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Sulfonyl *Bis*-N-Oxazolidinone (SBO): A New Versatile Dielectrophile with Sequential Reactivity

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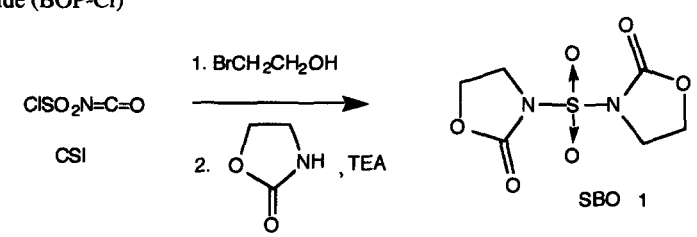
Abstract The sulfonyl*bis-N* -oxazolidinone (SBO) was designed as a biscarbamoylating reagent. Its synthesis was easily carried out starting from sulfuryl chloride, chlorosulfonyl isocyanate or sulfonyl*bis*-isocyanate, using oxazolidinone and/or 2-haloethanol in *one-pot* procedures. The structure of SBO was established by X-ray crystallography. The difference of reactivity of both electrophilic carbonyl centers allows the formation of dissymetric linkages. © 1997 Elsevier Science Ltd.

In order to develope a soft crosslinking and reticulation reagent for bionucleophiles, we envisioned to prepare the symmetric sulfonyl *bis-N*-oxazolidinone (SBO 1), in which both heterocyclic carbonyl groups can serve as electrophilic centers.

According to our previous papers [1-2], the preparation of SBO proceeds *via* the formation of chlorosulfonyl 2-bromoethylcarbamate by carbamoylation of CSI in dichloromethane, followed by the N-sulfamoylation of oxazolidinone. A subsequent heterocyclization gives the expected symmetric compound in a 80% yield (Scheme1). Relating to structural filiation, this compound can be considered as a sulfonyl analogue of carbonyl and phosphoryl reagents [3] such as carbonyldimidazole (CDI) and *bis*-oxazolidinone phosphoryl chloride (BOP-Cl)



-Scheme 1-

Alternatively, SBO 1 can also be prepared starting from sulfuryl chloride and oxazolidinone by substitution in dichloromethane/pyridine (65% yield, the easyest way), or from sulfonyl*bis*-isocyanate [4] and 2-haloethanol by addition-cyclization in dichloromethane/triethylamine (85% yield).

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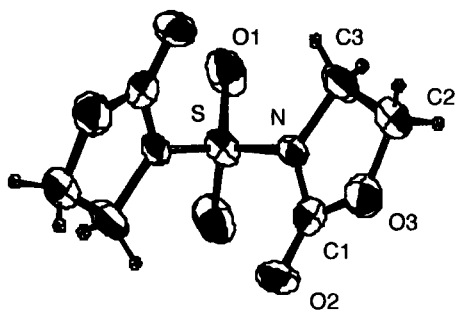
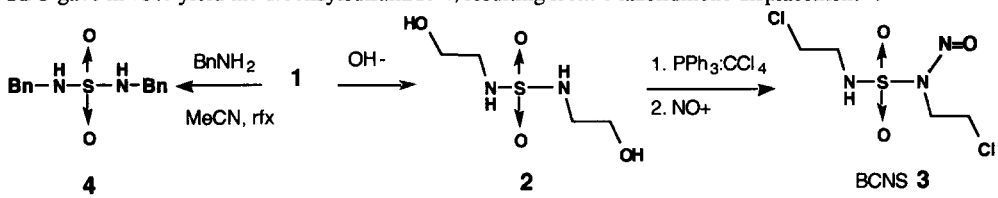
Among the spectroscopic data concerning SBO, reported in ref.8, the C=O group is characterized in IR by an absorbance at 1800 cm^{-1}, suggesting its strong electrophilic ability. The structural study was completed by a crystallographic analysis [5].



