Received: 18 October 2016 | Revised: 14 February 2017

DOI: 10.1002/hc.21370

RESEARCH ARTICLE

WILEY Heteroatom Chemistry

Investigation of the effect of medium in the preparation of alendronate: till now the best synthesis in the presence of an ionic liquid additive

Dávid Illés Nagy[1] | **Alajos Grün**[1] | **Sándor Garadnay**[2] | **István Greiner**[2] | **György Keglevich**[1]

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

[2]Gedeon Richter Plc., Budapest, Hungary

Correspondence
György Keglevich, Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest, Hungary.
Email: gkeglevich@mail.bme.hu

Funding information
Hungarian Research Development and Innovation Fund, Grant/Award Number: K119202

Abstract

The synthesis of the drug alendronate from γ-aminobutyric acid and phosphorus trichloride/phosphorous acid as the P-reagents is revisited using methanesulfonic acid and sulfolane as solvents and ionic liquids (ILs) as additives according to a novel approach. Besides elaborating efficient synthetic methods with a record yield of up to 80%, the misleading literature data were also clarified. It is a novel trend to use ILs as only catalysts or additives and not as solvents.

1 | INTRODUCTION

Alendronate is a prominent representative of hydroxymethylenebisphosphonic acid derivatives (dronic derivatives) used in the treatment of bone diseases, such as osteoporosis, Paget disease and tumor-induced hypercalcemia, but direct antitumor and antiparasitic activity were also detected.[1-6] It is known that the two phosphonic groups are capable of forming complex with calcium ions. Depending on their side chain, the bisphosphonates may belong to three generations of dronic derivatives. The first generation of dronic derivatives does not bear a nitrogen atom in the C-substituent. The representatives of the second and third generations have aminoalkyl or *N*-heterocyclic substituents, respectively. Alendronate belongs to the second generation of bisphosphonic derivatives,[7,8] and is still an important drug. As the best yields described are rather moderate (55%-67%), the synthesis of this valuable agent from γ-aminobutyric acid and P-reagents is still challenging.

Contract grant sponsor: Hungarian Research Development and Innovation Fund.

Contract grant number: K119202.

2 | RESULTS AND DISCUSSION

2.1 | A critical survey of the literature data: claims and facts

Many publications deal with the preparation of alendronate.[9-29] We have also studied its synthesis starting from γ-aminobutyric acid (GABA) (**1**) in methanesulfonic acid (MSA) as the solvent (Table 1; Scheme 1). The best result, a yield of 67% (with 100% purity), was obtained when phosphorus trichloride used as the P-reagent was applied in quantity of 3.2 equivalents at 75°C for 12 hour (Table 1, entry 6).

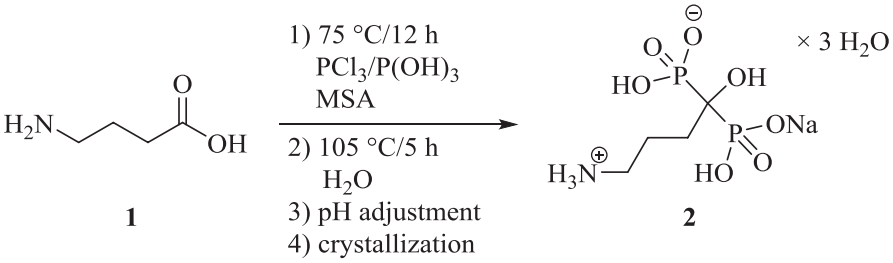
It was found that the addition of phosphorous acid to the reaction mixture was without any positive effect (Table 1, entries 3-5 and 6-8).[9]

However, others found that when GABA (**1**), phosphorus trichloride, and phosphorous acid were reacted in ratios of 1:2.1:1 or 1:2.4:1.5 equivalents in MSA at 65°C for 16-20 hours, the yields were 89% and 90%, respectively, considering pure samples.[10,11] According to our careful reproduction of these two preparations,[10,11] alendronate may be obtained in yields of only 35% and 43%, respectively, in purities of ca. 94% (see Supplementary Material). Hence, the

TABLE 1 Synthesis of monosodium alendronate trihydrate (**2**) from GABA (**1**) in MSA using phosphorus trichloride and phosphorous acid in different ratios

	Reactants				
Entry	**PCl_3 (equiv.)**	**H_3PO_3 (equiv.)**	**Purity (%)[a,b]**	**Yield of 2[b]**	**Ref.**
1	0	2	–	0	[9]
2	1	2	40[c]	22[c]	[9]
3	2	0	97	52	–
4	2	1	42[c]	43[c]	[9]
5	2	2	98	38	[9]
6	3.2	0	100	67[d]	–
7	3	1	97	61	–
8	3	2	98	63	–

