Heteroatom Chemistry
Volume 25, Number 3, 2014

The Synthesis of Pamidronic Derivatives in Different Solvents: An Optimization and a Mechanistic Study

Rita Kovács,[1] Alajos Grün,[1] Orsolya Németh,[1] Sándor Garadnay,[2] István Greiner,[2] and György Keglevich[1]

[1]*Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary*

[2]*Gedeon Richter Plc, 1475 Budapest, Hungary*

Received 10 February 2014; revised 19 March 2014

ABSTRACT: *The synthesis of pamidronic acid and sodium pamidronate dihydrate from β-alanine and P-reagents (phosphorus trichloride and phosphorous acid) was investigated at 75°C in different solvents, and the preparation was optimized. In sulfolane, the use of 2 equiv of phosphorus trichloride and phosphorous acid was found the optimum to lead to pamidronic acid in a yield of 63%. In methanesulfonic acid, 3.2 equiv of phosphorus trichloride was necessary without any phosphorous acid to give pamidronate dihydrate in the best yield (57%) after hydrolysis and pH adjustment. In the first case, the P-nucleophile may be* $(HO)_2P–O–PCl–O–P(OH)_2$ *or* $(HO)_2P–O–PCl_2$*, whereas in the second case, the P-reactant is probable* $Cl_2P–O–S(O)_2Me$*. It can be said that the mechanism proposed for the formation of pamidronic acid is highly influenced by the solvent used, as it determines the necessary P-reagent(s). Our results promote the "on purpose" planning of the synthesis of dronates.* © 2014 Wiley Periodicals, Inc. Heteroatom Chem. 25:186–193, 2014; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21155

INTRODUCTION

Carbon-substituted 1-hydroxy-1,1-bisphosphonic acids are efficient drugs used against bone diseases, such as osteoporosis, hypercalcemia, osteolytic 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].

Pamidronic acid belongs to the second generation of hydroxy-methylenebisphosphonic acids. The first synthesis of pamidronic acid was described in 1973, reacting β-alanine, 1.5 equiv of phosphorus trichloride, and 1.5 equiv of phosphorous acid in chlorobenzene at 132°C for 3 h. After hydrolysis and separation of the phases, the pamidronic acid was crystallized from the water phase in a yield of 59% [10]. Later on, the synthesis was accomplished applying 2 equiv of phosphorus trichloride and 1.5 equiv of phosphorous acid. The reaction was carried out in acetonitrile at 70–75°C for 6–9 h followed by hydrolysis and pH adjustment to afford monosodium pamidronate in a yield of 60% [11].

Correspondence to: György Keglevich; e-mail: gkeglevich@mail.bme.hu.

Contract grant sponsor: Hungarian Scientific and Research Fund.

Contract grant number: OTKA No K83118 and TÁMOP-4.2.1/B-09/1/KMR-2010–0002.

In another variation, monosodium pamidronate was prepared in methanesulfonic acid (MSA) as the solvent [12, 13] in a yield of 57% [12]. Using sulfolane as the solvent and utilizing microwave irradiation, McKenna et al. obtained monosodium pamidronate in a yield of 64% whereas under conventional thermal conditions the yield was 72% [14]. When pamidronic acid was the target, β-alanine, phosphorus trichloride, and phosphorous acid were reacted as shown above [10], or the components were measured in a molar ratio of 1:3.4:1.5 applying sulfolane as the solvent. After heating the components at 63–67°C for 3 h followed by hydrolysis at 0→100°C and cooling the reaction mixture to 0–5°C, the dronic acid was obtained in a yield of 63% and with a purity of 99% in a crystalline form [15]. In another variation, diphenyl ether was suggested as the solvent, but no preparative details were provided [16]. It is also possible to convert pamidronic acid to the disodium salt by treating with 2 equiv of sodium hydroxide [17].

In the literature, there are a variety of procedures for the preparation of dronic acids/dronates starting from the corresponding carboxylic acids and the P-reagents, such as phosphorus trichloride and phosphorous acid. However, the reactions were never optimized in respect of the ratio of the reactants and other reaction conditions. We tried to study the "black-box" of the synthesis of dronates by systematic investigations. It was shown via the example of risedronate [18, 19], zoledronate [18, 19], ibandronate [20], alendronate [20], etidronate [21], and fenidronate [22] that if MSA is the solvent, 3.2 equiv of phosphorus trichloride should be used as the P-reagent without any phosphorous acid.

