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Synthesis of 2-Phosphoro-1,2-thiazetidine 1,1-Dioxide

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ABSTRACT: *The reactions of phosphorochloridites* **5a–c** *with an equimolar amount of 1,2-thiazetidine 1,1-dioxide* **(2)** *or L(−)-3-carboethoxy-1,2-thiazetidine 1,1-dioxide* **(7)** *in the presence of triethylamine, affords the N-phosphitylated β-sultams* **6a–b** *and* **L(−)-8a,c.** *Their oxidation by addition of oxygen, sulfur, or selenium results in formation of stable organophosphorus β-sultams* **10a–b, L(−)-11a,c, 12a, 13a, L(−)-14c,** *and* **L(−)-15c.** © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 61–67, 1999

INTRODUCTION

The four-membered cyclic sulfonamides (1,2-thiazetidine 1,1-dioxides, *β*-sultams) have attracted much interest [1]. These compounds are regarded as sulfonyl analogs of *β*-lactam antibiotics as well as cyclic derivatives of taurine (2-aminoethanesulfonic acid). Taurine, present in mammals, shows various biological activities [2]. The mechanisms of its action are not yet well understood, and the investigation of new model derivatives of taurine, including substituted *β*-sultams, is highly desirable. In addition, *β*-sultams are convenient synthons in heteroatom chemistry [3].

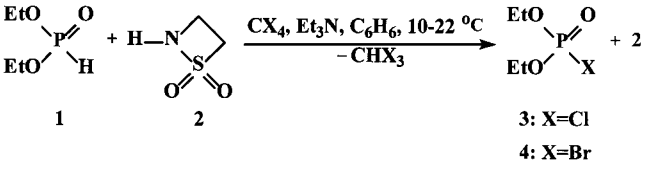
We have undertaken studies on the synthesis of a new class of *β*-sultams in which the four-membered ring bears an organophosphorus moiety. In this article, the results of the synthesis of 1,2-thiazetidine 1,1-dioxide, substituted on the nitrogen atom, is described.

RESULTS

A few synthetic approaches to *β*-sultams containing a direct bond between the tri- or tetracoordinated phosphorus atom and the nitrogen atom of the 1,2-thiazetidine 1,1-dioxide ring could be envisaged. The most simple among these is direct phosphitylation or phosphorylation of *β*-sultams at nitrogen.

Unfortunately, our attempts to synthesize N-phosphorylated sultams by the reaction of 1,2-thiazetidine-1,1-dioxide **(2)** with diethyl phosphorochloridate **(3)** and diethyl phosphorobromidate **(4)** generated *in situ* from diethyl phosphite **(1)** and carbon tetrachloride or carbon tetrabromide, respectively, in the presence of triethylamine in benzene solution (Atherton-Todd condition [4]) failed (Scheme 1).

No reaction between **2** and **3** was revealed by ^{31}P-NMR analysis of the reaction mixture. The formation of only one organophosphorus product with δ ^{31}P 2.8 characteristic of **3** was observed. Under identical conditions, in the reaction of phosphite **1** with



1 **2** **3: X=Cl** **4: X=Br**

SCHEME 1

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carbon tetrabromide in the presence of sultam **2** and triethylamine, the formation of a major product with δ ^{31}P −6.9 accompanied by a small amount of a second compound with δ ^{31}P −12.7 was observed. Monitoring of the reaction mixture by ^{31}P-NMR spectroscopy showed that the line at δ −6.9 slowly disappeared, while the one at δ −12.7 increased to become the only line after 6 days of reaction at 20–22°C.

The first observed product corresponding to the peak at δ −6.9 was identified as diethyl phosphorobromidate **(4)** by its reaction with cyclohexylamine providing diethyl cyclohexylphosphoroamidate and by spectral comparison with the pure bromidate **4** isolated by distillation of the product from the reaction between triethyl phosphite and bromine [5]. In the studied reaction, the bromidate **4** slowly underwent transformation to tetraethyl pyrophosphate (δ ^{31}P −12.7), most probably due to the presence of water.

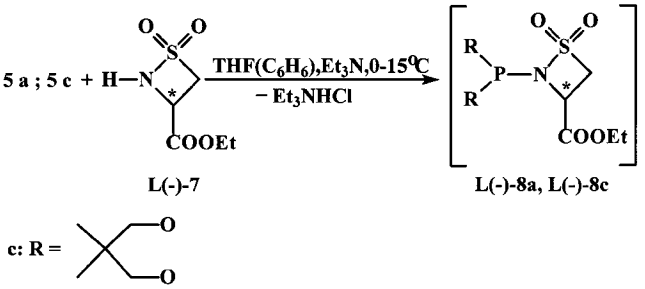
On the other hand, when **2** was reacted with the freshly prepared diethyl phosphorochloridite **(5a)** (δ ^{31}P 165) in the presence of triethylamine in THF solution at 0–15°C, the formation of a new product at δ 128.9 was observed in the ^{31}P-NMR spectrum of the reaction mixture. This line is characteristic for the expected 2-diethylphosphito-1,2-thiazetidine 1,1-dioxide **(6a).** Under the identical conditions, in the reaction of **2** with tetramethylphosphorodiamidous chloride **(5b),** N-phosphorodiamidous-1,2-thiazetidine 1,1-dioxide **(6b)** was obtained (Scheme 2).

