A New Family of 1,2,3-Oxathiazolidine-2,2-dioxide Phosphonate Derivatives: Synthesis, Characterization and Anticancer Evaluation.

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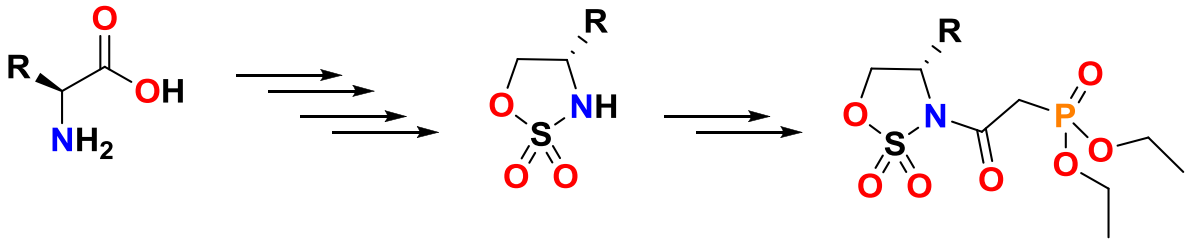
Abstract

An efficient synthesis of a new series of organophosphorus compounds having a cyclic sulfamidates moiety is described. The cyclic sulfamidate precursors were prepared from α-amino acids after four steps (Reduction, *N*-Boc protection, cyclisation and cleavage). The novel organophosphonates were synthesized within two steps starting from the cyclic sulfamidate (chloroacetylation following by phosphorylation *via* Arbuzov reaction). A particular compound **7-a** (diethyl phosphonate {2-[(4S)-4-benzyl-1,2,3-oxathiazolidin-3-yl-2,2-dioxyde]-2-oxoethyl}) was essayed for their *in vitro* cytotoxic activities against a panel of four cell lines (Jurkat, K562, U266, and A431). For all of these cells, the synthesized compound showed low cytotoxicity, even at high concentration levels (4 mM).



Keywords

Organophosphorus, Cyclic sulfamidates, Arbuzov reaction, anticancer activity.

Introduction

The past decades have seen many advances in the development of new and effective biomolecules for the treatment of various diseases. The chemistry of organophosphorus compounds has received considerable attention owing to their diverse biological activities.[1] Organophosphonate are analogs of phosphate esters with a non-hydrolysable C-P bond instead of a fragile O-P bond, which present the possibility of antimetabolic activity.[2]

The (α,β)-amidophosphonates constitute an important class of organophosphorus compounds with diverse biological activities, they can be used as antiviral agents,[4] anticancer agents,[5] antithrombotic agents,[6] antibiotic agents,[7] antibacterial agents,[8] potential antioxydants,[9] haptens of catalytic antibodies,[10] enzymes inhibitors,[11] anti-inflammatory agents,[12] antihypertensive agents[13] and carriers of hydrophilic organic molecules across phospholipid membrane,[14] they are also employed as insecticides and herbicides.[15]

In the literature several synthetic methods have been developed for the preparation of (α,β)-amidophosphonates.[16] Generally, the phosphonates derivative were prepared *via* Arbuzov reaction using trialkyphosphite under a variety of conditions.[17]

In recent years, cyclic sulfamidates have been utilized as a relevant precursor for the synthesis of potentially valuable new building-blocks in medicinal chemistry[18] and chiral auxiliaries in asymmetric synthesis.[19] Typically, these heterocyclic compounds is prepared from chiral and achiral amino alcohols and diols in several steps.[20]

In the spite of their importance, only few examples by Dolence et *al* [21] and Das et *al*. [22]are reported in the literature describing the use of the sulfamidates as precursors for the synthesis of phosphonates derivatives. In continuation of our interest towards development of new class of phosphonates derivative,[23] we report herein the synthesis of new amidophosphonates **(figure1)** using cyclic sulfamidates (1,2,3-oxathiazolidin-2,2-dioxide) as chiral precursors, which were prepared starting from commercially available α-amino acids.

Results and Discussion

Chemistry

The five membered cyclic sulfamidates **5 (a-c)** (1,2,3-oxathiazolidin-2,2-dioxide) is typically prepared, this heterocyclic compounds were synthetized from different chiral α-amino acids **1 (a-c)** as shown in scheme 1.

