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Synthesis of Novel Peptidosulfonamides Derived From Modified Oxazolidinones.

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ABSTRACT

The oxazolidin-2-ones are key intermediates in the synthesis of various compounds of interest in terms of reactivity. So, several aminoalcohols were prepared from oxazolidinone. The oxazolidinone may also be used as an intermediate in the preparation of peptidosulfonamide similar sulfonated a natural or synthetic peptide. The reactive condition typical for conversion of the cycle oxazolidinone from the aminoalcohol involves the use of a base hydroxyl, water and different types of organics co-solvents.

Keywords: Peptidosulfonamides; Sulfonamides; Oxazolidinones; reopening.

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INTRODUCTION

A large number of peptides, in most cases of low or relatively low molecular weight, exert immune-modulating activities. Most natural or synthetic peptides are generally very unstable in biological fluid environments and cross biological membranes poorly, toxic and antibacterial spectrum is limited, they are less active. In an attempt to overcome these obstacles, the peptides can be replaced by pseudo peptides. Bioisosteric replacement of a peptide bond with various surrogates is a widespread strategy for improving the biological activity, physicochemical properties, and the stability of peptides [1-3].

As an extension to the original peptides, several modified derivatives have been developed (e.g., azapeptides, depsipeptides, retro and retro-inverso peptides, phosphapeptides, ureidopeptides, and peptidosulfonamides) [4-5].

Over the last decade, the peptidosulfonamides have been recognized as emerging building blocks for preparing peptidomimetics and enzyme inhibitors [6-7]. Several papers have described the synthesis and biological interest of peptidosulfonamides by different methods [8-13]. The replacement of amide bonds in peptides by sulfonamide moieties resulted in peptidosulfonamidesincreases the flexibility of the backbone and is resistant to enzymatic degradation [8]. Although the sulfonamide-group is a weaker hydrogen bond acceptor, it still can form hydrogen bonds, mainly via the NH, which is a better hydrogen bond donor than an amide NH. The sulfonamide peptidomimetic is conveniently accessible and has been used for incorporation into peptides [14-17]. A disadvantage of peptidosulfonamides might be the presence of an additional carbon atom in each amino sulfonic acid residue, which is needed for stability reasons [18]. The peptides which contain a leucine, valine, Alanine and phenylalanine are more active than those containing amethionine, proline or isoleucine. From structural studies and functional bioactive peptides, changes in peptides can be provided at various levels of structural organization of the peptide or on the side chain or the peptide back bone itself.

In a previous work [19], we have easily achieved the coupling of amino esters with chloro sulfonyloxazolidinone, in the continuation of this work; we intend to prepare new peptidosulfonamides by reopening and oxidation of modified oxazolidinone cycles.

MATERIALS AND METHODS

All reagents and solvents were of commercial quality and used without further purification. All reactions were carried out under an inert atmosphere of nitrogen. Thethin layer chromatography (TLC) was performed on silica gel 60F254 plates (Merck Art. 5554). The products were found to UV light (254 nm) and by spraying ninhydrin in ethanol, followed by heating. Column chromatography silica gels were performed with silica Merck 60 H (Art. 9385). The uncorrected melting points were determined on a capillary electro thermal apparatus. Mass spectra were recorded on a JEOLSX102 high resolution mode on a positive or negative water micro mass ZQ by electron ionization (30eV). Elemental analysis was recorded on a EURO E.A 3700. Proton NMR spectra were recorded at room temperature on a WB unit360 or AC250 (Bruker). Chemical shifts(δ) are expressed in ppm relative to the signal of DMSO-d6 set at 2.49 ppm or $CDCl_3$ set at 7.24 ppm taken as internal reference. The multiplicity of signals is indicated by one (or more) letter(s) Singlet, (d) doublet, (t) triplet, (q) quartet,(dd) doublet of doublet, (m) multiplet.

The coupling constants are expressed in Hertz. Infrared spectra were recorded on a Perkin-ElmerFT-600.

