Site-Selective Dehydroxy-Chlorination of Secondary Alcohols in Unprotected Glycosides

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ABSTRACT: To circumvent protecting groups, the site-selective modification of unprotected glycosides is intensively studied. We show that site-selective oxidation, followed by treatment of the corresponding trityl hydrazone with tert-butyl hypochlorite and a H atom donor provides an effective way to introduce a chloride substituent in a variety of mono- and disaccharides. The stereoselectivity can be steered, and a new geminal dichlorination reaction is described as well. This strategy challenges existing methods that lead to overchlorination.

Site-selective modification of carbohydrates is challenging because of the presence of several or multiple hydroxyl groups with similar reactivity. Nonetheless, prior research has shown that it is possible to perform site-selective transformations such as esterification, sulfonylation, silylation, arylation, and alkylation on partially protected, or even unprotected, carbohydrates. The substitution of a secondary hydroxy group with a halogen in an unprotected carbohydrate is difficult, but it is used in the development of enzyme inhibitors and to prepare starting materials for further substitution and deoxygenation reactions. This transformation is currently achieved by reacting unprotected carbohydrates with sulfilimine or a combination of mesylic chloride and DMF, but this leads to simultaneous chlorination of the primary hydroxy group, producing 3,6-dichlorinated products. The combination of triphenylphosphine and tetrachloromethane has also been used, but also here the primary hydroxy group is converted into the chloride. Ring-opening of epoxides have been explored; however, their synthesis requires the use of protecting groups, and Payne rearrangement can result in mixtures of epoxides. Therefore, all-but-one protection of the hydroxy groups, followed by conversion of the remaining hydroxy group into a good leaving group and nucleophilic substitution, is the common path. This, however, becomes especially problematic when a halogen has to be introduced into a disaccharide or oligosaccharide. Furthermore, the removal of protecting groups has to be compatible with the halogen, which means that hydrogenolysis, for example, is hardly an option.

One approach that allows straightforward modification of unprotected glycosides is site-selective oxidation. Our group and the group of Waymouth have shown that the C3 position in pyranosides can be selectively oxidized with catalytic [(neocuproine)PdOAc]OTf. This method has successfully been applied to 1,4-linked glucans to introduce the keto functionality on the terminal residue. The keto group can serve as a handle for further modifications, for example in indium mediated allylations or to introduce epoxides. Moreover, it can be used to form oximes and hydrazones, which can be reduced to the corresponding amine to obtain aminoglycosides. However, it appeared challenging to convert the keto group into a chloride without involving a hydroxy group as an intermediate, which obviously would nullify the site selectivity.

In our search for such a strategy, we realized that hydrazones, readily available from ketones, can react both as electrophiles and nucleophiles, and can be used to functionalize unprotected carbohydrates. Baldwin et al. demonstrated that lithiated trityl hydrazones act as 1,2-diazaallyl anions and add to aldehydes. The resulting unstable aza-intermediate decomposes at room temperature in a carbon-centered radical that undergoes hydrogen atom transfer in the presence of a thiol. In 2016, Reyes and Rawal extended this work using tert-butyl hypochlorite (tBuOCl) as an effective electrophile. This leads overall to a rare “dehydroxy-chlorination” procedure.

With the regioselective oxidation and subsequent hydrazone formation in place, we realized that this strategy could meet the challenge to selectively introduce a chloride substituent in glycosides as this procedure does not have a hydroxy group as an intermediate.

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To investigate this strategy, previously reported keto-GlcNAc \(1a\) and keto-glucoside \(1b\)\(^{34,35}\) were converted into the corresponding \(E/Z\) trityl hydrazones \(2a\) and \(2b\) (Figure 2). Subsequently, GlcNAc derivative \(2a\) was studied first in the dehydroxy-chlorination reaction and was reacted with freshly prepared \(t\)BuOCl at \(-20^\circ\)C. The formed unstable azo-intermediate \(2a'\) was subjected to thermolysis using the conditions reported by Reyes and Rawal\(^{33}\) (40 \(^\circ\)C, 80 equiv of ethanethiol (EtSH)), which afforded \(3a\) in an excellent 80% yield (Figure 2A). This showed our hypothesis to be correct. NMR analysis established the structure of \(3a\) as a mixture of epimers (eq/ax: 1.4/1) with a slight preference for the equatorial chloride. The configuration of \(3a\)-ax was confirmed by its X-ray structure.