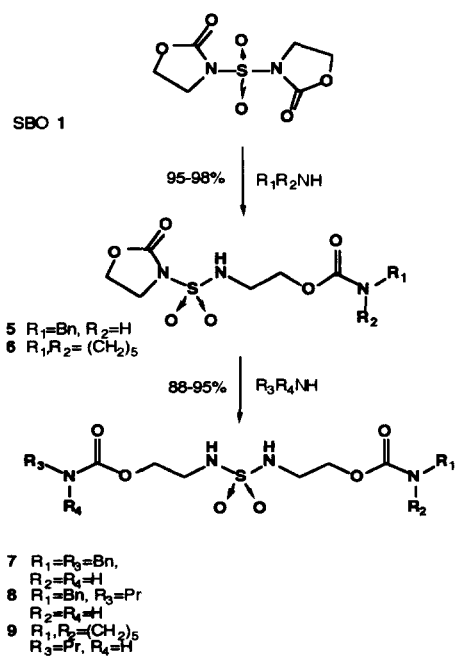
-Figure 1-

The Ortep view of the structure (Fig 1) shows an axial C_2 symmetry. The heterocyclic rings and sulfur atom are coplanar due to the sp^2 hybridization of nitrogen atoms (sum of angles around N= 358.5°) and each carbonyl group is anticoplanar with one S=O group. The angle between the heterocycle-containing planes is 87.5 ° and the intercarbonyl distance is 3.84 Å. A significant double-bond delocalization exists on the carboxylic group with bond lengths 1.20 Å (C_1-O_2) and 1.25 Å (C_1-O_3). On the other hand, both N-C_1 and N-C_3 lengths are equal (1.48 Å). By comparison, in the N-(N'-phenylsulfamoyl) 2-oxazolidinone [6], the partial double-bond character exists on the C-N bond: C_1-O_2= 1.198Å, C_1-O_3= 1.32Å, N-C_1= 1.367Å.

By saponification (2N NaOH in ethanol/water), SBO **1** furnished the *bis*-(2-hydroxyethyl) sulfamide **2** precursor of the nitrososulfamide **3** [2]. In the presence of benzylamine in boiling acetonitrile, SBO gave in 75% yield the dibenzylsulfamide **4**, resulting from oxazolidinone displacement [7].



-Scheme 2-



-Scheme 3-

The most interesting aspect of SBO chemistry regards its carbamoylating reactivity (Scheme 3). At room temperature in the presence of primary or secondary amines (*i.e.* benzylamine, propylamine, piperidine) as nucleophiles in stoechiometric conditions, SBO **1** gave the monocarbamates **5-6**. Then an excess of nucleophile (the same or other) lead to disubstituted adducts **7-9** [8].Opening of heterocycles proceeds via the N-CO cleavage, due to the preferential localization of negative charge on the sulfamide nitrogen atom [1]. Interestingly, the successive formation of *mono-* and *bis*-carbamoylated compounds shown in Scheme 3 can be followed by IR spectroscopy [8,9]. SBO **1** can be classified in the same category as anhydrides (ν C=O: 1800 cm^{-1}), whereas **5** and **6** are comparable to activated esters (1760 cm^{-1}). After the double addition, the resulting compounds **7, 8, 9** present a standard carbamate absorption (1680-1700 cm^{-1}).Such stepwise reactivity profile is well suited for the linkage of various nucleophiles under mild conditions, avoiding the formation of by-products. Moreover the unfolding of SBO during the *bis*-opening of oxazolidinones lead to interesting compounds with two different molecular entities held at a specific distance.

Work is currently in progress to evaluate the generality of this reaction and its application to the linkage and the reticulation of biomolecules, especially proteins.

Acknowledgments

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References and Notes

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5. Formula: $C_6H_8N_2O_6S$ (Mr=236.20), monoclinic, I2, a: 8.357(6), b: 5.409(7), c: 9.893(6),: β= 96.32(5), V: 445(3) Å^3, Z: 2, Dx= 1.765 Mg.m-3. λ (MoKα)= 0.70926 Å, μ= 3.605 cm^{-1}, F(000): 244, T (° K): 294, Final R: 0.087 for 360 observations. The values of bond distances and angles are reported in Tables 1 and 2.

