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$GaCl_3$-Catalyzed addition of thiols to glycals: a facile synthesis of 2-deoxy thioglycosides☆

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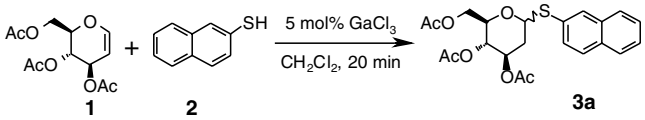
Abstract—Gallium(III) chloride catalyzes efficiently the addition of thiols to glycals under extremely mild conditions to afford 2-deoxy thioglycosides in high yields with a good α-selectivity. The reactions proceed rapidly at ambient temperature.

1,2-Unsaturated glycopyranosides, namely, glycals are versatile synthetic intermediates for elaboration to a number of functionalized glycosyl derivatives.[1] The major utility of glycals is their conversion to 2-deoxyglycosides which are well-known structural components of several biologically active compounds, especially antitumor–antibiotics such as anthracyclines, aureolic acids, orthosamycins, angucyclins and enediynes.[2] In particular, 2-deoxy-α-glycosides are present in many bioactive natural products including compactin, olivomycin, mithramycin, daunomycin, calicheamicin and many others.[3] In this context, several methods have been developed for the preparation of 2-deoxy sugars via multi-step sequences.[4] Of these, the acid-catalyzed addition of an alcohol to acetylated glycals appears to be the most direct method for the synthesis of 2-deoxy pyranosides.[5,6] In contrast to 2-deoxy glycosides, only a few methods have been reported so far for the preparation of 2-deoxy thioglycosides from glycals using HCl/^{i}Pr$_2$-NEt, *p*-TSA, CAN and $ReOCl_3(SMe_2)(Ph_3PO)$.[7] However, most of these methods involve either the use of oxidizing agents or strongly acidic conditions and are also limited to *O*-alkyl or *O*-benzyl glycals.[7] To date, the generality of this process to prepare 2-deoxy thiosugars has remained unattractive as the protected glycals often give rearranged products under acidic conditions.[8] Recently, there has been considerable interest in gallium mediated transformations.[9] Owing to their unique catalytic properties, gallium halides have been widely used for a variety of organic transformations. In particular, gallium(III) compounds are considered as effective Lewis acids to activate alkynes under extremely mild conditions.[10] However, there have been no reports on the use of gallium(III) chloride for the synthesis of 2-deoxy thiosugars from D-glycals.

As part of our continuing interest on the development of new synthetic methodologies,[11] we disclose our results on the gallium trichloride catalyzed synthesis of 2-deoxy-1-thioglycosides from D-glycals. Treatment of 3,4,6-tri-*O*-acetyl-D-glucal **1** with β-thionaphthol **2** in the presence of 5 mol % $GaCl_3$ in dichloromethane over 20 min at room temperature afforded the corresponding 2-deoxy-1-thioglycoside **3a** in 90% yield with the α-anomer as the major product (Scheme 1).

Encouraged by the results obtained with D-glucal and thionaphthol, we turned our attention to various glycals and thiols. Interestingly, several substituted thiophenols underwent addition reaction with glycals to provide the respective thioglycosides in 75–95% yields with a high α-selectivity (Table 1). The predominant formation of the α-anomer may arise from the thermodynamic anomeric effect. The effect of donating and withdrawing



Scheme 1.

Keywords: Glycals; Thiols; Gallium(III) halide; 2-Deoxy sugars; Thioglycosides.

