

A New Glycosylation Method: A Study of Microwave Effects at Low Temperatures



Introduction

Oligosaccharides are one of the most abundant classes of biologically active compounds with a variety of functions, including uses by our immune system, as energy sources, and as structural components. More specifically, oligosaccharides function as hormone regulators and play a role in cell to cell adhesion and cell recognition. Lewis X (Le^x) antigen (1) is a glycoconjugate (an oligosaccharide that is attached to a protein or lipid) that plays a role in selectin-mediated cell to cell adhesion. Shimizu and co-workers synthesized a thiomethyl Le^x derivative (2), **Figure 1**, in order to introduce a variety of functional groups at the thiomethyl position and to further study the antigen's mechanism of recognition.¹

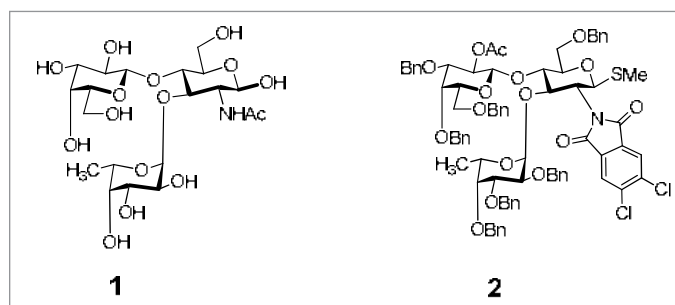
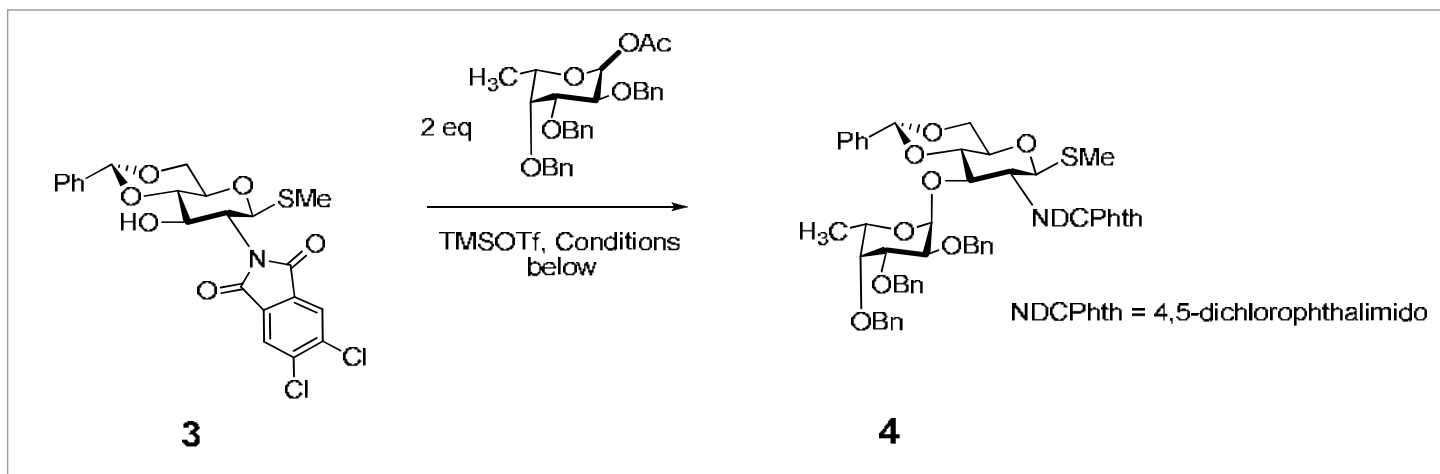


Figure 1. Le^x antigen and target synthesis

Microwave Versus Conventional

The Disaccharide synthesis is detailed in **Scheme 1**. The authors noted that the glycosylation between 3 and 4 could

be problematic due to the strong nucleophilicity of the thio moiety. The nucleophilic problems, especially when coupled with the steric hindrance of the sugar, made generating the desired product more difficult. Glycosylation in ether at -10 °C provided only a 27% yield. Using an ether/THF mixture increased the yield to 71% (details for all conditions shown in **Table 1**). The yields were increased tremendously when the authors used the CEM Discover® with CoolMate™ accessory (**Figure 2**).² Microwave irradiation at 300 W and 100 W resulted in a 90% and 83% yield respectively. A fiber optic probe was used to monitor the internal temperature, giving evidence that microwave irradiation has a profound effect on reaction rate at sub-ambient temperatures. The reactions using the CoolMate obtained higher yields with shorter reaction times.

