Efficient Synthesis of *O*-, *S*-, *N*- and *C*-Glycosides of 2-Amino-2-Deoxy-D-Glucopyranose from Glycosyl Iodides

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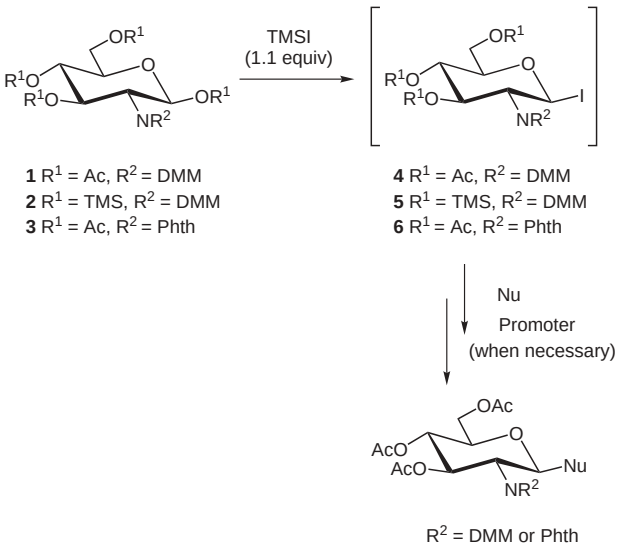
Dedicated to Prof. R. R. Schmidt.

Abstract: Glycosyl iodides of protected D-glucosamine are generated in situ under mild conditions and coupled with different kinds of nucleophiles, providing the corresponding β-glycosides in good yields.

Key words: carbohydrates, glycosyl iodides, glycosylations, stereoselective synthesis

Glycosides of 2-amino-2-deoxy sugars are present in the most important classes of glycoconjugates and naturally occurring oligosaccharides.[1] In particular, glycosides of *N*-acetylglucosamine are widely distributed in living organisms as building blocks of peptidoglycans and mucopolysaccharides. They are also encountered as components of human milk, blood group substances and bacterial lipopolysaccharide antigens, where they constitute part of the epitopes. Due to their great biological relevance, new and reliable methods to synthesize glycosides of 2-amino sugars are of outstanding importance.[2] Herein, we report an efficient method for the synthesis of *O*-, *S*-, *N*-, and *C*-glycosides of 2-amino-2-deoxy sugars from the corresponding in situ generated glycosyl iodides. Although the use of glycosyl halides in the formation of glycosidic bonds is largely documented in the literature,[3] glycosyl iodides have not been widely utilized as glycosyl donors,[4] mainly because they are too reactive and often difficult to handle and isolate.[5] Nevertheless, various methods to obtain glycosyl iodides have been introduced, some employing forcing conditions of rather limited applicability.[6] More reliable protocols include the generation of anomeric iodides under mild conditions from glycosyl phosphates,[7] phosphites[8] and hemiacetals.[9] Among them, the preparation of glycosyl iodides with iodotrimethylsilane (TMSI) from fully protected sugars, reported in 1980 by Thiem and Meyer, offers various practical advantages.[10] The use of TMSI for the generation of glycosyl iodides has been extended to different substrates, such as persilylated[11] and 1-*O*-acetylated benzylated sugars.[12] In particular Gervay et al. have extensively employed glycosyl iodides in the synthesis of *N*-, *C*- and *O*-glycosides and oligosaccharides.[13] The examples mentioned above evidenced the crucial role played by the protective groups of the monosaccharide precursor in determining the chemical stability of the corresponding iodide.[14] Only few examples of glycosyl iodides from 2-amino-2-deoxy sugars have previously been reported.[9b,15] In 1976 Lemieux[16] employed glycosyl deoxyphthalimido halides (including iodide) as glycosyl donors in the synthesis of three *O*-disaccharides. However, the glycosylating properties of the iodide were not further explored. The direct synthesis of glycosyl iodides from protected *N*-acetylglucosamine resulted unfeasible in our hands; we therefore employed the dimethylmaleolyl (DMM) as *N*-protecting group of acetylated or trimethylsilylated glucosamine derivatives. The treatment of compound **1**[17] with TMSI (1.1 equiv) in CH_2Cl_2 at room temperature resulted in the complete formation of the corresponding β-glycosyl iodide **4** in 30 minutes, as deduced by TLC analysis (Scheme 1). Since compound **4** was not isolable, we carried out the reaction in a NMR tube in $CDCl_3$ at 25 °C. After 30 minutes, the spectrum showed the complete formation of a new product with the anomeric proton as a doublet at δ = 6.56 ($J_{1,2}$ = 10.1 Hz), thus confirming the β-configuration.[18]



