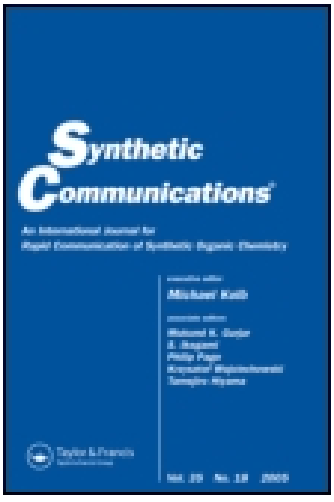

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Efficient Synthesis of Chiral 1,1′-Sulfonyl Bisaziridines

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Abstract: An efficient three-step synthesis of chiral 1,1′-(sulfonyl)bisaziridines is described. Preparation of these compounds was carried out easily starting from N,N′-sulfonyl bis-(α-L-aminoester) to afford the title compounds in very good yields. These 1,1′-(sulfonyl)bisaziridines can constitute interesting synthetic building blocks.

Keywords: Sulfonylbisaziridine, sulfamide, aziridine, heterocycle

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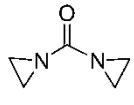
INTRODUCTION

Aziridines constitute an important class of heterocyclic compounds, which have found use in organic and medicinal chemistry.[1] They form a part of several natural products, and they are useful intermediates for the preparation of interesting biological molecules such as amino acids,[2] heterocycles,[3] and alkaloids.[4] Moreover, aziridines have important synthetic value, as they are able to react with various nucleophiles and to undergo regioselective ring-opening reactions.[5]

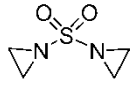
Among all the aziridine derivatives described in literature, 1,1′-sulfonylbisaziridine constitutes an original intermediate with potential applications in medicinal chemistry. Moreover, it can be considered as a sulfonyl equivalent of 1,1′-carbonylbisaziridine and also of TEPA (N,N′,N″-triethylenephosphoramide) compounds, such as thioTEPA (N,N′,N″-triethylenethiophosphoramide) which is well known for its anticancer properties.[6]

Despite their potential as synthetic intermediates for the preparation of compounds with potential biological interest, chiral 1,1′-sulfonylbisaziridines have received very little attention in the literature. Up to now, very few examples of such compounds have been reported. Only the synthesis of the nonsubstituted 1,1′-sulfonylbisaziridine has been previously described using direct coupling of aziridine with sulfuryl chloride.[7,8]

Herein, we report a simple and efficient method for the synthesis of chiral 1,1′-sulfonylbisaziridines from the ring-closing reaction of the bis-(chloroethylamino) precursor.



1,1'-carbonylbisaziridine



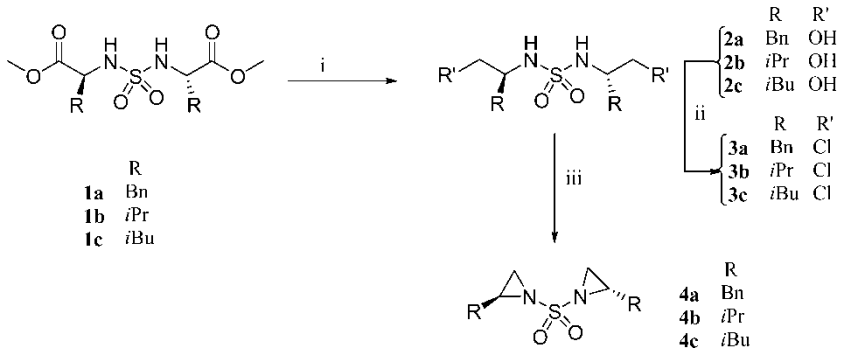
1,1'-sulfonylbisaziridine

ThioTEPA

CHEMISTRY

Chiral 1,1′-sulfonylbisaziridines **4a–c** have been obtained in three steps starting from N,N′-sulfonyl bis-(α-L-aminoester) **1a–c** prepared as previously described.[9] In the first step (Scheme 1), the reduction of **1a–c** with $LiAlH_4$ in anhydrous THF provided N,N′-bis (1-alkyl-2-hydroxyethyl) sulfamides **2a–c** in 80% yield. Chlorination of **2a–c** using SO_2Cl_2/TEA at $-78^{\circ}C$ furnished the corresponding N,N′-bis (1-alkyl-2-chloroethyl) sulfamides **3a–c** in high yields. At this stage, the aziridine rings were generated by a cyclization reaction using K_2CO_3 in acetonitrile (Scheme 1) to yield substituted 1,1′-sulfonylbisaziridines **4a–c**.

