Synthesis of *N*-Phosphoamino Acids with Long Dialkoxy Chains

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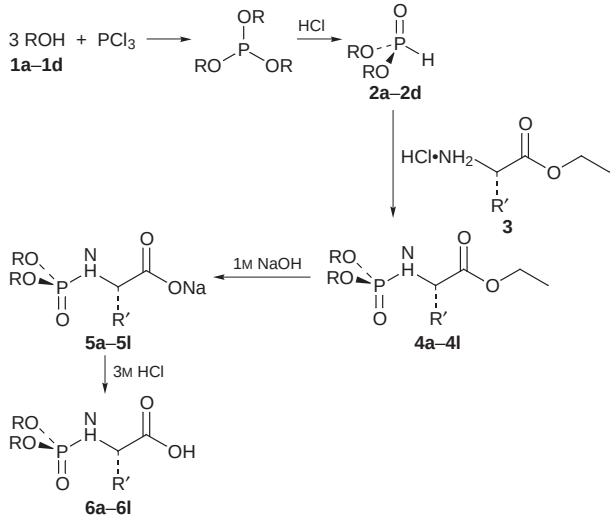
N-phosphoamino acids with long dialkoxy chains are synthesized and spectral data given.

Derivatives of *N*-phosphoamino acids and low-molecular weight peptides are of pharmaceutical interest[1] and several methods for their synthesis are known. In general, esters of the amino acids or peptides were phosphorylated with phosphoryl chloride or with dialkyl or diaryl phosphoro chlorides in non-aqueous solution.[5] Previously, the method of Todd *et al.*[7] has been successfully applied to synthesize *N*-dialkylphosphoryl glycine derivatives in anhydrous media.[8] Zhao *et al.*[8] reported that this reaction can be performed in weakly basic aqueous media in which the amino acids are more soluble. However, up to now, only *N*-phosphoamino acids with short dialkoxy chains have been synthesized by this method.[10,11]

In this paper, a series of *N*-phosphoamino acids with long dialkoxy chains **6** are synthesized in anhydrous media in high yield. The procedure can be described as in Scheme 1.



Scheme 1 Synthesis of *N*-phosphoamino acids with long dialkoxy chains

The synthesis of phosphites with long dialkoxyl chains (compounds **2a**–**2d**) is not very difficult but more attention should be paid to the temperature of the reaction. Because generally alcohol **1** has a high melting point, they should be warmed to the melting point. But too high a temperature will cause the formation of a large amount of by-products. Generally benzene is used as solvent. In this way, four phosphites **2a**–**2d** were synthesized in yields of 90–96%.

The synthesis of *N*-phosphoamino acids with long dialkoxy chains **6** is carried out generally by adding a carbon tetrachloride solution of dialkoxy phosphite **2** to an anhydrous organic mixture consisting of amino acid ester **3**, dichloromethane and triethylamine at 0 °C. The mixture is then stirred at room temperature for three hours before removal of solvent, and the white *N*-phosphoamino acid ester **4** is obtained. After saponifying the ester with 1 M NaOH (**5** is obtained) and acidifying with 3 M HCl, *N*-phosphoamino acid **6** is obtained in the yield 80–95%.

Techniques used: ^{31}P NMR, ^{1}H NMR, ^{13}C NMR, FAB-MS, elemental analysis

References: 12

Table I: Physical data of phosphites **2**

Table II: ^{1}H NMR and ^{13}C NMR data of phosphites **2**

Table III: Synthesis of *N*-phosphoamino acid esters **4** with a long dialkoxy chain

Table IV: FAB-MS, ^{1}H NMR and ^{13}C NMR data of **4h** (DNHP-L-Ala-OC_2H_5)

Table V: ^{31}P NMR data of the sodium salts of *N*-phosphoamino acids **5**

Table VI: Spectral data of **5a** (DEHP-L-Ala-ONa) and **5d** (DNDP-L-Ala-ONa)

Table VII: State, yield, FAB-MS and ^{31}P NMR of *N*-phosphoamino acids **6** with long dialkoxy chains

Table VIII: Elemental analysis data of compounds **6**

Table IX: ^{1}H and ^{13}C NMR data of compounds **6**

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