In first steps the α-amino acids were converted into the corresponding β-amino alcohols **2 (a-c)** by reduction reaction[24] with $NaBH_4$, I_2 in THF, in the second steps, the green chemistry conditions were respected where we converted the β-amino alcohols to their corresponding *N*-Boc derivatives **3(a-c)** using $(Boc)_2O$ under ultrasound irradiation.[25] The Cyclisation of the *N*-Boc protected β-aminoalcohols **3(a-c)** to form cyclic sulfamidates **4 (a-c)** was the key step of this synthesis, considering that we had to block the nucleophilicity of the nitrogen group by introducing the Boc group to allow the second nucleophilic attack on the sulfuryl chloride by

hydroxyl group. The second obstacle was to optimise the reaction conditions. We tried different temperatures, the best result was obtained at -20 °C, affording the cyclic product in good yield within 15 minute achieved the standard one-step cyclisation protocol. In all case the duration of the cyclisation step kept short (15 min) to obtain a good yield (**Table 3)**.

In the last step, and in continuation of our previous interest on the use of catalyst free, we herein use an efficient protocol for *N*-Boc deprotection under catalyst free conditions, finding that heating water (100°C) could efficiently catalyse the deprotection of *N*-Boc amino alcohols in good to excellent yields within 10-25 min proving the advantages of this method.[26]

In our study, the simplest and most typical reactions were used for the synthesis a new class of β-amidophosphonates **7(a-c)** using the cyclic sulfamidates **5(a-c)** as relevant precursor. This strategy involves two steps as shown in **Scheme 2**.

The starting chiral *N*-chloroacetyl (1,2,3)-oxathiazolidin-2,2-ones **6(a-c)** were easily prepared in good yields by treatment of the corresponding cyclic sulfamidates with K_2CO_3 in H_2O followed by chloroacetylation using chloroacetyl chloride[27]. The results are shown in **Table 1**.

The introduction of the phosphonate moiety was realised by a greener and efficient method developed by our group.[28] The corresponding amidophosphonates **7(a-c)** were obtained in good yields by phosphorylation of *N*-chloroacetyl cyclic sulfamidates derivatives under ultrasound irradiation **(Table 2)**. This protocol at a frequency of **40 KHz**, strongly accelerates the process of formation of P-C bonds compared to the classic Arbuzov reaction.

Biological evaluation

Cell cytotoxicity

The cytotoxicity of this new amidophosphonate was evaluated toward four cancer cell lines (Jurkat, K562, U266, and A431) using an MTT reduction assay (**Table S**). For all of these cells, synthesized compound (7a) showed low cytotoxicity, even at high concentration levels (**4** mM).

Experimental

Chemistry

General

All reagents and solvents were of commercial quality and used without further purification. Melting points were determined in open capillary tubes on an electro-thermal apparatus and uncorrected. IR spectra were recorded on a Perkin-Elmer FT-600 spectrometer. Proton nuclear magnetic resonance was recorded with an AC 250 and 400 MHz Brüker spectrometer using $CDCl_3$ or DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are reported in δ units (ppm). All coupling constants (***J***) are reported in Hertz. Multiplicity is indicated as **s** (singlet), **d** (doublet), **t** (triplet), **m** (multiplet) or combination of these signals. Elemental analysis was performed on a Euro-Vector 3000 C, H, N analyzer and. All reaction were monitored by TLC on Silica Merck 60 F254 (Art. 5554) precoated aluminum plates and were developed by spraying with ninhydrin and molybdenum bleu solution. Column chromatography was performed on Merck Silica gel (230-400 mesh). The Supplemental Materials contains complete characterization data for products **7a-c** (Figures S 1 – S 13).

General procedure for reduction of α-amino acids 2(a-c)

To a stirred solution of α-amino acids (1 equiv, 5 g) in THF (100 ml) at 0 °C, was added $NaBH_4$ (2.4 equiv.). A solution of iodine I_2 (1.1 equiv.) dissolved in THF was added dropwise at 0 °C. The resulting mixture was stirred under reflux for 18 h. The reaction was quenched by addition of methanol (20 mL). After evaporation of the solvent, a solution of KOH (20%, 100 mL) was added and the mixture was stirred for 4h. The crude products were extracted with AcOEt (3×100 mL), dried over $MgSO_4$, filtered, concentred under vacuum and recrystallized in diethyl ether.

***General procedure for N-tert*-butoxycarbonylation of β-amino alcohols 3(a-c)**

(S)-amino alcohols (1mmol) and di-*tert*-butyl dicarbonate [$(Boc)_2O$, 1.1 mmol] were placed in a glass tube under neat conditions and were sonicated for a suitable time. After completion of the reaction (as indicated by TLC), 5 mL of diethyl ether was added to the mixture, the resulting *tert*-butanol was freely soluble in diethyl ether and the *N*-Boc product was crystallized.

