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Synthesis of 1-Hydroxy-1,1-bisphosphonates

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INTRODUCTION

Derivatives of methylene bisphosphonic acids have become of great importance in recent years [1] because certain of them are clinically useful in the treatment of bone disease. The most effective compounds have an OH group and an alkyl substituent on the methylene carbon.

Several methods have been reported for the synthesis of 1-hydroxy-1,1-bisphosphonates. One can easily see two major synthetic pathways; the first is what we can call a direct synthesis and the second an indirect one. The direct synthesis is involved when a carboxylic acid (or the acid halide or anhydride) reacts with phosphorous acid (or phosphorus trichloride or phosphorus oxychloride) followed by hydrolysis. The indirect method is involved when an initial Arbuzov reaction gives an α-ketophosphonate from an acid halide and a dialkyl phosphite, followed by a second step that gives the 1-hydroxy-1,1-bisphosphonate through the further addition of the dialkyl phosphite to the carbonyl group of the α-ketophosphonate.

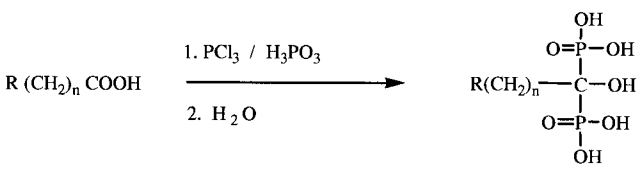
Historically, as far back as 1897, a prime example was the preparation of ethane-1-hydroxy-1,1-diphosphonic acid (EHDP) from acetylating agents and phosphorus (III) sources. EHDP and its salts have been known since the studies of von Baeyer and Hofmann [2]. They correctly represented the structure of the acid as $CH_3C(OH)(PO_3H_2)_2$, calling it *acetodiphosphorous acid*. Metal binding capacity of EHDP, suggested by the studies of von Baeyer and Hofmann, has encouraged a very close study of its preparation [3–7] and properties [8–10]. It is strange that a book [11] published in 1977 entitled "Phosphorus Chemistry in Everyday Living" does not mention these products, which, industrially, at that time, were used in the prevention of calcium and magnesium scale formation in boilers and pipes. One chapter in that book was devoted to "water softening with phosphates" only!

For a long period, these products were called 1-hydroxy-1,1-diphosphonates. A very good review [12] published in 1983 addressed with the role of phosphonates in living systems, and the fourth chapter concerned the chemical, biochemical, and medicinal properties of the diphosphonates with a part reserved for the synthesis of these products. At the present time, they are called 1-hydroxy-1,1-bisphosphonates.

SYNTHESIS OF 1-HYDROXY-1,1-BISPHOSPHONIC ACIDS

Direct Synthesis

They are prepared by reaction of a carboxylic acid with phosphorous acid and phosphorus trichloride, phosphorus pentachloride, or phosphorus oxychloride [13–20] followed by hydrolysis. It is often called a condensation reaction (Scheme 1).



SCHEME 1

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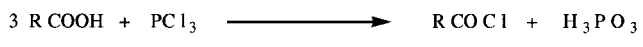
It is rather surprising to find this way of synthesis which is not common at all. In a large number of textbooks for students or for researchers, one can easily find that the classical way to obtain acid chlorides is to react carboxylic acids with phosphorus halides or phosphorus oxychloride [21–23]. The phosphorus chlorides PCl_3, PCl_5, and $POCl_3$ have been used to prepare acyl chlorides from carboxylic acids. All the reagents form intermediate mixed anhydrides so that the leaving group in the substitution is not OH but a derivative thereof. Each reagent has its unique characteristics. Phosphorus trichloride has been used extensively under a variety of conditions and detailed investigation of the reaction [24] shows that a 25–100% excess of the reagent is required, based on Scheme 2.

