Regioselective Reductive Ring Opening of Benzylidene Acetals Using Triethylsilane and Iodine

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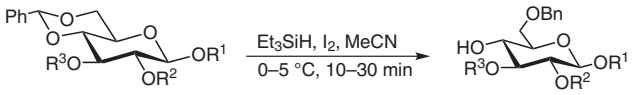
Abstract: Novel reaction conditions have been developed for the regioselective reductive ring opening of benzylidene acetals in carbohydrate derivatives using triethylsilane and molecular iodine. The reaction is fast, compatible with most of the functional groups encountered in the oligosaccharide synthesis, and yields were excellent. The reaction conditions are equally effective in thioglycosides.

Key words: carbohydrate, benzylidene acetal, regioselective, iodine, triethylsilane

Judicious protection of hydroxyl groups in the polyhydroxylated carbohydrate skeleton plays an important role in the synthesis of complex oligosaccharides and natural products.[1] Although chemistry for the selective protection and deprotection of carbohydrates has been extensively studied, there is still a need for improved methodology. Benzylidene acetals have found extensive application in oligosaccharide synthesis because of the group's utility for the simultaneous protection of two hydroxyl groups and its removal under acidic or neutral conditions.[2] Transformation of a benzylidene acetal to a benzyl or benzoyl group are useful conversions in the synthesis of oligosaccharides. The 4,6-*O*-benzylidene acetal in carbohydrate derivatives can be regioselectively opened to give either 6-O-benzylated or 4-O-benzylated derivatives depending on the reducing agent used.[2] For the selective removal of benzylidene acetasl a number of methods are available in the literature, including $NaBH_3CN$–HCl,[3] $NaBH_3CN$–TFA,[4] Et_3SiH–TFA,[5] Et_3SiH–$BF_3{\cdot}OEt_2$[6] for the preparation of 6-O-benzylated derivatives and $AlCl_3$–$LiAlH_4$,[7] DIBAL-H,[8] Me_3NBH_3–$AlCl_3$,[4] $BH_3{\cdot}$THF–TMSOTf,[9] Bu_2BOTf–$BH_3{\cdot}$THF,[10] $CoCl_2$–$BH_3{\cdot}$THF[11] and others[12] for the preparation of 4-O-benzylated derivatives. Nevertheless, many of these methods for the preparation of 6-O-benzylated carbohydrate derivatives have shortcomings such as formation of byproducts, use of expensive reagents, incompatibility with other functional groups, and harsh reaction conditions. Therefore, development of mild, efficient, and metal-free methodology for the regioselective ring opening of benzylidene acetals is still attractive. During the synthesis of complex oligosaccharides[13] we applied Et_3SiH–TFA[5] or Et_3SiH–$BF_3{\cdot}OEt_2$[6] to the regioselective opening of 4,6-O-benzylidene acetals in sugar derivatives to obtain 6-O-benzylated derivatives. However, in some cases we obtained poor yields because of the instability of some functional groups under the reaction conditions. Alternative use of $NaBH_3CN$–HCl·Et_2O requires repeated purification of the products to remove borate salts, and the Et_3SiH–TFA system did not work in D-galactose derivatives. Thus we sought to explore other possible reagent combinations for the reductive ring opening of benzylidene acetals of D-glucose and D-galactose derivatives. We envisaged that use of a Et_3SiH and molecular iodine combination could serve to improve the yield of the products. We disclose herein convenient reaction conditions for the regioselective ring opening of 4,6-*O*-benzylidene acetals of carbohydrate derivatives into 6-O-benzylated derivatives using a combination of triethylsilane–molecular iodine (Scheme 1).



Scheme 1 Regioselective ring opening of benzylidene acetal using triethylsilane and iodine.

