ORGANIC LETTERS

2009
Vol. 11, No. 3
609−612

Facile Synthesis of 2-*O*-Iodoacetyl Protected Glycosyl Iodides: Useful Precursors of 1→2-Linked 1,2-*trans*-Glycosides

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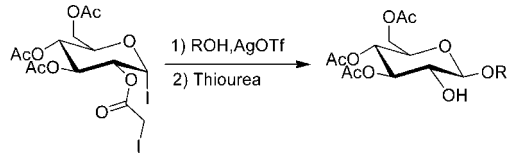
Received November 16, 2008

ABSTRACT



The preparation and utilization of novel iodide glycosyl donors, 2-*O*-iodoacetyl-glycopyranosyl iodides, is described. The mechanism for the reaction of iodine with carbohydrate cyclic ketene acetal was investigated through low-temperature NMR experiments. 2-*O*-Iodoacetyl-glycopyranosyl iodides can serve as effective glycosyl donors giving 2-*O*-iodoacetyl 1,2-*trans*-glycosides in high yields and excellent stereoselectivities. The 2-*O*-iodoacetyl group was removed selectively with thiourea to afford 2-hydroxy 1,2-*trans*-glycosides in high yield without affecting other protecting groups and anomeric configurations.

1→2-*O*-Linked 1,2-*trans*-glycosides are key subunits of many biologically important compounds such as vancomycin,[1] the immunosuppressant plakoside A,[2] and other useful agents.[3] Synthetic approaches to these glycosides have focused on two important concepts: regioselective protection and anomeric center activation. Many challenges have been overcome to create efficient stereoselective glycosyl donors as synthetic tools. Established donors include 2-*O*-protected glycosyl halides, trichloroacetimidates, thioglycosides, *n*-pentenyl glycosides, and glycals.[4] Most of these donors, however, require multistep syntheses that involve selective protection and deprotection procedures. The development of a direct and efficient glycosyl donor for the construction of 1→2-*O*-linked 1,2-*trans* glycosides is desirable but hitherto has not been forthcoming.

Glycosyl iodides display a significantly higher reactivity than the corresponding bromides and chlorides and show a greater reactivity toward nucleophilic displacement under neutral conditions.[5] Recent studies have shown that glycosyl iodides offer many advantages in terms of reaction times, efficiencies, and stereochemical outcomes.[6,7] Here, we report a series of novel iodide glycosyl donors for 1,2-*O*-glycosidation, namely, 2-*O*-iodoacetyl-glycopyranosyl iodides (**9**∼**12**).

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(1) Nicolaou, K. C.; Winssinger, N.; Hyghes, R.; Smethurst, C.; Cho, S. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 1084–1088.

(2) Nicolaou, K. C.; Li, J.; Zenke, G. *Helv. Chim. Acta* **2000**, *83*, 1977–2006.

(3) (a) Weinstein, D. S.; Nicolaou, K. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, *54*, 5–557. (b) Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072–3080. (c) Murakami, T.; Taguchi, K. *Tetrahedron* **1999**, *55*, 989–1004.

(4) For recent reviews, see: (a) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624. (b) Pellissier, H. *Tetrahedron* **2005**, *61*, 2947–2993.

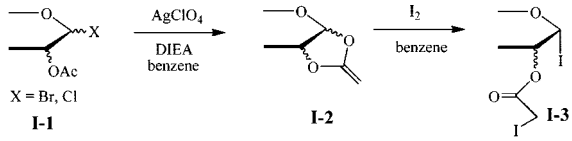
(5) (a) Hashimoto, S.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 4769–4772. (b) Schmid, U.; Waldemann, H. *Tetrahedron Lett.* **1996**, *37*, 3837–3840.

