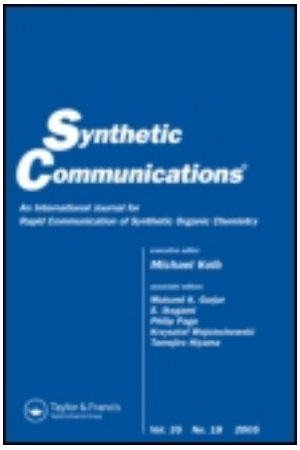

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Synthesis of Aminobisphosphonate

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SYNTHESIS OF AMINOBISPHOSPHONATE

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ABSTRACT

A new facile synthesis of aminobisphosphonate was reported. Dibenzylamine bisphosphonate (**1**) is prepared from dibenzylamine, triethyl orthoformate and diethyl phosphite. Deprotection by hydrogen transfer reaction and acid hydrolysis afforded aminobisphosphonate (**2**).

INTRODUCTION

Aminobisphosphonates have generated substantial interest recently for the treatment of bone diseases[1] and as plant growth regulators[2]. To date several methods have been used for the synthesis of aminobisphosphonates. The earliest of these methods was a three step synthesis of aminobisphosphonate (**2**) which involved the use of phosgene and debenzylation of *N,N*-dibenzylamine-bisphosphonate (**1**) by catalytic hydrogenation.[3] Sturtz *et. al.*[4] have reported two other methods. The first of these involves the treatment of methylenebisphosphonic acid tetraethylester with NaH to form the carbanion which was then reacted with a protected amine. Deprotection of the resultant aminobisphosphonate gave the desired product. Their second method involved

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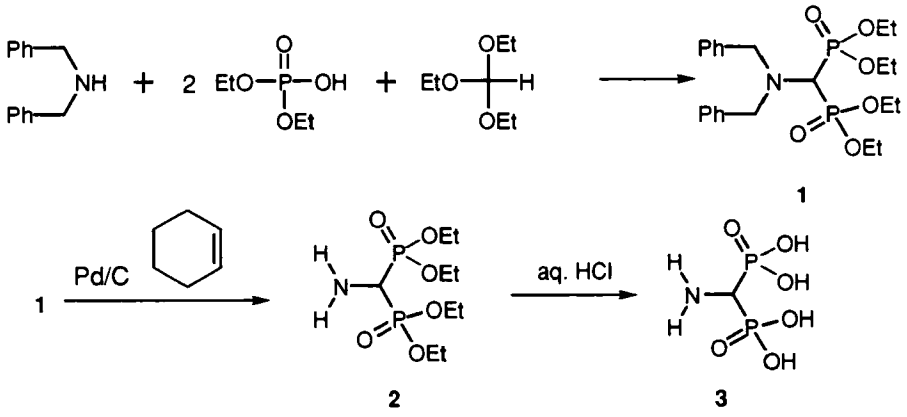
conversion of methylenebisphosphonate to diazomethylenebisphosphonate followed by a catalytic hydrogenation at 25 atm. H_2.

In this paper we report an new facile synthesis of aminobisphosphonate (Scheme 1). It is a shorter route than previously published syntheses as well as eliminating the need for highly toxic starting materials or vigorous reaction conditions. The synthesis is based on the triethyl orthoformate promoted P-C-P bond formation reaction first reported by Maier[3] and improved by Ebetino[5]. Triethyl orthoformate, diethyl phosphite and dibenzyl amine are reacted to form *N,N*-Dibenzylamine-bisphosphonate (**1**). Deprotection provides the desired aminobisphosphonates (**2** and **3**).

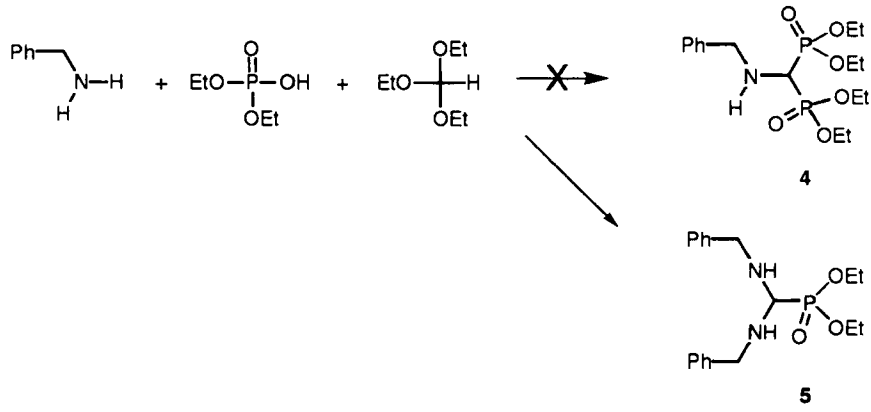
DISCUSSION

Our first approach to synthesis of **2** was to prepare the benzylbisphosphonate (**4**) (Scheme 2) by the conventional procedure[3] involving diethyl phosphite, triethyl carbonate and benzylamine. In our hands the reaction afforded a complex mixture containing only traces of the desired product. The dialkylated compound (**5**) was isolated in a 34% yield. The reactivity of triethyl orthoformate toward benzylamine was rather high even in the presence of four molar excess of diethyl phosphite. In order to structurally prevent dialkylation, benzyl amine was replaced with dibenzyl amine.

