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# Preparation of new imidazol-2-yl-(amino)methylphosphonates, phosphinates and phosphine oxides and their unexpected cleavage under acidic conditions

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ABSTRACT

The efficient synthesis of new imidazol-2-yl-(amino)methylphosphonic acids, phosphonates phosphinate esters and phosphine oxides is described. The synthetic methodology is based on nucleophilic addition of phosphorus species to imidazole-2 derived imines. Additionally, it was discovered that heating the imidazol-2-yl-(amino)methylphosphonates with aqueous HCl or $H_2SO_4$ leads to their decomposition resulting in a rupture of the C–P bond, elimination of the phosphorous-containing fragment and formation of the corresponding secondary imidazole-2 alkylamines. A mechanistic pathway for the cleavage is postulated.



## 1. Introduction

Imidazole is a common heterocyclic fragment of many highly significant naturally occurring small molecules, such as histidine, histamine, adenine, biotin etc.[1] Additionally, imidazole derivatives are well-known structural scaffolds in medicinal chemistry endowed with numerous important activities (Fig. 1). Members of this class of diazoles are known to possess antibiotic and antifungal activities.[2] In addition, these heterocycles include inhibitors of p38 MAP kinases, a subgroup of mitogen-activated protein kinases, thought to be involved in a variety of inflammatory and immunological disorders.[3]

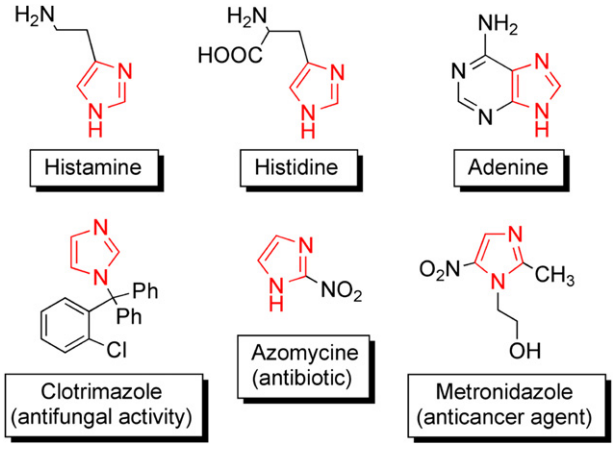


**Fig. 1.** Imidazole derivatives in nature and medicine.

On the other hand, as phosphorus analogues of natural aminocarboxylic acids, α-aminomethylphosphonic acids, their phosphonate and phosphinate esters and short peptides incorporating this fragment exhibit a variety of intriguing biological properties, and thus they have found diverse applications in many areas of modern medicine and agriculture.[4]

Based on the aforementioned facts, the union of a heteroaromatic fragment with a phosphorous-containing moiety could result in valuable chemical and biological properties of such heteroaromatic phosphonates and their derivatives, and thus the development of new protocols leading to these compounds would be especially desirable.[5]

As a part of our continuous interest in the preparation of new heteroaromatic phosphonates,[6] we describe the results of a study on the synthesis of new imidazol-2-yl-(amino)methylphosphonic acids, their phosphonate and phosphinate esters, and phosphine oxides and the unusual cleavage of these compounds under acidic conditions.

## 2. Results and discussion

### 2.1. Preparation of imdazol-2-yl-(amino) methylphosphonates phosphinates and phosphonic acids

Initially, we have examined the preparation of imdazol-2-yl-(amino)methylphosphonic and phenylphosphinic ethyl esters **3**

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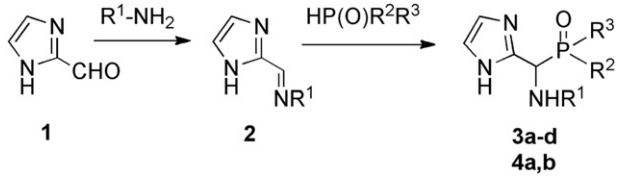
and diphenylphosphine oxides **4** by addition of, respectively, diethyl phosphite, ethyl phenylphosphinate, or diphenylphosphine oxide to imidazole derived imines **2**. Imines were prepared in situ from imidazole-2-carboxaldehyde (**1**) and secondary amines (benzyl and *n*-butyl amine) (Scheme 1, Table 1). Addition of phosphorus nucleophiles to imines **2** proceeded well at reflux in toluene. After 2 h the reaction was complete and the desired products **3a**–**d** and **4a**,**b** were formed. Diethyl phosphonate esters **3a**,**b** were isolated and characterized as oxalate salts obtained by treatment of the crude esters **3a**,**b** with oxalic acid [$(COOH)_2 \cdot 2H_2O$] in acetone. In turn, phosphinate esters **3c**,**d** and phosphine oxides **4a**,**b** were purified, without recourse to chromatography, by simple crystallization from a mixture of toluene/hexane.




**Scheme 1.** Synthesis of phosphonates and phosphinates **3a**–**d** and phosphine oxides **4a**,**b**.

**Table 1**
Prepared phosphonates and phosphinates **3a**–**d** and phosphine oxides **4a**,**b**

| Imine | $R^1$ | Product (%)[a] | $R^2$ | $R^3$ |
|---|---|---|---|---|
| **2a** | *n*-Bu | **3a** (48)[b] | OEt | OEt |
| **2b** | Bn | **3b** (41)[b] | OEt | OEt |
| **2a** | *n*-Bu | **3c** (82) | OEt | Ph |
| **2b** | Bn | **3d** (74) | OEt | Ph |
| **2a** | *n*-Bu | **4a** (48) | Ph | Ph |
| **2b** | Bn | **4b** (89) | Ph | Ph |

[a] Yield of the desired product after simple crystallization.
[b] Products isolated as an oxalate salts.

Imidazol-2-yl-(amino)methylphenylphosphinates **3c**,**d** were obtained as mixtures of two diastereoisomers (due to the presence of a chiral centre at P and α-C atoms) in approximately 1:1 ratio, as shown by their $^{31}P$ NMR spectra.

Subsequently, we became interested in the preparation of imidazol-2-yl-aminophosphonic acids **6**. Our interest in these compounds grew from the fact that biological activities presented by aminomethylphosphonic acids is often related to their strong affinity for binding metal ions.[4] In this context, heterocyclic aminophosphonic acids incorporating an imidazole moiety are especially interesting as they exhibit strong chelating activity towards transition metal ions [e.g., Cu(II) and Ni(II)].[7] The imidazol-2-yl-aminophosphonate derivatives presented here are unknown and could have valuable chemical and biological properties, and thus the synthesis of those compounds was desirable.

Imidazol-2-yl-aminophosphonic acids **6** were obtained using the protocol depicted in Scheme 2, based on the nucleophilic addition of silylated phosphorus esters[6g] to the corresponding imidazole-2 aldimines **2**. The aldimines, formed in situ, were reacted with silylated phosphorous esters to give the silylated esters **5**, as intermediates, which were subsequently desilylated producing the desired imidazol-2-yl-aminophosphonic acids **6a**–**e** as crystalline, non-hygroscopic white solids (Scheme 2, Table 2).

