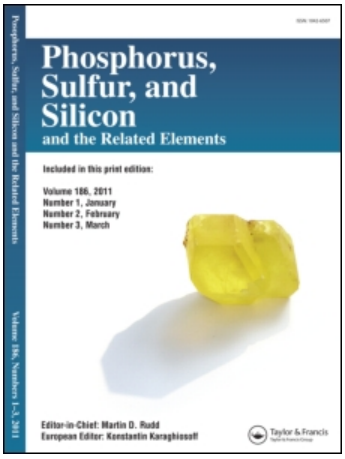

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A Convenient Two-Step One-Pot Synthesis of Alkylthiophosphoramidates Derivatives

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A CONVENIENT TWO-STEP ONE-POT SYNTHESIS OF ALKYLTHIOPHOSPHORAMIDATES DERIVATIVES

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N-thiophosphonylamino groups have been greatly overlooked as potentially potent, transition-state analogues, or tetrahedral—intermediate inhibitors of metalloproteases. Alkylthiophosphoramidates derivatives were synthesized by reaction of O-isopropyl phosphorodichloridothioate with an amino acid ester followed by hydrolysis in 2M NH_4OH. The reaction was monitored by ^{31}P NMR spectroscopy.

Keywords: Alkylthiophosphoramidates derivatives; amino acid ester; hydrolysis; O-isopropyl phosphorodichloridothioate; ^{31}P NMR spectroscopy

INTRODUCTION

The basis for the success of phosphonamidates as inhibitors of zinc metallopeptidases is presumably due to strong interactions of the phosphonyl oxygens with zinc (**II**).[1] Therefore, replacement of the phosphonyl oxygen by ligands which may form more favorable interactions with zinc should enhance the inhibitory potency of such compounds.[2] It is known that sulfur exhibits a high affinity for zinc (**II**), and that complexes with sulfur-containing ligands involve more covalent forces. As a consequence, the metal-ligand bonds in such zinc-sulfur complexes are correspondingly more stable.[3] Therefore simple modifications to the design of phosphonamidates which incorporate a sulfur atom ligand on the central phosphorus could enhance the chelation of the active-site zinc (**II**), thus resulting in enhanced inhibitory potency.[4–5]

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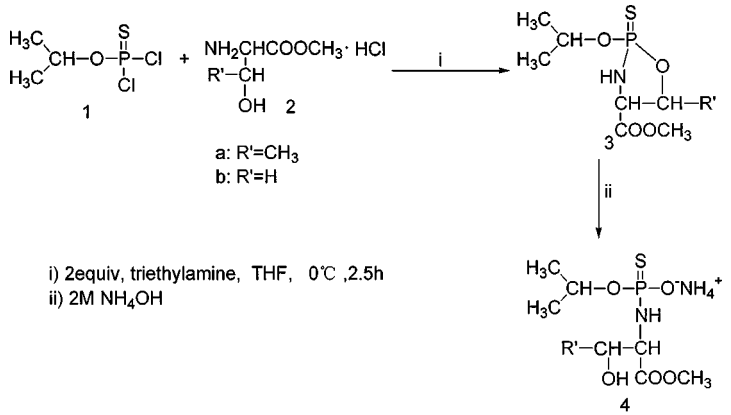
Recently Lu and co-workers had developed a method to synthesize N-phosphonamidothionate derivatives of glutamic acid.[6] The synthesis was a one-pot reaction involving three sequential steps. For example, methylphosphonothioic dichloride was treated with 3-hydroxypropionitrile and glutamic acid dimethyl ester to give the phosphonamidothionate ester. LiOH was used to hydrolyze the ester of the 2-cyanoethyl phosphates. In this paper, a similar pathway focused on utilizing a readily available O-isopropyl phosphorodichloridothioate to react with, serine and threonine methyl ester and then hydrolyzed in aqueous ammonia. In Scheme 1, it was shown that the five membered ring intermediate **3** from the reaction of O-isopropyl phosphorodichloridothioate **1** with amino acid methyl ester **2** without any purification were hydrolyzed immediately in aqueous ammonia. The desired alkylthiophosphoramidates derivatives were obtained.[7]



SCHEME 1 Synthetic pathway of alkylthiophosphoramidates derivatives.

RESULTS AND DISCUSSION

Reaction of amino acid methyl ester (**2**) with O-isopropyl phosphorodichloridothioate (**1**) were performed in THF at 0°C under a nitrogen atmosphere. Triethylamine was added via syringe to the stirred solution. The reaction was monitored by ^{31}P NMR spectroscopy. It was found that O-isopropyl phosphorodichloridothioate (**1**) with a ^{31}P NMR shift at 56.47 ppm was transferred into **3** (83 ppm) within approximately 2.5 h. The reaction mixture was filtered and concentrated in vacuo. After hydrolysis in NH_4OH, **4** were obtained in 91–93% yields by chromatography on a silica-gel column.

