Highly Stereoselective Synthesis of 2,3-Unsaturated Thioglycopyranosides Employing Molecular Iodine

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Abstract: Molecular iodine has been utilized for the first time for the thioglycosidation of D-glycals with various thiols to afford the corresponding 2,3-unsaturated thioglycosides in high yields. In the case of tri-*O*-acetyl-D-glucal, the α-anomer was obtained exclusively. The use of readily available iodine makes this method quite simple, more convenient, and practical.

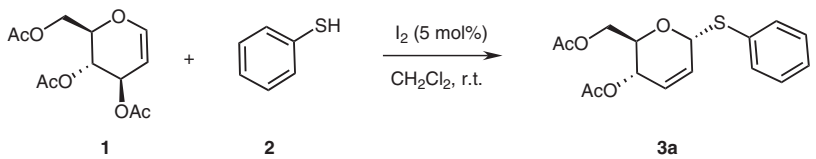
Key words: glycals, iodine, thioglycosides, thia-Ferrier rearrangement

Thioglycosides are important chiral building blocks for the synthesis of various biologically active natural products.[1] Thioglycosides are used as glycosyl donors as they are stable under mild acidic or basic conditions and can be selectively activated by thiophilic reagents.[2] They are usually prepared by the reaction of glycals with thiols in the presence of acid catalysts. The acid-catalyzed allylic rearrangement of glycals in the presence of alcohols or thiols is known as Ferrier rearrangement, which is widely used to prepare 2,3-unsaturated glycosides.[3] The reaction, as originally reported by Ferrier, involves intermediacy of a cyclic allylic oxocarbenium ion to which the nucleophile adds preferentially in quasi-axial orientation. Consequently, there have been some reports on the preparation of thioglycosides using Lewis acids such as $SnCl_4$,[4] $BF_3{\cdot}OEt_2$,[5] $LiBF_4$,[6] and $Sc(OTf)_3$.[7] However, many of these reagents are corrosive, moisture sensitive, and are required in stoichiometric amounts. Use of these reagents also lead to poor regioselectivity[4,5] and hence low yields due to the formation of mixture of products containing 3-thioglycals[4] and 1,3-dithioadducts.[5]

Recently, molecular iodine has gained importance as a low-cost, nontoxic, and readily available catalyst for various organic transformations affording the corresponding products with high selectivity in excellent yields.[8] The mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to perform several organic transformations using stoichiometric levels to catalytic amounts. Owing to advantages associated with this eco-friendly catalyst, molecular iodine has been explored as a powerful reagent in organic synthesis.[9]

In continuation of our interest on the use of molecular iodine for various organic transformations,[10] we herein report an efficient and practical method for the thiaglycosidation of glycals with thiols in dichloromethane using a catalytic amount of molecular iodine under mild conditions. Accordingly, treatment of tri-*O*-acetyl-D-glucal **1** with thiophenol (**2**) in the presence of 5 mol% of molecular iodine gave the 1-phenylthio-2,3-unsaturated glycoside **3a** in 85% yield (Scheme 1).

Similarly, various aryl and alkyl thiols reacted well with tri-*O*-acetyl-D-glucal to furnish the aryl and alkyl 2,3-unsaturated thioglycosides in high yields. It is of interest to note that α-anomer was exclusively obtained in this reaction (Table 1, entries **b**–**g**). In the case of propane-1,3-dithiol, monothioglycoside was obtained instead of dithioglycoside (Table 1, entry **g**). The reaction is highly stereoselective affording α-anomer exclusively with tri-acetyl glucal (Table 1, entries **a**–**g**). However, thioglycosidation of 3,4,6-tri-*O*-methyl-, 3,4,6-tri-*O*-benzyl-, and 3,4,6-tri-*O*-allyl-D-glucal with thiols gave the products in good yields, but with low selectivity when compared to acylated analogues. The predominant formation of α-anomer in the thiaglycosidation must arise from the thermodynamic anomeric effect.[11] The amount of the α-anomer increased with long reaction time because the configuration at the anomeric position isomerizes due to the exposure of the product to the acidic conditions. The ratio of α and β-anomers was determined on the basis of integrated ratios of anomeric hydrogens in the ^1H NMR



1 2 3a

Scheme 1 Reaction between glucal **1** and thiophenol (**2**)

