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Journal of Molecular Catalysis A: Chemical 223 (2004) 237–240
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
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Synthesis of 2,3-unsaturated glycopyranosides by Ferrier rearrangement in $FeCl_3$ based ionic liquid

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Received 10 February 2003; received in revised form 8 October 2003; accepted 1 November 2003
Available online 23 September 2004

Abstract

A novel and stereocontrolled glycosidation of 3,4,6-tri-*O*-acetyl-D-glucal with various alcohols to give the corresponding 2,3-unsaturated glycopyranosides using [bmim]Cl–1.5$FeCl_3$ based ionic liquid is presented. This ionic liquid has proved to be an efficient reaction medium, playing a dual role of a catalyst as well as of a solvent. Salient features of this simple methodology include non-hazardous reaction conditions, good yields in short reaction times and high anomeric selectivity.

Keywords: Ferrier rearrangement; Lewis acidic iron (III) chloride based ionic liquid; 2,3-Unsaturated glycopyranosides

1. Introduction

Glycosidation of organic compounds have attracted considerable attention in current synthetic organic chemistry related to both biomolecules and functional materials [1]. Lewis acid catalyzed allylic rearrangement of glycals, known as the Ferrier rearrangement, is the method of choice for the synthesis of 2,3-unsaturated glycopyranosides [2]. These have proven to be versatile intermediates in the synthesis of glycopeptide building blocks, uronic acids, modified carbohydrates, nucleosides and oligosaccharides. Valuable from synthetic pointstand is the preservation of the carbon–carbon double bond (Scheme 1), which can be further modified into a variety of derivatives. 2,3-Dideoxy sugars, which are easily derived from 2,3-unsaturated glycopyranosides, are common structural units in many significant molecules such as antibiotics.

New ways to achieve this transformation continues to receive attention in spite of the availability of the existing methods. A wide range of acid reagents such as $InCl_3$, $FeCl_3$, $BiCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, montmorillonite K10 have been used to effect this transformation [3–8]. Also, neutral conditions involving use of ionic liquids and reagents such as DDQ, *N*-iodosuccinimide, $CeCl_3{\cdot}7H_2O$ are known to bring about the glycosidation of glucals [9–12]. With a few exceptions, most of the methods have shortcomings such as long reaction times, highly acidic conditions and use of volatile organic solvents. Moreover, many of the Lewis acids are moisture sensitive and metal triflates are highly expensive. Therefore, the search for newer and efficient synthetic methodologies with greater efficiency and convenient procedures continues to be a challenge.

The toxic and/or hazardous properties of many solvents, notably chlorinated hydrocarbons, combined with serious environmental issues is making their use prohibitive. This is an important driving force in the quest for novel reaction media. Since the pioneering work of Seddon, ionic liquids have emerged as a new class of stable, inert solvents with unique properties [13–16]. Their purely ionic character makes them excellent solubilizers for a wide range of inorganic, organic as well as organometallic substrates, thus substituting polar

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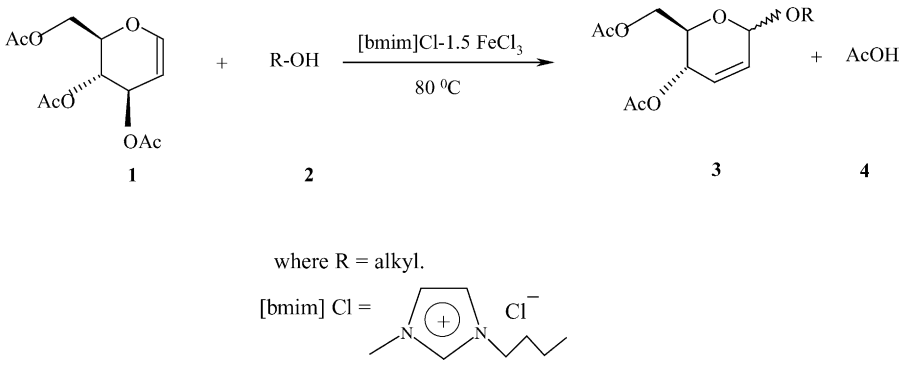
doi:10.1016/j.molcata.2003.11.044



