Tetrahedron 74 (2018) 975–986

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Perfluorophenyl phosphonate analogues of aromatic amino acids: Synthesis, X-ray and DFT studies

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ARTICLE INFO

Article history:
Received 11 December 2017
Received in revised form
5 January 2018
Accepted 9 January 2018
Available online 12 January 2018

Keywords:
Fluorinated aminophosphonates
Phenylglycine
Homophenylalanine
Amino acids
DFT calculations
X-ray analysis

ABSTRACT

Novel perfluorophenyl phosphonate analogues of phenylglycine and homophenylalanine were prepared in good to excellent yields, and subjected to solid state characterization by single-crystal X-ray diffraction analysis, and to investigations with the use of DFT methods.

The α-aminophosphonates have a big potential for biological activity, and through S_NAr reactions may give an entrance to further structurally variable analogues of both amino acids.

1. Introduction

α-Aminophosphonic acids and their derivatives constitute a class of compounds that are currently attracting interest due to their wide spectrum of biological activities and pharmacological properties.[1–3] Among the large family of α-aminophosphonates, various α-amino-phosphonoesters of type **1** (Fig. 1) exhibited anticancer (**1a**),[4,5] (Fig. 1) antioxidant,[5] antibacterial,[6] antimicrobial,[7] anti-protozoal,[8] and antiviral[9] activities. The biological activity of α-aminophosphonates can be explained by their structural similarity to the corresponding amino-acid derivatives in which the planar carboxylic group is replaced by tetrahedral phosphorus-containing moiety. The tetrahedral geometry of the phosphonate group can be considered as a bioisostere of the high-energy transition state of ester[10,11] or amide[12,13] bond hydrolyses. Therefore α-aminophosphonates can act as enzyme inhibitors.[14,15] Moreover, they are peptide mimetics.[16] The importance of α-aminophosphonates is reflected in a variety of existing synthetic approaches. However, surprisingly limited attention was paid to the synthesis of fluorine bearing phosphorus analogues of amino acids.[17] Combination of fluorine atoms with α-aminophosphonates offers opportunity to modulate physicochemical and biological properties, and to greatly improve the metabolic stability of the resulting molecules.[18–20] Presence of fluorine atoms can enhance compound lipophilicity, and improve the binding affinity to the target protein.[21–23] The exploitation of fluorine containing molecules has become an important strategy in protein biochemistry because it affords novel mechanism for molecular recognition.[24–27] Replacement of amino acids with their fluorinated analogues is shown to have application in studying amino acid interactions within the protein fold.[28,29] These interactions can be tracked with ^{19}F NMR spectroscopy also in living systems.[30]

Among the procedures affording α-aminophosphonates, the three-component Kabachnik-Fields reaction is an easily implemented synthetic approach. Consequently, it is the method of choice.[31–35] We initially used this procedure as well as its variations including syntheses under microwave irradiation, under solvent-free conditions, and with application of different catalysts however, none of the attempts resulted in the formation of desired fluorinated products. Therefore we built our synthetic protocol on preparation of aldimine followed by a hydrophosphonylation step

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https://doi.org/10.1016/j.tet.2018.01.019
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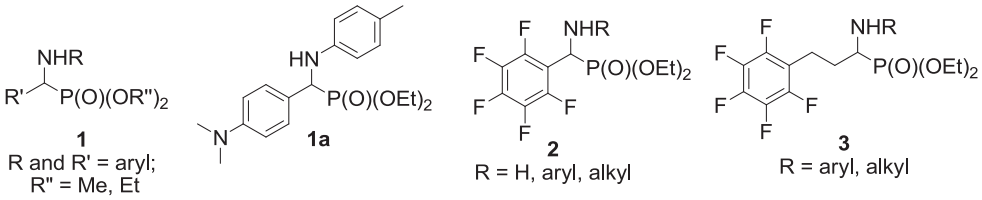
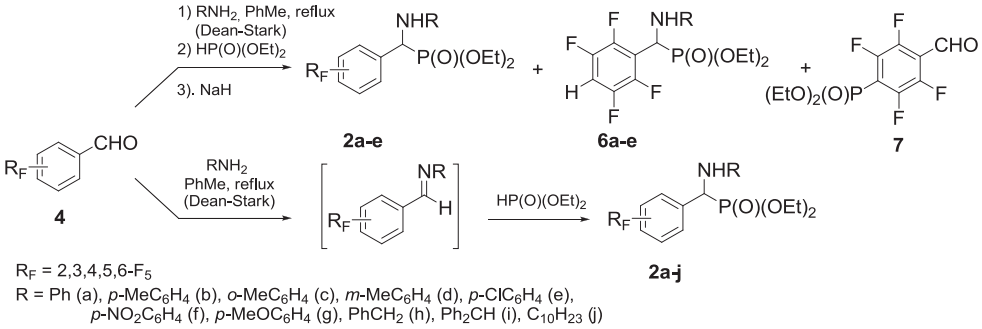


Fig. 1. α-Aminophosphonates of type **1**, targeted perfluorinated phosphono-phenylglycine **2** and homophenylalanine **3**.



