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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Microwave-assisted efficient synthesis of bisphosphonate libraries: a useful procedure for the preparation of bisphosphonates containing nitrogen and sulfur

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Abstract Microwave-assisted rapid and efficient procedure for the synthesis of bisphosphonate and their libraries is described in solvent-free medium. Bisphosphonates having nitrogen and sulfur are synthesized following this new procedure. This procedure is simple and can be useful for the generation of compound libraries of a class of bone-resorptive inhibitors such as *N*- and *N*-, *S*- containing bisphosphonates.

Keywords Bisphosphonates · Phosphorous acid · Phosphorous trichloride · Microwave-assisted

Introduction

Bisphosphonates (BPs) containing nitrogen are demonstrated as potent inhibitors of bone-resorptive and highly selective bone targeting agents (Abdou and Shaddy, 2009). These 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 (Abdou *et al.*, 2008). Over the past three decades, the discovery and development of bisphosphonic acids and their related BPs as a class of compounds for treatment of bone diseases has been a fascinating saga in medicinal chemistry (McClung and Geusens, 2001; Dunn and Goa, 2001). Recent studies show that the BPs containing nitrogen along with sulfur are emerging as excellent therapeutic agents for the treatment of arthritis particularly rheumatoid. The pharmaceutical importance of these molecules attracted many researchers and developed several methods (Lorin and Jonathan, 1996; Gallop *et al.*, 1994; Pavia *et al.*, 1993; Jung and Becksickinger, 1992; Dower and Fodor, 1991; Gold *et al.*, 1995). But many of these methods are suffering from drawbacks such as long reaction time and isolation of products. Therefore, we have developed a simple and efficient methodology for the synthesis of BPs under microwave irradiation.

Trying for development of novel synthetic procedures is desirable for the promising therapeutic areas to reach the demand for rapid synthesis of compound libraries for screening. Keeping this in view, we focused our attention on the development of new procedures for the generation of bisphosphonate libraries.

Microwave-assisted heating under controlled conditions has been shown to be invaluable technology for medicinal chemistry and drug discovery applications (Baxendale *et al.*, 2002; Artmann *et al.*, 2007; Appukkuttan and Eycken, 2006; Larhed and Hallberg, 2001; Wathey *et al.*, 2002). In recent years, microwave-assisted reactions have received much attention because of their simplicity in operation, enhanced reaction rates, and greater selectivity (Al Obeidi *et al.*, 2003; Kappe and Dallinger, 2006; Alcazar *et al.*, 2007; Varma 1999). In particular, solvent-free reactions have gained popularity as they provide an opportunity to work with open vessels (Zhang *et al.*, 2007; Sinnwell and Ritter, 2007; Barlow and Marder, 2003; Zhu *et al.*, 2004; Perelaer *et al.*, 2006; Jhung *et al.*, 2007; Millos *et al.*, 2007; Tsuji *et al.*, 2005; Tompsett *et al.*, 2006; Collins and Leadbeater, 2007). This avoids use of organic solvents and dramatically reduces reaction times, increases product

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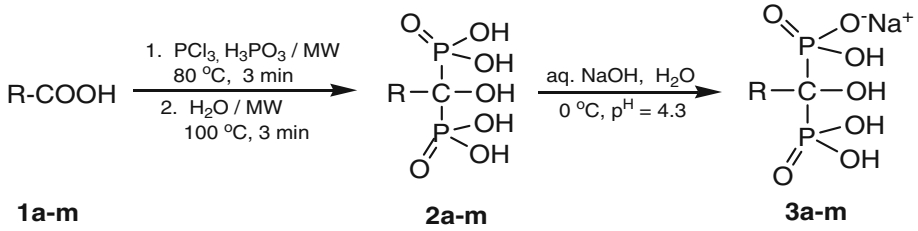
Scheme 1 Synthesis of bisphosphonic acids and their salts



