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Synthesis of new thiazole-2, -4, and -5-yl-(amino)methylphosphonates and phosphinates: unprecedented cleavage of thiazole-2 derivatives under acidic conditions

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ABSTRACT

An efficient and reliable synthesis of new thiazole-(amino)methylphosphonic, phosphinic acids, and phosphine oxides is reported. The synthetic protocol is based on nucleophilic addition of phosphorous species to thiazole derived imines. Unexpectedly, it was discovered that heating of thiazole-2-yl-(amino)-methylphosphonates and phosphinates with aqueous HCl leads to their decomposition resulting in a rupture of the C–P bond, rejecting of the phosphorus containing fragment and formation of the corresponding secondary *N*-(thiazole-2-yl-methyl)-alkylamines. Two alternative mechanisms for this cleavage are postulated.

1. Introduction

Small and simple heteroaromatics often have surprisingly complex biological properties and belong to one of the most important classes of compounds in medicinal chemistry.[1] Especially amines containing five-membered heteroaryl groups, such as furans, thiophenes, thiazoles, and pyrazoles are widely found in both natural products and drugs.[2] In particular, thiazoles and their derivatives attract continuous interest due to their remarkable characteristics[3] that recently found application in drug development for treatment of allergies,[4] hypertension,[5] inflammation,[6] schizophrenia[7] and also bacterial[8] and HIV infections,[9] and hypnotics.[10] More recently thiazole derivatives were used as fibrinogen receptor antagonists with antithrombotic activity[11] and as new inhibitors of bacterial DNA gyrase B subunit.[12]

On the other hand, α-aminoalkylphosphonic acids, as phosphorus analogues of natural α-aminocarboxylic acids, are known to exhibit significant biological activity.[13] Their diverse applications include inhibition of such important enzymes as synthase,[14] HIV protease,[15] renin,[16] and phosphatase.[17]

Additionally, they are considered as potent antibiotics,[18] antibacterial,[19] antiviral,[20] antifungal,[21] and antitumor agents.[22]

In light of the aforementioned observations the union of heteroaromatic fragments with a phosphorus-containing moiety could result in valuable chemical and biological properties of such heteroaromatic phosphonates and their derivatives.[23] In order to examine this hypothesis we have successfully prepared a range of aminophosphonates derived from pyridine,[24] furan,[25] imidazole,[26] pyrazole,[27] and thiazole,[28] and indeed those compounds presented interesting properties as very effective ligands for metal ions, especially Cu(II),[28,29] and promising enzyme inhibitors.[30]

Interestingly, during our studies on the synthesis of heteroaromatic aminophosphonates we discovered that in some cases the newly formed heteroaromatic aminophosphonates, in particular derivatives of 2- and 4-substituted pyridines, undergo decomposition resulting from C–P bond cleavage under acidic conditions and we have decided to embark on a program to study in detail this intriguing phenomena.[24] C–P bond cleavage is recognized to play a very important part in biological tasks exhibited by organophosphorus compounds and is present in living organisms and catalyzed by enzymes.[31] Both homolytic and heterolytic pathways for the C–P bond cleavage were postulated, but still the mechanism remains not well-understood, sometimes erroneous[32b] and merits further investigations.[24,32]

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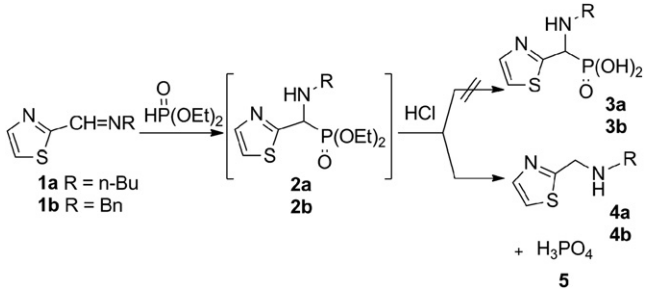
Herein, as a part of our study on the cleavage of the C–P bond in heteroaromatic aminophosphonates, we wish to present the results concerning our recent studies on the synthesis of new thiazole-(amino)methylphosphonic, phosphinic acids, and phosphine oxides and discovered, unprecedented cleavage of thiazole-2-aminophosphonates in acidic solutions.

2. Results and discussion

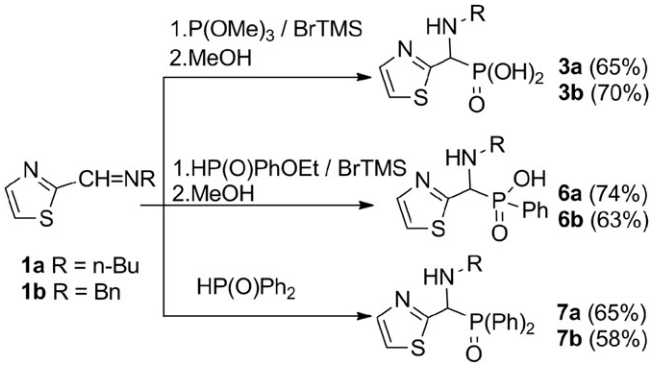
One of the most convenient synthetic protocols for the preparation of aminophosphonic acids is the nucleophilic addition of dialkyl or diaryl phosphites to imines or oxoiminium derivatives (often referred to as the Pudovik reaction) followed by acidic hydrolysis of the addition products, namely aminophosphonic acid esters, leading to the formation of the desired acids.[13,33] Usually this protocol can be performed in one-pot without isolation of the addition intermediates. In relation to another project, we needed to prepare thiazole-2-yl-(amino)methylphosphonic acids **3** and thus we have used the Pudovik reaction however, we could not isolate the expected phosphonic acids. The formation of the corresponding thiazole-2-yl-(amino)methylphosphonic acid esters **2** however, was clearly observed on ^{31}P and ^{1}H NMR spectra (these compounds were isolated and characterized) but their subsequent treatment with aqueous HCl did not result in formation of the desired acids **3**. A Similar result was obtained when the reaction was performed in one-pot without isolation of the products **2a**,**b**. Instead, on both occasions, after concentration of the crude reaction mixture, neutralization with aqueous Na_2CO_3, and extraction with CH_2Cl_2 the secondary amines **4** were isolated (Scheme 1).



