

Synthesis of New Ligands Derived from Polyphosphonates Partial Esters

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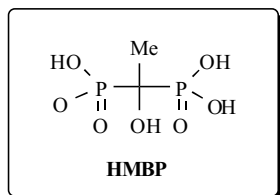
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Abstract: In the search for new chelation therapy drugs for the treatment of metal intoxications, some new polyphosphonated chelating ligands have been synthesized. They were obtained by means of an Arbuzov reaction followed by addition of the corresponding dialkylphosphite. The regioselective dealkylation was then carried out by using trimethylsilyl halide.

Keywords: Tetraphosphonate, chelating agents, restrained geometry, partial deprotection.

1-Hydroxymethylene-1,1-bisphosphonic acids (or HMBP throughout) are widely used for the treatment of diseases in the skeletal system, bone formation and resorption disorders [1] and also for the treatment of cancer [2-5]. It has been shown that bisphosphonates inhibit the development of bone metastasis in breast cancer patients [6]. These compounds containing a stable P-C-P bridge usually have low toxicity and high stability towards enzymatic degradation.

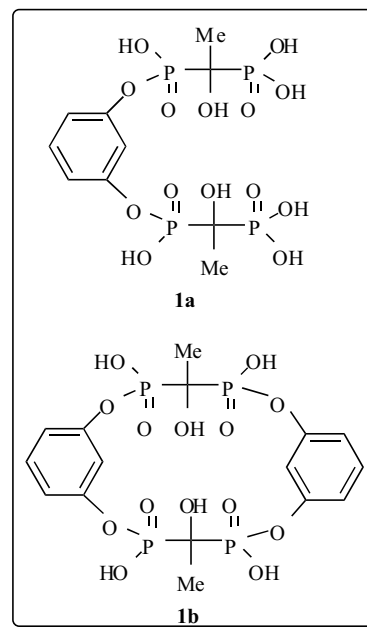


Another property of these compounds largely investigated is their chelating efficiency toward various metal ions. Bisphosphonates complexes of ^{99}Tc are routinely used in skeletal scintigraphy in the delineation of metastases. They are also efficient for the treatment of human metal intoxications. Recent works on coordination ability of HMBP in solution have shown their very high efficiency in binding metal or metalloid ions [7-10]. In the crystal state, our previous studies have shown that the structure of 1-hydroxyethyl-1,1-bisphosphonic acid-divalent metal (M II) salts did not show arrangements of discrete base motifs, but instead polymeric associations through hydrogen network and direct O.....M (II) coordination [11-13].

However, it has been observed that one of the major drawbacks of these products was their poor oral bioavailability due to a strong hydrophilicity [14] and their strong complexation of divalent cations [15].

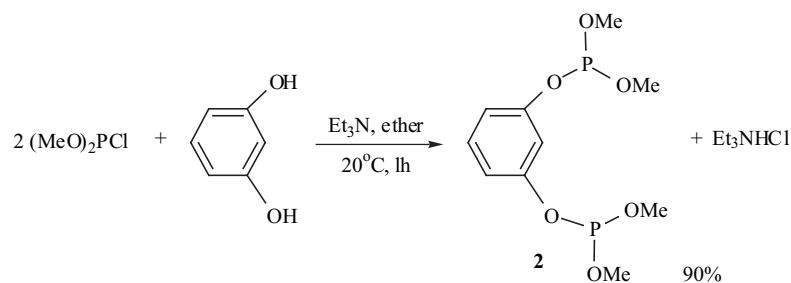
The purpose of this note has been to investigate new methods to prepare bidentate polyphosphonate compounds derived from 1,3-dihydroxybenzene, a modification that would have the advantage to increase the lipophilicity in HMBPs.

Our strategy is based on the synthesis of mixed dialkyl acylphosphonates by the Arbuzov reaction between mixed phosphites and acyl chloride as the primary step. The second step being the addition of dialkyl phosphite or mixed dialkylphosphite which is generated *in situ* to give mixed tetraalkyl 1-hydroxymethylene-1,1-bisphosphonate [16]. Synthesis of mixed dialkyl α -ketophosphonate is of practical value only with mixed phosphites in which there was clear selectivity between the different alkyl groups to be cleaved. Our previous studies have shown that the difference of reactivity between an alkyl group and a phenyl group is unusually high. In fact, the nucleophilic attack of the chloride anion is regioselective and concerns only the alkyl group [17]. In this paper, we describe an efficient procedure that allows the synthesis of new restrained aryl phosphonated chelating agents (**1a**) and (**1b**).

