HETEROCYCLES, Vol. 88, No. 1, 2014, pp. 201 - 206. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 24th June, 2013, Accepted, 30th July, 2013, Published online, 7th August, 2013
DOI: 10.3987/COM-13-S(S)44

# FORMATION OF 1,2-*CIS*-α-ARYL-GLYCOSIDIC LINKAGES DIRECTLY FROM 2-ACETAMIDO-2-DEOXY-D-GLUCOPYRANOSYL ACETATE BY THE MIXED ACTIVATING SYSTEM USING YTTERBIUM(III) TRIFLATE AND CATALYTIC BORON TRIFLUORIDE DIETHYL ETHERATE COMPLEX†

**Takashi Yamanoi,* Masanobu Midorikawa, and Yoshiki Oda**

The Noguchi Institute, 1-8-1 Kaga, Itabashi-ku, Tokyo 173-0003, Japan
E-mail: tyama@noguchi.or.jp

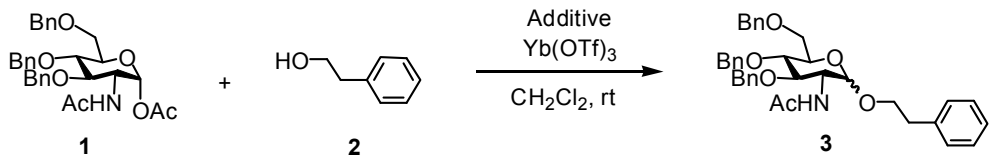
†Dedicated to Professor Dr. Victor Snieckus on his 77th birthday.

**Abstract** – We found that a mixed activating system using ytterbium(III) triflate and a catalytic boron trifluoride diethyl etherate complex efficiently promoted glycosidation of the 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-α-**D**-glucopyranosyl acetate in dichloromethane at room temperature to afford 2-acetamido-2-deoxy-**D**-glucopyranosides in good yields along with the formation of a considerable amount of α-isomers. Glycosylations of the aryl alcohols as the acceptors stereoselectively afforded aryl α-glycosides without producing any β-isomers.

Ytterbium(III) triflate ($Yb(OTf)_3$) is one of the useful activators in some glycosidation reactions.[1] Our investigation into the $Yb(OTf)_3$-promoted glycosidation showed that $Yb(OTf)_3$ was effective for several glycosyl acetates.[2] In addition, we found that a mixed activating system based on the combined use of $Yb(OTf)_3$ and a catalytic amount of boron trifluroride diethyl etherate ($BF_3{\cdot}OEt_2$) was useful for glycosidation using some of the less reactive glycosyl acetates.[3-5] Our attention was recently directed toward the formation of 2-acetamido-2-deoxy-**D**-glucopyranosidic linkages, and we conducted a preliminary investigation on glycosidation using 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-α-**D**-glucopyranosyl acetate (**1**)[6] as the glycosyl donor using a mixed activating system. The mixed activating system using $Yb(OTf)_3$ (1 equiv.)-$BF_3{\cdot}OEt_2$ (0.03 equiv.) successfully promoted the glycosidation of **1** with phenethyl alcohol (**2**) to produce the phenethyl 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-**D**-glucopyranosides (**3**) in a high yield of 95% with an α/β ratio of 40/60. Interestingly, this resulted in the production of a considerable amount of α-glycoside. It is known that glycosidations using

2-acetamido-2-deoxy-**D**-glucopyranosyl donors having a natural *N*-acetyl protecting group usually forms corresponding β-glycosides by the following mechanism. Stable oxazoline derivatives are generated by the effect of the neighboring-group participation of a C-2 acetamido function, and the consequent $S_N2$-like nucleophilic substitution of an alcohol to the oxazoline derivatives (or oxazolinium cation intermediate) under severe reaction conditions when using a strong Lewis or Brϕnsted acid leads to the production of the β-glycosides.[7] To the best of our knowledge, there have been no reports of glycosidations that directly produce 1,2-*cis*-α-glycosidic linkages from a 2-acetamido-2-deoxy-**D**-glucopyranosyl donor. The unusual reactivity and stereoselectivity of the glycosidation between **1** and **2** using our mixed activating system suggest that it may involve a different pathway that does not generate oxazoline intermediates.

