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First Synthesis of Anomeric Sulfimides - Efficient Glycosyl Donors

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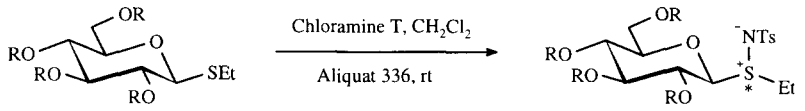
Abstract: Sugar-derived anomeric sulfimides were prepared in high yields from the corresponding thioglycosides and their ability to act as glycosyl donors was investigated.

Sulfimides are sulfur-nitrogen ylides which can be regarded as aza-analogues of sulfoxides. Although they are easily accessible by synthesis and their reactivity can be predicted to be intermediate between those of sulfonium ylides and of sulfoxides, sulfimides still constitute a miserably studied family of compounds.[1]

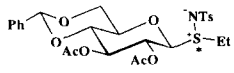
As part of our ongoing projects centred on diversely thio-functionalised sugars,[2] we have developed the synthesis of a new series of compounds, carbohydrate-derived sulfimides.[3]

The elaboration[4,5] of anomeric N-tosyl sulfimides **2** from readily available alkyl thioglycosides **1** is straightforward. In a preliminary study, we have focused on a series of diversely protected ethyl 1-thio-β-D-glucopyranosides **1a-f** which have appeared to be more reactive than their phenyl 1-thio counterparts.

Figure 1. *Preparation of sulfimides*



1 **2**

Compound	R = Ac **2a**	R = Bn **2b**	R = Piv **2c**	R = Bz **2d**	R = p-nitroBz **2e**	 **2f**
Reaction time (h)	3	2.5	16	2	24	4.5
Yield (%)	86	87	83	91	98	92
d.e. (%)	> 95	40	50	> 95	> 95	> 95

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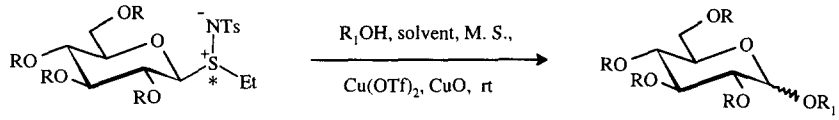
The sulfimides were formed in very good yields and the stereoselectivity attained was in general remarkably higher (Figure 1) than that observed in the synthesis of the corresponding sulfoxides. Depending mainly on the protective array of the sugar moiety, these new compounds can display a variable stability.[6]

Within the last decade, the development of new glycosylation methods[7] has focused on the glycosyl donating ability of anomeric thio-functions,[8-11] due to their high stability under many chemical conditions. More recently, anomeric sulfoxides[12] have made a conspicuous entrance and have proven to be efficient glycosylating agents.[13]

In order to test the potential glycosyl donating aptitude of the anomeric sulfimides - aza-analogues of the corresponding sulfoxides - ethyl 2,3,4,6-tetra-*O*-benzyl-1-*S*-(N-tosylimino)-1-thio-β-D-glucopyranoside **2b** was submitted to diverse glycosylation conditions using methanol as the test acceptor : the Kahne-type activation (Tf_2O or TMSOTf)[12] proved totally inefficient with this glycosyl donor, while other hard Lewis acids such as $BF_3.Et_2O$ only gave poor glycosylation yields, never exceeding 40 %. Attempted nucleophilic displacement of the anomeric group in alkaline medium (MeONa) led to complete degradation of the sulfimide. The use of oxidising reagents like *m*CPBA or MMPP did not promote the desired reaction and only produced moderate yields of the corresponding anomeric sulfoxides and sulfones. In contrast to the preceding cases, softer Lewis acids such as cupric salts were more efficient promoters for the glycosylation reaction.

We have observed for example that the fully benzylated representative **2b** can behave as an efficient glycosyl donor under copper(II) triflate[14] activation :[15,16]



2 **3**

Figure 2.

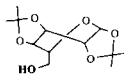
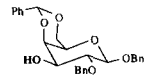
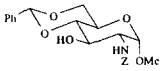
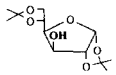
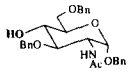
A brief study of the kinetics of the reaction has demonstrated that the per-benzylated sulfimide **2b** was rapidly activated and underwent complete transformation (in less than 5 min) in the presence of $Cu(OTf)_2$.
The reaction conditions with regard to stœchiometry were further investigated in dichloromethane, using 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose as the glycosyl acceptor :

Figure 3. *Stœchiometry variations*

Number of eq. of donor	*1*	*2*	*3*	*4*
Yield *(stepwise addition of 1 eq. every 5 min.)*	50 %	69 %	86 %	quant.
Yield *(all eq. at the start, 5 min.)*	50 %	79 %	quant.	--

The reaction conditions were found to be optimal when one used 1 equivalent of glycosyl donor **2b** in the case of the reaction with simple alcohols like methanol or isopropanol and 3 equivalents of **2b** in the case of the reaction with sugars as glycosyl acceptors. When the whole amount of donor was placed in the reaction flask at the start, then the reaction was completed in less than five minutes.

