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An Improved Synthesis of 2,3- and 3,4-Unsaturated Pyranosides: the Use of Microwave Energy

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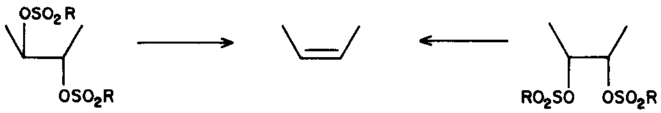
Abstract: Tipson-Cohen reactions of sugar derivatives containing contiguous sulfonyloxy groups have been studied in a microwave oven. Considerable rate increases and high yields of the unsaturated products have been observed.

Unsaturated carbohydrate derivatives have been subject of considerable interest for many years as versatile intermediates in a great number of natural products syntheses[1] and Diels-Alder reactions.[2] There are several methods in the literature concerning the introduction of double bonds into sugars,[3] and among them, the classical Tipson-Cohen procedure still provides an excellent alternative for these reactions.[1a,4,5] This method involves the action of sodium iodide and zinc dust in refluxing N,N-dimethylformamide on neighboring, secondary sulfonyloxy groups.

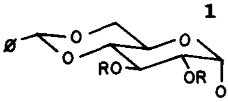
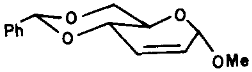
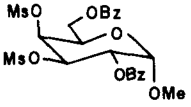
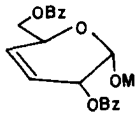
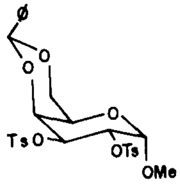
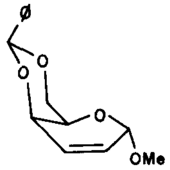


It is known that the reaction yields depend on the sulfonic ester environment in the molecules.[6,7] In some cases, especially when prolonged reaction times are required, decomposition of the products by the reagents may occur causing a yield decrease. The above mentioned factors were easily observed in our preparation of the 2,3-unsaturated carbohydrate 3 from the disulfonyloxy derivatives 1 or 2, according to the Tipson-Cohen procedure. The low reaction yields (42-53%) decreased further on longer reaction times (35-40%) (see table 1 - results almost identical with those reported by Horton *et al.*[5]).

To improve this reaction, we decided to employ microwave irradiation. This is becoming a standard technique in several areas of chemistry as an efficient source of energy.[8-12] In synthetic organic chemistry it has been used since 1986[9] and spectacular results have been reported,[9-12] indicating advantages of this new methodology when compared with conventional heating methods. These advantages, mainly faster and cleaner reactions due to less thermal decomposition of products and minimization of secondary processes,[10,12] seemed us very convenient for our purposes with the Tipson-Cohen reactions.

The results of some representative reactions are given in Table 1.

Table 1: Comparative results in representative Tipson-Cohen reactions using classical and microwave procedures (substrate, NaI and Zn dust in DMF).

Compound	Methodology	Reactional time	Yield[a] (%)	Product
 1 R=Ts	conventional[b]	2 h 4 h	53 40	 3
	microwave[b]	14 min	88	
2 R=Ms	conventional[b]	2 h 4 h	42 35	
	microwave[b]	8 min	89	
 4	conventional[c] microwave[c] microwave[e] microwave[f]	1h30[d] 2 min 4 min 12 min	93 90 81 79	 5
 6	microwave[b,g]	----	--	 7

[a] The yields are based on isolated products. [b] ratio substrate:NaI:Zn dust 1:50:54.[5] [c] ratio substrate:NaI:Zn dust 1:18:17.[1a] [d] the conventional conditions and results were taken from literature.[1a] [e] ratio substrate:NaI:Zn dust 1:9:8.5. [f] ratio substrate:NaI:Zn dust 1:4.5:4. [g] this reaction was also made at low, medium and medium-high power settings.

The microwave reactions were carried out in a commercial microwave oven (2450 MHz), at high power setting (700w), in a Teflon screw-capped vessel, always intercalating periods of heating (2-5 min) with periods of repose of the sample in the oven (30 sec-2 min). This was necessary to guarantee safe conditions and to prevent projection of the reaction medium, that may occur when non-homogeneous conditions provoke localized superheating.

In the preparation of the 2-ene pyranoside **3** from **1** and **2** excellent results were obtained. The reactions were completed in a few minutes (8-14 min) and the product was isolated in good yields (88-89%), showing a neat contrast with the results attained from the conventional manner. This new methodology was also convenient for the preparation of 3,4-unsaturated sugars, as shown for the reaction with the *galacto* di-*O*-mesyl derivative **4**.[1a] Using microwave irradiation, a very fast reaction (2 min) took place, yielding the 3-enoside **5** in 90%. In this particular case, it was also possible to reduce the excess of reagents (see Table 1), with no significant loss of the reaction efficiency. On the other hand, performing this reaction with the *galacto* 2,3-di-*O*-sulfonyloxy derivative **6**, complete decomposition of the starting material was observed, without detection of the elimination product **7**.

The above experiments indicate that, from a mechanistic point of view, the microwave-induced Tipson-Cohen reactions seem to be very similar with those induced by classical heating methods.[6,7] The steric and stereoelectronic interactions that affect the reaction transition state,[7,13] namely the effect of a vicinal axial and/or a β-*trans*-axial substituent regarding the position of the initial nucleophilic attack by iodide ion, must also be operative under microwave conditions.

Thus, the reaction with the *galacto* derivative **4** (having neither vicinal axial nor β-*trans*-axial substituents regarding the C-4 position) occurred faster than with the *gluco* derivatives **1** and **2** (having a β-*trans*-axial substituent regarding the C-3 position). Concerning the *galacto* sugar **6**, the disfavorable steric and stereoelectronic interactions (C-3 has both a β-*trans*-axial and a vicinal axial substituent) prevented the reaction occurrence.

It is noteworthy that the replacement of zinc dust by zinc-copper couple in the microwave reaction system[6b,14] gave the same olefinic products, but longer reaction times were needed and lower yields were obtained.[15]

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15. For example, the reaction with **1** using the substrate: sodium iodide: zinc-copper couple in molar proportions 1:5:5 took 15 min, furnishing **3** in 42% yield.

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