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Novel Procedure for the Synthesis of 1-Hydroxy-1,1-bisphosphonic Acids using Phenols as Medium

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Abstract: A facile synthetic route for the synthesis of bisphosphonates in phenols is described. Preparations of some of bisphosphonates, which are presently in clinical use such as risedronic acid and alendronate sodium, are synthesized following this new, simple method. This procedure can be useful for the synthesis of this class of bone-resorptive inhibitors in bulk quantities.

Keywords: alendronate, bisphosphonates, phenol, risedronic acid, sodium salt, zoledronic acid

INTRODUCTION

Bisphosphonates are analogs of pyrophosphate in which the oxygen of the P-O-P bond is replaced by a carbon atom, resulting in a metabolically stable P-C-P structure. Bisphosphonic acids are excellent antihypercalcemics and as such are used as therapeutic agents of choice for the treatment of a

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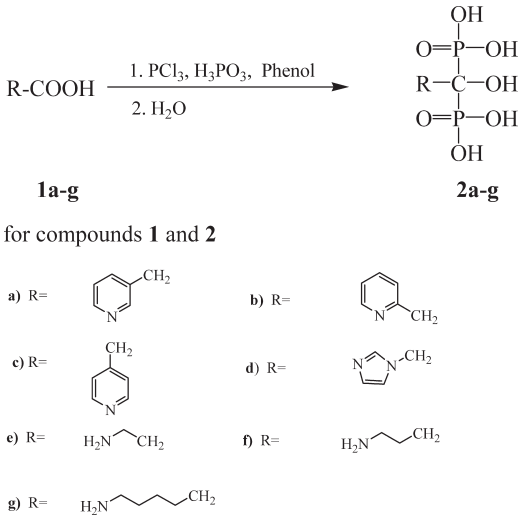
number of diseases characterized by abnormal calcium metabolism.[1] Bisphosphonates [in particular, 1-hydroxy-2-(pyridinyl)ethylidene bisphosphonic acid (risedronic acid, **2a**), 1-hydroxy-2-(1-imidazolyl) ethylidene bisphosphonic acid (zoledronic acid, **2d**), 3-amino-1-hydroxypropylidene bisphosphonic acid (pamidronic acid, **2e**), and 4-amino-1-hydroxy-butylidene bisphosphonic acid (alendronic acid, **2f**)] and their salts are used for the treatment of Paget's bone disease and osteoporosis.

RESULTS AND DISCUSSION

There are several methods reported[2–6] in the literature for the synthesis of 1-hydroxy alkylidene bisphosphonates. 1-Hydroxy alkylidene bisphosphonates and their pharmacologically active salts were prepared from the corresponding carboxylic acids with phosphorous acid and phosphorous trichloride, in solvents such as chlorobenzene,[2] methanesulphonic acid,[3] sulfolane,[4] ionic liquids,[5] and diphenyl ether.[6] All these processes have some disadvantages associated with their use, such as solid and unstirrable mass formation, which prevents uniform mixing. It is difficult to adapt these processes to an industrial scale, because the reaction mixture of the phosphonation step is not homogenous and tends to solidify, preventing stirring and leading to inconsistent yields. Methanesulphonic acid is helpful for solubilizing the reaction mass but, as reported,[3] involves safety risks in that this solvent gives rise to uncontrollable exothermic reactions, when the temperature of the reacting mixtures exceeds 85°C. Moreover, all processes may be suitable for preparation of small quantities of material but not practical for even pilot-scale preparation. Because of the therapeutic importance of this class of compounds, it became essential to develop an efficient and practical synthesis. We herein report a novel phenol-mediated procedure (Scheme 1), which circumvents these problems. Further, the solvent used can be recovered and recycled using known methods, which makes this procedure suitable for large-scale production.

