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Optimized Synthesis of Etidronate

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Abstract: The synthesis of Etidronate (as the disodium salt) by the reaction of acetic acid with phosphorus trichloride/phosphorus acid in methanesulfonic acid was studied and optimized. We showed that it is enough to use 3.2 equivalents of the phosphorus trichloride and there is no need to apply phosphorus acid. In the two-step variation of the synthesis, the acetyl chloride was formed by the reaction of acetic acid with phosphorus trichloride, thionyl chloride or triphosgene, then the intermediate was converted to etidronate by reaction with 2.2 equivalents of phosphorus trichloride. The work-up included in all cases hydrolysis and pH adjustment.

Keywords: Hydroxy-methylenebisphosphonic acid, Etidronate, Optimization, Intermediate.

1. INTRODUCTION

C-substituted-1-hydroxy-1,1-bisphosphonic acids are efficient drugs used against bone diseases, such as osteoporosis, hypercalcemia, osteolyc metastases and the Paget disease [1–5]. The 1-hydroxy-geminal bisphosphonic acids have a tridentate functionality to enable the binding of Ca^{2+} ions and to promote the affinity for species responsible for the accumulation of phosphates in the bone tissues [1-9].

Etidronic acid belongs to the first generation of hydroxymethylenebisphosphonic acids. The first synthesis of etidronic acid was described in 1897, reacting acetic acid and phosphorus trichloride at room temperature for 1 day and then at 120–130°C for 1 h. After hydrolysis and pH adjustment, the yield of etidronic acid was low [10]. Later on, the synthesis was accomplished applying 3.5 equivalents of phosphorous acid and the same amount of phosphorus trichloride in 1,4-dioxane as the solvent at 90–95°C followed by hydrolysis and precipitation by acetonitrile to give the product in a yield of 5% [11]. According to another method, penthyl acetate was the starting material and phosphorous acid was prepared *in situ* in the reaction mixture by the partial hydrolysis of phosphorus trichloride. The ester was heated with the mixture of the P-reactants in sulfolane (or in dimethylsulfolane) at ca 110°C for 4–6 h. The work-up including extraction and steam distillation of the remaining reactants and suspendation of the final product in water followed by filtration gave Etidronic acid in a yield of 41% [12]. In the very first publication on the preparation of etidronic acid, it was also claimed that the reaction of acetyl-chloride with phosphorous acid at 20°C for 1 day and then at ~125°C for 1 h led to the desired product [10]. It is noteworthy that the reaction of acetic acid with phosphorus trichloride also furnished Etidronic acid, moreover in a quite good yield of 70% [13]. Starting from pentyl acetate and using phosphorus-trioxide in the presence borotrifluoride in sulfolane, the yield of Etidronic acid was 22% after acidic hydrolysis [12]. No criterion of the Etidronate content was reported in the above-mentioned cases. It is probable that the yields were given for crude products.

According to another approach, etidronic acid was synthesized by the Arbuzov-reaction of acetyl chloride with tris(trimethylsylil)phosphite as the first step. Addition of a second molecule of tris(trimethylsylil)phosphite on the carbonyl unit of the intermediate so formed followed by migration of a trimethylsylil group and finally metanolysis afforded Etidronic acid [14]. Another possibility for the synthesis of Etidronic acid involves the addition of dialkyl phosphite on the carbonyl carbon of dialkyl oxoethylphosphonate [15, 16]. Acidic hydrolysis of the resulting tetraalkyl ester gives rise to the bisphosphonic acid [15]. It is also possible to accomplish the first addition step selectively under microwave condition [16, 17].

Based on the reaction of the corresponding 1-substituted acetic acid and phosphorus trichloride, we elaborated the rational synthesis of Risedronate and Zoledronate [18, 19], Ibandronate [20], as well as Alendronate [20]. According to this method, only 3.2 equivalents of phosphorus trichloride was used and no phosphorous acid was measured in. We were the first, who selected the reactants consciously, on the basis of the mechanism envisaged and partially proved [21]. We wished to see if our method works also for the synthesis of Etidronate.

