RESEARCH ARTICLE

A Study on the Synthesis of Risedronic Acid; The Role of an Ionic Liquid Additive

Dávid Illés Nagy¹, Alajos Grün¹, Júlia Sinkovicz¹, Sándor Garadnay², István Greiner² and György Keglevich^{1,*}

¹Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary; ²Gedeon Richter Plc., 1475 Budapest, Hungary

Abstract: *Background:* The synthesis of high value risedronic acid is not fully resolved, as, for the time being, the best method based on the preparation from 3-pyridylcarboxylic acid by reaction with phosphorus trichloride in methanesulfonic acid gives risedronic acid in a good yield, but in an unpure form.

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ARTICLE HISTORY

Methods: Alternative protocols realizing the synthesis in sulfolane as the solvent and/or in the presence of suitable IL additive were developed to obtain the target dronic acid in a pure form.

Results & Conclusion: Using phosphorus trichloride and phosphorous acid in two equivalents quantities together with 0.6 equivalents of [bmim][BF4] without any solvent, the method afforded the target dronic acid in a yield of 66% in a pure form.

Keywords: Risedronic acid, 3-pyridylacetic acid, P-reagents, sulfolane, ionic liquid additive, optimization.

1. INTRODUCTION

1-Hydroxy-methylenebisphosphonic (dronic) acid derivatives have two phosphonate groups connected to the same carbon atom. They are efficient drugs against bone diseases, such as osteoporosis, the Paget-disease, tumor-induced hypercalcaemia and osteolytic bone metastases. On the one hand, the dronic derivatives inhibit bone resorption, on the other hand, they have direct antitumor and antiparasitic activity [1-3]. The 1-hydroxy-geminal bisphosphonic acids have a tridentate functionality to enable the binding of Ca² ions, and thus to promote their accumulation in the bone mineral. The hydroxy group on the central carbon atom increases the affinity to the Ca^{2+} ions. The C-substituent on the methylene unit also has a significant impact on the biological activity. The first generation of dronic acid derivatives does not bear a nitrogen atom in the side chain, while the members of the second and third generation have an aminoalkyl or an N-heterocyclic substituent, respectively. These Ncontaining derivatives have a more significant biological effect. Risedronic acid is one of the most important and efficient members of the third generation of hydroxymethylenebisphosphonic derivatives [1-9]. Syntheses of the major representatives of dronic derivatives (pamidronic acid, alendronic acid, ibandronic acid, zoledronic acid, risedronic

*Address correspondence to this author at the Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary; E-mail: gkeglevich@mail.bme.hu

acid and/or their salts) together with the mechanisms for their formation have been reviewed and summarized by us [10]. The most preferred solvent in the preparation of dronic acid derivatives is methanesulfonic acid (MSA). In most syntheses of risedronic acid and its sodium salt, 3pyridylacetic acid (1) served as starting carboxylic acid [11]. Selected preparations of risedronic acid (2) derivatives utilizing phosphorus trichloride and phosphorous acid were summarized in Table 1. Beside these P-reagents, phosphoryl chloride or phosphorus trioxide was also applied using 3pyridylacetic acid in MSA. The reaction of heteroaryl acetic acid 1 with 2.1 equivalents of phosphorus trichloride and 1 equivalent of phosphorous acid in MSA furnished risedronic acid (2) in a yield of 38%, but no purity criterion was provided (Table 1/Entry 1) [12]. Using phosphorus trichloride and phosphorous acid in a molar ratio of 2:3 in a 1:3 mixture of MSA-diethyl carbonate as the solvent, risedronate (2-Na) was obtained in a yield of 73%. A purity of 99.9% was claimed that was established by HPLC (Table 1/Entry 2) [13]. However, the unusually good outcome for product 2-Na based on a complete purity may be questionable due to the considerable portion of the ballast represented by the excess of phosphorous acid (see later), and the Na salt of MSA formed from a part of the solvent on pH adjustment by NaOH. The inorganic impurities mentioned cannot be seen by HPLC. Our reproductive experiments showed that under the conditions described, the yield was even higher (89%), but the purity was only 82%. Using only 3.2 equivalents of phosphorus trichloride as the P-reagent in MSA, risedronic acid (2) was obtained in a yield of 74%, and in a purity of



Scheme (1). Preparation of risedronic acid (2) in MSA by an optimized method [11].

