Note

Cyanuric chloride/sodium borohydride: a new reagent combination for reductive opening of 4,6-benzylidene acetals of carbohydrates to primary alcohols

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Cyanuric chloride/Sodium borohydride: A new reagent combination for reductive opening of 4,6-benzylidene acetals of carbohydrates to primary alcohols

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Abstract

In the first such example, $NaBH_4$ in combination with cyanuric chloride (TCT) has been used to obtain 6-hydroxy-4-benzyl ether derivatives from 4,6-benzylidene acetals of carbohydrates. The nature of hydride donor determines the regioselectivity of acetal opening. High regioselectivity, scope for using a broad range of substrates, functional group tolerance, mild reaction conditions, easy handling process, inexpensive reagents and wide application mark the benefits of the newly developed reagent system.

Keywords

Benzylidene derivative reductive opening, Sodium borohydride, TCT, Primary OH

Success story of glycobiology is largely sustained by rapid progress in glycochemistry.[1] The glycochemical assembly of oligosaccharides from monosaccharide building blocks often requires orthogonally protected donors or acceptors due to the presence of several hydroxyl groups. Protection of a pair of appropriately oriented 1,3 and also 1,2 hydroxy groups as the *O*-benzylidene acetal[2] is one of the most frequently used reactions in glycochemistry.[3] This is because the acetals are highly stable under alkaline/basic conditions and their removal can be achieved at will using acidic reagents. These derivatives are therefore extremely useful in multi-step synthetic operations involving such substrates. A plethora of methods are available for regioselective opening of benzylidene acetals, but only a few of these are widely used.[4] In general Lewis acids such as $AlCl_3$,[5] $BF_3.Et_2O$,[6] or triflates[6-8] have been used in combination with hydrides such as $BH_3.THF$,[6-8] LAH,[9] and DIBAL-H[10] to open the benzylidene acetals towards primary alcohol. The reagent combinations used are mostly moisture sensitive ($AlCl_3$ or $BF_3.Et_2O$, triflates), expensive (metal triflates), lacking in functional group tolerance such as ester and amides (LAH,

DIBAL-H), unstable at room temperature (BH_3.THF needs additive), or dependent on the nature of the protective group[4] at C3 and often lead to complete hydrolysis of the acetal ring as a major side reaction.

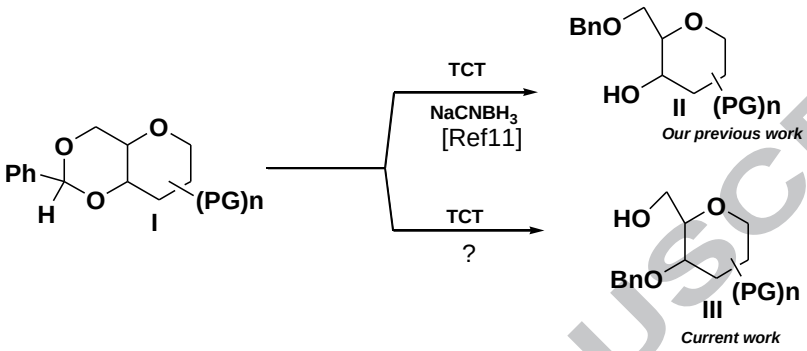
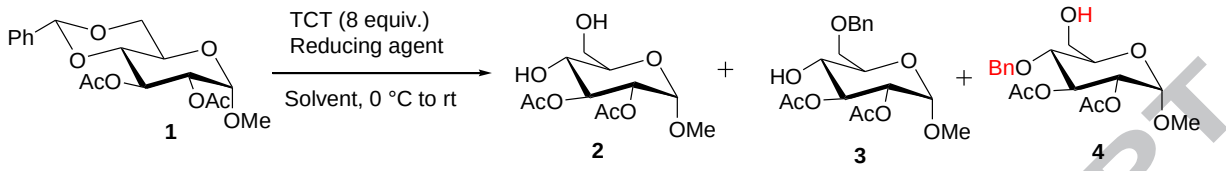