The appropriate carboxylic acid is taken and treated with phosphorous trichloride and phosphorous acid in phenolic compounds such as phenol, *p*-nitrophenol, or *p*-cresol. By conducting the reaction in a phenolic medium, the reaction mass remains fluid, thus allowing complete conversion of the starting material, providing excellent yields and purity of bisphosphonates, and making the process safe and convenient. During the preparation of alendronate sodium (**2f**), phenol was used for the reaction as a solvent. After completion of hydrolysis, the phenol layer was separated and fractionally distilled to obtain pure phenol (more than 99%). When *p*-nitrophenol and *p*-cresol were used as reaction solvents, these were recovered from the mother liquor by simply removing the solvents, followed by isolation from water. Further, the generality of this facile reaction was established by converting some



Scheme 1.

carboxylic acids to the corresponding bisphosphonates **2a–g** in good yields (Table 1).

Herein we have demonstrated a novel phenol-mediated reaction procedure for the preparation of various bisphosphonic acids and their sodium salts, suitable on a pilot scale. This approach is general, and it will be useful for the synthesis of various bisphosphonates.

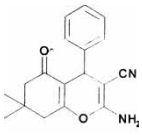
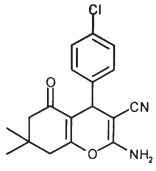
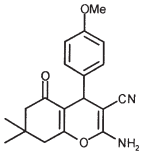
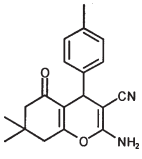
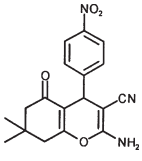
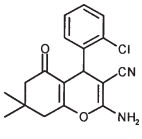
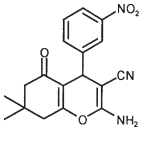
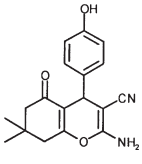
EXPERIMENTAL

Solvents and reagents were obtained from commercial sources and used without purification. The IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer FT-IR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300-MHz spectrometer. The chemical shifts are reported in δ ppm relative to TMS. The mass spectra were recorded on API 2000 Perkin-Elmer PE-SCIEX mass spectrometer.

1-Hydroxy-2-(3-pyridinyl)ethylidene Bisphosphonic Acid (Risedronic Acid, 2a): Typical Procedure

A mixture of 3-pyridylacetic acid (**1a**, 500.0 g, 3.65 mol), phosphorus acid (897.8 g, 10.95 mol), and *p*-nitrophenol (3000 g) was heated to 65°C, and phosphorus trichloride (1731 g, 12.59 mol) was slowly added over a period of 3 h at 65–70°C. The reaction mass was stirred at 65–70°C for 5 h and then cooled to

Table 1. Iodine-catalyzed synthesis of tetrahydrobenzo[b]pyran derivatives

Entry	Products	Time (h)	Yield (%)[a]	Mp (°C)
4a		3.2	92	231 (233[10])
4b		3.5	88	208 (207–209[10])
4c		3.5	90	199 (198–200[10])
4d		3.6	90	211 (208–210[10])
4e		4.0	85	133 (130–132[10])
4f		3.8	85	130 (130–132[10])
4g		4.0	86	215 (210–212[10])
4h		3.8	80	209 (206–208[11])

[a]Refers to isolated yield.

50°C. Precooled water (5000 ml) was added cautiously over a period of 1 h, and the contents were heated to reflux for 10 h. The reaction mass temperature was cooled to 10°C, and methanol (7500 ml) was added. The precipitated product was stirred at 0–5°C for 2 h. The product was filtered, washed with water (500 ml), and dried to get 952.5 g (87%) of **2a** monohydrate as a white solid. IR (KBr): 1184, 1073 cm^{-1}; ^{1}H NMR (300 MHz, D_2O/NH_3): δ 3.26 (t, $J = 12.1$ Hz, 2H), 7.55 (dd, $J = 8.2$, 5.5 Hz, 1H), 8.18 (d, $J = 5.5$ Hz, 1H), 8.32 (d, $J = 5.5$ Hz, 1H), 8.51 (s, 1H); ^{13}C NMR (75 MHz, D_2O/NH_3): δ 36.5, 73.8, 125.3, 137.1, 141.3, 145.3, 145.4, 146.1; ^{31}P NMR (D_2O/NH_3): δ 18.1; mass: 282.0 ($M^+ - 1$). Anal. calcd. for $C_7H_{13}NO_8P_2$: C, 27.92; H, 4.35; N, 4.65. Found: C, 27.64; H, 4.29; N, 4.69.

