Carbohydrate Synthesis

Potent, Versatile, and Stable: Thiazolyl Thioglycosides as Glycosyl Donors**

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The majority of biologically important carbohydrates exist as polysaccharides or glycoconjugates in which monosaccharide

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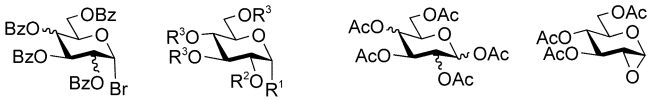
units are joined by *O*-glycosidic bonds.[1] The importance of chemical and/or enzymatic synthesis of complex oligosaccharides has come to the fore because of the low availability of these compounds from natural sources. As a result, many glycosyl donors have been developed and employed in oligosaccharide synthesis.[2,3] Despite enormous progress, no general glycosylation method for oligosaccharide synthesis in solution or on a polymer support has yet emerged.[4] Recently, we became interested in a class of glycosyl donors with the generic leaving group $SCR_1{=}NR_2$ (substituted thioimidoyl derivatives). We have already reported the synthesis of *S*-benzoxazolyl (SBox) glycosides and their evaluation in stereoselective 1,2-*cis* and 1,2-*trans* glycosylations.[5,6] We demonstrated that the SBox glycosides provide high stereoselectivity and remarkably high yields. The lower stability of the SBox glycosides toward some extreme reaction conditions (triflic acid (TfOH) or NaH) in comparison to the corresponding *S*-alkyl/aryl glycosides prompted us to continue the search for suitable leaving groups of this class. Here, we describe the synthesis of novel glycosyl donors, the thiazolyl (Taz) thioglycosides, their application in stereoselective glycosylations, and an evaluation of their usefulness in convergent oligosaccharide synthesis.

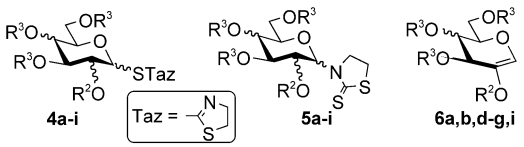
We reasoned that various synthetic precursors, such as anomeric halides (**1a–f**, Scheme 1), acetates (**2a–c**), or 1,2-anhydrosugars (**3**)



Scheme 1. Precursors for the synthesis of thiazolyl thioglycosides. **1a–c** and **2a–c** are derivatives of D-glucose, D-galactose, and D-mannose, as indicated. Bn = benzyl, Bz = benzoyl.

could serve as suitable precursors for the synthesis of thiazolyl thioglycosides (**4a–i**, Scheme 2). 2-Thiazoline-2-thiol (HSTaz) is an odorless solid, readily available from a variety of commercial sources; as a matter of fact, it is even cheaper than commonly used thiophenol. However, the ambiguous reactivity of HSTaz could lead to the formation of the *N*-linked product (**5a–i**). Also, the relatively high basicity of HSTaz ($pK_a = 13.01$) and its conjugate base would promote undesired β elimination, which would result in glycal (1,2-dehydro derivative) formation (**6a,b,d–g,i**).

In many cases the side reactions could be significantly suppressed by varying the reaction conditions. To our delight, conversion of **2** or **3** allowed formation of the desired *S*-linked derivatives with complete stereoselectivity and in high yields.



Scheme 2. Thiazolyl thioglycosides synthesized. **a**: $R^2 = R^3 =$ Bz (β-D-Glc), **b**: $R^2 = R^3 =$ Bz (β-D-Gal), **c**: $R^2 = R^3 =$ Bz (α-D-Man), **d**: $R^2 = R^3 =$ Ac (β-D-Glc), **e**: $R^2 = R^3 =$ Bn (β-D-Glc), **f**: $R^2 =$ Bn, $R^3 =$ Ac (β-D-Glc), **g**: $R^2 = R^3 =$ Ac (β-D-Gal), **h**: $R^2 = R^3 =$ Ac (α-D-Man), **i**: $R^2 = H, R^3 =$ Ac (β-D-Glc).

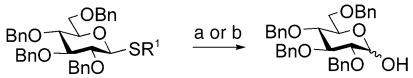
Similarly, derivatives of D-galactose (**4b**,**g**) and D-mannose (**4c**,**h**) were obtained. These results are summarized in Table 1.

