

ZrCl₄-Catalyzed Efficient Ferrier Glycosylation: A Facile Synthesis of Pseudoglycals

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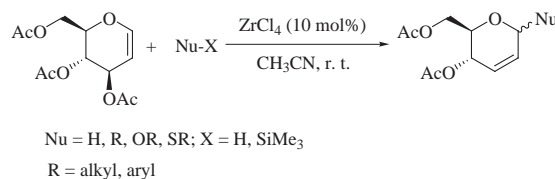
Abstract: The reaction of tri-*O*-acetyl-D-glucal with silyl nucleophiles, alcohols and thiols was effectively promoted by a catalytic amount of zirconium(IV) chloride to produce the corresponding pseudoglycals via Ferrier rearrangement.

Key words: zirconium(IV) chloride, Ferrier glycosylation, pseudoglycals

The acid-catalyzed allylic rearrangement of glycals in the presence of nucleophiles is known as Ferrier rearrangement,¹ which is widely employed to obtain 2,3-unsaturated glycosides (pseudoglycals). Pseudoglycals are valuable intermediates in the synthesis of glycopeptides, uronic acids, nucleosides and oligosaccharides² and also constitute the structural units of several antibiotics.³ These are very important class of compounds due to the presence of double bond between C(2) and C(3), which may be easily modified, for instance, by hydroxylation, hydrogenation, epoxidation and aminohydroxylation. A variety of acid catalysts are employed to promote the Ferrier glycosylation which include strong acids such as BF₃·Et₂O,⁴ SnCl₄,⁵ DDQ,⁶ TMSOTf,⁷ NIS,⁸ LiBF₄,⁹ trichloroacetimidate,¹⁰ montmorillonite K-10,¹¹ FeCl₃,¹² InCl₃,¹³ InBr₃,¹⁴ Sc(OTf)₃,¹⁵ Yb(OTf)₃,¹⁶ Dy(OTf)₃,¹⁷ I₂,¹⁸ CAN,¹⁹ BiCl₃,²⁰ ZnCl₂²¹ and others.²² All of these while offering some advantages, also suffer from disadvantages in terms of yield, reaction time, temperature, selectivity, cost of the reagent and use of a large amount of reagent or catalyst. Furthermore, some of these catalysts are used for either C-glycosylation with silyl nucleophiles or O- and S-glycosylation with alcohols and thiols respectively and a few of them are utilized for C-, O- and S-glycosylation in their individual reports. However, the wider acceptability of these reagents has not been demonstrated so far. Hence, the development of new reagents that leads to a potentially general and convenient procedures for this transformation is still of interest.

In continuation of our interest in exploring the utility of zirconium(IV) chloride (ZrCl₄) as a Lewis acid catalyst,²³ herein we wish to report a mild and efficient general method for the glycosylation of tri-*O*-acetyl-D-glucal with silyl nucleophiles, alcohols and thiols in CH₃CN using a catalytic amount of ZrCl₄ (10 mol%) for the first time

(Scheme 1). The reaction proceeds smoothly at room temperature and the products are obtained in good yields and in short reaction times.



Scheme 1

The results are summarized in Table 1, which reveal the scope and generality of this reagent system with respect to various nucleophiles. Initially, we examined the reaction of glucal with silyl nucleophiles to get the C-glycosylation products. In the first case, the treatment of 3,4,6-tri-*O*-acetyl-D-glucal with allyl trimethylsilane in the presence of 10 mol% ZrCl₄ at room temperature led to the formation of 2,3-unsaturated allyl glycoside in 94% yield with high α -selectivity (entry 1). Similarly, the reaction of the same glycal with trimethylsilyl azide and trimethylsilyl cyanide gave the corresponding glycosyl azide and cyanide in 86% and 85% yields, respectively (entry 2 and 3). The present protocol also behaved well with Et₃SiH to give the corresponding pseudoglycal in 93% yield within 5 minutes (entry 4). Interestingly, phenyl (trimethylsilyl)acetylene reacted smoothly to afford the corresponding alkynyl C-glycoside as α -anomer in 88% yield (entry 5). This success encouraged us to extend the generality of the reaction to other nucleophiles. The glycosylation of tri-*O*-acetyl-D-glucal with primary, secondary, allyl, benzyl and propargyl alcohols under the present reaction conditions furnished the corresponding 2,3-unsaturated glycopyranosides in high yields with α -anomer as the major product (entries 6–10). The versatility of this protocol was furthermore illustrated by making thioglycosides with thiophenol and ethane thiol (entries 11 and 12). The α -anomer was obtained as a major product in each reaction, the structure of which was characterized by spectroscopic data.