Excited about this result, we applied the same reaction conditions to glucoside \(2b\), which, to our surprise gave only 19% of the expected epimeric mixture of 3-chloro glycoside \(3b\). Instead, thioether \(4\) was isolated as the major product (74%) (Figure 2B). To circumvent thioether formation, we attempted the thermolysis reaction in the presence of triethylsilane, diethyl phosphite, methanol, 2-propanol, or acetic acid (Figure 2C). Four of these gave the desired chloride in low yield, but with good to excellent selectivity for the equatorial product. Dissatisfied by the yield, we attempted to avoid thioether formation by increasing the steric bulk of the thiol (Figure 2D). The yield of desired chloride \(3b\) increased to 41% when thermolysis was performed with 2-propanethiol (\(iPrSH\)) (entry 6). However, considerable amounts of thioether product were still isolated from the reaction mixture. The use of tert-butyl thiol (\(tBuSH\)) (entry 7) as the H atom donor completely circumvented thioether formation. Increasing the steric bulk of the thiol also had an effect on the stereocchemical outcome of the reaction. The product ratio shifted slightly in favor of the axial chloride (eq/ax: 1/1.4 (EtSH), 1/1.7 (\(iPrSH\)), 1/2.2 (\(tBuSH\))). Thermolysis with thiaoic acid (AcSH) was also tried. However, this gave a minimal amount of \(3b\) and, as expected, formation of the thioacetyl product (entry 8).

We also investigated the influence of the effect of the temperature on the thermolysis and found that a temperature of 60 \(^\circ\)C led to a considerably higher isolated yield (66%) and to a higher selectivity for the axial chloride (from 1/2.2 to 1/3.5; entries 7 and 9).

With these results in hand, we studied the substrate scope of the reaction (Figure 3). We prepared keto-sugars \(1c\)–\(1f\) via \([(\text{neocuproine})\text{PdOAc}]\)\(_2\)OTf oxidation, with the exception of the 4-keto sugar \(1c\) which was prepared with Oc\(_2\)SnCl\(_2\) and Br\(_2\)\(^{35,36}\). The keto-sugars were converted into the corresponding trityl hydrazones \(2c\)–\(2f\) and reacted with \(t\)BuOCl. Thermolysis with the optimized conditions gave chlorides \(3c\)–\(3f\) after column purification in good yields (65–74%). The major product invariably had the chloride substituent in the...
axial position, and in a number of cases the epimers could be separated by column chromatography. The isolated yields may be increased by omitting the column purification step, as was exemplified for 3-deoxy-3-chloro glycoside $3b$. On the 1 mmol scale, the tBuSH and trityl residues were readily removed by extraction, giving the desired pure $3b$ in an excellent 92% isolated yield. Especially the synthesis of disaccharides $3e$ and $3f$ in high yields shows the strength of this selective dehydroxy-chlorination approach, compared to the known chlorination methods in the literature.

Although tBuSH gave the desired chloro-glycosides in good yields, a major disadvantage is its obnoxious smell. Therefore, we performed the reaction with $2b$ using adamantantethiol and tert-nonyl mercaptan (tert-nonylSH) instead of tBuSH. These H atom donors gave chloro-glycoside $3b$ in 72% and 58% yield with again a higher selectivity for the axial chloride (entries 1 and 2, Table S1) and could be used as less odorous alternatives for tBuSH.

As an alternative approach, we performed thermolysis with lower amounts of thiol. Because lowering the thiol concentration might suppress the formation of substitution products, we also used AcSH and EtSH. When we subjected the in situ formed azo-intermediate of $2b$ to 4 equiv of thiol (entries 3–5, Table S1), the desired product $3b$ was isolated in moderate to good yield, without noticeable amounts of substitution products. Interestingly, the chloride substitution product $3b$ was obtained in 67% yield with an equatorial/axial ratio of 1/1.1 on a 2.5 mmol scale with AcSH as the H atom donor. This shows that when the equatorial chloride is desired, 4 equiv of AcSH can be used instead of tBuSH (e.g., the eq/ax ratio shifts from 1/3.5 to 1/1.1).