The synthesis of **2** shown in Scheme 1, involved the preparation of dibenzyl aminobisphosphonate **1** in one step followed by a debenzylation. Dibenzyl aminobisphosphonate tetraethyl ester was prepared in a single step by heating a solution of dibenzylamine, triethyl orthoformate and diethyl phosphite. It was necessary to remove the ethanol in order to obtain a high enough temperature for the reaction to reach completion. This procedure produced a 58% yield without optimization as opposed to 54% starting from methylenebisphosphonic acid tetraethylester which requires an additional step.[4] The debenzylation reaction was conveniently achieved by transfer hydrogenation[6] and proceeded quantitatively under mild conditions, eliminating the need for high pressure hydrogenation. Johnstone[6] reported yields of 90 to 100% for similar deprotection reactions. The final deprotection of **2** was realized by hydrolysis with aqueous hydrochloric acid.



Scheme 1: Synthesis of Aminobisphosphonate



Scheme 2: Attempted synthesis of Benzylamine-bisphosphonate

EXPERIMENTAL

All chemicals were obtained from Aldrich Chemical Co. and are used without further purification. NMR spectra were acquired on a General Electric GN-500 spectrometer at 500.1 MHz for ^{1}H, 125.8 MHz for ^{13}C and 202.5 MHz for ^{31}P. Mass spectra were recorded on a Finnigan MAT 900 High Resolution Mass Spectrometer operated in the electro-spray mode. Elemental analysis was performed by Galbraith Laboratories, Inc. (Knoxville, TX).

***N,N*-Dibenzylamine-bisphosphonate tetraethyl ester (1)** Triethylorthoformate (10.6 g, 72 mmol), diethyl phosphite (25.6 g, 186 mmol) and dibenzyl amine (11.8 g, 60 mmol) were combined and heated to reflux under argon for 5 hours. Heating was discontinued and the ethanol formed was removed by distillation. The temperature of the residue was then raised to 160°C and the solution was stirred under argon for an additional 19 hours. The reaction was cooled to room temperature, diluted with $CHCl_3$ (300 mL), washed with aqueous NaOH (2M, 3 x 60 mL) and brine (2 x 75 mL) then dried over sodium sulfate. The solvent was removed by rotary evaporation at reduced pressure (aspirator) and the remaining oil was purified by silica gel column chromatography (ethyl acetate-hexane-methanol 14:4:1) to yield 16.74 g (58%) as an oil. ^{1}H NMR ($CDCl_3$), δ: 7.54-7.16 (m, 10H, 2 x $C_6\underline{H}_5$-CH_2-), 4.21-4.04 (m, 8H, 4 x $OC\underline{H}_2CH_3$), 4.07-3.97 (m, 4H, 2 x C_6H_5-$C\underline{H}_2$-), 3.53 (t, 1H, *J* 20.1 Hz, N-C<u>H</u>-P), 1.30 (dt, 12H, *J* 2.42, 7.06 Hz, 4 x $OCH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$), δ: 129.37, 128.04, 127.05 ($\underline{C}_6H_5$-CH_2-) , 62.23 ($O\underline{C}H_2CH_3$), 56.36 (C_6H_5-$\underline{C}H_2$-), 54.94 (d, *J* 141.5 Hz, N-<u>C</u>H-P), 16.36 ($OCH_2\underline{C}H_3$); ^{31}P NMR ($CDCl_3$), δ: 21.94 [CH-($\underline{P}$(O)(OEt)$_2$)$_2$]; ESI (m/z): 484.2 (MH^+): HRMS: calc'd. 484.2018, found 484.2044.

Aminobisphosphonate tetraethyl ester (2) *N,N*-Dibenzylamine-bisphosphonate (**1**) (9.39 g, 19.4 mmol) was dissolved in dry methanol and added to a solution of methanol (10 mL) and cyclohexene (10 mL) over palladium on carbon (10% Pd, 5.0 g). The mixture was stirred at reflux under argon for 20 hours. The suspension was cooled to room temperature, filtered, the catalyst was washed with methanol (4 x 5 mL), and the washings were added to the filtrate. The solvent was removed by rotary evaporation at reduced pressure affording 5.88 g (100%) of a light brown oil. Only a single spot could be detected by TLC (r.f.