In conclusion, an efficient and stereoselective Ferrier glycosylation has been developed to produce structurally diverse C-, O- and S-glycopyranosides in the presence of a catalytic amount of ZrCl₄. The advantages of this protocol such as mild reaction conditions, shorter reaction times, simple experimental workup procedure and high yields of

the desired products are worthy of mention and make this method an attractive and useful addition to the present known methods.

Reaction of Tri-*O*-acetyl-D-glucal with *C*, *O* and *S*-Nucleophiles; General Procedure

To a stirred solution of the 3,4,6-tri-*O*-acetyl-D-glucal (0.272 g, 1 mmol) in CH₃CN (10 mL), were added nucleophile (1.1 mmol) followed by ZrCl₄ (10 mol%) and the reaction mixture was stirred at r.t. for the given time (see Table 1). After completion of the reaction, the solvent was evaporated in vacuo, extracted with EtOAc, washed with 10% aq NaHCO₃ and brine solution. The combined organic layers were dried (Na₂SO₄) and evaporated to give the corre-

sponding pseudoglycal, which was purified by column chromatography.

Spectral data (Entry 6)

$[\alpha]_D +77.6$ ($c = 1$, CHCl₃).

IR (neat): 2949, 1740, 1368, 1229, 1037, 698 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): $\delta = 7.3$ – 7.26 (m, 2 H), 7.2 – 7.18 (m, 3 H), 5.87 (dd, $J = 20.8, 10.3$ Hz, 2 H), 5.3 (d, $J = 8.4$ Hz, 1 H), 5.02 (br s, 1 H), 4.26 – 4.22 (m, 1 H), 4.16 – 4.09 (m, 2 H), 3.83 – 3.77 (m, 1 H), 3.55 – 3.49 (m, 1 H), 2.71 (t, $J = 7.2$ Hz, 2 H), 2.09 (s, 3 H), 2.04 (s, 3 H), 1.98 – 1.93 (m, 2 H).

¹³C NMR (100 MHz, CDCl₃): $\delta = 170.7, 170.2, 141.7, 129.0, 128.4$ (4 C), $127.9, 125.9, 94.5, 68.2, 66.9, 65.3, 63.2, 32.4, 31.3, 21.0, 20.7$.

HRMS (ESI): m/z calcd for C₁₉H₂₄O₆: 348.1573; found: 348.1640.

Table 1 ZrCl₄-Catalyzed Glycosylation of Tri-*O*-acetyl-D-glucal

Entry	Nu-X	Time (min)	Pseudoglycal	Yield (%) ^a	Ratio (α/β) ^b
1		3		94 ^{14a}	20:1
2	Me ₃ SiN ₃	8		86 ^{14a}	6:1
3	Me ₃ SiCN	10		85 ^{14a}	4:1
4	Et ₃ SiH	5		93 ^{13c}	—
5	Me ₃ Si-C≡C-Ph	8		88 ^{14b}	α
6	Ph-CH ₂ -CH ₂ -CH ₂ -OH	5		92	12:1
7	Ph-CH(OH)-CH ₃	8		89 ²¹	9:1
8	CH ₂ =CH-CH ₂ -OH	5		90 ^{13d}	12:1
9	Ph-CH ₂ -OH	6		94 ^{13d}	10:1
10	CH ₃ -C≡C-CH ₂ -OH	6		91 ²⁰	8:1
11	PhSH	4		86 ²⁰	7:1
12	EtSH	5		87 ^{15c}	6:1

^a Isolated yield are as pure anomeric mixtures after purification. The literature references are given for known products.

^b The α/β ratio was determined by integration of the anomeric protons in ¹H NMR spectra.

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