Synthesis of Sugar-Derived Alkyl Sulfones Using a Versatile Transsulfonylation Process

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Abstract: A range of sugar-derived alkyl sulfones were obtained from heteroaryl sulfones using an *ipso*-substitution/alkylation sequence.

Key words: heteroaryl sulfones, sugars, *ipso* substitution, benzothiazol-2-yl group, alkyl sulfones

In spite of the increasing attention given to sulfones in organic synthesis, in sugar chemistry the almost exclusive use of phenyl sulfones, in particular anomeric ones, has been reported emphasizing new methodologies to attain glycals,[1] *C*-glycosides[2, 3] and *C*-disaccharides.[4]

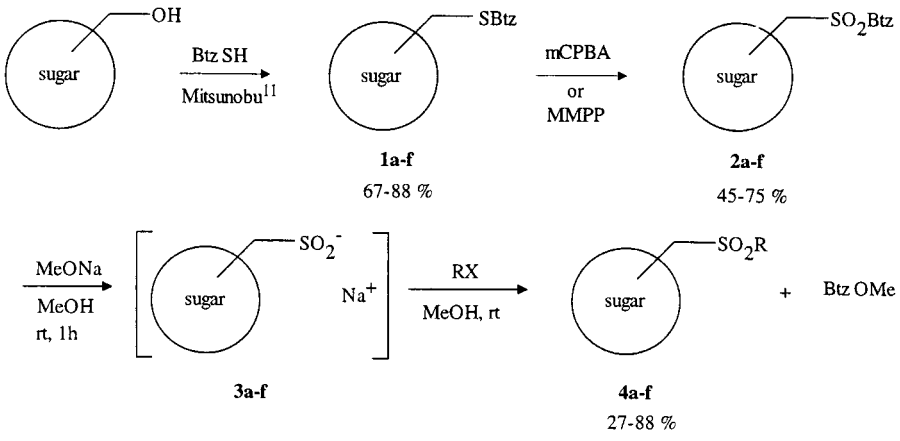
In other respects, non-anomeric sugar sulfones have been sparingly described although diverse analytical,[5] synthetic[6–8] or technical[9] applications have been outlined for such a family of compounds. Most of the sugar-derived sulfones described so far are arylsulfonyl derivatives, usually obtained either through oxidation of sulfide precursors[1, 10] or by arenesulfinate nucleophilic displacement of a halogenated sugar.[5, 6]

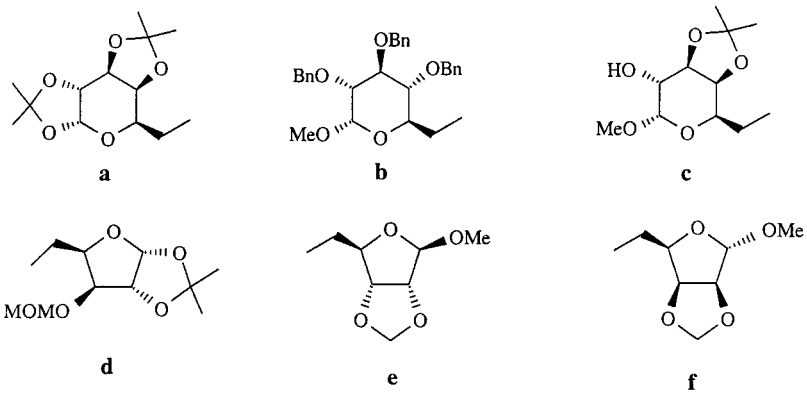
In the course of an ongoing program centered on novel synthetic pathways to chiral oxa- and aza-heterocycles,[7, 8] we needed a convenient odorless process to prepare miscellaneous sugar-derived sulfones.

