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Published in:
European Journal of Organic Chemistry

Link to article, DOI:
10.1002/ejoc.201600545

Publication date:
2016

Document Version
Peer reviewed version

Glycosylation with Disarmed Glycosyl Bromides Promoted by Iodonium Ions

Gyrithe Lanz and Robert Madsen*[a]

Abstract: Iodonium ions have been developed for activating glycosyl bromides in the coupling to glycosyl acceptors. The iodonium ions are generated from *N*-iodosuccinimide and a protic acid such as camphorsulfonic acid or triflic acid, where the latter gives the most reactive promoter system. The couplings occur with the release of iodine monobromide and the best results are obtained with benzoylated glycosyl donors and acceptors. In this way, disarmed glycosyl bromides can serve as glycosyl donors without the use of heavy metal salts.

Introduction

The most common glycosyl donors in the synthesis of oligosaccharides are glycosyl bromides, glycosyl trichloroacetimidates and thioglycosides.[1] Glycosyl bromides (and chlorides) are usually activated by silver salts which was first described by Koenigs and Knorr in 1901.[2] Although, the Koenigs-Knorr procedure has been the classical glycosylation method for more than a century, its use has been slowly declining due to the high costs of the promoters. The activation of glycosyl bromides has also been investigated with other metal salts such as $CdCO_3$[3] and the Helferich modification with various mercury salts.[4] However, these toxic compounds do not present an attractive alternative to the silver salts. Furthermore, $CoCO_3$, $InCl_3$, $Sn(OTf)_2$ and several zinc salts have been studied as promoters, but have shown limited reactivity and scope.[5] In 1975 Lemieux presented the halide ion-catalyzed glycosylation where perbenzylated glycosyl bromides are activated by in situ anomerization with tetrabutylammonium bromide.[6] This has been a useful protocol for synthesis of α-glucosides and -galactosides, but is limited to highly reactive donors and acceptors. As a result, there is still a need for inexpensive and benign promoters for the activation of glycosyl bromides to replace the use of the heavy metal salts.

We speculated whether a halonium ion would serve this purpose since NIS in the presence of an acid catalyst is a very powerful promoter for activation of thioglycosides and pent-4-enyl glycosides.[7] The idea was further fueled by earlier investigations by Field where I_2[8] and IBr[9] were employed for activation of peracetylated glycosyl bromides. I_2 could be used for coupling to primary alcohols where a β(1→6)-linked disaccharide was prepared in 73% yield after 16 h.[9] IBr also promoted the coupling to secondary alcohols to form β(1→2), β(1→3) and β(1→4) disaccharides in 35 – 73% yield although the reaction time was not reported.[9] The method was subsequently applied to methyl (1-bromo-1-deoxy-2,3,4-tri-*O*-pivaloyl-α-D-glucopyranosyl)uronate which underwent coupling to simple alcohols in the presence of IBr or NIS although long reaction times of 18 – 72 h were required.[10] Furthermore, NBS and a catalytic amount of ZnI_2 was used for promoting the coupling between 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**1**) and simple primary alcohols where the reactive reagent may be in situ formed NIS or IBr.[5a] However, the reactivity of these halogen-based promoters is insufficient for more widespread applications.

As a result, we herein describe the development of NIS and an acid catalyst for the activation of glycosyl bromides which allows for a more rapid coupling to sluggish monosaccharide acceptors.

Results and Discussion

The disarmed[7] glycosyl bromide **1** and different halogen electrophiles were selected for the initial experiments. First, cyclohexanol (**2**) was employed as the acceptor and the coupling to **1** was completed in 48 h with I_2 as the promoter to afford glycoside **3** in 73% yield (Table 1, entry 1). The same reaction with NIS went to completion in only 3 h to give the product in 95% yield (entry 2). No reaction occurred with NBS as the promoter while the glycosylation with IBr took about 24 h for complete conversion (results not shown). Surprisingly, the α-glycoside was formed in all cases and it was shown by NMR that the β-glycoside was generated simultaneously, but anomerization occurred during the course of the reaction. Field observed a similar formation of an α-anomer in a coupling between a peracetylated glycosyl bromide and a simple alcohol promoted by I_2.[11] The anomerization was attributed to the release of HI during the reaction, but with NIS as the promoter no protic acid is expected to be liberated. As a result, there must be a different explanation for the formation of the α-anomer in this case (*vide infra*).

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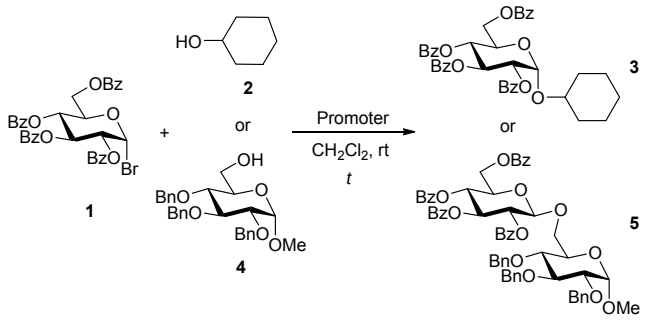
Table 1. Optimization of the iodonium-mediated glycosylation.



