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Tetrahedron Letters 46 (2005) 4701–4705
Tetrahedron Letters

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

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Received 21 April 2005; revised 12 May 2005; accepted 13 May 2005
Available online 31 May 2005

**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.


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 glycosides[8] 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, trichloroacetoimide, 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-workers[9] 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 (**1β**)[12] could be converted to octyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranoside (**2α** and **2β**)[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

*Keywords*: Microwave; Glycosylation; Carbohydrate; Methyl glycoside.
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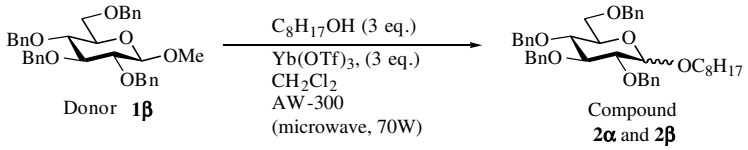
0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.05.046

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




| Time (min) | Conversion yield of **2** (**2α** and **2β** ratio) | **1α** and **1β** ratio[a] (%) |
|---|---|---|
| *(+) Microwave irradiation: observed reaction temperature = 120 °C* | | |
| 10 | 72% (46:26) | 18:10 |
| 20 | 78% (49:27) | 18:5 |
| 30 | 88% (57:31) | 8:3 |
| *(−) Microwave irradiation: setting reaction temperature = 120 °C* | | |
| 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.

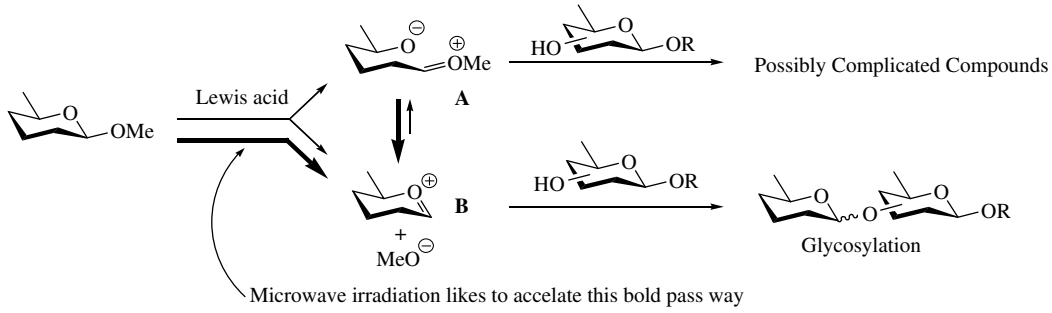



**Figure 1.** Pathways of activated methyl glucoside as a glycosyl donor.

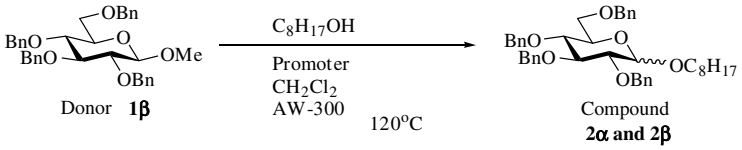
reformation of sugar rings producing the intermediates **B** from **A** could be thought of as a favorable pathway when compared to intermolecular reactions that might lead to complicated compounds. Although the glycosylated compound could be isolated without microwave irradiation, microwave irradiation 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).