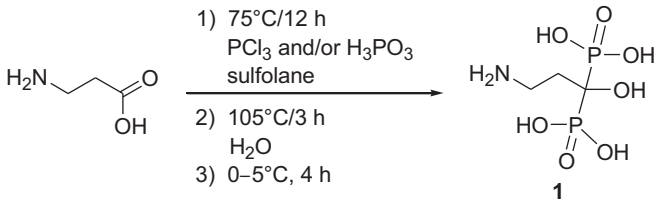
Not much is known about the mechanism of the reaction of carboxylic acids with P-reagents to afford dronic acids/dronates. However, there are interesting hints and ideas given by Lecouvey and Leroux on mechanistic aspects [23]. They also proposed that the first intermediate may be the acid chloride formed from the carboxylic acid by a reaction with phosphorus trichloride. This was proved by us experimentally [24]. It was a valuable observation of the French authors that phosphorous acid does not react with the carboxylic acid in itself, only if it was "partially replaced" by phosphorus trichloride. However, the exact and optimum ratio was not proposed and no explanation was given how the reaction takes place. The role of different solvents should also be considered. It can be said that not less important questions remained unanswered.

We now wished to study the preparation of pamidronic acid/pamidronate from β-alanine and P-reagents using sulfolane or MSA as the solvent. We were also interested in exploring further mechanistic details [24].

RESULTS AND DISCUSSION

The Synthesis of Pamidronate in Sulfolane

First, we wished to study the preparation of pamidronic acid (**1**) from β-alanine, phosphorus trichloride, and phosphorous acid using sulfolane as the solvent in details. The synthesis was carried out at 75°C for 12 h applying the P-reagents in different ratios. The reaction was followed by hydrolysis and crystallization (Scheme 1). Experimental data are listed in Table 1. When phosphorous acid or phosphorus trichloride was used alone in a quantity of 3.2 equiv, no pamidronate was formed (Table 1, entries 1 and 7). Applying phosphorus trichloride and phosphorous acid in ratios of 1:2 and 2:1, the yield was 44% and 42%, respectively (Table 1, entries 2 and 3). The outcome was the best, when phosphorus trichloride and phosphorous acid were measured in a ratio of 2:2. In this instance, the yield of dronic acid **1** was 63% (Table 1, entry 4). Modifying the 2:2 ratio to 3.2:2, the yield of compound **1** dropped to 55% (Table 1, entry 5), while a ratio of 3.2:1 led to even a lower yield of 34% (Table 1, entry 6). In all cases, completely pure or almost entirely pure (99%) product was obtained.

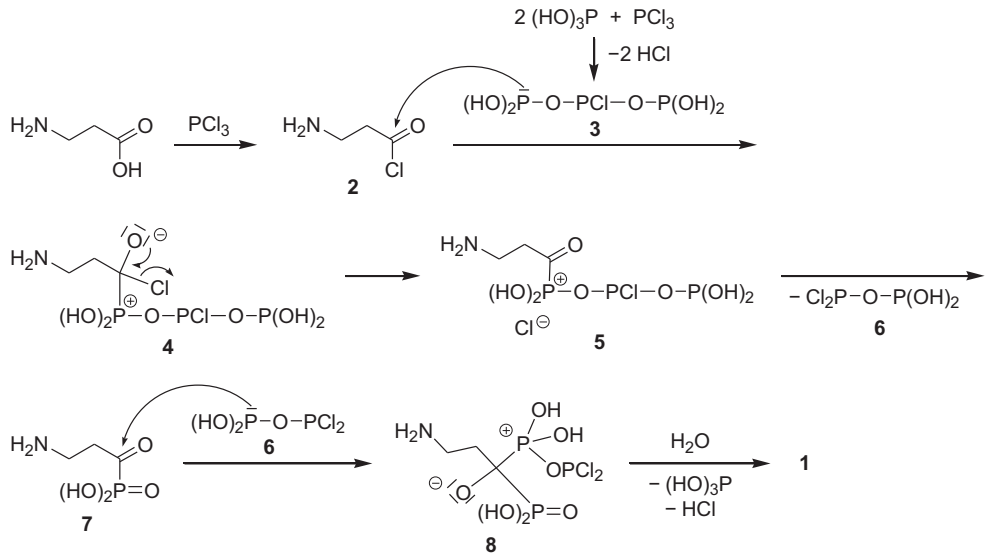


SCHEME 1

TABLE 1 Synthesis of Pamidronic Acid (**1**) from β-Alanine in Sulfolane Using Phosphorus Trichloride and Phosphorous Acid in Different Ratios

	Reactants			
Entry	*PCl_3 (equiv)*	*H_3PO_3 (equiv)*	*Purity[a] (%)*	*Yield of **1**[a,b] (%)*
1	0	3.2	0	0
2	1	2	99	44
3	2	1	99	42
4	2	2	100	63
5	3.2	2	100	55
6	3.2	1	99	34
7	3.2	0	–	0

[a]On the basis of potentiometric titration.
[b]From at least two parallel experiments.