Heteroaryl sulfones of type **2** can be readily prepared by oxidation with mCPBA or MMPP of the corresponding aza-heterocycle/thiosugar hybrids **1**, which were shown in our laboratory to be accessible by direct Mitsunobu thiosubstitution of protected sugars.[11]

Table 1. Introduced Substituent R through Transsulfonylation

Compound	R	Compound	R
4aa	Me	**4ai**	$(CH_2)_3CH_2Br$
4ab	Pr	**4aj**	$(CH_2)_5CH_2Br$
4ac	$(CH_2)_7Me$	**4b**	Me
4ad	$(CH_2)_{15}Me$	**4c**	Me
4ae	allyl	**4d**	Me
4af	farnesyl	**4e**	Me
4ag	CH_2Ph	**4f**	Me
4ah	CH_2CO_2Me		





Several aza-heterocyclic moieties can allow the above sequence and the corresponding heteroaryl sulfones **2** are generally prone to nucleophilic *ipso*-substitutions,[12] as previously exemplified for simple[13] or more complex benzothiazol-2-yl (Btz) sulfones such as the D-*galacto* derivative **2a**.[14] Other aza-heterocyclic ligands such as 2-pyrimidyl and 1-phenyltetrazol-5-yl were also tested, the transsulfonylation process (R = Me) being successful albeit with inferior yields[15] as compared to the efficient transformation of **2a** into the methyl sulfone **4aa**. Therefore only benzothiazol-2-yl sulfones were used throughout the entire study.

Base-catalyzed reaction of methanol with protected heteroarylsulfonyl sugars **2a–f** produced sugar sulfinates **3a–f**, which could be quenched with alkyl halides to yield sugar alkyl sulfones of type **4a–f** (Table 1).

An initial series of reactions was performed using solely the protected D-galactopyrano template **2a** bearing a 6-(benzothiazol-2-yl)sulfonyl moiety[14] and varying the electrophilic partner RX, either iodo reagents for **4aa–ad** or bromo reagents for **4ae–ah** (Tables 2 and 3).

As expected, an increase in length of the alkyl halide resulted in lower transsulfonylation yields. Attempts to build up bridged structures featuring two sugar sulfone units linked by a spacer chain (entries **4ai** and **4aj** using 1,4-dibromobutane and 1,6-dibromohexane, respectively) failed and only the corresponding bromoalkyl sulfones were obtained.

In order to extend the scope of this method, the same transsulfonylation process was applied to different pyrano- and furano-sugar templates **2b–2f** (Tables 3 and 4) using iodomethane as standard electrophilic reagent in the quenching step. The corresponding sugar methyl sulfones **4b–4f** were obtained in moderate to good yields (Table 2).

Further investigations towards an extension of the synthetic potential of this transsulfonylation process to secondary sites in sugars are in progress.

All common reagents and solvents were used as obtained from commercial suppliers without further purification, except Et_2O which was distilled over Na/benzophenone and mCPBA was dried over P_2O_5; petroleum ether = PE. Products were purified by flash chromatogra-

Table 2. 6-Alkylsulfonyl Derivatives **4**[a]

Entry	Starting Material	Product	Molecular Formula	MS (70 eV) (*m/z*)	Yield (%)	$[\alpha]_D$ (*c*, g/100 mL)[b]	mp (°C) (Solvent)
1	**2a**	**4aa**	$C_{13}H_{22}O_7S$ (322.37)	323	88	–53 (0.9)	140 (Et_2O)
2	**2a**	**4ab**	$C_{15}H_{26}O_7S$ (350.43)	351	80	–47 (0.7)	98 (Et_2O)
3	**2a**	**4ac**	$C_{20}H_{36}O_7S$ (420.56)	421	72	–48 (1.2)	88 (Et_2O)
4	**2a**	**4ad**	$C_{28}H_{52}O_7S$ (532.78)	533	37	–37 (1.0)	87 (PE/EtOAc)
5	**2a**	**4ae**	$C_{15}H_{24}O_7S$ (348.41)	349	81	–40 (1.0)	88 (Et_2O)
6	**2a**	**4af**	$C_{27}H_{44}O_7S$ (512.70)	513	27	–50 (1.0)	oil
7	**2a**	**4ag**	$C_{19}H_{26}O_7S$ (398.47)	398	73	–76 (1.0)	111 (Et_2O)
8	**2a**	**4ah**	$C_{15}H_{24}O_9S$ (380.41)	381	67	–82 (0.9)	oil
9	**2a**	**4ai**	$C_{16}H_{27}BrO_7S$ (443.35)	443	49	–48 (0.6)	155 (PE/EtOAc)
10	**2a**	**4aj**	$C_{18}H_{31}BrO_7S$ (471.40)	471	47	–46 (0.8)	75 (Et_2O)
11	**2b**	**4b**	$C_{29}H_{34}O_7S$ (526.65)	544	87	+47 (1.0)	83 (PE/EtOAc)
12	**2c**	**4c**	$C_{11}H_{20}O_7S$ (296.33)	297	67	+153 (1.0)	142 (Et_2O)
13	**2d**	**4d**	$C_{11}H_{20}O_7S$ (296.33)	314	63	–15 (0.8)	oil
14	**2e**	**4e**	$C_8H_{14}O_6S$ (238.25)	256	77	–193 (1.0)	88 (Et_2O)
15	**2f**	**4f**	$C_8H_{14}O_6S$ (238.25)	256	65 (2 steps)	+67 (1.0)	oil

