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Sulfonamide Ligands Attained Through Opening of Saccharin Derivatives

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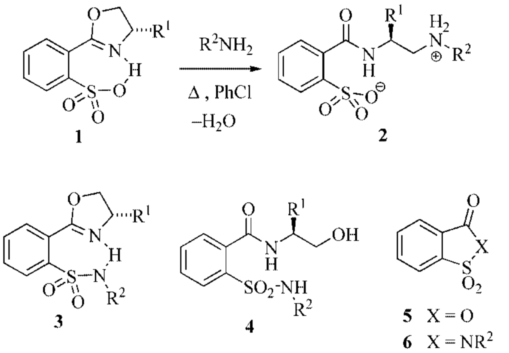
Literature *N*-alkylsaccharins (saccharin-R^2) have been shown in some cases to be *O*-alkylated regioisomers by crystallography (3 structures). The genuine former species react with (*S*)-$H_2NCHR^1CH_2OH$ at 101 °C in dioxane to provide 1,2-$C_6H_4(CONHCHR^1CH_2OH)(SO_2NHR^2)$ [R^1 = H, Me, *i*Pr, Bn, $(CH_2)_2SMe$; R^2 = Bn, *i*Pr, $CHPh_2$, CHMePh]. The (*i*Pr,Bn) compound is crystallographically characterised. If both R^1 and R^2 are sterically congested then reaction of the amino alcohol with the saccharin surrogate 1,2-$C_6H_4(CO_2Me)(SO_2NHR^2)$ is required. The saccharin-derived alcohols are converted into the oxazolines 1,2-C_6H_4(R^1-oxazoline)(SO_2NHR^2) (R^1 = H, Bn, Me, *i*Pr; R^2 = Bn, $CHPh_2$, *n*Pr, *i*Pr, *t*Bu, CHMePh). The dibenzyl compound is crystallographically characterised.

Introduction

Recently we proposed that, by unusual rearrangement chemistry, the amides **2** formed when the oxazolines **1** are heated with primary amines (Scheme 1).[1] Our initial assignment of structure **2** was based on extensive NMR studies as, at first, no example of this compound class could be crystallised. On the basis of NMR spectroscopic data alone, the structural assignment of **2** could not completely exclude the alternative possible structures **3** (the originally desired product of the reaction of **1** and R^2NH_2) and its hydrolysis product **4**. Thus, prior to successful crystallisation of **2**, an independent synthesis of **3** and **4** was sought. We had obtained the sulfonic acids **1** by opening of the anhydride **5** with amino alcohol derivatives. We envisaged that an alternative approach to the desired motif **3** would be opening of the saccharin **6** with similar α-amino acid derivatives affording the amide intermediate **4**, which could be cyclised to the oxazoline **3**. Surprisingly, despite the enormous abundance of saccharin literature, its opening (and opening of its derivatives) with amino acids (or their derivatives) is very poorly represented. Romani and co-workers opened compound **6** (R^2 = CO_2Bn) with α-amino acids, to afford 1,2-$C_6H_4(SO_2NHBz)[CONHCH(R^1)CO_2H]$ (R^1 = various amino acids) in good yields.[2] Whereas this has led to a widely used peptide-coupling procedure using a related compound **6** (R^2 = S-2-NO_2Ph) the intermediate amido sulfonamides were never isolated. In a single example, Proudfoot demonstrated that the saccharin **6** (R^2 = allyl) opened cleanly with $HNMe_2$ in dioxane.[3] However, to the best of our knowledge, studies of the reactions of *N*-substituted saccharins with 1,2-amino alcohols have never been carried out viz. the route we aimed to employ.



Scheme 1. Preparative routes to oxazoline sulfonic acids.

Results and Discussion

Opening of Saccharins with 1,2-Amino Alcohols

The saccharin starting materials **6** were prepared by either routine alkylation of saccharin **6a** (R^2 = H) in DMF with RX (Method A) or by Mitsonobu chemistry (Method B) on the equivalent alcohol. Alkylation methods led to the desired *N*-alkylation products **6b**–**g**; however, Mitsonobu chemistry tended to favour the corresponding *O*-alkylation **7b** and **7f** (Scheme 2), a fact not noted in the literature before.

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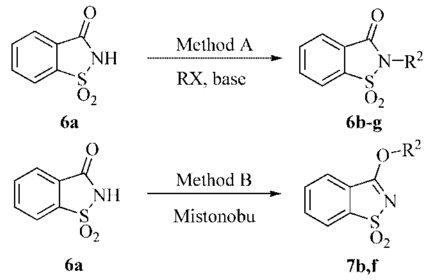


R^2	Conditions	Product	Yield (%)
CH_2Ph	**A**	**6b**	96
$CH(CH_3)_2$	**A**	**6c**	77
$CHPh_2$	**A**	**6d**	82
$CH(Me)Ph$	**A**	**6e**	92
CH_2CH_2Br	**A**	**6f**	68
$CH_2CH_2CH_3$	**A**	**6g**	71
CH_2Ph	**B**	**7b**	43
CH_2CH_2Br	**B**	**7f**	37

Scheme 2. Preparation of substituted saccharins.

Analysis of the ^1H NMR and IR spectra for the compounds **6f** and **7f**, did not afford explicit assignment of the connectivity. The structures were confirmed by X-ray crystallography on both compounds (Figures 1 and 2). It could be confirmed that the OCH_2 resonance ($\delta \approx 5$ ppm) appeared at higher frequency than the equivalent NCH_2 signal ($\delta \approx 4$ ppm) in the ^1H NMR spectra.

