

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

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-aminophosphonate (Phenylthiocarbamoylaminoalkylphosphonate) 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

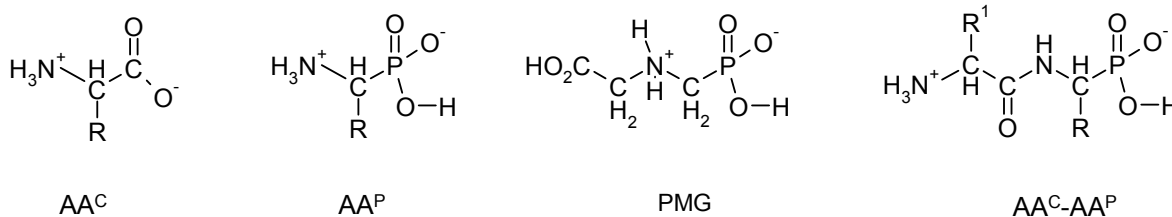
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1. Introduction

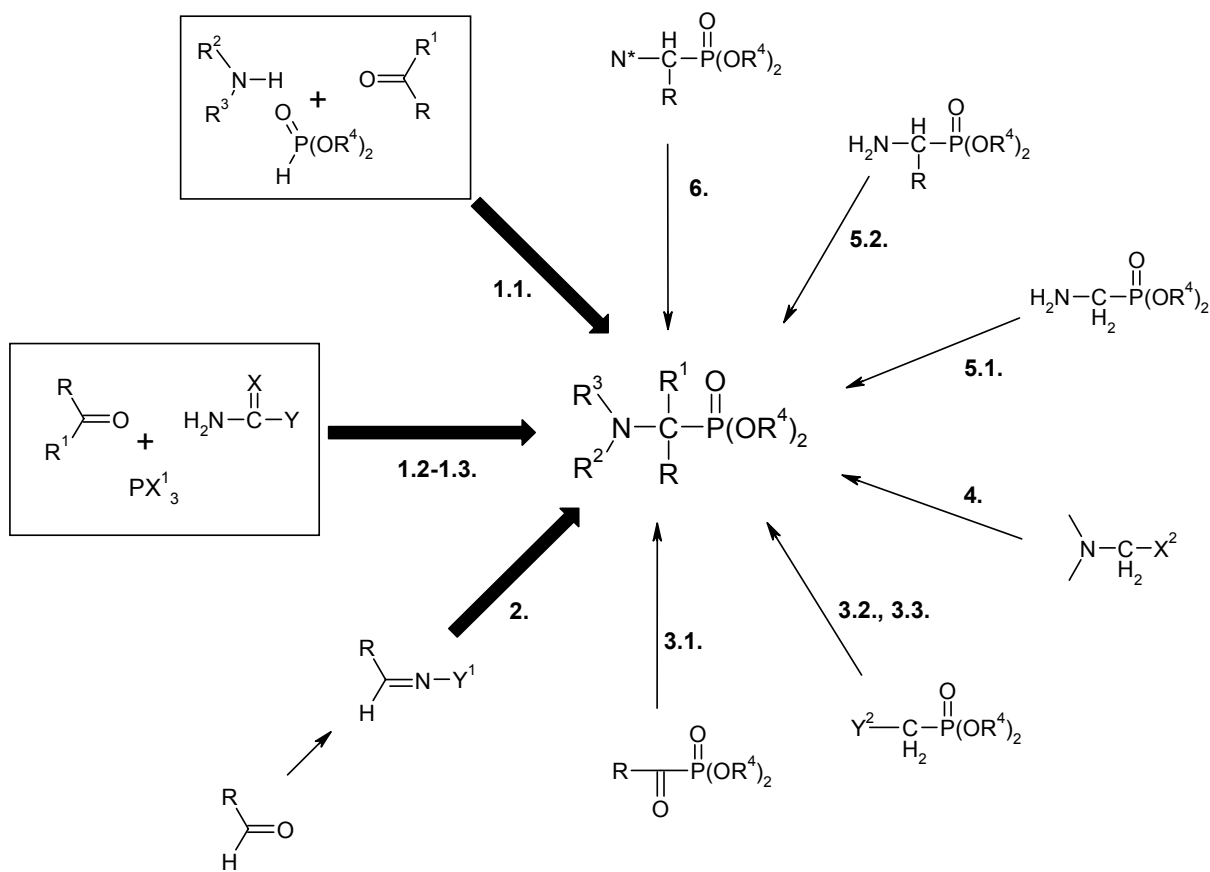
1-Aminoalkylphosphonic acids (AA^P) as structural analogues of protein amino acids (AA^C), are important inhibitors of enzymes of amino acid metabolism.¹⁻⁴ These properties have been spectacularly reflected in wide-world agrochemical applications of aminophosphonic herbicides, [e.g. phosphonmethylglycine (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}



Therefore, studies on the synthesis¹⁰⁻¹² 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 [$P+C+N \rightarrow P-C-N$]:
 - 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 [$P-H \rightarrow P-C-N$] (hydrophosphonylation and/or hydrophosphinylation of imines and trazines, hydrazones, azines and oximes, nitrones and nitriles).



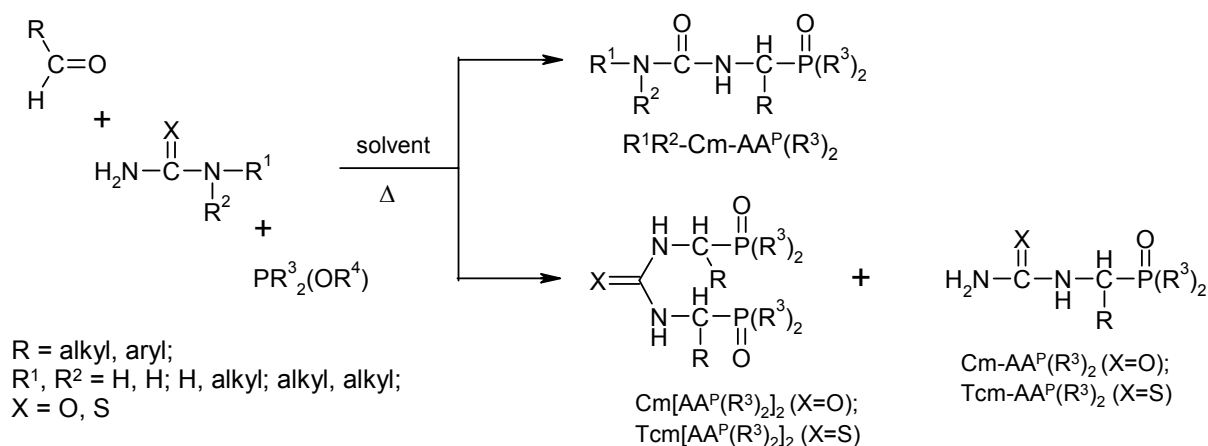
R, R¹ = H, alkyl, aralkyl, aryl; R², R³ = H, H; H, alkyl; H, aralkyl; H, aryl; cycloalkyl; alkyl, aryl;
 R⁴ = alkyl (Me, Et, iPr), aryl (Ph), aralkyl (Bn) and H; X = O, S; X¹ = Cl, HO, RO, ArO; X² = Cl, Br, RO;
 Y = BnO, PhNH; Y¹ = R, NH₂, RNH, R₂N, HO; Y² = Cl, HO (3.2.); Me, Ph, RO-C(O)-(3.3.);
 N* = N₃, NO₂, H₂N-NH

Scheme 1

3. Methods based on α -amination of functionalized alkylphosphonates [P-C + N \rightarrow 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 \rightarrow P-C-N + X] (Arbusov reaction derived methods).
5. Methods based on modifications of the carbon chain of 1-aminoalkylphosphonates [P-C(R)-N \rightarrow 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 \rightarrow P*-C-N] (oxidation of 1-aminoalkylphosphinic acids into 1-aminoalkylphosphonic analogues).
7. Methods based on modifications of nitrogenic functions [P-C-N \rightarrow P-C-N*] (reduction of 1-azidoalkylphosphonates and 1-nitroalkylphosphonates, reduction of oximes, hydrazones, azines, etc.)
8. Other methods.