[a] Satisfactory microanalyses obtained.
[b] Solvent $CHCl_3$.

Table 3. ^{1}H NMR Data for Sulfides, Sulfones and Alkylsulfones ($CDCl_3$/TMS), δ, J (Hz)

	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	Miscellaneous
4aa	d, 5.50 5.2	dd, 4.34 2.5	dd, 4.65 8.0	dd, 4.18 1.9	bd, 4.42 9.2	dd, 3.39 15.0	bd, 3.02	CH_3; 1.34 (2), 1.45 and 1.60, SO_2CH_3: s, 2.99
4ab	d, 5.48 4.9	dd, 4.33 2.6	dd, 4.65 7.8	dd, 4.17 1.2	bd, 4.40 9.4	dd, 3.38 15.5	bd, 2.97	CH_3: 1.36 (2), 1.45 and 1.59, propyl: 1.07, t, CH_3, 1.87, 3.05, 3.14, m, CH_2
4ac	d, 5.47 5.0	dd, 4.32 2.6	dd, 4.64 7.7	dd, 4.17 1.9	dt, 4.39 9.4	dd, 3.37 15.5	bd, 2.96	CH_3: 1.33 (2), 1.44 and 1.58, octyl: 0.87, t, CH_3, 1.27, 1.42, 1.81, 3.05, 3.14, m, CH_2
4ad	d, 5.48 5.0	dd, 4.34 2.6	dd, 4.65 7.8	dd, 4.19 1.9	dt, 4.40 9.5	dd, 3.39 15.4	bd, 2.97	CH_3: 1.35 (2), 1.45 and 1.60, hexadecyl: 0.89, t, CH_3, 1.26, 1.42, 1.83, 3.05, 3.16, m, CH_2
4ae	d, 5.51 5.0	dd, 4.34 2.6	dd, 4.65 7.7	dd, 4.18 2.0	dt, 4.43 9.5	dd, 3.49 15.5	dt, 2.89 1.9	CH_3: 1.34, 1.35, 1.44 and 1.61, allyl: 3.74, bdd, J = 18.8, 3.98, dd, J = 8.3, 5.92, m
4af	d, 5.60 4.9	dd, 4.38 2.7	dd, 4.67 7.7	dd, 4.17 1.8	m, 4.50 10.0	dd, 3.49 15.5	bd, 2.82	CH_3: 1.32, 1.37, 1.44 and 1.66, benzyl: 4.29, bd, 7.26, m, 7.46, m
4ag	d, 5.49 5.1	dd, 4.35 2.8	dd, 4.66 7.8	dd, 4.18 1.9	bd, 4.42 10.0	dd, 3.94 15.2	bd, 3.04	CH_3: 1.34 (2), 1.46 and 1.59, CO_2Me: 3.80, s, 3.97, d, 4.39, d, J = 15.6
4ah	d, 5.48 5.0	dd, 4.33 2.6	dd, 4.64 7.8	dd, 4.17 1.7	bd, 4.39 9.7	dd, 3.40 15.6	bd, 2.97	CH_3: 1.33 (2), 1.44 and 1.58, $(CH_2)_3CH_2Br$: 2.01, 3.14, m, CH_2
4ai	d, 5.47 4.8	dd, 4.32 2.6	dd, 4.63 7.8	dd, 4.17 1.9	bd, 4.39 9.5	dd, 3.42 15.5	bd, 2.96	CH_3: 1.33 (2), 1.44 and 1.58, $(CH_2)_3CH_2Br$: 1.48, 1.86, 3.10, m, CH_2