It was also expected that other β-sultams unsubstituted on the nitrogen atom could be used as the substrates of the investigated reaction. We have observed that L(−)-3-carboethoxy-1,2-thiazetidine-1,1-dioxide **(7)** reacted with **5a,** as well as with 2-chloro-5,5-dimethyl 1,3,2-dioxaphosphorinan **(5c),** and as a result, sultams **L(−)-8a** and **L(−)-8c** phosphitylated on the nitrogen atom were synthesized (Scheme 3).

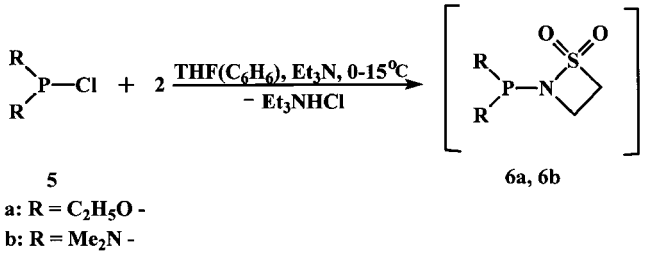
The sultams **6a,b, L(−)-8a,** and **L(−)-8c** showed relatively low stability, and we were not able to isolate these compounds from the reaction mixture in pure form. The crude 2-N-[L(−)-3-carboethoxy-1,2-thiazetidino-1,1-dioxo]-5,5-dimethyl-1,3,2-dioxaphosphorinan **(8c)** decomposed during attempted isolation from the reaction mixture by column chromatography on silica gel.

The easy hydrolytic cleavage of the phosphorus–nitrogen atom bond in **L(−)-8c** with the formation of 2-hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinan **(9),** as well as other unidentified products, was observed during this operation. In a separate experiment, the reaction between the sultam **L(−)-8c** and 3 equivalents of water, performed in benzene at room temperature, gave the phosphite **9** in quantitative yield (Scheme 4).

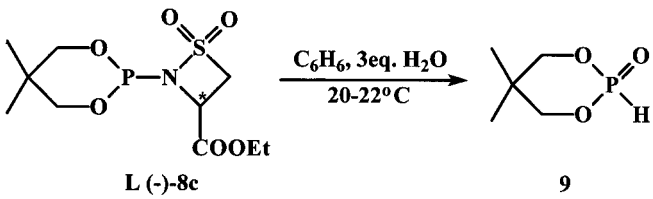
The observed facile cleavage of the P–N bond in the synthesized sultams by water, together with the observed location of their ^{31}P-NMR resonance lines in the range δ 106–132, is in full accord with the presence of a P^{III}–N functionality in their structures. The relatively high reactivity of N-phoshitylated β-sultams and the consequent difficulties in their separation from the reaction mixtures suggested that their transformation into compounds with a tetracoordinated phosphorus atom would be desirable. Toward this end, a reaction of the crude sultam **6a,** considered as a model compound, with 2-picoline N-oxide at 15–20°C in THF solution was carried out. As a result, a mixture of compounds was obtained. From this mixture, a major product with δ ^{31}P −6.9 was isolated by flash chromatography in 40% yield. The compound was identified as 2-diethylphosphoro-1,2-thiazetidine 1,1-dioxide **(10a).** The reactions of **6a** with either *m*-chloroperoxybenzoic acid



SCHEME 3



SCHEME 2



SCHEME 4

(MCPBA) in the presence of triethylamine or diphenyl selenoxide and anhydrous *t*-butyl hydroperoxide gave the same sultam **10a** in 35–49% yield, respectively (Scheme 5).

From the oxidants used, *t*-butyl hydroperoxide was selected as the most efficient one, and subsequently, other phosphitylated sultams were also oxidized to N-phosphoro derivatives **10b, L(−)-11a,** and **L(−)-11c** using this reagent (Scheme 6).

Similarly to the reactions shown in Schemes 4 and 5, the N-phosphitylated *β*-sultams underwent reactions of oxidative addition of elemental sulfur and selenium. In these reactions, performed in THF or benzene solution at room temperature, the 2-thio- and 2-selenophosphoro *β*-sultams **12a, 13a, L(−)-14c,** and **L(−)-15c** were obtained in satisfactory yields (Scheme 7).

The synthesized *β*-sultams, **10a, 10b, L(−)-11a, L(−)-11c, 12a, 13a, L(−)-14c,** and **L(−)-15c,** were isolated from the reaction mixtures by column chromatography, and they were fully characterized spectroscopically (^{1}H, ^{31}P-NMR, MS). They gave also the correct elemental analysis results. The compounds are stable oils **L(−)-11a** or low-melting crystalline substances **10a, 10b, L(−)-11c, 12a, 13a, L(−)-14c,** and **L(−)-15c),** and may be stored for a long time in the absence of moisture at a temperature near 0°C in a closed vessel under nitrogen without decomposition.