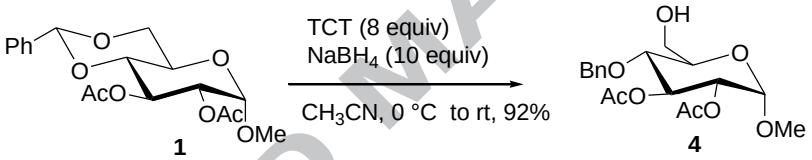
Fig 1: Cyanuric chloride (TCT) catalysed regioselective reductive ring opening of benzylidene acetals **I** to give primary alcohols **II** or secondary alcohols **III**

The use of harsh reaction conditions and environmentally hazardous expensive reagents always demand the development of new acid/reducing agent combinations. In continuation of our recent success in the regioselective benzylidene ring opening to afford secondary OH,[11] herein we present sodium borohydride in conjunction with cyanuric chloride [commercially known as 2,4,6-trichloro-1,3,5-triazene (TCT)] as an efficient, mild and inexpensive reagent combination for regioselective benzylidene ring opening towards primary OH. In order to find out the appropriate reducing agent which can work in combination with TCT to give reverse regioselectivity, we took 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-methyl-α-D-glucopyranoside as model substrate. A number of reducing agents were applied at room temperature under the condition optimized by us in our previous communication[11] (see SI, table 1). Depending on hydride donor and solvent, we initially obtained three products, namely **2**, **3**, and **4** (scheme 1). Reducing agents Et_3SiH and DIBAL-H gave only the 4-OH product in moderate to low yield (SI, Table1 entries 2, 3). $LiAlH_4$ and $NaB(OAc)_3H$ failed to give any desired product at room temperature even after prolonged reaction time (SI, Table 1, entries 4a, 5), though heating the reaction mixture to reflux with LAH yielded the corresponding 4,6-diol **2** exclusively (SI, Table 1 entry 4b).



Scheme 1: Opening of 4,6-*O*-benzylidene acetal in presence of TCT and different hydride donors (SI table1)

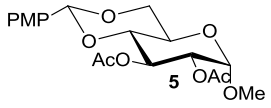
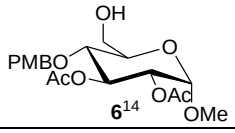
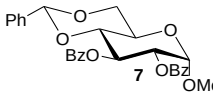
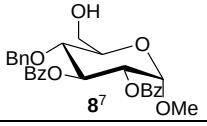
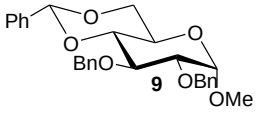
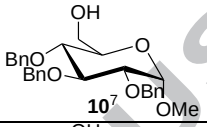
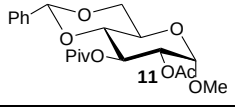
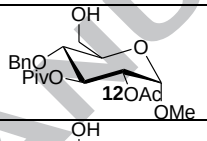
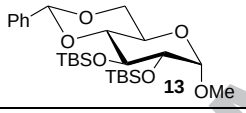
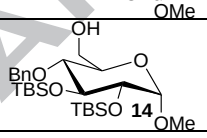
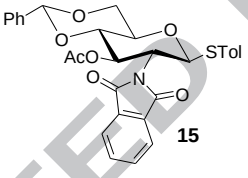
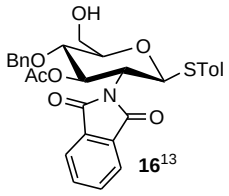
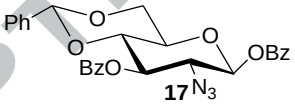
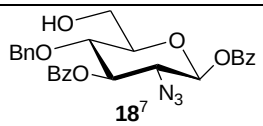
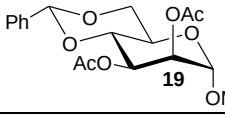
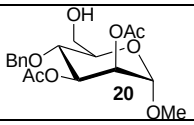
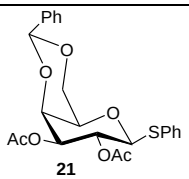
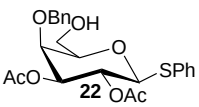
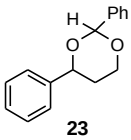
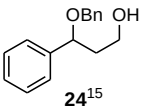
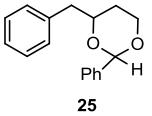
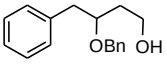
We then became interested to examine the fate of benzylidene derivative **1** using $NaBH_4$ and TCT in acetonitrile. To the best of our knowledge, there is no report of benzylidene ring opening using $NaBH_4$ as reducing agent. But we were delighted to see the complete consumption of the starting material **1** with formation of a new spot in TLC, Rf value of which was different from those of the products **2** and **3** (scheme 2). The structure of the product was assigned as **4**[12] on the basis of ^1H and ^{13}C NMR.



