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An armed-disarmed approach for blocking aglycon transfer of thioglycosides

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Abstract

Thioglycosides are used frequently as glycosyl donors and as mimetics of O-glycosides. While being very useful, thioglycosides are prone to a detrimental side reaction referred to as aglycon transfer. In this paper, it is shown that aglycon transfer can be blocked by matching thioglycoside-containing acceptors with more armed glycosyl donors.

Thioglycosides are extremely useful derivatives for the synthesis of oligosaccharides and glycosylated natural products.^{1,2} The sulfide group is easy to install and stable to a wide range of reaction conditions. In addition, thioglycosides can be activated directly as glycosyl donors using a variety of activating agents such as mercury salts, sulfonyl triflates, and alkylating agents.^{1,2} Moreover, thioglycosides can be readily converted into other glycosyl donors such as glycosyl sulfoxides,³ sulfones,⁴ and halides.⁵ As a result, they are versatile intermediates for carbohydrate synthesis. Thioglycosides have also been investigated extensively as mimetics of biologically relevant O-glycosides.⁶ S-glycosides are much more stable than O-glycosides to both chemical and enzymatic degradation and are typically much easier to synthesize. As a result, S-glycosides have been developed as glycosyl transferase inhibitors, agonists/antagonists for lectins, and as carbohydrate-based vaccine antigens.⁷

While being extremely useful, compounds containing thioglycoside aglycon groups are prone to a detrimental side reaction referred to as aglycon transfer.^{8–22} Strong electrophilic species such as activated glycosyl donors can react with the sulfur atom of a thioglycoside to produce a sulfonium ion (see Scheme 1). Cleavage of the bond between the anomeric carbon and the sulfur atom results in transfer of the aglycon to the electrophilic species. In the case of a glycosylation reaction, the aglycon is transferred to the glycosyl donor.

One strategy to block aglycon transfer is to introduce aglycon groups that decrease the nucleophilicity of the sulfur atom through steric hindrance and/or electronic deactivation such as the dicyclohexylmethyl group or 2,6-dimethylphenyl (DMP) group.^{16,17,22} While this approach is effective in many synthetic routes, there are a number of situations where the aglycon group cannot be modified. For example, many S-glycoside inhibitors and vaccine antigens have strict structural requirements for the aglycon group. Therefore, an alternative strategy that minimizes or eliminates aglycon transfer without modifying the aglycon is needed.

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Several reports have shown that the aglycon transfer process is affected by the protecting groups on the glycosyl acceptor and donor. For one to effectively utilize a protecting group strategy for blocking aglycon transfer, it is critical to understand how changes to protecting groups affect transfer and how best to implement this approach.

Aglycon transfer is thought to proceed via glycosylation of the sulfur atom to form a sulfonium ion followed by cleavage to give the transfer product. In principle, this process is reversible, which raises two important issues. First, the transfer process provides a pathway for cleavage and reformation of the bond between the anomeric carbon and the sulfur atom. Therefore, it provides a pathway for anomerization of the linkage. We recently showed that anomerization does in fact occur.²² Second, the transfer process permits equilibration between the activated species derived from the glycosyl donor and the activated species derived from the thioglycoside. Therefore, the relative energies of the two activated intermediates could have a significant effect on the transfer process with the reaction driven to the more stable intermediate (s). If this were true, one could avoid transfer by controlling the relative stabilities of the activated intermediates.

To effectively implement this approach, two important challenges must be addressed. First, one would have to prevent anomerization. This could be achieved by addition of a group that controls stereoselectivity via neighboring group participation. Second, one would like a rational means to control the relative reactivities of the activated species. However, the nature of the activated intermediate(s) and the factors that determine the relative stabilities are not well understood. Nevertheless, one can approximate the relative stabilities via an armed/disarmed analysis. The terms armed and disarmed refer to the relative ease or difficulty of activating a sugar as a glycosyl donor.^{23,24} In general, disarmed sugars have protecting groups that would destabilize an oxocarbenium ion such as electron withdrawing esters and azides. Armed sugars typically have protecting groups that are less destabilizing such as benzyl ethers or silyl ethers. Since the rates of activation can be evaluated experimentally, there is extensive information in the literature regarding factors that affect the armed/disarmed nature of a sugar.²⁵

