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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 4555–4558

Niobium(V) chloride catalyzed microwave assisted synthesis of 2,3-unsaturated *O*-glycosides by the Ferrier reaction

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Received 7 February 2005; revised 27 April 2005; accepted 5 May 2005

Abstract—$NbCl_5$ catalyzes the Ferrier reaction of per-*O*-acetylated glycals with primary, secondary, allylic, benzylic and monosaccharide alcohols to give 2,3-unsaturated α-glycosides in short reaction times under microwave irradiation conditions.

In the current era of chemical genetics, the importance of diversity oriented synthesis (DOS) of small molecule libraries with defined stereochemistry and interesting chemical skeletons has increased.[1] The starting template in the diversity oriented synthesis occupies a predominant role in dictating the resulting skeletal and stereochemical diversities.[2] A recent survey indicated that a large number of biologically active natural products are oxygen-rich compared with the corresponding congeners thus far synthesized from combinatorial libraries.[3] In view of the above facts, we became interested in initiating a diversity oriented synthesis using glycals as the starting template to enable oxygen-rich stereochemically pure scaffolds.

One of the important reactions to produce diversity in glycal chemistry is the Ferrier reaction that gives access to 2,3-unsaturated glycosides.[4] Some of the syntheses using 2,3-unsaturated glycosides as important intermediates comprise various natural products,[5] glycopeptides,[6] modified carbohydrate derivatives,[7] nucleosides and oligosaccharides.[8] The 2,3-double bond in the pyran ring can be subjected to stereoselective dihydroxylation, hydrogenation, epoxidation and amino hydroxylation reactions in order to achieve structural complexity and diversity.[9] The S_N2' attack of alcohols or allylic rearrangement of per-*O*-acetylated glycals was discovered by Ferrier using $BF_3{\cdot}Et_2O$ as the Lewis acid catalyst and is known as the Ferrier reaction.[4] Other reagents that effect this transformation include $InCl_3$,[10a] Montmorillonite K10,[10b] $SnCl_4$,[10c] $BiCl_3$,[10d] $FeCl_3$,[10e] $Sc(OTf)_3$,[10f] $ZnCl_2$,[10g] $LiBF_4$,[10h] $Dy(OTf)_3$[10i] and $ZrCl_4$.[10j] In addition to these Lewis acids, oxidizing agents such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),[11a] *N*-iodosuccinimide (NIS),[11b] iodine,[11c] iodonium dicollidine perchlorate (IDCP),[11d] ceric ammonium nitrate[11e] and $HClO_4$ on silica gel[11f] effect the Ferrier reaction to yield 2,3-unsaturated glycopyranosides. However, all these methods have drawbacks in generality, varied yields and stereoselectivity, long reaction times and practicality due to harsh reaction conditions. In view of the above, there exists a need to develop a practical stereoselective method that yields 2,3-dideoxy glycosides.

Thus in our efforts to utilize glycal chemistry to achieve diverse scaffolds, we focused on developing a practical, low-cost, eco-friendly, procedure for synthesizing 2,3-dideoxy glycopyranosides. The use of microwave reaction conditions with carbohydrate templates is not yet a mature subject, albeit various successful efforts in conventional organic synthesis exist. The use of microwaves in the Ferrier reaction were explored using Montmorillonite K10 and $InCl_3$. The microwave induced Montmorillonite K10[10b] mediated Ferrier rearrangement of per-*O*-acetylated glucal resulted in the formation of 2,3-unsaturated glucosides; the corresponding $InCl_3$[10a] reaction gave α-anomeric selectivity, however, 30 mol% of $InCl_3$ was required. Recently niobium(V) chloride has emerged as a Lewis acid for a variety of reactions.[12] In particular $NbCl_5$ has many advantages compared with other Lewis acids such as ease of handling, moisture stability, long shelf-life and economic viability, all factors that are required in DOS.[13] In this article, we describe

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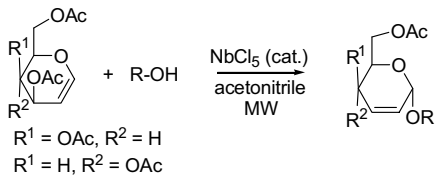
doi:10.1016/j.tetlet.2005.05.015



Scheme 1. Synthesis of 2,3-dideoxy glycopyranosides using $NbCl_5$.

a microwave assisted method for the synthesis of 2,3-unsaturated *O*-glycosides by the Ferrier reaction using a catalytic amount of niobium(V) chloride (Scheme 1).

