Tandem One-Pot Acetalation–Acetylation for Direct Access to Differentially Protected Thioglycosides and *O*-Glycosides with *p*-Toluenesulfonic Acid

Kwok-Kong Tony Mong,* Chin-Sheng Chao, Min-Chun Chen, Chun-Wei Lin

Department of Applied Chemistry, National Chiao Tung University, 1001 Ta-Hsueh Road, Hsinchu 300, Taiwan
Fax +886(3)5723764; E-mail: tmong@mail.nctu.edu.tw

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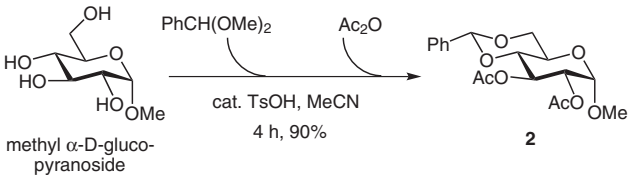
Abstract: A new tandem one-pot acetalation–acetylation procedure is reported which streamlines routine protecting-group manipulation of carbohydrate molecules in production of differentially protected *O*- and thioglycosides. This new procedure eliminates the use of highly toxic pyridine, and *p*-toluenesulfonic acid is employed as catalyst for acetalation and acetylation. Synthetic utility of the new procedure is demonstrated in the expeditious preparation of differentially protected glycosides from a wide variety of carbohydrate substrates including unprotected *O*-glycosides, thioglycosides, and *N*-acetyl neuraminic acid ester.

Key words: tandem, acetals, glycosides, oligosaccharides, protecting group

Preparation of carbohydrate building blocks has always been necessary for oligosaccharide synthesis; thus expeditious synthesis of such building blocks is highly desired. A logical approach toward this goal is to merge two or three sequential reactions into a tandem one-pot operation, which was realized in the preparation of peracetyl glycosyl bromide,[1] peracetyl glycosyl azide,[2] peracetyl glycosyl iodide,[3] peracetyl thioglycoside,[4] and regioselective one-pot protection of carbohydrates.[5]

Acetalation and acetylation are routine synthetic steps for protection of hydroxy function. Generally the former is effected with a free[6] or masked carbonyl function[7–10] in the presence of acid catalyst,[11–17] while the latter is usually promoted in the presence of excess pyridine.[18] However, owing to malodorous and toxic nature of pyridine, such acetylation procedure is gradually superseded by various acid-catalyzed protocols.[19, 20] Sequential acetalation and acetylation of unprotected glycoside substrates are widely employed for production of differentially protected *O*-glycosides and thioglycosides, and the latter constitutes a major class of useful building blocks in oligosaccharide synthesis.[21] As both acetalation and acetylation are catalyzed by acid, it is reasonable for us to merge them into a tandem one-pot operation. Such strategy has been demonstrated in one-pot acetalation–acetylation with immobilized $HClO_4$[22] and H_2SO_4.[23] Though both reported methods are found useful for production of differentially protected *O*-glycosides, preparation of synthetically useful thioglycoside was less discussed in their investigations. In addition, immobilization of acid on silica requires extra procedure rendering them less convenient in practice. Recently, iodine-catalyzed tandem acetonide formation–acetylation was reported, but it is not useful for making benzylidene acetal function.[10] To overcome such limitations and to develop a pyridine-free process, a new one-pot procedure is required. Herein we report the development of a versatile tandem one-pot acetalation–acetylation, which expedites the preparation of differentially protected *O*-glycosides and thioglycosides.

The key to effect a one-pot procedure is to explore the appropriate reaction conditions so that a practical acetylation rate is retained in the presence of the acid-labile acetal



