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Synthesis of thiazole aminophosphine oxides, aminophosphonic and aminophosphinic acids and Cu(II) binding abilities of thiazole aminophosphonic acids

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Abstract—A series of new aminophosphine oxides, aminophosphonic and aminophosphinic acids derived from thiazole was synthesized by addition of phosphine oxides or silylated phosphorus esters to the corresponding thiazole aldimines. The thiazole aldimines were obtained from 2-thiazole aldehyde and primary amines by a standard procedure. The corresponding phosphine oxides were obtained by alkylation of diethyl phosphite or ethyl phenylphosphinate with the appropriate Grignard reagents. The silylated phosphorus esters were prepared from trimethyl phosphite and from methyl- or phenylphosphinic ethyl ester by treatment with bromotrimethylsilane. The coordination ability towards Cu(II) ions are described for two obtained aminophosphonate ligands.

1. Introduction

Aminophosphonic acids, as phosphorus analogues of α-aminocarboxylic acids, are of great interest due to a significant biological activity.[1] Some of them are powerful herbicides and have found a wide commercial application, as for example, the phosphonomethylglycine (the glyphosate).[2] Some representatives of aminophosphonates have demonstrated promising enzyme inhibitory activity, as for example, HIV protease antagonists[3] and collagenase inhibitors[4] and biological activities are often related to their metal ion binding abilities.[1,5] In the last decades, an intensive synthetic work was performed in the preparation of aminophosphonates,[6] some of them being analogues of natural amino acids and others being analogues of important unnatural amino acids.[7]

To the best to our knowledge, aminophosphonates possessing a thiazole moiety are unknown. A basic difficulty in the synthesis of parent heterocyclic aminophosphonates[8] is an inapplicability of known, regular procedures for synthesis of the typical aminophosphonates. Therefore, there is a need to search for new methods, which could be more useful in preparation of heterocyclic aminophosphonates.

Recently, some heterocyclic derivatives of aminomethylphosphonic acid were prepared; for example, the furan derivatives,[8–10] imidazole and pyrazole derivatives,[11] thiophene derivatives,[12] and pyridine derivatives.[13,14] The prevailing synthetic route used in the preparation of these heterocyclic aminophosphonate derivatives was Fields' method,[15] and depended generally on addition of dialkyl phosphites to heterocyclic aldimines. This method was not suitable as a general synthetic procedure for most heterocyclic aminophosphonates, because, in some cases, decomposition of the heterocyclic moieties was observed, or, due to a cleavage of a C–P bond in the formed aminophosphonates.[13,14,16]

During the last few years, a new kind of silicon–phosphorus based reagent for synthesis of organophosphorus compounds has been developed.[17–20] Application of these reagents enabled the synthesis of heterocyclic α-aminophosphonate compounds.[18] It was found that silylated phosphorus acid esters were effective reagents for preparation of heterocyclic, fragile aminophosphonates from aldimines.[21–23]

In this paper, we wish to report the first synthesis of aminophosphonic and aminophosphinic acids derived from

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thiazole, by exploitation of the recently described methods. We report, additionally, the synthesis of thiazole aminophosphine oxides, which are parent compounds of the thiazole aminophosphonic and aminophosphinic acids. Earlier studies have shown that aminophosphonates bearing imidazole, pyrazole or pyridine moiety were effective ligands for metal ions, especially Cu(II).[24–27] The coordination properties of thiazole phosphonate ligands using potentiometric and spectroscopic methods are also reported here.

2. Results and discussion

2.1. Synthesis of aminophosphonic and aminophosphinic acids

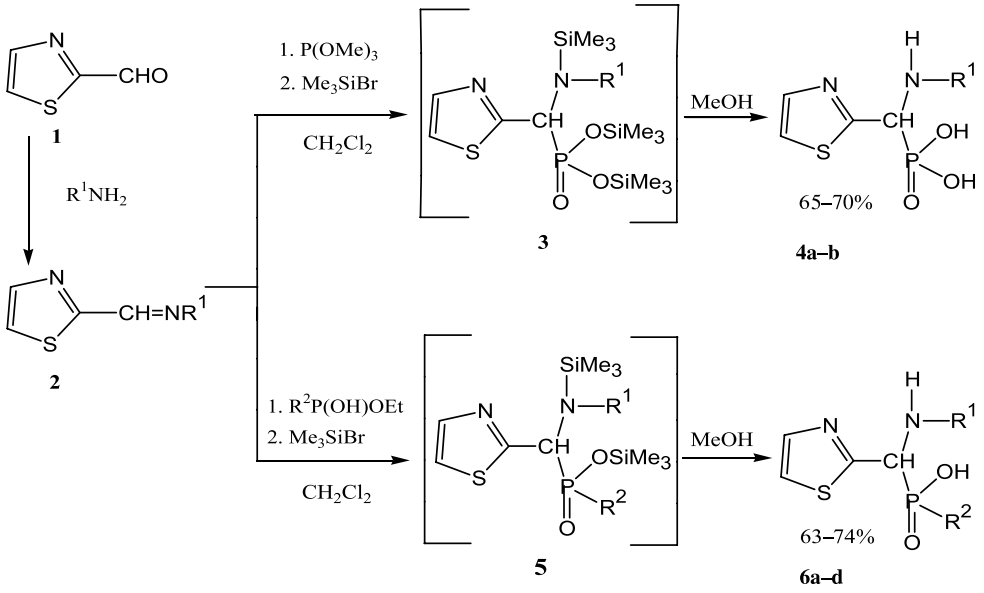
The syntheses of thiazole aminophosphonic and aminophosphinic acids are illustrated in Scheme 1. 2-Thiazole aldehyde[28] **1** reacted easily with aliphatic or aromatic primary amines in dichloromethane to give the corresponding aldimines **2**. The aldimines were reacted directly with silylated phosphorus esters to form the thiazole aminophosphonic, or aminophosphinic silylated esters **3** and **5**, as intermediates, which were then deprotected giving the thiazole aminophosphonic and aminophosphinic acids **4a**,**b** and **6a**–**d** (Scheme 1).

