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EXCLUSIVE FORMATION OF α-ANOMERS IN $NbCl_5$-PROMOTED FERRIER REARRANGEMENT FOR THE SYNTHESIS OF 2,3-UNSATURATED GLYCOSIDES [1]

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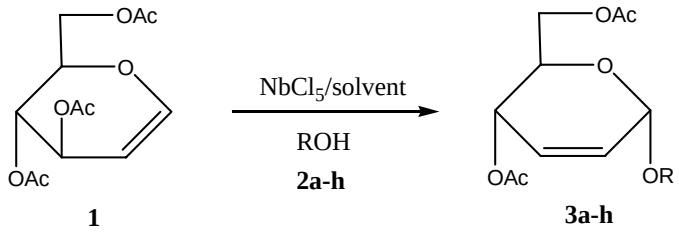
Abstract – $NbCl_5$-catalyzed reaction of primary and secondary alcohols with tri-*O*-acetyl-D-glucal is described. Exclusive formation of α-anomers of eight 2,3-unsaturated glycosides (**3a-h**) in high yields has been observed. Among eight unsaturated glycosides (**3a-h**) prepared, two of them (**3d,e**) are new. A new mechanism of the formation of (**3a-h**) from tri-*O*-acetyl-D-glucal and an alcohol assisted by $NbCl_5$ as a catalyst has been suggested.

INTRODUCTION

The initial discovery of $BF_3{\cdot}Et_2O$ as a Lewis acid catalyst by Ferrier and Prasad for transforming a glycal to a 2,3-unsaturated glycoside in the presence of an alcohol gave a big impetus to carbohydrate chemistry.[2] Since then many other acidic and oxidizing reagents have been employed for performing this reaction. A recent publication by Hotha and Tripathi cites several references concerning this type of transformation.[3] The unsaturated glycosides are an important class of compounds which can be transformed to a variety of other interesting and valuable carbohydrates.[4]

Due to our interest in Ferrier's rearrangement,[5,6] we focused our attention on the use of niobium pentachloride ($NbCl_5$) as a catalyst for carrying out such a transformation. This catalyst has been receiving increasing attention in organic synthesis.[7,8] Surprizingly, there is only one report in the literature on the use of this catalyst for the synthesis of 2,3-unsaturated glycosides assisted by microwaves.[3]

Generally, the Ferrier rearrangement is carried out in benzene or methylene chloride. Our aim was to see if it was possible to obtain the desired glycoside quickly using $NbCl_5$ in CH_2Cl_2 as solvent in a conventional manner; $NbCl_5$ is effectively a powerful activating agent for various organic reactions and certainly a strong Lewis acid.[8] In this communication, we report the synthesis of 2,3-unsaturated glycosides (**3a-h**) from tri-*O*-acetyl-D-glucal (**1**) and various alcohols (**2a-h**) (Scheme 1) in the presence of $NbCl_5$ using methylene chloride as well as THF as the solvent.



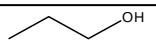
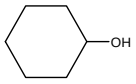
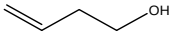
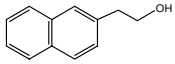
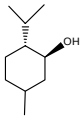
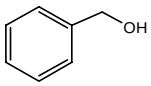
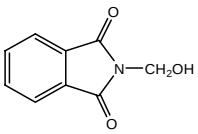
Scheme 1

RESULTS AND DISCUSSION

Initially, we expected that the reaction with tri-*O*-acetyl-D-glucal (**1**) and alcohols (**2a-g**) would go smoothly employing a catalytic amount of $NbCl_5$ (0.05 mole equiv.) in CH_2Cl_2. However, the reaction took place only in the presence of a large quantity of the catalyst (0.40 mole equiv. of $NbCl_5$) in this solvent. We noticed the precipitation of a solid arising probably from the complexation of $NbCl_5$ and the unsaturated carbohydrate. Therefore, more and more catalyst was needed to complete the reaction. Finally, 3,4,6-tri-*O*-acetyl-D-glucal (**1**) reacted with various alcohols (**2a-g**) in the presence of 0.4 mole equiv. of $NbCl_5$ to afford only 2,3-unsaturated α-D-glycosides (**3a-g**) in quite good yields (70-81%) as shown in Table 1 (Method A).