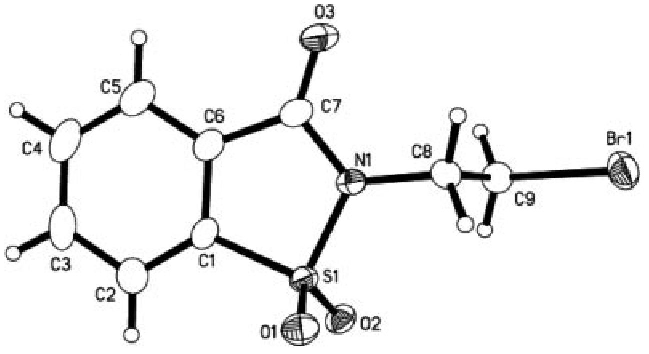


Figure 1. Crystallographic confirmation of the presence of an N–C linkage in *N*-alkylated saccharin **6f**. Displacement ellipsoids drawn at 50% probability level.

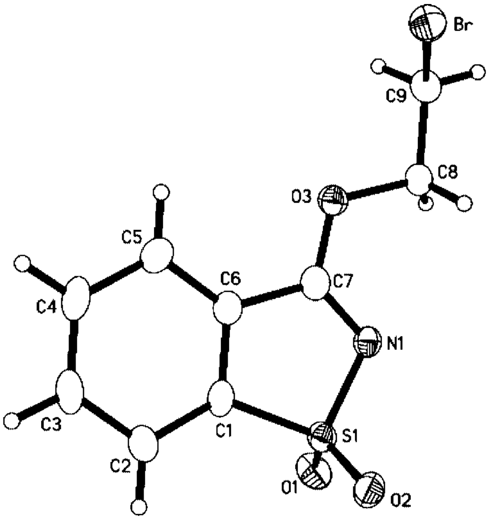


Figure 2. Crystallographic confirmation of the presence of an O–C linkage in *O*-alkylated saccharin **7f**. Displacement ellipsoids drawn at 50% probability level.

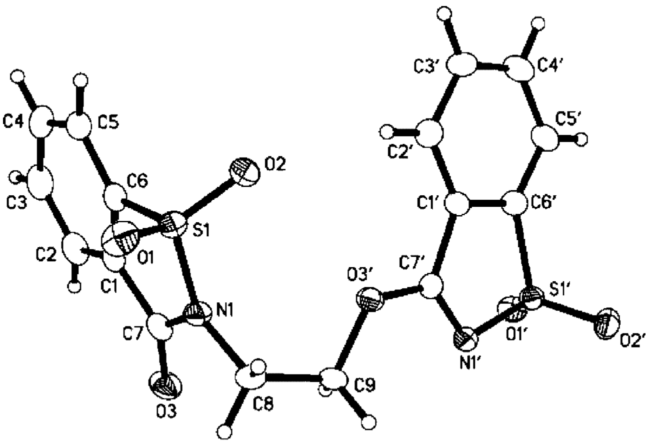
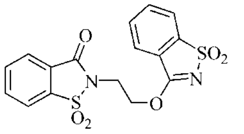
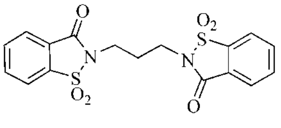


Figure 3. Crystallographic confirmation of the presence of an O–C linkage in the bis(sulfonamide) **8a** of Reid. Only one of two crystallographically independent molecules shown, displacement ellipsoids drawn at 50% probability level.



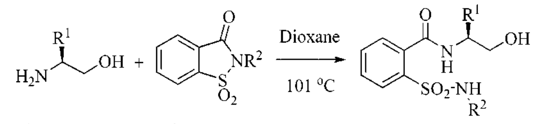
8a



8b

Attempts to prepare a methylene-spaced bis(saccharin) by the chemistry of Reid[4] were not successful. The report of this compound is in error; attempted alkylation of saccharin (method A) leads instead to a mixture of species. The major product is the *O*-alkylated compound **8a**, whose structure was determined crystallographically (Figure 3). The origin of this one example of *O*-alkylation by method A is the steric hindrance that bis(*N*-alkylation) would generate. This can be seen as the equivalent propyl derivative **8b** and all other species **6** were attained in good yield by simple alkylation.

The relatively unhindered saccharin **6a** opened in refluxing dioxane, b.p. 101 °C (or THF, b.p. 67 °C) with 1,2-amino alcohols to provide the required sulfonamide amides **4** in good yield (Scheme 3). The extremely polar nature of the primary sulfonamide **4aa** made it impossible to isolate it cleanly, so our attention was applied to *N*-substituted sulfonamides. The results of Scheme 3 were obtained using equimolar quantities of amino alcohol with **6b**, on scales >1 g to facilitate product separation. Alternatively, reactions could be driven to completion by using a higher loading of amino alcohol (1.5 equiv.) in refluxing dioxane for extended periods. It was noticeable that some amino alcohols were very much slower to react. This was exemplified by **4eb**, where after heating in dioxane for 16 h, only a 52% yield was achieved, whereas hardly any ring opening was observed in THF. All of the sulfonamides **4** are isolated as viscous oils, extensive drying under high vacuum is required to remove hydrogen-bonded solvents from these materials.



	R^1	**6**	R^2	**4**	R^1	R^2	Yield (%)
a	H	**a**	H	**ab**	H	Bn	90 (in THF)
b	Me	**b**	Bn	**ad**	H	$CHPh_2$	64 (at 130 °C)
c	*i*Pr	**c**	*i*Pr	**ac**	H	CHMePh	95
d	Bn	**d**	$CHPh_2$	**bb**	Me	Bn	64
e	$(CH_2)_2SMe$	**e**	CHMePh	**cb**	*i*Pr	Bn	69
		f	CH_2CH_2Br	**cc**	*i*Pr	*i*Pr	82
		g	$CH_2CH_2CH_3$	**cd**	*i*Pr	$CHPh_2$	73 (at 130 °C)
				ce	*i*Pr	CHMePh	0
				cg	*i*Pr	*n*Pr	51
				db	Bn	Bn	75 (in THF)
				eb	$(CH_2)_2SMe$	Bn	52

Scheme 3. Opening of saccharins **6** with 1,2-amino alcohols.

