Electronic Factors in the *C*-Glycosidation with Silylacetylene

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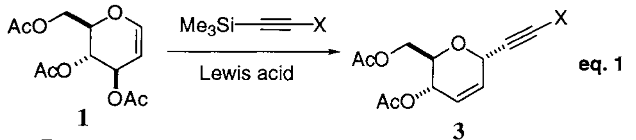
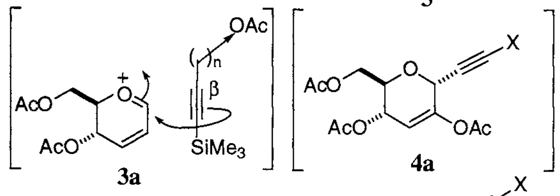
Two kinds of electronic factors have been clarified to control the reactivity in alkynylation of glycals with silylacetylenes. One is that the reactivity of nucleophile silylpropargyl alcohol derivative largely depends on the protecting group. The second factor is found in the similar electrophiles as oxocarbenium intermediates that were generated from glucals or galactals. Diminished reactivity was found with the 4-axial substituents such as acetoxy or methoxy group.

During our development of *C*-glycosidation with silyl acetylenes,[1] we found extremely low reactivity of silylpropargyl acetate (X = CH_2OAc) with tri-*O*-acetyl-D-glucal (**1**) under various acidic conditions (eg. $TiCl_4$ or $SnCl_4$) in dichloromethane solvent (eq. 1). We anticipated to improve this low reactivity since this type of glycoside product was considered as an attractive precursor to build up a cyclic ether unit of ciguatoxin.[2] The current reactions with protected silylpropargylic alcohols have been reinvestigated and finally we found a good condition. The process and factors connecting to the reactivity are described.





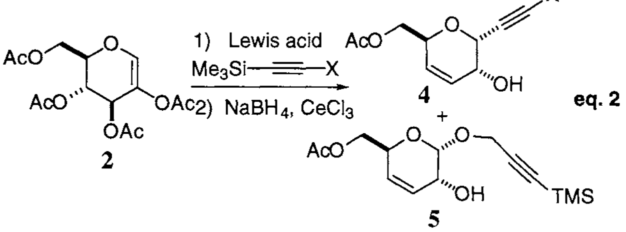


Table 1. Effects of the substituents X on the silylacetylene to the alkynylation of D-glucals **1** and **2**

Entry	SM	X	Lewis Acid[a]	Time /min	Product	Yield /%
1	1	$SiMe_3$	$SnCl_4$	20	**3**	98[c]
2	1	CH_2OAc	$SnCl_4$ or $TiCl_4$	20	**3**	0
3	1	$(CH_2)_2OAc$	$TiCl_4$	120	**3**	22
4	1	$(CH_2)_3OAc$	$TiCl_4$	100	**3**	36
5	1	$(CH_2)_4OAc$	$TiCl_4$	500	**3**	59
6	1	CH_2OPiv	$SnCl_4$	20	**3**	0
7	1	CH_2OBz	$SnCl_4$	20	**3**	0
8	1	CH_2OBn	$SnCl_4$	20	**3**	44
9	1	$CH_2OTBDMS$	$SnCl_4$	20	**3**	42
10	1	$CH_2OTBDPS$	$SnCl_4$	20	**3**	84
11	1	$CH_2OTBDPS$	$TiCl_4$	40	**3**	38
12	1	$CH_2OTBDPS$	$BF_3{\bullet}OEt_2$	35	**3**	44
13	2	$SiMe_3$	$SnCl_4$	20	**4**	76[c]
14	2	CH_2OBn	$SnCl_4$	20	**4**	27
15	2	$CH_2OTBDMS$	$SnCl_4$	40	**5**	35[b]
16	2	$CH_2OTBDPS$	$SnCl_4$	40	**4**	44

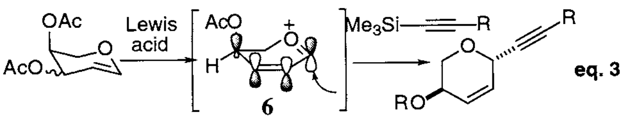
[a] Reaction conditions: entries 6-12 the reactions were carried out in the presence of $SnCl_4$ 0.2%, entries 14-16 , $SnCl_4$ 5%. [b] The *O*-glycoside compound was obtained as a product. [c] See Reference 3.

