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A mild and efficient one-pot synthesis of 1-hydroxymethylene-1,1-bisphosphonic acids. Preparation of new tripod ligands

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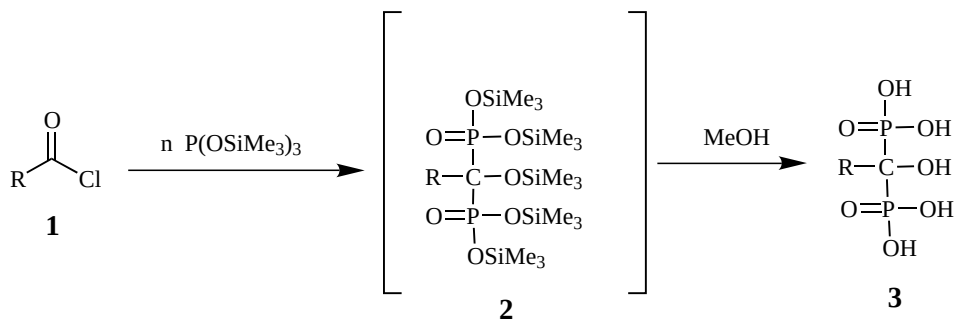
Abstract—A simple and efficient one-pot procedure for synthesis of 1-hydroxymethylene-1,1-bisphosphonic acids by reaction of acyl chlorides and tris(trimethylsilyl)phosphite is described. This method was applied to the synthesis of new phosphonated chelating tripod ligands. © 2001 Elsevier Science Ltd. All rights reserved.

For some years, there has been considerable interest in the derivatives of 1-hydroxymethylene-1,1-bisphosphonate because of their biological properties and medical applications. 1-Hydroxymethylene-1,1-bisphosphonates (HMBP) which are characterized by a P–C–P linkage, are stable analogues of pyrophosphate and are completely resistant to enzymatic hydrolysis. They are widely used in the treatment of a number of diseases characterized by an abnormal calcium metabolism.[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] It has been shown that HMBP inhibit the development of bone metastasis in breast[4,5] or prostate cancer patients.[6] Another approach is the use of the chelating properties of the 1-hydroxymethylene-1,1-bisphosphonic (HMBP) group for the treatment of human metal intoxications. Recent works on coordination ability of HMBP have shown their very high efficiency in binding of metal ions or metalloid ions.[7–9]

These numerous applications require then the development of an efficient and practical method to introduce the HMBP group. Several methods have been reported for the synthesis of HMBP. A common method involves the reaction of a carboxylic acid and phosphorus trichloride. In this case, the synthesis is carried out in the harsh acidic conditions and consequently it is not suitable for the polyfunctional substrates. The second pathway requires the synthesis of 1-hydroxymethylene-1,1-bisphosphonate (HMBP) tetraester obtained from the addition of dialkylphosphite to α-ketophosphonates followed by a dealkylation reaction. Unfortunately, HMBP tetraesters are not as stable as the correspond-



Scheme 1.

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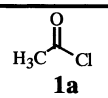
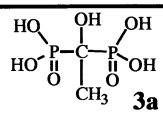
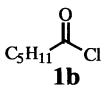
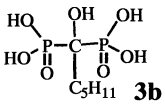
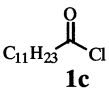
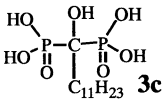
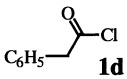
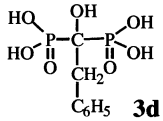
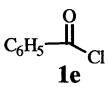
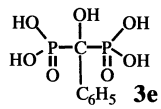
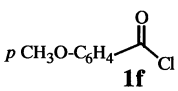
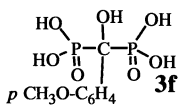
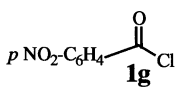
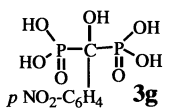
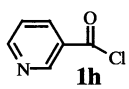
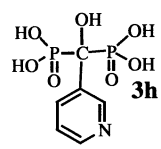
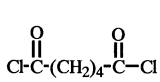
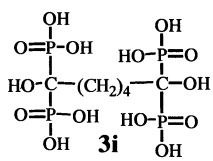
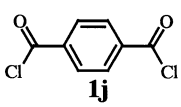
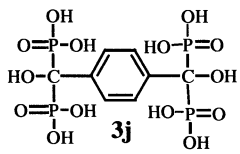
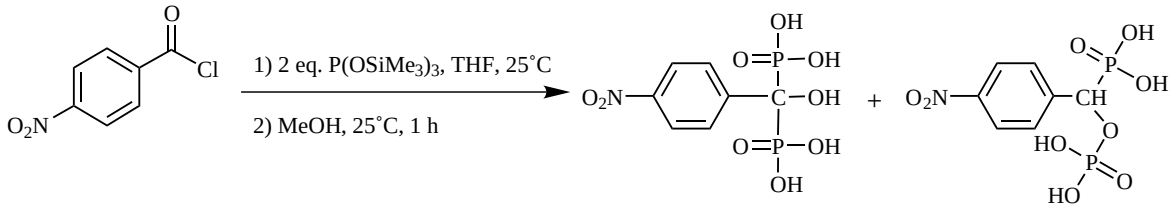
ing acids or salts due to the rearrangement HMBP tetraesters into the phosphonophosphate esters under basic conditions or thermically.[10–12]

Our group has previously described a one-pot procedure to obtain HMBP tetraesters from acyl chlorides and trimethylphosphite in the presence of protic reagent.[13] In this communication, we report a very mild and efficient one-pot method for the preparation of HMBP tetraacids (Scheme 1).