4aj	d, 5.50 5.0	dd, 4.34 2.6	dd, 4.65 7.8	dd, 4.18 1.6	bd, 4.44 9.5	dd, 3.43 15.5	bd, 2.87	CH_3: 1.34 (2), 1.44 and 1.61 farnesyl: 1.62, s, Me(13) and (17*E*); 1.68, s, Me(17*Z*); 1.76, s, 9Me; 1.94–2.16, m, $4CH_2$; 3.77, bdd, J = 14.2; 3.92, dd, J = 8.5 and 7.3; 5.06–5.14, m, H-12 and H-16; 5.32, bt
1b	d, 4.61 3.7	dd, 3.58 –	m, 4.05 9.5	dd, 3.46 –	m, 4.05 3.0	AB, 3.94 7.7	AB, 3.52 13.0	OCH_3: s, 3.40, OBn: 3 dd, 4.68; 4.81; 4.98, m, 7.23–7.48, Btz: H-4: d, 7.83, H-7: d, 7.75, H-5 and H-6: m, 7.23–7.48
1c	d, 4.79 4.1	m, 3.87 6.7	t, 4.29 6.2	m, 4.37 2.4	m, 4.37 5.5	AB, 3.74 6.8	AB, 3.62 13.9	CH_3: 2s, 1.39 and 1.54, OH: d, 2.32, J_{OH} = 6.2, OCH_3: s, 3.48, Btz: H-4: d, 7.96, H-7: d, 7.86, H-5 and H-6: bt, 7.78
1d	d, 5.95 3.7	d, 4.65 –	d, 4.23 3.1	dd, 4.75 6.3 7.7	AB, 3.77 and 3.59 13.4			CH_3: 2s, 1.32 and 1.46, OMOM: s, 3.45, Btz: H-4: d, 7.87, H-7: d, 7.76, H-5: t, 7.42, H-6: t, 7.30
1e	s 5.06 –	d, 4.61 6.0	d, 4.78 –	t, 4.60 7.9 7.9	AB, 3.64 and 3.56 14.0	2s, 4.96 and 4.99		OCH_3: s, 3.43, Btz: H-4: d, 7.89, H-7: d, 7.76, H-5: t, 7.43, H-6: t, 7.31
1f	s, 5.00	d, 4.52 5.1	dd, 4.72 3.7	m, 4.39 –	t, 4.07 dd, 4.23 11,1	2s, 3.71 and 3.69		OCH_3: s, 3.34, Btz: H-4: d, 7.87, H-7: d, 7.75, H-5: t, 7.42, H-6: t, 7.30
2b	d, 4.45 3.7	dd, 3.46 –	ft, 4.02 9.5	ft, 3.28	ft, 4.35 $J_{5,6b}$ = 10.4	dd, 3.82 14.8	dd, 3.54	OCH_3: s, 3.52, OBn: 4.60, 4.77, and 4.95, 3dd, 6H, 7.20–7.37, m, 15H, Btz: H-4: d, 8.21, H-7: d, 8.01, H-5 and H-6: m, 7.63
2c	d, 4.64 4.1	m, 3.79 6.6	t, 4.29 6.4	dd, 4.19 2.8	ddd, 4.76 $J_{5,6a}$ = 9.1 $J_{5,6b}$ = 3.3	dd, 403 15.2	dd, 3.84	OCH_3: s, 3.49, OH: d, 2.40, J = 4.1, CH_3: 2s, 6H, 1.30 and 1.46, Btz: H-4: d, 8.22, H-7: d, 8.02, H-5 and H-6: m, 7.64
2d	d, 5.78 3.7	d, 4.62 –	d, 4.25 3.3	m, 4.83 $J_{4,5a}$ = 8.0 $J_{4,5b}$ = 8.5	dd, 3.96 14.7 dd, 3.91	–	–	CH_3: 2s, 6H, 1.29 and 1.46, MOM: 3.41, s, 3H, CH_3, 4.72, AB, 2H, CH_2, J_{AB} = 6.8, Btz: H- 4: d, 8.22, H-7: d, 8.02, H-5 and H-6: m, 7.64