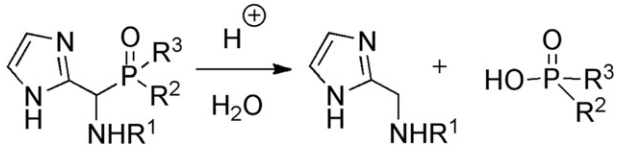
**Table 2**
Obtained imidazol-2-yl-(amino)methylphosphonic acids **6**

| Imine | $R^1$ | Product (%)[a] |
|---|---|---|
| **2a** | *n*-Bu | **6a** (54) |
| **2b** | Bn | **6b** (85) |
| **2c** | 2-$PyCH_2$ | **6c** (37) |
| **2d** | 3-$PyCH_2$ | **6d** (73) |
| **2e** | Imidazol-1-yl-$(CH_2)_3$ | **6e** (58) |

[a] Yield of the desired product after simple crystallization.

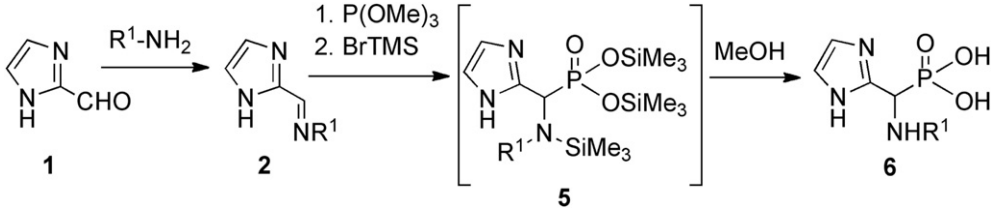
The use of bromotrimethylsilane (BrTMS) resulted in an easier silylation process of the alkyl phosphoesters[6g,11a] due to a higher reactivity of the BrTMS in comparison with chlorotrimethylsilane, frequently used in silylation reactions. Application of BrTMS gave excellent results and formed the desired imidazole-2 aminophosphonic acids by a direct way and in high yield and purity after simple crystallization.

It has to be noted, that the direct hydrolysis of the imidazol-2-yl-(amino)methylphosphonates **3a**,**b**, a classical method for the preparation of aminophosphonic acids, failed in our case. After heating of phosphonic esters **3a**,**b** ($R^2$=$R^3$=OEt) for 2 h at reflux in the presence of aqueous 6 M HCl, evaporation of the solvent, neutralization of the remaining residue with aqueous $Na_2CO_3$ and extraction with $CH_2Cl_2$, surprisingly, the secondary amines **7** were isolated. In turn, when the remaining aqueous layer was evaporated and $^{31}P$ NMR was recorded from the remaining residue, a sharp singlet at $\delta_P$ ~1.12 ppm corresponding to the formed phosphoric acid was observed. Later on, we observed that heating of phosphine oxides **4a**,**b** in 6 M HCl for 1 h also leads to their decomposition and formation of the corresponding amines **7** and phosphorus-containing fragment (diphenylphosphinic acid $HOP(O)Ph_2$).[9f] The general mechanism of the cleavage of the imidazole-2-aminophosphorus derivatives is depicted in Scheme 3.




**Scheme 3.** Decomposition of imidazole-2-yl-(amino)methylphosphorous derivatives **3**, **4** and **6** in the presence of a strong mineral acid.

Based on the obtained results, we postulate that the observed decomposition of imidazol-2-yl-(amino)methylphosphonates and phosphinates **3** and phosphine oxides **4** to secondary amines **7** and phosphorus-containing fragment is a result of the C–P bond cleavage. In fact, such a process (cleavage of C–P bond) is recognized to play an important role in biological tasks exhibited by organophosphorus compounds and is present in living organisms.[8]




**Scheme 2.** Preparation of imidazol-2-yl-(amino)methylphosphonic acids **6**.

### 2.2. Cleavage of the imidazol-2-yl-(amino) methylphosphonates phosphinates and phosphonic acids under acidic conditions

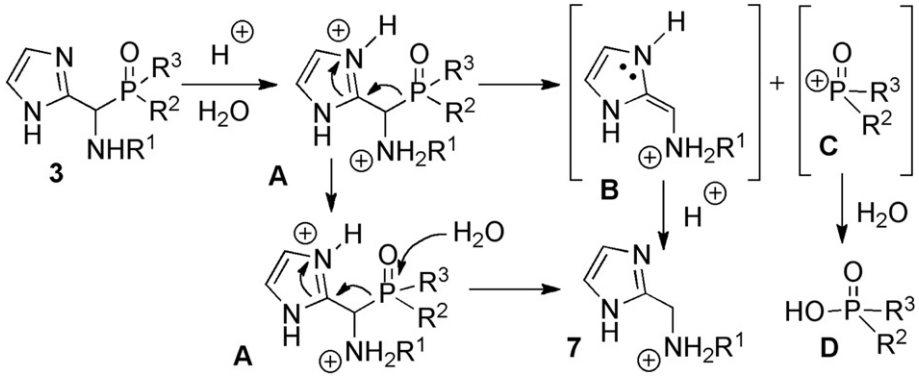
Taking into account literature reports[6,8,9] two alternative mechanistic pathways for the cleavage of the corresponding imidazole-2-yl-(amino)methylphosphorus derivatives under acidic conditions can be postulated (Scheme 4, $R^2$=$R^3$=OEt, OH, or Ph). The first proposed mechanistic pathway is a dissociative-type $S_N1(P)$ mechanism that relies upon the rupture of the C–P bond in protonated aminophosphonate **A** and subsequent formation of two intermediate products: an enamine-like moiety **B** and a metaphosphate-like moiety **C**. Intermediate **B** transforms into the secondary amine **7** by incorporation of a proton. In turn, **C** is actually closely associated with the well-known monomeric metaphosphate ($HOPO_2$).[10] As reactive intermediate, **C** can react with water to form, in the case of decomposition of imidazol-2-yl-(amino)methylphosphonic acids **6**, the phosphoric acid ($H_3PO_4$) **D** as a final product (Scheme 4). Similar mechanism of C–P bond cleavage can be postulated for imidazol-2-yl-(amino)methyldiphenylphosphine oxides **4a**,**b** (Scheme 4, $R^2$=$R^3$=Ph). In the latter case, the product **D** is the diphenylphosphinic acid, $HOP(O)Ph_2$.[9f] Phosphonic acids **6a**–**e** however, were found to be more stable and a longer reaction time was required to complete the cleavage process (Table 3).