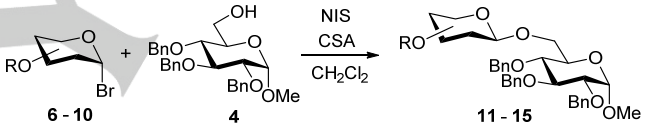
Entry	Acceptor	Promoter	*t* [h]	Product	Yield [%][a]
1	**2**	I_2[b]	48	**3**	73
2	**2**	NIS[c]	3	**3**	95
3	**4**	I_2[b]	48	**5**	10
4	**4**	NIS[b]	24	**5**	36
5	**4**	NIS[b]+TfOH[d]	1.5	**5**	88
6	**4**	NIS[b]+TfOH[e]	1	**5**	75
7	**4**	NIS[b]+TfOH[f]	3	**5**	80
8	**4**	NIS[c]+TfOH[g]	1	**5**	53
9	**4**	TfOH[h]	24	-	0
10	**4**	NIS[b]+PTSA[h]	5	**5**	59
11	**4**	NIS[b]+CSA[h]	2	**5**	87
12[i]	**2**	NIS[c]+CSA[h]	72	-	0

[a] Isolated yield. [b] 2.0 equiv. [c] 1.5 equiv. [d] 0.3 equiv. [e] 1.0 equiv. [f] 0.1 equiv. [g] 0.15 equiv. [h] 0.2 equiv. [i] With 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl chloride as the donor.

When the same reactions were performed with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**4**) as the acceptor, the coupling only formed the β-glycoside **5** as the product in 10 – 36% yield after 24 – 48 h (Table 1, entry 3 and 4). These yields are lower and the reaction times higher than reported by Field for similar couplings with peracetylated glycosyl bromides[8,9] which is probably due to the lower reactivity of the perbenzoylated counterpart **1**. However, when the glycosylation with NIS was carried out in the presence of an acid catalyst, the yields increased significantly and a much faster conversion was observed. With 0.3 equiv. of triflic acid (TfOH) the coupling went to completion in 1.5 h to afford glycoside **4** in 88% yield (entry 5). NIS is almost insoluble in dichloromethane, but reacts within a few minutes upon addition of TfOH. Increasing or decreasing the amount of TfOH gave slightly lower yields while a moderate yield was obtained with a lower amount of NIS (entries 6 – 8). No coupling occurred in the absence of NIS (entry 9) which underlines the importance of the iodonium ion for activation of the donor. Replacing TfOH with the weaker acid *p*-toluenesulfonic acid (PTSA) also afforded a moderate yield (entry 10) which was mainly due to concomitant hydrolysis of donor **1** since PTSA is a monohydrate and difficult to obtain in anhydrous form. However, it is noteworthy that a weaker sulfonic acid can catalyze the activation of NIS since this is usually performed with derivatives of TfOH. In fact, when camphorsulfonic acid (CSA) was employed, the glycosylation afforded glycoside **5** in 87% yield (entry 11) which is essentially the same as obtained with TfOH. No reaction occurred with the corresponding glycosyl chloride as the donor (entry 12) which illustrates the lower reactivity of this halide analogue. Accordingly, the optimization studies have shown that NIS in combination with triflic acid or camphorsulfonic acid can be utilized as a promoter for activation of glycosyl bromide **1** in dichloromethane at room temperature.

The substrate scope of this new method was then explored with different glycosyl donors and acceptors. First, a variety of glycosyl bromides were investigated with NIS/CSA as the promoter and **4** as the acceptor (Table 2). Good yields were also obtained with perbenzoylated mannosyl, galactosyl and 2-phthalimido-glucosyl bromides (entries 1 – 3) while the more reactive peracetylated and perbenzylated glucosyl bromides gave moderate yields (entry 4 and 5). In the latter two cases, several byproducts were also detected in small amounts, but none of these could be isolated in pure form and identified.

Table 2. Various donors in the iodonium-mediated glycosylation.[a]



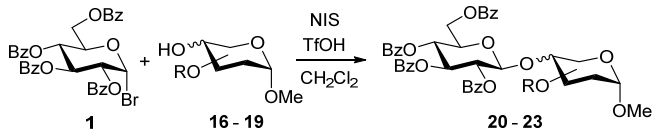
Entry	Donor	Product	Yield [%][b]
1	2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (**6**)	**11**[c]	76
2	2,3,4,6-Tetra-*O*-benzoyl-α-D-galactopyranosyl bromide (**7**)	**12**	73
3[d]	3,4,6-Tri-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide (**8**)	**13**	77
4[e]	2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**9**)	**14**	56
5	2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**10**)	**15**[f]	61

[a] Conditions: NIS (2.0 equiv.), CSA (0.2 equiv.), CH_2Cl_2, rt, 2 h. [b] Isolated yield. [c] With an α(1→6) linkage. [d] Reaction time 1 h. [e] 0.1 equiv. of CSA. [f] 1:3 α/β mixture.

Then, a number of acceptors were explored in the coupling to glucosyl bromide **1**. Several 2,3,6-protected methyl glycosides were selected since the hydroxy group at position 4 is usually the least reactive alcohol in monosaccharides. The glycosylation between **1** and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**16**) afforded the protected cellobioside **20** in 40% yield after 3 h (Table 3, entry 1). Extending the reaction time gave even lower yields (entry 2 and 3) and a byproduct was observed where the

benzyl ether at position 3 in **20** had been removed. This selective cleavage of the most hindered benzyl ether in disaccharides has been observed previously with the reagent I_2/Et_3SiH.[12] It indicates that the promoter system NIS/CSA is not fully compatible with less reactive benzyl-protected acceptors.