[a]On the basis of potentiometric titration.
[b]From at least three parallel experiments.
[c]For the crude product.
[d]Previously published yield: 57% (purity: 98%).[9]



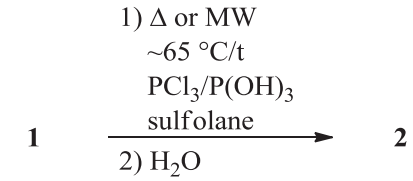
SCHEME 1 Preparation of alendronate in MSA[9]

statement of Polish authors on the yields of ca. 90% seems to be excessive, that is probably due to the neglect of purity criterions. In another case, when phosphorus oxychloride and phosphorous acid were measured as the P-reagents in ratios of 2:3 or 3:3, alendronate was obtained in a yield of 60% (in a purity of 97%).[12]

Another preferred solvent may be chlorobenzene, in which the P-reagents (PCl_3:H_3PO_3) were measured in ratios of 1.5:1.5, 2:3, or 1.5:1.5. The temperature was 100°C in each case, while the reaction time was 3 or 4 hour, and the yields were between 18% and 46%. No data were provided on the purities.[13-15] The synthesis of alendronate was described in a series of other solvents, eg, acetonitrile,[16] *n*-octane,[17,18] phenol and its derivatives,[19,20] anisole,[21] benzenesulfonic acid,[22] diphenyl ether,[23] etc. The yields were highly dependent on these solvents, and in most cases, the purity of the product was not reported. Using the P-reactants (PCl_3:H_3PO_3) in a ratio of 2:1.5 in the absence of solvent, the yield of alendronate was reported as 59%, but no purity criterion was provided.[24]

Alendronate was also synthesized in sulfolane under thermal and microwave (MW)-assisted conditions at ~65°C (Scheme 2).[25-27] The results were summarized in Table 2.

Using phosphorus trichloride and phosphorous acid in ratios of 2.5:3.5 and 3.4:1.5, pure alendronate was claimed to



SCHEME 2 Preparation of alendronate in sulfolane under thermal or MW conditions

have been prepared in yields of 55% and 69% from the thermal reactions (Table 2, entries 1 and 2).[25,26] Regardless of the application of conventional or MW heating, at a 3:3 ratio of P-reagents, the yield of the dronate under discussion was around 40% (Table 2, entries 3 and 4).[27]

Reproduction of the experiments covered by references[25,26] led to yields of 50% and 12%, respectively. It means that the 69%[26] was again excessive. Although at the molar ratio of 3.4 equivalents of phosphorus trichloride and 1.5 equivalents of phosphorous acid in sulfolane, the yield should be higher (see next chapter), the low outcome may be the consequence of the lower reaction temperature of 65°C, and the too short reaction time of 3 h (see Supplementary Material).

The ILs are considered green solvents, because of their low vapor pressure, high thermal stability, and they can be recycled or reused. To date, just two patents have dealt with

TABLE 2 Synthesis of alendronate in sulfolane under thermal and MW conditions

Entry	PCl_3:H_3PO_3 (equiv.:equiv.)	Condition	Temperature (°C)	Time (h)	Purity (%)	Yield (%)	Ref.
1	2.5:3.5	Thermal	60-65	12	99.9	55/50[a]	[25]
2	3.4:1.5	Thermal	63-67	3	99	69/12[a]	[26]
3	3:3	Thermal	65	3,5	–	38	[27]
4	3:3	MW	65	0,1	–	41	[27]

[a]According to our reproduction.

the synthesis of alendronic acid in ILs. De Ferra and co-workers employed $Bu_3N{\cdot}HCl$ as the solvent, and 2 equivalents of phosphorus trichloride together with 1 equivalent of phosphorous acid as P-reactants. The reaction was carried out at 60°C for 2 hour and the target dronate was obtained in a low yield (31%).[28]

In the other work described by Li and co-workers, GABA (**1**) was reacted with 2 equivalents of phosphorus trichloride and 1.5 equivalents of phosphorous acid in the presence of 0.5 equivalents of various ILs at 60°C for about 6 hour. The yield of pure alendronate was reported as 92%-94% depending on the ILs used that could be reused five times.[29] However, this outstanding result within the dronic acid/dronate discipline could not be reproduced by us. Applying the same conditions (60°C/15 hour), and performing a similar work-up (hydrolysis with the same amount of water, refluxing for 6 hour, adjusting the pH to 4.3, and recrystallization), we could prepare alendronate in a yield of 19% only. The purity was 95%. (The detailed procedure can be found in the Supplementary Material.)