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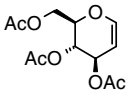
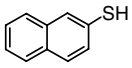
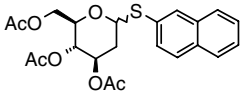
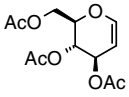
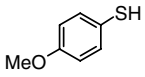
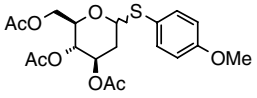
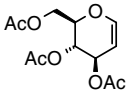
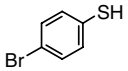
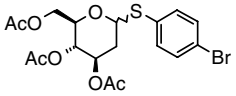
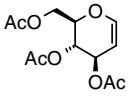
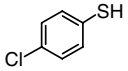
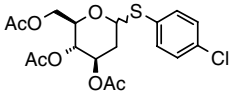
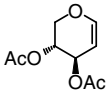
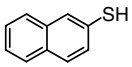
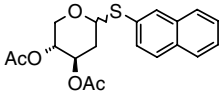
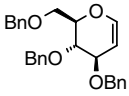
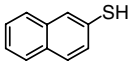
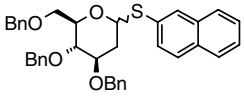
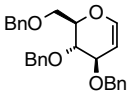
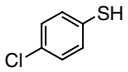
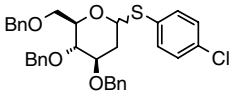
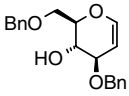
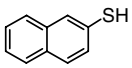
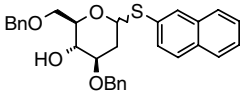
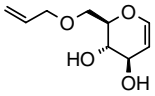
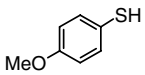
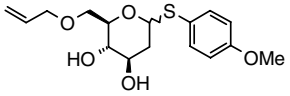
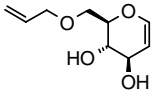
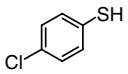
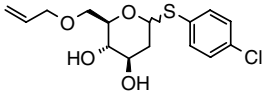
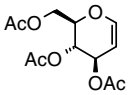
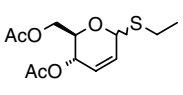
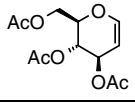
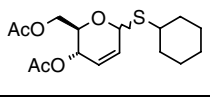
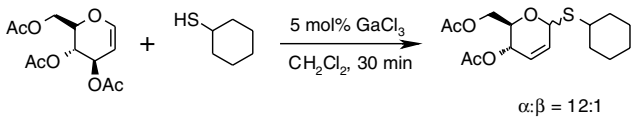
Table 1. $GaCl_3$-Catalyzed preparation of 2-deoxy thioglycosides

Entry	Glycal	Thiol	Product[a]	Time (min)	Yield[b] (%)	α:β
a				20	90	9:1
b				15	95	19:1
c				25	80	12:1
d				30	75	12:1
e				20	88	9:1
f				30	75	12:1
g				25	83	12:1
h				30	85	9:1
i				15	88	8:2
j				20	78	9:1
k				30	62	12:1
l				30	69	12:1

[a] All products were characterized by ^1H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yields.

substituents on the aromatic ring of the thiols had a considerable effect on the yields of the products formed. For example, *p*-methoxy-thiophenol (entry b) and tri-*O*-acetyl-D-glucal afforded the product in 95% yield, whereas *p*-bromo- and *p*-chloro-thiophenols (entries c and d) gave 2-deoxy thioglycosides in 80 and 75% yields,



Scheme 2.

respectively. Interestingly, 3,4-di-*O*-acetyl-D-xylal and β-thionaphthol gave the corresponding 2-deoxy-1-thioglycoside in 88% yield (entry e). Tri-*O*-benzyl-D-glucal and thionaphthol afforded the respective thioglycoside in a good yield (75%, entry f) after 30 min. In a similar manner, *p*-chloro-thiophenol reacted well with tri-*O*-benzyl-D-glucal to give the 2-deoxy thioglycoside in 83% yield (entry g).

Mono- and di-substituted D-glucals also underwent smooth addition to give the corresponding thioglycosides in good yields (entries h–j). Surprisingly, tri-*O*-acetyl-D-glucal underwent the Ferrier rearrangement with aliphatic thiols such as ethanethiol and cyclohexane thiol under the present reaction conditions (Table 1, entries k and l, Scheme 2).