Synthesis of*N*-chlorosulfonyloxazolidin-2-ones 1a-c

A solution of sulfuryl chloride (1equiv.) was added drop wise to a solution of oxazolidinone (0.1g, 1equiv.) in anhydrous methylene chloride (10 mL) in the presence of triethylamine (1.2 equiv.) and a catalytic amount of dimethyl aminopyridine at0 °C. The reaction was stirred under argon at 0° C for less than 1h.The reaction mixture was washed with HCl 0.1 N and then with water. The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuum. Theresidue was purified bycolumn chromatography on silica gel eluted withCH_2Cl_2, and chloro sulfonyloxazolidinone was obtained as crystals with a yield of80-88%.

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Coupling of chlorosulfonyloxazolidinone with amino esters

A solution of chlorosulfonyl oxazolidinone (0.2g, 1equiv.)in anhydrous methylene chloride isaddedto a solution of amino ester deprotected (1 equiv.) in the same solvent at 0°C in presence of triethylamine (1 equiv.).The evolution of the reaction was monitored by TLC. After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by column chromatography on silica gel eluted with CH_2Cl_2, to give the condensation product **2a-c**in good yields.

Opening reaction

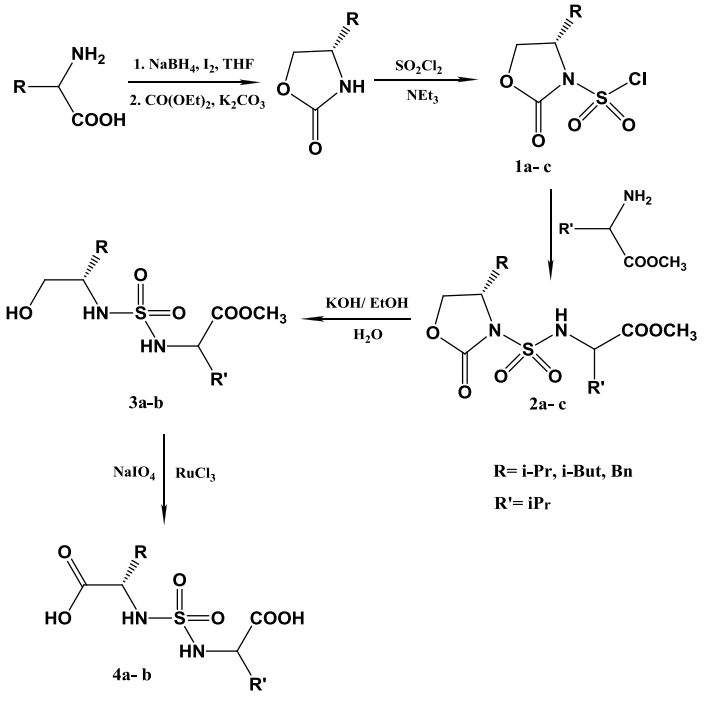
A solution of modified oxazolidinone (0.5g, 1.55mmol) in aqueous KOH (20% KOH inH_2O/ethanol, 1:1, 2.5 mL) was stirred atreflux for2 hours. The mixture was cooled to room temperature, neutralized with saturated NH_4Cl (25mL) and extracted with CH_2Cl_2 (2x20ml). The organic layer is dried over$MgSO_4$and concentrated under reduced pressure to give a white solid.

Oxidation reaction

A solution of *N*-[[(*S*)-(1-Hydroxy-3-methyl)-2-butyl] sulfonyl]-L-valine (0.1g, 0.337mmol) in methylene chloride (3 ml) was added to a solution of $NaIO_4$ (0.21, 3 equiv., 0.01mmol) in water, the mixture was cooled to 0°CandRuCl_3.nH_2O(0.02equiv, 0.21g) was added, the reaction mixture remains under magnetic stirring for8 hoursat20°C, then isopropanol (3ml) was added and the mixture is stirred for30 min at 20 °C, an oil which formed was filtered and concentrated under vacuum filtration. Theresidue was purified by column chromatography on silica gel eluted with CH_2Cl_2/MeOH: 7/3.

