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Microwave Induced Synthesis of *O*,*O*-Dialkyl Dialkylpyrophosphonates under Solvent Free Conditions: Markers of Nerve Agents

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This article describes a one pot, solvent free, microwave assisted synthesis of *O*,*O*-dialkyl dialkylpyrophosphonates (DADAPP) from *O*-alkyl alkylphosphonic chlorides **2a**–**j** with 4-dimethylaminopyridine (DMAP) in the presence of water under microwave irradiation. The reaction takes place by the phosphonium salts, which are converted into the DADAPPs **4a**–**j**. These DADAPPs are important markers of chemical warfare agents sarin, soman, and VX and their analogues. The method has several advantages over the conventional methods such as operational simplicity, high yield, and reduced reaction time.

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Introduction

The development of new efficient synthetic procedures for the verification analysis of chemical warfare agents (CWAs) and related compounds is a prominent area of contemporary research.[1–6] This field of synthesis and analysis has attracted the attention of several workers because of a strict verification program of the Chemical Weapons Convention (CWC). The CWC prohibits the production, storage, and use of chemical weapons and is administered by an international organization known as the Organization for Prohibition of Chemical Weapons (OPCW).[7–11]

The verification of CWC related chemicals (CRCs) involves chemical analysis of samples collected during inspections conducted under supervision of OPCW. The analysis is performed either on-site by the inspectors or, if deemed necessary, off-site by at least two laboratories designated by the OPCW.[11–13] The status of a designated laboratory can be achieved by successful performance in international official proficiency tests (OPTs) conducted by the OPCW. The OPTs are conducted according to standard procedures and performance of participants is judged as per the norms set by the OPCW.[14,15] The prerequisites for successful performance in OPTs depend on the availability of spectroscopic databases of CRCs. Consequently, a great deal of work has been devoted to the building up of spectroscopic libraries of CRCs.[16–21] In such analyses, final structures of analytes are confirmed by synthesizing the reference chemicals and matching the spectra (mostly gas chromatography/mass spectrometry (GC/MS) and ^{31}P NMR). Because OPTs are a time bound activity, i.e., the analysis results have to be submitted within a stipulated period of 15 days,[12–14] there is dire need to develop an efficient synthetic procedure that can be used to prepare several compounds simultaneously for screening by GC/MS and other spectroscopic techniques.

The chemicals relevant to the convention (CRCs) not only include the infamous chemical warfare agents (like sarin, soman, tabun, and VX) but also their precursors and degradation products. The CRCs that have been identified for the application of verification measures are listed in three schedules based on their past uses.[7,10]

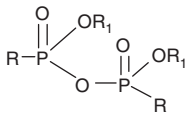

Fig. 1. General structure of *O*,*O*-dialkyl dialkylpyrophosphonates.

O,*O*-Dialkyl dialkylpyrophosphonates (DADAPPs) are often produced when highly toxic chemical warfare agents such as sarin, soman, VX, and their analogues are prepared in any laboratory or plant. Thus DADAPPs may be considered as important forensic markers for the verification of these agents and are covered in the list of CWC text under schedule 2B4.[8,22] However, the spectroscopic data of only a handful of DADAPPs are available in the literature. These compounds have been recently spiked in official proficiency tests as markers of nerve agents.[23] Thus, the generation of a spectroscopic database of DADAPPs is an important goal of the verification regime of the CWC. The general structure of such DADAPPs is shown in Fig. 1.

There are several methods for the synthesis of DADAPPs. The precedent literature revealed that the synthesis of DADAPPs is associated with several drawbacks such as prolonged reaction time, use of carcinogenic solvents, harsh reaction conditions, and tedious workup, and chromatographic techniques are often used to afford the compounds with desired purity.[24–27]

Recently, there has been considerable interest in the microwave induced synthesis of a variety of organic compounds because of the selective absorption of microwave energy by polar molecules.[28] Microwave assisted organic synthesis is known for the spectacular accelerations produced in many reactions as

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Table 1. Optimization of reaction conditions by performing the model reaction of *O*-ethyl methylphosphonic chloride with dimethyl amino pyridine (DMAP) under microwave irradiation

