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Direct glycosylation with anomeric hydroxy sugars by activation with 3-fluorophthalic anhydride and trifluoromethanesulfonic anhydride

Ju Yuel Baek, Bo-Young Lee, Rita Pal, Won-Yong Lee, Kwan Soo Kim *

Center for Bioactive Molecular Hybrids and the Department of Chemistry, Yonsei University, Seoul 120-749, Republic of Korea

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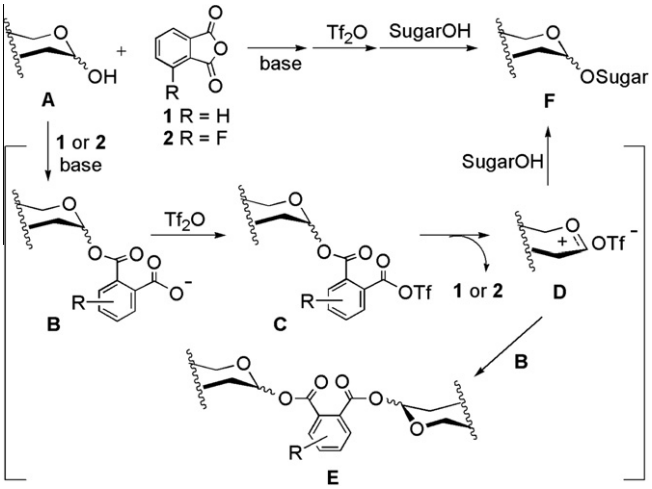
ABSTRACT

An efficient and direct one-pot glycosylation method using anomeric hydroxy sugars as glycosyl donors, employing 3-fluorophthalic anhydride and triflic anhydride as activating agents, has been developed. The present glycosylation utilizing 3-fluorophthalic anhydride resulted in few to no undesired self-condensed esters than the glycosylation using phthalic anhydride. Intermediates in the present glycosylation were identified by an NMR study.

A great deal of effort has been devoted to the development of efficient and stereoselective glycosylation methodologies[1] over the past decades due to important roles of complex oligosaccharides in many fundamental life-sustaining processes.[2] Devising new glycosyl donors and developing new activating systems for existing donors have led to major advances in this field. Glycosyl trichloroacetimidates,[3] thioglycosides,[4] glycosyl sulfoxides,[5] glycals,[6] *n*-pentenyl glycosides,[7] glycosyl fluorides,[8] glycosyl phosphates,[9] and glycosyl phosphites[10] have been the most widely used glycosyl donors for the synthesis of complex oligosaccharides. We have also reported 2′-carboxybenzyl (CB) glycosides,[11] glycosyl pentenoates,[12] and glycosyl benzyl and aryl phthalates[13] as new glycosyl donors. Glycosylation methodologies employing these aforementioned glycosyl donors consist of preparing the donor by conversion of an anomeric substituent into a latent leaving group in the first step. Activation of the isolated glycosyl donor by a promoter followed by formation of a glycosyl bond by the reaction between the activated donor and a nucleophilic glycosyl acceptor occurs in the second step. On the other hand, a direct glycosylation with anomeric hydroxy glycosyl donors, where the anomeric derivatization, activation, and glycosyl bond formation are combined in a one-pot procedure, would offer advantages over current stepwise glycosylation methods. Although there have been many reports on the direct glycosylation with C1-hydroxy glycosyl donors,[14] they have not attracted much attention partly because most have not been utilized for the practical synthesis of oligosaccharides. Recently, Gin and co-workers developed a new method for the glycosylation with anomeric hydroxy sugars involving oxosulfonium intermediates[15] and reported its application to the synthesis of complex oligosaccharides.[16]

We previously reported a new method for the one-pot direct glycosylation with anomeric hydroxy sugars employing phthalic anhydride and triflic anhydride (Tf_2O) as activators,[17] and successfully applied the new method to the synthesis of complex oligosaccahrides.[17,18] Although the new glycosylation method employing phthalic anhydride (**1**) proved to be efficient and stereoselective, it did give undesired self-condensed ester **E** (R = H) in certain cases. This probably resulted from the coupling of glycosyl phthalate anion **B** (R = H) and oxocarbenium ion **D** as shown in Scheme 1.[17]



Scheme 1.

