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Site-selective introduction of thiols in unprotected glycosides†

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Thioglycosides or S-linked-glycosides are important glycomimetics. These thioglycosides are often prepared by glycosylating deoxythio sugar acceptors, which are synthesized *via* elaborate protecting group manipulations. We discovered that a carbonyl group, formed by site-selective oxidation of unprotected saccharides, can be converted into a thiol moiety. The transformation involves S_N1-substitution of a chloro-azo intermediate, formed by oxidation of the corresponding trityl hydrazone, with a thiol. The prepared deoxythio sugars provide, in combination with the recently developed protecting group-free glycosylation of glycosyl fluorides, a protecting group-free synthesis of thioglycosides.

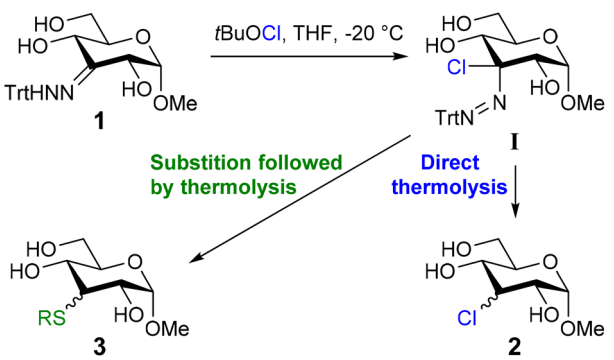
Introduction

Sulfur-substituted glycosides play an important role in carbohydrate chemistry and glycobiology. S-Linked-glycosides are more stable towards hydrolysis than their O-linked-glycoside counterparts, and have more conformational freedom, and sulfur therefore acts as a bioisostere in glycomimetics.[1,2] Enzymatic[3–5] or chemical[6–11] glycosylation of deoxythio sugar acceptors is commonly used to prepare *S*-glycosides. The acceptors used in the glycosylation reactions typically have a secondary thiol group either at the C2, C3 or C4 position, or a primary thiol at C6. The introduction of these thiol groups is mostly achieved *via* substitution of a triflate, tosylate, or iodide with thioacetate as the nucleophile. A different route uses a diazonium intermediate, prepared by oxidative deamination of amino sugars, and has been used specifically for *N*-acetylneuraminic acid derivatives.[12–14] The introduction of these leaving groups is designed in such a way that all-but-one hydroxy groups are protected.[15–24] This requires several protecting group manipulations, which are well-developed for monosaccharides but are challenging for larger carbohydrates.

The field of site-selective and late-stage modification of protection-group free mono- and oligosaccharides, however, is rapidly expanding and this should lead to alternative approaches.[25–29] Substitution reactions in unprotected carbohydrates are complicated, however, because of intramolecular competition of the hydroxy groups.[30] Another drawback is that the substitution reactions follow an S_N2-pathway and lead to inversion of configuration. Replacing a secondary hydroxy group in a glycoside with retention of configuration requires therefore either double inversion, or prior inversion of the stereochemistry of the hydroxy group.

Recently, we reported a method to combine palladium-catalyzed site-selective oxidation of carbohydrates[31–34] with subsequent trityl hydrazone formation, followed by conversion into the corresponding deoxychloro sugars (Scheme 1).[35] Subjecting trityl hydrazone **1** to *tert*-butyl hypochlorite (*t*BuOCl) leads to formation of a chloro-azo intermediate **I**. Upon thermolysis in the presence of a thiol as H-atom donor, chlorosugar **2** is formed and isolated as an epimeric mixture.

We noted that the use of ethanethiol occasionally led to the formation of the corresponding thioether **3a** as a side product. This unintentional thioether formation inspired us to study this side reaction for the formation of deoxythio glycosides. The possibility to capitalize on the well-developed site-selective



Scheme 1 Functionalization of carbohydrate-derived trityl hydrazones after treatment with *t*BuOCl *via* direct thermolysis with a sterically hindered H-atom donor to exclusively form deoxychloro sugar **2**, as reported previously, or *via* the here reported substitution-thermolysis sequence to form deoxythio sugar **3**.