Silylated in situ phosphoesters used for addition to the imines were prepared from trimethyl phosphite (in the case of preparation of thiazole aminophosphonic acids) or from methyl-, or phenylphosphinate ethyl ester (in the case of preparation of thiazole aminophosphinic acids), by treatment of the corresponding phosphoesters with bromotrimethylsilane. Nucleophilic addition of the silylated phosphorus esters to imines proceeded easily at room temperature for 24 h. Formed silylated phosphonic and phosphinic intermediates, **3** and **5** (Scheme 1) were then treated with methanol, as a dealkylating agent, to give the final aminophosphonic **4a**–**b** and aminophosphinic acids **6a**–**d**.

The silylated phosphoesters were found to be good nucleophiles toward the imines. The presence of a bulky trimethylsilyl group in the formed phosphonate or phosphonite-like ester increases the power of such a nucleophile due to formation of a stable, three-coordinated phosphorus moiety with a free electron pair at phosphorus. Also, lack of the possibility of tautomerization in the formed three-coordinated, silylated phosphorus ester into less nucleophilic four-coordinated phosphonate-like ester, additionally secure a nucleophilic character of the applied reagent.

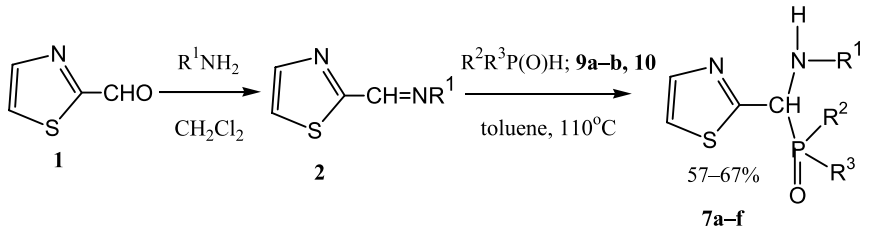
The use of bromotrimethylsilane (BrTMS) resulted in an easier silylation process of the alkyl phosphoesters, due to a higher reactivity of the BrTMS, in comparison with chlorotrimethylosilane, which is frequently used for silylation reactions.[17,18] Application of BrTMS for deprotection of phosphonate esters gave excellent results and allowed, in our case, to obtain the desired thiazole aminophosphonic and aminophosphinic acids by a direct way, in high yield and purity.

The described method presents a substantial improvement in the synthesis of heterocyclic aminophosphonic and aminophosphinic acids. After slight modifications, the present method can also be applied for synthesis of the monoalkyl esters of aminophosphonic acids, which are not easily available compounds.[22] Such a method is useful for synthesis of aminophosphonates possessing heterocyclic, fragile moieties.



4a: R^1 = *n*-Bu; **4b:** R^1 = CH_2Ph; **6a:** R^1 = *n*-Bu, R^2= Ph; **6b:** R^1 = CH_2Ph, R^2 = Ph; **6c:** R^1 = *n*-Bu, R^2 = CH_3; **6d:** R^1 = CH_2Ph, R^2 = CH_3.

Scheme 1. Synthesis of thiazole aminophosphonic and aminophosphinic acids.

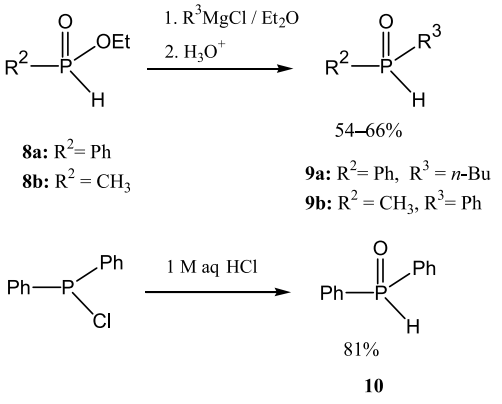


7a: R^1 = *n*-Bu, R^2= Ph, R^3 = *n*-Bu; **7b:** R^1 = CH_2Ph, R^2= Ph, R^3 = *n*-Bu
7c: R^1 = *n*-Bu, R^2 = CH_3, R^3= Ph; **7d:** R^1 = CH_2Ph, R^2 = CH_3, R^3 = Ph
7e: R^1 = *n*-Bu, R^2 = R^3 = Ph; **7f:** R^1 = CH_2Ph, R^2 = R^3 = Ph

Scheme 2. Synthesis of thiazole aminophosphine oxides.

