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Tris(pentafluorophenyl)borane catalyzed Ferrier azaglycosylation with sulfonamides and carbamates☆

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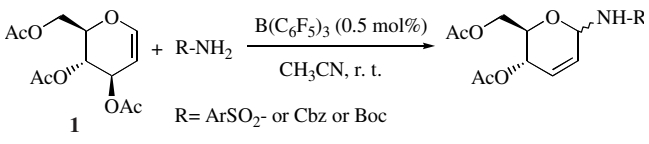
Abstract—The reaction of tri-*O*-acetyl-D-glucal with different nitrogen nucleophiles was effectively promoted by a catalytic amount of tris(pentafluorophenyl)borane for the first time in acetonitrile at room temperature to produce a variety of azapseudoglycals via Ferrier rearrangement in good yields and preferential anomeric selectivity.

Azaglycosylation is an important reaction in the synthesis of *N*-glycosides, due to the increasing importance of nucleosides having *N*-glycosidic linkages as pharmacological agents such as antibiotics, antineoplastic and antiviral compounds.[1] Among the *N*-glycosides, glycals having the double bond between C(2) and C(3) (*N*-pseudoglycals), represent a very important class of compounds because the double bond may be easily modified. Pseudoglycals are traditionally obtained by an acid catalyzed allylic rearrangement of glycals in the presence of nucleophiles, a reaction known as the Ferrier rearrangement.[2] Most of the Ferrier glycosylation reactions are known to occur with various nucleophiles such as carbon nucleophiles,[3] oxygen and/or sulfur nucleophiles[4] (alcohols and thiols) in the presence of acid catalysts. There are very limited reports of Ferrier rearrangement in the literature with nitrogen nucleophiles for the production of *N*-pseudoglycals where generally an azide nucleophile is used to obtain the glycosyl azides[5] and rarely others.[6] We were interested in a new protocol for direct conversion of glucals to *N*-pseudoglycals with sulfonamides and carbamates as nitrogen nucleophiles. Sulfonamides and carbamates are useful protecting groups for amines and can easily undergo further conversions using well-established protective group chemistry.[7] Furthermore, they play an important role in chemotherapy, and have been investigated for their anticancer properties.[8] Recently, Colinas and Bravo reported a method for sulfonamido-glycosylation of glycals,[9] however the products are 2-deoxy glycosides and not the Ferrier products (pseudoglycals). To our knowledge there is only one example known in the literature with methane sulfonamide[6c] but, there are no reports with benzyl or *t*-butyl carbamates affording the corresponding *N*-pseudoglycals.

In continuation of our interest in exploring the potential use of tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] as a Lewis acid catalyst,[10] herein we report a new and efficient protocol for the azaglycosylation of tri-*O*-acetyl-D-glucal with sulfonamides and carbamates to the corresponding *N*-pseudoglycals (Scheme 1). $B(C_6F_5)_3$ is gaining prominence as an unconventional and viable alternative for boron-based Lewis acids,[11] since it is commercially available, considerably more hydrolytically stable and comparable in Lewis acidity to BF_3, but without the problems associated with reactive B–F bonds. Furthermore, $B(C_6F_5)_3$ has not previously been used for Ferrier glycosylation with any kind of nucleophiles.

In a test reaction 1 mmol of tri-*O*-acetyl-D-glucal **1** was treated with 1 mmol of benzenesulfonamide **1a** and



Scheme 1.

