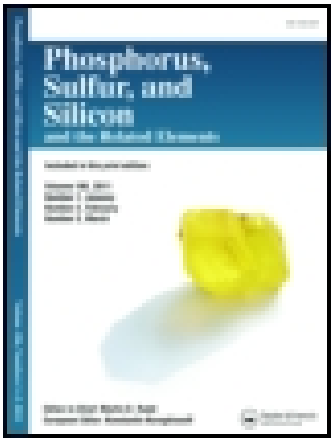

Phosphorus, Sulfur, and Silicon and the Related Elements

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ESTERIFICATION OF PHOSPHONIC AND PHOSPHINIC ACID ANALOGUES OF GLUTAMIC AND ASPARTIC ACIDS WITH ETHYL ORTHOFORMATE-SCOPE AND LIMITATIONS OF THE METHOD

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ESTERIFICATION OF PHOSPHONIC AND PHOSPHINIC ACID ANALOGUES OF GLUTAMIC AND ASPARTIC ACIDS WITH ETHYL ORTHOFORMATE—SCOPE AND LIMITATIONS OF THE METHOD

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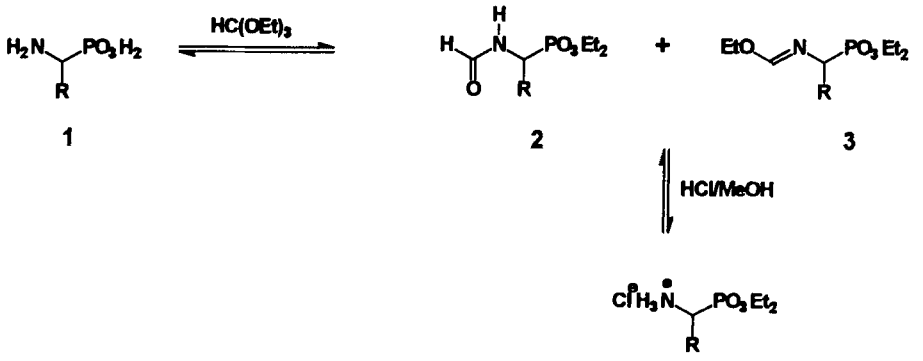
Reaction of C-ethyl esters of phosphonic- and phosphinic acid analogues of glutamic and aspartic acids with ethyl orthoformate provides the mixtures of N-formylamino- and N-ethoxymethyleneimino-derivatives with nearly quantitative yields. Scope and limitations of this procedure were studied by means of GC/MS technique.

Key words: Amino acid analogues, esterification, phosphonopeptides.

INTRODUCTION

Aminoalkylphosphonic acids (1) are widely recognized as antimetabolites of amino acids which display interesting and useful biological properties.[1,2] Their negligible mammalian toxicity, and the fact that they bear a very close chemical resemblance to their aminocarboxylic counterparts, makes them remarkably important structural units of phosphonopeptides and peptidomimetics. These peptides appeared to be promising enzyme inhibitors, antibacterials and anticancer drugs.[3–5]

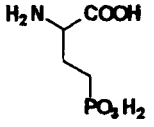
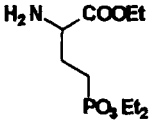
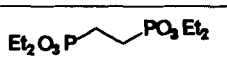
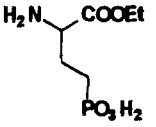
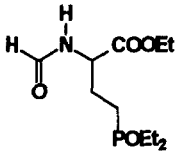
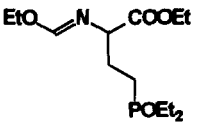
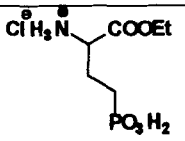
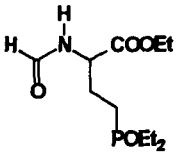
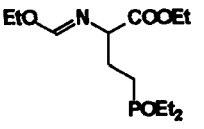
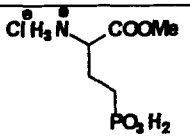
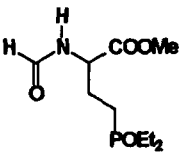
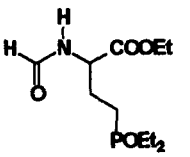
During the last twenty years a considerable progress in the synthesis of phosphonopeptides has been achieved.[3,6–10] However, the preparation of the peptides from aminoalkylphosphonic acids containing additional functional group in the side-chain is still a challenge.[11] This is mainly due to the lack of simple methods for the preparation of the properly blocked substrates from underivatized aminoalkylphos-