The reaction mechanism suggests a developing cationic charge to the β-carbon of the nucleophile silylacetylene that is usually stabilized by the silyl group.[1,3] On the other hand, this carbonium ion is destabilized by the presence of the electron-withdrawing acyloxy group at the propargylic position (eq. 1, X= $(CH_2)_nOAc$; and see **3a**). In principle any oxygen function has an electronegative property and thus affecting the destabilization, however this electronic factor would effect in a different degree to the reactivity depending upon the protective group. So we have systematically examined the substituent effect of propargylic alcohol protection (eq. 1 and eq. 2) and the results are summarized in Table 1. All of the silylpropargylic derivative having acyloxy groups (acetyl, pivaloyl or benzoyl as entries 2, 6 and 7) never afforded the product except in the cases when the carbon chain which connected to the acetate moiety was elongated (X = $(CH_2)_nOAc$, $n > 1$). The yields of products increased with the higher homologous acetates in longer reaction time as shown in entries 3, 4 and 5. This is due to the relief of the destabilization effect by the acetate group (screen effect).

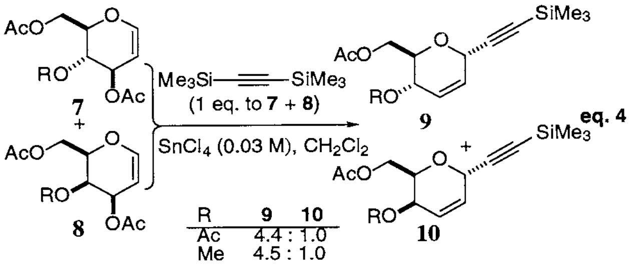
In order to overcome the problems of *C*-glycosidation of the propargylic alcohol (as entries 2, 6 and 7) which are so dramatically different from entry 1 in that **1** gave **3** (X = $SiMe_3$) in almost quantitative yield,[4] the benzyl- or *tert*-butyldimethylsilyl groups were employed as the protecting group for the propargylic alcohol to react with glucal **1**. The products **3** were obtained in moderate yields (entries 8 and 9). These results are not perfectly good but nevertheless quite encouraging that an etherial oxygen can weaken the electronic effect to provide products. Finally, we found that the reaction of *tert*-butyldiphenylsilylether (X= $CH_2OTBDPS$) with **1** afforded **3** as high as in 84% yield[5] (entry 10).

These facts indicate that different reactivities are primarily derived from different degree of electronegativity by the acyl groups to destabilize the cationic intermediate of the silylacetylenes. Reactivity difference is secondly attributed to steric factors as clearly seen in the cases between entries 9 and 10. The bulky SiPh$_2$^{t}Bu group would largely prevent the coordination of tin tetrachloride from the neighboring oxygen atom. Among the three Lewis acids in entries 10, 11 and 12, tin tetrachloride (the strongest acid) gave the best result. Under such best combination, **2** was reacted with various different protected propargylic alcohols (entries 14, 15 and 16). The reactions were carried out in high concentration of substrate and Lewis acid due to the lower reactivity of 2-acetoxy-D-glucal **2** with the silylpropargylalcohol to give **4** via **4a**.[3] The products[6] were obtained in moderate yield (entries 14, 15 and 16). In case of *tert*-butyldimethylsilyl protected alcohol (entry 15), the *O*-glycoside product **5** was observed under the condition of high concentration of Lewis acid which affected the deprotection of silyl group.

The second study will pay attention on the electronic factor at the C-4 protecting group of the electrophilic sugar for the approach of the silylacetylene nucleophile. In our previous studies, we reported the 1,4-*anti* selective introduction of carbon nucleophiles into pentose glycal.[7a] This selective *C*-glycosidation was observed during the course of synthetic studies on the ABC-segment of ciguatoxin leading to a single stereoisomer.[7b] The *C*-4-AcO-group in an axial orientation is more stable than the equatorial one by 1.5 kcal/mol.[7a, 8] At the transition state of the *C*-glycosidation (**6**), the orbital interaction results the nucleophilic addition from α-orientation at C-1 (eq. 3).

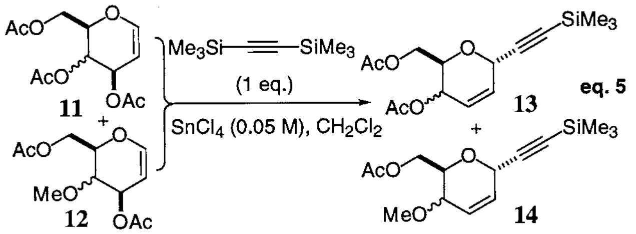


These reports prompted us to do following mixing experiments with glucal and galactal derivatives to investigate the stabilization effect at the C-4 position by employing two different protecting groups. This is the first C-glycosidation example of galactal with silylacetylene. The glucal type always gave higher yields than the galactal type during *C*-glycosidation (eq. 4). The reactions were carried out in the presence of SnCl$_4$ (0.03M) to afford the 1,4-*syn* and 1,4-*anti* products in almost similar ratio (around 4.5:1)[9] in both cases of different protecting groups. These results indicated the stereoelectronic effect at the C-1 on the approach of silylacetylene nucleophile into the *axial* face when the hexopyranoses were served as starting material.



