Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2023, **33**, 784–785

Mendeleev Communications

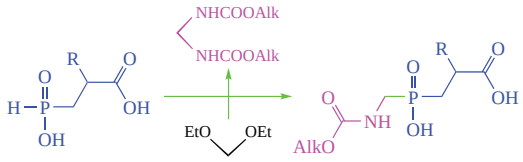
N + PC strategy for the synthesis of phosphinic pseudopeptides incorporating glycine isostere

Sofia R. Golovash, Alexey V. Borodachev, Maxim E. Dmitriev and Valery V. Ragulin*

Institute of Physiologically Active Compounds, Federal Research Center of Problems of Chemical Physics and Medicinal Chemistry, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax: +7 496 524 2650; e-mail: rvalery@dio.ru

DOI: 10.1016/j.mencom.2023.10.015

The reaction between dialkyl methylenebiscarbamates and phosphonous carboxylic acids affords N-protected phosphinic pseudopeptides incorporating glycine isostere. The compounds obtained are promising building blocks for subsequent peptide modification.



Keywords: phosphinic pseudopeptides, dialkyl methylenebiscarbamates, phosphonous carboxylic acids, glycine isostere, amidoalkylation.

Phosphinic pseudopeptides are the structural isosteres of natural peptides (Figure 1), in the molecules of which two amino acid components are linked by Zn-chelating $CH_2P(O)(OH)$ fragment that mimics the peptide C(O)NH bond in the transition state of peptide hydrolysis with tetra-coordinated carbon atom.[1–3] Therefore, phosphinic peptides are potent inhibitors of matrix metalloproteinases, which are a family of Zn-containing endoproteases involved in diverse biological processes.[4–6]

The currently prevailing strategy for the synthesis of phosphinic pseudodipeptides is based on the studies of the Ciba-Geigy company[7,8] devoted to methods for the synthesis of N,P-protected building blocks being the phosphonous isosteres of natural amino acids. The Michael–Pudovik addition of the latter to the corresponding N,P-substituted acrylates (NP + C approach) leads to the target phosphinic pseudopeptides.[2–4] However, the construction of an aminoalkylphosphonous N,P-diprotected block for the subsequent synthesis of the peptide is at least a four-step process, which is caused by the necessity of protection and deprotection at the phosphorus $\{P–CH(OEt)_2\}$ and nitrogen atoms.[7,8]

Synthesis of the phosphinic pseudopeptides containing glycine structural isostere is additionally complicated by the difficulty of using formaldehyde, existing in polymer form or in the form of an aqueous solution, which is usually incompatible with the employed synthetic procedure. Its synthetic equivalent, trimer of special formaldehyde Schiff base, 1,3,5-tris(diphenylmethyl)hexahydro-*s*-triazine, was proposed as a key building block for the synthesis of the phosphonous NP-component containing glycine isostere.[9] However, this approach also leads to an increase in the staging of the proposed synthetic scheme.

In the present report, to solve this problem, we propose a general synthesis of difficult-to-access phosphinic pseudopeptides incorporating glycine isostere by reversing the order for the construction of desired molecule.[10–12] The development of the N + PC methodology for the synthesis of pseudopeptides **1** by the reaction between phosphonous carboxylic diacids **2** and dialkyl methylenebiscarbamates **3** is described here (Scheme 1). Diacids **2** represent PC-component of the synthetic scheme, while compounds **3** being formaldehyde aminals would serve as a source of N-protected glycine 'tail'.

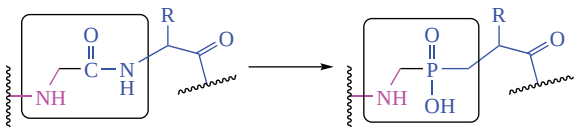


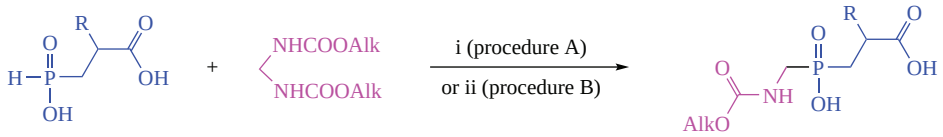
Figure 1 Example of replacement of glycylamido part in peptides by its phosphinic isostere.

The reactivity of phosphonous carboxylic diacids is noticeably higher than that of analogous esters, which is explained by the formation of highly reactive mixed phospho-carboxylic anhydrides (phospholactones).[12] Herein, isosteres of glycine (**2a**, R = H), alanine (**2b**, R = Me), leucine (**2c**, R = Bu^i), aspartic (**2d**, R = CH_2COOH) and glutamic [**2e**, R = $(CH_2)_2COOH$] acids were used in the form of the free carboxylic acids (see Scheme 1).

In this study, we also propose the convenient synthesis of dialkyl methylenebiscarbamates **3** by transacetalization of diethyl formal with two equivalents of the corresponding alkyl carbamate in acetic anhydride (Scheme 2). We have found that a near-optimal reaction requires at least two equivalents of trifluoroacetic acid (TFA) in solution. The obtained biscarbamates **3** are not acid stable, therefore the reaction should be carried out: (*a*) with slow addition of TFA to a stirred mixture of alkyl carbamate and formal, and (*b*) with a relatively short time (no more than 3–5 h).

