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A Convenient Preparation of Glycosyl Chlorides from Aryl/Alkyl Thioglycosides

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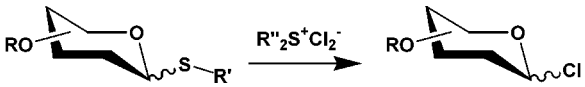
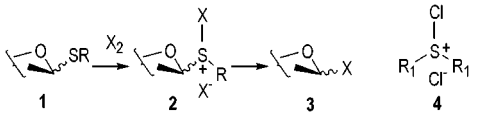
ABSTRACT



Because of the vast structural diversity encountered in the field of glycobiology, versatile methods for orthogonal oligosaccharide assembly are always of interest. Reported herein is the preparation of glycosyl chloride donors obtained by reaction of the corresponding thioglycoside precursors with chlorosulfonium chloride reagent 4. The crude chlorides thus obtained can be used directly in subsequent glycosylation reactions, and examples of the generality of this approach are provided.

Thioglycosides are now well established as stable and versatile synthons in the field of synthetic carbohydrate chemistry.[1−4] During the course of our work on oligosaccharide assembly,[5] we required a mild, versatile protocol for the conversion of thioglycosides protected with sensitive blocking groups into their corresponding glycosyl chlorides. Halogen activation[6,7] of thioglycosides is well-known, and the reaction proceeds under essentially neutral conditions. The mechanism of conversion involves the initial formation of glycosyl halosulfonium salt **2** from thioglycoside **1**, which subsequently heterolyzes to glycosyl halide **3** (Scheme 1).

Scheme 1



Recently, this approach has been extended to include reaction with mixed halogens (I−Br, I−Cl).[8] The utility of this classic halogen activation has been demonstrated in the assembly of higher oligosaccharides.[9] However, there is some concern that bromine can react with aromatic aryl protecting groups,[10] while the handling of chlorine gas is cumbersome. Here, we report a convenient method for the preparation of glycosyl chlorides from their precursor thioglycosides via chlorosulfonium salts generated in situ.

We envisaged that a preformed sulfonium salt such as **4** could effectively participate in the transfer of chlorine to thioglycoside **1** to generate **2**. Reagent **4** is readily prepared by treatment of an alkyl or aryl sulfoxide with oxalyl chloride

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under conditions similar to those utilized for the preparation of activated sulfoxides in the Swern oxidation.[11] Initial investigations were conducted on thioglycosides **7**, **15**, and **18** (Figure 1) with two chlorosulfonium salts, namely, **5** (**4**; R_1 = Me) and **6** (**4**; R_1 = Ph) as follows: The reaction was performed under an argon atmosphere on 0.1 mmol (1 equiv) of thioglycoside. To a stirred solution of oxalyl chloride (2 equiv) in dry CH_2Cl_2 (0.5 mL) at −78 °C was added dropwise a solution of either methyl or phenyl sulfoxide (3 equiv) in dry CH_2Cl_2 (1 mL).[12] After 5 min, when the evolution of the gas ceased, a solution of thioglycoside in dry CH_2Cl_2 (1 mL) was added dropwise, and the reaction mixture was allowed to attain room temperature over a period of 1.5 h. The mixture was diluted with CH_2Cl_2 (3 mL), washed with a 1:1 (v/v) mixture of aqueous saturated $NaHCO_3$ and 10% $Na_2S_2O_3$ (4 mL) and then H_2O (4 mL), and dried (Na_2SO_4), and the solvent was removed. The residue was analyzed by ^{1}H NMR spectroscopy.

