Thioureidoalkylphosphonates in the synthesis of 1-aminoalkylphosphonic acids. The Ptc-aminophosphonate method

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Dedicated to Prof. Dr hab. Heinz Heimgartner on the occasion of his 70th birthday

DOI: http://dx.doi.org/10.3998/ark.5550190.0012.617

Abstract

1-Aminoalkylphosphonic acids (AA^P) as structural analogues of protein amino acids (AA^C), are important inhibitors of amino acids metabolism. One of the three methods which have contributed to the development of the chemistry of 1-aminoalkylphosphonic acids is the Ptc-aminoalkylphosphonate (Phenylthio**c**arbamoylaminoalkylphosphonate) method which allows a time saving synthesis of structurally diverse AA^P of analytical purity on mmol-mol scale This review presents a comprehensive survey of this methodology development, with an emphasis on its scope and limitations.

Keywords: Amino acids, aminophosphonic acids, 1-aminoalkylphosphonic acids, Ptc-aminophosphonate method, Birum reaction, Birum-Oleksyszyn metod, Oleksyszyn method

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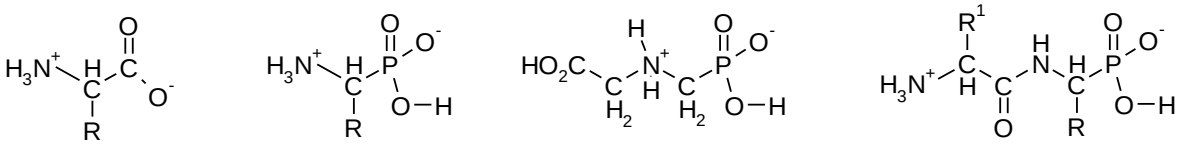
1. Introduction

1-Aminoalkylphosphonic acids (AA^P) as structural analogues of protein amino acids (AA^C), are important inhibitors of enzymes of amino acid metabolism.[1-4] These properties have been spectacularly reflected in wide-world agrochemical aplications of aminophosphonic herbicidals, [e.g. phosphonomethylglycine (PMG)[5-7] and also in bacteriostatic applications of mixed phosphono-carboxylic peptides (AA^C-AA^P), [e.g. *Phosphaline* (R=R^1=Me)].[8,9]



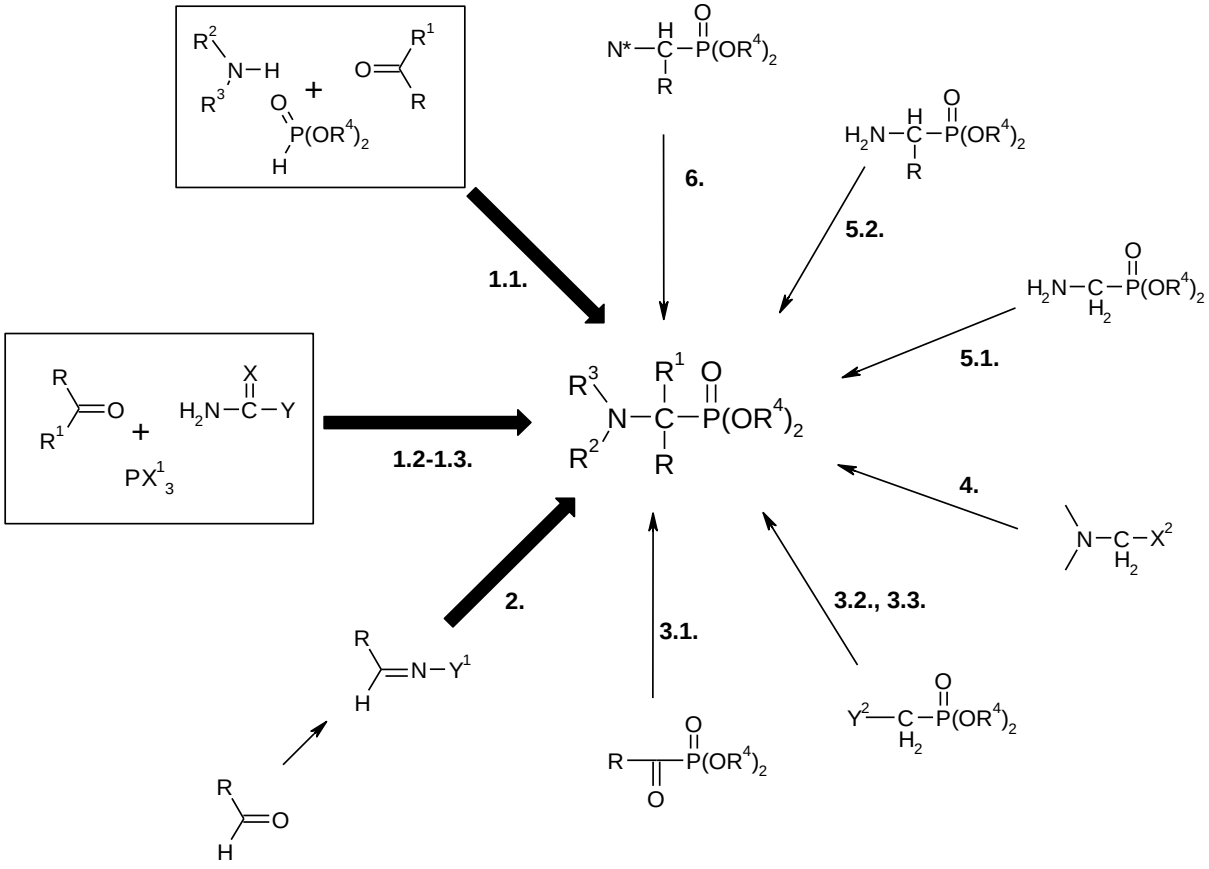
AA^C AA^P PMG AA^C-AA^P

Therefore, studies on the synthesis[10-12] and reactivity of 1-aminoalkylphosphonic acids and their derivatives (e.g. references 11, and 13-15) constitute an important topic in the chemistry and biochemistry of the P-C-N class phosphonates.

Thus, the numerous methods of synthesis of 1-aminoalkylphosphonic acids (1-aminoalkylphosphonates) published until now (according to Kafarski and Lejczak, over 6000 papers on the chemistry of aminophosphonates until 2001),[3] can be classified according to the system given below (Scheme 1):

1. Methods based on simultaneous formation of P-C-N systems [P+C+N → P–C–N]:
1.1. Kabachnik-Fields method;
1.2. Amidoalkylation of phosphorus(III) esters;
1.3. Amidoalkylation of phosphorus(III) halides.

2. Methods based on additions of the P-H functions to multiple C-N bonds [P–H → P–C–N] (hydrophosphonylation and/or hydrophosphinylation of imines and trazines, hydrazones, azines and oximes, nitrones and nitriles).



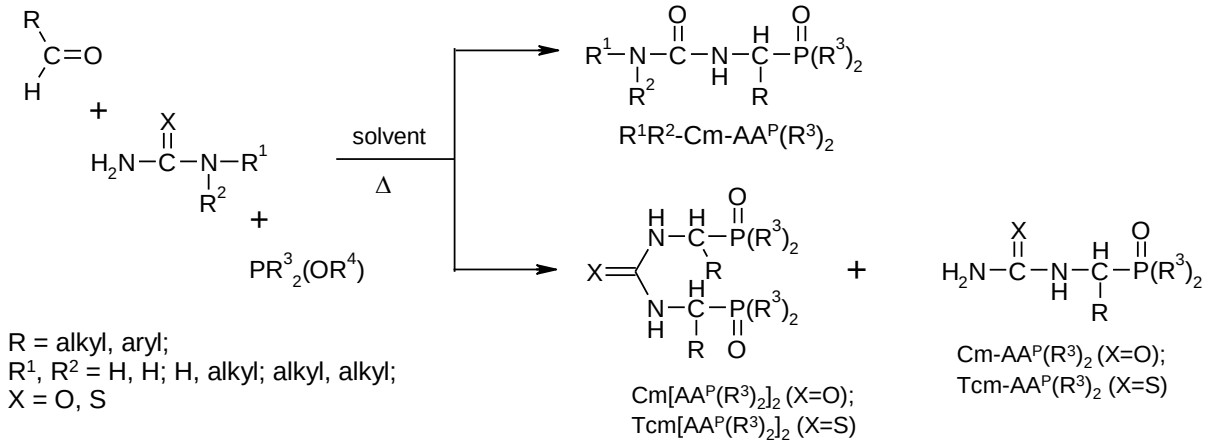
R, R^1 = H, alkyl, aralkyl, aryl; R^2, R^3 = H, H; H, alkyl;H, aralkyl; H, aryl; cycloalkyl; alkyl, aryl;
R^4 = alkyl (Me, Et, iPr), aryl (Ph), aralkyl (Bn) and H; X = O, S; X^1 = Cl, HO, RO, ArO; X^2 = Cl, Br, RO;
Y = BnO, PhNH; Y^1 = R, NH_2, RNH, R_2N, HO; Y^2 = Cl, HO (**3.2.**); Me, Ph, RO-C(O)-(**3.3.**);
N* = N_3, NO_2, H_2N-NH

Scheme 1

3. Methods based on α–amination of functionalized alkylphosphonates [P–C + N → P–C–N]:
3.1. Reductive amination of 1-ketophosphonates;
3.2. Nucleophilic aminations of alkylphosphonates;
3.3. Electrophilic aminations of alkylphosphonates).
4. Methods based on nucleophilic substitution with phosphoroorganic nucleophiles [P + X–C–N → P–C–N + X] (Arbusov reaction derived methods).
5. Methods based on modifications of the carbon chain of 1-aminoalkylphosphonates [P–C(R)–N → P–C(R*)–N]:

5.1. Nucleophilic or electrophilic alkylation of derivatives of phosphonoglycinate;
5.2. modifications of the carbon side chain of aminoalkylphosphonates.
6. Methods based on modifications of phosphorus functions [P–C–N → P*–C–N] (oxidation of 1-aminoalkylphosphinic acids into 1-aminoalkylphosphonic analogues).
7. Methods based on modifications of nitrogenic functions [P-C-N → P-C-N*] (reduction of 1-azidoalkylphosphonates and 1-nitroalkylphosphonates, reduction of oximes, hydrazones, azines, etc.)
8. Other methods.

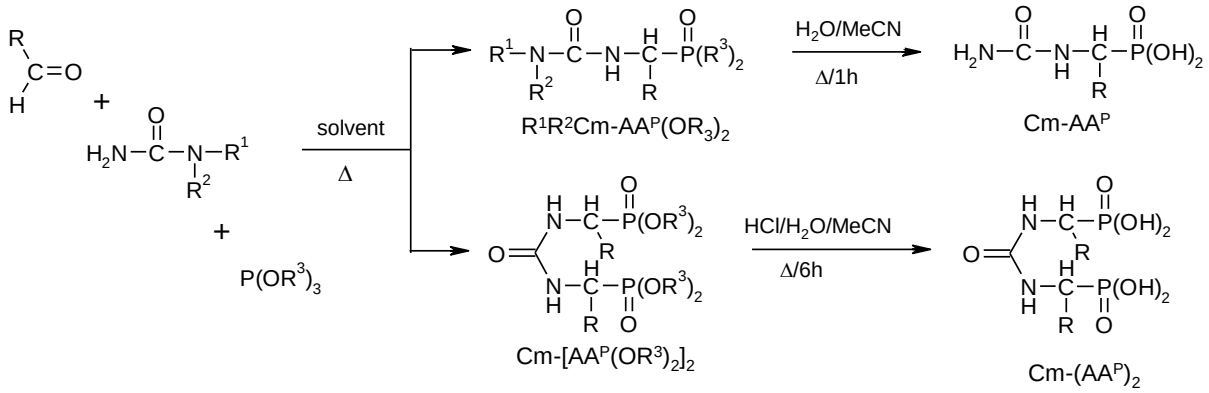
However, the crucial events in the chemistry of phosphonic analogues of protein amino acids (1-aminoalkylphosphonic acids bearing with the primary amino function: $R^2 = R^3 = H$; Scheme 1) took place in the late 1970s and were connected with two discoveries. The first was made by Birum[16] and is related to the easy and high yield reactions of ureas with aldehydes and esters of phosphorus(III) oxo-acids (Scheme 2). [In this review, the phosphonic acids and derivatives are named through abbreviations, the code for these abbreviations is listed in Section 4 (Table 12)].



Scheme 2

Their scope was extended by the use of other amide components, including sulfamides, sulfonamides and carbamates [patents of Birum[17-21]].

The products of the Birum condensation (Table 1) contain the P-C-N bond system characteristic for 1-aminoalkylphosphonic acids. However, attempts on their degradation, carried out by Birum for Cm-$AA^P(OPh)_2$ and/or Cm-$[AA^P(OPh)_2]_2$, revealed low to moderate stability of the ester functions and higher stability at applied conditions of the amide function (Scheme 3).

