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A high-yielding, one-pot preparation of unsymmetrical glycosyl disulfides using 1-chlorobenzotriazole as an in situ trapping/oxidizing agent

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ABSTRACT

A high-yielding, one-pot methodology for preparing unsymmetrical glycosyl disulfides derived from sugar, alkyl/aryl or cysteine thiols is reported using 1-chlorobenzotriazole (BtCl) as the oxidant. The highlight of the method is the low temperature of coupling (−78 °C) as well as the in situ trapping of the sulfenyl intermediate, which ensures that no homodimer of R^1SH (R^1SSR^1) is formed. The coupling efficiency is independent of sugar type, thiol position in the sugar, sugar-protecting groups, and the various products serve to illustrate the rapid synthetic access to a number of model systems in glycobiology.

The unsymmetrical disulfide functionality R^1SSR^2 plays a broad range of roles in Nature. For instance, it has long been known that *S*-allylmercaptocysteine and allicin, which are both present in freshly crushed garlic are responsible for the anti-infective properties of this vegetable.[1] Similarly, simple aryl–alkyl disulfides were recently shown to inhibit the growth of methicillin-resistant *S. aureus* and *B. anthracis* in vitro.[2] Use of the disulfide motif to connect a glycosyl unit to an alkyl or aryl chain[3] or to a different sugar has been shown to afford a novel class of disaccharide mimic,[4] while some neoglycoproteins represent further examples of interesting hybrid structures in which glycosyl units are attached to proteins through S–S linkages.[5] Mixed alkyl–glycosyl disulfides have been proposed as glycosyl donors in oligosaccharide synthesis,[6a,b] while phosphine-mediated mono-desulfurization of the disulfide linkage has been shown to produce thioglycosides.[7a–c] Diglycosyl disulfides have been shown to act as biologically active ligands in human tumor cell lines,[8] while specific binding of oligovalent aromatic mannosyl disulfide derivatives to the lectin, concanavalin A has also been recently reported.[9]

With regard to synthesis, a range of methods is available for disulfides containing at least one sugar unit. Thus, symmetrical diglycosyl disulfides can be readily obtained by oxidation of glycosyl thiols[10] or thiol equivalents such as glycosyldithiocarbamates,[11] or via reaction of benzyltriethylammonium tetrathiomolybdate with glycosyl halides.[12] Disulfides containing only one sugar unit such as glycosyl–alkyl/aryl disulfides can be prepared from glycosylsulfenyl halogenides,[13] glycosyl selenylsulfides, and [14] alkyl- and arylthiosulfonates,[15] via disulfide exchange[16] or by using diethyl azodicarboxylate as a glycosylsulfenyl transfer reagent.[17] By comparison, synthesis of the more challenging unsymmetrical diglycosyl disulfides was first reported by Szilágyi et al. through nucleophilic substitution of glycosyl methanethiosulfonates (MTS) with glycosyl thiolates.[4a] Pinto and co-workers prepared diglycosyl disulfides and selenosulfides using a similar approach,[4b] while diethyl azodicarboxylate (DEAD), a reagent introduced by Mukaiyama[18] for unsymmetrical disulfide synthesis back in the late 1960s, was demonstrated recently to be suitable for the synthesis of both symmetrical and unsymmetrical diglycosyl disulfides.[19]

Recently, we reported[20] an efficient one-pot method for synthesizing unsymmetrical disulfides that relied on the interception of a reactive sulfenyl derivative in situ generated using 1-chlorobenzotriazole (BtCl) as the oxidant. Thus, treatment of an alkyl, aryl or heteroaryl thiol R^1SH at −78 °C in CH_2Cl_2 with BtCl (1.5 equiv) together with benzotriazole BtH (1 equiv) to maximize trapping of the sulfenyl chloride intermediate as described previously[20a,c] produces a high yield of R^1SBt with virtually no trace of the corresponding homodimer of R^1SH (R^1SSR^1). Substitution of R^1SBt with a second thiol R^2SH at around −20 °C generates the desired unsymmetrical disulfide R^1SSR^2 together with small amounts of the homodimer R^2SSR^2 from reaction of the excess R^2SH with the excess BtCl used to drive the reaction to full conversion of R^1SH, Scheme 1.