Due to the chirality of phosphorus center, N-phosphoramidothionate derivatives **3** were obtained as a mixture of diastereoisomers which

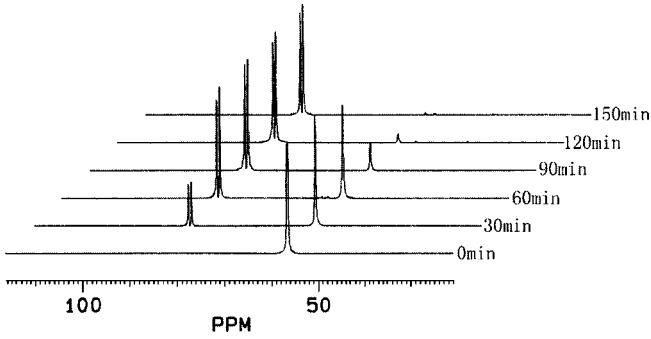
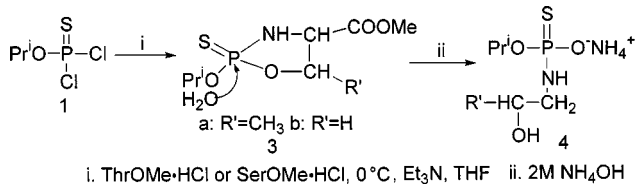


FIGURE 1 The stack ^{31}P NMR spectra of formation of compound **3a**.

yield a pair of peaks at about 83 ppm. For example, the formation of **3a** was followed by ^{31}P NMR spectroscopy as shown in Figure 1. The starting material O-isopropyl phosphorodichloridothioate (**1**) with a signal at 56.47 ppm gradually decreased as the solution of threonine methyl ester hydrochloride and triethylamine were added. At the same time a pair of new peaks at 83 ppm appeared. Triethylamine acted as a catalyst and also captured the hydrochloride acid produced in the reaction. The stacked ^{31}P NMR spectra for the formation of compound **3a** is shown in Figure 1.

Due to the β-OH of threonine, the threonine hydroxyl group was activated by Et_3N to increase its nucleophility to convert the phosphorus into the five membered ring transition state which in turn was hydrolyzed by aqueous ammonia to release the desired N-phosphonamidothionates **4a**. For compound **4b**, a similar reaction mechanism was proposed (Scheme 2).



SCHEME 2 The proposed mechanism of formation of compound **4**.

There was no attempt to isolate the reaction intermediate **3a**. However according to the ESI/MS/MS spectra **3a** existed ([**3a**+Na^+] m/z 276) (Figure 2).

The formation of **4a** was followed by ^{31}P NMR spectroscopy as shown in Figure 2. Compound **3a** with a pair of peaks at about 83 ppm gradually decreased as aqueous ammonia was added. Meanwhile a pair

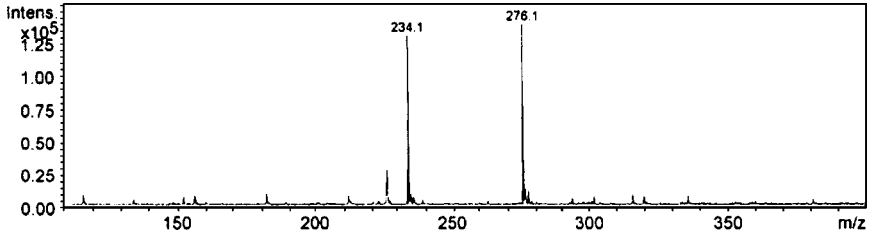


FIGURE 2 Positive ion ESI mass spectrum of intermediate **3a**.

of new peaks at 58 ppm permanently appeared. After 3 h the only pair of peaks at about 58 ppm were observed (Figure 3).

CONCLUSION

In this article a convenient and efficient approach to one-pot synthesis of alkylthiophosphoramidates derivatives under mild conditions has been developed. In the first step the two chloro substituents of O-isopropyl phosphorodichloridothioate are displaced by the amino acid ester to form a five membered ring intermediate. A more detailed investigation into these compounds and their biological activity is currently underway.

EXPERIMENTAL

General Information

All glassware was dried in an oven for at least 3 h at 120°C prior to use. Air sensitive materials were transferred under a nitrogen atmosphere.

