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Amino acids as suitable N-nucleophiles for the aza-Michael reaction of vinylphosphoryl compounds in water

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ABSTRACT

Application of water as a sole solvent promotes the aza-Michael reaction of diethyl vinylphosphonate and diphenylvinylphosphine oxide with α-substituted amino acid sodium salts generated in situ to afford the corresponding β-aminophosphonates and β-aminophosphine oxides in excellent yields and of high purity. The approach is equally suitable for the synthesis of both racemic and optically active compounds. In the case of glycine, the mono and bis(phosphonoethyl)-substituted products are formed in 6:4 ratio and when using a stoichiometric amount of the reactants, *N,N*-bis[2-(diethoxyphosphoryl)ethyl]glycine was the only product. In contrast, to perform the double phosphonoethylation of D,L-alanine, prolonged heating of the reaction mixture was required.

Both natural and synthetic aminophosphonic acid derivatives, being analogues of amino acids and competing with them for the active sites of enzymes, possess diverse biological activity which depends on the length of the alkyl chain between the phosphorus and nitrogen atoms and their substituents.[1] N-substituted amino acids and peptides bearing a terminal phosphorus moiety are also of interest in medicinal chemistry due to their valuable bioactivities. Thus, Phosphoramidon (isolated from *Actynomyces*) is effective as a metalloprotease inhibitor[2] and N-nucleoside phosphoramidates possess antitumor[3] or antiviral[4] properties. Among hydrolytically stable *N*-phosphonomethyl amino acids and peptides, *N*-(phosphonomethyl)glycine,[5] used worldwide as a herbicide, is a well known example. Furthermore, a number of compounds of this type demonstrate collagenase inhibiting properties,[1] antibacterial (alafosphalin or L-alanine-L-1-aminoethylphosphonic acid)[6] or antihypertensive[7] properties (CGS 24592). Recently, α-aminophosphonates obtained from cognitive function enhancing oligopeptides as the amine component were suggested as potential 'twin-drugs'.[8] Moreover, in view of the growing interest in new antagonists of excitatory amino acids which are involved in the pathology of a number of neurodegenerative disorders and epilepsy, a series of *N*-phosphonoalkyl-, -alkenyl,- and -arylglycines was tested on an NMDA (*N*-methyl-D-aspartate) competitive antagonist pharmacophore model.[9] In this case, the high receptor affinity was dictated by correct juxtaposition of the key NH_2, COOH, and $P(O)(OH)_2$ functions.

2-Aminoethylphosphonic acid (AEP) was the first identified natural phosphonate isolated from celiate protozoa by Horiguchi and Kandatsu[10] in 1959 and found also in numerous marine animals, coelenterates, flagellates, fungi, and even in the human body (in particular, in the human brain, heart, kidney, liver, intestine, spleen, adrenal glands, and aorta),[11] where it is primarily present in lipids (phosphonolipids), proteins, and polysaccharides, and its various derivatives possess diverse biochemical properties.[1b,11] Therefore, it can be suggested that *N*-phosphonoethyl modified amino acids or the corresponding peptidylphosphonates may be interesting as potential drug candidates. However, in contrast to the rather well developed area of *N*-phosphonomethyl substituted amino acids, publications on this topic are few in number. Thus, as early as 1979 the desired compounds were obtained in 43–65% estimated and 13–16% isolated yields via the aza-Michael addition of amino acid esters to diethyl vinylphosphonate in the presence of sodium ethanolate in EtOH by Issleib et al.[12] According to Bigge's report,[9] the reaction of glycine methyl ester hydrochloride and diethyl 2-bromoethylphosphonate in the presence of triethylamine provided the mixed ethyl–methyl ester of phosphonoethylated glycine (the yield was not given) which was transformed via an acidic hydrolysis into the corresponding tris-acid hydrochloride being a perspective NMDA antagonist. Later on, a similar strategy but using potassium carbonate (4 equiv) and an excess of glycine (4 equiv) in water (80 °C, 3 h) provided *N*-[2-(diethoxyphospho-