According to our previous experiences and on the basis of recent publications, ILs may promote certain reactions if they are used in small quantities as catalysts, additives, or cosolvents, and not as a solvent.[30-35] More and more reactions, such as multicomponent condensations, additions, acylations, esterifications, alkylations, oxidations and halogenations have been described in the presence of 10%-30% of a suitable IL to achieve better conversions in shorter reaction times. We have studied the synthesis of pamidronic acid in sulfolane,[36] and in the presence of IL additives.[37] As we have reached remarkable results, we wished to investigate the preparation of alendronic acid in these solvents too.

2.2 | Preparation of alendronate using sulfolane (A), sulfolane and ionic liquid additive (B) or ionic liquid additive alone (C): new results

In the first series of experiments, we studied the reaction of GABA (**1**) and phosphorus trichloride/phosphorous acid in sulfolane at 75°C according to the analogous procedures developed by us.[36] After heating for 3 hour, the mixture was hydrolyzed at 105°C (for 3 hour), the pH was set to 4.3 by the addition of 50% sodium hydroxide solution, and the mixture was stirred at 25°C (for 12 hour). The precipitated monosodium alendronate trihydrate (**2**) was removed by filtration. The final step comprised purification by recrystallization from hot water. The reaction was run with different ratios of the P-reagents (Table 3; Scheme 3). The use of phosphorous acid alone was inefficient (Table 3, entry 1). Using phosphorus trichloride and phosphorous acid in ratios of 1:1 and 1:2, the yield of dronate (**2**) was around 32% (Table 3, entries 2 and 3). The 2:1 and 2:2 ratio of the P-reagents led to yields of 37% and 46%, respectively (Table 3, entries 4 and 5). Three equivalents of phosphorus trichloride resulted in a yield of only 8% (Table 3, entry 6), but when 1 and 2 equivalents of phosphorous acid was used, the yield increased to 41% and 52%, respectively (Table 3, entries 7 and 8). It can be seen that the best results were obtained using phosphorus trichloride and phosphorous acid in ratios of 2:2 and 3:2 (Table 3, entries 5 and 8).

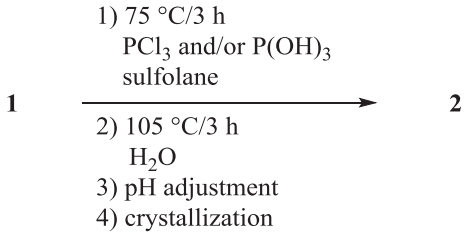
As mentioned in subchapter 2.1, ILs as additives may promote organic chemical reactions.[30-35,37] In the first approach, sulfolane was used as the solvent, but 0.3 equivalents of [bmim][BF_4] or [bmim][Cl] was used as an additive (Scheme 4). Phosphorus trichloride and phosphorous acid were both applied in a molar quantity of 2 equivalents. Table 4 shows that the two experiments provided alendronate (**2**) in yields of 72% and 48%, respectively, in a rather pure form (99/96%) (Table 4, entries 1 and 3). Applying phosphorus trichloride and phosphorous acid in a molar ratio of 3:2, the yields were 80% and 58% for the cases involving [bmim][BF_4] or [bmim][Cl] as the additive, respectively (Table 4, entries 2 and 4). The yields of 72% and 80% may be regarded excellent, if they are compared with the realistic yields of 12%-67% summarized in Table 5. Hence, the application of [bmim][BF_4] as an additive together with sulfolane as the solvent seems to be beneficial.

But what happens if IL additives are used without sulfolane as the solvent? Three ILs were used in a molar equivalent quantity of 0.1, 0.3, and 0.6 at a 3:2 or 2:2 molar ratio of

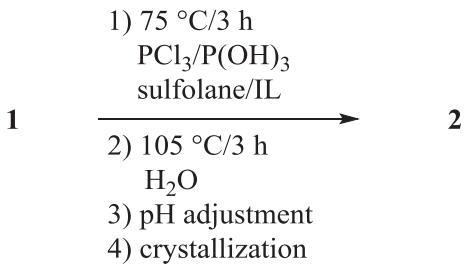
TABLE 3 Synthesis of monosodium alendronate trihydrate (**2**) from GABA (**1**) in sulfolane using phosphorus trichloride and phosphorous acid in different ratios

Entry	Reactants		Purity (%)[a,b]	Yield of 2[b]
	PCl_3 (equiv.)	H_3PO_3 (equiv.)		
1	0	3	–	0
2	1	1	99	32
3	1	2	100	31
4	2	1	100	37
5	2	2	100	46
6	3	0	100	8
7	3	1	100	41
8	3	2	99	52