1 2 3

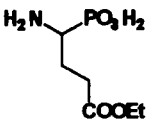
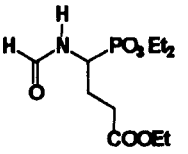
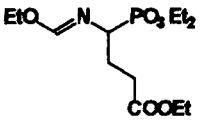
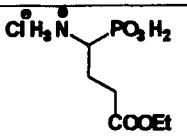
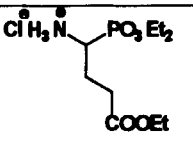
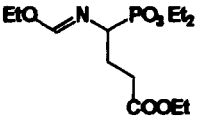
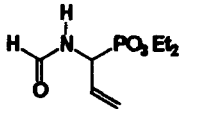
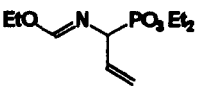
TABLE I

Reaction of phosphonic acid analogues of glutamic acid with ethyl orthoformate

Substrate	Product	Yield (%)	Yield of unreacted substrate (%)
		10	80
		4	
		76	9
		7	
		71.5	10
		7	
		63.5	15
		10	

phonic acids. One of the simplest procedures seems to be the reaction of amino-alkylphosphonic acids with orthoformates which yields the mixtures of 1-(N-formylamino)alkylphosphonate (**2**) and 1-(N-ethoxymethyleneimino)alkylphosphonate (**3**).[12–14] This mixture upon reaction with the solution of hydrogen chloride in meth-

TABLE I (*Continued*)

Substrate	Product	Yield (%)	Yield of unreacted substrate (%)
		40	22
		29	
		48	20
		4	
		14	
		10	