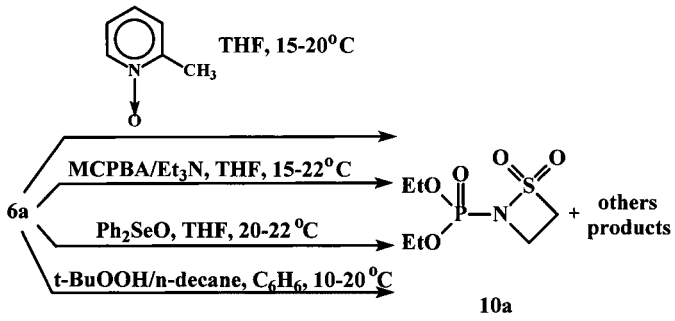
CONCLUSION

In this project, we have shown that the chloroanhydrides of phosphorous and amidophosphorous acids may be successfully used to perform phosphitylation on the nitrogen atoms, in *β*-sultams. The formed amidophosphites and phosphorous triamide are characterized by low stability toward water.

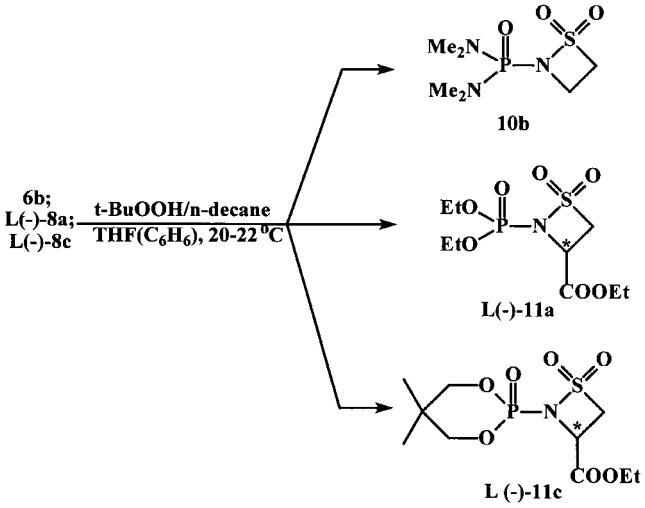
The oxidation of the phosphorus atom or addition of sulfur and selenium led to the synthesis of several not previously described N-phosphoro, N-thiophosphoro, and N-selenophosphoro *β*-sultams. Further studies on the reactivity and properties of these new types of organophosphorus derivatives are in progress.

EXPERIMENTAL

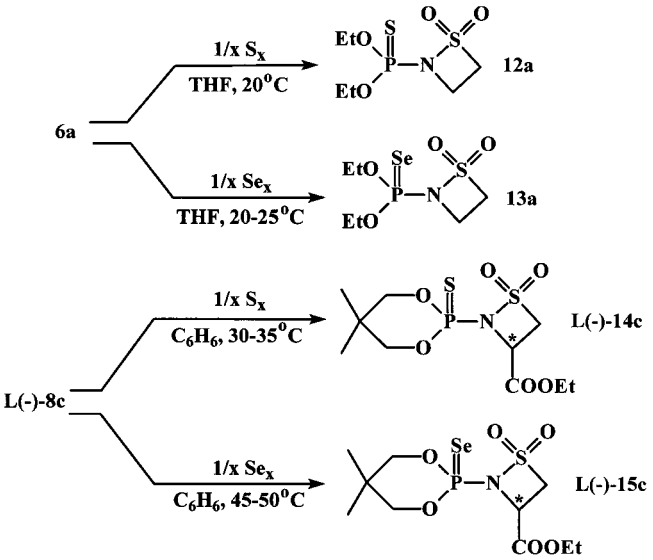
The solvents were dried by standard procedures before use. Triethylamine was refluxed over sodium and then distilled before use. Column flash chromatography was carried out with silica gel under a nitrogen pressure of 0.35 bar. Thin-layer chromatography was carried out on precoated plates (glass), silica gel 60 F_{254}. Melting points were determined with a Boetius apparatus and are uncorrected. IR



SCHEME 5



SCHEME 6



SCHEME 7

spectra were measured in solutions or in pellets using the ATI Mattson FT IR™ spectrometer. Optical rotations were measured on a Perkin Elmer 241 MC polarimeter. ^{1}H-NMR spectra were determined at 200.13 MHz with a Bruker AC 200 spectrometer using TMS as an internal standard. ^{31}P-NMR were taken on a Bruker AC 200 spectrometer at 81 MHz. Positive chemical shifts are downfield from 85% H_3PO_4 used as an external reference. LSIMS spectra were recorded on a Finnigan MAT 95 spectrometer in a glycerol matrix using cesium as the primary ion beam. CI/MS spectra were recorded on the same apparatus using isobutane as a reagent gas. The substrates, diethyl phosphite **(1)** [6], diethyl phosphorochloridite **(5a)** [7], 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinan **(5c)** [8], tetramethylphosphorodiamidous chloride **(5b)** [9], 1,2-thiazetidine 1,1-dioxide **(2)** [10], L(−)-3-carboethoxy-1,2-thiazetidine 1,1-dioxide **(7)** [11], 2-picoline N-oxide [12], and diphenyl selenoxide [13], were prepared according to the literature procedures.

