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Note

A facile Er(OTf)$_3$-catalyzed synthesis of 2,3-unsaturated O- and S-glycosides

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Abstract—Er(OTf)$_3$ is a useful catalyst for the Ferrier rearrangement furnishing high yields of O- and S-glycosides. The transformation has wide applicability, cleaner reaction profiles, mild reaction conditions, and high stereoselectivity and the catalyst, which is also commercially available, can be recovered and reused.

Keywords: O-Glycosylation; S-Glycosylation; Lewis catalyst; Erbium(III); Triflate

2,3-Unsaturated O-glycosides (pseudoglycals) are important building-blocks in many bioactive molecules.[1] Moreover, the 2,3 double bond in the pyran ring may be easily modified by dihydroxylation, hydrogenation, epoxidation, and aminohydroxylation to achieve structural complexity and diversity.[1l,2] A direct and straightforward method for the synthesis of 2,3-unsaturated glycosides is the acid-catalyzed allyl rearrangement of glycals in the presence of alcohols, which is known as the Ferrier reaction.[1b,3] This rearrangement is believed to involve a cyclic allylic oxocarbonium intermediate that is formed via displacement of the C-3 substituent in a glycal, followed by the preferential attack of a nucleophile from the quasi-equatorial orientation.[1a,4]

A wide range of acid and oxidizing reagents have been reported to promote this transformation such as $BF_3{\cdot}Et_2O$,[5] $SnCl_4$,[6] IDCP,[7] DDQ,[8] TMSOTf,[9] NIS,[10] $LiBF_4$,[11] trichloroacetimidate,[12] montmorillonite K-10,[13] $FeCl_3$,[14] $InCl_3$,[15] $InBr_3$,[16] Sc(OTf)$_3$,[17] Yb(OTf)$_3$,[18] Dy(OTf)$_3$,[19] I_2,[20] CAN,[21] $BiCl_3$,[22] $ZnCl_2$,[23] $ZrCl_4$,[24] $HClO_4$ on silica gel,[25] and $NiCl_5$.[26] All of these methods offer several advantages, but some of them suffer drawbacks in terms of yields and reaction time, while others suffer from the use of harsh reaction conditions, require non-catalytic amounts of reagents or are of high cost. Among them, lanthanide triflates have been found to be quite convenient for the O-glycosylation of glycals by Ferrier reaction and, as in many other cases, they can be used in sub-stoichiometric amounts. However, these useful catalysts also present some limitations; for example, Dy(OTf)$_3$ is used in an ionic liquid and other promoters were proposed for glucal substrates only and/or for only C- or O-, S- or N-glycosylation.[17–19] Therefore, the wider acceptability of these reagents has not been demonstrated so far and a need to develop a practical method yielding 2,3-dideoxyglycosides still exists.

In continuation of our interest in exploring the utility of Er(OTf)$_3$ as a Lewis acid catalyst,[27] we utilized glycal chemistry to achieve diverse building-blocks, developing a practical low-cost environmentally friendly procedure for their C- and N-glycosylation.[28] We now wish to report a mild and efficient general method for the glycosylation of tri-*O*-acetyl-D-glycals (Scheme 1).

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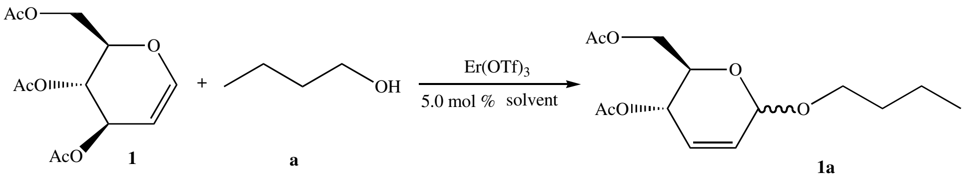

Scheme 1.

