Tetrahedron 65 (2009) 6341–6347

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

1,2-Cyclic sulfite and sulfate furanoside diesters: improved syntheses and stability

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ARTICLE INFO

Article history:
Received 1 April 2009
Received in revised form 20 May 2009
Accepted 4 June 2009
Available online 10 June 2009

Keywords:
Cyclic-sulfite
Cyclic-sulfate
Carbohydrates
Ionic liquids

ABSTRACT

The facile syntheses of 1,2- and 3,5-cyclic sulfite and sulfate furanoside diesters were conducted in molecular solvents and ionic liquids in the presence of immobilised morpholine. Molecular solvents and ionic liquids performed similarly with regards to overall yields. However, the use of ILs allowed for the reactions to be carried out under atmospheric conditions and showed good recyclability. Additionally, increases in product stability was achieved in ILs over organic solvents, in particular, in bis{(trifluoromethanesulfonyl)imide} and trispentafluoro-ethyltrifluorophosphate-based ionic liquids, which were also excellent media to control the hydrolysis of thionyl chloride and sulfuryl chloride.

1. Introduction

Thionyl chloride ($SOCl_2$) and sulfuryl chloride (SO_2Cl_2) are extensively used in industry for the manufacture of materials ranging from herbicides, drugs and dyestuffs to thermoplastics, surfactants and electrolytes.[1,2] In organic synthesis; they are primarily used as chlorination reagents,[2,3] while the reactivity of their respective cyclic sulfodiester derivatives is often compared with that of epoxides.[4,5] One limitation to the use of $SOCl_2$ and SO_2Cl_2 arises from their high reactivity towards moisture. Similarly, cyclic sulfite/sulfate esters have had limited applications due to problems associated with their syntheses[4,6,7] (e.g., difficulties in controlling cyclisation vs chlorination), as well as their variable reactivity towards nucleophiles.[8,9] For example, there are currently only two reported procedures used to prepare 1,2-cyclic sulfites from 1,2-diols. These involve thionyl chloride or *N*,*N*′-thionyl diimidazole in pyridine under anhydrous and temperature controlled conditions.[8,10] Similarly, this chemistry is not applicable to cyclic sulfates which are prepared from the cyclic sulfite precursors, via oxidation with ruthenium tetroxide, thus limiting their potential usage especially within an industrial setting.[5] These issues are further exacerbated in the case of partially protected sugar 1,2-diols which do not behave as standard diols, as the stereochemistry of anomeric position (alpha and beta configuration at C-1 of the sugar) controls the sulfite/sulfate formation, reactivity and stability, especially towards water.[11] This is particularly relevant as 1,2-cyclic sulfite and sulfate derivatives of carbohydrates have the potential to be versatile synthetic precursors to modified nucleosides, C-nucleosides and any derivatives where a ring opening via a nucleophilic substitution at the C-1 position of the sugar results in the regio- and stereo-selective introduction of the aglycon unit. Therefore, if the synthetic and stability problems related to these sulfur-containing reagents could be overcome, cyclic sulfites and sulfates would find a wider range of applications in organic synthesis and large scale productions, in particular in C-nucleoside chemistry. Herein, we report a simple procedure for which reaction and work-up conditions have been optimised in order to maximise conversion and minimise furanosyl cyclic sulfoester decomposition. Additionally, we have investigated the possibility of using non-molecular solvents in order to achieve higher conversions/yields by providing a stabilising media.

2. Results and discussion

2.1. Synthesis of cyclic sulfites and sulfates in ILs and molecular solvents

To date, the syntheses of cyclic sulfites from diols has to be carried out under strictly anhydrous conditions, with or without the use of triethylamine or pyridine as base[4,6] and this has resulted in varied success. Cyclic sulfates are commonly obtained by mild oxidation of the sulfite parents using Sharpless' conditions requiring the use of heavy metals.[12–14] In general, direct syntheses of cyclic sulfates from diols and SO_2Cl_2 generate several side products (competition between chlorination, multiple sulfurylation and cyclic sulfate formation) and average yields.[11] Only one report

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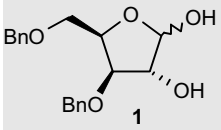
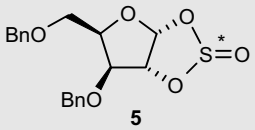
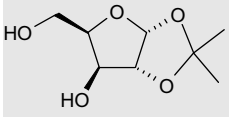
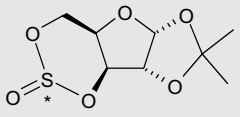
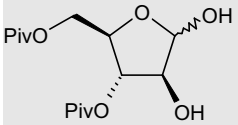
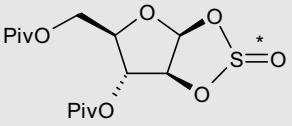
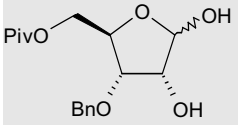
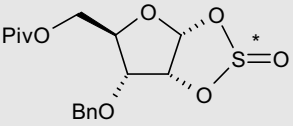
doi:10.1016/j.tet.2009.06.013

Table 1
Synthesis of cyclic sulfites from 1,2- and 3,5-partially protected furanose derivatives

Diols	Cyclic sulfites	Conditions	Isolated yields
 **1**	 **5**	$SOCl_2$ NEt_3, DCM	50
		$SOCl_2$ NEt_3, $[C_4mpyrr][NTf_2]$	67
		$SOCl_2$ PS-Morp, DCM	57
		$SOCl_2$ PS-Morp, $[C_4mpyrr][NTf_2]$	75
 **2**	 **6**	$SOCl_2$ NEt_3, DCM	62
		$SOCl_2$ NEt_3, $[C_4mpyrr][NTf_2]$	83
		$SOCl_2$ PS-Morp, DCM	55
		$SOCl_2$ PS-Morp, $[C_4mpyrr][NTf_2]$	83
 **3**	 **7**	$SOCl_2$ NEt_3, DCM	50
		$SOCl_2$ NEt_3, $[C_4mpyrr][NTf_2]$	38
		$SOCl_2$ PS-Morp, DCM	57
		$SOCl_2$ PS-Morp, $[C_4mpyrr][NTf_2]$	43
 **4**	 **8**	$SOCl_2$ NEt_3, DCM	74
		$SOCl_2$ NEt_3, $[C_4mpyrr][NTf_2]$	[a]
		$SOCl_2$ PS-Morp, DCM	78
		$SOCl_2$ PS-Morp, $[C_4mpyrr][NTf_2]$	[a]

[a] Product not extractable from the IL.