yields, and enhances product purities by reducing unwanted side reactions compared to conventional heating methods. Short reaction times make it ideal for rapid reaction scouting and optimization. Compound libraries can then be rapidly synthesized using this enabling technology. Thus, microwave irradiation has become a powerful synthetic tool for the rapid synthesis of a variety of biologically active compounds under solvent-free conditions. Synthesis of biologically active BPs achieved by several methods was reported in literature. In reported procedures, synthesis of BPs was carried out using organic solvents such as chlorobenzene, methanesulphonic acid (Kieczykowski *et al.*, 1995), sulfolane (Vijaykumar *et al.*, 2005), ionic liquids (Ferra *et al.*, 2003), diphenyl ether (Despande and Luthra, 2006) and phenol (Rao *et al.*, 2007a, b). The principal difficulty with all these procedures is using corrosive organic solvents and long reaction times, resulting in low yield and purities of the desired products. As part of our research, we envisaged to develop a synthetic procedure for the generation of high quality bisphosphonate libraries using microwave.

Results and discussion

We started our investigation with carboxylic acid **1a** to prepare bisphosphonic acid **2a** and subsequent conversion to its salt **3a**. We first reacted compound **1a** with phosphorous acid (H_3PO_3) and phosphorous trichloride (PCl_3) at various temperatures using microwave. Reactions performed at 50 °C were very slow whereas reactions performed at 100 °C were proceeded but the products obtained were contaminated with many side products. Decomposition was observed in the reactions performed at above 100 °C. It was thought that phosphorous trichloride is evaporated before the reaction takes place. Hence we used silica gel as solid support, mixed the reagents uniformly, and studied the reaction at various temperatures in microwave. We were delighted with the result when the reaction was finished in 3 min at 80 °C which was confirmed by ^{31}P NMR. Hydrolysis was also finished in 3 min at 100 °C in microwave. Afterward workup product **2a** was obtained in very good yield and in pure form without column chromatography. We applied this procedure to compounds **1b–m** to obtain products **2b–m** in excellent yields and in pure form without using any purification methods. (Scheme 1; Table 1). When this reaction was performed using silica gel as solid support and traditional heating at 100 °C, black polymeric material was obtained as a gummy mass.

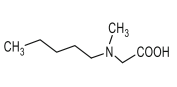
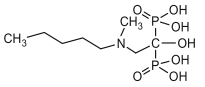
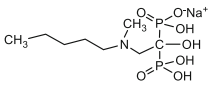
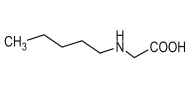
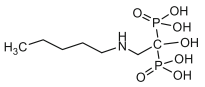
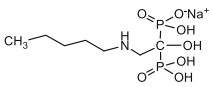
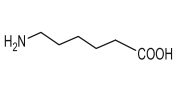
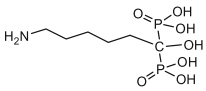
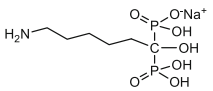
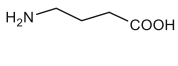
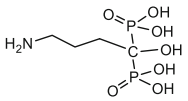
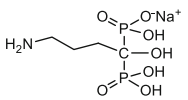
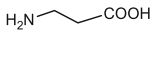
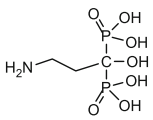
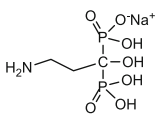
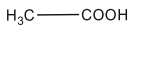
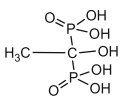
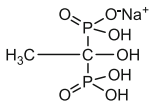
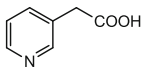
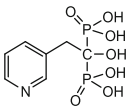
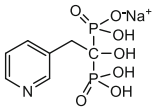
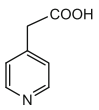
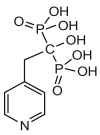
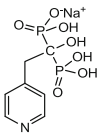
Having set of optimal conditions in hand, herein we report an efficient microwave-assisted solvent-free procedure for the synthesis of bisphosphonate libraries. A mixture of carboxylic acid **1**, phosphorous acid (H_3PO_3), phosphorous trichloride (PCl_3) using silica gel as solid support was irradiated in microwave unit at 80 °C for 3 min and the hydrolysis was carried out by addition of water followed by irradiation at 100 °C for 3 min (Scheme 1). After completion of hydrolysis, reaction mass was filtered and water miscible solvent (ex: MeOH, EtOH, acetone, etc.,) was added to the filtrate to get a solid. The solid was filtered and dried in oven at 40–60 °C under reduced pressure to obtain desired compound **2** in good to excellent yields. Using this procedure bisphosphonic acids **2a–m** are prepared.

