A facile one pot synthesis of bisphosphonic acids and their sodium salts from nitriles

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Abstract

A general and one pot synthesis for the preparation of bisphosphonic acids and their sodium salts (**2a-e**) from nitriles (**3a-e**) is described. This method involves hydrolysis of nitriles (**3a-e**) to the corresponding acids and subsequent bisphosphonation in a single solvent to produce bisphonates (**2a-e**). Preparations of some of bisphosphonates, which are presently in clinical use like risedronate (**2a**) sodium, ibandronate sodium (**2d**) are synthesized by following this new method. This method is useful for the preparation of other bisphosphonate compounds.

Keywords: Bisphosphonates, pamidronate, risedronate, ibandronate, alendronate, zolendronate

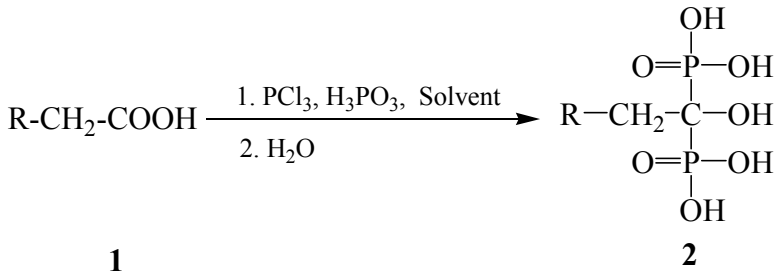
Introduction

Bisphosphonic acids and/or their salts 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] Bisphosphonates, in particular bisphosphonates, 1-hydroxy-2-(pyridinyl)ethylidene-1,1-bisphosphonic acid (risedronic acid **2a**), 1-hydroxy-3-(methylpentylamino)propylidene bisphosphonic acid (ibandronate **2d**), 3-amino-1-hydroxy propylidene bisphosphonic acid (pamidronate), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate) are used for the treatment of Paget`s disease of bone and osteoporosis. The synthesis of 1-hydroxyalkylidene-1,1-bisphosphonic acids (bisphosphonates) is based on reacting a carboxylic acid (**1**) with a mixture of phosphorous acid and phosphorous chloride such as PCl_3 or PCl_5, then quenching the reaction mixture with water followed by heating to hydrolyze the phosphonated reaction mass to get required product (**2**). 1-Hydroxyalkylidene-1,1 bisphosphonic acids were prepared using a solvent such as chlorobenzene,[2] methanesulphonic acid,[3] sulfolane,[4] ionic liquids[5] and diphenyl ether[6] as shown in Scheme 1. Our present work

envisages a new and direct method for the synthesis of bisphosphonic acids and their salts (**2a-e**) from nitrile compounds (**3a-e**) as a one-pot synthesis.

Results and Discussion

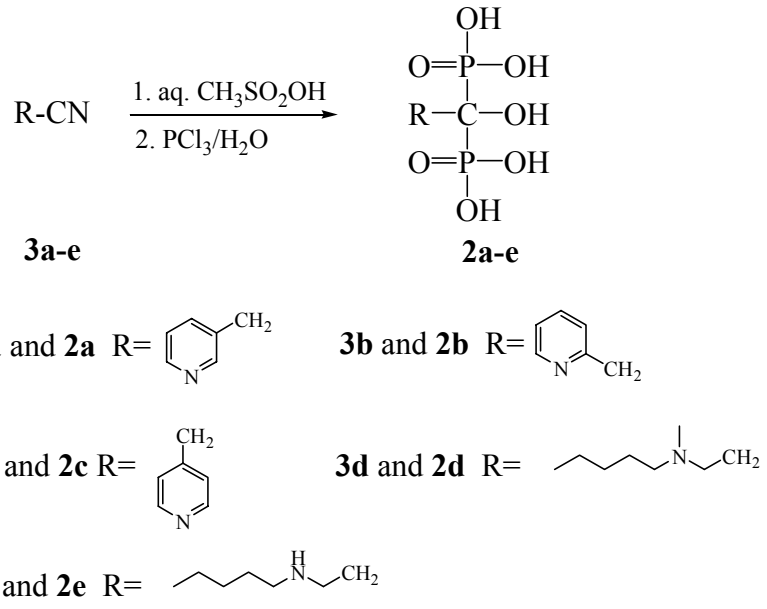
In our efforts to develop a simple and industrial feasible method for the synthesis of risedronic acid **2a**, experiments were carried out with known methods in the literature.[2-6] In all these methods (Scheme 1), it was obtained by the reaction of 3-pyridylacetic acid with phosphorous acid and phosphorous trichloride in a solvent such as chlorobenzene,[2] methanesulfonic acid,[3] sulfolane,[4] ionic liquids,[5] and diphenyl ether.[6] All the above processes have some disadvantages associated with their use such as solid mass formation which prevents uniform mixing. However methanesulphonic acid is helpful for solubilizing the reaction mass but it gave lower yield (40%, reported[3] 38%). Moreover they reported[2-6] the yields 50%, 38%, 70%, 49% and 77% respectively.