92% (Scheme 1) (Table 1/Entry 3) [11]. It was clarified by us that phosphorous acid is unnecessary, when phosphorus trichloride is applied in MSA as the solvent [11]. However, the preparation of pure risedronic acid from reaction mixtures containing MSA as the medium is complicated by the presence of MeSO₃Na.

In another case, when MSA was the solvent and 2 equivalents of phosphoryl chloride and 3 equivalents of phosphorous acid were the P-reagents, risedronic acid was obtained in a yield of 55% in a purity of 98% [14]. Carrying out the synthesis with 3 equivalents of phosphorus trioxide and 3.5 equivalents of phosphorous acid, a similar yield of 54% was claimed) [15].

Sulfolane is also a preferred solvent during the preparation of hydroxy-methylenebisphosphonic acid derivatives, but in the case of risedronate, this was a less used medium. McKenna and his co-workers reacted 3-pyridylacetic acid (1) with 3-3 equivalents of phosphorus trichloride and phosphorous acid in sulfolane under MW conditions. The crude risedronic acid (2) was obtained in a yield of 74% without purity criterions (Table 1/Entry 4) [16]. In another instance, phosphorus trichloride and phosphorous acid were applied in a ratio of 3.4:1.5 to afford risedronate in a yield of 54%. The purity of the product was 99% (Table 1/Entry 5) [17].

The preparation of risedronic acid derivatives was also performed in chlorobenzene using phosphorus trichloride and phosphorous acid in different quantities (1.5-3.5:1.5-3.5 equivalents). The yields fell in the range of 52–96%, but these data are not reliable at all, as they refer to crude products [18-22]. A typical example is shown in (Table 1/Entry 6) [20].

The synthesis of the target molecule was also carried out in toluene as the solvent [23]. In these instances, phosphoryl chloride and in the dronate discipline unusual reagents, for example, propylphosphonic anhydride (T3P), methanesulfonic acid anhydride or phosphorus pentachloride were used together with phosphorous acid in different ratios. Crude risedronic acid (2) was prepared in a yield of 58-90%, in claimed purities of around 98% [23]. These days, there is a demand to use more environmentally-friendly reagents and solvents in organic chemical syntheses. Ionic liquids (ILs) are considered green solvents, due to their low vapor pressure, high thermal stability, and recyclability. In addition, they are fine-tuneable solvents, as their properties including lipophilicity and polarity may be adjusted by selecting the appropriate cations and anions. It is a new tendency that the ILs are applied as only an additive or a catalyst in syntheses, and not as a solvent [24-30]. This approach was utilized by us in the preparation of a few important dronic acid derivatives, such as pamidronic acid [27], alendronate [28], ibandronate [29] and zoledronic acid [30]. The synthesis of hydroxy-methylenebisphosphonic acid derivatives was hardly performed in ILs as solvents; the preparation of risedronic acid was attempted in an IL only once. Reacting 3-pyridylacetic acid (1) with the mixture of 2 equivalents of phosphorus trichloride and 1 equivalent of phosphorous acid in tributylammonium chloride as the medium, a low yield of 12% was reported for crude risedronic acid (2) (Table 1/Entry 7) [31].

Generally, dronic acid derivatives cannot be synthesized in good yields in the absence of any solvent. However, risedronic acid could be prepared under solvent-free conditions, and quite good yields were claimed, but without providing purity criterions. The majority of the researchers applied

Entry	Solvent	Reactants (equiv.)	Product Form	Purity (%)	Yield	Refs.
1	MSA	PCl ₃ : H ₃ PO ₃ (2.1:1)	acid	-	38	[12]
2	MSA ¹	PCl ₃ : H ₃ PO ₃ (2:3)	Na*2.5H ₂ O	99.9 ² (82) ^{3,4}	73(89) ³	[13]
3	MSA	PCl ₃ (3.1)	acid	100^{4}	74	[11]
4	sulfolane	PCl ₃ : H ₃ PO ₃ (3:3)	acid*H ₂ O	-	74 ⁵	[16]
5	sulfolane	PCl ₃ : H ₃ PO ₃ (3.4:1.5)	Na	99	54	[17]
6	chlorobenzene	PCl ₃ : H ₃ PO ₃ (2.4:2.4)	acid	84 ²	58	[20]
7	[Bu ₃ NH][Cl]	PCl ₃ : H ₃ PO ₃ (2:1)	acid	-	26	[31]
8	-	$PCl_3 : H_3PO_3 (5:3)^5$	Na	-	86	[32]
9	-	PCl ₃ : H ₃ PO ₃ (2:1.5)	acid		67	[34]
10	-	PCl ₃ : H ₃ PO ₃ (2.5:2.2)	Na*2.5H ₂ O	99,9 ²	65	[35]

 Table 1.
 Selected Preparations of Risedronic Acid (2) Derivatives Utilizing Phosphorus Trichloride and Phosphorous Acid as the P-reagents in Different Solvents.