* Corresponding author. Tel.: +82 2 2123 2640; fax: +82 2 365 7608.
E-mail address: kwan@yonsei.ac.kr (K.S. Kim).

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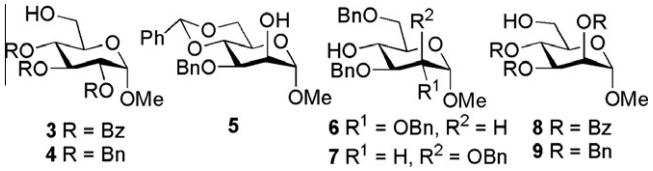


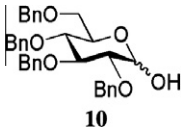
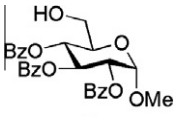
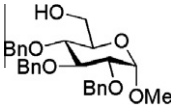
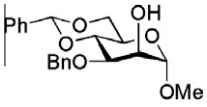
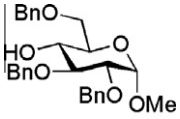
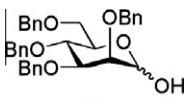
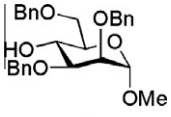
Figure 1. Glycosyl acceptors **3**–**9**.

We envisioned that if 3-fluorophthalic anhydride (**2**) was used as the activator instead of phthalic anhydride (**1**), the nucleophilicity of glycosyl fluorophthalate anion **B** (R = F) would become weaker than that of glycosyl phthalate anion **B** (R = H) such that the oxocarbenium ion **D** would preferentially react with the glycosyl acceptor (sugar-OH) over the less nucleophilic glycosyl fluorophthalate anion **B** (R = F). Herein, a one-pot direct glycosylation method with anomeric hydroxy sugars as glycosyl donors employing 3-fluorophthalic anhydride (**2**) and triflic anhydride as activating agents is reported.

Glycosylations of acceptors **3–7** (Fig. 1) with benzyl-protected glucosyl donor **10** and mannosyl donor **11** were carried out by the following sequence: (i) a solution of **10** or **11** (1.0 equiv), 3-fluorophthalic anhydride (**2**, 1.2 equiv), and 1,8-diazobicyclo[5,4,0] undec-7-ene (DBU, 1.2 equiv) in the presence of 4 Å molecular sieves was stirred for 15 min at room temperature in CH_2Cl_2 (2.0 mL/50 mg of the donor), (ii) the glycosyl acceptor (1.2 equiv) in CH_3CN (3.5 mL/50 mg of the donor) was added to the above solution at 0 °C and stirred for 15 min, and (iii) Tf_2O (1.5 equiv) in CH_2Cl_2 (1.5 mL/50 mg of the donor) was slowly added to the above solution at 0 °C, stirred for 15 min at 0 °C, and then subsequently warmed to room temperature for 30 min.

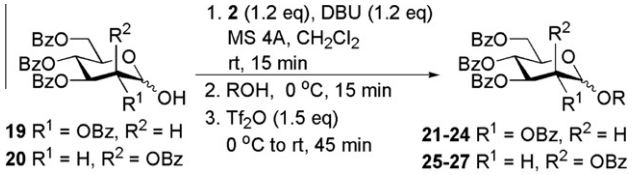
Indeed, glucosylations of primary alcohol acceptors **3** and **4** with the glucosyl donor **10** employing 3-fluorophthalic anhydride (**2**) provided desired disaccharides **12** and **13**, respectively, in high yields without generation of the undesired self-condensed esters, which were formed at approximately 10% in our original glucosylations of **3** and **4** with **10** employing phthalic anhydride (entries 1 and 2 in Table 1). Glucosylations of secondary alcohol acceptors **5** and **6** with **10** gave not only desired disaccharides **14** and **15**, respectively, but also a small amount of undesired self-condensed esters (entries 3 and 4). Nevertheless, the amounts (8% and 3%) of the self-condensed esters generated in the present glucosylations

