

## Selective removal of anomeric *O*-acetate groups in carbohydrates using $\text{HClO}_4\text{-SiO}_2$ <sup>☆</sup>

Pallavi Tiwari and Anup Kumar Misra\*

Medicinal and Process Chemistry Division, Central Drug Research Institute, Chattar Manzil Palace,  
Lucknow 226 001, UP, India

Received 23 January 2006; revised 27 February 2006; accepted 9 March 2006

**Abstract**—A convenient methodology has been developed for the selective removal of the anomeric acyl group of carbohydrate derivatives using  $\text{HClO}_4\text{-SiO}_2$  under acidic reaction conditions. Anomeric benzoyl groups can also be removed selectively following similar reaction conditions. The yields were excellent in all cases.

© 2006 Elsevier Ltd. All rights reserved.

Suitably protected 1-hydroxy sugars or glycosyl hemiacetals are useful synthetic intermediates for the preparation of several glycosyl donors such as glycosyl trichloroacetimidates,<sup>1</sup> glycosyl fluorides<sup>2</sup> and iodides<sup>3</sup> and glycosylation reactions towards the preparation of several bioactive molecules.<sup>4</sup> Glycosyl hemiacetals have successfully been used in dehydrative glycosylations for the synthesis of several complex oligosaccharides.<sup>5</sup> In general, protected glycosyl hemiacetals can be prepared by (a) deacetylation of glycosyl-1-*O*-acetates;<sup>6</sup> (b) acid hydrolysis of alkyl glycosides;<sup>7</sup> (c) hydrolysis of thioglycosides,<sup>8</sup> etc. Conventional methods for anomeric *O*-deacetylation of per-*O*-acetylated carbohydrate derivatives suffer from several shortcomings, which include, the use of highly toxic reagents, for example, hydrazine acetate,<sup>6a</sup> and heavy metal salts, for example, bis(tributyltin)oxide,<sup>6b</sup> tributyltin methoxide<sup>6c</sup> and mercuric chloride/mercuric oxide.<sup>6d</sup> Although there are a number of environmentally benign reagents (e.g., benzylamine,<sup>6e</sup> sodium methoxide,<sup>6f</sup> ammonium salts,<sup>6g,h</sup> piperidine,<sup>6i</sup>  $\text{Al}_2\text{O}_3$ ,<sup>6j</sup>  $\text{MgO}$ ,<sup>6k</sup> etc.) available for this transformation, most require longer reaction times leading to non selective de-*O*-acetylation and time-consuming purification steps. Therefore, the development of a metal-free, less-toxic reaction protocol, avoiding

purification steps, would extend the scope of this transformation.

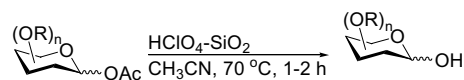
Recently, we have applied considerable effort towards the development of more environmentally benign catalysts for several important organic transformations.<sup>9</sup> During our study on the Helferich glycosylation of per-*O*-acetylated sugars using  $\text{HClO}_4$  adsorbed on  $\text{SiO}_2$ ,<sup>9b</sup> we observed that clean removal of the anomeric acetate group was taking place in each case instead of glycosylation. Taking cue from this observation, we explored the use of  $\text{HClO}_4\text{-SiO}_2$  for the anomeric deacetylation of 1-*O*-acetylated carbohydrate derivatives. We herein disclose our findings on the anomeric de-*O*-acetylation of carbohydrates under acidic reaction conditions using  $\text{HClO}_4\text{-SiO}_2$  (Scheme 1).

As a model system, per-*O*-acetylated  $\beta$ -D-glucose was treated with  $\text{HClO}_4\text{-SiO}_2$  varying the quantity of catalyst and reaction solvent at 70 °C. It was observed that use of 25 mg of  $\text{HClO}_4\text{-SiO}_2$  (0.012 mmol of  $\text{HClO}_4$ ) per mmol of per-*O*-acetylated  $\beta$ -D-glucose in acetonitrile at 70 °C resulted in clean formation of the hemiacetal in excellent yield without affecting other functional groups present in the substrate. In order to establish the reaction protocol, a series of protected mono- and disaccharides

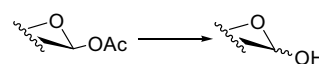
**Keywords:** Carbohydrate; Deacetylation; Acetates;  $\text{HClO}_4\text{-SiO}_2$ ; Hemiacetals.