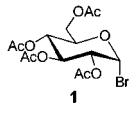
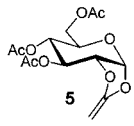
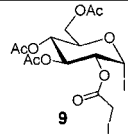
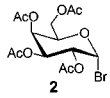
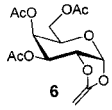
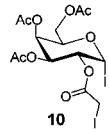
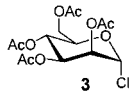
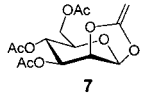
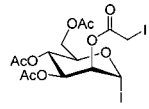
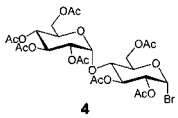
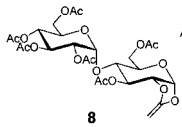
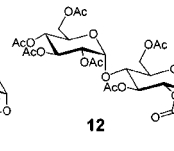
(6) (a) Perrie, J. A.; Harding, J. R.; King, C.; Sinnott, D.; Stachulski, A. V. *Org. Lett.* **2003**, *5*, 4545–4548. (b) Bhat, A. S.; Gervay-Hague, J. *Org. Lett.* **2001**, *3*, 2081–2084. (c) Hadd, M. J.; Gervay, J. *Carbohydr. Res.* **1999**, *320*, 61–69. (d) Gervay, J. *Org. Synth.: Theory Appl.* **1998**, *4*, 121–153. (e) Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961–6967.

10.1021/ol8026472 CCC: $40.75
Published on Web 12/31/2008

2-*O*-Iodoacetyl protected glycosyl iodides (**9**∼**12**) were readily synthesized from the *O*-acetyl glycosyl bromide or chloride via carbohydrate cyclic ketene acetal intermediates as shown in Table 1. Treatment of the glycosyl halides **1**∼**4**

Table 1. Synthesis of 2-*O*-Iodoacetyl-glycosyl Iodide



entry	substrate (**I-1**)	ketene acetal (**I-2**)	glycosyl iodide (**I-3**)	yield[a]
1	 **1**	 **5**	 **9**	87 %
2	 **2**	 **6**	 **10**	86 %
3	 **3**	 **7**	 **11**	81 %
4	 **4**	 **8**	 **12**	62 %

[a] Yields are obtained over two steps from **I-1**

with $AgClO_4$[8] in anhydrous benzene at room temperature for 1 h yielded the ketene acetals **5**∼**8** in 60∼90% yields. Unexpectedly, we found that carbohydrate ketene acetals **5**∼**8** showed good stability to water during workup. They could easily be purified by filtration through Celite to remove AgBr and finally washed with water to remove the residual $AgClO_4$, ammonium salts, and other water-soluble impurities. NMR analysis of these products indicated that no additional purification was necessary.

The ketene acetals **5**∼**8** reacted with iodine in the presence of 4 Å MS in benzene at ambient temperature to afford the glycosyl iodides **9**∼**12** as shown in Table 1. Glucosyl iodide derivative **9** was synthesized in 87% yield over two steps from the commercially available glucosyl bromide **1** (entry 1). Similarly, galactosyl iodide **10** and mannosyl iodide **11** were synthesized in 86% and 81% yields from galactosyl bromide **2** and mannosyl chloride **3**, respectively (entries 2 and 3). Maltosyl iodide **12** was synthesized in 62% yield from maltosyl bromide precursor **4**[9] which was readily available from the treatment of octa-*O*-acetyl-α-D-maltoside with 33% hydrogen bromide in AcOH (entry 4). Therefore, this synthetic procedure can be used with readily available monosaccharides and oligosaccharides.

The stability of 2-*O*-iodoacetyl-α-D-glycopyranosyl iodide derivatives is greatly dependent on the type of sugar. The order of stability for glycosyl iodides is as follows: glucosyl iodide **9** > galactosyl iodide **10** ≈ maltosyl iodide **12** > mannosyl iodide **11**. Especially, glucosyl iodide **9** is quite stable and can be stored for 5 months in the dark at room temperature or over one year at −18 °C. However, under concentrated conditions, mannosyl iodide **11** is so unstable that it has to be used for glycosylation without purification.