¹in 1:3 mixture of MSA and diethyl carbonate. ²On the basis of HPLC. ³Our reproduction. ⁴On the basis of acid-base titration. ⁵Under MW conditions.

phosphorus trichloride and phosphorous acid as the Preagents in molar ratios of 2:1.5 - 5:5. The crude product was isolated in yields of 65-86% (Table 1/Entries 8-10) [32-35]. In a special combination, phosphoryl chloride and phosphorous acid were used in an unnecessarily large excess of 3.2:9.7 affording dronic acid 2 in a yield of 60% [36].

Synthesis of the dronic acid under discussion was investigated in a series of other solvents (*e.g.* in acetonitrile [20, 37], *n*-octane [38, 39], ethyl acetate [23], dioxane [38], diphenyl ether [40], phenol derivatives [41] or diethyl carbonate [13] *etc.*) as well. However, in the lack of practical importance, these procedures are peripheral.

After the successful precedents in case of other dronic acid derivatives [27-30], we wished to develop an efficient and up-to-date synthesis of the high value (\pounds 160/g), third generation hydroxy-methylenebisphosphonic acid, risedronic acid (**2**) in sulfolane as the medium, and/or in the presence of an IL additive. The methods applying MSA as the solvent have the shortcoming of providing risedronic acid (**2**) in an unpure form.

2. EXPERIMENTAL

2.1. General

 31 P, 13 C and 1 H NMR spectra were obtained on a Bruker AV-300 spectrometer operating at 121.50 MHz, 75.5 MHz and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H₃PO₄ or TMS. The couplings are given in Hertz. The risedronic acid (**3**) content of the samples was determined by potentiometric acid-base titrations on a Mettler DL77 potentiometric titrator.

The titration curve for the risedronic acid (3) obtained from the reaction marked by Table 3/Entry 2 is shown in Fig. (1).

2.2. Reproduction of the Procedure of Vakamudi *et al.* for the Preparation of the Monosodium Salt of Risedronic Acid Hemi(pentahydrate) [13]

3.4 g (0.025 mol) of 3-pyridylacetic acid (1) and 6.1 g (0.074 mol) of phosphorous acid were added into the mixture

of 3.4 mL of MSA and 10.2 mL of diethyl carbonate on stirring. Then, 4.4 mL (0.05 mol) of phosphorus trichloride was added dropwise in ca. 30 min and the contents of the flask were stirred at 69 °C for 6 h. After cooling the mixture to 25 °C, 17 mL (0.94 mol) of water was added, and the mixture was stirred further at 105 °C for 5.5 h. The contents of the flask were cooled to 70 °C, and 17 mL isopropanol was added. Next, the mixture was cooled to 10 °C, and the pH was adjusted to 1.8 by adding ~12 mL of 50% aqueous sodium hydroxide. Then, the suspension was stirred further at the same temperature for 1 h, and the precipitate was removed by filtration, washed with 5 mL isopropanol, and finally dried. The crude risedronic acid obtained was added to 120 mL of water on stirring. Next, the mixture was cooled to 15 °C, and the pH was adjusted to 4.9 by adding 50% aqueous sodium hydroxide. The mixture was stirred at the same temperature for 15 min, and after the addition of 1 g of activated carbon for 20 min. The carbon was removed by filtration, washed with 20 mL of water, then the solution was cooled to 15 °C, and 20 mL of isopropanol was added, and the mixture stirred at 15 °C for 2 h, then at 0-5 °C for 1 h. 120 mL of cold isopropanol was added, and the contents of the flask were stirred at 0-5 °C for 2 h. The solid precipitate was filtered off, transferred to another flask, and suspended in a mixture of 60 mL of water and 60 mL of isopropanol. and the suspension stirred at 15 °C for 40 min. The solid phase was removed by filtration, washed with the mixture of cold isopropanol (5 mL) and cold water (5 mL), and dried to give 9,5 g (89%) of the monosodium salt of risedronic acid as a hemi(pentahydrate) in a purity of 82%. According to the patent [13], the product was claimed to have been isolated in a yield of 73%, and in a purity of 99.9%.

