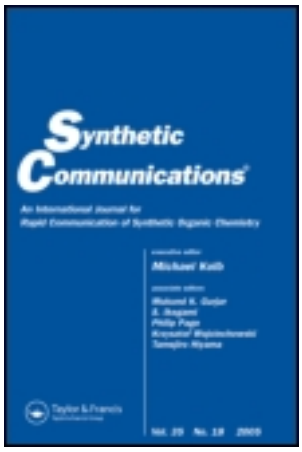

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Convenient Synthesis of Analogs of Aminomethylene *gem*-Diphosphonic Acid from Amines Without Catalyst

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ABSTRACT

A simple, novel, and convenient synthesis of analogs of aminomethylene *gem*-diphosphonic acids in one-pot from primary and secondary amines in moderate yields was reported without catalyst.

Key Words: Aminomethylene *gem*-diphosphonic acid; bisphosphonates; Primary and secondary amines; Aromatic and aliphatic analogs.

INTRODUCTION

Geminal bisphosphonates and the corresponding acids which are characterized by a P–C–P linkage are stable pyrophosphates analogs

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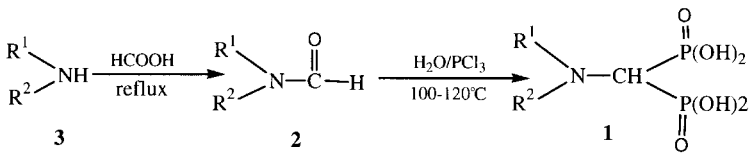
which are completely resistant to enzymatic hydrolysis. They are widely used in the treatment of a number of diseases characterized by an abnormal calcium metabolism, such as Paget's disease, osteoporosis.[1,2] Recently, a lot of studies have shown that the use of *bis*phosphonates might be considered as an improvement in the management of cancer.[3] Owing to the interest of this class of compounds, different synthetic routes have been reported in literature. For the main methods there are two categories. The first method involves the treatment of an amide with water and phosphorus trichloride in the presence of an organic base.[4–7] The second involves the bisphosphorylation of an amine with triethyl orthoformate and dialkyl phosphite. Subsequent hydrolysis of the aminomethylenebisphosphonate ester under acidic conditions gave the desired product.[8,9] However, to the best of our knowledge, simple and novel methods for the synthesis of aromatic and aliphatic analogs of aminomethylene *gem*-diphosphonic acids have rarely been reported.

In this paper, we wish to report a simple, novel, and convenient synthesis of aminomethylene *gem*-diphosphonic acids in one-pot from primary and secondary amines in moderate yields (Sch. 1) (Table 1). Amines (**3**) are formylated by formic acid to give the intermediate formamides (**2**) which are isolated unnecessarily and directly react with water and phosphorus trichloride without any catalysis to afford aminomethylene *gem*-diphosphonic acids (**1**). In this method we examined primary and secondary amines using as the starting materials, respectively, and found that the reaction of primary amines was carried out more easily than that of secondary amines. When di-isopropylamine is used as the starting material, no product was obtained due to a larger steric hindrance.

In summary, a facile and novel synthesis of compounds (**1a**–**1j**) in one-pot is described without any catalyst using amines as starting materials in modest yields. The synthesis pathway appears to provide a simple, general method for synthesis of aminomethylene *gem*-diphosphonic acids derivatives and it is also be applicable to a large scale production.



Scheme 1.

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Table 1. Results of the reactions.

Product	R^1	R^2	M.p. (°C)	Yield (%)[a]
1a	Phenyl	H	189–191[c]	60
1b	*o*-Methylphenyl	H	182–184[b]	40
1c	Cyclohexyl	H	261–263[c]	70
1d	3-(*N*,*N*-dimethylamino)-propyl	H	247–249[d]	72
1e	*n*-Octyl	H	272–274[c]	75
1f	Methyl	Methyl	240–242[b]	60
1g	Hydroxylethyl	Hydroxylethyl	>300[e]	45
1h	Ethyl	Ethyl	200–202	51
1i	*n*-Propyl	*n*-Propyl	196–198	60
1j	*n*-Butyl	*n*-Butyl	221–223	46

[a]Isolated yield.
[b]Hydrochloride.
[c]Monohydrate.
[d]Dihydrate.
[e]Tetrasodium salt.

