Facile Synthesis of Bisphosphonates

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Sodium hydride in polyethylene glycol has been used as a sustainable, non-volatile, and ecofriendly catalytic medium for the green synthesis of bisphosphonates with an alkyl/aryl/heterocyclic group fixed at the geminal carbon. All compounds (3a-j) were characterized by IR, ^1H and ^{31}P NMR, mass and elemental analysis. The easy recyclability of the reaction medium makes the reaction economically and potentially viable for commercial applications.

Key Words : Bisphosphonates, Green Synthesis, NaH in PEG.

1 INTRODUCTION

In conjunction with our interest in the development of synthetic methods for the preparation of bisphosphonate derivatives, we have focused our attention to the preparation of new bisphosphonate derivatives by direct insertion of alkyl/aryl/heterocyclic group at the geminal carbon of tetraethyl methylene bisphosphonate in the presence of sodiumhydride in PEG-600 at ambient temperatures. Bisphosphonates are an important class of pharmacologicallyactive molecules, which are widely used in the treatment of various bone diseases such as osteoporosis,[1] Paget's disease,[2] hypercalcaemia[3] and bone metastases secondary to breast cancer,[4] prostate cancer,[5] inhibition of tumor cell proliferation and invasion,[6] inhibition of tumor cell adhesion to bone,[7] inhibition of angiogenesis[8] or induction of apoptosis.[9] Some bisphosphonates also activate the $\gamma\delta$ -T cell population, which shows potential cytotoxic activity towards a broad spectrum of tumors.[10] Some others possess anti-inflammatory properties and may be effective in the treatment of rheumatoid arthritis[11] or exhibit anti-parasitic activity.[12]

In the recent years, PEG, a biologically acceptable polymer used extensively in drug delivery and in bioconjugates as tool for diagnostics, emerged as a powerful phase transfer catalyst and performs many useful organic transformations under mild reaction conditions. Moreover, PEG and its monomethyl ethers are inexpensive, thermally stable, recoverable, and are proved to be non-toxic phase-transfer catalysts. The PEG has hitherto not been widely used as a solvent medium but has been used as a support for various transformations.[13] This background prompted to use PEG as reaction medium for this reaction.

In this report, a series of new bisphosphonates with an alkyl/aryl/heterocyclic group fixed at the geminal carbon was synthesized, using alkyl/aryl/heterocyclic halides and tetraethyl methylene bisphosphonate in the presence of sodium hydride in PEG-600 at ambient temperatures.

2 EXPERIMENTAL

2.1 General

NMR spectra were recorded on a Bruker instrument at 400 MHz for ^1H NMR and 161.5 MHz for ^{31}P NMR in DMSO solution, using TMS as internal standard. Chemical shifts (δ) are indicated in ppm and coupling constants (J) in Hz. Mass spectra were recorded on ESI-MS mass spectrometer and IR spectra were measured on Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. Elemental analyses were performed on a Thermo Finnegan Instrument. All reagents were purchased from Sigma Aldrich and were used without further purification.

2.2 Synthesis

2.2.1 Typical procedure for the synthesis of Tetraethyl phenylmethylenediphosphonate (3g):

Tetraethylmethylenebisphosphonate (0.004 mol) was added drop wise to a dispersion of sodium hydride (80% in mineral oil, 0.004 mol) in 10 mL of PEG-600, Bromo benzene (0.004 mol) was added and the mixture was stirred for 2 hours at room temperature. After completion of the reaction as indicated by TLC, diluted HCl (5%) was added to the reaction mixture dropwise, and the product were extracted with dichloromethane. Drying extracts on sodium sulfate and evaporation afforded the product. The resulting product was purified by passing it over a silica gel column chromatography with EtOAc / hexane (1:4) as eluent. The remaining mixture was cooled in dry ice-acetone bath to precipitate the PEG and extracted with ether. The ether extract was dried over MgSO_4 and evaporated. The recovered PEG has been reused.[13b] The same procedure can be applied for the synthesis of 3b-j.