1-Hydroxy-2-(2-pyridinyl)ethylidene Bisphosphonic Acid (2b)

This compound was prepared in a way similar to **2a**, using 2-pyridylacetic acid (**1b**, 10.0 g, 72.99 mmol) and *p*-cresol, as a white monohydrate solid; yield: 18.1 g (82%). IR (KBr): 1215, 1058 cm^{-1}; ^{1}H NMR (300 MHz, D_2O/NH_3): δ 3.28 (t, $J = 12.1$ Hz, 2H), 7.16–7.20 (dd, $J = 7.4$, 6.0 Hz, 1H), 7.43–7.46 (d, $J = 7.4$ Hz, 1H), 7.63–7.68 (dd, $J = 8.5$, 7.4 Hz, 1H), 8.28 (d, $J = 5.2$ Hz, 1H); ^{13}C NMR (75 MHz, D_2O/NH_3): δ 37.7, 73.2, 125.0, 129.6, 140.8, 145.6, 153.4; ^{31}P NMR (D_2O/NH_3): δ 17.2; mass: 282.1 ($M^+ - 1$). Anal. calcd. for $C_7H_{13}NO_8P_2$: C, 27.92; H, 4.35; N, 4.65. Found: C, 15.10; H, 5.50; N, 4.20.

1-Hydroxy-2-(4-pyridinyl)ethylidene Bisphosphonic Acid (2c)

This compound was prepared in a way similar to **2a**, using 4-pyridylacetic acid (**1c**, 10.0 g, 72.99 mmol) and *p*-nitrophenol, as a white monohydrate solid; yield: 17.8 g (81%). IR (KBr): 1162, 1058 cm^{-1}; ^{1}H NMR (300 MHz, D_2O/NH_3): δ 3.14 (t, $J = 12.1$ Hz, 2H), 7.37 (d, $J = 4.4$, 1.7 Hz, 2H), 8.23–8.25 (dd, $J = 4.4$, 1.7 Hz, 2H); ^{13}C NMR (75 MHz, D_2O/NH_3): δ 39.5, 74.3, 128.3, 143.4, 155.4; ^{31}P NMR (D_2O/NH_3): δ 18.2; mass: 282.1 ($M^+ - 1$). Anal. calcd. for $C_7H_{13}NO_8P_2$: C, 27.92; H, 4.35; N, 4.65. Found: C, 27.76; H, 4.61; N, 4.72.

1-Hydroxy-2-(1-imidazolyl)ethylidene Bisphosphonic Acid (Zoledronic Acid, 2d)

This compound was prepared in a way similar to **2a**, using 1-imidazolylacetic acid (**1d**, 10.0 g, 79.36 mmol) and *p*-cresol, as a white solid; yield: 17.2 g (80%). IR (KBr): 1179, 1093 cm^{-1}; ^{1}H NMR (300 MHz, D_2O/NH_3): δ 4.63–4.66 (m, 2H), 7.34 (s, 1H), 7.48 (s, 1H), 8.68 (s, 1H); ^{13}C NMR

(75 MHz, D_2O/NH_3): δ 53.0, 73.2, 118.5, 124.2, 136.1; ^{31}P NMR (D_2O/NH_3): δ 16.1; mass: 271.0 ($M^+ - 1$). Anal. calcd. for $C_5H_{10}N_2O_7P_2$: C, 22.07; H, 3.70; N, 10.30. Found: C, 22.31; H, 3.72; N, 10.18.

(3-Amino-1-hydroxypropylidene)bisphosphonic Acid (Pamidronic Acid, 2e)

This compound was prepared in a way similar to **2a**, using 3-aminopropionic acid (**1e**, 10.0 g, 112.36 mmol) and *p*-cresol, as a white solid; yield: 14.9 g (57%). IR (KBr): 1152, 987 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ 2.17–2.28 (m, 2H), 3.24 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ 30.8, 36.2, 72.5; ^{31}P NMR (D_2O): δ 18.5; mass: 234.1 ($M^+ - 1$). Anal. calcd. for $C_3H_{11}NO_7P_2$: C, 15.33; H, 4.72; N, 5.96. Found: C, 15.41; H, 4.83; N, 5.88.