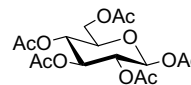
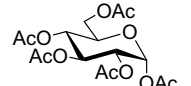
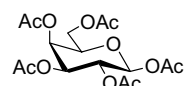
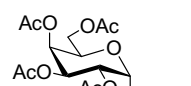
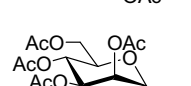
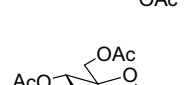
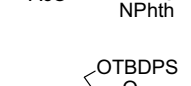
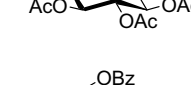
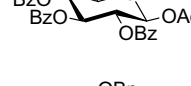
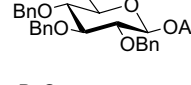
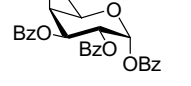
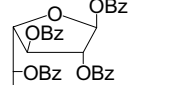
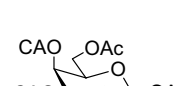
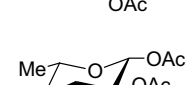
<sup>☆</sup> CDRI Communication No. 6929.

\* Corresponding author. Tel.: +91 522 2612411 18; fax: +91 522 2623938; e-mail: akmisra69@rediffmail.com

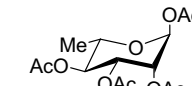
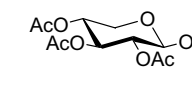
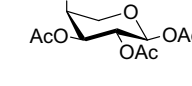
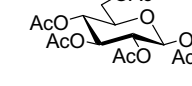
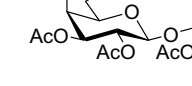
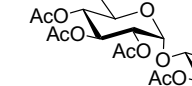


Scheme 1.

**Table 1.** Anomeric de-O-acylation of carbohydrate derivatives using  $\text{HClO}_4\text{-SiO}_2$ 


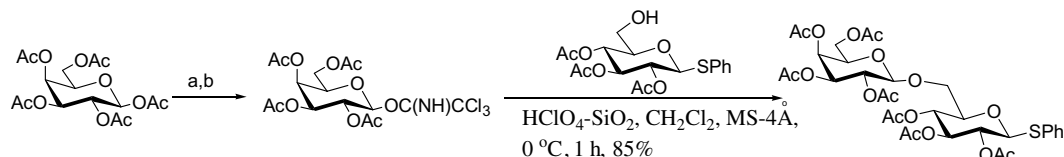
Entry	Substrates	Time (h)	Yield (%)	$\alpha/\beta$
1		1.5	92	2:1
2		1.5	90	2:1
3		1.5	95	5:2
4		1.5	92	2:1
5		1.0	92	1:0
6		1.5	90	1:2
7		1.5	90	2:1
8		1.5	95	1:1
9		1.5	80	2:1
10		2.5	90	5:2
11		2.5	85	1:0
12		1.5	85	5:2
13		1.0	90	1:1
14		1.0	82	2:1

**Table 1 (continued)**

Entry	Substrates	Time (h)	Yield (%)	$\alpha/\beta$
15		1.0	92	1:0
16		1.0	90	5:3
17		1.0	90	5:2
18		2.0	92	2:1
19		2.0	95	2:1
20		2.0	90	5:2

CAO: chloroacetyl group. All known compounds gave acceptable  $^1\text{H}$  NMR spectra, which matched the data reported in the literature.

were subjected to the deacetylation conditions and the results are presented in Table 1. The reaction was equally effective for the removal of both  $\alpha$ - and  $\beta$ -acetates. Anomeric benzoyl groups could also be removed in excellent yield using similar reaction conditions. Inter-glycoside linkages remained unaffected. Pure products could be obtained by removal of the catalyst by simple filtration and evaporation of the solvent. In order to justify the role of moisture present in the solvent in the anomeric deacylation, a parallel reaction was performed using distilled  $\text{CH}_3\text{CN}$  in place of commercial  $\text{CH}_3\text{CN}$ . In both cases the yields of the product and reaction times were almost similar indicating that the presence of moisture in the solvent did not have any effect on the reaction time and yield. No reaction or only very low yields of the product were obtained using other common apolar solvents, for example,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ , THF, etc. A typical experimental procedure is as follows: To a solution of 1-O-acetyl carbohydrate derivative (1.0 mmol) in  $\text{CH}_3\text{CN}$  (5 mL) was added  $\text{HClO}_4\text{-SiO}_2$  (25 mg) and the reaction mixture was stirred at  $70^\circ\text{C}$  for the appropriate time as mentioned in Table 1. After completion of the reaction (TLC), the reaction mixture was filtered through a Celite bed and washed with  $\text{CH}_2\text{Cl}_2$  and the filtrate evaporated under reduced pressure to furnish the pure glycosyl hemiacetal. Although, the crude product was sufficiently pure, analytical samples were prepared by passing the crude reaction product through a short column of  $\text{SiO}_2$ . **Caution:** Although no explosions were reported under these conditions, extreme care has to be exercised for large-scale reactions using  $\text{HClO}_4\text{-SiO}_2$ . The generation of the catalyst should be performed with special care and in a safe environment.