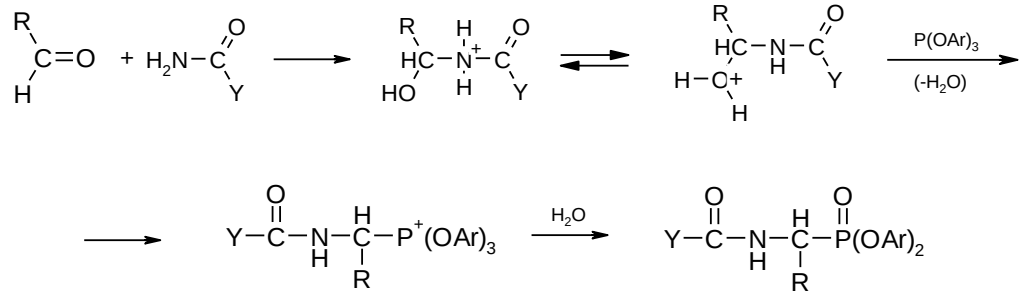


Scheme 3

As a matter of fact, the degradation of Pc-Ala^{P}(OEt)$_2$ and/or Pc-Pgly^{P}(OEt)$_2$ (R^1=Ph; R^2 = H; R^3 = Et) to the corresponding AA^{P}, carried out by Huber and Middlebrooks a few years later,[22] required relatively harsh conditions (72 h of reflux in 10 M HCl aq.).

The second contribution was made by Oleksyszyn, who not only recognized the practical value of the Birum condensations,[23-25] but also the Engelman and Pikl amidoalkylations of phosphorus trichloride[25-28] **(**Section 3).

In the Birum condensation, which formally can be considered as a variant of the Arbuzov reaction, and also as a type of the amidoalkylation of phosphorus(III) esters, the key electrophilic reagent prepared *in situ* from an amide substrate and an aldehyde, adds to the corresponding phosphite (phosphonite, phosphinite) afford the variety of structurally diverse P-C-N products (Scheme 4, Table 1).



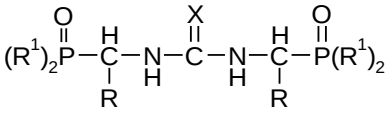
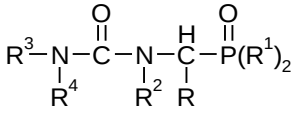
Y = NH_2, R-NH, R_2N; R = alkyl, aryl

Scheme 4

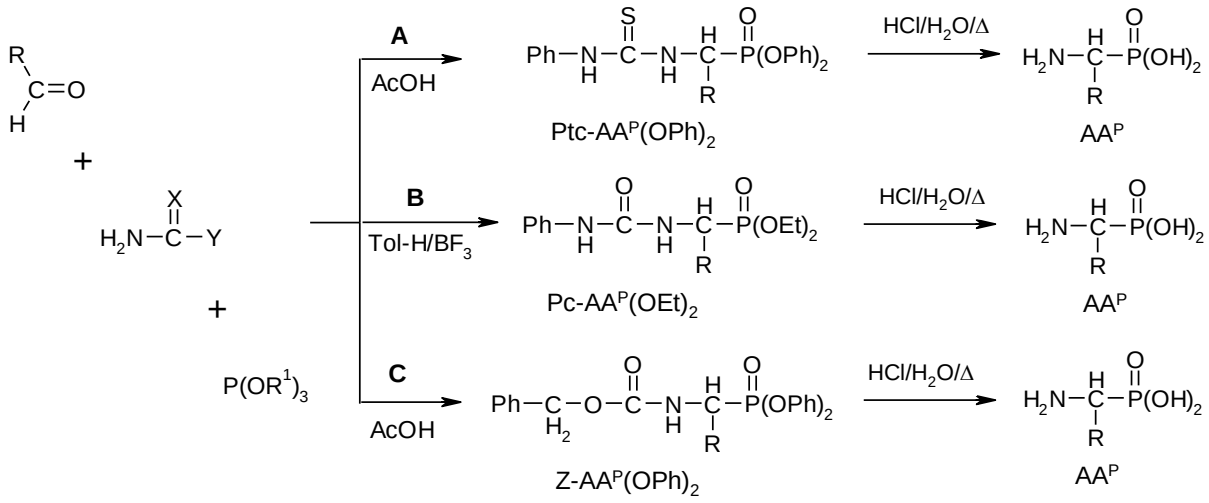
Modification of the Birum reaction, in which ureas (thiourea) were replaced by *N*-phenylthiourea (**A**: Ptc-aminophosphonate method[29,30] and/or by *N*-benzyl carbamates (**C**: Z-aminophosphonate method, Birum-Oleksyszyn method)[23,25] (Section 3.1.) (Scheme 5) and modification of the amidoalkylation Engelman-Pikl reaction by Oleksyszyn[25,28] (Section 3.2.)

created three excellent protocols exceeding earlier procedures in terms of simplicity and yields.[10-12]

Table 1. Characterization of representative products of the Birum condensation[16]

Structure							
							
Abbrev.	R	R^1	X	Conditions	Yields [%]	m.p. [°C][c,d]	^{31}P NMR [ppm]
Cm[Ala^P(OPh)$_2$]$_2$	Me	PhO	O	CH_2Cl_2/60-83°C/1h	100(88)	oil	19.7
					(62)	137±1[c]	19.7
						158±3[d]	20.1
Cm[Pgly^P(OPh)$_2$]$_2$	Ph	PhO	O	CH_2Cl_2/70-83°C/1h	(72)	190±1[c]	14.7
						182±1[d]	15.5
Cm[Ala^P(O-CET)$_2$]$_2$	Me	$ClCH_2CH_2O$	O	47-62°C/1h/90-95°C /0.5h	(89)	139±1	27.8
Tcm[Nval^P(OPh)$_2$]$_2$	Pr	PhO	S	PhMe/100-105°C/1h	100	140±2	18.1
							
Abbrev.	R	R^1	R^2N	R^4R^3N	Conditions	Yields [%]	m.p. [°C][c,d]	^{31}P NMR [ppm]
Dpc-Ala^P(OPh)$_2$	Me	PhO	H	Ph_2N	Ph-H/60°C	80		18.4[e]
Pc-Pgly^P(OEt)$_2$	Ph	EtO	H	Ph(H)N	PhMe/BF_3/100°C/1h	69	151±1	23.1
[a]Cm-Nval^P(Ph)$_2$	Pr	Ph	H	H_2N	PhMe/AcOH/RT/65-80°C/1.5h	69	151±1	44.4[f]
[b]Cm-Nval^P(Ph)$_2$	Pr	Ph	H	H_2N	PhMe/110°C/6h	69	151±1	32.4
Mcm-(Me)-Pgly^P(Ph)$_2$	Ph	Ph	Me	Me(H)N	PhCl/130°C/1h	100(75)	218±1.5	32.6

[a]Synthesized from $Ph_2P(OEt)$; [b]Synthesized from $Ph_2P(OPh)$. Yields: ^{31}P NMR or isolated yields (in brackets). M.p.: [(c)]I fraction & [(d)]II fraction. ^{31}P NMR: solutions in $CDCl_3$; PhH[(e)] or THF[(f)]



R = alkyl, aryl, aralkyl; R^1 = Et, Ph; X = O, S; Y = Ph-NH, BnO

Scheme 5

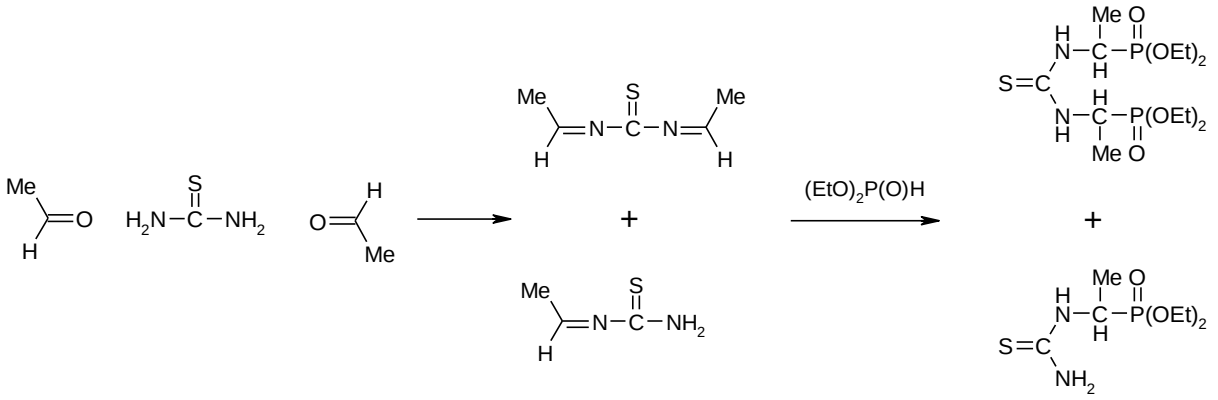
In this review, we present the results on the origin and developments of Ptc-aminophosphonate method.

2. The origin of the Ptc-aminophosphonate method

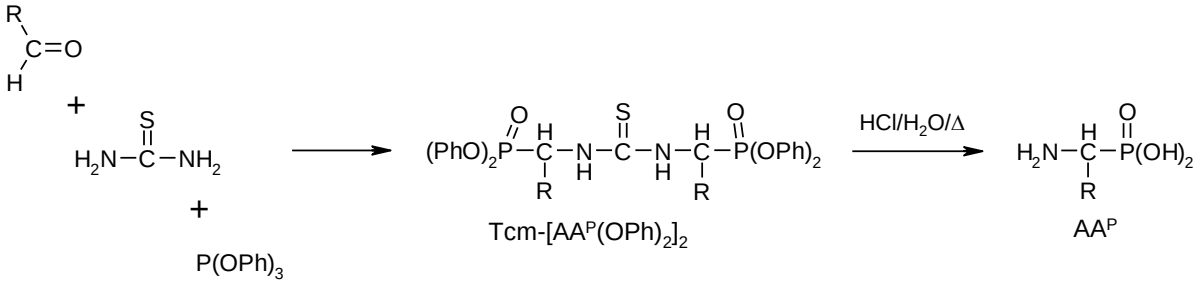
Until the 1980s the most efficient procedures for the synthesis of compounds containing the N-C-P bond system were based on an addition of a phosphorus nucleophile to imine bonds (usually imines derived from benzylamine and its analogs), followed by the amine group deprotection.[10,12] Therefore the 1-aminoalkylphosphonate research at these decades was directed mainly on the search for labile imine-derivatives – substrates for a phosphite addition. As a part of this research program, developed in the Stec laboratory,[31-34] we started with the examination on the addition of phosphorus nucleophiles into the C=N bond of thiourea-aldehyde adducts formed easily in aqueous acidic solutions of aldehydes and thiourea[35] (Scheme 6).

However, the deeper investigation of these additions carried out in wide set of reaction conditions and monitored by ^{31}P NMR, revealed the formation of compounds exhibiting characteristic for 1-aminoalkylphosphonate chemical shifts (~15-17 ppm) in low amounts.

Therefore, in an alternative approach, we applied the variant of the Birum reaction in which a toluene solution of alkanal, thiourea and triphenyl phosphite was converted upon heating (110^{o}C) into a mixture of thioureidoalkylphosphonate Tcm-AA^P(OPh)$_2$ and thiourylenebis(alkylphosphonate) Tcm-[AA^P(OPh)$_2$]$_2$. Their very slow hydrolytic degradation (24h of reflux in 10M HCl solution) gave the expected 1-aminoalkylphosphonic acids with yields of ca. 30-40% (Scheme 7).



Scheme 6

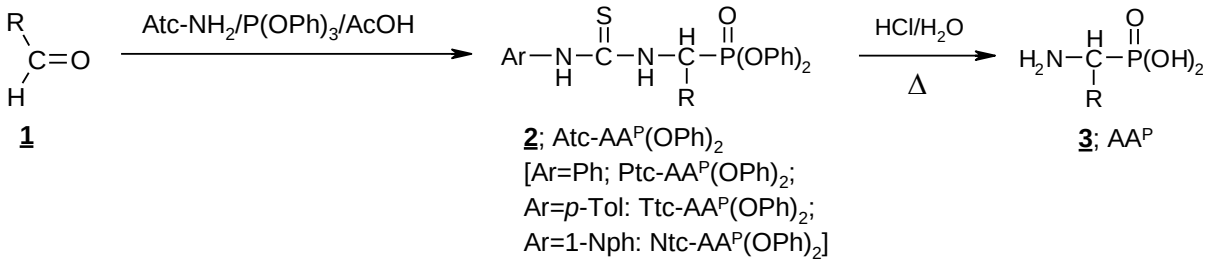


Scheme 7

However, due to the requirement of thermal activation, the applied conditions of condensation eliminated application of volatile, low molecular aldehydes (e.g. acetaldehyde). Also low yields of the degradation of so formed thiourylenebis(alkylphosphonates) Tcm-$[AA^{P}(OPh)_2]_2$ induced the search for more labile thiourea derivatives which afford more prone to the degradation tioureidoalkylphosphonates.