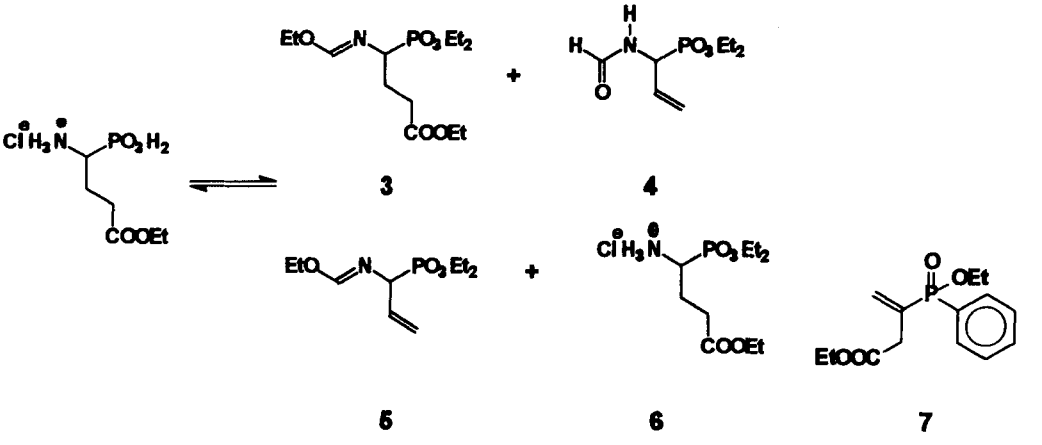


TABLE II

Reaction of phosphonic acid analogues of aspartic acid with ethyl orthoformate

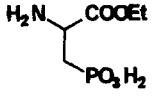
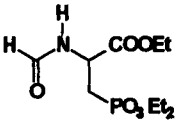
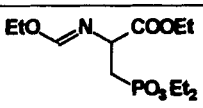
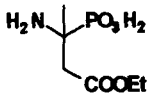
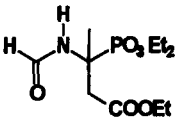
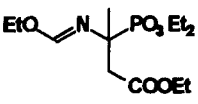
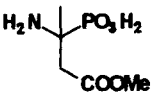
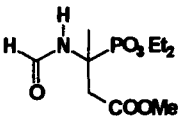
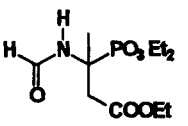
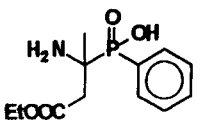
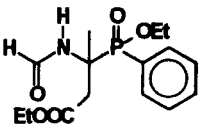
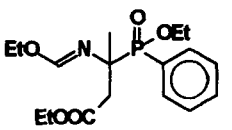
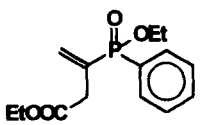
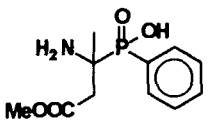
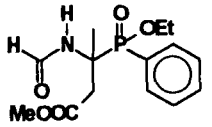
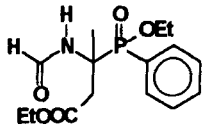
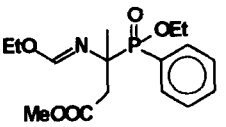
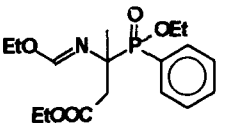
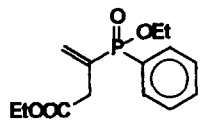
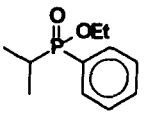
Substrate	Product	Yield (%)	Yield of unreacted substrate (%)
		90	0
		5	
		56	5
		36	
		46	11
		32	
		22	0
		64	
		7	

TABLE II (*Continued*)

Substrate	Product	Yield (%)	Yield of unreacted substrate (%)
		24	0
		21	
		22	
		10	
		5	
		5	

anol yields the desired hydrochloride of diethyl 1-aminoalkylphosphonate with a good yield.

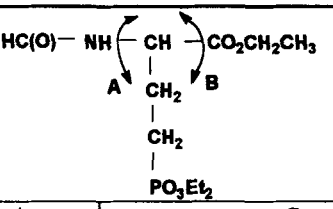
In this paper we report the usefulness of this procedure for the derivatization of phosphonic acid analogues of glutamic and aspartic acids.

RESULTS AND DISCUSSION

Reactions were carried out as described previously[12] and the composition of the product mixtures was studied by means of GC/MS technique. Results of the studies are summarized in Tables I (reaction of glutamic acid analogues) and II (reaction of aspartic acid analogues). As seen from Table I, underivatized phosphonic acid analogues of acidic amino acids are poor substrates and the esterification of their carboxylic acid groups should be performed prior the reaction with ethyl orthoformate. The C-ethyl esters readily reacted with ethyl orthoformate yielding the expected products **2** and **3** in good yields. The use of C-methyl esters is not recommended

TABLE III

Mode of fragmentation and principal ions in the mass spectrum of triethyl 2-(N-formylamino)-4-phosphonobutyrate



Ion	m/z (intensity, %)	Comments
$[MH]^+$	296 (1.4)	protonated molecular ion
$[AH^+]$	252 (6.2)	-
B	222 (30.6)	-
-	194 (99.3)	ion B minus $CH_2{=}CH_2$
-	165 (11.1)	$CH_2CH_2\text{-}PO_3Et_2$ fragment
-	152 (16.7)	$CH_3\text{-}PO_3Et_2$ fragment
-	125 (15.9)	$CH_3\text{-}P(OH)_2OEt$ fragment
-	109 (10.4), 81 (8.3), 65 (6.2)	products of $\text{-}PO_3Et_2$ group fragmentation
-	56 (100)	$[HC(O)\text{-}N{=}CH]^+$

because the transesterification of carboxylate moiety by orthoformate resulted in the production of the mixed esters.