**Table 2.** Microwave assisted glycosylation

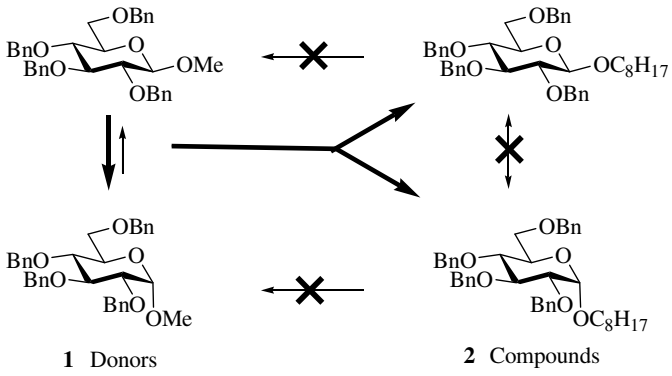



| Promoter | Donor (equiv) | Acceptor (equiv) | Microwave irradiation (W) | Time (min) | Conversion yield of **2** (**2α** and **2β** ratio) | Isolated yield of **2** (%) | **1α** and **1β** ratio[b] (%) |
|---|---|---|---|---|---|---|---|
| $Yb(OTf)_3$ | 1 | 1 | 70 | 10 | 1% | | 2:97 |
| | | | | 20 | 19% (11:8) | | 11:70 |
| | | | | 30 | 28% (16:12) | 27 | 16:56 |
| $Yb(OTf)_3$ | 1 | 2 | 70 | 10 | 18% (10:8) | | 9:71 |
| | | | | 20 | 30% (17:13) | | 10:60 |
| | | | | 30 | 37% (21:16) | 33 | 14:49 |
| $Yb(OTf)_3$ | 1 | 3 | 70 | 10 | 46% (28:18) | | 21:33 |
| | | | | 20 | 54% (33:21) | | 22:23 |
| | | | | 30 | 60% (37:23) | 60 | 18:21 |
| $Yb(OTf)_3$ | 2 | 1 | 70 | 10 | 21% (11:10) | | 11:68 |
| | | | | 20 | 37% (21:16) | | 17:46 |
| | | | | 30 | 43% (24:19) | 35 | 19:38 |
| $Yb(OTf)_3$ | 2 | 2 | 70 | 10 | 28% (15:13) | | 30:42 |
| | | | | 20 | 44% (26:18) | | 23:33 |
| | | | | 30 | 47% (29:18) | 50 | 27:20 |
| $Yb(OTf)_3$ | 2 | 3 | 70 | 10 | 40% (23:17) | | 20:40 |
| | | | | 20 | 50% (29:21) | | 19:31 |
| | | | | 30 | 56% (33:23) | 50 | 18:26 |
| $Yb(OTf)_3$ | 2 (α)[a] | 3 | 70 | 10 | 29% (17:12) | | 64:7 |
| | | | | 20 | 37% (22:15) | | 55:8 |
| | | | | 30 | 49% (31:29) | | 44:7 |
| | | | | 40 | 59% (37:22) | | 35:7 |
| | | | | 50 | 67% (41:26) | | 41:26 |
| $Yb(OTf)_3$ | 3 | 1 | 70 | 10 | 19% (10:9) | | 12:69 |
| | | | | 20 | 33% (19:14) | | 17:50 |
| | | | | 30 | 32% (18:14) | 37 | 25:24 |
| $Yb(OTf)_3$ | 3 | 2 | 70 | 10 | 41% (24:17) | | 20:39 |
| | | | | 20 | 54% (32:22) | | 23:23 |
| | | | | 30 | 59% (37:22) | 60 | 30:11 |
| $Yb(OTf)_3$ | 3 | 3 | 70 | 10 | 52% (46:26) | | 18:10 |
| | | | | 20 | 76% (49:17) | | 18:5 |
| | | | | 30 | 89% (57:31) | | 8:3 |
| $ZnCl_2$ | 1 | 3 | 60 | 10 | 14% (7:7) | | 13:73 |
| | | | | 20 | 30% (16:14) | | 12:57 |
| | | | | 30 | 43% (23:20) | | 18:39 |
| TMSOTf | 1 | 3 | 30 | 4 | 59% (39:20) | | 24:17 |
| | | | | 6 | 65% (43:22) | | 24:11 |
| | | | | 8 | 67% (45:22) | | 26:7 |