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



SCHEME 3 Synthesis of monosodium alendronate trihydrate (**2**) from GABA (**1**) using phosphorus trichloride and/or phosphorous acid in sulfolane



SCHEME 4 Synthesis of monosodium alendronate trihydrate (**2**) from GABA (**1**) using phosphorus trichloride and phosphorous acid in sulfolane with IL additive, or in IL

the P-reagents. The experimental data are listed in Table 6. Starting with [bmim][BF_4] as an additive, the following tendencies can be seen:

TABLE 5 Reliable Yields for Alendronate (**2**)

Yield (%)	67	35[a]	43[a]	60	50[a]	12[a]	19[a]
Reference	[9]	[10]	[11]	[12]	[25]	[26]	[29]

[a]After our careful reproduction.

- The IL additive has a significant effect on the yields, as compared with the blind probe experiment (Table 6, entries 1-6 vs entry 7). No alendronate was formed in the absence of any IL. This is a solvent-free accomplishment claimed to be successful according to a report.[24]
- The syntheses are more efficient at a 3:2 molar ratio of phosphorus trichloride and phosphorous acid, than at a 2:2 ratio. However, the differences are not so great to justify the 3:2 molar ratio instead of 2:2.
- The optimum choice is to measure in 0.3 equivalents of [bmim][BF_4] (Table 6, entries 3 and 4). The use of 0.6 or 0.1 equivalents of the IL leads to somewhat lower yields (Table 6, entries 1, 5 and 2, 6).

The tendencies are similar for the instances involving [bmim][Cl] and [bmim][PF_6] as additives (Table 6, entries 8-10 and 11-13, respectively). It is noteworthy that the use of [bmim][PF_6] leads to the target dronate (**2**) in lower purities. The PF_6^- anion is probable not intact during the dronate formation at 75°C.

TABLE 4 Synthesis of monosodium alendronate trihydrate (**2**) from GABA (**1**) using phosphorus trichloride and phosphorous acid in sulfolane together with 0.3 equivalents of [bmim][BF_4] or [bmim][Cl] Additive

Entry	Type of IL	Reactants		Purity (%)[a,b]	Yield of 2[b]
		PCl_3 (equiv.)	H_3PO_3 (equiv.)		
1	[bmim][BF_4]	2	2	99	72
2	[bmim][BF_4]	3	2	100	80
3	[bmim][Cl]	2	2	96	48
4	[bmim][Cl]	3	2	99	58

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

TABLE 6 Synthesis of monosodium alendronate trihydrate (**2**) from GABA (**1**) using phosphorus trichloride and phosphorous acid in different ratios without any solvent in the presence of [bmim][BF_4], [bmim][Cl] and [bmim][PF_6] as additives

Entry	Type of IL	Amount of IL (equiv.)	Reactants		Purity (%)[a,b]	Yield of 2[b]
			PCl_3 (equiv.)	H_3PO_3 (equiv.)		
1	[bmim][BF_4]	0.6	2	2	99	57
2	[bmim][BF_4]		3	2	98	63
3	[bmim][BF_4]	0.3	2	2	98	60
4	[bmim][BF_4]		3	2	98	66
5	[bmim][BF_4]	0.1	2	2	97	39
6	[bmim][BF_4]		3	2	90	46
7	[bmim][BF_4]	0	2	2	–	0
8	[bmim][Cl]	0.6	2	2	100	52
9	[bmim][Cl]	0.3	2	2	100	59
10	[bmim][Cl]	0.1	2	2	100	36
11	[bmim][PF_6]	0.6	2	2	77	56
12	[bmim][PF_6]	0.3	2	2	86	59
13	[bmim][BF_4]	0.1	2	2	95	54

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

In overall, the best results were obtained with [bmim][BF_4] as the additive. Using 0.3 equivalents of this IL, depending on the molar ratio of the P-reagents, alendronate (**2**) was obtained in yields of 60/66% (Table 6, entries 3 and 4).

Finally, [bmim][BF_4] was used in a larger portion (1.1 equivalents) to serve as a solvent. At a 3:2 molar ratio of phosphorus trichloride and phosphorous acid, alendronate (**2**) was formed only in ~5%. Hence, it is clear that the IL should not be used as a solvent, but only as an additive (Figure 1).

The ILs may further enhance the electrophilic character of carbonyl group as shown in Figure 2.