Reactions were monitored by TLC and ^{31}P NMR spectroscopy in $CDCl_3$ at 162 MHz

Entry	DMAP [mol-%]	Moisture [%]	Microwave power [W]	Time [min]	Conversion [%]
1	10	20	100	4	15
2	30	20	180	4	37
3	50	20	180	4	45
4	75	20	180	4	68
5	100	20	180	4	80
6	100	20	180	5	100
7	100	40	180	5	74
8	100	40	360	5	63[A]
9	100	15	180	5	90
10	100	20	100	5	50

[A] Other un-desired products were observed by TLC.

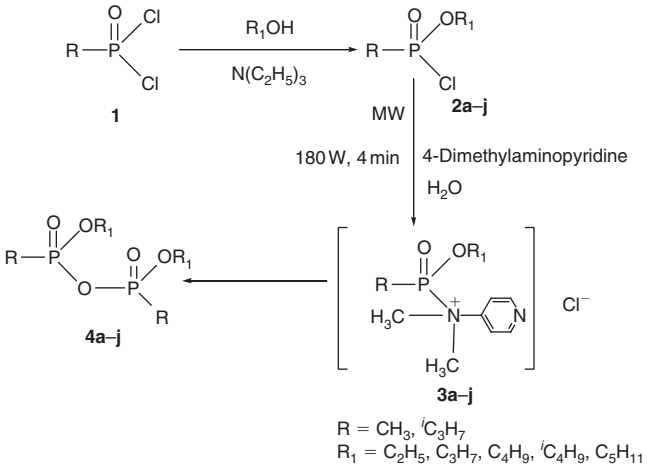
a consequence of the heating rate and cannot be easily reproduced by classical heating. It results in higher yields of products with easy workup and shorter reaction times.[29]

Results and Discussion

Inspired by the concept of microwave heating, it was thought that DADAPPs could be prepared from *O*-alkyl alkylphosphonochloridates **2a**–**j**. To address this possibility, we began the preparation of alkyl phosphonic dichloride **1** by the reported method.[30] The intermediate **1** was reacted with various alcohols in the presence of triethylamine at 0°C followed by heating at 50°C, to give rise to *O*-alkyl alkylphosphonic chlorides **2a**–**h**.[31]

After having the intermediate (*O*-alkyl alkylphosphonochloridates **2a**–**j**) in hand, we optimized the reaction conditions to obtain DADAPPs. In this regard, several reactions of *O*-ethyl methylphosphonic chloride with various bases such as dimethyl amino pyridine (DMAP), pyridine, triethylamine, diethyl aniline, *N*-methyl imidazole, and diisopropyl ethylamine were performed as a model reaction in the presence or absence of water under identical microwave power. The maximum yield was obtained when DMAP was used in the presence of water. Furthermore, to optimize the molar ratio of DMAP, various reactions of *O*-ethyl methylphosphonic chloride were also performed by changing the amount of DMAP, reaction time, amount of water, and microwave power. These reactions were monitored by TLC and ^{31}P NMR spectroscopy. The results obtained from this study (Table 1) revealed that the best results were obtained when the model reaction was performed with DMAP and water in a mole ratio of 1:1:0.2 at 180 W for 5 min (entry 6, Table 1). The results of ^{31}P NMR analysis also showed that DADAPP is formed by the formation of the corresponding phosphonium salt (Scheme 1).

After optimization, the general applicability of the method was tested with a diversity of structures (**2a**–**j**) and the results of the reactions are summarized in Table 2. The compounds **4a**–**j** were characterized by spectroscopic techniques such as infrared spectroscopy (FT-IR), NMR, GC/MS, and elemental analysis. The results of FT-IR analysis showed the characteristic strong and broad bands in the range of 975–969 cm^{-1}, attributable to the antisymmetric stretching of the P–O–P linkage.[32] The other frequencies assigned to the P–O–C, P–C, and P=O linkage were



Scheme 1.

compared with literature values and found to be within range.[33] It is worth noting that the signal of the *O*-alkyl alkylphosphonochloridates **2a**–**j** disappeared with the appearance of a new signal in the range of 22–31 ppm for **4a**–**j**. These compounds have shown two signals in the ^{31}P NMR spectra as a result of two stereogenic centres (Table 2). The results of the other analyses of **4a**–**j** are compiled in the experimental section.