Reaction of **1** *with Carbon Tetrachloride and Sultam* **2** *in the Presence of Triethylamine*

Into a stirred solution of 1.38 g (10 mmol) of **1,** 4.5 g (30 mmol) of CCl_4, and 1.07 g (10 mmol) of sultam **2** in 15 mL benzene at temperature 10–15°C, 1.01 g (10 mmol) of triethylamine in 5 mL benzene was added. The reaction mixture was stirred at a temperature of 15–20°C for 2 hours. The ^{31}P-NMR analysis of the reaction mixture showed the presence of only one product with δ 2.8. The stirring was continued for the next 15 hours, and still, the presence of only one product δ 2.8 that was identified as chloridate **3** was found in the reaction solution (Ref. [14] δ ^{31}P 2.8 for **3**).

Reaction of **1** *with Carbon Tetrabromide and Sultam* **2** *in the Presence of Triethylamine*

Into a stirred solution of 0.6 g (4.3 mmol) of phosphite **1,** and 2.1 g (6.3 mmol) of CBr_4 in 20 mL of benzene, 0.40 g (4.3 mmol) of sultam **2** and 0.43 g (4.3 mmol) of triethylamine in 5 mL of benzene were added at a temperature of 10°C. After 30 minutes, the presence of two organophosphorus products with δ −6.9 (42%) and −12.7 (41%) were found by ^{31}P NMR in the reaction mixture. The continuous analysis of the reaction mixture by ^{31}P-NMR spectroscopy showed that the line at δ −6.9 slowly disappeared, and, after 6 days, for the reaction performed at a temperature of 20–22°C, the presence of the major product with δ −12.7 was found in the reaction mixture. The line at δ −6.9 disappeared immediately after addition of cyclohexylamine to the reaction mixture. As a result, the formation of a new product with δ 8.66 was observed. This compound was isolated by flash column chromatography, eluent: hexane:chloroform:acetone (3:1:1), and identified as diethyl cyclohexylphosphoroamidate, mp 77–79°C (petroleum ether) (Ref. [15] mp 72–74°C, ^{31}P δ 8.8). The former product with δ −6.9 was identified as phosphorobromidate **4** and the latter as a tetraethyl pyrophosphate (Ref. [16] δ ^{31}P −12.8). The distilled sample of bromidate **4,** obtained by the reaction of bromine with triethyl phosphite according to a described procedure [5], showed δ ^{31}P −7.5 in $CDCl_3$ solution (Ref. [5] δ ^{31}P −9.7 in CH_3CH_2Cl).

Synthesis of 2-Phosphityl-1,2-thiazetidine 1,1-Dioxide. General Procedure

A solution of 5–10 mmol of the corresponding phosphorochloridite in 5 mL of dry THF or benzene was added at a temperature of 0–15°C with stirring, in an argon atmosphere, to a solution of sultam **2** or **L(−)-7** (2–10 mmol), triethylamine (2–10 mmol), and 400–600 mg of dry pulverized molecular sieves (3Å) in 15–30 mL THF or benzene. The reaction solution was stirred for 2–4 hours at room temperature. The amine hydrochloride was filtered off, the solvent evaporated *in vacuo* under argon, and the residual liquid maintained for 30 minutes under reduced pressure (1–2 mmHg) and analyzed by ^{31}P-NMR.

2-Diethylphosphito-1,2-thiazetidine 1,1-Dioxide (**6a**)

From the reaction of 1 g (6.4 mmol) of phosphorochloridite **5a,** 0.6 g (6.4 mmol) of sultam **2,** and 0.66 g (6.4 mmol) of triethylamine in 20 mL THF, the sultam **6a** was obtained in 52% yield, δ 128.9. The product was contaminated by 29% of phosphite **1,** ^{31}P δ 8.4 (Ref. [17] ^{31}P δ 7.5).

2-Tetramethylphosphorodiamidito-1,2-thiazetidine 1,1-Dioxide (**6b**)

In the reaction of 0.83 g (5.4 mmol) of phosphorochloridite **5b,** 0.55 g (5.4 mmol) of triethylamine and 0.5 g (5.4 mmol) of sultam **2** in 20 mL benzene, the sultam **6b,** δ ^{31}P 106, was obtained in 57% yield. In the obtained crude sample of sultam **6b,** the presence of 11.6% of tetramethyl phosphorodiamidous acid ^{31}P δ 24.1 (Ref. [18] δ ^{31}P 21.5) was found spectroscopically.

