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Preparation and Antimicrobial Studies of Acyclic Sulfamates

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A series of acyclic sulfamates have been prepared and tested for antimicrobial activity. Thus, the oxysulfonyl isocyanates, $ROSO_2NCO$ (**1a**, R = 4-methoxyphenyl; **1b**, R = phenyl; **1c**, R = 4-chlorophenyl and **1d**, R = 2,2,2-trifluoroethyl) have been prepared in 76–91% yield from chlorosulfonyl isocyanate. Treatment of **1a–d** with glycidol gave the glycidyl carbamates **2a–d**. Internal cyclisation afforded the corresponding 4-hydroxymethyl-2-oxazolidinones **3a–d**, which in turn were hydrolysed to give the free amino alcohols **4a–d**. The yields were in the range 39–85%. A preliminary agar diffusion test of **2a–d**, **3a–d**, **4a–d** indicated **2a–d** and **3c** to be possible antimicrobial agents. A more thorough analysis of these compounds revealed a minimum inhibition concentration (MIC) of 128 and 64 mg l^{-1} for glycidyl *p*-methoxyphenoxysulfonylcarbamate (**2a**) and glycidyl phenoxysulfonylcarbamate (**2b**) respectively, against *Branhamella catarrhalis*.

As part of a project studying the activation of 2-amino-1,3-propanediol derivatives, organic sulfamates, **5**, became available. Conversion into cyclic sulfamates has been applied by several groups as a means of activation of amino alcohols towards selective nucleophilic attack.[1] Although five-membered cyclic sulfamates, **6**, are the most commonly reported, these compounds are often too reactive to be isolated as such and disintegrate readily during storage.[2] An exception is the cyclic sulfamate moiety in the sweet-tasting 3,4-dihydro-1,2,3-oxathiazin-4-one derivatives, **7**, which have been found to be stable even in aqueous solution.[3] One reason for this difference in stability may be the lower ring strain in the six-membered ring systems. Andersen *et al.*[4] have compared acyclic and five-membered cyclic sulfamates and found the sulfur atom in the acyclic systems to be 1700 times more susceptible to attack by hydroxide anion than the corresponding sulfur atom in the cyclic systems. A lower rate of hydrolysis was therefore expected for the acyclic sulfamates than for the corresponding cyclic, five-membered systems.

In 1976, the cyclic sulfamidites **8a–c** (Fig. 1) were reported effectively to inhibit growth of *Staphylococcus aureus* and *Escherichia coli*.[5] However, there are, to our knowledge, no reports of antimicrobial studies of sulfamates in the literature. Owing to their structural resemblance to sulfamidites and sulfonamides, **9**, we decided to subject the sulfamates in our hands, **2a–d**, **3a–d**, and **4a–d** (Scheme 1) to preliminary testing for antimicrobial activity, with the purpose of revealing possible lead compounds for development of new antimicrobial agents.

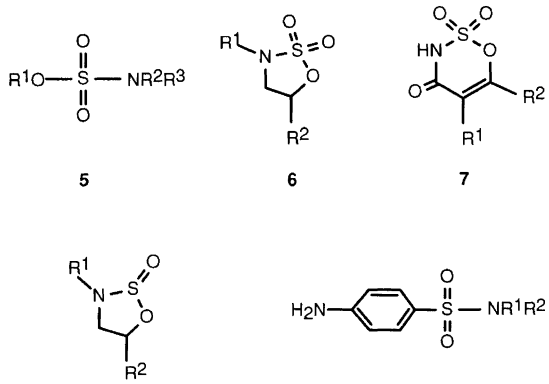

Fig. 1. For compounds **5**, **6**, **7** and **9**, R^1, R^2 and R^3 represent an alkyl or aryl group.

Synthesis. The glycidyl sulfonylcarbamates **2a–d** and the 4-hydroxymethyl-3-sulfonyl-1,3-oxazolidin-2-ones **3a–d** were prepared from the corresponding isocyanates **1a–d**

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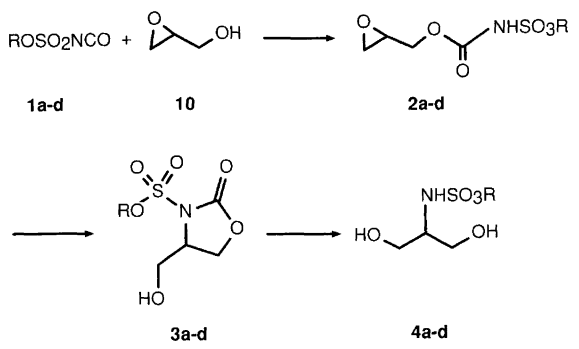


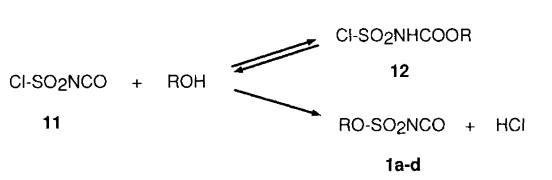
a: R = 4-MeOC$_6$H$_4$, b; R = Ph, c; R = 4-ClC$_6$H$_4$, d; R = F$_3$CCH$_2$

Scheme 1. Strategy for preparation of sulfamates **2a–d**, **3a–d** and **4a–d**.

according to a procedure reported by Hedayatullah and Brault.[6] By using glycidol, **10**, instead of the previously reported haloethanols[6] the 1,3-propanediols **4a–d** were obtained as shown in Scheme 1.

