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Efficient syntheses of zoledronic acid as an active ingredient of a drug against osteoporosis

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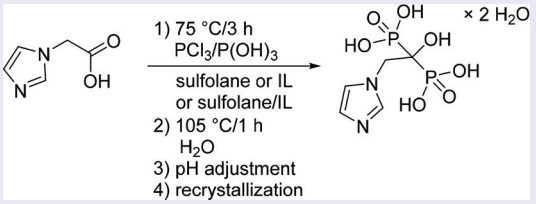
ABSTRACT

The reaction of 1*H*-imidazol-1-ylacetic acid and two equivalents of phosphorus trichloride/phosphorous acid at 75 °C in sulfolane, or in the presence of catalytic amounts of [bmim][BF_4] afforded zoledronic acid in yields up to 75%. The joint use of the ionic liquid additive and sulfolane as the solvent was synergetic affording highly valuable zoledronic acid in a record yield of 93%.

GRAPHICAL ABSTRACT



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1*H*-imidazol-1-ylacetic acid; ionic liquid additive; P-reagents; sulfolane; synthesis; zoledronic acid

Introduction

The α-hydroxy-methylenebisphosphonic (dronic) acid derivatives have two phosphonate groups connected to the same carbon atom. They are important drugs in the treatment of bone diseases, such as osteoporosis, the Paget-disease, tumor-induced hypercalcemia, so they are used as inhibitors of bone resorption. The compounds have also shown direct antitumor and antiparasitic activity.[1–4] The chemical structure of dronic acid derivatives enables them to form a complex with the Ca^{2+} ions, therefore, they are able to bind to the bone mineral. The hydroxy group on the central carbon atom increases the affinity to the Ca^{2+} ions. The side chain of the bisphosphonates has also a significant impact on the biological activity. The first generation of dronic acid derivatives does not bear a nitrogen atom in the C-substituent, while the members of the second and third generation have an aminoalkyl or a *N*-heterocyclic substituent, respectively. These *N*-containing derivatives have a more significant biological effect. Zoledronic acid is a prominent representative of the third generation of hydroxy-methylenebisphosphonic acid derivatives,

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This article is dedicated to Professor Dr. Marijan Mikolajczyk on the occasion of his 80th birthday.
Supplemental data (titration curve, ^{31}P NMR, ^{1}H NMR, and ^{13}C NMR spectra for compound 2) can be accessed on the publisher's website.

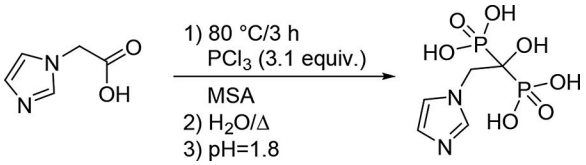
which is currently being used for therapeutic purposes.[1–9] It is the active ingredient of a high value drug against bone diseases.

The syntheses of the most important dronic acid derivatives, such as pamidronic acid, alendronic acid, ibandronic acid, zoledronic acid, risedronic acid, and/or their salts was summarized by us.[10] Until now, there were no comprehensive data on the mechanism of the formation of bisphosphonic acids. Therefore, the literature data have been surveyed, and our up-to-date conceptions summarized.[11] Although the most preferred solvent in the syntheses of dronic acid derivatives is methanesulfonic acid (MSA), the preparation of zoledronic acid was investigated only in two cases in this medium.[12,13] Imidazol-1-yl-acetic acid was reacted with 2.1 equivalents of phosphorus trichloride and 1 equivalent of phosphorous acid at 65 °C by Kieczykowski et al., and crude zoledronic acid was obtained in a yield of 31%.[12] The senior author of this paper together with coworkers proved that there is no need to use phosphorous acid if MSA is the solvent, as, due to its low nucleophilicity, phosphorous acid does not participate in the reaction. A reasonable yield of 53% was reached for pure zoledronic acid, when only 3.1 equivalents of phosphorus trichloride were used as the P-reactant, when MSA was the solvent (Scheme 1).[13]

The other frequently used solvent is sulfolane during the preparation of bisphosphonic derivatives. However, the synthesis of the target molecule in sulfolane was mentioned only in two cases.[14,15] Both P-reactants (PCl_3 and $P(OH)_3$) were applied by McKenna et al. in a quantity of 3 equivalents. Under thermal conditions, the yield was 67%, while on microwave (MW) irradiation, a somewhat higher (70%) outcome was disclosed, but the purities were not mentioned. The reaction temperature was 65 °C in both instances, but the reaction times were significantly different (3.5 h for normal heating, and 0.05 h for MW irradiation).[14] Performing the synthesis using 3.4 equivalents of phosphorus trichloride and 1.5 equivalents of phosphorous acid, zoledronic acid was claimed to have been obtained in a yield of 71%, but no purity criterion have been reported.[15]

