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Simple and Efficient Synthesis of New Chiral *N,N′*-Sulfonyl Bis-Oxazolidin-2-Ones

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ABSTRACT: *A series of new chiral N,N′-sulfonyl bis-oxazolidin-2-ones were synthesized starting from 2-aminoalcohols, sulfuryl chloride, and diethyl carbonate. This method utilizes natural amino acids as a source of chirality for the preparation of oxazolidinones.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:61–65, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20183

INTRODUCTION

Chiral oxazolidin-2-ones have emerged as a very important class of compounds in drug development especially in the area of antimicrobials [1–6], and they have been utilized as auxiliaries for a wide range of asymmetric transformations (Evans oxazolidinones) [7–11]. They are also found as a precursor in the synthesis of a variety of heterocyclic compounds, as a protecting group in organic synthesis, as ligands for metal catalysts, and as biologically active pharmaceutical agents [12–15]. In spite of these facts, very few reports in the literature have reported the synthesis and the use of *N*-sulfonyl oxazolidin-2-ones and bis-sulfonyl oxazolidin-2-one.

Previously, Dewynter et al. reported the synthesis of sulfonyl bis-oxazolidin-2-one **2** for development of soft crosslinking and reticulation reagent for bionucleophiles [16]. Lee et al. described the synthesis of the first hydrosoluble C-2 symmetric bis(oxazolidinone) [17] **1** as a potential bifunctional chiral auxiliary via regioselective intramolecular cyclization of the bis(carbamate). Due to our interest in the reactivity of *N*-sulfonyl oxazolidin-2-ones, we attempted their conversion to chiral bis *N,N′*-sulfonyl bis-oxazolidin-2-ones **3**.

Recently, we have reported the synthesis and the reactivity of the *N*-chlorosulfonyl oxazolidin-2-ones toward aminoesters [17]. In this paper, we have extended our studies in the chiral *N,N′*-sulfonyl bis-oxazolidin-2-ones C_2-symmetric and unsymmetric, in which both heterocyclic carbonyl groups can serve as electrophilic centers. Relating to structural filiation, these compounds can be considered as chiral *sulfa*-analogues of carbonyl and phosphoryl reagents such as carbonyldimidazole (CDI) and bis-oxazolidin-2-one phosphoryl chloride (BOP-Cl) [18].

To Dr Kamel Seghoum, *in memoriam*.

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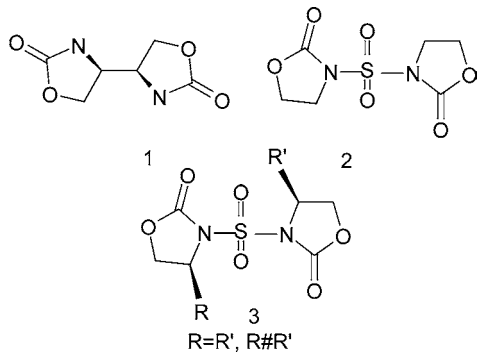