**Table 3**
Determination of kinetic parameters of the cleavage of selected imidazol-2-yl-(amino)methylphosphonates, phosphine oxides and phosphonic acids[a]

| Entry | Compound | Concn of acid mol $L^{-1}$ | Kinetic parameters | |
|---|---|---|---|---|
| | | | $10^{-4}$ $k_{obs}$ $s^{-1}$ | $k_H/k_D$ |
| 1 | **3d** | 1.0 ($H_2SO_4$) | 2.43 | 1.09 |
| | | 2.0 ($H_2SO_4$) | 4.92 | 1.21 |
| | | 1.0 ($D_2SO_4$) | 2.23 | |
| | | 2.0 ($D_2SO_4$) | 4.05 | |
| 2 | **4a** | 1.0 ($H_2SO_4$) | 0.317 | 1.06 |
| | | 2.0 ($H_2SO_4$) | 0.497 | 1.41 |
| | | 1.0 ($D_2SO_4$) | 0.298 | |
| | | 2.0 ($D_2SO_4$) | 0.354 | |
| 3 | **4b**[b] | 1.0 ($H_2SO_4$) | 0.191 | 1.33 |
| | | 2.0 ($H_2SO_4$) | 0.566 | 1.07 |
| | | 1.0 ($D_2SO_4$) | 0.143 | |
| | | 2.0 ($D_2SO_4$) | 0.530 | |
| 4 | **6a** | 1.0 ($H_2SO_4$) | 0.0310 | ~1.0 |
| | | 2.0 ($H_2SO_4$) | 0.0355 | |
| | | 1.0 ($D_2SO_4$) | 0.0312 | |
| 5 | **6b** | 1.0 ($H_2SO_4$) | 0.0671 | ~1.0 |
| | | 2.0 ($H_2SO_4$) | 0.0553 | |
| | | 1.0 ($D_2SO_4$) | 0.0682 | |

[a] Kinetic measurements were conducted in 50% (v/v) aqueous methanol solutions or 50% (v/v) $D_2O$ in $CD_3OD$. Experiments were run at 22 °C (except for acids **6a** and **6b** in which case the experiments were run at 90 °C). In all cases concentration of the starting material was 0.1 mol $L^{-1}$.

[b] For **4b** additional kinetic measurements were performed that allowed calculation of the activation parameters: $Ea$=79.15 [kJ $mol^{-1}$]; $\Delta H$=76.60 [kJ $mol^{-1}$]; and $\Delta S$=−76.15 [J $mol^{-1}$ $K^{-1}$].




**Scheme 4.** Possible mechanistic pathways of the cleavage.

The second postulated mechanism is an associative-type $S_N2(P)$ mechanism[9a,b] that involves a direct nucleophilic attack of water molecule at phosphorus in the protonated aminophosphonate **A** prior to the cleavage of the C–P bond. Further reorganizations lead to the formation of the same products as in the case of $S_N1(P)$ mechanism (Scheme 4).

*2.2.1. Kinetic measurements of the cleavage of the imidazol-2-yl-(amino)methylphosphonates, phosphinates and phosphonic acids under acidic conditions.* In order to gather more details about the observed decomposition mechanism, kinetic measurements were performed. For kinetic purposes, the cleavage of the selected imidazol-2-yl-(amino)methylphosphonate ester **3d**, phosphine oxides **4a**,**b** and phosphonic acids **6a**,**b** were run in 50% (v/v) aqueous methanol solutions, containing a well define quantity of $H_2SO_4$. All reactions were run directly in NMR tubes and the kinetics were measured with the use of $^{31}P$ NMR spectroscopy (Fig. 2).

The relative quantities of the phosphorus-containing products and starting materials were estimated from the corresponding integrated $^{31}P$ NMR signals. The appearance of a signal assigned to the phosphorus-containing fragment resulting from the C–P bond cleavage together with the decay of the signal corresponding to the starting material was observed (Fig. 2). A pseudo-first-order reaction was deduced and the rate constants for all experiments were determined (Table 3). It was found that the rate constants were considerably dependent on the concentration of the acid used. These results demonstrate that the protonation of imidazole-2-yl-(amino)methylphosphonates has a profound effect on the cleavage of the C–P bond. Kinetic measurements performed in deuterated solvents allowed calculation of isotope effects ($k_H/k_D$>1) showing that protons are involved in the rate-determining step. For compound **4b** additional kinetic measurements were carried out that allowed calculation of the activation parameters ($Ea$, $\Delta H$ and $\Delta S$, Table 3). Low value of the activation energy ($Ea$) calculated for the cleavage of **4b** confirms the observed facility of cleavage of this aminophosphine oxide under acidic conditions.

It has to be noted, that the corresponding imidazole-4(5)-yl-(amino)methylphosphonates[11a] and phosphine oxides[11b] are stable under acidic conditions and the cleavage of the C–P bond in the case of those compounds does not take place (this was proved experimentally). In this case, the reason for stability of these derivatives is that there is no possibility of formation of an

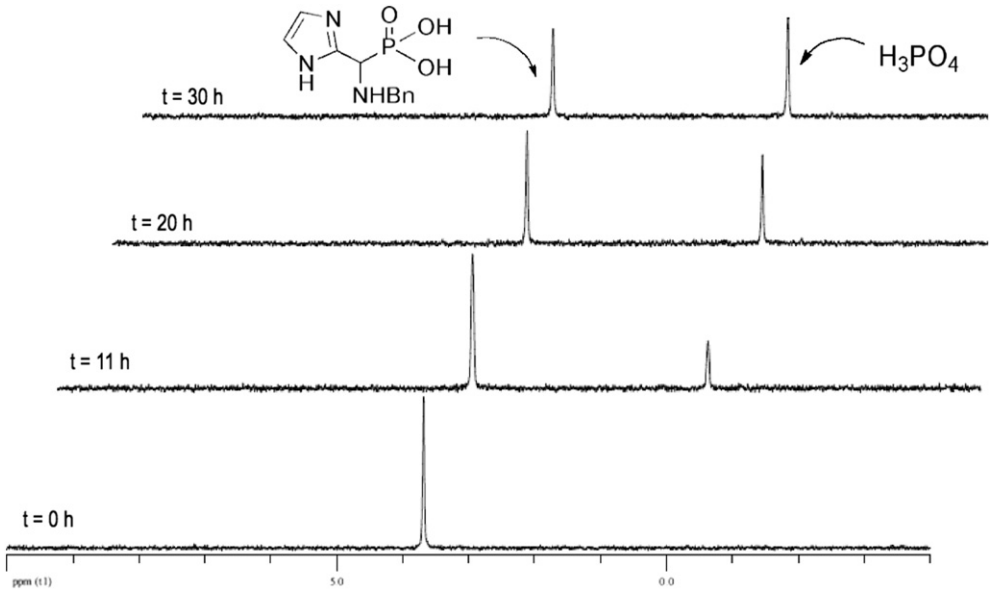
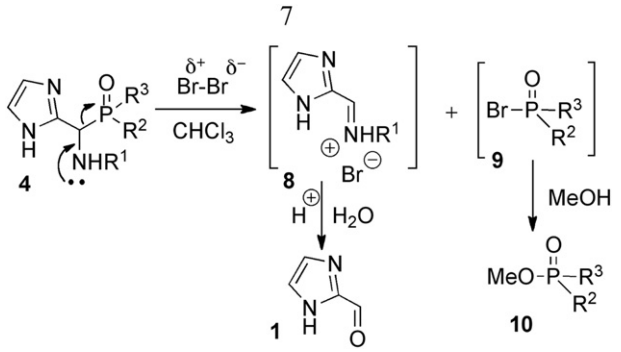