The sample (0.10*0.15*0.35 mm) was studied on an automatic diffractometer CAD-4 Enraf-Nonius with graphite monochromatized MoKα radiation. The cell parameters were obtained by fitting a set of 25 high-theta refections. The data collection ($2\Theta_{max}$= 50°, scan: $\omega/2\theta$ = 1, t_{max} = 50 s, range of HKL: H: 0.9 ; K: 0.6; L: -11.11, intensity controls without appreciable decay : 0.5%) gives 466 reflections from which 360 independent with I>3σ (I). After Lorenz and polarization corrections, the structure was solved by a direct method with the program SHELX-86 (Scheldrick, G.M., *Crystallographic computing3: Data Collection, Structure Determination, Proteins and Databases.* Sheldrick, Kruger and Goddard, Ed., Clarendon Press, Oxford, **1985**) which reveals all the non-hydrogen atoms of the compound. After anisotropic refinement (R=0.095), many hydrogen atoms were found with a Fourier Difference. The whole structure was refined by the full-matrix least-square techniques (use of F magnitude; x, y, z, $ß_{ij}$ for S,C,N and O atoms and x, y, z for H atoms; 68 variables and 360 observations; w = $1/s(F_O)^2=[s^2(I) + (0.04F_O^2)^2]^{-1/2}$) with the resulting R: 0.087, Rw: 0.076 and Sw: 1.453 (residual $\Delta\sigma \leq 0.28$ eÅ^{-3}). The atom scattering factors are taken from *International Tables for X-Ray Crystallography, Vol IV*; Kynoch Press, Birmingham, **1974.** The calculations were performed on a Hewlett Packard 9000-710 computer for the structure determination and on Digital Micro VAX computer with the MOLEN package for refinement (Fair, C.K. *MolEN. An Intelligent System for Crystal Structure Analysis.* Enraf-Nonius, Delft, The Netherlands, 1990) and Ortep calculations (Johnson, C.K. *Ortep. Report ORNL-3794.* Oak Ridge National Lab., Tennessee, USA, **1965**). The positional parameters are reported in Table 3.

-Table 1- Bond Distances in Angstroms

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
S	O_1	1.458(8)	O_3	C_2	1.46(1)	C_2	H_{2a}	0.93(1)
S	N	1.601(8)	N	C_1	1.48(2)	C_2	H_{2b}	1.02(2)
O_2	C_1	1.20(1)	N	C_3	1.48(1)	C_3	H_{3a}	0.93(1)
O_3	C_1	1.25(1)	C_2	C_3	1.43(2)	C_3	H_{3b}	0.98(1)

-Table 2- Bond Angles in Degrees

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
O_1	S	N	110.7(4)	O_3	C_1	N	108.3(8)	N	C_3	C_2	102.3(9)
C_1	O_3	C_2	113.(1)	O_3	C_2	C_3	107.1(9)	N	C_3	H_{3a}	112.1(9)
S	N	C_1	124.9(6)	O_3	C_2	H_{2a}	111.(1)	N	C_3	H_{3b}	107.(1)
S	N	C_3	125.8(7)	O_3	C_2	H_{2b}	106.(2)	C_2	C_3	H_{3a}	117.(1)
C_1	N	C_3	107.2(9)	C_3	C_2	H_{2a}	117.(2)	C_2	C_3	H_{3b}	110.(1)
O_2	C_1	O_3	130.(1)	C_3	C_2	H_{2b}	109.(1)	H_{3a}	C_3	H_{3b}	108.(1)
O_2	C_1	N	121.(1)	H_{2a}	C_2	H_{2b}	106.(1)				

Numbers in parentheses are estimated standard deviations on the least significant digit.

-Table 3- Positional Parameters and Their Estimated Standard Deviations				
Atom	x	y	z	B(A2)
S	1.000	0.051	0.0000	3.37(6)
O_1	0.861(1)	-0.094(2)	-0.0574(8)	5.0(2)
O_2	0.7228(8)	0.410(2)	0.0110(8)	5.3(2)
O_3	0.8314(8)	0.532(2)	0.2147(7)	4.5(2)
N	0.9531(8)	0.224(2)	0.1208(7)	2.9(2)
C_1	0.822(1)	0.408(3)	0.108(1)	4.3(3)
C_2	0.959(1)	0.316(1)	0.447(4)	6.5(4)
C_3	1.057(1)	0.281(3)	0.248(1)	4.4(3)
H_{2a}	0.9177	0.3903	0.3931	5*
H_{2b}	1.0258	0.5999	0.3455	5*
H_{3a}	1.1585	0.3373	0.2317	5*
H_{3b}	1.0707	0.1259	0.3002	5*
Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: (4/3) * [a2*B(1,1) + b2*B(2,2) + c2*B(3,3) + ab(*cos* γ)*B(1,2)+ ac(*cos* ß)*B(1,3) + bc(cos α)*B(2,3)] H atoms refined isotropically.				