Table 3. (continued)

	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	Miscellaneous
2e	s, 4.98	d, 4.55 5.7	d, 4.82 –	ft, 4.82 $J_{4,5a}$ = 6.7 $J_{4,5b}$ = 7.0	dd, 3.91 14.7 dd, 3.80	s, 4.97	s, 4.94	OCH_3: s, 3.31, Btz: H-4: d, 8.23, H-7: d, 8.03, H-5 and H-6: m, 7.63
2f	s, 4.95 –	d, 4.50 5.7	dd, 4.68 3.7	m, 4.61 $J_{4,5a}$ = 9.1	dd, 3.98 15.2 dd, 3.96	s, 4.90	s, 4.83	OCH_3: s, 3.25, Btz: H-4: d, 8.23, H-7: d, 8.02, H-5 and H-6: m, 7.62
4b	–	dd, 3.50 –	ft, 4.04 –	m, 3.25 –	ddd, 4.20 $J_{5,6a}$ = 2.2 $J_{5,6b}$ = 9.6	dd, 3.25 14.7	dd, 2.93	OCH_3: s, 3.46, OBn: 4.62, 4.82 and 4.97, 3dd, 6H, 7.24–7.40, m, 15H, SO_2CH_3: s, 2.92
4c	d, 4.76 3.0	s, 3.82 –	ft, 4.28 6.2	dd, 4.14 2.3	ddd, 4.61 $J_{5,6a}$ = 10.2	dd, 3.56 15.2	dd, 3.14	OCH_3: s, 3.51, OH: s, 2.38, CH_3: 2s, 6H, 1.35 and 1.51, SO_2CH_3: s, 3.05
4d	d, 5.92 3.7	d, 4.61 –	d, 4.15 3.3	m, 4.72 $J_{4,5a}$ 9.5	dd, 3.45 15.0 dd, 3.14	–	–	CH_3: 2s, 6H, 1.33 and 1.51, MOM: 3.39, s, 3H, CH_3, 4.65 and 4.74, AB, 2H, CH_2, J_{AB} = 6.9, SO_2CH_3: s, 3.03
4e	s, 5.05 –	d, 4.56 5.7	d, 4.76 –	ft, 4.74 $J_{4,5a}$ = 8.5 $J_{4,5b}$ = 5.0	dd, 3.44 14.5 dd, 3.21	s, 5.02	s, 4.99	OCH_3: s, 3.42, SO_2CH_3: s, 3.02
4f	s, 4.99 –	d, 4.55 5.7	dd, 4.66 3.7	m, 4.50 $J_{4,5a}$ = 9.1	dd, 3.45 15.2 dd, 3.34	s, 4.99	s, 4.92	OCH_3: s, 3.35, SO_2CH_3: s, 3.04

Table 4. Benzothiazol-2-yl Sulfides and Sulfones[a]

Entry	Starting Material	Product	Molecular Formula	MS (70 eV) (*m/z*)	Yield (%)	$[\alpha]_D$ (*c*, g/100 mL)[b]	mp (°C) (Solvent)
1		**1b**	$C_{35}H_{35}NO_5S_2$ (613.78)	614	88	+ 8 (0.9)	78 (PE/EtOAc)
2		**1c**	$C_{17}H_{21}NO_5S_2$ (383.48)	614	65	±78 (1.2)	oil
3		**1d**	$C_{17}H_{21}NO_5S_2$ (383.48)	383	29 (2 steps)	–58 (1.0)	oil
4		**1e**	$C_{14}H_{15}NO_4S_2$ (325.39)	325	67	+1 (1.0)	83 (Et_2O)
5		**1f**	$C_{14}H_{15}NO_4S_2$ (325.39)	325	72	+31 (1.0)	oil
6	**1b**	**2b**	$C_{35}H_{35}NO_7S_2$ (645.78)	647	70	+37 (1.0)	101 (Et_2O)
7	**1c**	**2c**	$C_{17}H_{21}NO_7S_2$ (415.48)	416	54	+54 (1.0)	120 (Et_2O)
8	**1d**	**2d**	$C_{17}H_{21}NO_7S_2$ (415.48)	416	45	–31 (1.0)	oil
9	**1e**	**2e**	$C_{14}H_{15}NO_6S_2$ (357.39)	358	55	–21 (1.0)	110 (E/EtOAc)
10	**1f**	**2f**	$C_{14}H_{15}NO_6S_2$ (357.39)	358	61	+45 (1.0)	oil