RESULTS AND DISCUSSION

The enantiomerically pure chiral oxazolidin-2-ones wereprepared in two steps starting fromthe corresponding amino acids (valine, leucine and phenylalanine). Reduction with sodium borohydride, followed by cyclization using diethyl carbonate [20]. The *N*-chlorosulfonyl-oxazolidinones **1a-c** were prepared from sulfurylchloride and chiral oxazolidin-2-one [19, 21], in the presence of triethylamine in anhydrous dichloromethane at 0°C.



Scheme 1: Synthesis of peptidosulfonamide.

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We considered the reactivity of*N*-chlorosulfonyl oxazolidin-2-ones with several amino esters under mild conditions at 0°C. Condensation products obtained previously can be used as aprecursor for the synthesis of peptidosulfonamide. while in the reaction with amino esters no inversion of configuration at asymmetric carbon was observed.

Several studies have been described in the literature [22] concerning the reopening of oxazolidinones in the reduction conditions such as LiOH/H_2O, KOH/EtOH, Cs_2CO_3, Ba $(OH)_2$, ...*ect.*

In our case we made the opening of oxazolidinones by action of KOH/EtOH on the compound **2**, the region selectivity is total with respect to CO_2 and SO_2 hydrolysis. The excess base causes saponification of the ester function, and provides access to the corresponding amino alcohols **3a-b**. Oxidation was carried out in the presence of $RuCl_3$ as catalyst and $NaIO_4$[23] as oxidizing agent. In the reduction and oxidation reactions, an asymmetric carbon does not change the initial configurations.

(S)-Methyl 2-((S)-4-isopropyl-2-oxooxazolidine-3-sulfonamido)-3-methylbutanoate(2a).
M.p. = 140–141◦C.yield = 87%.*Rf* = 0.4(CH_2Cl_2: MeOH/95:5). $[\alpha]_D$=+12.5 (*c*=1.0, CH_2Cl_2). IR (KBr): 3279, 1760, 1750, 1377, 1110 cm^{-1}.^{1}H NMR ($CDCl_3$, δ ppm): 0.92 (2d, *J*= 6.7 Hz, 6H, 2CH_3*i*Pr),1.05 (2d, *J*= 6.9 Hz, 6H, 2CH_3*i*Pr), 2.15(m, 1H, CH), 2.40 (m, 1H, CH), 3.70(s, 3H, OCH_3), 4.30-4.10 (m, 3H, *CHcyc, CH_2cyc), 4.25(m, 1H, *CH), 5.75(s, 1H, NH). ^{13}C NMR ($CDCl_3$, δ ppm): 18.9, 19.3, 29.3, 32.1, 51.9, 52.2, 60.9, 62.5, 151.6, 161.5. SM ESI$^+$ 30 eV*m/z*: 345 $[M + Na]^+$.Anal. Calc. for $C_{12}H_{22}N_2O_6S$: C 44.71, H 6.88, N 8.69. Found: C 44.75, H 6.85, N 8.75%. M=322..