Usually, the heterodisulfide can be separated chromatographically from the R^2SSR^2 homodimer by-product. This new method has been shown to work efficiently with a range of alkyl-, aryl-,

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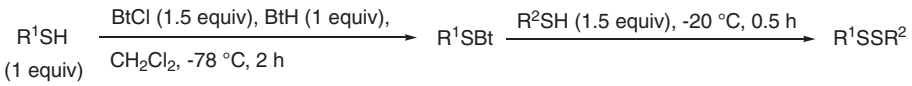
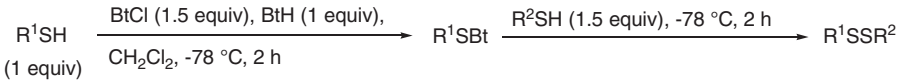


Scheme 1. General reaction scheme using the BtCl coupling methodology.



Scheme 2. Conditions for efficient coupling of sugar thiols.

and heteroarylthiols[20a,c] as well as biologically relevant cysteine.[20b] Generally, it was found that the reaction of aliphatic thiols was fast at −78 °C, and for the coupling of protected cysteines to afford unsymmetrical cystine derivatives it was found[20c] to be imperative to maintain the temperature at −78 °C throughout both the addition steps. In this Letter we report that our new mild method can also bring about an efficient coupling of different sugar thiols in a one-pot reaction that avoids the use of toxic activating or chlorinating agents, and in which the only by-product is the homodimer of R^2SH.

Initially, for optimization purposes, 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose[21] was reacted with either *n*-propylthiol or *p*-anisylthiol using the conditions described in Scheme 1 to return a modest yield of coupled heterodisulfide after chromatography. Mindful of the temperature aspect alluded to previously in the case of coupling cysteine derivatives,[20c] gratifyingly it was found that reducing the temperature in the second step to −78 °C and maintaining it at this temperature for two hours gave excellent yields (>80%) of the desired product. In the cases involving aliphatic or aromatic thiols (entries 1–4), the sugar thiol was added first. The full conditions are shown in Scheme 2.

Thereafter, a range of sugar thiols[21,22] was selected to probe the influence of the coupling partner, the position of the sulfhydryl group as well as the hydroxy-protecting group. In each case, the reaction proceeded smoothly to furnish the desired disulfide in good to excellent yield, see Table 1.

Entries 13 and 14 revealed that reversing the order of addition of the sugar thiols in this case had no effect on the overall outcome of the coupling in terms of yield. In the other entries the order of addition was not varied, but generally, results demonstrate that a particular sugar may act nucleophilically toward either the electrophilic BtCl reagent in the first step or the R^1SBt intermediate in the second (compare entries 5 and 7 for β-GlcSH and 6 and 8 for Gal-6SH). The only case where the yield was a little depressed (75%) was the diglycosyl disulfide involving the 4-SH of a protected glucose derivative (entries 13 and 14 in which the order of addition was varied), where steric considerations may have played a role. Similarly, the efficiency of the coupling was found to be independent of the protecting groups used in terms of electron-withdrawing (acetate) or electron-releasing (ketal), or the C-2 group (acetoxy or acetamido). However, it was found from the purification point of view that each sugar thiol R^1SH and R^2SH needed to

Table 1
One-pot diglycosyl disulfide synthesis using BtCl[a]