**Scheme 1.** Glycosylation of glucosamine**Table 1.** Effect of microwave irradiation at low temperature

Solvent	Microwave Power (W)	Temperature (°C)	Time (h)	Yield (%)
Ether	none	-10	1	27
Ether/THF (5/1)	none	-45	6	71
Ether	300 W	-10	1	90
Ether	100 W	-18	2.5	83
CH ₃ CN	300 W	-20	1	21
CH ₂ Cl ₂	300 W	-20	2.5	9

**Figure 2.** CEM CoolMate and Discover

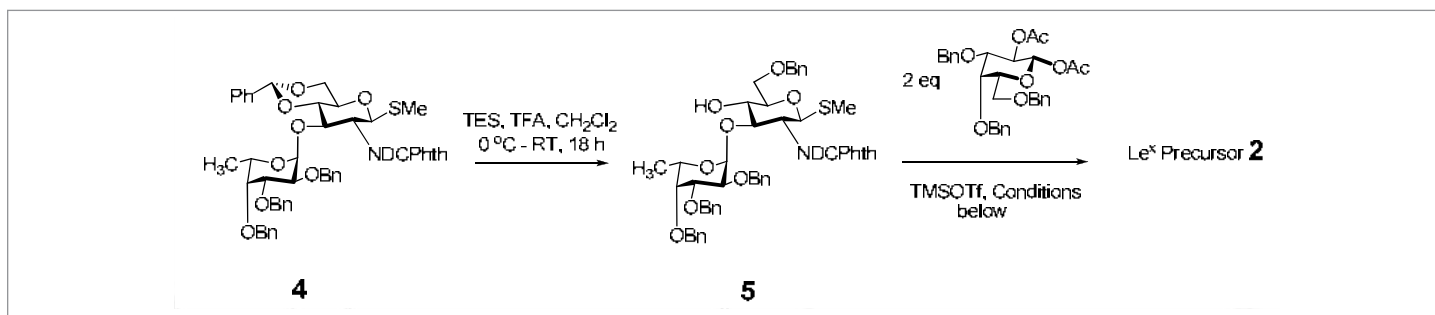
Challenging Trisaccharide Synthesis

For the trisaccharide synthesis (**Scheme 2**), selective reduction of the benzylidene group with triethylsilane and trifluoroacetic acid afforded **5** in 88 % yield. Glycosylation of the glucosamine unit in the presence of TMSOTf gave the desired product **2**. Many attempts under conventional methods to obtain product failed. The results of the trisaccharide synthesis are summarized in **Table 2**. Di- and trisaccharide byproducts were the only materials recovered from entry 4 and 5. It was unclear why the solvent affects the yield of desired product; however, ether consistently gave higher yields. Maintaining a temperature below 0 °C during the course of the reaction was crucial to

generate the desired product: entry 2 reached -5 °C, while entry 3 reached 30 °C and the isolated yield was decreased by half. The reduction in yield was attributed to the formation of di- and trisaccharide byproducts which were isolated and characterized.

Conclusion

Microwave irradiation at low temperatures was an effective method to control the reaction pathway and reduce byproducts in the synthesis of Le^x derivatives. In the words of the authors “microwave irradiation turned the ‘impossible’ into a ‘possible’.”



Scheme 2. Synthesis of thiomethyl Le^x derivative

Table 2. Results of trisaccharide synthesis using CoolMate

Entry	Solvent	Microwave Power (W)	Temperature (°C)	Time (h)	Yield of 2 (%)
1	Ether	None	-20 to RT	24	0
2	Ether	300	-20 to -5	5	82
3	Ether	300	-20 to 30	6	43
4	CH ₂ Cl ₂	300	-20 to 5	2	0
5	CH ₃ CN	300	-20 to 5	6	0

References and Remarks

¹ Shimizu, H.; Yoshimura, Y.; Hinou, H.; Nishimura, S.

Tetrahedron **2008**, 64, 10091 – 10096.

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² For information on the CoolMate including applications and

theory, see <http://www.cem.com/coolmate.html>

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