First, we tested the catalytic activity of $Er(OTf)_3$ in the glycosylation of 3,4,6-tri-*O*-acetyl-D-glucal **1** at room temperature in different solvents with 1.5 equiv of *n*-butanol. Preliminary results, which are shown in Table 1, revealed that catalytic activity of $Er(OTf)_3$ is very poor in non-polar solvents such as CH_2Cl_2, CH_3Cl, Et_2O, and THF (Table 1, entries 1–4), but it is still unsatisfactory in polar aprotic solvents such as CH_3CN and CH_3NO_2 (Table 1, entries 5 and 6). As could be predicted, better results were obtained when the reaction was performed under dry conditions. Thus, higher yields and shorter reaction times are reported for the glycosylation of **1** with *n*-butanol (Table 1, entries 7–10), but the best result was obtained in CH_3NO_2 where 90% of the product was obtained only after 2 h (Table 1, entry 10). Prolonged reaction times or higher amount of catalyst did not improve the reaction performance (Table 1, entries 11–13). $Er(OTf)_3$ can be almost quantitatively recovered and reused several times without significant loss of activity,[28] and yields over 80% were registered for four recyclings (Table 1, entry 14).

Based on the results reported in Table 1, we decided to explore the utility of erbium(III) triflate as Lewis acid catalyst as a general method for the O-glycosylation of tri-*O*-acetyl-D-glycals. The glycosylation of tri-*O*-acetyl-D-glucal with primary, secondary, benzyl, allyl, and propargyl alcohols proceeds smoothly at room temperature to afford the corresponding alkyl 2,3-unsaturated glycosides in high yields. The α-anomer is the major product (Table 2, entries 1–8), which may arise from the thermodynamic anomeric effect; product stereochemistry was confirmed from chemical shifts of the anomeric protons in the ^1H NMR spectrum. The resonance for H-1 of the α-glycosides occupies an upfield position compared to the β-glycosides; moreover, an NOE was observed between H-1 and H-4.

Table 1. Attempted O-glycosylation of 3,4,6-tri-*O*-acetyl-D-glucal **1** in various solvents

Entry	Solvent	Time (h)	Yield (%)
1	CH_2Cl_2	48	25
2	$CHCl_3$	24	18
3	Et_2O	48	15
4	THF	48	10
5	CH_3CN	48	35
6	CH_3NO_2	24	60
7	CH_2Cl_2 (dry)	12	46
8	Et_2O	12	25
9	CH_3CN (dry)	12	58
10	CH_3NO_2 (dry)	2	90
11	CH_3NO_2 (dry)	2	88[a]
12	CH_3NO_2 (dry)	2	81[b]
13	CH_3NO_2 (dry)	6	90
14	CH_3NO_2 (dry)		88
	Second recycle	2	86
	Third recycle	2	82
	Fourth recycle	2	

[a] Reaction conducted at 50 °C.

[b] 10 mol % of catalyst was used.

The generality of the present method was shown by exposing per-O-acetylated glucal to methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranoside and *N*-Boc-*O*-*tert*-butyl-L-threonine (Table 2, entries 9 and 10). Methyl 6-*O*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2,3,4-tri-*O*-methyl-α-D-glucopyranoside **1i** was obtained as anomeric mixture α/β 85/15 in 70% yield, while glycopeptide precursor **1j** was isolated only as the α-glycoside as already reported by Schmidt and co-workers.[18b]

The Ferrier rearrangement of the 2,3,6-tri-*O*-acetyl-D-glucal with phenols is not as easy a reaction as that with alcohols and only traces of glycosylated product were detected when **1** was reacted with 4-methoxyphenol in dry nitromethane and 5 mol % of $Er(OTf)_3$ (Table 2, entry 11). However, 35% yield was obtained when the amount of the catalyst was improved to 10 mol % and an 80% yield of the product was obtained when the reaction was conducted at 50 °C (Table 2, entries 12 and 13). Under the same experimental conditions, good results were observed for other phenols (Table 2, entries 14 and 15).

The Ferrier rearrangement of 3,4,6-tri-*O*-acetyl-D-galactal, **2**, is not as easy a reaction as that for a glucal analog and the few synthetically viable methods are restricted by the use of microwave heating,[13b,c,26] or strongly acidic conditions.[25] Thus, we deemed it pertinent to test our protocol on this substrate. Treatment of **2** with 1-octanol in the presence of 5 mol % $Er(OTf)_3$ in dry CH_3NO_2 resulted in the formation of the Ferrier adduct in only 15 min (Table 2, entry 16). To extend the scope of this reaction, we exposed different alcohols to **2** (Table 2, entries 17–19).

Finally, the versatility of $Er(OTf)_3$ was furthermore illustrated by synthesizing thioglycosides from ethanethiol and thiophenol (Table 2, entries 20 and 21). In all