2-Acetamido-2-deoxy-α-**D**-glucopyranosidic linkages are found in the *O*-glycans of gastric mucins,[8] lipopolysaccharides of bacteria,[9] tunicamycin,[10] etc.[11] Therefore, developing a convenient method for forming 1,2-*cis*-α-glycosidic linkages directly from 2-acetamido-2-deoxy-**D**-glucopyranose derivatives is one important goal in synthetic carbohydrate chemistry.[12] This study describes the detailed glycosidation properties involved in the formation of the 1,2-*cis*-α-glycosidic linkages from **1** by a mixed activating system using $Yb(OTf)_3$ and catalytic $BF_3{\cdot}OEt_2$.




**Scheme 1**

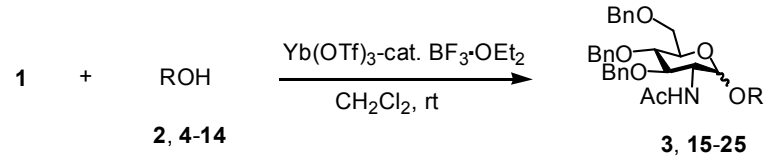
**Table 1**. Reaction of **1** with **2** in the presence of a Brϕnsted acid[a]

| Entry | Additive | Yield (%) | α/β |
|---|---|---|---|
| 1 | None | Trace | - |
| 2 | $BF_3{\cdot}OEt_2$ | 95 | 40/60 |
| 3 | TfOH | 68 | 47/53 |
| 4 | AcOH | 72 | 49/51 |

[a]Reaction conditions; molar ratio; **1**: **2**: $Yb(OTf)_3$: additive= 1.2: 1: 1: 0.03; overnight; room temperature.

A catalytic amount of $BF_3{\cdot}OEt_2$ is essential for promoting glycosidation because glycosidation does not proceed at all without $BF_3{\cdot}OEt_2$. We speculated that the $ROH{\cdot}BF_3$ complex formed in situ between $BF_3{\cdot}OEt_2$ and an alcohol would work as a Brϕnsted acid and influence the glycosidation reactivity as we previously reported for the glycosidation using **1**.[13] The effect of the Brϕnsted acids, AcOH, and TfOH, as additives was then examined (Scheme 1). The addition of a 3 mol% amount of AcOH or TfOH to the glycosidation process using **1** (1.2 equiv.), phenethyl alcohol (1 equiv.), and $Yb(OTf)_3$ (1 equiv.) in

$CH_2Cl_2$ at room temperature produced the glycoside **3** in 72% or 68% yields with α/β ratios of 49/51 or 47/53, respectively. The addition of AcOH or TfOH was also effective for the promotion of glycosidation using **1** as well as $BF_3{\cdot}OEt_2$, and these reactions produced a considerable amount of the α-glycoside. These results are shown in Table 1.




**Scheme 2**

**Table 2**. Reaction of **1** with various alcohols and aryl alcohols using the mixed activating system[a]

| Entry | Acceptor | Glycoside | Yield (%) | α/β Ratio | $^1$H NMR data of H-1 δ (ppm), *J* (Hz) | | $^{13}$C NMR data of C-1 δ (ppm) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | α-isomer | β-isomer | α-isomer | β-isomer |
| 1 | **2** | **3** | 95 | 40/60 | 4.68, 3.6 | 4.76, 7.6 | 97.7 | 99.8 |
| 2 | **4** | **15** | 83 | 19/81 | 4.78, 3.6 | 4.81, 8.4 | 97.5 | 99.8 |
| 3 | **5** | **16** | 86 | 51/49 | 4.90, 3.8 | 4.81, 7.7 | 97.2 | 99.3 |
| 4 | **6** | **17** | 94 | 37/63 | 4.80, 3.6 | 4.85, 7.6 | 96.9 | 99.0 |
| 5 | **7** | **18** | 71 | 38/62 | 4.76, 3.8 | 4.79, 7.7 | 97.6 | 99.8 |
| 6 | **8** | **19** | 72 | 27/73 | 4.91, 3.8 | 5.00, 7.9 | 96.2 | 98.1 |
| 7 | **9** | **20** | 68 | 53/47 | 4.92, 3.8 | 5.00, 8.1 | 95.9 | 98.0 |
| 8 | **10** | **21** | 71 | 31/69 | 4.94, 3.6 | 4.92, 7.9 | 95.8 | 97.7 |
| 9 | **11** | **22** | 67 | α | 5.47, 4.1 | - | 96.3 | - |
| 10 | **12** | **23** | 84 | α | 5.35, 3.4 | - | 97.2 | - |
| 11 | **13** | **24** | 57 | α | 5.54, 3.4 | - | 96.8 | - |
| 12 | **14** | **25** | 60 | α | 5.41, 3.4 | - | 96.2 | - |