Scheme 2: Opening of 4,6-*O*-benzylidene acetal to obtain 6-OH exclusively under TCT/$NaBH_4$ condition

Acetonitrile was found to be the best solvent for this transformation. Employment of other nonprotic solvents like DCM or THF (SI, table 1 entries 8, 9) failed to give the desired product in satisfactory yield, whereas a protic solvent such as MeOH led to the completely hydrolyzed product (**2**). The fact that $NaBH_4$ has not been utilised earlier for benzylidene opening led us to study the fate of **1** with $NaBH_4$ along with other Lewis or Bronsted acids (SI, Table2). Except dry HCl (SI, table 2, entry 15) all other acids failed to give satisfactory yield. However, TBS and other acid sensitive protecting groups are susceptible to cleavage in presence of dry HCl, which restricts its use.

Table 1: Substrate scope of the TCT/$NaBH_4$ mediated benzylidene ring opening

Entry	Substrate[a]	Product[b]	Yield[c] %(ref)
1	**1**	**4**[12]	92
2	 **5**	 **6**[14]	87
3	 **7**	 **8**[7]	85
4	 **9**	 **10**[7]	92
5	 **11**	 **12**	86
6	 **13**	 **14**	88
7	 **15**	 **16**[13]	89
8	 **17**	 **18**[7]	80
9	 **19**	 **20**	92
10	 **21**	 **22**	90
11	 **23**	 **24**[15]	85[d]
12	 **25**	 **26**[16]	87[d]

[a]In all cases standardised reaction conditions, i.e., 8 equiv. of TCT and 10 equiv. of $NaBH_4$ were used per equiv. substrate in 5 mL of solvent and the reactions were complete in 8 h. [b]Characterised through spectroscopic analysis. [c]Isolated yield after column chromatography. [d]Reactions were complete in 3.5 h.

With this newly developed efficient reaction condition (table 1, entry 1) for the regioselective 4,6-*O*-benzylidene cleavage in our hand, we next studied the substrate scope of the reaction. The mildness of the reaction conditions is obvious from the first experiment with the acetylated benzylidene derivative (table 1, entry 1). A series of 4,6-*O*-benzylidene protected glucosides (table 1, entries 2-8) were subjected to acetal ring opening using the optimised reaction conditions. The reactions proceeded smoothly leading to the formation of 6-OH in a regioselective manner without formation of the other regioisomer, i.e., 4-OH. Advantage of our reagent system over $LiAlH_4$-$AlCl_3$ system is that irrespective of the nature of protective group at C3 (OBn, OBz, OPiv, OTBDMS), the former gives O6-opened product exclusively (table 1, entries 2-8).[4] The survival of pivaloyl and silyl protecting groups constitutes an added advantage of the present process as the products can be used as monosaccharide building blocks for other transformations. In case of D-glucosamine and 2-azido derivatives **15** and **17**, the desired 6-OH products were obtained in good yields. Similarly, D-manno derivative **19** and D-galacto derivative **21** also afforded the corresponding products in good to excellent yields in a regiospecific manner. After getting encouraging results from carbohydrate derivatives, we next applied our reagent system for non-carbohydrate substrates **23** and **25**. Both these acetals underwent facile ring opening to provide primary –OH group without formation of the other regioisomer.