2.3. Preparation of Risedronic Acid Monohydrate (3) from 3-Pyridylacetic Acid (1), Phosphorus Trichloride and Phosphorous Acid in Sulfolane (Table 2/Entry 3)

1.7 g (0.013 mol) of 3-pyridylacetic acid (1) and 2.2 g (0.027 mol) of phosphorous acid were added into 5 mL of sulfolane on stirring. Then, 2.5 mL (0.029 mol) of phosphorus trichloride was added dropwise in *ca*. 30 min, and the contents of the flask were stirred at 75 °C for 3 h. After cool-



Fig. (1). Titration curve for the risedronic acid (3) obtained by the reaction presented in Table 3/Entry 2.

ing the mixture to 25 °C, 10 mL (0.56 mol) of water was added, and the mixture was stirred further at 105 °C for 1 h. Then, the solution was stirred at 0-5 °C for 3 h, and the precipitate was removed by filtration to give ~ 3 g of the crude product that was suspended in 30 mL of methanol, and the mixture was digested by stirring at 65 °C for 30 min. The solid product was filtered off to furnish 2.2 g (58%) of risedronic acid monohydrate (3) in a purity of 100%. ³¹P NMR $(D_2O) \delta$: 17.1, δ [42]: 18.1; ¹H NMR $(D_2O) \delta$: 3.31–3.23 (t, J $= 12.0, 2H, CH_2$, 7.54 (dd, J = 7.8 J = 5.6, 1H, NCHCH), 8.17 (d, J = 8.0, 1H, NCHCHCH), 8.32 (d, J = 5.2 1H, NCH), 8.52 (s, 1H, NCHC), δ [42]: 3.26 (t, J = 12.1, 2H), 7.55 (dd, J = 8.2, 5.5, 1H), 8.18 (d, J = 5.5, 1H), 8.32 (d, J =5.5, 1H), 8.51 (s, 1H); ¹³C NMR (D₂O) δ: 36.3 (s, CH₂), 73.6 (t, J = 130.7, P-C-P), 124.7 (s, NCHCH), 136.4 (t, J = 8.5 C), 142.1 (s, NCHCHCH), 144.8 (s, NCH), 146.2 (s, NCHC), δ [42]: 36.5, 73.8, 125.3, 137.1, 141.3, 145.3, 146.1.

2.4. Preparation of Risedronic Acid Monohydrate (3) from 3-Pyridylacetic Acid (1), Phosphorus Trichloride and Phosphorous Acid in the Presence of $[bmim][BF_4]$ (A), or in Sulfolane in the presence of $[bmim][BF_4]$ Additive (B) (Table 3/Entry 2, Table 4/Entry 1)

2.5 mL (0.029 mol) of phosphorus trichloride was added dropwise into the mixture of 1.7 g (0.013 mol) of 3-pyridylacetic acid (1), 2.2 g (0.027 mol) of phosphorous acid and 1.4 mL (0.008 mol) of [bmim][BF₄] (**A**), or into the mixture of 5 mL of sulfolane and 1.4 mL (0.008 mol) of [bmim][BF₄] (**B**) on stirring in *ca*. 30 min, and the contents of the flask were stirred at 75 °C for 3 h. Further processing including hydrolysis, crystallization and digestion was performed as described above (Chapter 4.3) to afford 2.5 g (66%, (**A**), Table **2**/Entry 2) and 2.5 g (65%, (**B**), Table **3**/Entry 1) of risedronic acid monohydrate (**3**) in a purity of 100% and 99%, respectively. ³¹P NMR (D₂O) δ : 17.2 and 17.1 respectively, δ [42]: 18.1.

3. RESULTS AND DISCUSSION

3.1. Syntheses of Risedronic Acid in Sulfolane

In the first series of experiments, the preparation of risedronic acid (3) by the reaction of 3-pyridylacetic acid (1) with phosphorus trichloride and phosphorous acid in sulfolane (Scheme 2) was optimized. The reaction was carried out with different ratios of the P-reagents. After a stirring at 75 °C for 3h, the mixture was hydrolyzed at 105 °C. On cooling, the target dronic acid (3) precipitated, and the crystals were removed by filtration. The final purification involved an extractive boiling with methanol. The purity was determined by potentiometric acid-base titration, NMR measurements, as well as HPLC. The shape of the curve in the acidbase titration diagram suggests the form of the product (if it is acid or a kind of salt), and the results of the titration determine the total dronic derivative content. The other impurities may be detected by ³¹P and ¹³C NMR, as well as HPLC measurements. Experimental data were summarized in Table 1.