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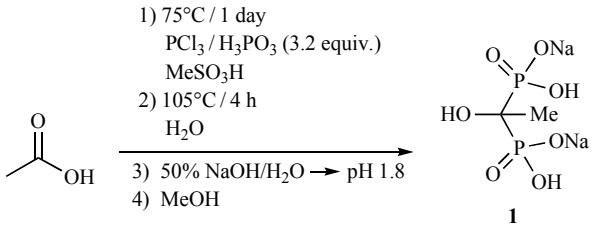

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Scheme 1.

Table 1. The Preparation of Etidronic Acid/Etidronate According to Scheme, Using the Phosphorus Trichloride and Phosphorous Acid Reactants in Different Ratio.

Reactants		Etidronate content[a] (%)	Yield[b] (%)	Entry
PCl_3 (equiv.)	H_3PO_3 (equiv.)			
0	3.2	–	0	1
1.1	2.2	c	<5	2
2.2	1.1	85[d]	38	3
3.2	0	90[d]	36	4

[a]On the basis of potentiometric titration.
[b]On the basis of the dronate content.
[c]No exact data, but the dronate content is less than 50%.
[d]From at least three parallel experiments.

2. RESULTS AND DISCUSSION

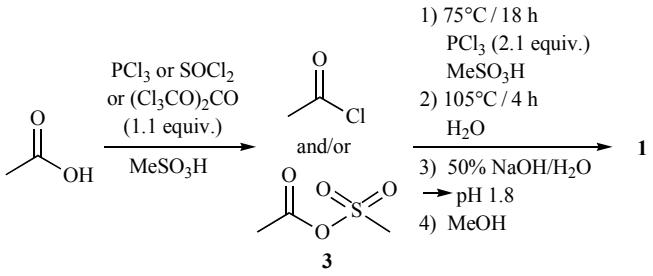
In the initial experiments we applied the phosphorus trichloride and phosphorous acid reactants in different ratios in reaction with acetic acid in methanesulfonic acid as the solvent at 75°C for 1 day (Scheme **1**). The reactions were followed by hydrolysis at 105°C for 4 h and then by pH adjustment by 50% NaOH/H_2O to pH = 1.8. The crude product (**1**) was obtained by precipitation using MeOH. Further purification comprised two additional precipitations from water solution and finally an extraction (digeration) of the solid product by MeOH on its boiling point.

The above procedure resulted in the formation of the disodium salt of Etidronic acid (**1**). The use of only 3.2 equivalents of phosphorous acid did not lead to the formation of the expected products (**1**) (Table **1**/Entry 1). Decreasing the quantity of phosphorous acid to 2.1 and 1.1 equivalents, and at the same time increasing the proportion of phosphorus trichloride to 1.1 and 2.1 equivalents, dronate **1** was obtained in a yield of *ca.* 5% and 38%, respectively (Table **1**/Entries 2 and 3). In the latter case, the dronate content was 85%. In the case, when only 3.2 equivalents of phosphorus trichloride was measured in (and no phosphorous acid was added), the yield of product **1** was 36%, while the dronate content was 90% (Table **1**/Entry 4). It can be seen that the best results were achieved, when phosphorus trichloride was the sole P-reactant, and when it was used in a 3.2 equivalent quantity. As in earlier cases [18–20], the phosphorous acid was not found to be of sufficient nucleophilicity.

The main impurity of crude Etidronate was $MeSO_3Na$ deriving from the reaction of MSA with NaOH. Purification of the crude product including two precipitations from water solution followed by digeration of the solid product was useful in getting rid of the $MeSO_3Na$ ballast, and led eventually to Etidronate with a dronate content > 90% according to potenciometric acid-base titration.

It was assumed by us that in the first step towards dronate formation, the starting carboxylic acid is transformed to the corresponding acid chloride by reaction with 1 equivalent of phosphorus trichloride [21]. In methanesulfonic acid as the solvent, it is also possible that a mixed anhydride formulated by $RC(O)O(O)_2SMe$ (**2**) is formed from the acid chloride. Thus, in the synthesis of Etidronate, the first intermediate is acetylchloride that may be converted to $MeC(O)O(O)_2SMe$ (**3**) by reaction with the solvent. For this, an experiment was carried out in which acetic acid was reacted with 1.1 equivalent of phosphorus trichloride in methanesulfonic acid in the first step. Then, the intermediates (acetyl chloride and $MeC(O)O(O)_2SMe$ (**3**)) formed were reacted further with 2.1 equivalents of phosphorus trichloride at 75°C for 18 h followed by the hydrolysis and other steps detailed above (Scheme **2**). In this case, product (**1**) was obtained in a yield of 32% with a dronate content of 88% (Table **2**/Entry 1). It can be seen that the one- and two-step procedures lead to quite similar results (Table **1**/Entry 4 vs. Table **2**/Entry 1). In another experiment, the *in situ* formed intermediates (acetylchloride and **3**) were reacted with 2.1 equivalents of phosphorous acid. The dronate **1**, was formed only in a low yield (*ca.* 5%) (Table **2**/Entry 2).