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7. In this case, SBO reacts as catecholsulfate (see ref 3, *vol 2*, p. 1020). Dibenzylsulfamide **3** is identified by NMR. mp: 181° C (Lit. 180-182° C, Helferich, B.; Wiehle, D. *J. Prakt. Chem.* **1961**, *14*, 177.

8.1 mp= 235-238°C. IR (KBr, ν cm^{-1}) 1800 (C=O), 1400 and 1190 (SO_2). ^1H NMR ($CDCl_3$, 250 MHz): 4.65 (t, J: 7.8 Hz, 2H, CH_2N), 4.15 (t, 2H, CH_2O). ^{13}C NMR (DMSOd6): 149.75 (C=O), 63.60 (C-N), 46.32 (C-O). MS (EI+) m/z 237 (M+H]+), 193 (M+H-CO_2]+). $C_6H_8N_2O_6S$.

5 mp= 99°C. IR (KBr, ν cm^{-1}) 3380, 3310, 1762, 1705, 1370, 1170 . ^1H NMR: 7.4-7.2 (m, 5H, ArH), 6.05 (t, 1H exch, NH carb), 5.30 (t, 1H exch, NH sulf), 4.45-4.30 (d+dd, 4H, Ph-CH_2+ NCH_2 oxaz), 4.22 (t, 2H, OCH_2 carb), 4.0 (dd, 2H, OCH_2 oxaz), 3.35 (q, 2H, $NHCH_2$).

6 mp= 108-109°C. IR (KBr, ν cm^{-1}): 3300, 1765, 1680, 1360, 1170. ^1H NMR: 6.0 (br.s, 1H exch, NH), 4.45 (dd, 2H, NCH_2 oxaz), 4.25 (t, 2H, OCH_2 carb), 4.05 (dd, 2H, OCH_2 oxaz), 3.40 (m, 6H, NCH_2 carb+pip), 1.7-1.5 (m, 6H, CH_2 pip).

7 mp= 156-158°C. IR (KBr, ν cm^{-1}): 3300, 3200, 1705, 1355, 1140. ^1H NMR (DMSO-d_6): 7.70 (t, 2H, NHCO), 7.28 (m, 10H, ArH), 7.05 (t, 2H, $NHSO_2$), 4.18 (d, 4H, CH_2Bn), 4.01 (t, 4H, CH_2O), 3.04 (q, 4H, CH_2NH). MS (EI+): 451, 318, 195, 185. ($C_{20}H_{26}N_4O_6S$).

8 mp=118-120°C. IR (KBr, ν cm^{-1}): 3460, 3400, 1695, 1320, 1150. ^1H NMR: 7.25 (m, 5H ArH), 5.50, 5.05 (2br.t, 2x1H exch, NH carb), 4.8 (m, 1H exch, NH sulf), 4.35 (d, 2H, $PhCH_2$), 4.25-4.10 (m, 4H, OCH_2), 3.35-3.20 (m, 4H, $SNHCH_2$), 3.05 (q, 2H, $CNHCH_2$) 1.50 (h, 2H, CH_2 Pr), 0.9 (t, 3H, CH_3 Pr).

9 mp<50°.IR (neat, ν cm^{-1}): 3400, 3350, 1705, 1680, 1300, 1160. ^1H NMR: 5.20 (t, 1H exch, NH carb), 4.9 (m, 2H exch, NH sulf), 4.20 (m, 4H, CH_2O), 3.40-3.20 (m, 8H, NCH_2 sulf+pip), 3.05 (q, 2H, $NHCH_2$ Pr), 1.60 (m, 2H, CH_2 Pr), 1.65 (m, 8H, CH_2 Pr+pip), 0.9 (t, 3H, CH_3 Pr).

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