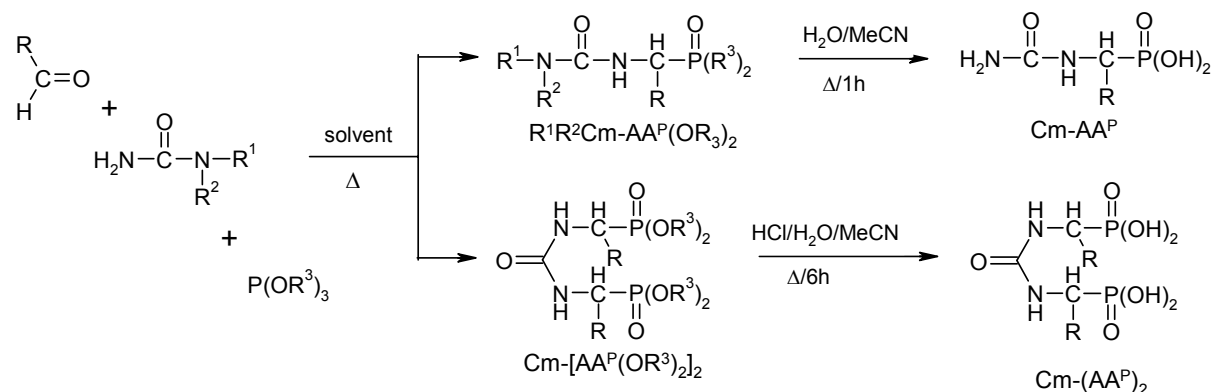
However, the crucial events in the chemistry of phosphonic analogues of protein amino acids (1-aminoalkylphosphonic acids bearing with the primary amino function: $R^2 = R^3 = H$; Scheme 1) took place in the late 1970s and were connected with two discoveries. The first was made by Birum¹⁶ and is related 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 Birum¹⁷⁻²¹].

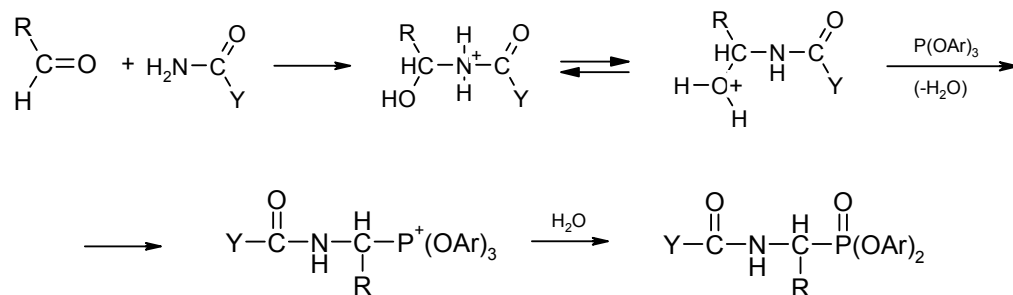
The products of the Birum condensation (Table 1) contain the P-C-N bond system characteristic for 1-aminoalkylphosphonic acids. However, attempts on their degradation, carried out by Birum for Cm-AA^P(OPh)₂ and/or Cm-[AA^P(OPh)₂]₂, revealed low to moderate stability of the ester functions and higher 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 (R¹=Ph; R² = H; R³ = 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 Píkl amidoalkylations of phosphorus trichloride²⁵⁻²⁸ (Section 3).

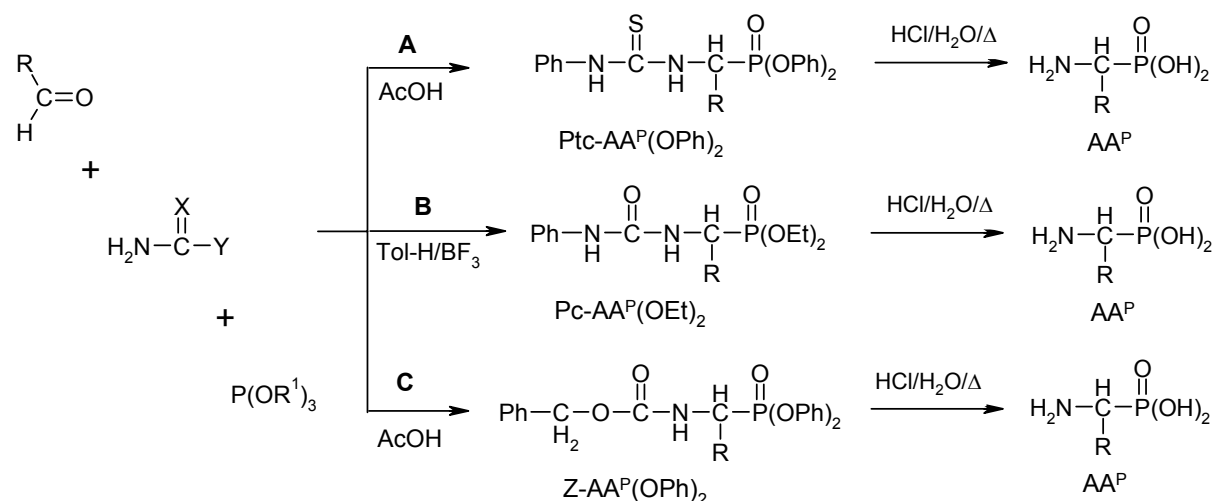
In the Birum condensation, which formally can be considered as a variant of the Arbuzov reaction, and also as a type of the amidoalkylation of phosphorus(III) esters, the key electrophilic reagent prepared *in situ* from an amide substrate and an aldehyde, adds to the corresponding phosphite (phosphonite,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



Y = NH₂, R-NH, R₂N; 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-Píkl reaction by Oleksyszyn^{25,28} (Section 3.2.)



Scheme 5

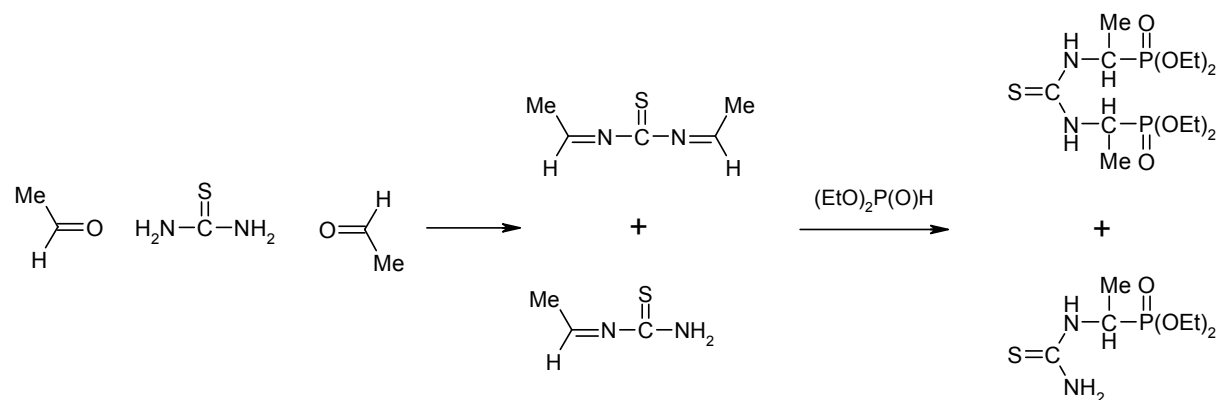
In this review, we present the results on the origin and developments of Ptc-aminophosphonate method.