Experimental

General

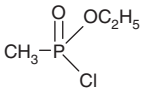
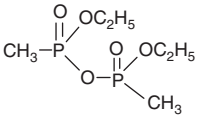
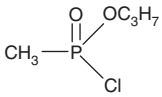
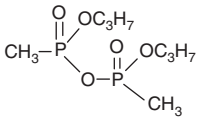
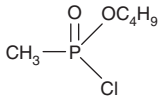
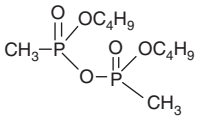
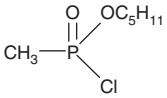
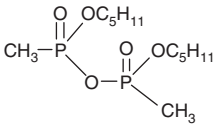
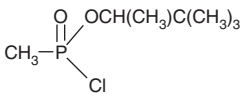
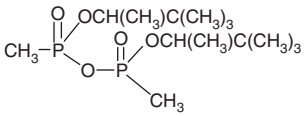
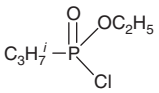
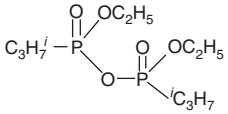
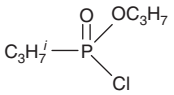
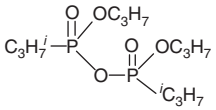
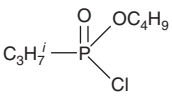
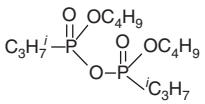
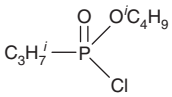
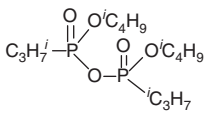
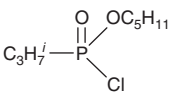
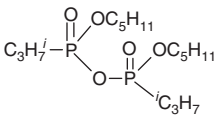
A domestic microwave oven (LG, Model MG-555F, New Delhi) with variable irradiating powers was used.

Boiling points are uncorrected. IR spectra were recorded on a Bruker FT-IR spectrometer model Tensor 27 using KBr disks. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ on a Bruker DPX Avance FT-NMR at 400, 200, and 162 MHz, respectively, using tetramethylsilane as an internal standard for ^{1}H and ^{13}C, and 85% H_3PO_4 as an external standard for ^{31}P. A Chemito GC model 1000 instrument was used with a flame ionization detector (FID). A capillary column (30 m × 0.25 mm I.D-BP5) packed with 5% phenyl and 95% dimethyl polysiloxane (SGE) coated on fused silica was employed. The injection port and detector block were maintained at 280 and 260°C, respectively, and the column oven was at a programmed temperature profile which started at 50°C, and was ramped up to 280°C at 25°C min^{-1}. Nitrogen was used as a carrier gas (at a flow rate of 30 mL min^{-1}). Air for the FID was supplied at 300 mL min^{-1} and hydrogen at 30 mL min^{-1}. In all analyses, 0.1 μL of sample was injected and peaks were recorded on an Iris32 data acquisition station. The GC-MS analyses were performed by electron ionization (EI, 70 eV) in full scan mode with an Agilent 6890 GC equipped with a model 5973 mass selective detector (Agilent Technologies, USA). An SGE BPX5 capillary column with 30 m length × 0.32 mm internal diameter × 0.25 μm film thickness was used with a temperature program of 80°C for 2 min and heating at 20°C min^{-1} to 280°C for 3 min. Helium was used as the carrier gas at a constant flow rate of 1.2 mL min^{-1}. The samples were analyzed in split less mode at injection temperature.