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oxidation of glycopyranosides in a formal deoxy-thiolation reaction would allow site-selective introduction of a thiol group in an unprotected carbohydrate. This potentially alleviates the need to pre-install a stereochemically defined leaving group.

We report here a new method to introduce a thioether or thioacetyl group in unprotected glycosides (Scheme 1) and its application in the synthesis of thioglycosides.

Results and discussion

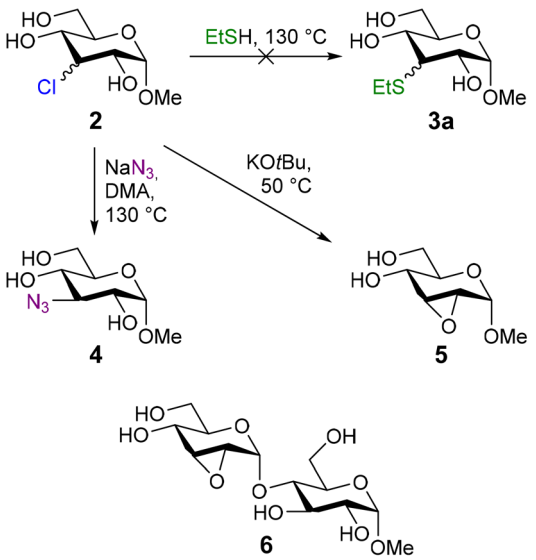
Initially, we hypothesized that during the dehydroxy-chlorination reaction of **1** with EtSH as H-atom donor, thioether **3a** was formed from 3-chloro-3-deoxy-glucoside **2**. In an attempt to reproduce this substitution reaction, we heated a solution of **2** and EtSH in dimethyl acetamide (DMA, Scheme 2).

No conversion of **2** was observed, however, even upon heating to 130 °C. In a second attempt, sodium ethanethiolate was used, but heating to 50 °C resulted in full conversion of **2** into a mixture of unidentifiable products. These results strongly indicated that thioether **3a** is formed *via* a different reaction pathway and not *via* S_N2 substitution of **2**.

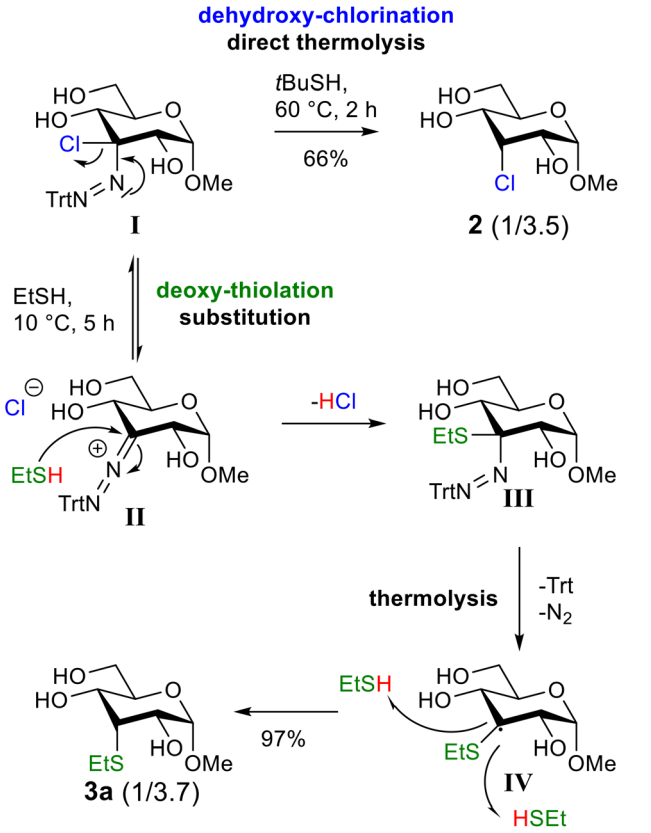
Although the introduction of a thiol moiety was not possible in this way, we were able to use the chloride as a leaving group in the synthesis of azide **4** (ESI†).[36] In accordance with earlier studies,[37] also the intramolecular substitution reaction of equatorial 3-chloro-deoxy-glycosides was feasible, even on disaccharides. Addition of *tert*-butoxide as a base afforded the corresponding 2,3-epoxides **5** and **6** cleanly.

