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Organosilicon based synthesis of new functionalized aminomethylenediphosphonates with moieties of amino acids

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ABSTRACT

The new functionalized aminomethylenediphosphonates with moieties of various amino acids are synthesized via unique reaction of tris(trimethylsilyl) phosphite and *N*-formyl amino acids at the presence of effective catalyst – trimethylsilyl triflate under mild conditions. The further treatment of aminomethylenediphosphonates with the methanol excess resulted in the water-soluble functionalized aminomethylenediphosphonic acids.

1. Introduction

The functionalized organophosphorus derivatives of aminocarboxylic acids and their corresponding peptides are the perspective organophosphorus biomimetics of natural phosphates and amino acids. These compounds are well known structural components of cells such as lipids and proteins. Many of these substances including non-hydrolysable P-C bonds interfere with various biochemical processes and possess a variety of biological activities [1–6]. Several phosphorus containing peptides with proline moieties have attached attention in the capacity of the competitive inhibitors of human immunodeficiency virus protease [7,8].

Also numerous methylenediphosphonic acids and their derivatives present great interest as effective polydentate ligands and biomimetics of natural pyrophosphates with multifactor activity. These compounds with stable P-C-P bonds possess a wide range of biomedical applications. So zoledronic acid as the most successful example is widely used in medicine as well known-drug – regulator of calcium metabolism, and some of the compounds with similar structure are used as effective functionalized antioxidants and cytoprotectors [9–18]. Aminomethylenediphosphonic acids as a subclass of diphosphonic acids are good complexones and effective ligands. So the aminomethylenediphosphonates are excellent chelators for heavy metal detoxification due to their coordination abilities over a broad range of pH [19–25].

However, the aminomethylenediphosphonic acids containing both P-C-P groups and moieties of amino acids are practically unavailable. Thus the search for convenient methods of synthesis of new types of functionalized aminomethylenediphosphonic acid is an area of active study.

Recently we synthesized aminomethylenediphosphonic acid with proline moiety using tris(trimethylsilyl) phosphite [26]. It should be noted that organosilicon synthons with highly reactive Si-O-P groups are widely used for creating of P-C bonds and synthesis of numerous functionalized organophosphorus compounds [27,28]. Also we developed the convenient synthetic methods for preparing of the some aminomethylenediphosphonates via applications of trimethylsilyl esters of trivalent phosphorus acids in organosilicon-mediated synthesis [29–31]. Also we first showed that various formamides reacts readily with tris(trimethylsilyl) phosphite excess

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only in the presence of trimethylsilyl triflate as effective catalyst to give corresponding aminomethylenediphosphonates with *N*-heterocycles moieties in high yield [26].

In this article we synthesized the new aminomethylenediphosphonic acids with moieties of various amino acids directly from available *N*-formyl amino acids which are well-known synthons in the chemistry of amino acids [32–36].

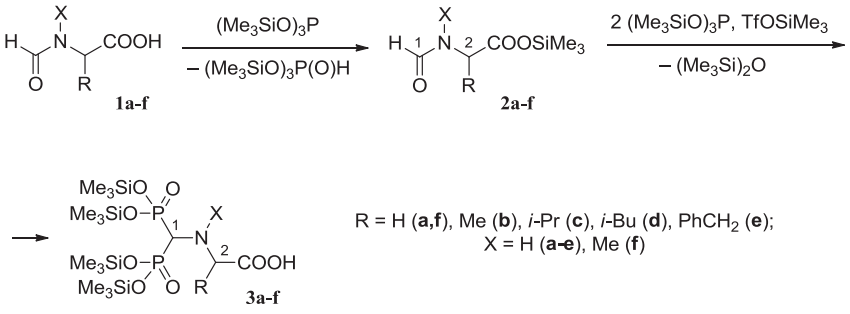
2. Results and discussion

Now we propose the convenient routes to new aminomethylenediphosphonic acids with moieties of various amino acids via reaction of tris(trimethylsilyl) phosphite to easily available *N*-formyl derivatives of amino acids which we obtained by treatment of amino acids with formic acid according to the usual methods described in Refs. [32–35]. We demonstrate that this reaction proceeds only at the presence of effective catalyst – trimethylsilyl triflate under mild conditions to give target diphosphonates **3**. This process is realized by us as one-pot synthesis of target products **3** directly from starting *N*-formyl amino acids and tris(trimethylsilyl) phosphite, but the synthesis of diphosphonates **3** was followed by the trimethylsilylation of starting formamides **1a-f** containing unprotected carboxyl groups with the formation of intermediates – trimethylsilyl esters **2a-f** (Scheme 1).