The acid catalysis in the reaction of aminoalkylphosphonic acids with ethyl orthoformate was reported to increase the yield of N-formyl derivative.[13,14] The use of C-ethyl 2-amino-4-phosphonobutyrate hydrochloride, however, did not result in any change of the reaction course. Quite surprisingly the reaction of C-ethyl 4-amino-4-phosphonobutyrate hydrochloride with ethyl orthoformate provided additionally the products of decarboxylation (compounds **4** and **5**). Also the removal of N-formyl group from **2** by hydrogen chloride providing compound **6** was observed in this case.

Another unexpected finding was the removal of the amino moiety which resulted in the formation of compound **7** observed when C-methyl and C-ethyl 3-amino-3-(P-phenyl)phosphino-butyrates were used as substrates. The mechanism of this interesting reaction remains to be determined.

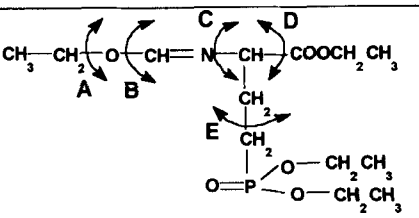
EXPERIMENTAL

Materials. All the reagents were of analytical purity. Ethyl orthoformate was purchased from Aldrich (Milwaukee, Illinois, USA). Aminophosphonic and -phosphinic acids, as well as their C-alkyl esters, were prepared according to the previously described procedure.[12]

Reaction of Aminophosphonates with Ethyl Orthoformate. A suspension of C-ethyl ester of aminoal-

TABLE IV

Mode of fragmentation and principal ions in the mass spectrum of triethyl 2-(N-ethoxymethyleneimino)-4-phosphonobutyrate



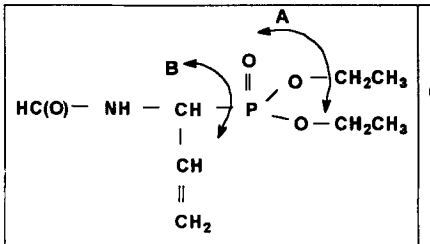
Ion	m/z (intensity, %)	Comments
$[MH]^+$	324 (1.4)	protonated molecular ion
A	294 (25.2)	-
B	278 (4.2)	-
-	249 (18.9)	ion B minus ethyl group from phosphonate moiety
$[CH]^+$	252 (10)	-
D	250 (49.6)	-
-	221 (55.2)	ion D minus ethyl group
-	192 (39.9)	ion D minus two ethyl group
E	172 (94.4)	-
-	148 (44.8)	$[C{=}CH\text{-}CH_2\text{-}P(O)(OEt)(OH)]^+$
-	136 (29.4)	$[CH_2{=}CH\text{-}PO_3HEt]^+$
-	121 (36.6)	$[CH_2CH_2\text{-}P(O)(OEt)]^+$
-	81 (25.9) 65 (10.5)	products of $-PO_3Et_2$ group fragmentation
-	56 (100)	$[H\text{-}C(O)\text{-}N{=}CH]^+$

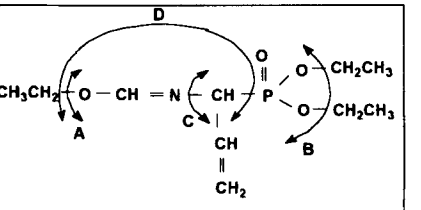
kylphosphonic acid (0.02 mol) in ethyl orthoformate (70 ml) was refluxed carefully in an apparatus for simple distillation for 3 h with removal of the formed ethanol. Then the unreacted substrate was filtered off and the filtrate evaporated *in vacuo* to give oily product which was analysed by means of GC/MS spectrometry.

