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

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This article is dedicated to Professor Armando José Latourrette de Oliveira Pombeiro

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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.

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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].

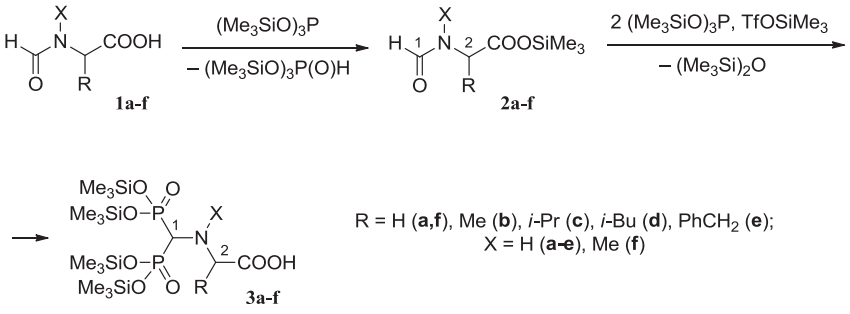
2. Results and discussion

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).

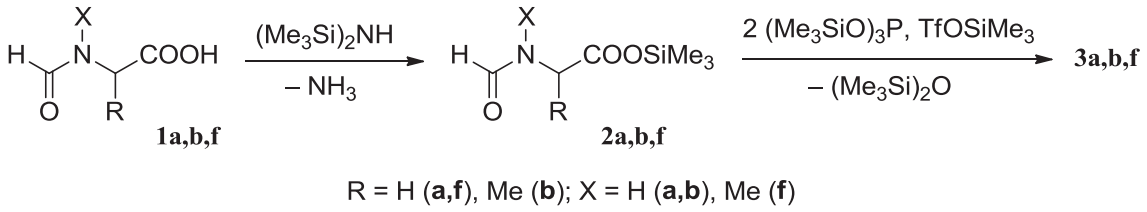
It should be noted that some of these esters **2a,b,f** were specially obtained by us via the interaction of the starting formamides **1a,b,f** and bis(trimethylsilyl)amine, and their further reaction with tris(-trimethylsilyl) phosphite under similar conditions also leads to diphosphonates **3a,b,f**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

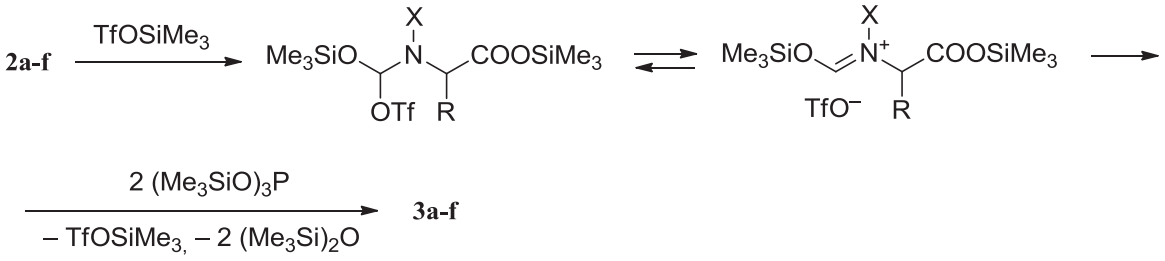
The obtained trimethylsilyl diphosphonates **3** are easily



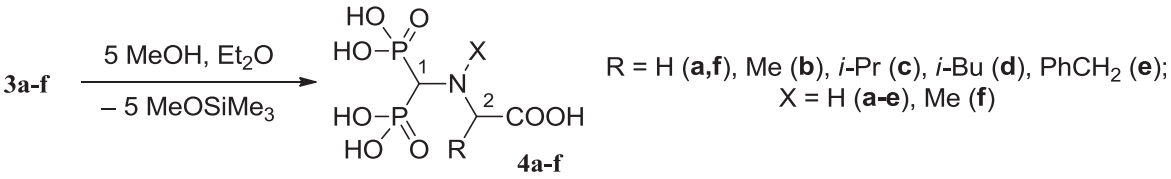
Scheme 1. Synthesis of aminomethylenediphosphonates **3a-f**.



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**.

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