Under the experimental conditions in Table 1, only α-glycosyl iodides were obtained without any trace of their *β*-anomers; this was verified by extensive NMR experiments and NOE measurements. The anomeric protons H-1 of compounds **9**, **10**, **11**, and **12** show the chemical shifts of 6.96, 7.03, 6.72, and 6.90 ppm, respectively.[10] Upon irradiation of H-2 of the α-glucosyl iodide **9** in a selective 1D NOE experiment,[11] strong interactions were observed with the anomeric proton H-1 (NOE 3.5%), the 1,3-diaxial proton H-4 (2.4%), and transdiaxial H-3 (1.1%), which suggested an α-configuration of the anomeric proton as shown in Figure 1. In addition, irradiation of the anomeric proton H-1 resulted in no detectable NOE signal except those of neighboring H-2.

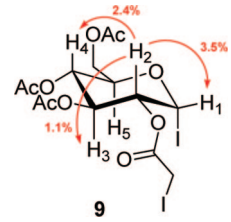


Figure 1. NOE measurements for *β*-glucosyl iodide **9** in toluene-d_8 at 298 K.

A detailed plausible mechanism for the formation of glycosyl iodides is depicted in Scheme 1. Reaction of electron-rich ketene acetal[12] with iodine would give a dioxocarbenium ion **13**. A nucleophilic ring opening of a dioxocarbenium ion **13** by an iodide first gives *β*-glycosyl

(7) (a) Schmid, U.; Waldmann, H. *Liebigs Ann./Relc.* **1997**, 2573–2577. (b) Tanaka, H.; Sakamoto, H.; Sano, A.; Nakamura, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **1999**, 1259–1260. (c) Caputo, R.; Kunz, H.; Mastroianni, D.; Palumbo, G.; Pedatella, S.; Solla, F. *Eur. J. Org. Chem.* **1999**, *314*, 7–3150.

(8) (a) Paulsen, H. *Angew. Chem., Int. Ed.* **1982**, *21*, 184–201. (b) Ness, R. K.; Fletcher, H. G.; Hudson, C. S. *J. Am. Chem. Soc.* **1951**, *73*, 296–300. (c) Hanessian, S.; Banoub, J. *Carbohyd. Res.* **1975**, *44*, C14–Cl7.

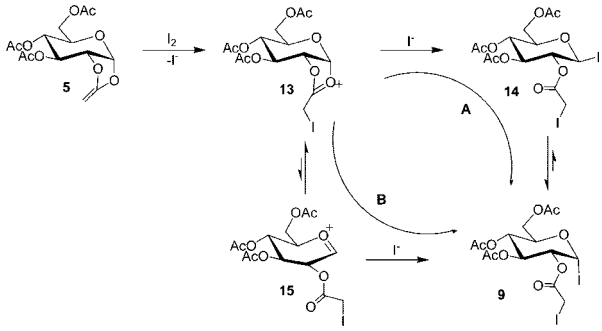
(9) Brauns, D. H. *J. Am. Chem. Soc.* **1929**, *51*, 1820–1831.

(10) $J_{1,2}$ values of H-1 at **9**, **10**, and **12** are 4.3 Hz, which suggests α-anomer. H-1 of **11** shows a broad single peak.

(11) Stott, K.; Keeler, J.; Shaka, Q. N.; Van, A. J. *J. Magn. Reson.* **1997**, *125*, 302–324.

(12) McElvain, S. M. *Chem. Rev.* **1949**, *45*, 453–492.

Scheme 1. Proposed Mechanism for Formation of Glucosyl Iodides **9**



iodide **14**, which rearranges[13] to the more stable α-glucosyl iodide **9** (path A). Alternatively, dioxocarbenium ion **13** can be equilibrated to the reactive but low-abundance oxocarbenium ion **15**, which is then attacked by an iodide anion and forms directly α-glycosyl iodide **9** without going through the *β*-anomer (path B). To investigate the mechanistic process, especially to detect *β*-glycosyl iodides, NMR experiments were performed at various temperatures.