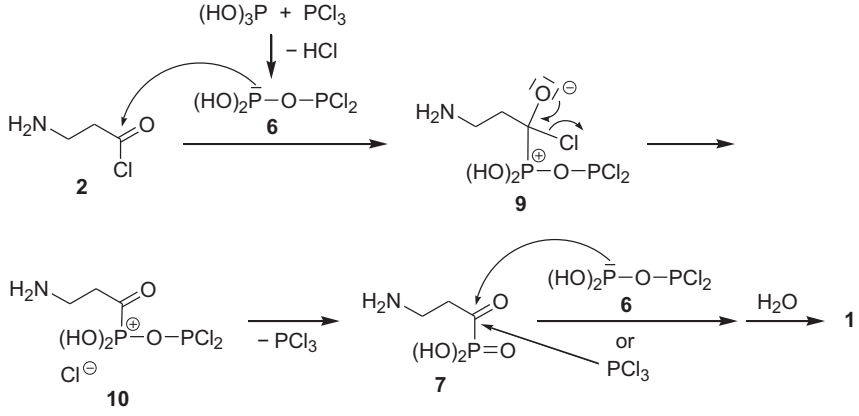


SCHEME 2

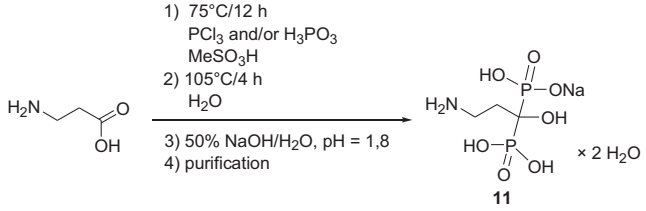
It is quite surprising that phosphorus trichloride did not react with β-alanine in sulfolane. Using MSA as the solvent, phosphorus trichloride was reactive [18, 20–22]. It is also noteworthy that the best yield (63%) was achieved at the 2:2 molar ratio of phosphorus trichloride and phosphorous acid. How can it be explained? A rational explanation may be that in the first step, β-alanine is converted to the appropriate acid chloride (**2**) by reaction with 1 equiv of phosphorus trichloride. The remaining phosphorus trichloride may react with the 2 equiv of phosphorous acid to furnish $(HO)_2P–O–PCl–O–P(OH)_2$ (**3**) that may react with the acid chloride (**2**) giving adduct **4** and then intermediate **5** that provides ketophosphonic acid **7** and $Cl_2P–O–P(OH)_2$ (**6**). Interaction of the latter two species **6** and **7** may lead to a second adduct **8**, whose hydrolysis may furnish pamidronic acid **1**, as well as phosphorous acid and hydrochloric acid as the by-products (Scheme 2).

If phosphorus trichloride and phosphorous acid are applied in a ratio of 3:2, then the 2 equiv of phosphorus trichloride that remains after the formation of the acid chloride (**2**) may react with the 2 equiv of phosphorous acid to give $Cl_2P–O–P(OH)_2$ (**6**). This P-nucleophile may also react with acid chloride **2** to afford adduct **9** and then intermediate **10**, whose stabilization leads to ketophosphonic acid **7** and phosphorus trichloride. Species **7** may then react with another unit of $(HO)_2P–O–PCl_2$ (**6**) or with phosphorus trichloride to provide dronic acid **1** after hydrolysis of the second adduct that was not shown in detail (Scheme 3).

Comparing the yields (55% vs. 63%), the reaction sequence shown in Scheme 3 seems to be somewhat less efficient than the other one shown in Scheme 2.



SCHEME 3



SCHEME 4

According to a literature method [17], applying sulfolane as the solvent along with phosphorus trichloride and phosphorous acid in a 3.4 equiv and a 1.5 equiv quantity, respectively, the yield of pure pamidronic acid (**1**) was claimed to be 63%, but no criterion of purity was provided. Our reproduction at the given molar ratio led to a yield of only 44% in a pure form. The purity was supported by potentiometric titration and NMR spectra. The yield of 44% is in accord with the fact that the molar ratio described earlier [17] is not optimal.