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ryl)ethyl]glycine isolated via low-pressure reverse-phase chromatography in quantitative yield.[13] This compound was used as an intermediate in the synthesis of a new type of tetranucleotide III, containing alternating achiral phosphonate (negatively charged) and *N*-ethyleneglycosyl amide (neutral) backbone linkages in dimer units. An alternative approach based on desulfurization of (thiocarbamoylmethyl)phosphonates by nickel boride allowed the corresponding *N*-(phosphonoethyl)-substituted glycine, alanine, and phenylalanine to be obtained in 40–50% yields.[14] In addition, a series of dipeptidyl β-aminophosphoryl compounds, useful as human calpain I inhibitors, was synthesized via a multistep procedure, but these compounds possess an α-keto function, mimicking peptide α-ketoesters and α-ketoacids.[15]

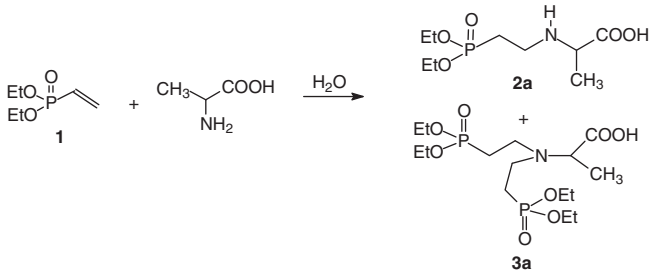
Relevant challenges of modern organic chemistry such as 'atom economy' and the application of 'environmentally friendly conditions' prompted us to improve the synthesis of β-aminophosphoryl compounds via the aza-Michael reaction of vinylphosphoryl compounds.[16,17] It was shown that the application of water as a sole solvent (without any catalyst or co-solvent) significantly accelerated the reaction and provided excellent yields, independently of the water-solubility of the starting substrate (in water or on-water reactions[18]), both of β-aminophosphonates possessing diverse biochemical properties such as antibacterial, anti-HIV, and protease-inhibiting activities,[19] and useful as synthetic nonviral vector-mediated gene transfer agents,[20] and the related β-aminophosphine oxides, exhibiting coordination properties towards a variety of metals.[21] These compounds also found applications as ligands for ruthenium-assisted enantioselective transfer hydrogenation of ketones[22] or building-blocks in the synthesis of *P,N*-ligands bearing phosphine donor moieties.[23]

These key points stimulated us to use amino acid derivatives as N-nucleophiles in aqueous aza-Michael reactions with vinylphosphoryl compounds and, in this Letter, we report on an efficient general approach to *N*-(phosphorylethyl)amino acids opening up the possibility of the facile, rapid, and cheap synthesis of these potential drug candidates.

In contrast to primary and secondary alkylamines, free amino acids do not react with vinylphosphoryl compounds in water in the absence of a catalyst even at elevated temperature, as was demonstrated in a model reaction of D,L-alanine and the water-soluble vinylphosphonate **1** (Table 1, entries 1,2). Such reduced reactivity of the free acid is connected with the formation of zwitterionic species. Using tertiary amines in catalytic amounts (10 mol % Et_3N, $^iPr_2NEt$, or 5 mol % DMAP) triggers the reaction, however, it stopped at a conversion level of ~30%, apparently due to the establishment of the equilibrium with participation of free D,L-alanine and **2a**, and their zwitterionic species formed in the presence of the tertiary amine. In these cases, the ^{31}P NMR spectra of the reaction mixtures demonstrated singlets at ca. δ 29 ppm and δ 33 ppm (approximately in 20:8 ratio) corresponding to the zwitterionic form of **2a** and its ammonium salt, along with the signal of the starting compound **1** at δ 17.2 ppm (Table 1, entries 3–5).

