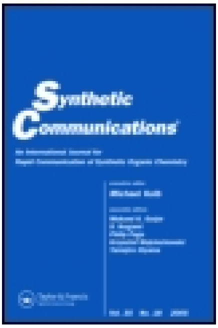

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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To cite this article: Julie A. Griffith , David J. McCauley , Richard E. Barrans Jr. & Albert W. Herlinger (1998) High Yield Synthesis of Tetraethyl Alkylene-Diphosphonates via the Michaelis-Arbuzov Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:23, 4317-4323, DOI: 10.1080/00397919808004465

To link to this article: http://dx.doi.org/10.1080/00397919808004465

SYNTHETIC COMMUNICATIONS, 28(23), 4317–4323 (1998)

HIGH YIELD SYNTHESIS OF TETRAETHYL ALKYLENEDIPHOSPHONATES VIA THE MICHAELIS-ARBUZOV REACTION

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Abstract

A high-yield synthesis of tetraethyl alkylenediphosphonates was achieved via the Michaelis-Arbuzov reaction. Application of optimized reaction conditions for a series of homologous alkylenediphosphonates establishes the generality of the approach.

Introduction

The useful properties of diphosphonates and diphosphonic acids have been recognized for many years. Important applications range from the treatment of osteoporosis to the functionalization of ion-exchange chromatographic resins.[1-3] Chemical applications frequently rely on the ability of diphosphonates to form stable complexes with a variety of metal ions.[4] Under acidic conditions, the metal-complexing ability of a diphosphonic acid exceeds that of analogous

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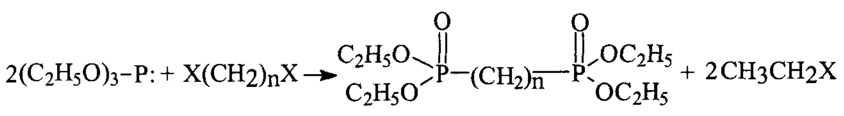
pyrophosphoric[5] or dicarboxylic acids.[6] Alkylenediphosphonic acids and their dialkyl-substituted derivatives are especially promising reagents for remediation of aqueous acidic mixed waste.[5] Efficient syntheses of diphosphonates is crucial for practical large-scale applications since an inexpensive source of starting materials would be required.

Tetraethyl alkylenediphosphonates are important synthetic reagents for the preparation of diphosphonic acids and their derivatives. The tetraethyl esters are easily hydrolyzed to the free acids.[7] The diphosphonic acids may then be re-esterified to a variety of symmetrically-substituted dialkyl esters.[8] The tetraethyl esters may also be selectively de-alkylated to give the diethyl esters of diphosphonic acids.[9]

Phosphonate compounds are normally prepared via the Michaelis-Arbuzov reaction, one of the most useful and well-characterized methods for the formation of phosphorus-carbon bonds.[10, 11] Phosphonates are formed when a trialkyl phosphite reacts with a primary haloalkane. Diphosphonates can be formed via this reaction if the haloalkane is replaced by a dihaloalkane (Figure 1).

FIG. 1



$$2(C_2H_5O)_3\text{-P:} + X(CH_2)_nX \rightarrow (C_2H_5O)_2\overset{O}{\overset{\|}{P}}-(CH_2)_n-\overset{O}{\overset{\|}{P}}(OC_2H_5)_2 + 2CH_3CH_2X$$

In dihaloalkane preparations, the distribution of substitution products depends upon the mole ratio of the reactants. Mono-substituted products predominate with an excess of dihaloalkane. Di-substituted product formation becomes more favorable as the phosphite-to-dihaloalkane mole ratio increases.[12, 13] Thus, the yield of the diphosphonate should improve when the phosphite-to-dihaloalkane mole ratio is increased. In this investigation, the reactant mole ratios were systematically varied to optimize diphosphonate formation.

Experimental

Diiodomethane, 1,2-dibromoethane, 1,3-dibromopropane, and 1,4-dibromobutane were obtained from Aldrich Chemical Company (Milwaukee, WI) and used without further purification. Triethyl phosphite purchased from Alfa Aesar (Ward Hill, MA) was used as received.

