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Thioglycosides Protected as Trans-2,3-Cyclic Carbonates in Chemoselective Glycosylations

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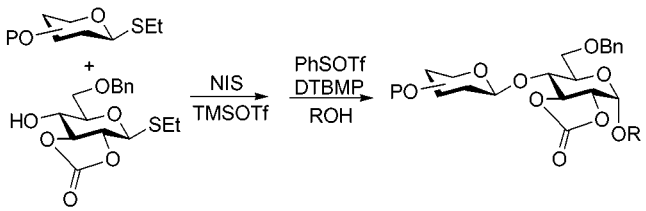
ABSTRACT



Thioglycosides protected as trans-2,3-cyclic carbonates have significantly lower anomeric reactivities than fully acylated and *N*-acyl-protected thioglycosides and can be used as acceptors in chemoselective glycosylations with a wide range of thioglycosyl donors. The resulting thioglycosides can be further activated to give 1,2-cis-linked glycosides.

Chemoselective glycosylations allow the rapid assembly of complex oligosaccharides without protecting group manipulations.[1] In a typical procedure, an activated (armed) thioglycoside, which bears an electron-donating protecting group (e.g., ether) at C-2, is coupled in a chemoselective manner with a less reactive thioglycoside (disarmed) usually having an electron-withdrawing ester protecting group at C-2.[2] Next, the anomeric center of the resulting disaccharide can be activated with a more powerful promoter and reaction with a suitable acceptor will yield a trisaccharide. The chemoselective assembly of more complex oligosaccharides requires a wider range of saccharide building blocks of different anomeric reactivity, and in this respect, Ley and co-workers were the first to show that thioglycosides, bearing a dispiroketal (dispoke) or cyclohexane-1,2-diacetal (CDA) protecting group, have reactivities between armed and disarmed thioglycosides.[3] Wong and co-workers have systematically examined the relative reactivity of a large number of *p*-methylphenyl thioglycosides, and this information was used to develop a computerized program for the design of synthetic schemes for "one-pot multistep" chemoselective assemblies of complex oligosaccharides.[4]

It is important to note that apart from thioglycosides, pentenyl glycosides,[5] glycals,[6] glycosyl fluorides,[7] and phosphoroamidate[8] have been employed in chemoselective glycosylations, however, fewer levels of anomeric reactivity have been described for these derivatives.

Thioglycosides of low anomeric reactivity usually have electron-withdrawing ester groups at the C-2 position, and this feature imposes serious limitations for chemoselective glycosylations. This type of functionality will perform neighboring group participation during glycosylations leading

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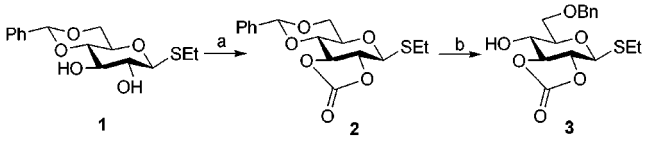
to the stereospecific formation of 1,2-trans glycosides and as a result, 1,2-cis glycosides cannot be introduced at a final stage of a chemoselective glycosylation sequence. To address this problem, we have developed a strategy whereby the anomeric reactivity of thioglycosides is controlled by the bulkiness of the anomeric thio group.[9] Although this approach widened the scope of chemoselective glycosylations, it is still hampered by the fact that the nature of the C-2 protecting group overrides the controlling effect introduced by leaving groups of different size. It is obvious that there is a great need for deactivated (disarmed) thioglycosides that can be used in chemoselective glycosylation and will give 1,2-cis glycosides.

We report here that trans-2,3-cyclic carbonates deactivate the anomeric center of thioglycosides both electronically and conformationally,[5] and as a result, such derivatives are significantly less reactive than corresponding thioglycosides that have ester-protecting groups at C-2. Importantly, it was anticipated that trans-2,3-cyclic carbonates cannot perform neighboring group participation during glycosylations and, therefore, under appropriate conditions should give α-glycosides as the major product.[10]

To explore the potential of trans-2,3-cyclic carbonates, compound **3** was prepared and its glycosyl accepting property was examined. Thus, treatment of thioglycoside **1** with phosgene in the presence of triethylamine as an acid scavenger gave **2** as crystalline material in a quantitative yield. Regioselective opening of the benzylidene acetal using sodium cyanoborohydride and hydrogen chloride in tetrahydrofuran provided the desired glycosyl acceptor **3** bearing a free hydroxyl at C-4 (Scheme 1).[11]