(S)-methyl 2-((S)-4-isobutyl-2-oxooxazolidine-3-sulfonamido)-3-methylbutanoate(2b). M.p. = 112-114 ◦C.yield = 89%. *Rf*= 0.50(CH_2Cl_2: MeOH/95:5). $[\alpha]_D$ =+2.56(*c*=1.0, CH_2Cl_2). IR (KBr): 3289, 1743, 1759, 1350, 1150 cm^{-1}.^{1}H NMR ($CDCl_3$,δ ppm): 0.91 (2d, *J* = 7.2 Hz, 6H, 2CH_3), 1.05 (2d, *J* = 6.5 Hz, 6H, 2CH_3), 1.50 (m, 2H, CH_2-*i*But), 1.80 (m, 1H, CH-*i*But); 2.20 (m, 1H, CH-*i*Pr), 3.75 (s, 3H, OCH_3); 4.25 (m, 1H, *CHcyc), 4.00 (m, 1H, *CH), 4.10-4.40 (2dd,J_1= 5.5, J_2 =13.6Hz, 2H, CH_2cyc), 5.30(s, H, NH).^{13}C NMR ($CDCl_3$, δppm): 18.9, 23.2, 24.5, 29.3, 42.8, 43.1, 51.9, 60.9, 65.6, 151.6, 159.5.SM ESI$^+$ 30 eV*m/z*: 337 $[M+1]^+$.Anal. Calc. for $C_{13}H_{24}N_2O_6S$: C 46.41, H 7.19, N 8.33. Found: C 46.35, H 7.21, N 8.36%.

(S)-Methyl 2-((S)-4-benzyl-2-oxooxazolidine-3-sulfonamido)-3-methylbutanoate (2c).
M.p. =115-116 ◦C.yield= 74%.*Rf*= 0.33 (CH_2Cl_2: MeOH/95:5). $[\alpha]_D$ =+4.78 (*c*=1.0, CH_2Cl_2).IR (KBr): 3270, 1765, 1750, 1370, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$,δ ppm): 0.9-1.0(2d, 6H, 2CH_3), 2.67(m, 1H, CH), 3.44(d, 1H, *CH), 3.68(s, 3H, OCH_3), 3.7 (dd, *J*=13.4 Hz, *J*=10.0 Hz, 1$H_b$cyc), 3.80 (dd, *J*=13.4 Hz, *J*=3 Hz, 1H, $H_a$cyc), 4.30 (m, 2H, CH_2-Ph), 4.70 (m, 1H, *CHcyc), 7.29-7.40(m, 5H, H-Ar),7.7 4(s, H, NH). ^{13}C NMR ($CDCl_3$, δppm):18.9,29.3,40.2, 47.7, 51.9, 60.9, 64.9, 126. 128, 128.8, 138, 151.6, 171.5. MS ESI$^+$ 30 eV*m/z*: 371 $[M + 1]^+$.Anal. Calc. for $C_{16}H_{22}N_2O_6S$: C 51.88, H 5.99, N 7.56. Found: C 51.82, H 6.03, N 7.55%.

(S)-Methyl2-((S)-1-(hydroxymethyl)-2-methylpropylsulfonamido)-3-methylbutanoate (3a)
M.p. = 180-182 °C.yield = 65%.*Rf* = 0.35 (CH_2Cl_2:MeOH/9:1).IR (KBr): 3380, 1715, 1155, 1370 cm^{-1}. ^{1}H NMR ($CDCl_3$,δ ppm):0.90 (2d, 6H, *J*= 7.2 Hz, 6H, 2CH_3), 1.00(d, *J*=6.2 Hz, 2CH_3), 2.05 (m, 1H, CH), 2.20(m, 1H, CH), 3.10 (m, 2H, CH_2), 3.70(m, 1H, *CH), 4.20(m, 1H, *CH), 5.60(s, 1H, 1OH), 6.55(d, *J*=8.2Hz, 1H, NH), 8.20(s, 1H, OH), ^{13}C NMR ($CDCl_3$, δ ppm): 18,20, 25, 33, 52, 63, 168. SM ESI$^+$ 30 eV*m/z*: 305.53 [M+ Na] $^+$.Anal. Calc. for $C_{10}H_{22}N_2O_5S$: C 42.54, H 7.85, N 9.92. Found: C 42.59, H 7.81, N 9.95 %.