Tetraethyl ethylenediphosphonate. This compound was prepared following the procedure of Ford-Moore and Williams.[14] Triethyl phosphite and 1,2-dibromoethane were reacted in various stoichiometric amounts. The reactants were heated with vigorous stirring to 160°C using a silicone oil bath. Bromoethane was removed by fractional distillation (b.p. 38-39°C, lit. 37-41°C) and the mono-substituted by-products, diethyl ethylphosphonate and diethyl 2-bromoethylphosphonate, were removed by distillation under reduced pressure: boiling points of 41-44°C/0.5 mmHg (lit. 55-60°C/2 mmHg) and 84-87°C/0.5 mmHg (lit. 99-115°C/1 mmHg), respectively. Tetraethyl ethylenediphosphonate remained in the reaction flask. Prolonged heating or attempts to purify the product by distillation resulted in decomposition. The purity of the product was established from the ^{31}P NMR spectrum in $CDCl_3$ recorded on a Varian VXR-400S spectrometer. A single ^{31}P resonance appears in the proton decoupled spectrum when the sample is pure.

Tetraethyl methylenediphosphonate, tetraethyl propylenediphosphonate, tetraethyl butylenediphosphonate. These diphosphonates were prepared as described above by replacing 1,2-dibromoethane with diiodomethane, 1,3-dibromopropane, or 1,4-dibromobutane, respectively. Product purity was established by ^{31}P NMR spectroscopy. In all cases, a single ^{31}P resonance was observed in the proton decoupled spectra.

Results

The tetraethyl esters of several diphosphonic acids were synthesized via the Michaelis-Arbuzov reaction. The haloalkane by-product was removed rapidly during the initial stage of the reaction to suppress isomerization of the triethyl phosphite. The desired product was obtained by removing the diethyl ethylphosphonate and the diethyl haloalkylphosphonate via vacuum distillation.

The triethyl phosphite-to-dibromoethane mole ratio was varied in a successful attempt to optimize the formation of the tetraethyl ethylenediphosphonate. The results are reported in Table I. The highest yield of the desired di-substituted product was obtained using a 4:1 phosphite-to-dihaloalkane mole ratio. A large amount of unreacted phosphite must be recovered when the reaction is carried out with higher mole ratios. The evolution of this fraction under reduced pressure is extremely rapid, difficult to control, and complicates product isolation.

Table I. Optimization of the Synthesis for Tetraethyl Ethylenediphosphonate

Triethyl phosphite (mol)	1,2-dibromoethane (mol)	Mole ratio	% Yield*
0.470	0.235	2:1	53.8
1.33	0.333	4:1	88.7
1.20	0.200	6:1	71.5
0.999	0.0999	10:1	64.8

*Average values.

The reactant mole ratios in the synthesis of tetraethyl methylenediphosphonate, tetraethyl propylenediphosphonate, and tetraethyl butylenediphosphonate were also varied to determine the generality of the findings. The results were similar to those reported in Table I. The results for the 2:1 and 4:1 mole ratios are contrasted in Table II.

Table II. Generality of the Optimized Michaelis-Arbuzov Reaction

Compound	% Yield (2:1)	% Yield (4:1)
Tetraethyl methylenediphosphonate	26.0*	24.5
Tetraethyl ethylenediphosphonate	53.8	88.7
Tetraethyl propylenediphosphonate	72.5*	89.5
Tetraethyl butylenediphosphonate	61.6 *	93.0

*From reference 15.

The highest yields for tetraethyl propylenediphosphonate and tetraethyl butylenediphosphonate were obtained using the 4:1 phosphite-to-dihaloalkane mole ratio. The yield of tetraethyl methylenediphosphonate at a 4:1 mole ratio showed no improvement over the 2:1 stoichiometry. Alternative synthetic methods for this compound with more acceptable yields have been reported.[16-18]

In conclusion, the synthesis of several valuable tetraethyl alkylenediphosphonates has been optimized by varying the mole ratio of the reactants used in the Michaelis-Arbuzov reaction. The general reaction conditions should be applicable for the synthesis of other tetraesters and higher homologues of alkylenediphosphonates.

Acknowledgments

The authors wish to thank Paul G. Rickert (ANL) for helpful discussions and suggestions. JAG wishes to thank the Department of Education for support through the GAANN fellowship program. The work at ANL was support under the auspices of the Office of Basic Energy Sciences, Division of Chemical Sciences, U.S. Department of Energy, under contract number W-31-109-ENG-38.

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7. The tetraethyl ester was refluxed for ~48 hr with conc. HCl. The solvent was removed under reduced pressure until precipitation. The diphosphonic acid was vacuum filtered and recrystallized twice from H_2O.

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(Received in the U.S.A. 01 June 1998)