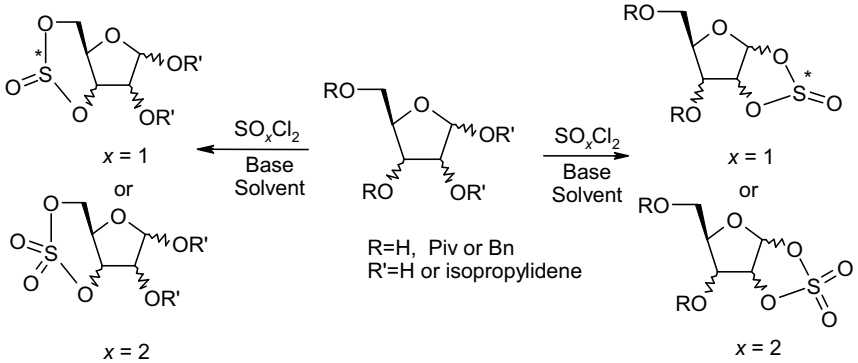
describes the direct formation of cyclic sulfates from diols but the procedure requires controlled conditions such as 0 °C, anhydrous atmosphere and slow reagent addition.[11]

Humenik reported that the formation of α-cyclic sulfites from 1,2-deprotected sugars of the type **5**, **7** and **8** (Table 1) was prevented through anomeric destabilisation of the C1–O-bond.[15] However Beaupere reported that such cyclic sulfites could be obtained for the pyranose form of arabinose.[8] In order to establish whether direct access to cyclic sulfites and sulfates species could be formed from 1,2- and 3,5-deprotected sugars (Scheme 1), the reactions of a series of sugar-diols (Table 1, **1**–**4**) and bases with thionyl chloride were investigated.

The synthesis of cyclic sulfite diester sugars was carried out at room temperature using triethylamine or immobilised morpholine in either anhydrous DCM under an atmosphere of argon, or in non-dried $[C_4mpyrr][NTf_2]$ in air. The isolated yields of the reaction products are summarised in Table 1. In both molecular and ionic solvents, the use of immobilised morpholine led to a reduction in side-product formation and allowed for an easier reaction workup. Upon aqueous work-up, rapid product hydrolysis could be observed with low recovery yields in the case of molecular solvents, but reduced hydrolysis was observed in the case of the IL. Further optimisation of the work-up conditions eliminated the need for an aqueous treatment. In this case, filtration, to remove solid supported morpholine, followed by flushing through a short pad of silica provided a method whereby high isolated yields could be achieved. Whilst the arabinose and ribose derivatives gave similar isolated yields in DCM, it was not possible to extract the riboside product **8** from the IL using diethyl ether, nor to perform an aqueous/DCM work-up due to rapid hydrolysis.

All reactions proceeded with the formation of a mixture of diastereoisomers. Initial spectroscopic analysis revealed that this was not a mixture of α and β isomers, but diastereoisomers due to the inherent chirality of tetrahedral sulfur (Fig. 1). The diastereoisomeric ratio being independent of the reaction conditions used.

Initial attempts to access the cyclic sulfates from the sulfite derived from 3,5-di-*O*-benzyl xylofuranose **1** using the standard Sharpless oxidation reaction conditions proved unsuccessful.[3] This was due to the rapid hydrolysis of the cyclic sulfate product which



Scheme 1. Preparation of the 1,2-cyclic sulfite and sulfate diester furanosides.

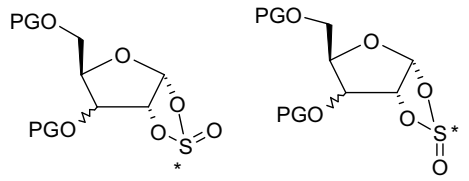


Figure 1. Structure illustrating the chiral configurations of the sulfur moiety.

occurs under the aqueous conditions required for this salt-catalysed oxidation.[16] This result was independent of the nature of the solvent and was attributed to the increased reactivity of the C-1–O–S linkage towards water once the sulfur center had been oxidised. Direct synthesis of the cyclic sulfate derived from 3,5-di-*O*-benzyl xylofuranose, **1**, was obtained with SO_2Cl_2 in the presence of base, and to the best of our knowledge, this is the first time SO_2Cl_2 has been used in one step procedure to form 1,2-carbohydrate cyclic sulfates. Again, the combined use of immobilised morpholine and [C_4mpyrr][NTf_2] further increased the yields compared with DCM, as shown in Table 2. A similar trend was also observed for the more robust cyclic sulfate derivative of 1,2-*O*-isopropylidene-α-xylofuranose, **2**. In the case of the arabinose derivative **3**, the synthesis of cyclic sulfate was lower yielding in both organic solvents and ILs compared with the other furanosides. The lower yields of the arabinose reactions may be attributed in part to the 60:40 α/β ratio of starting materials and the preferred cis configuration of the product, which favours the β isomer. In addition, the increased reactivity of the highly strained trans-cyclic sulfate, would increase the likelihood of product decomposition, resulting in lower yields. Reactions to form the cyclic sulfate from 3-*O*-benzyl-5-*O*-pivaloyl-D-ribofuranoside **4** resulted in no product being formed in either the organic solvent or ionic liquid. The benzyl protecting group at C-3 may be responsible for this lack of reaction since it hinders the α-face.