L(−)-2-Diethylphosphito-3-carboethoxy-1,2-thiazetidine 1,1-Dioxide (**8a**)

The reaction of 1 g (5.6 mmol) of sultam **L(−)-7,** $[\alpha]_D^{20} = -63.2$ ($CHCl_3$) with 0.56 g (5.6 mmol) of tri-

ethylamine and 0.87 g (5.6 mmol) of phosphorochloridite **5a** in 20 mL of dry THF was carried out during 24 hours at room temperature. The sultam **L(−)-8a** was obtained as a viscous liquid in 74% yield, δ ^{31}P 130.5. The crude product contained 20% of the phosphite **1.**

2-N-[L(−)-3-carboethoxy-1,2-thiazetidino-1,1-dioxo]-5,5-dimethyl 1,3,2-Dioxaphosphorinan (**8c**)

In the reaction of 0.46 g (2.8 mmol) of chloride **5c** with 0.5 g (2.8 mmol) of sultam **L(−)-7** and 0.28 g (2.8 mmol) of triethylamine in 25 mL benzene, the sultam **L(−)-8c** was obtained as a syrup. The crude product contained 74% of **L(−)-8c** δ ^{31}P 112.5 and 17% of **9,** δ ^{31}P 3.9, these values being calculated from integrated ^{31}P-NMR spectra. An attempt to isolate **L(−)-8c** by flash chromatography, eluent: hexane:acetone:chloroform (4:1:1), was unsuccessful. The formation of unidentified organophosphorus compounds with δ 138.0, 20–21, 7.0, 9.0, −12.5, −13.0, −13.8, −14.5, and −21.0 was indicated by ^{31}P-NMR spectroscopy during this operation.

The Reaction of **L(−)-8c** *with Water*

A solution of crude **L(−)-8c** 0.2 g (consisting of 77% of **8c,** δ ^{31}P 112.5, and 17.9% δ ^{31}P 3.61 of **9**) in 10 mL of benzene was stirred with 3 equivalents of water at room temperature for 72 hours. After this time, the formation of the phosphite **9,** in 90% yield, δ ^{31}P 3.64, $J_{P\text{-}H}$ 678 Hz was observed in the reaction solution (Ref. [19] δ ^{31}P-NMR 2.15, $J_{P\text{-}H}$ 688 Hz).

Oxidation of **6a**

1. *By 2-Picoline N-Oxide*

To a solution of sultam **6a,** freshly prepared from 0.6 g (6.4 mmol) of **2,** 1 g (6.4 mmol) of **5a,** and 0.64 g (6.4 mmol) of triethylamine in 15 mL of THF, was added with stirring at 15°C, 0.7 g (6.4 mmol) of 2-picoline N-oxide in 5 mL THF. Stirring was continued until the ^{31}P-NMR line of the substrate at δ 128.9 disappeared. The solvent was distilled off *in vacuo,* and, from the residual material, 2-diethylphosphoro-1,2-thiazetidine 1,1-dioxide (**10a**) was isolated by flash chromatography as a crystalline compound, 0.62 g, mp 33–34°C in 40% yield. Flash chromatography, eluent: hexane:chloroform:acetone (1:1:1); TLC, R_f = 0.4; hexane:chloroform:acetone (3:1:1), IR (CCl_4) ν_{max}/cm^{-1}; 814.7 (m), 982.5 (vs), 1027.6 (vs), 1117.3 (s), 1161.5 (s), 1212.3 (vs), 1275.6 (vs), 1348.8 (vs); ^{1}H-NMR ($CDCl_3$): δ 1.39 (dt, 6H, $^3J_{H\text{-}H}$ = 6.1 Hz, $^4J_{P\text{-}H}$ = 1.0 Hz); 3.62 (dt, 2H, $^3J_{H\text{-}H}$ = 6.1 Hz, $^4J_{P\text{-}H}$ = 1.1 Hz), 4.17–4.34 (m, 6H); ^{31}P-NMR ($CDCl_3$): δ −6.9; LSIMS m/z = 244{M+1}. Found %: C, 30.07; H, 5.79; N, 5.68; P, 12.74; S, 12.57; calcd for $C_6H_{14}NO_5PS$: C, 29.6; H, 5.8; N, 5.7; P, 12.7; S, 13.2.

2. *By m-Chloroperbenzoic Acid (MCPBA) in the Presence of Triethylamine*

The solution of sultam **6a,** prepared from 0.5 g (5.3 mmol) of **2,** 0.84 g (5.3 mmol) of **5a,** and triethylamine 1.36 g (13.4 mmol) in 20 mL of THF, was treated with stirring at a temperature of 15°C with 1.16 g (6.7 mmol) of MCPBA. The reaction mixture was stirred for 24 hours, and the filtered solution was concentrated. After flash chromatography, 0.45 g, 35% yield of sultam **10a** was obtained.