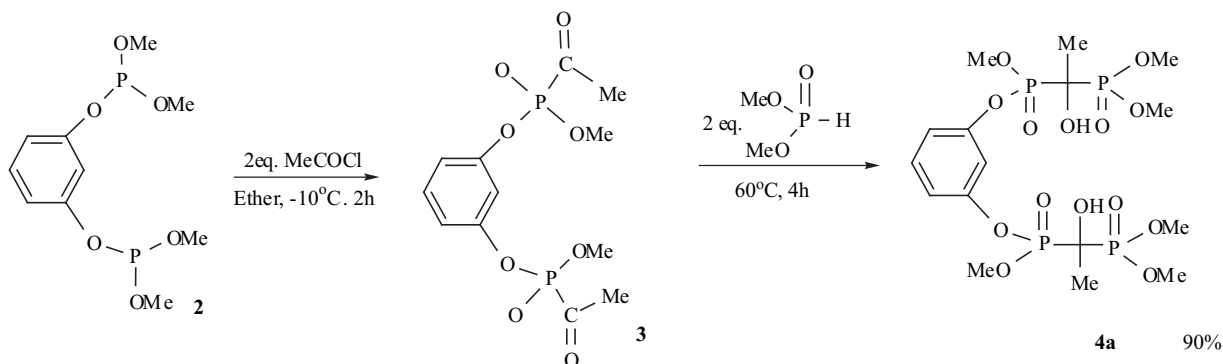


The mixed phosphite **2** is prepared by nucleophilic substitution of 1,3-dihydroxybenzene on chlorodimethylphosphite in the presence of triethylamine (scheme 1). The course of the reaction was monitored by ^{31}P NMR and

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Scheme 1.

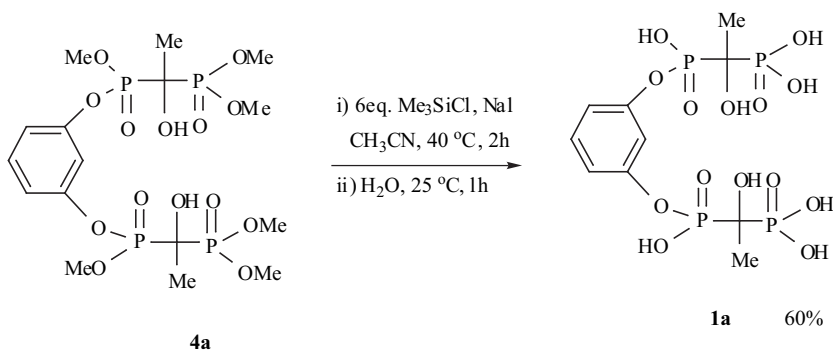


Scheme 2.

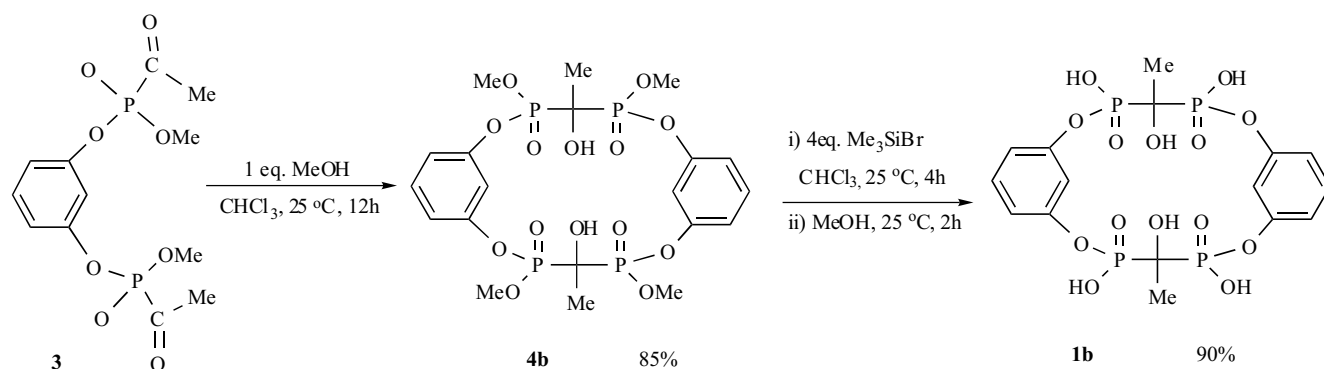
shown the formation of a main product ($\delta = 132.6$ ppm) after 1 hour of reaction. The mixed phosphite (**2**) was obtained after filtration of triethylammonium chloride in 90 % yield and was used without further purification.

