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$ZnCl_2$-catalyzed Ferrier reaction; synthesis of 2,3-unsaturated 1-*O*-glucopyranosides of allylic, benzylic and tertiary alcohols☆

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Abstract—Tertiary, allylic and benzylic alcohols react with 3,4,6-tri-*O*-acetyl-D-glucal in dichloromethane at 25°C in the presence of $ZnCl_2$ to afford the corresponding 2,3-unsaturated-1-*O*-glucopyranoside acetates in 65–91% yields, with selective formation of the α-anomer.

2-Deoxyglycoside derivatives of a wide range of compounds have been shown to be of immense biological importance.[1] A simple route to their preparation constitutes addition to 2,3-unsaturated glycopyranosides. These, in turn, can be prepared from the reaction of alcohols with 3,4,6-tri-*O*-acetyl-D-glycal in the presence of Lewis acid catalysts. Substitution occurs along with an allylic rearrangement, which is generally referred to as Ferrier rearrangement.[2] A variety of catalysts are employed in this reaction viz., $BF_3{\cdot}OEt_2$,[3] $SnCl_4$,[4] $FeCl_3$,[5] $InCl_3$,[6] $InBr_3$,[7] $Yb(OTf)_3$,[8] $Sc(OTf)_3$,[9] montmorillonite K-10,[10] $LiBF_4$[11] and $BiCl_3$.[12] Interestingly, zinc chloride has been tried as a catalyst along with hydrochloric acid in the reaction of D-glucal with *p*-nitrophenol in refluxing dioxan. However, formation of the glycoside was not observed.[13] Our earlier studies have revealed that the reaction of S_N1-active (allylic, benzylic and tertiary) halides with a variety of nucleophiles (-OH, -$OCOCH_3$, -SCN, -$SCOCH_3$, and -N_3), as their zinc salts afforded high yields of substitution products.[14] Also, *O*- and *S*-glucosides of several simple, long chain as well as terpenic alcohols, phenols and sterols have been synthesized from the reaction of α-glucopyranosyl bromide with the corresponding zinc salts.[15,16] In the present investigation, we examined the efficacy of zinc chloride as a catalyst in the preparation of 2,3-unsaturated glucopyranoside acetates of tertiary, benzylic and allylic alcohols, especially of monoterpene and isoprenyl alcohols, under Ferrier rearrangement conditions.

In a typical reaction, 3,4,6-tri-*O*-acetyl-D-glucal (5 mmol) was dissolved in anhydrous CH_2Cl_2 (10 ml), to which catalyst (10 mol%) was added, followed by addition of the substrate (5 mmol). After completion of reaction, the syrupy crude product, obtained after usual work-up, was subjected to column chromatography with 10% EtOAc in pet. ether (60–80°C) as eluent. The pure products, containing mixtures of α and β isomers were characterized by ^1H, ^{13}C and elemental analysis.

In the first instance, the reaction of D-glucal with *p*-menth-1-en-4-ol, an aroma chemical (Table 1, **1g**), was studied using various catalysts such as PTS, BF_3, BBr_3, ZnI_2, $SnCl_4$. In these cases, dehydration of the alcohol and dimerization of glucal[17] were predominant. However, in the presence of zinc chloride (10 mol%), these side reactions were considerably reduced and the glucoside was formed as the major product. Of the several solvents employed, the reaction in dichloromethane was rapid and the 2,3-unsaturated-1-*O*-glucopyranoside diacetate was obtained in good yield. The reaction of D-glucal with a selected group of monoterpenic and alkyl/aryl substituted alcohols together with the yields of the glucoside acetates obtained are summarized in Table 1 and Scheme 1. Product yields were better with benzylic alcohols than with allylic and tertiary alcohols. The anomeric ratios suggest selective axial approach by the nucleophile leading to the preferred formation of the α-isomers. The specific rotation of the products indicated that the allylic rearrangement in the aglycon did not occur which would have resulted in racemization of the aglycon, especially with regard to the monoterpenyl derivatives (entries **1a**, **1b**, **1f** and **1g**). In the case of the tertiary substrates, suppression of the competitive elimi-

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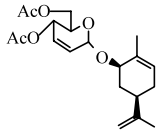
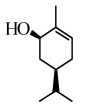
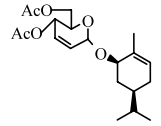
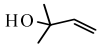
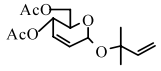
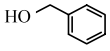
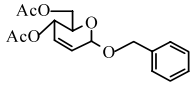
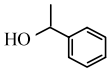
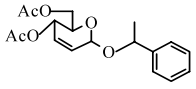
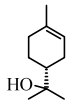
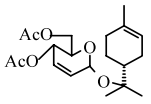
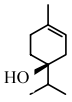
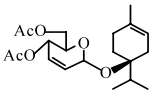
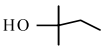
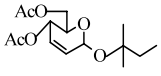
Table 1. Reactions of 3,4,6-tri-*O*-acetyl-D-glucal with allylic, benzylic, and tertiary alcohols using $ZnCl_2$ as catalyst in dichloromethane at 25°C

Entry	Substrate **1**	Product **2**	Reaction time (h)	Yield (%)[a]	Anomeric Ratio α/β[b]
a			8	70	3:1
b			6	80	3.5:1
c			6	65	2:1
d			2	91	3:1
e			6	81	1.5:1
f			12	60	1:1
g			10	65	1:1
h			12	74	1:1

a: Isolated yield as anomeric mixtures after purification. b: The anomeric ratio was determined by integration of the anomeric protons in the ^1H NMR spectra at 400 MHz.

nation reactions indicates a specific role for zinc chloride in the formation of a tight ion pair with the tertiary alcohol, which facilitates the substitution reaction.

Thus, a facile synthetic procedure, which is a variation of the Ferrier rearrangement, for the synthesis of 2,3-unsaturated-1-*O*-glucopyranosides from S_N1-active alcohols using the inexpensive catalyst, $ZnCl_2$, and a simple experimental protocol has been developed.

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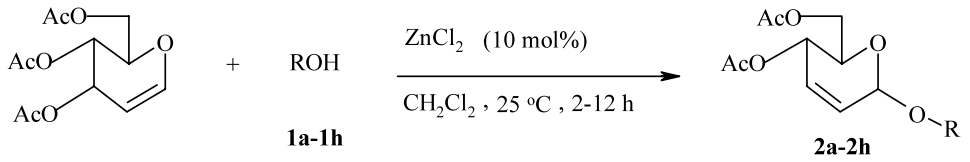

R = Allylic, benzylic, tertiary

Scheme 1.

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