Scheme 1. Cleavage of thiazole-2-yl-(amino)methylphosphonates **2** in acidic conditions.

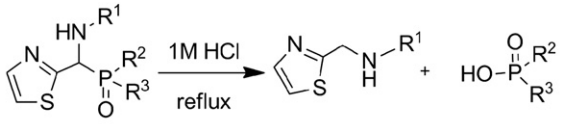
Following the hydrolysis of aminophosphonic acid esters **2** by ^{31}P NMR we could clearly observe the disappearance of the signal corresponding to the starting material **2** (δ_P ~23.0 ppm) and formation of another signal at about δ_P ~1.2 ppm that could be assigned to the formed phosphoric acid **5**. To confirm our assumption, after the complete disappearance of the signal corresponding to the esters **2** (δ_P ~23.0 ppm) the crude reaction mixtures were concentrated, dissolved in D_2O and ^{31}P NMR spectra were recorded showing a sharp singlet at δ_P=1.12 ppm corresponding to the phosphoric acid (for comparison: ^{31}P NMR spectrum of pure phosphoric acid in D_2O exhibits a singlet at 0.98 ppm).

In order to prepare the desired aminophosphonic acids **3** without using acidic conditions we applied a different strategy, namely addition of silylated phosphorus esters to aldimines prepared from 2-thiazolecarboxaldehyde (Scheme 2). Silylated phosphoesters were prepared in situ from trimethyl phosphite and bromotrimethylsilane (BrTMS). Subsequent treatment of the formed silylated intermediates with methanol, as a desilylating agent, led to the formation of expected aminophosphonic acids **3** in good yields. In turn, the use of silylated phosphoesters prepared from ethyl phenylphosphinate and BrTMS led to the formation of corresponding aminophosphinic acids **6** (Scheme 2). Additionally, we have prepared the thiazole-2-aminophosphine oxides **7**, parent compounds to the aminophosphonic and aminophosphinic acids, by the addition of diphenylphosphine oxide to thiazole-2 imines **1** (Scheme 2). In general, this one-pot procedure enabled an easy access to aminophosphonates **3**, **6**, and **7** in high yields and purity. All the synthesized compounds were characterized by standard spectroscopic techniques and the data obtained fully confirmed their structures.[28]



Scheme 2. Preparation of thiazole-2-yl-(amino)methylphosphonic and phosphinic acids **3** and **6**, and aminophosphine oxides **7**.

Interestingly, we discovered later on that the prepared thiazole-2-yl-(amino)methylphosphonic acids **3**, thiazole-2-yl-(amino) methylphosphinic acids **6**, and thiazole-2-yl-(amino)methyl-diphenylphosphine oxides **7** also undergo cleavage in acidic conditions (Scheme 3) similar to that observed earlier for thiazole-2-yl-(amino)methylphosphonic acid esters **2**. After heating of compounds **3**, **6**, and **7** for up to 3 h at reflux in the presence of aqueous 1 M HCl, evaporation of the solvent, neutralization of the crude reaction mixture with Na_2CO_3, and extraction with CH_2Cl_2 the secondary amines **4** were isolated and their structures were unambiguously confirmed by NMR spectroscopy (Scheme 3). The remaining aqueous layer was then acidified with aqueous 0.5 M HCl and dissolved in EtOH (in the case of **6** and **7**) and the resulting mixture was cooled down causing precipitation of the corresponding diphenylphosphinic acid **9** (in the case of aminophosphine oxides **7**) or phenylphosphonic acid **8** (in the case of aminophosphinic acids **6**), that were collected by filtration. The structures of compounds **9** and **8** were unambiguously confirmed by NMR techniques.



3a R^1 = n-Bu; R^2 = R^3 = OH	**4a** (75%)	**5** R^2 = R^3 = OH
3b R^1 = Bn; R^2=R^3 = OH	**4b** (80%)	**8** R^2 = OH; R^3 = Ph
6a R^1 = n-Bu; R^2 = OH; R^3 = Ph	**4a** (80%)	**9** R^2 = R^3 = Ph
6b R^1 = Bn; R^2 = OH; R^3 = Ph	**4b** (82%)	
7a R^1 = n-Bu; R^2 = R^3 = Ph	**4a** (90%)	
7b R^1 = Bn; R^2 = R^3 = Ph	**4b** (85%)	

Scheme 3. Cleavage of thiazole-2-yl-(amino)methylphosphonic and phosphinic acids **3** and **6**, and aminophosphine oxides **7** in acidic conditions.

