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A mild and efficient synthetic protocol for Ferrier azaglycosylation promoted by $ZnCl_2/Al_2O_3$

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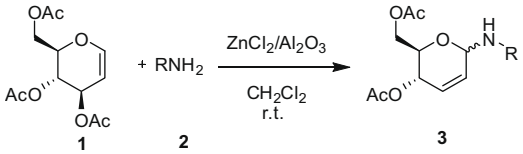
ABSTRACT

An improved method for the Ferrier sulfonamidoglycosylation of tri-*O*-acetyl-D-glucal with different *N*-nucleophiles has been developed. $ZnCl_2$ impregnated on activated alumina acts as an excellent reagent system for the conversion of 3,4,6-tri-*O*-acetyl-D-glucal into 2,3-unsaturated-*N*-pseudoglycals with good yields and preferential α-anomeric selectivity.

Ferrier rearrangement is a prominent reaction for the direct conversion of 3,4,6-tri-*O*-acetyl-D-glucal into 2,3-unsaturated glycosides.[1] Development of this method is of broad interest due to the considerable importance of 2,3-unsaturated glycosides, which serve as basic building blocks. In general, Ferrier glycosylation reactions occur when glucals are treated with nucleophiles such as carbon nucleophiles, oxygen and/or sulfur nucleophiles (alcohols and thiols) in the presence of Lewis acids or oxidants.[2] On the other hand, nitrogen nucleophiles have not been used extensively in the Ferrier rearrangement.[3] Azide is the typical nucleophile used to afford the *N*-pseudoglycals.[4] This prompted us to develop a mild protocol for the conversion of 3,4,6-tri-*O*-acetyl-D-glucal into *N*-pseudoglycals with sulfonamides, carbamates, amides and azides. Nucleosides having an *N*-glycosidic linkage represent highly valuable pharmacological agents such as antibiotic, antineoplastic and antiviral compounds.[5] Subsequent modification of the unsaturated part of the pseudoglycals via epoxidation, hydroxylation, hydrogenation or aminohydroxylation further enhances the synthetic utility of this conversion.

To date, there are only two known examples of the Ferrier sulfonamidoglycosylation of glycals in the presence of $B(C_6F_5)_3$[6] and $BF_3{\cdot}Et_2O$[7] as catalysts, respectively. Our group has been interested in new glycosylation techniques.[8] Recently, we demonstrated that the $ZnCl_2/Al_2O_3$ catalyzed Ferrier rearrangement of glucals with alcohols proceeds with high anomeric selectivity and in short reaction times.[9] To the best of our knowledge, the use of $ZnCl_2/Al_2O_3$ to promote the Ferrier sulfonamidoglycosylation of glycals has not been reported. Herein, we describe the synthesis of *N*-pseudoglycals by reaction of tri-*O*-acetyl-D-glucal (**1**) with nitrogen nucleophiles catalyzed by $ZnCl_2/Al_2O_3$ (Scheme 1).

Initially, a comparative study was carried out using tri-*O*-acetyl-D-glucal (**1**) and $TsNH_2$ as a model system with different Lewis acids (Table 1). Amongst the different catalysts tested, $ZnCl_2/Al_2O_3$[10] (Table 1, entry 10) was found to be superior in terms of reaction time, yield, reaction profile and selectivity. Moreover, the use of $Cu(OTf)_2$, $Yb(OTf)_2$, $IrCl_3$, $RuCl_3$ and $ZnCl_2$ as Lewis acid catalysts afforded the desired pseudoglycal products, albeit in longer reaction times, and moderate conversions and selectivities (Table 1, entries 1, 5 and 7–9). On the other hand, treatment of



1 2 3

R = $ArSO_2$, ArCO, Cbz or Boc

Scheme 1. A synthetic model for the Ferrier azaglycosylation.