[a]Reaction conditions; molar ratio; **1**: acceptor: $Yb(OTf)_3$: $BF_3{\cdot}OEt_2$= 1.2: 1: 1: 0.03; overnight; room temperature.

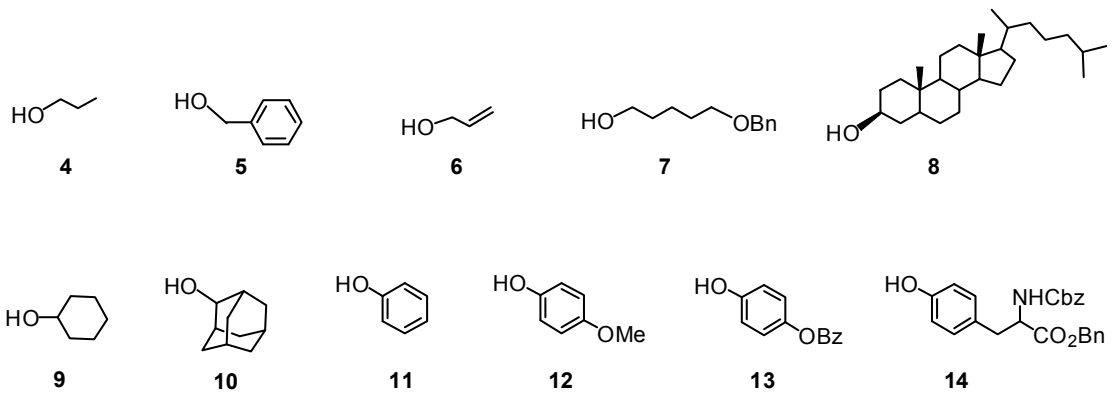
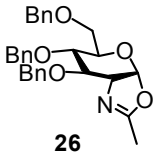



**Figure 1**

Next, we investigated the glycosidation of **1** with several types of alcohols under similar reaction conditions to examine the effect of alcohols on glycosidation's stereoselectivities (Scheme 2, Figure 1). The reactions using primary and secondary alcohols **2**, **4**-**10** gave the corresponding glycosides **3**, **15**-**21**, respectively in good yields with α/β ratios of ca. 1/1-1/5. Thus, each of these reactions gave a mixture of α- and β-glycosides. However, surprisingly, the reactions using aryl alcohols **11**-**14** gave aryl α-glycosides **22**-**25**, respectively in good yields with no production of the β-glycosides. The steric and electronic effects of the alcohols influenced the glycosidation's stereoselectivities. Table 2 summarizes these results and the $^{1}$H and $^{13}$C NMR data of H-1 and C-1, respectively from the α- and β-glycosides (**3**, **15**-**25**) produced.

**Table 3**. Reaction of **26** with **2** or **11**

| Entry | Acceptor | Yield (%) | α/β |
|---|---|---|---|
| 1 | **2** | 53 | β |
| 2 | **11** | No reaction | - |