**Fig. 2.** Kinetic experiment of the cleavage of **6b** in 1.0 M $H_2SO_4$ monitored by $^{31}P$ NMR.

appropriate resonance structure **B** (Scheme 4), responsible for cleavage in the postulated mechanisms.[9d–f]

### 2.3. Cleavage of the imidazol-2-yl-(amino)methylphosphine oxides in the presence of an electrophilic reagent and in aprotic solvent

In addition, we discovered that the cleavage of the imidazol-2-yl-(amino)methylphosphonates, phosphinates and phosphine oxides can occur in aprotic solvents (such as chloroform, dichloromethane etc.), by the use of electrophilic reagents (e.g., elemental bromine $Br_2$). Heating of aminophosphine oxide **4a** in $CHCl_3$ for 2 h in the presence of $Br_2$ leads (after evaporation of the solvent) to the mixture composed of imine **8** and diphenylphosphinic acid bromide **9** (Scheme 5). Subsequent treatment of the crude reaction mixture with methanol, acidification and extraction with $CH_2Cl_2$ allows isolation of the diphenylphosphinic acid methyl ester **10**[9f] in 80% yield (Scheme 5). From the aqueous phase (after neutralization) imidazole-2-carboxaldehyde (**1**) was isolated, as a product of the decomposition of imine **8** (Scheme 5). More insights into this particular cleavage reaction will be presented in a separate communication.[9h] On the basis these results however, the occurrence of the $S_N2(P)$ mechanism[9a,b] seems to be questionable.[9h]




**Scheme 5.** Cleavage of imidazol-2-yl-(amino)methylphosphonates in the presence of $Br_2$ in $CHCl_3$.

In summary, we have presented an efficient synthesis of new imidazol-2-yl-(amino)methylphosphonic acids, corresponding phosphonate and phosphinate esters, and phosphine oxides via nucleophilic addition of appropriate phosphorus species to imidazole-2 derived imines. The desired new compounds were obtained in good yields as crystalline, non-hygroscopic solids after simple crystallization. In addition, we have discovered that all the synthesized compounds were unstable and decompose under acidic conditions with formation of the corresponding secondary amines and corresponding phosphorous-containing fragment. The cleavage phenomenon was investigated and two possible mechanistic pathways were postulated, an associative-type $S_N2(P)$ mechanism and a dissociative-type $S_N1(P)$ mechanism. In light of the obtained results the dissociative-type $S_N1(P)$ mechanism seems to be the correct mechanistic pathway for the cleavage of the imidazol-2-yl(amino)methylphosphonate and phosphinate derivatives.

## 3. Experimental section

### 3.1. General

$^1H$ (300 MHz), $^{13}C$ (75 MHz) and $^{31}P$ (120 MHz) NMR spectra were recorded on a Bruker Avance TM DRX (300 MHz) spectrometer. Chemical shifts ($\delta$) are reported in parts per million relative to internal tetramethylsilane ($Me_4Si$, $\delta$ 0.0) for $^1H$ NMR, $CDCl_3$ ($\delta$ 77.0) for $^{13}C$ NMR and external 85% phosphoric acid ($\delta$ 0.0) for $^{31}P$ NMR. Coupling constants ($J$) are reported in hertz. HRMS analyses were performed on LCT Premier XE Waters apparatus, on mode ESI+ (TOF MS ES+). IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer. All reagents were used as received from the commercial supplier. All solvents for extractions and reactions were technical grade and were dried before use using standard techniques.

### 3.2. Preparation of diethyl imidazol-2-yl-(amino) methylphosphonates and phosphinates 3a–d

Neat secondary aromatic or aliphatic amine (5.0 mmol) was introduced at rt to a solution of imidazole-2-carboxaldehyde (**1**) (0.48 g, 5.0 mmol) in MeOH (100 mL) and the reaction was stirred

at reflux for 1 h. After that time, solvent was evaporated under reduced pressure affording crude imines **2** that were used directly in the next step. The crude imine (5.0 mmol) was dissolved in dry toluene (50 mL) and diethyl phosphite (0.65 mL, 5.0 mmol) or ethyl phenylphosphinate (0.75 mL, 5.0 mmol) was added. The mixture was heated to reflux for 2 h and then concentrated under reduced pressure affording crude esters **3** as thick oils or semi-solids. The phosphinate esters **3c**,**d** were recrystallized from a mixture of toluene/hexane. The phosphonate esters **3a**,**b** were characterized as oxalate salts. The oxalates were obtained in the following way; the crude ester (1.0 equiv) was dissolved in acetone (10 mL) and oxalic acid $(COOH)_2 \cdot 2H_2O$ (2.0 equiv) in acetone (10 mL) was added and the mixture was refrigerated. The separated precipitate was filtered, washed with cold acetone (10 mL) and dried on air.

*3.2.1. Imidazol-2-yl-methyl(N-butylamino)phosphonate diethyl ester (**3a**).* Oxalate; white solid; 0.90 g (yield 48%); mp 118–119 °C. $^1$H NMR ($D_2O$): $\delta_H$=7.20 (d, 1H, $J$=6.9 Hz, imidazole), 7.07 (d, 1H, $J$=6.7 Hz, imidazole), 4.21 (d, 1H, CH–P, $J_{H-P}$=13.1 Hz), 4.14 (m, 4H, $CH_2O$), 2.82 (m, 2H, $CH_2N$), 1.45 (m, 2H, $CH_2$), 1.22–1.10 (m, 8H, $CH_2$, $CH_3$ from OEt), 0.82 (t, 3H, $CH_3$, $J$=7.24 Hz). $^{31}$P NMR ($D_2O$): $\delta_P$=14.71. $^{13}$C NMR ($D_2O$): $\delta_C$=164.9 $(COOH)_2$, 136.8, 121.5, 121.0, 66.4, 62.8, 51.1 (d, $J_{C-P}$=129.4 Hz), 48.0, 28.7, 19.2, 15.5. IR, $\nu_{max}$ (KBr): 3405 (NH), 3110, 2981, 1925, 1720, 1632, 1562, 1198 (P═O), 1174, 1020 (P–O), 781, 743, 721, 695, 542, 531, 507 cm$^{-1}$. HRMS: calcd for $C_{12}H_{25}N_3O_3P$ $(M+H)^+$ 290.1634. Found 290.1628.