The preparation of the isocyanates **1a–d** is worthy of comment. Lohaus[7] has reported the synthesis of a large number of aryloxy- and 2,2,2-trifluoroethoxy-sulfonyl isocyanates from chlorosulfonyl isocyanate, **11**, and the respective alcohols as depicted in Scheme 2. The initial reaction between **11** and the alcohols was conducted at an elevated temperature forming the carbamates **12**. Subsequent reflux of the mixtures for several hours followed by filtration, concentration and distillation yielded pure isocyanates. In our hands, this method generally rendered lower yields than those reported by Lohaus,[7] mostly due to the high sensitivities of **1a–d** towards humidity. By omitting the filtration process, the yield of distilled **1a** was raised to 76%. For the synthesis of **1b** and **1c**, solutions of the crude products were used directly in the subsequent step. Compound **1d** was distilled together with the solvent. In these cases glycidol was added in portions until no remaining isocyanate could be detected by IR analysis of the reaction mixtures. The yields of **1b–d** reported were calculated from the amounts of glycidol consumed. The results are shown in Table 1.

The cyclisation of the glycidyl carbamates **2a–d** was expected to proceed in the presence of base, e.g. NaH or Et_3N as reported by Hedayatullah and Brault.[6] However, treatment of **2b** with NaH in refluxing THF afforded



a; R = 4-MeOC$_6$H$_4$, b; R = Ph, c; R = 4-ClC$_6$H$_4$, d; R = F$_3$CCH$_2$

Scheme 2. Lohaus protocol for the preparation of substituted sulfonyl isocyanates.[7]

Table 1. Yields of compounds **1a–d**, **2a–d**, **3a–d** and **4a–d**.

	Substituent R	**1** (%)	**2** (%)	**3** (%)	**4** (%)
a	4-MeOC$_6$H$_4$	76 (63)[a]	84[b]	80	49
b	Ph	91[c] (66)[a]	84	57	39
c	4-ClC$_6$H$_4$	89[b] (65)	74	65	78
d	F$_3$CH$_2$	83[b] (24)	79	48	85

[a]Yields reported by Lohaus.[6] [b]Crude product of 85% purity (^{1}H NMR). [c]Yields calculated on the basis of the consumption of **10** in the subsequent step.

only traces of **3b** along with several unidentified by-products. After **2b** had been refluxed in THF in the presence of Et_3N for 12 h, all substrate had been consumed to form essentially one product, **3b** (TLC). These conditions were further applied for the preparation of the oxazolidinones **3a–d** as reported in Table 1. Finally, alkaline hydrolysis of **3a–d** afforded the 1,3-propanediols **4a–d** in 39–85% yields.

Antimicrobial activity. As a preliminary screening for antimicrobial activity, an agar diffusion test was carried out for the sulfamates **2a–d**, **3a–d** and **4a–d** using *S. aureus*, *E. coli*, *Pseudomonas aeruginosa*, *Saccharomyces cerevisiae* and *Aspergillus niger* as test organisms. The following test conditions were applied. The sulfamates were dissolved in acetone (5 and 50 w%). Each solution was applied to 10 mm paper disks, which were placed on the surface of the nutrient agar after inoculation with suspensions of 3.5×10^6–8.0×10^7 colony forming units (CFU). The samples were incubated at 28 °C for 48 h. No significant effects were observed for the 5% solutions, except for substance **4c**, which exhibited an inhibition zone diameter of 24 mm. The results of the tests performed with 50% solutions are given in Table 2. The glycidyl carbamates **2a–d** and the 1,3-diol **4c** emerged as possibly antimicrobial.

The minimum inhibitory concentration (MIC/mg l^{-1}) of **2a–d** and **4c** was subsequently determined as given for the following 22 test strains: *Acinetobacter calcoaceticus*, *A. calcoaceticus* A787711, *Bacillus cereus*, *B. pumilus*, *Branhamella catarrhalis*, *Candida albicans*, *C. pseudotropicalis*, *E. coli* A4877, *E. coli* EDB, *E. coli* MB 3804, *Enterobacter cloacae*, *Enterococcus sp.*, *Klebsiella pneumoniae*, *Micrococcus luteus*, *Morganella morganii*, *P. aeruginosa*, *P. putida* A4858, *S. aureus*, *S. aureus* 4399, *S. epidermidis* MS I, *S. epidermidis* 1478, *Streptococcus agalactiae*, *Str. bovis* and *Yersinia enterocolitica*. The following conditions were applied: PDM agar (Biodisk AB, Stockholm, Sweden) was spot inoculated with samples of ca. 10^5 CFU of the test organisms and incubated at 37 °C for 24 h. The data revealed a moderate effect of glycidyl *p*-methoxyphenoxysulfonyl carbamate, **2a**, (MIC = 64 mg l^{-1}) and glycidyl phenoxysulfonyl carbamate, **2b**, (MIC = 128 mg l^{-1}) against *Br. catarrhalis*. For comparison, the following three antibiotics *ampicillin*, *doxycyclin* and *netilmicin* all gave MIC values against the bacteria in the range 0.25–1 mg l^{-1}.

Table 2. Agar diffusion test of 50% solutions of the sulfamates **2a–d**, **3a–d** and **4a–d**.