Complete conversion was observed over 24 h at rt when the proportion of tertiary amine (Et_3N) was increased up to 1 mol equiv. At that point, the ^{31}P NMR spectrum of the reaction mixture revealed a separated singlet at ~δ 29 ppm and two closely located signals at ca. δ 33.5 ppm in 18:78:4 ratio. These resonances were assigned to the zwitterionic form of **2a** and the corresponding ammonium salts **2a** and **3a**, respectively. Note that an increase in the reaction temperature up to 100 °C resulted in quantitative conversion in 3 h, however, the proportion of the double phosphonoethylation product **3a** also increased to 15% (Table 1, entry 7). A multinuclear NMR analysis of the crude products obtained by lyophilization of the reaction mixtures (entries **6** and **7**) revealed that the desired phosphorylated alanine **2a** was present as a mixture of the corresponding zwitterion and the salt with the starting amino acid, in a 3:1 ratio along with contamination due to compound **3a**. Isolation of the pure product via column chromatography (SiO_2, EtOH–NH_4OH = 70:30) proceeded with substantial loss of the product that was isolated as the ammonium salt.

Table 1
Aza-Michael reactions of diethyl vinylphosphonate **1** and D,L-alanine in water

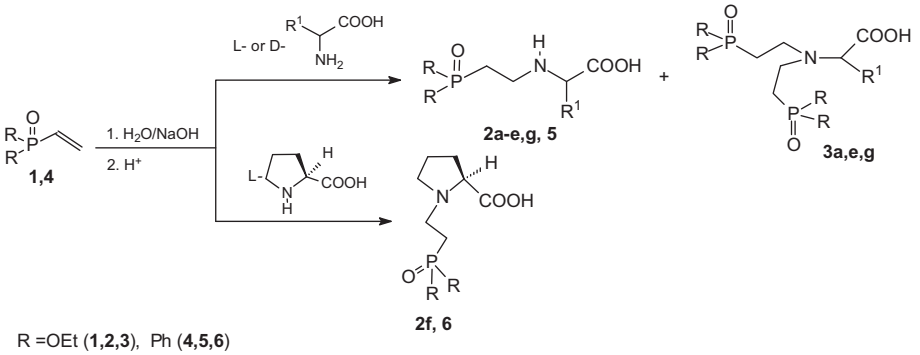


Entry	Base/Amount	Temperature (°C)	Time (h)	Yield[a] (%)		
				1	**2a**	**3a**
1	None	20	24	100	–	–
2	None	100	3	100	–	–
3	Et_3N/10 mol %	20	72	70	30	–
4	$^iPr_2NEt$/10 mol %	20	72	67	33	–
5	DMAP/5 mol %	20	72	69	31	–
6	Et_3N/1 equiv	20	24	0	96	4
7	Et_3N/1 equiv	100	3	0	85	15
8	$NaHCO_3$/1 equiv	20	24	100	–	–
9	K_2CO_3/1 equiv	20	24	62	38	–
10	NaOH/1 equiv	20	5	33	67	–
11	NaOH/1 equiv	20	20	5	95	–
12	NaOH/1 equiv	20	48	0	94	6

[a] Estimated yield according to ^{31}P NMR spectroscopic data.

Searching for a more convenient procedure to provide high conversion rates and easy isolation of the desired products we tested inorganic bases in this reaction. The screening revealed that the addition of the amino acid to vinylphosphonate **1** did not proceed in the presence of $NaHCO_3$ (1 equiv) and the reaction rate was much lower compared with that in the presence of Et_3N when K_2CO_3 was used as the base (38% conversion over 24 h at rt). At the same time, addition to vinylphosphonate **1** of the D,L-alanine sodium salt generated in situ under the action of NaOH proceeded readily under ambient conditions with a reaction rate comparable with that in the presence of Et_3N and provided an excellent yield of the *N*-[2-(diethoxyphosphoryl)ethyl]alanine **2a** sodium salt isolated via simple lyophilization of the reaction mixture (94% purity according to the ^1H and ^{31}P NMR spectroscopic data, 6% of **3a–Na** was present as the only impurity).