Since the substitution reactions on **2** with thiols did not give the thioether products, we focused our attention on the thermolysis step (Scheme 3, ESI Table S2†). In the dehydroxy-chlorination reaction, we did not observe the thioether product when we used a sterically hindered hydrogen atom donor (*tert*-butyl thiol) and quickly raised the temperature to 60 °C after addition of the thiol (Table S2,† entry 1). However, the thioether was the major product, when thermolysis of the chloro-azo intermediate was performed with an excess of ethanethiol at 40 °C for two hours. Under these conditions, chloride **2** was isolated in only 19% and thioether **3a** was obtained in 74% (Table S2,† entry 2). Recent work by Creary shows that chloro-azo compounds generate resonance-stabilized carbocations that undergo S_N1 substitution reactions.[38,39] This stabilization is also the reason why chloro-azo compounds undergo rapid solvolysis compared to regular alkyl chlorides. Based on Creary's work, we reasoned that the yield of the thioether product could be increased by slowly raising the temperature after addition of the thiol. We were pleased to observe that by decreasing the temperature of the thermolysis step to 10 °C and prolonging the reaction time to five hours, thioether **3a** was indeed formed in a near quantitative yield (97%) (Scheme 1).

We hypothesize that at lower temperature, the thermolysis of chloro-azo intermediate **I** is sufficiently slowed down to allow the formation of cation **II**, which readily reacts with the thiol, present in excess, to form the thioether-azo compound



Scheme 2 Substitution reactions of 3-chloro-deoxy-glucoside **2** and the structure of epoxide **6**.



Scheme 3 Direct thermolysis of **I** with *t*BuSH during the dehydroxy-chlorination reaction and the proposed mechanism for the deoxy-thiolation reaction by performing the thermolysis at lower temperature. The ratio for **3a** is given as an equatorial/axial ratio.

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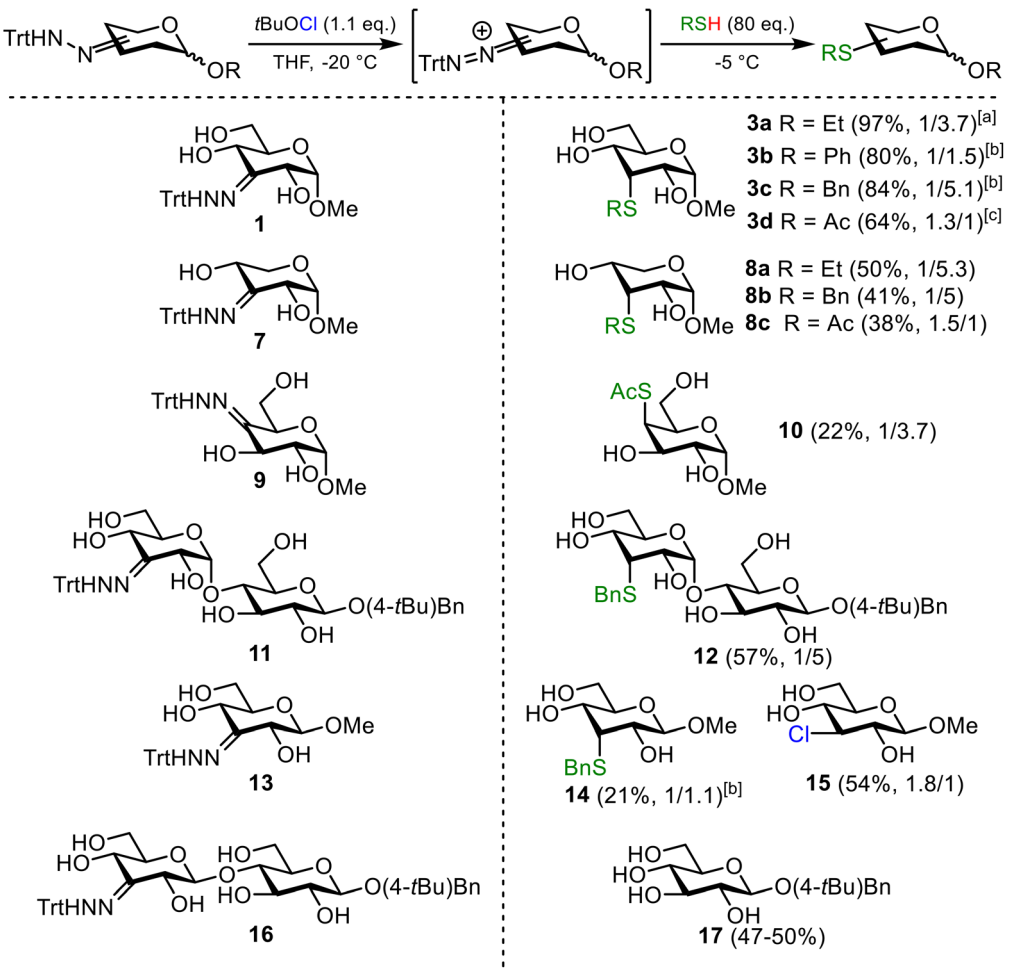
III (Scheme 3). At slightly elevated temperature, intermediate **III** undergoes subsequent thermolysis to produce thioether **3a**. Like in the dehydroxy-chlorination reaction,[35] the stereochemical outcome of this reaction is determined in the hydrogen atom-transfer step. The H-atom donor approaches the radical preferentially from the less hindered equatorial face of the substrate, which leads to an axial thioether substituent.