2. The origin of the Ptc-aminophosphonate method

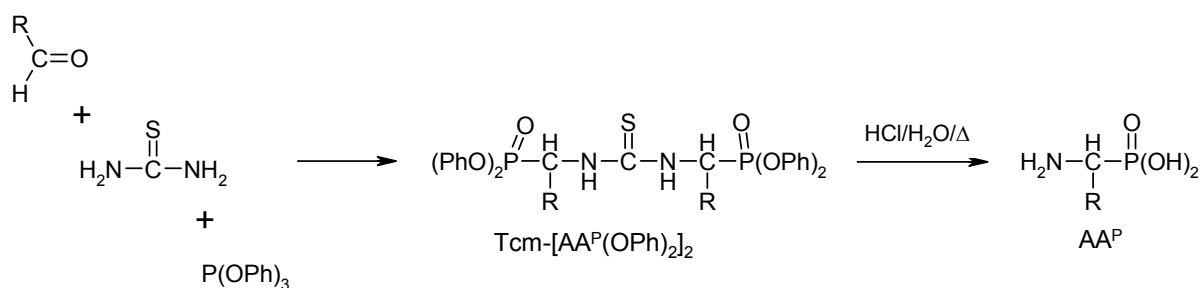
Until the 1980s the most efficient procedures for the synthesis of compounds containing the N-C-P bond system were based on an addition of a phosphorus nucleophile to imine bonds (usually imines derived from benzylamine and its analogs), followed by the amine group deprotection.^{10,12} Therefore the 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 thiourea³⁵ (Scheme 6).

However, the deeper investigation of these additions carried out in wide set of reaction conditions and monitored by ³¹P 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°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

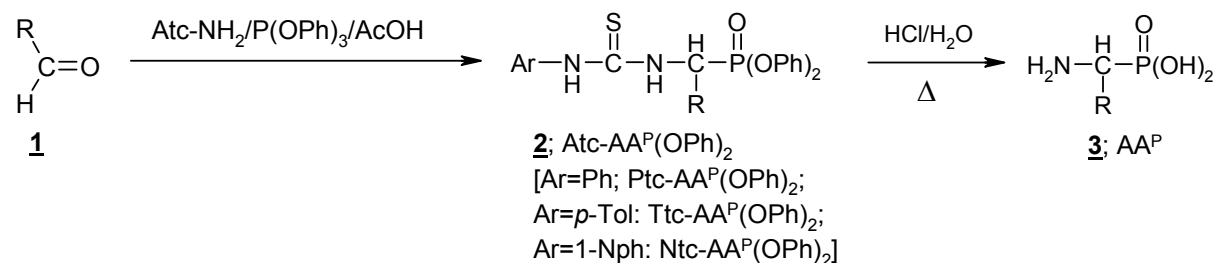


Scheme 7

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 thiouylenebis(alkylphosphonates) $\text{Tcm}-[\text{AA}^{\text{P}}(\text{OPh})_2]_2$ induced the search for more labile thiourea derivatives which afford more prone to the degradation thioureidoalkylphosphonates.

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 spontaneously, 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 [$\text{Ptc}-\text{AA}^{\text{P}}(\text{OPh})_2$], which in majority underwent spontaneous crystallization from the reaction mixtures. These $\text{Ptc}-\text{AA}^{\text{P}}(\text{OPh})_2$ compounds during acidic hydrolysis (6-8h of reflux in mixtures $\text{HCl}/\text{H}_2\text{O}/\text{AcOH}$) 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 acids⁴⁴⁻⁴⁶ suggested 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-NH₂: 0.02 mol) in one portion. Addition of Ptc-NH₂ 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 desiccator, 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-NH₂) 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			2M		H ₂ O		2M
							2→3	1→3			
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

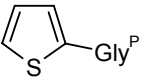
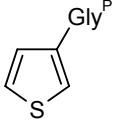
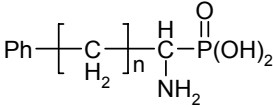
A mixture of triphenyl phosphite (0.02 mol), aldehyde (0.025 mol), *N*-phenylthiourea (Ptc-NH₂: 0.02 mol) in glacial acetic acid (10 ml) is stirred for 1 h at 80°C (oil-bath) and, without isolation, formed Ptc-AA^P(OPh)₂ is degraded. In cases when phenylthiourea is a reaction component, aqueous hydrochloric 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-AA ^P (OPh) ₂				AA ^P				Lit.
Structure	Abbrev.	Yield [%]	m.p. [°C]	³¹ P NMR [ppm]		Yield [%]	m.p. [°C]	³¹ P NMR [ppm]		
				CDCl ₃	AcOH			2M HCl	2M NaOH	
	PGly ^P	85	169-170	15.4	13.4	70	269-271	12.5	18.0	29
	2-MP-Gly ^P	85	169-170	15.0		70	252-254	13.4	19.0	
	3-MP-Gly ^P	82	154-158	15.7		90	234-236	13.2	18.6	
	4-MP-Gly ^P	90	192-195	15.5		97	246-248	13.3	18.7	
	2-NP-Gly ^P	68	164-166	13.7		45	246-249	10.8	17.2	
	3-NP-Gly ^P	76	146-149	14.5		90	231-233	11.2	17.1	
	4-NP-Gly ^P	34	165-168	14.1		37	223-224	10.9	16.8	
	2-CP-Gly ^P	81	130-134	14.5		49	235-237	11.8	18.0	
	4-BP-Gly ^P	68	177-179	14.7			254-256		18.1	
	1-Nph-Gly ^P	60	182-184	15.3		75	255-257	13.0	18.8	
	2-Nph-Gly ^P	70	177-179	15.5		91	235-237	12.9	18.4	
	2-Fu-Gly ^P	60	150-152	12.8		^a				

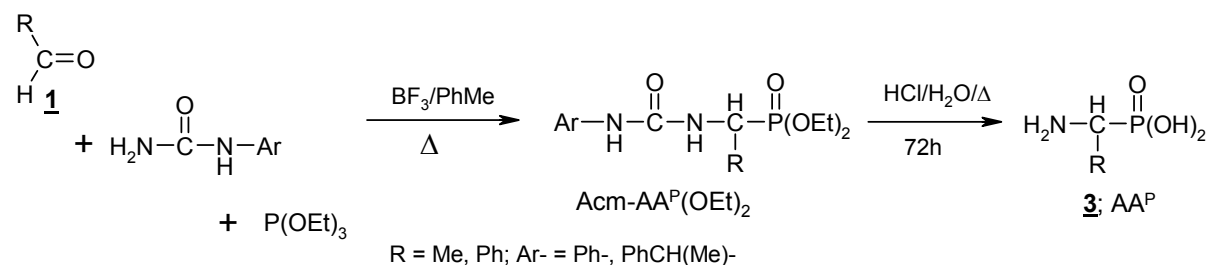
Table 3. Continued

	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

^aStandard 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 Middlebrooks²² 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