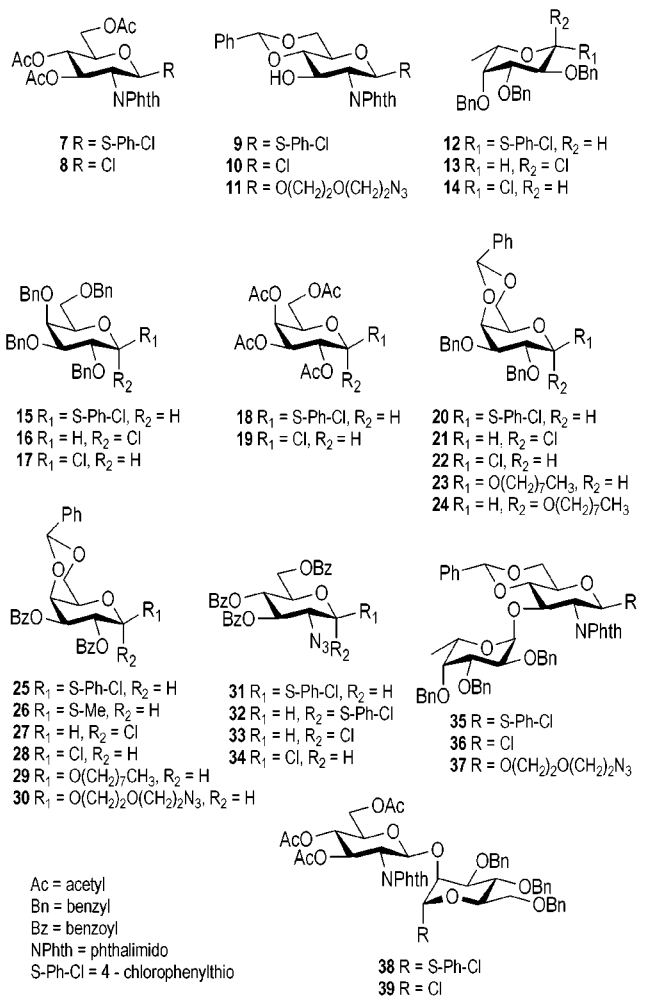

Figure 1.

With preformed salt **5**, thioglycosides **7** and **18** remained virtually unaffected while thioglycoside **15** gave only partial reaction, leaving substantial amounts of unreacted starting thioglycoside. On the other hand, all three thioglycosides, **7**, **15**, and **18**, were rapidly converted to their corresponding glycosyl chlorides using salt **6** with no evidence of starting materials remaining.[13] The rapid reaction with salt **6** indicated that the mechanism most likely involves the initial formation of **2**, which presumably occurs via chlorine transfer. Subsequent heterolysis of **2** leads to the kinetically controlled formation of **3**. The results also showed a clear difference in reactivity between salt **5** and **6** under the conditions described herein. Garcia et al. reported a similar observation in the direct glycosidation of 1-hydroxy glycosyl donors with sulfonium salts which were generated from phenyl sulfoxide/triflic anhydride and methyl sulfoxide/triflic anhydride.[14] It is known that the nucleophilicity of the sulfur atom of a thioglycoside is influenced by electronic effects from both the blocking groups of the sugar moieties ("armed-disarmed" concept)[15] and the alkyl/aryl substituents at the sulfur atom of the aglycon ("active-latent" concept).[16] Therefore, it was assumed that effective chlorine transfer and subsequent formation of glycosyl chlorides **3** might proceed if sulfonium salt **4** is less electronically favored than the glycosyl sulfonium salt **2**.

Our initial findings indicated that preformed **6** is an efficient chlorine transfer reagent; thus, the phenyl sulfoxide/oxalyl chloride combination was selected for further study. It was found that all of the thioglycosides shown in Figure 1 reacted readily with **6**, and the starting thioglycosides were totally consumed under these reaction conditions. The yields of glycosyl chlorides (Table 1) obtained were typically >90%.[17] Fortunately, ^{1}H NMR analysis of the crude products showed that the non-carbohydrate products in the mixture did not interfere with the assignment of the carbohydrate

