Notes

Preparation of (4-Amino-1-Hydroxybutylidene)bisphosphonic Acid Sodium Salt, MK-217 (Alendronate Sodium). An Improved Procedure for the Preparation of 1-Hydroxy-1,1-bisphosphonic Acids

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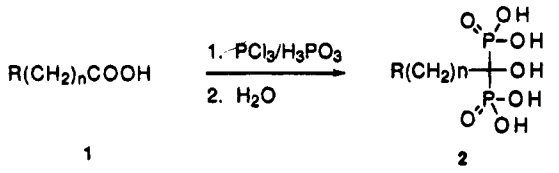
Introduction

Bisphosphonic acids are excellent antihypercalcemics and as such are rapidly evolving as therapeutic agents for the treatment of a number of diseases which are characterized by abnormal calcium metabolism.[1] They have demonstrated effectiveness in arresting bone deterioration and restoring normocalcemia in patients with hypercalcemia of malignancy, metastatic bone disease, Paget's disease, and osteoporosis, and they have the potential for other applications as well. To facilitate the further evaluation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (**2b**) as a therapeutic agent, it was essential to develop an efficient and practical synthesis to guarantee availability for its evaluation in clinical trials.

Several methods have been reported for the synthesis of 1,1-bisphosphonates. They have been prepared by reaction of a carboxylic acid with phosphorous acid and phosphorus trichloride (Scheme 1), phosphorus pentachloride, or phosphorus oxychloride,[2] by alkylation of tetraalkylmethyl bisphosphonate and related compounds,[2h,3] by Michael type addition to tetraethylethylidene bisphosphonate,[4] by [3 + 2] cycloaddition,[5] and by reaction of an acylphosphonate with a dialkyl phosphite in the presence of a catalytic amount of base.[2h,3b,6]

Scheme 1



1 2

The most expedient method for the preparation of 1-hydroxybisphosphonates, and the only method reported for the preparation 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, reacts a 4-aminobutyric acid (GABA) with phosphorus trichloride and phosphorous acid (Scheme 1).[7]

While the yield of this reaction is moderate, the use of inexpensive, readily available reagents, coupled with its simplicity, make it synthetically attractive. Unfortunately, the reaction has extremely poor physical characteristics making it impossible to scale up safely. The reaction mixture starts as a two-phase melt which gradually thickens, the volume of which increases due to entrained gases which are generated. A semisolid forms with concurrent loss of agitation. Upon cooling, the mixture forms a reactive brittle glass which must be quenched and worked-up. While this may be acceptable for preparations of small quantities of material, it is impractical for even modest scale preparations. The potential efficiency of this remarkable reaction attracted our attention and prompted further investigation. We wish to report herein an improved procedure which circumvents these problems. By running the reaction in methanesulfonic acid, the reaction remains fluid, thus allowing complete conversion of the carboxylic acid providing excellent yields and purity of 1-hydroxy-1,1-bisphosphonates.[8]

Results and Discussion

Since the reaction mixture starts as a two-phase melt, our initial efforts focused on increasing the amounts of the reagents, in particular the phosphorous acid, with the hope that the mixture would remain as a melt. Increasing the phosphorous acid had little effect upon the physical characteristics of the mixture while actually

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(7) See ref 2 for the preparation of a variety of 1-hydroxy-1,1-bisphosphonates. For preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid from 4-aminobutyric acid (GABA) see ref 2e,f,g.

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Table 1

compound	R	n	% yield[a]	lit. yield[ref]
2a	NH_2	2	57	72 (ref 2d)
2b	NH_2	3	89[b]	56 (ref 2e), 65 (ref 2g)
2c	NH_2	4	78	63 (ref 2g)
2d	NH_2	5	89	55 (ref 2c)
2e	CH_3	10	95[c]	–
2f	3-imidazoyl	1	31[d]	–
2g	3-pyridyl	1	38[d]	–
2h	4-aminophenyl	1	26	–
2i	Cl	3	30[e]	–

[a] Unless otherwise noted, yields pertain to the monosodium salt. With the exception of example **2b**, the yields were not optimized; the reactions were generally run once. [b] The yield of the free acid was 85%. [c] Isolated as a 40/60 mixture of mono- and disodium salts. [d] Isolated as the free acid. [e] Isolated as the tetrahydrofuran-2,2-bisphosphonic monosodium salt.

decreasing the yield, whereas increasing both the phosphorous acid and the PCl_3 had little effect either on the yield or the physical characteristics of the reaction. With other reagents, such as $POCl_3$, solidification occurred, and with PPA the mixture remained homogeneous, but no reaction took place.

