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Note

A highly efficient deprotection of the 2,2,2-trichloroethyl group at the anomeric oxygen of carbohydrates

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ABSTRACT

Commercially available zinc dust in the presence of ammonium chloride in acetonitrile at reflux removes the 2,2,2-trichloroethyl (TCE) group at anomeric centers with excellent yields (>95%) in short reaction times. This present method is easily implemented on substrates containing acyl and benzyl groups and large-scale reactions also proceed in high yield.

In the course of synthesizing oligosaccharides and glycoconjugates, manipulations of the anomeric protection of a sugar moiety usually play a key role.[1] To date, various groups have been developed to achieve chemoselective transformations or activations, such as acetyl, benzoyl, allyl, trimethylsilylethyl and phenylthiol.[2] Since Woodward first highlighted the elegance of the 2,2,2-trichloroethyl (TCE) ester group in his classical cephalosporin synthesis in 1966,[3] the TCE moiety has been the most widely used haloethyl protecting group for carbon, sulfuric and phosphorus acids.[4] Later, Lemieux, Ogawa and other chemists successfully introduced the TCE group for the protection of the anomeric center against standard reaction conditions in carbohydrate chemistry.[5,6] Despite these achievements, cleavage of TCE protection is sometimes still capricious in the syntheses of polyfunctional molecules. Hence the development of new methodologies for TCE deprotection remains a challenging task.[5a,7] For instance, in our continuous efforts toward carbohydrate-targeted drug delivery, we have encountered difficulties in selectively removing this group at the anomeric center. At the beginning of our work, we first investigated the TCE removal using the methods developed by other groups, such as Zn–AcOH,[5a] Zn–AcOH–NaOAc,[5a] Zn–pentane-2,4-dione[6b] and Zn/NMI.[6a] However, most methods have drawbacks. For example, the Zn–AcOH system suffers from long reaction times and low yields and the use of Zn–pentane-2,4-dione requires pre-activation of the zinc dust (Table 1).

Table 1
Comparison of the known methods of removal anomeric TCE on 2,2,2-trichloroethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **1a**

Entry	System	Temperature (°C)	Time (h)	Yield[a] (%)
1	Zn/AcOH[5a]	25	29	39.8
2	Zn/AcOH/AcONa[5a]	25	4	74.6
3	Zn/NMI[6b]	25	8	<10
4	Zn/pentane-2,4-dione[6c]	25	1.5	52.4
5	Zn/pentane-2,4-dione[6c]	50	10 min	75.6

[a] Isolated yields.

In our earlier research, Zn–NH_4Cl–EtOH had been successfully applied in the deprotection of 2-iodo-3-perfluoroalkyl group at the anomeric center of carbohydrates and other complex compounds.[8] Because most protective groups including ethers, esters, silyl ethers, and ketals all remained intact under refluxing conditions, we tried this elegant reductive approach in the deprotection of TCE groups at the anomeric center.[9] When a solution of 2,2,2-trichloroethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **1a** in ethanol was treated with non-activated Zn dust and NH_4Cl, and allowed to heat at reflux over a period of just 10 min, TLC revealed only the presence of one new component, which was revealed as the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose with the help of NMR and MS (Table 2, entry 1). Inspired by the fact that the 2,2,2-trichloroethyl could be easily removed using this simple system, we established optimal conditions. First, even if the reaction time was prolonged to 60 min, the starting material was not fully

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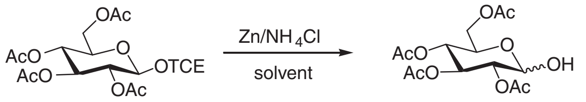
Table 2
Initial studies of TCE removal



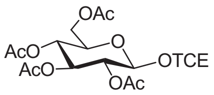
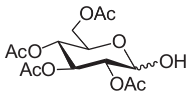
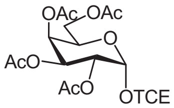
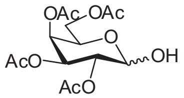
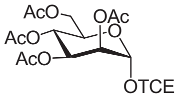
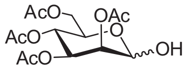
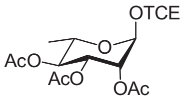
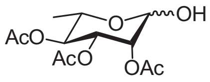
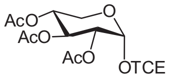
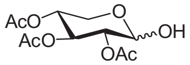
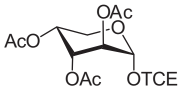
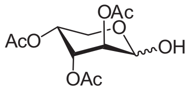
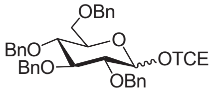
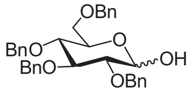
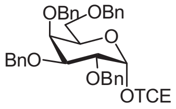
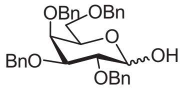
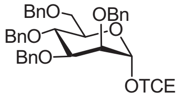
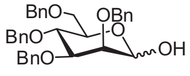
Entry	Catalyst (Zn/NH_4Cl) (equiv)	Solvent	Temp (°C)	Time (min)	Yield[a] (%)
1	5/5	EtOH	78	10	63
2	5/5	AcOH	90	10	56
3	5/5	Toluene	90	10	Trace
4	5/5	THF	66	10	84
5	5/5	CH_3CN	82	10	89
6	8/8	CH_3CN	82	5	98
7	8/0	CH_3CN	82	120	NR[b]
8	8/1	CH_3CN	82	90	98
9	8/4	CH_3CN	82	40	98
10	8/6	CH_3CN	82	15	98