2.2. Synthesis of thiazole aminophosphine oxides

In this paper, we describe a facile approach to new thiazole aminophosphine oxides, which are parent compounds to the thiazole aminophosphonic and aminophosphinic acids **4** and **6**. The method is based on addition of phosphinous acids (also called phosphine oxides, due to existence of such tautomeric a form) to thiazole aldimines **2**. Such addition of phosphine oxides to thiazole aldimines occurred readily in boiling toluene, to give the expected products, that is, the thiazole aminophosphine oxides **7a–f** (Scheme 2). As a result, a series of new thiazole aminophosphine oxides **7**, with varied substituents on phosphorus and nitrogen atoms, was obtained. Some of the thiazole aminophosphine oxides **7** were isolated and purified as oxalate salts. Oxalates were formed as crystalline solids when the aminophosphines **7** were treated with oxalic acid in acetone solution.



Scheme 3. Synthesis of phosphine oxides.

Phosphine oxides **9a–b** used in the presented synthetic procedure, were prepared from H-phosphinates (methyl- or phenylphosphinate ethyl esters) and Grignard reagents, according to a literature method [29] (Scheme 3). In turn, the diphenyl phosphine oxide (diphenylphosphinous acid, **10**) was simply obtained from chlorodiphenylphosphine and aqueous HCl, following the literature method.[30]

The synthesized thiazole aminophosphine oxides **7a–d** were mixtures of diastereoisomers (as shown by their NMR spectra). ^{31}P NMR shifts of the thiazole aminophosphine oxides depend largely on electronegativity of the substituent attached to the phosphorus atom. For example, the ^{31}P signals of diphenyl derivatives **7e**,**f** are placed between 30 and 32 ppm, compared to the corresponding signals of methyl-phenylphosphine derivatives **7c**,**d**, which are observed in the range of 41–44 ppm, and the *n*-butylphenyl-phosphine oxides **7a**,**b**, which are in the 42–46 ppm, respectively.

2.3. Complexation of Cu(II) ions by 4a and 4b

Coordination properties of the obtained products were measured for thiazole aminophosphonic acids **4a** and **4b**,

Table 1. Stability constants of proton (log *K*) and copper(II) complexes (log *β*)

	4a	**4b**	Imid-Bu[27]	Imid-Ph[27]	Pyrid-Bu[26]	Pyrid-Ph[26]
log *K*(HL)	8.67	7.56	10.22	9.06	10.14	9.04
log *K*(H_2L)	4.83	4.72	6.05	5.89	5.20	5.21
log *K*(H_3L)	—	—	4.30	4.07	1.72	3.82
log *β*(CuHL)	12.75	—	18.27	16.59	16.50	—
log *β*(CuL)	9.10	8.09	14.74	13.23	—	—
log *β*(CuH_2L_2)	—	—	35.04	32.11	31.35	29.11
log *β*($CuHL_2$)	—	—	28.93	25.77	26.81	25.01
log *β*(CuL_2)	14.45	13.17	20.67	18.10	20.90	19.38
log *β*($CuH_{-1}L_2$)	—	—	11.16	—	—	—
p*K*(CuHL)	3.65	—	3.53	3.36	—	—
p*K*(CuH_2L_2)	—	—	6.11	6.34	4.54	4.10
p*K*($CuHL_2$)	—	—	8.26	7.67	5.91	5.63
p*K*(CuL_2)	—	—	9.51	—	—	—

which were soluble in aqueous solutions. The thiazole aminophosphinic acids **6** and aminophosphine oxides **7** were not appropriate for potentiometric studies, due to precipitation of the ligands in a higher pH range. Both ligands (**4a**, **4b**) behave as H_2L acids. Two protonation constants of **4a** log $K=8.67$ and 4.83 may be assigned to amino and phosphonate functions, respectively. Similar log K values are observed for **4b**, 7.56 and 4.71. The protonation constant of benzylamino substituted nitrogen (**4b**) is distinctly lower than that of *N*-butylamino derivative (Table 1), while the basicities of the phosphonate function are rather similar to each other. The analogous derivatives with the imidazole[27] or pyridine[26] moiety behave in a similar way, although the basicities of amino groups of thiazole derivatives are much lower than those of imidazole, or pyridine aminophosphonates (Table 1). This indicates a much higher degree of electron withdrawing abilities of thiazole when compared to imidazole, or pyridine rings.