Keywords: Tris(pentafluorophenyl)borane; Azaglycosylation; Sulfonamides; Carbamates.
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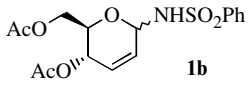
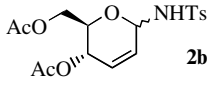
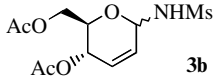
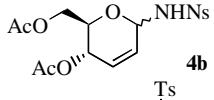
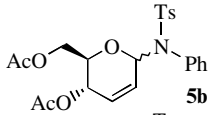
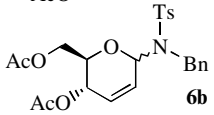
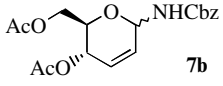
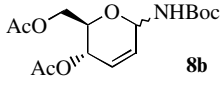
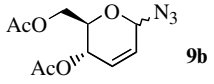
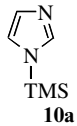
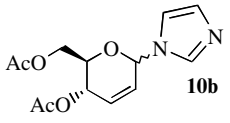
0.5 mol% of $B(C_6F_5)_3$ in acetonitrile for 4 h at room temperature to furnish benzenesulfonamido 2,3-unsaturated glycoside **1b** in 91% yield (Table 1, entry 1) with the α-anomer as the major product. This success encouraged us to exploit the generality of the reaction with different sulfonamides and the results are summarized in Table 1. *p*-Toluenesulfonamide **2a** ($TsNH_2$) and methanesulfonamide **3a** ($MsNH_2$) were reacted with glucal **1** under the present reaction conditions to give the corresponding pseudoglycals **2b** and **3b** in 92% and 90% yields, respectively, with the α-anomer as the major product. 4-Nitrobenzenesulfonamide ($NsNH_2$) **4a** reacted smoothly with glucal **1**, to give the corresponding pseudoglycal **4b** in 88% yield. Interestingly, extension of this reaction to *N*-substituted sulfonamides such as *N*-phenyl and *N*-benzyl toluenesulfonamides (**5a** and **6a**) furnished the corresponding pseudoglycals **5b** and **6b**, respectively, in good yields. We also extended the reaction conditions to benzyl carbamate ($CbzNH_2$) and *t*-butyl carbamate ($BocNH_2$) nucleophiles and found that these carbamates also reacted with glucal **1** to give the corresponding pseudoglycals **7b** and **8b** albeit in moderate yields (entries 7 and 8). Attempts made to improve the yields, such as increasing the amount of catalyst and/or reaction temperatures were unsuccessful. The products bearing benzyloxycarbonyl (Cbz) and *t*-butyloxycarbonyl (Boc) groups are potential precursors for the synthesis of glycosyl amines. In addition, we observed that the glycosylation of **1** with $TMSN_3$ was also successful furnishing the corresponding glycosyl azide in 94% yield (entry 9). However, the reaction of 1-trimethylsilyl imidazole with tri-*O*-acetyl-D-glucal **1** was unsuccessful (entry 10).

A comparative study was carried out using tri-*O*-acetyl-D-glucal and $TsNH_2$ as a model system with different Lewis acids (Table 2). For example, treatment of glucal **1** with $TsNH_2$ in the presence of 1 mol% of $BF_3{\cdot}Et_2O$, the led to a complex mixture, while with $AlCl_3$ there was no reaction. However, $InCl_3$ gave the product in a moderate yield and $Sc(OTf)_3$ was found to be as effective as $B(C_6F_5)_3$ for this conversion but with lower selectiv-

Table 1. $B(C_6F_5)_3$-catalyzed Ferrier azaglycosylation of tri-*O*-acetyl-D-glucal

Entry	Nucleophile	Time (h)	Pseudoglycal	Yield (%)[a]	Ratio (α/β)[b]
1	$PhSO_2NH_2$ **1a**	4	 **1b**	91	5/1
2	$TsNH_2$ **2a**	3	 **2b**	92	7/1
3	$MsNH_2$ **3a**	3	 **3b**	90	6/1
4	$NsNH_2$ **4a**	5	 **4b**	88	9/1
5	 **5a**	5	 **5b**	84	7/1
6	 **6a**	6	 **6b**	82	8/1
7	$CbzNH_2$ **7a**	10	 **7b**	71	12/1
8	$BocNH_2$ **8a**	16	 **8b**	56	15/1
9	$TMSN_3$ **9a**	2	 **9b**	94	5/1
10	 **10a**	24	 **10b**	0	—

[a] Isolated yields as anomeric mixtures after purification.
[b] The anomeric ratio was determined on the basis of the integration of the anomeric hydrogen in the ^1H NMR spectra.

Table 2. Comparative azaglycosylation study of tris-*O*-acetyl-D-glucal **1** with $TsNH_2$ using different Lewis acids

Entry	Lewis acid (0.5 mol%)	Time (h)	Yield (%)	Ratio (α/β)
1	$B(C_6F_5)_3$	3	92	7/1
2	$BF_3{\cdot}Et_2O$	1	Complex mixture	—
3	$AlCl_3$	8	No reaction	—
4	$InCl_3$	4	70	7/1
5	$Sc(OTf)_3$	3	88	6/1

ity. Among these catalysts, $B(C_6F_5)_3$ was found to be mild and more effective than others in terms of yields, reaction profiles and selectivity.

In summary, we have demonstrated a novel and efficient Ferrier azaglycosylation of tri-*O*-acetyl-D-glucal with sulfonamides, carbamates and azides using $B(C_6F_5)_3$ as catalyst. We believe this protocol will provide a useful entry to *N*-pseudoglycals under mild and simple conditions, with high yields.

