Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6211–6215

TETRAHEDRON LETTERS

Iodine catalyzes *C*-glycosidation of D-glucal with silylacetylene

Rungnapha Saeeng,[a,*] Uthaiwan Sirion,[a] Poolsak Sahakitpichan[b] and Minoru Isobe[c,*]

[a]*Department of Chemistry, Faculty of Science, Burapha University, Sangsook, Chonburi 20131, Thailand*
[b]*Chulabhorn Research Institute (CRI), Vibhavadee-Rangsit Highway, Bangkok 10210, Thailand*
[c]*Laboratory of Organic Chemistry, Graduate School of Bioagricultural Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan*

Received 22 May 2003; revised 13 June 2003; accepted 20 June 2003

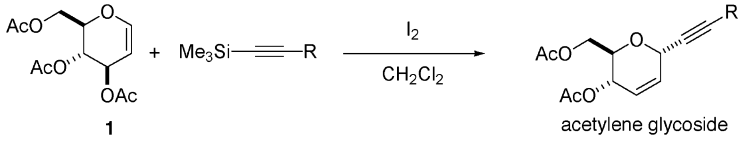
Abstract—A convenient method for *C*-glycosidation (alkynylation) with various silylacetylenes to D-glucal by iodine molecule via iodo–oxonium intermediates provided exclusively the α-acetylene glycoside products. Eleven successful examples are shown under this condition.

The direct formation of carbon–carbon bonds at the anomeric center of sugar nuclei still presents a significant challenge to synthetic chemists and several solutions to this problem have evolved.[1] *C*-Glycosidation is one of the key reactions for the introduction of carbon chain to a sugar ring. Silylacetylenes are considered to be sufficiently reactive to form acetylene glycosides which can be used as a carbon chiral pool for the synthesis of polyether natural products.[2] *C*-Glycosidation with silylacetylene compounds have been reported to proceed under various conditions by using Lewis acid[3] such as $SnCl_4$, $BF_3{\cdot}OEt_2$, $TiCl_4$ and recently[4] $InBr_3$. We reported here an easy handling and inexpensive iodine method to work in place as an efficient catalyst to promote the *C*-glycosidation of silylacetylenes.

Iodine has been employed as a catalyst to promote the *O*-glycosidation[5] and recently *C*-glycosidation of allytrimethylsilane.[6] However, no literature has been reported to date for the *C*-glycosidation of silylacetylene due to questions of potential reactivity between the acetylene moiety and iodine. We described now application of iodine to the *C*-glycosidation of tri-*O*-acetyl-D-glucal and silylacetylene with various types of R group at the other end of acetylene moiety (Eq. (1)).

Tri-*O*-acetyl-D-glucal **1** was treated with various silylacetylenes and iodine (1 equiv.) at room temperature to afford exclusively the α-acetylene glycoside products in high yields under mild conditions (Table 1).

The iodine-catalyzed *C*-glycosidation was first optimized with bis-trimethylsilylacetylene (entry 1). The reaction was carried out using iodine 0.5 M in dichloromethane (condition a)[7] to afford acetylene glycoside **2** in 78% isolated yield. In a dilute concentration solution of I_2 (0.08 M, condition b), only low yield of acetylene glycoside was observed. No reaction was obtained when using DMF as the solvent (condition c). Complete reaction was observed in 40 min (condition d) in acetonitrile. However the acetylene glycoside **2** was observed in lower yield than using CH_2Cl_2. Based on these results, the condition a was used as a general procedure for the *C*-glycosidation of other silylacetylenes; thus, the tri-*O*-acetyl-D-glucal (1 equiv.), silylacetylene (2 equiv.) and I_2 (1 equiv.) in 0.5 M concentration in dichloromethane. The methyl, phenyl and phenylthio groups at the other end of silylacetylenes were examined in entries 2–4, respectively. The reactions were completed in 45 min to 1 h due to the electronic effect of the electron donating substituents accompanied with the β-silyl stabilized carbocation intermediate. In the case of trimethylsilylphenyl-