In a set of initial experiments, methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) was allowed to stir with triethylsilane and iodine in MeCN at room temperature, varying the quantity of reagents. It was observed that treatment of compound **1** with 1.5 equiv. of Et_3SiH and 0.2 equiv. of iodine in MeCN could efficiently produce methyl 2,3-di-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranoside (**14**) in 10 min at room temperature. Reducing the quantity of reagents resulted in an incomplete transformation even after 5 h. Use of other organic solvents such as CH_2Cl_2, THF produced a similar result in the formation of compound **14**. Following these reaction condition, a series of 4,6-*O*-benzylidene acetal derivatives derived from D-glucose and D-galactose was transformed into the corresponding 6-O-benzylated derivatives (Scheme 1, Table 1). Noteworthy features are the absence of formation of 4-O-benzylated derivatives and stability of the majority of the functional groups used for the protection of hydroxy and amino groups in carbohydrates. Furthermore benzylidene acetals of thio- and selenoglycosides can also be regioselectively opened without any side reaction (Table 1, entries 8, 10 and 12); despite the fact that iodine has been used for thioglycoside activation.[14] The reaction conditions were equally effective in D-glucose and D-

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galactose derivatives unlike the Et_3SiH–TFA combination,[5] which can be used in D-glucose derivatives only. Finally, stereochemistry at the anomeric center does not influence the product formation. In order to establish the significant advantages of the present protocol, a comparative study was also carried out with the existing literature reported reaction conditions (Table 2) from which it is clear that the present reaction condition produces higher yields of the product in shorter time.

In summary, a novel, mild reaction condition has been developed for the regioselective reductive ring opening of benzylidene acetals in the carbohydrate backbone using triethylsilane and molecular iodine. This straightforward reaction is rapid and high yielding and can be scaled-up. Use of readily available reagents, without requirement of heavy metal salts, high boiling solvents or Lewis acids makes this reaction protocol an attractive alternative to existing methodology.

Table 1 Regioselective Ring Opening of Benzylidene Acetal of Carbohydrate Derivatives Using Et_3SiH and I_2

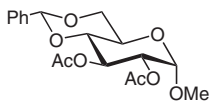
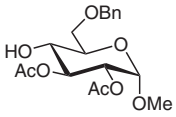
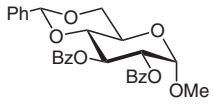
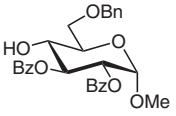
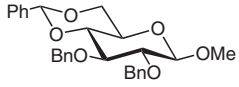
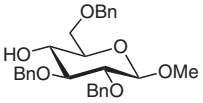
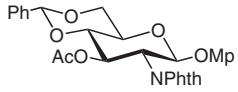
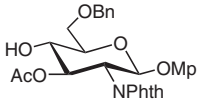
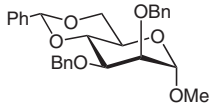
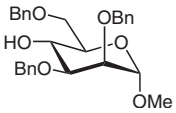
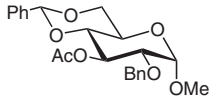
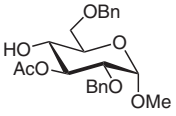
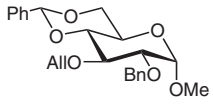
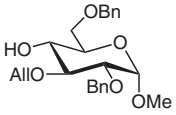
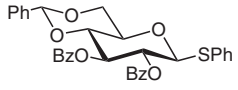
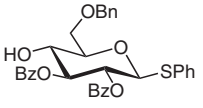
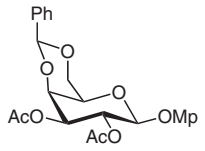
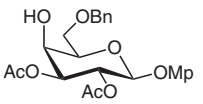
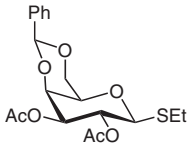
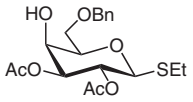
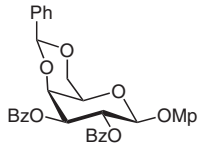
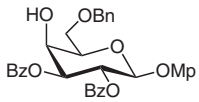
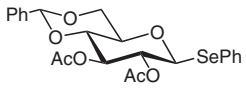
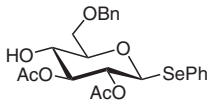
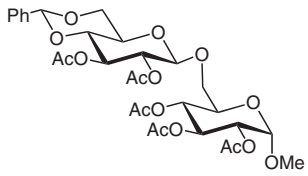
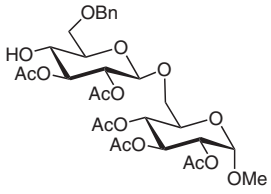
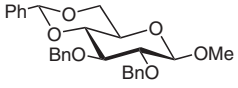
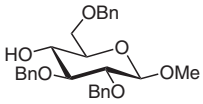
Entry	Substrates[a]	Products[a]	Time (min)	Yield (%)
1	 **1**	 **14**	10	95[15]
2	 **2**	 **15**	10	92[12b]
3	 **3**	 **16**	10	92[16]
4	 **4**	 **17**	15	87[17]
5	 **5**	 **18**	10	90[7]
6	 **6**	 **19**	10	92[18]
7	 **7**	 **20**	10	88[19]
8	 **8**	 **21**	10	82[20]
9	 **9**	 **22**	25	90