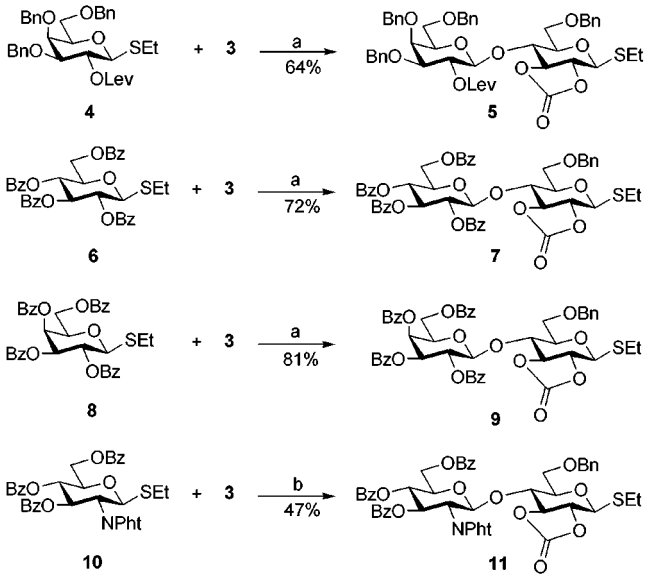
Scheme 1[a]



[a] Key: (a) phosgene (1.9 M solution in toluene), Et_3N, DCM, 100%; (b) $NaCNBH_3$, HCl/Et_2O, MS 3 Å, THF, 62%.

With thioglycoside **3** in hand, attention was focused on chemoselective glycosylations. In first instance, the electronically deactivated thioglycoside **4** was chosen as the glycosyl donor to investigate the relative reactivity of **3**. As expected, *N*-iodosuccinimide (NIS) and trimethylsilyl trifluoromethanesulfonate (TMSOTf)[12] mediated coupling of **3** with **4** gave disaccharide **5** in a yield of 64%. MALDI-TOF analysis of the crude reaction mixture indicated that no self-condensation or oligomerization of **3** had occurred. Furthermore, only the β-anomer was formed due to neighboring group participation by the Lev ester at C-2 of **4**. Additional experiments showed that thioglycoside **3** remains intact upon treatment with the following promoters of thioglycosides: NIS/TMSOTf, NIS/AgOTf,[12a] MeOTf[13] (in dichloromethane at room temperature). This finding prompted us to employ the highly deactivated donors **6**, **8**, and **10**, which can be activated with these promoters. Indeed, coupling of the fully benzoylated thioglucoside **6** with cyclic carbonate **3** in the presence of NIS/TMSOTf afforded disaccharide **7** in 72% yield. In a similar manner, disaccharide **9** was obtained in an excellent yield of 81% using the fully benzoylated thiogalactoside **8**. In both reactions, complete chemoselectivity was achieved and only β-glycosides were formed. Remarkably, the unreactive *N*-phthalimido derivative **10** was selectively activated by NIS/TMSOTf and reaction with **3** provided disaccharide **11** in 47% yield (Scheme 2). The results of these

Scheme 2[a]



[a] Key: (a) NIS, TMSOTf, MS 4 Å, DCM, 0 °C; (b) NIS, TMSOTf, MS 4 Å, DCM, rt.

glycosylations demonstrate that the anomeric reactivity of thioglycoside **3** is much lower than that of acylated derivatives.

In the next stage of the research, attention was turned to the use of 2,3-carbonates as glycosyl donors for the synthesis of α-glycosides and disaccharide **9** was chosen as the

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(10) During the preparation of this manuscript, Kerns et al. reported the use of oxazolidinone protected glucosamine derivatives for the synthesis of α-linked 2-amino glycosides. Benakli, K.; Zha, C.; Kerns, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 9461. For examples of using 2,3-cyclic carbonates as glycosyl donors, see: (a) Gorin, P. A.; Perlin, A. S. *Can. J. Chem.* **1961**, *39*, 2474. (b) Betaneli, V. I.; Ovchinnikov, M. V.; Backinowsky, L. V.; Kochetkov, N. K. *Carbohydr. Res.* **1980**, *84*, 211. (c) Kochetkov, N. K.; Torgov, V. I.; Malysheva, N. N.; Shashkov, A. S. *Tetrahedron* **1980**, *36*, 1099. (d) Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291.

