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A convenient method for the one-step synthesis of phosphonic peptides

Marcin Skoreński, Józef Oleksyszyn, Marcin Sieńczyk *

Division of Medicinal Chemistry and Microbiology, Faculty of Chemistry, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland

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ABSTRACT

A novel and efficient method for the synthesis of peptidyl derivatives of 1-aminoalkylphosphonate diaryl esters is presented. Phosphonic peptides were obtained in one step via an amidoalkylation reaction using amides of N-protected amino acids or peptides, triphenyl phosphite, and an appropriate aldehyde.

α-Aminoalkylphosphonate diaryl esters and their peptidyl derivatives compose a group of potent, irreversible, and highly selective inhibitors that exclusively react with the active site of serine proteases, examples of which include human neutrophil elastase, cathepsin G, dipeptidyl peptidase IV, and chymase.[1] Previous reports have described the usefulness of these compounds to target serine proteases of viruses[2] and bacteria, including proteases with a non-canonical catalytic triad.[3] In general, the elongation of aminophosphonates with peptide chains increases significantly their inhibitory potency toward target proteases, thus the most active derivatives of this class reported to date contain a peptide sequence structurally optimized for specific protease binding.[4] One of the greatest advantages of α-aminoalkylphosphonate aromatic esters over other classes of inhibitors such as peptide aldehydes, chloromethyl ketones, ketoesters, or ketoamides is their complete lack of reactivity with cysteine, threonine, and metalloproteinases.[5]

The method for the synthesis of simple Cbz-protected α-aminoalkylphosphonate diphenyl esters was first reported by Oleksyszyn et al., where triphenyl phosphite underwent an amidoalkylation reaction with benzyl carbamate and an appropriate aldehyde in acetic acid.[6] Several modifications of this reaction have since been reported including the addition of acetic anhydride or acetyl chloride.[7] Methods for the preparation of α-aminoalkylphosphonate diphenyl esters under mild conditions including the application of Lewis acids as catalysts have been developed.[8] Despite the variety of these methods, all require carbamates, thiocarbamates, or ureas as a reaction substrate.[9]

Although several methods for the synthesis of α-aminoalkylphosphonate diaryl esters have been reported in the literature, the synthesis of their peptidyl derivatives relies, to a great extent, on the stepwise (a successive deprotection-coupling sequence) synthesis in solution.[3] This approach can be limited; for example, incorporation of an amino acid containing a functional side chain requires a challenging use of protecting groups. One solution to overcoming these restrictions is the separate synthesis of the peptidyl fragment followed by coupling to a 1-aminoalkylphosphonate diaryl ester.[10] The ideal solution would be the application of α-aminoalkylphosphonate diaryl esters in solid phase peptide synthesis. Unfortunately, despite extensive research, this method has yet to be developed. An attempt to use α-aminoalkylphosphonate diaryl esters in solid phase synthesis was reported by Haemers et al., but this method did not incorporate elongation of the peptidyl chain.[11] Two interesting approaches for the synthesis of phosphonic peptides have been reported. The first method to convert amino acids or peptides into their corresponding phosphonic analogues is based on the oxidative decarboxylation, either electrochemical or with lead tetraacetate, followed by reaction with trialkyl or triaryl phosphite in the presence of $TiCl_4$.[12] The second method, reported only for the preparation of alkyl esters, involves the degradation of amino acids or dipeptides to bromo derivatives via the Hunsdiecker reaction, followed by a reaction with sodium diethyl phosphite.[13] Although the electrochemical oxidative decarboxylation approach via the formation of *N*-acyl-*N*,*O*-acetals is a very efficient method for the

* Corresponding author. Tel.: +48 71 320 2439; fax: +48 71 320 2427.
E-mail address: marcin.sienczyk@pwr.wroc.pl (M. Sieńczyk).