Table 1
Optimization of the catalyst for the Ferrier rearrangement[a]

Entry	Catalyst	Time (min)	Conversion (%)[b]	α:β[c]
1	$Cu(OTf)_2$	120	100	77:23
2	$FeCl_3$	120	Complex mixture	—
3	$FeCl_2$	120	Complex mixture	—
4	$Sn(OTf)_2$	180	Trace	—
5	$Yb(OTf)_2$	120	100	68:32
6	$PtCl_2$	180	No reaction	—
7	$IrCl_3$	120	91	73:27
8	$RuCl_3$	120	100	65:35
9	$ZnCl_2$	120	92	62:38
10	$ZnCl_2/Al_2O_3$[d]	20	100	88:12

[a] Reaction conditions: tri-*O*-acetyl-D-glucal (**1**) (100 mg, 0.37 mmol), $TsNH_2$ (1 equiv), catalyst (10 mol %), CH_2Cl_2 (1 mL).
[b] Determined by analysis of the ^1H NMR spectrum of the reaction mixture.
[c] The anomeric ratio was determined by integration of the anomeric hydrogen in the ^1H NMR spectrum.
[d] $ZnCl_2$ (1 equiv) on Al_2O_3 (5.3 equiv) was used per 1 equiv of tri-*O*-acetyl-D-glucal.

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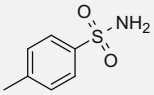
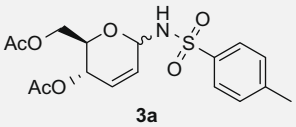
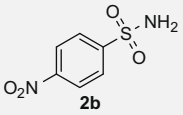
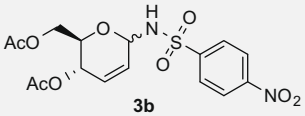
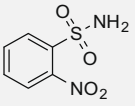
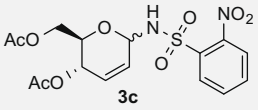
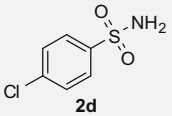
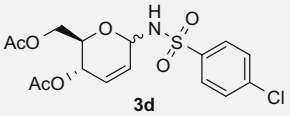
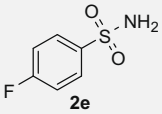
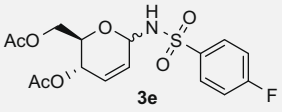
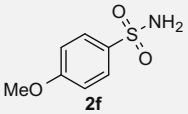
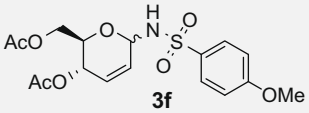
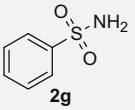
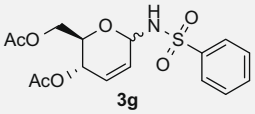
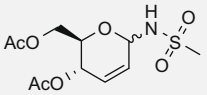
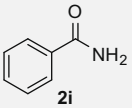
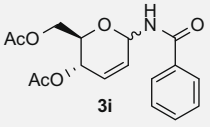
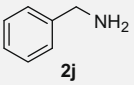
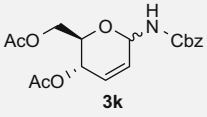
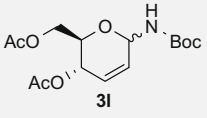
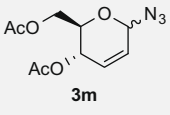
Table 2
Scope of the Ferrier azaglycosylation of tri-*O*-acetyl-D-glucals[11]

Entry	Nucleophile	Product	Yield[a] (%)	α:β[b]
1	 **2a**	 **3a**	96	88:12
2	 **2b**	 **3b**	84	90:10
3	 **2c**	 **3c**	80	79:21[11]
4	 **2d**	 **3d**	83	85:15[12]
5	 **2e**	 **3e**	88	91:9[13]
6	 **2f**	 **3f**	91	80:20[14]
7	 **2g**	 **3g**	90	91:9
8	 **2h**	 **3h**	88	85:15
9	 **2i**	 **3i**	54	74:26[15]
10	 **2j**	n.r.[c]	–	–
11	$CbzNH_2$ **2k**	 **3k**	80	92:8
12	$BocNH_2$ **2l**	 **3l**	70	84:16
13	$TMSN_3$ **2m**	 **3m**	92	86:14

[a] Isolated yields of anomeric mixtures after purification.
[b] The anomeric ratio was determined by integration of the anomeric hydrogen in the ^1H NMR spectrum.
[c] No reaction.

glucal **1** with $TsNH_2$ in the presence of 10 mol % of $FeCl_3$ or $FeCl_2$ led to a complex mixture of products (Table 1, entries 2 and 3), while with $Sn(OTf)_2$ and $PtCl_2$ no reaction was observed (Table 1, entries 4 and 6), even after prolonged reaction times.

