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First example of the carbon-Ferrier rearrangement of glycals with isocyanides: a novel synthesis of *C*-glycosyl amides

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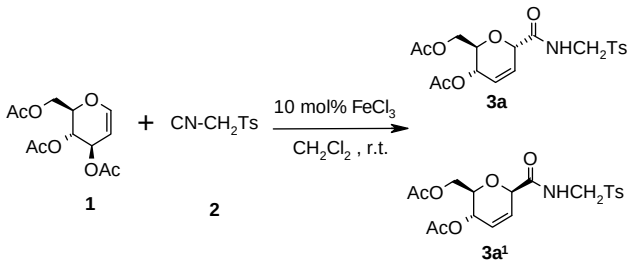
ABSTRACT

Glycals undergo smooth carbon-Ferrier rearrangement with isocyanides in the presence of a catalytic amount of $FeCl_3$ under mild reaction conditions to provide *C*-glycosyl amides in good yields with high α-selectivity. The use of $FeCl_3$ makes this method simple, convenient and cost-effective. This is the first report on carbon-Ferrier rearrangement using isonitriles as nucleophiles.

C-Glycosidation is an important tool for the synthesis of optically active compounds, since it allows the introduction of carbon chains to sugar chirons and the use of sugar nuclei as chiral pool reagents as well as carbon sources.[1] C-Glycosides are versatile chiral building blocks for the synthesis of many biologically interesting natural products such as palytoxin, spongistatin, halichondrin, and many others.[2] The discovery of naturally occurring C-nucleosides with important pharmacological properties gave impetus to synthetic efforts for preparing active carbohydrate analogs.[3] In addition, C-glycosides are potential inhibitors of carbohydrate-processing enzymes, and they are stable analogs of glycans involved in important intra- and inter-cellular processes.[4] Of these C-glycosides, 2,3-unsaturated glycosides (pseudoglycals) are versatile synthetic intermediates and also constitute the structural units of several antibiotics.[5] Pseudoglycals are traditionally obtained by an acid-catalyzed allylic rearrangement of glycals in the presence of nucleophiles, a reaction known as the Ferrier rearrangement.[6] Lewis acids are known to promote C-glycosidation with various nucleophiles such as allyltrimethylsilane, trimethylsilylcyanide, and alkynylsilanes.[7–9] However, there have been no reports on the allylic nucleophilic substitution of glycals (S_N2') with isocyanides to produce *C*-glycosyl amides.[10]

In continuation of our interest on glycosidation, we disclose a versatile approach for the preparation of *C*-glycosyl amides from glucal and isonitriles by means of a carbon-Ferrier rearrangement. Initially, we attempted the Passerini-type coupling of an isonitrile, a carboxylic acid, and a glycal instead of a carbonyl compound to produce ω-hydroxy carboxamides. Surprisingly, we observed the formation of glycosyl amides instead of open-chain hydroxyl amides. This provided incentive for an extensive study. Initially, we examined the reaction of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) with tosylmethylisocyanide (**2**, Tosmic) in the presence of 10 mol % of $FeCl_3$. The reaction was complete within 30 min, and the desired product was obtained in 92% yield as a mixture of α-**3a** and β-**3b** anomers in a 9:1 ratio favoring α-anomer **3a** (Scheme 1).

Similarly, various other D-glucal derivatives such as 3,4,6-tri-*O*-benzoyl-, 3,4,6-tri-*O*-benzyl-, 3,4,6-tri-*O*-methyl-, and 3,4,6-tri-*O*-allyl-D-glucal reacted effectively with isonitriles to produce the corresponding C-glycosides in good yields (Table 1, entries **b**–**k**). The reaction was also effective with the TBS derivative of D-glucal without affecting the TBS functionality (Table 1, entries **l** and **m**). This method is applicable for both ester and ether derivatives of D-glucal. In each case, the α-anomer was obtained predominantly. The ratio of anomers was determined by ^1H NMR spectroscopy of



Scheme 1.