Carbohydrate ketene acetal **5** from glucosyl bromide **1** was treated with 2 equiv of iodine in CD_2Cl_2 at 0 °C (Figure 2). After 5 min, the carbohydrate ketene acetal peaks at δ 3.43 and 3.36 ppm disappeared, and two new product peaks for H-1 of the glucosyl iodide **9** started to appear at δ 5.78 and 6.96 ppm (product ratio 14:1). The anomeric proton of the major *β*-product appeared as a doublet at δ 5.78 ppm (J = 9.4 Hz), while that of the minor α-product appeared at δ 6.96 ppm (J = 4.1 Hz). Upon warming to room temperature, the intensity of the proton at δ 5.78 was reduced, while the intensity of the proton at δ 6.96 was increased. After 30 min, most of the *β*-glucosyl iodide **14** rearranged to the α-glucosyl iodide **9**.

On the basis of these NMR experiments, the mechanism for the formation of 2-*O*-iodoacetyl-α-glycosyl iodides **9**, **10**, and **12** is explained by the following path A depicted in Scheme 1. However, attack on an unstable but more reactive oxocarbenium **15** equilibrated from **13** by an iodide ion (path B) should occur rarely since the peak indicating α-glycosyl iodides **9** did not appear until complete consumption of the ketene acetal **5** as shown in the ^{1}H NMR spectra (Figure 2). The formation of 2-*O*-iodoacetyl-α-mannosyl iodides **11** would be from a direct α-attack of iodine to produce the *β*-ketene acetal.

To evaluate its properties as a glycosyl donor, 2-*O*-iodoacetyl glucosyl iodide **9** was coupled with a variety of glycosyl acceptors in the presence of AgOTf.[8] In all of the cases examined, only 1,2-*trans*-*β*-glycoside products were obtained in good yields, as summarized in Table 2. Glycosylation of an unhindered aliphatic acceptor, benzyl alcohol **16**, was complete in 2 h at −10 °C to afford the 1,2-*trans*-*β*-glycoside **22** in 93% yield (Table 2, entry 1). Phenol derivatives **17** and **18** (entries 2 and 3) and the primary 6-OH of partially protected sugar **19** (entry 4) were also glycosylated after reaction for 3 h at −10 to 0 °C and gave rise to

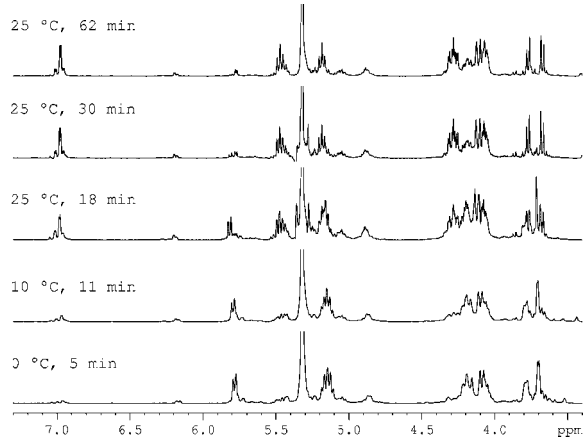
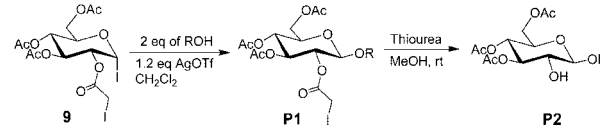
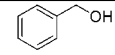
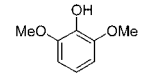
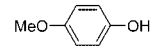
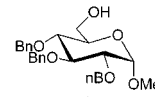
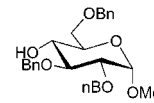
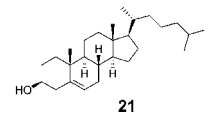


Figure 2. Reaction monitoring on the formation of glucosyl iodide **9** by ^{1}H NMR (600 MHz) analysis. Times indicated are cumulated ones from the injection of I_2 to **5** in CD_2Cl_2.