Unlike the reactions with $SOCl_2$ which formed only one anomeric species, the reactions with SO_2Cl_2 resulted in the formation of an anomeric mixture, leading to the formation of both cis and trans cyclic sulfates. However, in agreement with the synthesis of the cyclic sulfite, regardless of the reaction conditions used, the ratio of cis/trans ring systems remained independent of the furanoside stereochemistry.

Whilst both DCM and ILs offer a medium in which to perform the reactions of $SOCl_2$ and SO_2Cl_2 with partially protected furanosides to form cyclic sulfites and sulfates, a marked improvement is observed in the presence of solid supported morpholine. This base then negates the use of an aqueous work-up thus preventing loss of material due to hydrolysis of these very sensitive functionalities. Filtration through a pad of silica, rather than purification by column chromatography also improved the isolated yields.

Given that the cyclic sulfite/sulfate formation in non-dried ILs (in the absence of an inert atmosphere) shows enhanced yields and stability over the anhydrous DCM counterparts, a stability study of the moisture sensitive $SOCl_2$/SO_2Cl_2 reagents in a range of solvents was initiated. The stabilities were analysed over time using Raman spectroscopy in air and moisture equilibrated ILs. The stability was assessed by dissolving 10 mol % $SOCl_2$ and SO_2Cl_2 in a range of ILs and compared with a range of organic solvents. The results are summarised in Table 3 which shows the percentage of $SOCl_2$ and SO_2Cl_2 remaining after a 12 h and 72 h period.

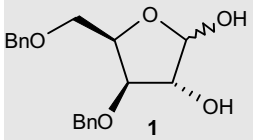
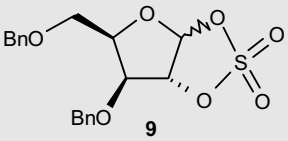
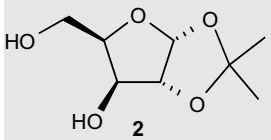
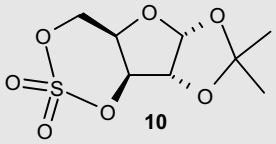
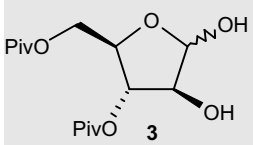
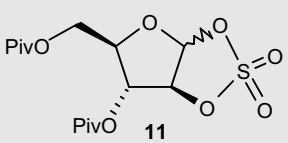
As expected, hydrophilic solvents, THF and [C_4mpyrr][OTf], showed low ability to stabilise both $SOCl_2$ and SO_2Cl_2 with either

Table 3
Stability of $SOCl_2$ and SO_2Cl_2 in a range of wet ILs and organic solvents stirred in air at 20 °C monitored by Raman spectroscopy. The composition for each reagent in the mixture is a percentage compared with the Raman taken after initial addition of the reagent to the solvent at time=0 h, normalised to the spectral features of the solvent

Solvent	Solvent/H_2O Mol ratio[a]	Time (h)	$SOCl_2$ (%)	SO_2Cl_2 (%)
[C_4mpyrr][NTf_2]	107:1	12	100	100
		72	100	15
[C_4mim][NTf_2]	61:1	12	95	92
		72	15	8
[C_4dmim][NTf_2]	48:1	12	84	90
		72	25	20
[C_4mpyrr][FAP]	307:1	12	100	100
		72	98	100
[C_4mpyrr][OTf]	1.5:1	12	0	0
THF	<1453:1	12	70	48
		72	0	0
Hexane	<1072:1	12	90	84
		72	50	30
Benzene	<461:1	12	94	92
		72	32	5
DCM	<1046:1	12	100	100
		72	0	0

[a] Water content determined at t=0 h.

Table 2
Synthesis of cyclic sulfates from 1,2- and 3,5-partially protected furanose derivatives

Diols	Cyclic sulfates	Conditions	Isolated yields
		SO_2Cl_2 NEt_3, DCM	43
		SO_2Cl_2 NEt_3, [C_4mpyrr][NTf_2]	62
		SO_2Cl_2 PS-Morp, DCM	47
		SO_2Cl_2 PS-Morp, [C_4mpyrr][NTf_2]	67
		SO_2Cl_2 NEt_3, DCM	61
		SO_2Cl_2 NEt_3, [C_4mpyrr][NTf_2]	73
		SO_2Cl_2 PS-Morp, DCM	55
		SO_2Cl_2 PS-Morp, [C_4mpyrr][NTf_2]	69
		SO_2Cl_2 NEt_3, DCM	27
		SO_2Cl_2 NEt_3, [C_4mpyrr][NTf_2]	30
		SO_2Cl_2 PS-Morp, DCM	35
		SO_2Cl_2 PS-Morp, [C_4mpyrr][NTf_2]	9

hydrolysis of the reagent or, in the case of the triflate anion, nucleophilic attack on the electron deficient sulfur centre being observed. Higher stability was displayed in more hydrophobic solvents with the $[FAP]^-$ based ionic liquid showing the highest degree stabilization of both reagents. In this case, only 2% degradation was observed over 72 h. Interestingly, despite the high levels of water found in the $[NTf_2]^-$ based ionic liquids compared with the organic solvents, similar stability of the $SOCl_2$ and SO_2Cl_2 was observed. Although both [C4mpyrr][NTf_2] and [C4mpyrr][FAP] were able to stabilize $SOCl_2$, only the $[FAP]^-$ based ionic liquids were able to stabilise SO_2Cl_2 reflecting the increased reactivity of the latter reagent. Even though the $[FAP]^-$ based ionic liquid clearly stabilise $SOCl_2$ and SO_2Cl_2 far better than the other solvents, due to the insolubility of the partially protected carbohydrates, the subsequent preparation of the cyclic sulfite/sulfates was not possible in this medium. Importantly, although DCM is the most commonly used solvent for cyclic sulfite/sulfate formation, this solvent showed very limited ability for the stabilisation of the reagents over time in air.