Table 1 Regioselective Ring Opening of Benzylidene Acetal of Carbohydrate Derivatives Using Et_3SiH and I_2 (continued)

Entry	Substrates[a]	Products[a]	Time (min)	Yield (%)
10	 **10**	 **23**	20	80[21]
11	 **11**	 **24**	25	88[22]
12	 **12**	 **25**		
13	 **13**	 **26**	30	85

[a] Mp: 4-methoxyphenyl, NPhth: N-phthalimido, All: allyl, Bn: benzyl, Bz: benzoyl. Known compounds gave ^1H NMR and ^{13}C NMR spectra that matched the data reported in the cited references.

Table 2 Comparison of Reaction Conditions for the Preparation of 6-*O*-Benzyl Carbohydrate Derivatives

Substrate	Product	Reagent	Time (min)	Yield (%)
 **3**	 **16**	$NaBH_3CN$–HCl·Et_2O	5	87[3]
		Et_3SiH–TFA	180	80[5]
		Et_3SiH–BF_3·OEt_2	240	84[a]
		Et_3SiH–I_2	10	92[a]

[a] This study.

Typical Experimental Conditions

To a solution of compound **1** (1 mmol) in MeCN (5 mL) were added triethylsilane (1.5 mmol) and iodine (0.2 mmol) at 0–5 °C, and the reaction mixture was allowed to stir at the same temperature for the appropriate time (Table 1). After completion of reaction (TLC), the reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was successively washed with sat. $NaHCO_3$ and H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using hexane–EtOAc (4:1) as eluent to furnish pure compound **14** (95%).[23]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(22) Zhang, Z.; Magnusson, G. *J. Org. Chem.* **1996**, *61*, 2383.
(23) Spectroscopic data for novel products are presented below. To aid assignments, data were taken after acetylation of the products.