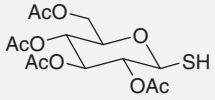
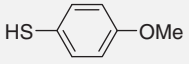
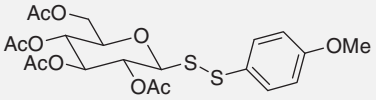
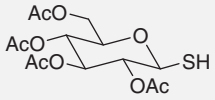
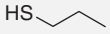
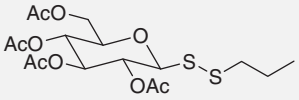
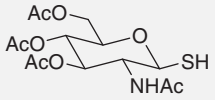
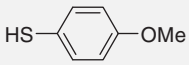
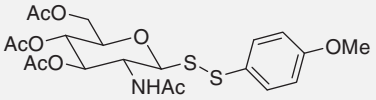
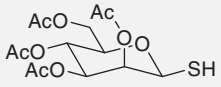
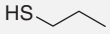
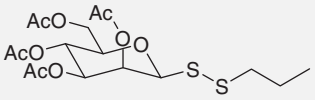
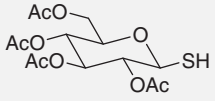
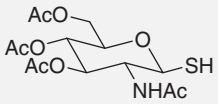
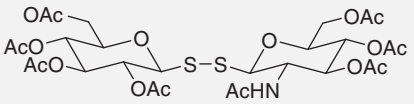
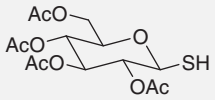
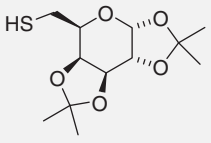
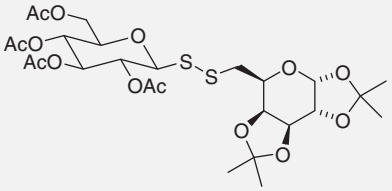
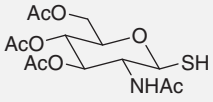
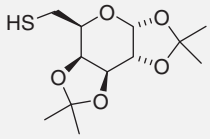
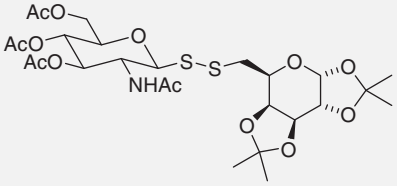
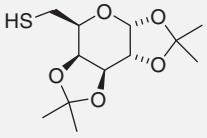
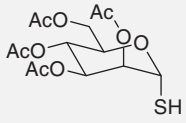
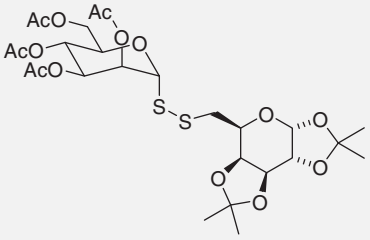
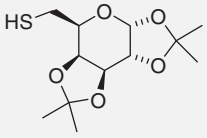
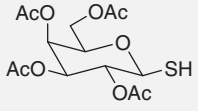
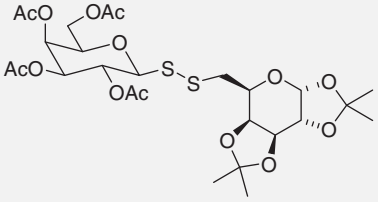
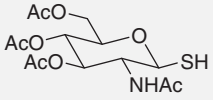
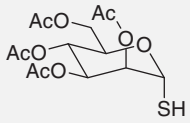
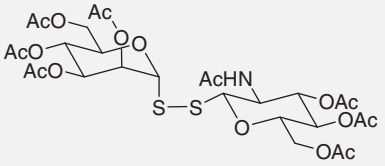
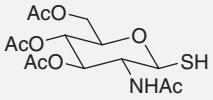
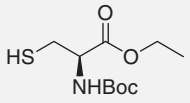
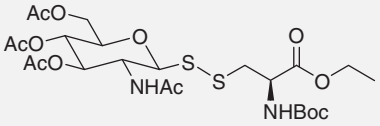
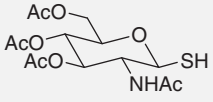
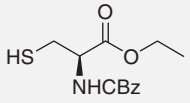
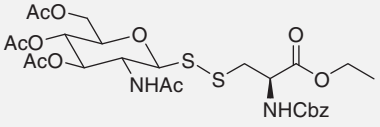
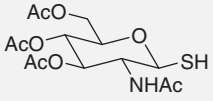
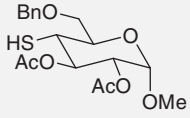
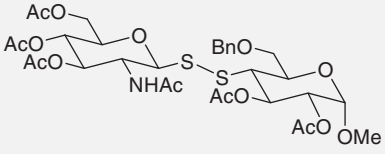
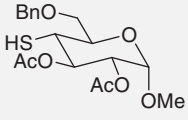
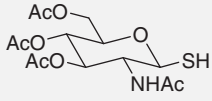
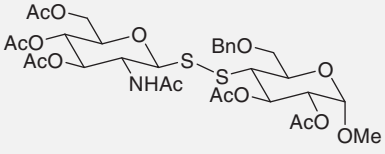
Entry	R^1SH	R^2SH	R^1SSR^2	Yield[b]
1				92
2				89
3				90
4				89
5				86
6				88