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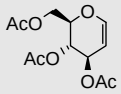
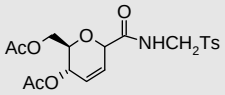
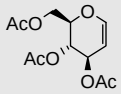
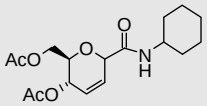
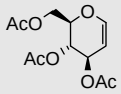
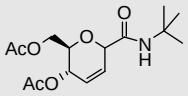
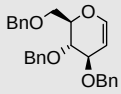
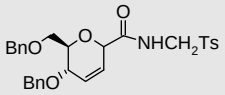
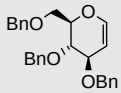
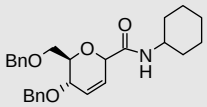
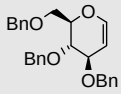
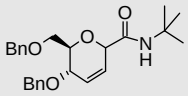
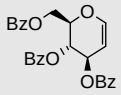
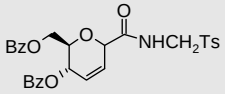
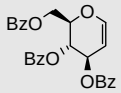
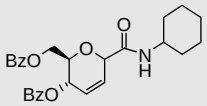
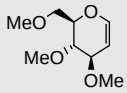
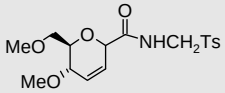
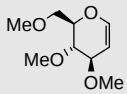
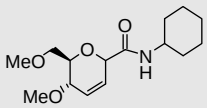
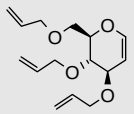
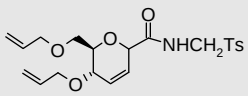
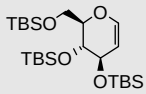
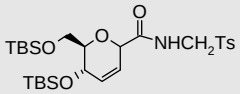
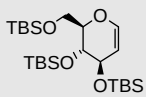
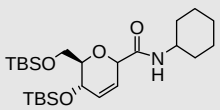
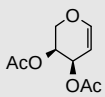
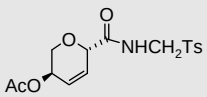
Table 1
$FeCl_3$-catalyzed Ferrier rearrangement of glycals with isocyanides

Entry	Glucal	Isonitrile	Product[a]	Time (min)	Yield[b] (%)	Ratio[c] (α:β)
a		Tosmic		30	92	9:1
b				30	85	9:1
c				50	75	9:1
d		Tosmic		35	90	9:1
e				45	85	6:1
f				56	70	9:1
g		Tosmic		30	85	9:1
h				45	80	9:1
i		Tosmic		25	90	9:1
j				30	85	6:1
k		Tosmic		45	75	9:1
l		Tosmic		50	70	9:1
m				40	65	7:1
n		Tosmic		30	89	—

[a] All products were characterized by NMR, IR, and the mass spectrometry.
[b] Yield refers to pure products after chromatography.
[c] Ratio was determined from the ^1H NMR spectrum of crude product.

the crude products obtained in the C-glycosidation. The predominant formation of the α-anomer may be explained by electronic effects on the oxocarbenium intermediate involved in this transformation. Kinetically preferred axial addition of the carbon nucleophile was observed in most cases.[11] The structures of **3a** and **3a′** were thoroughly studied by various NMR techniques including 1D ^{1}H NMR, homo-nuclear decoupling, double quantum filtered correlation spectroscopy (DQFCOSY), and nuclear Overhauser effect spectroscopy (NOESY). The spectral assignments were obtained from DQFCOSY experiments. Since the configurations at C2 and C3 are fixed, for the major isomer **3a**, the coupling constant between protons H2 and H3 ($^3J_{H2-H3}$ = 5.9 Hz) supports the equatorial disposition of H2 and H3, thereby implying axial orientation of the substituents at C2 and C3. The presence of NOE correlations between H1–H3 and H1–H6 suggest that all these three protons lie on the same side of the C3–C4–C5–C6 plane. These observations in turn indicate that the substituent at C6 is on the other side of this plane, which is additionally supported by the NOE correlation between NH and H2. The characteristic NOE's and energy-minimized structure of **3a** are shown in Figure 1.

For the minor isomer, a large coupling constant ($^3J_{H2-H3}$ = 9.2 Hz) between protons H2 and H3 indicates that they occupy axial positions in the six-membered ring. Further, the presence of a strong NOE correlation between H2 and H6 indicates that these protons occupy 1,3-diaxial positions, which in turn provides support for the equatorial orientation of all the three substituents on the ring. The characteristic NOE's and energy-minimized structure of **3a′** are shown in Figure 2.

