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$InCl_3$-catalyzed stereoselective synthesis of *C*-glycosyl heteroaromatics

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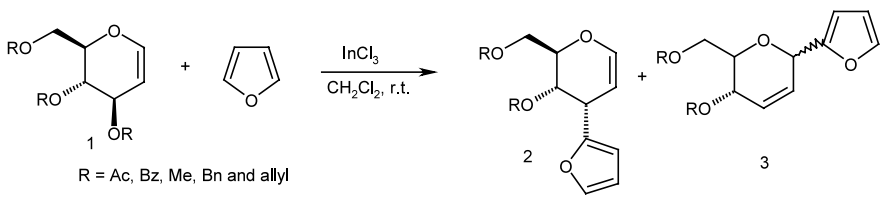
Abstract—Glycals react smoothly with furan in the presence of a catalytic amount of indium trichloride at ambient temperature to afford predominantly the *C*-3-substituted glycals in high yields. Other heteroaromatics including 2-benzyloxymethylfuran, thiophene and *N*-Boc protected indole afford exclusively *C*-1-glycosides in good yields with high β-selectivity under similar reaction conditions.

C-Glycosidation is an important transformation for the introduction of a carbon chain into sugars.[1] *C*-Glycosides bearing carbon-linked heterocyclics have attracted much synthetic interest because of their potential antiviral and antitumour activities.[2] Particularly, glycosyl furans are useful precursors for the synthesis of many *C*-glycosyl antibiotics.[3] Generally, *C*-glycosides are conveniently prepared from glycals. Glycals are ambident electrophiles capable of reacting at either *C*-1 or *C*-3 positions with nucleophiles either directly or via the intermediacy of a Ferrier rearrangement product.[4] Glycals are known to react with various nucleophiles[5–7] such as alcohols, thiols, silyl nucleophiles and malonates under the influence of either acids or oxidants to produce 2,3-unsaturated glycosides. Acid-catalyzed reactions of furan and pyrrole are limited and require careful control of the acidity to prevent side reactions. To date, acid-catalyzed reactions of furan and pyrrole remain a challenge for synthetic chemists because they tend to polymerize under most reaction conditions. As such, there are no reports on the *C*-glycosidation of glycals with such heterocycles. In recent years, $InCl_3$ has emerged as a mild Lewis acid for a variety of organic transformations.[8] Compared to conventional Lewis acids, indium trichloride has advantages of water stability, reusability and simplicity in operation. In addition, $InCl_3$ is found to be an efficient catalyst in promoting Ferrier rearrangement of glycals with alcohols.[9]

We wish to report a simple and efficient protocol for the *C*-glycosidation of glycals with furan, pyrrole, indole and thiophene using a catalytic amount of $InCl_3$. Thus, treatment of 3,4,6-tri-*O*-acetyl or benzoyl-D-glucal with furan in the presence of 10 mol% $InCl_3$ in dichloromethane at ambient temperature resulted in the formation of product **2** together with a trace amount of **3** (Scheme 1).



Scheme 1.

Keywords: indium reagents; glycals; *C*-glycosides; heteroaromatics.
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The products **2** and **3** were easily separated on silica gel column chromatography. Interestingly, the reaction of 3,4,6-tri-*O*-benzyl or methyl or allyl-D-glucal with furan or pyrrole gave exclusively *C*-3-adducts **2** without the formation of **3** under the reaction conditions. In all cases, the *C*-3-substituted glycals were obtained with inversion of configuration at the *C*-3-position in the glucal as confirmed by NOESY spectral analysis. The stereochemistry of product **2a** (Fig. 1) was established by detailed ^{1}H NMR and NOESY studies. The coupling constants $J_{H2-H3}=5.9$, $J_{H3-H4}=5.9$, $J_{H4-H5}=9.8$ Hz, are consistent with the proposed twist conformation with H4 and H5 each being axial. The structure is further supported by the presence of NOE cross peaks between H5–furan H(a), H3–H4, H6 and H6′ to furan H(a) in the NOESY spectrum.

Similarly in **2d** the six-membered pyranoside ring takes up a twist conformation with H4 and H5 axial, which is further confirmed by the large coupling constant for $J_{H4-H5}=9.3$ Hz and the presence of NOE cross peaks between H5–furan–H(a), H2–H3 and H6–furan–H(a) in the NOESY spectrum.

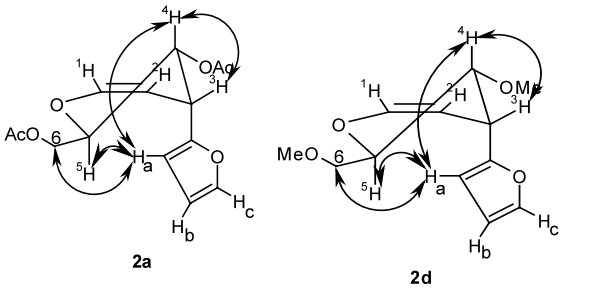


Figure 1. Important NOE's of compounds **2a** and **2d**.