**Scheme 2.** Reagents and conditions: (a)  $\text{HClO}_4\text{-SiO}_2$ ,  $\text{CH}_3\text{CN}$ ,  $70\text{ }^\circ\text{C}$ , 2 h, 95%; (b)  $\text{CCl}_3\text{CN}$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{CH}_2\text{Cl}_2$ , 80%.

In order to verify the synthetic utility of our method in comparison to other reported protocols, peracetylated galactose was transformed into its hemiacetal, which was then converted to the trichloroacetimidate derivative using trichloroacetonitrile and  $\text{K}_2\text{CO}_3$ . The peracetylated galactosyltrichloroacetimidate thus obtained was further used in the glycosylation reaction using  $\text{HClO}_4\text{-SiO}_2$  as the glycosylation activator<sup>10</sup> to prepare a novel disaccharide thioglycoside, which can be used as a disaccharide donor for the preparation of several oligosaccharides (Scheme 2).<sup>11</sup>

In summary, we have introduced a new method for the selective anomeric deacetylation or debenzoylation of carbohydrate derivatives under acidic reaction conditions. As the reaction does not require any toxic reagents and chromatographic purification, this environmentally benign reaction protocol should find application in synthetic organic chemistry.

### Acknowledgements

Instrumentation facilities from SAIF, CDRI are gratefully acknowledged. P.T. thanks CSIR, New Delhi, for providing a Senior Research Fellowship. This project was partly funded by the Department of Science and Technology (DST), New Delhi (SR/FTP/CSA-10/2002), India.

