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Efficient Synthesis Of Alkyl And Aryl 2,3-Unsaturated Glycopyranosides *via* Ferrier Rearrangement

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ABSTRACT

The reactions of 3,4,6-tri-*O*-acetyl-D-glucal with phenolic and aliphatic alcohol in various Lewis acid catalysts (namely $La(NO_3)_3.6H_2O$, $InCl_3$, $ZnCl_2$ and BF_3•OEt_2) have furnished the corresponding alkyl and aryl 2,3-unsaturated glycopyranosides *via* Ferrier rearrangement. BF_3•OEt_2 showed the best Lewis acids catalysts with excellent yields and minimum reaction times. The reactions performed in CH_3CN gave better yields and shorter reaction times compared to CH_2Cl_2. The electron withdrawing properties of aromatic ring resulting lower yields of aryl 2,3-unsaturated glycopyranosides compared to alkyl 2,3-unsaturated glycopyranosides under this condition. This study is significant in the preparation of *O*-glycosides *via* Ferrier rearrangement.

| Ferrier rearrangement | Lewis acids | alcohols | glycosides |

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1. INTRODUCTION

Ferrier rearrangement is an attractive methodology for the synthesis of glycoside derivatives with various alcohols. It is an efficient reaction for the substitution at the anomeric position with allylic rearrangement [1,2]. The Ferrier rearrangement involves the addition of nucleophile onto the intermediate allylic axycarbenium ion, preferentially in a quasi-axial orientation [1]. This rearrangement leads to the formation of alkyl and aryl 2,3-unsaturated-*O*-glycosides, which are versatile chiral intermediates in the synthesis of several biologically active natural products [1,2]. 2,3-unsaturated-*O*-glycosides are also important building blocks in the synthesis of some antibiotics [1].

A variety of reagents, Lewis acids and oxidants were reported to undergo Ferrier rearrangement [3]. $SnCl_4$, $LiClO_4$, $LiBF_4$ and $FeCl_3$ are common Lewis acid used to allow this rearrangement [1,2,4-6]. The requirement of an acid catalyst to bring about the Ferrier rearrangement precludes its applicability to substrates that are sensitive to acidic conditions [4]. The use of strongly acidic conditions frequently leads to the formation of undesirable side products competing with the main reaction [2]. Some of these acidic methods involve stoichiometric amounts of catalysts, strongly acidic conditions, long reaction times, unsatisfactory yields and low diastereoselectivity [3].

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This has led to the development of essentially neutral, mild and non-acidic alternative catalysts such as 2,3-dichloro-5,6-dicyano-*p*-bezoquinone (DDQ), N-iodosuccinimide (NIS), I_2, acidic Montmorillonite-K10, cerium ammonium nitrate (CAN), lanthanum (III) nitrate hexahydrate ($La(NO_3)_3.6H_2O$) and $InCl_3$ under different conditions [1-4, 7-10].

In this paper, we report Lewis acid-promoted allylic rearrangement of 3,4,6-tri-*O*-acetyl-D-glucal with 4-hydroxybenzaldehyde and aliphatic alcohols with different type of catalysts at different solvents. This study was used as model studies for the synthesis of glycosides bearing chalcone derivatives *via* Claisen-Schmidt condensation of aldehyde and acetophenone [11].

2. EXPERIMENTAL

2.1 Materials, method and instruments

Solvents were dried using standard method. All chemicals were used as received. All reactions were performed under nitrogen atmosphere. ^{1}H NMR spectra were recorded on a JEOL 500 MHz instrument using TMS as an internal standard. The IR spectra were obtained on a Perkin Elmer Instruments Spectrum Gx1v5.0 using NaCl disc. Reactions were monitored by thin-layer chromatography carried out on 0.2 mm Merck pre-coated silica gel plates (60 F_{254}).