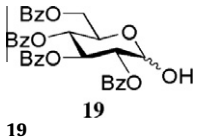
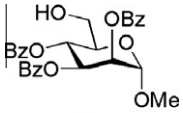
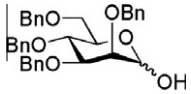
Table 1
Glycosylations with benzyl-protected donors **10** and **11**

Entry	Donor	Acceptor (ROH)	Product	Yield%[a] (ratio, α/β)[b]	Self-condensed ester, %
1	 **10**	 **3**	**12**	84 (1:1.4) 73 (1.6:1)	0 10[c]
2	**10**	 **4**	**13**	86 (1:1.5) 78 (1.2:1)	0 10[c]
3	**10**	 **5**	**14**	82 (1:5) 70 (1:7.5)	8 10[c]
4	**10**	 **6**	**15**	84 (1:1.8) 82 (1:7.5)	3 10[c]
5	 **11**	**3**	**16**	85 (10:1) 0	0
6	**11**	**5**	**17**	85 (α only)	0
7	**11**	 **7**	**18**	86 (1.8:1)	0

[a] Determined after isolation.
[b] The ratio was determined by ^1H NMR.
[c] The result from the original method employing phthalic anhydride, see Ref. 17.

Table 2
Glycosylations with benzoyl-protected donors **19** and **20**



Entry	Donor	Acceptor (ROH)	Product	Yield%[a] (ratio, α/β) [b]
1	 **19**	**3**	**21**	85 (β only)
2	**19**	**5**	**22**	84 (β only)
3	**19**	**6**	**23**	82 (β only)
4	**19**	 **8**	**24**	84 (β only)
5	 **20**	**3**	**25**	86 (α only)
6	**20**	**6**	**26**	84 (α only)
7	**20**	**7**	**27**	85 (α only)

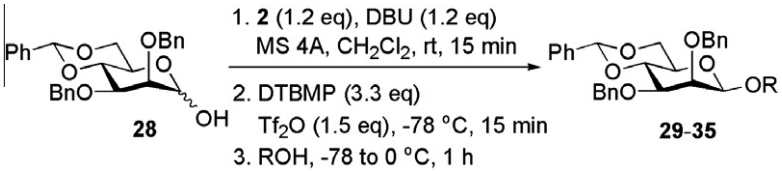
[a] Determined after isolation.
[b] The ratio was determined by ^{1}H NMR.

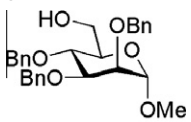
were less than those in our original glucosylations with **10** employing phthalic anhydride. On the other hand, mannosylations of acceptors **3**, **5**, and **7** with donor **11** were more satisfactory than the glucosylations, providing mannosyl disaccharides **16**, **17**, and **18**, respectively, in high yields without the formation of self-condensed esters (entries 5–7).[19]

Glycosylations of various acceptors with benzoyl-protected glucosyl donor **19** and mannosyl donor **20** were also examined under the same reaction conditions as described above, with the exception of using CH_2Cl_2 as the solvent (Table 2). Glucosylations of all primary and secondary alcohol acceptors **3**, **5**, **6**, and **8** with tetrabenzoyl glucose **19** exclusively afforded corresponding β-disaccharides **21**–**24**, respectively, in high yields (entries 1–4 in Table 2) while mannosylations of acceptors **3**, **6**, and **7** with tetrabenzoyl mannose **20** were completely α-selective, providing α-disaccharides **25**–**27**, respectively, in high yields (entries 5–7). The result indicates that the neighboring group participation by the benzoate at the C-2 position was fully operative in the present one-pot glycosylation.