The two-step procedure was also carried out using 1.1 equivalent of thionyl chloride or triphosgene in the first step, then following the synthesis of dronate **1** applying 2.2 equivalents of phosphorus trichloride as above. In these cases (Table **2**/Entries 3 and 4), the yields, in average (*ca.* 34%), were comparable with those obtained in the instances utilizing phosphorus trichloride as the only reagent (Table **1**/Entry 4 and Table **2**/Entry 1), but the dronate contents were even better, 99% and 100%, respectively.



Scheme 2.

Table 2. Synthesis of Etidronate 1 *Via* Acetyl Chloride as a Possible Intermediate.

Inorg. Halide[a]	P-Reactant[b]	Etidronate Content[c] (%)	Yield[d] (%)	Entry
PCl_3	PCl_3	88	32	1
PCl_3	H_3PO_3	e	<5	2
$SOCl_2$	PCl_3	99	25	3
$(Cl_3CO)_2CO$[d]	PCl_3	100	43	4

[a]Used in the acetyl chloride forming reaction (1.1 equivalent).
[b]Used in the dronate forming reaction (2.1 equivalent).
[c]On the basis of titration.
[d]85°C.
[e]No exact data, but the purity is less than 50%.

In the field of synthesis of dronates, the yields related to pure products are rarely higher than 46–53% [18,20]. This is the consequence of the rather complex purification procedure. Hence, our yields of 36–43% in respect of the best experiments must not be underestimated.

In the next variation, acetyl chloride was chosen as the starting material that was reacted with 2.2 equivalents of phosphorus trichloride under the conditions applied above (75°C/18h). This experiment gave the product (**1**) in a yield of 23%, and with a dronate content 60%. However, the interaction of acetyl chloride with phosphorous acid did not result in the formation of the product (**1**). These results confirm the involvement of acetyl chloride and a related anhydride (**3**) as possible intermediates in the synthesis of Etidronate starting from acetic acid. On the other hand, the poor nucleophilicity of phosphorous acid was again demonstrated.

3. CONCLUSION

In summary it was proved that the synthesis of Etidronate from acetic acid may be performed best by using only phosphorus trichloride as the P-reagent and applying it in a 3.2 equivalent quality. It is also possible to use 1.1 equivalent of another inorganic chloride (thionyl chloride or triphosgene), and then 2.1 equivalents of phosphorus trichloride in the second step. Of course, phosphorus trichloride may also be used in two separate steps.

4. MATERIALS AND METHODS

4.1. General

^{31}P NMR spectra were obtained on a Bruker AV-300 spectrometer at 121.50 MHz; chemical shifts are downfield relative to 85% H_3PO_4. The Etidronate content of the samples was determined by potenciometric acid-base titrations on a Mettler DL77 potenciometric titrator.

The titration curve for pure Etidronic acid purchased from Aldrich and for that of the sample obtained from the reaction marked by Table **1**/Entry 4 are shown in Figs. (**1** and **2**), respectively.