[a] Isolated yields.
[b] NR, no reaction.

consumed and the yield of product scarcely increased. Then, several solvents were tested. We found that the conversion proceeded much better in aprotic polar solvents especially in acetonitrile (entry 5 in Table 2). In addition, the NH_4Cl is indispensable to this reaction. The reaction did not occur at all without NH_4Cl (entry 7); moreover, the reaction times are shortened by using more NH_4Cl (entries 6 and 8–10).

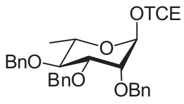
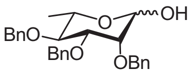
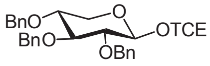
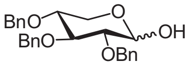
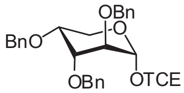
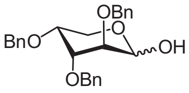
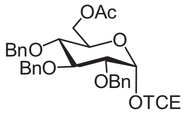
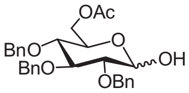
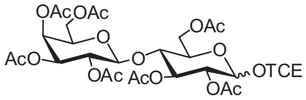
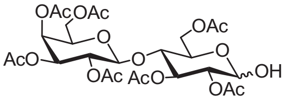
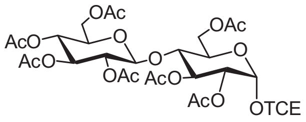
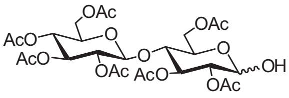
These findings prompted us to examine if this novel method could be effective with other trichloroethyl glycosides. The data listed in Table 3 represent our preliminary results of the deprotection under the specified conditions (8 equiv Zn powder, 8 equiv NH_4Cl, CH_3CN, reflux). All of the reactions of monosaccharide glycosides with acyl protection went to completion within 5 min (entries 1–6). Similarly, the deprotections are also nearly quantitative in the presence of benzyl ether protection (entries 7–13). As well, reactions of disaccharides proceeded smoothly in the presence of more zinc dust and ammonium chloride (16 equiv Zn powder, 16 equiv NH_4Cl, entries 14 and 15). The structure and stereochemistry of all products were elucidated by NMR and mass spectral

Table 3
Deprotection of anomeric O-TCE glycosides in refluxing acetonitrile[a]

Entry	Starting material	Product	Time (min)	Yield[b] (%)	α/β[c]
1	 **1a**	 **1b**	5	98[10]	2.7:1
2	 **2a**	 **2b**	5	98[10]	1.7:1
3	 **3a**	 **3b**	5	96[10]	>19:1
4	 **4a**	 **4b**	5	96[14]	>19:1
5	 **5a**	 **5b**	5	99[15]	1.9:1
6	 **6a**	 **6b**	5	97[15]	0.8:1
7	 **7a**	 **7b**	5	97[11]	1.8:1
8	 **8a**	 **8b**	5	98[10]	1.7:1
9	 **9a**	 **9b**	5	96[13]	>19:1

(*continued on next page*)

Table 3 (*continued*)

Entry	Starting material	Product	Time (min)	Yield[b] (%)	α/β[c]
10	 **10a**	 **10b**	5	98[11]	2.8:1
11	 **11a**	 **11b**	5	99[16]	0.8:1
12	 **12a**	 **12b**	5	98[16]	0.5:1
13	 **13a**	 **13b**	5	98[12]	1.8:1
14	 **14a**	 **14b**	20[d]	97[10]	1.9:1
15	 **15a**	 **15b**	20[d]	96[10,17]	1.9:1

[a] Reaction conditions: 1 equiv O-TCE glycosides, 8 equiv Zn powder, 8 equiv NH_4Cl, solvent, CH_3CN (2 mL), reflux.

[b] Isolated yields.

[c] α/β ratios were based on the integration of the corresponding anomeric protons in the ^1H NMR (500 MHz) spectra.

[d] 16 equiv Zn powder, 16 equiv NH_4Cl.

data.[17] In addition, the same methodology was also shown to be reliable on scales as large as 4.78 g (10 mmol) using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside as the substrate; the yield was excellent as well (98%).