Scheme 1. Glycosidation of 3,4,6-tri-*O*-acetyl-D-glucal by [bmim]Cl–1.5$FeCl_3$.

aprotic solvents. Coupled with the fact that they are easy to handle and non-explosive, ionic liquids provide a widely accessible temperature range with lack of flammability. Other important attributes of ionic liquids include negligible vapor pressure (thus reducing the degree of harmful emissions compared with conventional organic solvents), recylability (except in the case of acidic ionic liquids) and ease of separation of products from reaction mixture. Furthermore, a precision tuning of their properties such as melting point, viscosity, density and hydrophobicity can be achieved by suitable combination of cation and anion. Thus, as a result of their 'green' credentials and potential to enhance reaction rates and selectivities, ionic liquids opens a new frontier of reinventing organic reactions practiced in chemical industry.

In the light of their promising physical and chemical properties, chloroaluminate ionic liquids have been an active and exciting area of our investigation for quite some time [17–21]. However, chloroaluminate ionic liquids have the problem of the low tolerance to moisture necessitating the use of glovebox and Schlenk techniques in preparation and study of their properties. This problem is solved by replacing Al with less reactive metals. Recently, Freeman et al have prepared ionic liquids by just mixing either iron (II) chloride or iron (III) chloride with 1-butyl-3-methylimidazolium chloride [bmim]Cl. At room temperature, iron (III) chloride forms ionic liquid with [bmim]Cl from an apparent mole fraction of $FeCl_3$ ranging from 0.34 to 0.63 [22].

A novel aspect of these ionic liquids is their adjustable Lewis acidity; substantial variations in acidity can be effected simply by varying the molar ratio of the two components. The composition of iron (III) chloride ionic liquid is best described by the apparent mole fraction of $FeCl_3$, *N*. Chloroferrate melts are designated as *basic* when $N < 0.5$, *neutral* when $N = 0.5$ and *acidic* when $N > 0.5$, respectively.

In our initial ventures using chloroferrate ionic liquids, we have carried out Biginelli condensation and Friedel–Crafts sulphonylation reaction [23]. The remarkable Lewis acidity of these ionic liquids, prompted us to investigate Ferrier rearrangement in such a system. We herein report for the first time Ferrier rearrangement in Lewis acidic [bmim]Cl–1.5$FeCl_3$ ionic liquid.

2. Experimental

2.1. Materials

1-Methylimidazole and 1-chlorobutane were purchased from Lancaster and Merck, respectively, and were used without further purification. Iron (III) chloride was procured from M/s S.D. Fine Chemical Ltd., Mumbai, India.

3,4,6-Tri-*O*-acetyl-D-glucal was prepared as described by Roth and Pigman [24]. All alcohols were supplied by

Table 1
Influence of Lewis acidity on Ferrier rearrangement of 3,4,6-tri-*O*-acetyl-D-glucal with 1-butanol in [bmim]Cl–*x*$FeCl_3$[a]

No.	*N*	$FeCl_3$ w.r.t. D-glucal (mol%)	Amount of ionic liquid (mmol)	Yield[b] (%)
1	0.4	10	0.032	22
2	0.4	100	0.362	41
3	0.5	10	0.032	20
4	0.5	100	0.364	44
5	0.6	5	0.009	48
6	0.6	10	0.021	94

[a] Reactions were performed using 3,4,6-tri-*O*-acetyl-D-glucal (0.367 mmol), 1-butanol (0.403 mmol) in [bmim]Cl–*x*$FeCl_3$ at 80 °C and were quenched after 45 min.

[b] Yields were calculated on the basis of area normalization method using HPTLC analysis.