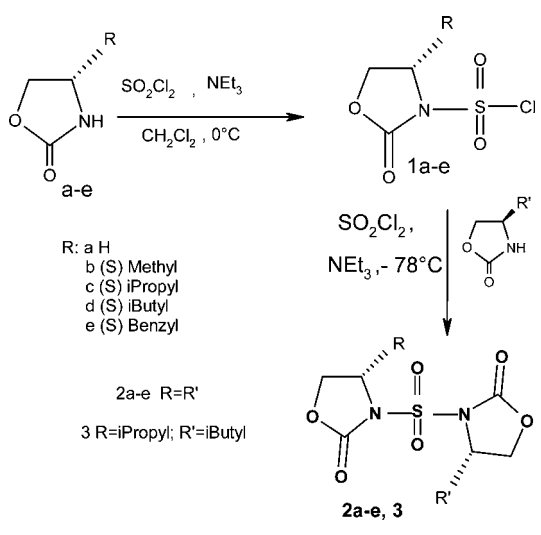
FIGURE 1

CHEMISTRY

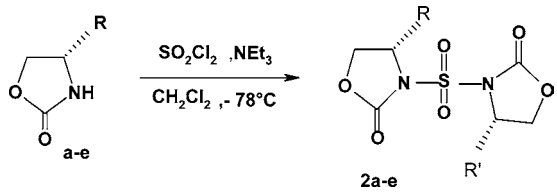
The purpose of using amino acids was to introduce the chirality in the target molecules. The reaction between amino alcohols and diethyl carbonate has proved to yield a direct route to oxazolidinones. The chiral oxazolidinon-2-ones can be prepared in two steps starting from the corresponding amino acids (Ala, Val, Leu, Phe), reduction with sodium borohydride, and cyclization using diethyl carbonate [19]. Sulfuryl chloride was used to introduce the chlorosulfonyl and sulfonyl moieties on oxazolidinone and bis-*N*-sulfonyloxazolidinon-2-ones (SBO).

Alternatively, SBO can be synthesized directly starting from sulfuryl chloride and oxazolidin-2-one, or in two steps by formation of *N*-chlorosulfonyloxazolidin-2-ones (CSO) as an intermediate.

The route to the C_2-symmetric and unsymmetric SBO **2a–e, 3** is outlined in Scheme 1. Different chiral chlorosulfonyloxazolidin-2-ones **1a–e** have been synthesized starting from sulfuryl chloride, and chiral oxazolidin-2-one by substitution in the presence of triethylamine in dichloromethane at 0°C under anhydrous argon atmosphere produces CSO in satisfactory yields.



SCHEME 1

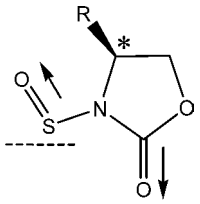


SCHEME 2

CSO 1 can be coupled with oxazolidin-2-one in anhydrous methylene chloride in the presence of TEA at −78°C to yield C_2-symmetric **2a–e** and unsymmetric **3** *N*,*N*′-sulfonyl bis oxazolidin-2-ones (SBO) in acceptable yield.

The symmetric *N*,*N*′-sulfonyl bis-oxazolidin-2-ones have been synthesized using sulfuryl chloride directly, starting from corresponding commercially available or easy accessible chiral oxazolidin-2-ones (Scheme 2). Starting materials were treated at −78°C with 1 eq. of sulfuryl chloride for 1 h leading to the title compounds in satisfactory yields.

The structure of all compounds was unambiguously confirmed by usual spectroscopic methods. For resulting compounds **2a–e**, IR spectra showed bands at 1782–1800 cm^{-1} (C=O), suggesting its strong electrophilic ability. Characteristic bands for the sulfonyl group appear at 1110–1170 cm^{-1} and 1350–1185 cm^{-1}. ^1H NMR spectra of the resulting compounds showed *dd* and multiplet system due to the diastereotopic methylene protons of oxazolidin-2-one heterocycle.



As revealed by X-Ray crystallographic analysis [16], each heterocyclic moiety and S=O group shows selective antiperiplanar orientation, which enhances values of α_D for the chiral C2-dimeric forms **2a–e**. SBO could be considered as a rigid skeleton grafted with substituents allowing structural and stereochemical diversity.

In conclusion, we have established a strategy described herein as effective method for the synthesis of a new variety of symmetric and unsymmetric SBO. Work is currently in progress to evaluate the reactivity of the chiral (SBO) to the primary or

secondary amines and the linkage and the reticulation of biomolecules, especially proteins. These compounds are currently being evaluated for biological activity, and the results of these investigations will be reported in due course.

EXPERIMENTAL

All commercial chemicals and solvents were used as received. All reactions were carried out under an inert atmosphere of argon. TLC analyses were performed on silica gel 60 F_{254} plates (Merck Art.1.05554). Spots were visualized under 254 nm UV illumination, or by ninhydrin solution spraying. Melting points were determined on a Büchi melting point 510 and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer FT–IR spectrometer S1000. ^{1}H and ^{13}C NMR spectra were determined with a AC-250 Brüker spectrometer. For ^{1}H-NMR spectra, chemical shifts are expressed in δ (ppm) downfield from tetramethylsilane, and coupling constants (J) are expressed in Hertz. Electron ionization mass spectra (30 eV) were recorded in positive or negative mode on a Water MicroMass ZQ. High-resolution mass spectra were measured on a Jeol SX102 mass spectrometer and recorded in FAB positive mode.