General procedure fort the cyclisation of *N*-Boc derivatives β-amino alcohols 4(a-c)

A solution of β-amino alcohols (1 mmol) in dry dichloromethane (5mL) and triethylamine (5 mmol) were taken in 50 mL round bottom flask under nitrogen and the solution was cooled to 0°C over 5 min. A solution of sulfuryl chloride (2 mmol) was added dropwise at -20°C over 15 min. After completion of the reaction, the organic layer was extracted with ethyl acetate (3×5mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product is purified over silica gel column chromatography eluted with (DCM-MeOH-9.5:0.5) to give yellow oil.

General procedure for the *N*-Boc deprotection of cyclic sulfamidates 5(a-c)

One millimoles of *N*-Boc cyclic sulfamidates and freshly double distilled water (10 mL) were loaded into 50 mL round bottomed flask related with depressurized system. The reaction mixture was heated in reflux for particular time and conducted under an argon atmosphere. After completion, the mixture was extracted with ethyl acetate (3×5mL) and concentrated in vacuum, all products were obtained pure.

General procedure for the choroacetylation of cyclic sulfamidates 6(a-c)

To a solution of (1,2,3)-oxathizolidin-2,2-dioxide (1 mmol) in H_2O (5mL) and K_2CO_3 (2 mmol) was added at 0°C chloroacetyl chloride (1.1 mmol). The reaction mixture was stirred for overnight at room temperature. The resulting mixture was then extracted with ethyl acetate (3 x 25mL). The organic layer was combined and dried over anhydrous sodium sulfate and concentrated. The crude product was crystallized in diethyl ether or purified by chromatography (CH_2Cl_2) to afford **6(a-c).**

General procedure for the phosphorylation of *N*-Acyl-(1,2,3)-oxathiazolidin-2,2-dioxide 7(a-c)

In a 10 mL round bottom flask taken a mixture of *N*-acylsulfamidate (1 mmol) with triethylphosphite (1mmol) was added. Then reaction mixture was subjected to the ultrasonication for appropriate time. After completion of the reaction, as indicated by TLC, silica gel, surplus reactants were removed by column chromatography eluted with AcOEt.

Diethyl phosphonate {2-[(4*S*)-4-benzyl-1,2,3-oxathiazolidin-3-yl-2,2-dioxide]-2-oxoethyl} (7-a)

Yield :91%, White oil, R_f: 0.60 (AcOEt), **IR (KBr: ν cm^{-1}): 1657 (C=O), 1131 & 1312 (SO_2).** **^{1}H NMR ($CDCl_3$, δ ppm:** 1.35 (t, 6H, C**H_3**-CH_2, $J_{1\text{-}2}$= 5.3 Hz), 2.76 (2dd, 1H, $J_{1\text{-}2}$=7.3 Hz), 3.33 (2dd, 1H, $J_{1\text{-}2}$=3.5 Hz), 3.70-3.91 (2dd, 2H, J_1= 5Hz, J_2=6.7 Hz), 4.20 (s, 2H), 4.15-4.24 (m, 4H), 4.69-4.75 (m, 1H), 7.22-7.33 (m, 5H). **^{13}C NMR ($CDCl_3$, δ ppm):** 16.4, 34.9, 37.6, 55.5, 62.8, 66.0, 127.3, 128.9, 129.4, 135.1, 165.0. **^{31}P NMR ($CDCl_3$, δ ppm) :** 19.5. **Elemental Analysis: Calcd,** C, 50.13; H, 6.17; N, 3.90; S, 8.92, **Found,** C, 50.10; H, 6.13; N, 3.87; S, 8.89.

Diethyl phosphonate {2-[(4*S*)-4-isobutyl-1,2,3-oxathiazolidin-3-yl-2,2-dioxide]-2-oxoethyl} (7-b)

Yield : 89%, White oil, R_f: 0.60 (AcOEt), **IR (KBr: ν cm^{-1}): 1657 (C=O), 1131 & 1312 (SO_2).** **^{1}H NMR ($CDCl_3$, δ ppm):** 0.90 (2d, 6H, $J_{1\text{-}2}$ = 6.1 Hz), 1.30 (t, 6H, $J_{1\text{-}2}$=5.9 Hz), 1.41 (m, 2H), 1.53 (m, 1H), 3.89-3.98 (dd, 2H, $J_{1\text{-}2}$ = 10.4 Hz), 4.14 (s, 2H), 4.15-4.24 (m, 4H), 4.46 (m, 1H). **^{13}C NMR ($CDCl_3$, δ ppm):** 16.3, 23.2, 24.8, 37.0, 40.6, 56.7, 61.5, 70.8, 168.4. **^{31}P NMR ($CDCl_3$, δ ppm) :** 19.5. **Elemental Analysis**: **Calcd,** C, 44.30; H, 7.44; N, 4.31; S, 9.85, **Found,** C, 44.28; H, 7.40; N, 4.30; S, 9.83.