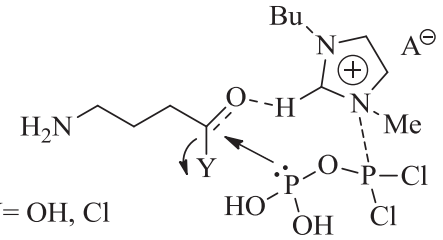


FIGURE 2 The possibly effect of the ILs

3 | SUMMARY

In summary, a detailed study on the synthesis of alendronate from γ-aminobutyric acid and phosphorus trichloride/phosphorous acid revealed that the best option is to apply the P-reagents in ratios of 2:2 or 3:2 in sulfolane in the presence of 0.3 equivalents of [bmim][BF_4] to give the target dronate in a yield of 72% and 80%, respectively. This is a new procedure, and the best ever published for alendronate. In the absence of sulfolane or IL, lower yields of 60/66% and 46/52%, respectively, were attained. The outcome of the former variation applying the P-reagents as above in the presence of the IL is comparable with that of the case using only 3.2 equivalents of phosphorus trichloride in MSA as the solvent (yields of 60/66% vs 67%). The misleading data published without purity criterions were clarified by reliable experiments that are reproducible and supplied with purity data. Our experimental data justified the recent finding that suitable ILs may have a beneficial effect on syntheses as additives or catalysts. Moreover, this also applies for organophosphorus syntheses.

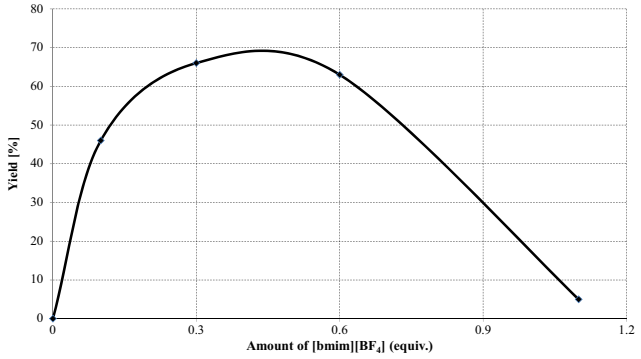


FIGURE 1 The effect of the amount of [bmim][BF_4] on the yield

4 | EXPERIMENTAL

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 alendronate content of the samples was determined by potentiometric acid-base titrations on a Mettler DL77 potentiometric titrator.

The titration curve for the pure alendronic acid standard purchased from Tokyo Chemical Industry Co., Ltd. (TCI), and for the sample obtained from the reaction marked by Table 3, entry 8 are shown in Figures 3 and 4, respectively.

4.2 | Preparation of monosodium alendronate trihydrate (2) from GABA (1), phosphorus trichloride, and phosphorous acid in MSA (Table 1, entry 6)

A quantity of 2.6 g (0.025 mol) of GABA (**1**) was added into 10.5 mL of MSA on stirring. Then, 7 mL (0.08 mol) of phosphorus trichloride was added dropwise in ca. 20 min to the solution. The contents of the flask were stirred at 75°C for 12 hour. After cooling to 25°C, 12 mL (0.67 mol) of water was added, and the mixture was stirred further at 105°C for 4 hour. On cooling, the pH was adjusted to 1.8 by adding ~12 mL of 50% aqueous sodium hydroxide. Then, the contents of the flask were stirred at 25°C for 12 hour. The precipitate was removed by filtration and dried to furnish 10.0 g (82%) of crude product (**2**) in a purity of 67%. The solid was taken up in sixfold amount (60 mL) of hot water, and the pH of the solution was adjusted to 4.5 by adding ~0.5 mL of 50% aqueous sodium hydroxide. Then, the contents of the flask were stirred at 25°C for 12 hour and finally at 0-5°C for 1 hour. The solid product was filtered off and dried to furnish 5.5 g (67%) of monosodium alendronate trihydrate (**2**) in a purity of 100%.

4.3 | Preparation of monosodium alendronate trihydrate (2) from GABA (1), phosphorus trichloride, and phosphorous acid in sulfolane (Table 3, entry 8)

A quantity of 2.6 g (0.025 mol) of GABA (**1**) and 4.1 g (0.05 mol) of phosphorous acid was added into 8 mL of sulfolane on stirring. Then, 6.6 mL (0.075 mol) of phosphorus

