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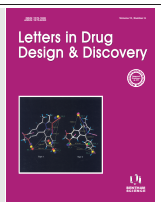

Efficient Synthesis of Pamidronic Acid Using an Ionic Liquid Additive

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Abstract: An efficient method was developed for the synthesis of pamidronic acid involving the reaction of *β*-alanine with three equivalents of phosphorus trichloride and two equivalents of phosphorous acid at 75 °C in the presence of 0.3 or 0.6 equivalents of [BMIM][PF_6] as an additive.

Keywords: Pamidronic acid, best synthesis, additive, ionic liquids, intermediate.

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1. INTRODUCTION

1-Hydroxy-1,1-bisphosphonic acid derivatives are of importance due to their activity against bone diseases, like osteoporosis, hypercalcemia, osteolyc metastases and the Paget's 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].

The pamidronic acid is a second generation hydroxymethylenebisphosphonic acid that was synthetized from *β*-alanine in various solvents (*e.g.* sulfolane, chlorobenzene, methanesulfonic acid (MSA) *etc.*), using, in most cases, phosphorus trichloride and/or phosphorous acid as the P-reagent, but phosphorus oxychloride was applied as well. The reaction temperature changed between 65–130 °C, while the reaction time fell in the range of 1-20 hours.

As the first case, *β*-alanine was reacted with 1.5 equivalents of phosphorus trichloride and the same amount of phosphorous acid at 132 °C in chlorobenzene, and the pure dronic acid was obtained in a yield of 59% [10]. Pamidronic acid was synthesized applying phosphorus trichloride and phosphorous acid in a molar ratio of 2:1.5 without any solvent. The yield was 61% [11]. Monosodium pamidronate was prepared in a yield of 60% from *β*-alanine using 2 equivalents of phosphorus trichloride and 1.5 equivalents of phosphorous acid at 70–75 °C in acetonitrile [12]. The synthesis was also carried out in MSA, and the yield was 57% [13-14]. The best yield (72%), was achieved by applying 3 equivalents of phosphorus trichloride and 3 equivalents of phosphorous acid at 65 °C in sulfolane [15]. Carrying out the reaction under microwave conditions at 65 °C for 3 min, McKenna *et al.* obtained sodium pamidronate in a yield of 64% [15].

In our earlier work, we studied the formation of pamidronic acid and sodium pamidronate from *β*-alanine at 75 °C using sulfolane and MSA as the solvent, respectively. The optimum molar ratio of phosphorus trichloride and phosphorous acid was 2:2 in sulfolane, and 3.2:0 in MSA. The optimized syntheses resulted in the formation pure pamidronic acid and sodium pamidronate in a yield of 63% and 57%, respectively [16]. We suggested a novel mechanism for the formation of pamidronic acid, which was based on the optimum molar ratio of the P-reactants. Hence, in sulfolane, $(HO)_2$P-O-PCl-O-P$(OH)_2$ or $(HO)_2$P-O-PCl_2 may be the P-nucleophile, while in MSA, Cl_2P-O-SO_2Me may be the active species reacting with the first acid chloride or anhydride type intermediates [16].

To date, just De Ferra and co-workers have employed ionic liquid (IL) (Bu_3N•HCl) as the solvent in the synthesis of pamidronate. *β*-Alanine was reacted with 2 equivalents of phosphorus trichloride and 1 equivalent of phosphorous acid at 65 °C for 2 h. The pure dronate was obtained in a low yield (26%) [17].

In most cases, MSA was used as the solvent in the synthesis of dronic acid derivatives. However, it is not a green solvent, and during the pH adjustment, it reacts with NaOH, and generates sodium mesylate, which is difficult to remove. The sulfolane is also a problematic solvent due to its price and disadvantageous properties (viscosity, hygroscopicity and melting point). ILs are regarded to be green solvents, and have low vapor pressure, high thermal stability, and can be recycled or reused. However, ILs were described only in one instance as the solvent in the synthesis of dronic acid derivatives [17]. It was a challenge for us to evaluate the role of ILs in the synthesis of pamidronic acid that is a suitable model. It is also an option to apply the ILs in a smaller quantity as a catalyst or as an additive. A number of examples are known, where ILs have been used as efficient catalysts [18-20].