We then, applied the present method to the stereospecific formation of 1,2-*cis*-β-mannopyranosyl linkages by employing 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranose (**28**) as the

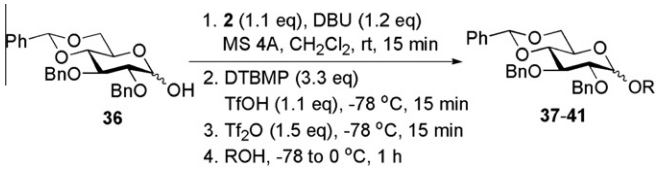
Table 3
Mannosylations with benzylidene-protected donor **28**



Entry	Acceptor (ROH)	Product	Yield%[a] (ratio, α/β) [b]
1	**3**	**29**	88 (1:50)
2	**4**	**30**	88 (1:50)
3	**5**	**31**	84 (β only)
4	**6**	**32**	85 (β only)
5	**7**	**33**	84 (1:19)
6	**8**	**34**	87(1:40)
7	 **9**	**35**	86 (1:18)

[a] Determined after isolation.
[b] The ratio was determined by LC–Mass.

Table 4
Glucosylations with benzylidene-protected donor **36**



Entry	Acceptor (ROH)	Product	Yield%[a] (ratio, α/β) [b]	Self-condensed ester, %
1	**3**	**37**	88 (1:1.4) [b]	0
			74 (α only)	20[d]
2	**8**	**38**	87 (30:1) [c]	4
			87 (18:1)	5[d]
3	**6**	**39**	85 (1:17)[b]	0
4	**5**	**40**	85 (2:1) [c]	0
5	**9**	**41**	87 (1:1.5) [b]	0

[a] Determined after isolation.
[b] The ratio was determined by ^{1}H NMR.
[c] The ratio was determined by LC–Mass.
[d] The result from the original method employing phthalic anhydride, see Ref. 17.

mannosyl donor, since the directing effect of the 4,6-*O*-acetal of the mannosyl donor on the mannopyranosylation is well established.[11a,12a,17,20] Mannosylations with the donor **28** were conducted under a slightly modified condition: 2,6-di-*t*-butyl-4-methylpyridine (DTBMP) was added to prevent cleavage of the acid-labile benzylidene group by triflic acid, and triflic anhydride was added before the acceptor in order to enhance the β-selectivity[21] (see Supplementary data for General Procedure). Mannosylations of all primary and secondary alcohol acceptors **3**–**9** with the 4,6-*O*-benzylidene-protected mannose **28** using 3-fluorophthalic anhydride and Tf_2O as activators were highly β-selective, providing β-mannopyranosides **29**–**35**, exclusively or predominantly in high yields without generation of the self-condensed esters (entries 1–7 in Table 3). Unlike glycosylations with donors **10** and **11**, the 4,6-*O*-benzylidene-protected mannosyl donor **28** did not generate the self-condensed ester even when Tf_2O was added prior to the acceptor.

We also applied the present modified one-pot glycosylation method to the glucosylation with 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranose (**36**). To compare these results with those from the original glucosylation employing phthalic anhydride, the glucosylation with **36** employing 3-fluorophthalic anhydride was conducted under the same condition as that of the original, under which triflic acid (TfOH) was added just before addition of Tf_2O.[17] The glucosylation of the benzoyl-protected primary alcohol glucose acceptor **3** with the benzylidene-protected glucosyl donor **36** employing 3-fluorophthalic anhydride provided desired disaccharides **37** without generation of the self-condensed ester, while the original glucosylation of **3** with **36** employing phthalic anhydride gave 20% of the self-condensed ester (entry 1 in Table 4). Although the glucosylation of **8** with **36** generated a small amount (4%) of the self-condensed ester (entry 2), glucosylations of other acceptors **6**, **5** and **9** with **36** did not produce self-condensed esters and provided desired disaccharides **39**, **40**, and **41**, respectively, in high yields (entries 3–5 in Table 4).