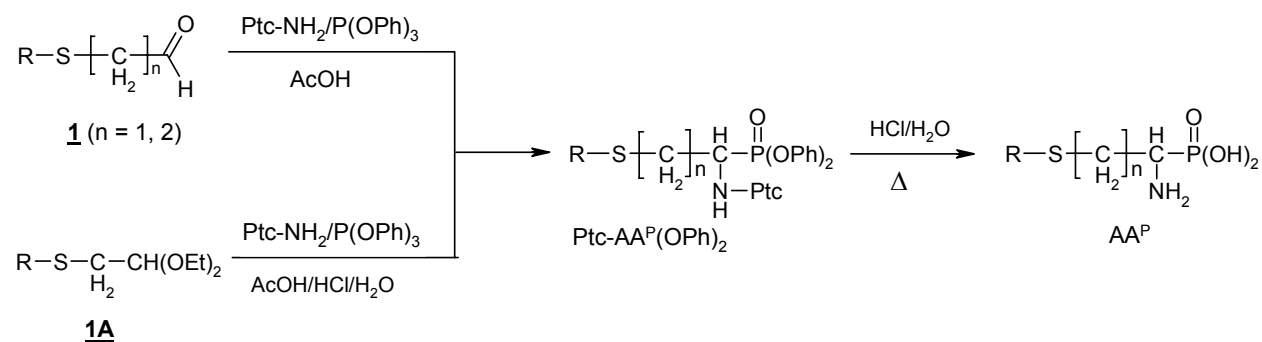
AA ^P	Atc-AA ^P (OPh) ₂			AA ^P			Lit.		
	Yield [%]	m.p. [°C]	³¹ P NMR ^a [ppm]	Yield [%]	m.p. [°C]	³¹ P NMR [ppm]			
	Ttc-AA ^P (OPh) ₂		<u>2</u> → <u>3</u>	AA ^P					
				2M HCl	H ₂ O	2M NaOH			
Ala ^P	85	164-166	18.8	93	275-276	16.8	14.3	22.3	
					275-276				29
Hala ^P	92	151-153	17.9	96	265-266	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

^aIn CDCl₃.

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-, alkylsulfanyl, alkylsulfonyl and sulfonic groups.

2.2.1. Synthesis of sulfur containing 1-aminoalkylphosphonic acids. These syntheses were performed starting from alkylthioacetaldehydes and/or 3-alkylthiopropional (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-aminothioalkylphosphonic acids

R =		Ptc-(R)AA ^P (OPh) ₂				AA ^P				Lit.
R ¹	n	Yield [%]	m.p. [°C]	³¹ P NMR [ppm]	Abbrev.	Yield [%]	m.p. [°C]	³¹ P NMR [ppm]		
				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 ₆ H ₁₃	2					HexHcys ^P	70	263- 265	15.8	20.3	57
n-C ₈ H 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 ₂ N-Ptc- Met ^P (OPh) ₂		41	186- 187								
R= BnOCH ₂		85- 90		17.2	15.6	Ser ^P	^b				

^aAs the result of the hydrolysis the mixture of Cys^P and Ser^P have been observed. ^bAs the result of the hydrolysis the mixture of C-N-P compounds (with ³¹P(δ)_{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 CHCl₃/MeOH (Table 1).

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.

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

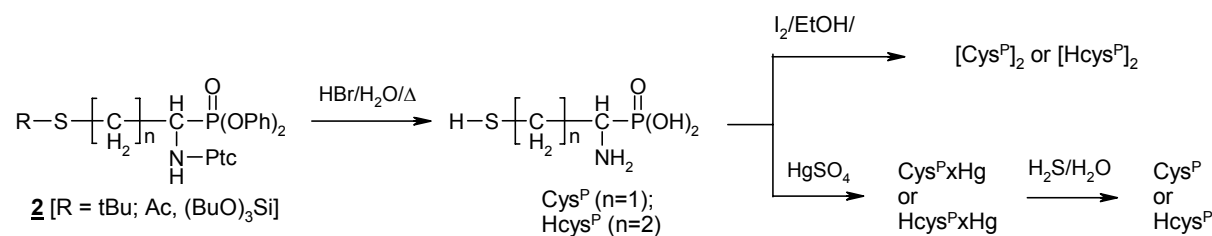
Compound Ptc-AA^P(OPh)₂ (0.01 mol) is dissolved in glacial acetic acid (5 ml) and 36% hydrochloric acid (20 ml), and the mixture is heated under reflux for 8 h. The solvents are evaporated under reduced pressure and the residue is dissolved in ethanol (20 ml). The solution is treated with methyloxirane 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-mercaptothioaldehyde - 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 ³¹P 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]₂⁵⁵ 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·Hg(II) which, according to microanalysis, possesses the formula C₂H₆NO₃PS×Hg(II)×H₂O. Treatment of a suspension of Cys^P·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 C₆H₂₀N₂O₆P₂S₂Hg₃.



Scheme 11

Phosphonocystine ([Cys^P]₂) [Kudzin, *Synthesis* 1981⁵⁵] and phosphonohomocystine ([Hcys^P]₂) [Kudzin&Stec, *Synthesis* 1980⁵⁶]:

To a solution of Ptc-(*t*-Bu)Cys^P(OPh)₂ or Ptc-(R)Hcys^P(OPh)₂, [R=*t*Bu-, Ac- or (tBuO)₃Si-] (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.

Phosphonocystine (Cys^P) and phosphonohomocystine (HCys^P) [Kudzin&Stec, *Synthesis* 1983⁵⁹]:

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*-phenylthiourea (9.06 g, 0.06 mol) in glacial acetic acid (50 ml). Stirring is continued for 1 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-(*t*Bu)Cys^P(OPh)₂ or Ptc-(*t*Bu)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).

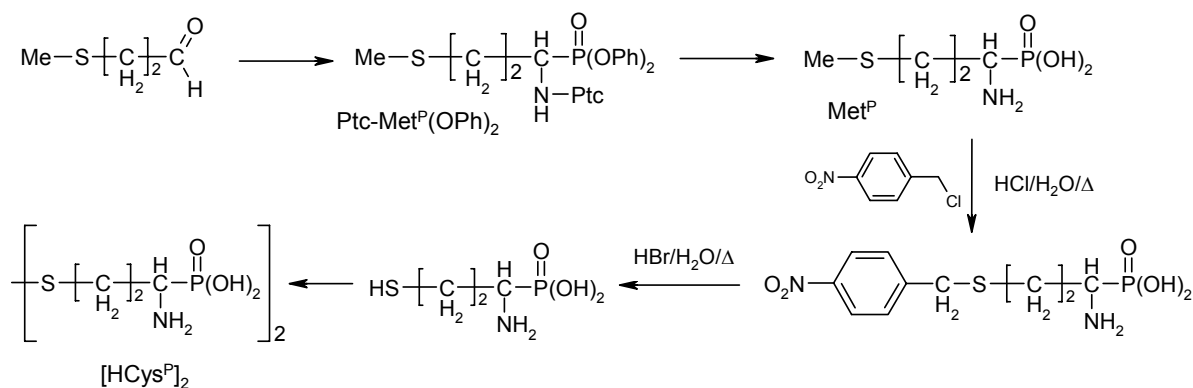
Table 6. Trifunctional thiolic 1-aminoalkylphosphonic acids

Ptc-(R)AA ^P (OPh) ₂					AA ^P					Lit.
R = R ¹ -S- (CH ₂) _n R ¹	Yield [%]	m.p. [°C]	³¹ P NMR [ppm]		Abbrev.	Yield [%]	m.p. [°C]	³¹ P NMR [ppm]		
	n		AcOH	CDCl ₃				10M HCl	2M KOH	
t-Bu	1	95	170- 171	16.5	Cys ^P	42	251- 252	14.5 12.9 ^b	19.5 19.5 ^c	59. 60, 61
t-Bu	1	95	170- 171	16.5	[Cys ^P] ₂	72	257- 259	13.2 ^a 12.6 ^b	17.7 18.4, 18.2 ^c	55
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-BuO) ₃ Si	2	76	147- 150	16.2	18.6	[HCys ^P] ₂	60	16.3; 16.0	20.0	
(4-O ₂ N-Bn)- Hcys ^P		66	246- 248			[HCys ^P] ₂	65	272- 274		58

^aIn TFA. ^bIn 2M HCl. ^cIn 2M NaOH.

