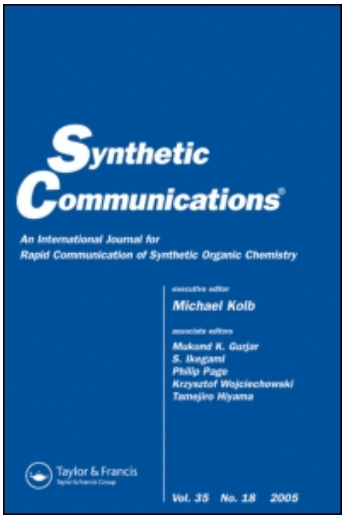

Synthetic Communications
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597304

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To cite this Article Babu, B. Sobhana and Balasubramanian, K. K.(1999) 'Lithium Tetrafluoborate Catalyzed Ferrier Rearrangement — Facile Synthesis of Alkyl 2,3-Unsaturated Glycopyranosides', Synthetic Communications, 29: 24, 4299 — 4305
To link to this Article: DOI: 10.1080/00397919908086589
URL: http://dx.doi.org/10.1080/00397919908086589

SYNTHETIC COMMUNICATIONS, 29(24), 4299–4305 (1999)

LITHIUM TETRAFLUOBORATE CATALYZED FERRIER REARRANGEMENT - FACILE SYNTHESIS OF ALKYL 2,3-UNSATURATED GLYCOPYRANOSIDES

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Abstract: Treatment of tri-*O* acetyl-**D**-galactal **1** and tri-*O*-acetyl-**D**-glucal **2** with diverse alcohols in the presence of $LiBF_4$ in CH_3CN, furnished alkyl 2,3-unsaturated glycopyranosides **3-18** (50- 86%).

2,3-Unsaturated glycosides have received wide attention in recent years particularly in the synthesis of several biologically active natural products and also as chiral synthons.[1] The various existing glycosidation methodologies have been extensively reviewed.[2] Ferrier rearrangement[3] is an important acid catalyzed glycosidation reaction essentially involving acetylated glycals, to afford 2,3-unsaturated glycosides through nucleophilic allylic displacement.

Ferrier rearrangement on tri-*O*-acetyl-**D**-galactal **1** has been less studied in contrast to tri-*O*-acetyl-**D**-glucal **2**. Apparently, Ferrier rearrangement on tri-*O*-acetyl-**D**-galactal **2** is known only with $SnCl_4$ as the catalyst.[4]

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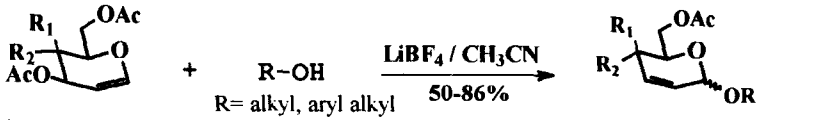
Although anhydrous lithium perchlorate in diethyl ether (LPDE) has gained importance as a versatile medium for bringing about many organic transformations[5], including carbon Ferrier rearrangement[6], in view of its oxidising property which may not desirable in some case, we were interested to examine the potential of lithium tetrafluoborate as a Lewis acid. Lithium tetrafluoborate ($LiBF_4$) is a mild Lewis acid, which has been used for deprotection of silyl ethers and also as a catalyst for the Diels-Alder reaction.[7] Since the counterion BF_4^- in $LiBF_4$ is non-nucleophilic and non-oxidizing unlike ClO_4^-, we were prompted to investigate the utility of $LiBF_4$ as a catalyst for the Ferrier rearrangement of glycals.

Herein, we present our preliminary results on the interesting utility of $LiBF_4$ in acetonitrile (LTAN) as an efficient system for the Ferrier rearrangement on tri-*O*-acetyl-**D**-galactal **1** and tri-*O*-acetyl-**D**-glucal **2** with various alcohols (primary, secondary, allylic, propargylic, benzylic etc.) leading to alkyl 2,3-unsaturated glycopyranosides **3-18**, in moderate to good yields.



R_1=OAc, R_2=H **1** R_1=OAc, R_2=H **3 - 10**

R_2=OAc, R_1=H **2** R_2=OAc, R_1=H **11 - 18**

When 1 equiv. of tri-*O*-acetyl-**D**-galactal **1** was treated with 1.2 equiv. of benzyl alcohol for 16 hours in LTAN at 50°C, benzyl 2,3-unsaturated galactopyranoside **3** was obtained[6] in 60% yield with the α-anomer as the major product. Likewise, other alcohols led to facile glycosidation upon reaction with

tri-*O*-acetyl-**D**-galactal **1** in LTAN affording the corresponding alkyl 2,3-unsaturated galactopyranosides **4-10** in moderate yields (see **Table**).

