Tetrahedron Letters 54 (2013) 5348–5350

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of glycosyl disulfides containing an α-glycosidic linkage

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ARTICLE INFO

Article history:
Received 10 June 2013
Revised 10 July 2013
Accepted 19 July 2013
Available online 29 July 2013

Keywords:
Glycosyl disulfide
Glycosyl thiol
DDQ
Synthesis

ABSTRACT

A wide range of symmetrical and unsymmetrical glycosyl disulfides is synthesized with focus on the use of α-glycosyl thiols. Oxidation of α-glycosyl thiols with iodine leads to symmetrical α,α-glycosyl disulfides, while unsymmetrical disulfides are readily synthesized from α- and β-glycosyl thiols under the action of DDQ. Thus, glycosyl disulfides containing at least one α-glycosidic linkage are made available.

Thioglycosides have been the subject of significant interest in the glycomimetic field due to their high stability and excellent similarity to native glycosides.[1] In comparison, glycosyl disulfides have not been investigated thoroughly and there are only a few reports on their chemical and biological applications. However, as glycomimetics, glycosyl disulfides sometimes display better binding interactions with protein receptors because of the increased conformational flexibility of the resulting molecules. For example, glycosyl disulfides exhibit potent inhibitory effects against the common plant lectin, concanavalin A, while the corresponding thiosugars showed no significant binding.[2] Conceivably, the three-bond interglycosidic linkage (–S–S–) could adjust the molecular shape to the active conformation in a more flexible manner, thereby influencing the biological activity. Glycosyl disulfides have been shown to act as biologically active ligands in human tumor cell lines.[3] Also, unsymmetrical disulfides have been employed as reductively activated prodrugs to improve the pharmacokinetic properties of the anticancer drug, paclitaxel.[4] In addition to biological applications, glycosyl disulfides have also been demonstrated to be efficient glycosyl donors for the synthesis of O-glycosides.[5]

A number of procedures are available in the literature for the synthesis of glycosyl disulfides. In general, symmetrical glycosyl disulfides are readily prepared by oxidation of the corresponding glycosyl thiols or thiol precursors. For example, galactosyl thiol was converted into a disulfide in very high yield by treatment with I_2.[6] GlcNAc thiol was oxidized by *m*CPBA to provide the corresponding disulfide in high yield.[7] The synthesis of unsymmetrical disulfides was less straightforward and often required activation of one of the sulfhydryl groups prior to the coupling reaction. Szilágyi and co-workers employed glycosylthio-phthalimides and -succinimides as glycosylsulfenyl donors to couple with various thiols to make mixed disulfides.[8] Another similar procedure involved in situ generation of glycosylsulfenyl benzotriazole intermediates which were then exposed to the second thiol to produce unsymmetrical disulfides.[9] The reactions were carried out in one-pot fashion at low temperature furnishing the mixed disulfides in high to excellent yields. Aversa et al. have reported a mild procedure for the synthesis of unsymmetrical disulfides,[10] in which a range of sulfenic acids was prepared in situ as the activated thiols. Prior to the above work, methanethiosulfonate was also introduced to an anomeric thiol and acted as an effective leaving group in the presence of another glycosyl thiol giving rise to mixed disulfides in good yields.[11] It should be noted here that glycomethanethiosulfonates were used earlier as glycosylating agents to construct S–S-linked glycoproteins.[12] Mixed glycosyl disulfides were also synthesized directly from two different thiols under the action of diethyl azodicarboxylate, in a one-pot fashion, in very good yields.[13] Despite the above progress on the synthesis of glycosyl disulfides, careful inspection reveals that normal α-glycosyl thiols, such as α-glucosyl thiol and α-galactosyl thiol, have not been used for the synthesis of disulfides (these thiols are thought to be less reactive due to stereoelectronic effects). Also, the synthesis of glycosyl disulfides through direct coupling of two thiols is rare in the literature. Therefore, we decided to explore the synthesis of glycosyl disulfides with a view to increase product variety by using α-glycosyl thiols and expand the arsenal of direct coupling methods.

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0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.07.093

Different glycosyl thiols were first prepared in order to carry out the synthesis of glycosyl disulfides. α-Glycosyl thiols **1** and **2** were synthesized from the corresponding benzylated 1,6-anhydrosugars following a stereospecific procedure developed in our laboratory,[14] and isolated exclusively as α-anomers from the reaction mixture. Thiol **1** was also converted into the acetylated 1-thiosugar **3**[15] in three steps, that is, Birch reduction, acetylation, and selective anomeric deacetylation. β-Glycosyl thiols **4**–**6** and α-mannosyl thiol **7** were readily prepared by standard literature procedures via reaction of the corresponding fully acetylated glycosyl bromide with thiourea and subsequent hydrolysis of the resulting thiouronium salt with an alkali metal disulfide.[16]

With the glycosyl thiols in hand, their transformation into disulfides was investigated, that is, the development of appropriate conditions to form both symmetrical and unsymmetrical glycosyl disulfides.