This simple equation does not account for the fact that all such reactions evolve hydrogen chloride. An explanation put forward by Cade and Gerrard [25] is that the reaction proceeds by the stepwise hydroxylation of phosphorus trichloride, producing the intermediates $HPOCl_2$ and HPO(OH)Cl, which may react with other molecules of carboxylic acid or degrade to hydrogen chloride and condensed phosphorus acids. The yield is very dependent on the conditions of the reaction. The rather complete study of this very complex reaction was done some years ago. The major contribution was a paper of J. B. Prentice and collaborators [26], which reported the isolation of about five intermediates when acetic anhydride reacts with phosphorous acid to form condensed species. The overall hypothetical reaction is as follows (Scheme 3).

Experience has shown that the reaction depicted in Scheme 4 does not take place.

Partial replacement of phosphorous acid by phosphorus trichloride, however, enables the reaction to proceed in a few hours at 100–150°, as evidenced by the presence of EHDP when such a mixture was hydrolyzed [4]. Alternatively, acetic acid can be replaced by acetyl chloride or acetic anhydride [5–7]. In order to obtain EHDP, one of the reactants must contain a hydrolyzable linkage, that is, it must react with water. It appears as if the capacity of the reactants to scavenge water actually serves as a driving force for the reaction. All the numerous articles, essentially patents, that have been published dealing with this subject are in accordance with this main idea. It is obvious that a great number of possibilities are offered with respect to that main idea.



SCHEME 2

To continue with a digest of this direct synthesis, one may understand the process as being initiated by the addition of the nucleophilic phosphorus atom of H_3PO_3 to the carbonyl carbon atom of the carboxylic acid (or to the carbonyl carbon atom of the acid halide) followed by the reformation of the carbonyl group to allow addition of a second phosphorous acid molecule. A valuable modification of this process was investigated to synthesize alendronate from γ-aminobutyric acid, methanesulfonic acid being used as a solvent able to give a medium that remains fluid, thus allowing complete conversion of the carboxylic acid to form the α-hydroxy-bisphosphonic acid in excellent yield [27] (Scheme 5).

For a long time, before this very good improvement based on the solvent effect was known, a great number of articles and patents were published that described this type of synthesis using either no solvent at all [28–49] or, in other cases, solvents such as chlorobenzene [50–56], tetrahydrofuran, sulfolane [57], or almost any inert organic solvent [58].