The bisphosphonic acids **2a–m** were converted into their sodium salts using NaOH (1.2 eq.) in aqueous medium. These salts precipitate as white solids upon addition of MeOH or EtOH as co-solvent. Filtration and drying were performed in oven at 60 °C under vacuum to obtain compounds **3a–m** in excellent yields (Table 1) in highly pure form without using any purification techniques. This makes the process simple convenient and time saving. Further the generality of this facile reaction procedure could be established for the generation of various bisphosphonate libraries. Products obtained by this procedure were converted into corresponding BPs in excellent yields (Table 1).

Conclusion

In summary, herein we have demonstrated an efficient, solvent-free, and microwave-assisted reaction procedure for the preparation of various bisphosphonic acids and their salts in highly pure form without using any purification methods. This procedure is environmentally friendly and useful for the synthesis of biologically important bisphosphonate libraries, valuable in drug discovery.

Table 1 Microwave-promoted synthesis of bisphosphonates

Compound	1a-h	2a-h	3a-3h	Yield (%)
a				72
b				76
c				65
d				78
e				67
f				78
g				86
h				82

Materials and methods

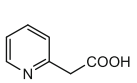
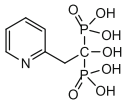
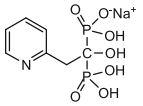
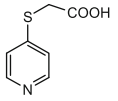
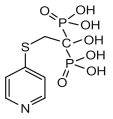
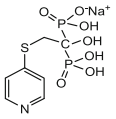
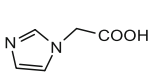
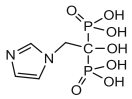
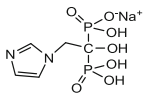
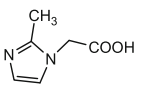
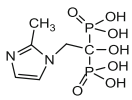
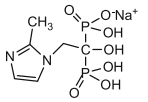
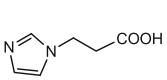
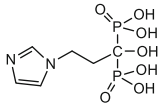
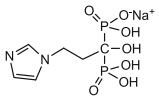
Chemistry

Microwave-assisted synthesis was carried out in an Initiator^{TM} 2.0 single mode MW at 2.45 GHz (Biotage AB, Uppsala). The reactions were performed in sealed vessels equipped with a teflon-coated stirred bar and under an argon atmosphere. A variable power was employed to reach the temperature desired and then to maintain it in the vessel during the period of time programmed. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded with a Bruker AM 300, 75, and 121.5 mHz NMR spectrometer, which provided all the necessary data for the full SCIEX-API 2000 mass spectrometer. IR spectra were measured with a Perkin-Elmer Spectrum One FT-IR spectrometer.

