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Glycosylation of 'basic' alcohols: methyl 6-(hydroxymethyl)picolinate as a case study

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ABSTRACT

Glycosylation is promoted by acid promoters rendering the reactions with basic acceptors challenging. This report presents an in depth study involving methyl 6-(hydroxymethyl)picolinate as the model acceptor and 22 glycosyl donors to afford the desired glycosides in good yields ranging from 46% to 85%. Several parameters were evaluated, including the protecting groups of the glycosyl donor, the leaving group at the anomeric center, and the promoter. The influence of the pyridine ring was evident with a benzene-based acceptor affording high yields of glycoside (79%) in comparison to the pyridine-based acceptor (46%). The present work provides a general and reliable access to pyridine-containing glycosides.

1. Introduction

Carbohydrates are present in nature as monomers (e.g., glucose is a source of energy) and oligomers (i.e., oligosaccharides) which are interconnected through glycosidic bonds. Glycosylation[1–9] is therefore one of the most important reactions in carbohydrate chemistry, challenged by the control of regioselectivity commonly achieved by protecting group strategies but also by the stereoselectivity of the glycosidic bond created requiring additional strategies based not only on protecting groups but also on specific reaction conditions.

Initially, picolinyl ethers have been identified as reactivity-enhancing replacements for benzyl ethers as exemplified for the glycosylation at the 4-position of a *N*-acetylglucosamine acceptor bearing a picolinyl group at the 3-position.[10] More recently, picolinyl and picoloyl substituents have been identified as protecting groups for the stereocontrol of glycosylation.[11–13] Nevertheless, this approach is usually using excess of promoters in order to balance the intrinsic basicity of the pyridine moiety and then catalyze the formation of the oxocarbenium intermediate. Surprisingly, a careful survey of the literature for the glycosylation of glycosyl acceptors with pyridine-containing acceptors did not afford many results and most of these were poor in terms of isolated yields of glycosides and are discussed below. Such glycosides containing a pyridine aglycone will find applications for the design of neutral nucleotide-diphosphate sugar analogues in the search for neutral inhibitors of glycosyltransferases.[14–17] After determining the optimal glycosylation conditions for these glycosides, the ester moiety will then be conjugated to a 5′-aminonucleoside to afford a neutral NDP-sugar analogue.

Pyridoxine can be glycosylated on the hydroxymethyl groups at positions 4′ or 5′, or both, and is better known as vitamin B_6. The 4′-glucosylated derivative is less stable to hydrolysis in the liver than its 5′-regioisomer. In an initial report, the hydrolysis of the glycosidic bond of glycosylated derivatives of pyridoxine by glycosidases has been studied (Table 1, entry 1).[18] In another series of experiments, the influence of borate was evaluated in order to obtain a regioselective glucosylation of pyridoxine at the 4′- or 5′-positions by microorganisms.[19,20] Enzymatic glycosylation could also be performed using α- and β-glucosidases (Table 1, entry 2).[21,22] Introduction of an additional fluorine atom at the 6-position of the pyridine ring afforded reporter molecules for the identification of genes encoding for β-galactosidase in the search for efficient molecules for the assessment of location, magnitude, and persistence of gene expression.[23] The glycosyl donors used in these reports are natural (oligo)saccharides, sucrose, or dextrins[19–22] but also chemically modified carbohydrates such as *p*-nitrophenyl[18] (PNP) or α-bromo[23] activated glycosides. Nevertheless, under the aforementioned conditions using enzymatic or microbial glycosylations, a maximum yield of 40% was achieved. In a similar enzymatic approach, the PNP-activated glucose was used as a donor

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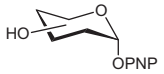
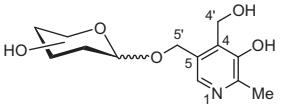
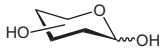
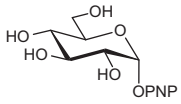
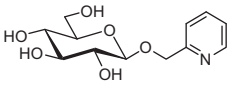
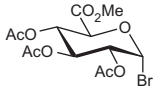
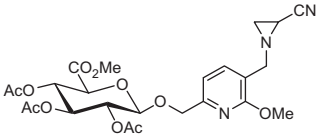
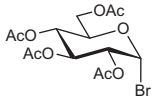
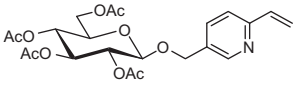
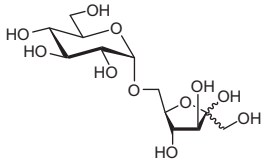
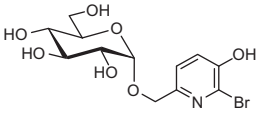
Table 1
Enzymatic and chemical approaches to the synthesis of glycosylated hydroxymethylpyridine derivatives

