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Note

Straightforward glycosylation of alcohols and amino acids mediated by ionic liquid

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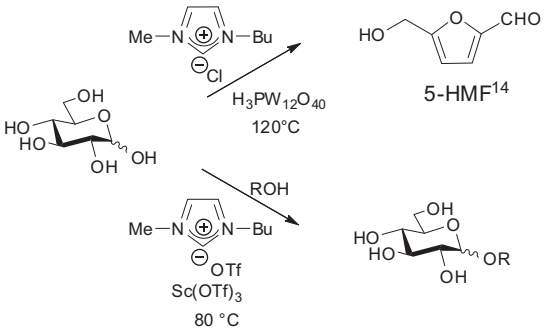
ABSTRACT

Green glycosylation of functionalized alcohols and α-amino acids, using an ionic liquid as a recyclable solvent, was performed in one step directly from the unprotected monosaccharide under scandium triflate or ferric chloride catalysis. Pure α- and β-glycosides could be obtained after specific enzymatic hydrolysis.

Carbohydrates play a fundamental role in many aspects of chemistry and biology. Therefore, the chemistry of glycosides and glycoconjugates has gained much attention for many years. In spite of continuous progress in O-glycosylation methodologies since the historical Koenigs–Knorr reaction, the chemical methods suffer from tedious protection/deprotection steps. Besides, an appropriate activating group must be introduced at the anomeric position, which induces supplementary waste. Such a reaction sequence for O-glycosylation leads to a poor atom economy and to a high E-factor. Indeed, these reaction metrics can now be easily calculated for a complete sequence and such a calculation is extremely instructive to figure out the greenness of a process.[1] Even enzymatic methods using glycosyltransferases require the introduction of an auxiliary such as an expensive sugar nucleotide. Moreover the nucleoside diphosphates generated during the reaction are potent glycosyltransferase inhibitors.[2] New enzymatic methods using glycosidases are emerging, such as the glycosynthase[3] or the transglycosidase[4] approach, but these methods are very specific and require activated sugars, such as fluoro or nitrophenyl glycosides, respectively.

When starting from unprotected carbohydrates, enzymatic reactions using glycosidases are driven more easily toward the hydrolysis than toward the formation of glycosides, since the natural medium of enzymes is water.[5,6] The thermodynamic enzyme-catalyzed equilibrium can be driven toward the formation of glycosides if a large excess of aglycone is used.[7] An alternative strategy was investigated with the use of ionic liquids to decrease the activity of water in glycosidase-catalyzed transglycosylations.[8,9]

We and others have recently shown that it was possible to use unprotected and non-activated monosaccharides in the O-glycosylation of alcohols in order to produce alkylpyranosides in the presence of an ionic liquid.[10–12] The reaction which goes through an oxocarbenium cation needs acidic conditions, either protonic or Lewis acid conditions. We must be aware that these conditions may lead to a secondary reaction, such as the dehydration of carbohydrates affording 5-hydroxymethylfurfural (5-HMF). Such a transformation in ionic liquid is now considered as a good oppor-



Scheme 1. Dehydration versus glycosylation.

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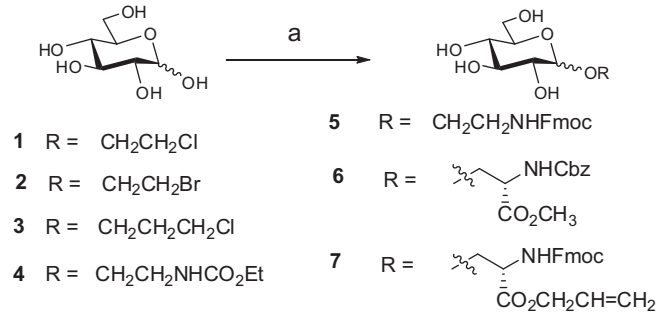
Table 1
Glycosylation of octanol

Carbohydrate	Catalyst (mol %)	Conditions	Isolated yield	α/β
Glucose	$Sc(OTf)_3$ (5)	80 °C 24 h	74	75/25
Glucose	$FeCl_3$ (5)	80 °C 3 h	67	55/45
N-Acetylglucosamine	$Sc(OTf)_3$ (5)	110 °C 24 h	60	79/21
N-Acetylglucosamine	$FeCl_3$ (100)	110 °C 2 h 30 min	34	100/0



Scheme 2. Reagents and conditions: (a) ROH, 5 equiv, $Sc(OTf)_3$ or $FeCl_3$ 0.05 equiv, [BMIM][OTf], 80 °C

tunity to easily produce biofuels or bioproducts from biomass.[13–15] Since we never observed the formation of 5-HMF when using butylmethylimidazolium triflate as the ionic liquid, we decided to apply our methodology (Scheme 1) to the straightforward O-glycosylation of functionalized alcohols including serine derivatives in order to propose convenient methodologies in the coupling of sugars with peptides.