Thus, treatment of acid chloride with 2 equiv. of tris(trimethylsilyl)phosphite at room temperature leads to the tetrakis(trimethylsilyl) ester of 1-trimethylsiloxy-1,1-bisphosphonic acid **2** in a single step within few minutes. The synthesis of **2** is based on an Arbuzov reaction to give a bis(trimethylsilyl) α-ketophosphonate followed by an immediate addition of a second equivalent of tris(trimethylsilyl)phosphite.[14] Hydrolysis of **2** was carried out in methanol at 25°C for 1 h. After evaporation of volatile fractions, HMBP tetraacids **3**

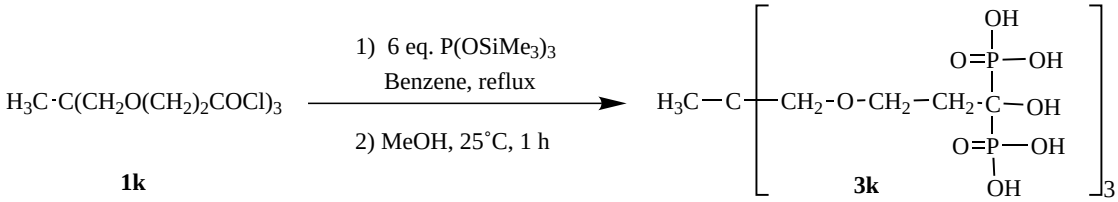
Table 1. HMBP derivatives **3a–i** produced via Scheme 1

Entry	1	n	Solvent	T °C	3	Yield %	$^{31}P\{^{1}H\}$ NMR (D_2O) ppm
1	 **1a**	2	/	25	 **3a**	98	19.4
2	 **1b**	2	/	25	 **3b**	97	20.4
3	 **1c**	2	/	25	 **3c**	97	19.6
4	 **1d**	2	/	25	 **3d**	90	19.0
5	 **1e**	2	/	25	 **3e**	91	16.0
6	 **1f**	2	THF	25	 **3f**	90	17.0
7	 **1g**	2	THF	-70	 **3g**	85	15.3
8	 **1h**	3	THF	25	 **3h**	61	13.6
9	 **1i**	4	/	25	 **3i**	91	20.0
10	 **1j**	4	/	25	 **3j**	86	16.1 ;16.2



1g **3g** **4g**

Scheme 2.



1k **3k**

Scheme 3.

were obtained very pure in very good yields. As shown in Table 1, the efficiency of the procedure was not affected by the nature of acid chlorides. In aromatic or aliphatic series, yields were always excellent. These results are very interesting because no method previously described allowed the synthesis of aromatic HMBP.

For the liquid acid chlorides **1a**–**e**,**i**–**j**, the reaction can be easily settled without solvent at room temperature. The reaction is strongly exothermic but no side reaction was observed. In particular, for the benzyl acetyl chloride, it has been shown that the Arbuzov reaction from this substrate and trimethylphosphite did not lead to the α-ketophosphonate but to the enol form.[15] The solid acid chlorides **1f**–**h** were solubilized in THF. The reaction was carried out at room temperature except for the substrate **1h**. In this case, it was necessary to work at −70°C due to the high reactivity of *p*-nitrobenzoyl chloride. At 25°C, the ^{31}P NMR experiments indicated that the HMBP tetraacid **3g** was formed but with 20% of phosphono phosphate derivative **4g** (Scheme 2).

Our method also allowed us to introduce two HMBP groups on the same molecule in good yield (entries 9–10). It was just necessary to use 4 equiv. of tris(trimethylsilyl)phosphite per molecule. No side products were observed in aromatic or aliphatic series.

These excellent results encouraged us to continue the synthesis of a new tripodal structure having HMBP functions as terminal groups (Scheme 3). Previously, we described the synthesis of chelating tripod ligands for the treatment of intoxication by actinides in the phosphonate series.[16] This new tripod having three HMBP groups was synthesized for the complexation of UO_2^{2+} and Co^{3+}. In fact, the two more acidic hydroxyl functions of the HMBP group would be able to bind to the metal to lead to a stable cycle (six atoms).

The synthesis was carried out from the acid chloride **1k** described by Martell et al.[17] and 6 equiv. of tris(trimethylsilyl)phosphite in refluxing benzene for 15 h (the reaction was monitored by ^{31}P NMR). After methanolysis, the tripod **3k** was obtained in 40% yield. In this case, the yield decreased sensitively due to the steric hindrance of HMBP groups.

In conclusion, the procedure described herein allowed to introduce the HMBP group from various aromatic or aliphatic acid chlorides. To our knowledge, the synthesis of the tripod having HMBP functions as terminal groups was carried out for the first time.

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