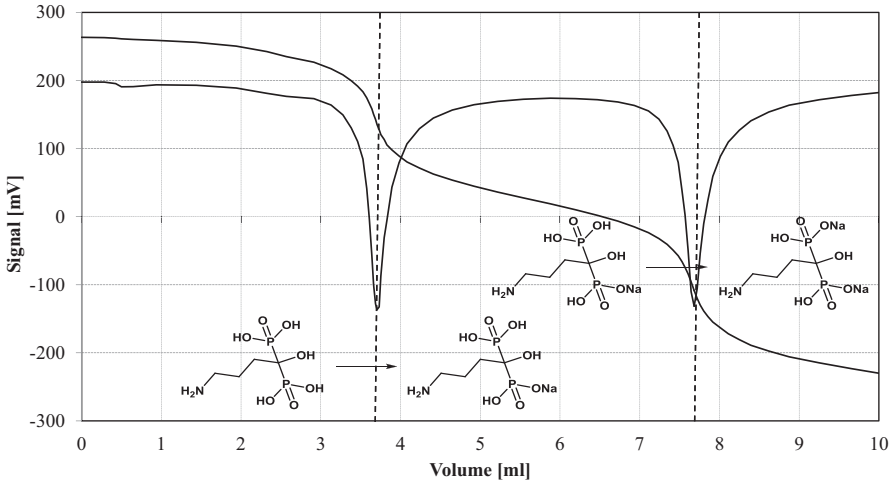


FIGURE 3 Titration curve for alendronic acid standard

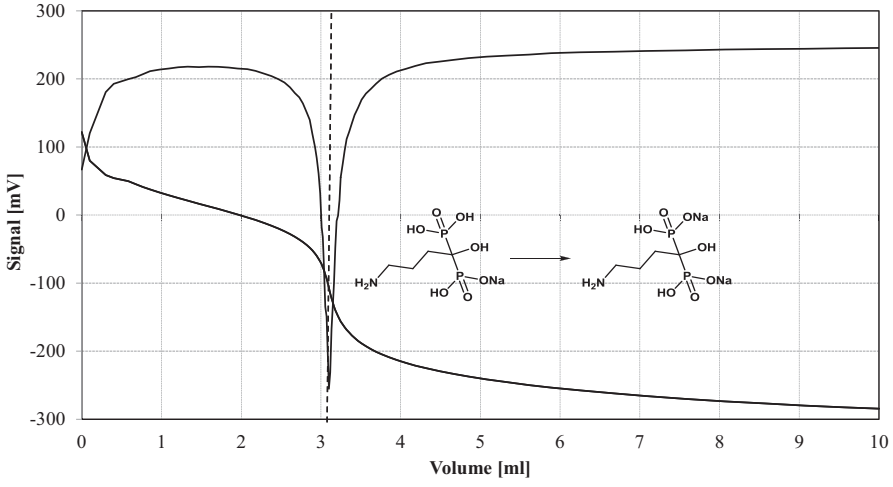


FIGURE 4 Titration curve for the monosodium salt of alendronic acid trihydrate (**2**) obtained by the reaction presented in Table 3, entry 8

trichloride was added dropwise in ca. 30 min, and the contents of the flask were stirred at 75°C for 3 hour. After cooling the mixture to 25°C, 22 mL (1.2 mol) of water was added, and the mixture was stirred further at 105°C for 3 hour. Next, the mixture was cooled to 25°C, and the pH was adjusted to 4.3 by adding ~4 mL of 50% aqueous sodium hydroxide. The stirring was continued for 12 hour, the precipitate was removed by filtration, and dried to give 6.0 g of the crude product. The solid was taken up in fourfold amount (24 mL) of hot water, and the solution stirred at 25°C for 12 hour. Finally, the solid was filtered off, and dried to furnish 4.3 g (52%) of monosodium alendronate trihydrate (**2**) in a purity of 99%. ^{31}P NMR (D_2O) δ: 17.9, δ[9]: 18.0, δ[12]: 18.6; ^{1}H NMR (D_2O) δ: 1.77-1.50 (m, 4H, $NCH_2CH_2CH_2$), 2.42 (t, *J*=6.9, 2H, NCH_2), δ[38]: 2.0-1.96 (m, 4H), 3.06-3.04 (t, 2H); ^{13}C NMR (D_2O) δ: 22.3 (t, *J*=6.7, NCH_2CH_2), 30.7 (s, $NCH_2CH_2CH_2$), 40.3 (t, *J*=4.4, NCH_2), 73.6 (t, *J*=134.7, PCP), δ[12]: 22.8 (t, *J*=6.9), 31.1 (s), 40.4 (s), 73.9 (t, *J*=127.6).