In a few instances, the synthesis of the target molecule was also performed in chlorobenzene or under solvent-free conditions.[16–22] Applying phosphorus trichloride and phosphorous acid in an amount of 3.7 equivalents, a quantitative yield was claimed, which is, however, not too probable.[16] In other cases, 1.9–3 equivalents of phosphoric acid were applied beside 2–4.7 equivalents of phosphorus trichloride, and yields of 41–79% without purity criterions were reported for crude zoledronic acid.[17–19]

Surprisingly, rather high yields (61–80%) were reported in the absence of any solvent, but according to our experiments, the synthesis of most bisphosphonates cannot be



Scheme 1. Preparation of zoledronic acid in MSA by an optimized method.[13] *Note*: MSA, methanesulfonic acid.

realized under solvent-free conditions with such good yields. Moreover, the P-reagents, phosphorus trichloride and phosphorous acid, or phosphoryl-chloride and phosphorous acid were used in unreasonably large quantities (3–9 equivalents) that presumably complicates the purification.[20–22]

Nowadays, environmentally-friendly methods including "green" reagents and solvents are in the focus. Thus, the application of ionic liquids (ILs) as solvents is an up-to-date trend. The ILs have a low vapor pressure, high thermal stability, and can be recycled or reused. In addition, they are considered fine-tunable solvents, as their properties including lipophilicity and polarity may be adjusted by selecting the appropriate cations and anions. It is a new endeavor that the ILs are applied in the syntheses as only additives or catalysts, and not as solvents.[23–30] This protocol was successful during the synthesis of pamidronic acid,[27] alendronate,[28] and ibandronate[29] elaborated by the authors of this article.

The synthesis of zoledronate was investigated in different ILs. De Ferra et al. used 2 equivalents of phosphorus trichloride and 1 equivalent of phosphorous acid in reaction with imidazolylacetic acid in the presence of tributylammonium chloride as the solvent. The product was obtained in a low yield (26%).[31]

In another case, phosphorus trichloride and phosphoric acid were reacted in a ratio of 2.5:1.7 equivalents in various ILs (e.g., 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4], 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6], 1-hydroxyethyl-2,3-dimethyl-imidazolium chloride, or 1-propyl-3-carbonitrile-imidazolium chloride, etc.) to furnish crude zoledronic acid in conversions around 90%. Pure sodium zoledronate was obtained in a yield of 60% after recrystallization.[32]

The syntheses of our target molecule was reported in many other solvents (e.g., in *p*-cresol,[33] *n*-octane,[34] cyclohexane,[17] dioxane,[34] diphenyl ether,[35] or diethyl and propylene carbonate,[36] etc.), but these methods are not typical, and the results are not notable.

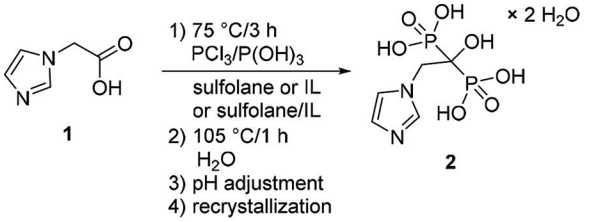
We wished to investigate the synthesis of the still important and valuable hydroxy-methylenebisphosphonic acid, zoledronic acid from 1*H*-imidazol-1-ylacetic acid and P-reagents in sulfolane, in the presence of an IL additive, as well as in the combination of sulfolane and an IL, to elaborate an efficient, and hence attractive preparation.

Results and discussion

The reaction of 1*H*-imidazol-1-ylacetic acid (**1**) with phosphorus trichloride and phosphorous acid measured in in different ratios was performed in different mediums at 75 °C for 3 h. After the reaction, the mixture was hydrolyzed at 105 °C for 1 h, the pH was set to 1.8, and the crude product precipitated removed by filtration. The crude product was purified by recrystallization from 1 M hydrochloric acid solution (Scheme 2).

Syntheses of zoledronic acid in sulfolane

In the first series of experiments, the reaction of imidazolylacetic acid (**1**) with the two P-reagents was performed in sulfolane as the solvent. The experimental data are listed in Table 1. Using 2 equivalents of phosphorus trichloride together with 1, 2, 3, and 4 equivalents of phosphorous acid, zoledronic acid dihydrate (**2**) was obtained in yields of 43, 74,



Scheme 2. The protocol for the preparation of zoledronic acid in the present study.

