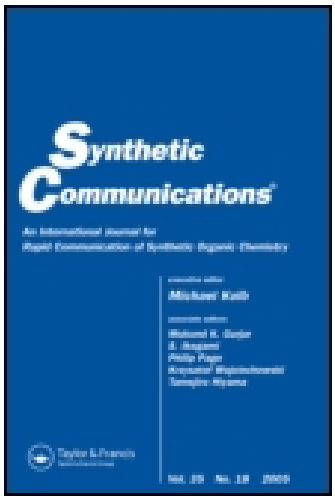

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A FACILE AND SELECTIVE HIGH YIELD SYNTHESIS OF SYMMETRIC DIALKYL-SUBSTITUTED METHYLENEBISPHOSPHONIC ACIDS

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A FACILE AND SELECTIVE HIGH YIELD SYNTHESIS OF SYMMETRIC DIALKYL-SUBSTITUTED METHYLENEBISPHOSPHONIC ACIDS

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ABSTRACT

Symmetric *P*,*P*′-dialkyl partial esters of methylenebisphosphonic acid were prepared in high yield and high selectivity from the corresponding acid chloride via a facile two-step, one-pot process. The newly developed synthesis, which does not require chromatographic or acid–base extractive purification, offers substantial advantages over previously used procedures.

Key Words: Phosphonic acids and derivatives; Esterification; Tetrazoles

INTRODUCTION

Bisphosphonic acids are among the most important of the organophosphorus compounds.[1,2] Ligands based on these acids form very stable complexes with a wide variety of metal ions,[3] and many practical

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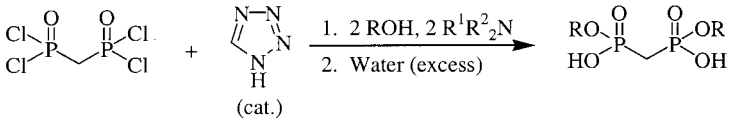
applications rely on the strong metal complexing ability of these molecules. For example, chelation of a cation by a bisphosphonate ligand increases its toxicological acceptability, facilitates its transport and ensures its selective concentration in target organs.[2] Bisphosphonic acids, their salts and tetraesters are widely used for treatment of diseases of the skeletal system as well as bone formation and resorption disorders.[4] Our interest in bisphosphonic acids is derived from their ability to strongly chelate actinides under highly acidic conditions and their potential for use in transuranic and mixed waste treatment.[5,6] The chelating ability of alkylenebisphosphonic acids has been utilized in metal ion separations in aqueous solution and on ion exchange and extraction chromatographic resins.[6,7,8] Partial functionalization of an alkylenebisphosphonic acid with an organic moiety enhances its solubility in non-aqueous solvents, while leaving the remaining acidic hydrogens available for exchange with the metal for charge neutralization.[8] Further, the lower acidity of the dialkyl partial esters is expected make them good candidates as drugs for treatment of bone diseases since this should lead to better binding to bone, improved bio-availability and superior therapeutic behavior.[9]

Utilization of partial esters of methylenebisphosphonic acid has been limited by the difficulty in obtaining pure compounds having exactly the desired number of ester substituents. A selective preparative method that has been used successfully to prepare *P*,*P*′-dialkyl and *P*,*P*′-disilyl partial esters is the dicyclohexylcarbodiimide-promoted coupling of methylenebisphosphonic acid with an alcohol of choice.[8,10] This procedure, which may not be applicable for some silicon-containing alcohols,[11] requires long reaction times at elevated temperature and a series of tedious acid–base extractions that generate large volumes of waste. Selective synthetic procedures have also been developed for preparing partial esters of dichloromethylenebisphosphonic acid from tetraesters using tertiary and secondary amines as dealkylating reagents.[12,13] Partial deprotection of the bisphosphonate, however, reportedly requires the presence of an activating group at the bridging methylene to instigate dealkylation.[12]

We report here a highly efficient two-step, one-pot method for selectively forming *P*,*P*′-dialkyl partial esters of methylenebisphosphonic acid from the acid chloride using 1*H*-tetrazole to control the regio-selectivity of the reaction. Our methodology draws upon work recently reported by Zhao and Laundry for the formation of mixed dialkyl monophosphonates.[14] In the first step of the synthesis, a catalytic amount of 1*H*-tetrazole is used to promote the condensation of methylenebis(phosphonic dichloride) with two equivalents of alcohol under mild, anhydrous conditions in the presence of a hindered base. In the second step, the partial



R = hexyl, cyclohexyl, octyl, 2-ethylhexyl, 2, 4, 4-trimethylpentyl, 3-trimethylsilylpropyl

$R^1R^2{}_2N$ = diisopropylethylamine

Figure 1.

ester is formed directly by quenching the unreacted P-Cl groups with water (Figure 1).

