

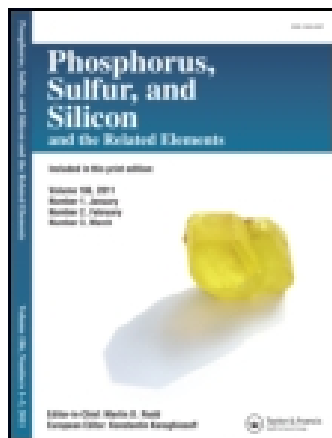
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Synthesis of Alkyl Methylphosphonic Acid Esters

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A synthesis and isolation scheme is described for producing mono alkyl esters of methylphosphonic acid based upon stoichiometric addition of alcohol to methylphosphonic dichloride. Solvent extraction is applied to the reaction mixture to separate the monoalkyl esters in reasonable yield from dialkyl methylphosphonate and unsubstituted methylphosphonic acid. The single-alkylated materials are important hydrolysis products of the G-series nerve agents, and are not generally available from chemical suppliers.

Keywords Cyclohexyl methylphosphonic acid; isopropyl methylphosphonic acid; methylphosphonic dichloride

INTRODUCTION

The development of analytical techniques for the detection and analysis of G-series nerve agent hydrolysis products (alkyl methylphosphonic acid esters) is hampered by the lack of available reference materials. With the exception of pinacolyl methylphosphonic acid ester, these materials are not commercially available.¹ The rapid environmental hydrolysis of the G-series nerve agents produces a relatively persistent alkyl methylphosphonic acid ester as the primary product.² Further hydrolysis affords methylphosphonic acid. The goal of this work is to devise a simple synthesis and separation for G-series nerve agent hydrolysis products that can be performed in most research

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laboratories, which results in material suitable for use in chemical warfare analysis methodologies.

Several published reports describe the synthesis of alkyl methylphosphonic acid esters. Chittenden et al. described a synthetic path to these compounds through methyl phosphonothioic acids.³ This procedure is complex and requires the synthesis of starting materials. Timperly et al. detailed their production through an Arbuzov synthesis.⁴ A direct route from partial hydrolysis of methylphosphonic dichloride has been successfully employed,^{5,6} with overall yields in the 12% to 47% range.⁵ This latter procedure requires the reaction of methylphosphonic dichloride with water resulting in a hydrolytically unstable, glassy anhydride that is used as a starting material for esterification. This method, as well as that of Timperly et al., apparently requires vacuum distillation to obtain pure product.

The synthesis and extraction techniques developed in this study can be applied using commonly available equipment and materials to rapidly produce high purity (98+%) alkyl methylphosphonic acid esters. An additional advantage of the method described here is that vacuum distillation is not required to obtain a pure product.

Our approach is based on the direct reaction of alcohols (isopropanol and cyclohexanol) with methylphosphonic dichloride (Figure 1) in toluene solvent, followed by hydrolysis of monochloride to produce the desired alkyl methylphosphonic acids. The desired product is isolated from other products by solvent extraction. The overall synthetic approach, combined with solvent extraction-based purification, results in gram quantities (typical yield of >30%) of high-purity (98+%) product. Inherent to the reaction is the production of transient pyrophosphonate species (Figure 2) which are easily hydrolyzed to the suite of idealized products shown in Figure 1.

Since the alkyl methylphosphonic acids were not amenable to direct Gas Chromatographic (GC) analysis, reaction aliquots and samples from extractions were treated with ethereal diazomethane to create methyl derivatives⁷ prior to analysis by Gas Chromatography-Mass Spectrometry (GC-MS). This technique has been applied to acidic phosphate-related components in nuclear defense wastes.⁸ Many of

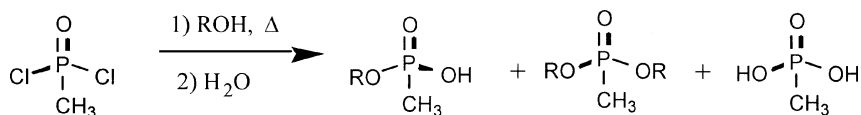


FIGURE 1 Reaction between methylphosphonic dichloride and alcohol resulting in a statistical production of products.

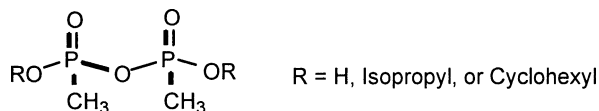


FIGURE 2 Pyrophosphonate artifacts.

the alkyl organophosphorus compounds have relatively straightforward mass spectral fragmentation patterns.⁸ As analytical methylation and silylation are likely to be used by other researchers for analysis of monoalkyl methylphosphonic acid esters, GC and MS data for the compounds synthesized in this work are provided in Tables I and II.

