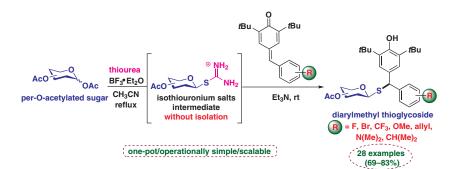
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Abstract An efficient one-pot protocol has been developed for the direct preparation of diarylmethyl thioglycosides starting from per-O-acetylated sugars via glycosyl isothiouronium salts. The one-pot reaction conditions involve rapid conversion of the per-O-acetylated sugar with thiourea in the presence of boron trifluoride etherate as catalyst to give the corresponding glycosyl isothiouronium salt, which is subsequently treated with a *para*-quinone methide in the presence of a base to give the a diarylmethyl thioglycoside in excellent yield.

Keywords diaryl thioglycosides, one-pot reaction, thioureas, *para-*quinone methides

Sulfur-containing functionalized carbohydrates are a remarkably important class of compounds that find widespread use as pharmaceuticals. Amongst them, thioglycosides are an important class of sugar derivatives that are considered as useful simulants of biologically relevant Oglycosides, because they are known to resist enzymatic hydrolysis and can consequently be used as enzyme inhibitors in various biochemical studies.

S-Glycosides are valuable glycomimetic derivatives that find a wide range of applications in pharmaceutical science.

1a,c,4 Protected thioglycosides are often used in synthetic carbohydrate chemistry as versatile glycosyl donors because of their stability during various chemical transformations and the ease with which they can be converted into a variety of other functionalities. In addition, these derivatives serve as versatile intermediates in organic synthesis.

Among the several glycosyl donors, thioglycosides are considered to be versatile intermediates because of their high degree of stability in many organic reactions. These derivatives are routinely used as glycosyl donor building blocks in producing a variety of glycosidic linkages;^{7a,8}

moreover, they are also found in various drugs, natural products, and medicinally active agents,⁹ including an hS-GLT1 inhibitor, a ligand of lectin A, a cytotoxic Hsp90 inhibitor, inhibitors of galactosidase and glycosidase,¹⁰ and various antimicrobial agents (Figure 1). Interestingly, another representative natural product bearing a C–S glycosidic bond is the clinically used antibiotic lincomycin A¹¹ (Figure 1). These derivatives clearly hold great potential in medicinal chemistry as well as in carbohydrate chemistry. Therefore, the development of highly efficient synthetic methods to access functionalized sulfur-containing carbohydrates is particularly appealing.

Thioglycoside derivatives are commonly prepared treating per-O-acetylated glycosyl precursors with a thiophenol in the presence of a Lewis acid, ¹² by substituting the halogen atom of an acetohaloglycoside with a thiolate anion, ¹³ or by a reaction of a 1-thioglycopyranose with an alkyl halide (Scheme 1a). ¹⁴

An alternative route to access (het)arylthioglycosides involves the use of thioglycosides as nucleophiles under transition-metal catalysis (Scheme 1b).^{15,16} These derivatives have also been prepared from carbohydrate sulfenates¹⁷ or by free-radical addition of 1-thiosugars to alkenes.¹⁸

Despite these significant recent improvements, it is surprising to find that there have been no reports of the preparation of diarylmethyl thioglycosides from *para*-quinone methides (*p*-QMs) through the generation in situ of glycosyl isothiouronium salts from per-O-acetylated sugars (Scheme 1c).

In recent years, *p*-QMs have been explored extensively because of their unique ability to act as powerful Michael acceptors with a variety of nucleophiles to generate highly functionalized diarylmethane derivatives. Anand's group and others have reported that a diversity of nucleophiles, including cyanides, malonates, glycine Schiff bases, dicyanoolefins, the Seyferth–Gilbert reagent, allenic

group.