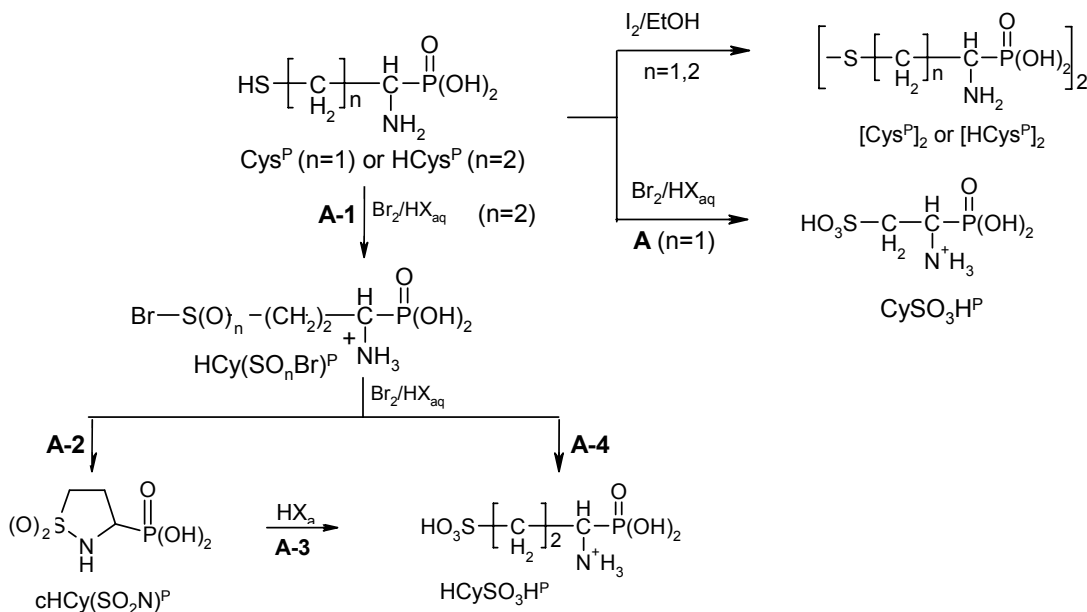
For the preparation of phosphonohomocystine Tishler and co-workers proposed method presented schematically on Scheme 12.

2.2.1.1. Functionalization of sulfur containing 1-aminoalkylphosphonic acids. Oxidation of phosphonic analogues of the thio- amino acids, namely Cys^P and/or Hcys^P afford, depending on the applied conditions, disulfide derivatives [Cys^P]₂⁵⁵ and [Hcys^P]₂⁵⁶ 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-induced dephosphonylation of 1-aminoalkylphosphonic acids will be discussed in a separate paper⁶³). In such conditions, the oxidation proceeded gradually with the formation of a mixture of intermediary derivatives, slowly rearranging into the final $\text{HCySO}_3\text{H}^{\text{P}}$ (Scheme 13).⁶²



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

Scheme 13

Preparation of phosphonocysteic acid [CySO₃H^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 CySO₃H^P (0.20 g; 97.5%) of analytical purity.

Preparation of phosphonohomocysteic acid [HCySO₃H^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 HCySO₃H^P (0.61 g; 96%) of analytical purity.

In a number of works, modifications of the thioether function of 1-amino-n-thiaalkylphosphonic acids were conducted, affording corresponding sulfinyl- and/or sulfonyl,^{57,58,64} as well as trimethylsulfonium derivatives.^{58,65}

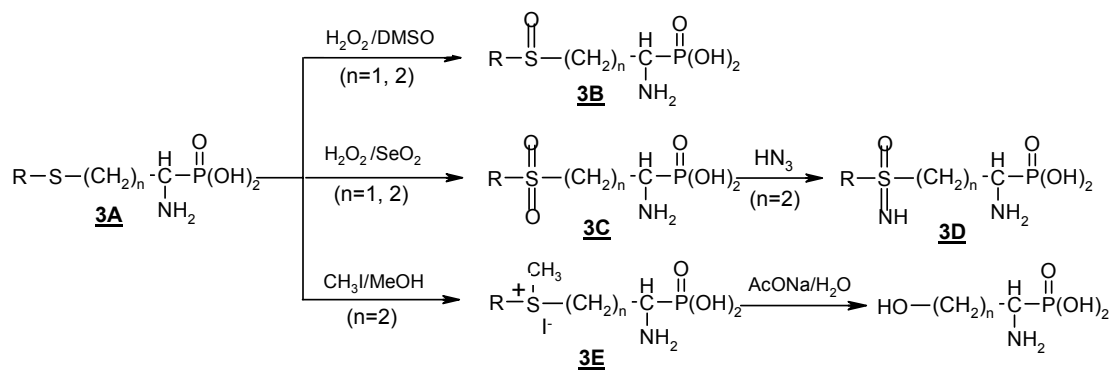
The synthesis of the sulfinyl **3B** and sulfonyl **3C** derivatives of the sulfur-containing amino acids **3A** elaborated by us, was based on the selective oxidation of the latter compounds.

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) dioxide⁶⁶ 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-H₂O₂-SeO₂ 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. [°C]	³¹ P NMR [ppm]		Lit.	
R ¹	n			2M NaOH	2M HCl		
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							
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	

^aIn TFA.

Preparation of the sulfinyl derivatives 3B of the amino acids 3A. General procedure [Kudzin *et al.*, *Heteroatom Chem.* 1994⁶⁴]:

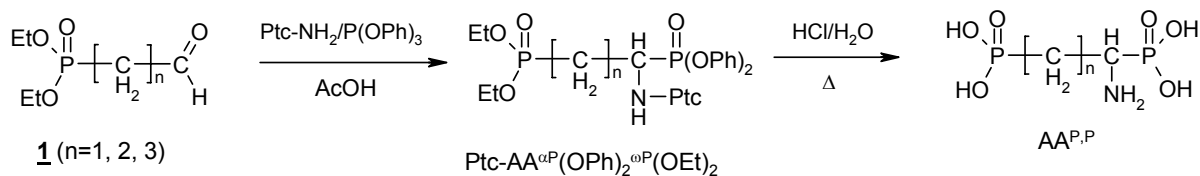
Each of the amino acids 3A (5 mmol) was added in one portion into a cooled (10°C) and well-stirred mixture of hydrogen peroxide (30% aq., 2 ml), water (2 ml), and dimethyl sulfoxide (3 ml), and the reaction mixture was stirred for 0.5 h at room temperature. After dilution with acetone (30 ml), the mixtures 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.* 1994⁶⁴]:

Each of the amino acids 3A (5 mmol) was added in one portion into a cooled (10°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 50W×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^{αP}(OPh)₂^{ωP}(OEt)₂ afforded the title AA^{αP,ωP} (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.	³¹ P NMR	Yield	m.p.	³¹ P NMR	
	[%]	[°C]	[ppm] ^a	[%]	[°C]	2M HCl 2M NaOH	
Asp ^{P,P}	75	150-	15.6;	70	233-235	13.6; 14.3;	71
		151	16.3;		22.07;		
			26.0; 26.7		22.9; 23.6 22.12		
Glu ^{P,P}	70	145-	17.3; 17.4	65	233-235	15.0; 19.6	71
		147	31.2; 31.4		234-236	21.9; 22.0;	
					237-239	23.3; 23.4	
HGlu ^{P,P}	58	oil	18.3; 32.4	50	235-237	15.9; 29.0	71
HGlu ^{γ-P}	73	oil	16.6 ^b	70	158-159	15.8	74

³¹P NMR spectra of Ptc-AA^P(OPh)₂ and Ptc-AA^{P,P}(OPh)₂ were recorded in (a)CDCl₃ 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/H₂O (1:1) to give corresponding thioureidoalkylphosphonate Ptc-AA^{P,P}(OPh)₂ (n=1,2) as crystalline compounds pure as indicated by their ³¹P 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

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 paper⁷⁶).

