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Environmentally Benign Synthesis of 2,3-Unsaturated Glycopyranosides in Task-Specific Ionic Liquid

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Abstract A green reaction condition has been developed for the synthesis of 2,3-unsaturated glycopyranosides by the Ferrier rearrangement of glycals using alcohols and thiols in 1-butyl-3-methylimidazolium trifluoromethanesulfonate ([BMIM]·OTf) in excellent yield. [BMIM]·OTf has been applied as a task specific ionic liquid organo-catalyst. Operational simplicity, environmentally benign reaction condition, use of task specific ionic liquid, short reaction time, high yields are the notable features of this methodology.

Keywords Ferrier rearrangement · Ionic liquid · Environmentally benign · 2,3-unsaturated glycosides · Glycal

1 Introduction

2,3-Unsaturated glycosides or pseudoglycals are useful intermediates for the synthesis of pharmacologically active molecules [1, 2]. They have been successfully used as chiral building blocks in the multi-step synthesis of several antibiotics [3, 4]. Conventionally, 2,3-unsaturated glycosides are prepared by the allylic rearrangement of acyloxy glycals (popularly known as Ferrier Rearrangement) catalyzed by a Lewis acid [5, 6]. Because of their synthetic utility several reports have appeared in the literature for the improvement of the Ferrier reaction using a variety of metallic and non-metallic catalysts [7–17]. Besides these, a number of heterogeneous catalysts have also been applied for this transformation [18–22]. Ferrier rearrangement of acetoxy glycals has also been carried out under microwave irradiation [23–26]. Despite of their strong influence in the preparation of 2,3-dideoxy glycopyranosides, many of the above-mentioned catalysts suffer from several shortcomings, such as lack of environmentally friendliness, use of strong acidic catalyst, use of expensive catalysts, requirement for the preparation of catalysts, oxidizing conditions, longer reaction times, use of organic solvents, unsatisfactory yields, use of an excess of reagent or catalysts etc. As a consequence, there is a constant need to develop an environmentally benign mild reaction condition for the preparation of 2,3-unsaturated glycopyranosides using less hazardous catalyst and reaction medium.

As a part of the current thrust in the development of environmentally friendly catalytic processes, we set out to explore the potential of 1-butyl-3-methylimidazolium trifluoromethanesulfonate ([BMIM]·OTf) as a task-specific ionic liquid in the Ferrier rearrangement of acetoxy glycals as catalyst and reaction medium. Room temperature ionic liquids have attracted significant attention of synthetic chemists for their capability to act as green reaction medium as well as organo-catalyst [27–35]. In the recent past, several organic transformations have been carried out in the ionic liquids under green reaction conditions [36–43]. Earlier, Salunkhe et. al. [44] reported a comparative investigation on the metal nitrate catalyzed Ferrier rearrangement of glycal derivatives in organic solvents and ionic liquids and showed that the use of ionic liquid improves yield of the products and stereoselectivity. We report herein, Ferrier rearrangement of acetoxy glycals with alcohols and thiols for the preparation of 2,3-

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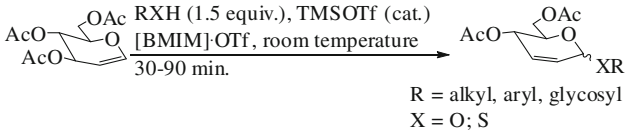


Scheme 1 Ferrier rearrangement of acetoxy glycals in ionic liquid [BMIM]·OTf at room temperature

unsaturated *O*- and *S*-glycosides using [BMIM]·OTf as organo-catalyst as well as solvent under an environmentally benign reaction condition avoiding organic solvents and hazardous chemicals (Scheme 1).

