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Microwave-induced synthesis of 2,3-unsaturated *O*-glycosides under solvent-free conditions

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Abstract—Microwave irradiation of a mixture of tri-*O*-acetyl-D-glucal **1** and an appropriate alcohol **2a–f**, in the presence of Montmorillonite K-10 as a catalyst, provided unsaturated glycosides **3a–f** in much shorter time and in yields comparable with conventional heating.

Since its discovery in 1969,[1] Ferrier's rearrangement has gained a great significance in the area of carbohydrate chemistry. The unsaturated glycosides obtained initially through this reaction play an important role in the transformation of these compounds into other interesting carbohydrates.[2,3] For example, the double bond formed between C-2 and C-3 atoms by the reaction of tri-*O*-acetyl-D-glucal and *N*-hydroxymethylphthalimide could easily be converted to *N*-phthaloylmethyl α-D-mannopyranoside.[3] This product along with other unsaturated *N*-phthaloylmethyl glycosides have been found to reduce plasma cholesterol and triglyceride levels significantly in mice.[3]

There has been a growing interest in the application of microwave-assisted reactions in the field of organic chemistry, as is evident by the number of reviews that have appeared since 1991.[4–8] Indeed, there has been a tremendous advancement in the synthesis of organic compounds using microwave irradiation.[9] With this idea in view and analyzing the great utility of the unsaturated glycosides obtained by the Ferrier rearrangement, we decided to investigate this rearrangement to obtain the unsaturated sugars through the intervention of microwaves. In general, these reactions are clean, efficient and require very little time. Recent microwave activated reactions in the carbohydrate field gave impetus for the development of solvent-free methods with rate enhancement. The literature mentions the reaction of phenols with tri-*O*-acetyl-D-glucal using microwave irradiation technique.[10] When we tried to repeat this procedure employing cyclohexanol **2f** in place of phenol, we did not obtain any product. However, irradiation of a mixture of tri-*O*-acetyl-D-glucal **1**, an appropriate alcohol **2a–f** and Montmorillonite K-10 (catalyst) was irradiated in a domestic microwave oven, the allylic rearrangement occurred to give the unsaturated glycosides **3a–f**. To our knowledge, no microwave-mediated Ferrier rearrangement of tri-*O*-acetyl-D-glucal and an alcohol using Montmorillonite K-10 catalyst under dry conditions has been performed.

Table 1 records the yields obtained by conventional heating as well as by microwave irradiation.

The unsaturated glycosides **3a–f** have been obtained in 71–87% yields (Table 1). Only α-anomers (Scheme 1) have been isolated and their structures inferred by

Table 1. Comparison of conventional and microwave-mediated methods for the synthesis of **3a–f**

Entry	Reaction time (min)		$[\alpha]_D^{21}$	Yields (%)
	Conventional	Microwave		
3a	90	10[a]	+46	77
3b	150	10[a]	+55	79
3c	90	10[a]	+47.5	81
3d	90	15[a]	ND[c]	71
3e	90	15[a]	ND[c]	71
3f	120	20[b]	+111	87

[a] 650 W.

[b] 360 W/4×5 min. In this case the reaction was performed in a sealed tube.

[c] Since these are diastereoisomeric mixtures, the specific rotations were not obtained.

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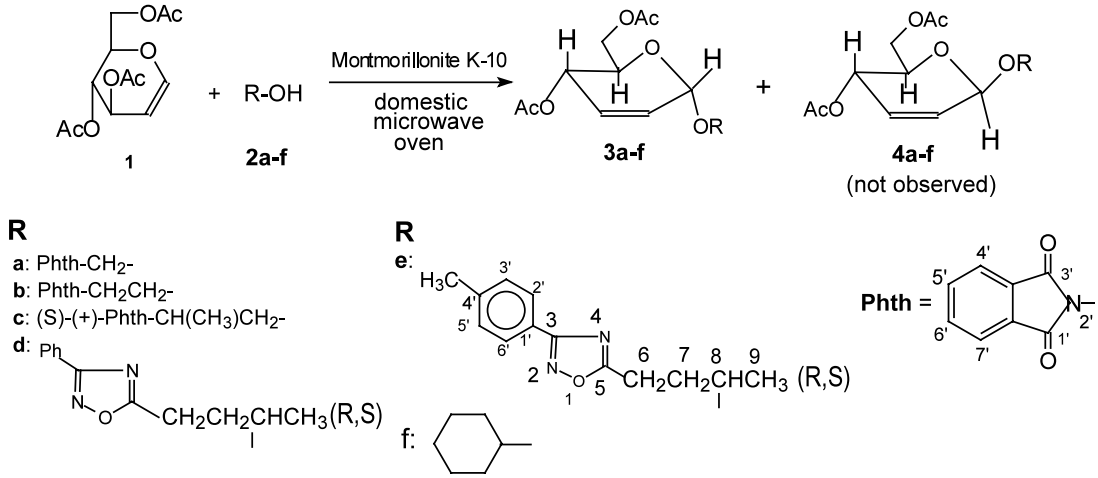

Scheme 1. Glycosidations of **1** with alcohols (**2a**–**f**) in the presence of Montmorillonite K-10.

spectroscopic means. We also examined other catalysts. This includes silica gel and ferric chloride, but either no reaction occurred or there was an extensive decomposition with these acids. Compounds **3a**[3] and **3f**[2c] are known, although they were prepared differently. Unsaturated glycosides **3d** and **3e** have also been synthesized recently using conventional heating and their structures established.[11] A comparison of the physical and spectroscopic properties of **3a**,**d**,**e**,**f** with those obtained previously gave satisfactory results.

In order to confirm the configuration at C-1 in these unsaturated glycosides, we chose compounds **3b**,**d**,**e** and obtained their two-dimensional spectra by applying the nuclear Overhauser enhancement spectroscopy (NOESY) technique. The spectra clearly showed the spatial interaction between H-1 and H-4 and demonstrated that H-1 and H-4 are on the same side.

Microwave method (solvent-free conditions): Microwave irradiation was performed in the domestic multimode oven.[12] An intimate mixture of **1** (1 mmol), **2a**–**f** (1.5 mmol) and Montmorillonite K-10 (25 mg, 50% w/w of **1**) was put in an open glass test tube, and then irradiated in the domestic microwave oven for a specified time, as indicated in Table 1, cooled and dissolved in ethyl acetate giving a colorless solution. Filtration to remove Montmorillonite K-10 and solvent evaporation left a solid mass which was chromatographed over a silica gel column employing *n*-hexane–ethyl acetate (9:1) as eluent. The fractions containing **3** ($R_f \approx 0.6$) were combined and solvent evaporated to provide chromatographically pure products. These were further purified by crystallization and recrystallization from ethanol. For comparison purposes, the synthesis of **3a**–**f** have also been carried out by conventional heating.[13]

In conclusion, a rapid, clean and efficient synthesis of 2,3-unsaturated glycosides **3a**–**f** containing *N*-phthalimidoalkyl or 1,2,4-oxadiazol-5-yl functions as aglycones by microwave irradiation is reported. The anomeric configurations of 2,3-unsaturated glycosides **3b**,**d**,**e** have been determined by nuclear Overhauser enhancement spectroscopy (NOESY) experiment which confirmed the spatial interactions between H-1 and H-4.

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