Table 2
Effect of temperature[a]

No.	Temperature (°C)	Time (h)	Yield[b] (%)
1	30	3.5	89
2	60	1.5	90
3	80	0.45	94

[a] Reactions were performed using 3,4,6-tri-*O*-acetyl-D-glucal (0.367 mmol), 1-butanol (0.403 mmol) and [bmim]Cl–1.5$FeCl_3$ ($N = 0.6$, 0.021 mmol).

[b] Yields were calculated on the basis of area normalization method using HPTLC analysis.

M/s S.D. Fine Chemical Ltd. and were distilled prior to use.

2.2. Reaction procedure

2.2.1. Preparation of [bmim]Cl–$xFeCl_3$ based ionic liquid

A 100 ml round bottom flask was charged with 1-methylimidazole (22 ml, 276 mmol) and 1-chlorobutane (33 ml, 287 mmol) and heated to 75 °C for 48 h. The excess 1-chlorobutane was removed in vacuo at 80 °C. The resulting viscous liquid on refrigeration gave a white solid ([bmim]Cl) which was dried under vacuo. The ionic liquid was prepared by direct mixing of anhydrous $FeCl_3$ and [bmim]Cl [23].

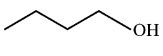
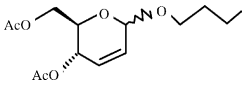
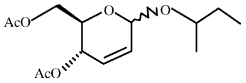
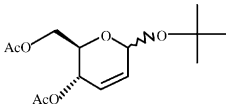
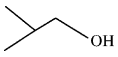
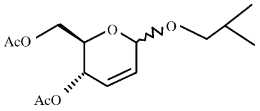
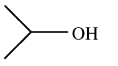
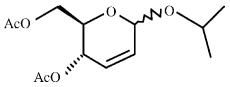
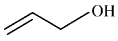
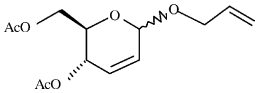
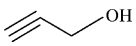
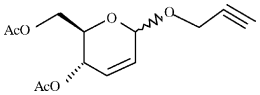
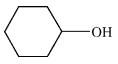
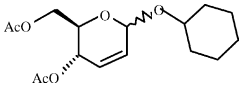
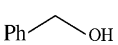
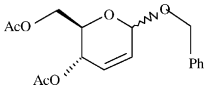
2.2.2. Glycosidation procedure

To a weighed quantity of ionic liquid (N = 0.6, 0.119 mmol) was added 3,4,6- tri-*O*-acetyl-D-glucal **1** (0.5 g, 1.83 mmol) and alcohol **2** (2.01 mmol). The contents were stirred at 80 °C for the specified time as indicated in Table 3. After complete conversion of 3,4,6-tri-*O*-acetyl-D-glucal (monitored by TLC), the reaction mixture was quenched with cold aqueous solution of sodium bicarbonate and extracted with diethyl ether (2 ml × 10 ml). The combined organic extract was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography on silica gel (M/s S.D. Fine Chemical Ltd., 60–120 mesh, petroleum ether (60–80):EtOAc, 7:3) to afford the pure glycoside 3. NMR spectra were recorded on a Varian—VXR spectrometer in $CDCl_3$ using TMS as internal standard.

2.2.3. High performance thin layer chromatography (HPTLC)

The reactions were performed using **1** (0.367 mmol) under the conditions mentioned in Tables 1 and 2, followed by usual work-up. The crude products were diluted with 15 ml of dichloromethane. The samples were assayed employing the CAMAG Linomat IV sample applicator (5 μl sample applied for each analysis) on silica gel 60 F_{254} pre-coated plates. The plates were developed in a twin trough chamber using petroleum ether:ethyl acetate (7/3, v/v) mobile phase and derivatised (by dipping in derivatising agent (1% anisalde-