hSGLT1 inhibitor

Glucosidase inhibitor

Cytotoxic agent

Antimicrobial agent Leaf-closure β-glucosidase inhibitor

Irreversible glycoside inhibitor

polymer precursor

Lincomycin A

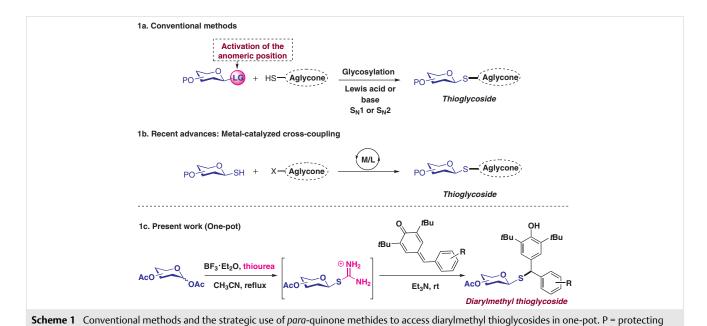
Figure 1 Some examples of biologically active thioglycosides

esters, styrenes, and β-naphthols, can be used in 1,6-conjugate additions to p-QMs.

Despite these tremendous achievements, the development of new nucleophiles, such as various S-glycosides, for the 1,6-conjugate addition of p-QMs is still in great demand. The chemistry of p-QMs is well explored in organic synthesis and physical organic chemistry, but less so in carbohydrate chemistry. Keeping in mind the high reactivity of p-QMs toward nucleophiles, we surmised that these units

might server as versatile diarylmethylating agent for the synthesis of diarylmethane S-glycosides.

The direct one-pot conversion of glycosyl isothiouronium salts derivatives into glycosyl thiol derivatives under phase-transfer conditions is a well-established process.²³ Therefore, glycosyl isothiouronium salts might be used for 1,6-conjugate addition of p-OMs in the presence of base to generate glycosyl thiols in situ. However, to the best of our knowledge, there are no reports that describe the synthesis



Generally, the most-often-employed approaches involve cleavage of a glycosyl isothiouronium salt by treatment with potassium carbonate and sodium hydrogen sulfite or metabisulfite in water-acetone media, followed by reaction of the resulting acetylated 1-thioglycose with an alkyl or aryl halide.²⁴ In most cases, the presence of water in the reaction mixture does not permit the use of water-sensitive alkylation and acylation agents. Consequently, the 1-thiosugar formed has to be isolated before alkylation, making the approach more laborious. The synthesis of alkyl- or arylthioglycosides and glycosyl thioesters via isothiouronium salts by using a base at room temperature has been recently described.²⁵

We attempted to develop a one-pot reaction protocol for the direct preparation of diarylmethyl thioglycoside from per-O-acetylated sugars via glycosyl isothiouronium derivatives through the strategic use of *p*-QMs in the presence of alkylamines in acetonitrile. Reports in the literature suggest that alkylamines are stronger bases but weaker nucleophiles than thiols; therefore, by converting the isothiouronium salts into more-nucleophilic thiolate anions, they should react readily with thioaldoses.

To standardize the reaction protocol, 2,3,4,6-tetra-0-acetyl- β -D-galactopyranose (1; 1.0 mmol) was treated with a mixture of thiourea (1.1 mmol) and boron trifluoride

etherate (1.1 mmol) in acetonitrile, and the mixture was heated to 80 °C for 30 minutes. TLC showed complete conversion of the sugar per-O-acetate into slower-moving Sglycosyl isothiouronium salts. The mixture was then cooled to room temperature, and the p-QM derivative 2a (1.1 mmol) and excess alkylamine were added sequentially. The mixture was then stirred at room temperature for a further one hour. Various organic bases, such mono-, di-, or trialkylamines, were found to be suitable for use in synthesis of the thioglycoside by the described procedure (Table 1). In the case of triethylamine, the reaction proceeded smoothly at room temperature to give the diarylmethyl S-glycoside 3a²⁶ as a diastereomeric mixture (dr 1:1) in 83% yield (Table 1, entry 1); no improvement in the yield of 3a was observed in the presence of diethylamine, DIPEA, DBU, or DABCO (Table 1, entries 2–6), even with longer reaction times. Lessbasic amines, for example pyridine, were unable to cleave the glycosyl isothiouronium salt (entry 7).

After completion of the reaction, as monitored by TLC (hexane: EtOAc 1:1), the solvent was evaporated and the resulting syrup was diluted with CH₂Cl₂ and washed with water, which on evaporation gave the pure diaryl thioglycoside **3a** in 83% yield as a diastereomeric mixture in a one-pot process starting from the per-O-acetylated sugar.