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

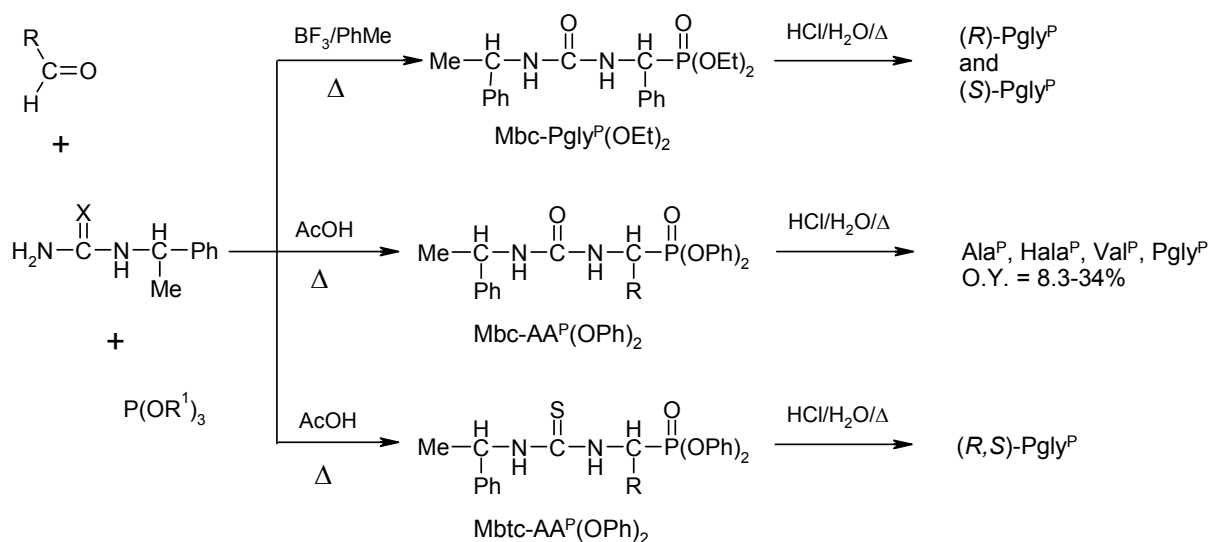
R, R ¹	$\text{O}_2\text{N}-\overset{\text{R}^1}{\underset{\text{R}}{\text{C}}}-\overset{\text{H}_2}{\text{C}}-\overset{\text{H}_2}{\text{C}}-\overset{\text{H}}{\underset{\text{N}-\text{Ptc}}{\text{C}}}-\overset{\text{O}}{\parallel}{\text{P}}(\text{OPh})_2$			$\text{O}_2\text{N}-\overset{\text{R}^1}{\underset{\text{R}}{\text{C}}}-\overset{\text{H}_2}{\text{C}}-\overset{\text{H}_2}{\text{C}}-\overset{\text{H}}{\underset{\text{NH}_2}{\text{C}}}-\overset{\text{O}}{\parallel}{\text{P}}(\text{OH})_2$				
	Yield [%]	m.p. [°C]	³¹ P NMR [ppm] ^a AcOH CDCl ₃	Yield [%]	m.p. [°C]	³¹ P NMR TFA ^a / H ₂ O 2M NaOH HCl ^b		
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

³¹P NMR: ^aTFA; ^b2M HCl; ^c2M AcOH/AcONa-D₂O; ^dEtOH-D₂O (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*⁷-1-methylbenzylaminoureidophosphonates (Scheme 18).^{77,78}

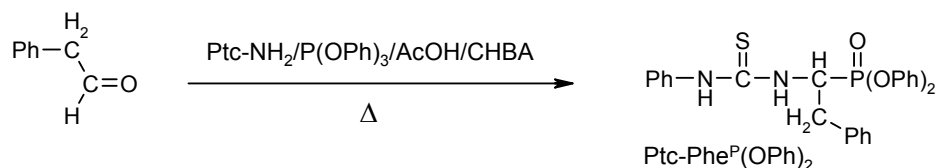
In a similar approach, applied for both levorotatory and dextrorotatory *N*-(1-methylbenzyl)-thioureas [(*R*)-Bmtc-NH₂ and (*S*)-Bmtc-NH₂], temporary Bmtc-Ala^P(OPh)₂ obtained, as well as the product of their final acidic hydrolysis – phosphonoalanine (Ala^P) did not exhibit remarkable optical activity²⁹ (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 $\text{Ptc-Phe}^{\text{P}}(\text{OPh})_2$ in acetic acid-chiral Bronsted acids (CHBA)



AcOH/(2 <i>R</i> ,3 <i>R</i>)-(+)-tartaric acid (10%)									
$^{31}\text{P}(\delta)$	[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%)									
$^{31}\text{P}(\delta)$	[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 <i>S</i>)-(+)-camphorsulfonic acid (10%)									
$^{31}\text{P}(\delta)$	[ppm]	38.3	36.1	33.7	19.7	16.4	4.1	1.4	-18.7
	[%]		10	6	7	10	40	10	4

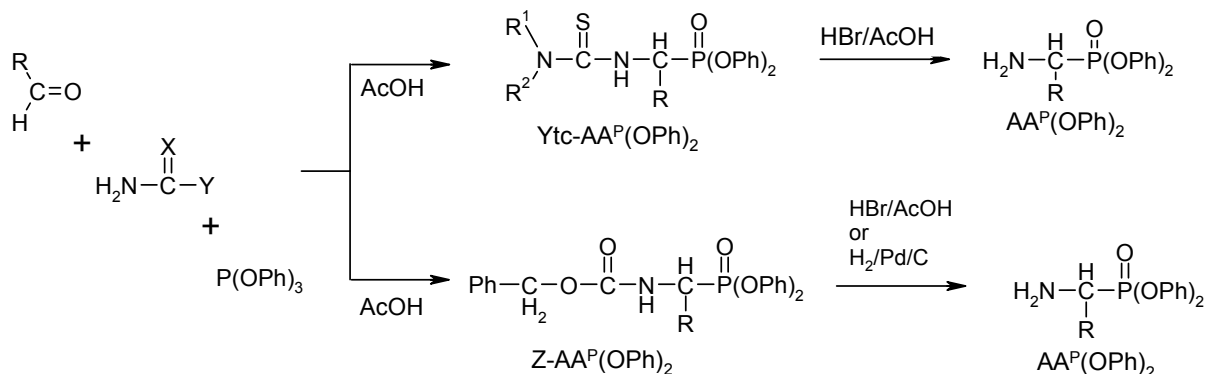
$^{\text{a}}\delta(^{31}\text{P})$: $(\text{PhO})_3\text{P}$ $127\pm 1\text{ppm}$; $(\text{PhO})_2\text{P}(\text{O})\text{H}$ $0\pm 0.5\text{ppm}$; $(\text{PhO})\text{P}(\text{O})(\text{OH})_2$ -4.7ppm ; $(\text{PhO})_3\text{P}(\text{O})$ - $17.5\pm 1\text{ppm}$ ⁷⁹