In a typical experiment,[14] per-*O*-acetylated glucal in the presence of an alcohol was treated with one mole percent of $NbCl_5$ in acetonitrile and irradiated with microwaves in an open vessel for the specified time (Table 1) in order to afford the corresponding 2,3-unsaturated glycosides in good yields with α-stereoselectivity. All the reactions were complete in less than 3 min. It is interesting to note that the reaction of 3,4,6-tri-*O*-acetyl glucal with benzyl alcohol at room temperature required 1 h to yield benzyl 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-eno α-D-glucopyranoside, whereas the corresponding reaction under microwave conditions was complete in two minutes (entry 6, Table 1), thereby making this reaction a microwave oven-induced reaction enhancement (MORE) technique.[15] The generality of this new reagent was shown by exposing per-*O*-acetylated glucal to various alcohols including allylic, benzylic, aliphatic, phenolic and monosaccharide donors. We also tested our protocol on 3,4,6-tri-*O*-acetyl galactal using various aglycones. It is pertinent to mention that not many methods are available for the Ferrier reaction of 3,4,6-tri-*O*-acetyl galactal. Treatment of 3,4,6-tri-*O*-acetyl galactal in the presence of an alcohol with $NbCl_5$ (cat.) in acetonitrile and irradiation with microwaves for less than 3 min resulted in the formation of the Ferrier product 4,6-di-*O*-acetyl-2,3-dideoxy-D-*threo*-hex-2-eno-α-D-galactopyranoside along with a minor quantity of 2-deoxy-α-D-*lyxo*-hexopyranoside.[16] In order to understand the scope of this reaction we exposed different aglycones to 3,4,6-tri-*O*-acetyl galactal (entries 11–20, Table 1). In almost all the reactions, the ratio of the Ferrier product versus the 2-deoxy

Table 1. $NbCl_5$ catalyzed microwave assisted synthesis of 2,3-unsaturated Ferrier rearranged products

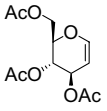
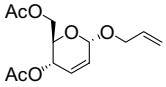
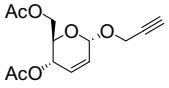
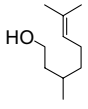
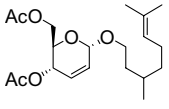
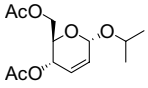
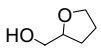
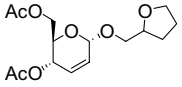
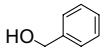
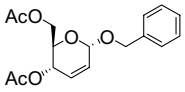
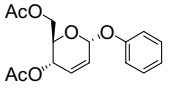
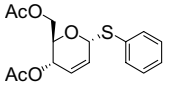
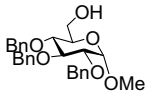
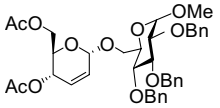
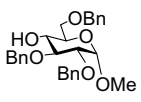
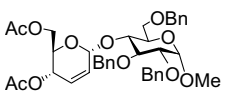
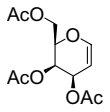
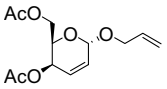
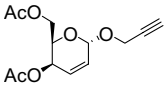
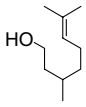
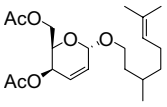
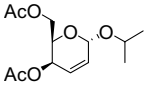
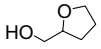
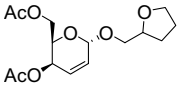
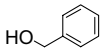
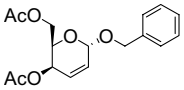
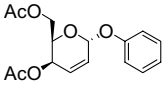
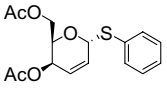
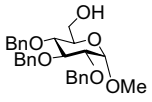
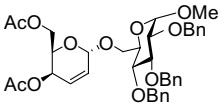
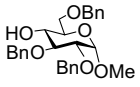
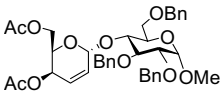
Entry	Substrate	Alcohol	Product	Time (min)	Yield (%)
1				2.0	95
2				2.5	92
3				2.0	80
4				1.5	85
5				2.0	93
6				2.0	97
7				3.0	84
8				2.0	87
9				3.0	90
10				3.0	87

Table 1 (*continued*)

Entry	Substrate	Alcohol	Product	Time (min)	Yield (%)
11				1.5	79
12				2.5	73
13				3.0	72
14				2.0	69
15				2.0	74
16				1.0	80
17				2.0	76
18				2.5	73
19				3.0	74
20				3.0	68

compound was found to be 4:1 after isolation of the respective compounds by conventional silica gel column chromatography. ^{1}H and ^{13}C NMR spectra of all the compounds were in conformity with those reported values.[17]

In conclusion, we disclosed herein a practical methodology for the synthesis of 2,3-dideoxy glycopyranosides in a stereoselective manner using a catalytic quantity of $NbCl_5$ under microwave irradiation conditions. Our current endeavors are devoted to the incorporation of this protocol into our diversity oriented synthesis pathway development programs using glycals as starting templates.

Acknowledgements

We thank the Director, NCL for a Start-up grant and DST, New Delhi for the financial support. We thank Dr. K. N. Ganesh for support and encouragement. A.T. thanks the CSIR, New Delhi for a Junior Research Fellowship.

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14. Typical experimental procedure: to a mixture of glycal (1 mmol) and alcohol (1.5 mmol) in acetonitrile (2 mL) was added $NbCl_5$ (0.01 mmol) and the mixture irradiated with microwaves (Kenstar Model No. OM-9918C; 2450 MHz, 2350 W) for the specified period of time in an open vessel. After completion of the reaction, the reaction mixture was diluted with water and extracted twice with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulphate and concentrated in vacuo. The product was purified by silica gel column chromatography using ethyl acetate and light petroleum (60–80 °C).
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17. All new compounds gave satisfactory ^1H NMR, ^{13}C NMR and CHNS analysis.