Compound	Observed inhibition zone diameters/mm				
	S. aureus	*E. coli*	*P. aeruginosa*	*S. cerevisiae*	*A. niger*
2a	16	13	12	18	0
2b	15	14	13	28	0
2c	24	17	14	20	16
2d	16	16	14	0	0
3a	11	0	0	10	0
3b	12	10	10	0	0
3c	10	10	0	0	0
3d	0	0	0	0	0
4a	0	0	0	0	0
4b	13	11	12	0	0
4c	14	12	0	13	18
4d	0	11	0	0	0

Compounds **2c**, **2d** and **4c** showed no significant activity (MIC $\geqslant$ 1024). Whether **2a** and **2b** may serve as lead compounds for development of sulfamates suitable for use as antiseptics will depend on their toxicities and environmental degradabilities.

Experimental

All reactions were carried out under a nitrogen atmosphere. The chemicals were commercial products of *p.a.* quality and used directly as received unless otherwise stated. All solvents were dried prior to use as described elsewhere.[8] Melting points were determined on a Büchi apparatus and are uncorrected. TLC was performed on Merck 5554 Fertigplatten, DC-Alufolien, Kieselgel 60_{254}, using UV light at 254 nm and 5% alcoholic molybdophosphoric acid for detection. Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX 400 FT NMR system, using $SiMe_4$ as an internal standard. IR spectra were recorded on a Nicolet 20-SXC FT-IR spectrometer. Mass spectra were recorded on an AEI MS-902 double focusing mass spectrometer (Nier–Johnson geometry). The samples were inserted directly and ionized by electron impact. Exact mass measurements were carried out by peak matching with perfluorokerosene as the standard for mass references.

Preparation of the isocyanates **1a–d**. The procedures are modifications of the methods earlier described by Lohaus.[7]

p-*Methoxyphenoxysulfonyl isocyanate,* **1a**. A solution of chlorosulfonyl isocyanate, **11**, (15.00 g, 106 mmol) in toluene (40 ml) was added to a solution of *p*-methoxyphenol (13.14 g, 106 mmol) in toluene (90 ml) at 40 °C, over a period of 30 min. The reaction mixture was then refluxed for 10 h and finally stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue distilled under reduced pressure. This gave 18.57 g (76% yield) of **1d** as a clear, colourless liquid, b.p. 101–103 °C, 0.7 mmHg (lit.[7] 96–99 °C, 0.2 mmHg, 63% yield). The product was immediately dissolved in dry CH_2Cl_2. ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 3 H), 6.92–6.97 (m, 2 H), 7.26–7.30 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 55.7, 115.1, 122.8, 129.6, 143.2, 159.3. IR (neat): 3287 (w), 2950 (w), 2252 (s), 1737 (w), 1595 (m), 1503 (s), 1485 (m), 1443 (m), 1410 (s), 1301 (m), 1255 (s), 1205 (s), 1169 (s), 1145 (s), 1105 (m), 1031 (m), 932 (w), 891 (m), 838 (m), 809 (m), 746 (m), 699 (m) cm^{-1}. MS (170 °C, 30 eV) [*m/z* (% rel. int.)]: 229 (3), 203 (31), 124 (21), 123 (100), 109 (6), 95 (10), 80 (2).

Phenoxysulfonyl isocyanate, **1b**. A solution of phenol (1.00 g, 10.6 mmol) in chlorobenzene (8 ml) was heated to 40 °C. To this solution **11** (1.51 g, 10.6 mmol) in chlorobenzene (7 ml) was added dropwise, keeping the temperature below 50 °C. After the addition, the mixture was refluxed for 10 h and then cooled to room temperature. The reaction was analysed for completeness by IR and used directly without purification in the following reaction with glycidol, **10**. The yield of **1b** was 91%, estimated on the basis of the glycidol consumed in the next step. Work-up of the isocyanate for spectroscopic characterization was carried out by evaporation of the solvent and distillation of the residue. This afforded a 61% yield of **1b** as a clear oil, b.p. 80–83 °C, 0.1 mmHg (lit.[7] 106–109 °C, 10 mmHg, 66% yield). ^{1}H NMR ($CDCl_3$): δ 7.32–7.05 (m). ^{13}C NMR ($CDCl_3$): δ 121.6, 128.5, 130.3, 149.8. IR (neat) 3426 (w), 3318 (w), 2249 (s), 1589 (w), 1489 (s), 1412 (s), 1205 (s), 1172 (s), 1142 (s), 1024 (w), 918 (s), 888 (s), 786 (s), 753 (m), 732 (m), 689 (m) cm^{-1}.

p-*Chlorophenoxysulfonyl isocyanate,* **1c**. A solution of *p*-chlorophenol (6.36 g, 49.5 mmol) in chlorobenzene (25 ml) was heated to 40 °C. To this mixture was added dropwise a solution of **11** (7.00 g, 49.5 mmol) in chlorobenzene (25 ml), maintaining the temperature at 40 °C. When the addition was completed, the reaction was refluxed for 10 h and then stirred at room temperature

overnight. Owing to the instability of the isocyanate, this mixture was usually used directly in the subsequent step. The yield was 89%, calculated on the basis of the amount glycidol (**10**) consumed in the following step. Work-up of the isocyanate for spectroscopic characterization was carried out by evaporation of the solvent and distillation of the residue. This afforded a 72% yield of **1c** as a clear oil, b.p. 87–89 °C, 0.4 mmHg (lit.[7] 91–95 °C, 0.2 mmHg, 65% yield). ^{1}H NMR ($CDCl_3$): δ 7.31 (br d, J=8.8 Hz, 2 H), 7.45 (br d, J=8.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 123.1, 129.6, 130.7, 148.1. IR (neat) 3248 (w), 3103 (w), 2254 (s), 1654 (w), 1485 (s), 1416 (s), 1206 (m), 1178 (m), 1150 (m), 1090 (m), 1016 (m), 890 (m), 838 (m), 779 (m), 739 (w) cm^{-1}.