2. RESULTS AND DISCUSSION

The preparation of pamidronic acid (**2**) and its salt from β-alanine (**1**) and P-reagents was found to be a good model reaction in our earlier studies [16]. For this, we decided to choose this model to investigate the possibility of applying

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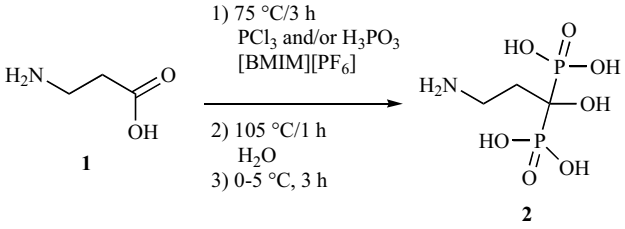
Table 1. Preparation of Pamidronic Acid (2) Using Phosphorus Trichloride (2 equivalents) and Phosphorous Acid (2 equivalents) in Different Amounts of [BMIM][PF_6] as the Solvent.

Entry	Amount of [BMIM][PF_6]		Purity[a,b] (%)	Yield of 2[b]
	mL	equiv.		
1	10	2	>99	42
2	3	0.6	>99	70
3	1.5	0.3	>99	71
4	1	0.2	>99	65
5	0.5	0.1	>99	64
6	0	0	>99	44
7[c] [11]	0	0	no data	61

[a]On the basis of potentiometric titration.
[b]From at least two parallel experiments.
[c]Using 2 equivalents of phosphorus trichloride and 1.5 equivalents of phosphorous acid.



Scheme (1).

ionic liquids as solvent, or only as additive in the synthesis of dronic acid derivatives. Phosphorus trichloride and phosphorous acid were applied in different ratios as the P-reactants. In the first approach, 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]) was chosen as the ionic liquid to be tested. Heating at 75 °C for 3 h on intensive stirring was followed by hydrolysis at 105 °C for 1 h. Then, pamidronic acid (**2**) precipitated on cooling. The purification involved digestion in methanol (Scheme **1**).

First, the effect of the quantity of the IL chosen was evaluated. The results are summarized in Table **1**. It was found that decreasing the quantity of the IL from 10 mL to 3 mL, 1.5 mL, 1 mL, 0.5 mL and finally to 0 mL, the yields of pamidronic acid followed a function going through maximum, and were 42%, 70%, 71%, 65%, 64% and 44%, respectively (Table **1**/Entries 1-6). In the absence of any solvent using 2 equivalents of phosphorus trichloride and 1.5 equivalents phosphorous acid at 100 °C for 4 h, the yield reported was 61%, however, no data on the purity was provided [11]. It can be concluded that it is not advisable to use [BMIM][PF_6] as the solvent. The application of a quantity of only 0.6 or 0.3 equivalents is more appropriate. Hence, it is better to measure in the IL as an additive and not as the solvent.

Accepting the "message" of the previous experiments that it is better to use only 0.3 or 0.6 equivalents of

Table 2. Synthesis of Pamidronic Acid (2) from *β*-Alanine (1) in the Presence of 3 mL (0.6 equivalents) of [BMIM][PF_6] Using Phosphorus Trichloride and Phosphorous Acid in Different Ratios.

Entry	Reactants		Purity (%)[a,b]	Yield of 2[b]
	PCl_3 (equiv.)	H_3PO_3 (equiv.)		
1	0	3	-	0
2	1	1	>99	41
3	1	2	>99	37
4	2	1	>99	49
5	2	2	>99	70
6	3	0	-	0
7	3	1	>99	41
8	3	2	>99	72

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

[BMIM][PF_6], we sought to find the best quantity and molar ratio of phosphorus trichloride and phosphorous acid. The results obtained in the presence of 3 mL (0.6 equivalents) of [BMIM][PF_6] are listed in Table **2**. It can be seen that using phosphorus trichloride or phosphorous acid alone, there was no formation of pamidronic acid (Table **2**/Entries 1 and 6). Applying phosphorus trichloride and phosphorous acid in a ratio of 1:1, 1:2, 2:1 and 2:2, the yields of the target dronic acid (**2**) were 41%, 37%, 49% and 70%, respectively (Table **2**/Entries 2-5). The use of 3 equivalents of phosphorus trichloride together with 1 or 2 equivalent(s) of phosphorous acid led to a yield of 41% and 72%, respectively (Table **2**/Entries 7 and 8). In all cases, pure pamidronic acid was formed according to the titrations. One may conclude that the molar ratios of 2:2 and 3:2 are the most advantageous in respect of phosphorus trichloride and phosphorous acid. In these cases, the yields exceeded 70%.