General Procedure for the Preparation of Diethyl Dimethylpyrophosphonate *4a*

4-DMAP (1.22 g, 0.01 mol) was placed in a conical flask and *O*-ethyl methylphosphonic chloride (1.32 g, 0.01 mol) was added

Table 2. Synthesis of *O*,*O*-dialkyl dialkylpyrophosphonates 4a–j using microwave irradiation

Entry	Substrate	Product	Yield[A] [%]	Boiling point [°C mmHg^{-1}]	^{31}P NMR [δ ppm][B]
4a			86.2	115/2	22.49, 22.18
4b			90.5	120/2	26.32, 26.01
4c			92.4	135/1.5	26.26, 25.94
4d			90.3	145/1.5	26.26, 25.94
4e			87.6	160/1.5	22.61–20.96
4f			88.7	132/1	28.25, 28.19
4g			85.4	149/1	28.59, 28.53
4h			93.1	158/1	28.59, 28.53
4i			88.4	160/1	28.30, 28.23
4j			93.7	165/1	31.70, 31.64

[A] Isolated yield.
[B] ^{31}P NMR Spectra were recorded in $CDCl_3$ at 162 MHz; all the reactions were completed within 5–6 min at 180 W.

and mixed well. After microwave irradiation at 180 W for 4 min the formation of a salt was observed, this was dissolved by the addition of one drop of water. The reaction mixture was further irradiated at 180 W for 1 min. The reaction mixture was monitored by ^{31}P NMR spectroscopy until the signal of *O*-ethyl methylphosphonic chloride disappeared. The reaction mass was washed and extracted into *n*-pentane (4 × 25 mL) and the solvent was evaporated to afford pure diethyl dimethylpyrophosphonate without use of column chromatography. ν_{max} (liquid film)/cm^{-1} 2885 (C–H), 1230 (P=O), 1095 (P–O–C), 972 (P–O–P), 690 (P–C). δ_H 4.17 (m, *J* 7.36, 4H, CH_2), 1.35 (d, *J* 7.54, 6H, CH_3), 0.92 (t, *J* 6.35, 6H, CH_3). δ_C 46.50 (CH_2), 21.06 (CH_3), 10.53 (CH_3).

m/z (EI) 230 (4.06%), 203 (74.19), 186 (15.20), 175 (72.14), 157 (75.10), 143 (87.43), 97 (61.70), 79 (100), 65 (10.07), 47 (32.10). (Found: C 31.30, H 7.02. $C_6H_{16}O_5P_2$ requires C 31.31, H 7.01%.)

Dipropyl Dimethylpyrophosphonate **4b**

ν_{max} (liquid film)/cm^{-1} 2889 (C–H), 1235 (P=O), 1080 (P–O–C), 970 (P–O–P), 698 (P–C). δ_H 4.17 (m, *J* 7.45, 4H, CH_2), 1.60 (m, *J* 7.23, 4H, CH_2), 1.40 (d, *J* 7.50, 6H, CH_3), 0.88 (t, *J* 6.39, 6H, CH_3). δ_C 44.67 (CH_2), 20.09 (CH_3), 18.95 (CH_2), 10.35 (CH_3). *m/z* (EI) 259 (M+H$^+$, 5.03%), 217 (9.85), 187 (4.52), 175 (100), 157 (72.15), 143 (23.25), 97 (50.11), 79 (30.13), 41 (11.10). (Found: C 37.23, H 7.80. $C_8H_{20}O_5P_2$ requires C 37.22, H 7.81%.)

Dibutyl Dimethylpyrophosphonate **4c**

ν_{max} (liquid film)/cm^{-1} 2888 (C–H), 1237 (P=O), 1088 (P–O–C), 975 (P–O–P), 696 (P–C). δ_H 4.10 (m, *J* 6.88, 4H, CH_2), 1.62–1.70 (m, *J* 7.31, 8H, CH_2), 1.40 (d, *J* 6.59, 6H, CH_3), 0.93 (t, *J* 6.75, 6H, CH_3). δ_C 44.56 (CH_2), 21.05 (CH_2), 18.45 (CH_2), 15.97 (CH_3), 10.23 (CH_3). *m/z* (EI) 286 (4.85%), 231 (9.98), 201 (8.78), 175 (100), 157 (50.25), 143 (14.15), 97 (40.78), 79 (19.05), 41 (10.85). (Found: C 41.95, H 8.47. $C_{10}H_{24}O_5P_2$ requires C 41.96, H 8.45%.)