*3.2.2. Imidazol-2-yl-methyl(N-benzylamino)phosphonate diethyl ester (**3b**).* Oxalate; white solid; 0.84 g (yield 41%); mp 187–188 °C. $^1$H NMR ($D_2O$): $\delta_H$=7.33–7.09 (m, 7H, Ph and imidazole), 4.28 (1H, CHP, d, $J_{H-P}$=12.7 Hz), 4.01 (m, 4H, $CH_2O\times2$), 3.78 (m, 2H, $CH_2N$), 1.11 (m, 6H, $CH_3\times2$). $^{31}$P NMR ($D_2O$): $\delta_P$=17.62. $^{13}$C NMR ($D_2O$): $\delta_C$=164.3 $(COOH)_2$, 140.9, 136.4, 132.6, 130.0, 129.9, 129.4, 120.1, 65.7, 51.9, 50.8 (d, $J_{C-P}$=128.7 Hz), 15.6. IR, $\nu_{max}$ (KBr): 3400–3350 (NH), 3131, 2985, 2652, 1923, 1727, 1634 [$(COOH)_2$], 1457, 1271, 1217 (P═O), 1044 (P–O), 961, 914, 752, 708, 565, 494 cm$^{-1}$. HRMS: calcd for $C_{15}H_{23}N_3O_3P$ 324.1477. Found 324.1468.

*3.2.3. Imidazol-2-yl-methyl(N-butylamino)phenylphosphinate ethyl ester (**3c**).* Yellowish solid; 1.31 g (yield 82%); mp 85–90 °C. $^1$H NMR ($CDCl_3$): $\delta_H$=7.81–7.26 (m, 5H, Ph), 7.00 (d, $J$=7.0 Hz, 1H, imidazole), 6.88 (d, $J$=7.2 Hz, 1H, imidazole), 4.44–4.41 (d, 1H $J_{H-P}$=8.2 Hz, CH–P diastereoisomer 1). 4.39–4.36 (d, 1H, $J_{H-P}$=8.1 Hz, CH–P diastereoisomer 2), 4.18–4.01 (m, 2H, $CH_2O$), 2.50–2.39 (m, 2H, $CH_2N$), 1.37–1.14 (m, 7H, $CH_2$, $CH_3$), 0.80–0.74 (m, 3H, $CH_3$). $^{31}$P NMR ($CDCl_3$): $\delta_P$=37.51 and 37.12 (two diastereoisomers). $^{13}$C NMR ($CDCl_3$): $\delta_C$=133.9, 133.0, 131.9, 128.9, 128.7, 128.6, 127.4, 65.1, 47.6 (d, $J_{C-P}$=79.9 Hz diastereoisomer 1), 46.8 (d, $J_{C-P}$=80.1 Hz diastereoisomer 2), 38.2, 37.1, 24.5, 15.8, 9.6. IR, $\nu_{max}$ (KBr): 3410 (NH), 3114, 2956, 2874, 2782, 1509, 1440, 1205 (P═O), 1174, 1026 (P–O), 784, 752, 727, 708, 698, 574, 552, 532, 509 cm$^{-1}$. HRMS: calcd for $C_{16}H_{25}N_3O_2P$ $(M+H)^+$ 322.1684. Found 322.1691.

*3.2.4. Imidazol-2-yl-methyl(N-benzylamino)phenylphosphinate ethyl ester (**3d**).* Yellowish solid; 1.30 g (yield 74%); mp 131–133 °C. $^1$H NMR (DMSO-$d_6$): $\delta_H$=7.67–6.92 (m, 10H Ph and imidazole), 4.16 (d, 1H, CHP, $J_{H-P}$=8.3 Hz diastereoisomer 1), 4.12 (d, 1H, CHP, $J_{H-P}$=8.3 Hz diastereoisomer 2), 4.10–3.67 (m, 4H, $CH_2O$, $CH_2N$), 1.21–1.02 (m, 3H, $CH_3$). $^{31}$P NMR (DMSO-$d_6$): $\delta_P$=36.06 and 36.14 (two diastereoisomers). $^{13}$C NMR (DMSO): $\delta_C$=142.8, 139.5, 139.3, 132.2, 131.9, 131.8, 131.7, 128.3, 128.1, 128.0, 127.9, 61.3, 56.2 (d, $J_{C-P}$=77.0 Hz diastereoisomer 1), 54.7 (d, $J_{C-P}$=76.9 Hz diastereoisomer 2), 50.9, 16.2. IR, $\nu_{max}$ (KBr): 3412 (NH), 3184, 3058, 2979, 2902, 2848, 2782, 1592, 1539, 1455, 1440, 1205 (P═O), 1123, 1035 (P–O), 959, 776, 749, 697, 569, 551, 525, 510 cm$^{-1}$. HRMS: calcd for $C_{19}H_{23}N_3O_2P$ $(M+H)^+$ 356.1528. Found 356.1508.

### 3.3. Preparation of imidazol-2-yl-(amino)methylphosphine oxides 4a,b

Protocol described above for the preparation of esters **3a**–**d** was followed. Here, *H*-diphenylphosphine oxide was used as a nucleophilic reagent for addition to the double bond of imine. Reagents were refluxed in toluene for 1 h. After work-up, crude imidazol-2-yl-aminodiphenylphosphine oxides **4**, were purified by crystallization from mixture toluene/hexane.

*3.3.1. Imidazol-2-yl-methyl(N-butylamino)diphenylphosphine oxide (**4a**).* White solid; 0.84 g (yield 48%); mp 138–144 °C. $^1$H NMR (DMSO-$d_6$): $\delta_H$=7.83–7.25 (m, 12H, imidazole and Ph), 6.84 (br s, 1H, NH), 4.89 (d, 1H, CH–P, $J_{H-P}$=11.9 Hz), 2.38–2.31 (m, 2H, $CH_2N$), 1.21–1.16 (m, 2H, $CH_2$), 1.08–0.95 (m, 2H, $CH_2$), 0.74–0.61 (m, 3H, $CH_3$). $^{31}$P NMR (DMSO-$d_6$): $\delta_P$=28.88. $^{13}$C NMR (DMSO): $\delta_C$=143.9, 133.4, 132.1, 131.8, 131.7, 131.4, 129.2, 128.6, 128.6, 128.4, 127.9, 57.5 (d, $J_{C-P}$=83.3 Hz), 48.3, 31.6, 20.1, 14.1. IR, $\nu_{max}$ (KBr): 3432 (NH), 3303 (NH), 3138, 3061, 2959, 2926, 2894, 2827, 1591, 1553, 1485, 1438, 1172 (P═O), 1122, 1098 (P–O), 1070, 1037, 855, 743, 726, 693, 561, 542, 525, 439 cm$^{-1}$. HRMS: calcd for $C_{20}H_{25}N_3OP$ $(M+H)^+$ 354.1735. Found 354.1719.