Selecting the appropriate hydrazone turned out to be crucial for this deoxy-thiolation reaction. Treatment of a readily prepared dinitrophenyl chloro-azo glucoside[35] with EtSH did not give any conversion, whereas the use of the unsubstituted phenyl hydrazone led to decomposition (ESI Scheme S3†). This shows that trityl hydrazones provide the right balance between stability and reactivity in this reaction.

This new deoxy-thiolation reaction nicely complements the scarce methods available in literature for this transformation. A recent and comprehensive overview by Li *et al.* describes the deoxygenative functionalization of aldehydes, ketones and carboxylic acids.[40] Reductive thioetherification (or "reductive sulfanylation") of ketones has been elaborated by Roth *et al.* and for benzylic compounds recently by Perrio *et al.*[41,42] Both methods apply a combination of a thiol and a Brønsted – (triflic acid, CF_3CO_2H) or Lewis acid (BF_3) with either Et_3SiH or BH_3 as a reducing agent. As expected, these reagents are not compatible with unprotected carbohydrates and our attempts to use these methods for the deoxy-thiolation of methyl 3-keto-glucose met with failure. Copper- or photochemical mediated oxidation of hydrazones to the corresponding diazo intermediate and subsequent carbene insertion into the S–H bond of a thiol has been reported, but is restricted to benzylic ketones.[43–45] Conversion of tosylhydrazones under thermal basic conditions in the presence of thiols, can also lead to thioether formation.[46] The group of König reported that tosylhydrazones can be used in an umpolung difunctionalisation reaction with photoredox catalysis.[47,48] Although focusing on aromatic aldehydes as starting materials, also cyclic ketones were successfully explored and we expect that this approach can be adapted for the synthesis of thioethers. Currently, the chlorination of trityl hydrazone followed *in situ* by nucleophilic substitution of the chloride and subsequent thermolysis, is the only viable method for deoxy-thiolation in carbohydrates and therefore we continued by exploring its scope.



Scheme 4 Synthesis of deoxythio sugars. The major products are drawn. In brackets the isolated yields and the equatorial/axial ratio. Reactions with monosaccharides were performed on 0.4 mmol scale, with disaccharides on 0.25 mmol scale. [a] Raised to 10 °C; [b] raised to 15 °C; [c] Raised to 5 °C.