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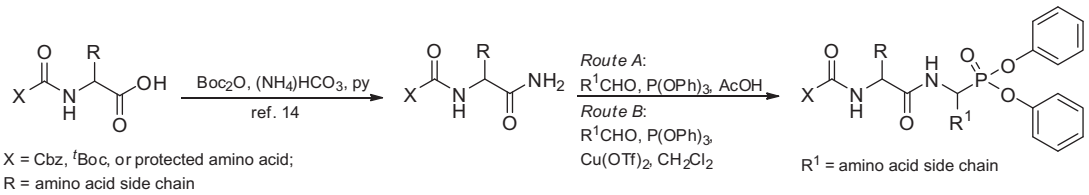


Scheme 1. The general synthesis of peptidyl derivatives of α-aminophosphonate diphenyl esters from N-protected amino acid or peptide amides—routes A and B.

Table 1
Yields and products obtained via amide-based amidoalkylation

Product	Formula	Isolated yield (%)	
		Route A	Route B
1	Cbz-Pro-Ala^{P}(OPh)$_2$	4	25
2	Cbz-Pro-Leu^{P}(OPh)$_2$	15	38
3	Cbz-Pro-Phg^{P}(OPh)$_2$	8	31
4	Cbz-Ala-Ala^{P}(OPh)$_2$	9	11
5	Cbz-Ala-nVal^{P}(OPh)$_2$	15	30
6	Cbz-Ala-Leu^{P}(OPh)$_2$	19	36
7	Cbz-Phe-Ala^{P}(OPh)$_2$	7	19
8	Cbz-Phe-Leu^{P}(OPh)$_2$	12	31
9	Cbz-Phe-nVal^{P}(OPh)$_2$	8	16
10	^{t}Boc-Abu-Gly-Leu^{P}(OPh)$_2$	<4%	26
11	Cbz-Val-Pro-Val^{P}(OPh)$_2$	<4%	16
12	Cbz-Val-Pro-nVal^{P}(OPh)$_2$	<4%	29
13	Cbz-Val-Pro-Leu^{P}(OPh)$_2$	<4%	29
14	Cbz-Val-Pro-Ala^{P}(OPh)$_2$	<4%	11
15	Cbz-Val-Pro-Abu^{P}(OPh)$_2$	<4%	19
16	Cbz-Val-Pro-Phe^{P}(OPh)$_2$	<4%	19
17	Cbz-Val-Pro-hPhe^{P}(OPh)$_2$	<4%	31
18	Cbz-Phe-Pro-Val^{P}(OPh)$_2$	<4%	12
19	Cbz-Phe-Pro-Leu^{P}(OPh)$_2$	<4%	24
20	Ac-VFLLAla^{P}(OPh)$_2$	<4%	18
21	Ac-VFLLLeu^{P}(OPh)$_2$	<4%	26
22	Ac-PVFLLAla^{P}(OPh)$_2$	<4%	15
23	Ac-PVFLLLeu^{P}(OPh)$_2$	<4%	21

synthesis of phosphonic diaryl ester derivatives, it requires access to specialized electrochemical equipment that may limit its broader application.

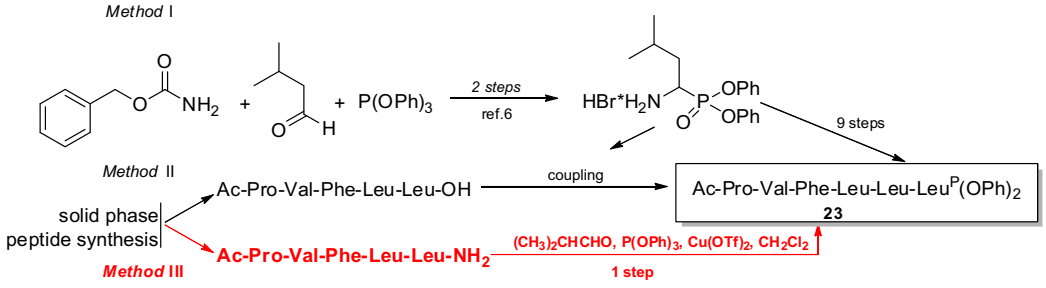
Herein we present a novel method for the synthesis of phosphonic peptides using amides of N-protected amino acids or peptides as the starting substrates.