Table 3
Glycosidation of 3,4,6-tri-*O*-acetyl-D-glucal by [bmim]Cl–1.5$FeCl_3$

No.	Alcohol	Product	Time (h)	Yield[a] (%)	Anomeric ratio[b] (α:β)
1			0.45	89	Only α observed
2			1.0	82	70:30
3			0.45	85	Only α observed
4			1.0	81	86:14
5			1.0	82	70:30
6			0.45	80	60:40
7			1.15	78	60:40
8			1.0	90	Only α observed
9			1.0	87	70:30

Reaction conditions: 3,4,6-tri-*O*-acetyl-D-glucal (1.83 mmol), alcohol (2.01 mmol), [bmim]Cl–$FeCl_3$ (N = 0.6, 0.119 mmol); Temperature: 80 °C.

[a] Isolated yields as pure anomeric mixtures after purification.

[b] The anomeric ratio was determined on the basis of the anomeric hydrogens in the ^{1}H NMR spectra at 300 MHz.

hyde (w/v), 1% concentrated H_2SO_4 (w/v) and 1% glacial acetic acid (w/v) in methanol) and subsequently heating in an oven at 100 °C for 10 min. The plates were scanned on a CAMAG TLC Densitometric Scanner 3 (tuned at 500 nm) equipped with the Cats 3.0 version software to obtain the chromatograms.

3. Results and discussion

We report here our recent findings on the *O*-glycosidation of acetylated glucals with alcohols to give the corresponding 2,3-unsaturated glycopyranosides in [bmim]Cl–1.5$FeCl_3$ ionic liquid. As can be seen from Scheme 1, our approach is elegantly simple.

To gain some preliminary information of this synthetically useful reaction, screening experiments were performed. For all these studies, 1-butanol was the alcohol of choice. In order to establish the influence of Lewis acidity on the reaction, 3,4,6-tri-*O*-acetyl-D-glucal was allowed to react with 1-butanol in different melt compositions, i.e. $N = 0.4$–0.6. As anticipated, best results were obtained with increase in the Lewis acidity i.e. $N = 0.6$, [bmim]Cl–$FeCl_3$ (Table 1).

Further, we observed that at room temperature the reaction was too sluggish; it took 3.5 h for the completion of the reaction. On the other hand, when the reaction was carried out at 80 °C, maximum yield was obtained within a short reaction time of 45 min using 1-butanol (Table 2). Hence, all further investigations were carried out at 80 °C.

Having established what appeared to be the optimal conditions, we switched our attention to generalize this reaction. A variety of alcohols were then reacted with this remarkably simple procedure and the results are summarized in Table 3. As shown, the glycosidation of 3,4,6-tri-*O*-acetyl-D-glucal with primary, secondary, tertiary, allyl, propargyl and cyclohexyl alcohols proceeded smoothly under similar conditions to give the corresponding 2,3-unsaturated glycopyranosides in good yields with high stereoselectivities. A noteworthy point is that in all the products α-anomer is predominant which can be attributed to the anomeric effect. The experimental procedure is simple and does not require the use of expensive or corrosive reagents. The only cases where the above-mentioned glycosidation were not feasible were compounds with phenolic/thiol groups. Green coloration was obtained, suggesting a strong complexation of the catalyst to these substrates.

4. Conclusion

In conclusion, we have developed a new and efficient method for the synthesis of 2,3-unsaturated glycopyranosides by the glycosidation of 3,4,6-tri-*O*-acetyl-D-glucal with various alcohols using [bmim]Cl–1.5$FeCl_3$ ionic liquid. The highlighting features of this method, which include simple and ecofriendly protocol, good yields and high level of stereoselectivity should find widespread application for the synthesis of biologically important natural products. Further studies in this subject are in progress.

Acknowledgements

This paper is dedicated to late Dr. Bhushan M. Khadilkar. We gratefully acknowledge BRNS (99/37/39/BRNS/1749) for financial assistance and the G.D. Gokhale Trust for awarding fellowship to one of the authors. RSIC-IIT, Mumbai is gratefully acknowledged for recording the NMR spectra.

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