EXPERIMENTAL

All melting points were determined on a Yanaco apparatus and they are uncorrected. NMR spectra were measured on a Brucker AC-P200 NMR instrument in D_2O or $+K_2CO_3$ and chemical shifts are expressed as δ units, TMS being used as an internal standard for ^1H NMR and 85% H_3PO_4 as an external standard for ^{31}P NMR spectroscopy. Elemental analysis was carried out with a Yanaco CHNCORDER MT-3 Analyzer. All the amines were redistilled before being used, except compound **1f** synthesized by directly using DMF as the starting material.

General Procedure

A 100 mL flask fitted with a reflux condenser and a distillation apparatus and charged with 15 mmol of amines (**3**) and 19.5 mmol of anhydrous formic acid. The mixture was refluxed for 5 hr, water produced and excess formic acid was removed continuously by the distillation during reaction to give the intermediate (**2**), and the resultant mixture was cooled to room temperature and 34 mmol of water was added. The flask was fitted with a mechanical stirrer instead of distillation apparatus, and 31 mmol of phosphorus trichloride was slowly added dropwise at such a rate that the internal temperature did not

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rise above 25°C with vigorous stirring in ice-water bath. After the completion of the addition, the reaction mixture was heated to 100–120°C and maintained at this temperature over 0.5 hr until solidified. It was quenched with 30 mL of water and hydrolyzed at reflux for 1 hr. The amino*bis*phosphonic acid crystallizes directly from the aqueous reaction mixture after cooling to room temperature. Appropriate ethanol was added and the pH was adjusted to 1–2, while the sodium salt was obtained upon cooling and adjusting the pH to 7–8 with aq. 20% NaOH.

***N*-Phenyl-aminomethylene-1,1-bisphosphonic Acid (1a).** Preparation procedure was the same as above. The crystal was collected by filtration, washed with cool water, recrystallized from water and dried in vacuo at 45°C to give pale white crystals as a monohydrate. ^{1}H NMR (D_2O) δ 6.89–7.47 (m, 5H, aromatic), 3.94 (t, $J_{H-P} = 19.87$ Hz, 1H, CH–P); ^{31}P NMR (D_2O) δ 16.80; Anal. Calcd for $C_7H_{11}NO_6P_2 + H_2O$: C, 29.49; H, 4.60; N, 4.91. Found: C, 29.21; H, 4.33; N, 4.70.

***N*-*o*-Methylphenyl-aminomethylene-1,1-bisphosphonic Acid (1b).** The crystal was collected by filtration, washed with ethanol, recrystallized from water/ethanol = 4 : 6 (v/v) to give a pale white crystalline as hydrochloride.^{1}H NMR (D_2O) δ 6.76–7.47 (m, 4H, aromatic), 2.25 (s, 3H, CH_3), 4.13 (t, $J_{H-P} = 19.82$, 1H, CH–P); ^{31}P NMR (D_2O) δ 17.66; Anal. Calcd for $C_8H_{13}NO_6P_2 + HCl$: C, 30.25; H, 4.44; N, 4.41. Found: C, 30.18; H, 4.12; N, 4.61.

***N*-Cyclohexyl-aminomethylene-1,1-bisphosphonic Acid (1c).** The desired product crystallized directly from the aqueous reaction mixture after cooling. Crystals were filtrated, washed with cool water, recrystallized from water and dried at 100°C to afford a white crystalline monohydrate ^{1}H NMR ($D_2O + K_2CO_3$) δ 1.33–2.08 (m, 11H, cyclohexyl), 3.23 (t, $J_{H-P} = 17.24$, 1H, CH–P); ^{31}P NMR ($D_2O + K_2CO_3$) δ 11.79; Anal. Calcd for $C_7H_{17}NO_6P_2 + H_2O$: C, 28.87; H, 6.58; N, 4.81. Found: C, 28.54; H, 6.55; N, 4.45.

***N*-3-(*N*,*N*-Dimethylamino)propyl-aminomethylene-1,1-bisphosphonic Acid (1d).** Preparation procedure was the same as above to obtain a white crystalline as dihydrate. ^{1}H NMR ($D_2O = K_2CO_3$) 2.91 (s, 6H, $2CH_3$), 2.22 (m, 2H, CH_2), 3.45 (m, 4H, CH_2–N), 3.25 (t, $J_{H-P} = 17.65$ Hz, 1H, CH–P); ^{31}P NMR ($D_2O + K_2CO_3$) δ 9.97; Anal. Calcd for $C_6H_{20}NO_6P_2 + 2H_2O$: C, 23.08; H, 7.10; N, 8.97. Found: C, 23.01; H, 7.23; N, 8.85.