After optimization of the procedure, other substituted racemic and optically active L- or D-amino acids were used in reaction with **1** in the presence of NaOH to afford the corresponding sodium salts in excellent yields (Scheme 1). The above-mentioned side-reaction of double phosphonoethylation of D, L-alanine was observed also in the reaction of **1** with aspartic acid and in that with glycine. In the first case, the side product **3e** was formed in a negligible amount (5%, NMR-estimated yield) while in the case of glycine the proportions of mono and diphosphonoethylated products **2g–Na** and **3g–Na**, respectively, were comparable to each other (6:4). In other words, the nucleophilic properties of glycine sodium salt are close to those of *N*-[2-(diethoxyphosphoryl)ethyl]glycine, **2g–Na**. Indeed, when the reactants were used in a stoichiometric ratio, bis(phosphorylethyl)-substituted glycine sodium salt **3g–Na** was formed as the sole product (the ^{31}P NMR spectrum demonstrated a singlet at ca. δ 33.4) and the corresponding free acid **3g** was isolated in high yield after acidification (see ESI for experimental details). Alternatively, the presence of an α-substituent in the



Scheme 1. Aza-Michael addition of amino acids to vinylphosphoryl compounds.

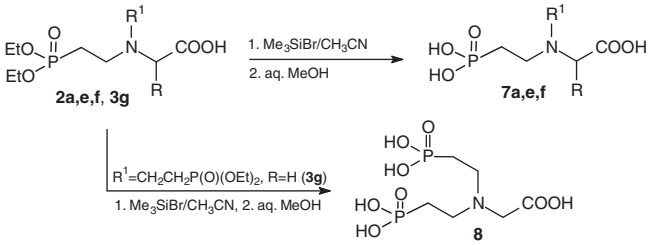
amino acid inhibited the double phosphonoethylation. Thus, it required 2 days at 70 °C to achieve an 85% conversion in the reaction of D,L-alanine and vinylphosphonate **1** used in a 1:2 ratio.

The reactivity of the amino acid sodium salts decreased along the series proline > alanine ≈ glycine > phenylalanine, that is, the reactivities were similar to those found for the addition of amines to vinylphosphoryl compounds in water, that is, secondary amines were more reactive than primary ones and additional steric hindrance decreased the reaction rate.[16,17] It should be noted that the addition of amino acids can be performed in water also for the water-insoluble diphenylvinylphosphine oxide **4**, however, in this case elevated temperatures were used to reduce the reaction time.

The final products were isolated in high yields as the corresponding sodium salts via lyophilization of the crude reaction mixtures. It should be emphasized that despite the fact that diethyl phosphonates are inclined to partial hydrolysis to monoesters if the reaction proceeds in the presence of sodium hydroxide, we did not observe such a process under the reaction conditions employed and the singlet chemical shifts in the ^{31}P NMR spectra and integral intensities in the ^{1}H NMR spectra of the crude products isolated via lyophilization, confirmed these observations.

Alternatively, these salts can be transformed into the corresponding free acids **2a**–**g**, **3a**,**g**, **5**, and **6** via acidification with HCl, removal of the water in vacuo, and treatment of the residue with ethanol to remove the precipitated sodium chloride.[24] Naturally, for such a transformation it is more convenient to use the crude reaction mixtures rather than the isolated sodium salts. However, under this work-up procedure, some product loss was observed due to the limited solubility of the products in their zwitterionic form in EtOH and, in some cases, the corresponding free acids were isolated as strong complexes with the residual NaCl which could be removed by repeated recrystallization. Therefore, the application of cation exchange chromatography (Dowex 50WX8) was found to be the most convenient procedure for the isolation of the phosphorylated free amino acids as stable hydrates.