The Synthesis of Pamidronate in MSA

Recalling our general method elaborated for the synthesis of dronates, we wished to apply this also to the preparation of pamidronate (**11**). In these experiments, the solvent was MSA instead of sulfolane. The effect of the molar ratios of phosphorus trichloride and phosphorous acid on the outcome was investigated in reactions carried out at 75°C for 12 h. The reaction was followed by hydrolysis, pH adjustment, digestion in MeOH, treatment by MeOH in water at pH 5.5–6, and another digestion in MeOH (Scheme 4). Experimental details are listed in Table 2.

Using phosphorous acid alone, there was no reaction (Table 2, entry 1). When 1.1 equiv of phosphorus trichloride was applied together with 2.2 equiv of phosphorous acid, the yield of the monosodium salt of pamidronic acid dihydrate (pamidronate dihydrate, **11**) was very low (3%) and the purity was also insufficient (Table 2, entry 2). Increasing the proportion of the phosphorus trichloride to 2.2 equiv and adding 1.1 or 2.2 equiv of phosphorous acid to the mixture, the yield of the product (**11**) was 28% and 27%, respectively, with a purity of 97/96% (Table 2, entries 3 and 4). The best results were obtained when 3.2 equiv of the phosphorus trichloride was used as the only reagent. In this case, the yield of pamidronate dihydrate was 57% and the purity was 99% (Table 2, entry 5).

TABLE 2 Synthesis of Pamidronate Dihydrate (**11**) from β-Alanine in MSA Using Phosphorus Trichloride and Phosphorous Acid in Different Ratios

	Reactants			
Entry	*PCl_3 (equiv)*	*H_3PO_3 (equiv)*	*Purity[a] (%)*	*Yield of **11**[a,b] (%)*
1	0	3.2	0	0
2	1.1	2.2	58	3
3	2.2	1.1	97	28
4	2.2	2.2	96	27
5	3.2	0	99	57

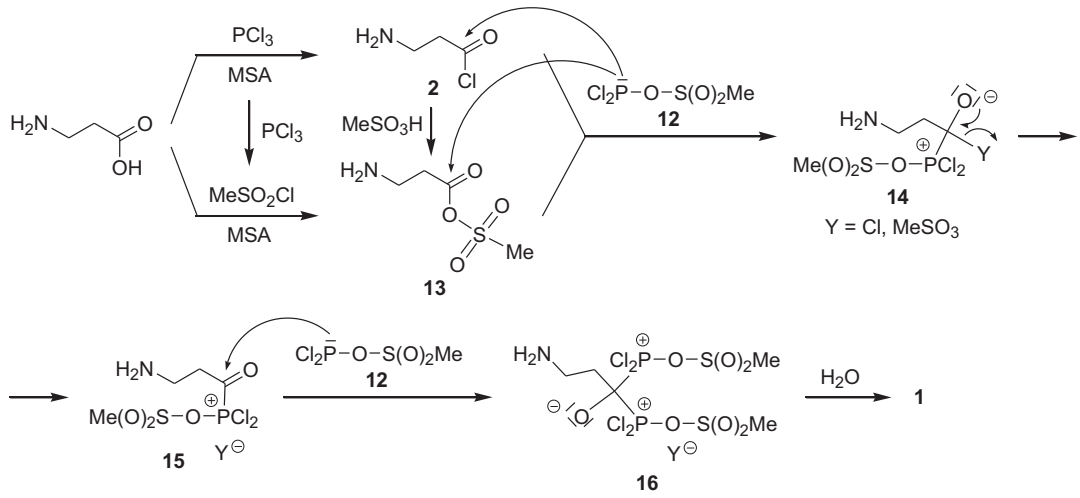
[a]On the basis of potentiometric titration.
[b]From at least two parallel experiments.

It is a noteworthy experience that phosphorus trichloride was not of enough reactivity in sulfolane as the solvent; however, using MSA as the solvent, the best results were obtained with phosphorus trichloride alone (without phosphorous acid). It is possible that phosphorus trichloride is more reactive in the more polar solvent of MSA. It is, however, more probable that phosphorus trichloride forms an anhydride with MSA that can be formulated as Cl_2P–O–$S(O)_2Me$ (**12**). Considering also that in the first step not only an acid chloride (**2**), but a mixed anhydride (**13**) may also be formed (the latter in two ways, either via **2** or by the reaction of β-alanine with $MeSO_2Cl$), the reaction sequence represented by Scheme 5 may be proposed. Then, the carbonyl carbon of species **2** and **13** is attacked by the P atom of mixed anhydride **12** to furnish adduct **14** that is stabilized by the loss of $Y^{\ominus}$ (that is $Cl^{\ominus}$ or $MeSO_3^{\ominus}$). α-Keto intermediate **15** so formed reacts then with another unit of the mixed anhydride **12** to give adduct **16**, and after hydrolysis pamidronic acid **1** that is transformed to its sodium salt dihydrate (**11**) by pH adjustment. It is also possible that intermediate **15** is somehow stabilized before the attack of a second unit of Cl_2P–O–$S(O)_2Me$ (**12**).