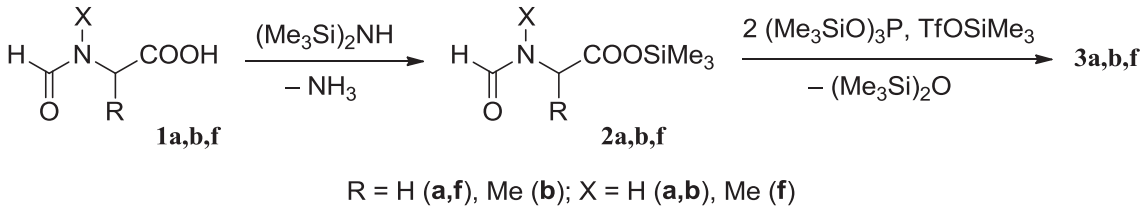
It should be noted that some of these esters **2a,b,f** were specially obtained by us via the interaction of the starting formamides **1a,b,f** and bis(trimethylsilyl)amine, and their further reaction with tris(-trimethylsilyl) phosphite under similar conditions also leads to diphosphonates **3a,b,f** in high yields (Scheme 2).

It is known that trimethylsilyl triflate was successfully used as a catalyst for the activation of double bonds [26,37]. Evidently, in this way the catalytic effect of trimethylsilyl triflate is similarly connected with its ability to generate highly reactive electrophilic carbonio-immonium ions as intermediates in the course of this reaction (Scheme 3).

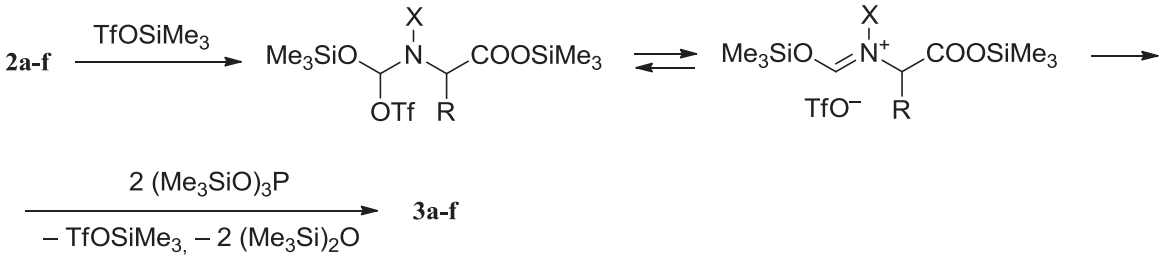
The obtained trimethylsilyl diphosphonates **3** are easily



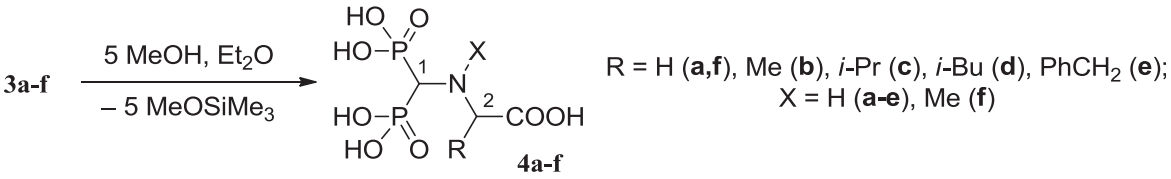
Scheme 1. Synthesis of aminomethylenediphosphonates **3a-f**.



Scheme 2. Synthesis of aminomethylenediphosphonates **3a,b,f** via specially obtained trimethylsilyl esters **2a,b,f**.



Scheme 3. The possible route of formation of aminomethylenediphosphonates **3a-f**.



Scheme 4. Synthesis of aminomethylenediphosphonic acids **4a-f** via methanolysis of corresponding trimethylsilyl diphosphonates **3a-f**.

converted to the corresponding acids **4**. So, trimethylsilyl esters **3** readily react with methanol excess under mild conditions to form water-soluble functionalized aminomethylenediphosphonic acids **4** as white crystals (Scheme 4).

The structures of diphosphonic acids and their precursors **2**–**4** with moieties of amino acids were confirmed by the ^{1}H, ^{13}C, ^{31}P NMR spectra where the characteristic signals of corresponding moieties were observed. The numbers of the carbon atoms used for the description of the ^{1}H, ^{13}C NMR spectra for compounds **2**–**4** in the experimental section are shown in the Schemes 1–4.

3. Conclusions

Summarizing, we have confirmed convenient methods for synthesis of new functionalized aminomethylenediphosphonic acids and their derivatives with various amino acids moieties via the unique reaction of tris(trimethylsilyl) phosphite with *N*-formyl amino acids catalyzed by trimethylsilyl triflate. The resulting compounds are the promising synthons for preparation of functionalized organophosphorus substances with various amino acids and peptides moieties. Also these compounds are the perspective polydentate ligands and biologically active substances with versatile properties.