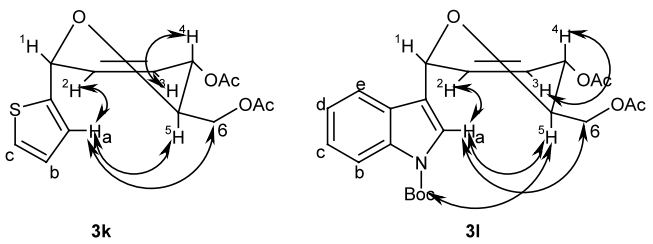
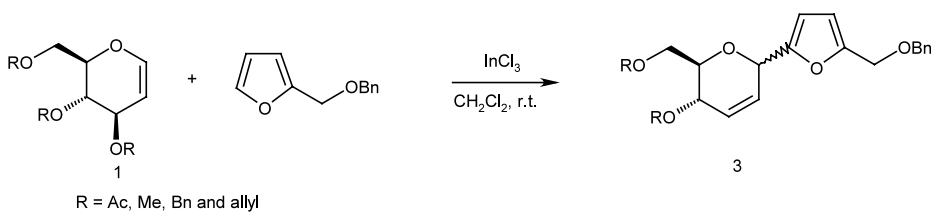


Figure 2. Important NOE's of compounds **3l** and **3k**.

Furthermore, *N*-Boc protected indole and thiophene gave the corresponding *C*-1-glycosides in good yields with high β-selectivity. In product **3k** (Fig. 2), the small coupling constants $J_{H1-H2}=1.9$, and $J_{H3-H4}=1.8$ Hz, and the large coupling constant $J_{H4-H5}=8.5$ Hz, are consistent with a twist conformation of the sugar six-membered ring with H4 and H5 each being axial, which is further supported by the presence of NOE cross peaks between H5–thiophene H(a), H2–thiophene H(a) and H3–H4 in the NOESY spectrum. The conformation of the pyranoside six-membered ring in the product **3l** is a twist conformation which is consistent with the coupling constants $J_{H4-H5}=8.8$, $J_{H3-H4}=1.8$ and $J_{H1-H2}=1.5$ Hz; the structure was further confirmed by the presence of NOE cross peaks between Ha indole–H5, Boc–H5, Ha–indole–H6 and H3–H4 in the NOESY spectrum. Similarly, 2-benzyloxymethylfuran reacted well with D-glycals to afford the corresponding *C*-1-derivatives **3f–i** in high yields with high β-selectivity (Scheme 2).

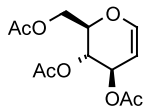
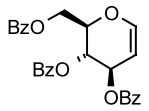
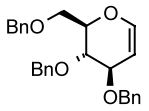
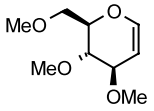
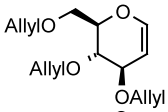
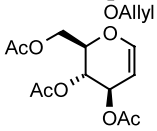
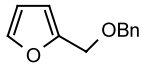
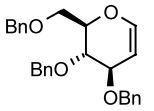
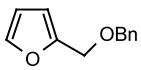
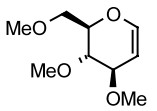
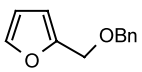
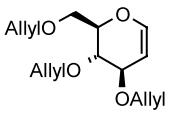
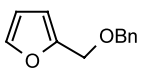
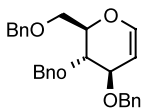
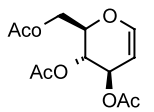
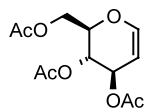
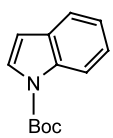
The selectivity for the formation of the β-isomer at C(1) is consistent with previous observations.[10] However, the coupling of furan and pyrrole with glycals proceeds with inversion of configuration at the *C*-3 position. The major *C*-3-adduct was obtained as the α-epimer, which was confirmed by comparison with the spectroscopic data reported in the literature for *C*-3-substituted glycals.[11] The reactions are faster with furan and 2-benzyloxymethylfuran whereas thiophene, indole and pyrrole took longer for achieve complete conversion. Several examples illustrating this simple and efficient procedure for the synthesis of *C*-3-substituted glycals are listed in Table 1.[12]

In summary, we have developed a novel and efficient protocol for the synthesis of a new class of sugar derivatives, *C*-3-substituted glycals using catalytic amount of $InCl_3$. In addition to its simplicity, high efficiency and mild reaction conditions, this method provides an easy access to *C*-3-substituted glycals, which makes it a useful and attractive process for the synthesis of *C*-glycosyl heteroaromatics.



Scheme 2.

Table 1. $InCl_3$-catalyzed *C*-glycosidation of D-glycals with heteroaromatics

entry	Glycal	nucleophile	Product[a]	Time(h)	Yield(%)[b]
a			**2a** **3a**	3.5	85 15
b			**2b** **3b**	4.0	80 10
c			**2c**	1.5	92
d			**2d**	1.0	94
e			**2e**	2.0	84
f			**3f**	4.0	90
g			**3g**	2.5	87
h			**3h**	2.0	85
i			**3i**	2.5	89
j			**2j**	8.0	65
k			**3k**	8.0	68 c
l			**3l**	10.0	70 c

a) All products were characterized by ^1H & ^{13}C NMR spectra.
b) Isolated and unoptimized yields.
c) 5-10% of the α-isomer was also observed by ^1HNMR.