Similarly, di-*O*-acetyl-L-arabinal also underwent the Ferrier-type rearrangement to produce *C*-glycosyl amide **3n** with α-selectivity.[12] The presence of strong correlations between H1′/H5 and H1/H2 and of medium correlations between H1′/H2 protons and the coupling constants $^3J_{H1-H2}$ = 5.2 and $^3J_{H1'-H2}$ = 7.4 Hz provides ample support for the structure shown in Figure 3, with substituents at C4 *trans* to the *O*-acetyl group at C1. The characteristic

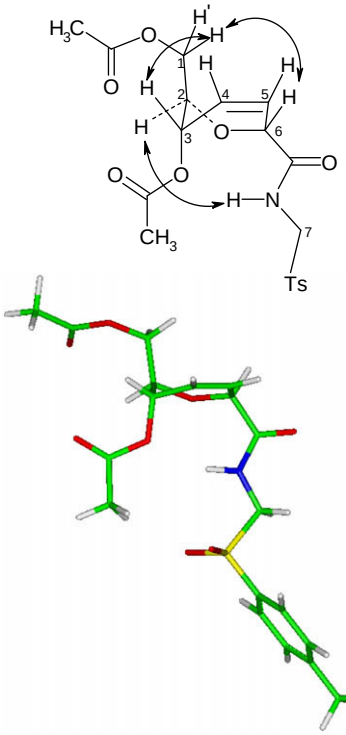


Figure 1. Characteristic NOE's and energy-minimized structure of **3a**.

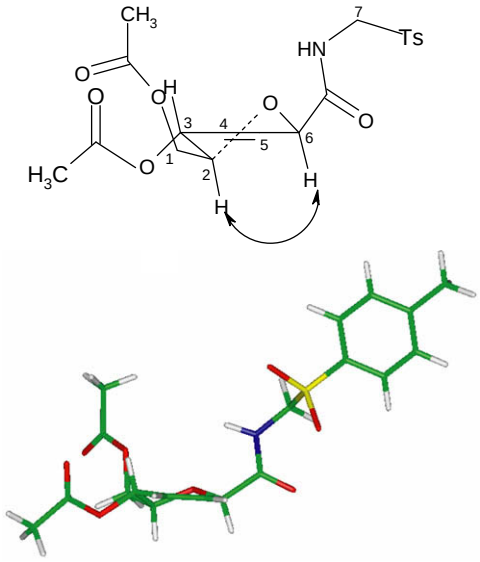


Figure 2. Characteristic NOE's and energy-minimized structure of **3a′**.

NOE's and energy-minimized structure of **3n** are shown in Figure 3.

The products were characterized by ^{1}H, ^{13}C NMR, and IR spectra and by mass spectrometry. In the absence of catalyst, no reaction was observed even after an extended reaction time (12 h). As solvent, Dichloro methane gave the best results. In all the cases, the reactions proceeded rapidly at room temperature under mild conditions. The reactions were clean, and no side products were detected under these conditions as determined from the NMR spectra of the crude products. There are several advantages in the use of $FeCl_3$ as catalyst for this transformation, which include high conversions, short reaction times and high α-selectivity. In addition, this method avoids the use of expensive reagents, and does not require any additives or stringent reaction conditions. This method is quite simple and convenient, affording the desired products in good yields.

The efficacy of various metal halides such as $FeCl_3$, $InBr_3$, $InCl_3$, $GaCl_3$, YCl_3, and $YbCl_3$ was studied for this transformation. Of these catalysts, $FeCl_3$ was found to be more effective in terms of conversion. For example, treatment of 3,4,6-tri-*O*-acetyl-D-glucal with Tosmic in the presence of 10 mol % $FeCl_3$ and 10 mol % $InCl_3$ over 30 min afforded 92% and 75% yields, respectively.

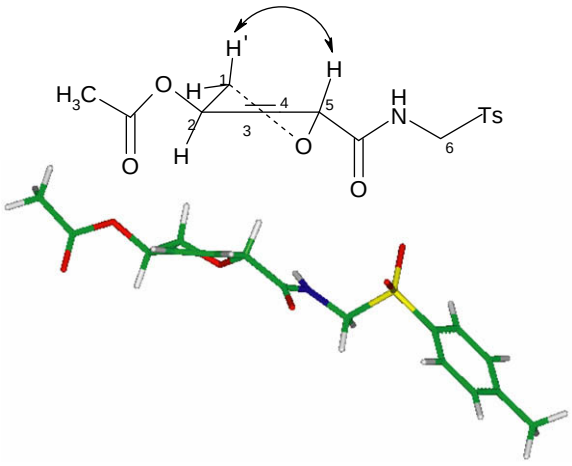
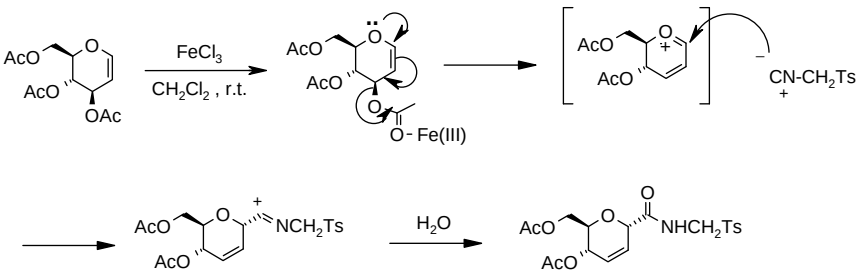


Figure 3. Characteristic NOE's and energy-minimized structure of **3n**.