Finally, we investigated whether the reaction with $2b$ could be performed in MeOH (entries 6 and 7, Table S1), because minimally protected oligosaccharides have limited solubility in THF. Chloride $3b$ was not formed, but surprisingly, $\alpha,\alpha$-dichloro compound $5$ was isolated in 22% yield (Figure 4).

The yield of $5$ increased to 34% when 2.2 equiv of tBuOCl was used. Although the yield is not yet up to standards, this finding, which is currently under study, provides potentially an efficient entry into this motif in carbohydrate chemistry. gen-Dihalo glycosides are rare but are used in nucleoside chemistry as viral reverse transcriptase inhibitors.37

We demonstrated already in earlier work that nucleophilic attack on the keto group in 3-ketoglucoside $2b$ takes place preferentially from the top face.26 Similarly, epoxidation of the corresponding exocyclic alkylidene with dimethyldioxirane takes place from the top face.38,39 In both cases, attack via the bottom face is less favorable because of a 1,3-diaxial interaction with the methoxy substituent on the anomeric center. We hypothesized that the stereoselectivity of both steps in the dehydroxy-chlorination reaction, and so chloride introduction and hydrogen atom-transfer, is also determined by 1,3-diaxial interactions and that the second step will...
determine the final stereochemical outcome (vide infra). To underpin this hypothesis, the 2,4-dinitrophenyl hydrazones of methyl α- and β-glucosides 6a and 6b were prepared. Treatment of these hydrazones with tBuOCl gave stable azo-intermediates (Figure 5A/B). NMR analysis revealed that 6a cleanly converted into a single azo-product 7a, whereas β-glucoside 6b gave a mixture of the two epimeric products, 7b. This result confirmed that 1,3-diaxial interactions indeed determine the stereochemical outcome of the reaction with tBuOCl. On the basis of these results, we argue that treatment of the trityl hydrazone of tert-BuOCl. On the basis of these results, we argue that treatment of the trityl hydrazone of tert-BuOCl will also predominantly form a single azo-intermediate (vide infra). The H atom donor affects the stereochemical outcome of the reaction (Figure 5C). Chloride 3g was isolated in 84% yield with a lower stereoselectivity (1/1.7) compared to the reaction with α-glucose 2b 1/3.9 (entry 2, Table S1), further confirming that the anomeric configuration influences the stereochemical outcome.

In conclusion, we have developed a novel approach for the site-selective dehydroxy-chlorination of glycosides. Our methodology involves site-selective oxidation, followed by conversion of the ketone to the corresponding trityl hydrazone. Chlorination of this trityl hydrazone with tBuOCl and subsequent thermolysis of the intermediate with a suitable H atom donor give the desired chloro-sugars as mixtures of the equatorial and the axial chloride. The choice of H atom donor is crucial to obtain a high yield in the chlorination reaction and steers the stereoselectivity. A bulky thiol such as tert-butyl thiol and tert-nonyl mercaptan leads to a preference for the axial chloride substituent, whereas the use of 4 equiv of AcSH provides a near one to one mixture of epimers. The dehydroxy-chlorination of the disaccharides cellobiose and maltose, in high yield, shows that this method can be extended beyond monosaccharides for the selective introduction of a chloride in glycosides, which is a considerable advantage over existing methods. Apart from the (known) utility of chlorosugars per se, we are currently studying the reactivity of the chloro substituent, in particular in nucleophilic substitution reactions. The serendipitously observed geminal dichlorination of substrate 2b will elicit further study on this reaction as well.

**Figure 5.** (A/B) Synthesis of the azo-intermediates 7a and 7b. The yield of 7b could not be determined because it could not be isolated from 6b. (C) Proposed mechanism for the dehydroxy-chlorination reaction. (D) Synthesis of 3g. The eq/ax ratio was determined by NMR analysis.

Accession Codes

CCDC 2150508, 2150537, and 2150551 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data_request/cif](https://www.ccdc.cam.ac.uk/data_request/cif) or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at [https://pubs.acs.org/doi/10.1021/acs.oglett.2c01992](https://pubs.acs.org/doi/10.1021/acs.oglett.2c01992).

Detailed experimental procedures, synthesis diagrams, X-ray structures of compounds 1d, 2d, 3a, and 3b, and copies of NMR and HRMS spectra (PDF)

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Notes
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