Direct Transformation of Unprotected Sugars to Aryl 1-Thio-β-glycosides in Aqueous Media Using 2-Chloro-1,3-dimethylimidazolinium Chloride

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Aryl 1-thioglycosides have directly been synthesized in good yields from the corresponding unprotected sugars and thiols without protection of the hydroxy groups by using 2-chloro-1,3-dimethylimidazolinium chloride (DMC) as dehydrative condensing agent. The reaction proceeded in a mixed solvent of water and acetonitrile under mild reaction conditions, leading to the predominant formation of β-anomers.

There has been a growing research interest in thioglycosides in carbohydrate chemistry.[1] Aryl 1-thioglycosides are useful precursors of glycosyl fluorides, glycosyl bromide, and glycosyl sulfoxides.[2] Thioglycoside derivatives are also employed as efficient glycosyl donors or glycosyl acceptors for chemical or enzymatic glycosylations.[3] In addition, they are stable *O*-glycoside analogues, which can be utilized as enzyme inhibitors in various biochemical studies.[4]

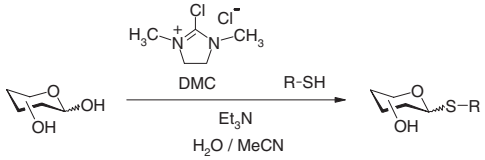
In general, thioglycoside derivatives are synthesized by the reaction of a peracetylated sugar with a thiol in the presence of a Lewis acid,[5] or by substituting the bromine of an acetobromoglucose with a thiolate anion.[6] Thioglycosides can also be prepared by treating 1-thiosugars with an electrophile like alkyl halides.[7] All of these procedures require multistep reactions including protection and deprotection of the hydroxy groups. Direct methods for preparation of thioglycosides from hemiacetals have been demonstrated in trifluoroacetic acid. However, these methods show poor selectivity concerning the anomeric configuration and are accompanied by the formation of dithioacetals as by-products.[8]

In a series of our investigation of the direct activation of unprotected sugars,[9] we have recently reported the synthesis of 1,6-anhydrosugars[10] via an intramolecular dehydration reaction in aqueous media by using 2-chloro-1,3-dimethylimidazolinium chloride (DMC).[11] The reaction proceeds via a reactive intermediate that is formed as a result of a preferential attack of the anomeric hydroxy group toward DMC.[12] Then, an intramolecular nucleophilic attack of the 6-hydroxy group to the anomeric carbon gives rise to the 1,6-anhydrosugar.

We postulated that if the reaction is carried out in the presence of a thiol, a direct introduction of a thioaryl group to the anomeric carbon would be possible, affording the corresponding 1-thioglycoside. The present paper describes a DMC-mediated intermolecular dehydration reaction between the anomeric hydroxy group of unprotected sugars and aromatic thiols to give the corresponding aryl 1-thioglycosides.

It was predicted that more than 2 equivalents of base would be necessary to scavenge hydrogen chloride liberated and to activate a hydroxy group in the course of the reaction. We screened various bases as well as their equivalency using D-glucose as a model substrate, and finally found that the use of triethylamine (Et_3N) is effective for promotion of the reaction. It was also predicted that a considerable amount of 1,6-anhydrosugar would be formed as by-product. Interestingly, the addition of acetonitrile greatly reduced the formation of 1,6-anhydroglucose, leading to the preferential formation of thioglycoside.[13]

Table 1. Direct synthesis of aryl thioglycosides from unprotected sugars[a]



Entry	Sugar	H_2O/MeCN, Temp/°C	RSH (equiv)	Yield/%[b] (β/α)
1	D-Glucose	1/1, −15	 (5)	quant. (6.7/1)
2	D-Glucose	1/1, 0	 (7)	93 (4.5/1)
3	D-Glucose	1/1, 0	 (3)	90 (10/1)
4	D-Glucose	1/1, r.t.	 (5)	90 (β)
5	D-Glucose	1/1, 0	 (5)	91 (β)
6	Cellobiose	4/1, 0	 (5)	quant.(β)
7	Lactose	4/1, 0	 (5)	quant.(β)
8	Laminaribiose	4/1, 0	 (5)	quant.(β)
9	Melibiose	4/1, 0	 (5)	quant.(β)

[a]The reactions were carried out using 3 equiv of DMC and 10 equiv of Et_3N. The reaction time: 1 h. [b]Determined by ^{1}H NMR by comparing the integrals of the anomeric proton of the product and that of unprotected sugar in D_2O.