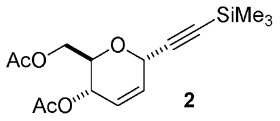
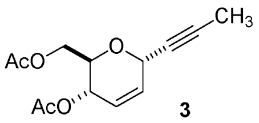
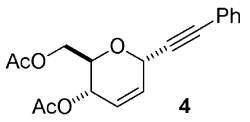
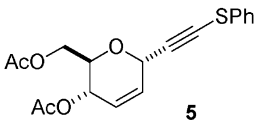
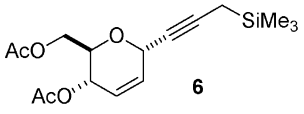
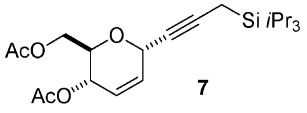
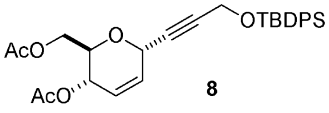
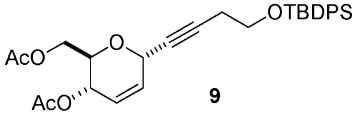
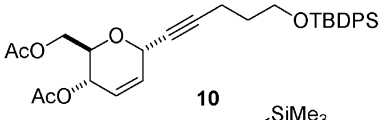
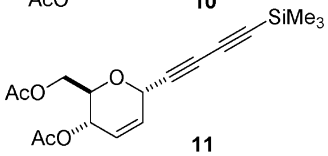
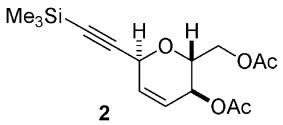
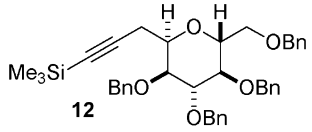
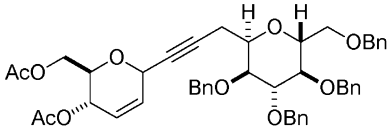


(1)

* Corresponding authors. Fax.: +66-38-390-354 (R.S.); Fax.: +81-52-789-4111 (M.I.); e-mail: rungnaph@buu.ac.th; isobem@agr.nagoya-u.ac.jp

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01540-5

Table 1. *C*-Glycosidation of tri-*O*-acetyl-D-glucal with various silylacetylenes

entry	silylacetylene	time (h)	Conditions	product	yield (%)
1	Me_3Si—≡—$SiMe_3$	16 h 16 h 16 h 40 min	a b c d	 **2**	78 11 0 33
2	Me_3Si—≡—CH_3	1 h	a	 **3**	80
3	Me_3Si—≡—Ph	1 h	a	 **4**	90
4	Me_3Si—≡—SPh	45 min	a	 **5**	38 (87)*
5	Me_3Si—≡—H	24 h	a	No reaction	0
6	Me_3Si—≡—$SiMe_3$	2 h	a	 **6**	30
7	Me_3Si—≡—Si iPr_3	3.5 h	a	 **7**	53
8	Me_3Si—≡—OTBDPS	4 h	a	 **8**	74
9	Me_3Si—≡—OTBDPS	1 h	a	 **9**	83
10	Me_3Si—≡—OTBDPS	45 min	a	 **10**	80
11	Me_3Si—≡≡—$SiMe_3$	5 h	a	 **11**	67
12	 **2**	24 h	a	No reaction	0
13	 **12**	2.5 h	a	 **13**	88

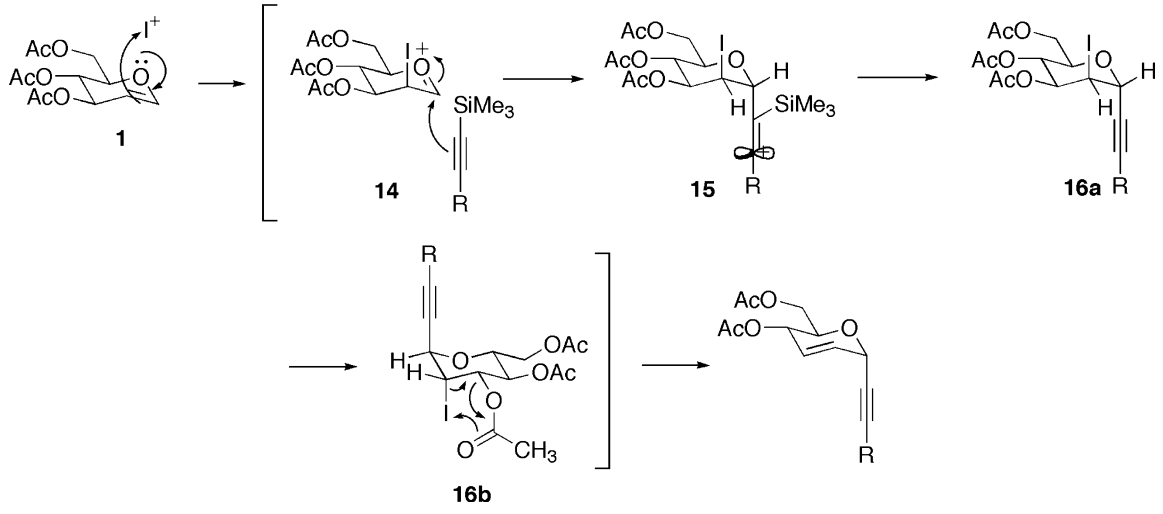
Condition ***a*** 0.5 M I_2, CH_2Cl_2, ***b*** 0.08 M I_2, CH_2Cl_2, ***c*** 0.5 M I_2, DMF, ***d*** 0.5 M I_2, CH_3CN
*compound **5** (38%) and diiodovinylsulfide-glycoside (49%)[8]

