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A Glycosylation Protocol Based on Activation of Glycosyl 2-Pyridyl Sulfones with Samarium Triflate

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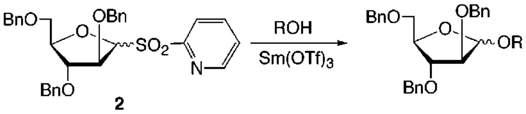
ABSTRACT



Reaction of glycosyl 2-pyridyl sulfones (e.g., 2) with alcohols and samarium(III) triflate affords glycosides in moderate to excellent yields. Benzylated sulfones can be activated in preference to their benzoylated counterparts, and the methodology has been used to prepare di- and trisaccharides containing both furanose and pyranose residues. Thioglycosides do not react under these conditions, and the sulfones are inert to the *N*-iodosuccinimide/silver triflate promoter system commonly used to activate thioglycosides. This selectivity allowed the efficient preparation of oligosaccharides via orthogonal glycosylation protocols.

Oligosaccharides are key players in a number of biological recognition processes,[1] and their preparation has attracted the attention of synthetic chemists for many years.[2] Although a number of glycosylation procedures are available, there is still a need for the development of glycosyl donors that can be activated selectively in the presence of other potential donors. Such compounds allow the efficient synthesis of oligosaccharides via orthogonal glycosylation protocols.[3] These methodologies are attractive alternatives to more classical approaches, which often involve a number of tedious (and yield lowering) protection and deprotection steps on precious oligosaccharide intermediates.

In this paper we report that hydrolytically stable glycosyl 2-pyridyl sulfones can be used as glycosylation agents. Although thioglycosides[4] and glycosyl sulfoxides[5] have found widespread application as donor species in the synthesis of oligosaccharides, the corresponding sulfones have not been widely investigated. To the best of our knowledge, the only previous reports of glycoside bond formation using sulfone donors were published by Ley and co-workers about 10 years ago.[6] This work, an extension of their studies on the formation of tetrahydropyran and tetrahydrofuran acetals, showed that two different glycosyl phenyl sulfones could be activated with magnesium bromide etherate and coupled to simple alcohols. In one case, a carbohydrate alcohol was used to form a disaccharide.[6b] Best yields were obtained upon either heating or ultrasonication. A related study is detailed in a report by Sanders and Kiessling.[7] In this work it was shown that heating glucose 1,2 cyclic sulfites with simple alcohols and lanthanide triflates afforded glucosides. We have now found that benzylated glycosyl 2-pyridyl sulfones (e.g., **2**) react with a range of simple and carbohydrate alcohols upon activation with samarium(III) triflate ($Sm(OTf)_3$) to yield α:β mixtures of glycosides in moderate to excellent yield.

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[6] (a) Brown, D. S.; Ley, S. V.; Vile, S. *Tetrahedron Lett.* **1988**, *29*, 4873. (b) Brown, D. S.; Ley, S. V.; Vile, S.; Thompson, M. *Tetrahedron* **1991**, *47*, 1329. (c) Charreau, P.; Ley, S. V.; Vettiger, T. M.; Vile, S. *Synlett* **1991**, 415.

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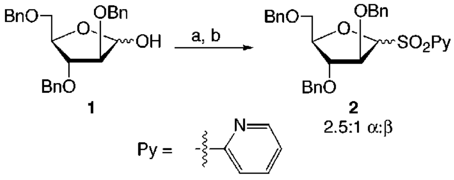
10.1021/ol005579k CCC: $19.00

Scheme 1. Synthesis of Sulfones[a]



[a] Legend: (a) PySSPy, *n*-Bu$_3$P, CH_2Cl_2, rt; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 75% (two steps).

The sulfone starting materials are readily prepared as illustrated in Scheme 1.[8] Reaction of the commercially available benzylated arabinofuranose derivative **1** with dipyridyl disulfide and tri-*n*-butylphosphine provided an anomeric mixture of pyridyl thioglycosides in excellent yield. Subsequent oxidation with *m*-CPBA afforded the target sulfones. Two other sulfones, possessing the mannopyranosyl, **3**,[8] and galactopyranosyl, **4**, stereochemistry (Figure 1), were synthesized in an analogous fashion. For **2** and **3**, the α-sulfone could be separated from its *β*-isomer, but for **4** this was not possible. It was found, however, that both isomers could be used in the glycosylation reactions with equal efficiency and consequently the sulfones were isolated and used as anomeric mixtures. The preparation of the benzoylated pyridyl sulfones, *p*-cresyl sulfones, and pyridyl sulfoxides (see below) is outlined in the Supporting Information and proceeded without incident.