The structures of all compounds were unambiguously confirmed by the usual spectroscopic and spectrometric analysis. In compound **4c**, we notice



Scheme 1. Reagents and conditions: (i) $LiAlH_4$, THF, 0°C 1 h, and reflux 3 h (80%); (ii) SO_2Cl_2, Et_3N, CH_2Cl_2, −78°C 3 h, and rt 10 h (70%), (iii) K_2CO_3, CH_3CN, rt 5 h (85%).

the nonequivalence of the methylene protons in the *iso*butyl group that appear in the NMR spectrum as two multiplets at δ 1.25 and δ 1.52. Similarly, the two protons of the aziridine rings methylene group were nonequivalent. For the three final derivatives **4a–c,**the different NMR spectra showed a pair of doublets, due to the adjacent methine proton at C-2, at δ 2.15 and δ 2.62 ($\Delta\delta \sim 0.50$ ppm) with coupling constants $J = 4.60$ Hz and $J = 6.90$ Hz in the cyclic system. Moreover, all the compounds exhibited characteristic absorption bands (SO_2) in the infrared spectrum at 1110–1170 cm^{-1} and 1340–1390 cm^{-1}.

CONCLUSION

An expedient route has been developed for the preparation of bis-aziridinyl-sulfones (**4a–c**). The synthesis has been performed easily starting from N,N′-sulfonyl bis-L-amino esters. The strategy we describe is highly flexible and applicable to the synthesis of an array of scaffolds with different modifications on the side chain. This work now provides reliable access to this class of derivatives and opens the way to further applications. Work along this line is currently in progress.

EXPERIMENTAL

General

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrometer. Proton nuclear magnetic resonance was determined with an AC 250-MHz Bruker spectrometer. 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), q (quadruplet), m (multiplet) and combination of these signals. Electron ionization mass spectra (30 eV) were recorded in positive or negative mode on a Water MicroMass ZQ. Optical rotations were measured in a 1-cm cell on a Perkin-Elmer polarimeter. All reactions were monitored by TLC on silica Merck h60 F_{254} precoated aluminium plates and were developed by spraying with ninhydrin solution. Column chromatographies were performed on Merck silica gel (230–400 mesh).

General Procedure for the Reduction of N,N′-sulfonyl-bis-L-aminoesters

One equiv. of bis-L-aminoestersulfone **1** in anhydrous THF was added dropwise to 3.5 eq. of lithium aluminium hydride in the same solvent at 0°C, and the medium was refluxed with stirring for 3.5 h. The reaction was cooled in an ice bath, and the excess of lithium aluminium hydride was neutralized by addition of THF-H_2O (4/1). The resulting solution was stirred for 1 h and then filtered through Celite®. The solvent was removed under reduced pressure, and the solution was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum.

Data

S,S-N,N′-bis (1-Benzyl-2-hydroxyethyl) sulfamide (2a): White solid; yield 80%, mp 97–98°C; TLC: $R_f = 0.70$ (CH_2Cl_2-MeOH, 9 : 1); $[\alpha]_D = +36.26^\circ$ (c = 0.10 MeOH); IR (KBr, ν cm^{-1}) 3668 (OH), 3328, 3258 (NH), 1330 and 1134 (SO_2). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 2.75–3.0 (m, 8H, $CH_2Ph + CH_2OH$), 3.30–3.75 (m, 6H, C ∗ H + OH + NH), 7.30 (m, 10H, H arom); ^{13}C NMR ($CDCl_3$, 250 MHz) δ: 38.16, 46.74, 55.20, 127.18, 128.65, 129.40, 136.43; MS ESI$^+$ 30 eV m/z: 387 $[M + Na]^+$.