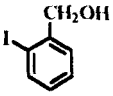
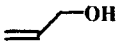
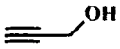
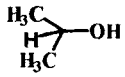
A noteworthy point is that in all the products α-anomer is predominant which can be attributed to the anomeric effect. No significant enhancement in the intensity of the anomeric proton was observed when the signal due to H-5 is irradiated, thus confirming that H-1 and H-5 are *trans* to each other. We may also note that in the case of tri-*O*-acetyl-**D**-galactal **1** the formation of alkyl 2-deoxy glycopyranosides are either not observed, or observed only as a minor reaction.

We have extended this $LiBF_4$ mediated Ferrier rearrangement to tri-*O*-acetyl-**D**-glucal **2**. Treatment of tri-O-acetyl-D- glucal **2** with benzyl alcohol in LTAN at ambient temperature itself gave the benzyl glucopyranoside **11** in 86% with α- anomer as the major product. Likewise, other alcohols led to facile glycosidation upon reaction with tri-*O*-acetyl-**D**-glucal **2** in LTAN affording the corresponding alkyl 2,3-unsaturated glycopyranosides **11-18** in good yields.

To the best of our knowledge, this is the first instance of $LiBF_4$ mediated Ferrier rearrangement. We have also examined the catalytic ability of several other fluoborates such as $C_6H_5CH_2(C_2H_5)_3NBF_4$, $(n\text{-}Bu)_4NBF_4$, $NaBF_4$, KBF_4/ 18 crown 6, NH_4BF_4 in dry CH_3CN which were all found to be ineffective.

In summary, we have observed that $LiBF_4$ in CH_3CN (LTAN) is a useful catalyst, enabling a practical method for the synthesis of alkyl 2,3-unsaturated glycopyranosides[8]. The cyclisation of 2'-iodobenzyl glycosides **4** and **12** to form chiral isochromans is currently under investigation.

Table. LTAN mediated glycosylation of alcohols with **1** and **2**

Alcohol	Product	Time(hrs)	Yield (%)	α:β[#]
	**3**	16	60	9:1
	11	4	86	4:1
	**4**	20	58	10:1
	12	36	56	6:1
	**5**	16	56	9:1
	13	3	76	9:1
	**6**	16	50	12:1
	14	6	70	9:1
	**7**	16	52	9:1
	15	4	80	8:1
H_3C-OH	**8**	26	50	α-only[$]
	16	8	58	4:1[$]
$H_3C(CH_2)_{11}-OH$	**9**	10	60	10:1
	17	3	85	9:1
	**10**	18	62	9:1
	18	10	60	10:1

[#] Anomeric ratios were determined by ^1H and ^{13}C NMR (400 MHz) spectroscopy

[$] Reaction was successfully scaled upto 20 gm of **1** and **2**

EXPERIMENTAL

To a mixture of tri-*O*-acetyl-D-galactal **1** or tri-O-acetyl-D-glucal **2** (1 mmol) and the -OH nucleophile (1.1 to 1.6 mmol), was added anhydrous $LiBF_4$ (ACROS Organics or Fluka or Janssen 1.2 mmol) in dry CH_3CN (1 mL) at ambient temperature (in the case of tri-O-acetyl-D-galactal **2**, at 50°C). The contents were stirred for the required time (see Table) and the reaction is monitored by TLC. The reaction mixture was quenched by the addition of aqueous sodium hydrogen carbonate (10%, 25 mL), extracted with dichloromethane (3 x 25 mL) dried over anhydrous sodium sulphate, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to obtain the products.

2'-Iodobenzyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-eno-pyranoside (3) ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 2.06 (s, 3H, - $OCOCH_3$), 2.09 (s, 3H, - $OCOCH_3$),4.24 (d, 2H, J=6.35Hz, $6H_A$, $6H_B$), 4.43-4.47(m, 1H, 5-H), 4.57(d, A of AB, J=12.69Hz, $PhCH_A$), 4.83(d, B of AB, 1H, J=12.69Hz, $PhCH_B$), 5.04(d,d, 1H, J=5.13Hz, 2.93Hz, 4-H), 5.23(d, 1H, J= 2.93Hz, 1-H), 6.08-6.18(m, 2H, 2-H, 3-H), 7.00(m, 1H, Ar-H), 7.34-7.43(m, 2H, Ar-H), 7.82- 7,85(m, 1H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 20.75 (q), 20.79 (q), 62.61 (t), 62.61(d), 67.01(d), 73.69(t), 93.48(d), 98.13(s), 125.40(d), 129.14(d), 129.40(d), 130.28(d), 139.25(d), 139.79(s), 170.15(s), 170.44(s).

ACKNOWLEDGMENTS

We thank: Department of Science and Technology, India, for financial support; RSIC, IIT, Chennai, SPIC Science Foundation, Chennai and Sun

Pharmaceuticals Advanced Research Centre, Baroda for spectral data; Dr.K.Vijayakumaran, Director, R&D, Chimique Laboratories, Chennai and Dr.Indrapal Singh Aidhen, IIT, Chennai for useful discussions.

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Accepted / April 01, 1999