**26**

**Figure 2**

Furthermore, to clarify the difference in the reaction mechanism, we performed glycosidation using 3,4,6-tri-*O*-benzyl-1,2-oxazoline-glucopyranose (**26**),[14] considered to be one of the glycosyl intermediates, under the same reaction conditions (Figure 2). The reactions of **26** (1.2 equiv.) with **2** or **11** were examined in the presence of $Yb(OTf)_3$ (1 equiv.) and $BF_3{\cdot}OEt_2$ (0.03 equiv.) in $CH_2Cl_2$ at room temperature. The reaction using **2** gave β-glycoside in 53% yield with no production of the α-glycoside, while the reaction using **11** did not produce glycoside at all. These results are shown in Table 3. The reactivity and stereoselectivity of glycosidation using **26** were found to be quite different from those of glycosidation using **1**. In addition, we confirmed that the β-anomer of **22** was not isomerized to the α-anomer at all under the acidic conditions in the presence of $Yb(OTf)_3$ (1 equiv.) and $BF_3{\cdot}OEt_2$ (0.03 equiv.) in $CH_2Cl_2$ at room temperature. Therefore, the α-glycosides formed by the glycosidation using **1** are not a conversion product of in situ acid-catalyzed anomerization from the β-glycosides.

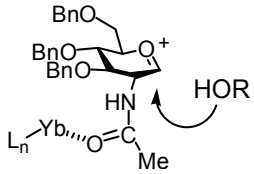



**Figure 3**

We speculated that the complex of ytterbium metal and **1** through the carbonyl group of **1** might be formed as a glycosyl cation intermediate, as shown in Figure 3. This complex formation would prevent the production of the oxazoline derivative because of the decrease in the Lewis basicity of the oxygen atom of the carbonyl group and allow an alcohol to attack the glycosyl cation intermediate from the α-face, resulting in the formation of the 1,2-*cis*-α-glycosidic linkages. However, we have not yet found a sufficient explanation for the high α-stereoselectivities of the glycosidations using aryl alcohols.

In summary, we found that several 2-acetamido-2-deoxy-**D**-glucopyranosides were directly synthesized from glycosyl acetate **1** in good yields along with the formation of a considerable amount of α-isomers by a mixed activating system using $Yb(OTf)_3$-catalytic $BF_3{\cdot}OEt_2$. The reactions using the aryl alcohols as acceptors only afforded aryl α-glycosides with no production of β-glycosides.[15] This novel glycosidation approach for forming 2-acetamido-2-deoxy-**D**-glucopyranosidic linkages is applicable for the synthesis of natural products.

## REFERENCES AND NOTE


1. S. Kobayashi, M. Sugiura, H. Kitagawa, and W. W.-L. Lam, *Chem. Rev.*, 2002, **102**, 2227.
2. (a) T. Yamanoi, Y. Iwai, and T. Inazu, *Heterocycles,* 2000, **53**, 1263; (b) T. Yamanoi and I. Yamazaki, *Tetrahedron Lett*., 2001, **42**, 4009.
3. T. Yamanoi, Y. Iwai, and T. Inazu, *J. Carbohydr. Chem*., 1998, **17**, 819.
4. It was found that $Yb(OTf)_3$ was basically ineffective for the less reactive glycosyl acetates such as 2,3,4,6-tetra-*O*-benzyl-**D**-glucopyranosyl acetate. J. Inanaga, Y. Yokoyama, and T. Hashimoto, *Tetrahedron Lett*., 1993, **34**, 2791.
5. Several glycosidation methods using the combination of two Lewis acids have been reported. For example, (a) The combination of bismuth(III) triflate and $BF_3{\cdot}OEt_2$ was a useful activating system for the glycosidation of sialyl acetate derivatives. K. Ikeda, Y. Torisawa, T. Nishi, J. Minamikawa, K. Tanaka, and M. Sato, *Bioorg. Med. Chem*., 2003, **11**, 3073; (b) The activating system using silver perchlorate-lithium perchlorate was useful for ribofuranosylation. T. Mukaiyama and N. Shimomura, *Chem. Lett.*, 1993, 781; (c) The activating system using $Yb(OTf)_3$-zinc chloride was effective for the glycosidation of glycosyl fluoride. S. Hosono, W.-S. Kim, H. Sasai, and M. Shibasaki, *J. Org. Chem*., 1995, **60**, 4. Other references are cited therein.
6. R. Harrison and H. G. Fletcher, *J. Org. Chem*., 1965, **30**, 2317.
7. For example, (a) M. Kiso and L. Anderson, *Carbohydr. Res.,* 1985, **136**, 309; (b) G. Arsequell, L. Krippner, R. A. Dwek, and S. Y. C. Wong, *J. Chem. Soc., Chem. Commun.,* 1994, 2383; (c) I. Carvalho, S. L. Scheuerl, K. P. R. Kartha, and R. A. Field, *Carbohydr. Res*., 2003, **338**, 1039; (d) A β-glycosidation method has been reported directly from 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-α-