The general synthetic approach is outlined in Scheme 1. The starting amides of N-protected amino acids or dipeptides were prepared using ammonium hydrogen carbonate in the presence of pyridine and di-*tert*-butyl dicarbonate (Boc_2O) according to a previously described procedure.[14] In the next step an amidoalkylation reaction was performed either following the conditions of the original Oleksyszyn protocol (Scheme 1, route A), or a modified procedure under mild conditions using copper(II) triflate as the catalyst (Scheme 1, route B). The peptides used in this study were prepared by SPPS on Rink amide resin using HBTU in the presence of DIEA as the coupling agent. Fmoc deprotection was performed using 20% piperidine/DMF solution. Peptides were cleaved from the resin with TFA/H_2O/TIPS (95:2.5:2.5, v/v) and used in the next step without any further purification.

An amidoalkylation of simple N-protected amides of amino acids resulted in the formation of phosphonic dipeptides **1**–**9**, with higher yields being obtained when the synthesis followed route B (11–38%, Table 1). The preparation of tripeptides **10**–**19** as well as polypeptides **20**–**23** required milder reaction conditions (Route B) since the amidoalkylation in acetic acid resulted in poor yields of isolated products (<4%). The one-step preparation of phosphonic peptides was performed with the application of copper(II) triflate in dichloromethane at room temperature. In general, the yields were higher and the products more easily isolated for all the reactions performed under mild conditions with $Cu(OTf)_2$ as the reaction mixture were less complex.

Additionally, we checked to see if any stereoselectivity could be induced when structurally diverse chiral amides were used. Surprisingly, we noticed a 1:1 ratio of both diastereoisomers. This contrasted with the previous report by Oshikawa et al. who observed the formation of an excess of one diastereoisomer when chiral carbamates [(−)-menthyl carbamate; 1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-3,2′-indan)-2-yl carbamate) or chiral ureas ((*R*)-(+)- and (*R*)-(−)-(1-phenylethyl)urea] were used in the amidoalkylation reaction.[15]

In comparison to the classical approach to phosphonic oligopeptide synthesis in solution, our amide-based method presents a clear advantage. The standard synthesis of Cbz-Val–Pro-Phe^{P}(OPh)$_2$ (**16**) in solution requires five steps, whereas in our amide-based protocol the target peptide can be synthesized in a single step from the corresponding protected dipeptide amide Cbz-Val–Pro-NH_2. Moreover, when the synthesis of longer phosphonic peptides is required [Ac-PVFLLLeu^{P}(OPh)$_2$, **23**], peptide amides can be prepared simply on a solid support followed by a modified amidoalkylation reaction with triphenyl phosphite and the appropriate aldehyde (Scheme 2, method III). This also represents an improvement on the classical three-step protocol where the peptide synthesized by SPPS is next coupled to a deprotected 1-aminoalkylphosphonate diaryl ester (Scheme 2, method II). When we compared the yield of Ac-VFLLLeu^{P}(OPh)$_2$ (**21**) synthesized by the three approaches, we determined that the most efficient methods were II and III (approx.



Scheme 2. Different approaches for the synthesis of peptide derivatives of α-aminoalkylphosphonate diphenyl esters.

25% and 26% yields, respectively, with the assumption of 100% yield for the starting peptide synthesis on solid support), whereas the total yield using method I was estimated not to exceed 5%.

In addition, an amide-based amidoalkylation procedure can be used successfully for combinatorial applications. By using a mixture of aldehydes, two or four phosphonic peptides were obtained in one reaction mixture (see Supplementary data). Such an approach can be used for combinatorial screening of serine proteases with a preference for an optimal peptidyl inhibitor P1 residue.

In conclusion we have demonstrated a novel method for the one-step synthesis of peptidyl derivatives of α-aminoalkylphosphonate diphenyl esters. Importantly, this procedure allows for the preparation of short peptidyl derivatives and can be used successfully to synthesize longer phosphonic peptides in a single step, even when peptide labile side protecting groups are present. The target compounds were obtained in good to moderate yields. Our results suggest a combinatorial application of this method and further research on this subject will be published in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.049.

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