*3.3.2. Imidazol-2-yl-methyl(N-benzylamino)diphenylphosphine oxide (**4b**).* White solid; 1.71 g (yield 89%); mp 162–168 °C. $^1$H NMR ($CDCl_3$): $\delta_H$=7.71–7.12 (m, 17H, Ph and imidazole), 6.86 (br s, 2H, NH amine, NH imidazole) 4.87 (d, 1H, CH–P, $J_{H-P}$=11.4 Hz), 3.87 (d, 1H, $PhCH_2$, $J$=13.1 Hz), 3.60 (d, 1H, $PhCH_2$, $J$=13.2 Hz). $^{31}$P NMR ($CDCl_3$): $\delta_P$=33.22. $^{13}$C NMR ($CDCl_3$): $\delta_C$=143.2, 139.1, 132.0, 131.9, 131.7, 131.3, 131.2, 130.9, 128.7, 128.5, 128.4, 128.3, 128.2, 127.7, 127.0, 56.8 (d, $J_{C-P}$=83.7 Hz), 52.4 (d, $^3J_{C-P}$=13.8 Hz). IR, $\nu_{max}$ (KBr): 3436 (NH), 3292 (NH), 3137, 3057, 2971, 2895, 1962, 1590, 1552, 1490, 1438, 1167 (P═O), 1123, 1100 (P–O), 1070, 1025, 850, 789, 738, 693, 566, 554, 525, 435 cm$^{-1}$. HRMS: calcd for $C_{23}H_{23}N_3OP$ $(M+H)^+$ 388.1579. Found 388.1584.

### 3.4. Preparation of imidazol-2-yl-methyl(amino)phosphonic acids 6a–e

To a solution of crude imine **2** (prepared as described above, 2.5 mmol) in dry $CH_2Cl_2$ (25 mL) was added trimethyl phosphite (0.32 g, 2.5 mmol), followed by bromotrimethylsilane (1.6 g, 10 mmol). The mixture was stirred for 24 h at room temperature and evaporated under reduced pressure. The resulted oil was treated with methanol (5 mL) and refrigerated for several hours. The products, imidazole-2-yl-(amino)methylphosphonic acids (**6a**–**c**) separated as white solids and were collected by filtration, washed with methanol/diethyl ether 1:1 (20 mL) and dried in air. In the case of imidazole-2-yl-(amino)methylphosphonic acids **6d**,**e**, methanol from reaction mixture was evaporated under reduced pressure and the products were crystallized from acetone/water solution (1:1) (10 mL).

*3.4.1. Imidazol-2-yl-methyl(N-butylamino)phosphonic acid (**6a**).* White solid; 0.31 g (yield 54%); mp 224–226 °C. $^1$H NMR ($D_2O$): $\delta_H$=7.34 (s, 2H, imidazole), 4.67 (d, 1H, CHP, $J_{H-P}$=17.1 Hz), 2.98–2.80 (m, 2H, $CH_2N$), 1.50–1.44 (m, 2H, $CH_2$), 1.18–1.03 (m, 2H, $CH_2$), 0.80 (t, 3H, $CH_3$, $J$=7.2 Hz). $^{31}$P NMR ($D_2O$): $\delta_P$=4.07. IR, $\nu_{max}$ (KBr): 3410 (NH), 3143 (NH), 2965, 2937, 2875, 2687, 2563, 1922, 1616, 1516, 1471, 1308, 1110 (P═O), 1074 (P–O), 975, 901, 785, 744, 677, 577, 551, 511,

484 $cm^{-1}$. HRMS: calcd for $C_8H_{17}N_3O_3P$ $(M+H)^+$ 234.1008. Found 234.1007.

*3.4.2. Imidazol-2-yl-methyl(N-benzylamino)phosphonic acid (**6b**).* White solid; 0.56 g (yield 85%); mp 216–219 °C. $^1H$ NMR (0.1 M $D_2SO_4$): $\delta_H$=7.25 (s, 2H, imidazole), 7.22–7.09 (m, 5H, Ph), 4.98 (d, 1H, CHP $J_{H-P}$=17.9 Hz), 4.39 (d, 1H, $J$=13.2 Hz, $NCH_2Ph$), 4.22 (d, 1H, $J$=13.2 Hz, $NCH_2Ph$); $^{31}P$ NMR (0.1 M $D_2SO_4$): $\delta_P$=2.24. $^{13}C$ NMR (0.1 M $D_2SO_4$): $\delta_C$=133.2, 130.0, 128.3, 128.0, 127.6, 126.5, 119.4, 50.8, 49.3 (d, $J_{C-P}$=134.4 Hz). IR, $\nu_{max}$ (KBr): 3472, 3443 (NH), 3148, 3033, 2941, 2733, 2533, 2433, 1874, 1617, 1495, 1457, 1332, 1200, 1167, 1092 (P=O), 1060 (P–O), 978, 876, 753, 693, 605, 573, 504, 484 $cm^{-1}$. HRMS: calcd for $C_{11}H_{15}N_3O_3P$ $(M+H)^+$ 268.0851. Found 268.0874.

*3.4.3. Imidazol-2-yl-methyl(N-2-pyridylmethylamino)phosphonic acid (**6c**).* White solid; 0.24 g (yield 37%); mp 146–148 °C. $^1H$ NMR ($D_2O$): $\delta_H$=8.39 (d, 1H, 6-Py, $J$=5.6 Hz), 8.02 (m, 1H, 4-Py), 7.92 (d, 1H, 3-Py, $J$=7.9 Hz), 7.81 (t, 1H, 5-Py, $J$=6.6 Hz), 7.22 (s, 2H, 4(5)-imidazole), 4.34 (d, 1H, CHP, $J_{H-P}$=21.4 Hz), 4.12 (dd, 1H, $CH_aH_b$, $J$=16.3 Hz), 4.08 (dd, 1H, $CH_aH_b$, $J$=16.3 Hz). $^{31}P$ NMR ($D_2O$): $\delta_P$=11.20. $^{13}C$ NMR ($D_2O$+NaOD): $\delta_C$=153.6 (d, 2-imidazole, $^2J_{C-P}$=4.2 Hz), 148.9, 146.5, 145.2, 140.8, 126.7 (d, $J$=3.5 Hz), 125.7 (d, $J$=1.8 Hz), 118.8, 60.2 (d, *C*HP, $^1J_{C-P}$=128.0 Hz), 42.9 (d, *C*$H_2$, $^3J_{C-P}$=12.3 Hz). IR, $\nu_{max}$ (KBr): 3321 (NH), 3295 (NH), 2852, 2674, 2567, 1630, 1603, 1524, 1470, 1287, 1171 (P=O), 1080 (P–O), 908, 772, 552 $cm^{-1}$. HRMS: calcd for $C_{10}H_{14}N_4O_3P$ $(M+H)^+$ 269.0804. Found 269.0802.