Table 1 summarizes the synthesis of various aryl 1-thioglycosides by the reaction of unprotected sugars and aromatic thiols. In case of using benzenethiol, *p*-toluenethiol, and 4-methoxybenzenethiol, the corresponding β-thioglycosides were obtained preferentially (Entries 1–3). When 4-nitrobenzenethiol and 2-pyridinethiol were reacted with D-glucose in the presence of DMC, the corresponding thioglycosides having β-configuration were exclusively obtained (Entries 4 and 5). The present reaction could successfully be applied to disaccharides (Entries 6–9). Cellobiose (β-1,4), laminaribiose (β-1,3), melibiose (α-1,6) have been transformed to the corresponding 2-pyridyl thioglycosides in excellent yields without affecting the inner glycosidic bonds.

The following is a typical procedure for synthesis of thioglycoside (Entry 5). DMC was added to a mixture of D-glucose, Et_3N, and 2-pyridinethiol in water/acetonitrile (1/1 (v/v)), and the reaction mixture was stirred for 1 h at 0 °C. After removing the solvent, the residue was purified by using silica

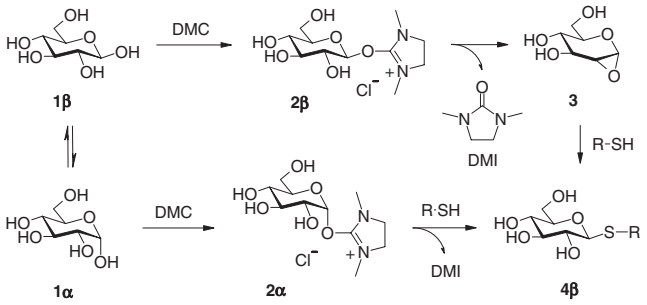


Figure 1. Plausible reaction mechanism.

gel column chromatography to give 2-pyridyl 1-thio-β-D-glucopyranoside.

The ^{1}H NMR of the product showed a signal around 5 ppm ($J_{1,2} = 10$ Hz) derived from the anomeric proton. The large coupling constant clearly indicated that the anomeric configuration of the product was β-type. A signal of anomeric carbon around 87 ppm in the ^{13}C NMR supported the formation of *S*-glycosidic bonds.[14] One of the characteristic features of the present reaction is that thioglycosides are produced directly from hemiacetals. It is therefore predicted that a furanose ring formation would take place as a side reaction. The NMR spectroscopic study of all products showed no signals characteristic of aryl 1-thiofuranoside derivatives at around 83 and 70 ppm ascribable to C4 and C5, respectively.[15]

The reaction mechanism involves the initial formation of the β-glycosyl intermediate **2β** as a result of a nucleophilic attack of β-glucose (**1β**) to the 2 position of DMC promoted by triethylamine as a general base (Figure 1). The resulting intermediate is then converted to the 1,2-anhydro intermediate **3** by the neighboring group participation of the 2-hydroxy group enhanced by the action of triethylamine, producing 1,3-dimethylimidazolidin-2-one (DMI). At this stage, two triethylamines are converted to the corresponding HCl salts. A thiol attacks to the anomeric carbon of **3** from the β side, giving rise to β-thioglycoside (**4β**). On the other hand, α-glucose (**1α**) that is in equilibrium with **1β** also reacts with DMC to give the corresponding α-glycosyl intermediate **2α**, which was attacked by thiol to afford **4β**. The participation of 1,2-anhydrosugar **3** is strongly supported by the results that 2-deoxy-D-glucose was converted to the corresponding thioglycoside with lower stereoselectivity ($\beta/\alpha = 1.6/1$) (data not shown).

In conclusion, we achieved a one-step and highly β-selective synthesis of aryl 1-thioglycosides by using DMC as a dehydrative condensing agent under mild reaction conditions. The reaction requires no protection of the hydroxy groups and proceeds smoothly in aqueous media. The present method would be a general and practical tool for the synthesis of aryl β-thioglycoside starting from not only unprotected mono- or disacchcrides but also unprotected oligosaccharides of higher molecular weights.

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13 The minimum acetonitrile concentration to prevent the 1,6-anhydrosugar formation was 35 vol %; under a lower concentration, the 1,6-anhydrosugar was formed as by-product. The role of acetonitrile has not been made clear.

14 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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