4-Methoxyphenyl 2,3,4-Tri-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranoside (Acetylated 22)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.17 (m, 5 H, ArH), 6.87 (d, *J* = 9.0 Hz, 2 H, ArH), 6.70 (d, *J* = 9.0 Hz, 2 H, ArH), 5.40 (d, *J* = 3.3 Hz, 1 H, H-4), 5.31 (dd, *J* = 7.9 Hz each, 1 H, H-2), 4.99 (dd, *J* = 10.4, 3.4 Hz, 1 H, H-3), 4.83 (d, *J* = 7.9 Hz, 1 H, H-1), 4.48 (d, *J* = 11.9 Hz, 1 H, $PhCH_{2a}$), 4.36 (d, *J* = 11.9 Hz, 1 H, $PhCH_{2b}$), 3.87–3.84 (m, 1 H, H-5), 3.68 (s, 3 H, OCH_3), 3.52–3.44 (m, 2 H, H-$6_{a,b}$), 2.01, 1.99, 1.93 (3 s, 9 H, 3 $COCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3, 170.1, 169.5 (3 *C*OCH_3), 156.0–114.9 (ArC), 101.1 (C-1), 73.9, 72.9, 71.5, 69.4, 67.9, 67.8, 55.8, 21.1, 21.0, 20.9 (3 CO*C*H_3). ESI-MS ($C_{26}H_{30}O_{10}$): *m/z* = 525.1 [M + Na]$^+$.

Phenyl 2,3,4-Tri-*O*-acetyl-6-*O*-benzyl-1-seleno-β-D-glucopyranoside (Acetylated 25)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.21 (m, 10 H, ArH), 5.15 (t, *J* = 9.2 Hz, 1 H, H-3), 5.01 (t, *J* = 9.8 Hz, 1 H, H-2), 4.97 (t, *J* = 9.2 Hz, 1 H, H-4), 4.88 (d, *J* = 9.9 Hz, 1 H, H-1), 4.53–4.46 (2 d, *J* = 11.8 Hz, 2 H, $PhCH_2$), 3.67–3.63 (m, 1 H, H-5), 3.56–3.54 (m, 2 H, H-$6_{a,b}$), 2.14, 2.05, 1.96 (3 s, 9 H, 3 $COCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4, 169.6, 169.4 (3 *C*OCH_3), 138.2–127.6 (ArC), 81.4 (C-1), 78.9, 74.4, 73.9, 71.3, 69.4 (2 C), 21.1, 20.9 (2 C) (3 CO*C*H_3). ESI-MS ($C_{25}H_{28}O_8Se$): *m/z* = 559.1 [M + Na]$^+$.

Methyl (2,3,4-Tri-*O*-acetyl-6-*O*-benzyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (Acetylated 26)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.24 (m, 5 H, ArH), 5.43 (t, *J* = 10.0 Hz each, 1 H, H-3_A), 5.16 (t, *J* = 9.4 Hz each, 1 H, H-4_A), 5.03 (t, *J* = 9.5 Hz each, 1 H, H-3_B), 4.96 (dd, *J* = 7.9 Hz each, 1 H, H-2_B), 4.90 (t, *J* = 9.4 Hz each, 1 H, H-4_B), 4.88 (d, *J* = 3.6 Hz, 1 H, H-1_A), 4.82 (dd, *J* = 10.1, 3.6 Hz, 1 H, H-2_A), 4.55 (d, *J* = 11.9 Hz, 1 H, $PhCH_{2a}$), 4.52 (d, *J* = 7.9 Hz, 1 H, H-1_B), 4.48 (d, *J* = 11.9 Hz, 1 H, $PhCH_{2b}$), 3.94–3.89 (m, 2 H, H-6_{abA}), 3.65–3.61 (m, 1 H, H-5_B), 3.55–3.51 (m, 3 H, H-5_A, H-$6_{a,bB}$), 3.37 (s, 3 H, OCH_3), 2.06, 2.03, 1.98, 1.89 (4 s, 18 H, 6 $COCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4, 170.1, 170.0, 169.7, 169.6, 169.4 (6 *C*OCH_3), 137.9–128.1 (ArC), 101.2 (C-1_B), 96.8 (C-1_A), 73.9, 73.7, 73.3, 71.6, 71.2, 70.6, 69.7, 69.4, 69.2, 68.5, 68.3, 55.5 (OCH_3), 21.1 (2 C), 21.0 (2 C), 20.9 (2 C). ESI-MS ($C_{30}H_{40}O_{16}$): *m/z* = 679.2 [M + Na]$^+$.