*3.4.4. Imidazol-2-yl-methyl(N-3-pyridylmethylamino)phosphonic acid (**6d**).* White solid; 0.48 g (yield 73%); mp 216–218 °C. $^1H$ NMR ($D_2O$+NaOD): $\delta_H$=8.02 (br s, 1H, 6-Py), 7.98 (s, 1H, 2-Py), 7.38 (d, 1H, 4-Py, $J$=6.6 Hz), 7.03 (t, 1H, 5-Py, $J$=6.6 Hz), 6.63 (s, 2H, 4(5)-imidazole), 3.53 (d, 1H, CHP, $J_{H-P}$=17.3 Hz), 3.37 (dd, 1H, $CH_aH_b$, $J$=13.1 Hz), 3.29 (dd, 1H, *C*$H_aH_b$, $J$=13.1 Hz). $^{31}P$ NMR ($D_2O$+NaOD): $\delta_P$=13.80. $^{13}C$ NMR ($D_2O$+NaOD): $\delta_C$=148.4, 147.3 (d, 2-imidazole, $^2J_{C-P}$=4.4 Hz), 147.1, 137.4, 134.9, 123.9, 123.8, 121.4, 57.0 (d, *C*HP, $^1J_{C-P}$=132.0 Hz), 49.7 (d, *C*$H_2$, $^3J_{C-P}$=13.1 Hz). IR, $\nu_{max}$ (KBr): 3434 (NH), 2742, 2551, 1962, 1620, 1461, 1429, 1125 (P=O), 1035 (P–O), 980, 882, 505 $cm^{-1}$. HRMS: calcd for $C_{10}H_{14}N_4O_3P$ $(M+H)^+$ 269.0804. Found 269.0802.

*3.4.5. Imidazol-2-yl-methyl[(N-imidazol-1-yl-n-propyl)amino]phosphonic acid (**6e**).* White solid; 0.41 g (yield 58%); mp 116–118 °C. $^1H$ NMR ($D_2O$): $\delta_H$=8.58 (s, 1H, 2-imidazole), 7.34 (s, 1H, 5-imidazole), 7.28 (s, 1H, 4-imidazole), 7.24 (s, 2H, 4(5)-imidazole), 4.27 (d, 1H, CHP, $J_{H-P}$=18.1 Hz), 4.15 (m, 2H, $CH_2$ imidazole), 2.56 (dt, 1H, $NHCH_aH_b$, $J$=7.2, 12.3 Hz), 2.72 (dt, 1H, $NHCH_aH_b$, $J$=7.2, 12.3 Hz), 2.01 (quintet, 2H, $CH_2$, $J$=7.2 Hz). $^{31}P$ NMR ($D_2O$): $\delta_P$=6.29. $^{13}C$ NMR ($D_2O$): $\delta_C$=141.4 (d, 2-imidazole, $^2J_{C-P}$=4.2 Hz), 134.4, 129.0, 121.5, 119.8, 119.7, 54.0 (d, *C*HP, $J$=122.6 Hz), 46.3 (s, *C*$H_2$ imidazole), 44.6 (d, $NHCH_2$, $J$=7.5 Hz), 27.1 (s, *C*$H_2$). IR, $\nu_{max}$ (KBr): 3339 (NH), 2942, 2795, 2694, 2531, 1961, 1659, 1627, 1465, 1122 (P=O), 1081 (P–O), 995, 900, 775, 573 $cm^{-1}$. HRMS: calcd for $C_{10}H_{17}N_5O_3P$ $(M+H)^+$ 286.1069. Found 286.1052.

### 3.5. Cleavage of imidazol-2-yl-(amino)methylphosphonates under acidic conditions and isolation of the products

A sample of corresponding imidazole-2-yl-(amino)methylphosphonate **3**, or phosphine oxide **4** (1.0 mmol) was dissolved in HCl (25 mL of 6 M aqueous solution) and heated at reflux for 2 h. In the case of imidazole-phosphonic acids **6** (1.0 mmol) the reaction solution (50 mL of 6 M HCl) was refluxed for 6–8 h. After that time, the reaction mixture was cooled down to room temperature, $CH_2Cl_2$ was added (25 mL) and the resulting liquid mixture was alkalized with solid $Na_2CO_3$. Then the formed layers were separated and the aqueous layer was washed with $CH_2Cl_2$ (3×15 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtrated and concentrated under reduced pressure affording the amines **7**, as semi-solids. The amines were purified as oxalate salts. For this, the obtained amines (1 equiv) were dissolved in acetone (10 mL) and acetone solution of oxalic acid (2 equiv) (5 mL) was added. The separated oxalates of amines were filtered off and dried on air. In the case of cleavage of imidazole-phosphonic acids **6c**–**e**, the reaction mixture was evaporated to dryness, remaining residue was dissolved in water (25 mL), resulting solution was made alkaline with solid $Na_2CO_3$ and again evaporated to dryness. Obtained solid residue was mixed with acetone (30 mL), stirred, filtered and again washed twice with acetone (2×10 mL). Then, oxalic acid (2 equiv) dissolved in acetone (10 mL) was added to the combined acetone filtrate and cooled. The formed solid oxalates were filtered off, and dried.

*3.5.1. N-(Imidazol-2-yl-methyl)-butylamine (**7a**).* Oxalate, white solid; 0.17 g (yield 72%); mp 205–206 °C. $^1H$ NMR ($D_2O$): $\delta_H$=7.37 (s, 2H, imidazole-4, imidazole-5), 4.48 (s, 2H, $CH_2N$), 2.97 (t, 2H, $J$=7.29 Hz, $CH_2$), 1.49–1.43 (m, 2H, $CH_2$), 1.19–1.09 (m, 2H, $CH_2$), 0.70 (t, 3H, $J$=7.2 Hz, $CH_3$). IR, $\nu_{max}$ (KBr): 3393 (NH), 3141, 2961, 2932, 2873, 1922, 1622 [$(COOH)_2$], 1439, 1299, 1221, 1102, 906, 757, 721, 710, 623, 556, 495 $cm^{-1}$. HRMS: calcd for $C_8H_{16}N_3$ $(M+H)^+$ 154.1344. Found 154.1332.

*3.5.2. N-(Imidazol-2-yl-methyl)-benzylamine (**7b**).* Oxalate, white solid; 0.21 g (yield 78%); mp 206–208 °C. $^1H$ NMR ($D_2O$): $\delta_H$=7.14 (s, 1H, imidazole-4), 7.09 (s, 5H, Ph), 7.06 (s, 1H, imidazole-5), 4.34 (s, 2H, $CH_2$), 4.02 (s, 2H, $CH_2N$). $^{13}C$ NMR ($D_2O$): $\delta$=160.6 $(COOH)_2$, 135.5 (2-imidazole), 129.7, 129.6, 129.1, 128.9, 128.5, 120.7 (4,5-imidazole), 51.4 ($CH_2$), 39.2 ($CH_2$). IR, $\nu_{max}$ (KBr): 3421 (NH), 3070, 3020, 2984, 2887, 2790, 2724, 1738 [$(COOH)_2$], 1621, 1497, 1467, 1439, 1303, 1214, 1105, 919, 750, 738, 710, 699, 582, 494 $cm^{-1}$. HRMS: Calcd for $C_{11}H_{14}N_3$ $(M+H)^+$ 188.1188. Found 188.1174.