2,2,2-Trifluoroethoxysulfonyl isocyanate, **1d**. To a mixture of 2,2,2-trifluoroethanol (4.50 g, 45.0 mmol) in chlorobenzene (20 ml) at 30 °C was added dropwise a solution of **11** (6.36 g, 45.0 mmol) in chlorobenzene (30 ml), maintaining the starting temperature. When the addition was complete, the mixture was refluxed for 10 h. The reaction was then cooled and distilled (45–55 °C, 15 mmHg), giving a solution of the isocyanate **1d** in chlorobenzene which was used directly in the next step. The yield of **1d** was 83%, calculated on the basis of the amount of glycidol, **10**, consumed in the next step, (lit.[7] 54–55 °C, 16 mmHg, 24% yield). IR (CH_2Cl_2): 2256 cm^{-1}.

Preparation of the carbamates **2a–d**: *Glycidyl* p-*methoxyphenoxysulfonylcarbamate,* **2a**. To an ice-cooled solution of glycidol, **10**, (6.00 g, 81.1 mmol) in CH_2Cl_2 (100 ml) was added a solution of *p*-methoxyphenoxysulfonyl isocyanate, **1a**, (18.57 g, 81.1 mmol) in CH_2Cl_2 (200 ml), over a period of 40 min, keeping the temperature below 7 °C. After the addition, the reaction was stirred for 30 min at the same temperature. At this point, no isocyanate band was observed in the IR spectrum of the reaction mixture. The solvent was then evaporated off under reduced pressure, giving 29.14 g of a clear, colourless oil. Crystallization from dichloromethane–hexane afforded 20.65 g (84% yield) of **2a** as a white product with m.p. 92–93 °C. ^{1}H NMR ($CDCl_3$): δ 2.72 (ddd, J= 2.9, 2.5, 4.6 Hz, 1 H), 2.90 (br t, J=4.4 Hz, 1 H), 3.23–3.26 (m, 1 H), 3.81 (s, 3 H), 4.01 (dd, J=6.4z, 12.2 Hz, 1 H), 4.65 (dd, J=2.4, 12.2 Hz, 1 H), 6.88–6.93 (m, 2 H), 7.21–7.25 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 44.6, 55.7, 67.4, 114.9, 122.8, 143.2, 149.5, 158.8. IR (KBr): 3630–2340 [br m signal with maxima: 3067 (m), 3001 (m), 2912 (m), 2842 (m)], 1771 (s), 1503 (s), 1397 (m), 1301 (w), 1254 (m), 1176 (s), 1149 (s), 1107 (m), 1029 (m), 899 (m), 868 (s), 838 (m), 800 (m), 694 (m) cm^{-1}. MS (180 °C, 70 eV) [*m/z* (% rel. int.)] 303 (16, M^+), 223 (3), 192 (3), 124 (13), 123 (100), 109 (2), 95 (2). Observed: M^+ 303.0411. Calc. for $C_{11}H_{13}NO_7S$: 303.0413.

Glycidyl phenoxysulfonylcarbamate, **2b**. To a crude chlorobenzene solution of phenoxysulfonyl isocyanate, **1b**, cooled in an ice–water bath, were added portions of glycidol, **10**, dissolved in CH_2Cl_2 (0.72 g, 9.7 mmol in 11 ml) until the isocyanate band was no longer detected in the IR spectrum of the reaction mixture. The solvent was then evaporated off and the residue crystallized from CH_2Cl_2 at 4 °C. This afforded 1.99 g of **2b** as a white, crystalline product, m.p. 102.5–103.5 °C. A second crystallization of the mother liquor furnished another 0.25 g of the a product with m.p. 101.5–102.5 °C, giving a total yield of 2.24 g (84%) of **2b**. ^{1}H NMR ($CDCl_3$): δ 2.71 (dd, J=2.4, 4.4 Hz, 1 H), 2.88 (br t, J=4.4 Hz, 1 H), 3.21–3.25 (m, 1 H), 4.00 (dd, J=6.4, 12.2 Hz, 1 H), 4.63 (dd, J=2.4, 12.2 Hz, 1 H), 7.31–7.45 (m, 5 H), 8.00 (br s, 1 H). ^{13}C NMR ($CDCl_3$): δ 44.7, 49.1, 67.4, 121.8, 128.0, 130.1, 149.4, 149.8. IR (KBr): 3077 (w), 2902 (w), 2855 (w), 1766 (s), 1490 (s), 1436 (w), 1389 (s), 1248 (m), 1184 (s), 1164 (s), 922 (m), 886 (s), 875 (s), 787 (m), 769 (m), 738 (w), 616 (w), 591 (m), 555 (m) cm^{-1}. MS (170 °C, 20 eV) [*m/z* (% rel. int.)]: 274 (3), 273 (18, M^+), 243 (3), 242 (25), 199 (18), 194 (6), 193 (56), 180 (10), 178 (4), 173 (4), 163 (9), 162 (92), 134 (3), 199 (2), 107 (2), 106 (3), 95 (7), 94 (100), 93 (45), 86 (3), 66 (3), 65 (17), 58 (3), 57 (7). Observed: M^+ 273.0309. Calc. for $C_{10}H_{11}NO_6S$: 273.0307.