General Procedure

Synthesis of N-chlorosulfonyloxazolidin-2-ones. To a solution of oxazolidin-ones **1–5** (10 mmol, 1 eq.) and triethylamine (0.670 mL, 0.486 g, 12 mmol, 1.2 eq.) in 20 mL, anhydrous methylene chloride in the presence of a catalytic quantity of dimethylamino pyridine (DMAP) at 0°C was added dropwise a solution of sulfuryl chloride (10 mmol, 1.350 g, 0.833 mL) in the same solvent (10 mL). The reaction was stirred under argon at 0°C for less than 1 h. The solvent was concentrated to 20 mL under reduced pressure, and the solution was washed with HCl 0.1 N and water. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. Recrystallization from the crude product in $CHCl_3$–hexane 1/5 or flash chromatography (CH_2Cl_2) afforded chlorosulfonyl oxazolidin-2-one **1a–e** in 67–80% yields.

N-chlorosulfonyl-oxazolidin-2-one **1a**. Yield: 75%; mp 89–90°C. R_f 0.65 (CH_2Cl_2: MeOH 95:5). ^{1}H NMR ($CDCl_3$, δ): 4.20 (t, 2H, J = 6.6 Hz), 4.50 (t, 2H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, δ): 150, 63, 46. IR (KBr): 1800, 1405, 1188 cm^{-1}; MS ESI$^+$ 30 eVm/z: 208 [M + Na]$^+$. HRMS [calcd. for $C_3H_4ClNO_4S + H^+$: m/z [M + H]$^+$ (185.9628): found 185.9623.

(S)-4-Methyl-N-chlorosulfonyl-oxazolidin-2-one **1b.** Yield: 79%; mp 47–48°C. R_f 0.70 (CH_2Cl_2: MeOH 95:5). $[\alpha]_D = -12.1$ (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, δ): 4.6 (m, 2H), 4.10 (m, 2H), 1.60 (d, J = 6.1 Hz, 3H).^{13}C NMR ($CDCl_3$, δ): 150, 70, 56, 19. IR (KBr): 1785, 1385, 1175 cm^{-1}; MS ESI$^+$ 30 eV m/z: 222 [M + Na]$^+$. HRMS calcd for $C_4H_6ClNO_4S + H^+$: m/z [M + H]$^+$ 199.9784, found 199.9779.

(S)-4-Isopropyl-N-chlorosulfonyl-oxazolidin-2-one **1c**. Yield: 88%; mp 42–43°C. R_f = 068 (CH_2Cl_2: MeOH 95:5). $[\alpha]_D = +3.5$ (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, δ): 4.20–4.40 (m, 2H); 2.50 (m, 1H); 1.00 (2d, J = 9.0 Hz, 6H).^{13}C NMR ($CDCl_3$, δ): 150, 64, 63, 29, 18, 14. IR (KBr): 1790, 1400, 1188 cm^{-1}. MS ESI$^+$ 30 eVm/z: 250 [M + Na]$^+$. HRMS calcd for $C_6H_{10}ClNO_4S + H^+$: m/z [M + H]$^+$ 228.0097, found 228.0092.

(S)-4-Isobutyl-N-chlorosulfonyl-oxazolidin-2-one **1d.** Yield: 82%; mp 38–39°C. R_f = 064 (CH_2Cl_2: MeOH 95:5). $[\alpha]_D = +7.4$ (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, δ): 4.40 (m, 2H), 4.20 (m, 2H), 2.10 (m, 1H), 1.70 (m, 2H), 1.00 (2d, J = 9.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, δ): 150, 68, 58, 41, 24, 23, 21. IR (KBr): 1793, 1415, 1191 cm^{-1}. MS ESI$^+$ 30 eV m/z: 264 [M + Na]$^+$. HRMS calcd for $C_7H_{12}ClNO_4S + H^+$: m/z [M + H]$^+$ 242.0254, found 242.0249.