4.2. Preparation of the Disodium Salt of Etidronate (1) in a One Step Reaction

1.4 mL (0.025 mol) of acetic acid was added into 10.5 mL of MSA on stirring. Then 7 mL (0.08 mol) of phosphorus trichloride was added dropwise in ca. 30 min and the contents of the flask were stirred at 75°C for 24 h. After cooling the mixture to room temperature, 25 mL (1.39 mol) of water was added and the mixture was stirred further at 105°C for 4 h. The pH was adjusted to 1.8 by adding ~12 mL of 50% aqueous sodium hydroxide to the mixture. Then 127 mL of methanol was added, the mixture stirred for 45 min and the precipitate was filtered. The crude product was dissolved in 10 mL of hot water and 50 mL of methanol was added, then the precipitate was filtered off and dried to give 7.6 g of Etidronate disodium salt in a purity of 57 %. The precipitation was repeated twice by adding 50 mL of methanol to the 10 mL water solution of the crude product. Then the solid product was suspended in the 50 mL mixture of methanol–water 94:6 and the mixture was digested by stirring at 65°C for 30 min, then the mixture was filtered. This procedure was repeated twice to afford 2.5 g (36%) of Etidronate disodium salt **1** in a dronate content of 90%. ^{31}P NMR (D_2O) δ 19.2, δ [22] 19.9 for the acid, ^{13}C (D_2O) δ 22.1 (s. CH_3), 74.0 (t, J = 136.5, P–C–P), δ [22] 21.5 (s, CH_3), 72.3 (t, J = 152.0, P–C–P) for the acid.

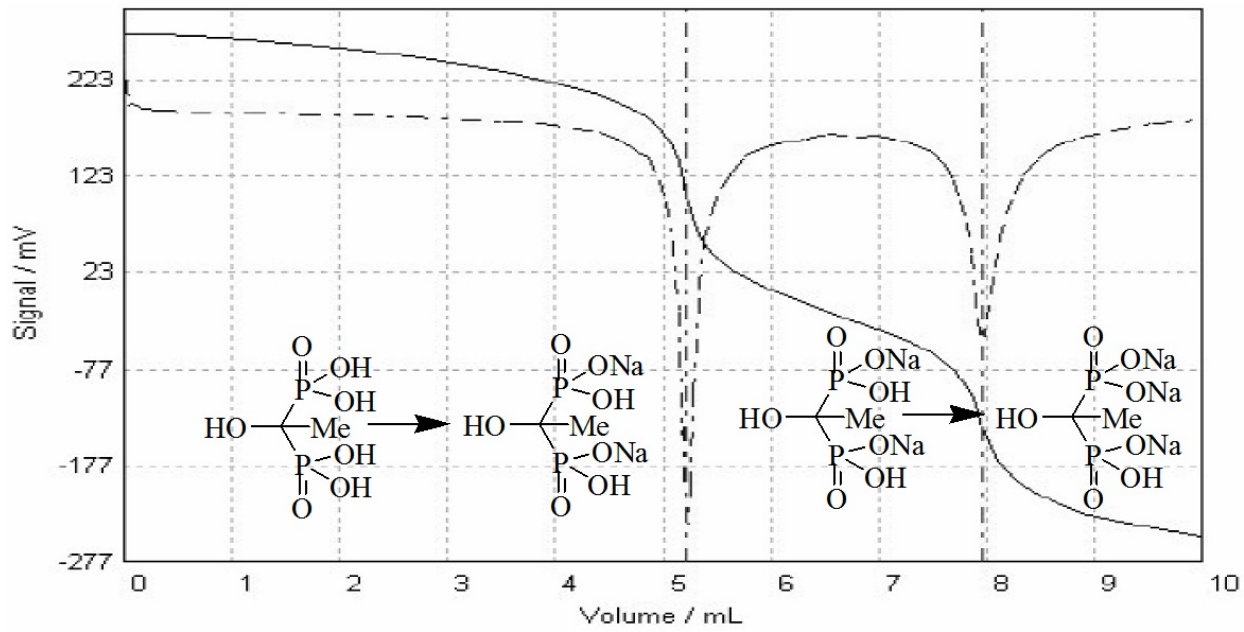


Fig. (1). Titration curve for etidronic acid.