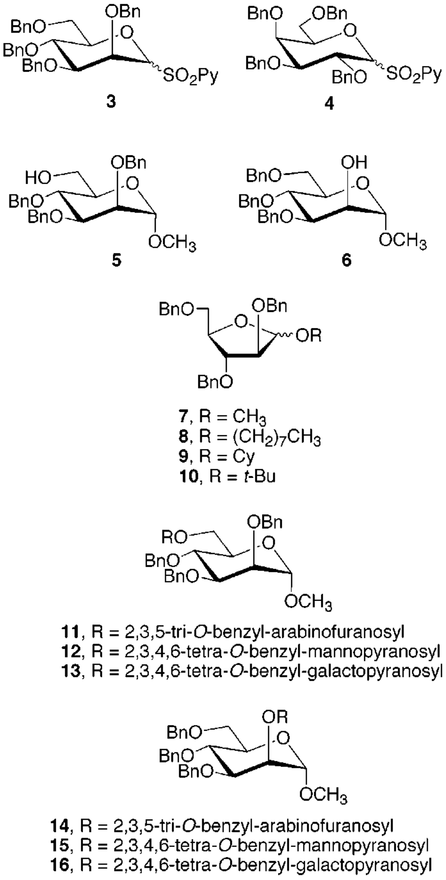
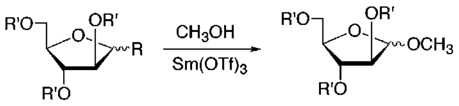


Figure 1.

With a route available for the efficient preparation of the required donors, we first explored the possibility that the pyridyl sulfones could be activated in preference to other potential glycosylation agents. Accordingly, we reacted a panel of glycosyl sulfones, sulfoxides, and thioglycosides with methanol in the presence of a stoichiometric amount of Sm(OTf)$_3$[9] as detailed in Table 1.

Table 1. Reaction of Various Protected Arabinofuranoside Derivatives with Sm(OTf)$_3$ and Methanol[a]



entry	R	R′	yield (%)[b]	α:*β* ratio[c]
1	SO_2Py	Bn	92	5:1
2	SPy	Bn	NR[d]	
3	SO_2Cr[e]	Bn	49	4:1
4	SCr	Bn	NR	
5	SO_2Py	Bz	tr[f]	
6	SPy	Bz	NR	
7	SO_2Cr	Bz	NR	
8	SCr	Bz	NR	
9	SOPy	Bn	81	5:1
10[g]	SO_2Py	Bn	93	7:1

[a] Conditions: donor (1.0 equiv), methanol (20 equiv), Sm(OTf)$_3$ (1.0 equiv). The reactions were carried out on a 0.2 mmol scale in 10 mL of refluxing CH_2Cl_2 under argon for 18 h. [b] Isolated yield after chromatography. [c] Ratio determined by integration of OCH_3 and H-1 resonances in the ^1H NMR spectrum. The α- and *β*-glycosides of **7** were inseparable by chromatography. [d] No reaction observed by TLC. This was confirmed by ^1H NMR spectroscopy of the products isolated after chromatography of the reaction mixture. [e] Cr = *p*-$CH_3C_6H_4$. [f] As detected by TLC. Following chromatography of the reaction mixture, 90% of the unreacted sulfone was recovered. [g] Yb(OTf)$_3$ used in place of Sm(OTf)$_3$.

Among the substrates tested, the benzylated glycosyl pyridyl sulfones were the best, providing methyl glycoside **7** in 92% yield (entry 1). The pyridyl nitrogen appears to be important for the reaction to proceed efficiently; when the benzylated *p*-cresyl sulfone was used, the yield dropped to 49% (entry 3). Both benzylated thioglycosides (entries 2 and 4) do not react as determined by TLC. This was confirmed by ^1H NMR spectroscopy of the products that were recovered after chromatography of the reaction mixture. In contrast to the benzylated sulfones, which provided moderate to excellent yields of **7**, the benzoylated sulfones were much poorer reaction substrates. Only the benzoylated pyridyl sulfone (entry 5) provided any product, in trace amounts. The benzylated sulfoxides (entry 9) were also activated under these conditions, giving an 81% yield of the product. We have found that ytterbium(III) triflate could be used as the

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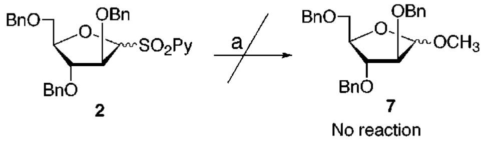
(8) Urban, D.; Skrydstrup, T.; Beau, J. M. *J. Org. Chem.* **1998**, *63*, 2507.

