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Microwave-assisted saccharide coupling with *n*-pentenyl glycosyl donors☆

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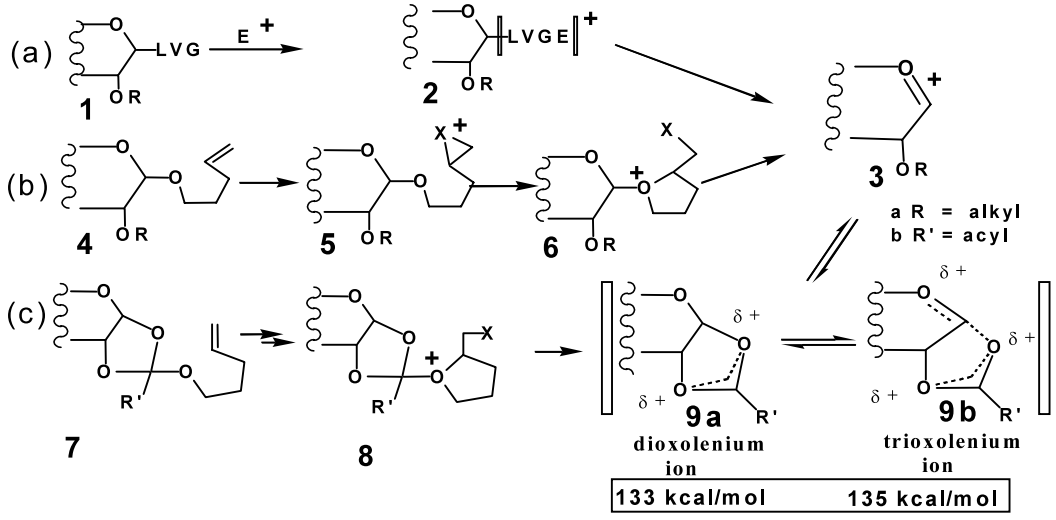
Abstract—*n*-Pentenyl glycosides, armed and disarmed, and *n*-pentenyl orthoesters couple with acceptors, hindered and unhindered, within 25 min under microwave activation. The reaction takes place in acetonitrile under neutral conditions with *N*-iodosuccinimide as promotor, which are therefore ideal for use with reactants bearing acid-labile protecting groups.

The pioneering 1986 report of Westaway,[1a] Majetich[1b] and their co-workers on the use of microwave activation for chemical reactions continues to inspire increasing interest in this novel synthetic tool. The impressive versatility of the technique may be judged by recent reviews[2,3] and monographs.[4] Major attributes of the method include faster reaction times and 'cleaner' reactions, and although the science which underlies these salutary effects remains debatable, the accruing advantages are indisputable, having been demonstrated even in enzymic reactions.[5]

Abramovitch[6] and Loupy[2] have postulated that reactions in which 'polarity is increased—from the ground state towards the transition state' are ideal candidates for microwave assistance. This postulate, added to the fact that microwave heating is less destructive of the substrate than thermal heating,[7] holds promise for



Scheme 1.

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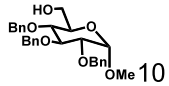
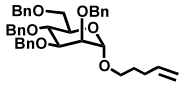
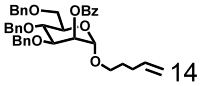
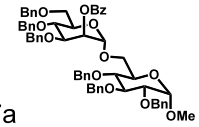
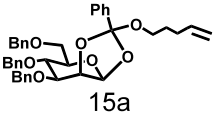
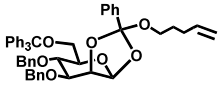
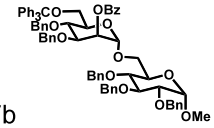
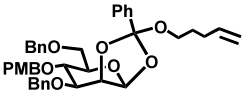
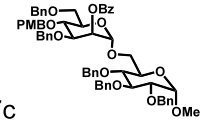
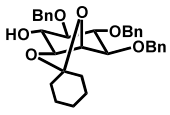
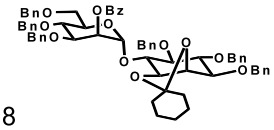
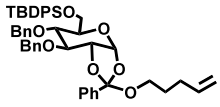
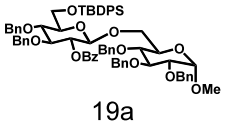
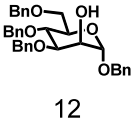
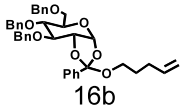
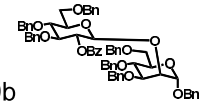
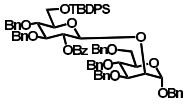
application to carbohydrates which are notoriously sensitive to heat. Apropos, experiments on installing/removing protecting groups,[8] nucleophilic displacements,[9] enzyme-catalysed glycosidation[10a] and, very recently, glycosylation of oxazolidine donors[10b] have been successful. In this communication we report the first examples, to our knowledge, of non-enzymatic saccharide coupling induced by microwave irradiation.