Scheme 1 One-pot acetalation–acetylation of methyl α-D-glucopyranoside

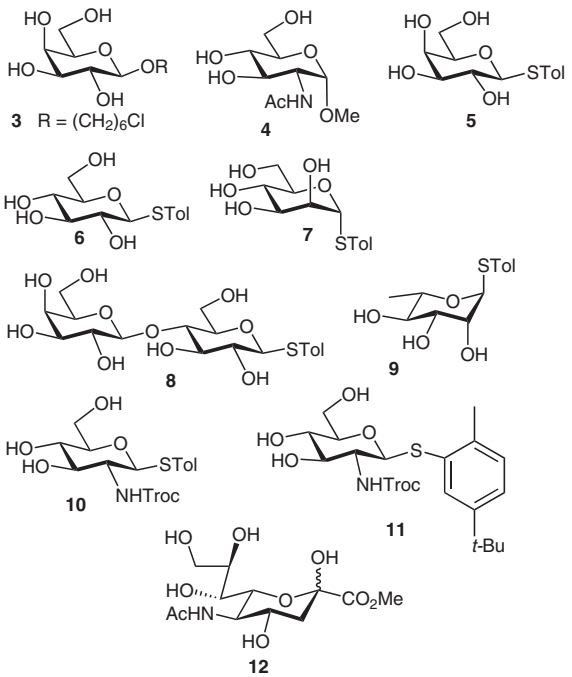


Figure 1 *O*-Glycosides **3** and **4**, thioglycosides **5**–**11**, and NANA ester **12**

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function. Referring to the reported procedures, the amount of acid used in acetalation spans from 5–20 mol%.[11,14,15] Thus in our model study, a suspension of methyl α-D-glucopyranoside and benzaldehyde dimethyl acetal in acetonitrile were treated with 10 mol% of TsOH (0.05 M, Scheme 1). The reaction proceeded smoothly at room temperature and upon complete conversion into acetal intermediate, acetic anhydride (Ac_2O, 1.5 equiv per OH) was added to give the expected 2,3-di-*O*-acetyl-4,6-*O*-benzylidene α-D-gluco-pyranoside **2** in excellent 90% yield.

Being encouraged by the preliminary result, we next examined the one-pot acetalation–acetylation of unprotected *O*-glycosides **3**, **4**,[24] thioglycosides **5**–**11**,[25] and *N*-acetyl neuraminic acid ester (NANA ester) **12**[26] (Figure 1), and the results were detailed in Table 1.[27]

Table 1 One-Pot Acetalation–Acetylation of *O*-Glycosides **3** and **4**, Thioglycosides **5**–**11**, and NANA ester **12**

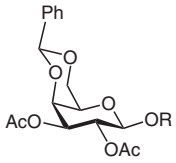
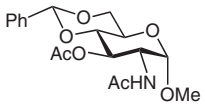
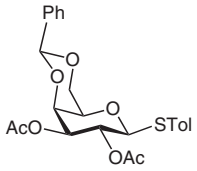
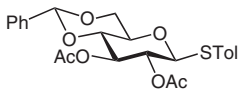
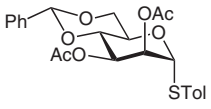
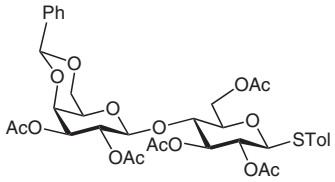
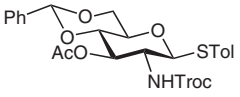
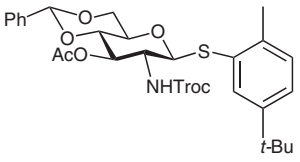
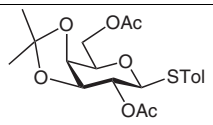
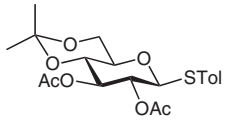
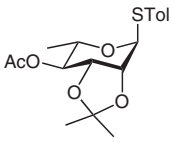
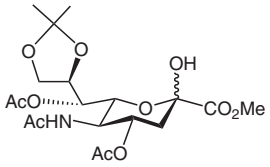
Entry	Substrate	Product	TsOH (mol%, M)	Acetalation/acetylation temp (°C)	Time (h)	Yield (%)
1	3	 **13**	10 (0.031)	25/40	4	81
2	4	 **14**	10 (0.041)	25/40	4	76
3	5	 **15**	10 (0.032)	25/40	5	77
4	6	 **16**[23]	10 (0.032)	25/40	4.5	75
5	7	 **17**	10 (0.01)	25/50	6	70
6	8	 **18**[28]	10 (0.014)	50/50	10	82
7	10	 **19**[29]	32 (0.019)	25/40	4	70
8	11	 **20**	10 (0.027)	25/40	6	75