General method for the preparation of BPs **1a–m** to **3a–m**

A mixture of 3-(4-methyl pentylamino)-propionic acid (5 g, 2.38 mmol), phosphorous acid (5.87 g, 7.16 mmol), phosphorous trichloride (16.4 g, 11.93 mmol), and silica gel (5 g) were mixed thoroughly and subjected to microwave irradiation for 3 min at 80 °C. After completion of starting material as confirmed by ^{31}P NMR, water (50 mL) was added to the resulting reaction mixture and again subjected to microwave irradiation for 3 min at 100 °C. The resulting reaction mixture was cooled to room

Table 1 continued

Compound	1i-m	2i-m	3i-3m	Yield (%)
i				81
j				81
k				80
l				72
m				79

temperature and filtered and the cake was washed with water (10 mL). The filtrate was added to methanol (80 mL) and stirred well for 1 h and precipitated bisphosphonic acid was filtered and washed with methanol (10 mL) to obtain product **2a** (yield 3.8 g).

A stirred mixture of the above-obtained bisphosphonic acid **2a** (3 g) in water (30 mL) was adjusted to pH 4.3 by adding 40 % NaOH solution (~2 mL) at 0 °C to obtain a clear solution. To this clear solution methanol (45 mL) was added and continued stirring for 1 h at 0 °C and precipitated solid was filtered and dried to obtain bisphosphonate sodium salt **3a** (2.85 g). All the products were confirmed by its IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and mass spectral data.

Results for individual compounds

*[1-Hydroxy-3-(methylpentylamino)-propylidene]-bisphosphonic acid monosodium (ibandronate sodium, **3a**)*

Yield: 72 %; white solid; spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 3166, 2962, 2320, 1667, 1259, 1034 cm^{-1}; ^{1}H NMR (D_2O, 300 mHz, δ, ppm): 0.78 (t, $J = 6.9$ Hz, 3H), 1.23–1.26 (m, 4H), 1.60–1.62 (m, 2H), 2.21–2.30 (m, 2H), 2.74 (s, 3H), 2.94–2.98 (m, 1H), 3.06–3.12 (m, 2H), 3.43–3.47 (m, 1H); ^{13}C NMR (D_2O, 75.5 mHz, δ, ppm): 13.43, 21.85, 23.56, 28.20, 39.74, 53.24, 56.7, 72.56; ^{31}P NMR (D_2O, 121.5 mHz, δ, ppm): 17.69; MS (ESI, *m*/*z*): 318.0 $[M-H]^+$.

*1-Hydroxy-3-(pentylamino)-propylidene bisphophosnic acid monosodium (**3b**)*

Yield: 76 %; white solid; spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 3680, 2951, 2430, 1470, 1400, 102 cm^{-1}; ^{1}H NMR (D_2O, 300 mHz, δ, ppm): δ 0.80 (t, $J = 6.6$ Hz, 3H), 1.23–1.27 (m, 4H), 1.54–1.59 (m, 2H), 2.14–2.27 (m, 2H), 2.90–2.95 (m, 2H), 3.23–3.27 (m, 2H); ^{13}C NMR (D_2O, 75.5 mHz, δ, ppm): 13.38, 21.82, 25.66, 28.17, 29.95, 44.45, 48.06, 72.78; ^{31}P NMR (D_2O, 121.5 mHz, δ, ppm): 18.23; MS (ESI, *m*/*z*): 304.2 $[M-H]^+$.

*6-Amino-1-hydroxyhexylidene)-bisphosphonic acid monosodium (neridronate sodium, **3c**)*

Yield: 65 %; white solid; spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 3275, 2889, 1640, 1470, 1266, 952 cm^{-1}; ^{1}H NMR (D_2O, 300 mHz, δ, ppm): 1.28–1.35 (m, 2H), 1.50–1.63 (m, 2H), 1.73–1.77 (m, 2H), 1.81–1.88 (m, 2H), 2.85–2.95 (m, 2H); ^{13}C NMR (D_2O, 75.5 mHz, δ, ppm): 23.48, 26.7, 34.1, 39.61, 76.26; ^{31}P NMR (D_2O, 121.5 mHz, δ, ppm): 19.4; MS (ESI, *m*/*z*): 276.1 $[M-H]^+$.