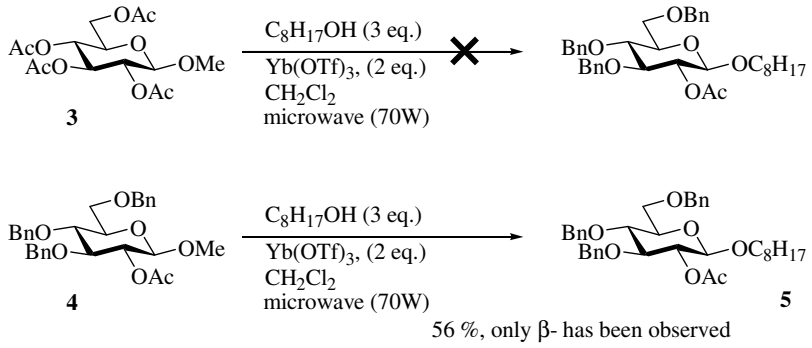
[a] **1α** was used as a donor.
[b] **1α** and **1β** were observed by HPLC analysis.[11] Both the starting material and epimerized compound were observed.

Finally, we would like to emphasize that this reaction system is very sensitive to donor reactivity. In addition to the activation that has a dependency on the length of the alkyl chains, the hydroxyl protecting groups on donors also affected deeply. Although methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) could not be activated, methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (**4**)[14] were converted to octyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (**5**)[15] with 1-octanol. We could not observe any α-glycosylated product, which suggests that neighboring effects work well even in this microwave irradiation glycosylation system (Scheme 2).

As shown here, methyl glycosides can be converted to glycoside derivatives with microwave irradiation efficiently. Methyl glycosides are widely available, and relatively easy to prepare compared with other monosaccharide donors. And as discussed in Scheme 1, microwave irradiation had activated methyl glycosides




**Scheme 1.** Reaction pathway from methyl glycosides with microwave irradiation.




**Scheme 2.** Microwave-assisted glycosylations for acetyl protected methyl glycosides.

selectively in spite of other existing glycosyl bonds, for example, octyl glycoside. The present finding that methyl glycosides can behave as donors as well may begin an era of oligosaccharide syntheses at the industrial level.

## Acknowledgements

The authors would like to thank Dr. Hiroshi Ohrui, Tohoku University, Japan, for valuable discussions.

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11. Typical procedure for the glycosylations was as follows: Microwave irradiation reactions were performed in a CEM Discover microwave system. To a mixture of predried donor **1β** (120 mg), AW-300 (300 mg), and promoter in $CH_2Cl_2$ (3 mL) in a CEM equipped pressure vessel was added 1-octanol. The reaction vessel was sealed and heated in an oil bath at 120 °C (without microwave irradiation case) or set in a 'Discover' for microwave assisted reactions. Although 'Discover' can incorporate both temperature and pressure feedback system, we have set just microwave irradiation power and observed actual reaction temperature and pressure. Every 10 min, the reaction vessel was once cooled with 'Discover CoolMate' and sampled, which was further treated as follows: It was diluted with ethyl acetate and washed with satd aq $NaHCO_3$. Repeating this procedure cyclically, the reaction mixture was finally diluted with ethyl acetate and neutralized with satd aq $NaHCO_3$. The aqueous layer was extracted with ethyl acetate and combined organic extracts were dried over $MgSO_4$. The resulting mixture was purified by silica gel chromatography. Elution with *n*-hexane/ethyl acetate (4:1) gave isolated **2α** and **2β**. The sampled reaction mixture was monitored by HPLC. Unless mentioned, conversion yield were determined by HPLC and we have confirmed that these conversion yield were much good with the isolated yield. HPLC conditions;

column Inertsil C8-3, 4.5∅ × 250 mm (GL Science Inc.), $CH_3CN/H_2O$ = 85:15 with 0.1% TFA, 1.0 ml/min, 254 nm UV detector, rt = 10 min for **1α**, 12 min for **1β**, 42 min for **2α** and 48 min for **2β**.

12. Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**1α**) and methyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (**1β**) were prepared by benzylation (NaH, BnBr, DMF) of methyl α-glucopyranoside and methyl β-glucopyranoside, respectively, and confirmed by comparison with references as **1α** for, Bessodes, M.; Shamsazar, J.; Antonakis, K. *Synthesis* **1988**, 560–562, and **1β** for; France, R. R.; Compton, R. G.; Davis, B. G.; Fairbanks, A. J.; Rees, N. V.; Wadhawan, J. D. *Org. Biomol. Chem.* **2004**, *2*, 2195–2202.
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