4. Experimental

The ^{1}H, ^{13}C and ^{31}P NMR spectra were registered on a Bruker Avance-400 spectrometer (400, 100, and 162 MHz, respectively) against TMS as internal standard (^{1}H and ^{13}C) and 85% H_3PO_4 in D_2O as external standard (^{31}P). High resolution mass spectra (HRMS) were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI).

All reactions were carried out under dry argon in anhydrous solvents. The starting tris(trimethylsilyl) phosphite was prepared as described in Refs. [27,28]. The starting *N*-formyl amino acids were prepared as described in Refs. [32–36].

4.1. Trimethylsilyl N-formylglycinate *2a*

A mixture of *N*-formylglycine (0.1 mol, 10.3 g) and bis(-trimethylsilyl)amine (0.2 mol, 33.3 g) was refluxed with stirring until the ammonia evolution ceased. The residue was distilled to obtain 12.6 g of **2a**, yield 72%, bp 112°C (2 mm Hg). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.15 s (Me_3Si), 3.88 d (C^2H_2, $^{3}J_{HH}$ 5.2 Hz), 7.41 br.s (NH), 8.07 s (C^1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: −0.7 s (Me_3Si), 40.6 s (C^2), 161.3 s (C^1), 169.4 s (CO).

Esters **2b,f** were prepared similarly (see supplementary data).

4.2. Trimethylsilyl N-{bis[bis(trimethylsiloxy)phosphoryl]methyl} glycinate *3a*

a. Trimethylsilyl trifluoromethanesulfonate (0.004 mol, 0.89 g), was added under stirring to a mixture of tris(trimethylsilyl) phosphite (0.079 mol, 23.5 g) and *N*-formylglycine **1a** (0.0175 mol, 1.8 g) in methylene chloride (10 mL). The mixture was kept at 20°C for 2 h. The solvent was removed and then an excess of tris(-trimethylsilyl) phosphite and bis(trimethylsilyl) phosphite were distilled off under vacuum of 0.5 mm Hg to obtain 9.8 g of diphosphonate **3a**, yield 92%, thick oil. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: −0.36 s (Me_3Si), −0.32 s (4 Me_3Si), 2.54 t (C^1H, $^{2}J_{PH}$ 20.8 Hz), 3.11 s (C^2H_2). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: −1.7 s (Me_3Si), −0.3 s (4 Me_3Si), 49.7 t (C^2, $^{3}J_{PC}$ 7.2 Hz), 53.7 t (C^1, $^{1}J_{PC}$ 152.3 Hz), 169.9 s (CO). ^{31}P NMR (162 MHz, $CDCl_3$), δ, ppm: 0.7 s. According to the ^{31}P NMR spectrum, the substance contains bis(trimethylsilyl) phosphite, δ, ppm: −13.9 s (3 mol. %). It should be noted that this impurity was converted to phosphorous acid and removed during the synthesis of the corresponding acid **4a** (cf. in Ref. [13]).

Diphosphonates **3b-f** were prepared similarly (see supplementary data).

b. Trimethylsilyl trifluoromethanesulfonate (0.004 mol, 0.89 g), was added with the stirring to solution of tris(trimethylsilyl) phosphite (0.06 mol, 17.9 g) and trimethylsilyl *N*-formylglycinate **2a** (0.02 mol, 3.5 g) in methylene chloride (10 mL). Diphosphonate **3a** (11.5 g, yield 94%), was obtained similarly to example *a*. Diphosphonates **3b,f** were prepared similarly.

4.3. N-(Diphosphonomethyl)glycine *4a*

Methanol (10 mL) was added to solution of diphosphonate **3a** (0.016 mol, 9.8 g) in ether (15 mL) under stirring and cooling to 10°C, The mixture was kept at 20°C for 12 h, then white crystals were filtered, washed with cold ether (10 mL), and kept in vacuum 0.5 mm Hg for 0.5 h to give 4.0 g of acid **4a**, yield 95%, mp 192°C (decomp.). ^{1}H NMR (400 MHz, D_2O), δ, ppm: 3.33 t (C^1H, $^{2}J_{PH}$ 18.4 Hz), 3.75 s (C^2H_2). ^{13}C NMR (100 MHz, D_2O), δ, ppm: 47.1 s (C^2), 52.8 t (C^1, $^{1}J_{PC}$ 126.2 Hz), 168.5 s (CO). ^{31}P NMR (D_2O, 162 MHz), δ, ppm: 7.4 (s). HRMS (ESI), *m/z* $[M\text{-}H]^+$, calcd 248.9764, found 248.9751. Anal. Calcd for $C_3H_9NO_8P_2$ (%): C, 14.47; H, 3.64. Found: C, 14.22; H, 3.68.

Diphosphonic acids **4b-f** were prepared similarly (see supplementary data).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jorganchem.2018.07.007.

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