Due to oil formation only one example could be crystallised. The structure of **4cb** (Figure 4) shows the extensive hydrogen-bonding network of intramolecular H bonds between the carbonyl amide O1 (as an H-bond acceptor), and the sulfonamide proton on N2 (as an H-bond donor). The hydroxy proton on O4 is also H-bonded with the sulfonyl oxygen atom O2. The amide proton at N1 forms an intermolecular H-bond to the O4 atom of another molecule, forming a dimeric lattice. This structure also explains the experimental observation of why removal of hydrogen-bonding solvents was often so difficult. Prolonged high-vacuum drying at 40 °C for several days (a few weeks in some cases) is required to produce solids. Both EtOH and MeOH bond very strongly in the H-bonding pocket produced by these molecules.

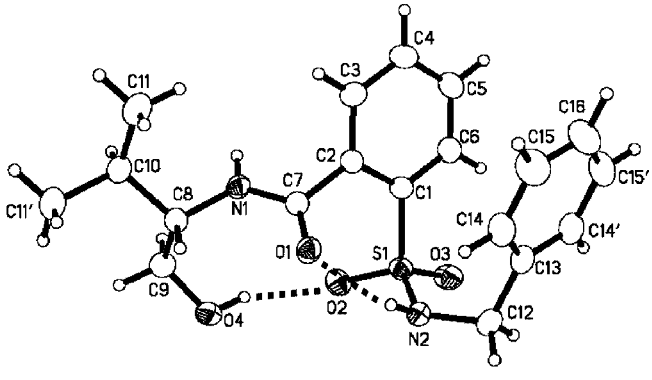
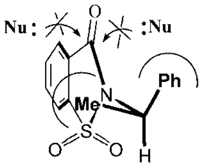


Figure 4. Molecular structure of **4cb** showing intramolecular hydrogen bonding (solid dotted lines). Selected H-bonding contacts [Å; °]: O(4)···O(2) 2.894(2), O(4)–H(4)–O(2) 163.9, N(2)···O(1) 2.864(2), N(2)–H(2)–O(1) 149(2). Displacement ellipsoids drawn at 50% probability level.

The direct ring opening of hindered alkyl saccharins (**6c–e**) under dioxane reflux proved challenging. Varying success, depending on the steric requirements of the alkyl group (R^1) in the incoming amino alcohol, was attained. Whereas all the substituted saccharins **6b–e** could be ring-opened by 2-ethanolamine under the standard conditions, when L-valinol was employed as a nucleophile, the saccharins **6c–6e** were very sluggish to react, requiring large excesses of valinol and elevated temperatures in some cases. It was noticeable that the isopropyl derivative **6c** was also slower to react than the diphenyl derivative **6d** as monitored by TLC analysis and ^1H NMR spectroscopy. In the case of **6e** no product formation was observed at all even under sealed-tube conditions. A number of additives were attempted to see if ring opening of hindered saccharin **6e** could be induced. Catalytic DMAP (10 mol-%) or Lewis-acidic $La(OTf)_3·9H_2O$ or $Sc(OTf)_3$ (both at 5 mol-%) had no effect; neither did pre-treatment of **6e** with $(Me_3O)BF_4$ in an attempt to improve its reactivity by *O*-alkylation.

The path of the sterically encumbered amine nucleophile into the exocyclic carbonyl group of the saccharin ring **6e** appears completely blocked. The presence of the sulfonyl functionality in the ring enforces the alkyl group to adopt the conformation shown in structure **9**. The resulting transition state after nucleophilic attack is very cluttered, and interaction with L-valinol seems especially disfavoured. This lack of reactivity led us to develop an alternative method to such hindered species.



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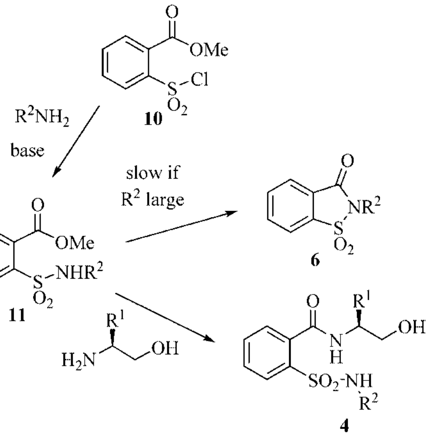
In an attempt to determine the scope of this steric effect, the synthesis of sterically more encumbered saccharin derivatives was carried out. Previous reports on the synthesis of saccharin derivatives that cannot be prepared by simple S_N2 chemistry generally utilise the cyclisation of species **11** (Scheme 4). The sulfonyl chloride **10** makes an excellent precursor to the sulfonamides **11** and, in fact, these latter compounds serve as a source of *N*-alkylsaccharins **6**.

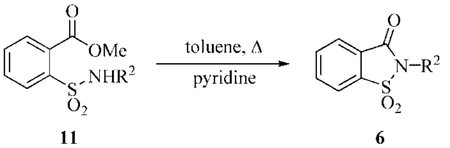
Base-catalysed cyclisation via the methoxy ester **11** is usually very slow, and this often depends on the nature of group R^2, both from a steric and electronic perspective. Preparation of **6e** and the *tert*-butyl derivative **6h** by this methodology proved difficult, with a very poor yield of the saccharin produced allowing direct synthesis of **4ch** (Scheme 4). By comparison, phenylsaccharin **6i** readily cyclised in high yield (Scheme 5).