We performed an NMR study to detect intermediates in the glycosylation with 4,6-*O*-benzylidene mannose **28** as the model donor. Intermediates in the reaction of 3-fluorophthalic anhydride (**2**) and **28** in the first step of the mannosylation would be mannosyl 3′-fluorophthalates **42**α and **42**β and mannosyl 6′-fluorophthalates **43**α and **43**β (Fig. 2). When a mixture of **28** (α/β = 2.1:1) (1.0 equiv) and **2** (1.2 equiv) in CD_2Cl_2 at 25 °C in the NMR tube was treated with DBU (1.2 equiv), the ^{1}H NMR spectrum showed anomeric proton resonances at δ 6.31 and 6.34 for α-mannosyl fluorophthalates **42**α and **43**α and at δ 5.90 and 6.00 for β-mannosyl fluorophthalates **42**β and **43**β. Almost the same amount of regioisomers **42** and **43** were formed while the anomeric ratio, (**42**α + **43**α)/(**42**β + **43**β), was around 1.6:1. This ratio was unchanged at 25 °C; however, during the temperature change from 25 to 35 °C, ^{1}H NMR indicated that β-anomers slowly converted to the corresponding stable α-anomers (see Supplementary data). After 30 min at 35 °C, almost all β-anomers were converted into α-anomers, showing only two anomeric proton signals at δ 6.31 and 6.34. The reaction mixture in the NMR tube was then cooled down to −40 °C, and DTBMP (3.0 equiv) and Tf_2O (1.5 equiv) were added sequentially. Immediately after addition of Tf_2O, the ^{1}H NMR spectrum showed an anomeric proton peak at δ 6.03 for α-mannopyranosyl triflate **44**, the same species as that was produced in the original mannosylation.[17] The ^{13}C NMR spectrum at −40 °C also indicated the formation of **44** with an anomeric carbon peak at 105.4. The NMR study supported both the mechanism depicted in Scheme 1 and the involvement of the α-mannopyranosyl triflate **44** in the β-mannosylation with 4,6-*O*-benzylidene mannose **28** (see Supplementary data).

In conclusion, we described here an efficient direct glycosylation method with anomeric hydroxy sugars as glycosyl donors employing 3-fluorophthalic anhydride and Tf_2O as activating agents. Few or no undesired self-condensed esters were formed in the present glycosylation employing 3-fluorophthalic anhydride, as compared with our original glycosylation employing phthalic anhydride. Glycosyl 3′-fluorophthalates and glycosyl 6′-fluorophthalates were identified as intermediates in the first step of the present glycosylation reaction, while α-mannosyl triflate was detected in the second step of the mannosylation with 4,6-*O*-benzylidene mannose, based on the NMR study.

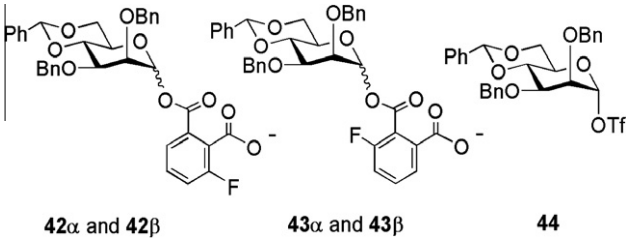


Figure 2. Intermediates identified in the mannosylation with

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.064.

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19. All acceptors, donors, and product disaccharides are same as those in our original work. See: Ref. 17.
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21. We have previously observed that the order of addition of reagents affected the stereoselectivity of the mannosylation: the β-selectivity increased when Tf_2O was added prior to the acceptor in mannosylations with 2′-carboxybenzyl 4,6-*O*-benzylidene mannosides as donors. See: Ref. 11a.