Dipentyl Dimethylpyrophosphonate **4d**

ν_{max} (liquid film)/cm^{-1} 2887 (C–H), 1235 (P=O), 1090 (P–O–C), 978 (P–O–P), 705 (P–C). δ_H 4.10 (m, *J* 6.97, 4H, CH_2), 1.70 (m, *J* 7.09, 8H, CH_2), 1.40 (d, *J* 7.16, 6H, CH_3), 1.32 (m, *J* 7.57, 4H, CH_2), 0.90 (t, *J* 7.06, 6H, CH_3). δ_C 46.50 (CH_2), 23.06 (CH_2), 21.05 (CH_3), 18.36 (CH_2), 14.36 (CH_2), 9.98 (CH_3). *m/z* (EI) 315 (5.29%), 245 (14.12), 175 (100), 157 (30.15), 143 (11.10), 97 (31.03), 79 (17.45), 41 (5.45). (Found: C 45.85, H 8.99. $C_{12}H_{28}O_5P_2$ requires C 45.86, H 8.98%.)

Dipinacolyl Dimethylpyrophosphonate **4e**

ν_{max} (liquid film)/cm^{-1} 2885 (C–H), 1240 (P=O), 1095 (P–O–C), 980 (P–O–P), 698 (P–C). δ_H 4.10 (m, *J* 7.35, 2H, CH_2), 1.40 (d, *J* 7.16, 6H, CH_3), 1.22 (dd, *J* 7.45, 6H, CH_3), 0.83 (s, *J* 6.58, 18H, CH_3). δ_C 62.16 (CH), 23.15 (C), 19.56 (CH_3), 14.36 (CH_3), 9.98 (CH_3). *m/z* (EI) 452 (7.23%), 202 (14.12), 175 (100), 157 (47.09), 143 (18.20), 97 (20.15), 85 (15.78), 69 (16.17), 57 (20), 41 (37.10). (Found: C 49.10, H 9.40. $C_{14}H_{32}O_5P_2$ requires C 49.12, H 9.42%.)

Diethyl Diisopropylpyrophosphonate **4f**

ν_{max} (liquid film)/cm^{-1} 2888 (C–H), 1240 (P=O), 1085 (P–O–C), 973 (P–O–P), 695 (P–C). δ_H 4.19 (m, *J* 7.18, 4H, CH_2), 2.08 (m, *J* 6.85, 2H, CH), 1.13 (t, *J* 6.73, 6H, CH_3), 0.98 (d, *J* 6.95, 12H, CH_3). δ_C 67.98 (CH_2), 27.70 (CH), 18.19 (CH_3), 12.30 (CH_3). *m/z* (EI) 286 (13.63%), 259 (8.75), 244 (72.72), 231 (18.18), 215 (40.90), 202 (30.90), 187 (100), 171 (54.50), 152 (63.63), 125 (68.18), 65 (48.18), 43 (59.09). (Found: C 41.97, H 8.46. $C_{10}H_{24}O_5P_2$ requires C41.96, H 8.45%.)

Dipropyl Diisopropylpyrophosphonate **4g**

ν_{max} (liquid film)/cm^{-1} 2890 (C–H), 1240 (P=O), 1093 (P–O–P), 974 (P–O–P), 698 (P–C). δ_H 4.21 (m, *J* 8.16, 4H, CH_2), 2.10 (m, *J* 6.73, 2H, CH), 1.70 (m, *J* 6.78, 4H, CH_2), 1.25 (m, *J* 6.73, 12H, CH_2), 0.94 (t, *J* 7.24, 6H, CH_3). δ_C 68.30 (CH_2), 27.76 (CH), 23.88 (CH_2), 16.17 (CH_3), 10.35 (CH_3). *m/z* (EI) 315 (M+H, 13.63%), 273 (24.27), 243 (5.45), 231 (100), 213 (28.15), 187 (45.63), 171 (30.09), 145 (17.47), 125 (70.87), 65 (11.65), 43 (25.24). (Found: C 45.84, H 8.96. $C_{12}H_{28}O_5P_2$ requires C 45.86, H 8.98%.)

