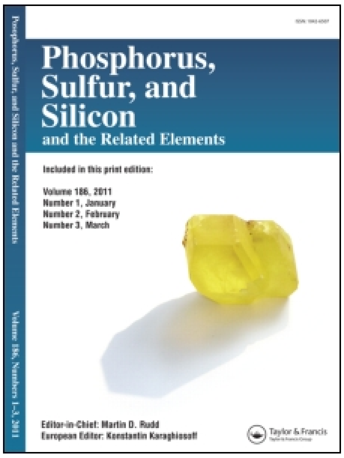

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MICROWAVE SYNTHESIS OF TRICHLORFON AND ITS ANALOGUES

Abdollah Javidan[a]; A. R. Banan[a]
[a] Department of Chemistry, Imam Hossein University, Tehran, I. R. Iran

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MICROWAVE SYNTHESIS OF TRICHLORFON AND ITS ANALOGUES

Abdollah Javidan and A. R. Banan
Department of Chemistry, Imam Hossein University,
Tehran, I. R. Iran

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The synthesis of dialkyl-(2,2,2-trichloro-1-Hydroxyethyl) phosphonates using dialkyl hydrogen phosphite and chloral hydrate under solvent-free condition by microwave irradiation is reported. The products were chrachetrized using ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectroscopy.

Keywords: Anticholinestrase; insecticide; microwave; organophosphorus compounds; trichlorfon

INTRODUCTION

Dialkyl-(2,2,2-trichloro-1-hydroxyethyl)phosphonates are important from the point of view of biologic activity, and the agrochemical and medicine industries, for example, trichlorfon (**3a**) or dimethyl-2,2,2-tricholoro-1-hydroxyethyl phosphonate is a pesticide.[1–4] Since this compound is less toxic than DDT, it is a good candidate to replace for DDT. Trichlorfon, which is well known as metrifonate in the medicine industry, is under investigation as an affecting drug for alzheimer's disease and anticholinestrase.[5]

In recent years, there has been growing interest in the application of microwave irradiation in chemical reaction enhancement because of its cleaner reactions, decreased reaction time, and easier workup.[6–8] In continuation of our ongoing efforts in this area, for the above reasons, and in view of our general interest in microwave synthesis, we wish to report here the synthesis of these organophosphorus compounds using microwave irradiation. This procedure is a general method for

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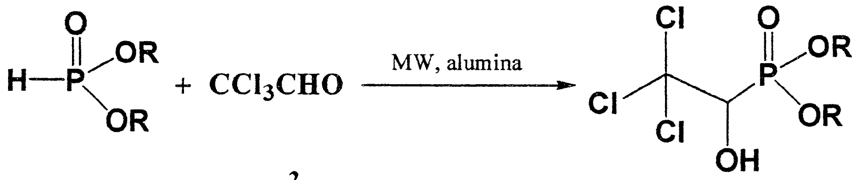
Address correspondence to Abdollah Javidan, Department of Chemistry, Imam Hossein University, P.O. Box 16575-347, Tehran, I. R. Iran. E-mail: ajavidan@ihu.ac.ir

synthesis of dialkyl-2,2,2-tricholoro-1-hydroxyethyl phosphonates **3a–c** by microwave irradiation, which in previous preparations required heating starting materials for several hours in the reflux condition. The data obtained show that the reaction time can be reduced to minutes in good yields.

RESULTS AND DISCUSSION

For our study we worked with neat dialkylphosphites **1** and chloral hydrate **2** using a domestic microwave oven under solvent-free conditions in the presence of alumina or silica gel. The synthetic conventional method for these compounds was the same as previously reported procedures.[9–12] The reactions are completed within minutes and in good-to-excellent yields (65–93%, Table I). To evaluate the effect of microwave irradiation, we tried several experiments on compounds **3a** (3, 6, 9, and 12 min). We observed that increasing the reaction time had no significant effect on the yields to product. In addition, when we exposed the reaction mixture to microwave irradiation for 30 min the product decomposed.



1a, R= Methyl
1b, R=Ethyl
1c, R=isopropyl

2

3a, R= Methyl
3b, R=Ethyl
3c, R=isopropyl

SCHEME 1

The structure of the products was assigned with ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectroscopic analysis and comparison with authentic samples.[13–15] The existence of signal at 18.84 ppm and disappearance of the signal at 11 ppm in the ^{31}P-$\{^1$H$\}$ NMR spectrum of crude product shows the presence of trichlorfon **3a**. The ^{1}H NMR spectrum showed two doublets at 3.89 and 3.93 ppm, confirming the presence of two diasteretopic methoxy groups.