The survey of thiourea structures suggested the use of *N*-phenylthiourea as an amide substrate for these tri-component condensations. It is easily degradable under acidic hydrolysis to *N*-phenylisothiocyanate and ammonia.[36]

The mechanistic analysis of this condensation, confirms the Birum suggestions on the role of acidic catalyst in the reactions (Table 2). We have found, that the condensations carried out in glacial acetic acid occur spontanously, usually with a slight exothermic effect. The application of *N*-phenylthiourea as the amide component of condensation, resulted in the high yields formations of the corresponding *N*-phenylthioureidoalkylphosphonates [Ptc-$AA^{P}(OPh)_2$], which in majority underwent spontaneous crystallization from the reaction mixtures. These Ptc-$AA^{P}(OPh)_2$ compounds during acidic hydrolysis (6-8h of reflux in mixtures $HCl/H_2O/AcOH$) underwent the quantitative degradations to the corresponding 1-aminoalkylphosphonic acids (Scheme 8).



Scheme 8

Diphenyl Ptc-aminoalkylphosphonates have also attracted considerable interest as model compounds for structural studies.[37-42]

2.1. Synthesis of bifunctional 1-aminoalkylphosphonic and 1-aminoaralkylphosphonic acids

The application of the tri-component condensation of *N*-phenylthiourea, alkanals or aromatic aldehydes and triphenyl phosphite gave various diphenyl 1-(Ptc-amino)alkylphosphonates, which upon hydrolytic, acidic degradation afforded bifunctional 1-aminoalkylphosphonic and 1-aminoaralkylphosphonic acids (Tables 2 and 3). Using this protocol we have synthesized several phosphonic analogs of the protein amino acids, including Ala^P, Val^P, Leu^P, Ile^P, Phe^P, as well as their homologs, compounds known from their biological activity.[1-4,43] Herbicidal properties of the aryl-containing 1-aminophosphonic acids[44-46] sugested us the synthesis of their analogs (Table 2).

Preparation of thioureidoalkylphosphonates Ptc-AA^P(OPh)$_2$ [Kudzin&Stec, *Synthesis* **1978**][29]

To a solution of triphenyl phosphite (0.02 mol) and aldehyde (0.025 mol) in glacial acetic acid (10 ml) is added the powdered *N*-phenylthiourea (Ptc-NH$_2$: 0.02 mol) in one portion. Addition of Ptc-NH$_2$ is accompanied with a slight exothermic effect. The reaction mixture is stirred at room temperature for 0.5 h and for next 0.5 h at 80°C (oil-bath). After cooling of the reaction mixture to room temperature, water (5 ml) is added and the solution was maintained at room temperature for 10 h. The precipitate is filtered off, washed with acetic acid/water (1:1), dried over potassium hydroxide in an evacuated dessicator, and recrystallized from chloroform/methanol. The yields and physical constants of all products Ptc-AA^P(OPh)2 are given in Table 2.

Preparation of 1-aminoalkylphosphonic acid; Procedure A [Kudzin&Stec, *Synthesis* **1978**][29]

Compound **Ptc-AA^P(OPh)$_2$** (0.005 mol) is dissolved in a mixture of glacial acetic acid (1 ml) and hydrochloric acid (36 %, 10 ml) and heated under reflux for 7 h. The solvents are evaporated under reduced pressure and the residue is dissolved in ethanol (20 ml). The ethanolic solution of the amino acid hydrohalide is treated with methyloxirane until pH 6 is reached. The precipitated aminoalkanephosphonic acid is filtered off, washed with ethanol, and dried in vacuum over potassium hydroxide. Recrystallization from ethanol/water gives the desired aminoalkanephosphonic acid. The yields and analytical data are collected in Table 2 and 3.

Preparation of 1-aminoalkylphosphonic acid; Procedure B [Kudzin&Stec, *Synthesis* **1978**][29] When *N*-Ph-CH(Me)-thiourea (Bmtc-NH_2) were applied, the formed thioureidophosphonate Bmtc-$AA^P(OPh)_2$ (5 mmol) is heated under reflux for 3 h in acetic anhydride/acetic acid (5 ml and 1 ml, respectively). Aqueous hydrobromic acid (d=1.38 g/ml, 5 ml) is then added dropwise and heating is continued for 7 h.] The solvents are evaporated under reduced pressure and the residue is dissolved in ethanol (20 ml). The ethanolic solution of the amino acid hydrohalide is treated with methyloxirane until pH 6 is reached. The precipitated aminoalkylphosphonic acid is filtered off, washed with ethanol, and dried in vacuum over potassium hydroxide. Recrystallization from ethanol/water gives the desired aminoalkanephosphonic acid. The yields and analytical data are collected in Table 2 and 3.

Table 2. Bifunctional 1-aminoalkylphosphonic acids

AA^P	Ptc-$AA^P(OPh)_2$						AA^P				Lit.
	Yield [%]	m. p. [°C]	^{31}P NMR [ppm]		Yield [%]		m. p. [°C]	^{31}P NMR [ppm]			
			AcOH	$CDCl_3$	**2**→**3**	**1**→**3**		2M HCl	H_2O	2M NaOH	
Ala^P	85	156-157	17.6		93	91	275-276	16.8	14.3	22.3	29
$Hala^P$	86	159-161	16.7		98	86	265-266	16.8	13.7	22.0	
$Nval^P$	89	155-156	16.8		97	83	262-264	16.8	13.9	22.0	
Val^P	77	158-159	16.2	17.5	92	72	261-262	15.7	13.0	21.2	
$Nleu^P$	81	161-162	16.9	18.0		80	262-264	16.5	14.	21.7	
Leu^P						80	266-268	16.2	13.4	21.2	
							279-280				47
$Ileu^P$						85	261-263	15.0	12.0	20.6	
							271-272				47
$Tleu^P$	80	181-182		16.9		88	245-250	15.3	13.0	20.8	
							245-253				48
$Hnle^P$	78	157-159		16.9		80	267-269	16.5	14.	21.7	
							269-271				49
							274-277				50

Preparation of 1-aminoalkylphosphonic acids; "One-pot" procedure C [Kudzin&Stec, *Synthesis* **1978**][29]

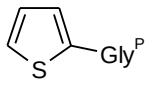
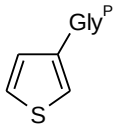
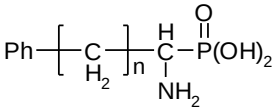
A mixture of triphenyl phosphite (0.02 mol), aldehyde (0.025 mol), *N*-phenylthiourea (Ptc-NH_2: 0.02 mol) in glacial acetic acid (10 ml) is stirred for 1 h at 80°C (oil-bath) and, without isolation, formed Ptc-$AA^P(OPh)_2$ is degraded. In cases when phenylthiourea is a reaction component, aqueous hydrochloric acid (36 %, 20 ml) is used for cleavage of the N-C(S) bond. Bmtc-

$AA^P(OPh)_2$ derivatives required treatment with acetic anhydride/ acetic acid followed by aqueous hydrobromic acid as stated above. Isolation is analogous to that described for procedure **A**.

Table 3. Bifunctional 1-aminoaralkylphosphonic acids

AA^P		$Ptc\text{-}AA^P(OPh)_2$				AA^P				Lit.
$Ar-C(H)(NH_2)-P(O)(OH)_2$		Yield [%]	m.p. [°C]	^{31}P NMR [ppm]		Yield [%] **1**→**3**	m.p. [°C]	^{31}P NMR [ppm]		
								2M HCl	2M NaOH	
Structure	Abbrev.			$CDCl_3$	AcOH					
Gly^P	$PGly^P$	85	169-170	15.4	13.4	70	269-271	12.5	18.0	29
Me-Gly^P	2-MP-Gly^P	85	169-170	15.0		70	252-254	13.4	19.0	
Me-Gly^P	3-MP-Gly^P	82	154-158	15.7		90	234-236	13.2	18.6	
Me-Gly^P	4-MP-Gly^P	90	192-195	15.5		97	246-248	13.3	18.7	
NO_2-Gly^P	2-NP-Gly^P	68	164-166	13.7		45	246-249	10.8	17.2	
O_2N-Gly^P	3-NP-Gly^P	76	146-149	14.5		90	231-233	11.2	17.1	
O_2N-Gly^P	4-NP-Gly^P	34	165-168	14.1		37	223-224	10.9	16.8	
Cl-Gly^P	2-CP-Gly^P	81	130-134	14.5		49	235-237	11.8	18.0	
Br-Gly^P	4-BP-Gly^P	68	177-179	14.7			254-256		18.1	
Gly^P	1-Nph-Gly^P	60	182-184	15.3		75	255-257	13.0	18.8	
Gly^P	2-Nph-Gly^P	70	177-179	15.5		91	235-237	12.9	18.4	
O-Gly^P	2-Fu-Gly^P	60	150-152	12.8		[a]				

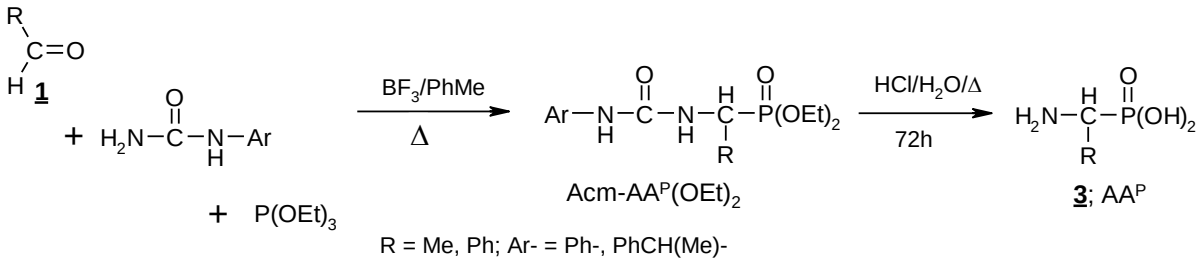
Table 3. Continued

	2-Tf-Gly^P	59			13.1	[a]				
	3-Tf-Gly^P	43			14.2	[a]				
										
Ph-2-Ala^P (n=1)	Phe^P	70	170-171	16.7	16.5	80	267-269	14.8	20.4	29
Ph-3-Hala^P (n=2)	Hphe^P	80	181-182	17.7		85	257-259	15.8	21.3	
							249-252			51

[a]Standard hydrolytic degradations of the corresponding Ptc-Hetgly^P(OPh)$_2$ [AcOH/10M HCl (1:1), 8h of reflux] afforded multicomponent mixtures of compounds with characteristic for the P-C-N system chemical shifts.

Other *N*-aryl-thioureas led to the corresponding Atc-AA^P(OPh)$_2$ isolated in comparable yields, which during subsequent hydrolytic degradation afforded also AA^P in high yields (Table 4).

Huber and Middlebrooks[22] also applied the Birum reaction for the synthesis of Ala^P(41%) and Pgly^P(46%) in accordance with Scheme 9.



Scheme 9

Tri-component condensations of aldehydes, triphenyl phosphite and thiourea afforded 1-thioureidophosphonates, intermediates in the syntheses of 1-guanidinophosphonic acids.[52-54]

Table 4. Bifunctional 1-aminophosphonic acids obtained by degradation of other Atc-$AA^P(OPh)_2$

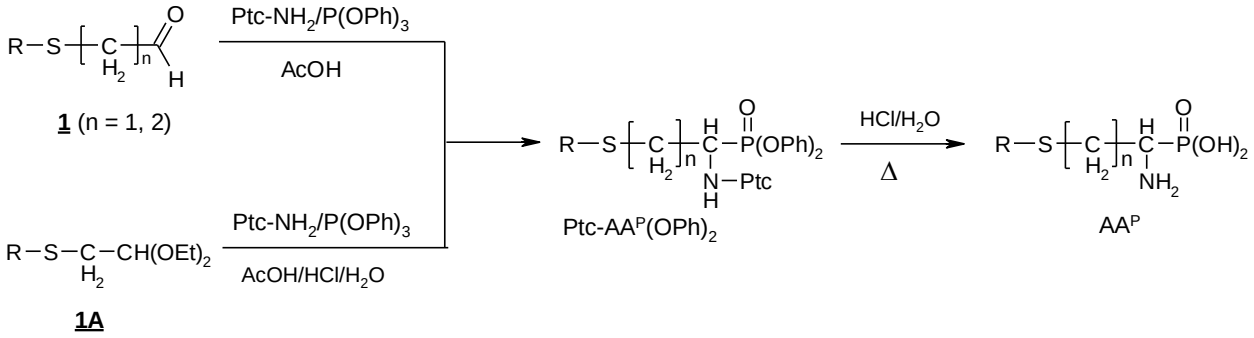
AA^P	Atc-$AA^P(OPh)_2$				AA^P				Lit.
	Yield [%]	m.p. [°C]	^{31}P NMR[a] [ppm]	Yield [%]	m.p. [°C]	^{31}P NMR [ppm]			
	Ttc-$AA^P(OPh)_2$			**2**→**3**		2M HCl	H_2O	2M NaOH	
Ala^P	85	164-166	18.8	93	275-276	16.8	14.3	22.3	
					275-276				29
$Hala^P$	92	151-153	17.9	96	265-266	16.8	13.7	22.0	
					265-266				29
$Nval^P$	90	159-161	17.8	94	262-264	16.8	13.9	22.0	
					262-264				29
Val^P	80	170-172	17.1	90	261-262	15.7	13.0	21.2	
					261-262				29
$Nleu^P$	88	169-171	17.9	95	262-264	16.5	14.	21.7	
					262-264				29
$Pgly^P$	79	160-163	15.1	93	269-271	12.5		18.0	
					269-271				29
	Ntc-$AA^P(OPh)_2$				AA^P				
Ala^P	82	157-159	18.6	93	275-276	16.8	14.3	22.3	
					275-276				29
$Hala^P$	84	165-167	17.6	92	265-266	16.8	13.7	22.0	
					265-266				29
$Nval^P$	86	158-159	17.5	94	262-264	16.8	13.9	22.0	
					262-264				29
Val^P	73	182-184	17.0	87	261-262	15.7	13.0	21.2	
					261-262				29
$Nleu^P$	85	125-127	17.8	91	262-264	16.5	14.	21.7	
					262-264				29
$Pgly^P$	80	194-195.5	15.2	90	269-271	12.5		18.0	
					269-271				29

[a]In $CDCl_3$.