According to the calculations based on potentiometric data, **4a** and **4b** form two major complexes CuL and CuL_2 (Table 1, Fig. 1). The stability constants of the **4a** complexes are distinctly higher than those of **4b** due to the higher basicity of the amino function of the ligand. The d–d transitions observed around 640–660 and 610–630 nm indicate the involvement of two or four nitrogen donors in the binding of Cu(II) ion in CuL and CuL_2, respectively, (Table 2).[24–27] Also, EPR parameters, especially the values

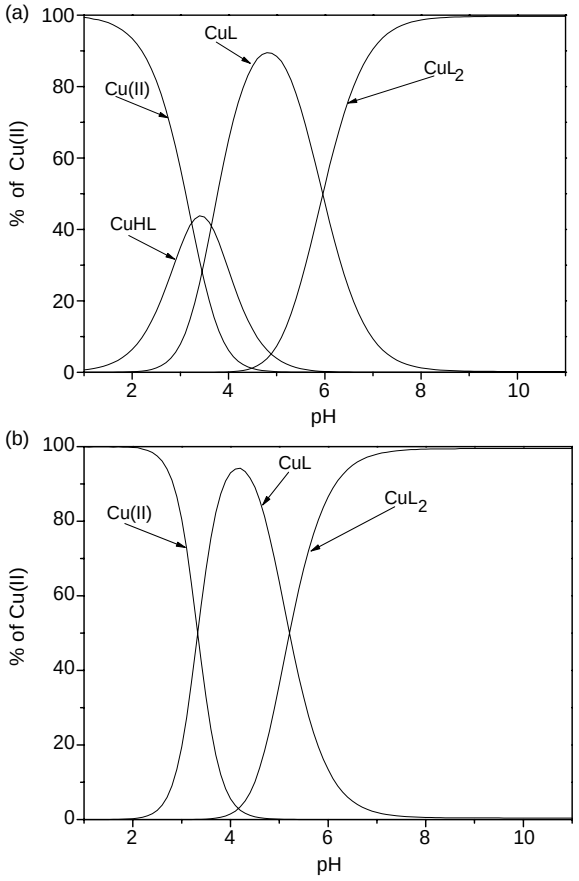


Figure 1. Species distribution curves for the complexes formed in the (a) Cu(II)-**4a**; (b) Cu(II)-**4b** system as a function of pH. $C_{Cu(II)}=1.0\times10^{-3}$ mol dm^{-3}, $C_L=4.0\times10^{-3}$ mol dm^{-3}.

Table 2. Spectroscopic parameters for Cu(II) complexes formed by studied ligands

Ligands		UV–vis		EPR	
		λ (nm)	ε (dm^3 mol^{-1} cm^{-1})	A_{II}	g_{II}
L1-**4a**	CuHL	693	48	140	2.347
	CuL	643	76	155	2.290
	CuL_2	612	86	187	2.222
L2-**4b**	CuL	667	86	155	2.281
	CuL_2	634	84	190	2.231

of $A_{II}=155$ and 190 G support such a coordination mode.[24–27] In the CuHL, species observed for **4a** the coordination mode $\{N_{thiazole}, PO_3^{2-}\}$ seems to be the most likely. The d–d trasition at 693 nm support the one nitrogen coordination (Table 2).[26] Thus, thiazole and amino nitrogen are basic for the metal ion coordination although the presence of the phosphonate function modulates the binding ability of the aminophosphonic acid distinctly. The thiazole moiety with its least basic nitrogen donor is a very effective chelating agent for Cu(II) ions although both pyridine and imidazole derivatives are more powerful ligands.

3. Conclusions

New thiazole aminophosphine oxides, thiazole aminophosphonic and aminophosphinic acids were synthesized in a simple way, from the corresponding aldimines and secondary phosphine oxides, or silylated phosphorus esters. It was demonstrated that thiazole aminophosphonic acids are effective ligands for complexation of Cu(II) ions.

4. Experimental

NMR spectra were recorded on a Bruker Avance TM DRX spectrometer, in D_2O, 10% D_2O/D_2SO_4, or $CDCl_3$ solutions, respectively. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. MS analyses were determined on a Finnigan TSQ 700 instrument (electrospray ionization on mode: ESI +Q1MS) in Department of Chemistry, University of Wrocław. Melting points were determined using an Electrothermal 9200 apparatus and a Boetius hot-stage apparatus and were uncorrected. Elemental analyses were done in Department of Chemistry, University of Wrocław. All commercially available materials were used as received from the supplier (Aldrich Company).

4.1. Synthesis of reagents

Ethyl methylphosphinate (**8b**) was prepared from methyldichlorophosphine, as described in the literature.[31]

4.1.1. *n*-Butylphenylphosphine oxide[32] (9a). To a 2.0 M solution of *n*-BuMgCl (10.0 mL, 20.0 mmol) in dry diethyl ether (20 mL) ethyl phenylphosphinate (1.70 g, 10.0 mmol) was added dropwise at 0 °C with stirring. Then, the reaction mixture was refluxed for 2 h, cooled (ice bath) and aqueous

25% H_2SO_4 (30 mL) was slowly added. The organic layer was separated and discarded. The remaining aqueous layer was extracted with CH_2Cl_2 (5×30 mL). The combined organic extracts were shaken with the solid K_2CO_3 and dried over anhydrous Na_2SO_4. After evaporation of the filtrate, the crude *n*-butylphenylphosphine oxide **9a** was obtained as colorless oil. Yield: 66% (1.2 g). ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.13–6.59 (dt, 1H, P–*H*, J_{H-P}=463 Hz, J=3.7 Hz), 7.61–7.36 (m, 5H, Ph*H*), 1.93–1.83 (m, 2H, PCH_2(CH_2)$_2$$CH_3$), 1.54–1.13 (m, 4H, CH_2(CH_2)$_2$$CH_3$), 0.92–0.87 (m, 3H, C$H_3$). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 29.66 (s).