After identifying the optimal one-pot conditions for this transformation (Table 1, entry 1), we examined the substrate scope of this transformation by using a wide range of p-QMs $\mathbf{2a}$ - \mathbf{n}^{27} bearing various substituents on the phenyl ring together with various easily accessible per-O-acetylated sugars (Table 2). Most of the p-QMs employed in the re-

 Table 1
 One-Pot Protocol for the Synthesis of Diarylmethyl Thioglycoside 3a, and Screening of Various Amines^a

Entry	Base	Equiv	Time (h)	Yield ^b (%)
1	Et ₃ N	2	2	83
2	DIPEA	2	2	77
3	DBU	2	2	69
4	DABCO	2	2	68
5	MeNH ₂	2	2	68
6	Et ₂ NH	2	2	78
7	ру	2	2	ND^c
8	Et ₃ N	4	6	84

^a Reaction conditions: **1a** (1.0 mmol), thiourea (1.1 mmol), BF₃-Et₂O (1.1 mmol), MeCN (5 mL), 80 °C then **2a** (1.1 mmol), base (2 mmol), rt.

^b Isolated yield after silica gel chromatography.

c ND = not detected.

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To elaborate the substrate scope further, this one-pot method was extended to 1,6-conjugate addition of several per-O-acetylated disaccharide moieties with wide range of p-QMs **2** to give corresponding desired diarylmethyl thioglycosides **4a**–**f**²⁸ (Table 3). The reaction conditions were successfully applied to the preparation of diarylthioglycosides from D- or L-sugars as well as from disaccharides. The reaction proceeded smoothly at room temperature affording the products in high yields. A series of thioglycosides of

Table 2 Substrate Scope of a Diverse Range of *p*-QMs **2a–n** and Various Per-O-acetylated Sugars^a

b Isolated yield after silica gel chromatography (dr ≈ 1:1).

^a Reaction conditions: 1 (1.0 mmol), thiourea (1.1 mmol), BF₃·Et₂O (1.1 mmol), MeCN (5 mL), 80 °C; then 2 (1.1 mmol), Et₃N (2 mmol), rt.

a Reaction conditions: 1 (1.0 mmol), thiourea (1.1 mmol), BF₃:Et₂O (1.1 mmol), MeCN (5 mL), 80 °C; then 2 (1.1 mmol), Et₃N (2 mmol), rt.

^b Isolated yield after silica gel chromatography (dr \approx 1:1)

mono- and disaccharides were prepared by using this onepot procedure in short reaction times not exceeding two hours.

Based on the above results and previously reports,²⁹ a plausible mechanism for the formation of **3** and **4** is proposed (Scheme 2). The reaction is probably initiated by BF₃-induced formation of the 1,2-acyloxonium ion as an intermediate that reacts with nucleophiles in only one possible way, leading exclusively to 1,2-*trans*-substitution products. The isothiourea intermediates obtained in 30 minutes without isolation can be directly converted into thioglycosides by 1,6-conjugate addition under basic conditions.

In conclusion, we have demonstrated the first strategic use of *p*-QMs to access diarylmethyl *S*-glycosides from the per-O-acetyl sugars through sequential thioglycosidation

via *S*-glycosyl isothiouronium salts. The reaction conditions are operationally simple, mild, reproducible, high-yielding, and can be scaled up for large-scale preparation. We therefore believe that this method will open a route to novel diarylmethyl thioglycosides as a novel and largely unexplored structural class of glycomimetic compounds.

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Scheme 2 Plausible mechanism of the reaction.

Supporting information for this article is available online at $\frac{1}{1000} \frac{1}{1000} \frac$

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- (26) (3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl 2,3,4,6-Tetra-O-acetyl-1-thiohexopyranoside (3a); Typical Procedure
 - Thiourea (84 mg, 1.1 mmol) and BF₃·Et₂O (136 μ L, 1.1 mmol) were added to a solution of 2,3,4,6-tetra-O-acetyl- β -D-galactopyranose (**1a**; 390 mg, 1.0 mmol) in MeCN (5 mL), and the mixture was refluxed at 80 °C until the starting material was fully consumed (TLC; 30 min). The mixture was then cooled to rt, and Et₃N (279 μ L, 2.0 mmol) and *p*-QM **2a** (353 mg, 1.2

mmol) were added with stirring. The mixture was kept at rt for 2 h then diluted with CH2Cl2 and washed with H2O. The resulting organic phase was dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel; hexane-EtOAc (5:1)] to a give a colorless oil; yield: 546 mg (83%; dr 1:1).