2.2. Synthesis of trifunctional 1-aminoalkylphosphonic acids

This section presents the synthetic protocols leading to 1-aminoalkanephosphonic acids bearing the third additional function, including mercapto, alkylthio-, alkylsulfinyl, alkylsulfonyl and sulfonic groups.

2.2.1. Synthesis of sulfur containing 1-aminoalkylphosphonic acids. These syntheses were performed starting from alkylthioacetaldehydes and/or 3-alkylthiopropanals (obtained by addition of corresponding thiols to acrolein) (Scheme 10).



Scheme 10

Alkylthioacetaldehydes were released by hydrolysis of corresponding acetals **1A**, obtained from thiolates and bromoacetal, and applied for the reaction with *N*-phenylthiourea and triphenyl phosphite without or after prior isolation. The yields and reduced characteristics of obtained 1-amino-(2-alkylthioethyl)phosphonic and 1-amino-(3-alkylthiopropyl)phosphonic acids, are summarized in Table 5.

Table 5. Trifunctional sulfur-containing 1-aminothiaalkylphosphonic acids

Ptc-(R)AA^P(OPh)$_2$						AA^P					Lit.
R = R^1-S-(CH$_2$)$_n$		Yield [%]	m.p. [^{o}C]	^{31}P NMR [ppm]		Abbrev.	Yield [%]	m.p. [^{o}C]	^{31}P NMR [ppm]		
R^1	n			AcOH	CDCl$_3$				TFA	2M KOH	
Me	1	94	136-138	15.2	15.6	MeCys^P	92	258-260	14.0	18.1	55
Et	1	92	135-137	15.2	15.6	EtCys^P	90	257-260	13.9	18.1	
Pr	1	91	142-144	15.2	15.6	PrCys^P	91	251-252	14.1	18.1	

Table 5. Continued

iPr	1	90	150-157	15.2	15.5	iPrCys^P	73	253-255	14.0	18.1	
Bu	1	95	111-112	15.2	15.6	BuCys^P	91	259-261	14.0	18.1	
Bn	1	97	141-143	14.9	15.1	BnCys^P	[a]				
Me	2	85	175-177	16.2	17.0	Met^P	80	270-272	16.0	20.3	56
Et	2	80		16.2	17.2	Eth^P	75	261-263	16.2	20.1	
Pr	2	78		16.4	17.2	PrHcys^P	64	276-278	15.9	20.1	
Bu	2	72		16.3	16.9	BuHcys^P	69	273-275	16.1	20.1	
n-C_6H_{13}	2					HexHcys^P	70	263-265	15.8	20.3	57
n-C_8H_{17}	2					OctHcys^P	80	262-264	15.4	20.2	
n-$C_{10}H_{21}$	2					DecHcys^P	80	260-262	15.3	20.2	
n-$C_{12}H_{25}$	2					Ddec-Hcys^P	80	252-254	15.4	20.2	
n-$C_{16}H_{33}$	2					Hdec-Hcys^P	70	207-209	15.0	20.3	
Bn	2	90	99-100	16.2	17.2	BnHcys^P	64	270-272		20.1	56
Me	2	86	175-177			Met^P	95	274-275			58
Et	2	88	157-158			Eth^P	64	272-273			
Ntc-Met^P(OPh)$_2$		56	153-155								
4-O_2N-Ptc-Met^P(OPh)$_2$		41	186-187								
R= $BnOCH_2$		85-90		17.2	15.6	Ser^P	[b]				

[a]As the result of the hydrolysis the mixture of Cys^P and Ser^P have been observed. [b]As the result of the hydrolysis the mixture of C-N-P compounds (with $^{31}P(\delta)_{2M\ NaOH}$ = 18.1 (32%); 14.8 (14%); 13.6 (44%) ppm) have been obtained.

Diphenyl 2-alkylthio-1-(*N*-phenylthioureido)ethylphosphonates and 3-alkylthio-1-(*N*-phenylthioureido)propylphosphonates [Kudzin&Stec, *Synthesis* **1980;**[56] Kudzin, *Synthesis* **1981**[55]]

Method A. To a solution of triphenyl phosphite (6.2 g, 0.02 mol) and aldehyde (**1**, 0.025 mol) in glacial acetic acid (10 ml), powdered *N*-phenylthiourea (3.02 g, 0.02 mol) is added in one portion. The reaction mixture is stirred at room temperature for 0.5 h and for 0.5 h at 80°C (oil bath temperature). After cooling of the mixture to room temperature, water (5 ml) is added and the solution is maintained at room temperature for 10 h. The precipitate is filtered off, washed with acetic acid/water (1:1; 2×10 ml), dried over potassium hydroxide in an evacuated desiccator, and recrystallized from $CHCl_3$/MeOH (Table l).

Method B. [Kudzin, Synthesis **1981**[55]**]:** A mixture of the *O,O*-diethyl acetal of the alkanethioacetaldehyde **1A** (0.02 mol), glacial acetic acid/water (98:2; 10 ml) and *p*-toluenesulfonic acid (0.2 g) are heated under reflux for 5 min. The mixture is diluted with glacial acetic acid (5 ml), cooled to ~50°C, and *N*-phenylthiourea (1.6 g,0.01 mol) and triphenyl phosphite (3.1 g, 0.01 mol) are added. The reaction mixture is stirred at ~40°C for 2 h. Water (3-5 ml) is added and after 8 h, the crystalline compounds Ptc-$AA^P(OPh)_2$ are separated and purified as described above.

l-Amino-2-alkylthioethylphosphonic and 1-amino-3-alkylthiopropylphosphonic acids 3 [Kudzin&Stec, *Synthesis* **1980**[56]; Kudzin, *Synthesis* **1981**[55]]

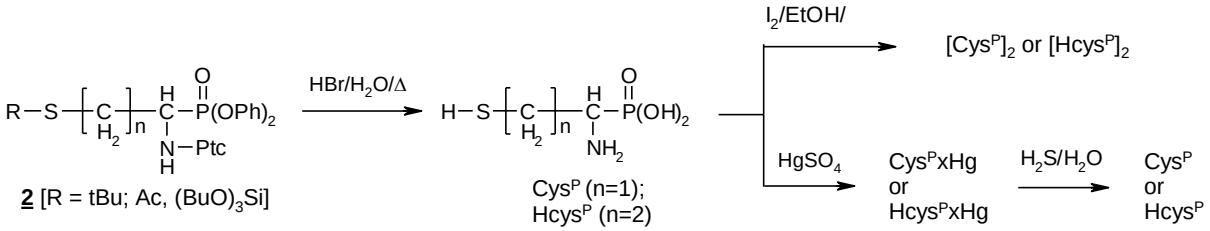
Compound Ptc-$AA^P(OPh)_2$ (0.01 mol) is dissolved in glacial acetic acid (5 ml) and 36% hydrochloric acid (20 ml), and the mixture is heated under reflux for 8 h. The solvents are evaporated under reduced pressure and the residue is dissolved in ethanol (20 ml). The solution is treated with methyloxirane until pH 6 is reached. The precipitate is filtered off, washed with ethanol, and dried under vacuum over potassium hydroxide. Recrystallization from ethanol/water gives the pure aminoalkylphosphonic acid.

Since mercaptoethanal as well as 3-mercaptopropanal - carbonyl precursors of Cys^P and $Hcys^P$ do not exist in the free forms, we used *S*-protected [Ac, tBu, $(BuO)_3Si$] thioalkanals. The obtained corresponding Ptc-$AA^P(OPh)_2$ derivatives, underwent the acidic-hydrolytic degradation with simultaneous deprotection of the phosphonic, amino and thiol functions affording corresponding 1-amino-2-mercaptoethylphosphonic acid [Cys^P] or 1-amino-3-mercapto-propylphosphonic acid [$HCys^P$] in high ^{31}P NMR yields (Scheme 11).

Because of difficulties in isolation of Cys^P and/or $HCys^P$ from their reaction mixtures these amino acids were converted into insoluble disulfide forms $[Cys^P]_2$[55] and $[Hcys^P]_2$,[56] or precipitated in the form of their mercury salts, and subsequently regenerated by saturating with hydrogen sulfide.[59]

Thus, Cys^P by pretreatment with aqueous mercury sulfate afforded the crystalline salt $Cys^P \cdot Hg(II)$ which, according to microanalysis, possesses the formula $C_2H_6NO_3PS \times Hg(II) \times H_2O$. Treatment of a suspension of $Cys^P \cdot Hg(II)$ in water with hydrogen sulfide liberates free phosphonocysteine (Cys^P) which upon ion-exchange chromatography was isolated in crystalline form (platelets). A similar sequence can be applied to the synthesis of phosphonohomocysteine

(Hcys^P) starting from 3-(*t*-butylthio)propanal. In this case, the mercury salt Hcys^P·Hg(II) used for the isolation of Hcys^P is assumed to have the formula $C_6H_{20}N_2O_6P_2S_2Hg_3$.



Scheme 11

Phosphonocystine ([Cys^P]$_2$) [Kudzin, Synthesis **1981**[55]] **and phosphonohomocystine (**[Hcys^P]$_2$**)** [Kudzin&Stec, *Synthesis* **1980**[56]**]:**

To a solution of Ptc-(t-Bu)Cys^P(OPh)$_2$ or Ptc-(R)Hcys^P(OPh)$_2$, [R=tBu-, Ac- or (tBuO)$_3$Si-] (0.01 mol) in glacial acetic acid (10 ml) aqueous hydrobromic acid (*d*= 1.38 g/ml, 20 ml) is added and the mixture is heated under reflux for 14 h. The solvents are evaporated under reduced pressure. The residue is dissolved in ethanol (10 ml) and treated with a solution of iodine (1.4 g, 0.052 mol) in ethanol (10 ml). The mixture is stirred for 15 min and propylene oxide is added until pH 6 is reached. The precipitated crude phosphonocystine [Cys^P]$_2$ or phosphonohomocystine [Hcys^P]$_2$ is filtered off, washed with ethanol (10 ml) and water (10 ml), and dissolved in ethanol/water/36% hydrochloric acid (10:10:1.5). The amino acids are again precipitated with propylene oxide, filtered off, washed with ethanol and water, and dried in vacuum over potassium hydroxide. Yields and physical yields are collected in Table 6.

Phosphonocysteine (Cys^P**) and phosphonohomocysteine (H**Cys^P**)** [Kudzin&Stec, Synthesis **1983**[59]**]:**

Triphenyl phosphite (18.6 g, 0.06 mol) is added in one portion to a stirred solution of the aldehyde t-butylthioethanal or 3-(t-butylthio)propanal (0.05 mol) and *N*-pheny1thiourea (9.06 g, 0.06 mol) in glacial acetic acid (50 ml). Stirring is continued for l h, the mixture allowed to stand at room temperature over night, and then diluted with water (5 ml). After 2 h, the precipitated phosphonates Ptc-(tBu)Cys^P(OPh)$_2$ or Ptc-(tBu)HCys^P(OPh)$_2$ is filtered off, washed with acetic acid/water and . The crude phosphonate is dissolved in a mixture of glacial acetic acid (50 ml) and 40% hydrobromic acid (100 ml) and this solution is heated at reflux temperature for 16 h. The resultant mixture is cooled to room temperature, diluted with water (100 ml), extracted with benzene (2×50 ml), and evaporated to dryness under reduced pressure. The solid residue is dissolved in methanol (125 ml), and a solution of mercury(II) sulfate (30 g) in sulfuric acid (30 g) and water (125 ml) is added. After 3 h, the precipitated salt (Cys^P**)**×Hg(II) or (HCys^P**)**×Hg(II) is isolated by suction, washed with water (2×30 ml), and dried to constant weight in a dessicator over solid phosphorus pentoxide and potassium hydroxide under reduced pressure. The salt (Cys^P**)**×Hg(II) or (HCys^P**)**×Hg(II) (10 g) is suspended in water (100 ml). This suspension is saturated with hydrogen sulfide and stirred at room temperature for 3 h. The precipitated solid is

filtered off, washed with water (2×30 ml), and the combined filtrate is concentrated in vacuo to a volume of ~25 ml. The solution is passed through a Dowex 50W×2 column and the fractions containing Cys^P or $HCys^P$ (ninhydrin or thiomercurimetric test) are collected. The combined fractions containing Cys^P or $HCys^P$, respectively, are concentrated under reduced pressure to a volume of ~5 ml and amino acids Cys^P or $HCys^P$ are precipitated with ethanol (25 ml).