(9) Activation could also be achieved by using 0.5 equiv of Sm(OTf)$_3$; however, reactions times were significantly longer.

promoter with equal efficiency (entry 10). In all cases, mixtures of glycosides were formed, with the α-isomer predominating.

We have also determined that these pyridyl sulfones are not activated by the *N*-iodosuccinimide/silver triflate[10] promoter system used to activate thioglycosides. Attempted reaction of **2** with methanol as outlined in Scheme 2 yielded only the unreacted sulfones.

Scheme 2[a]



[a] Legend: (a) CH_3OH, *N*-iodosuccinimide, silver triflate, CH_2Cl_2, 0 °C to rt, 18 h.

Although we have not carried out any mechanistic investigations, the activation of these sulfones is most likely via "remote activation" [11] by complexation of the metal ion with the pyridyl nitrogen and one of the sulfone oxygens. Subsequent cleavage of the C1−S bond in this activated complex would lead to an oxonium ion, which is, in turn, trapped by the alcohol. The reactivity trends and product ratios detailed in Table 1 are easily rationalized. The lower reactivity of the benzoylated substrates relative to their benzylated counterparts is presumably due to their disarmed nature.[12] The lack of stereocontrol in these glycosylations is expected given that the donors possess nonparticipating benzyl protecting groups on O-2.

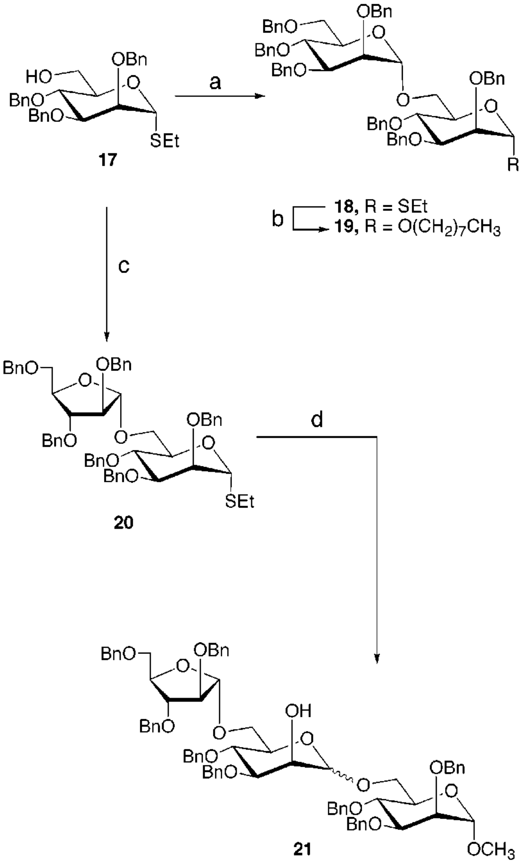
We next investigated the glycosylation of other simple alcohols by **2** (Table 2, entries 2−4). Under the same conditions as those used for the synthesis of **7** (20 equiv of the alcohol, refluxing dichloromethane, 1 equiv of Sm($(OTf)_3$), good to excellent yields of glycosides were obtained with 1-octanol, cyclohexanol, and *tert*-butyl alcohol. Again, mixtures of glycosides were formed, but the α-isomer was favored.

Table 2. Synthesis of Glycosides by Reaction of Glycosyl 2-Pyridyl Sulfones with Various Alcohols in the Presence of Samarium Triflate[a]

entry	sulfone	alcohol	product/yield (%)[b]	α:*β* ratio[c]
1	**2**	CH_3OH	**7**/92	5:1
2	**2**	octanol	**8**/94	2:1
3	**2**	cyclohexanol	**9**/76	4:1
4	**2**	*t*-BuOH	**10**/81	3:2
5	**2**	**5**	**11**/75	2.7:1
6	**2**	**6**	**14**/71	2:1
7	**3**	**5**	**12**/53	2:1
8	**3**	**6**	**15**/89	10:1
9	**4**	**5**	**13**/56	4:1
10	**4**	**6**	**16**/40	4.5:1