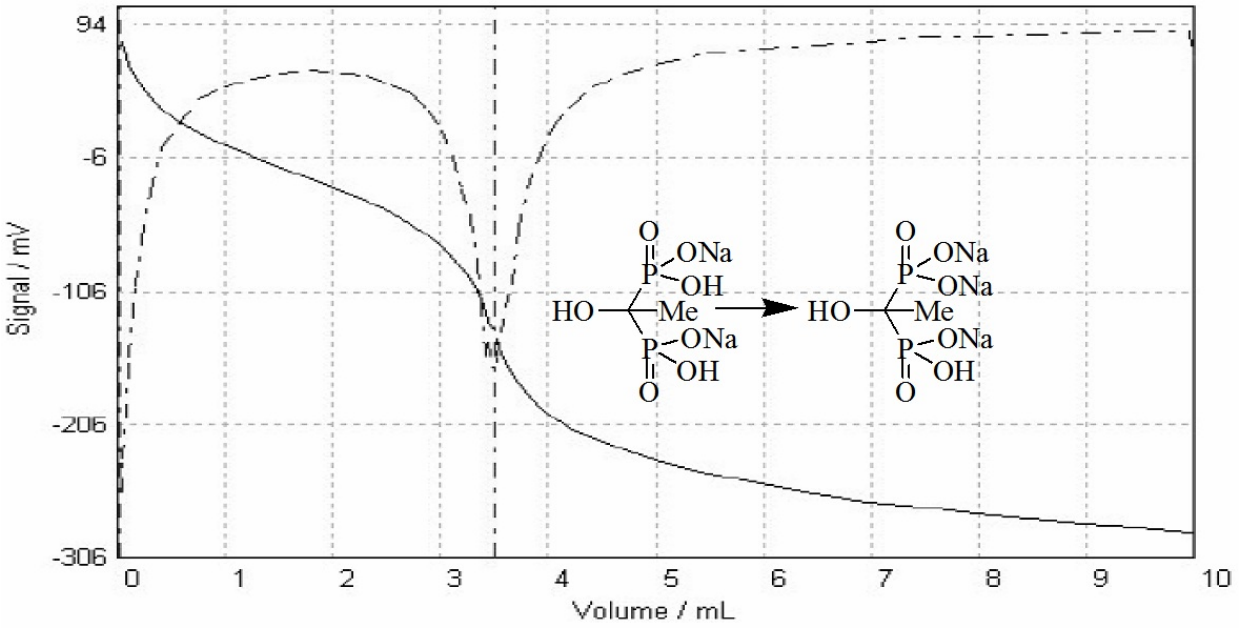


Fig. (2). Titration curve for the disodium salt of Etidronic acid (**1**) obtained by the reaction marked by Table **1**/Entry 4.

4.3. Preparation of Etidronate Disodium Salt in a Two-Step Reaction Using Only Phosphorus Trichloride (Table 2/Entry 1)

1.4 mL (0.025 mol) of acetic acid was dissolved in 10.5 mL of methanesulfonic acid on stirring. 2.3 mL (0.026 mol) of phosphorus trichloride was added dropwise and the mixture was stirred at 26°C for 6 h. Then 4.8 mL (0.055 mol) of phosphorus trichloride was added dropwise and the mixture was stirred at 75°C for 18 h. Further processment including hydrolysis, pH adjustment and precipitation with MeOH was performed as described above to afford 13.0 g of crude **1**. After the two precipitations with MeOH and three digestions with MeOH/water 94:6, 2.3 g (32%) of Etidronate disodium salt was obtained in a dronate content of 88%. ^{31}P NMR (D_2O) δ 19.3, δ [22] 19.9 for the acid.

4.4 Preparation of Etidronate Disodium Salt (1) in a Two-Step Reaction Using Phosphorus Trichloride and then thionylchloride (Table 2/Entry 3)

1.4 mL (0.025 mol) of acetic acid was dissolved in 10.5 mL of methanesulfonic acid on stirring. 1.9 ml (0.026 mol) of thionyl chloride was added dropwise and the mixture was stirred at 26°C for 6 h. Further processment including the second step, hydrolysis, pH adjustment and precipitation with MeOH was performed as described above, 1.6 g (25%) of Etidronate disodium salt was obtained in a dronate content of 99%. ^{31}P NMR (D_2O) δ 19.0, δ [22] 19.9 for the acid.

4.5. Preparation of Etidronate Disodium Salt (1) in a Two-Step Reaction Using Phosphorus Trichloride and then triphosgene (Table 2/Entry 4)

1.4 mL (0.025 mol) of acetic acid was dissolved in 10.5 mL of methanesulfonic acid on stirring. 2.6 g (0.026 mol) of triphosgene was added and the mixture was stirred at 85°C for 6 h. Further processment including the second step, hydrolysis, pH adjustment and precipitation with MeOH was performed as described above, 2.7 g (43%) of Etidronate disodium salt was obtained in a dronate content of 100%. ^{31}P NMR (D_2O) δ 19.3, δ [22] 19.9 for the acid.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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