Diethyl phosphonate {2-[(4*S*)-4-isopropyl-1,2,3-oxathiazolidin-3-yl-2,2-dioxide]-2-oxoethyl} (7-c)

Yields : 87%, White oil, R_f: O.61 (AcOEt), **IR (KBr: ν cm^{-1}): 1657 (C=O), 1131 & 1312 (SO_2).** **^{1}H NMR ($CDCl_3$, δ ppm):** 0.83-0.87 (t, 6H, $J_{1\text{-}2}$=6.8 Hz), 1.27 (t, 6H, $J_{1\text{-}2}$= 5.9Hz), 2.07 (d, 2H), 2.33 (m, 1H), 3.59-3.74 (2dd, 2H, $J_{1\text{-}2}$=9.8Hz), 4.09-4.14 (m, 4H), 4.38-4.43 (m, 1H). **^{13}C NMR ($CDCl_3$, δ ppm):** 16.3, 23.2, 24.8, 37.0, 40.6, 56.7, 61.5, 70.8, 168.4. **^{31}P NMR ($CDCl_3$, δ**

ppm) : 19.5. **Elemental Analysis**: **Calcd,** C, 42.44; H, 7.12; N, 4.50; S, 10.30, **Found,** C, 42.40; H, 7.09; N, 4.48; S, 10.27.

Biological evaluation

Cell lines and culture conditions

Jurkat (acute T cell Leukemia, ATCC TIB-152), K562 (chronic myelognous leukemia, ATCC CLL-243) and U266 (multiple myeloma, ATCC TIB-196) were routinely cultured in RPMI-1640 supplemented with 10% Fetal Bovine Serum (FBS, IDBIO, Limoges, France), 100U/ml penicillin, 100µg/ml streptomycin), 2mM L-glutamine, 1mM sodium pyruvate, 1% vitamins and 1% non-essentials amino-acids). A431 (vulvar epidermoid carcinoma, ATCC CRL-1555) was cultured in DMEM supplemented with 10% FBS, 100U/ml penicillin, 100µg/ml streptomycin), 2mM L-glutamine, 1mM sodium pyruvate. The cells were cultured at 37°C in a fully humidified 5% CO_2 incubator. All supplements and culture were purchased from Gibco-BRL Life Technologies, Cergy-Pontoise, France.

Cell viability assay

The cytotoxicity activity was evaluated using the MTT assay (3-(4,5-dimethylthiazol-2-yl)-phenyl-tetrazolium bromide). Briefly, tumor cell lines were added into 96-well tissue culture plates in culture medium. Compounds were prepared at a concentration of 4000µM in 10% DMSO in complete culture medium (v/v). The solutions were used at concentration range from 4000 µM to 7.8 µM. Cells were incubated with or without drugs for 72 h. Then, the MTT solution was added at a final concentration of 0.5mg/ml per well and cells were incubated for 3h at 37°C. The purple formazan crystals were dissolved by adding 200µl DMSO. The absorbance was read using a microplate spectrophotometer (Triad, Dynex Technologies) at 595 nm. The

results were compared with those of a control reference plate fixed on the treatment day and the growth inhibition percentage was calculated for each drug contact period. The concentration required for 50% inhibition of cell viability (IC_{50}) was calculated using the software OriginPro (OriginLab, Northampton, USA). Assays were performed in hexaplicate on three independent experiments.

Conclusion

In this work, we reported efficient and operationally simple methods for the synthesis a novel class of β-amidophosphonates using the chiral cyclic sulfamidates as precursors. A chiral molecule (**7-a)** was evaluated from their anticancer activities. For all of these evaluations, this compound showed a low cytotoxicity, even at high concentration levels.