Entry	Donor	Glycoside	Method	Yield (%)	Ref.
1			Enzymatic	32[a]	18
2				44[b]	22
3				24	24
4				45[c]	25
5			Chemical	24[c]	26
6				<5[d]	27

[a] Yield reported for galactose derivatives.
[b] The 4′-regioisomer was also isolated in a 28:72 mixture with the desired 5′-derivative.
[c] Yield calculated over two steps from the data reported through the orthoester intermediate.
[d] Yield calculated from the reported data for the multi-step process.

for the glucosylation of a series of aliphatic and benzylic alcohols in the presence of a glucosidase providing the desired β-D-glucosides in less than 35% yield (Table 1, entry 3).[24] While these synthetic strategies, inspired by natural enzymes or microorganisms did not require extensive protecting group chemistry and provided the desired glycosides in high anomeric stereoselectivities, the yields obtained remained quite low and did not call for applications in organic synthesis.

In an organic chemistry approach, a handful of reports have been identified in the literature in which chemical synthesis has been applied. The glucuronylation of ciamexon (an immunomodulating agent with application in diabetes) was achieved from the corresponding α-glucuronopyranosyl bromide donor using silver(I) salt as a promoter leading to the desired glucuronide in 45% yield (Table 1, entry 4).[25] The reaction conditions were quite sensitive and the use of basic medium (*sym*-collidine) influenced the reaction affording a large portion of undesired orthoester. This problem could be overcome by using excess of silver triflate (AgOTf, 3 equiv) most probably in order to balance the basicity of the pyridine acceptor. The formation of the orthoester intermediate could not be prevented in the glycosylation between acetobromoglucose and 2-vinyl-5-hydroxymethylpyridine derivative using AgOTf as the promoter[26] in a study for the design of peptide functionalizing agents (Table 1, entry 5). Again, an excess of promoter (1.5 equiv) was used but led to exclusive formation of the orthoester intermediate in 73% yield since the same amount of acceptor was used and its basicity could therefore not be totally balanced. A subsequent rearrangement in the presence of trimethylsilyl triflate (TMSOTf) afforded the desired glycoside in 32% yield corresponding to an overall yield of only 24% over two steps.

Finally, isomaltulose was used as a precursor for α-glucosylated hydroxymethylpyridine derivatives (Table 1, entry 6).[27] Acid dehydration of isomaltulose afforded a glucosylated furfural which could be transformed into a pyridine moiety through two additional synthetic steps. The overall process did not afford the desired compounds in good yields (<5%) but represents yet another possibility for the construction of the pyridine scaffold from a furane moiety intermediate.

2. Results and discussion

Methyl 6-(hydroxymethyl)picolinate **2a** was chosen as the glycosyl acceptor. After reductive desymmetrization of a diester precursor,[28] the subsequent glycosylation was then investigated with a large series of glycosyl donors and glycosylation conditions to address the scope and limitation of such chemical glycosylation of hydroxymethylpyridine derivative. This general investigation of the glycosylation of hydroxymethylpyridine was therefore undertaken based on the literature overview presented above leading to at least two observations: (1) enzymatic or chemical glycosylations are possible, but (2) the yields obtained are rather poor. The chemical glycosylation was studied here with 22 donors and under 43 glycosylation conditions in order to provide a general and useful methodology for the synthesis of a large series of glycosylated hydroxymethylpyridine derivatives.

2.1. Galactosyl donors

The first type of glycosylation investigated employed galactosyl donors in order to address the influence of protecting groups on the carbohydrate moiety as well as the different leaving groups at the anomeric position on the outcome of the glycosylation reaction. Galactosylation is usually simpler to be studied in comparison to glucosylation providing in most cases higher reactivities of the glycosyl donors, improved yields, and better selectivities.[29–31] In all cases, the promoter was a Lewis acid used in excess in the