The anomeric configuration has been ascertained by obtaining the NOESY spectra of compounds (**3d** and **3e**). In both cases, H-1 showed a spatial interaction with H-4 proton, thus confirming the identity of these compounds as α-anomers. Furthermore, no interaction between H-1 and H-5 has been observed.

Table 1. Synthesis of 2,3-unsaturated *O*-glycosides (**3a-h**) from tri-*O*-acetyl-D-glucal (**1**)

	Alcohol	Product	Method A (0.4 equiv. $NbCl_5/CH_2Cl_2$) Time (min.)	Method A Yield (%)[a]	Method B (0.1 equiv. $NbCl_5$/THF) Time (min.)	Method B Yield (%)[a]	Yield (%)[c] (Reference)
2a		**3a**	60	70	50	74	95 (11)
2b		**3b**	30	75	50	71	87 (6)
2c		**3c**	30	81	50	87	64 (9)
2d		**3d**[b]	30	74	50	73	-
2e		**3e**[b]	60	77	50	75	(10)[d]
2f		**3f**	30	74	50	73	97 (2)
2g		**3g**	60	78	50	80	77 (6)
2h	CH_3CH_2OH	**3h**	-	-	50	72	(12)[d]

[a] Yield of purified product; [b] The spectral data are given in the experimental part; [c] Yields reported are the ones obtained by other procedures; [d] Yield not reported.

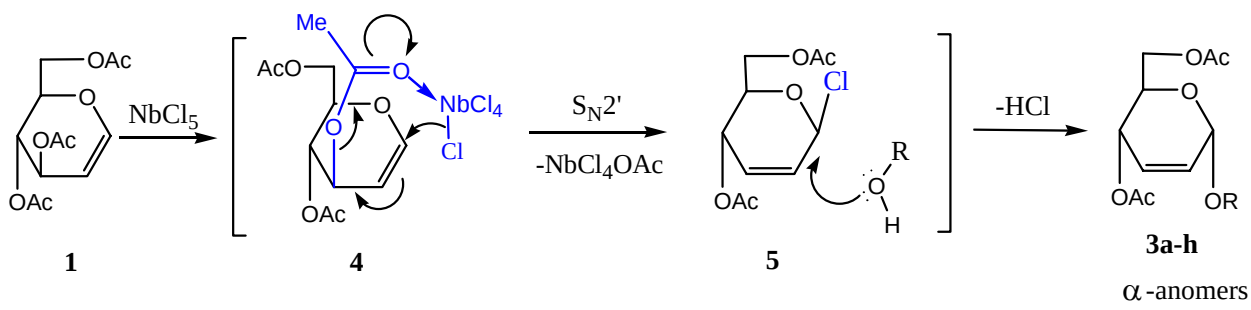
We tried to improve the above-mentioned method by using other solvents. As described above, addition of just 0.1 mol equivalent of $NbCl_5$ in CH_2Cl_2 either failed to react or gave only a very poor yield of the unsaturated glycosides at room temperature (Table 1). Addition of a few drops of acetonitrile to the CH_2Cl_2 solution improved the yield to some extent, but not satisfactorily. The introduction of a couple drops of DMF to the methylene chloride solution did not increase the yield as well. Finally, we found that replacement of methylene chloride with dry tetrahydrofuran and using 0.1 equiv of $NbCl_5$ gave a smooth reaction in 50 min. at reflux temperature, the complex remained soluble in the THF solution. The yields in this reaction are higher than those obtained when the condensation was performed in CH_2Cl_2, and ranged between 71-87% (Table 1, Method B), only the α-anomers have been formed. The use of THF as solvent for affecting Ferrier rearrangement at reflux temperature has not yet been reported in the literature (Table 1, Method B). Although, Ferrier´s rearrangement has recently been carried out in acetonitrile using

microwave radiation,[3] no report yet appeared about such reaction in solution employing conventional heating. Therefore, our findings are the new ones.