Table 1 (*continued*)

Entry	R^1SH	R^2SH	R^1SSR^2	Yield[b]
7				89
8				80
9				93
10				80
11				83
12				88
13				75
14				75

[a] See Refs. 21,22 for the preparation of the sugar thiols.
[b] Isolated yield after chromatography.

have a reasonably different R_f on TLC by virtue of having a different set of protecting groups (acetate or ketal), or a different C-2 substituent (OAc vs NHAc). This ensured that the unsymmetrical disulfide could be efficiently separated chromatographically from the homodimer R^2SSR^2 by-product. Finally, efficient coupling could be achieved by varying the position of the thiol group (positions 1, 4, and 6) as well as using different sugar configurations (glucose, mannose, galactose). Coupling was also independent of the thiol anomeric configuration and in all cases, the thiol group of R^1SH was carried through with retention of configuration into the disulfide product as reflected in the product anomeric coupling constants. Cysteine derivatives (entries 11 and 12) could also be coupled as models for glycopeptide conjugate synthesis. All products gave satisfactory analytical and spectral data, two examples of which are given.[23,24]

In conclusion, our BtCl technology, involving a low reaction temperature, small excess of reagent and with only one of the homodimers observed as a by-product, offers a much milder coupling protocol for sugar disulfide synthesis compared to other methods. The extremely mild conditions of coupling bode

well for achieving oligosaccharide coupling via a disulfide linkage.

General experimental procedures: To a stirred solution of 1-chlorobenzotriazole (0.058 g, 0.375 mmol) and benzotriazole (0.030 g, 0.250 mmol) in CH_2Cl_2 (3 mL) under N_2 at −78 °C was added dropwise a solution of R^1SH (0.250 mmol) dissolved in CH_2Cl_2 (1 mL). The solution was allowed to stir for 2 h at −78 °C. R^2SH (0.375 mmol) in CH_2Cl_2 (1 mL) was then added slowly at −78 °C and the solution stirred for a further 2 h. The reaction was quenched with a solution of $Na_2S_2O_3$ (0.10 g in 3 mL of H_2O). CH_2Cl_2 (25 mL) was added together with saturated aq Na_2CO_3 (10 mL) and the solution stirred rapidly for 20 min. The CH_2Cl_2 layer was then separated and the aqueous fraction extracted with CH_2Cl_2 (2 × 25 mL). TLC analysis showed that the organic layer contained no BtH. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography using petroleum ether/EtOAc mixtures to afford the corresponding unsymmetrical disulfide.