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%); $Z-Leu^P(OPh)_2$ (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 [$Z-AA^P(OPh)_2 \rightarrow AA^P(OPh)_2$] 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

$\text{Me}-\overset{\text{O}}{\parallel}{\text{S}}-\text{NH}_2$	$\text{Me}-\overset{\text{O}}{\parallel}{\text{S}}-\underset{\text{H}}{\text{N}}-\underset{\text{Me}}{\overset{\text{H}}{\text{C}}}-\overset{\text{O}}{\parallel}{\text{P}}(\text{OPh})_2$	20.0 (20%)	17.7 (40%)	
$\text{Et}-\text{O}-\overset{\text{S}}{\parallel}{\text{C}}-\text{NH}_2$	$\text{Et}-\text{O}-\overset{\text{S}}{\parallel}{\text{C}}-\underset{\text{H}}{\text{N}}-\underset{\text{Me}}{\overset{\text{H}}{\text{C}}}-\overset{\text{O}}{\parallel}{\text{P}}(\text{OPh})_2$	18.8 (40%)	17.5 (18%)	16.0 (10%)
$\text{Et}-\text{S}-\overset{\text{S}}{\parallel}{\text{C}}-\text{NH}_2$	$\text{Et}-\text{S}-\overset{\text{S}}{\parallel}{\text{C}}-\underset{\text{H}}{\text{N}}-\underset{\text{Me}}{\overset{\text{H}}{\text{C}}}-\overset{\text{O}}{\parallel}{\text{P}}(\text{OPh})_2$	18.9 (42%)	16.7 (25%)	
$\text{H}_2\text{N}-\overset{\text{S}}{\parallel}{\text{C}}-\text{S}-\text{S}-\overset{\text{S}}{\parallel}{\text{C}}-\text{NH}_2$	$\left[\text{S}-\overset{\text{S}}{\parallel}{\text{C}}-\underset{\text{H}}{\text{N}}-\underset{\text{Me}}{\overset{\text{H}}{\text{C}}}-\overset{\text{O}}{\parallel}{\text{P}}(\text{OPh})_2 \right]_2$	Multicomponent mixture		
$\text{N}\equiv\text{C}-\text{NH}_2$	$\text{N}\equiv\text{C}-\underset{\text{H}}{\text{N}}-\underset{\text{Me}}{\overset{\text{H}}{\text{C}}}-\overset{\text{O}}{\parallel}{\text{P}}(\text{OPh})_2$	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 $Z\text{-AA}^{\text{P}}(\text{OPh})_2$ ^{92,93} made the continuation of this approach for the synthesis of these precursors of $\text{AA}^{\text{P}}(\text{OPh})_2$ not reasonable.

3. Other modifications

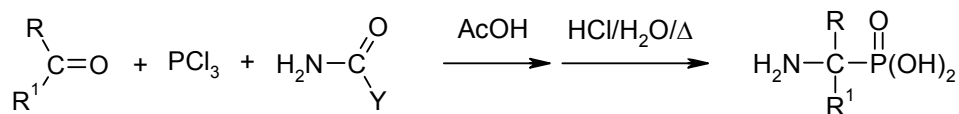
3.1. Z-Aminophosphonate Method (Birim-Oleksyszyn Method)

Modifications of the Birum reaction by the use of easily degradable benzyl carbamate^{10-12,25,30} present the base of the Z-aminophosphonate method (Birim-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 $\text{AA}^{\text{P}}(\text{OPh})_2$. 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*-phenylurea²² optically active *N*-(1-methylbenzyl)ureas^{77,78} and carbamates,⁷⁸ *O,O*-diethyl phosphoramidothioate,^{97,98} or *O*-ethyl, *O*-phenyl phosphoramidothioate,⁹⁷ *O,O*-dipropyl phosphoroamidate,⁹⁹ *N*-acyl-4-aminobutanal,¹⁰⁰ 2-amino-5-phenyl-1,3,4-oxadiazole or 1,3,4-thiadiazole¹⁰¹ have also been applied.

3.2. Oleksyszyn Method

The first essential modification of the Engelman and Píkl 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, R¹ = 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 Wrocław 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 alkanooates,⁴⁸ *p*-toluenesulfonamide,^{125,126,127} *O,O*-diethyl phosphoramidothioate,¹¹⁵ or *O*-ethyl, *O*-phenyl¹¹⁵ diethyl phosphoramidate or phosphorothioamidate,¹¹⁵ 1,3-oxazolidin-2-one¹²⁸ and 5,5-dimethylhydantoin.^{129,130}

In others, phosphorus trichloride was replaced by various chlorophosphites,^{115,125,127,131-133} dichlorophosphites,^{123,131,132,134,135} dithioisopropyl-chlorophosphites¹³¹ and PhOPCl₂/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/SO₂Cl₂^{137,139} and also (RO)₂P(O)H/Ac₂O/HCl mixtures,¹³⁹ as well as PCl₃/P(OMe)₃^{140,141} and PCl₃/AcOH/SO₂Cl₂¹¹⁷ mixtures. Amidoalkylation of phosphorous acid^{25,105,106,109} and alkylphosphonic acids in RP(O)(OH)₂/Ac₂O mixtures (R=Me, Ph)¹⁰⁵ were also applied.

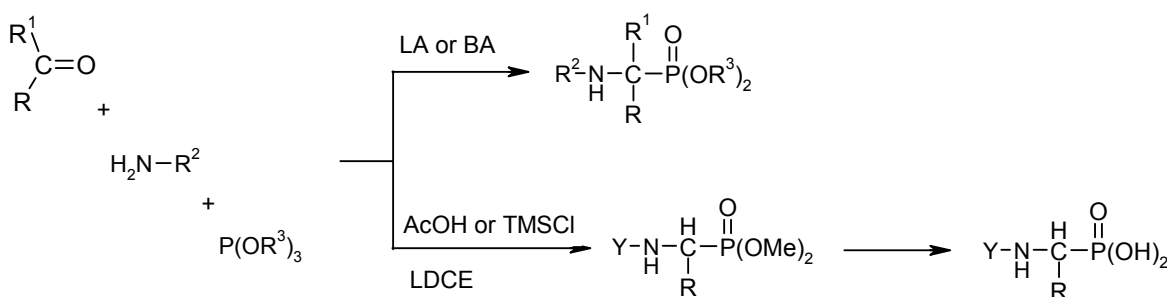
The application of dichloroalkylphosphines and/or dichloroarylphosphines,^{28,102-104,112-114, 142,143} a functionalized or nonfunctionalized phosphonites^{144,145} and hypophosphorous acid¹¹¹ (for the preparation of 1-aminoalkylphosphinic acids), or chlorodialkylphosphines^{105,116} allowed on the preparation of 1-aminoalkylphosphinic acids and/or 1-aminoalkanephosphine oxides, respectively.