Additionally, in order to gather more evidence about the cleavage of the thiazole-2-yl-(amino)methylphosphonates we decided to carry out kinetic measurements. We used ^{31}P NMR spectroscopy as a tool for the kinetic experiments.[24b] During the course of measurements we have discovered that the cleavage of the aminophosphonic acids **3** as well as aminophosphinic acids **6**

proceeds to fast, hence it was impossible to perform reliable kinetic measurements. In turn the aminodiphenylphosphine oxides **7** were found to be more durable compounds and therefore kinetic experiments were carried out using those compounds.

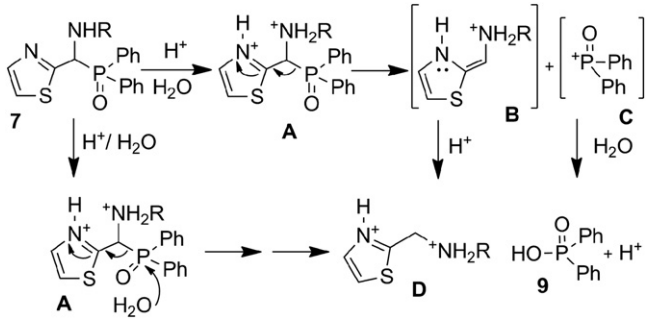
For the purpose of kinetic measurements, the cleavage of a representative sample, the aminophosphine oxide **7a** was run in 50% (v/v) aqueous methanol solution, containing a definite quantity of HCl (Table 1). The use of aqueous methanol was necessary to avoid the precipitation of the formed diphenylphosphinic acid **9**, during the course of experiments. The kinetics were run directly in NMR tube. The relative quantities of the phosphorus-containing product and starting material were estimated from the corresponding integrated ^{31}P NMR signals. In this case, the appearance of a signal assigned to diphenylphosphinic acid **9** ($\delta_P \sim 25$ ppm), together with the subsequent decay of a signal corresponding to the starting aminophosphine oxide **7a** ($\delta_P \sim 31$ ppm) was observed. On the basis of ^{31}P NMR data, the rate constants (k_{obs}) were calculated. It is noteworthy, that the rate constants were calculated from estimated ^{31}P NMR integrated signals and, therefore, these results should not be considered as exact data for mere kinetic studies, but rather as general information assisting in understanding of the cleavage process. The measured cleavages followed pseudo-first-order kinetics and it was found that the rate constants (k_{obs}) were strongly dependent on the concentration of the hydrochloric acid (Table 1).

Table 1
Rate constants for cleavage of thiazole-2-yl-(*N*-butylamino)methyldiphenylphosphine oxides **7a** conducted at 80 °C

Compound	Concentration of compound mol L^{-1}[a]	Concentration of HCl mol L^{-1}	10^2 k_{obs} h^{-1}
7a	0.05	0.5	0.56
	0.05	1.0	5.76
	0.05	2.0	11.34

[a] All experiments were run in 50% aqueous methanol solutions.

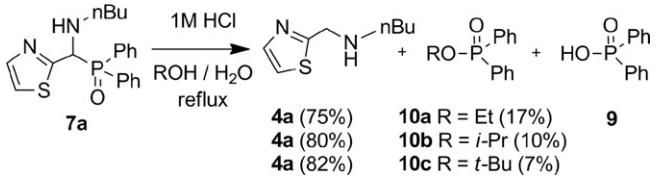
Taking into account the obtained data, literature reports[34] and our previous experience[24] two alternative mechanisms of the cleavage of the thiazole-2-aminophosphine oxides **7** in acidic conditions can be proposed (Scheme 4).



Scheme 4. Possible mechanisms for the cleavage of thiazole-2-yl-(amino)methyldiphenylphosphine oxides **7**.

The first, dissociative-type mechanistic pathway (Scheme 4) relies upon the rupture of the C–P bond in protonated aminophosphine oxide **A** and the formation of two intermediate products: an enamine-like moiety **B** and a metaphosphate-like moiety **C**. The intermediate **C** is actually the 'protonated' metaphosphate (a phosphinylium,[35] or phosphacylium cation[36]) and is closely associated with the well known monomeric metaphosphate ($HOPO_2$).[37,38] The metaphosphates, as transient species, are postulated as the putative intermediates in biological phosphoryl-transfer reactions[38] and also in many fragmentations of organophosphorus compounds.[37,38] The **C** as reactive intermediate can therefore react with water to form the final product, i.e., diphenylphosphinic acid **9**. In turn the enamine-like intermediate **B** transforms into the amine **D** by incorporation of a proton. In turn the second, associative-type mechanism would involve a direct nucleophilic attack of a solvent molecule (H_2O in the presented case) at phosphorus in the protonated aminophosphine oxide **A** prior to the cleavage of the C–P bond (Scheme 4). Further reorganizations would lead to the formation of the final products, i.e., the secondary amine **D** and diphenylphosphinic acid **9**. A driving force that triggers the cleavage of the C–P bond in both mechanisms seems to be the presence of a positive charge on protonated nitrogen in the aminophosphonate **A**. Assuming a similar behavior of all the other presented here thiazole-2-aminophosphonates **2**, **3**, and **6** in the presence of an acid, the two alternative mechanisms (Scheme 4) may also be used to explain the cleavage of those compounds. Examining both proposed mechanisms (Scheme 4), it is clear, that the corresponding thiazole-4 and -5 derivatives should not have decomposed in this way in acidic conditions. In order to examine this hypothesis, we have additionally synthesized appropriate thiazole compounds **11**–**13** and **14**–**16** (Scheme 6 in further section of the text).