Figure 4. *Reaction with the per-benzylated donor* **2b**

solvent →	Et_2O		CH_2Cl_2		CH_3CN	
R_1OH ↓	yield (%)	α/β[1]	yield (%)	α/β[1]	yield (%)	α/β[1]
methanol	93	65:35	98	55:45	93	30:70
isopropanol	96	75:25	98	50:50	98	30:70
	91	80:20	quant.	60:40	quant.	20:80
	-	-	50 [2]	45:55	68 [2]	25:75
	89	65:35	84	80:20	95	25:75
	86	65:35	76 *+ 4* [3]	65:35	76 *+ 12* [3]	55:45
	52	≥ 95:5	39	≥ 95:5	42	≥ 95:5

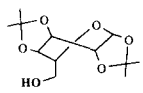
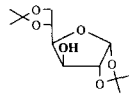
(1) α/β ratios were determined by ^1H NMR. The analysis was based on the spectra of the pure isomers isolated on an analytical scale.

(2) These yields were obtained using only one equivalent of the glycosyl donor.

(3) The yields in italics correspond to rearranged products resulting from the 5,6 → 3,5 migration of an isopropylidene group.

The preceding results could be extended to the case of the per-acetylated donor **2a** : using 2 equivalents of **2a** in CH_2Cl_2, the 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose acceptors were transformed into disaccharides with high β stereoselectivity (Figure 5).

Figure 5. *Reaction with the per-acetylated donor* **2a**

R_1OH		
yield (%)	72	33 + *26 rearranged product*
α/β	0 : 100	0 : 100

In summary, we have described the preparation of a new series of compounds - carbohydrate-derived sulfimides. These anomeric sulfimides **2** can be easily prepared from the corresponding thioglycosides **1**, using a cheap and handy reagent (Chloramine T). They were obtained with high yields and good stereoselectivities (in most cases only one epimer was formed).

These anomeric sulfimides appear to be promising glycosyl donors. No intermediate purification was required prior to their use in glycosylation reactions.

In comparison with other glycosylation methods such as Kahne's procedure, the yields and stereoselectivity are similar but the reaction conditions are milder, the reaction time is quite short - especially

for activated donors - the reaction proceeds at room temperature and the promoter is easy to manipulate and can be stored over a long period without significant loss of activity.

Extension of this study to miscellaneous series of sugars is currently under way in our laboratory.

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References and notes

1. G. Smith, T. J. Sparey and P. C. Taylor, *J. Chem. Soc. Perkin Trans I* (1996) 313-317 and references cited.
2. selected references for a) sulfoxides : S. Cassel, P. Chaimbault, M. Lafosse; C. Lorin and P. Rollin, *Sulfur Lett.*, **20** (1996) 63-70 b) vinyl sulfides : L. Brochard, C. Lorin, N. Spiess and P. Rollin, *Tetrahedron Lett.*, **39** (1998) 4267-4270.
3. see related study in : H. Yuasa, T. Kajimoto and C.-H. Wong, *Tetrahedron Lett.*, **35** (1994) 8243-8246.
4. C. R. Johnson, K. Mori and A. Nakanishi, *J. Org. Chem.*, **44** (1979) 2065-2067.
5. In a typical procedure, a dichloromethane solution of the thioglycoside **1** was treated with 1.5 equivalent of Chloramine T and one drop of Aliquat 336®. The suspension was stirred at room temperature and after completion of the reaction, the mixture was diluted with dichloromethane. The organic phase was washed with 5 % aqueous NaOH, dried over $MgSO_4$, filtered and the filtrate evaporated under reduced pressure.
6. Fully satisfactory spectroscopic data (250 MHz ^{1}H-NMR and mass spectrometry) were obtained for compounds **2a-f**.
7. K. Toshima and K. Tatsuta, *Chem. Rev.*, **93** (1993) 1503-1531.
8. P. J. Garegg, *Adv. Carbohydr. Chem. Biochem.*, **52** (1997) 179-205.
9. J.-R. Pougny, *J. Carbohydr. Chem.*, **5** (1986) 529-535.
10. A. Marra, F. Gauffeny and P. Sinaÿ, *Tetrahedron*, **47** (1991) 5149-5160.
11. P. Fügedi, P.J. Garegg, S. Oscarson, G. Rosén and B.A. Silwanis, *Carbohydr. Res.*, **211** (1991) 157-162.
12. L. Yan and D. Kahne, *J. Am. Chem. Soc.*, **118** (1996) 9239-9248 and references cited.
13. D. Crich and S. Sun, *J. Am. Chem. Soc.*, **120** (1998) 435-436.
14. T. Mukaiyama, T. Nakatsuka and S.-I. Shoda, *Chem. Lett.* (1979) 487-490; see also A. Dondoni, A. Marra, M.-C. Scherrmann, A. Casnati, F. Sansone and R. Ungaro, *Chem. Eur. J.*, **3** (1997) 1774-1782.
15. NB : the sulfimides **2** involved in the glycosylation reactions were used without purification.
16. The dried perbenzylated sulfimide **2b** (3 equivalents) was dissolved in the anhydrous solvent (Et_2O, CH_2Cl_2 or CH_3CN); the glycosyl acceptor (1 equivalent) and CuO (1 equivalent) were added. The mixture was then stirred with powdered molecular sieves (3 or 4 Å depending on the solvent) for about 15 min in order to remove traces of water, then treated with $Cu(OTf)_2$ (3.3 equivalents). After 5 min stirring (in the case of the per-benzylated donor), two drops of triethylamine were added and the mixture was stirred for another 5 min, filtered over Celite®, and the filtrate was evaporated under reduced pressure. The disaccharides **3** were purified by silica gel column chromatography.