3 RESULTS AND DISCUSSION

In an initial endeavor, we carried out the reaction of Bromobenzene (1g), Tetraethylmethylenebisphosphonate (2) in the presence of sodium hydride in various solvents at ambient temperature (Table-2). Excellent results were obtained, when the reaction was

Table 1 Spectral Data of Synthesized compounds (3a-j)

Compound Name	NMR (DMSO- <i>d</i> ₆) δ		IR (KBr) $\nu_{\max}$ cm ⁻¹ P=O, P-C	ESI-MS m/z (M ⁺)	Elem. Anal. (C& H)	
	¹ H	³¹ P			Calcd.	Found
3a Tetraethylquinolin-2-yl methylenediphosphonate (C ₁₈ H ₂₇ NO ₆ P ₂)	7.54 – 7.68 (m, 6H), 5.14 (d, 1H, <i>J</i> = 9.6 Hz), 4.07-3.81 (m, 8H), 1.23 (t, 6H, <i>J</i> = 4.4 Hz), 1.01 (t, 6H, <i>J</i> = 6.4 Hz)	29.63	1220, 755	415	52.05 6.55	52.01 6.53
3b Tetraethylisoquinolin-1-yl methylene diphosphonate (C ₁₈ H ₂₇ NO ₆ P ₂)	7.58 – 7.74 (m, 6H), 4.93 (d, 1H, <i>J</i> = 9.6 Hz), 3.87-3.67 (m, 8H), 1.21 (t, 6H, <i>J</i> = 4.0 Hz), 1.06 (t, 6H, <i>J</i> = 6.4 Hz)	33.6	1234, 763	415	52.05 6.55	52.01 6.53
3c Tetraethyl(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) methylene diphosphonate (C ₁₃ H ₂₄ N ₂ O ₈ P ₂)	6.85 (s, 1H), 6.34 (s, 1H), 5.42 (s, 1H), 5.09 (d, 1H, <i>J</i> = 9.2 Hz), 4.05-3.68 (m, 8H), 1.17 (t, 6H, <i>J</i> = 4.8 Hz), 1.06 (t, 6H, 4.0 Hz)	31.9	1217, 812	398	39.20 6.07	39.16 6.02
3d Tetraethyl(6-hydroxy pyridin-2-yl)methylene diphosphonate (C ₁₄ H ₂₅ NO ₇ P ₂)	6.54 (m, 3H), 5.05 (d, 1H, <i>J</i> = 9.4 Hz), 3.73-4.06 (m, 8H), 1.19 (t, 6H, <i>J</i> = 4.0 Hz), 1.08 (t, 6H, <i>J</i> = 6.8 Hz)	31.6	1232, 786	381	44.10 6.61	44.03 6.57
3e Tetraethyl(2-amino-6-methylpyrimidin-4-yl) methylenediphosphonate (C ₁₄ H ₂₇ N ₃ O ₆ P ₂)	6.58 (s, 1H), 5.62 (s, 2H), 5.13 (d, 1H, <i>J</i> = 9.4 Hz), 4.08-3.76 (m, 8H), 2.24 (s, 3H), 1.19 (t, 6H, <i>J</i> = 4.4 Hz), 1.07 (t, 6H, <i>J</i> = 6.4 Hz)	35.62	1225, 754	395	42.53 6.88	42.49 6.84
3f Tetraethyl(3-cyano pyridine-2-yl)methylene diphosphonate (C ₁₅ H ₂₄ N ₂ O ₆ P ₂)	7.12-7.17 (m, 3H), 5.10 (d, 1H, <i>J</i> = 9.4 Hz), 4.07-3.83 (m, 8H), 1.13 (t, 6H), 1.07 (t, 6H, <i>J</i> = 6.8 Hz)	32.41	1232, 764	390	46.16 6.20	46.11 6.16
3g Tetraethyl phenyl methylenediphosphonate (C ₁₅ H ₂₆ O ₆ P ₂)	6.81-6.93 (m, 5H), 4.96 (d, 1H, <i>J</i> = 9.4 Hz), 4.04-3.69 (m, 8H), 1.18 (t, 6H, <i>J</i> = 4.0 Hz), 1.06 (t, 6H, <i>J</i> = 6.4 Hz)	20.63	1219, 744	364	49.45 7.19	49.39 7.16
3h Tetraethyl(3-methyl-4-nitro phenyl) methylene diphosphonate (C ₁₆ H ₂₇ NO ₈ P ₂)	7.26-7.34 (m, 3H), 5.22 (d, 1H, <i>J</i> = 9.6 Hz), 3.75-4.07 (m, 8H), 1.21 (t, 6H, <i>J</i> = 5.2 Hz), 1.06 (t, 6H, <i>J</i> = 7.2 Hz)	31.52	1217, 734	423	45.39 6.43	45.36 6.39
3i Tetraethyl(3-aminophenyl) methylenediphosphonate (C ₁₅ H ₂₇ NO ₆ P ₂)	6.21-6.32 (m, 4H), 5.38 (s, 2H), 5.04 (d, 1H, <i>J</i> = 9.6 Hz), 3.76-4.10 (m, 8H), 1.17 (t, 6H, <i>J</i> = 5.6 Hz), 1.11 (t, 6H, <i>J</i> = 7.2 Hz)	29.61	1242, 765	379	47.49 7.17	47.45 7.13
3j Tetraethyl(4-amino-2-nitrophenyl)methylene Diphosphonate (C ₁₅ H ₂₆ N ₂ O ₈ P ₂)	7.12-7.23 (m, 3H), 5.52 (s, 2H), 5.13 (d, 1H, <i>J</i> = 9.6 Hz), 4.09-3.78 (m, 8H), 1.19 (t, 6H, <i>J</i> = 4.0 Hz), 1.05 (t, 6H, <i>J</i> = 6.4 Hz)	29.37	1256, 823	424	42.46 6.18	42.41 6.14