Table 1. Formation of Glycosyl Chlorides from Thioglycosides

thioglycoside	glycosyl chloride	α:β ratio	δ (ppm) and *J* (for H-1) (in $CDCl_3$)
7	**8**	0:1	6.21 (*J* 10.3 Hz, β)
9	**10**	0:1	6.13 (*J* 10.0 Hz, β)
12	**13/14**	4.8:1	6.15 (*J* 3.4 Hz, α)
			5.14 (*J* 8.8 Hz, β)
15	**16/17**	3:2	6.15 (*J* 3.4 Hz, α)
			5.16 (*J* 8.3 Hz, β)
18	**19**	0:1	5.27 (*J* 8.8 Hz, β)
20	**21/22**	10:1	6.22 (*J* 3.9 Hz, α)
			5.20 (*J* 8.8 Hz, β)
25	**27/28**	9:1	6.65 (*J* 3.9 Hz, α)
			5.57 (*J* 8.8 Hz, β)
26	**27/28**	4:1	6.65 (*J* 3.9 Hz, α)
			5.57 (*J* 8.8 Hz, β)
31	**33/34**	6.7:1	6.28 (*J* 3.4 Hz, α)
			5.36 (*J* 8.9 Hz, β)
32	**34**	0:1	5.36 (*J* 8.9 Hz, β)
35	**36**	0:1	6.18 (*J* 9.3 Hz, β)
38	**39**	1:0	5.93 (*J* 1.5 Hz, α)

(12) Either the addition of the oxalyl chloride solution to a solution containing the sulfoxide or the reverse addition did not lead to any notable deleterious effects in the formation of reagents **5** or **6**.

ring proton signals.[18] The survival of the benzylidene ring in compounds **9**, **20**, **25**, **26**, and **35** indicated that the reaction conditions described herein are essentially neutral. Interestingly, α-thioglycoside **32** gave only β-chloride **34**, while β-thioglycoside **31** gave a mixture of α- and β-chlorides, indicating the importance of the anomeric configuration of the starting material. Kovac and Lerner[9f] previously reported differences in the outcome of glycosyl chloride formation during chlorine activation of 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-1-thio-α- and -β-D-glucopyranosides. They likewise observed that the α-thioglycoside gave only the β-chloride while the β-thioglycoside led to a mixture of chlorides and additionally demonstrated that no anomerization had occurred in either case. This concurs with our current findings.[19] Crich et al. noted that sulfoxidation of protected α-mannothioglycosides proceeds with high stereoselectivity[20] and proposed that the stereoselective outcome of sulfur oxidation is dependent upon the orientation of the two lone electron pairs on the sulfur atom. In the case of the α-thioglycoside, both steric and exo-anomeric effects may be responsible for the high stereoselectivity observed. For the corresponding β-thioglycosides, the two lone pairs are sterically less distinguishable, resulting in mixtures of sulfoxides. It is possible that similar factors, which are governed primarily by the anomeric configuration of the starting thioglycoside, lead to the formation of **2** having a preferred conformation. Such a conformation, along with the nature of the substituent at C-2, may in turn influence the anomeric outcome of subsequent glycosyl chloride formation.

The utility of the crude chlorides shown in Figure 1 as donors in typical Koenigs−Knorr type glycosidations[3,21] was demonstrated for select glycosyl acceptors to obtain glycosides **11** (82%), **23** (26%), **24** (56%), **29** (44%), **30** (85%), and **37** (82%). It was noted that the non-carbohydrate byproducts in the crude chlorides did not interfere with the glycosidation reactions. Isolation of chlorides **8** (92%) and **34** (87%) was achieved.

In summary, a mild method for the preparation of glycosyl chlorides from aryl/alkyl thioglycosides has been described. The protocol outlined herein avoids the handling of chlorine gas, and use of the S−Ph−Cl aglycon minimizes the unpleasant aspects of generating volatile sulfur-containing byproducts. The reaction sequence is readily amenable to scale-up. The procedure additionally allows for the convenient generation of a wide variety of glycosyl chloride donors in high yield and should find utility in oligosaccharide assembly.

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Supporting Information Available: Spectral data for compounds **7**−**39** and the experimental details for the glycosylation reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) In certain instances, the ^{1}H NMR spectrum revealed the presence of the hydrolysis product (<10%), presumably produced during the aqueous workup.

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