Table 1: Synthesis of thiazolyl thioglycosides **4a-i**.

Precursor	Conditions[a]	Products	Yield [%]
1a	HSTaz, NaH, MeCN, RT	**4a**, **5a**, **6a**	49, 0, 41
1a	NaSTaz, [15]crown-5, MeCN, RT	**4a**, **5a**, **6a**	50, 0, 41
1a	KSTaz, [18]crown-6, MeCN, RT	**4a**, **5a**, **6a**	41, 0, 39
1a	NaSTaz, [15]crown-5, acetone, RT	**4a**, **5a**, **6a**	60, 0, 20
1b	KSTaz, [18]crown-6, MeCN, RT	**4b**, **5b**, **6b**	90, 0, 0
1c	KSTaz, [18]crown-6, MeCN, RT	**4c**, **5c**, **6a**	70, 0, 0
1d	NaSTaz, [15]crown-5, MeCN, RT	**4d**, **5d**, **6d**	53, 11, 13
1e	NaSTaz, [15]crown-5, acetone, RT	**4e**, **5e**, **6e**	55, 38, 0
1f	NaSTaz, [15]crown-5, MeCN, RT	**4f**, **5f**, **6f**	46, 28, 21
2a	HSTaz, $BF_3{\cdot}Et_2O$, 3-Å MS, CH_2Cl_2, 45 °C	**4d**, **5d**, **6d**	91, 0, 0
2b	HSTaz, $BF_3{\cdot}Et_2O$, 3-Å MS, CH_2Cl_2, 45 °C	**4g**, **5g**, **6g**	85, 0, 0
2c	HSTaz, $BF_3{\cdot}Et_2O$, 3-Å MS, CH_2Cl_2, 45 °C	**4h**, **5h**, **6d**	70, 0, 0
3	HSTaz, $ZnCl_2$, CH_2Cl_2, RT	**4l**, **5l**, **6i**	78, 0, 0

[a] MS = molecular sieves.

Having synthesized a number of thiazolyl thioglycosides (**4a–i**), our attention turned to an evaluation of their stability toward hydrolysis in the presence of acidic thiophilic reagents (*N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS)/TfOH), common conditions for the thioglycoside hydrolysis.[7,8] For these studies per-benzylated **4e** was compared with ethyl per-*O*-benzyl-1-thio-β-D-glycopyranoside (**7**, Scheme 3)[9] and its 1-*S*-phenyl counterpart, **8**.[10] Thus, **4e**, **7**,



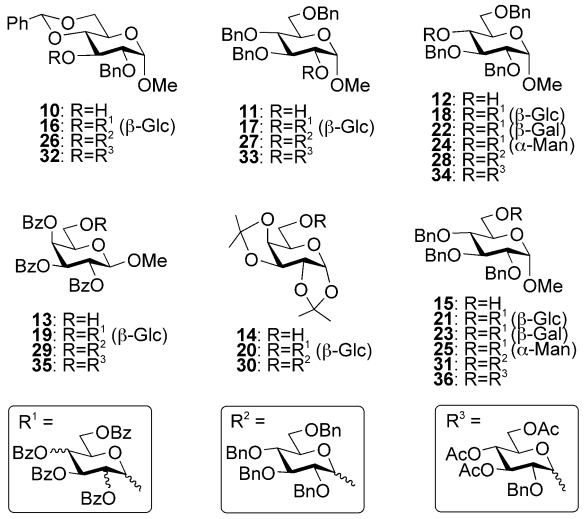
Scheme 3. Stability of STaz versus SEt/SPh toward acidic hydrolysis. Conditions: a) NIS/TfOH, aqueous dichloromethane (RT, 1 h); b) NBS, aqueous acetone (RT, 1 h).

or **8** was treated under standardized conditions to afford hemiacetal **9**. We were thrilled to find that **4e** appears to be much more stable than either **7** or **8**. For example, treatment of **4e** with NIS/TfOH in aqueous CH_2Cl_2 (conditions a) resulted in trace amounts of **9** (< 5 %) in 1 h, while hydrolysis of either **7** or **8** was complete in less than 5 min.