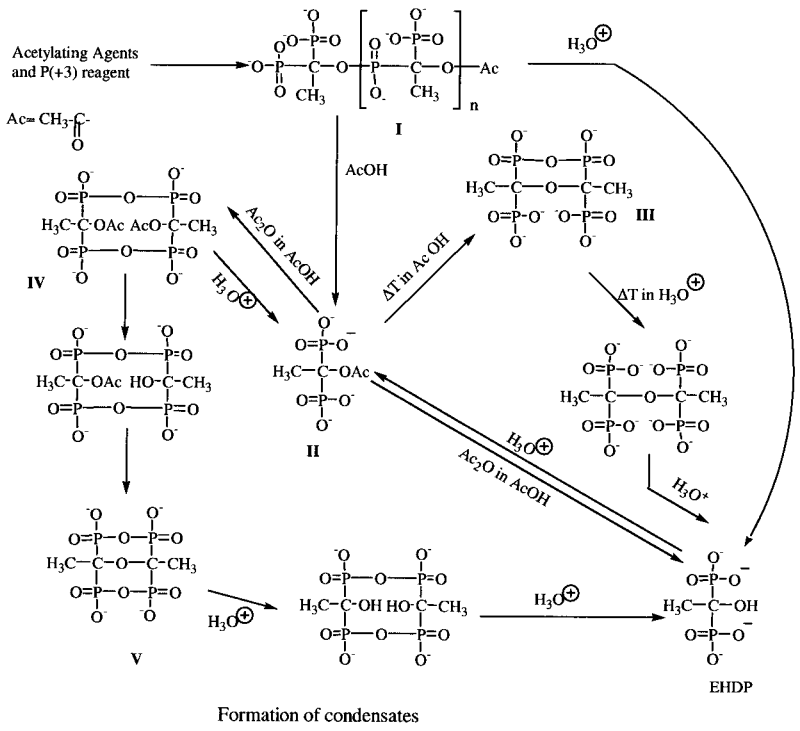
Use of Tris(trimethylsilyl) Phosphite

A few years ago, the use of tris(trimethylsilyl) phosphite was limited to acylphosphonic acid synthesis [59]. This phosphite (1 equivalent) was reacted with acetyl chloride or benzoyl chloride to give the corresponding silylated ester, and after alcoholysis, the resulting acylphosphonic acid was obtained. It was then shown that the action of two equivalents of these phosphites on benzoyl chloride led to a tetrakis(trimethylsilyl) ester of 1-trimethylsiloxybenzyl-1,1-bisphosphonic acid in a single step. After hydrolysis with a mixture of methanol and aniline, the monoanilinium salt of the 1-hydroxy-1,1-bisphosphonic acid was obtained in 93% yield (Scheme 6).

Dealkylation of Esters by HCl

Acidic hydrolysis of tetraalkyl 1-hydroxy-1,1-bisphosphonates requires strong experimental conditions. Usually, boiling a 6 M HCl solution [52, 60] or a more concentrated medium is used over a few hours. On the other hand, pinacol derivatives are cleaved very easily with cold dilute HCl solution [61, 62]. Water itself is able to very quickly hydrolyze only one bond of the pinacolate ester.

A recent improvement for this acidic hydrolysis has been reported with some *p*-substituted-benzyl 1-hydroxy-1,1-bisphosphonates [63]. The *p*-methylbenzyl ester requires only 45 minutes with 6 M HCl at room temperature. Especially with the *p*-methoxybenzyl ester, the rate of hydrolysis is very fast. At room temperature, it takes no more than a few min-



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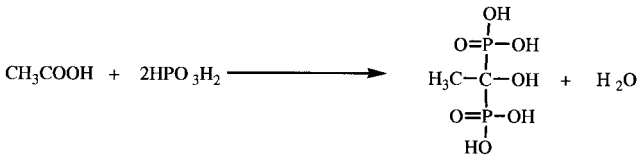

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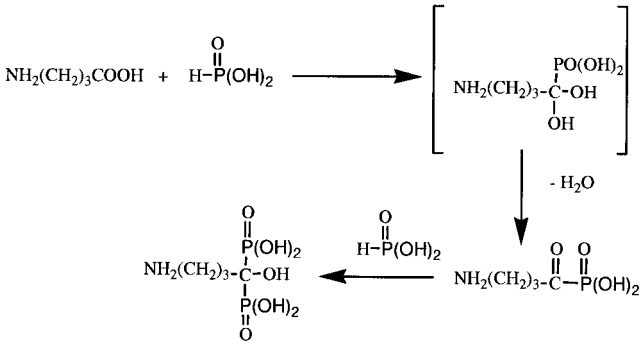


SCHEME 5

utes, and with trichloroacetic acid solution about one minute.

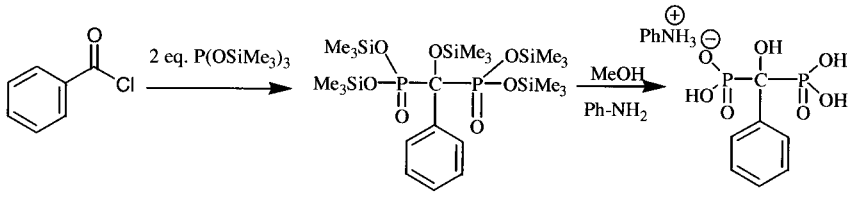
Dealkylation of Esters by Me_3SiX

Tetralkyl 1-hydroxy-1,1-bisphosphonates can be converted into tetrakis(trimethylsilyl) esters on treatment with bromotrimethylsilane [64] or iodotrimethylsilane [65, 66], also a known behavior of dialkyl phosphonates [67] or dialkyl acylphosphonates [68]. Alternatively, tetrakis(trimethylsilyl) esters can be obtained by using chlorotrimethylsilane with sodium iodide [69]. Tetrakis(trimethylsilyl) esters were solvolyzed by alcohol or water under mild conditions (Scheme 7). Chlorotrimethylsilane with sodium iodide was used recently for the synthesis of dihydroxy tetraphosphonic acids [70].