Table 3. Various acceptors in the iodonium-mediated glycosylation.[a]



Entry	Acceptor	*t* [h]	Product	Yield [%][b]
1[c]	Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**16**)	3	**20**	40
2[c]		6		33
3[c]		24		27
4[d]	Methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (**17**)	24	**21**	81
5	Methyl 2,3,6-tri-*O*-benzoyl-α-D-mannopyranoside (**18**)	2	**22**	80
6	Methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside (**19**)	6	**23**[e]	80

[a] Conditions: NIS (2.0 equiv.), TfOH (0.2 equiv.), CH_2Cl_2, rt. [b] Isolated yield. [c] With NIS (2.0 equiv.) and CSA (0.2 equiv.) as the promoter. [d] With 0.3 equiv. of TfOH. [e] 1:2 α/β mixture.

Accordingly, the studies continued with benzoyl-protected glycosides as acceptors. Methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (**17**) is a very unreactive acceptor due to the axial hydroxy group and the electron-withdrawing ester moieties.[13] No glycosylation occurred between **1** and **17** within 48 h when using NIS and CSA as the promoter. However, with NIS and TfOH the coupling went to completion to furnish the β(1→4)-linked disaccharide **21** in 81% yield (Table 3, entry 4). Attempts to lower the amount of NIS and TfOH led to a decrease in the yield of **21** (results not shown). The glycosylation between **1** and methyl 2,3,6-tri-*O*-benzoyl-α-D-mannopyranoside (**18**) occurred more readily and afforded disaccharide **22** in 80% yield after 2 h (entry 5). The same yield was obtained in the coupling to glucose acceptor **19** although in this case the product **23** was isolated as an 1:2 α/β mixture (entry 6). Attempts to perform the reaction between **1** and **19** with NIS and CSA only led to a lower yield of the disaccharide after 2 d which further underlines the importance of TfOH for coupling to benzoyl-protected acceptors.

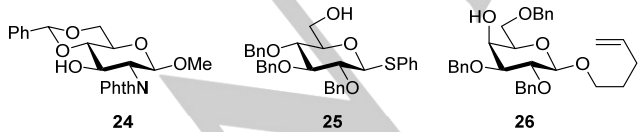
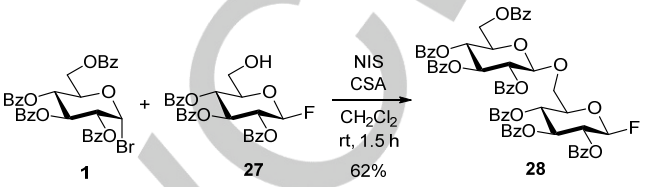


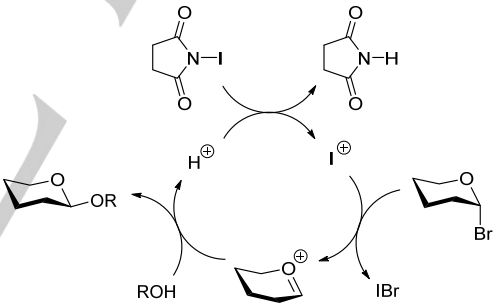
Figure 1. Unsuccessful acceptors in the glycosylation.

Several acceptors with additional functional groups were also investigated in the coupling with bromide **1** under the conditions in Table 2. Benzylidene- and phthalimido-protected glucosamine **24** is known to react very sluggishly at the 3 position (Figure 1) and indeed no conversion of **24** was observed in the reaction with bromide **1**, NIS and CSA. Thioglycoside **25** underwent reaction at sulfur and was converted into 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose in the presence of **1**, NIS and CSA. Pent-4-enyl glycoside **26** decomposed under the reaction conditions, which is presumably due to a higher reactivity of the pent-4-enyl moiety as compared to the bromide in **1**. Glycosyl fluoride **27**, however, was not affected by the promoter system and a coupling with **1** could be achieved to furnish β(1→6)-linked disaccharide **28** in 62% yield (Scheme 1).



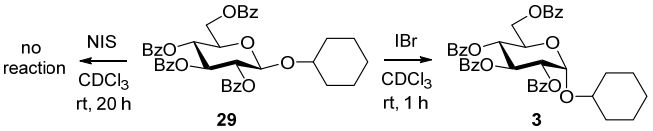
Scheme 1. Glycosylation with glycosyl fluoride acceptor.

The mechanism of the glycosylation is expected to involve the formation of the iodonium ion which activates the glycosyl bromide and expels IBr (Scheme 2). The formation of the latter was confirmed by adding styrene to the reaction in Table 1, entry 2 after 5 h. A ^{13}C NMR spectrum of the crude reaction mixture showed the presence of 1-bromo-2-iodo-1-phenylethane which was also generated in a separate experiment by adding IBr to styrene.



Scheme 2. Mechanism of the glycosylation reaction.

All the glycosylations with donor **1** gave the expected β-glycoside except for cyclohexyl glucoside **3** and disaccharide **23**. In the first case, the β-glycoside was also formed but isomerizes into the more stable α-anomer during the reaction. To further probe the anomerization cyclohexyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (**29**) was prepared from bromide **1**, cyclohexanol and Ag_2O. No reaction occurred when **29** was exposed to 2 equiv. of NIS for 20 h, while complete anomerization into **3** was observed upon reaction with IBr for 1 h (Scheme 3).



Scheme 3. Anomerization of **29** monitored by ^{13}C NMR.