Also, the thiazolylthio moiety was found to be stable toward common protective-group manipulations involving strong bases. For example, conversion of **4d** into **4e** by sequential deacetylation (NaOMe/MeOH) and benzylation (BnBr/NaOH in *N*,*N*-dimethylformamide) proceeded in high overall yield (83%).

Having established the relative stability of the STaz glycosides, we turned our attention to an investigation of their glycosyl donor properties. It should be noted that, although **4d**[11] and a number of thiazolyl thiofuranosides[12] have been reported, to the best of our knowledge this class of compounds has never been glycosidated. We discovered that the STaz glycosides could be activated under a range of reaction conditions, for example, with MeOTf, a common activator for the glycosidation of thioglycosides, as well as AgOTf or $Cu(OTf)_2$. It should be highlighted that virtually no reaction takes place in the presence of NIS/catalytic TfOH, whereas the reaction is smoothly driven to completion in the presence of stoichiometric amounts of TfOH.

Per-benzoyl derivatives of glucose, galactose, and mannose (**4a–c**) were chosen to perform test reactions for the synthesis of 1,2-*trans*-linked disaccharides. Differently protected glycosyl acceptors **10–15**[13–17] were selected for this purpose (Scheme 4). Disaccharides **16–25** were obtained in



Scheme 4. Glycosyl acceptors **10–15** and disaccharides **16–36** formed by use of thiazolyl thioglycosides.

the presence of each promoter; representative reactions are highlighted in Table 2. Complete stereoselectively was achieved reliably with the assistance of a participating substituent at the C-2 position.[18]

We also chose to demonstrate that 1,2-*cis*-glycosides could be obtained with the use of the STaz glycosides bearing a nonparticipating substituent at the C-2 position, for example, **4e** or **4f**. Although stereoselectivity is average in 1,2-dichloroethane (DCE), similar to that with the *S*-alkyl/aryl glycosides, it is apparent that these results can be significantly improved by varying common factors that influence the stereoselectivity at the anomeric center.[4] Some of these studies are outlined in Table 3. Thus, the use of partially

Table 2: Synthesis of 1,2-*trans*-linked disaccharides **16–25**.

Donor	Acceptor	Promoter	Time	Product	Yield [%]
4a	**10**	AgOTf	16 h	**16**	91
4a	**11**	MeOTf	20 h	**17**	99
4a	**12**	NIS/TfOH	16 h	**18**	93
4a	**13**	AgOTf	2 h	**19**	90
4a	**14**	MeOTf	1 h	**20**	82
4a	**15**	$Cu(OTf)_2$	4 days	**21**	99
4b	**12**	AgOTf	40 min	**22**	92
4b	**15**	AgOTf	30 min	**23**	84
4c	**12**	AgOTf	6 days	**24**	85
4c	**15**	AgOTf	6 days	**25**	87

Table 3: AgOTf-promoted synthesis of 1,2-*cis*-linked disaccharides **26–36**.

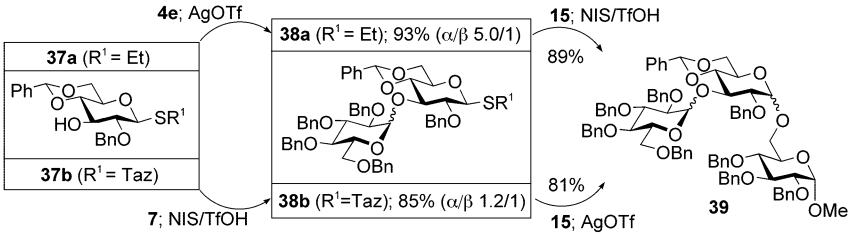
Donor	Acceptor	Solvent[a]	Product	Yield [%]	α/β ratio
4e	**10**	DCE	**26**	96	2.9/1
4e	**10**	T/D	**26**	85	7.7/1
4e	**11**	DCE	**27**	88	1.5/1
4e	**11**	T/D	**27**	97	4.5/1
4e	**12**	T/D	**28**	95	3.5/1
4e	**13**	T/D	**29**	82	4.1/1
4e	**14**	T/D	**30**	76	4.0/1
4e	**15**	T/D	**31**	85	2.7/1
4f	**10**	DCE	**32**	78	1.5/1
4f	**11**	DCE	**33**	88	9.3/1
4f	**12**	DCE	**34**	89	>19/1
4f	**13**	DCE	**35**	74	4.8/1
4f	**15**	DCE	**36**	70	2.7/1

[a] T/D = toluene/dioxane, 1/1 (v/v).

acetylated glycosyl donors or a toluene/dioxane participating solvent mixture[19] in the presence of $Cu(OTf)_2$ or AgOTf was found to be especially beneficial.