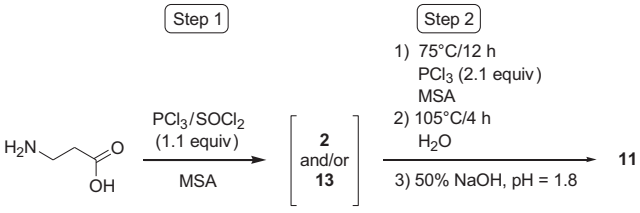
In a separate experiment, MSA and 1 equiv of phosphorus trichloride were stirred in an ethereal solution at 26°C. After a reaction time of 6 h, ^{31}P NMR analysis revealed a signal at δ_P 178.3 ($CDCl_3$) that may support the structure Cl_2P–O–SO_2Me, and hence its intermediacy in the above reaction. The predicted ^{31}P NMR chemical shift was δ_P 179.3 $\pm$ 5.4 using ACD/Chem Sketch software version 4.55/2002.

The reaction sequence shown in Scheme 5 may be of general value, and hence may be valid for the formation of other dronic acids as well. In this sense, the mechanism proposed for the formation of zoledronate and risedronate must be refined [18].

Then, we wished to prove the first and second step of the mechanism suggested in Scheme 5. For this, the optimized synthesis of pamidronate dihydrate **11** was accomplished in two steps: reacting β-alanine first with 1.1 equiv of phosphorus trichloride or with thionyl chloride at 26°C for 4 h, and then



SCHEME 5



SCHEME 6

TABLE 3 Preparation of Pamidronate Dihydrate (**11**) in Two Steps Using Different Reactants

Entry	*Inorganic Halide (1.1 equiv)*	*Reactant (2.1 equiv)*	*Purity[a] (%)*	*Yield of **11**[a,b] (%)*
1	PCl_3	PCl_3	91	37
2	PCl_3	H_3PO_3	96	4
3	$SOCl_2$	PCl_3	97	37
4	$SOCl_2$	H_3PO_3	0	0

[a]On the basis of potentiometric titration.
[b]From at least two parallel experiments.

with 2.1 equiv of phosphorus trichloride at 75°C for 12 h. In both steps, MSA was the solvent. The reaction sequence is shown in Scheme 6, whereas the experimental data are listed in Table 3.

It can be seen that using either phosphorus trichloride or thionyl chloride in the first step and then phosphorus trichloride in the second step, dronate dihydrate **11** was obtained in a yield of 37% (Table 3, entries 1 and 3). Using, however, phosphorous acid in the second step, the yield of product **11** was only, in the best case, 4% (Table 3, entries 2 and 4). It can be seen that phosphorous acid is not nucleophilic enough to participate in the dronate-forming reaction. It can be also concluded that the two-step variation is less efficient than the other version, reacting the components all at once (57% vs. 37%, Table 2, entry 5 vs. Table 3, entry 1). However, the intermediacy of acid chloride **2** and mixed anhydride **13** was confirmed by these experiments.

It should be mentioned that the optimized syntheses may afford pamidronic acid (**1**) in a yield of 63% or sodium pamidronate dihydrate (**11**) in a yield of 57%. Both products were obtained in a pure form. In the context of literature data, our yields are reasonable.

In summary, the synthesis of pamidronic acid and sodium pamidronate was investigated and optimized using sulfolane and MSA, respectively, as the solvent at 75°C. Novel mechanisms were suggested on the basis of the optimum set and molar ratio of the P-reactants. Hence, in sulfolane, $(HO)_2P$–O–PCl–O–$P(OH)_2$ or $(HO)_2P$–O–PCl_2 may be the P-nucleophile, while in MSA, Cl_2P–O–$S(O)_2Me$ may be the active species reacting further with the first acid chloride intermediate whose presence was proved by separate two-step syntheses. Our results provide a better understanding of the formation of dronates in the reaction of carboxylic acids and P-reagents and make possible to select the optimum conditions. This is the first case that the role of the solvent was pointed out in the selection of the suitable set of the P-reagents and in the course of the reaction.

