Microwave-Induced, $InCl_3$-Catalyzed Ferrier Rearrangement of Acetylglycals: Synthesis of 2,3-Unsaturated Glycopyranosides[1]

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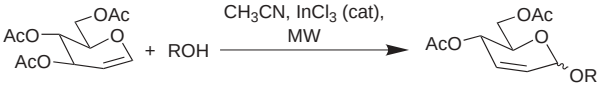
Received 28 May 2003

Abstract: Indium(III) chloride catalyzed, microwave assisted Ferrier rearrangement on different per-*O*-acetylglycals leads to an efficient synthesis of 2,3-unsaturated *O*-glycosides in good to excellent yields.

Key words: indium(III) chloride, microwave, Ferrier rearrangement, glycals, *O*-glycosides

2,3-Unsaturated glycosides or pseudoglycals represent a very important class of compounds where the double bond can easily be modified, e.g., by hydroxylation, hydrogenation, epoxidation and amino hydroxylation. These are also versatile chiral intermediates[2a,b] in the synthesis of glycopeptides,[2c] modified carbohydrates,[2d] nucleosides,[2e,f] uronic acids,[2g,h] oligosachharides[2i,j] and several biologically active natural products.[2k] 2-Deoxy- and 2,3-dideoxy sugars derived from 2,3-unsaturated glycosides constitute the structural motifs of several antibiotics[3] and they are also found to reduce the plasma cholesterol and triglyceride levels significantly in mice.[4] 2,3-Unsaturated glycosides are generally accessed via a strong Lewis acid[5] [boron trifluoride etherate or titanium(IV) chloride or tin(IV) chloride] mediated Ferrier rearrangement[6] of sugar derivatives. Other reagents used to effect this transformation include indium(III) halides,[7] acidic montmorillonite K10,[8] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone,[9] trimethylsilyl triflate,[10] trichloroacetimidate,[11] *N*-iodosuccinimide[12] and triflates like scandium triflate,[13] Ytterbium triflate[14] are also known to bring about the Ferrier rearrangement under different conditions. However, many of these methods suffer from generality and have limitations like strong oxidizing conditions, high acidic medium, low yields, reaction temperature, longer reaction time, compatibility with functional groups present, the catalyst and reagents used, their amounts and especially the cost of the reagents used. Therefore, there is still a need for a general procedure for the Ferrier rearrangement. Accordingly, as a part of our endeavour[15] to develop an efficient, mild, rapid, eco-friendly procedure for *O*- and *C*-glycosylation, we have explored the use of microwaves for Ferrier rearrangement. Although microwave-assisted reactions are widely applied in other domains of organic synthesis, their use in carbohydrate area has been rather limited. Herein, we now report, an $InCl_3$-catalyzed, microwave-assisted Ferrier rearrangement of different per-*O*-acetylglycals to synthesize 2,3-unsaturated *O*-glycosides. Although the Ferrier rearrangement has been reported[7e] by using $InCl_3$, the authors had confined their findings only with glucal. Above all, these reactions were not performed under microwave conditions. Besides that, they have used CH_2Cl_2–CH_3CN mixed solvent system and performed the reaction at ambient temperature. On the contrary, we have chosen a polar solvent like CH_3CN to perform these transformations under microwave condition,[16] a representative example is shown in Scheme 1. To our knowledge, this is the first report of *O*-glycosylation through Ferrier rearrangement illustrating the value of microwave coupled with $InCl_3$ in glycal chemistry.



Scheme 1

Typically, the per-*O*-acetylglycals, alcohols and $InCl_3$ were taken in acetonitrile in an open vessel and irradiated with microwaves to afford the 2,3-unsaturated products in good to excellent yields (Table 1). The reactions were complete in a few seconds. The reaction mixture was diluted with ethyl acetate, subsequently washed with water and concentrated. All the products were characterized through ^{1}H NMR, COSY, IR and mass spectral data.[18] Anomeric ratios of these products were determined from ^{1}H NMR.

It is interesting to note that all glycals, other than arabinal, furnished only axial products with all the alcohols. The case of allyl alcohol with galactal and benzyl alcohol with rhamnal could be treated as exception where also the stereoselectivities are high though not 100%. It seems that the stereochemical outcome is guided by the stereochemistry of the C-5 substituent. The relative stereochemistry was found to be *trans* as was evident from $J_{1,2}$ values[18] of major/only isomers. In the case of arabinal, where the substituents at C-5 are only H atoms, the selectivity becomes less as is clear from the products. The yields of the reactions are good to excellent. Only in case of galactal with propargyl alcohol and arabinal with pent-4-en-1-ol yields were found to be moderate (50%). Repetition of the reactions with increased amounts of reagents from 2 equivalents to 5 equivalents improved the yields by 5–10% only.