3. *By Diphenyl Selenoxide*

To a solution of sultam **6a,** obtained from 0.3 g (3.2 mmol) of **2,** 0.5 g (3.2 mmol) of **5a,** and 0.32 g (3.2 mmol) of triethylamine in 20 mL of THF, 0.8 g (3.2 mmol) of diphenyl selenoxide in 5 mL THF was added with stirring at a temperature of 15°C. Stirring was continued for 20 hours, and, after filtration, the solvent was distilled off *in vacuo.* After flash chromatography, 0.38 g, 49% yield of sultam **10a,** δ ^{31}P −6.9 was obtained.

4. *By t-Butyl Hydroperoxide*

A solution of 1.38 g (14.8 mmol) of sultam **2,** 2.35 g (15 mmol) of **5a,** and 1.5 g (14.8 mmol) of triethylamine in 40 mL of benzene was stirred for 2 hours. After this time, 2.35 g (15 mmol) of *t*-butyl hydroperoxide (98% in *n*-decane) was added dropwise and the mixture was stirred for 3 hours. The mixture was filtered, and the solvent was evaporated from the filtrate. From the residue, the sultam **10a** was separated by flash chromatography, 1.37 g, 38% yield. The product was identical with that synthesized according to the described procedures (1–3) (TLC, ^{1}H, ^{31}P-NMR, MS).

Reaction of Sultams **6b, L(−)-8a**, *and* **L(−)-8c** *with t-Butyl Hydroperoxide*

The reactions were performed according to the described procedure (4), and the sultams **10b, L(−)-11a,** and **L(−)-11c** were synthesized.

2-(Tetramethylphosphorodiamido)-1,2-thiazetidine 1,1-Dioxide (**10b**)

The reaction of sultam **6b,** prepared from 0.5 g (5.4 mmol) of **2,** 0.83 g (5.4 mmol) of chloride **5b,** and 0.54 g (5.4 mmol) of triethylamine, was treated with 0.9 g (5.7 mmol) of *t*-butyl hydroperoxide at room

temperature in THF solution. The reaction mixture was stirred for 2 hours at room temperature and filtered. The solvent was evaporated, and the product was separated chromatographically as a crystalline compound, 0.64 g, 50% yield, mp 93–94°C. Flash chromatography, eluent: acetone:chloroform:hexane (2:1:1); TLC, R_f = 0.22; acetone:chloroform:hexane (3:1:1); IR (in KBr pellet) ν_{max}/cm^{-1}: 513.18 (m), 569.76 (w), 674.40 (m), 704.26 (m), 755.19 (m), 788.10 (w), 810.70 (w), 979.78 (s), 993.11 (vs), 1102.23 (m), 1140.20 (w), 1154.53 (m), 1188.62 (w), 1224.63 (vs), 1301.50 (m), 1323.74 (vs), 1489.23 (w), 1636.57 (w), 2817.35 (w), 2904.70 (w), 3430.96 (w); ^{1}H-NMR ($CDCl_3$) δ 2.72 (s, 6H), 2.77 (s, 6H), 3.57 (t, 2H), 4.19 (dt, 2H, $^3J_{H\text{-}H}$ = 7.0 Hz, $^3J_{P\text{-}H}$ = 3.5 Hz); ^{31}P-NMR ($CDCl_3$) δ 10.8; MS/CI m/z = 242 {M + 1}. Found %: C, 30.17; H, 6.54; N, 17.33; P, 12.85; S, 13.35; calcd for $C_6H_{16}N_3O_3PS$; C, 29.9; H, 6.7; N, 17.4; P, 12.9; S, 13.3.

L(−)-2-Diethylphosphoro-3-carboethoxy-1,2-thiazetidine 1,1-Dioxide (**11a**)

In the reaction of crude **L(−)-8a,** freshly prepared from 1 g (5.6 mmol) of **L(−)-7** and 0.87 g (5.6 mmol) of **5a** in the presence of 0.56 g (5.6 mmol) of triethylamine, with 0.9 g (5.6 mmol) of *t*-butyl hydroperoxide in 20 mL of THF, the sultam **L(−)-11a,** 1.1 g, 63% yield as a oily liquid was obtained. Flash chromatography eluent: hexane:acetone:chloroform (4:1:1); TLC; R_f = 0.36, hexane:acetone:chloroform (3:1:1); IR (CCl_4); IR ν_{max}/cm^{-1}; 772.70 (m); 1031.20 (vs); 1128.34 (m); 1164.28 (s); 1209.91 (vs); 1276.98 (s); 1347.88 (s); 1750.32 (s); 2912.88 (w); 2985.69 (w); ^{1}H-NMR ($CDCl_3$); δ: 1.29 (tdd, 6H, $^3J_{H\text{-}H}$ = 7.1 Hz, $^4J_{P\text{-}H}$ = 2.1 Hz); 1.24 (t, 3H, $^3J_{H\text{-}H}$ = 7.2 Hz); 4.07–4.56 (m, 9H); ^{31}P-NMR ($CDCl_3$), δ −8.17 pm; MS/CI m/z = 316 {M + 1}. Found %: C, 34.55; H, 5.66; N, 4.40; P, 9.90; S, 10.71; calcd for $C_9H_{18}NO_7PS$: C, 34.2; H, 5.7; N, 4.4; P, 9.8; S, 10.2; $[\alpha]_D^{20}$ = −73.62, ($CHCl_3$).