The fundamental process for activation of the anomeric center is depicted in Scheme 1a.[11] Several leaving groups (LVGs) allow direct or remote[12] activation leading to the crucial oxocarbenium ion **3**. In the case of *n*-pentenyl glycosides (NPGs) pioneered in this laboratory[13] (Scheme 1b), the road to oxocarbenium ion **3** traverses increasingly polar intermediates, **5** and **6**, that should present ideal opportunities for microwave assistance in keeping with the Abramovitch/Loupy postulate.[2,6]

Our initial work focused on the approach outlined in Scheme 1b. Thus, coupling of the 'armed' NPG donor

Table 1. Microwave-promoted coupling of *n*-pentenyl donors and acceptors

Entry	Acceptor	Donor	Product	Yield%
i	 10	 13	Several	-
ii	10	 14	 17a	26
iii	10	 15a	17a	77
iv	10	 15b	 17b	56
v	10	 15c	 17c	53
vi	 11	15a	 18	73
vii	10	 16a	 19a	65
viii	 12	 16b	 19b	60
ix	12	16a	 20	41

[a]For experimental conditions see footnote.[14] [b]Yields are unoptimized.

13 and 2 equiv. of the glucoside acceptor **10** in acetonitrile solution containing 2.2 equiv. of *N*-iodosuccinimide (NIS) under microwave irradiation for 25 min[14] showed no evidence of a coupled product (Table 1, entry i). By contrast, the 'disarmed' analogue **14**, under similar conditions, afforded disaccharide **17a**, albeit in poor (unoptimized) yield (Table 1, entry ii). Nevertheless, it was encouraging that some coupling had occurred. *n*-Pentenyl orthoesters (NPOEs), e.g. **7** (Scheme 1c) offer another avenue to the oxocarbenium ion **3** as shown in Scheme 1c.[15] Notably, the di/trioxolenium complex **9a**/**b**, can also capture the acceptor-OH at the anomeric center,[16] and the fact that the complex **9**, is ~30 kcal/mol lower in energy[17] than the disarmed oxocarbenium ion **3** (R = acyl) makes **9** more accessible. Indeed *manno* NPOE **15a**, reacted[14] with acceptor **10** to give disaccharide **17a** in 77% yield—in contrast to the 26% yield obtained with NPG **14** (Table 1, entry ii versus iii). The reaction of the *gluco* NPOE **16a** with acceptor **10** (Table 1, entry vii) also resulted in successful coupling to give disaccharide **19a** in 65% yield. It was of interest to see how acceptors with hindered hydroxyl groups would fare. The inositol (**11**) and mannoside (**12**) acceptors had previously been coupled with *manno* (**15a**) and *gluco* (**16b**) NPOEs under Lewis acid promoted conditions furnishing yields of **18** and **19b** in 80–90% and 84%, respectively.[18] These couplings were therefore repeated under our optimized microwave conditions. Yields of 73 and 60% were obtained (Table 1, entries vi and viii), somewhat lower than the Lewis acid conditions; however the resulting reaction mixtures were much cleaner, containing less side products.