Scheme 1 Synthesis of glycosides and disaccharides via in situ formed glycosyl iodides

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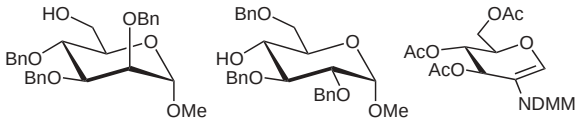
Tetra-*O*-trimethylsilylated glucosamine **2**, prepared as described by Uchiyama and Hindsgaul,[11a] reacted with TMSI under the same conditions and provided even more rapidly (20 min) the very unstable glycosyl iodide **5**. In order to assess the influence of the glucosamine N-protection on the glycosyl iodide formation, we also studied the reaction with TMSI of the *N*-phthalimido protected derivative **3**.[19] Compound **3** reacted sluggishly when treated with TMSI at room temperature, both in CH_2Cl_2 and in toluene. However, the complete formation of the β-glycosyl iodide **6** took place in 45 minutes in toluene at 80 °C (Scheme 1). The same reaction was carried out into a NMR tube (C_6D_6, 75 °C); after 1 hour, a new single product was observed in the spectrum, exhibiting an anomeric signal at δ = 6.90 ($J_{1,2}$ = 10.0 Hz), which confirmed the β-configuration.[20] Subsequently, we explored the glycosylating properties of the in situ generated glycosyl iodides **4**–**6**.[21] First, the glycosylation of simple alkyl alcohols was examined. As shown in Table 1 (entries 1–4, 10–15), donors **4**–**6** afforded the corresponding glycosides in good to excellent yields. It should be emphasized that no promoter was added to the reaction mixtures and exclusively β-glycosides were obtained, thus implying an effective anchimeric assistance from the *N*-protecting groups. Moreover, the efficiency of the glycosylation was mostly unaffected by the nature of the *O*-protecting groups (compare entries 1–4 with 10–13). As expected, the more challenging couplings with less reactive glycosyl acceptors **7** and **8** (Figure 1) required the addition of silver trifluoromethanesulfonate (AgOTf) as a promoter.

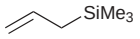


7 **8** **9**

Figure 1 Glycosyl acceptors **7**, **8** and glycal **9**

The primary acceptor **7** gave the corresponding β-disaccharide in good yield (entry 5), whereas the sterically hindered, unreactive O-4 unprotected glycoside **8** provided the β-disaccharide in 51% unoptimized yield (entry 6). In order to explore in more detail the versatility of these new intermediates, the reactivity of **4** with nucleophiles other than alcohols was also investigated (Table 1). When thiophenol was allowed to react with **4** in the absence of acidic promoter, the corresponding β-phenyl thioglycoside was obtained in 94% yield (entry 7). Allyl trimethylsilane, selected as a representative C-nucleophile, reacted smoothly with intermediate **4** in the presence of $BF_3{\cdot}OEt_2$ as a promoter to afford the β-*C*-allyl glycoside in 80% yield (entry 8). This result is particularly remarkable, as it could open a new and easy access to the challenging synthesis of *C*-glycosides of 2-amino-2-deoxy sugars, a class of carbohydrate analogues of great pharmaceutical interest.[22] Finally, the possibility of generating *N*-glycosidic linkages by reaction with suitable *N*-nucleophiles was studied. Preliminary explorations with primary and secondary amines in the absence of promoter invariably led to 1,2-elimination and the corresponding glycal **9** (Figure 1) was obtained in almost quantitative yields.