The signal for methine proton of trichlorfon appeared as a doublet at 4.54 ppm with $J = 15$. $^2J_{\text{P-H}} = 11.5$ Hz. With respect to the relationship between the magnitude of $^2J_{\text{P-H}}$ and dihedral angle observed in

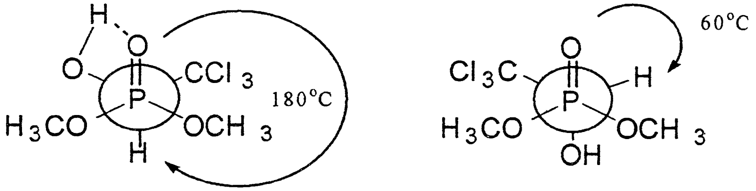
TABLE I Preparation of **3a–c** Using Microwave Irradiation under Solvent-Free Conditions

Starting phosphite	(R)	Molar ratio of (phosphite/chloral)	Catalyst	Reaction time (min)	Conversion (%)*
1a	Methyl	1: 1.01	Silica gel	1.5**	3a (60)
1a	Methyl	1: 1.01	Alumina	3 (240)	3a (70)
1a	Methyl	1: 1.01	Alumina	6 (240)	3a (74)
1a	Methyl	1: 1.01	Alumina	9 (240)	3a (71)
1a	Methyl	1: 1.01	Alumina	12 (240)	3a (67)
1b	Ethyl	1: 1.16	Alumina	4 (300)	3b (76)
1c	Isopropyl	1: 1.20	Alumina	3 (420)	3c (65)
1c	Isopropyl	1: 1.40	Alumina	7	3c (82.5)
1c	Isopropyl	1: 2.00	Alumina	8	3c (93)

*Based on the ^{31}P NMR of crude reaction mixture.
**450 W.

organophosphorus compounds and the present data, the conformation of this compound has been assigned. The observed $^2J_{P-H} = 11.5$ Hz in trichlorfon **3a** suggests that the preferred conformation is *anti* (a) in which the hydrogen group is anti to phosphoryl group ($\theta = 180^\circ$) but the coupling constant of the alternative conformation (b) ($\theta = 60^\circ$) is around 24 Hz.[16] Existence of hydrogen bonding between hydrogen and the oxygen of the phosphoryl group has been reported in the literature.[16] The proton of the OH group appears at 5.48 ppm as a broad peak.

Further evidence for determination the structure of the products were obtained from ^{13}C NMR analysis. In the ^{13}C NMR, the CHOH carbon appeared at 79.98 ppm as a doublet with ^1J(PC) = 662.5 Hz. This large value of ^1J(PC) is consistant with coupling of phosphorus with adjacent carbon.[16] The most downfield shift of CCl_3 carbon at 97.7, which split with phosphorus, appears as a doublet and is in agreement with the phosphorus attached to three electronegative chlorine atoms. The presence of hydroxyl group was indicated by a broad absorption band at 3350 cm^{-1} in the infrared spectrum.



a **b**

FIGURE 1

CONCLUSION

In this article a straightforward method for formation of dialkyl-(2,2,2-trichloro-1-Hydroxyethyl) phosphonates using dialkyl hydrogen phosphate and chloral hydrate under solvent-free conditions using microwave irradiation has been reported. This method is superior to the reported method from the point of view of green chemistry, yields, and short reaction time.

EXPERIMENTAL

General

^{1}H, ^{13}C, and ^{31}P NMR spectra were obtained using a Bruker 250 spectrometer using $CDCl_3$ as solvent and TMS as internal standard or 85% H_3PO_4 as external standard. Melting points were determined on a Metler 9100 electrothermal and are uncorrected. IR spectra were recorded on a Perkin-Elmer IR-738 spectrometer. All reagents and chemicals were obtained from Merck or Aldrich Chemical Company and were used as received unless otherwise noted. The starting materials, 1a, 1b, and 1c, were prepared as described in the literature.[17,18] A domestic microwave oven operating at 2450 MHz was used at power 600 W for all the microwave experiments except that.

General Procedure

Method A (Conventional)

Reactions were performed under the same conditions using an oil bath at the reflux temperature as previously reported.[9] The product was extracted with benzen, the organic phase was dry over MgSO4, filtered, and put away until the title compound was isolated as white crystal.