As no previous examples of α,α-linked glycosyl disulfides exist in the literature, our first goal was to synthesize symmetrical α,α-disulfides with thiols **1**–**3** as the starting materials. Hence, **1** was treated with I_2 in the presence of pyridine under standard conditions.[17] As expected, the reaction took place smoothly and gave rise to α,α-disulfide **8** in 70% yield (Scheme 1). Similarly, oxidation of thiol **2** with I_2 under the same conditions led to the desired α,α-disulfide **9** in very good yield (77%). The acetyl-protected thiol **3** was also oxidized effectively with I_2 to produce disulfide **10** in 88% yield.

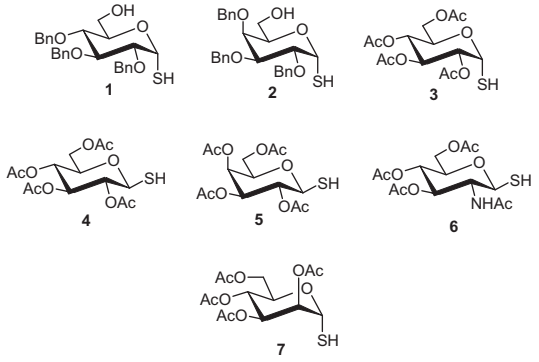
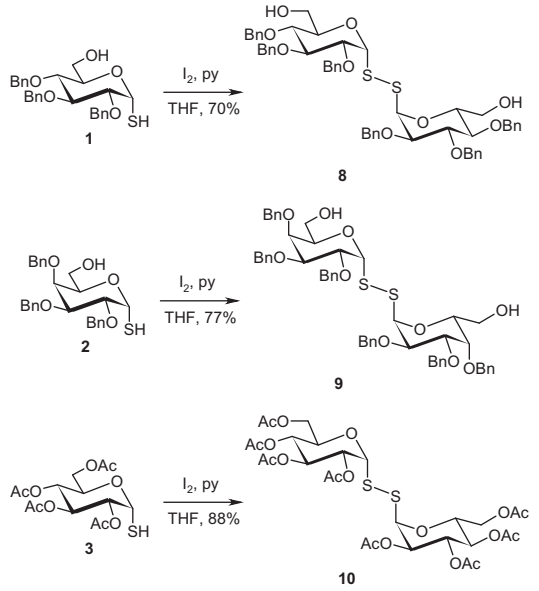


Figure 1. Prepared glycosyl thiols **1**–**7**.

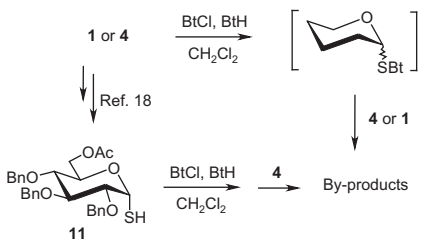


Scheme 1. Synthesis of symmetrical disulfides **7** and **8**.

Next, we turned our attention to the investigation of the synthesis of unsymmetrical disulfides with α-glycosyl thiols as building blocks. As mentioned above, in the literature, mixed disulfides have been readily prepared from glycosyl thiols via glycosylsulfenyl benzotriazole intermediates.[9] Following this procedure, activation of thiol **1** with BtCl/BtH was conducted to generate in situ the SBt intermediate, which was then treated with a solution of thiol **4**[16b] in CH_2Cl_2, but unfortunately, no α,β-linked disulfide was produced (Scheme 2). The reversed operation, that is, activation of thiol **4** under the same conditions followed by the addition of thiol **1**, did not furnish the desired product either. We speculated that the free 6-OH group of thiol **1** might interfere with the reaction, hence, **1** was converted into thiosugar **11**[18] as reported previously, and then treated with **4**, but again the reaction was found to be unsuccessful. The products obtained in these reactions appeared to be composed of β-thiosugars only, indicating that dimerization of **4** predominated under the current conditions due, presumably, to the higher nucleophilicity of β-glycosyl thiol. In comparison with α-thiols, β-thiols exhibit greater lone pair repulsion between the anomeric sulfur and endocyclic oxygen, and such interactions can cause the energy of the lone pair of the sulfur to be increased and the lone pair thus becomes a better nucleophile.[19] In comparison, the orientation of these lone pairs relative to each other in α-anomers is such that any repulsion is minimized, resulting in them being poorer nucleophiles.