As a result, the anomerization in Table 1, entry 2 is most likely caused by the Lewis acidity of the liberated IBr. I_2 and the corresponding interhalogens are known to catalyze protecting group transformations and serve as an alternative to protic acids.[14] In addition, ICl was shown recently to mediate the anomerization (and cleavage) of nucleosides.[15] It has also been debated whether the actual catalyst is HI or HBr generated in trace amounts from a reaction with the alcohol (or water).[15,16] However, in this context it should be noted that I_2 in refluxing methanol does not lead to anomerization of methyl β-glycosides[17] and we therefore believe the Lewis acidity of IBr is responsible for the anomerization of simple glycosides. Separate NMR experiments revealed that 0.1 equiv. of HBr was not sufficient for anomerization of **29** at room temperature, but with 3 equiv. of HBr complete isomerization of **29** into **3** was observed in 30 min.

NIS is commercially available and was used without further purification in this study. However, the classical procedure for preparation of NIS employs the silver salt of succinimide which is treated with I_2 in dioxane.[18] Since the entire purpose of this study is to avoid heavy metal salts, it was decided to investigate a cheaper source of NIS. In fact, NIS can also be prepared by mixing equimolar amounts of *N*-chlorosuccinimide and NaI in acetone followed by filtration to remove NaCl and concentration of the filtrate.[19] This affords a crude NIS and when used directly in the coupling between bromide **1** and acceptor **4** as described in Table 1, entry 11, the product **5** was obtained in a 62% unoptimized yield. Although, the yield is lower than achieved with the commercial NIS sample in Table 1, the experiment illustrates that an inexpensive source of the promoter can be employed. It was also attempted to generate NIS in situ by using *N*-chlorosuccinimide and NaI directly in the glycosylation. However, when replacing NIS with these two components, the coupling between **1** and **4** only afforded a 49% yield of **5**. Most likely, the decrease in yield is due to the change in solvent since NIS is formed less efficiently from *N*-chlorosuccinimide and NaI in dichloromethane than in acetone.

Conclusions

In summary, NIS and a catalytic amount of a protic acid has been developed as a promoter for activating glycosyl bromides. The most powerful system consists of NIS and TfOH which allows for coupling to rather unreactive monosaccharides while the combination of NIS and CSA requires a more reactive acceptor. The glycosylations proceed with the release of IBr which may cause anomerization of simple alkyl β-glycosides into the more stable α-anomers. The NIS/TfOH system constitutes the most potent promoter for activating glycosyl bromides which does not involve a heavy metal salt.

Experimental Section

General methods: Reactions were conducted under an argon or nitrogen atmosphere. CH_2Cl_2 was obtained from a PureSolv™ solvent purification system. Cyclohexanol was redistilled prior to use while camphorsulfonic acid was recrystallized from EtOAc and *N*-chlorosuccinimide from glacial acetic acid. TLC was performed on aluminum plates coated with silica gel 60. The plates were developed by UV or by dipping in a solution of cerium(IV)sulfate (2.50 g) and ammonium molybdate (6.25 g) in 10% sulfuric acid (250 mL) followed by heating. Purification was carried out with HPLC grade solvents by flash chromatography on silica gel (Merck 40 – 60 micron) or by dry column vacuum chromatography (DCVC)[20] on silica gel (Merck 15 – 40 micron). NMR spectra were recorded on a Bruker Ascend 400 spectrometer. Chemical shifts were measured relative to the signals of residual $CHCl_3$ (δ_H = 7.26 ppm) or $CDCl_3$ (δ_C = 77.0 ppm). New compounds were further assigned by COSY, HSQC and HMBC experiments. HRMS was performed on a Bruker SolariX XR ESI/MALDI-FT-ICR-MS instrument equipped with a 7 T magnet. The instrument was run in the MALDI mode and externally calibrated with sodium trifluoroacetate cluster ions.

General glycosylation procedure: The donor (1.5 equiv.) and the acceptor (1.0 equiv.) were dissolved in dry CH_2Cl_2 (2 mL) at room temperature under an inert atmosphere followed by addition of NIS (2.0 equiv.) and a catalytic amount of the acid (0.1 - 0.3 equiv.). The reaction was stirred until complete consumption of the starting material was observed by TLC. The mixture was evaporated onto silica or diluted with CH_2Cl_2, washed with saturated aqueous sodium thiosulfate and water, dried and the solvent removed in vacuo. Finally, the product was purified by DCVC or flash column chromatography.

Cyclohexyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (3): Cyclohexanol (1.00 mmol) and 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (0.50 mmol) were dissolved in dry CH_2Cl_2 (2 mL) at room temperature under an inert atmosphere followed by addition of the promoter (0.75-1.00 mmol). After 3 – 48 hours full conversion to cyclohexyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside was observed. The solvent was evaporated and the residue purified by flash column chromatography (6:1 toluene/acetone). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.05 (m, 2H), 8.03–7.94 (m, 4H), 7.91–7.87 (m, 2H), 7.55–7.25 (m, 12H), 6.22 (t, *J* = 9.9 Hz, 1H), 5.67 (t, *J* = 9.9 Hz, 1H), 5.52 (d, *J* = 3.8 Hz, 1H), 5.29 (dd, *J* = 10.2, 3.8 Hz, 1H), 4.63–4.57 (m, 2H), 4.52–4.42 (m, 1H), 3.69–3.56 (m, 1H), 2.04–1.91 (m, 1H), 1.78–1.39 (m, 5H), 1.38–1.07 ppm (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.3, 166.0 (2xC), 165.5, 133.5, 133.4, 133.2 (2xC), 130.0–128.4, 94.8, 77.7, 72.3, 70.8, 69.9, 68.0, 63.4, 33.6, 31.7, 25.6, 24.1, 23.8 ppm. NMR data are in accordance with literature values.[21]

Methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (5): General glycosylation procedure with CSA (0.2 equiv.) and a reaction time of 2 hours. Purification by flash column chromatography (19:1 toluene/acetone) resulted in 87% yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.98 (m, 2H), 7.94–7.88 (m, 4H), 7.88–7.81 (m, 2H), 7.56–7.01 (m, 27H), 5.91 (t, *J* = 9.6 Hz, 1H), 5.70 (t, *J* = 9.7 Hz, 1H), 5.62 (dd, *J* = 9.7, 7.8 Hz, 1H), 4.91 (d, *J* = 10.9 Hz, 1H), 4.84 (d, *J* = 7.8 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 1H), 4.69 (d, *J* = 11.5 Hz, 1H), 4.63 (dd, *J* = 12.0, 3.4 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.58–4.48 (m, 3H), 4.31 (d, *J* = 11.2 Hz, 1H), 4.17 (d, *J* = 9.1 Hz, 1H), 4.12 (ddd, *J* = 13.4, 5.9, 3.3 Hz, 1H), 3.90 (t, *J* = 9.3 Hz, 1H), 3.80–3.69 (m, 2H), 3.45 (dd, *J* = 9.7, 3.5 Hz, 1H), 3.40 (t, *J* = 9.3 Hz, 1H), 3.23 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.2, 165.9, 165.2, 165.0, 138.8, 138.3, 138.2, 133.5, 133.3, 133.2 (2xC), 129.9–127.5, 101.4, 98.0, 81.9, 79.8, 77.4, 75.6, 74.8, 73.4, 72.9, 72.2, 71.9, 69.8, 69.5, 68.4, 63.3, 55.1 ppm. NMR data are in accordance with literature values.[22]

Methyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (11): General glycosylation procedure with CSA (0.2 equiv.) and a reaction time of 2 hours. Purification by flash column chromatography (97:3 toluene/acetone) resulted in 76% yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.12–7.99 (m, 4H), 7.94–7.87 (m, 2H), 7.85–7.79 (m, 2H), 7.65–7.13 (m, 27H), 6.07 (t, *J* = 10.1 Hz, 1H), 5.88 (dd, *J* = 10.1, 3.3 Hz, 1H), 5.73 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.16 (d, *J* = 1.7 Hz, 1H), 5.02 (d, *J* = 11.1 Hz, 1H), 5.00 (d, *J* = 11.1 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.71–4.60 (m, 4H), 4.41 (ddd, *J* = 9.9, 4.3,

2.3 Hz, 1H), 4.34 (dd, *J* = 12.0, 4.4 Hz, 1H), 4.04 (t, *J* = 9.3 Hz, 1H), 3.94 (dd, *J* = 10.9, 5.1 Hz, 1H), 3.86 (dd, *J* = 10.1, 5.1 Hz, 1H), 3.81 (dd, *J* = 11.0, 1.5 Hz, 1H), 3.58 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.56–3.49 (m, 1H), 3.45 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.2, 165.5 (2xC), 165.4, 138.8, 138.3 (2xC), 133.5 (2xC), 133.3, 133.2, 130.0–127.7, 98.0, 97.9, 82.2, 80.3, 77.8, 75.8, 75.1, 73.6, 70.4, 70.1, 70.0, 69.0, 67.0, 66.8, 62.8, 55.3 ppm. NMR data are in accordance with literature values.[23]

Methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (12): General glycosylation procedure with CSA (0.2 equiv.) and a reaction time of 2 hours. Purification by flash column chromatography (97:3 toluene/acetone) resulted in 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.6 Hz, 2H), 8.03 (d, *J* = 7.6 Hz, 2H), 7.90 (d, *J* = 7.7 Hz, 2H), 7.78 (d, *J* = 7.7 Hz, 2H), 7.70–6.99 (m, 27H), 5.99 (bs, 1H), 5.86 (t, *J* = 9.1 Hz, 1H), 5.61 (d, *J* = 10.4 Hz, 1H), 4.91 (d, *J* = 10.9 Hz, 1H), 4.79–4.65 (m, 4H), 4.64–4.54 (m, 2H), 4.52 (d, *J* = 3.5 Hz, 1H), 4.46–4.34 (m, 2H), 4.30–4.17 (m, 2H), 3.92 (t, *J* = 9.2 Hz, 1H), 3.81–3.68 (m, 2H), 3.44–3.32 (m, 2H), 3.22 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.1, 165.7 (2xC), 165.2, 138.9, 138.3, 138.2, 133.7, 133.4 (2xC), 133.2, 130.1–127.6, 102.1, 98.0, 82.0, 79.9, 77.6, 75.6, 74.8, 73.4, 71.7, 71.5, 69.8, 69.7, 68.8, 68.2, 62.0, 55.1 ppm. NMR data are in accordance with literature values.[24]