(4-Amino-1-hydroxybutylidene)bisphosphonic Acid Monosodium (Alendronate Sodium, 2f)

This compound was prepared in a way similar to **2a**, using 4-aminobutanoic acid (**1f**, 10.0 g, 97.09 mmol) and phenol, but pH was adjusted to 4.3 with 40% sodium hydroxide solution before diluting with methanol. The product was filtered and dried to get the trihydrate product as a white solid; yield: 15.8 g (50%). IR (KBr): 1176, 1064 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ 1.89–1.92 (m, 4H), 2.92 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ 22.5, 30.9, 40.2, 73.8; ^{31}P NMR (D_2O): δ 18.6; mass: 248.1 ($M^+ - 1$). Anal. calcd. for $C_4H_{18}NNaO_{10}P_2$: C, 14.78; H, 5.58; N, 4.31. Found: C, 15.10; H, 5.50; N, 4.20.

(6-Amino-1-hydroxyhexylidene)bisphosphonic Acid (Neridronic Acid, 2g)

This compound was prepared in a way similar to **2a**, using 6-aminohexanoic acid (10.0 g, 76.34 mmol) and *p*-cresol, as a white solid; yield: 11.2 g (53%). IR (KBr): 1147, 996 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ 1.29–1.33 (m, 2H), 1.51–1.61 (m, 2H), 1.73–1.78 (m, 2H), 1.82–1.87 (m, 2H), 2.90–2.94 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ 23.4, 26.6, 26.8, 34.0, 39.5, 74.5; ^{31}P NMR (D_2O): δ 19.5; mass: 276.0 ($M^+ - 1$). Anal. calcd. for $C_6H_{17}NO_7P_2$: C, 26.00; H, 6.18; N, 5.05. Found: C, 26.24; H, 6.06; N, 5.15.

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REFERENCES

1. (a) Geusens, P.; McClung, M. Review of risedronate in the treatment of osteoporosis. *Expert Opin. Pharmacother.* **2002**, *2*, 2011; (b) Dunn, C. J.; Goa, K. L. Risedronate: A review of its pharmacological properties and clinical use in resporptive bone disease. *Drugs* **2001**, *61*, 685.
2. (a) Benedict, J. J.; Perkin, C. M. Pharmaceutical compositions containing geminal diphosphonates. *Eur. Pat. Appl. EP* 186,405, 1986; *Chem. Abstr.* **1986**, *105*, 232453; (b) Jary, J.; Rihakova, V.; Zobacova, A. 6-Amino-1-hydroxyhe-4- oxyliclene diphosphonic acid, salts and a process for production thereof. US Patent 4,304,734, 1981. *Chem. Abstr.* **1982**, *96*, 69215; (c) Jaeggi, K. A.; Widler, L. Subtituted alkanediphosphonic acids and pharmaceutical use. US Patent 4,939,130, 1990; *Chem. Abstr.* **1991**, *114*, 62355.
3. Kieczkowski, G. R.; Jobson, R. B.; Melillo, D. G.; Reinhold, D. F.; Grenda, V. J.; Shinkai, I. Synthesis of novel (1-alkanoyloxy-4-alkanoylaminobutyliclene)-1,1-bisphosphonic acid derivatives. *J. Org. Chem.* **1995**, *60*, 8310.
4. Vijay Kumar, P. M.; Trinadhrao, C.; Rajamannar, T. A process for preparation of bisphosphonic acid compounds. PCT Int. Pat. WO 44,831, 2005; *Chem. Abstr.* **2005**, *142*, 463876.
5. De Ferra, L.; Turchetta, S.; Massardo, P.; Casellato, P. Preparation of bisphosphonic acids and salts therof. PCT Int. Pat. WO 93,282, 2003; *Chem. Abstr.* **2003**, *139*, 365070.
6. Despande, P. B.; Luthra, P. K. US Patent Appl. 258, 625, 2006; *CAPLUS* **2006**, 1204267.