[a] Conditions. (1) For sulfone **2** with simple alcohols: donor (1.0 equiv), alcohol (20 equiv), $Sm(OTf)_3$ (1.0 equiv). The reactions were carried out on a 0.2 mmol scale in 10 mL of refluxing CH_2Cl_2, under argon for 18 h. (2) For sulfones **2**, **3**, and **4** with carbohydrate alcohols: donor (1.3 equiv), alcohol (1.0 equiv), $Sm(OTf)_3$ (1.0 equiv). The reactions were carried out on a 0.14 mmol scale in 10 mL of toluene at 70 °C, under argon for 18 h. [b] Isolated yield after chromatography. [c] When the two glycosides were separable (entries 6, 7, 9 and 10), the ratio was determined by recovered product yields. In all other cases, the ratio was determined by integration of OCH_3 or H-1 resonances in the ^1H NMR spectrum.

Scheme 3[a]



[a] Legend: (a) **3**, $Sm(OTf)_3$, toluene, 70 °C, 75%, α:*β* 3:1; (b) *n*-octanol, NIS, AgOTf, −78 to 0 °C, 66%, α:*β* 1.4:1.0; (c) **2**, $Sm(OTf)_3$, toluene, 70 °C, 71%, α:*β* 3:1; (d) **5**, NIS, AgOTf, 0 °C, 75%, α:*β* 1.3:1.

Encouraged by the results with these simple alcohols, we then tested the ability of **2** to glycosylate carbohydrate alcohols **5**[13] and **6**[14] (Table 2, entries 5 and 6). The disaccharide products (**11** and **14**) were obtained in good yield. As in the other glycosylations, the α-glycosides predominated. The glycosylation of alcohols **5** and **6** by the mannosyl and galactosyl sulfones **3** and **4** was also explored as detailed in Table 2 (entries 7−10). With the carbohydrate

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alcohols, better yields were obtained if the reactions were carried out in toluene at 70 °C. Despite the relatively high temperatures required, the only detectable side product was the hydrolyzed sulfone. In general (Table 2), the furanose derivatives gave better yields; however, the stereoselectivity for the α-linked disaccharide was higher in the pyranose series.

On the basis of the results presented in Table 1, we were confident that we could rapidly assemble oligosaccharides by the selective coupling of glycosyl 2-pyridyl sulfones to thioglycoside acceptors. This was demonstrated by the synthesis of disaccharide **19** and trisaccharide **21** (Scheme 3). Deprotection of these oligosaccharides would provide fragments of the lipoarabinomannan (LAM) found in the cell wall complex of *Mycobacterium tuberculosis*.

Both oligosaccharides were synthesized without difficulty as outlined in Scheme 3. Reaction of thioglycoside **17**[15] with sulfone **3** provided a 75% yield disaccharide **18** in a 3:1 α:β ratio. The α-glycoside was separated by chromatography and then coupled to *n*-octanol using a promoter system of *N*-iodosuccinimide and silver triflate. Following column chromatography, disaccharide **19** was obtained pure in 66% yield. The synthesis of trisaccharide **21** proceeded along similar lines. Coupling of thioglycoside **17** with sulfone **2** provided a 3:1 α:β mixture of disaccharides in 71% yield. The desired α-glycoside **20** could be isolated pure after chromatography. Reaction of this thioglycoside with **5** and *N*-iodosuccinimide/silver triflate provided a 75% yield of trisaccharide **21** as a 1.3:1 α:β mixture, which could not be separated.

In summary, we report here a novel glycosylation procedure in which glycosyl 2-pyridyl sulfones are coupled to alcohols using samarium triflate as the promoter. Moderate to excellent yields of simple glycosides and oligosaccharides are obtained. The sulfones can be activated selectively in the presence of thioglycosides. This enabled the rapid synthesis of oligosaccharides **19** and **21** in two−three steps from monosaccharide building blocks **2**, **3**, and **17**. We have also demonstrated that the sulfones are not activated by a standard method for activating thioglycosides (*N*-iodosuccinimide/silver triflate). In its present form the method is limited by the high temperatures required for the reaction to proceed and by the fact that disarmed (acylated) sulfones do not serve as glycosylation partners. The latter limitation is the most serious in that it prohibits controlling the stereochemistry of glycosylation via neighboring group participation of O-2 protecting groups on the donor. We are currently investigating methods by which both of these limitations can be overcome.

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Supporting Information Available: General procedure, scheme detailing the preparation of the sulfones and thioglycosides not described in the text, experimental data, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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