Table 2. Gycosylation and Deprotection



entry	acceptor (ROH)	P1	yield[a]	P2	yield[b]
1	 **16**	**22**	93%	**28**	92%
2	 **17**	**23**	57% 96%[c]	**29**	98%
3	 **18**	**24**	93%	**30**	91%
4	 **19**	**25**	76%	**31**	73%
5	 **20**	**26**	82%[d]	**32**	84%
6	 **21**	**27**	61%	**33**	97%

[a] Isolated yields of **P1** prepared from **9**. [b] Isolated yields of **P2** prepared from **P1**. [c] 3 equiv of **9** was used. [d] 2.4 equiv of AgOTf was used.

the 1,2-*trans*-β-glycoside products in acceptable yield. The hindered phenol **17**[14] was glycosylated with 3 equiv of glucosyl iodide **9** in 96% yield (entry 2). Glycosylation of the highly hindered secondary 4-OH of **20** was complete after 18 h at an elevated temperature of 10 °C (entry 5). Glycosylation of cholesterol **21** was carried out at 0 °C due to the limited solubility of cholesterol at low temperature (entry 6). It is noteworthy that 2-*O*-iodoacetyl glucosyl iodide **9** can be used in glycosylation with a variety of glycosyl acceptors, it giving 1,2-*trans*-β-glycosides in good yields. Reactions using **10**, **11**, and **12** also showed complete stereoselection yielding only 1,2-*trans*-β-glycosides with excellent yields in glycosylation.

Selective removal of the iodoacetyl group at C-2 in 2-*O*-iodoacetyl-glycosides (**22**∼**27**) using thiourea[15] proceeded successfully without affecting other protecting groups and anomeric configurations, affording good yields of the expected products (73%∼98%, Table 2). While little is known about the properties of the iodoacetyl group in carbohydrate chemistry, we have successfully demonstrated its advantages as a protecting group. In this regard, it can be easily removed under mild conditions after glycosylation.

In conclusion, a facile method for the preparation of 2-*O*-iodoacetyl-protected glycosyl iodides from glycosyl bromides or chlorides via carbohydrate cyclic ketene acetals has been established. Glycosyl iodides protected with the 2-*O*-iodoacetyl group serve as efficient and stereoseletive glycosyl donors for the preparation of the 1→2-linked 1,2-*trans*-glycosides. Glycosylation of various acceptors with 2-*O*-iodoacetyl protected glycosyl iodides and subsequent selective removal of the 2-*O*-iodoacetyl group gives the corresponding 2-hydroxy 1,2-*trans*-glycosides in high yield and with excellent stereoselectivity. Therefore, the glycosylation protocol outlined herein provides a useful method for the synthesis of oligosaccharides and glycoconjuates containing 1→2-*O*-linked 1,2-*trans*-glycosides.

Acknowledgment. Support of this work by the National Center for Inter-University Research Facilities in Seoul National University is greatly appreciated.

Supporting Information Available: Experimental details and spectral data (^{1}H and ^{13}C NMR, and HRMS) of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8026472

(13) Gervay, J.; Nguyen, T. N.; Hadd, M. J. *Carbohydr. Res.* **1997**, *300*, 119–125.

(14) (a) Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Bando, T.; Hughes, R.; Winssinger, N.; Natarajan, S.; Koumbis, A. E. *Chem.*−*Eur. J.* **1999**, *5*, 2648–2667. (b) Thompson, C.; Ge, M.; Kahne, D. *J. Am. Chem. Soc.* **1999**, *121*, 1237–1244. (c) Nicolaou, K. C.; Mitchell, H. J.; Delft, F. L.; Rübsam, F.; Rodriguez, R. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1871–1874. (d) Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 3471–3475.

(15) Kováč, P.; Glaudemans, C. P. J. *Carbohyd. Res.* **1985**, *140*, 313–318.