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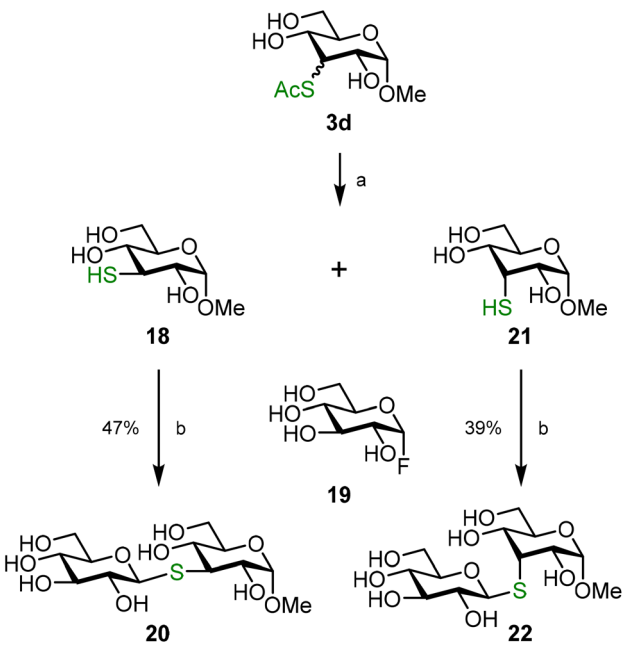
With the optimized conditions for the deoxy-thiolation reaction in hand, we first investigated the introduction of different thiol moieties at the C3 position of glucose. Performing the reaction with thiophenol (PhSH) and benzyl thiol (BnSH) gave the corresponding thioethers **3b** and **3c** in high yields (Scheme 4), again favoring the products with an axial thio-substituent. The excess of PhSH and BnSH was readily removed by extraction which eased column purification. Pleasingly, substitution with thioacetic acid (AcSH) gave **3d** as an epimeric mixture, with a slight preference for the equatorial thioacetate product. This tendency of thioacetic acid to provide the equatorial substituted product had already been observed in the dehydroxy-chlorination reaction.[35] The stereochemical outcome of the reaction is determined during the H-atom transfer step. As is in the dehydroxy-chlorination reaction, sterically hindered H-atom donors gave primarily the axial products, while small H-atom donors, such as thioacetic acid gave a slight preference for the equatorial product. Although the level of stereoselectivity is currently suboptimal, the result is important as it means that the C3 hydroxy group in glucose can be substituted for a C3 thiol group with overall retention of configuration. The acetyl group is readily removed by hydrolysis, liberating the thiol for use as a nucleophile in further glycosylation reactions, *vide infra*. This reaction was scaled to 6.0 mmol, which gave **3d** in 58% yield. The yield was somewhat lower than expected, which is attributed to competing acetyl migration.[23,49] The substitution reaction was also attempted with ten equivalents of 2,3,4,6-tetra-*O*-acetyl-β-thioglucose. Unfortunately, exclusively chloride **2** was isolated, indicating that the substitution with a sterically hindered thiol under the used reaction conditions is unsuccessful. Increasing the equivalents of the nucleophile to 80 was not considered for practical reasons.

Subsequently, the carbohydrate scope was expanded (Scheme 4). Xylose derivative **7** was equipped with several thio-substituents in moderate yields (**8a–c**). Installing a thio-substituent at the C4 position turned out to be challenging due to side product formation and the desired thioether product **10** was isolated in 22% yield. The synthesis of C3′-thio-substituted maltose **12** in 57% yield shows the versatility of this novel strategy which is not limited to monosaccharides. The axial and equatorial epimer were separated by column chromatography.

In cases in which carbocation formation is slow or does not occur, the chlorosugar instead of the thiosugar is obtained. The trityl hydrazone of *N*-acetyl glucosamine for example, solely provided the chlorosugar. We hypothesize that the electron withdrawing effect of the acetamido group prevents carbocation formation. To substantiate our hypothesis, acetylated glucose **1** was subjected to the deoxy-thiolation conditions with EtSH. Also here, the thioether was not formed and only the corresponding chlorosugar was obtained (ESI Scheme S5†).