Scheme 2. A plausible reaction mechanism.

The scope and generality of this process are illustrated with respect to various glucal derivatives and isonitriles, and the results are presented in Table 1.[13] Mechanistically, the reaction proceeds via an oxocarbenium ion intermediate by a Ferrier rearrangement. Subsequent axial attack of the isonitrile on the oxocarbenium ion would give a carbimminium intermediate which is probably hydrolyzed to the product amide (Scheme 2).

In summary, we have described a novel method for the synthesis of *C*-pseudoglycals from glycals and isonitriles using a catalytic amount of $FeCl_3$ under mild reaction conditions. This method provides high yields of *C*-glycosyl amides in short reaction times with high anomeric selectivity, which makes it a useful process for carbon–carbon bond formation at the anomeric position of sugars.

Acknowledgement

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12. For C-glycosides derived from di-*O*-acetyl-L-arabinal, the α-configuration corresponds to a *trans* relationship between the substituents at C1 and C4 (Table 1).
13. *Experimental procedure*: To a stirred solution of glucal triacetate (0.5 mmol) in Dichloro methane (2 mL) were added Tosmic (0.6 mmol) and $FeCl_3$ (10 mol %). The resulting mixture was stirred at room temperature for 30 min. After complete conversion as indicated by TLC, the reaction mixture was diluted with water and extracted with Dichloro methane (3 × 10 mL), and the combined organics were dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo, followed by purification on silica gel using hexane–ethyl acetate (3:1), afforded the pure *C*-glycosyl amide. Spectral data for selected products: *Major isomer* **3a**: $[\alpha]_D^{27}$ 11.6 (*c* 2.5, chloroform); IR (KBr): ν_{max}: 3393, 2924, 2853, 1740, 1694, 1597, 1513, 1453, 1372, 1322, 1232, 1143, 1084, 1045, 758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (m, 2H, Ar), 7.27 (t, *J* = 6.9 Hz, 1H, NH), 7.31 (m, 2H, Ar), 5.98 (ddd, *J* = 10.5, 3.0, 1.7 Hz, 1H, H4), 5.86 (dt, *J* = 10.4, ~2.9 Hz, 1H, H5), 5.06 (ddt, *J* = 5.9, 1.7, ~3.0 Hz, 1H, H3), 4.70 (dd, *J* = 13.9, 7.4 Hz, 1H, H7), 4.54 (q, *J* = ~2.8 Hz, 1H, H6), 4.51 (dd, *J* = 13.9, 6.4 Hz, 1H, H7′), 4.21 (dd, *J* = 11.9, 3.7 Hz, 1H, H1), 4.17 (dd, *J* = 11.9, 7.5 Hz, 1H, H1′), 3.90 (ddd, *J* = 7.5, 5.9, 3.7 Hz, 1H, H2), 2.46 (s, 3H, Me), 2.19 (s, 3H, OAc), 2.14 (s, 3H, OAc). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 170.1, 168.2, 145.5, 133.5, 129.9, 128.8, 127.6, 124.8, 72.8, 71.9, 64.0, 62.6, 59.6, 21.6, 20.8, 20.6. LC–MS: *m/z*: 448.0 (M+Na). HRMS calcd for $C_{19}H_{23}NO_8NaS$: 448.1015; found: 448.1012.