The next series of experiments was carried out in the presence of 1.5 mL (0.3 equivalents) of [BMIM][PF_6]. The tendency was exactly the same that was observed using twice as much IL (Table **3**). The best results (70/71% yield) were obtained using phosphorus trichloride and phosphorous acid in a ratio of 2:2 and 3:2 (Table **3**/Entries 4 and 6).

The reacting species that was added to the C=O group of *β*-alanine is obviously Cl_2P-O-P$(OH)_2$.

It can be concluded that it is enough to use [BMIM][PF_6] as an additive in a quantity of 0.3 or 0.6 equivalents, and the best is, when phosphorus trichloride and phosphorous acid are applied in a ratio of 2:2 or 3:2. The novel method afforded pamidronic acid in better yields, than the earlier procedures [16].

Although the use of 0.3 or 0.6 equivalents of [BMIM][PF_6] was rather efficient both at a 2:2 or 3:2 molar ratio of phosphorus trichloride and phosphorous acid, we wished to try out a few other ILs such as, 1-butyl-3-

Table 3. Synthesis of Pamidronic Acid (2) from *β*-Alanine (1) in the Presence of 1.5 mL (0.3 equivalents) of [BMIM][PF_6] Using Phosphorus Trichloride and Phosphorous Acid in Different Ratios.

Entry	Reactants		Purity (%)[a]	Yield of 2[b]
	PCl_3 (equiv.)	H_3PO_3 (equiv.)		
1	1	1	>99	42
2	1	2	>99	35
3	2	1	>99	47
4	2	2	>99	71
5	3	1	>99	41
6	3	2	>99	70

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

methylimidazolium chloride ([BMIM][Cl]), 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF_4]), and 1-ethyl-3-methylimidazolium ethanesulfonate ([EMIM][$EtSO_3$]). The results are summarized in Table **4**. For comparison purposes, the relevant results obtained with the use of [BMIM][PF_6] are also included.

It can be seen that the yields of dronic acid **2** were lower in all cases applying ILs other than [BMIM][PF_6]. Using 0.3 equivalents of [BMIM][BF_4] and [BMIM][Cl] together with a molar ratio of 3:2 of phosphorus trichloride and phosphorous acid, the yield of product **2** was 61% and 33%, respectively (Table **4**/Entries 2 and 3), as compared to the outcome of 70% obtained with [BMIM][PF_6] under similar conditions (Table **4**/Entry 1). Similarly, measuring [BMIM][Cl] or [EMIM][$EtSO_3$], and applying the P-reagents in a 2:2 molar ratio, the yield of dronic acid **2** was 40% and 48%, respectively, that is lower than the yield of 70% obtained with [BMIM][PF_6] (Table **4**/Entries 4-6). As can be seen, indeed, [BMIM][PF_6] is the best choice for an IL to be used as catalyst in our model reaction.

3. SUMMARY

It was found that the synthesis of pamidronic acid from *β*-alanine and P-reagents, like phosphorus trichloride and phosphorous acid may be advantageously carried out in the presence of [BMIM][PF_6] as an additive. Hence, using the above components in a molar ratio of 1:2:2:0.3, after a reaction at 75 °C for 3 h, the product was obtained in a yield of 71%.

4. EXPERIMENTAL

4.1. General

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

The titration curve for pure pamidronic acid (**2**) synthesized by us (Table **2**/Entry 8) is shown in Fig. (**1**).