The formation of amides from esters at high temperatures has been previously demonstrated for a variety of substrates.[5] Utilising the methoxy ester **11** as a saccharin surrogate, we could prepare the hindered saccharin substrates (Scheme 4). The amides could be easily separated from the saccharin by-product using chromatography. The preferred procedure was the use of dioxane or toluene in a sealed tube at 130 °C, as dioxane reflux was not as effective in this case. A tertiary sulfonamide derivative **12** was also attempted to see if amide formation was possible without the



4	Yield (%)	R¹	R²
4ce	73	*i*Pr	CHMePh
4ch	45	*i*Pr	*t*Bu

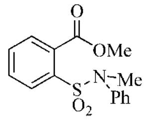
Scheme 4. Synthesis of sulfonamides **4** via methoxy ester **11**.



R²	Yield (%)	
*t*Bu	15	**6h**
Ph	66	**6i**
CH(Me)Ph	10	**6e**

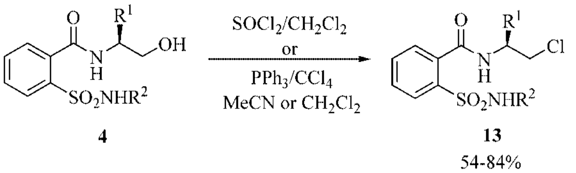
Scheme 5. Synthesis of sterically encumbered saccharin derivatives.

presence of an acidic proton. No sign of reaction was observed, indicating that the presence of the acidic sulfonamide proton was critical to the reaction.



12

Upon completion of the amide series **4ab**–**4eb**, the amide was cyclised to the desired oxazoline ring using established literature procedures. Denmark[6] et al. have established a reliable procedure whereby the alcohol functionality is mesylated, and subsequent treatment with base forms the oxazoline ring. This and other one-pot procedures for oxazoline formation proved ineffective in our hands. A two-step procedure via the chloride was thus adopted. Chlorination of alcohols using PPh_3/CCl_4 was found to be optimal for producing **13** very cleanly in high yields (54–84%, Scheme 6).



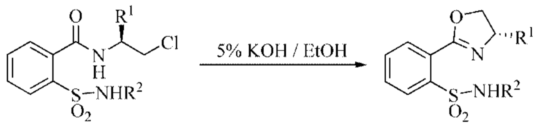
13	R¹	R²	Conditions	Yield (%)
ab	H	Bn	$SOCl_2/CH_2Cl_2$	82
ad	H	$CH(Ph)_2$	PPh_3/CCl_4 (5equiv.) $MeCN/CH_2Cl_2$, r.t., 78 h	54
bb	Me	Bn	PPh_3/CCl_4 (5equiv.) MeCN, r.t. 2 h	75
cb	*i*Pr	Bn	PPh_3/CCl_4 (5equiv.) MeCN, r.t., 5 h	84
cc	*i*Pr	*i*Pr	PPh_3/CCl_4 (5equiv.) MeCN, r.t., 48 h	60
cd	*i*Pr	$CH(Ph)_2$	PPh_3/CCl_4 (5equiv.) MeCN / CH_2Cl_2, r.t., 78 h	65
ce	*i*Pr	(R)-CH(Me)Ph	PPh_3/CCl_4 (5equiv.) MeCN, r.t., 48 h	71
cg	*i*Pr	*n*Pr	PPh_3/CCl_4 (5equiv.) MeCN, r.t., 24 h	67
ch	*i*Pr	*t*Bu	PPh_3/CCl_4 (5equiv.) MeCN, r.t. 24 h	61
db	Bn	Bn	PPh_3/CCl_4 (1.5equiv.) MeCN, r.t., 24 h	71

Scheme 6. Conversion of amino alcohols **4** to chlorides **13**.

Purification only required the removal of triphenylphosphane oxide by flash chromatography. Initially, the reactions were run in CH_2Cl_2 and were only complete after a 48–72 h period; however, when MeCN was used, the reaction was much faster taking just 5 h. Previous reports have shown that MeCN has a dramatic rate-accelerating effect on the dissociation of a chlorine atom from CCl_4,[7] often the rate-determining step in this reaction. Two reactions were run using a 50:50 mixture of CH_2Cl_2/MeCN in order to aid solubility (Entries **13ad** and **13cd**).

Cyclisation of the chlorides **13ab**–**db** was achieved by treatment with 5% ethanolic KOH, producing near quantitative yields of the corresponding oxazolines **3ab**–**db** (Scheme 7) in all cases. Recrystallisation of the oxazolines proved somewhat difficult, although it was not required for purification in many cases. However, suitable crystals of **3db** for X-ray analysis were produced when a CH_2Cl_2 solution was slowly concentrated (Figure 5). This confirmed that we had synthesised the desired architecture of the ligand. In this case the oxazoline is not in a protonated state, unlike the sulfonic acids previously synthesised by us,[1] although hydrogen bonding between the oxazoline nitrogen atom and the sulfonamide proton is evident.

These ligands, and their precursors, were subsequently tested for activity in the copper-catalysed 1,4-conjugate addition of organometallic reagents to enones. It was found that in the addition of diethylzinc to cyclohexenone, the ligands gave very strong rate acceleration but led to poor enantioselectivity, less than 10%. However, subsequent biological screening revealed significant antibacterial activity for some of the compound library prepared.



13 **3**

Entry	13	R^1	R^2	Product	Yield (%)
1	**ab**	H	Bn	**3ab**	81
2	**ad**	H	CH(Ph)$_2$	**3ad**	86
3	**bb**	Me	Bn	**3bb**	92
4	**cb**	*i*Pr	Bn	**3cb**	93
5	**cc**	*i*Pr	*i*Pr	**3cc**	98
6	**cd**	*i*Pr	CH(Ph)$_2$	**3cd**	44[a]
7	**ce**	*i*Pr	(R)-CH(Me)Ph	**3ce**	76
8	**cg**	*i*Pr	*n*Pr	**3cg**	92
9	**ch**	*i*Pr	*t*Bu	**3ch**	66
10	**db**	Bn	Bn	**3db**	96

[a] Due to the product being inseparable from the starting material, quoted yield is calculated from NMR data.