*3.5.3. N-(Imidazol-2-yl-methyl)-N-(2-pyridylmethyl)-amine (**7c**).* Oxalate, white solid; 38 mg (yield 37%); mp 176–177 °C. $^1H$ NMR ($D_2O$): $\delta_H$=8.54 (d, 1H, $J$=7.2 Hz, 6-PyH), 8.26 (t, 1H, $J$=7.9 Hz, 4-PyH), 7.73 (d, 1H, $J$=7.9 Hz, 3-PyH), 7.71 (t, 1H, $J$=7.2 Hz, 5-PyH), 7.27 (s, 2H, imidazole-4, imidazole-5), 4.24 (s, 4H, 2×$CH_2$). $^{13}C$ NMR ($D_2O$): $\delta$=161.1 $(COOH)_2$, 147.8, 144.4 (1-Py), 142.8, 135.8 (1-imidazole), 128.4, 127.9, 120.8 (4,5-imidazole), 47.2 ($CH_2$), 40.4 ($CH_2$). IR, $\nu_{max}$ (KBr): 3421 (NH), 3071, 3031, 2779, 1743 [$(COOH)_2$], 1621, 1523, 1476, 1208 [$(COOH)_2$], 712, 487 $cm^{-1}$. HRMS: calcd for $C_{10}H_{13}N_4$ $(M+H)^+$ 189.1140. Found 189.1132.

*3.5.4. N-(Imidazol-2-yl-methyl)-N-(3-pyridylmethyl)-amine (**7d**).* Oxalate, white solid; 0.20 g (yield 73%); mp 201–202 °C. $^1H$ NMR ($D_2O$+$D_2SO_4$): $\delta_H$=8.77 (s, 1H, 2-PyH), 8.62 (d, 1H, $J$=7.8 Hz, 6-PyH), 8.54 (d, 1H, $J$=7.8 Hz, 4-PyH), 7.91 (t, 1H, $J$=7.8 Hz, 5-PyH), 7.30 (s, 2H, imidazole-4, imidazole-5), 4.60 (s, 2H, $CH_2$), 4.45 (s, 2H, $CH_2$). $^{13}C$ NMR ($D_2O$+$D_2SO_4$): $\delta$=160.3 $(COOH)_2$, 148.3, 142.1, 142.1, 134.7, 130.1, 127.7, 120.7 (4,5-imidazole), 47.2 ($CH_2$), 39.7 ($CH_2$). IR, $\nu_{max}$ (KBr): 3444 (NH), 3408 (NH), 3024, 2787, 1733 [$(COOH)_2$], 1622, 1500, 1219 [$(COOH)_2$], 709, 592, 493 $cm^{-1}$. HRMS: calcd for $C_{10}H_{13}N_4$ $(M+H)^+$ 189.1140. Found 189.1152.

*3.5.5. N-(Imidazol-2-yl-methyl)-N-(imidazol-1-yl-n-propyl)-amine (**7e**).* Oxalate, white solid; 0.25 g (yield 86%); mp >260 °C (dec). $^1H$ NMR ($D_2O$): $\delta_H$=8.66 (s, 1H, imidazole-2), 7.43 (s, 2H, imidazole-4, imidazole-5), 7.41 (s, 1H, imidazole-5), 7.35(s, 1H, imidazole-4), 4.58 (s, 2H, $CH_2$–imidazole-2), 4.24 (t, 2H, $J$=7.5 Hz, $CH_2$–imidazole-1), 3.14 (t, 2H, $J$=7.5 Hz, $CH_2N$), 2.23 (q, 2H, $J$=7.5 Hz, $CH_2$). $^{13}C$ NMR ($D_2O$): $\delta$=165.3 $(COOH)_2$, 135.5, 134.7, 121.6,

121.1, 120.0, 119.9, 46.0 ($CH_2$), 44.8 ($CH_2$), 40.0 ($CH_2$), 26.8 ($NCH_2CH_2$). IR, $\nu_{max}$ (KBr): 3443 (NH), 3433 (NH), 2711, 1869, 1744 [$(COOH)_2$], 1645, 1619, 1452, 1416, 1235 [$(COOH)_2$], 1030, 719, 595, 557, 494, 473 $cm^{-1}$. HRMS: calcd for $C_{10}H_{16}N_5$ $(M+H)^+$ 206.1406. Found 206.1403.

### 3.6. Cleavage of imidazol-2-yl-(amino)-methyldiphenylphosphine oxides 4 in the presence of elemental bromine and isolation of the products

A sample of imidazole-2-yl-(*N*-butylamino)-methyldiphenylphosphine oxide **4a** (353 mg, 1.0 mmol) was dissolved in $CHCl_3$ (25 mL), containing 320 mg of $Br_2$ (2.0 mmol). Then concentrated sulfuric acid (196 mg, 2.0 mmol) was added and the mixture was stirred at room temperature for 2 h, until bromine disappeared. Methanol (10 mL) was added and the mixture was stirred for additional 5 h, then evaporated under reduced pressure. The obtained oily residue was treated with 0.5 M $H_2SO_4$ (20 mL) and extracted with methylene chloride (2×25 mL). The combined extracts were dried (anhyd $Na_2SO_4$), filtered and evaporated to afford methyl diphenylphosphinate **10**[9f] as an oil that solidifies with time (186 mg, ~80%). The remaining aqueous, acidic solution was neutralized with solid $Na_2CO_3$ and evaporated to dryness. The obtained solid residue was treated with 25 mL methanol, stirred, filtered and the filtrate evaporated to dryness, to give imidazole-2-carboxaldehyde **1** (79 mg, ~80%).

### 3.7. Kinetic measurements

Solutions of the corresponding imidazol-2-yl-(amino)methyl phosphinate, phosphine oxide or phosphonic acid ($c$ 0.1 mol $L^{-1}$) in aqueous 50% methanol, containing an appropriate quantity of $H_2SO_4$ (1.0 or 2.0 M solutions) in NMR tubes were prepared. The $^{31}P$ NMR spectra were consecutively recorded after desired period of time. The use of different concentrations of $H_2SO_4$ allowed calculating the pseudo-first-order rate constants ($k_{obs}$). The rate constants were determined by plotting the dependence of $\log(a-x)$ on time (where the '$a$' is a relative quantity of the starting material and the '$a-x$' represents a relative quantity of unreacted starting material).

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