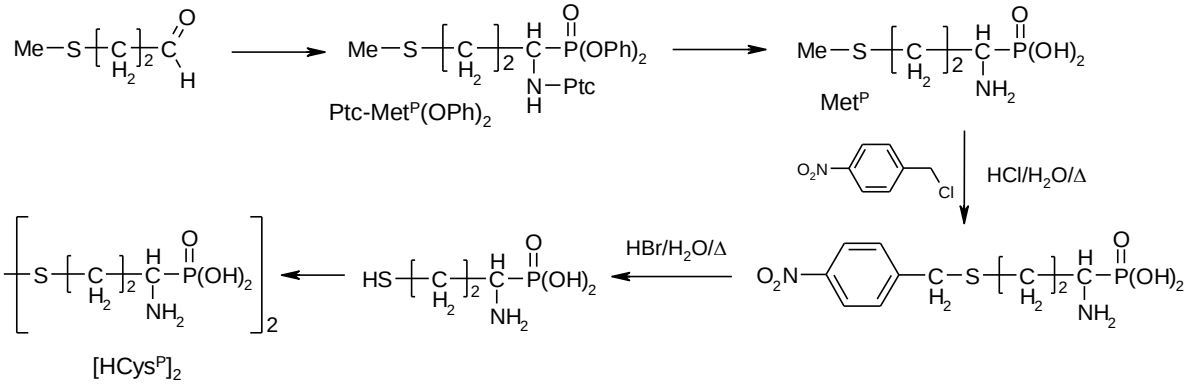
Table 6. Trifunctional thiolic 1-aminoalkylphosphonic acids

Ptc-(R)$AA^P(OPh)_2$						AA^P					Lit.
R = R^1-S-$(CH_2)_n$		Yield [%]	m.p. [°C]	^{31}P NMR [ppm]		Abbrev.	Yield [%]	m.p. [°C]	^{31}P NMR [ppm]		
R^1	n			AcOH	$CDCl_3$				10M HCl	2M KOH	
t-Bu	1	95	170-171		16.5	Cys^P	42	251-252	14.5	19.5	59.
								228-234	12.9[b]	19.5[c]	60, 61
t-Bu	1	95	170-171		16.5	$[Cys^P]_2$	72	257-259	13.2[a]	17.7	55
									12.6[b]	18.4, 18.2[c]	
t-Bu	2	90	134-135		16.5	$HCys^P$	53	251-252	21.1	16.6	59
						$[HCys^P]_2$	77	271-273	16.3; 16.0	20.0	56
Ac	2	83	131-136	15.9	16.7	$[HCys^P]_2$	70		16.3; 16.0	20.0	
$(t\text{-}BuO)_3$ Si	2	76	147-150	16.2	18.6	$[HCys^P]_2$	60		16.3; 16.0	20.0	
(4-O_2N-Bn)-$Hcys^P$		66	246-248			$[HCys^P]_2$	65	272-274			58

[a]In TFA. [b]In 2M HCl. [c]In 2M NaOH.

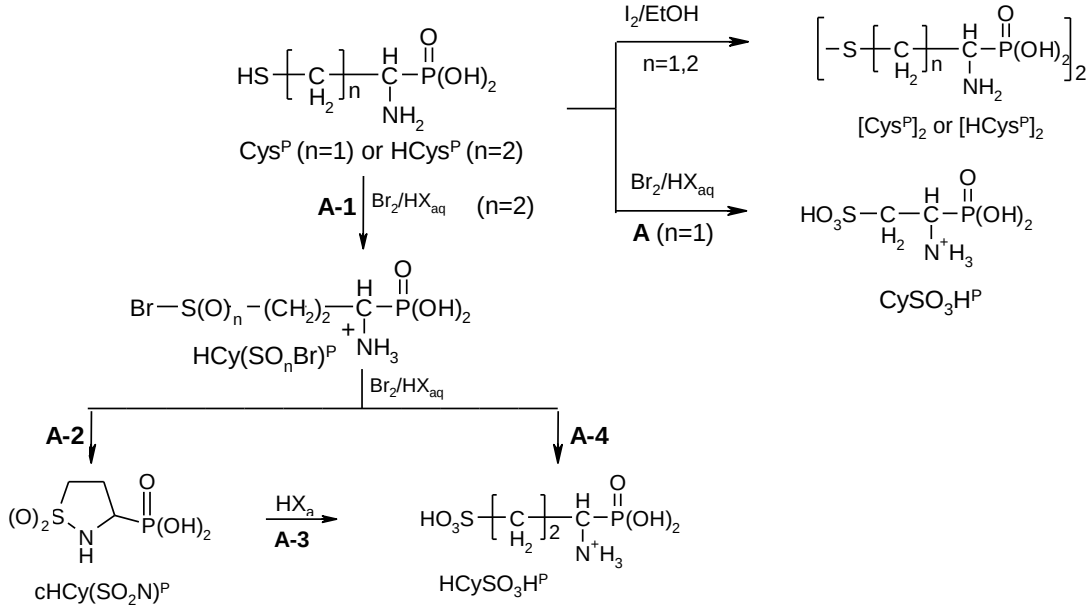
For the preparation of phosphonohomocystine Tishler and co-workers proposed method presented schematically on Scheme 12.

2.2.1.1. Functionalization of sulfur containing 1-aminoalkylphosphonic acids. Oxidation of phosphonic analogues of the thiolo-amino acids, namely Cys^P and/or $Hcys^P$ afford, depending on the applied conditions, disulfide derivatives $[Cys^P]_2$[55] and $[Hcys^P]_2$[56] or sulfonic derivatives Cys^P or $Hcys^P$ (**A**)[62] (Scheme 12).



Scheme 12

The bromine-induced oxidation of phosphonohomocysteine Hcys^P was found to occur in a far more complicated manner. The reaction occurred with splitting of the P-C bond, unless it was carried out in a strong acidic medium (5M HCl) (the bromine-induce dephosphonylation of 1-aminoalkylphosphonic acids will be discussed in a separate paper[63]). In such conditions, the oxidation proceeded gradually with the formation of a mixture of intermediary derivatives, slowly rearranging into the final HCySO$_3$H^P (Scheme 13).[62]



A-1 – bromine promoted oxidation of Hcys^P {Hcys^P → Hcy(SBr)^P [n=0; $\delta(^{31}P)_{2M\ HCl}$ = 15.7 ppm] → Hcy[S(O)Br]^P [n=1; $\delta(^{31}P)_{2M\ HCl}$ = 14.7 ppm] → Hcy[S(O)$_2$Br]^P [n=2; $\delta(^{31}P)_{2M\ HCl}$ = 13.9 ppm]}; **A-2** – cyclization of Hcy[S(O)$_2$Br]^P to cHcy[S(O)$_2$N]^P [$\delta(^{31}P)_{2M\ HCl}$ = 20.1 ppm]; **A-3** – hydrolysis of the sulfonamide bond {cHcy[S(O)$_2$N]^P → HcySO$_3$H^P}; **A-4** – hydrolysis Hcy[S(O)$_2$Br]^P to HcySO$_3$H^P [$\delta(^{31}P)_{2M\ HCl}$ = 15.1 ppm].

Scheme 13

Preparation of phosphonocysteic acid [$CySO_3H^P$] [Kudzin *et al., Pol. J. Chem.* **2005**[62]]
Phosphonocysteine (1mmol; 0.16 g) was dissolved in 2 M hydrochloric acid (2.5 ml) and treated drop by drop with stirring at ambient temperature with bromine (3.3 mmol; 0.5 g). The mixture was allowed to react for 24 h and concentrated to dryness under reduced pressure at 50°C (10 mm Hg and 0.2 mm Hg) affording the desired product $CySO_3H^P$ (0.20 g; 97.5%) of analytical purity.

Preparation of phosphonohomocysteic acid [$HCySO_3H^P$] [Kudzin *et al., Pol. J. Chem*. **2005**[62]]**:**
Phosphonohomocysteine (2.9 mmol; 0.50 g) in 5M hydrochloric acid (4 ml) solution was cooled to ca. 0°C (dry ice/acetone bath) and treated drop by drop with stirring with bromine (9.57 mmol; 1.53 g). The mixture was allowed to react for 24 h, heated under reflux temperature for 2 h and concentrated to dryness under reduced pressure at 50°C (10 mm Hg and 0.2 mm Hg) affording the desired product $HCySO_3H^P$ (0.61 g; 96%) of analytical purity.

In a number of works, modifications of the thioether function of 1–amino-n-thiaalkyl-phosphonic acids were conducted, affording corresponding sulfinyl- and/or sulfonyl,[57,58,64] as well as trimethylsulfonium derivatives.[58,65]

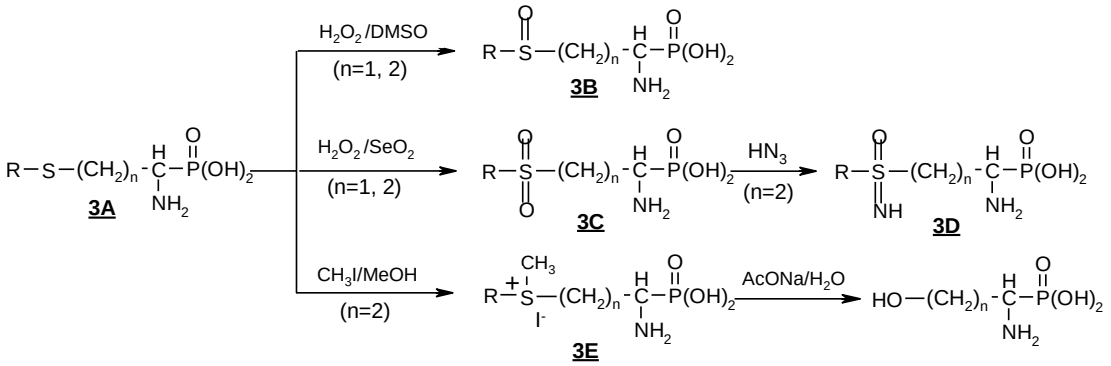
The synthesis of the sulfinyl **3B** and sulfonyl **3C** derivatives of the sulfur-containing amino acids **3A** elaborated by us, was based on the selective oxidation of the latter compounds.

Hydrogen peroxide was found to be useful as a selective oxidant in the case of simple sulfides.[66] However, its application for the oxidation of sulfides bearing an acidic function is limited by the fact that, in the presence of such a group, the subsequent oxidation of the sulfoxides initially formed to sulfones is facilitated. For this reason, the oxidations of amino acids related to methionine have been carried out using hydrogen peroxide in nearly stoichiometric amounts and/or carrying out the reaction at low temperature with careful TLC monitoring of the reaction's progress.[58,67]

We have found, moreover, that the addition of DMSO, used in excess to the oxidant, to the reaction mixture of the amino acids **3A**, and hydrogen peroxide, enables the selective course of the oxidation **3A**→**3B**, at ambient temperature, in spite of the large excess of oxidant used. The opposite effect was observed with the use of selenium (IV) dioxide[66] as a catalyst. The acceleration of the second oxidation stage (**3B**→**3C**) results in a fast and almost quantitative conversion of the amino acids **3A** to their sulfonyl derivatives **3C** (**3A**→**3B**→**3C**).

The latter reagent has also been successfully applied in the oxidation system TFA-H_2O_2-SeO_2 for the oxidation of surfactant derivatives of 1-aminothiaalkylphosphonic acids to their sulfonyl analogs.[57] The yields and physical and analytical properties of the amino acids **3B** and **3C** are summarized in Table 7.

S-Alkylphosphonomethionines **3E** (n=2) were found to be unstable in basic conditions. They were converted into phosphonohomoserine [$Hser^P$] *via* elimination of corresponding thioether molecules.[68,69] 1-Amino-3-sulfonylalkylphosphonic acids **3C** – were converted into sulfoxyiminium derivatives **3D**[70] (Scheme 14).