It should be noted that we previously published a single example of the reaction between biscarbamate **3c** and ester of phosphonous acid **2c**, the obtained N-protected peptide (ethyl ester) was not isolated but was converted into free amino phosphinic acid by hydrolysis.[13] Nevertheless, a general approach to the synthesis of difficult-to-access N-protected phosphinic pseudopeptides incorporating glycine isostere is urgently needed for the development of subsequent peptide synthesis of phosphinic tripeptides, powerful inhibitors of Zn-metalloproteinases.[1–4]

An initial attempt to perform mild amidoalkylation of phosphonous carboxylic acids **2a**–**e** using dialkyl methylenebiscarbamates **3a**–**c** and one equivalent of trifluoroacetic anhydride (TFAA) in dichloromethane in accordance with the previously proposed procedure[11] was ineffective. Methylene-



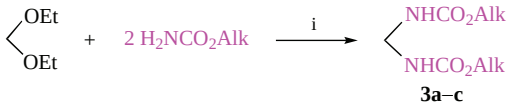
2a–e **3a–c** **1a–h** (yields, %, A/B)

2a R = H
2b R = Me
2c R = Bu^i
2d R = CH_2COOH
2e R = $(CH_2)_2COOH$

3a Alk = Me
3b Alk = Et
3c Alk = Bn

1a Alk = Bn, R = H (43/76)
1b Alk = Et, R = Me (n.d./63)
1c Alk = Bn, R = Me (29/67)
1d Alk = Me, R = Bu^i (46/71)
1e Alk = Et, R = Bu^i (58/68)
1f Alk = Me, R = CH_2COOH (n.d./51)
1g Alk = Bn, R = CH_2COOH (42/n.d.)
1h Alk = Et, R = $(CH_2)_2COOH$ (n.d./55)

Scheme 1 *Reagents and conditions*: i, EtOAc, $(CF_3CO)_2O$ (2–4 equiv.), room temperature (procedure A); ii, AcCl Ac_2O (2 : 1), ~5 → 20 °C (procedure B).



3a–c

a Alk = Me
b Alk = Et
c Alk = Bn

Scheme 2 *Reagents and conditions*: i, Ac_2O, CF_3CO_2H (2–2.2 equiv.), room temperature.

biscarbamates **3** were surprisingly less reactive than substituted alkane-1,1-diylbiscarbamates used earlier.[11] We have found that replacing dichloromethane with ethyl acetate improves the efficiency of this approach (procedure A) and provides yields of 29–58% (see Scheme 1). However, the use of stronger dehydration and acylation conditions created by the AcCl/Ac_2O mixture (procedure B) makes it possible to achieve noticeably better results. In addition, this procedure is experimentally simpler and more convenient.

Obtained pseudopeptides, N-protected α-amino phosphinic acids **1a–h,** are the mixtures of conformers which may be associated with the presence of a chiral carbon atom and amide nitrogen in the molecule.

In summary, we proposed a convenient general strategy for the synthesis of previously unknown N-protected phosphinic pseudopeptides **1** incorporating glycine isostere.

This paper is dedicated to the memory of Nikolay S. Zefirov (1935–2017).

The synthesis and study of compounds reported in the paper was financially supported by the Russian Science Foundation (grant no. 23-23-00158).

Online Supplementary Materials

Supplementary data associated with this article (synthesis and characterization of compounds **1a–h**, **2a–e** and **3a–c**, copies of their NMR spectra, and HRMS for **1a–h**) can be found in the online version at doi: 10.1016/j.mencom.2023.10.015.

References

1 M. Matziari, K. Bauer, V. Dive and A. Yiotakis, *J. Org. Chem*., 2008, **73**, 8591.
2 A. Mucha, *Molecules*, 2012, **17**, 13530.
3 D. Georgiadis and V. Dive, *Top. Curr. Chem*., 2015, **360**, 1.
4 S. Vassiliou, E. Węglarz-Tomczak, Ł. Berlicki, M. Pawelczak, B. Nocek, R. Mulligan, A. Joachimiak and A. Mucha, *J. Med. Chem*., 2014, **57**, 8140.
5 P. Kokkala, T. Rajeshkumar, A. Mpakali, E. Stratikos, K. D. Vogiatzis and D. Georgiadis, *Org. Lett*., 2021, **23**, 1726.
6 M. Hori and K. Nishida, *Cardiovasc. Res*., 2009, **81**, 457.
7 E. K. Baylis, C. D. Campbell and J. G. Dingwall, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2845.
8 P. P. McCleery and B. Tuck, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1319.
9 J. Buchardt, M. Ferreras, C. Krog-Jensen, J.-M. Delaisse, N. T. Foged and M. Meldal, *Chem. – Eur. J*., 1999, **5**, 2877.
10 V. V. Ragulin, L. F. Rozhko, I. W. Saratovskikh and N. S. Zefirov, *Patent JP 2001213887*, 2001.
11 M. E. Dmitriev and V. V. Ragulin, *Tetrahedron Lett.*, 2012, **53**, 1634.
12 M. E. Dmitriev, S. R. Golovash, A. V. Borodachev and V. V. Ragulin, *J. Org. Chem*., 2021, **86**, 593.
13 M. E. Dmitriev and V. V. Ragulin, *Russ. J. Gen. Chem*., 2013, **83**, 1888 (*Zh. Obshch. Khim*., 2013, **83**, 1681).

Received: 19th June 2023; Com. 23/7195