Table 1 Coupling Reactions with Various Nucleophiles of β-Glycosyl Iodides Generated in situ from *N*-Protected Glucosamine Precursors **1**–**3**

Entry	Donor	Nucleophile (equiv)	Promoter (equiv)	Yield (%)[a]
1	**4**	MeOH (10)	–	94
2	**4**	AllOH (10)	–	92
3	**4**	*i*-PrOH (10)	–	81
4	**4**	BnOH (10)	–	74
5	**4**	**7** (1.1)	AgOTf (1)	81
6[b,c]	**4**	**8** (1.1)	AgOTf (1)	51
7	**4**	PhSH (10)	–	94
8	**4**	 (1.2)	$BF_3{\cdot}OEt_2$ (1)	80
9[c]	**4**	$TMSN_3$ (2)	$BF_3{\cdot}OEt_2$ (1)	80
10	**5**	MeOH (10)	–	88
11	**5**	AllOH (10)	–	90
12	**5**	*i*-PrOH (10)	–	79
13	**5**	BnOH (10)	–	74
14	**6**	AllOH (10)	–	78
15	**6**	*i*-PrOH (10)	–	74

[a] Isolated total yields based on the donor precursors **1**–**3**.
[b] Reaction started at 0 °C and performed in the presence of 2,6-di-*t*-Bu-4-Me pyridine (1 equiv) as an acid scavenger.
[c] After iodide formation, the solvent was removed in vacuo and the residue coevaporated twice with dry toluene to remove TMSOAc, which can compete as a nucleophile in the following coupling reaction.

Eventually, we found that the treatment of **4** with trimethylsilyl azide in the presence of $BF_3{\cdot}OEt_2$ afforded the β-glycosyl azide in 80% yield (entry 9). Glycosyl azides are important intermediates in the synthesis of *N*-glycoconjugates, which largely occur in many biologically relevant natural products. In conclusion, we have shown that β-glycosyl iodides of suitably protected D-glucosamine derivatives can be generated in situ under mild conditions and stereoselectively coupled with various nucleophiles, giving access to *O*-, *S*-, *C*- and *N*-glycosides of 2-amino-2-deoxy sugars. Due to the high biological relevance of carbohydrate structures containing 2-amino sugars, the promising versatility exhibited by these intermediates is worth to be further explored and extended to new substrates. These studies are currently in progress in our laboratory.

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(18) ^{1}H NMR (Bruker Avance 400, 400 MHz, $CDCl_3$) for compound **4**: δ = 6.56 (d, 1 H, *J* = 10.1 Hz, H-1), 5.55 (t, 1 H, *J* = 9.7 Hz, H-3), 5.21 (t, 1 H, *J* = 9.7 Hz, H-4), 4.44 (t, 1 H, H-2), 4.28 (dd, 1 H, *J* = 12.5 Hz, *J* = 4.7 Hz, H-6), 4.15 (dd, 1 H, *J* = 2.3 Hz, H-6′), 3.85 (ddd, 1 H, H-5), 2.14 (s, 3 H, Ac), 2.08 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 1.99 (s, 3 H, DMM), 1.91 (s, 3 H, DMM).
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(20) ^{1}H NMR (Bruker Avance 400, 400 MHz, C_6D_6, 75 °C) for compound **6**: δ = 7.65–7.01 (m, 4 H, Ar), 6.90 (d, 1 H, *J* = 10.0 Hz, H-1), 6.02 (t, 1 H, *J* = 9.7 Hz, H-3), 5.38 (t, 1 H, *J* = 9.7 Hz, H-4), 4.98 (t, 1 H, H-2), 4.27 (dd, 1 H, *J* = 12.4 Hz, *J* = 4.7 Hz, H-6), 4.08 (dd, 1 H, *J* = 2.0 Hz, H-6′), 3.49 (m, 1 H, H-5), 1.88 (s, 3 H, Ac), 1.83 (s, 3 H, Ac), 1.72 (s, 3 H, Ac).
(21) To a solution of compound **1** and **2** (0.66 mmol, 1 equiv) in CH_2Cl_2 (3 mL) at 0 °C TMSI (1.1 equiv) was added under inert atmosphere. The reaction mixture was stirred at r.t. until disappearance of the starting material (about 30 min), then cooled to –78 °C. On the other hand, compound **3** (0.63 mmol, 1 equiv) was dissolved in toluene (3 mL) and TMSI (1.1 equiv) was added at 0 °C under inert atmosphere. The solution was stirred at 80 °C for 45 min, then the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (3 mL) under inert atmosphere and the solution cooled at –78 °C. The nucleophile and the acidic promoter (when necessary, see text) were added, the solution was allowed to reach r.t. and stirred for 6–8 h. Standard workup and silica gel chromatography gave the β-glycoside. When silylated compound **2** was employed as starting material (entries 10–13 in Table 1), MeOH was added after glycosylation to remove the trimethylsilyl groups. After stirring 20 min, the solvent was evaporated in vacuo and the crude residue was submitted to standard acetylation.
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