R	9 10
Ac	4.4 : 1.0
Me	4.5 : 1.0

Following experiments were attempted by mixing equimolar amounts of each set of two compounds having the same orientation (eq. 5). When 4-acetoxy and 4-methoxy in either of the glucal or galactal combination were subjected to the *C*-glycosidation conditions, the ratio of the product was 1:1. The effect of the protecting group at the C-4 of the hexopyranose were not observed in these mixing reactions.



11-(4-αOAc) + **12**-(4-αOMe) → **13**-(4-αOAc) + **14**-(4-αOMe)
1 : 1
11-(4-βOAc) + **12**-(4-βOMe) → **13**-(4-βOAc) + **14**-(4-βOMe)
1 : 1

The substitutent effects at the C-4 position are completely opposite between the pento- and hexo-pyranoside cases.

The present studies on electronic factors of the nucleophilic silylacetylene and the electrophilic sugar derivative have now been reported to advance further development of *C*-glycosidation reactions.

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References and Notes

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3 An intermediate **4a** in eq. 2 is reported in the following paper. T. Tsukiyama and M. Isobe, *Tetrahedron Lett.*, **33**, 7911 (1992).

4 T. Tsukiyama, S. C. Peters, and M. Isobe, *Synlett*, **1993**, 413.

5 Compound 3 (X = CH$_2$OTBDPS), ^{1}H-NMR (300 MHz, CDCl$_3$), δ 1.05 (9H, s, *t-Bu*), 2.08 (3H, s, *Ac*), 2.10 (3H, s, *Ac*), 4.01 (1H, ddd, *J* = 9.0, 5.0, 2.5 Hz, H-5), 4.16 (1H, dd, *J* = 12.5, 2.5 Hz, H-6a), 4.24 (1H, dd, *J* = 12.5, 5.0 Hz, H-6b), 4.38 (2H, d, *J* = 2.0 Hz, H-3'), 4.94 (1H, brs, H-1), 5.30 (1H, dm, *J* = 9.0 Hz, H-4), 5.73 (1H, dt, *J* = 11.0, 1.5 Hz, H-3), 5.78 (1H, dt, *J* = 11.0, 1.5 Hz, H-2), 7.35-7.48 (6H, m, *Ph*), 7.68-7.74 (4H, m, *Ph*); MS (EI) *m/z* 449 (M$^+$-OAc); Found: C, 68.75; H, 6.83%. Anal. Calcd for C$_{29}$H$_{34}$O$_6$Si; C, 68.75 ; H, 6.76%.

6 Compound 4 (X = CH$_2$OTBDPS), ^{1}H-NMR (300 MHz, CDCl$_3$), δ 1.04 (9H, s, *t-Bu*), 1.73 (1H, br, *OH*), 2.08 (3H, s, *Ac*), 4.10 (2H, d, *J* = 5.0 Hz, H-6), 4.23 (1H, m, H-2), 4.34-4.41 (1H, m, H-5), 4.41 (2H, d, *J* = 1.5 Hz, H-3'), 4.85 (1H, dd, *J* = 5.5, 1.5 Hz, H-1), 5.61 (1H, dt, *J* = 10.5, 2.0 Hz, H-4), 5.76 (1H, dt, *J* = 10.5, 2.0 Hz, H-3), 7.36-7.49 (6H, m, *Ph*), 7.67-7.74 (4H, m, *Ph*); MS (EI) *m/z* 464 (M$^+$); Found: C, 69.81; H, 7.08%. Anal. Calcd for C$_{27}$H$_{32}$O$_5$Si; C, 69.80; H, 6.94%.

7 a) S. Hosokawa, B. Kirschbaum, and M. Isobe, *Tetrahedron Lett.*, **39**, 1917 (1998). b) S. Hosokawa and M. Isobe, *Synlett*, **1996**, 351.

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9 a) The yield of product from *C*-glycosidation of Bistrimethylsilylacetylene with **7** (R= Ac) and (R= Me) were 85 and 56% and the yield with **8** (R= Ac) and (R= Me) were 68 and 60%, respectively. b) The mixing reaction as eq. 4 and eq. 5 were conducted with only 1 equiv. of the reagent and interrupted while starting materials were remained, so that the products were kinetically controlled and the yields being 10~60%.