To evaluate the armed-disarmed strategy, a series of glycosylations were carried out with the aim of synthesizing a GalNAc α 1–3Gal derivative. This disaccharide is known to be expressed in humans and was needed as a glycan for our group's carbohydrate microarray.^{26–28} The relative armed/disarmed nature of the glycosyl donor and acceptor was systematically varied. First, the disarmed donor **1**²⁹ was coupled with armed acceptor **2**³⁰ (see Scheme 2).³¹ One would anticipate that an oxocarbenium ion (or other activated intermediate) derived from the armed **2** would be more stable than an oxocarbenium ion derived from the disarmed **1**. Therefore, aglycon transfer was expected to be favorable. In fact, aglycon transfer was the major pathway (85% of **3**³², $\alpha:\beta = 2.5:1$) and no disaccharide was formed. Next, we examined disarming the thioglycoside by substituting the benzyl ethers with electron withdrawing benzoyl esters. In addition to disarming the thioglycoside, the benzoyl ester at the 2 position should maintain the beta stereochemistry at the anomeric center via neighboring group participation. Glycosylation of disarmed acceptor **4**²⁶ with disarmed donor **1** produced the desired disaccharide (**5**)²⁶ in 40% yield along with 30% transfer product **3** ($\alpha:\beta = 1:1$). Next, armed donor **6**²⁹ was coupled with armed acceptor **2**. The reaction produced a very complex mixture of products. From this mixture, the transfer product (**7**, all β)³³ could be isolated in 30% yield, but the desired product was not obtained. The extensive formation of side products may have resulted from polymerization and/or anomerization. Finally, we coupled the disarmed thioglycoside **4** with the armed donor **6**. Based on the mechanistic analysis, this is the preferred matching and transfer should be unfavorable. Indeed, disaccharide **8**³⁴ was produced in 79% yield and no transfer product was observed.

The results demonstrate that aglycon transfer can be avoided by modifying the protecting groups on the glycosyl donor and acceptor to ensure that the thioglycoside acceptor is more disarmed than the glycosyl donor. The approach provides a complement to existing strategies based on modifying the aglycon group. Given the work involved in changing protecting groups, this approach is best implemented in the planning stages of a synthesis.

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31. Procedure for the glycosylation reactions: A mixture of donor **6** (98 mg, 0.16 mmol, 2 eq) and acceptor **4** (46 mg, 0.08 mmol, 1 eq) was dried under vacuum for 1 hr and then dissolved in dichloromethane (1 mL). Molecular sieves was added to the solution and the reaction was cooled to –20 °C. TMSOTf (1 drop) was added and the mixture was stirred at –20 °C for 0.5 hr. The reaction was quenched by addition of saturated NaHCO₃ (1 mL). The organic layer was separated, dried over Na₂SO₄, and concentrated in vacuo. The crude product was purified by column chromatography (1:1 ethyl acetate/hexanes) to give the desired product, phenyl (2-azido-3,4,6-tri-O-benzyl-2-deoxy- α -D-galactopyranosyl)-(1 $\rightarrow$ 3)-2,4,6-tri-O-benzoyl-1-thio- β -D-galactopyranoside (**8**), (64 mg, 79% yield).
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34. Phenyl (2-azido-3,4,6-tri-O-benzyl-2-deoxy- α -D-galactopyranosyl)-(1 $\rightarrow$ 3)-2,4,6-tri-O-benzoyl-1-thio- β -D-galactopyranoside (**8**), (64 mg, 79% yield): *R*_f = 0.4 (1:2 ethyl acetate/hexanes); ¹H NMR (CDCl₃) δ 8.08–8.01 (m, 6H), 7.61–7.50 (m, 5 H), 7.48–7.43 (m, 4 H), 7.33–7.17 (m, 18 H), 7.10–7.08 (m, 2 H), 5.91 (d, *J* = 3.2 Hz, 1 H), 5.64 (t, *J* = 10.0 Hz, 1 H), 5.24 (d, *J* = 3.6 Hz, 1 H), 4.85 (d, *J* = 10.0 Hz, 4.66 (d, *J* = 11.2 Hz, 1 H), 4.58 (dd, *J* = 11.6, 7.2 Hz, 1 H), 4.46–4.36 (m, 3 H), 4.30–4.21 (m, 4 H), 4.12 (m, 1 H), 3.74 (m, 1 H), 3.70 (dd, *J* = 10.4, 3.2 Hz, 1 H), 3.44 (dd, *J* = 10.8, 2.8 Hz, 1 H), 3.38 (dd, *J* = 9.6, 7.2 Hz, 1 H), 3.23 (d, *J* = 1.2 Hz), 3.17 (dd, *J* = 9.6, 5.6 Hz, 1 H); ¹³C NMR (CDCl₃) δ 166.0, 165.7, 164.7, 138.1, 138.0, 137.5, 133.3, 133.2, 131.9, 130.1, 129.9, 129.8, 129.5, 129.4, 129.1, 128.8, 128.5, 128.44, 128.42, 128.36, 128.32, 128.16, 128.1, 127.97, 127.8, 127.7, 127.6, 127.5, 94.2, 86.0, 77.4, 75.0, 74.4, 73.7, 73.3, 73.2, 72.5, 70.1, 69.1, 68.9, 65.6, 62.7, 59.2; HRMS, *C* alcd for [MNH₄]⁺ C₆₀H₅₉N₄O₁₂S: 1059.3850. Found: 1059.3873.

Scheme 1.
Aglycon Transfer of Thioglycosides

Scheme 2.

Effects of varying the armed/disarmed nature of the glycosyl donor and acceptor on the outcome of the glycosylation reaction