2.2 Synthesis of 1-(3-acetyl-6-propoxy-3,6-dihydro-2H-pyran-2-yl)propan-2-one (3)

Catalysed by ($La(NO_3)_3.6H_2O$): $La(NO_3)_3.6H_2O$ (0.022g, 0.05mmol, 10 mol%) was added to the mixture of 3,4,6-tri-*O*-acetyl-D-glucal (0.136g, 0.5mmol) and propanol (0.041mL, 0.55mol, 1.1eq) in dry dichloromethane (2mL). The mixture was stirred at room temperature for 24 h. Water was added and the organic layer was extracted with ethyl acetate, dried over $MgSO_4$, filtered and concentrated. The crude was separated by column chromatography (hexane:ethyl acetate, 14:1) to furnish **3** (0.07g, 52%) as yellow waxy solid. R_f 0.83(hexane:ethyl acetate, 6:1). IR (neat) υ_{max} in cm^{-1}: 2963, 2937, 2879, 1746, 1661, 1605, 1435, 1371, 1234, 1185, 1036; ^{1}H NMR ($CDCl_3$): 5.91 (d, *J* = 5.2Hz, 3-H), 5.82 (dd, *J* = 10.4, 11.2Hz, 1H, 2-H), 5.26 (d, *J* = 9.2Hz, 1H, 4-H), 5.01 (s, 1H, 1-H), 4.20 (dd, *J* = 5.2, 5.2Hz, 1H, 6_a-H), 4.14 (dd, *J* = 1.7, 1.7Hz, 1H, 6_b-H), 4.07 (m, 1H, 5-H), 3.67 (m, 1H, 7_a-H), 3.44 (m, 1H, 7_b-H), 2.05 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO), 1.59 (q, 2H, 8-H_2), 0.91 (t, *J* = 7.4Hz, 3H, 9-H_3).

Catalysed by ($InCl_3$): To a mixture of 3,4,6-tri-*O*-acetyl-D-glucal (0.136g, 0.5mmol) and propanol (0.041mL, 0.55mol 1.1eq) in dry dichloromethane was added anhydrous $InCl_3$ (0.022g, 0.1mmol, 20mol%) (2 mL). The mixture was stirred at room temperature for 17 h and quenched with aqueous $NaHCO_3$, The mixture was extracted with dichloromethane, dried over $MgSO_4$, filtered and concentrated. The crude was separated by column chromatography (hexane: ethyl acetate, 14:1) to obtain **3** (0.07g, 52%) as yellow waxy solid. R_f 0.83 (hexane: ethyl acetate, 6:1). IR and ^{1}H NMR data are similar with those reported earlier.

Catalysed by ($ZnCl_2$): Propanol (0.041mL, 0.55mmol, 1.1 eq) was added to 3,4,6-Tri-*O*-acetyl-D-glucal (0.136g, 0.5mmol) in dry dichloromethane. Anhydrous zinc chloride (0.089g, 0.65mmol, 1.3eq) was added and the mixture was stirred at room temperature for 30 min. The supernatant was decanted from the gelatinous solid, neutralized with saturated $NaHCO_3$ solution and extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude was separated by column chromatography (hexane:ethyl acetate, 14:1) to give **3** (0.09g, 66%) as yellow waxy solid. IR and ^{1}H NMR data were similar with those reported earlier.

Catalysed by (BF_3•OEt_2): BF_3•OEt_2 (0.127mL, 1.0mmol, 2.0eq) was added to a stirred solution of 3,4,6-tri-*O*-acetyl-D-glucal (0.136g, 0.5mmol) and propanol (0.041mL, 0.55mmol, 1.1eq) in dry dichloromethane (2mL). The mixture was stirred at room temperature for 30 min. The reaction mixture was treated with saturated $NaHCO_3$, followed by diethyl ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude was separated by column chromatography (hexane:ethyl acetate, 14:1) to give **3** (0.09g, 66%) as yellow waxy solid. R_f 0.83 (hexane: ethyl acetate, 6:1). IR and ^{1}H NMR data were similar with those reported earlier.

2.3 Synthesis of 4-[(2-acetonyl-3-acetyl-3,6-dihydro-2H-pyran-6-yl)oxy]benzaldehyde (5)

Catalysed by ($La(NO_3)_3.6H_2O$): $La(NO_3)_3.6H_2O$ (0.022g, 0.05mmol, 10 mol%) was added to a mixture of 3,4,6-tri-*O*-acetyl-D-glucal (0.136g, 0.5mmol) and 4-hydroxybenzaldehyde (0.067g, 0.55mmol, 1.1eq) in dry dichloromethane (2 mL). The mixture was stirred at room temperature for 17 h. Water was added to the reaction mixture, and extracted into ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude was separated by column chromatography (hexane:ethyl acetate, 10:1) to obtain **5** (0.06g, 37%) as yellow waxy solid. R_f 0.33 (hexane: ethyl acetate, 6:1); IR (neat) υ_{max} in cm^{-1}: 2924, 1744, 1720, 1641, 1452, 1368, 1273, 1228, 1155, 1098**;** ^{1}H NMR ($CDCl_3$): 9.86 (s, 1H, CHO), 7.81 (d, *J*=8.6Hz, 2H, Ar-H), 6.93 (d, *J*=8.6Hz, 2H, Ar-H), 5.70-6.13 (m, 2H, 2-H and 3-H), 5.29 (bs, 1H, 1-H), 5.10 (d, 1H, *J*=10.3Hz, 4-H), 3.90-4.41 (m, 3H, 5-H, 6_a-H, 6_b-H), 2.09 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO).