2 Results and Discussion

In a set of initial experiments, triacetoxy-D-glucal (**1**) was allowed to react with 2-propanol (1.5 equiv. to 5.0 equiv.) in 1-butyl-3-methylimidazolium trifluoromethanesulfonate ([BMIM]·OTf; 0.5–1.0 mL/mmol of substrate) by addition of a catalytic amount (~1.0 μL) of trimethylsilyl trifluormethanesulfonate (TMSOTf) at room temperature. After some experimentation, it was observed that use of 2-propanol (1.5 equiv.) in [BMIM]·OTf (0.5 mL/1 mmol of substrate) in the presence of catalytic TMSOTf furnished 82% yield of compound **3** (α/β: 4/1) at room temperature in 40 min. Under similar reaction condition various aliphatic alcohols and hydroxy sugar derivatives reacted with triacetoxy-D-glucal (**1**) to furnish alkyl 2,3-unsaturated glucopyranosides and disaccharides in excellent yield (Table 1). A variety of functional groups such as allyl, propargyl, isopropylidene, benzyl, isopropyl groups remained unaffected under the reaction conditions and formation of by-products was not observed. The reaction condition has been successfully applied for the reaction of aryl thiols with compound **1** to furnish 2,3-unsaturated thioglucosides in good to excellent yield. It is worth mentioning that formation of further rearranged product was not observed using thiols, which were evidenced earlier in this reaction. Competitive reaction for the formation of 2-deoxy glycoside derivatives was not observed in all cases. Similar to triacetoxy-D-glucal (**1**), a set of aliphatic alcohols and monosaccharide acceptor were reacted with triacetoxy-D-galactal (**2**) under similar reaction condition to furnish 2,3-unsaturated galactopyranosides in satisfactory yield. In the case of triacetyl-D-galactal (**2**) the reactions took longer time and the yields were slightly lower in comparison to its D-glucal counterpart. Reaction of triacetyl-D-galactal (**2**) with thiols resulted in the formation of some 2-deoxy products together with the expected 2,3-unsaturated products, which can be explained from the structure of the starting substrate (Table 1, entry 20). In most of the cases, a mixture two anomers of 2,3-unsaturated glycosides (α and β were obtained, the ratio of which were determined by comparing the integration values of the peaks in ^{1}H NMR, ^{13}C NMR (Table 1). The α-configuration of the major product was confirmed from the positions of the anomeric protons in the ^{1}H NMR and ^{13}C NMR spectra. In the ^{1}H NMR spectrum, the H-1 of the α-glycoside appears in an up field position compared to its β-isomer. The α-stereochemistry of the anomeric center of the major products was further confirmed from the NOE study. A strong NOE between H-1 and H-4 was observed in the D-glucal derived and such interaction was absent in the D-galactal derived product. [BMIM]·OTf acts as a task specific ionic liquid which plays dual role as an organo-catalyst as well as reaction medium. Addition of a catalytic amount of TMSOTf as activator to the reaction medium drives the reaction towards the formation of products and [BMIM]·OTf acts as a source of triflate ion to maintain the catalyst concentration in the reaction. In a control reaction, treatment of compound **1** with 2-propanol in [BMIM]·OTf in the absence of catalytic TMSOTf did not produce any product and the substrate remained unaffected even after 24 h at room temperature justifying the requirement of a catalytic TMSOTf for the initiation of the reaction. Other available room temperature ionic liquids ([BMIM]·Cl, [BMIM]·BF_4 and [BMIM]·PF_6) were also tested for their efficacy in the Ferrier reaction and [BMIM]·OTf was found best in terms of solubility of the substrates, yield of product and reaction time (Table 2). Acting as an organo-catalyst, [BMIM]·OTf has strong influence on the reaction providing the OTf- counter anion to facilitate the formation of the products. The experimental condition is simple and isolation of the products and recovery of the ionic liquid can be achieved using EtOAc and H_2O which are recommended solvents [45] to carry out green reactions.

3 Conclusion

In conclusion, a green reaction condition has been developed for the Ferrier rearrangement of acetoxy glycal derivatives using alcohols and thiols in a task-specific room temperature ionic liquid ([BMIM]·OTf) avoiding the use of hazardous chemicals. The reaction is reasonably fast, clean, environmentally benign, high yielding with high anomeric selectivity. Therefore, this reaction condition provides a better and practical alternative to the existing procedures for this reaction.

4 Experimental

Typical experimental procedure for the Ferrier rearrangement of 3,4,6-tri-O-acetylated-D-glucal (**1**): To a

Table 1 Ferrier rearrangement of glycals in [BMIM]·OTf catalyzed by TMSOTf at room temperature