β-Glycosides give mixed results in the reaction. Performing the deoxy-thiolation reaction on methyl-β-glucoside **13** gave the expected benzyl thiol **14** in 21% yield, together with 54% of the corresponding chloride **15** and a small amount of a ring-contracted side product.[50,51] With cellobiose **16** as substrate, only the deglycosylated product **17** was isolated. Based on recent work by Hansen *et al.*,[52] we hypothesize that in alpha-glycosides a driving force for carbocation formation is the release of steric strain upon departure of chloride. The destabilization by the 1,3-diaxial interaction between the axial azobenzene substituent and the anomeric position is less pronounced in beta-glycosides and therefore, we reason that these substrates are less reactive.

An important application of unprotected thiosugars resides in protection-group free glycosylation reactions.[25] Whereas, the group of Pedersen used *in situ* generated thiosugars for the synthesis of thiotrehalose,[53] Withers and co-workers reported in the early 2000s the chemoenzymatic synthesis of thioglycosides from deoxythio sugars and glycosyl fluoride donors.[3–5] The recent advances in development of methods to chemically activate the anomeric position in unprotected donors led to a steep growth in the development of protection-group free glycosylation reactions.[54–59] In particular, the finding by Schepartz and Miller that unprotected glycosyl fluoride donors can be activated with calcium hydroxide and selectively coupled to sucrose acceptors[60] or phenolic acceptors[61] paved the path for the synthesis of S-linked glycosides. Both Tang *et al.* and Zhang *et al.* independently showed that the same activation conditions can be used for the synthesis of S-linked disaccharides and oligosaccharides.[7,62] We here illustrate the versatility of the combination of, now readily available, deoxythio sugars and glucosyl fluorides by preparing disaccharides from thiosugars **18** and **21**. To separate the epimeric mixture obtained from the deoxy-thiolation reaction, **3d** was per-acetyl-



Scheme 5 Synthesis of disaccharides **20** and **22**. Reagents and conditions: (a) i. Ac_2O, pyridine, 1.5 h, 98%; ii. NaOMe, MeOH, 1 h, **18**: 83%, **21**: 70%; (b) $Ca(OH)_2$, H_2O, 5 h.

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ated. Column chromatography gave pure fractions of the axial and the equatorial isomer, together with a mixed fraction due to the minor difference in R_f value. Thiosugars **18** and **21** were obtained by full deacetylation of the pure fractions and these thiosugars were then coupled to donor **19**, which gave *S*-glycosides **20** and **22** (Scheme 5). Interestingly, we found that the products could be isolated without derivatization, making protecting groups in these reactions obsolete.

Conclusions

The discovery of a new deoxy-thiolation reaction allows the protecting group-free synthesis of deoxythio sugars. In combination with the site-selective oxidation of unprotected carbohydrates, which can be carried out in several ways, this satisfies an unmet need. Trityl-hydrazones, prepared from the corresponding keto-saccharides, provide chloro-azo intermediates upon treatment with *t*BuOCl. By selecting the appropriated thermolysis conditions, these chloro-azo intermediates can be converted either into chlorides, as shown previously, or into thioethers and thioacetates. The use of thioacetate as nucleophile gives mainly the product with overall retention of configuration. This versatile deoxy-thiolation reaction provides an efficient entry to the synthesis of thioglycosides with minimal use of protecting groups.

The chlorosugars allow the introduction of an azide *via* S_N2 substitution and in addition allow the introduction of an epoxide. This is versatile in particular for disaccharides as it avoids elaborate protecting group strategies. The current protocol is effective in particular for alpha-glucosides, and current studies aim to control the formation of the intermediate resonance-stabilized carbocation. In our opinion this is the key to expand the scope of this reaction further.

Author contributions

N. R. M. R. performed the experiments and analysed the data. M. D. W., A. J. M. conceived and directed the project. N. R. M. R., M. D. W., and A. J. M. prepared the manuscript. All authors discussed the experimental results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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