The procedure, which does not require chromatographic or acid–base extractive purification, offers substantial advantages over the previously used carbodiimide-promoted coupling route.[8,10]

EXPERIMENTAL

General Methods

All reagents supplied by Aldrich were used as received without further purification. Methylenebis(phosphonic dichloride) was handled under anhydrous conditions. Anhydrous solvents were dispensed from Aldrich Sure-Seal bottles and all glassware was oven dried at 120°C. The purity of the compounds was established by ^{1}H and ^{31}P NMR spectroscopy, potentiometric titration, elemental analysis and infrared spectroscopy. The ^{1}H and ^{31}P NMR spectra were recorded on a VXR 400 MHz spectrometer using $CDCl_3$ as the solvent. The δ values in parts per million (ppm) are relative to internal $CHCl_3$ and external 85% H_3PO_4, respectively. The equivalent weight of the partial esters was determined by titration with 0.1 M NaOH in an isopropanol–toluene mixture using an Orion EA 940 pH meter. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Infrared spectra were obtained on a Mattson Genesis series FTIR spectrometer operating in the 4000–400 cm^{-1} region using a liquid IR cell with NaCl windows. Spectra were recorded for 0.10 M solutions of the partial esters in CCl_4 using 64 scans at 4 cm^{-1} resolution with solvent as the background. Melting points were a measured using an Arthur H. Thomas, Hoover capillary melting point apparatus with a calibrated thermometer.

General Synthetic Procedure for the Preparation of *P*,*P*′-Dialkyl Partial Esters of Methylenebisphosphonic Acid

Methylenebis(phosphonic dichloride) (4.00 mmol) and 1*H*-tetrazole (0.6 mmol) were placed in a 100 mL Schlenk flask and dissolved in 50 mL of toluene with vigorous stirring under a nitrogen atmosphere. When dissolution was complete, a solution of the alcohol (7.92 mmol) and diisopropylethylamine (8.80 mmol) in 20 mL of toluene was added dropwise through an addition funnel over a 2.0 h period. After stirring overnight at room temperature under an atmosphere of nitrogen, the reaction mixture was quenched with 30 mL of water. The mixture was stirred for 15 min, transferred to a separatory funnel and the organic phase was washed with two 30 mL portions of 0.1 M HCl. The tetrazole and amine partition into the aqueous phase as their respective salts, while the desired product remains in the organic phase. The final product was obtained by removing the solvent and residual water under reduced pressure at 60°C. Typical yields are 85–95%.

***P*,*P*′-Di-*n*-hexyl methylenebisphosphonic acid, H_2DH[MBP]:** This novel compound was obtained as a white solid in 89% yield, m.p. 39.5–40.5°C. ^{1}H NMR ($CDCl_3$, δ): 10.89 (s, 2 H, OH), 4.06 (dt, 4 H, $J_{P,H} = J = 6.8$ Hz, OCH_2), 2.42 (t, 2 H, $J_{P,H} = 21.6$ Hz, P-CH_2-P), 1.65 (p, 4 H, $J = 6.9$ Hz, OCH_2CH_2), 1.22–1.38 (m, 12 H, CH_2), 0.88 (t, 6 H, $J = 6.8$ Hz, CH_3); ^{31}P NMR ($CDCl_3$, δ): 19.4 (s). Equiv. Wt.: calcd 172.2 g/mol, found 174.0 g/mol. Anal. calcd for $C_{13}H_{30}O_6P_2$: C, 45.35; H, 8.78, found: C, 45.32; H, 9.19.