Methyl 3,4,6-tri-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (13): General glycosylation procedure with CSA (0.1 equiv.) and a 1 hour reaction time. Purification by flash column chromatography (1:3:3 EtOAc/hexane/ toluene) resulted in 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.89 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.82–7.71 (m, 2H), 7.63–7.16 (m, 26H), 7.02 (dd, *J* = 6.6, 2.9 Hz, 2H), 6.28 (dd, *J* = 10.7, 9.3 Hz, 1H), 5.69 (t, *J* = 9.6 Hz, 1H), 5.64 (d, *J* = 8.5 Hz, 1H), 4.85 (d, *J* = 10.9 Hz, 1H), 4.73–4.52 (m, 6H), 4.43–4.38 (m, 2H), 4.30–4.21 (m, 1H), 4.15–4.11 (m, 2H), 3.84 (t, *J* = 9.3 Hz, 1H), 3.72 (dd, *J* = 10.3, 4.7 Hz, 1H), 3.68 (dd, *J* = 10.3, 3.8 Hz, 1H), 3.39 (dd, *J* = 9.7, 3.5 Hz, 1H), 3.26 (t, *J* = 9.4 Hz, 1H), 3.15 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.0 (2xC), 166.3, 165.8, 165.3, 138.8, 138.6, 137.9, 134.2 (2xC), 133.5, 133.4, 133.2, 130.0–123.6, 98.7, 98.0, 82.0, 79.8, 77.8, 75.8, 74.9, 73.5, 72.3, 71.2, 70.5, 69.3, 68.9, 63.5, 55.1, 54.9 ppm. NMR data are in accordance with literature values.[25]

Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (14): General glycosylation procedure with CSA (0.2 equiv.) and a reaction time of 2 hours. Purification by flash column chromatography (97:3 toluene/acetone) resulted in 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.23 (m, 15H), 5.17 (t, *J* = 9.4 Hz, 1H), 5.11–4.95 (m, 3H), 4.86 (d, *J* = 10.9 Hz, 1H), 4.82–4.76 (m, 2H), 4.65 (d, *J* = 12.1 Hz, 1H), 4.58–4.50 (m, 3H), 4.23 (dd, *J* = 12.3, 4.6 Hz, 1H), 4.11 (d, *J* = 12.2 Hz, 1H), 4.06 (d, *J* = 10.5 Hz, 1H), 3.97 (t, *J* = 9.2 Hz, 1H), 3.76 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.72–3.62 (m, 2H), 3.51 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.42 (t, *J* = 9.4 Hz, 1H), 3.36 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.95 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.7, 170.4, 169.4, 169.1, 138.7, 138.1 (2xC), 128.6–127.6, 100.7, 98.1, 82.0, 79.8, 77.7, 75.8, 75.0, 73.4, 73.0, 71.8, 71.3, 69.7, 68.4, 68.2, 62.0, 55.2, 20.7 (2xC), 20.6 (2xC) ppm. NMR data are in accordance with literature values.[26]

Methyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (15): General glycosylation procedure with CSA (0.1 equiv.) and a reaction time of 2 hours. Purification by flash column chromatography (1:4:4 EtOAc/hexane/toluene) resulted in an α/β mixture (1:3) in 61% yield. HSQC (400 MHz, $CDCl_3$) showed the α anomer at 4.98/97.35 ppm and 4.54/98.08 ppm while the β anomer was observed at 4.60/98.16 ppm and 4.35/103.93 ppm. For the mixture: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.09 (m, 46.66H), 4.99–4.95 (m, 2.66H), 4.91–4.89 (m, 1.33H), 4.84–4.48 (m, 16H), 4.45 (d, *J* = 11.0 Hz, 0.33H), 4.41 (d, *J* = 12.1 Hz, 0.33H), 4.34 (d, *J* = 7.8 Hz, 1H), 4.18 (dd, *J* = 10.8, 1.9 Hz, 1H), 3.99 (t, *J* = 9.3 Hz, 1H), 3.97 (d, *J* = 9.3 Hz, 0.33H), 3.85–3.38 (m, 13.33H), 3.34 (s, 1H), 3.32 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.0 (2xC), 138.9, 138.6 (2xC), 138.5 (3xC), 138.4, 138.3 (2xC), 138.2, 138.1, 128.6–127.6, 103.9, 98.1, 98.2, 97.4, 84.9, 82.3, 82.2, 82.1, 81.8, 80.3, 80.1, 79.9, 78.1, 78.0, 77.9, 77.7, 75.8 (3xC), 75.6, 75.1 (2xC), 75.0 (3xC), 73.6, 73.5 (3xC), 72.5, 70.5, 70.4, 70.0, 69.1, 68.7, 68.6, 66.2, 55.3 (2xC) ppm. NMR data are in accordance with literature values.[26]

Methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (20): General glycosylation procedure with CSA (0.2 equiv.) and a reaction time of 3 – 24 hours. Purification by flash column chromatography (4:4:1 toluene/hexane/EtOAc) resulted in 27 – 40% yield (corrected for small impurities which could not be removed). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.80 (m, 8H), 7.61–7.03 (m, 27H), 5.61 (d, *J* = 9.5 Hz, 1H), 5.55 (t, *J* = 9.6 Hz, 1H), 5.47 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.07 (d, *J* = 11.2 Hz, 1H), 4.85 – 4.71 (m, 4H), 4.70–4.37 (m, 3H), 4.34 (d, *J* = 12.1 Hz, 1H), 4.31–4.22 (m, 1H), 3.97 (t, *J* = 9.4 Hz, 1H), 3.88 (t, *J* = 9.2 Hz, 1H), 3.75–3.67 (m, 2H), 3.57–3.34 (m, 3H), 3.28 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.1, 165.8, 165.1, 164.8, 139.3, 138.4, 137.9, 133.4, 133.3, 133.2, 133.0, 129.9–127.2, 100.4, 98.5, 80.0, 78.8, 77.3, 75.4, 73.64, 73.6, 73.2, 72.3, 71.8, 69.9, 69.5, 67.6, 63.2, 55.4 ppm. NMR data are in accordance with literature values.[22]

Methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (21): General glycosylation procedure with TfOH (0.3 equiv.) and a reaction time of 24 hours. Purification by DCVC (0-70% EtOAc in hexane) resulted in a white solid in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05–7.92 (m, 8H), 7.88–7.77 (m, 6H), 7.61–7.24 (m, 19H), 7.13 (t, *J* = 7.8 Hz, 2H), 5.87–5.81 (m, 2H, 3-H, H-3'), 5.71–5.62 (m, 2H, H-2', H-4'), 5.26 (dd, *J* = 10.7, 3.6 Hz, 1H, H-2), 5.20 (d, *J* = 3.6 Hz, 1H, H-1), 5.09 (d, *J* = 7.8 Hz, 1H, H-1'), 4.73 (dd, *J* = 11.7, 4.7 Hz, 1H, H-6a), 4.58–4.52 (m, 2H, H-4, H-6b), 4.47 (dd, *J* = 12.2, 3.3 Hz, 1H, H-6a'), 4.42–4.34 (m, 2H, H-6b'), 3.96 (dt, *J* = 9.8, 3.9 Hz, 1H, H-5'), 3.34 ppm (s, 3H, OMe). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.1, 166.1, 166.0 (2xC), 165.5, 165.3, 165.2, 133.8, 133.5, 133.4, 133.2, 133.1 (2xC), 133.0, 130.1 – 128.2, 101.3 (C-1'), 97.3 (C-1), 74.9 (C-4), 72.8 (C-3'), 72.4 (C-5'), 72.2 (C-2'), 70.5 (C-3), 69.7 (C-2), 69.5 (C-4'), 67.9 (C-5), 64.2 (C-6), 62.6 (C-6'), 55.5 ppm (OMe). HRMS: *m/z* calcd for $C_{62}H_{52}O_{18}$: 1107.3046 $[M + Na]^+$; found: 1107.3069.

Methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-α-D-mannopyranoside (22): General glycosylation procedure with TfOH (0.2 equiv.) and a reaction time of 2 hours. Purification by flash column chromatography (1:4:4 EtOAc/hexane/toluene) resulted in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.71 (m, 14H), 7.61–7.17 (m, 21H), 5.87 (dd, *J* = 9.5, 3.5 Hz, 1H, H-3), 5.79 (t, *J* = 9.7 Hz, 1H, H-3'), 5.62 (dd, *J* = 3.4, 1.9 Hz, 1H, H-2), 5.56–5.51 (m, 2H, H-2', H-4'), 5.07 (d, *J* = 7.9 Hz, 1H, H-1'), 4.83 (d, *J* = 1.8 Hz, 1H, H-1), 4.69 (dd, *J* = 11.9, 1.7 Hz, 1H, H-6a), 4.56–4.47 (m, 2H, H-4, H-6b), 4.13–4.06 (m, 3H, H-5, H-6'), 3.78 (dt, *J* = 9.7, 3.7 Hz, 1H, H-5'), 3.41 ppm (s, 3H, OMe). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.9 (3xC), 165.4, 165.1, 165.0 (2xC), 133.5, 133.4 (3xC), 133.3, 133.1 (2xC), 130.0–128.3, 101.3 (C-1'), 98.6 (C-1), 74.5 (C-4), 72.9 (C-3'), 72.3 (C-5'), 72.2 (C-2'), 70.5 (C-2), 70.2 (C-3), 69.44 (C-4'), 69.39 (C-5), 62.8 (C-6'), 62.5 (C-6), 55.5 ppm (OMe). HRMS: *m/z* calcd for $C_{62}H_{52}O_{18}$: 1107.3046 $[M + Na]^+$; found: 1107.3079.

Methyl 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside (23): General glycosylation procedure with TfOH (0.2 equiv.) and a reaction time of 6 hours. Purification by DCVC (0 – 18% EtOAc in toluene/hexane) resulted in both anomers in the ratio 1:2 (α/β) in 80% yield. α-form: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.10 (m, 2H), 8.03–7.99 (m, 2H), 7.90–7.86 (m, 4H), 7.77–7.73 (m, 4H), 7.70–7.66 (m, 2H), 7.62–7.17 (m, 21H), 6.10 (t, *J* = 9.5 Hz, 2H, H-3, H-3'), 5.79 (d, *J* = 3.8 Hz, 1H, H-1'), 5.68 (t, *J* = 9.8 Hz, 1H, H-4'), 5.28 (dd, *J* = 10.5, 3.9 Hz, 1H, H-2'), 5.16 (d, *J* = 3.5 Hz, 1H, H-1), 5.09 (dd, *J* = 10.2, 3.5 Hz, 1H, H-2), 4.90 (dd, *J* = 12.1, 1.8 Hz, 1H, H-6a), 4.77 (dd, *J* = 12.1, 4.1 Hz, 1H, H-6b), 4.52–4.42 (m, 3H, H-4, H-5', H-6a'), 4.39–4.35 (m, 1H, H-5), 4.31 (dd, *J* = 12.2, 3.5 Hz, 1H, H-6b), 3.47 ppm (s, 3H, OMe). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.3, 166.1, 166.0, 165.8, 165.6, 165.2, 165.0, 133.6, 133.5, 133.4 (2xC), 133.2 (3xC), 130.2–128.2, 96.9 (C-1), 96.7 (C-1'), 73.7 (C-4), 72.6 (C-2), 72.5 (C-3), 71.0 (C-