To confirm the presence of metaphosphate-like moiety as a reactive intermediate that forms during the cleavage, additional experiments were carried out. Since, the metaphosphate ($HOPO_2$) is considered as a strong electrophile,[37] one of the most commonly used diagnostic tests for an involvement of this intermediate is phosphorylation of alcohols, especially hindered alcohols.[37,38] Therefore, a representative sample of aminophosphine oxide **7a** was heated at reflux for 1 h in aqueous solutions of different alcohols in the presence of 1 M HCl (Scheme 5).

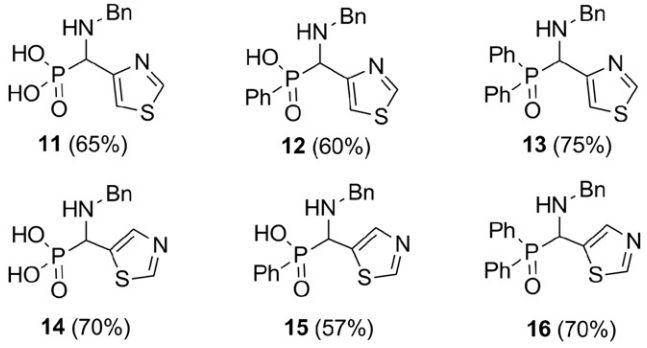


Scheme 5. Cleavage of thiazole-2-yl-(*N*-butylamino)-methyldiphenylphosphine oxide **7a** in 50% aqueous alcohols.

It was expected that if the 'protonated' metaphosphate (a phosphinylium cation)[35] is involved in the cleavage then the formation of phosphoesters (in this case the corresponding alkyl esters of diphenylphosphinic acid) would confirm, to some extent, its presence and hence support the dissociative-type mechanistic pathways. The formation of phosphoesters however, can also be explained using the second, associative-type mechanism. The cleavages of **7a** were carried out in 50% aqueous solutions of various alcohols. The solutions containing ethanol, isopropanol or *tert*-butanol and a definite amount of 1 M HCl were heated for 1 h at reflux and the progress of the reaction was monitored by ^{31}P NMR spectroscopy. After that time the reaction mixtures were cooled down to room temperature and after usual work-up (see Experimental part) the corresponding *N*-(thiazole-2-ylmethyl)butan-1-amine (**4a**) was isolated accompanied by expected phosphinic alkyl esters **10a**–**c** and diphenylphosphinic acid (**9**). The structures of the phosphoesters **10a**–**c** were confirmed by standard spectroscopic techniques. Due to the steric hindrance represented by the R substituent of the alcohol the yields of the isolated phosphoesters **10a**–**c** were the highest for EtOH than for *i*-PrOH and the lowest in the case of *t*-BuOH. The formation of the phosphoesters is consistent with the both proposed mechanisms of the cleavage of the aminophosphine oxide **7a**. The formation of the **10a**–**d** and diphenylphosphinic acid **9**, with the amounts corresponding to the molar ratio of alcohol and water, additionally verifies this assumption.

As mentioned above, we decided to prepare the corresponding thiazole-4 and -5 aminophosphonates **11**–**13** and **14**–**16** and analyze their behavior in acidic conditions. The aforementioned

compounds **11**–**16** (Scheme 6) were prepared in good yields using protocol depicted earlier in Scheme 2 and characterized by standard spectroscopic techniques.



Scheme 6. Structures of the synthesized thiazole-4 and thiazole-5-yl-(amino)methyldiphenylphosphonates **11**–**13** and **14**–**16**.

Subsequently, the obtained thiazole aminophosphonates and phosphinates **11**–**16** were heated at reflux in 1 M aqueous HCl for 3 h. In all cases decomposition was not detected and the tested compounds were found to be stable. This fact additionally confirms the proposed mechanism (Scheme 4). Under used acidic conditions surely protonation of nitrogen atoms in thiazole-2, -4, and -5-aminophoshonates occurs. However, only in the case of thiazole-2 derivatives the existence of delocalisation (intermediate **B**, Scheme 4) possible by the presence of a positive charge at thiazolyl nitrogen (intermediate **A**, Scheme 4) can trigger further events leading to the final secondary amine and corresponding phosphorus-containing product, respectively (Scheme 4). In the case of thiazole-4 and -5-aminophoshonates **11**–**13** and **14**–**16** the formation of aforementioned intermediates is not possible and thus those compounds are stable under acidic conditions and no cleavage is observed.

In conclusion, we have successfully synthesized new thiazole-2, -4, and -5-(amino)methylphosphonic and phosphinic acids, and phosphine oxides using nucleophilic addition of phosphorous species to thiazole derived imines. We have discovered that thiazole-2 derivatives undergo unexpected decomposition under acidic conditions resulting from C–P bond cleavage that leads to the formation of secondary *N*-(tiazol-2-yl-methyl)-alkylamines and corresponding phosphorus-containing product. The kinetic measurements of the cleavage of thiazole-2-yl-(amino)methyldiphenylphosphine oxides were performed to assist in elucidation of the mechanistic pathway. Based on the obtained results two mechanisms can be postulated namely, a dissociative-type and an associative-type mechanism. Additionally, cleavages of thiazole-2-yl-(*N*-butylamino)-methyldiphenylphosphine oxide **7a** in 50% aqueous solutions of different alcohols and isolation of corresponding phosphoesters **10a**–**c** was performed, which is consistent with the both proposed mechanistic pathways.