Glycidyl p-*chlorophenoxysulfonylcarbamate,* **2c**. A solution of crude *p*-chlorophenoxysulfonyl isocyanate (**1c**) (maximum 49.5 mmol) in chlorobenzene was cooled to 2 °C in an ice–water bath. To the solution were added aliquots of a solution of glycidol, **10** (3.25 g, 43.9 mmol), in CH_2Cl_2 (21 ml) until no isocyanate was detected by IR. The mixture was filtered, and the solvent evaporated off to yield 92 g (74%) of **2c** as a white, crystalline product, m.p. 102.5–103.5 °C. ^{1}H NMR ($CDCl_3$): δ 2.73 (dd, J=2.4, 4.4 Hz, 1 H), 2.90 (t, J=4.40 Hz, 1 H), 3.24–3.28 (m, 1 H), 4.02 (dd, J=6.4, 12.2 Hz, 1 H), 4.67 (dd, J=2.4, 12.2 Hz, 1 H), 7.27–7.30 (m, 2 H), 7.39–7.42 (m, 2 H), 7.95 (br s, 1 H). ^{13}C NMR ($CDCl_3$): δ 44.7, 49.2, 67.5, 123.2, 130.2, 133.7, 148.1, 149.4. IR (KBr): 3104 (w), 3078 (w), 2906 (w), 2858 (w), 2819 (w), 1768 (s), 1485 (s), 1434 (w), 1392 (m), 1344 (w), 1241 (m), 1187 (s), 1174 (s), 1163 (s), 1091 (m), 1013 (w), 918 (m), 894 (s), 875 (s), 841 (m), 766 (m), 653 (w), 593 (m), 575 (m) cm^{-1}. MS (180 °C, 40 eV) [*m/z* (% rel. int.)]: 309 (4), 307 (10, M^+), 278 (3), 276 (7), 229 (10), 228 (4), 227 (31), 212 (4), 199 (3), 198 (29), 197 (9), 196 (87), 180 (11), 131 (2), 130 (32), 129 (31), 128 (100), 127 (79), 111 (3), 101 (11), 100 (5), 99 (34), 86 (3), 75 (4), 73 (8), 65 (5), 63 (6), 57 (9). Observed: M^+ 306.9919. Calc. for $C_{10}H_{10}ClNO_6S$: 306.9917.

Glycidyl 2,2,2-trifluoroethoxysulfonylcarbamate, **2d**. A solution of 2,2,2-trifluoroethoxysulfonyl isocyanate, **2a**, in chlorobenzene as described above was cooled to 2 °C in an ice–water bath and a solution of glycidol, **10**, (2.75 g, 37.2 mmol in 35 ml chlorobenzene) was added

in portions until no isocyanate band was observed in the IR spectrum of the reaction mixture. The solution was then filtered, giving 7.96 g of a white, crystalline material, m.p. 78 °C. A second crystallization of the mother liquor afforded another 0.20 g of white crystals with m.p. 68.5–69.5 °C, giving an overall yield of 8.16 g (79%) of **2d**. ^{1}H NMR (acetone-d_6): δ 2.69 (dd, J=2.4, 5.4 Hz, 1 H), 2.80 (br t, J=4.9, 4.4 Hz, 1 H), 3.21–3.26 (m, 1 H), 4.00 (dd, J=6.3, 12.2 Hz, 1 H), 4,61 (dd, J=2.4, 12.2 Hz, 1 H), 4.98 (q, J=8.3 Hz, 2 H), 11.14 (br s, 1 H). ^{13}C NMR (acetone-d_6): δ 44.4, 49.4, 68.1 (q, $^2J_{CF}$= 38.6 Hz), 68.4, 123.4 (q, J_{CF}=275.8 Hz), 151.2. IR (KBr): 3064 (w), 2879 (w), 2853 (w), 2812 (w), 1772 (s), 1489 (m), 1455 (w), 1387 (m), 1344 (w), 1308 (m), 1280 (m), 1259 (m), 1173 (s), 1049 (s), 970 (m), 926 (m), 902 (m), 886 (m), 832 (m), 771 (m), 601 (m), 558 (m) cm^{-1}. MS (180 °C, 50 eV) [*m/z* (% rel. int.)]: 279 (0.6, M^+), 250 (6), 249 (16), 248 (100), 247 (4), 207 (3), 206 (9), 205 (43), 204 (21), 192 (5), 186 (2), 181 (2), 180 (31), 163 (4), 147 (6), 137 (3), 136 (68), 122 (8), 117 (2), 110 (6), 106 (25), 87 (2), 86 (17), 83 (5), 80 (5), 79 (3), 75 (2), 74 (4), 63 (4), 61 (5), 57 (8), 56 (9). Observed: M^+ 279.0024. Calc. for $C_6H_8F_3NO_6S$: 279.0018.