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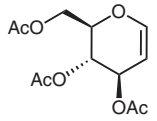
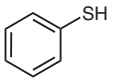
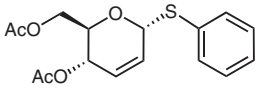
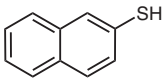
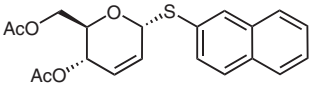
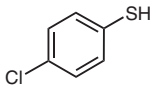
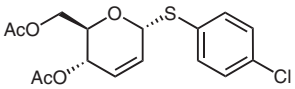
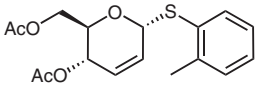
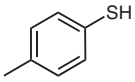
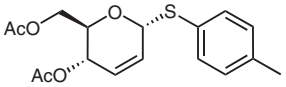
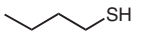
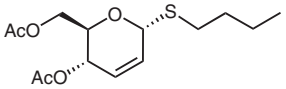
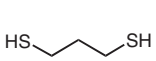
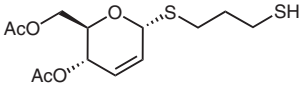
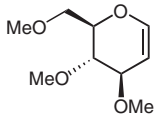
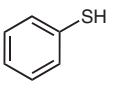
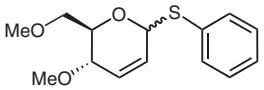
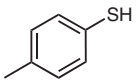
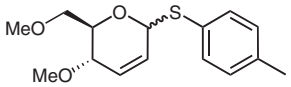
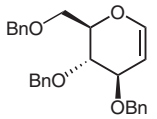
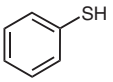
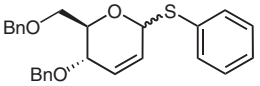
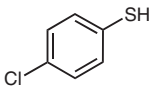
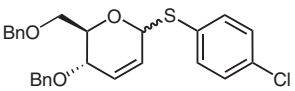
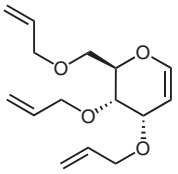
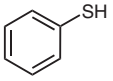
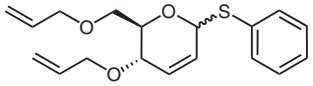
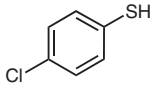
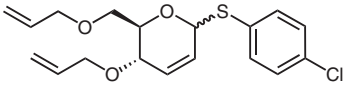
spectrum of the product and also by isolation of pure isomers on column chromatography. The configuration of the products was assigned by comparison of their spectral data with authentic compounds.[4] The spectroscopic data of the products was identical with the data reported in the literature. The results are summarized in Table 1. The scope and generality of the reaction is illustrated with respect to various thiols and glycals. This method offers significant advantages such as high yields, short reaction times, high α-selectivity, and mild conditions over classi-

Table 1 Iodine-Catalyzed Thioglycosidation of Glycals

Entry	Glycal	Thiol	Product	Time (min)	Yield (%)[a]	Ratio of α/β anomers[b]
a				20	85	–
b				20	80	–
c				15	90	–
d				15	85	–
e				15	89	–
f				20	80	–
g				20	71	–
h				25	80	9:1
i				25	83	9:1
j				30	70	4:1
k				30	75	4:1
l				25	80	5:1
m				25	82	5:1

[a] Yield refers to pure products after chromatography.
[b] Ratio was determined on the basis of the integrated ratios of the anomeric hydrogens in the ^{1}H NMR spectra and also by isolation of pure isomers by column chromatography.

cal thia-Ferrier conditions. No 3-thioglycals and 1,3-dithioadducts were formed under these reaction conditions, which are normally observed with a stoichiometric amount of either $BF_3{\cdot}OEt_2$ or $SnCl_4$.

In conclusion, iodine has proved to be an effective catalyst for the synthesis of thioglycosides from glycals and thiols by means of thia-Ferrier rearrangement. The method has advantages of mild reaction conditions, high conversions, short reaction times, remarkable selectivity, and simple experimental/workup procedures, which makes it a useful and alternative process for the synthesis of thioglycosides.

Melting points were recorded on a Büchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR and ^{13}C spectra were recorded on Gemini-200 spectrometer (200 MHz) in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. Column chromatography was performed using E. Merck 100–200 mesh silica gel.

Thioglycoside 3a; Typical Procedure

A mixture of 3,4,6-tri-*O*-acetyl-D-glucal (**1**; 272 mg, 1 mmol), thiophenol (**2**; 108 mg, 1 mmol), and I_2 (20 mg, 5 mol%) in CH_2Cl_2 (15 mL) was stirred at r.t. for 0.5 h. After complete conversion, as indicated by TLC, the mixture was diluted with sat. aq $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc–hexane, 2:8) to afford the pure thioglycoside **3a** as a solid; yield: 320 mg (85%); mp 58–60 °C.