2-N-[L(−)-3-Carboethoxy-1,2-thiazetidino-1,1-dioxo]-2-oxo-5,5-dimethyl 1,3,2-Dioxaphosphorinan (**11c**)

To a solution of crude **L(−)-8c,** prepared from 0.5 g (2.8 mmol) of **L(−)-7,** 0.46 g (2.8 mmol) of **5c,** and 0.28 g (2.8 mmol) of triethylamine in 20 mL benzene, 0.44 g (3.6 mmol) of *t*-butyl hydroperoxide was added at 10°C with stirring. The reaction mixture was stirred at room temperature for 24 hours, and the filtered reaction solution was concentrated *in vacuo*. After chromatography, a 0.42 g, 46% yield of sultam **L(−)-11c,** a crystalline compound, with mp 140–142°C, was obtained. Flash chromatography, eluent: hexane:acetone:chloroform (4:1:1); TLC, R_f = 0.24; hexane:acetone:chloroform (3:1:1); IR (KBr pellet) ν_{max}/cm^{-1} 538.82 (m), 644.08 (w), 776.55 (m), 848.48 (w), 972.72 (m), 1001.31 (vs), 1047.51 (vs), 1144.33 (m), 1168.55 (m), 1210.04 (vs), 1234.13 (m), 1273.44 (m), 1346.93 (vs), 1373.41 (w), 1480.46 (w), 1758.79 (s), 2984.19 (w); ^{1}H-NMR ($CDCl_3$): δ 0.98 (s, 3H); 1.26 (s, 3H); 1.32 (t, 3H); 4.08–4.61 (m, 9H); ^{31}P-NMR ($CDCl_3$): δ −14.2; MS/CI m/z = 328 {M + 1}. Found %: C, 36.62; H, 5.51; N, 4.25; P, 9.47; S, 9.70; calcd for $C_{10}H_{18}NO_7PS$: C, 36.7; H, 5.5; N, 4.3; P, 9.5; S, 9.8; $[\alpha]_D^{20}$ = −65.51 ($CHCl_3$).

Reactions of Sultams **6a** *and* **L(−)-8c** *with Sulfur and Selenium. The Synthesis of Sultams* **12a, 13a, L(−)-14c**, *and* **L(−)-15c**. *General Procedure*

The dry pulverized sulfur or selenium (3.7–26 mmol) was added into a stirred freshly prepared solution of the corresponding phosphitylated sultam (3.0–25 mmol) in THF or benzene solutions at room temperature. The stirring was continued at temperature 20–45°C for 15–36 hours, and the reaction mixture was filtered. The solvent was distilled off from the filtrate at 25–30°C, and, from the residual liquid material, the sultams were isolated by flash column chromatography.

2-Diethythiophosphoro-1,2-thiazetidine 1,1-Dioxide (**12a**)

In the reaction of crude **6a,** freshly prepared from 1.00 g (10 mmol) of **2,** 1.56 g (10 mmol) of **5a,** and 1.01 g (10 mmol) of triethylamine, with 0.44 g of sulfur in 20 mL THF, the sultam **12a,** 1.8 g, 73% yield was obtained as a crystalline compound with mp 42–44°C. Flash chromatography, eluent: hexane:chloroform:acetone (8:1:1); TLC; R_f = 0.28, hexane:chloroform:acetone (3:1:1); IR (CCl_4), ν_{max}/cm^{-1} 650.2 (s), 821.5 (s), 970.3 (s), 1020.6 (s), 1100.7 (m), 1160 (s), 1354.4 (s), 2906.7 (w), 2983.1 (m); ^{1}H-NMR ($CDCl_3$): δ 1.36 (dt, 6H, $^3J_{H\text{-}H}$ = 7.06 Hz, $^4J_{P\text{-}H}$ = 0.84 Hz), 3.58 (dt, 2H, $^3J_{H\text{-}H}$ = 6.68 Hz, $^4J_{P\text{-}H}$ = 1.48 Hz), 4.01–4.31 (m, 6H); ^{31}P-NMR ($CDCl_3$): δ 57.36; MS/CI m/z = 260 {M + 1}. Found %: C, 28.08; H, 5.7; N, 5.37; P, 12.29; S, 25.07; calcd for $C_6H_{14}NO_4PS_2$: C, 27.79; H, 5.44; N, 5.40; P, 11.94; S, 24.73.