1 **2**

Scheme 1

Because of the therapeutic importance of this class of compounds, it became essential to develop an efficient and practical synthesis method. We report a new simple procedure to synthesize risedronic acid **2a** with a better yield 79% and its sodium salt 71% directly from 3-pyridinecarbonitrile **3a** in a suitable solvent (Scheme 2). Hydrolysis of 3-pyridinecarbonitrile **3a** in aqueous methanesulfonic acid[7] produces the corresponding carboxylic acid *in situ* and is allowed to react with phosphorous trichloride and the resulting phosphonated reaction mass on further hydrolysis yielded the bisphosphonic acids at pH < 2 or its monosodium salt at pH 4.2-4.5 in good yields. The commercially available aqueous methanesulfonic acid (85%) is cheaper than methanesulfonic acid and is used both as acid catalyst in the first operation and as solvent in the subsequent phosphonylation reaction. This process is industrially much favored because the entire process is carried out in a single solvent which itself promotes the acid catalyzed hydrolysis of nitrile group. Further, to evaluate this methodology we have tried to prepare various bisphosphonates and got the required product in good yield.



Scheme 2

In summary, a one-pot synthesis of bisphosphonic acids and/or sodium salts (**2a-e**) from corresponding nitriles (**3a-e**) is described. The inexpensive and readily available starting material and reaction solvent make this procedure a practical and simple one-pot method for the preparation of bisphosphonic acid and/or its sodium salt. Finally, this methodology can be used for making other bisphosphonate drugs such as zoledronic acid and minodronic acid.

Experimental Section

General Procedures. The IR spectra were recorded on a Perkin Elmer Spectrum of FTIR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 300 MHz and 75 MHz spectrometer respectively. Chemical shifts are reported in ppm downfield from TMS as internal standard. Mass spectra were measured on Perkin Elmer PE SCIEX-API 2000 mass spectrometer.

1-Hydroxy-2-(3-pyridyl)ethylidene bisphosphonic acid (risedronic acid, 2a). Aqueous methanesulfonic acid (85%, 432.5 mL) was added to 3-pyridinecarbonitrile[8] **3a** (100.0 g, 0.847 mol) and heated to 98-100 °C for 8 h. Then, cooled the reaction temperature to 65 °C and phosphorus trichloride (396.0 g, 2.880 mol) was added over 25 min. After 5 h. stirring at 65-70 °C, the reaction mass temperature was cooled to 30 °C and pre-cooled water (1000 mL) was added very slowly in 30 min. The reaction mass temperature was heated to 98 °C. After 15 h stirring, the temperature was cooled to 50 °C and methanol (1500 mL) was added. After 2 h. stirring at 5-10 °C, the product was collected by filtration and dried to yield **2a** (201.5 g, 79%) as

a white monohydrate solid; purity[9] 99.1% (by HPLC); IR (KBr, cm^{-1}) 3189, 3091, 3069, 1635, 1617, 1262, 1073; ^{1}H NMR (D_2O/ NH_3) δ 3.26 (t, 2H, *J*=12.1 Hz), 7.54, (dd, 1H, *J*=8.2, 5.5 Hz), 8.18 (d, 1H, *J*=8.2 Hz), 8.32 (d, 1H, *J*=5.5 Hz), 8.51, (s, 1H); ^{13}C-NMR (300 MHz, D_2O/ NH_3) δ 36.5, 73.8, 125.3, 137.1, 141.3, 145.4, 146.1; ^{31}P NMR (D_2O/NH_3) δ 18.1; MS (ESI, *m/z*): 282.0 $[M-H]^+$.

Risedronic acid monosodium salt (2a sodium). Monosodium salt was obtained by the above procedure with 3-pyridinecarbonitrile **3a** (100.0 g, 0.847 mol). But, pH was adjusted to 4.3 with 30% sodium hydroxide solution before diluting with methanol (1500 mL). The resulting product was filtered and dried to yield **2a** sodium **(**210 g, 71%) as a white crystalline hemipentahydrate solid; purity[9] 99.8% (by HPLC); IR (KBr, cm^{-1}) 3621, 3566, 3364, 1689, 1655, 1211, 1134, 1065; ^{1}H NMR (D_2O) δ 3.37 (t, 2H, *J*=12.1 Hz), 7.84, (m, 1H), 8.50 (d, 2H, *J*=7.2 Hz), 8.66 (s, 1H); ^{13}C-NMR (300 MHz, D_2O) δ 36.4, 73.9, 126.3, 138.4, 138.9, 142.7, 149.4; ^{31}P NMR (D_2O) δ 17.1; MS (ESI, *m/z*): 284.1 $[M+H]^+$.

