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Acetals in amidoalkylation of phosphonous carboxylic diacids

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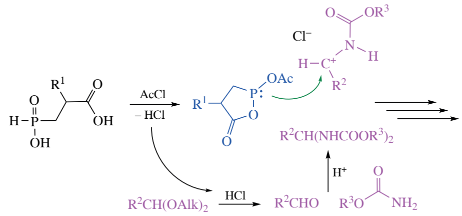
The use of free phosphonous carboxylic diacids in three-component carbamate version of the Kabachnik–Fields reaction in acetyl chloride medium allows introducing acetals into the reaction sphere to result in phosphinic peptides. The employment of low-stable and functionally substituted aldehydes in the form of acetals provides phosphinic peptides that are difficult to obtain by other methods.



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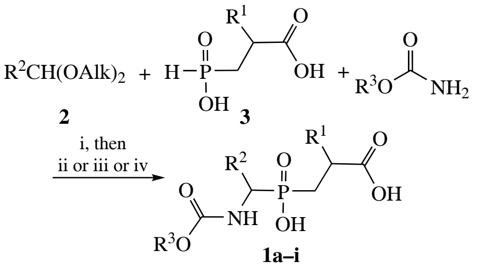
Aldehydes are widely applied in many chemical reactions, but in some cases this application is limited due to the high volatility of their lower homologs. The use of formaldehyde is also limited because of its existence in polymeric form or as an aqueous solution. Some aldehydes, such as phenylacetaldehyde, have high CH acidity and can enter into side reactions. In this regard, the idea of replacing aldehydes with their acetals is promising.

In this work we studied the use of acetals in the three-component Kabachnik–Fields reaction. We developed a carbamate version of this reaction with the aim of constructing an *N*-protected α-amino phosphorylic function in the molecules of phosphinic pseudopeptides **1** (Scheme 1). In these compounds, the natural peptide NHC(O) bond in the dipeptide part is replaced by a non-hydrolyzable methylenephosphorylic $CH_2P(O)OH$ moiety which links two amino acid components in the molecule of the resulting phosphinic isostere of the dipeptide.[1–3] In this case, conditions are created for a very close imitation of the transition state of peptide hydrolysis with a tetracoordinated carbon atom.[3–5] Therefore, phosphinic peptides are potent inhibitors of matrix metalloproteinases representing a family of Zn-containing endoproteases involved in a variety of biological processes.[6–10]

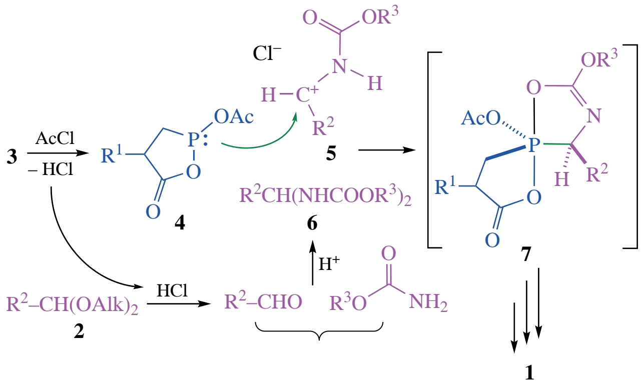


1a $R^1 = R^2 = H$, $R^3 = Bn$, 29% (ii)
1b $R^1 = R^3 = Me$, $R^2 = Bn$, 58% (ii), 43% (iii)
1c $R^1 = Me$, $R^2 = CH_2CO_2Et$, $R^3 = Bn$, 67% (ii), 45% (iii)
1d $R^1 = Bu^i$, $R^2 = H$, $R^3 = Et$, 34% (ii)
1e $R^1 = Bu^i$, $R^2 = Bn$, $R^3 = Me$, 54% (ii)
1f $R^1 = R^2 = Bn$, $R^3 = Et$, 48% (ii)
1g $R^1 = Bn$, $R^2 = R^3 = Me$, 65% (ii), 43% (iii)
1h $R^1 = CH_2CO_2H$, $R^2 = Me$, $R^3 = Bn$, 59% (iv)
1i $R^1 = CH_2CO_2H$, $R^2 = CH_2CO_2Et$, $R^3 = Bn$, 67% (iv)

Scheme 1 *Reagents and conditions*: i, AcCl, room temperature, 2–20 h; ii, EtOAc–H_2O, then crystallization; iii, EtOAc–H_2O, then column chromatography; iv, C_6H_6–H_2O, isolation from the aqueous phase.