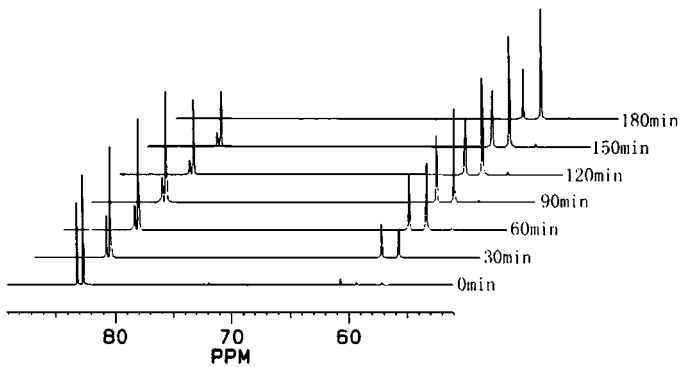


FIGURE 3 The stack ^{31}P NMR spectra of formation of compound **4a**.

THF and triethylamine were dried over Na and CaH_2 respectively. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AM 500 spectrometer. TMS ($\delta = 0.0$) and D_2O ($\delta = 4.80$ ppm) were references for ^1H and ^{13}C NMR spectra respectively. ^{13}C NMR spectra were all taken under ^1H decoupled and ^{31}P coupled conditions. ^{31}P NMR spectra were taken on Bruker AC 200 spectrometer at 81 MHz under ^1H decoupled conditions. ^{31}P NMR chemical shifts are reported in ppm downfield (+) or upfield (−) from external 85% H_3PO_4 as reference. Mass spectra were conducted on Bruker Esquire-LC mass spectrometer operated in positive and negative ion mode.

Synthesis of O-Isopropyl Phosphorodichloridothioate (1) and Amino Acid Methyl Ester Hydrochloride (2)

The preparation of O-isopropyl phosphorodichloridothioate (**1**) and amino acid methyl ester hydrochloride (**2**) were carried out according to the literature.[8,9] All physical constants and spectroscopies data of the products synthesized agreed with the literature.

General Procedure for Synthesis of N-Phosphoramidothionates

A solution of amino acid methyl ester hydrochloride (**2**, 1 mmol) and triethylamine (0.3 mL, 2 mmol) in THF (3 mL) was added via syringe to a stirred solution of O-isopropyl phosphorodichloridothioate (**1**, 0.193 g, 1 mmol) in THF (2 mL) at 0°C under a nitrogen atmosphere. The resulting solution was stirred for 2.5 h. After hydrolysis in NH_4OH, the residue was purified by column chromatography on silica (200–300 mesh, 40 g) with elution by 2-propanol-NH_4OH-H_2O. Pooling and evaporation of appropriate fractions gave the product **4** as a white foam.

Compound **4a** (diastereoisomers): 2-propanol-NH_4OH-H_2O (33:1:1) as eluent ($R_f = 0.76$ for TLC). 0.247 g (yield 91.2%). ^{31}P NMR (D_2O, δ: ppm, J: Hz): δ 59.48, 57.90; ^1H NMR (500MHz, D_2O): δ 4.63 (1H, m, OC*H*Me_2), 4.24 (1H, m, H-β), 3.78 (1H, m, H-α), 3.62 (3H, s, OC*H*$_3$), 1.10–1.30 (9H, m, OCH(C*H*$_3$)$_2$, γ-CH_3); ^{13}C NMR (500MHz, D_2O): δ 176.70 (*C*OOMe), 71.93 (O*C*H(CH_3)$_2$), 68.19 (C-β), 64.23 (O*C*H$_3$), 50.73 (C-α), 25.85 (CH_3), 23.68 (CH_3), 20.11 (C-γ); ESI-MS (pos.): m/z 272 $(M+H)^+$; ESI-MS (neg.): m/z 270 $(M-H)^-$. Anal. Calcd for $C_8H_{18}NO_5PS$: C, 35.42; H, 6.64; N, 5.17. Found: C, 35.29; H, 6.62; N, 5.22.

Compound **4b** (diastereoisomers): 2-propanol-NH_4OH-H_2O (33:1:1) as eluent ($R_f = 0.72$ for TLC). 0.241g (yield 93.3%). ^{31}P NMR (D_2O, δ: ppm, J: Hz): δ 57.8, 56.2; ^1H NMR (500 MHz, D_2O): δ 4.66 (1H,

m, OC*H*Me_2), 3.63 (3H, s, OCH_3), 3.57 (1H, m, H-α), 3.51 (2H, m, H-β), 1.30 (6H, m, OCH(CH_3)$_2$); ^{13}C NMR (500 MHz, D_2O): δ 178.88 (*C*OOMe), 72.44, 72.41 (O*C*H(CH_3)$_2$), 63.10 (C-β), 55.09 (O*C*H_3), 45.80, 45.73 (C-α), 28.63 (CH_3), 26.86 (CH_3); ESI-MS (pos.): m/z 258 $(M+H)^+$; ESI-MS (neg.): m/z 256 $(M-H)^-$. Anal. Calcd for $C_7H_{16}NO_5PS$: C, 32.68; H, 6.23; N, 5.45. Found: C, 32.56; H, 6.21; N, 5.44.

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