Similar effects have been observed previously for PCl_3 and $POCl_3$ where higher stability was observed in ionic liquids when compared with commonly used organic solvents. No hydrolysis was found in wet [C4mpyrr][NTf_2] for PCl_3 and [C5mim][FAP] for $POCl_3$ over one week open to air and this behaviour was attributed to the distribution of water molecules in the ILs.[17] In the present study only $[FAP]^-$ based ionic liquids provided the enhanced stability for both sulfur containing electrophiles ($SOCl_2$, SO_2Cl_2). This may reflect the increased hydrolytic instability of the sulfur reagents compared with the phosphorus based reagents. It was, therefore, informative to examine the kinetics of the hydrolysis. For the organic solvents, a gradual degradation of the solute is observed, whereas in the $[NTf_2]^-$ based ionic liquids, the solutes remained stable for a period of time before rapid hydrolytic reaction occurred (see the Supplementary data). This reflected the need for a critical amount of water to be present in the IL before hydrolysis became significant. During hydrolysis, chloride is released into the solution which creates a binary ionic liquid consisting of both hydrophilic, Cl^-, and hydrophobic, $[NTf_2]^-$, anions. This increases the hydrophilicity of the media raising the water content further which, in turn, results in more hydrolysis and rapid decomposition.

3. Conclusions

This study has shown that hydrophobic ILs offer a means to stabilise $SOCl_2$ (in particular [C4mpyrr][NTf_2] and [C4mpyrr][FAP]) and SO_2Cl_2 (in particular [C4mpyrr][FAP]) while maintaining the reactivity of these reagents towards nucleophiles such as diols. The stabilisation of these highly reactive species could find application in large scale synthesis allowing more widespread use. Both $SOCl_2$ and SO_2Cl_2 showed excellent reactivity at room temperature in ionic liquid media when compared to the same reactions in organic solvent. The syntheses of cyclic sulfites and sulfates have also been improved upon when carried out in ILs, due to improved stability and use of simple reaction conditions (room temperature in air). For the first time, direct access to cyclic sulfates of highly reactive modified furanosides has been achieved and the synthetic medium, i.e., the hydrophobic ILs, provided a stabilising environment that limited product decomposition. Further improvements were obtained by the introduction of an immobilised base (which can be recycled by simple NEt_3/DBU/DCM wash), which resulted in higher yields of cyclic sulfite and sulfate formation. Owing to the solubility of the diols and relative stability of $SOCl_2$ and SO_2Cl_2 in organic solvents, only DCM could be used. In this case the ILs, which can be recycled, provide a green alternative for this procedure. These highly reactive cyclic sulfite/sulfates are ideal intermediates for further elaboration towards substituted nucleosides and work is currently ongoing in this area.

4. Experimental

4.1. General

1-Butyl-3-methylimidazolium bis{(trifluoromethyl)sulfonyl}imide ([C4mim][NTf_2]), 1-butyl-2,3-dimethylimidazolium bis{(trifluoromethyl)sulfonyl}imide ([C4dmim][NTf_2]), 1-butyl-1-methyl-pyrrolidinium bis{(trifluoromethyl)sulfonyl}imide ([C4mpyrr][NTf_2]) and 1-butyl-1-methyl-pyrrolidinium trifluoromethanesulfonate ([C4mpyrr][OTf]) were prepared in house using standard literature methods[18,19] from the appropriate halide salt. 1-Butyl-1-methyl-pyrrolidinium tris(pentafluoroethyl)trifluorophosphate ([C4mpyrr][FAP]) was obtained from Merck. Bromide content was measured for each ionic liquid using ion chromatography. In each case, the bromide levels were below 5 ppm. The ionic liquids were used without drying and their water content was analysed via Karl Fischer titration. All organic solvents for the stability studies were HPLC grade solvents which were further distilled either over sodium/benzophenone or calcium hydride.

4.2. Spectroscopic details

All the Raman data was collected on an Avalon 785 instrument at 25 °C and normalised to the solvent features. $SOCl_2$ frequencies-346 cm^{-1}, SO wag, 490 cm^{-1}, SCl_2 stretch, 286 cm^{-1}, SCl_2 rock, 444 cm^{-1}, SCl_2 stretch, 1230 cm^{-1}, SO stretch. SO_2Cl_2 frequencies-346 cm^{-1}, SO wag, 490 cm^{-1}, SCl_2 stretch, 286 cm^{-1}, SCl_2 rock, 444 cm^{-1}, SCl_2 stretch, 1230 cm^{-1}, SO stretch. All ^1H and ^{13}C NMR spectra were been recorded on a Bruker Avance 300 or 500 at 25 °C in $CDCl_3$ referenced to 0.00 ppm using TMS for the ^1H NMR and 77.00 ppm using $CDCl_3$ for the ^{13}C NMR unless otherwise stated. The chemical shifts are reported in parts per million (ppm).

4.3. 3,5-Di-*O*-benzyl-D-xylofuranose (1)[20]