Method B (MW)

General method. In a mortar, dialkyl hydrogen phosphite **1a–c** (46 mmol) and alumina or (silica gel) was ground with a pestle, and 48 mmol of chloral hydrate was added. The mixture was transfer to a Teflon vessel and irradiated in microwave oven for the time specified in Table I. As this study was done only for the comparison, the products were not isolated, and after evaporation of the solvent the resulting mixture was analyzed by ^{31}P NMR.

(3a). m.p. 75–76°C (lit. 76–78°C). ^{31}P NMR ($CDCl_3$) δ: 18.83. ^{1}H NMR ($CDCl_3$) δ: 3.88 (d, $^{3}J_{P-H} = 6.5$ Hz, 3H, $POC\underline{H}_3$), 3.93 (d, $^{3}J_{P-H} = 6.5$ Hz, 3H, $POC\underline{H}_3$), 5.45 (d, $^{2}J_{P-H} = 11.75$, 1H, $C\underline{H}OH$), 5.48 (s, 1H, OH). ^{13}C {^{1}H}NMR ($CDCl_3$) δ 54.22 (d, $^{2}J_{P-C} = 27.5$ Hz, $PO\underline{C}H_3$), 54.80 (d, $^{2}J_{P-C} = 27.5$ Hz, $PO\underline{C}H$), 79.98 (d, $^{1}J_{P-C} = 665$ Hz, $\underline{C}HOH$), 97.75 (d, $^{2}J_{P-C} = 6.8$ Hz, $\underline{C}Cl$). IR (KBr) cm^{-1}: 3350, 3042, 2980, 2940, 1270, 1200 (P=O).

(3b). m.p. 54–55°C (lit. 55–56°C). ^{31}P NMR ($CDCl_3$) δ: 16.37. ^{1}H NMR ($CDCl_3$) δ: 1.38 (t, $^{4}J_{P-H} = 7.0$, 6H, $POCH_2C\underline{H}_3$), 4.28 (m, 4H, $POC\underline{H}_2CH_3$), 4.49 (d, $J = 11.75$, 1H, $C\underline{H}OH$), 5.86 (s, 1H, OH). ^{13}C{1H}NMR ($CDCl_3$) δ16.36 (d, $^{3}J_{P-C} = 5$ Hz, $POCH_2\underline{C}H_3$), 16.46 (d, $^{3}J_{P-C} = 5$ Hz, $POCH_2\underline{C}H$), 64.28 (d, $^{2}J_{P-C} = 27.5$ Hz, $PO\underline{C}H_2CH_3$), 64.33 (d, $^{2}J_{P-C} = 27.5$ Hz, $PO\underline{C}H_2CH_3$), 78.99 (d, $\underline{C}$(P)OH,$^{1}J_{P-C} = 657.5$ Hz), 98.04 (d, 1C, $^{2}J_{P-C} = 40$ Hz, $\underline{C}Cl$). IR (KBr) cm^{-1}: 3355, 3100, 3020, 2980, 1280, 1230, 1205 (P=O).

(3c). m.p. 108–109°C (lit. 105–106°C). ^{31}P NMR ($CDCl_3$) δ: 14.49. ^{1}H NMR ($CDCl_3$) δ: 1.39 (d, $^{3}J_{H-H} = 7.0$, 8.1, 6H, $CH(C\underline{H}_3)_2$, 1.39 (d, $^{3}J_{H-H} = 7.0$, 6H, $CH(C\underline{H}_3)_2$, 4.39 (d, 1H, $J = 11.75$, $C\underline{H}OH$), 4.86 (m, 1H, $C\underline{H}(CH_3)_2$), 5.49 (sb, 1H, OH).^{13}C{1H}NMR ($CDCl_3$) δ: 23.74 (d, $^{3}J_{P-C} = 25$ Hz, $CH(\underline{C}H_3)_2$), 24.34 (d, $^{3}J_{P-C} = 25$ Hz, $CH(\underline{C}H_3)$), 24.44 (d, $^{3}J_{P-C} = 25$ Hz, $CH(\underline{C}H_3)_2$),73.17 (d, $^{2}J_{P-C} = 30$ Hz, $\underline{C}H(CH_3)_2$), 73.83 (d, $^{2}J_{P-C} = 32.5$ Hz, $\underline{C}H(CH_3)_2$), 80.20 (d, $^{1}J_{P-C} = 655$ Hz, $\underline{C}$(P)OH), 98.27 (d, $^{2}J_{P-C} = 37.5$ Hz, $\underline{C}Cl_3$). IR (KBr film) cm^{-1}: 3350, 3065, 3010, 2950, 1290, 1270, 1200 (P=O).

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