Additionally, we decided to evaluate the applicability of the STaz method to chemoselective glycosylation strategies for convergent oligosaccharide synthesis. We assumed that STaz glycosides could be activated over *O*-pentenyl glycosides (with MeOTf, AgOTf, or $Cu(OTf)_2$) or thioglycosides (with AgOTf or $Cu(OTf)_2$), as found for SBox glycosides.[5,6] Conversely, it should be possible to activate other glycosyl donors over STaz glycosides, for example, bromides (with Koenigs–Knorr or Helferich conditions), trichloroacetimidates (with trimethylsilyl triflate), and even "stable" glycosyl donors such as *S*-alkyl/phenyl or *O*-pentenyl glycosides (with NIS/cat. TfOH).[2,3] To prove this hypothesis we synthesized trisaccharide **39** through two conceptually different approaches: activation of the STaz moiety in **4e** over the SEt moiety in **37a**[20] with AgOTf and activation of the SEt moiety in **7** over the STaz group in **37b** with NIS/cat. TfOH (Scheme 5). The obtained disaccharides **38a** and **38b** were coupled with **15** to provide **39**, which was isolated in 83 and 69% overall yields over the two-step activation sequence STaz–SEt–OMe and SEt–STaz–OMe, respectively.

Based on the presented results, we conclude that the STaz glycosides can be successfully applied to the synthesis of both 1,2-*trans*- and 1,2-*cis*-glycosides. In addition, a fully orthogonal character of thiazolylthio and ethylthio moieties has



Scheme 5. Selective activation of STaz over SEt and vice versa. Tf = trifluoromethanesulfonyl.

been discovered. These derivatives fulfill major requirements for the "ideal" glycosyl donor: accessibility, high stability toward protecting group manipulations, mild activation conditions, orthogonality toward other glycosyl donors, and good stereoselectivity. Many other synthetic strategies can be developed with these unique glycosyl donors, further evaluation of which is underway in our laboratory.

Experimental Section

Preparation of the STaz glycosides:

Method A from glycosyl halides: [15]Crown-5 (or [18]crown-6, 0.6 mmol) and NaSTaz (or KSTaz, 6.0 mmol) were added to a stirred solution of a glycosyl halide (**1a–f**, 3.0 mmol) in acetone (or MeCN, 4 mL) under argon. The reaction mixture was stirred for 1 h at RT. The mixture was then diluted with toluene (30 mL) and washed with 1% aqueous NaOH (15 mL) and water (3 × 10 mL). The organic phase was separated, dried, and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane gradient elution) to afford the STaz glycoside (**4a–d**).

Method B from glycosyl acetates: A solution of a glycosyl acetate (**2a–c**, 0.128 mmol), HSTaz (0.256 mmol), and activated 3-Å molecular sieves (100 mg) in CH_2Cl_2 (1.0 mL) was stirred under argon for 30 min at RT. $BF_3{\cdot}Et_2O$ (0.256 mmol) was added dropwise and the reaction mixture was left for 45 min at RT. Additional portions of HSTaz (0.256 mmol) and $BF_3{\cdot}Et_2O$ (0.256 mmol) were added and the reaction mixture was left for 1 h under reflux conditions (45 °C). Upon completion, the STaz glycoside (**4d**, **g**, or **h**) was isolated and purified as described in Method A.

Method C from Brigl's anhydride **3**: HSTaz (0.347 mmol) and $ZnCl_2$ (0.0087 mmol) were added to a stirred solution of **3** (0.174 mmol) in anhydrous CH_2Cl_2. The reaction mixture was stirred for 10 min at RT. Et_3N was then added dropwise until a neutral pH value was reached. The mixture was subjected to aqueous work-up and column chromatography to afford **4i**.