4.1.2. Methylphenylphosphine oxide[33] (9b). The title compound was prepared using PhMgCl (2.0 M solution in diethyl ether, 16.0 mL, 32.0 mmol) and ethyl methylphosphinate **8b** (1.7 g, 16.0 mmol). The procedure for preparation of **9a** was exactly followed and **9b** obtained as colorless oil. Yield: 54% (1.2 g). ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.24–6.65 (dq, 1H, P–*H*, J_{H-P}=476.3 Hz, J=3.8 Hz), 7.64–7.29 (m, 5H, Ph*H*), 1.77 (dd, 3H, P–CH_3, J=13.9, 3.8 Hz). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 22.30 (s).

Aldimines **2** were prepared from 2-formylthiazole (**1**) and primary amines, according to the following procedure: aldehyde **1** (0.47 g, 2.5 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and an appropriate amine was added (2.5 mmol). The mixture was stirred for 24 h at room temperature and dried over anhydrous Na_2SO_4, filtered and the filtrate evaporated to give the crude imines **2**, which were used directly in a next step.

4.2. General procedure for preparation of 2-thiazole aminophosphonic acids 4a–b and aminophosphinic acids 6a–d

To a solution of crude imine **2** (2.5 mmol) in dichloromethane (25 mL) trimethyl phosphite was added (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 (thiazole aminophosphonic acids **4a**–**b**) separated as white solids and were collected by filtration, washed with diethyl ether and dried.

Phosphinic acids **6a**–**d** were obtained in the following way: the ethyl phenylphosphinate (**8a**) (0.45 g, 2.5 mmol), or ethyl methylphosphinate (**8b**) (0.28 g, 2.5 mmol), was added to solution of crude imine **2** in dry CH_2Cl_2 (25 mL). Bromotrimethylsilane (1.2 g, 7.5 mmol) was then added and the whole mixture was stirred for 24 h, at room temperature. After this, the mixture was evaporated, the resulted oil treated with 5 mL MeOH and refrigerated for several hours. The separated products were filtered and dried to give the aminophosphinic acids **6a**–**d** as white solids.

4.2.1. Thiazole-2-yl-methyl(*N*-butylamino)phosphonic acid (4a). A white solid. Yield: 0.40 g (65%), mp 220–224 °C. ^{1}H NMR; δ_H (D_2O/10% D_2SO_4; 300 MHz): 7.67 (d, 1H, thiazole-4, J=3.4 Hz), 7.55 (d, 1H, thiazole-5, J=3.4 Hz), 4.82 (d, 1H, C*H*–P, J=16.6 Hz), 2.89–2.68 (m, 2H, NHCH_2), 1.38–1.26 (m, 2H, C$H_2$$CH_2$), 1.08–1.01 (m, 2H, CH_2CH_2), 0.57–0.48 (m, 3H, CH_3). ^{31}P NMR; δ_P (D_2O/D_2SO_4; 121.5 MHz): 6.91 (s). IR, ν_{max} (KBr): 3439 (NH); 3109; 2964; 2837; 2811; 2681; 2328; 1616; 1558; 1492; 1466; 1385; 1225; 1185 (P=O); 1076; 984; 926; 850; 748; 642; 567 cm^{-1}. MS; (ESI+Q1MS): 273.2 (100, M^++Na). Anal. Calcd for $C_8H_{15}N_2O_3PS$, requires C, 38.39; H, 6.04; N, 11.19; found: C, 38.34; H, 6.18; N, 11.10%.

4.2.2. Thiazole-2-yl-methyl-(*N*-benzylamino)phosphonic acid (4b). A white solid. Yield: 0.50 g (70%), mp 185–187 °C. ^{1}H NMR; δ_H (D_2O/10% D_2SO_4; 300 MHz): 7.56 (d, 1H, thiazole-4, J=3.3 Hz), 7.40 (d, 1H, thiazole-5, J=3.3 Hz), 6.99–6.89 (m, 5H, Ph*H*), 4.86 (d, 1H, C*H*–P, J=18.7 Hz), 3.94 (s, 2H, NHCH_2Ph). ^{31}P NMR; δ_P (D_2O/D_2SO_4; 121.5 MHz): 6.06 (s). IR, ν_{max} (KBr): 3492, 3407 (NH); 3040; 2886; 2614; 2486, 2398; 1662; 1576; 1456; 1466; 1382; 1277; 1187 (P=O); 1118; 937; 864; 743; 636; 555; 490, 460 cm^{-1}. MS; (ESI+Q1MS): 307.2 (100, M^++Na). Anal. Calcd for $C_{11}H_{13}N_2O_3PS$, requires C, 46.48; H, 4.61; N, 9.85; found: C, 46.40; H, 4.75; N, 9.81%.