Next we examined a number of solvents, concentrating first on ethereal solvents (ether, THF, DME, and dioxane) in which phosphorous acid is soluble. We were encouraged by the fact that these mixtures were homogeneous at the onset. As the reaction proceeds, however, a dense lower layer forms which eventually solidifies, leaving a clear ethereal upper layer. Other common non-ethereal solvents offered no advantage over the neat reaction. We also tried using high speed stirring with inert solvents such as hexane and chlorobenzene hoping to form a dispersion and prevent solidification. While agitation was maintained, a dispersion was not obtained; instead, the thick mixture coated the sides of the flask. Methanesulfonic acid has been used as a solvent for phosphorus pentoxide reactions[9] and was therefore tried. When we examined methanesulfonic acid (MSA), we were pleased to find that the reaction remained fluid at concentrations of 2.5 M (4 mL/g) and below, thus allowing for complete conversion of the carboxylic acid.[10] It is desirable to keep the MSA at a minimum; the MSA reacts with the PCl_3, the reaction is faster at higher concentration, and the MSA must be removed at the end. Therefore, the reaction is normally run 2.5 M in methanesulfonic acid.

With a solvent identified, we reexamined the stoichiometry of the reaction. The prior art suggests using 1.5 equiv of both PCl_3 and H_3PO_3 for this reaction.[3] We found that a larger excess ($\geq$2 mol) of PCl_3 was required to effect completion, while only 0.75 equiv of H_3PO_3 was needed.[11]

Our initial experiments were run at reflux (internal temperature of 75 °C). Routine operational hazards evaluation revealed that under adiabatic conditions the reaction becomes self-heating at 85 °C, and an uncontrolled exotherm occurs at >140 °C. This 10 °C temperature differential was of some concern upon scale-up, prompting us to examine lower reaction temperatures to obtain a greater margin of safety. At 55 °C the reaction takes 3 days, while at 65 °C the reaction is complete after an overnight age.

Upon completion of the reaction, it is quenched with water and hydrolyzed at reflux. The bisphosphonic acid crystallizes directly from the aqueous reaction mixture after cooling and adjusting the pH to 1.8, while the monosodium salt is obtained upon cooling and adjusting the pH to 4.3. Both are analytically pure as isolated.

The reaction appears to be quite general for a variety of unhindered carboxylic acids, see Table 1. The conversion is lower for β-substituted acids and does not work with α-substituted acids.

Experimental Section

General. All chemicals were purchased from Aldrich and were used as is. Assays were performed by the analytical department of Merck & Co., Inc.

General Procedure for the Preparation of Bisphosphonic Acids and Their Sodium Salts. Preparation of (4-Amino-1-hydroxybutylidene)bisphosphonic Acid Monosodium Salt (2b). A 250 mL flask was fitted with a mechanical stirrer, a thermocouple, an addition funnel, and a reflux condenser through which was circulated −10 °C brine and connected to a caustic scrubber. The system was flushed with nitrogen and charged with 4-aminobutyric acid (20 g, 0.19 mol),[12] phosphorous acid (16 g, 0.19 mol), and methanesulfonic acid (80 mL). The mixture was heated to 65 °C, PCl_3 (35 mL, 0.40 mol) added over 20 min, and the mixture maintained at 65 °C overnight (generally 16−20 h). The clear, colorless solution was cooled to 25 °C and quenched into 0−5 °C water (200 mL) with vigorous stirring. The reaction flask was rinsed with an additional 100 mL of water and the combined solution refluxed for 5 h. The solution was cooled to 20 °C, the pH adjusted to 4.3 with 50% NaOH (ca. 80 mL), and the resulting suspension aged for 2 h at 0−5 °C. The product was collected by filtration, washed with cold water (2 × 50 mL) and 95% ethanol (100 mL), and dried (air drying then *in vacuo* at 40 °C) yielding 56.4 g (89% yield) of **2b** as the monosodium salt trihydrate: mp 257−262.5 °C; MS (FAB) *m/z* 248 (M − Na); ^{1}H NMR (D_2O) δ 3.02 (2H, m), 1.99 (4H, m); ^{13}C NMR (D_2O) δ 74.3 (t, J_{C-P} = 135 Hz), 40.8, 31.4, 23.0 (t, J_{C-P} = 6.6 Hz); ^{31}P NMR (H_3PO_4/D_2O) δ 18.7; Titration (NaOH) 99.7%, (complexometric) 99.9%; KF 16.6% (theory 16.6%). Anal. Calcd for $C_4H_{12}NNaO_7P_2 + 3H_2O$: C, 14.77; H, 5.54; N, 4.31; Na, 7.08; P, 19.08. Found: C, 14.67; H, 5.58; N, 4.22; Na, 7.00; P, 19.00; residual Cl < 0.05%.