In general, all the reactions were complete within 15–30 min and the products were obtained in 62–95% yields. All the products were characterized by IR, ^{1}H NMR and mass spectroscopy and also by comparison with authentic compounds.[7] Among various Lewis acids such as $GaCl_3$, $InCl_3$, $ZrCl_4$, $BiCl_3$, YCl_3 and $CeCl_3\cdot 7H_2O$ studied for this reaction, $GaCl_3$ was found to be the most effective in terms of conversion. Furthermore, glycals underwent the well-known Ferrier transformation rather than addition when $InCl_3$, $ZrCl_4$, $BiCl_3$, YCl_3 and $CeCl_3\cdot 7H_2O$ were used. The results obtained with various aromatic thiols and glycals are presented in Table 1. The reaction conditions are compatible with various hydroxyl protecting groups such as acetyl, allyl and benzyl ethers. Both acetyl and benzyl derivatives of D-glucal were equally effective for this conversion. Furthermore, this method is especially useful to obtain 2-deoxy thioglycosides from D-glucal and *p*-methoxy-thiophenol without the formation of any side products such as disulfides and quinones, which are generally observed using the reported reagents.[7] For example, 3,4,6-tri-*O*-acetyl-D-glucal and *p*-methoxy-thiophenol in the presence of $GaCl_3$ gave the corresponding 2-deoxy thioglycoside in 95% yield, whereas the same reaction using CAN failed to give the desired product. In addition to this, treatment of 3,4,6-tri-*O*-acetyl-D-glucal with β-thionaphthol in the presence of $GaCl_3$ gave the 2-deoxy thioglycoside in 90% yield while CAN afforded the same product in 35% yield along with 2,3-unsaturated thioglycoside in 40% arising from thio-Ferrier rearrangement. The experimental procedure is quite simple, convenient and does not involve a tedious work-up procedure for the isolation of the products.[12]

In conclusion, we have developed a novel and efficient approach for the preparation of 2-deoxy-1-thioglycosides through the addition of thiols to glycals using gallium trichloride as the catalyst. This method offers significant advantages such as mild reaction conditions, short reaction times, high yields and no side products such as disulfide or glycal-rearranged products, which makes it an attractive process for the preparation of synthetically challenging thioglycosides.

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12. *Typical experimental procedure*: To a stirred solution of glucal triacetate (1 mmol) and the thiol (1.1 mmol) in methylene dichloride (10 mL) was added $GaCl_3$ (5 mol %) and stirring continued at room temperature for 15–30 min (Table 1). The progress of the reaction was monitored by TLC. After complete conversion as indicated by TLC, the reaction mixture was quenched with saturated ammonium chloride solution. The resulting mixture was extracted with methylene dichloride (3×10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products thus obtained were purified by column chromatography (silica gel 60–120 mesh) using a gradient mixture of ethyl acetate and *n*-hexane (1:9) to furnish pure thioglycosides. Spectral data for selected compounds:

Compound (**3a**): IR (KBr): ν 2921, 2859, 1740, 1441, 1369, 1235, 1050, 809, 746, 653 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.95–1.05 (m, 1H), 1.95–2.10 (m, 6H), 2.15–2.20 (s, 3H), 2.22–2.32 (m, 1H), 2.80–2.90 (m, 1H), 3.66 (d, 1H, $J = 9.6$ Hz), 4.25–4.40 (m, 2H), 4.97–5.10 (m, 1H), 5.58 (s, 1H), 7.20 (d, 2H, $J = 7.5$ Hz), 7.39 (t, 1H, $J = 5.3$ Hz), 7.50 (t, 1H, $J = 5.3$ Hz), 7.65–7.78 (m, 2H), 8.10 (d, 1H, $J = 7.7$ Hz).

Compound (**3b**): IR (KBr): ν 3067, 2951, 2873, 1740, 1539, 1467, 1431 1369, 1230, 1086, 1040, 1004, 891, 813, 751, 632 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 2.01 (s, 3H), 2.03 (s, 3H), 2.06 (s, 3H), 2.14 (d, 1H, $J = 6.0$ Hz), 2.31 (d, 1H, $J = 6.0$ Hz), 3.37–3.50 (m, 1H), 3.95 (d, 1H, $J = 15.6$ Hz), 4.20 (d, 1H, J =7.2 Hz), 4.33–4.40 (m, 1H), 4.87 (t, 1H, $J = 14.5$ Hz), 5.54 (d, 1H, $J = 6.0$ Hz), 7.26 (d, 2H, $J = 9.5$ Hz), 7.50 (d, 2H, $J = 9.5$ Hz).

Compound (**3c**): IR (KBr): ν 2908, 2848, 2352, 1735, 1584, 1488, 1451, 1367, 1234, 1174, 1035, 927, 817, 749, 673 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.95–2.18 (m, 10H), 2.30 (d, 1H, $J = 12.0$ Hz), 3.70–3.90 (m, 4H), 4.06–4.20 (m, 2H), 4.30 (d, 1H, $J = 4.8$ Hz), 4.62 (d, 1H, $J = 9.6$ Hz), 5.95 (d, 1H, $J = 4.8$ Hz), 6.80 (d, 2H, $J = 9.6$ Hz), 7.45 (d, 2H, $J = 9.6$ Hz).