4.2. Typical Procedure for the Preparation of Pamidronic Acid (2) from β-Alanine (1), Phosphorous Trichloride and Phosphorous Acid in the Presence of [BMIM][PF_6] (Table 2/Entry 8)

2.2 g (0.025 mol) of *β*-Alanine (**1**) and 4.3 g (0.053 mol) phosphorous acid were added into 3 mL (0.015 mol) of 1-butyl-3-methylimidazolium hexafluorophosphate on stirring. Then, 7 mL (0.080 mol) of phosphorous trichloride was added dropwise in *ca*. 30 min, and the contents of the flask were stirred at 75 °C for 3 h. After cooling the mixture to 26 °C, 10 mL (0.53 mol) of water was added and the mixture was stirred further at 105 °C for 1 h. Then, the mixture was stirred at 26 °C for 12 h, and finally at 0-5 °C for 3 h. The precipitate was removed by filtration to give ~5 g of the crude product that was suspended in 15 mL of methanol, and the mixture was digested by stirring at 65 °C for 30 min. The solid product was filtered off to furnish 4.2 g (72%) of pamidronic acid (**2**) in a purity of >99%. ^{31}P NMR (D_2O) δ: 17.6, δ [16]: 17.6; ^{13}C NMR (D_2O) δ: 72.8 (t, J = 132.8,

Table 4. The Effect of Different ILs on the Synthesis of Pamidronic Acid (2) from *β*-Alanine (1) Using Phosphorus Trichloride and Phosphorous Acid.

Entry	Type of IL	Quantity of IL	Reactants		Purity (%)[a]	Yield of 2[b]
			PCl_3 (equiv.)	H_3PO_3 (equiv.)		
1	[BMIM][PF_6]	0.3	3	2	>99	70
2	[BMIM][BF_4]	0.3	3	2	>99	61
3	[BMIM][Cl]	0.3	3	2	>99	33
4	[BMIM][PF_6]	0.6	2	2	>99	70
5	[BMIM][Cl]	0.3	2	2	>99	40
6	[EMIM][$EtSO_3$]	0.6	2	2	>99	48

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

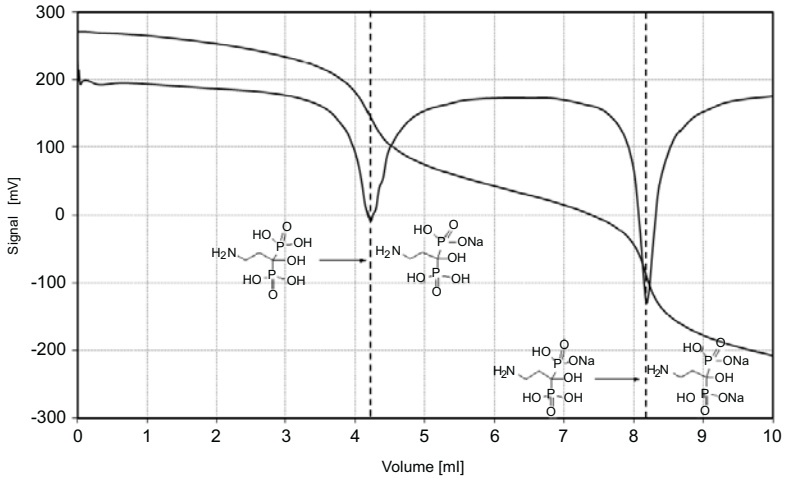


Fig. (1). Titration curve for pure pamidronic acid (**2**) obtained by the reaction presented in Table **2**/Entry 8.

PCP), 36.5 (t, J = 7.5, NCH_2CH_2), 30.8 (s, NCH_2), δ [16]: 75.3 (t, J = 133.0, PCP), 39.0 (t, J = 7.7, NCH_2CH_2), 33.3 (s, NCH_2).

CONFLICT OF INTEREST

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

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REFERENCES

[1] Russell, R. G. G. Bisphosphonates: The first 40 years. *Bone*, **2011**, *49*, 2-19.

[2] Russell, R. G. G. Bisphosphonates: Mode of action and pharmacology. *Pediatrics*, **2007**, *119*, S150-S162.