The exclusive formation of α-anomer requires some comments. Niobium pentachloride could complex with the carbonyl oxygen atom of the *O*-acetyl group at C-3 as shown in Scheme 2. Then one of the chlorine atoms of niobium pentachloride could attack at C-1 via a 8-membered transition state to furnish 4,6-di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl chloride (**5**) by a S_N2' mechanism. This β-anomer could revert to α-anomer after some time, but as soon as **5** is formed, it reacts with the alcohol instantaneously before anomerization of **5** to α-anomer. This leads to the privileged formation of the α-unsaturated glycosides (**3a-h**).

In order to get more perception about the formation of 4,6-di-*O*-acetyl-2,3-dideoxy-β-D-hex-2-enopyranosyl chloride (**5**) as an intermediate, we conducted the reaction between (**1**) and $NbCl_5$ in refluxing THF without alcohol. [13] After cooling the reaction contents and evaporating the solvent, the ^{1}H NMR spectrum of the crude mixture showed an absortion as a broad singlet at δ 5.90 ppm indicating the presence of presumably (**5**). However, NOESY spectrum does not show any spatial interaction between H-1 and H-5. Therefore, it is concluded that compound (**5**) forms first and then anomerizes quickly to its α-anomers. A closely related product, viz., 2,4,6-tri-*O*-acetyl-3-deoxy-α-D-*erythro*-hex-2-enopyranosyl chloride has been reported in the literature.[14] This product showed H-1 proton at δ 6.28 ppm, which is close to the α-anomer of **5**. This way, our assumption for the proposed mechanism seems more appropriate.

Although the previous authors [3] also reported the formation of α-anomers using $NbCl_5$, but no insight was given regarding the mechanism of formation. Therefore, we feel that this proposed mechanism is an important literature addition in this rearrangement.



Scheme 2. Mechanism of formation of α-anomers

One of the referees suggested to try the Ferrier's rearrangement using tri-*O*-benzyl-D-glucal and an alcohol in the presence of $NbCl_5$ to clarify the mechanism. Initially, we tried to do the reaction with alcohols (**2a,c,f**) and **1**, and verified on the tlc plates (10% EtOAc in $CHCl_3$), where the products of the reaction and tri-*O*-benzyl-D-glucal appeared to have the same R_f values, although it was a mixture. Finally, we performed to do the same reaction using **1** and ethanol (**2h**), which showed a better separation of the starting tri-*O*-benzyl-D-glucal and the allylic rearrangement products. Separation of the spots with R_f value of 0.40 (dichloromethane) followed by the ^{1}H NMR spectrum showed it to contain a mixture of ethyl 4,6-di-*O*-benzyl-2,3-dideoxy-α,β-D-*erythro*-hex-2-enopyranosides in the ratio of (1:1) in 60% yield. The literature search revealed that such reaction was done earlier in the presence of $BF_3{\cdot}Et_2O$ where α:β ratio was (2:1).[15] In summary, the mechanism of the Ferrier rearrangement with C-3 *O*-acetyl group is different that the one with C-3 *O*-benzyl function.

In conclusion, we have shown that the reaction of tri-*O*-acetyl-D-glucal with various alcohols does occur in methylene chloride as solvent, but using a large amount of niobium pentachloride as a catalyst. However, when the same reaction was carried out in THF, only 0.1 mol equivalent of $NbCl_5$ could be used, the unsaturated glycosides being obtained solely as α-anomers in quite good yields. It is worth mentioning that proposal of eight-membered transition state in Ferrier's rearrangement has not been encountered in the literature. Also, the use of THF at reflux temperature is being reported for the first time.

EXPERIMENTAL

General experimental procedures

All commercially available reagents were used as received. All reactions were monitored by TLC analysis (TLC plates GF_{254} Merck). Air- and moisture-sensitive reactions were performed under inert atmosphere techniques. Column chromatography was performed on silica gel 60 (230-240 mesh, Merck). Optical rotations were recorded using a Perkin-Elmer 241 polarimeter. NMR spectra were recorded with a Bruker AMX 300 spectrometer and referenced as following: ^{1}H (300 MHz), internal $SiMe_4$ at δ = 0.00 ppm, ^{13}C (75 MHz), internal standard at δ = 77.23 ppm. Exact mass spectra were recorded on a Finnigan Mat 95 XL spectrometer.