1-Hydroxy-2-(2-pyridyl)ethylidene bisphosphonic acid monosodium (2b). This compound was prepared in a similar way to **2a sodium**, using 2-pyridinecarbonitrile **3b** (10.0 g, 0.085 mol) procured from Aldrich chemicals, as a white hemipentahydrate solid (21 g, 71%); purity[9] 99.4% (by HPLC); IR (KBr, cm^{-1}) 3190, 3186, 1638, 1625, 1215, 1058; ^{1}H NMR (D_2O) 3.54 (t, 2H, *J*=12.9 Hz), 7.73 (dd, 1H, *J*=7.9, 7.1 Hz), 7.82, (d, 1H, *J*=8.2 Hz), 8.29, (dd, 1H, *J*=9.1, 8.2 Hz), 8.49 (d, 1H, *J*=6.1 Hz); ^{13}C-NMR (300 MHz, D_2O) δ 37.7, 73.3, 125.1, 129.8, 140.7, 145.9, 153.4; ^{31}P NMR (D_2O) δ 17.0; MS (ESI, *m/z*): 284.1 $[M+H]^+$.

1-Hydroxy-2-(4-pyridyl)ethylidene bisphosphonic acid monosodium (2c). This compound was prepared in a similar way to **2a sodium**, using 4-pyridinecarbonitrile **3c** (10.0 g, 0.085 mol) procured from Aldrich chemicals, as a white monohydrate solid (20.5 g, 75%); purity[9] 99.2% (by HPLC); IR (KBr, cm^{-1}) 3242, 3107, 1644, 1626, 1224, 1058; ^{1}H NMR (D_2O) 3.37 (t, 2H, *J*=12.1 Hz), 7.88 (d, 2H, *J*=6.0 Hz), 8.42 (d, 2H, *J*=6.0 Hz); ^{13}C-NMR (300 MHz, D_2O) δ 39.6, 74.5, 129.6, 140.7, 159.2; ^{31}P NMR (D_2O) δ 17.2. MS (ESI, *m/z*): 284.1 $[M+H]^+$.

1-Hydroxy-3-(methylpentylamino)propylidene bisphosphonic acid monosodium (ibandronate sodium, 2d). This compound was prepared in a similar way to **2a sodium**, but isolated from ethanol, using N-methylpentylamino propionitrile[10] **3d** (50.0 g, 0.325 mol) as a white monohydrate solid (75.4 g, 65%); purity[11] 99.2% (by HPLC); IR (KBr, cm^{-1}) 3164, 2922, 2852, 1667, 1191, 1067; ^{1}H-NMR (300 MHz, D_2O) δ 0.78 (t, 3H, *J*= 6.9 Hz), 1.21-1.25 (m, 4H), 1.61-1.63 (m, 2H), 2.22-2.28 (m, 2H), 2.74 (s, 3H), 2.94-2.98 (m, 1H), 3.10-3.25 (m, 2H), 3.43-3.49 (m, 1H); ^{13}C-NMR (300 MHz, D_2O) δ 13.4, 21.8, 23.5, 28.1, 28.2, 39.7, 53.2, 56.7, 72.6; ^{31}P NMR (D_2O) δ 17.7; MS (ESI, *m/z*): 318.1 $[M-H]^+$.

1-Hydroxy-3-(pentylamino)propylidene bisphosphonic acid mono sodium (2e). This compound was prepared in a similar way to **2a sodium**, but isolated from ethanol, using N-pentylamino propionitrile[10] **3e** (10.0 g, 0.071 mol) as a white monohydrate solid (15.7 g, 64%); purity[11] 99.1% (by HPLC); IR (KBr, cm^{-1}) 3127, 2957, 2871, 1640, 1607, 1156, 1081; ^{1}H-NMR (300 MHz, D_2O) δ 0.79 (t, 3H, *J*= 6.9 Hz), 1.23-1.25 (m, 4H), 1.54-1.59 (m, 2H), 2.14-2.27 (m,

2H), 2.91-2.95 (m, 2H), 3.24-3.25 (m, 2H); ^{13}C-NMR (300 MHz, D_2O) δ 13.4, 21.8, 25.7, 28.2, 30.0, 44.5, 48.1, 72.8; ^{31}P NMR (D_2O) δ 18.2; MS (ESI, *m/z*): 306.2 $[M+H]^+$.

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9. Analytical HPLC were run with Zorbax SB-C8, 5µ (150 X 4.6 mm) column for compounds 2a, 2b, and 2c at 262nm. Retention times were 8.9, 4.5 and 8.1 respectively (CH_3CN : 0.15 M Na_2HPO_4 : 0.01 M $[(C_4H_9)N^+Br^-]$).
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11. Analytical HPLC were run with Intersil C8-3, 5µ (250 X 4.6 mm) column for compounds 2d and 2e using Refractive Index Detector. Retention times were 6.7 and 6.6 respectively (CH_3OH: 0.2 M CH_3COONH_4).