The successes listed in Table 1 (entries iv–vi) augured well for use with substrates bearing acid labile protecting groups. In this context, a recent communication from our laboratory[19] reported that ytterbium (III) triflate was specifically suited for use with NPOE donors, especially those with acid labile protecting groups such as present in **15b** and **15c**. Microwave-induced coupling of the latter NPOEs with acceptor **10** provided modest yields (Table 1, entries iv and v). However, it is notable that again the product mixtures were extremely 'clean,' allowing ready isolation of the disaccharide products **17b** and **17c**, and recycling of the starting material.

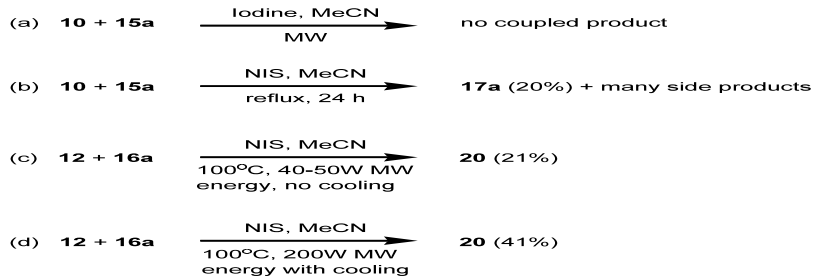
That the results in Table 1 were indeed attributable solely to microwave irradiation was an obvious concern. We therefore investigated the reaction using an alternative activator. Independent experiments had shown that donors **14** and **15** (**a**, **b** or **c**) were not activated by molecular iodine either thermally or by microwave radiation. The result in Scheme 2a in which iodine was replaced by NIS under the experimental conditions[14] of entry (iii), show that **15a** is not activated by iodine under microwave conditions.

On the other hand, were the results in Table 1 merely thermally induced? The experiment in entry (iii) was again repeated, except under 24 h reflux (Scheme 2b). Coupled product **17a** was indeed obtained, but the reaction was very messy, giving several side products.

Performing the reactions in a focused microwave instrument involves first setting a target temperature for the reaction. Irradiation with microwave energy results in the reaction reaching this temperature rapidly. Subsequent maintenance of this target temperature however only requires small bursts of microwave energy. A feature of the CEM 'Explorer' focused microwave instrument is the ability to maintain the target temperature while subjecting the reaction mixture to continuous irradiation with microwaves by cooling the reaction vessel with a stream of nitrogen.

To further test for thermal versus microwave effects, we took advantage of this feature described above.[14] Thus, reaction of compounds **12** and **16a** at 100°C with 200 W of microwave energy with simultaneous cooling gave product **20** in 41% yield (Table 1, entry ix and Scheme 2d). When the same reaction carried out without cooling, the microwave energy absorbed was only 40–50 W and the product **20** was isolated in only 21% (Scheme 2). This observation suggested that the applied microwave energy rather than heat alone had a substantial effect on the yields.

In conclusion, the *n*-pentenyl family of glycosyl donors, disarmed and orthoester, undergo ready coupling with hindered or unhindered acceptors. When the reactions are performed in a focused microwave the yields range from excellent to modest, and the reactions are always rapid and 'clean'. The ability to tolerate acid-labile protecting groups as well as short reaction time are attractive advantages of this coupling procedure.



Scheme 2.

Acknowledgements

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14. *A typical procedure for the glycosidation is as follows*: Acceptor (1 equiv.) and and *n*-pentenyl donor (2 equiv.) were dissolved together in a small amount of toluene and azeotroped to dryness. The residue was dried overnight under vacuum, and then dissolved in dry acetonitrile (1 mL), and transferred to a microwave vessel (10 mL). NIS (2.2 equiv.) was added to the solution and the sealed vessel was subjected to microwave reaction under cooling in a CEM 'Explorer' focused microwave reactor. The settings for temperature, time and power were: 100°C, 25 min and 200 W, respectively. After the reaction was complete, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and quenched with 10% sodium thiosulfate solution. The organic layer was extracted with CH_2Cl_2, washed with water, and dried over sodium sulfate. The solvents were removed, and the residue was purified by column chromatography.
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