Minor isomer **3a′**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.72 (m, 2H, Ar), 7.31 (m, 2H, Ar), 7.23 (t, *J* = 6.6 Hz, 1H, NH), 5.80 (dt, *J* = 10.5, ~1.6 Hz, 1H, H4), 5.76 (dt, *J* = 10.5, ~1.6 Hz, 1H, H5), 5.28 (ddd, *J* = 9.2, 3.3, 1.6 Hz, 1H, H3), 4.73 (dd, *J* = 13.9, 7.4 Hz, 1H, H7), 4.56 (dt, *J* = 3.3, ~1.6 Hz, 1H, H6), 4.44 (dd, *J* = 13.9, 5.7 Hz, 1H, H7′), 4.31 (dd, *J* = 12.4, 2.6 Hz, 1H, H1), 4.25 (dd, *J* = 12.4, 5.2 Hz, 1H, H1′), 3.76 (ddd, *J* = 9.2, 5.2, 2.5 Hz, 1H, H2), 2.46 (s, 3H, Me), 2.17 (s, 3H, OAc), 2.10 (s, 3H, OAc).
Major isomer **3b**: $[\alpha]_D^{27}$ 49.8 (*c* 1.0, chloroform); IR (KBr) ν_{max}: 3408, 2929, 1715, 1656, 1515, 1455, 1374, 1346, 1177, 1068, 986, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.55 (d, *J* = 8.2 Hz, 1H), 5.92–5.81 (m, 2H), 5.12–5.05 (m. 1H), 4.63–4.59 (m, 1H), 4.22–4.10 (m, 2H), 3.95–3.85 (m, 1H), 2.16 (s, 3H), 2.10 (s, 3H), 1.98–1.10 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 170.2, 169.9, 145.0, 133.1, 73.0, 71.6, 64.3, 62.2, 47.0, 32.9, 25.3, 24.6, 20.8, 20.6. LC–MS: *m/z*: 362.0 (M+Na). HRMS calcd for $C_{17}H_{25}NO_6$ Na: 362.1579; found: 362.1591.
Major isomer **3d**: $[\alpha]_D^{20}$ −7.7 (*c* 1.13, chloroform); IR (KBr) ν_{max}: 3132, 2929, 2856, 2657, 1630, 1510, 1384, 1255, 1086, 835, 773, 699, 624 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.79–7.67 (m, 3H), 7.38–7.18 (m, 12H), 5.98–5.84 (m, 2H), 4.62–4.39 (m, 7H), 3.80–3.63 (m, 3H), 3.49 (dd, *J* = 9.8, 7.5 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 144.9, 137.5, 133.6, 129.6, 128.6, 128.3, 128.2, 127.6, 127.5, 127.3, 125.9, 125.3, 74.5, 73.3, 72.7, 70.6, 69.2, 68.7, 59.6, 21.4. LC–MS: *m/z*: 544.2 (M+Na). HRMS calcd for $C_{29}H_{31}NO_6NaS$: 544.1769; found: 544.1761.
Major isomer **3i**: $[\alpha]_D^{20}$ −28.4 (*c* 1.15, chloroform) IR (KBr) ν_{max}: 3350, 2989, 2930, 2826, 1693, 1596, 1514, 1456, 1396, 1322, 1144, 1087, 753 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75–7.70 (m, 3H), 7.30 (d, *J* = 8.3 Hz, 2H), 5.87–6.60 (m, 2H), 4.54–4.67 (m, 2H), 4.40–4.44 (m, 1H), 3.52–3.71 (m, 2H), 3.46 (s, 3H), 3.38 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 145.5, 133.4, 129.7, 128.7, 126.9, 125.4, 74.2, 72.6, 71.4, 71.2, 59.8, 59.2, 56.1, 21.5. LC–MS: *m/z*: 392.1 (M+Na). HRMS calcd for $C_{17}H_{23}NO_6NaS$: 392.1143; found: 392.1154.
Compound **3n**: $[\alpha]_D^{20}$ −136.7 (*c* 0.6 in chloroform); IR (KBr) $\nu_{(max)}$: 3344, 2927, 2857, 1734, 1693, 1596, 1515, 1372, 1322, 1238, 1144, 1086, 954, 815, 752 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.75 (m, 2H, Ar), 7.33 (m, 2H, Ar), 7.31 (t, *J* = 7.0 Hz, 1H, NH), 5.93 (dt, *J* = 10.5, ~1.7 Hz, 1H, H3), 5.76 (dt, *J* = 10.5, ~2.3 Hz, 1H, H4), 5.27(m, 1H, H2), 4.71 (dd, *J* = 14.2, 7.3 Hz, 1H, H6), 4.60 (dd, *J* = 14.2, 6.8 Hz, 1H, H7′), 4.50 (q, *J* ~ 2.3 Hz, 1H, H6), 4.17 (dd, *J* = 11.2, 5.2 Hz, 1H, H1), 3.60 (dd, *J* = 11.2, 7.4 Hz, 1H, H1′), 2.44 (s, 3H, Me), 2.09 (s, 3H, OAc). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 168.6, 145.4, 133.4, 129.9, 128.8, 128.1, 125.8, 73.7, 65.3, 63.6, 59.4, 21.6, 20.8. LC–MS: *m/z*: 376 (M+Na). HRMS calcd for $C_{16}H_{19}NO_6NaS$: 376.0830; found, 376.0828.