(S)-4-Benzyl-N-chlorosulfonyl-oxazolidin-2-one **1e**. Yield: 85%; mp 80–81°C; R_f = 0.74 (CH_2Cl_2: MeOH 95:5). $[\alpha]_D = -6.5$ (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, δ): 7.20–7.42 (m, 5H), 4.70 (m, 1H), 4.30 (m, 2H), 3.60 (dd, J = 13.4 Hz, J = 3 Hz, 1H), 3.05 (dd, J = 13.4 Hz, J = 10.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, δ): 150, 134, 130, 128, 67, 60, 38. IR (KBr): 1780, 1395, 1170 cm^{-1}. MS ESI$^+$ 30 eVm/z: 298 [M + Na]$^+$. HRMS calcd for $C_{10}H_{10}ClNO_4S + H^+$: m/z [M + H]$^+$ 276.0097, found 276.0092.

*Preparation of Symmetric N,N'-sulfonyl bis-oxazolidin-2-ones (**2a–e**): Procedure 1*

Oxazolidin-2-one (2 eq.) in anhydrous CH_2Cl_2 (20 mL) was added sequentially to a 100-mL round bottom flask fitted with argon balloon. The solution was cooled to −78°C; triethylamine (2.78 mL, 2.02 g, 22 mmol, 2.2 eq.) and catalytic quantity of DMAP added slowly, and the resulting solution was stirred for 30 min. A solution of sulfuryl chloride in the same solvent (0.83 mL, 1.35 g, 10 mmol, 1 eq.) was added slowly over 1 h, and the resulting yellow solution was stirred for 3 h. The reaction mixture was washed with HCl 0.1 N and water. The organic layer is dried over magnesium sulfate, concentrated and separated by chromatography on silica gel (eluted with CH_2Cl_2/CH_2OH 9.5: 0.5) to afford bis-N,N'-sulfonyl bis-oxazolin-2-one as white solid in acceptable yields.

*Preparation of Symmetric and Unsymmetric N,N′-sulfonyl Oxazolidin-2-ones (**2a–e, 3**): Procedure 2*

Coupling of Chlorosulfonyl Oxazolidin-2-ones with Oxazolidin-2-ones. To a stirred solution of oxazolidin-2-one (1 eq., 5 mmol) in anhydrous CH_2Cl_2 (20 mL) in the presence of triethylamine (1.2 eq., 6 mmol, 0.60 g, 0.82 mL) and catalytic amount of (DMAP) at −78% was added chlorosulfonyl oxazolidin-2-one (5 mmol, 1 eq.) in the same solvent (15 mL). The reaction mixture was stirred for 3 h at −78°C under argon. The reaction was monitored by TLC. The resulting reaction solution was allowed to warm up to room temperature for 1 h. The reaction mixture was diluted with 20 mL of methylene chloride and washed with HCl 0.1 N and water. The organic layer is dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluted with CH_2Cl_2/EP 9:1) to afford of *N,N′*sulfonyl bis-oxazolidin-2-one as white solid in good yields.

N,N′-Sulfonyl bis-oxazolidin-2-one **2a**. Yield: 70%; mp 235–238°C. $R_f = 0.62$ (CH_2Cl_2: MeOH 95:5). ^{1}H NMR ($CDCl_3$, δ): 4.65 (t, $J = 7.7$ Hz, 2H); 4.15 (t, $J = 7.7$ Hz, 2H). ^{13}C NMR ($CDCl_3$, δ): 149.2, 63.5, 46.5. IR (KBr, ν): 1800, 1405, 1188 cm^{-1}. MS ESI$^+$ 30 eV*m/z*: 259 [M + Na]$^+$. HRMS calcd for $C_6H_8N_2O_6S$ + H$^+$: *m/z* [M + H]$^+$ 237.0314, found 237.0313.

N,N′-Sulfonyl-bis-[(4S)-methyl-oxazolidin-2-one] **2b**. Yield: 80%; mp 108–110°C. R_f: 0.75 (CH_2Cl_2: MeOH 95:5). $[\alpha]_D = -144$ ($c = 1$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, δ): 4.72–4.60 (2dd, $J = 11.2$, 7.4, 4.3 Hz, 4H), 4.12 (m, 2H), 1.65 (d, $J = 6.1$ Hz, 3H).^{13}C NMR ($CDCl_3$, δ): 150.3, 71.2, 56.4, 18.5. IR (KBr, ν): 1795, 1375, 1185 cm^{-1}; MS ESI$^+$ 30 eV*m/z*: 287 [M + Na]$^+$. HRMS calcd for $C_8H_{12}N_2O_6S$ + H$^+$: *m/z* [M + H]$^+$ 264.9784, found 264.9779.