EXPERIMENTAL

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 pamidronate content of the samples was determined

by potentiometric acid–base titrations on a Mettler DL77 potentiometric titrator.

The titration curve for pure pamidronic acid (**1**) synthesized by us (Table 1, entry 4) and the monosodium salt of pamidronic acid (**11**) obtained by the reaction (Table 2, entry 5) is shown in Figs. 1 and 2, respectively.

*Preparation of Pamidronic Acid (**1**) in Sulfolane (Table 1, Entry 4)*

β-Alanine (2.2 g, 0.025 mol) and phosphorous acid (4.1 g, 0.050 mol) were added to 8.0 mL of sulfolane on stirring. Then, 4.4 mL (0.050 mol) of phosphorus trichloride was added dropwise in ca. 15 min, and the contents of the flask were stirred at 75°C for 3 h. After cooling the mixture to 0–5°C, 22.3 mL (1.2 mol) of water was added and the mixture was stirred further at 105°C for 3 h. Then, the mixture was cooled to 0–5°C and stirred for 4 h. The precipitation was removed by filtration. 3.7 g (63%) of pamidronic acid (**1**) was obtained in a purity of 100%. ^{31}P NMR (D_2O) δ: 17.6, δ [25]: 16.8; ^{13}C NMR (D_2O) δ: 75.3 (t, J = 133.0, PCP), 39.0 (t, J = 7.7, NCH_2CH_2), 33.3 (s, NCH_2), δ [25]: 72.3 (t, J = 134.8, PCP), 36.1 (s, NCH_2CH_2), 31.2 (s, NCH_2).

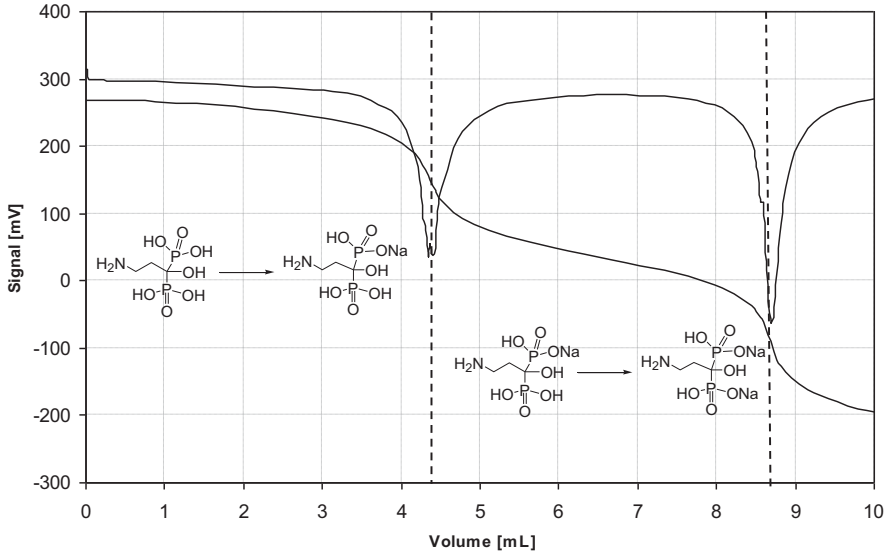


FIGURE 1 Titration curve for pure pamidronic acid (**1**) obtained by the reaction presented in Table 1 (entry 4).

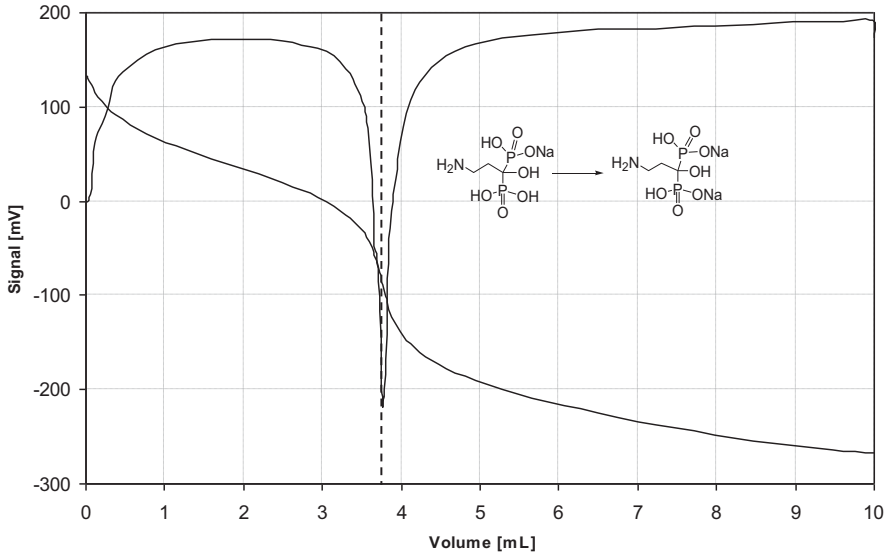


FIGURE 2 Titration curve for the monosodium salt of pamidronic acid (**11**) obtained by the reaction presented in Table 2 (entry 5).