4.4 | Preparation of monosodium alendronate trihydrate (2) from GABA (1), phosphorus trichloride, and phosphorous acid in sulfolane with IL additive (A) or in the presence of IL (B) (Table 4, entry 2, Table 6, entry 4)

A quantity of 2.6 g (0.025 mol) of GABA (**1**) and 4.3 g (0.053 mol) of phosphorous acid was added into a mixture of 8 mL of sulfolane and 1.4 mL (0.008 mol) of [bmim][BF_4] (**A**), or into 1.4 mL (0.008 mol) of [bmim][BF_4] (**B**) 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 3 hour. After cooling the mixture to 25°C, 10 mL (0.5 mol) of water was added, and the mixture was stirred further at 105°C for 3 hour. Next, the mixture was cooled to 25°C, and the pH was adjusted to 4.6 by adding ~4 mL of 50% aqueous sodium hydroxide. Then, the contents of the flask were stirred at the same temperature for 12 hour and finally at 0-5°C for 2 hour. Further work-up including filtration of the crude product, and purification by recrystallization from water was performed as described above to afford 6.5 g (80%, (**A**), Table 4, entry 2), 5.5 g (66%, (**B**), Table 6, entry 4) of monosodium alendronate trihydrate (**2**) in a purity of 100% and 98%, respectively. ^{31}P NMR (D_2O) δ: 17.9 for the product obtained from the experiment marked by Table 4, entry 2, δ[9]: 18.0, δ[12]: 18.6.

ACKNOWLEDGMENTS

The research was supported by Gedeon Richter Plc and by the Hungarian Research Development and Innovation Fund (K119202). We thank Orsolya Németh for participating in the synthetic work.

REFERENCES

[1] R. G. G. Russell, *Bone* **2011**, *49*, 2.
[2] R. G. G. Russell, *Pediatrics* **2007**, *119*, 150.
[3] F. H. Ebetino, A. L. Hogan, S. Sun, M. K. Tsoumpra, X. Duan, J. T. Triffitt, A. A. Kwaasi, J. E. Dunford, B. L. Barnett, U. Oppermann, *Bone* **2011**, *49*, 20.
[4] C. M. Szabo, Y. Matsumura, S. Fukura, M. B. Martin, J. M. Sanders, S. Sengupta, J. A. Cieslak, T. C. Loftus, C. R. Lea, H. J. Lee, A. Koohang, R. M. Coates, H. Sagami, E. Oldfield, *J. Med. Chem.* **2002**, *45*, 2185.
[5] M. J. Rogers, S. Gordon, H. L. Benford, F. P. Coxon, S. P. Luckman, J. Monkkonen, J. C. Frith, *Cancer* **2000**, *88*, 2961.
[6] A. S. Massey, S. Pentlavalli, R. Cunningham, C. M. McCrudden, E. M. McErlean, P. Redpath, A. A. Ali, S. Annett, J. W. McBride, J. McCaffrey, T. Robson, M. E. Migaud, H. O. McCarthy, *Mol. Pharm.* **2016**, *13*, 1217.
[7] H. R. Hudson, N. J. Wardle, S. W. A. Blight, I. Greiner, A. Grün, G. Keglevich, *Mini Rev. Med. Chem.* **2012**, *12*, 313.
[8] W. K. Sietsema, F. H. Ebetino, A. M. Salvagno, J. A. Bevan, *Drugs Exp. Clin. Res.* **1989**, *15*, 389.
[9] R. Kovács, A. Grün, S. Garadnay, I. Greiner, G. Keglevich, *Curr. Org. Synth.* **2013**, *10*, 640.
[10] G. R. Kieczykowski, R. B. Jobson, D. G. Melillo, D. F. Reinhold, V. J. Grenda, I. Shinkai, *J. Org. Chem.* **1995**, *60*, 8310.
[11] G. R. Kieczykowski, R. B. Jobson, D. G. Melillo, US4922007, 1990, *Chem. Abstr.* **1990**, *113*, 132508.
[12] A. Grün, R. Kovács, S. Garadnay, I. Greiner, G. Keglevich, *Lett. Drug Des. Discov.* **2015**, *12*, 253.
[13] M. I. Kabachnik, T. Y. Medved, N. M. Dyaglova, Y. M. Polikarpov, B. K. Shcherbakov, F. I. Bel'skii, *B Acad. Sci. USSR Ch.* **1978**, *27*, 374.
[14] L. Widler, K. A. Jaeggi, M. Glatt, K. Müller, R. Bachmann, M. Bisping, A. R. Born, R. Cortesi, G. Guiglia, H. Jeker, R. Klein, U. Ramseier, J. Schmid, G. Schreiber, Y. Seltenmeyer, J. R. Green, *J. Med. Chem.* **2002**, *45*, 3721.
[15] H. Blum, K. H. Worms, DE2534391, 1977, *Chem. Abstr.* **1977**, *87*, 68491.
[16] V. G. Gore, V. K. Shukla, M. M. Ghadge, R. M. Avadhut, US2009/198062, 2009, *Chem. Abstr.* **2008**, *148*, 100730.
[17] S. C. Pandey, H. Haider, S. Saxena, M. K. Singh, R. K. Thaper, S. K. Dubey, WO2006/134603, 2006, *Chem. Abstr.* **2006**, *146*, 62922.
[18] S. C. Pandey, H. Haider, S. Saxena, M. K. Singh, R. K. Thaper, S. K. Dubey, US2009/312551, 2009, *Chem. Abstr.* **2006**, *146*, 62922.
[19] S. R. Danda, N. K. A. S. S. Garimella, S. R. V. N. Divvela, R. Dandala, S. Meenakshisunderam, US2007/173645, 2007, *Chem. Abstr.* **2007**, *147*, 189284.
[20] D. V. N. S. Rao, R. Dandala, G. K. A. S. S. Narayanan, R. Lenin, M. Sivakumaran, A. Naidu, *Synth. Commun.* **2007**, *37*, 4359.
[21] U. P. Senthilkumar, T. Arulmoli, V. S. Lakshmipathi, S. M. Rao, US2007/66569, 2007, *Chem. Abstr.* **2007**, *146*, 296069.
[22] D. V. Yanvarev, A. N. Korovina, N. N. Usanov, S. N. Kochetkov, *Russ. J. Bioorg. Chem.* **2012**, *38*, 224.
[23] P. B. Deshpande, P. K. Luthra, US2006/258625, 2006, *Chem. Abstr.* **2006**, *145*, 511840.
[24] X. Chen, X. Huang, Y. Jiang, H. Li, L. Qu, Z. Qu, D. Wei, Y. Zhao, C. Qu, L. Qu, J. Yuan, Y. Zhao, *Int. J. Mass Spectrom.* **2010**, *295*, 85.