S,S-N,N′-bis (1-Isopropyl-2-hydroxyethyl) sulfamide (2b): White solid; yield 80%; mp 110–112°C; TLC: $R_f = 0.54$ (CH_2Cl_2-MeOH, 9 : 1), $[\alpha]_D = -6.26^\circ$ (c = 0.74 MeOH); IR (KBr, ν cm^{-1}) 3471 (OH), 3282, 3220 (NH), 1326 and 1118 (SO_2); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.85 (2 × d, $J = 6.4$ Hz, 12H, $4CH_3$), 1.82 (m, 2H, 2CH), 3.0 (m, 2H, 2C ∗ H), 3.40 (m, 4H, $2CH_2$), 4.72 (m, 2H, 2OH), 6.3 (d, $J = 8.2$ Hz, 2H, 2NH); ^{13}C NMR ($CDCl_3$, 250 MHz) δ: 16.70, 17.80, 27.45, 40.40, 52.60; MS ESI$^-$ 20 eV m/z: 267.05 $[M\text{-}H]^-$; ESI$^+$ 30 eV m/z: 291.16 $[M + Na]^+$.

S,S-N,N′-bis [1-Isobutyl-2-hydroxyethyl) sulfamide (2c): White solid; yield 83%; mp 100–102°C; TLC: $R_f = 0.37$ (CH_2Cl_2-MeOH, 9 : 1); $[\alpha]_D = +21.26^\circ$ (c = 0.10 MeOH); IR (KBr, ν cm^{-1}) 3668 (OH), 3328,

3258 (NH), 1330, 1134 (SO_2); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.85 (2 × d, $J = 6.0$ Hz, 12H, $4CH_3$), 1.25 (m, 4H, $2CH_2$ *i*Bu), 1.70 (m, 2H, 2CH *i*Bu), 3.30–3.50 (m, 4H, 2C ∗ H + 2NH), 3.65 (s, 2H, 2 OH), 3.75 (m, 4H, $2CH_2O$); ^{13}C NMR ($CDCl_3$, 250 MHz) δ: 22.38, 22.69, 24.53, 41.07, 54.64, 64.90; MS ESI$^+$ 30 eV m/z: 319.34 $[M + Na]^+$, 297.34 $[M + H]^+$; ESI$^-$ 20 eV m/z: 295.17 $[M\text{-}H]^-$.

General Procedure for Chlorination

The compound N,N -bis (1-alkyl-2-hydroxyethyl) sulfamide **2** was dissolved in dry dichloromethane under an argon atmosphere. Triethylamine (2.5 eq.) was added to the solution at −78°C. Sulfuryl chloride (0.5 eq.) was added dropwise to the solution, and the reaction mixture was kept under constant stirring at −78°C for 3 h. The reaction mixture was allowed to warm to room temperature for 10 h. The mixture was washed with HCl 1 N and water. The organic layer was dried over anhydrous sodium sulfate and removed under reduced pressure. The residue was purified on a silica-gel column (CH_2Cl_2) to afford the expected product **3** in good yield.

Data

S,S-N,N′-bis (1-Benzyl-2-chloroethyl) sulfamide (3a): White oil; yield 82%, R_f =0.50 (CH_2Cl_2); $[\alpha]_D = -2.72°$ (c = 0.11, $CHCl_3$); IR (CCl_4, ν cm^{-1}): 3228 (NH), 1292 and 1149 (SO_2); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.8–3.15 (m, 4H, CH_2-Ph), 3.30–3.80 (m, 2H, ∗CH), 4.20 (2 × d, $J = 2.8$ Hz, $J = 2.5$ Hz, 1H), 5.50 (m, 2H, 2NH), 7.30 (m, 10H, H arom); ^{13}C NMR ($CDCl_3$, 250 MHz) δ: 39.16, 46.74, 53.20, 127.24, 128.75, 129.65, 136.45; MS ESI$^+$ 30 eV m/z: 422.92 $[M + Na]^+$; ESI$^-$ 20 eV 399 $[M-H]^-$.

S,S-N,N′-bis (1-Isopropyl-2-chloroethyl) sulfamide (3b): White solid; yield 70%; $R_f = 0.60$ (CH_2Cl_2); mp 80–82°C; $[\alpha]_D = +59°$ (c = 0.38, $CHCl_3$); IR (KBr, ν cm^{-1}): 3298 (NH), 1326 and 1137 (SO_2); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.96 (2 × d, $J = 6.9$ Hz, 12H, $4CH_3$), 2.00 (m, 2H, 2CH *i*Pr), 3.42 (m, 2H, 2C ∗ H), 3.80 (m, 4H, $2CH_2Cl$), 4.50 (d, $J = 9.0$ Hz, 2H, 2NH); ^{13}C NMR ($CDCl_3$) δ: 17.70, 18.8, 31.5, 48.40, 54.80; MS ESI$^+$ 30 eV m/z: 328.88 $[M + Na]^+$, ESI$^-$ 20 eV m/z: 303.99 $[M-H]^-$.