Synlett 2003, No. 11, Print: 02 09 2003. Web: 05 08 2003.
Art Id.1437-2096,E;2003,0,11,1607,1610,ftx,en;D12103ST.pdf.
DOI: 10.1055/s-2003-40991

Table 1 $InCl_3$-induced Microwave-assisted Synthesis of 2,3-Unsaturated Ferrier Rearranged Products with Different Alcohols

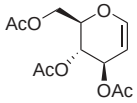
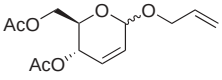
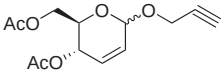
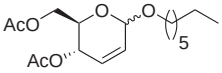
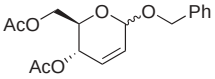
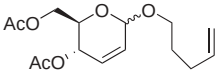
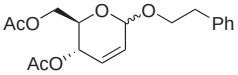
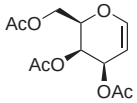
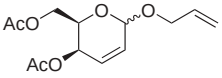
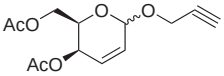
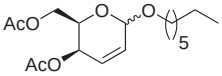
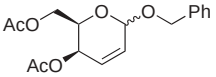
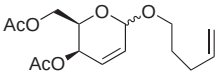
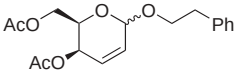
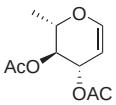
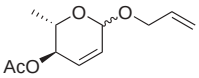
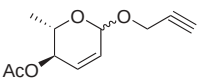
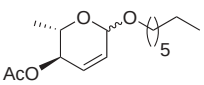
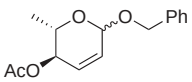
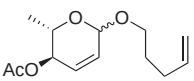
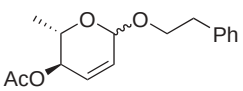
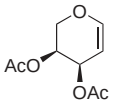
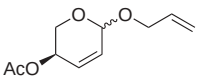
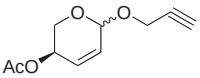
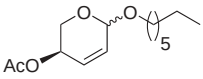
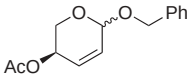
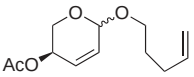
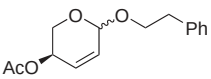
Substrate	R-OH (R =)	Product	Time (sec)	Yield[a]	(α/β)	ref.
	allyl		50	81%	8/1	[17a]
	propargyl		50	50%	α[b]	[17b]
	heptyl		20	97%	α[b]	[17c]
	benzyl		20	85%	α[b]	[17d]
	pent-4-enyl		50	68%	α[b]	[17e]
	phenethyl		50	93%	α[b]	[13]
	allyl		55	75%	α[b]	[17f]
	propargyl		60	70%	α[b]	[17f]
	heptyl		60	79%	α[b]	[18]
	benzyl		60	72%	α[b]	[17f]
	pent-4-enyl		60	78%	α[b]	[18]
	phenethyl		60	80%	α[b]	[18]
	allyl		20	85%	α[b]	[17g]
	propargyl		20	98%	α[b]	[17g]
	heptyl		20	65%	α[b]	[18]
	benzyl		20	84%	6/1	[17h]
	pent-4-enyl		20	70%	α[b]	[18]
	phenethyl		20	65%	α[b]	[18]

Table 1 $InCl_3$-induced Microwave-assisted Synthesis of 2,3-Unsaturated Ferrier Rearranged Products with Different Alcohols (continued)

Substrate	R-OH (R =)	Product	Time (sec)	Yield[a]	(α/β)	ref.
	allyl		50	62%	3/1	[18]
	propargyl		50	69%	3/1	[17i]
	heptyl		20	96%	3/1	[18]
	benzyl		20	63%	4/1	[17j]
	pent-4-enyl		20	50%	4/1	[18]
	phenethyl		20	76%	4/1	[18]

[a] Isolated yields.
[b] No β-glycoside could be detected by NMR.

In conclusion, the present method of $InCl_3$ catalyzed Ferrier rearrangement of acetylglycals provides an efficient alternative to the existing methodologies to synthesize 2,3-unsaturated *O*-glycosides. The process is operationally simple and high yielding. The use of catalytic amount of $InCl_3$, easy work-up and short reaction time makes this procedure further an attractive alternative to those existing.

Acknowledgement

We express our esteemed gratitude to Professor J. Iqbal and Dr. R. Rajagopalan for their continuous encouragement to this work. We thank the members of the Analytical Research Department of Discovery Research for the services provided.