**D**-glucopyranosyl diethyl phosphate in the presence of bis(trifluoromethanesulfonyl)imide via the α-glycosyl triflate intermediate, not the oxazoline derivative. R. Aihara, S. Nakamura, and S. Hashimoto, *Angew. Chem. Int. Ed*., 2005, **44**, 2245.

8. For example, M. Kawakubo, Y. Ito, Y. Okimura, M. Kobayashi, K. Sakura, S. Kasama, M. N. Fukuda, M. Fukuda, T. Katsuyama, and J. Nakayama, *Science*, 2004, **305**, 1003. Other references cited therin.
9. For example, (a) L. Feng, A. V. Perepelov, G. Zhao, S. D. Shevelev, Q. Wang, S. N. Senchenkova, A. S. Shashkov, Y. Geng, P. R. Reeves, Y. A. Knirel, and L. Wang, *Microbiology*, 2007, **153**, 139; (b) A. N. Kondakova, R. Fudala, S. N. Senchenkova, A. S. Shashkov, Y. A. Knirel, and W. Kaca, *Carbohydr. Res*., 2003, **338**, 1191; (c) A. D. Cox, J.-R. Brisson, P. Thibault, and M. B. Perry, *Carbohydr. Res*., 1997, **304**, 191; (d) H. Parolis, S. M. R. Stanley, A. Dell, and A. J. Reason, *Carbohydr. Res*., 1995, **266**, 95.
10. For example, (a) A. Takatsuki, K. Arima, and G. Tamura, *J. Antibiot*., 1971, **24**, 215; (b) T. Suami, H. Sasai, K. Matsuno, N. Suzuki, Y. Fukuda, and O. Sakanaka, *Tetrahedron Lett*., 1984, **25**, 4533; (c) A. Tordai, L. F. Brass, and E. W. Gelfand, *Biochem. Biophys. Res. Commun*., 1975, **65**, 248.
11. K.-F. Mo, X. Li, H. Li, L. Y. Low, C. P. Quinn, and G.-J. Boons, *J. Am. Chem. Soc*., 2012, **134**, 15556.
12. Manabe *et al.* reported the synthetic approach of the 2-acetamido-2-deoxy-α-**D**-glucopyranosides through the glycosidation using a *N*-benzyl-2,3-oxazolidinone-protected glucosamine derivative. (a) S. Manabe, K. Ishii, and Y. Ito, *J. Am. Chem. Soc*., 2006, **128**, 10666; (b) S. Manabe, K. Ishii, and Y. Ito, *J. Org. Chem.*, 2007, **72**, 6107. The typical approaches for the preparation of the 2-amido-2-deoxy-α-**D**-glucopyranosides utilized the glycosyl donors having an azido group or a benzylideneamino group at C-2. For example, (c) J. Park, S. Kawatkar, J.-H. Kim, and G.-J. Boons, *Org. Lett*., 2007, **9**, 1959; (d) E. A. Mensah, F. Yu, and H. M. Nguyen, *J. Am. Chem. Soc*., 2010, **132**, 14288.
13. The addition of a Brϕnsted acid, such as hydrochloric or carboxylic acid, dramatically accelerated the aldol and allylation reactions catalyzed by a Lewis acid in water. K. Manabe, Y. Mori, S. Nagayama, K. Odashima, and S. Kobayashi, *Inorg. Chim. Acta*, 1999, **296**, 158.
14. P. Rollin and P. Sinay, *J. Chem. Soc., Perkin Trans. 1*, 1977, **22**, 2513.
15. We have applied the reaction to the synthesis of a β-cyclodextrin derivative conjugated with a 2-acetamido-2-deoxy-**D**-glucopyranoside residue. Y. Oda, M. Miura, K. Hattori, and T. Yamanoi, *Chem. Pharm. Bull*., 2009, **57**, 74.