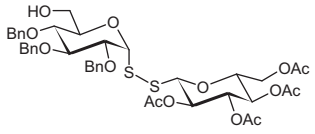
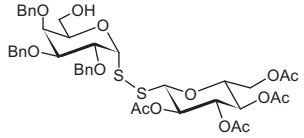
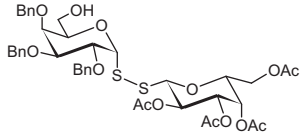
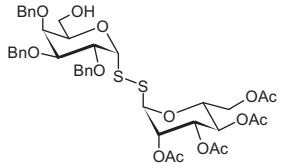
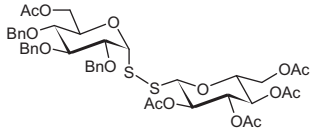
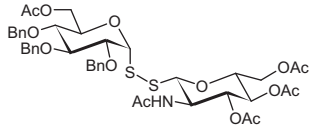
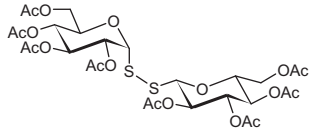
The setback with the Bt procedure led us to seek an alternative method. Wang and co-workers have developed a new method for the synthesis of unsymmetrical disulfides from simple aliphatic and aromatic thiols using DDQ as the oxidant.[20] This method is particularly interesting due to its apparent selectivity for the exclusive formation of unsymmetrical disulfides in spite of two different thiols being present in the reaction mixture in equimolar ratio before addition of DDQ. We anticipated that this method might also be applicable to the synthesis of mixed glycosyl disulfides. As a test reaction, thiols **1** and **4** were first mixed together and then treated with DDQ following Wang's procedure.[20] As expected, the desired disulfide **12** was produced smoothly as indicated by TLC and was isolated in 67% yield (Table 1, entry 1). Subsequently, a mixture of thiols **2** and **4** was subjected to the same conditions, and the unsymmetrical α,β-linked disulfide **13** was produced in good yield (60%). Suitable crystals of **13** were obtained for X-ray analysis by slow crystallization from dichloromethane and cyclohexane at room temperature. The crystallographic data clearly show that a disulfide linkage had formed (Fig. 1). To further exploit the DDQ procedure for the synthesis of mixed glycosyl disulfides, reactions of **2** with thiols **5**[16a] and **7**[16a] were also carried out in the presence of DDQ. They proceeded satisfactorily and the desired disulfides **14** and **15** were isolated from the reaction mixtures in 62% and 64% yields, respectively.

It should be mentioned here that the above reaction yields are generally good but not excellent due to the formation of small amounts of symmetrical β,β-disulfides, however, these are in line with similar results obtained by Wang for secondary thiol starting



Scheme 2. Attempted synthesis of a disulfide following Hunter's procedure.[9]

Table 1
Synthesis of unsymmetrical glycosyl disulfides

Entry	Glycosyl thiols	Product	Yield (%)
1	**1** + **4**	 **12**	67
2	**2** + **4**	 **13**	60
3	**2** + **5**	 **14**	62
4	**2** + **7**	 **15**	64
5	**11** + **4**	 **16**	78
6	**11** + **6**	 **17**	62
7	**3** + **4**	 **18**	32

materials. The homo-coupling of β-glycosyl thiols took place relatively easily in all the reactions and were difficult to suppress under the current conditions as a result of the higher nucleophilicity of β-thiols. In spite of this, the DDQ procedure is still very effective for the synthesis of glycosyl disulfides containing an α-glycosidic linkage. To further demonstrate the effectiveness of this method, we also investigated the use of the fully protected thiol **11** as an α-thiosugar building block. As expected, coupling of α-thiol **11** with β-thiol **4,** under the same conditions as above proceeded smoothly to give α-linked disulfide **16** in a very good yield (78%). Similarly, when **11** was exposed to β-GlcNAc thiol **6**[21] in the presence of DDQ, the desired mixed disulfide **17** was produced readily in 62% yield. At this point, we speculated that fully acetylated α-thiosugars might not be suitable for this coupling as the electron-withdrawing acetyl groups would further reduce the reactivity of the anomeric sulfhydryl group, which would render the homo-coupling of β-thiosugars more prominent. Indeed, when α-thiol **3** was mixed with β-thiol **4** and treated with DDQ, the α,β-linked disulfide **18** was isolated in only 32% yield (entry 7) with concomitant formation of the symmetrical β,β-disulfide as the major product.

In summary, a series of symmetrical and unsymmetrical glycosyl disulfides containing normal α-linkages has been synthesized directly from the corresponding glycosyl thiols by oxidation with either I_2 or DDQ. All the disulfides were produced in generally good yields, which dispelled our initial concerns regarding the relatively low reactivity of α-glycosyl thiols. In particular, the DDQ-mediated formation of unsymmetrical disulfides is very intriguing, and a mechanistic study is in progress.

Acknowledgments

This work was supported by the University College Dublin and the Natural Science Foundation of Zhejiang Province (R4110195). R.S. is grateful for a demonstratorship from the UCD School of Chemistry and Chemical Biology.

Supplementary data

Supplementary data (experimental procedure, characterization data and X-ray crystallographic data of compound **13**, as well as copies of the ^{1}H and ^{13}C NMR of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.093.

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