The first studies were carried out with lanthanide or scandium triflate as the catalyst.[12] Indeed, since $FeCl_3$ is a more accessible catalyst than $Sc(OTf)_3$, it was interesting to test it. As a matter of fact, Fischer-type glycosylation of methanol in the presence of $FeCl_3$ gave methyl glucofuranosides from glucose and methyl galactofuranosides from galactose.[16] Later on, Plusquellec and coworkers have shown that the direct O-glycosylation of reducing sugars in the presence of 3 equiv of $FeCl_3$ afforded furanosides in good to excellent yields in THF.[17] In contrast, α-pyranosides were produced from *N*-acetylglucosamine in THF[17] and from peracetylated glycosamines in dichloromethane.[18] In both cases $FeCl_3$ was used in substoichiometric amounts. We found that a catalytic amount of $FeCl_3$ is sufficient to promote the glucosylation of octanol in butylmethylimidazolium triflate ([BMIM][OTf]). The glycosylation reaction is faster under $FeCl_3$ than under $Sc(OTf)_3$ catalysis, but yields and selectivities are similar (Table 1). Curiously, the glycosylation of octanol with *N*-acetylglucosamine requires 1 equiv of $FeCl_3$, affording pure α derivative. Note that such total α selectivity was previously observed in $FeCl_3$-promoted glycosidation of *N*-acetylglucosamine[17] and glycosamine peracetates.[18]

In order to prepare glycoconjugates (Scheme 2) we planned to investigate glycosylation of alcohols bearing halogen and nitrogen functionality as a linker. Halogenoalcohols could be easily glycosylated in butylmethylimidazolium triflate under $Sc(OTf)_3$ catalysis (Table 2). The yield is quantitative when using 3-chloropropanol.[12] Curiously 2-chloro and 2-bromoethanol gave only moderate yields, even if the reaction time is extended to 24 h. Poor yields were observed when preparing **1** and **2** with 2-chloroethanol[19] and 2-bromoethanol,[20] respectively, using the same alcohol as the solvent. With 2-azidoethanol or *N*-acylethanolamine, we did not succeed in obtaining the corresponding glycosides. The replacement of the amide by a carbamate function, allowed us to prepare free sugars carrying a linker prone to be coupled with any derivative bearing carboxylic acid function (Table 2).

Finally, serine protected by ester and carbamate groups, except *t*-butyloxycarbamate, could be glycosylated, affording a mixture of α- and β serine derivatives (Table 3).

By enzymatic hydrolysis, α and β derivatives could be obtained as pure anomers. As an example (Scheme 3) the mixture of α and β-glucosylserines (**6**) was purified by enzymatic hydrolysis using α or β-glucosidase from *Saccharomyces cerevisiae* in a phosphate buffer (pH 7.1) to afford quantitatively either β or α glucosylserine.

Table 2
Glucosylation of functionalized alcohols as linkers in [BMIM][OTf]

Aglycone	Conditions	Product (isolated yield, %)	α/β
HO–(CH2)2–Cl	$Sc(OTf)_3$, 5%, 80 °C, 3 h	**1** (52)	55/45
HO–(CH2)2–Br	$Sc(OTf)_3$, 5%, 80 °C, 3 h	**2** (41)	55/45
HO–(CH2)3–Cl	$Sc(OTf)_3$, 5%, 80 °C, 24 h	**3** (100)	71/29
HO–(CH2)2–NHCO2Et	$Sc(OTf)_3$, 5%, 80 °C, 24 h	**4** (41)	54/46
HO–(CH2)2–NHFmoc	$Sc(OTf)_3$, 5%, 80 °C, 24 h	**5** (53)	54/46

Table 3
Glucosylation of serine derivatives in [BMIM][OTf]

Aglycone	Conditions	Product (isolated yields, %)	α/β
HO–CH(NHCbz)–CO2Me	$Sc(OTf)_3$, 5%, 80 °C, 24 h $FeCl_3$ 5%, 80 °C, 5 h	**6** (62) **6** (62)	54/46 50/50
HO–CH(NHFmoc)–CO2Allyl	$Sc(OTf)_3$, 5%, 80 °C, 20 h	**7** (71)	55/45