Scheme 7. Base cyclisation of chlorides **13** using ethanolic KOH.

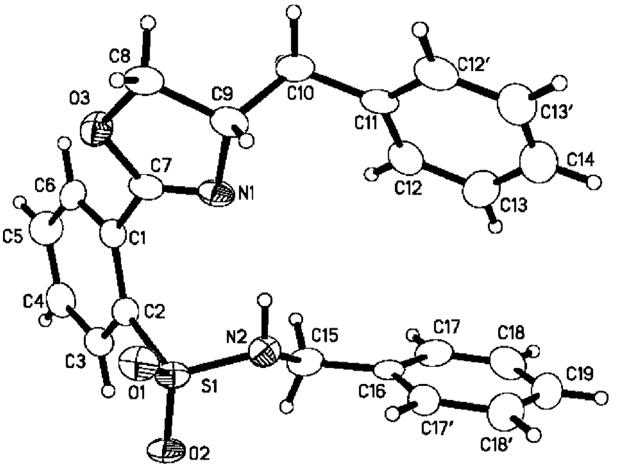


Figure 5. Crystal structure of ligand **3db**. Displacement ellipsoids drawn at 50% probability level.

Conclusions

Crystallographic studies of alkylation products of saccharin have revealed *O*-alkylated imides instead of the *N*-alkyl species suggested in the parent literature in some cases. Care must be taken in distinguishing these as their NMR and IR spectra are often surprisingly similar. Mitsonobu approaches favour *O*-alkylation. Ring opening of *N*-alkylsaccharins with 1,2-amino alcohols leads to direct formation of the sulfonamides **4** if the alkyl substituent in the saccharin is not too large. In the latter case **4** can still be attained by the use of 1,2-C$_6$H$_4$(CO$_2$Me)(SO$_2$Cl) through stepwise treatment with R$_{\text{large}}$NH$_2$ and subsequently the amino alcohol. The alcohols **4** are converted into the oxazolines **3** via the intermediate chlorides **13** followed by base-induced cyclisation. Whereas the final oxazoline sulfonamides were not of utility in copper-catalysed conjugate addition, this class of compounds and their precursors constitutes an interesting scaffold for biological studies and preliminary research is now focused in this area.

Experimental Section

General: Representative general experimental procedures are listed below. Full experimental procedures and data for compounds **3ab**–**db**, **4ab**–**4eb**, **6b**–**6g**, **7b**, 7f, **8a**–**b**, **11e**, **11h**, **11i**, **13ab**–**13db** is available in the Supporting Information. Procedures involving moisture-sensitive reagents or intermediates were performed under argon or nitrogen using standard Schlenk techniques. Tetrahydrofuran and Et$_2$O were distilled from sodium/benzophenone ketyl. Other solvents were dried appropriately and stored over molecular sieves (4 Å). Light petroleum refers to the fraction boiling in the range 40–60 °C. IR spectra were recorded with a Perkin–Elmer 983G (KBr disc), Perkin–Elmer 882 or a Nicolet Avatar 360 FT-IR infrared spectrophotometer. The term "solid state" refers to direct analysis of the oil/solid, using a Nicolet Avatar 360 FT-IR reflecting probe. ^{1}H and ^{13}C NMR spectra were recorded with either JEOL (GX 270) or Bruker (AM400, AV400 and DRX500) spectrometers at ambient temperature unless otherwise noted. Tetramethylsilane was used as an internal standard and *J* values are given in Hz. Mass spectra were obtained with a Micromass 70E (electron impact ionisation, EI+), Micromass LCT (electrospray ionisation, ES+) and VG AutoSpec (fast-atom bomdardment, FAB+) machines. Specific rotations were measured with a Jasco DIP370 Digital polarimeter at ambient conditions and are given in units of 10^{-1}°cm^{2}g^{-1}; (*c* in g/100 mL). Appropriate *N*-substituted saccharins were prepared according to literature routes.[8]

Crystallographic Data: Colourless crystals of **6f**, **8a** were grown from isopropyl alcohol, **7f** from ethanol, **3db** from CH$_2$Cl$_2$ and **4cb** from CH$_2$Cl$_2$. All single-crystal diffraction data were collected using graphite-monochromated Mo-K_α X-ray radiation with a Bruker SMART APEX, except for **7f** which was collected with a SMART1000 CCD area detector diffractometer, each equipped with an Oxford Cryostream cooling device. All data were collected at 150 K. Details of the individual data collections and refinements are given in Table 1. All structures were solved by direct methods using SHELXS-97 or SIR-92 (**7f**). All structures were refined by least-squares full-matrix refinement against F^2 using SHELXL-97 and all non-H atoms refined with anisotropic atomic displacement parameters (adps). Hydrogen atoms were geometrically placed and refined as part of a riding model, except for those bound to N and O in **4cb** and N in **3db** which were located from difference Fourier maps and the OH group was refined as a rigid rotor and the NH atoms were refined freely in both structures. Crystallographic data for all compounds are summarised in Table 1. CCDC-604476 to -604480 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for the Preparation of Oxazolinesulfonamides 3: Compound **13** (4.8 mmol) was added to a stirred solution of 5% ethanolic KOH (20 mL). The reaction mixture was stirred at room temperature for the stated amount of time, followed by the addition of CH$_2$Cl$_2$ (50 mL). The reaction mixture was then acidified by the

Table 1. Crystallographic data for **3eb**, **4cb**, **6f**, **7f** and **8a**.