Xylose (1 equiv) was dissolved in acetone (100 cm^3) and to this was added copper sulfate (2 equiv) and sulfuric acid (0.1 equiv) the reaction mixture was stirred at room temperature for 12 h. The copper sulfate was then filtered and the filtrate neutralised with ammonia and passed through a pad of Celite. The acetone was then removed in vacuo to give yellow syrup. To the syrup was added 0.1 M HCl (50 cm^3) and the solution stirred overnight. The resulting mixture was extracted with chloroform, and the combined extracts were washed with saturated $NaHCO_3$ solution (50 cm^3). The aqueous was further extracted with ethyl acetate and the organic phases combined, dried and concentrated and used in the next reaction with no further purification. The material was dissolved in DMF (100 cm^3) and to this was added sodium hydride (3.5 equiv), benzyl bromide (2.5 equiv) and tetrabutylammonium iodide (0.1 equiv). The reaction mixture was then stirred at room temperature for 12 h. Workup was then carried out by addition of water and extraction with DCM. The organic phase was then concentrated and purified by column chromatography. After purification the material was stirred in TFA/water (4:1) until no starting material remained as determined by TLC analysis. The solution was then diluted with ethyl acetate and potassium carbonate solution added. The pH was adjusted to 7 and extraction with ethyl acetate was carried out. The organic phase was then dried and concentrated to yield (**1**) as a mixture of anomers. ^1H NMR (500 MHz, MeOD) δ 7.33–7.29 (m, 10H, Ph), 5.33 (d, 1H, J=7.0 Hz, H-1α), 5.10 (d, 1H, J=2.5 Hz, H-1β), 4.72 (d, 1H, J=5.3 Hz, CH_2Ph), 4.67 (d, 1H, J=6.1 Hz, CH_2Ph), 4.57–4.50 (m, 6H, CH_2Ph), 4.42 (d, 1H, J=10.3 Hz, H-3β), 4.38 (d, 1H, J=8.6 Hz, H-4α), 4.13 (d, 1H, J=14.7 Hz, H-2α), 4.04 (t, 1H, J=6.3 Hz, H-2β), 3.91 (dd, 1H, J=3.7, 8.5 Hz, H-3α), 3.80–3.59 (m, 2H, H-5bα/β), 3.54 (d, 1H, J=10.0 Hz, H-4β). ^{13}C NMR (125 MHz, MeOD) δ 141.3, 141.2, 141.0, 140.9 (PhØ), 130.0, 129.8, 29.6, 129.2, 128.6, 128.5, 128.3, 128.1, 128.0, 127.8 (Ph), 105.3 (C-1α), 98.2 (C-1β), 85.4 (C-2β), 85.2 (C-2α), 82.0 (C-3α), 81.6

(C-3β), 78.6 (C-5β), 76.2 (C-4α), 75.0 (CH_2Ph), 74.8 (CH_2Ph), 73.5 (CH_2Ph), 73.2 (CH_2Ph), 71.8 (C-5α), 70.9 (C-4β). HRMS (ES) *m*/*z* ($M+H^+$) calculated for $C_{19}H_{23}O_5$ 353.1365, found 353.1374. IR ν_{max} (thin film, $CHCl_3$) 3398, 2927, 751, 697.

4.4. 1,2-*O*-Isopropylidene-α-D-xylofuranose (2)

Xylose (1 equiv) was dissolved in acetone (100 cm^3) and to this was added copper sulfate (2 equiv) and sulfuric acid (0.1 equiv) the reaction mixture was stirred at room temperature for 12 h. The copper sulfate was then filtered and the filtrate neutralised with ammonia and passed through a pad of Celite. The acetone was then removed in vacuo to give yellow syrup. To the syrup was added 0.1 M HCl (50 cm^3) and the solution stirred overnight. The resulting mixture was washed with chloroform until the pH was raised to 8. The aqueous phase was extracted with ethyl acetate and the organic phases combined, dried and concentrated to yield (**2**) as a colourless oil. ^{1}H NMR (500 MHz, MeOD) δ 5.22 (d, 1H, *J*=6.15 Hz, H-1), 3.81 (d, 1H, *J*=6.15 Hz, H-2), 3.51 (dt, 1H, *J*=4.75, 10.65 Hz, H-4), 3.45 (d, 1H, *J*=4.75 Hz, H-3), 3.11 (m, 2H, H-5a,b), 0.79 (s, 3H, CH_3), 0.64 (s, 3H, CH_3). ^{13}C NMR (125 MHz, MeOD) δ 107.2 (C-1), 87.6 (C-2), 82.8 (C-4), 76.7 (C-3), 61.5 (C-5), 27.7 (CH_3), 26.7 (CH_3). HRMS (ES) *m*/*z* ($M-H^+$) calculated for $C_8H_{13}O_5$ 189.0763, found 189.0790. IR ν_{max} (thin film, $CHCl_3$) 3451, 2979, 1374. $[\alpha]_D$ −19.7 (*c* 1.1, H_2O) [lit.[21] −18.9 (H_2O)].

4.5. 3,5-Di-*O*-pivaloyl-D-arabinofuranose (3)

1,2-*O*-Isopropylidene-β-D-arabinofuranoside was prepared as per literature procedures.[22,23] 1,2-*O*-isopropylidene-β-D-arabinofuranoside (750 mg, 3.9 mmol) was dissolved in dry pyridine/dry dichloromethane (50 cm^3/50 cm^3). To this solution was added dropwise at 0 °C a solution of pivaloyl chloride (1.1 cm^3, 8.7 mmol) in DCM (10 cm^3). The resulting solution was warmed up at room temperature and was stirred overnight. The solvent was then concentrated in vacuo. The white residue was dissolved in chloroform (100 cm^3), washed with a solution of saturated sodium hydrogen carbonate, brine, and water then dried, filtered and concentrated in vacuo to afford the crude as an oil. Purification by flash chromatography (hexane/ethyl acetate (9:1)) yielded 3,5-di-*O*-pivaloyl-1,2-*O*-isopropylidene-β-D-arabinofuranoside as a yellow oil. This intermediate was then treated with a mixture TFA/water (4:1) at 0 °C. The resulting solution was stirred for 3 h and then diluted with DCM (25 cm^3). A saturated solution of $NaHCO_3$ was added and solid $NaHCO_3$ was added until the pH was neutral. The aqueous layer was extracted with DCM and the combined organic layers were washed with brine and water then dried, and concentrated in vacuo. Purification by flash chromatography (chloroform to chloroform/ethanol (95:5)) gave (**3**) (1.0 g, 88%) as an α/β mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (d, *J*=4.2 Hz, 2H, H-1α, H-1β), 4.94 (t, 1H, H-3α), 4.70 (dd, 1H, *J*=2.5, 5.6 Hz, H-3β), 4.45–4.22 (m, 5H, H-5a,bα, H-5a,bβ, H-4β), 4.16 (d, 1H, *J*=4.7 Hz, H-2α), 4.13–4.06 (m, 2H, H-2β, H-4α), 3.84–3.83 (m, 1H, H-3α), 3.26 (br, 1H, OH), 1.24 (s, 18H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7, 178.6 (C-OPiv), 103.2 (C-1α), 97.4 (C-1β), 81.7 (C-3α), 81.4 (C-3β), 80.4 (C-4α), 80.1 (C-4β), 79.5 (C-2α), 76.8 (C-2β), 65.3 (C-5β), 63.8 (C-5α), 39.3, 39.1 (C-qPiv), 27.5, 27.4 (C-MePiv). HRMS (ES) *m*/*z* ($M+Na^+$) calculated for $C_{15}H_{26}O_7Na$ 341.1576, found 341.1575. IR ν_{max} (thin film, $CHCl_3$) 3448, 2973, 1734.