Method A: In a typical experiment, $NbCl_5$ (40 mg, 0.15 mmol) was added to a stirred solution of tri-*O*-acetyl-D-glucal (**1**) (100 mg, 0.37 mmol) dissolved in anhydrous methylene chloride (10 mL) at 0ºC under a nitrogen atmosphere. After a few minutes, the appropriate alcohol (**2**) (3.0 mmol) was added into the flask and the contents stirred at rt. In general, it took 30 min to an hour for the completion of the reaction (see Table 1). Then, the crude material was washed with a saturated aqueous solution of $NaHCO_3$ and extracted with AcOEt. Work-up, followed by chromatography, provided unsaturated glycoside (**3**).

Method B: $NbCl_5$ (27 mg, 0.1 mmol) was added to a stirred solution of tri-*O*-acetyl-D-glucal (**1**) (272 mg, 1 mmol) dissolved in anhydrous THF (2.0 mL) at 0ºC under a nitrogen atmosphere. After a few minutes, the appropriate alcohol (**2**) (1.5 mmol) was added and the mixture was refluxed for 50 min. The contents were cooled, and the work-up, as described above, afforded the unsaturated glycoside (**3**). All products were fully characterized by IR, ^{1}H- and ^{13}C- NMR spectra.

*2-Naphtalenoethyl 4,6-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (***3d***):* oil; $[\alpha]_{20}^{D}$ = + 73 (c 0.55, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO), 3.1 (t, 2H, *J* =7.0 Hz, CH_2), 3.83 (dt, 2H, *J* =9.6, 7.0 Hz, OCH_2), 3.96 (ddd, 1H, *J* =9.5, 5.4, 2.4 Hz, H-5), 4.03 (dd, 1H, *J* =2.4, 12.3 Hz, H-6), 4.13 (dd, 1H, *J* =5.4, 12.3 Hz, H-6'), 5.03 (brs, 1H, H-1), 5.28 (dd, 1H, *J* =9.6, 1.5 Hz, H-4), 5.81 (ddd, 1H, *J* =10.2, 2.4, 1.8 Hz, H-2), 5.87 (brd, 1H, *J* =10.2 Hz, H-3), 7.36-7.49 (m, 3H, ar.), 7.68 (brs, 1H, ar.), 7.77-7.83 (m, 3H, ar.). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.7, 20.9, 36.4, 62.8, 65.1, 66.8, 69.4, 94.4, 125.4, 126.0, 127.2, 127.4, 127.6, 127.7, 127.9, 129.1, 132.1, 133.5, 136.2, 170.2, and 170.7. Anal. Calcd for $C_{22}H_{24}O_6$, 1/4·H_2O: C, 67.94; H, 6.35. Found: C, 67.80; H, 6.55. $[M+Na]^+$ = Calcd. 407.1471. Found: 407.1473.

*(1S,2R,5S)-Menthyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (***3e***):* oil; $[\alpha]_{20}^{D}$ = + 46 (c 0.75, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (d, 3H, *J* =7.0 Hz, CH_3), 0.91 (2d, 6H, *J* =7.0 Hz, $2CH_3$), 0.77-2.05 (m, 9H, $3CH_2$, 3CH), 2.08 (s, 3H, CH_3CO), 2.11 (s, 3H, CH_3CO), 3.42 (dt, 1H, *J* =10.6, 4.5 Hz, CHO), 4.16-4.23 (m, 3H, H-6, H-6', H-5), 5.10 (brs, 1H, H-1), 5.29 (brd, 1H, *J* =10.5 Hz, H-4), 5.87 (brs, 2H, H-2, H-3). 13C NMR (75.5 MHz, $CDCl_3$): δ 16.6, 21.1, 21.4, 21.5, 22.8, 23.5, 26.0, 32.1, 34.7, 43.7, 49.2, 63.7, 65.7, 67.1, 81.5, 96.5, 128.4, 129.0, 170.7, 171.2. Anal. Calcd for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75. Found: C, 65.22; H, 8.81.

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