***P*,*P*′-Dicyclohexyl methylenebisphosphonic acid, H_2DcH[MBP]:** This partial ester, reported in the literature to be an oil,[15] was isolated as a white solid in 94% yield, m.p. 133–135°C. ^{1}H NMR ($CDCl_3$, δ): 10.38 (s, 2 H, OH), 4.50 (m, 2 H, CH), 2.43 (t, 2 H, $J_{P,H} = 21.6$ Hz, P-CH_2-P), 1.15–2.02 (m, 20 H, CH_2); ^{31}P NMR ($CDCl_3$, δ): 18.4 (s). Equiv. Wt.: calcd 170.1 g/mol, found 179.5 g/mol. Anal. calcd for $C_{13}H_{26}O_6P_2$: C, 45.89; H, 7.70, found: C, 46.33; H, 8.01.

***P*,*P*′-Di-*n*-octyl methylenebisphosphonic acid, H_2DO[MBP]:** This compound was isolated as a white solid in 94% yield, m.p. 54–56°C (lit. 55°C).[16] ^{1}H NMR ($CDCl_3$, δ): 10.11 (s, 2 H, OH), 4.06 (dt, 4 H, $J_{P,H} = J =$ 6.9 Hz, OCH_2), 2.42 (t, 2 H, $J_{P,H} = 21.6$ Hz, P-CH_2-P), 1.65 (p, 4 H, $J = 7.0$ Hz, OCH_2CH_2), 1.20–1.39 (m, 20 H, CH_2), 0.88 (t, 6 H, $J = 7.0$ Hz, CH_3); ^{31}P NMR ($CDCl_3$, δ): 19.4 (s). Equiv. Wt.: calcd 200.2 g/mol, found 204.0 g/mol.

***P*,*P*′-Di(2-ethylhexyl) methylenebisphosphonic acid, H_2DEH[MBP]:** This dialkyl ester was isolated as a colorless oil in 92% yield. ^{1}H NMR ($CDCl_3$, δ): 10.46 (s, 2 H, OH), 3.97 (m, 4 H, OCH_2), 2.43 (t, 2 H,

$J_{P,H} = 21.8$ Hz, P-CH_2-P), 1.55 (m, 2 H, CH), 1.22–1.42 (m, 16 H, CH_2), 0.87 (m, 12 H, CH_3); ^{31}P NMR ($CDCl_3$, δ): 19.4 (s). Equiv. Wt.: calcd 200.2 g/mol, found 199.2 g/mol. Anal. calcd for $C_{17}H_{38}O_6P_2$: C, 50.99; H, 9.56, found: C, 51.37; H, 9.89.

***P,P′*-Di(2,4,4-trimethylpentyl) methylenebisphosphonic acid, H_2DTMP-[MBP]:** This novel C_8 ester of methylenebisphosphonic acid was isolated as a white solid in 93% yield, m.p. 67–70°C. ^{1}H NMR ($CDCl_3$, δ): 10.44 (s, 2H, OH), 3.72–3.92 (m, 4 H, OCH_2), 2.42 (t, 2 H, $J_{P,H} = 21.8$ Hz, P-CH_2-P), 1.83 (m, 2 H, CH), 0.97–1.28 (m, 4 H, CH_2), 0.97 (d, 6 H, $J = 6.8$ Hz, CHCH_3), 0.89 (s, 18 H, CCH_3); ^{31}P NMR ($CDCl_3$, δ): 19.3 (s). Equiv. Wt.: calcd 200.2 g/mol, found 207.4 g/mol. Anal. calcd for $C_{17}H_{38}O_6P_2$: C, 50.99; H, 9.56, found: C, 51.14; H, 10.00.

***P,P′*-Di[3-(trimethylsilyl)propyl] methylenebisphosphonic acid, H_2DTMSP[MBP]:** This compound was obtained as a white solid in 90% yield, m.p. 39–41°C (lit. 32–34°C).[10] ^{1}H NMR ($CDCl_3$, δ): 10.31 (s, 2 H, OH), 4.01 (dt, 4 H, $J_{P,H} = J = 7.2$ Hz, OCH_2), 2.43 (t, 2 H, $J_{P,H} = 21.6$ Hz, P-CH_2-P), 1.65 (m, 4 H, OCH_2CH_2), 0.48 (m, 4 H, $OCH_2CH_2CH_2$), 0.01 (s, 18 H, CH_3); ^{31}P NMR ($CDCl_3$, δ): 19.3 (s). Equiv. Wt.: calcd 202.3 g/mol, found 203.9 g/mol.