4.2.3. Thiazole-2-yl-methyl-(*N*-butylamino)-phenylphosphinic acid (6a). A white solid. Yield: 0.57 g (74%), mp 157–160 °C. ^{1}H NMR; δ_H (D_2O/10% D_2SO_4; 300 MHz): 8.61 (d, 1H, thiazole-4, J=3.3 Hz), 8.57 (d, 1H, thiazole-5, J=3.3 Hz), 8.00–7.82 (m, 5H, Ph*H*), 5.23 (d, 1H, C*H*–P, J=19.6 Hz), 3.59–3.51 (m, 2H, NHCH_2), 2.07–1.97 (m, 2H, C$H_2$$CH_2$), 1.75–1.62 (m, 2H, CH_2CH_2), 1.19 (t, 3H, CH_3, J=7.3 Hz). ^{31}P NMR; δ_P (D_2O/D_2SO_4; 121.5 MHz): 19.62 (s). MS; IR, ν_{max} (KBr): 3394 (NH); 3060; 2961; 2777; 1591; 1487; 1441; 1316; 1216 (P=O); 1131; 990; 938; 750; 718; 695; 547; 505 cm^{-1}. (ESI+Q1MS): 333.3 (100, M^++Na). Anal. Calcd for $C_{14}H_{19}N_2O_2PS$, requires C, 54.18; H, 6.17; N, 9.03; found: C, 54.15; H, 6.21; N, 8.97%.

4.2.4. Thiazole-2-yl-methyl-(*N*-benzylamino)-phenylphosphinic acid (6b). A white solid. Yield: 0.53 g (63%), mp 217–220 °C. ^{1}H NMR; δ_H (D_2O/10% D_2SO_4; 300 MHz): 8.50 (d, 1H, thiazole-4, J=3.3 Hz), 7.30 (d, 1H, thiazole-5, J=3.3 Hz), 8.20–8.03 (m, 10H, Ph*H*), 5.22 (d, 1H, C*H*–P, J=18.7 Hz), 4.71 (s, 2H, NHCH_2Ph). ^{31}P NMR; δ_P (D_2O/D_2SO_4; 121.5 MHz): 19.64 (s). IR, ν_{max} (KBr): 3620; 3446 (NH); 3047; 2963; 2930; 2848; 2730; 2603; 1617; 1476; 1437; 1366; 1169 (P=O); 1131; 1026; 997; 918; 891; 743; 732; 695; 645; 602; 566; 510 cm^{-1}. MS; (ESI+Q1MS): 345.3 (100, M^++1). Anal. Calcd for $C_{17}H_{17}N_2O_2PS$, requires C, 59.29; H, 4.98; N, 8.13; found: C, 59.18; H, 5.02; N, 8.09%.

4.2.5. Thiazole-2-yl-methyl-(*N*-butylamino)-methylphosphinic acid (6c). A white solid. Yield: 0.41 g (67%), mp 168–172 °C. ^{1}H NMR; δ_H (D_2O/10% D_2SO_4; 300 MHz): 8.59 (d, 1H, thiazole-4, J=3.3 Hz), 8.57 (d, 1H, thiazole-5, J=3.3 Hz), 5.26 (d, 1H, C*H*–P, J=17.6 Hz), 3.56–3.50 (m, 2H, NHCH_2), 1.79–1.70 (m, 2H, C$H_2$$CH_2$), 1.40–1.32 (m, 2H, CH_2CH_2), 1.17 (t, 3H, CH_3, J=7.3 Hz), 1.02 (d, 3H, PCH_3, J=14.3 Hz). ^{31}P NMR; δ_P (D_2O/D_2SO_4; 121.5 MHz): 29.80 (s) ppm. IR, ν_{max} (KBr): 3313 (NH); 3243; 2951; 2908; 2878; 1587; 1487; 1421; 1198 (P=O); 1123; 995; 928; 755; 708; 695; 504 cm^{-1}

MS; (ESI+Q1MS): 271.3 (100, M^++Na). Anal. Calcd for $C_9H_{17}N_2O_2PS$, requires C, 43.54; H, 6.90; N, 11.28; found: C, 43.45; H, 7.01; N, 11.21%.

4.2.6. Thiazole-2-yl-methyl-(*N*-benzylamino)methylphosphinic acid (6d). A white solid. Yield: 0.50 g (72%), mp 210–214 °C. ^{1}H NMR; δ_H (D_2O/10% D_2SO_4; 300 MHz): 8.50 (d, 1H, thiazole-4, J=3.3 Hz), 8.25 (d, 1H, thiazole-5, J=3.3 Hz), 8.20–8.03 (m, 5H, Ph*H*), 4.90 (d, 1H, C*H*–P, J=17.7 Hz), 4.64 (s, 2H, NHCH_2Ph), 1.10 (d, 3H, PCH_3, J=14.3 Hz). ^{31}P NMR; δ_P (D_2O/D_2SO_4; 121.5 MHz): 30.45 (s) ppm. IR, ν_{max} (KBr): 3386 (NH); 3045; 2960; 2928; 2863; 1604; 1485; 1326; 1181 (P=O); 1154; 938; 887; 733; 649; 596; 561; 504 cm^{-1}. MS; (ESI+Q1MS): 305.3 (100, M^++Na). Anal. Calcd for $C_{12}H_{15}N_2O_2PS$, requires C, 51.06; H, 5.36; N, 9.92; found: C, 50.99; H, 5.43; N, 9.87%.

