<table>
<thead>
<tr>
<th>Title</th>
<th>Organocatalytic direct α-selective N-glycosylation of amide with glycosyl trichloroacetimidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Li, Shanji; Kobayashi, Yusuke; Takemoto, Yoshiji</td>
</tr>
<tr>
<td>Citation</td>
<td>Chemical and Pharmaceutical Bulletin (2018), 66(7): 768-770</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2018-06-01</td>
</tr>
<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/2433/235932">http://hdl.handle.net/2433/235932</a></td>
</tr>
<tr>
<td>Type</td>
<td>Journal Article</td>
</tr>
<tr>
<td>Textversion</td>
<td>publisher</td>
</tr>
</tbody>
</table>

Kyoto University
Organocatalytic Direct α-Selective N-Glycosylation of Amide with Glycosyl Trichloroacetimidate

Shanji Li, Yusuke Kobayashi, and Yoshiji Takemoto

Organocatalytic Direct α-Selective N-Glycosylation of Amide with Glycosyl Trichloroacetimidate

Received April 1, 2018; accepted April 16, 2018


Through the synergistic catalytic effect of the halogen bond (XB) donor and thiourea catalyst, a direct α-selective N-glycosylation of the amide residue of asparagine derivative was achieved using readily accessible glycosyl trichloroacetimidate. n-Butyl methyl ether was found to be the most suitable solvent for the α-selectivity.

Key words glycosylation; organocatalyst; halogen bond; hydrogen bond; green chemistry

N-Glycosides are found in a variety of bioactive compounds, including natural products. Sugar moieties are known to extend the diversity of molecules, altering their property, structure, and biological activities. However, synthetic methods for N-glycosides have not been well developed as compared with the preparation of O-glycosides. In particular, stereoselective synthesis of α-N-glycosides is one of the most challenging issues despite their potentials as therapeutic compounds. In 2003, DeShong’s group investigated several other etheric solvents (entries 8–12), and found that dimethoxyethane (DME) and n-butyl methyl ether improved α/β-selectivity (α:β=80:20) (entries 11 and 12). The anomic configuration of major product was unambiguously determined as α-isomer (α-2a) by an X-ray crystallographic analysis.

With the suitable catalyst and solvent in hand, we next screened the reaction conditions for the direct α-N-glycosylation of asparagine derivative 3 with glycosyl donor 1 (Table 1). According to our previous work, 2-iodoimidazolium salt (XB1) was examined in conjunction with HB1 in dichloromethane. As we expected, the combination of HB1 and XB1 was essential for the production of desired N-glycoside 2a (entries 1–3), although almost no α/β selectivity was observed (entry 3). A control experiment with non-halogenated azolium 5 did not furnish 2a at all (entry 4), indicating that XB interaction would play an important role. The chemical yields were slightly improved using XB2 and XB3 (entries 5 and 6), whereas the undesired glycosyl trichloroacetamide 4 was obtained in these cases. Further investigation was carried out with XB3 from the viewpoint of its easy preparation. A slight improvement of α/β-selectivity (α:β=65:35) was observed when diethyl ether was used as solvent (entry 7). Encouraged by this result, we next investigated several other etheric solvents (entries 8–12), and found that dimethoxyethane (DME) and n-butyl methyl ether improved α/β-selectivity (α:β=80:20) (entries 11 and 12). The anomic configuration of major product was unambiguously determined as α-isomer (α-2a) by an X-ray crystallographic analysis.

With the suitable catalyst and solvent in hand, we next screened the reaction conditions for the direct α-N-glycosylation of asparagine derivative 3 with glycosyl donor 1 (Table 1). According to our previous work, 2-iodoimidazolium salt (XB1) was examined in conjunction with HB1 in dichloromethane. As we expected, the combination of HB1 and XB1 was essential for the production of desired N-glycoside 2a (entries 1–3), although almost no α/β selectivity was observed (entry 3). A control experiment with non-halogenated azolium 5 did not furnish 2a at all (entry 4), indicating that XB interaction would play an important role. The chemical yields were slightly improved using XB2 and XB3 (entries 5 and 6), whereas the undesired glycosyl trichloroacetamide 4 was obtained in these cases. Further investigation was carried out with XB3 from the viewpoint of its easy preparation. A slight improvement of α/β-selectivity (α:β=65:35) was observed when diethyl ether was used as solvent (entry 7). Encouraged by this result, we next investigated several other etheric solvents (entries 8–12), and found that dimethoxyethane (DME) and n-butyl methyl ether improved α/β-selectivity (α:β=80:20) (entries 11 and 12). The anomic configuration of major product was unambiguously determined as α-isomer (α-2a) by an X-ray crystallographic analysis.
investigated several additives and HB donors in order to improve the $\alpha/\beta$-selectivity, and to suppress the undesired glycosyl trichloroacetamide 4 (Table 2).

When 1.0 equiv of thiophene was added, the yield of 2a increased to 64% along with the decrease of byproduct 4, and the $\alpha/\beta$-selectivity has reached to 82 : 18 (entry 1). Ten equiv of thiophene, however, diminished the yield of 2a, probably due to the inhibition of the catalysts (entry 2). To our disappointment, further improvement was not observed, although several different thiophene derivatives (entries 3–8) and other nucleophilic additives, such as $N,N$-dimethylaminopyridine-$N$-oxide (DMAPO), $N$-formylmorpholine (NFM), 15) triphenylphosphine oxide, and tri(2-thienyl) phosphine (entries 9–12), were screened as additives. Then, we examined the HB donors HB2 19) and HB3 17) bearing superior HB-donating abilities (entries 13 and 14). The ratio of the desired product 2a to the byproduct 4 was improved, presumably because of their stronger anion binding abilities, while there is still room for improvement of the $\alpha/\beta$-selectivity. It is worthy to note that trimethylsilyl trifluoromethanesulfonate (TMSOTf), one of the most commonly used Lewis acids, was not effective to obtain $N$-glycoside 2a, and the undesired glycosyl trichloroacetamide 4 was just produced in high yield (entry 15).

In conclusion, we have found that XB donor/ thiourea co-catalytic system was effective even in polar solvent, enabling a direct $\alpha$-selective $N$-glycosylation of amide with glycosyl trichloroacetimide. We believe that this methodology would be applied to the synthesis of a variety of $\alpha$-$N$-glycosides.

**Experimental**

To a solution of glycosyl donor 1 (41.1 mg, 0.06 mmol), glycosyl acceptor 3 (15.3 mg, 0.05 mmol), and thiophene (4.2 mg, 0.05 mmol) in $n$-butyl methyl ether (1.0 mL) were successively added activated MS4Å (100.0 mg), XB3 (3.3 mg, 0.005 mmol), and HB1 (2.5 mg, 0.005 mmol), and the reaction mixture was stirred at room temperature for 24 h. Direct purification on silica gel column chromatography gave $\alpha$-2a (21.9 mg, 53%) and $\beta$-2a (4.8 mg, 11%) as white solid (Table 2, entry 1).

**Acknowledgments**

This work is supported in part by Takeda Science Foundation and Grants-in-Aid for Scientific Research (16H06384) from Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

**Conflict of Interest**

The authors declare no conflict of interest.

**Supplementary Materials**

The online version of this article contains supplementary materials.

**References**

17) See the Supplementary Materials for details.