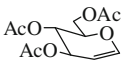
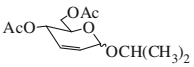
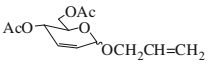
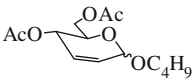
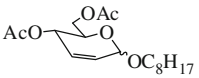
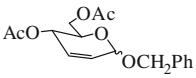
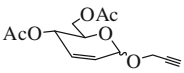
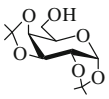
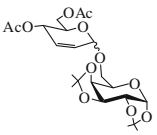
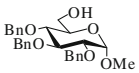
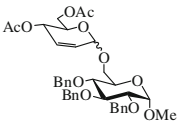
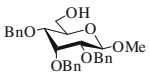
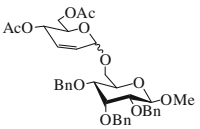
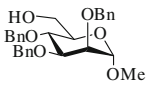
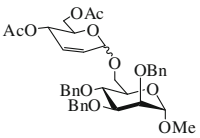
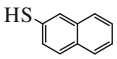
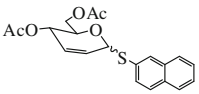
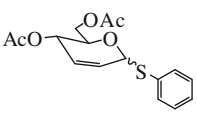
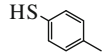
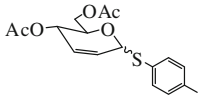
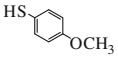
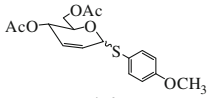
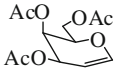
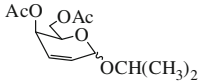
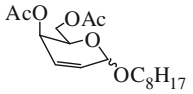
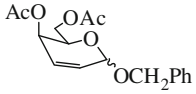
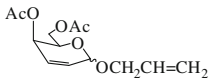
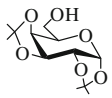
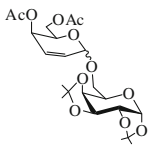
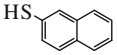
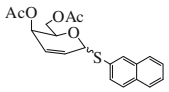
Sl. No.	Glycal	Alcohol/thiol	Product	Time (min)	Yield[a] (%)	α/β[b]	Ref.
1	 **1**	2-Propanol	 **3**	40	82	4:1	[5]
2	**1**	Allyl alcohol	 **4**	45	80	6:1	[46]
3	**1**	1-Butanol	 **5**	40	82	4:1	[47]
4	**1**	1-Octanol	 **6**	45	77	4:1	[47]
5	**1**	Benzyl alcohol	 **7**	30	78	6:1	[48]
6	**1**	Propargyl alcohol	 **8**	30	74	10:1	[48]
7	**1**		 **9**	40	72	6:1	[5]
8	**1**		 **10**	40	74	9:1	[22]
9	**1**		 **11**	40	70	8:1	–
10	**1**		 **12**	40	72	10:1	–
11	**1**		 **13**	30	76	1:0	[49]
12	**1**		 **14**	30	74	14:1	[50]

Table 1 continued

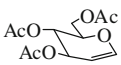
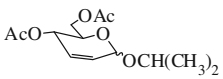
Sl. No.	Glycal	Alcohol/thiol	Product	Time (min)	Yield[a] (%)	α/β[b]	Ref.
13	**1**		 **15**	30	75	12:1	[22]
14	**1**		 **16**	30	72	1:0	–
15	 **2**	2-Propanol	 **17**	100	72	1:0	[22]
16	**2**	1-Octanol	 **18**	100	74	2:1	[22]
17	**2**	Benzyl alcohol	 **19**	100	76	1:0	[22]
18	**2**	Allyl alcohol	 **20**	90	74	16:1	[25]
19	**2**		 **21**	100	72	1:0	[22]
20	**2**		 **22**	90	52[c]	9:1	–

[a] Isolated yield

[b] α/β-ratio was determined from the integration values of the peaks in ^{1}H NMR spectrum

[c] Together with 2-deoxy thioglycoside (~25%)

Table 2 Comparison of the yields of the Ferrier rearrangement of tri-*O*-acetyl-D-glucal (**1**) in the presence of 2-propanol using different ionic liquids (IL)

Sl. No.	Substrate	Product	Ionic liquid	Time (min)	Yield (%)
1	 **1**	 **3**	[BMIM]·[BF_4]	150	65
2			[BMIM]·[PF_6]	150	52
3			[BMIM]·[OTf]	40	82
4			[BMIM]·[Cl]	180	46

mixture of compound **1** (1.0 mmol) and aliphatic alcohol (1.5 mmol) or sugar alcohol (1.2 mmol) or thiol (1.2 mmol) in [BMIM]·OTf (0.5 mL) was added TMSOTf (1.0 μL) and the reaction mixture was allowed to stir at room temperature for appropriate time mentioned in Table 1. The reaction mixture was poured into water and extracted with ethyl acetate. The EtOAc layer was successively washed with satd. $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product, which was passed through a short pad of SiO_2 using EtOAc-hexane (3:1) as eluant to furnish anomeric mixture of the product. The aqueous layer was

evaporated to dryness and the crude mass was passed through a short pad of SiO_2 using EtOAc as eluant to furnish [BMIM]·OTf, which was dried at 70–80 °C under reduced pressure before its reuse. Spectral data of the major isomers those are not reported earlier are as follows:

Methyl 6-O-(4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl)-2,3,4-tri-O-benzyl-β-D-allopyranoside (11): Yellow oil; R_f: 0.5 (hexane:EtOAc; 3:1); IR (neat): 2944, 2347, 1754, 1390, 1251, 1053, 766 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.37–7.26 (m, 15 H, Ar–H), 5.82 (br s, 2 H, H-2′, H-3′), 5.31–5.28 (m, 1 H, H-4′), 5.11 (br s, 1 H, H-1′), 4.92–4.86 (m, 2 H), 4.82–4.76 (m, 2 H), 4.68–4.24 (m, 4 H), 4.23–3.92 (m, 5 H), 3.82-3.78 (m, 1 H), 3.52 (s, 3 H, OCH_3), 3.42–3.39 (m, 1 H), 3.18–3.16 (m, 1 H), 2.05, 2.03 (2 s, 6 H, 2 $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 170.8, 170.2, 138.9–127.3 (Ar–C, C-2′, C-3′), 101.9, 94.7, 78.9, 75.8, 74.4 (2 C), 72.8, 71.9, 71.4, 67.6, 66.7, 65.1, 62.6, 56.9, 20.9, 20.7; ESI–MS: *m/z* 699.2 $[M+Na]^+$.

Methyl 6-O-(4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl)-2,3,4-tri-O-benzyl-α-D-mannopyranoside (12): Yellow oil; R_f: 0.4 (hexane:EtOAc; 4:1); IR (neat): 2937, 2355, 1767, 1386, 1246, 1063, 769 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.37–7.26 (m, 15 H, Ar–H), 5.88–5.78 (m, 2 H, H-2′, H-3′), 5.32–5.28 (m, 1 H, H-4′), 5.23 (br s, 1 H, H-1′), 4.98 (d, $J = 11.2$ Hz, 1 H, $PhCH_2$), 4.77–4.59 (m, 6 H, H-1, $PhCH_2$), 4.21–4.17 (m, 1 H), 4.11–3.97 (m, 4 H), 3.91–3.67 (m, 4 H), 3.30 (s, 3 H, OCH_3), 2.09, 2.04 (2 s, 6 H, 2 $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 170.8, 170.2, 138.6–125.0 (Ar–C, C-2′, C-3′), 98.8, 94.7, 80.0, 74.9, 74.6 (2 C), 72.6, 71.9, 71.6, 67.2, 66.8, 65.2, 62.7, 54.7, 20.9, 20.7; ESI–MS: *m/z* 699.2 $[M + Na]^+$.

p-Methoxyphenyl 4,6-di-O-acetyl-2,3-dideoxy-erythro-hex-2-eno-1-thio-α-D-pyranoside (16): Yellow oil; R_f: 0.6 (hexane:EtOAc; 4:1); IR: (neat): 2932, 2367, 1765, 1366, 1043, 769 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.49 (d, $J = 9.0$ Hz, 2 H, Ar–H), 6.86 (d, $J = 9.0$ Hz, 2 H, Ar–H), 6.06–6.03 (m, 1 H, H-2), 5.85–5.82 (m, 1 H, H-3), 5.60 (br s, 1 H, H-1), 5.37–5.35 (m, 1 H, H-4), 4.50–4.47 (m, 1 H), 4.26–4.22 (m, 2 H, H-6), 3.79 (s, 3 H, OCH_3), 2.11, 2.10 (2 s, 6 H, 2 $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 170.8, 170.4, 160.0, 135.0 (2 C), 128.8, 127.5, 125.1, 114 (2 C), 84.7, 67.2, 65.4, 63.3, 55.4, 21.1, 20.9; ESI–MS: *m/z* 375.1 $[M + Na]^+$.

2-Napthyl 4,6-di-O-acetyl-2,3-dideoxy-threo-hex-2-eno-1-thio-α-D-pyranoside (22): Yellow oil; R_f: 0.6 (hexane: EtOAc; 4:1); IR: (neat): 2936, 1738, 1388, 1246, 1068, 796, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.05–7.44 (m, 7 H, Ar–H), 6.26–6.24 (m, 1 H, H-2), 6.14–6.11 (m, 1 H, H-3), 5.97 (br s, 1 H, H-1), 5.16–5.14 (m, 1 H, H-4), 4.75–4.72 (m, 1 H, H-5), 4.33–4.27 (m, 2 H, H-6), 2.08, 1.96 (2 s, 6 H, 2 $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 170.6, 170.3, 133.7–124.7 (Ar–C, C-2, C-3), 83.5, 67.5, 63.4, 62.7, 20.9, 20.8; ESI–MS: *m/z* 395.1 $[M + Na]^+$.

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