Previous attempts to replace aldehydes with the corresponding acetals **2** under acidic catalysis in acetic anhydride in the amidoalkylation of phosphonous acids **3** were unsuccessful.[11,12] The relatively mild conditions of acid catalysis (trifluoroacetic or *p*-toluenesulfonic acids) in acetic anhydride did not allow a positive result to be achieved.[12] In this regard, the replacement of aldehydes and carbamates with pre-synthesized dialkyl alkylidene biscarbamates in the Kabachnik–Fields reaction is a successful approach in the synthesis of *N*-protected α-amino phosphorylic compounds.[11,12] The more severe conditions for amidoalkylation of phosphonous acids **3** in acetyl chloride medium look favorable for the use of acetals and the generation of aldehydes. However, in this case, a partial dealkylation of the carboxylic ester in the phosphinic peptide molecule is observed leading to the mixture of ester and acidic forms of the formed phosphinic peptides.[13,14] Therefore, phosphonous acids containing the isostere of the corresponding amino acid in the form of a carboxylic ester in the amidoalkylation procedure were replaced by free phosphonous carboxylic diacids.[15,16]

Surprisingly, we found a noticeable acceleration of the reaction, which is explained by the formation of a highly reactive intermediate, a mixed phospho-carboxylic anhydride (phospha lactone) **4** with a tricoordinated phosphorus atom (Scheme 2).[15] The latter acts as a nucleophile and is directly involved in the formation of the P–C bond as a result of nucleophilic attack of the acyliminium cation **5** (see Scheme 2) and the probable formation of an unstable spirobicyclic intermediate, spirophosphorane **7**, which we hypothesized earlier.[15]



Scheme 2

As also shown earlier, the source of generation of the electrophilic component of the reaction, highly reactive acyliminium cation **5**, is dialkyl alkylidene biscarbamate **6**, a relatively stable reaction intermediate that is easily formed during the interaction of an aldehyde and carbamate (see Scheme 2).[11–16] It is important to note that in both cases the process is catalyzed by dry hydrogen chloride, which is formed during the acetylation and dehydration of phosphonous carboxylic diacid **3** with the generation of phospha lactone **4**.[15] We believe that the participation of acetals in the formation of phosphorus–carbon bonds in the process under study can occur according to Scheme 2.

Thus, sufficiently favorable conditions are created for introducing acetals into the reaction with *in situ* generation of the corresponding aldehydes. We studied formaldehyde diethyl acetal, acetaldehyde diethyl acetal, phenylacetaldehyde dimethyl acetal, and ethoxycarbonylacetaldehyde diethyl acetal (general formula **2**) in the amidoalkylation of phosphonous carboxylic diacids **3** containing the structural isostere of glycine (R = H), alanine (R = Me), leucine (R = Bu^i), phenylalanine (R = Bn), and aspartic acid (R = CH_2COOH) in acetyl chloride medium (see Scheme 1).[†] We found that under these conditions, aldehydes are generated from the corresponding acetals forming the desired *N*-protected phosphinic peptides **3a–i** in yields of 43–67%. The lower yields were observed in cases of more stable formaldehyde diethyl acetal: 29% for **1a** and 34% for **1d**. This was confirmed by ^{31}P NMR spectroscopy data when the content of the target products (δ_P ~ 40–50) in the reaction mixture was not higher than ~50–55%.

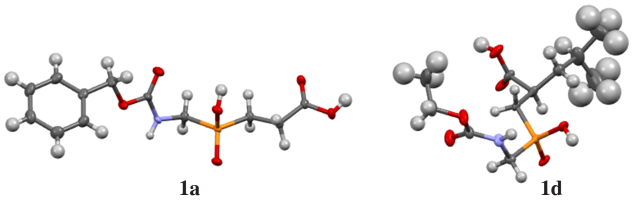


Figure 1 Molecular structure of **1a** and **1d** based on X-ray diffraction.