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(16) **A Typical Procedure**: To a solution of glycal (50 mg) and alcohol (2 equiv) in acetonitrile (1 mL) $InCl_3$ (30 mol%) was added and the mixture irradiated with microwaves (LG model: MC-804AAR) for the appropriate time (see Table 1). The reaction mixture was then diluted with ethyl acetate and washed with water, dried (Na_2SO_4) and evaporated to dryness. The residue was purified on silica gel (100–200 mesh) to afford the desired 2,3-unsaturated products as summarized in Table 1.
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(18) All new compounds were fully characterized. Spectral and analytical data were in good agreement. Spectral data of **(2*S*,3*R*,6*R*)-2-methyl-6-phenethyloxy-3,6-dihydro-2*H*-3-pyranyl acetate**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.16 (d, 3 H, *J* = 6.4 Hz, H-6), 2.08 (s, 3 H, Ac), 2.93 (t, 2 H, *J* = 7.1 Hz, PhC*H*$_2$), 3.76 (t, 1 H, *J* = 7.1 Hz, OC*H*$_2$), 3.83–3.90 (m, 1 H, H-5), 3.98 (t, 1 H, *J* = 7.1 Hz, OC*H*$_2$), 4.95 (br s, 1H, H-1), 5.03 (dd, 1 H, *J* = 9.3 Hz, 1.5 Hz, H-4), 5.77 (dd, 1 H, *J* = 10.3 Hz, 1.9 Hz, H-2), 5.84 (dd, 1 H, *J* = 10.3 Hz, 1.9 Hz, H-3), 7.20–7.32 (m, 5 H, Ph). IR (Neat): 1745, 1374, 1237, 1107, 1039, 918 cm^{-1}. LC-MS (CI): *m/z* 277 (M^+ + 1).
(6*S*,2*R*,3*R*)-2-Methylcarbonyloxymethyl-6-(2-propynyloxy)-3,6-dihydro-2*H*-3-pyranyl acetate: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.076, 2.084 (2 s, 6 H, 2Ac), 2.93 (t, 1 H, *J* = 2.4 Hz, acetylene H), 4.22–4.32 (m, 5 H, H-5, H-6, OC*H*$_2$), 5.04 (dd, 1 H, *J* = 5.4 Hz, 2.4 Hz, H-4), 5.29 (d, 1 H, *J* = 2.9 Hz, H-1), 6.04 (dd, 1 H, *J* = 10.3 Hz, 2.9 Hz, H-2), 6.15 (ddd, 1 H, *J* = 10.0 Hz, 5.4 Hz, 1.0 Hz, H-3). IR (Neat): 1743, 1590, 1372, 1234, 1102, 1039, 757 cm^{-1}. LC-MS (CI): *m/z* 269 (M^+ + 1).
(6*S*,2*R*,3*R*)-2-Methylcarbonyloxymethyl-6-(4-pentenyloxy)-3,6-dihydro-2*H*-3-pyranyl acetate: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.08, 2.09 (2 s, 6 H, 2Ac), 1.66–1.78 (m, 2 H, OCH$_2$C*H*$_2$CH$_2$-), 2.10–2.20 (m, 2 H, OCH$_2$CH$_2$C*H*$_2$-), 3.50–3.59 (m, 1 H, OC*H*$_2$CH$_2$CH$_2$-), 3.75–3.84 (m, 1 H, OC*H*$_2$CH$_2$CH$_2$-), 4.20–4.09 (m, 2 H, H-6), 4.33–4.40 (m, 1 H, H-5), 4.95–5.04 (m, 3 H, H-4 and CH=C*H*$_2$), 5.06 (d, 1 H, *J* = 2.0 Hz, H-1), 5.77–5.87 (m, 1 H, C*H*=CH$_2$), 6.03 (dd, 1 H, *J* = 10.2 Hz, 2.9 Hz, H-2), 6.15 (ddd, 1 H, *J* = 10.0 Hz, 5.4 Hz, 1.0 Hz, H-3). IR (Neat): 1744, 1372, 1232, 1106, 1049, 912 cm^{-1}. LC-MS (CI): *m/z* 299 (M^+ + 1).
(3*R*,6*R*)-3-Allyloxy-3,6-dihydro-2*H*-3-pyranyl acetate (major isomer): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.09 (s, 3 H, Ac), 3.80–3.87 (m, 1 H, OC*H*$_2$CH=CH$_2$), 4.07 (dd, 1 H, *J* = 7.8 Hz, 1.5 Hz, H-5a), 4.09–4.20 (m, 1 H, OC*H*$_2$CH=CH$_2$), 4.24 (dd, 1 H, *J* = 6.4 Hz, 1.5 Hz, H-5b), 4.94–4.97 (m, 1 H, H-4), 5.05 (d, 1 H, *J* = 2.4 Hz, H-1), 5.18–5.33 (m, 2 H, OCH$_2$CH=C*H*$_2$), 5.83–5.98 (m, 1 H, OCH$_2$C*H*=CH$_2$), 6.04 (dd, 1 H, *J* = 10.0 Hz, 3.0 Hz, H-2), 6.09 (dd, 1 H, *J* = 10.2 Hz, 4.9 Hz, H-3). IR (Neat): 1738, 1373, 1238, 1102, 1042, 959 cm^{-1}. LC-MS (CI): *m/z* 199 (M^+ + 1).