IR (neat): 3644, 3021, 2967, 1752, 1522, 1348, 1225, 1157, 1052, 760, 668 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.49–7.46 (m, 1 H), 7.39-7.34 (m, 2 H), 7.31-7.19 (m, 3 H), 7.15-7.13 (m, 1 H), 5.43 (s, 0.6 H), 5.38 (s, 0.4 H), 5.35-5.33 (m, 1 H), 5.29-5.22 (m, 1.5 H), 5.15 (s, 0.5 H), 4.91-4.85 (m, 1 H), 4.14-4.03 (m, 3 H), 3.60-3.55 (m, 1 H), 2.14 (s, 3 H), 2.07 (s, 3 H), 2.05 (s, 3 H), 1.95 (s, 3 H), 1.3 (s, 18 H). 13 C NMR (100 MHz, CDCl₃): δ = 170.3, 170.2, 170.1, 170.0, 169.5, 169.4, 153.2, 153.1, 140.9, 140.5, 136.1, 135.8, 130.3, 130.2, 128.6, 128.5, 128.4, 128.3, 127.5, 127.2, 125.1, 125.0, 83.7, 83.4, 74.3, 74.2, 72.0, 71.9, 67.4, 67.3, 67.2, 61.5, 61.4, 53.3, 52.7, 34.4, 34.3, 30.3, 30.1, 20.9, 20.8, 20.7, 20.6, 20.5. HRMS (ESI-TOF): m/z [M + NH₄]⁺ calcd for C₃₅H₅₀-NO₁₀S: 676.3150; found: 676.3152.

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(28) Compound 4a (Table 3); Typical Procedure

Thiourea (84 mg, 1.1 mmol) and BF₃·Et₂O (136 µL, 1.1 mmol) were added to a solution of peracetyl-β-D-lactose (678 mg, 1.0 mmol) in MeCN (10 mL), and the mixture was refluxed at 80 °C until the starting material was completely consumed (TLC, 30 min). The mixture was then cooled to rt and Et₃N (279 μ L, 2.0 mmol) and p-QM 2a (353 mg, 1.2mmol) were added with stirring. The mixture was kept at rt for 2 h then diluted with CH₂Cl₂ and washed with H₂O. The resulting organic phase was dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, hexane-EtOAc (1:1)] to give a colorless oil; yield: 748 mg (79%; dr 1:1).

IR (neat): 3617, 2958, 2568, 1753, 1623, 1374, 1225, 1165, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.46 - 7.41$ (m, 1 H), 7.37-7.33 (m, 2 H), 7.31-7.26 (m, 2 H), 7.22-7.18 (m, 1 H), 7.12-7.11 (m, 1 H), 5.39 (br s, 1 H), 5.33-5.32 (m, 1 H), 5.22-5.14 (m, 1 H), 5.08-5.03 (m, 2 H), 5.00-4.89 (m, 2 H), 4.50-4.34 (m, 2 H), 4.12-4.02 (m, 4 H), 3.86-3.82 (m, 1 H), 3.77-3.2 (m, 1 H), 3.28-3.23 (m, 1 H), 2.17 (s, 3 H), 2.13 (s, 2 H), 2.04 (s, 12 H), 1.95 (s, 3 H), 1.38 (s, 18 H). 13 C NMR (100 MHz, CDCl₃): δ = 170.3, 170.1, 170.0, 169.7, 169.6, 169.5, 169.1, 169.0, 153.2, 153.1, 140.9, 140.4, 136.1, 135.8, 130.3, 130.2, 128.6, 128.5, 128.4, 128.2, 128.1, 127.6, 127.2, 125.1, 124.9, 124.8, 101.2, 101.1, 82.8, 82.4, 77.2, 76.4, 76.3, 74.1, 73.9, 71.1, 70.6, 70.5, 70.4, 69.1, 66.5, 62.3, 62.2, 60.7, 53.3, 52.5, 34.4, 34.3, 30.4, 30.2, 20.9, 20.8, 20.7, 20.6, 20.5, 20.4. HRMS (ESI-TOF): m/z [M + NH₄]⁺ Calcd for C₄₇H₆₆⁻ NO₁₈S: 964.3995; found: 964.3968.

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