The use of acetals of acetic and phenylacetic aldehydes gives good results and makes it possible to prepare phosphinic peptides containing N-terminal isosteres of alanine (**1g**,**h**) and phenylalanine (**1b**,**e**,**f**) in yields of 48–65% (see Scheme 1). As functionally substituted acetal, we took ethoxycarbonylacetic aldehyde acetal, which allowed us to construct an isostere of the N-terminal aspartate component (in the form of ethyl ester) in the molecule of the resulting phosphinic peptide. In this manner, phosphinic peptides **1c** and **1i** were isolated in 67% yields.

The structures of compounds **1a** and **1d** were confirmed by the X-ray single crystal diffraction (Figure 1).[‡] The data on their molecular and crystal structure, H-bond network in crystals and H-bond distances are given in Online Supplementary Materials.

In conclusion, an effective procedure for amidoalkylation of free phosphonous carboxylic diacids **3** using dialkyl acetals **2** in acetyl chloride at room temperature is proposed. The potential of this approach lies in the possibility of using low-stable and functionally substituted aldehydes in the form of acetals, which opens access to hard-to-reach and new phosphinic peptides.

Dedicated to the memory of Anatoly A. Petrov (1913–1992).

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7650.

[†] *Phosphinic peptides* **1a–i** *(general procedure, see Scheme 1, step i).* The corresponding acetal **2** (1.1–1.2 mmol) was slowly added dropwise to freshly prepared solution of the corresponding phosphonous carboxylic diacid **3** (1.0 mmol) and alkyl carbamate (1.0 mmol) in acetyl chloride (5–6 ml) at room temperature. The resulting mixture was stirred for 2 to 20 h (^{31}P NMR monitoring). After completion of the reaction, chloroform (5 ml) was added and the mixture was evaporated *in vacuo*.

Isolation of **1a–g** *(step ii).* The residue was partitioned between ethyl acetate and water (3–5 : 1). The precipitated unreacted alkyl carbamate was filtered off, and the organic part of filtrate was evaporated *in vacuo*. The wet residue was treated with diethyl ether and left for a while. Usually, the phosphinic peptides were isolated as white solids. The exceptions are **1a** and **1d**, which were isolated by silica gel column chromatography (chloroform–2-propanol, 2→10%). The eluate was evaporated *in vacuo*, the residue crystallized spontaneously or after treatment with diethyl ether.

Alternative isolation of **1b**,**c**,**g** *(step iii).* The residue obtained after *in vacuo* evaporation of the organic phase (see step ii) was subjected to column chromatography (chloroform–2-propanol, 2→10%). The eluate was concentrated *in vacuo* when the residue crystallized spontaneously or after treatment with diethyl ether.

Isolation of **1h**,**i**. The residue was partitioned between benzene and water (1 : 5). The precipitated carbamate was filtered off, and the aqueous part of the filtrate was additionally washed with benzene and then evaporated *in vacuo*. The wet residue was treated with light petroleum (40–70) and left for a while. Then the light petroleum was decanted from a semi-crystalline residue, which was tritutated with diethyl ether to afford phosphinic peptides **1h**,**i** as solids.

[‡] *Crystal data for* **1a**. $C_{12}H_{16}NO_6P$, M_r = 301.23, space group $P2_1/c$, at 120 K, a = 30.000(1), b = 4.8905(2) and c = 9.4021(4) Å, β = 94.638(4)°, V = 1374.9(1) Å^3, Z = 4, d_{calc} = 1.455 g cm^{-3}, R_1 = 0.0471 [for 2371 reflections with $2\theta < 52°$ and $I > 2\sigma(I)$ from 2673 unique reflections], wR_2 = 0.1325, GOF = 1.101.