Method D from thioglycosides: The solution of **37a** (0.128 mmol) and 3-Å molecular sieves (70 mg) in CH_2Cl_2 (2 mL) was stirred under argon for 1 h. A freshly prepared solution of Br_2 in CH_2Cl_2 (1.2 mL, 1/165 (v/v)) was then added and the reaction mixture was left for 5 min at RT. The CH_2Cl_2 was then evaporated off under reduced pressure at RT. The crude residue was treated with NaSTaz (0.51 mmol) in dry MeCN (1 mL) under an argon atmosphere for 2 h at RT. The mixture was then diluted with toluene, the solid was filtered-off, and **37b** was isolated and purified as described in Method A.

Preparation of di- and trisaccharides:

Typical AgOTf-promoted glycosylation procedure: A mixture the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and 3-Å molecular sieves (200 mg) in CH_2Cl_2 (2 mL) was stirred under argon for 1.5 h. Freshly conditioned AgOTf (0.22 mmol) was added and the reaction mixture was stirred for 1–2 h at RT, then diluted with CH_2Cl_2. The solid was filtered off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was subjected to aqueous work-up and column chromatography.

All synthesized compounds have adequate ^1H and ^{13}C NMR spectroscopy data and high-resolution MS data (see the Supporting Information).

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[1] A. Varki, *Glycobiology* **1993**, *3*, 97–130.
[2] K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503–1531.
[3] K. C. Nicolaou, H. J. Mitchell, *Angew. Chem.* **2001**, *113*, 1624–1672; *Angew. Chem. Int. Ed.* **2001**, *40*, 1576–1624.
[4] A. V. Demchenko, *Curr. Org. Chem.* **2003**, *7*, 35–79.
[5] A. V. Demchenko, N. N. Malysheva, C. De Meo, *Org. Lett.* **2003**, *5*, 455–458.
[6] A. V. Demchenko, M. N. Kamat, C. De Meo, *Synlett* **2003**, 1287–1290.
[7] M. S. Motawia, J. Marcussen, B. L. Moeller, *J. Carbohydr. Chem.* **1995**, *14*, 1279–1294.
[8] H. I. Duynstee, M. C. de Koning, H. Ovaa, G. A. van der Marel, J. H. van Boom, *Eur. J. Org. Chem.* **1999**, 2623–2632.
[9] F. Dasgupta, P. J. Garegg, *Acta Chem. Scand.* **1989**, *43*, 471–475.
[10] R. J. Ferrier, R. W. Hay, N. Vethaviyasar, *Carbohydr. Res.* **1973**, *27*, 55–61.
[11] L. Cottier, G. Descotes, W. Kudelska, *C. R. Seances Acad. Sci. Ser. II* **1992**, *314*, 657–660.
[12] V. Ferrieres, S. Blanchard, D. Fischer, D. Plusquellec, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3515–3518.
[13] I. E. Valashek, M. K. Shakhova, V. A. Minaev, G. I. Samokhvalov, *Zh. Obshch. Khim.* **1974**, *44*, 1161–1164.
[14] J. M. Kuester, I. Dyong, *Justus Liebigs Ann. Chem.* **1975**, 2179–2189.
[15] P. J. Garegg, H. Hultberg, *Carbohydr. Res.* **1981**, *93*, C10-C11.
[16] Y. Kondo, *Agric. Biol. Chem.* **1975**, *39*, 1879–1881.
[17] M. Sollogoub, S. K. Das, J.-M. Mallet, P. Sinay, *C. R. Acad. Sci. Ser. II* **1999**, *2*, 441–448.
[18] A. F. Bochkov, G. E. Zaikov, *Chemistry of the O-glycosidic bond: formation and cleavage*, Pergamon, **1979**.
[19] A. Demchenko, T. Stauch, G. J. Boons, *Synlett* **1997**, 818–820.
[20] P. J. Garegg, I. Kvarnstrom, A. Niklasson, G. Niklasson, S. C. T. Svensson, *J. Carbohydr. Chem.* **1993**, *12*, 933–953.

