

A novel glycosylation concept; microwave-assisted acetal-exchange type glycosylations from methyl glycosides as donors

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Abstract—Efficient microwave-assisted glycosylations from methyl glucopyranosides are described. We have discussed the effects of microwave irradiation on this unique glycoside exchanging reaction from view points such as amount of Lewis acid promoters and acceptors, hydroxyl protecting groups of methyl glucopyranosides donors for reactivity, and neighboring effect.
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Since the mid-1980s, microwaves are being widely used in chemical reactions.^{1,2} Even in the field of carbohydrate research, there are already many reports involving microwave applications, especially in aspects of glycosylations,³ glycopeptide syntheses,⁴ protecting group chemistry,⁵ and so on, and even a review has already been published.⁶ Fundamentally, the microwave effect should mainly be related to heat effects, and many reports have thus focused on ‘improvement of reactions’.

Glycosylation, which is the conjugation of a sugar and an alcohol, has been well studied especially over the past quarter century.⁷ In general, alkyl glycosides are not suitable for glycosyl donors, because they require harsh acidic conditions to break the glycosyl bonds, with the exception of 4-pentenyl glycosides⁸ which are able to be activated in intramolecular systems. In order to form new glycosyl bonds, glycosyl donors bearing efficient leaving groups at their anomeric centers (e.g., halide, fluoride, thioalkyl groups, trichloroacetimidate, 4-pentenyl glycoside, etc.) are typically activated by heavy metal salts, Lewis acids, etc. Although methyl glycosides are

often used for protecting the anomeric center, they *never* act as glycosyl donors in the formation of new glycosyl linkages except in a case of the report from Mukaiyama and co-workers⁹ which has required silyl-protection for acceptor hydroxyl groups to achieve higher glycosylation yields.

Despite these historical backgrounds, we have found a new glycosylation system that with microwave irradiation has lead to newly glycosylated compounds, allowing methyl glucopyranosides as donors, as simple to exchange glycosyl bonds.¹⁰

According to our fundamental experiment,¹¹ methyl 2,3,4,6-tetra-*O*-benzyl- β -D-glucopyranoside (**1 β**)¹² could be converted to octyl 2,3,4,6-tetra-*O*-benzyl- α , β -D-glucopyranoside (**2 α** and **2 β**)¹³ with 1-octanol and a Lewis acid promoter at 120 °C. The conversion yield, however, was not higher than 46% after 1 h. The exact same conditions (reaction scale, amount of reagent, etc.) plus microwave irradiation gave a quicker and higher yield, for example, 72% for 10 min and 88% for 30 min (Table 1).

There are two possibilities for the mechanism that cleaves acetal C–O bonds under acidic conditions, either for sugar rings to intermediate **A** or for glycosyl bond to intermediate **B** in Figure 1, although the intramolecular

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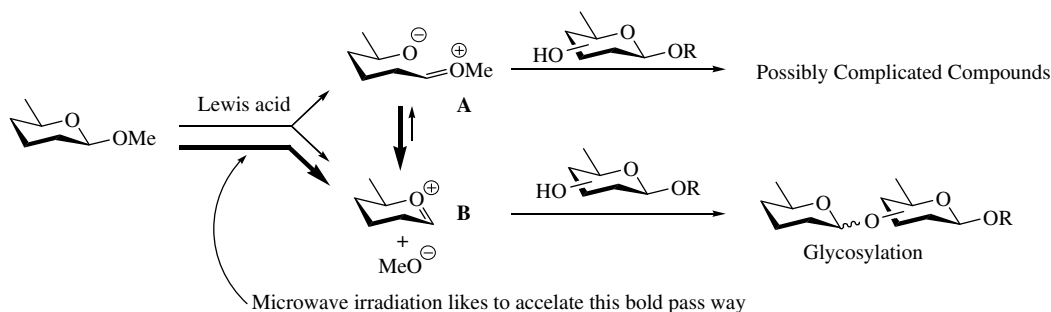
Table 1. Methyl glucoside reactions as glycosyl donors with/without microwave irradiation

Donor **1β** $\xrightarrow[\text{CH}_2\text{Cl}_2, \text{AW-300 (microwave, 70W)}]{\text{C}_8\text{H}_{17}\text{OH (3 eq.)}, \text{Yb(OTf)}_3 \text{ (3 eq.)}}$ Compound **2α and 2β**

Time (min)	Conversion yield of 2 (2α and 2β ratio)	1α and 1β ratio ^a (%)
<i>(+) Microwave irradiation: observed reaction temperature = 120 °C</i>		
10	72% (46:26)	18:10
20	78% (49:27)	18:5
30	88% (57:31)	8:3
<i>(-) Microwave irradiation: setting reaction temperature = 120 °C</i>		
30	43% (25:18)	17:39
60	46% (27:19)	18:36

Conversion yield was determined by HPLC.¹¹

^a **1α** and **1β** were observed by HPLC analysis.¹¹ Both the starting material and epimerized compound were observed.

**Figure 1.** Pathways of activated methyl glucoside as a glycosyl donor.

reformation of sugar rings producing the intermediates **B** from **A** could be thought of as a favorable pathway when compared to intermolecular reactions that might lead to complicated compounds. Although the glycosylated compound could be isolated without microwave irradiation, microwave irradiation had obviously accelerated to leave methoxy anion to lead oxocarbenium cation **B** or conversion from the intermediates **A** to **B**.

Based on these results, we have examined the practical conditions required for this ‘acetal bonds exchange type’ microwave supported glycosylations from methyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (**1β**). First, we have demonstrated the efficiency of the amount of acceptor and promoter used, 1-octanol and ytterbium triflate, respectively. As seen in Table 2, more acceptor and more promoter gave better results. For example, the use of three each equivalent amounts of 1-octanol and ytterbium triflate led to 72% conversion yield in only 10 min. The products were a mixture of α- and β-glycosylated compounds, **2α** and **2β**, as ca. 1:1 to 1.6:1. When methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**1α**) was chosen as a starting donor, the reaction speed was slower but the resulting yield was better than that from β-donor. (See in Table 2 for the cases of 2 equiv of Yb(OTf)₃ and 3 equiv of 1-octanol to compare.) This would cause methyl α-glucopyranoside to be less reactive than methyl β-glucopyranoside, and the epimerization from β-methoxy group to α-methoxy

group at the anomer position was more favorable than the reverse. We considered at first whether the boiling point of the acceptor was involved in the yields or not, but we could not reach a definitive conclusion because of two issues: (i) the boiling point of 1-octanol is lower than the reaction temperature (bp = 196 °C, reaction temp. = 120 °C); (ii) there was no parallel connection with the yield and the boiling point when other acceptors were tested (data is not shown here).

The required microwave power was different for each promoter. As shown in Table 2, Ytterbium triflate and zinc chloride required 70 W and 60 W, respectively, but in case of trimethylsilyl triflate (TMSOTf), 30 W was enough. The reaction was very fast and gave an excellent reaction yield even for 6 min. When we irradiated compound **1β** by 50 W with TMSOTf as a promoter for 10 min, the material seemed to decompose and we could not detect the reaction by TLC at all.

Next, we tested for epimerization possibilities for resulting of both α- and β-octyl glucopyranosides, **2α** and **2β**, under the typical microwave irradiation reaction conditions, but epimerization was not observed at all. From this point on, we concluded that the reaction has proceeded via ‘one way’, which means even though both methyl glycoside and octyl glycoside are ‘alkyl glycosides’, only methyl glycoside can behave as a donor (Scheme 1).

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