[a] Satisfactory microanalyses obtained.
[b] Solvent $CHCl_3$.

phy on silica gel (36–63 mesh). Mps were measured with a Kofler hot stage apparatus and are uncorrected. Specific optical rotations were measured with a Perkin–Elmer (model 41) polarimeter in $CHCl_3$ using a 1.00 dm cell. ^1H NMR spectra were recorded on a Bruker AM 300 spectrometer in $CDCl_3$ using TMS as internal standard. MS were recorded on a VG Analytical 70-VS mass spectrometer. Elemental analysis: Centre National de la Recherche Scientifique, Service Central d'Analyse, Vernaison, France.

Benzothiazol-2-yl Sulfides 1; General Procedure:
To a solution of the protected sugar (11 mg, 0.25 mmol) in anhyd toluene (5 mL) were added, under argon, 2-mercaptobenzothiazole

(84 mg, 0.50 mmol), Ph_3P (131 mg, 0.50 mmol) and diisopropyl azodicarboxylate (DIAD) (0.1 mL, 0.50 mmol). The mixture was stirred and heated at 80 ˚C for 8 h. After concentration under reduced pressure, the sulfide was purified by flash chromatography (petroleum ether/EtOAc 8:2 for **1b**, **1e**, and **1f**; petroleum ether/EtOAc 7:3 for **1c** and **1d**).

Benzothiazol-2-yl Sugar Sulfones 2; General Procedure:

Oxidation with mCPBA:

Dried commercial mCPBA (70% estimated peracid content, 154 mg, ca. 0.62 mmol) was added to the sulfide (0.26 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h at r.t. (monitored by TLC), then extracted with aq $NaHCO_3$ (3 × 5 mL); the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (flash silica gel column, petroleum ether/EtOAc).

Oxidation with MMPP:

Technical magnesium monoperoxyphtalate hexahydrate (80% peracid content, 180 mg, 0.29 mmol) was added to the sulfide (0.26 mmol) in CH_2Cl_2/EtOH (9:1) (5 mL). The mixture was refluxed with stirring for 2 h (monitored by TLC); after cooling, the mixture was treated in the way described above. Eluents used for chromatography: **2a**: petroleum ether/EtOAc 8:2; **2b**: petroleum ether/EtOAc 8:2 then 7:3; **2e**: petroleum ether/EtOAc 7:3; **2c**, **2d**, and **2f**: petroleum ether/EtOAc 7:3 then 6:4.

Alkyl Sugar Sulfones 4; General Procedure:

The heteroaryl sulfone (0.24 mmol) was dissolved in anhyd MeOH (5 mL), 1 M NaOMe (1 mL) was added until the pH value reached 8–9. The mixture was stirred at r.t. for 45 min., TLC showed the complete formation of the sulfinate and 2-methoxybenzothiazole. The sulfinate was then quenched by MeI (2 mL, 2.4 mmol) or another alkylating reagent (1.2 mmol) at r.t. overnight. After neutralization with acid resin (Dowex 50, 120 mg), the solvent was removed under reduced pressure. The residue was chromatographed (flash silica gel column, petroleum ether/EtOAc). Eluents used for chromatography: **4ab**, **4ad**, **4aj**: petroleum ether/EtOAc 9:1 then 8:2; **4ac**, **4ah**, and **4ai**: petroleum ether/EtOAc 8:2; **4aa** and **4b**: petroleum ether/EtOAc 8:2 then 7:3; **4ae**, **4af**, and **4ag**: petroleum ether/EtOAc 7:3; **4d**, **4e**, and **4f**: petroleum ether/EtOAc 7:3 then 6:4; **4c**: petroleum ether/EtOAc 3:7.

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(15) Transsulfonylation yields for 2-pyrimidyl and 1-phenyltetrazol-5-yl D-*galacto* derivatives: 54% and 68%, respectively.