It can be seen that using phosphorus trichloride alone in sulfolane, no matter if the P-reagent was measured in a 2 or 3.2 equivalents' quantity, risedronic acid **3** (containing 1 molecule of crystalline water) was formed in low yields of



Scheme (2). Preparation of risedronic acid (3) in sulfolane.

Table 2.	Synthesis of risedronic acid (3) from 3-pyridylacetic				
	acid (1) in sulfolane using phosphorus trichloride				
	and phosphorous acid in different ratios.				

Entw	Reac	tants	Durity (0/) ^{a,b}	Yield of 3 ^b	
Entry	PCl ₃ (equiv.)	H ₃ PO ₃ (equiv.)	Furity (%)		
1	2	0	98	2	
2	2	1	98	39	
3	2	2	100	58	
4	2	3	100	60	
5	2	4	98	57	
6	3.2	0	100	4	
7	3	1	100	29	
8	3	2	100	49	
9	3	3	100	51	

^aOn the basis of potentiometric titration. ^bFrom at least five parallel experiments.

2-4% (Table 2/Entries 1 and 6). Using a 2:1 mixture of phosphorus trichloride and phosphorous acid, the product (3) was obtained in a yield of 39% (Table 2/Entry 2). Repeating the experiments with 2, 3 and 4 equivalents of phosphorous acid, the yields were 58%, 60% and 57%, respectively (Table 2/Entries 3-5). As practically similar results (ca. 59% yields) were obtained, the best molar ratio of the P-reagents is 2:2. Applying phosphorus trichloride in a quantity of 3.2 equivalents together with 1, 2 and 3 equivalents of phosphorous acid, risedronic acid (3) was obtained in yields of 29%, 49% and 51%, respectively (Table 2/Entries 7-9). It can be seen that the results of the experiments with 3 equivalents of phosphorus trichloride (Table 2/Entries 7-9) are more modest, than those with 2 equivalents of this reagent (Table 2/Entries 2-4). It is also evident that the earlier yield of 54%, obtained in sulfolane using phosphorus trichloride and phosphorous acid in quantities of 3.4 and 1.5 equivalents [17], could be improved by us to 58% by the application of the Preagents in a ratio of 2:2 that is better than the results obtained in MSA, as refers to pure product [11].

3.2. Syntheses of Risedronic Acid in the Presence of an Ionic Liquid

According to our earlier experiments, ILs as additives promoted the efficient syntheses of dronic acid derivatives, pamidronic acid, ibandronate and zoledronic acid [27, 29, A Study on the Synthesis of Risedronic Acid

$$1 \xrightarrow{1) 75 °C/3 h} PCl_3/P(OH)_3 \longrightarrow 3$$

$$1 \xrightarrow{IL additive} 2) 105 °C/1 h H_2O$$
3) crystallization
4) MeOH digestion

Scheme (3). Preparation of risedronic acid (3) in the presence of an ionic liquid.

30]. This was also tried in the synthesis of risedronic acid (Scheme 3).

Measuring in the P-reagents in a quantity of 2-2 equivalents, and applying [bmim][BF₄] in portions of 0.9, 0.6 and 0.3 equivalents, risedronic acid 3 was obtained in yields of 58%, 66% and 51%, respectively (Table 3/Entries 1, 2 and 4). As earlier [27-30], with increasing quantities of the IL additive, the yields followed a curve with a maximum. The presence of 0.6 equivalents of $[bmim][BF_4]$ was the optimum promoting a record yield of 66%. Applying phosphorus trichloride and phosphorous acid in a ratio of 3:2 at a 0.6 and 0.3 equivalents quantity of the IL, the yields were 65% and 60%, respectively (Table 3/Entries 3 and 5). As a blind probe comparison, one of the above experiments was also performed in the absence of [bmim][BF₄] to provide a lower yield of 35% (Table 3/Entry 6). Another IL, $[bmim][PF_6]$ was also tested as an additive at a 2:2 ratio of the P-reagents. The presence of 0.6 and 0.3 equivalents of the IL led to yields of 57% and 51%, respectively. The preparation of risedronic acid (3) seems to be more advantageous in the presence of [bmim][BF₄] as an additive, than in sulfolane or MSA as the solvents. This statement is justified by the yields of 66%, 58% and 59%, respectively. Moreover, the solventfree accomplishments are always preferable.