***N*-Octyl-aminomethylene-1,1-bisphosphonic Acid (1e).** Preparation procedure was the same as above to obtain a white slice crystalline as monohydrate. ^{1}H NMR ($D_2O + K_2CO_3$) 0.754 (t, $J = 6$ Hz, 3H, CH_3), 1.16–1.62 (m, 12H, CH_2), 3.22 (t, $J = 7.39$ Hz, 3H, CH_2–N), 2.99 (t, $J_{H-P} = 16.45$ Hz,1H, CH–P); ^{31}P NMR ($D_2O + K_2CO_3$) δ 11.49; Anal. Calcd for $C_9H_{23}NO_6P_2 + 2H_2O$: C, 31.86; H, 8.02; N, 4.13. Found: C, 31.76; H, 8.22; N, 3.82.

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***N*,*N*-Dimethyl-aminomethylene-1,1-bisphosphonic Acid (1f).** Crystals were filtrated, washed with ethanol, recrystallized from water/ethanol and dried at 100°C to afford a white crystalline as hydrochloride. ^{1}H NMR (D_2O) δ 2.97 (s, 6H, CH_3), 3.53 (t, $J_{H-P} = 19.49$ Hz, 1H, CH–P); ^{31}P NMR (D_2O) δ 9.52; Anal. Calcd for $C_3H_{11}NO_6P_2 + HCl$: C, 14.10; H, 4.70; N, 5.48. Found: C, 13.83; H, 4.50; N, 5.48.

***N*,*N*-Dihydroxylethyl-aminomethylene-1,1-bisphosphonic Acid (1g).** The resulting reaction mixture was cooled to room temperature, and pH was adjusted to 7–8 with aq. 20% NaOH. Appropriate ethanol was added to give a white crystal which was purified by recrystallizing from ethanol/water to furnish **1g** as tetrasodium salt. ^{1}H NMR (D_2O) δ 2.50–2.92 (m, 4H, CH_2–N), 3.88–4.35 (m, 4H, HO–CH_2), 3.56 (t, $J_{H-P} = 19.45$ Hz, 1H, CH–P); ^{31}P NMR (D_2O) δ 9.94; Anal. Calcd for $C_5H_{11}NNa_4O_6P_2$: C, 17.92; H, 3.31; N, 4.18. Found: C, 17.71; H, 3.40; N, 4.25.

***N*,*N*-Diethyl-aminomethylene-1,1-bisphosphonic Acid (1h).** Crystals were filtrated, washed with ethanol, recrystallized from water/ethanol and dried at 100°C to afford a white crystalline. ^{1}H NMR (D_2O) δ 1.17 (t, $J = 7.22$ Hz, 6H, CH_3), 3.45 (q, $J = 6.5$ Hz, 4H, CH_2), 3.63 (t, $J_{H-P} = 20.16$ Hz, 1H, CH–P); ^{31}P NMR (D_2O) δ 9.93; Anal. Calcd for $C_5H_{15}NO_6P_2$: C, 24.30; H, 6.12; N, 5.67. Found: C, 24.62; H, 6.10; N, 6.00.

***N*,*N*-Dipropyl-aminomethylene-1,1-bisphosphonic Acid (1i).** Preparation procedure was the same as above to obtain a white crystalline. ^{1}H NMR (D_2O) δ 0.688 (t, $J = 7.29$ Hz, 6H, CH_3), 1.50 (q, $J = 7.55$ Hz, 4H, CH_2), 3.36 (q, $J = 6.65$ Hz, 4H, CH_2–N), 3.53 (t, $J_{H-P} = 20.44$ Hz, 1H, CH–P); ^{31}P NMR (D_2O) δ 9.69; Anal. Calcd for $C_7H_{19}NO_6P_2$: C, 30.55; H, 6.96; N, 5.09. Found: C, 30.71; H, 6.94; N,5.24.

***N*,*N*-Dibutyl-aminomethylene-1,1-bisphosphonic Acid (1j).** Preparation procedure was the same as above to obtain a white crystalline. ^{1}H NMR (D_2O) δ 0.835 (t, $J = 7.29$ Hz, 6H, CH_3), 1.25 (q, $J = 7.25$ Hz, 4H, CH_2), 1.59 (q, $J = 6.35$ Hz, 4H, CH), 3.42 (br, 4H, CH_2–N), 3.54 (t, $J_{H-P} = 15.2$ Hz, 1H, CH–P); ^{31}P NMR (D_2O) δ 9.37; Anal. Calcd for $C_9H_{23}NO_6P_2$: C, 35.65; H, 7.65; N, 4.62. Found: C, 35.59; H, 7.55; N, 4.43.

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