Scheme 14

Table 7. Sulfinyl, sulfonyl and sulfonic derivatives of 1-aminothioalkylphosphonic acids

AA^P			Yield	m.p.	^{31}P NMR [ppm]		Lit.
R^1-S(O)-(CH$_2$)$_n$		Abbrev.	[%]	[^{o}C]	2M NaOH	2M HCl	
R^1	n						
Me	1	Mcys(SO)^P	88	194-196	16.5; 17.1	10.9; 11.2	64
Et	1	Ecys(SO)^P	86	192-196	16.6; 17.3	10.9; 11.3	
Me	2	Met(SO)^P	85	185-187	19.0; 19.5	14.0	
				188-190			58
Et	2	Eth(SO)^P	93	194-196	19.4	14.0	64
Hex	2	Hex(SO)^P	83	234-236	19.2	14.5[a]	57
Oct	2	Oct(SO)^P	86	200-202	19.2	14.5[a]	
Dec	2	Dec(SO)^P	81	197-200	19.2	14.6[a]	
Ddec	2	Ddec(SO)^P	85	188-191	19.3	14.6[a]	
Hdec	2	Hdec(SO)^P	83	183-185	19.0	14.7[a]	
R^1-S(O)$_2$-(CH$_2$)$_n$							
R^1	n						
Me	1	Mcys(SO)$_2^P$	90	250-252	16.1	10.1	64
Et	1	Ecys(SO)$_2^P$	89	258-260	16.2	10.2	
Me	2	Met(SO)$_2^P$	86	254-256	19.0	13.6	
				258-260			58
Et	2	Eth(SO$_2$)^P	93	255-257	19.0	13.6	64
Hex	2	Hex(SO$_2$)^P	92	264-266	18.7	14.3[a]	57
Oct	2	Oct(SO$_2$)^P	96	252-254	18.8	14.1[a]	
Dec		Dec(SO$_2$)^P	93	236-238	18.9	14.2[a]	
Ddec	2	Ddec(SO$_2$)^P	97	237-239	18.9	14.2[a]	
Hdec	2	Hdec(SO$_2$)^P	98	247-249	18.9	14.2[a]	
HO-S(O)$_2$-CH$_2$		Cys^{P}A	97(100)	250-256	18.0	11.9	62
HO-S(O)$_2$-(CH$_2$)$_2$		HCys^{P}A	96(100)	232-238	20.5	14.8	

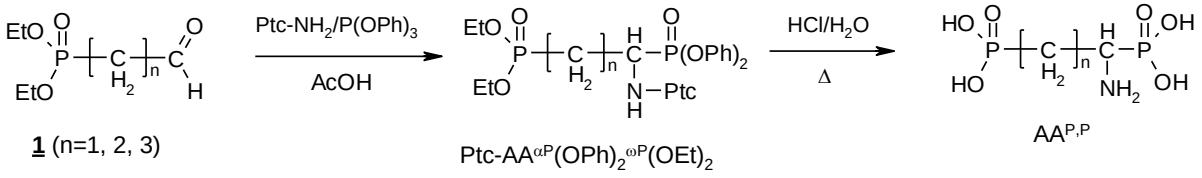
[a]In TFA.

Preparation of the sulfinyl derivatives 3B of the amino acids 3A. General procedure [Kudzin *et al*., *Heteroatom Chem*. **1994**[64]]:
Each of the amino acids **3A** (5 mmol) was added in one portion into a cooled (10°C) and well-stirred mixture of hydrogen peroxide (30% aq., 2 ml), water (2 ml), and dimethyl sulfoxide (3 ml), and the reaction mixture was stirred for 0.5 h at room temperature. After dilution with acetone (30 ml), the mixtures were left in the refrigerator for 2 h. The solvent layer was removed, and the residue was dissolved in distilled water (25 ml). The aqueous solutions of the amino acids **3B** were passed through a Dowex 50W×2 column, the fractions containing the amino acids (ninhydrin test) being collected and evaporated to dryness. The amino acids **3B** were recrystallized from water-ethanol mixtures.

Preparation of the sulfonyl derivatives 3C of the amino acids 3A. General procedure[Kudzin *et al., Heteroatom Chem.* **1994**[64]]:
Each of the amino acids **3A** (5 mmol) was added in one portion into a cooled (1O°C) and well-stirred solution of hydrogen peroxide (30% aq., 2 ml), water (3 ml), and selenic acid (0.01 g). The reaction mixture was stirred at room temperature for 0.5 h, diluted with acetone (30 ml), and left in the refrigerator for 2 h. The precipitated amino acids **3C** were isolated by decantation, dissolved in distilled water (25 ml), and purified on a Dowex 5OW×2 column. The fractions containing the amino acids (ninhydrin test) were collected and evaporated to dryness, and the pure compounds **3C** were recrystallized from water/ethanol mixtures.

2.2.2. Synthesis of 1-aminoalkyldiphosphonic acids. 1-Aminoalkyldiphosphonic acids – phosphonic analogs of protein acidic amino acids and their homologs were also synthesized by the Ptc-aminophosphonate method.

Thus, the condensation of the corresponding terminal phosphonoalkanals **1** (n=1, 2 and 3) with *N*-phenylthiourea and triphenyl phosphite, and subsequent acidic degradation of temporary formed corresponding thioureidoalkylphosphonates Ptc-$AA^{\alpha P}(OPh)_2{}^{\omega P}(OEt)_2$ afforded the title $AA^{\alpha P,\omega P}$ (Scheme 15, Table 8).



Scheme 15

Terminal phosphonoalkanals **1** (n=1-3) were obtained in Arbuzov reaction from corresponding halogenoacetals and triethyl phosphite, and subsequent hydrolysis of formed ω-phosphonyloacetals.[71]

Table 8. Bisacidic 1-aminoalkylphosphonic acids

AA^P	Ptc-$AA^P(OPh)_2$			AA^P				Lit.
	Yield [%]	m.p. [°C]	^{31}P NMR [ppm][a]	Yield [%]	m.p. [°C]	^{31}P NMR 2M HCl	^{31}P NMR 2M NaOH	
$Asp^{P,P}$	75	150-151	15.6; 16.3; 26.0; 26.7	70	233-235	13.6; 14.3; 22.9; 23.6	22.07; 22.12	71
					233-235			72
					234-236			73
$Glu^{P,P}$	70	145-147	17.3; 17.4 31.2; 31.4	65	236-238	15.0; 19.6	21.9; 22.0; 23.3; 23.4	71
					237-239			72
$HGlu^{P,P}$	58	oil	18.3; 32.4	50	235-237	15.9; 29.0	13.6; 25.6	71
$HGlu^{\gamma\text{-}P}$	73	oil	16.6[b]	70	158-159	15.8	21.8	74

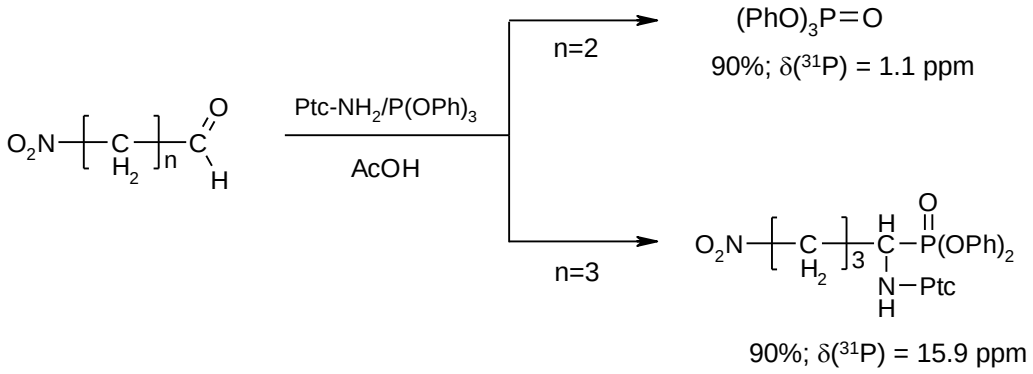
^{31}P NMR spectra of Ptc-$AA^P(OPh)_2$ and Ptc-$AA^{P,P}(OPh)_2$ were recorded in [(a)]$CDCl_3$ or [(b)]AcOH.

Synthesis of 1-aminoalkyl-1,n-diphosphonic acids 3 (n = 1, 2, 3). General procedure A [Kudzin *et al., J. Organometal. Chem*. **1994**[71]]

Triphenyl phosphite (0.015 mol; 4.65 g) was added in one portion to a solution of aldehyde **1** (0.01 mol) and N-phenylthiourea (0.015 mol; 2.26 g) in glacial acetic acid (20 ml). The mixture was stirred at 60°C for 1 h, left to stand overnight at room temperature and then diluted with water (2 ml). After 6 h the precipitate was filtered off and washed with AcOH/H_2O (1:1) to give corresponding thioureidoalkylphosphonate Ptc-$AA^{P,P}(OPh)_2$ (n=1,2) as crystalline compounds pure as indicated by their ^{31}P NMR spectra. The products were purified for microanalysis by recrystallization from chloroform-methanol (5:1). Thioureidoalkylphosphonate Ptc-$HGlu^{P,P}(OPh)_2$ (n=3) was isolated as an oil by chromatography on a silica column [eluent: chloroform-methanol (10:1)]. Thioureidoalkylphosphonates Ptc-$AA^{P,P}(OPh)_2$ were dissolved in glacial acetic acid (50 ml) and hydrochloric acid (100 ml, 1:1) and the solution was heated under reflux for 12 h. The mixture was then cooled to room temperature, diluted with water (100 ml),and extracted with toluene (2×50 ml). The aqueous layer was evaporated to dryness under reduced pressure, and the solid residue was dissolved in water (10 ml). The solution was passed through Dowex 50 W×8 column and fractions containing amino acids AA^{PP} (ninhydrin test) were collected. The combined fractions containing $AA^{P,P}$, respectively, were concentrated under reduced pressure to ca. 5 ml and 1-aminoalkyldiphosphonic acids were precipitated with ethanol (25 ml), and dried to constant weight in a dessicator under reduced pressure over solid phosphorus pentoxide and potassium hydroxide.

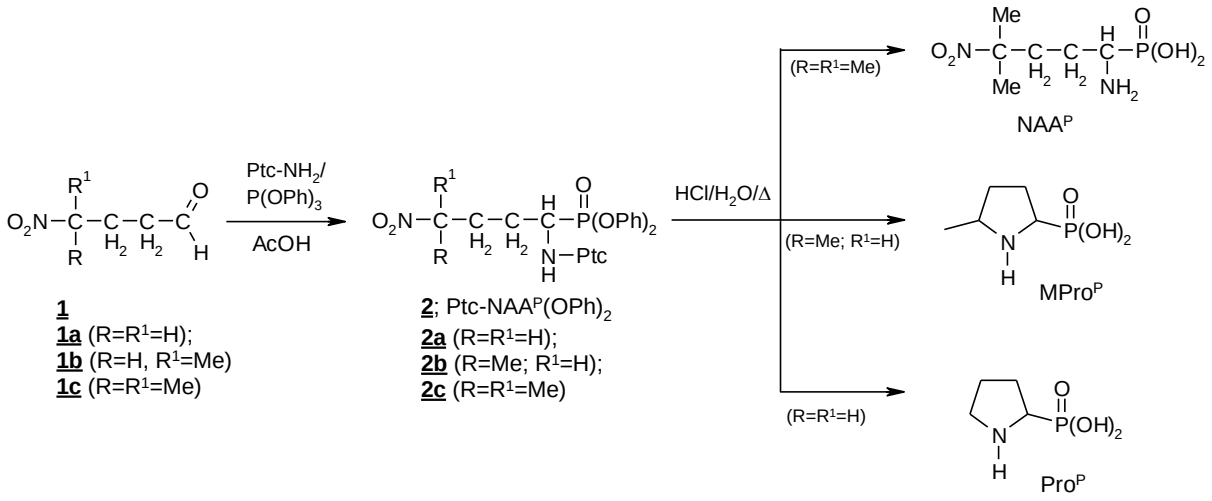
2.2.3. Synthesis of ω-nitro-1-aminoalkylphosphonic acids. The biological activity of *Fosmidomycin* (Fr 31546) induced our interest in the preparation of its amino analogs.[75] We have

found that the reaction of 3-nitropropanal and 4-nitrobutanal (precursors of analogs of Fr 31546) with Ptc-NH_2 and triphenyl phosphite occurs in different modes, dependent on the structure of applied ω-nitroalkanal (Scheme 16).



Scheme 16

Starting from 4-nitroalkanals **1**, easily prepared from acrolein and the corresponding nitroalkanes, the representative Ptc-1-amino-4-nitroalkylphosphonates [Ptc-$NAA^P(OPh)_2$] were obtained in good to high yields (Table 9). However, their subsequent acidic hydrolysis afforded products of structure dependent on the structure of the starting Ptc-$NAA^P(OPh)_2$.