Using the optimized reaction conditions, the scope of the Ferrier azaglycosylation promoted by $ZnCl_2/Al_2O_3$ was examined. The results are summarized in Table 2. Generally, the reactions provided 2,3-unsaturated pseudoglycals in high to excellent yields with good anomeric selectivities. For example, sulfonamides **2a** and **2f** bearing electron-donating groups gave the corresponding pseudoglycals **3a** and **3f** in excellent yields and selectivities (Table 2, entries 1 and 6), while sulfonamides **2b–e** bearing electron-withdrawing groups provided lower yields of the desired products, but typically with slightly higher selectivities (Table 2, entries 2–5). In addition, the aromatic sulfonamide [benzenesulfonamide (**2g**)] and methanesulfonamide (**2h**) ($MsNH_2$) proved to be excellent nucleophiles providing the corresponding products in high yields and selectivities (Table 2, entries 7 and 8). Interestingly, extension of this reaction to other nitrogen nucleophiles such as benzamide **2i** furnished the corresponding pseudoglycal **3i**, in moderate yield and selectivity (Table 2, entry 9). To our knowledge, this is the first attempt using benzamide as a nucleophile in Ferrier glycosylation with tri-*O*-acetyl-D-glucal (**1**). This result encouraged us to further exploit the Ferrier azaglycosylation with benzyl carbamate ($CbzNH_2$), *t*-butyl carbamate ($BocNH_2$) and trimethylsilyl azide ($TMSN_3$) as nucleophiles. Reaction of carbamates **2k** and **2l** with glucal **1** furnished the corresponding pseudoglycals **3k** and **3l**, in good yields and selectivities (Table 2, entries 11 and 12). These products can be easily transformed into the corresponding amines by removal of the protecting group. Likewise, the glycosylation of glucal **1** with $TMSN_3$ gave the corresponding glycosyl azide in 92% yield (Table 2, entry 13). In contrast, reaction of benzylamine **2j** with tri-*O*-acetyl-D-glucal (**1**) was unsuccessful (Table 2, entry 10).

In summary, we have demonstrated a new protocol for the Ferrier azaglycosylation with various nitrogen nucleophiles under the influence of $ZnCl_2/Al_2O_3$. The main advantages of this method are high anomeric selectivity and short reaction times. Low cost reagents and no aqueous work-up are required, and the catalyst could be recycled (up to three times).