Table 1 One-Pot Acetalation–Acetylation of *O*-Glycosides **3** and **4**, Thioglycosides **5**–**11**, and NANA ester **12** (continued)

Entry	Substrate	Product	TsOH (mol%, M)	Acetalation/acetylation temp (°C)	Time (h)	Yield (%)
9	5	 **21**	10 (0.023)	40/40	12	70
10	6	 **22**	10 (0.023)	25/40	7	52
11	9	 **23**[22]	5 (0.018)	25/40	4	75
12	12	 **24**	10 (0.021)	25/35	8	74

One-pot benzylidenation–acetylation of unprotected glycoside substrates **3**–**8** and **10**–**11** produced the expected glycosyl acetal derivatives **13**–**20** in 70–82% yield within 4–10 hours (Table 1, entries 1–8).[30] Owing to variation in physicochemical properties, optimization of reaction conditions was required for particular glycoside substrates. A point in case is the acetalation of mannopyranoside, which suffers from competitive formation of 2,3:4,6-*O*-bis(acetal) derivative. As a consequence, previous one-pot acetalation–acetylation of methyl α-D-mannopyranoside met with difficulty.[22] In our optimized one-pot procedure, a 'diluted' suspension of thiomannopyranoside **7** (1 g in 35 mL of MeCN) and a stoichiometric amount of acetalating agent [1.05 equiv of $PhCH(OMe)_2$] were used. Gratifyingly, formation of bis(acetal) derivative was largely suppressed and the desired 3-*O*-acetyl-4,6-*O*-benzylidene thiomannopyranoside **17** was obtained in satisfactory 70% yield (Table 1, entry 5).

One-pot isopropylidenation–acetylation of carbohydrate substrates **5**, **6**, **9**, and **12** was conducted in acetone,[31] from which the corresponding glycosyl ketal derivatives **21**–**24** were furnished in 52–75% yield at reasonable time frames (Table 1, entries 9–12). Isopropylidenation of thiogalactopyranoside **5** at room temperature gave a mixture of 3,4-*O*- and 4,6-*O*-isopropylidene ketal derivatives, while elevating the reaction temperature to 40 °C led to the exclusive formation of 3,4-*O*-isopropylidene ketal derivative **21** (Table 1, entry 9). Close examination revealed that 4,6-*O*-isopropylidene ketal derivative was formed preferentially in the beginning, but was gradually isomerized to **21**. Thus, longer reaction time and higher reaction temperature would favor the formation of 3,4-*O*-isopropylidene galactopyranosyl derivative. It should be mentioned that camphorsulfonic acid (CSA)[32] and trimethylsilyl chloride (TMSCl)[33] were also employed as catalyst, though the results were inferior to those obtained by using TsOH catalyst. Isopropylidenation of thioglucopyranoside **6** gave 4,6-*O*-isopropylidene ketal derivative **22** as the single regioisomer in a modest 52% yield along with 15% per-*O*-acetyl thioglucopyranoside. Formation of the latter is attributed to the cleavage of inherently less stable 4,6-*O*-isopropylidene ketal function in conjunction with acetylation (Table 1, entry 10).[34,35]

Other than glycoside substrates, the present procedure is also applicable to carbohydrate hemiacetals as exemplified in the one-pot isopropylidenation–acetylation of NANA ester **12**, which gave NANA ester ketal derivative **24** in 74% yield (Table 1, entry 12). As previously reported, the tertiary C-2 hydroxy function of **12** was unacetylated.[20] To prove the suitability of the procedure for a larger scale operation, 10 g of per-*O*-acetyl thiolactoside was deacetylated to thiolactoside **8**, which after neutralization and purification, underwent the now routine one-pot procedure to give lactosyl benzylidene acetal **18** in reproducible yield.[36]

In summary, an unprecedented TsOH-catalyzed one-pot acetalation–acetylation was developed, which streamlines the routine protecting-group manipulation procedures and obviate the use of toxic pyridine in preparation of a wide diversity of differentially protected thioglycosides.