thioacetylene (entry 4), the 1:1.3 mixture of acetylene glycoside **5** and diiodovinylsulfideglycoside were obtained in 87% total yeilds. The formation of diiodovinylsulfide (49%) was resulted from the iodine addition to acetylene moiety.[8] Without substituent at the end of acetylene, no reaction was observed due to the lack of substitution stabilized effect (entry 5).[3]

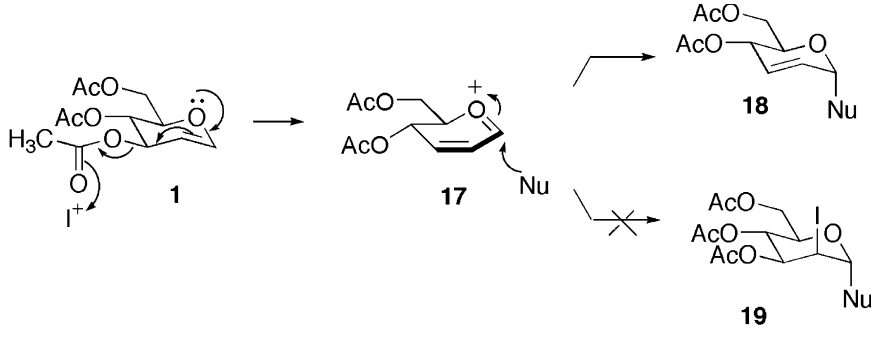
Extended carbon bonds of silylacetylenes were investigated in entries 6–11[9,10] to result in the formation of the acetylene glycosides in moderate to high yields. In the case of entries 8–10, when the homologation of carbon chain between the acetylene and TBDPS–ether was increased, the reaction was completed in the shorter time due to the relief of the destabilization effect by the ether group.[10] The efficiency of iodine was also tested to promote the *C*-glycosidation on the larger silylacetylene compounds (entries 12 and 13). The silylacetylene glycoside **2** failed to react with the D-glucal (entry 12) because of the destabilized effect of the ether ring oxygenation. Contrast to the result in entry 13, silylpropargyl-sugar **12** smoothly reacted with D-glucal to furnish exclusively the α-acetylene glycoside product **13** in 88% yield proving the generality of this methodology.

In terms of reaction mechanism, this process could involve the generation of different oxonium cation species from the Ferrier rearrangement of Lewis acid catalyzed *C*-glycosidation as depicted in Schemes 1 and 2.