63, and 66%, respectively, mostly in 99–100% purity (Table 1, entries 1–4). It can be seen that the optimal molar ratio of the P-reactants is 2:2, as this combination led to a yield of 74%. When only phosphorus trichloride served as the P-reagent in a quantity of 3.2 equivalents, the yield of product **2** was only 10% (Table 1, entry 5). However, adding also 1, 2, and 3 equivalents of phosphorous acid to the mixture, zoledronic acid (**2**) was prepared in yields of 60, 71, and 75%, respectively, in purities of 98, 99, and 100%, respectively (Table 1, entries 6–8). One may see that the yields of the target product applying the P-reagents in a 2:2 or 3:3 ratio are comparable (Table 1, entries 2 and 8). The use of 2 equivalents of the P-reactants is optimal, as the 3 equivalents quantity has a minimal impact on the yield. The need for the equivalent quantities of phosphorus trichloride and phosphorous acid is justified by the assumption that the nucleophilic agent reacting with the carbonyl group of imidazolylacetic acid (**1**) is Cl_2P-O-$P(OH)_2$ formed from the P-reagents. It may also be assumed that the C=O function of the carboxylic acid (**1**) is reactive enough to be attacked by the $-P(OH)_2$ moiety of the Cl_2P-O-$P(OH)_2$ species.[37]

Syntheses of zoledronic acid in the presence of an ionic liquid

In the next stage of our work, ILs were utilized in the preparation of zoledronic acid. As was mentioned above, it is a new approach to apply ILs as only catalytic additives.[23–30] For this, we wished to perform the **1** → **2** model reaction in the presence of different quantities of a suitable IL. Pre-experiments revealed that from among the earlier applied [bmim][PF_6] and [bmim][BF_4], the latter onium salt is the more efficient.

The second series of reactions was performed in the presence of 1.2, 0.6, 0.3, and 0.1 equivalents of [bmim][BF_4], and also in the absence of the IL. Table 2 elucidates that the yields (and purities) were practically not dependent on the 2:2 or 3:2 ratio of the

Table 1. Synthesis of zoledronic acid (**2**) from 1*H*-imidazol-1-ylacetic acid (**1**) in sulfolane using phosphorus trichloride and phosphorous acid in different ratios.

	Reactants			
Entry	PCl_3 (equivalents)	$P(OH)_3$ (equivalents)	Purity (%)[a,b]	Yield of 2[b]
1	2	1	98	43
2	2	2	100	74
3	2	3	99	63
4	2	4	99	66
5	3.2	0	100	10
6	3	1	98	60
7	3	2	99	71
8	3	3	100	75

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

Table 2. Synthesis of zoledronic acid (**2**) from 1*H*-imidazol-1-ylacetic acid (**1**) in the presence of [bmim][BF_4] additive using phosphorus trichloride and phosphorous acid in different ratios.

Entry	Amount of [bmim][BF_4] (equivalents)	Reactants		Purity (%)[a,b]	Yield of 2[b]
		PCl_3 (equivalents)	$P(OH)_3$ (equivalents)		
1	1.2	2	2	98	49
2		3	2	98	48
3	0.6	2	2	99	75
4		3	2	99	75
5	0.3	2	2	96	61
6		3	2	98	62
7	0.1	2	2	97	35
8		3	2	97	36
9	0	2	2	100	39

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

phosphorus trichloride and phosphorous acid reagents. Applying 1.2, 0.6, 0.3, and 0.1 equivalents of [bmim][BF_4], zoledronic acid (**2**) was obtained in *ca.* 49, 75, 62, and 36%, respectively, in purities of 96–99% (Table 2, entries 1/2, 3/4, 5/6, and 7/8, respectively). The control experiment ran in the absence of the IL furnished the target compound in a yield of 39% (Table 2, entry 9). It can be seen that increasing the quantity of [bmim][BF_4] from 0.1 to 1.2 equivalents, the yields follow a curve with a maximum at 0.6 equivalents of the additive. From among the two experiments affording a yield of 75% (Table 1, entries 3 and 4), the one requiring only 2 equivalents of both P-reagents is the optimum. It may be concluded that (1) a catalytic amount of the selected IL is suitable to promote the reaction under discussion, (2) sulfolane used as a solvent may be substituted by [bmim][BF_4] as an additive.

Syntheses of zoledronic acid in the mixture of sulfolane and ionic liquid additive

Finally, we wished to investigate the use of [bmim][BF_4] additive in sulfolane as the solvent. Catalytic amounts of 0.6 and 0.3 equivalents were tested at a 2:2 and 3:2 molar ratios of phosphorus trichloride and phosphorous acid. As can be seen from Table 3, the joint use of 0.6 equivalents of the IL additive and sulfolane as the solvent, led to yields of 93 and 91% that were associated with purities of 99 and 98%, respectively (entries 1 and 2). The application of only 0.3 equivalents of [bmim][BF_4] resulted in somewhat lower yields of 89 and 87% (Table 3, entries 3 and 4). The massage of these experiments is that the use of a catalytic amount of [bmim][BF_4] together with sulfolane is synergetic, as their joint use led to yields around or higher than 90%. The 93% yield of zoledronic acid (**2**) obtained using the P-reagents in 2 equivalent quantities in the presence of a catalytic amount of

Table 3. Synthesis of zoledronic acid (**2**) from 1*H*-imidazol-1-ylacetic acid (**1**) in sulfolane in the presence of [bmim][BF_4] using phosphorus trichloride and phosphorous acid in different ratios.