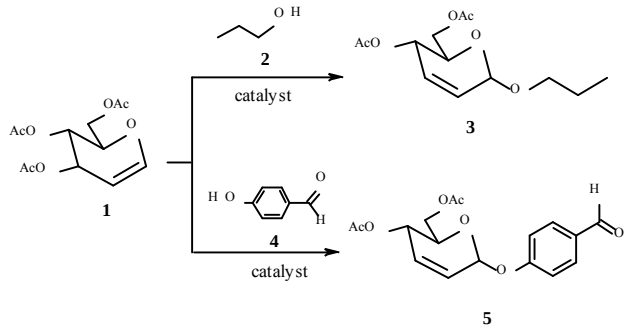
Catalysed by ($InCl_3$)**:** $InCl_3$ (0.022g, 0.1mmol, 20mol%) was added to a mixture of 3,4,6-tri-*O*-acetyl-D-glucal (0.136g, 0.5mmol) and 4-hydroxybenzaldehyde (0.067g, 0.55mmol, 1.1eq) in dry dichloromethane (2 mL). The reaction was stirred at room temperature for 5 h and quenched with aqueous $NaHCO_3$. The organic layers were extracted with dichloromethane, dried over $MgSO_4$, filtered and concentrated. The crude was separated by column chromatography (hexane: ethyl acetate, 10:1) to obtain **5** (0.05g, 29%) as yellow waxy solid. R_f 0.33 (hexane: ethyl acetate, 6:1). IR and ^{1}H NMR data were similar with those reported earlier.

Catalysed by ($ZnCl_2$): Anhydrous zinc chloride (0.089g, 0.65mmol, 1.3eq) was added into a mixture of 3,4,6-Tri-*O*-acetyl-D-glucal (0.136g, 0.5mmol) and 4-hydroxybenzaldehyde (0.067g, 0.55mmol, 1.1eq) in dry dichloromethane. The mixture was stirred for 3 h. The supernatant was decanted from the gelatinous solid, neutralized with saturated $NaHCO_3$ and extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude was separated by column chromatography (hexane:ethyl acetate, 10:1) to furnish **5** (0.08g, 52%) as yellow waxy solid. R_f 0.33 (hexane: ethyl acetate, 6:1). IR and ^{1}H NMR data were similar with those reported earlier.

Catalysed by (BF_3•OEt_2): BF_3•OEt_2 (0.127mL, 1.0mmol, 2.0eq) was added to a mixture of 3,4,6-tri-*O*-acetyl-D-glucal (0.136g, 0.5mmol) and 4-hydroxybenzaldehyde (0.067g, 0.55mmol, 1.1eq) in dry dichloromethane (2mL). The mixture was stirred at room temperature for 1 h. The reaction mixture was treated with saturated $NaHCO_3$, and the aqueous layer was extracted with diethyl ether. The combined organics were washed with brine, dried over $MgSO_4$, filtered, concentrated. The crude was separated by column chromatography (hexane:ethyl acetate, 10:1) to give **5** (0.09g, 39%) as yellow waxy solid. R_f 0.33 (hexane: ethyl acetate, 6:1). IR and ^{1}H NMR data were similar with those reported earlier.

3. RESULTS & DISCUSSION

The synthesis of 1-(3-acetyl-6-propoxy-3, 6-dihydro-2H-pyran-2-yl)propan-2-one, **3** and 4-[(2-acetonyl-3-acetyl-3,6-dihydro-2H-pyran-6-yl)oxy]benzaldehyde **5** *via* Ferrier rearrangement in different types of Lewis acids is shown in Scheme 1.



Scheme 1 Synthesis of glycosides **3** and **5**

The IR spectrum of **3** showed the presence of $\upsilon_{C=O}$ at 1746 cm^{-1} and paraffinic chains at 2963 cm^{-1}. IR showed the absorption bands at 1661 cm^{-1} (C=C of glucal), 1435 cm^{-1} (CH_3 of the acetates group) and 1234 cm^{-1} (C-O-C). The presence of paraffinic chain was confirmed by the protons resonances at δ 1.59 (q, 2H, 8-H_2) and δ 0.91 (t, J = 7.4Hz, 3H, 9-H_3) in the ^{1}H NMR spectrum. The CH_3 of the acetates appeared as two singlets at δ 2.05and δ 2.04, while the protons of 3-H and 2-H were observed at δ 5.91 and δ 5.02. The resonance of C-1 appeared as a singlet at δ 5.01 (s, 1H, 1-H). The IR and ^{1}H NMR spectra of **3** are shown in Figure 1a and Figure 2a.

