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Microwave-induced, Montmorillonite K10-catalyzed Ferrier rearrangement of tri-*O*-acetyl-D-galactal: mild, eco-friendly, rapid glycosidation with allylic rearrangement

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Abstract—Montmorillonite K10 was found to catalyze, under microwave irradiation, rapid *O*-glycosidation of 3,4,6-tri-*O*-acetyl-D-galactal to afford exclusively the alkyl and aryl 2,3-dideoxy-D-*threo*-hex-2-enopyranosides with very high α-selectivity and without the formation of the 2-deoxy-D-*lyxo*-hexopyranosides. Under these conditions, 3,4,6-tri-*O*-acetyl-D-glucal as usual also underwent the Ferrier rearrangement.

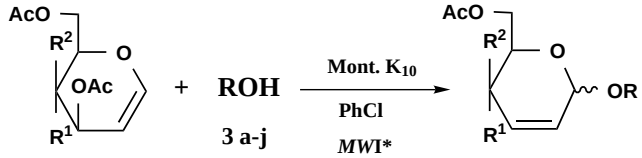
1. Introduction

2,3-Unsaturated glycosides (pseudoglycals) are versatile synthetic intermediates and also constitute the structural units of several antibiotics.[1] Allylic rearrangement of glycals, otherwise known as the Ferrier rearrangement,[2] in the presence of a nucleophile generally leads to the formation of 2,3-unsaturated glycosides. 2,3-Unsaturated *O*-aryl glycosides, in turn can be transformed to *C*-aryl glycosides through [1,3] sigmatropic rearrangement.[3] The Ferrier rearrangement of 3,4,6-tri-*O*-acetyl-D-galactal is not as easy a reaction as that of 3,4,6-tri-*O*-acetyl-D-glucal, since it leads to 2-deoxy-D-*lyxo*-hexopyranosides by the addition of the OH nucleophile to the galactal double bond.[4]

A wide range of acid reagents[5] such as $BF_3{\cdot}Et_2O$, cation-exchange resin, $InCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, Montmorillonite K10 (Mont. K10) and neutral reagents[6] such as DDQ, I_2, and *N*-iodosuccinimide have been described for the glycosidation of glucals. But there are only a few catalysts available for the Ferrier rearrangements of 3,4,6-tri-*O*-acetyl-D-galactal like $SnCl_4$,[7] DDQ,[6b] $LiBF_4$[6c] in contrast to other known Lewis acid catalyst, which mostly lead to 2-deoxy-D-*lyxo*-hexopyranosides. Except for the $SnCl_4$ method of glycosidation, which is the only synthetically viable method for the Ferrier rearrangement of 3,4,6-tri-*O*-acetyl-D-galactal for the synthesis of both alkyl and aryl galactosides, the other methods are restricted to the synthesis of only the 2,3-unsaturated alkyl galactosides. Even in the $SnCl_4$-catalyzed reaction, the Ferrier rearrangement is accompanied by the formation of minor amounts of the aryl 2-deoxy-D-*lyxo*-hexopyranosides and a bicyclic aryl 2-deoxy galactoside derivative.[8]

Herein, we report the Mont. K10-catalyzed, microwave-induced Ferrier rearrangement of 3,4,6-tri-*O*-acetyl-D-galactal with alcohols and phenols in an open vessel, giving 4,6-di-*O*-acetyl-2,3-dideoxy-D-*threo*-hex-2-enopyranosides with very high α-selectivity (Scheme 1).

As a part of our endeavor to develop an efficient, mild, rapid, eco-friendly method for *O*- and *C*-glycosidation, the use of microwaves for Ferrier rearrangement was explored. Although Mont. K10-catalyzed glycosidation of 3,4-di-*O*-acetyl-L-rhamnal and 3,4,6-tri-*O*-acetyl-D-



1 R^1 =H , R^2 = OAc
2 R^1 = OAc, R^2 = H
4 a-j R^1 = H, R^2 = OAc
5 a-j R^1 = OAc, R^2 = H

Scheme 1.

Keywords: galactal; glucal; Montmorillonite K10; Ferrier rearrangement; microwave irradiation.

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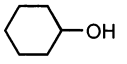
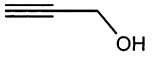
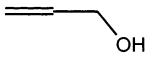
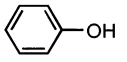
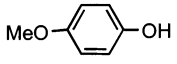
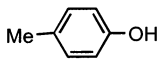
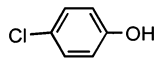
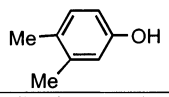
glucal has been previously reported,[9] the authors have not extended this reaction either with tri-*O*-acetyl-D-galactal or to phenols. Earlier, our laboratory reported[10] the solvent-free microwave-induced Ferrier rearrangement of glucals with phenols in a sealed vessel which always carries the hazard of explosion. We have now adopted the microwave oven-induced reaction enhancement (MORE) technique,[11] wherein the reaction is carried out in an open vessel.