Gas Chromatography and Mass Spectrometry. A Hewlett-Packard 5890 series II gas chromatograph with an electron impact (electron energy of 70 eV) mass spectrum detector was used. The 25 m × 0.25 mm HP1 110/8/300 capillary column was used. The column temperature was set up to 110°C for 3 minutes and then increased at a rate of 8°C min^{-1} to 300°C. The modes of fragmentation were determined using the literature data.[13-15] Similarly as described in the literature the molecular ions of these derivatives were observed in low abundance. The representative modes of fragmentations alongside with the principal ions in the mass spectra of the expected products **2** and **3** obtained starting from 2-amino-4-phosphonobutyric acid are given in Tables III and IV. The fragmentation pathways and principal ions of decarboxylation products **4** and **5** are given in Table V, whereas the data for compound **7** are collected in Table VI.

TABLE V

Mode of fragmentation and principal ions in the mass spectrum of compounds **5** and **6**





Ion	m/z intensity	Comments	Ion	m/z intensity	Comments
$[MH]^+$	222 (1.9)	protonated molecular ion	$[MH]^+$	250 (1.0)	protonated molecular ion
$[M]^+$	221 (19.0)	isotopic peak	$[M]^+$	249 (8.1)	isotopic peak
$[AH]^+$	193 (7.6)	-	$[AH]^+$	221 (3.8)	-
-	166 (2.5)	$[NHCH_2PO_3Et_2]^+$	B	193 (7.5)	EtOCH=N-CH-PO_3H_2 CH=CH_2
-	149 (1.9)	$[H_2C$=CH-CHPO_3EtH]	$[C\text{-}1]^+$	176 (3.8)	-
-	138 (18.4)	HPO_3Et_2	-	165 (28.8)	$[HN$=CH$PO_3Et_2]^+$
-	111 (29.7)	H_3PO_3Et	-	138 (74.4)	HPO_3Et_2
B	84 (100)	-	-	111 (58.1)	H_3PO_3Et
-	65 (3.2)	product of -PO_3Et_2 group fragmentation	$[DH]^+$	84 (100)	-
-	56 (5.1)	$[H\text{-}C(O)\text{-}N$=$CH]^+$	-	65 (2.1)	product of -PO_3Et_2 group fragmentation
-	-	-	-	56 (4.0)	$[H\text{-}C(O)\text{-}N$=$CH]^+$

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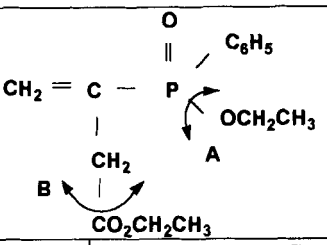
TABLE VI

Mode of fragmentation and principal ions in the mass spectrum of compound 7



Ion	m/z (intensity, %)	Comments
$[MH]^+$	283 (2.0)	protonated molecular ion
$[M]^+$	282 (12.6)	isotopic peak
-	253 (3.5)	isotopic peak minus ethyl group
A	237 (23.8)	-
B	209 (100)	-
-	185 (12.6)	CH_3-P(OH)(OEt)C_6H_5
-	157 (11.2)	CH_3-P(OH)$_2C_6H_5$
-	141 (83.2)	$[HPO_2(C_6H_5)]^+$ fragment
-	125 (7.7)	$[HPO(C_6H_5)]^+$ fragment
-	105 (3.5)	$[CP(OH)(OEt)]^+$
-	77 (42.6)	-C_6H_5
-	67 (8.4)	H_4PO_2

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