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glycosyl donor and 1,2:3,4-di-*O*-isopropylidene-α-D-galactose (**12**) was used as the model acceptor. As expected, NIS/TMSOTf or MeOTf failed to activate **9**. When dimethyl(thiomethyl)sulfonium triflate (DMTST)[14] was used as the promoter, several unidentified products were formed along with the desired trisaccharide and unreacted starting material. Fortunately, PhSOTf, which was generated in-situ by the reaction of PhSCl with AgOTf,[15] proved to be the activator of choice and gave trisaccharide **13** in a yield of 74% as a mixture of anomers (α/β = 2/5) when the coupling was performed in dichloromethane at −78 °C. Interestingly, a similar yield and stereochemical outcome was obtained when Crich's reverse addition protocol[16] was adopted. A low α-selectivity (α/β = 3/2) was obtained when diethyl ether was used as the reaction solvent. Fortunately, mainly the α-glycoside (α/β = 5/1) was obtained when the reaction was performed in a mixture of toluene/1,4-dioxane (1/3, v/v)[17] at 0 °C albeit in a somewhat lower yield (64%). When glycosyl acceptor **14,** having a secondary hydroxyl was coupled with **9**, using the same activator and solvent mixture, trisaccharide **15** was formed with highly α-stereoselectivity in a reasonable yield (α/β = 8/1, 51%) (Scheme 3).

In conclusion, it is demonstrated that thioglycosides protected as trans-2,3-cyclic carbonates have significantly lower anomeric reactivities than fully acylated and *N*-acyl-protected thioglycosides and as a result these derivatives can be used as acceptors in chemoselective glycosylations with a wide range of C-2 alkylated or acylated thioglycosyl donors. Its synthetic value was further demonstrated by employing trans-2,3-cyclic carbonate protected thioglycosides as glycosyl donors and under the appropriate conditions the substrates provided mainly 1,2-cis-linked glycosides. The use of trans-2,3-cyclic carbonate protected thioglycosides provides a new level of anomeric reactivity and therefore widens the scope of existing chemoselective glycosylation strategies. In particular, these new substrates make it possible to synthesize trisaccharides having the 1″,2″-trans and 1′,2′-cis glycosidic linkage sequences.

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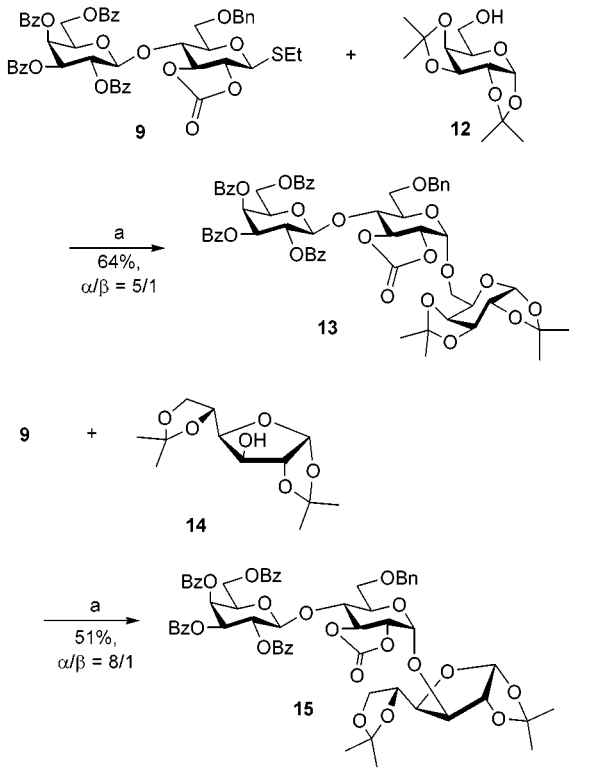
Scheme 3[a]



[a] Key: (a) PhSCl, AgOTf, DTBMP, MS 4 Å, toluene/1,4-dioxane (1/3, v/v), 0 °C.

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Supporting Information Available: Detailed experimental procedures with spectroscopic data for compounds **2**, **3**, **5**, **7**, **9**, **11**, **13**, and **15** as well as the ^{1}H NMR and ^{13}C NMR spectra of those compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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