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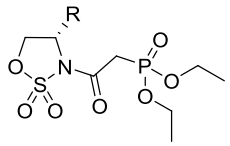
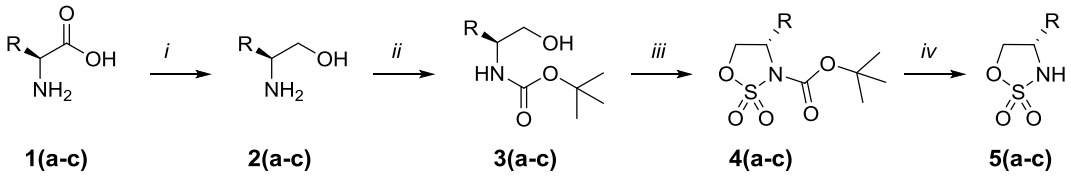
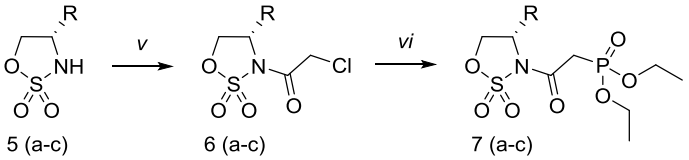


Figure 1: General structure of β-amidophosphonates.



i*).** $NaBH_4$,I_2, THF, Reflux. ***ii*).** $(Boc)_2O$,)))), rt.iii*).** SO_2Cl_2, TEA,-20°C. **i*v*).** H_2O, Reflux

Scheme 1: General procedure for the synthesis of cyclic sulfamidates.



v). $ClCOCH_2Cl$, K_2CO_3, H_2O, rt. *vi*). $P(OEt)_3$,)))), rt.

Scheme 2: General procedure for the synthesis of β-amidophosphonates.

Table 1: Synthesis of cyclic sulfamidates.

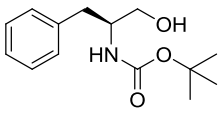
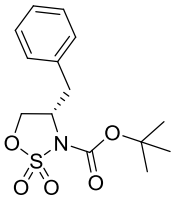
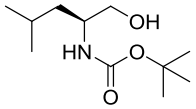
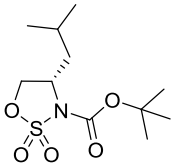
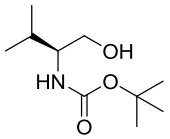
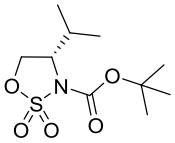
Entry	Substrate	Product	Yield (%)
01			92
02			87
03			85

Table 2: *N*-Boc deprotection of cyclic sulfamidates.

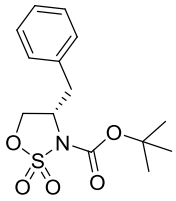
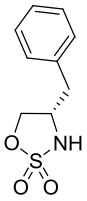
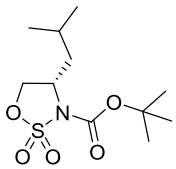
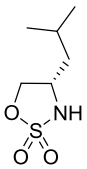
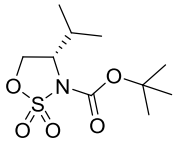
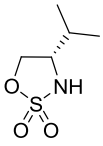
Entry	Substrate	Product	Yield (%)
01			>95
02			>95
03			>95

Table 3: Chloroacetylation of cyclic sulfamidates.

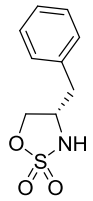
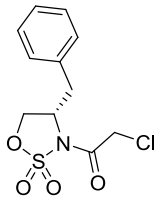
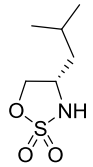
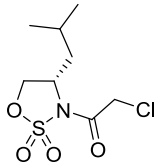
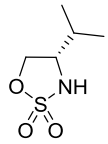
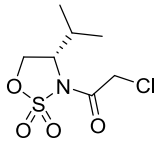
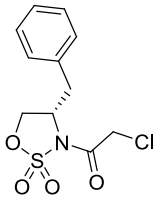
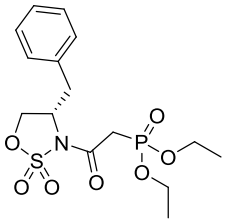
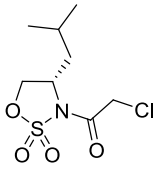
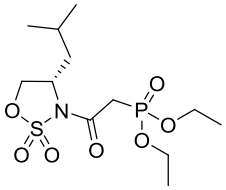
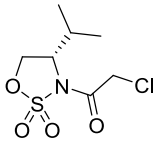
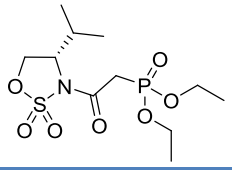
Entry	Substrate	Product	Yield (%)
01			82
02			80
03			79

Table 4: Phosphorylation of *N*-acetyl-(1,2,3)-oxathiazolidin-2,2-ones.

Entry	Substrate	Product	Yield (%)	Time (min)
01			91	10
02			89	12
03			87	14