SYNTHESIS OF 1-HYDROXY-1,1-BISPHOSPHONATES

Addition of Dialkyl Phosphites to Dialkyl Acylphosphonates

The first presumed synthesis of 1-hydroxy-1,1-bisphosphonate esters by the base-catalyzed addition of



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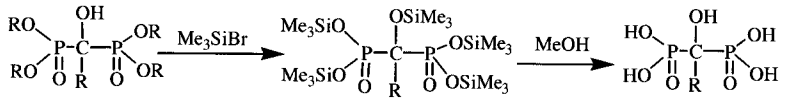

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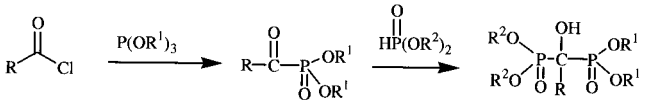

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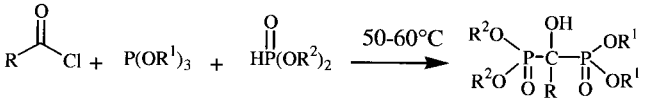


SCHEME 9

a dialkyl phosphite to a dialkyl acylphosphonate was described in 1956 [71]. However, six years later, a ^{31}P and ^{1}H NMR study showed that the synthesized compounds were not 1-hydroxy-1,1-bisphosphonate esters but rather isomeric compounds containing two chemically different phosphorus–carbon bonds, a tetraalkyl phosphono-phosphate being formed [72]. The standard procedure for the synthesis of 1-hydroxy-1,1-bisphosphonates is, in the first step, a Michaelis–Arbuzov reaction of an acyl halide with a trialkyl phosphite to give a dialkyl acylphosphonate, followed by an addition of a dialkyl phosphite in neutral medium (Scheme 8). This method was shown to be applicable to the synthesis of not only symmetrical methyl esters ($R^1 = R^2 = Me$) [17, 73–76] but also of unsymmetrical esters ($R^1 = Me$; $R^2 = Ph$) [77].

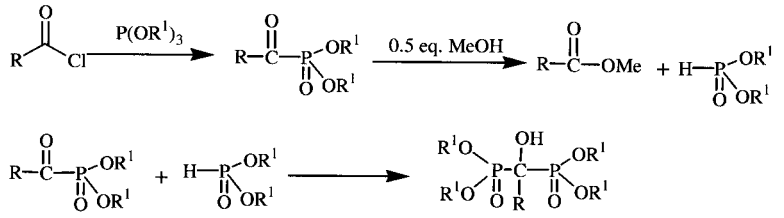
This procedure was used to synthesize a series of 1-hydroxy-1,1-bisphosphonates with several aminophenylmethane groups on the side chain [52]. Recently, it was shown that the addition of a dimethyl phosphite across the α-carbonyl group of a dimethyl acylphosphonate to give the 1-hydroxy-1,1-bisphosphonate was successfully achieved in high yield by carrying out the reaction in toluene in the presence of di-*n*-butylamine as catalyst [78]. The choice of the solvent was found to be important in this reaction. In toluene, the 1-hydroxy-1,1-bisphosphonate was only slightly soluble, so that, in this solvent, the product precipitated as it formed, thus preventing the formation of the phosphate-phosphonate.