3. Experimental section

3.1. General

^{1}H (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 (δ) are reported in parts per million relative to internal tetramethylsilane (Me_4Si, δ 0.0) for ^{1}H NMR, $CDCl_3$ (δ 77.0) for ^{13}C NMR and external 85% phosphoric acid (δ 0.0) for ^{31}P NMR. Coupling constants (J) are reported in hertz. Infrared spectra (IR) were taken as neat and only the most representative frequencies (in cm^{-1}) are reported. Reported melting points are uncorrected. 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. The thiazole-2-yl-(amino)methylphosphonic acids **3a**, **3b**, thiazole-2-yl-(amino) methylphosphinic acids **6a**, **6b** and thiazole-2-yl-(amino)methyldiphenylphosphine oxides **7a**, **7b** were obtained using a procedure described previously by us.[28]

3.2. Synthesis of thiazole-2-yl-(amino)methylphosphonate diethyl esters 2a,b

Neat secondary aromatic or aliphatic amine (5.0 mL) was injected at room temperature to a solution of 2-thiazolecarboxaldehyde[39] (0.56 g, 5.0 mmol) in CH_2Cl_2 (30 mL) and the reaction was stirred overnight. After that time, anhydrous $MgSO_4$ was added and the mixture was stirred for additional 0.5 h. After removal of the drying agent the reaction was concentrated under reduced pressure affording crude imines **1a**,**b** that were used directly in the next step. The imines (5.0 mmol) were dissolved in dry toluene (30 mL) and diethyl phosphite (0.65 mL, 5.0 mmol) was added. The mixture was heated to reflux for 2 h and then concentrated under reduced pressure. The resulting oily residue was dissolved in toluene (10 mL) then hexane was added (2 mL) and the mixture was placed in the freezer for crystallization. The precipitated thiazole-2-yl-(amino)methylphosphonate diethyl esters were collected by filtration, washed with cold Et_2O (10 mL) and dried in air.

*3.2.1. Thiazole-2-yl-methyl(N-butylamino)phosphonate diethyl ester (**2a**).* White solid (680 mg, 45%), mp=125–127 °C. ^{1}H NMR ($CDCl_3$): δ_H 7.70 (d, 1H, thiazole-4, J=3.0 Hz), 7.15 (d, 1H, thiazole-5, J=3.2 Hz), 5.02 (d, 1H, CH–P, J=12.5 Hz), 4.03–3.74 (m, 4H, 2×OCH_2), 2.70–2.55 (m, 2H, NCH_2), 1.45–1.39 (m, 2H, NCH_2CH_2), 1.21–1.17 (m, 2H, $NCH_2CH_2CH_2$), 1.15 (t, 3H, J=7.0 Hz), 1.00 (t, 3H, J=7.1 Hz), 0.82 (t, 3H, J=7.1 Hz). ^{13}C NMR ($CDCl_3$): δ_C 169.5, 142.7, 120.5, 56.2 (d, CH–P, J=96.5 Hz), 59.2, 47.7, 30.2, 24.2, 14.0, 12.1. ^{31}P NMR ($CDCl_3$): δ_P 23.4 (s). FTIR (neat) ν_{max} (cm^{-1}): 3276 (N–H st), 1180 (P=O). CIMS m/z: 307.1 ([M+H], 80). HRMS calcd for $C_{12}H_{24}N_2O_3PS$ $(M+H)^+$ 307.1167. Found, 307.1171.

*3.2.2. Thiazole-2-yl-methyl(N-benzylamino)phosphonate diethyl ester (**2b**).* White solid (850 mg, 51%), mp=117–120 °C. ^{1}H NMR ($CDCl_3$): δ_H 7.81–7.20 (m, 7H, thiazole-4, thiazole-5, Ph), 4.98 (d, 1H, CH–P, J=12.9 Hz), 4.01 (s, 2H, CH_2Ph), 3.95–3.71 (m, 4H, 2×OCH_2), 1.15 (t, 3H, J=7.0 Hz), 1.00 (t, 3H, J=7.1 Hz). ^{13}C NMR ($CDCl_3$): δ_C 169.2, 142.9, 140.1, 127.1, 126.5, 129.5, 60.2 (d, CH–P, J=98.2 Hz), 58.2, 49.7, 12.9. ^{31}P NMR ($CDCl_3$): δ_P 24.8 (s). FTIR (neat) ν_{max} (cm^{-1}): 3269 (N–H st), 1174 (P=O). CIMS m/z: 340.1 ([M+H], 95). HRMS calcd for $C_{15}H_{22}N_2O_3PS$ $(M+H)^+$ 341.1010. Found, 341.1014.

3.3. Cleavage of thiazole-2-yl-(amino)methylphosphonic acids 3 in acidic conditions and isolation of the products

A sample of corresponding thiazole-2-yl-(amino)methylphosphonic acids **3a** or **3b** (1.0 mmol) was dissolved in HCl (25 mL of 1 M aqueous solution) and heated at 80 °C for 3 h. The resulting reaction mixture was cooled down to room temperature and CH_2Cl_2 was added (25 mL). The resulting solution was alkalized with solid Na_2CO_3 (1.6 g, 15 mmol) and the layers were separated. The aqueous layer was additionally washed with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtrated, and concentrated under reduced pressure affording the amines **4a** and **4b** as yellow oils.