IR (KBr): 3458, 3059, 2926, 1742, 1581, 1475, 1440, 1372, 1232, 1124, 1046, 975, 899, 784, 745 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.52–7.47 (m, 2 H), 7.31–7.24 (m, 3 H), 6.05 (dt, *J* = 2.4, 10.3 Hz, 1 H), 5.85 (dt, *J* = 1.5, 10.3 Hz, 1 H), 5.74–5.70 (m, 1 H), 5.37–5.32 (m, 1 H), 4.43 (td, *J* = 2.4, 6.3 Hz, 1 H), 4.27 (dd, *J* = 6.3, 11.8 Hz, 2 H), 2.11 (s, 3 H), 2.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 170.2, 134.8, 132.6, 129.8, 128.9, 128.7, 128.5, 127.6, 127.1, 83.6, 67.3, 65.4, 63.2, 63.0, 20.9.

ESI-MS: *m*/*z* = 345 (M + Na)$^+$.

HRMS: *m*/*z* calcd for $C_{16}H_{18}O_5S$ + Na: 345.0772; found: 345.0762.

3b

Solid.

IR (KBr): 2926, 1744, 1644, 1587, 1500, 1369, 1056, 947, 854, 784, 635 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.70 (m, 4 H), 7.3–7.40 (m, 3 H), 6.40 (d, *J* = 6.0 Hz, 1 H), 5.10 (dd, *J* = 4.5 Hz, 1 H), 4.90 (t, *J* = 5.2 Hz, 1 H), 4.30–4.40 (m, 3 H), 4.25 (dt, *J* = 4.5, 2.2 Hz, 1 H), 2.04 (s, 3 H), 2.02 (s, 3 H).

ESI-MS: *m*/*z* = 372 (M + Na)$^+$, 395.

3c

Liquid.

IR (neat): 2925, 1743, 1477, 1437, 1231, 1086, 1055, 976, 905, 785, 649 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.49 (d, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 5.90–6.00 (m, 1 H), 5.83–5.89 (m, 1 H), 5.29–5.37 (m, 1 H), 5.65–5.68 (m, 1 H), 4.39 (q, *J* = 4.3 Hz, 1 H), 4.22 (d, *J* = 4.3 Hz, 2 H), 2.11 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.15, 169.78, 133.95, 133.40, 132.96, 129.10, 128.17, 128.13, 83.65, 67.47, 65.01, 62.90, 20.93, 20.73.

ESI-MS: *m*/*z* = 356 (M$^+$), 321, 245, 214, 154, 112, 83, 43.

3d

Liquid.

IR (neat): 2928, 2190, 1749, 1646, 1565, 1499, 1451, 1370, 1239, 1052, 809, 780, 656 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (m, 1 H), 7.14 (m, 3 H), 6.09–6.06 (m, 1 H), 5.88–5.82 (m, 1 H), 5.72–5.69 (m, 1 H), 4.42–4.35 (m, 1 H), 4.32–4.23 (m, 1 H), 4.16 (d, *J* = 2.0 Hz, 1 H), 2.42 (s, 3 H), 2.11 (s, 3 H), 2.03 (s, 3 H).

LC-MS: *m*/*z* = 336 (M + Na)$^+$, 359.

3e

Liquid.

IR (neat): 2925, 2090, 1741, 1641, 1492, 1451, 1370, 1231, 1052, 809, 780 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ = 7.35 (d, *J* = 7.5 Hz, 2 H), 7.08 (d, *J* = 7.5 Hz, 2 H), 6.01–6.06 (m, 1 H), 5.80–5.84 (m, 1 H), 5.61–5.64 (m, 1 H), 5.30–5.35 (m, 1 H), 4.38– 4.44 (m, 1 H), 4.16–4.27 (m 2 H), 2.34 (s, 3 H), 2.11 (s, 3 H), 2.07 (s, 3 H).

ESI-MS: *m*/*z* = 336 (M + Na)$^+$, 359.

3f

Liquid.

IR (neat): 2958, 2928, 2869, 1744, 1645, 1455, 1370, 1233, 1050, 975, 905, 792 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.96–5.87 (m, 1 H), 5.77–6.72 (m, 1 H), 5.48 (br s, 1 H), 5.33–5.28 (m, 1 H), 4.27–4.11 (m, 3 H), 2.76–2.56 (m, 2 H), 2.08 (s, 6 H), 1.68–1.58 (m, 2 H), 1.49–1.37 (m, 2 H), 0.94 (t, *J* = 7.6 Hz, 3 H).

ESI-MS: *m*/*z* = 325 (M + Na)$^+$.

HRMS: *m*/*z* calcd for $C_{14}H_{22}O_5S$ + Na: 325.1085; found: 325.1088.

3g

Liquid.