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

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References and Notes

(1) Kartha, K. P. R.; Jennings, H. J. *J. Carbohydr. Chem.* **1990**, *9*, 777.
(2) Kumar, R.; Tiwari, P.; Maulik, P. R.; Misra, A. K. *Eur. J. Org. Chem.* **2006**, 74.
(3) Mukhopadhyay, B.; Kartha, K. P. R.; Russell, D. A.; Field, R. A. *J. Org. Chem.* **2004**, *69*, 7758.
(4) (a) Tai, A.-A.; Kulkarni, S. S.; Hung, S.-C. *J. Org. Chem.* **2003**, *68*, 8719. (b) Tiwari, P.; Kumar, R.; Maulik, R.; Misra, A. K. *J. Carbohydr. Chem.* **2005**, *24*, 723. (c) Lin, C.-C.; Huang, L.-C.; Liang, P.-H. *J. Carbohydr. Chem.* **2006**, *25*, 303. (d) Dasgupta, S.; Rajput, V. K.; Roy, B.; Mukhopadhyay, B. *J. Carbohydr. Chem.* **2007**, *26*, 91. (e) Valerio, S.; Iadonisi, A.; Adinolfi, M.; Ravidà, A. *J. Org. Chem.* **2007**, *72*, 6097.
(5) (a) 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 (London)* **2007**, 896. (b) Français, A.; Urban, D.; Beau, J.-M. *Angew. Chem. Int. Ed.* **2007**, *46*, 8662.
(6) (a) De Belder, A. N. *Adv. Carbohydr. Chem. Biochem.* **1965**, *20*, 219. (b) De Belder, A. N. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 179.
(7) Kihlberg, J.; Frejd, T.; Jansson, K.; Magnusson, G. *Carbohydr. Res.* **1986**, *152*, 113.
(8) (a) Barili, P. L.; Berti, G.; Catelani, G.; Colonna, F.; Marra, A. *Tetrahedron Lett.* **1986**, *27*, 2307. (b) Foster, A. B.; Overend, W. G.; Stacey, M.; Wiggins, L. F. *J. Chem. Soc.* **1949**, 2542.
(9) Hung, S.-C.; Chen, C.-S. *J. Chin. Chem. Soc.* **2000**, *47*, 1257.
(10) Mukherjee, D.; Ali Shah, B.; Gupta, P.; Taneja, S. C. *J. Org. Chem.* **2007**, *72*, 8965.
(11) Freudenberg, K.; Hixon, R. M. *Ber. Dtsch. Chem. Ges.* **1923**, *56*, 2119.
(12) Winnik, F. M.; Carver, J. P.; Krepinsky, J. J. *J. Org. Chem.* **1982**, *47*, 2701.
(13) Wood, H. B. Jr.; Diehl, H. W.; Fletcher, H. G. Jr. *J. Am. Chem. Soc.* **1957**, *79*, 1986.
(14) Lipták, A.; Imre, J.; Nanási, P. *Carbohydr. Res.* **1981**, *92*, 154.
(15) Boulineau, F. P.; Wei, A. *Carbohydr. Res.* **2001**, *334*, 271.
(16) Kartha, K. P. R. *Tetrahedron Lett.* **1986**, *27*, 3415.
(17) (a) Chen, C.-T.; Weng, S.-S.; Kao, J.-Q.; Lin, C.-C.; Jan, M.-D. *Org. Lett.* **2005**, *7*, 3343. (b) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.
(18) (a) Chen, C.-T.; Weng, S.-S.; Kao, J.-Q.; Lin, C.-C.; Jan, M.-D. *Org. Lett.* **2005**, *7*, 3343. (b) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.
(19) Bizier, N. P.; Atkins, S. R.; Helland, L. C.; Colvin, S. F.; Twitchell, J. T.; Cloninger, M. J. *Carbohydr. Res.* **2008**, *343*, 1814; and references therein.
(20) Chao, C.-S.; Chen, M.-C.; Lin, S.-C.; Mong, K.-K. T. *Carbohydr. Res.* **2008**, *343*, 957; and references therein.
(21) (a) Qiu, D.; Koganty, R. R. *Tetrahedron Lett.* **1997**, *38*, 45. (b) Mong, T. K.-K.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4087. (c) Fan, R.-H.; Achkar, J.; Hernández-Torres, J. M.; Wei, A. *Org. Lett.* **2005**, *7*, 5095. (d) Lopin, C.; Jacquinet, J.-C. *Angew. Chem. Int. Ed.* **2006**, *45*, 2547. (e) Manabe, S.; Ishii, K.; Ito, Y. *J. Org. Chem.* **2007**, *72*, 6107.
(22) Mukhopadhyay, B.; Russell, D. A.; Field, R. A. *Carbohydr. Res.* **2005**, *340*, 1075.
(23) Mukhopadhyay, B. *Tetrahedron Lett.* **2006**, *47*, 4337.