*3.3.1. N-(Thiazol-2-ylmethyl)butan-1-amine (**4a**).* Yellow oil (127 mg, 75%). ^{1}H NMR ($CDCl_3$): δ_H 7.74 (d, 1H, thiazole-4, J=3.2 Hz), 7.17 (d, 1H, thiazole-5, J=3.4 Hz), 4.04 (s, 2H, CH_2), 2.64–2.59 (m, 2H, CH_2), 1.67 (br s, 1H, NH), 1.47–1.22 (m, 4H, CH_2CH_2), 0.85–0.811 (m,

3H, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 165.5, 144.9, 126.5, 55.4, 50.2, 35.7, 24.2, 14.0. FTIR (neat) ν_{max} (cm^{-1}): 3332 (N–H st). CIMS *m*/*z*: 171.0 ([M+H], 100). HRMS calcd for $C_8H_{15}N_2S$ $(M+H)^+$ 171.0878. Found, 171.0883.

3.3.2. N-(Thiazol-2-ylmethyl)benzyl-1-amine[40] (***4b***). Yellow oil (162 mg, 80%). ^1H NMR ($CDCl_3$): δ_H 7.74 (d, 1H, thiazole-4, *J*=3.2 Hz), 7.39–7.27 (m, 3H, Ph), 7.17–7.11 (m, 3H, thiazole-5, Ph), 4.10 (s, 2H, CH_2), 3.91 (s, 2H, CH_2), 1.89 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ_C 167.5, 145.8, 141.1, 128.0, 127.3, 126.9, 121.8, 56.4, 50.1. FTIR (neat) ν_{max} (cm^{-1}): 3327 (N–H st). CIMS *m*/*z*: 204.0 ([M+H], 100). HRMS calcd for $C_{11}H_{13}N_2S$ $(M+H)^+$ 204.0721. Found, 204.0719.

3.4. Cleavage of thiazole-2-yl-(amino)methylphosphinic acids 6 in acidic conditions and isolation of the products

The amines **4a** and **4b** were isolated in the same manner as it is described for thiazole-2-yl-(amino)methylphosphonic acids **3**. The remaining aqueous layer was acidified with HCl (about 5 mL of 0.5 M aqueous solution) and evaporated to dryness under reduced pressure. The resulting residue was dissolved in EtOH (10 mL) and placed in the refrigerator overnight. The precipitated phenylphosphinic acid **8** was collected by filtration and dried in air (white solid, 75–78%).

3.4.1. Phenylphosphonic acid[41] (***8***). White solid (105 mg, 75% from cleavage of **6a**) and (111 mg, 78% from cleavage of **6b**), mp=161–163 °C. ^1H NMR (DMSO-d_6): δ_H 7.38 (br s, 2H, OH), 7.75–7.69 (m, 2H, Ph), 7.51–7.46 (m, 3H, Ph). ^{31}P NMR (DMSO-d_6): δ_P 14.62 (s). CIMS *m*/*z*: 159.0 ([M+H], 100).

3.5. Cleavage of thiazole-2-yl-(amino) methyldiphenylphosphine oxides 7 in acidic conditions and isolation of the products

A sample of corresponding thiazole-2-yl-(amino)methyldiphenylphosphine oxides **7a** or **7b** (1.0 mmol) were dissolved in HCl (25 mL of 1 M aqueous solution) and heated at 80 °C for 3 h. After that time the reaction mixture was cooled down and let to stand overnight at room temperature. The precipitated diphenylphosphinic acid **9** was collected by filtration and dried on air (white solid, 70–74%). The filtrate was alkalized with an excess of solid Na_2CO_3 and the amines **4a** and **4b** were isolated in the same manner as it is described for thiazole-2-yl-(amino)methylphosphonic acids **3**.

3.5.1. Diphenylphosphinic acid[42] (***9***). White solid (154 mg, 70% from cleavage of **7a**) and (160 mg, 74% from cleavage of **7b**), mp=130–133 °C. ^1H NMR ($CDCl_3$): δ_H 10.01 (br s, 1H, OH), 7.67–7.61 (m, 4H, Ph), 7.50 (d, 4H, *J*=8.0 Hz, Ph), 7.35–7.29 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): δ_C 134.3 (d, *J*=10.2Hz), 132.5 (d, *J*=145.3 Hz), 130.9 (d, *J*=14.9 Hz), 128.0. ^{31}P NMR ($CDCl_3$): δ_P 26.14 (s). HRMS calcd for $C_{12}H_{12}O_2P$ $(M+H)^+$ 219.0497. Found, 219.0493.

3.6. Kinetic measurements

Solutions of the corresponding thiazole aminophosphine oxide (*c* 0.05 mol L^{-1}) in aqueous 50% methanol, containing an appropriate quantity of HCl (0.5, 1.0 and 2.0 mL^{-1} solutions) in NMR tubes were prepared and thermostated at 80 °C for a desired period of time (10, 15, 30, 60, 90, 120 min, respectively). The ^{31}P NMR spectra were consecutively recorded. The use of different concentrations of HCl 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 aminophosphine oxide and the '$a-x$' represents a relative quantity of unreacted aminophosphine oxide).