The products were white hygroscopic solids. Their rather high melting points as well as the presence in their IR spectra of absorption bands at 1609–1626 cm^{-1} which are characteristic[25] for an ammonium species $>NH_2^+$ are indicative of the zwitterionic structures of **2a**–**g**, **5**, and **6**. Since the chiral carbon atom of the amino acid is not affected during the reaction, using optically active starting materials, the sodium salts and the corresponding *N*-[2-(diethoxyphosphoryl)ethyl]-amino acids were obtained in optically pure form. The pattern of CD spectra of the products **2a**–**f** is similar to those observed for the corresponding amino acids and their optical rotation values (see ESI) confirm this supposition.



2a, **7a**: R^1= H, R=CH$_3$; **2e**, **7e**: R^1 = H, R = CH$_2$COOH; **2f, 7f:** R^1, R = (CH$_2$)$_3$

Scheme 2. Synthesis of free *N*-(2-phosphonoethyl)amino acids.

Finally, β-aminophosphonates **2a**–**g** could be easily converted into free phosphonic acids via treatment with Me_3SiBr in acetonitrile followed by methanolysis of the intermediate silyl esters (Scheme 2) as was exemplified by the synthesis of the mono(phosphonoethylated) amino acids **7a**,**e**,**f**, and the bis(phosphonoethylated) glycine **8**. This procedure is convenient, as a typical acidic hydrolysis resulted either in partial decomposition of the product via a retro-addition affording the parent amino acid in the case of concentrated HCl or proceeded very slowly (3 equiv 6 N HCl, 24 h, 75%).

In conclusion, using water to accelerate the aza-Michael reaction for vinylphosphoryl compounds, even for those that are insoluble in water, we have developed an effective procedure for the synthesis of *N*-(2-diethoxyphosphonoethyl)-amino acids and their analogues with phosphine oxide moieties using racemic or optically active amino acids as the *N*-nucleophiles. Excluding the reaction with glycine, where the products of mono and double phosphonoethylations were formed in similar amounts, the sodium salts of α-substituted amino acids were formed in near quantitative yields. The sodium salts could be further used either in solution in water or in a pure form after removal of the water for further synthetic procedures, or transformed into the corresponding free acids. This cheap and green approach represents a straightforward procedure to a range of biologically active drug candidates or complexing agents.

Acknowledgments

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Supplementary data

Supplementary data (detailed experimental procedures including the syntheses, physicochemical data, and full NMR assignments for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.111.

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24. *N*-[2-(Diethoxyphosphoryl)ethyl]- and *N*-[2-(diphenylphosphoryl)ethyl]-amino acids (**2a**–**f**, **5**,**6**) (*general procedure*): (a) *Sodium salts*: a mixture of diethyl vinylphosphonate **1** (0.41 g, 2.5 mmol) or diphenylvinylphosphine oxide **4** (0.57 g, 2.5 mmol), the corresponding amino acid (2.5 mmol), and NaOH (0.10 g, 2.5 mmol) in H_2O (5 ml) was stirred either under ambient conditions (for the reaction of **1**) or at reflux (in the case of **4**). The reaction was completed in 2 h in the case of proline (both for **1** and **4**), 10 h (reaction of L-methionine and **4**), 72 h for the reaction of **1** and L-phenylalanine and 48 h for the reaction of vinylphosphonate **1** with other amino acids. The corresponding sodium salts were isolated as white hygroscopic powders by lyophilization of the crude reaction mixture. (b) *Free acids*: After completion of the reaction, the mixture was acidified with 5.4 N HCl (0.46 ml, 2.5 mmol) in H_2O (2 ml) and then concentrated to dryness under reduced pressure. The residue was dissolved in EtOH (10 ml), precipitated NaCl was filtered, and the filtrate was concentrated in vacuo and dried over P_2O_5 to give the crude final products. If necessary, the products were additionally purified by recrystallization or precipitation. Otherwise, the reaction mixture was loaded onto a Dowex 50WX8-H^+column and eluted with EtOH–NH_4OH = 7:3. The fraction from the cation exchange column was evaporated to the dryness, dissolved in MeOH, and the final acid precipitated with Et_2O.
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