IR (neat): 2926, 1743, 1649, 1372, 1222, 1103, 1042 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.90 (dt, *J* = 1.5, 10.1 Hz, 1 H), 5.76 (dt, *J* = 1.5, 10.1 Hz, 1 H), 5.51–5.47 (m, 1 H), 5.35–5.25 (m, 1 H), 4.25 (t, *J* = 4.6 Hz, 1 H), 4.19 (dd, *J* = 3.1, 9.3 Hz, 2 H), 1.95–1.97 (m, 2 H), 2.88–2.58 (m, 4 H), 2.09 (s, 6 H), 1.27 (t, *J* = 7.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.0, 189.7, 148.3, 146.4, 118.1, 100.0, 96.5, 93.5, 84.4, 53.0, 49.1, 40.3, 20.5.

ESI-MS: *m*/*z* = 343 (M + Na)$^+$.

HRMS: *m*/*z* calcd for $C_{13}H_{20}O_5S_2$ + Na: 343.0649; found: 343.0648.

3h

Liquid.

IR (neat): 3054, 2962, 2822, 1581, 1472, 1384, 1313, 1193, 1106, 974, 848, 782 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.51–7.45 (m, 2 H), 7.27–7.16 (m, 3 H), 6.02–5.89 (m, 1 H), 5.69–5.65 (m, 1 H), 4.11 (dd, *J* = 2.2, 4.4 Hz, 1 H), 4.15–4.07 (m, 1 H), 3.90–3.86 (m, 1 H), 3.64–3.58 (m, 2 H), 3.38 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.7, 131.2, 128.7, 128.5, 128.2, 127.0, 96.1, 84.0, 81.7, 72.2, 71.5, 69.2, 56.2, 29.7.

ESI-MS: *m*/*z* = 289 (M + Na)$^+$.

HRMS: *m*/*z* calcd for $C_{14}H_{18}O_3S$ + Na: 289.0874; found: 289.0871.

3i
Liquid.

IR (neat): 2926, 2822, 1730, 1588, 1463, 1382, 1314, 1193, 1110, 1051, 975, 949, 849, 782, 749, 711, 527 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.51–7.60 (m, 1 H), 7.08–7.13 (m, 3 H), 5.94–6.05 (m, 2 H), 5.68–5.70 (m, 1 H), 4.07–4.13 (q, *J* = 2.6 Hz, 1 H), 3.93–3.97 (t, *J* = 1.5 Hz, 1 H), 3.54–3.60 (d, *J* = 3.7 Hz, 2 H), 3.42 (s, 3 H), 3.30 (s, 3 H), 2.30 (s, 3 H).

ESI-MS: *m*/*z* = 280 $(M + Na)^+$, 303.

3j
Liquid.

IR (neat): 3030, 2919, 2862, 1725, 1645, 1493, 1452, 1371, 1306, 1206, 1179, 1080, 1023, 949, 849, 809, 780, 738, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.3 Hz, 2 H), 6.99–7.10 (d, *J* = 8.3 Hz, 2 H), 7.23–7.30 (m, 10 H), 5.95–5.97 (m, 1 H), 5.62–5.63 (m, 1 H), 4.50–4.58 (m, 2 H), 3.75–3.72 (m, 2 H), 2.31 (s, 3 H).

ESI-MS: *m*/*z* = 422 $(M + H)^+$, 455.

3k
Liquid.

IR (neat): 2920, 2865, 1763, 1678, 1532, 1521, 1470, 1078, 932, 742, 698, 535 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.48–7.45 (m, 1 H), 7.41 (d, *J* = 7.9 Hz, 2 H), 7.3–7.20 (m, 10 H), 7.13 (d, *J* = 7.9 Hz, 2 H), 5.96 (dt, *J* = 10.1, 1.4 Hz, 2 H), 5.67–5.60 (m, 1 H), 4.60–4.40 (m, 5 H), 3.71 (d, *J* = 3.6 Hz, 2 H).

LC-MS: *m*/*z* = 452.5 $(M + Na)^+$, 475.5.

3l
Liquid.

IR (neat): 2924, 2855, 1743, 1646, 1544, 1549, 1458, 1089, 922, 741, 693, 585 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.50–7.30 (m, 2 H), 7.27–7.20 (m, 3 H), 5.91–5.70 (m, 3 H), 5.60 (d, *J* = 5.1 Hz, 1 H), 5.30–5.10 (m, 3 H), 4.00–3.90 (m, 6 H), 3.70–3.20 (m, 2 H).

LC-MS: *m*/*z* = 318 $(M + Na)^+$, 341.

3m
Liquid.

IR (neat): 2958, 2924, 2854, 2362, 1736, 1646, 1459, 1375, 1270, 1081, 996, 922, 770 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 6.7 Hz, 2 H), 7.23 (d, *J* = 6.7 Hz, 2 H), 5.76–6.02 (m, 6 H), 5.63–5.65 (m, 1 H), 5.16–5.30 (m, 4 H), 3.96–4.22 (m, 6 H), 3.60 (d, *J* = 3.0 Hz, 2 H).

ESI-MS: *m*/*z* = 352 $(M + Na)^+$, 375.

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