S,S-N,N′-bis (1-Isobutyl-2-chloroethyl) sulfamide (3c): Yellow oil; yield 80%, $R_f = 0.62$ (CH_2Cl_2); $[\alpha]_D = -29°$ (c = 0.01, CH_2Cl_3); IR (CCl_4, ν cm^{-1}): 3289 (NH), 1322 and 1126 (SO_2); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.98 (2 × d, $J = 6.0$ Hz, 12H, $4CH_3$), 1.50 (m, 4H, $2CH_2$ *i*Bu), 1.70 (m, 2H, 2CH *i*Bu), 3.65 (dd, 2H, $J = 2.6$, 3.6 Hz, 2CH), 3.70 (m, 2H, 2C ∗ H), 3.90 (dd, 2H, $J = 3.6$, 4.10 Hz, 2CH), 4.42 (s, 1H, NH); ^{13}C NMR

($CDCl_3$, 250 MHz) δ: 21.61, 21.88, 23.40, 40.46, 47.38, 52.18. MS ESI^+ 30 eV m/z: 333.34 $[M+H]^+$, ESI^+ 20 eV m/z: 331.10 $[M-H]^-$.

Typical Experimental Procedure for the Synthesis of 4a–c

A solution of **3** (0.10 g, 0.2 mmol) and K_2CO_3 (0.05 g, 0.3 mmol) in CH_3CN (20 ml) was stirred at room temperature for 5 h. The reaction was monitored by TLC. Then the reaction mixture was filtered and concentrated under vacuum. The residue was purified on a silica-gel column using chloroform as the eluent.

Data

S,S-N,N′-bis(2-Benzylaziridin-1-yl) sulfone (4a): Yellow oil yield 90%; $R_f = 0.60$ (CH_2Cl_2); $[\alpha]_D = -12^\circ$ (c = 0.01, CH_3OH); IR (CCl_4, ν cm^{-1}): 3289 (NH), 1322 and 1126 (SO_2); ^1H NMR ($CDCl_3$, 250 MHz) δ: 2.17 (d, $J = 4.4$ Hz, 2H, $2C_3H$), 2.71 (m, 2H, $2C_3H$), 2.76–3.12 (m, 6H, 2 $CH_2Ph + 2C*H$), 7.33 (m, 10H, H arom); ^{13}C NMR ($CDCl_3$, 250 MHz) δ: 39.60, 41.20, 43.40, 126.98, 128.64, 129.25, 136.93; MS ESI^+ 30 eV m/z: 351.06 $[M+Na]^+$.

S,S-N,N'-bis(2-Isopropylaziridin-1-yl) sulfone (4b): White solid; yield 85%; $R_f = 0.75$ (CH_2Cl_2); mp 60–61°C; $[\alpha]_D = +82.90^\circ$ (c = 0.38, $CHCl_3$); IR (KBr ν cm^{-1}): 1312 and 1120 (SO_2); ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.10 (d, 12H, $J = 6.70$ Hz, $4CH_3$), 1.54 (m, 2H, 2CH), 2.24 (m, 2H, $2C_3H$), 2.62 (m, 4H, $2C_3H + 2C*H$). ^{13}C NMR ($CDCl_3$, 250 MHz) δ: 17.80, 18.80, 33.54, 40.20, 41.50. MS (ESI^+, 30 eV): 255.20 $[M+Na]^+$.

N,N′-bis (2-Isobutylaziridin-1-yl) sulfone (4c): Yellow oil; yield 90%; R_f =0.75 (CH_2Cl_2); $[\alpha]_D = -64.94^\circ$ (c = 0.97, CH_2Cl_2); IR (CCl_4, ν cm^{-1}): 1332 and 1144 (SO_2); ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.8 (2 × d, $J = 2.0$, 3.30 Hz, $4CH_3$), 1.30 (m, 2H, 2CH *i*Bu), 1.55 (m, 2H, 2CH), 1.84 (m, 2H, 2CH), 2.15 (d, $J = 4.60$ Hz, 2H, $2C_3H$), 2.62 (d, $J = 6.90$ Hz, 2H, $2C_3H$), 2.78 (m, 2H, $2C*H$); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 22.05, 22.77, 26.65, 34.57, 39.34, 40.32. MS ESI^+ 30 eV m/z: 283.28 $[M+Na]^+$, 261.29 $[M+H]^+$.

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