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12. *Experimental procedure*: A mixture of glycal (5 mmol), nucleophile (7 mmol) and $InCl_3$ (10 mol%) in dichloromethane (15 mL) was stirred for an appropriate time (Table 1). After complete conversion as monitored by TLC, the reaction mixture was diluted with water and extracted with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure product.

Compound **2a**: Liquid, $[\alpha]_D$ 171.4 (*c*, 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, $J=2.4$, 1H, *H*c), 6.52 (dd, $J=1.8$, 5.9, 1H, *H*1), 6.33 (dd, $J=2.4$, 3.3, 1H, *H*b), 6.13 (d, $J=3.3$, 1H, *H*a), 5.06 (dd, $J=5.9$, 9.8, 1H, *H*4), 4.81 (t, $J=5.9$, 1H, *H*2), 4.30 (m, 2H, -CH_2O), 4.15 (ddd, $J=3.1$, 4.3, 9.8, 1H, *H*5), 4.02 (dt, $J=1.8$, 5.9, 1H, *H*3), 2.09 (s, 3H, COCH_3), 1.98 (s, 3H, COCH_3). ^{13}C NMR ($CDCl_3$, proton decoupled): δ 20.6, 33.8, 62.5, 67.7, 70.8, 98.3, 108.9, 110.1, 142.4, 143.9, 153.3, 169.7, 170.6.

Compound **2d**: Liquid, $[\alpha]_D$ 188.2 (*c*, 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, $J=1.8$, 1H, *H*c), 6.49 (dd, $J=1.4$, 5.8, 1H, *H*1), 6.33 (dd, $J=1.8$, 3.1, 1H, *H*b), 6.13 (d, $J=3.1$, 1H, *H*a), 4.75 (t, $J=5.8$, 1H, *H*2), 3.99 (ddd, $J=2.4$, 5.2, 9.3, 1H, *H*5), 3.87 (dt, $J=1.4$, 5.8, 1H. *H*3), 3.68 (dd, $J=5.2$, 10.6, 1H, H6′), 3.66 (dd, $J=5.8$, 9.3, 1H, *H*4), 3.63 (dd, $J=5.2$, 10.6, 1H, *H*6), 3.47 (s, 3H, OMe), 3.41 (s, 3H, OMe). ^{13}C NMR ($CDCl_3$, proton decoupled): δ 33.5, 57.4, 59.4, 71.5, 73.2, 75.2, 97.9, 108.9, 108.4, 110.1, 141.9, 144.0, 154.5.

Compound **3k**: Liquid, $[\alpha]_D$ 188.2 (*c*, 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, $J=8.0$, 1H, Hc), 7.02 (t, $J=8.0$, 1H, Hb), 7.03 (d, $J=7.8$, 1H, Ha), 6.20 (ddd, $J=1.8$, 3.5, 10.3, 1H, H2), 5.95 (dt, $J=1.9$, 10.3, 1H, H3), 5.53 (d, $J=1.8$, 1H, H1), 5.35 (dq, $J=1.8$, 8.5, 1H, H4), 4.22 (m, 1H, H6), 4.12 (m, 1H, H6′), 3.87 (ddd, $J=2.7$, 5.5, 8.5, 1H, H5), 2.06 (s, 3H, COCH_3) 2.10 (s, 3H, COCH_3).

Compound **3l**: Liquid, $[\alpha]_D$ 60.5 (*c*, 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, $J=7.9$, 1H, *H*e), 7.80 (d, $J=7.8$, 1H, *H*b), 7.50 (s, 1H, *H*a), 7.35 (t, $J=8.2$, 1H, *H*d), 7.25 (t, $J=8.2$, 1H, *H*c), 6.26 (ddd, $J=1.5$, 3.0, 10.2, 1H, *H*2), 6.00 (dt, $J=1.8$, 10.2, 1H, *H*3), 5.58 (d, $J=1.5$, 1H, *H*1), 5.37 (dt, $J=1.8$, 8.8, 1H, *H*4), 4.24 (dd, $J=6.4$, 12.1, 1H, *H*6), 4.02 (dd, $J=2.8$, 12.1, 1H, *H*6′), 3.80 (ddd, $J=2.8$, 6.4, 8.8, 1H, *H*5), 1.93 (s, 3H, COCH_3), 2.08 (s, 3H, COCH_3), 1.69 (s, 9H, Boc). ^{13}C NMR ($CDCl_3$, proton decoupled): δ 20.6, 28.1, 29.3, 34.1, 65.3, 63.6, 68.0, 70.2, 84.1, 115.3, 118.5, 120.3, 122.7, 124.0, 124.6, 125.2, 126.3, 129.2, 130.3, 131.7, 135.7, 149.5, 170.4, 170.8.