Reaction between Acyl Halides and a Mixture of Trialkyl and Dialkyl Phosphites

A one-pot method of synthesis of 1-hydroxy-1,1-bisphosphonates, one that avoided the formation of an intermediate dialkyl α-ketophosphonate, was developed by Burgada et al. 1-Hydroxy-1,1-bisphosphonates were synthesized in good yield by adding an acyl halide to a mixture of trialkyl phosphite and dialkyl phosphite at 50–60°C (Scheme 9). This method was applicable to the synthesis of symmetrical esters, such as methyl esters or tetramethyldioxaphospholane esters [62] and also to unsymmetrical esters such as methyl and tetramethyldioxaphospholane esters [61]. Recently, we also showed that this procedure was suitable for the preparation of dihydroxytetraphosphonates [70].

Addition of a Protic Reagent to a Dialkyl Acylphosphonate

Recently, our group developed an original one-pot strategy to prepare symmetrical 1-hydroxy-1,1-bisphosphonate esters without the use of a dialkyl phosphite by introducing a protic reagent at a strategic point [79]. An acyl halide was added to a trialkyl phosphite at a temperature of between −10°C and 0°C. The reaction was exothermic and the corresponding dialkyl α-ketophosphonate was quickly generated. As soon as the reaction was complete (monitoring by ^{31}P NMR spectroscopy), one half of



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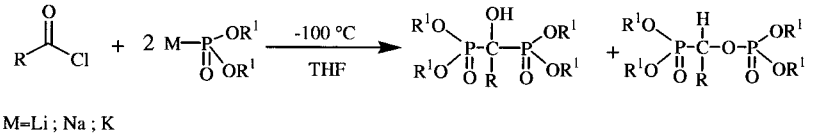


M=Li ; Na ; K

SCHEME 11

an equivalent of a protic reagent such as methanol or water was then added. Under such conditions, solvolysis of the dialkyl α-ketophosphonate yields a dialkyl phosphite. The latter compound then adds to the carbonyl group of an unreacted dialkyl α-ketophosphonate molecule with the formation of a 1-hydroxybisphosphonate ester (Scheme 10). This approach was applied with success for the synthesis of several *p*-substituted benzyl 1-hydroxy-1,1-bisphosphonate esters [63].

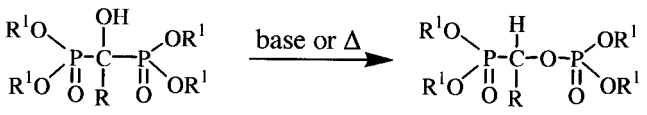
Michaelis–Becker Reaction

A single-step preparation of 1-hydroxy-1,1-bisphosphonates by addition of potassium dialkyl phosphite anions to acid chlorides has been reported [80]. The addition reaction between the anion of a dialkyl phosphite to an acid chloride at low temperature led to the tetraalkyl 1-hydroxy-1,1-bisphosphonate (Scheme 11). This method is, however, limited by the rearrangement of 1-hydroxybisphosphonates to tetraalkyl phosphono-phosphates [72]. It was shown that the nature of the alkoxide metal counterion and the nature of phosphonic ester alkyl groups were the factors that govern the outcome of the reaction.

Rearrangement of 1-Hydroxy-1,1-bisphosphonates

Although the 1-hydroxy-1,1-bisphosphonic acids and their salts are quite stable compounds, such is not the case for the corresponding 1-hydroxy-1,1-bisphosphonate esters. An NMR study revealed the rearrangement of these compounds to the corresponding phosphate-phosphonates by heating or by reaction with a base [72] (Scheme 12). The ^{31}P NMR spectra showed conclusively the transition from one type of phosphorus resonance for the 1-hydroxy-1,1-bisphosphonate to two equal resonances of the phosphate-phosphonate.

Pudovik and coworkers showed that sodium alkoxides and dialkylamines promote rearrangement [81]. When R is an alkyl group, rearrangement of 1-hydroxy-1,1-bisphosphonates occurs without added base if the temperature exceeds 120°C [73, 82].



SCHEME 12

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