(24) Compound **4** was obtained by literature procedure reported in: Ahn, Y. M.; Gray, G. R. *Carbohydr. Res.* **1997**, *298*, 279.
(25) Unprotected thioglycosides **5**–**10** were derived from the corresponding peracetyl thioglycosides by Zemplèn deacetylation. Peracetyl thioglycosides were prepared by literature procedure reported in ref. 20.
(26) Compound **12** was obtained by literature procedure reported in: Kondo, H.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1992**, *114*, 8148.
(27) Preparatory procedures of compounds **3** and **11** were described in supporting information.
(28) Larsen, K.; Olsen, C. E.; Motawia, M. S. *Carbohydr. Res.* **2003**, *338*, 199.
(29) Mong, T. K.-K.; Huang, C.-Y.; Wong, C.-H. *J. Org. Chem.* **2003**, *68*, 2135.
(30) **General One-Pot Benzylidenation–Acetylation Procedure for the Preparation of 2 and 13–20**
TsOH (10–32 mol%, Table 1) was added into a stirring mixture of carbohydrate substrate (1.0 equiv of methyl α-D-glucopyranoside, **3**–**8**, **10**, or **11**) and $PhCH(OMe)_2$ (1.5 equiv) in MeCN under N_2. Upon complete conversion into benzylidene acetal intermediate as assessed by TLC, Ac_2O (1.5 equiv per OH, total OH equals to the sum of OH of acetal intermediate plus MeOH released from acetalating reagent) was added, and the reaction temperature was brought up to 40 or 50 °C (Table 1). Specific reaction conditions are detailed in the supporting information. Upon complete acetylation as assessed by TLC, excess EtOAc (4 × volume of MeCN used) was added to the mixture, which was then washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated for purification by flash column chromatography over SiO_2. Elution with EtOAc–hexane mixture afforded the compounds **2** and **13**–**20**.
(31) **General One-Pot Isopropylidenation–Acetylation Procedure for Preparation of 21–24**
TsOH (5–10 mol%, Table 1) was added into a stirring mixture of unprotected thioglycoside (1.0 equiv of **5**, **6**, **9**, or NANA ester **12**), and $Me_2CH(OMe)_2$ (1.5 equiv) in acetone. The mixture was stirred at r.t. or 40 °C under N_2. Upon complete conversion into glycosyl ketal intermediate as assessed by TLC, Ac_2O (1.5 equiv per OH, total OH equals to OH from glycosyl acetal intermediate plus MeOH released from acetalating reagent) was added, and the reaction temperature was brought up to 35 or 40 °C (Table 1). Specific reaction conditions for preparation of compounds **21**–**24** were detailed in the supporting information. Upon complete acetylation as assessed by TLC, excess EtOAc (4 × volume of MeCN used) was added to the mixture, which was then washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated for purification by flash column chromatography over SiO_2. Elution with EtOAc–hexane mixture afforded compounds **21**–**24**.
(32) Ziegler, T.; Herold, G. *Liebigs Ann. Chem.* **1994**, 859.
(33) Nishida, Y.; Dohi, H.; Uzawa, H.; Kobayashi, K. *Tetrahedron Lett.* **1998**, *39*, 8681.
(34) In *Monosaccharides: Their Chemistry and their Roles in Natural Products*; Collins, P. M.; Ferrier, R. J., Eds.; John Wiley and Sons: New York, **1996**, 389–405.
(35) Lu, K.-C.; Hseih, S.-Y.; Patkar, L. N.; Chen, C.-T.; Lin, C.-C. *Tetrahedron* **2004**, *60*, 8967.
(36) For acid-catalyzed one-pot acetalation–acetylation, unnecessary prolonged reaction time would compromise the yield of reaction due to the cleavage of the acetal function.