carried out in PEG-600.

It was also found that PEG-600 also affects the yield of product. When sodium hydride is replaced with sodium borohydride in the reaction, the products are formed in lower yields (>30%) with longer

reaction time (24h). In this reaction, sodium hydride acts as base and abstracts proton from active methylene group of Tetraethylmethylene bisphosphonate, PEG catalyzes by increasing electrophilicity of C-X carbon through a hydrogen bonding by hydroxyl oxygen

Table 3 One pot synthesis of bisphosphonate derivatives using NaH/PEG.

Compound	R	Yield(%) ^a	Compound	R	Yield(%) ^b
1a & 3a		65	1f & 3f		59
1b & 3b		62	1g & 3g		70
1c & 3c		66	1h & 3h		71
1d & 3d		65	1i & 3i		68
1e & 3e		64	1j & 3j		67

^aisolated yield
$$\text{R-X} + \begin{array}{c} \text{O} \\ || \\ \diagdown \text{P} \diagup \\ | \quad | \\ \text{OEt} \quad \text{OEt} \\ / \quad \backslash \\ \text{O} \end{array} \xrightarrow[\text{PEG-600}]{\text{NaH, rt}} \begin{array}{c} \text{O} \\ || \\ \diagdown \text{P} \diagup \\ | \quad | \\ \text{OEt} \quad \text{OEt} \\ / \quad \backslash \\ \text{O} \end{array}$$

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All the products purified by column chromatography and were characterized by elemental analysis, IR,¹H-,³¹P-NMR, and MS spectral data it is summarized in Table 1.

4 CONCLUSIONS

In this study, NaH in PEG has been utilized for the efficient one pot synthesis of new bisphosphonate derivatives. The advantages of this procedure are reusability of PEG, operational simplicity and reasonable yields.

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