4.6. 3-*O*-Benzyl 5-*O*-pivaloyl-D-ribofuranose (4)

1,2-*O*-Isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-D-ribofuranoside was prepared from (**2**) as per literature procedure.[24] 1,2-*O*-Isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-D-ribofuranoside (6.58 g, 21.4 mmol), was dissolved in dry THF (300 cm^3), cooled to 0 °C and benzyl bromide (5.48 g, 32 mmol) was added. To this solution was added slowly a suspension of NaH (0.77 g, 32 mmol) in THF (20 cm^3). The reaction was stirred at room temperature for 12 h under argon. Water (5 cm^3) was then added and some of the THF removed under reduced pressure prior to addition of EtOAc (100 cm^3) and an aq NH_4Cl solution (100 cm^3). The aqueous layer was extracted with EtOAc (2×100 cm^3) and the combined organic fractions were washed with brine and dried ($MgSO_4$). The crude was then dissolved in THF (200 cm^3) and TBAF (1 M in THF, 23.5 cm^3, 23.5 mmol) was added. The resulting solution was stirred overnight then concentrated to 20 cm^3. After addition of EtOAc (100 cm^3), the organic layer was washed with an aq NH_4Cl solution (100 cm^3), dried ($MgSO_4$) filtered and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate (4:1)). 1,2-*O*-Isopropylidene-3-*O*-benzyl-D-ribofuranoside (4.60 g, 16.4 mmol) was dissolved in DCM (150 cm^3) under argon and stirred at 0 °C. Triethylamine (6.90 cm^3, 49.3 mmol), dimethylaminopyridine (0.2 g, cat) and pivaloyl chloride (2.43 ml, 19.7 mmol) were added successively to the solution. After 24 h, a 0.5 M HCl solution was added. The organic layer was then washed with a saturated NH_4Cl solution and brine, then dried ($MgSO_4$) and concentrated in vacuo. The residue was then dissolved in a TFA/water (4:1) mixture (40 cm^3) and stirred at room temperature for 3 h. The TFA was partially removed under reduced pressure (residual volume ~5 cm^3) and EtOAc (100 cm^3) was added. The organic layer was washed with saturated $NaHCO_3$ and brine then dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate (1:1)) to yield (**4**) (3.21 g, 9.9 mmol) as a 1:1 mixture of anomers (46% overall yield over four steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.32 (m, 5H, Ph), 5.32 (s, 1H, H-1α), 5.28 (br s, 1H, H-1β), 4.68 (d, 1H, *J*=11.9 Hz, CH_2Ph), 4.65 (d, 1H, *J*=11.8 Hz, CH_2Ph), 4.62 (d, 1H, *J*=12.0 Hz, CH_2Ph), 4.57 (d, 1H, *J*=11.7 Hz, CH_2Ph), 4.31 (dd, *J*=4.2, 12.0 Hz, H-4α), 4.11–4.21 (m, 6H, H-2α, H-3β, H-4β, H-5bα, H-5a,bβ), 4.06 (d, 1H, *J*=4.6 Hz, H-2β), 4.00 (dd, 1H, *J*=4.3, 12.0 Hz, H-5aα), 3.86 (dd, *J*=4.4, 5.6 Hz, H-3α), 3.22 (br s, 1H, OH), 3.00 (br s, 2H, OH), 2.68 (br s, 1H, OH), 1.18 (s, 9H, Piv-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9 (Piv-CO), 178.5 (Piv-CO), 137.0 (PhØ), 129.1, 128.9, 128.4 (Ph), 102.6 (C-1α), 97.4 (C-1β), 79.8 (C-2β), 79.2 (C-2α), 79.0 (C-3β), 78.2 (C-3α), 73.9 (C-4α), 73.7 (CH_2Ph), 73.5 (CH_2Ph), 70.9 (C-4β), 65.3 (C-5α), 64.1 (C-5β), 39.3, 39.2 (C-qPiv), 27.6 (MePiv). HRMS (ES) *m*/*z* ($M+Na^+$) calculated $C_{17}H_{24}O_6Na$ 347.1471, found 347.1475. IR ν_{max} (thin film, $CHCl_3$) 3401, 2967, 1728, 738, 696.

4.7. Synthesis of cyclic sulfites and sulfates in organic solvent or ILs using triethylamine

To DCM or IL (2 cm^3) stirred under argon, was added diol (0.30 mmol) and triethylamine (0.90 mmol). To the resulting suspension were added thionyl or sulfuryl chloride (0.36 mmol) and the reaction mixture allowed to stir gently at room temperature overnight. Workup was then carried by extraction with water to remove the triethylamine. The organic fraction was then passed through a pad of silica and concentrated to yield the sulfite or sulfate. Those carried out in IL were extracted from the IL using diethyl ether prior to extraction with water then filtration through silica. (For yields see Tables 1 and 2.)