General Purification Procedure for Partial Esters

A product of high purity is obtained upon washing the crude product with 0.1–0.2 M HCl. This ensures that all unreacted amine and tetrazole partition into the aqueous phase as salts and obviates the foaming that can be problematic if the product is washed with water. If necessary, purification of an alcohol-containing product could be achieved by the acid–base extraction method described previously for the carbodiimide-promoted coupling procedure.[8,10]

RESULTS AND DISCUSSION

A highly efficient and facile method for selectively forming *P,P′*-dialkyl partial esters of methylenebisphosphonic acid has been developed. The reaction sequence, shown in Figure 1, utilizes 1*H*-tetrazole to catalyze the coupling of methylenebis(phosphonic dichloride) with two equivalents of alcohol under mild conditions. The procedure has general synthetic applicability for the preparation of a variety of water immiscible diesters of methylenebisphosphonic acid. A number of primary alkyl, cyclic secondary alkyl and silicon-containing alcohols were successfully utilized in this

procedure. The yield of high purity partial ester achieved using this method is higher than that previously obtained using carbodiimide-promoted coupling procedures.[8,10] The extraction performance of the product formed by the 1*H*-tetrazole catalyzed esterification of methylenebis(phosphonic dichloride) is as good if not better than the performance of the product formed by the latter route.[17]

The ^{31}P NMR spectra of the partial esters consist of a single sharp resonance. The position of this resonance ($\delta \sim 19$) is not strongly influenced by the nature of the alkyl-substituent. The ^{1}H NMR spectra of the esters exhibit resonances of the expected intensity and splitting patterns in the appropriate spectral regions. There is no evidence of unreacted alcohol being present in these samples. The infrared spectra of the partial esters are indicative of a strongly hydrogen-bonded dialkyl alkylenebisphosphonic acid. These characteristic spectral features are not given here since they have been previously discussed in detail for H_2DEH[MBP][18,19] and H_2DTMSP[MBP].[10] The phosphoryl band position ($\sim$1240 cm^{-1}) is not strongly influenced by the nature of the alkyl-substituent. Small differences are observed in the 3000–2800 cm^{-1} region due to differences in the alkyl chains. The most notable difference is the simplified two-band spectrum exhibited in this region by the dicyclohexyl partial ester H_2DcH[MBP].

The 1*H*-tetrazole catalyzed coupling reaction was investigated in a variety of aromatic (benzene and toluene) and chlorinated hydrocarbon (CH_2Cl_2 and $CHCl_3$) solvents. Aromatic solvents afforded the highest yields and best purity. Toluene, with its lower vapor pressure and toxicity, appears to be the solvent of choice. Reactions carried out in halogenated solvents afforded lower yields, and the purity of the product was lowered by the presence of hydrocarbon by-products.

The procedure is carried out using a small excess of the acid chloride to prevent the formation of the triester, which is not easily removed. The formation of a small amount of the parent acid or the monoester is not a concern since both are water-soluble and partition into the aqueous phase when the reaction is quenched. Features of the process which are critical to successfully obtaining the desired product in high purity are careful control of reagent stoichiometry, use of anhydrous solvents, and slow simultaneous addition of alcohol and hindered base to the acid chloride. Advantages of this method over existing preparative methods include: higher yields, shorter reaction times, milder conditions, less expensive and less toxic starting reagents, smaller secondary waste streams and simpler isolation and purification procedures.

The procedure is not applicable for the preparation of water-soluble partial esters of methylenebisphosphonic acid, nor does it work well with tertiary or highly hindered secondary alcohols. Reaction of phenol or a

fluoroalkyl alcohol with methylenebis(phosphonic dichloride) produces a mixture of all possible bisphosphonate esters. Work to expand the applicability of the 1*H*-tetrazole catalyzed esterification of methylenebis(phosphonic dichloride) to a wider range of alcohols is currently in progress in our laboratory.

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