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Microwave-induced, $InCl_3$-catalyzed Ferrier rearrangement of acetylglycals: synthesis of 2,3-unsaturated *C*-glycosides☆

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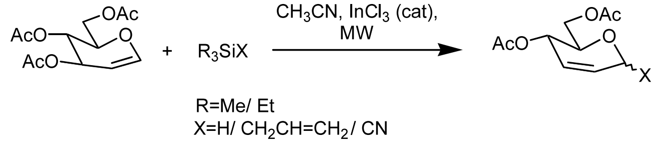
Abstract—Indium(III) chloride-catalyzed, microwave-assisted Ferrier rearrangement of different per-*O*-acetylglycals leads to an efficient synthesis of 2,3-unsaturated *C*-glycosides in good to excellent yields. © 2003 Elsevier Science Ltd. All rights reserved.

C-Glycosides are versatile chiral building blocks for the synthesis of many biologically interesting and potential natural products such as palytoxin,[1] spongistatin[2] and halichondrin.[3] The discovery of naturally occurring *C*-nucleosides with important pharmacological properties[4] gave impetus to synthetic efforts for preparing active carbohydrate analogs. In addition, *C*-glycosides are potential inhibitors of carbohydrate processing enzymes and they are stable analogs of glycans involved in important intra- and intercellular processes.[5,6] Among these *C*-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. 2,3-Unsaturated glycosides are generally accessed via a strong Lewis acid[7,8] (boron trifluoride etherate or titanium(IV) chloride) mediated Ferrier rearrangement[6,9] of sugar derivatives. A few examples are also known in the literature where Ferrier rearrangement has been achieved with indium(III) halides,[10] montmorillonite K10,[11] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone,[12] trimethylsilyl triflate[13] and trichloroacetimidate.[14] However, many of these methods lack generality and have limitations in terms of yields, stereoselectivities, reaction temperature, time, compatibility with functional groups present, the catalyst and reagents used, and their amounts. Therefore, there is still a need for a general procedure for the Ferrier rearrangement. Accordingly, as a part of our endeavor 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 the area of carbohydrates has been rather limited. Herein, we now report, for the first time, an $InCl_3$-catalyzed, microwave-assisted Ferrier rearrangement of different per-*O*-acetylglycals to synthesize 2,3-unsaturated *C*-glycosides, representative examples are shown in Scheme 1.

Although the Ferrier rearrangement has been reported[10a] using $InCl_3$ under non-microwave conditions, these findings are mainly confined to allyltrimethyl silane as the nucleophile in dichloromethane. In contrast, we chose acetonitrile as the reaction medium to perform these transformations under microwave irradiation.[15]

Typically, the per-*O*-acetylglycals, silanes 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 and the work-up procedure was very simple as the products were isolated by merely diluting the reaction mixture with ethyl acetate and subsequently washing with



Scheme 1.

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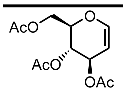
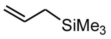
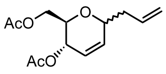
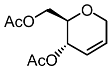
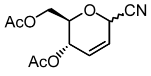
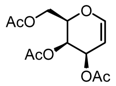
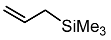
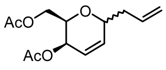
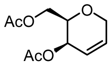
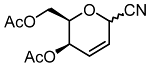
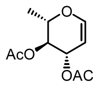
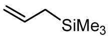
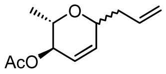
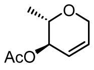
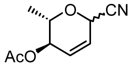
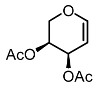
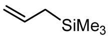
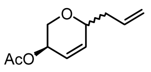
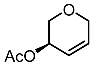
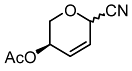
Table 1. $InCl_3$-induced microwave-assisted synthesis of 2,3-unsaturated Ferrier rearranged products with different silanes

Substrate	Silanes	eq. of silane	Product	Time (sec)	Yield[a] (α/β)	ref.
		3		30	95% (19/1)	10c
	Et_3SiH	5		20	71% ----	16a
	Me_3SiCN	6		30	89% (6/4)	10c
		5		40	90% (99/1)	10c
	Et_3SiH	3		20	96% ----	16b
	Me_3SiCN	6		30	79% (6/4)	10c
		3		20	85% (13/1)	10a
	Et_3SiH	5		20	72% ----	17
	Me_3SiCN	6		20	71% (6/4)	16c
		3		30	89% (19/1)	17
	Et_3SiH	5		20	79% ----	17
	Me_3SiCN	6		30	72% (10/1)	17

[a] Isolated yields.

water. All the products were characterized by ^1H NMR, COSY, IR and mass spectral data. The purity and the anomeric ratios of these products were determined by HPLC.

It is interesting to note that the reaction of 3,4,6-tri-*O*-acetyl-D-glucal with allyltrimethyl silane, when performed without microwave-assistance under reflux using the same quantity of $InCl_3$, was complete within 15 min but the yield was only 50%. However, a high yield[10a] of the same product was obtained at room temperature using 1.5–2.0 equiv. of $InCl_3$ in dichloromethane, whereas conducting the reaction using a catalytic amount of $InCl_3$ furnished the starting per-*O*-acetylglycals. While the yields of all the reactions were high, the 1,5-*anti* diastereoselectivities in the cyanation of 3,4-di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol; 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol and 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol were poor (α:β = 6:4). 3,4-Di-*O*-acetyl-1,5-anhydro-2-deoxy-L-*arabino*-pent-1-enitol, on the other hand provided high selectivity (α:β = 10:1). It was also observed that the reaction time was greatly reduced under microwave irradiation when compared to the conventional reflux method using catalytic $InCl_3$ or the room temperature method using a stoichiometric amount of $InCl_3$.

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 *C*-glycosides. The process is operationally simple, high yielding and the use of a catalytic amount of $InCl_3$, easy work-up and short reaction times makes this procedure an attractive alternative to those existing.

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15. **A typical procedure**: To a solution of glycal (50 mg) in acetonitrile (1 mL), $InCl_3$ (20 mol%) was added followed by silane 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 product in the yield given in Table 1.
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17. All new compounds were fully characterized. Spectral and analytical data were in good agreement.