3.7. Cleavage of 7a in the presence of 50% aqueous alcohols

A sample of thiazole-2-yl-methyl(*N*-butylamino)-diphenylphosphine oxide (**7a**) (370 mg, 1.0 mmol) was dissolved in aqueous-alcoholic solution (1:1, v/v) (10 mL) and 1 M HCl was added (10 mmol). The following alcohols were used ethanol, isopropanol, and *tert*-butanol. The reaction mixture was heated to reflux for 1 h and then cooled down to room temperature and left overnight. The formed diphenylphosphinic acid (**9**) crystallized from the reaction mixtures was collected by filtration and dried on air. The filtrate was treated with 5% aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give an oil, which was a mixture of *N*-(thiazol-2-ylmethyl)butan-1-amine (**4a**) and corresponding alkyl phosphoesters **10a**–**c**. To separate the products the mixture was treated with 1 M aqueous HCl (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried over $MgSO_4$ and concentrated affording pure esters **10a**–**c** as oily products that solidified after several hours. The aqueous layer was alkalized with solid Na_2CO_3 and extracted with CH_2Cl_2 (3×15 mL). The organic layer was dried over $MgSO_4$ and concentrated producing the secondary amine **4a**.

3.7.1. Ethyl diphenylphosphinate[43] (***10a***). Yellow oil (41 mg, 17%). ^1H NMR ($CDCl_3$): δ_H 7.70–7.63 (m, 4H, Ph), 7.43–7.31 (m, 6H, Ph), 4.16–4.09 (m, 2H, CH_2), 1.30 (t, 3H, *J*=7.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 139.9 (d, *J*=11.1 Hz), 133.7 (d, *J*=143.4 Hz), 130.9 (d, *J*=12.9 Hz), 127.0, 59.0, 16.7. ^{31}P NMR ($CDCl_3$): δ_P 30.84 (s). HRMS calcd for $C_{14}H_{15}O_2P$ $(M)^+$ 246.0810. Found, 246.0816.

3.7.2. Isopropyl diphenylphosphinate[44] (***10b***). White solid (26 mg, 10%), mp=98–100 °C. ^1H NMR ($CDCl_3$): δ_H 7.75–7.68 (m, 4H, Ph), 7.45–7.33 (m, 6H, Ph), 4.65–4.58 (m, 1H, CH), 1.29 (t, 6H, *J*=6.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 140.1 (d, *J*=10.9 Hz), 135.1 (d, *J*=140.4 Hz), 131.0 (d, *J*=11.9 Hz), 127.0, 71.2, 19.7. ^{31}P NMR ($CDCl_3$): δ_P 31.45 (s). CIMS *m*/*z*: 261.0 ([M+H], 100).

3.7.3. tert-Butyl diphenylphosphinate[44] (***10c***). White solid (20 mg, 7%), mp=108–111 °C. ^1H NMR ($CDCl_3$): δ_H 7.74–7.66 (m, 4H, Ph), 7.41–7.32 (m, 6H, Ph), 1.39 (s, 9H, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 138.1 (d, *J*=11.9 Hz), 137.2 (d, *J*=141.7 Hz), 130.3 (d, *J*=12.1 Hz), 125.9, 90.1, 27.4. ^{31}P NMR ($CDCl_3$): δ_P 29.32 (s). CIMS *m*/*z*: 275.1 ([M+H], 100).

3.8. Synthesis of thiazole-4 and thiazole-5-(amino)methylphonates 11–16

Nucleophilic addition of phosphorous species to thiazole-4 and -5 derived imines was applied using a protocol described previously by us (reaction scale here was 560 mg, 5.0 mmol of corresponding thiazole aldehydes).[28] Thiazole-4-carboxaldehyde and thiazole-5-carboxaldehyd used for the preparation of imines were purchased from commercial supplier (Aldrich). Compounds **11**–**16** are new and their characterization is presented below.

3.8.1. Thiazole-4-yl-methyl-(N-benzylamino)phosphonic acid (***11***). White solid (910 mg, 65%), mp=171–173 °C. ^1H NMR (D_2O/10% D_2SO_4): δ_H 8.90 (d, 1H, thiazole-2, *J*=2.0 Hz), 7.65–7.20 (m, 6H, thiazole-5, Ph), 5.19 (d, 1H, CH–P, *J*=14.9 Hz), 4.68 (s, 2H, CH_2Ph). ^{13}C NMR (D_2O/10% D_2SO_4): δ_C 156.0, 151.9, 139.1, 126.9, 126.4, 126.2, 125.8, 61.0 (d, CH–P, *J*=97.2 Hz), 56.1. ^{31}P NMR (D_2O/10% D_2SO_4): δ_P 7.02 (s). FTIR (neat) ν_{max} (cm^{-1}): 3280 (N–H st), 1187 (P=O). CIMS *m*/*z*: 285.0 ([M+H], 95). HRMS calcd for $C_{11}H_{14}N_2O_3PS$ $(M+H)^+$ 285.0384. Found, 285.0386.