RESULTS AND DISCUSSION

Attempting to form monoalkyl phosphonic esters from direct reaction of alcohols with methylphosphonic dichloride creates a mixture of products. Upon hydrolysis of these mixtures, depending upon conditions, a statistical mixture of methylphosphonic acid, dialkyl methylphosphonate, and the desired monoalkyl methylphosphonic ester results (Figure 1). Linear alkyl pyrophosphonates of the type shown in Figure 2 were found when hydrolysis was done at ambient temperature. The linear pyrophosphonates either form during hydrolysis of the phosphoryl chlorides or result from *in situ* side reactions involving the alcohols, which generate water. Pienaar⁵ and Petrov⁶ report that the reaction of water with methylphosphonic dichloride initially results in a cyclic dimer. In our approach, the alkyl ester is formed first, allowing alkylated linear species to form upon hydrolysis. The pyrophosphonate dimers are readily hydrolyzed by quenching the reaction with water at toluene reflux temperature.

The mixture of products (Figure 1) is purified by first partitioning the highly acidic aqueous phase from the toluene. The dialkyl

TABLE I GC and GC-MS Data for Derivatives of Cyclohexyl and Isopropyl Methylphosphonic Acids

Compound (R ₁ O)(R ₂ O)P(O)CH ₃	GC Index	EI-MS m/z (Relative intensity)	MW (CI)
R1 = CH ₃ , R2 = isopropyl	982	93(100), 111(97), 137(38), 79(21)	152
R1 = TMS, R2 = isopropyl	1107	153(100), 169(20), 75(18), 195(8)	
R1 = CH ₃ , R2 = cyclohexyl	1383	111(100), 93(27), 79(9)	192
R1 = TMS, R2 = cyclohexyl	1492	153(100), 169(43), 75(11)	

methylphosphonate ester, as well as most of the unreacted alcohol, is extracted into the toluene layer. The desired product and methylphosphonic acid form a separate layer.

An approach fashioned after the work of Hardy and Seargill⁹ was used to remove methylphosphonic acid. These authors found that dibutyl phosphate could be isolated from technical butyl phosphate mixtures by extracting with carbon tetrachloride. We have found that the difference in polarity between methylphosphonic acid and monoalkyl methylphosphonic acid esters can be exploited in a similar fashion. Extracting the aqueous mixture with chloroform, and subjecting it to successive partitions with water, affords a clean separation of the monoalkylester. The extracted monoalkylated materials were nearly colorless and displayed GC traces in which >98% of the peak area was product, suggesting that further purification of these materials for use as analytical or experimental standards was not necessary. The overall levels of by-products found in the extracts were comparable to that found in samples of previously available¹ commercial isopropyl methylphosphonic acid (<2%). Examination of the GC-MS trace for the cyclohexyl analogue afforded similar impurity levels; however, no standard material was available for comparison. Finally, distillation under vacuum afforded only one fraction, with very little residue left in the distillation pot. GC-MS traces of this distillate were not markedly different from the extracts.

The solvent extraction efficiency was investigated by diazomethane derivatization and GC-MS analysis of each step. Initial removal of dialkyl methylphosphonates by toluene was found to be very efficient. Nearly all of the methylphosphonic acid remains in the aqueous phase upon partitioning with chloroform. Residual traces of methylphosphonic acid were removed by back-extracting the chloroform with water. Isopropyl methylphosphonate has a moderate extraction distribution from chloroform to water, so only two back extractions with water were performed. The cyclohexyl compound did not exhibit significant loss during this step and three back extractions were done to remove methylphosphonic acid from the chloroform. In both cases, the end products were found to be 98+% monoalkyl methylphosphonates in terms of the total peak area in the GC-MS traces. It is recognized, however, that ion production mechanisms in the mass spectrometer are very different for the components; therefore, TIC areas cannot be used for precise quantification. The isopropyl methylphosphonate obtained from this procedure, when derivatized, exhibited a GC trace virtually identical to that obtained from the commercial sample.