In summary, TCT/$NaBH_4$ has proven to be a mild, inexpensive, nontoxic, functional group tolerant and environmentally benign reagent system for the generation of orthogonally protected monosaccharide units. The high regioselectivity and substrate diversity add to the advantages of the current methodology over the already existing ones. It is now obvious that TCT can serve as a switchable catalyst for the generation of 6-OH and 4-OH in benzylidene acetal opening based on the type of reducing agent used. The applicability of the reagent system to non-sugar derivatives is another merit of the process. Finally, this is the first report of use of $NaBH_4$ for benzylidene ring opening.

1. Experimental section

General procedure for 4,6-*O*-arylidene ring opening using TCT/$NaBH_4$ (1).

To solution of benzylidene acetal (1 mmol) in acetonitrile (10 mL) at 0 °C was added $NaBH_4$ (10 equiv, 380 mg) and allowed to stir for 5 min. Then TCT (8 equiv, 1.47 g) was added to the mixture. After stirring for the required time, the reaction was quenched by the addition of

ethyl acetate (5 mL). The mixture was filtered through a small pad of celite using ethyl acetate (10 mL × 4) as eluent. The filtrate was concentrated at reduced pressure to yield the crude product. The residue was purified by flash column chromatography on silica gel to give the corresponding products.

1.1. Methyl 2,3-di-*O*-acetyl-4-*O*-benzyl-α-D-mannopyranoside (20).

Prepared by the general procedure 1 using **19** (368 mg, 1mmol) and column chromatography on silica gel (20% EtOAc/hexane then 30% EtOAc/hexane) to afford **20** as gum in 92% (338 mg) yield. Rf = 0.38 (40% EtOAc/hexane); $[\alpha]_D$ = +29.0 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) ῡ 3476, 1749, 1368, 1244, 1224, 1083 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.26 (m, 5H), 5.34 (dd, *J* = 3.6, 10.0 Hz,1H), 5.24 (dd *J* = 2.0, 3.2 Hz, 1H), 4.71-4.63 (m, 3H), 3.92 (t, *J* = 10.0 Hz, 2H), 3.84-3.78 (m, 1H), 3.75-3.71 (m, 1H), 3.36 (s, 3H, OMe), 2.09 (s, 3H, OAc), 1.98 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 169.8, 137.8, 128.5, 128.4, 127.8, 127.6, 127.6, 98.5, 74.8, 72.5, 71.6, 71.5, 69.9, 61.6 ,55.0, 20.8, 20.8; HRMS (ESI^+) m/z calcd for $C_{18}H_{24}NaO_8$ $(M+Na)^+$ 391.1369, found 391.1358.

Acknowledgments

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Supplementary material

Copies of ^1H and ^{13}C NMR, 2D spectra of selected compounds and HRMS files. This material is available free of charge via the Internet at http://--- /."

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Cyanuric Chloride/sodiumborohydride: A new reagent combination for reductive opening of benzylidine acetals

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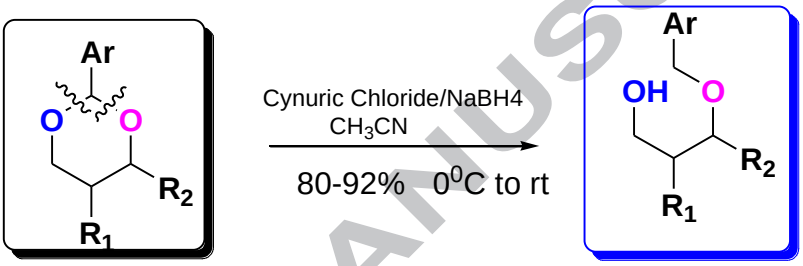

Highligts

- First report of benzylidine acetals reductive opening towards 6-OH using cyanuric chloride/ $NaBH_4$ reagent system.
- Inexpensive reagent, mild reaction condition, high yield with broad functional group tolerance
- High regioselectivity of reagent system.
- Application to both carbohydrate and non-carbohydrate systems.