3,4,6-Tri-*O*-acetyl-D-galactal **1** in the presence of alcohols/phenols **3** and Mont. K10 (100% w/w) in chlorobenzene, when irradiated with microwaves at power level (PL) 2, yielded exclusively the alkyl/aryl 2,3-dideoxy-D-*threo*-hex-2-enopyranosides **4a**–**j** in reasonably good yields with very high α-selectivity as summarized in Table 1. The reactions were completed in a very short period, in general to afford the alkyl or aryl 2,3-dideoxy-D-*threo*-hex-2-enopyranosides. All these compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectral data. It is interesting to note that the reaction of 3,4,6-tri-*O*-acetyl-D-galactal, benzyl alcohol **3b** and Mont. K10, when performed without microwave irradiation, but under reflux conditions in 1,2-dichloroethane, not only required longer time, viz. 24 hours, but resulted in a low yield (30%) of benzyl 4,6-di-*O*-acetyl-2,3-dideoxy-D-*threo*-hex-2-enopyranoside **4b**. No reaction was observed in the absence of Mont. K10 both under microwave irradiation and reflux conditions. Also, the galactal **1** with phenol **3g** and Mont. K10 under reflux conditions in 1,2-dichloroethane for about 30 hours, yielded phenyl 4,6-di-*O*-acetyl-2,3-dideoxy-D-*threo*-hex-2-enopyranoside **4g**, albeit in very low yield (~20%) and the reaction did not go to completion. Thus we find that the Mont. K10-catalyzed reaction of 3,4,6-tri-*O*-acetyl-D-galactal **1** with alcohols and phenols, generally leads to easy allylic rearrangement. It is also observed that the reaction time is greatly reduced under microwave irradiation when compared to the conventional reflux method.

Table 1. Glycosidation of 3,4,6-tri-*O*-acetyl-D-galactal **1**

Entry	3 (ROH)	Time[a] (min.)	Product 4	
			Yield[b] (%)	Anomeric ratio[c] (α/β)
a	CH_3CH_2OH	14	82	>95%α
b	$C_6H_5CH_2OH$	9	85	Only α observed
c		15	60[d]	>95%α
d		6	72	>95%α
e		10	68	Only α observed
f		8	75	>95%α
g		7	70	10:0.5
h		10	63	>95%α
i		6	84	Only α observed
j		15	52[d]	Only α Observed

[a] All the reactions were irradiated at PL=2 in a domestic microwave oven (2450 MHz, 980 W). [b]Isolated yields after column chromatography. [c]α:β ratio as determined by ^{1}H-NMR spectroscopy (300 MHz) and/or isolation of pure isomer. [d] yield based on the isolated product, since the reaction did not go to completion.

Similarly, we found that 3,4,6-tri-*O*-acetyl-D-glucal **2** with alcohols/phenols **3** in the presence of Mont. K10 as catalyst and under microwave irradiation afforded the alkyl or aryl 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosides, **5a**–**j** in very good yields as summarized in Table 2.

The yields and the stereoselectivity were in the range observed previously with other catalysts. The predominant α-selectivity follows the anomeric effect.[12]

In summary, our present methodology has the following advantages: (a) the catalyst, Mont. K10 clay can be easily recovered and reused. (b) Short reaction times (in order of minutes) and generally good yields. (c) No need for perfectly dry solvents and reagents. In conclusion, we have developed a mild and eco-friendly approach for the glycosidation of glycals, particularly for 3,4,6-tri-*O*-acetyl-D-galactal to afford the corresponding alkyl and aryl 2,3-dideoxy-D-*threo*-hex-2-enopyranosides.

2. General experimental procedure

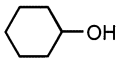
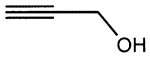
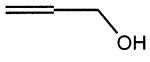
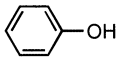
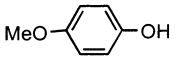
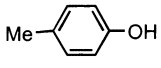
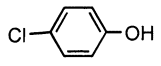
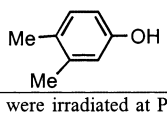
2.1. Glycosidation using alcohols

To a mixture of glycal **1** or **2** (1 mmol) and alcohols (3.0 or 6–8 equiv. in the cases of low boiling alcohols such as ethanol) in PhCl (5 mL) taken in a conical flask (100 mL) was added Mont. K10 (100% w/w). Then a funnel was placed on the top of the flask and the contents were irradiated with microwaves at PL = 2. The course of the reaction was monitored using TLC. After completion of the reaction, the solution was filtered and the filtrate was concentrated in vacuo. The product was purified using column chromatography.

2.2. Glycosidation using phenols

To a mixture of glycal **1** or **2** (1 mmol) and phenols (3.0 equiv.) in PhCl (5 mL) taken in a conical flask (100 mL) was added Mont. K10 (100% w/w). Then a funnel was placed on the top of the flask and the contents were

Table 2. Glycosidation of 3,4,6-tri-*O*-acetyl-D-glucal **2**

Entry	3 (ROH)	Time[a] (min.)	Product 5	
			Yield[b] (%)	Anomeric ratio[c] (α/β)
a	CH_3CH_2OH	8	87	6:1
b	$C_6H_5CH_2OH$	3	90	8:1
c		10	73	5:1
d		3	78	6:1
e		7	80	4.5:1
f		4	93	7:1
g		3	82	10:1
h		3	85	8.2:1
i		2	90	7:1
j		5	74	9:1

[a] All the reactions were irradiated at PL=2 in a domestic microwave oven (2450 MHz, 980 W).
[b]Isolated yields after column chromatography. [c]$\alpha:\beta$ ratio as determined by ^{1}H-NMR spectroscopy (300 MHz) and/or isolation of pure isomer.

irradiated with microwaves at PL = 2. The course of the reaction was monitored using TLC. After the completion of the reaction, the reaction mixture was filtered, extracted with dichloromethane and washed with aqueous NaOH (10%), followed by water. The organic layer was then dried and evaporated. The crude product was purified using column chromatography.

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