Acknowledgements

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10. Sigma–Aldrich aluminium oxide, neutral, 150 mesh, STD grade was used for all reactions. Alumina was freshly prepared by heating at 200 °C under vacuum for 5 h and flushed with nitrogen. Alumina (5.3 equiv) was combined with 1 equiv of activated $ZnCl_2$ (heated under vacuum at 160 °C for 2 h), and to this mixture about 3 mL of dry THF or CH_2Cl_2 was added with stirring for 5 min. The solvent was removed and the remaining solid was dried under vacuum.
11. *Typical experimental procedure*: To a stirred mixture of tri-*O*-acetyl-D-glucal (**1**) (100 mg, 0.37 mmol) and nitrogen nucleophile **2** (1 equiv) in CH_2Cl_2 (0.2 mL) was added 250 mg of $ZnCl_2/Al_2O_3$ at ambient temperature. The mixture was stirred for the appropriate amount of time (Table 2), and the extent of the reaction was monitored by TLC analysis. The reaction mixture was filtered and the solid residue was washed with CH_2Cl_2 (5 mL). The combined filtrate was concentrated under vacuum to give the product which was purified by silica gel column chromatography (EtOAc/hexane = 1:2). The products were identified by IR, ^1H and ^{13}C NMR and mass spectroscopy. Spectroscopic data for selected products (major anomers): *4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl-2′-nitrophenylsulfonamide* (**3c**): ^1H NMR ($CDCl_3$, 400 MHz): δ 8.16–8.23 (m, 1H), 7.85–7.88 (m, 1H), 7.69–7.77 (m, 2H), 6.49 (d, J = 10.0 Hz, 1H), 5.76–5.96 (m, 2H), 5.67 (d, J = 9.2 Hz, 1H), 5.27 (d, J = 9.2 Hz, 1H), 4.10 (q, J = 6.8 Hz, 1H), 3.70–3.73 (m, 1H), 3.10 (d, J = 12.0 Hz, 1H), 2.07 (s, 3H), 2.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 170.0, 135.2, 133.9, 133.2, 131.6, 131.1, 127.8, 126.0, 125.2, 125.1, 67.1, 64.1, 61.5, 20.9, 20.7; IR ($CHCl_3$) 3285, 1738, 1539, 1367, 1236, 1170, 1032, 742 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{19}N_2O_9S$: 415.0811, found: 415.0816.
12. *4,6-Di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl-p-chlorophenylsulfonamide* (**3d**): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.88 (d, J = 6.9 Hz, 2H), 7.49 (d, J = 6.9 Hz, 2H), 5.94 (d, J = 6.9 Hz, 1H), 5.78–5.84 (m, 2H), 5.62 (d, J = 7.8 Hz, 1H), 5.23 (dd, J = 8.7, 1.8 Hz, 1H), 3.93 (dd, J = 12.3, 3.6 Hz, 1H), 3.55–3.63 (m, 2H), 2.04 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.6, 170.1, 140.0, 139.4, 130.7, 129.3, 128.9, 128.7, 126.5, 67.2, 64.3, 61.9, 20.9, 20.7; IR ($CHCl_3$): 3269, 1738, 1371, 1338, 1236, 1167, 1036, 756 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{19}ClNO_7S$: 404.0571, found: 404.0574.
13. *4,6-Di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl-p-fluorophenylsulfonamide* (**3e**): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.93–7.98 (m, 2H), 7.17–7.23 (m, 2H), 5.94 (d, J = 8.4 Hz, 1H), 5.79–5.84 (m, 2H), 5.62 (d, J = 5.7 Hz, 1H), 5.24 (dd, J = 9.0, 2.1 Hz, 1H), 3.94 (dd, J = 12.9, 4.5 Hz, 1H), 3.54–3.60 (m, 2H), 2.03 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.6, 170.0, 137.5, 130.6, 130.0, 129.9, 126.6, 116.4, 116.1, 67.1, 64.3, 61.9, 20.9, 20.7; IR ($CHCl_3$): 3282, 1738, 1591, 1371, 1338, 1236, 1155, 1033, 754 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{19}FNO_7S$: 388.0866, found: 388.0869.
14. *4,6-Di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl-p-methoxyphenylsulfonamide* (**3f**): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.86 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 5.92 (d, J = 10.2 Hz, 1H), 5.68–5.82 (m, 2H), 5.59 (d, J = 7.5 Hz, 1H), 5.26 (dd, J = 8.7, 1.5 Hz, 1H), 3.90 (dd, J = 10.2, 3.0 Hz, 1H), 3.87 (s, 3H), 3.50–3.58 (m, 2H), 2.03 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.8, 170.2, 163.1, 133.1, 130.6, 129.6, 128.7, 126.8, 114.2, 66.8, 64.4, 62.0, 55.8, 21.0, 20.8; IR ($CHCl_3$): 3420, 1647, 1238, 1165, 1034, 721 cm^{-1}; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{17}H_{21}NO_8SNa$: 422.0886, found: 422.0888.
15. *4,6-Di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl-benzamide* (**3i**): ^1H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, J = 7.6 Hz, 2H), 7.45–7.48 (m, 1H), 7.36–7.40 (m, 2H), 6.51 (d, J = 10.0 Hz, 1H), 6.17 (d, J = 9.6 Hz, 1H), 5.83–5.93 (m, 2H), 5.26 (d, J = 9.6 Hz, 1H), 4.11–4.22 (m, 2H), 3.91–3.94 (m, 1H), 2.03 (s, 3H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.9, 170.3, 166.7, 133.4, 132.2, 129.8, 129.6, 128.7, 127.2, 75.5, 74.3, 64.6, 63.1, 21.0, 20.9; IR ($CHCl_3$): 3406, 1741, 1526, 1237, 1041 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{20}NO_6$: 334.1291, found: 334.1286.