The synthesis of 4-[(2-acetonyl-3-acetyl-3,6-dihydro-2H-pyran-6-yl)oxy]benzaldehyde **5** was characterized by IR spectrum with absorption bands at 1273cm^{-1} (C-O-C of benzoate group), 1228cm^{-1} (C-O-C of acetates), 1744cm^{-1} (C=O of the acetates) and 1720cm^{-1} (HC=O). The vibration frequency at 1641 cm^{-1} (C=C of glucal) and 1452 cm^{-1} (CH_3 of the acetates group) were also observed. ^{1}H NMR spectrum revealed the presence of aromatic protons at δ 7.81 (d, J=8.6Hz, 2H, Ar-H) and δ 6.93 (d, J=8.6Hz, 2H, Ar-H). The proton resonance at δ 9.86 (s, 1H, CHO), δ 5.70-6.13 (m, 2H, 2-H and 3-H), δ 5.29 (bs, 1H, 1-H), δ 2.09 (s, 3H, CH_3CO) and δ 2.05 (s, 3H, CH_3CO) confirmed the attachment of 4-hydoxybenzaldehyde to the 3,4,6-tri-*O*-acetyl-D-glucal (**1**). The IR and ^{1}H NMR spectra of **5** are shown in Figure 1b and Figure 2b.

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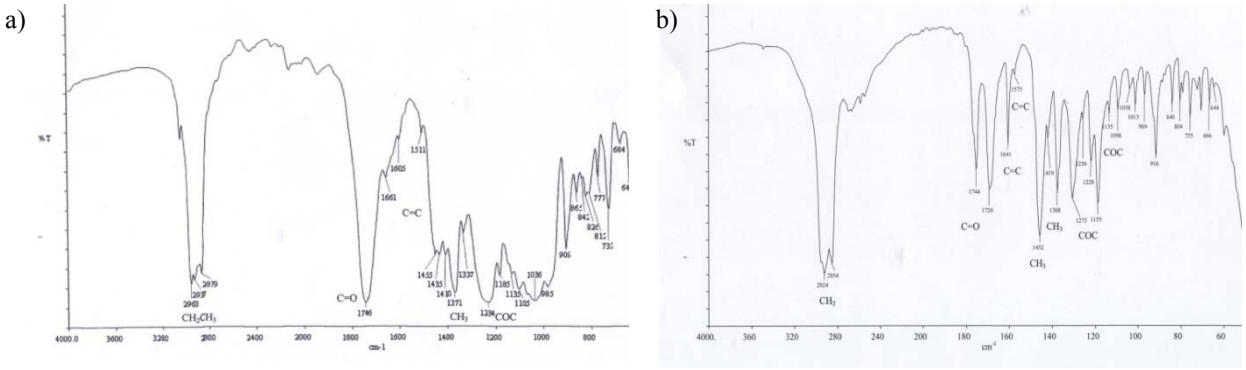