General experimental procedure: To a stirred solution of tri-*O*-acetyl-D-glucal (0.272 g, 1 mmol) and the *N*-nucleophile (1 mmol) in acetonitrile (5 mL) was added tris(pentafluorophenyl)borane (0.5 mol%) and the stirring continued for the given time (Table 1) at room temperature. After completion of the reaction (monitored by TLC), the solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel to give the corresponding azapseudoglycal in good yields. The products obtained were identified by IR, ^1H and ^{13}C NMR and mass spectroscopy.[12]

Acknowledgements

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12. Spectroscopic data for selected products (major anomers): (**1b**): ^1H NMR ($CDCl_3$, 400 MHz): δ 7.98–7.94 (m, 2H), 7.63–7.49 (m, 3H), 5.96 and 5.85 (ABq, J_{AB} = 10.4 Hz, 2H), 5.66 (br s, 2H), 5.28 (d, J = 8.8 Hz, 1H), 3.92 (dd, J = 3.6, 8.4 Hz, 1H), 3.53 (dt, J = 2.8, 9.2 Hz, 1H), 3.34 (dd, J = 2.4, 12.4 Hz, 1H), 2.05 (s, 3H), 2.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.1, 141.5, 132.9, 130.6, 129.0 (2C), 127.1 (2C), 126.6, 77.1, 66.7, 64.2, 61.7, 20.9, 20.8; IR (neat): 3256, 1740, 1233, 1160, 1029, 684 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}NO_7S$, 369.0882; found, 369.0878. (**4b**): ^1H NMR ($CDCl_3$, 400 MHz): δ 8.38 (d, J = 8.8 Hz, 2H), 8.15 (d, J = 8.8 Hz, 2H), 6.3 (d, J = 8.8 Hz, 1H), 5.98 and 5.85 (ABq, J_{AB} = 10.4 Hz, 2H), 5.66 (d, J = 8.8 Hz, 1H), 5.25 (d, J = 8.8 Hz, 1H), 3.88 and 3.85 (ABq, J_{AB} = 12.0 Hz, 1H), 3.63–3.62 (m, 2H), 2.05 (s, 3H), 2.0 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 170.1, 150.1, 147.1, 131.0, 128.6 (2C), 126.2, 124.3 (2C), 77.1, 67.2, 64.4, 61.7, 20.9, 20.7; IR (neat): 3256, 1744, 1532, 1233, 1164, 1037, 624 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}N_2O_9S$, 414.0733; found, 414.0728. (**6b**): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.77 (d, J = 8.3 Hz 2H), 7.35–7.18 (m, 7H), 6.1 (s, 1H), 5.63 and 5.45 (ABq, J_{AB} = 10.5 Hz, 2H), 5.16 (d, J = 7.5 Hz 1H), 4.35–4.08 (m, 2H), 4.06–3.9 (m,

2H), 3.82 (t, $J=3.6$, 8.4 Hz, 1H), 2.42 (s, 3H), 2.1 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.5, 170.1, 143.6, 137.2, 136.5, 129.8, 129.3, 129.1 (2C), 128.3 (2C), 128.2 (2C), 128.0 (2C), 127.3, 83.2, 74.0, 64.4, 63.0, 47.1, 21.5, 20.9, 20.7; IR (neat): 1740, 1349, 1225, 1161, 1043, 772 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{27}NO_7S$, 473.1508; found, 473.1502. (**7b**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.32 (m, 5H), 5.95 and 5.87 (ABq, $J_{AB}=10.4$ Hz, 2H), 5.73 (br s, 1H), 5.56 (br s, 1H), 5.29 (d, $J=8.8$ Hz, 1H), 5.15 (s, 2H), 4.25 and 4.14 (ABq, $J_{AB}=12.4$ Hz, 2H, the 4.25 ppm peaks are further split into doublets with $J=4.8$ Hz and the 4.14 ppm peaks are further split into doublets with $J=2$ Hz), 3.92–3.89 (m, 1H), 2.07 (s, 3H), 2.05 (s, 3H); ^{13}C NMR($CDCl_3$, 100 MHz): δ 170.9, 170.2, 155.1, 135.9, 129.8, 129.6, 128.6 (2C), 128.4 (2C), 127.5, 74.5, 67.2, 64.7, 64.5, 62.9, 21.0, 20.8; IR (neat): 3350, 1740, 1519, 1233, 1049, 698 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}NO_7$, 363.1318; found, 363.1321. (**8b**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.93 and 5.83 (ABq, $J_{AB}=10.4$ Hz, 2H), 5.68 (br s, 1H), 5.39 (br s, 1H), 5.28 (d, $J=8.8$ Hz, 1H) 4.25–4.15 (m, 2H), 3.93–3.91 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 170.1, 154.3, 129.4, 127.9, 80.4, 73.7, 67.5, 64.8, 63.0, 28.2 (3C), 20.9, 20.7; IR (neat): 3354, 1740, 1511, 1233, 1045, 976 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{23}NO_7$, 329.1475; found, 329.1469.