2-Diethylselenophosphoro-1,2-thiazetidine 1,1-Dioxide (**13a**)

In the reaction of 0.67 g of selenium with crude sultam **6a,** obtained from 0.92 g (8.6 mmol) of **2,** 1.34

g (8.6 mmol) of **5a,** and triethylamine 0.87 g (8.6 mmol) in 15 mL of THF, **13a,** 1.62 g, was obtained in 61.8% yield as colorless crystals with mp 29–31°C. Flash chromatography, eluent: hexane:chloroform:acetone (7:1:1); TLC; R_f = 0.49, hexane:chloroform:acetone (3:1:1); IR (CCl_4): ν_{max}/cm^{-1}, 812.5 (m), 970.2 (vs), 1020.6 (vs), 1100.7 (s), 1160.6 (vs), 1210.2 (vs), 1354.4 (vs), 2906.7 (w), 2983 (m); ^{1}H NMR ($CDCl_3$): δ 1.38 (dt, 6H, $^3J_{H-H}$ = 7.06 Hz, $^4J_{P-H}$ = 0.76 Hz), 3.6 (dt, $^3J_{H-H}$ = 6.6 Hz, $^4J_{P-H}$ = 1.64 Hz), 4.13–4.31 (m, 6H); ^{31}P-NMR ($CDCl_3$): δ 61.34, $J^{31}P-^{77}Se$ = 938 Hz; MS/CI, m/z = 308{M + 1} for ^{80}Se. Found %: C, 23.80; H, 4.71; N, 4.53; P, 12.09; S, 10.21; calcd for $C_6H_{14}NO_4PSSe$: C, 23.53; H, 4.60; N, 4.57; P, 10.11; S, 10.47.

2-N-[L(−)-3-Carboethoxy-1,2-thiazetidino-1,1-dioxo]-2-thiono-5,5-dimethyl 1,3,2-Dioxaphosphorinan (**14c**)

In the reaction of 0.12 g (3.7 mmol) of sulfur with crude sultam **L(−)-8c,** obtained from 0.5 g (2.7 mmol) of **L(−)-7,** 0.47 g (2.7 mmol) of **5c,** and 0.28 g (2.7 mmol) of triethylamine in 20 mL of benzene, the sultam **L(−)-14c,** 0.36 g, was obtained in 38% yield as a crystalline compound with mp 110°C. Flash chromatography, eluent: hexane:acetone:chloroform (8:1:1); TLC, R_f = 0.35, hexane:acetone:chloroform (3:1:1); IR (in KBr pellet): ν_{max}/cm^{-1}, 678.89 (w), 711.58 (w), 774.66 (m), 840.63 (m), 875.09 (w), 915.04 (w), 966.17 (s), 991.11 (vs), 1041.67 (vs), 1082.41 (w), 1140.90 (m), 1167.55 (s), 1214.33 (vs), 1356.15 (s), 1378.30 (m), 1473.50 (w), 2976.47 (w); ^{1}H-NMR ($CDCl_3$): δ 1.04 (s, 3H), 1.20 (s, 3H), 1.32 (t, 3H), 4.00–4.54 (m, 9H); ^{31}P-NMR ($CDCl_3$): δ 52.0; MS/CI m/z = 344 {M + 1} for ^{80}Se. Found %: C, 34.98; H, 5.01; N, 4.10; P, 9.18; S, 18.58: calcd for $C_{10}H_{18}NO_6PS_2$: C, 35.0; H, 5.3; N, 4.1; P, 9.0; S, 18.7; $[\alpha]_D^{20}$ = −59.25 ($CHCl_3$).

2-N-[L(−)-3-Carboethoxy-1,2-thiazetidino-1,1-dioxo]-2-seleno-5,5-dimethyl 1,3,2-Dioxaphosphorinan (**15c**)

In the reaction of 0.32 g (4 mmol) of selenium with crude **L(−)-8c,** obtained from 0.38 g (2.3 mmol) of **5c,** 0.4 g (2.38 mmol) of **L(−)-7,** and 0.23 g (2.3 mmol) of triethylamine in 20 mL of benzene, the sultam **L(−)-15c,** 0.42 g, was obtained in 48% yield as colorless crystals with mp 117°C. Flash chromatography, eluent: hexane:acetone:chloroform (8:1:1); TLC, R_f = 0.4, hexane:acetone:chloroform (4:1:1); IR (KBr pellet): ν_{max}/cm^{-1} 645.12 (w), 771.32 (m), 818.14 (m), 870.78 (w), 914.96 (w), 984.45 (vs), 1039.87 (s), 1075.99 (w), 1138.16 (w), 1166.69 (m), 1211.48 (s), 1357.20 (m), 1378.07 (w), 1473.34 (w), 1751.98 (m), 2887.10 (w), 2974.76 (w), 3048.10 (w); ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 3H); 1.17 (s, 3H); 1.32 (t, 3H); 4.00–4.57 (m, 9H); ^{31}P NMR ($CDCl_3$): δ 55.9, $J^{31}P-^{77}Se$ = 988 Hz; MS/CI m/z = 392 {M + 1} for ^{80}Se. Found %: C, 30.69; H, 4.74; N, 3.61; P, 8.20; S, 8.49; calcd for $C_{10}H_{18}NO_6PSSe$: C, 30.8; H, 4.6; N, 3.6; P, 7.9; S, 8.2; $[\alpha]_D^{20}$ = −60.08, ($CHCl_3$).

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