*(4-Amino-1-hydroxybutylidene)-bisphosphonic acid monosodium (alendronate sodium, **3d**)*

Yield: 78 %; white solid; spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2925, 2225, 1770, 1417, 1377, 104 cm^{-1}; ^1H NMR (D_2O, 300 mHz, δ, ppm): 1.90–1.92 (m, 4H), 2.93 (m, 2H); ^{13}C NMR (D_2O, 75.5 mHz, δ, ppm): 22.8, 31.0, 40.3, 74.82; ^{31}P NMR (D_2O, 121.5 mHz, δ, ppm): 18.7; MS (ESI, *m/z*): 248.0 $[M-H]^+$.

*3-(Amino-1-hydroxypropylidene)-bisphosphonicacid monosodium (pamidronate sodium, **3e**)*

Yield: 67 %; white solid; spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 3192, 2322, 1630, 1509, 1286, 915 cm^{-1}; ^1H NMR (D_2O, 300 mHz, δ, ppm): 2.15–2.29 (m, 2H), 3.16–3.27 (m, 2H); ^{13}C NMR (D_2O, 75.5 mHz, δ, ppm): 31.3, 36.6, 73.08; ^{31}P NMR (D_2O, 121.5 mHz, δ, ppm): 18.45; MS (ESI, *m/z*): 236.1 $[M+H]^+$.

*1-Hydroxy ethylidine bisphosphonic acid monosodium (etidronate sodium, **3f**)*

Yield: 78 %; white solid; spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 3148, 2026, 1620, 1382, 1216, 1052, 951 cm^{-1}; ^1H NMR (D_2O, 300 mHz, δ, ppm): δ 1.3 (s, 3H). ^{13}C NMR (D_2O, 75.5 mHz, δ, ppm): 2.8, 62.7; ^{31}P NMR (D_2O, 121.5 mHz, δ, ppm): 17.5; MS (ESI, *m/z*): 207.2 $[M+H]^+$.

*1-Hydroxy-2-(3-pyridinyl)-ethylidene bisphosphonic acid monosodium (risedronate sodium, **3g**)*

Yield: 86 %; white solid; spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 3368, 2151, 1690, 1568, 1349, 1133 cm^{-1}; ^1H NMR (D_2O, 300 mHz, δ, ppm): 3.35 (t, $J = 12.0$ Hz, 2H), 7.81 (dd, $J = 8.1$, 5.5 Hz, 1H), 8.46 (d, $J = 6.6$ Hz, 2H), 8.63 (s, 1H); ^{13}C NMR (D_2O, 75.5 mHz, δ, ppm): 36.3, 73.9, 125.1, 137.2, 141.1, 145.4, 145.2, 145.8; ^{31}P NMR (D_2O, 121.5 mHz, δ, ppm): 18.1; MS (ESI, *m/z*): 282.1 $[M-H]^+$.

*1-Hydroxy-2-(4-pyridinyl)-ethylidene bisphosphonic acid monosodium (**3h**)*

Yield: 82 %; white solid; spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 3448, 3107, 2134, 1644, 1344, 1091 cm^{-1}; ^1H NMR (D_2O, 300 mHz, δ, ppm): 3.33 (t, $J = 12.3$ Hz, 2H), 7.37 (d, $J = 5.7$, Hz, 2H), 8.43 (d, $J = 5.7$ Hz, 2H); ^{13}C NMR (D_2O, 75.5 mHz, δ, ppm): 40.1, 76.3, 129.5, 140.5, 159.5; ^{31}P NMR (D_2O, 121.5 mHz, δ, ppm): 17.16; MS (ESI, *m/z*): 282.0 $[M-H]^+$.