In summary, we have demonstrated a facile, highly efficient removal of TCE protecting groups in the presence of either acetyl or benzyl protection. The time required for the desired deprotective reactions are remarkably short (5–20 min) and the yields are exceptionally high (>95%). All the applied reagents were directly applied without any pretreatment. In particular, the zinc dust does not need to be activated before use. Furthermore, the reaction could be done in neutral media and in large scale; therefore, multiple bicarbonate washes for removal of acetic acid are avoided. Thus, we expect that this methodology will find widespread use in the deprotection of this class of protecting group. Further exploration of this methodology is currently under study in our laboratory.

1. Experimental

1.1. General experimental methods

^1H NMR spectra were recorded on a Bruker DRX-500 MHz spectrometer using tetramethylsilane as internal standard and $CDCl_3$ as solvent. Silica gel (10–40 μ, Yantai, China) was used for column chromatography. TLC plates (10–40 μ, Yantai, China) were used to monitor the reactions.

1.2. General experimental procedure

To a solution of 2,2,2-trichloroethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (96 mg, 0.2 mmol) in CH_3CN (2 mL), were added Zn powder (104 mg, 1.6 mmol) and NH_4Cl (85 mg, 1.6 mmol). After being heated at reflux for 5 min, the mixture was filtered. The filtrate was concentrated to a residue that was purified by silica gel column chromatography (petroleum ether–EtOAc 3:1) to give 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (69 mg, 98%).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.08.007.

References

1. (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155–173; (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235; (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531; (d) Ogawa, T. *Chem. Soc. Rev.* **1994**, 397–407; (e) Oscarson, S. In *Organic Chemistry of Sugars*; Levy, D. E., Fügedi, P., Eds.; CRC Press: Boca Raton, FL, 2006; p 53; (f) Wang, C. C.; Lee, J. C.; Luo, S. Y.; Kulkarni, S. S.; Huang, Y. W.; Lee, C. C.; Chang, K. L.; Hung, S. C. *Nature* **2007**, *446*, 896–899.
2. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience: New York, 2007.
3. Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbruggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852–853.
4. (a) Weissman, S. A.; Zewge, D. *Tetrahedron* **2005**, *61*, 7833–7863; (b) Ingram, L. J.; Taylor, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 3503–3506; (c) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience: New York, 2007. pp 573, 646, 963.
5. (a) Lemieux, R. U.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4069–4075; (b) Lemieux, R. U.; Abbas, S. Z.; Chung, B. Y. *Can. J. Chem.* **1982**, *60*, 68–75; (c) Koike, K.; Mori, M.; Ito, Y.; Nakahara, Y.; Ogawa, T. *Glycoconjugate J.* **1987**, *4*, 109–116; (d) Koike, K.; Mori, M.; Ito, Y.; Nakahara, Y.; Ogawa, T. *Agric. Biol. Chem.* **1990**, *54*, 2931–2939; (e) Mori, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, *195*, 199–224; (f) Macindoe, W. M.; Ijima, H.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1995**, *269*, 227–257; (g) Takeda, T.; Kanemitsu, T.; Shimizu, N.; Ogihara, Y.; Matsubara, M. *Carbohydr. Res.* **1996**, *283*, 81–93.
6. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience: New York, 2007. p 79; (b) Somsák, L.; Czifrák, K.; Veres, E. *Tetrahedron Lett.* **2004**, *45*, 9095–9097; (c) Bogdan, D.; Aleksander, Z. *Carbohydr. Res.* **1987**, *164*, 470–476.
7. Winnik, F. M.; Carver, J. P.; Krepinsky, J. J. *J. Org. Chem.* **1982**, *47*, 2701–2707.
8. (a) Yu, B.; Zhang, J.; Lu, S.; Hui, Y. *Synlett* **1998**, 29–30; (b) Yu, B.; Li, B.; Zhang, J.; Hui, Y. *Tetrahedron Lett.* **1998**, *39*, 4871–4874.
9. (a) Somsák, L. *Chem. Rev.* **2001**, *101*, 81–135; (b) Ali, A. M.; Hill, B.; Taylor, S. D. *J. Org. Chem.* **2009**, *74*, 3583–3586.
10. Misra, A. K.; Agnihotri, G. *Carbohydr. Res.* **2004**, *339*, 885–890.
11. Dasgupta, S.; Bimalendu, R.; Balaram, M. *Carbohydr. Res.* **2006**, *341*, 2708–2713.
12. Bozhena, S. K.; Yury, E. T.; Gerald, B. P.; Nikolay, E. N. *J. Org. Chem.* **2008**, *73*, 8411–8421.
13. Kim, I. S.; Kim, S. J.; Lee, J. K.; Li, Q. R.; Jung, Y. H. *Carbohydr. Res.* **2007**, *342*, 1502–1509.
14. Hennen, W. J.; Sweers, H. M.; Wang, Y. F.; Wong, C. H. *J. Org. Chem.* **1988**, *53*, 4939–4945.
15. Zhang, J.; Kovac, P. *J. Carbohydr. Chem.* **1999**, *18*, 461–469.
16. Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641–2647.
17. Mandal, P. K.; Misra, A. K. *Synlett* **2007**, 1207–1210.