2'), 70.0 (C-3'), 69.3 (C-4'), 69.2 (C-5'), 68.4 (C-5), 63.6 (C-6), 62.6 (C-6'), 55.7 ppm (OMe). HRMS: *m/z* calcd for $C_{62}H_{52}O_{18}$: 1107.3046 $[M + Na]^+$; found: 1107.3068. β-form: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–7.94 (m, 10H), 7.81–7.74 (m, 4H), 7.59–7.14 (m, 21H), 6.09 (t, *J* = 9.5 Hz, 1H, H-3), 5.77 (t, *J* = 9.6 Hz, 1H, H-3'), 5.55 (dd, *J* = 9.6, 8.0 Hz, 1H, H-2'), 5.43 (t, *J* = 9.5 Hz, 1H, H-4'), 5.18 (dd, *J* = 10.2, 3.6 Hz, 1H, H-2), 5.11 (d, *J* = 3.6 Hz, 1H, H-1), 5.00 (d, *J* = 7.9 Hz, 1H, H-1'), 4.61 (dd, *J* = 12.0, 1.1 Hz, 1H, H-6a), 4.51 (dd, *J* = 12.1, 4.3 Hz, 1H, H-6b), 4.21 (t, *J* = 9.5 Hz, 1H, H-4), 4.11 (m, 2H, H-5, H-6a'), 3.86 (m, 2H, H-5', H-6b'), 3.36 ppm (s, 3H, OMe). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.1, 166.0, 165.8 (2xC), 165.4, 165.1, 164.9, 133.4 (3xC), 133.32 (3xC), 133.2, 130.0–128.4, 101.1 (C-1'), 96.9 (C-1), 76.8 (C-4), 73.1 (C-3'), 72.5 (C-5'), 72.2 (C-2'), 72.1 (C-2), 70.3 (C-3), 69.5 (C-4'), 68.5 (C-5), 62.7 (C-6'), 62.5 (C-6), 55.6 ppm (OMe). HRMS: *m/z* calcd for $C_{62}H_{52}O_{18}$: 1107.3046 $[M + Na]^+$; found: 1107.3069.

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl fluoride (28): General glycosylation procedure with CSA (0.2 equiv.) and a reaction time of 1.5 hours. Purification by DCVC (0 – 6% acetone in toluene) resulted in 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05–7.81 (m, 14H), 7.53–7.26 (m, 21H), 5.91 (t, *J* = 9.7 Hz, 1H, H-3'), 5.74 (t, *J* = 8.5 Hz, 1H, H-3), 5.65 (t, *J* = 9.7 Hz, 1H, H-4'), 5.53 (dd, *J* = 9.5, 8.1 Hz, 1H, H-2'), 5.50–5.42 (m, 2H, H-2, H-4), 5.27 (dd, *J* = 51.5, 5.8 Hz, 1H, H-1), 5.02 (d, *J* = 7.9 Hz, 1H, H-1'), 4.61 (dd, *J* = 12.2, 3.0 Hz, 1H, H-6a'), 4.45 (dd, *J* = 12.2, 4.9 Hz, 1H, H-6b'), 4.18–4.11 (m, 3H, H-5, H-5', H-6a), 3.95 ppm (dd, *J* = 12.3, 8.2 Hz, 1H, H-6b). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.3, 165.9, 165.5, 165.4, 165.3 (2xC), 165.0, 133.8, 133.7 (2xC), 133.6 (2xC), 133.4, 133.3, 130.1–128.4, 106.6 (d, *J* = 220.2 Hz, C-1), 102.1 (C-1'), 74.5 (d, *J* = 3.6 Hz, C-5), 72.9 (C-3'), 72.5 (C-5'), 71.9 (C-2'), 71.6 (d, *J* = 23.4 Hz, C-2), 71.4 (d, *J* = 13.9 Hz, C-3), 69.7 (C-4'), 69.2 (C-6), 68.6 (C-4), 63.0 ppm (C-6'). NMR data are in accordance with literature values.[27]

Acknowledgements

Financial support from the Danish Council for Independent Research | Natural Sciences is gratefully acknowledged. We thank Ida S. A. Jensen and Christine T. Poulsen for investigating the reactivity of glycosyl chlorides.

Keywords: glycosides • glycosyl bromide • halogens • promoter • synthetic methods

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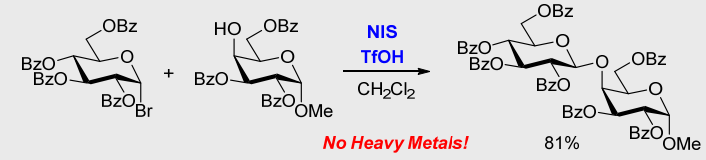

N-Iodosuccinimide and triflic acid has been developed as a promoter system for activating disarmed glycosyl bromides. Glycosylations with these donors can then be performed with a more benign promoter instead of the commonly employed silver and mercury salts.

Glycoside Synthesis

*Gyrithe Lanz, Robert Madsen**

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