	3eb	**4cb**	**6f**	**7f**	**8a**
Empirical formula	$C_{23}H_{22}N_2O_3S$	$C_{19}H_{24}N_2O_4S$	$C_9H_8BrNO_3S$	$C_9H_8BrNO_3S$	$C_{16}H_{12}N_2O_6S_2$
M_r	406.49	376.46	290.13	290.13	392.40
Cell setting, space group	triclinic, $P1$	orthorhombic, $P2_12_12_1$	monoclinic, $P2_1/n$	monoclinic, $P2_1/c$	triclinic, $P\bar{1}$
Temperature [K]	150(2)	150(2)	150(2)	150(2)	150(2)
a [Å]	5.8503(15)	8.5173(10)	10.3122(9)	7.5511(12)	6.194(2)
b [Å]	7.736(2)	12.5191(14)	18.944(2)	17.164(3)	10.840(4)
c [Å]	22.170(6)	18.195(2)	11.5524(10)	8.0984(13)	12.625(4)
α [°]	87.995(4)	90	90	90	86.406(5)
β [°]	85.686(4)	90	109.501(1)	92.108(3)	80.673(5)
γ [°]	89.818(4)	90	90	90	79.499(6)
V [Å^3]	1000.0(8)	1940.1(4)	2127.4(3)	1048.9(3)	821.9(5)
Z	2	4	8	4	2
$D_{\text{calcd.}}$ [Mg·m^{-3}]	1.350	1.289	1.812	1.837	1.586
μ [mm^{-1}]	0.19	0.19	4.05	4.10	0.36
Crystal form, colour	tablet, colourless	block, colourless	lath, colourless	plate, colourless	column, colourless
Crystal size [mm]	0.41 × 0.33 × 0.03	0.33 × 0.18 × 0.14	0.24 × 0.12 × 0.07	0.40 × 0.19 × 0.02	0.27 × 0.07 × 0.04
Absorption correction	none	none	multi-scan	multi-scan	none
$T_{\text{min.}}$ [°]	–	–	0.564	0.091	–
$T_{\text{max.}}$ [°]	–	–	0.753	0.164	–
No. of measured/independent/observed reflections [$I > 2\sigma(I)$]	8314/7675/5077	16999/4563/4446	18343/4922/3995	6360/2385/1585	7082/3592/2567
R_{int}	0.100	0.034	0.030	0.071	0.056
R [$F^2 > 2\sigma(F^2)$], $wR(F^2)$, S	0.075, 0.188, 0.94	0.035, 0.099, 1.10	0.037, 0.094, 1.02	0.036, 0.078, 0.87	0.048, 0.098, 0.93
$(\Delta/\sigma)_{\text{max}}$	0.001	0.002	<0.0001	0.001	0.001
$\Delta\rho_{\text{max}}$, $\Delta\rho_{\text{min}}$ [e·Å^{-3}]	0.89, –0.36	0.25, –0.23	2.06, –1.06	0.56, –0.57	0.44, –0.40
Flack parameter	0.05(12)	0.01(7)			

addition of an aqueous 2.0 M HCl solution, the organic phase was extracted, washed with H_2O (40 mL), brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo to give a pale yellow oil. Purification by flash chromatography (CH_2Cl_2) gave **3** as a colourless oil.

***N*-Benzyl-2-[(4*S*)-4-benzyl-4,5-dihydro-1,3-oxazol-2-yl]benzenesulfonamide (3db):** Prepared from **13db** (1.30 g, 2.93 mmol), stirring for 3 h. Purification by flash chromatography (CH_2Cl_2) gave **3db** (1.14 g, 95%) as a white solid. R_f = 0.35 (CH_2Cl_2). M.p. 90–93 °C (dec., CH_2Cl_2). $[\alpha]_D$ = –25.8 (c = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (br. s, 1 H, SO_2NH, exchanges with H_2O), 8.04 (dd, J = 7.2, 1.7 Hz, 1 H, Ar), 7.77 (dd, J = 7.2, 1.7 Hz, 1 H, Ar), 7.54 (m, 2 H, Ar), 7.19–7.10 (m, 10 H, Ar), 4.68–4.63 (m, 1 H, C*H*N), 4.47 (dd, J = 9.5, 8.5 Hz, 1 H, $OCH_{2\alpha}$), 4.17 (dd, J = 9.5, 8.5 Hz, 1 H, $OCH_{2\beta}$), 4.11 (d, J = 14.0 Hz, 1 H, $NHCH_{2\alpha}Ph$), 4.04 (d, J = 14.0 Hz, 1 H, $NHCH_{2\beta}Ph$), 3.06 (dd, J = 14.0, 7.2 Hz, 1 H, $CHCH_{2\alpha}Ph$), 2.84 (dd, J = 14.0, 7.2 Hz, 1 H, $CHCH_{2\beta}Ph$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 139.7, 137.7, 136.8, 131.9, 131.1, 131.0, 129.8, 129.2, 128.7, 128.4, 127.9, 127.5, 126.7, 126.0, 72.2, 68.6, 47.5, 41.4 ppm. IR (solid state): $\tilde{\nu}$ = 1644, 1452, 1438, 1370, 1327, 1310, 1252, 1165, 1137, 1103, 1059, 1026, 963, 781, 770, 732, 699 cm^{-1}. MS (EI+): calcd. for $C_{23}H_{22}N_2O_3S$ 406.1351, found 406.1353 [M]$^+$.

General Procedure for the Reaction of Saccharin 6 with 1,2-Amino Alcohols. Preparation of 4: The required 1,2-amino alcohol (40.0 mmol, see Scheme 3 for range employed) was added to a stirred solution of the appropriate *N*-alkylsaccharin **6** (40.0 mmol) in dioxane (60 mL). The reaction mixture was refluxed for 8–96 h, until no further saccharin was consumed according to TLC analysis. For the preparation of **4ab** and **4db** the reactions were carried out in THF (b.p. 67 °C). For **4ad**, **4cd**, **4ce** and **4ch** the reaction was performed in dioxane or toluene in a sealed tube at 130 °C (6–20 h). The solvent was evaporated in vacuo to yield a colourless viscous oil. Purification by gradient chromatography (CH_2Cl_2 followed by CH_2Cl_2/MeOH 5%) gave **4**, which was isolated as a viscous oil. After several days of drying and standing under high vacuum (0.1 Torr, 20–40 °C), in most cases the oils solidified to white solids (yields 52–95%).