[25] G. P. Sing, H. S. Jadhav, N. V. Maddireddy, D. Srivastava, WO2007/10556, 2007, *Chem. Abstr.* **2007**, *146*, 142830.
[26] V. M. Patel, T. R. Chitturi, R. Thenatti, WO2005/044831, 2005, *Chem. Abstr.* **2005**, *142*, 463876.
[27] D. A. Mustafa, B. A. Kashemirov, C. E. McKenna, *Tetrahedron Lett.* **2011**, *52*, 2285.
[28] L. De Ferra, S. Turchetta, P. Massardo, P. Casellato, WO2003/093282, 2003, *Chem. Abstr.* **2003**, *139*, 365070.
[29] E. Hao, X. Jiang, Y. Liu, Q. Zhang, D. Wang, M. Xie, H. Wang, H. Guo, G. Li, CN104558028, 2015, *Chem. Abstr.* **2015**, *162*, 577267.
[30] Q. Zhang, S. Zhang, Y. Deng, *Green Chem.* **2011**, *13*, 2619.
[31] S. Feng, G. Yanlong, Z. Qinghua, D. Youquan, *Catal. Surv. Asia* **2004**, *8*, 179.
[32] H. Olivier-Bourbigou, L. Magna, D. Morvan, *Appl. Catal. A* **2010**, *373*, 1.
[33] N. Z. Kiss, G. Keglevich, *Tetrahedron Lett.* **2016**, *57*, 971.
[34] D. Z. Troter, Z. B. Todorović, D. R. Đokić-Stojanović, O. S. Stamenković, V. B. Veljković, *Renew. Sust. Energy Rev.* **2016**, *61*, 473.
[35] H. Guo, X. Qi, Y. Hiraga, T. M. Aida, R. L. Smith Jr., *Chem. Eng. J.* **2017**, *314*, 508.
[36] R. Kovács, A. Grün, O. Németh, S. Garadnay, I. Greiner, G. Keglevich, *Heteroatom Chem.* **2014**, *25*, 186.
[37] A. Grün, D. I. Nagy, S. Garadnay, I. Greiner, G. Keglevich, *Lett. Drug Des. Discov.* **2016**, *13*, 475.
[38] D. A. Mustafa, B. A. Kashemirov, C. E. McKenna, *Tetrahedron Lett.* **2011**, *52*, 2285.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Nagy DI, Grün A, Garadnay S, Greiner I, Keglevich G. Investigation of the effect of medium in the preparation of alendronate; till now the best synthesis in the presence of an ionic liquid additive. *Heteroatom Chem*. 2017;00:e21370. https://doi.org/10.1002/hc.21370