Crystal data for **1d**. $C_{11}H_{22}NO_6P$, M_r = 295.27, space group $P2_1/n$, at 120 K, a = 14.6797(5), b = 5.7170(2) and c = 19.4331(8) Å, β = 105.737(4)°, V = 1569.8(1) Å^3, Z = 4, d_{calc} = 1.249 g cm^{-3}, R_1 = 0.0549 [for 3380 reflections with $2\theta < 56°$ and $I > 2\sigma(I)$ from 3732 unique reflections], wR_2 = 0.1272, GOF = 1.05.

The experiments were performed on a STOE diffractometer equipped with an Image Plate detector and Oxford Cryosystems Cryostream cooler [λ(MoKα) = 0.71073 Å, graphite monochromator, φ-scans].

Data reduction with empirical absorption correction of experimental intensities (Scale3AbsPack program) was made with a CrysAlisPro software, the structures were solved by a charge flipping method using Superflip program.[17] All non-hydrogen atoms were refined anisotropically by a full-matrix least squares method using SHELX-2018 program.[18]

CCDC 2334586 (**1d**) and 2334587 (**1a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

References

1 V. Dive, D. Georgiadis, M. Matziari, A. Makaritis, F. Beau, P. Cuniasse and A. Yiotakis, *Cell. Mol. Life Sci.*, 2004, **61**, 2010; https://doi.org/10.1007/s00018-004-4050-y.

2 M. Matziari, K. Bauer, V. Dive and A. Yiotakis, *J. Org. Chem.*, 2008, **73**, 8591; https://doi.org/10.1021/jo8014215.

3 A. Mucha, *Molecules*, 2012, **17**, 13530; https://doi.org/10.3390/molecules171113530.

4 D. Georgiadis and V. Dive, *Top. Curr. Chem.*, 2015, **360**, 1; https://doi.org/10.1007/128_2014_571.

5 M. Talma, M. Maślanka and A. Mucha, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 1031; https://doi.org/10.1016/j.bmcl.2019.02.034.

6 *Zinc Metalloproteases in Health and Disease*, ed. N. M. Hooper, CRC Press, London, 1996; https://doi.org/10.1201/9781482272765.

7 M. Whittaker and A. Ayscough, *Celltransmissions*, 2001, **17**, 3; https://www.sigmaaldrich.com/deepweb/assets/sigmaaldrich/marketing/global/documents/970/949/celltrans17_1.pdf.

8 B. Pirard and H. Matter, *J. Med. Chem.*, 2006, **49**, 51; https://doi.org/10.1021/jm050363f.

9 A. Mucha, P. Kafarski and Ł. Berlicki, *J. Med. Chem.*, 2011, **54**, 5955; https://doi.org/10.1021/jm200587f.

10 M. Hori and K. Nishida, *Cardiovasc. Res.*, 2009, **81**, 457; https://doi.org/10.1093/cvr/cvn335.

11 M. E. Dmitriev and V. V. Ragulin, *Russ. J. Gen. Chem.*, 2012, **82**, 1882; https://doi.org/10.1134/S107036321211028X.

12 M. E. Dmitriev and V. V. Ragulin, *Tetrahedron Lett.*, 2012, **53**, 1634; https://doi.org/10.1016/j.tetlet.2012.01.094.

13 L. F. Rozhko and V. V. Ragulin, *Amino Acids*, 2005, **29**, 139; https://doi.org/10.1007/s00726-005-0194-9.

14 M. E. Dmitriev and V. V. Ragulin, *Tetrahedron Lett.,* 2010, **51**, 2613; https://doi.org/10.1016/j.tetlet.2010.03.020.

15 M. E. Dmitriev, S. R. Golovash, A. V. Borodachev and V. V. Ragulin, *J. Org. Chem.*, 2021, **86**, 593; https://doi.org/10.1021/acs.joc.0c02259.

16 S. R. Golovash, A. V. Borodachev, M. E. Dmitriev and V. V. Ragulin, *Mendeleev Commun.*, 2023, **33**, 784; https://doi.org/10.1016/j.mencom.2023.10.015.

17 L. Palatinus and G. Chapuis, *J. Appl. Crystallogr.*, 2007, **40**, 786; https://doi.org/10.1107/S0021889807029238.

18 G. M. Sheldrick, *Acta Crystallogr.*, 2015, **C71**, 3; https://doi.org/10.1107/S2053229614024218.

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