4.3. General procedure for preparation of 2-thiazole aminophosphine oxides (7a–f)

To a solution of crude imine **2** (2.5 mmol) in dry toluene (25 mL), the appropriate phosphine oxide (**9** or **10**) was added (2.5 mmol). The mixture was stirred overnight at room temperature and then refluxed for 2 h to complete the reaction. After evaporation of the solvent, crude thiazole aminophosphine oxides were obtained as solids, or thick oils. Compounds **7e** and **7f** (solids) were purified by crystallization from toluene–hexane solution. Compounds **7a–d** (oils) were purified as oxalate salts, obtained by the following procedure: the crude product (~2.5 mmol) was dissolved in acetone (10 mL) and treated with acetone solution of oxalic acid (10 mL, containing 0.61 g $(COOH)_2\cdot 2H_2O$). After cooling, the separated crystals were collected by filtration and dried on air to give oxalates **7a–d**, as white, crystalline solids.

Oxalates **7a–d**, treated with an excess of aqueous sodium bicarbonate and extracted with methylene chloride give the pure thiazole aminophosphine oxides, as thick oils.

4.3.1. Thiazole-2-yl-methyl(*N*-butylamino)-butylphenylphosphine oxide, oxalate (7a). A crystalline solid. Yield: 0.79 g (67%), mp: 104–106 °C. ^{1}H NMR; δ_H (D_2O; 300 MHz): 7.70–7.37 (m, 7H, thiazole-4, thiazole-5, Ph*H*), 5.63 (d, 0.5H, C*H*–P, J=11.6 Hz), 5.58 (d, 0.5H, C*H*–P, J=11.6 Hz), 3.98–3.76 (m, 4H, NHCH_2, PCH_2), 1.59–1.20 [(m, 8H, NHCH$_2$(CH_2)$_2$ and PCH$_2$(CH_2)$_2$)], 0.97–0.80 (m, 6H, 2×CH_3). ^{31}P NMR; δ_P (D_2O; 121.5 MHz): 46.61 (s) and 45.83 (s), in a ratio 1:0.80 (two diastereomers). IR, ν_{max} (KBr): 3489; 3410 (NH); 3110; 2956; 2806; 1742; 1662; 1479; 1445; 1403; 1174 (P=O); 786; 741; 696; 551; 482 cm^{-1}. MS; (ESI+Q1MS): 373.4 (100, M^++Na). Anal. Calcd for $C_{18}H_{27}N_2OPS\cdot 2\times(COOH)_2$, requires C, 49.81; H, 5.89; N, 5.28; found: C, 49.80; H, 5.94; N, 5.25%.

4.3.2. Thiazole-2-yl-methyl(*N*-benzylamino)-butylphenylphosphine oxide, oxalate (7b). A crystalline solid. Yield: 0.73 g (58%), mp 120–122 °C. ^{1}H NMR; δ_H (D_2O; 300 MHz): 7.48–7.19 (m, 12H, thiazole-4, thiazole-5, 2×Ph*H*), 4.73 (d, 0.5H, C*H*–P, J=14.6 Hz), 4.69 (d, 0.5H, C*H*–P, J=14.6 Hz) 4.05–3.99 (m, 2H, NHCH_2Ph), 2.41–2.36 (m, 2H, PCH_2), 1.50–1.45 [(m, 4H, PCH$_2$(CH_2)$_2$)], 0.97–0.92 (m, 3H, CH_3). ^{31}P NMR; δ_P (D_2O; 121.5 MHz): 43.02 (s) and 42.31 (s), in a ratio 1:0.83 (two diastereomers). IR, ν_{max} (KBr): 3491; 3415 (NH); 2965; 2810; 1668; 1481; 1449; 1408; 1183 (P=O); 792; 744; 690; 541; 531; 491 cm^{-1}. MS; (ESI+Q1MS): 407.5 (100, M^++Na). Anal. Calcd for $C_{21}H_{25}N_2OPS\cdot 2\times(COOH)_2$, requires C, 53.19; H, 5.18; N, 4.96; found: C, 53.08; H, 5.34; N, 4.75%.

4.3.3. Thiazole-2-yl-methyl(*N*-butylamino)-methylphenylphosphine oxide, oxalate (7c). A crystalline solid. Yield: 0.67 g (62%), mp 132–135 °C. ^{1}H NMR; δ_H (D_2O; 300 MHz): 7.67–7.47 (m, 7H, thiazole-4, thiazole-5, Ph*H*), 5.63 (d, 0.5H, C*H*–P, J=12.6 Hz), 5.59 (d, 0.5H, C*H*–P, J=12.6 Hz), 3.95–3.90 (m, 2H, NHCH_2), 1.54–1.49 (m, 4H, CH_2CH_2), 1.57 (d, 1.5H, PCH_3, J=13.0 Hz), 1.47 (d, 1.5H, PCH_3, J=13.0 Hz), 0.87–0.84 (m, 3H, CH_3). ^{31}P NMR; δ_P (D_2O; 121.5 MHz): 44.21 and 43.83 (s), in a ratio 1:0.90 (two diastereomers). IR, ν_{max} (KBr): 3465; 3389 (NH); 3090; 2951; 2803; 1656; 1471; 1408; 1204; 1186 (P=O); 780; 739; 678; 541; 491 cm^{-1}. MS; (ESI+Q1MS): 331.4 (100, M^++Na). Anal. Calcd for $C_{15}H_{21}N_2OPS\cdot 2\times(COOH)_2$, requires C, 46.72; H, 5.16; N, 5.74; found: C, 46.58; H, 5.24; N, 5.70%.