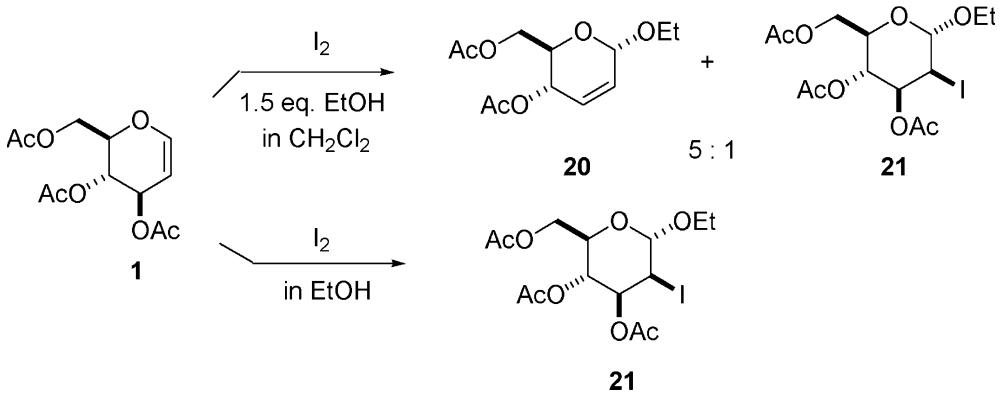
We believe the *C*-glycosidation reaction was initiated by the attack of a soft electrophilic iodonium to the double bond of tri-*O*-acetyl-D-glucal to form an iodo–oxonium carbocation **14**[11] (mechanism 1, Scheme 1) rather than attack to the acetate group at C-3 as Ferrier rearrangement in mechanism 2 (Scheme 2). This intermediate **14** can coordinate with silylacetylene at the anomeric position C-1 from the α-side. Concerted elimination of iodide and acetyl group at the C-3 position of intermediate **16b** resulted in the formation of acetylene glycoside. The iodo–oxonium mechanism was proposed on the basic of our result of the *O*-glycosidation of D-glucal with ethanol by iodine as shown in Scheme 3. It was observed that, upon treatment with 1.5 equiv. EtOH in CH_2Cl_2, the *O*-glycoside product was obtained as a 5:1 mixture of **20** and **21**. Without CH_2Cl_2, the *O*-glycosidation proceeds smoothly to give exclusively the iodo–tetrahydropyran product **21**[11] in the case of EtOH as a solvent. This result seems to indicate that the glycosidation should proceed via the



Scheme 1. Plausible mechanism 1.



Scheme 2. Ferrier rearrangement mechanism 2.



Scheme 3. *O*-Glycosidation of D-glucal and EtOH.

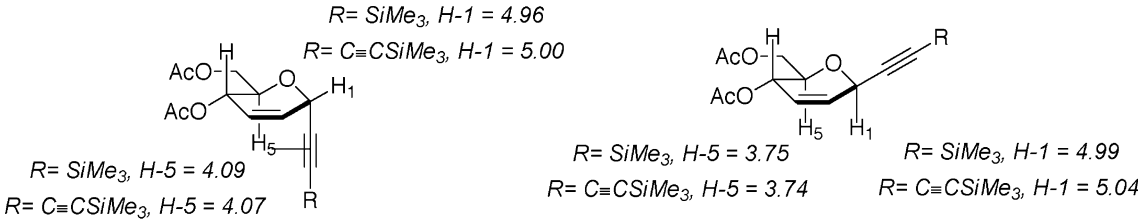


Figure 1. Chemical shifts of the α- and β-acetelene glycosides.

iodo–oxonium intermediate **14** to obtain the iodo–tetrahydropyran intermediate **16a**, then followed by iodine–acetate elimination.

The stereochemistry at the C-1 position of the acetylene glycoside products was proved to be exclusively α-orientation in all cases. The α-acetylene glycoside products were chemically proven through partial hydrogenation of the acetylene group to the corresponding vinyl one, the vinyl α-proton showing NOE with the H-5. Here we have established an empirical rule as follow. The chemical shifts of the H-5 in ^{1}H NMR were found between 4.07 and 4.09 ppm in case of R = TMS or C≡CTMS due to the anisotropic effect of the α-acetylene at the C-1 (Fig. 1). Comparing with the β-acetylene glycosides without anisotropic effect, the chemical shifts at the H-5 were observed between 3.74 and 3.77 which were summarized from a report by Tanaka et. al.[12] from epimerization product via cobalt complex. All of the H-5 chemical shifts of acetylene glycoside products in our experiments were observed at 4.05–4.18 ppm.[13] These results confirmed the α-oreintation of the acetylene glycoside products.

In conclusion, we have developed a convenient and easy procedure with high stereoselectivity for the *C*-glycosidation with various silylacetylenes using iodine-promoted reaction. The possible iodo–oxonium mechanism is also proposed in this report.

Acknowledgements

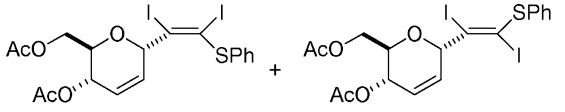
This research was financially supported by a grant from Thailand Toray Foundation, Faculty of Science (Burapha University) and JSPS Core University Exchange Program to R.S. Special thanks are due to Dr. Masaki Kuse (Nagoya University) and Dr. Roderick Bates (CRI) for mechanism discussion and to Mr. S. Kitamura for combustion analyses. The first author R.S. stayed in Nagoya University during the period of March–June, 2003.