4.8. Synthesis of cyclic sulfites and sulfates in organic solvent or ILs using immobilised base

To DCM or IL (2 cm^3) stirred under argon was added diol (0.30 mmol) and immobilised morpholine (Stratospheres® PL-MPH) (0.90 mmol). To the resulting suspension was added thionyl or sulfuryl chloride (0.36 mmol) and the reaction mixture was allowed to stir gently at room temperature overnight. For reactions in DCM, workup was then carried by filtration to remove the immobilised morpholine, followed by washing through with DCM.

The filtrate was then passed through a pad of silica and concentrated to yield the sulfite or sulfate. For reactions in ILs reaction product was extracted form the IL using diethyl ether prior to filtration through silica. (For yields see Tables 1 and 2.)

4.9. 3,5-Di-*O*-benzyl-1,2-*O*-sulfinyl-α-D-xylofuranose (5)[8]

Mixture of two diastereoisomers at the sulfur centre obtained in a 5:2 ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.26 (m, 10H, Ph), 5.94 (d, 1H, J=6.4 Hz, H-1), 4.70–4.51 (m, 5H, 2×CH_2Ph, H-2), 4.48 (dt, 1H, J=5.4, J=10.0 Hz, H-4), 3.96 (d, 1H, J=5.3 Hz, H-3), 3.75 (dd, 2H, J=3.5 Hz, 10.2 Hz, H-5a,b). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1 (CØ), 137.5 (CØ), 128.5, 128.4, 128.0, 127.9, 127.5 (Ph), 99.9 (C-1), 81.2 (C-3), 79.7 (C-4), 79.3 (C-2), 73.6 (CH_2Ph), 72.1 (CH_2Ph), 68.0 (C-5). HRMS (ES) m/z ($M+Na^+$) calculated for $C_{19}H_{20}O_6SNa$ 399.0878, found 399.0870. IR ν_{max} (thin film, $CHCl_3$) 2924, 2868, 1216 (S=O), 740, 697.

4.10. 1,2-Isopropylidene-3,5-*O*-sulfinyl-α-D-xylofuranose (6)[25]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (d, 1H, J=3.7 Hz, H-1), 4.95 (d, 1H, J=11.9 Hz, H-5a), 4.91 (d, 1H, J=2.3 Hz, H-4), 4.62 (d, 1H, J=3.7 Hz, H-2), 4.18 (d, 1H, J=3.5 Hz, H-3), 4.17 (d, 1H, J=13.1 Hz, H-5b), 1.49 (s, 3H, CH_3), 1.44 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 112.6 (CØ), 104.9 (C-1), 83.6 (C-2), 71.2 (C-3), 69.3 (C-4), 55.7 (C-5), 26.6 (CH_3), 26.2 (CH_3). HRMS (ES) m/z ($M+NH_4^+$) calculated for $C_8H_{16}NO_6S$ 254.0687, found 254.0698. IR ν_{max} (thin film, $CHCl_3$) 2923, 1380, 1190 (S=O). $[\alpha]_D$ +37.6 (c 0.065, $CHCl_3$) [lit.[25] +47 ($CHCl_3$)].

4.11. 3,5-Di-*O*-pivaloyl-1,2-*O*-sulfinyl-D-arabinofuranose (7)

Mixture of two diastereoisomers at the sulfur centre obtained in a 7:3 ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (d, 1H, J=4.1 Hz, H-1), 6.38 (d, 1H, J=5.1 Hz, H-1′), 5.33 (d, 1H, J=4.1 Hz, H-2), 5.12 (dd, 1H, J=5.1 Hz, H-2′), 4.53–4.43 (m, 2H, H-3, H-3′), 4.38–4.35 (m, 2H, H-4, H-4′), 4.25–4.20 (m, 3H, H-5a,b, H-2), 4.08 (dd, 2H, J=7.1 J=11.7 Hz, H-5a′,b′), 1.24 (s, 18H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7, 178.6 (C-OPiv), 111.2 (C-1), 110.1 (C-1′), 90.7 (C-2), 86.7 (C-2′), 85.5 (C-4), 85.4 (C-4′), 77.9 (C-3), 76.8 (C-3′), 63.9 (C-5), 62.9 (C-5′), 39.3, 39.1 (C-qPiv), 27.5, 27.4 (C-MePiv). HRMS (ES) m/z ($M+Na^+$) calculated for $C_{15}H_{24}O_8SNa$ 387.1090, found 387.1091. IR ν_{max} (thin film, $CHCl_3$) 2974, 1734, 1159 (S=O).

4.12. 3-*O*-Benzyl-5-*O*-pivaloyl 1,2-*O*-sulfinyl-D-ribofuranose (8)

Mixture of two diastereoisomers at the sulfur centre obtained in a 1:1 ratio. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.32 (m, 5H, Ph), 6.45 (d, 1H, J=3.9 Hz, H-1), 6.32 (d, 1H, J=4.8 Hz, H-1′), 5.24 (dd, 1H, J=4.2, 4.5 Hz, H-2), 4.92 (dd, 1H, J=5.3, 4.9 Hz, H-2′), 4.90–4.10 (m, 2×CH_2Ph, H-4, H-4′, H-5a,b, H-5a′,b′), 3.91 (dd, 1H, J=4.5, 8.1 Hz, H-3), 3.83 (dd, 1H, J=5.4, 9.3 Hz, H-3′). ^{13}C NMR (70 MHz, $CDCl_3$) δ 178.3 (C-OPiv), 136.6, 129.2, 129.1, 129.0, 128.7, 128.6 (Ph), 110.1 (C-1′), 108.5 (C-1), 83.1 (C-2′), 79.5 (C-2), 78.1 (C-4), 77.7 (C-4′), 73.1 (C-3), 72.8 (C-3′), 61.8 (CH_2Ph), 39.3, 27.5 (C-MePiv). HRMS (ES) m/z ($M+Na^+$) calculated for $C_{17}H_{22}NaO_7S$ 393.0984, found 393.0989. IR ν_{max} (thin film, $CHCl_3$) 2395, 1728, 1215 (S=O), 757, 669.