3.8.2. Thiazole-4-yl-methyl-(N-benzylamino)-phenylphosphinic acid (***12***). White solid (1.0 g, 60%), mp=189–192 °C. ^1H NMR (D_2O/10% D_2SO_4): δ_H 8.87 (d, 1H, thiazole-2, *J*=2.1 Hz), 7.71–7.29 (m, 6H,

thiazole-5, 11Ph), 5.21 (d, 1H, CH–P, J=16.9 Hz), 4.70 (s, 2H, CH_2Ph). ^{13}C NMR (D_2O/10% D_2SO_4): δ_C 157.2, 154.4, 139.1, 132.3, 131.8, 129.9, 128.1, 127.5, 126.2, 126.0, 125.5, 62.0 (d, CH–P, J=97 Hz), 56.1. ^{31}P NMR (D_2O/10% D_2SO_4): δ_P 18.72 (s). FTIR (neat) ν_{max} (cm^{-1}): 3456 (N–H st), 1170 (P=O). HRMS calcd for $C_{17}H_{18}N_2O_2PS$ $(M+H)^+$ 345.0748. Found, 345.0751.

*3.8.3. Thiazole-4-yl-methyl-(N-benzylamino)-diphenylphosphine oxide (**13**).* White solid (1.5 g, 75%), mp=139–142 °C. ^{1}H NMR ($CDCl_3$): δ_H 8.93 (d, 1H, thiazole-2, J=2.0 Hz), 7.71–7.21 (m, 6H, thiazole-5, 16Ph), 5.19 (d, 1H, CH–P, J=17.1 Hz), 4.23 (s, 2H, CH_2Ph). ^{13}C NMR ($CDCl_3$): δ_C 162.1, 157.8, 140.0, 133.7, 133.5, 133.0, 132.6, 132.4, 132.3, 131.8, 129.9, 128.1, 127.5, 126.2, 126.0, 63.4 (d, CH–P, J=96.9 Hz), 57.3. ^{31}P NMR ($CDCl_3$): δ_P 30.52 (s). FTIR (neat) ν_{max} (cm^{-1}): 3435 (N–H st), 1187 (P=O). HRMS calcd for $C_{23}H_{22}N_2OPS$ $(M+H)^+$ 405.1112. Found, 405.1114.

*3.8.4. Thiazole-5-yl-methyl-(N-benzylamino)phosphonic acid (**14**).* White solid (980 mg, 70%), mp=169–170 °C. ^{1}H NMR (D_2O/10% D_2SO_4): δ_H 8.84 (d, 1H, thiazole-2, J=2.1 Hz), 7.70–7.36 (m, 6H, thiazole-4, Ph), 5.10 (d, 1H, CH–P, J=16.3 Hz), 4.72 (s, 2H, CH_2Ph). ^{13}C NMR (D_2O/10% D_2SO_4): δ_C 157.2, 152.7, 138.9, 126.6, 126.2, 126.0, 125.9, 63.0 (d, CH–P, J=98.1 Hz), 54.1. ^{31}P NMR (D_2O/10% D_2SO_4): δ_P 6.91 (s). FTIR (neat) ν_{max} (cm^{-1}): 3287 (N–H st), 1182 (P=O). HRMS calcd for $C_{11}H_{14}N_2O_3PS$ $(M+H)^+$ 285.0384. Found, 285.0385.

*3.8.5. Thiazole-5-yl-methyl-(N-benzylamino)-phenylphosphinic acid (**15**).* White solid (970 mg, 57%), mp=195–199 °C. ^{1}H NMR (D_2O/10% D_2SO_4): δ_H 8.82 (d, 1H, thiazole-2, J=2.1 Hz), 7.71–7.25 (m, 6H, thiazole-4, 11Ph), 5.25 (d, 1H, CH–P, J=17.0 Hz), 4.71 (s, 2H, CH_2Ph). ^{13}C NMR (D_2O/10% D_2SO_4): δ_C 157.0, 154.1, 138.7, 132.2, 132.0, 129.7, 127.7, 127.4, 126.3, 125.8, 125.5, 63.2 (d, CH–P, J=96.7 Hz), 57.1. ^{31}P NMR (D_2O/10% D_2SO_4): δ_P 19.8 (s). FTIR (neat) ν_{max} (cm^{-1}): 3451 (N–H st), 1182 (P=O). HRMS calcd for $C_{17}H_{18}N_2O_2PS$ $(M+H)^+$ 345.0748. Found, 345.0750.

*3.8.6. Thiazole-5-yl-methyl-(N-benzylamino)-diphenylphosphine oxide (**16**).* White solid (1.4 g, 70%), mp=145–147 °C. ^{1}H NMR ($CDCl_3$): δ_H 8.97 (d, 1H, thiazole-2, J=2.2 Hz), 7.68–7.25 (m, 6H, thiazole-4, 16Ph), 5.21 (d, 1H, CH–P, J=17.3 Hz), 4.19 (s, 2H, CH_2Ph). ^{13}C NMR ($CDCl_3$): δ_C 162.0, 157.5, 139.6, 132.9, 133.7, 133.1, 132.3, 132.1, 132.0, 131.6, 130.0, 128.5, 127.7, 126.0, 125.8, 63.1 (d, CH–P, J=97.2 Hz), 57.7. ^{31}P NMR ($CDCl_3$): δ_P 31.21 (s). FTIR (neat) ν_{max} (cm^{-1}): 3429 (N–H st), 1190 (P=O). HRMS calcd for $C_{23}H_{22}N_2OPS$ $(M+H)^+$ 405.1112. Found, 405.1115.

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Supplementary data

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