2-[(Benzylamino)sulfonyl]-*N*-[(1*S*)-1-hydroxymethyl-2-methylpropyl]benzamide (4cb): Prepared from L-valinol (3.96 g, 38.4 mmol) and **6b** (10.5 g, 38.4 mmol) in dioxane (60 mL), refluxing for 72 h. Purification by flash chromatography gave **4cb** as a viscous oil. After several days of drying and standing under high vacuum, the oil solidified to a white solid (10.0 g, 69%). R_f = 0.36 (5% MeOH/CH_2Cl_2). M.p. 136–137 °C (CH_2Cl_2). $[\alpha]_D$ = –28.9 (c = 1.0, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (dd, J = 7.9, 1.0 Hz, 1 H, Ar), 7.60–7.46 (m, 3 H, Ar), 7.22–7.18 (m, 5 H, Ar), 6.72 (t, J = 7.0 Hz, 1 H, SO_2NH), 6.39 (d, J = 8.9 Hz, 1 H, CON*H*), 4.18 (dd, J = 13.8, 7.0 Hz, 1 H, $PhCH_{2\alpha}$), 4.00 (dd, J = 13.8, 5.2 Hz, 1 H, $PhCH_{2\beta}$), 3.88–3.82 (m, 1 H, NC*H*), 3.78 (dd, J = 12.2, 6.3 Hz, 1 H, $CH_{2\alpha}OH$), 3.65 (dd, J = 12.2, 3.0 Hz, 1 H, $CH_{2\beta}OH$), 2.95 (br. s, 1 H, O*H*), 1.80 (oct, J = 6.9 Hz, 1 H, $CHMe_2$), 1.00 (d, J = 6.9 Hz, 3 H, *Me*), 0.99 (d, J = 6.9 Hz, 3 H, *Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 137.7, 136.2, 135.6, 132.7, 130.1, 129.3, 128.5, 128.4, 128.1, 127.7, 63.0, 58.1, 47.6, 29.1, 19.7, 19.1 ppm. IR (solid state): $\tilde{\nu}$ = 3512, 3232, 1640, 1565, 1431, 1330, 1215, 1166, 1015, 749, 736, 701 cm^{-1}. MS (FAB+): calcd. for $C_{19}H_{24}N_2O_4S$ 377.1535, found 377.1352 [M + H]$^+$. $C_{19}H_{24}N_2O_4S$ (376.47): calcd. C 60.62, H 6.43, N 7.44; found C 60.65, H 6.41, N 7.40.

General Procedure for the Preparation of *N*-Alkylated Saccharin Derivatives 6: The appropriate alkyl halide (10.0 mmol) was added to a stirred solution of sodium saccharin dihydrate (10.0 mmol) in DMF (20 mL). The reaction mixture was refluxed at 90 °C for 24–48 h, after which time a white precipitate had formed. The reaction mixture was cooled and CH_2Cl_2 (10 mL) and water (10 mL) were added. The reaction mixture was transferred to a separating funnel and 2 M HCl (10 mL) was added. The layers were separated and the aqueous layer washed with more CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried with $MgSO_4$ and concentrated in vacuo to yield a colourless viscous oil. Purification was carried out by either flash silica column chromatography or by recrystallisation as stated for each compound.

2-(2-Bromoethyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide (6f): Prepared from sodium saccharin dihydrate (5.00 g, 20.7 mmol) and 1,2-dibromoethane (1.80 mL, 20.9 mmol) in DMF (20 mL). Purification by flash silica chromatography followed by recrystallisation from *i*PrOH gave **6f** (2.67 g, 44%) as white crystals. R_f = 0.58 (50% EtOAc/light petroleum). M.p. 96–98 °C (*i*PrOH; ref.[9] 99 °C, aq. EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.08 (m, 1 H, Ar), 7.96–7.84 (m, 3 H, Ar), 4.17 (t, J = 7.6 Hz, 2 H, NCH_2), 3.67 (t, J = 7.6 Hz, 2 H, CH_2Br) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 137.4, 135.0, 134.4, 126.9, 125.3, 121.0, 39.8, 26.8 ppm. IR (solid state): $\tilde{\nu}$ = 2360, 2340, 1732, 1462, 1446, 1335, 1296, 1257, 1229, 1176, 1162, 1033, 960, 752 cm^{-1}. MS (EI+): calcd. for $C_9H_8BrNO_3S$ 290.9388, found 290.9383 $[M]^+$. $C_9H_8BrNO_3S$ (290.13): calcd. C 37.26, H 2.78, N 4.83; found C 37.38, H 2.81, N 4.78.

General Procedure for the Preparation of *O*-Alkylated Saccharin Derivatives 7: Anhydrous benzyl alcohol (5.5 mmol) was added to a stirred solution of saccharin **6a** (5.5 mmol) and triphenylphosphane (6.8 mmol) in dry THF (20 mL) under an inert gas. The reaction mixture was cooled to 0 °C and diethyl azodicarboxylate (6.8 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 16 h, after which time the solvent was concentrated in vacuo. Purification by flash silica chromatography and subsequent recrystallisation from cold EtOH gave the desired *O*-alkylated product.