### References and notes

- (a) Pougny, J.-R.; Jacquinet, J.-C.; Nassr, M.; Duchet, D.; Milat, M.-L.; Sinaÿ, P. *J. Am. Chem. Soc.* **1977**, *99*, 6762–6763; (b) Schmidt, R. R.; Jung, K.-H. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1996; pp 283–312.
- Caputo, R.; Kunz, H.; Mastroianni, D.; Palumbo, G.; Pedatella, S.; Solla, F. *Eur. J. Org. Chem.* **1999**, 3147–3150.
- Yokoyama, M. *Carbohydr. Res.* **2000**, *327*, 5–14.
- (a) Schmidt, R. R.; Klotz, W. *Synlett* **1991**, 168–170; (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235.
- (a) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597–7598; (b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269–4279; (c) Garcia, B. A.; Gin, D. Y. *Org. Lett.* **2000**, *2*, 2135–2138; (d) Nguyen, H. M.; Poole, J. L.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 414–417.
- (a) Excoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohydr. Res.* **1975**, *39*, 368–373; (b) Watanbe, K.; Itoh, K.; Araki, Y.; Ishido, Y. *Carbohydr. Res.* **1986**, *154*, 165–176; (c) Nudelman, A.; Herzig, J.; Gottlieb, H. E.; Keinan, E.; Sterling, J. *Carbohydr. Res.* **1987**, *162*, 145–152; (d) Sambaiah, T.; Fanwick, P. E.; Cushman, M. *Synthesis* **2001**, 1450–1452; (e) Conchie, J.; Levvy, G. A. *Methods Carbohydr. Chem.* **1963**, *2*, 345–347; (f) Itoh, K.; Takamura, H.; Watanbe, K.; Araki, Y.; Ishido, Y. *Carbohydr. Res.* **1986**, *156*, 241–246; (g) Blazejewski, J.-C.; Dorme, R.; Wakselman, C. *Synthesis* **1985**, 1121–1122; (h) Mikamo, M. *Carbohydr. Res.* **1989**, *191*, 150–153; (i) Rowell, R. M.; Feather, M. S. *Carbohydr. Res.* **1967**, *4*, 486–491; (j) Schneider, G.; Weisz-Vincze, I.; Vass, A.; Kovacs, K. *Tetrahedron Lett.* **1972**, *32*, 3349–3352; (k) Herzig, J.; Nudelman, A. *Carbohydr. Res.* **1986**, *153*, 162–167.
- Koto, S.; Morishima, N.; Miyata, Y.; Zen, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2639–2640.
- (a) Xie, J.; Molina, A.; Czernecki, S. *J. Carbohydr. Chem.* **1999**, *18*, 481–498; (b) Barua, P. M. B.; Sahu, P. R.; Mondal, E.; Bose, G.; Khan, A. T. *Synlett* **2002**, 81–84; (c) Uchiro, H.; Wakiyama, Y.; Mukaiyama, T. *Chem. Lett.* **1998**, 567–568; (d) Misra, A. K.; Agnihotri, G. *Carbohydr. Res.* **2004**, *339*, 885–890.
- (a) Misra, A. K.; Tiwari, P.; Agnihotri, G. *Synthesis* **2005**, *2*, 260–266; (b) Misra, A. K.; Tiwari, P.; Madhusudan, S. K. *Carbohydr. Res.* **2005**, *340*, 325–329; (c) Tiwari, P.; Agnihotri, G.; Misra, A. K. *Carbohydr. Res.* **2005**, *340*, 749–752; (d) Kumar, R.; Tiwari, P.; Maulik, P. R.; Misra, A. K. *J. Mol. Catal. A: Chem.* **2006**, *247*, 27–30.
- (a) Mukhopadhyaya, B.; Maurer, S. V.; Rudolph, N.; van Well, R.; Russell, D.; Field, R. A. *J. Org. Chem.* **2005**, *70*, 9059–9062; (b) Du, Y.; Wei, G.; Cheng, S.; Hua, Y.; Linhardt, R. J. *Tetrahedron Lett.* **2006**, *47*, 307–310.
- 1,2,3,4,6-Penta-*O*-acetyl- $\beta$ -D-galactose (585 mg, 1.5 mmol) and  $\text{HClO}_4\text{-SiO}_2$  (35 mg) were mixed in  $\text{CH}_3\text{CN}$  (5 mL) and stirred at  $70\text{ }^\circ\text{C}$  for 1.5 h. The reaction mixture was filtered through Celite, rinsed with  $\text{CH}_2\text{Cl}_2$  and concentrated. To a mixture of the crude product (496 mg, 1.42 mmol) and  $\text{CCl}_3\text{CN}$  (570  $\mu\text{L}$ , 5.68 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added anhydrous  $\text{K}_2\text{CO}_3$  (1.0 g) and the reaction mixture was stirred at room temperature for 3 h. After completion (TLC), the reaction mixture was filtered, rinsed with  $\text{CH}_2\text{Cl}_2$ , concentrated and passed through a short pad of  $\text{SiO}_2$  to give per-*O*-acetylated galactosyl trichloroacetimidate (560 mg). To a mixture of per-*O*-acetylated galactosyl trichloroacetimidate (560 mg, 1.1 mmol) and phenyl 2,3,4-tri-*O*-acetyl-1-thio- $\beta$ -D-glucopyranoside (398 mg, 1.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added powdered MS-4 Å (500 mg) and the reaction mixture was stirred under Ar for 30 min at  $0\text{ }^\circ\text{C}$ . To the cooled reaction mixture was added  $\text{HClO}_4\text{-SiO}_2$  (30 mg) and the reaction mixture was stirred at  $0\text{ }^\circ\text{C}$  for 1 h. After completion of the reaction (TLC), the reaction mixture was filtered through a Celite bed and washed with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with satd aq  $\text{NaHCO}_3$  and water, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Column chromatography of the crude product over  $\text{SiO}_2$  using hexane-EtOAc (3:1) furnished phenyl (2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-galacto-pyranosyl)-(1 $\rightarrow$ 6)-2,3,4-tri-*O*-acetyl-1-thio- $\beta$ -D-glucopyranoside (618 mg, 85%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.48–7.32 (m, 5H, aromatic protons), 5.39–5.33 (dd,  $J=9.5$  and  $2.4$  Hz, 1H), 5.28 (d,  $J=7.9$  Hz, 1H), 5.21–5.17 (m, 1H), 5.15–5.02 (m, 1H),

5.00–4.80 (m, 3H), 4.73–4.65 (t,  $J = 8.7$  Hz each, 1H),  
4.54–4.48 (dd,  $J = 8.8$  Hz, 8.8 Hz, 1H), 4.17–4.06 (m, 2H),  
3.89–3.82 (m, 1H), 3.74–3.67 (m, 2H), 2.10, 2.08, 2.07,  
2.06, 2.03, 1.98, 1.96 (7s, 21H, 7COCH<sub>3</sub>); <sup>13</sup>C NMR

(75 MHz, CDCl<sub>3</sub>):  $\delta$  171.2, 170.6, 170.4, 170.0, 169.4 (2C),  
168.9, 132.9–128.1 (aromatic carbons), 100.9, 85.4, 77.3,  
76.6, 76.0, 73.7, 70.6, 69.0, 68.5, 68.3, 61.1, 60.7, 20.6 (2C),  
20.5 (2C), 20.3 (2C), 20.0.