N,N′-Sulfonyl-bis-[(4S)-isopropyl-oxazolin-2-one] **2c**. Yield: 76%; mp 120–122°C; $R_f = 0.71$ (CH_2Cl_2: MeOH 95:5). $[\alpha]_D = +32.5$ ($c = 1$, CH_2Cl_2). ^{1}H NMR($CDCl_3$, δ): 4.50 (m, 4H), 4.25 (m, 2H), 2.25 (m, 2H), 0.95 (2d, $J = 9.1$ Hz, 12 H). ^{13}C NMR ($CDCl_3$, δ): 151.2, 63.2, 60.1, 30.1, 18.6, 14.5. IR (KBr,ν): 1795, 1485, 1185 cm^{-1}. MS ESI$^+$ 30 eV *m/z*: 343 [M + Na]$^+$. HRMS calcd for $C_{12}H_{20}N_2O_6S$ + H$^+$: *m/z* [M + H]$^+$ 321.1197, found 321.1192.

N,N′-Sulfonyl-bis-[(4S)-isobutyl-oxazolidin-2-one] **2d**. Yield: 68%; mp 112–114°C; $R_f = 0.71$ (CH_2Cl_2: MeOH 95:5). $[\alpha]_D = +117.4$ ($c = 1$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, δ): 4.55–4.30 (2dd, $J = 3.8$, 8.6, 6.2 Hz, 4H), 4.50 (m, 2H), 2.1 (m, 2H), 1.65 (m, 4H), 1.05 (2d, $J = 9.2$ Hz, 12H). ^{13}C NMR ($CDCl_3$, δ) 152.7, 68.2, 59.4, 41.2, 24.3, 23.1, 21.8. IR (KBr,ν): 1794, 1405, 1189 cm^{-1} . MS ESI$^+$ 30 eV *m/z*: 371 [M + Na]$^+$. HRMS calcd for $C_{14}H_{24}N_2O_6S$ + H$^+$: *m/z* [M + H]$^+$ 349.0264, found 349.0259.

N,N′-Sulfonyl-bis-[(4S)-benzyl-oxazolidin-2-one] **2e**. Yield = 72%; mp 125–127°C; $R_f = 0.77$ (CH_2Cl_2: MeOH 95:5). $[\alpha]_D = -34.5$ ($c = 1$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, δ): 7.40 (m, 10H), 4.87 (m, 2H,); 4.61–4.25 (2dd, $J_{vc} = 3.9$, 8.7, 9.2 Hz, 4H); 3.68–3.00 (2dd, $J_c = 3.7$, 9.1, 13.6 Hz, 4H).^{13}C NMR ($CDCl_3$, δ): 154.7, 136.4, 135.3, 131.4, 128.4, 127.5, 126.7, 68.2, 60.1, 41.2. IR (KBr, ν): 1782, 1392, 1175 cm^{-1}. MS ESI$^+$ 30 eV *m/z*: 439 [M + Na]$^+$. HRMS calcd for $C_{20}H_{22}N_2O_6S$ + H$^+$: *m/z* [M + H]$^+$ 417.0135, found 417.0143.

N,N′-Sulfonyl-4S-isopropyl,4′S-isobutyl-bis-oxazolidin-2-one **3**. Yield = 65%; mp 100–102°C; ^{1}H NMR ($CDCl_3$, δ): 4.60 (m, 1H); 4.05–4.35 (m, 4H); 3.70 (m, 1H); 1.70 (m, 2H); 1.55 (m, 2H); 1.00 (2d, $J = 6.7$ Hz, 6H); 0.90 (d, $J = 6.9$ Hz, 6H). ^{13}C NMR ($CDCl_3$, δ): 160.2, 156.3, 68.4, 66.8, 58, 56, 41.8, 31.9, 25.1, 23.2, 21.1, 18.1, 17.2. MS ESI$^+$ 30 eV *m/z*: 385 [M + Na]$^+$. HRMS calcd for $C_{13}H_{22}N_2O_6S$ +H$^+$: *m/z* [M + H]$^+$ 438.9784, found 438.9779.

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