The mechanisms of the Engelman-Píkl-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, R¹ = H, alkyl; H, aryl; H, aralkyl; R² = alkyl, aryl; R³ = Me, Et; Y = Me₂N, PhO

Scheme 21

The reported modifications of this procedure are based on the use of LPDE catalysis,¹⁴⁷⁻¹⁴⁹ the use of Brønsted acids {BA: sulfonic acid functionalized ionic liquid,¹⁵⁰ silica-sulfuric acid,¹⁵¹ oxalic acid¹⁵² and/or boric acid¹⁵³ or Lewis acids [LA: CAN,¹⁵⁴ VCl₃,¹⁵⁵ TiCl₄,¹⁵⁶ Cu(OTf)₂,¹⁵⁷ AlCl₃¹⁵⁸ or Sc tris(dodecyl sulfate),¹⁵⁹ or a realization of tri-component condensation under solvent-free conditions using Al(H₂PO₄)₃ as an efficient and reusable heterogeneous catalyst¹⁶⁰ or without catalyst.¹⁶¹

4. Nomenclature and applied abbreviations code

The compounds discussed are listed in Table 12 together with the code used to identify them in tables and schemes. This system of abbreviations used for assignment of aminoalkylphosphonic acids and derivatives has already been applied in the fragmentary form in our earlier papers¹³⁻¹⁵ and its full version will be published elsewhere.

Table 12. Codes used for the representative phosphonic acid and derivatives¹³⁻¹⁵

Code	Compound name
AA ^P s	1-Aminoalkylphosphonic Acids ¹³
AA ^P (OR) ₂	Dialkyl 1-Aminoalkylphosphonate; Dialkyl Phosphono-Amino-Acidate ^a
Gly ^P (OMe) ₂	Dimethyl 1-Aminomethylphosphonate; Dimethyl Phosphonoglycinate ^a
(AC)-AA ^P	1-(N-Acylamino)alkylphosphonic Acid ¹³ ; (ACyl)-PhosphonoAmino Acid ^a
Ac-AA ^P	1-(N-Acetylamino)alkylphosphonic Acid ¹³
Ac-Ala ^P	Acetyl-phosphonoalanine ^a ; 1-(N-Acetylamino)ethylphosphonic Acid
Bz-AA ^P	1-(N-Benzoylamino)alkylphosphonic Acid ¹³
TFA-AA ^P	1-(N-Trifluoroacetylamino)alkylphosphonic Acid ¹⁴

Table 12. Continued

Mca-AA ^P	1-(<i>N</i> -Chloroacetyl amino)alkylphosphonic Acid ¹⁵
(Ac)-AA ^P (OR) ₂	Dialkyl Acetylphosphono-Amino Acidate ^a ; Dialkyl 1-(<i>N</i> -Acetyl amino)alkylphosphonate ¹³
Ac-Ala ^P (OR) ₂	Dialkyl Acetylphosphonoalaninate ^a ; Dialkyl 1-(<i>N</i> -Acetyl amino)ethylphosphonate ¹³
PTC-AAs	1-(Phenylthiocarbamoyl)-Amino Acids ^{162, 163}
Ptc-AA ^P s	1-(Phenylthiocarbamoyl amino)alkylphosphonic Acids ^a
Ptc-AA ^P (OR) ₂	Dialkyl 1-(Phenylthiocarbamoyl amino)alkylphosphonate ^a ;
Ptc-AA ^P (OAr) ₂	Diaryl 1-(Phenylthiocarbamoyl amino)alkylphosphonate ^a ; Diaryl 1-(3-Phenylthioureido)alkylphosphonate ^{55,56}
Ptc-AA ^P (OPh) ₂	Diphenyl 1-(Phenylthiocarbamoyl amino)alkylphosphonate ^a ; Diphenyl 1-(<i>N</i> -Phenylthioureido)alkylphosphonate ^{39,41,55,56}
Ptc-Ala ^P (OPh) ₂	Diphenyl Phenylthiocarbamoyl-phosphonoalaninate ^a ; Diphenyl 1-(3-Phenylthioureido)ethylphosphonate ³⁸
Ptc-Hala ^P (OPh) ₂	Diphenyl Phenylthiocarbamoyl-phosphonohomoalaninate ^a ; <i>O,O</i> -Diphenyl 1-(3-phenylthioureido)butanephosphonate ⁴⁰
Ptc-tLeu ^P (OPh) ₂	Diphenyl Phenylthiocarbamoyl-phosphonotertleucinate ^a ; <i>O,O</i> -Diphenyl 2-methyl-1-(3-phenylthioureido)propanephosphonate ³⁷
Ptc-Nleu ^P (OPh) ₂	Diphenyl Phenylthiocarbamoyl-phosphononorleucinate ^a ; <i>O,O</i> -diphenyl 1-(3-phenylthioureido)-pentanephosphonate ⁴⁰
Pc-AA ^P	1-(Phenylcarbamoyl amino)alkylphosphonic Acid ^a
Pc-AA ^P (OAr) ₂	Diaryl 1-(Phenylcarbamoyl amino)alkylphosphonate ^a
Pc-Pgly ^P (OEt) ₂	Diethyl Phenylcarbamoyl-phosphonophenylglycinate ^a Diethyl 1-(3-Phenylureido)ethylphosphonate ¹⁶
Ac*-AA ^P (OPh) ₂	Diphenyl 1-(Arylcarbamoyl amino)alkylphosphonate ^a
Dpc-Ala ^P (OPh) ₂	Diphenyl Diphenylcarbamoyl-phosphonoalaninate ^a ;
Atc-AA ^P	1-(Arylthiocarbamoyl amino)alkylphosphonic Acid ^a ;
Tc-AA ^P	1-(Thiocarbamoyl amino)alkylphosphonic Acid ^a ; 1-(Thioureido)alkylphosphonic acid ⁵³
Atc-AA ^P (OAr) ₂	Diaryl 1-(Arylthiocarbamoyl amino)alkylphosphonate ^a
Tc[AA ^P (OAr) ₂] ₂	Tetraaryl Thiocarbamoyl[di(1-aminoalkylphosphonate)] ^a ; Tetraaryl Thiourylene[dialkyl]diphosphonate) ²⁹
Tc-AA ^P (OPh) ₂	Diphenyl 1-(Thiocarbamoyl amino)alkylphosphonate ^a
Tc[AA ^P (OPh) ₂] ₂	Tetraphenyl Thiocarbamoyl-[di(aminoalkylphosphonate)] ^a ; Tetraphenyl (Thiourylenedialkyl)-diphosphonate) ²⁹
Tc[Nva ^P (OPh) ₂] ₂	Tetraphenyl Thiocarbamoyl-[di(phosphononorvalinate)] ^a ; Tetraphenyl (Thiourylenedibutyl)diphosphonate) ¹⁶
Cm-Hala ^P	Carbamoyl-phosphonohomoalanine ^a ; 1-Ureidopropylphosphonic acid ¹⁶

Table 12. Continued

Cm[Ala ^P (OCET) ₂] ₂	Tetrakis(2-Chloroethyl) Carbamoyl-[di(phosphonoalaninate)] ^a ; Tetrakis(2-Chloroethyl) (Urylenediethyl)diphosphonate ¹⁶
Cm[Ala ^P (OPh) ₂] ₂	Tetraphenyl Carbamoyl-[di(phosphonoalaninate)] ^a ; Tetraphenyl (Urylenediethyl)diphosphonate ¹⁶
Cm[Pgly ^P (OPh) ₂] ₂	Tetraphenyl Carbamoyl-[di(phosphonophenylglycinate)] ^a ; Tetraphenyl (Urylenedibenzyl)diphosphonate ¹⁶
AA ^P (H)s	1-Aminoalkylphosphinic Acids
Ala ^P (H)	1-Aminoethylphosphinic Acid; Phosphinoalanine

^aConvention applied in this paper. ^bName formed by analogy to the Birum's nomenclature.

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