

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

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Version of record first published: 21 Aug 2006.

To cite this article: Mingshu Wu, Ruyu Chen & You Huang (2004): Convenient Synthesis of Analogs of Aminomethylene gem-Diphosphonic Acid from Amines Without Catalyst, *Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry*, 34:8, 1393-1398

To link to this article: <http://dx.doi.org/10.1081/SCC-120030688>

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SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 8, pp. 1393–1398, 2004

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

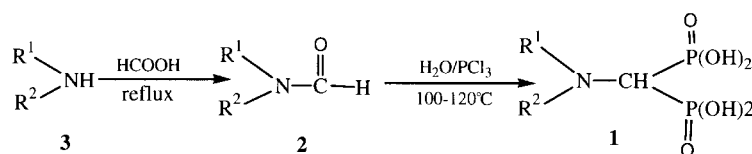
Geminal bisphosphonates and the corresponding acids which are characterized by a P–C–P linkage are stable pyrophosphates analogs

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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 *bisphosphonates* 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.



Table 1. Results of the reactions.

Product	R ¹	R ²	M.p. (°C)	Yield (%) ^a
1a	Phenyl	H	189–191 ^c	60
1b	<i>o</i> -Methylphenyl	H	182–184 ^b	40
1c	Cyclohexyl	H	261–263 ^c	70
1d	3-(<i>N,N</i> -dimethylamino)-propyl	H	247–249 ^d	72
1e	<i>n</i> -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	<i>n</i> -Propyl	<i>n</i> -Propyl	196–198	60
1j	<i>n</i> -Butyl	<i>n</i> -Butyl	221–223	46

^aIsolated yield.

^bHydrochloride.

^cMonohydrate.

^dDihydrate.

^eTetrasodium salt.

EXPERIMENTAL

All melting points were determined on a Yanaco apparatus and they are uncorrected. NMR spectra were measured on a Bruker AC-P200 NMR instrument in D₂O or +K₂CO₃ and chemical shifts are expressed as δ units, TMS being used as an internal standard for ¹H NMR and 85% H₃PO₄ as an external standard for ³¹P 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



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 aminobisphosphonic 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. ¹H NMR (D₂O) δ 6.89–7.47 (m, 5H, aromatic), 3.94 (t, *J*_{H–P} = 19.87 Hz, 1H, CH–P); ³¹P NMR (D₂O) δ 16.80; Anal. Calcd for C₇H₁₁NO₆P₂ + H₂O: 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. ¹H NMR (D₂O) δ 6.76–7.47 (m, 4H, aromatic), 2.25 (s, 3H, CH₃), 4.13 (t, *J*_{H–P} = 19.82, 1H, CH–P); ³¹P NMR (D₂O) δ 17.66; Anal. Calcd for C₈H₁₃NO₆P₂ + 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 ¹H NMR (D₂O + K₂CO₃) δ 1.33–2.08 (m, 11H, cyclohexyl), 3.23 (t, *J*_{H–P} = 17.24, 1H, CH–P); ³¹P NMR (D₂O + K₂CO₃) δ 11.79; Anal. Calcd for C₇H₁₇NO₆P₂ + H₂O: 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. ¹H NMR (D₂O + K₂CO₃) 2.91 (s, 6H, 2CH₃), 2.22 (m, 2H, CH₂), 3.45 (m, 4H, CH₂–N), 3.25 (t, *J*_{H–P} = 17.65 Hz, 1H, CH–P); ³¹P NMR (D₂O + K₂CO₃) δ 9.97; Anal. Calcd for C₆H₂₀NO₆P₂ + 2H₂O: 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. ¹H NMR (D₂O + K₂CO₃) 0.754 (t, *J* = 6 Hz, 3H, CH₃), 1.16–1.62 (m, 12H, CH₂), 3.22 (t, *J* = 7.39 Hz, 3H, CH₂–N), 2.99 (t, *J*_{H–P} = 16.45 Hz, 1H, CH–P); ³¹P NMR (D₂O + K₂CO₃) δ 11.49; Anal. Calcd for C₉H₂₃NO₆P₂ + 2H₂O: C, 31.86; H, 8.02; N, 4.13. Found: C, 31.76; H, 8.22; N, 3.82.



***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. ¹H NMR (D₂O) δ 2.97 (s, 6H, CH₃), 3.53 (t, *J*_{H-P} = 19.49 Hz, 1H, CH-P); ³¹P NMR (D₂O) δ 9.52; Anal. Calcd for C₃H₁₁NO₆P₂ + HCl: C, 14.10; H, 4.70; N, 5.48. Found: C, 13.83; H, 4.50; N, 5.48.

***N,N*-Dihydroxyethyl-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. ¹H NMR (D₂O) δ 2.50–2.92 (m, 4H, CH₂-N), 3.88–4.35 (m, 4H, HO-CH₂), 3.56 (t, *J*_{H-P} = 19.45 Hz, 1H, CH-P); ³¹P NMR (D₂O) δ 9.94; Anal. Calcd for C₅H₁₁NNa₄O₆P₂: 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. ¹H NMR (D₂O) δ 1.17 (t, *J* = 7.22 Hz, 6H, CH₃), 3.45 (q, *J* = 6.5 Hz, 4H, CH₂), 3.63 (t, *J*_{H-P} = 20.16 Hz, 1H, CH-P); ³¹P NMR (D₂O) δ 9.93; Anal. Calcd for C₅H₁₅NO₆P₂: 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. ¹H NMR (D₂O) δ 0.688 (t, *J* = 7.29 Hz, 6H, CH₃), 1.50 (q, *J* = 7.55 Hz, 4H, CH₂), 3.36 (q, *J* = 6.65 Hz, 4H, CH₂-N), 3.53 (t, *J*_{H-P} = 20.44 Hz, 1H, CH-P); ³¹P NMR (D₂O) δ 9.69; Anal. Calcd for C₇H₁₉NO₆P₂: 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. ¹H NMR (D₂O) δ 0.835 (t, *J* = 7.29 Hz, 6H, CH₃), 1.25 (q, *J* = 7.25 Hz, 4H, CH₂), 1.59 (q, *J* = 6.35 Hz, 4H, CH), 3.42 (br, 4H, CH₂-N), 3.54 (t, *J*_{H-P} = 15.2 Hz, 1H, CH-P); ³¹P NMR (D₂O) δ 9.37; Anal. Calcd for C₉H₂₃NO₆P₂: C, 35.65; H, 7.65; N, 4.62. Found: C, 35.59; H, 7.55; N, 4.43.

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Received in Japan October 20, 2003



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