4.13. 3,5-Di-*O*-benzyl-1,2-*O*-sulfanyl-D-xylofuranose (9)

Mixture of two diastereoisomers at the anomeric centre obtained in a 5:2 ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.18 (m, 20H, Ph), 6.37 (d, 1H, J=4.5 Hz, H-1α), 6.23 (s, 1H, H-1β), 5.51 (t, 1H, H-2α, J=4.5 Hz), 5.2 (d, 1H, J=5.7 Hz, H-2β), 4.60–4.50 (m, 9H, H-4α, 2×CH_2Ph), 4.36 (dt, 1H, J=10.6, 5.4 Hz, H-4β). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.0, 137.5, 137.2 (CØ), 127.6, 127.4, 127.2, 126.9, 126.5 (Ph), 91.5 (C-1), 90.8 (C-1′), 78.7 (C-4), 78.3 (C-4′), 73.9 (CH_2Ph), 72.4 (CH_2Ph), 72.3 (CH_2Ph), 71.8 (CH_2Ph), 69.5 (C-3), 69.1 (C-3′), 66.7 (C-5), 66.3 (C-5′). HRMS (ES) m/z ($M-H^+$) calculated for $C_{19}H_{19}O_7S$ 391.0869, found 391.0852. IR ν_{max} (thin film, $CHCl_3$) 2927, 2862, 1212 (S=O), 1092 (S=O), 756, 698.

4.14. 1,2-Isopropylidene-3,5-*O*-sulfanyl-D-xylofuranose (10)[25]

Mixture of two diastereoisomers obtained in a 10:1 ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (d, 1H, J=3.7 Hz, H-1), 6.00 (d, 1H, J=3.7 Hz, H-1′), 5.28 (d, 1H, J=2.7 Hz, H-3), 5.18 (d, 1H, J=2.0 Hz, H-4′), 4.98 (d, 1H J=12.9 Hz, H-5a′), 4.95 (d, 1H, J=3.5 Hz, H-2′), 4.83 (d, 1H, J=12.9 Hz, H-5b′), 4.73 (d, 1H, J=3.7 Hz, H-2), 4.57 (dt, 1H, J=2.7, 5.6 Hz, H-4), 4.26 (s, 1H, H-4′), 3.76 (dd, 1H, J=5.5, 11.2 Hz, H-5a), 3.66 (dd, 1H, J=8.6, 11.2 Hz, H-5b), 1.55 (s, 3H, CH_3), 1.51 (s, 1H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 113.7 (CØ), 113.3 (CØ), 104.9 (C-1′), 104.8 (C-1), 89.8 (C-3), 86.5 (C-4′), 82.8 (C-2), 82.2 (C-2′), 78.8 (C-4), 72.4 (C-3′), 70.4 (C-5′), 64.8 (C-3), 38.1 (C-5), 26.5 (CH_3), 26.2 (CH_3), 26.1 (CH_3′), 25.8 (CH_3′). HRMS (ES) m/z ($M+H^+$) calculated for $C_8H_{13}O_7S$ 270.0647, found 270.0652. IR ν_{max} (thin film, $CHCl_3$) 2989, 1375, 1262 (S=O), 1192 (S=O).

4.15. 3,5-*O*-Pivaloyl-1,2-*O*-sulfanyl-D-arabinofuranose (11)

Mixture of two diastereoisomers at the anomeric centre obtained in a 3:2 ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (d, J=4.7 Hz, 1H, H-1α), 6.38 (d, 1H, J=5.1 Hz, H-1β), 5.73 (t, 1H, J=4.1 Hz H-2α), 5.43 (m, 2H, H-2β, H-3α), 5.33 (dd, 1H, J=4.4, 2.7 Hz, H-3β), 4.58–4.3 (m, 6H, H-4α, H-4β, H-5a,bα, H-5a,bβ), 1.24 (s, 18H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 176.6 (C-OPiv), 92.1 (C-1α), 89.8 (C-1β), 83.7 (C-2α), 42.4 (C-2β), 79.4 (C-4α), 79.2 (C-4β), 74.3 (C-3α), 71.3 (C-3β), 62.7 (C-5α), 60.7 (C-5β), 37.9, 37.6 (C-qPiv), 26.1, 26.0 (C-MePiv). HRMS (ES) m/z ($M+OH^+$) calculated for $C_{15}H_{25}O_{10}S$ 397.1174, found 397.1168. IR ν_{max} (thin film, $CHCl_3$) 2977, 1745, 1281 (S=O), 1193 (S=O).

4.16. Preparation of non-dried IL solutions

For the study of the stability of $SOCl_2$ and SO_2Cl_2 in non-dried ILs, all the ILs were left open to the air prior to use to allow air equilibration. A sample of each IL was removed for water content analysis via Karl Fischer titration.

4.17. Stability of $SOCl_2$ and SO_2Cl_2 in non-dried ILs and organic solvents

All experiments carried out in non-dried ILs and organic solvents were carried out in oven dried glassware with a headspace of air. In each case the storage vessels were sealed to avoid evaporation of either the $SOCl_2$/SO_2Cl_2 or the organic solvent. To 1 cm^3 of solvent was added 29 μL of $SOCl_2$ or 33 μL of SO_2Cl_2 to obtain a 10 mol % solution. After 15 min stirring the samples were placed in a quartz cuvette and a Raman spectrum taken. For the kinetic experiments the solution was stirred in the quartz cuvette and spectra taken every 30 min.

Acknowledgements

We would like to thank QUILL, Merck KGaA for the donation of ionic liquids and an EPSRC (Portfolio Partnership), and EC-Marie Curie FP6 EST program (MEST-CT-2005-020351) for funding.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.013.

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