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23. *Entry 9*: (0.149 g, 93%) as a clear oil; $[\alpha]_D^{20}$ −16.0 (*c* 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2)/cm^{-1} 1751 (C=O), 1370 ($C(CH_3)_2$), 499 (S–S); δ_H (400 MHz, $CDCl_3$), dashed assignments refer to the ketal sugar: 1.27 (6H, s, CH_3), 1.36 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.91 (3H, s, CH_3), 2.00 (6H, s, CH_3), 2.10 (3H, s, CH_3), 2.91 (1H, dd, *J* 7.6 Hz and 13.5 Hz, H-6'), 3.02 (1H, dd, *J* 5.8 Hz and 13.5 Hz, H-6'), 3.93 (1H, t, *J* 6.4 Hz, H-5), 4.07 (3H, m, H-6 and H-5'), 4.21 (1H, d, *J* 8.0 Hz, H-2'), 4.25 (1H, dd, *J* 3.0 and 5.0 Hz, H-4'), 4.58 (2H, m, H-1 and H-3'), 5.01 (1H, dd, *J* 3.0 Hz and 10.0 Hz, H-3), 5.24 (1H, t, *J* 10.0 Hz, H-2), 5.36 (1H, d, *J* 3.0 Hz, H-4), 5.45 (1H, d, *J* 5.2 Hz, H-1'); δ_C (100.58 MHz, $CDCl_3$): 20.3 (CH_3), 20.4 (CH_3), 20.4 (CH_3), 20.5 (CH_3), 24.3 (CH_3), 24.9 (CH_3), 25.8 (CH_3), 26.0 (CH_3) 39.4 (C-6'), 61.5 (C-6), 66.1 (C-5'), 66.9 (C-2), 67.2 (C-4), 70.4 (C-2'), 70.9 (C-3'), 71.7 (C-4' and C-3), 74.7 (C-5), 91.2 (C-1), 96.5 (C-1'), 108.6 ($C(CH_3)_2$), 109.1 ($C(CH_3)_2$), 169.2 (C=O), 169.7 (C=O), 169.9 (C=O), 170.2 (C=O); HRMS: *m/z* 661.1626 (M^++Na), $C_{26}H_{38}NaO_{14}S_2$ requires 661.1601.
24. *Entry 12*: (0.142 g, 88%) as a colourless solid, mp 183–185 °C (EtOH); $[\alpha]_D^{20}$ −52.6 (*c* 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2)/cm^{-1} 3337 (NH), 1744 (C=O), 1694 (C=O), 1660 (C=O), 495 (S–S); δ_H (400 MHz, $CDCl_3$): 1.22 (3H, t, *J* 7.2 Hz, CH_3), 1.87 (3H, s, CH_3), 1.97 (3H, s, CH_3), 1.99 (6H, s, CH_3), 3.07 (1H, dd, *J* 7.6 Hz and 13.8 Hz, SCH_2), 3.30 (1H, dd, *J* 4.2 Hz and 13.8 Hz, SCH_2), 3.75 (1H, m, H-5), 4.14 (5H, m, H-2, H-6 and OCH_2), 4.65 (1H, br s, CHN), 4.73 (1H, d, *J* 10.4 Hz, H-1), 5.07 (3H, m, Bn and H-4), 5.23 (1H, t, *J* 9.8 Hz, H-3), 5.72 (1H, d, *J* 8.0 Hz, NH), 6.04 (1H, d, *J* 8.8 Hz, NH), 7.28 (5H, m, Ar-H)); δ_C (100.58 MHz, $CDCl_3$): 14.0 (CH_3), 20.5 (CH_3), 20.5 (CH_3), 20.5 (CH_3), 23.0 (CH_3), 42.5 (SCH_2), 52.5 (C-2), 53.7 (CN), 61.9 (C-6), 62.1 (OCH_2), 67.0 (Bn), 68.2 (C-4), 73.4 (C-3), 76.1 (C-5), 89.3 (C-1), 128.0 (Ar), 128.1 (Ar), 128.4 (Ar) 136.2 (Ar), 155.7 (C=O), 169.2 (C=O), 170.2 (C=O), 170.4 (C=O), 170.5 (C=O), 170.7 (C=O); HRMS: *m/z* 667.1622 (M+Na)$^+$, $C_{27}H_{36}NaN_2O_{12}S_2$ requires 667.1607; Found: C, 49.98; H, 5.41; N, 4.07; S, 9.66. $C_{27}H_{36}NaN_2O_{12}S_2$ requires C, 50.30; H, 5.63; N, 4.35; S, 9.95.