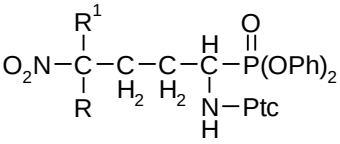
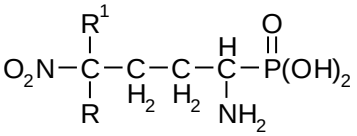


Scheme 17

Thus, the degradation of diphenyl 1-Ptc-amino-4-methyl-4-nitropentylphosphonate [1-(*N*-phenylthioureido)-4-methyl-4-nitropentylphosphonate] afforded 1-amino-4-nitro-4-methyl-pentylphosphonic acids [**2c**→NAA^P] whereas degradation of diphenyl 1-Ptc-amino-4-nitro-pentylphosphonate [1-(*N*-phenylthioureido)-4-nitropentylphosphonate] (**2b**) occurred with intermolecular rearrangement giving 4-methylpyrrolidinephosphonic acid ($MPro^P$). Similarly,

degradation of diphenyl 1-Ptc-amino-4-nitrobutylphosphonate [1-(*N*-phenylthioureido)-4-nitrobutylphosphonate] (**2a**) afforded 2-pyrrolidinephosphonic acid (Pro^P) (Scheme 17, Table 9) (the details on these rearrangements will be published in a separate paper[76]).

Table 9. Ptc-amino-4-nitroalkylphosphonates and products of their degradation

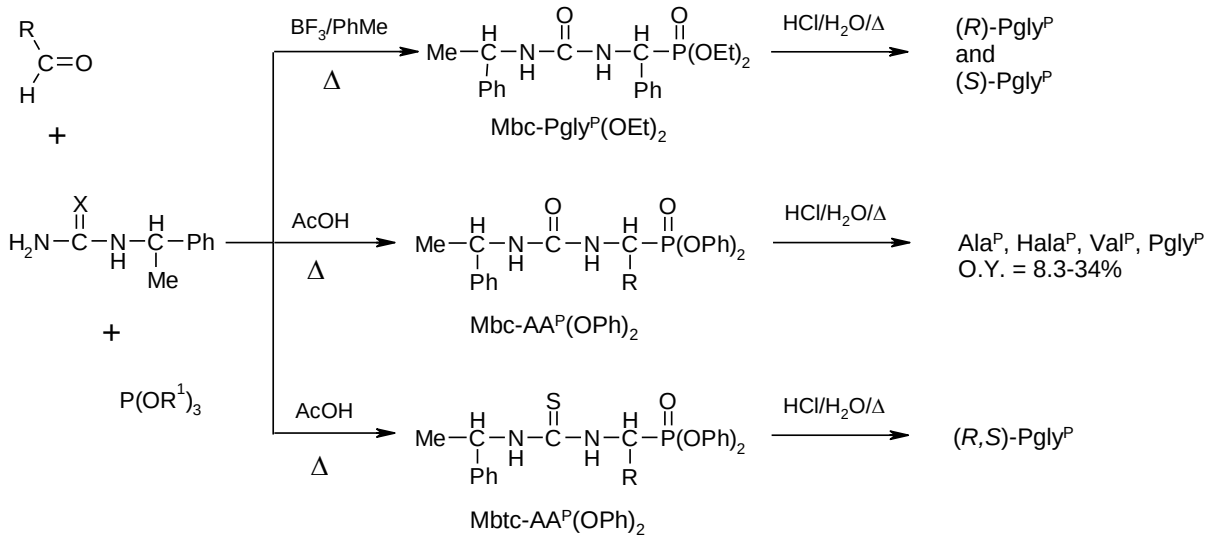
R, R^1									
	Yield [%]	m.p. [°C]	^{31}P NMR [ppm][a]		Yield [%]	m.p. [°C]	^{31}P NMR		
			AcOH	$CDCl_3$			TFA[a]/ HCl[b]	H_2O	2M NaOH
R=R^1=H	70	145-150		17.7	-	glass	17.5[a]	12.3[c]	20.9
R=H; R^1=Me	70	145-152		17.8	-	glass		13.8[d]	18.7
R=R^1=Me	80	135-145	15.9	16.5	80	>250°C (dec.)	15.2[b]	12.3[d]	20.8

^{31}P NMR: [a]TFA; [b]2M HCl; [c]2M AcOH/AcONa-D_2O; [c]EtOH-D_2O (1:1).

2.2.4. Application of the Ptc-aminophosphonate and related protocols for the synthesis of optical pure 1-aminoalkylphosphonic acids. The Ptc-aminophosphonate method was adapted for the preparation of both levorotatory and dextrorotatory 1-aminoalkylphosphonic acids *via* the hydrolysis of the corresponding intermediary *N*'-1-methylbenzylaminoureidophosphonates (Scheme 18).[77,78]

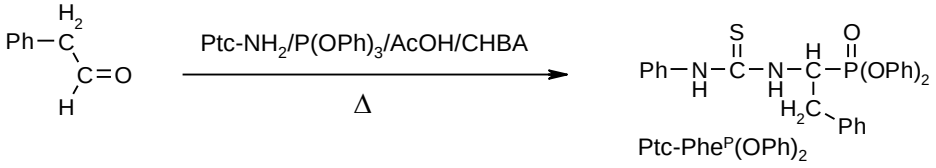
In a similar approach, applied for both levorotatory and dextrorotatory *N*-(1-methylbenzyl)-thioureas [(*R*)-Bmtc-NH_2 and (*S*)-Bmtc-NH_2], temporary Bmtc-$Ala^P(OPh)_2$ obtained, as well as the product of their final acidic hydrolysis – phosphonoalanine (Ala^P) did not exhibit remarkable optical activity[29] (Scheme 18).

Results of the reaction of benzylacetaldehyde, with *N*-phenylthiourea and triphenyl phosphite in acetic acid containing 10% of chiral Bronsted acids are summarized in Table 10.



Scheme 18

Table 10. The partial ^{31}P NMR spectra of reaction mixture of synthesis of Ptc-Phe^{P}(OPh)$_2$ in acetic acid-chiral Bronsted acids (CHBA)



AcOH/(2*R*,3*R*)-(+)-tartaric acid (10%)									
^{31}P(δ)	**[ppm]**	**37**	**35.4**	**17.4**	**16.2**	**15.**	**1.3**		**-18.7**
	[%]	8.5	1.5	5	**28**	16	24		2
AcOH/(+)-2,3-dibenzoyl-D-tartaric acid (10%)									
^{31}P(δ)	**[ppm]**	**37**	**33.4**	**33.5**	**17.2**	**16.3**	**6.6**	**2.8**	**-18.7**
	[%]	8.5	1.5	5	5	**28**	16	24	2
AcOH/(1*S*)-(+)-camphorsulfonic acid (10%)									
^{31}P(δ)	**[ppm]**	**38.3**	**36.1**	**33.7**	**19.7**	**16.4**	**4.1**	**1.4**	**-18.7**
	[%]		10	6	7	**10**	40	10	4

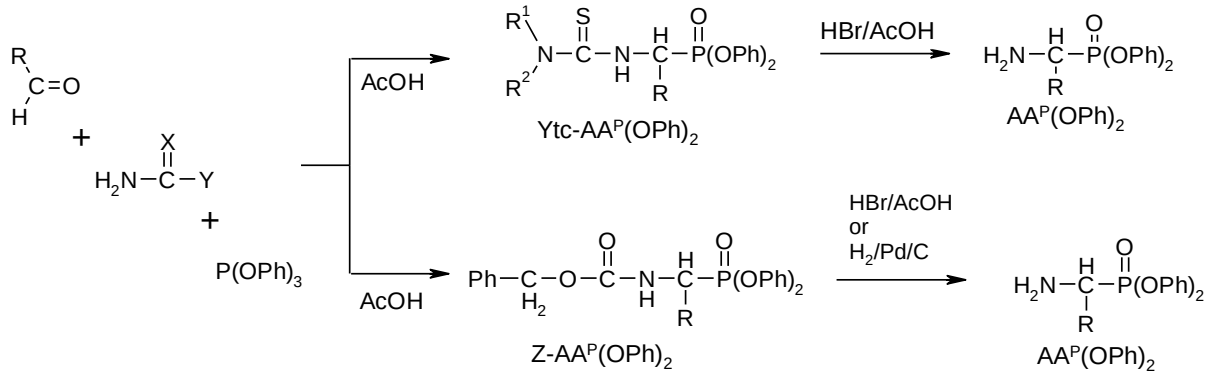
[a]δ(^{31}P): $(PhO)_3P$ 127±1ppm; $(PhO)_2P(O)H$ 0±0.5 ppm; $(PhO)P(O)(OH)_2$ -4.7 ppm; $(PhO)_3P(O)$ -17.5±1ppm[79]

These results show that this approach for the preparation of optically active 1-aminoalkylphosphonic acids cannot be considered as an effective one.

2.2.5. Application of the Ptc-aminophosphonate and related methods for synthesis of diphenyl 1-aminoalkylphosphonates. Diphenyl Z-aminoalkylphosphonates – are applied as the

substrates in preparation of diphenyl 1-aminoalkylphosphonates and subsequently for *P*-terminal phosphono-peptides synthesis.[24,80-91]

Since intermediary structures, Z-AA^{P}(OPh)$_2$, could be isolated from the reaction mixtures in moderate yields [e.g. Z-Gly^{P}(OPh)$_2$ (45-56%); Z-Ala^{P}(OPh)$_2$ (42%); Z-Val^{P}(OPh)$_2$ (50%); Z-Leul^{P}(OPh)$_2$ (51%); Z-Pgl^{P}(OPh)$_2$ (50%) or Z-Phe^{P}(OPh)$_2$ (32%)][24,80] we undertook investigations on the further modification of the thioureido-moiety of easily isolable Atc-AA^{P}(OPh)$_2$. We applied amides more prone for the selective amino-group deprotection [Z-AA^{P}(OPh)$_2$ → AA^{P}(OPh)$_2$] derivatives (Scheme 19).



Scheme 19

The types of starting amides and structures of the corresponding diphenyl 1-amidoalkylphosphonates are summarized in Table 11.

Table 11. Amides and the corresponding diphenyl 1-amidoalkylphosphonates

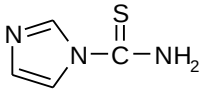
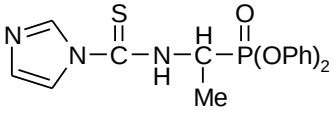
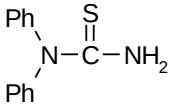
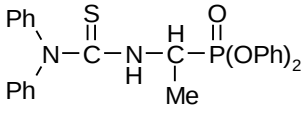
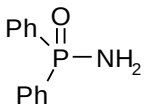
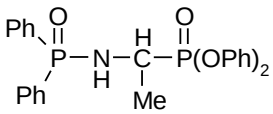
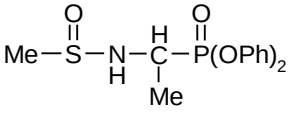
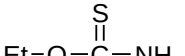
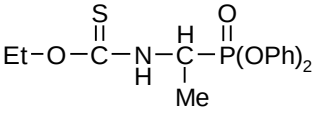
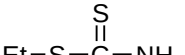
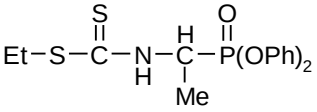
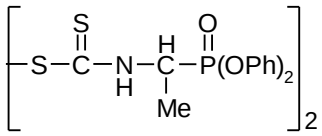
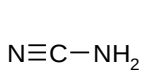
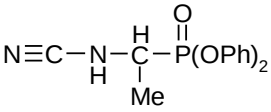
Starting amides	**Expected product**	^{31}P NMR δ(^{31}P) vs RA [%]
		Broad signal 19±4 ppm
		21.2 (20%) 20 (40%)
		29.4; 28.3 (33%); 19.2; 18.7 (20%)

Table 11. Continued

		20.0 (20%)	17.7 (40%)	
		18.8 (40%)	17.5 (18%)	16.0 (10%)
		18.9 (42%)	16.7 (25%)	
		Multicomponent mixture		
		19.3 (45%)	16.3 (46%)	

The low degree of the conversions of listed amides into the corresponding 1-amidoalkylphosphonates (Table 10), as well as, problems from their isolation from the reaction mixtures, in the light of recent reports on almost quantitative synthesis of Z-$AA^P(OPh)_2$[92,93] made the continuation of this approach for the synthesis of these precursors of $AA^P(OPh)_2$ not reasonable.

3. Other modifications

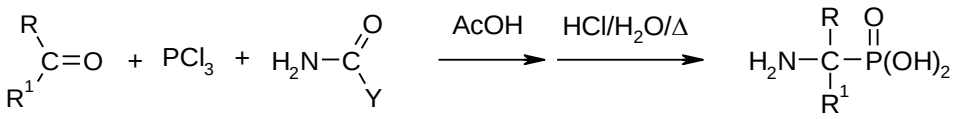
3.1. Z-Aminophosphonate Method (Birum-Oleksyszyn Method)

Modifications of the Birum reaction by the use of easily degradable benzyl carbamate10-12,25,30 present the base of the Z-aminophosphonate method (Birum-Oleksyszyn Method) (**C**),[23-25,46,80-91,93-96] (Scheme 3), allowing the synthesis of structurally diverse AA^P and also their diester derivatives $AA^P(OPh)_2$. The yields of the Oleksyszyn and Tyka protocol are greatly improved when reactions are carried out in the presence of Lewis acids.[92,93]

In other modifications *N*-phenylurea[22] optically active *N*-(1-methylbenzyl)ureas[77,78] and carbamates,[78] *O*,*O*-diethyl phosphoramidothioate,[97,98] or *O*-ethyl, *O*-phenyl phosphoramido-thioate,[97] *O*,*O*-dipropyl phosphoroamidate,[99] *N*-acyl-4-aminobutanal,[100] 2-amino-5-phenyl-1,3,4-oxadiazole or 1,3,4-thiadiazole[101] have also been applied.