[3] Breuer, E. The development of bisphosphonates as drugs, In *Analogue-Based Drug Discovery*; Fischer, J.; Ganelli, C. R. (Eds.); Wiley: 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. Highly potent geminal bisphosphonates. From pamidronate disodium (Aredia) to zoledronic acid (Zometa). *J. Med. Chem.*, **2002**, *45*, 3721-3738.

[5] Hudson, H. R.; Wardle, N. J.; Blight, S. W. A.; Greiner, I.; Grün, A.; Keglevich, G. *N*-Heterocyclic dronic acids; applications and synthesis. *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. Molecular mechanisms of action of bisphosphonates. *Bone*, **1999**, *24*(Suppl.), 73S-79S.

[7] Russell, R. G. G.; Croucher, P. I.; Rogers, M. J. Bisphosphonates: pharmacology, mechanisms of action and clinical uses. *Osteoporosis Int.*, **1999**, *9*, S66-S80.

[8] Russell, R. G. G.; Rogers, M. J. Bisphosphonates: from the laboratory to the clinic and back again. *Bone*, **1999**, *25*, 97-106.

[9] Roelofs, A. J.; Thompson, K.; Gordon, S.; Rogers, M. J. Molecular mechanisms of action of bisphosphonates: Current status. *Clin. Cancer. Res.*, **2006**, *12*, 6222-6230.

[10] Krueger, F.; Bauer, L.; Michel, W. 1-Hydroxy-3-aminopropane-1,1-diphosphonic acid – prepn. from beta-alanine and phosphorus trihalide, used as complexant. *DE2130794*; *Chem. Abstr.*, **1973**, *78*, 528.

[11] Zhibo, Q.; Xiaolan, C.; Chen, Q.; Lingbo, Q.; Jinwei, Y.; Donghui, W.; Huina, L.; Xiaoying, H.; Yuqin, J.; Yufen, Z. Fragmentation pathways of eight nitrogen-containing bisphosphonates (BPs) investigated by ESI-MS^n in negative ion mode. *Int. J. Mass. Spectrom*., **2010**, *295*, 85-93.

[12] Gore, V. G.; Shukla, V. K.; Ghadge, M. M.; Avadhut, R. M. Novel process for the preparation of bisphosphonic acids. *WO2008004000*; *Chem. Abstr.*, **2008**, *148*, 100730.

[13] Kieczykowski, G. R.; Jobson, R. B.; Melillo, D. G.; Reinhold, D. F.; Grenda, V. J.; Shinkai, I. Preparation of (4-amino-1-hydroxybutylidene)bisphosphonic acid sodium salt, MK-217 (alendronate sodium). An improved procedure for the preparation of 1-hydroxy-1,1-bisphosphonic acids. *J. Org. Chem.*, **1995**, *60*, 8310–8312.

[14] Xie Y.; Ding H.; Qian L.; Yan X.; Yang C.; Xie Y. Synthesis and biological evaluation of novel bisphosphonates with dual activities on bone in vitro. *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 3267–3270.

[15] Mustafa, D. A.; Kashemirov, B. A.; McKenna, C. E. Microwave-assisted synthesis of nitrogen-containing 1-hydroxymethylenebisphosphonate drugs. *Tetrahedron Lett.*, **2011**, *52*, 2285-2287.

[16] Kovács, R.; Grün, A.; Németh, O.; Garadnay, S.; Greiner, I.; Keglevich, G. The synthesis of pamidronic derivatives in different solvents: An optimization and a mechanistic study. *Heteroatom Chem.*, **2014**, *25*, 186-193.

[17] De Ferra, L.; Turchetta. S.; Massardo, P.; Casellato, P. Preparation of biphosphonic acids and salts thereof. *WO2003093282*, **2003**.

[18] Martínez-Palou, R. J. Ionic liquid and microwave-assisted organic synthesis: A "green" and synergic couple. *Mex. Chem. Soc.*, **2007**, *51*, 252-264.

[19] Zhang, Q.; Zhang, S.; Deng, Y. Recent advances in ionic liquid catalysis. *Green Chem.*, **2011**, *13*, 2619-2637.

[20] Olivier-Bourbigou, H.; Magna, L.; Morvan, D. Ionic liquids and catalysis: Recent progress from knowledge to applications. *Appl. Catal. A.*, **2010**, *373*, 1-56.