3-(2-Bromoethoxy)benzo[*d*]isothiazole 1,1-Dioxide (7f): Prepared from saccharin **6a** (2.00 g, 10.9 mmol), triphenylphosphane (3.59 g, 13.7 mmol), anhydrous 2-bromoethanol (0.78 mL, 10.9 mmol), diethyl azodicarboxylate (2.15 mL, 13.7 mmol) and dry THF (20 mL). Purification by flash silica chromatography (25–100% CH_2Cl_2/light petroleum) and subsequent recrystallisation from cold EtOH gave **7f** (1.23 g, 37%) as colourless crystals. Also isolated from the reaction mixture was compound **6f** (0.74 g). R_f = 0.40. M.p. 172–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.89 (m, 1 H, Ar), 7.82–7.71 (m, 3 H, Ar), 4.89 (t, J = 6.0 Hz, 2 H, OCH_2CH_2Br), 3.74 (t, J = 6.0 Hz, 2 H, OCH_2CH_2Br) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 143.5, 134.4, 133.6, 126.4, 123.5, 122.0, 70.5, 27.1 ppm. IR (solid state): $\tilde{\nu}$ = 2361, 1615, 1556, 1457, 1414, 1357, 1327, 1273, 1175, 1273, 1175, 1166, 957, 819, 788, 771, 752 cm^{-1}. MS (EI+): calcd. for $C_9H_8BrNO_3S$ 290.9418, found 290.9405 $[M]^+$. $C_9H_8BrNO_3S$ (290.13): calcd: C 37.26, H 2.78, N 4.83; found C 37.14, H 2.74, N 4.84.

2-{2-[(1,1-Dioxo-1,2-benzisothiazol-3-yl)oxy]ethyl}-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide (8a): Prepared according to the general procedure for the synthesis of **6**. Prepared from sodium saccharin dihydrate (1.44 g, 7.02 mmol) and 1,2-dibromoethane (0.3 mL, 3.51 mmol) in DMF (25 mL). Purification by recrystallisation from CH_2Cl_2 gave **8a** (0.77 g, 56%). R_f = 0.75 (CH_2Cl_2). M.p. > 260 °C (dec., CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, J = 6.5, 1.5 Hz, 1 H, Ar), 7.94–7.85 (m, 5 H, Ar), 7.76 (dt, J = 7.5, 1.0 Hz, 1 H, Ar), 7.71 (dt, J = 7.5, 1.0 Hz, 1 H, Ar), 4.91 (t, J = 6.2 Hz, 2 H, NCH_2), 4.27 (t, J = 6.2 Hz, 2 H, CH_2O) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 169.2, 158.9, 143.5, 137.7, 135.2, 134.6, 134.2, 133.6, 127.5, 127.4, 125.5, 124.0, 121.8, 121.2, 67.9, 38.0 ppm. IR (solid state): $\tilde{\nu}$ = 1739, 1616, 1556, 1462, 1403, 1322, 1258, 1179, 1159, 1122, 1058, 1040, 953, 930, 788, 755 cm^{-1}. MS (FAB+): calcd. for $C_{16}H_{13}N_2O_6S_2$ 393.0215, found 393.0206 $[M + H]^+$. $C_{16}H_{12}N_2O_6S_2$ (392.41): calcd: C 48.97, H 3.08, N 7.14; found C 48.80, H 3.00, N 7.1.

General Procedure for the Preparation of Sulfonamide Methyl Ester 11: Triethylamine (5.1 mmol) was added in one portion to a stirred solution of methyl 2-(chlorosulfonyl)benzoate (4.3 mmol) in dry CH_2Cl_2 (20 mL) (inert gas, room temperature). The reaction was quenched by the addition of 2.0 M HCl (5 mL). The organic fraction was extracted and washed with 2.0 M HCl (2 × 50 mL), brine (50 mL), and then dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2) gave **11** as either a viscous colourless oil or a foamy white solid.

General Procedure for the Preparation of Chloro Sulfonamides 13: Triphenylphosphane (1.30 mmol) and carbon tetrachloride (5 mL, 51.7 mmol) were added to a stirred solution of **4** (1.30 mmol) in the stated solvent (5 mL) at room temperature for the stated time, until complete conversion according to TLC was noted. The reaction mixture was concentrated in vacuo, to give a crude colourless oil. Purification by flash chromatography gave **13** as either a viscous colourless oil or a foamy white solid.

Supporting Information (see footnote on the first page of this article): Full experimental procedures and data for compounds **3ab**–**db**, **4ab**–**4eb**, **6b**–**6i**, **7b**, **7f**, **8a**–**b**, **11e**, **11h**, **11i**, **13ab**–**13db** together with graphical images of their ^{13}C NMR spectra.

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[1] R. I. Robinson, J. C. Stephens, S. M. Worden, A. J. Blake, C. Wilson, S. Woodward, *Eur. J. Org. Chem.* **2004**, 4596–4605.
[2] S. Romani, G. Bovermann, L. Moroder, E. Wuensch, *Synthesis* **1985**, 512–513.
[3] J. R. Proudfoot, U. R. Patel, A. B. Dyatkin, *J. Org. Chem.* **1997**, *62*, 1851–1853.
[4] E. E. Reid, L. M. Rice, C. H. Grogan, *J. Am. Chem. Soc.* **1955**, *77*, 5628–5630.
[5] For example, benzoic acid ethyl ester has been shown to yield 2-(benzoylamino)ethanol (77%), when refluxed at 150 °C in 2-aminoethanol as reported by: A. P. Phillips, R. Baltzly, *J. Am. Chem. Soc.* **1947**, *69*, 200–203.
[6] S. E. Denmark, R. A. Stavenger, A.-M. Faucher, J. P. Edwards, *J. Org. Chem.* **1997**, *62*, 3375–3389.
[7] R. Apple, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801–811.
[8] See Supporting Information.
[9] L. L. Meritt, S. Levey, H. B. Cutter, *J. Am. Chem. Soc.* **1939**, *61*, 15–16.

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