Preparation of the 1,3-oxazolidin-2-ones **3a–d**: *4-hydroxymethyl-3-(*p*-methoxyphenoxysulfonyl)-1,3-oxazolidin-2-one,* **3a**. A solution of **2a** (18.00 g, 59.4 mmol) and triethylamine (6.00 g, 59.4 mmol) in THF (300 ml) was refluxed for 11 h and then stirred at room temperature overnight. At this time, only traces of starting material were detected by TLC. The solvent was evaporated off under reduced pressure, and the residue dissolved in CH_2Cl_2 (200 ml) and washed with aq. HCl (0.1 M, 100 ml), water (2 × 100 ml) and brine (100 ml). Drying ($MgSO_4$) and removal of the solvent under reduced pressure afforded 14.46 g of a yellow oil (80% yield, 85% pure by ^{1}H NMR), which was crystallized (CH_2Cl_2–*n*-hexane) at −40 °C. Unfortunately, these crystals melted below room temperature (18 °C), giving 3.85 g of a colourless, viscous oil (21% yield). However, the crude product was found to be pure enough for further reactions. ^{1}H NMR ($CDCl_3$): δ 1.63–1.66 (m, 1 H), 3.65 (ddd, J=2.4, 5.9, 11.0 Hz, 1 H), 3.71–3.77 (m, 1 H), 3.82 (s, 3 H), 4.22–4.26 (m, 1 H), 4.41 (d, J=5.9 Hz, 2 H), 6.91–6.95 (m, 2 H), 7.30–7.34 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 55.7, 58.7, 61.6, 65.4, 115.0, 123.0, 142.8, 151.3, 159.1. IR (neat): 3733–2794 [broad signal with the following maxima: 3546 (w), 3400 (w), 2934 (w), 2842 (w)], 1794 (s), 1626 (w), 1594 (m), 1503 (s), 1466 (m), 1400 (m), 1301 (m), 1254 (s), 1172 (s), 1141 (s), 1104 (m), 1064 (m), 1031 (m), 935 (w), 883 (m), 841 (m), 805 (m), 755 (w), 734 (w), 697 (m), 641 (m) cm^{-1}. MS (180 °C, 40 eV) [*m/z* (% rel. int.)]: 303 (8, M^+), 223 (3), 192 (2), 124 (12), 123 (100), 109 (2), 95 (7). Observed: M^+ 303.0411. Calc. for $C_{11}H_{13}NO_7S$: 303.0413.

4-Hydroxymethyl-3-phenoxysulfonyl-1,3-oxazolidin-2-one, **3b**. A solution of **2b** (7.00 g, 25.6 mmol) and triethylamine (2.59 g, 25.6 mmol) in THF (500 ml) was refluxed for 12 h and then stirred at room temperature overnight. The solvent was then removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (300 ml) and washed with aqueous HCl (0.1 M, 1 × 150 ml), water (3 × 100 ml) and brine (100 ml). Drying ($MgSO_4$) and evaporation of the solvent under reduced pressure gave 6.85 g of a light brown, viscous oil. Purification of 3.00 g of the crude product by flash chromatography (acetone–*n*-hexane = 35 : 65) afforded 1.76 g of **3b** as a clear, colourless oil (57% yield). The rest of the crude product was hydrolysed without prior purification. ^{1}H NMR ($CDCl_3$): δ 2.43–2.48 (m, 1 H), 3.52–3.60 (m, 1 H), 3.67–3.75 (m, 1 H), 4.19–4.26 (m, 1 H), 4.33–4.42 (m, 2 H), 7.30–7.47 (m, 5 H). ^{13}C NMR ($CDCl_3$): 59.0, 61.4, 65.8, 121.9, 128.4, 130.3, 149.4, 151.7. IR (neat): 3550 (br, w), 2928 (w), 1791 (s), 1586 (w), 1488 (w), 1403 (s), 1187 (s), 1137 (s), 1070 (m), 1033 (w), 918 (w), 879 (s), 782 (s), 755 (w), 691 (w), 658 (m), 635 (m) cm^{-1}. MS (180 °C, 70 eV) [*m/z* (% rel. int.)]: 273 (9, M^+), 243 (3), 242 (24), 194 (4), 193 (28), 178 (3), 163 (9), 162 (86), 107 (2), 106 (3), 95 (7), 94 (100), 93 (48), 86 (4), 77 (10), 66 (6), 65 (44), 64 (7) 63 (4), 51 (4). Observed: M^+ 273.0309. Calc. for $C_{10}H_{11}NO_6S$: 273.0307.