0.28 in 14:4:1 EtOAc/Hexane/MeOH)) and the purity was confirmed by ^{1}H and ^{13}C NMR. ^{1}H NMR ($CDCl_3$), δ: 4.23-4.12 (m, 8H, 4 x $OC\underline{H}_2CH_3$, lit. 4.3), 3.38 (t, 1H, *J* 20.6 Hz, N-C<u>H</u>-P, lit. 3.4), 2.22 (bs, 2H, $\underline{H}_2N$-CH-P, lit. 1.9), 1.30 (t, 12H, *J* 7.09 Hz, 4 x $OCH_2C\underline{H}_3$, lit. 1.3); ^{13}C NMR ($CDCl_3$), δ: 63.01 ($O\underline{C}H_2CH_3$), 47.99 (d, *J* 144.3 Hz, N-<u>C</u>H-P), 16.32 ($OCH_2\underline{C}H_3$); ^{31}P NMR ($CDCl_3$), δ: 21.61 [CH-(<u>P</u>(O)$(OEt)_2)_2$]; ESI (m/z): 304.5 (MH^+); HRMS: calc'd. 303.1000, found 303.0993

Aminobisphosphonate (**3**) Aminobisphosphonate tetraethylester (**2**) (2.07 g 6.8 mmol) was heated to reflux with aqueous hydrochloric acid (40 mL, 37%) for 2 h. To the reddish solution was added active carbon (1 g) and the suspension filtered, yielding a clear solution. The residual acid was removed under reduced pressure until crystallization started. Methanol (10 mL) was added and suspension cooled to -10°C. The precipitate was filtered, washed with methanol and dried in vacuum desiccator. Yield 1.29 g (83 %) of white crystals, m.p. 290-292°C. ^{1}H NMR (D_2O) δ: 3.46 (t, 1H, *J* 17.9 Hz, CH). ^{13}C NMR (D_2O) δ: 57 ppm. ^{31}P NMR (D_2O) δ: 9.06 ppm. FAB m/z 190 ($M\text{-}H^+$), HRMS: calc'd. 189.9670, found 189.9679, Elemental analysis: ($CH_7NO_6P_2$, 191.017) calc'd: C 6.29, H 3.69), N 7.33 %; found: C 6.29, H 3.90, N 7.03 %.

1,1-di-(*N*-benzylamino)-1-(diethyl phosphonate) mathane (**5**) Benzylamine (5.5 mL, 50 mmol) was added to the mixture of triethyl orthoformate (8.5 mL, 50 mmol) and diethyl phosphite (26.3 mL, 200 mmol) at 160°C via syringe over 30 min. with the removal of the ethanol byproduct by distillation. The mixture was heated for additional 30 min., cooled then diluted with water (50 mL) and ethyl acetate (80 mL). The pH was adjusted to 5-6 with aqueous hydrochloric acid (1N) and the ethyl acetate was removed under reduced pressure. The aqueous layer was washed with ethyl acetate (50 mL) and the aqueous layer was evaporated to dryness. The residual white solid was dissolved in the mixture of chloroform (100 mL) and aqueous sodium hydroxide (2N, 30 mL). The organic phase was washed with aqueous sodium hydroxide (2N, 20 mL), water (20 mL) then dried (Na_2SO_4) and solvent removed under reduced pressure. The oily residue was purified by silica gel column chromatography ($CHCl_3$-MeOH 9:1) to yield 3.23 g of light yellow oil. ^{1}H ($CDCl_3$) δ: 7.4-7.2 (m, 10H, 2x Ph), 4.07 (q, 2H, *J* 7.1 Hz, CH_2), 4.02 (d, 1H, *J* 20.1 Hz, CH), 3.96 (q, 2H, *J* 7.1 Hz, CH_2), 3.81 (d, 2H, *J* 13.3 Hz,

CH_2), 3.54 (d, 2H, *J* 13.3 Hz, CH_2), 2.38 (bs, 2H, 2x NH), 1.27 (t, 3H, *J* 7.1Hz, CH_3), 1.12 (t, 3H, *J* 7.1Hz, CH_3). ^{13}C ($CDCl_3$) δ: 139.25 (C-1'); 135.67 (C-1'); 128.64 (1C, C-3'); 128.60 (1C, C-3'); 128.40 (2C, C-3'); 128.28 (4C, C-2'); 127.84 (C-4'); 127.04 (C-4'); 62.91, 62.86 (CH_2, Et); 62.75, 62.70 (CH_2, Et); 60.17 (CH_2, Bn); 58.95 (CH_2, Bn); 51.23, 51.09 (CH); 16.38, 16.34 (CH_3, Et); 16.19, 16.15 (CH_3, Et). ^{31}P ($CDCl_3$) δ: 23.75 ppm. CI-MS (NH_3) m/z: 91, 196, 334 ($M+H^+$ -Et).

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