3.2. Oleksyszyn Method

The first essential modification of the Engelman and Pikl reaction, reported by Oleksyszyn, Tyka and Mastalerz in 1978,[28,25] was based on the replacement of *N*-(hydroxymethyl)amides by hydroxyamides, prepared *in situ* from carbamates and carbonyl compounds (Scheme 20; Y=OBn).



R, R^1 = H, H; H, alkyl; H, aryl; alkyl, alkyl; cycloalkyl; alkyl, aryl; Y = H, alkyl, aryl, BnO

Scheme 20

This procedure was subsequently modified by Oleksyszyn[28,102-106] and other members of the Wroclaw Amino Acid School[46,48,96,107-113] becoming one of the most commonly used for the preparation of structurally diverse aminophosphonates.[10,12]

These modifications applied the use of carbamates and/or various amides,[44,48,104,105,107,110-121,122-124] bisamides[105,109,119] or formed in situ 1-(acylamino)alkyl alkanoates,[48] *p*-toluene-sulfonamide,[125,126,127] *O,O*-diethyl phosphoramidothioate,[115] or *O*-ethyl, *O*-phenyl[115] diethyl phosphoramidate or phosphorthioamidate,[115] 1,3-oxazolidin-2-one[128] and 5,5-dimethyl-hydantoin.[129,130]

In others, phosphorus trichloride was replaced by various chlorophosphites,[115,125,127,131-133] dichlorophosphites,[123,131,132,134,135] dithioisopropyl-chlorophosphites[131] and $PhOPCl_2$/AcCl mixture.[136] Also two- and tricomponent mixtures of dialkyl phosphites were applied, including $(RO)_2P(O)H$/AcCl,[105,120,137,138] $(PhO)_2P(O)H$/AcCl,[126] $(RO)_2P(O)H/AcOH/SO_2Cl_2$[137,139] and also $(RO)_2P(O)H/Ac_2O$/HCl mixtures,[139] as well as $PCl_3/P(OMe)_3$[140,141] and $PCl_3/AcOH/SO_2Cl_2$[117] mixtures. Amidoalkylation of phosphorous acid[25,105,106,109] and alkylphosphonic acids in $RP(O)(OH)_2/Ac_2O$ mixtures (R=Me, Ph)[105] were also applied.

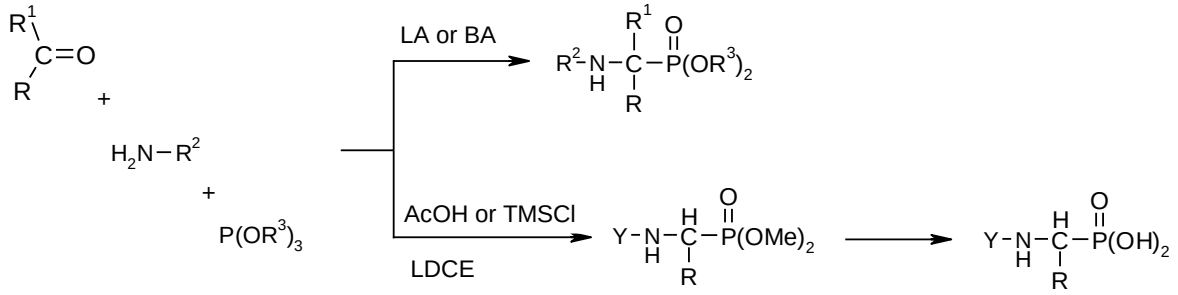
The application of dichloroalkylphosphines and/or dichloroarylphosphines,[28,102-104,112-114, 142,143] a functionalized or nonfunctionalized phosphonites[144,145] and hypophosphorous acid[111] (for the preparation of 1-aminoalkylphosphinic acids), or chlorodialkylphosphines[105,116] allowed on the preparation of 1-aminoalkylphosphinic acids and/or 1-aminoalkanephosphine oxides, respectively.

The mechanisms of the Engelman-Pikl-Oleksyszyn reaction have been in detail examined by Oleksyszyn[25,105] and Soroka.[48,107,109] Recently discussion on the mechanism of amidoalkylation of hydrophosphoryl compounds was also presented by Dmitriev and Ragulin.[146]

3.3. Synthesis of 1-*N*-alkyl(aryl)aminoalkylphosphonates

The Birum-type condensations of carbonyl compounds, trialkyl phosphites and amines, hydrazines or hydroxylamines affords the corresponding 1-*N*-alkyl(aryl)aminoalkyl-

phosphonates, substituted hydrazinealkyl- and/or hydroxylalkylphosphonates, respectively (Scheme 21).



R, R^1 = H, alkyl; H, aryl; H, aralkyl; R^2 = alkyl, aryl; R^3 = Me, Et; Y = Me_2N, PhO

Scheme 21

The reported modifications of this procedure are based on the use of LPDE catalysis,[147-149] the use of Bronsted acids {BA: sulfonic acid functionalized ionic liquid,[150] silica-sulfuric acid,[151] oxalic acid[152] and/or boric acid[153] or Lewis acids [LA: CAN,[154] VCl_3,[155] $TiCl_4$,[156] $Cu(OTf)_2$,[157] $AlCl_3$[158] or Sc tris(dodecyl sulfate),[159] or a realization of tri-component condensation under solvent-free conditions using $Al(H_2PO_4)_3$ as an efficient and reusable heterogeneous catalyst[160] or without catalyst.[161]

4. Nomenclature and applied abreviations code

The compounds discussed are listed in Table 12 together with the code used to identified them latter in tables and schemes. This sytem of abbreviations used for assingement of aminoalkylphosphonic acids and derivatives has already been applied in the fragmentary form in our earlier papers[13-15] and its full version will be published elsewhere.

Table 12. Codes used for the representative phosphonic acid and derivatives[13-15]

Code	Compound name
AA^Ps	1-**A**minoalkyl**p**hosphonic **A**cids[13]
$AA^P(OR)_2$	Dialkyl 1-Aminoalkylphosphonate; Dialkyl Phosphono-Amino-Acidate[a]
$Gly^P(OMe)_2$	Dimethyl 1-Aminomethylphosphonate; Dimethyl **P**hosphono**gly**cinate[a]
(AC)-AA^P	1-(*N*-**Ac**yl**a**mino)alkyl**p**hosphonic **A**cid[13]; (**AC**yl)-**P**hosphono**A**mino Acid[a]
Ac-AA^P	1-(*N*-**Ac**etyl**a**mino)alkyl**p**hosphonic Acid[13]
Ac-Ala^P	**Ac**etyl-**p**hosphono**ala**nine[a]; 1-(*N*-Acetylamino)ethylphosphonic Acid
Bz-AA^P	1-(*N*-**B**en**z**oyl**a**mino)alkyl**p**hosphonic Acid[13]
TFA-AA^P	1-(*N*-**T**ri**f**luoro**ac**etyl**a**mino)**a**lkyl**p**hosphonic Acid[14]

Table 12. Continued

Mca-AA^P	1-(*N*-Chloroa**c**etyl**a**mino)**a**lkyl**p**hosphonic Acid[15]
(Ac)-AA^P(OR)$_2$	Dialkyl **Ac**etylphos**p**hono-**A**mino **A**cidate[a];
	Dialkyl 1-(*N*-**Ac**etyl**a**mino)**a**lkyl**p**hosphonate[13]
Ac-Ala^P(OR)$_2$	Dialkyl **Ac**etyl**p**hosphono**ala**ninate[a];
	Dialkyl 1-(*N*-Acetylamino)ethylphosphonate[13]
PTC-AAs	1-(**P**henyl**t**hio**c**arbamoyl)-**A**mino **A**cid**s**[162, 163]
Ptc-AA^{P}s	1-(**P**henyl**t**hio**c**arbamoylamino)alkyl**p**hosphonic Acids[a]
Ptc-AA^P(OR)$_2$	Dialkyl 1-(**P**henyl**t**hio**c**arbamoylamino)alkylphosphonate[a];
Ptc-AA^P(OAr)$_2$	Diaryl 1-(**P**henyl**t**hio**c**arbamoylamino)alkylphosphonate[a];
	Diaryl 1-(3-Phenylthioureido)alkylphosphonate[55,56]
Ptc-AA^P(OPh)$_2$	Diphenyl 1-(**P**henyl**t**hio**c**arbamoylamino)alkylphosphonate[a];
	Diphenyl 1-(*N*-Phenylthioureido)alkylphosphonate[39,41,55,56]
Ptc-Ala^P(OPh)$_2$	Diphenyl **P**henyl**t**hio**c**arbamoyl-**p**hosphono**ala**ninate[a];
	Diphenyl 1-(3-Phenylthioureido)ethylphosphonate[38]
Ptc-Hala^P(OPh)$_2$	Diphenyl **P**henyl**t**hio**c**arbamoyl-**p**hosphono**h**omo**ala**ninate[a];
	O,O-Diphenyl 1-(3-phenylthioureido)butanephosphonate[40]
Ptc-tLeu^P(OPh)$_2$	Diphenyl **P**henyl**t**hio**c**arbamoyl-**p**hosphono**t**ert**leu**cinate[a];
	O,O-Diphenyl 2-methyl-1-(3-phenylthioureido)propanephosphonate[37]
Ptc-Nleu^P(OPh)$_2$	Diphenyl **P**henyl**t**hio**c**arbamoyl-**p**hosphono**n**or**leu**cinate[a];
	O,O-diphenyl 1-(3-phenylthioureido)-pentanephosphonate[40]
Pc-AA^P	1-(**P**henyl**c**arbamoylamino)alkyl**p**hosphonic **A**cid[a]
Pc-AA^P(OAr)$_2$	Diaryl 1-(**P**henyl**c**arbamoylamino)alkylphosphonate[a]
Pc-Pgly^P(OEt)$_2$	Diethyl **P**henyl**c**arbamoyl-**p**hosphono**p**henyl**gly**cinate[a]
	Diethyl 1-(3-Phenylureido)ethylphosphonate[16]
Ac*-AA^P(OPh)$_2$	Diphenyl 1-(**A**ryl**c**arbamoylamino)alkylphosphonate[a]
Dpc-Ala^P(OPh)$_2$	Diphenyl **D**i**p**henyl**c**arbamoyl-**p**hosphono**ala**ninate[a];
Atc-AA^P	1-(**A**ryl**t**hio**c**arbamoylamino)alkyl**p**hosphonic **A**cid[a];
Tc-AA^P	1-(**T**hio**c**arbamoylamino)alkyl**p**hosphonic **A**cid[a];
	1-(Thioureido)alkylphosphonic acid[53]
Atc-AA^P(OAr)$_2$	Diaryl 1-(**A**ryl**t**hio**c**arbamoylamino)alkylphosphonate[a]
Tc[AA^P(OAr)$_2$]$_2$	Tetraaryl **T**hio**c**arbamoyl[di(1-aminoalkylphosphonate)][a];
	Tetraaryl Thiourylene[dialkyl)diphosphonate)][29]
Tc-AA^P(OPh)$_2$	Diphenyl 1-(**T**hio**c**arbamoylamino)alkylphosphonate[a]
Tc[AA^P(OPh)$_2$]$_2$.	Tetraphenyl **T**hio**c**arbamoyl-[di(aminoalkylphosphonate)][a];
	Tetraphenyl (Thiourylenedialkyl)-diphosphonate)[29]
Tc[Nva^P(OPh)$_2$]$_2$.	Tetraphenyl **T**hio**c**arbamoyl-[di(**p**hosphono**n**or**va**linate)][a];
	Tetraphenyl (Thiourylenedibutyl)diphosphonate)[16]
Cm-Hala^P	**C**arba**m**oyl-**p**hospono**h**omo**ala**nine[a]; 1-Ureidopropylphosphonic acid[16]

Table 12. Continued

$Cm[Ala^P(OCET)_2]_2$	Tetrakis(2-Chloroethyl) **C**arba**m**oyl-[di(**p**hosphono**ala**ninate)][a]; Tetrakis(2-Chloroetyl) (Urylenedietyl)diphosphonate[16]
$Cm[Ala^P(OPh)_2]_2$	Tetraphenyl **C**arba**m**oyl-[di(**p**hosphono**ala**ninate)][a]; Tetraphenyl (Urylenediethyl)diphosphonate[16]
$Cm[Pgly^P(OPh)_2]_2$	Tetraphenyl **C**arba**m**oyl-[di(phosphono**p**henyl**gly**cinate)][a]; Tetraphenyl (Urylenedibenzyl)diphosphonate[16]
$AA^P(H)s$	1-Aminoalkylphosphinic Acids
$Ala^P(H)$	1-Aminoethylphosphinic Acid; Phosphinoalanine

[a]Convention applied in this paper. [b]Name formed by analogy to the Birum's nomenclature.

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