(4-Amino-1-hydroxybutylidene)bisphosphonic Acid (2b). To obtain the free acid, the above procedure is followed and the pH is adjusted to 1.8 instead of 4.3. Isolation and drying is identical, providing 44.0 g (85% yield) of white crystalline **2b** as a monohydrate. Anal. Calcd for $C_4H_{13}NO_7P_2 + H_2O$: C, 17.97; H, 5.62; N, 5.24; P, 23.21. Found: C, 17.84; H, 5.55; N, 5.16; Na, 0.05; P, 23.02. Titration (NaOH) 99.5%, (complexometric) 99.8%; LOD 6.79% (theory 6.74%).

(3-Amino-1-hydroxypropylidene)bisphosphonic Acid Monosodium Salt (2a). Yield 57%: ^{1}H NMR ($NaOD/D_2O$): δ 2.88 (t, J = 7.6 Hz, 2H), 1.90−2.04 (m, 2H); ^{13}C NMR (DCl/D_2O) δ 72.3 (t, J_{C-P} = 148 Hz), 36.3, 31.0 (t, J_{C-P} = 7.4 Hz); ^{31}P NMR (H_3PO_4/D_2O) δ 18.0; MS (ESI) *m/z* 258 (M + 1). Anal. Calcd for $C_3H_{10}NNaO_7P_2 + H_2O$: C, 13.10; H, 4.40; N, 5.09; Na, 8.36; P, 22.52. Found: C, 13.12; H, 4.21; N, 4.95; Na, 8.20; P, 22.63; residual Cl < 0.05%.

(4-Amino-1-hydroxypentylidene)bisphosphonic Acid Monosodium Salt (2c). Yield 78%: ^{1}H NMR ($NaOD/D_2O$) δ 2.62 (t, J = 7.2 Hz, 2H), 1.78−1.90 (m, 2H), 1.51−1.61 (m, 2H), 1.4 (pent, J = 7.2 Hz, 2H,); ^{13}C NMR ($NaOD/D_2O$) δ 77.4 (t, J_{C-P} = 135 Hz), 41.3, 36.7, 33.7, 22.3 (t, J_{C-P} = 5.8 Hz); ^{31}P NMR (H_3PO_4/D_2O): δ 19.1; MS (ESI) 286 (M + 1). Anal. Calcd for $C_5H_{14}NNaO_7P_2 + 1.4\ H_2O$: C, 19.35; H, 5.46; N, 4.51; Na, 7.41;

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(10) Similar results were obtained with benzenesulfonic acid; sulfuric acid did not work.

(11) If the reaction is run without H_3PO_3, a yield of ca. 30% is obtained. This is consistent with the formation of 0.33 a mol of H_3PO_3 from the reaction of the carboxylic acid with 0.33 a mol of PCl_3. The H_3PO_3 for this reaction can be generated *in situ* from PCl_3 and 3 mol of water.

(12) This reaction has been run on a 14 kg scale producing the monosodium salt in 87% yield and the acid in 82% yield.

P, 19.96. Found: C, 19.22; H, 5.33; N, 4.39; Na, 7.46; P, 20.37; residual Cl < 0.05%.

(4-Amino-1-hydroxyhexylidene)bisphosphonic Acid Monosodium Salt (2d). Yield 89%: ^{1}H NMR (NaOD/D_2O) δ 3.0 (t, J = 7.4 Hz, 2H), 1.84–2.01 (m, 2H), 1.69 (pent, J = 7.4 Hz, 2H), 1.54–1.66 (m, 2H), 1.37 (pent, J = 7.4 Hz, 2H); ^{13}C NMR (NaOD/D_2O) δ 76.9 (t, J_{C-P} = 133 Hz), 40.8, 36.3, 30.2, 27.8, 24.5 (t, J_{C-P} = 5.5 Hz); ^{31}P NMR (H_3PO_4/D_2O) δ 19.3; MS (ESI) 300 (M + 1). Anal. Calcd for $C_5H_{14}NNaO_7P_2$ + 0.5 H_2O: C, 23.39; H, 5.56; N, 4.55; Na, 7.46; P, 20.10. Found: C, 23.39; H, 5.70; N, 4.51; Na, 7.49; P, 20.17; residual Cl < 0.05%; KF 2.55%, TG 3.2% (theory 2.92).