*3-(*p*-Chlorophenoxysulfonyl)-4-hydroxymethyl-1,3-oxazolidin-2-one,* **3c**. A solution of **2c** (3.50 g, 11.4 mmol) and triethylamine (1.15 g, 11.4 mmol) in THF (330 ml) was refluxed for 4 h, after which time no trace of the starting material could be observed on TLC. The solvent was evaporated off and the residue dissolved in CH_2Cl_2 (250 ml), followed by washing with aqueous HCl (0.1 M, 150 ml), water (3 × 150 ml) and brine (150 ml). The organic solution was dried ($MgSO_4$) and filtered. Evaporation of the solvent yielded 3.71 g of a colourless oil. Purification by flash chromatography (acetone–*n*-hexane = 30 : 70) furnished 2.28 g of **3c** as a clear, oily product (65% yield) which crystallized upon standing. M.p. 91–92 °C. ^{1}H NMR ($CDCl_3$): δ 1.88 (br s, 1 H), 3.66–3.69 (m, 1 H), 3.86–3.89 (m, 1 H), 4.30–4.35 (m, 1 H), 4.45 (d, J=5.9 Hz, 2 H), 7.33–7.44 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 58.8, 61.5, 65.6, 123.5, 130.3, 134.0, 147.9, 151.2. IR (KBr): 3519 (s), 1775 (s), 1483 (s), 1425 (s), 1400 (s), 1377 (w), 1221 (m), 1177 (s), 1150 (m), 1133 (m), 1089 (m), 1066 (m), 1012 (w), 875 (m), 854 (m), 776 (m), 720 (w), 664 (w), 622 (w), 574 (w) cm^{-1}. MS (180 °C, 40 eV) [*m/z* (% rel. int.)] 309 (4, M+2), 307 (11, M^+), 278 (3), 276 (8), 229 (9), 228 (3), 227 (28), 214 (2), 212 (4), 199 (3), 198 (26), 197 (9), 196 (82), 131 (3), 130 (32), 129 (30), 128 (100), 127 (71), 111 (3), 101 (11), 100 (4), 99 (34), 86 (3), 75 (3), 73 (8), 65 (6), 64 (4), 63 (6). Observed: M^+ 306.9923. Calc. for $C_{10}H_{10}ClNO_6S$: 306.9917.

4-Hydroxymethyl-3-(2,2,2-trifluoroethoxysulfonyl)-1,3-oxazolidin-2-one, **3d**. A solution of **2d** (8.00 g, 28.7 mmol) and triethylamine (2.90 g, 28.7 mmol) in THF (500 ml) was refluxed for 3 h. The reaction mixture was cooled

and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (200 ml) and washed with aqueous HCl (0.2 M, 200 ml), water (3 × 100 ml) and brine (100 ml). Drying ($MgSO_4$) and evaporation of the solvent under reduced pressure afforded 7.70 g of a light yellow oil. Purification by flash chromatography (acetone–*n*-hexane = 40:60) furnished 3.80 g of **3d** as a light pink oil (48% yield). ^{1}H NMR (acetone-d_6): δ 2.87 (br s, 1 H), 3.84 (dd, J = 1.5, 12.2 Hz, 1 H), 4.03 (dd, J = 3.4, 12.2 Hz, 1 H), 4.53 (dd, J = 2.9, 8.3 Hz, 1 H), 4.61–4.68 (m, 1 H), 4.71 (t, J = 8.30 Hz, 1 H), 4.73–5.12 (m, 2 H). ^{13}C NMR (acetone-d_6): δ 60.3, 61.6, 67.4, 68.4 ($^2J_{CF}$ = 36.8 Hz), 123.2 (J_{CF} = 277.60 Hz), 152.7. IR (neat): 3457 (br, w), 2986 (w), 2924 (w), 2853 (w), 1790 (s), 1652 (w), 1476 (w), 1411 (m), 1332 (w), 1284 (m), 1182 (s), 1075 (m), 1033 (s), 961 (w), 862 (w), 829 (w), 808 (w) cm^{-1}. MS (180 °C, 50 eV) [*m/z* (% rel. int.)] 250 (6), 249 (13), 248 (100), 247 (4), 207 (2), 206 (4), 205 (40), 204 (20), 192 (5), 147 (6), 122 (10), 86 (17), 83 (3). Observed: $M-32$ 247.9841. Calc. for $C_5H_5NFO_5S$: 247.9841.

Preparation of the sulfamates **4a–d**: *2-[(p-methoxyphenoxy)sulfonamido]-1,3-propanediol,* **4a**. To a solution of **3a** (4.30 g, 14.2 mmol) in 96% ethanol (40 ml) was added aqueous sodium hydroxide (2 M, 40 ml) and the mixture was stirred for 1 h at room temperature. The reaction was monitored by TLC and after 1 h diethyl ether (100 ml) was added, and the pH adjusted to approximately pH 3 by addition of aqueous, 2 M HCl. The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 50 ml). The combined organic layers were washed with 10% aq. $NaHCO_3$ (50 ml) and brine (50 ml) and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure to yield a crude crystalline product. Recrystallization from ethyl acetate afforded 1.93 g (49%) of **4a** as a white crystalline material, m.p. 96–97 °C. ^{1}H NMR (CD_3OD): 3.49 (q, J = 5.37 Hz, 1 H), 3.67 (d, J = 5.37 Hz, 4 H), 3.79 (s, 3 H), 4.85 (s, 3 H), 6.93 and 7.27 (AA′BB′ system, 4 H). ^{13}C NMR (CD_3OD): δ 56.10, 59.18, 61.91, 115.54, 124.21, 145.48, 159.56. IR (KBr): 3329 (br, s), 3252 (s), 2973 (w), 2938 (w), 2889 (w), 1592 (w), 1506 (s), 1457 (m), 1444 (m), 1362 (s), 1289 (w), 1247 (s), 1198 (m), 1169 (m), 1153 (s), 1118 (w), 1009 (w), 1073 (s), 1063 (s), 1025 (m), 1006 (m), 970 (m), 880 (m), 837 (m), 799 (m), 693 (w), 573 (w) cm^{-1}. MS *m/z* [(% rel. int.)]: 278 (2, $M+1$), 277 (11, M^+), 246 (2), 125 (7), 124 (100), 123 (40), 122 (6), 109 (18), 95 (3), 94 (2), 81 (4), 64 (2). Observed: M^+ 277.0620. Calc. for $C_{10}H_{15}NO_6S$: M 277.0616.