*Preparation of Pamidronic Acid (**1**) in Sulfolane According to the Literature Method*

β-Alanine (2.2 g, 0.025 mol) and phosphorous acid (3.1 g, 0.034 mol) were added to 8.0 mL (3.4 mol) of sulfolane on stirring. Then, 7.4 mL (0.085 mol) of phosphorus trichloride was added dropwise in ca. 15 min, and the contents of the flask were stirred at 75°C for 3 h. After cooling the mixture to 0–5°C, 22.3 mL (1.2 mol) of water was added and the clear solution was stirred further at 105°C for 3 h in the presence of 0.5 g of activated carbon. Then, the mixture was filtered and the filtrate was cooled to 0–5°C and stirred for 4 h. The precipitation was removed by filtration. Repeating the experiment three times, 2.5 g (44%) of pamidronic acid (**1**) was obtained as an average in a purity of 100%. ^{31}P NMR (D_2O) δ: 17.6, δ [25]: 16.8 [17].

*Preparation of the Monosodium Salt of Pamidronate (**11**) Starting from β-Alanine in a One-Step Reaction (Table 2, Entry 5)*

β-Alanine (2.2 g, 0.025 mol) was added to 10.5 mL of MSA on stirring. Then, 7.0 mL (0.080 mol) of phosphorus trichloride was added dropwise in ca. 15 min, and the contents of the flask were stirred at 75°C for 24 h. After cooling the mixture to 26°C, 12 mL (0.67 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, the mixture was stirred for 2 h and the precipitate was removed by filtration. The crude product was suspended in 50 mL of methanol and the mixture was digested by stirring at 65°C for 30 min. Then, the solid product was suspended in 18 mL of water, the pH was adjusted to 5.5–6.0, and 50 mL of MeOH was added. The mixture was stirred for 1 h, and the solid phase was filtered off. Another digestion of the solid product in 50 mL of MeOH led to 4.2 g (57%) of pamidronate dihydrate (**11**). ^{31}P NMR (D_2O) δ: 17.7, δ [26]: 18.4, ^{13}C NMR (D_2O) δ: 75.1 (t, $J = 132.7$, PCP), 36.8 (t, $J = 5.3$, NCH_2CH_2), 34.1 (s, NCH_2) δ [26]: 73.1, 36.6, 31.3. TG and DTG thermal examinations revealed the loss of one molecule of water in the range of 162–228°C and the loss of the other molecule of water in the range of 228–282°C in a two-step process.

*Preparation of Pamidronate Monosodium Salt (**11**) Applying Phosphorus Trichloride in a Two-Step Reaction (Table 3, Entry 1)*

β-Alanine (2.2 g, 0.025 mol) was dissolved in 10.5 mL of MSA on stirring. Phosphorus trichloride (2.6 mL, 0.030 mol) was added dropwise and the mixture was stirred at 26°C for 6 h. Then, 4.6 mL (0.053 mol) of phosphorus trichloride was added dropwise and the mixture was stirred at 75°C for 18 h. Furthermore, the process includes hydrolysis and pH adjustment that was performed as described above to afford 13.0 g of crude product. After digestion with MeOH carried out similarly as above, 2.8 g (37%) of pamidronate monosodium salt (**11**) was obtained in a purity of 100%. ^{31}P NMR (D_2O) δ: 17.7, δ [26]: 18.4.

*Preparation of Pamidronate Monosodium Salt (**11**) with Thionyl Chloride and Phosphorus Trichloride in a Two-Step Reaction (Table 3, Entry 3)*

β-Alanine (2.2 g, 0.025 mol) was dissolved in 10.5 mL of MSA on stirring. Thionyl chloride (2.0 mL, 0.027 mol) was added dropwise and the mixture was stirred at 26°C for 6 h. Furthermore, the process includes the second step with phosphorus trichloride, hydrolysis, pH adjustment, and digestion with MeOH was performed as described above to afford 2.7 g (37%) of pamidronate monosodium salt (**11**) in a purity of 100%. ^{31}P NMR (D_2O) δ: 17.7, δ [26]: 18.4.