*1-Hydroxy-2-(2-pyridinyl) ethylidene bisphosphonic acid monosodium (**3i**)*

Yield: 81 %; white solid; spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 3256, 2435, 2112, 1656, 1248, 1059 cm^{-1}; ^1H NMR (D_2O, 300 mHz, δ, ppm): 3.61 (t, $J = 13.0$ Hz, 2H), 7.71–7.78 (m, 1H), 7.85 (d, $J = 8.1$ Hz, 1H), 8.26 (d, $J = 7.$ 8 Hz, 1H), 8.48 (d, $J = 5.4$ Hz, 1H); ^{13}C NMR (D_2O, 75.5 mHz, δ, ppm): 37.5, 71.5, 125.1, 130.1, 141.0, 145.5, 152.1; ^{31}P NMR (D_2O, 121.5 mHz, δ, ppm): 16.87; MS (ESI, *m/z*): 281.9 $[M-H]^+$.

*1-Hydroxy-2-(4-pyridylmercapto) ethylidene bisphosphonic acid monosodium (**3j**)*

Yield: 81 %; white solid; spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 3256, 2310, 1633, 1483, 1279, 1064, 956 cm^{-1}; ^1H NMR (D_2O, 300 mHz, δ, ppm): 3.70 (t, $J = 11.7$ Hz, 2H), 7.75 (d, $J = 5.7$ Hz, 2H), 8.25 (d, $J = 5.4$ Hz, 2H) ^{13}C NMR (D_2O, 75.5 mHz, δ, ppm): 36.9, 72.9, 122.4, 139.1, 165.5; ^{31}P NMR (D_2O, 121.5 mHz, δ, ppm): 16.85; MS (ESI, *m/z*): 315.9 $[M+H]^+$.

*1-Hydroxy-2-(1-imidazolyl) ethylidene bisphosphonic acid monosodium (zoledronate sodium, **3k**)*

Yield: 80 %; white solid; spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 3160, 2765, 1586, 1491, 1371, 1053 m^{-1}; ^1H NMR (D_2O, 300 mHz, δ, ppm): 4.54–4.63 (m, 2H), 7.27 (s, 1H), 7.43 (s, 1H), 8.62 (s, 1H); ^{13}C NMR (D_2O, 75.5 mHz, δ, ppm): 53.6, 71.4, 118.8, 124.5, 136.6; ^{31}P NMR (D_2O, 121.5 mHz, δ, ppm): 14.63; MS (ESI, *m/z*): 273.2 $[M+H]^+$.

*1-Hydroxy-2-(2-methyl-1-imidazolyl)-ethylidene bisphosphonic acid monosodium (**3l**)*

Yield: 72 %; white solid; spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 3208, 1891, 1609, 1341, 1246, 984 cm^{-1}; ^1H NMR (D_2O, 300 mHz, δ, ppm): 2.38 (s, 3H), 4.31–4.38 (m, 2H), 6.78 (s, 1H), 7.22 (s, 1H); ^{13}C NMR (D_2O, 75.5 mHz, δ, ppm): 11.2, 50.6, 73.5, 116.9, 124.1, 145.9; ^{31}P NMR (D_2O, 121.5 mHz, δ, ppm): 15.23; MS (ESI, *m/z*): 286.0 $[M-H]^+$.

*1-Hydroxy-2-(1-imidazolyl) propylidene bisphosphonic acid monosodium (**3m**)*

Yield: 79 %; white solid; spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 3216, 2283, 1580, 1472, 1266, 971 cm^{-1}; ^1H NMR (D_2O, 300 mHz, δ, ppm): 2.39 (m, 2H), 4.47 (d, $J = 7.6$ Hz, 2H), 7.31 (s, 1H), 7.45 (s, 1H), 8.67 (s, 1H); ^{13}C NMR (D_2O, 75.5 mHz, δ, ppm): 34.8, 46.0, 72.9, 120.0, 122.2, 135.0; ^{31}P NMR (D_2O, 121.5 mHz, δ, ppm): 18.09; MS (ESI, *m/z*): 285.0 $[M-H]^+$.

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