References

1. (a) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, 1995; (b) Levy, D. E.; Tang, C. *The Chemisty of C-Glycosides*; Pergamon: Oxford, 1995; (c) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913–9959.
2. (a) Takai, S.; Isobe, M. *Org. Lett*. **2002**, *4*, 1183–1186; (b) Hosokawa, S.; Isobe, M. *J. Org. Chem*. **1999**, *64*, 37–48; (c) Saeeng, R.; Isobe, M. *Heterocycles* **2001**, *54*, 789–798; (d) Saeeng, R.; Isobe, M. *Tetrahedron Lett*. **1999**, *40*, 1911–1914.
3. (a) Ichikawa, Y.; Isobe, M.; Konobe, M.; Goto, T. *Carbohydr. Res*. **1987**, *171*, 193–199; (b) Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun*. **1998**, 2665–2676.
4. Yadav, J. S.; Reddy, B. V. S.; Raju, A. K.; Rao, C. V. *Tetrahedron Lett*. **2002**, *43*, 5437–5440.
5. Capaccio, C. I.; Varela, O. *J. Org. Chem*. **2002**, *67*, 7839–7846.
6. Yadav, J. S.; Reddy, B. V. S.; Rao, C. V.; Chand, P. K.; Prasad, A. R. *Synlett* **2001**, 1638–1640.
7. **General procedure**: To a solution of tri-*O*-acetyl-D-glucal (0.5 mmol) and the trimethylsilylacetylene nucleophile (1.0 mmol) in anhydrous CH_2Cl_2 was added iodine (0.5 mmol) at room temperature. After TLC showed the

complete conversion, the reaction was diluted with CH_2Cl_2 and washed with a 5:1 (v/v) mixture of satd aq. $Na_2S_2O_3$ and satd aq. $NaHCO_3$, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography.

8. The diiodovinylsulfideglycoside was obtained as a mixture in 49%.



9. (a) Tsukiyama, T.; Isobe, M. *Tetrahedron Lett*. **1992**, *33*, 7911–7914; (b) Tsukiyama, T.; Peter, S. C.; Isobe, M. *Synlett* **1993**, 413–414.
10. Isobe, M.; Saeeng, R.; Nishizawa, R.; Konobe, M.; Nishikawa, T. *Chem. Lett*. **1999**, 467–468.
11. The electrophilic iodonium attacks at the β-side due to stereoelectronic effect. This evidence can be observed from the *trans*-relationship of the proton at C-1 and C-2 of α-ethoxy-β-iodo glycoside **21** which show the coupling constant value $J_{2,3}=4.5$ Hz.
12. (a) Tanaka, S.; Tsukiyama, T.; Isobe, M. *Tetrahedron Lett*. **1993**, *34*, 5757–5760; (b) Tanaka, S.; Isobe, M. *Tetrahedron* **1994**, *50*, 5633–5644.
13. Compound **2**: Mp = 61–62°C; $[\alpha]_D^{26}=-47.8$ (*c* 1.95, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 1.85 (3H, d, $J=2.0$ Hz, H-3′), 2.07 (3H, s, *Ac*), 2.09 (3H, s, *Ac*), 4.09 (1H, ddd, $J=9.0$, 5.0, 3.0 Hz, H-5′), 4.20 (1H, dd, $J=12.0$, 3.0 Hz, H-6a), 4.24 (1H, dd, $J=12.0$, 5.0 Hz, H-6b), 4.92 (1H, m, H-1), 5.27 (1H, ddd, $J=9.0$, 4.0, 2.0 Hz, H-4), 5.73 (1H, dt, $J=10.0$, 2.0 Hz, H-2), 5.86 (1H, ddd, $J=10.0$, 4.0, 2.0 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 3.7, 20.8, 21.0, 63.1, 64.1, 64.9, 69.7, 75.1, 83.3, 124.8, 129.9, 170.4, 171.0; IR (KBr): 2956, 2923, 2287, 2219, 1740, 1437, 1371, 1230, 1053, 809 cm^{-1}. Anal calcd for $C_{13}H_6O_5$: C, 61.90; H, 6.39. Found: C, 61.93; H, 6.33.