(S)-methyl2-((N-((S)-1-hydroxy-4-methylpentan-2-yl)sulfamoyl)amino)-3 methylbutanoate (3b).
M.p.= 165-167 °C.Yield = 75%.*Rf* = 0.30(CH_2Cl_2:MeOH/9:1). IR (KBr): 3417, 1720, 1172, 1377 cm^{-1}.^{1}H NMR ($CDCl_3$,δ ppm): 0.92 (2d, *J*=6.7 Hz, 6H, 2CH_3), 1.03 (2d, *J*= 6.9 Hz, 6H, 2CH_3). 1.40(m, 2H, CH_2), 2.25 (m, 2H, 2CH), 3.40-3.90 (m, 3H, CH_2-O,*CH),5.30 (d, 1H, *J*= 8.5 Hz, NH), 5.80(s, 1H, 1OH),7.60(d, 1H, *J*= 5.3Hz, NH), 10.5 (1H, s, OH), ^{13}C NMR ($CDCl_3$, δ ppm): 18, 20, 22, 23, 29, 43.5, 50, 46, 63, 165, SM ESI$^+$ 30 eV*m/z* : 319.15 [M+ Na]$^+$.Anal. Calc. for $C_{12}H_{26}N_2O_5S$: C 46.43, H 8.44, N 9.02. Found: C 46.48, H 8.49, N9.06%.

(2S,2'S)-2,2'-(sulfonylbis(azanediyl))bis(3-methylbutanoic acid) (4a).
Yellow oil. yield = 80 %.*Rf* = 0.2(CH_2Cl_2:MeOH/8:2).IR (KBr): 2980,2683, 1723, 1712, 1377, 1163 cm^{-1}.^{1}H NMR ($CDCl_3$,δ ppm): 0.93 (2d, *J*= 6.1 Hz, 6H, 2CH_3), 1.15 (2d, *J*= 6.9 Hz, 6H, 2CH_3),2.25(m,2H, 2CH), 4.10(m, 2H, 2*CH), 5.20(d, *J*=7.1Hz, 1H, NH),11.23 (s, 2H, 2OH).^{13}C NMR ($CDCl_3$, δppm): 18.4, 18.6, 22.5, 22.8, 26.3, 27.6, 63, 175.8, 179. SM ESI$^+$ 30 eV*m/z* : 319.15 [M+ Na]$^+$. Anal. Calc. for $C_{10}H_{20}N_2O_6S$: C 40.54, H 6.78, N 9.42.

Found: C 40.57, H 6.83, N 9.45 %**.**

(S)-2-((N-((S)-1-carboxy-2-methylpropyl)sulfamoyl)amino)-4-methylpentanoic acid(4b).
yellow oil .Yield = 89 %; *Rf* = 0.18(CH_2Cl_2:MeOH/8:2).IR (KBr): 2894, 2689, 1736, 1726, 1367, 1159 cm-^{1}.^{1}H NMR ($CDCl_3$,δ ppm): 0.94 (2d, *J*=6.7Hz, 6H, $2CH_3$),1.14 (2d, *J*=7.2 Hz, 6H, $2CH_3$), 1.65(m, 1H, CH*i*But), 1.70 (m, 1H, CH_2*i*But), 2.25(m,1H, CH*i*Pr), 4.00(m, 1H, *CH), 4.10(m, 1H, *CH), 5.20(d, *J*=8.3Hz, 1H, NH), 10.85(s, 2H, 2OH), ^{13}C NMR ($CDCl_3$, δppm): 18.1, 18.2, 21.5, 24.8, 26.3, 26.9, 39.4, 62.15, 175.4, 1177.6. SM ESI^{+} 30 e*V m/z*: 309.05 [M-H]$^{+}$.Anal. Calc. for $C_{11}H_{22}N_2O_6S$: C 42.57, H 7.14, N 9.03. Found: C 42.54, H 7.09, N 9.06 %.

CONCLUSION

In conclusion, we have developed a novel method for the efficient preparation of a new peptidosulfonamides structure (a dipeptide linkedby a bridgesulfone). This is ostere was successfully prepared starting from modified sulfamoyloxazolidinone by reopening of oxazolidinone cycles then catalytic oxidation using $RuCl_3$and $NaIO_4$ as oxidizing agent.

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