3.3. Syntheses of Risedronic Acid in Sulfolane in the Presence of an Ionic Liquid Additive

Finally, the preparation of risedronic acid (3) was attempted in sulfolane as the solvent together with an IL additive (Scheme 4, Table 4). As can be seen, the use of



Scheme (4). Preparation of risedronic acid (3) in sulfolane using an ionic liquid additive.

[bmim][BF₄] led to comparable results (Table 4/Entries 1 and 2) with those obtained without sulfolane.

One may see that the use sulfolane is unnecessary when $[bmim][BF_4]$ additive is applied in the synthesis under discussion.

It is clear that from the variations investigated, the route utilizing the P-reagents in a 2 equivalents quantity in the presence of 0.6 equivalents of [bmim][BF₄] is the most appropriate. This protocol furnishes risedronate in a yield of 66% in an entirely pure form. This approach is better than a previous one realizing the synthesis in MSA in the presence of 3.2 equivalents of phosphorus trichloride to afford the target dronic acid in a purity of only 92%, and in a yield of 74% [11], as the quantity of the dronic acid is very similar in both cases ($0.66x1 \approx 0.74x \ 0.92$), however, there is no need for an additional purification in the new procedure.

It is interesting to compare the best set of parameters for the more important dronic acid derivatives. The methods are similar but significantly different. E.g. for ibandronate [29], at a 3:2 ratio of phosphorus trichloride and phosphorous acid, in the presence of 0.1 equivalents of [bmim][BF₄], a yield of 90% was reported for a pure product. The optimum conditions for zoledronic acid involved a 2:2 ratio of the Preagents, and the use of 0.3 equivalents of the same IL. However, in this case, there was a need for sulfolane as the solvent. In this way, pure zoledronic acid was obtained in a yield of 89% [30]. As regards risedronic acid [present paper], at a molar ratio of 2:2, in the presence of 0.6 equivalents of the IL, a maximum yield of 66% could be achieved for pure compound, moreover in the absence of sulfolane.

Entry	Amount of (hmim)(DE 1 (aguin))	Read	tants	D ensity $(0/)^{a,b}$	Yield of 3 ^b
	Amount of [bmim][br 4] (equiv.)	PCl ₃ (equiv.)	H ₃ PO ₃ (equiv.)	rurny (76)	
1	0.9	2	2	99	58
2	- 0.6	2	2	100	66
3		3	2	100	65
4	0.2	2	2	100	51
5	0.3	3	2	100	60
6	0	2	2	100	35

 Table 3.
 Synthesis of Risedronic Acid (3) from 3-Pyridylacetic Acid (1) in the Presence of [bmim][BF4] Additive Using Phosphorus Trichloride and Phosphorous Acid in Different Ratios.

^aOn the basis of potentiometric titration. ^bFrom at least five parallel experiments.

 Table 4.
 Synthesis of Risedronic Acid (3) from 3-Pyridylacetic Acid (1) in Sulfolane in the Presence of 0.6 Equivalents of [bmim][BF₄] or [bmim][PF₆] Using Phosphorus Trichloride and Phosphorous Acid in Different Ratios.

Entry	Type of IL	Rea	ctants	Durity (0/)a,b	Viold of 2 ^b
		PCl ₃ (equiv.)	H ₃ PO ₃ (equiv.)	runy (78)	Tield of 5
1	[hmim][PF]	2	2	99	65
2	լ տուղլ ու 4յ	3	2	100	67
3	[bmim][PF ₆]	2	2	95	49

^aOn the basis of potentiometric titration. ^bFrom at least five parallel experiments.

CONCLUSION

In conclusion, the high-value drug, risedronic acid used in the treatment of bone deceases could be prepared from 3pyridylacetic acid applying two equivalents of the P-reagents (phosphorus trichloride and phosphorous acid) in the absence of any solvent, using only 0.6 equivalents of [bmim][BF₄] as a catalytic additive. The optimized method afforded the target dronic acid in a yield of 66% in a pure form. This method is more advantageous than the previous protocol applying 3.2 equivalents of phosphorus trichloride in MSA as the solvent that furnishes risedronic acid in a better yield (74%) but in a purity of only 92%.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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