Dibutyl Diisopropylpyrophosphonate **4h**

ν_{max} (liquid film)/cm^{-1} 2881 (C–H), 1236 (P=O), 1092 (P–O–P), 980 (P–O–P), 690 (P–C). δ_H 4.20 (m, *J* 7.83, 4H, CH_2), 2.12 (m, *J* 6.75, 2H, CH), 1.67 (m, *J* 7.03, 4H, CH_2), 1.40 (m, *J* 6.75, 4H, CH_2), 1.22 (m, *J* 6.70, 12H, CH_2), 0.92 (t, *J* 7.24, 6H, CH_3). δ_C 66.33 (CH_2), 27.74 (CH), 26.14 (CH_2), 18.83 (CH_2), 16.15 (CH_3), 15.98 (CH_3). *m/z* (EI) 343 (M+H, 13.63%), 287 (20.38), 243 (8.95), 231 (100), 213 (25.24), 187 (29.12), 171 (23.30), 145 (13.10), 125 (56.31), 65 (10.05), 43 (19.13). (Found: C 49.10, H 9.43. $C_{14}H_{32}O_5P_2$ requires C 49.12, H 9.42%.)

Diisobutyl Diisopropylpyrophosphonate **4i**

ν_{max} (liquid film)/cm^{-1} 2889 (C–H), 1238 (P=O), 1085 (P–O–P), 969 (P–O–P), 690 (P–C). δ_H 3.93 (m, *J* 6.96, 4H, CH_2), 2.05 (m, *J* 7.05, 2H, CH), 1.88 (m, *J* 7.43, 2H, CH), 1.05 (d, *J* 7.39, 12H, CH_3), 0.81 (d, *J* 7.39, 12H, CH_3). δ_C 66.20 (CH_2), 27.74 (CH), 26.05 (CH), 18.83 (CH_3), 18.72 (CH_3). *m/z* (EI) 343 (M+H, 13.63%), 287 (8.03), 243 (10.05), 231 (100), 213 (24.27), 187 (24.85), 171 (25.13), 145 (58.25), 125 (56.31), 57 (11.33), 43 (30.15). (Found: C 49.10, H 9.43. $C_{14}H_{32}O_5P_2$ requires C 49.12, H 9.42%.)

Dipentyl Diisopropylpyrophosphonate **4j**

ν_{max} (liquid film)/cm^{-1} 2890 (C–H), 1236 (P=O), 1089 (P–O–P), 974 (P–O–P), 698 (P–C). δ_H 4.21 (m, *J* 8.16, 4H, CH_2), 2.10 (m, *J* 6.75, 2H, CH), 1.70 (m, *J* 7.03, 4H, CH_2), 1.34 (m, *J* 6.75, 4H, CH_2), 1.26 (m, *J* 6.75, 4H, CH_2), 1.20 (m, *J* 6.70, 12H, CH_3), 0.90 (t, *J* 7.15, 6H, CH_3). δ_C 66.33 (CH_2), 27.74 (CH), 26.14 (CH_2), 18.83 (CH_2), 16.15 (CH_3), 15.16 (CH_3), 10.98 (CH_3). *m/z* (EI) 370 (13.63%), 301 (38.38), 259 (11.23), 243 (25.92), 231 (100), 213 (25.24), 187 (32.40), 171 (24.83), 145 (11.15), 125 (78.70), 43 (23.10). (Found: C 51.85, H 9.81. $C_{16}H_{36}O_5P_2$ requires C 51.88, H 9.80%.)

Conclusion

In conclusion, we have developed a rapid and efficient method for the synthesis of *O*,*O*-dialkyl dialkylpyrophosphonates **4a**–**j** with excellent yields. The main advantage of this method is that reactions were clean and had operational simplicity. Because column chromatography was not required to purify the pure products, this method is more attractive for organic chemists.

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