Scheme 1. Products formed by reactions of 2,3,4,5,6-pentafluorobenzaldehyde **4** with anilines and diethyl phosphite in the presence of NaH, and formation of perfluorophenyl phosphonate analogues of phenylglycine **2a-j**.

to afford novel perfluorophenyl phosphonates of type **2** and phospha homophenylalanine analogues of type **3** (Fig. 1).

Structures of the obtained perfluorophenyl phosphonate analogues of phenylglycine and homophenylalanine were studied in details by spectroscopic, crystallographic and computational methods. Such an approach provided valuable information in regard to preferable conformation, hydrogen bonds as well as other interactions present in the crystals investigated.

2. Results and discussion

2.1. Synthesis of α-aminophosphonates *2a-2j*

Preparation of perfluorinated α-aminophosphonates **2** and **3** was planned by applying a *one-pot* two step synthesis carried out under thermal conditions from commercially available 2,3,4,5,6-pentafluorobenzaldehyde **4** or from the prepared 3-(2,3,4,5,6-pentafluorophenyl)propanal **5** as starting materials.

At the outset, a modified strategy was investigated for the preparation of α-aminophosphonates **2**, by the use of sodium hydride with diethyl phosphite to form *in situ* the phosphite anion. Nevertheless, preliminary reactions performed with aniline, toluidines and *p*-chloroaniline led to the formation of the expected aminophosphonates **2a-e** along with a mixture of side-products **6a-e** and **7** (Scheme 1).

Structures of the side-products **6a-e** were proposed based on detailed analyses of MS, ^{19}F NMR and ^{31}P{/^{1}H} NMR spectra obtained for partially separated reaction mixtures. The resulted data are presented in Table 1.

The analyzed mas spectra besides the signals derived from protonated molecular ions of compounds **6a-e**, showed fragment ions signals corresponded to the loss of HP(O)(OEt)$_2$ from [M+H]$^+$. In the ^{19}F NMR spectra signals consistent with structures of para substituted in the fluorophenyl rings derivatives were observed. Formation of tetrafluoro α-aminophosphonate derivatives **6a-e** was likely due to a nucleophilic aromatic substitution of fluorine atom in para position of **2a-e** by hydride ion derived from NaH used as a base in the upper branch of reactions in Scheme 1, for deprotonation of diethyl phosphite but it acted also as nucleophile attacking fluorinated ring of the synthesized α-aminophosphonate. Similarly, phosphonate **7** was the result of the phosphite anion nucleophilic attack on the unreacted pentafluorobenzaldehyde **4**. To avoid these side-reactions, procedure without the base was then applied. Aminophosphonates **2a-j** were produced in good to excellent yields

Table 1
Spectrometric and spectroscopic data obtained for **6a-e**.

Side-product	MS *m/z*	^{19}F NMR δ [ppm][a]	^{31}P{/^{1}H} NMR δ [ppm][a]
6a	[M+H]$^+$ 392 [M+H-(HP(O)(OEt)$_2$)]$^+$ 254	−138.47 (s, 2F), −142.86 to −142.98 (m, 2F)	18.94–18.88 (m)
6b	[M+H]$^+$ 406 [M+H-(HP(O)(OEt)$_2$)]$^+$ 268	−133.11 to −133.20 (m, 2F), −138.55 (s, 2F)	19.05–18.99 (m)
6c	[M+H]$^+$ 406 [M+H-(HP(O)(OEt)$_2$)]$^+$ 268	−132.01 to −132.12 (m, 2F), −141.28 to −141.41 (m, 2F)	19.09–19.03 (m)
6d	[M+H]$^+$ 406 [M+H-(HP(O)(OEt)$_2$)]$^+$ 268	−131.81 to −131.94 (m, 2F), −141.06 to −141.19 (m, 2F)	18.98–18.92 (m)
6e	[M+H]$^+$ 426 [M+H-(HP(O)(OEt)$_2$)]$^+$ 288	−138.24 (s, 2F), −142.93 to −143.06 (m, 2F)	18.59–18.54 (m)

[a] Spectra performed in $CDCl_3$ for partially separated reaction mixtures.