(1-Hydroxydodecylidene)bisphosphonic Acid Sodium Salt (2e). Yield 95%: ^{1}H NMR (NaOD/D_2O) δ 1.75–1.96 (m, 2H), 1.43–1.55 (m, 2H), 1.25–1.31 (m, 16H), 0.81 (t, J = 6.3 Hz, 3H); ^{31}P NMR (NaOD/H_3PO_4/D_2O): δ 13.8; MS (ESI) 392/369 (M + 1). Anal. Calcd for $C_{12}H_{27}Na_{1.6}O_7P_2$: C, 37.72; H, 7.12; Na, 9.63; P, 16.21. Found: C, 38.12; H, 6.85; Na, 9.62; P, 15.74.

(2-(3-Imidazoyl)-1-hydroxyethylidene)bisphosphonic Acid (2f). Yield 31%: ^{1}H NMR (NaOD/D_2O) δ 7.74 (s, 1H), 6.91 (s, 1H), 3.24 (t, J = 12.6 Hz, 2H), ^{13}C NMR (NaOD/D_2O) δ 135.5 (d, J = 12 Hz), 130.2 (t, J = 8.4 Hz), 123.4 (broad s), 74.0 (t, J = 129 Hz), 30.2; ^{31}P NMR (H_3PO_4/D_2O) δ 17.3; MS (ESI) m/z 273 (M + 1). Anal. Calcd for $C_5H_{10}N_2O_7P_2$ + H_2O: C, 20.69; H, 4.14; N, 9.67. Found: C, 20.67; H, 3.74; N, 9.80; residual Cl < 0.05%.

(2-(3-Pyridyl)-1-hydroxyethylidene)bisphosphonic Acid (2g). Yield 38%: ^{1}H NMR (NaOD/D_2O): δ 8.49 (d, J = 1.5 Hz, 1H), 8.26 (dd, J = 5, 1.5 Hz, 1H), 7.90 (dt, J = 7.8, 1.9 Hz, 1H), 7.29 (dd, J = 7.8, 5 Hz, 1H), 3.29 (t, J = 12 Hz, 1H); ^{13}C NMR (NaOD/D_2O) δ 144.5, 133.5 (d, J = 4.3 Hz), 130.5 (t, J = 6.5 Hz), 129.8, 116.6, 76.3 (t, J = 133.8 Hz), 39.5; ^{31}P NMR (NaOD/H_3PO_4/D_2O) δ 12.7; MS (ESI) m/z 284 (M + 1). Anal. Calcd for $C_7H_{11}NO_7P_2$ + H_2O: C, 27.92; H, 4.35; N, 4.65; P, 20.57. Found: C, 28.00; H, 4.42; N, 4.60; P, 20.69; Na < 0.01; residual Cl < 0.13%; KF 5.87% (theory 5.98).

(2-(4-Aminophenyl)-1-hydroxyethylidene)bisphosphonic Acid Monosodium Salt (2h). Yield 26%: ^{1}H NMR (NaOD/D_2O) δ 7.27 (d, J = 8.1 Hz, 2H), 6.75 (d, J = 8.1 Hz, 2H), 3.20 (t, J = 12.5 Hz, 2H); ^{13}C NMR (NaOD/D_2O) δ 144.4, 133.6 (t, J = 7.7 Hz), 130.8 (t, J = 6.4 Hz), 116.5, 76.9 (t, J = 133.6 Hz), 39.9; ^{31}P NMR (H_3PO_4/D_2O): δ 18.4; MS (ESI) m/z 320 (M + 1). Anal. Calcd for $C_8H_{12}NNaO_7P_2$ + 1.5 H_2O: C, 27.76; H, 4.32; N, 4.05; Na, 6.64; P, 17.90. Found: C, 27.80; H, 4.53; N, 4.08; Na, 6.70; P, 18.07; KF 7.8% (theory 8.1%).

Tetrahydrofuranyl-2,2-bisphosphonic Acid Sodium Salt Monohydrate (2i). Yield 30%: ^{1}H NMR (NaOD/D_2O) δ 3.80–3.86 (m, 2H), 2.21 (sept, J = 7.6 Hz, 2H), 1.91 (pent, J = 6.8 Hz, 2H); ^{13}C NMR (NaOD/D_2O) δ 83.5 (t, J_{C-P} = 139 Hz), 69.5 bs, 30.9, 27.4; ^{31}P NMR (H_3PO_4/D_2O) δ 19.1; MS (ESI) m/z 255 (M + 1). Anal. Calcd for $C_4H_9NaO_7P_2$ + H_2O: C, 17.66; H, 4.08; Na, 8.45; P, 22.77. Found: C, 17.67; H, 4.04; Na, 8.30; P, 22.90; residual Cl < 0.05%; KF 6.4% (theory 6.6%).

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