Entry	Amount of [bmim][BF_4] (equivalents)	Reactants		Purity (%)[a,b]	Yield of 2[b]
		PCl_3 (equivalents)	$P(OH)_3$ (equivalents)		
1	0.6	2	2	99	93
2		3	2	98	91
3	0.3	2	2	99	89
4		3	2	99	87

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

[bmim][BF_4] in sulfolane means a record not only in the carrier of zoledronic acid, but also in the discipline of all dronic acid derivatives. The importance of the, for the time being, highest realistic yield is underlined by the high price of zoledronic acid.

Summary

In summary, our study on the synthesis of zoledronic acid from 1*H*-imidazol-1-ylacetic acid and phosphorus trichloride/phosphorous acid revealed that it is a good option to apply the P-reagents in a ratio of 2:2 in sulfolane, or in 0.6 equivalents of [bmim][BF_4] at a temperature of 75 °C giving the target dronic acid in a yield of 74 and 75%, respectively. It is noteworthy, that combining the former variations (using the IL catalyst in sulfolane), zoledronic acid, a high value drug, was obtained in a record yield of 93% due to synergism of the two effects.

Experimental

Preparation of zoledronic acid dihydrate (2) from 1H-imidazol-1-ylacetic acid (1), phosphorus trichloride and phosphorous acid in sulfolane (Table 1, entry 2)

1.6 g (0.013 mol) of 1*H*-imidazol-1-ylacetic 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 cooling to 25 °C, 10 mL (0.56 mol) of water was added to the mixture, and it was stirred further at 105 °C for 1 h. After cooling to 25 °C, the pH was adjusted to 1.8 by adding ~5 mL of 50% aqueous sodium hydroxide. Then, the suspension was stirred at 0–5 °C for 3 h, and the precipitate was filtered off and dried. The crude product (4.6 g) was taken up in a fivefold amount (23 mL) of hot 1 M hydrochloric acid, and the contents of the flask were stirred at 26 °C for 12 h. The precipitate was removed by filtration, and dried to furnish 2.9 g (74%) of zoledronic acid dihydrate (**2**) in a pure form. ^{31}P NMR (D_2O) δ: 17.5, δ[13]: 16.0; ^{1}H NMR (D_2O) δ: 4.50–4.46 (m, 2H, NCH_2), 7.07 (s, 1H, NCH), 7.33 (s, 1H, NCH), 8.19 (s, 1H, NCHN), δ[14]: 4.58–4.54 (m, 2H), 7.13 (s, 1H), 7.39 (s, 1H), 8.17 (s, 1H); ^{13}C NMR (D_2O) δ: 52.1 (t, $J = 2.8$, NCH_2), 72.8 (t, $J = 124.5$ P-C-P), 121.8 (s, NCH), 123.1 (s, NCH), 137.3 (s, NCHN), δ[33]: 53.0, 73.2, 118.5, 124.2, 136.1.

Preparation of zoledronic acid dihydrate (2) from 1H-imidazol-1-ylacetic acid (1), phosphorus trichloride and phosphorous acid in the presence of [bmim][BF_4] (A) or in sulfolane with [bmim][BF_4] additive (B) (Table 2, entry 3 and Table 3, entry 1)

2.5 mL (0.029 mol) of phosphorus trichloride was added dropwise into the mixture of 1.6 g (0.013 mol) of 1*H*-imidazol-1-ylacetic acid (**1**), 2.2 g (0.027 mol) of phosphorous acid and 1.4 mL (0.008 mol) of [bmim][BF_4] (**A**), or into the mixture of 5 mL of sulfolane and 1.4 mL (0.008 mol) of [bmim][BF_4] (**B**) on stirring in *ca*. 30 min, and the contents of the flask were stirred at 75 °C for 3 h. Further process including hydrolysis, pH adjustment, filtration and recrystallization was performed as described above to afford 2.9 g (75%, (**A**), Table 2, entry 3) and 3.6 g (93%, (**B**), Table 3, entry 1) of zoledronic acid dihydrate (**2**) in a purity of 99%. ^{31}P NMR (D_2O) δ: 17.6 and 17.3 respectively, δ[13]: 16.0.

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