4.3.4. Thiazole-2-yl-methyl(*N*-benzylamino)-methylphenylphosphine oxide, oxalate (7d). A crystalline solid. Yield: 0.65 g (57%), mp 142–145 °C. ^{1}H NMR; δ_H (D_2O; 300 MHz): 7.50–7.21 (m, 12H, thiazole-4, thiazole-5, 2×Ph*H*), 4.64 (d, 0.5H, C*H*–P, J=12.6 Hz), 4.60 (d, 0.5H, C*H*–P, J=12.6 Hz), 4.04–4.00 (m, 2H, NHCH_2Ph), 1.60 (d, 1.5H, PCH_3, J=12.9 Hz), 1.45 (d, 1.5H, PCH_3, J=12.9 Hz). ^{31}P NMR; δ_P (D_2O; 121.5 MHz): 41.22 and 40.31 (s), in a ratio 1:0.88 (two diastereomers). IR, ν_{max} (KBr): 3466; 3398 (NH); 2954; 2812; 1675; 1443; 1440; 1194 (P=O); 801; 756; 692; 547 cm^{-1}. (ESI+Q1MS): 365.4 (100, M^++Na). Anal. Calcd for $C_{18}H_{19}N_2OPS\cdot 2\times(COOH)_2$, requires C, 50.58; H, 4.44; N, 5.36; found: C, 50.55; H, 4.48; N, 5.23%.

4.3.5. Thiazole-2-yl-methyl(*N*-butylamino)-diphenylphosphine oxide (7e). A white solid. Yield: 0.59 g (65%), mp 110–112 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.88–7.18 (m, 12H, thiazole-4, thiazole-5, 2×Ph*H*), 5.03 (d, 1H, C*H*–P, J=12.6 Hz), 2.67–2.51 (m, 2H, NHCH_2), 1.42–1.20 (m, 4H, CH_2CH_2), 0.85 (t, 3H, CH_3, J=7.5 Hz). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 Hz): 30.93 (s). IR, ν_{max} (KBr): 3445; 3275 (NH); 3054; 2923; 2868; 1627; 1592; 1484; 1435; 1379; 1182 (P=O); 1116; 999; 829; 722; 690; 644; 554; 507 cm^{-1}. (ESI+Q1MS): 393.4 (100, M^++Na). Anal. Calcd for $C_{20}H_{23}N_2OPS$, requires C, 64.85; H, 6.26; N, 7.56; found: C, 64.80; H, 6.34; N, 7.49%.

4.3.6. Thiazole-2-yl-methyl(*N*-benzylamino)-diphenylphosphine oxide (7f). A white solid. Yield: 0.58 g (58%), mp 138–141 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.84–7.15 (m, 17H, thiazole-4, thiazole-5, 3×Ph*H*), 4.98 (d, 1H, C*H*–P, J=12.3 Hz), 3.95–3.90 (m, 2H, NHCH_2Ph). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 Hz): 31.45 (s). IR, ν_{max} (KBr): 3434 (NH); 3054; 2923; 2855; 2606; 2206; 1634; 1497; 1436; 1380; 1315; 1187 (P=O); 1166; 1124; 1073; 1038; 1021; 917; 857; 799; 699; 555; 507; 489 cm^{-1}. (ESI+Q1MS): 427.5 (100, M^++Na). Anal. Calcd for

$C_{23}H_{21}N_2OPS$, requires C, 68.30; H, 5.23; N, 6.93; found: C, 68.23; H, 5.36; N, 6.87%.

4.4. Potentiometric and spectroscopic studies of Cu(II) complexes with 4a and 4b

4.4.1. Potentiometric measurements. The purities and exact concentrations of the stock solutions of the ligands were confirmed pH-metrically by the Gran method.[34] The concentration of the Cu(II) stock solution was measured gravimetrically via precipitation of the quinolin-8-olate.

The stability constants both for protons and Cu(II) complexes of the studied ligands were determined by pH-metric titration of 1.5–2.0 cm^3 samples at the pH range 2.5–11.0. The ligand concentration 2.5–3.0 mmol dm^{-3}; metal to ligand molar ratios 1:2, 1:4, 1:6; ionic strength adjusted to 0.1 mol dm^{-3} with KNO_3; duplicate pH titration calibrated in concentration;[35] temperature 25 °C.

The pH was measured with MOLSPIN automatic titration system with a microcombined glass-calomel electrode calibrated daily. Titration data were used to calculate the stability constants ($\beta_{pqr}=[M_pH_rL_q]/[M]^p[H]^r[L]^q$) with a SUPERQUAD computer program.[36] Standard deviations quoted refer to random errors only.

4.4.2. Spectroscopic measurements. The absorption spectra were recorded on a Beckman DU 650 spectrophotometer. The EPR spectra were recorded, in 1:2 ethane-1,2-diol/water (v/v), on a Bruker ESP 300E spectrometer at the X-band (9.3 GHz) at 120 K. The concentrations used in the spectroscopic measurements were similar to those given for potentiometric titrations. The results of potentiometric and spectroscopic studies are collected in Tables 1 and 2.

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