To synthesize tetraalkyl 1-hydroxymethylene-1,1-bisphosphonates, several methods are described in the literature [18]. In this case, we preferred to use two steps for the preparation of compound (**4a**) in order to characterise each intermediate (scheme 2). The first Arbuzov reaction between the phosphite (**2**) and two equivalents of acetyl chloride was carried out at -10 °C for two hours. The reaction was monitored by ^{31}P NMR and showed the presence of one product ($\delta = -8.4$ ppm) characteristic of the α -diketodiphosphonate (**3**). The second step was the addition of dimethyl phosphite on the crude product (**3**). The solution was heated for 4 hours at 60 °C. At the end of the reaction, the ^{31}P spectrum showed the presence of two doublets due to the presence of two inequivalent phosphorus $\delta_1 = 16.1$ ppm and $\delta_2 = 19.8$ ppm with a coupling constant of 42.5 Hz. The 1-hydroxymethylene-1,1-bisphosphonate (**4a**) was obtained in 90 % yield.

The main difficulty in preparing 1-hydroxymethylene-1,1-bisphosphonate partial esters (**1**) is the selective dealkylation at specific positions. Several low selective methods such as acidic hydrolysis have already been published [19-21] but the obvious way to synthesize (**1a**) is the dealkylation of the methyl groups using silylhalides followed by hydrolysis [22]. Vepsalainen and co-worker have shown from previous studies that the order of the silylation depends on the nature of the alkyl group of phosphonic ester [23,24]. These authors have been able to determine that the phenyl ester was less sensible than the methyl ester towards the silylation reaction while tris trimethylsilyl esters are more easily hydrolysed than the phenyl ester. In our case, we carried out the deprotection step by using a mixture of trimethylsilyl chloride and sodium iodide followed by hydrolysis to give (**1a**) in 60 % yield (scheme 3). The formation of the partial ester (**1a**) was readily followed by ^{31}P NMR spectroscopy. It showed two doublets different from the starting product, due to the presence of two inequivalent phosphorus $\delta_1 = 16.8$ ppm and $\delta_2 = 21.0$ ppm with a 38.0 Hz coupling constant [25].



Scheme 3.



Scheme 4.

To prepare the cyclic polyphosphonate (**1b**), a similar strategy could be used but a method described earlier was preferred [16,26]. 1-Hydroxymethylene-1,1-bisphosphonate tetraester is directly obtained from α -diketodiphosphonate by introducing a protic reagent (scheme 4).

After the preparation of α -diketodiphosphonate (monitored by ^{31}P NMR), 1 equivalent of methanol is added and the solution stirred for 12 hours at room temperature. Under these conditions, solvolysis of half the quantity of compound (**3**) yielded methylphenylphosphite. This compound then reacted with the carbonyl groups of half the quantity of unreacted compound (**3**) and lead to the formation of the cyclic tetraphosphonate (**4b**). After evaporation of volatile fractions, (**4b**) was obtained as a white powder in 85 % yield. The ^{31}P NMR spectrum showed the presence of one product ($\delta = 15.6$ ppm) characteristic of the symmetric compound (**4b**). This cyclic compound was further confirmed by electrospray ion trap mass spectrometry analysis ($\text{MH}^+ = 617$).

Dealkylation of methylphosphonate groups using trimethylsilyl bromide (4 eq.) in dichloromethane for 4 hours at room temperature, followed by treatment with methanol, afforded the partially deprotected tetraphosphonate (**1b**) in 90 % yield [27]. No side reactions such as phenyl phosphonate hydrolysis were observed during the deprotection process.

In conclusion, the procedure described herein allows an efficient access to new restrained polyphosphonate ligands. Further studies on the scope and synthetic applications of this methodology are in progress.

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- [27] **1b**: ^1H NMR (500 MHz, D_2O) δ 1.47-1.53 (6H, m), 6.95 -7.20 (8H, m). ^{31}P NMR (162 MHz, D_2O) δ 16.3. ^{13}C NMR (100.6 MHz, D_2O) δ 20.4, 77.2 (t, $J_{\text{PC}} = 131$ Hz), 113.9, 117.8, 130.4, 151.3.