2-(Phenoxysulfonamido)-1,3-propandiol, **4b**. Treatment of **3b** (3.00 g, 11.0 mmol) according to the procedure given for preparation of **4a** afforded 1.63 g of a dark yellow oil, which was crystallized from ethyl acetate. This gave 1.06 g of **4b** as a white crystalline product, m.p. 70–71 °C. ^{1}H NMR (CD_3OD): δ 3.51 (q, J = 5.37 Hz, 1 H), 3.67 (d, J = 5.37 Hz, 4 H), 6.62 (s, 3 H), 7.26–7.29 (m, 1 H), 7.33–7.42 (m, 4 H). ^{13}C NMR (CD_3OD): δ 59.16, 61.87, 123.03, 127.61, 130.67, 152.16. IR (KBr): 3499 (m), 3348 (m), 3128 (m), 3074 (m), 2962 (w), 2903 (w), 1486 (s), 1373 (w), 1345 (m), 1321 (m), 1261 (w), 1189 (s), 1170 (s), 1148 (m), 1104 (m), 1066 (m), 1047 (s), 1012 (m), 967 (s), 914 (w), 886 (m), 863 (s), 783 (m), 735 (m), 690 (m), 563 (w), 525 (m) cm^{-1}. MS [*m/z* (% rel. int.)] 247 (0.7, M^+), 216 (11), 157 (5), 137 (4), 122 (11), 119 (2), 95 (13), 94 (100), 93 (6), 77 (3), 66 (3), 65 (10), 60 (4). Observed: M^+ 247.0517. Calc. for $C_9H_{13}NO_5S$: M 247.0514.

2-(p-Chlorophenoxysulfonamido)-1,3-propanediol, **4c**. A solution of **3c** (2.72 g, 8.8 mmol) in 96% ethanol was treated according to the procedure given for **4a**, using 2 M aqueous NaOH (30 ml) as the base. After filtration of $MgSO_4$, the crude product solution was concentrated until crystallization started. The crude suspension of crystals was stored at −20 °C overnight and filtered to yield 1.61 g of **4c** as a white, crystalline product. Evaporation of the mother liquor and subsequent recrystallization (diethyl ether) afforded another 0.51 g of product, yielding a total of 85%, m.p. 99–100 °C. ^{1}H NMR (acetone-d_6): δ 2.82–2.86 (m, 3 H), 3.57–3.62 (m, 1 H), 3.73–3.81 (m, 4 H), 7.42–7.48 (m, 4 H). ^{13}C NMR (acetone-d_6): δ 59.2, 61.8, 124.8, 130.5, 132.3, 150.4. IR (KBr): 3514 (m), 3319 (m), 3114 (w), 2968 (w), 2931 (w), 1485 (s), 1464 (m), 1361 (s), 1199 (m), 1171 (s), 1108 (m), 1085 (m), 1072 (m), 1053 (s), 1010 (w), 976 (m), 869 (s), 835 (m), 747 (s), 576 (m), 557 (m), 493 (w) cm^{-1}. MS (170 °C, 70 eV) [*m/z* (% rel. int.)]: 281 (1.4, M^+), 252 (2), 250 (5), 131 (2), 130 (32), 129 (11), 128 (100), 127 (10), 123 (2), 122 (19), 101 (2), 99 (7), 94 (3), 73 (3), 65 (5), 64 (3), 63 (3). Observed: M^+ 281.1025. Calc. for $C_9H_{12}ClNO_5S$: 281.0128.

2-(2,2,2-Trifluoroethoxysulfonamido)-1,3-propanediol, **4d**. To a solution of **3d** (1.50 g, 5.4 mmol) in ethanol (96%, 30 ml) was added 2 M aqueous NaOH (30 ml) and the mixture was stirred for 2 h at room temperature. The mixture pH was then adjusted to 4 by addition of 2 M HCl. The solvent was evaporated off and the white residue was washed with dry diethyl ether (3 × 50 ml). The combined ether phases were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield 1.09 g (78%) of **4d** as a yellow oil. The product purity was estimated to >95% by ^{1}H NMR. ^{1}H NMR (CD_3OD): δ 3.41 (m, 1 H), 3.62 (dd, J = 5.4, 11.2 Hz, 2 H), 3.66 (dd, J = 5.9, 11.2 Hz, 2 H), 4.57 (q, J = 8.3 Hz, 2 H). ^{13}C NMR (CD_3OD): δ 59.4, 62.3, 66.0 ($^2J_{CF}$ = 36.8 Hz), 124.4 (J_{CF} = 275.8 Hz). IR (neat): 3829–2440 [br signal with the following maxima: 3307 (s) 2967 (m), 2896 (m)], 1635 (w), 1454 (m), 1421 (w), 1366 (m), 1282 (m), 1182 (s), 1117 (w), 1049 (m), 1009 (m), 965 (m), 887 (w), 809 (w) cm^{-1}. MS (170 °C, 40 eV) [*m/z* (% rel. int.)]: 222 (44), 205 (4), 147 (2), 1367 (5), 123 (5), 122 (100), 94 (31), 83 (8), 80 (3), 69 (2), 65 (2), 64 (4), 62

(3), 61 (6), 60 (3), 59 (8), 58 (7), 57 (2), 56 (3). Observed: $M-31$ 222.0048. Calc. for $C_4H_7FNO_4S$: 222.0050.

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