REFERENCES

[1] Russell, R. G. G. Bone 2011, 49, 2–19.
[2] Russell, R. G. G. Pediatrics 2007, 119, S150–S162.
[3] Breuer, E. In Analogue-Based Drug Discovery; Fischer, J.; Ganelli, C. R. (Eds.); Wiley-VCH: Weinheim, Germany, 2006; Ch. 15.
[4] Widler, L.; Jaeggi, K. A.; Glatt, M.; Müller, K.; Bahmann, R.; Bisping, M.; Born, A.-R.; Cortesi, R.; Guiglia, G.; Jeker, H.; Klein, R.; Ramseier, U.; Schmid, J.; Schreiber, G.; Seltenmeyer, Y.; Green, J. R. J Med Chem 2002, 45, 3721–3738.
[5] Hudson, H. R.; Wardle, N. J.; Blight, S. W. A.; Greiner, I.; Grün, A.; Keglevich, G. Mini-Rev Med Chem 2012, 12, 313–325.
[6] Rogers, M. J.; Frith, J. C.; Luckman, S. P.; Coxon, E. P.; Benford, H. L.; Mönkkönen, J.; Auriola, S.; Chilton, K. M.; Russell, R. G. G. Bone 1999, 24(Suppl.), 73S–79S.
[7] Russell, R. G. G.; Croucher, P. I.; Rogers, M. J. Osteoporosis Int 1999, 9, S66–S80.
[8] Russell, R. G. G.; Rogers, M. J. Bone 1999, 25, 97–106.
[9] Roelofs, A. J.; Thompson, K.; Gordon, S.; Rogers, M. J. Clin Cancer Res 2006, 12, 6222–6230.
[10] Krueger, F.; Bauer, L.; Michel, W. German Patent 2130794; Chem Abstr 1973, 78, 528.
[11] Gore, V. G.; Shukla, V. K.; Ghadge, M. M., Avadhut, R. M. World Patent 2008/4000; Chem Abstr 2008, 148, 100730.
[12] Kieczykowski, G. R.; Jobson, R. B.; Melillo, D. G.; Reinhold, D. F.; Grenda, V. J.; Shinkai, I. J Org Chem 1995, 60, 8310–8312.

[13] Xie Y.; Ding H.; Qian L.; Yan X.; Yang C.; Xie Y. Bioorg Med Chem Lett 2005, 15, 3267–3270.
[14] Mustafa, D. A.; Kashemirov, B. A.; McKenna, C. E. Tetrahedron Lett 2011, 52, 2285–2287.
[15] Patel, V. M.; Chitturi, T. R.; Thennati, R. World Patent 2005/44831 2005; Chem Abstr 142, 463876.
[16] Deshpande, P. B.; Luthra, P. K. World Patent 2007096896 2007; Chem Abstr 145, 511840.
[17] Shinal, E. C. World Patent 2000/34293 2000; Chem Abstr 133, 34404.
[18] Keglevich, G.; Grün, A.; Aradi, K.; Garadnay, S.; Greiner, I. Tetrahedron Lett 2011, 52, 2744–2746.
[19] Garadnay, S.; Grün, A.; Keglevich, G.; Neu, J. World Patent 2012107787 2012; Chem Abstr 157, 356874.
[20] Keglevich, G.; Grün, A.; Kovács, R.; Garadnay, S.; Greiner, I. Curr Org Synth 2013, 10, 640–644.
[21] Kovács, R.; Nagy, D. I.; Grün, A.; Balogh, G. T.; Garadnay, S.; Greiner, I.; Keglevich, G. Lett Drug Des Discovery 2013, 10, 733–737.
[22] Grün, A.; Kovács, R.; Nagy, D. I.; Garadnay, S.; Greiner, I.; Keglevich, G. Lett Org Chem 2014, 11, 368–373.
[23] Lecouvey, M.; Leroux, Y. Heteroatom Chem 2000, 11, 556–561.
[24] Keglevich, G.; Grün, A.; Kovács, R.; Koós, K.; Szolnoki, B.; Garadnay, S.; Neu, J.; Drahos, L.; Greiner, I. Lett Drug Des Discovery 2012, 9, 345–351.
[25] Guénin, E.; Monteil, M.; Bouchemal N.; Prangé T.; Lecouvey, M. Eur J Org Chem 2007, 3380–3391.
[26] Lenin, R.; Raju, R. M.; Rao, D. V. N. S.; Ray, U. K. Med Chem Res 2013, 22, 1624–1629.