Table 1 exhibits the GC, electron ionization (70 eV) mass spectrometry (EI-MS) data, and chemical ionization mass spectrometry

TABLE II GC and GC-MS Data for Pyrophosphonate Methyl Derivatives

Pyrophosphonate Compounds (R ₁ O)P(O)(CH ₃) OP(O)(CH ₃)(OR ₂)	EI-MS m/z (Relative Intensity)	MW (CI)
R1 = R2 = CH ₃	157(100), 93(52), 172(22), 89(11), 202(9), 187(8)	202
R1 = CH ₃ , R2 = isopropyl	171(100), 189(84), 111(88), 93(80), 157(44), 79(30)	230
R1 = R2 = isopropyl	175(100), 157(95), 97(44), 79(33), 143(22), 201(16)	258
R1 = CH ₃ , R2 = cyclohexyl	189(100), 111(80), 93(31), 157(28), 171(16), 211(8)	

(CI-MS) data for the methyl and trimethylsilyl derivatives of isopropyl and cyclohexyl methylphosphonates. Table 2 addresses the EI-MS and CI-MS data obtained for selected pyrophosphonates. The MS ions are listed in relative abundance to the base ion. Authentic isopropyl methylphosphonate,¹ was used for GC-MS comparisons. We noted a discrepancy between previously reported data⁵ for isopropyl methylphosphonate and that which we obtained using diazomethane for derivatizing our isopropyl methylphosphonate product. In light of our experience in interpreting mass spectra of these types of compounds, the presence of readily interpretable fragment ions, and the verification of molecular weight by CI-MS, we believe the data reported in Table 1 and Table 2 to be correct.

Based on our studies of isopropyl methylphosphonic acid and cyclohexyl methylphosphonic acids, we believe this synthesis would be generally applicable for producing alkyl methylphosphonic acid esters from other unhindered alcohols in the C₄–C₇ range.

EXPERIMENTAL

Alkyl methylphosphonic acid esters were prepared as follows. Alcohol (16.5 mmol of either cyclohexanol [1.64 g] or isopropanol [0.992 g]) was dissolved in 2.0 mL of dry toluene and placed in an additional funnel that had been swept with dry nitrogen. Methylphosphonic dichloride (2.18 g, 16.5 mmol), dissolved in 2.0 mL of dry toluene, placed into a dried 100-mL round-bottomed flask maintained under dry nitrogen, and equipped with a reflux condenser. Alcohol was added dropwise to the round-bottomed flask at ambient temperature. The reaction was stirred for 15 min before bringing to reflux at 105°C for 2 h.

The reaction mixture was quenched while still warm (*ca.* 80°C) with two equivalents of water (0.60 mL), and then refluxed for an additional

10 min. The reaction was cooled and the organic phase (approximately 4.0 mL of yellow liquid) was separated from the denser aqueous layer.

Methylphosphonic acid was removed by adding 5.0 mL of chloroform to the acidic extract and back-extracting the chloroform two times (isopropyl synthesis) or three times (cyclohexyl synthesis) with 3.0 mL portions of water. The chloroform extracts were dried over sodium sulfate followed by quantitative removal of the chloroform under vacuum. Overall yields of purified extracted product were 38% for isopropyl methylphosphonic acid and 31% for cyclohexyl methylphosphonic acid (based on the weight of purified product remaining after removal of chloroform).

The temperature-programmed GC retention indices for methyl derivatives and trimethylsilyl (TMS) derivatives were determined by a linear interpolation between bracketing *n*-alkanes on a capillary column coated with a 1.0 μm film of poly (5% diphenyl/95% dimethylsiloxane). Trimethylsilyl derivatives were created using bis-(trimethylsilyl)trifluoroacetamide (BSTFA).¹⁰ GC-EI-MS data (70 eV) were collected using a Hewlett-Packard Model 5890 GC (Agilent, Palo Alto, CA, USA) interfaced with a Hewlett-Packard 5972 mass spectrometer through a heated transfer line (280°C). Splitless sample introduction (injection port at 250°C) was followed by separation on a Restek (Bellefonte, PA, USA) Rtx-5 capillary column [30-m \times 0.25-mm i.d., d_f = 0.25 μm film of bonded poly (5% diphenyl/95% dimethylsiloxane) stationary phase]. After an initial hold at 45°C for 2 min, the column was programmed to 250°C at 8°C/min and held at this final temperature for 5 min. This program was adequate to elute all expected products and dimers from the chromatographic system. GC-CI-MS data were determined using a Hewlett-Packard Model 5890 GC interfaced with a JEOL SX102/SX102 mass spectrometer (Peabody, MA, USA) operated in the CI mode (source temperature 190°C, source pressure 2×10^{-4} torr) using isobutane reagent gas to observe *M*+1 ions. The JEOL instrument used a column identical to that used to collect EI-MS data.

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