Fig.1 a) FT-IR spectrum of **3** and b) FT-IR spectrum of **5**

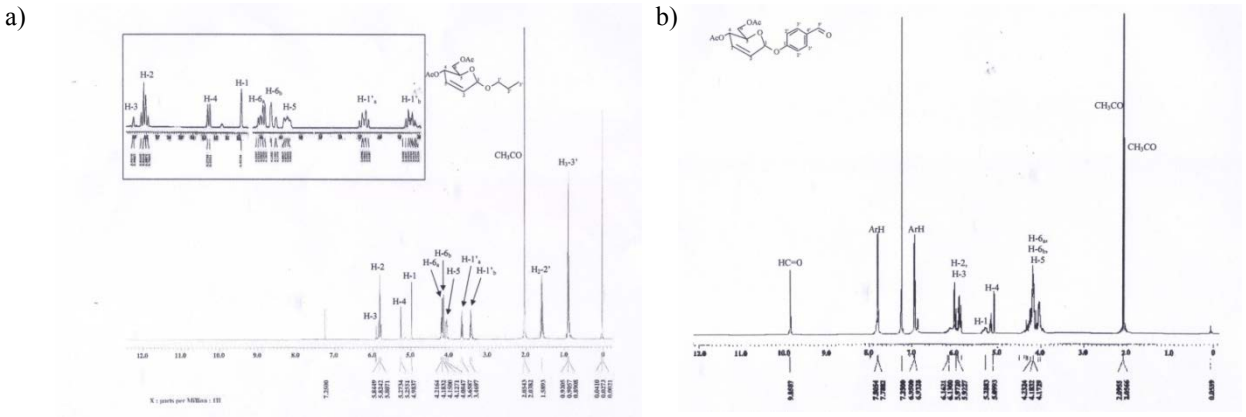


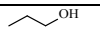
Fig. 2 a) ^{1}H NMR spectrum of **3** and b) ^{1}H NMR spectrum of **5**

The reaction of **1** with **2** and **4** respectively, in the presence of $La(NO_3)_3.6H_2O$ in CH_2Cl_2 afforded the desired products with moderate yields (entry 1(i,iii) in Table 1). Performing the reactions in CH_3CN were not increased the corresponding products despite longer reaction times (24 h).

In the reaction of **1** with **2** and **4** respectively, in the presence of $InCl_3$ as an activator, neither afforded **3** nor **5** with higher yield. Using $ZnCl_2$ as an activator only showed little effect on the reaction times and yield. The choice of CH_3CN as solvent, on the other hand, afforded 73% yield of **3** after stirring 30 min (entry 3(ii) in Table 1).

The reaction depicted in Scheme 1 afforded **3** and **5,** where each compound present as a mixture of α- and β-anomers. In all cases the α isomer was produced predominantly, and the different catalysts had little influence in the anomeric ratios. On TLC, their spots completely overlapped, and their separation was not achieved. The results of the reaction are presented in Table 1.

Table 1 Yield of 3 and 5 in various catalysts and solvents.

Entry	Cat.	Alcohol	Solvent/rt	Time	Yield (%)	α/β[a]
1	$La(NO_3)_3$.$6H_2O$		i) CH_2Cl_2	24 h	52	70:30
			ii) CH_3CN	24 h	59	80:20
			iii) CH_2Cl_2	17h	37	85:15
			iv) CH_3CN	17h	41	80:20
2	$InCl_3$		i) CH_2Cl_2	17h	52	85:15
			ii) CH_3CN	6 h	52	85:15
			iii) CH_2Cl_2	5 h	29	90:10
			iv) CH_3CN	45 min	37	90:10
3	$ZnCl_2$		i) CH_2Cl_2	30 min	66	90:10
			ii) CH_3CN	30 min	73	95:5
			iii) CH_2Cl_2	3 h	52	85:15
			iv) CH_3CN	4 h	41	85:15
4	BF_3•OEt_2		i) CH_2Cl_2	30 min	66	95:5
			ii) CH_3CN	15min	92	98:2
			iii) CH_2Cl_2	30 min	40	80:20
			iv) CH_3CN	15min	50	85:15

[a]*Anomeric ratios were determined by ^1H NMR spectroscopy.*

Encouraged by the initial results using $La(NO_3)_3.6H_2O$, $InCl_3$ and $ZnCl_2$ as activators, the choice of the Lewis acids was extended to BF_3•OEt_2. Interestingly, higher yields were obtained in the presence of BF_3•OEt_2 as the activator (entries 4(i,ii) in Table 1).

BF_3•OEt_2 has taken a strong prevalence among other catalysts involved in the reactions. The reaction of **1** with **2,** in the presence of BF_3•OEt_2 in CH_3CN afforded 92% of **3** in 15 min with α/β (98:2). The reaction of **1** with **4** however, afforded lower yields compared to that of **3**. This is due to the electron withdrawing properties of the aromatic ring in benzaldehyde, which under the acidic condition become a weaker nucleophile as compared to alkyl, resulting in lower yields [12].

Notably, the solvents have an important influence on the reaction efficiencies. The effect of different types of solvents was also studied. The polarity of the solvents tends to influence the reaction kinetics. CH_3CN gave better yields and shorter reaction times compared to CH_2Cl_2. The overall reactions is shown in Table 1.

4. CONCLUSION

The feasibility of using BF_3•OEt_2 has been demonstrated to furnish the corresponding alkyl and aryl 2,3-unsaturated glycopyranosides *via* Ferrier rearrangement. BF_3•OEt_2 exhibited excellent Lewis acids catalysts and minimum reaction times compare to other catalysts. This research is significant in the preparation of *O*-glycosides *via* Ferrier rearrangement.

ACKNOWLEDGEMENTS

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